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SYNTHETIC APPROACHES TOWARDS PENTACYCLIC TRITERPENES

by

© Richard Farayola Lawuyi B.Sc., M.Sc.

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
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ABSTRACT

An overall approach to the total synthesis of pentacyclic triterpenes such as β -amyrin, friedelin and taraxerol based on the construction of BCDE tetracyclic intermediates is reported.

During the course of our investigation a simple reagent, diethylaluminum ethoxide was utilised for the first time for the intramolecular aldol-cyclisation of the diastereomeric diketones of 2-keto-1-methyl-1-(2-(3-keto-4,4-trimethylcyclohexyl ethyl)-6-methoxy-3,4-dihydronaphthalene 99a and 99b and 1 α -[2-(3'-keto-1',4'4-trimethylcyclohexyl)-ethyl] 8-hydroxy, 1 β , 4 $\alpha\beta$, 8 $\alpha\beta$ -trimethyl-dodecahydro-phenanthr-10(10a), 4b(5)-diene-2-one 85a (and 85b). With this reagent tetracyclic compounds 8-methoxy-3,3,10 $\beta\alpha$, 12 $\alpha\beta$ -tetramethyl-1,2, 5,6,10 β ,11,12,12 α ,octahydro-3H-chrysen-4-one 100a and 8-methoxy-3,3,10 $\beta\beta$, 12 $\alpha\beta$ -tetramethyl-1,2,5,6,10 β ,11,12,12 α -octahydro-(3H)-chrysen-4-one 100b and the pentacyclic 2,2,4 α ,12 α ,12 β ,14 α -hexamethyl-9-hydroxy-1,2,3,4,4 α ,5,6,6 α ,8,8 α ,9,10,11,12 β ,13,14,1-hexa decahydrop-1-picenone 80 have been synthesized in high yield.

While the conjugate methylation of 8-methoxy-3,3-10 $\beta\beta$, 12 $\alpha\beta$ -tetramethyl-1,2,5,6,10 β ,11,12,12 α -octahydro-(3H)-chrysen-4-one, 100b a precursor of friedelin is still under investigation, the synthesis of 8-methoxy-3,3,10 $\beta\alpha$,12 $\alpha\beta$ -tetramethyl-1,2,4,6,10 β ,11,12,12 α -octahydro-(3H)-chrysen-4-ol 162 a precursor of β -amyrin containing three asymmetric centers in the correct stereochemistry, was successful.

A variety of investigations using the tetracyclic compounds 100a and 100b are reported.

To Tinu, Niyi, and Bisi and the
memory of my mum Efunleye Agbeke, and
Dad, Olawuyi Amao.

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INTRODUCTION

The triterpenes constitute that homogeneous group of natural products containing thirty carbon atoms divisible into isoprene units - (polyprenoids). Triterpenes may be classified as acyclic such as squalene, or cyclic. The cyclic triterpenes are almost invariably pentacyclic but the group also includes a small number of tetracyclic secondary alcohols and derived acids² such as lanosterol.

The pentacyclic triterpenes are ubiquitous in nature, mainly in the plant kingdom including fungi where they have been found to occur in all parts of the plant, in resins and plant saps, either in the free state or in combination with sugars and acids as glycosides and esters respectively.² They also occur to some extent in the animal kingdom, in the liver oils of sharks³, yeasts⁴ and the Nigerian crude petroleum extracts.⁵

While no biological activity has been established for a large number of pentacyclic triterpenes, some such as acetylaleuritolic acid isolated from the seeds of Phytolacca americana and Jatropha macrorrhiza has been shown to have substantial antitumour activity.⁶

(A) The Biogenetic Isoprene Rule⁷

Considerable progress has been made during the last sixty years in the chemistry of pentacyclic triterpenes. It was largely the intensive work of several groups like Ruzicka⁸ and Jeger, Barton⁹, Cornforth¹⁰, Popjak¹¹, Arigoni¹², Robinson¹³, Stork¹⁴, Bloch¹⁵,

Acetylaleuritolic acid

Woodward¹⁶ and their collaborators that laid the foundations for our understanding of the chemistry of all terpenes.

Although most of the structural work and all the impressive achievements therefrom must be associated with Leopold Ruzicka^{7,8}, the polyisoprenic character of triterpenes resulting in obvious regularities of structure had also been studied by Bloch¹⁵ (1955) Channon¹⁷ (1926) and Robinson¹³ (1934). Ruzicka's findings culminated in the biogenetic 'isoprene rule' of 1953.

According to the biogenetic 'isoprene rule'²⁰, the basic

building block of the terpenes is isopentenyl pyrophosphate. Two molecules of isopentenyl pyrophosphate condense in a head to tail fashion to form geranyl pyrophosphate; multiple linkings of isopentenyl pyrophosphate lead to C_{10} , C_{15} and C_{20} intermediates which may further dimerize in a tail to tail fashion to produce precursors of C_{20} , C_{30} and C_{40} terpenes. The general precursor of triterpenes is an all trans-squalene^{7,8} and has been isolated from such varied natural sources as hair oil, human ear wax and fungi. The biogenetic relationship between squalene and pentacyclic triterpenes is also an extension of the 'isoprene rule' (Fig. 1). All known pentacyclic triterpenes can be derived from different modes of conformations of an all trans-squalene molecule^{8,14,18,19} followed by concerted 1,2-shifts of hydrides or methyl groups in a stereoelectronically controlled anti-parallel, trans-diaxial orientations. The mechanism for the conversion of squalene epoxide to the polycyclic systems was proposed by Stork¹⁴ and Eschenmoser⁸ and many attempts have been made to provide experimental basis for the cyclization.

As shown in Fig. 1 friedelin thus represents the final stage of the transformation of the chair-chair-chair-boat carbonium ion while germanicol, β -amyrin (oleanene), taraxerol, multiflorenol, and glutinone (alnusenone) represent pauses along the complex pathway of rearrangements.

B. Structure Elucidation of Pentacyclic Triterpenes

Our knowledge of the structure of many pentacyclic triterpenes

4

Cyclization of Squalene-2-3-epoxide
through the chair-chair-chair-boat-unfolded

Sev. Steps

3a

cont'd p. 5

3a

-H17 α

HO

4a

Germanicol

H17-21 α

H13 β -17 α

-H12

HO

5

β -Amyrin

CH₃14 α -13 α

-H15

HO

6

Taraxerol

Fig. 1

CHART 1. A SKELETAL CORRELATION OF MAIN PENTACYCLIC TRITERPENES.

has again been associated with Leopold Ruzicka and his collaborators. The problems often encountered were considerable, arising from the superfluity of the contiguous methyl groups and multiring systems. Functional groups are often situated at the remote end of the molecule and when not, are hindered and unreactive.

The rapid development of physical techniques, some automated and computerized, during the last two decades both in instrumentation and interpretation has revolutionized the older approaches to structure determination. Growth in this area has thus been explosive as a result of new advances in isolation techniques, physico-chemical measurements, new concepts and synthetic methods so much so, that two of the most intriguing and time-consuming problems in organic chemistry, structure determination and total synthesis, have become less tedious.

Notable Routes to the Synthesis of Pentacyclic Triterpenes Skeletons

A synthetic chemist, confronted with a pentacyclic molecule with no molecular symmetry, a plethora of angular methyl groups

Alnusenone

and difficult stereochemical characteristics, is definitely faced with a formidable, talent-demanding synthetic challenge. Some elegant synthetic successes have been scored as reviewed by ApSimon and Hooper in 1973.²¹

The reduced picene-type pentacyclic triterpenes contain seven or more contiguous asymmetric centres and eight or more methyl groups with some at the ring junctions. A preliminary evaluation reveals that the construction of the pentacyclic basic frame-work which has the correct stereochemistry is not only of foremost concern but also a stereoselective provisional inclusion of any other functional groups must be taken into account. This section will describe the strategies that have been developed for the construction of the pentacyclic skeletons together with the provisions for subsequent introduction of substituents by Ireland^{22,23,24}, Kametani^{25,26} and ApSimon^{27,28,29}.

Ireland's Approaches to the Pentacyclic Skeleton

Ireland and his collaborators completed the total synthesis of the pentacyclic triterpene alnusenone²² in 1973 and Friedelin²⁴ in 1976. The general features of the basic skeleton of alnusenone that bear consideration in this case are the trans-anti-trans-anti-cis system, the exocyclic double bond, the carbonyl, and the methyl groups.

The diether 9 was chosen as the key synthetic intermediate. The pentacyclic diether seems admirably and appropriately suited as an attractive synthon by virtue of the presence of the vicinal

9

angular methyl groups (future 16 and 17 positions) that could prove most troublesome, the trans-anti-trans system, and the two alkoxy-phenyl groups which are relatively inert handles while other structural changes are being performed as well as a useful tool for the introduction of the carbonyl and methyl groups in the terminal rings. The aromatic rings also function to enhance the facile construction of the diether intermediate through the use of Friedel-Crafts type cyclization³⁰. The transformation of the alkoxy-phenyl groups to the A and B rings of alnusenone had already been developed in the total synthesis of the diterpene, ($\pm$) rimuene.³¹

At the outset, the structure of diether 9 suggests many modes of synthesis. The choice of the synthetic scheme $A + DE \rightarrow ACDE \rightarrow ABCDE$ approach was based on the fact that particularly poor yields were realized in the final stages of other schemes that had been previously explored in a preliminary fashion. A scheme that would pass through the tricyclic ketone 10 was envisioned. The tricyclic enone 10 was prepared by Robinson annelation of vinyl ketone 11 and β -tetralone derivative 12 in 72% yield. (Scheme 1). This was followed by Nagata hydrocyanation under controlled conditions to give either the trans or the cis cyano-ketone 17 or 13. The cyano-ketone 17 was transformed to the cyano-olefin 18 with methyl magnesium iodide followed by thionyl chloride and dehydrohalogenation. The Nagata modified Wolff-Kishner reduction of the cyano-olefin 18 afforded the methylated olefin 19 which was cyclized to the

10

required diether 9 in a total yield of 31% starting from tetralone. The cis-cyano isomer 13 was also treated along similar lines to give the pentacyclic species 16.

Polyolefinic Cyclization

In order to circumvent some of the manifold obstacles²² associated with the subsequent transformation of the diether 9 (e.g. selective reduction of the two dissimilar A and E aromatic rings and the improvement in the total yield), other approaches were investigated. Johnson and coworkers³² have shown that the cyclisation of some polyenic derivatives with internal disubstituted double bonds gives predominantly decalin products with the desired stereochemistry.

SCHEME 1

Johnson³² has also developed stereoselective synthesis and cyclisation of squalene-like polyenes. Such non-enzymatic approaches that mimic sterol biosynthetic procedures could be adapted to generate trans-fused polycyclic systems from readily available acyclic precursors. Very efficient systems were then sought that could be prepared from the aldehyde 21 to yield a pentacyclic skeleton. The answer

was found in model studies and in Johnson's work.³² While model studies have shown that the labile aldehyde³³ group is a very poor initiator of such cationic cyclization, a less sensitive but effective source of cationic character would be much more suited. Johnson³² has amply

demonstrated that cyclic allylic alcohols such as 2-cyclopentenol units are excellent intermediates for such fused 2-cyclohexenone ring systems after cyclization followed by ring enlargement.

The polyolefinic cyclization approach was therefore attempted.

At the inception of this scheme, two types of cyclic allylic alcohols were considered for the cationic cyclization^{23,24}, (a) 3-methyl-2-cyclopentenol 22 and (b) 4-methyl-2-cyclohexenol 23 systems. Both schemes will be discussed.

(a) 3-Methyl-2-cyclopentenol route

The cyclopentenone 25 was readily obtained from the aldehyde 24 in four steps with a yield of 28% (Scheme 2). Thus, carbonyl addition with 4-trimethylsilylhomopargylmagnesium chloride, followed by hydration with simultaneous desilylation of the acetylenic alcohol gave an hydroxy ketone which on oxidation afforded the cyclopentenone 25.

Lithium aluminum hydride reduction afforded the 3-methyl-2-cyclopentenol system 22. Cyclization of this alcohol 22 resulted in the formation of both the para and ortho methoxy isomers 27 and 29 in a poor yield. The condition used in the model studies was found to be rather unsatisfactory often producing mixture of inseparable products. Oxidative ring enlargement^{32a} of the major isomer 22 completed a successful route for the transformation of the aldehyde 24 to the desired key intermediate enone 28.

SCHEME 2

LAH

and isomer **26**

Although this route was found to be less efficient as a result of problems associated with the acid-catalysed cyclization step, the results of Johnson and coworkers³² subsequent work showed that the overall yield of 28 could be drastically improved by a different route.

(b) 4-Methyl-2-cyclohexenol route

The additional advantages in this system over the previously mentioned are that the E ring is six-membered and the pentacyclic products also bears the C-4a methyl group at the cis D/E ring junction. The synthesis of the allylic cyclohexenol 23 was also established in a model series. The enone 32 was readily obtained from the dienol 31 in six steps with 70% overall yield (Scheme 3). The dienol 31 on oxidation with Collins reagent gave the aldehyde which was transformed to its corresponding acid with alkaline silver nitrate. Methylation, hydride reduction and Robinson annelation smoothly afforded the enone 32. Hydride reduction of the enone 32 followed by cyclization resulted in the desired olefin 34 which on hydroboration followed by hydrolysis and oxidation afforded the ketone 35. However all efforts to convert the carbonyl function to the geminal-dimethyl group were unsuccessful. Apparently, the steric congestion due to the C-14a methyl group and the hydrogens around C-2 (compound 35) as a result of the cis-D/E ring fusion hinder effectively the approach of any attacking nucleophiles. However in a very meagre yield the ketone 35 was converted to the C-2 oxirane³⁵ followed by hydrolytic rearrangement and subsequent

SCHEME 3

$[\text{CrO}_3 \cdot \text{Py}, \text{CH}_2\text{Cl}_2]$

$[\text{AgNO}_3, \text{aqNaOH}, \text{EtOH}]$

$[\text{LiN}(\text{iPr})_2, \text{THF HMPA}, \text{CH}_3\text{I}]$

$[\text{LAH}, \text{Et}_2\text{O}]$

$[\text{CrO}_3 \cdot \text{Py}, \text{CH}_2\text{Cl}_2]$

$[\text{C}_4\text{H}_9\text{N}, \text{C}_6\text{H}_6, \text{CH}_3\text{COCH=CH}_2]$
 $\text{NaOAc}, \text{aqHOAc}.$

methylation to give the aldehyde 36.

But again, all efforts to reduce the aldehyde 36 to the alcohol and then to the methyl group failed abysmally. This is probably due to the fact that the aldehyde functional group being in the α -configuration is effectively blocked by the C-14 α methyl group also in the α -configuration. Such a situation has been postulated to be responsible for the ease of acid-catalyzed rearrangement of alnusenone 7, friedelin 8 and multiflorenol to the β -amyrin 5 structure.

1. The Total Synthesis of dl-alnusenone by Ireland.²²

With the diether 9 in hand the stage was set for the final series of transformations to incorporate the requisite substituents as in alnusenone (Scheme 4).

The strategy was to protect the A ring by conversion to a phenol while the E ring was being reduced. Thus the selective ether cleavage of the diether 9 was achieved with lithium diphenyl phosphide followed by Birch reduction of the E ring after demethylation of the A ring. This was followed by remethylation of the A ring and acidification to afford the enone 28. Hydride reduction of the enone 28 to the pseudo-equatorial alcohol followed by the directed Simmons-Smith cyclopropanation furnished the cyclopropanol which on Collins oxidation and the directed geminal-dimethylation gave the ketone 39. The cyclopropane moiety was then cleaved with lithium in liquid ammonia followed by Wolff-Kishner reduction of the carbonyl group to give the mono-ether aromatic pentacycle 41 which on Birch reduction followed by acidification and dimethylation finally completed the synthesis of dl-alnusenone-4,5-ene.

2. Total Synthesis of ($\pm$) Friedelin by Ireland.²⁴

The successful synthesis of dl-alnusenone paved the way for another attempt at a closely related pentacyclic triterpene friedelin 8. Some modifications were however necessary to avoid the poor yields in the selective reduction steps and cyclization of the diether 9 encountered in the alnusenone synthesis. In the previous

SCHEME 4

Diether 9 $\downarrow$ LiPPh_2 , THF $\downarrow$ 42% Li/NH_3 , glyme, CH_3I $\downarrow$ 85% $\text{LiAl(O-}^t\text{Bu)}_3\text{H}$, $\text{THF-C}_6\text{H}_6$

dl-Alnusenone 7

Friedelin

preparation of alnusenone, the aromatic E ring of the diether 9 was reduced first and methylated before reduction and methylation of the A ring; this procedure was reversed to A ring reduction before the E ring. One reason for such a detour was that the severe steric strain to be generated from the cis D/E ring junction might hinder the cyclization step of the acetylenic alcohol 45. This could be avoided or postponed to when less sensitive transformations were being performed. It was also felt that the initial Birch reduction of the E ring was responsible for the poor overall yield of 14% in the transformations of the E ring; secondly, the ease of reduction of the aromatic A ring calls for this to be reduced first.

The synthetic plan thus, calls for preparation of the diether 43 having the locations of the ethoxy and methoxy interchanged compared with alnusenone intermediate diether 9. This was achieved in 25% overall yield along the same lines as reported for (dl)-alnusenone 7 (Scheme 5). The diether 43 was then selectively reduced. The reduction started with ether cleavage of the E ring with lithium diphenyl phosphide , Birch reduction, followed by remethylation of the resulting ion and acid cleavage to give the enone 44. Epoxidation of the ring A double bond followed by Eschenmoser cleavage⁴² of the derived epoxide gave on methylation the acetylenic tertiary alcohol 45. On treatment with

SCHEME 5

44 45 46

trifluoroacetic acid the alcohol 45 cyclized in 98% yield to furnish directly, the enol trifluoro acetate 46. Cyclopropanation of the enol acetate 46 as its lithium enolate was achieved with lithium diisopropylamide and the Simmons-Smith reagent. Reduction of the aromatic cyclopropanol 47 with lithium in ammonia followed by acid treatment afforded the enone with the substitution and stereochemistry required for the A/B ring system.

The final series of transformations to friedelin were along the same lines as in the dl-alnusenone synthesis. It took eleven more steps in 26% overall yield from the enone 48. The overall yield of the friedelin synthesis was 0.3% in thirty-one steps.

Kametani's Approaches to the Pentacyclic Skeleton

Kametani and coworkers^{25,26} focussed their scheme on the pentacyclic diaromatic diether 9, the same key intermediate, employed in Ireland's route. Their scheme was based on the results of earlier work^{26,36,37} on atisine and estrone following the observation that the intramolecular cycloaddition of O-quinodimethanes³⁸ could proceed stereoselectively as well as regio selectively.

