

APPROACHES TO THE SYNTHESIS OF CADINENE SESQUITERPENES AND THE BIRCH
REDUCTION OF SOME 4-ALKYL- $\Delta^{1,9}$ -2-OCTALONES

BY

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ABSTRACT

Part of this thesis describes the investigation of several synthetic approaches to the cadinane group of sesquiterpenes. The first approach investigated the preparation of a possible key intermediate of type 118 using the known octalone 114 as starting material. However all attempts to obtain octalone 116, a necessary intermediate in this sequence were unsuccessful. This precluded further use of this approach. The second approach involved preparation of several cross-conjugated dienone systems (125, 133, 139 and 141) and the study of 1,4-conjugate addition of an alkyl group by means of cuprous ion catalyzed Grignard reagents and lithium dialkylcuprate reagents. Use of reagents in which the alkyl group was methyl or primary effected the desired 1,4-conjugate addition. However when isopropylmagnesium bromide or lithium diisopropylcuprate reagents were tried no addition products were detected. Evidence is presented which indicates that enolization of the keto system was the main reaction pathway in these cases. The final and most successful approach described is the condensation-annellation approach where condensation between a vinyl ketone such as 144 and a substituted cyclohexanone derivative of type 143 was investigated. Octalones 162 were prepared by the enamine-annellation reaction employing vinyl ketone 144 and the enamine of keto alcohol 158. The stereochemistry of octalones 162 was then established. The mixture of epimeric octalones 162 was degraded to decalones 165a and 165b. The stereochemistry of these decalones was unambiguously shown by a combination of chemical and spectroscopic methods.

Octalones (162a + 162c) were converted into thioketal 166 by treatment with ethanedithiol and boron trifluoride etherate. Thioketal 166 was converted into alcohol 167 by desulphurization employing Raney nickel. Treatment of alcohol 167 with chromium trioxide in pyridine afforded octalone 168. Octalone 168 was converted into (+)-cadinene dihydrochloride by treatment of the former with methyllithium followed by treatment of the resultant 3° alcohol with anhydrous hydrogen chloride in ether.

The Birch reduction of octalones of type 170 is described. The octalones were prepared by 1,4-conjugate addition of lithium dialkylcuprate reagents to the cross-conjugated dienones of type 171. The preparation of the corresponding authentic cis- and trans-fused decalones is described. The results of Birch reduction of octalones 188 to 192 revealed a higher percentage of cis-fused decalone product than normally obtained in other substituted $\Delta^{1,9}$ -2-octalone systems. The results also indicated that as the bulk of the C₄ substituent was increased the product ratio of cis-fused decalone to trans-fused decalone also increased. The substituent at the C₁₀ position also effected the ratio of cis:trans decalone obtained. Possible explanations for these results are presented.

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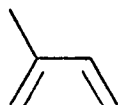
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INTRODUCTION

I. General

Terpenoids are a class of naturally occurring compounds characterized by a common building block, the isoprene unit (1). Terpenoids are

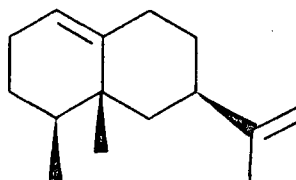


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subdivided according to the number of isoprene units embodied in their structure. The group containing three such units, that is fifteen carbon atoms, are called sesquiterpenes. There is an ever widening variety of compounds which fall into this class - at least forty different types to date (1). They may be acyclic, monocyclic, bicyclic, tricyclic or tetracyclic. Generally, each skeletal type can possess stereochemical variations, positional isomerism, as well as a range of functional groups, such as, ketones, alcohols, lactones and oxides.

The common biogenesis of terpenoids was postulated by Ruzicka, Eschenmoser and Heusser, in 1953, as the Isoprene Rule (2). The latter was restated as the Biogenetic Isoprene Rule by Ruzicka, Eschenmoser, Jeger and Arigoni, in 1955, to include compounds formed

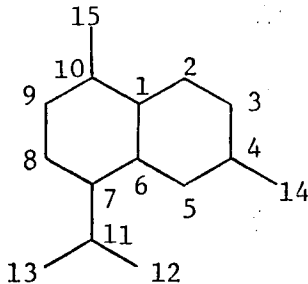
by the union of isoprene units followed by skeletal rearrangements (3). For example, this rule allowed compounds such as eremophilene (2) to be formally classified as sesquiterpenes.



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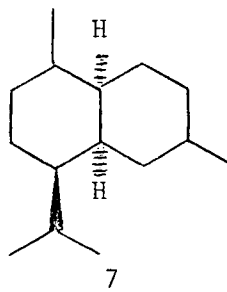
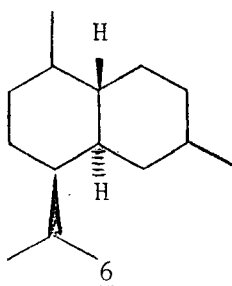
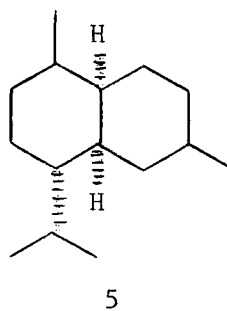
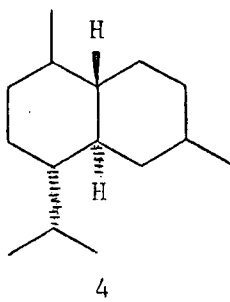
Although sesquiterpenes have been recognized for over a century, it has not been until recent years that meaningful structural elucidation has been carried out. This is mainly attributable to the fact that sesquiterpenes usually occur in essential oils as very complex mixtures. In past years fractional distillation was the only means used for separation. Hence, much work was carried out with substances which were not homogeneous and often erroneous conclusions resulted. Only in recent years with the advent of separation techniques such as gas-liquid chromatography (g.l.c.) and thin layer chromatography has separation of these complex mixtures been realized.

One of the largest groups of sesquiterpenes is the cadinane class, which contains the basic skeleton and numbering system shown in 3. The

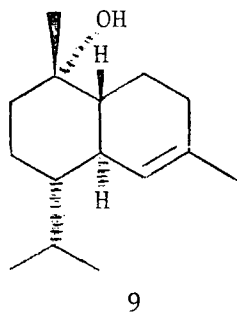
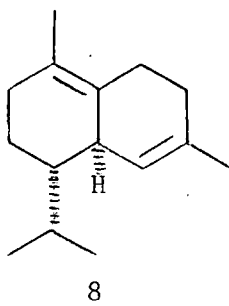


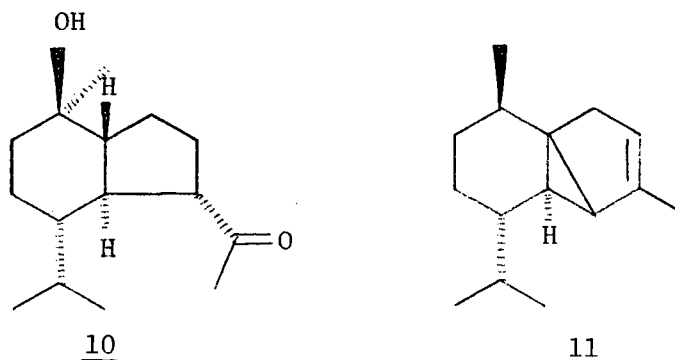
3

basic cadinane class has been divided into four subgroups, differing only in the relative stereochemistry at C_1 , C_6 and C_7 . These classifications are exemplified by the following structural formulae: cadinane (4), muurolane (5), bulgarane (6) and amorphane (7) (4).



Naturally occurring compounds belonging to the cadinane class occur as hydrocarbons, for example, δ -cadinene (8) (4,5,6), alcohols, for example, Γ -cadinol (9) (5,7), in ring contracted and oxygenated forms, for example, oplopanone (10) (8,9) and tricyclic structural variants, for example, α -cubebene (11) (10).





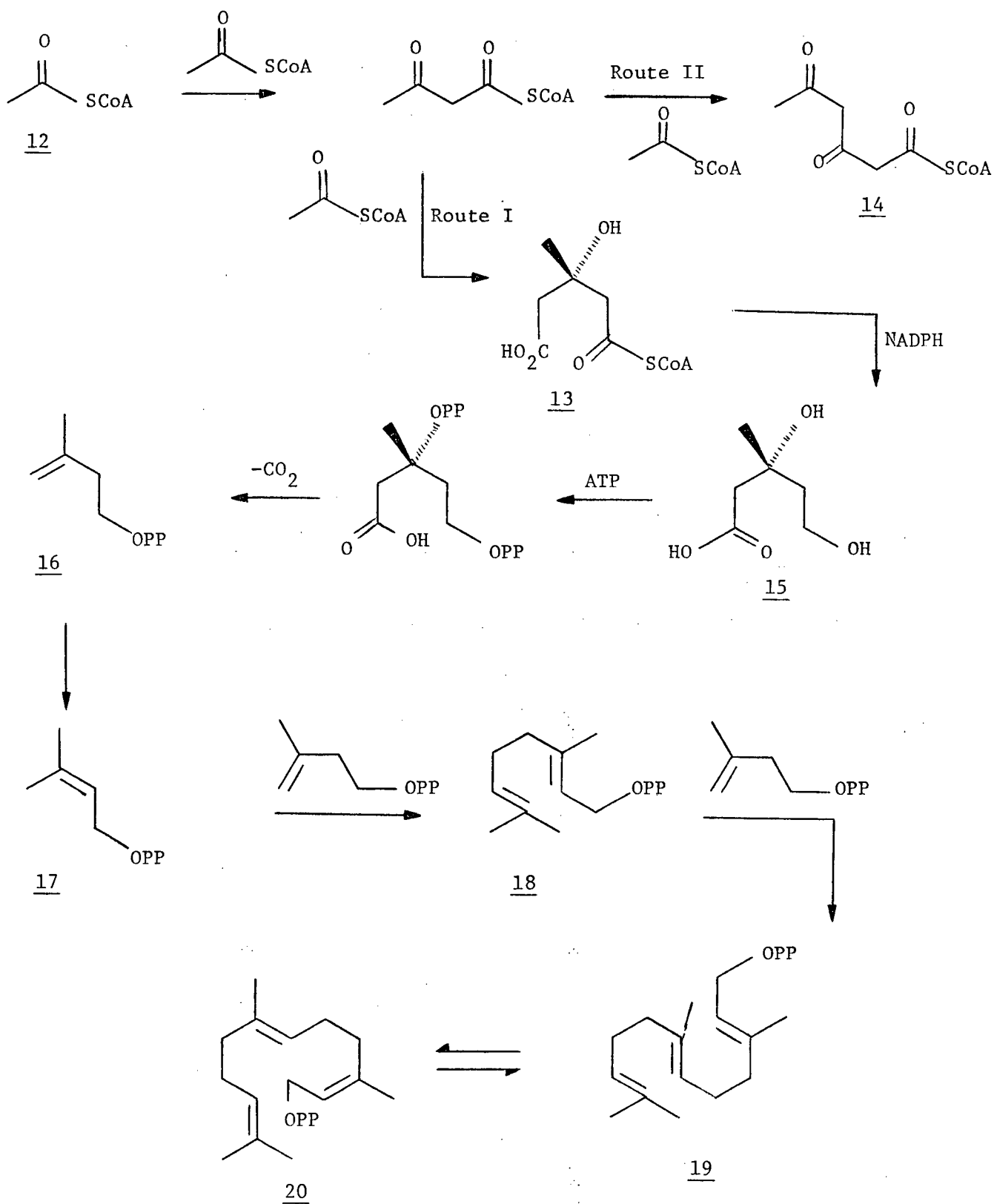
The work of natural product chemists in structural elucidation and synthesis of terpenoids is essential for a firm foundation for more biological investigations of terpenoids. Thus, the work described in this thesis is, in part, concerned with gaining a general synthetic entry into the cadinane class of sesquiterpenes.

II. Sesquiterpene Biosynthesis

Sesquiterpenes are believed to be derived by the union of three biological C_5 isoprenoid units, followed by a variety of cyclization modes, with or without skeletal rearrangements. It is generally believed (1,11) that the C_5 unit arises from acetyl CoA (12) by three successive condensations (Chart I, Route I) to afford β -hydroxy- β -methyl glutaryl CoA (13). An alternate mode of condensation of acetyl CoA gives rise to a straight chain derivative 14, which is believed to be the precursor of two groups of natural products, the acetogenins and the phenolic resins (Chart I, Route II).

