STUDIES TOWARD TOTAL SYNTHESSES OF DRIMANE TYPE ANTIFEEDANTS FROM THUJONE

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ABSTRACT

This thesis concerns studies directed towards a total synthesis of the drimane type dialdehyde 90 from thujone 47. The naturally occurring drimane dialdehydes have potent antifeedant activity. Development of a versatile synthesis of the drimane type dialdehydes from thujone was the main objective of this research.

The decalone 80 was considered an efficient intermediate leading to the drimane dialdehydes. Much work was devoted to develop syntheses of such C7-decalones from thujone 47. The previously known enone 48, obtained in an efficient manner from thujone 47, is subjected to reduction via catalytic or Birch reduction to afford, in quantitative yield, the cis-fused ketone 62. Deoxygenation of the ketone 62 by Wolff-Kishner reduction afforded 72 in excellent yield. Detailed studies had shown that ozone selectively reacted at the activated tertiary carbon of the isopropyl side chain in molecules such as 72. Thus, the tricyclic alkane 72 was converted to the tertiary alcohol 73 by ozonation. The alcohol 73 was then elaborated to the key intermediate 80 via cyclopropane ring opening, free radical rearrangement and ozonation. The stereochemistry of the various products 62, 72, 73 and 80 with respect to the A/B fusion was established through correlation with the absolute structure and stereochemistry of the diketone 66 the latter being one of the ozonation products of ketone 62. Diketone 66 was subjected to X-ray diffraction analysis.

The drimane skeleton was then constructed via formylation of 80 to 81 and the latter converted to 82, via reaction with phenylselenyl chloride followed by oxidative elimination of the resultant product. Conjugate addition of cyanide to the unsaturated keto-aldehyde 82 afforded 83. The latter was converted into the unsaturated aldehyde 85 via reduction of its (n-butylthio)methylene derivative, followed by borohydride reduction and mild hydrolysis. Protection of the aldehyde group in 85 gave 86 and the nitrile group in the latter was then reduced to give 88. The latter was then hydrolyzed to the drimane dialdehyde 90. The synthesis of 90 was accomplished in sixteen steps with an overall yield of 4% from thujone 47, thereby
indicating that the individual steps in the sequence proceed in excellent yield. The biological activity of compound 90 will be evaluated.

Approaches towards a total synthesis of the natural drimane polygodial 1 are also shown.
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</tr>
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<td>hexamethyl phosphoric triamide</td>
</tr>
<tr>
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<td>LDA</td>
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<td>W-K-H</td>
<td>Huang Minlong modification of Wolff-Kishner reaction</td>
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I wish to express my sincere appreciation to Professor James P. Kutney for the opportunity to pursue this project and for his guidance and valuable advice, both during the progress of this research and in the preparation of this thesis.

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1 INTRODUCTION

1.1 Antifeedants

An antifeedant has been defined by Munakata\(^1\) as a chemical which inhibits feeding but does not kill the insect directly, the insect often remaining near the treated plant material and possibly dying through starvation. It is not, however, identical with an olfactory repellent which is usually a volatile compound which repels the insect before it starts to eat.

As we know, insecticides, together with herbicides, are currently the most important chemicals used in the protection of food and other crops. Insecticides can be divided into true insecticides and indirectly acting insecticides. Most insecticides used today belong to the first group, e.g. synthetic organic chlorinated compounds, organophosphines and so on. The indirectly acting group consists of repellents, attractants, pheromones, insect growth regulators, and antifeedants. Although the first group are effective, relatively cheap and easy to use, many of these compounds are quite toxic to vertebrates, fish or beneficial lower forms of life. Some are extremely persistent in the environment and many accumulate in animals. Some pest insects have become resistant, requiring highly and possibly phytotoxic dosages and many agents are non-selective thereby toxic to beneficial insects\(^2\).

Therefore, many efforts have been devoted to the group of "indirectly acting" insecticides which lack these disadvantages. These compounds are of natural origin, more easily degradable, and furthermore, it is unlikely that they will accumulate and pollute the environment. It is also expected that, in general, such specific compounds will be less toxic to human beings than many of the synthetic pesticides and useful insects will not be disturbed.
1.2 Drimane type antifeedants

The naturally occurring antifeedants can be divided according to their general chemical nature, e.g. as alkaloids, terpenes, flavonoids, carbohydrates and others. Our attention will be focussed on the natural sesquiterpenoid dialdehydes within the drimane series, which have relatively simple structures and known strong antifeedant activity. The specific compounds are polygodial 1, warburganal 2 and cinnamodial 3, since these exhibit strong antifeedant activity. An analogous set of functionalities is found in the rearranged drimane muzigodial 4 which also exhibits strong antifeedant activity. A common structural feature in these drimanes is the presence of a Δ7,8-ene-11,12β-dialdehyde functionality and, with the exception of polygodial, a 9α-hydroxy group.

Interestingly, Kubo and Ganjian reported that these four insect antifeedants 1-4 taste very hot (spicy) to humans. They suggested that the 9β-aldehyde combined with the enal moiety is responsible for the hot taste, which is associated with its antifeedant activity. Based on these structural features, several other synthesized analogues have been investigated for their biological activity.
1.3 Review of total syntheses of polygodial and warburganal

As was mentioned in the last section, natural antifeedants are of potential value in new biorational methods of insect control. Therefore much effort has been devoted to developing total syntheses of these compounds since, in most cases, only minute amounts of material can be obtained from natural sources.

Syntheses of the drimanes 1 to 4 have exploited a variety of methods, which can be roughly divided into two parts: first, constructing an appropriately functionalized decalin ring system, and then introducing the sensitive hydroxy-ene-dialdehyde function into ring B. The most commonly used decalin ring systems are the epimeric esters 5, the diene diester 6, the decalones 7 and 8 shown below:

Several efficient synthetic routes to polygodial and warburganal are now presented.

The starting diester 6 was obtained in independent studies by Tanis and Nakanishi\textsuperscript{11} (83% yield) and Howell et al\textsuperscript{12} (94% yield). Both studies involved the Diels-Alder reaction of 1,3,3-trimethyl-2-vinyl-1-cyclohexene 2 and dimethyl acetylene-dicarboxylate (DMAD). The efficient Tanis route afforded (±)-polygodial 1 and (±)-warburganal 2, but the Howell synthetic route was shorter.
and of higher yield. It is therefore in Scheme 1. The diester 6 was reductively rearranged using palladium on carbon and an acid catalyst directly to a trans-fused drimane system 10 in 80% yield. Reduction of this diester gave diol 11 and the latter served as the pivotal starting material for several sesquiterpene natural product syntheses. Oxidation of this diol 11 provided (±)-polygodial in 95% yield by using the method developed by Omura and Swern. The triol 12 was obtained from diol 11 via acetylation followed by allylic oxidation with selenium dioxide and then cleavage of the resultant acetate groups. The direct oxidation of triol 12 is accomplished in 45% yield by using a modified Swern oxidation.
Another synthesis of (±)-polygodial 1 starting from bicyclofarnesic acid 14, the latter being obtained by cyclization of monocyclofarnesic acid 13, has been developed by Kato et al.16 (Scheme 2) Esterification of 14 and oxidation of the ester with singlet oxygen produced the allylic alcohol 15 in a modest yield of 33%. Treatment of the alcohol 15 with acid gave drimenin 16, which was converted into cinnamolide 17 via reduction and reoxidation. Saponification of lactone 17 and treatment of the resulting sodium salt simultaneously with acid and diazomethane gave a mixture of 18 and 17, which could then be separated. Oxidation of the alcohol 18 into the corresponding aldehyde and protection of the latter gave the acetal 19. Reduction of the ester function in 19 followed by oxidation provided the monoacetal 20.
which could be hydrolyzed to (±)-polygodial 1. The total synthesis of polygodial 1 in this sequence was completed with a fairly poor yield.

Scheme 3 illustrates a much more desirable route to 1 and obviously would provide an alternative route from 14 since drimenol 21 is readily available via hydride reduction of 14.

Oxidation of 21 with pyridinium chlorochromate in dichloromethane, followed by protection of the resultant aldehyde, gave 22. Allylic oxidation of the latter using selenium dioxide and bis (4-methoxyphenyl) selenoxide as co-oxidant afforded 23 in 45% yield, which upon acid treatment afforded polygodial 1 in an overall yield of 30%.

The classical acid-catalyzed cyclization of methyl farnesoate 24 produced methyl 9-epibicyclofarnesate 25 and the latter was used as the starting material for the first synthesis of (±)-warburganal18. (Scheme 4) Selenium dioxide oxidation of 25 gave a mixture from which the aldehyde ester 26 was obtained in 61% yield. Protection of the aldehyde function,
followed by reduction of the ester function and oxidation of the resulting alcohol with Collins reagent (chromium trioxide-pyridine complex in dichloromethane), gave the aldehyde 28. The enolate derived from 28 by treatment of 28 with one equivalent of lithium hexamethyldisilazamide (LHMDS) was oxidized with MoO$_5$-hexamethyl phosphoric triamide (HMPT) complex to give the hydroxylated aldehyde in a low 24% yield. Hydrolysis of the dioxolane group in compound 28 provided (±)-warburganal 2.

In 1980, 5,5,8a-trimethyl-trans-1-decalone 7 was introduced as a starting material for the synthesis of warburganal 2. Kende and Blacklock$^{19}$ reported the synthesis outlined in Scheme 5.

Decalone 7 was converted into the selectively protected unsaturated ketone 29 via formylation, dehydrogenation with dichlorodicyanobenzoquinone (DDQ) and reaction with
ethylene glycol. Addition of [methoxy(trimethylsilyl)-methyl]lithium gave a diastereoisomeric mixture of alcohols 30, which underwent elimination of trimethylsilanol to afford a 1:3 mixture of the (E)-isomer 31 and (Z)-isomer 32 respectively. Epoxidation of 31 with m-chloroperbenzoic acid (m-CPBA) gave exclusively the α-epoxide 33 which could be hydrolyzed under mild acid conditions to (±)-warburganal 2. Epoxidation of 32 gave a 4:1 mixture of the β- and α-epoxides 34 and 35, respectively, and these could be hydrolyzed to a mixture of (±)-warburganal and (±)-epiwarburganal.

Scheme 5
At the same time, another approach to (±)-warburganal 2 was completed by Goldsmith and Kezar\textsuperscript{20}. (Scheme 6)

Formylation of the decalone 7, followed by a selenation procedure gave the unsaturated keto-aldehyde 36 in a high yield (91%). Selective protection of the aldehyde group in compound 36 and addition of methyllithium gave the tertiary alcohol 37, which was then dehydrated using the Burgess reagent\textsuperscript{21} to 38. Osmylation of diene 38 gave diol 39, and further oxidation of 39 with dicyclohexylcarbodiimide (DCC) in DMSO, followed by hydrolysis of the acetal, afforded (±)-warburganal in 15\% overall yield.

In yet another approach, Jansen \textit{et al.}\textsuperscript{22} introduced decalone 8, which has the carbonyl group at position C7, as a starting material. The carbonyl function is ideally located for the introduction of the other necessary functional groups, and thus provided a very efficient route to polygodial and warburganal. (Scheme 7)
The drimane skeleton was constructed via formylation of 8 and conjugate addition of cyanide to the unsaturated keto-aldehyde 40. The resultant keto-aldehyde 41 was converted into the unsaturated aldehyde 42 via reduction of its (n-butylthio)methylene derivative, followed by borohydride reduction and mild hydrolysis. Protection of the aldehyde group in 42 gave 43 and the nitrile group in the latter was then reduced by diisobutylaluminium hydride (DIBAH) to give 44. The axial aldehyde group in 44 was epimerized to its equatorial epimer.
with the help of potassium tert-butoxide in tert-butanol. (±)-Polygodial was then readily available after hydrolysis of 45. According to the work of Tanis and Nakanishi, the enolate of compound 45, derived from lithium diisopropylamide (LDA), was easily deprotonated and subsequently oxidized with MoO₅-hexamethyl phosphoric triamide (HMPT) complex (see Scheme 4) to 46, which was then hydrolyzed to (±)-warburganal.

In summary, the above discussion provides some of the highlights in the synthetic studies leading to the drimane antifeedants. Other studies are detailed in an excellent recent review.

1.4 Object of our research

The monoterpene thujone 47 is the major component of the Western red cedar (Thuja plicata) leaf oil. A considerable amount of synthetic work utilizing thujone as a chiral synthon has been completed in our group during the past few years. These studies have shown that thujone 47 can be a viable chiral synthon for synthesizing a variety of natural products and biologically important molecules. (See Figure 1)

Since the structures and activities of these insect antifeedants are now known, our goal was to develop general synthetic routes to many of these drimanes from thujone 47. The synthetic strategies would be applicable to not only the natural products but would also provide simple structural analogues. It would be possible to then study these compounds at a molecular level and to define the structure and the stereochemistry responsible for the important biological activity.