The basic strategy was conceived on the idea that carbon atoms 6, 6a, 6b, 7 and C_{6b}-CH₃ could serve as an isoprene unit. At the inception of this work two main approaches were considered: (a) The double cycloaddition approach which essentially is a one

step intermolecular double cycloaddition of the bis-O-quinodimethanes 55 with isoprene and

(b) The stepwise and stereoselective synthesis, in which the cycloaddition of benzocyclobutenes to isoprene produces tetralin compounds corresponding to A and B rings, followed by alkylation and an intramolecular cycloaddition to complete the synthesis of the key pentacyclic intermediate 56 to be transformed to the diether 9.

(a) The Double Cycloaddition Approach

Attempt was made to add 1,2-di(1-cyano-4-methoxybenzocyclobutenyl) ethane 55 to isoprene in one step. The convergent synthesis of the key intermediate in this scheme, the bisbenzocyclobutene 54 was straightforward as depicted below (Scheme 6). Knoevenagel condensation of 2-bromo-5-ethoxybenzaldehyde 49 with cyanoacetic acid gave in 82% yield the α -cyanocinnamic acid 50 followed by hydride reduction and decarboxylation to furnish O-bromophenylpropionitrile 51. Treatment of the O-bromophenylpropionitrile 51 with sodamide in liquid ammonia afforded in 77% yield the benzocyclobutene 52 which on condensation with 2-(2-bromoethoxy)tetrahydropyran gave the 1-cyanobenzocyclobutenyl ethyl alcohol on acid hydrolysis. The resulting alcohol was converted to the iodide 53 via the tosylate and on further treatment with 1-cyano-4-methoxybenzocyclobutene afforded the 1,2-di(1-cyano-4-methoxybenzocyclobutenyl) ethane 54 which, unfortunately did not give the desired pentacyclic diether 56 on heating with excess isoprene.

SCHEME 6

It however gave the bistetralin derivative 57 formed by cycloaddition of isoprene to each half of the bis-0-quinodimethane 55. As a result of this failure attention then turned on the stepwise synthesis.

Stepwise and Stereoselective Synthesis

In this approach benzocyclobutene 58 was added to isoprene to produce the tetralin compound 59, this was followed by addition of the iodide 53 and completed by an intramolecular cycloaddition as below (Scheme 7). The benzocyclobutene iodide 53, embodying the potential D and E rings of the triterpene was prepared as in the previous route. The tetralin compound 59, the potential A and B rings, on the other hand, was synthesized from benzocyclobutene 58 and excess isoprene in 42% yield by heating at 180° for two hours (Scheme 7). Two products were obtained as a result of an intermolecular cycloaddition of the quinodimethane 61 to either of the double bonds of the isoprene. Alkylation of the 1-cyano-2-isopropenyl tetralin 59 with the iodide 53 in the presence of sodamide in the liquid ammonia afforded the dicyano olefin 62. The cycloaddition of the benzocyclobutene 62 to the desired pentacyclic compound was completed by heating in dry toluene at 210-215° for three hours. Hydride reduction of the resulting pentacyclic species 56, followed by the Nagata modification of the Wolff-Kishner³⁹ reduction of the resulting diimine resulted in the pentacyclic diaromatic diether 9 also used by Ireland. The other pentacyclic isomer in which the diether groups were reversed as in friedelin synthesis was also prepared in a similar manner.

The yield of 56 from 62 is 60%.

The high regioselectivity realised in this scheme has been attributed to the strong electron-attracting power of the cyano group and the electron releasing effect of the methyl group of the olefin 63. The stereoselectivity is provided by controtatory ring opening of the cyclobutene 62 through the less sterically demanding 0-quinodimethane intermediate 63 whose simultaneous intramolecular cycloaddition could proceed most favourably through the exo-chair 64 conformation.

SCHEME 8

A nonstereoselective version of the second approach was also performed (Scheme 8). In this case the benzocyclobutenyl iodides 53 were applied as the A and B ring systems while the tetralin compounds would correspond to the D and E rings. The diastereomeric mixture of the 1-cyano-2-methyl-2-vinyltetralin 60 on alkylation with the iodide 53 in the presence of sodamide afforded in 86% yield the 1,1,2,2-tetrasubstituted tetralin 65 as a stereoisomeric mixture. The tetralin compound 65 on thermolysis at 210-215° furnished a stereoisomeric mixture of the dicyano derivatives 67 via the O-quinodimethane intermediate 66. Separation by column chromatography gave the pure pentacyclic dinitrile 67a in 33% yield with the correct stereochemical arrangement.

ApSimon's Approaches to the Pentacyclic Skeleton

Of the various approaches^{27,28,29,40,41} to the pentacyclic skeleton being studied in this laboratory one has been completed and the last step of another is still being investigated. The first based on an ABC + E ring construction was directed towards the synthesis of the $\alpha\beta$ -unsaturated ketone 68.

The enone 68 is a very attractive precursor for most reduced-picene type triterpenes because it is endowed with five methyl groups and three of the nine asymmetric centres as in friedelin. It also possesses requisite functional groups to introduce the remaining methyl groups and the double bond found in the pentacyclic triterpenes. The basic strategy of the convergent

FIG. 2

68

synthesis is as shown in Schemes 9 to 12. The obvious advantages of this route are (i) the synthons are so designed as to be useful for more than one route, (ii) the rapid provision of polycyclic species (iii) fewer steps than those previously discussed.

The tosylate²⁹ 70 and tricyclic²⁹ enone 69 served as the starting materials. The tosylate was prepared as follows: (Scheme 10). Treatment of the cyclohexenone 74 with malononitrile gave the dicyanoketone 75 which on ketalization, alkaline hydrolysis and decarboxylation afforded the acid 78. Hydride reduction of the acid 78 followed by tosylation gave the tosylate 70 in 26% overall yield from the dicyanoketone 75.

On the other hand, the tricyclic enone 69 was prepared by Robinson annelation of the β -tetralone with ethylvinyl ketone (Scheme 9). Alkylation of the tricyclic enone 69 with the tosylate 70 in the presence of potassium tert-pentoxide in dry benzene afforded the diastereomeric mixture of diketone²⁹ 71 as a crystalline solid.

However all attempts to affect the desired cyclisation of the diketone 71 with a variety of bases were not successful, while p-toluenesulfonic acid gave a product which was later identified as 79 (Scheme 11). However, when the diketone 71 was subjected to catalytic hydrogenation followed by p-toluene sulfonic acid in boiling xylene, the desired pentacyclic ketone 72 along with another product which was not further identified were obtained.

The second approach also aimed at the total synthesis of pentacyclic triterpenes such as friedelin has as its prime

SCHEME 10

SCHEME 11

Friedelin

Conjugate-
Addition

Conjugate-
Addition
Alkylation

Birch reduction
acetylation and
photolysis

target, the dienolate 80. The dienolate 80 is far better suited than the

enone 68 since it possesses six methyl groups, four of the nine asymmetric centres in friedelin, no aromatic ring to be reduced, and other functional groups in place for the incorporation of the remaining substituents and control of the missing stereochemical features. The diketone 85 was prepared as follows: (Scheme 13).

Robinson annelation of the bicyclic enone 81 via the dienolate (on with sodium methoxide in methanol and ethylvinyl

ketone gave the tricyclic enone 82. This was followed by protection of the hydroxyl group in preparation for the alkylation. Alkylation of the enone 83 with the tosylate 70 was readily achieved with potassium tert-pentoxide in dry benzene to give the diketone 85 on acid hydrolysis. With the diketone 85 in hand the stage was then set for the cyclization. Treatment of the diketone 85 with p-toluene sulfonic acid did not give the desired pentacyclic enone 80 but a rearranged product in which the 1,10 double bond has become saturated and the C₅-methyl group has migrated to carbon 10.

Scheme 13

70potassium t-pentoxide,
benzene H^+

pTsoH

The undesirable rearrangement was of great concern and an attempt was later made to remove the 1,10 double bond. However it was with great dismay to observe that similar rearrangement occurred on catalytic hydrogenation. Apparently slow protonation of the 1,10 double bond was occurring on prolonged hydrogenation followed by methyl migration and hydride shift with the hydroxyl group facilitating the rearrangement. The corresponding benzyl ethers of the diketone 85 were also found to show similar rearrangement on catalytic hydrogenation.

RESULTS AND DISCUSSION

The Development of a Synthetic Strategy

Despite the formidable synthetic challenges, as outlined in the introduction, there have been some elegant forays into the pentacyclic arena. These synthetic schemes have been patterned on

FIG. 3

ring construction approaches such as:

- (i) $AB + DE \rightarrow ABDE \rightarrow ABCDE$ (oleanenes)^{45,46}
- (ii) $A + B \rightarrow AB \rightarrow ABC \rightarrow ABCE \rightarrow ABCDE$ (germanicol)⁴⁷
- (iii) $CDE \rightarrow ACDE \rightarrow ABCDE$ (alnusenone)⁴⁸
- (iv) $CD \rightarrow CDE \rightarrow BCDE \rightarrow ABCDE$ (lupeol)⁴⁹
- (v) $AB + DE \rightarrow ABCDE$ (δ -amyrin)⁵⁰

For the last nine years this laboratory has been preoccupied with the development of efficient, versatile and stereoselective reaction schemes that would also provide a general and broad entry into pentacyclic triterpenes.^{21,27,28,40,41}

Fig. 4 illustrates some of the regularities in the substitution patterns and structural features in the oleanane series. It is to be noted that multiflorenol, alnusenone and friedelin have similar BCDE ring systems and substitution patterns namely, the trans-anti-trans-anti-cis ring junctions, angular methyl groups or hydrogens.

The work described in this thesis is centered on synthetic studies leading towards a BCDE ring system fragment capable of conversion into a variety of the species as shown in Fig. 4.

The work described falls into three different categories representing different strategies:

Section 1. Approaches to the construction of the BCDE ring system - attempted condensation of 6-methoxy-1-methyl-2-tetralone 90 with 3,6,6,-trimethyl-3-vinylcyclohexanone 91 (Scheme 14).

Section 2. Approaches to the construction of the BCDE ring system - cyclization studies on the bicyclic diastereomeric diketones

β -amvrin5 taraxerol 6 multiflorenol 4 alnusenol 7 friedelin 8

FIG. 4

Scheme 14

99a and 99b, 2-keto-1-methyl-1 [2-(3-keto-1,4,4-trimethyl cyclohexyl) ethyl]-6-methoxy-3,4-dihydronaphthalene (Scheme 15).

Scheme 15

(ii) Approaches to the construction of the ABCDE ring system.

Cyclization studies on the diastereomeric tricyclic diketone 85, 1 α -[2-3'-keto-]';4',4'-trimethylcyclohexyl)-ethyl]-8 β -trimethyl-trans-anti-dodecahydro-phenanthr-10(10a), 4b(5)-diene-2-one

Section 3. Further transformations of tetracyclic compound 100a, 8-methoxy-3,3,10 α , 12 $\alpha\beta$ -tetramethyl-1,2,5,6,10 β ,11,12,12 $\alpha\beta$ -octahydro-(3H)-chrysen-4-one and 100b, 8-methoxy-3,3,10 β , 12 $\alpha\beta$ -tetramethyl-1,2,5,6,10 β ,11,12,12 α -octahydro-(3H)-chrysen-4-one.

At this point, a brief outline of the general synthetic plan underlying our preliminary efforts is presented (Chart 2).

CHART 2

CHART 2A

Two approaches to the synthesis of the species 100A and 100B were investigated in order to ascertain the stereochemical arrangement of the C-10b and the C-12a methyl groups after the cyclization step (Chart 2). One of the approaches is discussed in Section 1 (Scheme 16) while the other, Scheme 18, (p.87) is dealt with in Section 2 along with some applications of the cyclization reactions to the the synthesis of the pentacyclic compound(80).

Section 1. Approach A

Approaches to the construction of the BCDE ring system

Attempted condensation of 6-methoxy-1-methyl-2-tetralone with 3,6,6-trimethyl-3-vinylcyclohexanone (Scheme 16).

The synthesis of tosylate 95 required the construction of the dienone 92, for further cyclization to the compound 100a or 100b. 6-Methoxy-1-methyl-2-tetralone 90 was prepared from the commercially available 6-methoxy-1-tetralone⁽⁸⁾ according to a variation of the method originally developed by Stork⁵¹ and later modified by Ireland³³. While the Grignard methylation step proceeded in much higher yield than reported³³, all efforts to substitute the commercially available meta-chloroperbenzoic acid in the epoxidation step were unsuccessful. A complex mixture of rearranged products was often obtained along with small amounts of the desired β -tetralone.

The enone (91) on the other hand was prepared from Robinson annelation of methyl vinyl ketone and 3-methyl-2-butanone to afford 3,6,6-trimethylcyclohexenone followed by a 1,4 addition of

Scheme 16

the vinyl group. Thus the base-catalyzed reaction of methyl vinyl ketone and 3-methyl-2-butanone was carried out according to the modified method of ApSimon and co-workers²⁷ to give the desired cyclohexenone 74 along with its isomer (102). The (1,4) vinylation of the enone 74 however presented some problems.

The use of lithium organocuprates reagents in 1,4 conjugate addition is well known.^{53a,53b} The copper-catalyzed conjugate addition of Grignard reagents to cyclohexenones had been used in a variety of syntheses such as the lycopodine alkaloids^{53c}, substituted hydroazalenes⁵⁴ and steroids⁵⁵. However addition of the cyclohexenone 74 dropwise to a stirred ethereal suspension of vinyl

magnesium bromide and cuprous bromide at 0 to -10° (salt and ice-water bath) with stirring for extra 1 hour resulted in a mixture of starting material, the 1,2 and 1,4 conjugate addition products. All efforts to make improvements by altering the reaction conditions resulted in failure.

Based upon the postulate that lack of regiospecificity was due to insolubility of the cuprous bromide in ether, attention was drawn to the solubility advantages offered by some Cu(I) halide complexes such as nBu_3PCuI ⁵⁶ and Me_2SCuBr ⁵². The synthesis of the white crystalline tetrakis[iodo(tri-n-butylphosphine) copper(1)] nBu_3PCuI , was readily achieved according to a modification of a method described by Kauffman and Teter.⁵⁶ The conversion of the

cyclohexenone 74 to the desired vinylcyclohexanone (91) was accomplished with vinylmagnesium bromide and catalytic amount of $n\text{-Bu}_3\text{PCuI}$.⁷³ Thus, to a stirred solution of the cyclohexenone and a catalytic amount of the copper additive in THF (tetrahydrofuran) at -55 to -65° (acetone-dry-ice bath) was added the vinylmagnesium bromide dropwise. The reaction mixture was left to stir overnight and then quenched with ice/ $3N$ HCl mixture. The pure enone 91 was obtained by distillation in 85% yield. Because of the instability and high boiling point of $n\text{-Bu}_3\text{P}$ (b.p. 150° 50 mm), and its persistent disagreeable odour, another copper additive Me_2SCuBr was substituted for $n\text{-Bu}_3\text{P}$ in the reaction. The Me_2SCuBr was prepared according to a modification of the method described by House.⁵⁸ The white crystalline Me_2SCuBr was found to be more stable and could be stored in the fridge for several weeks with no decomposition. The vinylcyclohexanone was also obtained in the same high yield with the Me_2SCuBr additive. The spectral properties confirm the identity of the vinylcyclohexanone (enone) 91.

With the β -tetralone 90 and the enone 91 in our hands preparations were then made for the condensation step.

Cross-aldol condensation can in principle be performed under two main sets of conditions. Stabilized enol derivatives such as the trimethylsilyl ethers can be condensed with ketones, aldehydes, ketals and acetals under the influence of Lewis acid catalyst. The same reaction can also be carried out with preformed metal enolates and carbonyl compounds.

Some steric problems were anticipated because of the geminal dimethyl groups and the C₃-methyl of the enone (91) and we therefore found chelating Lewis-acid catalysts particularly attractive. We developed immediate interest in the results of Mukaiyama's studies⁶⁰ that silyl enol ethers react with aldehydes and ketones in the presence of titanium tetrachloride to give cross-aldol addition products in good yields under very mild conditions. Titanium not only forms very strong bond with oxygen (O-Ti = 158±8 kcal) but also when bearing chlorine ligands, it powerfully activates the carbonyl carbon for nucleophilic reactions. The postulate was that silyl enol ether 104 would readily attack carbonyl compound activated by titanium tetrachloride to form an aldol product through a stable six-membered transition state⁶⁰ as shown below. This exceptional chelating property of titanium tetrachloride towards carbonyl oxygens led us to pursue the condensation reaction.

To this end the silyl enol ether 103 was conveniently prepared according to a variation of a procedure described by House.⁶¹ The conversion of the enone 91 to its silyl enol ether 103 was achieved with lithium diisopropylamide and chlorotrimethylsilane in 1,2-dimethoxyethane. The silyl enol ether in dichloromethane was then added dropwise to a stirred solution of equimolar amounts of β -tetralone 90 also in dichloromethane and freshly distilled titanium tetrachloride under argon at 0°. The blue-black reaction mixture was further stirred for one hour, quenched with ice water and extracted with ether. Purification yielded a mixture of the starting tetralone 90,

104 138 TiCl_4

106 107

the enone 91 and some aromatized tetralone 108.

These results suggested to us that although the enolate of the silyl enol ether 103 was being formed no nucleophilic addition was occurring due to competitive enolization of the β -tetralone and subsequent aromatization. The formation of such naphthalenic derivative 108 is not without precedents.⁴¹ Such naphthalenic products had been obtained during the attempted acid-catalyzed condensation of the diketone 99b (Section 2 of Discussion).

Several attempts were further made to effect the reaction under varying conditions such as low temperatures (-40 to -65°), shorter reaction times, catalytic quantities of titanium tetrachloride, but all were unsuccessful. A simultaneous mode of addition whereby both the silyl enol ether 103 and the β -tetralone were added at the same time with syringes to the methylene chloride solution of titanium tetrachloride was not successful.

The titanium tetrachloride condensation having failed, a much milder Lewis acid was sought. The organoaluminum compounds have recently been reported to be excellent and highly effective reagents in aldol synthesis.⁶² Yamamoto has found that dialkylaluminum chloride in the presence of zinc generates aluminum enolate from α -halo ketones to effect a facile nucleophilic addition to carbonyl compounds⁶² as shown on p.74.