Reduction of β -hydroxy- β -methyl glutaryl CoA (13) with nicotinamide-adenine dinucleotide phosphate (NADPH) affords mevalonic acid (15). This intermediate is phosphorylated with adenine triphosphate (ATP) and

Chart I



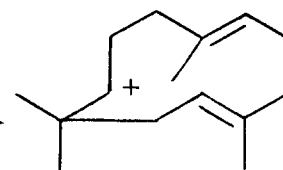
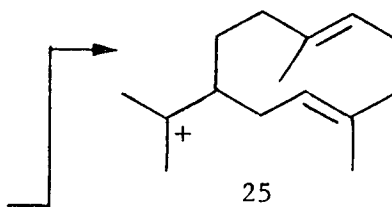
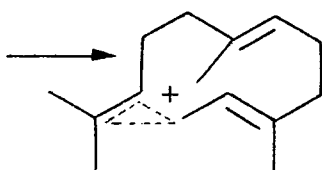
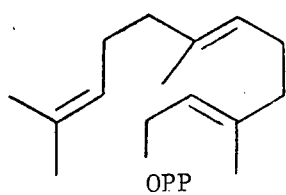
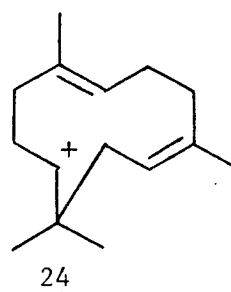
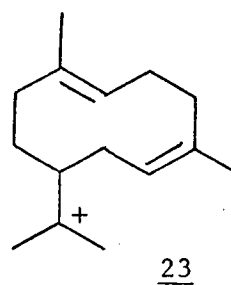
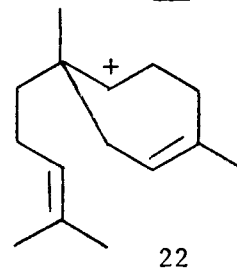
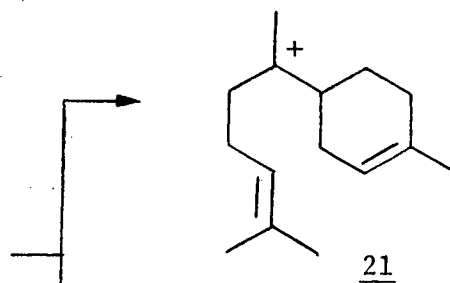
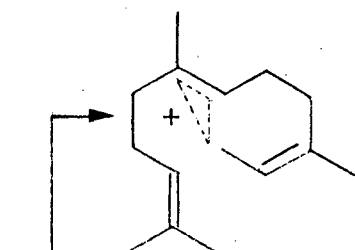
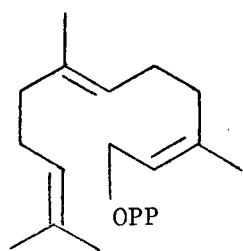
subsequently decarboxylates to form isopentenyl pyrophosphate (16). Isomerization of the terminal double bond of 16 affords dimethylallyl pyrophosphate (17), which upon condensation with 16 affords geranyl pyrophosphate (18), the monoterpene precursor. Further condensation of geranyl pyrophosphate (18) with isopentenyl pyrophosphate yields farnesyl pyrophosphate (19), the active precursor of the sesquiterpenes.

It is believed (12) that all sesquiterpenes can be formed from either trans- or cis-farnesyl pyrophosphate, (19) and (20) respectively, by processes involving in vivo transformations formally resembling cationically induced transannular cyclizations. It is understood of course, that in this discussion the representation of formal charges is only a convenient symbolism, as in living systems farnesyl pyrophosphate is probably enzyme bound and the cyclizations probably fully or partially concerted.

In the representation shown in Chart II, the initial step is shown as the ionization of the allylic pyrophosphate group from 19 or 20. The central or terminal double bond can participate with the resulting cation from cis-farnesyl pyrophosphate (20) to give rise to cations 21 to 24, while for steric reasons only the terminal double bond can interact with the cation from trans-farnesyl pyrophosphate giving rise to cations 25 and 26. These resulting cations 21 to 26 can undergo proton loss, interaction with nucleophiles or a series of further rearrangements.

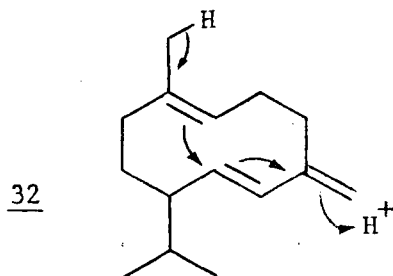
Germacrene D (27), a naturally occurring ten-membered carbocyclic ring compound, has recently been isolated by Hirose et al. (13) from the essential oil of Pseudotsuga japonica. Its presence has also been

Chart II



noticed in a variety of other essential oils (13). It has been postulated that germacrene D (27) could be a crucial intermediate in the biosynthesis of several cadinene compounds (13). While no in vivo experimental work has been done to verify its intermediacy in biosynthesis, laboratory results strongly support this hypothesis (see Chart III).

Germacrene D (27), was smoothly converted into a mixture of γ -muurolene (28), α -amorphane (29), δ -cadinene (8) and γ -cadinene (30), thermally, on silica gel or by acid isomerization. From chemical and spectroscopic data, Hirose (13) proposed that the preferred conformation of germacrene D is 31, where there are transannular interactions between the endocyclic double bonds. It was suggested (13) that at least the γ -isomers of the cadinane group most probably arise through this intermediate and the cyclization was postulated as in 32.



Several other postulates for the biosynthesis of cadinenes have been proposed and are represented diagrammatically in Chart IV. Cation 21 was postulated to deprotonate with subsequent double bond isomerization to afford triene 33, followed by cyclization to afford cation 34. This cation could then be deprotonated to yield, for example, δ -cadinene (8).

Chart III

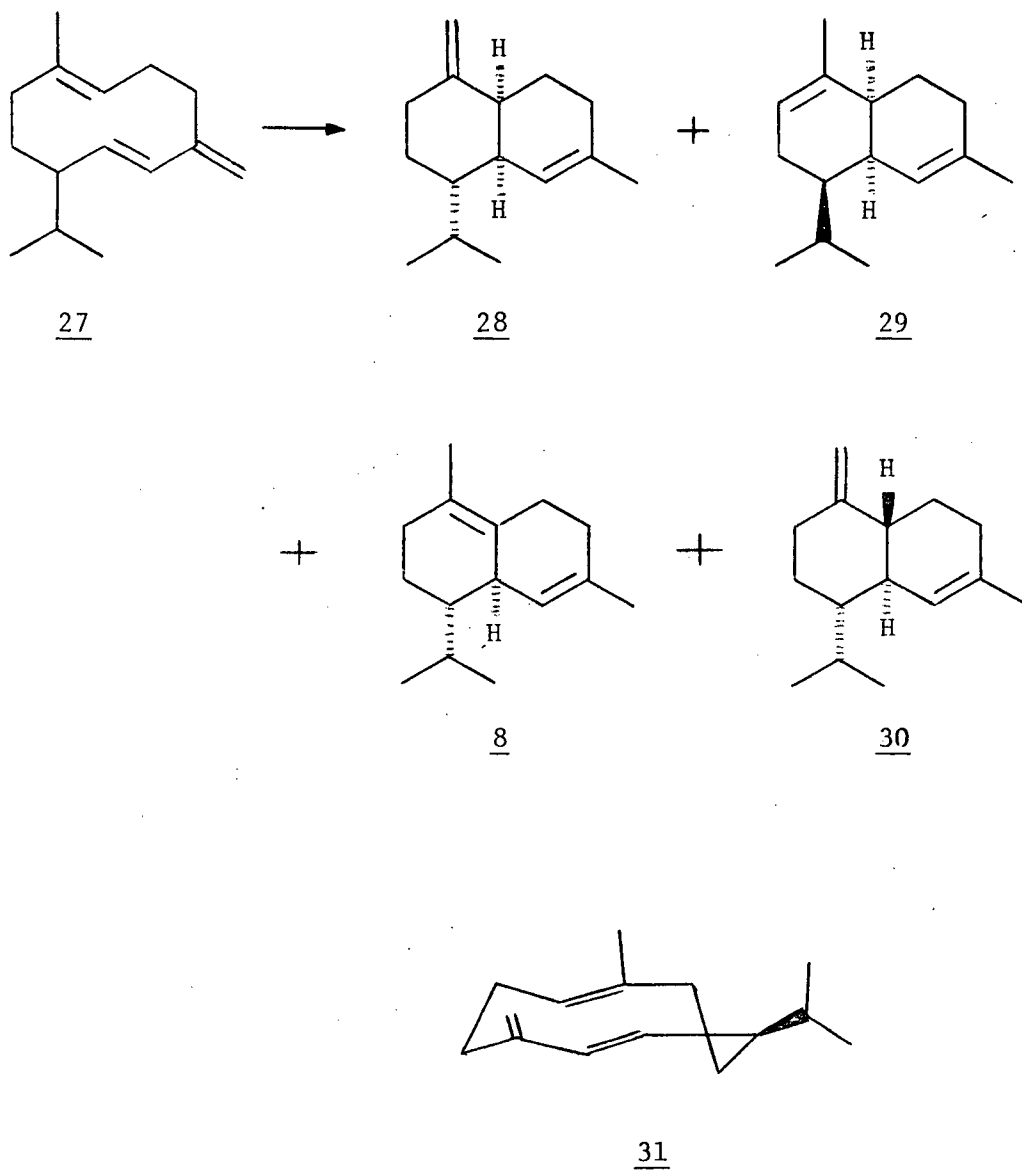
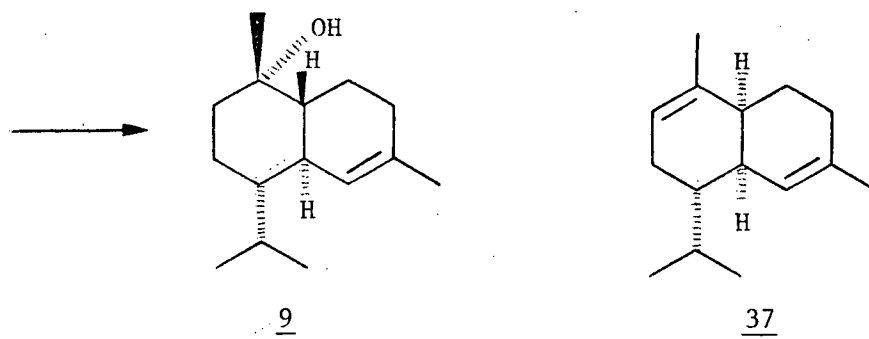
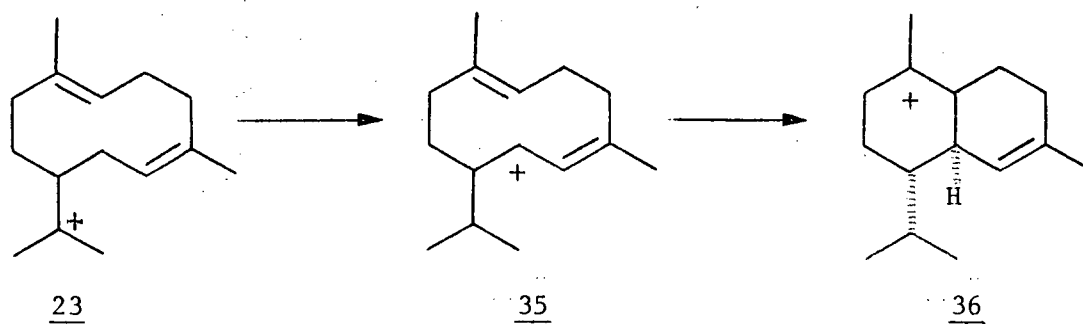
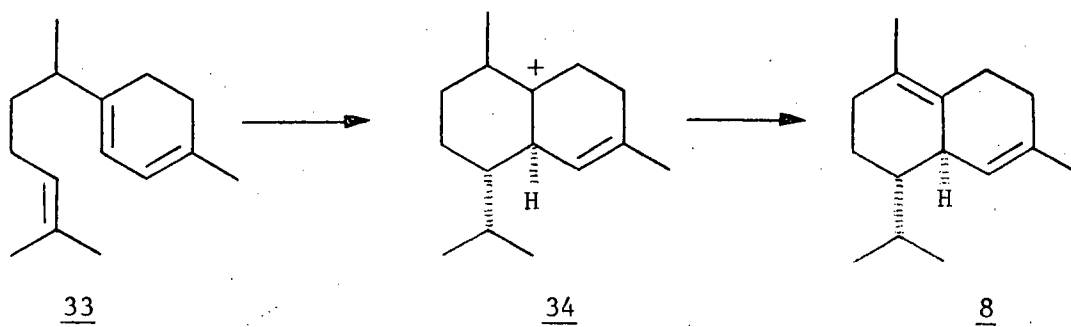
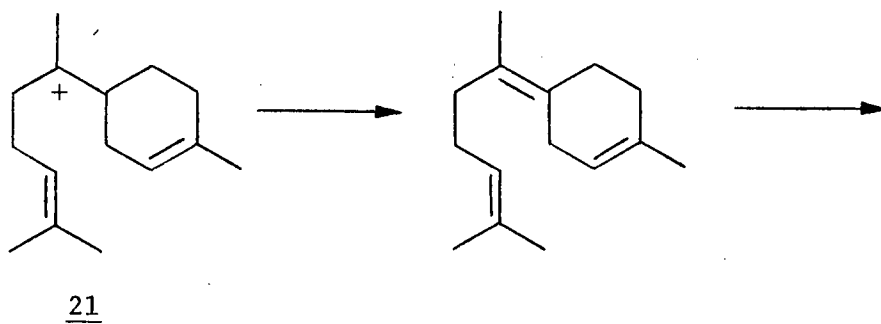
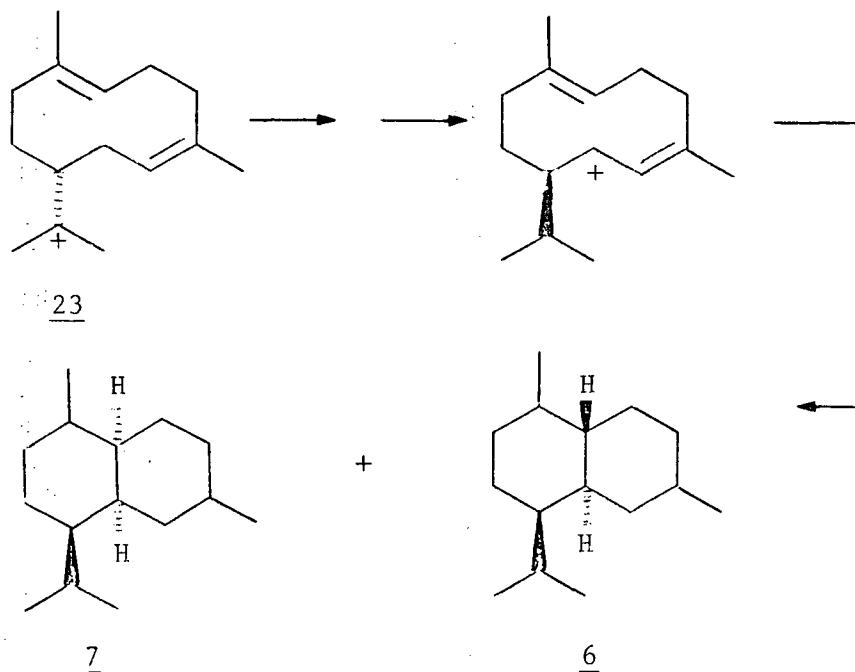