From Figure 1, the chiral sesquiterpene 52, available from thujone 47, has the desired decalin ring skeleton. If the C7-isopropyl group could be converted into the 7-decalone system, similar in structure to the racemic structure 8 employed by Jansen (Scheme 7), an attractive route to the chiral polygodial family is near in hand. Studies in this direction are presented in the next section.
Figure 1
2 Results and Discussion

2.1 Approaches to the synthesis of the drimane type antifeedants from thujone.

2.1.1 First approach

The initial approach was based on the previously known sequence developed in Dr. Kutney's group. (See Scheme 8)

Robinson annelation of thujone 47 with ethyl vinyl ketone (EVK) and cyclization of the resultant intermediate, proceeds stereospecifically to afford the tricyclic enone 48. This enone 48 was converted to 50 via ketalization to 49, followed by treatment of 49 with potassium permanganate in basic solution. Treatment of 50 with aqueous hydrobromic acid gave the bromo-dienone 51. The overall yield of 51 from the readily available thujone 47 is 25%, so
that the various reactions proceed in excellent yields. The present research extends from the bromide 51. (See Scheme 9)

Scheme 9
The syntheses of 52 and 53 were established in our group several years ago\textsuperscript{25,26}. Reduction of 51 with excess of tri-n-butyltin hydride (TBTH) in benzene gave (+)-\beta-cyperone 52 in 79\% yield. The latter was then converted to 53 in 54\% yield by initial treatment of 52 with N-bromosuccinimide (NBS) in water and THF (1:1 v/v) followed by reaction of the resultant bromohydrin in refluxing benzene containing a catalytic amount of p-toluenesulfonic acid. Reduction of the carbonyl group of 53 was considered necessary at this stage. This product 54, as a mixture of C3-alcohols, was treated with a mixture of osmium tetroxide and sodium periodate at ambient temperature to afford the dienone 55 in 70\% yield.

The parallel study starting from 51 provided the alternative series of compounds (Scheme 9) possessing the C9-cyano group. In this study, the conversion of 51 to 59 was accomplished by treatment of 51 with potassium cyanide in DMSO. The cyano group could serve as the aldehyde function, as required for the polygodial series. The overall yield from 51 to 60 was 38\%, so that again, the individual conversions in this sequence proceeded in good yield.

At this point in the study, the unsaturated ketone 55 thus obtained, could be converted to the desired trans A/B fused system by catalytic reduction of the olefinic double bonds. The resultant product could be elaborated to the required C7-decalone 58 by Baeyer-Villiger reaction, followed by saponification and oxidation as shown in Scheme 9.

However this consideration was abandoned when a more efficient method to these compounds was developed.
2.1.2 Second approach

In 1981, Dr. Piotrowska* involved in steroid syntheses in Dr. Kutney's group, found that ozone selectively reacted at the tertiary carbon of the isopropyl side chain of compounds such as the sesquiterpene analogue 61. In her study, compounds 63 and 65 were obtained from the so called "dry ozonation"27 of compound 61 at -78°C. It was only a preliminary investigation, but such a novel reaction was worthy of further study in our program. The initial results established that the ratio of the tertiary alcohol 63 with respect to methyl ketone 65 was 2:1 (Scheme 10).

A more detailed study of this interesting ozonation reaction was undertaken by Y. H. Chen in our research group. In ethyl acetate as the solvent and employing a low

*: Personal communication from Dr. K. Piotrowska.
temperature for the ozonation reaction (-40°C), it was possible to convert 62 in an overall 70% yield, to a mixture of the tertiary alcohol 64 and methyl ketone 66 in a 2:1 ratio respectively. Subsequent treatment of 64 with concentrated hydrochloric acid afforded the five-membered ring system 67* shown in Scheme 10.

With this data on hand, it was of interest to evaluate this approach for our purpose. The available tricyclic intermediate 68, obtained from ketalization of 62, was chosen and similar ozonization conditions indeed afforded a 1:1 ratio of the alcohol 69 and methyl ketone 70 (68%) (Scheme 11). Treatment of 69 with concentrated hydrochloric acid gave the five-membered ring compound 67. Purification of 67 was difficult due to its instability to column

\[ \text{Scheme 11} \]

*: Personal communication from Y. H. Chen.
chromatography (silica gel and alumina) so the crude product was treated directly with tri-n-butyltin hydride (TBTH) in refluxing benzene to afford the rearranged six-membered ring alkene 71. The mechanism concerning the rearrangement will be discussed later. The overall yield from the alcohol 69 to the final product 71 was consistently in the 40-46% range.

2.2 Outline of the present work.

In summary, the above studies appeared well suited for our objective to provide a versatile synthetic route for a family of chiral polygodial analogues. An outline of the presently completed study is provided in Scheme 12 and 13. Details of the various reactions are given in the following sections.
Scheme 12
In summary, the cis-decalone analogue 80 was synthesized in seven steps from 48 in 27% overall yield and 80 was then converted to the drimane-type dialdehyde 90 in eight steps with an overall yield of 27%. The stereochemistry of the various compounds was established through correlation with the absolute structure of diketone 66 (Scheme 10), the latter being obtained by X-ray analysis.

2.2.1 Studies of the stereochemistry of tricyclic ketone 62 and reduction to 72

![Scheme 14 Diagram]

The starting material, tricyclic enone 48, was prepared in a large quantity via the previously published procedure\textsuperscript{25} involving Robinson annelation of thujone 47 with ethyl vinyl ketone (Scheme 12). Catalytic hydrogenation of 48, using Pd/C as a catalyst in ethanol, afforded the A/B cis fused product 62 in quantitative yield. The stereochemistry of 62 at C4...
and C5 was first investigated by a detailed proton NMR study. The C4 and C5 methine protons appeared as multiplets at 2.59 and 1.70 ppm respectively, while the C4 methyl group revealed a doublet at 0.94 ppm. These assignments were established from the following decoupling studies. There are three multiplets, each integrating for one proton, resonating at 2.15, 2.42 and 2.59 ppm in the spectrum. On the basis of their chemical shifts, they must be attached to C2 and C4. Irradiation of the signal at 2.59 ppm resulted in the three-proton doublet at 0.94 ppm, to collapse into a singlet (Figure 2b), thereby implying that the multiplet at 2.59 ppm was due to the proton at C4, and the doublet at 0.94 ppm was, in turn, due to the C14 methyl group. Conversely, irradiation of the signal at 0.94 ppm changed the splitting pattern at 2.59 ppm from a multiplet to a poorly resolved doublet (Figure 2c). Also as a result of irradiation of the C4 proton signal at 2.59 ppm, the multiplet at 1.70 ppm, integrating for one proton, became a doublet of doublets, thereby allowing assignment of the multiplet at 1.70 ppm to be that of the C5 proton. The C15 methyl signal was then easily recognized at 1.23 ppm since it is the only three proton singlet in the spectrum. (see Figure 2)

Having located these key protons in the NMR spectrum, we started to investigate the stereochemistry at C4 and C5 by a Nuclear Overhauser Effect (NOE) difference experiment. The NOE data have considerable potential in the elucidation of configuration at specific centers in organic molecules. The maximum value that the Overhauser effect can have is determined by the nature of the nuclear species involved, and it is proportional to 1/r^6, where r is the distance between the nuclei concerned. Therefore NOE data are obtained for nuclei in close proximity. Examination of a molecular model of \( \text{C2} \) showed that the distances between the C14 methyl group and the C5 proton, and also the C15 methyl group and the C5 proton are small if these nuclei are on the same side of the molecule. Therefore irradiation of the \( \beta \) oriented C15 methyl or C14 methyl signals should enable determination of the configurations at C4 and C5.
$^1$H-NMR (400 MHz, CDCl$_3$) of tricyclic ketone 62
a) normal 400 MHz spectrum.
b) homonuclear spin decoupling at 2.59 ppm.
c) homonuclear spin decoupling at 0.94 ppm

Figure 2
Nuclear Overhauser difference experiments on the tricyclic ketone:

a) off resonance spectrum
b) irradiation at 1.23 ppm
c) irradiation at 0.94 ppm

Figure 3
X-ray diffraction analysis of diketone 66

Figure 4
Irradiation at 1.23 ppm (C15 methyl) resulted in the enhancement of the multiplet at 2.59 ppm due to the C4 proton, but revealed no effect on the multiplet at 1.70 ppm due to the C5 proton (Figure 3b). Irradiation at 0.94 ppm (C14 methyl) gave only a very small enhancement at 1.70 ppm (Figure 3c). These observations indicated that the C4 proton is on the same side as the C15 methyl group, namely, the C14 methyl group is α-oriented, however the nature of the ring A/B fusion (cis or trans) remained unclear. (See Figure 3)

In order to settle this question and to allow assignments in subsequent synthetic intermediates, as outlined in Schemes 12 and 13, a suitable crystalline compound for X-ray analysis was required. The tosylhydrazone 92 failed to yield suitable crystals. Fortunately, the compound 66 obtained from ozonolysis of 62, provided satisfactory crystals upon recrystallization from hexanes. The subsequent X-ray analysis of 66 clearly revealed the C14α-methyl orientation and cis A/B ring fusion as shown in Scheme 14 and Figure 4. As a result, it is possible to assign cis A/B ring fusion in all compounds arising from 62.

At this stage we investigated whether we could develop a trans A/B fused system via reduction of compound 48. The classical Birch reduction of α,β-unsaturated ketones involves transfer of electrons with the formation of a carbanion species which leads, after suitable work up, to a saturated ketone28. A detailed study on the Birch reduction of α,β-unsaturated ketone was published by Stork. In his publication29 Stork indicated "that the saturated ketone formed by such a reduction is not simply the more stable of the two isomers at the β-carbon. The energies of the stereoelectronically allowed transition states, rather than those reduction products, determine the stereochemistry of the latter". In this postulate, Stork argues that transition states such as 93A and 93B (Scheme 15) are involved and 93A would be favored since a maximum overlap of the p-orbitals occurs. On this basis, an octalone system, upon Birch reduction, is expected to yield the A/B trans fused system. Another study by Djerassi, Stork et al30 showed that the reduction of 96 indeed afforded the A/B trans fused compound 97. This result indicates that the α-isopropyl group at C7, which is axially oriented in a conformation similar to 93A, would be expected to provide some steric hindrance to approach
of the proton, at the C5 carbon, from the α-face. Clearly this steric effect is not a dominant role.

Scheme 15
If we consider our study involving the Birch reduction of 48, the favored transition state, according the Stork hypothesis, would be 94A. In fact, the result obtained was the cis-fused system 95B and this would require the less favored transition state 94B. It was clear that our system does not follow the Stork hypothesis.

In another study, it was shown that small variations in the trans/cis product ratio were observed when methyl substituents were at the angular position and at various positions on ring B of the parent octalone, and it was suggested by Robinson\textsuperscript{31} that the stereoselectivity of the reduction might be explained by assuming that the $\beta$-carbon atom is trigonal in the transition state for protonation. Substituents were considered to influence the reduction stereochemistry by causing small changes in the position of the equilibrium involving the two half-chair conformations, 93C and 93D, of ring A of the species undergoing protonation.

Applying this hypothesis to compound 48, and assuming a 6,6-fused ring system, the thermodynamically stable intermediate 94C should be also greatly preferred in the protonation process. (See Scheme 16)
Various laboratories have studied the Birch reduction of 6,5-fused compounds (See Table 1) and their results are summarized in a review article by Caine. It is clear that in these instances a mixture of cis and trans fused products, with the cis isomer predominating, is obtained.

<table>
<thead>
<tr>
<th>Reactant</th>
<th>Reaction conditions</th>
<th>Product</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1" alt="Reactant" /></td>
<td>Li/NH$_3$</td>
<td><img src="image2" alt="Product" /></td>
</tr>
<tr>
<td><img src="image3" alt="Reactant" /></td>
<td>Li/NH$_3$, Et$_2$O, NH$_4$Cl</td>
<td><img src="image4" alt="Product" /></td>
</tr>
<tr>
<td><img src="image5" alt="Reactant" /></td>
<td>Li/NH$_3$, Et$_2$O, NH$_4$Cl</td>
<td><img src="image6" alt="Product" /></td>
</tr>
</tbody>
</table>

Table 1: Birch reduction of 6,5-fused bicyclic α,β-unsaturated ketones.

Based on various postulates and experimental results as shown above, it appears more appropriate to consider compound 48 as a 6,5-fused system. In our study, however, the cis-fused product was exclusive and no trans-fused system could be detected.

