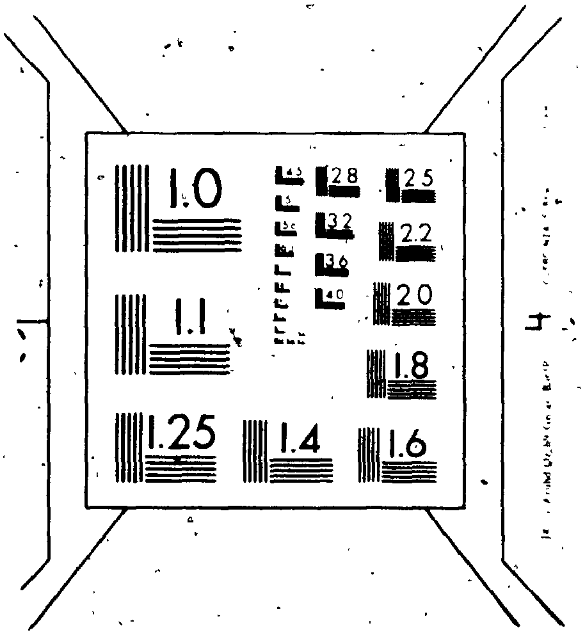
1



39056

National Library of Canada
Bibliothèque nationale du Canada

CANADIAN THESES ON MICROFICHE
THÈSES CANADIENNES SUR MICROFICHE

NAME OF AUTHOR/*NOM DE L'AUTEUR* Mr. Kazuyuki Yamasaki

TITLE OF THESIS/*TITRE DE LA THÈSE* Studies Directed Towards the Total Synthesis of Some Higher 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* 1978

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

Permission is hereby granted to the NATIONAL LIBRARY OF CANADA to microfilm this thesis and to lend or sell copies of the film.

The author reserves other publication rights, and neither the thesis nor extensive extracts from it may be printed or otherwise reproduced without the author's written permission.

L'autorisation est, par la présente, accordée à la BIBLIOTHÈQUE NATIONALE DU CANADA de microfilmer cette thèse et de prêter ou de vendre des exemplaires du film.

L'auteur se réserve les autres droits de publication; ni la thèse ni de longs extraits de celle-ci ne doivent être imprimés ou autrement reproduits sans l'autorisation écrite de l'auteur.

DATED/*DATÉ* Oct 23, 1978 SIGNED/*SIGNÉ*

PERMANENT ADDRESS/*RÉSIDENCE FIXE*
1330-5, Arinocho Kamite, Kitaku
Kobe-shi, Hyogoken, Japan

NL-91 (11-73)

National Library of Canada

Cataloguing Branch
Canadian Theses Division

Ottawa, Canada
K1A 0N4

Bibliotheque nationale du Canada

Direction du catalogage
Division des theses canadiennes

NOTICE

The quality of this microfiche is heavily dependent upon the quality of the original thesis submitted for microfilming Every effort has been made to ensure the highest quality of reproduction possible

If pages are missing, contact the university which granted the degree

Some pages may have indistinct print especially if the original pages were typed with a poor typewriter ribbon or if the university sent us a poor photocopy

Previously copyrighted materials (journal articles, published tests, etc.) are not filmed

Reproduction in full or in part of this film is governed by the Canadian Copyright Act, R S C 1970, c C-30 Please read the authorization forms which accompany this thesis.

THIS DISSERTATION
HAS BEEN MICROFILMED
EXACTLY AS RECEIVED

AVIS

La qualite de cette microfiche depend grandement de la qualite de la these soumise au microfilmage Nous avons tout fait pour assurer une qualite superieure de reproduction

S il manque des pages, veuillez communiquer avec l universite qui a confere le grade

La qualite d impression de certaines pages peut laisser a desirer, surtout si les pages originales ont ete dactylographiees a l aide d un ruban use ou si l universite nous a fait parvenir une photocopie de mauvaise qualite

Les documents qui font deja l objet d un droit d auteur (articles de revue, examens publies, etc) ne sont pas microfilmes

La reproduction, même partielle, de ce microfilm est soumise à la Loi canadienne sur le droit d auteur, SRC 1970, c C-30 Veuillez prendre connaissance des formules d autorisation qui accompagnent cette thèse

LA THÈSE A ÉTÉ
MICROFILMÉE TELLE QUE
NOUS L'AVONS REÇUE

NL-339 (3/77)

STUDIES DIRECTED TOWARDS THE TOTAL SYNTHESIS OF SOME HIGHER TERPENOIDS

by

Kazuyuki Yamasaki, B.Eng., M.Eng. (Kyoto University)

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
Ottawa, Ontario

September, 1978

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

....
Thesis Supervisor

C.H. Amberg
....
Chairman, Department of Chemistry

....
External Examiner

Carleton University

ABSTRACT

Several approaches to the total synthesis of clerodane diterpenes and pentacyclic triterpenes were investigated.

In Part I, the synthesis of 2,2-ethylenedithio-4aα,5-dimethyl 1-(3-oxobutyl)-1,2,3,4,4a,7,8,8aβ-octahydronaphthalene (67) is described. This compound is considered to be a potentially useful synthon for the synthesis of some trans-clerodanes.

In Part II, two approaches to a key synthetic intermediate (144) in our synthetic plans for dl-friedelin are reported.

The first approach led to the synthesis of 2-allyloxy-1,4aβ,7,7-tetramethyl-3,4,4a,5,6,7,8,8aβ-octahydronaphthalene (177). Rigorous proof for the stereochemical assignment of its ring junction is presented in addition to the results on the attempted Claisen rearrangement of the molecule.

In the second approach the effective synthesis of 3,3,10aβ-trimethyl-1,2,3,4,4aβ,5,8,9,10,10a-decahydrophenanthren-7(6H)-one (221) was achieved. The D/E ring junction of the molecule was firmly established to be cis by the use of ^{13}C nmr spectra. This synthetic intermediate can serve as the key substance for a synthetic entry to friedelin as well as β-amyrin. Logistically possible synthetic pathways to correlate this compound with friedelin are discussed.

ACKNOWLEDGEMENTS

I would like to express my hearty thanks to Professor John W. ApSimon whose enthusiasm, interest, and understanding have guided this work, and whose help has made my stay at Carleton University possible during the period of this research.

The friendly advice of Messrs. Nguyen D. Tho and Jean D. Burnell is greatly acknowledged.

Valuable suggestions and comments from Dr. S. Badripersaud are deeply appreciated.

Continual help from Mr. Karl Diedrich was essential to the research reported in this thesis.

I am indebted to Dr. Alain Fruchier (Université de Montpellier) for the 100 MHz nmr spectra of some synthetic samples.

I appreciate the encouragement given by Prefessor Mamoru Ohashi (The University of Electro-Communications, Tokyo).

Financial assistance in the form of teaching assistantship and scholarship from Carleton University is greatly acknowledged.

Finally, I wish to thank my parents for their complete support during my education.

TABLE OF CONTENTS

PART I

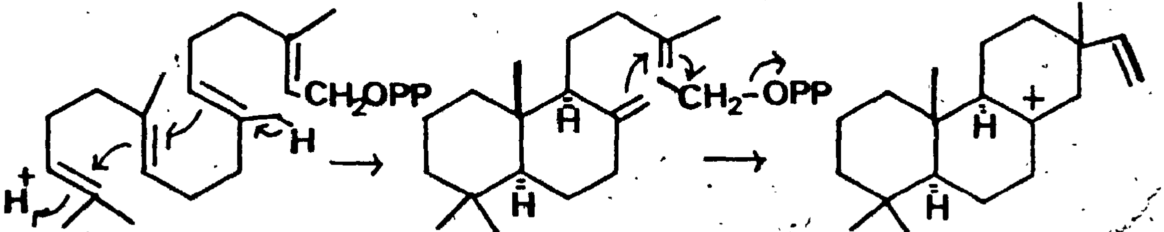
INTRODUCTION

The diterpenoids form a large group of C_{20} substances derived biogenetically from geranylgeranyl pyrophosphate (1).[1] They exhibit a wide range of biological activity, and are mainly of plant or fungal origin.[2] Amongst them, perhaps the best known substances are gibberellin plant growth hormones.[3] Resin acids are other representatives of the diterpenoids and are believed to possess a mild antibiotic action against microbial decay of wood fibres.[4]

Based on the Biogenetic Isoprene Rule[5] the major structural varieties within the class can be rationalized in terms of the stepwise cyclization of the biogenetic precursor, geranylgeranyl pyrophosphate (1). Such biogenetic consideration has led to the understanding of the structural relationships among the main diterpenes.[6]

The major mode of cyclization of geranylgeranyl pyrophosphate (1) is initiated by protonation of a double bond in contrast to triterpenoids and steroids both of which arise from attack on squalene epoxide (see Introduction to Part II of this thesis p.28), resulting in the formation of the bicyclic labdadienol pyrophosphate (2) (Scheme 1).[7] In the next cyclization the pyrophosphate group serves as a leaving group, and thus the pimarane skeleton (3) is formed (Scheme 1). The tricyclic pimarane cation (3) may readily act as a progenitor of various tricyclic and tetracyclic diterpenes through rearrangement, and cyclization. Further structural variations among the tricyclic and tetracyclic diterpenes emerge as a result of secondary rearrangement, ring cleavage, contraction and expansion.[8]

Scheme 1



(1)

(2)

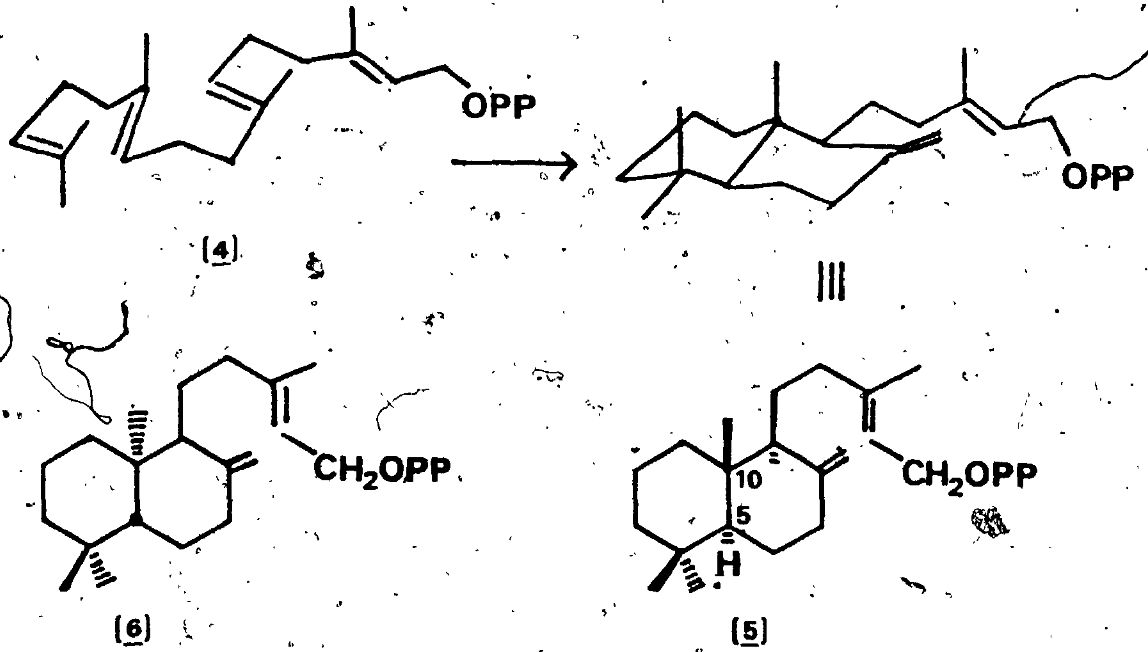
(3)

geranylgeranyl
pyrophosphate

One of the most notable characteristics of the diterpenoids is the appearance of the normal and antipodal A/B ring junctions. The former belongs to the same optical series as steroids, whereas the latter belongs to the opposite series. The formation of both series depends on the mode of the cyclization of all-trans-geranylgeranyl pyrophosphate (4) in the most stable all chair conformation giving rise to the normal A/B ring junction, as in the bicyclic labdane pyrophosphate (2) bearing the stereostructure (5) with regard to the absolute stereochemistry at C-5 and C-10 (for the numbering system of labdanes; see APPENDIX I p. 165).

On the other hand a different mode of coiling of geranylgeraniol pyrophosphate (1) on an enzyme surface is also possible, by which the antipodal A/B ring junction as found in (6) results.[9] The cyclization leading to the normal A/B ring junction series can be visualized as in Scheme 2.

Scheme 2



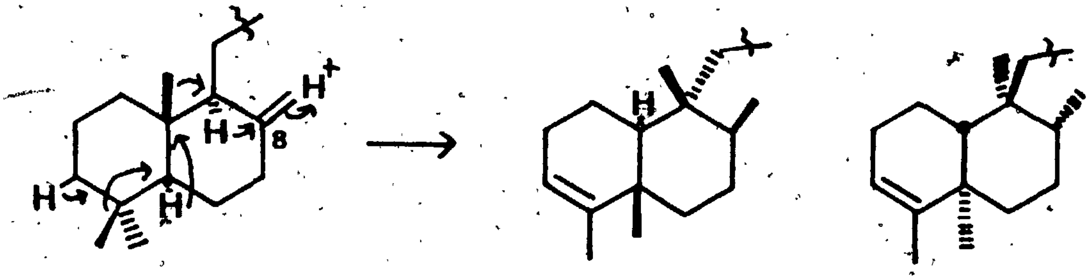
Thus, examples of both series are widespread in nature and are occasionally found in the same plants. About 700 different diterpenes have been recorded[10] with frequent reports of new species appearing[11].

Clerodane Diterpenoids:

The bicyclic diterpenes whose origin in biogenesis is the labdadienol pyrophosphate (2) may be classified into two subgroups; labdanes and clerodanes. Some fifty diterpenes belonging to the latter group, the clerodanes have been isolated,[10] and particularly extensive studies on the chemotaxonomy of the Solidago species, probably the richest source of these diterpenes, by two groups[12a,12b] have revealed a few interesting facets inherent in these diterpenes.

Biosynthetically, these diterpenes are derivable from the labdanes by way of a Wagner-Meerwein type rearrangement.[13] This rearrangement consists of a number of methyl and hydride shifts as illustrated in Scheme 3, and is initiated by protonation of the C-8 double bond, and is terminated by the formation of a double bond on ring A (for the numbering system; see APPENDIX I p. 165).

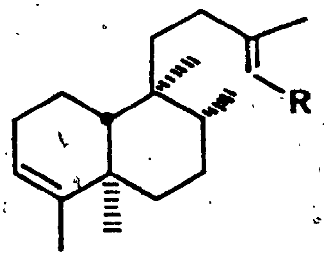
Scheme 3



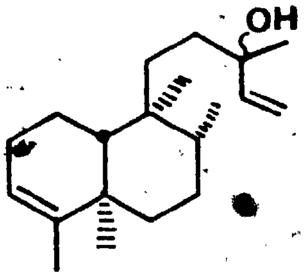
(5) (7) (8)

Occurrence of both series (normal and antipodal), represented by (7) and (8), is also observed. Mechanistically, the overall rearrangement is in conformity with the postulate that all the migrating groups involved be located in a trans-diaxial relationship to each other.[14] However, the findings that some members of this class of diterpene possess a cis-A/B ring fusion have revealed that this postulate no longer holds in explaining these instances. In order to accommodate these facts, it has been suggested that the syn-1,2-rearrangement necessary for the occurrence of the cis-A/B ~~ring-~~fusion in nature must be operative during the biogenesis of these species.[14]

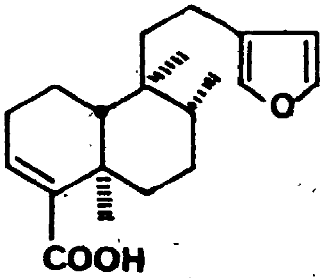
Another interesting feature is the variety of oxygenation patterns found in this class of diterpene.[15] Oxygenation occurs at nuclear sites as well as on the side chain portion, and interestingly the oxidation level of the side chain frequently involves the formation of a furan ring. The variations of oxygenation are exemplified by the following representatives of the class ((9), (10), (11), and (12)).



(9) R=CH_2OH kolavenol
(10) R=COOH kolavenic acid

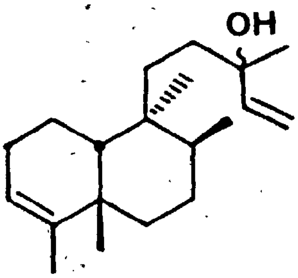


(11) kolavelool

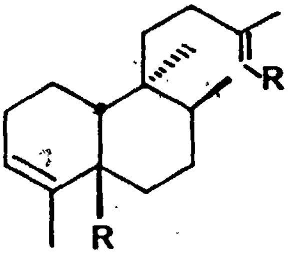


(12) hardwickic acid

Kolavenol (9) represents the *trans*-fused clerodanes and was found in the oleoresin of *Hardwickia pinnanate* with a series of closely related diterpenes.[16] They were kolavenic acid (10), kolavelool (11), and hardwickic acid (12).

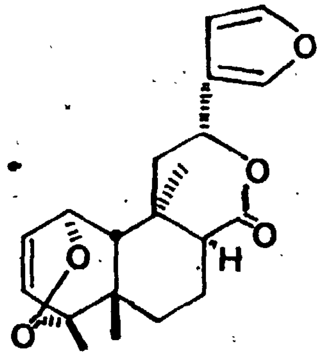


(13) plathytenol



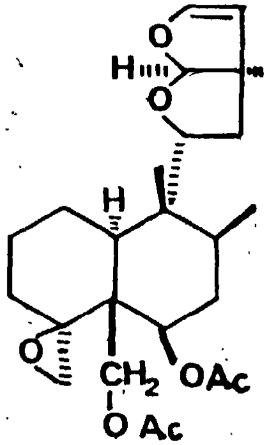
(14) R=CH$_2$OH cistodiol

(15) R=COOH cistodioic acid

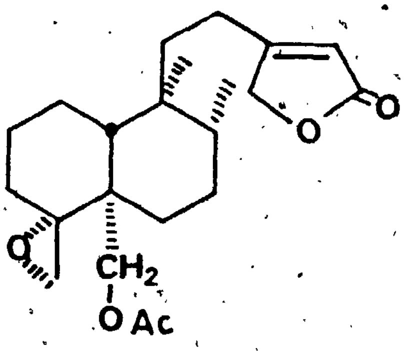


(16) columbin

Some representatives of the *cis*-fused clerodanes are displayed above. Plathytenol (13) was isolated from *Plathymenia reticulata*.[17] Both cistodiol (14) and cistodioic acid (15) were isolated from *Cistus monspeliensis*.[18] Columbin (16) is the most important bitter principles of the Colombo root (*Jateorrhiza palmeta*), and its structure was elucidated by Barton's group[19] based on chemical degradation studies. Probably one of the most highly oxygenated examples of this class is a bitter principle, clerodin (17). The structure of clerodin (17) was established by X-ray analysis[20] and complementary studies using chemical degradation methods[21]. Regardless of the A/B ring fusion (*cis* or *trans*), most members of the diterpenes belonging to the clerodanes are bitter principles and do not exhibit any significant biological activity; in this context, however, several new clerodanes such as ajugarin (18) have been found to possess insect antifeedant activity against African army worms.[22]



(17) clerodin

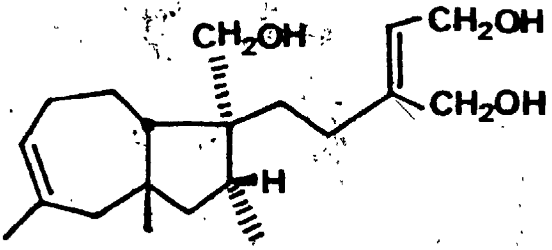


(18) ajugarin 1

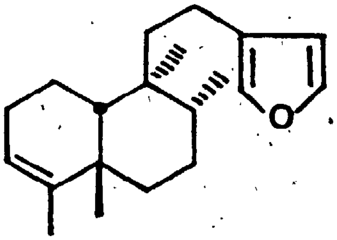
From the synthetic point of view, the varying nature of the side chain in addition to four contiguous asymmetric centers on the bicyclic skeleton (i.e. C-5, C-8, C-9, and C-10) renders these diterpenes attractive molecules for study. Consequently, a number of synthetic approaches directed towards the clerodanes have emerged quite recently,[23a,23b] one of which will be summarized in the following section and it is this part of the thesis that is concerned with the elaboration of another synthetic route.[24]

Synthesis of the Clerodanes:

A few years ago, Tokoroyama and coworkers[25] reported a highly imaginative and stereospecific total synthesis of portulal (19)[26], a unique diterpene with a perhydroazulene skeleton and clerodane-type side chain, which shows plant growth-regulating activity. Close resemblance of the stereostructure of portulal (19) with that of the furanoid *cis*-clerodane (20)[27] led them to choose (20) as their second synthetic target since most of the synthetic problems anticipated in this route had already been solved in the portulal synthesis.[23b]



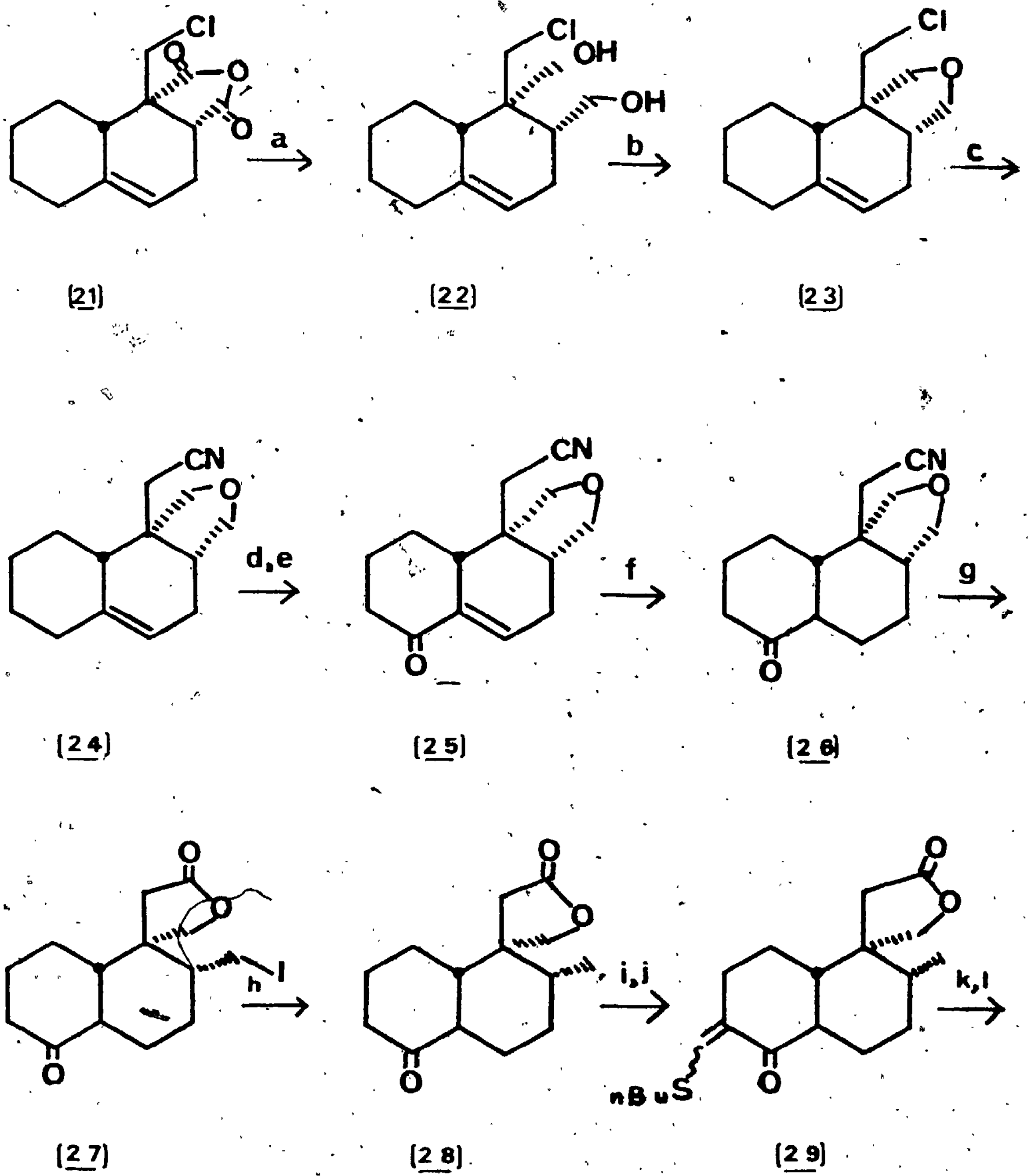
(19) portulal



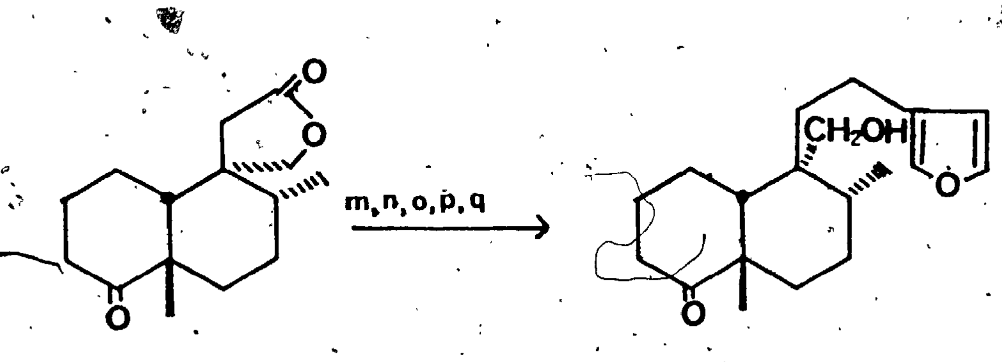
(20)

Their approach as outlined in Scheme 4 starts from the intermediate (21)[28], which has been used for the portulal synthesis. This intermediate possesses the correct stereochemistry for (20) at C-8, C-9, and C-10 as well as a side chain suitable for modification to that of (20). Compound (24) was derived from (21), which had been prepared by a Diels-Alder reaction of chloromethylmaleic anhydride with 1-vinylcyclohexene.

Scheme 4



Scheme 4 continued

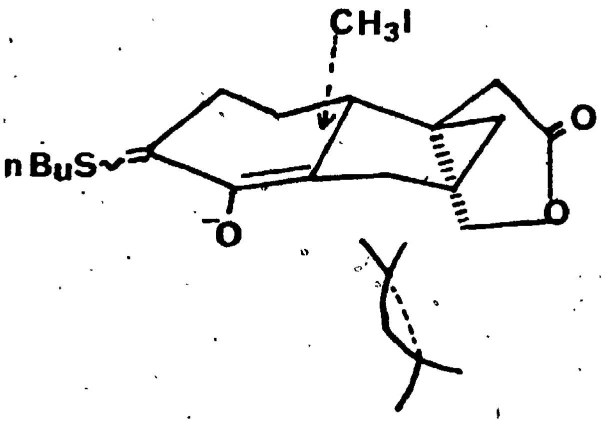


[30] [31]

Reagents: (a) $LiAlH_4$; (b) tosyl chloride, pyridine; (c) NaCN, NaI, DMSO; (d) SeO_2; (e) MnO_2 ; (f) H_2, 10% Pd/C, ethanol; (g) HI, CH_3COOH; (h) Zn, CH_3COOH; (i) NaH, $HCO_2C_2H_5$; (j) nBuSH; (k) t-AmOK, CH_3I; (l) OH^-; (m) β-furyllithum ; (n) $NaAlH_2(OCH_2CH_2OCH_3)_2$, ethanol; (o) $(CH_3CO)_2O$, pyridine; (p) Li, liq. NH_3; (q) OH^-.

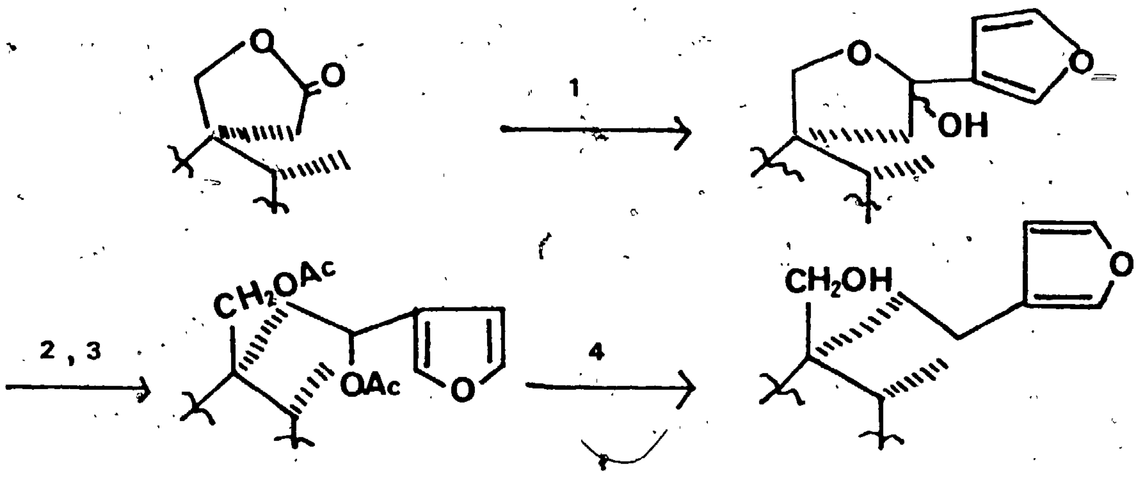
Initial attempts to replace chlorine on the side chain by cyanide ion directly failed probably because of the neopentyl type of substitution, but eventually it was overcome by conducting the substitution reaction on the cyclic ether (23). First, compound (21) was reduced with lithium aluminium hydride to afford the diol (22). Treatment of this diol with tosyl chloride and pyridine gave the cyclic ether (23). Heating this ether with sodium cyanide and sodium iodide in dimethyl sulphoxide at 120° replaced the chlorine by the cyanide group to give (24) (94%).

It must be noted that asymmetric centres at C-8, C-9, and C-10 are rigorously established in one step by a Diels-Alder reaction, and that compound (24) carries these correctly disposed centres. Oxidation first with selenium dioxide and then with manganese dioxide created a carbonyl group at C-4 of the cyclic ether (24) (25%). Compound (25) thus obtained was subjected to hydrogenation over 10% Pd/C in ethanol, yielding (26). Cleavage of the cyclic ether and concomitant hydrolysis of the cyano group in ketone (26) was effected upon treatment with hydroiodic acid to afford the lactone (27), the iodine of which was removed reductively in the next step (i.e. (27)-(28)). Initial attempts to introduce an angular methyl group at C-5 of the lactone (28) by addition of Simmons-Smith reagent[29] to an enol acetate prepared from (28) were unsuccessful, and hence an alternative method, developed by Ireland and Marshall[30], involving the prior blocking of the C-3 by n-butylthiomethylene group in order to direct the angular methylation, was employed. Thus methylation with methyl iodide followed by the deblocking of the protecting group was conducted with reasonable success (i.e. (29)-(30)). The stereochemistry of the methyl group introduced was assumed to be β because of steric hindrance on the α-side exerted by the lactone ring (see below).



In fact, compound (30) was obtained as the sole product (59%) when the n-butylthiomethylene derivative (29) was methylated with methyl iodide in the presence of a large excess of base. The furan ring could be incorporated in the lactone (30) in the identical manner to that used on the model compound[25]. Thus the sequence involved was; 1) addition of β-furyllithium ; 2) reduction of the resultant hemiketal with Vitride reagent ($NaAlH_2(OCH_2CH_2OCH_3)_2$); 3) *in situ* acetylation ; 4) hydrogenolysis with lithium in liquid ammonia. The whole sequence is shown in Scheme 5.

Scheme 5

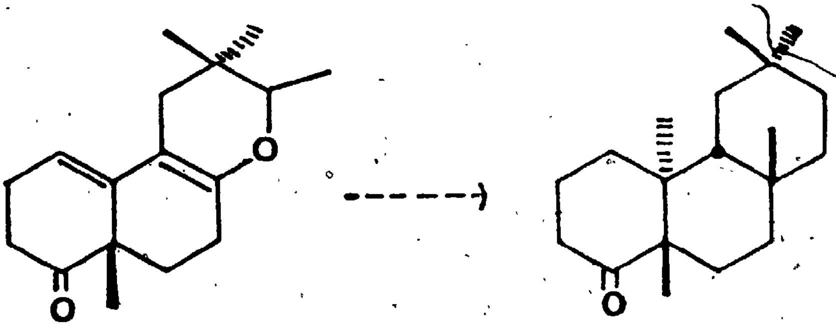


Accordingly, compound (31) was obtained.[23b] Modification of the A ring, probably by reaction with methyl Grignard reagent or addition of methyllithium , and subsequent dehydration in addition to removal of the hydroxyl group at C-20 in (31) would complete this synthesis.

RESULTS AND DISCUSSION

In our plans for the total synthesis of pentacyclic triterpenes, a novel approach relying on the conversion of compound (32)* to (33) (Scheme 6), which would lead to an appropriately functionalized building block for the CDE ring unit of some triterpenes (see Introduction to PART II of this thesis, p. 28), was investigated in these laboratories a few years ago.

Scheme 6

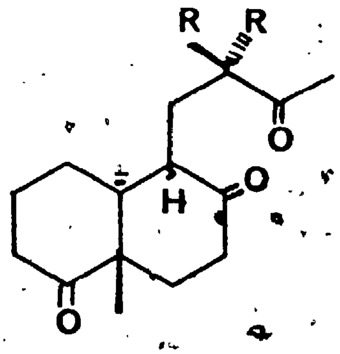


(32) (33)

Although the approach in its original form produced discouraging results, the intermediate (34) which is logistically located in this synthetic scheme attracted our attention during the investigation.

---

* Except for the structures representing natural products, all structural formulae containing one or more asymmetric carbons depict one enantiomer but refer to racemic compounds throughout. In the text only an enantiomer bearing a direct relationship to the natural series is shown for convenience.

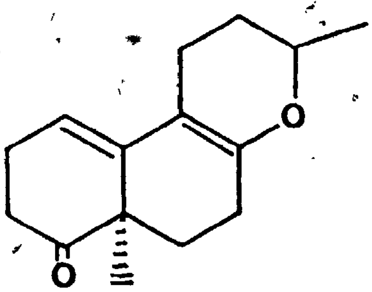


(34) $R=CH_3$

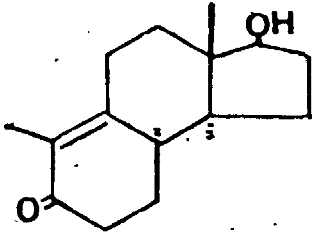
(35) $R=H$

If the three ketone moieties in a similar molecule (35) were carefully differentiated so that they could be manipulated successively at appropriate stages in a synthesis, the triketone (35) would be suitable for possible conversion to such a clerodane skeleton as present in kolavenol (9). The relationship in structure between the two is obvious and furthermore the two ketones on the A and B ring of (35) are ideally disposed so as to introduce three methyl groups at C-4, C-8, and C-9, the third ketone on the side chain being a means by which various functionalities would be added. These considerations led us to consider a suitably constructed synthon analogous to the ketone (35) as a synthetic goal.

As a consequence, a program was initiated that was aimed primarily at the synthesis of diene (36) and secondly at its further elaboration to the clerodane framework. The original version of th[illegible]te leading to (32) had been exploited by the Hoffman-La R[illegible] group[31] during their work directed towards the total synthesis of 19-norsteroids, especially centred on asymmetric induction during the synthesis.



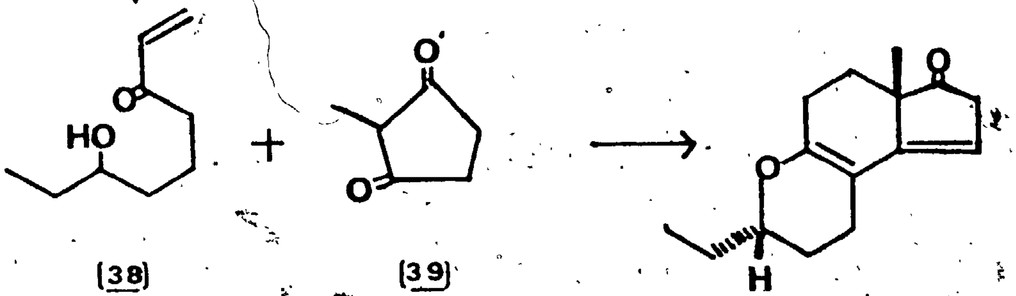
(36)



(37)

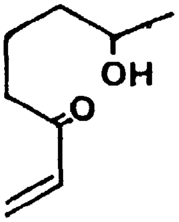
Some members of the steroids occupy a central role in human contraception.[32] The first paper of the Hoffman-La Roche group in this series which was published in 1971[33] described a unique synthesis of the BCD tricyclic building block (37) for 19-nor-steroids based on the novel condensation of 7-hydroxy-1-nonen-3-one (38) with 2-methylcyclopentane-1,3-dione (39) as is shown in Scheme 7.

Scheme 7

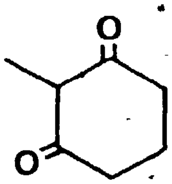


(38) (39) (40)

It was thus thought that the condensation of 7-hydroxy-1-octene-3-one (41) and 2-methylcyclohexane-1,3-dione (42) could be accomplished in a similar fashion.

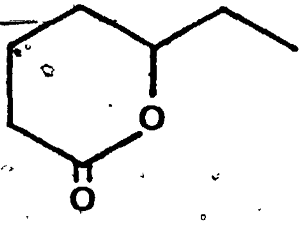


[41]

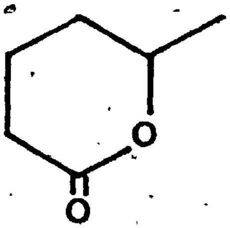


[42]

Since Saucy and coworkers[34] had reported the direct preparation of the enone (38) from the δ-lactone (43) by the Grignard reaction with vinylmagnesium chloride in tetrahydrofuran at -50°, the logical precursor of the similar enone (41) in our case was the corresponding δ-lactone (44).



[43]

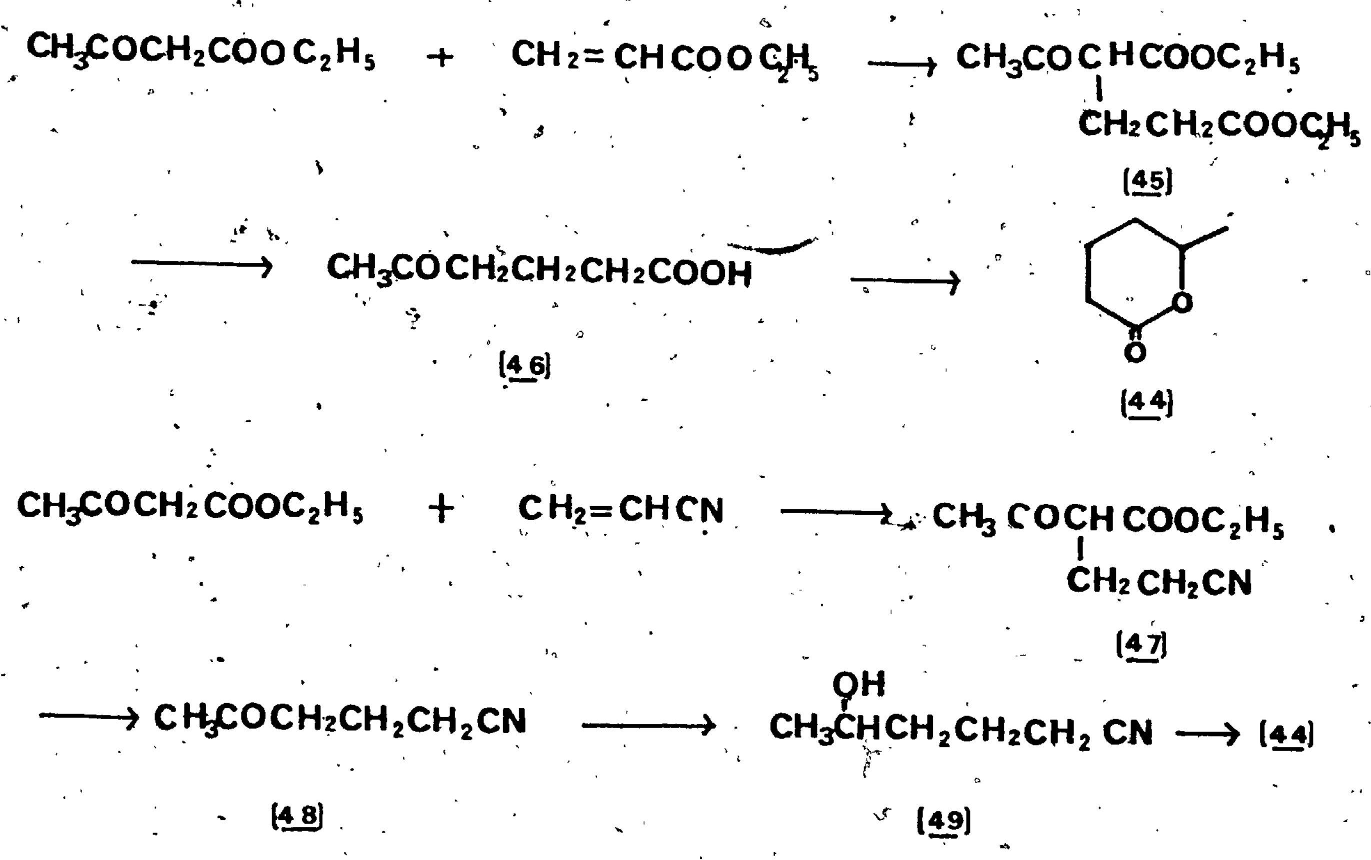


[44]

We therefore set out to prepare the lactone (44). In one route, according to Korte and coworkers[35], ethyl acetoacetate was condensed with ethyl acrylate in the presence of sodium methoxide to give the adduct (45), which was in turn decarboxylated in dilute sulphuric acid to furnish the ketoacid (46). Reduction of this acid with sodium borohydride followed by vacuum distillation yielded the required δ-lactone (44) in 18% overall yield.

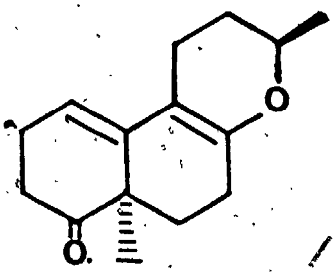
The other route, quite similar to the foregoing one, was developed when ethyl acrylate was not available. In this route, adduct (47) prepared from the base-condensation of ethyl acetoacetate and acrylonitrile was decarboxylated by refluxing in aqueous potassium carbonate solution, producing the ketonitrile (48) in this case. Sodium borohydride reduction of the nitrile (48) and hydrolysis of the resultant alcohol (49) with sodium hydroxide afforded the δ-lactone (44) after vacuum distillation. Thus, this alternative route also gave the same lactone, but with much less efficiency (4% overall yield). The two routes are shown below (Scheme 8).

Scheme 8

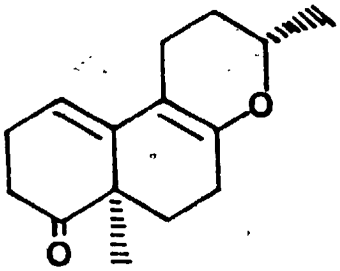


Carefully controlled reaction of the lactone (44) with vinylmagnesium bromide at -90° (dry ice-ether bath) was found to give the expected vinyl ketone (41) after some experimentation. As Saucy[34] pointed out concerning the preparation of the similar ketone (38), the success of this transformation appears to be critically dependant upon the low temperature at which the Grignard reaction is conducted. Since the vinyl ketone (41) proved to be unstable even when it was stored in a refrigerator, it was used in the next step immediately after its preparation and without purification.

Condensation of the crude (41) with 2-methylcyclohexane-1,3-dione (42), in a similar manner to the reaction of (38) and (39) (Scheme 7), was carried out in boiling toluene-acetic acid mixture, producing the diene (36) in ca. 40% yield. The product (36) was shown by nmr to be a single isomer of the two conceivable diastereoisomers (50) (trans-racemate) and (51) (cis-racemate).



(50)

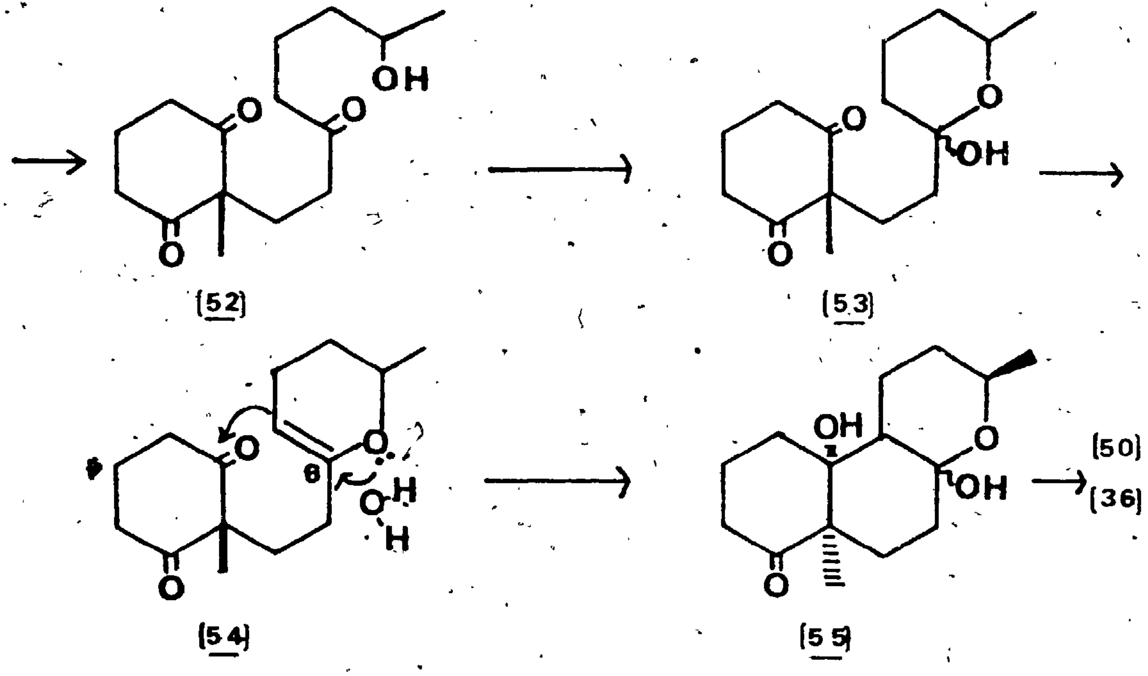


(51)

Based on the Saucy's findings[34] that the trans-compound (40) predominated in the condensation mixture as proved by the use of an optically active lactol, the trans-structure (50) was tentatively assumed in our case.

The formation of diene (36) (or (50)) can be explained by adoption of the mechanism[31] that was proposed to account for the formation of (40) and related compounds (see Scheme 9).

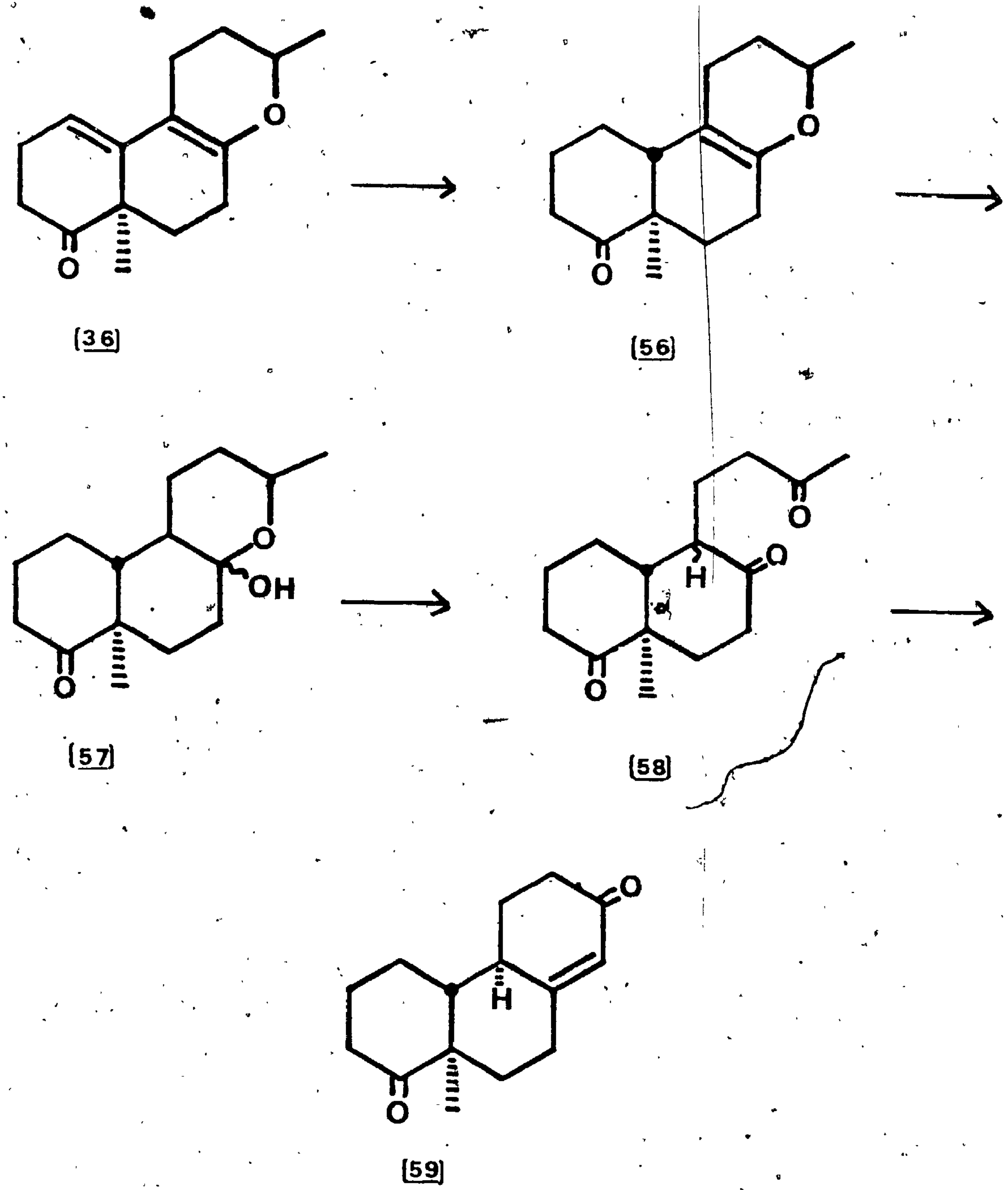
Scheme 9



The initial step consists of a Michael addition leading to the adduct (52) which would first cyclize to hemiketal (53) and then this species gives (54) upon dehydration. A second cyclization presumably assisted by attack of a water molecule at C-8 would take place in the intermediate (54), resulting in the formation of the tricyclic (55). Elimination of two molecules of water then yields the diene (36).

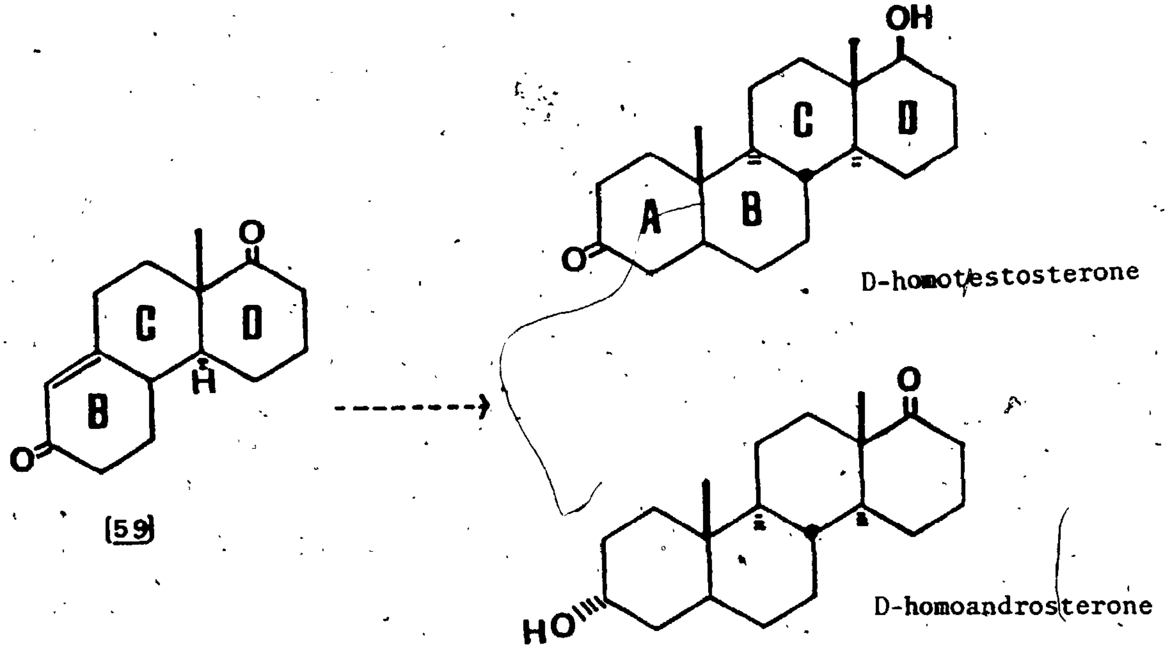
Hydrogenation of the diene (36) in toluene over a palladiumcatalyst gave the enol ether (56) as an only isolable product in nearly quantitative yield, leaving the enol double bond present in the diene (36) intact. The trans-stereochemistry with respect to the A/B ring junction had been expected on the basis of analogous hydrogenations[33,34], and it was finally confirmed to be trans when the enol ether (56) was converted into the known steroidal intermediate (59)[36a,36b] via the sequence shown in Scheme 10 (p. 21). Thus the enol ether (56) was hydrated with 1N sulphuric acid in acetone to afford the hemiketal (57), which was then oxidized with Jones' reagent to give the triketone (58). These hydration and oxidation steps could be carried out in one pot by adding a solution of chromium trioxide in 6N sulphuric acid to the acetone solution containing (57). At this stage it was noticed that the prolonged treatment of the hemiketal (57) with Jones' reagent significantly diminished the yield of the triketone probably because of the strong acidity of the medium. The final cyclization of (58) to (59) was effected either by refluxing in benzene with p-toluenesulphonic acid or in methanol with potassium hydroxide. The latter conditions (base-treatment) were found to be superior to the former acid-catalyzed cyclization, for the product obtained in the former process seemed to be contaminated by impurities which we were unable to remove completely. The yield from the abovementioned operations was in the range of 20-30% and the overall yield from the lactone (44) was ca. 8%. The final product (59) was identical in all respects with an authentic sample kindly provided by Professor S. Danishefsky (University of Pittsberg). In this manner, the expected trans-stereochemistry at the A/B ring junction was confirmed at this point.

Scheme 10



As the following scheme (Scheme 11) indicates, it is interesting to note that the tricyclic compound (59) can be considered as a BCD ring synthon for the synthesis of some homosteroids. Further work on the possible transformation into these steroids was not undertaken in view of the poor yield of the overall processes, however taking Saucy's report[34] into account, it would be envisaged that the tricyclic compound (59) might be available in optically active form by way of this approach should optically active (44) be obtained.

