STEREOSELECTIVE TOTAL SYNTHESES OF TETRACYCLIC SESQUITERPENES: (±)-ISHWARONE AND (±)-ISHWARANE

by

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to the required standard

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ABSTRACT

This thesis describes a stereoselective total synthesis of (±)-ishwarone 12 and (±)-ishwarane 13 via the trans-fused octalone 226 as the key intermediate.

The first synthetic attempt toward the octalone 226 involved a Lewis acid-catalyzed Diels-Alder reaction between 1,3-butadiene and the unsaturated keto ester 258, obtained from the known diene ester 261 by selective hydrogenation and allylic oxidation. Two isomeric Diels-Alder adducts, 272 and 273, were isolated in moderate yield. The relative stereochemistry of these adducts was determinated by chemical correlation with compounds of known structure and stereochemistry.

In a second approach to the synthesis of the octalone 226, 3,4-dimethyl-2-cyclohexen-1-one (227) was treated with vinyl magnesium bromide in the presence of cuprous iodide and dimethylsulfide to afford the adduct 142, which was converted into the aldehyde 304. Reaction of the latter with dibromomethylenetriphenylphosphorane afforded the dibromo olefin 305. Trapping the lithium acetylide generated from the dibromo olefin 305 with gaseous formaldehyde provided the ketal propargylic alcohol 306 which was elaborated into the keto allylic alcohol 291 by acid hydrolysis and hydrogenation. Mesylation of the keto allylic alcohol 306, followed by treatment of the resultant mesylate with excess potassium tert-butoxide gave the desired octalone 226.

The ketone group of 226 was protected as the corresponding 5,5-dimethyl-1,3-dioxane derivative 324. Addition of dibromocarbene to the latter

compound gave the dibromocyclopropane derivative 325.

Model studies were carried out with 7,7-dibromonorcarane (185) and its derivatives. Subjection of 185 to a sequence involving lithium-halogen exchange and alkylation afforded the benzyl ether 329. This compound was converted by hydrogenolysis into the bromohydrin 331, which upon mesylation gave the bromo mesylate 332. Treatment of 7-exo-bromo-7-endo-methylnorcarane 336 (obtained from dibromonorcarane 185) with an alkyllithium and methyl chloroformate produced the monoester 338. The latter, upon reduction, provided the exo-hydroxymethyl derivative 339. Mesylation of this primary alcohol proved to be unsuccessful. When dibromonorcarane 185 was treated with two equivalents of an alkyllithium, followed by methyl chloroformate, the diester 359 was obtained. Reduction of this compound, followed by mesylation of the resultant diol 361 gave the dimesylate 362. The latter was converted into the dichloride 363 by treatment with lithium chloride in hexamethylphosphoramide.

Conversion of the dibromocyclopropane derivative 325 into the benzyl ether 327 ($R=PhCH_2$) or the diester 369 by means of reaction conditions used in the model studies were unsuccessful. However, compound 325 could be monomethylated to afford a mixture of exo and endo isomers 366 and 372. The exo-isomer 366 was converted into the endo-monoester 367. Reduction of the latter, followed by deprotection of the ketone yielded the desired keto alcohol 368. Mesylation of 368 could not be achieved without decomposition. However, this alcohol underwent ester formation with p-nitrobenzyl chloride to give the p-nitrobenzoate derivative 380. Attempted intramolecular alkylation of this keto p-nitrobenzoate 380 to give (±)-ishwarone 12 was unsuccessful.

The ketal olefin 324 reacted stereoselectively with the carbenoid derived from dimethyl diazomalonate to give the diester 369 as the only adduct. This compound was reduced to the diol 389. Hydrolysis of the ketal functionality, followed by mesylation of the resulting diol 383 afforded the keto dimesylate 384. Intramolecular alkylation of this keto dimesylate gave no recognizable product. When the dimesylate 384 was treated with anhydrous lithium chloride, the crystalline dichloride 391 was obtained. Base-promoted intramolecular alkylation of the latter provided the keto chloride 392 which was reduced immediately by means of lithium triethylborohydride. Oxidation of the resulting alcohol 393 gave (±)-ishwarone 12 which upon Wolff-Kishner reduction furnished (±)-ishwarane 13.

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INTRODUCTION

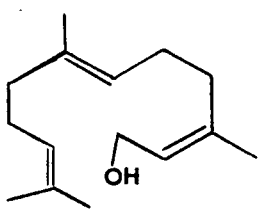
I. Perspective

From the active study on the constituents of the essential oils obtained from fragrant plants during the turn of the century, a family of natural products having empirical formulas containing a multiple of five carbons has been recognized. These compounds have been named terpenoids. Thus, compounds containing two C_5-units are called monoterpenes; three units, sesquiterpenes; four units, diterpenes; five units, sesterterpenes; six units, triterpenes; and compounds having more than six units belong to the carotenoid family. Due to the elegant work of Ruzicka and his colleagues[1] it is now known that most terpenoids have a remarkable familial resemblance in which their structures can be dissected into isopentane skeletal units linked head to tail. This unique and striking property has been formulated as the "isoprene rule"[1] and the latter has been used as a potent guide in the structural elucidation of new terpenoids.

The early work on terpenoid chemistry was mainly restricted to hydrocarbon monoterpenes and simple sesquiterpenes, partly due to their volatility which allowed them to be separated easily from other more complex molecules merely by distillation, and partly due to the relative simplicity of their structures. However, in the last two decades, the chemistry of terpenoid compounds has expanded very rapidly mainly due to the availability of more sophisticated isolation techniques (gas-liquid chromatography, thin-layer chromatography, high pressure liquid chromatography, etc.) and modern physical methods for structural analysis (fourier-transform nuclear magnetic resonance spectroscopy, ^{13}C nuclear magnetic resonance spectroscopy, x-ray

crystallography, mass spectrometry, etc.). Many new compounds with novel structures have been obtained and identified by these techniques.

One large group of terpenoids are the sesquiterpenes which are formed by linking three isoprene units together in various ways. Thus, more than 80 different carbon skeletons have been found in the sesquiterpene family of natural products. These skeletons vary from the rather simple acyclic system of farnesol 1 to the complex polycyclic system of cyclosativene 2. The degree of oxygenation also varies a great deal, ranging from hydrocarbons with no oxygen (e.g. cyclosativene 2) to compounds which are highly oxygenated (e.g. tutin 3). Recently, researchers have reported the isolation of sesquiterpenes containing functional groups which, up to the present time, have not been commonly found in natural products (e.g. halogen in laurintenol 4, isonitrile in 9-isocyanopupukeanone 5).



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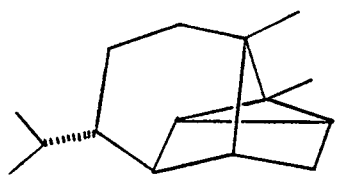

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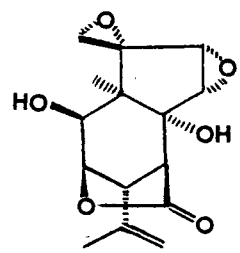

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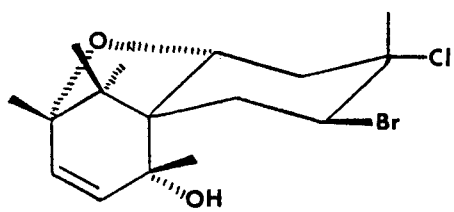

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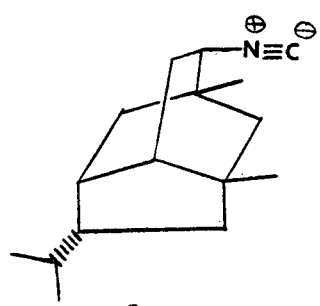

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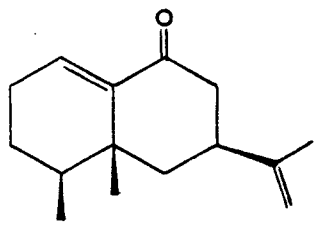
The structural elucidation of a relatively large numbers of sesquiterpenes with the eremophilane skeleton has been reported.[2,3]

However, the structure of the first member of this class, eremophilone 6 (isolated by Simonsen and co-workers in 1932[4]), puzzled chemists for several years. This bewilderment was mainly due to the fact that this compound did not obey the "isoprene rule" as originally formulated. The correct skeleton was eventually proposed by Penfold and Simonsen.[5] About fifteen years later, the structure and stereochemistry of hydroxydihydro-eremophilone 7, one of the congeners isolated with eremophilone 6, were defined by means of x-ray crystallography[6] and the original proposal[5] regarding the carbon skeleton of eremophilane sesquiterpenoids was confirmed.



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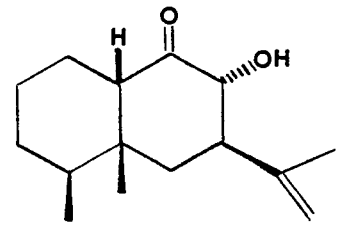

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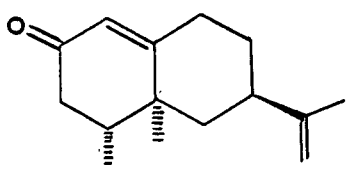
Valencane-type sesquiterpenoids, although very closely related in structure to the eremophilanes, are less frequently encountered in nature. In 1965, several new sesquiterpenes belonging to the valencane class, (for example, nootkatone 8, nootakene 9 and valencene 10), were isolated and characterized.[7]



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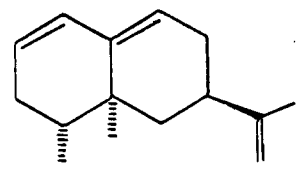

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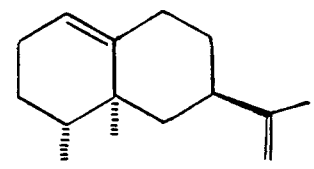

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The common structural features between the eremophilane- and valencane-

type sesquiterpenoids are a pair of cis-vicinal methyl groups at C_4 and C_5 of the bicyclic system and a three carbon "isopropyl"-type unit as a side chain at C_7*. The relative stereochemistry of this isopropyl-type moiety is cis with respect to the methyl groups in eremophilane-type sesquiterpenoids but is trans in the valencane family.

To account for the biosynthesis of these two classes of sesquiterpenoids, a 1,2-methyl shift from a eudesmane-type precusor was first suggested by Robinson to Penfold and Simonsen as early as 1939.[5] Since then, various biogenetic schemes involving 1,2-alkyl migration have been postulated. McSweeney and co-workers[8] have postulated that the above mentioned stereochemical differences between the eremophilane- and valencane-type compounds is due to biogenetic-type cyclization of two different conformers of a substituted cyclodeca-1,6-diene, followed by appropriate 1,2-alkyl rearrangements (see scheme 1).

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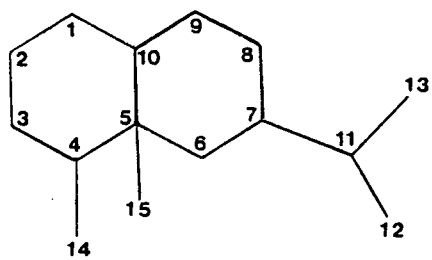
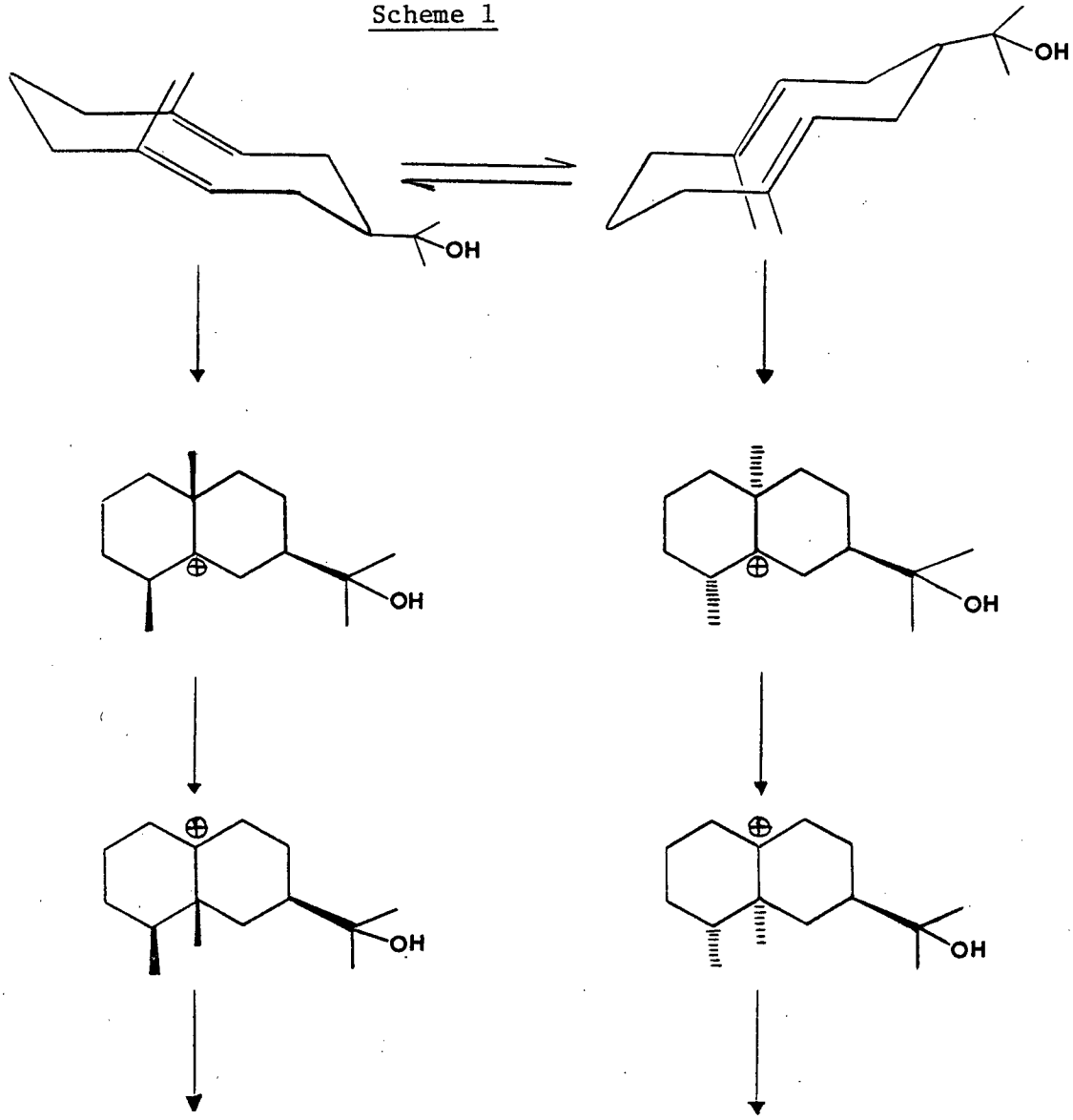
* The numbering system commonly employed for eremophilanes and valencanes is as shown below

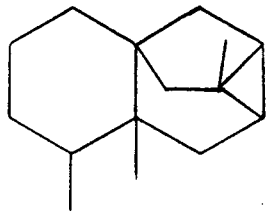


Scheme 1



eremophilane Valencane

In 1969, the structural elucidation of the first member of a new class of sesquiterpenoids (ishwarane-type sesquiterpenoids) was reported.[10] Although it is clear that this new class is structurally related to the eremophilane-valencane type terpenoids, the ishwaranes contain a novel tetracyclic carbon skeleton 11. It is reasonable to postulate that the unique carbon framework of this class of compounds is derived biogenetically



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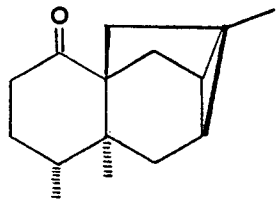
from the same intermediate which leads to the valencane sesquiterpenoids, with participation of the side chain in subsequent electrophilic cyclizations. Due to the unusual structural features present in the ishwaranes, studies concerning the chemistry and total synthesis of this group of compounds have been actively pursued by several research groups since the first reports appeared.

II. Isolation and Structural Elucidation of Ishwarone and Related Sesquiterpenoids

Ishwarone, the first member of a relatively small class of sesquiterpenoid with a unique tetracyclic structure, was originally isolated from the roots of Aristolochia indica and given its name by Rao and co-workers[9] as early as 1935. However, these researchers only recognized the ketonic nature of ishwarone and proposed its molecular formula as $C_{15}H_{22}O$. Its unique skeletal structure was not fully revealed until the late sixties, when a full structural elucidation was accomplished by means of chemical degradation and spectroscopic evidence.[10-12] Ishwarone and its parent hydrocarbon ishwarane, also a natural product isolated from the roots of Aristolochia indica[13] and from the dried petals of Cymbopetalum penduliforum (Dunal) Baill[14], have been identified as 12 and 13 respectively.



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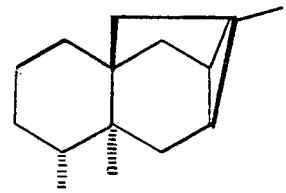

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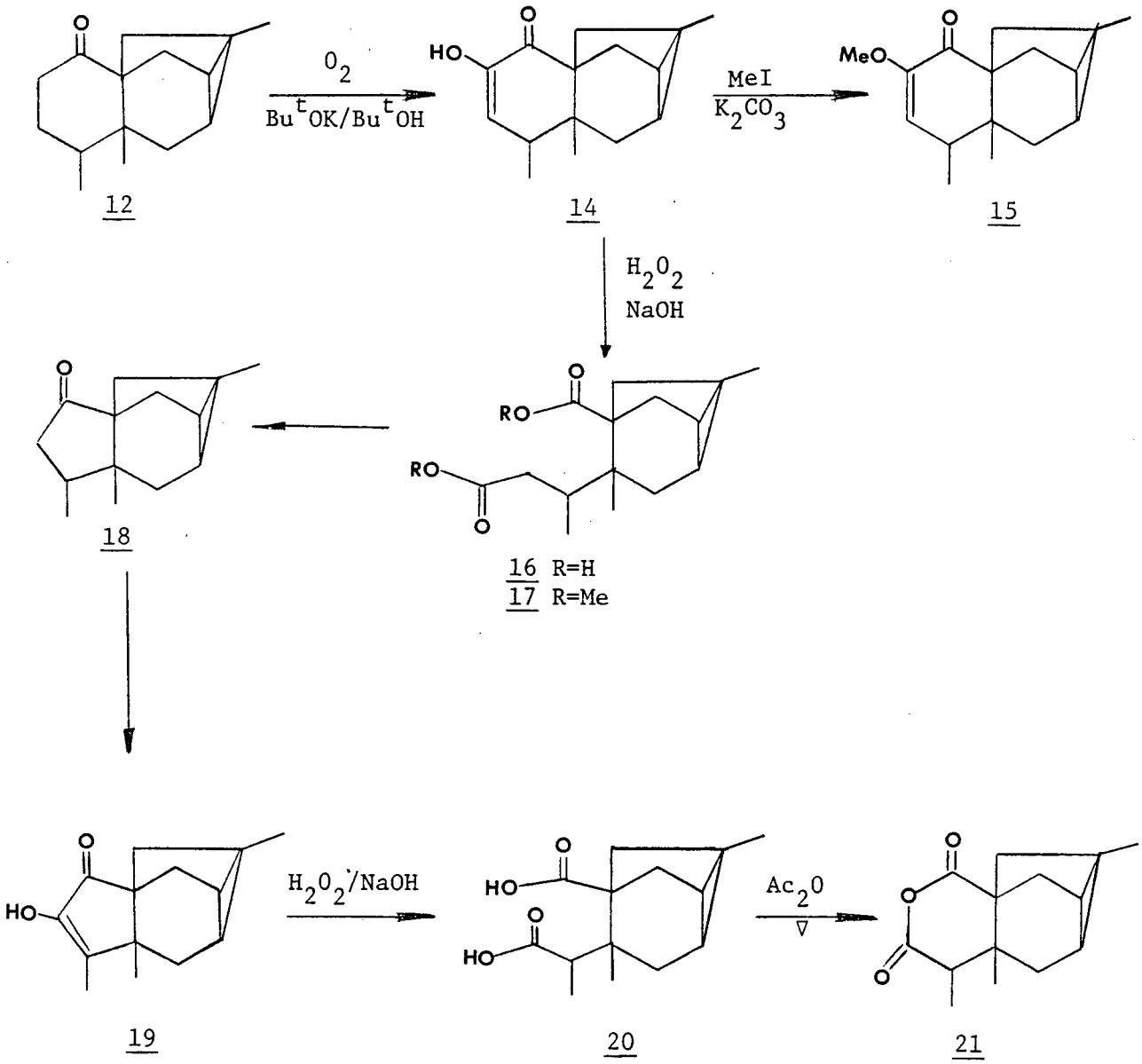
Ishwarone was found to be resistant to hydrogenation even though the molecular formula, $C_{15}H_{22}O$, indicated five degrees of unsaturation. Therefore, after taking into account the presence of the ketone group (indicated by a strong absorption at 1706 cm^{-1} in the infrared spectrum), it appeared that the molecule was tetracyclic in structure. Indeed, the absence of appropriate signals due to ethylenic unsaturation in infrared (i.r.), proton nuclear magnetic resonance (p.m.r.) and Raman spectra supported the tetracyclic nature of ishwarone.

The p.m.r. spectrum of ishwarone showed two 3-proton singlets at δ0.75 and δ1.15 which could be attributed to the presence of two tertiary methyl groups. There was also a 3-proton doublet at δ0.85 with a coupling constant J=6.5 Hz, probably due to a secondary methyl group. Other than these distinct methyl signals, the most important information observed from the p.m.r. was a multiplet corresponding to one proton at δ0.55. This resonance signal, in conjunction with the presence of absorption at 3020 cm^{-1} in Raman spectrum, strongly implied the presence of a cyclopropyl moiety. Indeed, this suggestion was supported by the fact that ishwarone was unstable to acid and exhibited a positive color reaction with tetranitromethane, even though the molecule contained no olefinic double bonds.

In attempts to determine the position of the methyl groups, ishwarone 12 was oxidized with oxygen in the presence of potassium

t-butoxide and tertiary butanol to afford the diosphenol 14. When the allylic proton of the corresponding methyl ether 15 was exchanged for deuterium ($NaOCH_3/CH_3OD$), both of the doublets in the p.m.r. spectrum, due to the secondary methyl group and the olefin proton,



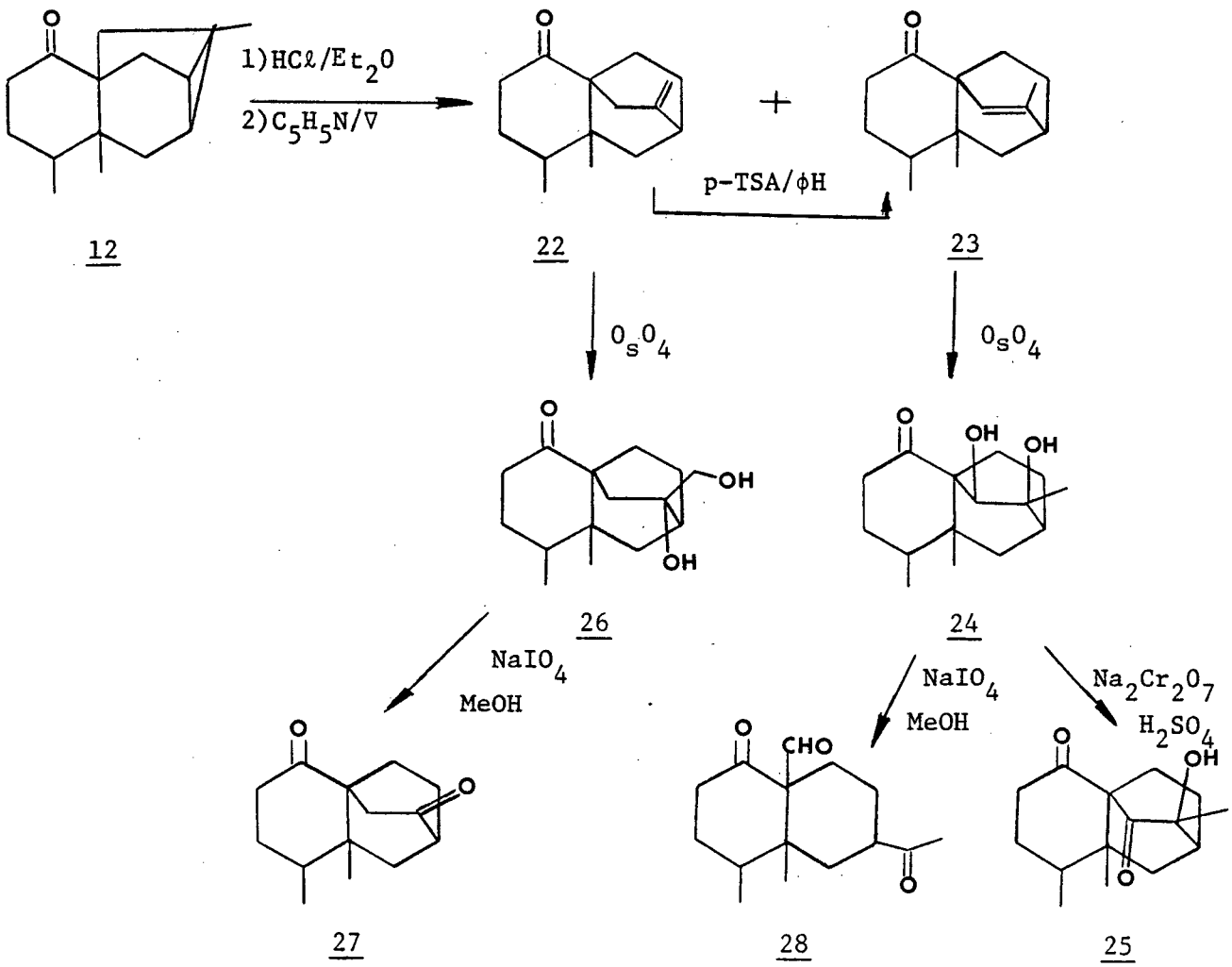
collapsed to singlets. When the ishwarone diosphenol 14 was further oxidized with alkaline hydrogen peroxide, a dicarboxylic acid, ishwaric acid 16, was isolated. Pyrolysis of this acid or Dieckman condensation

of the corresponding dimethyl ester 17 (followed by hydrolysis and decarboxylation) furnished norishwarone 18, the latter compound contained a five membered ring ketone, as indicated clearly by a strong absorption at 1728 cm^{-1} in the i.r. spectrum. Subsequently, this cyclopentanone underwent Barton oxidation (oxidation with oxygen in the presence of strong base such as potassium t-butoxide) smoothly to provide the corresponding diosphenol 19. The p.m.r. of this enol ketone lacked the doublet signal due to the secondary methyl group in comparison to the diosphenol 14 obtained directly from ishwarone. Instead, a new signal at δ1.87, which corresponded to a vinyl methyl group, was present. Oxidation of this new diosphenol with alkaline hydrogen peroxide led to a new dicarboxylic acid, norishwaric acid 20. Brief treatment of the latter with refluxing acetic anhydride, afforded norishwaric anhydride 21. The i.r. spectrum of this compound exhibited absorptions at 1760 and 1800 cm^{-1}. These absorption positions are identical with those found for glutaric anhydride.

From these chemical and spectroscopic evidences, a 1,4-relationship between the secondary methyl group and the ketone functionality was clearly demonstrated.

When treated with dry hydrogen chloride in ethyl ether at 0°, followed by brief contact with boiling pyridine, ishwarone rearranged to two isomeric olefinic ketones via ring opening of the cyclopropyl moiety. Furthermore, one of the products, the exocyclic olefinic ketone 22, could be converted (p-toluenesulfonic acid in refluxing benzene) into the other isomeric product, the endocyclic olefin 23. The latter compound (named isoishwarone) reacted with osmium tetroxide to form the keto diol 24 which

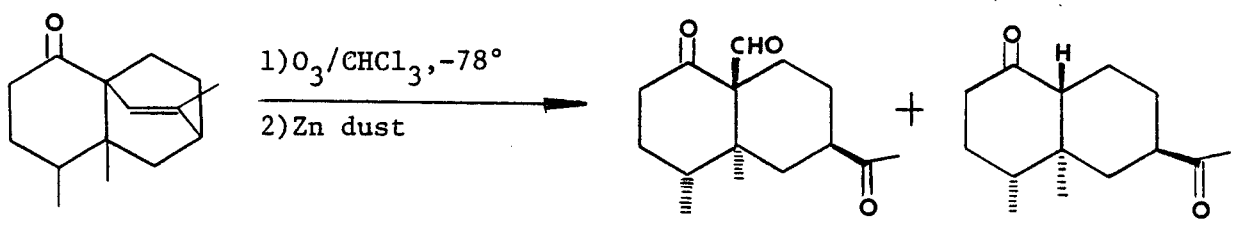
was then oxidized by the Kiliani reagent (prepared by the addition of 60 g of sodium dichromate to a solution of 80 g of conc. sulfuric acid in 270 g of water) to give the diketo alcohol 25. The carbonyl absorptions in the i.r. spectrum of this compound indicated that one carbonyl group was like a normal cyclohexanone (1705 cm^{-1}) while the other was reminiscent of a bicyclo[2.2.2]octanonesystem (1722 cm^{-1}). Further evidence for the latter point was obtained by cleavage of the keto diol 26 (obtained by osmium tetroxide hydroxylation of the exocyclic olefin 22) to the dione 27. The presence of bands at 1702 and 1726 cm^{-1} in the i.r. spectrum of



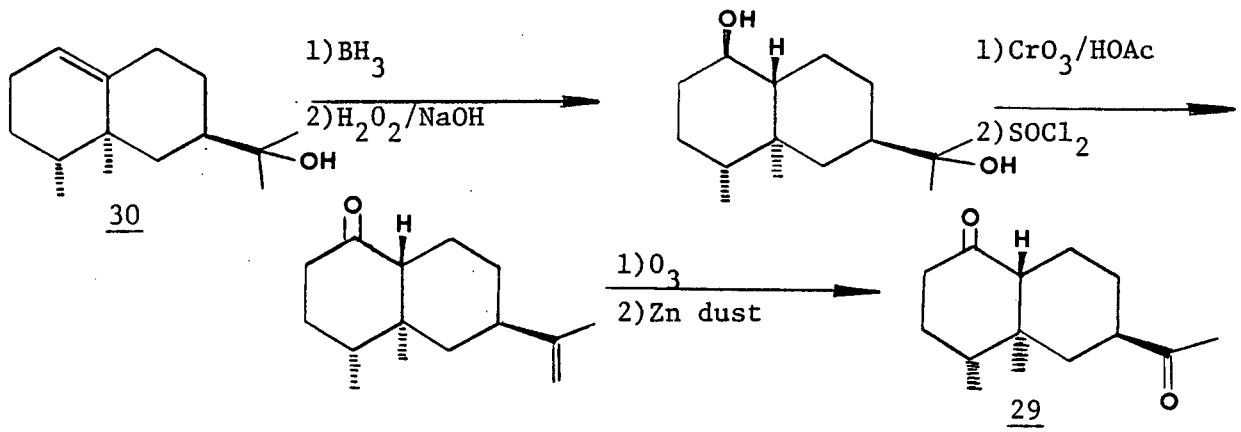
27 tended to confirm the presence of a cyclohexanone-type carbonyl and a bicyclo[2.2.2.]octanone moiety.

Even though the results described above indicated the presence of a bicyclo[2.2.2.]octene system in isoishwarone 23, the position of the vinyl methyl group was not yet secured. This problem was solved by periodate cleavage of the keto diol 24. The p.m.r. spectrum of the diketo-aldehyde 28, thus obtained, showed a 3-proton singlet at δ2.17 for the methyl group of the acetyl moiety and a 1-proton singlet at δ10.05 for the aldehyde proton. The lack of coupling in the downfield signal (δ10.05) clearly implied that the aldehyde group must be adjacent to a quaternary center as indicated in 28.

At this stage, the relative stereochemistry of the vicinal methyl groups and the bicyclo[2.2.2.]octene moiety had not been established. Conclusive chemical evidence which unambiguously defined the stereochemistry was needed. One way in which this could be done would be to correlate isoishwarone with other sesquiterpenes of known structure and absolute stereochemistry. Therefore, isoishwarone 23 was subjected to ozonolysis to provide the diketo aldehyde 28 as well as the diketone 29. The latter was found to be identical with an authentic sample of the same compound prepared from valerinol 30, the stereochemistry of which had been fully established.

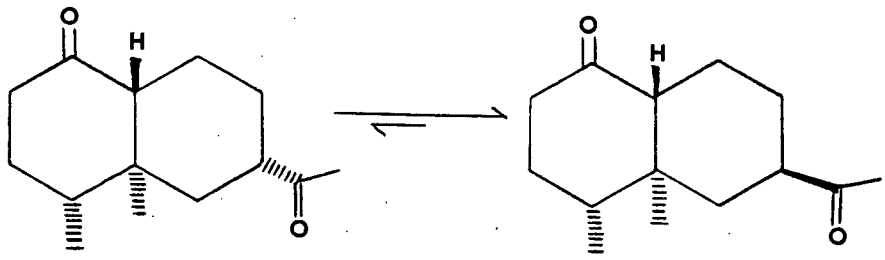


23 28 29



30 29

Although the cis-vicinal relationship of the methyl groups at C_4 and C_5 in isoishwarone* had thus been verified, the trans relationship between the acetyl group and the methyl groups in dione 29 could not be accepted without question. Clearly, the β-acetyl function in 29 could have been derived by equilibration, during the ozonolysis procedures, from the thermodynamically less stable α-acetyl isomer 31 (acetyl group axial).



31 29

In order to clarify the stereochemistry at C_7, the ethylene ketal 32 of isoishwarone 23 was hydroborated to give the ketal alcohol 33. After removal of the ketal protecting group with aqueous acid, the β-hydroxy ketone 34 was treated with base to provide keto aldehyde 35 via a retro-aldol reaction. The bicyclo[2.2.2.]octane bridge was therefore cleaved

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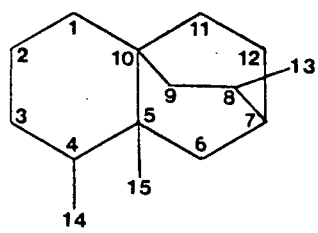
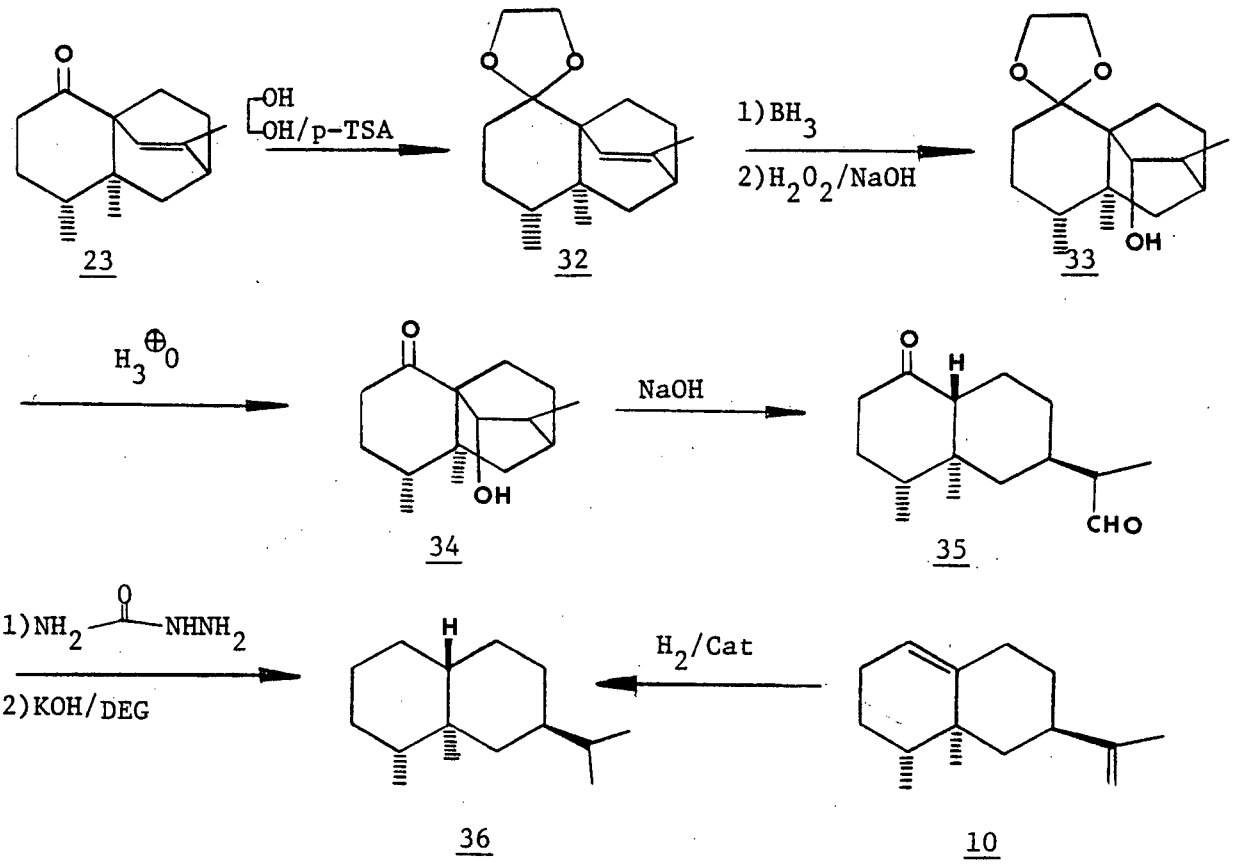
* The numbering system of isoishwarane and derivatives is

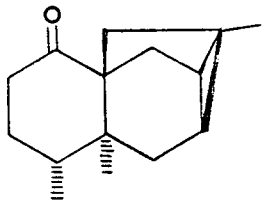


into a simple system without the possibility of affecting the stereochemistry at C_7. The bis-semicarbazone of this keto aldehyde was converted into a single hydrocarbon which was identical in all respects with an authentic sample of (+)-nootkatane 36 obtained by hydrogenation of valencene 10. The latter is a naturally occurring sesquiterpene with fully established structure and configuration.



23 32 33 34 35 36 10

From these results, the basic structure as well as the stereochemistry of isoishwarone 23 was completely solved. Therefore, ishwarone itself must be represented by structure 12 or 37. However, no differentiation of these positional isomers could be made at this stage of the structural elucidation work.



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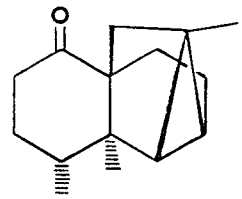
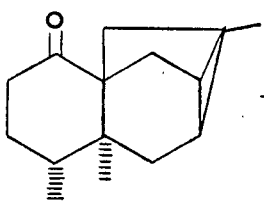


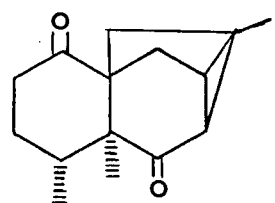
37

Treatment of ishwarone with ozone afforded a small amount of oxoishwarone 38 having two carbonyl absorptions in the i.r. spectrum at 1718 and 1689 cm^{-1}. The i.r. stretching band at 1689 cm^{-1} indicated that the newly formed carbonyl group should be conjugated with the cyclopropyl moiety. Indeed, this interpretation was supported by the ultraviolet (U.V.) spectrum which exhibited λ_{max} 210 nm (ε5020) and λ_{max} 290 nm (ε70). Heating oxoishwarone 38 with concentrated hydrochloric acid, resulted in ring cleavage to yield the monochloride 39 which, upon exposure to base, cyclized back to oxoishwarone. Similarly, reaction of oxoishwarone 38 with hot hydrobromic acid or trifluoroacetic acid gave the monobromide 40 or the trifluoroacetate 41 respectively.



12

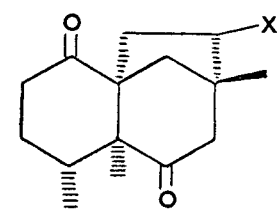
O_3



38

HX

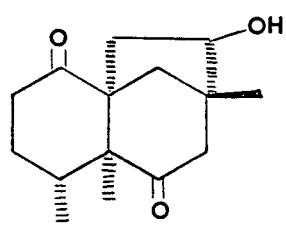
B⊖



39 X=Cl
40 X=Br
41 X=$O\overset{O}{\overset{\|}{C}}CF_3$

NaOH/meOH

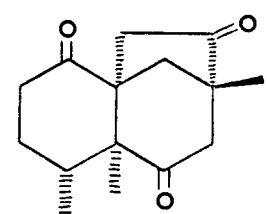
X = $O\overset{O}{\overset{\|}{C}}CF_3$



42

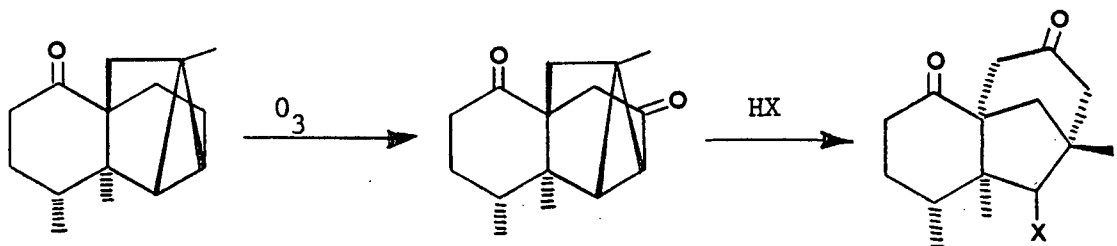
CrO_3

HOAc



43

In each of the p.m.r. spectra of the monochloride 39 and the monobromide 40, the proton adjacent to the halogen appeared as an 8-line signal with coupling constants J=1.5, 4.5 and 7.5 Hz. These observations could be rationalized by proposing that, in each case, the proton adjacent to the halogen atom experienced two vicinal couplings and one long-range W-type coupling. On the other hand, if ishwarone had possessed the structure 37, the corresponding oxoishwarone would have been 44, and the monohalides would have possessed the structures 45 and 46

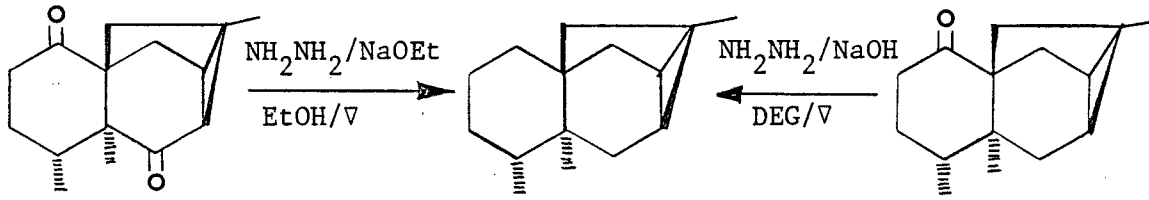


37 44 45 X=Cl
46 X=Br

Obviously, one would expect that the protons adjacent to halogen in the latter compounds would have given rise to singlets in the p.m.r. spectra. In addition to the spectroscopic evidence, the structure of monobromide 40 has been confirmed by the x-ray crystallography technique.[15] Therefore, ishwarone must be represented by structure 12 instead of 37.

The trifluoroacetate 41 was hydrolysed with alcoholic sodium hydroxide to give the diketo-alcohol 42. Oxidation of this alcohol gave the triketone 43 which showed in the i.r. spectrum a new carbonyl stretching absorption at 1745 cm^{-1}, typical of a five-membered ring ketone. These chemical transformations added another piece of evidence to support the structure of ishwarone.

In order to ensure that no rearrangement had been involved in the ozone oxidation of ishwarone, oxoishwarone 38 was subjected to Wolff-Kishner reduction. A single hydrocarbon was isolated and characterized as ishwarane 13, which had also been obtained from the reduction of ishwarone itself. It is pertinent to note that ishwarane is also a naturally occurring compound, having been obtained from the hexane extract of the roots of Aristolochia indica[13] or the dried petals of Cymbopetalum penduliforum (Dunal) Baill.[14]

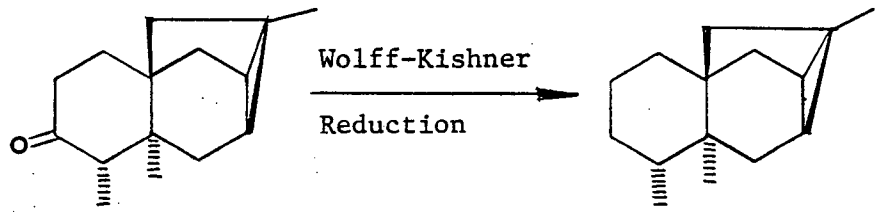


38 13 12

In 1973 the isolation of another sesquiterpene belonging to the ishwarane family was reported. From the fresh roots of Aristolochia debitis Sieb. et Zucc.[16], three sesquiterpenic ketones were obtained. One of these compounds exhibited an i.r. stretching band at 3030 cm^{-1} and a multiplet signal at δ0.6 in the p.m.r. spectrum. These spectral data indicated the presence of a cyclopropyl moiety. For biogenetic reasons, it was suspected to be a positional isomer of ishwarone. Indeed, this assumption was proved by reducing the ketone to the corresponding hydrocarbon, which was identified by spectroscopic data as ishwarane 13.

When refluxed in D_2O-dioxane in the presence of sodium bicarbonate, this new sesquiterpene afforded a trideuterio derivative. Although the p.m.r. spectrum of the parent sesquiterpene showed a 3-proton doublet at δ0.89 (secondary methyl group), the corresponding signal of the trideuterio derivative appeared as a 3-proton singlet. Based on these

data, as well as on the optical rotation dispersion curve of the natural product (from which it was concluded that the conformation of the cyclohexanone ring was in a chair form with the secondary methyl group in an equatorial orientation), this new compound was formulated as 3-oxoishwarone 47.



47 13

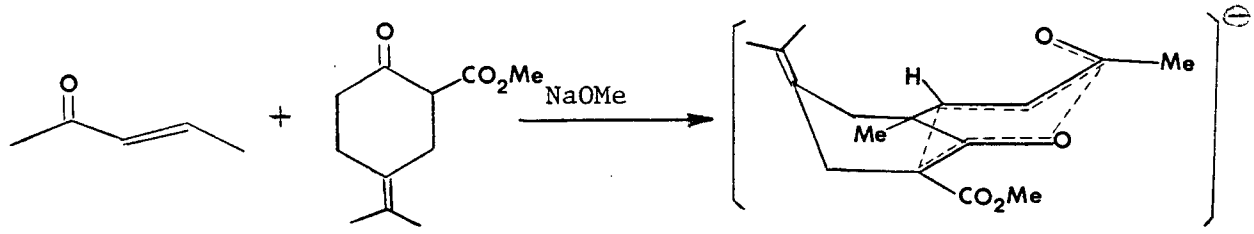
III. Synthesis of cis-4,10-Dimethyl Octalones and Related Systems

The cis-relationship of the vicinal dimethyl groups in ishwarone and ishwarane represents one of the interesting structural features of this class of compounds. Furthermore, the 7-methyl-tricyclo[3.2.1.$0^{2.7}$]-octane system present in these compounds represents a structurally novel moiety not found in many natural products. It is therefore pertinent to discuss how each of these structural features has been obtained previously by synthesis.

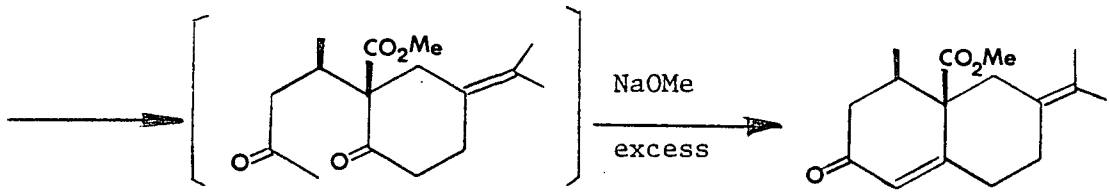
Procedures leading to cis-vicinal dimethyl groups in octalone systems are relatively well documented in the literature, mainly due to considerable efforts which have been directed towards the synthesis of eremophilane and valencane-type sesquiterpenoids.

The construction of appropriate synthetic precursors containing the necessary cis-vicinal dimethyl groups has been attempted in various ways.

The well-known Robinson annulation procedure has been widely adapted. In a synthetic sequence leading to the preparation of (±)-isonootkatone (α-vetivone) 51[17], the first eremophilane sesquiterpene obtained by total synthesis, the β-keto ester 48 underwent Michael addition with trans-pent-3-en-2-one in the presence of a small amount of sodium ethoxide. Subsequent treatment of the resulting intermediate with excess methoxide, afforded the crystalline bicyclic keto-ester 50 as the main product. The stereochemical outcome of the overall annulation reaction, resulting in a cis-orientation of the methyl and the angular



48 49



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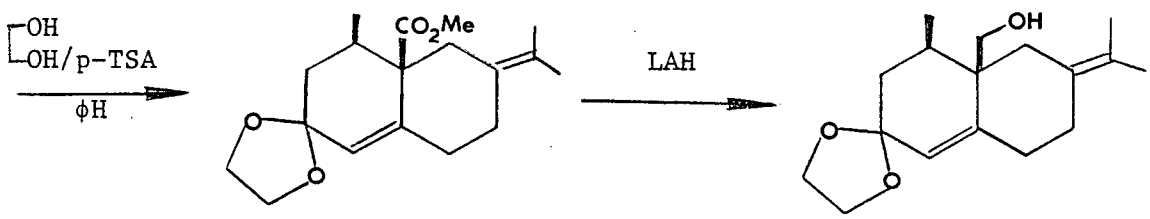
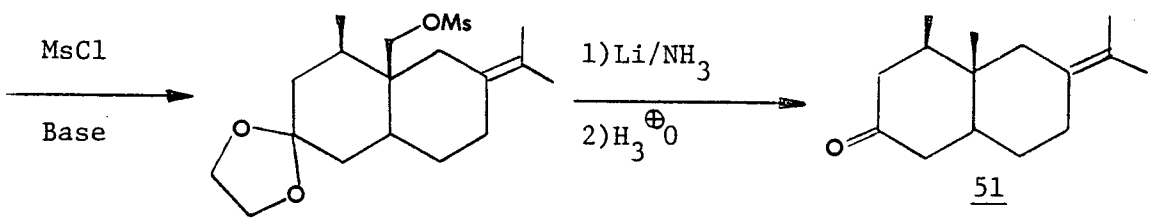
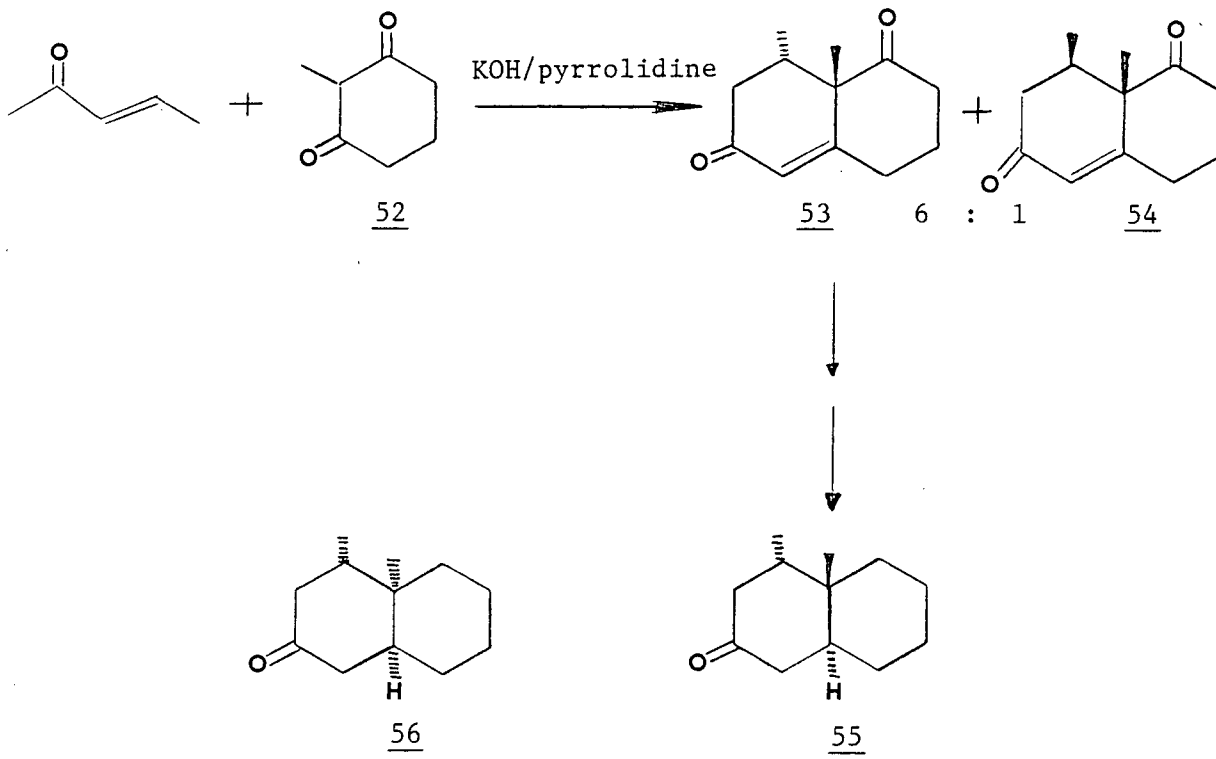




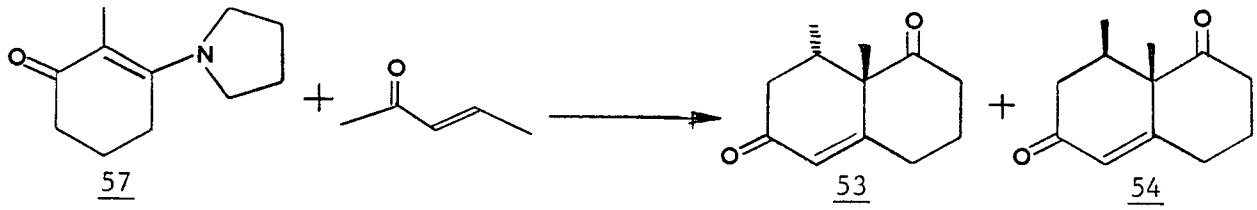
51

carbomethoxy groups, was rationalized by proposing that steric and electronic factors in the Michael addition step would favour the transition state 49. The latter would result in the observed configuration in the product. After protecting the ketone functionality in 50 as the corresponding ethylene ketal, the carbomethoxy moiety was transformed into a methyl group *via* metal hydride reduction, mesylation of the alcohol and lithium-ammonia reduction of the primary mesylate. (±)-Isonootkatone 51 was then readily isolated after acid hydrolysis of the ketal.

Even though Marshall and co-workers[17] found that the Robinson annulation of the cyclic keto ester 48 with *trans*-pent-3-en-2-one gave ketone 50 with the required *cis*-stereochemical relationship between the methyl and carbomethoxy groups, related studies[18] with 2-methylcyclohexan-1,3-dione 52 provided different results. Condensation of the dione with *trans*-pent-3-en-2-one in the presence of potassium hydroxide and pyrrolidine gave the *trans* isomer 53 as the predominant annulation product. The stereochemistry of the latter was firmly established by comparing the optical rotatory dispersion measurement of the optically resolved decalone 55 (obtained from the dione 53 *via* selective protection of the enone moiety, Wolff-Kishner reduction, regeneration of the enone functionality and lithium-ammonia reduction) with that of its optically pure epimer 56.



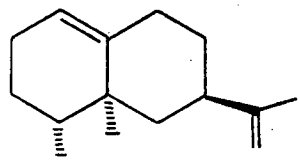
Instead of direct condensation of 2-methylcyclohexan-1,3-dione 52 with trans-pent-3-en-2-one, Coates and Shaw[19] used the pyrrolidine enamine 57 of the dione in the annulation process. These workers found that this procedure also led to a mixture of trans- and cis-isomers 53 and 54. However, it was found that the ratio of these isomers varied significantly with the polarity of the solvent employed as the reaction medium. Thus, when benzene was used as solvent, the



Reaction Condition	Total % Yield	Ratio of Two Isomers
ϕH/HOAc/NaOAc	64	10 : 1
DMF/HOAc/NaOAc	27	1 : 1

trans-isomer 53 was the major component in the crude product (trans/cis

10/1). However, the ratio was changed to approximately 1 to 1 by replacing benzene with N,N-dimethylformamide. Several eremophilane sesquiterpenes, such as (±)-valencene 10[20], (±)-valerinol 30[20], (±)-eremopnilene 58[20], (±)-eremoligenol 59[20] and (±)-calarene 60[21], have been synthesized from the cis-dimethyl octalone 54.



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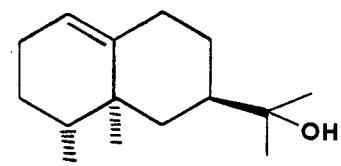

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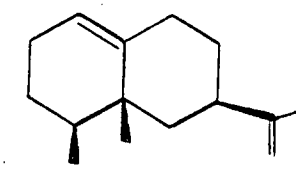

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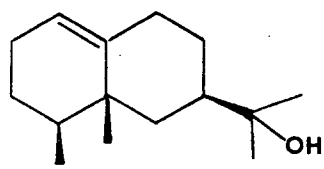

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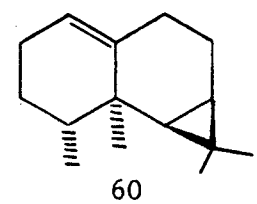
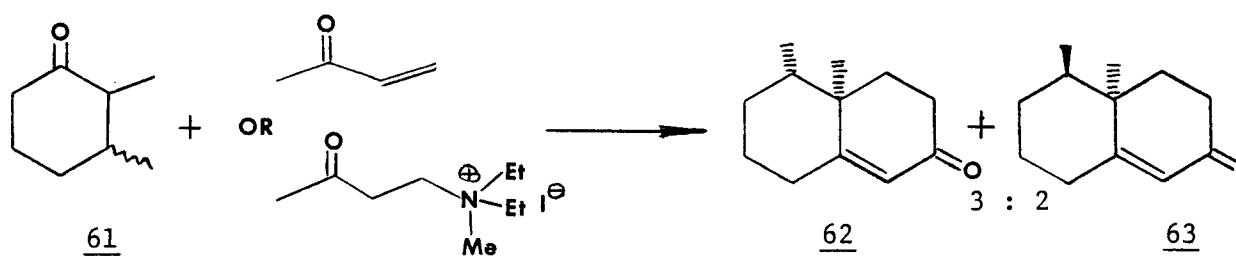


60

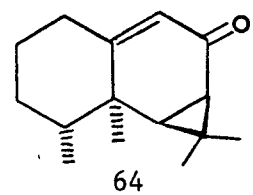
The use of 2-methylcyclohexanone derivatives in the construction of cis-4,10-dimethyloctalone systems has also been investigated. Independently, Piers et al[22] and Ourisson et al[23] have found that 2,3-dimethylcyclohexanone 61 underwent Robinson annulation with methyl vinyl ketone and/or its equivalent such as 4-diethylamino-2-butanone methiodide.



61 62 63

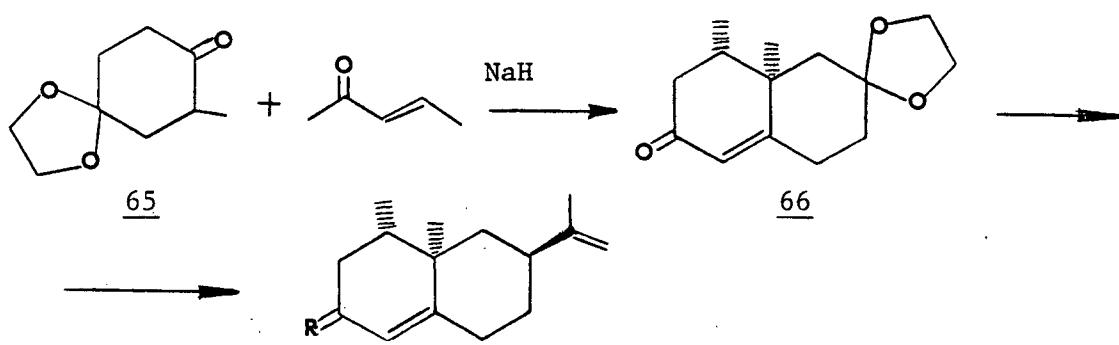
The octalone isolated from the reaction consisted of a mixture of two epimers 62 and 63 in the ratio of approximately 3:2, respectively. However, the total yield of the product was very low (ca. 15%). Although

Ourisson's group converted the cis-isomer 62 into (±)-aristolone 64, the inefficiency associated with the annulation step made this a rather impractical approach to the total synthesis of eremophilane sesquiterpenoids.