At this stage, it was considered necessary to get rid of the carbonyl group of 62, so that the products from ozonolysis could be efficiently used in later stages of the synthetic route. The first approach involved conversion of ketone 62 to the tosylhydrazone 92 in 97% yield,
followed by reduction to the corresponding methylene derivative with sodium borohydride or catechoborane (Scheme 14). The results are listed in Table 2. Although the results were reasonably satisfactory, high cost of catecholborane and more difficult handling conditions particularly in scale-up encouraged us to evaluate the classical Huang Minlong modification of the Wolff-Kishner reaction (W-K-H). Thus ketone 62 was treated with hydrazine and potassium hydroxide in the high boiling point solvent, diethylene glycol (DEG), to give the desired hydrocarbon 72. The IR spectrum of this compound indicated the absence of the carbonyl group absorption. The yields were consistently high (85%-89%) and were independent of the scale of the reaction (Table 2). In summary, this latter procedure was employed for all future studies.

<table>
<thead>
<tr>
<th>Method</th>
<th>Time (h)</th>
<th>Yield</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium Borohydride\textsuperscript{33}</td>
<td>12</td>
<td>58%</td>
<td>lower yield, easy to handle, not feasible for large quantity</td>
</tr>
<tr>
<td>Catechoborane\textsuperscript{34}</td>
<td>3</td>
<td>75%</td>
<td>fairly high yield, anhydrous conditions, not feasible for large quantity, expensive.</td>
</tr>
<tr>
<td>W-K-H\textsuperscript{35}</td>
<td>8</td>
<td>87%</td>
<td>high yield, low cost, can handle large quantity</td>
</tr>
</tbody>
</table>

Table 2: Reduction of 62
It is known that ozone reacts slowly with saturated hydrocarbons with oxygen insertion into the C-H bond. Insertion occurs preferentially at the tertiary carbon atoms, resulting in alcohols and ketones. This type of reaction had been little used until 1975 when Cohen et al reported the dry ozonation method for hydroxylation of saturated compounds. The main idea was to use silica gel as the reaction matrix based on the fact that silica gel absorbs ozone efficiently at low temperature (its concentration being about 4.5% by weight at -78°C). In practice, the silica gel is preabsorbed with the organic substrate, cooled to -78°C and then saturated with ozone; it is then allowed to warm slowly to room temperature and the product is eluted in the normal fashion. It has also been observed that ozone cleaves not only C-H bonds, but also C-CH₃ bonds, which occurs by a direct insertion of ozone into these bonds (Scheme 18).
As mentioned earlier, Dr. Piotrowska in our laboratory had made preliminary study of this reaction, and a more detailed study was now undertaken. Application of this dry ozonation procedure to ketal 68 afforded 60% of alcohol 69 and a small amount of ketone 70. However, application of this technique to our synthesis presented difficulties: the progress of this reaction was not easily monitored, and there were technical limitations to the scale of the experiment. However, these difficulties can be overcome by the use of a solvent37, although ozone is only slightly soluble in organic solvents (about 0.1-0.3% by weight at -78°C38 and reaction time may be longer. To perform the reaction, all the compounds under study were dissolved in ethyl acetate and a stream of ozone was then passed through the solution at -40°C±10°C for 8-10 hours. The reaction was quenched by dimethyl sulfide (DMS). The expected alcohol and ketone products were separated by silica gel chromatography. In this manner, the tricyclic alkane 72 afforded a mixture of the alcohol 73 and ketone 74 in a 1:1 ratio (overall yield 66-70%). The IR spectra indicated the presence of hydroxyl group in 73 and carbonyl absorption in 74, and while 1H-NMR spectra showed that the two doublets at δ=0.89 and 0.96ppm in the starting material 72 (C12 and C13 methyl groups), had collapsed to two
singlets at $\delta=1.18$ and 1.27ppm in 73 and one singlet at $\delta=2.03$ppm in 74. If the temperature of the ozonation process was raised to 0°C, many products were observed even after a short time of reaction (30 minutes). The reaction was very slow when conducted below -50°C, for example, at -60 to -70°C, only 10% of substrate was converted after 18 hours. Compounds 91 and 98 were also investigated for comparison. The results and conditions are listed in Table 3.

<table>
<thead>
<tr>
<th>Substrate</th>
<th>time(h)</th>
<th>temp(°C)</th>
<th>conversion(%)</th>
<th>yield(%)</th>
<th>alcohol/ketone</th>
</tr>
</thead>
<tbody>
<tr>
<td>68</td>
<td>6</td>
<td>-40</td>
<td>75</td>
<td>68</td>
<td>1/1</td>
</tr>
<tr>
<td>68</td>
<td>8</td>
<td>-40</td>
<td>100</td>
<td>45</td>
<td>1/1</td>
</tr>
<tr>
<td>72</td>
<td>1</td>
<td>0</td>
<td>70</td>
<td>side products</td>
<td></td>
</tr>
<tr>
<td>72</td>
<td>8</td>
<td>-40</td>
<td>70</td>
<td>66-75</td>
<td>1.2/1</td>
</tr>
<tr>
<td>62</td>
<td>10</td>
<td>-40</td>
<td>100</td>
<td>67</td>
<td>2.4/1</td>
</tr>
<tr>
<td>91</td>
<td>3</td>
<td>0</td>
<td>100</td>
<td>89*</td>
<td>1.5/1*</td>
</tr>
<tr>
<td>98</td>
<td>3</td>
<td>0</td>
<td>100</td>
<td>79*</td>
<td>1.4/1*</td>
</tr>
</tbody>
</table>

*: Relative percentage of area in glc.

Table 3: Ozonation results of several compounds

From the above studies, it was concluded that: a) higher yields of products are generally obtained when a molecule has a minimum number of tertiary carbon atoms, b) the distribution of alcohol vs ketone is not controllable by the reaction temperature and time, c) a carbonyl or a ketal group at ring A does not improve the yield, but it does shorten the reaction time.

The separated ketone 74 was reduced to alcohol 75 in 93% yield with NaBH4, and this product, together with alcohol 73, provide a convenient family of cyclopropylcarbinols which can undergo an important cyclopropane ring opening reaction discussed in the next section.
2.2.3 Synthesis of decalone 80

In Scheme 8, presented earlier, cyclopropyl ring opening was achieved in a manner to that studied by Julia et al\textsuperscript{39} while in Schemes 10 and 11, an alternate ring opening reaction was observed. It was therefore appropriate to treat the cyclopropylcarbinols 73 and 75 obtained above, with concentrated hydrochloric acid at both 0°C and room temperature for 2 hours, in order obtain chlorides 76 and 77 respectively (Scheme 12). The IR spectra of these products indicated the absence of hydroxyl groups. The parent mass of 76 at 240 (m/z) is consistent with the molecular formula C\textsubscript{15}H\textsubscript{25}\textsuperscript{35}Cl and at 242 (m/z) for the natural \textsuperscript{37}Cl isomer (C\textsubscript{15}H\textsubscript{25}\textsuperscript{37}Cl). The \textsuperscript{1}H-NMR spectra of these compounds were consistent with the five-membered ring structure shown in 76 (Scheme 19) Thus the spectrum revealed a typical ABX coupling system, that is, two well resolved doublet of doublets at $\delta=3.45$ppm (1H,dd,$J=11.4$Hz) and $\delta=3.61$ppm (1H,dd,$J=11.8$Hz) consistent with methylene protons on
a carbon atom attached to the chlorine. Purification of this mixture of chlorides was not successful because these compounds are extremely unstable to both silica gel and alumina chromatography. Even a rapid filtration of the reaction mixture through a short silica gel column results in a partial decomposition. Actually, we found that it was convenient to carry the reaction mixture directly into the next step of the sequence.

In related studies, involving an attempted conversion of 73 with 48% hydrobromic acid to the corresponding five-membered ring bromide (76, replaced Cl by Br), a more complex mixture of products, as determined by glc, and conjugated diene products (UV absorption) were noted.

At this stage, consideration of the ring opening of 76 and 77 to a six-membered ring B, for example to compound 99, was considered since subsequent displacement of chloride by cyanide would allow convenient entry into the C9-aldehyde series. (see Schemes 9 and 13).

McCormick et al.\textsuperscript{40, 41} reported a high yielding, stereoselective conversion of secondary and tertiary cyclopropylcarbinols into homoallylic bromides or iodides by treatment with magnesium bromide or iodide in refluxing anhydrous ether. In this study, they also reported in another publication\textsuperscript{42} that a combination of magnesium halide and zinc halide provided a striking increase in both reaction rate and regioselectivity in conversions involving a bicyclic system.

On this basis, alcohol 73 was treated with one molar equivalent of magnesium bromide together with one molar equivalent of zinc bromide in refluxing anhydrous ether. However, incomplete conversion of substrate to the five-membered ring product was observed. In another study, a mixture of zinc bromide and aqueous hydrobromic acid\textsuperscript{43} was utilized to promote this transformation, but with similar results to those noted above.

The crude product 76 was treated with excess tri-n-butyltin hydride (TBTH) initiated by azobisisobutyronitrile (AIBN) in refluxing toluene for 8 hours to afford the rearranged six-membered ring product 78, the overall yield from 73 to 78 was 52-56%. The crude chloride 77 was converted to 79 in the same conditions described above (the overall yield from 75 to
was 53%). The six-membered ring structure of \(78\) was supported by the \(^1\)H-NMR spectra. There are four methyl signals in the spectra at \(\delta=0.88\ ppm\ (3H,d,J=6.6, C4-CH_3), 0.94\ ppm\ (3H,s, C10-CH_3), 1.655\ ppm\ (3H,s, C11-CH_3)\) and \(1.660\ ppm\ (3H,s, C11-CH_3)\) which are consistent with the structure of \(78\). If B ring was five-membered one more methyl signal, a doublet, would be observed.

There is little doubt that the above conversion of \(76\) to \(78\) involves a radical process. Thus homolytic fission of the C-halogen bond, initiated by the tri-n-butyltin radical, generates intermediate \(101\). Rearrangement of \(101\) as shown in Scheme 20 affords \(102\), which is finally converted to \(78/79\). It is logical to assume that the rearrangement, \(101 \rightarrow 102\), could involve a concerted 1,2-shift although mechanistic studies were not performed here.

\[
R\text{-}X + (n\text{-C}_4\text{H}_9)_3\text{Sn} \rightarrow R' + (n\text{-C}_4\text{H}_9)_3\text{Sn-X}
\]

\[
R' + (n\text{-C}_4\text{H}_9)_3\text{SnH} \rightarrow R\text{-}H + (n\text{-C}_4\text{H}_9)_3\text{Sn}^-
\]

\(X=\text{Halide}\)

\[\text{CH}_2\text{Cl} \quad \text{Bu}_3\text{Sn}^+ \quad \text{R} \quad \text{Bu}_3\text{Sn}^+ \quad \text{R}\]

\(76\) \(R=\text{CH}_3\)

\(77\) \(R=\text{H}\)

\(101\)

\[
\rightarrow \quad \text{H}^+ \rightarrow \quad \text{H}^+ \rightarrow \quad \text{R}
\]

\(102\)

\(78\) \(R=\text{CH}_3\)

\(79\) \(R=\text{H}\)

Scheme 20
In our initial studies with TBTH and the chlorides 76 and 77, refluxing benzene was utilized as the reaction medium. In this case, a 50% yield of 78 or 79 was obtained in a 24 h reaction time. Subsequent studies in refluxing toluene increased the yield (generally 52-56%) and reduced the reaction time to 8 hours.

With the alkenes 78 and 79 in hand, the important intermediate decalone 80 was readily available. Alkene 78 or 79 (or the mixture) was treated with ozone at -60°C (chloroform/dry ice) for 20 minutes. After decomposition of the resultant intermediate ozonide under reductive conditions employing dimethyl sulfide (DMS) at higher temperature, decalone 80 was obtained in 90-93% yield. The IR spectrum of the product showed a carbonyl absorption at 1705 cm⁻¹ and the ¹H-NMR spectrum indicated disappearance of the methyl proton singlets at δ=1.655 and 1.660 ppm normally due to the unsaturated side chain in the substrate 78.