Scheme 11

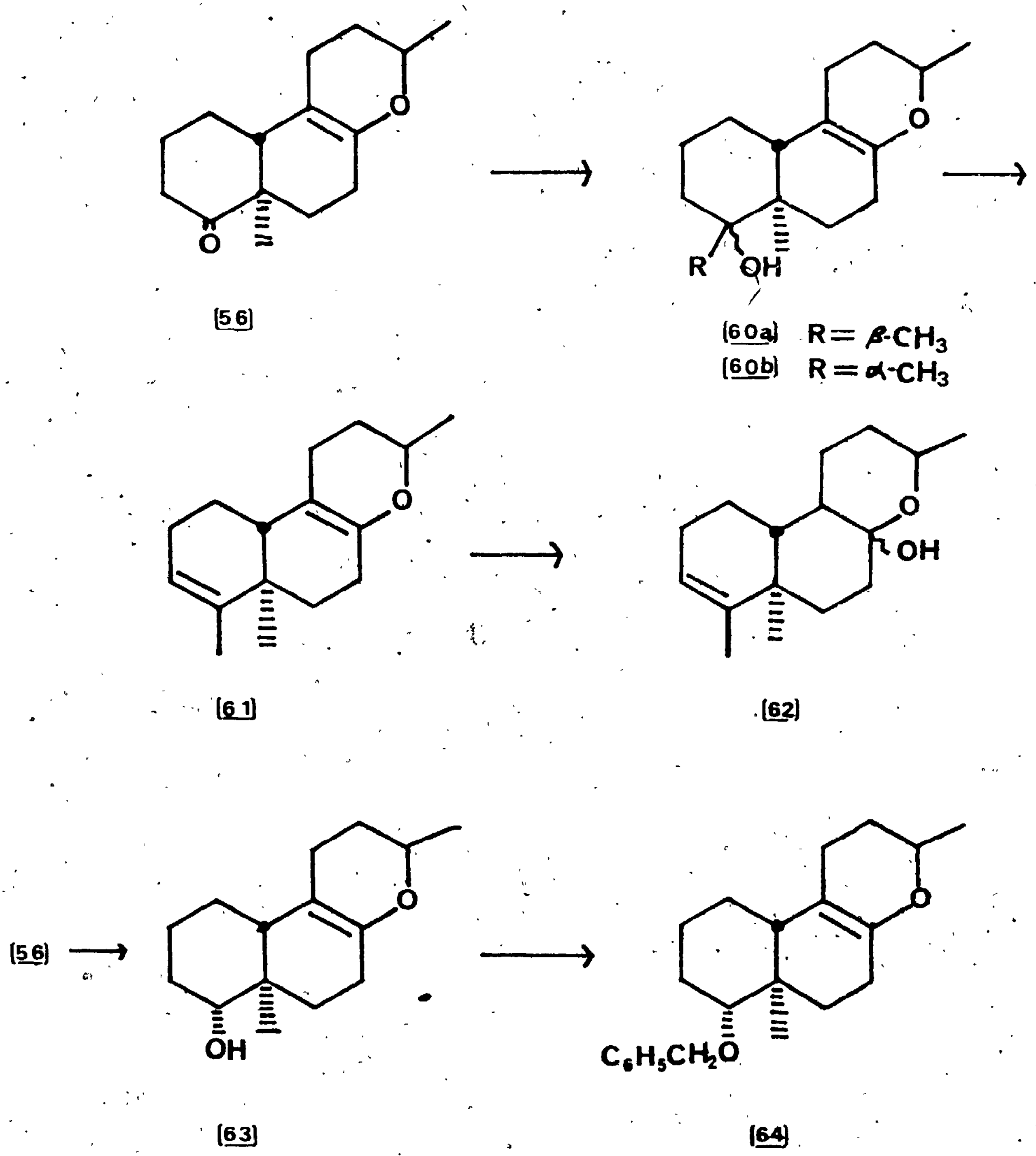


Having thus established the *trans*-A/B ring structure, we next turned our attention to the modification of ring A such that it would embody the A ring structure present in the naturally occurring clerodanes.

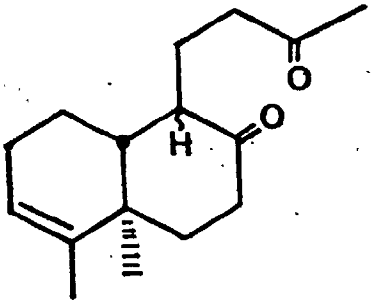
Scheme 12 (p. 24) shows the conversions performed along these lines. Addition of methyl Grignard reagent to the enol ether (56) proceeded readily, and the resulting mixture of alcohols (60a) and (60b) was dehydrated to (61) upon refluxing with hydrochloric acid in methanol (31%). A commonly used dehydration procedure involving treatment of the alcohols with thionyl chloride in pyridine at 0° produced a complex mixture from which only a trace of (61) was detectable. As before ((56)-(57)), the hydration of (61) with 1N sulphuric acid in acetone gave the hemiketal (62) in good yield (83%).

In attempts to postpone the abovementioned operations, if possible, to a later stage in the synthesis, the alcohol (63) obtainable by reduction of the enol ether (56) with lithium aluminium hydride was subjected to benzyl ether formation so that it could carry the hydroxyl group protected until the rest of the molecule was modified as desired. This consideration arose from the fear that a double bond formed on ring A prior to the construction of the other parts of the target molecule might not be compatible with the experimental conditions used as the synthesis proceeds. Alcohol (63) was thus refluxed with sodium hydride in dry benzene-dimethyl formamide mixture. In this manner, there was obtained benzyl ether (64) in 68% yield. However, the same hydration procedure as well as its slight modification (stirring with 1N sulphuric acid in acetone-tetrahydrofuran or in THF only) failed to yield the expected hydrated compound for unknown reason, resulting in the complete recovery of the starting material in both cases. These transformations are depicted in Scheme 12.

Scheme 12



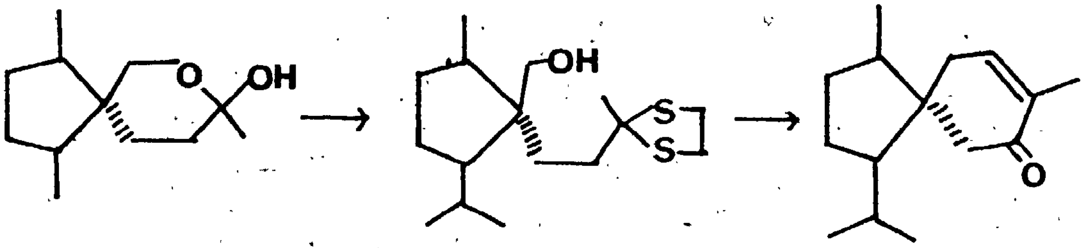
Hence it was decided to carry out further transformations using (62). The next stage required the ether ring cleavage of (62). Oxidation of (62) with Jones' reagent as described previously (e.g. (57)-(58)) would afford a diketone (65) similar to (58) in which C-8 and C-13 are not discriminated chemically, as a result, it would be impossible or very difficult to pursue our synthetic task.



(65)

To overcome the problem, the hydroxy ketone was fixed in the open form by thioketalization. The choice of this condition for an opening of a cyclic hemiketal such as (62) was guided by an example found in Trost's total synthesis of acorenone B (Scheme 13)[37].

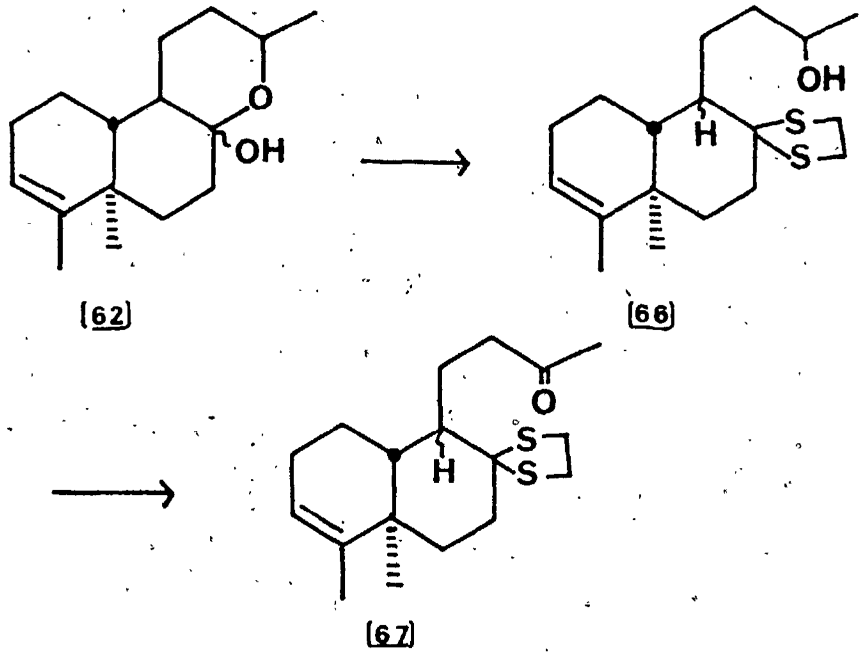
Scheme 13



acorenone B

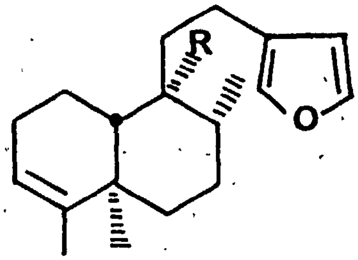
Thus, treatment of the hemiketal (62) with 1,2-ethanedithiol in dry toluene followed by addition of boron trifluoride-etherate with ice-cooling furnished the thioketal derivative (66) in 64% yield. This compound was then oxidized to (67) by Sarret oxidation (chromium trioxide in pyridine) in a rather poor yield of 45%. It is anticipated that the yield of the last stage can be improved by the use of a different oxidizing reagent. These two steps are shown in Scheme 14.

Scheme 14

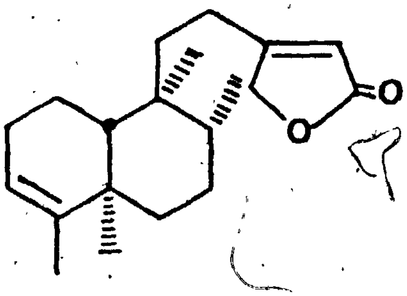


Since compound (67) possesses the A ring structure of some clerodanes, the construction of the entire framework now apparently entails introduction of the vicinal dimethyl groups at C-8 and C-9 in addition to attachment of the proper side chain in the correct oxidation states found in nature. Besides the ketone group at C-13 which can be utilized for the construction of the side chain, compound (67) bears a latent ketone moiety now protected as a dithioketal, , which can be demasked and utilized in introducing the vicinal dimethyl groups. Therefore it appears that this intermediate (67) can serve as a valuable synthetic precursor in the preparation of several members of the clerodane family and particularly among others such clerodanes as kolavenol (9), junceic acid (68)[38], furan (69)[39], and solidagolactone (70)[40].

Other research priorities precluded further work on this project but we anticipate future work to commence in our laboratories in the near future.



(68) R=COOH
(69) R=CH_3



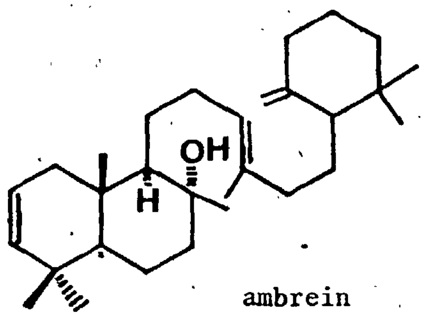
(70)

PART II

INTRODUCTION

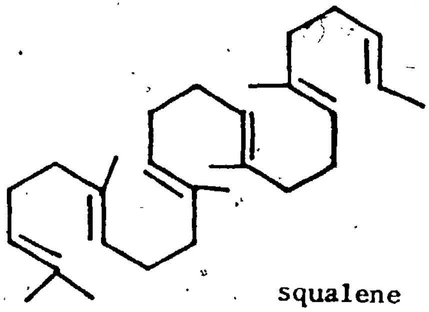
The triterpenoids constitute by far the largest terpenoid class and are characterized as possessing a skeleton of thirty carbon atoms divisible into six isoprene units.[1,41] Their occurrence in nature has been known for over one hundred years, for the most part in plants although a few examples are found in the animal kingdom as well[42].

The triterpenoids may be classified into three major groups as follows; 1) the acyclic terpenoids (ambrein* (71) and squalene (72)); 2) the tetracyclic triterpenoids[43] (lanosterol (73)); 3) the pentacyclic triterpenoids.



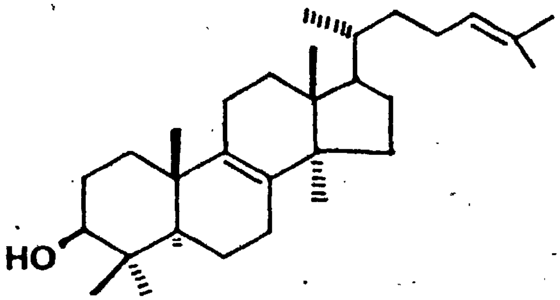
ambrein

[71]



squalene

[72]



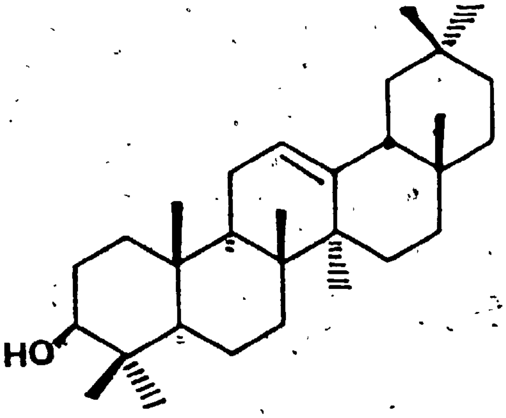
lanosterol

[73]

---

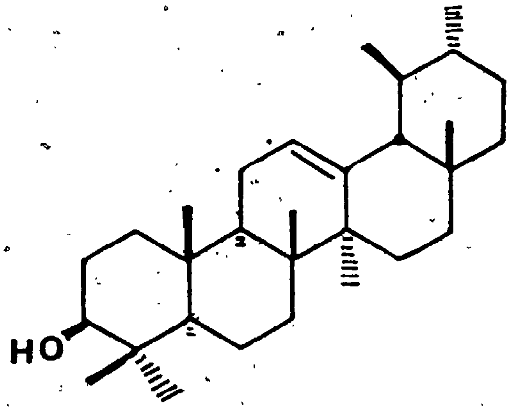
*Although ambrein is obviously not acyclic, it is traditionally classified with squalene as a non-tetracyclic, nor pentacyclic species.

Squalene (all trans-form) is now accepted as the biological precursor of all triterpenoids[41] and its biosynthesis has been established in detail.[44] Lanosterol (73) has also received much attention concerning steroid biosynthesis.[44] The third group (the pentacyclic triterpenoids) is the largest in number and the parent substances of the group, β-amyrin (74), α-amyrin (75), and lupeol (76), were formulated correctly in 1937[45], 1949[46], and 1951[47] respectively. Especially they provided, together with the steroids, the experimental bases for conformational analysis[48].



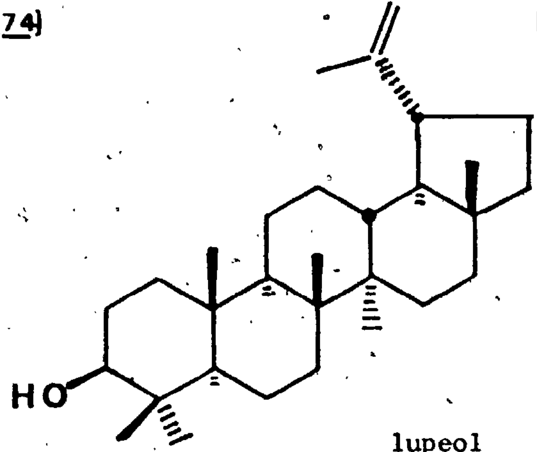
β-amyrin

[74]



α-amyrin

[75]



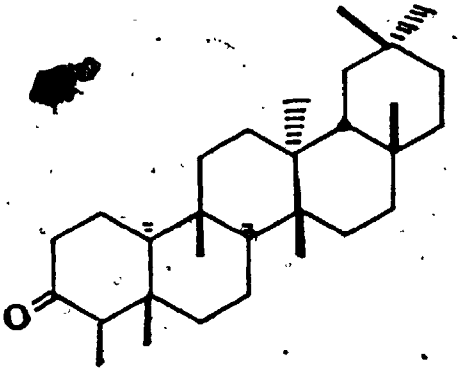
lupeol

[76]

The diverse structures and configurations of basic triterpene skeletons are derivable, according to the Biogenetic Isoprene Rule[5], from squalene epoxide by cyclization in various conformations. Recently the structural relationships among the triterpenes based on this principle have been ably reviewed by Connolly and Overton[49].

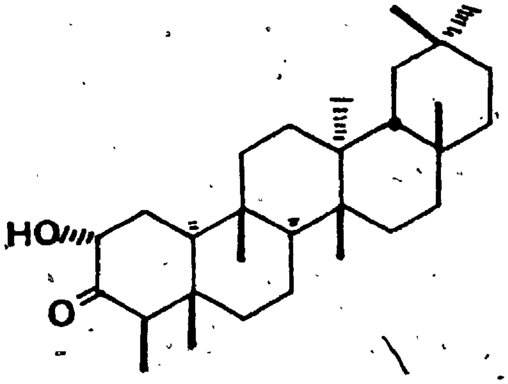
Friedelin:

Among nearly 750 naturally occurring triterpenes known to date[10], friedelin (77) occupies an important place in the triterpene chemistry. Its isolation dates back to as early as 1807 although it was later shown that the substance regarded as homogeneous at the time of discovery contained both friedelin (77) and cerin (78).[50]



friedelin

[77]



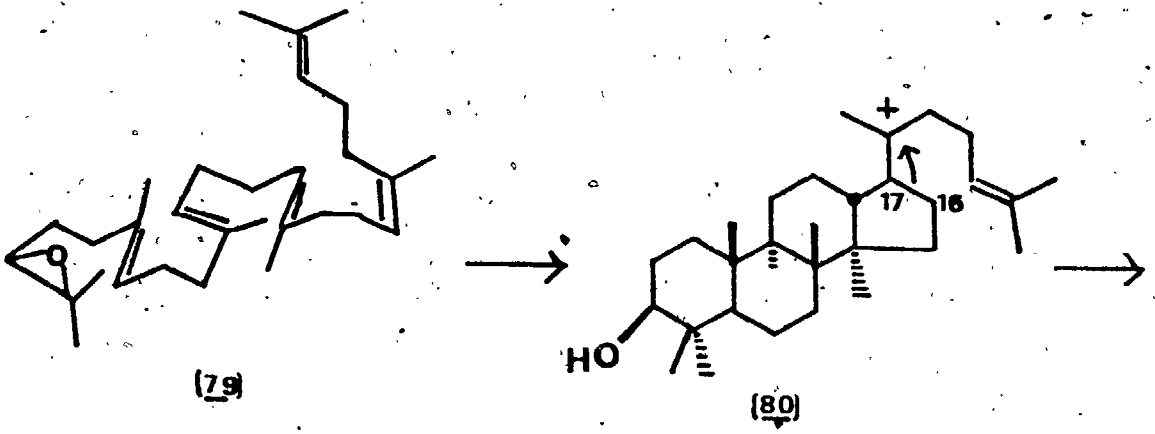
cerin

[78]

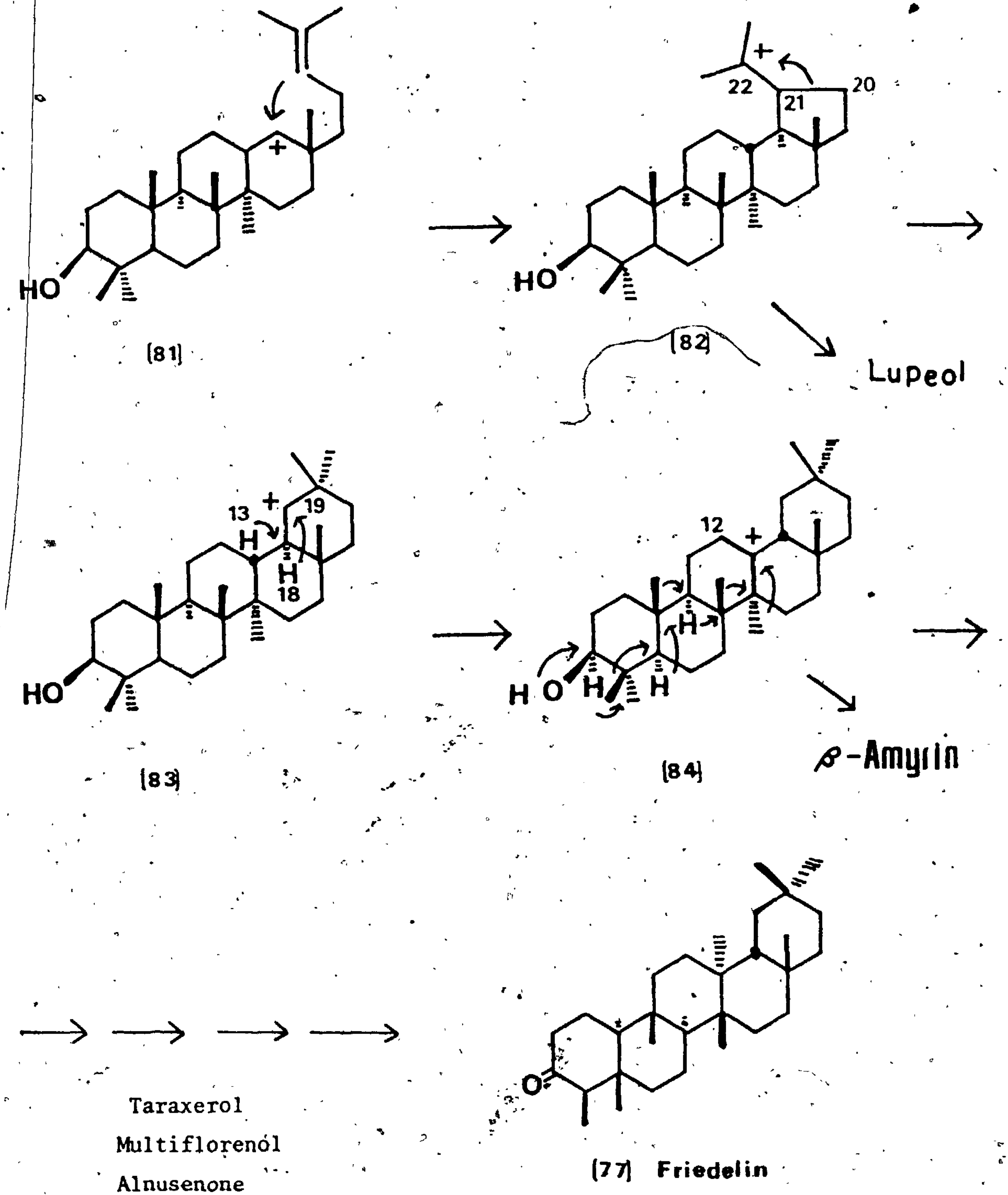
Biosynthetically, friedelin (77) is located at the end of the pathway by which the majority of the known pentacyclic triterpenes are produced *in vivo*.[49,51] In detail, cyclization of squalene

1,2-epoxide (79) when it is folded in the chair-chair-boat conformation (as is shown in Scheme 15) leads to cation (80). This intermediate ion (80) pauses for reorganization by migration of the C-16 methylene group (for the numbering of the system; see APPENDIX II p. 166) to the next cation (81), and then it continues along the pathway to the pentacyclic cation (82) after further cyclization, from which the lupane group such as lupeol (76) is derived. Ring expansion in (82) to a six-membered E ring (i.e. C-20 migrates from C-21 to C-22) results in the formation of a new intermediate (83). The wide variety of pentacyclic triterpenes belonging to oleananes are of this origin. Two subsequent 1,2-hydride shifts in cation (83) and elimination of a proton from C-12 in the resulting cation (84) produces β-amyrin (74). A series of further hydride and methyl shifts ultimately generates friedelin (77) as indicated in Scheme 15, during which process various triterpenes, taraxerol, multiflorenol and alnusenone, are directly derivable by the loss of a proton from the corresponding intermediate ions.

Scheme 15



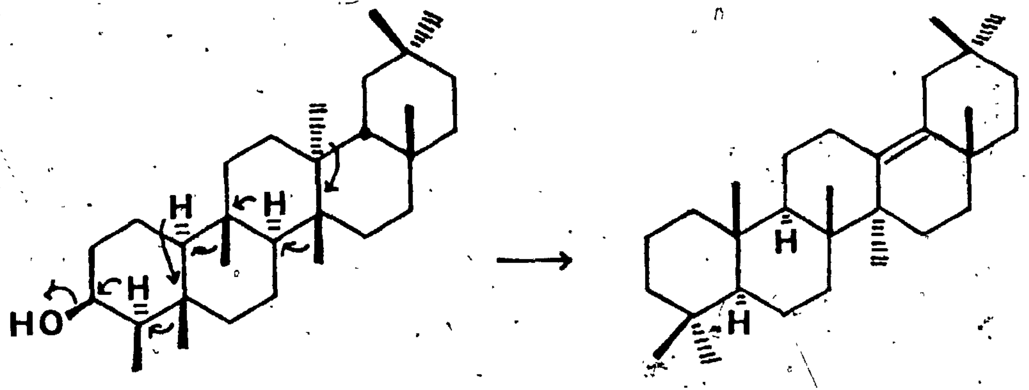
Scheme 15 continued



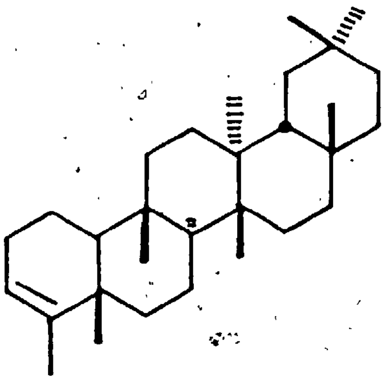
The foregoing scheme principally based on Ruzicka's proposal[5] for the formation of β-amyrin (74) from squalene has been verified experimentally due to the efforts of several groups. First, Barton and coworkers[52] identified (S)-squalene 2,3-epoxide as the exclusive biogenetic precursor of β-amyrin (74) in pea seedlings. More recently Tomita and coworkers[53] have demonstrated that ^{13}C-labelling patterns in some oleanene-type pentacyclic triterpenes biosynthesized from $(4-^{13}C)$-mevalonic acid in tissue cultures of Isodon japonicus Hara are entirely consistent with the Ruzicka's pathway (Scheme 15).

A characteristic feature of the friedelin framework can be seen in a back-bone rearrangement that takes place in friedelin-3β-ol (85) upon treatment with acid.[54] This rearrangement as indicated in Scheme 16 converts (85) into a δ-amyrin skeleton, olean-13(18)-ene (86), and hence it is considered to be the retro-biogenetic route of friedelin (77). Δ³-Friedelin (87)[55] as well as Δ²-friedelin (88)[56] experiences the same rearrangement in acid.

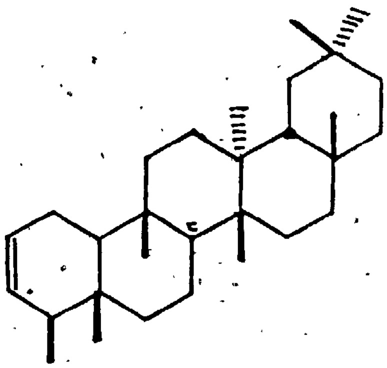
Scheme 16



(85) (86)

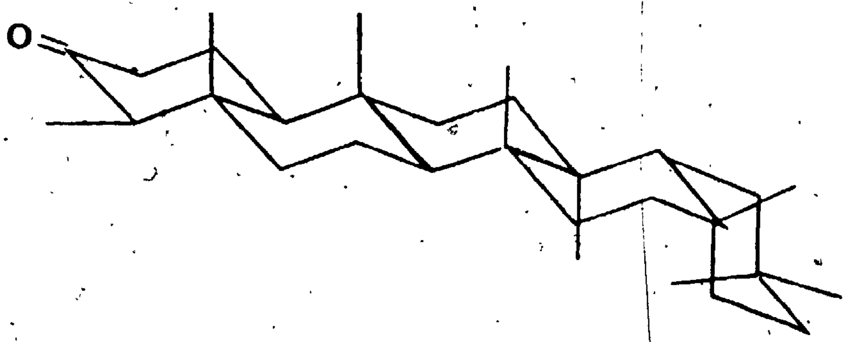


[87]

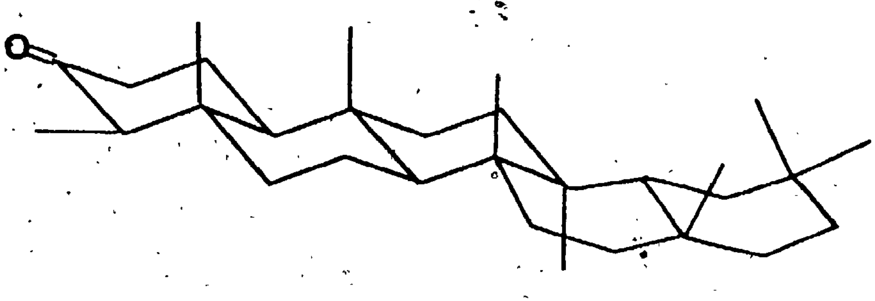


[88]

It has been suggested by Spring and coworkers[55] that these acid-catalyzed Wagner-Meerwein rearrangements are promoted by the severe nonbonded interactions present in the cis-D/E ring system. Regardless of the conformation of friedelin (77) in question as to whether it is the all chair conformation (89)[54] or the chair-chair-chair-boat-boat conformation (90)[57], evidently the congested enviroment around the D/E ring system would be responsible for the back-bone rearrangement. The perspective view of both conformations is shown on the next page (p. 35).



(89)

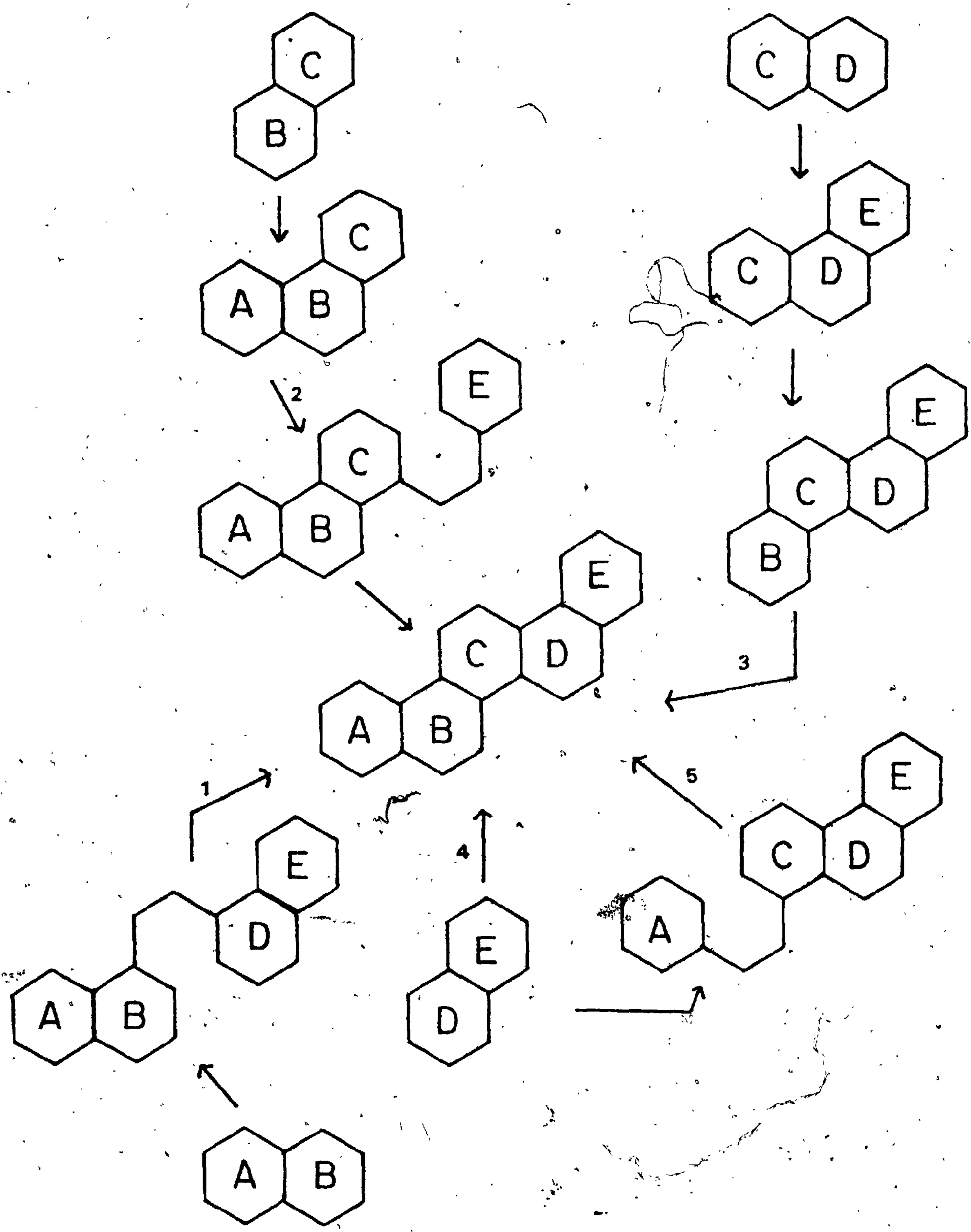


(90)

Triterpene Syntheses:

The synthetic challenges presented by the triterpenes particularly the pentacyclic series involve two aspects; one concerns the methods for the assembly of policyclic systems, and the other is concerned with steric control in complex reactions. The former aspect has been undoubtedly developed in the steroid field, the total synthesis of which began in 1950's. On the other hand, the latter is of newer advent both conceptually and practically; an increasing number of innovations in synthetic methodology that appear year after year have addressed this problem. As a result, ealier syntheses of symmetrical triterpenes were, although of a pioneering nature, nonstereoselective in general, but recent syntheses of several unsymmetrical pentacyclic triterpenes have shown the progress not only in the methodology but also in the sophisiticated planning of the synthetic routes prior to experimentation. The total syntheses of triterpenes that had been achieved up to 1972 have been comprehensively reviewed by ApSimon and Hooper[58]. Since most of the strategies and tactics involved in the triterpene synthesis were put into practice in the steroid synthesis, it would seem logical to classify the synthetic approaches according to the sequences in which rings are constructed as is customary in the steroid field[59]. The following is the brief summary of some examples of the triterpene syntheses, emphasizing the routes sought for construction of the pentacyclic array rather than the details. Considering its importance to the theme of this thesis, the total synthesis of friedelin will be described independantly with some experimental details.

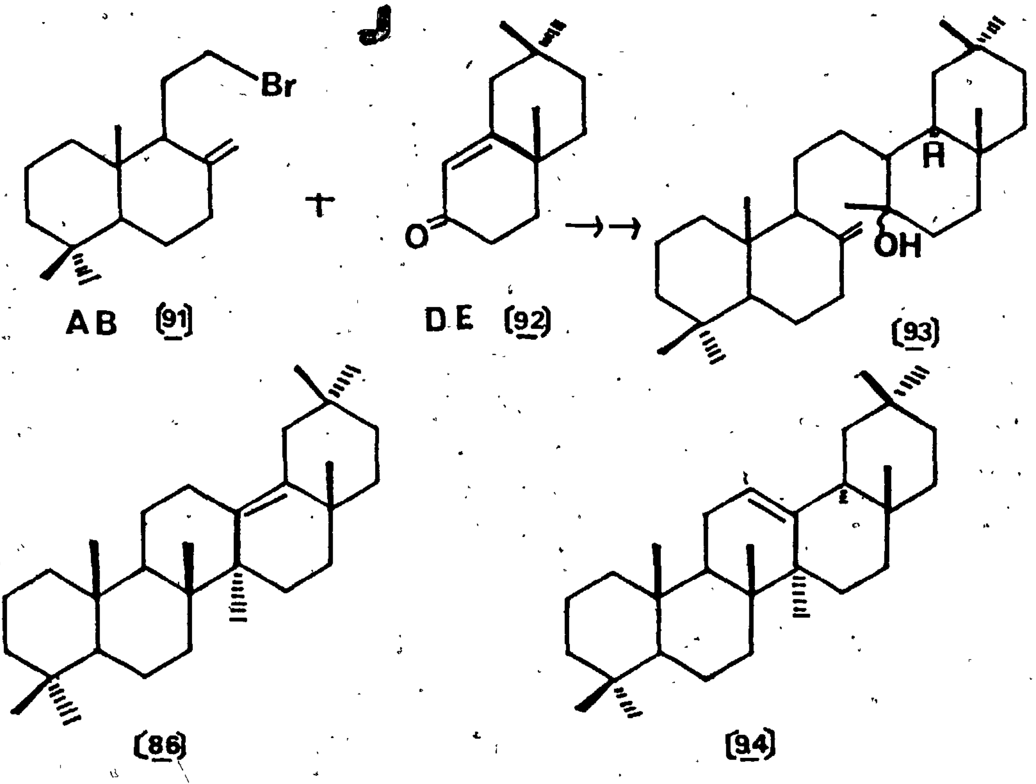
Some Possible Ring Constructions for the Pentacyclic Framework



1) The AB-ABDE-ABCDE Route:

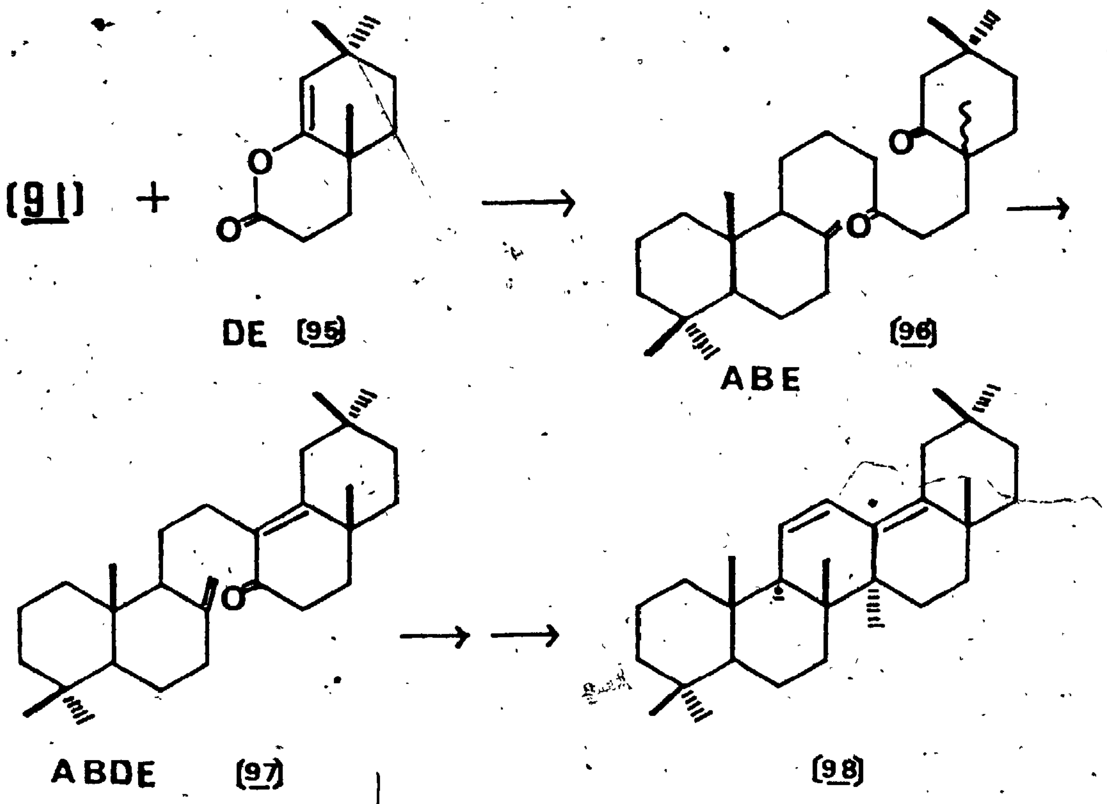
In the first instance, the pioneering work of Barltrop and coworkers[60] on the synthesis of oleanenes is formulated as an AB-ABDE-ABCDE route. Their route (see Scheme 17) began with a preformed AB fragment (91) derivable from sclareol, into which a CD ring precursor (92) was combined. The resulting ABDE portion was converted to (93), which in turn cyclized to produce pentacyclic hydrocarbons upon treatment with aluminum chloride. Two pentacyclic substances, olean -13(18)-ene (86) and 18α-olean-12-ene (94) were obtained in low yields together with their epimers from the hydrocarbon mixture.

Scheme 17



In the synthesis of olean-11,13(18)-diene (98), Corey and coworkers[61] followed a slightly different approach (Scheme 18). Reaction of the Grignard reagent prepared from the bromide (91) with the enol-lactone (95) (the DE ring unit in this synthesis) gave a mixture of stereoisomeric diketones (96). Intramolecular aldol condensation of (96) resulted in the formation of the α,β-unsaturated ketone (97) which had previously been synthesized[60]. The conversion of the enone (97) to a pentacyclic material proceeded with great difficulty. In any event, olean-11,13(18)-diene (98) was separated from the acid-catalyzed cyclization mixture in poor yield.

Scheme 18

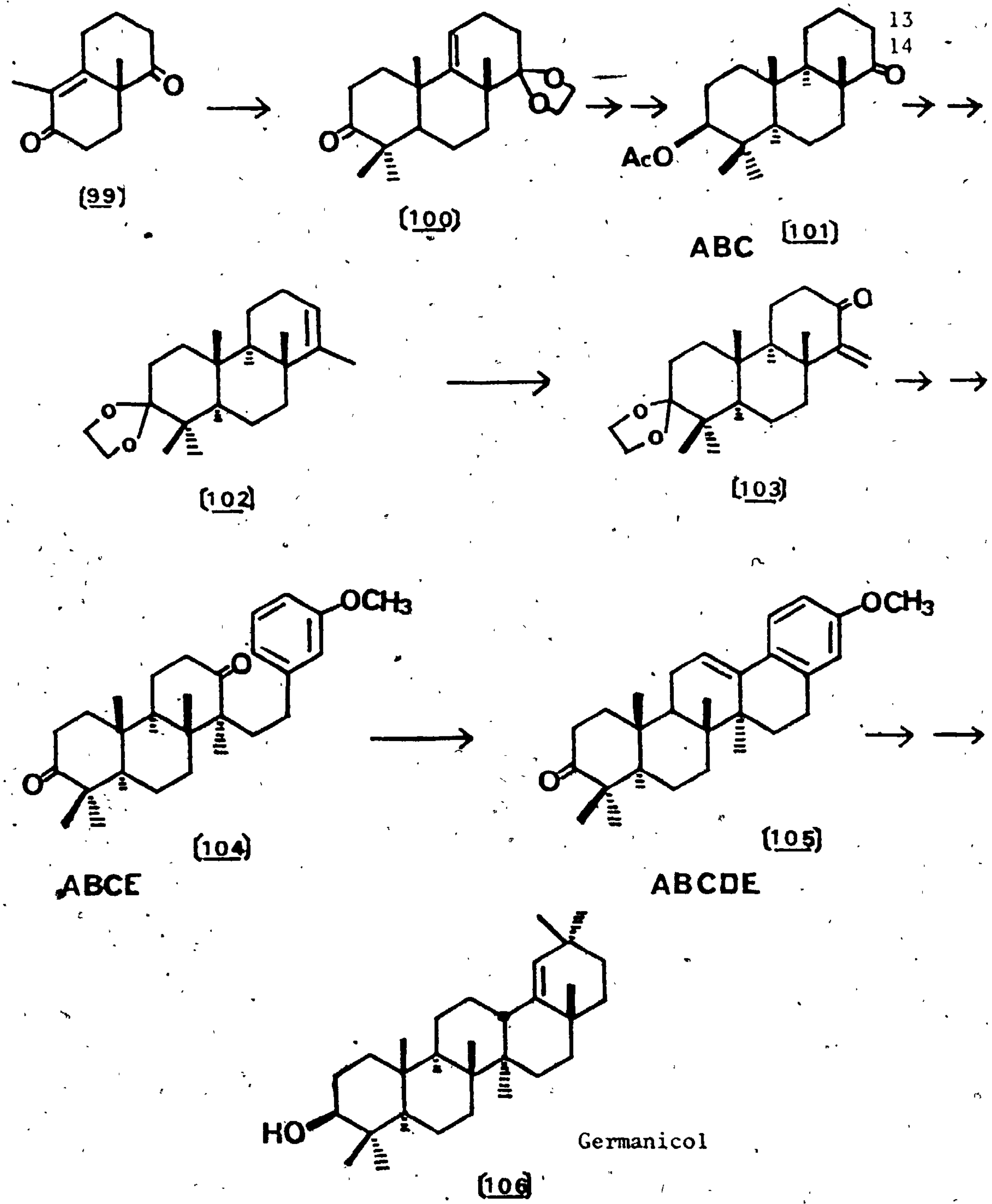


The approach of Sondheimer and Ghera[62] to olean-13(18)-ene (86) and 18α-olean-12-ene (94) was based on a similar strategy although quite different in detail. However, they could detect (86) and (94) only by the combined technique of gas chromatography and mass spectroscopy. All these syntheses of oleananes depending on the AB-ABDE-ABCDE route suffer from a serious drawback, that is, a complex mixture of stereoisomers is produced at the final stage as the result of the non-stereospecific cyclization forming the C ring and probably acid-catalyzed methyl group migrations. Other synthetic efforts being made in this direction may lead to better specificity.[77]

2) The BC-ABC-ABCE-ABCDE Route:

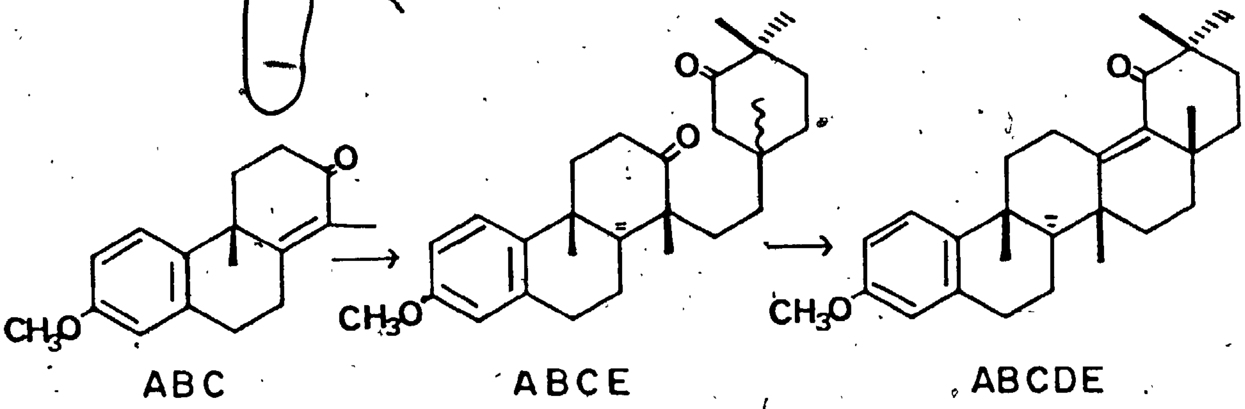
This route is best illustrated by Ireland's synthesis of germanicol[63]. This brilliantly designed synthesis (Scheme 19) started with an easily available BC ring portion (99), onto which ring A was annelated ((99)-(100)). After several routine procedures, the ABC ring portion (101) with the required trans-anti-trans-configuration was made in an efficient manner. Between two approaches that were investigated for the modification of this material, that is -stereoselective introduction of a E ring unit at C-14 and functionality for the D ring formation at C-13, only one route is shown in Scheme 19. This rather difficult task was elegantly solved by the use of photosensitized oxygenation ((102)-(103)), and thus compound (103) was furnished with an α,β-unsaturated ketone moiety that underwent conjugate addition of m-methoxybenzylmagnesium chloride followed by angular methylation, leading to (104). Compound (104) thus obtained was subjected to cyclodehydration, affording the pentacyclic material (105) from which germanicol (106) was finally elaborated.

Scheme 19



A conceptually similar approach (AB-ABC-ABCE-ABCDE) has been under study at Carleton in conjunction with a friedelin synthesis (Scheme 20).[64]

Scheme 20

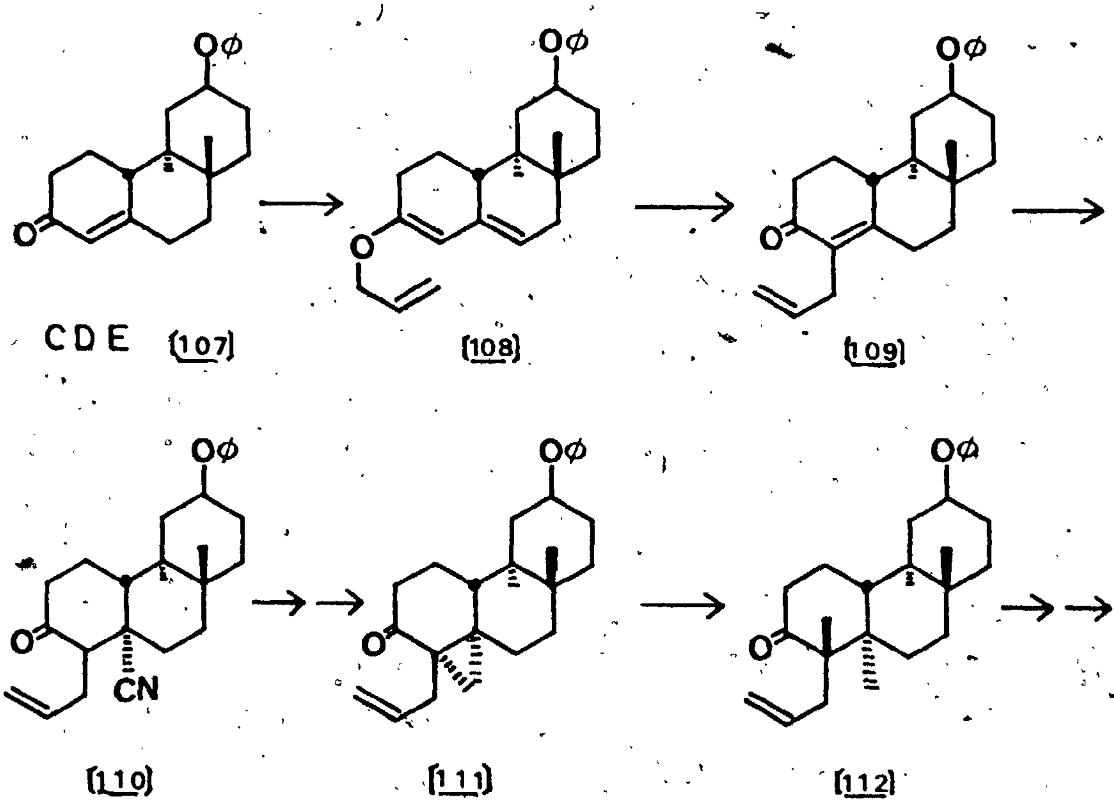


3) The CD-CDE-BCDE-ABCDE Route:

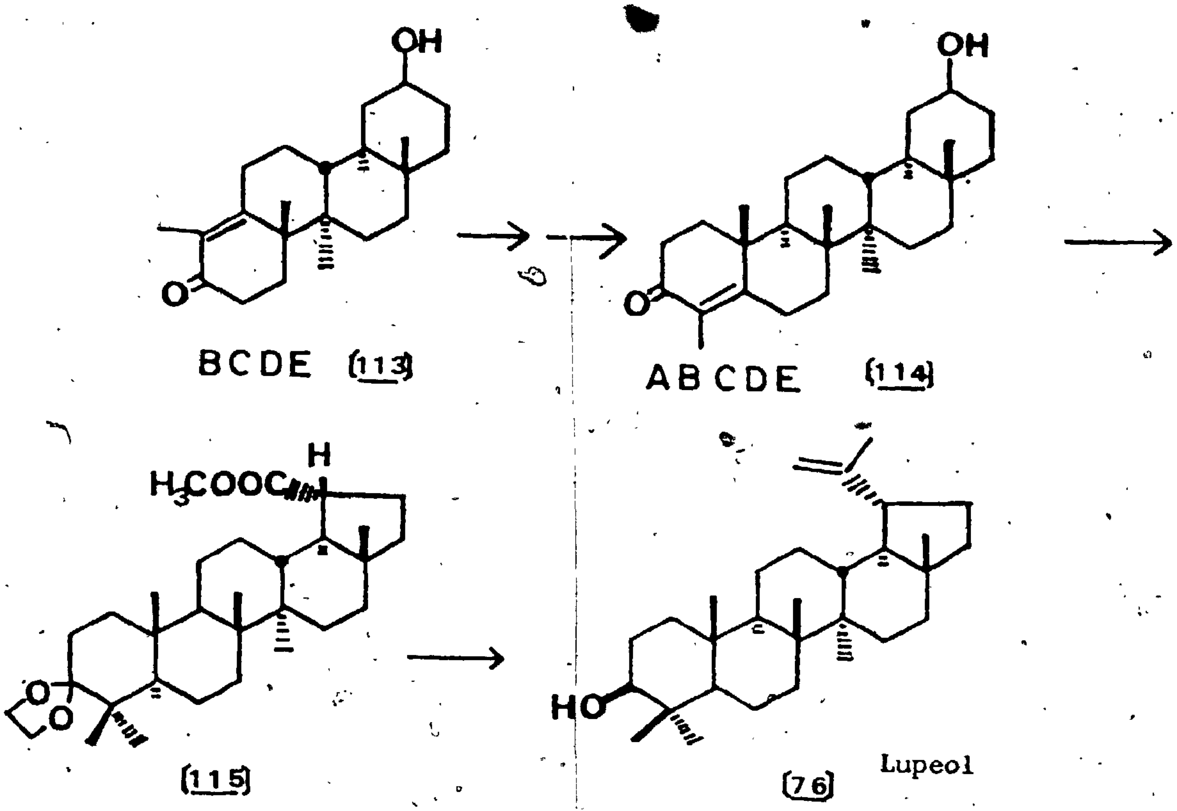
The synthesis of lupeol (76) by Stork and coworkers[65] set out with the initial construction of the CDE ring (107) followed by the stepwise addition of ring B and ring A in this order. The principal problem in the synthesis, the introduction of the two vicinal methyl groups in a trans-diaxial fashion, was solved here in an elegant manner. Thus the allyl enol ether (108) prepared from (107) was rearranged thermally to the allyl ketone (109), upon which hydrocyanation[66] was effected to introduce one of the two angular methyl groups ((109)-(110)). The crucial feature of the synthesis, introduction of the adjacent methyl group in a trans-relationship, was achieved through reductive alkylation of the cyclopropane derivative (111) which was obtained by manipulation of the hydrocyanation product (110), giving (112).

Attachment of ring B was carried out following the Fujimoto-Belleau reaction ((112)-(113)). The regio- and stereospecific construction of ring A was efficiently solved *via* the enolate trapping method again, which led to the desired ABCDE unit (114). Modification of ring A into that of lupeol (76) by the use of reductive alkylation once more and ring contraction of the E ring eventually yielded (115), a relay compound, which had been converted into lupeol by the same authors in the natural series. Stork's synthesis of lupeol is outlined in Scheme 21.