64

While the use of 2,3-dimethylcyclohexanone in Robinson annulation appeared to be rather unsuccessful, certain other 2-methylcyclohexanone derivatives do find use in constructing the eremophilane skeleton. For example, McGuire, Odom and Pinder[24] obtain the ketal enone 66 in 56% yield (based on unrecovered starting material) by condensing the monoketal 65 with trans-pent-3-en-2-one in the presence of sodium hydride. Evidence for the cis-relationship between the methyl groups was obtained by comparing



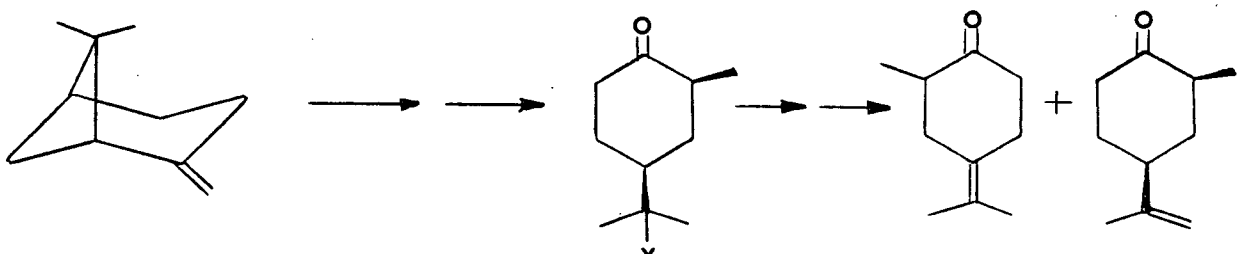
65 66

8 R=O
10 R=H_2

the p.m.r. spectrum of the product 66 with that of authentic nootkatone 8. The intermediate 66 was converted into (±)-valencene 10[27] and (±)-nootkatone 8.[27]

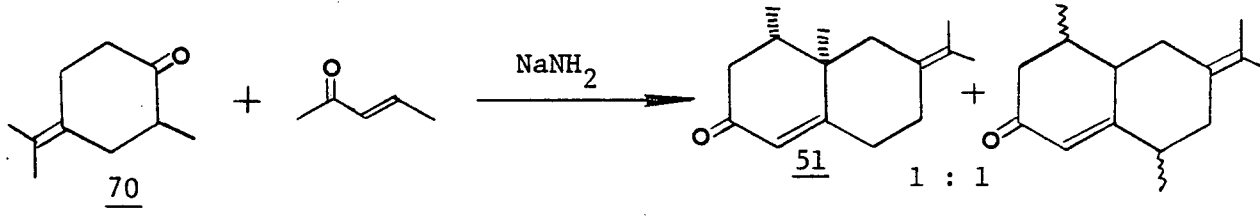
Van der Gen and co-workers have reported the synthesis of optically

active eremophilane-type sesquiterpenoids using as starting materials optically active cyclohexanones derived from monoterpenes such as β-pinene and sabinene. β-Pinene 67 was converted into 2-methyl-4-isopropylidenecyclohexanone 70 or 2-methyl-4-isopropenylcyclohexanone 71 via the chloride 68 or the acetate of the alcohol 69.[25]

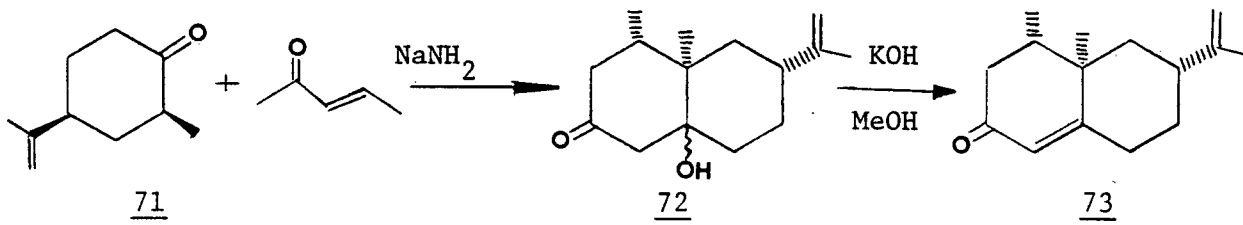


67 — 68 X=Cℓ; 69 X=OH — 70 — 71

The sodium enolate of each of these ketones was condensed with trans-pent-3-en-2-one. In the case of the isopropylidene isomer 70, a mixture of bicyclic ketones was obtained in 50% yield. From these crude products, (±)-isonootkatone (α-vetivone) 51 was isolated in 21% yield while the rest of the product consisted of compounds which arose from condensation on the less substituted position of the 2-methylcyclohexanone. On the other



70 — 51

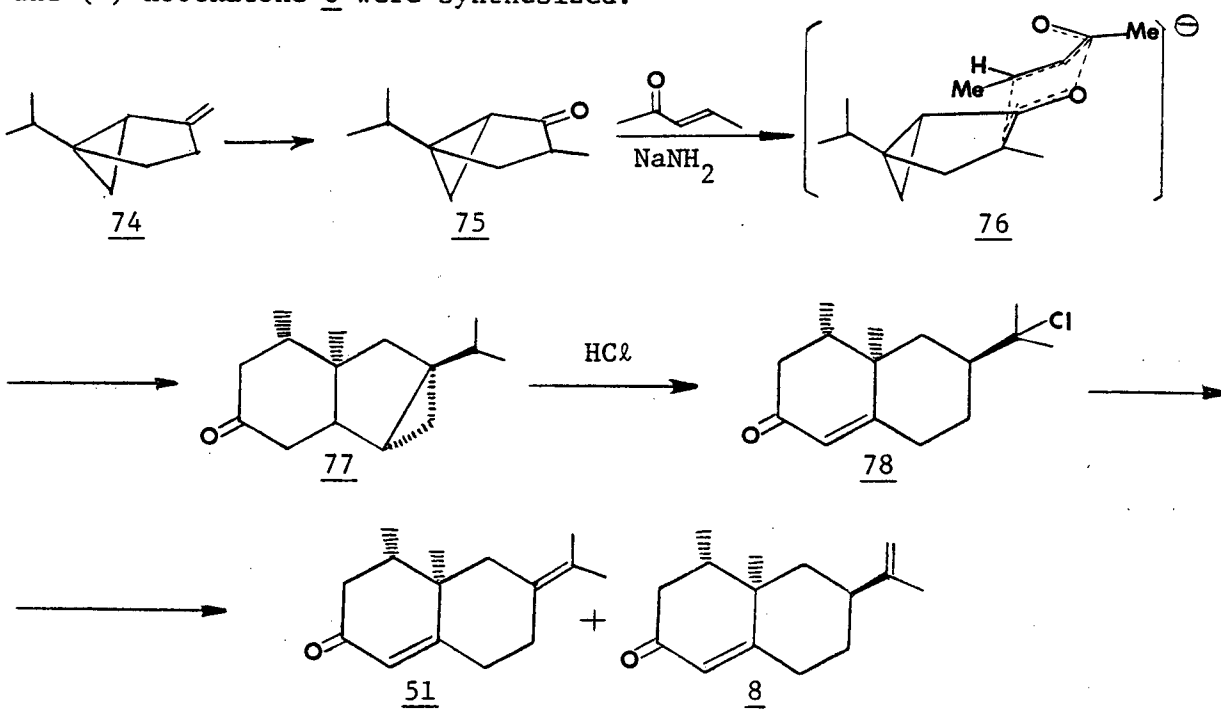


71 — 72 — 73

hand, a similar condensation involving the isopropenyl isomer 71 gave the ketol 72 which, upon refluxing with potassium hydroxide in methanol,

generated a 29% yield of (±)-7-epi nootkatone 73.

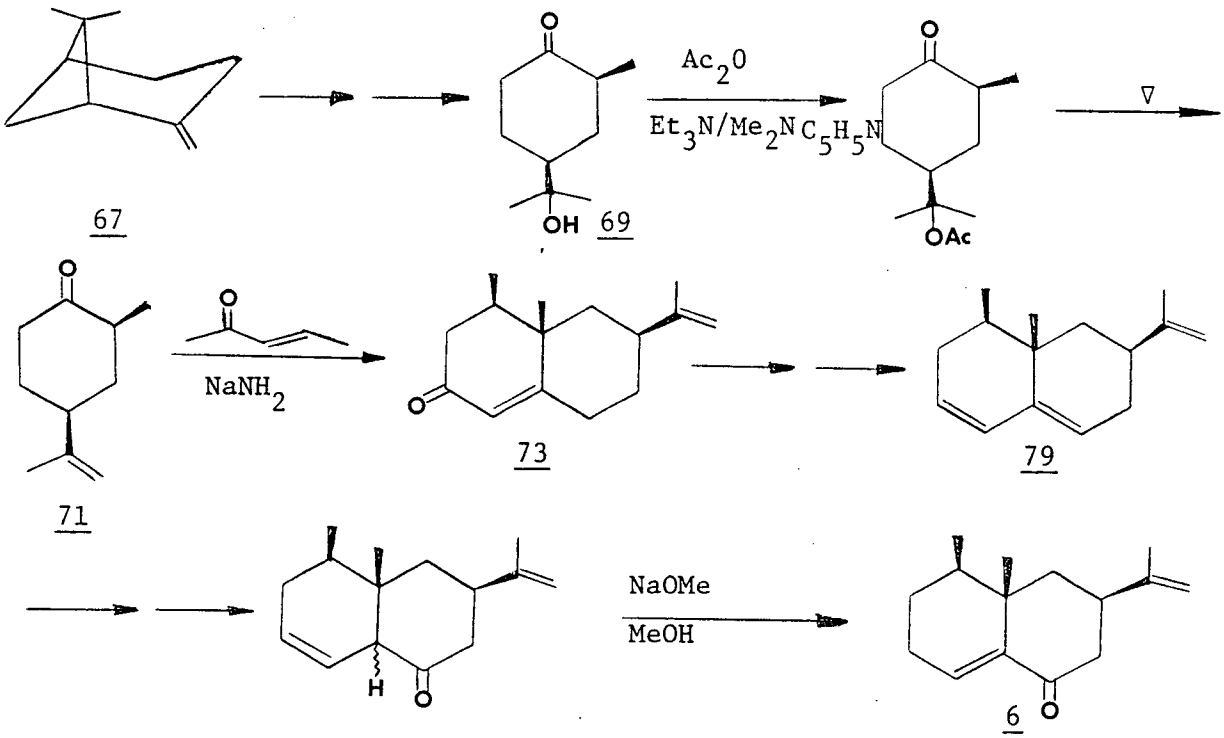
Sabinene 74 was transformed efficiently into 3-methylsabinaketone 75.[26] Treatment of this ketone with trans-pent-3-en-2-one in the presence of sodium amide gave an optically pure tricyclic enone 77 in good yield (ca. 67%). The assignment of product stereochemistry was based on the assumption that a transition state represented by 76, in which steric effects were the main factors to govern the reaction, was involved. The enone 77 was subsequently treated with hydrogen chloride and from the resultant monochloride 78, (-)-isonootkatone (α-vetivone) 51 and (-)-nootkatone 8 were synthesized.



74 75 76 77 78 51 8

Recently, McMurry and his co-workers[27] have modified Van der Gen's procedure[25] to obtain 7-epinootkatone 73 in higher yield. Furthermore, the former workers subsequently transformed compound 73 into eremophilone 6, the first non-isoprene sesquiterpene isolated from nature. Keto alcohol 69, obtained from β-pinene 67, was acylated with acetic anhydride in the

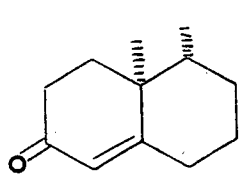
presence of triethylamine and 4-(N,N-dimethylamino)-pyridine.



Pyrolysis of the resultant acetate, afforded, in good overall yield from β-pinene 2-methyl-4-isopropenylcyclohexanone 71. The latter was subjected to Robinson annulation with trans-pent-3-en-2-one in the presence of sodium amide as base. The product, 7-epinootkatone 73 was isolated by column chromatography instead of molecular distillation. In this manner, the yield of the desired octalone was improved from 29%[25] to 50% (basedon recovered starting material). The dieneone 73 was then converted into triene 79 which upon epoxidation and subsequent treatment with lithium perchlorate, yielded two epimeric β,γ-unsaturated ketones. Both ketones provided (±)-eremophilone 6 by bringing the double bond into conjugation with strong base.

It has been pointed out that, with ordinary unactivated cyclohexanone derivatives, the Robinson annulation process often provides unsatisfactory

results because of competing polymerization of the vinyl ketones and, in the case of unsymmetrical cyclohexanones, because of the difficulty of controlling the site of condensation. Many modifications, such as the utilization of Mannich bases, β-haloketones, enamines, α-silyl enones etc., have been developed in order to overcome these problems. Some of these methods have achieved a certain degree of success.[28] Another entirely different approach to solve these difficulties involves the use of highly reactive alkylating reagents (halo ethers, halo ketals, allylic halides, etc.) which contain a latent ketone group. Indeed, Piers and co-workers[22] have demonstrated that cis-5,10-dimethyl octalone 62 could be efficiently obtained from 2,3-dimethylcyclhexanone by this approach.



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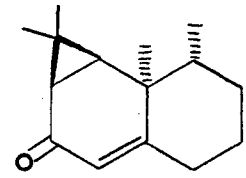
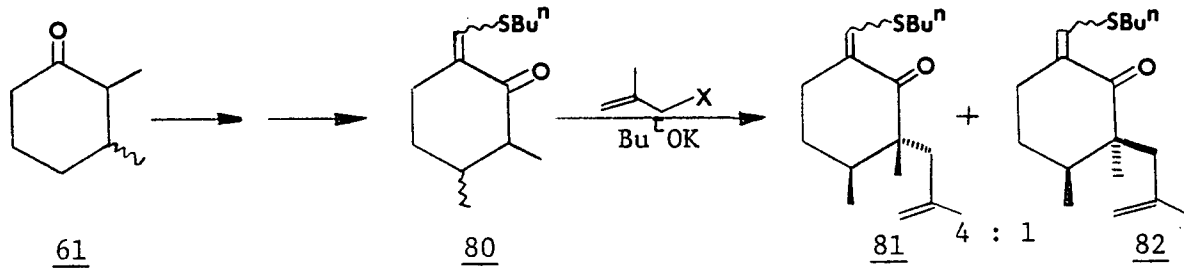


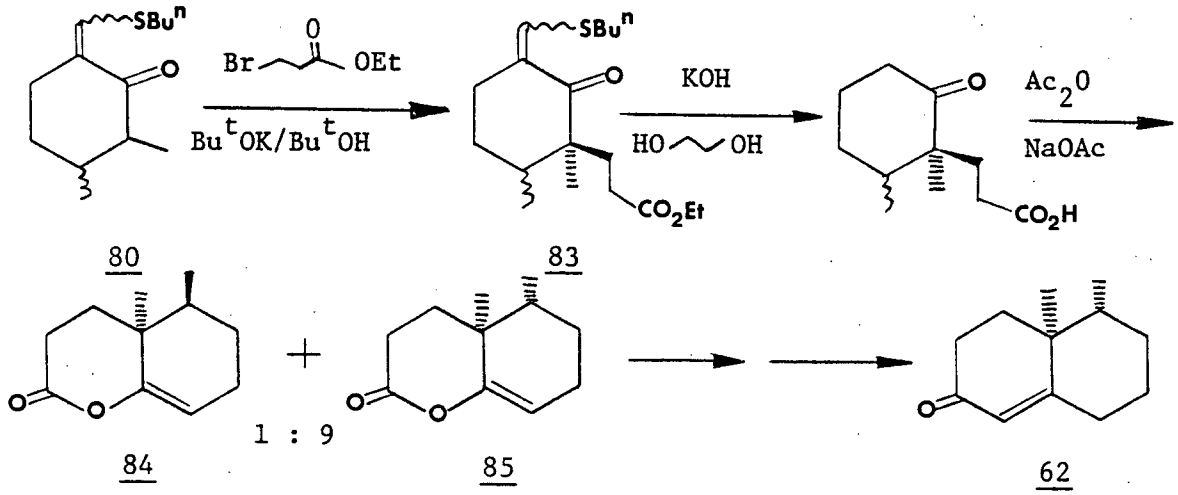
64

In their total synthesis of (±)-aristolone 64, Piers et al[29] observed that alkylation of the n-butylthiomethylene derivative of 2,3-dimethyl-cyclohexanone 80 with methallyl halide gave, in fairly good yield, a mixture of the cis and trans-isomers 81 and 82 (ca. 4:1, respectively). This result encouraged them to investigate the utilization of other potentially useful alkylating reagents in the stereoselective synthesis of octalone 62

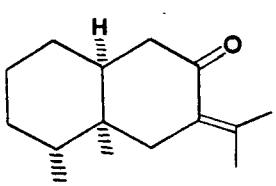


61 80 81 82

Alkylation of the n-butylthiomethylene derivative 80 with ethyl 3-bromopropionate gave a mixture of keto esters 83 in excellent yield.[30] Removal of the blocking group and enol-lactonization of the resultant keto acids furnished two crystalline epimers 84 and 85 in high overall yield. The major isomer 85, favoured by a 9:1 ratio, was eventually



converted into octalone 62 via addition of methyllithium, acid hydrolysis, and base promoted cyclization. From this important intermediate, several sesquiterpenes, such as (±)-fukinone 86[30], (±)-eremophilenlide 87[31], (±)-tetrahydroligularenolide 88[31], (±)-aristolochene 89[31], (±)-isoishwarane 90[34] and (±)-ishwarane 13[32-34] have been synthesized.



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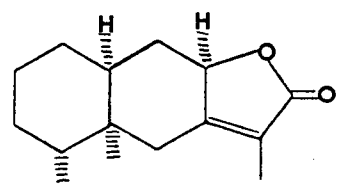

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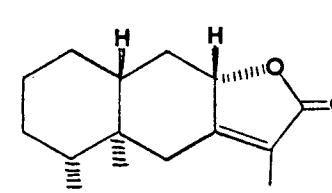

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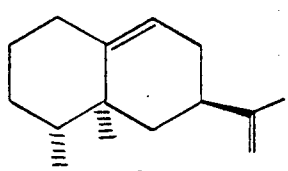

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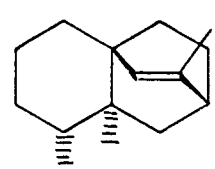

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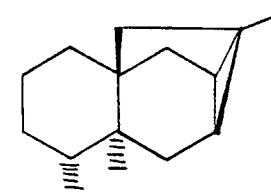
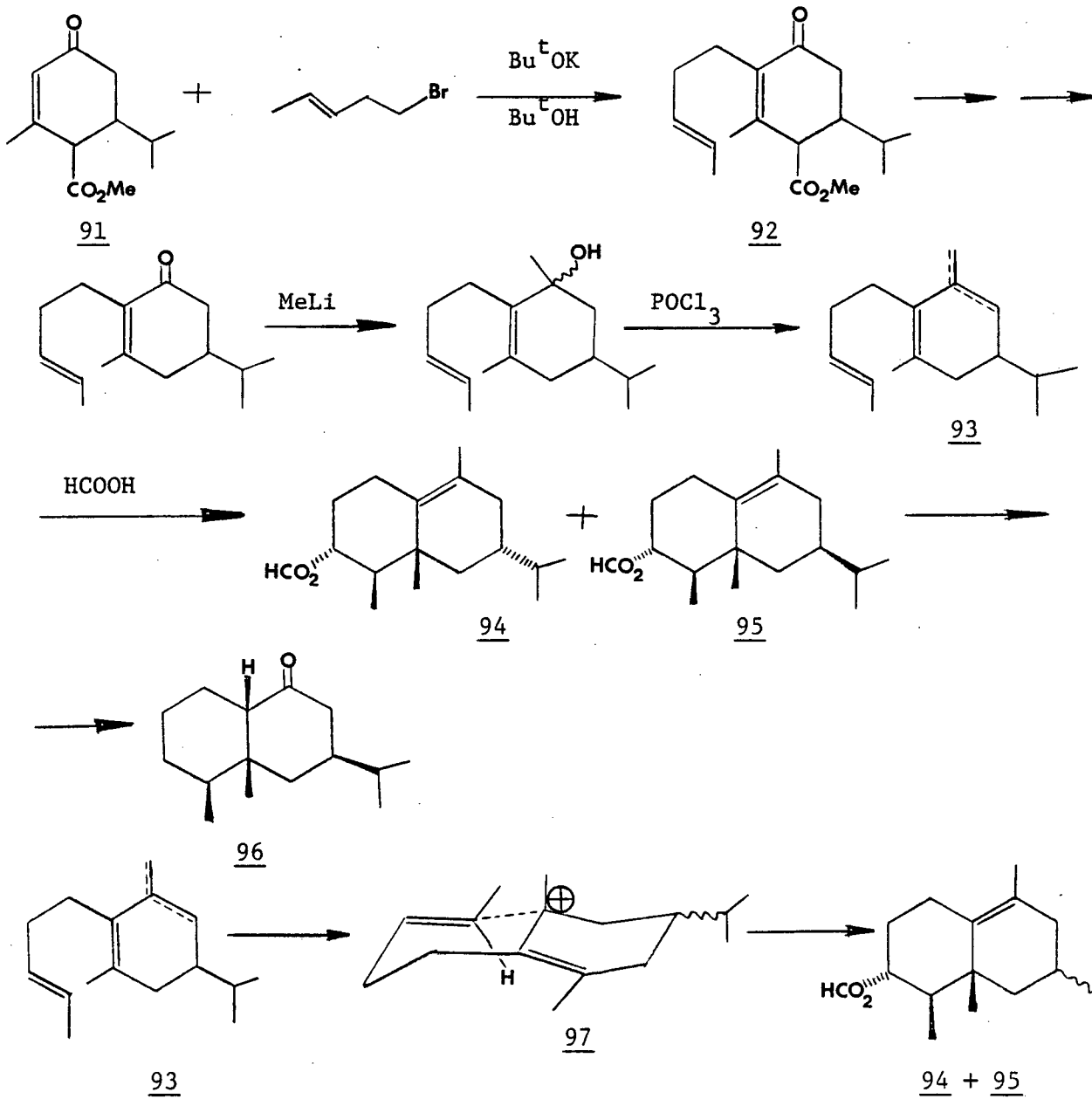
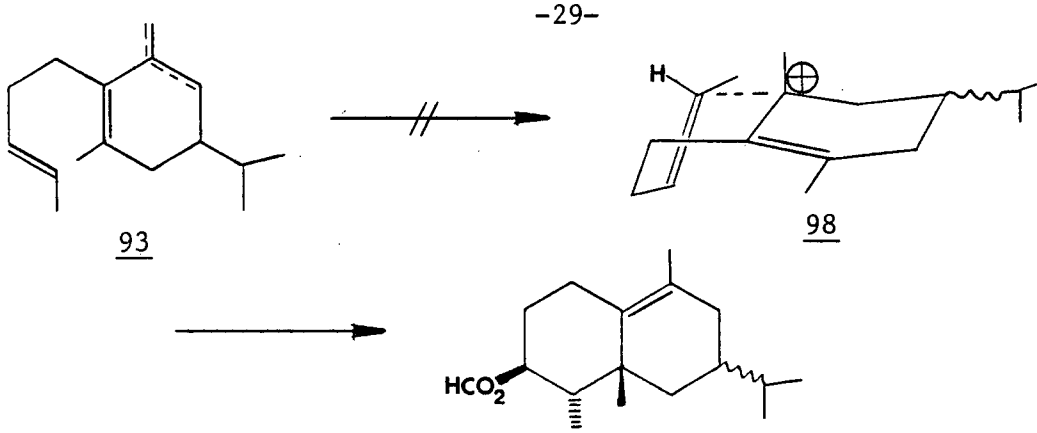


13

Although the Robinson annulation and related processes seem to be the most commonly used methods to obtain octalones with cis-vicinal methyl groups at C_4 and C_{10}, compounds of this type are also available by acid initiated π-cyclization of polyenes. Brown and co-workers[35] have used this type of reaction as the key step in their synthesis of (±)-tetrahydroeremophilone 96. The keto ester 91 was first transformed into a mixture of trienes 93 by standard reactions.

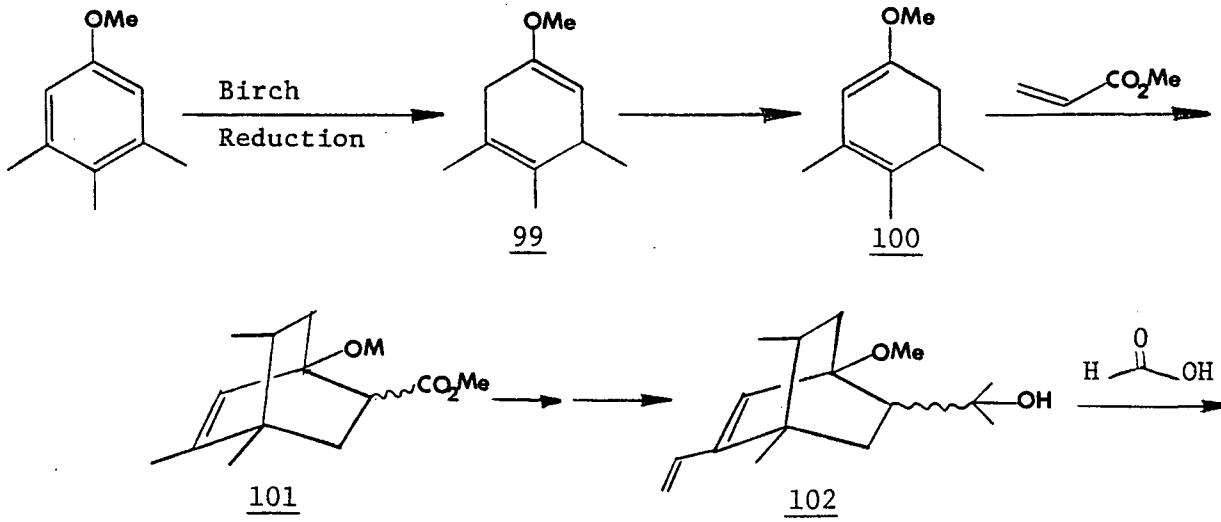




93 98

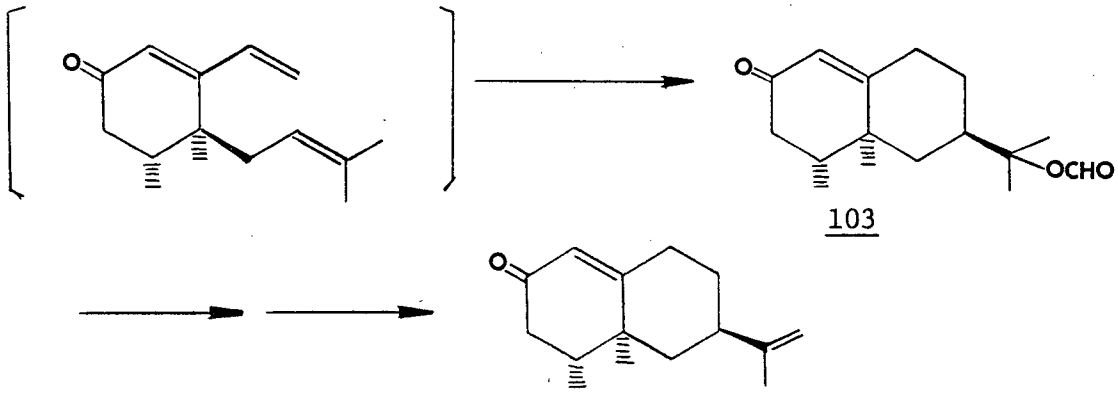
Cyclization proceeded smoothly in anhydrous formic acid to yield two esters 94 and 95, epimeric at the isopropyl side chain. The stereoselectivity involved in the formation of only cis-vicinal dimethyl products has been explained by proposing the chair-like character of the incipient ring in the transition state 97. On the other hand, the trans-relationship could be obtained only through the less favourable boat-like transition state 98.

The Diels-Alder reaction is one of the most powerful tools in modern synthetic organic chemistry. Its versatility has been demonstrated in many areas. Dastur[36,37], in applying this reaction to the formation of (±)-nootkatone 8, achieved high stereoselectivity with respect to the introduction of the cis-vicinal methyl groups at C_4 and C_5. The diene 99, obtained by Birch reduction of 3,4,5-trimethylanisole, underwent in situ



99 100

101 102

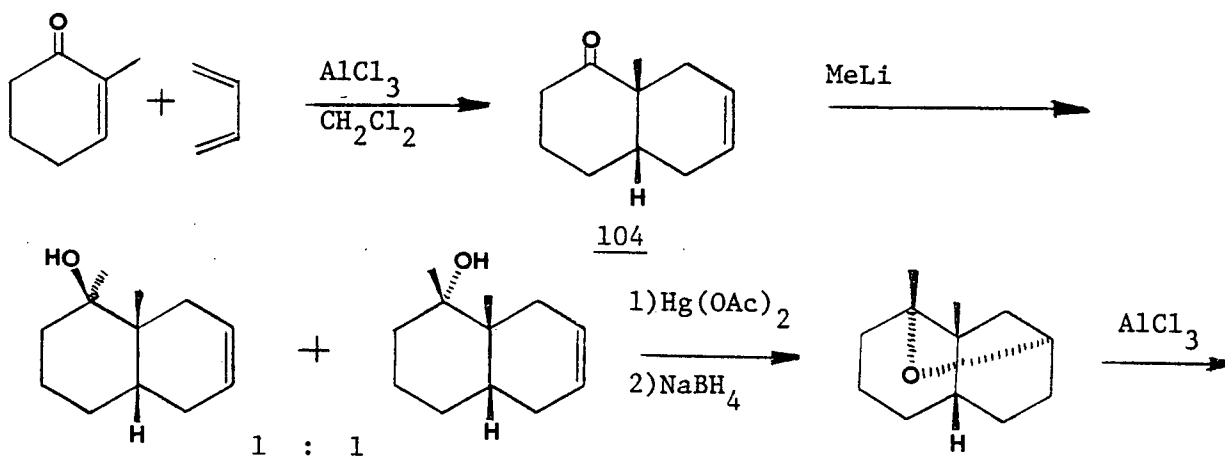


103

8

Diels-Alder reaction with methyl acrylate in good yield. Due to steric factors, the methyl acrylate was expected to approach the diene from the side of the molecule opposite to the secondary methyl group (c.f. 100), thus affording a product with the methyl groups in a cis-relationship. Indeed, one major adduct 101 was obtained. The latter was subsequently transformed into the tertiary alcohol 102, which upon solvolysis in formic acid yielded the octalone ester 103. Upon subjection to hydrolysis and dehydration, the latter gave (±)-nootkatone 8. Not a trace of the corresponding trans-4,5-dimethyl compound could be detected in the reaction product.

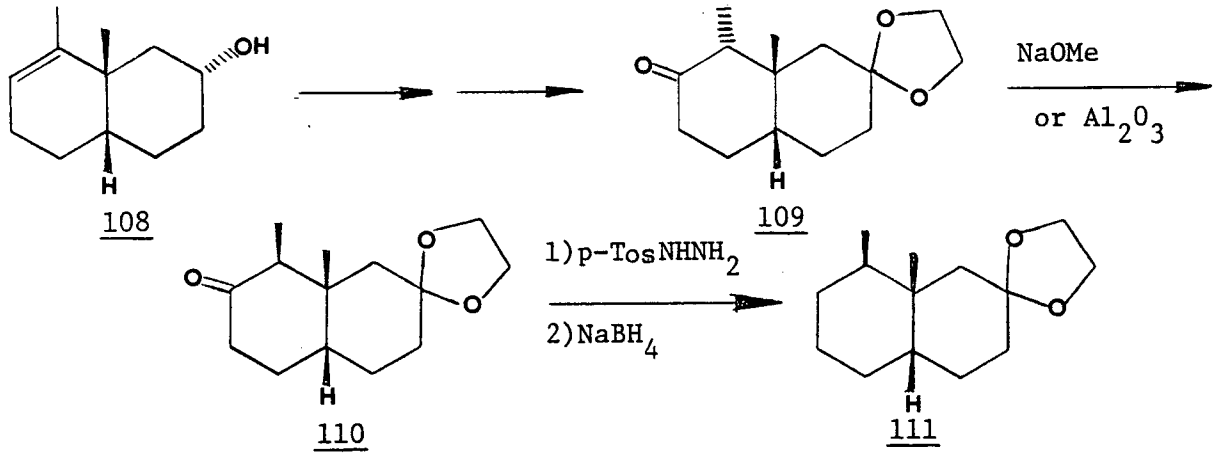
Kitahara et al[38] used the Diels-Alder reaction to provide the simple cis-octalone 104. Addition of methylithium to this ketone gave the trans- and cis-isomers 105 and 106 as 1:1 mixture. Intramolecular oxymercuration, followed by reduction, furnished the internal ether 107. Cleavage of the ether linkage resulted in the formation of the unsaturated alcohol 108. After



104

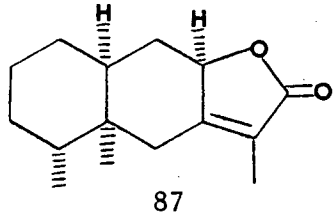
105 1 : 1 106

107



108 109 110 111

conversion of this alcohol into the ketone ketal 109 via standard procedures, the latter compound could readily be transformed (sodium methoxide in methanol or chromatography on alumina) into the thermodynamically more stable isomer 110, possessing a cis-relationship between the two methyl groups. The keto group of 110 was then removed by sodium borohydride reduction of the corresponding tosylhydrazone. The ketal 111 was later used in the total synthesis of (±)-eremophilenolide 87[39] and (±)-furanoeremophilane 112.[39]



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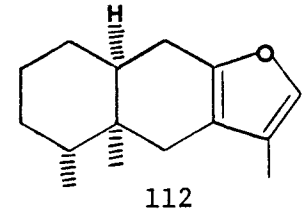
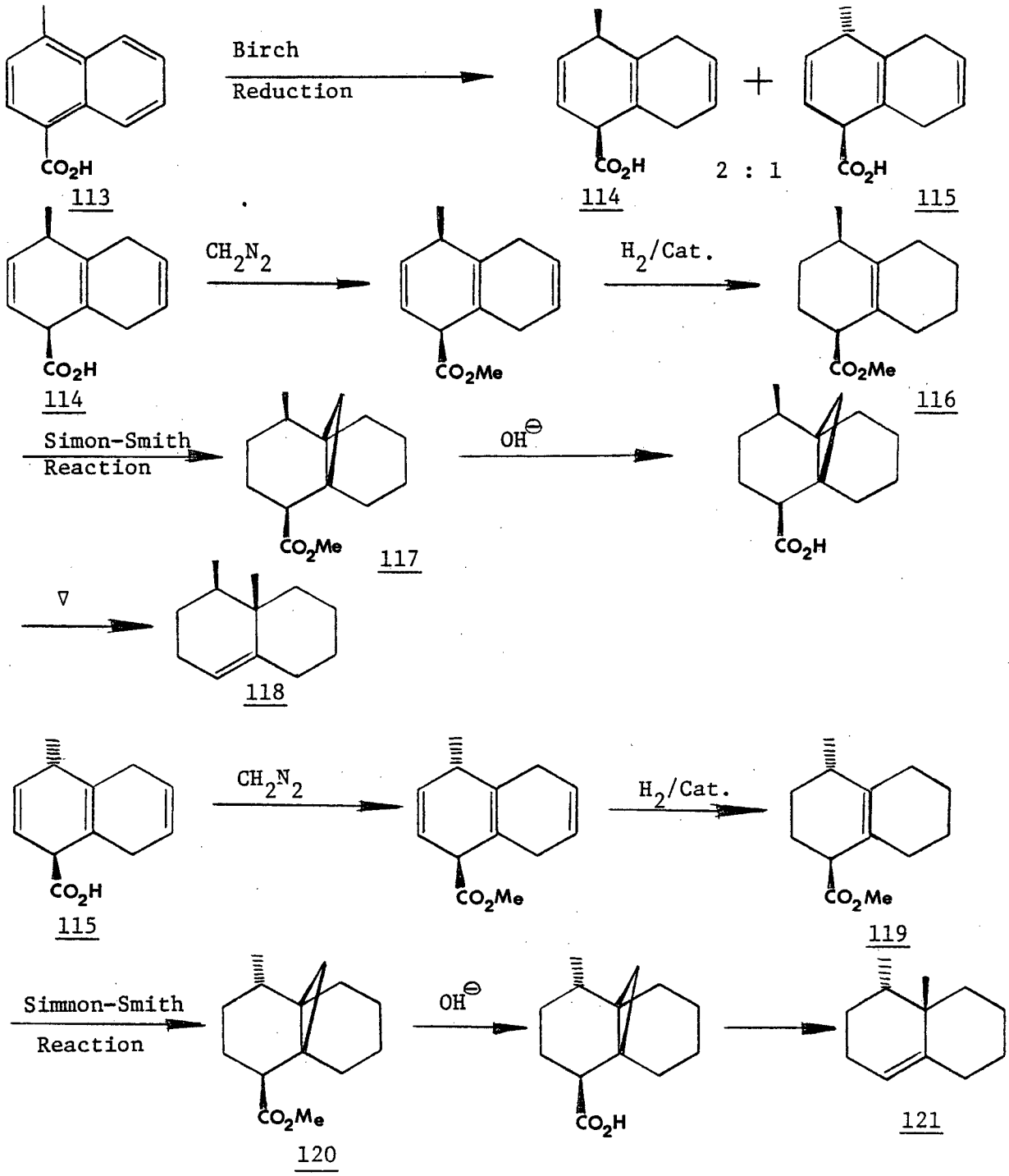


112

Sims and Selman[40] have reported the stereoselective introduction of an angular methyl group into polycyclic systems via regioselective opening of a cyclopropane ring. This method offers promise as an alternative solution for the introduction of cis-vicinal methyl groups into an intermediate suitable for the synthesis of eremophilane sesquiterpenes. Sims and Selman found that Birch reduction converted 4-methyl-1-naphthoic acid 113 into two epimeric acids, 114 and 115, in the ratio of approximately 2:1, respectively. Separation of the isomers could be effected by fractional

recrystallization. Conversion of the cis-isomer 114 into the corresponding ester, followed by hydrogenation of the latter afforded the octalin 116.

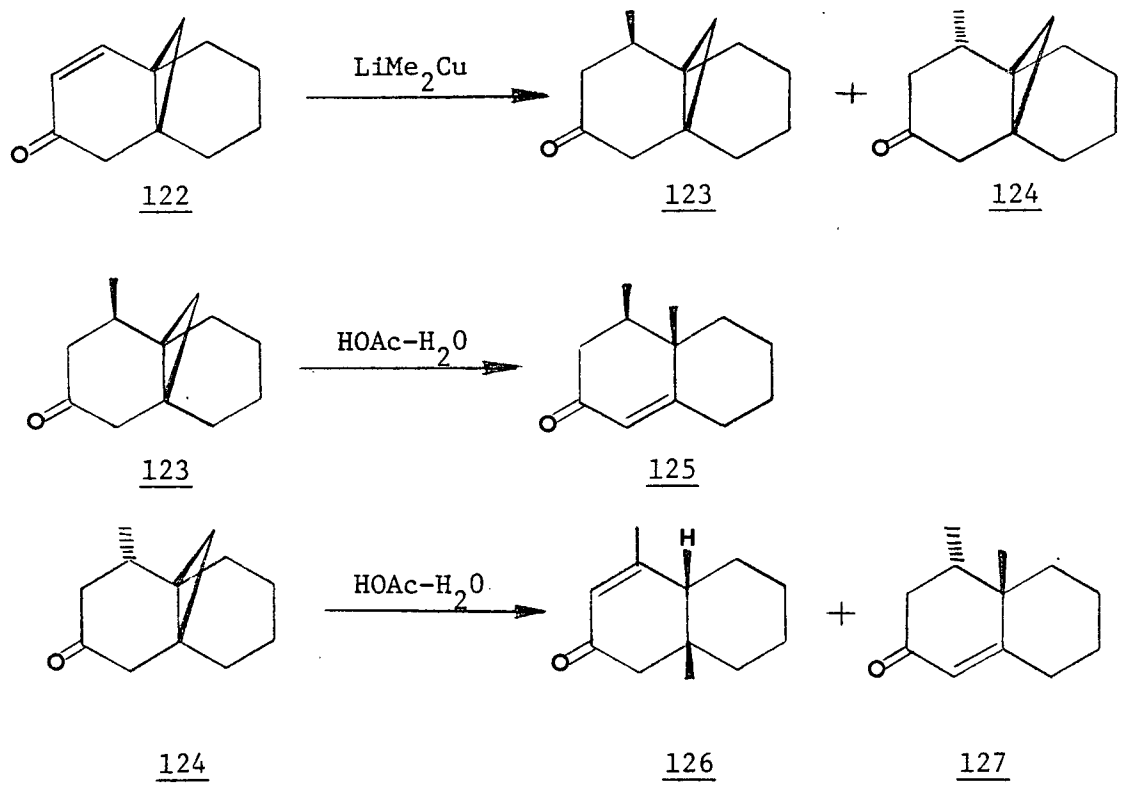


113 114 115 116 117 118 119 120 121

Cyclopropanation of 116 by the Simmon-Smith reaction resulted in the formation

of a single isomer 117. Thermal decarboxylation of the acid obtained by saponification of 117 afforded the octalin 118 via a regiospecific ring opening of the cyclopropyl moiety. A similar set of reactions, involving the intermediates 119 and 120, resulted in the conversion of the trans-isomer 115 into the octalin 121.

Marshall and Ruden[41,42] also investigated the possibility of regioselectively cleaving cyclopropyl systems by acid. These workers found that the cyclopropyl enone 122 reacted smoothly with lithium dimethylcuprate in dioxane to give a reaction product which appeared to be homogeneous. However, upon subjection to acid cleavage, this material provided a mixture of products consisting mainly of compound 126, with lesser amounts of the cis- and trans-octalones 125 and 127 also being present. It thus appeared that the conjugate addition of lithium dimethylcuprate to enone 122 resulted in a mixture of the cis- and trans-isomers



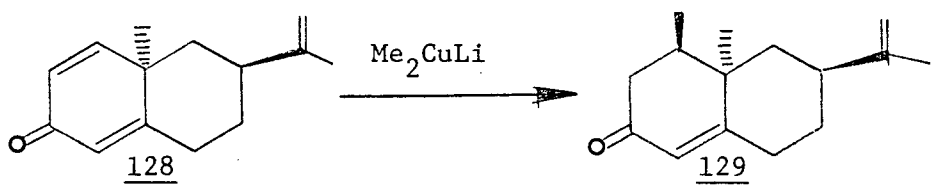
122 123 124

123 125

124 126 127

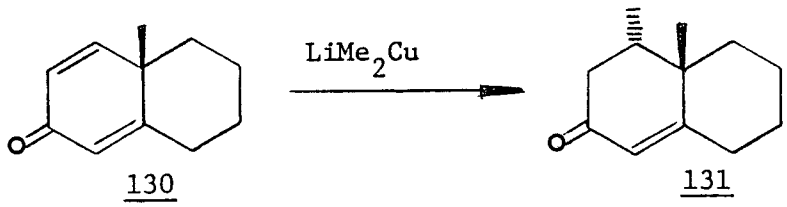
123 and 124. In order to gain more information concerning the regioselectivity of the acid cleavage of the cyclopropyl ring, Marshall and Ruden explored the reaction further with a mixture of ketones 123 and 124 in a ratio of approximately 1:3, respectively. It turned out that the reaction product contained 25% of the cis-octalone 125. Therefore, it was proposed that the cis-isomer 123 must be opened up unidirectionally to give the cis-octalone 125 whereas the trans-isomer 124 was cleaved by acid in the opposite sense to provide the rearranged enone 126.

Conjugate addition of lithium dialkylcuprates to enones has been successfully applied in many total synthesis. From studies of this type of reaction using simple conjugated enones as substrates, it has been concluded that the stereochemical outcome of the reaction is highly subject to electronic and steric controls. For example, Schudel et al.[43] found that reductive methylation of dienone 128 with lithium dimethylcuprate, gave almost exclusively 4-epinootkatone 129 in excellent yield.

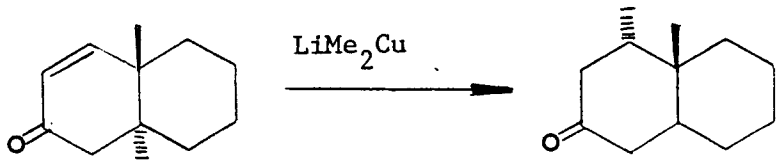


128 129

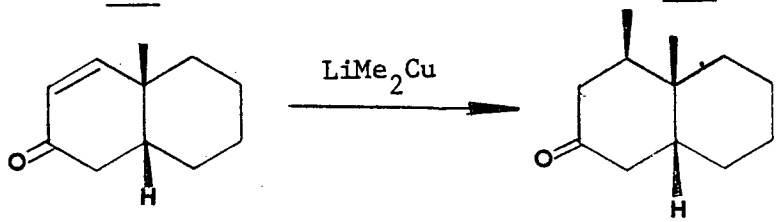
Similarly, Warne[44] observed that 1,4-addition occurred from the α-faces of the dienone 130 and the octalone 132 to give exclusively the products 131 and 133, respectively, each possessing vicinal methyl groups in a trans-relationship. However, the cis-fused octalone 134 afforded product 135 with completely different stereochemistry.[45]



130 131

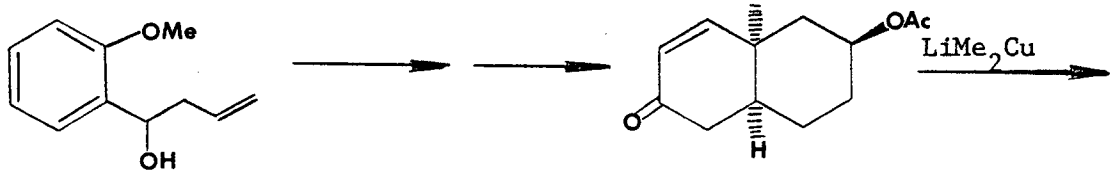


132 133

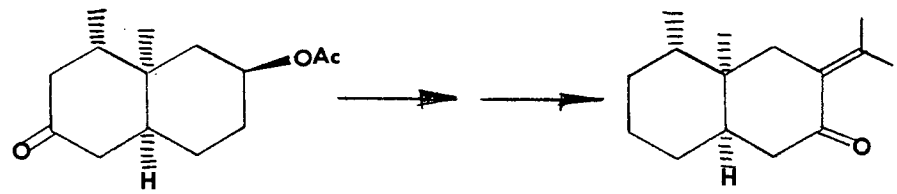


134 135

Marshall and Cohen[46] employed this type of chemistry to advantage in their stereoselective synthesis of (±)-fukinone 86. The crystalline cis-fused octalone 137, obtained from the benzylic alcohol 136 via standard transformations, reacted with lithium dimethylcuprate to provide a single stereoisomer 138 in fairly good yield. This keto acetate 138 was then converted into fukinone 86 by standard reactions.



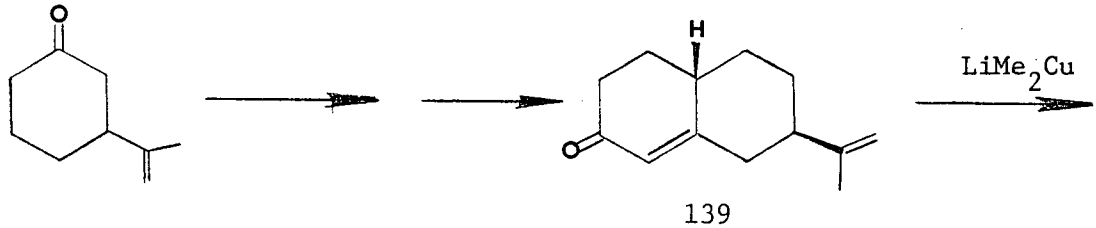
136 137



138 86

On the other hand, Piers and Keziere[47,48] generated the characteristic eremophilane skeletone in a slightly different manner. 3-Isopropenylcyclo-

hexanone was converted into the octalone 139 via several steps. The stereoselective introduction of the angular methyl group was achieved by 1,4-addition of lithium dimethylcuprate to the enone 139. Borohydride reduction of the tosylhydrazone derivative of the resultant product 140, followed by catalytic hydrogenation, afforded (±)-7β-eremophilane 141.



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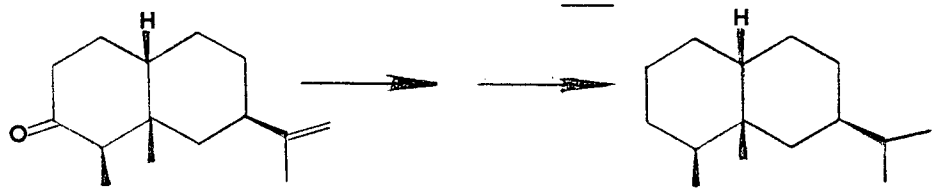
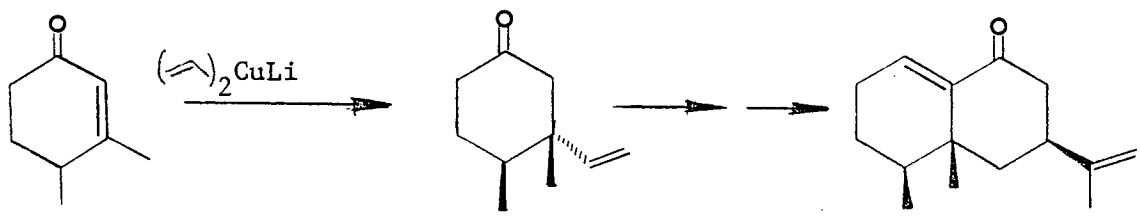
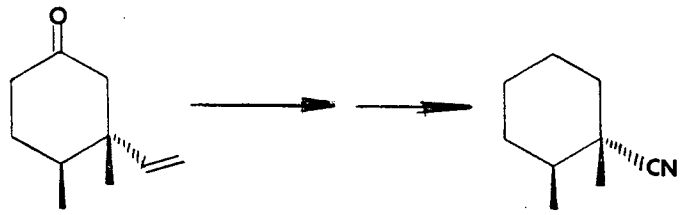


140 141

More recently, Ziegler and co-workers[49,50] have reported two different approaches to the total synthesis of eremophilone 6. In each case, the intermediate 142 served as the starting material. This compound could be conveniently prepared by the addition of lithium divinylcuprate to 3,4-dimethylcyclohexenone. This reaction proceeded stereoselectively, as expected, to give only 3,4-cis-dimethyl-3-vinylcyclohexanone 142. The stereochemistry of the product was determined by its conversion into cis-1,2-dimethylcyclohexylnitrile 143, a known compound with established stereochemistry. The assignment of the stereochemistry was further confirmed by converting the unsaturated ketone 142 into (±)-eremophilone 6.



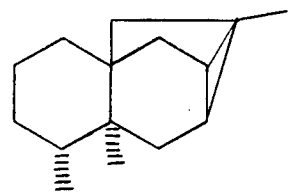
142 6



142 143

IV. Synthesis of Tricyclo[3.2.1.$0^{2.7}$]octane Systems and the Total Synthesis of Ishwarane

In connection with the possibility of synthesizing ishwarane-type compounds with carbon skeleton 11, it is clear from the above discussion

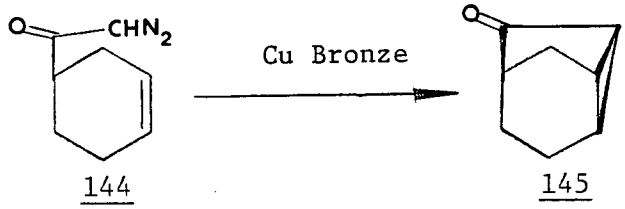


11

that the stereochemical problems associated with the synthesis of cis-vicinal methyl groups on decalin-type systems can be solved in a variety of ways. However, the formation of the 7-methyltricyclo[3.2.1.$0^{2.7}$]octane system present in ishwaranes 11 and the inherent stereochemical problems associated with this moiety impose a challenge in designing the synthesis of ishwarane-type sesquiterpenes.

In recent years, several tricyclo[3.2.1.$0^{2.7}$]octane-6-one systems have been synthesized and used as convenient precusors for bicyclo[3.2.1]octane or bicyclo[2.2.2]octane systems. Most of these investigations have utilized the copper-catalyzed intramolecular addition of a carbenoid to a carbon-carbon double bond. For example, tricyclo[3.2.1.$0^{2.7}$]octan-6-one 145 was obtained by LeBel and Hubbler in 1963 from thermal decomposition of the cyclohexenyl diazomethyl ketone 144 in the presence of copper bronze.[51] Similarly, House, Boots and Jones[52] applied this type of reaction to the

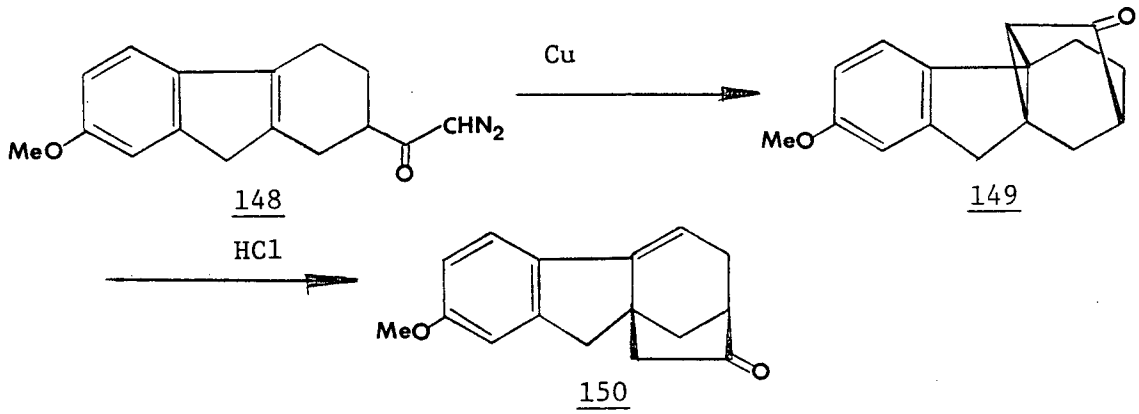
bicyclic diazo ketone 146 and isolated the tetracyclic ketone 147 in moderate yield.



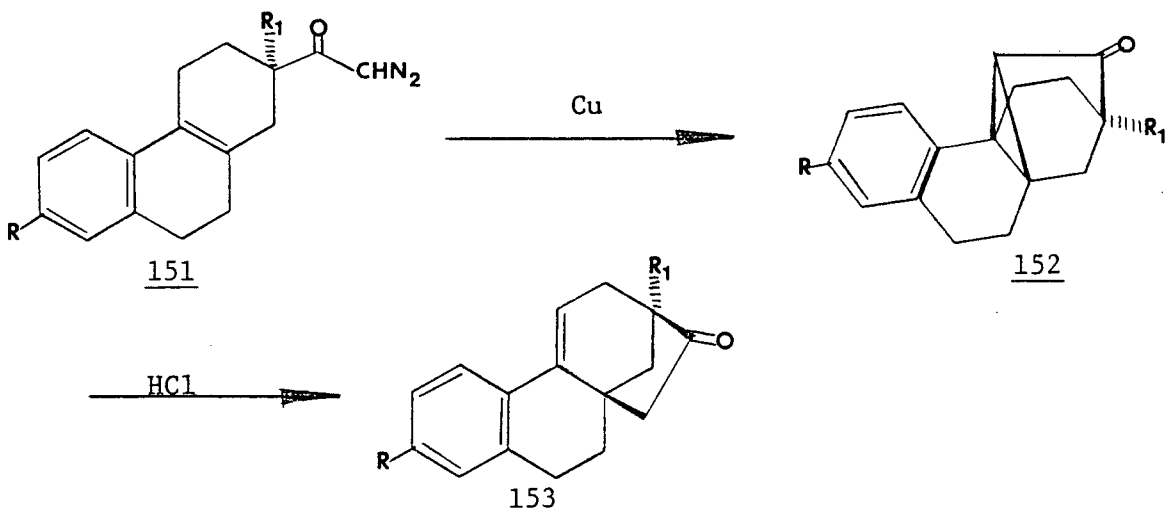
144 145

146 147

Chakrabortty et al.[53] have used similar tricyclic systems to generate the bicyclo[3.2.1]octane moiety in their model study for the synthesis of gibberellane and kaurane-phyllocladene type diterpenoids. The ketones 149 and 152, obtained from the diazoketones 148 and 151



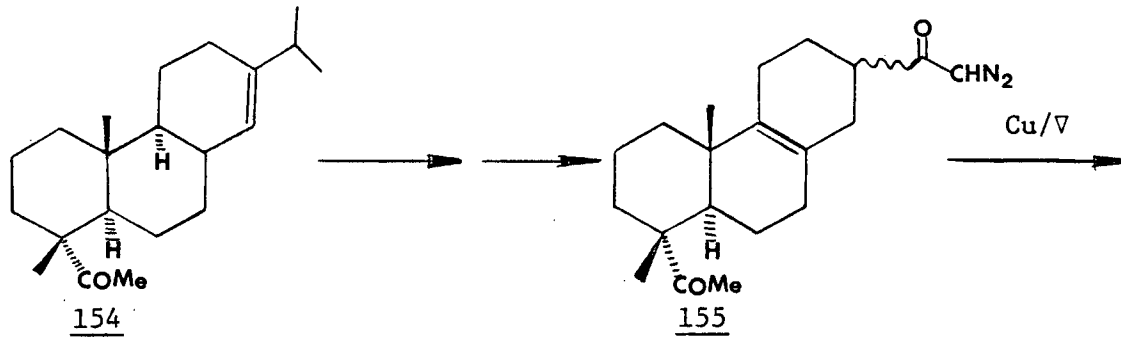
148 149 150



151 152 153

respectively, were rearranged with acid to the bicyclooctanones 150 and 153, respectively, in excellent yield. However, the yields of the carbenoid reactions (formation of 149 and 152) varied from poor to moderate.

In a report concerning the synthesis of (+)-kaurene 160 and (+)-phyllocladene 161 from (-)-abietic acid 154, Tahara, Shimagaki, Ohara and Nakata[54] employed the formation of the tricyclo[3.2.1.$0^{2,7}$]octanone system as a key reaction. In their sequence, the diazoketone 155 (mixture of epimers) derived from (-)-abietic acid 154, was converted by thermolysis in the presence of copper, into a 1:1 mixture of the pentacyclic keto esters 156 and 157. The yield of this reaction was not specified. The keto esters 156 and 157 were subsequently transformed into intermediates 158 and 159, respectively, via reductive cleavage of the cyclopropane ring and modification of the carbomethoxy functionality into a methyl group. From these intermediates 158 and 159, (+)-kaurene 160 and (+)-phyllocladene 161 were obtained, respectively, via standard reactions.