The α -bromo enone 113 was readily synthesized from the silyl enol ether 103 and cupric bromide.⁶³ The α -bromo enone 113 was also satisfactorily obtained from the enone 91 and cuprous bromide in refluxing methanol though with less purity.⁶⁴ The identity of the bromo enone 113 was established by infra red, n.m.r. and mass spectroscopy. The condensation reaction was then carried out. A solution of the β -tetralone 90 and bromo enone 113 in THF was added to a stirred suspension of activated zinc dust, cuprous bromide and diethylaluminum chloride in THF-hexane at -20° under argon. Addition of pyridine, removal of the cooling bath and aqueous

work-up afforded a mixture of starting β -tetralone, with some

brominated and unbrominated enone. Moreover all attempts to apply this reaction to the condensation of the β -tetralone 90 with the bromo enone 113 under various conditions were not successful.

Preformed lithium enolates have commonly been used as reactants in aldol condensation with other carbonyl compounds⁶⁵, with lithium serving as the chelating metal cation in non-polar solvents at low temperatures. The addition of either anhydrous magnesium bromide or zinc chloride as an etherate has been reported⁶⁵ to enhance the stability of the six-membered cyclic metal-chelated intermediate resulting in a high yield of a single aldol product.

Subsequent dehydration of the resulting aldol product or products would then afford an $\alpha\beta$ -unsaturated ketone.

The lithium enolate of the enone 91 was readily prepared with lithium diisopropylamide in dimethoxyethane, while further addition of an excess of a saturated ethereal solution of magnesium bromide or zinc chloride was used to generate the magnesium or zinc enolate respectively. Subsequent addition of the β -tetralone 90 however failed to generate the much desired aldol product. Again all attempts to achieve the condensation under various base-catalyzed reaction conditions met with failure.

The Grignard reagent diisopropylamidomagnesium bromide ($i\text{-C}_3\text{H}_7$)₂ NMgBr has been reported⁶⁶ to be an effective aldol condensing agent and has successfully been used by Kishi and his group in the synthesis of monensin.⁶⁶ This reagent possesses a

combination of the complexing character due to magnesium and basicity

required to achieve the condensation desired but unfortunately efforts to accomplish the condensation with this reagent were not successful.

It was then plain to us that that the β -tetralone 90 in the presence of trace amounts of acid or base when in solution exists predominantly in the enol or enolate form, and this probably accounts for the absence of any activity of the carbonyl group, stabilization of the enolate being provided by the aromatic ring.

The α -keto dianions 121 have recently been reported to be an extremely reactive class of new intermediates.^{67,68}

Our speculation was that the difficulties would be solved using the dianion of the enone 91. The dianion 122 was prepared

according to a variation of the method of Kowalski.⁶⁷ The bromo-enone

SCHEME 17

113 was treated with 1.10 equivalents of lithium hexamethyldisilazide (or LDA at -55°) (acetone dry ice bath) followed by 4.0 equivalents of tert-butyllithium still at -55° to deprotonate the disilazane, to exchange the bromine and to destroy the tert-butyl bromide produced. Evidence for the presence of the dianion 122 was established by quenching a cold sample of the reaction mixture with deuterioacetic acid in deuterium oxide to afford the dideuteriated enone 124.

Quenching a cold sample of the reaction mixture with excess chlorotrimethylsilane at -55° followed by warming to room temperature gave the disilylated enone 125. Addition of the β -tetralone to the dianion, however, did not afford the desired product. Both the starting β -tetralone 90 and enone 91 were recovered on workup.

Finally, having failed to achieve any results with the activation of the enone 91 we then proceeded to activate the β -tetralone carbonyl since it is the real cause of the inactivity. Indirect electrophilic activation of the carbonyl is well known.^{69,70} The reaction of enol silyl ethers with ketals, acetals and some ortho esters in the presence of catalytic amounts of trimethylsilyl trifluoromethane sulfonate to afford the aldol condensation products has been reported to proceed in good yields by Noyori.⁶⁹ The electrophilic attack of the silyl triflate 127 on an oxygen atom of the acetal 128 generates the reactive oxonium intermediate 129 that exists in resonance with the methyl carboxonium ion/methoxytrimethyl silane contact pair, followed by nucleophilic displacement by the enol silyl ether to give the condensation

product 130.

However, two different attempts to prepare the ketal of β -tetralone resulted in failure and route A was therefore abandoned.

2

SECTION 2. APPROACH B.

Approaches to the construction of the BCDE ring system - Aldol-cyclization studies on the bicyclic diketone, 2-keto-1-methyl-1-[2-(3-keto-1,4,4-trimethylcyclohexyl)ethyl]-6-methoxy-3,4-dihydronaphthalene diastereoisomers (99a and 99b) and the tricyclic diketone, 1 β -4 α -8 $\alpha\beta$ -trimethyl-trans-anti-dodecahydrophenanthr-10(10a), 4b(5)-diene-2-one (85).

The unsuccessful attempts to achieve the desired condensation in route A (Section 1) led us to reinvestigate route B (Scheme 18) more carefully.

Several years ago, our laboratory began an investigation into the synthetic possibilities in the pentacyclic triterpenes area.^{27,29,52a} Many objectives were then defined. Primarily, it was hoped to achieve the total synthesis of at least some of the naturally occurring pentacyclic triterpenoid compounds (Fig. 4). Moreover, several means were sought to develop a rapid entry to the general ring system, thus allowing for some further deep-seated structural modifications leading to a wide variety of pentacyclic species.

The basic strategy was then presented.⁴¹ The plan entailed the synthesis of tetracyclic intermediates of the types 100a and 100b in the hope that such a structure would prove amenable to subsequent manipulations towards the target compounds in the friedelin and β -amyrin series. In particular, the initial intention was to reach tetracycles 100a and 100b through suitable cyclization of diketone 99a and 99b. The route outlined in Scheme 15 (p. 58.) holds very high promise as a result of the parallel study shown in Scheme 11 (p. 48) in which one of the tricyclic diastereomeric diketones (73) was cyclized with para-toluene sulphonic acid to give a product which readily crystallised, the spectral data and x-ray analysis showed the product to be the compound 72. Both this compound and the tetracyclic species can be seen as excellent synthons for friedelin.

In the previous investigation⁴¹ in our laboratory, the diastereoisomeric bicyclic diketones 99a and 99b when treated with tert-butylmagnesium chloride gave the tetracyclic compound 100a in 45% yield, a trace of its diastereomeric 100b and the bicyclic keto-alcohol 131 (Scheme 18). The tetracyclic compound 100a was then viewed as an appropriate precursor for β -amyrin while 100b would be ideal for friedelin.

In order to continue the previous study, our two main objectives were to devise more efficient methods to produce the tosylate 70 in ample quantities and more importantly to cyclize both diastereomeric bicyclic diketones 99a and 99b in acceptable yields. The problem associated with the previous synthesis of the tosylate 70 was the unacceptably low overall yield at the end of an extremely long route and with some difficult steps. A substantial modification of the old route was then sought.

An improved route to the tosylate 70 (Scheme 19) was realized by the 1,4-vinylation of cyclohexenone followed by protection of the carbonyl as the ethylene ketal. Hydroboration and peroxide treatment of the protected ketone 132 afforded the alcohol 133. The alcohol 133 proved to be rather unstable, often giving a crystalline dimeric product on storage and therefore had to be used immediately. The alcohol 133 gave the tosylate 70 on treatment with p-toluenesulfonic chloride and pyridine in 92% yield thus completing a much shorter and very efficient synthesis of the tosylate. Although the alcohol 133 could also be converted to the mesylate, the p-toluenesulfonate ester offers the additional advantage in that it is crystalline solid and

SCHEME 19

could easily be purified by crystallisation before use. The identity of the tosylate 70 was confirmed by I.R., N.M.R. and mass spectral data. The melting point was also identical with that of authentic sample. The preparation of the tetralone 90 was achieved as discussed in Section 1. The stage was then set for the alkylation reaction, which was conveniently accomplished with potassium-tert-pentoxide as in Scheme 18 (p. 86) to afford the diastereomeric bicyclic diketones 99a and 99b after deketalization and chromatographic separation of the reaction products. With the two diastereomeric bicyclic diketone 99a and 99b in our hands attention was then directed towards the crucial cyclization step.

The aldol-cyclization of only one of the diastereomeric ketones in the previous study with $t\text{BuMgCl}$ to the compound 100a and the reduction of the other 99b mostly to the keto-alcohol 131 was a crucial step to be improved. The reduction of the bicyclic diketone 99b to the keto-alcohol doubtless occurred through the coordination of the magnesium atom with the carbonyl oxygen followed by the transfer of a β -hydrogen from the Grignard reagent to the carbonyl carbon in a six-membered transition state to afford an olefin and the keto-alcohol as below.

Aldol Cyclization of the Bicyclic Diketones 99a and 99b with Bases.⁸⁰

The name 'aldol' is a generic term derived from the fact that the end product of acetaldehyde self-condensation with a base is both an aldehyde and an alcohol. It is now generally applied to carbon-carbon bond formation when an enol (or enolate) of one carbonyl adds to

another carbonyl group, be it an aldehyde or ketone, followed by protonation.⁸¹ This fundamental reaction has been disguised under various names depending on the choice of carbonyl compound. However all such variations have now been conveniently classed as 'aldol condensation' type reactions.⁸¹ The reaction is among the oldest classes in organic chemistry and is now not only fully associated with the creation of 1,3-oxygen-oxygen but also 1,3-nitrogen-oxygen heteroatom-heteroatom relationships.⁸⁰

Over the past few years, the advent of macrolide and ionophore antibiotics⁸² as viable targets for synthetic organic chemists has aroused a tremendous surge of renewed interest in the development of the stereoregulated aldol condensation. The syntheses of target molecules such as erythromycin aglycones, erythronolide A and erythronolide B (Scheme 20) illustrates the utility and prominence of the aldol condensation. The most serious problems associated with the aldol process are the stereochemical aspects. Considerable progress has however, been made in the understanding of the underlying mechanism and the development of stereoregulated aldol processes.⁸²

Four possible product stereoisomers (two new chiral centers) are possible in the crossed-aldol condensation of any two achiral carbonyl compounds. Abundant evidence now exists that relates diastereoselection (A as opposed to B) to enolate geometry,^{83,84} and enantioselection (A(+) as opposed to A(-)) to resident chirality in either or both condensation partners or their enolates.⁸⁵ (Fig. 5).

When catalyzed by acids the reaction is thought to follow the path as illustrated below (Scheme 21).

In spite of all the equilibria steps good yields of aldol condensation products are often obtained especially if the initially formed aldol product is further transformed (e.g. by dehydration⁸⁷ or cyclization⁸⁸) or is continuously removed from the reaction medium as it is formed⁸⁹, this serves to displace the various prior equilibria in favour of the final product. The second or ring closure step in the Robinson annelation provides a good example.

SCHEME 20

R = H, Erythronolide B

R = OH, Erythronolide A

A (+)

B (+)

A (-)

Erythro
Syn

B (-)

Threo
AntiFIG. 5

SCHEME 21

For the present study a convenient point to start the investigation was, firstly, to find conditions to avoid the ketone reduction in the aldol condensation of the bicyclic diketones 99a and 99b with tert-butyl-magnesium chloride. This, in principle, can be achieved by modification of reaction conditions or by the use of Grignard reagents with no β -hydrogen atoms. Very low reaction temperatures and dilute reagents are known to favour carbonyl addition in preference to reduction.⁷³

However, addition of excessively dilute tetrahydrofuran (THF) solutions of tert-butylmagnesium chloride to a stirred dilute dimethoxyethane (DME) solution of the diastereomeric bicyclic diketones 99a and 99b at -78° and at various temperatures under argon and sometimes followed by further stirring at room temperature afforded mostly the starting material. Further dilution of the reagents and shorter reaction times did not help either.

Tritylmagnesium chloride has no β -hydrogens and it was postulated that this would be the solution to our reduction problem. The tritylmagnesium chloride was readily prepared from trityl chloride and magnesium turnings in tetrahydrofuran as a yellow solution. Refluxing of this Grignard reagent with the bicyclic diketone 99a and 99b resulted in four new compounds (by thin layer chromatography, (t.l.c.) and some starting material. The infra red spectrum of the crude reaction mixture showed a strong peak at 1675 cm^{-1} indicative of an α,β -unsaturated ketone as a condensation product. The nuclear magnetic resonance (n.m.r.) spectrum suggested the presence of much triphenyl methane and all efforts to remove this were unsuccessful. It should be noted that House et al.⁶¹ had expressed having similar difficulty in removing triphenylmethane from their preparation of silylenol ethers with triphenylmethyllithium and triphenylmethylpotassium.

Following our failure to purify the condensation products, it was reasoned that greater success might be achieved by the use of basic catalysts.

Enolization of the desired carbonyl group will lead to aldol cyclization (Fig. 6) through a six-membered ring transition state. On the other hand enolization of the undesired carbonyl group would not result in any cyclization since nucleophilic addition to such a highly hindered carbonyl would be greatly disfavoured, and in any case an eight-membered transition state would be involved.

The lower the strength of a base the greater is its selectivity.⁹⁰ Common hydroxide bases such as those of sodium, potassium and barium have been used frequently with water or alcohol as solvent on acidic substrates to achieve aldol condensation.⁹¹ The aldol process has also been carried out under much milder conditions using hydroxide bases in combination with phase transfer catalysts.⁹² This method when applied with and without phase transfer catalyst dicyclohexyl-18-crown-6 or triethylbenzylammonium chloride under Makosza conditions⁹² was unsuccessful. Thus in a typical run, a solution of the diketone (99a) and (99b) in acetonitrile containing 50% sodium hydroxide in water and a catalytic amount of phase transfer catalyst (dicyclohexyl-18-crown-6 or triethylbenzylammonium chloride (TEBA)) was stirred for 30 minutes at room temperature. In all cases the starting material was recovered on work-up. Variations in reaction conditions such as temperature and solvent changes did not help.

Next, another Grignard reagent somewhat similar to tert-butylmagnesium chloride, diisopropylamidomagnesium bromide was used. The reagent has been remarkably successful as a base-aldol catalyst in the synthesis of monesin by Kishi.⁶⁶ The reagent was prepared from diisopropylamine, ethyl bromide and magnesium. However no reaction was noted. Reflux of the diketones with glycine and catalytic amount of perchloric acid in acetonitrile was also attempted.

Again no cyclisation was observed.

Next we decided to test the possibility of selective enolization of the carbonyl groups. To a solution of lithium diisopropylamide in dimethoxyethane at 0° was added the bicyclic diketones (99a and 99b) in dimethoxyethane under argon and the solution was stirred for 30 minutes. Tlc indicated mostly starting material in the reaction medium, half of which was withdrawn with a syringe and worked up and the other half quenched with trimethylsilyl chloride. Purification by preparative thin layer chromatography (p.l.c.) of the isolated portion afforded mostly the starting diketones 99a and 99b. On the other hand, the trimethylsilyl chloride - quenched portion gave a silylenol derivative whose structure was unequivocally assigned as 139. Obviously, enolization of the carbonyl of the highly hindered cyclohexanone ring (1,1,4,4-tetrasubstituted) is much more difficult to achieve than the less hindered tetralone portion.

The structure of 139 was confirmed by spectral methods as well as by elemental analysis. The infra red (i.r.) spectrum showed a carbonyl absorption at 1695 cm^{-1} and a C=C-O absorption at 1675 cm^{-1} . The n.m.r. spectrum contains singlets at 0.26 δ (9H) for the $\text{Si}(\text{CH}_3)_3$; 0.77 δ , 0.93 δ , 1.00 δ , 1.33 δ (3H each) for the C_1 - CH_3 , gem-dimethyls, and C_1 - CH_3 respectively, a doublet at 3.33 δ (2H, $J = 4\text{ Hz}$) for the two benzylic protons; and a triplet at 4.87 δ (1H, $J = 4\text{ Hz}$) for the

99a and 99b

homobenzylic proton. The mass spectrum shows a molecular ion at M/e 428, and a base peak at m/e 261, arising from β -cleavage of the side chain. It also contains the very diagnostic fragment of trimethylsilylenol ethers at m/e 73 as the second most abundant peak (see p 102). It was clear then to us that the preferred enolization of the carbonyl at C-2 was the cause of the lack of condensation.

The question was then asked if the undesired carbonyl was being enolized with base catalysts, how could aldol condensation ever be achieved with the basic tert-butylmagnesium chloride? Our postulate then was that the answer probably lies in the complexing ability of magnesium. Magnesium coordinates to the two carbonyl

oxygen thus situating them in close proximity for addition to take place to form a six-membered ketoalkoxide metal-chelate. In this manner either carbonyl can be enolized but not both, with only the desired enolate leading to the tetracyclic compound.

In contrast the conversion of the bicyclic diketone 99a in our preliminary studies to the compounds 100a and 101 with para-toluenesulphonic acid cannot involve such a mechanism^{41,134} (see p. 103).

Aldol Cyclization with Lewis Acids

As has been pointed out, the success of the aldol condensation is mainly attributable to the formation of an intermediate metal-chelate that allows the equilibrium leading to the aldol product to be much more favourable. In the case of an intramolecular aldol condensation involving a diketone in which both carbonyls carry α -hydrogens another possible equilibrium exists between the metal-chelates in which the more thermodynamically stable intermediate will lead to the aldol-cyclized product. Such metal-chelate formation has been found to be favoured by the use of organo-metallic catalysts of Li⁹³, Mg⁶⁵, Zn⁶⁵, Hg⁹⁴, B⁹⁵, Al⁹⁶, and Ti^{60, 97}, although the di-, tri- and tetravalent metal cations form more stable metal-chelates than the lithium or potassium. External addition of di- or trivalent metal salts such as zinc chloride⁶⁵, magnesium bromide⁶⁵ and aluminum chloride^{73,76} has also been found to be very effective in displacing the final equilibrium step towards the aldol product.

As a result of our failures to produce ample amounts of species 100b and following up with the postulate that a diketo metal-chelate complex is a desirable intermediate, it was reasoned that greater success might be achieved with a more highly complexing cation such as aluminum.⁹⁶ Aluminum is also easier to work with than Boron or Titanium.

There are very few reports on the use of organoaluminum compounds as aldol-condensing agents.^{96,98,99,100,101} This is probably due to the fact that no standard methodology has yet been developed for transforming the carbonyl compounds into reactive aluminum enolates. Dauben et al.¹⁰⁰ have used aluminum t-butoxide in refluxing benzene to cyclize the diketone 141 to the bicyclic enone 142 in 34% yield. When potassium t-butoxide in t-butyl-alcohol was used only an intractable oily mixture was obtained.