Scheme 21



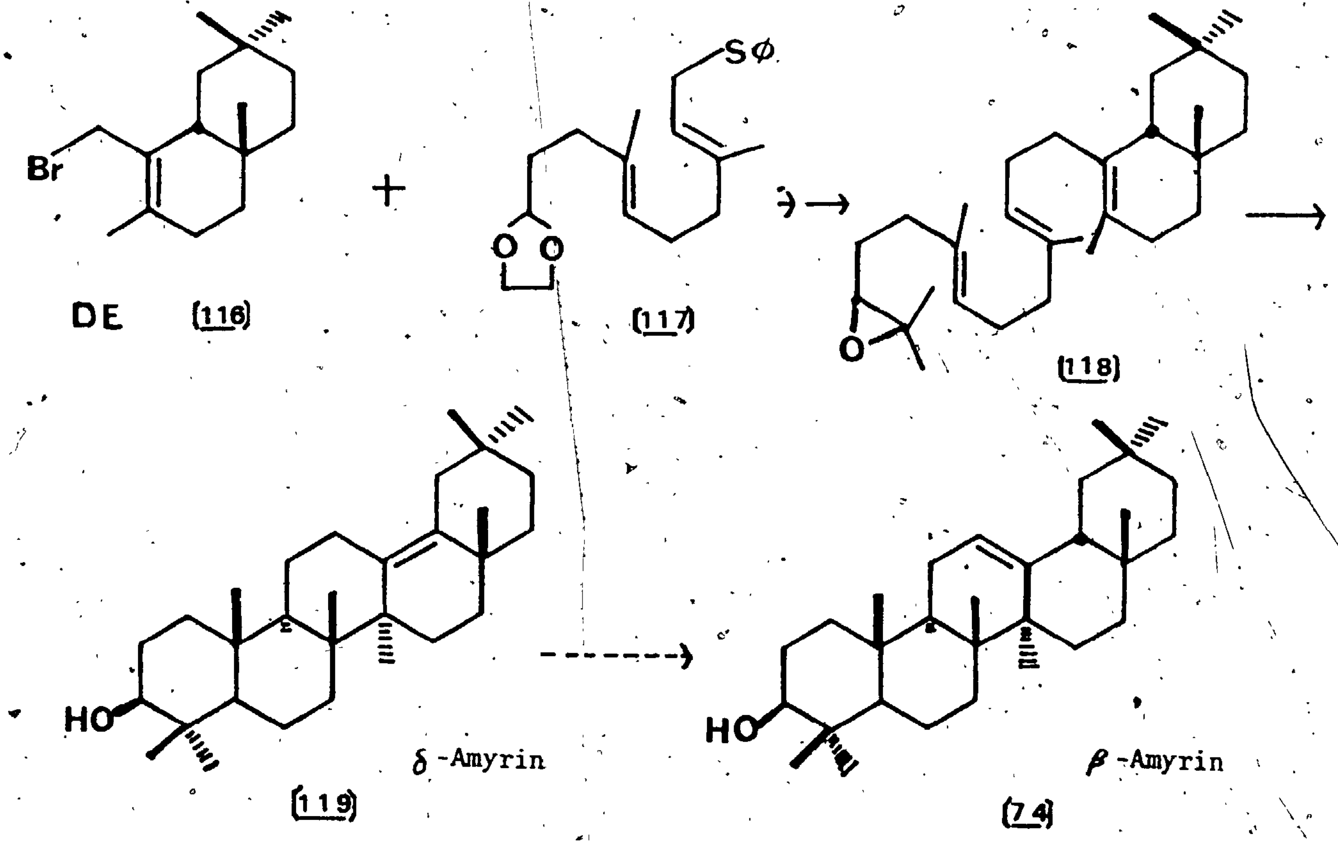
Scheme 21 continued



4) The DE-ABCDE Route:

The highly efficient synthesis of δ-amyrin (119) by van Tamelen and coworkers[67] has resulted from the accumulation of their extensive studies on the biomimetic cyclization of terminal epoxides[68]. As Scheme 22 indicates, a preformed DE ring component (116) was coupled with the phenyl thioether (117) to give the required epoxide (118) for their purpose. Stannic chloride-catalyzed cyclization effected the one-step transformation of the epoxide (118) into dl-δ-amyrin (119) (8%), surprisingly enough with five asymmetric centres being established at one time during cyclization. This entirely different approach of a biogenetically patterned synthesis which attempts to delineate in vivo syntheses of terpenoids might compete favourably with conventional multi-stage laboratory syntheses in the future as van Tamelen pointed out[68].

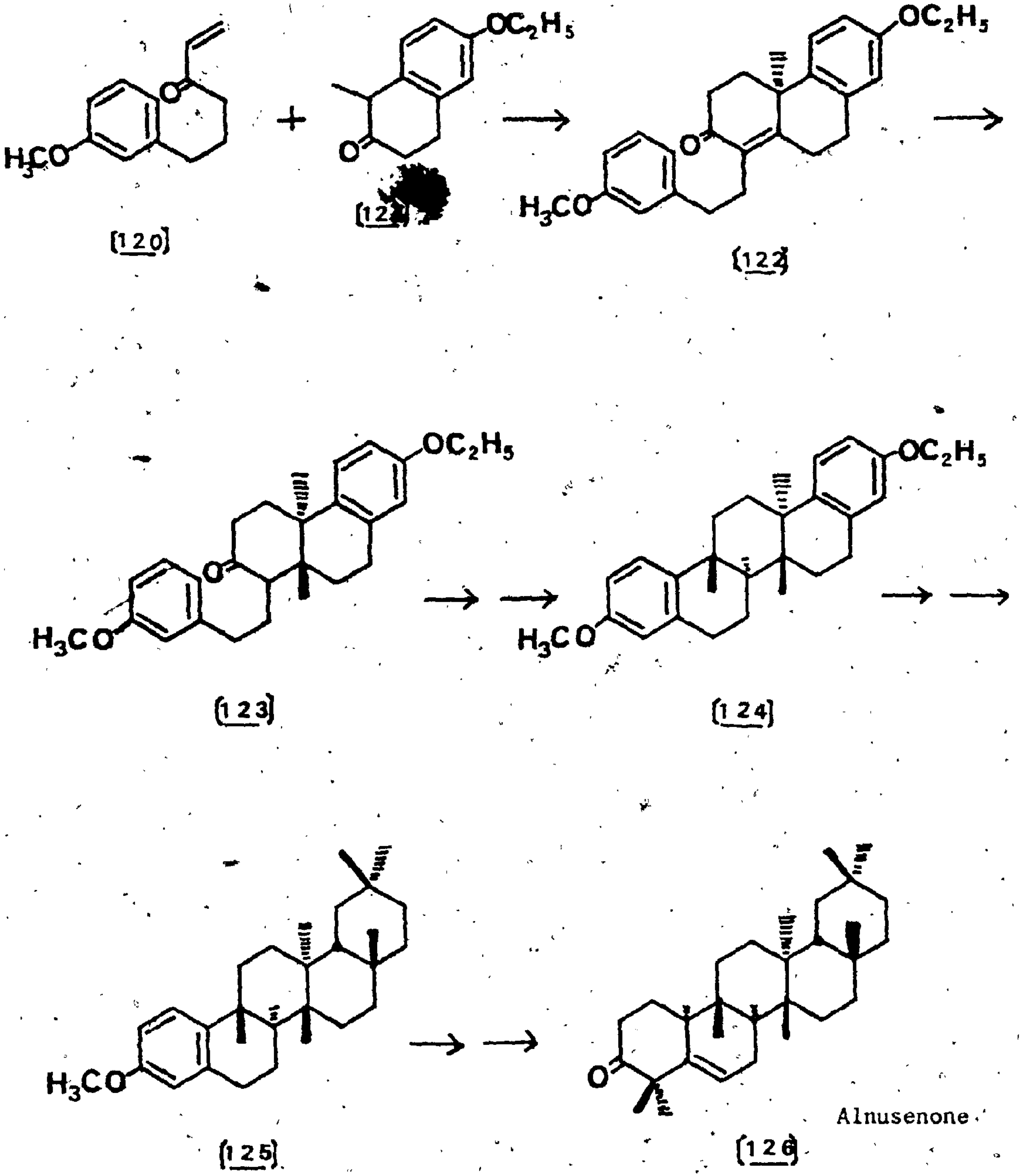
Scheme 22



5) The DE-ACDE-ABCDE Route:

The approach, DE-ACDE-ABCDE route, has been used by Ireland and coworkers[69] in their successful synthesis of alnusenone (126), and ultimately has led to the completion of a friedelin synthesis[70a,70b]. The convergent nature of the synthesis and the high stereoselectivity achieved in creating asymmetric centres have made this synthesis a monumental step in the triterpene synthesis. The alnusenone synthesis according to Ireland is briefly presented in Scheme 23. Tetralone (DE ring element, (<u>121</u>)) was combined with a tris-annelating agent (<u>120</u>) which had been used by Smith and coworkers[71] in connection with a steroid total synthesis. Thus, in a single step, the ACDE fragment (<u>122</u>) was synthesized efficiently. This one-step synthesis of the fragment constitutes the fundamental pattern in their following syntheses of shionone[72] and friedelin[70a,70b]. Nagata's hydrocyanation (kinetically controlled conditions)[66] allowed the stereoselective introduction of an angular methyl group into (<u>122</u>) in the desired <u>trans</u>-fashion. This procedure as previously utilized in Stork's lupeol synthesis (i.e. (<u>109</u>)-(<u>110</u>)) is, in general, a remarkable solution for the construction of a <u>trans</u>-fused CD ring system with its two angular methyl groups common to this class of triterpenes. As verified by a model study on tetracyclic analogs in their earlier experiments, the Friedel-Crafts cyclialkylation of the tricyclic ether (<u>123</u>) generated the <u>trans</u>-fused system (<u>124</u>) predominantly. Modification of the aromatic ring E to that of alnusenone (<u>126</u>) was completed through a series of reactions, despite some difficulties, details of which will be presented later in the friedelin synthesis. Birch reduction of the aromatic A ring of (<u>125</u>) and then methylation of the resulting enone provided alnusenone (<u>126</u>). It should be noted that the aromatic A and E ring have been differentiated <u>a priori</u> so as to set the stage for separate Birch reductions.

Scheme 23



[120] [121] [122]

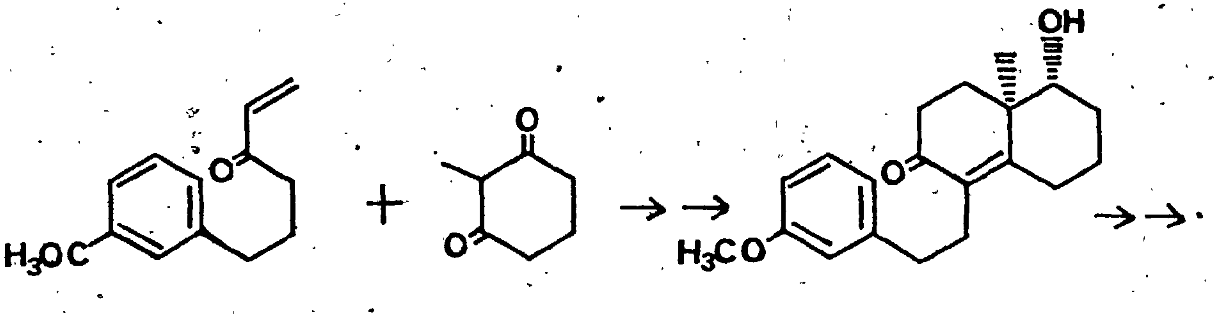
[123] [124]

[125] [126]

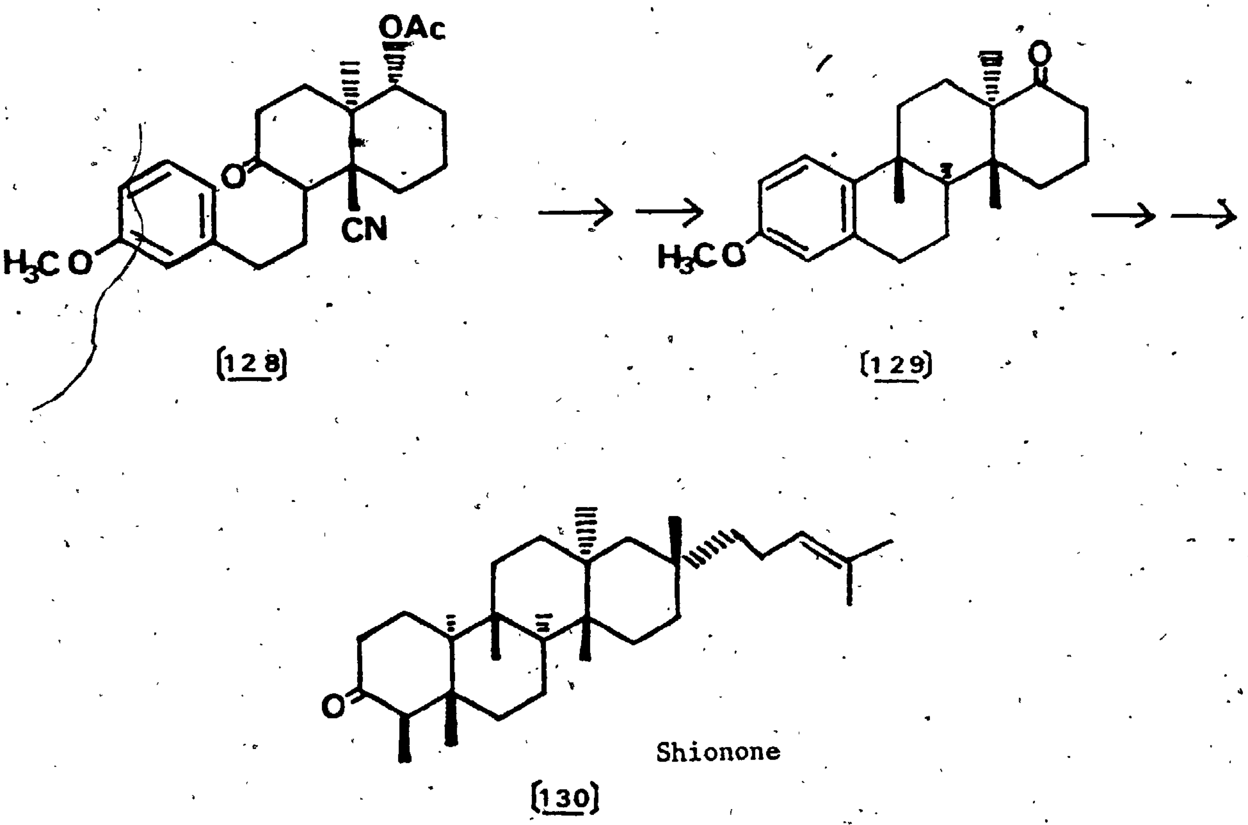
Alnusenone

Ireland[72] has contributed another highly efficient synthesis, that of shionone (130), based on a similar strategy. Therefore, as was the case in the alnusenone synthesis (Scheme 23), the correct stereochemical disposition of the angular methyl groups about the tetracyclic intermediate (129) was the initial objective. Among three different routes that had been sought, the most successful one was patterned closely after the route for the construction of alnusenone intermediates. Annelation of 2-methylcyclohexane-1,3-dione with the Smith's tris-annelating agent (120) followed by reduction gave (127). An analogous scheme to that used for the alnusenone synthesis employing Nagata's hydrocyanation procedures produced (128). By cyclialkylation of this material the tetracyclic intermediate (129) was made available. Conversion of this tetracyclic material to shionone (130) entailed addition of the side chain and modification of the aromatic A ring, the latter being one of the subjects to be presented in the next section. Ireland's synthesis of shionone is outlined in Scheme 24.

Scheme 24



Scheme 24 continued



(128)

(129)

Shionone

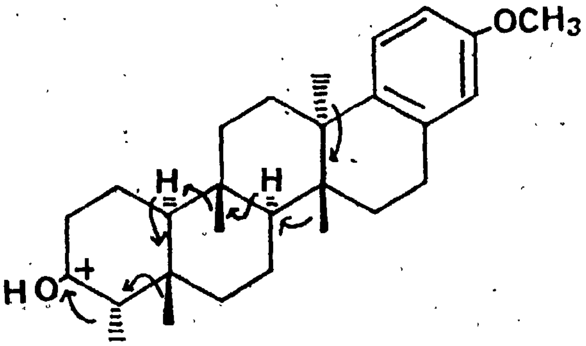
(130)

Total Synthesis of Friedelin:

Friedelin (77) is characterized as having nine contiguous asymmetric centres including five angular methyl groups, and its total synthesis has been the ultimate goal of synthetic efforts in these laboratories and others for a decade.

Recently Ireland's group[70a,70b] has announced the first total synthesis of fridelin in 31 steps. In their synthesis, the route that was investigated (CDE-ACDE-ABCDE) parallels that used for their alnusenone synthesis (Scheme 23) in many aspects: alnusenone (126) differs only in the substitution pattern of dimethyl groups on ring A from that of friedelin (77). As a consequence, it was first envisaged that the pentacyclic intermediate (124) used in the alnusenone synthesis would be a key intermediate in this case as well. However, on the basis of the following considerations certain modifications of the route planned initially were necessary; 1) in the alnusenone synthesis the aromatic ring E of the diether (124) was converted to that of alnusenone prior to the modification of the aromatic A ring, but the sequence resulted in a low overall yield principally as the result of the initial Birch reduction; 2) the completed CDE ring system would experience severe steric strain and this would cause a back-bone rearrangement triggered by the acid-catalyzed cyclization of ring A which was successful in the shionone synthesis[72]. Therefore it was decided to postpone the modification of the aromatic E ring to a later stage, that is, after completion of the A-ring, and by this alternative it was hoped to be able to circumvent these two problems. In order to implement the new strategy, it was necessary to prepare the pentacyclic diether (131) in which the locations of ethoxy and methoxy groups are interchanged from those in (124). The main stream of their synthesis of friedelin is outlined in Scheme 25 (pp. 53-54).

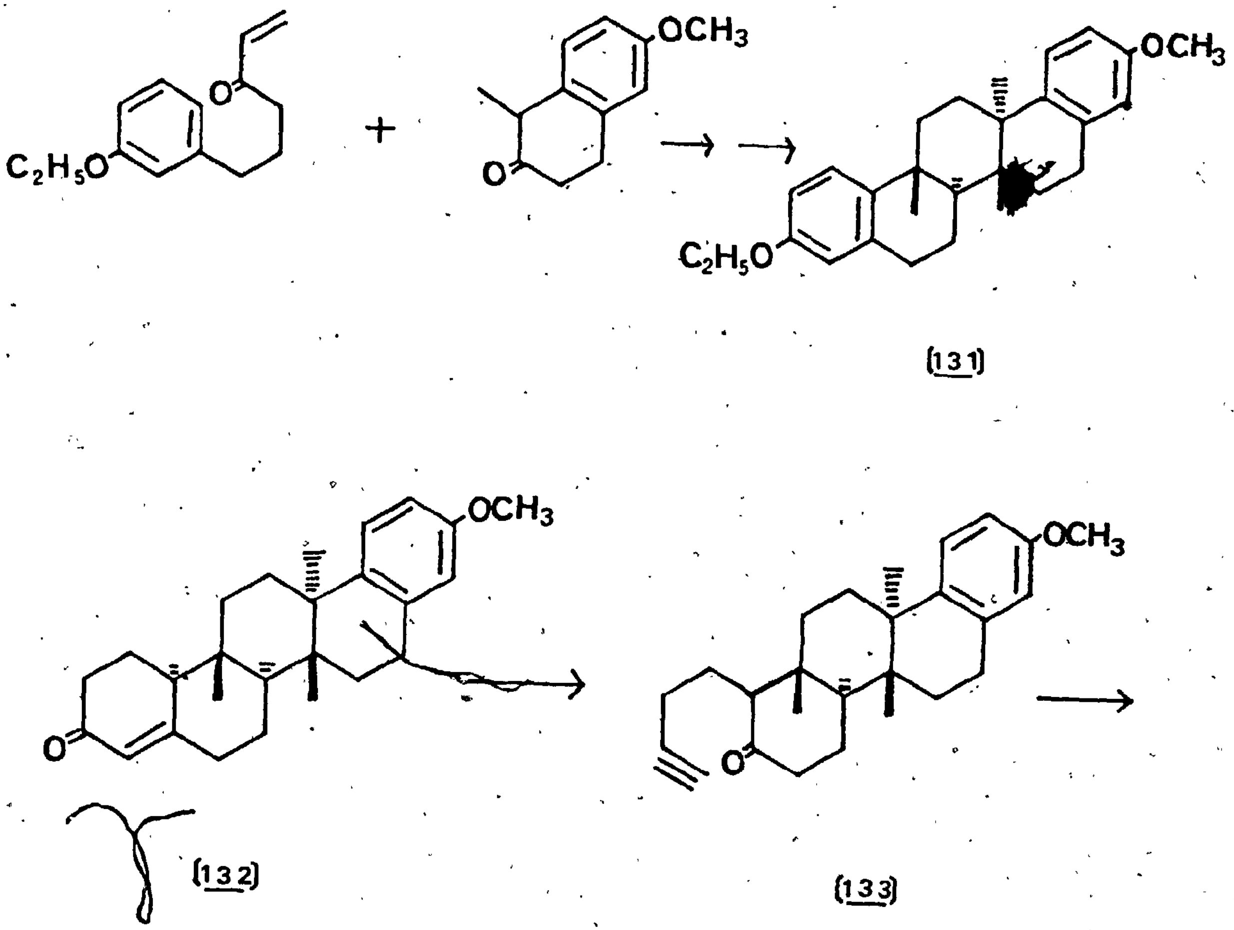
The diether (131) was prepared in a convergent manner similar to that used in the previous examples (see Scheme 23 and 24). The selective reduction of the aromatic A ring of (131) in the presence of another aromatic ring (ring E) was feasible because an aromatic ring bearing an alkoxy group can be reduced to a desired dihyroaromatic system as seen in (132), whereas an aromatic ring containing a hydroxyl group remains intact by virtue of the high reduction potential of a phenoxide ion relative to that of anisole. In order to satisfy this requirement the methoxy group on ring E was selectively cleaved according to the method of Mann[73]. This operation and the following Birch reduction of the resultant phenol afforded the pentacyclic enone (132) as expected after remethylation of the phenol in 56% yield. The problems associated with the modification of the aromatic A ring to that of the natural product had been solved in the synthesis of shionone (i.e. (129)-(130) in Scheme 24). Between two methods developed during the course of the synthesis, the one relying on the sequences exploited by Eschenmoser and coworkers[74] proved to be more successful than the other depending the orientation of the Simmons-Smith methylenation[29] by the alcohol function in an allylic system[75]. Thus, being guided by this experience, the Eschenmoser fragmentation was carried out on the enone (132), and the alcohol (134) was obtained upon treatment of the ketone (133) with methyl lithium. Cyclization of the alcohol (134) in trifluoroacetic acid led to an enol trifluoroacetate (135) in excellent yield. The stereochemical outcome of the cyclization could be predicted to lead to the desired C-4a methyl orientation due to the control provided by the axial C-8 methyl group. The lithium enolate derived with the action of lithium diisopropylamide was trapped by the Simmons-Smith reagent to give a good yield of the cyclopropanol (136). Since cleavage of the cyclopropanol with acid was found to be inefficient in the present case probably due to the back-bone rearrangement of the intermediate cation such as (139), direct Birch reduction of the cyclopropanol (136) followed by acid-catalyzed opening of the cyclopropanol ring was attempted, successfully yielding (137).



(139)

Then the stage was set for completion of the E ring of the natural product and this was carried out in a fashion analogous to that used in the alnusenone synthesis as delineated in Scheme 26 (p. 56) with all operations.

Scheme 25

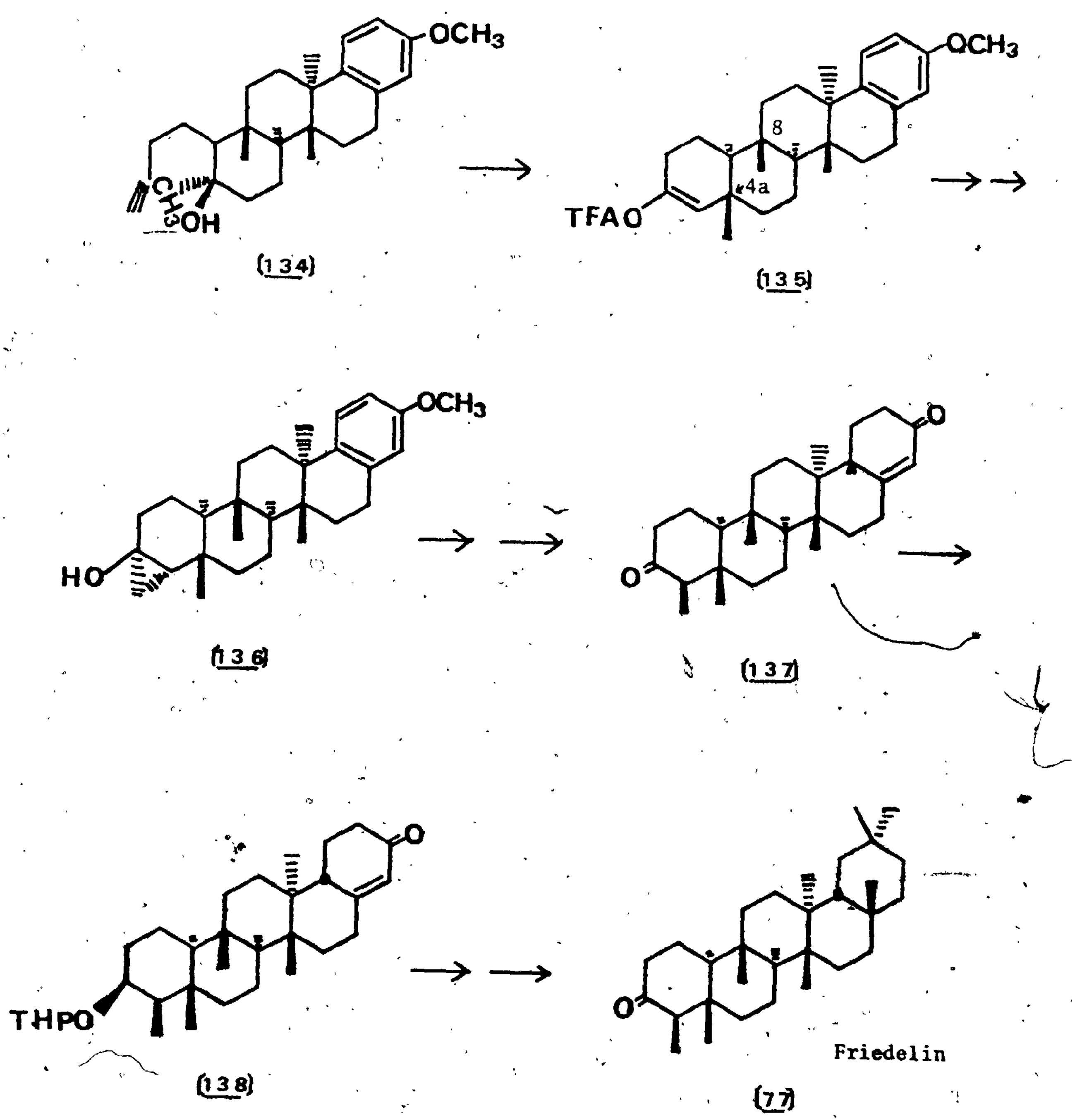


(131)

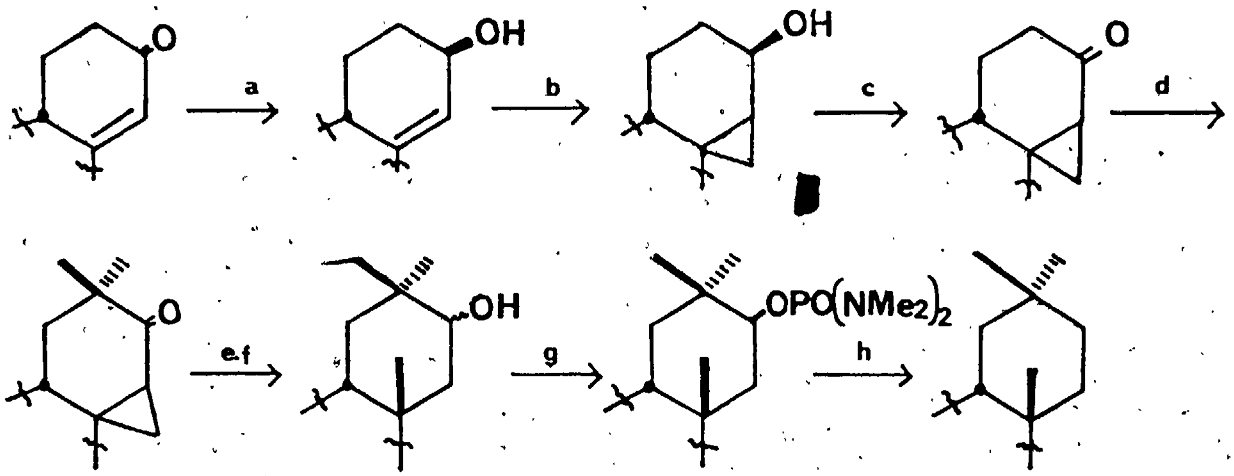
(132)

(133)

Scheme 25 continued



Scheme 26



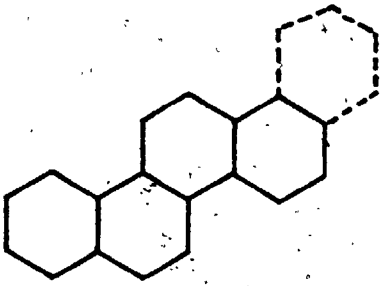
Reagents: (a) Li(OtBu)$_3$AlH, THF, C_6H_6, reflux; (b) Zn-Ag, CH_2I_2, THF; THF; (c) $CrO_3 \cdot 2py$, CH_2Cl_2; (d) KOt-Bu, CH_3I, THF; (e) Li, NH_3, THF, t-BuOH; (f) $LiAlH_4$, THF; (g) $ClPO(NCH_3)_2$, DME; HMPA, nBuLi; (h) Li, $C_2H_5NH_2$, t-BuOH.

In execution, it was necessary to protect the C-3 hydroxyl group as the tetrahydropyranyl ether in (138), which was the only difference from the alnusenone case. In the event, the first total synthesis of dl-friedelin (77) was thus completed in 31 steps with the overall yield of 0.3%.

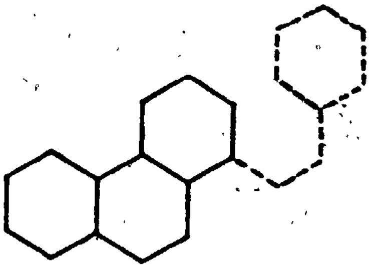
Ingeniously designed routes, being combined with highly stereospecific reactions that were carefully selected, have undoubtedly stemmed from the accumulation of the group's long continuing efforts, and hence the synthesis itself shall be recorded as one of the achievements in the history of natural products chemistry.

RESULTS AND DISCUSSION

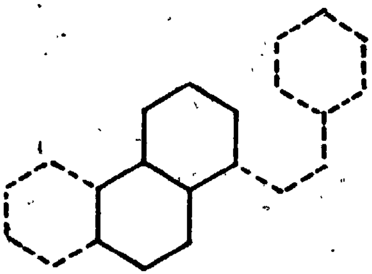
Some of the successful synthetic schemes leading to the pentacyclic triterpenes have been discussed in the previous section. The most notable synthetic achievements to date are Stork's synthesis of lupeol[65], Ireland's syntheses of germanicol[63], alnusenone[69], shionone[72], and friedelin[70a], and van Tamelen's synthesis of δ-amyrin[67]. Independantly to these workers, the problems associated with the total synthesis of the pentacyclic triterpenes have been under investigation in these laboratories for nearly a decade. Our concerns have been principally focused on the following routes; ABC-ABCD-ABCDE; ABC-ABCE-ABCDE; BC-BCE-BCDE-ABCDE; DE[illegible]DE-ABCDE.



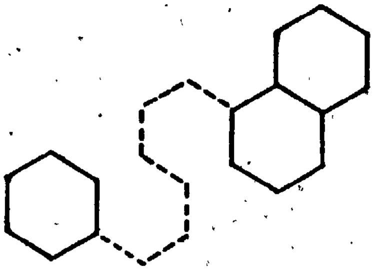
ABC→ABCD→ABCDE



ABC→ABCE→ABCDE

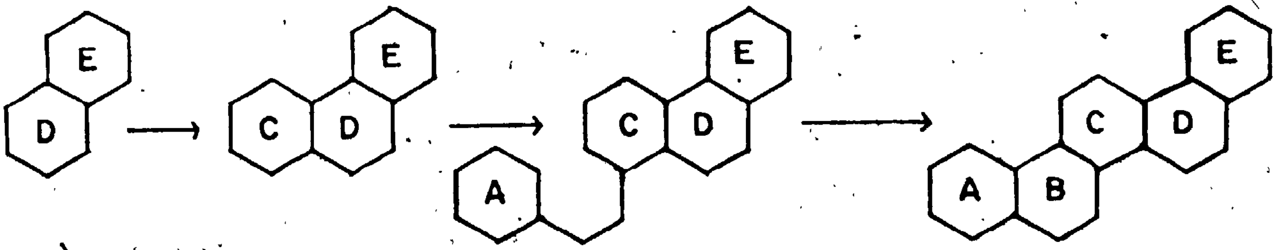


BC→BCE→BCDE→ABCDE



DE→ADE→ABCDE

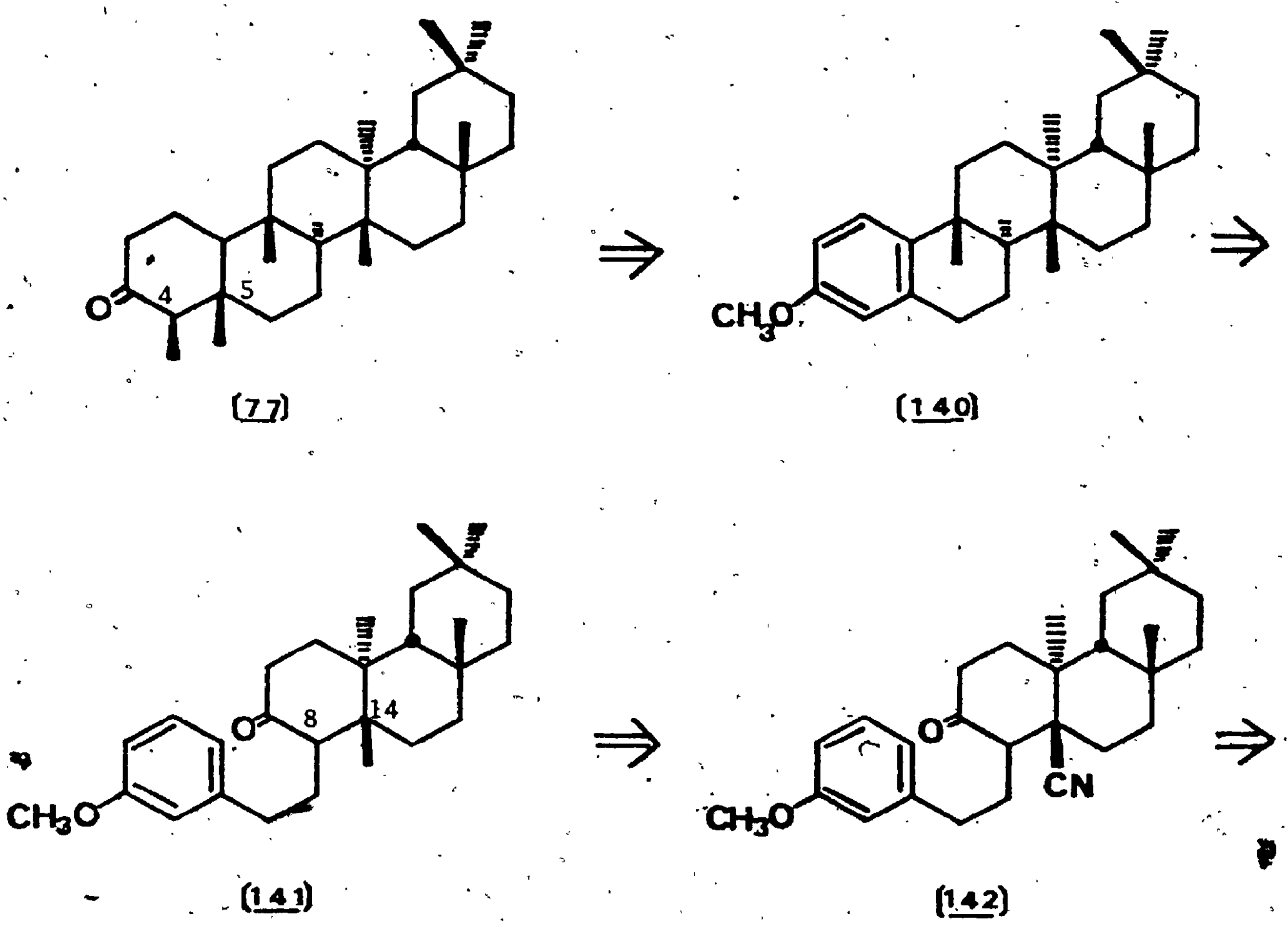
Although some measure of success has been achieved in each route, other potential approaches that are more economical, stereoselective and versatile may be envisioned in order to implement the approaches currently being investigated. In searching for such approaches, we have realized that a scheme relying on the route -DE-CDE-ACDE-ABCDE- would be worthwhile exploring.



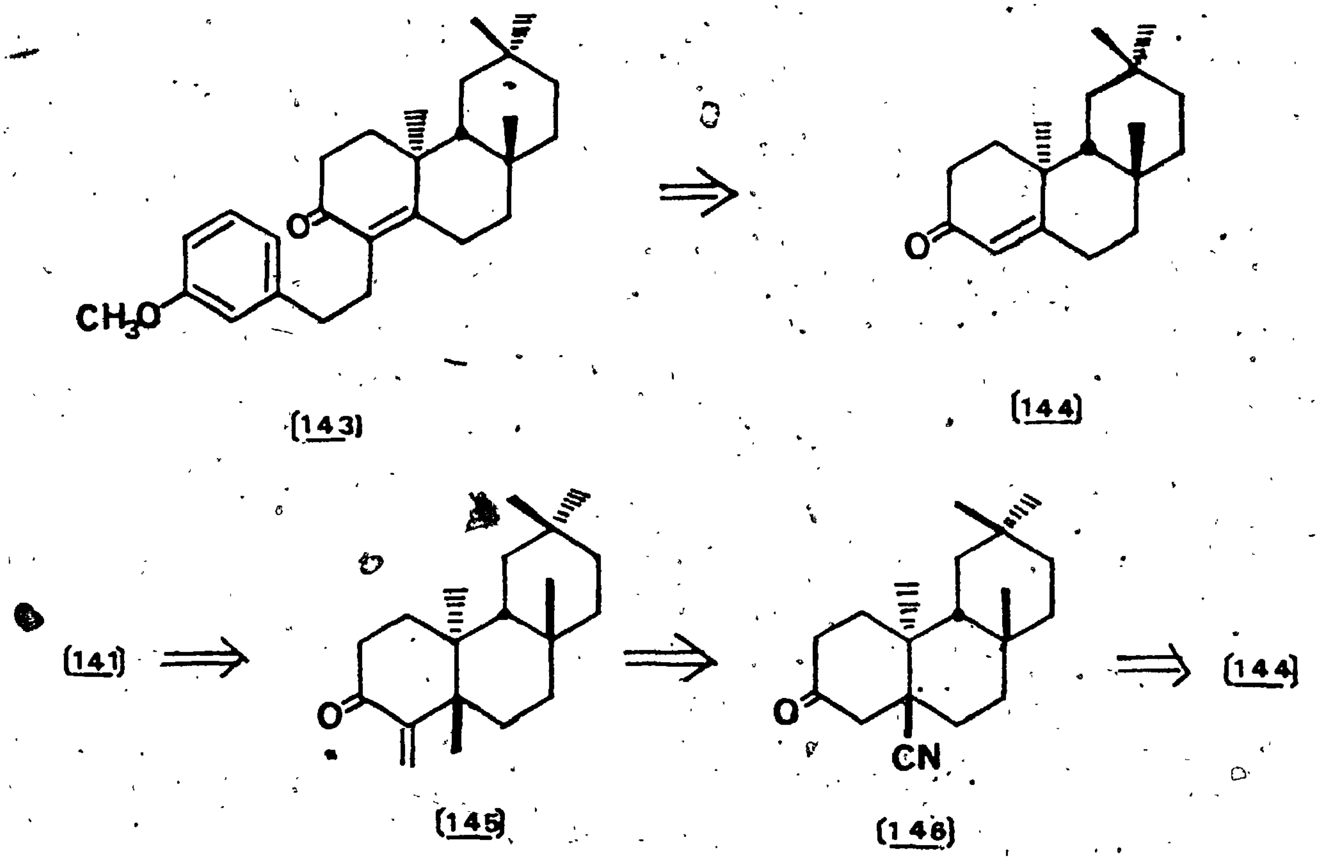
As previously mentioned, the earlier synthetic schemes which are patterned on the AB-ABDE-ABCDE approach- applied in the construction of the oleanane group- suffer seriously from poor yields and lacks of stereochemical control during the final cyclization stages. Without these drawbacks, the approach starting with a preformed DE ring skeleton would be attractive as had been illustrated in the van Tamelen synthesis of δ-amyrin[67] (Scheme 22) that foreshadowed the viability of the approach. An obvious advantage pertaining to the DE ring approach is the early solution in the construction of the _cis_-D/E ring junction that is the common feature in a number of naturally occurring triterpenes. As a logical consequence, it is likely that in such approaches the same _cis_-DE ring synthon would ultimately become the DE ring skeleton, and thus might serve as a general synthetic entry to the triterpenes.

Recognizing the difficulty that is related to the AB-ABDE-ABCDE approach, an alternative route still utilizing the DE ring synthon, that is DE-CDE-ACDE-ABCDE in which ring C is added to the preformed DE ring followed by assembly of the remaining A and B rings, was in our mind at the outset of the work. The ultimate objective of our work is the total synthesis of friedelin (77) and therefore a brief outline of the general synthetic plan that would possibly terminate in the synthesis of the natural product is presented in a retrosynthetic sense (Scheme 27).

Scheme 27



Scheme 27 continued



Ireland and coworkers[72] have elegantly accomplished the regioselective introduction of the two vicinal methyl groups at C-4 and C-5 through either the Simmons-Smith methylenation of an allylic alcohol system or the Eschenmoser cleavage of a keto epoxide[74], both of which are expected to be obtainable from a methoxylated aromatic ring such as that present in the pentacyclic ether (140), therefore this compound can be considered as a immediate precursor to friedelin. However, a problem exists in the use of latter method when it is applied to the present case such that it would presumably cause the back-bone rearrangement (as in compound (139)), and thus it seems likely that the choice would be restricted only to the former process (Simmons-Smith methylenation). Other experience from the Ireland's laboratory has also demonstrated that the Friedel-Crafts type cyclialkylation is of general utility, both stereochemically and practically, for the preparation of tetracyclic and pentacyclic ethers similar to (140), and for this reason the cyclialkylation of (141) would probably at least produce the required B/C *trans*-fused ether (140) predominantly in this case.

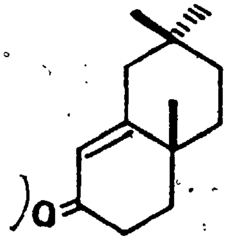
The angular methyl group at C-14 in (141) is expected to be introduced by the hydrocyanation[66] on the enone (143), as has been demonstrated by Ireland[69,70a,72] on similar enones. Incorporation of a *m*-methoxyphenylethyl side chain into (144) is not hard to envision, and the alkylation of (144) with either *m*-methoxyphenyl ethyl bromide or *m*-methoxyphenacyl bromide would probably yield (143). It is expected that the order of introduction of the angular methyl group at C-14 and the side chain at C-8 can be interchangeble, that is; first the hydrocyanation of (144) is carried out a[illegible]hereafter the attachment of the side chain follows presumably *via* the 1,4-conjugate addition of *m*-methoxyphenyl magnesium bromide to (145). By way of both routes, it is believed that compound (143) would be derivable from (144).

As the foregoing retrosynthetic analysis indicates, it is clear that the prime synthetic target for our route patterned on CDE-ACDE-ABCDE path should be the tricyclic enone (144). Two discrete routes that would lead to (144) were designed at the inception of the work, and it is the observations which have resulted from the initial phases of our investigations along these lines that are reported in this part of the thesis.

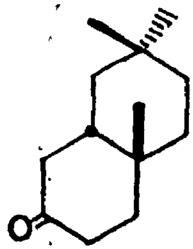
The DE-CDE Ring Approach:

The first approach towards the synthesis of the enone (144) involves the initial construction of a preformed DE ring unit and its subsequent conversion to a tricyclic compound by annelation, thus being formulated as a DE-CDE route.

There have been a number of reports regarding the construction of such preformed DE ring synthons. Halsall and Thomas[76] described the synthesis of the bicyclic intermediates (147) and showed that the hydrogenation of this decalone gave a single compound for which they assigned the cis-structure (148).

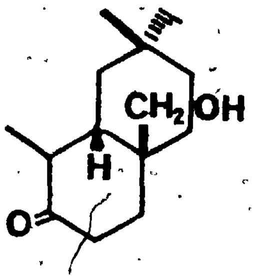


(147)

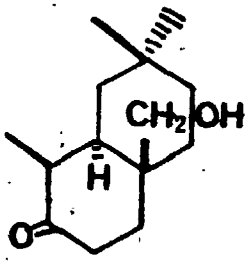


(148)

Recently the process has been repeated by Heathcock and coworkers[77], and a more rigorous stereochemical proof for the decalone (148) has been presented. Similar cis- and trans-decalones, (149) and (150), have been prepared in these laboratories.[64,78]

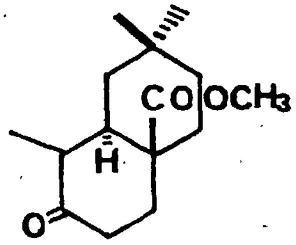


(149)

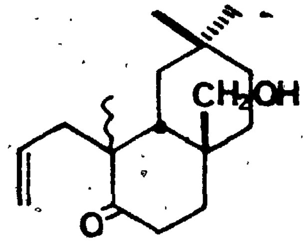


(150)

Comparison of the physical properties of the cis-(149) with those of trans-(150) has enabled the establishment of the cis-stereochemistry of (149) since the trans-decalone (150) was derived from the parent ester (151) whose trans-structure was determined by X-ray analysis.

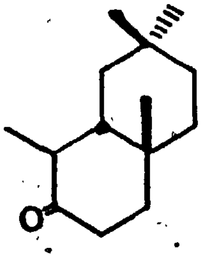


(151)

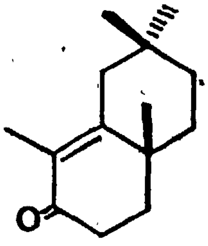


(152)

Unfortunately, all attempts to functionalize the C-1 position of the cis-decalone (149) failed except on only one occasion in which a low yield of the allyl derivative (152) was obtained. In view of these discouraging results, our interest was next turned to a cis-decalone (153) in the hope that the molecule would provide less steric hindrance towards an incoming alkylation agent.



(153)



(154)

Although compound (153) appeared to be derivable from (149) of known cis-stereochemistry, it was felt that the direct route relying on the hydrogenation of (154) would offer some advantages. Thus, the preparation of (149) is already laborious and therefore the need for extra steps in the synthesis in order to achieve the conversion of (149) to (153) does not seem to justify the synthesis by this route. On the other hand, there is good reason to believe that the hydrogenation of (154) will give the cis-decalone (153) predominantly.

The stereochemistry of the hydrogenation of α,β-unsaturated bicyclic ketones has been widely investigated. It has been proposed that the stereochemical outcome in the various substituted decalones was controlled by the nature of the angular substituents.[79] In principle, when the angular substituent is carboethoxy or carbomethoxy, a trans-product results exclusively; whereas when the substituent is hydroxymethyl or methyl, a cis-product predominates. This, however, is not the sole controlling factor and the influence of the angular substituent can be affected by small changes in the other positions of the molecules as well as by solvent. For instance, the addition of acid to the system is known to increase the amount of a cis-compound in the hydrogenation of some decalone derivatives.[80] Despite the variations in the cis/trans product ratio caused by these changes, the postulate above with regard to the role of the angular substituent appears to be true in a general sense on condition that neutral media and palladium-carbon as a catalyst are used in the hydrogenation. In order to clarify the points that have been argued, a tabular survey for the hydogenation of several 2-decalones was prepared (Table 1).

Table 1 The Hydrogenation of Some 2-Decalones.

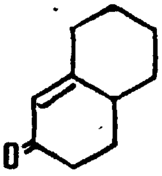
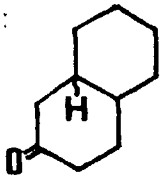
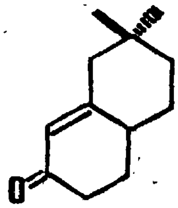
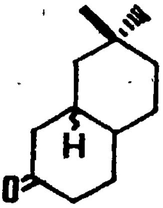
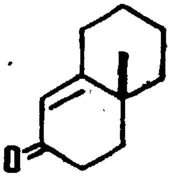
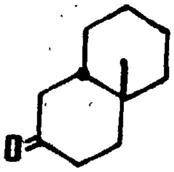
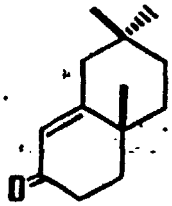
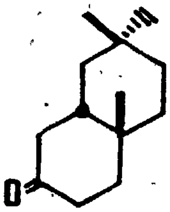
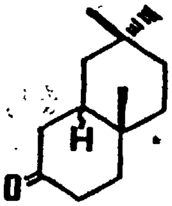
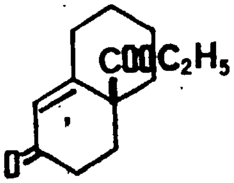
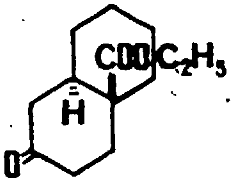
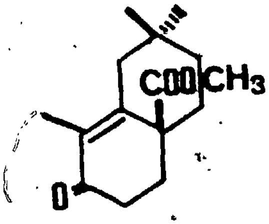
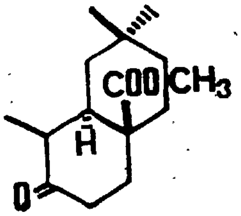
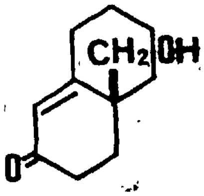
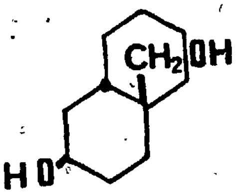
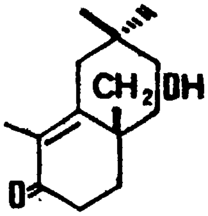
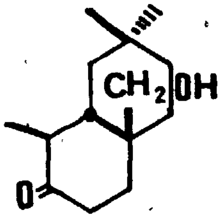
Entry	Decalones	Products		Conditions	References
1			cis/trans 53:47 93:7 62:38	10% Pd/C ethanol ethanol, aq. HCl ethanol,aq. NaOH	81
2			cis/trans 70:30 >95 30:70	10% Pd/C ethanol ethanol, aq. HCl ethanol,aq. NaOH	82
3			cis/trans 93:7	10% Pd/C ethanol, aq. HCl	83
4				10% Pd/C ethyl acetate	76
			mixture	acetic acid	

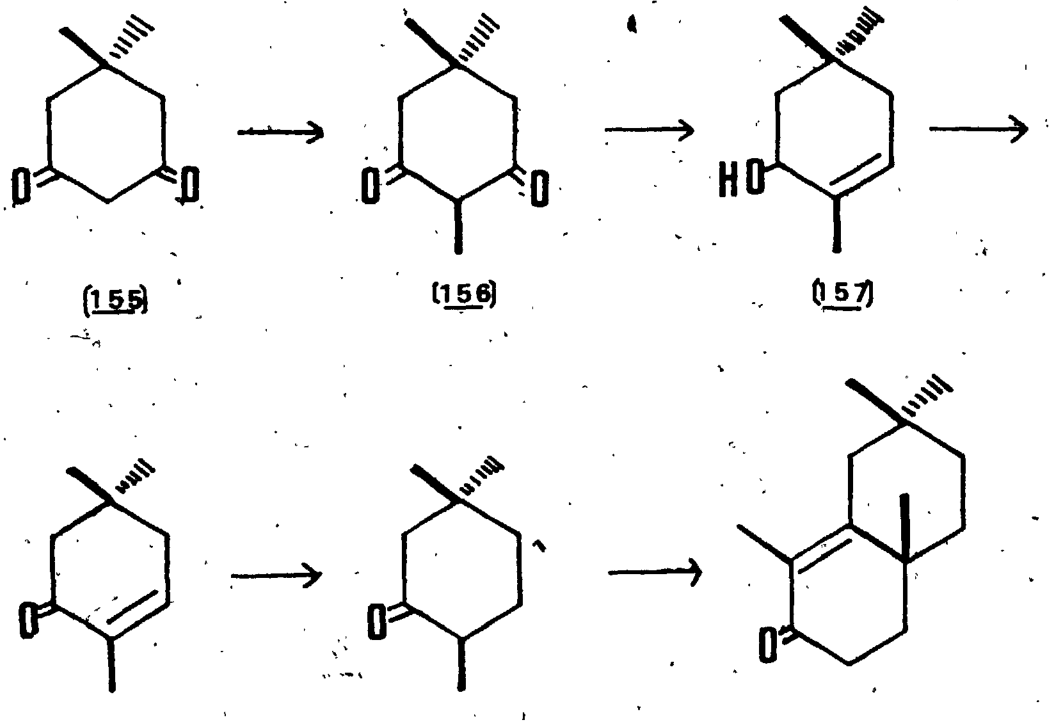
Table 1 continued

Entry	Decalones	Products	Conditions	References
5				79
6			10% Pd/C ethanol, aq. HCl	64,78
7			Pt ethanol	79
8			10% Pd/C ethanol, aq. HCl	64,78

Based on the work of Halsall[76] and Heathcock[77] in the preparation of the ketone (148), it was anticipated that the hydrogenation of (154) should afford the cis-decalone (153) with a high degree of stereospecifity. Examination of the literature also seems to support this view (see Entry 3,4 in Table 1). Consequently, it was decided to prepare the bicyclic enone (154) and the hydrogenation of the substance was subsequently executed.

Our synthesis of this material, following Heathcock's method[77] is outlined in Scheme 28.

Scheme 28

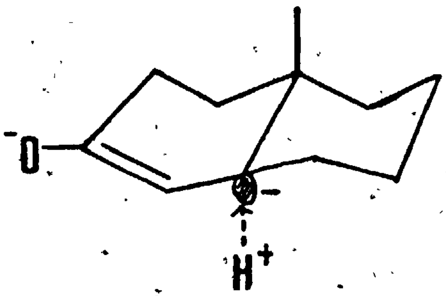


Methyl dimedone (156) prepared from commercially available dimedone (155) by Heathcock's procedure (methyl iodide, sodium hydroxide, water, at reflux)[84] was reduced with lithium aluminium hydride in ether to produce the allylic alcohol (157) in 65% yield. Oxidation of this alcohol (sodium dichromate in aqueous sulphuric acid-benzene at 0°) followed by catalytic hydrogenation of the resulting enone (158) on 10% Pd/C in ethyl acetate gave the monoketone (159) in 74% yield. Employing the convenient acid-catalyzed Robinson annelation procedure developed by Still and VanMiddlesworth[85] (treatment with methyl vinyl ketone in benzene at 0°, together with a small amount of conc. sulphuric acid), the desired decalone (154) could be prepared in 48% yield (71% conversion). By this route the decalone (154) was thus made available from dimedone (155) in an overall yield of 23%.

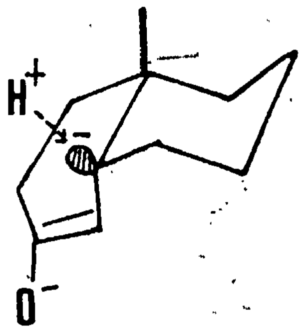
Hydrogenation of the enone (154) on palladium-carbon in ethyl acetate proceeded in high yield (92%) to afford a crystalline saturated ketone as the only isolable product, the stereochemistry of which is rigidly established later. Although it was likely, by analogy to some of the examples in Table 1 (pp. 64-65), that the hydrogenation product has the cis-ring junction, definite proof for its stereochemistry was felt to be necessary at this stage prior to further experimentation.

In this connection, it was thought that Birch reduction of the same enone (154) would give the trans-ketone (163) (p. 70) isomeric to the cis-(153) and hence the obtention of the samples in both series would be of value for identification purpose.

Concerning the stereochemistry of the metal-ammonia reduction of α,β-unsaturated ketones in which the β-carbon atom is located at the fusion of two six-membered rings, Barton and Robinson[86] postulated that the reductions, in general, lead to the formation of the thermodynamically more stable isomer at the β-position. However, using results of reduction in the octalone series, Stork and Darling[87] later concluded that regardless of the relative stability of the two possible octalones, the product is always derived from the more stable one of the two transition states, (160a) and (160b), for protonation in which overlap of the β-carbon with π-orbitals of the metal enolate is maintained.