Chart IV



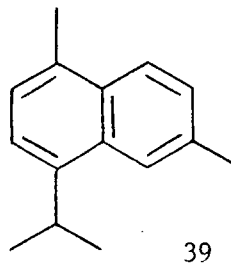
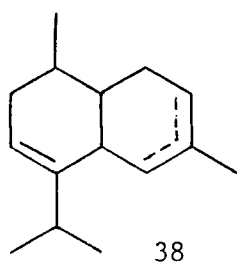
A second proposal involved cation 23, which could undergo a 1,3-hydride shift to cation 35, followed by cyclization to yield cation 36. Hydration of this cation from the α -face would give rise to Γ -cadinol (9), while deprotonation from C_9 or from C_1 would afford α -muurolene (37) or δ -cadinene (8), respectively. The other members of the cadinane family can be derived by analogous processes. For example, if cation 23 were to undergo two 1,2-hydride shifts and then followed through the above processes, the stereochemistry of the bulgarane (6) and amorphane (7) groups would result. These theoretical cyclizations have received some experimental support by Hirose and coworkers (4), who have artificially generated some of the above cations in the laboratory and have indeed isolated a mixture of cadinane-type sesquiterpenoids as the rearrangement products.



III. Structural Elucidation and Stereochemical Studies

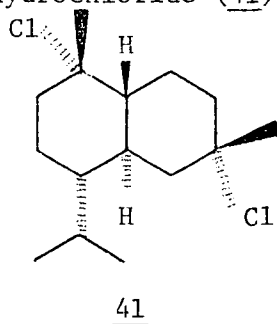
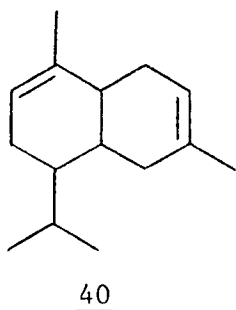
Since part of this thesis is concerned with gaining a synthetic entry into the cadinane class of sesquiterpenes, it is pertinent to discuss the studies which led to the establishment of the structure and stereochemistry of the cadinene group. Since publications dealing with this topic are numerous and complex, it is necessary to limit this discussion to several examples. Hence, only the establishment of structure and stereochemistry of β -cadinene, using classical methods, of α -cadinene, using modern chemical and spectroscopic methods, and of cadinene dihydrochloride, using a combination of methods, will be discussed in any detail.

Semmler and Stenzel (14), in 1914, and Ruzicka and coworkers (15), in 1924, proposed structure 38 for cadinene. While the location of the



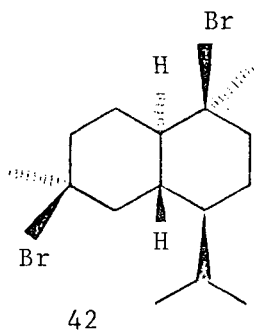
double bonds remained uncertain, Ruzicka confirmed the basic carbon skeleton by dehydrogenation of cadinene to cadalene (39).

Campbell and Soffer (16), in 1942, proposed structure 40 for cadinene regenerated from cadinene dihydrochloride (41). The latter

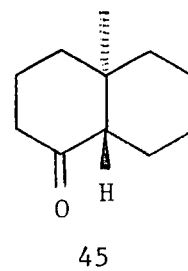
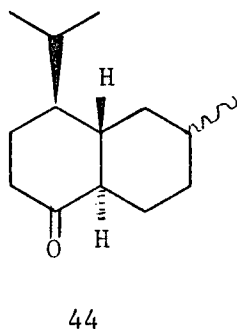
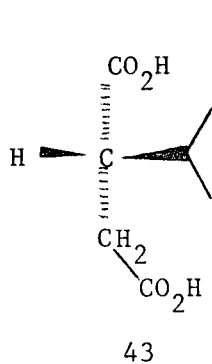


compound was first prepared in 1840 by Soubeiran and Capitaine from cubeba oil (17). From that time forward this derivative, along with the corresponding dihydrobromide, have played a major role in identification and isolation of cadinene compounds. These crystalline derivatives circumvented the major problem that plagued workers in this field, that is, the inseparability of the structurally similar cadinene compounds.

The structure and stereochemistry of (-)-cadinene dihydrobromide was determined by Hanic in 1958 (18). He carried out an X-ray structural determination to confirm structure 42 or its mirror image for (-)-cadinene dihydrobromide.



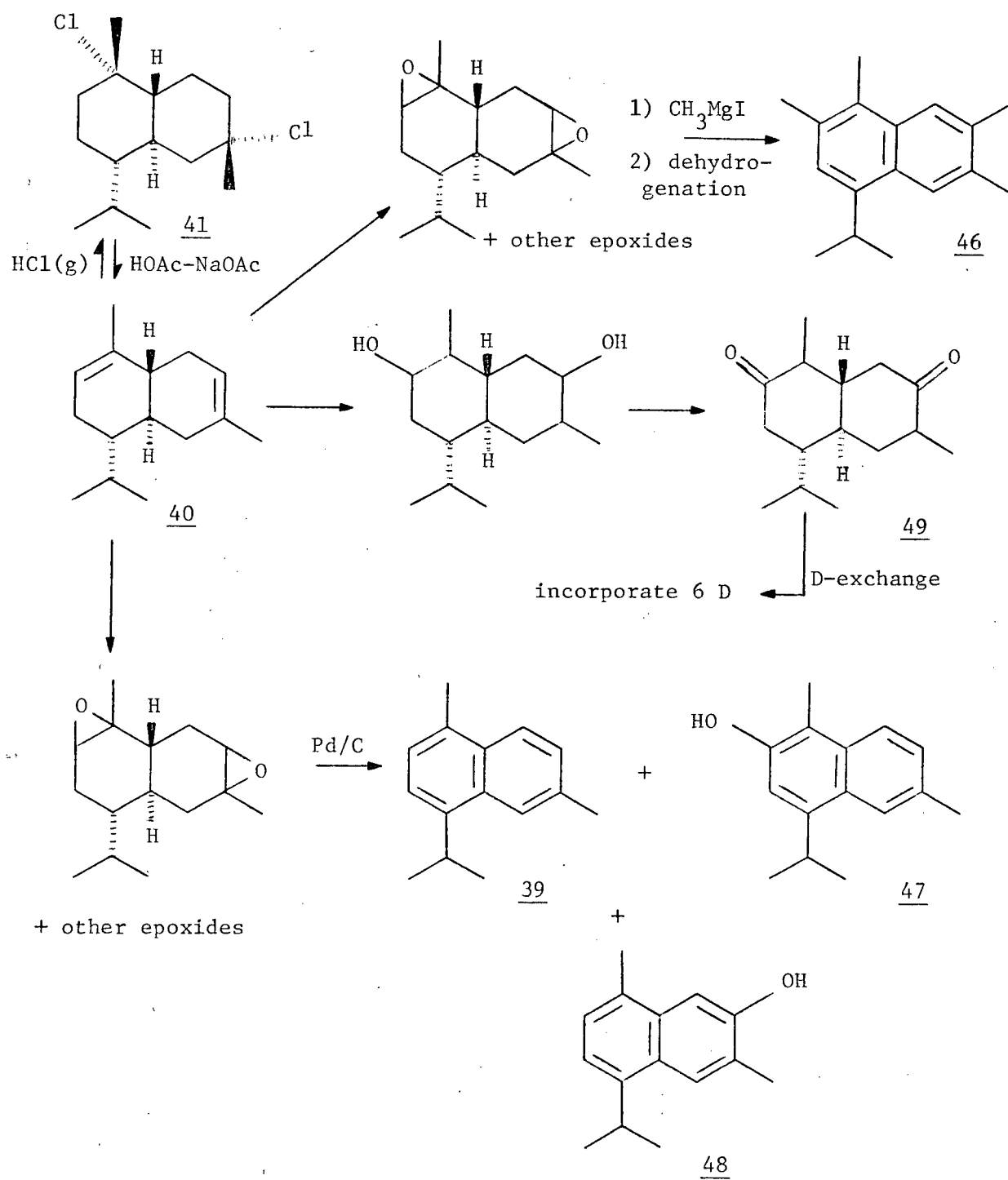
The dipole moment of this compound was determined and found to be in good accord with structure 42 (19). The absolute configuration of 42 was then investigated by Herout *et al.* (19,20). The relative configuration at positions 1, 6 and 7 is maintained during formation of the dihydrohalide derivatives; hence, the determination of the absolute configuration of only one of these centers was necessary to fix the absolute configuration of the naturally occurring cadinene compounds. (-)-Cadinene dihydrochloride was dehydrohalogenated with glacial acetic acid-sodium acetate to yield a mixture of hydrocarbons with β -cadinene (40) predominating. This mixture was then subjected to oxidative degradation to obtain only slightly racemized D-(+)-isopropylsuccinic acid (43). This fixes the absolute configuration at C₇.



The optical rotatory dispersion (o.r.d.) curve of a degradation product of α -cadinol was also investigated. The o.r.d. curve of the degradation product, decalone 44, bore a mirror image relationship to the o.r.d. curve of decalone 45, of known absolute configuration. These results are in agreement with the assigned absolute configuration shown in structure 42 for (-)-cadinene dihydrobromide.