2.2.4 Synthesis of drimane dialdehyde 90 (see Scheme 13)

As shown in Scheme 7, the C8-aldehyde function of 40 was introduced via formylation of decalone 8 with ethyl formate and sodium hydride in ether at room temperature. When we applied the same condition to decalone 80, no reaction was observed at room temperature over a 24 hour period and a similar result was observed at elevated temperature. It was clear that stronger base such as KH or CsH₄ was required.
Gas evolution readily commenced when substrate 80 was added to a suspension of potassium hydride in THF at room temperature and upon addition of ethyl formate, formylation occurred in 20 minutes. The product, isolated in 89% yield, was the C8 formyl compound 81. (See Table 4). It should be noted, as shown in Table 4, that THF is a superior solvent to ether in this process.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base</th>
<th>Solvent</th>
<th>Temperature</th>
<th>Yield</th>
<th>Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NaH</td>
<td>ether</td>
<td>R.T. or Reflux</td>
<td>----</td>
<td>24h</td>
</tr>
<tr>
<td>2</td>
<td>NaH</td>
<td>THF</td>
<td>R.T. or Reflux</td>
<td>----</td>
<td>24h</td>
</tr>
<tr>
<td>3</td>
<td>KH</td>
<td>ether</td>
<td>R.T.</td>
<td>81%</td>
<td>30min</td>
</tr>
<tr>
<td>4</td>
<td>KH</td>
<td>THF</td>
<td>R.T.</td>
<td>89%</td>
<td>20min</td>
</tr>
</tbody>
</table>

Table 4: Formylation of 80

Compound 81 is easily purified through a silica gel column or by extraction with potassium hydroxide solution, but somewhat unstable even when stored at 0°C. Consequently it was best to perform the next reaction without delay. This compound showed in the IR spectrum a weak absorption for the OH (enolic) function and a strong carbonyl absorption.

The olefinic bond in 82 was introduced via a selenylation-deselenylation reaction with 81. Liotta et al reported that the rate of selenation with PhSeCl/pyridine can be roughly correlated with the percent enolic character of the starting β-dicarbonyl compound. When the substrate in question exists to a substantial extent in its enol form, selenation is instantaneous at room temperature. In our case, compound 81 exists entirely in the enol form as supported by two singlets shown in the 1H-NMR spectrum at δ=8.56 and 14.29ppm. Compound 81 was therefore readily converted to the corresponding unsaturated derivative 82 by a) selenation using a 1:1 complex of phenylselenenyl chloride/pyridine and b) in situ oxidation with 30% H2O2. The isolated yield of 82 was 86%. The UV spectrum showed the conjugated
absorption at 238 nm, the IR spectrum indicated the conjugated C=O absorption at 1680 cm\(^{-1}\) and the \(^1\)H-NMR spectrum revealed the olefinic proton at \(\delta=7.45\) ppm as well as the aldehyde proton at \(\delta=10.09\) ppm. The resultant keto aldehyde 82 smoothly underwent a conjugate addition with cyanide to give 9-nitrile 83. The crude product was purified by extraction with potassium hydroxide solution, then acidification, extraction again with organic solvent. Further purification with column chromatography on either silica gel or alumina was not successful since all the crude product would be consumed on the column. The crude product showed the cyano group absorption at 2236 cm\(^{-1}\) in IR spectrum, and \(^1\)H-NMR spectrum gave singlets at \(\delta=4.01, 8.98\) and 15.04 ppm supporting the structure of 83. The stereochemistry at C9 was not clear, although it could be assumed that the nitrile group was \(\beta\)-oriented.

The conversion of the formyl ketone moiety in 83 into the \(\alpha,\beta\)-unsaturated aldehyde 85 was performed via the following two steps. 1) protection of the aldehyde group of 83 by n-butylmercaptan, 2) reduction of the carbonyl group of the (n-butylthio)methylene derivative 84 with sodium borohydride, followed by hydrolysis promoted by mercuric chloride. The overall yield in the conversion 82 \(\rightarrow\) 85 was 52%. The UV spectrum of 85 showed the conjugated absorption at 224 nm, and the \(^1\)H NMR spectrum indicated the aldehyde and olefinic protons at \(\delta=7.05, 9.51\) ppm respectively.

Protection of the aldehyde group of 85, so that the nitrile could be reduced to an aldehyde, with ethylene glycol catalyzed by p-toluenesulfonic acid, provided ketal 86 in 71% yield along with the isomeric ketal 87 in 18% yield. The IR spectra showed no carbonyl group in these products while \(^1\)H-NMR spectra revealed one olefinic proton at \(\delta=6.05\) ppm for 86 and two olefinic protons at \(\delta=5.53, 6.62\) ppm for 87. Since the double bond is expected to move back into conjugation on deprotection of the ketal, compound 87 could be utilized. Examination of the \(^1\)H-NMR spectrum of 86 revealed the proton attached to the C9 atom, which carries the cyano group, at \(\delta=2.79\) ppm (singlet 1H). On the basis of its chemical shift, the C10 methyl group was also easily noted at \(\delta=1.24\) ppm (singlet 3H). Irradiation of the
C10 methyl proton resonance (δ=1.24ppm) resulted in an enhancement of a signal at δ=2.79ppm (C9-H) (Figure 5). From the more stable conformation of 86 (See 86A), it was clear that irradiation of the C10 methyl protons would be expected to provide an enhancement to the C9 axial proton in 86-1 and similarly to the C9 equatorial proton in 86-2. Since the distance between these protons and the corresponding methyl protons should be similar in the two possible isomers (86-1 and 86-2). In conclusion, NOE experiment cannot clearly establish the stereochemistry at C9.

Nitrile 86 was reduced to the corresponding aldehyde 88 with DIBAH at -60°C to -50°C in three hours (85% yield). This reduction was done at this temperature, because at the lower temperature of -78°C, the reaction would not proceed to completion, whilst at room temperature, a low yield of aldehyde was obtained. Nitrile 87 was reduced to aldehyde 88 with DIBAH at -78°C for two hours.
Nuclear Overhauser difference experiments on nitrile 86 (400 MHz, CDCl₃)

a) off resonance spectrum
b) irradiation at 1.24 ppm

Figure 5
We surprisingly found that nitrile 84 was resistant to DIBAH reduction. When excess DIBAH was added to 84, only alcohol 103 was found even after 12 hours at room temperature. (see Scheme 21).

![Scheme 21](image)

With 88 and 89 in hand, we were ready to perform the final steps of the sequence. Ketal 88 was hydrolyzed in an acetone/water mixture with an acid (p-toluenesulfonyl acid) catalyst at room temperature for three hours to give our target compound 90 in 93% yield. As we expected, hydrolysis of 89 provided the same compound 90 in 77% yield (overall from 87). The IR spectrum of this compound showed a saturated aldehyde at 1718 cm\(^{-1}\) and a conjugated aldehyde at 1665 cm\(^{-1}\), and the \(^1\)H-NMR spectrum revealed the two aldehyde protons at \(\delta=9.44\) and 9.79 ppm.

Another NOE difference experiment was applied to 90 as shown in Figure 6. Irradiation at the C10 methyl protons resonance at \(\delta=1.26\) ppm (3H,s) resulted in an enhancement of the C9 proton at \(\delta=3.33\) ppm (1H,d, J=3) and C9 aldehyde proton at \(\delta=9.79\) ppm (1H,d, J=3). Similar arguments concerning NOE results and stereochemistry at C9, to those presented above for 86, apply in this case and therefore NOE data cannot establish the C9 configuration in the final product 90. However it should be noted that the acidic treatment in the conversions, 88→90 and 89→90 may well provide the C9 α-orientation for the aldehyde function. In the latter case, this functionality is in a more favored equatorial orientation.
Nuclear Overhauser difference experiments on drimane dialdehyde 2Q (400 MHz, CDCl₃)
   a) off resonance spectrum
   b) irradiation at 1.50 ppm

Figure 6

2.3 Approach to the natural drimane antifeedants

As was seen in Section 1.2, the naturally occurring drimane antifeedants have a trans A/B ring fusion coupled with the functional groups in ring B and gem-dimethyl group in ring A. An approach to a trans decalone with a gem-dimethyl group in ring A, which will eventually lead to the natural drimane antifeedants, is now presented. From our previous work, the enone 48 could not be converted to a trans A/B ring juncture by either catalytic hydrogenation or the Birch reduction (Section 2.2.1 and Scheme 14). As mentioned earlier, the 6,5-fused system plays an important part in formation of the cis A/B fusion, it was therefore decided to study molecules of the 6,6-fused system. Reductive alkylation of the
trienone 53, available from Scheme 9, did not give the desired diene 106 (Scheme 22). However, an efficient sequence has been developed by Dr. Cheng* based on a large amount of work in the model studies (Scheme 23). This study will provide a novel entry to the natural products of the polygodial family.

The reaction sequence is as follows:

1. Treatment of 53 with Li/NH3 followed by CH3I gives compound X (Scheme 22).
2. Compound 52, treated with NaOCH3 in CH3I/DMSO, yields a mixture of 105 and 106.
4. Compound 108 is treated with Li/NH3 to give 109.

Scheme 23

*: Personal communication with Dr. K. P. N. Cheng.
Alkylation of 52 with methyl iodide and sodium methoxide in DMSO provided the dienes 105 and 106 in a 2:1 ratio. The former was then readily epimerized to 106 via catalysis with iodine in refluxing hexane. The diene 106 could be converted to the trans A/B fused compound 109 by reduction followed by selective ozonation of the more active exocyclic double bond of diene 107 to give enone 108. Finally the latter could be elaborated to the chiral trans decalone 109 by Birch reduction. The chiral decalone 109 can be easily converted to the chiral natural products polygodial and warburganal by performing the procedures described in Scheme 7 and 13.

2.4 CONCLUSION

Polygodial 1 exhibits a number of interesting biological properties, including a marked antifeedant activity against insects, and tastes very hot to humans. However, in spite of various efforts made in recent years, the biochemical mechanism for these activities still remains obscure. D' Ischia et al\textsuperscript{47} have suggested that the biological activity of polygodial is related to its ability to react with amino groups. Based on this hypothesis and experiments, epi-polygodial 110 and the cis -fused isomer 111 were observed non-active\textsuperscript{9,47}, but the cis- fused dialdehyde 112 was found active to some insects\textsuperscript{48}. 
The newly synthesized drimane dialdehyde 90 possesses the following structural features: a cis A/B ring junction, one methyl group in ring A and the required dialdehyde functionality in ring B. Detailed evaluation of its biological activity will reveal whether this thujone-derived intermediate, with only one methyl group in ring A, will possess this important activity. This result could lead to a new family of antifeedants from the readily available and inexpensive thujone. Regardless, the above studies have provided considerable chemistry relating to the synthesis of the drimane type dialdehydes both in the natural and unnatural series. It is clear that the information derived can be extended to other terpenoid synthesis.
3. Experimental

3.1 General

Unless otherwise specified, all reagents were supplied by the Aldrich Chemical Company and used without further purification. Petroleum ether refers to the fraction boiling in the range 30-60°C. Anhydrous tetrahydrofuran (THF), diethyl ether and toluene were purified by distillation from a mixture of the solvent with sodium and benzophenone. Anhydrous benzene was obtained by distillation from a mixture of benzene and calcium hydride and dry methanol from a mixture with magnesium and iodine. Ozone was produced by a Welsbach Ozonator.

The compounds were characterized by their melting points on a Nalge melting point apparatus and are uncorrected. The infrared spectra were recorded on Perkin-Elmer 710B and 1710 (Fourier Transform I.R.) spectrometers either in chloroform solution (using sodium chloride cells of 0.1mm path length) or as a neat liquid film (using sodium chloride plate). The ultraviolet spectra were recorded on a Cary 15 spectrometer in 1cm quartz cells, the extinction coefficients ($\log \epsilon_{\text{max.}}$) being given in parentheses, and the wavelength(s) of the maxima in nanometers. The mass spectra were recorded on AEI-MS-9 (low resolution) or KRATOS-MS-50 (high resolution) spectrometers. The $^1$H NMR spectra were recorded on either Bruker WH-400 or Varian XL-300 spectrometers and the chemical shifts are reported in ppm relative to tetramethylsilane (internal standard). The optical rotations were recorded on a Perkin-Elmer 141 automatic polarimeter in a 10 cm cell at ambient temperature using the solvent and concentrations (g/100ml) indicated in parentheses following the recorded rotation values. The elemental analyses were determined by combustion analysis by Mr. P. Borda, Microanalytical Laboratory, The University of British Columbia. The X-ray diffraction analysis was performed by Dr. S. Rettig on a RIGAKU AFC6 diffractometer. Column chromatography was performed using 230-400 mesh silica gel supplied by E. Merck Co. Unless otherwise stated, all reactions
were monitored by thin layer chromatography (TLC) analyses, which were carried out on commercial aluminium-backed silica gel plates (Merck art 5554). Visualization was accomplished with ultraviolet light and/or by spraying with 5% ammonium molybdate-10% aqueous sulfuric acid, followed by heating. Gas-liquid chromatography (GLC) was performed on a Hewlett Packard model 5890 gas chromatograph, using a flame ionization detector and a 25m x 0.21mm fused silica capillary column coated with DB1701.