154 155

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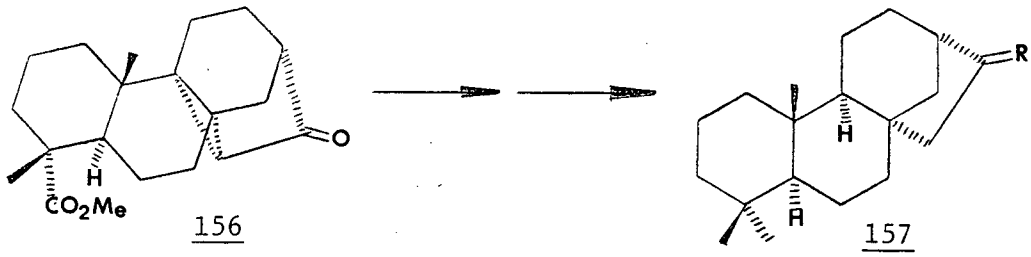
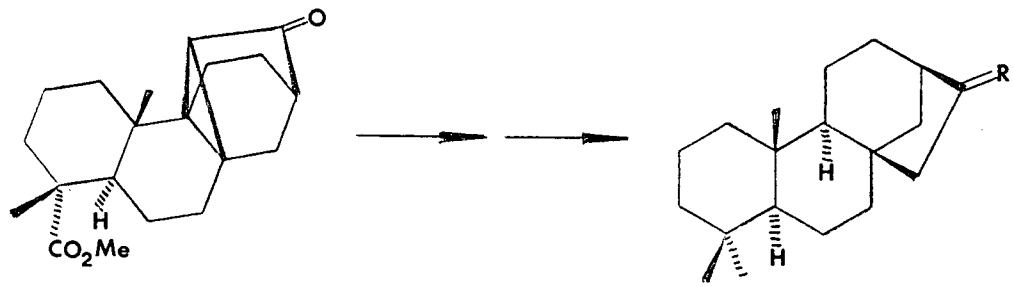
156 157



156 157

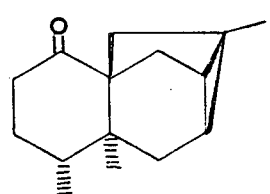
158 R=O
160 R=CH_2



157

159 R=O
161 R=CH_2

Application of this type of methodology to the synthesis of ishwarone 12 and ishwarane 13 would, at first sight, seemed to be



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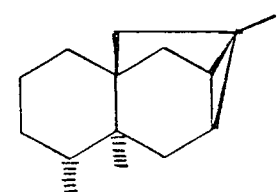
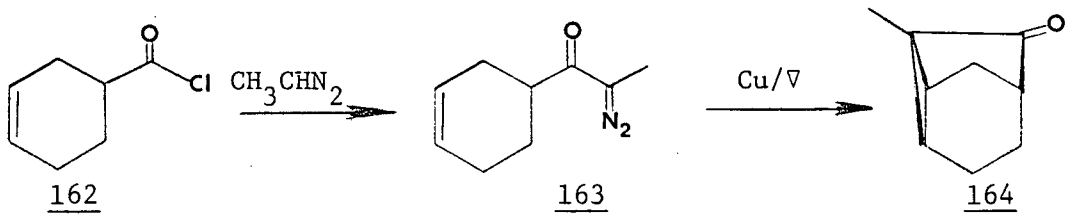


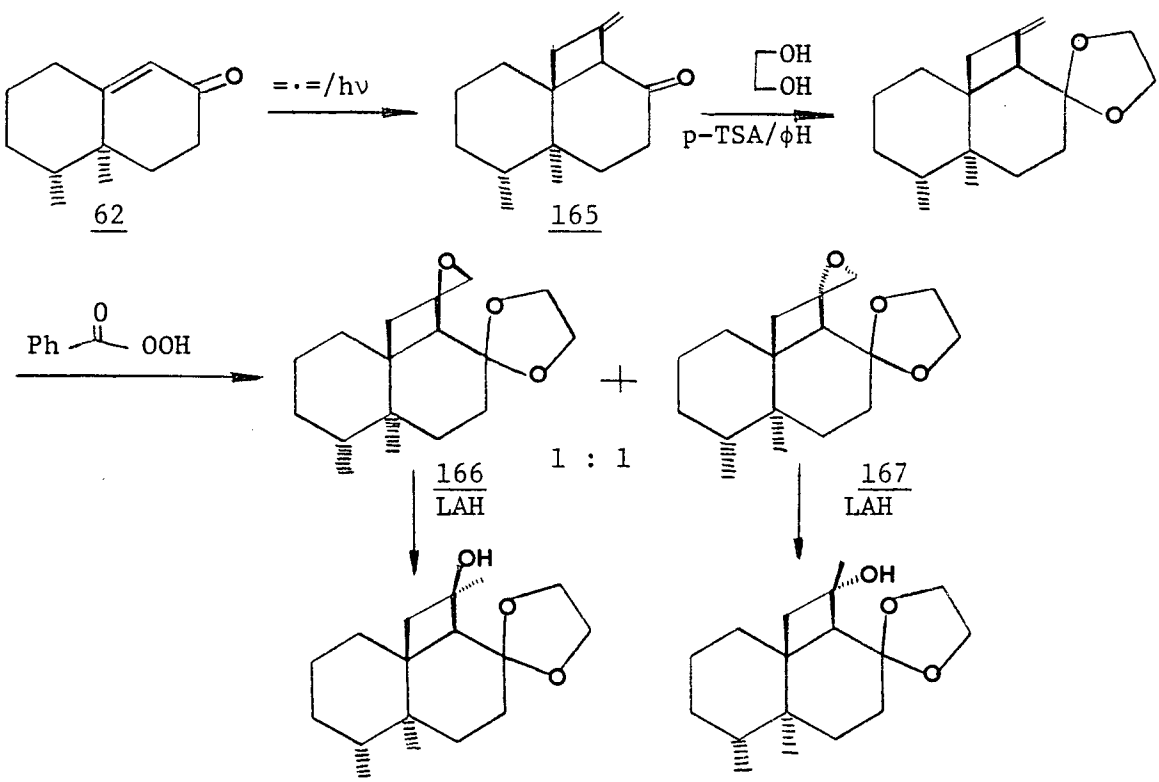
13

possible. In these cases, however, it would be necessary to use appropriately substituted diazoethyl cyclohexenyl ketones. Scanio and Lickei[55], using a simple model system, have investigated the feasibility of this approach. The diazoketone 163, resulting from the reaction of diazoethane with the acyl chloride 162, underwent intramolecular carbene addition to afford the desired tetracyclic ketone 164 in unspecified yield. However, extension of this methodology to the attempted total synthesis of ishwarone 12 and ishwarane 13 has so far been unsuccessful.[56]

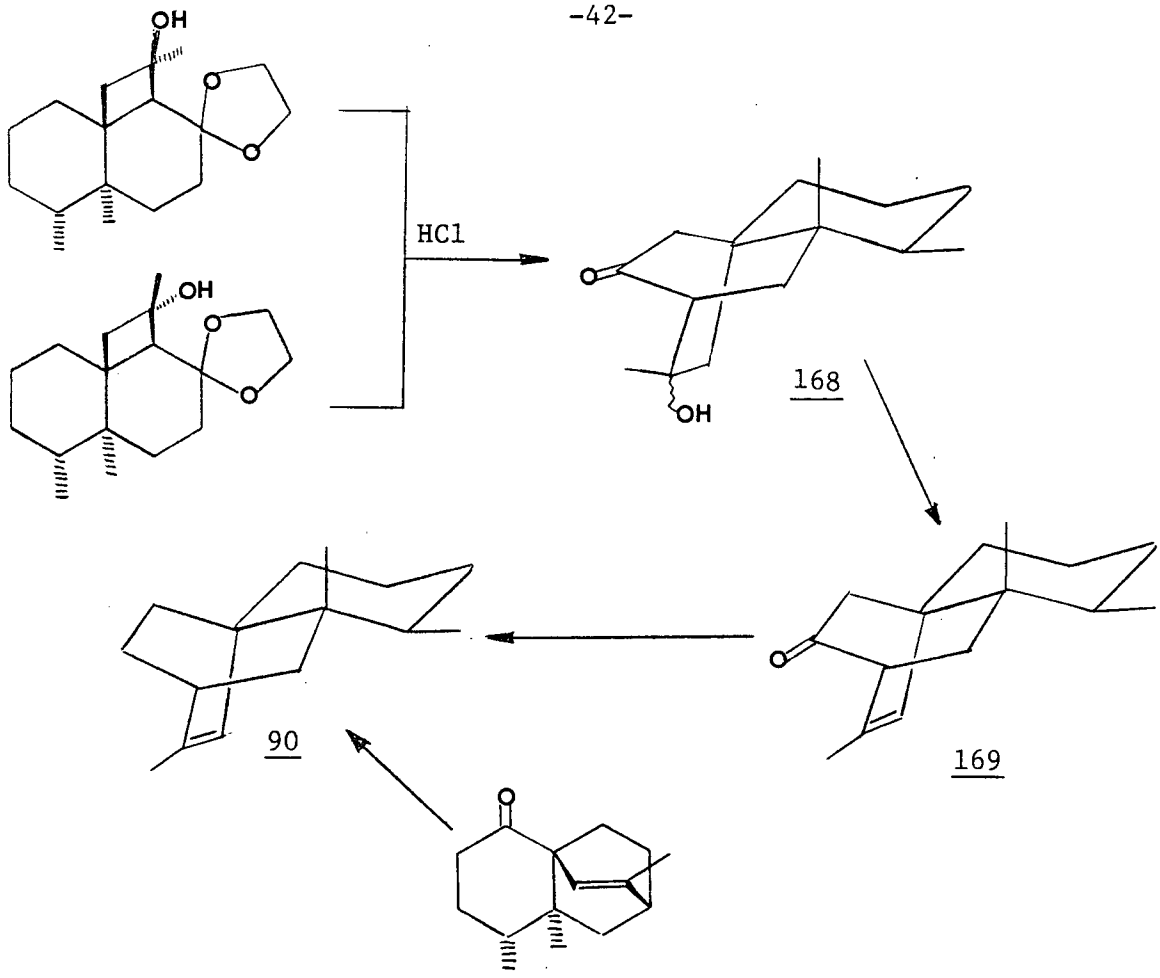


162 163 164

The first total synthesis of ishwarane was reported by Kelly, Zamecnik and Beckett[32-34] in the early seventies. Instead of using carbene addition as the key reaction, these workers employed the more traditional intramolecular alkylation to form the tricyclo-[3.2.1.$0^{2.7}$]octanone system from a bicyclo[2.2.2]octanone precusor. Thus, octalone 62 with defined stereochemistry, underwent photoaddition with allene to give the 1:1 adduct 165 stereo- and regioselectively.[34] Successive subjection of 165 to ketalization and epoxidation gave the two isomeric epoxides 166 and 167, which were obtained in approximately equal amounts. Fortunately, the lack of stereoselectivity at this stage did not affect the efficiency of the synthesis, since both epoxides were



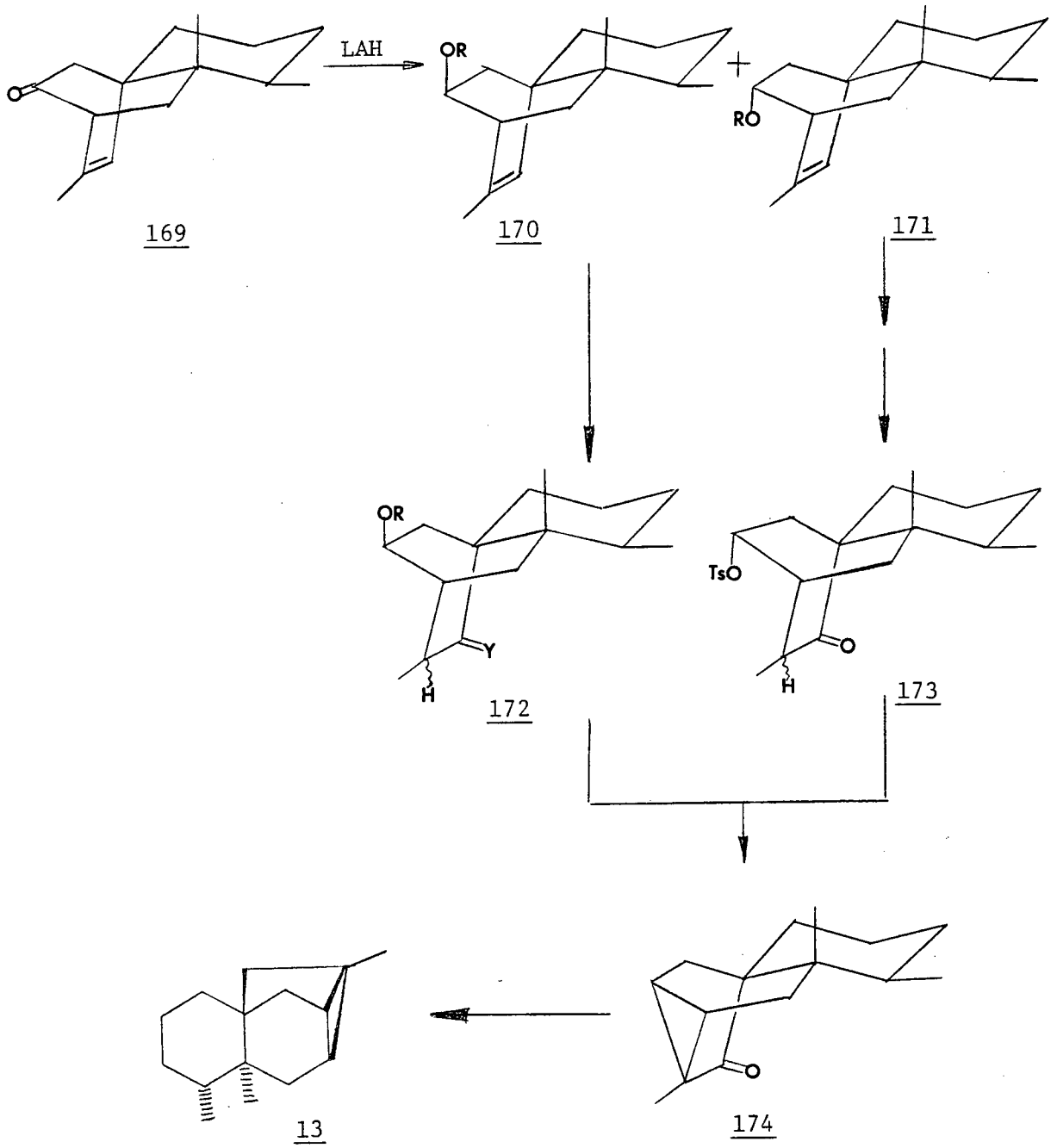
62 165



23

converted to the same mixture of epimeric keto alcohols 168. Thus treatment of the mixture of 166 and 167 with lithium aluminium hydride, followed by acid-promoted rearrangement of the resulting ketal alcohols, afforded 168 in good yield. This latter mixture of ketols was dehydrated to the tricyclic unsaturated ketone 169. This important enone underwent Huang-Minlon reduction to give a hydrocarbon identical with isoishwarane 90 prepared from isoishwarone 23.

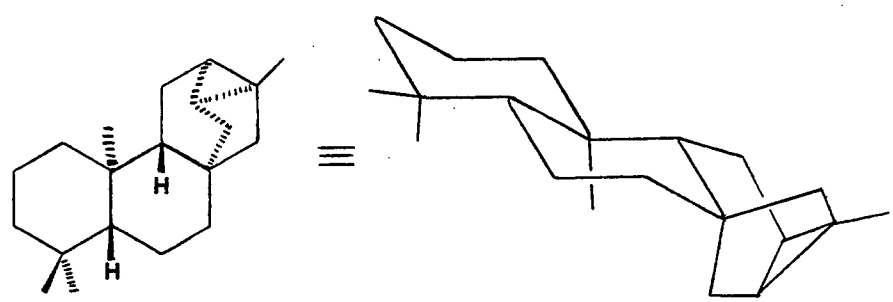
When the ketone 169 was reduced with lithium aluminium hydride, equal amounts of the epimeric alcohols 170(R=H) and 171(R=H) were obtained. The exo-alcohol 170(R=H), after being protected as the corresponding benzyl ether 170($R=PhCH_2$), was subjected to hydroboration and the resultant product



was oxidized with Jones' reagent. The keto benzyl ether 172 (R=$PhCH_2$, Y=O) thus obtained was smoothly hydrogenolized to the corresponding keto alcohol 172(R=H, Y=O). Intramolecular alkylation of the corresponding keto tosylate 172(R=Ts, Y=O) into the cyclopropyl ketone 174 was achieved in high yield

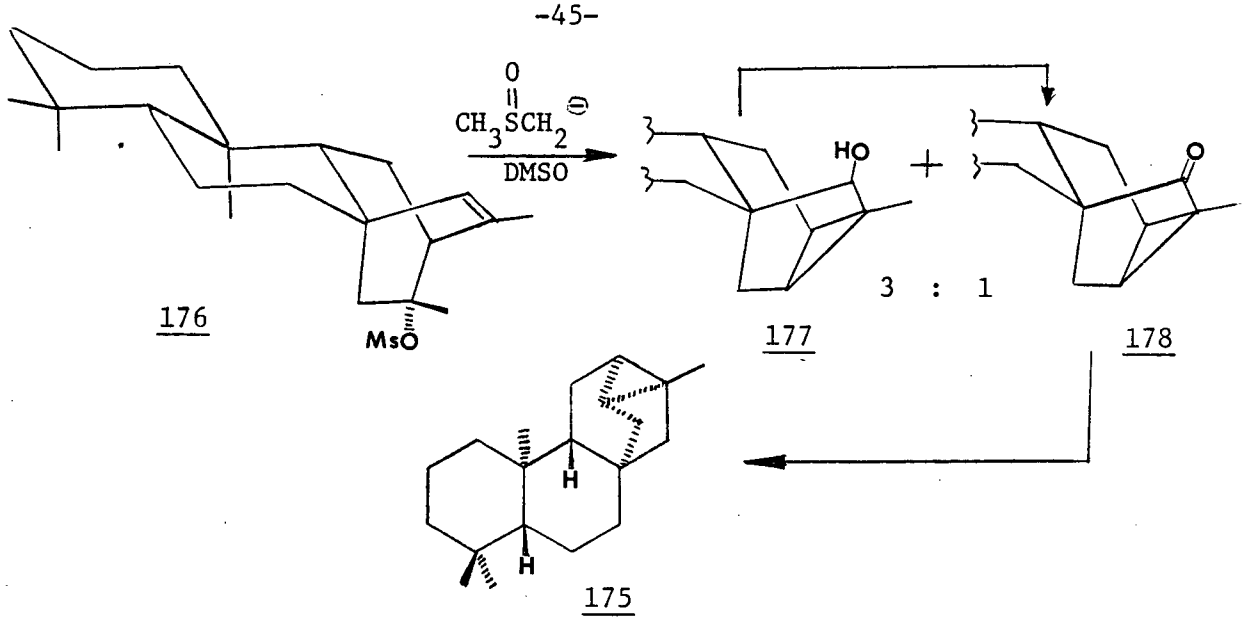
by heating the former with excess methylsulfinyl carbanion in dimethyl sulfoxide. Similarly, the endo-alcohol 171 was transformed into the same cyclopropyl ketone 174 in a somewhat lower yield. Finally, ishwarane 13 was obtained from ketone 174 by subjection of the latter to a modified Wolff-Kishner reaction.

Direct intramolecular nucleophilic displacement of the tosylate functionality of compound 173 would be mechanistically unfavourable. Therefore, Kelly proposed that the overall conversion of 173 into 174 involved a double displacement mechanism, in which the tosylate group of 173 was first replaced by the methylsulfinyl carbanion (or a molecule of solvent) and the resultant intermediate then underwent "normal" intramolecular displacement by the enolate.[34] This proposal was supported by further investigations which resulted in the total synthesis of trachylobane 175 using the same basic approach.[57]



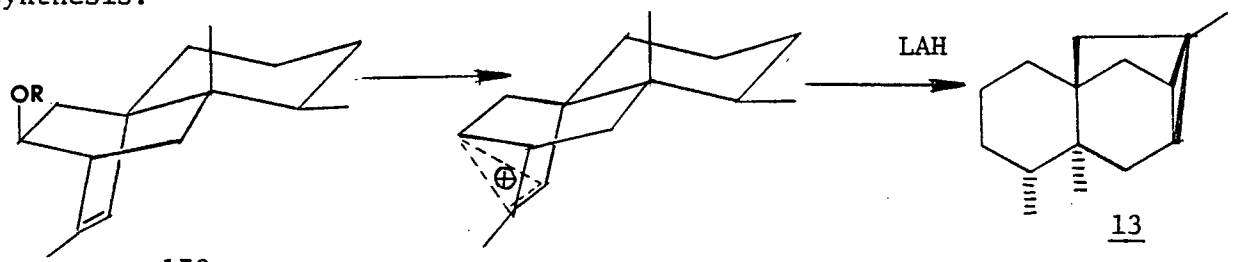
175

Solvolytic cyclization of a homoallyic mesylate has been utilized successfully by Kelly to synthesize (±)-trachylobane 175.[58] Upon heating in dimethylsulfoxide, the mesylate 176 was converted into a mixture of an alcohol 177 and the cyclopropyl ketone 178 in the ratio of approximately 3:1, respectively. Direct oxidation of the crude product mixture with Jones' reagent allowed the isolation of ketone 178, the immediate precusor of trachylobane, in high yield.



176 177 178 175

This encouraging result, however, was not applied to the synthesis of ishwarane until very recently. Based on this methodology, Kelly and Alward[59] found that ishwarane 13 could be obtained from the homoallyic alcohol 170 (R=H) by refluxing its corresponding mesylate 170 (R=Ms) in ether in the presence of lithium aluminium hydride. This process improved the overall yield of ishwarane 13 from the alcohol 170 (R=H) to 65%, as compared with the 23% overall yield obtained from the classical stepwise synthesis.[33,34]

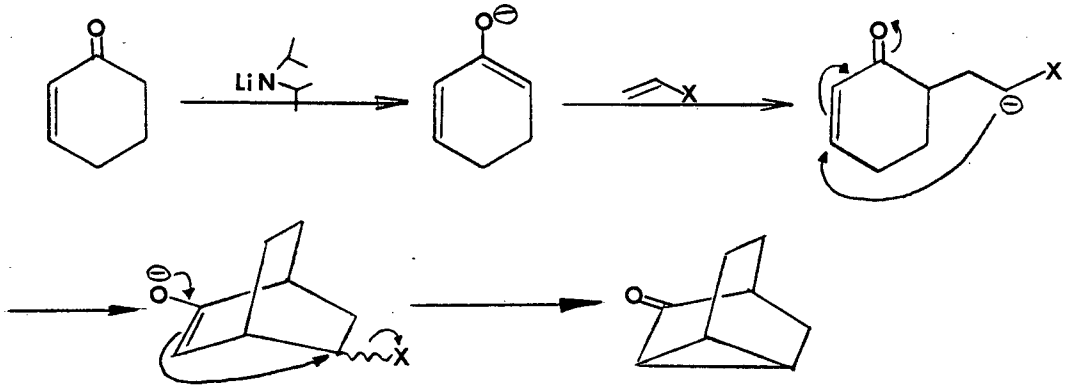


170 13

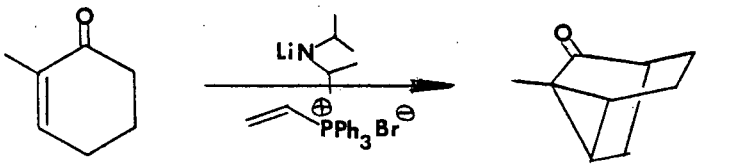
In 1975, Cory and Chan[60] reported that the tricyclo[3.2.1.$0^{2.7}$]octan-6-one system could be obtained in a one step synthesis. The success of this "bicycloannulation process" was based on the assumption that the kinetic enolate of an α,β-unsaturated cyclohexanone would react with a suitable Michael acceptor. The stabilized anion, thus formed, would undergo internal 1,4-conjugate addition to give another enolate. If

the activating group of the Michael acceptor is also a good leaving group, subsequent intramolecular displacement by the enolate would generate the desired tricyclic octanone system (see scheme 2).

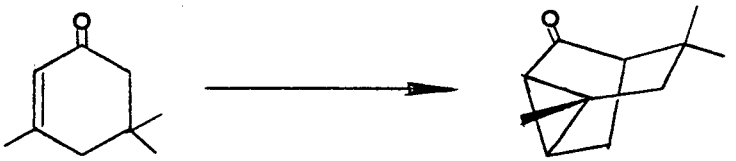
Scheme 2



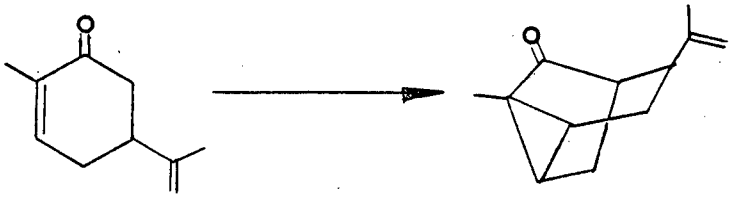
Indeed, each of the cyclohexenones 179, 180 and 181, after brief treatment with lithium diisopropylamide, reacted with vinyltriphenylphosphonium bromide to give the corresponding tricyclic ketones 182, 183 and 184 in yields of about 10, 22 and 18% respectively.



179 182

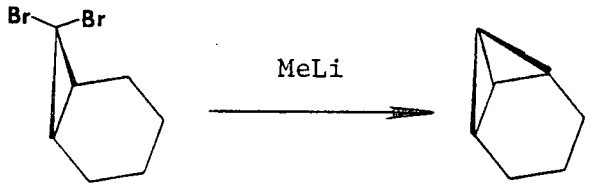


180 183



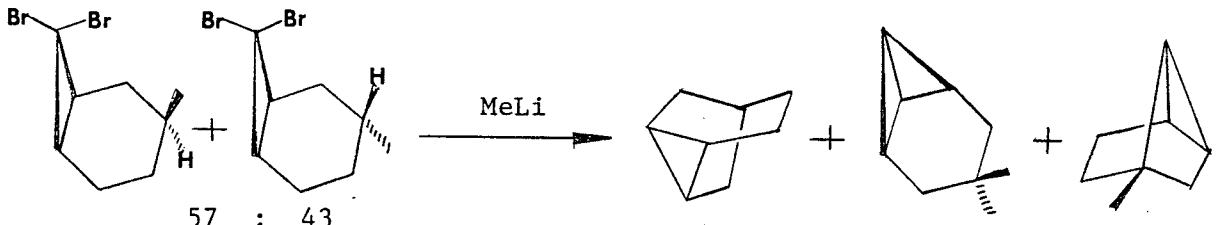
181 184

Intramolecular carbene insertion into a carbon hydrogen bond is a well known reaction. Moore and co-workers[61] discovered that the bicyclobutane 186 could be obtained as the predominant product when the dibromocyclopropane 185 was treated with an excess of methyllithium.



185 186

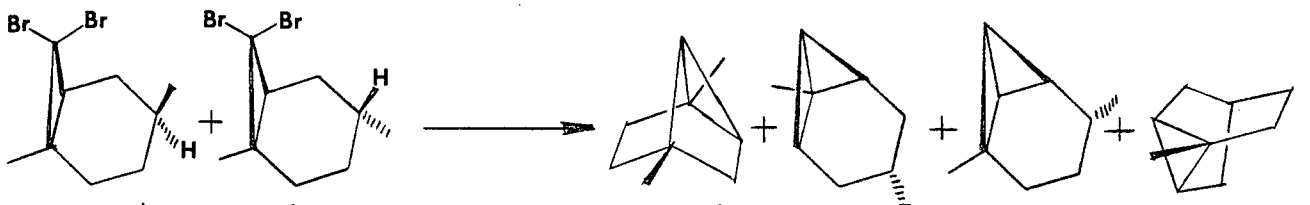
Recently, Paquette and his associates[62,63] found that tricyclo[3.2.1.$0^{2,7}$]-octane 189 could be obtained efficiently from the 7,7-dibromonorcarane 187 containing a syn methyl group at the C_4 position. On the other hand, the corresponding anti-isomer 188 gave, under the same conditions the bicyclobutane derivatives 190 and 191. However, the site selectivity decreased



57 : 43 60 : 28 : 12

187 188 189 190 191

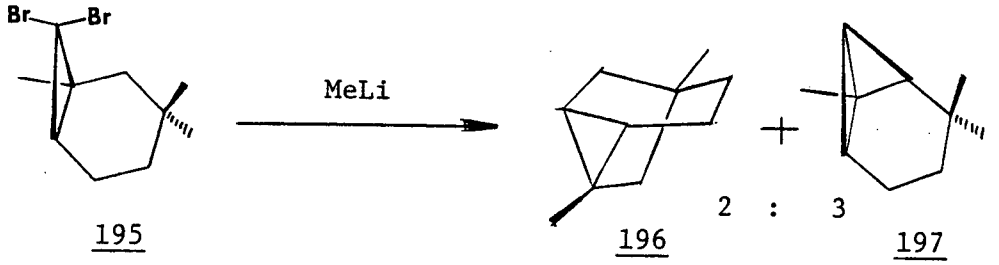
when more substituent groups were present.[63] For example, the tricyclooctane 194 became the minor product when the disubstituted dibromonorcarane 192 and its epimer 193 were used in the reaction.



4 : 6 6 : 50 : 28 : 16

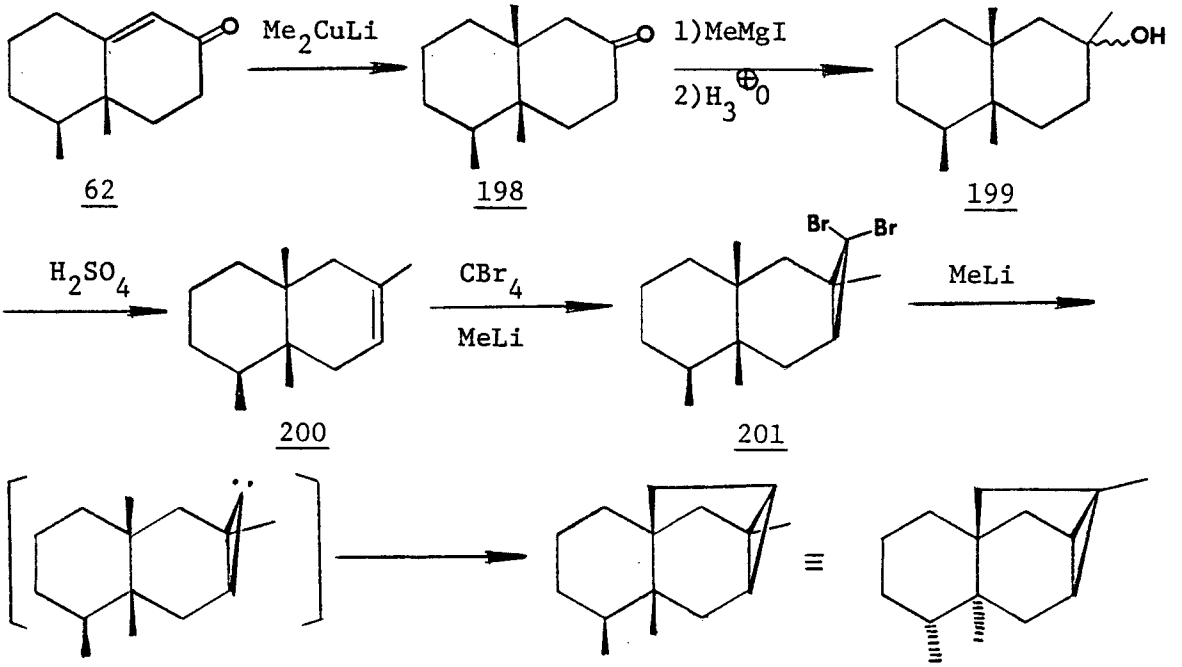
192 193 194

Independently, Cory, Burton and McLaren[64] observed that the dibromonorcarane 195, when treated with methyllithium, gave two products, 196 and 197, in the ratio of about 2:3, respectively.



195 196 197

In 1977, Cory and McLaren[65] reported a new, short synthesis of (±)-ishwarane 13 based on the type of methodology just described. In this sequence, octalone 62 was treated with lithium dimethylcuprate in order to obtain the cis-decalone 198.



62 198 199

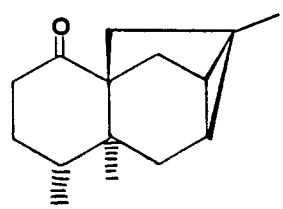
200 201

202 13

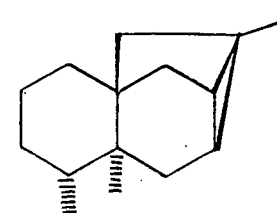
The saturated ketone was allowed to react with methyl Grignard reagent to form the tertiary alcohol 199. The bicyclic olefin 200 was isolated in good overall yield by brief exposure of alcohol 199 to mineral acid. Reaction of 200 with dibromocarbene generated from carbon tetrabromide and one equivalent of methyllithium at low temperature gave the adduct 201. The latter was not isolated but was treated immediately with another equivalent of methyllithium to form the cyclopropylidene carbene intermediate 202. This reactive intermediate underwent the expected insertion reaction to form (±)-ishwarane 13, which was isolated from the reaction products in 26% yield.

V. The Problem

Since the structures of ishwarone and ishwarane were proposed as 12 and 13 respectively, studies concerning the total synthesis of this class of sesquiterpenoids have been actively pursued. However, up to the present time, the efforts reported in the literature have been successful in achieving only the total synthesis of ishwarane 13. Therefore, the objective of the work described in this thesis was to carry out a stereoselective total synthesis of ishwarone 12.



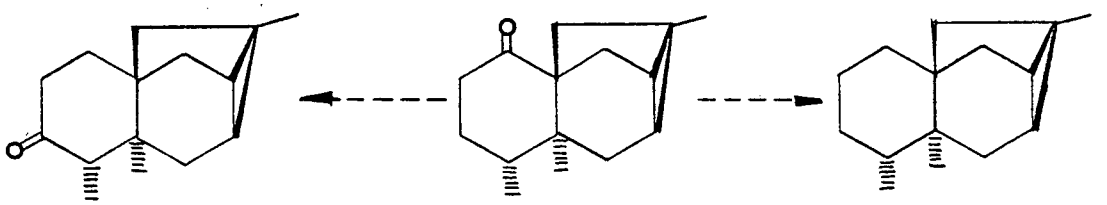
12



13

Apart from the fact that ishwarone 12 has not yet been obtained by total synthesis, one of the major advantages in choosing ishwarone (rather

than ishwarane 13) as the primary synthetic target has to do with the possibility of transforming 12 into other members of this class of sesquiterpenoids. For example, ishwarane 13 can be obtained by Wolff-Kishner reduction of the ketone functionality in ishwarone. Also, ishwarone 12 can be transformed at least in theory into 3-oxoishwarane 47 by a 1,3-transposition of carbonyl functionality via standard reactions.

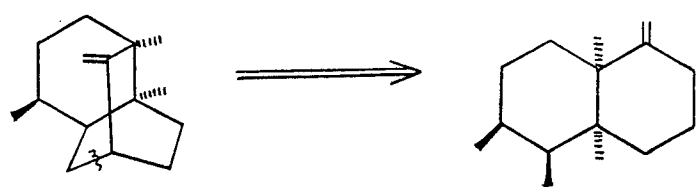


47 12 13

DISCUSSION

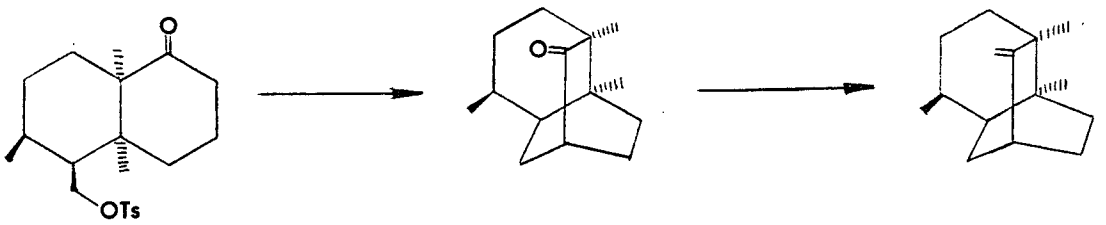
I. General

In planning a prospective pathway for the total synthesis of a complex natural product such as a polycyclic sesquiterpene, it is advantageous to study carefully a molecular model of the compound and reduce the complex framework to simpler possible precursors. The theoretical cleavage of a bond in a polycyclic skeleton will often yield an intermediate having a less complex ring structure. The cyclization of this appropriately functionalized intermediate would give back the desirable polycyclic compound. The usefulness of this approach has been demonstrated by many successful total syntheses of natural products. For example, in the synthesis of (±)-seychellene 203 reported by Piers, de Waal and Britton[66], theoretical cleavage (see 203) of the bicyclo[2.2.2]octane moiety produced a simplified bicyclic system 204. The appropriately functionalized intermediate 205 having the skeleton of 204 underwent base-promoted intramolecular



203 204

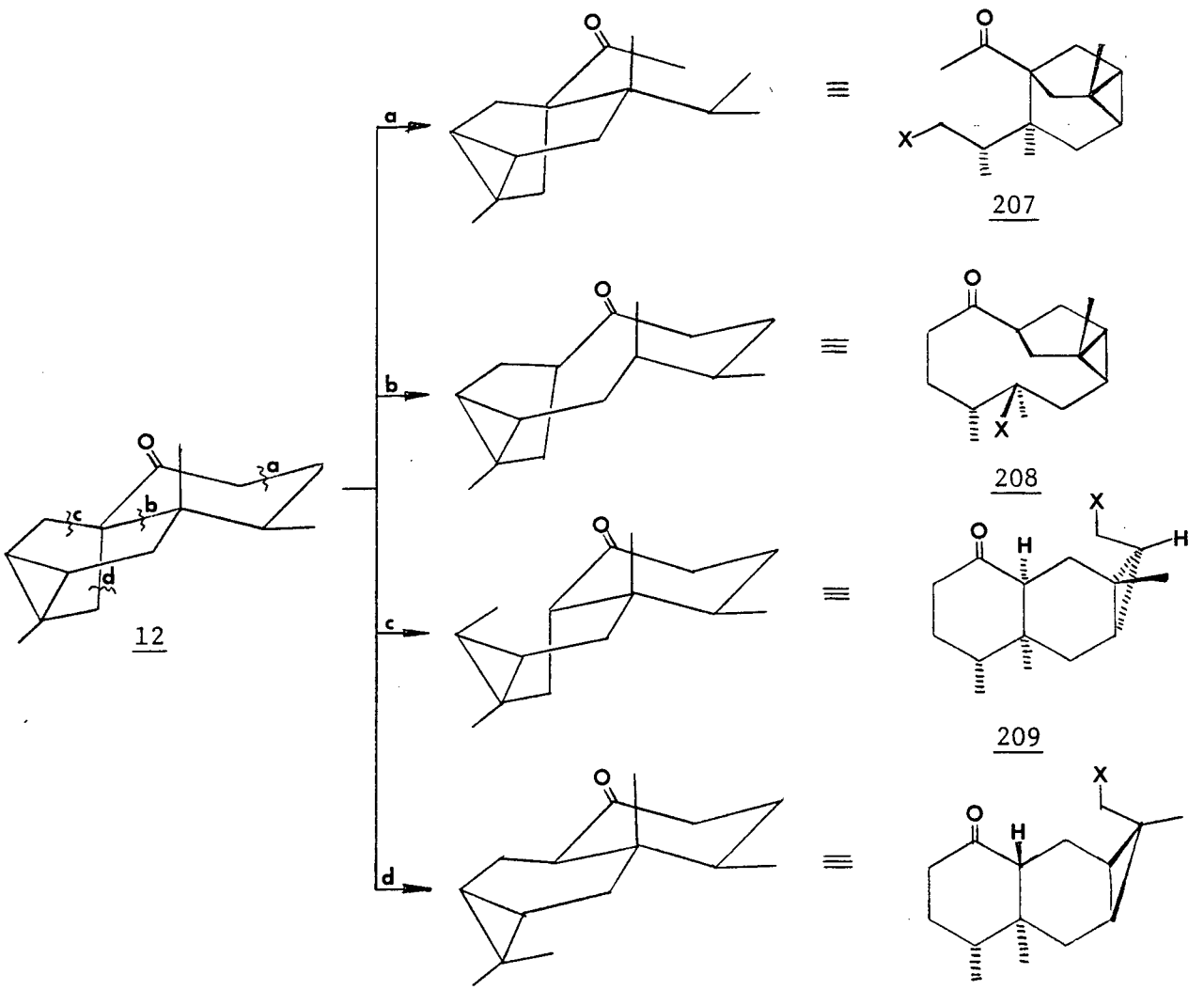
cyclization to generate the tricyclic ketone 206, which was then elaborated into (±)-seychellene by standard reactions.



205 206 203

Following this general approach, various theoretical carbon-carbon bond cleavages in ishwarone 12 were considered. Since we wished to regenerate the tetracyclic skeleton by intramolecular alkylation, only bonds in close proximity to the ketone group were taken into consideration (see Scheme 3).

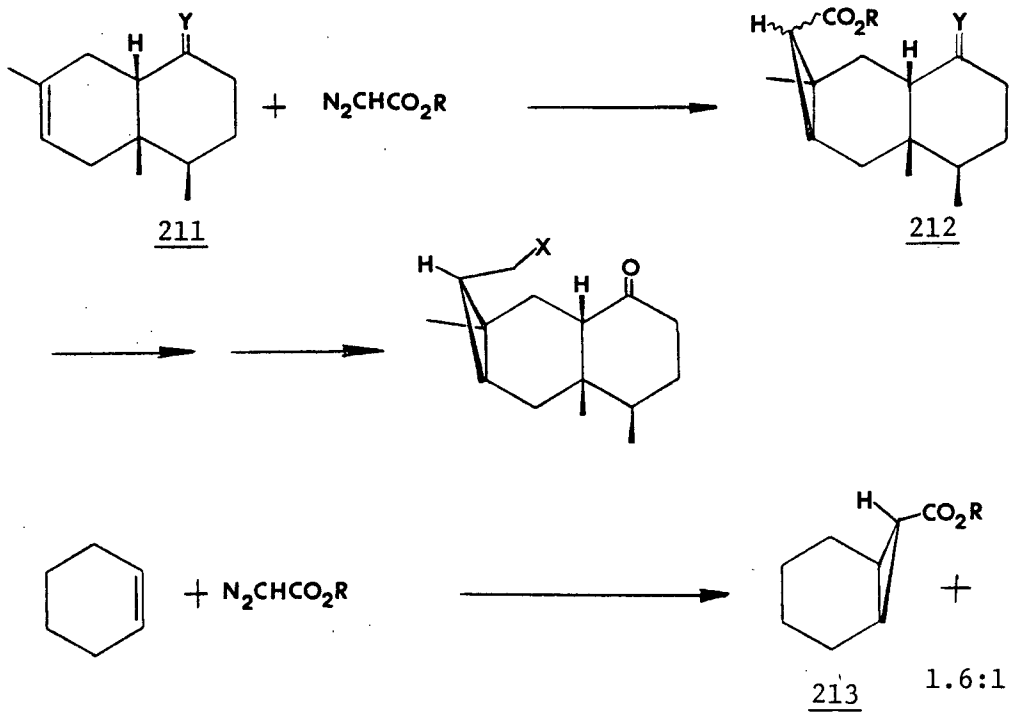
Scheme 3



12 207 208 209 210

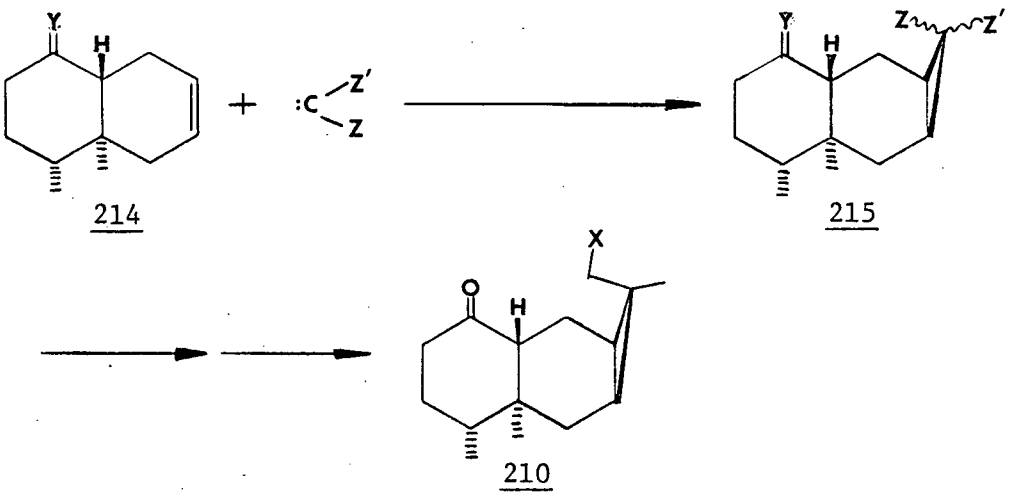
Of the four possible intermediates 207, 208, 209 and 210 obtained by theoretical breakage of bonds a, b, c and d, respectively, those with obvious structural complexity were not considered further. It was quite clear that the stereoselective syntheses of compounds of the type depicted in 207 and 208 would be quite difficult, and hence, the possible use of these intermediates in the synthesis of (±)-ishwarone 12 was not investigated.

The intramolecular cyclization of 209 seemed, at first sight, to be an attractive possibility. However, a synthetic pathway to ishwarone 12 via this intermediate was eventually excluded, mainly because the endo stereochemistry of the CH_2X group (see 209) would not be easily obtained. For example, the skeleton of 209 might be derived from the intermolecular carbenoid addition of diazoacetate to the olefin 211 (Y=O or protecting group), but the desired endo-isomer of 212 would be expected to be the minor product. For instance, cyclohexene reacted with diazoacetate to give the exo-isomer 213 as the major product.[67] Furthermore, in order

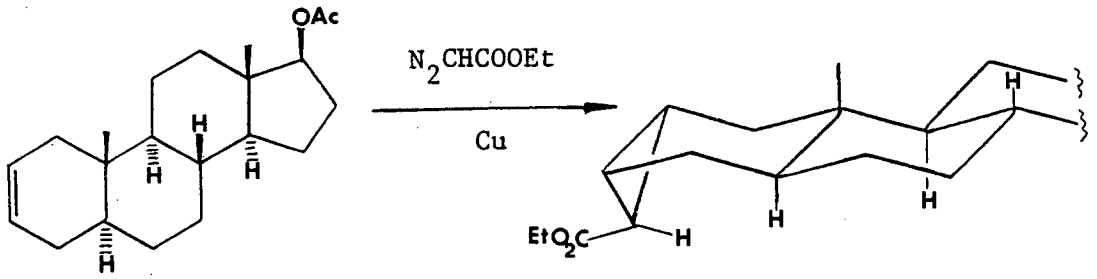


to obtain the required cis-stereochemistry between the cyclopropyl moiety and the angular methyl group, it would be necessary for the olefin 211 (Y=0 or protecting group) to have a cis-ring junction. Clearly, this stereochemical arrangement would be thermodynamically less stable than the corresponding trans-isomer. Hence, great care would have to be taken to prevent epimerization to the trans-fused isomer.

On the other hand, intermediate 210 seemed to be a better choice. Carbenoid addition to the thermodynamically favoured trans-fused olefin 214 (Y=0 or protecting group) would be expected to give the required trans-stereochemistry between the cyclopropane ring and the angular methyl group (see 215). This type of stereoselectivity has been demonstrated by the reaction between diazoacetate and 17β-hydroxyandrost-2-ene acetate 216. Only one isomer, 2α,3α-exo-carboethoxymethano-5α-androstan-17β-ol acetate 217, was isolated in about 45% yield.[68]

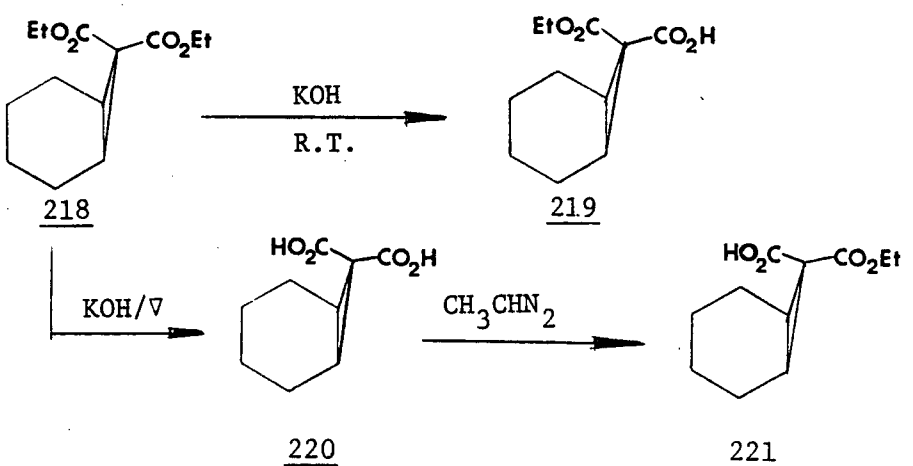


214 215 210



216 217

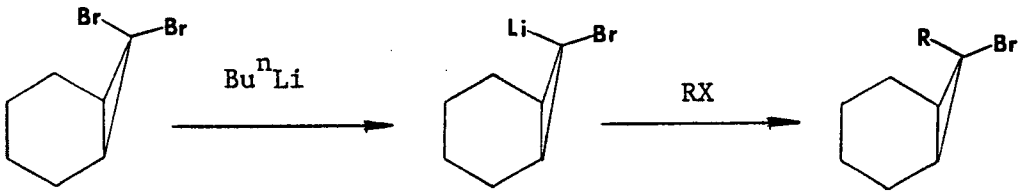
Obviously, the stereochemistry on the cyclopropane ring in 215 would be difficult to control if an unsymmetrical carbenoid ($Z \neq Z'$) was employed. This problem could be avoided by using a symmetrical carbenoid ($Z=Z'$) precursor. Assuming that steric hindrance between the endo and exo-faces of the adduct 215 would be sufficiently different to allow for selective transformation of the Z functional groups, an intermediate of the type depicted in 210 might be obtained from the adduct 215 ($Z=Z'$). Indeed, this assumption has been validated in closely related cases. For example, the two ester groups in 7,7-dicarboethoxynorcarane 218 exhibit quite different reactivities.[69] Hydrolysis of the diester with a limited amount of base at room temperature afforded only the endo half ester 219. Complete hydrolysis required much more drastic conditions, such as a large excess



218 219 220 221

of base and high temperatures. The dicarboxylic acid 220 derived from 218 reacted with diazoethane to provide only the exo half ester 221.

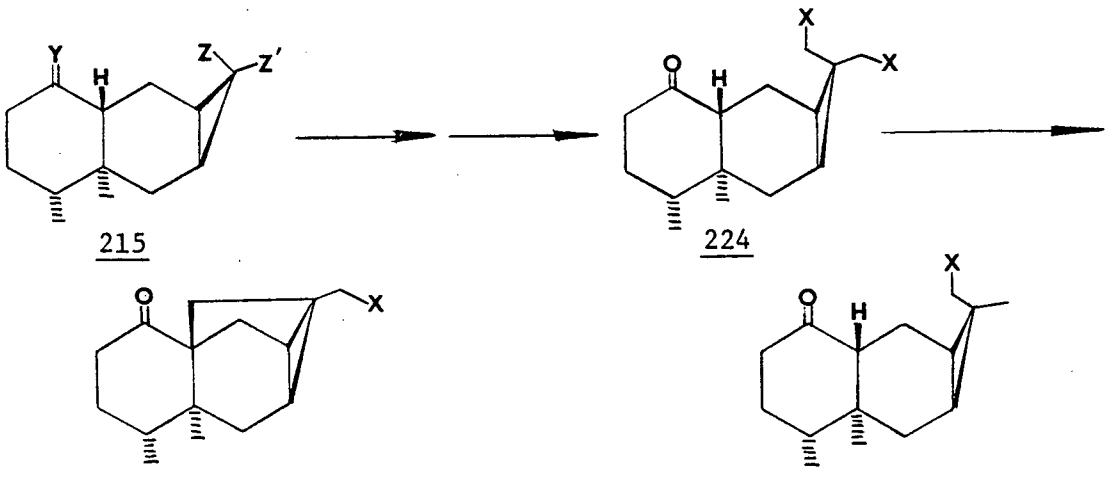
Recently, Kitatani, Hiyama and Nozaki[70,71] demonstrated that 7,7-dibromonorcarane 185 could be metalated selectively with n-butyllithium under thermodynamically controlled conditions to give the endo litho compound 222. Subsequent alkylation with reactive alkyl halides provided



185 222 223

predominately or exclusively the 7-endo-alkyl-7-bromonorcarane 223.

If the carbene adduct 215 (Z=Z′) could not be elaborated selectively into 210, it still might be possible to transform the adduct into an intermediate of general structure 224. Intramolecular cyclization of the

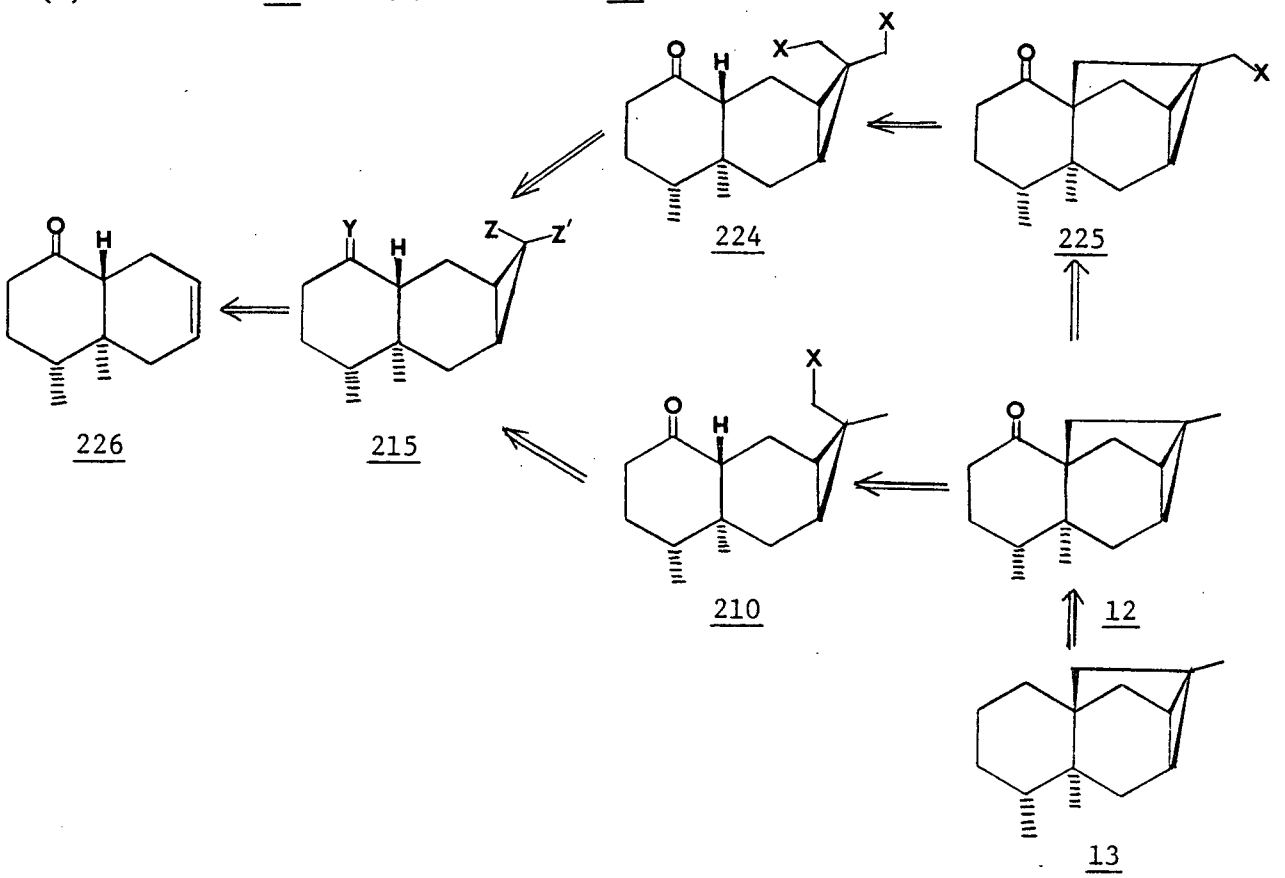


215 224 225 210

latter would provide the compound 225 with the skeleton of the ishwaranes.

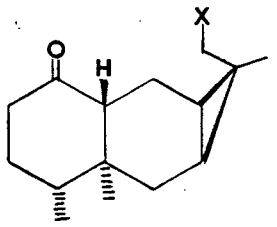
Further elaboration of functional groups would give ishwarone 12 and ishwarane 13 from this tetracyclic intermediate. This alternative would eleminate the difficulties which could arise in attempting to differentiate between the exo and endo functional groups on the cyclopropane ring.

After considering the potential versatility and availability of all of the possible precursors, intermediate 215 (Z=Z´) seemed to be the best choice for our purpose. This proposal required the stereoselective synthesis of the keto olefin 226 as the first key intermediate and the stereoselective transformation of this olefin into 210 or 225 via the carbenoid adduct 215. Indeed, the feasibility of this synthetic proposal has been demonstrated by the stereoselective total synthesis of (±)-ishwarone 12 and (±)-ishwarane 13.[72]

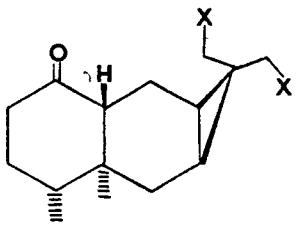


II. Attempted Synthesis of the Keto Olefin 226 via a Diels-Alder Reaction

Having considered some of the possible approaches to the synthesis of ishwarane-type sesquiterpenes, we chose to use the intramolecular cyclization of an intermediate such as 210 or 224 as the key step to form the tricyclo[3.2.1.$0^{2.7}$]octane moiety present in these natural products. The stereoselective synthesis of these intermediates would require the selective addition of a suitable carbenoid to the keto olefin 226. Therefore, our first objective was the synthesis of the bicyclic keto olefin 226.



210



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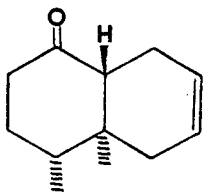
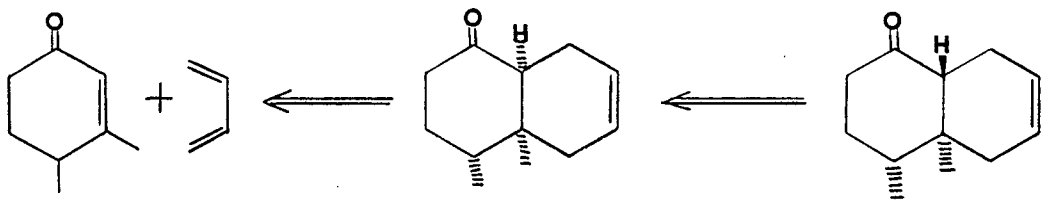


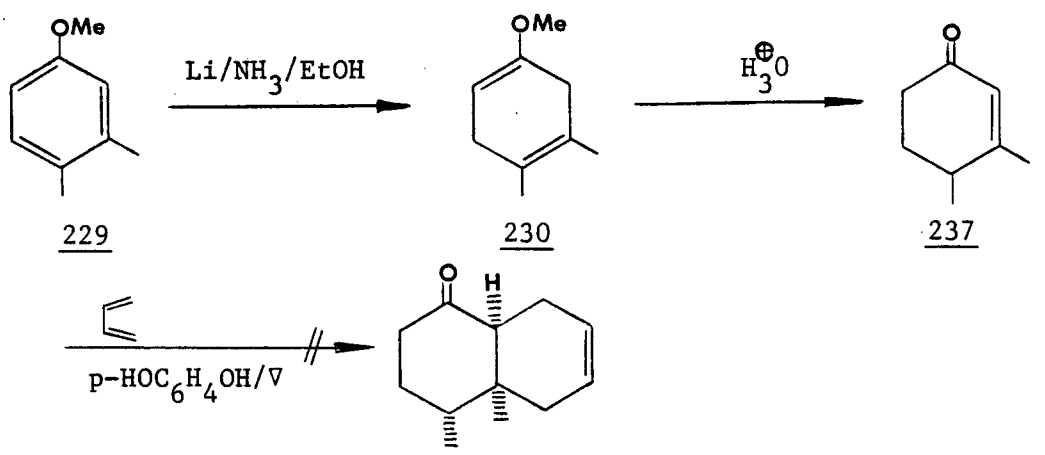
226

At the outset of our work, there was no report in the literature concerning the synthesis of the keto olefin 226 or of a closely analogous compound. The synthesis of this intermediate 226 would require unambiguous formation of the cis-vicinal dimethyl groups. From a perusal of the structural formula of this compound, one might expect that the formation of the bicyclic olefin 226 could be economically achieved by a Diels-Alder reaction between 3,4-dimethyl-2-cyclohexen-1-one 227 and 1,3-butadiene followed by epimerization of the resultant adduct 228 (cis- to trans-ring junction).



227 228 226

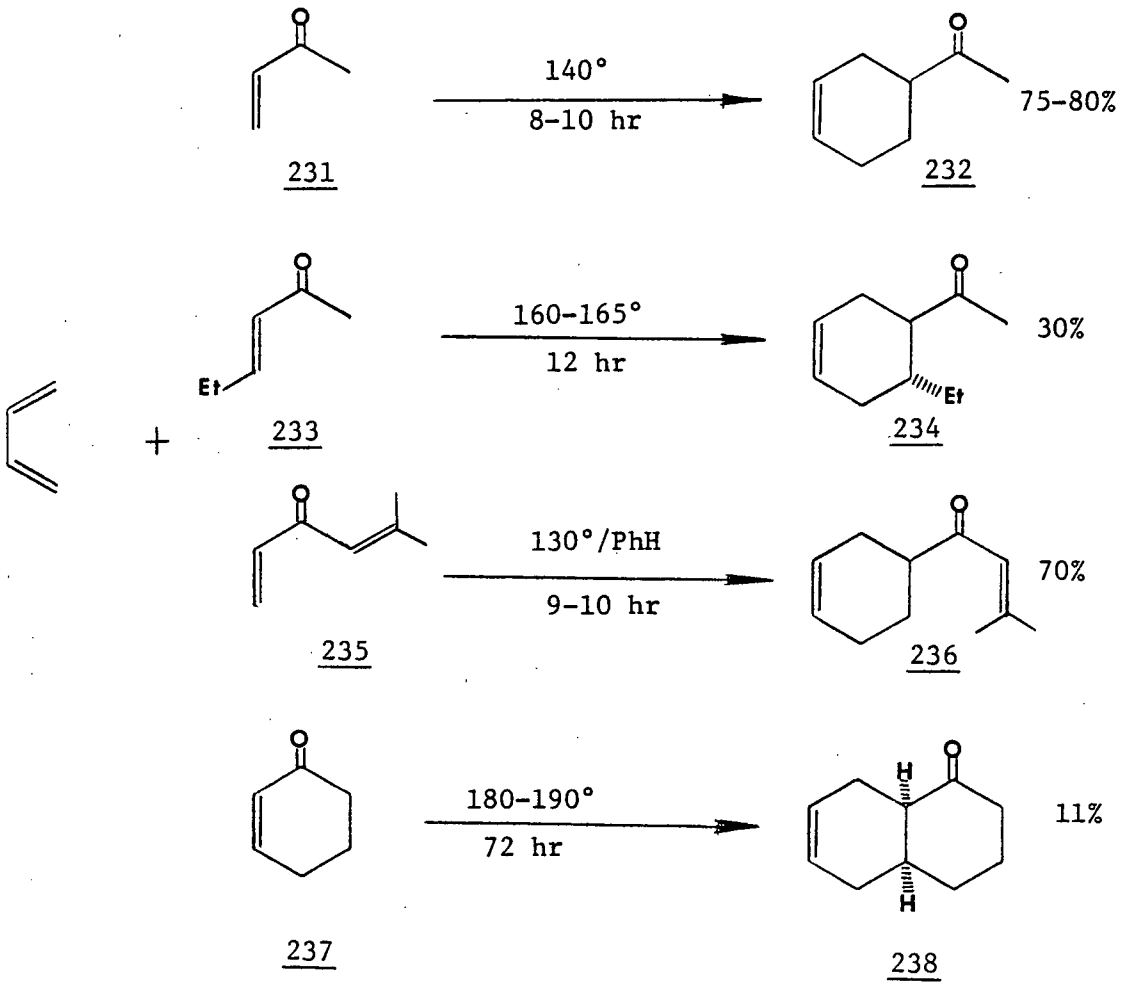
3,4-Dimethyl-2-cyclohexen-1-one 227 was obtained by Birch reduction (lithium-liquid ammonia-alcohol) of 3,4-dimethylanisole 229, followed by acid hydrolysis of the resultant intermediate 230.[73] In our hands, this enone 227 did not react with 1,3-butadiene to give the expected 1:1 adduct under different sets of conditions (various temperatures and various reaction times). From the various experiments, either recovery of the dienophile (under less drastic conditions) or extensive polymerization of starting materials (at higher temperatures and longer reaction times) was observed. The unsuccessful attempts were probably due to the low reactivity of the cyclohexenone 227 in the Diels-Alder reaction. It has been reported that the reactivity of unsaturated ketones in Diels-Alder reactions decreased significantly when alkyl or aryl substituents were present at the β-position.[74] For example, methyl vinyl ketone 231 reacted readily with 1,3-butadiene to afford the adduct



229 230 237

228

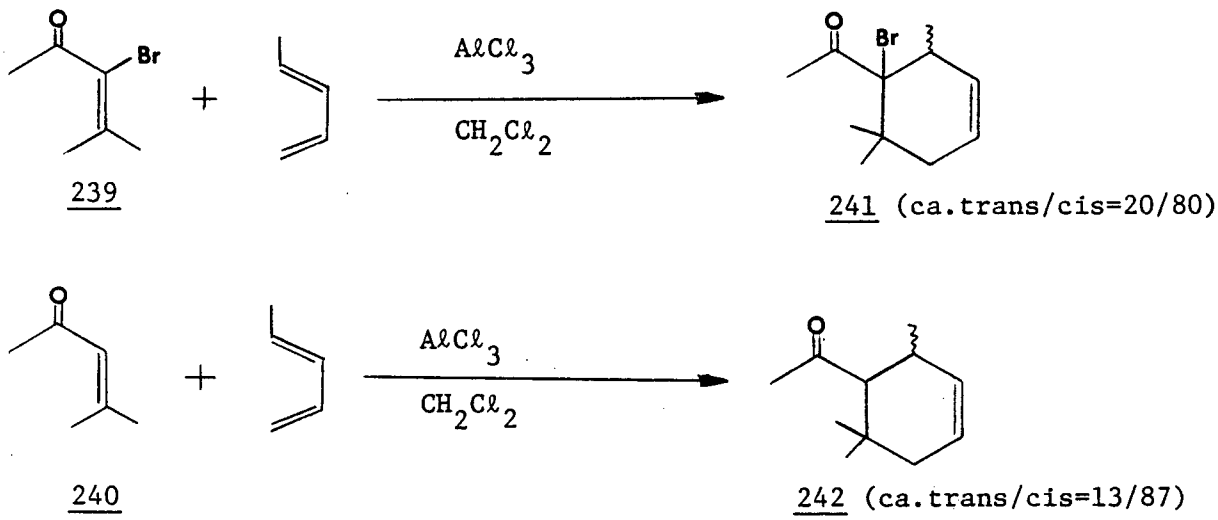
232 in 75-80% yield[75] while trans-3-hexene-2-one 233 gave the adduct 234 in only 30% yield even at higher reaction temperatures and longer reaction times.[76] Furthermore, 5-methyl-1,4-hexadien-3-one 235 reacted regioselectively with 1,3-butadiene at the non-substituted vinyl moiety to produce the 1:1 adduct 236 in 70% yield.[74] It should also be noted that the dienophilic properties of cyclic α,β-unsaturated ketones have been reported to be less significant than those of acyclic vinyl ketones.