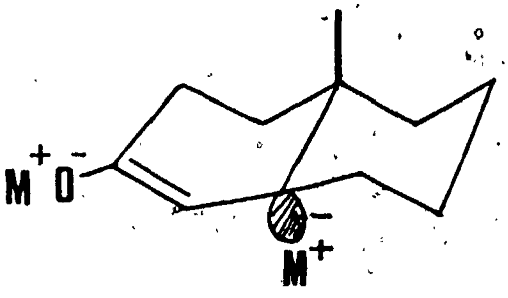


(160a)

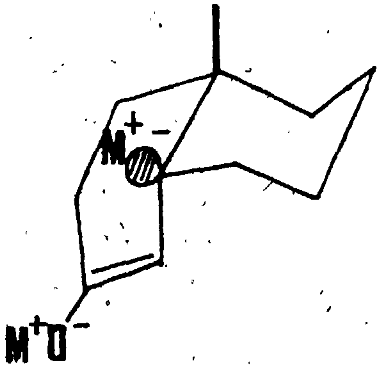


(160b)

The Stork and Darling rule has been widely applied for correctly predicting the stereochemical outcome of a large number of metal-ammonia reductions. However, there seems to be a even greater preference for the formation of the trans-product than would be predicted by analysis of nonbonded interactions if equilibrium is established between the configurations that are allowed on stereoelectronic grounds (i.e. overlap of orbitals). It has been therefore suggested that there is a kinetic preference for the formation of dianion (161a) over that of (161b), and that this intermediate (161a) undergoes protonation more rapidly than equilibration.[88]



(161a)



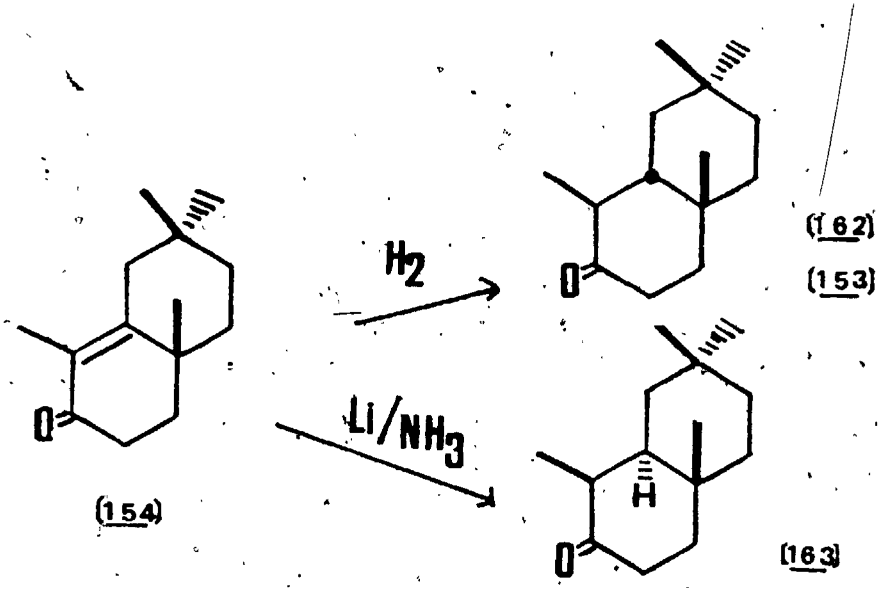
(161b)

Based on the preceding arguments, in the Birch reduction of (154) a intermediate resembling (160a) or (161a) should be favoured over the other one leading to a cis-product, and the intermediate would be expected, upon protonation, to yield the trans-product. The decalone (154) was therefore reduced with lithium in ammonia to afford a single product in a yield of 82%, and as expected the product thus obtained in Birch reduction proved not to be identical with the hydrogenation product (162).

Consistent with the prediction regarding the stereochemical outcome of both hydrogenation and Birch reduction, the results appeared to show that compound (162) from the hydrogenation would be the cis-decalone (153) whereas compound (163) from the Birch reduction should be trans-fused (see Scheme 29).

In order to ascertain the expected stereochemistry of both materials ((162) and (163)), an effort was made to correlate (163) with (151) of unambigious trans-stereochemistry that had been determined by X-ray analysis.

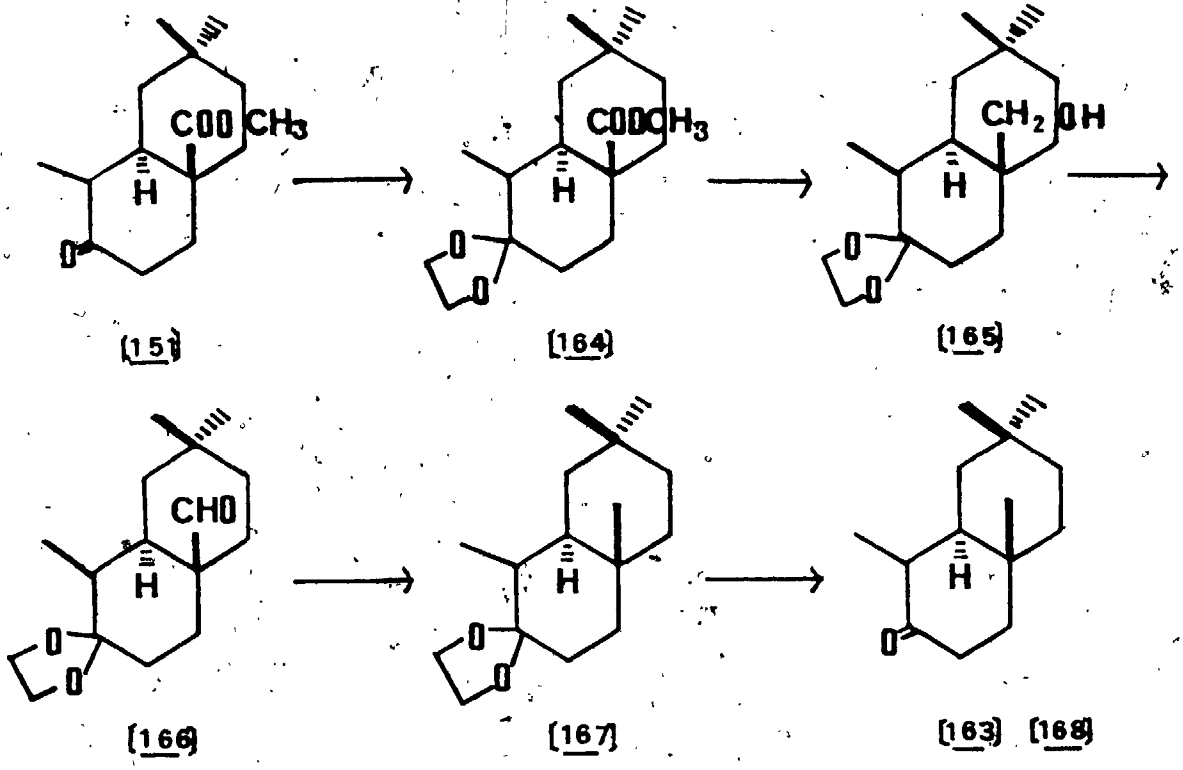
Scheme 29



Thus, the following transformations of the *trans*-ketone (151) as outlined in Scheme 30 were carried out. Ketone (151) had already been transformed to the corresponding alcohol (165) through (164) (Work performed by Dr. Badripersaud). Corey oxidation[89] of the alcohol (165) gave the corresponding aldehyde (166) in 89% yield. Aldehyde (166) was then subjected to Wolff-Kishner reduction conditions[90] to afford the ketal (167) contaminated by the *trans*-ketone (168) which was clearly formed during the work up of the reduction products by acid. Acid-hydrolysis of the mixtures, (167) and (168), in boiling acetone with dilute oxalic acid furnished the crystalline *trans*-ketone (168) (85%).

With the ketone (168) of known *trans*-stereochemistry in our hands, direct comparison of this material with the previous ketone (163) which had been obtained from the Birch reduction of (154) was possible. As we expected, compound (168) with the unambiguous

Scheme 30

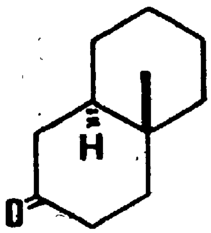


trans-ring junction was indeed identical with the ketone (163), thereby establishing the trans-ring nature of (163). Inasmuch as the trans-ketone (163) has the same molecular weight that the hydrogenation product (162) does, but shows distinctive differences in ^{1}H and ^{13}C nmr, and in melting point, the ketone (162) must bear the cis-junction; evidently ketone (162) is identical with the cis-decalone (153) (p. 62).

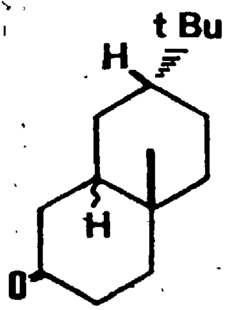
Of particular use in the assignment of stereochemistry that substantiated the above conclusion is the ^{13}C chemical shifts of decalones (162) and (163) (for the complete assignment of the chemical shifts; see APPENDIX III p. 167). A significant feature of their ^{13}C spectra is that the angular carbon atom in the cis-fused decalone (162) has a chemical shift of 27.5 ppm whereas the corresponding absorption in the trans-isomer (163) appears at 15.9 ppm. This observation can be attributed to the fact that a trans-decalone has a greater number of γ-interactions which contribute to the shielding of the angular carbon atom.[91] The chemical shifts of the angular carbon atom in some cis- and trans-2-decalones are collected in Table 2 for reference purpose.

Table 2

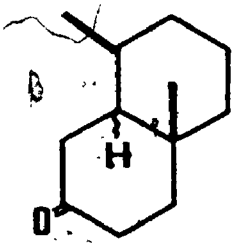
Decalones	Chemical shifts of angular carbon atoms (ppm)			Reference
	cis	trans	$\Delta\delta$ cis-trans	
(169)	---	14.9	---	92
(170)	27.0	17.2	9.8	93
(171)	27.7	18.6	9.1	94
(172)	26.2	19.6	6.6	94



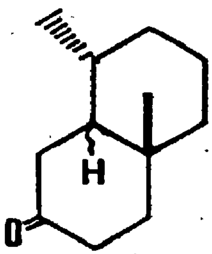
(169)



(170)



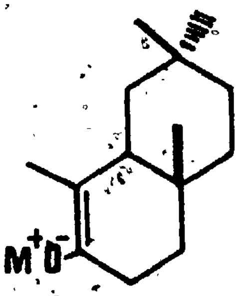
(171)



(172)

The observed difference in chemical shifts, 11.6 ppm between (162) and (163), is somewhat larger than the values quoted in Table 2, but in complete accordance with Stother's observations[95] that the shielding of the steroidal C-19 methyl carbon differs by 11-12 ppm between 5α- and 5β-steroids. Therefore it can be concluded that the ^{13}C nmr data for the compounds (162) and (163) are the direct reflection of their stereochemistry at the ring junction.

Having unequivocally established the stereochemistry of (162), we then set out to study the functionalization of C-1 which had been unsuccessful on compound (149). In view of the previous experiences from our laboratory, attempts were made to generate a metal enolate such as (173) and trap it with a suitable alkylating reagent.



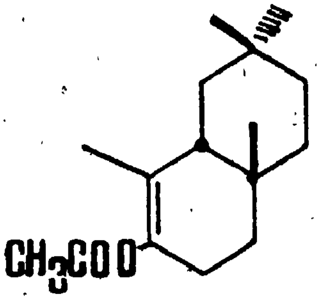
(173)

The main reason for this choice was that the regiospecific generation of a metal enolate coupled with quenching by an alkylating reagent precludes the need for either blocking or additional activating groups.

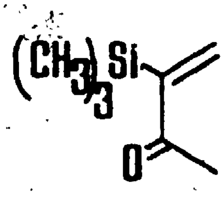
Principally there are two methods available at present for such regiospecific or regioselective formation of a metal enolate from an unsymmetrical ketone; a more highly substituted metal enolate can be prepared by reaction of an enol ester (formed under thermodynamic conditions) with an organometallic reagent, and similarly a silyl enol ether can be used as a precursor of either a more or less highly subsituted metal enolate depending upon the conditions under which it is generated (thermodynamic or kinetic control). Although, by the second method, it is often difficult to obtain a single enolate (i.e. a single silyl enol ether) of an unsymmetrical ketone under equilibrating conditions, the method offers such an advantage over the first one that it can avoid the formation of base (lithium t-butoxide) whose presence in the reaction medium might complicate the alkylation reaction by enhancing di- or poly-alkylation.[96]

The above consideration led us to attempt the preparation of a silyl enol ether from ketone (162), only to recover the ketone quantitatively under several conditions. By contrast, it was feasible to prepare the corresponding enol acetate (174) from the ketone (162) by following the procedure of House and coworkers[97] (acetic anhydride and catalytic amount of perchloric acid). The product was, in fact, the more highly substituted enol acetate (174) and no appreciable amount of the less highly substituted isomer ($\Delta^{2,3}$ isomer) was detected by nmr.

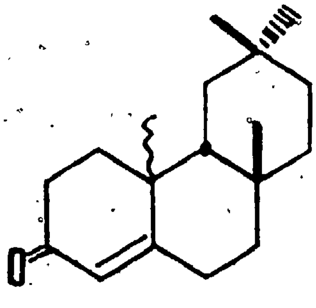
In one experiment the lithium enolate (173) (M=Li) generated from the corresponding enol acetate (174) upon treatment with methyllithium was allowed to react with α-trimethylsilylvinyl ketone (175)[98], and the reaction produced an ill-defined ketone in less than 10% yield which was suspected to be a tricyclic ketone (176) on the basis of ir and nmr spectra.



(174)

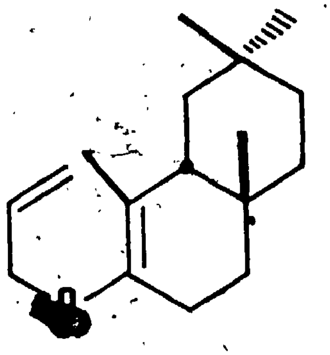


(175)

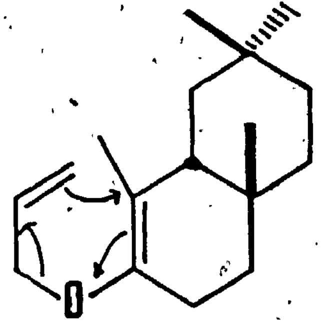


(176)

As we had observed before,[64] the lithium enolate (173) (M=Li) failed to react with allyl bromide in a number of solvents (ether, tetrahydrofuran, and 1,2-dimethoxyethane). While these experiments did not show any encouraging results, there was obtained, a new product in a yield of over 80% to which structure (177) was assigned when the alkylation was conducted in Hexamethylphosphoramide (HMPA). Characteristically, the nmr spectrum of this product contains a methylene peak appearing as a multiplet centered at δ 4.10 ppm, which can be assigned to be the methylene group lying between the oxygen atom and the vinyl group. The formation of (177) is not entirely unanticipated and resulted from the exclusive O-alkylation of the lithium enolate (173) in HMPA. A reasonable rationalization for the formation may be made using the following argument[99]; a very aprotic solvent such as dimethyl sulphoxide or HMPA has the ability to solvate a metal cation so strongly that a relatively free enolate anion is available in the solution and as the result, the enolate anion is apt to be captured by an alkylating reagent, forming an O-alkylated product.

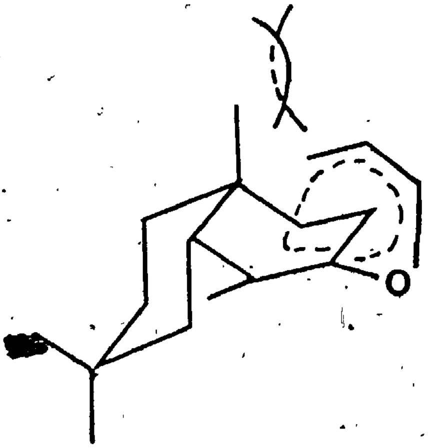


(177)

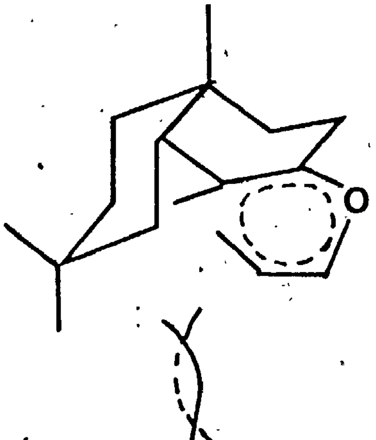


(178)

It was felt that compound (177) would undergo Claisen rearrangement readily by which one could introduce an allyl side chain at the C-1 of (177) as shown in (178). However, the question as to the stereochemistry of the allyl side chain would remain even if the Claisen rearrangement took place as expected; it would be either 1α-(equatorial)- or 1β-(axial)-allyl system. While axial attack is generally favoured on stereoelectronic grounds,[100] the approach seems to be offset or at least disfavoured by the steric factor provided by the angular methyl group in the case at hand (see (178a)). In a similar manner, equatorial attack (from α-face) would have to face the steric hindrance exerted by the E ring (particularly by the methylene group at C-8; see (178b)). Accordingly no rational prediction about the geometry around C-1 could be made *a priori*.



(178a)



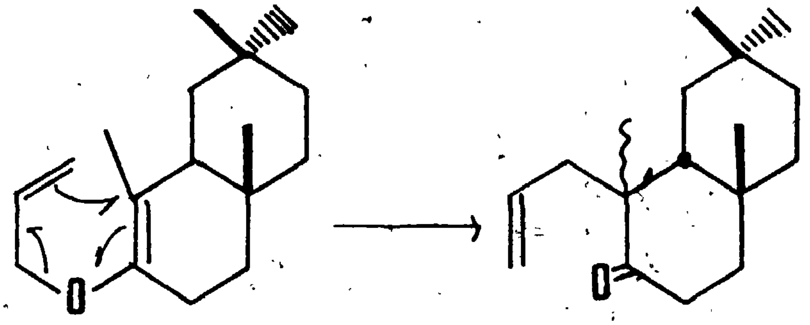
(178b)

In attempts to effect the Claisen rearrangement under a variety of conditions, the reaction displayed its capricious nature. Pyrolysis of the chromatographically pure (177) in a sealed Pyrex tube (200-220°, 20 min) afforded as high as 28% yield of a new product to which we assigned structure (179), together with the original ketone (162).

In boiling 2,2-oxydiethanol (bp 201°) the ketone (162) was produced quantitatively. This abnormal fragmentation to give (162) can be explained by the mechanism (Scheme 31) involving a (1,5)-sigmatropic hydrogen shift with extrusion of allene (retro-ene reaction[101]).

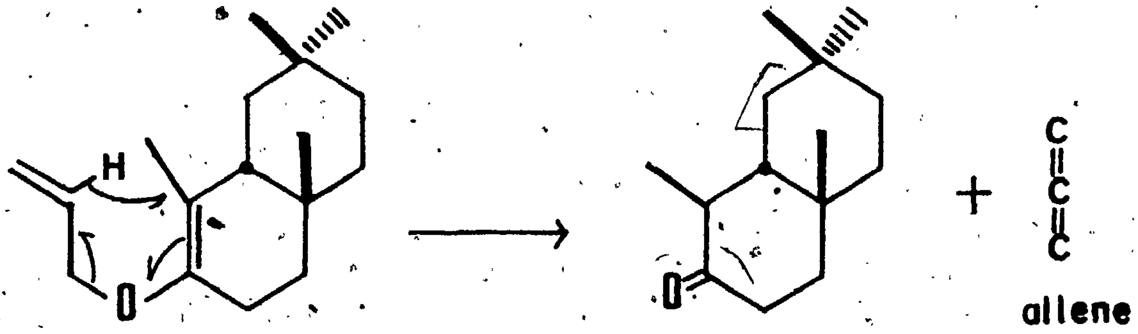
It sounds reasonable to assume that in the case above the Claisen rearrangement being normally a low energy process requires a transition state whose energy is raised by the steric factors,

Scheme 31



(177) (179)

Claisen rearrangement



(162)

Retro-ene reaction

and therefore the seemingly anomalous process which leads to the observed homolytic cleavage in a formal sense would become competitive with normal rearrangement.

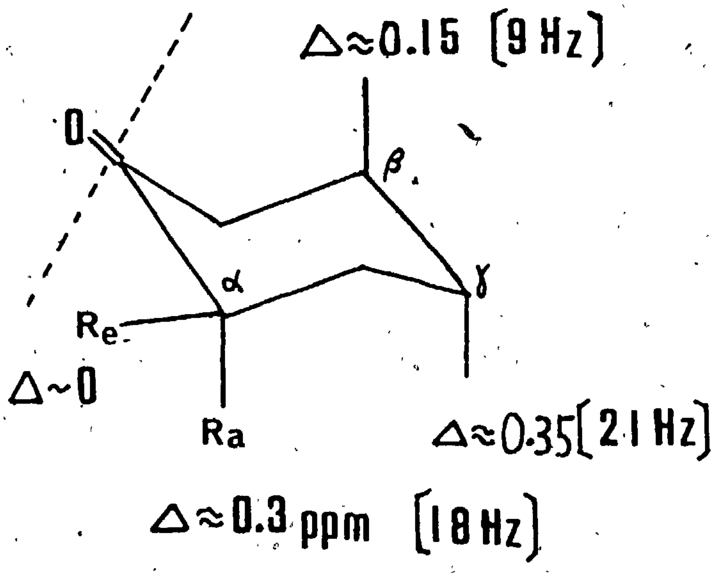
After some experimentation it was found that in boiling diglyme (diethyleneglycol dimethyl ether) the unfavourable fragmentation could be minimized to some extent which, however, was far from satisfactory, whereby as high as 45% of the desired (179) was obtained. The problem on the stereochemistry of the newly introduced allyl group at C-1 remained, as yet, to be solved.

In this connection, it was thought that the solvent-induced shifts of the C-1 methyl group would be of some use in determining the stereochemistry of the methyl group and hence the remaining allyl group could be defined spatially relative with the methyl group. Generally, the solvent shifts induced by replacing deuterochloroform by benzene ($\Delta = \delta\, CDCl_3 - \delta\, C_6H_6$) are negative for protons lying in front of a carbonyl group and positive for protons lying behind it.[102a,102b] Thus the solvent shifts are useful in establishing the spatial relationship between a ketone and protons whose resonances can be discerned in both solvents.

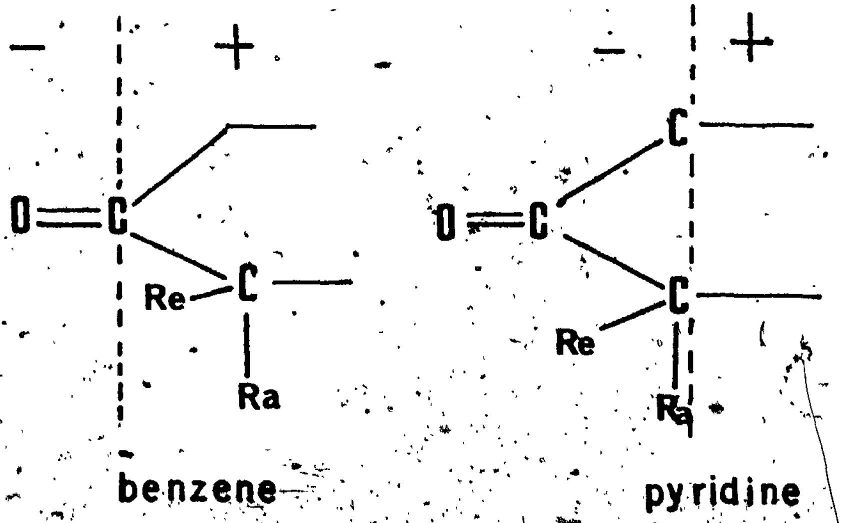
This relation is illustrated in the figure (p.80) using cyclohexane as an example where equatorial protons or methyl groups adjacent to the carbonyl group are barely influenced while those in axial positions are strongly shielded.

The situation is somewhat different in pyridine,[103] here the solvent shifts ($\Delta = \delta\, CDCl_3 - \delta\, C_5H_5N$) are negative for protons lying in front of a carbonyl group in a similar manner to the benzene-induced shifts, but the values are, by contrast, zero or

Figure Benzene-induced Shifts

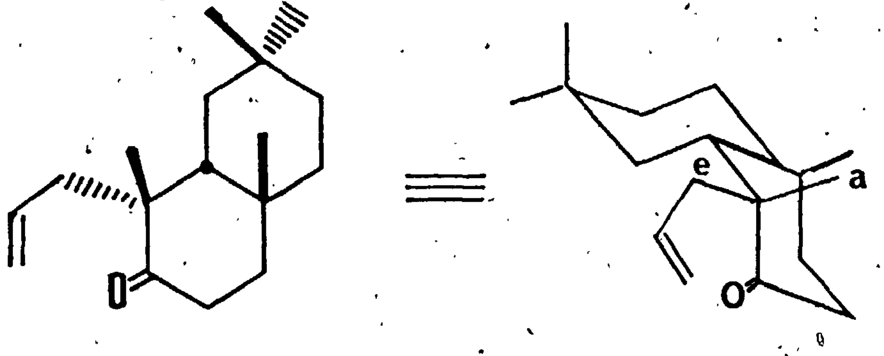


small (negative or positive) for protons located near a plane perpendicular to the carbonyl double bond and passing through α-carbon atoms. In other words, a change of sign occurs near a plane bisecting the molecular plane at the α-carbon atoms perpendicularly in pyridine shifts, while in the case of benzene shifts the reference plane can be drawn as cutting through the carbonyl carbon (see the illustrations below).

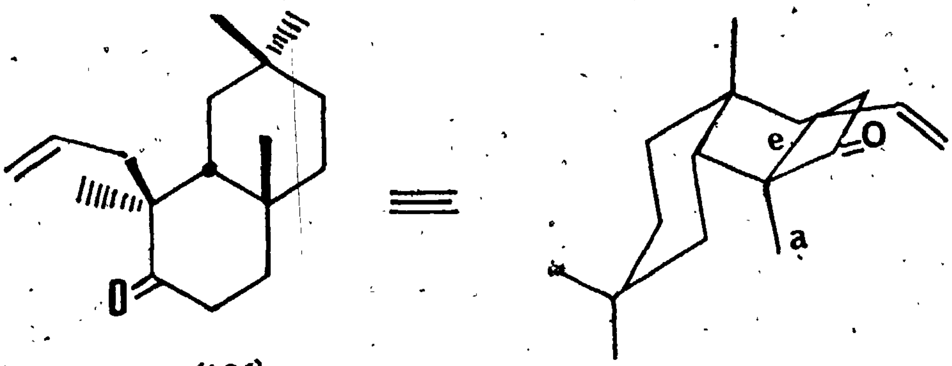


As the foregoing arguments imply, one can distinguish an equatorial methyl group from that in an axial position by combining both solvent shifts with certain reliability if the value in benzene is small (negative) or zero and the corresponding value in pyridine is appreciably negative. If the benzene induced shift has a positive value in the order of 10 Hz and the shift in pyridine is small (-5 to -4 Hz) or zero, the methyl group can be said to be axial.

In ketone (179) the values of the methyl resonance at C-1 were measured to be 6 Hz in both benzene and pyridine. These values suggest an axial rather than an equatorial methyl group, and therefore it seems likely that the C-1 methyl group of (179) occupies an axial position. Based on this finding it was proposed that compound (179) has a α-allyl group and a β-methyl group (as represented by the stereostructure (180)), nevertheless we could not preclude the possibility that were the allyl group on the β-face of the molecule, the D ring might be forced to exist as a half-boat form because of the severe 1,3-diaxial interaction between the allyl and angular methyl groups, in which case the α-methyl group at C-1 would become psuedo-axial as in (181). Taking this situation for granted, the stereochemical assignment around C-1 must be reversed. For this reason the structure (180) should be considered as tentative only.



(180)

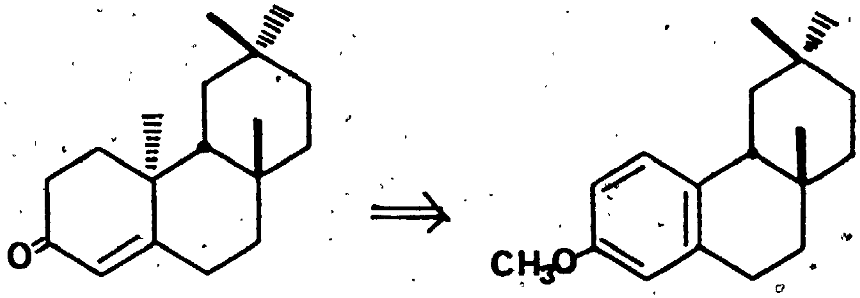


(181)

Since only (181) bearing a α-methyl group at C-1 can be of use in the synthesis of the tricyclic synthon (144), and in view of the relatively low yield of the Claisen rearrangement, taken together with the uncertainty about the structure of the product as to whether it is (180) or (181), we have at this stage regretfully abandoned further investigation of its use for the preparation of (144) in favour of the route described in the following section.

The CDE Ring Approach:

In parallel to the DE-CDE ring approach that has been discussed in the preceding section, an alternative route (the CDE approach) to the key synthon (144) in our synthetic plan has been explored. The main strategy of this approach is to initially synthesize the CDE ring skeleton and then convert it into the required enone (144). At the outset of this work the tricyclic intermediate (182) was in mind as our prime synthetic objective.

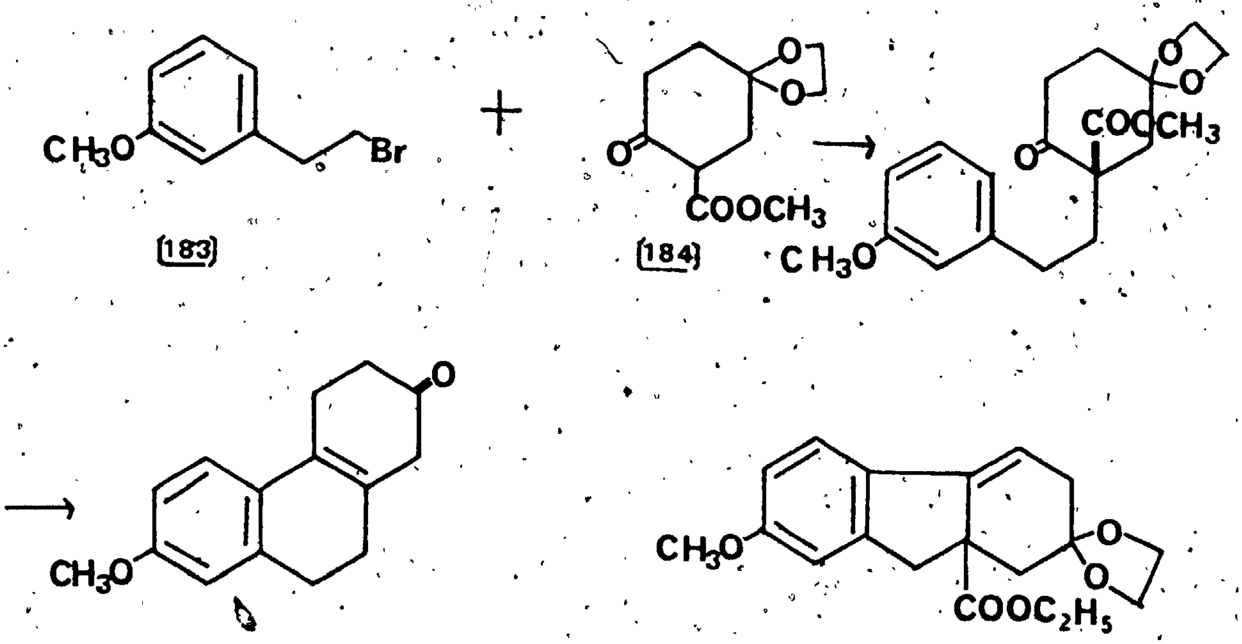


(144) (182)

The substance (182) provides not only the correct stereochemistry at the D/E ring junction but also the opportunity for elaboration of the C ring of the target molecule (144), because compound (182) has a methoxy aromatic ring which should give access to the enone system present in (144).

The construction of such a CDE ring synthon, although conceptually new in the triterpene syntheses, has several literature precedents.[104a,104b] In connection with the synthesis of cassaine analogs, Daum and coworkers[104a] reported the preparation of the tetrahydrophenanthrone (185) from the bromide (183) and the keto ester (184) according to the scheme below (Scheme 32).

Scheme 32

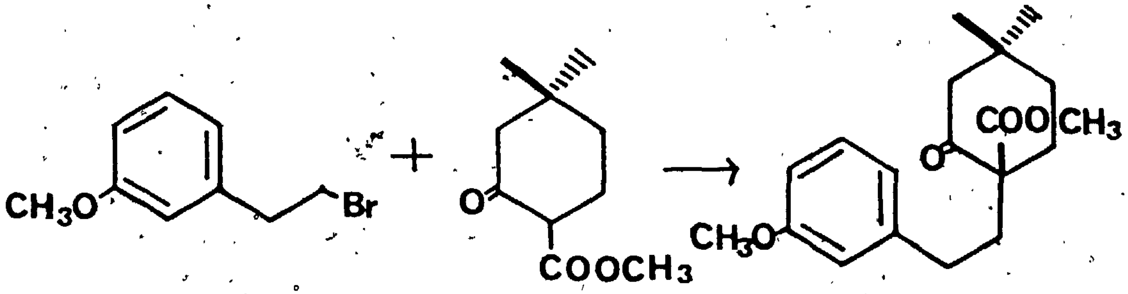


(183) (184) (185) (186)

Thomson[104b] reported the synthesis of compound (186) as a model compound for a gibberellic acid synthesis by a similar route. Both routes involve condensation of a halide with the anion of the keto ester and subsequent acid-catalyzed cyclization that led to compounds (185) and (186) respectively.

One can therefore foresee that the basic skeleton for the key substance (182) could be constructed based on the same idea, and the starting point of this research was then set at effecting the alkylation of the ketoester (187) with the bromide (185). (Scheme 33).

Scheme 33

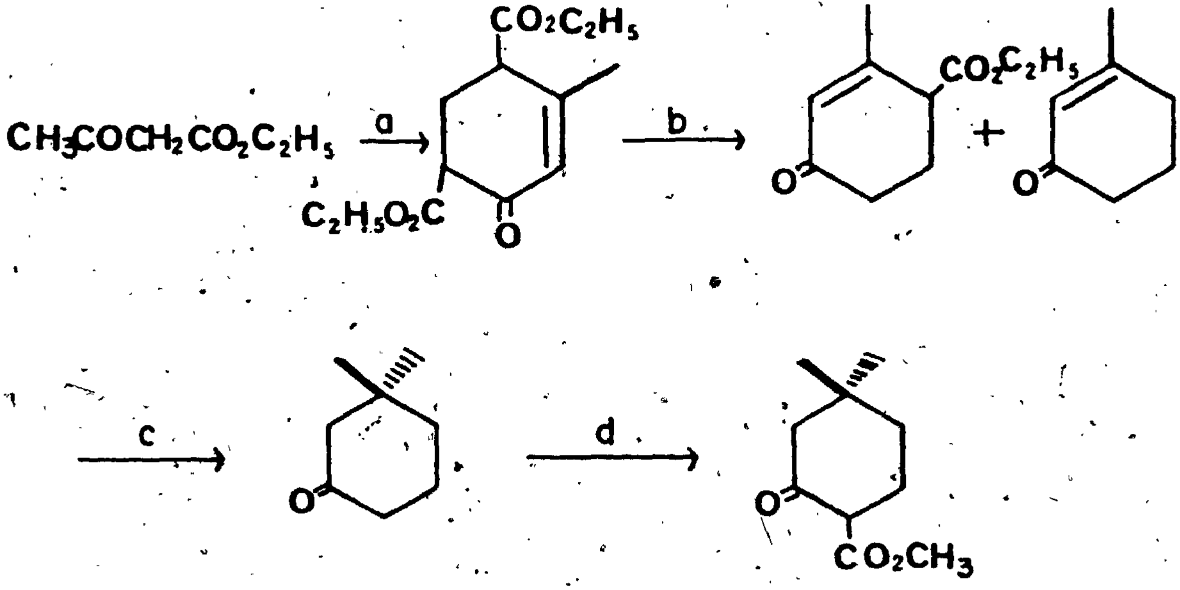


(183) (187) (188)

The keto ester (187) can be prepared readily and the method used to synthesize this compound has been published from our laboratory.[78] Scheme 34 outlines its preparation, and the only modification in the present route differing from the previous one can be seen in step (d) where Deslongchamps's method[105] for carbomethoxylation of cyclohexanone was employed. Following this scheme, the ketoester (187) was synthesized in an overall yield of 25% from ethyl acetoacetate.

Condensation of the keto ester (187) with the bromide (183) in the presence of base (potassium t-butoxide) proceeded in a yield of about 31% to give compound (188) (Scheme 33).
m-Methoxyphenylethyl tosylate as an alkylating agent offered no advantages over the bromide (183), but rather complicated the

Scheme 34



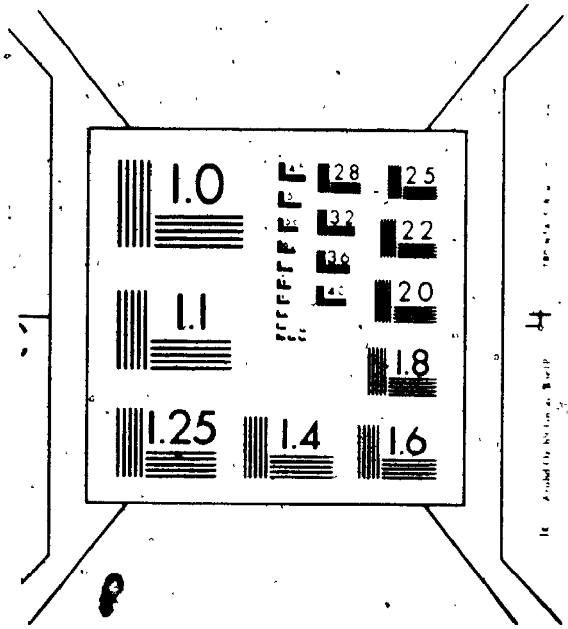
(187)

Reagents: (a) HCHO, piperidine; (b) H_2SO_4; (c) CH_3MgI, CuI; (d) $CO(OCH_3)_2$, NaH, KH.

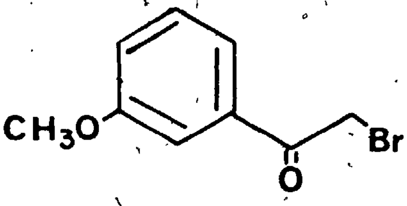
separation of the product (188) because the unreacted tosylate in the reaction mixture made separation by distillation impracticable.

The condensation reaction was always accompanied by the formation of a side product (m-methoxystyrene) which apparently resulted from elimination of bromine or the tosylate group in the alkylating agent by base. In order to avoid this unfavourable side reaction, m-methoxyphenacyl bromide (189) containing no

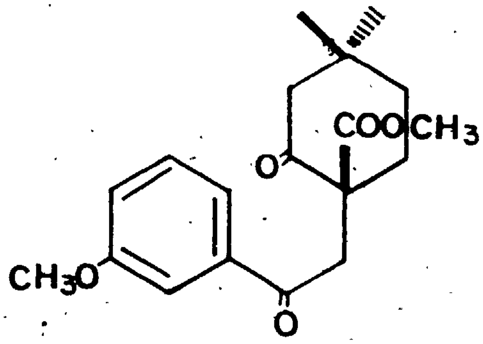
2



hydrogens at the benzylic position was used in the alkylation, nevertheless the yield of (188) turned out not to be as high as we expected (54%) since in this case the extra carbonyl group in the product (190) had to be removed reductively by hydrogenation in an acidic medium.



(189)

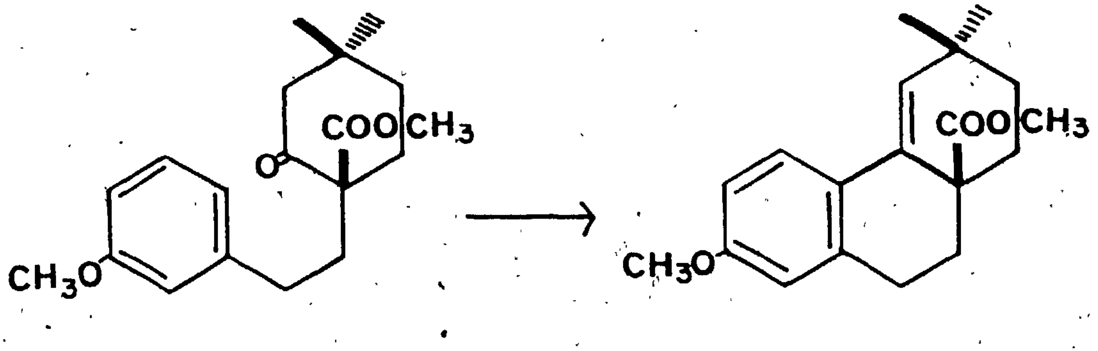


(190)

Finally after the abovementioned experiments it was concluded that the first alkylation method (as shown in Scheme 33 p. 85) would be the best in terms of reproducibility and purity of the product although the yield was not entirely satisfactory.
The alkylated product (188) was cyclized efficiently by refluxing in benzene with p-toluenesulphonic acid, providing a tricyclic compound (191) in a yield of 83% (Scheme 35).

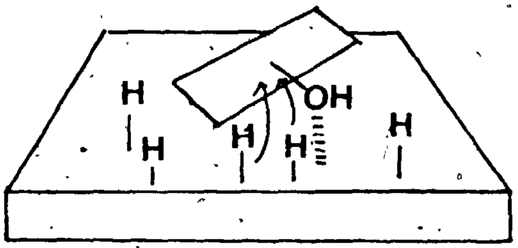
2

Scheme 35



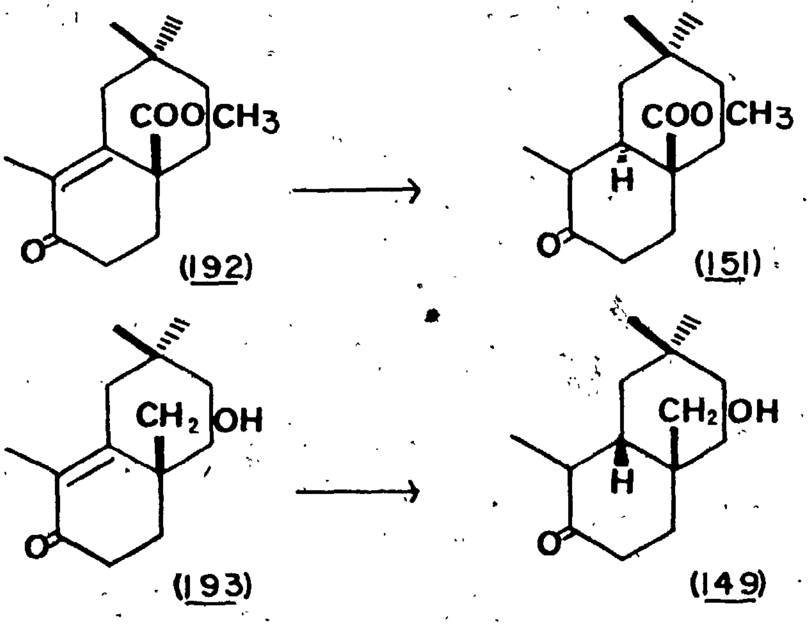
(188) (191)

Compound (191), being essentially flat, would probably approach a catalyst face only from α-face upon hydrogenation because of the steric effect provided by the angular carbomethoxy group, and for this reason it seems almost likely that the hydrogenation of (191) would produce the *trans*-stereochemistry at the D/E ring junction. By contrast, if the angular substituent contained a hydroxyl group, the catalyst surface would be able to approach to the molecule preferentially from β-face by virtue of directing effect by the hydroxyl group, thereby a *cis*-stereochemistry would be expected.[106a,106b] This sort of attractive interaction between the catalyst surface and a part of the reducible molecule, particularly a hydroxyl group, has been known for a long time and recently generalized in the term "haptophilicity" by Thompson.[106b] According to his definition, the directing effect of a hydroxyl group in heterogeneous catalytic hydrogenation arises from the fact that the hydroxyl group binds to the catalyst surface in such a way as to make delivery of hydrogen from its side of the reducible molecule possible. This hypothesis is illustrated in the model shown below.[106b]



Perhaps one illustrative example of the concept can be found in the hydrogenation of decalones (192) and (193) (Scheme 36; see also Entries 6 and 8 in Table 1 p. 65)[64,78].

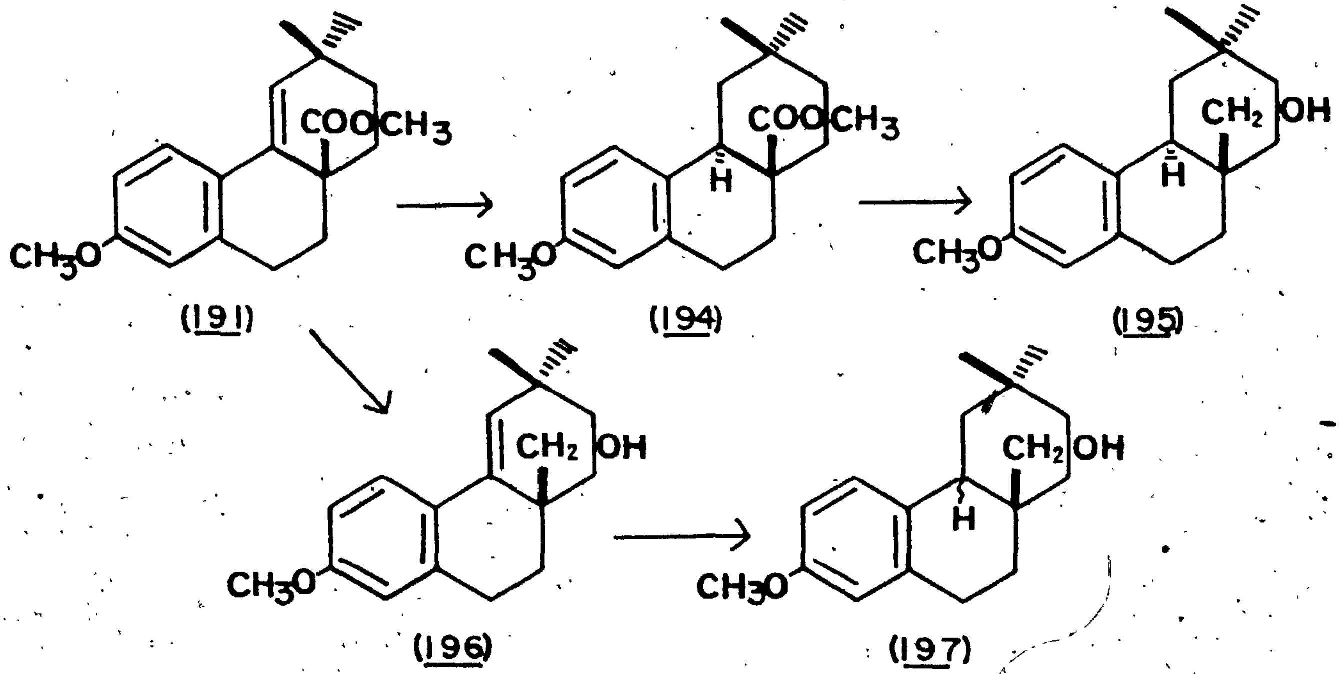
Scheme 36



Hydrogenation of the ester (192) yielded decalone (151) with unambiguous *trans*-stereochemistry, by contrast compound (193) differing from (192) only with respect to its angular substituent gave the *cis*-fused alcohol (149). Here, the haptophilic properties of the angular hydroxymethyl group undoubtedly reversed the stereochemical course of the hydrogenation.

It remains, however , to determine whether or not this concept can be utilized in directing the stereochemistry of double bond hydrogenation in a compound such as (191), although *a priori* we concluded that catalytic hydrogenation of (191) would lead to a *trans*-D/E ring junction whereas reduction of the corresponding alcohol (196) should provide the *cis*-fused product (197) as the major material (see Scheme 37). Accordingly, compound (196) was prepared by lithium aluminium hydride reduction of (191) in a nearly quantitative yield.

Scheme 37

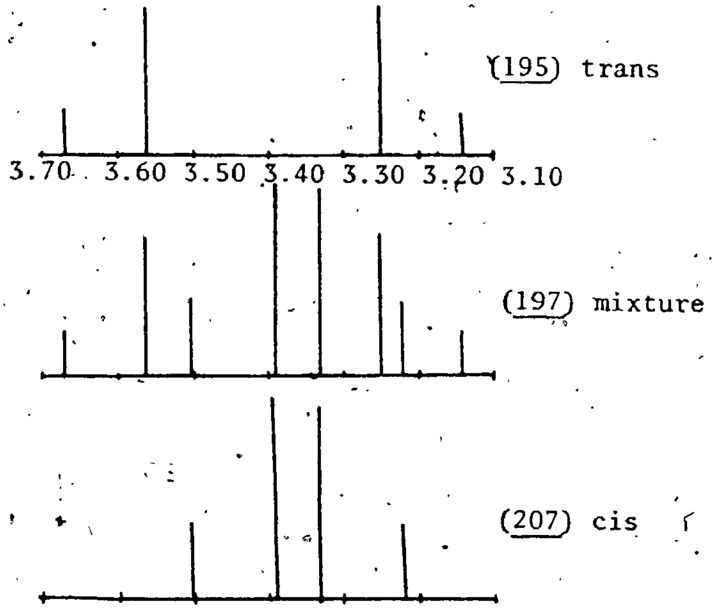


With both samples (191) and (196) in hand, we first carried out the hydrogenation of (191) on 10% Pd/C in toluene. Compound (191) upon hydrogenation gave what appeared to be a single ester (194) in 98% yield, and this ester was further reduced with lithium aluminium hydride to the corresponding alcohol (195) (94%). Under similar hydrogenation conditions the alcohol (196) was reduced catalytically to give the alcohol of ambiguous stereochemical purity (197) which later proved to be a mixture of the cis- and trans-alcohols, (195) and (207). These sequences are shown in Scheme 37 (p. 90).

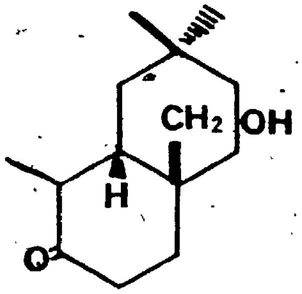
Examination of the ^1H nmr spectra of both alcohols (195) and (197) revealed a remarkable difference in the region between δ 3.10 and 3.70. The signals due to the angular hydroxymethyl group (CH_2-OH) of (195) appear at δ 3.20 and 3.61 as a pair of doublets (AB type) whereas the alcohol (197) exhibits two pairs of doublets, one at δ 3.20 and 3.61 and the other at δ 3.30 and 3.42 in the corresponding region. Assuming that the stereochemistry of (195) be trans, that is, the first pair of the doublets appearing at δ 3.20 and 3.61 represent the trans-nature of the ring junction, we were inclined to suppose that the third pair of peaks at δ 3.30 3.42 would belong to the true cis-isomer. These relationships can be visualized in the diagram (p. 92).

In assigning the stereochemistry of the bicyclic alcohols, (149) and (150), whose structures are closely related to those of (195) and (197), ApSimon and coworkers[78] have utilized the line width of the angular hydroxymethyl absorption in nmr and concluded that the trans-fused (150) has the line width at half-height ($W_{\frac{1}{2}}h$)

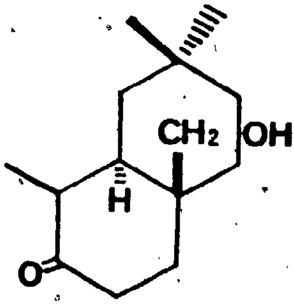
Diagram representing the ^1H nmr signals for the angular hydroxymethyl groups (CH_2-OH).



of 3Hz as opposed to the values (1Hz) for the cis-fused (149). This argument is based on the postulate of Spencer and coworkers[107] that the W½h for the trans-decalins is always larger than that for cis-decalins.



(149)



(150)

The $W_{\frac{1}{2}h}$ for the first pair of doublets at δ 3.20 and 3.61 (see the diagram) and that for the second pair at δ 3.20 and 3.61 in (197) have the same value of 3Hz, in contrast, the corresponding value for the last pair at δ 3.30 and 3.42 (also in (197)) is relatively smaller (around 2Hz).

Applying Spencer's rule in the present case, the following arguments can be proposed; the first and second pairs are due to the angular hydroxymethyl group with the trans-fusion and hence compound (195) contains only the trans-isomer, whilst compound (197) is composed of the cis- and trans-isomers since the last pair can be regarded as arising from the cis-isomer. As the foregoing arguments imply, the hydrogenation of (191) was believed to produce the trans-isomer (194) of stereochemical purity but that of the alcohol (196) was not stereospecific, resulting in the formation of a mixture of the cis- and trans-isomers (197).

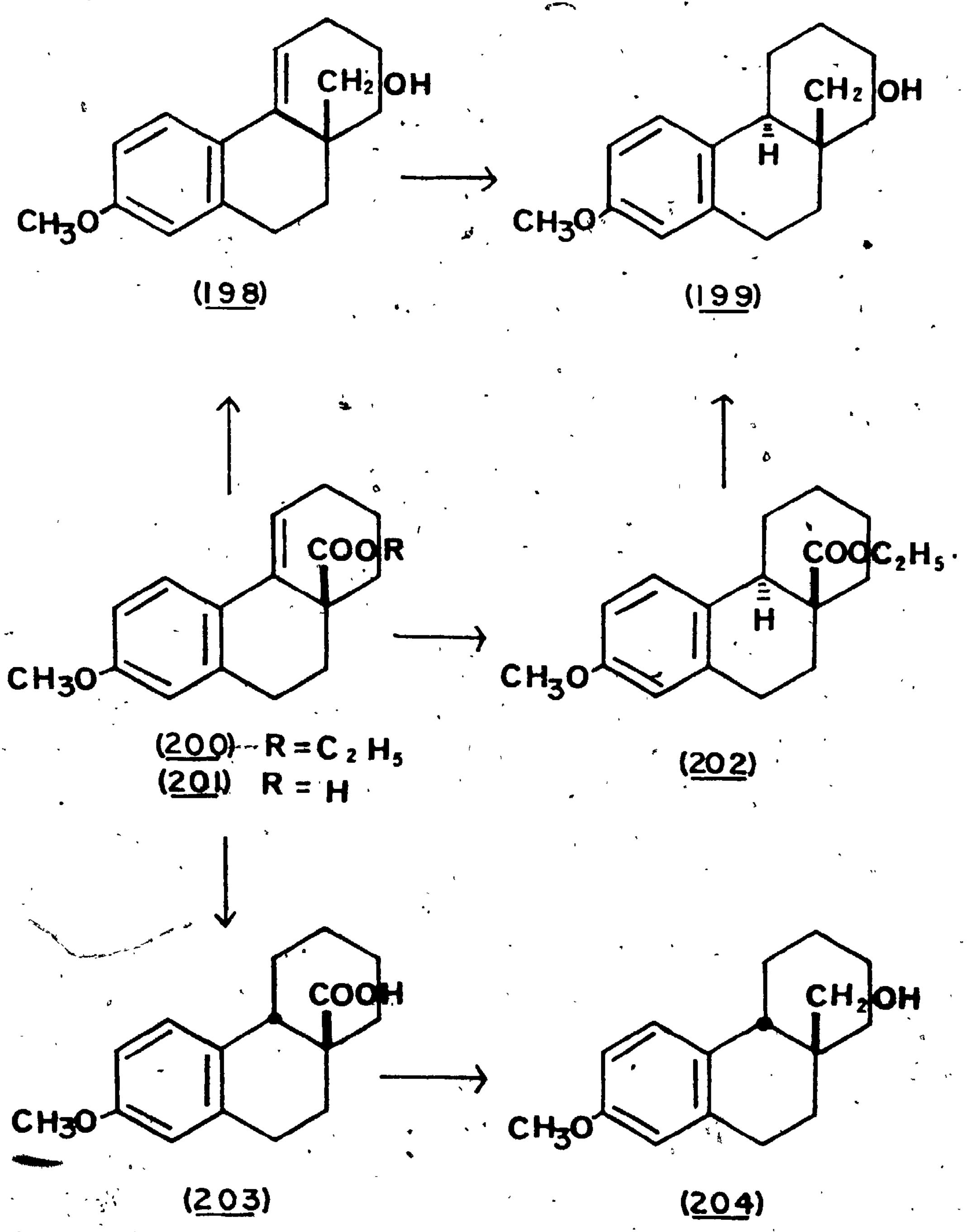
Accordingly, it was thought that changing solvent might affect the stereochemical course of the hydrogenation and that hopefully it would increase the portion of the cis-isomer by enhancing the haptophilicity of the hydroxyl group to a dgree which would be synthetically useful. Unfortunately little is known concerning the solvent effects on hydrogenation[80,108] and therefore prediction of the stereochemical outcome seemed impossible. For this reason, the hydrogenation of the alcohol (196) was conducted in a number of solvents. Normally the hydrogenation was found to give a mixture of the cis- and trans-isomers as revealed by nmr, but exceptionally in acetonitrile it produced the cis-isomer predominantly, in this case, however the rate of hydrogenation was too slow to be of synthetic utility.