As mentioned earlier the major product from dehydrohalogenation of cadinene dihydrochloride was β -cadinene (40). Thus, this hydrocarbon was the first cadinene compound to be readily available for investigation. However "the very pure β -cadinene" (21) obtained as "regenerated cadinene" was shown to be a mixture with at least nine components (22). Campbell and Soffer (16) treated the diepoxide of regenerated cadinene with methylmagnesium iodide and subjected the resultant product to dehydrogenation, thus obtaining a 3% yield of 2,7-dimethylcadalene (46) (see Chart V). Sutherland and collaborators (23) repeated this epoxidation experiment and isolated at least four different diepoxides. One of the diepoxides formed was then dehydrogenated on palladised charcoal at 265° for 1 h to give a mixture of cadalene (39), 2-hydroxycadalene (47) and 7-hydroxycadalene (48).

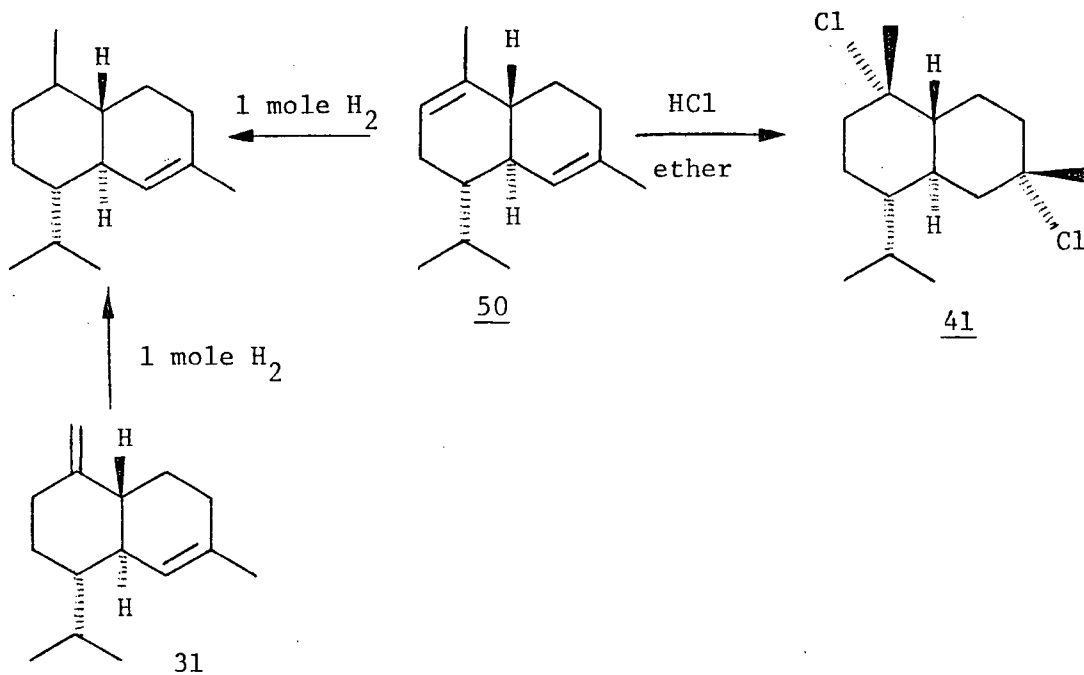
Chart V



Herout et al. (22) reinvestigated their "very pure β -cadinene". By an elaborate combination of separation techniques they isolated β -cadinene which formed one crystalline diepoxide, identical with the one which had been dehydrogenated by Sutherland. Herout then carried out a hydroboration-oxidation of β -cadinene to obtain diketone 49, which upon deuterium exchange incorporated six deuterium atoms. Hence, all these results substantiate structure 40 for β -cadinene.

Naya and Kotake (24) using modern techniques elucidated the structure of the most recently isolated cadinene, α -cadinene (50). Their work is in striking contrast to the inconsistencies and structural controversies of the earlier structural elucidations. The sesquiterpene, $C_{15}H_{24}$, was isolated, in 1969, from Japanese hop (Humulus lupulus L.). The nuclear magnetic resonance (n.m.r.) spectrum of this compound gave evidence for an isopropyl group, τ 9.22 and τ 9.09 as a pair of three-proton doublets, two vinyl methyl groups, τ 8.35 as broad three-proton singlets, and two vinyl hydrogens, τ 4.68 and τ 4.48 as one-proton multiplets. The mass spectrum showed a molecular ion peak at m/e 204, a base peak at m/e 105, and an abundant peak at m/e 161 (M-43).

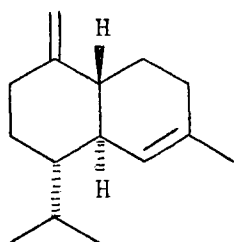
Upon partial hydrogenation with platinum oxide in methanol-ether α -cadinene (50) gave a single product, which was identical with the dihydro compound prepared from γ -cadinene (31). Treatment of hydrocarbon 50 with dry hydrogen chloride in ether afforded (-)-cadinene dihydrochloride (41). The infrared (i.r.) spectrum of α -cadinene was distinct from that of β -cadinene. Therefore, the Japanese workers proposed structure 50 for α -cadinene.



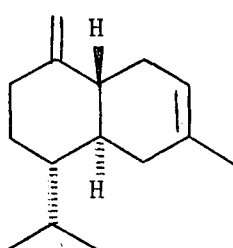
In 1966, Westfelt (25) isolated γ -cadinene (31) from a high boiling fraction of Swedish sulfate turpentine. Bhattacharyya isolated the closely related γ_2 -cadinene (51) from Indian vetiver oil (26).

Herout and Santany (27) proposed structure 8 for δ -cadinene. After some controversy (28), Hirose et al. (4) and Dev et al. (5), in 1968, independently confirmed structure 8 for δ -cadinene. A compound of structure 52 was mistakenly called δ -cadinene (28) but Sutherland et al. (6) showed 52 to be a distinct cadinene compound and named it ω -cadinene.

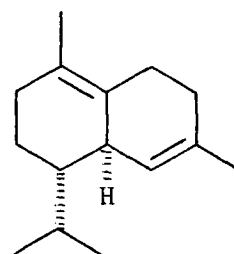
Westfelt et al., in 1964, (29) isolated ϵ -cadinene (53) which was different from the previously isolated ϵ -cadinene (21). Westfelt's definitive work showed ϵ -cadinene to have structure 53 and the previously isolated compound to be ϵ -muurolene (54).



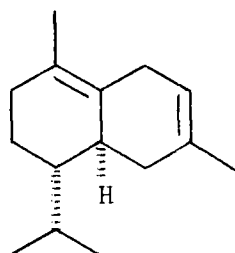
31



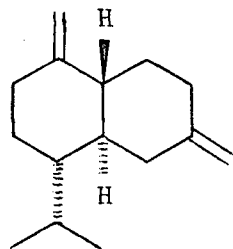
51



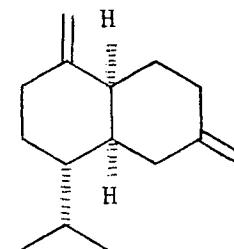
8



52

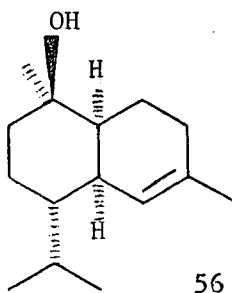


53

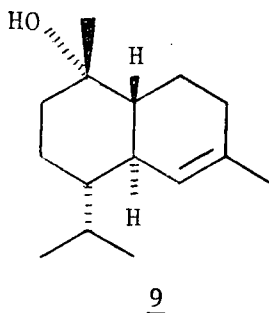
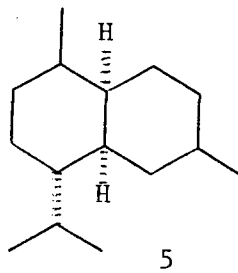
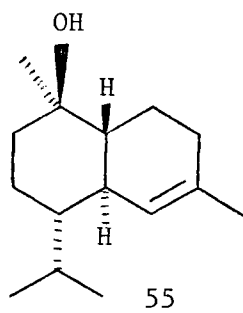


54

Two cadinols have been isolated to date. They are α -cadinol (55) and Γ -cadinol (9) (30,7). There have been at least eight publications dealing with the structure of δ -cadinol, with chemical and spectral evidence being put forward to support four different structures. This alcohol has been named δ -cadinol (5,31,30), abicaulol (32), cedrelanol (33), and (-)-torreyol (34). It is now becoming clear that this alcohol does not belong to the cadinane class but rather to the muurolane class (5). Thus, δ -cadinol is now proposed to possess structure 56 (5).



56

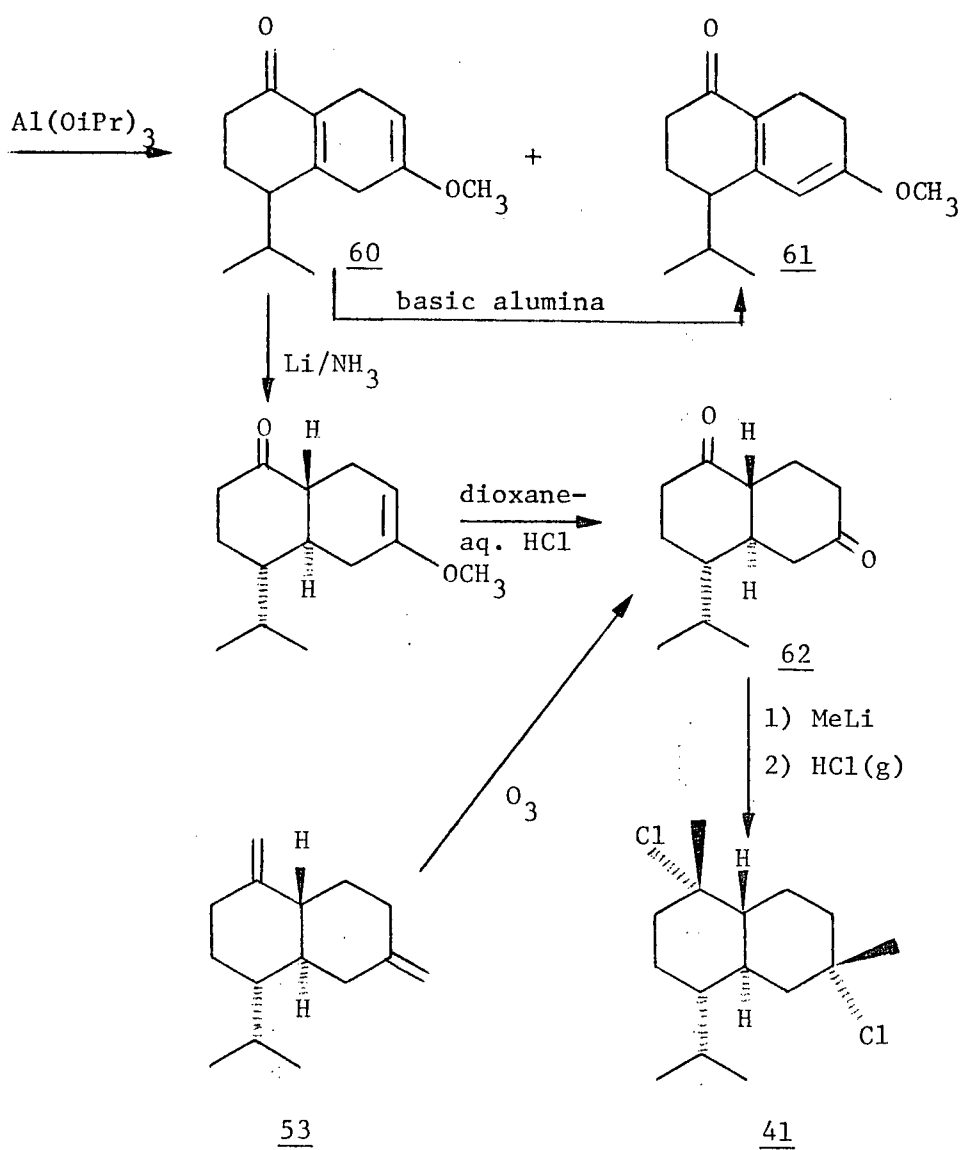
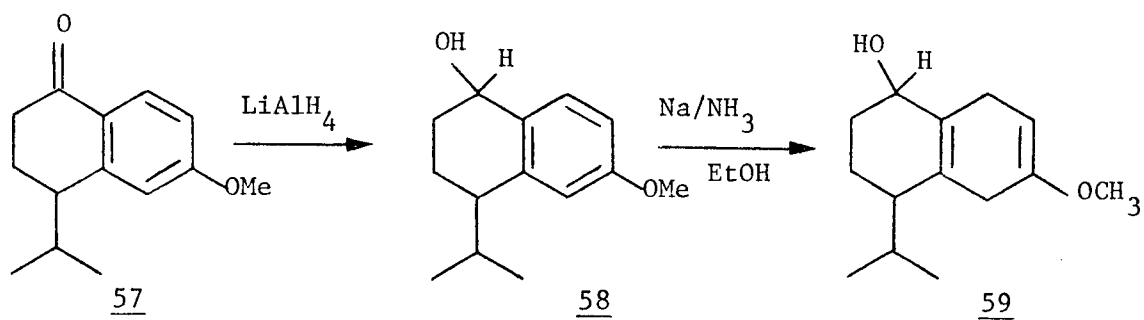


IV. Synthetic Approaches to the Cadinane-type Sesquiterpenes

At the time this work was undertaken there were no published syntheses of cadinene hydrocarbons. However recently several syntheses have been published.