This has been illustrated by the fact that reaction of 2-cyclohexen-1-one 237 with 1,3-butadiene gave the octalone 238 in only 11% yield.[77]

In 1973, Cookson and his colleagues[78] reported that 3-bromo-4-

methyl-3-penten-2-one 239 and 4-methyl-3-penten-2-one 240 reacted with 1,3-pentadiene in methylene chloride containing aluminium chloride to give the corresponding 1:1 adduct 241 and 242, respectively, as mixtures of stereoisomers. These results led us to investigate the

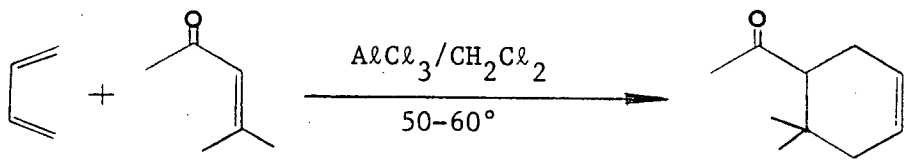


239 241 (ca.trans/cis=20/80)

240 242 (ca.trans/cis=13/87)

possibility of using Lewis acids to catalyse the reaction between 3,4-dimethyl-2-cyclohexen-1-one 227 and 1,3-butadiene.

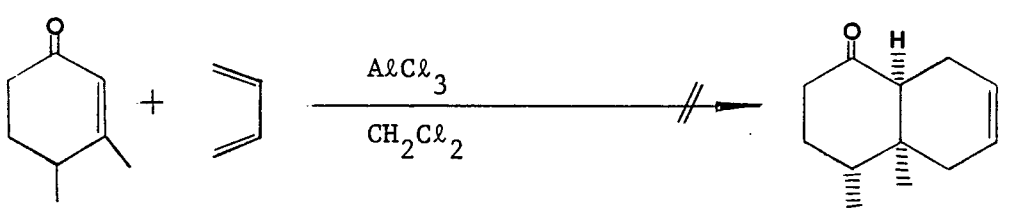
In preliminary studies, it was found that 4-methyl-3-penten-2-one 240 and excess 1,3-butadiene in methylene chloride in the presence of a catalytic amount of aluminium chloride (approximately 20-30 mole %) proceeded smoothly when the mixture was heated at 50-60° for 15-20 hours. Under these conditions, the 1:1 adduct 243 was isolated in fairly good yield. However, when the reaction was carried out at lower temperatures, only the starting material, the enone 240, was recovered.



240 243

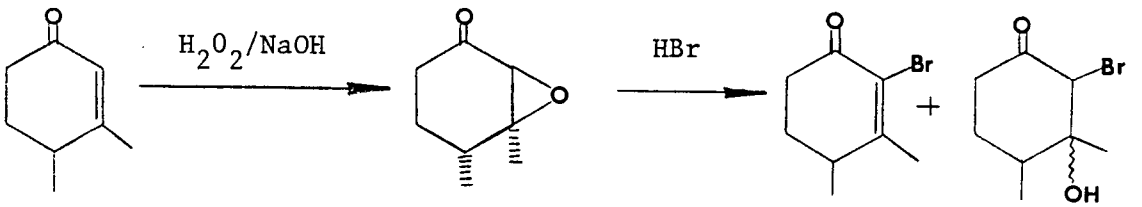
The reaction product 243 was identified by spectral data. The i.r. spectrum showed the presence of an olefinic carbon-hydrogen stretching absorption at 3060 cm^{-1} and a carbonyl stretching absorption at 1710 cm^{-1}. In the p.m.r. spectrum, the two olefinic protons of the product appeared as an unresolved multiplet at δ5.60 while the gem-dimethyl groups and the acetyl methyl group were observed as singlets at δ0.93, δ1.00 and δ2.10 respectively.

These results indicated that at least a simple β,β-disubstituted enone could react with 1,3-butadiene under favourable conditions to give the expected Diels-Alder adduct in practical yield. However, all attempts to carry out a similar reaction between 3,4-dimethyl-2-cyclohexen-1-one 227 and 1,3-butadiene were unsuccessful. Under most of the reaction conditions which were tried, the starting enone 277 was recovered. When forcing conditions (higher temperatures, increased amounts of catalyst) were used, extensive polymerization of starting materials was observed.



227 228

The possibility of using 2-bromo-3,4-dimethyl-2-cyclohexen-1-one 244 as a dienophile was also explored briefly. The synthesis of the bromo enone 244 could not be achieved satisfactorily by the sequence used in the formation of 3-bromo-4-methylpent-3-en-2-one 239 from 4-methylpent-3-en-2-one 240 (bromination of the double bond and dehydrobromination of the resulting α,β-dibromo ketone with alcoholic potassium hydroxide[79]) due to the instability and complexity of products formed in this reaction sequence. However, the desired compound was obtained in about 20% overall yield from the enone 227 via epoxidation, followed by treatment of the resultant epoxide 245 with hydrobromic acid.



227 245 244 246

By means of a standard procedure[80], the enone 227 was converted into the epoxy ketone 245 in good yield. The p.m.r. spectrum of the distilled product indicated that one isomer was obtained predominantly (ca. 9:1 by p.m.r.). The epoxy proton of the major isomer was observed as a singlet at δ2.93 while the tertiary methyl group and the secondary methyl group appeared as a singlet (δ1.42) and a doublet (δ1.08, J=7.0 Hz), respectively. On the basis of the mechanism of the reaction and the steric effect between the methyl groups ($A^{1.2}$ strain) in enone 227, the predominant epoxy ketone 245 was tentatively predicted to possess a cis-relationship

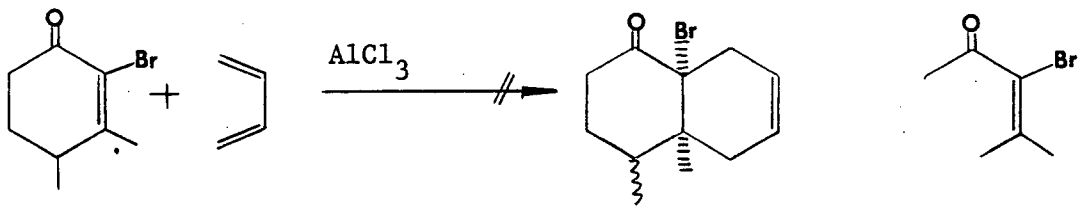
between the two methyl groups.

The mixture of the epoxy ketones was stirred with 30% hydrobromic acid in acetone to give a complex mixture of products.[81] The i.r. spectrum of this material indicated the presence of an α,β-unsaturated ketone and a saturated ketol. By means of careful column chromatography of the mixture on silica gel (elution with gradually increasing amounts of ether in benzene), the desired 2-bromo-3,4-dimethyl-2-cyclohexen-1-one 244 was obtained as a pale yellow oil. The i.r. spectrum of this material exhibited a strong α,β-unsaturated carbonyl absorption at 1680 cm^{-1} and a strong stretching band for the conjugated carbon-carbon double bond at 1600 cm^{-1}. The tetrasubstituted pattern of the double bond was established from the p.m.r. spectrum, which exhibited no signal which could be attributed to an olefinic proton. The vinyl methyl group appeared as a singlet at δ2.13. The secondary methyl group gave rise to a doublet (δ1.27) with a coupling constant of 7.0 Hz.

The i.r. spectrum of a more polar minor component eluted from the chromatography column showed a broad band at 3500 cm^{-1} (O-H stretching frequency) and strong absorptions at 1730 and 1710 cm^{-1}. The position of the absorption due to the carbonyl stretch (ca. 1730 cm^{-1}) indicated the presence of an α-bromo ketone moiety. Although it seemed reasonable to propose that the minor component was 2-bromo-3,4-dimethyl-3-hydroxycyclohexanone 246, the lack of success in attempted cycloadditions between bromo enone 244 and 1,3-butadiene (see below), precluded attempts to convert this material into the bromo enone 244.

Cycloaddition of 2-bromo-3,4-dimethyl-2-cyclohexen-1-one 244 with 1,3-butadiene was attempted in the presence of aluminum chloride with

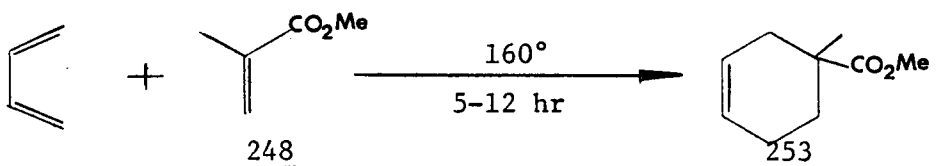
methylene chloride or benzene as solvent at different temperatures (from room temperature to 60°). However, no 1:1 adduct 247 was obtained under any of the reaction conditions used. The inability of this bromo enone



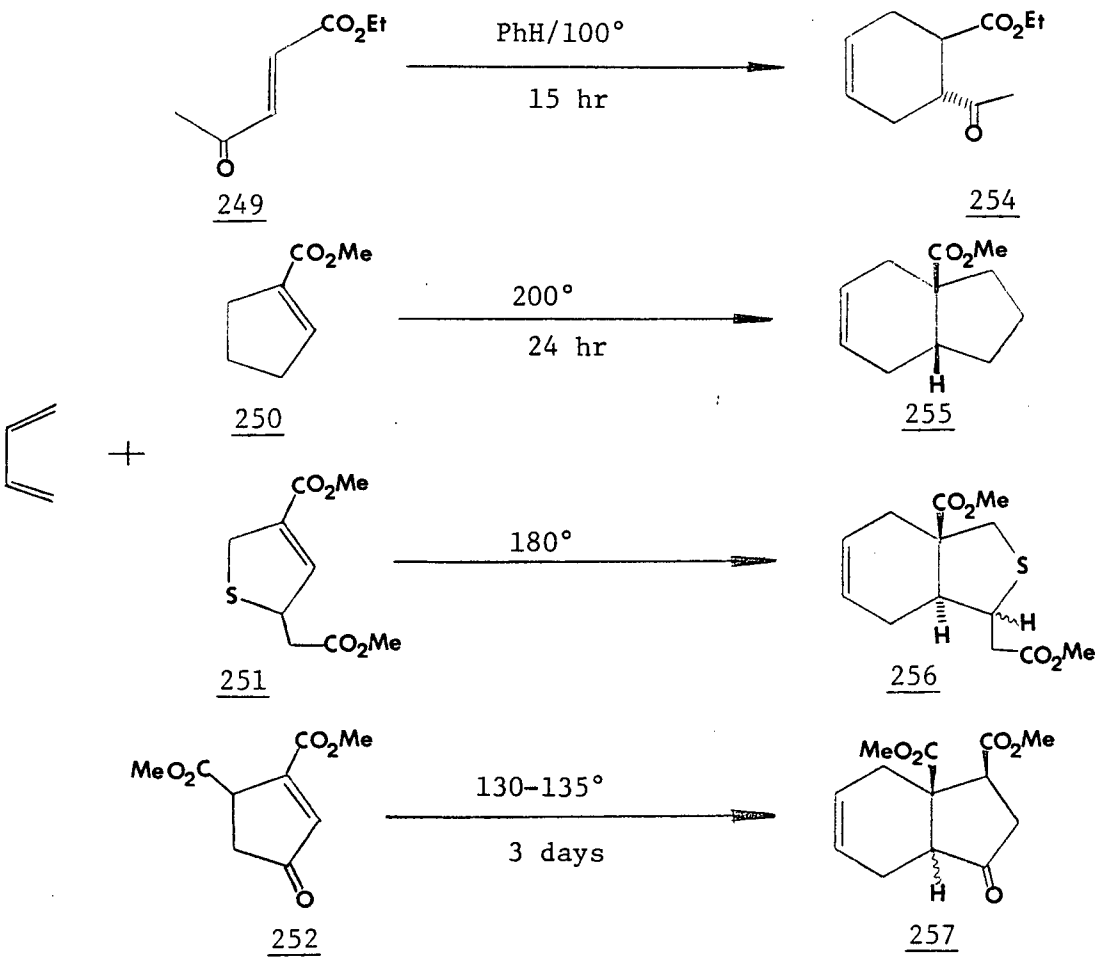
244 247 239

244 to undergo cycloaddition with the conjugated diene in comparison with 3-bromo-4-methyl-3-penten-2-one 239 was probably a reflection of the decreasing dienophilic properties of cyclic α,β-unsaturated ketones as compared with acyclic analogues.[74]

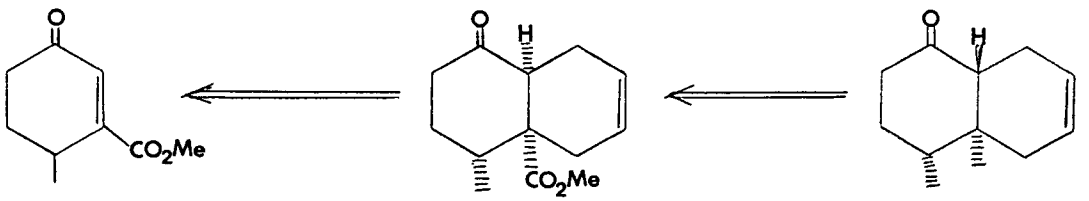
Due to the inability of β-alkyl substituted cyclic α,β-unsaturated ketones to participate in the Diels-Alder reaction with unactivated dienes, it was decided to replace this type of dienophile with a more active one. Since it had been reported that aliphatic α,β-unsaturated esters such as methyl methacrylate 248[82], ethyl β-acetylacrylate 249[83], and even the cyclic analogues 250[84], 251[85] and 252[86] readily reacted with 1,3-butadiene to give the corresponding adducts 253, 254, 255, 256 and 257, respectively, it was felt that 3-carbomethoxy-4-methyl-2-cyclohexen-1-one 258 might react with 1,3-butadiene to give the desired adduct 259 which could then be transformed



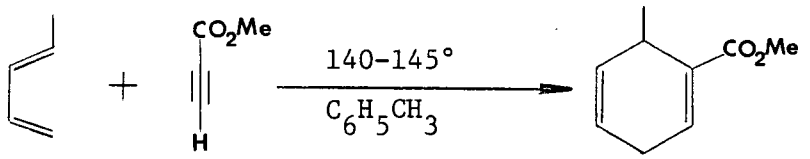
248 253



into keto olefin 226 by standard reactions.



In 1956, Petrov and Rall[86] reported that methyl propiolate 260 condensed with 1,3-pentadiene to give the unconjugated cyclic diene 261. Following their procedure, a colorless oil was obtained. The i.r. spectrum

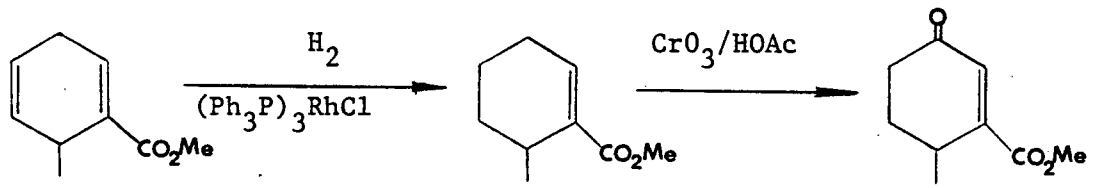


260 261

of this material exhibited a carbonyl absorption for an α,β-unsaturated ester at 1720 cm^{-1}. The unconjugated diene system was evidenced by the p.m.r. spectrum. The olefinic protons of the disubstituted carbon-carbon double bond appeared as a two-proton multiplet at δ5.82, while the vinyl proton on the double bond conjugated with the ester group gave rise to a multiplet at δ7.08. The chemical shift of this proton indicated that it was at the β-carbon of the unsaturated ester moiety. A three-proton singlet at δ3.86 was attributed to the methyl group of the methyl ester moiety, while signals at δ2.98 and δ3.32 were assigned to the allylic methylene and allylic methine protons respectively. The downfield shift of these protons as compared with the chemical shifts of ordinary allylic methylene and methine protons (at approximately δ2.3 and δ2.6 respectively) indicated that these protons were located between two unconjugated double bonds. The secondary methyl group was evidenced by a doublet at δ1.26 with a coupling constant of 7.0 Hz.

The less substituted double bond in the diene ester 261 was selectively hydrogenated with tris(triphenyl)rhodium chloride as catalyst to afford the α,β-unsaturated ester 262. The presence of the unsaturated ester functionality in compound 262 was evidenced by a carbonyl absorption at 1710 cm^{-1} and a carbon-carbon double bond stretching absorption at 1640 cm^{-1} in its i.r. spectrum. In the p.m.r. spectrum, the multiplets due to the allylic methylene and allylic methine protons of this ester had shifted upfield (δ2.18 and δ2.68,

respectively) in comparison with the analogus signals in the diene ester 261. These upfield shifts were expected since the additive effect of the second double bond had been eliminated. The only signal in the olefinic region of the p.m.r. spectrum (a one-proton triplet at δ7.06 with J=4.0 Hz) could be assigned to the β-proton of the α,β-unsaturated ester moiety. The methyl group of the methyl ester functionality appeared as a singlet at δ3.84, while the secondary methyl group exhibited a doublet at δ1.20 with a coupling constant of 7.0 Hz.

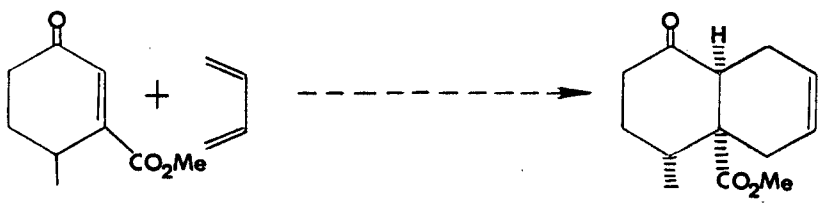


261 262 258

Allylic oxidation of the unsaturated ester 262 was attempted with a number of different oxidizing agents, such as chromium trioxide-pyridine complex[88], tert-butyl chromate[89], N-bromosuccinimide in moist dioxane[90] and chromic acid.[91] In most of the cases, the results were unsatisfactory. However, the keto ester 258 could be obtained in acceptable yield by addition of excess chromium trioxide (about three equivalents) in portions to a solution of the unsaturated ester 262 in glacial acetic acid containing small amounts of water. It was advantageous to stop the reaction when the ratio of the starting ester 262 to the keto ester 258 had reached about 1:1. Addition of further amounts of chromium trioxide to force the reaction toward completion generally resulted in the generation of complex product mixtures and low recovery of material. The keto ester 258, a pale yellow oil,

could be isolated in approximately 50% yield (based on unrecovered starting material) by subjection of the crude product mixture to molecular distillation and column chromatography on silica gel, with a 4:1 mixture of petroleum ether-ether being used as the eluting solvent. The presence of the γ-oxo-α,β-unsaturated ester functionality in compound 258 was evidenced by the strong carbonyl absorptions at 1685 and 1720 cm^{-1} in the i.r. spectrum. In the p.m.r. spectrum, the olefinic proton appeared as a singlet at δ6.58. The sharp singlet at δ3.78 was associated with the methyl ester while the multiplet at δ2.96 could be assigned to the allylic methine proton. The three-proton doublet at δ1.24 with coupling constant of 7.0 Hz was attributed to the secondary methyl group.

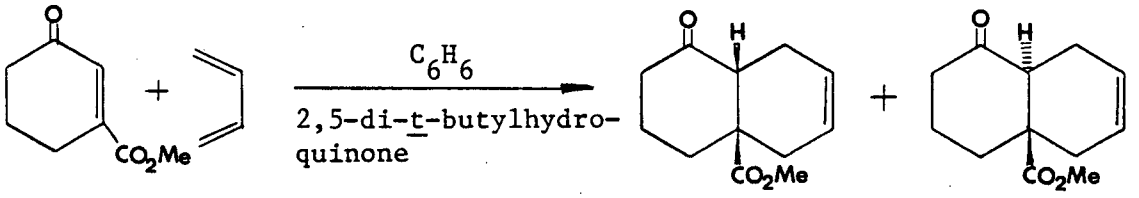
With the keto ester 258 in hand, the next step involved the Diels-Alder reaction between this compound and 1,3-butadiene. It was hoped that the diene would, for steric reasons, attack 258 from the face opposite to the secondary methyl group to produce the bicyclic keto ester 259 in which the methyl group and the carbomethoxy moiety would be cis to one another.



258 259

To the best of our knowledge at the time when we began this investigation, there was no previous report regarding the attempted use of the cyclic keto ester 258 or a closely related analog in Diels-Alder reaction. However, during the time that our study was underway, Torii, Kumitomi and Okamoto[92] reported that the keto ester 263 underwent a Diels-Alder reaction

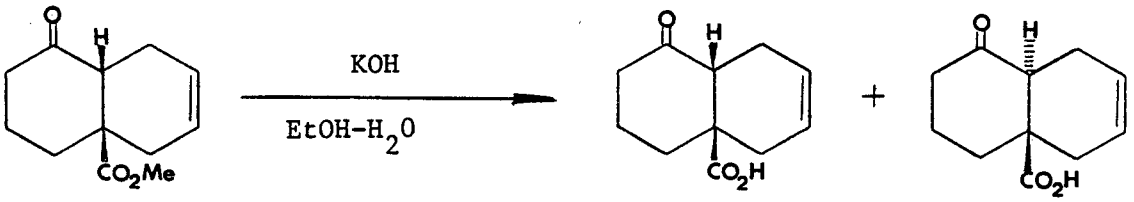
with 1,3-butadiene at 130-140° to afford exclusively the cis-adduct 264. When the reaction was carried out at temperatures above 150°, a



263 264 265

temperature	ratio of 264/265
130-140°	100:0
>150°	3:1

mixture of the cis and trans products 264 and 265 (ca. 3:1) was isolated. These workers also demonstrated that the cis-adduct 264, upon hydrolysis with wet alcoholic potassium hydroxide, provided a mixture of the cis and trans keto acids 266 and 267 in which the trans-isomer 267 predominated (266:267≈1:4).



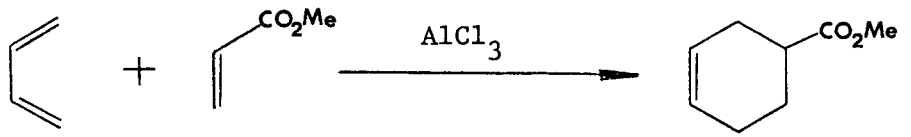
264 266 267

This result clearly implied that the trans-isomer 267 was thermodynamically more stable than the cis-isomer 266.

In our hands, the thermal cycloaddition of the keto ester 258 with 1,3-butadiene proved to be very sluggish. Treatment of the dienophile 258 with excess 1,3-butadiene in the presence of a catalytic amount of hydroquinone

in a sealed tube for three to four days at temperatures up to approximately 160° resulted only in recovery of the keto ester 258 and/or excessive polymerization of starting materials. The use of still more forcing conditions (e.g. heating a mixture of 258 and 1,3-butadiene at 180-200° in a sealed bomb with a glass lining for four days) also failed to produce any of the desired Diels-Alder product.

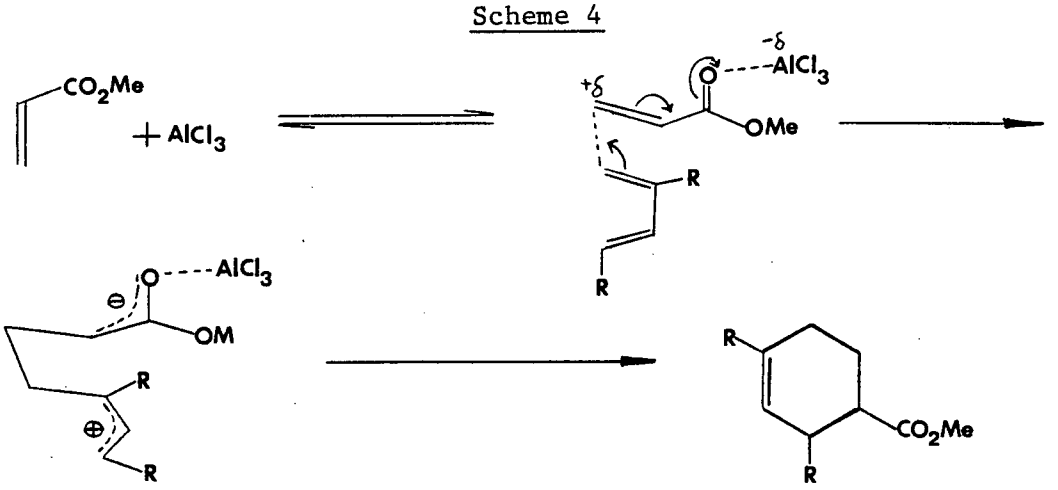
In the sixties, Inukai and his colleagues[93] showed that methyl acrylate reacted with 1,3-butadiene very rapidly in the presence of anhydrous aluminum chloride to give the corresponding Diels-Alder product. They reported that when the reaction was carried out for three hours at 10-20°, methyl 3-cyclohexene-1-carboxylate 268 could be obtained in 65% yield. However, without aluminum chloride as catalyst, not a trace of the product was detected after 96 hours at room temperature. With regards to



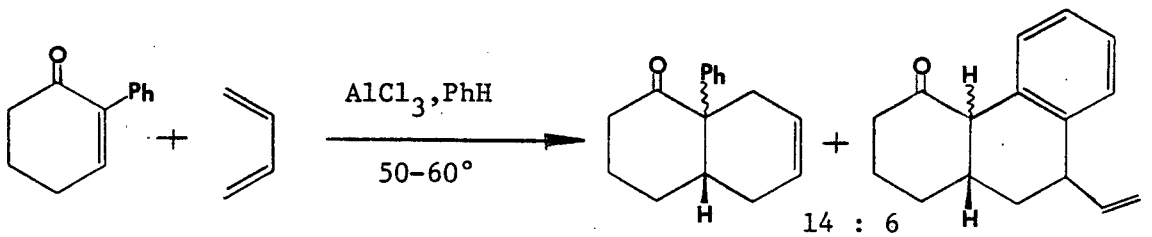
268

reaction mechanism, Inukai and Kojima[94,95] postulated that the catalyst first coordinated with the electron withdrawing group of the dienophile and that this complex then reacted with the diene in a stepwise ring formation involving a very short-lived zwitterionic intermediate (see Scheme 4). This type of stepwise mechanism was further supported by the

Scheme 4



observations of Thompson and Melillo[96] in a study of the catalyzed reaction between 1,3-butadiene and 2-phenyl-2-cyclo-hexen-1-one 269. Along with the expected adduct 270 (mixture of cis and trans-isomers),

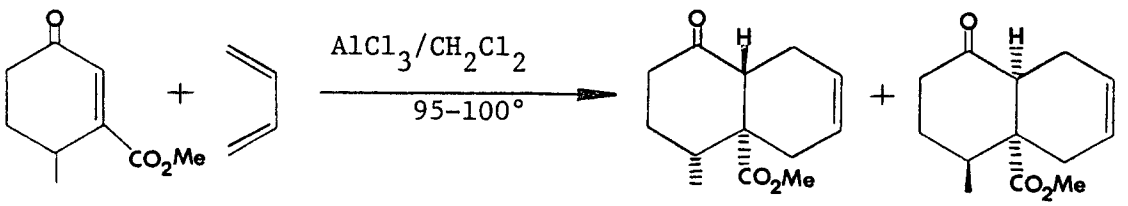


269 270 271

these workers also isolated the tricyclic ketone 271 (mixture of isomers). The latter was proposed to arise from the internal trapping of the zwitterionic intermediate by electrophilic attack on the phenyl moiety.

Encouraged by the results observed by Inukai's group on the catalytic Diels-Alder reaction[93], we chose to explore the effect of a Lewis acid on the reaction between the keto ester 258 and 1,3-butadiene. Unfortunately, it was found that no reaction occurred when butadiene was bubbled into a methylene chloride solution of the keto ester-aluminium chloride complex for three to four hours at room temperature. Similarly, when a methylene

chloride solution of the dienophile-aluminum chloride complex was saturated with 1,3-butadiene, and then kept at room temperature for three to four days, no Diels-Alder product was produced. However, when a solution of the keto ester 258 in methylene chloride was heated at 95-100° with excess 1,3-butadiene in the presence of aluminum chloride in a sealed tube for one day, a mixture of 1:1 Diels-Alder adducts was isolated from other polymeric products. On the basis of a g.l.c. analysis, the Diels-Alder adduct mixture consisted of two major products (1:1 ratio), which were later shown to be 272 and 273. The yield of this mixture was found to vary significantly (from 20-50% yield) with the amount of Lewis acid as well as the purity of the catalyst. The best results were obtained by using an approximately 2:1 ratio of the keto ester 258 to freshly



258 272 273

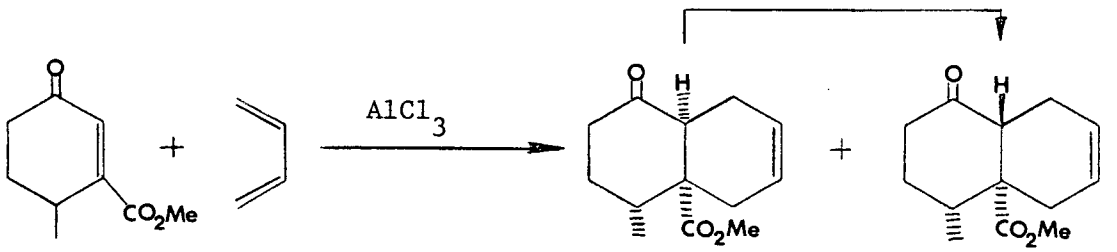
sublimed aluminum chloride. Other Lewis acids such as boron trifluoride etherate and copper tetrafluoroborate were also tried, but the results were unsatisfactory. Boron trifluoride etherate gave the same major products (also in a ratio of approximately 1:1), but with more side products and lower yields. Although copper tetrafluoroborate was reported by Corey[97] to be an effective catalyst for Diels-Alder reactions, it seemed to be ineffective in our case. At room temperature, no reaction was observed after one day, while at 60-70°, excessive polymerization of

starting materials was observed.

The physical and spectral properties of the 1:1 Diels-Alder adduct mixture were in agreement with structures 272 and 273. Thus the i.r. spectrum showed a strong olefinic carbon-hydrogen stretching absorption at 3080 cm^{-1} and a broad carbonyl absorption ($\sim$1720 cm^{-1}) for the ester and cyclohexanone-type carbonyl groups. This mixture of isomers was partially separated by a careful gradient column chromatography over silica gel, with mixtures of petroleum ether and ether being used as eluting solvent. The keto ester 272 was obtained as a colorless oil which crystallized upon standing. Recrystallization from petroleum ether gave pure white needles (m.p. 96-97°). In the p.m.r. spectrum of this material, the olefinic protons appeared as a multiplet at δ5.68 while the methyl group of the ester functionality gave rise to a singlet at δ3.62. The bridgehead proton was observed as an unresolved multiplet at δ2.88-3.06. A doublet at δ0.99 with a coupling constant of 6.0 Hz was attributed to the secondary methyl group.

Isomer 273 was very difficult to purify. It was eventually obtained from the above-mentioned column chromatography as colorless oil containing a small amount of the isomer 272 as an impurity. By comparing the p.m.r. spectrum of the keto ester 272 with that derived from this material, it was possible to assign the proton resonances of the isomer 273. Although the spectrum of the latter was very similar to that of compound 272, there were small differences. The vinyl protons of 274 gave rise to a signal at δ5.60 (broad doublet) and the secondary methyl group produced a doublet (J=6.0 Hz) at δ0.89. The methyl group of the ester functionality gave rise to a three-proton singlet at δ3.74 and the bridgehead proton produced an unresolved doublet of doublets at δ3.17.

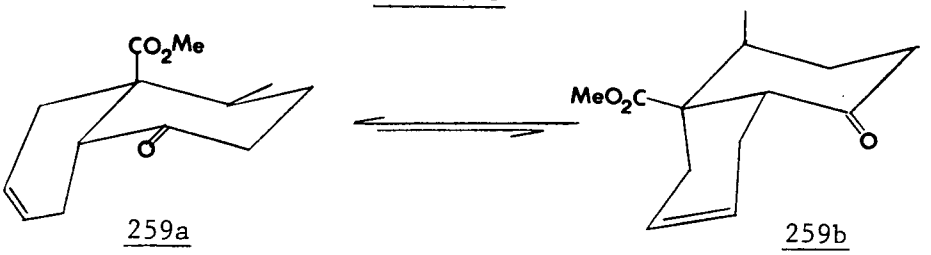
At this point, the stereochemistry of both of the Diels-Alder adducts 272 and 273 remained unknown. It had been expected, on the basis of the mechanism of the Diels-Alder reaction and of steric effects associated with the secondary methyl group, that 1,3-butadiene would attack the keto ester 258 from the less hindered face (away from the secondary methyl group) to give the all cis compound 259 as the initial product. Perhaps, under the reaction conditions, this primary product could undergo partial (or complete) epimerization to afford the trans keto ester 272 as another possible major component in the mixture.



258 259 272

On the basis of conformational analyses of structures 272 and 259 (see Scheme 5), it was expected that the trans-isomer 272 should be

Scheme 5



259a ⇌ 259b

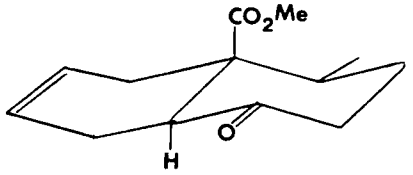
259a

1 gauche COOMe-CH_3
1 gauche CH_2-CH_3
1 syn-axial COOMe-H
1,3-diaxial COOMe-sp^2(>=0)
2 syn-axial CH_2-H
1,3-diaxial CH-sp^2(>=<)

259b

1 gauche COOMe-CH_3
2 syn-axial CH_3-H
1 syn-axial CH_2-H
1,3-diaxial CH_2-sp^2(>=0)
1 syn-axial COOMe-H
1,3-diaxial COOMe-Sp^2(>=<)
1,3-diaxial sp^2(>=0)-sp^2(>=<)

259b-259a* = (2 syn-axial CH_3-H
+ 1,3-diaxial sp^2(>=0)-sp^2(>=<) -
(1 gauche CH_2-CH_3 + 1 syn-axial CH_2-H)
≃ [1.8-(0.8+0.9)]Kcal/mole
≃ 0.1 Kcal/mole



272

1 gauche COOMe-CH_3
1 gauche CH_2-CH_3
2 syn-axial COOMe-H
1,3-diaxial COOMe-sp^2(>=0)
1,3-diaxial COOMe-sp^2(>=<)

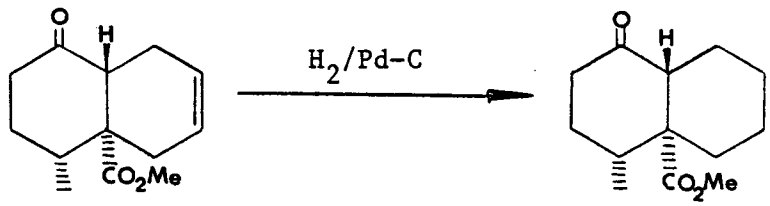
259b-272 = (2 syn-axial CH_2-H)
-(1 syn-axial COOMe-H)
= (1.8 - 0.55)Kcal/mole
= 1.25 Kcal/mole

---

* The conformational energy associated with a 1,3-diaxial interaction between two Sp^2 centers (>C=O and >C=C<) was assumed to be small and negligible.

thermodynamically more stable than the cis-isomer 259 and should therefore be the predominant isomer under epimerization conditions. Therefore the crystalline isomer 272 was subjected to equilibriation by treatment with sodium methoxide in dry methanol. After five hours at reflux, only the starting material was recovered. This indicated that the compound probably possessed a trans-ring junction. However, due to the ambiguity associated with estimating the effect of the double bond in the conformational analysis, it was felt to be advantageous to remove the double bond in order to simplify the analysis.

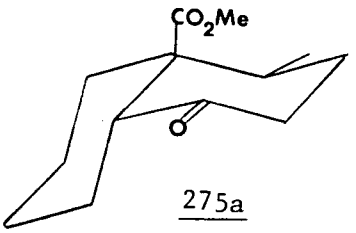
Upon hydrogenation of compound 272 in the presence of palladium-on-carbon, the decalone 274 was obtained as white needles, after recrystallization from petroleum ether. This crystalline product exhibited physical properties in accord with the structure proposed. In the i.r. spectrum, the carbonyl stretching absorptions of the ester group and the ketone functionality appeared at 1720 and 1710 cm^{-1}, respectively. The p.m.r. spectrum of 274 showed no signals due to olefinic protons. The sharp singlet at δ3.60 was attributed to the methyl group of the ester moiety, while the doublet (J=6.0 Hz) at 0.93 was assigned to the secondary methyl group.



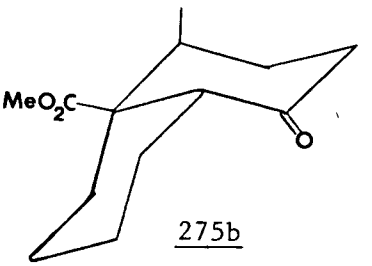
272 274

The decalone ester 274 was subjected to epimerization conditions by treatment with sodium methoxide in hot methanol. After the solution had been refluxed for five hours, the only compound isolated possessed a g.l.c. retention time identical with that of the starting material. Indeed, the i.r. and p.m.r. spectra of this component were identical with those of the starting material, decalone 274. On the basis of conformational analyses (see Scheme 6), it could be seen that the trans-decalone 274 should be considerably more stable than the cis-decalone 275, and equilibration should thus favour the former compound. On this basis, it was concluded that the decalone 274 and, in turn, the unsaturated keto ester 272, must possess trans-fused ring systems.

Scheme 6



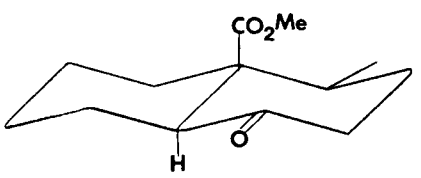
275a



275b

1 gauche COOMe-CH_3
1 gauche CH_2-CH_3
1 syn-axial COOMe-H
1,3-diaxial COOMe-sp^2(>=0)
2 syn-axial CH_2-H
1 syn-axial CH-H

1 gauche COOMe-CH_3
2 syn-axial CH_3-H
2 syn-axial COOMe-H
1 syn-axial CH_2-H
2 1,3-diaxial CH_2-sp^2(>=0)



274

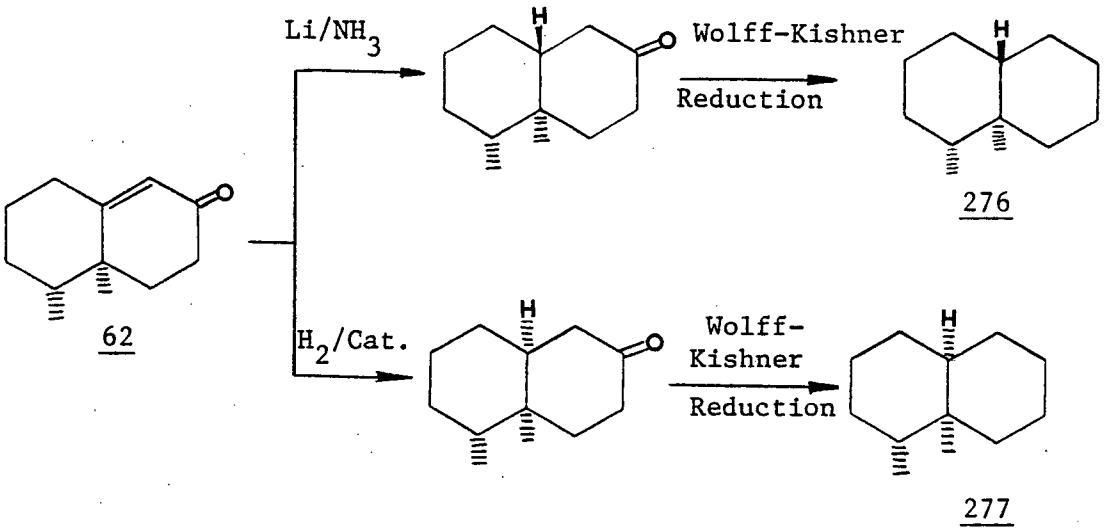
1 gauche COOMe-CH_3
1 gauche CH_2-CH_3
3 syn-axial COOMe-H
1 1,3-diaxial COOMe-sp^2(>=0)

275b-275a = (1 syn-axial COOMe-H
+ 1,3-diaxial CH_2-sp^2(>=0)
- (1 gauche CH_3-CH_2)
= (0.55 + 0.35 - 0.8) Kcal/mole
= 0.1 Kcal/mole

275a - 274 = (2 syn-axial CH_2-H
+1 syn-axial CH-H) -
(2 syn-axial COOMe-H)
= (3 x 0.9 - 1.1) Kcal/mole
= 1.6 Kcal/mole

At this point, the stereochemical relationship between the secondary methyl group and the angular ester group in compound 272 and 275 was not yet defined. However, in previous studies in our laboratory, the decalins 276 and 277 had been prepared unambiguously from the octalone 62[98] (see Scheme 7). Therefore, correlation

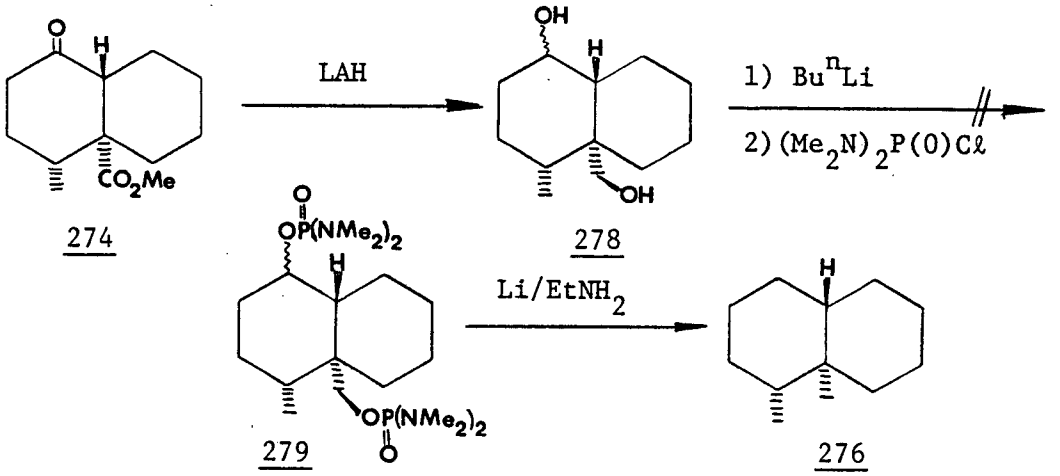
Scheme 7



of the keto ester 274 with the decalin 276 would provide unambiguous evidence regarding the relative stereochemistry of the methyl group and the ester functionality in 274.

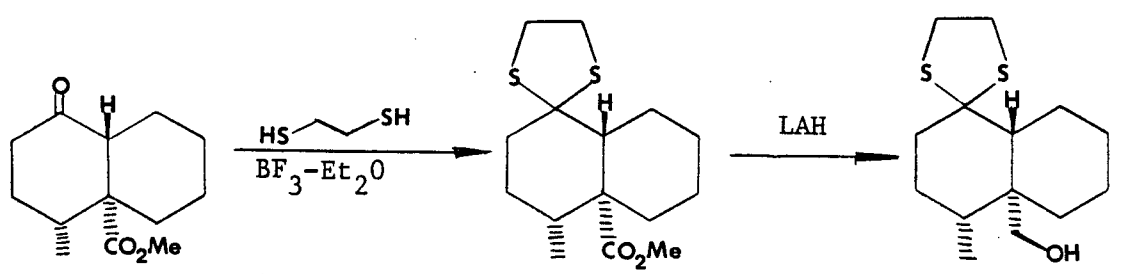
Initially, we chose to reduce the keto ester 274 to the diol(s) 278, which, hopefully, could be transformed into the decalin 276 by Ireland's reductive deoxygenation procedure[99] employing N,N,N',N'-tetramethylphosphorodiamidates 279 as intermediate(s). Although reduction of 274 to the diol(s) 278 proceeded smoothly with excess lithium aluminum hydride in refluxing ether, the attempted conversion of 278 into

the corresponding phosphorodiamidates 279 was unsuccessful. Therefore, this approach to the transformation of 274 into the decalin 276 was abandoned.

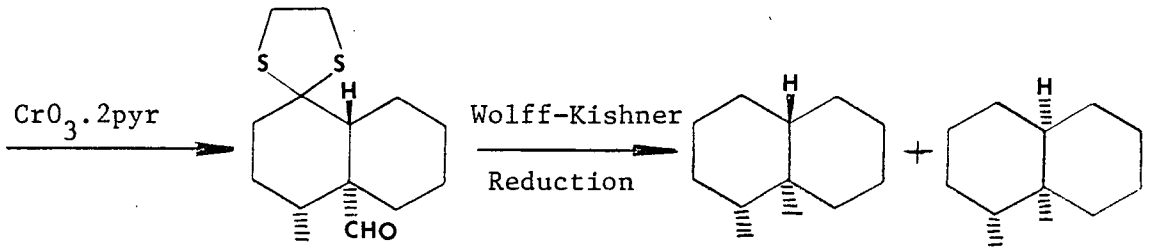


274 278 279 276

In another approach, the ketone functionality of the decalone ester 274 was first converted into the corresponding dithioketal 280 by allowing the former to react with ethanedithiol in the presence of boron trifluoride etherate. The dithioketal ester 280 was then reduced smoothly with excess lithium aluminium hydride to afford the corresponding alcohol 281 in excellent yield. The spectral properties of this compound were in full agreement with the assigned structure. Thus, the hydroxy group produced a broad absorption at 3467 cm^{-1} in the i.r. spectrum. The presence of the dithioketal moiety and the primary alcohol group was evidenced by the p.m.r. spectrum which exhibited a four-proton multiplet at δ3.20 and a two-proton sharp singlet at δ3.90.



274 280 281



282 276 277

Oxidation of 281 with chromium trioxide-pyridine complex[100] produced a crystalline product 282 in good yield. A strong absorption at 1720 cm^{-1}, in association with an absorption at 2710 cm^{-1} in the i.r. spectrum, indicated that the primary alcohol group had been oxidized to the corresponding aldehyde. The tertiary nature of the aldehyde functionality was shown by the p.m.r. spectrum of 282 which showed the aldehyde proton as a sharp singlet at δ10.23. Interestingly, the doublet for the secondary methyl group in 282 had shifted up-field to δ0.88 in comparison to the corresponding doublet in the dithioketal alcohol 281 (δ0.97).

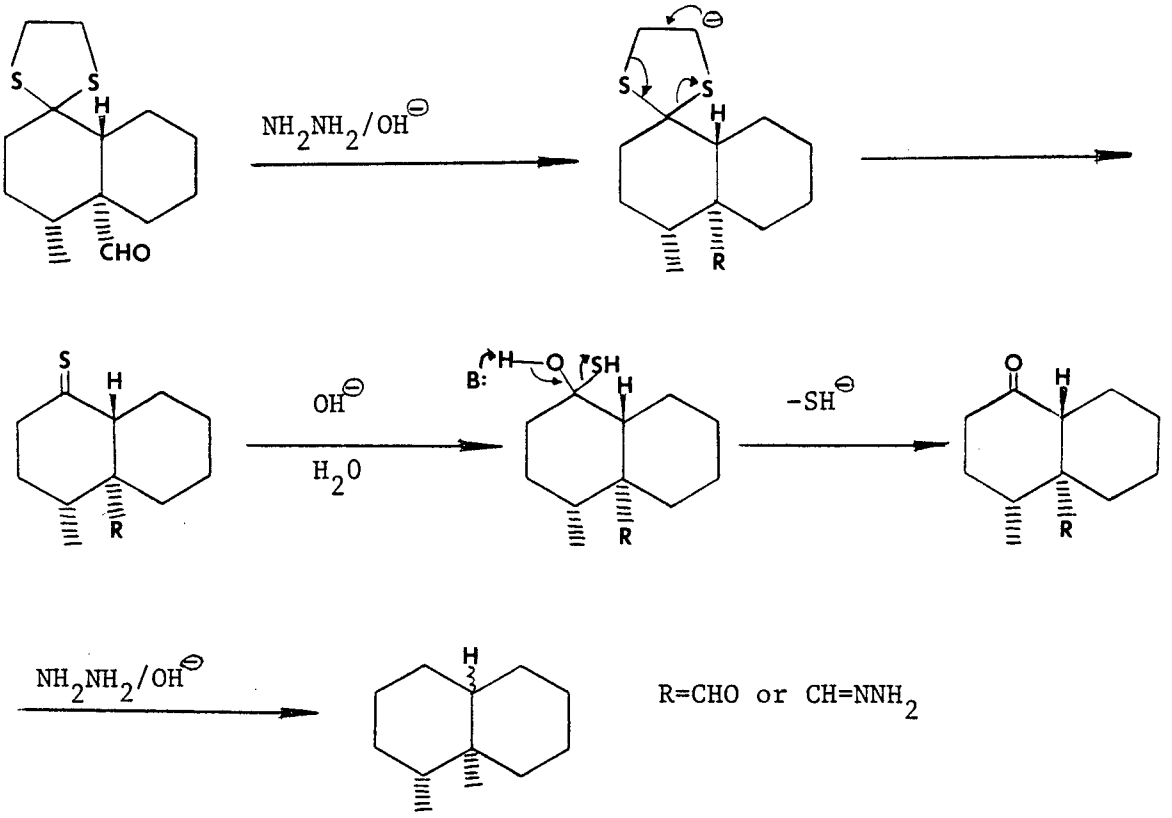
When the pure dithioketal aldehyde was subjected to Wolff-Kishner reduction, desulfurization also occurred.[101] The product appeared to be homogeneous by g.l.c. analysis and its retention time was identical with that of the hydrocarbon 276 as well as that of the decalin 277. The i.r. spectrum of this product indicated that the aldehyde functionality had been reduced to the corresponding methyl group. However, a careful comparison of the p.m.r. spectrum of the reduction product with those of authentic samples of the decalins 276 and 277 clearly showed that this material was actually a mixture of 276 and 277. The tertiary methyl group of pure 276 appeared as singlet at δ0.70 while the secondary methyl group gave rise to a poorly resolved doublet at δ0.74 (J=5.0 Hz). On the other hand, the signal due to the tertiary methyl group of the decalin 277

appeared as a sharp singlet at δ0.83 and the secondary methyl group produced a doublet at δ0.75 (J=6.2 Hz).

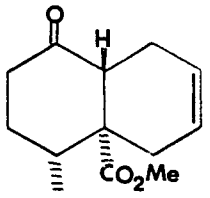
In the p.m.r. spectrum of the Wolff-Kishner reduction product, there was a strong singlet at δ0.68 which could be attributed to the tertiary methyl group of the decalin 277. The characteristic pattern for the secondary methyl group of the decalin 277, however, could not be observed clearly due to interference by the signal attributed to the secondary methyl group of the decalin 276 which appeared at δ0.72 as a doublet with a coupling constant of 6.0 Hz. The tertiary methyl group of decalin 277 appeared as a sharp signal at δ0.80. From this spectrum, the ratio of the decalins 276 and 277 in the Wolff-Kishner reduction product was estimated to be approximately 60:40, respectively.

The formation of the epimeric decalins 276 and 277 from the Wolff-Kishner reduction of the dithioketal aldehyde 282 can be rationalized by assuming that the dithioketal moiety first underwent base-promoted fragmentation to generate a bicyclic ketone (see Scheme 8). Base-catalyzed epimerization of the ketone, followed by Wolff-Kishner reduction of the carbonyl group could lead to a mixture of hydrocarbons.[102] Indeed, Heathcock and colleagues[103] have reported that ethylene ketals are subjected to fragmentation (to afford the corresponding ketones which then undergo 1,2-addition with the excess alkyllithium) when treated with very strong bases such as n-butyllithium. Since protons adjacent to sulfur atoms are more acidic than those adjacent to oxygen atoms, it appears that dithioketals might be even more susceptible to this kind of fragmentation than the corresponding ketals.

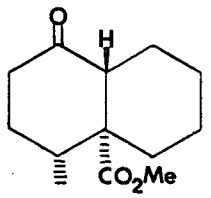
Scheme 8



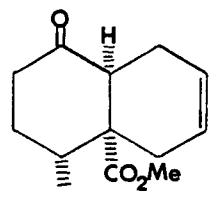
The product obtained from the Wolff-Kishner reduction of the dithioketal aldehyde 282 was, unfortunately, a mixture of the epimeric decalins 276 and 277. However, the presence of vicinal cis-dimethyl groups in both components clearly defined the relative stereochemistry of the secondary methyl group and the angular ester functionality in the keto ester 272. These results, in conjunction with the previously described failure of the crystalline ester 272 and its dihydro derivative 274 to epimerize under basic conditions, clearly showed that these compound possessed a cis-relationship between the methyl group and the ester functionality and a trans-relationship between the bridgehead proton and the angular carbomethoxy moiety.



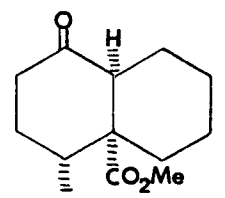
272



274



259



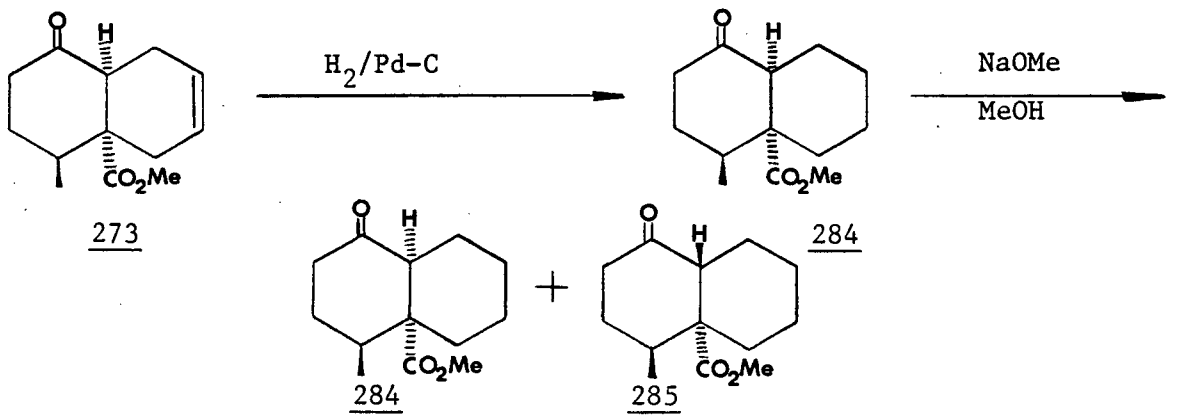
275

As pointed out previously, conformational analyses had indicated that the initial expected product 259 from the Diels-Alder reaction should be thermodynamically less stable than the trans-epimer 272 (see Scheme 5). In the case of the dihydro derivatives 274 and 275, it was expected that the trans-isomer 274 would be the predominant isomer under equilibration conditions (see Scheme 6). Therefore, if the other component isolated from the Diels-Alder reaction had possessed the all cis-stereochemistry (259), it, and/or its dihydro derivative 275, would be expected to epimerize under basic conditions to the thermodynamically more stable isomers 272 and 274, respectively.

When the oily component obtained from the Diels-Alder reaction was treated with sodium methoxide in methanol, a mixture of the starting keto ester and a new isomer 283 (ratio ≈ 7:1), was obtained. By comparing the p.m.r. spectrum of this mixture with that of the starting keto ester, it was possible to assign some of the proton resonances of the new isomer. Of particular interest were the signals due to the secondary methyl groups and the methyl groups of ester functionalities. The doublet (J=6.0 Hz) due to the secondary methyl group of the starting material appeared at δ0.89, while the corresponding signal for the new isomer appeared at δ1.23 (J=6.0 Hz). The three-proton singlets for the methyl group of the carbomethoxy moieties appeared at δ3.74 (starting material) and δ3.64 (new isomer).

When these data were compared with those obtained from the first Diels-Alder product 272 (secondary methyl doublet at δ0.99, J=6.0 Hz, and the singlet due to the carbomethoxy functionality at δ3.62), it was clear that the second Diels-Alder product must have possessed a trans stereochemical relationship between the secondary methyl group and the angular methyl ester moiety. Hence, this compound was assigned structure 273.

Upon hydrogenation, the unsaturated keto ester 273 was converted into the dihydro derivative 284. The i.r. spectrum of the latter compound showed carbonyl stretching absorptions at 1720 cm^{-1} (ester) and 1700 cm^{-1} (ketone). The p.m.r. spectrum, which contained no signals due to olefinic protons, exhibited a three-proton singlet at δ3.70 (methyl ester) and a three-proton doublet (J=6.0 Hz) at δ0.86 (secondary methyl group).



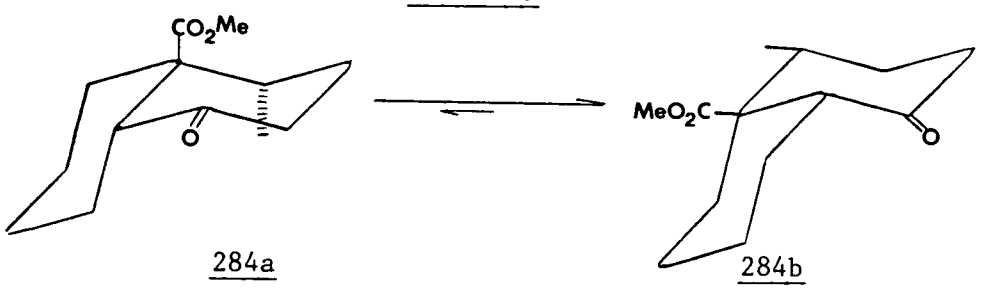
When the keto ester 284 was subjected to equilibration conditions (sodium methoxide in methanol), a mixture of two major components, in a ratio of approximately 55:45, was obtained. A g.l.c. analysis indicated that the predominant component was the starting material, keto ester 284. These epimeric keto esters were separated by means of preparative t.l.c. (with a mixture of 3:7 ether-hexane being employed as the developing solvent). The p.m.r. spectrum of the new isomer showed that the secondary methyl group of this keto ester 285 gave rise to a doublet (J=6.5 Hz) at δ1.20. Thus,

epimerization had caused a significant downfield shift of this signal, since the corresponding absorption in the starting material 284 was at δ0.86. On the other hand, epimerization had caused an upfield shift of the signal due to the carbomethoxy group (δ3.70 in 284 and δ3.62 in 285). When the p.m.r. spectrum of keto ester 285 was compared with that of decalone 274, it was quite clear that the two compounds were different. The p.m.r. spectrum of 274 showed a singlet at δ3.60 (methyl ester) and a doublet (J=6.0 Hz) at δ0.73 (secondary methyl group).

Conformational analyses involving the isomeric keto esters 284 and 285 indicated that the isomer with a cis-ring junction (284) should be slightly more stable than the trans-isomer (see Scheme 9). The calculated conformational energy difference between the more stable conformer 284b of the cis-isomer and the rigid conformation 285 of the trans-isomer was roughly 0.4 kcal/mole. This small difference in free energy indicated that the more stable isomer at equilibrium should be only slightly favoured (in the ratio of approximately 65:35). Indeed, the ratio of the two products obtained from the epimerization experiment was approximately 55:45.

Although the saturated keto ester 284 and in turn, the unsaturated keto ester 273 isolated from the Diels-Alder reaction, could now be assigned to have cis-ring junctions and a trans-relationship between the secondary methyl group and the tertiary ester functionality, it was felt desirable to obtain further unambiguous evidence to support these conclusions. To this end, it was decided to convert the saturated keto ester 284 into the decalin(s) 286 and/or 287, which were available from a previous study in

Scheme 9



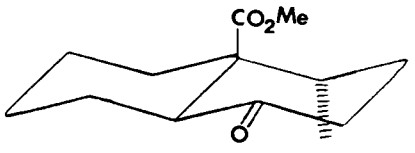
284a

284b

1 syn-axial COOMe-H
1 1,3-diaxial COOMe-sp^2(>=O)
1 syn-axial CH_3-H
2 1,3-diaxial CH_2-CH_3
1 syn-axial CH_2-H

1 gauche COOMe-CH_3
1 gauche CH_3-CH_2
2 syn-axial COOMe-H
2 syn-axial sp^2(>=O)-H
1 syn-axial CH_2-H

284a-284b = (1 syn-axial CH_3-H
+ 2 1,3-diaxial CH_2-CH_3)-(1 gauche
COOMe-CH_3 + 1 gauche CH_3-CH_2
+ 1 syn-axial COOMe-H)
= (0.9 + 2x3.7)-(2x0.8+0.55)
= 6.15 Kcal/mole



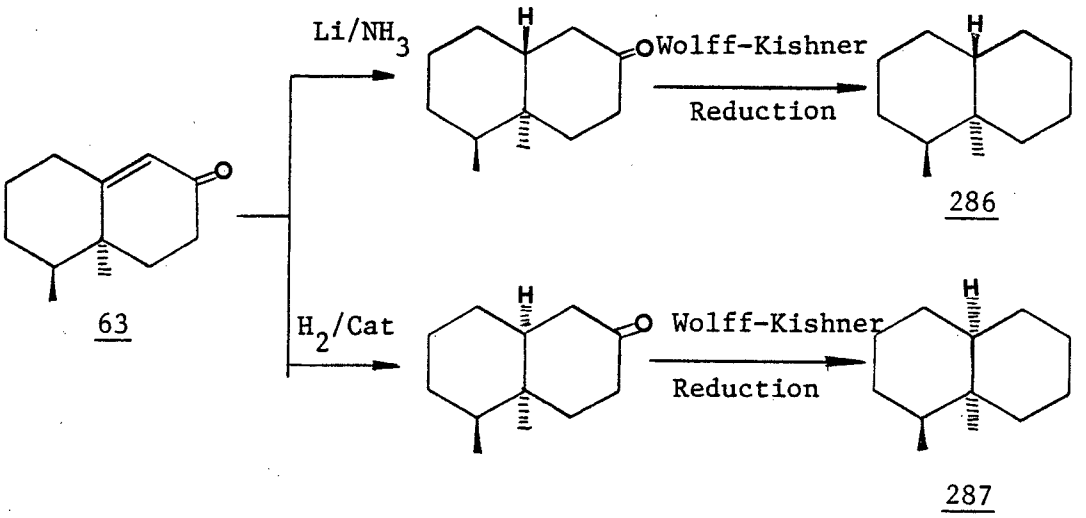
285

285-284b = (1 syn-axial COOMe-H +
2 syn-axial CH_3-H)-(1 gauche
COOMe-CH_3 + 1 gauche CH_3-CH_2 +
1 syn-axial sp^2(>=O)-H)
= (0.55 + 1.8)-(2 x 0.8 + 0.35)
= 0.4 Kcal/mole

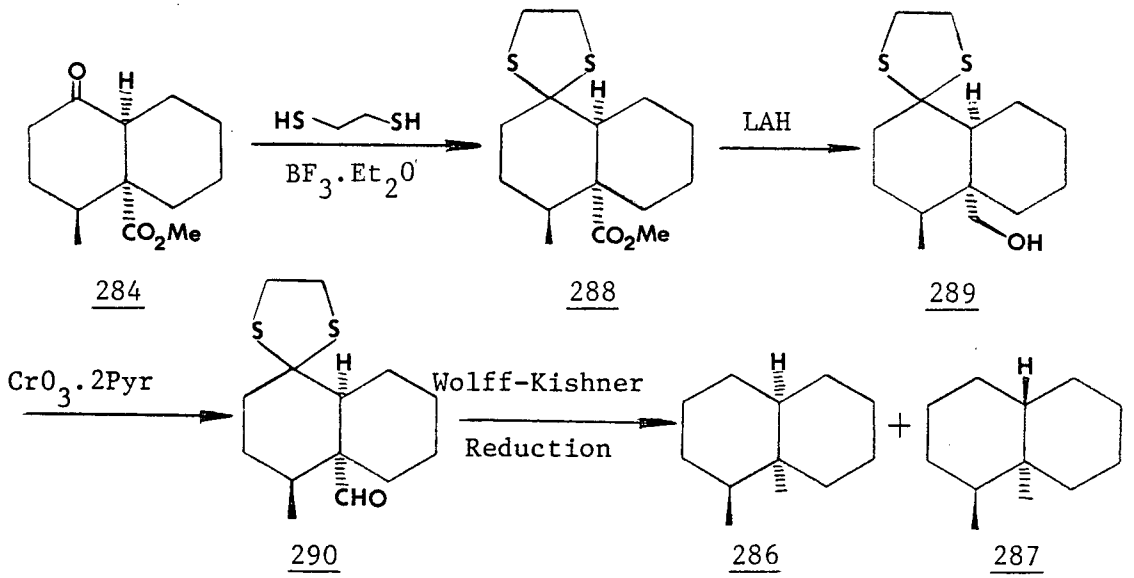
1 1,3-diaxial COOMe-sp^2(>=O)
3 syn-axial COOMe-H
3 syn-axial CH_3-H

our laboratory. The authentic samples of 286 and 287 were prepared from the octalone 63, the stereochemistry of which was known[97] (see Scheme 10).