In the meantime, the hydrogenation of alcohol (198) that is astonishingly similar to our system was reported by Thompson and coworkers[109]. Their results (shown in Scheme 38) showed that compound (198) upon hydrogenation gave cis- and trans-mixtures rich in the trans-isomer (199) (trans/cis 94:6 in ethanol) whose cis-composition was increased as the polarity of the solvent was decreased, and that the parent ester (200) was hydrogenated to provide the trans-ester (202) which was in turn correlated with (199).

Their observations seem to agree with ours besides the high percentage of the trans-isomer in the hydrogenation product, and thus support our speculation concerning the stereochemical outcome of the hydrogenation (p. 93 1.6). Additionally, it was reported that lithium-ammonia reduction of the carboxylic acid (201) yielded a single carboxylic acid (203) to which they assigned the cis-ring junction. Lithium aluminium hydride reduction converted the carboxylic acid (203) to the alcohol (204), which was not identical with the previous alcohol (199). Accordingly their stereochemical assignments for (199) and (204), and hence for (202) and (203) are self-consistent within their system.

Having been encouraged by these results, we decided to prepare the corresponding acid (205) (Scheme 39) and undertake the lithium-ammonia reduction of this compound. On the assumption that a minor difference in structure between (201) and (205) would not cause significant changes in the stereochemical course of the reduction, a cis-product was expected upon the reduction of the acid (205).

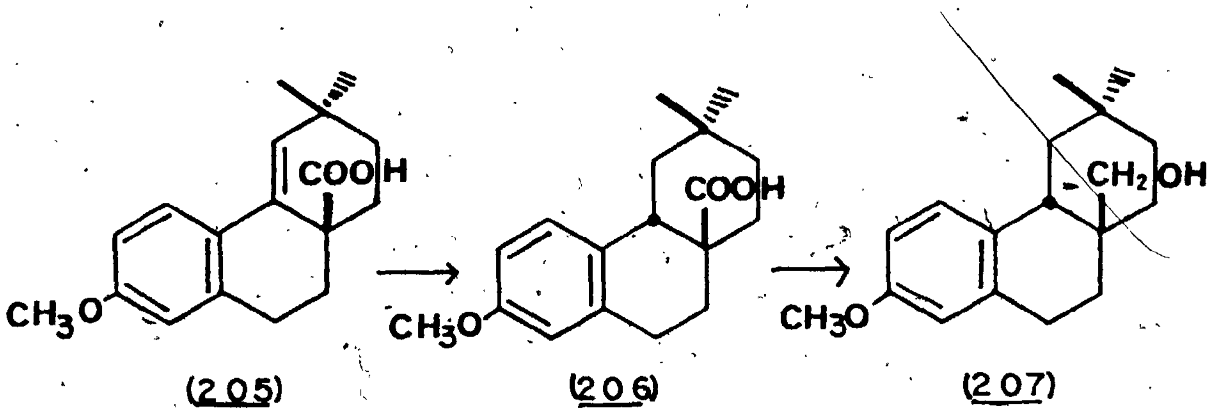
Scheme 38


CH₂OH
CH₃O
(198)
CH₂OH
H
CH₃O
(199)
COOR
CH₃O
(200) R = C₂H₅
(201) R = H
COOC₂H₅
H
CH₃O
(202)
COOH
CH₃O
(203)
CH₂OH
CH₃O
(204)

Saponification of the ester (191) with potassium hydroxide in methanol under reflux proceeded extremely slowly as Thompson[110] pointed out, but replacing the solvent from methanol to methoxyethanol (bp 124°) greatly facilitated the saponification. In this manner, a reasonable yield (71%) of the carboxylic acid (205) could be obtained during a reasonable length of time (48 hr).

Following Thompson's conditions for the reduction of (201) to (203), the acid (205) was treated with lithium in liquid ammonia to give a saturated carboxylic acid (206) in a yield of 74%, and this acid was reduced with lithium aluminium hydride to a hydroxymethyl compound (207) which was not identical with (195) obtained through a hydrogenation and lithium aluminium hydride reduction sequence from (191) (see Scheme 37).

Scheme 39



Consistent with our prediction on the assignments of the angular hydroxymethyl peaks, the nmr spectrum of compound (207) displayed the characteristic pattern appearing at δ 3.30 and 3.42 which had been supposed to represent the cis-ring junction. This result, taken together with our previous stereochemical assignments for (195) and (197), suggested that if Thompson's assignments for (199) and (204) were correct, so would be ours for (195) and (207). We were therefore confident that the alcohol (195) posesses the trans-ring junction and thus the other alcohol (207) has the cis.

Inasmuch as our stereochemical assignments were dependant upon the preceding arguments, there is one weakness in our logic, that is, only evidence relying on the $W\frac{1}{2}h$ values (refer to p. 93) can allow us to distinguish the cis- and trans- isomers. Interestingly, ^{13}C nmr data for both alcohols (195) and (207) displayed a marked contrast in chemical shift of their angular hydroxymethyl groups (C^*H_2-OH); the chemical shift for (195) is 59.2 ppm while the corresponding shift for (207) is 69.2 ppm.

Although the observed shifts themselves have no reference values for comparison, the difference between the two, 10 ppm, is in accord with those between cis- and trans- decalones (Table 2 p. 72). Considering the fact that the angular grouping in a trans-decalin is always shielded significantly when it is compared to its counterpart in a cis-series, these observations suggest that the alcohol (195) has a trans-decalin structure while the other alcohol (207) is cis-fused. Thus the ^{13}C data for the alcohols (195) and (207) appear to support our original assignments based on the coupling patterns for stereochemistry at the ring junction (p. 91). These assignments were later confirmed when the ^{13}C data for a pair of hydrocarbons, (218) and (182), that were derived from (195) and (207) respectively became available.

Our results as well as Thompson's[109] in which the lithium-ammonia reduction of the unsaturated carboxylic acids was achieved with complete stereocontrol are of particular interest since they might assist in an appreciation of the stereochemically controlling factors in reductions of this type.

The reduction of a styrene type system with alkali metal in liquid ammonia has been known for years and generally believed to proceed via a dianion intermediate followed by successive protonations.[111] The reduction is initiated by the addition of two electrons to the reducible double bond, and the dianion intermediate thus formed undergoes protonation in such a way that more basic position (homo-benzylic) protonates first and protonation of the less basic position (benzylic) follows. The course of the reduction may be represented in the fashion shown below (Scheme 40).

Scheme 40

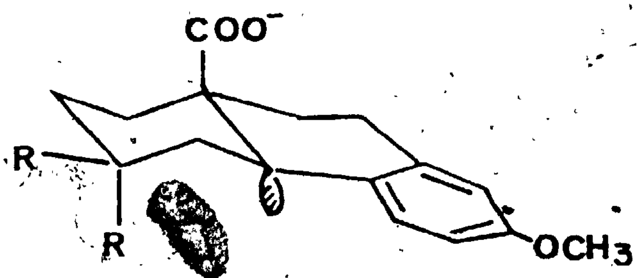
$$C_6H_5CH{=}CHR + 2e^- \longrightarrow C_6H_5\bar{C}H{-}\bar{C}HR \xrightarrow{NH_3} C_6H_5\bar{C}H{-}CH_2R$$

$$\xrightarrow{NH_3} C_6H_5CH_2{-}CH_2R$$

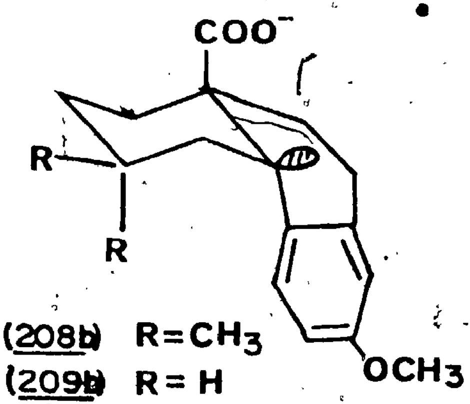
Concerning a cyclic stilbenoid system in which the reduction results in the formation of one or two new asymmetric centres, Smith[112] has, on the above assumption, proposed that two factors control the stereochemistry of the proton addition to the dianion or monoanion intermediate; 1) the relative stabilities of the available conformations of the intermediate (conformational factor); 2) the relative degrees of steric hindrance to the different approaches of the proton donor to the negative charge in these conformations (steric approach factor).

In order to discuss our results (i.e. (205)-(206)), we will not consider the first protonation step (protonation to the homobenzylic position) since it requires little activation energy relative to the following protonation step (to the benzylic position) and it does not decide the crucial stereochemistry at the ring junction. The factors governing the second protonation step in the intermediate monoanion will then be of more importance and of our major concern. The addition of the first proton to the dianion gives two conceivable preferred conformations for the resulting monoanion, (208a) and (208b), that would eventually lead to the trans- and cis- ring junction correspondingly upon protonation. Both conformations (208a) and (208b) should provide good ring overlap with the benzylic anion.

Thompson and coworkers[109], in explaining their results, have claimed that the stability of the cis-junction in their system renders the conformation (209b) favoured over (209a) under equilibrium and the equilibrium mixture consisting of largely the cis-conformer (209b) gives rise to the cis-product (203)



(208a) R = CH_3
(209a) R = H



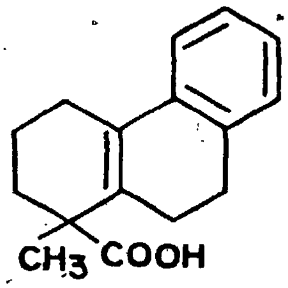
(208b) R=CH_3
(209b) R = H

(Scheme 38) upon protonation the rate of which is comparable in both conformers. This argument can be interpreted, according to Smith's proposal[112], as follows; the cis-conformer (209b) is favourable compared to the trans-one (209a) by the conformation factor because the steric factor is estimated to be nearly equal in both conformers. This latter point concerning the steric approach factor does not sound unreasonable provided that both axial and equatorial proton approaches are energetically similar. The conformational factor is itself very difficult to assess, and the assumption that the cis-ring structure is more stable than the trans-one in the system (i.e. (209a) $<$ (209b)) is not, to our best knowledge, as persuasive as they asserted; for instance it is known that trans-9-methyldecalin is more stable in energy by ca. 1 Kcal/mole than cis-9-methyldecalin.[113]

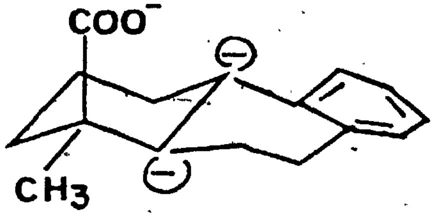
In one experiment, the ester (191) was reduced with lithium-ammonia to give a mixture of the cis- and trans- alcohols, (195) and (207), as judged by nmr. Although this experiment has not been repeated, it is at least suggestive that the conformer (208a) in the form of either ester or hydroxymethyl anion ($-CH_2-O^-$) at the angular position is as favourable as the conformer (208b), thus yielding a mixture of alcohols upon protonation. For these reasons, we are not entirely in agreement with Thompson's explanation[109] and are inclined to propose that conformers (208a) and (208b) are equally stable or the relative stabilities of both conformers are not as distinctly different as to be decisive in leading to preference of one conformer over the other. Thus one may imagine that the steric factor outweighs the conformational factor in our system since the approach of a proton donor to the anion in the conformation (208b) can avoid 1,3-diaxial interaction provided by one of the geminal methyl groups and accordingly, the formation of the cis-isomer will be favoured. However, this rationalization cannot be extended to explain Thompson's results because both (209a) and (209b) have no gem-dimethyl group.

Therefore it is apparent that we cannot make any commitments on the factors deciding the stereochemical course of the reduction but we feel that the carboxylic acid function present in our system system as well as Thompson's might play an important role, that is, it either contributes to stabilize significantly conformers (208b) and (209b) relative to (208a) and (209a) or assists in the approach of the proton donor from its side of the molecules.

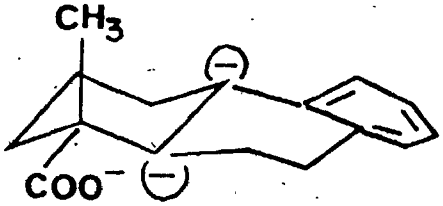
Contrary to our opinion, Ghatak and coworkers[114] have reported that in the lithium-ammonia reduction of the unsaturated carboxylic acid (210), the electronic repulsion of the carboxylic acid anion and the anionic centre destabilizes the energy state of conformer (210a) in which both anions are placed in a *cis*-relationship and as a result conformer (210b) is favoured. Should this be the case, conformers (208b) and (209b) would evidently be disfavoured. In view of our results as well as Thompson's, we cannot agree that Ghatak's view is generally applicable.



(210)



(210a)

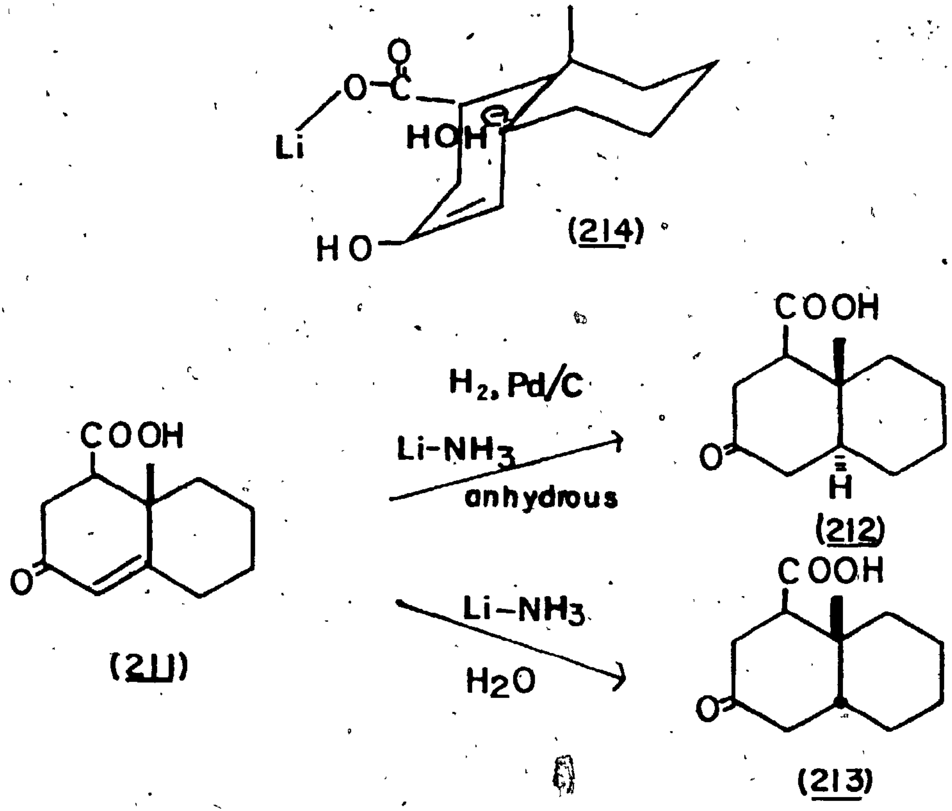


(210b)

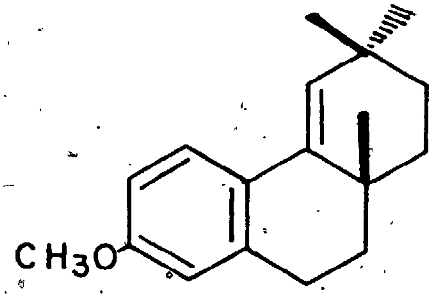
In connection with the role of a carboxyl substituent during the reduction, McMurry and coworkers[115] have recently reported very interesting observations on the Birch reduction of

9-methyl-1-carboxy-Δ^4-3-octalone (211). They have revealed that while the Birch reduction under anhydrous conditions follows normal course to give exclusively the trans-product (212), in the presence of water the cis-product (213) predominates (cis/trans, 75:25) in the reduction mixture (Scheme 41). In order to explain this striking result, they have suggested that the intermediate carbanion (214) is protonated from the β-face by water molecule confined in the solvent shell of the β-oriented lithium carboxylate grouping. This rationalization seems to hold in our case, and hence it is quite likely that the carboxyl grouping would probably assist or direct the approach of a proton donor from its side of the reducible molecule by virtue of some kind of attractive interaction between the acid function and the proton donor.

Scheme 41



In conclusion, the question on the role of the angular carboxylic acid group has not been fully answered, and this question would hopefully be answered if the behaviour of molecules such as (196), (198) or (215) in lithium-liquid ammonia were to be studied. These studies are currently being continued by Mr. D. Moir in our laboratories.



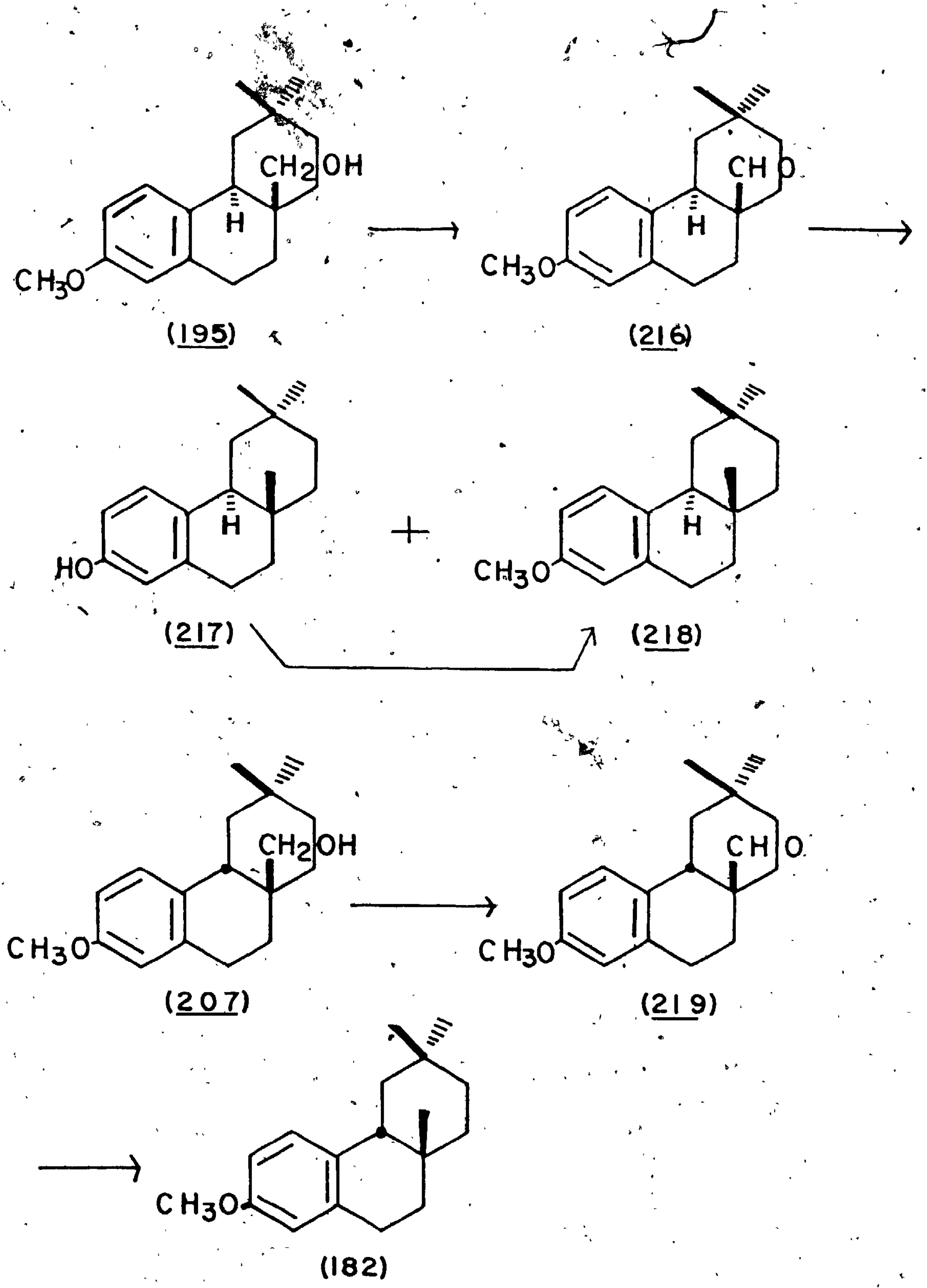
(215)

With both alcohols (195) and (207) in hand, we next turned our attention to the conversion of the angular hydroxymethyl group into a methyl group. This task was not so easy as it would appear because the hydroxyl group to be removed is of the neopentyl type. Therefore, in a similar fashion to the conversion, (165)→(168) (scheme 30), the trans-tricyclic alcohol (195) was oxidized to the corresponding aldehyde (216) by Corey oxidation (97%). Aldehyde (216) was then subjected to Wolff-Kishner reduction. During the reduction the consistent formation of a side product which proved to be a phenol (217) on the basis of its spectral data was noticed besides the expected reduction product (218). This seemingly unusual observation has been confirmed by an earlier report in which the cleavage of C-O bond in a phenyl ether under drastic conditions similar to those used in the present Wolff-Kishner reduction was described.[116]

Consequently, a crude mixture of hydrocarbon (218) and phenol (217) was treated with methyl iodide in the presence of sodium hydride at room temperature,[117] and this remethylation procedure afforded the hydrocarbon (218) as the sole product in 85% yield (overall yield 73% from (195)). Scheme 42 outlines the conversion of (195) to (218). Likewise in the *cis*-series alcohol (207) was transformed into the corresponding hydrocarbon (182) by way of the intermediate aldehyde (219) (overall yield from (207); 73%). This sequence is also shown in Scheme 42 (p. 106).

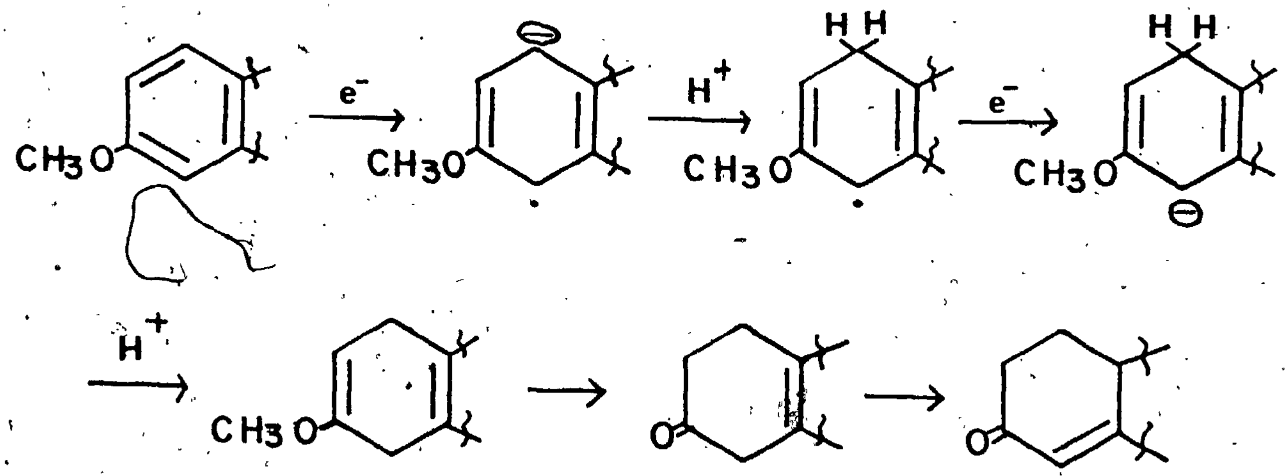
Having thus obtained both hydrocarbons (182) and (218), it became possible to compare their spectroscopic properties. Among them ^{13}C nmr spectra of these compounds were undoubtedly the most useful in assigning the stereochemistry at the ring junction. Thus, ^{13}C nmr peak due to the angular methyl group of the hydrocarbon (182) appears at 27.5 ppm, being strongly indicative of the *cis*-nature of its ring junction. The corresponding signal for the other hydrocarbon (218) is located at 15.2 ppm and this can be assigned as being due to the angular methyl group of a decalin system bearing a *trans*-ring fusion (for the attempted complete assignments of the signals; see APPENDIX IV p. 168; and for some discussion, refer to pp. 71-73). The ^{13}C nmr data for these hydrocarbons have thus convinced us that compound (182) has the *cis*-ring junction and its counterpart (218) is *trans*-fused, and hence our assignments for the stereochemistry of the parent alcohols (195) and (207) are correct.

Scheme 42


CH2OH
CH3O
(195)
CHO
CH3O
(216)
HO
H
(217)
CH3O
H
(218)
CH2OH
CH3O
(207)
CHO
CH3O
(219)
CH3O
(182)

Since the initial synthetic objective (182) was constructed quite efficiently (overall yield from (191); 39%), preliminary studies on the synthetic pathway towards the key synthon (144) were undertaken. It was evident that one could modify a methoxy aromatic ring to a enone system by Birch reduction, however apparently the enone system thus produced would not be transformed to the angular-substituted enone such as that in (144). In the light of the known mechanism for Birch reduction[118], the reduction involving a methoxy aromatic ring can be written as follows (Scheme 43).

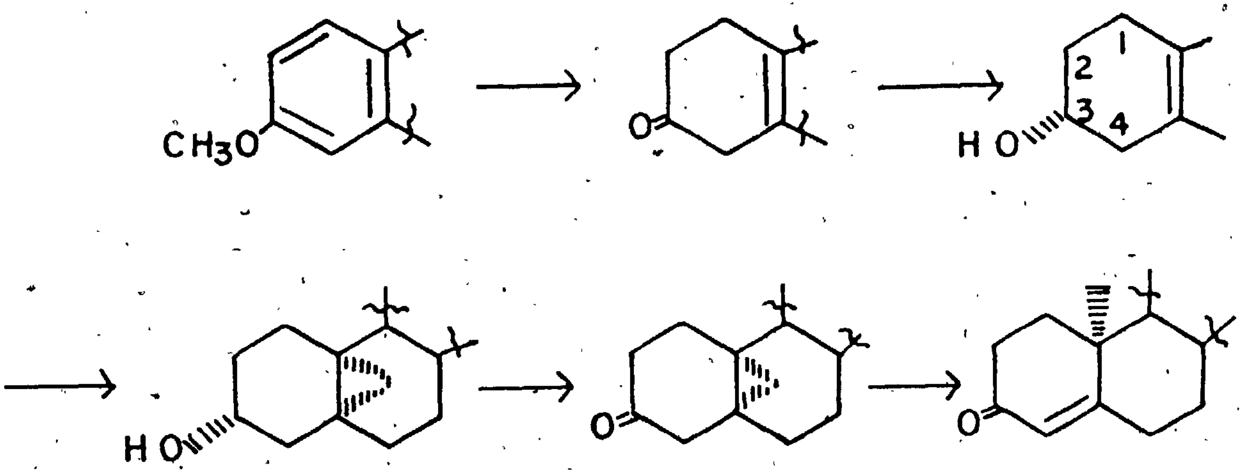
Scheme 43



It is well known that the reduction of anisole gives the intermediate product (2,5-dihydroanisole) which upon mild hydrolysis is converted to a β,γ-enone and further acid treatment isomerizes it to a α,β-enone.[119]

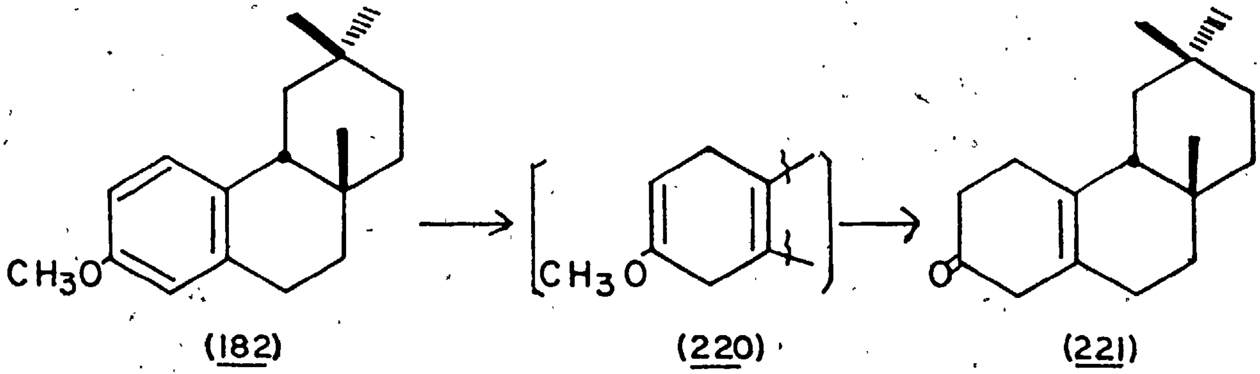
In 1965 the Syntex group[120], as a part of their exhaustive synthetic studies of steroids, developed a unique method to construct the A ring portion of 10α-androst-4-en-3-ones which is identical with that of (144). Their synthesis was critically dependent upon the isolation of the intermediate β,γ-enone system obtained by the Birch reduction and stereochemically controlled Simmons-Smith methylenation[75]. As illustrated in Scheme 44, the 3-hydroxyl group provides stereochemical control in the addition of the Simmons-Smith reagent. Cleavage of the α-cyclopropane with base (t-butoxide-dimethyl sulphoxide) leads to 10α-androst-4-en-3-one analogs.

Scheme 44



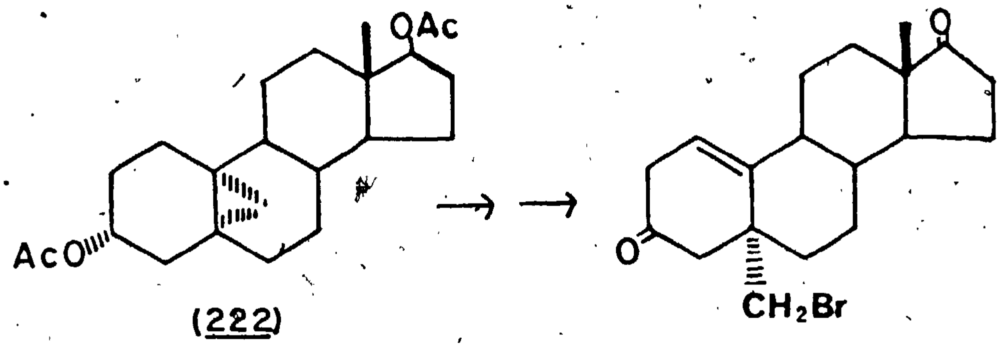
Based on this strategy and following a recent report by Wiesner and coworkers[121] hydrocarbon (182) was reduced in lithium-liquid ammonia to an intermediate product (probably (220)) which upon mild acid treatment (oxalic acid, ethanol) gave the expected β,γ-enone (221) in a yield of 89% (Scheme 45).

Scheme 45



If the Simmons-Smith methylenation of (221) and the following manipulations as outlined in Scheme 44 proceed precisely according to our plan, compound (221) should be convertible to the important tricyclic synthon (144) for our triterpene synthesis. Additionally, it is notable that the Syntex group[119] also reported the transformation of the α-cyclopropane steroidal diacetate (222) into (223) by the sequence involving bromination, debromination (lithium carbonate, dimethylformamide) and oxidation (Scheme 46).

Scheme 46

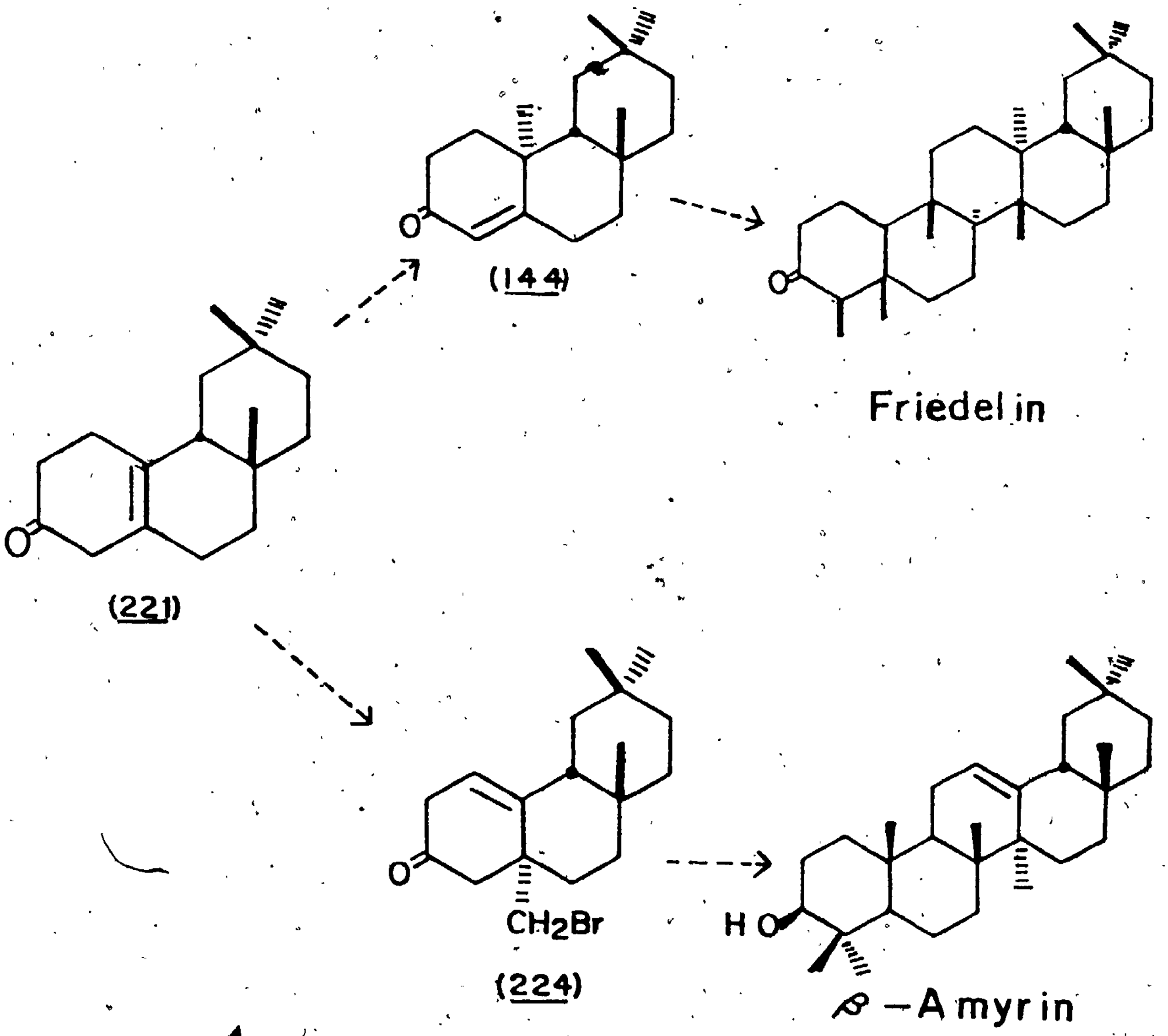


(222)

(223)

This finding is particularly interesting since it suggests the possibility of compound (221) being convertible into (224) which can be considered as a potential synthon that might be correlated to β-amyrin (74). Therefore, these considerations have led us to conclude that compound (221) would be a valuable synthon for the synthetic entry to such triterpenes as friedelin (77), β-amyrin (74) and related species. Scheme 47 manifests the relationships between the synthetic intermediates and the natural products.

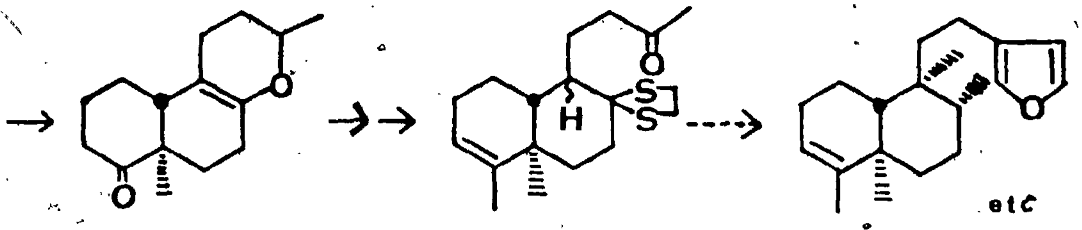
Scheme 47



Summary of the Synthetic Routes Described in this Thesis

PART I

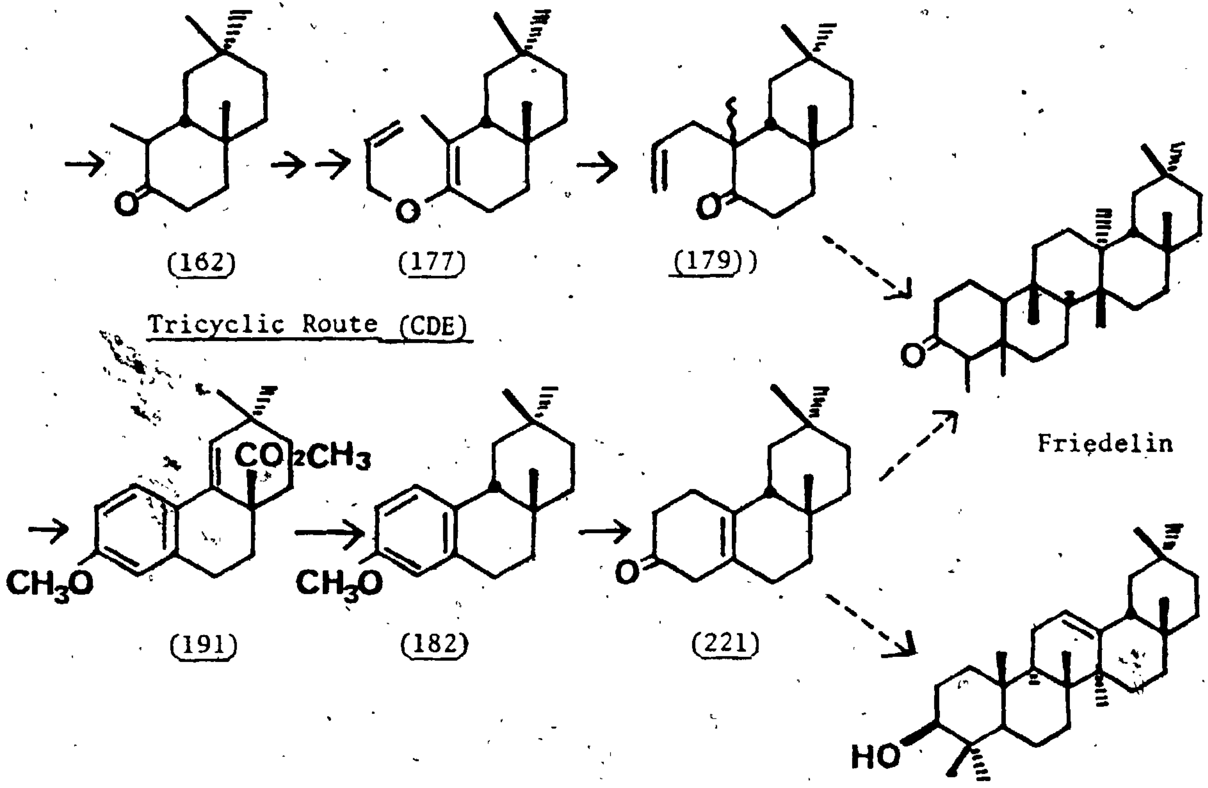
Clerodane Route



(56) (67)

PART II

Bicyclic Route (DE-CDE)



(162) (177) (179)

Tricyclic Route (CDE)

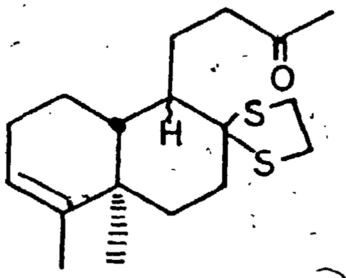
(191) (182) (221)

Friedelin

β-Amyrin

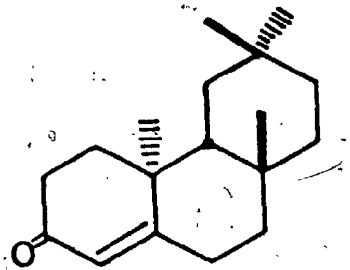
CONCLUSION

Exploratory investigations on the Saucy routes have resulted in the synthesis of a novel synthon (67) that can be applied to the synthesis of several trans-clerodanes.

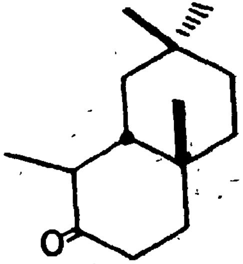


(67)

Between the two routes sought in order to synthesize the key CDE ring intermediate (144), the bicyclic approach starting with the cis-octalone (162) has proved not to be very promising because of the difficulties encountered at the alkylation stage on the C-1 of the molecule, thereby preventing its further use at this stage of our studies.

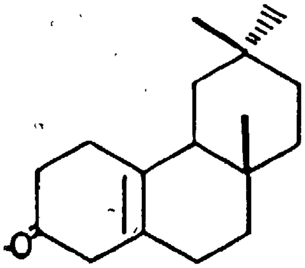


(144)



(162)

By contrast, the tricyclic ketone (221) which was made available quite efficiently has potential value in our synthetic plans for the pentacyclic triterpenes.



(221)

Additionally, during our investigations it has been illustrated that the ^{13}C chemical shifts of the angular methyl group in decalones and tricyclic compounds are intrinsically useful in determining the stereochemical nature of the ring junction.

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 AEI 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 Arbor, Michigan.

All reactions and chromatograms were routinely monitored by thin-layer chromatography (TLC) (Merck 60 PF-254 plates, 0.25 mm), using 1:5 hexane-ethyl acetate as eluent. Spots were developed by exposing to iodine vapour. 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. Silica gel (Davison Chemical Co., grade 923, 100-200 mesh) was used for column chromatography.

The term "dry benzene" and "dry toluene" refer to benzene or toluene which was distilled and stored over sodium. "Dry tetrahydrofuran" was 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°.

Unless otherwise specified, "working-up" procedure means; extraction of the reaction mixture with ether (x3), washing of the extracts with water (x3) and with brine (x1), drying of the organic phase over anhydrous magnesium sulphate or sodium sulphate, filtration, and evaporation of the solvents at 40-50° _in vacuo_.

Ethyl 2-Acetylpentanedioate (45). Sodium (6 g, 0.26 mol) was dissolved in 150 ml of absolute ethanol and to this was added 660 g (5.1 mol) of ethyl acetoacetate. Ethyl acrylate (500 g, 0.56 mol) was then added to the solution under reflux. The resulting mixture was refluxed overnight, when the orange-coloured mixture was cooled and poured into 500 ml of dil.(10N) sulphuric acid solution. The organic phase was separated and washed with water (x5) and dried over anhydrous sodium sulphate. Concentration and distillation under reduced pressure gave 709 g (62%) of (45) as a yellow oil: bp 100-115°/1.0 mm (lit.^{35} 91-95° /0.05 mm); ir (neat) 1735 (ester) and 1710 cm^{-1} (carbonyl); nmr (CCl_4) δ 1.23, 1.27 (two t, each 3H, J=7Hz, $-O-CH_2-\underline{CH_3}$), 1.93-2.44 (m, 4H, C-2 and C-3 H), 2.16 (s, 3H, C-6 H), 3.44 (t, 1H, J=7Hz, C-4 H), and 4.07, 4.13 (two t, each 3H, J=7Hz, $-O-\underline{CH_2}-CH_3$).

5-Oxohexanoic Acid (46). Following Korte's procedure^{35}, ester (45) (709 g, 3.08 mol) was refluxed in 1.5 l of water and 150 ml of conc. sulphuric acid overnight. During reflux the ethanol formed was distilled off through a distillation head.

Upon cooling, ammonium sulphate was added to salt out the organic substance. The organic material was extracted with ether (x3), washed with water (x5), saturated sodium bicarbonate solution and brine, and dried over anhydrous sodium sulphate. Evaporation of the solvent gave an oil which was distilled to separate 314 g (78%) of the ketoacid (46) at reduced pressure: bp 126-130°/1.0 mm (lit.[35] 95°/0.01 mm); ir (neat) 3400-2900 (broad, carboxylic acid) and 1710 cm^{-1} (broad, carbonyl and carboxylic acid); nmr (CDCl$_3$) δ 1.67-2.68 (m, 6H, C-2, C-3, and C-4 H), 2.13 (s, 3H, C-6 H), and 11.3 (s, 1H, acid proton).

6-Methyloxacyclohexan-2-one (44). To a solution of 314 g (2.41 mol) of the ketoacid (46) in 1.5 l of water containing 240 g (2.4 mol) of sodium bicarbonate was added 46 g (1.2 mol) of sodium borohydride portionwise at 0°. The resulting solution was stirred at room temperature overnight and then acidified with dil. (3N) hydrochloric acid solution. Stirring was further continued for 4 hr, and the reaction mixture was saturated with sodium chloride. The usual work-up, followed by vacuum distillation afforded 99.6 g (36%) of the lactone (44) as a colourless oil which solidified upon refrigeration: bp 76-78°/0.5 mm (lit.[35] 59-60°/0.01 mm); ir (neat) 1720 cm^{-1} (lactone); nmr (CCl$_4$) δ 1.33 (d, 3H, J=7Hz, C-6 CH$_3$) and 4.10-4.60 (m, 1H, C-6 H).

Ethyl 2-(2-cyanoethyl)-3-oxobutanoate(47) This compound was prepared according to the method of Albertson[122]. To a solution of 15 g (0.65 mol) of sodium in 800 ml of absolute ethanol was added 1230 g (9.45 mol) of ethyl acetoacetate dropwise. With stirring 500 g (9.45 mol) of acrylonitrile was then added over a period of 4 h, and the reaction mixture was refluxed for a further 4 h. Upon cooling, the mixture was poured into 500 ml of dil. (10N) sulphuric acid solution. The organic phase was separated and washed with water (x5). After drying over anhydrous sodium sulphate the organic material was concentrated and distilled under reduced pressure to afford 551 g (32%) of the nitrile (47): bp 105-140°/2.0 mm (lit.[122] 121°/2 mm); ir (neat) 1735 (ester) and 1710 cm^{-1} (carbonyl); nmr (CCl_4) δ 1.28 (t, 3H, J=7Hz, $-COO-CH_2-\underline{CH_3}$), 2.00-2.56 (m, 4H, C-2 and C-3 H), 2.23 (s, 3H 3H, C-6 H), 3.52 (t, 1H, J=7Hz, C-4 H), and 4.17 (q, 2H, J=7Hz, $-COO-\underline{CH_2}-CH_3$).

5-Oxohexanenitrile (48). Sodium carbonate (600 g, 5.6 mol) and the ketonitrile (47) (551 g, 3.02 mol) in 3 l of water were refluxed overnight. Upon cooling, ammonium sulphate was added to salt out the organic substance. Extraction with ether (x3) and the normal work-up left a yellow oil which was distilled under reduced pressure to separate 156 g (47%) of the title nitrile (48): bp 75-80°/1 mm (lit.[122] 86.5°/5.2 mm); ir (neat) 2253 (nitrile), and 1712 cm^{-1} (carbonyl); nmr (CCl_4) δ 1.67-2.73 (m, 6H C-2, C-3, and C-4 $\underline{CH_2}$) and 2.13 (s, 3H, C-6 H).

5-Hydroxyhexanenitrile (49). To a solution of 156 g (1.40 mol) of the ketonitrile (48) in 400 ml of water containing 3 g of sodium hydroxide was added 26 g (0.67 mol) of sodium borohydride.

portionwise at ice-bath temperature. Addition was continued over a period of 1 h and the mixture was stirred overnight at room temperature. The solution was then acidified with dil. (3N) hydrochloric acid solution and stirred for 3 h. Solid ammonium sulphate was added to salt out the organic substance. After the normal work-up and vacuum distillation there was obtained 143 g (90%) of the hydroxynitrile as a viscous oil which solidified upon refrigeration: bp 120-135°/1 mm; ir (neat) 3230 (hydroxyl) and 2270 cm^{-1} (cyano); nmr ($CDCl_3$) δ 1.27 (d, 3H, J=7Hz, C-6 H) and 3.86 (sex, 1H, J=7Hz, C-5 H).

The hydroxynitrile (49) (143 g, 1.26 mol) was added dropwise to 500 ml of 10% aqueous sodium hydroxide solution under reflux. Reflux was further continued for 3 h and the solution was stirred at room temperature overnight. The reaction mixture was acidified with dil. (6N) sulphuric acid solution and the following work-up gave 37.9 g (28%) of the lactone (44) after vacuum distillation.

7-Hydroxy-1-octen-3-one (41). Vinylmagnesium bromide in tetrahydrofuran was prepared according to the method of D. Seyferth[123]. Thus, magnesium turnings (12.2 g, 0.53 g atoms) were placed in a flask and dry THF was added to cover the magnesium. About 5 ml of vinyl bromide was added to the flask. After the exothermic reaction had started, 300 ml of dry THF was added. Then, vinyl bromide (51.5 g, 0.48 mol) diluted with 100 ml of THF was added dropwise at such a rate that gentle reflux was maintained. Upon completion of addition the solution was further refluxed for 30 min. The Grignard solution thus prepared was cooled to -90° (dry ice-ether bath), then a solution of 54.5 g (0.48 mol) of (44) in 100 ml of THF was added during 30 min. The solution was stirred for another 30 min at -90° and allowed to warm to room temperature. The resulting solution was quenched by adding saturated ammonium chloride solution and extracted with ether (x3). Drying over anhydrous sodium sulphate and evaporation of the solvent gave crude (41) as a yellow oil (61.2 g, 90%). A sample was distilled to afford a colourless oil: bp 100-110°/1.0 mm; ir (neat) 3400 (hydroxyl) and 1690 (carbonyl); uv$_{max}$ (CH_3OH) 210 nm (ϵ = 5200); nmr ($CDCl_3$) δ 1.20 and 1.37 (d, 3H, J=7Hz C-8 H), 3.54-3.94 and 4.13-4.56 (m, 1H, C-7 H), and 4.93-6.36 (m, 3H, vinyl protons); ms m/e (relative intensity) 142 (M^+,9), 115 (12), 83 (100), 70 (24), 55 (65).

3,6aα-Dimethyl-1,2,3,5,6,6a,9-heptahydronaphtho[2,1-b]-pyran-7(8H)-one (36). The procedure of G. Saucy and coworkers[34] was followed. A mixture of crude (41) (6.00 g, 42.0 mmol), 2-methylcyclohexane-1,3-dione (42) (4.75 g, 37.6 mmol), toluene (120 ml), and acetic acid (50 ml, distilled over phosphorus pentoxide) was refluxed under nitrogen for 2 h, during which time the water formed was removed by a Dean-Stark trap. The reaction mixture was cooled, triturated with benzene and the crystals were filtered, and washed with benzene. 2-Methylcyclohexane-1,3-dione (1.27 g, 10.1 mmol) was recovered. The combined filtrates were washed with water (x3) and saturated sodium bicarbonate solution (x3), dried over [illegible]ydrous sodium sulphate and concentrated *in vacuo*. The residue (brown crystals)

(5.63 g) were chromatographed on aluminium oxide (Woelm neutral grade I). Elution with hexane and hexane-10% ethyl acetate afforded 4.14 g (43%, 65% based on the unrecoverd dione) of yellow crystalline (36). Recrystallization of a small quantity of this material from hexane-ethyl acetate (3:1) gave an analytical sample of (36) as yellow needles: mp 109-112°; ir (KBr) 1729 and 1713 cm^{-1} (carbonyl), and 1643 cm^{-1} (diene); uv_{max} (C_2H_5OH) 254 nm (ε =27000); nmr ($CDCl_3$) δ 1.20 (s, 3H, C-6a CH_3), 1.28 (d, 3H, J=6Hz, C-3 CH_3), 3.84 (m, 1H, C-3 H), and 5.44 (t, 1H, C-10 H).

Anal. Calcd for $C_{15}H_{20}O_2$: C, 77.55; H, 8.68.

Found : C, 77.61; H, 8.65.

3,6aα-Dimethyl-1,2,3,5,6,6a,9,10,10aβ-nonahydronaphtho[2,1-b]-pyran-7(8H)-one (56). A solution of 300 mg (1.26 mmol) of (36) in toluene (30 ml) was hydrogenated at room temperature using 10% Pd/C catalyst (30 mg). The uptake of hydrogen (ca. 30 ml) stopped after 1½ h. The catalyst was removed by filtration through a pad of Celite, washed with toluene and the combined filtrates were evaporated under reduced pressure to give 276 mg (91%) of yellowish crystalline (56). A sample was recrystallized from hexane-petroleum ether (1:1) to afford an analytical sample mp 71-73°; ir (KBr) 1736, 1712 (carbonyl) and 1674 cm^{-1}(enol ether) ; nmr ($CDCl_3$) δ 1.14 (s, 3H, C-6a CH_3), 1.26 (d, 3H, C-3 CH_3), and 3.76 (m, 1H, C-3 H); ms m/e (relative intensity) 234 (M^+ , 100), 219 (62), and 163 (42).

Anal. Calcd for $C_{15}H_{22}O_2$: C, 76.88; H, 9.46.

Found : C, 76.87; H, 9.45.

4a-Hyroxy-3,6aα-dimethyl -1,2,3,4a,5,6,6a,9,10,10aβ,10b-undecahydronaphtho[2,1-b]-pyran-7(8H)-one (57).

According to the published procedure[34], a solution of crude (56) (4.42 g, 18.5 mmol) in 50 ml of acetone and 20 ml of 1N sulphuric acid was stirred at room temperature overnight. The solution was diluted with brine and extracted with ether (x3). The ether extract was washed with water (x2), saturated sodium bicarbonate solution (x2) and brine. Drying over anhydrous sodium sulphate and concentration under reduced pressure gave 4.43 g of crude (57) as a yellow oil. This oil was chromatographed on aluminium oxide (Woelm neutral grade 2). Elution with hexane-ether (1:1) gave 3.76 g (80%) of the hemiketal (57) as crystals with a yellow tinge. Recrystallization of the material from hexane afforded colourless crystals: mp 120-121°; ir (KBr) 3430 (hydroxy) and 1700 cm^{-1} (carbonyl); nmr ($CDCl_3$) δ 1.09 (d, 3H, J=6Hz, C-3 CH_3), 1.13 (s, 3H, C-6a CH_3), and 4.04 (m, 1H, C-3 H); ms m/e (relative intensity) 252 (M^+,100), 234 (39), and 180 (47).

Anal. Calcd. for $C_{15}H_{23}O_3$: C, 71.39; H, 9.59.
Found : C, 71.37; H, 9.63.

8aα-Methyl-5-(3'-oxobutyl)-3,4,4aβ,7,8,8a-hexahydronaphthalene-1,6(2H, 5H)-dione (58). To a solution of crude (57) (4.0 g, 16 mmol) in 150 ml of acetone was added a solution of chromium trioxide (8.0 g, 80 mmol) in 50 ml of 6N sulphuric acid dropwise at 0°. The mixture was stirred at 0° for 3 h and supernatant solution was decanted from the black mass. This was diluted with brine and the organic substance was extracted with ether (x3). The ether extract was washed with water (x2), saturated sodium bicarbonate (x2), and brine. The organic phase was dried over anhydrous sodium sulphate, and evaporated to give crude (58) as a yellow viscous oil (2.36 g, 59%). This oil was purified by preparative tlc (hexane-ethyl acetate (3:1)) and recrystallized from hexane-ethyl acetate (4:1) to afford a sample of the triketone (58) as needles with a yellow tinge: mp 79-82° (lit.[124], mp 86°); ir (KBr) 1700 cm^{-1} (carbonyl); nmr ($CDCl_3$) δ 1.37 (s, 3H, C-8a CH_3) and 2.13 (s, 3H, C'-4 H); ms m/e (relative intensity) 250 (M^+, 100), 245 (54), 175 (73), 137(38), 124((35), and 55 (51).