The same aluminum reagent had been used to cyclize the triketone 143 to the enone 144 by Wendler et al.⁹⁹

Tsuji et al.¹⁰¹ in their synthesis of muscone used diisobutylaluminum phenoxide in the presence of a tertiary amine to cyclize the diketone 145 to the enone 146 in 85% yield.

Similar successful intramolecular aldol reactions had been carried out by Nozaki and coworkers¹⁰² via organoaluminum enolates generated from carbonyl compounds with diethylaluminum 2,2,6,6-tetramethylpiperidide at low temperatures.

Several aspects of the aluminum-catalyzed intramolecular aldol cyclizations are noteworthy:

- a. "The combined acid-base attack of the reagents as well as the intimate ion-pair character of the reacting species".^{101,102}
- b. Metal-chelate formation and dehydration of the intermediate aldol product that help to shift the prior equilibria to the final enone product.
- c. Very high regioselectivity.¹⁰¹

After some initial screening experiments the diisobutylaluminum phenoxide was our choice. It was conveniently prepared from diisobutylaluminum hydride (DIBAL-H) and phenol. The solution of di-i-butylaluminum hydride in heptane was added to a solution of phenol (slight excess) and pyridine at 0°. The solution was gently refluxed under argon and the diketone in THF added in a dropwise manner. The progress of the reaction was monitored by t.l.c. After 1 hour the reaction mixture was quenched and the products isolated. Infrared spectroscopy showed both carbonyl groups had been reduced to alcohols and all changes in solvents (toluene, THF, CH₂Cl₂) and reaction times provided no improvement. Our next choice was diethylaluminum ethoxide which is commercially available although a literature search revealed it is not a commonly used reagent.

To a solution of the diketone 99a and 99b as a 1:1 diastereomeric

99a and 99b in methylene chloride was added excess diethylaluminum ethoxide in toluene (10 fold) dropwise with stirring at room temperature under argon. The reaction mixture was kept at 60-80° for 72 h. Thin layer chromatography showed the presence of two overlapping non-polar products after 24 hours and no starting material was left after 72 hours. The reaction mixture was quenched with ice or cold ether and ice, stirred for a further 4 h and then filtered. The organic materials were separated and concentrated. Separation of the two products was difficult but was finally achieved on plc after three developments. The two crystalline products were obtained in 88% yield. The two products were assigned the structures 100a and 100b on the basis of their spectral data and also comparison of 100a with an authentic sample.

The spectral and physical characteristics of the two diastereomeric products deserve some comments. While the infrared, ultraviolet and mass spectra are identical, the ^{13}C , ^1H nmr spectra and melting points are very different. The ir spectrum contains amongst others the 1675 cm^{-1} peak, indicative of α,β -unsaturated ketone; the ultraviolet spectrum (MeOH) contains absorption maxima at 285 ($\epsilon = 1918$), 274 ($\epsilon = 2830$) and 242 ($\epsilon = 6393$). Woodward and Fieser rules predicted λ_{max} of 259 for the α,β unsaturated chromophore. In the mass spectrum the molecular ion peak at 338 was noticeable and the base peak at m/e 323 resulting from loss of a methyl group. In the spectrum of the proton nmr of compound 100a the $\text{C}_{12\alpha\beta}$ -methyl group resonates at 0.90 δ the geminal dimethyl groups at 1.17 δ and the benzylic methyl group at 1.47 δ whereas

100b

in the case of 100b the C_{12aδ}-methyl group resonates at 1.03δ and almost overlapping with the geminal dimethyl groups at 1.40δ, and 1.13δ, and the benzylic methyl group at 1.40δ. The confinement of the methyl groups to a much narrower range reflects the steric overcrowding in the case of compound 100b. The methoxy groups in both compounds resonate at 3.77δ and the chemical shifts for the remaining protons are also comparable including the signal for aromatic protons.

In the ¹³C nmr of 100a (Figure 7) the carbonyl carbons showed signals at 187.1δ compared with 181.6δ for 100b, the olefinic carbons resonate at 144.0δ and 136.9δ compared with 157.1δ and 141.1δ for 100b. The methyl carbons resonate at 24.7δ, 24.9δ, 23.8δ and 26.0δ in contrast to 25.0δ, 24.8δ, 26.4δ and 29.6δ for 100b. All the spectra data of 100a are in excellent agreement with that of authentic sample. The melting point of compound 100b is 129-130° while that of 100a is 89-90° again in good agreement with the previously synthesized 100a.

100a

FIG. 7

Aldol Cyclization of the Tricyclic Ketone (85)

A separate study²⁸ in this laboratory some few years back aimed at the total synthesis of pentacyclic triterpenes has as its specific goal the synthesis of the pentacyclic intermediate of the type 80 via the tricyclic ketone 85 with the hope that such a structure would prove more suited to further manipulation towards the target compound 8 (see pp. 51 and 52). The compound 80 contains six of the eight methyl groups in friedelin and four of the eight asymmetric centres and therefore requires fewer steps to friedelin than in the case of the compound 100b.

The requisite functional groups such as the hydroxyl, the olefinic bonds are also in place for further functionalization to achieve the friedelin structure. Most importantly, the intention was to reach the compound 80 by the aldol cyclization of the tricyclic diketone 85, which was readily prepared along similar lines as the dicyclic diketone 99a and 99b. Our achievement of the aldol cyclization of the bicyclic diketones 99a and 99b led immediately to attempts to reexamine the cyclization of the more complex tricyclic diketone. Previously attempted cyclizations²⁸ employed catalysts such as *t*-butylmagnesium chloride, potassium hydroxide, and *p*-toluenesulfonic acid where rearrangement was found to be prevalent to afford precursors of mostly unnatural products.

Having successfully developed diethylaluminum ethoxide for the aldol cyclization of the bicyclic ketone 99a and 99b the stage was set for the cyclization of the more complex tricyclic diketone 85 although the presence of the hydroxyl and olefinic bonds was of some concern. However no dehydration or any rearrangement was noticed when the alcohol obtained by hydride reduction of the α,β -unsaturated compound 100a was refluxed with the reagent in toluene or xylene.

We therefore decided it reasonable to proceed with the cyclization of the tricyclic diketone 85 which was refluxed in toluene and methylene chloride with diethylaluminum ethoxide (excess) for 72 hours under argon, affording two main products in 78% yield with similar polarities very close to that of the starting material and some minor non-polar products. The two main products were purified by preparative thin layer chromatography (p.t.c.). The least polar product was assigned the structure 80 on the basis of its spectral data.

The mass spectrum of the pentacyclic product 80 is noteworthy. While the mass spectrum of the starting tricyclic diketone 85 showed the molecular ion peak M/e 426 and a major fragment at m/e 408 corresponding to the loss of H_2O (M/e 426-18) followed by a further loss of a methyl group to afford another fragment at M/e 393 (M/e -18-15), the base peak is however at m/e 259 corresponding to the loss of the cyclohexanone appendage (M/e 426-167) (see p. 115).

On the other hand, in the mass spectrum of the product 80 the parent ion peak is at M/e 408, followed by another fragment at m/e 393 corresponding to the loss of the methyl group (M/e 408-15). The m/e 259 is absent, and other major fragments visible in that of the starting tricyclic ketone are absent. The infrared spectrum showed the hydroxyl absorption at 3450 cm^{-1} , the α,β -unsaturated carbonyl peak at 1685 with $\text{C}=\text{C}-\text{C}=\text{O}$ peak at 1655 and the 1,10 and 7,8 olefinic bonds at 1605. The n.m.r. spectrum however displayed the six methyl groups at 0.83 δ 1.10 δ 1.20 δ and 1.27 δ the ring protons at 1.60 δ to 2.20 δ the secondary alcohol proton (C_4-H) at 3.60 δ as a triplet ($J = 7\text{ Hz}$),

the hydroxyl proton at 4.73 δ and the olefinic protons at 5.63 δ as a poorly resolved triplet. It can be concluded from the above data that the undesired rearrangement did not occur upon cyclization.

Compound 80 showed the expected spectroscopic behaviour. The ultraviolet (U.V.) spectrum showed weak absorptions at 254 (ϵ = 4447), 248 (ϵ = 5100) and 220 (ϵ = 8690). Woodward and Fieser rules predicted an absorption maximum of 259 nm (ϵ = < 10,000). The ^{13}C n.m.r. spectrum showed the six methyl groups at 20.7 δ , 24.7 δ , 25.1 δ , 25.8 δ , 26.3 δ and 27.8 δ . The nine methylene carbon resonate at 32.7 δ , 33.2 δ , 34.8 δ , 35.5 δ , 36.3 δ , 36.8 δ , 38.7 δ , 44.1 δ , 49.6 δ . The five quaternary carbons resonate at 35.0 δ , 36.0 δ , 37.5 δ , 49.8 δ , 52.0 δ , the carbinol carbon at 77.1 δ , the CH olefinic carbons at 118.4 δ and 128.3 δ , the fully substituted olefinic carbons at 146.5 δ , 147.7 δ , 144.9 δ and 144.6 δ . The weak peaks at 179.6 δ and 181.4 δ were assigned to the carbonyl carbon. These two peaks reflect the diastereomeric nature of 80. The low value reflects an upfield shift as a result of steric effects and α,β -unsaturation. Some of the carbon resonances show slight variations when compared with those of friedelin and β -amyrin, reflecting the α - and β -effects of functional groups and less 1,3 diaxial interactions in compound 80. Nevertheless the results are comparable with literature values of closely related systems.^{103,135,136,137}. The mass spectrum of the second product does not show the molecular ion peak but displays a peak at 449. Its i.r. spectrum contains the hydroxyl peak at 3400 cm^{-1} (weak), the α,β -unsaturated carbonyl peak at 1685, the C=C-CO bond peak at 1650 cm^{-1} (weak), and the C=C bonds peak at 1575 cm^{-1} . The n.m.r. spectrum shows the six methyl peaks at 0.83 δ , 0.97 δ , 1.13 δ , 1.17 δ , 1.25 δ and 1.37 δ , the ring protons at 1.60-2.20 δ , the secondary alcohol proton at 3.70 δ as a

triplet ($J = 7\text{Hz}$) and the poorly resolved olefinics at 5.63 δ .

Efforts are still underway to determine the structure of this second compound.

80

FIG. 9

The ^{13}C n.m.r. chemical shifts assignments for the Sp^2 carbon atoms and those bearing heteroatoms were mostly derived from literature values of similar systems^{103, 135}. Approximate calculations of chemical shifts were first made for Sp^3 carbon atoms unsubstituted by heteroatoms from data available in standard tables^{136, 137} followed by comparison with literature values of similar polycyclic carbon atoms. Some of the assignments are interchangeable.

Section 3. Further transformations of compounds 100a, 8-methoxy-3,3,10b α , 12a δ -tetramethyl-1,2,5,6-10b,11,12,12a-octahydro-(3H)-chrysen-4-one and 100b, 8-methoxy-3,3,10b δ , 12a δ -tetramethyl-1,2,5,6,10b, 11,12,12a-octahydro-(3H)-chrysen-4-one.

120

With the compound 100a destined to β -amyrin in hand, preparations were then initiated to shift the double bond to the 4b,5 position.

The essence of the synthetic plan (Scheme 22) was to prepare its enol acetate, followed by hydrolysis with BF_3 or NaBH_4 , reduction of the resulting β,γ -unsaturated ketone with lithium aluminum hydride, acetylation and eventual cleavage of the acetate by photolysis to afford compound 163. The most general method⁷¹ for the preparation of enol acetate is by treatment of the carbonyl compound with acetic anhydride and catalytic amount of aqueous perchloric acid, another is by isopropenyl acetate with p-toluenesulfonic acid.⁷⁷

Although the carbonyl of 161 could perhaps also be removed by Clemensen or Wolff-Kishner reduction, the hydroxyl route is not only milder but, most importantly, would enable us to determine the stereochemistry of the future DE ring junction.¹⁰⁴ A solution of the compound 100a in ethyl acetate was added dropwise with stirring to a solution of acetic anhydride also in ethyl acetate followed by catalytic amount of perchloric acid at room temperature under argon. When the reaction was complete, three products of higher polarity than the starting material were detectable on tlc (alumina). After work-up and separation by chromatography, one major (most polar) and two minor products were isolated. The major product was assigned the structure 164 on the basis of its spectral data. The mass spectrum showed the parent ion at M/e 464 and an intense peak at 421 ($M-43$) due to loss of the CH_3CO group. The infrared spectrum showed an unusually strong peak at 1680 cm^{-1} , the ^1H n.m.r. spectrum did not show any aromatic protons and a singlet appeared at 2.18 ppm. The mass spectra of the other

SCHEME 22

minor products showed the parent ion peaks at M/e 394 and 380 but were not further characterized. It was then clear to us that Friedel-Crafts acylation was successfully competing with the desired enol acetylation. Change of solvent (CCl_4) or reaction time (20 min. to 16h) did not result in any improvement. Furthermore, refluxing of the compound **100a** with isopropenyl acetate and catalytic amount of *p*-toluenesulfonic acid in toluene afforded mainly the starting material.

At this point one other method for preparing β,γ -unsaturated ketone was examined.¹³³ Quenching of the enolate of **100a** under kinetic conditions should result in the desired β,γ -unsaturated ketone. To this end a solution of the compound in DME was added

dropwise to a solution of lithium diisopropylamide (prepared from methylolithium and diisopropylamine) at 0° with triphenylmethane as indicator. The reaction mixture was then quenched with acetic acid still at 0° and quickly extracted with pentane. On isolation, however, mostly starting material and some condensation products were recovered.

As a result of this failure, a reevaluation of our strategy was undertaken. It was then realized that the silylenol ether 165 would serve the same purpose as the much sought enol acetate. Treatment of the silylenol ether with tetrabutylammonium fluoride (TBAF) would give the desired β,γ -unsaturated ketone 161. The lithium enolate of the compound 100a was again prepared and quenched with chlorotrimethylsilane at 0° . On work up a less polar product was obtained which after purification by chromatography was assigned the structure 165 on the basis of its spectral data. The mass spectrum showed the expected parent ion peak at M/e 410 a mass fragment at 395 corresponding to a loss of methyl group ($M/e - 15$) and the base peak at m/e 73 very diagnostic of the presence of trimethyl silyl group. Compound 165 showed the expected conjugated double bond absorption in the i.r. spectrum at 1610 cm^{-1} and a shoulder at 1575 cm^{-1} (aromatic $C=C$). In the ^1H n.m.r. spectrum as expected the benzylic protons appeared as a doublet at 3.67δ ($J = 4\text{ Hz}$), the homobenzylic proton at 5.90δ , triplet ($J = 4\text{ Hz}$), the trimethylsilyl group as three singlets at 0.30δ , 0.37δ and 0.45δ , and the methoxy as a singlet at 4.07δ . In the U.V.

SCHEME 23

spectrum however a maximum at 288 nm was observed and an extinction coefficient of $\epsilon = 750$. Woodward-Fieser rules predicted a maximum at 289 nm and extinction coefficient of 8000-20,000. The unusually low extinction coefficient could be attributed to the non-coplanarity of the conjugated double bonds^{105, 106} as observed from the Dreiding model. In the ^{13}C nmr, the olefinic carbons were observed at 180.1 δ (C_4), 111.2 δ (C_{4a}), 156.8 δ (C_{4b}), 111.2 δ (C_5).

With the silyl enol ether 165 firmly in hand, we then proceeded to remove the trimethylsilyl group with tetrabutyl ammonium fluoride (TBAF). A solution of the silyl enol ether in THF was stirred with TBAF at room temperature for 2h. On isolation and purification the isolated product was assigned the structure 161 in accordance with its spectral data. The i.r. spectrum showed the expected saturated carbonyl absorption at 1700 cm^{-1} and the double bond at 1605 cm^{-1} . Weaker absorptions were also observed at 1675 cm^{-1} and were attributed to the presence of traces of species 100a. The ^1H nmr spectrum showed the expected $\text{C}_5\text{-H}$ proton at 5.60 ppm as an unresolved multiplet and the $\text{C}_6\text{-H}$ proton at 3.60 ppm.

Our inability to isolate enone 161 as a pure compound led us to suspect its stability. Indeed to our dismay, storage of the enone 161 in the fridge for two days resulted in recovery of the starting compound 100a. To prove also that isomerization was occurring treatment of the enone 161 with acetic acid gave the starting species 100a. This thus demonstrates that the exocyclic double bond was migrating to afford the more stable thermodynamic starting tetracyclic compound 100a.

At this point it was clear to us that the relative instability of the unconjugated system would not permit the isolation and prolonged storage of the β,γ -unsaturated ketone: it has to be used immediately on preparation. Since conjugation with the carbonyl was the driving force for the rearrangement it was decided that the enone 161 should be reduced to the alcohol in situ. To this end the unconjugated enone 161 was prepared as above and its ethereal solution added to a stirred slurry of lithium aluminum hydride in ether at room temperature. After work up and purification by preparative layer chromatography, a more polar compound was isolated and assigned the structure 162. As expected the i.r. spectrum showed the hydroxyl absorption at 3440 cm^{-1} , the C=C at 1610 cm^{-1} and the aromatic C=C at 1575 cm^{-1} .

In the ^1H nmr spectrum the methoxy group appeared as a singlet

at 3.77 δ and the benzyl proton (C_6 -H) as a doublet at 3.80 δ ($J = 2\text{Hz}$) and the C_4 -H as a doublet at 3.88 ($J = 2\text{Hz}$). The mass spectrum showed the parent ion peak at M/e 340, a major fragment at m/e 325 corresponding to the loss of a methyl group ($M/e - 15$) and another at 307 corresponding to a further loss of water.

Determination of the stereochemistry of the future DE ring junction and the hydroxyl.

Deconjugation of the enone 100a double bond will create a new asymmetric centre at C-4a thus resulting in two diastereomers i.e. the cis and the trans DE ring junctions (Scheme 23a). The stereochemistry of reduction of carbonyl compounds by metal hydrides has been well studied but has been the subject of considerable controversy.^{107,108,109} All metal-hydride-ketone reductions are believed to have transition states that resemble the reactants in geometry and the reduction stereochemistry is the result of such factors as steric interference, torsional strain and electrostatic effects in the transition state. The stereochemical courses of reduction of the cis 161b and the trans 161a enones would be expected to be different. In case of the trans enone 161a the 1,3 diaxial interaction between the metal hydride and C_{12a} -CH₃ would hinder the approach of the hydride from the β -face (steric approach control)^{107,108} (Fig.10). Approach of the hydride from the less hindered α -face would result in the β -axial alcohol 162b. On the other hand, in case of the cis enone 161b the 1,3 diaxial interaction is absent, (Fig. 11) approach of the metal hydride from either face is probable although an axial-equatorial coupling ($J_{ae} = 2\text{ Hz}$) implies attack of the metal hydride from the β -face

unfavourable

III

FIG. 10

favourable

|||

Fig. 11

to afford an α -axial alcohol 162 .