Scheme 10



In the conversion of the saturated keto ester 284 into the corresponding decalin, the ketone group was first protected as the corresponding dithioketal. Treatment of the keto ester 284 with ethanedithiol in the presence of boron trifluoride afforded the dithioketal ester 288 in excellent yield. The spectral properties of 228 were in agreement with the assigned structure. The presence of the carbonyl group of the ester was shown by an absorption at 1720 cm^{-1} in the i.r. spectrum. The p.m.r. spectrum showed an unresolved doublet centered at δ0.83 for the secondary methyl group while the protons due to the dithioketal moiety and the methyl group of the carbomethoxy functionality appeared as a multiplet at δ3.30 and a singlet at δ3.72, respectively.



284 288 289

290 286 287

Reduction of the ester 288 to give the alcohol 289 was achieved smoothly by treatment of the former with lithium aluminium hydride in refluxing tetrahydrofuran.

The i.r. spectrum of the product 289 indicated the presence of the hydroxyl functionality by a broad absorption at 3450 cm^{-1}. In the p.m.r. spectrum, the methylene protons adjacent to the hydroxyl group appeared as a pair of doublets (AB system) at δ3.69 and 3.58, with a coupling constant of 11.0 Hz. A multiplet at δ3.25 was attributed to the dithioketal protons. The hydroxyl proton gave rise to a singlet at δ2.62. Finally, an unresolved upfield doublet at δ0.83 was assigned to the secondary methyl group.

The alcohol 289 was oxidized with chromium trioxide-pyridine complex[100] to afford the corresponding aldehyde 290 in 76% yield. The presence of aldehyde functionality was supported by absorptions at 2717 and 1720 cm^{-1} in the i.r. spectrum. A downfield singlet at δ9.35 in the p.m.r. spectrum also confirmed the presence of a tertiary aldehyde group. The signal attributed to the dithioketal protons appeared as a multiplet at δ3.28, while the secondary methyl group produced an unresolved doublet

at δ0.78.

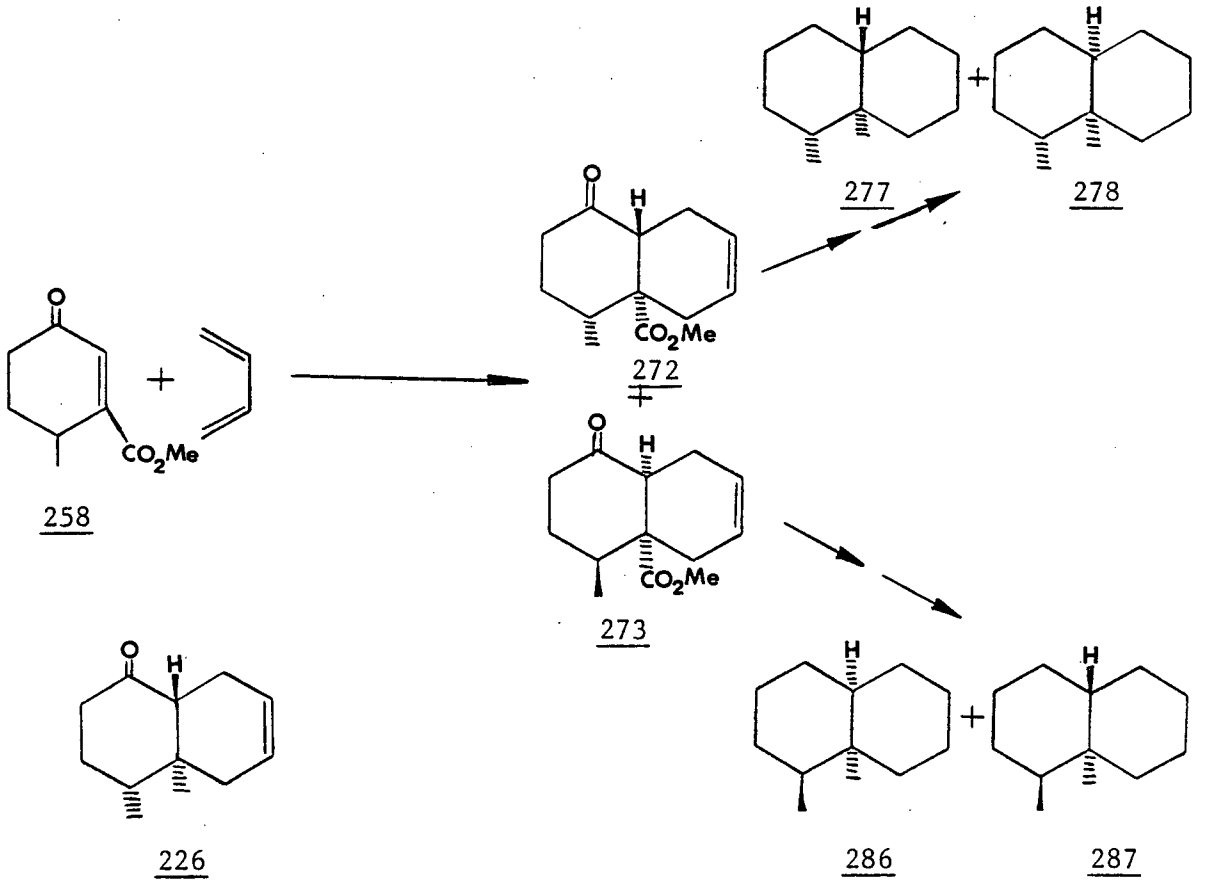
Reduction of the dithioketal aldehyde under Wolff-Kishner reduction conditions afforded a colorless oil which appeared to be homogeneous by analysis on several different g.l.c. columns. The retention time of this material was identical with those of the authentic decalins 286 and/or 287. However, a careful study of the p.m.r. spectrum of this material showed that it was actually a mixture of the decalins 286 and 287.

In the p.m.r. spectrum of the pure authentic decalin 286, the tertiary methyl group appeared at δ0.92 while the secondary methyl group was located as a doublet (J=4.5 Hz) centered at 0.97. On the other hand, the tertiary methyl group of the pure authentic decalin 287 gave rise to a sharp singlet at δ1.02. The pattern of the secondary methyl group was very distinctive. It appeared as a broad unresolved signal at δ0.82.

The p.m.r. spectrum of the mixture of hydrocarbons obtained from the Wolff-Kishner reduction of the dithioketal aldehyde 290 contained all of the signals which would be expected from a mixture of 286 and 287. Two sharp singlets at δ0.93 and δ1.02 could be assigned to the tertiary methyl groups of the decalins 286 and 287, respectively. The doublet signal due to the secondary methyl group of 286 could not be identified easily due to interference from the tertiary methyl signal of the hydrocarbon 287. However, the characteristic unresolved signal for the secondary methyl group of 287 was observed at δ0.82. From the integration of this p.m.r. spectrum, the ratio of the decalins 286 and 287 in the Wolff-Kishner reduction product was estimated to be approximately 1:1. The formation of

these hydrocarbons from the pure dithioketal aldehyde 290 could be explained by the postulation described previously (see Scheme 8). On the basis of this correlation, it could be concluded that the oily Diels-Alder product 273 possessed a trans stereochemical relationship between the secondary methyl group and the ester functionality.

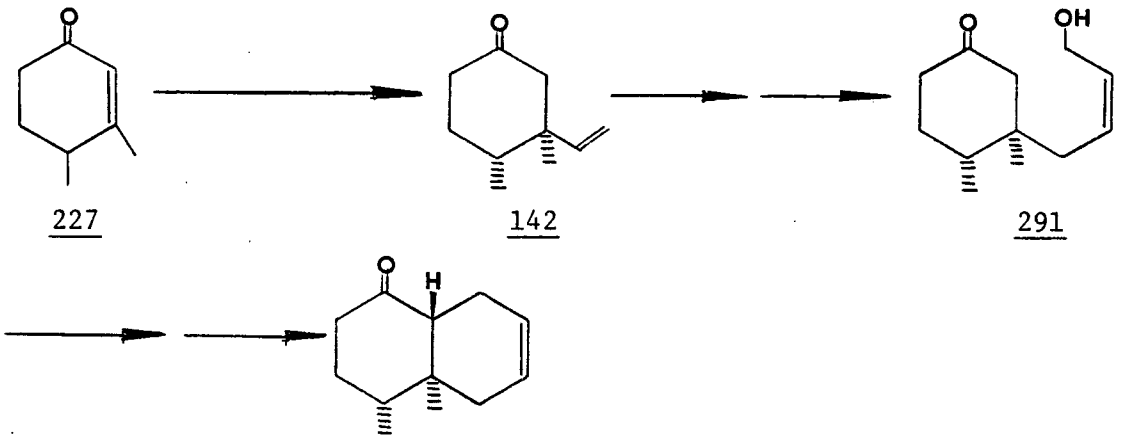
The established relationship between the keto ester 272 and the decalins 276 and 277, as well as the conversion of the keto ester 273 into the decalins 286 and 287, clearly indicated that the Diels-Alder reaction between the keto ester 258 and 1,3-butadiene had not taken place with the hoped-for (and expected) stereoselectivity. Although the desired bicyclic keto ester 272 had been obtained in four steps from the commercially available methyl propiolate 260, the formation of equal amounts of the isomer 273, along with the necessity for a tedious separation of



isomers, and the capricious nature of the Diels-Alder reaction made this overall synthetic approach experimentally unsatisfactory. Therefore it was decided to attempt the synthesis of the keto olefin 226 by another synthetic sequence.

III. Synthesis of the Keto Olefin 226 via Intramolecular Alkylation

The difficulties encountered in the attempted synthesis of the bicyclic keto olefin 226 via a Diels-Alder reaction led us to investigate a synthetic sequence in which the construction of the cis-vicinal methyl groups could be unambiguously achieved at an early stage. Although many methods which had resulted in the formation of cis-vicinal methyl groups in octalone systems had been documented, the one reported by Ziegler and his colleagues[49,50] seemed to be the most suitable for our purposes. These workers had reported that 1,4-addition of lithium divinylcuprate to 3,4-dimethyl-2-cyclohexen-1-one 227 resulted in the efficient formation of cis-3,4-dimethyl-3-vinylcyclohexanone 142 as the sole product. This cyclohexanone not only possessed the desired stereochemistry with respect to the vicinal methyl groups, but also contained the vinyl group as a "handle" to allow for further elaboration to the bicyclic keto olefin 226.



227 142 291

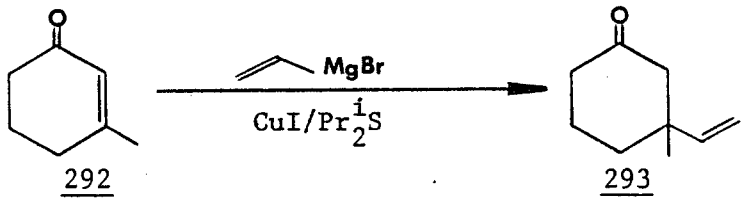
226

We chose as our first synthetic objective, the allylic alcohol, which could then hopefully serve as a direct precusor for the synthesis of the bicyclic keto olefin 226. When 3,4-dimethyl-2-cyclohexen-1-one 227 was treated with a large excess of lithium divinylcuprate in the presence of tri-n-butylphosphine as a stabilizing agent[104], the cyclohexanone 142 was formed as the only product. The physical and spectral properties of this material were in agreement with those previously reported.[50] Thus, the i.r. spectrum clearly showed the presence of the vinyl group (band at 3030, 1630 and 920 cm^{-1}) and the ketone carbonyl functionality (1710 cm^{-1}). In the p.m.r. spectrum of 142, the tertiary vinyl group gave rise to three different pairs of doublets. The downfield pair of doublets (J=18.0 and 9.0 Hz) at δ5.78 could be assigned to the internal vinyl proton. The second pair of doublets at δ4.99 with coupling constants of 9.0 and 1.5 Hz was attributed to the terminal vinyl proton which was cis with respect to the internal vinyl proton. Finally, the pair of doublets at highest field (δ4.95, J=18.0 and 1.5 Hz) could readily be assigned to the terminal olefinic proton which was trans to the internal vinyl hydrogen. Other signals of note in the p.m.r. spectrum of 142 were those associated with the secondary methyl group, which gave rise to a doublet at δ0.91 (J=6.0 Hz) and the tertiary methyl group which produced a sharp singlet at δ0.90.

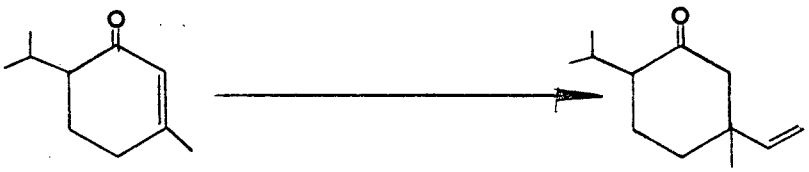
Although the conjugate addition of lithium divinylcuprate to the cyclohexenone 227 proceeded smoothly to give the adduct 142 in excellent yield, there were some drawbacks to the reaction. First of all, a fairly large excess of lithium divinylcuprate was required for the reaction. In addition to being somewhat wasteful, this requirement led to the necessity,

in large-scale reactions, of handling large volumes of vinyllithium solution. Thirdly, in large scale reactions, the relatively copious amounts of insoluble copper salts made work up rather tedious. Finally, the fact that vinyllithium was no longer commercially available caused yet another obstacle. In view of these inconveniences, it was decided to investigate the copper-catalyzed 1,4-addition of vinyl magnesium halide to the cyclohexenone 227 as an alternative method.

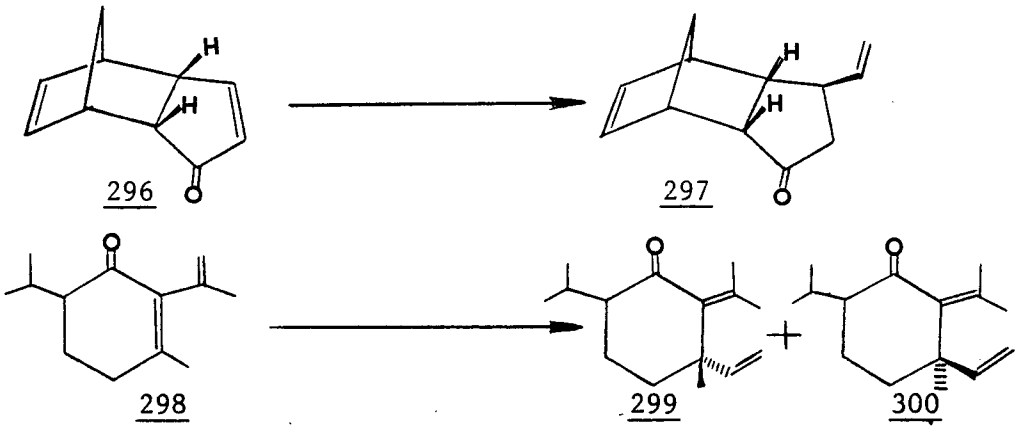
The conjugate addition of alkyl magnesium halides to α,β-unsaturated enones in the presence of cuprous halides was well documented.[105] However, the use of alkenyl magnesium halides, especially vinyl magnesium halide itself, was less familiar. Nevertheless, Alexandre and Rouessac[106,107] had reported that in the presence of diisopropylsulfide and a catalytic amount of cuprous iodide, vinyl magnesium halide reacted with various cyclic α,β-unsaturated ketones to afford the corresponding 1,4-adducts in good to excellent yields. Thus cyclohexanones 293, 295, and 297 were obtained from corresponding enones 292, 294 and 296, respectively. The enone 298, under the same conditions, gave rise to two cyclohexanones 299 and 300 in the ratio of approximately 4:1.



292 293

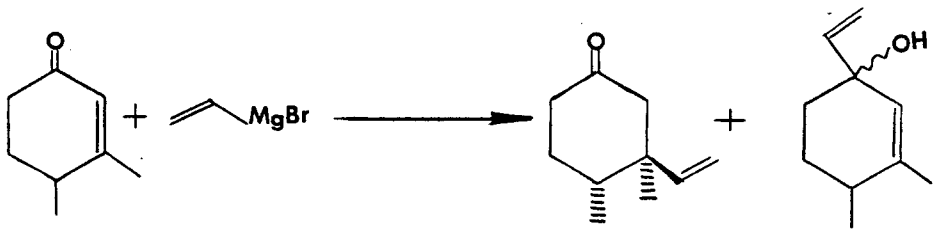


294 295



Addition of 3,4-dimethyl-2-cyclohexen-1-one 227 to a cold solution (0°) of vinyl magnesium bromide (prepared according to the procedure of Seyferth[108]) in tetrahydrofuran containing dimethylsulfide and a catalytic amount of cuprous iodide resulted in the formation of only small amounts (10-20%) of the desired 1,4-adduct. The i.r. spectrum of the crude product showed a strong absorption at 3450 cm^{-1} which could be attributed to a hydroxyl functionality. Presumably, 1,2-addition to the carbonyl group had competed with 1,4-addition. It was known that this type of competition reaction could sometimes be minimized by employing an inverse addition procedure in which the Grignard reagent was added to a solution of the enone.[105] Indeed, when a solution of vinyl magnesium bromide was added dropwise to a tetrahydrofuran solution of 3,4-dimethyl-2-cyclohexen-1-one 227 in the presence of cuprous iodide and dimethylsulfide, the formation of the 1,4-adduct was improved dramatically. Hence, homogeneous cis-3,4-dimethyl-3-vinylcyclohexanone 142 could be isolated in approximately 65% yield by direct distillation of the crude product. The physical and spectroscopic properties of this compound were identical in all respects with those of an authentic sample obtained as described previously. The presence of a minor alcoholic component (presumably 301, resulting from competitative 1,2-addition) was shown by a broad

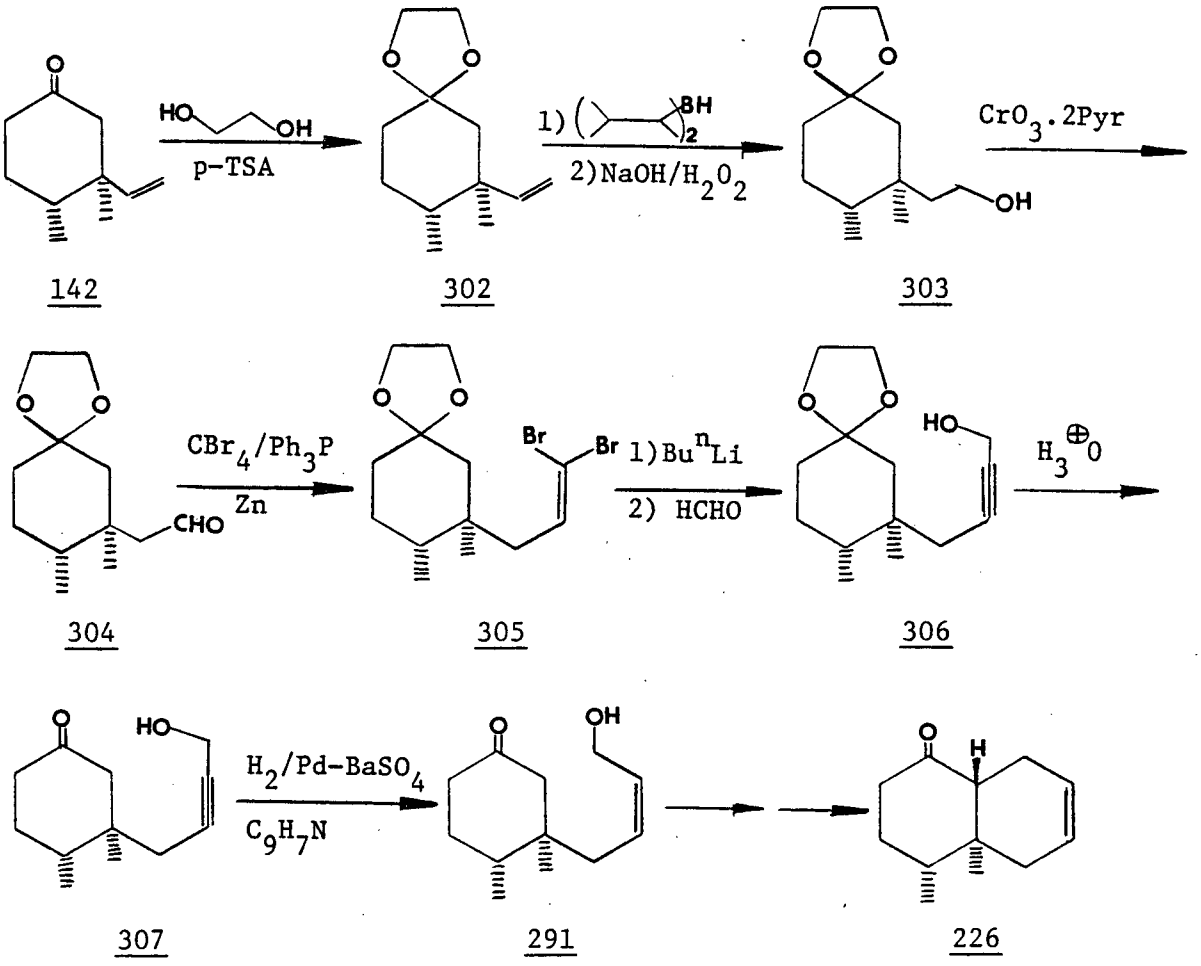
hydroxyl stretching absorption at 3450 cm^{-1} in the i.r. spectrum of the crude product. This compound seemed to be thermally unstable because, upon distillation of the crude product, significant amounts of water were collected. In all probability, the tertiary alcohol 301 underwent catalytic thermal dehydration to give water and highly volatile hydrocarbon products.



227 142 301

When a procedure for the formation of the cyclohexanone 142 via 1,4-addition of vinyl magnesium bromide had been secured, an investigation aimed at the conversion of 142 into the allylic keto alcohol 291 was begun. Ziegler and coworkers[49,50] had shown that the ketal aldehyde 304 could be obtained efficiently in three steps from the ketone 142. We felt that the former intermediate 304 could serve as a useful intermediate in our synthesis of the keto olefin 226. For example, it was hoped that 304 could be transformed efficiently into the dibromo olefin 305. Treatment of the latter with two equivalents of n-butyllithium, followed by trapping of the resulting lithium acetylide with formaldehyde, should afford the propargylic alcohol 306. Sequential subjection of 306 to hydrolysis and semi-hydrogenation would furnish the desired allylic keto alcohol 291, from which the keto olefin 226

would be obtained via intramolecular alkylation.



The ethylene ketal 302 of cis-3,4-dimethyl-3-vinylcyclohexanone was obtained efficiently by refluxing a benzene solution of the cyclohexanone 142 and ethylene glycol in the presence of a catalytic amount of p-toluenesulfonic acid (Dean-Stark apparatus). The spectral data obtained from the product 302 were in full agreement with the assigned structure. Of particular interest was the absence of a carbonyl absorption in the i.r. spectrum. In the p.m.r. spectrum, the vinyl group gave rise to three pairs of doublets in a pattern very similar to that observed in the spectrum of the ketone 142. A four-proton multiplet at δ3.90 could be attributed to the protons of the ethylene

ketal moiety. The secondary and tertiary methyl groups were evidenced by a doublet (J=6.0 Hz) at δ0.79 and a sharp singlet at δ1.00, respectively.

Hydroboration of the ketal olefin 302 with disiamylborane[50] (formed by the reaction of dimethylsulfide-borane complex with 2-methyl-2-butene[109]) afforded the ketal alcohol 303 as colorless viscous oil. The presence of a primary alcohol functionality in this compound was shown by a strong, broad absorption at 3450 cm^{-1} in its i.r. spectrum, and by a two-proton triplet (J=7.0 Hz) at δ3.69 in its p.m.r. spectrum. The p.m.r. signals for the methyl groups and the ketal protons were found at positions very similar to those of the corresponding signals in the ketal olefin 302.

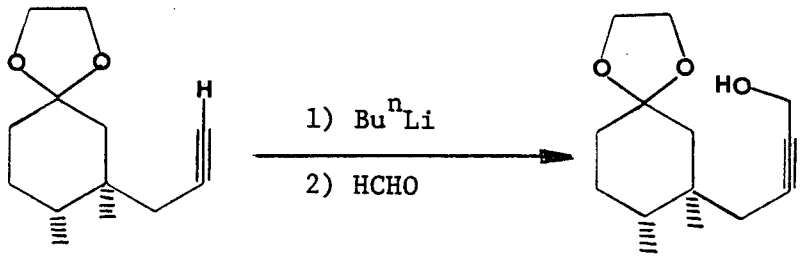
Oxidation of the primary alcohol 303[50] was achieved by chromium trioxide-pyridine complex.[100] The i.r. spectrum of the product 304 exhibited no absorption due to a hydroxy group, but showed two absorptions (2755, 1715 cm^{-1}) which were clearly indicative of the presence of an aldehyde functionality. In the p.m.r. spectrum, a downfield triplet at δ9.87 with a coupling constant of 3.0 Hz was characteristic of an aldehyde proton. The methylene protons adjacent to the aldehyde group appeared as a doublet at δ2.35 with a coupling constant of 3.0 Hz. The signals due to the ketal protons (δ3.90, multiplet) and the secondary methyl group (δ0.85, doublet, J=6.0 Hz) were at the same positions as the corresponding signals in the ketal alcohol 303. However, the singlet due to the tertiary methyl group had shifted downfield from δ0.90 to δ1.06 when the primary alcohol group was oxidized to the aldehyde.

Addition of this aldehyde 304 to a solution of dibromomethylene-triphenylphosphorane (generated *in situ* by the reaction of carbon tetrabromide with triphenylphosphine in the presence of zinc dust[110]) resulted

in the smooth formation of the 1,1-dibromoolefin 305. The p.m.r. spectrum of this material did not exhibit any signals at chemical shift values higher than δ6.43. This observation, in conjunction with the absence of a carbonyl stretching absorption in the i.r. spectrum, clearly indicated that the aldehyde group had undergone the Wittig reaction with dibromomethylenetriphenylphosphorane to give the expected olefin. The most interesting feature in the p.m.r. spectrum of 305 was that the vinyl proton and the allylic methylene protons formed an ABX system. The vinyl proton, which constituted the X part of the system, appeared as a "triplet" (overlapped pair of doublets) instead of the more commonly observed four-line pattern, while the allylic methylene protons, the AB part of the system, gave rise to an eight-line multiplet. By means of calculation[111], it was determined that the chemical shift positions of the methylene protons were δ1.91 and δ2.26 with the coupling constants being J_{AB} = 15.0 Hz and $J_{AX}=J_{BX}$=7.0 Hz. On the other hand, the position of the vinyl proton was found to be δ6.43, with a coupling constant $J_{AX}=J_{BX}$=7.0 Hz. The protons associated with the ketal functionality gave rise to a multiplet at δ3.91, and the three-proton signals due to the tertiary and secondary methyl groups appeared at δ0.92 (singlet) and δ0.86 (doublet, J=6.0 Hz), respectively.

In order to add the last necessary carbon atom to the side chain of 305, the latter was allowed to react with two equivalents of n-butyllithium at -78° to form the corresponding lithium acetylide.[110] Attempted trapping of this anion at -78° by means of treatment with gaseous formaldehyde (obtained from the pyrolysis of paraformaldehyde) proved to be only mildly successful, since varying amounts of the corresponding acetylene 308 were obtained as a side product. However, it was

found that when the acetylene was converted back to the lithium acetylide (treatment with n-butyllithium) and the acetylide was allowed to react with gaseous formaldehyde at 0°, the propargylic alcohol 306 was formed in excellent yield. Therefore, the tetrahydrofuran solution of the



308 306

lithium acetylide, obtained directly from the reaction between the 1,1-dibromoolefin 305 and n-butyllithium was warmed to ice-bath temperature before gaseous formaldehyde was bubbled into the solution. By means of this modified procedure, an excellent yield (98%) of the desired propargylic alcohol 306 was obtained directly from the 1,1-dibromoolefin 305 without formation of the acetylene 308. The spectral properties of the alcohol 306 were in agreement with the assigned structure. Thus, in the i.r. spectrum, the hydroxyl group produced a broad band at 3475 cm^{-1} and a weak absorption due to the triple bond stretching was located at 2255 cm^{-1}. In the p.m.r. spectrum, the signal due to the methylene protons adjacent to the hydroxyl group appeared as a triplet at δ4.19 (J=2.0 Hz). The formation of a triplet signal instead of the expected singlet was due to long range coupling with the other propargylic methylene protons transmitted through the triple bond.[112] This long range coupling also affected the multiplicity of the other propargylic methylene group. Thus, the propargylic

methylene protons adjacent to the quaternary center produced an unresolved triplet at δ2.14. The presence of the ketal functionality was evidenced by a four-proton multiplet at δ3.87.

At this stage of the synthesis, it was deemed necessary to remove the ketal protecting group before the propargylic alcohol was hydrogenated to the allylic alcohol. This was achieved by subjecting the ketal propargylic alcohol 306 to acid hydrolysis in aqueous methanol. The corresponding keto propargylic alcohol 307 was obtained in 92% yield. The regeneration of the keto functionality was shown by the strong carbonyl stretching absorption in the i.r. spectrum at 1700 cm^{-1} as well as by the disappearance of the signal due to ketal protons in the p.m.r. spectrum. The other spectral data derived from compound 307 were very similar to those of the synthetic precursor 306.

The next transformation in the synthetic sequence involved the cis hydrogenation of the triple bond present in the keto propargylic alcohol 307. Although a number of different catalysts have been employed to effect this type of conversion[113], the Lindlar catalyst has found the widest usage. Indeed, when the keto propargylic alcohol 307 was hydrogenated in ethanol in the presence of the catalyst and a trace of quinoline, the keto allylic alcohol 291 was obtained as the sole product in excellent yield. However, it was subsequently found that it was more convenient to carry out the hydrogenation in ethanol in the presence of commercially available palladium-on-barium sulfate catalyst and few drops of purified quinoline.*[114] Under these conditions, the allylic alcohol 291 was isolated

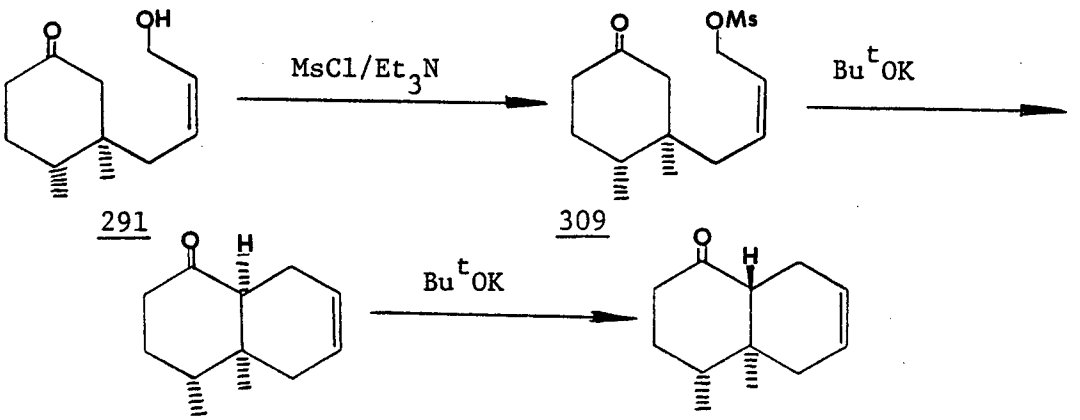
* Cram and Allinger[114] suggested that satisfactory results could be obtained only by use of synthetic quinoline. However, we found that commercial quinoline, carefully purified by Vogel's procedure[115], was satisfactory.

in 95% yield as viscous colorless oil.

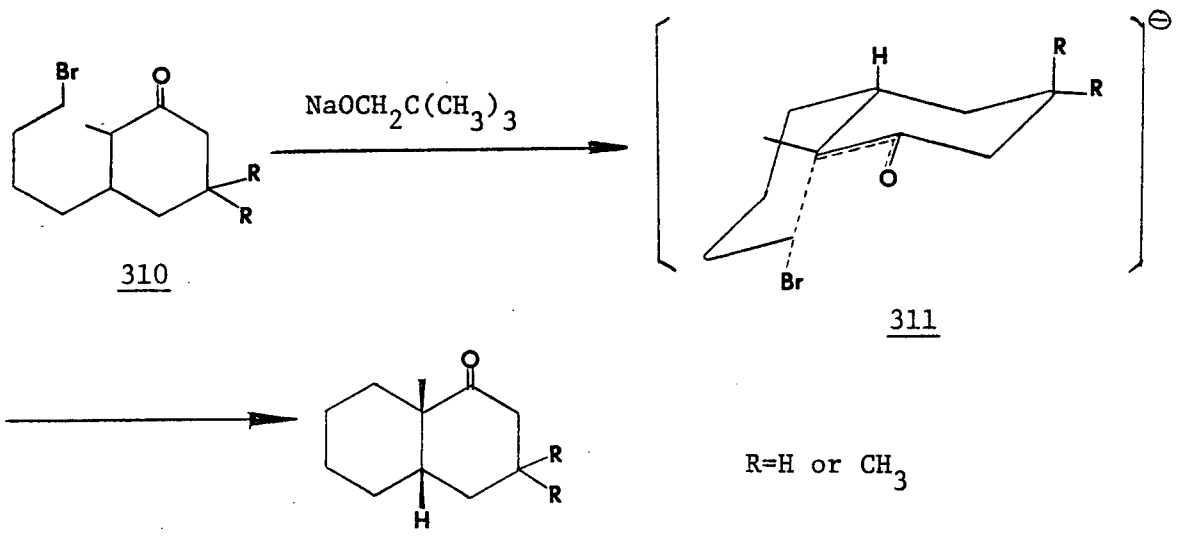
The i.r. spectrum of compound 291 showed absorption bands at 3450 cm^{-1}(O-H), 3050 cm^{-1} (olefinic C-H) and 1710 cm^{-1} (C=O). In the p.m.r. spectrum, a multiplet at δ5.62 was attributed to the two vinyl protons. The methylene protons adjacent to the hydroxyl functionality appeared as a doublet at δ4.12, with a coupling constant of 5.5 Hz. Three-proton signals at δ0.80 (singlet) and δ0.93 (doublet) could be assigned to the tertiary and secondary methyl groups, respectively.

With the achievement of our first synthetic objective, the keto allylic alcohol 291, the next step was to convert the hydroxyl group of 291 into a good leaving group so that a subsequent intramolecular alkylation could be achieved. Hence, we chose to explore the possibility of forming the corresponding tosylate or mesylate from the keto allylic alcohol 291, although it was recognized that these derivatives might not be stable enough to be isolated and purified. Following the procedure of Crossland and Servis[116], the crude keto mesylate 309 was obtained as an orange-yellow oil in excellent yield (96%). The i.r. spectrum of this crude product exhibited no absorption due to hydroxyl stretching, but showed strong bands at 1350 and 1170 cm^{-1} for the sulfonate functionality, as well as a carbonyl absorption at 1710 cm^{-1}. In the p.m.r. spectrum, the vinyl protons gave rise to a multiplet at δ5.80 and the methylene protons adjacent to the methanesulfonate group appeared as a doublet (J=6.0 Hz) at δ4.78. The signal due to the methyl group of the OMs group was a sharp singlet at δ3.08. Finally, high-field signals at δ0.90 (singlet) and δ1.03 (doublet, J=6.0 Hz) were assigned to the tertiary and secondary methyl groups respectively. Due to the fact that the mesylate 309 was

too unstable to allow for purification, it was used directly in the next transformation.

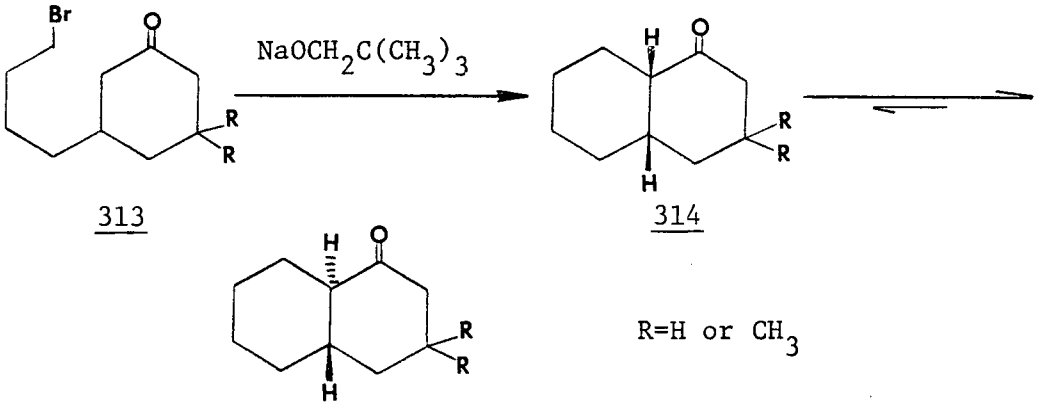


In 1961, Conia and Ronessac[117] had reported that 3-(ω-bromobutyl)-2-methylcyclohexanone 310 (R=H or CH_3) underwent stereoselective intramolecular alkylation to afford the corresponding cis-fused decalone 312 (R=H or CH_3) as the sole product. The stereochemical outcome of this reaction was rationalized by postulating that the cyclization took place via the transition 311, in which the alkylation occurred from an axial direction. When the cyclohexanone 313 (R=H or CH_3) was subjected to the



312

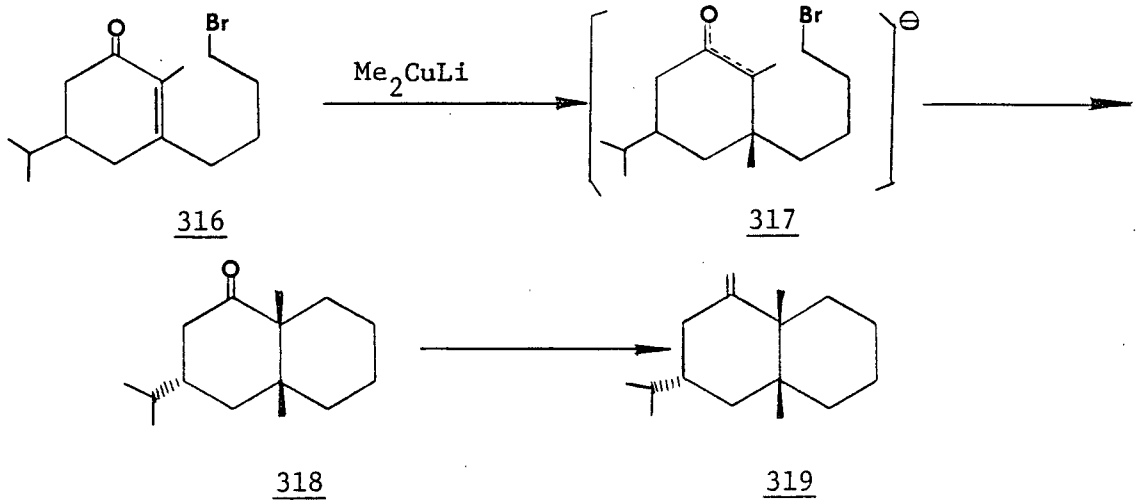
same reaction conditions, a mixture of the cis and trans isomers 314



313 314 315

(R=H or CH_3) and 315 (R=H or CH_3) was obtained, in which the latter predominated. Presumably, the cis-decalone 314 (R=H or CH_3) was initially formed and was subsequently epimerized to the thermodynamically more stable trans-fused ketone 315 (R=H or CH_3).

More recently, Posner and his colleagues[118,119] observed that the enolate 317, formed by conjugated addition of lithium dimethylcuprate to the enone 316, underwent intramolecular alkylation with a high degree of stereoselectivity. In this reaction, only the cis-fused decalone 318 was formed. The stereochemistry of the latter compound was proved by its conversion into (±)-valerane 319, a sesquiterpene with known configuration.



316 317

318 319

On the basis of these precedents, it was expected that the intramolecular alkylation of the keto mesylate 309 would initially give the cis-fused octalone 228. However, presence of excess base would facilitate epimerization and, in this manner, it was hoped that the desired trans-isomer 226 would be obtained directly from the reaction mixture.

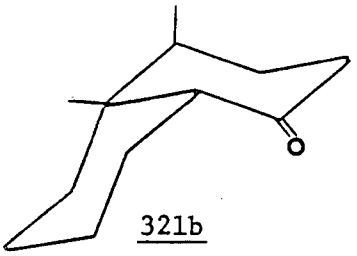
Indeed, when the keto mesylate 309 was treated with four equivalents of potassium tert-butoxide in dry tert-butyl alcohol at room temperature, a homogeneous oily compound was obtained in 63% overall yield from the keto allylic alcohol 291. The product exhibited spectral properties in good agreement with those expected for the octalone 226. The i.r. spectrum showed absorptions at 3050 and 1660 cm^{-1} due to the cis disubstituted carbon-carbon double bond, and a carbonyl absorption at 1705 cm^{-1}. In the p.m.r. spectrum, the signal due to the tertiary methyl group was at extraordinarily high field (δ0.66). The secondary methyl group appeared as a doublet (J=6.0 Hz) at δ0.95. Finally, a broad singlet at δ5.58 could be attributed to the olefinic protons.

Although it seemed highly likely that the octalone thus obtained should have the desired trans-ring junction, this point could not be proven from the available data. Hence, it was decided to convert this compound into the corresponding dihydro derivative and then treat the latter compound with strong base under equilibration conditions. On the basis of conformational analyses of the decalones 320 and 321 (see Scheme 11), it seemed that the trans-isomer 320 would be considerably more stable than the corresponding cis-isomer 321.

The octalone 226 obtained from intramolecular cyclization of the keto mesylate 309 was hydrogenated with palladium-on-carbon in methanol

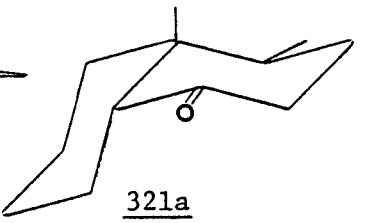
to afford the dihydro derivative 320. Apart from the absence of appropriate absorptions due to the presence of a disubstituted carbon-carbon double bond, the spectral data (i.r., p.m.r.) obtained from the dihydro

Scheme 11



321b

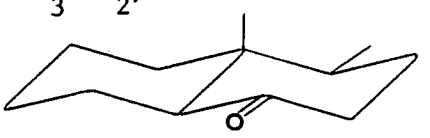
1 gauche CH_3-CH_3
4 syn-axial CH_3-H
2 syn-axial $sp^2(>=0)$-H
1 syn-axial CH_2-H



321a

1 gauche CH_3-CH_3
1 gauche CH_3-CH_2
1 syn-axial CH_3-H
1 1,3-diaxial CH_3-$sp^2(>=0)$
3 syn-axial CH_2-H

321b-321a=(1 syn-axial CH_3-H +
1 syn-axial $sp^2(>=0)$-H)-(1 gauche CH_3-CH_2)
= (0.85 + 0.35) - (0.8)
= 0.4 Kcal/mole



320

1 gauche CH_3-CH_3
1 gauche CH_3-CH_2
3 syn-axial CH_3-H
1 1,3-diaxial CH_3-$sp^2(>=0)$

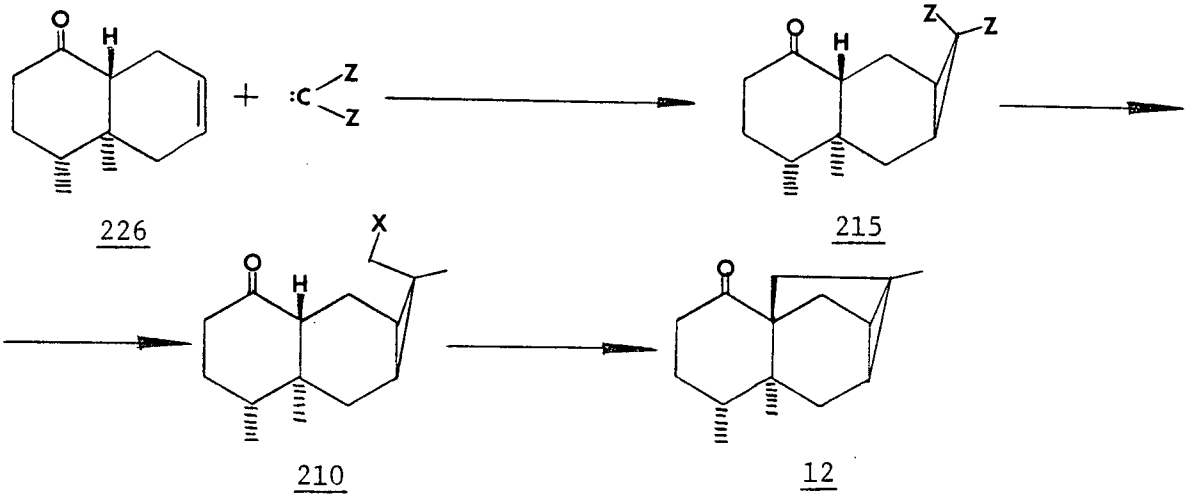
321a-320 = 1 syn-axial CH_3-H
= 0.85 Kcal/mole

derivative 320 were very similar to those of the starting material 226.

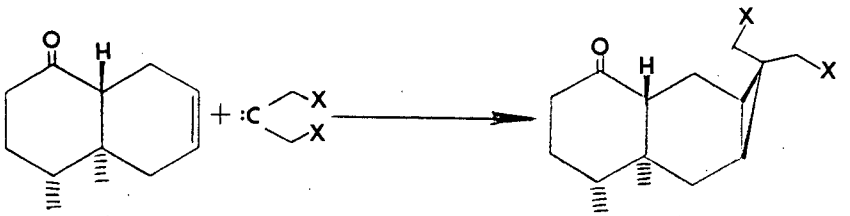
The decalone 320 was subjected to equilibration conditions by treatment with potassium tert-butoxide in dry tert-butyl alcohol for 2 hours at room temperature. The isolated material was shown to be identical with the starting bicyclic ketone in all respects. Therefore, it could be concluded that the decalone had a trans-fused ring junction (as represented by structure 320), and, in turn, that the octalone obtained from the intramolecular cyclization of 309 possessed the desired stereochemistry as shown by structure 226.

IV. Attempted Synthesis of (±)-Ishwarone via Dibromocyclopropane Derivatives

In accord with our synthetic plans, it was envisaged that the unsaturated keto olefin 226 would be transformed by reaction with a suitable carbene (or carbenoid) into an appropriate cyclopropane derivative such as 215 or 224. Intermediate 215 seemed to be an attractive possibility because, potentially, the exo and the endo positions on the cyclopropane ring (Z) could be modified separately to afford a compound with general structure 210, which could then serve as a direct precursor for our final target compound, ishwarone 12.

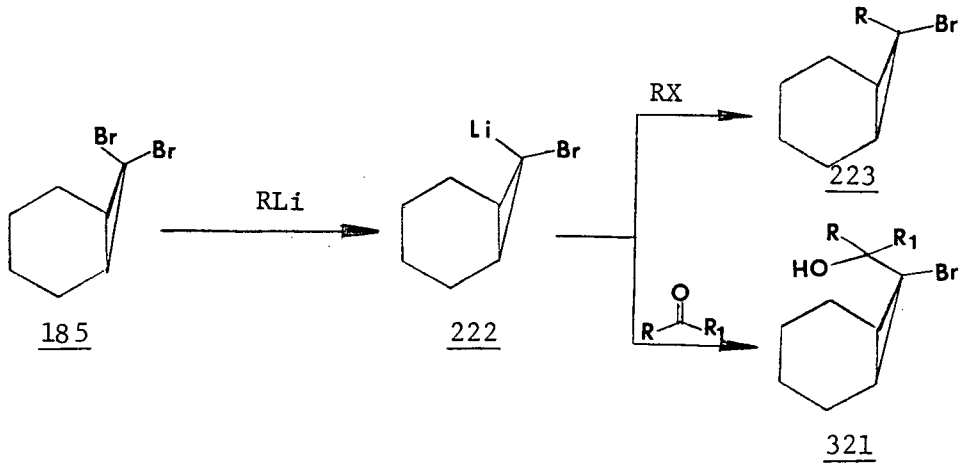


226 215 210 12



226 224

Recently, Kitatani, Hiyama and Nozaki[70,71] reported that 7,7-dibromonorcarane 185 underwent halogen-lithium exchange stereoselectively when treated with an alkyllithium. The resulting carbenoid* reacted with various alkylating agents to give 7-alkyl-7-bromonorcaranes 223 in good to excellent yields. It also had been observed independently by Hiyama et al[121] and Seebach et al[122] that lithium carbenoids of this type reacted with aldehydes and/or ketones to give the corresponding bromohydrins 321. Interestingly, when the dibromide 185 was allowed to



185 222 223 321

react with two equivalents of an alkyllithium in the presence of diethyl carbonate, 7,7-dicarboethoxynorcarane 218 could be obtained in 72% yield.

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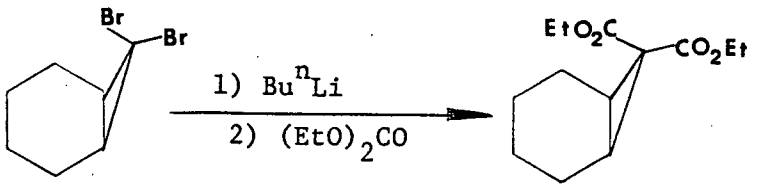
* A species containing a carbanion on the same carbon as a good leaving group (such as bromide) has been named a carbenoid because such a species can readily decompose to a carbene.[120]

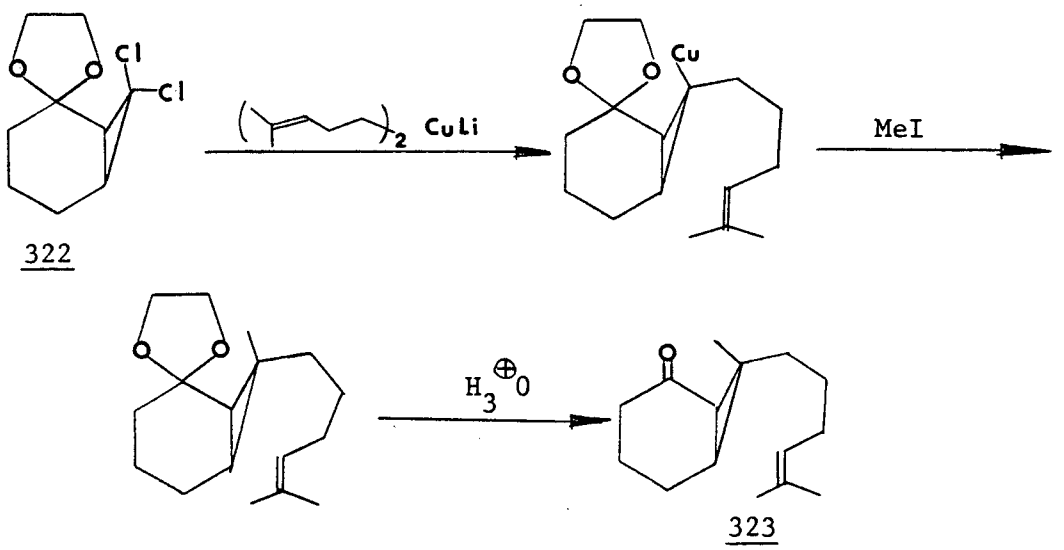
This type of reaction could possibly be extended to allow for the



185 218

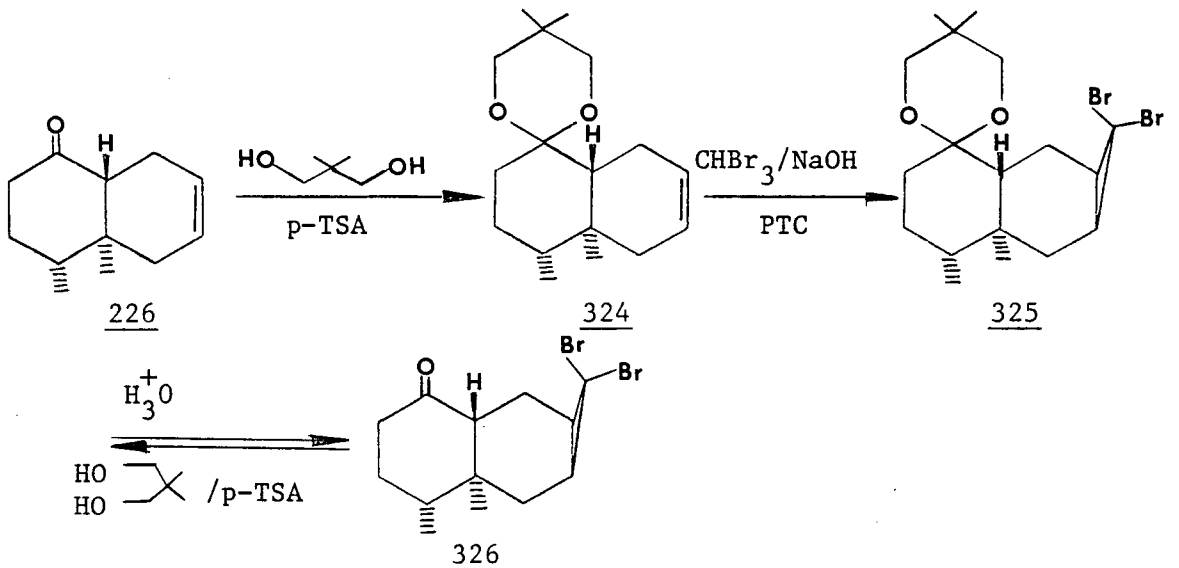
conversion of an intermediate like 215 (Z=Br) into a compound with general structure 224, another possible intermediate in our projected synthetic routes.

Hiyama and coworkers[123] also found that gem-dihalocyclopropanes could be dialkylated stereoselectively by treatment with a lithium dialkylcuprate reagent, followed by trapping of the resultant organocopper intermediate with different alkylating agents. Thus, for example, the dichlorocyclopropane derivative 322 was transformed into the ketone 323 in good overall yield.



322 323

On the basis of these encouraging results documented in the literature, it was decided to investigate the possibility of synthesizing (±)ishwarone 12 via the intermediacy of the dibromocyclopropane derivative 215 (Z=Br, Y=0 or protecting group). To this end, the carbonyl group of the keto olefin 226 was first protected as the corresponding 5,5-dimethyl-1,3-dioxane derivative 324. Thus, treatment of 226 with 2,2-dimethyl-1,3-propanediol under standard ketalization conditions afforded the crystalline ketal olefin 324 in very good yield. The i.r. data obtained

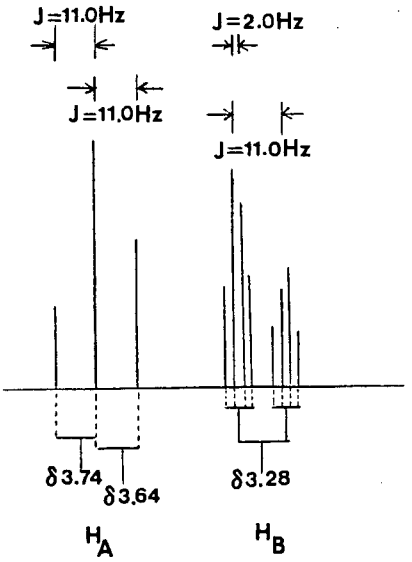


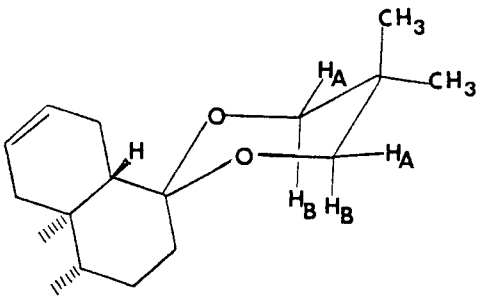
226 324 325

326

from this compound was consistent with the formation of the ketal, since no carbonyl absorption could be observed. In the p.m.r. spectrum, the olefinic protons gave rise to a multiplet at δ5.62. The bridgehead proton appeared as an unresolved doublet of doublets at δ2.82. Signals due to the three tertiary methyl groups were observed at δ0.69, 0.80 and 1.18, while the secondary methyl group gave rise to a doublet (J=6.0 Hz) at δ0.84. Of particular interest in this spectrum was the pattern due to the four ketal protons, which gave rise to an eleven-line signal between

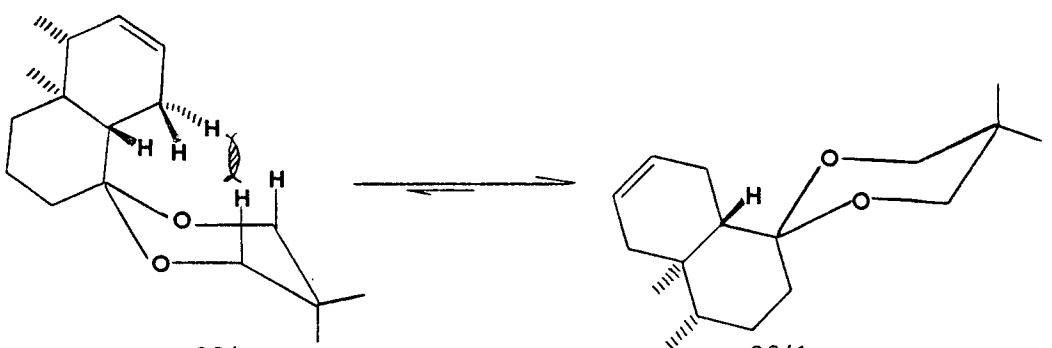
δ3.18 and 3.82 as depicted below:





324b

On the basis of conformational analysis, it was anticipated that conformer 324b would be considerably more stable than conformer 324a, due to the presence in the latter of severe steric interaction between the allylic methylene protons and the axial protons of the dioxane ring. On the basis of this rigid conformation the downfield



324a 324b

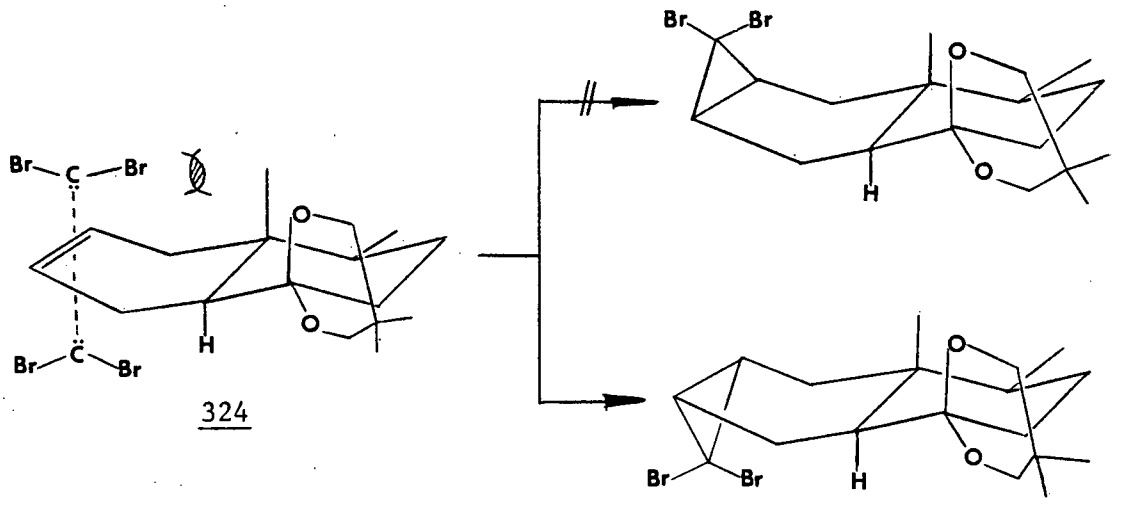
resonance of the ketal signal, which appeared as a "triplet" (overlapping pair of doublets at δ3.64 and δ3.74, with coupling constants of 11.0 Hz

for both doublets) could be assigned to the equatorial protons (H_A) of the dioxane moiety in 324b. On the other hand, the pair of quartets at high field (δ3.28, J=11.0 and 2.0 Hz) was attributed to the two axial protons (H_B) of the ketal functionality. The formation of a pair of quartets instead of a doublet for these protons could be rationalized by postulating long range W-type coupling with one of the gem-dimethyl groups.