10aα-Methyl-3,4,4aβ,4bα,5,9,10,10a-octahydrophenanthrene-1,7(2H, 6H)-dione (59).

(a) A mixture of crude (58) (1.05 g, 4.85 mmol), benzene (50 ml), and p-toluenesulphonic acid (200 mg) was refluxed for 4 h under a stream of nitrogen. The solution was cooled, washed with brine (x2) and dried (anhydrous sodium sulphate). Removal of solvent at reduced pressure gave 0.92 g of brown oil, which was chromatographed on silica gel. Elution with hexane-ether (1:2) afforded an oily fraction (243 mg) which ha a uv_{max} (C_2H_5OH) at 240 nm and showed two broad absorptions in ir at 1710 and 1665 cm^{-1}. This fraction was not homogeneous on tlc but appeared as two closely located spots. Attempts to purify this material by a second column chromatography failed.

(b) To a solution of 1.7 g (6.8 mmol) of crude (58) in 50 ml of methanol (distilled over Drierite) was added 0.3 g (5.4 mmol) of potassium hydroxide pellets. The resulting red solution was refluxed for 2 h under nitrogen. Upon cooling, the solution was diluted with benzene (100 ml). The benzene solution was washed with water (x3), dil. hydrochloric acid (3N) and brine. Drying over sodium sulphate and removal of the solvent gave 1.54 g of an oil which was then chromatographed on silica gel. Elution with dichloromethane afforded 309 mg (25%) of yellow crystalline (59). Recrystallization of this material from hexane-benzene yielded a sample of (59) as yellow plates: mp 120-122° (lit.[36a] 120°, lit.[36b] 125°); ir (KBr) 1712 (carbonyl) and 1688 cm^{-1} (enone); uv_{max} (C_2H_5OH) 240 nm (ε =26000); nmr ($CDCl_3$) δ 1.28 (s, 3H, C-10a CH_3) and 5.86 (s, 1H, C-8 H); ms m/e (relative intensity) 232 (M^+, 100), 176 (21), 149 (35), 148 (44), and 110 (23). On admixture with an authentic (±)-specimen of this substance provided by Professor S. Danishefsky, the melting point was undepressed.

7α-Hydroxy-3,6aα,7β-trimethyl-1,2,3,5,6,6a,7,8,9,10,10aβ-undecahydronaphtho[2,1-b]-pyran (60a) and 7β-Hydroxy-3,6aα,7α-trimethyl-1,2,3,5,6,6a,7,8,9,10,10aβ-undecahydronaphtho[2,1-b]-pyran (60b). Magnesium turnings (1.42 g, 59.3 mg atoms) were placed in a flask and anhydrous ether was added to cover the magnesium. Methyl iodide (8.20 g, 5.82 mmol) diluted with 50 ml of anhydrous ether was added dropwise to the flask while maintaining a gentle reflux. After addition was completed, the solution was allowed to reflux for ½ h. The Grignard solution thus prepared was cooled to 0° and to this a solution of (56) (13.0 g, 55.5 mmol) in 70 ml of anhydrous ether was added dropwise at 0°. The mixture was further stirred at 0° for ½ h and the temperature was raised to allow boiling. Reflux was continued for ½ h. Upon cooling, the reaction mixture was quenched by adding saturated ammonium chloride. The ether layer was separated and the aqueous layer was extracted with ether (x2). The combined ether extracts were washed with water (x1), dil. (3N) hydrochloric acid (x1) and brine. Evaporation of the solvent under reduced pressure gave an oily substance which was chromatographed on silica gel. Elution with hexane-10% ethyl acetate left 10.3 g (70%) of (60a) and (60b) as a yellow oil. Preparative tlc (hexane-20% ethyl acetate) of the above mixture separated (60a) and (60b) in a ratio of 60:40.* Bulb to bulb distillation of the less polar substance (R_f=0.59) at oil pump pressure furnished (60a) as oily crystals: bp 70-90°/1.0 mm; ir (neat) 3450 (hydroxyl) and 1678 cm^{-1} (enol ether); nmr ($CDCl_3$) δ 0.92 (s, 3H, C-6a CH_3), 1.13 (s, 3H, C-7 CH_3), 1.27 (d, 3H, J=6Hz, C-3 CH_3), and 3.83 (m, 1H, C-3 H); ms m/e (relative intensity) 250 (M^+, 13), 232 (29), 217 (100), and 175 (19).

---

* The assignment of the stereochemistry of the C-7 methyl group as to whether it is axial (β) or equatorial (α) was made based on the observed difference in chemical shift when both isomers were complexed with $Eu(fod)_3$ in solution. Thus, upon addition of about 25 mg of the shift reagent the C-6a methyl group signal of (60a) experienced 9Hz downfield shift while the same methyl in (60b) only moved 2Hz in chemical shift. These results indicate that the hydroxyl group of (60a) is equatorial (α), as a result the C-7 methyl group is axial (β) whereas the C-7 methyl group in (60b) is equatorial (α).

Similarly bulb to bulb distillation of the more polar substance (R_f=0.53) at oil pump pressure furnished (60b) as a yellow oil: bp 120-135°/1.0 mm; ir (neat) 3450 (hydroxyl) and 1675 cm^{-1} (enol-ether); nmr ($CDCl_3$) δ 0.97 (s, 3H, C-6a CH_3), 1.25 (s, 3H, C-7 CH_3), 1.27 (d, 3H, J=6Hz, C-3 CH_3), and 3.83 (m, 1H, C-3 H); ms m/e (relative intensity) 250 (M^+,100), 232 (20), 217 (48), 175 (16), and 151 (88).

F. 3,6aα,7-Trimethyl-1,2,3,5,6,6a,9,10,10aβ-nonahydronaphtho-[2,1-b]-pyran (61).

(a) To a solution of the alcohols (60a) and (60b) (300 mg, 1.2 mmol) in 20 ml of dry pyridine (distilled over potassium hydroxide) was added 1 ml of thionyl chloride dropwise at 0°. The resulting brown mixture was diluted with water and extracted with ether (x3). The ether extract was washed with water (x2), dil. (3N) hydrochloric acid (x3), then with water again (x2) and brine. Removal of the solvent gave an oil which showed at least five spots on tlc (hexane-ether). The nmr spectrum of this oil displayed a small broad peak at around δ 5.20 probably due to a olefinic proton.

(b) A mixture of (60a) and (60b) , 8 ml of conc. hydrochloric acid and 70 ml of methanol was refluxed overnight. Upon cooling, the reaction mixture was diluted with water. The organic substance was extracted with ether, washed with water and saturated sodium bicarbonate solution, and dried over sodium sulphate. Evaporation of the solvent under reduced pressure gave a yellowish oil (5.52 g). This oil was chromatographed on silica gel. Elution with hexane-5% ethyl acetate gave 2.27 g (42%) of the olefin (61) as a colourless oil. Bulb to bulb distillation of a small quantity of (61) afforded a sample: bp 80-90°/1. mm; ir (neat) 1676 cm^{-1} (enol ether); nmr ($CDCl_3$) δ 0.93 (s, 3H, C-6a CH_3), 1.23 (d, 3H, J=6Hz, C-3 CH_3), 3.67 (m, 1H, C-3 H), and 5.30 (m, 1H C-8 H); ms m/e (relative intensity) 232 (M^+, 100), 217 (58), 175 (23), 164 (50), 154 (36), and 108 (32).

4a-Hydroxy-3,6aα,7-trimethyl-1,2,3,4a,5,6,6a,9,10,10aβ,10b-undecahydronaphtho[2,1-b]-pyran (62). Compound (61) (2.27 g, 9.78 mmol) was dissolved in acetone (70 ml) and hydrated with 30 ml of dil. (1N) sulphuric acid. After 20 h with stirring at room temperature, brine was added. Organic material was extracted with ether (x3) and the ether extract was washed with water (x2), saturated sodium bicarbonate solution (x2), and brine. Drying over sodium sulphate and concentration *in vacuo* gave 2.03 g (83%) of yellow crystalline (62). This material was twice recrystallized from hexane-petroleum ether (1:1) to yield a sample of analytical purity: mp 105-107°; ir (Nujol) 3450 cm^{-1} (hydroxyl); nmr ($CDCl_3$) δ 0.97 (s, 3H, C-6a CH_3), 1.27 (d, 3H, J=6Hz, C-3 CH_3), 3.94 (m, 1H, C-3 H), and 5.23 (m, 1H, C-8 H); ms m/e (relative intensity) 250 (M^+, 31), 232 (100), 207 (52), 140 (37), and 108 (97).

Anal. Calcd. for $C_{16}H_{26}O_2$: C, 76.75; H, 10.47.

Found : C, 76.62; H, 10.50.

7α-Hydroxy-3,6aα-dimethyl-1,2,3,5,6,6a,7β,8,9,10,10aβ-undecahydronaphtho[2,1-b]-pyran (63). A solution of (56) (550 mg, 2.4 mmol) in 30 ml of dry tetrahydrofuran was added to a slurry of lithium aluminium hydride (100 mg, 2.6 mmol) in 30 ml of dry THF at 0° under nitrogen with stirring. The reaction mixture was stirred at 0° for 1 h and left overnight with stirring at room temperature. The excess lithium aluminium hydride was destroyed by adding saturated sodium sulphate solution. The white precipitate was removed by filtration through a pad of Celite and washed with ether. The combined filtrates were dried over anhydrous sodium sulphate. The solvent was removed *in vacuo* to give 515 mg of colourless oil, which was crystallized from hexane-ether (3:1) to afford 303 mg (54%) of the alcohol (63) as colourless crystals. Recrystallization from the same solvents yielded a sample of analytical purity: mp 96-98°; ir (KBr) 3400 (hydroxyl) and 1680 cm^{-1} (enol ether); nmr (CDCl$_3$) δ 0.82 (s, 3H, C-6a CH$_3$), 1.25 (d, 3H, J=6Hz, C-3 CH$_3$), 3.28 (doublet of doublets, 1H, J_1=10Hz J_2=5Hz, C-7 H), and 3.74 (m, 1H, C-3 H).

Anal. Calcd. for $C_{15}H_{24}O_2$: C, 76.23; H, 10.24.
Found : C, 76.26; H, 10.20.

7α-Benzyloxy-3,6aα-dimethyl-1,2,3,5,6,6a,7β,8,9,10,10aβ-undecahydronaphth [2,1-b]-pyran (64). Crude alcohol (63) (3.76 g, 15.5 mmol) in 40 ml of dry dimethylformamide (distilled under vacuum and stored over 4A molecular sieves) was added to a slurry of 5 g (0.2 mol) of sodium hydride in 100 ml of dry tetrahydrofuran under reflux. After 2 h reflux, distilled benzyl chloride (2.75 g

2.17 mmol) was added dropwise and reflux was continued overnight. Upon cooling, saturated aqueous sodium sulphate solution was carefully added to the reaction mixture. The organic substance was extracted with ether and the extract was washed with hydrochloric acid (3N), water (x2) and brine. Drying over anhydrous sodium sulphate and evaporation of the solvent gave an oil which was distilled under reduced pressure to afford 3.45 g (68%) of the benzyl ether (64) as an oil: bp 120-130°/0.5 mm; ir (neat) 1670 cm^{-1} (enol ether); nmr (CCl_4) δ 1.20 (s, 3H, C-6a CH_3), 1.22 (d, 3H, J=6Hz, C-3 CH_3), 4.47 (q, 2H, -O-CH_2-), and 7.20 (s, 5H, aromatic protons); ms m/e (relative intensity) 326 (M^+, 20), 235 (15), 193 (61), and 91 (100).

Attempted Hydration of (64). The above benzyl ether (1.50 g, 4.63 mmol) in 50 ml of tetrahydrofuran and 20 ml of 1N sulphuric acid was stirred at room temperature for 3 days. The solution was diluted with brine and extracted with ether. The normal "work-up" gave 1.29 g of an oil which was distilled under vacuum to afford a viscous oil (bp 130-135°/0.5 mm). The spectral properties of this oil were identical with those of the starting material. Replacing the solvent from THF to acetone or acetone-THF did not produce any detectable amount of the hydrated substance as judged by the mass spectra of the resulting oils.

2,2-Ethylenedithio-1-(3-hydroxybutyl)-4aα,5-dimethyl-1,2,3,4,4a,7,8,8aβ-octahydronaphthalene (66). The procedure of Trost and coworkers[37] was followed. To a solution of 921 mg (3.69 mmol) of crude (62) and 752 mg (8.60 mmol) of 1,2-ethanedithiol in 30 ml of dry toluene was added 150 mg (1.06 mmol) of boron trifluoride-etherate with ice-cooling. The reaction mixture was allowed to stand in a refrigerator for 4 days and then diluted with ether. The solution was washed with saturated sodium carbonate solution and brine, dried over anhydrous sodium sulphate, and evaporated under reduced pressure. The residual oil was chromatographed on silica gel and elution with dichloromethane gave 774 mg (64%) of crystalline (66). Recrystallization from dichloromethane-hexane (1:1) gave a sample of (66) as white plates for analysis: mp 93-94°; ir (Nujol) 3350 cm^{-1} (hydroxyl); nmr (CDCl$_3$) δ 1.00 (s, 3H, C-4a CH$_3$), 1.23 (d, 3H, J=6Hz, C-3' CH$_3$), 3.26 (s, 4H, -S-$\underline{CH_2}$-$\underline{CH_2}$-S-), 3.94 (m, 1H, C-3' H), and 5.27 (m, 1H, C-6 H); ms m/e (relative intensity) 326 (M$^+$, 28) and 131 (100).

Anal. Calcd. for $C_{18}H_{30}S_2O$: C, 66.20; H, 9.26; S, 19.64.
Found : C, 66.29; H, 9.31; S, 19.70.

2,2-Ethylenedithio-4aα,5-dimethyl-1-(3-oxobutyl)-1,2,3,4,4a,7,8,8aβ-octahydronaphthalene (67). To a solution of chromium trioxide (400 mg, 4 mmol) in 20 ml of dry pyridine was added 320 mg (0.982 mmol) of (66) in 10 ml of dry pyridine. Stirring was continued for 4 h at room temperature. The reaction mixture was treated with methanol for 30 min and then diluted with water (30 ml). The organic substance was extracted with ethyl acetate, and the ether extract was washed successively with dil. (3N) hydrochloric acid (x3), saturated sodium bicarbonate solution and brine. Drying over magnesium sulphate followed by evaporation of the solvent gave 273 mg of an oily substance which was purified by preparative tlc (hexane-ethyl acetate 4:1) to afford 146 mg (46%) of crystalline (67) and 61 mg of recovered (66). Recrystallization from hexane-petroleum ether (1:1) yielded a sample of analytical purity as white prisms: mp 71-72°; ir (KBr) 1717 cm^{-1} (carbonyl); nmr ($CDCl_3$) δ 1.00 (s, 3H, C-4a CH_3), 2.13 (s, 3H, C-3' CH_3), 3.23 (s, 4H, -S-$\underline{CH_2}$-$\underline{CH_2}$-S-), and 5.20 (m, 1H, C-6 H).

Anal. Calcd. for $C_{18}H_{28}S_2O$: C, 66.61; H, 8.70; S, 19.76.
Found : C, 66.60; H, 8.69; S, 19.73.

2,5,5-Trimethylcyclohexane-1,3-dione (156). This compound was prepared according to the procedure of Heathcock and coworkers[84]. A solution containing 100 g (0.71 mol) of commercial dimedone (155), methyl iodide (190 g, 1.34 mol), and sodium hydroxide in 1000 ml of water refluxed for 24 h. The mixture was cooled to 0°, filtered and the resulting solid was air-dried. Recrystallization from ethyl acetate gave 85.5 g of (156) as a white solid. The mother liquor from 1st recrystallization was extracted with 10% sodium carbonate, and acidification of the aqueous extract with dil. (3N) hydrochloric acid gave another crop of methyldimedone (156) (3.7 g, after recrystallization). The combined yield of (156) was 89.2 g (82%): mp 160-161° (lit.[84] 158-159°).

2,5,5-Trimethylcyclohex-2-en-1-ol (157). To a solution of 48.6 g (0.32 mol) of methyldimedone (156) in 400 ml of anhydrous ether was added a solution of 12 g (0.32 mol) of lithium aluminium hydride in 300 ml of ether dropwise. Stirring was continued at room temperature overnight. Excess lithium aluminium hydride was decomposed by adding 10% aqueous ammonium chloride solution. The resulting granular solids were filtered through a pad of Celite and filtrate was washed with brine and dried over anhydrous magnesium sulphate. Ether was removed under reduced pressure to give 35 g (80%) of a colourless oil: ir (neat) 3350 cm^{-1} (hydroxyl); nmr (CCl_4) δ 0.90 (s, 3H, C-5 CH_3), 0.97 (s, 3H, C-5 CH_3), 1.73 (s, 3H, C-2 CH_3), and 5.40 (m, 1H, C-3 H).

<u>2,5,5-Trimethylcyclohex-2-en-1-one (158)</u>. A solution of 26 g (0.087 mol) of sodium dichromate, 20 ml of conc. sulphuric acid and 20 ml of glacial acetic acid in 200 ml of water was cooled to 0°. To this was added a solution of 35 g (0.25 mol) of the allyl alcohol (157) in 300 ml of benzene dropwise over a period of 2 h with stirring. Stirring was continued at room temperature for a further 10 h. The benzene layer was separated and the aqueous layer was diluted with water and extracted with benzene The combined benzene extracts were washed with water (x2), saturated sodium bicarbonate solution (x1) and brine, then dried over anhydrous sodium sulphate. The solvent was removed under reduced pressure to leave a faintly yellow oil (29.1 g, 83%): ir (neat) 1679 cm^{-1} (carbonyl); nmr (CCl_4) δ 1.07 (s, 6H, <u>gem</u>-dimethyl), 2.20 (s, 3H, C-2 CH_3), and 6.75 (m, 1H, C-3 H).

2,5,5-Trimethylcyclohexanone (159). The enone (158) (29.0 g, 0.207 mol) was hydrogenated over 4 g of 10% Pd/C in 250 ml of ethyl acetate. The mixture was filtered through Celite and the solvent was removed under reduced pressure to give a colourless oil which was distilled to separate 26.5 g (90%) of the title ketone (159): bp 70-72°/10 mm (lit.[77] 75-80°/10 mm); ir (neat) 1712 cm^{-1} (carbonyl); nmr (CCl_4) δ 0.87 (s, 3H, C-5 CH_3), 0.97 (s, 3H, C-5 CH_3), and 1.00 (d, 3H, J=6Hz, C-2 CH_3).

1,4a,7,7-Tetramethyl-4,4a,5,6,7,8-hexahydronaphthalen-2(3H)-one (154). A mixture of 17.5 g (0.12 mol) of the ketone (159), 10.5 g (0.13 mol) of freshly distilled ethyl vinyl ketone and 50 ml of benzene was cooled to 0°. Then the mixture was stirred while 1.5 ml of conc. sulphuric acid was added dropwise, and it was allowed to stand at 0° for 2 h. The orange mixture was then stirred and second portions of ethyl vinyl ketone (5 ml) and sulphuric acid (0.5 ml) were added. After an additional 2 h, final portions of ethyl vinyl ketone (5 ml) and sulphuric acid (0.5 ml) were mixed with the dark coloured mixture. After standing for two days in a refrigerator, the reaction mixture was decanted from the black polymer and poured into 200 ml of ether. The polymer was rinsed with ether. The combined ether solutions were dried over magnesium sulphate and the solvent was evaporated at reduced pressure to yield a light yellow oil (25 g). Short-path distillation through a Vigreux column separated the starting ketone (159) (6.1 g) at water pump pressure (25 mm) and the product was collected at 0.5 mm as a faintly yellow liquid (bp 60-75°, 15.0 g).

A solution containing 15.0 g of the aforementioned product and sodium ethoxide (3 g of sodium in 400 ml of absolute ethanol) was heated at 40-50° for 2½ h. The solution was stirred under nitrogen at room temperature overnight. The resulting solution was poured into water. The organic substance was extracted with ether. Removal of ether under reduced pressure after drying (magnesium sulphate) and distillation under vacuum yielded 11.9 g (48%) of the bicyclic enone (154) as a colourless oil: bp 120-122°/1.5 mm; ir (neat) 1667 cm^{-1} (enone); nmr (CCl_4) δ 0.83 (s, 3H, C-7 CH_3), 1.07 (s, 3H, C-7 CH_3), 1.20 (s, 3H, C-4a CH_3), and 1.70 (s, 3H, C-1 CH_3); ms m/e (relative intensity) 206 (M^+, 100), 191(78), 164 (57), 149 (61), 138 (70), 93 (48), 91((61), and 79 (57).

1,4aβ,7,7-Tetramethyl-1,4,4a,5,6,7,8,8aβ-octahydronaphthalen-2(3H)-one (153) or (162). The enone (154) (854 mg, 4.15 mmol) in 50 ml of ethyl acetate was hydrogenated over 100 mg of 10% Pd/C for 42 h. The palladium-carbon was filtered through Celite and the solvent was removed under reduced pressure to yield a colourless oil, which was chromatographed on silica gel. Elution with hexane-ethyl acetate (5:1) gave 793 mg (92%) of the title ketone. Recrystallization from hexane afforded a sample of analytical purity as colourless needles: mp 78-79°; ir (KBr) 1716 cm^{-1} (carbonyl); nmr ($CDCl_3$) δ 0.89 (s, 3H, C-7 CH_3), 0.90 (s, 3H, C-7 CH_3), 0.93 (d, 3H, J=7Hz, C-1 CH_3), and 1.28 (s, 3H, C-4a CH_3); ms m/e (relative intensity) 208 (M^+, 100), 146 (59), 123 (68), 97 (50), 69 (50), and 55 (59).

Anal. Calcd. for $C_{14}H_{24}O$: C, 80.71; H, 11.61.
Found : C, 80.80; H, 11.56.

1,4aβ,7,7-Tetramethyl-1,4,4a,5,6,7,8,8aα-octahydronaphthalen-2(3H)-one (163) or (168). A solution of 960 mg (4.66 mmol) of the enone (154) in dry ether was added dropwise to lithium (1.5 g, 210 mg atoms) in 100 ml of distilled liquid ammonia and the blue solution was stirred for 30 min. An excess of ammonium chloride was added and ammonia was allowed to evaporate. Addition of water followed by the normal work-up gave 830 mg of crystals. Recrystallization from aqueous methanol yielded 787 mg of the title ketone (82%). Another recrystallization from the same solvent gave a sample of analytical purity as fine flakes: mp 61-62°; ir (KBr) 1712 cm^{-1} (carbonyl); nmr ($CDCl_3$) δ 0.87 (s, 3H 3H, C-7 CH_3), 0.95 (s, 3H, C-7 CH_3), 0.95 (d, 3H, J=6Hz, C-1 CH_3), and 1.05 (s, 3H, C-4a CH_3); ms m/e (relative intensity) 208 (M^+, 66), 123 (18), 97 (41), 69 (54), 55 (77).

Anal. Calcd. for $C_{14}H_{24}O$: C, 80.71; H, 11.61.
Found : C, 80.71; H, 11.67.

2-Ethylenedioxy-4aβ-formyl-1,7,7-trimethyl-1,2,3,4,4a,5,6,7,8,8aα-decahydronaphthalene (166). Pyridinium chlorochromate (645 mg, 3.00 mmol) and sodium acetate (272 mg, 2.00 mmol) were suspended in 30 ml of dry methylene chloride, and the alcohol (165)^{64} was rapidly added at room temperature. The reaction mixture was stirred for 4 h and diluted with ether. The solvent was decanted and the black solid was washed twice with ether.

The combined ether solutions were passed through a Florisil column and evaporation of the solvents at reduced pressure afforded 476 mg (89%) of the aldehyde (166) as a yellow oil. Crystallization of this oil from hexane gave a sample of (166) as white particles, mp 61-64°. Attempts to further purify this material failed: ir (CCl_4) 1723 cm^{-1} (aldehyde); nmr ($CDCl_3$) δ 0.83 (d, 3H, J=6Hz, C-1 CH_3), 0.92 (s, 6H, C-7 CH_3), 3.93 (s, 4H, $-O-\underline{CH}_2-\underline{CH}_2-O-$), and 11.3 (s, 1H, aldehyde proton); ms m/e (relative intensity) 238 (M^+-28, 24), 100 (45), 99 (100), and 86 (57).

2-Ethylenedioxy-1,4aβ,7,7-tetramethyl-1,2,3,4,4a,5,6,7,8,8aα-decahydronaphthalene (167) and 1,4aβ,7,7-Tetramethyl-1,4,4a,5,6,7,8,8aα-octahydronaphthalen-2(3H)-one (168). A solution containing 521 mg (1.99 mmol) of the aldehyde (166), 50 ml of diethyleneglycol, and 990 mg (20 mmol) of hydrazine hydrate (99%) was warmed to 100° over a 1 h period. After cooling, 1.12 g (20 mmol) of potassium hydroxide was added and the resulting mixture was boiled slowly with concurrent distillation of water for 2 h. Refluxing was continued for an additional 3 h. The mixture was then cooled, acidified with dil. (3N) hydrochloric acid and extracted with ether (x3). The ether extract was washed with water and dried over magnesium sulphate, and the solvent was evaporated to give 323 mg (64%) of a faintly yellow oil: ir ir (neat) 1715 cm^{-1} (carbonyl); nmr (CCl_4) δ 3.87 (s, $-O-\underline{CH}_2-\underline{CH}_2-O-$). This material which is considered to be a mixture of (167) and (168), 217 mg, was refluxed in 60 ml of acetone and 10 ml of oxalic acid solution (5%) for 3 h. Normal work-up with ether afforded 152 mg of the ketone (<u>168</u>) as white needles. Recrystallization of this material from aqueous methanol gave a sample whose physical properties were identical with those of (<u>163</u>).

<u>Attempted Silyl-enolation of Ketone (162).</u>

(a) The procedure of House and coworkers[125] was followed. To a solution of 32.6 mg (0.29 mmol) of chlorotrimethylsilane and 60.6 mg (0.60 mmol) of triethylamine in 25 ml of dry dimethylformamide was added 41.8 mg (0.21 mmol) of the <u>cis</u>-ketone (<u>162</u>). The reaction mixture, from which yellow solids separated immediately upon addition, was refluxed for 24 h. After cooling, the mixture was diluted with 100 ml of pentane, and washed with cold aqueous sodium bicarbonate solution. The pentane solution was washed with portions of cold dil. hydrochloric acid (3N) and cold aqueous sodium bicarbonate solution. The resulting pentane phase was dried over sodium sulphate and concentrated to give 39.5 mg of colourless oil. IR and nmr spectra of this oil did not show any differences from those of (<u>162</u>).

(b) The ketone (<u>162</u>) (0.26 mmol) was refluxed in 15 ml of dry glyme for 1 h, together with sodium hydride (30 mg, 60% dispersion). Upon cooling, triethylamine (30 mg, 0.30 mmol) and chlorotrimethylsilane (30 mg, 0.27 mmol) were added. The resultant solution was stirred for another 15 min and diluted with pentane. Work-up as described above gave 47.3 mg of oil. Both ir and nmr spectra of the sample were identical with those of the starting ketone.

2-Acetyl-1,4aβ,7,7-tetramethyl-3,4,4a,5,6,7,8,8aβ-octahydronaphthalene (174). A solution of 1.16 g (5.58 mmol) of the *cis*-ketone (162) and 10 g of acetic anhydride in 50 ml of carbon tetrachloride was stirred, and to this were added 5 drops of perchloric acid. The solution was then stirred at room temperature for 4 h. The resulting mixture was washed with water (x2) and saturated sodium bicarbonate solution. After drying over magnesium sulphate , the solvent was removed at reduced pressure to give a brown oil which was distilled to separate 1.20 g (80%) of the enol acetate (174) as a colourless oil: bp 50-53°/0.5 mm; ir (neat) 1762 cm^{-1} (enol acetate); nmr (CCl_4) δ 0.90 (s, 6H, *gem*-dimethyl), 0.97 (s, 3H, C-4a CH_3), and 2.03 (s, 6H, C-1 CH_3 and $-OOC-\underline{CH_3}$); ms m/e (relative intensity) 250 (M^+,15), 209 (27), 208 (100), 193 (63), 123 (28), 55 (22).

Attempted Annelation of 3-Trimethylsilyl-3-buten-2-one (175) with Lithium Enolate (173). The lithium enolate (173) was prepared from the enol acetate (174) (523 mg, 2.09 mmol) and methyllithium (4.6 mmol) in 8 ml of freshly distilled 1,2-dimethoxyethane (DME) under nitrogen. After cooling to -78° a solution of the vinyl ketone (175) (366mg, 2.52 mmol) which was prepared according to the method of Ganem[98] in DME (4 ml) was added and the yellow reaction mixture was stirred at -78° for ½ h. The solution was allowed to reach room temperature over a period of 1 h and quenched by adding water. The organic substance was extracted with ether and the ether extract was washed with water (x2), brine, dried over potassium carbonate and concentrated *in vacuo* to afford an orange oil. This crude oil was refluxed in 5% sodium methoxide in methanol solution for 3 h. Normal work-up with ether gave 212 mg of yellow oil which was chromatographed on 2 mm preparative tlc (hexane-ethyl acetate, 4:1) to separate 56 mg of faintly yellowish oil (176): ir (neat) 1668 cm^{-1} (enone); nmr (CDCl$_3$) δ 0.90 (br. s, 9H), and 5.87 (br. s, olefinic proton).

Attempted Alkylation of Enol Acetate (174). Methyllithium (4.4 mmol, obtained by concentrating a ether solution under reduced pressure) and 1 mg of 2,2'-bipyridyl were dissolved in dry DME (10 ml) and stirred at 0° for ½ h. Enol acetate (174) (500 mg, 2.00 mmol) in 5 ml of DME was added dropwise to the above solution. To the resulting deep red solution was added 240 mg (2.2 mmol) of allyl bromide. The reaction mixture was stirred for 10 min and a allowed to warm to room temperature. A solution of saturated sodium bicarbonate was added and the organic phase was extracted with ether. The ether extract was washed with brine and dried over anhydrous magnesium sulphate. Evaporation of the solvent gave 380 mg of crystalline substance which turned out to be the *cis*-ketone (162). No alkylation product was detected by nmr. A similar procedure was repeated in ether and tetrahydrofuran, where the ketone (162) was recoverd nearly quantitatively.

2-Allyloxy-1,4aβ,7,7-tetramethyl-3,4,4a,5,6,7,8,8aβ-octahydronaphthalene (177). Methyllithium (18.4 mmol, obtained by concentrating an ether solution under reduced pressure) and a few milligram of *o*-phenanthroline were dissolved in 100 ml of hexamethylphosphoramide (distilled at reduced pressure and stored over 4A molecular sieves) and the resulting solution was cooled to 0°. Enol acetate (174) (2.08 g, 8.33 mmol) was added dropwise through a syringe. To the deep red solution that resulted, allyl bromide (0.83 ml, 9.6 mmol) was added quickly and stirred for 5 min. The reaction mixture was allowed to warm to room temperature during another 10 min. Saturated sodium carbonate solution was poured into the solution and the organic phase was extracted with water. The ether extract was then stirred with 50 ml of dil. (3N) hydrochloric acid for 1 h. The ether phase was separated, washed with saturated sodium bicarbonate solution and brine. Drying over magnesium sulphate and concentration under reduced pressure gave 2.15 g of a yellow oil. Distillation of the oil at oil pump pressure separated 1.78 g (86%) of colourless oil , and a sample was further distilled to afford (177) of analytical purity: bp 78-80°/0.5 mm; ir (neat) 1687 cm^{-1} (enol ether); nmr (CCl_4) δ 0.90 (s, 9 H, C-4a and C-7 gem-dimethyl), 1.40 (s, 3H, C-1 CH_3), 3.84-4.18 (m, 2H, $-O-\underline{CH_2}-$), 4.94-5.40 (m, 2H, $-CH=\underline{CH_2}$), and 5.91-6.21 (m, 1H, $-\underline{CH}=CH_2$); ms m/e (relative intensity) 248 (M^+, 100), 123 (52), 110 (59), 95 (62), 69 (67), and 55 (59).

Anal. Calcd. for $C_{17}H_{28}O$: C, 82.20; H, 11.36.
Found : C, 82.15; H, 11.31.

1-Allyl-1,4aβ,7,7-tetramethyl-1,4,4a,5,6,7,8,8aβ-octahydronaphthalen-2(3H)-one (179). The allyl ether (177) (100 mg, 0.403 mmol) was sealed in a pyrex tube under nitrogen and pyrolyzed at 200-220° for 15 min. The brown residue was dissolved in chloroform and separated by preparative tlc (hexane-10% ethyl acetate) to give 28 mg (28%) of the title compound (179) as a colourless oil together with 26 mg of the *cis*-ketone (162). A sample was distilled at oil pump pressure to afford analytically pure (179): bp 65-68°/0.03 mm; ir (CCl_4) 1700 cm^{-1} (carbonyl); nmr ($CDCl_3$) δ 0.87 (s, 3H, C-7 CH_3), 0.90 (s, 3H, C-7 CH_3), 1.27 (s, 3H, C-1 CH_3), 1.33 (s, 3H, C-4a CH_3), 4.87-5.30 (m, 2H, $-CH{=}\underline{CH_2}$), and 5.45-6.12 (m, 1H, $-\underline{CH}{=}CH_2$); ms m/e (relative intensity) 248 (M^+,45), 233 (13), 55 (68), and 41(100).

Anal. Calcd. for $C_{17}H_{28}O$: C, 82.20; H,11.36.

Found : C, 82.30; H,11.30.

The allyl ether (177) (225 mg, 0.91 mmol) was refluxed in ethylene glycol for 1½ h. Upon cooling, the solution was diluted with ether (100 ml) and washed with water (x3), dried over magnesium sulphate. Evaporation of the solvent under reduced pressure gave 216 mg of oil which was separated to afford 60 mg (27%) of (179) and 25 mg of (162).

When 600 mg (2.42 mmol) of (177) was boiled in 2,2-oxydiethanol for 4h, only the ketone (483 mg, 93%) was isolated.

Refluxing 125 mg (0.502 mol) of the ether (177) in diglyme (diethyleneglycol dimethyl ether) resulted in the formation of 56 mg (45%) of (179) and 17 mg of the ketone (162).

2-Methoxycarbonyl-5,5-dimethylcyclohexanone (187).

Dry methyl carbonate (270 g, 3.00 mol) and sodium hydride (72 g, 3.00 mol) in 500 ml of dry tetrahydrofuran were heated at reflux temperature with mechanical stirring. To this suspension was added dropwise 125 g (1.03 mol) of 3,3-dimethylcyclohaxanone[78] in 200 ml of dry THF. Two minutes after the addition, about 1 g of potassium hydride was added to initiate the reaction. The solution was refluxed for an additional 1½ h. The mixture was then cooled in an ice bath for 30 min and hydrolyzed by the careful addition of 3M aqueous acetic acid solution. The organic material was extracted with chloroform, washed with saturated sodium bicarbonate solution, and brine. Drying over anhydrous sodium sulphate and removal of solvent under reduced pressure gave a yellow oil from which the title keto ester (187) (115 g, 65%) was distilled under vacuum: bp 78-83°/1.0 mm; ir (neat) 1746, 1723, 1657, and 1623 cm^{-1} (α-ketoester); nmr (CCl_4) δ 0.97 (s, 6H gem-dimethyl) and 3.70 (s, 3H, $-COO-CH_3$).

2-Methoxycarbonyl-5,5-dimethyl-2-(m-methoxyphenethyl)-cyclohexanone (188).

(a) The procedure of Daum and coworkers[104a] was followed. Potassium (11.7 g, 0.30 mol) was dissolved in 250 ml of dry t-butanol. To this was added dropwise 50.6 g (0.30 mol) of the above ketoester (187) diluted with 100 ml of t-butanol. An additional 100 ml of t-butanol was added, followed by the addition of 2-(m-methoxyphenyl)-ethyl bromide (183) diluted with 100 ml of t-butanol. The reaction mixture was refluxed with mechanical stirring for 80 h. The cooled reaction mixture was poured into ice-water. Ether was added and the organic layer was separated. The ether layer was washed with dil. (3N) hydrochloric acid, saturated sodium bicarbonate solution and brine. After drying over sodium sulphate, the solvent was removed in vacuo to leave a yellow oil. This oil was distilled under high vacuum; the first fraction (13.2 g) contained the starting ketoester (187) and m-methoxystyrene; the second fraction (10.2 g) which boiled at 63-83° contained the ester and the bromide (183); the third fraction that boiled at 83-85° was chiefly the bromide (183); the final fraction that boiled at 168-172° (0.3 mm) was collected (a yellow viscous oil, 27.2 g, 31%): ir (neat) 1734 (ester); and 1712 cm^{-1} (carbonyl); nmr ($CDCl_3$) δ 0.89 (s, 3H, C-5 CH_3), 1.03 (s, 3H, C-5 CH_3), 3.70 (s, 3H, $-COOCH_3$), 3.76 (s, 3H, $-OCH_3$) and 6.62-7.30 (m, 4H, aromatics); ms m/e (relative intensity) 318 (M^+, 6), 184 (33), 152 (21), 135 (27), 134 (100), and 121 (23).

(b) Potassium (5.0 g, 0.13 mol) was dissolved in 200 ml of dry benzene containing 20 ml of t-pentyl alcohol under reflux. To the solution was added 19.5 g (0.106 mol) of the ketoester (187) diluted with 50 ml of dry benzene while ca. 50 ml of benzene was being removed through a Dean-Stark trap. Then, a solution of m-methoxyphenylethyl tosylate (32.7 g, 0.107 mol) in 100 ml of benzene was added dropwise with stirring under reflux. Reflux was continued for 24 h. The cooled reaction mixture was poured into ice-water and benzene was added. The benzene layer was separated and the aqueous layer was extracted with benzene (x2). The combined benzene extracts were washed with water, dil. (3N) hydrochloric acid, saturated sodium bicarbonate solution, and brine. The solvent was removed *in vacuo* to leave a yellow oil. This oil was chromatographed on silica gel. Elution with hexane-ethyl acetate (10:1) separated the starting ketoester (187) (7.1 g) and yielded 10.2 g (30%) of (188) as a yellow viscous oil.

2-Methoxycarbonyl-5,5-dimethyl-2-(m-methoxyphenacyl)-cyclohexanone (190). Potassium (2.3 g, 0.06 mol) was dissolved in 120 ml of [illegible] benzene containing 7 ml of *t*-pentyl alcohol under reflux. A solution of 8.2 g (0.06 mol) of the ketoester (187) in 50 ml of benzene was added dropwise to the above solution and benzene was distilled off through a Dean-Stark trap simultaneously. *m*-Methoxyphenacyl bromide (189) (13.7 g, 0.06 mol) was then added portionwise and the resulting deep red solution was refluxed under nitrogen overnight. The work-up procedure described above produced a viscous reddish oil. This oil was chromatographed on silica gel to separate 8.0 g (54%) of the title compound (190) as a red solid. A sample was recrystallized from ethanol to give amorphous powders: mp 92-93°; ir (KBr) 1735 (ester), 1712 (carbonyl), and 1684 cm^{-1} (carbonyl): nmr ($CDCl_3$) δ 0.94 (s, 3H, C-5 CH_3), 1.07 (s, 3H, C-5 CH_3), 3.74 (s, 3H, $COOCH_3$), 3.80 (s, 3H, OCH_3), and 6.80-7.54 (m, 4H, aromatic protons).

Anal. Calcd. for $C_{19}H_{24}O_5$: C, 68.66; H, 7.27.
Found : C, 68.64; H, 7.24.

The product (190) (5.4 g, 16 mmol) was hydrogenated over 500 mg of 10% Pd/C in 100 ml of acetic acid. After hydrogen uptake had ceased (ca. 3 h), the solution was diluted with chloroform (200 ml) and filtered through Celite. The chloroform solution was washed with water (x3), saturated sodium bicarbonate solution (x3), and brine. The extract was dried over sodium sulphate and evaporated at reduced pressure to leave a yellow oil which was purified on silica gel column (eluted with benzene) to separate 4.6 g (89%) of (188).

7-Methoxy-10a-methoxycarbonyl-3,3-dimethyl-1,2,3,9,10,10a-hexahydrophenanthrene (191). Compound (188) (10 g, 0.31 mol) and 2.5 g of p-toluenesulphonic acid in 400 ml of dry benzene were refluxed under nitrogen for 12 h. Upon cooling, the reaction mixture was passed through a short column packed with neutral aluminium oxide (Woelm). Concentration of the solution under reduced pressure yielded the cyclized material (191) (7.8 g, 83%) as a yellow solid. An analytical sample of (191) was obtained by recrystallization from hexane as colourless crystals: mp 74-75°; ir (KBr) 1712 cm^{-1} (ester); nmr ($CDCl_3$) δ 1.05 (s, 3H, C-3 CH_3); 1.10 (s, 3H, C-3 CH_3), 3.54 (s, 3H, $COO\underline{CH_3}$), 3.72 (s, 3H, $O\underline{CH_3}$), 5.94 (s, 1H, C-4 H), and 6.50-7.57 (m, 3H, aromatic); ms m/e (relative intensity) 300 (M^+, 100), 285 (100), 241 (31), and 225 (42).

Anal. Calcd. for $C_{19}H_{24}O_3$: C, 75.97; H, 8.05.
Found : C, 75.98; H, 8.08.

7-Methoxy-10aβ-methoxycarbonyl-3,3-dimethyl-1,2,3,4,4aα,9,10,10a-octahydrophenanthrene (194). Ester (191) (382 mg, 1.27 mmol) was hydrogenated over 70 mg of 10% Pd/C in 50 ml of toluene. After 12 h, palladium-carbon was removed by filtration through a pad of Celite and the solution was concentrated to yield 376 mg (98%) of the hydrogenated product (194) as white powders. A sample was recrystallized from hexane-ethyl acetate (3:1): mp 91-92°; ir (KBr) 1739 cm^{-1} (ester); nmr ($CDCl_3$) δ 1.02 (s, 6H, C-3 gem-dimethyl), 3.54 (s,3H, $COOCH_3$), 3.75 (s, 3H, OCH_3), and 6.50-7.23 (m, 3H, aromatic); ms m/e (relative intensity) 302 (M^+,100),242 (100), 186 (19), and 171 (19).

Anal: Calcd. for $C_{19}H_{26}O_3$: C, 75.46; H, 8.67.

Found : C, 75.48; H, 8.60.

10aβ-Hydroxymethyl-7-methoxy-3,3-dimethyl-1,2,3,4,4aα,9,10,10a-octahydrophenanthrene (195). A slurry of 100 mg (2.50 mmol) of lithium aluminium hydride in 40 ml of dry ether was stirred under nitrogen while the ester (194) (670 mg, 2.22 mmol) in 50 ml of dry ether was added dropwise. The mixture was then refluxed for 4 h. Excess lithium aluminium hydride was destroyed by adding saturated sodium sulphate solution. The resulting suspension was diluted with dil. (3N) hydrochloric acid and the ether layer was separated. The ether layer was washed with water (x2) and dried over sodium sulphate. Removal of ether under reduced pressure gave 569 mg (94%) of the alcohol (195) as a white powder. Recrystallization twice from hexane-ethyl acetate (4:1) afforded a sample of analytical purity: mp 119-120°; ir (Nujol) 3270 cm^{-1}

(hydroxyl); nmr ($CDCl_3$) δ 1.04 (s, 3H, C-3 CH_3), 1.07 (s, 3H, C-3 CH_3), 3.20 (d, 1H, J=11Hz, C-10a $\underline{CH_2}$-OH), 3.61 (d, 1H, J=11Hz, C-10a -$\underline{CH_2}$-OH), 3.79 (s, 3H, $O\underline{CH_3}$), and 6.60-7.14 (m, 3H, aromatic); ms m/e (relative intensity) 274 (M^+,100), 243 (34), 173 (19), and 147 (21).

Anal. Calcd. for $C_{18}H_{26}O_2$: C, 78.79; H, 9.55.
Found : C, 78.84; H, 9.48.

10a-Hydroxymethyl-7-methoxy-3,3-dimethyl-1,2,3,9,10,10a-hexahydrophenanthrene (196). A slurry of 352 mg (8.8 mmol) of lithium aluminium hydride in 50 ml of dry ether was stirred under nitrogen during addition of a solution containing 2.80 g (9.3 mm mmol) of the ester (191) in 50 ml of dry ether. After addition was completed, the mixture was refluxed for 4 h, and stirred overnight at room temperature. Excess lithium aluminium hydride was destroyed by adding saturated sodium sulphate solution. The resulting suspension was diluted with dil. (3N) hydrochloric acid. The organic layer was separated, washed with sodium bicarbonate solution and brine. Drying over sodium sulphate and removal of solvent in vacuo gave 2.55 g of semi-solids. The solids were purified by column chromatography (silica gel, eluted with hexane-ethyl acetate) to afford 2.49 g (97%) of the title alcohol (196) as white powders. The material was recrystallized from hexane to give a sample of analytical purity: mp 55-56°; ir (KBr) 3400 cm^{-1} nmr ($CDCl_3$) δ 1.03 (s, 3H, C-3 CH_3), 1.07 (s, 3H, C-3 CH_3) 3.46 (s, 2H, C-10a -$\underline{CH_2}$-OH), 3.76 (s, 3H, $O\underline{CH_3}$), 5.84 (s, 1H, C-4 H), and 6.50-7.42 (m, 3H, aromatic).

Anal. Calcd. for $C_{18}H_{24}O_2$: C, 79.37; H, 8.88.

Found : C, 79.41; H, 8.90.

Catalytic Hydrogenation of (196). A solution of 550 mg (2.00 mmol) of the alcohol (196) in 50 ml of toluene was hydrogenated at room temperature over 50 mg of 10% Pd/C for 20 h. Palladium-carbon was removed by filtration through Celite. Concentration of the solvent provided 564 mg of a white solid. Some material was recrystallized to give a sample that melted at 59-61°. The mass spectrum of the sample showed a molecular ion peak at m/e 274. The nmr spectrum of this solid showed a complex pattern of peaks at 3.10-3.70 which was analyzed to be composed of two pairs of doublets (see p. 92), and on this basis the product was found to be a mixture of (195) and (207).

The hydrogenation was carried out in the following solvents; ethanol, ethanol-10% aqueous sodium hydroxide, acetic acid, and acetonitrile. After work-up, the residue was examined by nmr. The cis- and trans- mixtures were obtained in these solvents except acetonitrile, in which the cis-product (207) was produced predominantly, but the time for hydrogenation of 30 mg of (196) was ca. 150 h.

10a-Carboxy-7-methoxy-3,3-dimethyl-1,2,3,9,10,10a-hexahydrophenanthrene (205). Ester (191) (1.03 g, 4.44 mmol) in 70 ml of methoxyethanol was refluxed with 2 g (36 mmol) of potassium hydroxide for 48 h under nitrogen. The cooled reaction mixture was acidified with dil. (3N) hydrochloric acid and extracted with ether. The ether extract was washed with water (x2) and brine, and dried over sodium sulphate. Removal of ether under reduced pressure gave 695 mg (71%) of the acid (205). A sample was recrystallized twice from ethanol to afford a white powder: mp 180°-dec. ir (KBr) 3300-2400, 1735, and 1690 cm^{-1} (carboxylic acid); nmr (CDCl$_3$) δ 1.03 (s, 3H, C-3 CH$_3$), 1.10 (s, 3H, C-3 CH$_3$), 3.75 (s, 3H, OCH$_3$), 5.90 (s, 1H, C-4 H), 6.45-7.50 (m, 3H, aromatic), and 7.91 (s, 1H, COOH); ms m/e (relative intensity) 286 (M$^+$,64), 271 (100), and 241 (15). The combustion analysis of this solid did not give correct percentage for C and H.

10aβ-Carboxy-7-methoxy-3,3-dimethyl-1,2,3,4,4aβ,9,10,10a-octahydrophenanthrene (206). The procedure of Thompson and coworkers[109] was followed. A solution of 300 mg (1.05 mmol) of the acid (205) in 20 ml of dry 1:1 tetrahydrofuran-ether was added to a stirred solution of 100 mg (19 mg-atoms) of lithium in 60 ml of distilled liquid ammonia. After 30 min the blue reaction mixture was quenched by adding solid ammonium chloride, and ammonia was allowed to evaporate. To this, dil. (3N) hydrochloric acid was added and the organic substance was extracted with ether. The ether extract was washed with water (x2) and brine, and dried over sodium sulphate. Removal of the solvent under reduced pressure provided 274 mg of crude solid which was recrystallized from ethanol to give 222 mg (74%) of the title acid (206) as fine needles. The material was further recrystallized from ethanol to afford a sample for combustion analysis; mp 175-182° with partial sublimation; ir (KBr) 3450, 3200, and 1723 (carboxylic acid); nmr ($CDCl_3$) δ 0.90 (s, 3H, C-3 CH_3), 1.03 (s, 3H, C-3 CH_3), 3.74 (s, 3H, OCH_3), and 6.50-7.06 (m, 3H, aromatic); ms m/e 288 (M^+,100), 242 (63), and 186 (11).

Anal. Calcd. for $C_{18}H_{24}O_3$: C, 74.97; H, 8.39.
Found : C, 74.79; H, 8.46.

10aβ-Hydroxymethyl-7-methoxy-3,3-dimethyl-1,2,3,4,4aβ,9,10,10a-octahydrophenanthrene (207). A slurry of 68 mg (1.7 mmol) of lithium aluminium hydride in 20 ml of dry tet[illegible]ydrofuran was stirred under nitrogen during dropwise addition of a solution containing 555 mg (1.9 mmol) of the acid (206) in 50 ml of dry THF. Upon completion of addition, the mixture was refluxed for 2 h. The cooled reaction mixture was titrated with saturated sodium sulphate solution and the solids formed were removed by filtration through Celite. The filtered solution was dried over sodium sulphate and the solvent was removed at reduced pressure to leave 498 mg (96%) of the alcohol (207) as an amorphous solid. Two recrystallizations from hexane afforded an analytical sample: mp 97-98°; ir (KBr) 3350 cm^{-1} (hydroxyl); nmr ($CDCl_3$) δ 0.87 (s, 3H, C-3 CH_3), 1.00 (s, 3H, C-3 CH_3), 3.30 (d, 1H, J=11Hz, -CH_2-OH) 3.42 (d, 1H, J=11Hz, -CH_2-OH), 3.74 (s, 3H, OCH_3), and 6.54-6.96 (m, 3H, aromatic); ms m/e (relative intensity) 274 (M^+, 100), 256 (22), and 243 (22).

Anal. Calcd. for $C_{18}H_{26}O_2$: C, 78.79; H, 9.55.
Found : C, 78.80; H, 9.59.

10aβ-Formyl-7-methoxy-3,3-dimethyl-1,2,3,4,4aα,9,10,10a-octahydrophenanthrene (216). Pyridinium chlorochromate (213 mg, 0.98 mmol) was suspended in 20 ml of dry methylene chloride, and the *trans*-alcohol (195) (181 mg, 0.66 mmol) was added rapidly at room temperature. The reaction mixture was stirred for 3 h. The resulting solution was diluted with ether, the solvent was decanted from the black mass and the mass was washed with ether. The combined ether solutions were passed through a Florisil column and the solvent was removed at reduced pressure to give 174 mg (97%) of the aldehyde (216) as fine white crystals. Recrystallization of the material from aqueous methanol afforded a sample of analytical purity as fine needles: mp 86-87°; ir (KBr) (CCl_4) 1714 cm^{-1} (aldehyde); nmr ($CDCl_3$) δ 1.03 (s, 6H, C-3 *gem*-dimethyl), 3.74 (s, 3H, OCH_3), and 6.54-7.30 (m, 3H, aromatic), and 9.57 (s, 1H, aldehyde).

Anal. Calcd. for $C_9H_{12}O$: C, 79.37; H, 8.88.

Found : C, 79.40; H, 8.86.

7-Hydroxy-3,3,10aβ-trimethyl-1,2,3,4,4aα,9,10,10a-octahydrophenanthrene (217) and 7-Methoxy-3,3,10aβ-trimethyl-1,2,3,4,4aα,9,10,10a-octahydrophenanthrene (218).

Aldehyde (216) (1.10 g, 4.05 mmol), 50 ml of distilled diethylene glycol, and 7.5 ml (0.15 mol) of hydrazine hydrate were warmed to 120° over a 1 h period and maintained at this temperature for 2 h. Upon cooling 2.8 g (0.05 mol) of potassium hydroxide was added, and the mixture was brought to boiling point with concurrent removal of water by distillation over a period of

3h. Reflux was continued for a further 6 h. After cooling, the mixture was acidified with dil. hydrochloric acid (3N) and extracted with ether. The ether extract was washed with water (x5), then brine and dried over magnesium sulphate. Concentration at reduced pressure left 894 mg of crystalline material that showed two spots on tlc. Some material (200 mg) was chromatographed on preparative tlc (hexane-25% ethyl acetate) to separate 98 mg of less polar substance (Rf=0.84, hexane-10% ethyl acetate) and 75 mg of more polar substance (Rf=0.64).

The more polar substance was recrystallized from methanol (twice) to afford a sample of the phenol (217) as an amorphous soild: mp 92-94°; ir (CCl_4) 3640 (phenol) and 1510 cm^{-1} (aromatic) nmr ($CDCl_3$) δ 0.65 (s, 3H, C-10a CH_3), 0.98 (s, 3H, C-3 CH_3), 1.03 (s, 3H, C-3 CH_3), 5.74 (br., 1H, -OH), and 6.33-7.00 (m, 3H, aromatic).

Anal. Calcd. for $C_{17}H_{24}O$: C, 83.55; H, 9.90.
Found : C, 83.49; H, 9.90.

Recrystallization of the less polar substance from methylene chloride-methanol (1:3) gave a sample of the hydrocarbon (218) as prisms with yellow tinge: mp 43-44°; ir (KBr) 1612 and 1501 cm^{-1} (aromatic ring); uv_{max} (CH_3OH) 218 (ε =7940), 278 (2340), and 287 nm (2060); nmr ($CDCl_3$) δ 0.67 (s, 3H, C-10a CH_3), 0.97 (s, 3H, C-3 CH_3), 3.76 (s, 3H, OCH_3), and 6.55-7.20 (m, 3H, aromatic); ms m/e (relative intensity) 258 (M^+,100).

Anal. Calcd. for $C_{18}H_{26}O$: C, 83.67; H, 10.14.
Found : C, 82.60; H, 10.06.

Phenol (217) was methylated according to the method of Stoochnoff and Benoition[117]. Thus, the phenol (50 mg, 0.2 mmol) was dissolved in 50 ml of dry tetrahydrofuran containing 10 mg (0.4 mmol) of suspended sodium hydride (98% dry). To this, was added 230 mg (0.9 mmol) of methyl iodide and the mixture was stirred at room temperature overnight. Water was added to destroy the remaining sodium hydride and the organic substance was extracted with ether. The ether extract was washed with water and brine, and dried over magnesium sulphate. Removal of the solvent at reduced pressure left 45 mg (85%) of chromatographically pure hydrocarbon (218).

Similarly, the remaining mixtures of the phenol (217) and the hydrocarbon (218) were treated with 100 mg (4.2 mmol) of sodium hydride (98% dry) and 2.4 g (10 mmol) of methyl iodide. The solution was left at room temperature overnight with stirring. Work-up as above gave 667 mg of hydrocarbon (218). The combined yield of the two steps Wolff-Kishner-methylation amounts to ca. 75%.