It is important to note that the numbering system employed for the compounds prepared conforms with that used for the natural drimane sesquiterpenoids. This is done in order to allow facile comparison with compounds within the drimane family. However the corresponding names according to IUPAC system are shown in parentheses.
A mixture of tricyclic enone 48 (8.00 g, 36.7 mmol), potassium hydroxide (1g, 17.8 mmol) and 10% palladium on active charcoal (2 g) in ethanol (800 ml) was hydrogenated at room temperature and atmospheric pressure. Hydrogen absorption ceased after 3.5 hours. The mixture was filtered through a celite plug and the filtrate evaporated. Water (100 ml) was added to the residue, the mixture was extracted with methylene chloride (2x100 ml) and dried over sodium sulfate. Evaporation of the solvent at reduced pressure afforded the saturated ketone 62 as a colorless oil (7.99 g, 99%).

The physical properties of 62 are as follows:

IR ν max. (neat): 2942, 2846 (C-H, st.), 1702 (C=O, st.) cm⁻¹.

¹H-NMR (400 MHz, CDCl₃) δ: 0.20(1H,dd, J=9,4, C8-H), 0.43(1H,dd, J=6,4, C8-H), 0.85(3H,d, J=8, C11-CH₃), 0.91(3H,d, J=8, C11-CH₃), 0.94(3H,d, J=7, C4-CH₃), 1.18(1H,t, J=11.2), 1.23(3H,s, C10-CH₃), 1.33(1H,h, J=8, C11-H), 1.61-1.83(5H,m), 2.15(1H,m, C2-H), 2.42(1H,m, C2-H), 2.59(1H, m, C4-H).

MS m/z: 220(M⁺), 205, 177, 136, 124, 105, 93, 86, 82, 67, 55, 41. High resolution mass measurement: calculated for C₁₅H₂₄O: 220.1821; found: 220.1815.

Elemental analysis: calculated for C₁₅H₂₄O: C 81.76, H 10.98; found: C 81.67, H 11.00. 

3.3 (5β)-4α,10β-dimethyl-3-(1,3-dioxolan-2-yl)-7α-isopropyl-tricyclo[4.4.0.0⁵,10.0⁷,9]-decane 68
A solution of ketone 62 (3.53 g, 16 mmol), ethylene glycol (2.1 g, 33.9 mmol) and p-toluenesulfonic acid (50 mg, 0.26 mmol) in benzene (70 ml) was heated at reflux with a Dean-Stark apparatus for 4 hours. The solution was cooled and ether (100 ml) was added. The solution was washed with saturated aqueous sodium bicarbonate (50 ml) and water (2x50 ml), then dried over sodium sulfate. The solvent was evaporated. The residue was filtered through a short column of silica gel using a solvent of ether/pet. ether (1:9 v/v). The solvent was evaporated to give the pure ketal 68 (3.67 g, 87%) as a colorless oil.

The physical properties of 68 are as follows:

IR ν_max. (neat): 2940, 2855 (C-H st.), 1110 (C-O SL) cm⁻¹.

¹H-NMR (400 MHz, CDCl₃) δ: 0.10(1H,dd,J=8.4, 4.8, C8-H), 0.37(1H,dd,J=4.8,3.8, C8-H), 0.84(3H,d,J=7.2, C11-CH₃), 0.88(3H,d,J=7.2, C11-CH₃), 0.98(3H,d,J=7.2,C4-CH₃), 1.00(3H,s, C10-CH₃), 1.02-1.97(10H,m), 3.97-4.00(4H,m).

MS m/z: 264(M⁺), 249, 235, 221, 99.

3.4 (5B)-4,4,10β-trimethyl-7α-isopropyl-tricyclo[4.4.0.0⁶,10]-dec-3-one 21

(5B)-2,4,4,10β-tetramethyl-7α-isopropyl-tricyclo[4.4.0.0⁶,10]-dec-3-one 28

{(6β)-1β,5,5-trimethyl-8α-isopropyl-tricyclo[4.4.0.0⁶,10]-dec-4-one
91
A solution of enone 48 (1.1 g, 5 mmol) in dry THF (13 ml) was added dropwise to a solution of lithium (0.09 g, 13 mmol) in liquid ammonia (38 ml) (purified by distillation from lithium). After addition was complete the blue solution was stirred for 10 minutes, then dry THF (40 ml) was added. Removal of ammonia was completed by heating under reflux and, after allowing the mixture to cool (argon protection), methyl iodide (7.5 g, 52.8 mmol) was added and the mixture was heated at reflux for 1 hour. After stirring at room temperature for 5 hours, the mixture was poured into water and extracted with ether (3x50 ml). The ethereal solution was washed with brine and dried over magnesium sulfate. Column chromatography on silica gel using 5% ether/pet. ether gave the desired ketone 91 (0.632 g, 54%) as a colorless oil plus compound 98 (0.470 g, 40%).

The physical properties of 91 are as follows:
IR ν max. (neat): 2940, 2850 (C-H st.), 1700 (C=O st.) cm⁻¹.

¹H-NMR (400MHz, CDCl₃) δ: 0.18(1H, dd, J=8, 4.8, C8-H), 0.39(1H, dd, J=4.8, 4, C8-H), 0.84(3H, d, J=6.4, C11-CH₃), 0.86(1H, m), 0.90(3H, d, J=6.4, C11-CH₃), 0.96(3H, s, C10-CH₃), 1.22(3H, s, C4-CH₃), 1.32(3H, s, C4-CH₃), 1.28-1.38(2H, m), 1.47(1H, dd, J=12, 7.6), 1.72(1H, dd, J=12, 7.2), 1.83(2H, m), 2.13(1H, m, C2-H), 2.70(1H, m, C2-H).

MS m/z: 234(M⁺), 219, 201, 191, 105, 96, 81, 49, 55, 43.

The physical properties of 98 are as follows:
IR ν max. (neat): 2925, 2850 (C-H st.), 1695 (C=O st.) cm⁻¹.
$^1$H-NMR (400MHz, CDCl$_3$) δ: 0.14(1H,dd,J=8,4.8, C8-H), 0.41(1H,dd,J=4.8,4, C8-H), 0.83(3H,d,J=5.6, C2-CH$_3$), 0.88(3H,d,J=6.8, C11-CH$_3$), 0.95(3H,s, C10-CH$_3$), 0.98(3H,d,J=6.8, C11-CH$_3$), 1.06-1.80(7H,m), 2.91(1H,m, C2-H).

MS m/z: 248(M$^+$), 233, 205, 149, 136, 123, 114, 107, 96, 81, 71, 55, 41.

3.5 (5β)-4α,10β-dimethyl-7α-isopropyl-tricyclo[4.4.0$^5$,10$^7,9$]-dec-3-tosylhydrazone 92

{(6β)-1β,5α-dimethyl-8α-isopropyl-tricyclo[4.4.0$^8$,10]-dec-4-tosylhydrazone 92}

A solution of tricyclic ketone 62 (19.655 g, 89.1 mmol) in benzene (1500 ml) with p-toluenesulfonyl hydrazide (17.425 g, 93.7 mmol) and boron trifluoride etherate (1 ml) was stirred under argon at room temperature for 6 hours. The benzene was evaporated under reduced pressure. The residue was diluted with water (500 ml) and extracted with ether (2x500 ml). The extracts were dried over sodium sulfate and the solvent was evaporated. Recrystallization from ether/pet. ether gave hydrazone 92 as white crystals (33.53 g, 97%).

Mp: 88.5-89.5°C

Elemental analysis: calculated for C$_{22}$H$_{32}$N$_2$O$_2$S: C 68.00, H 8.30, N 7.21; found: C 68.16, H 8.43, N 7.25.

3.6 (5β)-4α,10β-dimethyl-7α-isopropyl-tricyclo[4.4.0$^5$,10$^7,9$]-decane 72

{(6β)-1β,5α-dimethyl-8α-isopropyl-tricyclo[4.4.0$^8$,10]-decane 72}
3.6.1 Method A

To a solution of tosylhydrazone 92 (6.20 g, 15.9 mmol) in methanol (200 ml) was added sodium borohydride (11.3 g, 339 mmol) in small portions during one hour and the resulting mixture was heated under reflux for an additional 8 hours. The solvent was removed under reduced pressure. The residue was dissolved in ether and the ethereal solution was washed with water, 10% sodium carbonate solution, 1N hydrochloric acid and water, then dried over sodium sulfate. The solvent was removed under reduced pressure. Chromatography of the residue on a silica gel column using petroleum ether as eluant gave 72 (1.90 g, 58%) as a colorless oil.

3.6.2 Method B

To a solution of tosylhydrazone 92 (20.45 g, 52.7 mmol) in chloroform (100 ml) at -15°C under argon, catecholborane (6.31 ml, 58 mmol) was added and the hydroboration was allowed to proceed at -10°C for one hour. Sodium acetate trihydrate (20.1 g, 155 mmol) was then added, and the reaction mixture was brought to a gentle reflux for 3 hours, cooled to room temperature, and filtered. The solid material on the filter was washed with chloroform (50 ml), and the combined filtrates were evaporated under reduced pressure. The remaining oil was purified by chromatography on a silica gel column with hexanes as eluant to afford 72 (8.14 g, 75%) as a colorless oil.
3.6.3 Method C

A mixture of the carbonyl substrate 62 (30 g, 136.4 mmol) and hydrazine (21.8 g, 681.8 mmol) in diethylene glycol (300 ml) was heated from 100-130°C for 1.5 hours (water and excess hydrazine were distilled). After cooling, potassium hydroxide (45.8 g, 818.4 mmol) was added to the reaction mixture and heating was continued at 200-210°C for 6 hours. The cooled reaction mixture was added to water (300 ml), extracted with ether (2x250 ml), washed with brine and dried over sodium sulfate. The solvent was removed and the residue was purified on a silica gel column using pet. ether as eluant to give the ketone-free compound 72 (24.5 g, 87%) as a colorless oil.

The physical characteristics of 72 are as follows:

IR $\nu_{\text{max}}$ (neat): 3035, 2995, 2925, 2860 (C-H st.), 1470, 1385 (C-H bend) cm$^{-1}$

$^1$H-NMR (400 MHz, CDCl$_3$) $\delta$: 0.07(1H,dd,J=8,5, C8-H), 0.40(1H,dd,J=10,5, C8-H), 0.81(3H,d,J=6.8, C4-CH$_3$), 0.89(3H,d,J=6.6, C11-CH$_3$), 0.96(3H,d,J=6.6, C11-CH$_3$), 0.95(3H,s, C10-CH$_3$), 1.10-1.63(12H,m).

MS m/z: 206(M$^+$), 191, 163, 123, 110, 95, 81, 55. High resolution mass measurement: calculated for C$_{15}$H$_{26}$: 206.2034; found: 206.2033.

Elemental analysis: calculated for C$_{15}$H$_{26}$: C 87.30, H 12.70; found: C 87.24, H 12.75.

3.7 (5$\beta$)-4$\alpha$,10$\beta$-dimethyl-7$\alpha$-isopropinol-tricyclo[4.4.0.0$^8$]5.10.7.9]-decane 73

(5$\beta$)-7$\alpha$-acetyl-4$\alpha$,10$\beta$-dimethyl-tricyclo[4.4.0.0$^8$]5.10.7.9]-decane 74

((6$\beta$)-1$\beta$,5$\alpha$-dimethyl-8$\alpha$-isopropinol-tricyclo[4.4.0.0$^8$]5.10.7.9]-decane 73

(6$\beta$)-8$\alpha$-acetyl-1$\beta$,5$\alpha$-dimethyl-tricyclo[4.4.0.0$^8$]5.10.7.9]-decane 74
Ozone was bubbled through a solution of \(\text{72} \) (24 g, 116.5 mmol) in ethyl acetate (500 ml) containing sodium bicarbonate (9.8 g) at \(-40^\circ\text{C}\) (acetonitrile/dry ice bath) for eight hours. The excess ozone was removed under a stream of argon and then dimethyl sulfide (5 ml) was added to the solution. The reaction mixture was allowed to warm to room temperature and stirred for one hour. Filtration and concentration, followed by flash chromatography on a silica gel column (hexanes-ethyl acetate as eluant, 17:3, v/v) provided alcohol \(\text{73} \) (10 g, 38.7\%) and ketone \(\text{74} \) (7.7 g, 32.3\%) and starting material \(\text{72} \) (6.9 g, 28.7\%). The total yield was 71\% based on the recovered starting material.

The physical properties of \(\text{73} \) are as follows:

IR \(\nu_{\text{max}}\) (neat): 3405 (O-H, St.), 3050, 2903, 2850 (C-H st), 1140 (C-O St.) cm\(^{-1}\).