The generation of dihalocarbenes can be carried out via a variety of methods, such as the pyrolysis of sodium trihaloacetates[124], the thermal decomposition of phenyl(trihalomethyl)mercury[125], and the dehydrohalogenation of haloforms with strong base.[126] One of the most simple procedures was the dehydrohalogenation of haloforms with aqueous sodium (or potassium) hydroxide in the presence of a phase transfer agent.[127] Following the procedure reported by Makosza and Fedoryuski[128], the ketal olefin 324 was transformed into the dibromo ketal 325, using triethylbenzylammonium chloride as the phase transfer agent. Although, in pure form, the dibromo ketal 325 was quite stable, the crude product obtained from the dibromocarbene addition reaction proved to be subject to some decomposition. For example, when the crude material was allowed to stand at room temperature, the ketal moiety was partially lost, as shown by the increase of carbonyl absorption in the i.r. spectrum. This behaviour became even more pronounced when vaccum distillation of the material was attempted. Rapid column chromatography did not entirely solve the problem either, since fractions containing substantial amounts of carbonyl compound were obtained. Presumably, some impurities in the crude product were catalyzing the decomposition of the ketal functionality.

In order to avoid this problem, the crude product obtained from the dibromocarbene addition reaction was immediately hydrolysed with aqueous mineral acid, and the resultant material was purified by column chromatography over silica gel, with 4:1 petroleum ether-ether being used as eluting solvent. A white crystalline compound (ketone 326) was obtained in approximately 80% yield. On the basis of g.l.c. and spectral analysis, it was clear that this compound was stereochemically homogeneous.

The stereochemistry of compounds 325 and/or 326 was assigned as shown on the basis of steric considerations. That is, it was expected that the addition of dibromocarbene to the olefinic double bond of 324 would occur from the side opposite to the angular methyl group.



324

325

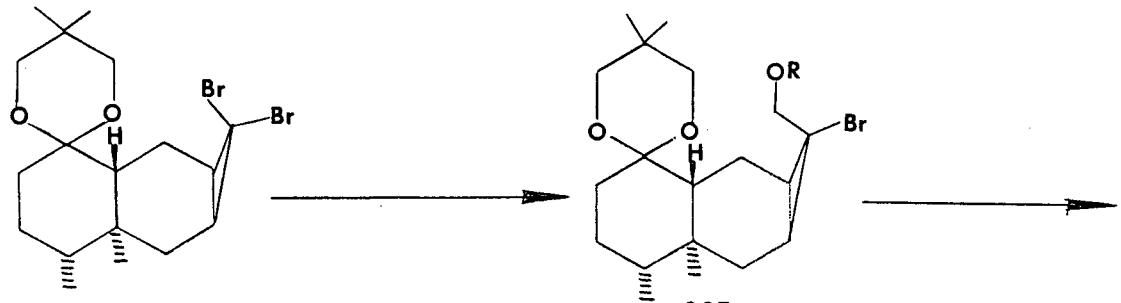
In the i.r. spectrum of the keto dibromide 326, a sharp, strong absorption at 1710 cm^{-1} indicated the presence of the ketone group. In the region associated with carbon-hydrogen bond stretching, a shoulder was observed at 3100 cm^{-1}. This absorption was assigned to stretching of the carbon-hydrogen bonds of the cyclopropane ring. In the p.m.r.

spectrum, the signal due to the tertiary methyl group was found at unusually high field (δ0.57). This was thought to be due to the anisotropic effect of the ketone functionality. The secondary methyl group gave rise to a doublet at δ0.93, with a coupling constant of 6.0 Hz. Finally, a one-proton multiplet at δ1.14-1.32 was assumed to be due to one of the cyclopropyl protons.

The purified keto dibromide 326 was ketalized by means of a standard procedure. The ketal dibromide 325 thus obtained was a very viscous pale yellow oil. This material was purified further by column chromatography on silica gel. The viscous pale yellow oil was clearly much more stable than the crude product isolated from the dibromocarbene addition reaction. The p.m.r. spectrum of this material showed singlets due to the tertiary methyl groups at δ0.66, 0.72 and 1.16. The secondary methyl group produced a doublet (J=5.0 Hz) at δ0.83. The bridgehead proton associated with the two six-membered rings gave rise to a broad pair of doublets at δ2.65-2.81 with coupling constants of 13.0 and 4.0 Hz. In the region of δ3.17-3.75, the four ketal protons formed a complex multiplet signal which could not be analysed easily. Thus, although the pure ketal dibromide 325 could not be isolated directly from the crude product of the carbene addition reaction (324 to 325), it could be obtained in about 70% overall yield by this indirect route (324 → 325 → 326 → 325).

One of the possible planned synthetic sequences involved the projected subjection of the dibromide 325 to a stereoselective halogen-lithium exchange to produce an intermediate which upon alkylation with a suitably functionalized alkylating agent would give the endo-alkylated product 327. Subsequent halogen-lithium exchange of the exo-bromide, followed by methylation of

the resultant intermediate and deprotection of the alcohol and ketone functionalities would provide the desired precursor 210 (X=OH) which, hopefully, could be converted into (±)-ishwarone 12. In order to obtain some evidence regarding the feasibility of such a synthetic sequence, it was decided to use 7,7-dibromonorcarane 185 as a model to investigate some of these reactions.



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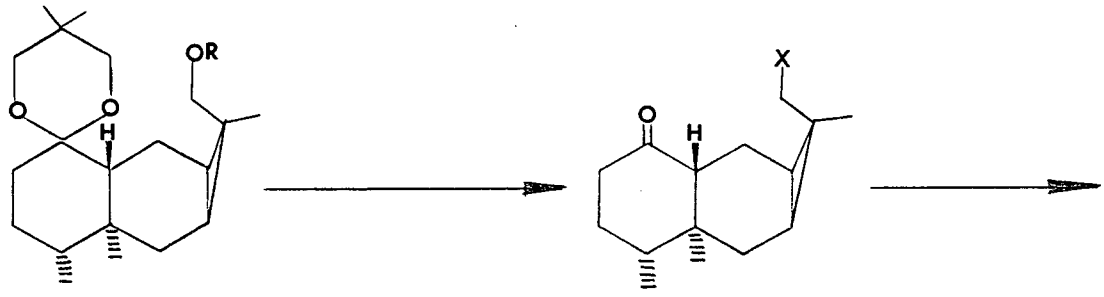

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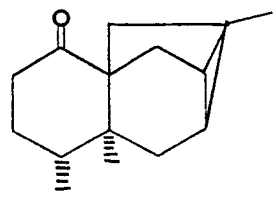
210



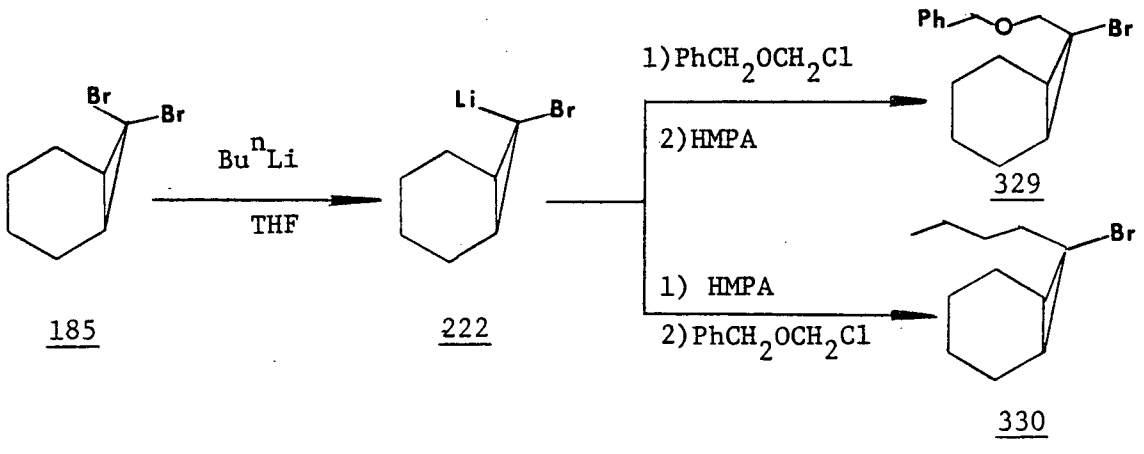
12

A. Model Studies Employing Norcarane Derivatives

An alkyl chloromethyl ether seemed to be a good choice as an alkylating agent for a conversion of the type 325 to 327. However,

use of the commercially available chloromethyl methyl ether would impose possible difficulties because the sensitivity of the cyclopropane ring to acidic conditions would limit the choice of reagents which could be used to cleave the methyl ether to the corresponding primary alcohol (328 to 210, X=OH). A better choice appeared to be chloromethyl benzyl ether since the primary alcohol functionality could then be liberated from the benzyl ether by hydrogenolysis under neutral conditions. Fortunately, chloromethyl benzyl ether was readily available from the reaction of benzyl alcohol and formaldehyde with hydrogen chloride according to a procedure reported by Graham and McQuillin.[129]

Addition of chloromethyl benzyl ether to a cold (-95°) tetrahydrofuran solution of 7-endo-litho-7-exo-bromonorcarane 222 (formed by treatment of 7,7-dibromonorcarane with n-butyllithium as described by Hiyama et al[70,71]) resulted in the formation of only small amounts of the desired 7-endo-benzyloxymethyl-7-exo-bromonorcarane 329. In attempts to facilitate the alkylation step, it was decided to add anhydrous hexamethylphosphoramide (HMPA) as a co-solvent. However, it was found that the sequence in which the hexamethylphosphoramide and the alkylating agent were added was very crucial. Introduction of the hexamethylphosphoramide before the alkylating reagent ($PhCH_2OCH_2Cl$) resulted in the formation of a

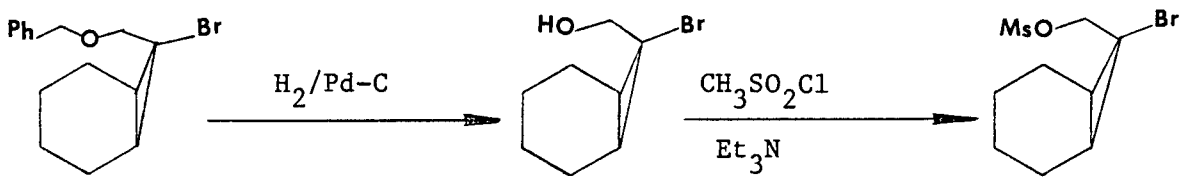


major product which was clearly not the desired material 329. On the basis of the i.r., p.m.r. and the mass spectra (m/e 230 and 232), this product was assigned the structure 330. Clearly, upon addition of the hexamethylphosphoramide, the carbenoid 222 had reacted rapidly with the n-butyl bromide which had been formed during the initial halogen-lithium exchange reaction. In order to overcome this problem, hexamethylphosphoramide was added simultaneously with or after the introduction of chloromethyl benzyl ether. By means of this simple experimental modification, it was possible to obtain the benzyl ether 329 as the predominant product. Column chromatography of the crude product gave the benzyl ether 329 in 35 to 49% yield, depending upon the amount of chloromethyl benzyl ether used. The i.r. spectrum of the product, a pale yellow oil, exhibited bands at 3050, 730 and 690 cm^{-1} due to the aromatic ring and a weak shoulder at 3090 cm^{-1} indicative of the presence of cyclopropyl protons. In the p.m.r. spectrum, the aromatic protons of the benzyl group were evidenced by a multiplet at δ7.37 which integrated for five protons. The methylene protons for the benzyl group were located at δ4.62 as a sharp singlet. The methylene protons of the ether moiety were found as a singlet at δ3.80.

Hydrogenolysis of the benzyl ether 329 with palladium-on-carbon at room temperature and atmospheric pressure, smoothly afforded 7 -exo-bromo-7-endo-hydroxymethylnorcarane 331. After this material had been distilled and cooled, it solidified to form a wax like substance. The presence of the primary alcohol functionality was supported by a broad absorption at 3403 cm^{-1} in the i.r. spectrum and by a sharp singlet at δ3.95 for the methylene protons adjacent to the hydroxyl group in the p.m.r. spectrum.

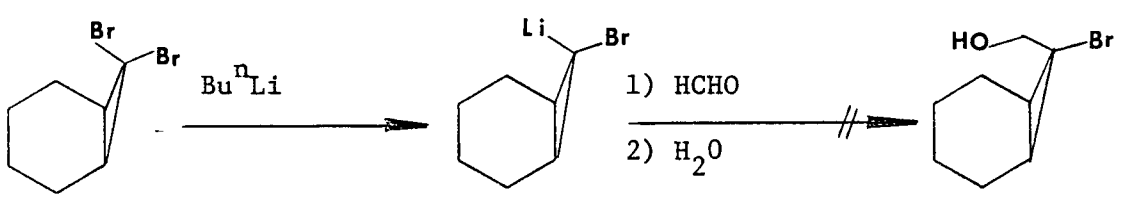
The bromohydrin 331 was efficiently converted into the corresponding mesylate 332 (97% yield) by the procedure reported by Crossland and Servis.[116]

This solid mesylate seemed to be fairly stable at low temperature, since no substantial decomposition was observed after the compound had been kept at low temperature(0°) for a long period of time. The i.r. spectrum of 332 exhibited strong absorptions at 1360 and 1170 cm^{-1} which could be attributed to the presence of the sulfonate group. In the p.m.r. spectrum, the methyl group of methanesulfonate moiety gave rise to a sharp singlet at δ2.63 while the methylene protons adjacent to the sulfonate were located at δ4.63 as a singlet.



329 331 332

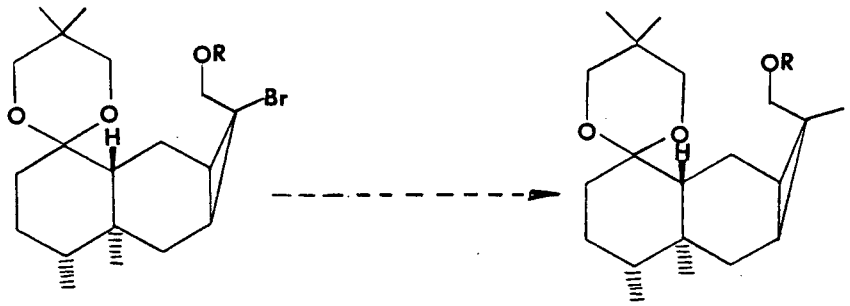
Since Hiyama et al.[121] and Seebach et al.[122] had both observed that the lithium carbenoid 222 could be trapped with aldehydes to give the corresponding bromohydrins, it was at least theoretically possible that the bromohydrin 331 could be obtained directly by passing gaseous formaldehyde into a solution of the lithium carbenoid 222. However, this proved



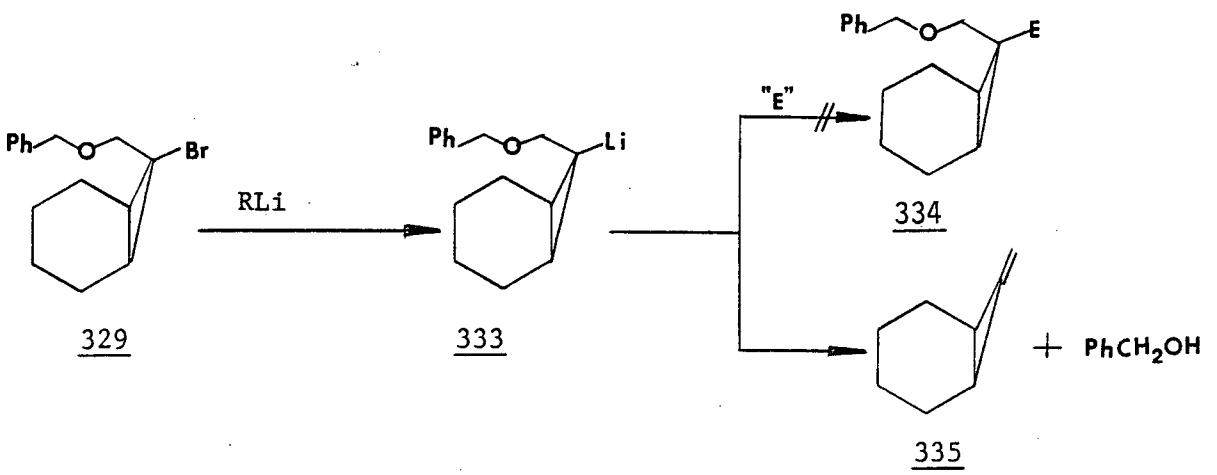
185 222 331

to be unsuccessful in practice. When the reaction was attempted at the necessary low temperatures (-95°), gaseous formaldehyde seemed to condense and polymerize rapidly and thus was not efficiently trapped. On the other hand, it is now well known that at higher temperatures (at which gaseous formaldehyde can be trapped efficiently by carbanions) carbenoids of the type 222 are not thermally stable, but decompose rapidly to carbenes.[120] Therefore, we were not able to obtain the bromohydrin 331 directly from 222 even though several attempts were made.

In order to gain some insight into the possibility of replacing the second bromo group in a compound such as 327 to give a gem-dialkylated cyclopropane derivative such as 328, the benzyl ether 329 was treated with an alkyllithium reagent. It was hoped that the corresponding cyclopropyl-



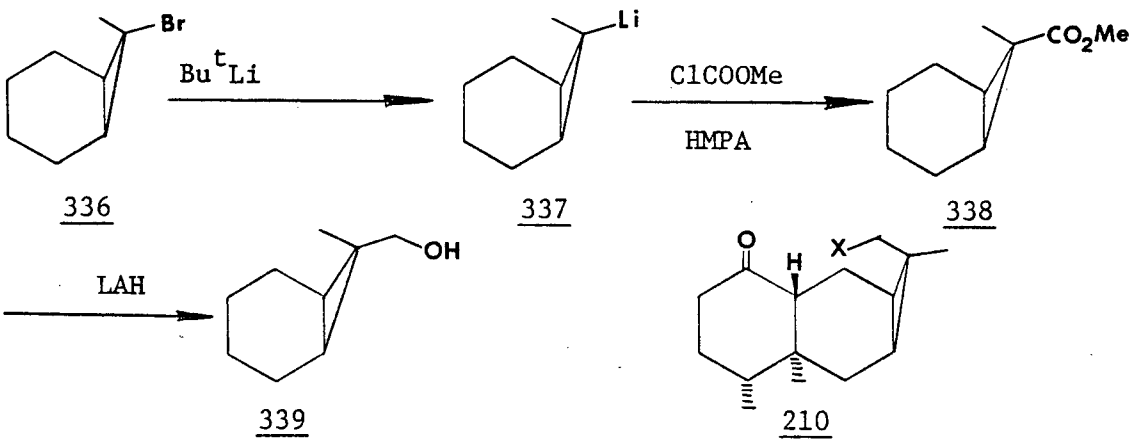
327 328



329 333 334 335

lithium intermediate 333 would be formed, which could then be trapped by an electrophile such as methyl iodide to give the desired derivative 334. However, all attempts to accomplish this transformation were unsuccessful. In most of the attempts, a complex mixture of products was obtained, although g.l.c. analyses indicated that the same major product had been formed in each case. A sample of this major component, collected by preparative g.l.c., was identified as benzyl alcohol by comparison with an authentic sample. In hindsight, the lack of success in these attempts was not entirely unexpected, since it is very reasonable to propose that the lithium compound 333, formed from 329 by metal exchange, could readily undergo 1,2-elimination to give the lithium alkoxide ($PhCH_2OLi$) and the olefin 335.

In view of this failure, it was decided to continue this aspect of the study using the readily available 7-endo-methyl-7-exo- hydroxymethyl - norcarane 339 as a substrate. Although this compound did not possess stereochemistry directly analogus to that of intermediates (e.g. 210) which could eventually become part of a synthesis of (±)-ishwarone, it was nevertheless felt that a study of the chemical behavior of 339 might supply some insight into the chemical properties of a compound such as 210 (X=OMs or halogen).



336 337 338

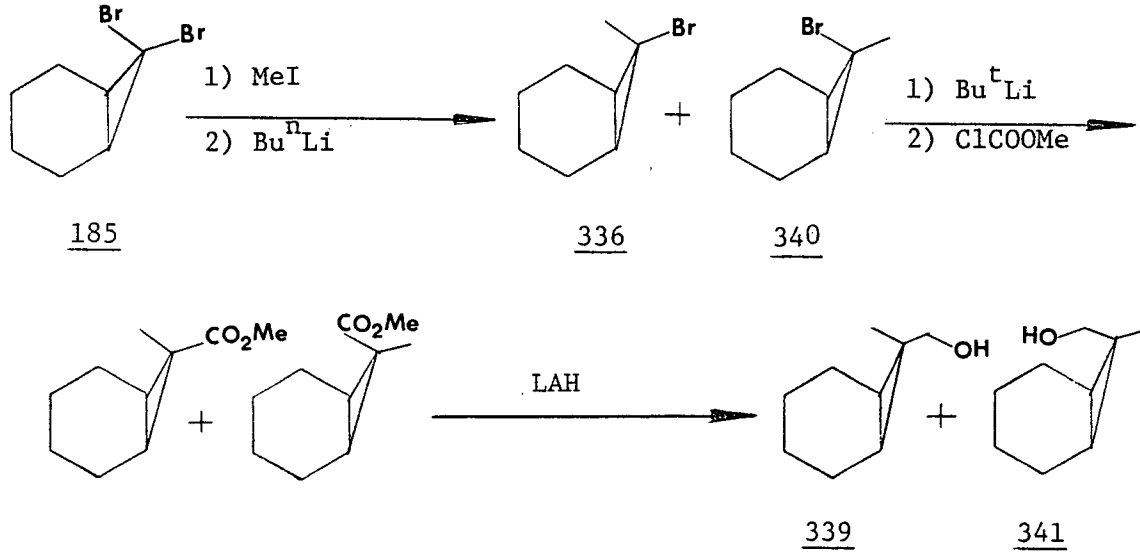
339 210

When the monobromide 336[70,71] was mixed with two equivalents of t-butyllithium in anhydrous ether at low temperature (-78°), lithium exchange proceeded smoothly. Successive addition of methyl chloroformate and dry hexamethylphosphoramide to the solution of the resultant cyclopropyllithium derivative gave 7-endo-methyl-7-exo-carbomethoxynorcarane 338 in about 60% yield. The i.r. spectrum showed a strong carbonyl absorption for the ester functionality at 1720 cm^{-1}. The stretching band due to the cyclopropyl protons was located at 3040 cm^{-1}. In the p.m.r. spectrum, sharp singlet signals at δ1.20 and δ3.57 could readily be attributed to the tertiary methyl group on the cyclopropane ring and the methyl group of the ester functionality, respectively.

This monoester 338 was reduced by treatment with lithium aluminum hydride in ether at room temperature. The resultant product, the alcohol 339, was isolated as a colorless viscous oil. The spectral properties of this material were in good agreement with the structure assigned. Thus, the i.r. spectrum showed a broad, strong band at 3400 cm^{-1} for the hydroxyl group. The absorption due to cyclopropane hydrogen stretching was found at 3020 cm^{-1}. In the p.m.r. spectrum, a sharp singlet at δ3.20 was due to the methylene protons adjacent to the hydroxyl group. A broad singlet at δ2.05 was attributed to the hydroxyl proton, while a sharp three-proton singlet at δ1.06 could be assigned to the tertiary methyl group. Finally, the two cyclopropyl protons gave rise to a multiplet at δ0.72.

When a mixture of the epimeric monobromides 336 and 340 (ca. 4:1) (obtained by the treatment of the dibromide 185 with alkyllithium in the presence of methyl iodide[70,71]) was subjected to the same reaction sequence

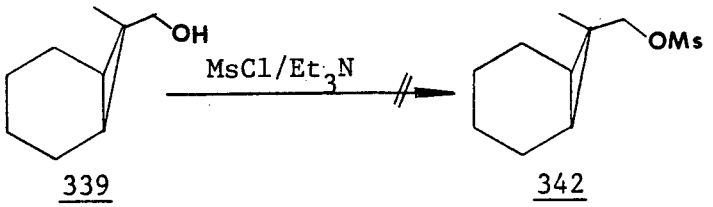
(i.e. lithiation, acylation with methyl chloroformate, and reduction with lithium aluminium hydride), a mixture of alcohols 339 and 341, in a ratio of approximately 7:3 was obtained. The i.r. and p.m.r. spectra of this material were very similar to those of the alcohol 339. However, in the p.m.r. spectrum, there was another sharp singlet at δ3.65 which could be assigned to the methylene protons adjacent to the hydroxyl group of epimeric 7-endo- hydroxylmethyl -7-exo-methylnorcarane 341.



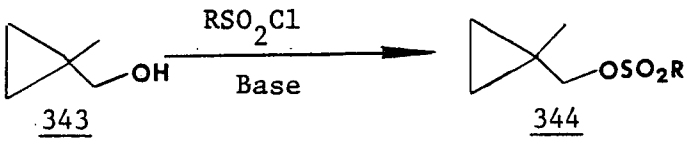
185 336 340 339 341

Mesylation of the primary alcohol 339 was attempted with methanesulfonyl chloride and triethylamine in methylene chloride and/or tetrahydrofuran solution at 0°.[116] However, no mesylate corresponding to the structure 342 could be isolated. Modifications involving removal of the triethylammonium salt by filtration and rapid evaporation of the solvent (instead of the normal aqueous work-up procedure) were tried, but, again isolation of the mesylate 342 was unsuccessful. Although the mesylate 344 (R=Me) and tosylate 344 (R=p-$CH_3C_6H_4$) of (1-methylcyclopropyl)carbinol 343, as well as the mesylate or tosylate 346 of the parent cyclopropylcarbinol

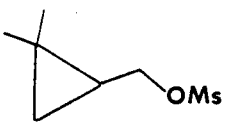
345, have been isolated successfully, the thermal instability of these compound was well known.[130-132] Furthermore, solvolysis studies have



339 342



343 344



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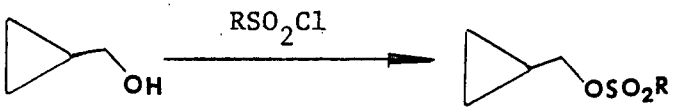
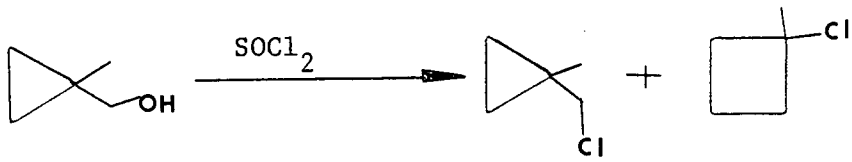


345 346

shown that the presence of methyl substituents on the ring would enhance the rate of solvolysis significantly. For example, the rate of solvolysis of the mesylate 344 was approximately five times faster than the solvolysis rate of the mesylate 346. Of even more interest was the fact that the relative rate of solvolysis of the mesylate 347 was ninety-six times faster.[132] Assuming that the effect of substituents on the rate of solvolysis was additive, it is possible to postulate that the mesylate 342 would solvolyze even faster than the mesylate 347. This inherent instability would account for the fact that the mesylate 342 could not be isolated from the reaction mixture.

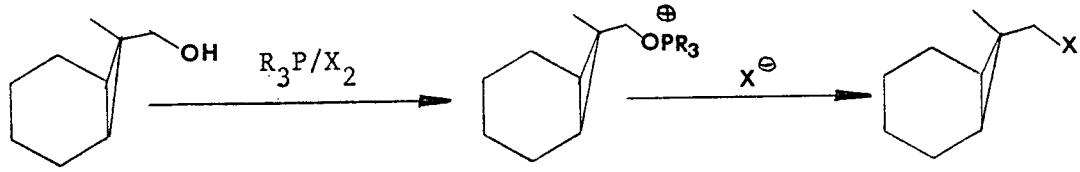
Although (1-methylcyclopropyl)carbinol 343 has been converted into the corresponding chloride 348 by treatment with thionyl chloride[131], the product was contaminated with significant amounts of the rearranged product 1-chloro-1-methylcyclobutane 349. Therefore, it was felt that this type

of procedure would be a poor choice for our purposes. Other reagents which could be employed for the synthesis of halides from alcohols,



343 348 349

(e.g., N-halosuccinimde and triphenylphosphite[133], carbon tetrahalide and tertiary phosphines[134], phosphorous tribromide[135], triphenylphosphine and halogen[136], dimethylbromosulfonium bromide[137]) usually proceed via a pathway involving a cationic-type transition state (cf. 350) which in the case of our desired transformation could well favour rearrangement to 352 rather than give 351.*



339 350 351

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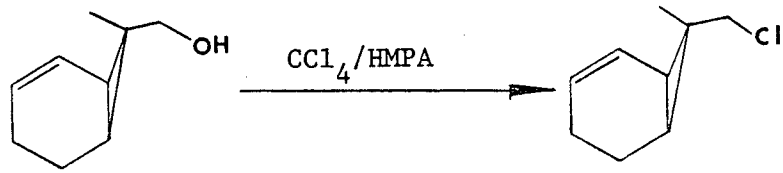
* Recently, Harding and Trotter[138] have reported that the alcohol i was transformed into the corresponding chloride ii by treatment with carbon tetrachloride and hexamethylphosphoramide.



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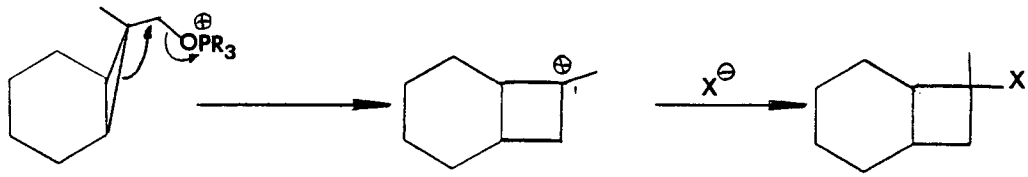
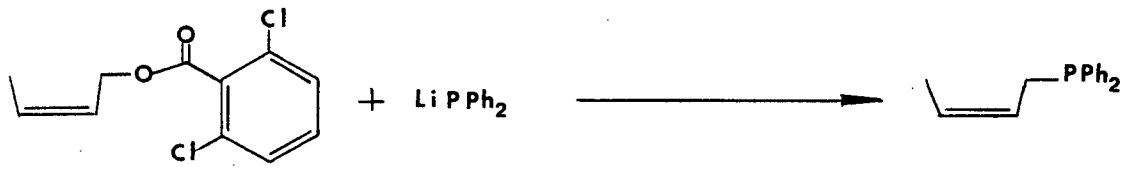


350 352

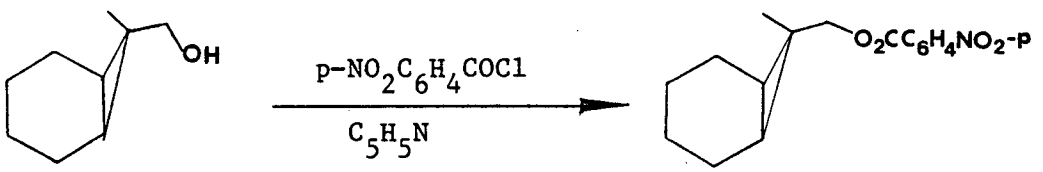
Acyloxy groups ($RCOO^-$) have received limited use as leaving groups in organic synthesis. However, it would be expected that the presence of a strongly electron attracting moiety in the R portion of such a group would enhance the leaving-group ability of the species. Indeed, this type of rationalization has been demonstrated by the reaction of the 2,6-dichlorobenzoate 353 with lithium diphenylphosphide to give product 354.[139,140] Since one might expect that a p-nitrobenzoate anion might also be a fairly good leaving group, it was decided to investigate the possibility of preparing the p-nitrobenzoate derivative of the alcohol 339.



353 354

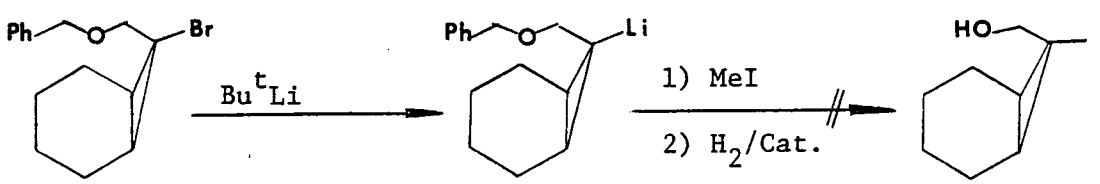
Treatment of the alcohol 339 with recrystallized p-nitrobenzoyl chloride in the presence of pyridine afforded the p-nitrobenzoate 355. The spectral data obtained from the latter were in agreement with the

assigned structure. In the i.r. spectrum, the ester functionality gave rise to a strong absorption at 1725 cm^{-1}. The presence of an aromatic ring was confirmed by absorption bands at 3030 and 1610 cm^{-1}, while the presence of a nitro group in the molecule was evidenced by strong absorptions at 1530 and 1350 cm^{-1}. In the p.m.r. spectrum, the aromatic protons gave rise to a multiplet at δ8.16 while the methylene protons adjacent to the ester moiety produced a singlet at δ4.00. Finally a sharp singlet and a multiplet located at δ1.12 and 0.86, respectively, could be assigned to the tertiary methyl group and the two cyclopropyl protons. It was thus clear that a p-nitrobenzoate of the type 355 could easily be prepared and that this type of substance was sufficiently stable to allow for isolation and characterization.



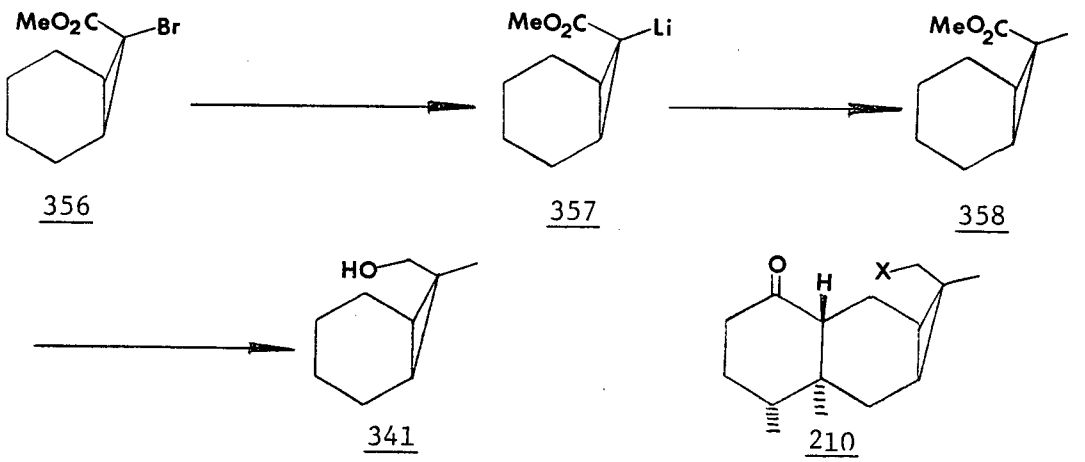
339 355

As was discussed previously, the epimer 341 of the alcohol 339 could not be prepared from the benzyl ether 329 by halogen-lithium exchange followed by methylation and deprotection of the primary alcohol.



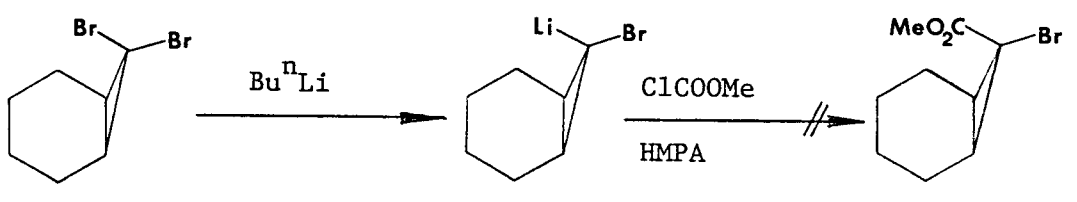
329 341

It was therefore decided to attempt the preparation of the monobromo ester 356 as an alternative starting material for the synthesis of the alcohol 341. Since halogen-lithium exchange is a very fast reaction, it was felt that treatment of 356 with an alkyllithium at low temperature would afford the litho ester 357, which upon alkylation with methyl iodide would give 358 Reduction of the latter compound would then afford the alcohol 341 which would possess sterochemistry similar to the prospective intermediate 210 (X=OH).



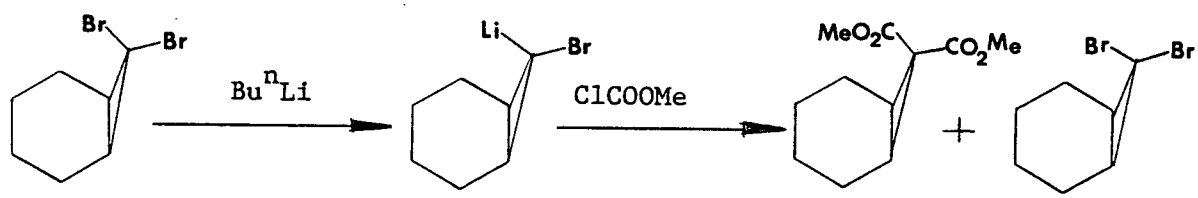
356 357 358 341 210

The attempted synthesis of the monobromo ester 356 involved an experimental procedure very similar to that employed for the synthesis of the benzyl ether 329, except that the lithium carbenoid 222 was trapped with methyl chloroformate instead of with chloromethyl benzyl ether. Thus, treatment of a tetrahydrofuran solution of 222 (prepared



185 222 356

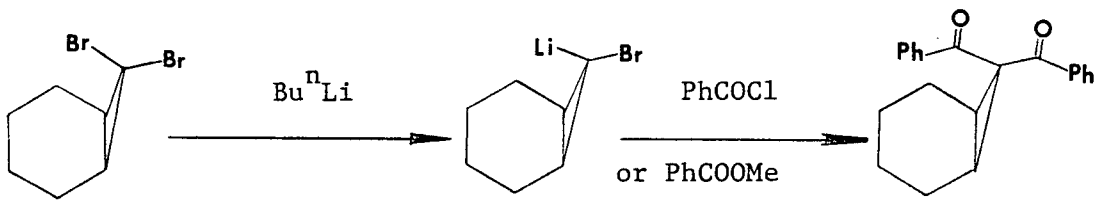
from dibromide 185 by exchange with one equivalent of n-butyllithium[70,71] with a large excess of distilled methyl chloroformate followed by hexamethylphosphoramide at -95° for 1 hour and then at -78° for 4 hours resulted in the isolation of a colorless oil. A g.l.c. analysis of the reaction product indicated that it consisted of two major components which differed very significantly in g.l.c. retention times. By means of a co-injection experiment, one of the major components was identified as the starting material, 7,7-dibromonorcarane 185. The other major component was later identified as 7,7-dicarbomethoxynorcarane 359, by comparison with an authentic sample prepared by treatment of 7,7-dibromonorcarane 185 with two equivalents of an n-butyllithium, followed by acylation of the resultant intermediate(s) with methyl chloroformate (see below).



185 222 359 185

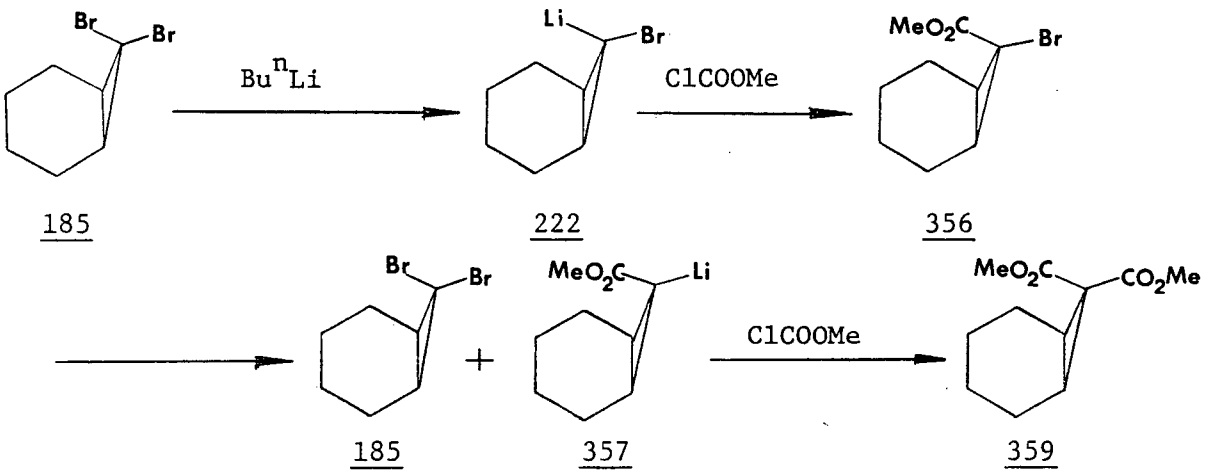
The yield of 7,7-dicarbomethoxynorcarane 359 from the above-described reaction was approximately 30%. A similar type of observation had been made by Seebach and his colleagues.[122] These workers found that when 7-bromo-7-lithionorcarane was allowed to react with methyl benzoate or benzoyl chloride, a 25 to 32% yield of the diketone 360 was formed.

In order to account for these types of transformations (185 to 359; 185 to 360), it seems reasonable to propose that the rate of acylation



185 222 360

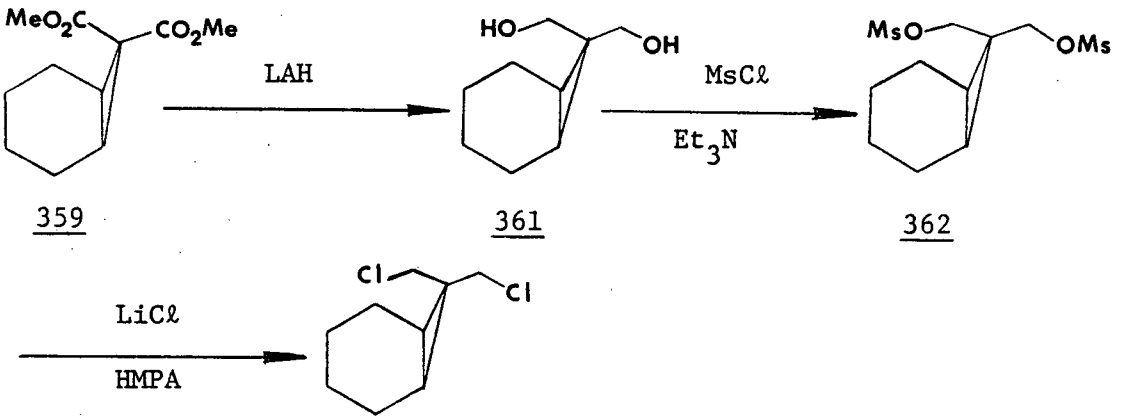
of the lithio derivative 222 was much slower than the rate of bromine-lithium exchange involving 222 and the initial acylated product 356. Thus, as soon as 356 was formed, it would react with the lithio derivative 222 to afford 7,7-dibromonorcarane 185 (the original starting material) and the new lithio derivative 357, which would then acylate to give the final product 359. In any case, it was clear that this type of reaction could not be used to effect the synthesis of the desired monobromo ester 356.



When a solution of 7,7-dibromonorcarane 185 was treated successively with two equivalents of n-butyllithium and excess methyl chloroformate, 7,7-dicarbomethoxynorcarane 359 could be isolated in 55% yield. The i.r.

spectrum of 359 showed a strong carbonyl absorption at 1720 cm^{-1}, while, in the p.m.r. spectrum, the two methyl groups of the ester functionalities gave rise to three-proton singlets at δ3.66 and 3.75.

Reduction of the diester 359 with lithium aluminum hydride afforded the diol 361 in very good yield. This compound exhibited a broad, strong absorption at 3400 cm^{-1} in the i.r. spectrum. In the p.m.r. spectrum, the cyclopropyl protons gave rise to a multiplet at δ0.90. Two singlets at δ3.46 and δ3.90 were attributed to the two sets of methylene protons adjacent to the hydroxyl groups. Finally, the two hydroxyl protons were observed as a broad singlet at δ3.46.



359 361 362

363

Conversion of the diol 361 into the dimesylate 362 was accomplished by means of a standard procedure.[116] The spectroscopic data obtained from the crude product were in good agreement with the assigned structure. In the i.r. spectrum, strong absorptions at 1355 and 1165 cm^{-1} were assigned to the stretching bands of the sulfonate moiety. In the p.m.r. spectrum, a signal at δ3.05, which integrated for six protons was attributed to the methyl groups of the two mesylate functionalities. The methylene protons adjacent to the two mesylate groups appeared as two singlets at δ4.00 and

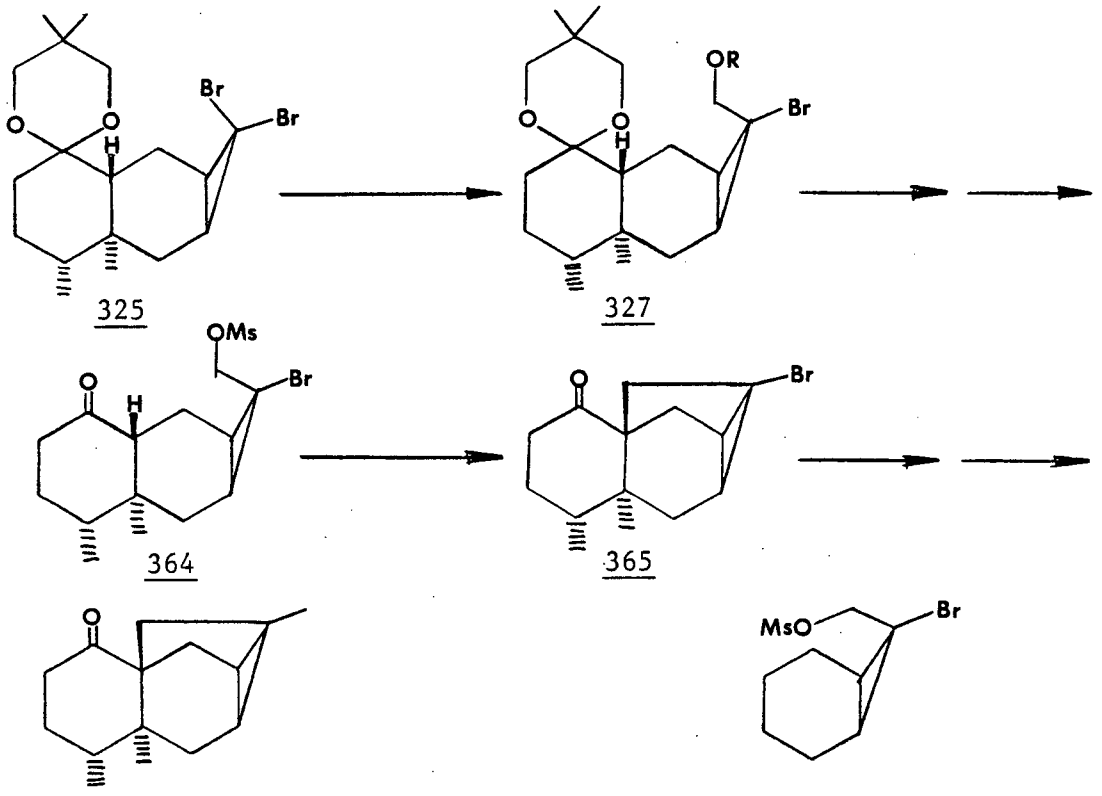
δ4.43. Due to the fact that the dimesylate 362 did not appear to be very stable, the crude product was immediately used in the next transformation.

When the crude dimesylate 362 was stirred with anhydrous lithium chloride in hexamethylphosphoramide, the dichloride 363 was formed in excellent yield. In the p.m.r. spectrum of 363, the methylene protons adjacent to the chlorine atoms gave rise to two singlets at δ3.50 and 3.87. It was thus clear that a dimesylate of the type 362 could easily be prepared and was sufficiently stable to allow for isolation. Furthermore, both of the neopentyl type mesylate groups could be readily displaced by chloride ion to produce the corresponding dichloride 363.

B. Attempted Synthesis of (±)-Ishwarone from the Dibromocyclopropane Derivative 325

On the basis of the results obtained from the model studies, it was possible to propose a number of routes which could possibly be used in the transformation of the dibromide 325 into ishwarone 12. Firstly, subjection of 325 to bromine-lithium exchange, followed by alkylation of the resultant intermediate with chloromethyl benzyl ether might afford the ketal benzyl ether 327 ($R=PhCH_2$). Since model studies had shown that the mesylate 332 was quite stable, it was thought that 327 ($R=PhCH_2$) could be converted by standard methodology into the keto mesylate 364, which could then be subjected to intramolecular alkylation to provide 365. After protection of the ketone functionality (e.g. ketal), the last required methyl group could be introduced by bromine-lithium exchange,

followed by methylation of the resulting cyclopropyllithium derivative.

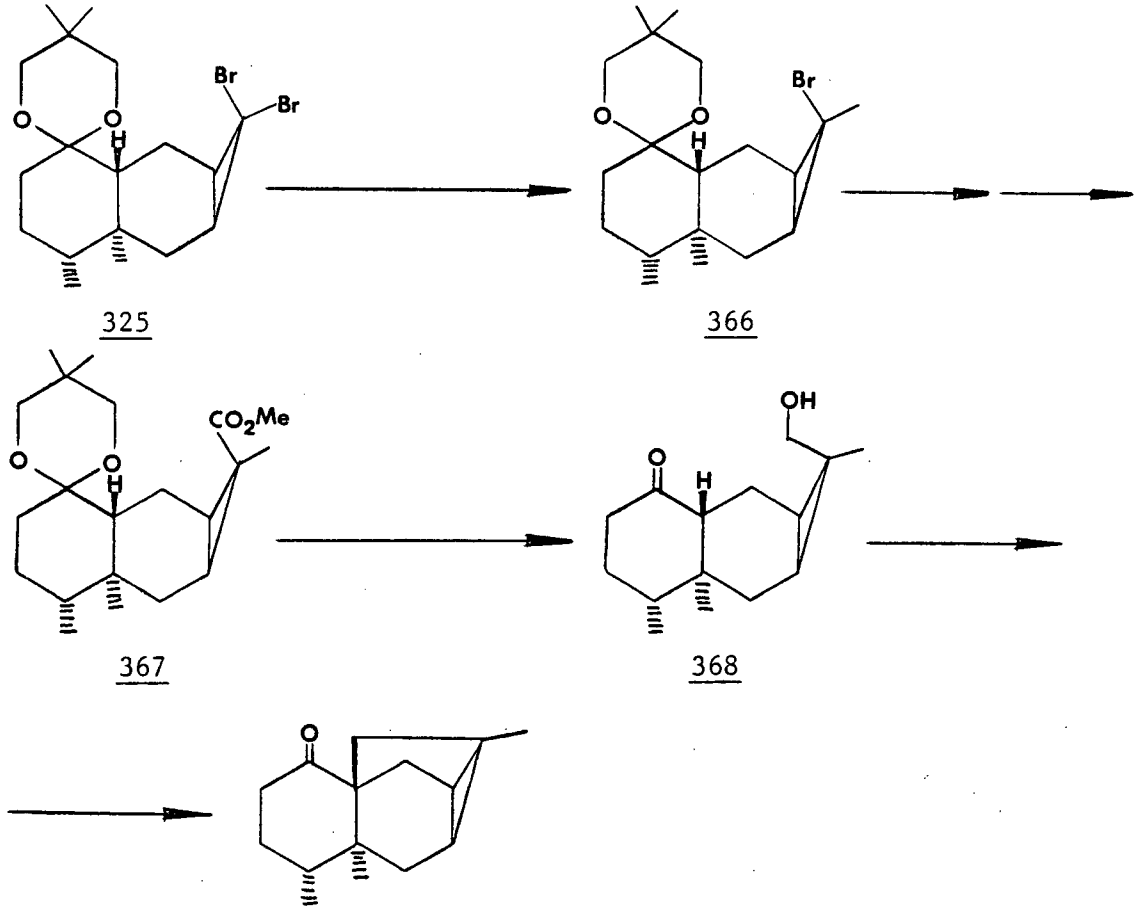


325 327

364 365

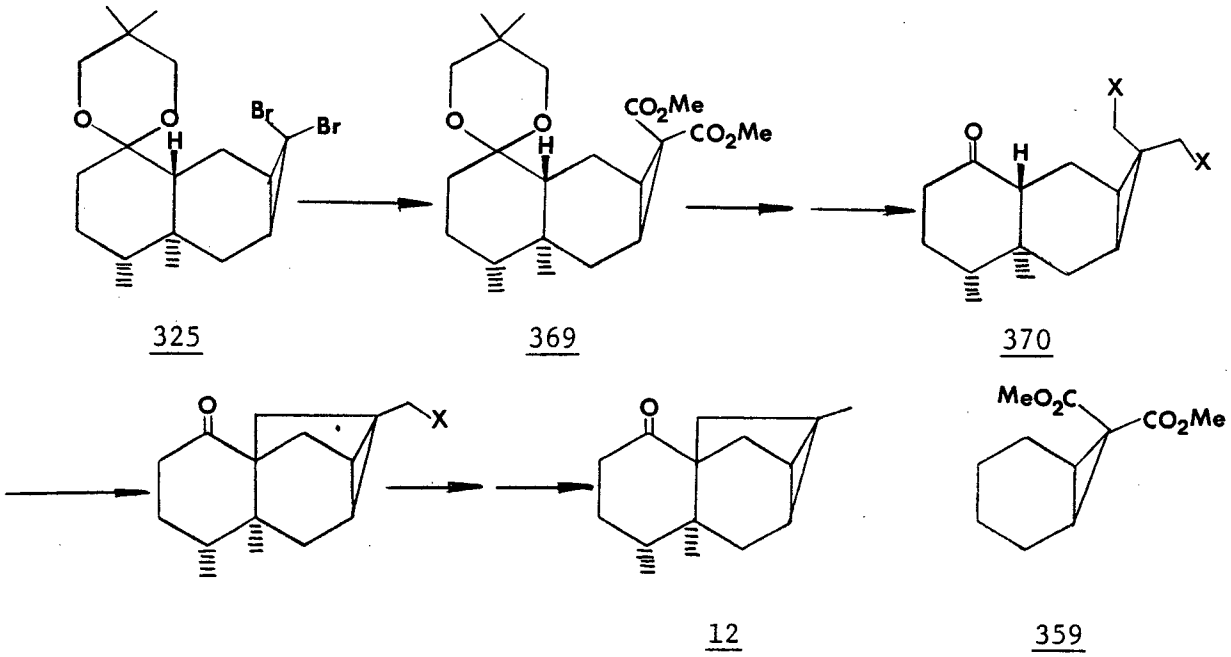
12 332

Alternatively, it was thought that it might be possible to subject 325 to the metal exchange-methylation sequence under conditions which would afforded the exo-methyl derivative 366 as the major product. Trapping the carbanion generated from this compound with methyl chloroformate, would then give the ketal ester 367. Conversion of the latter intermediate into the keto alcohol 368 would be straightforward. Theoretically, ishwarone 12 could be obtained directly from this keto alcohol 368 by intramolecular alkylation after the alcohol functionality had been converted into a suitable leaving group.



325 366 367 368 12

A third possible route which was considered was based on the observation that 7,7-dibromonorcarane 185 could be converted into the corresponding diester 359. Thus, by means of a similar transformation, the dibromide 325 would afford the diester 369. Subjection of the latter compound to a straight forward sequence of reactions would provide the dimesylate 370 (X=OMs), which presumably could be transformed into the dichloride 370 (X=Cℓ) if necessary. Intramolecular alkylation followed by reductive removal of the second mesylate (or chloride) would give ishwarone 12.



325 369 370

12 359

We chose first to explore the possibility of converting the dibromide 325 into the benzyl ether 327 (R=$PhCH_2$). To this end, a solution of compound 325 in tetrahydrofuran was treated with one equivalent of n-butyllithium at -95° for approximately 30 minutes, and to the resultant solution (presumably containing the carbenoid 371) was added excess chloromethyl benzyl ether and hexamethylphosphoramide.* However, the expected benzyl ether 327 (R=$PhCH_2$) was not obtained. Instead, g.l.c. and t.l.c. analyses showed that the product consisted of a complex mixture of many compounds. Attempts to improve this reaction by changing reaction conditions were unsuccessful. Apparently,

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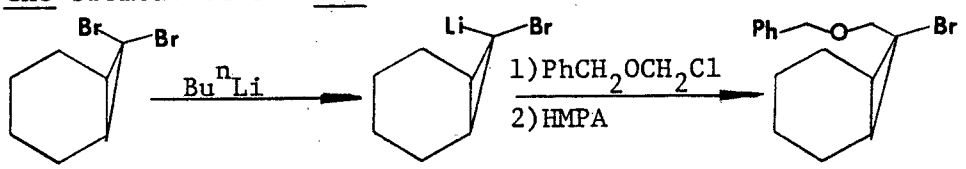
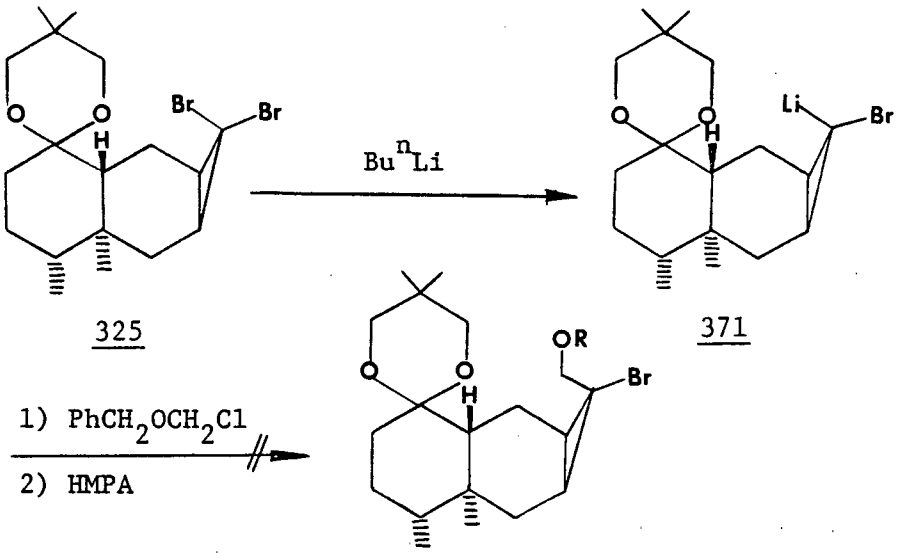
* These conditions were essentially identical with those used to convert 7,7-dibromonorcarane 185 into the benzyl ether of 7-endo-hydroxymethyl-7-exo-bromonorcarane 329.



185 329

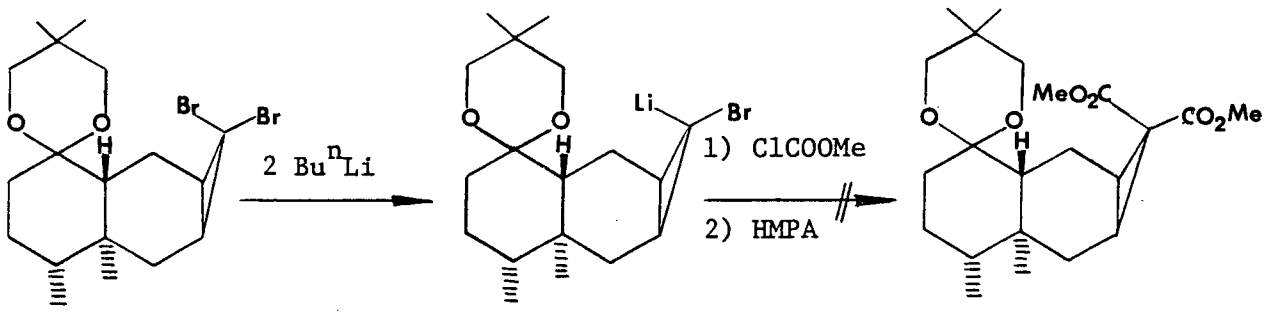
the reaction of the carbenoid with chloromethyl benzyl ether at -95°



325 371 327

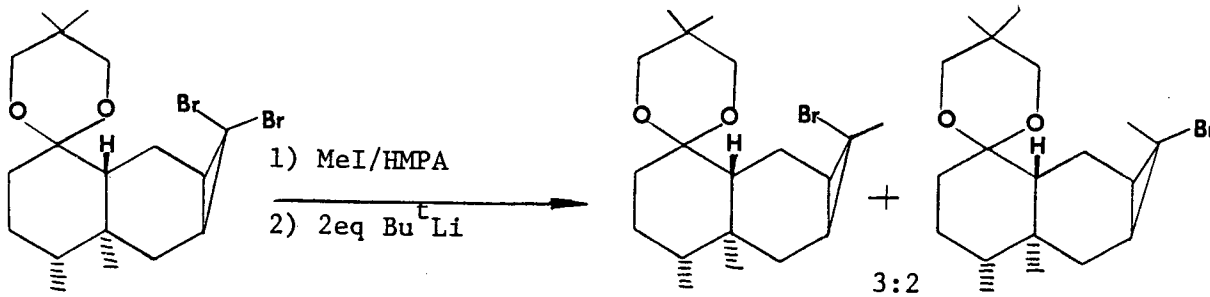
was very sluggish, while, at higher temperature, the inherent thermal instability of the lithium carbenoid caused it to decompose to form other side products.

In view of this failure, it was decided to attempt the conversion of 325 into the corresponding diester 369 under conditions which had previously successfully transformed 7,7-dibromonorcarane 185 into 7,7-dicarbomethoxynorcarane 359. Thus, a solution of compound 325 in dry tetrahydrofuran at -95° was treated with two equivalents of n-butyllithium, and to the resultant solution was added excess methyl chloroformate followed by dry hexamethylphosphoramide. However, spectral and g.l.c. analysis of the mixture of products showed that little, if any, of the desired diester 369 had been formed. Again, altering reaction conditions failed to have a positive effect on the reaction.



325 371 369

At this stage, it was decided to attempt the conversion of the dibromide 325 into the exo-methyl derivative 366. To this end, a pentane solution of two equivalents of t-butyllithium was added to a cold (-95°) solution of one equivalent of the dibromide 325, containing 3.5 equivalents of methyl iodide and 10% by volume of hexamethylphosphoramide. G.l.c. analysis of the product indicated the presence of two major components in a ratio of approximately 3:2. These major products were separated by means of column chromatography over silica gel. The first component which was eluted from the column was obtained in 58% yield. On the basis of the reaction conditions employed, it was expected that the major methylated product should have the cyclopropyl methyl group in an exo orientation and therefore this compound was tentatively assigned structure 366. This assignment was subsequently substantiated by p.m.r. data derived from a number of derivatives in this series of compounds (see later).