10aβ-Formyl-7-methoxy-3,β-dimethyl-1,2,3,4,4aβ,9,10,10a-octahydrophenanthrene (219). Pyridinium chlorochromate (1.47 g, 6.80 mmol) was suspended in 70 ml of dry methylene chloride, and the cis-alcohol (1.25 g, 4.53 mmol) (207) was added quickly. The reaction mixture was stirred at room temperature for 5 h. The resulting black solution was diluted with ether, the solvent was decanted, and the black solid was washed with ether. The combined ether solutions were passed through a Florisil column and the solvent was removed under reduced pressure to leave 1.19 g (96%) of the aldehyde (219). Recrystallization of the material twice from aqueous methanol afforded a sample of analytical purity as fine needles with a yellow tinge: mp 100-102°; ir (CCl_4) 1718 cm^{-1} (aldehyde); nmr ($CDCl_3$) δ 0.93 (s, 3H, C-3 CH_3), 1.03 (s, 3H, C-3 CH_3), 3.74 (s, 3H, OCH_3), 6.50-7.10 (m, 3H, aromatic) and 9.40 (s, 1H, aldehyde proton).

Anal. Calcd. for $C_9H_{12}O$: C, 79.37; H, 8.88.
Found : C, 79.30; H, 8.86.

7-Methoxy-3,3,10aβ-trimethyl-1,2,3,4,4aβ,9,10,10a-octahydrophenanthrene (182). Aldehyde (219) (2.88 g, 10.5 mmol), 70 ml of distilled diethylene glycol, and 25 ml (0.49 mol) of hydrazine hydrate (100%) were warmed to 100° over a 2 h period and maintained at this temperature for 2 h. Upon cooling, potassium hydroxide (5.6 g, 0.10 mol) was added and the mixture was boiled with concurrent removal of water by distillation over a period of 3 h. The solution was refluxed for a further 12 h. After cooling, the mixture was acidified with dil. (3N) hydrochloric acid and extracted with ether. The ether extract was washed with water and brine, and dried over magnesium sulphate. Concentration at reduced pressure gave 2.38 g of crystalline material. This material was methylated in 50 ml of dry tetrahydrofuran using sodium hydride (200 mg, 8.33 mmol) and methyl iodide (4.00 g, 16.5 mmol). Work-up with ether afforded hydrocarbon (182) (2.02 g, 75%). A sample of the material was twice recrystallized from methanol to give the hydrocarbon as colourless needles, mp 65-66°; ir (KBr) 1600 and 1510 cm^{-1} (aromatic ring); uv_{max} (CH_3OH) 220 (ε=5210), 280 (1740), and 285 nm (1610); nmr ($CDCl_3$) δ 0.89 (s, 6H, C-3 gem-dimethyl), 1.00 (s, 3H, C-10a CH_3), 3.76 (s, 3H, OCH_3), and 6.57-7.06 (m, 3H, aromatic); ms m/e (relative intensity) 258 (M^+,100).

Anal. Calcd. for $C_{18}H_{26}O$: C, 83.67; H, 10.14.
Found : C, 83.55; H, 10.15.

3,3,10aβ-Trimethyl-1,2,3,4,4aβ,5,8,9,10,10a-decahydrophenanthren-7(6H)-one (221). The procedure of Wiesner and coworkers[121] was followed. A solution of 600 mg (2.32 mmol) of the cis-hydrocarbon (182) in 50 ml of dry 1:1 tetrahydrofuran, t-butanol was added over 15 min to a stirred solution of lithium (320 mg, 45.7 mg-atoms) in distilled ammonia (ca. 100 ml). The mixture was stirred at acetone-dry ice temperature for 1 h. The blue reaction mixture was quenched by adding absolute methanol, and ammonia was allowed to evaporate. The residue was dissolved in water (100 ml) and extracted with ether (x4). The ether extract was dried by passing through a pad of magnesium sulphate and concentrated to afford a colourless oil. This oil was immediately dissolved in cold absolute ethanol (100 ml) and treated with 1M aqueous oxalic acid solution (30 ml) for 30 min at 0°. The mixture was neutralized by dropwise addition of saturated sodium carbonate solution. Normal work-up with ether gave 512 mg (89%) of the ketone (221) as a yellow oil which solidified upon refrigeration, but melted at room temperature. The material was distilled under vacuum to afford a colourless oil: bp 95-100°/1.0 mm; ir (neat)

1718 cm^{-1} (carbonyl); uv_{max} (CH_3OH) transparent beyond 210 nm ; nmr ($CDCl_3$) δ 0.87 (s, 3H, C-10a CH_3) and 0.90 (s, 6H, C-3 gem-dimethyl); ms m/e (relative intensity) 246 (M^+,100), 231 (100), 217 (86), 105 (38), 91 (41), 79 (31), 69 (31), and 55 (34).

Anal. Calcd. for $C_{17}H_{26}O$: C, 82.87; H, 10.64.

Found : C, 82.90; H, 10.68.

REFERENCES

1. P. de Mayo, "The Higher Terpenoids", Vol. III, Interscience Publishers Inc., New York, 1959.

2. J. Simonsen and D. H. R. Barton, "The Terpenes", Vol. III, Cambridge Press, Cambridge, 1951.

3. P. W. Brian, J. F. Groe and J. MacMillain in "Progress in the Chemistry of Organic Natural Products", Vol. 18, L. Zechmeister, Ed., Springer-Verlag, Vienna, 1969, p. 350.

4. J. R. Hanson in "Chemistry of Terpenes and Terpenoids", A. A. Newman, Ed., Academic Press, London, 1972, p. 193.

5. L. Ruzicka, A. Eschenmoser and H. Heuser, Experientia, 9, 359 (1953); A. Eschenmoser, L. Ruzicka, O. Jeger and D. Arigoni, Helv. Chim. Acta., 38, 1890 (1955).

6. K. Nakanishi in "Natural Products Chemistry", Vol. I, K. Nakanishi, T. Goto, S. Ito, S. Natori and S. Nozoe, Ed., Kodansha and Academic Press, Tokyo and New York, 1974, p. 185.

7. J. R. Hanson in "Progress in the Chemistry of Organic Natural Products", Vol. 29, L. Zechmeister, Ed., Springer-Verlag, Vienna, 1971, p. 395.

8. R. McCrindle and K. H. Overton in "Chemistry of Carbon Compounds", Vol. 2c, Elsevier, London, 1969, p. 373.

9. Reference 4, p. 156.

10. T. K. Devon and A. I. Scott, "Handbook of Naturally Occurring Compounds", Vol. 2, Academic Press, New York, 1972.

11. For example, "Terpenoids and Steroids", Vol. 1-7, The Chemical Society, London, 1971-1977.

12.(a) T. Anthonesen, P. M. McCabe, R. McCrindle and R. D. H. Murry, Tetrahedron, 25, 2233 (1969) and subsequent papers in the series.

12.(b) S. Kusumoto, T. Okazaki, A. Osuga and M. Kotake, Tetrahedron Letters, 4325 (1968) and subsequent papers in the series.

13. J. R. Hanson in "Progress in Phytochemistry", Vol. 3, L. Reinhold and Y. Liwshits, Ed., Interscience Publishers, London, 1972, p. 231.

14. R. M. Coates in "Progress in the Chemistry of Organic Natural Products", Vol. 33, W. Hertz, H. Grisebach and G. W. Kimby, Ed., Springer-Verlag, Wien, 1976, p. 74.

15. Reference 13, p. 268.

16. R. Misra, R. C. Pandy and S. Dev, Tetrahedron Letters, 3751 (1964).

17. T. J. King and S. Rodrigo, Chem. Commun., 683 (1969).

18. G. Berti, O. Livi and S. Sernini, Tetrahedron Lett., 1401 (1970).

19. D. H. R. Barton and D. Elad, J. Chem. Soc., 2085 (1956).

20. G. A. Sim, J. A. Hamon, J. C. Raul and J. M. Robertson, Proc. Chem. Soc., 75 (1961).

21. D. H. R. Batron, H. T. Cheng, A. D. Cross, L. M. Jackman and M. Martin-Smith, J. Chem. Soc., 5061 (1961).

22. I. Kubo, Yue-Wei Lec, V. Balogknair, K. Nakanishi and A. Chappya, J. Chem, Soc.,Chem. Commun., 949 (1977).

23. (a) S. Takahashi, T. Kusumi and H. Kakisawa, Abstracts of Papers, the Annual Meeting of the Chemical Society of Japan, 2U02, Apr. 1977.

23. (b) R. Kawasaki and T. Tokoroyama, ibid., 2U03, Apr. 1977; T. Tokoroyama, Private Communications.

24. J. W. ApSimon and K. Yamasaki, Chem. Letters, 1453 (1977).

25. R. Kanazawa, H. Kotsuki and T. Tokoroyama, Tetrahedron Lett., 3651 (1975).

26. S. Yamazaki, S. Tamura, F. Marumo and Y. Saito, Tetrahedron Letters, 3651 (1969).

27. A. B. Anderson, R. McCrindle and E. Nakamura, J. Chem. Soc., Chem. Commun., 453 (1974); J. Chem. Soc., Perkin I, 1590 (1976).

28. T. Tokoroyama, K. Matsuo, R. Kanazawa, H. Kotsuki and T. Kubota, Tetrahedron Lett., 3093 (1974).

29. H. E. Simmons and R. D. Smith, J. Am. Chem. Soc., 81, 4256 (1956).

30. R. E. Ireland and J. A. Marshall, J. Org. Chem., 27, 1615 (1962).

31. N. Cohen, Acc. Chem. Res., 9, 412 (1976).

32. R. Wiechert, Angew. Chem. Int. Ed. Engl., 16, 506 (1977).

33. G. Saucy, R. Borer and A. Furst, Helv. Chim. Acta., 54, 2034 (1971).

34. G. Saucy and R. Borer, Helv. Chim. Acta., 54, 2121 (1971).

35. F. Korte and H. Machleidt, Chem. Ber., 88, 1676 (1955).

36.(a) G. Stork, S. Danishefsky and M. Ohashi, J. Am. Chem. Soc., 89, 5459 (1967).

36.(b) Y. Pietrasanta and B. Pucci, Tetrahedron Lett., 1901 (1974).

37. B. M. Trost, K. Hiroi and N. Holy, J. Am. Chem. Soc., 97, 5873 (1975).

38. M. S. Henderson, R. D. H. Murry, R. McCrindle and D. McMaster, Can. J. Chem., 51, 1322 (1973).

39. R. McCrindle and E. Nakamura, Can. J. Chem., 52, 2029 (1974).

40. T. Okazaki, A. Otsuka and M. Kotake, Nippon Kagaku Kaishi, 583 (1973).

41. L. Ruzicka, Proc. Chem. Soc., 341 (1959).

42. J. Simonsen and W. C. J. Ross, "The Terpenes", Vol. IV, Cambridge Press, Cambridge, 1957.

43. G. Ourisson, P.Crabbé and O. R. Roding, "Tetracyclic Triterpenes", Holden-Day Inc., California, 1964.

44. J. D. Cornforth, Quart. Rev., 23, 125 (1969).

45. R. O. Haworth, Ann. Rep., 34, 327 (1937).

46. A. Meisels, O. Jeger and L. Ruzicka, Helv. Chim. Acta., 32, 1075 (1949).

47. T. R. Ames, T. G. Halsall and E. R. H. Jones, J. Chem Soc., 450 (1951).

48. D. H. R. Barton and G. A. Morrison in "Progress in the Chemistry of Organic Natural Products", Vol. 19, L. Zechmeister, Ed., Springer-Verlag, Wien, 1961.

49. J. D. Connollyand K. H. Overton in "Chemistry of Terpenes and Terpenoids", A. A. Newman, Ed., Academic Press, London, 1972.

50. Reference 1, p. 202.

51. J. H. Richards and J. B. Hendrickson, "The Biosynthesis of Steroids, Terpenes and Acetogenins", W. A. Benjamin Inc., New York, 1964.

52. D. H. R. Barton, T. R. Jarman, K. G. Watson, D. A. Widdowson, R. B. Boar and K. Pamps, J. Chem. Soc., Chem. Commun., 861 (1974).

53. S. Seo, Y. Tomita and K. Tori, J. Chem. Soc., Chem. Commun., 274 (1975).

54. E. J. Corey and J. J. Ursprung, J. Am. Chem. Soc., 78, 5014 (1956).

55. F. S. Spring, J. M. Beaton, R. Stevenson and J. M. Stewart, Chem. and Ind. (London), 1054 (1956).

56. H. Dutler, O. Jeger and L. Ruzicka, Helv. Chim. Acta., 38, 1268 (1955).

57. T. Kikuchi, M. Niwa and N. Masaki, Tetrahedron Letters, 5249 (1972).

58. J. W. ApSimon and J. W. Hooper in "The Total Synthesis Natural Products", J. W. ApSimon, Ed., Vol. 2, John Wiley and Sons Inc., New York, 1973.

59. R. T. Blickenstaff, A. C. Ghosh and G. C. Wolf, "Total Synthesis of Steroids", Academic Press, New York, 1974.

60. J. A. Barltrop, J. D. Littlehailes, J. D. Rushton and N. A. J. Rogers, Tetrahedron Letters 429 (1962).

61. E. J. Corey, H. J. Hess and S. Proskow, J. Am. Chem. Soc., 90, 1031 (1968).

62. E. Ghera and F. Sondheimer, Tetrahedron Letters, 3887 (1964).

63. R. E. Ireland, S. W. Baldwin, D. J. Dawson, M. I. Dawson, J. E. Dolfin, J. Newbould, W. S. Johnson, M. Brown, R. J. Crawford, P. F. Hudrlik, G. H. Rasmussen and K. K. Schmiegel, J. Am. Chem. Soc., 92, 5743 (1970).

64. S. Badripersaud, Ph.D. Dissertation, Carleton University, 1976.

65. G. Stork, S. Uyeo, T. Wakamatsu, P. Grieco and J. Lapowitz, J. Am. Chem. Soc., 93, 4945 (1971).

66. W. Nagata and M. Yoshioka in "Organic Reactions", Vol. 25, John Wiley and Sons Inc., New York, 1977.

67. E. E. van Tamelen, M. P. Seiler and W. Wiercuga, J. Am. Chem. Soc., 94, 8229 (1972).

68. E. E. van Tamelen, Acc. Chem. Res., 8, 152 (1975).

69. R. E. Ireland, M. I. Dawson, S. C. Welch, A. Hagenbach, J. Border and B. Trus, J. Org. Chem., 95, 7829 (1973).

70.(a) R. E. Ireland and D. M. Walba, Tetrahedron Lett., 1071 (1976).

70.(b) D. M. Walba, Ph.D. Dissertation, California Institute of Technology, 1976.

71. G. H. Douglas, J. M. H. Graves, D. Hartley, G. A. Hughes, B. J. McLonghlin, J. Siddall and H. Smith, J. Chem. Soc., 5072 (1963).

72. R. E. Ireland, C .J. Kowalski, J. W. Tilley and D. Walba, J. Am. Chem. Soc., 96, 3333 (1974) and J. Org. Chem., 40, 990 (1975).

73. F. G. Mann and M. J. Pragnell, Chem. and Ind. (London), 1386 (1964).

74. D. Felix, J. Schreiber, G. Ohloff and A. Eschenmoser, Helv. Chim. Acta., 54, 2896 (1971).

75. S. Winstein, J. Sonnerberg and L. De Vries, J. Am. Chem. Soc., 81, 6523 (1959).

76. T. G. Halsall and D. B. Thomas, J. Chem. Soc., 2431 (1956).

77. J. E. Ellis, J. S. Dutcher and C. H. Heathcock, J. Org. Chem., 41, 2670 (1976).

78. J. W. ApSimon, S. Badripersaud, T. T. T. Nguyen and R. Pike, Can. J. Chem., 56, 1646 (1978).

79. L. S. Minckler, A. S. Hussey and R. H. Baker, J. Am. Chem. Soc., 78, 1009 (1956).

80. H. O. House, "Modern Synthetic Reactions", 2nd ed., W. A. Benjamin Inc., California, 1972, p. 27.

81. R. L. Augustine, J. Org. Chem., 23, 1853 (1958).

82. R. L. Augustine and A. D. Broom, J. Org. Chem., 25, 802 (1960).

83. H. O. House, R. W. Giese, K. Kronberger, J. P. Kaplan and J. F. Simeone, J. Am. Chem. Soc., 92, 2800 (1969).

84. J. E. Ellis, J. S. Dutcher and C. H. Heathcock, Synth. Commun., 4 71 (1974).

85. W. C. Still and F. L. VanMiddlesworth, J. Org. Chem., 42, 1258 (1977).

86. D. H. R. Barton and C. H. Robinson, J. Chem. Soc., 3054 (1954).

87. G. Stork and S. D. Darling, J. Am. Chem. Soc., 86, 1761 (1964).

88. D. Caine in "Organic Reactions", Vol. 23, John Wiley and Sons Inc., New York, 1976.

89. E. J. Corey and J. W. Suggs, Tetrahedron Letters, 2647 (1975).

90. L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis", Vol. 1, John Wiley and Sons Inc., 1967, p. 435.

91. J. B. Stothers, "Carbon-13 NMR Spectroscopy", Academic Press, New York, 1972, p. 60.

92. S. H. Grover, D. H. Marr, J. B. Stothers and C. T. Tan, Can. J. Chem., 53, 1351 (1975).

93. H. O. House and M. J. Lush, J. Org. Chem., 42, 183 (1977).

94. D. Caine and T. L. Smith Jr., J. Org. Chem., 43, 755 (1977).

95. J. L. Gough, J. P. Guthrie and J. B. Stothers, J. Chem. Soc., Chem. Commun., 979 (1972).

96. Reference 80, p. 568.

97. H. O. House, L. J. Czuba, M. Gall and H. D. Omstead, J. Org. Chem., 34, 2324 (1969).

98. B. Ganem, Ph.D. Dissertation, Columbia University, 1972.

99. Reference 80, p. 527.

100. R. F. Church, R. E. Ireland and J. A. Marshall, J. Org. Chem., 27, 1118 (1962).

101. H. M. R. Hoffman, Angew. Chem. Int. Ed. Engl., 8, 556 (1969).

102. (a) D. H. Williams and N. S. Bhacca, Tetrahedron, 21, 1641 (1965).

102.(b) D. H. Williams and N. S. Bhacca, Tetrahedron, 21, 2021 (1965).

103. D. H. Williams, Tetrahedron Lett., 2035 (1965).

104.(a) S. J. Daum, P. E. Shaw and R. L. Clarke, J. Org. Chem., 32, 1430 (1967).

104.(b) H. W. Thompson, J. Org. Chem., 32, 3712 (1967).

105. L. Ruest, G. Blowin and P. Deslongchamps, Synth. Commun., 6, 169 (1976).

106.(a) H. W. Thompson, J. Org. Chem., 36, 2577 (1971).

106.(b) H. W. Thompson and R. E. Naipawer, J. Am. Chem. Soc., 95, 6379 (1973).

107. K.L. Williamson, T. Howell and T. A. Spencer, J. Am. Chem. Soc., 88, 325 (1966).

108. R. L. Augustine, "Catalytic Hydrogenation", Marcel Dekker, New York, 1965, pp. 34-49.

109. H. W. Thompson, E. Mcpherson and B. L. Lences, J. Org. Chem., 41, 2903 (1976).

110. Reference 109, Experimental Section (p. 2905).

111. H. Smith, "Organic Reactions in Liquid Ammonia", Interscience Publishers, New York, 1963, p. 226.

112. Reference 111, p. 228.

113. E. L. Eliel, N. L.Allinger, S. J. Angyal and G. Morrison, "Conformational Analysis", Interscience Publishers, New York, 1965, p. 231.

114. U. R. Ghatak, N. R. Chatterjee, A. K. Banerjee, J. Chakravatry and R. E. Moore, J. Org. Chem., 12, 3739 (1969).

115. J. E. McMurry, L. C. Blaszczak and M. A. Johnson, Tetrahedron Lett., 1633 (1978).

116. R. Stoermor and B. Kahlert, Chem. Ber., 34, 1812 (1801) quoted in "The Chemistry of the Ether Linkage", S. Patai, Ed., Interscience Publishers, London, 1967, p. 47.

117. B. A. Stoochnoff and N. L. Benoiton, Tetrahedron Lett., 21 (1973).

118. Reference 111, p. 245.

119. A. J. Birch, J. Chem. Soc., 430 (1944).

120. R. Ginsing and A. D. Cross, J. Am. Chem. Soc., 87, 4629 (1965).

121. K. Wisner, I. H. Sanchez, K. S. Atural and S. F. Lee, Can. J. Chem., 55, 1091 (1977).

122. F. F. Albertson, J. Am. Chem. Soc., 72, 2594 (1950).

123. D. Seyferth in "Organic Synthesis", Vol. 39, M. Tishler, Ed., John Wiley and Sons Inc., New York, 1959, p. 10.

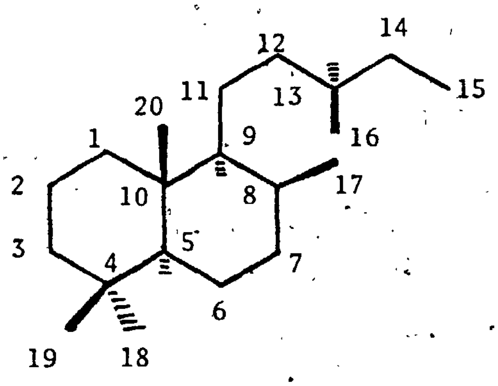
124. B. Pucci, Ph.D. Dissertation, Université de Montpellier, 1976.

125. H. O. House, L. J. Gzuba, M. Gall and H. D. Olmstead, J. Org. Chem., 34, 2324 (1968).

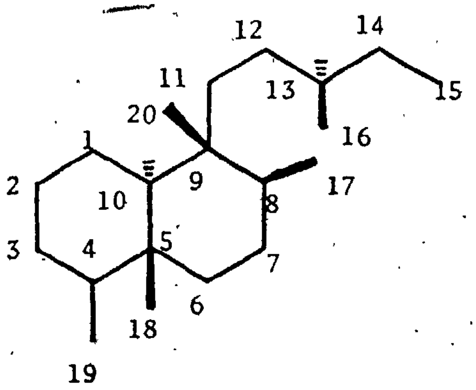
APPENDIX I

The Numbering of Bicyclic Diterpenes

The following numbering system for the bicyclic diterpenes has been used in this thesis.



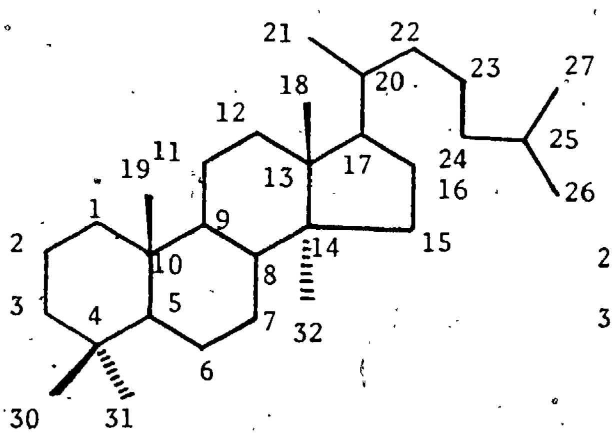
labdane



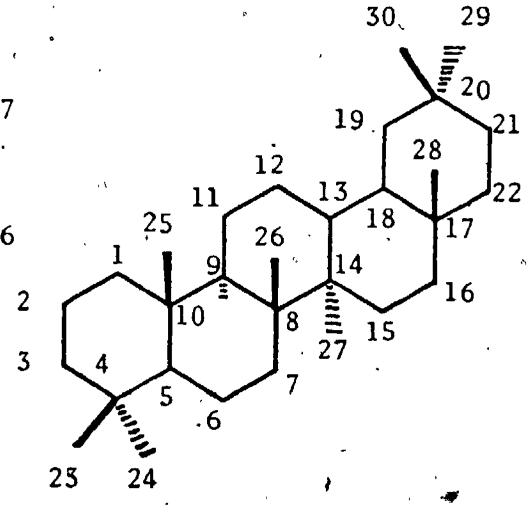
clerodane

APPENDIX II

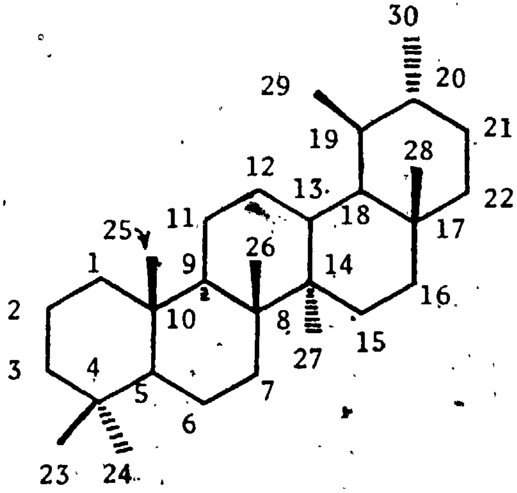
The Systematic Numbering of Typical Triterpene Skeleta



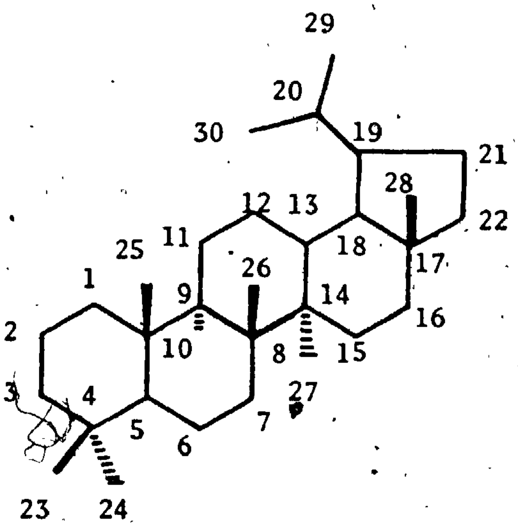
lanostane



oleanane



ursane

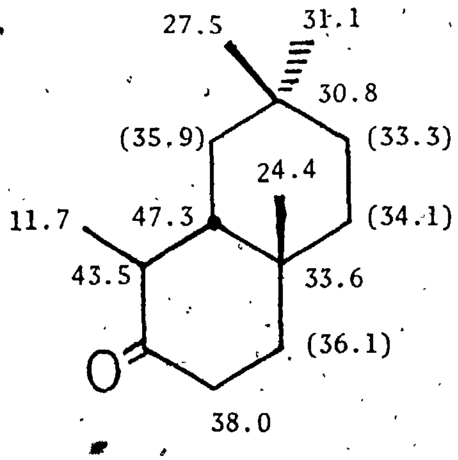


lupane

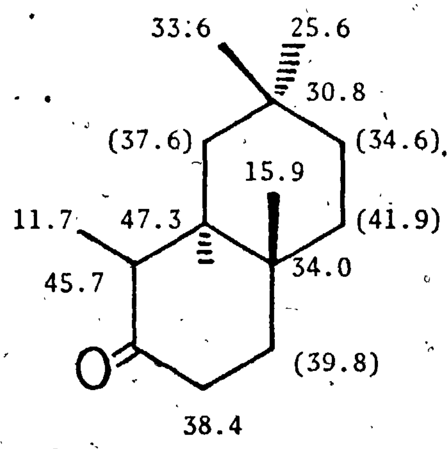
APPENDIX III

^{13}C Chemical Shifts of cis- and trans-2-Octalones, (162) and (163).

The natural abundance ^{13}C NMR spectra data of the octalones are summarized in the following formulae.



(162)



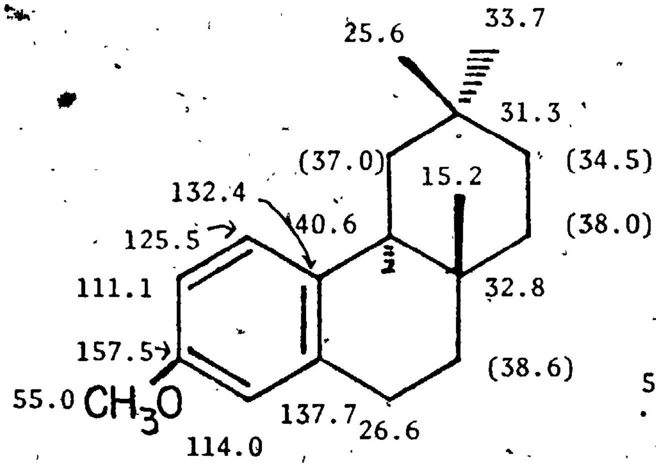
(163)

(a) The spectra were taken in $CDCl_3$ solution.
(b) Chemical shfits are given in ppm relative to internal TMS.
(c) The assignments in parentheses are tentative and may be interchangeble.
(d) The ^{13}C chemical shifts reported above were determined based on the reference shifts for the similar decalones (cf. refernces 92-94).
(e) The spectra were recorded on a Varian XL-100 NMR spectrometer.

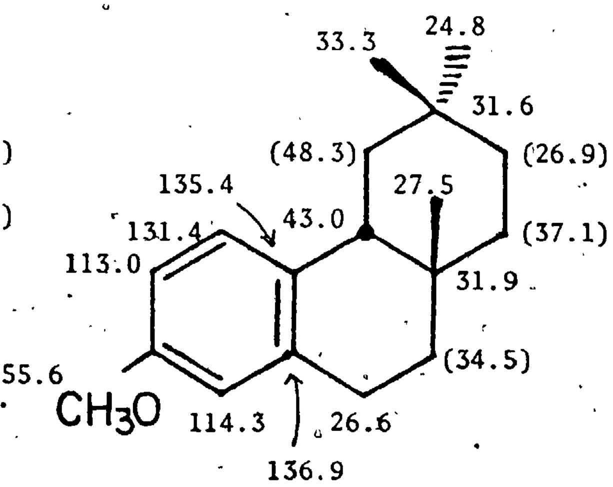
APPENDIX IV

^{13}C Chemical Shifts of cis- and trans-Tricyclic Hydrocarbons, (182) and (218).

The natural abundance ^{13}C NMR spectra data of the hydrocarbons are summarized in the following formulae.



(218)



(182)

(a) Chemical shifts are in ppm relative to internal TMS.

(b) The assignments in parentheses are tentative and may be interchangeble.

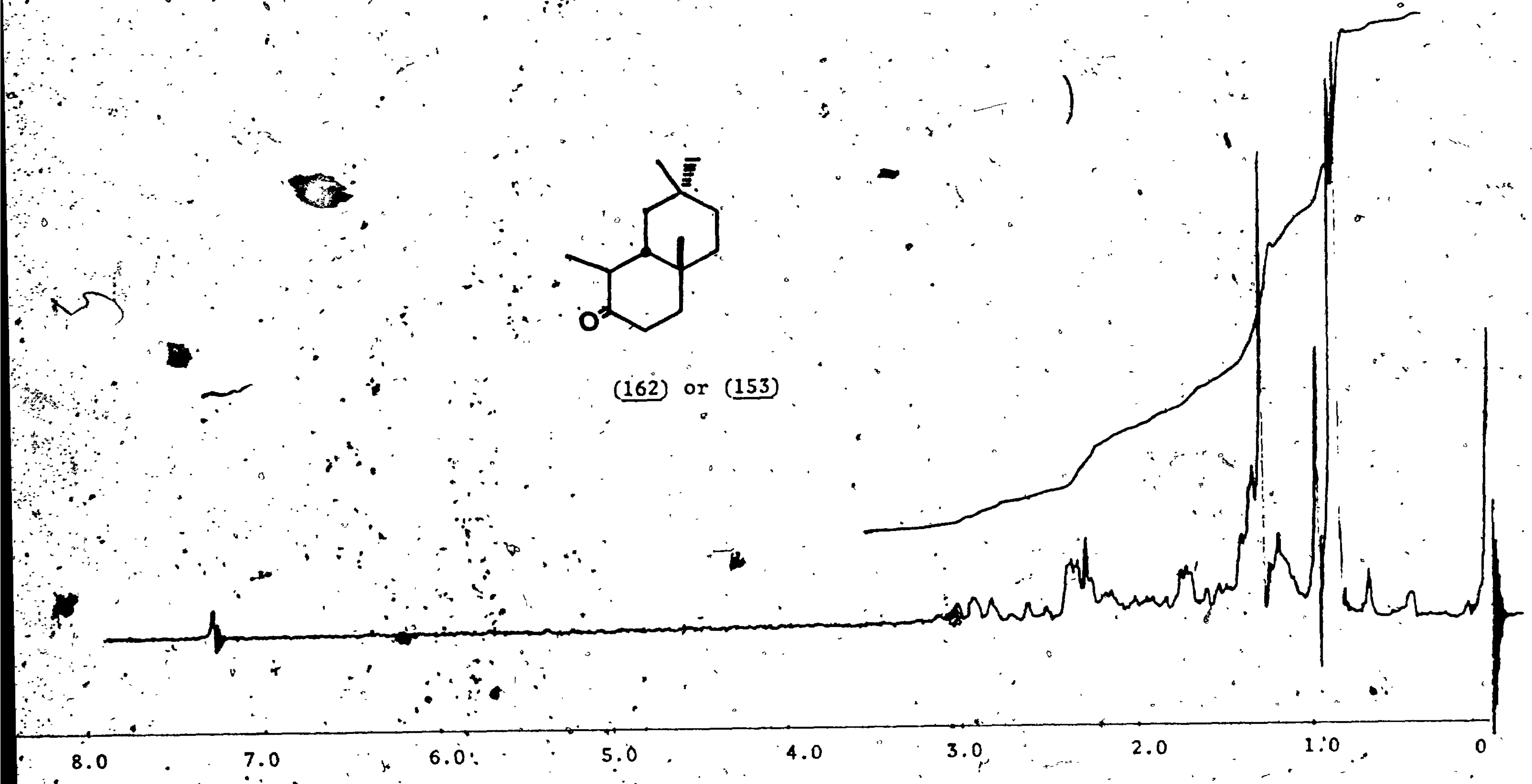
(c) The chemical shifts were determined as previously mentioned (cf. footnote (d), p. 167).

APPENDIX V

Selected ^{1}H NMR (60MHz) Spectra of Synthetic Intermediates

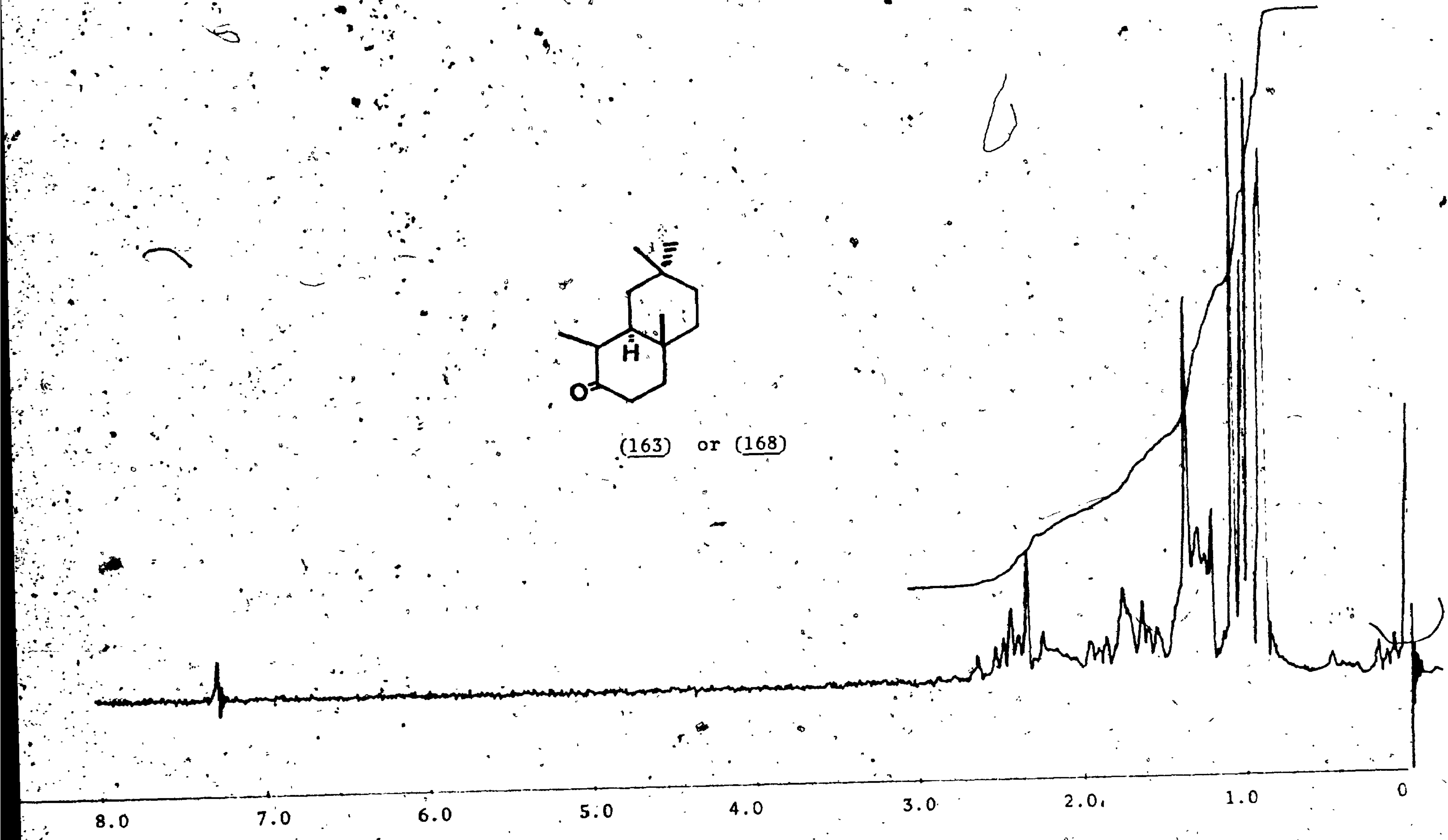
---

* All the spectra were taken in $CDCl_3$ solution.

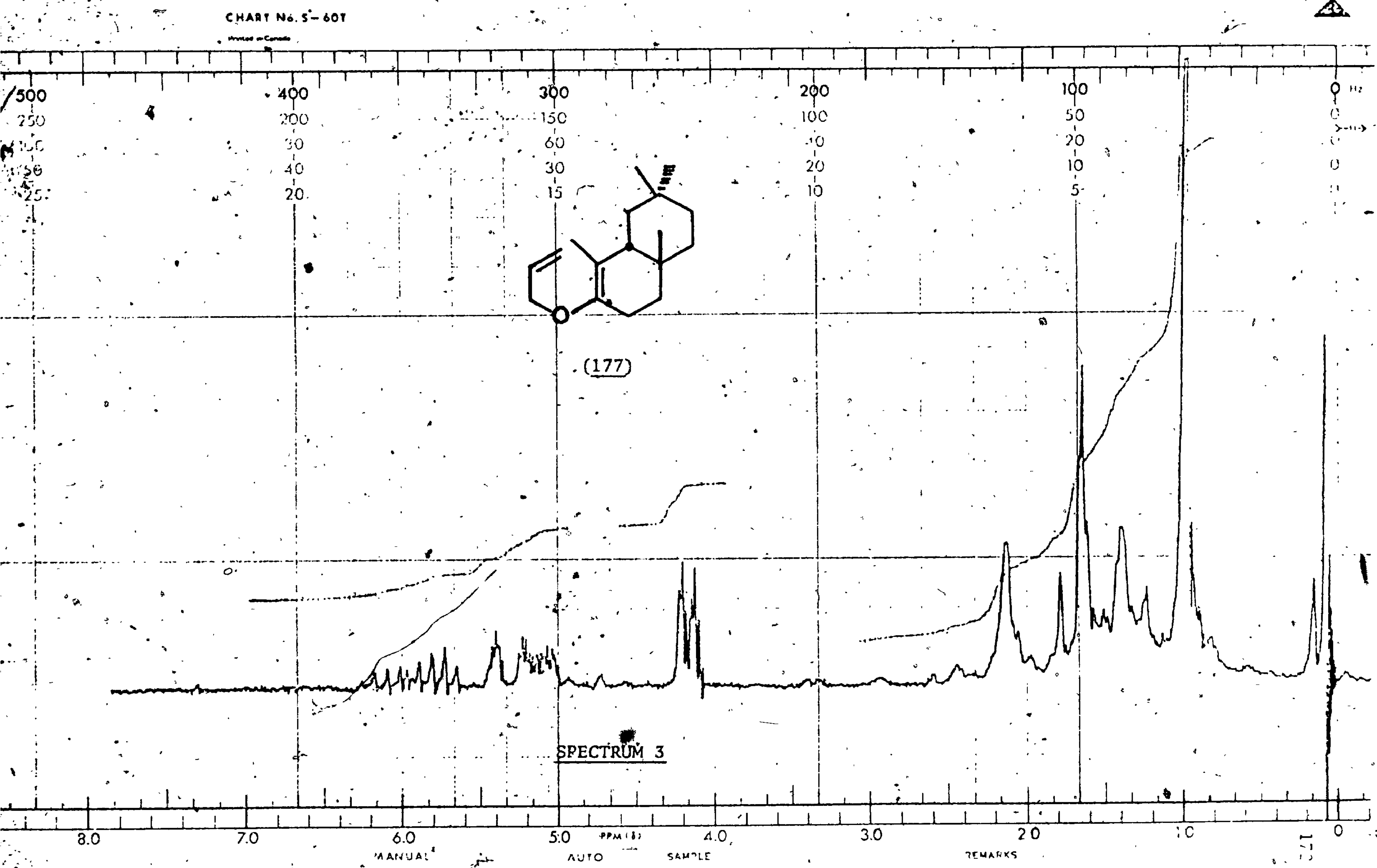


(162) or (153)

SPECTRUM 1

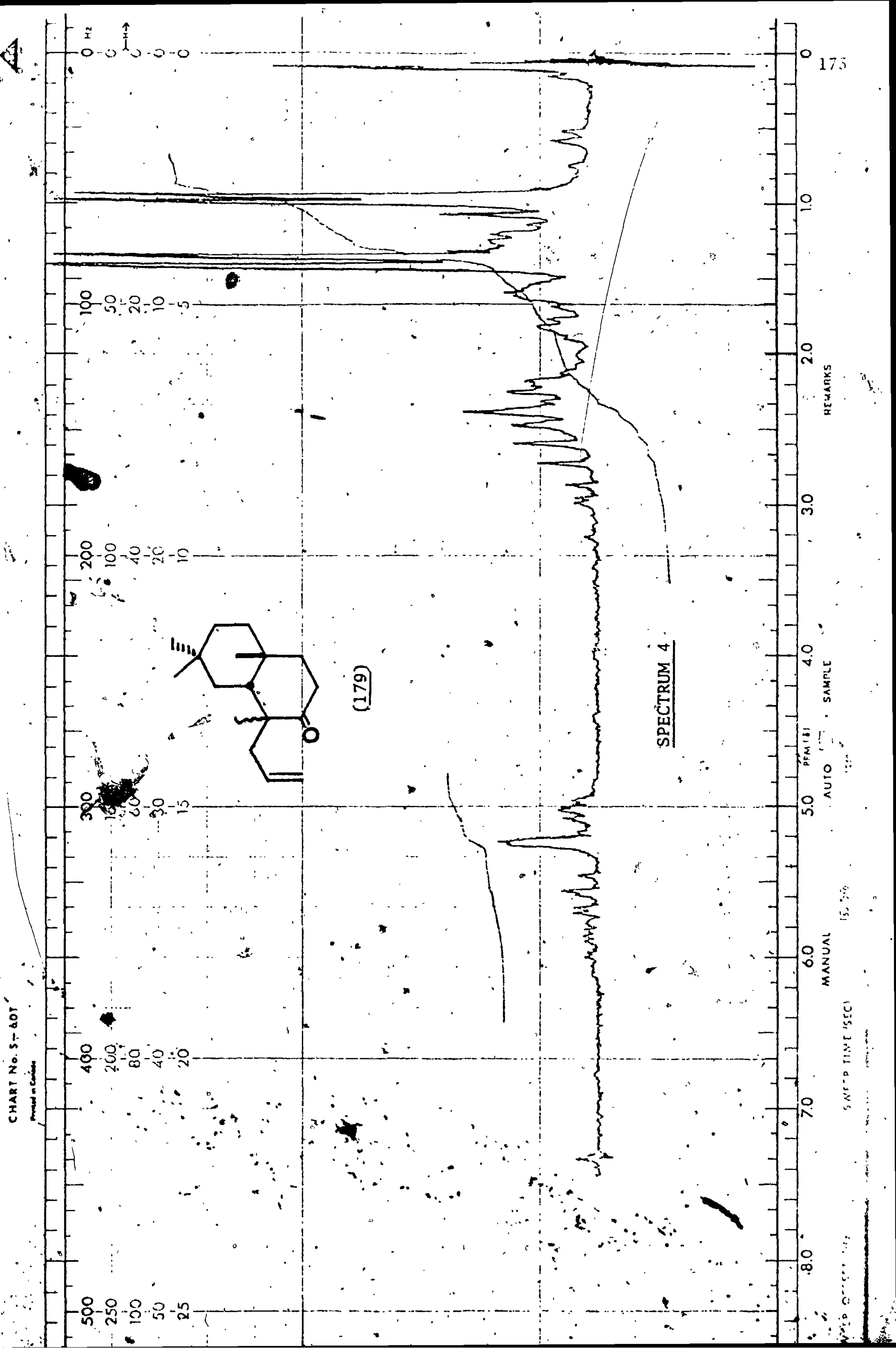


SPECTRUM 2



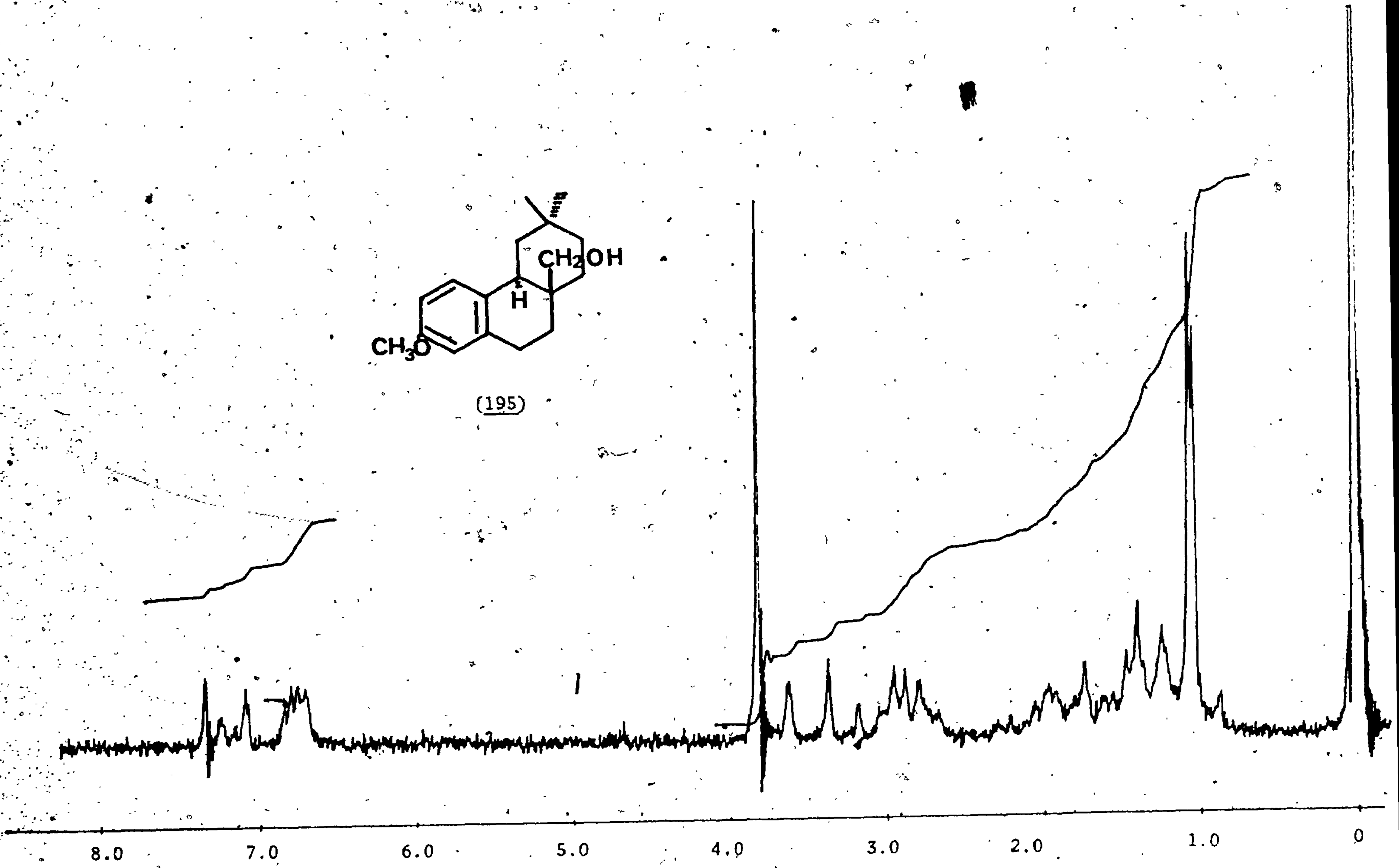
(177)

SPECTRUM 3



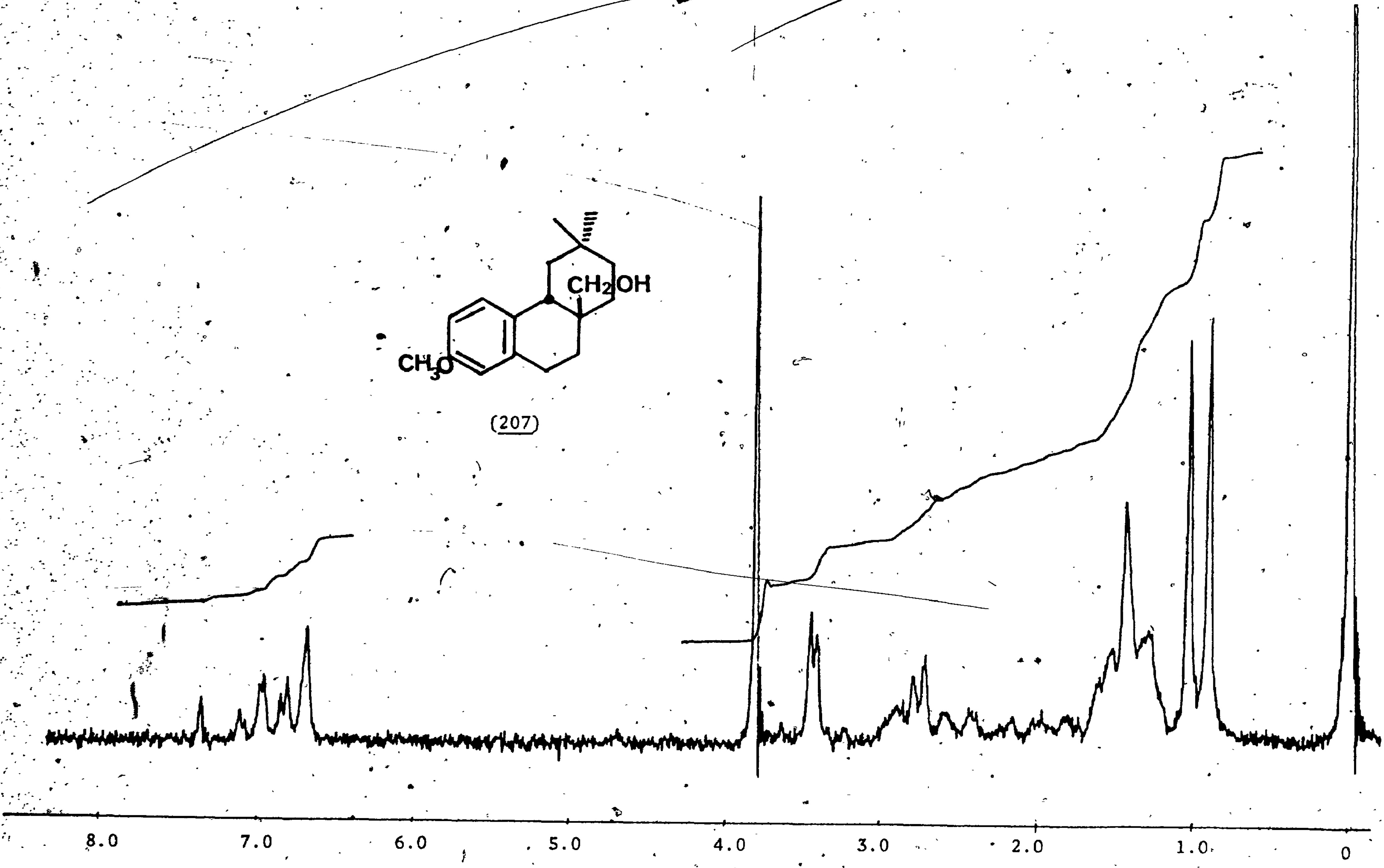
(179)

SPECTRUM 4



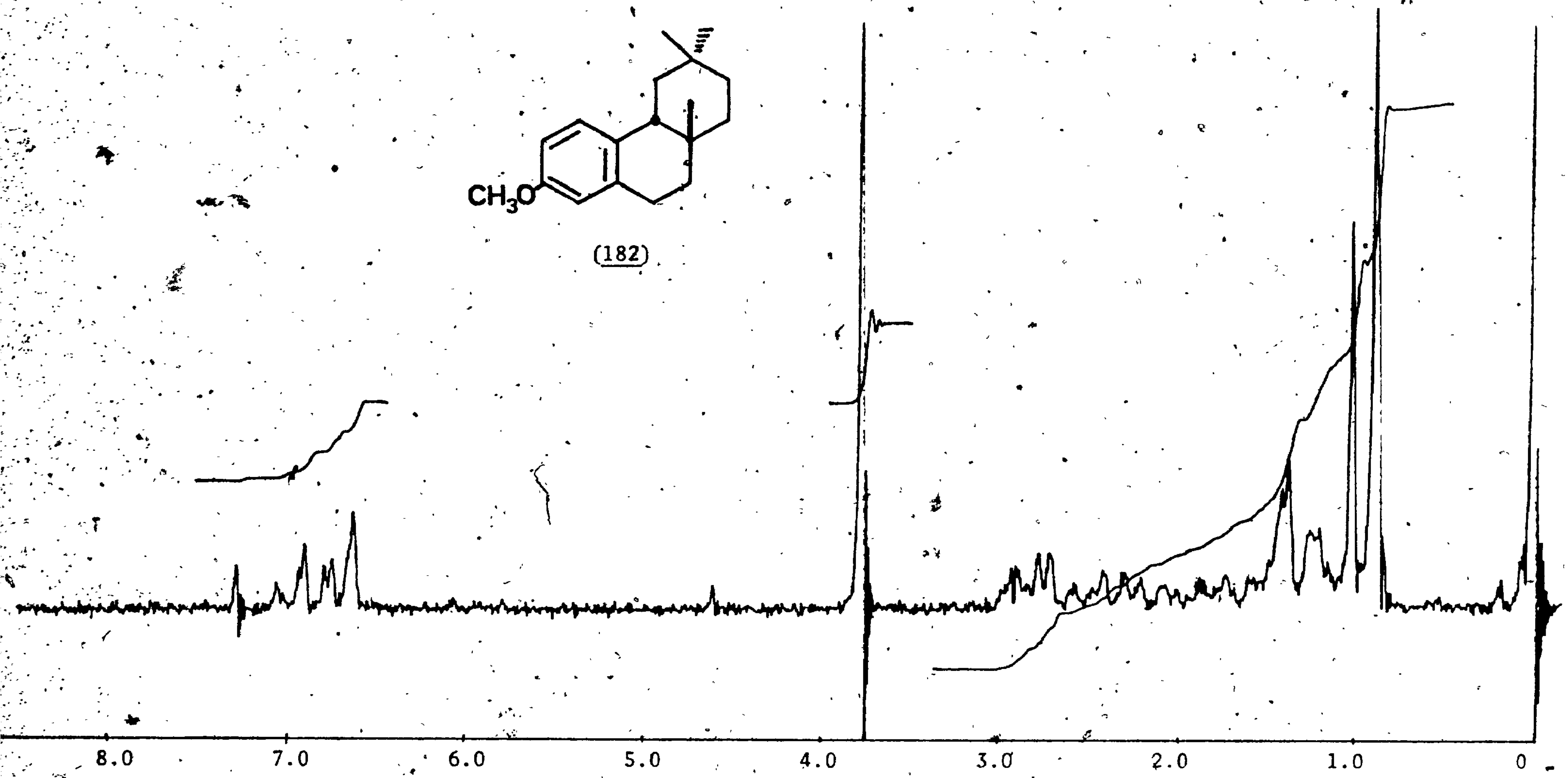
(195)