In 1960 Dev et al. (35,36) synthesized diketone 62 for comparison with the ozonolysis product from ϵ -cadinene (53). Their approach is outlined in Chart VI. The route involved the reduction of 4-isopropyl-6-methoxytetralone (57) with lithium aluminum hydride to give alcohol 58. Birch reduction of 58 with sodium in liquid ammonia containing ethanol as co-solvent and proton source proceeded in 65% yield to afford alcohol 59. This two-step sequence was necessary since Birch reduction of the starting tetralone 57 resulted in the formation

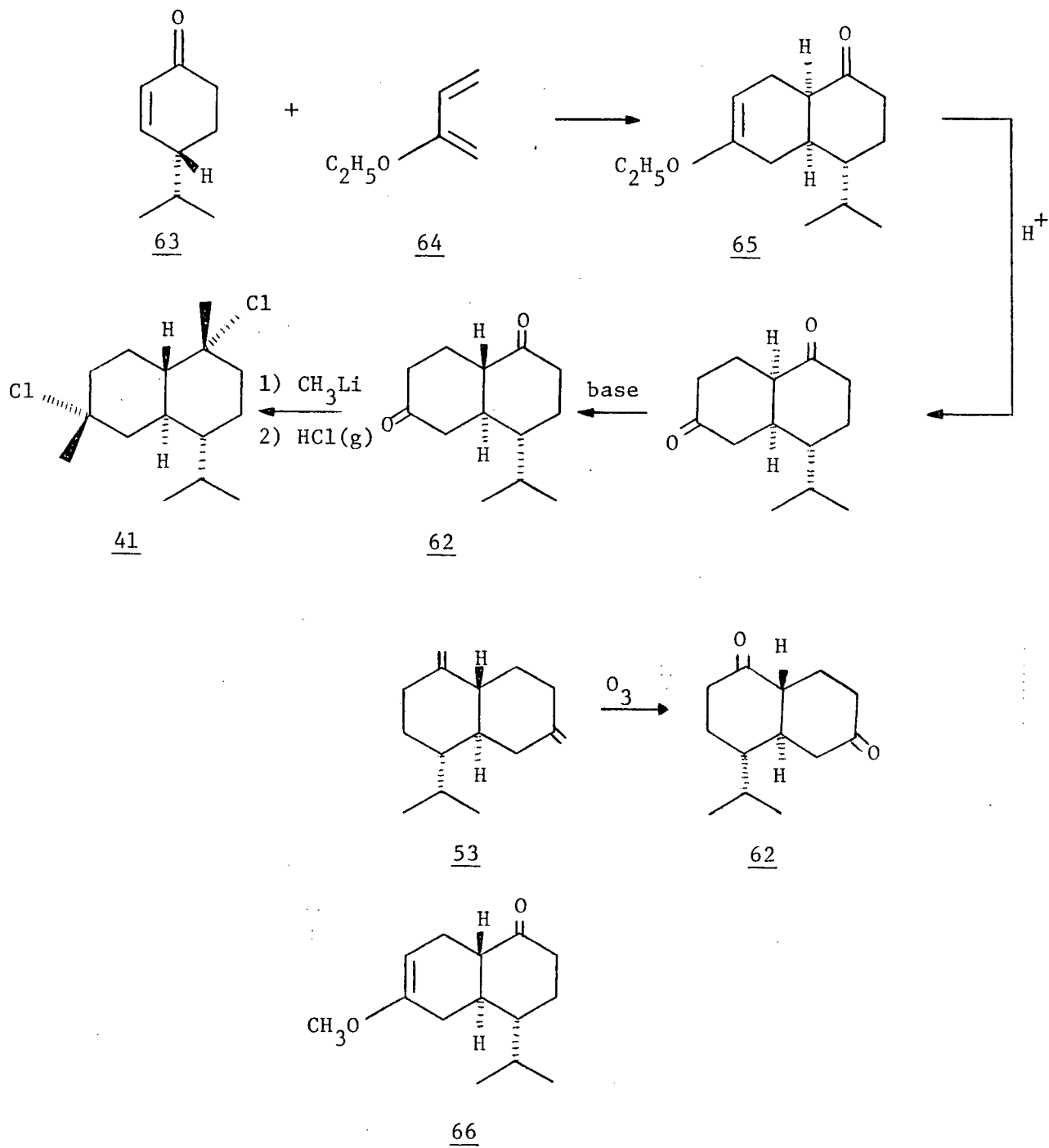
Chart VI



of a major by-product, the hydrogenolysis product. Oppenauer oxidation of 59 afforded a mixture of octalone enol ethers 60 and 61. Octalone enol ether 60 was isomerized to the fully conjugated octalone enol ether 61 when subjected to chromatography on basic alumina. Octalone enol ether 60 was reduced with lithium in liquid ammonia, followed by treatment of the resulting product with aqueous hydrochloric acid to afford, in 30% yield, (\pm)-4-isopropyl-trans-decalin-1,6-dione (62). The stereochemistry of this product was predicted from mechanistic considerations of the Birch reduction. The infrared spectrum of dione 62 was identical with that of the ozonolysis product of ϵ -cadinene (53). Dione 62 was treated with excess methyllithium and the resulting glycol treated with gaseous hydrogen chloride to afford, in 20% yield, (\pm)-cadinene dihydrochloride (41). The synthetic material was identical (infrared spectrum, mixed melting point) with an authentic sample prepared from (\pm)- δ -cadinene and anhydrous hydrogen chloride.

More recently, Soffer and Gunay (37,38) prepared (+)-cadinene dihydrochloride starting from the monoterpenoid (-)-cryptone (63). Their synthesis is outlined in Chart VII. The crucial step in their synthesis involved the Diels-Alder addition of the dienophile, 2-ethoxybutadiene-1,3 (64) to (-)-cryptone. Addition of the dienophile from the side trans to the bulky isopropyl group afforded syn-cis-decalone enol ether 65. This was followed by acid hydrolysis of the decalone enol ether 65 and base-promoted epimerization of the cis ring junction to the more stable (+)-4-isopropyl-trans-decalin-1,6-dione (62). This compound was shown to be the enantiomer of the product of

Chart VII

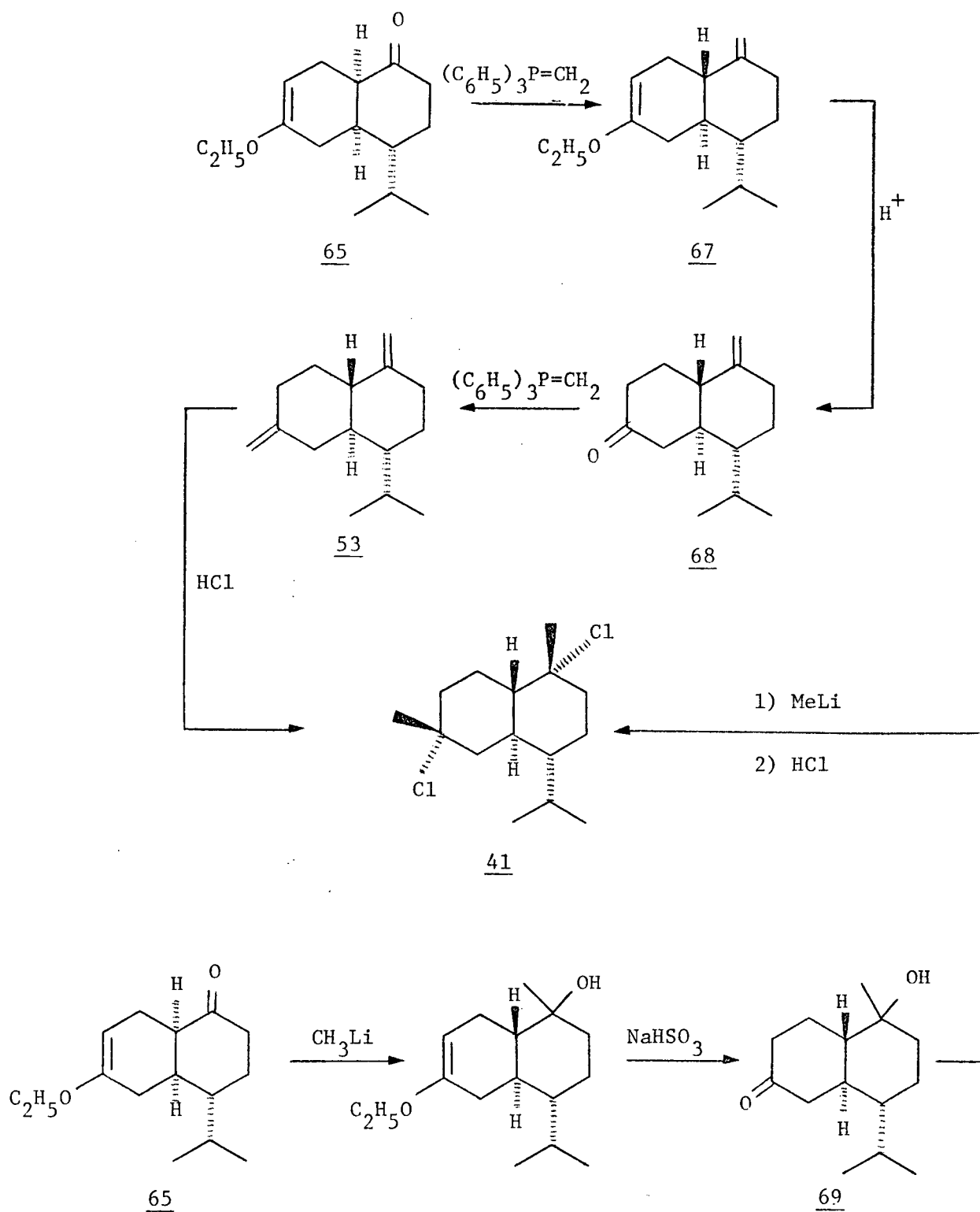


ozonolysis of ϵ -cadinene. The optically active diketone 62 was treated with excess methyllithium and then dry hydrogen chloride to afford (+)-cadinene dihydrochloride, m.p. 116-117°. This product was identical with an authentic sample obtained from reaction of (-)- γ_2 -cadinene with hydrogen chloride.

Within the past year several syntheses of cadinene hydrocarbons have been reported. In each case, either the decalone enol ether 65 or the decalone enol ether 66 was used as the starting material.

Soffer and Burk (39), utilized the cis-decalone enol ether 65 as their starting material. Treatment of the latter with either methylenetriphenylphosphorane or methyllithium afforded the corresponding trans-fused product. Hence, they proposed that first a fast reversible enolization-epimerization took place, followed by a nucleophilic attack on the carbonyl carbon. Therefore, they converted in one step, the cis-decalone enol ether 65 into the trans olefinic enol ether 67 employing methylenetriphenylphosphorane. Hydrolysis of the enol ether group was effected, in 60% yield, by treatment with 0.5 N hydrogen chloride in 95% ethanol for 25 min at room temperature. The trans nature of the ring junction was shown by a strong positive Cotton effect in the o.r.d. curve of the resulting product 68. The olefinic ketone 68 was converted in 70% yield into (+)- ϵ -cadinene by a second Wittig reaction using methylenetriphenylphosphorane. The synthetic ϵ -cadinene was identical with the naturally occurring compound in all respects. The synthetic (+)- ϵ -cadinene was converted at low temperature into (+)-cadinene dihydrochloride. This crystalline derivative was obtained by a second pathway (see Chart VIII). Methyllithium was

Chart VIII



added to cis-decalone enol ether 65, followed by thorough extraction of the ether with sodium bisulfite solution yielding directly the hydrolysis product 69. Treatment of 69 with methyllithium, followed by anhydrous hydrogen chloride afforded (+)-cadinene dihydrochloride.