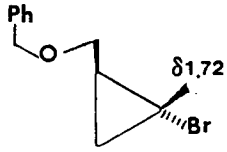
325 366 372

In the p.m.r. spectrum of compound 366, the ketal protons were observed as a multi-line signal between δ3.12 and 3.70, with a pattern very similar to that of 325 (see p-112) except that the high field signal assigned to the axial ketal protons gave rise to as a pair of unresolved quartets. The chemical shifts for the equatorial protons were found at δ3.63 and 3.55, with a coupling constant of 11.0 Hz for both signals. On the other hand, both axial ketal protons had a chemical shift at δ3.22 with a coupling constant of 11.0 Hz. The coupling constant for the large range W-type coupling between these protons and one of the gem-dimethyl group in the ketal moiety could not be measured from the spectrum due to the poor resolution of the signal. A doublet of doublets at δ2.62-2.78, with coupling constants of 12.0 Hz and 3.0 Hz, was attributed to the bridgehead proton associated with the two six-membered rings. A sharp three-proton singlet at δ1.74 was assigned to the tertiary methyl group on the cyclopropane ring. The other three tertiary methyl groups gave rise to singlets at δ0.64, 0.72 and 1.13, while the secondary methyl group produced a doublet at δ0.79, with a coupling constant of 6.0 Hz.

The second major component (38% yield) obtained from the above-mentioned column chromatography was clearly epimeric with the first compound and was therefore assigned structure 372. In the p.m.r. spectrum, the pattern for the signal of the ketal protons was exactly the same as that of

the corresponding signal derived from compound 325 (see p-112). Hence, a pair of doublets at δ3.63 and 3.54 (both with J=12.0 Hz) could be assigned to the equatorial ketal protons, while a pair of quartets at δ3.21 (J=12.0 Hz and 3.0 Hz) was assigned for the axial ketal protons. The bridgehead proton adjacent to the ketal functionality was found as an ill-resolved doublet of doublets at δ2.61-2.78, with coupling constants of about 14.0 Hz and 4.0 Hz. The tertiary methyl group on the cyclopropyl ring gave rise to a singlet at δ1.62. The other tertiary methyl groups gave rise to singlets at δ0.64, 0.71 and 1.12. The secondary methyl group was located at δ0.77 (J=6.0 Hz).

The fact that the signal for the cyclopropyl methyl group of the minor isomer 372 appeared at higher field (δ1.62) than the corresponding signal (δ1.74) for the epimeric compound 366 provided some evidence for the stereochemical assignments. On the basis of examples found in the literature, it was expected that the more sterically congested cyclopropyl methyl group (in 372) would resonate at higher field than the less congested cyclopropyl methyl group in 366. For example, the chemical shifts for the sterically congested cyclopylmethyl groups in compounds



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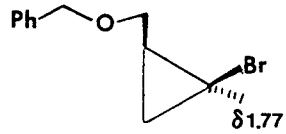

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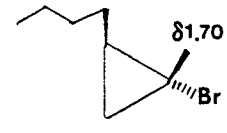

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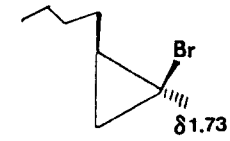

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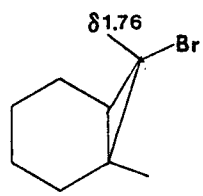

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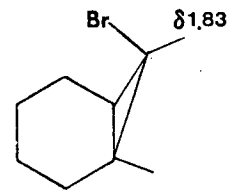

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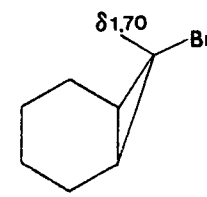

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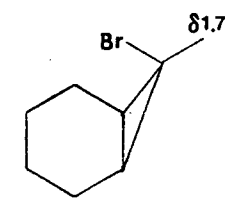

340

373, 375, 377 and 336 were found at higher field than the corresponding signals for the epimeric compounds 374, 376, 378 and 340.[71]

Treatment of compound 366 with two equivalents of t-butyllithium in pentane at -78°, followed by trapping the resultant cyclopropyllithium derivative with freshly distilled methyl chloroformate afforded the corresponding ester 367 in 71% yield. The i.r. spectrum of 367 showed a strong carbonyl absorption at 1720 cm^{-1}, indicating the presence of the ester group. In the p.m.r. spectrum, the ketal protons gave rise to a multiplet at δ3.16-3.74. Although the pattern of this multiplet appeared to be very similar to the analogous signals in the bromo ketal, detailed analysis could not be achieved due to interference from the signal due to the methyl group of the ester moiety, which gave rise to a sharp singlet at δ3.66. The bridgehead proton associated with the two six-membered rings produced an unresolved doublet of doublets at δ2.64-2.81. The signal due to the cyclopropyl methyl group was found at δ1.24, while the other three tertiary methyl groups appeared as sharp singlets at δ0.66, 0.78 and 1.16. Finally, the secondary methyl group produced a doublet (J=5.0 Hz) at δ0.80.

Reduction of the ketal ester 367 with lithium aluminum hydride produced the ketal alcohol 379 in good yield. The presence of a hydroxyl group in 379 was revealed by a strong broad absorption at 3500 cm^{-1} in its i.r. spectrum. Furthermore, the p.m.r. spectrum of this compound exhibited a two-proton singlet at δ3.58, which could be attributed to the methylene protons adjacent to the hydroxyl group. The other signals in the p.m.r. spectrum were very similar to those of compound 367.

Hydrolysis of the ketal moiety in compound 379 was accomplished efficiently by treatment of this material with aqueous hydrochloric acid

in acetone. The spectral data obtained from the product 368 were in good agreement with the assigned structure. In the i.r. spectrum, strong absorptions at 3450 cm^{-1} and 1705 cm^{-1} could be attributed to the presence of the hydroxyl group and the ketone functionality, respectively. The p.m.r. spectrum of this compound exhibited a two-proton singlet at δ3.56* for the methylene protons adjacent to the hydroxyl group, and two three-proton singlets at δ1.13 and 0.66 for the tertiary methyl groups. The secondary methyl group gave rise to a doublet at 0.86, with coupling constant of 6.0 Hz.

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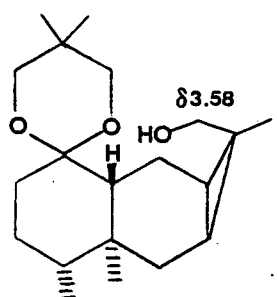
* A comparison of the chemical shifts of the methylene protons of the hydroxymethyl groups in compounds 379 and 368 with those of the analogous protons in compounds 381 and 382 (prepared from 372 via a route analogous to that employed for the conversion of 366→367→379→368) provided further corroboration for the stereochemical assignments made for this series of compounds. Thus, in compounds 379 and 368, this signal appeared as singlets at δ3.58 and 3.56, respectively, whereas, in the compounds 381 and 382, the singlets could be found at δ3.30 and 3.26 respectively. In the epimeric 7-methyl-7-hydroxymethylnorcaranes 341 and 339 (of established stereochemistry), the methylene protons of the hydroxymethyl group appeared as singlets at δ3.65 and 3.20, respectively (see page 122 and 123).



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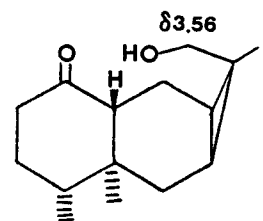

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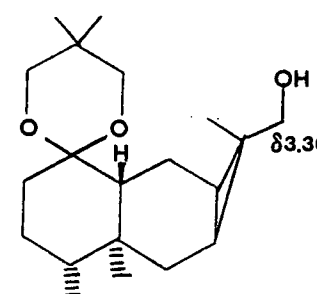

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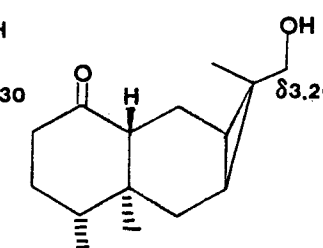

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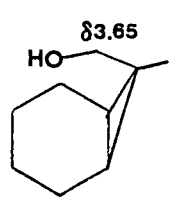

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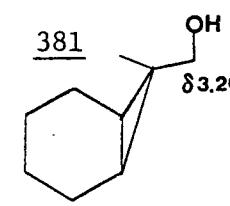

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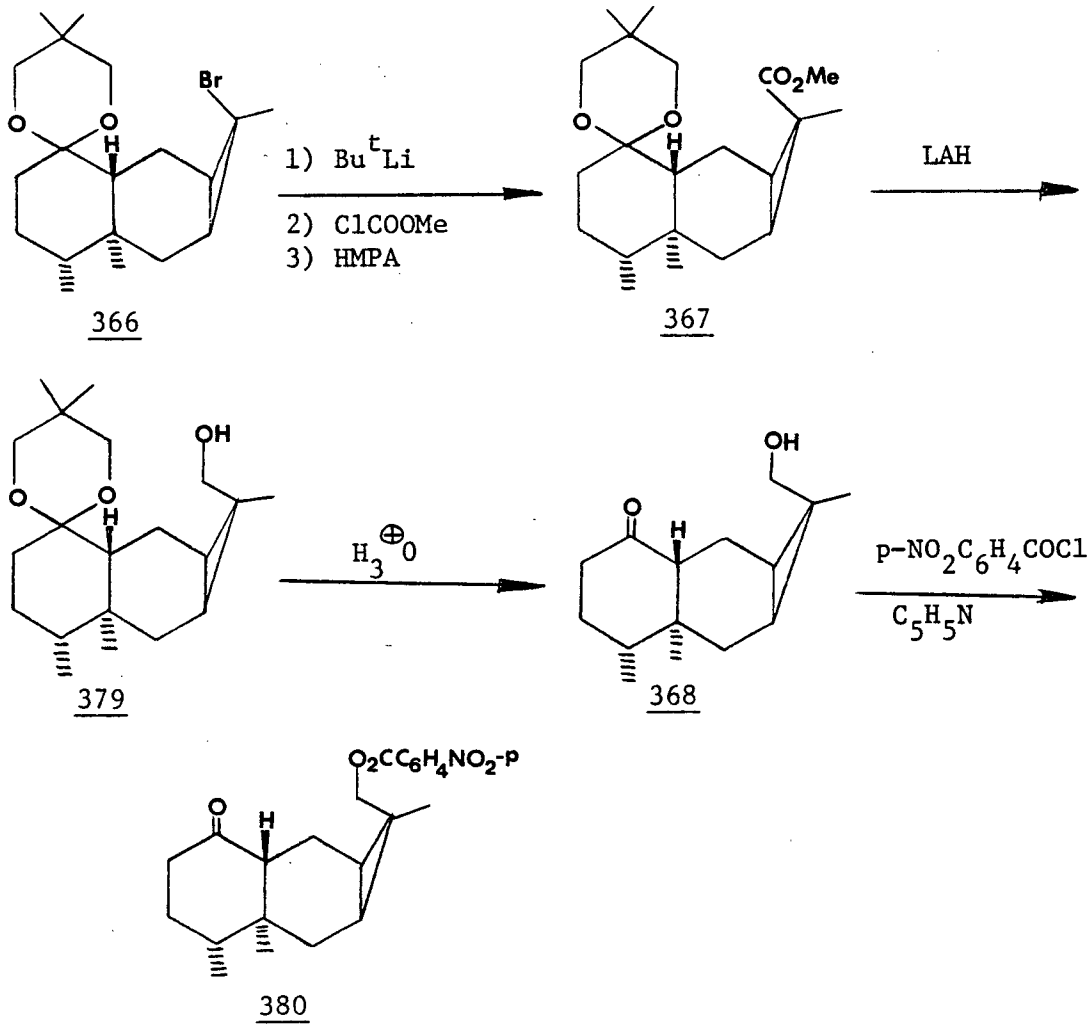
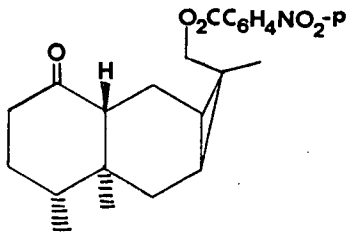


366 367 379 368 380

As might have been indicated by the model studies on norcarane derivatives, conversion of the hydroxy ketone 368 into a derivative in which the hydroxyl group had been transformed into a good leaving group proved to be problematic. For example, attempts to prepare and isolate the corresponding mesylate were consistently unsuccessful, presumably due to the instability of the cyclopropylcarbinyl mesylate system. In view of these failures, it was decided to prepare the p-nitrobenzoate 380 with the hope that the p-nitrobenzoate anion would serve as a leaving group for an intramolecular cyclization step. Thus, the keto alcohol 368

was treated with recrystallized p-nitrobenzoyl chloride and pyridine at 0° and the keto ester 380 was isolated from the crude product by means of preparative t.l.c. The spectral properties of this compound were in agreement with the structure 380. Thus, in the i.r. spectrum, a strong absorption at 1720 cm^{-1} indicated the presence of the aryl ester functionality and the nitro group was evidenced by strong absorptions at 1525 and 1345 cm^{-1}. The ketone carbonyl group gave rise to a strong band at 1705 cm^{-1}. In the p.m.r. spectrum, a four-proton multiplet at δ8.28 was attributed to the aromatic protons. The methylene protons adjacent to the ester group gave rise to a sharp singlet at δ4.38, while the two tertiary methyl groups produced singlets at δ1.20 and 0.66. The presence of a secondary methyl group was evidenced by a poorly resolved doublet at δ0.90, with a coupling constant of 6.0 Hz.

Attempts to effect the intramolecular cyclization of the p-nitrobenzoate 380 were carried out with different bases (e.q. potassium tert-butoxide, potassium hydride) in different solvents (e.g. tert-butyl alcohol, tetrahydrofuran) under a variety of conditions. Unfortunately, in all cases, either the starting material 380 was recovered, or the keto alcohol 368 was isolated as the only product. In no case was it possible to detect any of the desired product (±)-ishwarone 12.



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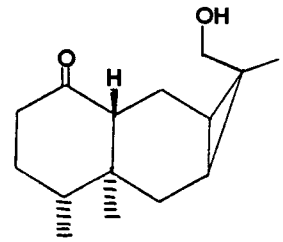

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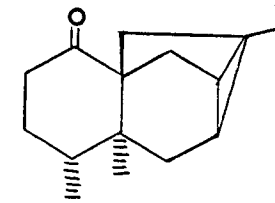
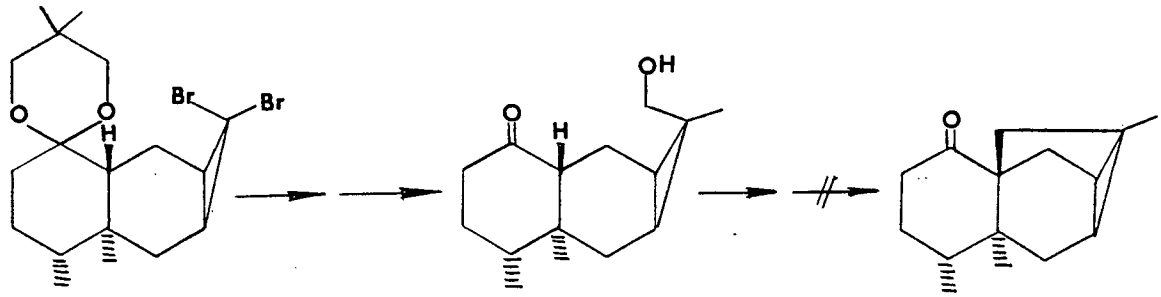


12

The projected conversion of the keto alcohol 368 into (±)-ishwarone 12 remains an attractive possibility. It seems quite likely that some method could be invented which would effect this transformation. However, at the same time at which the above study was being carried out, an alternative synthetic route to (±)-ishwarone 12 was also being investigated. This alternative, which is described in the following section of this thesis, proved to be successful and, therefore, attempts to effect the conversion of 368 into (±)-ishwarone 12 were discontinued.

V. Total Synthesis of (±)-Ishwarone and (±)-Ishwarane

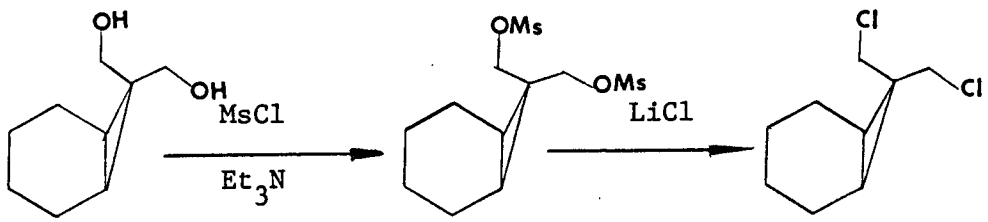
The difficulties encountered in the attempted synthesis of (±)-ishwarone 12 via the keto alcohol 368 (obtained from compound 325) were related to lack of success in finding a suitable leaving group for the intramolecular cyclization step. It was felt that the unsuccessful attempts to prepare the corresponding mesylate from the keto alcohol 368 was at least partially due to the electron donating effect of the methyl group. This effect would enhance the ease of solvolysis of the mesylate derivative. On this basis, one could at least qualitatively



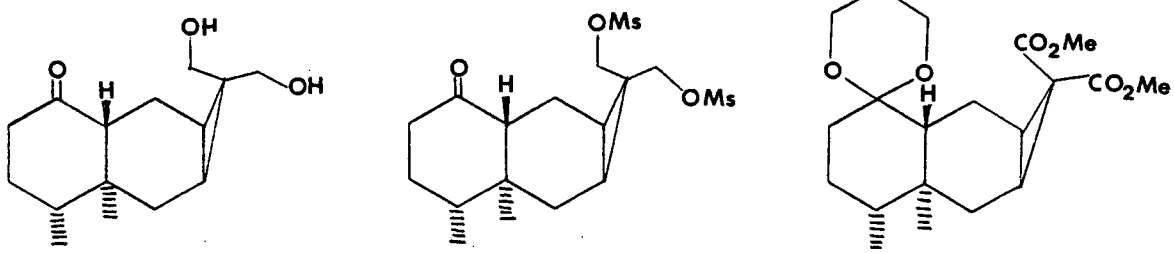
325 368 12

account for the fact that the keto mesylate was apparently too unstable to allow for isolation.

In the previously described model studies with norcarane derivatives, it had been found that the diol 361 could be converted successfully into the dimesylate 362, which in turn could be transformed into the dichloride 363. These encouraging results led us to investigate the synthesis of the keto diol 383 which, upon mesylation, should afford the dimesylate 384.

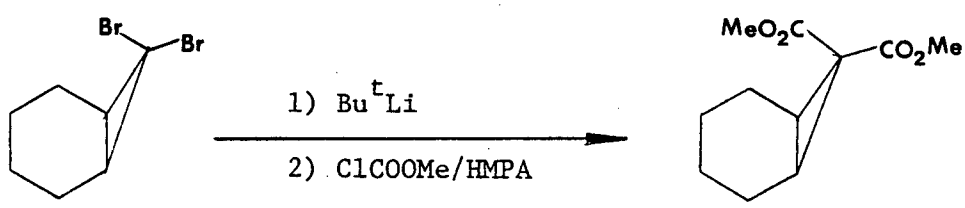


361 362 363

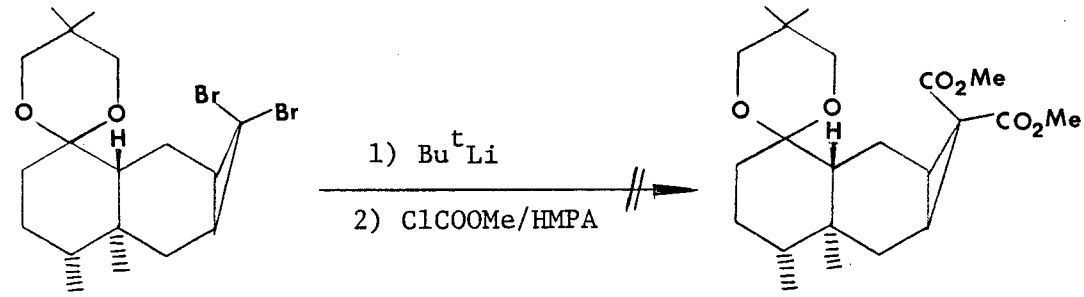


383 384 369

The most logical precursor for the keto diol 383 would be the ketal diester 369. Although, in the model studies, it was shown that 7,7-dibromonorcarane 185 could be transformed into the diester 359, the attempted conversion of the ketal dibromide 325 into the diester 369 proved to be unsuccessful. However, it was also possible to consider

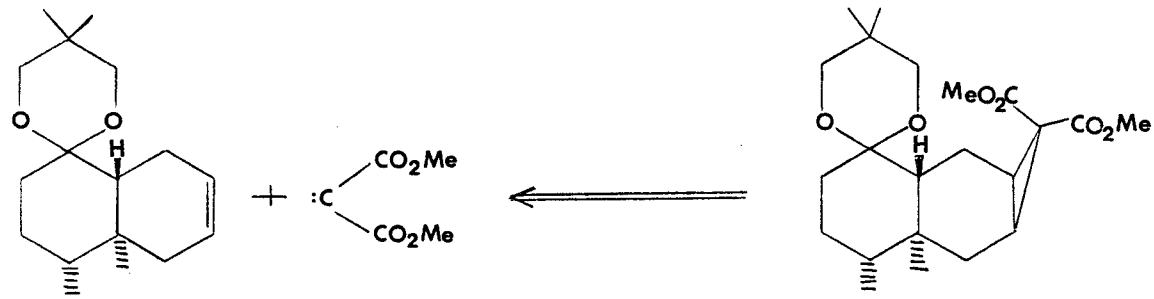


185 359



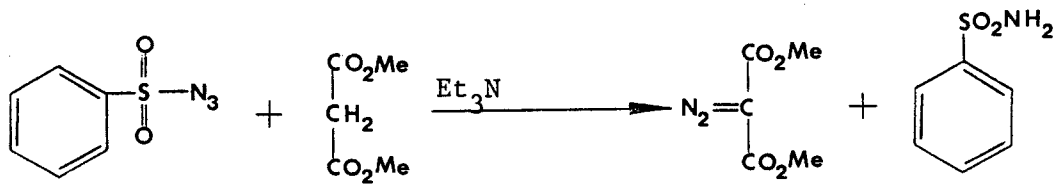
325 369

the diester 369 as the product of a reaction between the ketal olefin 324 and a carbenoid derived from dimethyl malonate.



324 369

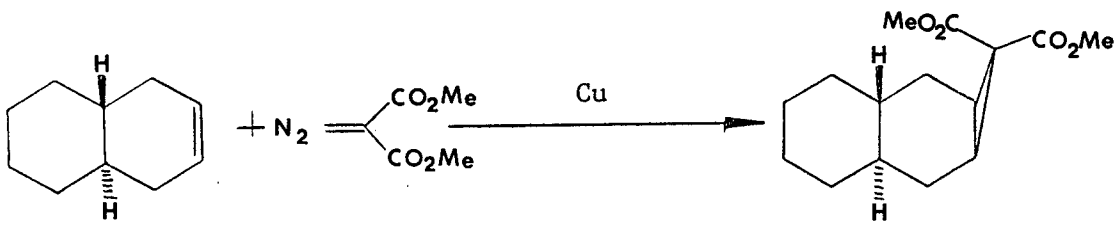
Dimethyl diazomalonate 386 was prepared by the reaction of dimethyl malonate with tosyl azide 385[141] in the presence of triethylamine, according to the procedure of Peace, Carman and Wulfman.[142]



385 386

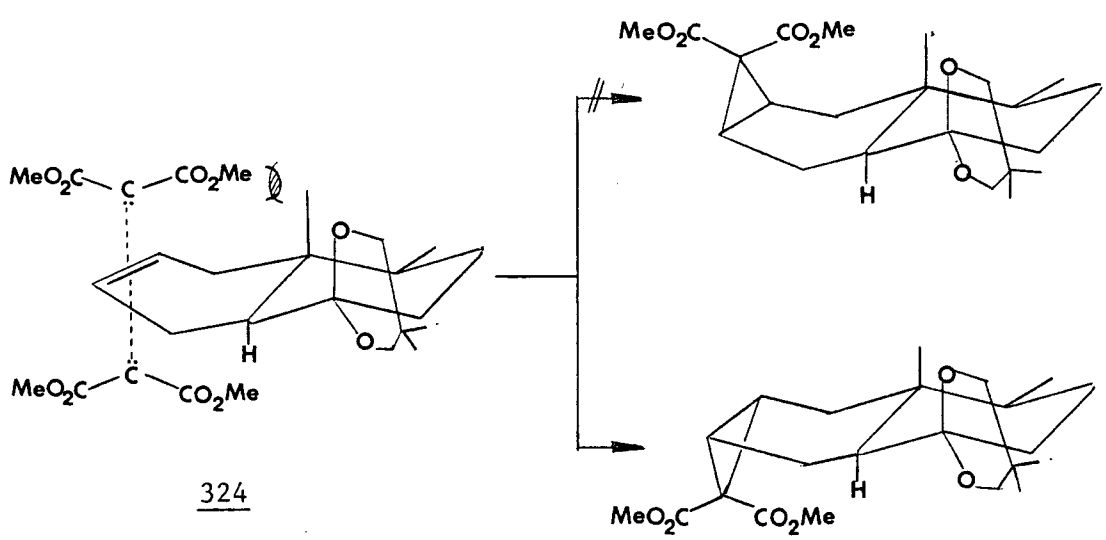
The reaction of diazomalonate with various acyclic and monocyclic olefins had been reported.[143] However, to our knowledge, the only report of an analogous reaction between diazomalonate and a bicyclic olefin

involved the simple octalin 387[144] as substrate. Therefore, no literature precedent which would provide the basis for predicting the stereochemical outcome of the projected reaction between the ketal olefin 324



387 386 388

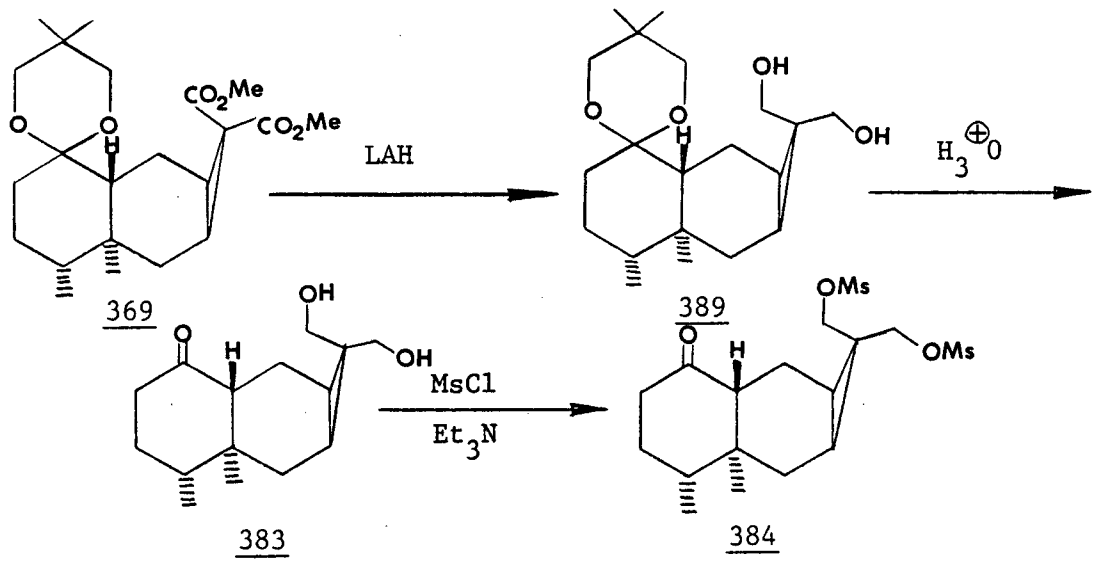
and dimethyl diazomalonate 386 existed. However, on the basis of steric considerations, it appeared highly likely that the carbenoid formed by thermal decomposition of diazomalonate in the presence of copper bronze (or a copper salt), would add to the carbon-carbon double bond of 324 from the side opposite to the angular methyl group (see below). Thus, only the trans product 369 would be expected.



324 369

Reaction between the ketal olefin 324 and excess dimethyl diazomalonate 386 in the presence of copper bronze at 130-140° gave an 80% yield of a single adduct which was assigned structure 369. The spectral properties of this compound were in agreement with the assigned structure. In the i.r. spectrum, the presence of the cyclopropane-type protons and of the ester groups was revealed from absorptions at 3105 and 1730 cm^{-1}, respectively. In the p.m.r. spectrum, the ketal protons appeared as a multi-line signal. The pattern was similar to that obtained from the ketal olefin 324 (see p-112), but due to the interference of the strong singlets due to the methyl groups of the methyl ester functionalities (δ3.68 and 3.74), detailed analysis of this pattern could not be achieved. The secondary methyl group in the molecule gave rise to a doublet(J=6.0 Hz) at δ0.80, while the tertiary methyl groups produced singlets at δ0.66, 0.82 and 1.15.

Reduction of the ketal diester 369 with lithium aluminum hydride in anhydrous ether provided the ketal diol 389 as a white powder in 94% yield. The presence of the hydroxyl groups in this molecule was shown by a broad absorption at 3300 cm^{-1} in its i.r. spectrum. In the p.m.r. spectrum, a broad eight-proton multiplet between δ3.60 and 3.90 could be attributed to the methylene protons of the ketal functionality and to the two hydroxymethyl groups. Singlets at δ0.63, 0.75 and 1.10 were attributed to the tertiary methyl groups, while a doublet at δ0.63 with a coupling constant of 6.0 Hz was assigned to the secondary methyl group.

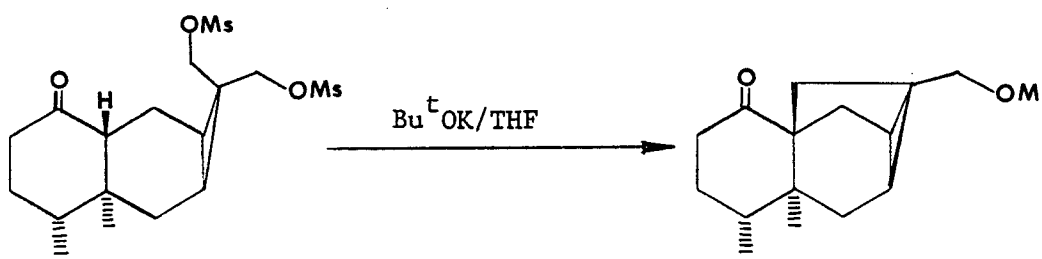


Hydrolysis of the ketal diol 389 to the keto diol 383 was achieved by treatment of the former with hydrochloric acid in aqueous acetone. In the i.r. spectrum of 383, absorptions at 3300 and 1700 cm^{-1} could be attributed to the presence of hydroxyl groups and a ketone carbonyl group, respectively. In the p.m.r. spectrum, the methylene protons of the endo hydroxymethyl group gave rise to an AB pair of doublets at δ3.45 and 3.61, with a coupling constant of 12.0 Hz. The corresponding AB pair of doublets for the exo hydroxymethyl group appeared at δ3.70 and 3.90, with a coupling constant also equal to 12.0 Hz. An upfield singlet at δ0.66 and a doublet at δ0.91, with coupling constant of 6.0 Hz, were attributed to the tertiary and secondary methyl groups, respectively.

Treatment of the keto diol 383 with methanesulfonyl chloride in the presence of triethylamine afforded the keto dimesylate 384 as a pale yellow viscous oil. The i.r. spectrum of the crude product exhibited strong absorptions at 1355 and 1170 cm^{-1} which were due to the stretching bands of the sulfonate moiety. The carbonyl group gave rise to a strong band at 1700 cm^{-1}. In the p.m.r. spectrum, the methylene protons of

the exo CH_2OMs group gave rise to a singlet at δ4.30, while the corresponding signal for the endo CH_2OMs group was an AB pair of doublets at δ3.96 and 4.04. Other signals of particular interest were a singlet at δ0.66 and an unresolved doublet at 0.90, which were assigned to the tertiary and secondary methyl groups respectively. The methyl groups of the methanesulfonate moiety gave rise to the singlets at δ3.03 and 3.06.

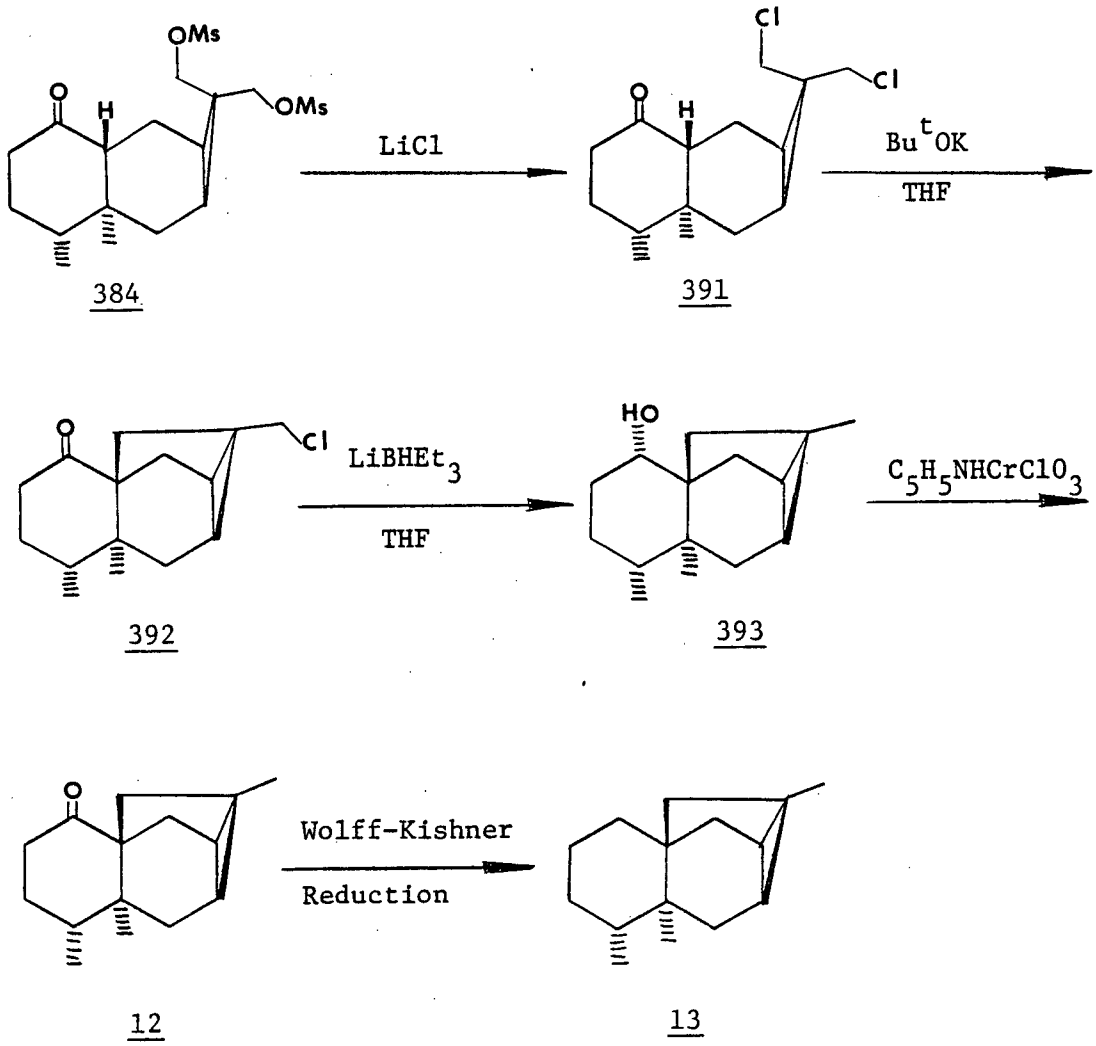
Because it appeared to be rather unstable, the crude keto dimesylate 384 was not purified, but was used immediately for the next step. All attempts to effect conversion of the keto dimesylate 384 into the tetracyclic keto monomesylate 390 via a base-promoted intramolecular alkylation reaction failed. Although it appeared to be highly probable that the desired transformation had occurred, the desired product 390 was apparently not sufficiently stable under the reaction conditions to allow for isolation. Therefore, it was felt that if the mesylate group of 384 were replaced by a "poorer" leaving group such as chloride, then the corresponding tetracyclic keto chloride might be stable enough to be isolated.



384 390

The keto dichloride 391 was prepared smoothly by stirring the crude dimesylate 384 with anhydrous lithium chloride in a mixture of hexamethylphosphoramide and ether. The product, obtained in 91% overall yield from

keto diol 383, exhibited spectral properties in agreement with structure 391. Thus, the i.r. spectrum showed a carbonyl absorption at 1706 cm^{-1}.



In the p.m.r. spectrum, the protons of the endo chloromethyl group gave rise to an AB pair of doublets at δ3.36 and 3.66, with a coupling constant of 11.0 Hz, while the corresponding signals for the exo chloromethyl group

were located at δ3.61 and 3.81, with a coupling constant of 12.0 Hz. The tertiary and secondary methyl groups exhibited a singlet at δ0.62 and a doublet (J=6.5 Hz) at δ0.92, respectively.

When the keto dichloride 391 was treated with a slight excess of freshly prepared potassium tert-butoxide in tetrahydrofuran, intramolecular alkylation proceeded smoothly to afford the tetracyclic keto chloride 392 in excellent yield. In the p.m.r. spectrum of the product 392, a sharp two-proton singlet at δ3.60 could be attributed to the protons of the chloromethyl group. A singlet at δ0.73 and a doublet at δ0.87 (J=6.0 Hz) were assigned to the tertiary and secondary methyl groups, respectively. Although this cyclopropylcarbinyl chloride could be isolated, it did not appear to be very stable and it therefore was used immediately for the next reaction.

Reduction of halides and mesylates (or tosylates) to hydrocarbons can be achieved by a variety of reducing agents, for example, lithium triethylborohydride ("super hydride")[145-147], potassium tri-s-butylborohydride - cuprous iodide complex[148], complex metal hydrides of copper (i.e. Li_4CuH_5)[149] and lithium alkylcopper hydride (LiCuHR)[150]. Due to the commercial availability of lithium triethylborohydride, we chose to investigate the reduction of the keto monochloride 392 with this reagent.[145] When 392 was treated with four equivalents of the reducing agent in tetrahydrofuran, it was converted smoothly into the alcohol 393. The isolated product exhibited a strong,broad absorption at 3350 cm^{-1} in its i.r. spectrum. In the p.m.r. spectrum, the presence of two tertiary methyl groups was shown by two three-proton singlets at δ1.03 and 1.13. The

secondary methyl group gave rise to a doublet at δ0.77, with a coupling constant of 5.5 Hz. A high field multiplet at δ0.55 was assigned to one of the cyclopropyl protons. An unresolved multiplet at δ3.42, with width at half-height of 6.0 Hz, was attributed to the proton adjacent to the hydroxyl group. Judging from the p.m.r. spectrum and taking into account the steric hindrance exerted by the angular methyl group, the stereochemistry of the hydroxyl group was tentatively assigned to be cis to the angular methyl group.

Oxidation of the alcohol 393 with pyridinium chlorochromate[151] in methylene chloride gave a ketonic compound 12 in 69% overall yield from the keto dichloride 391. The i.r. spectrum of this compound exhibited a strong absorption at 1700 cm^{-1} due to the carbonyl group and a weak band (shoulder) at 3030 cm^{-1} due to the presence of cyclopropane-type protons. In the p.m.r. spectrum, the tertiary methyl groups gave rise to singlets at δ0.74 and 1.16. Finally, a doublet at δ0.87, with a coupling constant of 6.5 Hz, was assigned to the secondary methyl group. These spectral data were in full agreement with those reported for the natural product (+)-ishwarone 12.[12]

In order to confirm the structure of the final product, the synthetic (±)-ishwarone 12 was converted into (±)-ishwarane 13 by Wolff-Kishner reduction as reported.[12] The i.r. spectrum of the product, which showed no carbonyl absorption, exhibited a band at 3040 cm^{-1} which was attributed to the presence of cyclopropane-type protons. In the p.m.r. spectrum, the cyclopropyl protons appeared as a multiplet at δ0.52. The tertiary methyl groups produced singlets at δ0.78 and 1.14, while the secondary methyl group gave rise to a doublet at δ0.74, with a coupling

constant of 6.5 Hz. The spectral properties and g.l.c. retention times of this product were identical with those of authentic (±)-ishwarane 13*.[57]

In conclusion, a stereoselective total synthesis of (±)-ishwarone and (±)-ishwarane was carried out. To our knowledge, the work described herein constitutes the first total synthesis of (±)-ishwarone. Potentially, the sequence could be extended further to include the synthesis of 3-oxoishwarane, and thus all presently known members of the ishwarane class of sesquiterpenoids could be obtained from this sequence.

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* We are grateful to Professor R. B. Kelly for a sample of authentic (±)-ishwarane.

EXPERIMENT

Melting points, which were determined with a Fisher-Johns melting point apparatus, and boiling points are uncorrected. Infrared spectra were recorded on a Perkin-Elmer model 710 spectrophotometer. The proton magnetic resonance spectra were taken in deuterochloroform solution on Varian Associates Spectrometers, models T-60 and/or HA-100 or XL-100. Signal positions are given in parts per million (δ) with tetramethylsilane as an internal reference; the multiplicity, integrated peak areas, and proton assignments are indicated in parentheses. Gas-liquid chromatography (g.l.c.) was carried out with a Varian Aerograph model 90-P gas chromatograph, or with a Hewlett-Packard model 5832A gas chromatograph. The following columns were employed.

Column	Length	Stationary Phase	Support	Mesh
A	10' x ¼"	20% SE-30	Chromosorb W	60/80
B	"	10% SE-30	"	"
C	"	10% OV-210	"	"
D	5' x ¼"	20% SE-30	"	"
E	"	10% SE-30	"	"
F	6' x 1/8"	10% OV-210	"	110/120

The specific column used along with column temperature and carrier gas (helium) flow-rate (in ml/min) are indicated in parentheses. Column chromatography was performed using florisil (Fischer Scientific Co.) or neutral silica gel (Camag or Macheray, Nagel and Co., or E. Merck, Silica Gel 60). The alumina Act III used in filtration columns was obtained by deactivating neutral alumina Act I (Alumina Woelm B, Act I) with 6% of

water. Thin layer chromatography was carried out with commercial silica gel plates (Eastman Chromagram Sheet Type 13181) or with 20 x 5 cm glass plates coated with 0.5 mm of neutral silica gel (silica gel GF 254, E. Merck) and activated by heating in an oven for 12-24 hours. Preparative thin layer chromatography was carried out with 20 x 20 cm glass plates coated with 1 mm of neutral silica gel (silica gel GF 254, E. Merck) and activated by heating in an oven for 12-24 hours. The high resolution mass spectra were recorded on an AEI MS-902 mass spectrometer. Microanalyses were performed by Mr. P. Borda, Microanalytical Laboratory, University of British Columbia.

Dried solvents were used in all reactions. Dry tetrahydrofuran and hexamethylphosphoramide were distilled from lithium aluminum hydride. Methylene chloride was distilled from phosphorous pentoxide and methanol was obtained by distillation over magnesium methoxide. tert-Butyl alcohol was distilled from a solution of potassium t-butoxide in the alcohol. Benzene was distilled from metallic potassium. Petroleum-ether was obtained by distillation from potassium permangenate. Anhydrous ether was obtained commercially.

Preparation of 2-Carbomethoxy-1-methyl-1,4-dihydrobenzene 261

A mixture of 3.2 g of methyl propiolate (38.1 mmole), 6.4 g of distilled 1,3-pentadiene (94.1 mmole) and 0.1 g of hydroquinone in 20 ml of toluene was heated in two sealed tubes at 140-145° for approximately 10 hrs. After cooling, the reaction mixtures obtained from the tubes were combined. The solvent and excess pentadiene were evaporated to give 4.1 g of a colorless oil. Distillation of the crude product gave 3.8 g (66%) of a colorless oil, b.p., 92-98° at 16-20 mm (lit. b.p.88-90°

at 20 mm[87]); i.r. (film), ν_{max} 3050, 1720, 1670, 1640 cm^{-1}; p.m.r., 1.26 (d, 3H, secondary methyl, J=7.0 Hz), 2.98 (m, 2H, allylic methylene), 3.32 (m, 1H, allylic methine), 3.86 (s, 3H, -COOMe), 5.82 (m, 2H, vinyl proton), 7.08 (m, 1H, -CH=CCOOMe).

Preparation of Methyl 6-methylcyclohexenecarboxylate 262

To a solution of 2-carbomethoxy-1-methyl-1,4-dihydrobenzene 261 (12.0g, 78.95 mmoles) in 100 ml of benzene was added 800 mg of tris-(triphenylphosphine)rhodium chloride. The resulting solution was hydrogenated at atmospheric pressure and room temperature. After one equivalent of hydrogen had been absorbed, the brick red solution was filtered through a short column of alumina (Act III), and the column was eluted with approximately 1ℓ of benzene. The solvent was evaporated under reduced pressure to give a deep yellow oil. Short path distillation gave 9.80 g (80%) of a colorless oil, b.p., 86-87° at 24 mm; i.r. (film), ν_{max} 1710, 1640 cm^{-1}; p.m.r., 1.20 (d, 3H, secondary methyl, J=7.0 Hz), 2.18 (m, 2H, allylic methylene), 2.68 (unresolved m, 1H, allylic methine), 3.84 (s, 3H, -COOMe), 7.06 (t, 1H, -CH=CCOOMe, J=4.0 Hz).

Anal. Calcd. for $C_9H_{14}O_2$: C, 70.10; H, 9.15. Found: C, 69.88; H, 8.99.

Preparation of 3-Carbomethoxy-4-methyl-2-cyclohexen-1-one 258

To a stirred solution of 10.0 g of methyl 6-methylcyclohexencarboxylate 262 (64.93 mmoles) in 60 ml of glacial acetic acid and 1 ml of water was added 10.0 g of chromium trioxide (100 mmoles) over a period of 30 minutes while the temperature of the solution was kept below 40° with a cold water bath. Then, after stirring for 2 hrs. at 40-50°, another 10.0 g of chromium trioxide was added in portions and the mixture was stirred

for another 2 hrs. It was cooled with an ice-bath and neutralized with 10% sodium hydroxide solution. The mixture was extracted with ether and the combined ethereal solution was washed with water, saturated sodium bicarbonate solution, water and brine. It was then dried over anhydrous magnesium sulfate. After filtration, the solvent was evaporated to give a golden yellow oil. Short path distillation of the crude product gave 7.0 g of a pale yellow oil, b.p. 85-140° at 16-20 mm. Analysis of this material by g.l.c. (column A, 175°, 70 ml/min) showed that this distillate was a mixture containing approximately 25% of the starting material 262 and 75% of the product 258. This material was subjected to column chromatography on silica gel (350 g) with a 4:1 petroleum ether (30-60°) - ether mixture being used as eluting solvent. Those fractions containing pure starting material were combined to give a total of 1.53 g of colorless oil after distillation. Combining the other fractions gave 5.03 g (56%, based on unrecovered starting material) of 3-carbomethoxy-4-methyl-2-cyclohexen-1-one 258, isolated as a dark yellow oil. Distillation gave 4.92 g of a pale yellow oil, b.p., 114-120° at 15-18 mm; i.r. (film), ν_{max} 1720, 1685 cm^{-1}; p.m.r., 1.24 (d, 3H, secondary methyl, J=7.0 Hz), 2.96 (m, 1H, allylic methine), 3.78 (s, 3H, COOMe), 6.58 (s, 1H, $-\overset{O}{\overset{\|}{C}}\underline{CH}=C-COOMe$).

Mol. Wt. Calcd. for $C_9H_{12}O_3$: 168.0788. Found (high resolution mass spectrometry): 168.0786.

Diels-Alder Reaction of 3-Carbomethoxy-4-methyl-2-cyclohexen-1-one 258 with 1,3-Butadiene

To a suspension of 1.20 g (8.98 mmoles) of freshly sublimed anhydrous aluminium trichloride in 20 ml of anhydrous methylene chloride was added

3.60 g (21.43 mmoles) of 3-carbomethoxy-4-methyl-2-cyclohexen-1-one 258. A deep yellow homogeneous solution was formed. This solution was transferred to two thick wall glass tubes. Another 14 ml of anhydrous methylene chloride was added to each tube. Then each tube was charged with approximately 20 ml of liquid 1,3-butadiene.

The sealed tubes were heated at about 95-100° for one day. After cooling to room temperature, the reaction mixtures were diluted with chloroform and the combined solution was washed with dilute hydrochloric acid and then with water and brine. After drying with anhydrous magnesium sulfate, the solvent was evaporated to give a gummy yellow oil. The latter was extracted twice with 100 ml portions of refluxing methanol. The combined methanolic extracts were filtered through a bed of Celite and the filtrate was concentrated on a rotary evaporator. The residue was diluted with ether and dried over anhydrous magnesium sulfate. Removal of solvent and distillation of the residue (air bath temperature up to 140° at 0.05 mm) gave 3.28 g of a light yellow oil. Redistillation of the mixture, with air bath temperature at 90-109° and 0.08 mm, gave 2.84 g of a slightly yellow oil. G.l.c. analysis (column C, 180°, 70 ml/min) showed that this material consisted of two major components in a ratio of approximately 1:1. The mixture was subjected to column chromatography on 300 g of silica gel using petroleum ether with increasing amounts of ether as eluting solvent. The first isomer 272 (420 mg, 21%) which was eluted from the column was obtained as a crystalline compound, m.p., 96-97° (recrystallized from petroleum ether); i.r. ($CHCl_3$), ν_{max}, 3080, 1720 cm^{-1}; p.m.r., 0.99 (d, 3H, secondary methyl, J=6.0 Hz), 2.88-3.06 (m, 1H, bridgehead proton), 3.62 (s, 3H, COOMe), 5.68 (m, 2H,

vinyl protons).

Anal. Calcd. for $C_{13}H_{18}O_3$: C, 70.24; H, 8.16. Found: C, 70.20; H, 8.21.

The second isomer 273 (350 mg, 18%) which was eluted from the column was isolated as a pale yellow viscous oil [b.p. 95-105° (air bath temperature) at 0.1 mm)]; i.r. (film), ν_{max}, 3080, 1720 cm^{-1}; p.m.r., 0.89 (d, 3H, secondary methyl, J=6.0 Hz), 3.17 (unresolved d of d, bridgehead proton), 3.74 (s, 3H, COOMe), 5.60 (broad d, 2H, vinyl protons, J=6.0 Hz).

Mol. Wt. Calcd. for $C_{13}H_{18}O_3$: 222.1257. Found (high resolution mass spectrometry): 222.1256.

Attempted Epimerization of the Keto Ester 272

Approximately 14 mg of metallic sodium was added to 10 ml of stirred anhydrous methanol. After all of the sodium had reacted, a solution of 100 mg (0.45 mmole) of the keto ester 272 in 10 ml of anhydrous methanol was introduced dropwise. The resulting solution was refluxed under a nitrogen atmosphere for 5 hrs. After cooling most of the solvent was removed under reduced pressure and the residue was diluted with water and acidified with dilute hydrochloric acid. The mixture was then extracted with ether. The combined ether extracts were washed with water, saturated aqueous sodium bicarbonate, water and then brine. After drying with anhydrous magnesium sulfate and evaporating off the solvent, a light yellow oil was obtained. Distillation of this material at 110-117° (air bath temperature) and 0.35 mm gave 73 mg (73%) of colorless oil which solidified upon cooling (m.p., 95-96°). G.l.c. retention times (columns A and C, 150°, 100 ml/min) and i.r. and p.m.r. spectra of this material were identical with those of the starting

material (keto ester 272).

Hydrogenation of the Keto Ester 272

To a solution of 0.20 g (0.90 mmole) of the unsaturated keto ester 272 in 10 ml of ethanol, was added 15.2 mg of 5% palladium-on-carbon. The mixture was hydrogenated at atmospheric pressure and room temperature. After approximately one equivalent of hydrogen had been absorbed, the mixture was filtered through celite. Evaporation of the solvent from the filtrate gave a viscous colorless oil which crystallized upon standing. Recrystallization from hexanes gave 0.16 g (79%) of compound 274 as white needles, m.p., 63-65°; i.r. ($CHCl_3$), ν_{max} 1720, 1710 cm^{-1}; p.m.r., 0.93 (d, 3H, secondary methyl, J=6.0 Hz), 2.39 (m, 3H, protons α to the keto carbonyl group), 3.60 (s, 3H, COOMe).

Anal. Calcd. for $C_{13}H_{20}O_3$: C, 69.61; H, 8.99. Found: C, 69.79; H, 8.97.

Attempted Epimerization of the Keto Ester 274

Approximately 46 mg of metallic sodium was added to 10 ml of stirred anhydrous methanol. After all of the sodium had reacted, a solution of 76 mg (0.34 mmole) of the saturated keto ester 274 in 3 ml of anhydrous methanol was introduced. The mixture was refluxed under nitrogen for 5 hrs. Most of the solvent was removed and the residue was diluted with water. The aqueous solution was then extracted with ether. The combined ether extracts were washed with water and brine. Evaporation of the solvent after drying over anhydrous magnesium sulfate gave 60 mg (79%) of a slightly yellow oil which was shown by g.l.c. analysis (column A and C, 150°, 100 ml/min) to be one component with a retention time identical with that of the starting keto ester 274. The i.r. and p.m.r. spectra of the product were identical with those of the starting material.

Preparation of the Dithioketal Ester 280

About 2 ml of ethanedithiol was added to a round bottomed flask containing 366 mg (1.63 mmole) of the saturated keto ester 274 under a nitrogen atmosphere. The mixture was stirred until all of the keto ester had dissolved. The solution was cooled with an ice bath, and then approximately 1 ml of boron trifluoride etherate was added slowly. The resulting mixture was stirred at 0° for 1½ hour. The ice bath was removed and the mixture was allowed to warm to room temperature. After having been stirred at room temperature for another 15 minutes, the mixture was poured into 5% aqueous potassium hydroxide and the aqueous layer was extracted with ether. The combined ether extracts were washed twice with 5% aqueous potassium hydroxide and then with water until the extracts were not alkaline. After another washing with brine, the solution was dried with anhydrous magnesium sulfate. Evaporation of the solvent gave 561 mg of a viscous oil. Distillation (air bath temperature 146-160° at 0.6 mm) of this material afforded 495 mg (100%) of a colorless viscous oil; i.r. (film), ν_{max} 1720 cm^{-1}; p.m.r., 0.88 (d, 3H, secondary methyl, J=6.0 Hz), 2.95 (m, 1H, bridgehead proton), 3.18 (m, 4H, dithioketal protons), 3.70 (s, 3H, COOMe).

Mol. Wt. Calcd. for $C_{15}H_{24}O_2S_2$: 300.1224. Found (high resolution mass spectrometry): 300.1218.

Preparation of the Dithioketal Alcohol 281.

A solution of 495 mg (1.65 mmole) of the dithioketal ester 280 in 6 ml of anhydrous tetrahydrofuran was added to a solution of 217 mg (5.71 mmole) of lithium aluminum hydride in 20 ml of anhydrous tetrahydrofuran under a nitrogen atmosphere. The mixture was refluxed for 2 hrs., and then cooled to room temperature. Powdered sodium sulfate

decahydrate was added cautiously. When all the excess lithium aluminum hydride had been destroyed, the mixture was filtered through Celite and the solid was washed with ether. The filtrate was concentrated under reduced pressure and the residue was diluted with ether. The resultant solution was dried with anhydrous magnesium sulfate. Removal of the solvent afforded 467 mg of crude product. Distillation (air bath temperature 145-160° at 0.4 mm) of this material gave 435 mg (97%) of the dithioketal alcohol 281 as a viscous colorless oil; i.r. (film), ν_{max} 3467 (broad), 1024 cm^{-1}; p.m.r., 0.97 (d, 3H, secondary methyl, J=5.0 Hz), 3.20 (m, 4H, dithioketal protons), 3.93 (s, 2H, $-C\underline{H}_2OH$).

Mol. Wt. Calcd. for $C_{14}H_{24}OS_2$: 272.1286 Found (high resolution mass spectrometry): 272.1269

Preparation of the Dithioketal Aldehyde 282

To a solution of 1.10 g (13.92 mmoles) of dry pyridine in 16 ml of dry methylene chloride, was added carefully, with vigorous stirring, 660 mg (6.66 mmoles) of dry chromium trioxide. After the resultant solution had been stirred for 15 mins. at room temperature, a solution of 300 mg (1.10 mmole) of the dithioketal alcohol 281 in a minimum amount of methylene chloride was added. The reaction mixture was stirred at room temperature for 30 mins., and was then decanted into a separatory funnel. The residue was washed twice with ether. The combined organic solution was washed successively with 5% aqueous potassium hydroxide, water, dilute hydrochloric acid, saturated aqueous sodium bicarbonate, water, and brine. After drying and evaporation of solvent, 251 mg (84%) of a slightly yellow solid was obtained as the crude product. Recrystallization of the solid from ether-petroleum ether gave 185 mg (62%) of the

dithioketal aldehyde 282 as colorless crystals; m.p., 83-85°; i.r. ($CHCl_3$), ν_{max} 2710, 1720 cm^{-1}; p.m.r., 0.88 (d, 3H, secondary methyl, J=6.0 Hz), 3.28 (m, 4H, dithioketal protons), 10.23 (s, 1H, CHO).

Mol. Wt. Calcd. for $C_{14}H_{22}OS_2$: 270.1109. Found (high resolution mass spectrometry): 270.1120.

Wolff-Kishner Reduction of the Dithioketal Aldehyde 282

To 20 ml of diethylene glycol was added approximately 0.5 g of metallic sodium. The mixture was carefully heated by means of a steam bath until all of the sodium had reacted.

To a two-necked flask fitted with a thermometer and a short path distillation apparatus, was added 18 ml (19.8 mmole) of the sodium diethylene glycolate solution (prepared as described above), 185 mg (0.685 mmole) of the dithioketal aldehyde 284 and 3 ml of hydrazine hydrate. The resultant mixture was heated slowly and the low-boiling material was allowed to distill until the internal temperature of the mixture had reached 180°. The mixture was then refluxed for 21 hours. Distillation was then continued until the internal temperature of the reaction mixture reached 210° and refluxing was carried out at this temperature for another 25 hours.

After having been cooled to room temperature, the reaction mixture and the total distillate which had been collected were combined, diluted with water, and thoroughly extracted with ether. The combined ether extracts were washed with water until the washings were no longer alkaline, and then dried with anhydrous magnesium sulfate. Evaporation of the solvent under reduced pressure at low temperature (cold water bath), gave 133 mg of a pale yellow oil as the crude product. Distillation of this material at 110-120° (air bath temperature) and water aspirator

pressure gave 92.3 mg (81%) of a colorless oil; i.r. (film), no carbonyl absorption. Analysis of the distillate by g.l.c. (column A, 120°, 70 ml/min) showed only one peak. However, the p.m.r. spectrum of this material indicated that it was a mixture of the epimeric hydrocarbons 276 and 277 in a ratio of approximately 55:45 (estimated from the integration of the methyl groups in the p.m.r. spectrum); p.m.r., 0.68 (s, 3H, tertiary methyl of hydrocarbon 276), 0.71 (d, 3H, secondary methyl of hydrocarbon 277, J=6.5 Hz), 0.78 (s, 3H, tertiary methyl of hydrocarbon 277). This spectrum was identical with the combination of the p.m.r. spectra of authentic hydrocarbons 276 and 277.[98] Also, the g.l.c. retention time of the product was identical with those of the authentic samples.

Epimerization of the Keto Ester 273

Approximately 14 mg of metallic sodium was added to 10 ml of anhydrous methanol. After all the metal had reacted, a solution of 100 mg (0.450 mmole) of the keto ester 273 in 10 ml of anhydrous methanol was added dropwise over a period of 30 minutes. The solution was then stirred at room temperature under an inert atmosphere (nitrogen) for another 4 hours. The solvent was removed under reduced pressure and the residue was diluted with water, and acidified with a few drops of dilute hydrochloric acid. The mixture was extracted with ether. The combined ether extracts were washed thoroughly with water and brine and then dried over anhydrous magnesium sulfate. Evaporation of the ether gave 87 mg (87%) of a pale yellow oil. Distillation of this material at 100-115° (air bath temperature) and 0.35 mm gave 79 mg (79%)

of a colorless oil. G.l.c. analysis (column D, 165°, 100 ml/min) showed that the latter was a mixture of starting material 273 and a new product, presumably 283 in a ratio of approximately 8:1 respectively. This new keto ester 283 was not obtained pure. However, by comparing the p.m.r. spectrum of this material with that of the keto ester 273, it was possible to assign the following signals to 283: 1.23 (d, 3H, secondary methyl, J=6.0 Hz), 3.64 (s, 3H, COOMe), 5.60 (broad m, 2H, vinyl protons).

Hydrogenation of the Keto Ester 273

To a solution of the keto ester 273 (462 mg, 2.08 mmoles) in 25 ml of ethanol was added 26 mg of 5% palladium-on-carbon. The mixture was hydrogenated at atmospheric pressure and room temperature till the absorption of hydrogen ceased. The mixture was filtered through Celite. The solid was washed with ethanol. The combined alcoholic solution was evaporated to give a slightly yellow oil which upon distillation (air bath temperature 106-118° at 0.3 mm) gave 457 mg (98%) of the saturated keto ester 284 as a colorless oil; i.r. (film), ν_{max} 1720, 1700 cm^{-1}; p.m.r., 0.86 (d, 3H, secondary methyl, J=6.0 Hz), 2.96 (m, 1H, bridgehead proton), 3.70 (s, 3H, COOMe).

Mol. Wt. Calcd. for $C_{13}H_{20}O_3$: 224.1390. Found (high resolution mass spectrometry): 224.1413.