SPECTRUM 5[illegible]

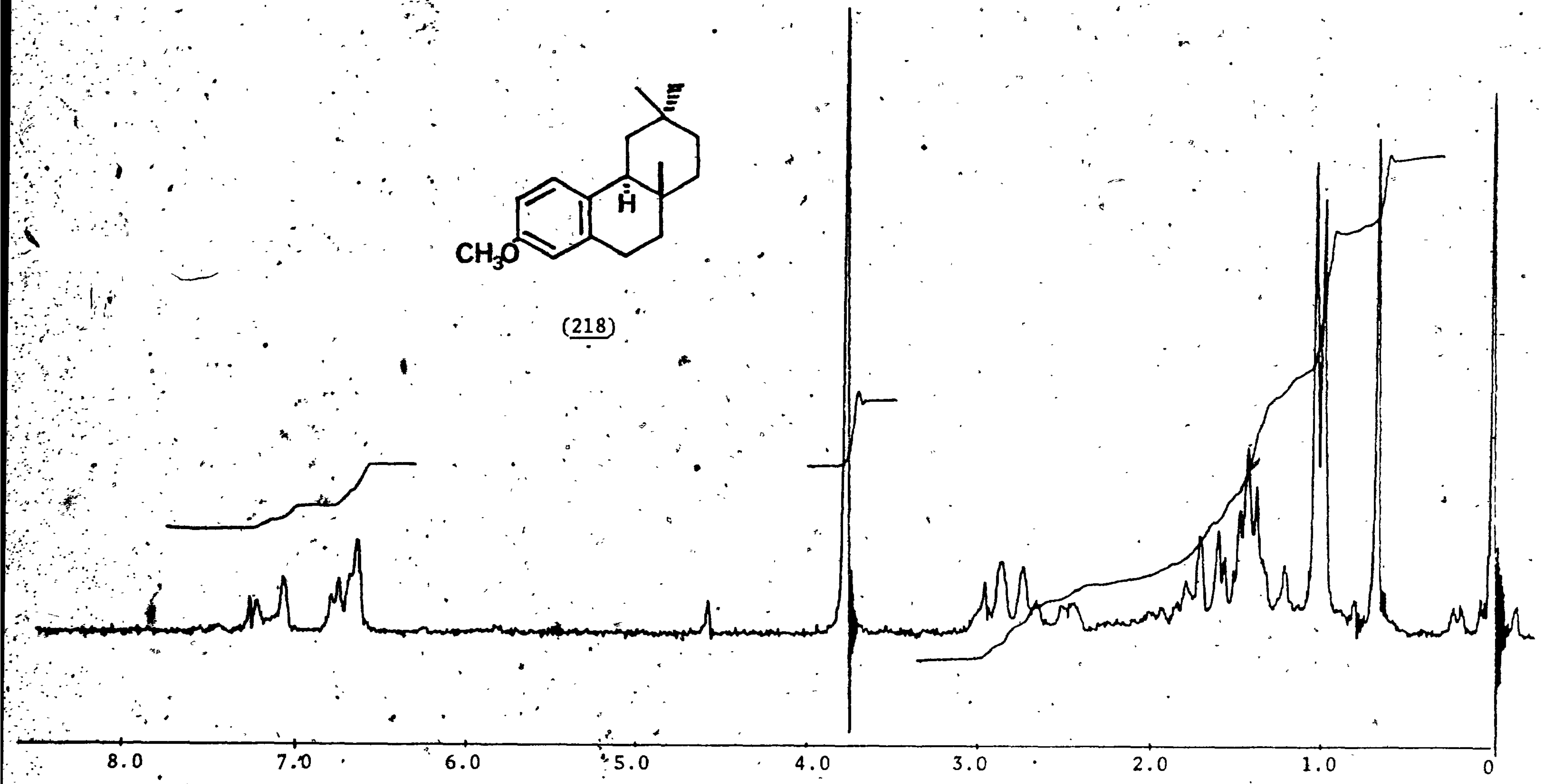


(207)

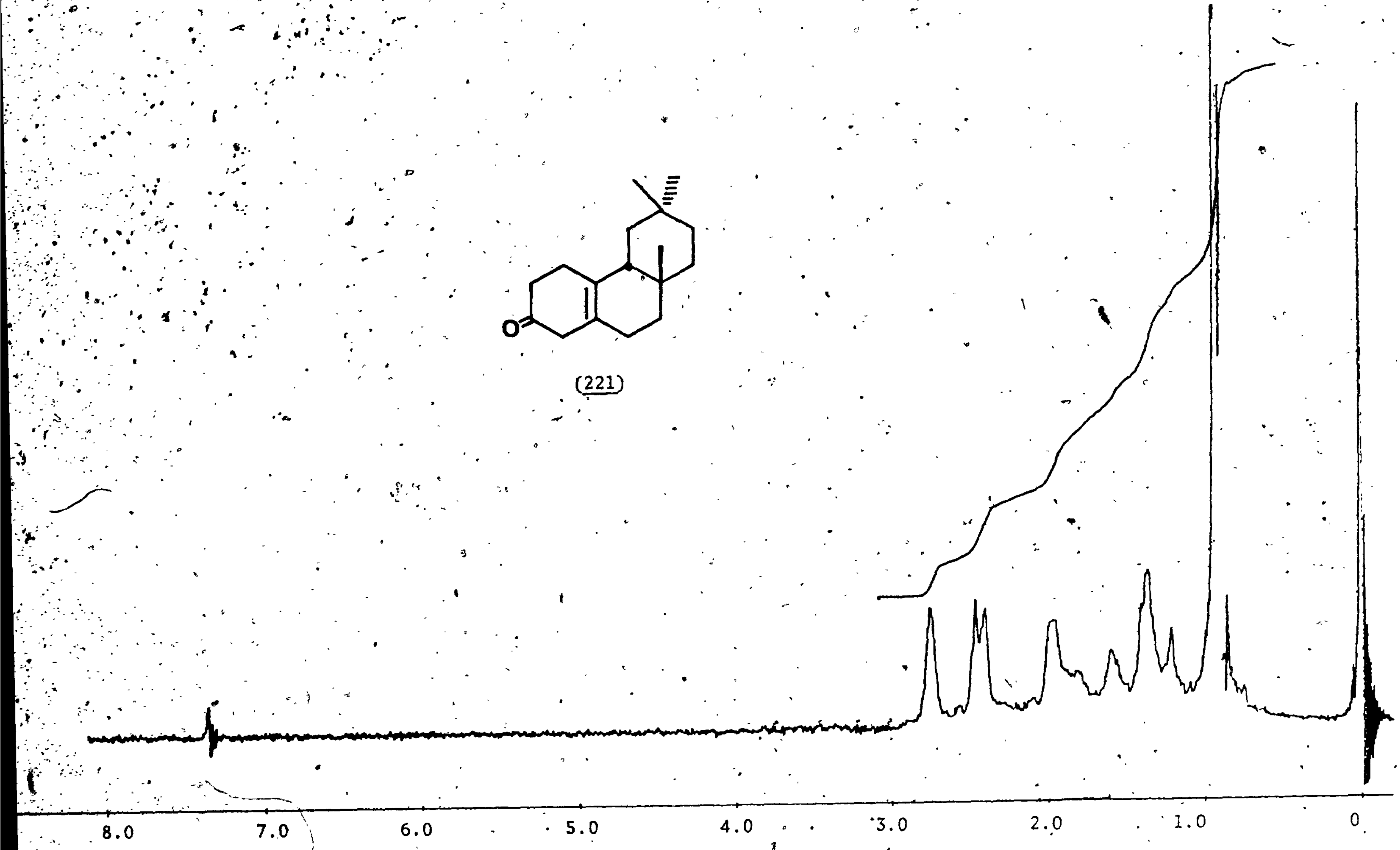
SPECTRUM 6



SPECTRUM 6



SPECTRUM 7



SPECTRUM 8

APPENDIX VI

Selected Mass Spectra of Synthetic Intermediates

CHART 1

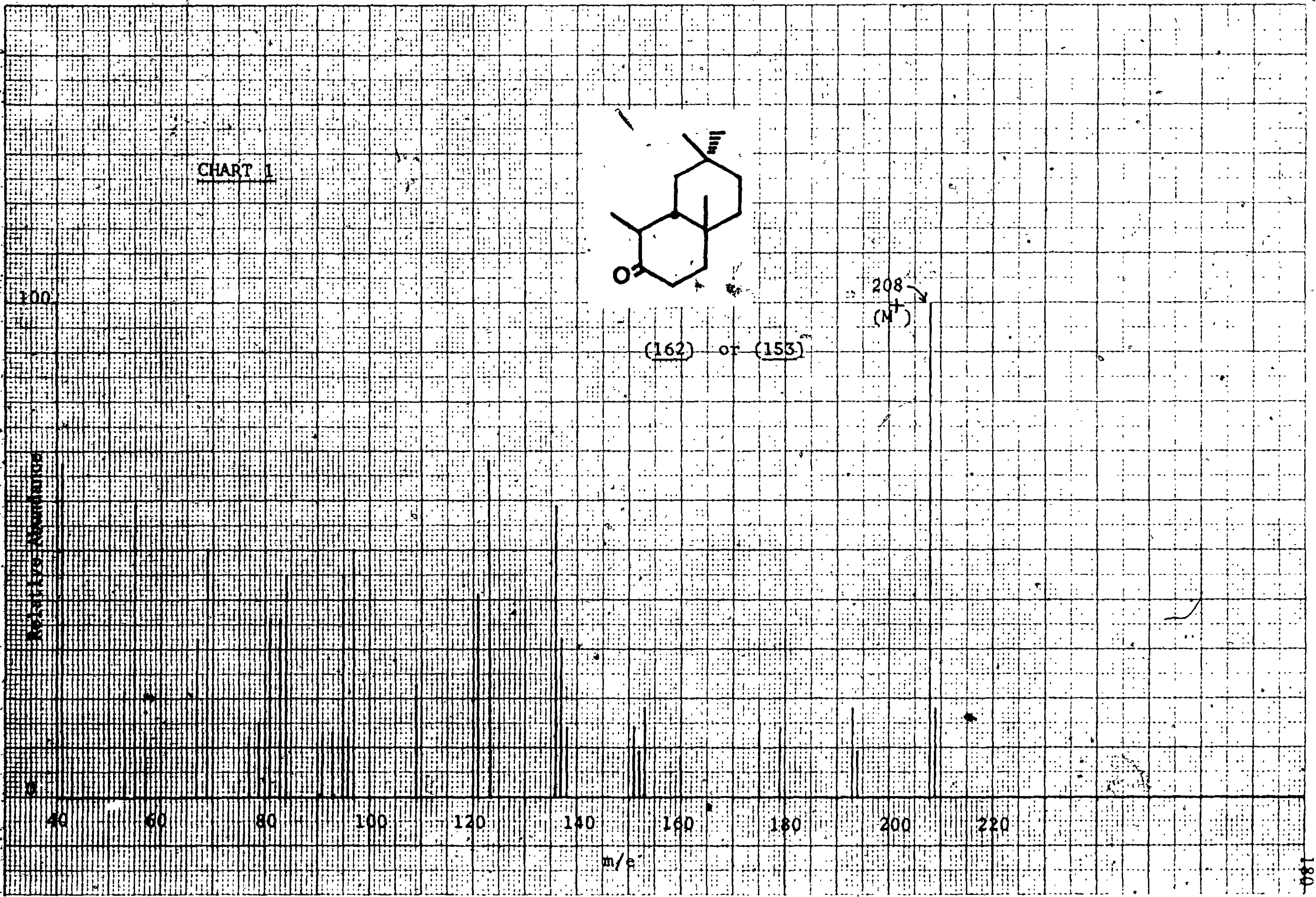
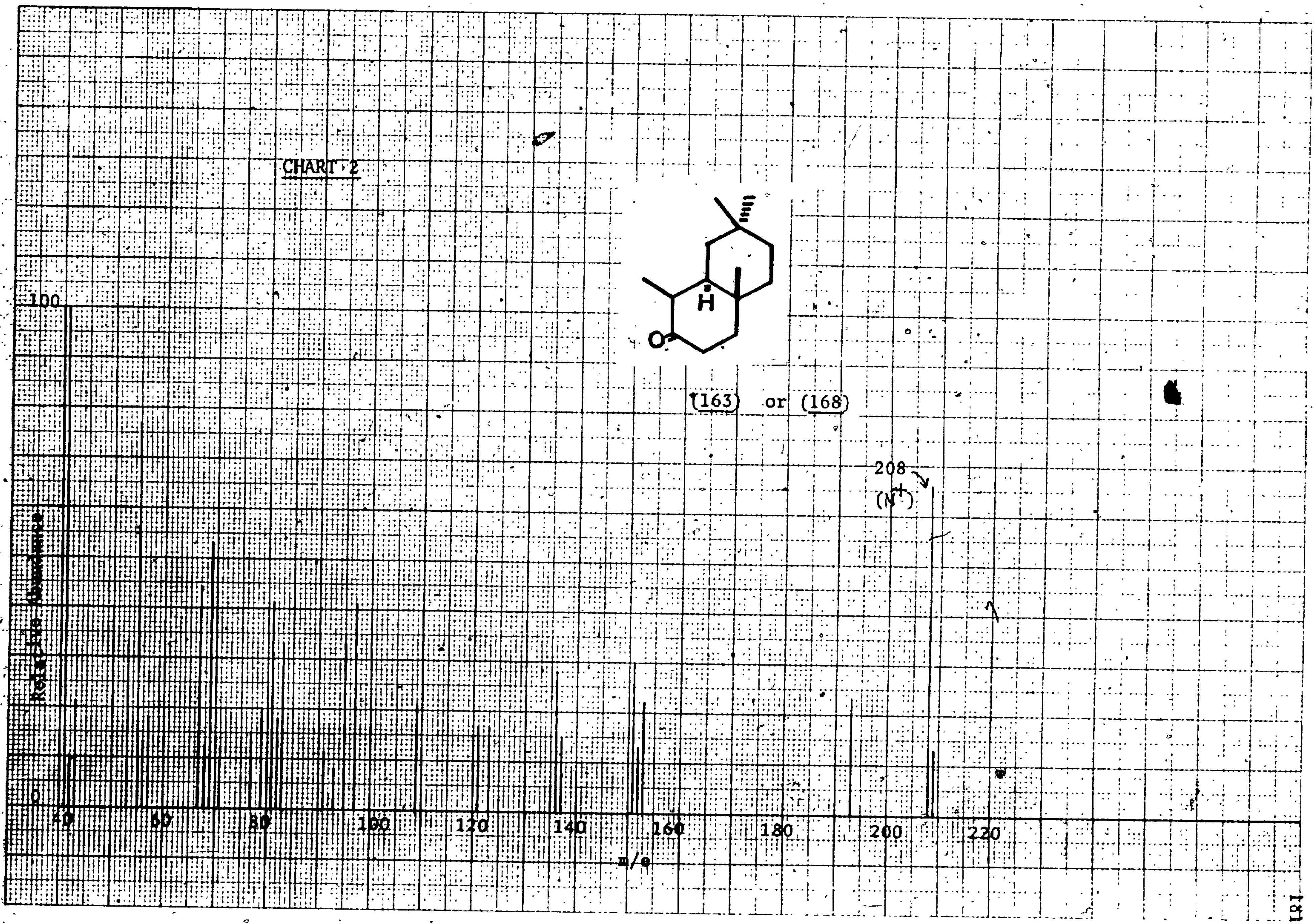
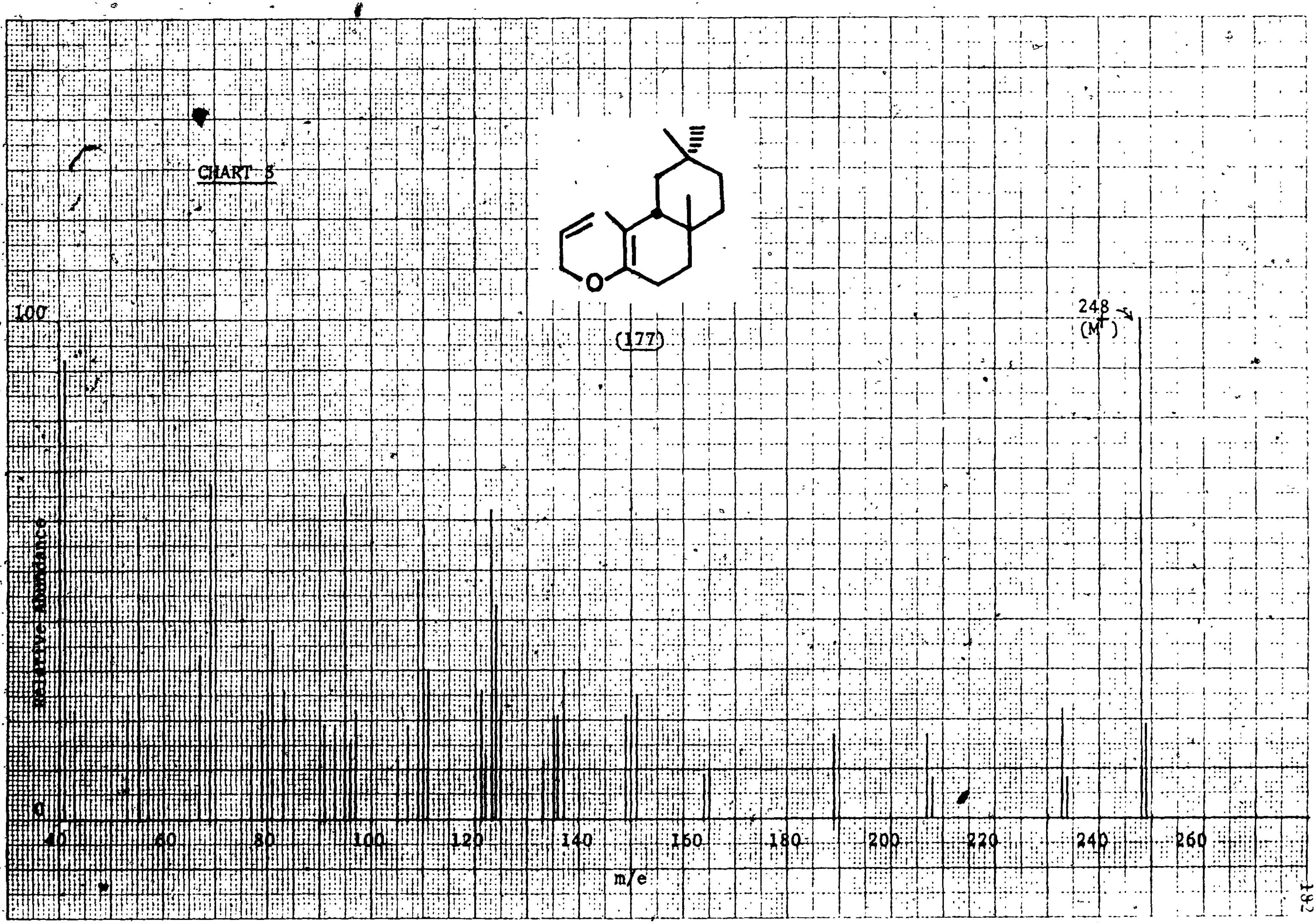

100
Relative Abundance
0
208
(M+)
(162) or (153)
40
60
80
100
120
140
160
180
200
220
m/e

CHART 2



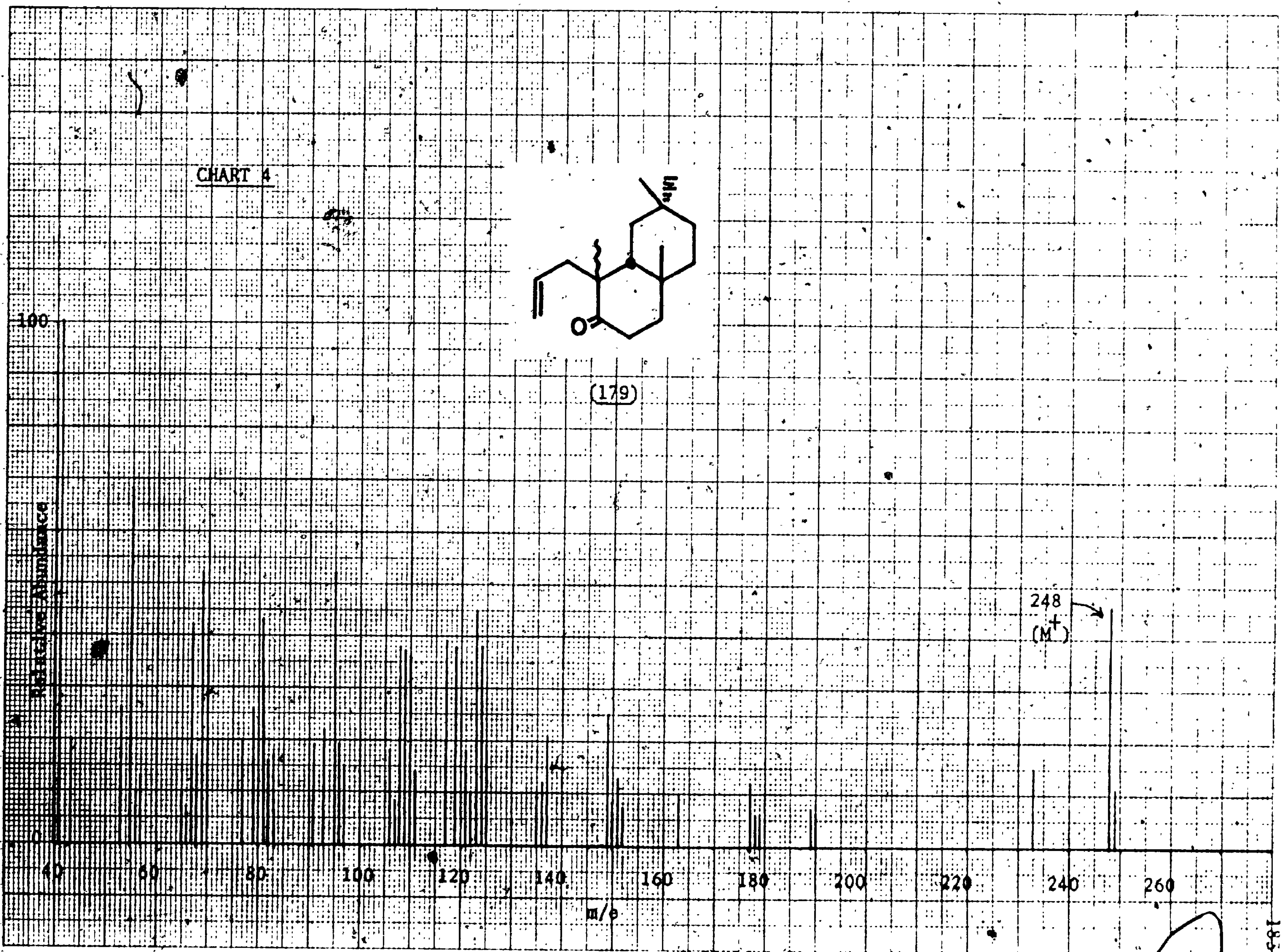
(163) or (168)

CHART 5


100
0
Relative Abundance
248
(M⁺)
40
60
80
100
120
140
160
180
200
220
240
260
m/e

(177)

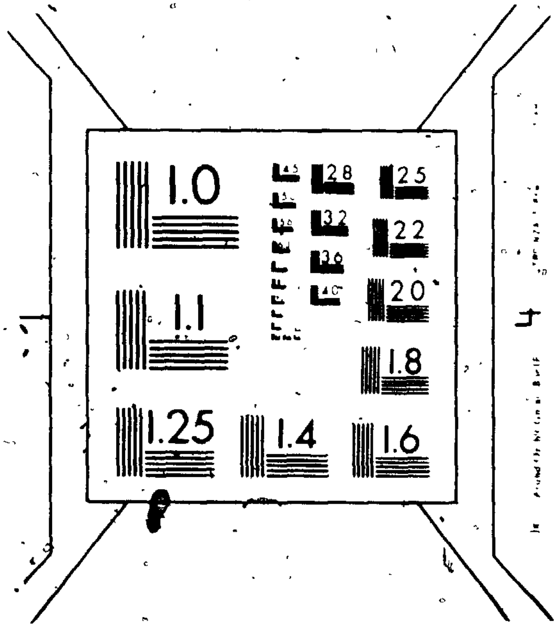
CHART 4



(179)

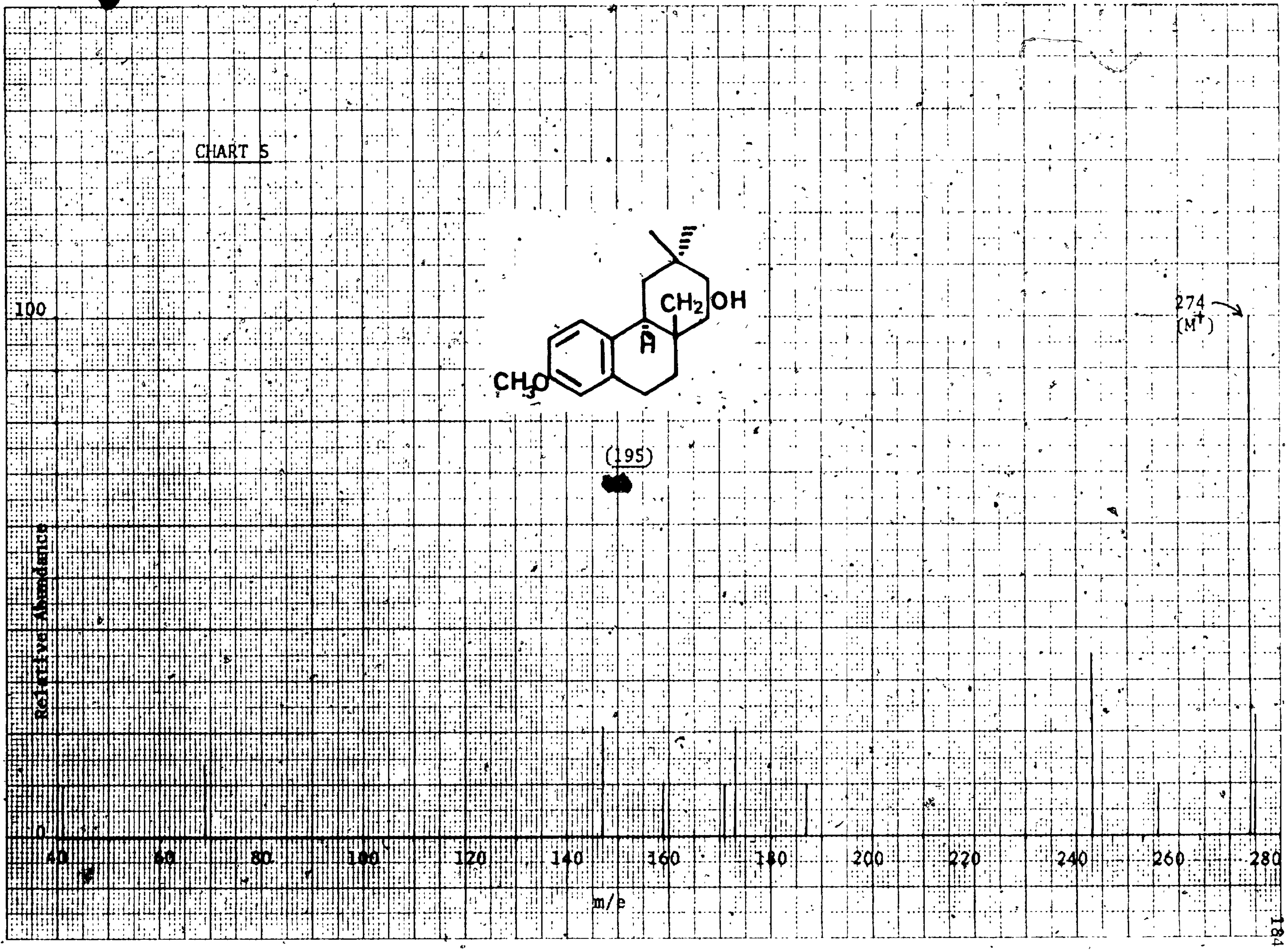
100
0
Relative Abundance
40
60
80
100
120
140
160
180
200
220
240
260
m/e
248
(M+)
O

3 OF/DE 3



ARC - 374

CHART 5


100
0
Relative Abundance
40
60
80
100
120
140
160
180
200
220
240
260
280
m/e
274
(M+)
(195)
CH3O
CH2OH
H

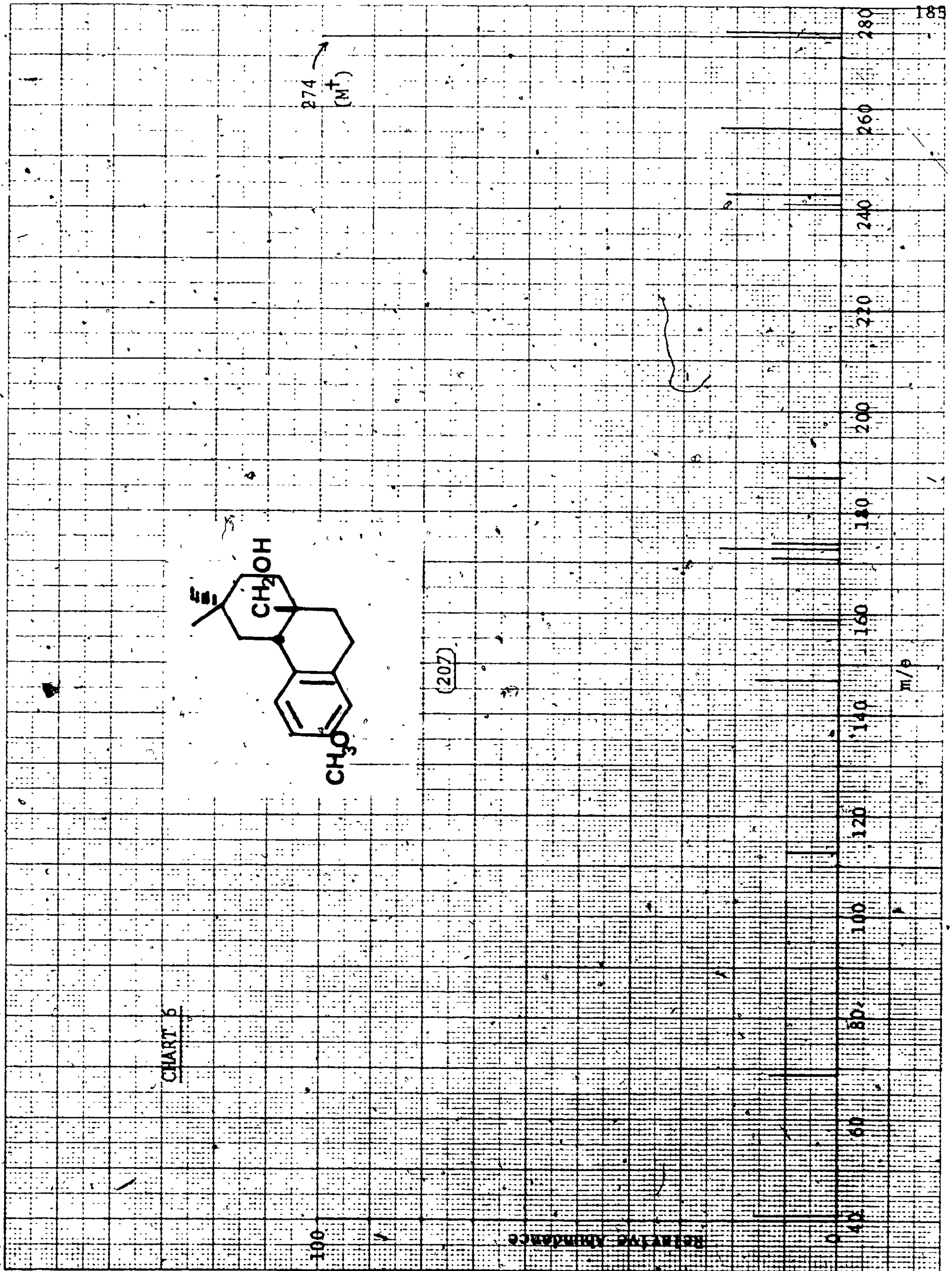
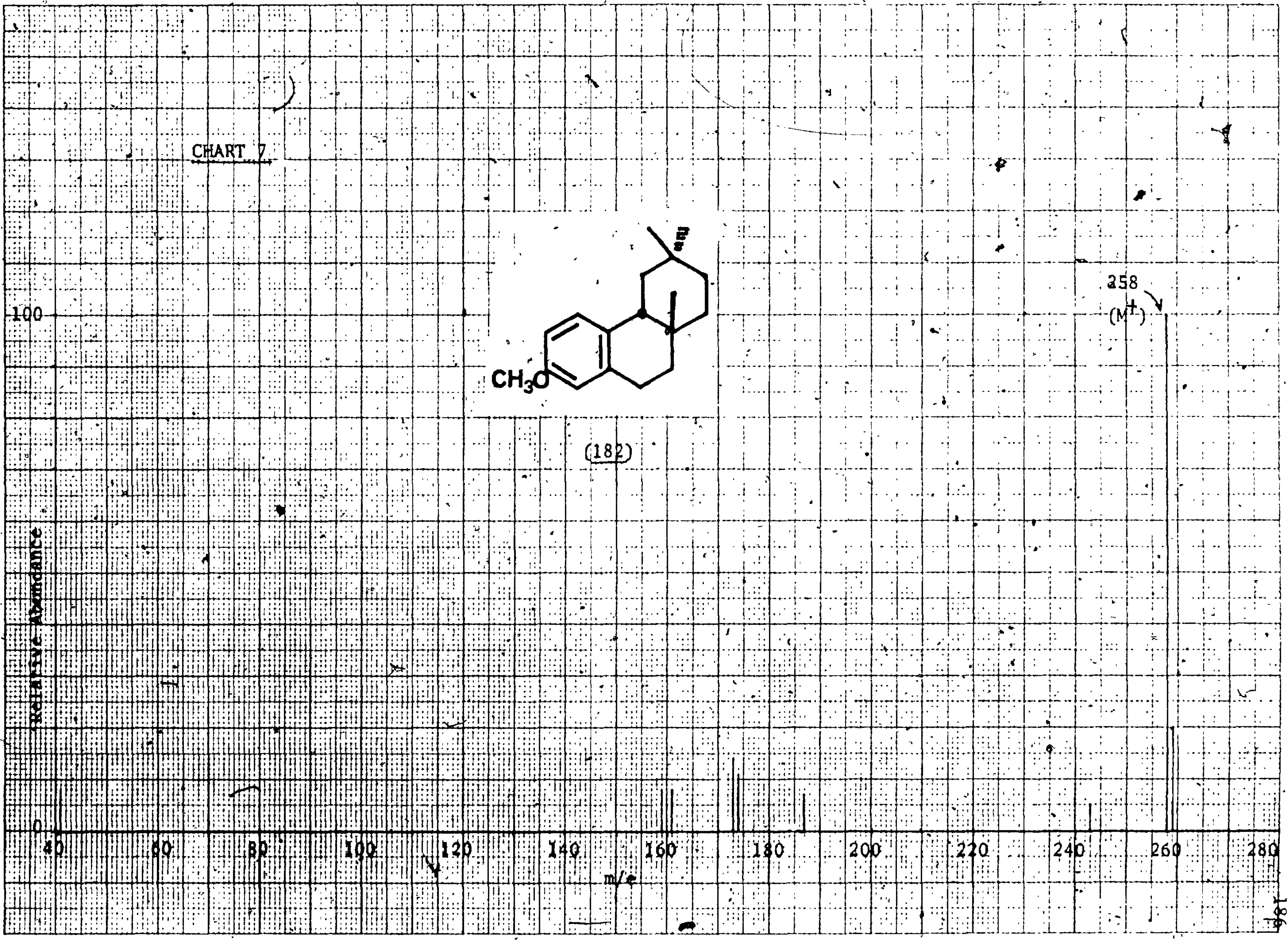


CHART 6

274
(M$^+$)
(207)
CH$_2$OH
CH$_3$O
m/e
40
60
80
100
120
140
160
180
200
220
240
260
280
Relative Abundance
100
0

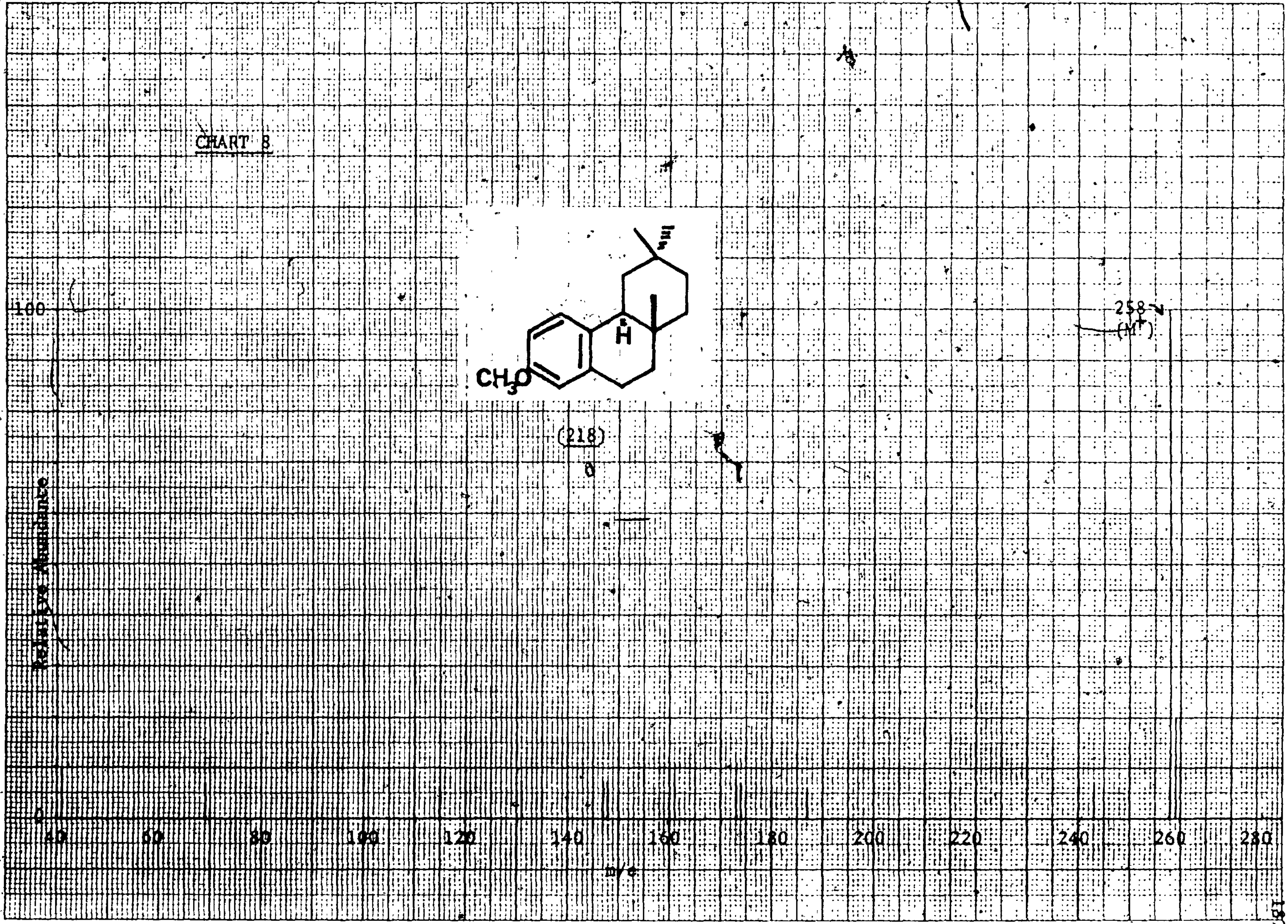
CHART 7



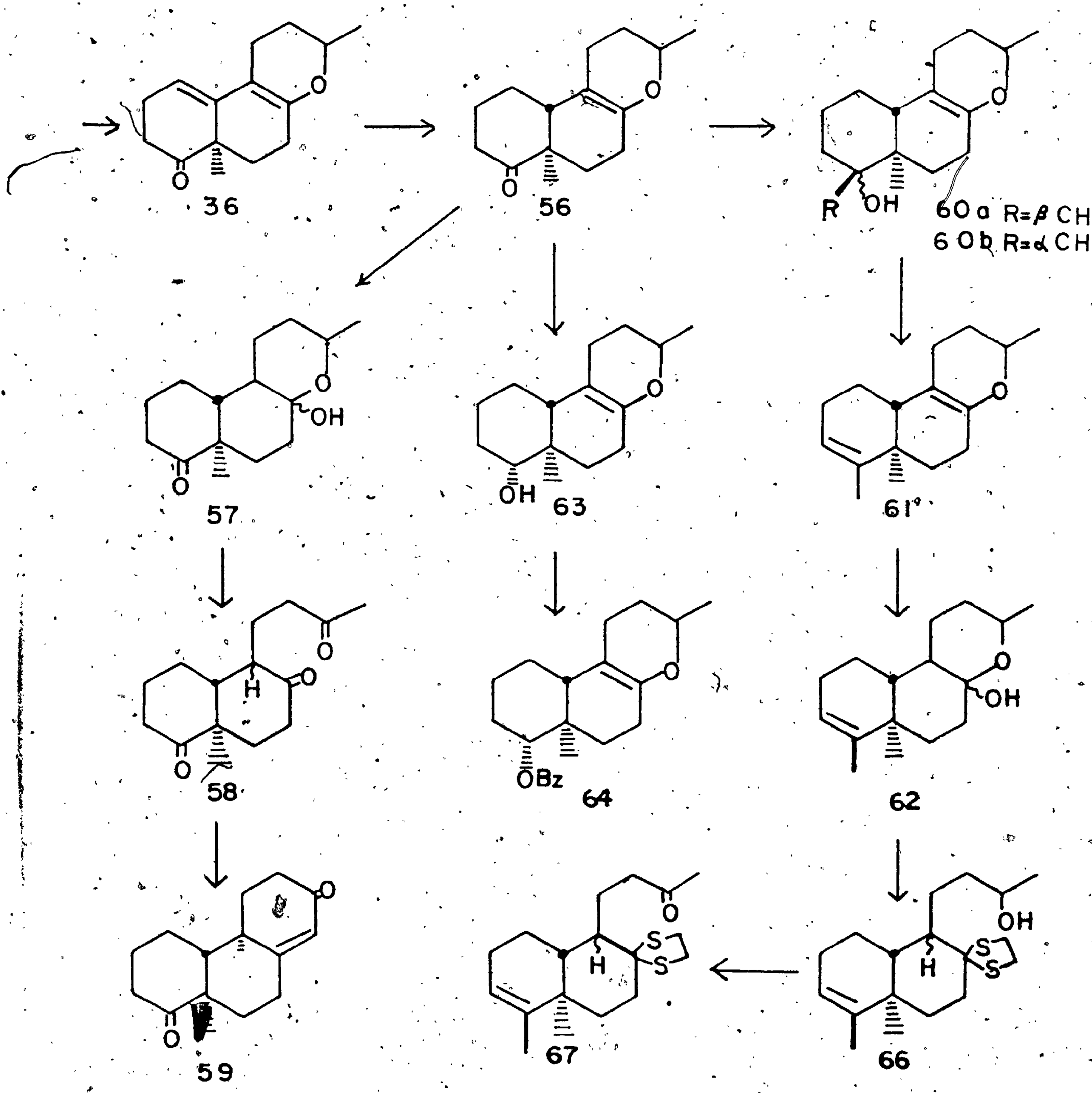
100
0
Relative Abundance
CH$_3$O
258
(M^{+})
40
60
80
100
120
140
160
180
200
220
240
260
280
m/e

(182)

CHART 8

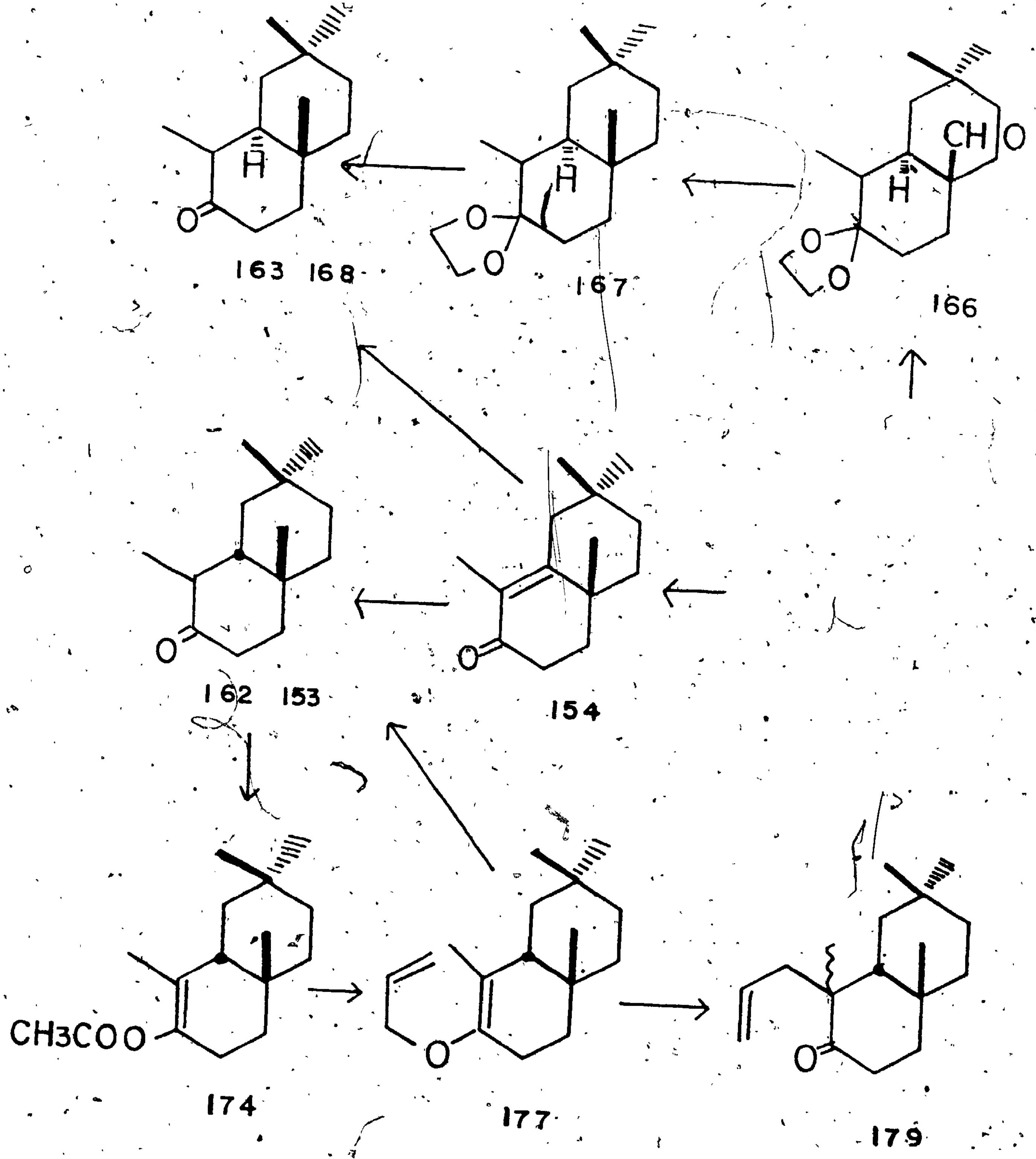

100
0
Relative Abundance
40
60
80
100
120
140
160
180
200
220
240
260
280
m/e
258
(M+)
(218)
CH$_3$O
H

FLOW SHEET I



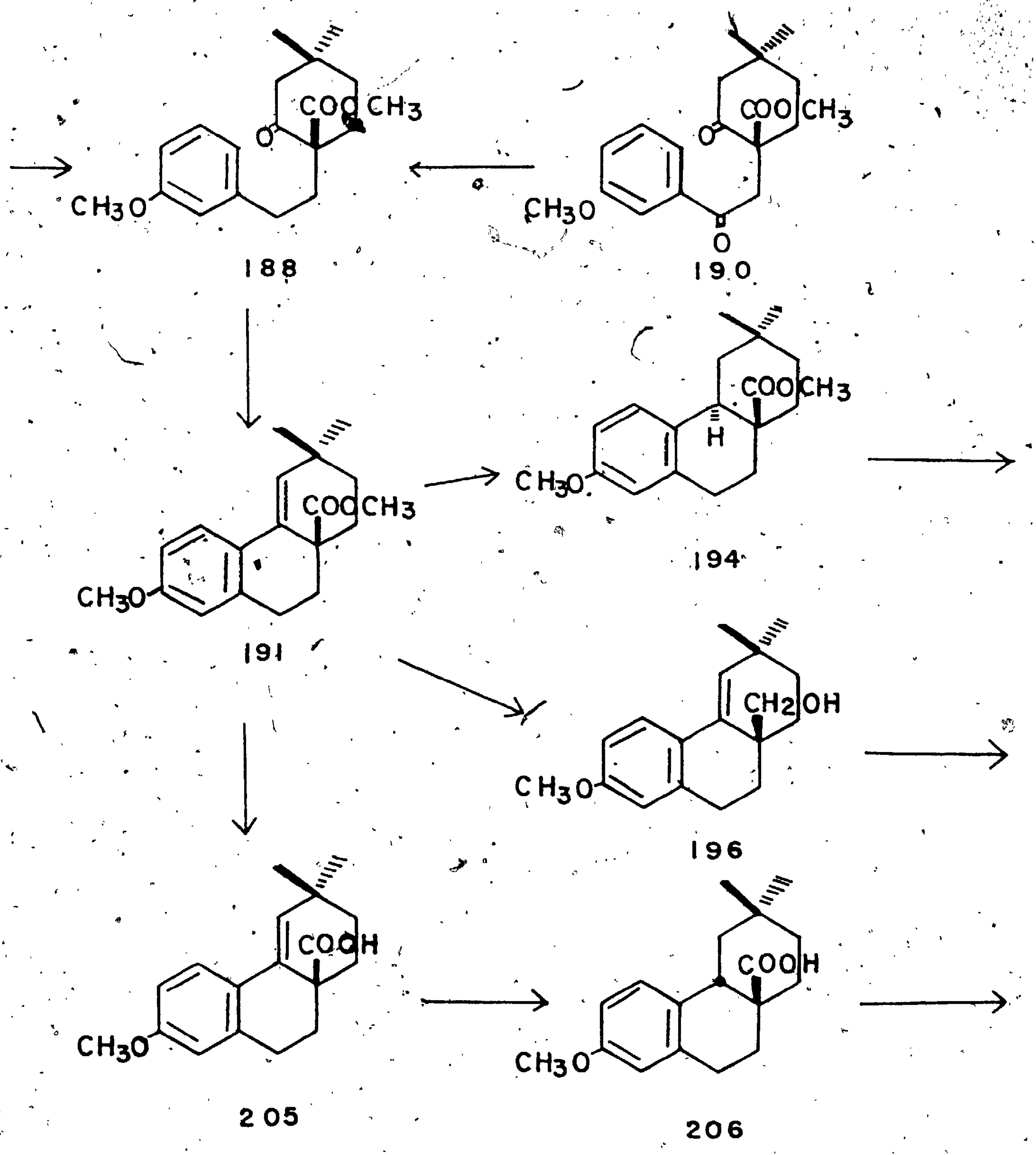
O
O
36
O
O
56
O
R
OH
60a R=β CH
60b R=α CH
O
OH
O
57
O
OH
63
O
61
O
O
H
O
58
O
OBz
64
O
OH
62
O
O
59
O
S
S
H
67
OH
S
S
H
66

FLOW SHEET 2



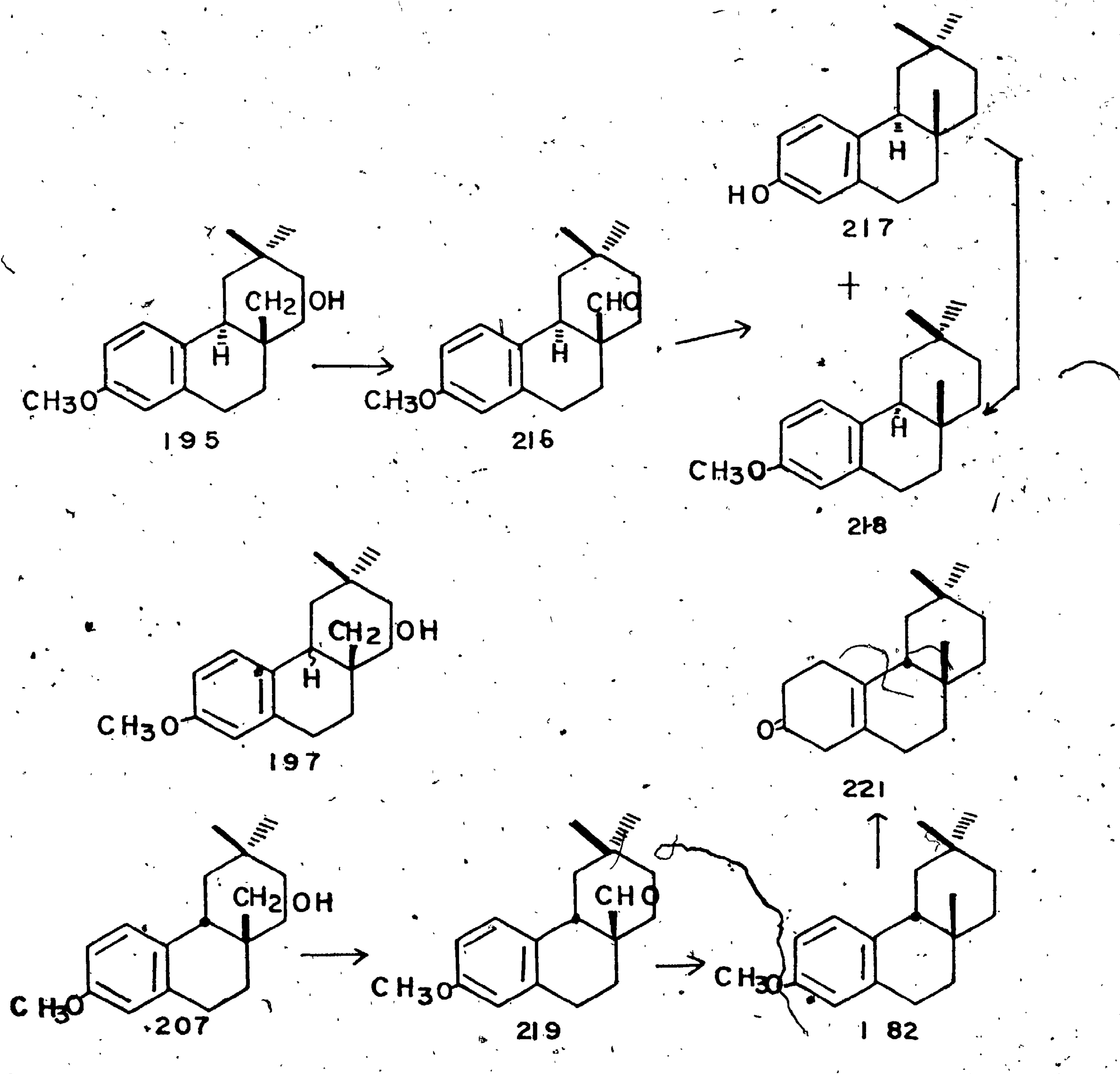
H
O
163 168
H
O
O
167
CHO
H
O
O
166
O
162 153
O
154
CH3COO
174
O
177
O
179

FLOW


COOCH3
CH3O
188
COOCH3
CH3O
O
190
COOCH3
CH3O
191
COOCH3
H
CH3O
194
CH2OH
CH3O
196
COOH
CH3O
205
COOH
CH3O
206

1 of

SHEET 3


HO
217
+
CH2 OH
CH3O
195
CHO
CH3O
216
CH3O
218
CH2 OH
CH3O
197
O
221
CH2 OH
CH3O
207
CHO
CH3O
219
CH3O
182

2 of 2

END

21 08 79

FIN

ARC - 375