Kelly and Eber (40) utilized the trans-decalone enol ether 66 as starting material for their synthesis of γ_2 -cadinene. Their synthesis is outlined in Chart IX. Lithium aluminum hydride reduction of 66 afforded, in 73% yield, alcohol 70. Hydrolysis of the enol ether group was effected in 95% yield by treatment of 70 with oxalic acid in methanol. The resulting keto alcohol 71 was converted into the diol 72 by the Grignard reaction, using methylmagnesium iodide. Selective dehydration of the tertiary alcohol was successfully carried out, in 80% yield, by stirring with p-toluenesulfonic acid in benzene at 52° for 2 h. Sarett oxidation of the secondary alcohol of 73 gave a 65% yield of octalone 74. This compound was smoothly converted into γ_2 -cadinene by reaction with methylenetriphenylphosphorane. Treatment of synthetic γ_2 -cadinene with hydrogen chloride gave a 60% yield of cadinene dihydrochloride. The spectral data of synthetic γ_2 -cadinene were identical in all respects with those of the naturally occurring compound.

Vig and coworkers (41) recently synthesized (\pm)- γ -cadinene by the method outline in Chart X. The key step in this synthesis involved a Diels-Alder reaction which fixed the position of the $\Delta^{4,5}$ double bond. The starting material for their synthesis was 2-isopropyl-4-carbethoxybutanal 75 prepared by the alkylation of the piperidine enamine of isovaleraldehyde with ethyl acrylate. Wittig reaction of

Chart IX

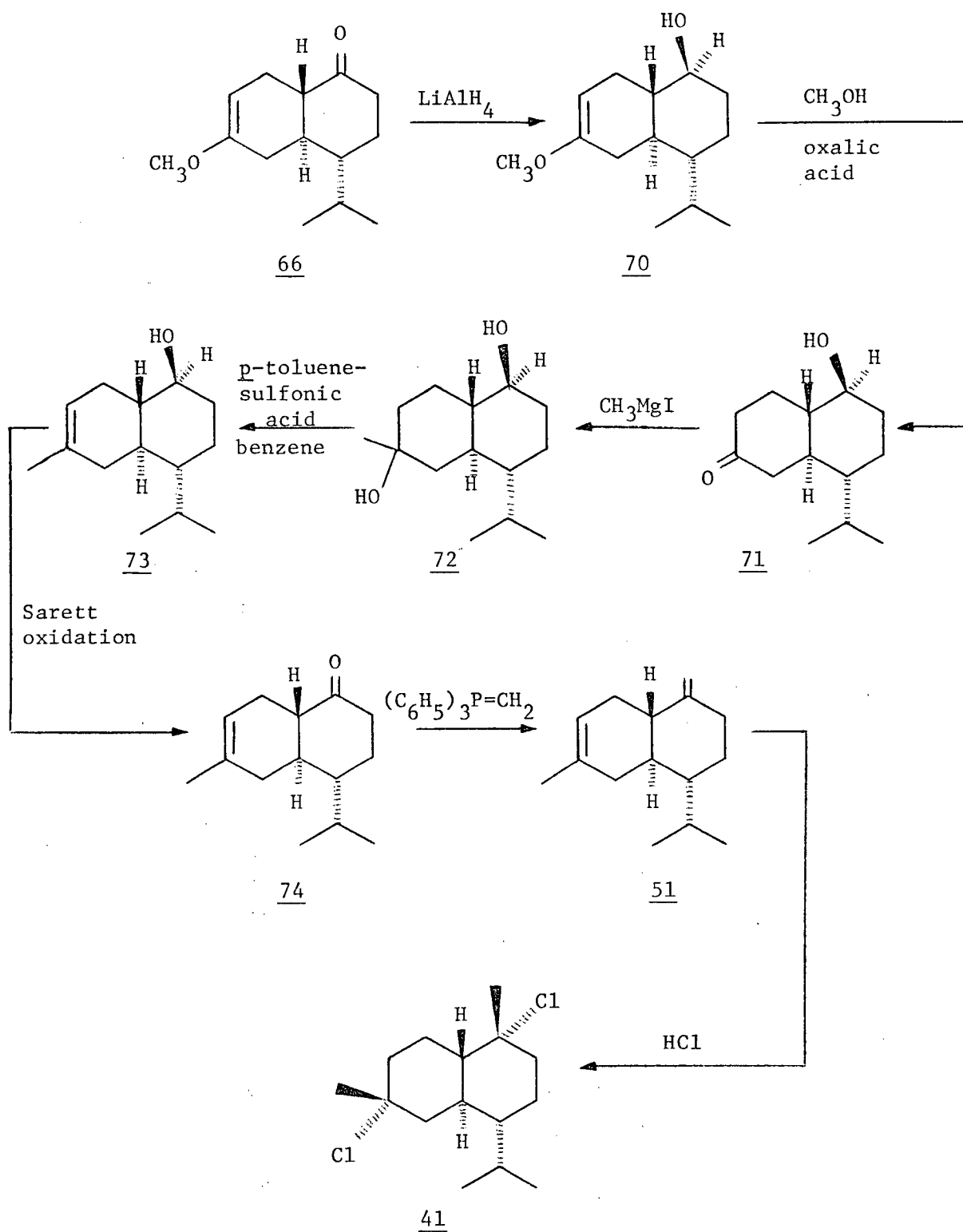
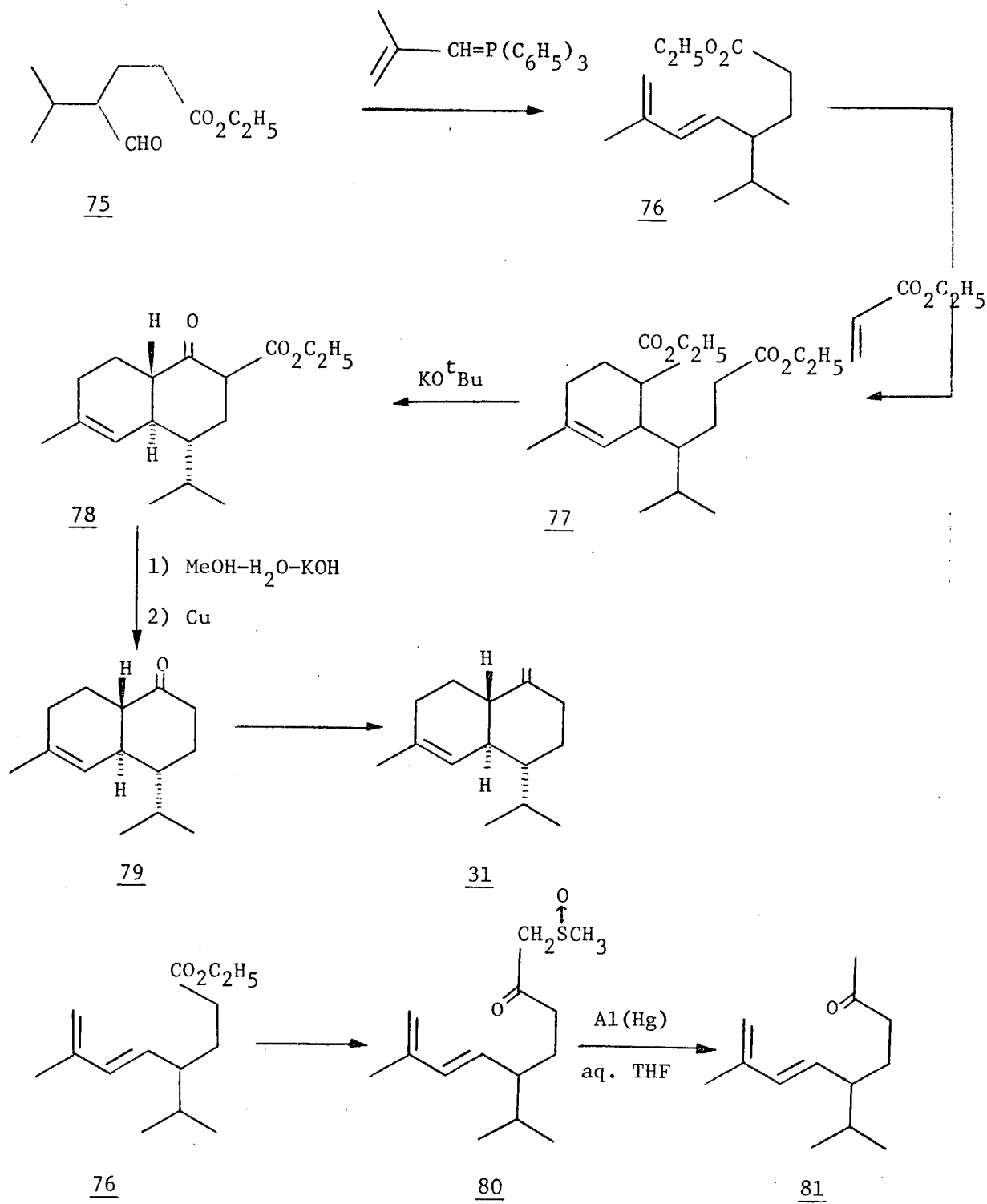


Chart X

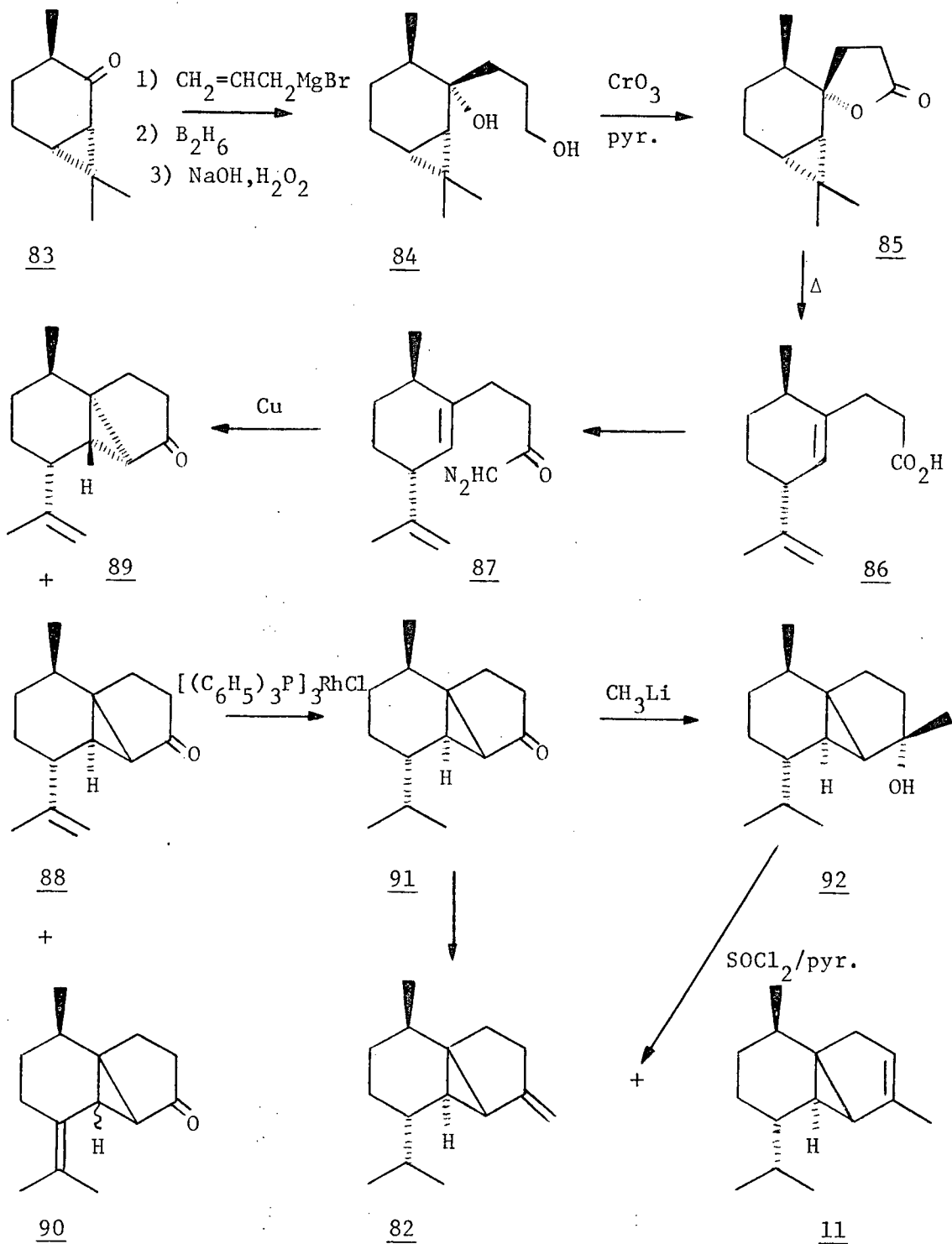


75 with methallylidenetriphenylphosphorane gave, in 65% yield, diene ester 76. Formation of β -keto-sulfoxide 80, followed by reduction with aluminum amalgam in aqueous tetrahydrofuran converted diene ester 76 in compound 81, which was identical with naturally occurring (\pm)-solanone (81). This conversion confirmed the structure of diene ester 76. The Diels-Alder addition of ethyl acrylate to diene ester 76 afforded mainly 1-methyl-4-carbethoxy-3-(isopropyl-3-carbethoxy-n-propyl)-cyclohex-1-ene (77). This diester 77 was subjected to potassium tert-butoxide in tert-butanol to afford, in 65% yield, the Dieckmann condensation product, keto ester 78. Hydrolysis of 78 with aqueous methanolic potassium hydroxide, followed by decarboxylation over copper powder afforded octalone 79. This octalone was subjected to Wittig reaction with methylenetriphenylphosphonium iodide in sodium hydride-dimethylsulfoxide to yield, in 75% yield, (\pm)- γ -cadinene (31). The synthetic material gave an infrared spectrum identical with that of the naturally occurring γ -cadinene.