\(^1\text{H-NMR} \) (400 MHz, CDCl\(_3\)) \(\delta\): 0.43(1H,dd,\(J=5.2,4.4\), C8-H), 0.48(1H,dd,\(J=5.8,4.4\), C8-H), 0.83(3H,d,\(J=6.4\), C4-CH\(_3\)), 0.98(3H,s, C10-CH\(_3\)), 1.18(3H,s, C11-CH\(_3\)), 1.27(3H,s, C11-CH\(_3\)), 1.00-1.51(10H,m), 1.62(1H,br, O-H), 1.75(1H,t,J=12)

MS m/z: 204(M\(^+\)-H\(_2\)O), 189, 161, 133, 119, 105, 95, 91, 81, 67, 59, 55, 41, 32. High resolution mass measurement: calculated for C\(_{15}\)H\(_{26}\)O: 222.1984; found: 222.1982.

Elemental analysis: calculated for C\(_{15}\)H\(_{26}\)O: C 81.02, H 11.78; found: C 80.80, H 11.53.

The physical properties of \(\text{74} \) are as follows:

IR \(\nu_{\text{max}}\) (neat): 3000, 2925, 2859(C-H st), 1680(C=O st.) cm\(^{-1}\).

\(^1\text{H-NMR} \) (400 MHz CDCl\(_3\)) \(\delta\): 0.86(3H,d,\(J=6.4\), C4-CH\(_3\)), 1.03(3H,s, C10-CH\(_3\)), 1.04-1.73(12H,m), 2.03(3H,s, C11-CH\(_3\)), 2.10(1H,t,J=12).

MS m/z: 206(M\(^+\)), 191, 177, 163, 95, 81, 43. High resolution mass measurement for C\(_{14}\)H\(_{22}\)O: 206.1671; found: 206.1662.
Elemental analysis: calculated for C_{14}H_{22}O: C 81.50, H 10.75; found: C 81.56, H 10.90.

3.8 (5\beta)-4\alpha,10\beta-dimethyl-3-(1,3-dioxolan-2-yl)-7\alpha-isopropinol-tricyclo[4.4.0.0^4,8.10.0^7,9]-decane 69 and (5\beta)-7\alpha-acetyl-4\alpha,10\beta-dimethyl-3-(1,3-dioxolan-2-yl)-tricyclo[4.4.0.0^4,8.10.0^7,9]-decane 70

{(6\beta)-1\beta,5\alpha-dimethyl-4-(1,3-dioxolan-2-yl)-8\alpha-isopropinol-tricyclo[4.4.0.0^8,10]-decane 69 and (6\beta)-8\alpha-acetyl-1\beta,5\alpha-dimethyl-4-(1,3-dioxolan-2-yl)-tricyclo[4.4.0.0^8,10]-decane 70}

Compounds 69 and 70 were prepared as described for 73 and 74. Thus compound 68 (190 mg/200 ml ethyl acetate) gave 69 (46 mg, 22.8%) and 70 (50 mg, 26.3%) and starting material (48 mg, 25.2%).

The physical properties of 69 are as follows:

IR \nu_{\text{max}} (neat): 3601 (O-H St.), 2950, 2875 (C-H St.), 1110 (C-O st.) cm^{-1}.

\textsuperscript{1}H-NMR (400 MHz, CDCl\textsubscript{3}) \delta: 0.38(1H,dd,J=5.2,4, C8-H), 0.43(1H,dd,J=8.8,4, C8-H), 0.84(3H,d,J=7, C4-CH\textsubscript{3}), 1.03(3H,s, C10-CH\textsubscript{3}), 1.19(3H,s, C11-CH\textsubscript{3}), 1.27(3H,s, C11-CH\textsubscript{3}), 1.30-1.67(8H,m), 1.95(1H,m), 2.17(1H,m), 3.80-3.99(4H,m).

\textsuperscript{13}C-NMR (75MHz, CDCl\textsubscript{3}) \delta: 7.727, 11.856, 21.610, 27.582, 27.630, 28.461, 31.000, 33.237, 33.989, 34.525, 35.742, 39.135, 45.868, 64.052, 65.593, 70.756, 111.217.

MS m/z: 280(M\textsuperscript{+}), 262, 247, 99, 59, 55, 41.

The physical properties of 70 are as follows:
IR ν max. (neat): 2953, 2882 (C-H st.), 1684 (C=O st.), 1102 (C-O st.) cm⁻¹

¹H-NMR (300 MHz, CDCl₃) δ: 0.89 (3H, d, J=7.5, C₄-CH₃), 1.01 (1H, m), 1.07 (3H, s, C₁₀-CH₃), 1.26-1.83 (8H, m), 1.96 (1H, m), 2.10 (3H, s, C₁₁-CH₃), 2.56 (1H, t, J=13.5), 3.80-3.99 (4H, m).

MS m/z: 264 (M⁺), 221, 179, 99, 55, 43.

3.9 (5β)-4α,10β-dimethyl-7α-(1'-hydroxy ethyl)-tricyclo[4.4.0.0².⁷]decane 75

{(6β)-1β,5α-dimethyl-8α-(1'-hydroxy ethyl)-tricyclo[4.4.0.0⁸.¹⁰]-decane 75}1

[Diagram]

To a solution of ketone 74 (5.2 g, 25 mmol) in methanol (70 ml) was added sodium borohydride (0.58 g, 15 mmol) at 0°C. The reaction mixture was stirred at 0°C for 20 minutes, then the methanol was evaporated. Ether was added to the residue and the solution was washed with water and brine. The solvent was removed under reduced pressure and the residue was purified by chromatography on a silica gel column (ether-pet/ether as eluant, 1:1, v/v) to afford alcohol 75 (4.8 g, 93%) as a colorless oil.

The physical properties of 75 are as follows:
IR ν max. (neat): 3325 (O-H, s), 3050, 2900 (C-H, s), 1100 (C-O, s.) cm⁻¹
¹H-NMR (300 MHz, CDCl₃) δ: 0.24 (1H, dd, J=9, 4.8, C₈-H), 0.56 (1H, dd, J=6, 4.8, C₈-H), 0.82 (3H, d, J=6.6, C₄-CH₃), 0.98 (3H, s, C₁₀-CH₃), 1.21 (3H, d, J=6.6, C₁₁-CH₃), 0.88-1.67 (11H, m), 1.72 (1H, t, J=11.4), 3.42 (1H, q, J=6.6, C₁₁-H).
MS m/z: 208(M+), 190(M+H2O), 175, 164, 149, 135, 123, 95, 81, 67, 55, 43. High resolution mass measurement for C14H24O: 208.1827; found: 208.1829.

Elemental analysis: calculated for C14H24O: C 80.71, H 11.61; found: C 80.50, H 11.54.

3.10 (5β)-8-chloromethyl-4α,9β-dimethyl-7α-isopropylidene-bicyclo[4.3.0]-9-nonane 76
{(6β)-9-chloromethyl-1β,5α-dimethyl-8α-isopropylidene-bicyclo[4.3.0]-nonane 76}

![Chemical structure diagram]

Compound 73 (6.08 g, 27.4 mmol) was dissolved in dichloromethane (150 ml) and added to ice cold concentrated hydrochloric acid (150 ml). The mixture was stirred rapidly at 0°C for two hours. The mixture was poured into water (200 ml), and the aqueous layer was extracted with dichloromethane (3x70 ml). The combined organic extracts were washed with saturated aqueous sodium bicarbonate solution (2x70 ml), dried over sodium sulfate, and the solvent was evaporated. The yellow oil was carried over to next step without purification.

The physical characteristics of 76 are as follows:

IR ν max. (neat): 2905, 2850 (C-H st.), 1654 (C=C st.), 718 (C-Cl st) cm⁻¹.

¹H-NMR (400 MHz, CDCl₃) δ: 0.87(3H,d, J=7, C4-CH₃), 1.14(3H,s, C9-CH₃), 1.65(3H,s, C11-CH₃), 1.73(3H,s, C11-CH₃), 0.89-1.59(7H,m), 1.90(1H,m), 2.11(2H,d,br,J=10, C6-H), 2.50(1H,m,br, C8-H), 3.45(1H,dd,J=11,4, C10-H), 3.61(1H,dd,J=11,8, C10-H).

Compound 77 was prepared from 75 as described for 76. The crude oil product was carried over to next step without purification.

3.11 (5β)-4α,10β-dimethyl-7-isopropylidene-bicyclo[4.4.0]10-decane 78

To a solution of crude 76 from 3.10 in dry toluene (250 ml) under argon was added tri-n-butyltin hydride (11.9 g, 41.1 mmol). AIBN (300 mg, 1.9 mmol) was then added and the reaction mixture was heated at reflux under argon for two hours. A further portion of AIBN (300 mg) was added and the reaction maintained at gentle reflux for an additional 6 hours. The solvent was evaporated and the residue chromatographed on silica gel with hexanes to give 78 (3.16 g, 56% calculated from 73) as a colorless oil.

The physical properties of 78 are as follows:

IR ν max. (neat): 2920 (C-H st.), 1660 (C=C st.) cm⁻¹.
\[ ^1 \text{H-NMR (400 MHz, CDCl}_3 \text{)} \delta: 0.88(3H,d,J=6.6, \text{C4-CH}_3), 0.94(3H,s, \text{C10-CH}_3), 1.11-1.62(10H,m), 1.65(3H,s, \text{C11-CH}_3), 1.66(3H,s, \text{C11-CH}_3), 1.83-1.98(2H,m), 2.41(2H,m). \]

MS m/z: 206(M\(^{+}\)), 191, 163, 109, 95, 81, 67, 55, 41. High resolution mass measurement: calculated for C\(_{15}\)H\(_{26}\): 206.2034; found: 206.2037.

Elemental analysis: calculated for C\(_{15}\)H\(_{26}\): C 87.30, H 12.70; found: C 87.05, H 12.60.

Compound 79 was prepared from 77 as described for 78. The total yield from 75 to 79 was 53%.

The physical characteristics of 79 are as follows:
IR \( \nu \text{ max. (neat)} \): 2950, 2930, 2859 (C-H st.), 1660 (C=C st.), 829 (C-H bend) cm\(^{-1}\).
Partial \(^1\text{H-NMR (1:1 C11-isomers) (300 MHz, CDCl}_3 \text{)} \delta: 0.83, 0.87(3H,two sets,d,J=6, \text{C4-CH}_3), 0.95(3H, two sets,s, \text{C10-CH}_3), 1.56(3H,two sets,d,J=4.2, \text{C11-CH}_3), 5.13(1H,two sets,m,C11-H). \]
MS m/z: 192(M\(^{+}\)), 177, 163, 109, 95, 81, 67, 55, 41. High resolution mass measurement for C\(_{14}\)H\(_{24}\): 192.1878; found: 192.1870.

3.12 (5\( \beta \))-4\( \alpha \),10\( \beta \)-dimethyl-octahydro-7-(6\( H \))-naphthalenone 80

\{(8\( \alpha \)\( \beta \))-4\( \alpha \)\( \beta \),8\( \alpha \)-dimethyl-octahydro-2-(1\( H \))-naphthalenone 80\}

\[
\begin{align*}
\text{Ozone was bubbled through a solution of 78 (2.30 g, 11.2 mmol) in ethyl acetate (70 ml) at -60°C. After 20 minutes, the system was flushed with argon until no blue color in the}
\end{align*}
\]
solution, and dimethyl sulfide (1.12 ml, 15.2 mmol) was added. The solution was then allowed to warm up slowly to 0°C in one hour, then stirred at ice bath temperature for one hour, finally at room temperature for one hour. The solvent was removed and residue was purified by flash chromatography (ether/pet. ether, 2:8, v/v) to give decalone 80 (1.83 g, 91%) as a colorless oil.

79 provided 80 in the same way to give a yield of 90%.

The physical properties of 10 are as follows:

\[ [\alpha]_D^{18} = +12.9^\circ \] (0.940, methanol).

IR \( \nu_{\text{max.}} \) (neat): 2900, 2845 (C-H st.), 1705 (C=O st.) cm\(^{-1}\).

\(^1\)H-NMR (300 MHz, CDCl\(_3\)) \( \delta \): 0.80(3H,d, J=7, C4-CH\(_3\)), 1.05(3H,s, C10-CH\(_3\)), 1.06-2.03(10H,m), 2.12-2.56(4H,m).

MS m/z: 180(M+), 123, 109, 95, 81, 69, 55, 41. High resolution mass measurement for C\(_{12}\)H\(_{20}\)O: 180.1514; found 180.1514.

Elemental analysis: calculated for C\(_{12}\)H\(_{20}\)O: C 79.94, H 11.18; found: C 80.00, H 11.30.