In order to confirm our stereochemical assignments some simplification and clarification of the nmr spectra were required. Lanthanide nmr shift reagents are extremely valuable for the chemical shift and structural assignments.¹¹⁰⁻¹¹⁴ Shift reagents are lanthanide β -diketonates, which are Lewis acids and function by complexing to the nucleophilic centers of the compound being analysed. They induce large paramagnetic shifts in the signals of protons in the immediate vicinity of the metal and small in distant rings. The shifts induced can give valuable insight into the structure and conformation of the rings especially where a hydroxyl group resides. The induced shifts are attributed to pseudocontact and dipolar interaction between the shift reagent and the nucleophile.¹¹⁰ The chemical shift of a given peak is dictated by the new environment of the nuclei in the complexed and uncomplexed molecules. The new environment in turn depends on the stability of the complex formed and the amount of shift reagent added. Usually addition of aliquots of the shift reagent to the sample produces varying changes in the chemical shifts of the protons. The relationship thus provides one with some information about the stereochemistry of substitution around the lanthanide metal atom. While a variety of combination of β -diketonates and lanthanide metals exist, the most common ones are the fluorinated octanediones and heptanediones of Eu (111), Yb (111) and Pr (111).

Despite many assumptions¹¹⁸ entailed in the application of lanthanide shift reagents, extremely accurate results have often been obtained^{104,115,116}. The McConnell-Robertson equation relates

the induced chemical shift of a given nucleus $\Delta\nu_1$ and the location of the nucleus ν_1 , to its distance r , from the lanthanide ion and θ , the angle between the principal magnetic axis of the complex.¹¹⁷ K is a constant.

$$\frac{\Delta\nu_1}{\nu_1} = K \frac{(3\cos^2\theta - 1)}{r^3}$$

The Angle Factor in McConnell-Robertson Equation.

The angle term in the McConnell-Robertson equation determines the direction and magnitude of the induced shift. When the angle θ is less than 55° , the induced shifts are downfield for Eu, and when it is greater than 55° but less than 125° the shifts are in the

opposite direction, that is, upfield. The direction of shift and the magnitude therefore corresponds to the term $3\cos^2 \theta - 1$, remaining negative for some range of angles. One would therefore expect that, in the presence of Eu shift reagent, some peaks will be shifted downfield, others upfield while some will remain unchanged.^{146,147,148} The DE ring junction stereochemistry in compound 162.

The magnitude of the vicinal couplings between various protons can be simply related to the dihedral angles through the Karplus relationship.¹²² A coupling constant of 2Hz strongly indicates an axial-equatorial coupling and absence of axial-axial coupling.¹²³ It has been shown that in proton-proton coupling, the orientation of the electronegative group affects the coupling constant 3J .^{123,124} In steroids, the J_{ae} of structure 169 below is about 5.5 ± 1 Hz for $R = OH$ or OAc while for 163 the J_{ae} is in the range of 2.5-3.2 Hz that is, the electronegative group exerts its maximum effect when it is trans-coplanar to one of the coupled protons thus resulting in minimum J_{ae} . Having established the relative stereochemistry of the C_4-H and $C_{4a}-H$, that of the DE ring junction was investigated with $Eu(fod)_3$.¹²⁵ It was anticipated that because of the two possible sites for complexation the methoxy and the hydroxyl, the preferential site would be the more basic, hydroxyl group.¹¹⁴ The nmr spectra of the alcohol were then obtained in the presence of varying aliquots of the $Eu(fod)$ solution. In the preliminary investigation $Eu(dpm)_3$ was found to be rather unsatisfactory due to its poor solubility in $CDCl_3$.¹¹⁴ $Eu(fod)_3$

$$J_{ae} = 5.5 \pm 1 \text{ Hz}$$

169

$$J_{ae} = 2.5 - 3.2 \text{ Hz}$$

168

R = OH or OAc

provided the best results as illustrated on the graph below. It could be seen that the least shifted methyl group signal is that of $C_{10b}\text{-CH}_3$, while the most shifted is the $C_{12a}\text{-CH}_3$ signal. From the distance and angle measurements of the Dreiding model for a trans DE ring junction (see Table I, p. 136) one would expect the least shifted to be that of $C_{12a}\text{-CH}_3$ (57° , 6.0 cm) the critical angle being 55° . Similarly for cis DE ring junction one would expect the $C_{10b}\text{-CH}_3$ (benzylic) signal to be the least shifted (58° , 6.3 cm) which is in accord with the experimental results. It is therefore concluded that the alcohol 162 DE ring junction is cis.

Determination of Stereochemistry of D/E ring Junction of Alcohol
162 . Graph plot of $[\text{Eu}(\text{fod})_3]$ and shift change.

Graph 1

Table I: Dreiding Models Measurements
Trans Ring Junction Alcohol 162b

Methyl	Angle θ *	Distance R **
C _{12a} -Methyl	57°	6.0
Geminal Dimethyl	38°	12.0
	15°	17.2
C _{10b} -Methyl (benzylic)	38°	19.1
C _{4a} -4	24°	13.8

Cis Ring Junction. Alcohol 162

Methyl	Angle θ	Distance R
C _{12a} -Methyl	40°	15.2
Geminal dimethyl	22°	16.3
	42°	12.0
C _{10b} -Methyl (benzylic)	58°	6.3
C _{4a} -H	16°	13.8

* θ is the angle between the lanthanide-nucleophile bond axis and a line drawn from the nucleus of interest to the lanthanide ion. The nucleus of a methyl group is assumed to be the center of the circle described by the three hydrogens.¹¹⁴

** R is the distance from the lanthanide ion to the nucleus of interest.

Conjugate methylation of the enone 100b, 8-methoxy-3,3,10b8, 12a8-tetramethyl-1,2,5,6,10b,11,12,12a-octahydro-(3H)-chrysen-4-one.

While the stereochemistry of the DE ring junction of the alcohol 162 was being determined, preliminary preparations were being made to methylate enone 100b (destined for friedelin) at the β -carbon. As has been discussed in section 1, the most popular method to effect a conjugate addition to an enone is through organocuprate reagents. Since our main objective was to introduce the methyl group at the α -face, the feasibility of such a methylation was first examined. An examination of the Dreiding model of the enone 100b shows that the α -face of the double bond is not as hindered as the β -face. Consequently, approach of the methyl group from the β -face is not favoured due to the 1,3 diaxial interaction with the C_{12a} -methyl, while approach from the relatively unencumbered α -face will result in the desired α -methyl at the β -carbon. The enone 100b was then treated with methylmagnesium bromide in the presence of tetrakis iodo (tri-n-butylphosphine)-copper (I), nBu_3PCuI ^{73, 128} as discussed in section 1. However only the starting enone was recovered on work-up. Changes in reaction time (4-12 h) and temperature (-60° to 25°) resulted in no observable reaction.

It is known that presence of Cu(II) and other metal impurities in the Cu(I) salts used to form organocuprate reagents often resulted in side reactions or lack of reaction and $Me_2S-CuBr$ is often preferred.⁵⁸ The

$\text{Me}_2\text{S-CuBr}$ was prepared according to a modification of the method of House and coworkers.⁵⁸ Excess methyl sulfide was added to pulverized cuprous bromide, stirred and filtered. Hexane was then added and the white crystals that appeared were washed until colorless, and dried under argon. The conjugate methylation was then attempted with $\text{Me}_2\text{S-CuBr}$ and methyllithium. A colorless solution of the $\text{Me}_2\text{S-CuBr}$ in methyl sulfide and ether was added dropwise with stirring at room temperature to an ether solution of methyllithium until a yellow precipitate that was produced dissolved. At this point, a solution of the enone 100b in ether was added and the reaction mixture stirred for one hour. On work-up only the starting enone was again recovered.

Following these failures, we then turned our attention to another method closely related to the Michael reaction involving conjugate addition of the cyanide ion to the β -carbon often referred to a hydrocyanation.¹²⁶ According to Nagata¹²⁶ hydrocyanation with preformed diethylaluminum cyanide results in the formation of mostly thermodynamically more stable cyano-isomer while kinetically controlled conditions ($\text{Et}_3\text{Al-HCN}$) furnish the less stable cyano-isomer. Although it is not really apparent to us which isomer represents the less or more stable, we decided to carry out a trial experiment with the commercially available diethylaluminum cyanide. Treatment of the enone 100b with diethylaluminum cyanide in benzene and toluene at room temperature again resulted only in the starting enone. Changes in reaction time (1 to 24h) or solvent

(THF) or temperature (0° to reflux) did not result in any improvement either. It must be mentioned that in all the three reactions above, traces of some deconjugation through enolization and α -protonation on work-up were observed.

In view of the unfavourable results of these conjugate ~~addition~~ experiments, the kinetically controlled ($\text{Et}_3\text{Al-HCN}$) hydrocyanation was not carried out, instead we decided to attempt another procedure to introduce the methyl group that does not involve conjugate addition. The Simmons-Smith reaction¹²⁷ involves transfer of a methylene group from a ZnCH_2I complex to a double bond to form a cyclopropyl derivative, an hydroxyl group being used to direct its orientation. The eventual opening of the resulting cyclopropane ring could afford a methyl group with the desired stereochemistry.

A preliminary analysis of the hydride reduction of the enone 100b predicts the formation of an alcohol with a β -axial C_4 -hydroxyl function in the wrong orientation to direct the Simmons-Smith methylenation in the required direction. Nevertheless, we decided to proceed with the reaction for two reasons. Firstly, the desired α -alcohol might be produced and secondly, further conformational analysis with shift reagents would enable us to compare our previous results for alcohol 162.

Attack of the hydride from the relatively hindered β -face is unfavourable due to the 1,3-diaxial interaction with the $\text{C}_{12a\beta}$ -methyl while the approach from the unencumbered α -face will lead to the β -axial alcohol (Fig. 12). Reduction of the enone 100b with LAH afforded

FIG. 12

the colourless crystalline alcohol 166 (m.p. 91°). The mass spectrum showed the parent ion peak at M/e 340, the base peak at m/e 325 corresponding to loss of a methyl group, and another major fragment at m/e 307 corresponding to a further loss of H_2O . The i.r. spectrum showed a weak hydroxyl absorption at 3400 cm^{-1} and $C=C$ bond absorption at 1605 cm^{-1} . The 200 MHz 1H n.m.r. spectrum showed singlets at 0.85 δ and 1.04 δ (gem-dimethyl), 1.15 δ ($C_{12a}-CH_3$) 1.39 δ (benzylic methyl), the benzylic protons as a poorly resolved multiplet (two overlapping doublets) at 2.80 δ , the methoxy group at 3.78 δ , the C_4 -methine proton at 4.47 δ singlet, and the aromatic protons at 6.54-7.22 δ (multiplet).

In the ^{13}C n.m.r. spectrum the $HO-C_4$ carbon showed a signal at 79.7 δ ppm the methoxy at 55.0 δ and the olefinic carbons at 139.4 δ and 138.1 δ (Figure 13). Proposed ^{13}C resonance assignments for the alcohol 166 are also indicated in this Figure.

FIG. 13

In order to confirm the stereochemistry of the hydroxyl of the alcohol 166 the ^1H n.m.r. spectra were obtained in the presence of varying aliquots of $\text{Eu}(\text{fod})_3^{110}$. The results are as illustrated in Graph 2. It could be seen from the Graph 2 that the signals for geminal dimethyl groups are the most shifted by the lanthanide ion and almost equally while the signals for the C_{12a} - and benzylic methyl groups are the least shifted and also almost together. An examination of the distance and angle measurements from the Dreiding models (see Table II, p. 145) shows that for an equatorial alcohol all the four methyls should be shifted in a mixed pattern and within a narrow range. On the other hand, for the β -axial alcohol, the signals for the geminal dimethyl group should be most shifted while the benzylic and the C_{12a} -methyl the least shifted (the critical angle being 55°) which agrees well with the experimental result. It is therefore concluded that the orientation of the hydroxyl of the alcohol 166 is the undesired β -axial as predicted by the principle of steric approach control. The Simmons-Smith methylenation route was therefore not attempted.

Finally one other route that was being developed for the conjugate methylation but proved to be rather unpredictable involved refluxing of the enone 100b with diethylaluminum ethoxide, in excess dichloromethane and xylene for 3 days. On hydrolytic work-up, some starting material and two other products were recovered. One was tentatively assigned the structure 167 and the other was not fully characterized. The mass spectra of 167 and the other material showed parent ion peaks at 356 and 368 respectively. The alcohol 167 shows no u.v. activity. Its i.r. spectrum shows a weak hydroxyl absorption at 3400 cm^{-1} , and the aromatic $\text{C}=\text{C}$ at 1600 cm^{-1} . The ^1H n.m.r. spectrum shows five

Determination of the stereochemistry of the hydroxyl of alcohol 166.
Graph plot of $[\text{Eu}(\text{fod})_3]$ and shift change.

Graph 2

Table II. Dreiding Model Measurements
Equatorial Alcohol

Methyl	Angle θ^*	Distance R^*
C _{12a} -Methyl	22°	18.6 cm
Geminal Dimethyl	eq. 43° Ax. 22°	11.5 16.7
C _{10b} -Methyl (benzylic)	40°	17.5

β -axial alcohol

C _{12a} -Methyl	58°	10.6
Geminal Dimethyl	eq. 38° Ax. 48°	12.9 9.8
C _{10b} -Methyl (benzylic)	64°	14.8

* Angle θ and Distance R are as defined on p. 135.

methyl singlets at 0.87 δ , 1.07 δ , 1.17 δ , 1.30 δ and 1.40 δ the ring protons at 1.53-2.17 δ benzylic protons at 2.80 δ as a poorly resolved doublet the methoxy at 3.80 δ , HO-C_4 -proton at 4.50 δ also as a poorly resolved doublet and the aromatic protons at 6.60-7.27 δ . Efforts are continuing to investigate this unusual reaction.

Summary of Discoveries

A summary of the discoveries in this thesis is as follows:

SECTION 1

Our first approach to the synthesis of the compounds 100a and 100b, precursors of β -amyrin and friedelin respectively, involving the coupling of β -tetralone 90 and enone 103 was not successful due to the enolic nature of the β -tetralone.

SECTION 2

In an alternate route, while conventional bases and acids failed to cyclize the bicyclic diketones 99a and 99b, diethylaluminum ethoxide was found to be very successful. With the same reagent the synthesis of the pentacyclic compound 80, a precursor of friedelin with six methyl groups and four of the desired asymmetric centres was achieved.

SECTION 3

Further transformations of the compound 100a were described. Although the enol acetate route for the synthesis of β,γ -unsaturated ketone 161 failed due to extensive Friedel-Crafts acylation of the aromatic ring, the silylenol ether approach was very successful.

Conventional conjugate addition methods have failed in the conversion of 100b to 170 or 171. Hydride reduction of the compound 100b gave predominantly the undesired equatorial epimeric alcohol.

A new approach to effect the conjugate methylation is being investigated.

Suggestions for Future WorkFriedelin Route:

1. The enone 100b is now firmly in hand although its conjugate methylation has not been successful. Since our original work more attractive reagents have surfaced.¹²⁸ One involves treatment of the enone with tin reagents such as Me_3SnLi , $\text{Me}_3\text{SnCuMe}_2\text{S}$, $[\text{Me}_3\text{SnCuSPh}]\text{Li}$, $[\text{nBu}_3\text{SnCuSPh}]\text{Li}$ followed by a base and the alkylating agent.

2. Another attractive approach involves addition of cyanotrimethylsilane.¹²⁹ Utimoto has recently showed that cyanotrimethylsilane adds to some α,β -unsaturated ketone in a conjugate manner under the catalytic action of Lewis acids such as triethylaluminum, aluminum chloride, and stannous chloride and the resulting product on hydrolysis affords β -cyano ketones.¹²⁹

3. Another feasible route to the conjugate addition is to build in a potential methyl group such as an epoxide in the C ring before cyclization of the diketone. Such a transformation could be achieved with dimethylsulfoxonium methylide.¹³⁰ Based on the present work, it is expected that the second carbonyl, being more hindered, would not be as reactive.

4. An unusual but attractive approach that is being pursued involves methylation at the α -carbon atom¹³³, hydride reduction of the carbonyl followed by the type of rearrangement already discussed in the Introduction on catalytic hydrogenation with Pd/C.²⁸

B-Amyrin Route:

Having successfully synthesized the alcohol 162, the stage is then set for the removal of the hydroxyl group and the reduction of the aromatic ring. A very efficient method for such removal especially with apparently hindered alcohols has been achieved by Ireland²² by means of the lithium methylamine reduction of the tetramethylphosphorodiamidate (TMPDA) derivative. The reaction resulted in both removal of the TMPDA group and the reduction of the aromatic ring. An alternative method is to cleave the acetate derivative by pyrolysis.¹³²

EXPERIMENTAL

General

All melting and boiling points were uncorrected. The melting points were measured on Fisher-Johns apparatus. Infrared (ir) spectra were recorded on a Perkin-Elmer Model 237B or 683 Infrared Spectrophotometer in chloroform unless otherwise specified. Absorption frequencies are reported in cm^{-1} . Nuclear magnetic resonance (nmr) spectra were measured on Varian T-60 or EM 360. The high resolution ^1H and ^{13}C nuclear magnetic resonance spectra were obtained on Varian XL 200 (Carleton University) or Bruker 250 instrument (Agriculture, Canada). Chemical shifts expressed in ppm (δ scale) using tetramethylsilane (TMS) as internal standard, and are expressed with the following designations: (s), singlet; (d), doublet; (t) triplet; (m), multiplet; (br), broad. Ultraviolet (uv) spectra were recorded on a Perkin-Elmer 202 Ultraviolet-Visible spectrometer in methanol unless otherwise indicated. The mass spectra were measured on a VG 7070 E (University of Ottawa). Combustion analyses were performed by Spang Microanalytical Laboratory, Ann Arbor, Michigan and Guelph Chemical Labs. Ltd. Guelph, Ontario.

All reactions and chromatograms were routinely monitored by analytical thin layer chromatography (tlc) on precoated silica gel plates (Merck 60, PF-254, 0.25 mm). Plates were visualized under uv light or by exposure to iodine vapour or by spraying with ceric sulfate and heating. Preparative thin-layer chromatography (plc) was carried out on Merck 60 F-254 precoated silica gel plates of

2.0 or 0.25 mm thickness. Bands were visualized under ultraviolet source or by staining a thin edge with ceric sulfate or heating. Silica gel (Davidson Chemical Co., grade 923, 100-200 mesh) was used for column chromatography. Flash chromatography refers to elution of material on a silica gel pad (silica gel 60H-E.M. Reagents, sintered glass funnel) using water aspirator suction. Preparative HPLC was performed with Waters Prep-500 Liquid Chromatography instrument, on Prep-pak silica gel columns (Waters Associates).