Interesting structural variants of the cadinene skeleton are exemplified by α -cubebene (11) and β -cubebene (82). Recently two syntheses of these compounds have appeared in the literature (42,43). Both syntheses employed as the key step the intramolecular cyclization of an olefinic diazoketone to generate the tricyclic skeleton. The reaction sequence of Yoshikoshi and coworkers (42) is outlined in Chart XI.

Treatment of (-)-trans-caran-2-one (83) with allylmagnesium bromide, followed by hydroboration-oxidation yielded 20% of crystalline diol 84. Oxidation with chromium trioxide in pyridine afforded the

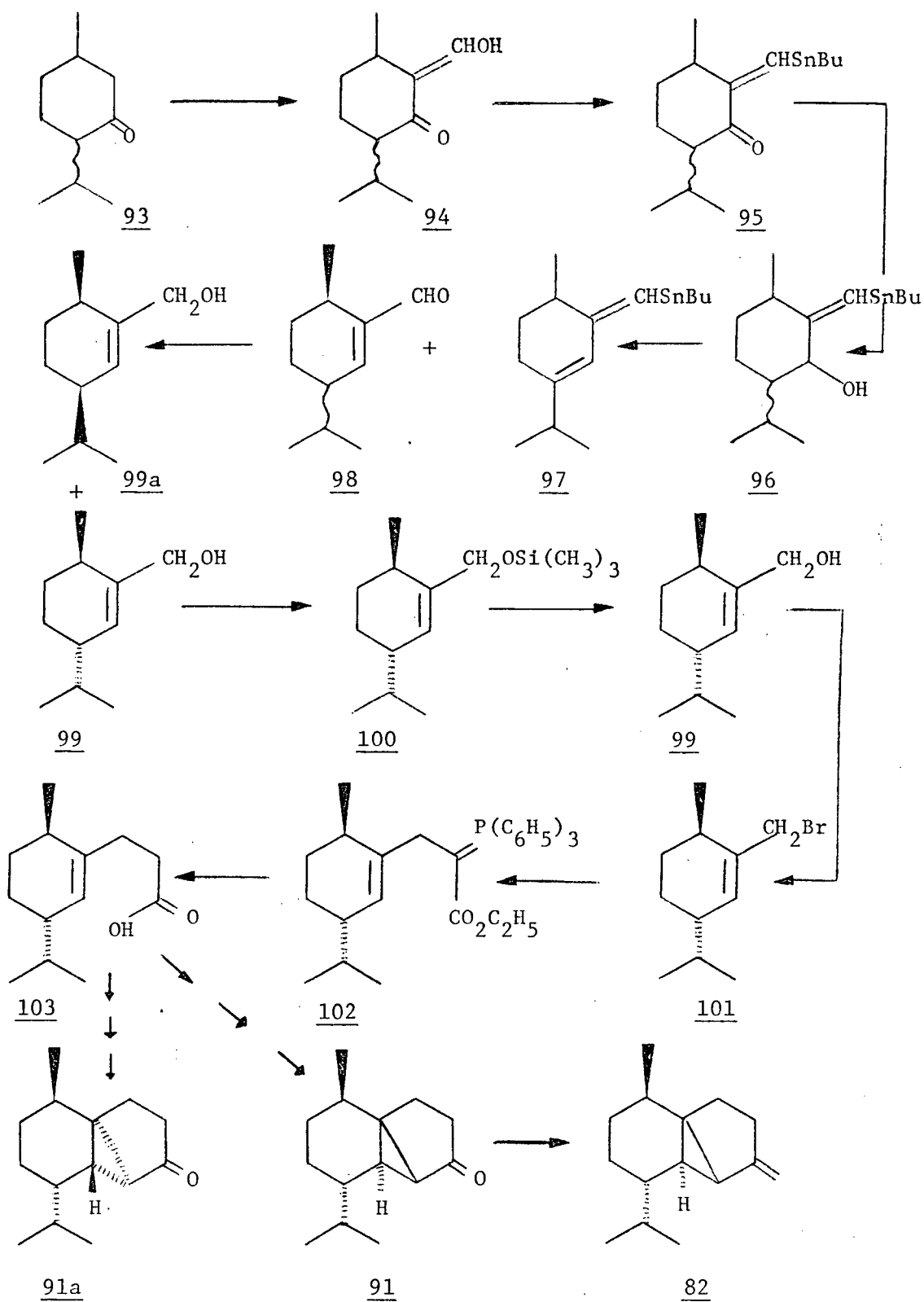
Chart XI



spirolactone 85 in quantitative yield. Pyrolysis of lactone 85 in a sealed tube at 250° with a small amount of pyridine present afforded a 70% yield of diene acid 86. The diazoketone 87 was prepared from the acid 86 by standard procedures. Treatment with copper powder in refluxing cyclohexane gave a mixture of cyclopropyl ketones 88, 89 and 90 in 11, 13 and 1% yields respectively, from spirolactone 85. Hydrogenation of ketone 88 using tris(triphenylphosphine)chlororhodium as catalyst afforded ketone 91 which was identical with the ozonolysis product of β -cubebene. Treatment of this ketone 91 with methylenetriphenylphosphorane afforded synthetic β -cubebene (82) which was identical in all respects with the naturally occurring compound. Addition of methyllithium to ketone 91 resulted in attack of the methyl group from the side opposite to the cyclopropane ring to afford cubebol (92). Dehydration of cubebol with thionyl chloride-pyridine yielded α -cubebene (11) and β -cubebene (82) in a 7:2 ratio. The synthetic compounds were identical in every respect with the naturally occurring compounds.

The synthesis of Piers and coworkers (43) is outlined in Chart XII. Hydroxymethylene derivative 94 was formed, in 88% yield, by condensation of commercial (\pm)-menthone and (\pm)-isomenthone with ethyl formate in the presence of sodium methoxide in benzene. Treatment of 94 with n-butanethiol in the usual manner gave an 89% yield of the n-butylthiomethylene derivative 95. Reduction of 95 with basic methanolic sodium borohydride afforded β -hydroxythioenol ether 96 in quantitative yield. Hydrolysis of 96 with 1% hydrochloric acid in aqueous acetone afforded a mixture of thioenol ether 97 and the desired α,β -unsaturated aldehyde 98, in a ratio of 5:4, respectively. Sodium borohydride

Chart XII



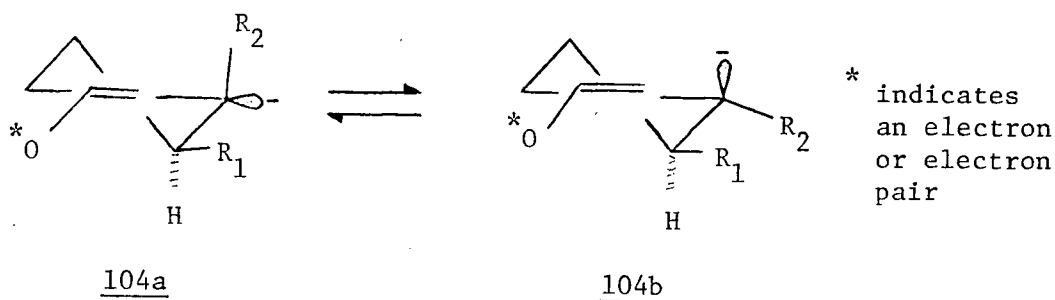
reduction of aldehyde 98 provided, in 91% yield, alcohol 99 and alcohol 99a, epimeric at the carbon bearing the isopropyl group. Preparation of the corresponding trimethylsilyl ether derivatives, followed by preparative g.l.c. isolation afforded epimerically pure trimethylsilyl ether 100. The stereochemistry of this compound was demonstrated to be that shown in structure 100 by an independent synthesis. The trimethylsilyl ether grouping was then hydrolyzed with hot 2% aqueous ethanol to regenerate, in 98% yield, alcohol 99. Treatment of 99 with phosphorus tribromide in benzene-pyridine at 0° gave a 77% yield of allylic bromide 101. The latter compound was then converted into the corresponding Wittig reagent 102 by treatment with two equivalents of carbethoxymethylenetriphenylphosphorane in refluxing ethyl acetate for 2.5 h. Hydrolysis of phosphorane 102 was achieved with 10% potassium hydroxide in refluxing methanol to afford, in 69% yield, olefinic carboxylic acid 103. This compound was converted in the usual manner to the corresponding diazoketone, followed by cyclization with cupric sulfate in refluxing cyclohexane, to afford in a 5:3 ratio cyclopropyl ketones 91a and 91. Wittig reaction of 91 with methylenetriphenylphosphorane afforded a quantitative yield of (+)- β -cubebene, possessing spectral properties identical with those of naturally occurring β -cubebene.

V. Studies of the Birch Reduction of α,β -Unsaturated Ketones

Since part of this thesis is concerned with the stereochemistry of the Birch reduction of α,β -unsaturated ketones, it is appropriate to briefly review the theories which have been proposed on this subject.

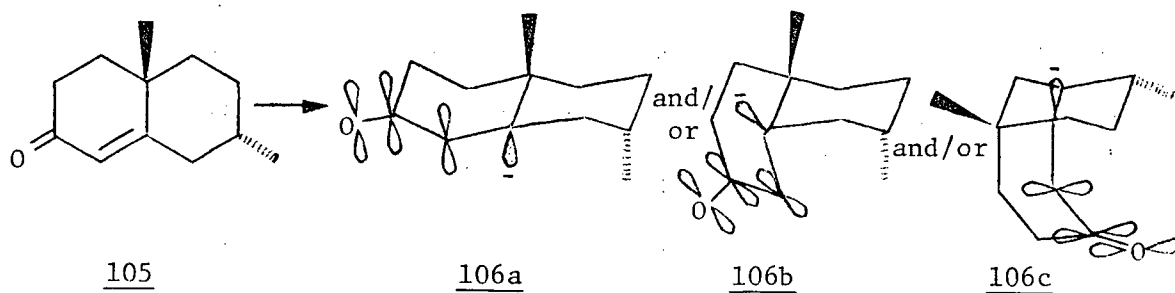
In 1954, Barton observed that in Birch reductions where stereo-isomeric products were possible, the thermodynamically more stable product was almost always formed (44). To account for these results he proposed

the formation of a tetrahedral carbanion which was readily capable of inversion (e.g., 104a \rightleftharpoons 104b).



The electron pair was assumed to have spatial requirements between that of a C-H and a C-C bond. Hence, the carbanion would assume its more stable configuration, which, upon protonation would afford the thermodynamically more stable product.

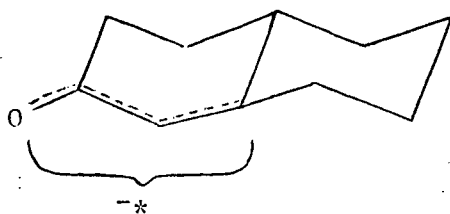
Stork and Darling (45) questioned the validity of Barton's theory when they observed that in several Birch reductions which they performed the products obtained were not only the less stable isomers but also that none of the more stable isomers could be detected. For example, in the Birch reduction of trans-7,10-dimethyl- $\Delta^{1,9}$ -2-octalone (105), they found exclusively the trans-fused decalone product. Since in this case one of the conformations of the cis enolate anion 106c is of lower energy than the corresponding trans-intermediate 106a; Barton's theory would predict the cis-fused decalone as product.