3.13 9-cyano-4,10\(\beta\)-dimethyl-7-isopropyl-1,8,9,10-tetrahydro-3-(2H)-naphthalenone 59

(5-cyano-1,4a\(\beta\)-dimethyl-7-isopropyl-4,4a,5,6-tetrahydro-2-(3H)-naphthalenone 59)

\[ \begin{array}{c}
\text{Br} \\
\text{O} \\
\text{51}
\end{array} \rightarrow \begin{array}{c}
\text{KCN} \\
\text{DMSO} \\
\text{CN}
\end{array} \rightarrow \begin{array}{c}
\text{CN} \\
\text{59}
\end{array} \]

Bromo-dienone 51\(^{22}\) (1.00 g, 3.4 mmol) was added to a stirred mixture of potassium cyanide (0.241 g, 3.7 mmol) in dimethyl sulfoxide (10 ml) at 110°C. The mixture was heated at 110-120°C for 17 hours. The reaction mixture was cooled, diluted with water (400 ml), and
extracted with ether (3×100 ml). The ether extract was washed with 6N hydrochloric acid and water, and dried over sodium sulfate. After removal of the solvent, the residue was purified by silica gel chromatography to give yellow crystals (0.478 g, 59%).

The physical properties of 59 are as follows:

mp: 94.5-95.5°C

UV \( \lambda_{\text{max}} \) (CH\(_3\)OH): 295 nm.

IR \( \nu_{\text{max}} \) (CH\(_2\)Cl\(_2\)): 2955, 2930 (C-H st), 2240 (C=N st), 1655 (C=O st.), 1620, 1590 (C=C st.) cm\(^{-1}\).

\(^1\)H-NMR (300 MHz, CDCl\(_3\)) \( \delta \): 1.14 (3H, d, J=6.6, C11-CH\(_3\)), 1.17 (3H, d, J=6.6, C11-CH\(_3\)), 1.18 (3H, s, C10-CH\(_3\)), 1.75 (1H, m), 1.90 (3H, s, C4-CH\(_3\)), 2.37-2.69 (6H, m), 2.79 (1H, dd, J=6.1, C9-H), 6.44 (1H, s, C6-H).

\(^13\)C-NMR (75MHz, CDCl\(_3\)) \( \delta \): 10.434, 20.684, 21.145, 21.294, 27.191, 33.432, 35.747, 35.827, 38.350, 118.901, 120.229, 129.919, 129.978, 149.480, 150.247, 197.586.

MS m/z: 243 (M\(^+\)), 228, 215, 200, 188, 172, 91, 77, 43.

3.14 9-cyano-4,10\( \beta \)-dimethyl-7-isopropenyl-1,8,9,10-tetrahydro-3-(2H)-naphthalenone 60

{5-cyano-1,4\( \alpha \)-dimethyl-7-isopropenyl-4,4a,5,6-tetrahydro-2-(3H)-naphthalenone 60}

\[ \begin{align*}
\text{CN} & \quad \text{CN} \\
\text{O} & \quad \text{O} \\
\text{59} & \quad \text{60}
\end{align*} \]

1) To a solution of cyano-dienone 59 (0.516 g, 2.12 mmol) in THF and water (50 ml, 1:1 v/v) was added N-bromosuccinimide (2 g, 11.3 mmol) and the mixture was stirred for 22 hours. The reaction mixture was diluted with water (100 ml) and extracted with ether (2×100
ml). The organic layer was washed with water, dried over sodium sulfate and the solvent was removed. 2) To this residue in dry toluene (20 ml) was added 2,2-dimethyl-1,3-propanediol (1.3 g, 12.5 mmol) and p-toluenesulfonic acid (5 mg) and the reaction was heated at reflux under argon for 30 minutes. It was then cooled, diluted with water (50 ml) and extracted with ether (3x50 ml). The combined organic extracts were washed with water (2x50 ml), dried over sodium sulfate, and concentrated. The residue was purified by silica gel chromatography (ether/pet. ether, 4:6, v/v) to give a colorless oil (0.326 g, 64%).

The physical characteristics of 60 are as follows:

UV \( \lambda_{\text{max}} \) (CH\(_3\)OH): 313 nm.

IR \( \nu_{\text{max}} \) (neat): 2925 (C-H st.), 2245 (ON st.), 1650 (C=O st.), 1665, 1620, 1595 (C=C st.) cm\(^{-1}\).

\(^1\)H-NMR (300MHz, CDCl\(_3\)) \( \delta \): 1.22 (3H, s, C10-CH\(_3\)), 1.80 (2H, m), 1.96 (3H, s, C4-CH\(_3\)), 2.05 (3H, s, C11-CH\(_3\)), 2.40-2.70 (4H, m), 2.63 (1H, dd, \( J = 6,1 \), C9-H), 5.23 (1H, s, C13-H), 5.28 (1H, s, C13-H), 6.73 (1H, s, C6-H).

MS m/z: 241 (M\(^+\)), 226, 213, 198, 115, 56, 43.

3.15 4,10\( \beta \)-dimethyl-3-hydroxy-7-isopropenyl-1,2,3,8,9,10-hexahydro-naphthalene 54

\{1,4a\( \beta \)-dimethyl-2-hydroxy-7-isopropenyl-2,3,4,4a,5,6-hexahydro-naphthalene 54\}

To a mixture of 53 (0.216 g, 1 mmol) in methanol (5 ml) and a methanol solution of cerium chloride heptahydrate (0.4 M, 2.5 ml) was added sodium borohydride (0.038 g, 1 mmol) over 1 minute and the reaction stirred for 10 minutes. Water (50 ml) was added to the
mixture, and the mixture was extracted with ether (3x30 ml). The organic extracts were washed with water (30 ml) and dried over sodium sulfate. Evaporation of the solvent and purification of the residue on a silica gel column (ether/pet. ether, 5:5, v/v) gave alcohol 54 (0.169 g, 81%) as a colorless oil.

The physical properties of 54 are as follows:

IR $\nu_{\text{max.}}$ (neat): 3320 (O-H st), 2905 (C-H st), 1649, 1610, 1585 (C=C st) cm$^{-1}$.

$^1$H-NMR (400 MHz, CDCl$_3$) $\delta$: 1.02 (3H, s, C10-CH$_3$), 1.35-1.58 (5H, m), 1.72-1.82 (2H, m), 1.86 (3H, s, C4-CH$_3$), 1.99 (3H, s, C11-CH$_3$), 2.05-2.13 (2H, m), 4.15 (1H, t, $J$=8, C3-H), 4.96 (1H, s, C13-H), 5.15 (1H, s, C13-H), 6.74 (1H, s, C6-H).

MS m/z: 218(M$^+$), 203, 185, 177, 157, 143, 129, 115, 105, 91, 84, 77, 55, 51.

3.16 7-acetyl-4,10\(\beta\)-dimethyl-3-hydroxy-1,2,3,8,9,10-hexahydronaphthalene 55

{7-acetyl-1,4\(a\)\(\beta\)-dimethyl-2-hydroxy-2,3,4,4\(a\),5,6-hexahydronaphthalene 55)

To a suspension of osmium tetraoxide (6.6 mg, 0.026 mmol) and sodium periodate (0.397 g, 1.85 mmol) in ether and water (3.2 ml, 1:1 v/v) was added 54 (0.188 g, 0.86 mmol) and the mixture was stirred vigorously for 75 hours at ambient temperature. The reaction mixture was filtered through a celite pad and the precipitate was washed thoroughly with ether. The combined ether layers were washed with excess 10% sodium sulfide solution, the aqueous layer containing a black precipitate was filtered and the filtrate was extracted with ether. The combined ether layers were washed with brine, dried over magnesium sulfate and
concentrated. The residue was purified on a silica gel column (ether/pet ether, 4:6, v/v) to give a colorless oil (0.133 g, 70%).

The physical properties of 55 are as follows:

UV $\lambda_{\text{max}}$ (CH$_3$OH): 293 nm.

$^1$H-NMR (300 MHz, CDCl$_3$) $\delta$: 0.99 (3H, s, C10-CH$_3$), 1.22-1.55 (5H, m), 1.75-1.88 (2H, m), 1.95 (3H, s, C4-CH$_3$), 2.11 (2H, m), 2.38 (3H, s, C11-CH$_3$), 2.50 (2H, m), 4.18 (1H, br, C3-H), 7.17 (1H, s, C6-H).

MS m/z: 220 (M$^+$), 205, 177, 91, 43.

3.17 4$\alpha$,10$\beta$-dimethyl-cis-perhydro-7-oxonaphthalene-8-carboxaldehyde

(5$\alpha$,8$\alpha$-dimethyl-cis-perhydro-3-oxonaphthalene-2-carboxaldehyde)

The formylation of 80 was performed by suspending potassium hydride (1.33 g, 33.3 mmol) in dry THF (120 ml). To this suspension was added a mixture of 80 (6.00 g, 33.3 mmol) and ethyl formate (5.00 g, 66.6 mmol) in dry THF (10 ml) over 5 minutes. After stirring at room temperature for 20 minutes, the solvent was evaporated and ether (100 ml) was added to the residue. The ethereal solution was extracted twice with 4N potassium hydroxide (50 ml). The combined alkaline solution was acidified with concentrated hydrochloric acid and extracted with ether. The ethereal solution was washed with brine and dried. Evaporation of ether gave 81 (6.17 g, 89%) as a light yellow liquid.

The physical properties of 81 are as follows:
3.18 4α,10β-dimethyl-1,2,3,4,5β,6,7,10-octahydro-7-oxonaphthalene-8-carboaldehyde 82

{5α,8αβ-dimethyl-3,4,4αβ,5,6,7,8,8a-octahydro-3-oxonaphthalene-2-carboaldehyde 82 }

To an ice cooled solution of benzene selenenyl chloride (5.68 g, 29.7 mmol) in dichloromethane (300 ml) were added pyridine (2.58 g, 32.6 mmol) and 81 (6.17 g, 29.7 mmol) in dichloromethane (25 ml). The reaction mixture was stirred for 1 hour and washed with 4N hydrochloric acid (25 ml) and brine (25 ml). The dichloromethane solution was cooled to 0°C, 30% hydrogen peroxide (4.5 ml) was added in three portions with intervals of 20 minutes, and the reaction was stirred at 0°C for another 30 minutes. the solvent was then evaporated and the residue was purified by column chromatography on silica gel using pet. ether/ether (4:1 v/v) as eluant to give 82 (5.26 g, 86%) as a colorless oil.

The physical properties of 82 are as follow.

\[ [\alpha]_D^{20} = 96.16^\circ, \text{(1.016, methanol).} \]
UV $\lambda_{\text{max}} = 238, (3.836)$. 

IR $\nu_{\text{max}}$ (neat): 2920, 2856(C-H st.), 1680(C=O st.), 1617(C=C st.) cm$^{-1}$. 

$^1$H-NMR (400 MHz, CDCl$_3$) $\delta$: 0.91(3H,d,J=6.8, C4-CH$_3$), 1.21(3H,s, C10-CH$_3$), 1.07-2.05(8H,m), 2.42(2H,m, C6-H), 7.45(1H,s, C9-H), 10.09(1H,s, aldehyde-H). 

MS m/z: 206(M$^+$), 191, 178, 110, 95. High resolution mass measurement: calculated for C$_{13}$H$_{18}$O$_2$: 206.1307; found: 206.1303. 

Elemental analysis: calculated for C$_{13}$H$_{18}$O$_2$: C 75.67, H 8.79; found: C 75.55, H 8.94.

3.19 4$\alpha$,10$\beta$-dimethyl-8-(hydroxymethylene)-cis-perhydro-7-oxonaphthalene-9-carbonitrile $\mathbf{83}$. 

{5$\alpha$,8$\alpha$β-dimethyl-2-(hydroxymethylene)-cis-perhydro-3-oxonaphthalene-1-carbonitrile $\mathbf{83}$} 

\[ \begin{align*} 
\text{CHO} & \quad \text{KCN} \quad \text{CN} \\
\text{82} & \quad \text{83} \\
\end{align*} \]

To a solution of $\mathbf{82}$ (3.00 g, 14.6 mmol) in dioxane (43 ml) and water (4.3 ml) was added a solution of potassium cyanide (0.919 g, 14.6 mmol) in dioxane (4.3 ml) and water (1 ml). The reaction mixture was stirred at room temperature for 30 minutes, and then the dioxane was evaporated. The residue was treated with 4N potassium hydroxide (20 ml) and extracted with ether. The basic solution was acidified with concentrated hydrochloric acid (5 ml) and washed with ether. The ethereal solution was washed with brine and dried. The ether was evaporated to give crude $\mathbf{83}$ (2.41 g, 71%) as a yellow oil.

The physical characteristics of $\mathbf{83}$ are as follows:

IR $\nu_{\text{max}}$ (neat): 3621(O-H st.), 3019, 2964, 2933(C-H st.), 2236(C=N st.), 1220(C-O st.) cm$^{-1}$. 