Anhydrous solvents were dried immediately prior to use. Benzene, toluene, xylene, tetrahydrofuran (THF), dioxane, dimethoxyethane and ether were all dried over sodium with some benzophenone as indicator and distilled over sodium. Hexamethylphosphoramide (HMPA) was distilled at reduced pressure prior to use. Chlorotrimethylsilane was treated with triethylamine and magnesium sulfate and then filtered before use.

Abbreviations

THF	Tetrahydrofuran
DMSO	Dimethyl sulfoxide
DME	Dimethoxyethane
TMSCl	Chlorotrimethylsilane
Py	Pyridine
DMF	N,N-dimethylformamide
Ts, tosyl	p-toluenesulfonyl
tlc	Thin layer chromatography
plc	Preparative thin layer chromatography

THP	tetrahydropyranyl
H.P.L.C.	High performance liquid chromatography
L.S.R.	Lanthanide shift reagent
Bu ₄ N ⁺ F ⁻ , TBAF	Tetrabutyl ammonium fluoride

3,6,6-Trimethyl-2-cyclohexenone (74)

To a stirred solution of potassium hydroxide (56g, 1 mol) in absolute ethanol (250 mL) at ice-bath temperature was added dropwise freshly distilled 3-methyl-2-butanone (172g, 2 mol) in anhydrous ether (100 mL) during 40 min. Stirring was maintained for another 1 h at 0° and freshly distilled methyl vinyl ketone (210g, 3 mol) in anhydrous ether (100 mL) added dropwise during 1 h. The reaction mixture was stirred for another 3 h at 0° and 4 h at room temperature and then added to ice-water mixture. The organic layer was separated and then combined with ethereal extract of the aqueous phase. The combined ethereal extract was washed with HCl (3N, 3 x 200 mL), NaHCO₃ (3 x 100 mL), dried over magnesium sulfate and concentrated. Distillation yielded 85.1 g of a yellowish liquid mixture 130°/3.3 torr. Purification by HPLC yielded 88.5 g (32%) of a colourless liquid 74 that has infrared (neat) absorptions at 1672 cm⁻¹ (unsaturated C=O), 1635 cm⁻¹ (C=C). NMR (CDCl₃) δ 1.10 (6H, s, gem-dimethyl) 1.83 (2H, t, C₅-H), 1.92 (3H, s, C₃-CH₃) 2.33 (2H, t, C₄-H) and 5.75 (1H, s, C₂-H).

Tetrakis[iodo(tri-n-butylphosphine)Copper(I)]⁵⁶

Tri-n-butylphosphine (12.5 mL, 0.05 mol) was vigorously shaken up with a decolourised solution of potassium iodide (130 g, 0.78 mol) in water (100 mL) and copper(I) iodide (15 g, 0.069 mol). Vigorous shaking was continued until the greasy reaction mixture became crystalline. After filtration, the white crystalline solid was washed with saturated potassium iodide solution (3 x 10 mL), distilled water (3 x 10 mL), cold 95% ethanol (3 x 10 mL) and then dried. Recrystallization in ethanol and acetone mixture (1:1) yielded 16.8 g (86%) of a colourless crystalline solid m.p. 74°, literature mp 75°.

3,6,6-Trimethyl-3-vinylcyclohexanone ⁹¹ ⁷³

A stirred solution of enone 74 (27.6 g, 0.2 mol) and tetrakis [iodo(tri-n-butylphosphine)copper(I)] (3.93 g, 0.01 mol) in THF (200 mL) was cooled to -65° and then vinylmagnesium bromide (167 mL, 1.5 M, 0.25 mol) was added dropwise over a period of 40 min. while the temperature was kept between -40° and -65° for an additional 4 h. The reaction mixture was then left to stir overnight and gradually warmed to room temperature. The reaction mixture was then added to ammonium chloride - ice mixture, allowed to stand for 2 h and then partitioned between hexane and aqueous NH₄Cl. After the organic layer was separated and then combined with extract of aqueous phase, it was washed with cold HCl (3 x 15 mL) NaHCO₃ (1 x 50 mL) and brine (1 x 50 mL) and then dried over magnesium sulfate. After

removal of the solvent, distillation at water pressure yielded 28.3 g (85%) of a colourless oil 91 b.p. 108-110/25 torr. A collected sample of the vinylketone 91, a colourless liquid, has infrared absorptions at 1700 cm^{-1} (nonconjugated C=O), 1649 cm^{-1} (C=C). The nmr spectrum has absorptions at δ 1.05 (3H, s, $\text{C}_3\text{-CH}_3$), 1.07 (3H, s, $\text{C}_6\text{-CH}_3$), 1.12 (3H, $\text{C}_6\text{-CH}_3$), 1.73 (4H, s, $\text{C}_4\text{-CH}_2$ and $\text{C}_5\text{-CH}_2$), 2.24 (1H, s, $\text{C}_2\text{-H}$), 2.54 (1H, s, $\text{C}_2\text{-H}$), 4.7-5.4 (2H, m, CH=CH_2), 5.5-6.1 (1H, m, CH=CH_2), mass spectrum m/e (rel intensity) 166(M^+ , 24), 95 (52), 69(100), 68(40), 67(60), 55(37).

Trimethylsilyloxy-3,6,6-trimethyl-3-vinyl-1-cyclohexene 103

An ethereal methylolithium solution (200 mL, 1.4 M, 0.28 mol) was concentrated at reduced pressure to about one-tenth its original volume and the residue redissolved in dry 1,2-dimethoxyethane (200 mL). The reaction mixture was cooled to 0° and diisopropylamine (39.3 mL, 28.3 g, 0.28 mol) added dropwise during 30 min. under argon. The vinylketone 91 (33.2 g, 0.2 mol) was then added dropwise and the stirring continued for 1 h at ice-bath temperature. The reaction mixture was then quenched with freshly distilled chlorotrimethylsilane from triethylamine (50 mL, 0.42 mol). Stirring was continued for another 15 min at 0° and 15 min at room temperature. The resulting mixture was then partitioned between hexane and cold aqueous NaHCO_3 . The organic layer was separated and then combined with the aqueous extracts. The combined hexane extract was washed with water (3 x 100 mL), brine (1 x 100 mL) and dried over magnesium sulfate. After removal of the solvent, purification by HPLC yielded

29.6 g (62%) of a colourless liquid. $\text{ir } 1650 \text{ cm}^{-1}$ ($\text{C}=\text{C}-\text{OSi}$) shoulder at 1620 cm^{-1} ($\text{C}=\text{C}$). NMR δ 0.20 (9H, s, $-\text{Si}(\text{CH}_3)_3$), 1.02, 1.04 (6H, 2s, gem-dimethyl), 1.07 (3H, s, C_3-CH_3), 1.50 (4H, s, C_4-CH_2 , C_5-CH_2), 4.57 (1H, s, C_2-CH), 4.80-5.20 (2H, m, $\text{CH}=\text{CH}_2$) 5.62-6.10 (1H, m, $\text{CH}=\text{CH}_2$).

3,6,6-Trimethyl-3-vinylcyclohexanone ethylene ketal 132

To a stirred solution of 3,6,6-trimethyl-3-vinylcyclohexanone 91 (18.2 g, 0.11 mol) in dry benzene (200 mL) was added ethylene glycol (20 mL) and para-toluenesulfonic acid (300 mg). The flask was fitted with a condenser and Dean-Stark water aspirator, and the reaction mixture refluxed overnight. The benzene layer was washed with water (3 x 50 mL), brine (1 x 100 mL) and dried over magnesium sulfate. Removal of solvent yielded 20.1 g (96%) of a colourless oil. ir (neat) loss of $\text{C}=\text{O}$. NMR (CDCl_3) δ 0.95 (3H, s, gem-dimethyl), 1.08 (3H, s, gem-dimethyl), 1.05-1.22 (6H, m, C_2-CH_2 , C_4-CH_2 , C_5-CH_2), 3.97 (4H, s, $-\text{O}-\text{CH}_2-\text{CH}_2-\text{O}-$) 4.73-5.16 (2H, m, $\text{CH}_2=\text{CH}$), 5.70-6.33 (1H, m, $\text{CH}_2=\text{CH}$).

3-(2-Hydroxyethyl)-3,6,6-trimethylcyclohexanone ethylene ketal 133

To a stirred solution of 9-borabicyclononane (9-BBN) (240 mL, 0.5M, 0.12 mol) in THF at 0°C under argon was added dropwise the ethylene ketal 132 (21.0 g, 0.10 mol) in dry THF (200 mL). Stirring was maintained for additional 24 h at room temperature, at which time no starting material was observable on tlc. The reaction mixture was then oxidised by dropwise addition of 3N sodium hydroxide (50 mL) followed by 30% hydrogen peroxide (50 mL)

at ice-bath temperature followed by gradual warming to room temperature. The THF was removed under reduced pressure and the residue extracted with ether (3 x 200 mL). The combined ethereal extract was washed with cold HCl (3N, 3 x 100 mL), water (3 x 100 mL), brine (1 x 100 mL) and dried over anhydrous magnesium sulfate. After removal of the ether, purification by HPLC yielded 21.5 g (94%) of 133 as a colourless oil. ir (neat) 3388 cm^{-1} (OH); NMR (CDCl_3) δ 0.96 (6H, s, gem-dimethyl), 1.00 (3H, s, C-3 CH_3), 3.74 (2H, t, $J = 8\text{ Hz}$, CH_2OH), 3.99 (4H, s, $-\text{O}-\text{CH}_2-\text{CH}_2\text{O}-$).

3-(2-p - toluenesulphonyloxyethyl)-3,6,6-trimethylcyclohexanone ethylene ketal 70.

A solution of para-toluenesulfonylchloride (38.0 g, 0.2 mol) in anhydrous ether (200 mL) was added dropwise to a stirred solution of the alcohol 133 (22.8 g, 0.1 mol) in anhydrous ether (100 mL) and dry pyridine (32 g, 0.4 mol) at ice-bath temperature. The ice-bath was removed and reaction stirred for extra 24 h at room temperature. No starting material was observed at this time. The reaction mixture was filtered and then poured into ice-cold water (300 mL). The organic layer was quickly washed with ice-cold HCl (3N, 3 x 100 mL), NaHCO_3 (1 x 100 mL) and dried over magnesium sulfate. After removal of the ether, 35.2 g (92%) of a white crystalline solid was obtained. Further crystallization in acetone afforded 33.4 g (87%) of pure 70 mp $111-112^\circ$; ir (CHCl_3) 1595 cm^{-1} (phenyl), 1420 cm^{-1} and 1195 cm^{-1} ($-\text{OSO}_2-$), NMR (CDCl_3) δ 0.89 (3H, s, C_3-CH_3), 0.92 (6H, s, gem-dimethyl), 1.40 (6H, broad s, C_2-CH_2 , C_4-CH_2 , C_5-CH_2),

2.47 (3H, s, Ar-CH₃), 3.90 (4H, s, -O-CH₂-CH₂-O-), 4.17 (2H, t, J = 7.5 Hz, CH₂-OTs), 7.41 (2H, d, J = 8 Hz, Ar), 7.87 (2H, d, J = 8 Hz).

Mass spectrum, molecular ion, m/e 382.

Anal. Calcd. for C₂₀H₃₀O₅S: C, 62.87; H, 7.85; S, 8.39;

Found: C, 62.88; H, 7.75; S, 8.27.

1-Methyl-6-methoxy-3,4-dihydronaphthalene 105²²

To a solution containing 6-methoxy-1-tetralone (35.2 g, 0.2 mol) in dry benzene (200 mL) was added methylmagnesium bromide (100 mL, 2.1M, 0.21 mol) solution in anhydrous ether dropwise with stirring. The reaction mixture was stirred at room temperature for 3 h and then quenched with ice and aqueous ammonium chloride mixture. The organic layer was separated and the aqueous layer extracted with ether (3 x 200 mL). The combined ethereal extract was washed with HCl (1N, 1 x 100 mL), saturated brine (1 x 100 mL) and dried over magnesium sulfate. Concentration at reduced pressure gave an orange liquid which on distillation yielded 31.4 g (90%) yellow liquid. b.p. 108-112/4.5 torr., literature bp 93-94⁰/1 torr.²²

IR (CHCl₃) 1640 cm⁻¹ (C=C), 1605 cm⁻¹ (ArH). NMR (CDCl₃)

δ 2.00 (3H, s, x=C-CH₃), 2.56-2.80 (4H, m, benzylic and homobenzylic H), 5.70 (1H, br. m, C=C-H), 6.57-7.33 (3H, m, ArH).

1-Methyl-6-methoxy-3,4-dihydro-2-(1H)-naphthalenone²² gō

To a stirred solution of 1-methyl-6-methoxy-3,4-dihydronaphthalene (17.4 g, 0.1 mol) in anhydrous ether (200 mL) at 0° was added an ethereal solution of freshly prepared and standardized solution of monoperphthalic acid (390 mL, 0.388 M, 0.12 mol) dropwise under argon such that the internal temperature was between -5° and +5°. On completion of addition, the reaction mixture was left to stir at 0° for 5 h and then overnight. Meanwhile ice-cold 40% sulfuric acid (200 mL) was prepared and added dropwise with stirring still maintained. The reaction mixture was then left to stir at room temperature under argon for 2 days. The organic layer was then separated and combined with the ethereal extracts (3 x 200 mL). The combined organic extract was washed with saturated aqueous sodium bicarbonate solution (3 x 100 mL), saturated brine (3 x 100 mL) and dried with magnesium sulfate. After concentration at reduced pressure, distillation yielded 17.6 g (93%) of a colourless oil, b.p. 128-129°/0.9 torr, that crystallized in the fridge m.p. 30-32°, literature bp 100-110/0.2 torr.²² Ir (CHCl₃) 1705 cm⁻¹ (C=O), 1605 cm⁻¹ (ArH). NMR (CDCl₃) δ 1.43 (3H, d, J = 7 Hz, -CH₃) 2.40-2.67 (2H, m, homobenzylic CH₂), 2.97*3.18 (2H, m, benzylic CH₂) 3.30-3.67 (1H, q, J = 7 Hz, (HCO) 3.80 (3H, s, O-CH₃), 6.77-7.27 (3H, m, ArH).

Monoperphthalic acid⁴³

Recrystallized phthalic anhydride (66 g, 0.45 mol) and sodium perborate (92 g, 0.60 mol) was added to water (280 mL). The mixture was stirred at 0° for 3 h. It was then shaken with ether (200 mL) and acidified with ice-cold 30% sulfuric acid (120 mL). The ether layer was separated and the aqueous portion extracted with ether (3 x 100 mL). The combined ethereal extract was washed with 40% ammonium sulfate solution (3 x 200 mL) and dried in a refrigerator over anhydrous magnesium sulfate. A 5 mL portion when treated with 20% potassium iodide solution (60 mL) and then titrated with 0.1 N sodium thiosulfate solution yielded 0.38 mol (84%) of monoperphthalic acid.

2-Bromo-3,6,6-trimethyl-3-vinylcyclohexanone⁶⁴ 113

Cupric bromide (0.448 g, 2 mmol) and enone 91 (0.168 g, 1 mmol) was added to methanol (40 mL). The reaction mixture was refluxed for 24 h, cooled and then poured into water and the resulting mixture extracted with chloroform. The extract was washed with water (1 x 50 mL), brine (1 x 50 mL) and dried over magnesium sulfate. Removal of solvent at reduced pressure yielded 194 mg of a yellow liquid. Purification by preparatory chromatography gave 182 mg (74%) of a yellow crystalline solid, which was recrystallized in chloroform and hexane. m.p. 77°-79°. Ir (CHCl₃) 1720 cm⁻¹ (-C=O) 1635 cm⁻¹ (-C=C-). NMR (CDCl₃) δ 1.03 (3H, s, C3-CH₃), 1.18-1.23 (6H, 2s, gem-dimethyl), 1.63-2.10 (4H, m, C4-CH₂ and C5-CH₂), 4.97-5.10 (2H, m, C=CH₂), 5.27 (1H, s, C2-H) 5.60-6.27 (1H, m, CH=C).

1,2-Dilithio-3,6,6-trimethyl-3-vinyl-1-cyclohexen-1-one.⁶⁷ 122

A solution of bromoenone 113 (245 mg, 1mmol) in 1,2-dimethoxyethane under argon was added dropwise to a solution of lithium diisopropylamide (14 mg, 1.3 mmol) in DME (3 mL) with stirring over a 4 min period and the reaction mixture allowed to stir for another 15 min still at 0°C. Meanwhile the ice-bath was replaced with an acetone-dry ice mixture. The reaction mixture was then treated at -65°C with tert-butyllithium solution in pentane (2.7 mL, 2M, 5.4 mmol). The acetone-dry ice bath was then removed for 10 min. thus completing the formation of the dianion.

Proof for the formation of dianion 122

The existence of the dianion was established by both deuteration and silylation. When a cold (-65°C) solution of the dianion was quenched with excess deuterioacetic acid in deuterium oxide with stirring and then allowed to warm to room temperature, the enone-d₂ 124 obtained gave the following spectral data: Ir (CHCl₃) 1700 cm⁻¹ (C=O) NMR (CDCl₃), δ 1.00-1.03 (9H, 3s, C3-CH₃ and gem-dimethyl), 1.70 (C4-CH₂ and C5-CH₂), 4.90-5.33 (2H, m, CH₂=C) 5.63-6.10 (1H, m, CH=C).

On the other hand when the dianion was quenched with excess chlorotrimethylsilane and triethylamine at -65°C followed by warming to room temperature, the disilylated enol ether 125 obtained gave the following spectral data: Ir (CHCl₃), 1645 cm⁻¹ (C=C-O) NMR (CDCl₃), δ 0.07 (9H, s, (CH₃)₃-Si-C), 0.13 (9H, s, (CH₃)₃-Si-O), 0.83-1.06 (9H, m, gem-dimethyl and C3-CH₃), 1.40 (4H, s, C4-CH₂ and C5-CH₂) 4.73-5.06 (2H, m, CH₂=C), 5.57-6.03 (1H, m, CH=C).

Attempted cross-aldol condensation between the dianion 122 and β -tetralone 90.