Epimerization of the Keto Ester 284

To 7 ml of dry methanol was added 46 mg of metallic sodium. After the reaction between the methanol and sodium was complete, 152 mg (0.68 mmole) of the keto ester 284 in 7 ml of dry methanol was added to the reaction flask. The mixture was then gently stirred for approximately 5 hours. After the methanol had been removed, the residue was diluted

with water and acidified with a few drops of dilute hydrochloric acid. The aqueous solution was extracted thoroughly with ether. The combined ether extracts were washed with water, brine and then dried with anhydrous magnesium sulfate. Removal of solvent and distillation of the resulting yellow oil (air bath temperature 110-120° at 0.4 mm) gave 134 mg (88%) of a colorless oil. Analysis of this distillate by g.l.c. (column E, 165°, 70 ml/min) showed that it consisted of a mixture of the starting keto ester 285 and a new compound in a ratio of approximately 55:45, respectively. These components were separated by preparative t.l.c. (using hexane-ether 7:3 as eluting solvent). The new epimeric keto ester 285, after distillation, exhibited the following spectral properties; i.r. (film), ν_{max} 1730, 1710 cm^{-1}; p.m.r., 1.20 (d, 3H, secondary methyl, J=6.5 Hz), 3.62 (s, 3H, COOMe).

Mol. Wt. Calcd. for $C_{13}H_{20}O_3$: 224.1395. Found (high resolution mass spectrometry): 224.1412.

Preparation of the Dithioketal Ester 288

To 457 mg (2.04 mmoles) of the keto ester 284 was added 2 ml of ethanedithiol. The solution was cooled with an ice bath and 1 ml of boron trifluoride etherate was added. The reaction mixture was left at 0° for 1½ hours (with occasional stirring), diluted with 5% aqueous potassium hydroxide and thoroughly extracted with ether. The combined ethereal extracts were washed twice with 5% aqueous potassium hydroxide and then with water until the aqueous layer was no longer alkaline. After the organic layer had been dried over anhydrous magnesium sulfate, the solvent was removed to give a viscous yellow oil as the crude product. Distillation of this material at 132-150° (air bath temperature) and

0.15 mm gave 573 mg (94%) of the dithioketal ester 288 as a colorless viscous oil; i.r. (film), ν_{max} 1720 cm^{-1}, p.m.r., 0.83 (unresolved d, 3H, secondary methyl, J=5.0 Hz), 3.30 (m, 4H, dithioketal protons), 3.72 (s, 3H, COOMe).

Mol. Wt. Calcd for $C_{15}H_{24}O_2S_2$: 300.1236. Found (high resolution mass spectrometry): 300.1217.

Preparation of the Dithioketal Alcohol 289

To a suspension of 670 mg (17.63 mmoles) of lithium aluminum hydride in 20 ml of dry tetrahydrofuran was added a solution of 573 mg (1.91 mmoles) of the dithioketal ester 288 in 10 ml of dry tetrahydrofuran. The mixture was refluxed gently for 3 hours under an atmosphere of nitrogen. After the reaction mixture had been cooled to room temperature, powdered sodium sulfate decahydrate was added cautiously to destroy the excess lithium aluminum hydride. The mixture was filtered through Celite and the solid residue was washed with ether. The combined organic filtrates were evaporated to give a yellow viscous oil which was diluted with ether and dried with magnesium sulfate. Removal of the solvent and distillation [170-180° (air bath temperature) at 0.35 mm] of the residue gave 430 mg (83%) of the dithioketal alcohol 289 as a colorless viscous oil; i.r. (film), ν_{max} 3450 (broad), 1031 cm^{-1}; p.m.r., 0.83 (unresolved d, 3H, secondary methyl), 2.62 (s, 1H, -OH), 3.25 (m, 4H, dithioketal protons), 3.58 and 3.69 (AB pair of doublets, 2H, $C\underline{H}_2OH$, J=11.0 Hz).

Mol. Wt. Calcd. for $C_{14}H_{24}OS_2$: 272.1284. Found (high resolution mass spectrometry): 272.1268.

Preparation of the Dithioketal Aldehyde 290

To a solution of 1.50 g (18.99 mmoles) of pyridine in 20 ml of dry methylene chloride was added 957 mg (9.57 mmoles) of dry chromium trioxide. After the resulting mixture had been stirred for 15 minutes at room temperature, a solution of 430 mg (1.58 mmoles) of the dithioketal alcohol 289 in 4 ml of dry methylene chloride was added with vigorous stirring. The mixture was stirred for another 30 minutes and then the solution was decanted into a separatory funnel. The residue in the reaction flask was washed with ether. The combined reaction mixture and ether washings were washed successively with 5% aqueous potassium hydroxide, water, dilute hydrochloric acid, saturated aqueous sodium bicarbonate and brine. After the organic layer had been dried over anhydrous magnesium sulfate, the solvent was evaporated to afford 354 mg of a yellow oil. Distillation of this material at 155-170° (air bath temperature) and 0.4 mm gave 326 mg (76%) of the dithioketal aldehyde 290 as a colorless oil; i.r. (film), ν_{max}, 2717, 1720 cm^{-1}; p.m.r., 0.78 (unresolved d, 3H, secondary methyl, J=5.0 Hz), 3.28 (m, 4H, dithioketal protons), 9.35 (s, 1H, CHO).

Mol. Wt. Calcd for $C_{14}H_{22}OS_2$: 270.1112. Found (high resolution mass spectrometry): 270.1112.

Wolff-Kishner Reduction of the Dithioketal Aldehyde 290

To 20 ml of diethylene glycol was added 500 mg of sodium. The mixture was carefully warmed by a steam bath until all of the sodium had reacted.

To 274 mg (1.01 mmole) of the dithioketal aldehyde 290 was added 20 ml of sodium diethylene glycolate solution (prepared as described above). After

3 ml of hydrazine hydrate had been added, the mixture was heated slowly and the low-boiling material was allowed to distill until the internal temperature of the reaction solution reached 180°. The mixture was then refluxed for 18 hours. Subsequently, the distillation was continued until the internal temperature reached 210° and then refluxing was continued for another 24 hours. All of the distilled material was combined with the cooled reaction mixture. The combined material was diluted with water and the resulting mixture was extracted thoroughly with ether. The combined ether extracts were washed with water and brine and then dried over anhydrous magnesium sulfate. Evaporation of the solvent afforded 173 mg of a yellow oil as the crude product. Distillation of this material at 120-125° (air bath temperature) and water-aspirator pressure furnished 118 mg (70%) of a colorless oil; i.r. (film), no carbonyl absorption. G.l.c. analysis (column A, 130°, 100 ml/min) of this oil showed only one major peak with a retention time identical with those of the authentic hydrocarbons 286 and 287. However, the p.m.r. spectrum of the product indicated that it was a mixture of the epimeric hydrocarbons 286 and 287, in the ratio of approximately 1:1 estimated from the integration of the signals due to the methyl groups; p.m.r., 0.93 (s, 3H, tertiary methyl of hydrocarbon 286), 0.98 (d, 3H, secondary methyl of hydrocarbon 286, J=4.0 Hz), 0.83 (unresolved signal, 3H, secondary methyl of hydrocarbon 287), 1.03 (s, 3H, tertiary methyl of hydrocarbon 287). This spectrum was identical with the combination of the p.m.r. spectra of authentic samples of 286 and 287.[98]

Preparation of cis-3,4-Dimethyl-3-Vinylcyclohexanone 142

To a mixture of 9.63 g (0.396 mole) of magnesium, 100 ml of dry tetrahydrofuran and a few crystals of iodine in a 3-necked flask fitted with a dropping funnel, a dry-ice condenser and a nitrogen inlet, was added a small amount of vinyl bromide. When the formation of the vinyl magnesium bromide had started, a solution of 58.7 g (0.268 mole) of vinyl bromide in 100 ml of dry tetrahydrofuran was added dropwise to maintain a gentle reflux. After the addition was complete, the mixture was heated to reflux for 30 minutes and the tetrahydrofuran solution was then decanted into a flame dried dropping funnel.

To a mixture of 12.53 g (0.101 mole) of 3,4-dimethyl-2-cyclohexen-1-one, prepared according to the procedure of Birch and co-workers[73] and 3.79 g (19.95 mmoles) of cuprous iodide in 300 ml of dry tetrahydrofuran at ice-bath temperature and under a nitrogen atmosphere, was added 20 ml of dimethylsulfide to form a black homogeneous solution. The freshly prepared solution of vinyl magnesium bromide was added slowly (over a period of 1 hour) to the reaction flask with vigorous stirring. After the addition was complete, the solution was stirred for another 2 hours at 0°. The mixture was poured into 500 ml of saturated aqueous ammonium chloride and the resultant mixture was extracted with ether. The combined ether extracts were washed successively with dilute ammonium hydroxide, water and brine, and then dried over anhydrous magnesium sulfate. Evaporation of the solvent gave 22.6 g of a yellow oil. Fractional distillation of this material gave 9.99 g (65%) of cis-3,4-dimethyl-3-vinylcyclohexanone 142 as a very pale yellow oil; b.p. 115-120° at 36-38 mm (lit. b.p., 51-54° at 0.3 mm[50]); i.r. (film), ν_{max} 3030, 1710, 1630, 920 cm^{-1}; p.m.r., 0.90

(s, 3H, tertiary methyl), 0.91 (d, 3H, secondary methyl, J-6.0 Hz), 4.95 (d of d, 1H,  , J=18.0 and 1.5 Hz), 4.99 (d of d, 1H,  , J =9.0 and 1.5 Hz), 5.78 (d of d, 1H, , J=18.0 and 9.0 Hz).

Preparation of the Ethylene Ketal of cis-3,4-Dimethyl-3-vinylcyclohexanone 142

A solution of 19.51 g (128.3 mmole) of cis-3,4-dimethyl-3-vinylcyclohexanone 142, 16.70 g (269.4 mmole) of ethylene glycol, and 405 mg (2.35 mmole) of p-toluene sulfonic acid in 70 ml of dry benzene was refluxed for 18 hours under a nitrogen atmosphere using a Dean-Stark trap to remove the water. The reaction mixture was cooled to room temperature, diluted with benzene and successively washed with saturated aqueous sodium bicarbonate, water and brine, and then dried over anhydrous magnesium sulfate. Removal of the solvent gave a yellow oil. Distillation of this material at 112-114° (14 mm) gave 21.10 g (84%) of the olefinic ketal 302 as a very pale yellow oil (lit. b.p., 71-73° at 0.3 mm[50]); i.r. (film), ν_{max} 3110, 1635, 905 cm^{-1}; p.m.r., 0.79 (d, 3H, secondary methyl, J=6.0 Hz), 1.00 (s, 3H, tertiary methyl), 3.90 (m, 4H, ethylene ketal), 4.92 (d of d, 1H,  , J=18.0 and 1.5 Hz), 4.95 (d of d, 1H,  , J=10.0 and 1.5 Hz), 5.72 (d of d, 1H, J=18.0 and 10.0 Hz).

Preparation of the Ketal Alcohol 303

To a solution of 61.5 g (0.879 mole) of 2-methyl-2-butene in 450 ml of dry tetrahydrofuran at 0° under nitrogen was added 34 ml (0.354 mole) of dimethylsulfide-borane complex. After the resulting solution had been stirred for 30 minutes at 0°, a solution of 25.40 g (0.130 mole) of the ketal olefin 302 in 200 ml of dry tetrahydrofuran was added dropwise. The ice bath was removed after all the ketal olefin 302 had been added and the

mixture was stirred at room temperature for another 3 hours. The solution was cooled to 0° and cautiously treated with 517 ml of 3N sodium hydroxide followed by 517 ml of 30% hydrogen peroxide solution. The mixture was allowed to warm to room temperature, stirred for another 3 hours, and then poured into a mixture of ice and water. The resulting mixture was thoroughly extracted with ether. The combined ether extracts were washed with saturated aqueous sodium bicarbonate, water and brine. The organic layer was dried over anhydrous magnesium sulfate. Evaporation of the solvent, followed by distillation (air bath temperature 115-120° at 0.2 mm) of the residual material gave 21.87 g (79%) of the ketal alcohol 303 as a viscous colorless oil (lit. b.p., 98-102° at 0.05 mm^{50}); i.r. (film), ν_{max} 3450 cm^{-1}; p.m.r., 0.85 (d, 3H, secondary methyl, J=6.0 Hz), 0.90 (s, 3H, tertiary methyl), 2.05 (broad s, 1H, OH), 3.69 (t, 2H, $C\underline{H}_2OH$, J=7.0 Hz), 3.90 (m, 4H, ketal protons).

Preparation of the Ketal Aldehyde 304

To a solution of 38 g (0.481 mole) of dry pyridine in 600 ml of dry methylene chloride was added cautiously 24 g (0.24 mole) of anhydrous chromium trioxide. The mixture was stirred for 30 minutes, and then a solution of the ketal alcohol 303 (8.57 g, 0.04 mole) in 30 ml of dry methylene chloride was added in one portion. After the reaction mixture had been stirred for another 30 minutes, the methylene chloride solution was decanted and the residue was triturated with ether. After the combined organic solution had been washed successively with 5% aqueous potassium hydroxide, saturated aqueous sodium bicarbonate, water, and brine, it was dried over anhydrous magnesium sulfate. Removal of the solvent, followed by distillation (air bath temperature 95-106°, 0.25 mm) of the residue gave

7.17 g (85%) of the ketal aldehyde 304 as a colorless oil (lit. b.p., 83-85° at 0.05 mm[50]); i.r. (film), ν_{max} 2755, 1715 cm^{-1}; p.m.r., 0.85 (d, 3H, secondary methyl, J=6.0 Hz), 1.06 (s, 3H, tertiary methyl), 2.35 (d, 2H, $C\underline{H}_2CHO$, J=3.0 Hz), 3.90 (m, 4H, ethylene ketal), 9.87 (t, 1H, CHO, J=3.0 Hz).

Preparation of the Ketal Dibromide 305

To a suspension of 5.35 g (0.0821 g/atom) of zinc dust and 21.0 g (80.15 mmoles) of triphenylphosphine in 280 ml of dry methylene chloride was added 26.57 g (80.03 mmoles) of carbon tetrabromide. The mixture was stirred at room temperature under nitrogen for 27 hours.[110]

To this pale brown mxiture was added a solution of 8.51 g (40.14 mmoles) of the ketal aldehyde 304 dissolved in a minimum amount of dry methylene chloride. After the reaction mixture had been stirred at room temperature for another 1½-2 hours, approximately 200 ml of petroleum ether (30-60°) was added and the resulting mixture was filtered. The solid residue was redissolved in 60 ml of methylene chloride, the resulting solution was diluted again with 200 ml of petroleum ether, and then filtered. This process was repeated twice and all of the filtrates were combined. Removal of the solvent gave a mixture of a light yellow oil and a white solid. The crude product was diluted with a small amount of ether and filtered. The solid residue was washed with ether. The removal of the solvent from the filtrate, followed by flash distillation of the residue at 114-124° (air bath temperature) and 0.25-0.3 mm gave 11.33 g (77%) of the ketal dibromide 305 as a very pale yellow oil; i.r. (film), ν_{max} 1615 cm^{-1}; p.m.r., 0.86 (d, 3H, secondary methyl, J=6.0 Hz), 0.92 (s, 3H, tertiary methyl), 1.91 and 2.26 (8-line multiplet,

the AB protons of the ABX system, 2H, allylic methylene, $J_{AX}=J_{BX}=7.0$ Hz, $J_{AB}=15.0$ Hz), 3.91 (m, 4H, ethylene ketal protons), 6.43 (t, the X proton of the ABX system, 1H, vinyl proton, $J_{AX}=J_{BX}=7.0$ Hz).

Mol. Wt. Calcd. for $C_{13}H_{20}Br_2O_2$: 367.9840. Found (high resolution mass spectrometry): 367:9810.

Preparation of the Ketal Propargyl Alcohol 306

To a cold (-78°) stirred solution of 7.86 g (21.36 mmoles) of the ketal dibromide 305 in 100 ml of dry tetrahydrofuran under an atmosphere of nitrogen was added 21 ml (49.77 mmoles) of a solution of n-butyllithium in hexane (2.37M). The mixture was stirred at -78° for 1½ hours and then was allowed to warm to ice bath temperature. Gaseous formaldehyde, obtained by pyrolyzing 8g of paraformaldehyde at 160-190° (oil bath temperature), was swept into the reaction flask with a stream of nitrogen. The resulting mixture was stirred vigorously for another 30 minutes and then about 30 ml of saturated aqueous ammonium chloride was added. The resulting mixture was diluted further with water and the aqueous layer was extracted with ether. The solid paraformaldehyde left in the reaction flask was washed twice with ether. The combined ether extracts were washed with water and brine, and dried over anhydrous magnesium sulfate. Evaporation of the solvent gave 5.106 g of a very pale yellow viscous oil. Distillation of this material at 135-145° (air bath temperature) and 0.4 mm afforded 5.003 g (98%) of the propargyl alcohol 306 as a colorless viscous oil; i.r. (film), ν_{max} 3475 (broad, 2325, 2255 cm^{-1}; p.m.r., 0.82 (d, 3H, secondary methyl, J=6.0 Hz), 0.90 (s, 3H, tertiary methyl), 2.14 (unresolved t, 2H, $C\underline{H}_2C\equiv C$), 3.09 (broad s, 1H,

disappeared upon addition of D_2O, OH), 3.87 (m, 4H, ethylene ketal protons), 4.19 (t, 2H, $C\equiv CCH_2OH$, J=2.0 Hz).

Mol. Wt. Calcd. for $C_{14}H_{22}O_3$: 238.1546. Found (high resolution mass spectrometry): 238.1569.

Hydrolysis of the Ketal Propargyl Alcohol 306

A solution of 5.37 g (22.14 mmoles) of the ketal propargyl alcohol 306, 22 ml of 3N hydrochloric acid and 22 ml of water in 300 ml of methanol was stirred at room temperature for 3 hours. Most of the methanol was removed under reduced pressure. The residue was diluted with water and thoroughly extracted with ether. The combined ether extracts were washed with saturated aqueous sodium bicarbonate, water and brine, and then dried over anhydrous magnesium sulfate. Removal of the solvent, followed by distillation of the residue at 130-140° (air bath temperature) and 0.5 mm afforded 3.95 g (92%) of a colorless viscous oil which crystallized upon refrigeration. Recrystallization from ether-petroleum ether gave the keto alcohol 307 as white crystals; m.p., 43-45°: i.r. (film), ν_{max} 3500 (broad, 2320, 2260, 1700 cm^{-1}; p.m.r., 0.80 (s, 3H, tertiary methyl), 0.93 (d, 3H, secondary methyl, J=6.0 Hz), 3.03 (broad s, 1H, disappeared upon the addition of D_2O, OH), 4.29 (broad s, 2H, changed into t upon the addition of D_2O, CH_2OH, J=2.0 Hz).

Anal. Calcd. for $C_{12}H_{18}O_2$:C, 74.19; H, 9.34. Found: C,74.28; H, 9.30.

Hydrogenation of the Keto Propargylic Alcohol 307

To a solution of 2.73 g (14.07 mmoles) of the keto propargylic alcohol 307 in 50 ml of ethanol was added 548 mg of 5% palladium-on-barium sulfate and four drops of purified quinoline. The mixture was hydrogenated

at room temperature and atmospheric pressure until approximately one equivalent of hydrogen had been absorbed. The insoluble material was filtered through a bed of celite and the residue was washed with ethanol. The combined ethanolic solution was evaporated under reduced pressure to give a yellow oil which upon distillation at 132-140° (air bath temperature) and 0.4 mm gave 2.621 g (95%) of the keto alcohol 291 as a colorless viscous oil: i.r. (film), ν_{max} 3450 (broad), 3050, 1710 cm^{-1}; p.m.r., 0.80 (s, 3H, tertiary methyl), 0.93 (d, 3H, secondary methyl, J=6.0 Hz), 3.58 (broad s, 1H, OH), 4.12 (d, 2H, $C\underline{H}_2OH$, J=5.5 Hz), 5.62 (m, 2H, vinyl protons).

Mol. Wt. Calcd. for $C_{12}H_{20}O_2$: 196.1457. Found: (high resolution mass spectrometry): 196.1463.

Preparation of the Keto Mesylate 309

To a cold (0°) solution of 2.712 g (13.83 mmoles) of the keto allylic alcohol 291 and 2.103 g (20.82 mmoles) of dry triethylamine in 50 ml of dry methylene chloride was added slowly 1.748 g (15.27 mmole) of methanesulfonyl chloride. The reaction mixture was stirred at 0° for 30 minutes under a nitrogen atmosphere. The cloudy suspension was poured into ice water and the organic phase was separated. The organic layer was washed three times with ice cold water and once with brine. After the solution had been dried over anhydrous magnesium sulfate, the solvent was evaporated to give 3.64 g (96%) of the crude keto mesylate 309 as an orange yellow oil: i.r. (film), ν_{max} 3060, 1710, 1350, 1170 cm^{-1}; p.m.r., 0.90 (s, 3H, tertiary methyl), 1.03 (d, 3H, secondary methyl, J=6.0 Hz), 3.08 (s, 3H, CH_3SO_3), 4.78 (d, 2H, $C\underline{H}_2OMs$, J=6.0 Hz), 5.80 (m, 2H, vinyl protons).

Due to the fact that the keto mesylate 309 was quite unstable, this compound was not purified further, but was used directly for the next synthetic transformation.

Preparation of the Bicyclic Keto Olefin 226

To 100 ml of dry tert-butyl alcohol in a three-necked flask fitted with a condenser, a dropping funnel and a nitrogen inlet tube was added 1.1 g of metallic potassium. The mixture was brought to reflux until all of the metallic potassium had reacted with the alcohol, and was then cooled to room temperature.

A solution of 3.644 g of the crude keto mesylate 309 in 30 ml of dry tert-butyl alcohol was added dropwise. When the addition was complete, the mixture was diluted with another 75 ml of dry tert-butyl alcohol to facilitate the stirring, and the orange red suspension was stirred for 2½ hours at room temperature. The reaction mixture was treated with aqueous ammonium chloride and the resultant mixture was thoroughly extracted with ether. The combined ether extracts were washed with water and dried over anhydrous magnesium sulfate. Removal of the solvent gave a reddish brown crude product. Distillation of this material at 62-75° (air bath temperature) and 0.15 mm gave 1.558 g (63% based on the keto allylic alcohol 291) of the bicyclic keto olefin 226 as a colorless oil: i.r. (film), ν_{max} 3050, 1705, 1660 cm^{-1}, p.m.r., 0.66 (s, 3H, tertiary methyl), 0.95 (d, 3H, secondary methyl, J=6.0 Hz), 5.58 (broad, s, 2H, vinyl protons).

Anal. Calcd. for $C_{12}H_{18}O$: C, 80.85; H, 10.18. Found: C, 80.51; H, 10.01.

Hydrogenation of the Bicyclic Keto Olefin 226

A mixture of 223 mg (1.253 mmole) of the bicyclic keto olefin 226 and 52.6 mg of 5% palladium-on-carbon in 10 ml of methanol was hydrogenated at room temperature and atmospheric pressure until no more hydrogen was absorbed. The mixture was filtered through a celite bed and the residue was washed with methanol. Evaporation of the solvent followed by distillation of the residue at 160-172° (air bath temperature) and water aspirator pressure (approximately 16-20 mm) gave 186 mg (83%) of the decalone 320 as a colorless oil: i.r. (film), ν_{max} 1710 cm^{-1}; p.m.r., 0.66 (s, 3H, tertiary methyl), 0.88 (d, 3H, secondary methyl, J=6.0 Hz).

Mol. Wt. Calcd. for $C_{12}H_{20}O$: 180.1507. Found (high resolution mass spectrometry): 180.1514.

Attempted Epimerization of the Decalone 320

To 10 ml of dry tert-butyl alcohol was added 43 mg of potassium metal. After all the potassium had reacted, a solution of 180 mg (1.0 mmole) of the decalone 320 in 2 ml of dry tert-butyl alcohol was added. The mixture was stirred under a nitrogen atmosphere at room temperature for 22 hours, was then diluted with water and thoroughly extracted with ether. The combined ether extracts were washed with water and brine, and dried over anhydrous magnesium sulfate. Evaporation of the solvent gave a small amount of yellow oil. Distillation of this material at 165-176° (air bath temperature) and water aspirator pressure afforded 129 mg (72%) of a colorless oil which was identical with the starting material, decalone 320 in all respects: i.r. (film), ν_{max} 1710 cm^{-1}; p.m.r., 0.68 (s, 3H, tertiary methyl), 0.86 (d, 3H, secondary methyl,

J=6.0 Hz).

Preparation of the Bicyclic Ketal Olefin 324

A solution of the octalone 226 (5.20 g, 29.21 mmoles), 2,2-dimethyl-1,3-propanediol (4.50 g, 43.27 mmoles), and p-toluenesulfonic acid (520 mg) in 200 ml of dry benzene was refluxed for 20 hours under a Dean-Stark water separator. The cooled solution was diluted with ether and washed with saturated aqueous sodium bicarbonate. The organic layer was washed with water and brine and then dried over anhydrous magnesium sulfate. Evaporation of the solvent gave a pale yellow viscous oil which solidified upon cooling in the refrigerator. Recrystallization of the solid from hexane furnished 6.52 g (85%) of the ketal olefin 324 as white crystals: m.p., 100.5-102.5° i.r. ($CHCl_3$), ν_{max} 3030, 1650 cm^{-1}; p.m.r., 0.69 (s, 3H, tertiary methyl), 0.80 (s, 3H, tertiary methyl), 0.84 (d, 3H, secondary methyl, J=6.0 Hz), 1.18 (s, 3H, tertiary methyl), 2.82 (unresolved d of d, 1H, bridgehead proton), 3.28 (pair of quartets, 2H, axial protons of the ketal, J=11.0 Hz and 2.0 Hz), 3.64 and 3.74 (pair of doublets, 2H, equatorial protons of the ketal, J=11.0 Hz), 5.62 (m, 2H, vinyl protons).

Anal. Calcd. for $C_{17}H_{28}O_2$: C, 77.22; H, 10.67. Found: C, 77.08; H, 10.55.

Preparation of the Keto Dibromide 326

To a mixture of 358 mg (1.36 mmoles) of the ketal olefin 324, 82.3 mg (0.36 mmole) of triethylbenzylammonium chloride, a catalytic amount of ethanol, and 5 g (19.76 mmoles) of bromoform was added dropwise 10 ml of 50% aqueous sodium hydroxide. The heterogeneous mixture was warmed with a sand bath at 40-50° for 2-3 hours. The mxiture was poured into

water and extracted thoroughly with methylene chloride. The combined organic extracts were washed with water and dried with anhydrous magnesium sulfate. Evaporation of the solvent gave a dark brown oil, which was dissolved in 20 ml of methanol and 1 ml of 1N hydrochloric acid was added. The resulting solution was stirred at room temperature for 4 hours and then concentrated. The residual material was diluted with saturated aqueous sodium bicarbonate and the aqueous layer was extracted with ether. Removal of the solvent from the combined ether extracts after drying over anhydrous magnesium sulfate afforded a dark brown oil which was purified by column chromatography on 200 g of silica gel using 4:1 petroleum ether (30-60°)-ether as eluting solvent. Combining all of the fractions containing the desired keto dibromide 326 furnished 378 mg (80%) of this compound as very pale yellow crystals. An analytical sample was obtained by recrystallization from ether: m.p., 130-131.5°; i.r. ($CHCl_3$), ν_{max} 3100, 1710 cm^{-1}; p.m.r., 0.57 (s, 3H, tertiary methyl), 0.93 (d, 3H, secondary methyl, J=6.0 Hz), 1.14-1.32 (m, 1H, cyclopropyl proton).

Mol. Wt. Calcd. for $C_{13}H_{18}Br_2O$: 351.9693. Found (high resolution mass spectrometry): 351.9686.

Preparation of the Ketal Dibromide 325

A solution of the keto dibromide 326 (351 mg, 1.00 mmole), 2,2-dimethyl-1,3-propanediol (1.5 g, 14.42 mmoles) and p-toluenesulfonic acid (10 mg) in 25 ml of dry benzene was refluxed under a Dean-Stark water separator for 20 hours. The cooled solution was diluted with ether and washed with saturated aqueous sodium bicarbonate. The organic layer was dried over anhydrous magnesium sulfate and concentrated, affording 463 mg

of a viscous pale yellow oil. Column chromatography of this material on 50 g of silica gel using 4:1 petroleum ether - ether as the eluting solvent mixture yielded 405 mg (93%) of the ketal dibromide 317 as a viscous pale yellow oil: i.r. (film), no carbonyl absorption; p.m.r., 0.66 (s, 3H, tertiary methyl), 0.72 (s, 3H, tertiary methyl), 0.83 (d, 3H, secondary methyl, J=5.0 Hz), 1.16 (s, 3H, tertiary methyl), 2.65-2.81 (d of d, 1H, bridgehead proton, J=13.0 and 4.0 Hz), 3.17-3.75 (m, 4H, ketal protons).

Mol. Wt. Calcd. for $C_{18}H_{28}Br_2O_2$: 438.0419, 436.0429 and 434.0475. Found (high resolution mass spectrometry): 438.0417, 436.0436 and 434.0456.

Preparation of the Benzyl Ether 329

To a solution of 1.01 g (3.97 mmoles) of 7,7-dibromonorcarane[128] in 10 ml of dry tetrahydrofuran cooled to -95° with a liquid nitrogen-toluene bath and kept under an atmosphere of nitrogen, was added 1.6 ml (4.13 mmoles) of a solution of n-butyllithium in hexane (2.58 M). After 20 minutes, a solution of 1.26 g (8.05 mmoles) of chloromethyl benzyl ether[129] in 2 ml of dry hexamethylphosphoramide was added, followed by another 2 ml of dry hexamethylphosphoramide. The mixture was stirred at -95° for 30 minutes and then at -78° for 4 hours. It was then poured into vigorously stirred dilute aqueous sodium hydroxide. The aqueous layer was extracted with pentane. The combined extracts were washed with water and brine and dried over anhydrous magnesium sulfate. Evaporation of the solvent afforded 1.244 g of a yellow oil which was subjected to column chromatography over 150 g of silica gel using 5% ether in petroleum ether as the eluting solvent. The desired product, benzyl ether 329, was obtained as a pale yellow oil (0.583 g, 49%).

Distillation at 110-120° (air bath temperature) and 0.2 mm gave a colorless oil: i.r. (film), ν_{max} 3090, 3050, 730, 690 cm^{-1}; p.m.r., 3.80 (s, 2H, C=C$\underline{H_2}$O), 4.62 (s, 2H, O$\underline{CH_2}$Ph), 7.37 (m, 5H, C_6H_5).

However, an analytical pure sample of 329 could not be obtained. The compound showed no parent peak in the mass spectrum but gave a strong peak at m/e 215 which corresponded to M^+-Br.

Hydrogenolysis of the Benzyl Ether 329

To a solution of 301 mg (1.02 mmole) of the benzyl ether 329 in 15 ml of 95% ethanol was added 61 mg of 10% palladium-on-carbon and the resulting mixture was hydrogenated at room temperature and atmospheric pressure for 1 hour. By then, approximately 1 equivalent of hydrogen had been consumed. The mixture was filtered through Celite and the residue was washed with ethanol. Removal of the solvent from the filtrate gave a pale yellow oil. Distillation of this material at 75-80° (air bath temperature) and 0.2 mm afforded 195 mg (93%) of the alcohol 331 as a colorless oil which solidified upon cooling: m.p., 36-37.5°; i.r. ($CHCl_3$), ν_{max} 3403 (broad) cm^{-1}; p.m.r., 3.95 (s, 2H, $\underline{CH_2}$OH).

Anal. Calcd. for $C_8H_{13}BrO$: C, 46.85; H, 6.39. Found: C, 46.56; H, 6.38.

Preparation of the Mesylate 332

To a solution of 150 mg (0.732 mmole) of the alcohol 331 and 303 mg (3.00 mmoles) of dry triethylamine in 6 ml of dry methylene chloride at 0° under a nitrogen atmosphere was added 218 mg (1.904 mmole) of freshly distilled methanesulfonyl chloride. After the resulting mixture had been stirred at 0° for 30 minutes, it was poured into ice-cold water. The aqueous layer was extracted thoroughly with methylene chloride. The

combined methylene chloride extracts were dried with anhydrous magnesium sulfate and the solvent was evaporated to give 200 mg (97%) of the mesylate 332 as a pale yellow oil which solidified upon cooling: m.p. 56-58.5°; i.r. (film), 3080, 1360, 1170 cm^{-1}; p.m.r., 2.63 (s, 3H, CH_3SO_3), 4.63 (s, 2H, $\underline{CH_2}OHs$).

An analytical sample of 332 could not be obtained due to the instability of the compound in the attempted recrystallization from petroleum ether. The compound showed no parent peak in the mass spectrum but exhibited strong peaks at m/e 203, 189(187), and 188(186) which corresponded to M^+-Br, M^+-CH_3SO_3 and M^+-CH_3SO_3H, respectively.

Preparation of 7-endo-methyl-7-exo-carbomethoxynorcarane 338

To a cold (-78°) solution of 560 mg (2.96 mmoles) of 7-exo-bromo-7-endo-methylnorcarane[70,71] in 15 ml of anhydrous ether under a nitrogen atmosphere was added 3.3 ml (6.67 mmoles) of a solution of tert-butyllithium in pentane (2.02 M). The mixture was kept at -78° for 30 minutes and 0.74 ml (9.50 mmoles) of distilled methyl chloroformate was added dropwise. After the addition was complete, 1.5 ml of dry hexamethylphosphoramide was introduced by means of a syringe. The mixture was kept at -78° for another 4 hours and then poured into water. The aqueous layer was extracted with petroleum ether (b.p. 35-65°). The combined organic extracts were washed with water and dried with anhydrous magnesium sulfate. Removal of the solvent gave 357 mg of a pale yellow oil. Distillation of the latter at 100-120° (air bath temperature) and water aspirator pressure gave 320 mg (64%) of 7-endo-methyl-7-exo-carbomethoxynorcarane 338 as a colorless oil: i.r. (film), ν_{max} 3040, 1720 cm^{-1}; p.m.r., 1.20 (s, 3H, tertiary methyl),

3.57 (s, 3H, COOMe).

Mol. Wt. Calcd. for $C_{10}H_{16}O_2$: 168.1151. Found (high resolution mass spectrometry): 168.1151.

Preparation of 7-endo-methyl-7-exo-hydroxymethylnorcarane 339

A mixture of 300 mg (7.89 mmoles) of lithium aluminum hydride and 150 mg (0.89 mmole) of the monoester 338 in 30 ml of anhydrous ether was stirred at room temperature under an atmosphere of nitrogen for 20 hours. The excess hydride was destroyed by addition of powdered sodium sulfate decahydrate. The resultant mixture was filtered and the collected material was washed with ether. The ethereal solution was dried over anhydrous magnesium sulfate. Evaporation of the solvent gave a very pale yellow viscous oil. Distillation of this material at 100-110° and aspirator pressure gave 101 mg (81%) of the primary alcohol 339 as a colorless viscous oil: i.r. (film), ν_{max} 3400 (broad), 3020 cm^{-1}; p.m.r., 0.72 (m, 2H, cyclopropyl protons), 1.06 (s, 3H, tertiary methyl), 2.05 (broad s, 1H, OH), 3.20 (s, 2H, CH_2OH).

Mol. Wt. Calcd. for $C_9H_{16}O$: 140.1211. Found (high resolution mass spectrometry): 140.1201.

Preparation of the p-Nitrobenzoate 355

A solution of 100 mg (0.71 mmole) of the alcohol 339, 200 mg (1.08 mmole) of recrystallized p-nitrobenzoyl chloride and 200 mg (2.53 mmoles) of dry pyridine in 10 ml of dry methylene chloride was kept at 0° for 24 hours. The mixture was poured into water and the aqueous layer was extracted with ether. The combined ether extracts were dried over anhydrous magnesium sulfate and then concentrated to give a bright yellow

oil which solidified upon cooling. Recrystallization from petroleum ether gave yellow crystals: m.p., 70-73°; i.r. (film), ν_{max} 3030, 1725, 1610, 1530, 1350 cm^{-1}; p.m.r., 0.86 (m, 2H, cyclopropyl protons), 1.13 (s, 3H, tertiary methyl), 4.00 (s, 2H, $\underline{CH_2}OOCAr$), 8.16 (m, 4H, $\underline{p}$-$NO_2C_6H_4COO$).

Mol. Wt. Calcd. for $C_{16}H_{19}NO_4$: 289.1291. Found: (high resolution mass spectrometry): 289.1314.

Preparation of the Diester 359

To a solution of 856 mg (3.37 mmoles) of 7,7-dibromonorcarane[128] in 10 ml of dry tetrahydrofuran under a nitrogen atmosphere at -95° was added a solution of 3.8 ml (7.41 mmoles) of n-butyllithium in hexane (1.95 M). After 30 minutes, 1.27 g (13.46 mmoles) of methyl chloroformate was added, followed by 1 ml of dry hexamethylphosphoramide. After another 30 minutes at -95°, the solution was warmed to -78°, kept at this temperature for 3 hours and then poured into water. The aqueous layer was extracted with pentane. The combined pentane extracts were washed thoroughly with water and brine, and then dried over anhydrous magnesium sulfate. Removal of the solvent gave 852 mg of a pale yellow oil. Distillation of this material at 80-105° (air bath temperature) and 0.3 mm gave 591 mg of a colorless viscous oil which was 80% pure by g.l.c. analysis (column F, 90° for 10 minutes and then column temperature raised to 180° with the rate of 25°/min, 180 ml/min). The distillate was subjected to column chromatography on 60 g of silica gel. The fractions from the column which were eluted with 1:9 ether-petroleum ether gave 410 mg (57%) of the crystaline diester 359. Recrystallization from pentane gave colorless crystals; m.p., 92-95° (lit. m.p. 88.5-89°[142]); i.r. ($CHCl_3$), ν_{max} 1720 cm^{-1}; p.m.r., 3.66 (s, 3H, COOMe), 3.75 (s, 3H, COOMe).

Preparation of the Diol 361

To a suspension-solution of 200 mg (7.14 mmoles) of lithium aluminium hydride in 20 ml of anhydrous ether was added a solution of 200 mg (0.94 mmole) of the diester 359 in 5 ml of anhydrous ether. The resulting mixture was stirred at room temperature for 24 hours under a nitrogen atmosphere. The excess hydride was destroyed by addition of powdered sodium sulfate decahydrate. The mixture was filtered through Celite and the collected material was washed with more ether. The combined ethereal solution was dried over anhydrous magnesium sulfate. Evaporation of the solvent from the filtrate gave 125 mg (85%) of the diol 354 as a colorless viscous oil which crystallized upon cooling. Recrystallization from petroleum ether-ether gave white crystals, m.p., 71-72.5°; i.r. ($CHCl_3$), ν_{max} 3400 (broad) cm^{-1}; p.m.r., 0.90 (m, 2H, cyclopropyl protons), 3.46 (s, 2H, $\underline{CH_2}OH$), 3.46 (broad, s, 2H, disappeared upon addition of D_2O, OH), 3.90 (s, 2H, $\underline{CH_2}OH$).

Anal. Calcd. for $C_9H_{16}O_2$: C, 69.19; H, 10.32. Found: C, 69.11; H, 10.50.

Preparation of the Dimesylate 362

To a solution of 100 mg (0.64 mmole) of the diol 361 and 241 mg (2.39 mmoles) of dry triethylamine in 7 ml of dry methylene chloride at 0° was added 183 mg (1.60 mmole) of distilled methanesulfonyl chloride. The mixture was kept at 0° for 30 minutes and then poured into ice-cold water. The aqueous layer was extracted with ether. The combined ether extracts were washed thoroughly with ice-cold water and brine and then dried over anhydrous magnesium sulfate. Evaporation of the solvent gave

202 mg of the dimesylate 362 as a yellow oil; i.r. (film), ν_{max} 3065, 1355, 1165 cm^{-1}; p.m.r., 3.05 (s, 6H, CH_3SO_3), 4.00 (s, 2H, $\underline{CH_2}OMs$), 4.43 (s, 2H, $\underline{CH_2}OMs$).

Due to the fact that the dimesylate 362 was quite unstable, this compound was not purified further, but was used directly for the next transformation.

Preparation of the Dichloride 363

To a solution of 202 mg (0.64 mmole) of the crude dimesylate 362 in 5 ml of dry hexamethylphosphoramide was added 200 mg (4.71 mmoles) of anhydrous lithium chloride. The mixture was stirred under a nitrogen atmosphere at room temperature for 20 hours, and was then poured into water. The aqueous solution was extracted with pentane. The combined pentane extracts were washed thoroughly with water and dried over anhydrous magnesium sulfate. Evaporation of the solvent gave 110 mg (89%) of the dichloride 363 as a pale yellow oil; i.r. (film), ν_{max} 3030 cm^{-1}; p.m.r., 3.50 (s, 2H, $\underline{CH_2}Cl$), 3.87 (s, 2H, $\underline{CH_2}Cl$).

The analytical sample was obtained by preparative t.l.c. with pentane being used as the developing solvent.

Mol. Wt. Calcd. for $C_9H_{14}Cl_2$: 192.0465 and 194.0432. Found (high resolution mass spectrometry): 192.0472 and 194.0443.

Preparation of the Ketal Monobromides 366 and 372

To a cold (-95°, liquid nitrogen-toluene bath) solution of 268 mg (0.61 mmole) of the ketal dibromide 325, 500 mg (3.52 mmoles) of methyl iodide and 0.4 ml of dry hexamethylphosphoramide in 4 ml of dry tetrahydrofuran was added 0.7 ml (1.35 mmole) of a solution of tert-butyllithium

in pentane (1.93 M). The mixture was stirred at -95° for 1 hour, was warmed to -78° and then stirred at this temperature for an additional 4 hours. Water (10 ml) was added and the resultant mixture was extracted with hexane. The combined hexane extracts were washed with water and brine, and then dried over anhydrous magnesium sulfate. Removal of the solvent gave 288 mg of a viscous yellow oil. G.l.c. analysis (column F, 150° for 5 minutes and then raised to 200° for 15 minutes with the rate of 25°/min, 180 ml/min) of this material showed that it consisted mainly of two components in a ratio of approximately 3:2. The crude product was subjected to chromatography on 25 g of silica gel, with 9:1 hexane-benzene being employed as the eluting solvent mixture.

The major isomer 366 (130 mg, 58%), which was the first component to be eluted from the column, was obtained as a pale yellow viscous oil and exhibited the following spectral properties: i.r. (film), no carbonyl absorption; p.m.r., 0.64 (s, 3H, tertiary methyl), 0.72 (s, 3H, tertiary methyl), 0.79 (d, 3H, secondary methyl, J=6.0 Hz), 1.13 (s, 3H, tertiary methyl), 1.74 (s, 3H, tertiary methyl), 2.62-2.78 (d of d, 1H, bridgehead proton, J=12.0 and 3.0 Hz), 3.22 (a pair of unresolved quartets, 2H, axial protons of the ketal, J=11.0 Hz), 3.55 and 3.64 (a pair of doublets, 2H, equatorial protons of the ketal, J=11.0 Hz).

Mol. Wt. Calcd. for $C_{19}H_{31}BrO$: 370.1522 and 372.1467. Found (high resolution mass spectrometry): 370.1537 and 372.1440.

The minor isomer 372 (85 mg, 38%), also obtained as a pale yellow viscous oil, exhibited the following spectral properties: i.r. (film), no carbonyl absorption; p.m.r., 0.64 (s, 3H, tertiary methyl), 0.71 (s, 3H, tertiary methyl), 0.77 (d, 3H, secondary methyl, J=6.0 Hz),

1.12 (s, 3H, tertiary methyl), 1.62 (s, 3H, tertiary methyl), 2.61-2.78 (unresolved d of d, 1H, bridgehead proton, J=14.0 and 4.0 Hz), 3.20 (pair of quartets, 2H, axial protons of the ketal, J=12.0 and 3.0 Hz), 3.54 and 3.63 (pair of doublets, 2H, equatorial protons of the ketal, J=12.0 Hz).

Mol. Wt. Calcd. for $C_{19}H_{31}BrO$: 370.1522 and 372.1467. Found (high resolution mass spectrometry): 370.1507 and 372.1488.

Preparation of the Ketal Ester 367

To a cold (-78°) solution of 144 mg (0.39 mmole) of the ketal bromide 366 in 8 ml of anhydrous ether under a nitrogen atmosphere was added slowly 0.45 ml (0.87 mmole) of a solution of tert-butyllithium in pentane (1.93 M). After the resultant solution had been stirred at -78° for 1 hour, 0.25 ml (3.23 mmoles) of methyl chloroformate was added, followed by 0.8 ml of dry hexamethylphosphoramide. The mixture was maintained at -78° for another 4 hours, and then was diluted with water. The resultant mixture was extracted with petroleum ether, the combined extracts were washed thoroughly with water and brine, and then dried over anhydrous magnesium sulfate. Evaporation of solvent gave 112 mg of a pale yellow oil which was chromatographed over 15 g of silica gel, with 9:1 petroleum ether-ether being used as the eluting solvent mixture. The fractions containing the ketal ester 367 were combined to afford 97 mg (71%) of the desired material as pale yellow crystals; m.p., 120-123°; i.r. ($CHCl_3$), ν_{max} 1720 cm^{-1}; p.m.r., 0.66 (s, 3H, tertiary methyl), 0.78 (s, 3H, tertiary methyl), 0.80 (d, 3H, secondary methyl, J=5.0 Hz), 1.16 (s, 3H, tertiary methyl), 1.24 (s, 3H,

tertiary methyl), 2.64-2.81 (unresolved d of d, 1H, bridgehead proton), 3.16-3.74 (m, 4H, ketal protons), 3.66 (s, 3H, COOMe).

Mol. Wt. Calcd. for $C_{21}H_{34}O_4$: 350.2432. Found (high resolution mass spectrometry): 350.2457.

Preparation of the Ketal Alcohol 379

To a suspension-solution of 104 mg (2.73 mmoles) of lithium aluminum hydride in 5 ml of anhydrous ether was added a solution of 97 mg (0.277 mmole) of the ketal ester 367 in 7 ml of anhydrous ether. The mixture was stirred for 20 hours at room temperature under a nitrogen atmosphere. The excess lithium aluminum hydride was destroyed by addition of powdered sodium sulfate decalhydrate. The mixture was filtered and the collected material was washed with more ether. The combined ethereal solution was dried with anhydrous magnesium sulfate. Removal of the solvent from the filtrate afforded 63 mg (71%) of the ketal alcohol 379 as a very visous oil which could not be distilled; i.r.($CHC\ell_3$), ν_{max} 3400 (broad) cm^{-1}; p.m.r., 0.66 (s, 3H, tertiary methyl), 0.78 (s, 3H, tertiary methyl), 0.80 (d, 3H, secondary methyl, J=4.0 Hz), 1.10 (s, 3H, tertiary methyl), 1.15 (s, 3H, tertiary methyl), 2.56-2.83 (unresolved d of d, 1H, bridgehead proton), 3.06-3.75 (m, 4H, ketal protons), 3.58 (s, 2H, $\underline{CH_2}OH$).

Mol. Wt. Calcd. for $C_{20}H_{34}O_3$: 322.2506. Found (high resolution mass spectrometry): 322.2508.

Preparation of the Keto Alcohol 368

To a solution of 63 mg (0.20 mmole) of the ketal alcohol 379 in 3 ml of reagent grade acetone, 3 ml of methanol and 1 ml of water was

added 6 drops of 1N hydrochloric acid. The mixture was stirred under nitrogen for 3 hours. The solution was concentrated under reduced pressure and the residual material was diluted with saturated aqueous sodium bicarbonate. The resulting mixture was extracted with ether. Concentration of the combined ethereal solution, after it had been washed with water and brine, and dried over anhydrous magnesium sulfate, gave 56 mg of the keto alcohol as a viscous oil. This crude material was purified by means of preparative t.l.c. using 2:1 mixture of benzene and ethyl acetate as eluting solvent mixture to give 46 mg (97%) of the desired keto alcohol as a colorless viscous oil: i.r.($CHC\ell_3$), ν_{max} 3500 (broad), 1705 cm^{-1}; p.m.r., 0.66 (S, 3H, tertiary methyl), 0.86 (d, 3H, secondary methyl, J=6.0 Hz), 1.13 (s, 3H, tertiary methyl), 3.56 (s, 2H, $\underline{CH_2}OH$).

Mol. Wt. Calcd for $C_{15}H_{24}O_2$: 236.1771. Found (high resolution mass spectrometry): 236.1776.

Preparation of the Keto p-Nitrobenzoate 380

To a solution of 45 mg (0.19 mmole) of the keto alcohol 368 in 5 ml of dry methylene chloride was added 100 mg (0.54 mmole) of recrystallized p-nitrobenzoyl chloride and 100 mg (1.27 mmole) of dry pyridine. The mixture was kept at 0° for 24 hours and then diluted with water. The product was extracted into ether. The combined ether extracts were dried over anhydrous magnesium sulfate. Removal of the solvent yielded 95 mg of a yellow viscous oil as crude product. The desired keto p-nitrobenzoate 371, isolated from this crude material by means of preparative t.l.c. with 2:1 benzene-ethyl acetate being used as developing solvent, was obtained as a pale yellow viscous oil (67 mg, 91%); i.r. (film), ν_{max}

3100, 3070, 1720, 1705, 1609, 1525, 1345 cm^{-1}; p.m.r., 0.66 (s, 3H, tertiary methyl), 0.90 (unresolved d, 3H, secondary methyl, J=6.0 Hz), 1.20 (s, 3H, tertiary methyl), 4.38 (s, 2H, $\underline{CH_2}OCOAr$), 8.28 (m, 4H, $\underline{p}$-$NO_2C_6\underline{H}_4COO$).

Mol. Wt. Calcd. for $C_{22}H_{27}O_5$: 385.1889. Found (high resolution mass spectrometry): 385.1889.

Preparation of the Ketal Diester 369

To a mixture of 786 mg (2.98 mmoles) of the ketal olefin 324 and 64 mg of copper bronze[152] heated with an external oil bath at 130-140° under a nitrogen atmosphere was added, dropwise, 2.04 g (12.90 mmoles) of dimethyl diazomalonate.[142] Nitrogen was evolved immediately. After the addition of the diazomalonate had been completed, the mixture was stirred at 130-140° for another 1½ hour. When the mixture was cooled to room temperature, it solidified. The solid mixture was digested with a small amount of methylene chloride, and the resulting suspension was filtered through a short florisil column. The column was eluted with methylene chloride. Removal of the solvent from the eluant gave a crude product which was digested with ether. The resulting solution-suspension was filtered. Removal of the solvent from the filtrate afforded 2.29 g of a yellow semi-solid viscous oil. The latter material was chromatographed on 230 g of silica gel with a 1:3 mixture of ethyl acetate and petroleum ether being used as the eluting solvent. Evaporation of the solvent from the fractions containing the desired product gave 931 mg (80%) of a nearly colorless viscous oil which crystallized upon standing. Recrystallization from hexane gave 599 mg

of colorless crystals. Concentration of the mother liquor gave another 150 mg of the ketal diester 369 (total yield 64%) as colorless crystals, m.p. 132-133.5°; i.r. ($CHCl_3$), ν_{max} 3105, 1730 cm^{-1}; p.m.r., 0.66 (s, 3H, tertiary methyl), 2.62-2.82 (m, 1H, bridgehead proton), 3.14-3.80 (m, 4H, ketal protons), 3.68 (s, 3H, COOMe), 3.74 (s, 3H, COOMe).

Anal. Calcd. for $C_{22}H_{34}O_6$: C, 66.98; H, 8.69. Found: C, 67.09; H, 8.50.

Preparation of the Ketal Diol 389

To a solution-suspension of 500 mg (13.16 mmoles) of lithium aluminum hydride in 50 ml of anhydrous ether was added, over a period of 30 minutes, a solution of 532 mg (1.35 mmole) of the ketal diester 369 in 50 ml of anhydrous ether. The mixture was stirred at room temperature under a nitrogen atmosphere for 20 hours. After the reaction mixture had been diluted with methylene chloride (approximately 20 ml), the excess lithium aluminum hydride was destroyed by addition of excess powdered sodium sulfate decahydrate. The resultant mixture was diluted with more methylene chloride and then filtered through a Celite bed. The collected material was triturated and washed with methylene chloride. Removal of the solvent from the combined filtrate, after drying over anhydrous magnesium sulfate, gave a white solid. This solid was washed three times with small amounts of ether to furnish 371 mg of the ketal diol 389. Concentration of the ethereal washings gave another 58 mg of the ketal diol 389 (total yield 429 mg, 94%) with m.p. 170-172°. An analytical sample, obtained by recrystallization of a small amount of this material from acetone, exhibited m.p. 173-174.5°; i.r. (nujol mull), ν_{max} 3300 (broad) cm^{-1}; p.m.r., 0.63 (s, 3H, tertiary methyl), 0.75 (s, 3H, tertiary methyl), 0.78 (d, 3H, secondary methyl, J=6.0 Hz), 1.10

(s, 3H, tertiary methyl), 2.40 (broad s, 2H, OH), 3.60-3.96 (m, 8H, $\underline{CH_2}OH$ and ketal protons).

Anal. Calcd. for $C_{20}H_{34}O_4$: C, 70.97; H, 10.12. Found: C, 70.89; H, 10.00.

Hydrolysis of the Ketal Diol 389

To a solution of the ketal diol 389 (371 mg, 1.10 mmole) in 60 ml of reagent grade acetone and 5 ml of water was added 5 drops of 4N hydrochloric acid. The solution was stirred under nitrogen at room temperature for 3 hours. After anhydrous sodium bicarbonate had been added, most of the solvent was removed under reduced pressure. The residue was diluted with water and the aqueous layer was extracted thoroughly with methylene chloride. The combined extracts were washed with water and dried over anhydrous magnesium sulfate. Removal of the methylene chloride gave 259 mg of a pale yellow oily solid which was triturated with a small amount of ether. Filtration gave 147 mg of the desired keto diol 383 as a white powder. Concentration of the filtrate gave another 85 mg (total yield 232 mg, 84%) of the desired product, which exhibited m.p. 138-139.5°; i.r. (nujol mull), ν_{max} 3300 (broad), 1700 cm^{-1}; p.m.r., 0.66 (s, 3H, tertiary methyl), 0.91 (d, 3H, secondary methyl, J=6.0 Hz), 1.00-1.15 (m, 2H, cyclopropyl protons), 2.35 (broad s, 2H, disappeared upon addition of D_2O, OH), 3.45, 3.61 (AB pair of doublets, 2H, $\underline{CH_2}OH$, J=12.0 Hz), 3.70, 3.90 (AB pair of doublets, 2H, $\underline{CH_2}OH$, J=12.0 Hz).

Anal. Calcd. for $C_{15}H_{24}O_3$: C, 71.39; H, 9.59. Found: C, 71.00; H, 9.52.

Preparation of the Keto Dimesylate 384

To an ice-cold solution of the keto diol 383 (232 mg, 0.921 mmole) in 20 ml of methylene chloride under an atmosphere of nitrogen was added 290 mg (2.87 mmoles) of dry triethylamine and 266 mg (2.32 mmoles) of methanesulfonyl chloride. The mixture was stirred at 0° for 30 minutes, was diluted with ether and then washed four times with ice-cold water. The organic phase was wahsed with brine and dried over magnesium sulfate. Evaporation of the solvent gave 413 mg of a slightly yellow viscous oil as the crude product; i.r. (film), ν_{max} 1700, 1355, 1170 cm^{-1}; p.m.r., 0.66 (s, 3H, tertiary methyl), 0.90 (unresolved d, 3H, secondary methyl), 3.03 (s, 3H, $\underline{CH_3}SO_3$), 3.06 (s, 3H, $\underline{CH_3}SO_3$), 3.96, 4.04 (AB pair of doublets, 2H, $\underline{CH_2}OMs$, J=11.0 Hz), 4.30 (s, 2H, $\underline{CH_2}OMs$).

Due to the fact that this dimesylate 384 was quite unstable, this crude product was used immediately in the next transformation without further purification.

Preparation of the Keto Dichloride 391

To a solution of the crude keto dimesylate 384 (413 mg, obtained from mesylation of 232 mg of the keto diol 383) in 15 ml of anhydrous ether and 30 ml of dry hexamethylphosphoramide was added 2.1 g of anhydrous lithium chloride. The mixture was stirred overnight under an atmosphere of nitrogen, and then poured into approximately 150 ml of water. The resultant mixture was extracted with ether. The combined ether extracts were washed thoroughly with water and dried over anhydrous magnesium sulfate. Evaporation of the solvent gave 310 mg of a slightly

yellow viscous oil which solidified upon cooling. The crude product was recrystallized from hexane to give 242 mg (91%) of the keto dichloride 391 as creamy colored crystals which exhibited m.p. 133-135°*; i.r. ($CHCl_3$), ν_{max} 1706 cm^{-1}; p.m.r., 0.62 (s, 3H, tertiary methyl), 0.92 (d, 3H, secondary methyl, J=6.5 Hz), 3.36, 3.66 (AB pair of doublets, 2H, $\underline{CH_2}Cl$, J=11.0 Hz), 3.61, 3.81 (AB pair of doublets, 2H, $\underline{CH_2}Cl$, J=12.0 Hz).

Anal. Calcd. for $C_{15}H_{22}Cl_2O$: C, 62.29; H, 7.67. Found: C, 62.27; H, 7.85.

Intramolecular Alkylation of the Keto Dichloride 391

To a small amount of dry tert-butyl alcohol was added 36 mg of potassium metal. The mixture was warmed briefly to ensure that all the potassium had reacted. The excess tert-butyl alcohol was removed under reduced pressure (vacuum pump). To the remaining potassium tert-butoxide (white powder) was successively added 10 ml of dry tetrahydrofuran, and a solution of 178 mg (0.615 mmole) of the keto dichloride 391 in 5 ml of dry tetrahydrofuran. The resulting orange yellow solution was stirred under a nitrogen atmosphere at room temperature for 1½ hour. Aqueous ammonium chloride was added and the resulting mixture was extracted with pentane. The combined extracts were washed with water and brine, and

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* A sample of the keto dichloride 391 which was obtained by means of preparative t.l.c. using 7:3 hexane-ether as the developing solvent, and which was not recrystallized, exhibited m.p. 74-76°.

dried over anhydrous magnesium sulfate. Evaporation of the solvent gave 141 mg (91%) of a pale yellow oil which was used in the subsequent transformation without further purification because of its thermal instability; i.r. (film), ν_{max} 1700 cm^{-1}, p.m.r., 0.73 (s, 3H, tertiary methyl), 0.87 (d, 3H, secondary methyl, d=6.0 Hz), 3.60 (s, 2H, $\underline{CH_2}Cl$).

Reduction of the Keto Monochloride 392

To a cold (0°) solution of 141 mg of the crude keto monochloride 392 in 10 ml of dry tetrahydrofuran was added 2.8 ml (2.8 mmoles) of a solution of lithium triethylborohydride in tetrahydrofuran (1M). The mixture was stirred for 20 hours at room temperature under a nitrogen atmosphere. The excess reducing agent was destroyed by addition of 4 ml of water. Approximately 3 ml of 3N sodium hydroxide and 3 ml of 30% hydrogen peroxide solution were carefully added to the reaction mixture. The mixture was stirred for another 4 hours at room temperature, was diluted with water and then thoroughly extracted with ether. The combined etheral extracts were washed with water and brine, and then dried over anhydrous magnesium sulfate. Evaporation of the solvent gave 148 mg of the alcohol 393 as a pale yellow oil. Distillation at 100-110° (air bath temperature) and 0.5 mm (lit.b.p. 114° at 1 mm[12]) yielded 128 mg (94% based on the keto dichloride 391 used) of a colorless viscous oil; i.r. (film), ν_{max} 3350 (broad) cm^{-1}; p.m.r., 0.55 (m, 1H, cyclopropyl proton), 0.77 (d, 3H, secondary methyl, d=5.5 Hz), 1.03 (s, 3H, tertiary methyl), 1.13 (s, 3H, tertiary methyl), 3.42 (m, 1H, $\underline{CH}OH$).

Preparation of (±)-Ishwarone 12

To a suspension of chromium trioxide (282 mg, 2.82 mmoles) in 20 ml

of methylene chloride was added 330 mg (2.86 mmoles) of pyridinium hydrochloride. The mixture was stirred for 1 hour to form a bright yellow-orange suspension-solution. To this suspension-solution was added a solution of 128 mg (0.58 mmole) of alcohol(s) 393 in a minimum amount of methylene chloride. The reaction mixture was stirred at room temperature for 2 hours, was diluted with ether and then filtered through a short florisil column. The column was eluted with ether. Evaporation of the solvent from the eluant gave 115 mg of a yellow oil. Distillation of the crude product at 120-130° under water aspirator pressure gave 92 mg (73%) of colorless oil which solidified upon cooling. Recrystallization from pentane gave (±)-ishwarone 12 as colorless crystals which exhibited m.p. 80-81°; i.r. (film), ν_{max} 3030, 1700 cm^{-1}; p.m.r., 0.56 (m, 1H, cyclopropyl proton), 0.74 (s, 3H, tertiary methyl), 0.87 (d, 3H, secondary methyl, d=6.5 Hz), 1.16 (s, 3H, tertiary methyl). The spectral properties of this synthetic (±)-ishwarone 12 were in full agreement with those of natural ishwarone.[12]

Mol. Wt. Calcd. for $C_{15}H_{22}O$: 218.1671. Found (high resolution mass spectrometry): 218.1679.

Wolff-Kishner Reduction of (±)-Ishwarone 12 to (±)-Ishwarane 13

To 20 ml of diethylene glycol was added 0.5 g of metallic sodium. The mixture was warmed with a steam bath until the reaction between the sodium and diethylene glycol was complete. To the resultant solution was added 31 mg (0.14 mmole) of ishwarone 12 and 3 ml of hydrazine hydrate. The solution was heated slowly with distillation (the distillate was saved) until the internal temperature reached 180° and was then refluxed at this

temperature for 18 hours. The solution was again slowly distilled (the distillate was saved) until the internal temperature had reached 210°. After the reaction mixture had been refluxed for 6 hours, it was cooled, combined with the two distillates obtained as described above, and then poured into water. The resultant mixture was extracted with ether. The combined ether extracts were washed with water and brine and dried over anhydrous magnesium sulfate. Evaporation of ether and subsequent distillation of the crude product at 90-120° (air bath temperature) and water aspirator pressure gave 23.5 mg (81%) of (±)-ishwarane 13 as a colorless oil; i.r. (film), no carbonyl absorption; p.m.r., 0.52 (m, 2H, cyclopropyl protons), 0.74 (d, 3H, secondary methyl, J=6.5 Hz), 0.78 (s, 3H, tertiary methyl), 1.14 (s, 3H, tertiary methyl). This material exhibited spectral data (i.r., p.m.r., and mass spectrum), and g.l.c. retention time (column F, 120° for 5 minutes and then raised to 200° for 10 minutes with the rate of 25°/min, 180 ml/min) identical with those of authentic (±)-ishwarane.[34]

Mol. Wt. Calcd. for $C_{15}H_{24}$: 204.1898. Found (high resolution mass spectrometry): 204.1878.

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