$^1$H-NMR (400MHz, CDCl$_3$) $\delta$: 0.91(3H,d,J=5.2, C4-CH$_3$), 1.15(3H,s, C10-CH$_3$), 1.22-2.00(8H,m), 2.53(1H,d,J=20, C6-H), 2.56(1H,dd,J=20,4.6, C6-H), 4.01(1H,s, C9-H), 8.98(1H,s, olefin-H), 15.04(1H,s, O-H).

MS m/z: 233(M$^+$), 215, 206, 178, 110, 95, 81, 77, 67, 53, 41. High resolution mass measurement: calculated for C$_{14}$H$_{19}$NO$_2$: 233.1415; found: 233.1415.

3.20 8-[(butylthio)methylene]-4a,8a$\beta$-dimethyl-cis-perhydro-7-oxonaphthalene-9-carbonitrile 84.

{2-[(butylthio)methylene]-5a,10$\beta$-dimethyl-cis-perhydro-3-oxonaphthalene-1-carbonitrile 84)  

A solution of 83 (2.41 g, 10.4 mmol), 1-butanethiol (1.0 ml) and p-toluenesulfonic acid (14 mg) in dry benzene (60 ml) was refluxed for 3 hours in a Dean-Stark apparatus. After cooling, the reaction mixture was washed with saturated sodium bicarbonate solution (10 ml), water (10 ml) and brine (10 ml) and dried. The benzene was evaporated and the residue was purified by column chromatography on silica gel using ether/pet. ether (3:7 v/v) as eluant to give compound 84 (2.77 g, 88%) as white crystals.

The physical properties of 84 are as follows:

mp=85-86°C.

IR $\nu_{max}$. (CHCl$_3$): 2990, 2950, 2933, 2852(C-H st.), 2220(ON st.), 1660(C=O st.), 1545(C=C st.) cm$^{-1}$.

$^1$H-NMR (400 MHz, CDCl$_3$) $\delta$: 0.85(3H,d,J=6.4, C4-CH$_3$), 0.95(3H,t,J=8), 1.38(3H,s, C10-CH$_3$), 1.02-2.25(12H,m), 2.32(1H,dd,J=20,10, C6-H),
2.43(1H, dd, J=20.8, C6-H), 2.94(2H, t, J=8.4, S-CH2), 3.37(1H, s, C9-H), 7.89(1H, s, olefin-H).

MS m/z: 305(M+), 248, 217, 109, 89, 67, 55, 44. High resolution mass measurement: calculated for C18H27NOS: 305.1805; found: 305.1809.

Elemental analysis: calculated for C18H27NOS: C 70.77, H 8.91, N 4.59, S 10.50; found: C 70.63, H 8.72, N 4.41, S 10.39.

3.21 4α,10β-dimethyl-8-formyl-1,2,3,4,5β,6,9,10-octahydonaphthalene-9-carbonitrile 85.

{5α,8αβ-dimethyl-2-formyl-1,4,4αβ,5,6,7,8,8α-octahydro-naphthalene-1-carbonitrile 85}

To a solution of 84 (1.623 g, 5.3 mmol) in methanol (15 ml) was added sodium borohydride (62 mg, 1.6 mmol) at 0°C. The reaction mixture was stirred for 15 minutes, and then the methanol was evaporated. Ether was added to the residue, and the solution was washed with water and brine. The ether was evaporated and the residue was dissolved in methanol (25 ml). Mercuric chloride (2.44 g, 9.0 mmol) and 4N hydrochloric acid (7.5 ml) were added to this solution. The reaction mixture was stirred at room temperature for 16 hours and then filtered. The methanol was evaporated, and ether (100 ml) was added. The etheral solution was washed with saturated sodium bicarbonate solution with brine and dried. The ether was evaporated and the residue was purified by column chromatography on silica gel using ether/pet. ether (3:7 v/v) as eluant to give 85 (0.712 g, 84%) as white crystals.

The physical properties of 85 are as follows:
mp=103-104.5°C.

$[\alpha]_D^{15}=149.8$, (0.990, methanol).

UV $\lambda_{\text{max}}=224$, (4.129).

IR $\nu_{\text{max.}}$ (CHCl$_3$): 2915, 2850(C-H st.), 2220(C=N st.), 1683(C=O st.), 1659(C=C st.),

$^1$H-NMR (400 MHz, CDCl$_3$) $\delta$: 0.91(3H,d, $J=5.2$, C$_4$-CH$_3$), 1.36(3H,s, C$_{10}$-CH$_3$),

1.05-2.13(8H,m), 2.31(1H,dd,$J=20.4,9.2,3.5$, C$_6$-H), 2.45(1H,ddd,$J=20.4,7.6,4$, C$_6$-H),

3.30(1H,s, C$_9$-H), 7.05(1H,dd,$J=4,3.5$, C$_7$-H), 9.51(1H,s, aldehyde-H).

MS m/z: 217(M$^+$), 200, 190, 146, 110, 105, 95, 81, 77, 55, 41. High resolution mass measurement for C$_{14}$H$_{19}$NO: 217.1471; found: 217.1469.

3.22 4$\alpha$,10$\beta$-dimethyl-8-(1,3-dioxolan-2-yl)-1,2,3,4,5$\beta$,6,9,10-octahydro-naphthalene-9-carbonitrile 86

4$\alpha$,10$\beta$-dimethyl-8-(1,3-dioxolan-2-yl)-1,2,3,4,5$\beta$,8,9,10-octahydro-naphthalene-9-carbonitrile 87

{5$\alpha$,8$\alpha$$\beta$-dimethyl-2-(1,3-dioxolan-2-yl)-1,4,4$\alpha$$\beta$,5,6,7,8,8$a$-octahydro-naphthalene-1-carbonitrile 86

5$\alpha$,8$\alpha$$\beta$-dimethyl-2-(1,3-dioxolan-2-yl)-1,2,4$\alpha$$\beta$,5,6,7,8,8$a$-octahydro-naphthalene-1-carbonitrile 87}

A solution of 85 (712 mg, 3.3 mmol), ethylene glycol (0.83 ml), and p-toluenesulfonic acid (5 mg) in benzene (9 ml) was refluxed for 3 hours in a Dean-Stark apparatus. The reaction mixture was cooled, ether (50 ml) was added, and the solution was washed with saturated sodium bicarbonate solution and dried. The solvent was evaporated and the residue was
purified by column chromatography on silica gel using ether/pet. ether (3:7 v/v) as eluant to
give ££ (615 mg, 71%) and 87 (156 mg, 18%).

The physical properties of ££ are as follows:

[a] D

15

=109.60, (0.920, methanol).

IR ν max. (neat): 2950, 2900(C-H st.), 2220(C≡N st.), 1680(C=C st.) cm⁻¹.

1H-NMR (400 MHz, CDCl3) δ: 0.79(3H,d,J=7, C4-CH₃), 1.24(3H,s, C10-CH₃), 0.85-
2.14(10H,m), 2.79(1H,s, C9-H), 3.85-4.04(4H,m), 5.19(1H,s, C8-CH),
6.05(1H,dd,J=4.3,5, C7-H).

MS m/z: 261(M⁺), 246, 221, 138, 110, 95, 86, 73, 55, 41. High resolution mass
measurement for C₁₆H₂₃NO₂: 261.1729; found: 261.1724.

Elemental analysis: calculated for C₁₆H₂₃NO₂: C 73.53, H 8.87, N 5.36; found: C
73.31, H 8.98, N 5.36.

1H-NMR of 87 (400 MHz, CDCl3) δ: 0.84(3H,d,J=7, C4-CH₃), 1.30(3H,s, C10-
CH₃), 1.19-2.32(9H,m), 2.85(1H,d,J=4.4, C9-H), 3.83-4.05(4H,m), 5.14(1H,d,J=6, C8-
H), 5.53(1H,dd,J=10,2, olefin-H), 6.02(1H,dd,J=10,2, olefin-H).

3.23 4α,10β-dimethyl-8-(1,3-dioxolan-2-yl)-1,2,3,4,5β,6,9,10-
octahydro-naphthalene-9-carboxaldehyde 88.

{5α,8αβ-dimethyl-2-(1,3-dioxolan-2-yl)-1,4,4αβ,5,6,7,8,8α-
octahydro-naphthalene-1-carboxaldehyde 88}

A solution of 86 (250 mg, 0.96 mmol) in dry toluene (19 ml) was cooled to -60°C under
argon, and a solution of diisobutylaluminium hydride (1.0M, hexane solution) (1.80 ml) was
added. The reaction mixture was stirred at -60°C for 3 hours and then poured into saturated ammonium chloride solution (15 ml). The layers were separated and the aqueous was extracted 5 times with ether (100 ml). The combined organic solutions were dried, and the solvent was evaporated. The residue was purified by column chromatography on silica gel using ether/pet. ether (3:7 v/v) as eluant to give \( \text{88} \) (215 mg, 85%) as a colorless oil.

The physical characteristics of \( \text{88} \) are as follows:

\[ [\alpha]_D^{21} = 311^\circ, \text{ (0.820, methanol).} \]

IR \( \nu_{\text{max.}} \text{ (neat): } 2900, 2835 (\text{C-H st.}), 2690 (\text{C-H st. aldehydic}), 1705 (\text{C=O st.}), 1655 (\text{C=C st.}) \text{ cm}^{-1}. \]

\[ ^1\text{H-NMR (400 MHz, CDCl}_3\text{)} \delta: 0.84(3\text{H,d,J}=7, \text{ C4-CH}_3), 1.10(3\text{H,s, C10-CH}_3), 0.93-2.25(10\text{H,m}), 2.67(1\text{H,d,J}=5, \text{ C9-H}), 3.80-4.10(4\text{H,m}), 5.16(1\text{H,s, C8-CH}), 6.20(1\text{H,dd,J}=4.4,3.6, \text{ C7-H}), 9.50(1\text{H,d,J}=5, \text{ aldehyde-H}). \]

MS m/z: 264(M\(^+\)), 249, 235, 73, 55, 45, 41. High resolution mass measurement for \( \text{C}_{16}\text{H}_{24}\text{O}_3 \): 264.1726; found: 264.1723.

Elemental analysis: calculated for \( \text{C}_{16}\text{H}_{24}\text{O}_3 \): C 72.70, H 9.15; found: C 73.00, H 9.30.

Compound \( \text{87} \) (188 mg, 0.72 mmol) in toluene (15 ml) was reduced by DIBAH (toluene solution, 1.5M) (1.3 ml) at -78°C in 2 hours by the above procedure to give \( \text{89} \). The crude product was hydrolyzed in the next reaction without further purification.

3.24 4\( \alpha \),10\( \beta \)-dimethyl-1,2,3,4,5\( \beta \),6,9,10-octahydropaphthalene-9,8-dicarboxaldehyde \( \text{90} \).

\( \{5\alpha,8\alpha\beta\}-\text{dimethyl-1,4,4a\beta,5,6,7,8,8a-octahydropaphthalene-1,2-dicarboxaldehyde 90} \)
A solution of 88 (92 mg, 0.35 mmol) and p-toluenesulfonic acid (8 mg) in acetone (7 ml) and water (1.7 ml) was stirred for 2 hours at room temperature. The acetone was evaporated, and water/ether were added. The aqueous was extracted with ether, and the combined ethereal solution was washed with saturated sodium bicarbonate solution, with water, and brine and then dried. The ether was evaporated and the residue was chromatographed on silica gel using ether/pet. ether (3:7 v/v) as eluant to give 90 (71 mg, 93%) as a colorless oil.

The physical properties of 90 are as follows:

$[a]_D^{16}=393^\circ$, (0.700, methanol).
UV $\lambda_{max.}=229$, (4.026).
IR $\nu_{max.}$ (neat): 2920, 2860(C-H st.), 2820, 2715(C-H st. aldehydic), 1718(C=O st.), 1665(C=O conjugated st.), 1300(C-H bend aldehydic) cm$^{-1}$.

$^1$H-NMR (300 MHz, CDCl$_3$) $\delta$: 0.86(3H,d,J=7, C4-CH$_3$), 1.26(3H,s, C10-CH$_3$), 1.05-2.50(10H,m), 3.33(1H,d,J=3, C9-H), 7.09(1H,dd,J=4.3,3.8, C7-H), 9.44(1H,s, C8-aldehyde-H), 9.79(1H,d,J=3, C9-aldehyde-H).

MS m/z: 220(M$^+$), 202, 192, 177, 121, 109, 95, 91, 81, 77, 67, 55, 41. High resolution mass measurement for C$_{14}$H$_{20}$O$_2$: 220.1461; found: 220.1462.

Elemental analysis: calculated for C$_{14}$H$_{20}$O$_2$: C 76.33, H 9.15; found: C 76.38, H 9.20.

Crude product of 89 from last step in acetone (15 ml), water (3.6 ml) and 1N hydrochloric acid (2 ml) was refluxed for 6 hours to give 90 (121 mg, 77% from 87).
REFERENCES