The final reaction mixture containing the dianion as in (a) was cooled to -65° (acetone-dry ice bath) and β -tetralone (323 mg, 1.70 mmol) added dropwise with stirring under argon. Stirring was continued for 3 h at same temperature. It was then quenched with cold 5% HCl, extracted with ether (3 x 20 mL) and dried over sodium sulfate anhydrous. After removal of the solvent, 920 mg of a crude product was obtained. Mass spectrum, tlc, ir and nmr spectra showed that no cross-aldol condensation product was present.

General Procedure for the Preparation of the Enolates of 3,6,6-trimethyl-3-vinyl-1-cyclohexanone⁶⁵ 91

Methylolithium in ether (10 mL, 1.4M, 14 mmol) was concentrated under reduced pressure in argon and the residue redissolved in 1,2-dimethoxyethane (10 mL). The solution was then treated with diisopropylamine (1.5g, 14 mmol) still at 0° , to the reaction mixture was added dropwise with stirring over a 5 min period the enone 91 (1.99g, 12 mmol) and the resulting solution left to stir for further 30 min. The zinc and magnesium enolates⁴³ were prepared by the addition of saturated ethereal solution of equimolar amounts of zinc chloride and magnesium bromide respectively to the preformed lithium enolate in ether or 1,2-dimethoxyethane solution at 0°C .

2-Keto-1-methyl-1[2-(3-keto-1,4,4-trimethyl cyclohexyl)ethyl]-6-methoxy-3,4-dihydronaphthalene 99a and 99b.

Potassium metal (546 mg, 13.96 mmol) was added to dry benzene (150 mL) and t-pentyl alcohol (1.85g, 20.94 mmol) with stirring under argon. The reaction mixture was refluxed until all the potassium was completely dissolved (8 h). It was then cooled to room temperature and tetralone 98 (2.45g, 13.96 mmol) dissolved in dry benzene (20 mL) added dropwise. The benzene/t-pentyl alcohol was then distilled off while some more benzene was added to keep a constant volume over a period of 2 h. The reaction mixture was again cooled to room temperature and the tosylate 70 (5.35g, 13.96 mmol) dissolved in dry benzene (20 mL) added dropwise. The resulting mixture was stirred at room temperature for 6 h and then refluxed for 24 h. The resulting mixture was then cooled to room temperature shaken with 3 drops of 10% sulfuric acid, extracted with ether (3 x 100 mL) and dried over anhydrous sodium sulfate. Evaporation of the solvent and purification by column chromatography yielded 4.90 g of a yellow oil.

A solution of the oil in acetone (200 mL) and sulfuric acid (50 mL, 1N) was refluxed for 3h, cooled, diluted with water (200 mL) and extracted with chloroform (3 x 150 mL). The combined extract was washed with 5% sodium bicarbonate solution (1 x 100 mL), saturated, brine (3 x 100 mL) and dried over anhydrous sodium sulfate. Evaporation of the solvent and purification by flash chromatography yielded 3.43 g (69%) of pure (99a) and (99b). The diastereomeric

compounds (99a) and (99b) exhibited the following spectral characteristics:

Ir: (CHCl₃) 1700 cm⁻¹ (C=O) 1650 cm⁻¹ (aromatic); NMR: (CDCl₃)

δ 0.77 (3H, s, C₁-CH₃ of cyclohexyl), 1.00 (6H, s, gem-dimethyl of cyclohexyl), 1.33 (3H, s, C₁-CH₃ of dihydronaphthalene) 1.53 (4H, s, C₅-CH₂ and C₆-CH₂ of cyclohexyl), 1.87-2.27 (6H, m, C₁-CH₂ and C₂-CH₂ of ethyl, and a singlet at 2.10 (-CH₂-CO of cyclohexyl)), 2.47-2.77 (2H, m, -CH₂-CO of dihydronaphthalene), 2.93-3.20 (2H, m, benzylic-CH₂), 3.87 (3H, s, -O-CH₃), 6.83-7.40 (3H, m, aromatic); mass spectrum m/e (rel intensity) 356 (M⁺, 15), 203 (100), 175 (33).

UV λ_{max} 317, 285, 255(ε = 6218)

Anal. Calcd. for C₂₃H₃₂O₂: C, 77.54; H, 8.98; found: C, 77.25; H, 9.11.

8-Methoxy-3,3,10bα, 12aβ-tetramethyl-1,2,5,6,10b,11,12,12a-octahydro-(3H)-chrysen-4-one (100a) and 8-methoxy-3,3,10bβ, 12aβ-tetramethyl-1,2,5,6,10b,11,12,12a-octahydro-(3H)-chrysen-4-one. (100b).

A solution of diethylaluminum ethoxide in toluene (25% by weight)(1.4 mL, 10 mmol) was added dropwise to the diketone 99a and 99b (356 mg, 1 mmol) in dichloromethane (10 mL) at 0°C with stirring under argon. Stirring was maintained for 6 h at room temperature after completion of addition. The reaction mixture was then kept at 60-80° with stirring for 3 days. Tlc showed two yellow non-polar spots and no starting material left. The reaction mixture was then cooled to room temperature diluted with toluene (10 mL) and poured into solid ice. The resulting

mixture was stirred for 5 h and the organic layer separated. The aqueous layer was extracted with ether (3 x 50 mL). The combined organic extract was then dried over anhydrous sodium sulfate and evaporated. Purification by column chromatography afforded 148 mg (70%) of pure 100a and 159 mg (76%) of pure 100b, 100a being a little less polar than 100b on tlc. Both crystallized at 0° white platelets from hexane/ether (4:1) solution.

Spectral characteristics of 100a

m.p. 88°

Ir (CHCl₃) 1675 cm⁻¹ (α-β-unsaturated C=O), 1625 (C=C), 1600 (aromatic) ¹H (CDCl₃) δ 0.90 (3H, s, C_{12aβ}-CH₃), 1.17 (6H, s, gem-dimethyl), 1.47 (3H, s, 10ba-CH₃), 1.67-2.27 (8H, m, C₁-CH₂, C₂-CH₂, C₁₁-CH₂ and C₁₂-CH₂), 2.37-2.73 (2H, m, C₅-CH₂), 2.80-2.07 (2H, m, C₆-CH₂), 3.77 (3H, s, -OCH₃), 6.53-7.27 (3H, m, aromatic).

¹³C NMR (CDCl₃) δ 23.81, 24.79, 24.94, 26.01, 20.95, 33.17, 33.66, 35.03, 35.97, 37.18, 38.82, 39.85, 46.17, 55.15, 112.58, 112.78, 127.41, 136.93, 137.53, 138.65, 144.83, 157.13, 187.10.

UV (MeOH)_{λ_{max}} 285 (ε = 1918), 274 (ε = 2830) 242 (ε = 6393), 218 (ε = 10,868).

Mass spectrum m/e (rel intensity) 338 (M⁺, 35) 324 (25) 323 (100), 305 (24) 295 (26), 97 (20), 86 (25), 84 (41) 82 (43), 41 (26).

Anal. Calcd for C₂₃H₃₀O₂: C, 81.67; H, 8.87. Found: C, 81.71; H, 9.07.

Compound (100b)

m.p. 128°

Ir (CHCl₃), 1675 cm⁻¹ (α-β unsaturated C=O), 1625 (C=C), 1600 (aromatic)¹H NMR (CDCl₃), δ 1.03 (C_{12aβ}-CH₃), 1.08 and 1.13 (6H, 25, gem-dimethyl),1.40 (3H, s, C_{10bβ}-CH₃), 1.60-2.30 (8H, m, C₁-CH₂, C₂-CH₂, C₁₁-CH₂,C₁₂-CH₂), 2.33-2.83 (4H, m, C₅-CH₂, C₆-CH₂), 3.77 (3H, s, -OCH₃), 6.50-

7.27 (3H, m, aromatic).

¹³C NMR (CDCl₃) δ 24.50, 24.87, 25.06, 26.44, 29.60, 31.46, 34.45,

34.81, 35.01, 36.70, 38.30, 39.44, 46.03, 55.13, 76.38, 77.01, 77.64,

112.65, 112.68, 127.40, 136.71, 137.96, 138.22, 141.19, 157.15,

187.00.

UV (MeOH) λ_{max} 285 (ε = 1918), 274 (ε = 2830) 242 (ε = 6393), 218 (ε = 10,868).Mass spectrum m/e (rel intensity) 338 (M⁺, 20), 324 (22), 323 (88),

295 (25), 239 (19), 171 (19), 86 (67), 84 (100), 73 (34), 47 (27)

Exact mass: 338.2242 (calcd for C₂₃H₃₀O₂ 338.2246).8-Methoxy-4-trimethylsilyloxy-3,3-10ba, 12aβ-tetramethyl-1,2,6,10b,11,12-hexahydrochrysene (165)

The silyl enol ether 165 was prepared according to a modified procedure reported by House et al.⁶⁶ To a solution of lithium diisopropylamide (prepared from 1 mmol of methyl lithium and

1 mmol of diisopropylamine) in dimethoxyethane was added dropwise with stirring under argon at 0° 100a (320 mg, 0.95 mmol) in DME (1 mL). The red coloured reaction mixture was stirred for 10 min and then quenched with tetramethylsilyl chloride already treated with triethylamine. The resulting solution was stirred at 0° for 10 min, at room temperature for 15 min and then partitioned between pentane and cold aqueous 5% sodium bicarbonate solution. The organic layer was separated, washed with water, brine and dried over anhydrous sodium sulfate. After removal of the solvent purification by preparative layer chromatography gave 348 mg (89%) of (165) as a syrupy liquid.

Ir (CHCl₃) 1610 cm⁻¹ (C=C, with shoulders at 1635 cm⁻¹ (C=C, with shoulders at 1635 cm⁻¹ C=C-O-Si₁, and 1575 cm⁻¹ for the aromatic C=C). ¹H NMR (CDCl₃), δ 0.30, 0.37, 0.45 (9H, 3s, Si(CH₃)₃), 1.22 (3H, s, C_{12aβ}-CH₃), 1.37 (3H, s, gem-dimethyl) 1.57 (3H, s, C_{10ba}-CH₃) 1.68-2.08 (8H, m, C₁-CH₂, C₂-CH₂, C₁₁-CH₂ and C₁₂-CH₂), 3.67 (2H, d, J = 3.5 Hz, C₆-CH₂), 4.07 (3H, s, -OCH₃), 5.90 (1H, t, J = 3.5 Hz, C₅-CH) 6.87-7.53 (3H, m, aromatic).

¹³C NMR (CDCl₃) δ 24.50, 24.63, 24.83, 24.93, 29.15, 35.77, ~~35.83~~, 38.13, 38.16, 41.33, 43.56, 43.58, 50.23, 54.64, 98.32, 111.20, 111.25, 112.53, 112.58, 126.56, 126.63, 133.43, 134.43, 151.64, 156.84, 180.10.

UV(ether)_{λ_{max}} 314(528), 288 (750), 227 (4453).

mass spectrum m/e (rel intensity) 410 (M⁺, 36), 395 (37), 305 (37), 73 (100).

Exact mass 410.2646 (calcd for $C_{26}H_{38}O_2Si$ 410.2641).

8-Methoxy-3,3-10b α , 12a β -tetramethyl-1,2,4,6,10b,11,12,12a-octahydro-
(3H)-chrysen-4-ol (162b).

The silylenol ether 165 (180 mg, 0.44 mmol) dissolved in tetrahydrofuran (4 mL) was stirred with a solution of tetrabutylammonium fluoride (1 mL, 1M, 1 mmol) for 4 h at room temperature. The reaction mixture was then added to a suspension of lithium aluminum hydride (50 mg, 1.3 mmol) in tetrahydrofuran (4 mL) and then refluxed for 4 h under argon. The cooled reaction mixture was then added to a mixture of water-ammonium chloride and tetrahydrofuran at -60° (dry ice-acetone bath) and then allowed to warm up to room temperature. The resulting suspension was filtered, the organic layer separated, and the aqueous layer extracted with additional ether (25 mL). The combined extracts were washed with water (3 x 20 mL), and dried over anhydrous sodium sulfate. After the solvent had been removed, purification of the crude oil by column chromatography gave 40 mg (27%) of pure (162b) and a minor product which was not further identified.

Ir ($CHCl_3$) 3440 cm^{-1} (-OH), shoulder at 1625 (C=C), 1610 (aromatic C=C).

^1H NMR (CDCl_3), δ 0.95 (3H, s, $\text{C}_{12\text{aB}}\text{-CH}_3$), 1.10, 1.11 (6H, 2s, gem-dimethyl) 1.12 (3H, s, $\text{C}_{10\text{bA}}\text{-CH}_3$), 1.54-1.72 (4H, m, $\text{C}_1\text{-CH}_2$, $\text{C}_2\text{-CH}_2$), 2.08-2.24 (2H, m, $\text{C}_{12}\text{-CH}_2$) 2.50-2.74 (2H, m, $\text{C}_{11}\text{-CH}_2$), 3.76-3.92 (6H, m, $-\text{OCH}_3$ as singlet at 3.80, $\text{C}_6\text{-CH}_2$ and $\text{C}_4\text{-C-H}$;
 OH
 Eu(dpm)_3 shift reagent shows the latter two as doublets with $J = 2$ Hz, $J = 3$ Hz respectively; 6.66-7.60 (3H, m, aromatic).

UV (MeOH) λ_{max} 198 ($\epsilon = 2604$), 220 ($\epsilon = 1681$) 660 ($\epsilon = 274$).

Mass spectrum m/e (rel intensity), 340 (9), 338 (9), 325 (30), 322 (24), 307 (64), 305 (21), 237 (24), 219 (28), 211 (38), 185 (24), 175 (20), 173 (27), 171 (26), 91 (22), 86 (26), 85 (25), 84 (42), 83 (46), 81 (37), 71 (28), 69 (29), 67 (20), 57 (54), 55 (58), 49 (51), 43 (100) 41 (69), 39 (23), 29 (21), 27 (21).

Exact mass 340.2434 (calcd. for $\text{C}_{23}\text{H}_{32}\text{O}_2$ 340.2402).

2-Trimethylsilyloxy-1-methyl(2-(3-keto-1,4,4-trimethylcyclohexyl)-ethyl)-6-methoxy-3,4-dihydronaphthalene⁶⁶ 139.

To a solution of lithium diisopropylamide in dry dimethoxy ethane (5 mL, 0.7 mmol) was added the diketone 99a and 99b (0.222g, 0.62 mmol) of dry dimethoxy ethane was added 0.222 g (0.62 mmol) of diketone at 0°C with stirring for 10 min, the resulting solution was then quenched with chlorotrimethylsilane already treated with triethylamine. The reaction mixture was then partitioned between pentane and cold 10% sodium bicarbonate solution to yield 245 mg of crude 139 after work-up. Purification by preparative layer chromatography afforded 292 mg (91%) of pure 139.

Ir (CHCl₃) 1695 cm⁻¹ (C = O), 1675 cm⁻¹ (C=C-O-Si(CH₃)₃), 1605 cm⁻¹ (aromatic C=C).

¹H NMR (CDCl₃) δ 0.26 (9H, s, Si-(CH₃)₃), 0.77 (3H, s, C - CH₃), 0.93 and 1.00 (6H, 2s, gem-dimethyl), 1.33 (3H, s, C₁-CH₃) 1.40-1.93 (8H, m, C₅¹-CH₂, C₆¹-CH₂, and -CH₂-CH₂ of ethyl), 2.03 (2H, s; C₂¹-CH₂), 3.33 (2H, d, J = 4 Hz, C₄-CH₂), 3.73 (3H, s, -OCH₃), 4.87 (1H, t, J = 4Hz, C₃-CH), 6.53-7.20 (3H, m, aromatic-CH).

¹³C NMR (CDCl₃) δ 24.49, 24.64, 24.93, 28.71, 29.16, 31.50, 35.77, 35.82, 38.16, 41.32, 43.58, 50.24, 54.64, 76.08, 76.72, 77.36, 97.23, 98.31, 111.19, 112.58, 126.56, 133.43, 134.43, 151.64, 156.72, 186.60.

UV (ether) λ_{max} 302 (ε = 1355), 290 (ε = 1868) 243 (ε = 3724), 222 (5935).

Mass spectrum m/e (rel. intensity) 428 (M⁺, 10), 262 (32), 261 (100), 245 (11), 189 (16), 75 (22), 73 (49).

Exact mass 428.2728 (Calcd for C₂₆H₄₀O₃Si 428.2746).

8-Methoxy-3,3,10b β ,12a β -tetramethyl-1,2,5,6,10b,11,12-12a-octahydro-(3H)-chrysen-4-ol. 166.

To a suspension of lithium aluminium hydride (10 mg, 0.26 mmol) in dry ether (2 mL) was added the enone 100b (50 mg, 0.15 mmol) in ether (5 mL) at 0° and the reaction stirred for 10 min.

The reaction mixture was then cooled under dry ice-acetone bath and quenched with solid ice-ammonium chloride mixture. After work-up, preparative layer chromatography gave 45 mg (88%) of pure 166 as white powdery crystals.

m.p. 91°

Ir (CHCl₃) 3410 cm^{-1} (OH), 1600 cm^{-1} (C=C, and aromatic C=C).

¹H NMR (CDCl₃), δ 0.85 (3H, s, C_{12aB}-CH₃), 1.04 (3H, s, gem-dimethyl), 1.15 (3H, s, gem-dimethyl), 1.30 (3H, s, C_{10aB}-CH₃), 1.61-1.86 (8H, m, C₁-CH₂, C₂-CH₂, C₁₁-CH₂, C₁₂-CH₂), 2.80 (2H, m, C₅-CH₂), 3.77 (3H, s, -OCH₃), 4.00-4.08 (2H, m, C₆-CH₃), 4.47 (1H, s, C₄-CH₃) 6.54-7.22 (3H, m, aromatic).

¹³C NMR (CDCl₃) δ 18.50, 23.37, 26.68, 28.53, 30.96, 32.50, 34.09, 35.95, 36.55, 37.02, 38.03, 39.07, 40.40, 55.07, 79.76, 112.14, 112.47, 127.15, 134.02, 136.91, 138.13, 139.40, 156.80.

UV (ether) 325 (ϵ = 485), 306 (ϵ = 713), 285 (ϵ = 1128), 278 (ϵ = 1104), 224 (ϵ = 3917).

Mass spectrum m/e (rel intensity) 340 (M⁺, 17), 326 (24), 325 (100), 322 (32), 308 (16), 307 (60), 239 (15), 211 (23), 171 (20).

Exact mass 340.2434 (calcd for C₂₃H₃₂O₂ 340.2402).

Attempted conjugate methylation of the enone 100b using lithium dimethylcuprate via Me_2SCuBr ⁶³.

To a colourless solution of Me_2SCuBr (0.10 g) in methyl sulfide and dry ether (1 mL each) was added dropwise with stirring while maintaining the temperature at 0° , methyllithium in ether (1.5 mL, 1.4M, 2.1 mmol). At this point the earlier formed precipitate just dissolved to form a pale yellow solution. To the solution was added the enone 100b (302 mg, 0.9 mmol) in ether (0.5 mL) and the resulting mixture from which a yellow precipitate $(\text{MeCu})_n$, separated was stirred still at 0° , for 40 min and then partitioned between ether and aqueous ammonium chloride and ammonium hydroxide.

After work-up, tlc, ir and nmr spectra showed no reaction had occurred. *Tetrakis[~~iodo~~(tri-n-butylphosphine)copper(1)] also was substituted for Me_2SCuBr .

* Attempted methylation of the enone¹²⁸ 100b using lithium dimethylcuprate via tetrakis[iodo(tri-n-butylphosphine) copper(1)]⁷³

To a solution of the enone 100b (30 mg, 0.089 mmol) and $(\text{nBu}_3\text{P})_4\text{CuI}$ (10 mg) in dry tetrahydrofuran (5 mL) was added methylmagnesium bromide (0.3 mL, 3M, 1 mmol) at -65° (dry ice-acetone bath) with stirring overnight. The reaction mixture was then quenched with ice-cold 3 M HCl. After work-up, tlc, ir and nmr spectra showed no reaction had occurred.

Attempted hydrocyanation of the enone¹²⁶ 100b.

A solution of the enone 100b (338 mg, 1 mmol) in benzene (4 mL) was added dropwise to diethylaluminum cyanide in toluene (2 mL, 1.4M, 2.8 mmol) at 0° with stirring. Stirring was maintained for 30 min at 0° and 1 h at room temperature. The reaction mixture was then quenched with solid ice - 10% sodium hydroxide mixture. After stirring for 30 min, the resulting mixture was extracted with ether (3 x 20 mL). The combined organic extract was washed with water (1 x 20 mL), saturated aq.-sodium chloride and dried over anhydrous magnesium sulfate. After removal of solvent, tlc, ir and nmr spectra showed no reaction had occurred.

1-[2-(3-Keto-1,4,4-trimethylcyclohexyl)ethyl]-2-methyl-6-methoxynaphthalene. 101

A suspension of p-toluenesulfonic acid (360 mg, 1.9 mmol) and enone 100a (280 mg, 0.79 mmol) in para-xylene (15 mL) was refluxed for 24 h, at this time tlc showed no starting material was left. The reaction mixture was then cooled, washed with 10% sodium bicarbonate (1 x 10 mL), water (3 x 10 mL) saturated brine (1 x 20 mL) and dried over magnesium sulfate. After solvent removal, preparative layer chromatography gave 100 mg (37% of a

colourless crystalline solid 101.

m.p. 109-110°

Ir (CHCl₃) 1700 cm⁻¹ (C=O), 1615 and 1600 (C=C).

NMR (CDCl₃), δ 1.10 (3H, s, C₇-CH₃) 1.17 (6H, s, gem-dimethyl),
1.17-1.77 (6H, s(b), C₅-CH₂, C₆-CH₂ C₂-(ethyl)-CH₂) 2.18 (2H,
s, C₂-CH₂), 2.30 (2H, d, J = 5Hz, C₁-(ethyl)-CH₂), 2.52 (3H, s,
C₂-CH₃) 4.00 (3H, s, -OCH₃), 7.23-8.18 (5H, m, aromatic).

UV (MeOH) $\lambda_{\max}$ 273, 285 ($\epsilon = 8.1 \times 10^3$), 290.

Mass spectrum m/e (rel intensity) 338 (M⁺, 100), 199 (12), 185 (98)
139 (28).

Anal. Calcd. for C₂₃H₃₀O₂: C, 81.67; H, 8.87. Found: C, 81.38; H, 9.17.

Attempted cyclization of 99b using di-isopropylamidomagnesium bromide.⁶⁶

(a) Preparation of di-isopropylamidomagnesium bromide.

Ethyl bromide (0.95 mL, 12.5 mmol) was added to a suspension of magnesium (0.3 g, 12.5 mmol) in tetrahydrofuran (10 mL). The reaction mixture was refluxed for 40 min under argon, cooled to room temperature and freshly distilled diisopropylamine (2 mL) added. The reaction mixture was again refluxed for 40 min and kept warm.

(b) The Reaction.

To a cooled solution of the dione 99b (600 mg, 1.69 mmol) in THF (10 mL) (acetone-dry ice bath) under argon was added dropwise with stirring 3 mL of the above prepared Grignard. The resulting mixture was allowed to warm up to room temperature and then refluxed for 18 h. After cooling to room temperature, it was quenched with ammonium chloride-ice mixture, extracted with ether (3 x 10 mL), washed 10% HCl (1 x 10 mL) water, brine, and then dried over sodium sulfate. After solvent removal, 610 mg of a crude was obtained whose spectral characteristic and tlc were identical with the starting dione 99b.

Attempted cyclization of 99b using sodium hydroxide and phase transfer catalyst under Mokosza conditions.¹¹⁹

A mixture of dione 99b (253 mg, 0.99 mmol), 50% sodium hydroxide (2 mL), acetonitrile (2 mL), and benzyltriethylammonium chloride (100 mg), or dicyclohexyl-18-crown-6 (50 mg) was stirred at room temperature for 30 min. The reaction mixture was then quenched with 10% hydrochloric acid, washed with water (3 x 15 mL), brine (1 x 15 mL) and dried over sulfate. After removal of solvent, tlc, ir and nmr spectra of the crude product showed no reaction had occurred.

Attempted cyclization of 99b using lithium diisopropylamide.

To a solution of diketone 99b (500 mg, 1.32 mmol) in dimethoxyethane (10 mL) at 0° was added dropwise lithium diisopropylamide in DME (1 mL, 1 mmol) with stirring under argon. The mixture was stirred for 2 h at 0° and 3 more h at room temperature. The reaction mixture was then quenched with cold 10% HCl, washed with water (3 x 10 mL), saturated brine (1 x 10 mL) and dried over magnesium sulfate. After the solvent had been removed, the tlc and spectral characteristics of the isolated products showed no reaction did occur.

Attempted cyclization of diketones 99a and 99b using glycine and perchloric acid.⁴⁴

A mixture of diketones 99a and 99b (700 mg, 2.7 mmol), glycine (450 mg, 6 mmol), 70% HClO₄ (410 mg) in acetonitrile

(15 mL) was refluxed for 2 days. It was then cooled and the solvent removed with oil pump. The resulting crude residue was extracted with chloroform, washed with 10% sodium bicarbonate, water, brine and dried over magnesium sulfate. After solvent removal, tlc, ir and nmr showed no cyclization had occurred.

Cyclization of diketone 99b using tritylmagnesium chloride.

(a) Preparation of $(C_6H_5)_3C MgCl$.

To a suspension of magnesium metal (1.5 mg, 63 mmol) in tetrahydrofuran (20 mL) under argon was added triphenylmethyl chloride (15 g, 54 mmol) in THF (10 mL). The reaction mixture was then refluxed for 8 h.

(b) Cyclization.

To the diketone 99b (3.78 g, 14.8 mmol) in THF (20 mL) was added tritylmagnesium chloride (10 mL of above) dropwise with stirring under argon. The reaction mixture was then refluxed overnight, cooled, quenched with ammonium chloride-ice mixture and extracted with ether (3 x 15 mL). The combined ether extract was then washed with water, saturated brine and dried. After solvent removal, tlc showed no starting material was left, new products and substantial amount of triphenylmethane which could not be removed by chromatography, were however obtained.

Attempted cross-aldol condensation between β -tetralone 90 and 1-trimethylsilyloxy-3,6,6-trimethyl-3-vinyl-1-cyclohexene 103 using titanium tetrachloride⁶⁵.

To a solution of β -tetralone 90 (190 mg, 1 mmol) in dichloromethane (10 mL) and freshly distilled TiCl_4 (0.11 mL, 1 mmol) at -60° was added dropwise the silylenol ether 91 (238 mg, 1 mmol) in dichloromethane (10 mL) under argon and with stirring for 2 h. The reaction mixture was allowed to warm up to room temperature, and then quenched with cold water (10 mL). The organic layer was separated and aqueous layer extracted with ether (3 x 10 mL). The combined organic layer was washed with water (3 x 20 mL), brine (1 x 20 mL) and dried over magnesium sulfate. After concentration, tlc and spectra data showed that the desired cross-aldol condensation did not take place.

Attempted cross-aldol condensation between β -tetralone 90 and 3,6,6-trimethyl-3-vinyl-1-cyclohexanone 91 using lithium diisopropylamide.

To a stirred solution of enone 91 (332 mg, 2 mmol) and lithium diisopropylamide (2 mL, 1 M, 2 mmol) in dimethoxyethane (5 mL) at 0° was added the β -tetralone 90 (380 mg, 2 mmol) in dimethoxyethane (1 mL) dropwise under argon. The resulting mixture was then stirred at room temperature for 1 h. It was then quenched with 10% hydrochloric acid, extracted with ether (3 x 20 mL), washed with water (3 x 20 mL), brine (1 x 20 mL) and then dried

over magnesium sulfate. After concentration, tlc and spectra data showed the desired reaction did not take place.

Attempted cross-aldol condensation between β -tetralone 90 and 2-bromo-3,6,6-trimethyl-3-vinylcyclohexanone 113 using diethylaluminum chloride.⁶²

To a stirred suspension of bromo enone 113 (490 mg, 2 mmol), activated zinc dust (196 mg, 3 equiv.), cuprous bromide (22 mg, 0.15 equiv.) in THF (10 mL) and diethylaluminum chloride (2.3 mL, 4 mmol) in toluene at -65° (acetone-dry ice bath) under argon was added dropwise β -tetralone 90 (380 mg, 2 mmol) in THF (2 mL). The reaction mixture was stirred for 1 h and then allowed to warm up to room temperature. It was then stirred for another 30 min. pyridine (10 mL) was added followed by aqueous work-up tlc and spectral data showed that the desired reaction did not occur.

Attempted preparation of 1-methyl-2,6,6-trimethoxy-3,4-dihydro-2(1H)-naphthalene. 152

To a stirred mixture of β -tetralone 90 (200 mg, 1.05 mmol) in dichloromethane (5 mL), methanol (15 mL) and p-toluene-sulfonic acid (10 mg) at 0° was added trimethyl orthoformate (0.35 mL, 320 mg, 3 mmol) dropwise under argon. The reaction mixture was stirred at 0° for 3 h and overnight at room temperature. The reaction mixture was then filtered through basic alumina and extracted with dichloromethane. After solvent removal, tlc and spectral data indicated that no ketal was formed.

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Attempted preparation of 8-Methoxy-4-acetoxy-3,3,10b α , 12a β -tetramethyl-1,2,6, 10b, 11, 12-hexahydrochrysene (160) using acetic anhydride and perchloric acid.

To a stirred solution of acetic anhydride (1 mL) and ethyl acetate (5 mL) was added the compound 100a (140 mg, 0.41 mmol) in ethyl acetate (5 mL), followed by perchloric acid (0.01 mL) in ethyl acetate (5 mL). The reaction mixture was stirred at room temperature for 20 min, added to a slurry of ice and sodium bicarbonate and stirring maintained until evolution of carbon dioxide ceased. The organic layer was separated, and the aqueous layer extracted with ethyl acetate. The combined organic extract was washed with water (3 x 20 mL), brine (1 x 20 mL) and then dried over sodium sulfate anhydrous. After evaporation of the solvent, tlc, nmr, ir and mass spectra showed the presence of starting material as well as mono, di and trisubstituted acetoxy derivatives.

Preparation of 8-Methoxy-4-acetoxy-3,3, 10b α , 12a β -tetramethyl-1,2, 6,10b, 11,12-hexahydrochrysene 160 using acetic anhydride and lithium diisopropylamide.

To a stirred solution of lithium diisopropylamide (1 mmol) in DME (5 mL) at 0° and under argon was added dropwise a solution of compound 100a (300 mg, 0.85 mmol) in DME (1 mL). Stirring was continued for 10 min and the reaction mixture quenched with

freshly distilled acetic anhydride (0.5 mL). The resulting solution was then stirred at room temperature for 20 min. After work-up tlc and spectral data revealed the presence of 65% starting material and 30% of the acetoxy derivative. The mixture was not dealt with any further.

8-Methoxy-3,3, 10ba, 12a β -tetramethyl-1,2, 4a,6,10b,11,12,12a-octahydro-(3H)-chrysen-4-one. 161

To a stirred solution of the silyl ether 165 (45 mg, 0.11 mmol) in THF (2 mL) was added BuN⁺F⁻ (35 mg, 0.13 mmol) in THF (1 mL) at room temperature under argon. Stirring was continued for 2 h. The reaction mixture was then cooled to -65⁰ (dry ice-acetone bath) followed by dilute acetic acid (acetic acid, 0.5 mL, water 5 mL). The resulting solution was then stood at -65⁰ for 10 min, allowed to warm up to room temperature and then divided between cold ether and water. After work-up it gave 226 mg of a mixture of two isomers, the deconjugated ketone and the α,β -unsaturated ketone. Complete purification of the deconjugated ketone could not be achieved.

Reaction of diethylaluminum ethoxide with 1 α -[2-(3'-keto-1', 4', 4'-trimethylcyclohexyl)-ethyl]8-hydroxy-1 β , 4 $\alpha\beta$, 8 $\alpha\beta$ -trimethyl-dodecahydrophenanthrene-10(10a), 4b(5)-diene-2-one 85a (and 85b.)

To a stirred solution of 85a and 85b (225 mg, 0.53 mmol) in dichloromethane (10 mL) was added dropwise 25% diethylaluminum ethoxide in toluene (10 mL, 19 mmol) under argon. The reaction mixture was kept at 60-80° with stirring for 5 days. The resulting mixture was then poured into solid ice followed by stirring for 6 h. After ether extraction and concentration preparative thin layer chromatography gave two main oily products, the less polar 80 (62 mg), and more polar syrupy liquid (110 mg) which could not be identified. The spectral characteristics of 80 are as follows:

IR (CHCl₃) 3450 cm⁻¹ (OH), 1685 (C=C-CO), 1655 (C=C) 1605 (C=C-CO).
 NMR (CDCl₃) 0.83, 1.10, 1.20, 1.27 (18H, s, 5 CH₃), 1.60 and 2.57 (19H, m, ring H's) 3.60 (1H, m, HO-C-CH). 5.60 (2H, m, vinyl H's).
 Mass spectrum: m/e (rel intensity) 408 (M⁺, 1.4), 322 (7.0), 299 (51.4), 227 (5.9) 199 (8.5), 149 (7.1), 125 (13.2), 97 (16.5) 85 (30.1), 83 (19.9), 81 (16.2), 71 (27.1), 69 (28.5), 57 (88.4), 56 (39.9), 45 (56) 43 (100).
 UV(MeOH) $\lambda_{\max}$ 220 (ϵ = 8690), 248 (ϵ = 5100) 254 (ϵ = 4447).
¹³C 20.7, 24.7, 25.1, 25.8, 26.3, 27.8, 32.7, 33.2, 34.8, 35.0, 35.5, 36.0, 36.3, 36.8, 37.5, 38.7, 44.1, 49.6, 49.8, 52.0, 77.1, 118.4, 128.3, 144.9, 144.6, 146.5, 147.7, 179.3, 179.6.
 Exact mass 408.2983 (calcd for C₂₈H₄₀O₂ 408.3028).

Reaction of diethylaluminum ethoxide with 8-methoxy-3,3,10b δ ; 12a δ -tetramethyl-1,2,5,6-10b, 11,12,12a-octahydro-(3H)-chrysen-4-one 100b

A solution of diethylaluminum ethoxide (14 mL, 10 mmol) in toluene (25% by weight) was added dropwise at room temperature to a stirred methylene chloride solution (10 mL) of 100b (65 mg, 0.2 mmol) and xylene. The reaction mixture was then refluxed for three days. Methylene chloride being added to keep the volume constant. The reaction mixture was then allowed to cool followed by hydrolytic work-up to yield 48 mg of a crude mixture of two products which were purified by plc.

The mass spectrum of the more polar product 168 showed the parent ion peak 368 and was not further identified. The less polar product 167 showed the following spectral characteristics.

Ir(CHCl₃), 3400 cm⁻¹ (OH), 1600 cm⁻¹ (C=C).

NMR (CDCl₃), 0.87, 1.00, 1.17, 1.27, 1.40 (each 3H, s, ring CH₃), 1.57-2.17 (13H, m, ring protons), 2.77 (2H, poorly resolved doublet J = 3Hz, benzylic protons), 3.73 (3H, s, OCH₃) 4.47 (1H, poorly resolved doublet, ^{OH}_{C-H}) 6.53-7.23 (3H, m, aromatic).

Mass spectrum m/e (rel intensity) 356 (M⁺, 2.3), 340 (22.3), 326 (24.1) 325 (100.0), 173 (21.1), 69 (25.7), 57 (21.0) 55 (29.6), 43 (29.4), 41 (47.0).

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APPENDICES

APPENDIX I

Systematic Numbering of Pentacyclic and Tetracyclic Skeletons.

I.U.P.A.C. Organic Numbering.

Triterpene Numbering.

I.U.P.A.C. Organic Numbering.

APPENDIX II

Selected ^1H NMR Spectra

^1H NMR Spectrum of **80** 90

^1H NMR Spectrum of 100a

^1H NMR Spectrum of 100b

¹H NMR Spectrum of 139

2C4

^1H NMR Spectrum of 162 with Eu^{+++}

¹H NMR Spectrum of 162

162

¹H NMR Spectrum of 165

207

APPENDIX III
Selected ^{13}C NMR Spectra

^{13}C NMR Spectrum of 80

^{13}C NMR Spectrum of 100a

^{13}C NMR Spectrum of 100b

¹³C NMR Spectrum of 152

APPENDIX IV

Selected Mass Spectra

C

Mass Spectrum of 85

Mass Spectrum of 100b

220

Mass Spectrum of 139

5.00

3.00

1.00

APPENDIX V

Flow Charts of Synthetic Routes followed in this work.

FLOW CHART 1: Preparation of the Tosylate 70

133, R = OH
70, R = TsO

FLOW CHART 2: Preparation of β -tetralone 90

FLOW CHART 3: Approach A

FLOW CHART 4: Approach B

227

FLOW CHART 5: β -Amyrin Route

FLOW CHART 6: Friedelin Route

FLOW CHART 7: Pentacycle 80 Route

END

0 1 1 1 1 8 5

FIN