To account for this apparent anomaly, Stork and Darling (45) modified Barton's theory to include a stereoelectronic requirement. They stated that only transition states which maintained continuous overlap between the enolate system and the forming C-H bond at the β -carbon were allowed. In the above example this requirement means that only transition states resembling 106a and 106b would be stereoelectronically allowed. Hence, of the two allowed transition states, the one resembling 106a is of lower energy and protonation would lead to the trans-fused decalone.

Robinson (46) continued the investigation with a study of the sodium-liquid ammonia reductions of $\Delta^{1,9}$ -2-octalones and found that the observed stereoselectivity was far greater than could be accounted for when only thermodynamic stabilities of stereoelectronically allowed transition states were taken into account.

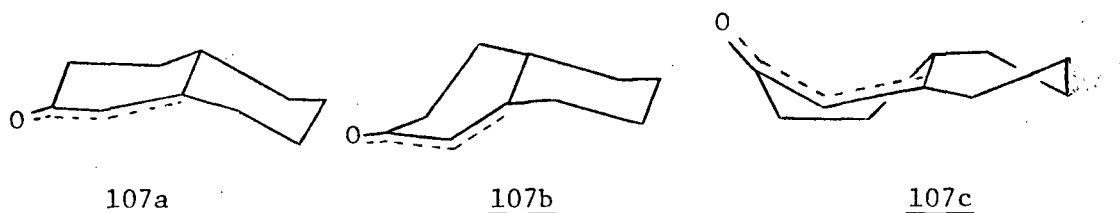
In contrast to previous workers in this area, Robinson maintained that the transition state for protonation would resemble the highly basic anion intermediate 107 where the β -carbon atom remained essentially trigonal. Robinson pointed out that in the reduction of cycloalkyl halides, which have tetrahedral carbanion intermediates, the product



* indicates an unpaired electron or an electron pair

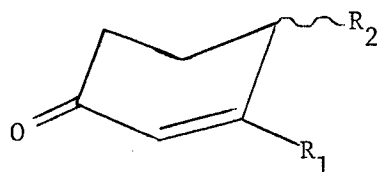
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stability does correlate with the observed stereoselectivity. Therefore, if the Birch reduction did involve a tetrahedral carbanion as an intermediate, the same trend would be expected. Since this is not the case, Robinson felt that the transition state for protonation should be similar to the conformation of the intermediate anion 107, in which the β -carbon is trigonal. In particular, he proposed three possible conformations for the transition state for protonation 107a, 107b and 107c. Considering angle and torsional strain, Robinson



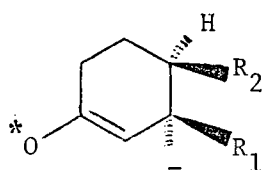
concluded that 107a would yield the trans-decalone, that 107b would yield the cis-decalone, and that 107c would generally involve too high an energy (large angle strain, lack of planarity of the conjugated system) to be a likely transition state. Further examination of 107a and 107b indicated, according to Robinson, that conformation 107a would be the only one in which the three trigonal carbon atoms could be accommodated with minimal strain. Hence, for this reason, Robinson predicted a high proportion of trans-fused decalone products in all $\Delta^{1,9}$ -2-octalone reductions of the type studied.

Johnson and coworkers (47) also investigated the geometry of the β -carbon atom in the protonation transition state. They studied Birch reductions of compounds of type 108. Because of $A^{(1,2)}$ strain

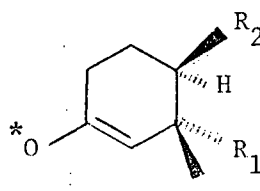


108

(48), R_2 would be more stable in the axial orientation in the cyclohexenone relative to the alternate conformation with R_2 equatorial. If the β -carbon atom is trigonal in the transition state for protonation, Johnson postulated that the products should reflect the conformational composition of the starting material, that is to say the major product should be the 3,4-cis isomer. On the other hand, if the transition state for protonation is tetrahedral, the products should reflect the thermodynamic stabilities of the carbanion intermediates 104a and 104b.



104a

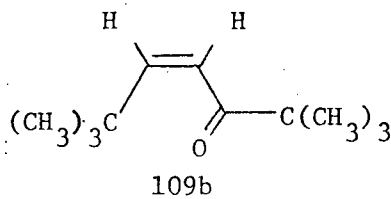
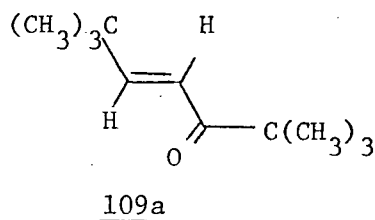


104b

The results obtained from their experiments indicated that the configuration of the β -carbon in the protonation transition state varied from tetrahedral for small R groups to trigonal when R_1 was phenyl and capable of delocalizing the negative charge. Thus, when R_1 and R_2 were methyl groups the product consisted of trans- and cis-3,4-dimethylcyclo-

hexanone in a ratio of 84:16 respectively, while when R_1 and R_2 were phenyl groups, 98% of the product was the 3,4-cis isomer.

House and coworkers (49,50) in an elegant series of experiments further investigated the nature of the pathway involved in the Birch reduction of α,β -unsaturated ketones. Although their experiments will not be discussed in detail, it is pertinent to note the main conclusions resulting from their work. Using electron paramagnetic resonance (e.p.r.) studies, House resolved several important mechanistic features of the Birch reduction of enones. Firstly, he demonstrated an initial rapid reversible electron addition to unreduced enones, while calculations showed approximately 40-50% of the unpaired electron resided at the β -carbon atom. Furthermore, reduction of trans-enone 109a and cis-enone 109b indicated that the initially formed anion radicals were different but rapidly equilibrated to the more stable form. In the



presence of proton donors or lithium cations the lifetime of this anion radical was substantially lowered. To explain this observation House proposed the formation of an O-H bond in the former case and a covalent Li-O bond or tight ion pair in the latter. Moreover, studies of polarographic reduction potentials demonstrated that then and only then could a second electron be added to an aliphatic enone system; that is

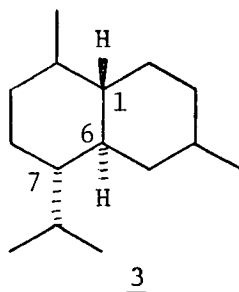
to say, free dianion intermediates are generally not formed. Lastly, by isotope studies, House demonstrated that donation of a proton, not a hydrogen atom, was the non-reversible step leading to the final product.

As for the nature of the geometry of the β -carbon atom in the intermediate anion, House favored a pyramidal configuration by analogy with isoelectronic enamines and anilines.

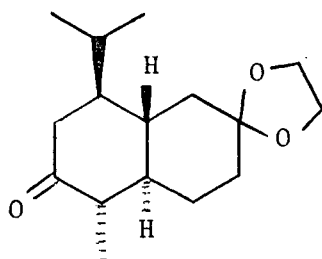
DISCUSSION

I. General

As mentioned previously, the main purpose of the work described in this thesis was to develop a general synthetic entry into the cadinane type of sesquiterpenes. On inspection of the general structural formula for the cadinenes, it became obvious that the most important and difficult part of any synthetic approach would be the control of the relative stereochemistry at C₁, C₆ and C₇.



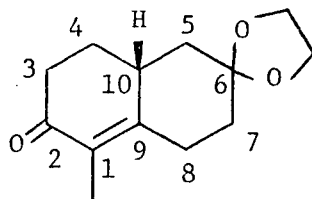
The first objective was, therefore, to synthesize a compound with fixed stereochemistry at these positions and with functionalities in both rings A and B which would allow elaboration to the cadinene compounds. Thus, a compound such as decalone 118 was envisaged as a possible key synthetic intermediate.



118

II. Conjugate Addition Approach

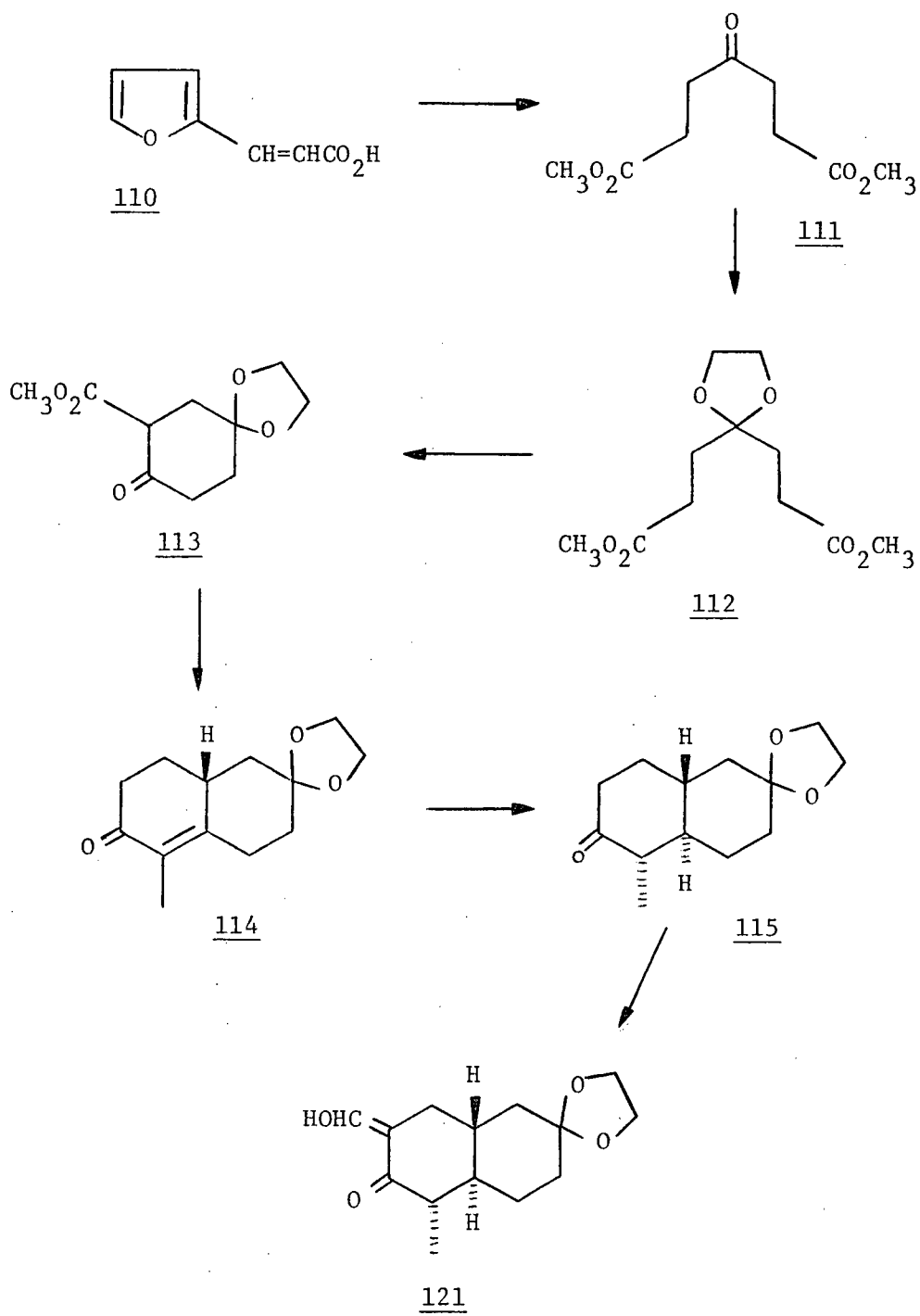
The starting material which was initially chosen for the synthesis of the required crucial intermediate of type 118 was the well-known ketal octalone 114. This compound was prepared (see Chart XIII) by a



114

combination of the procedures of Sarett et al. (51) and Ireland et al. (52). Thus, treatment of commercial furylacrylic acid (110) with hydrogen chloride in methanol, followed by esterification of the resulting product, using methanol in the presence of a catalytic amount of concentrated sulphuric acid afforded, in 84% yield, dimethyl- α -ketopimelate (111). Treatment of the latter under the usual ketalization conditions (p-toluenesulfonic acid, ethylene glycol) resulted in a mixture of starting material and dimethyl- γ -ethylenedioxy-pimelate (112). It was found that careful fractional distillations coupled with repeated

Chart XIII



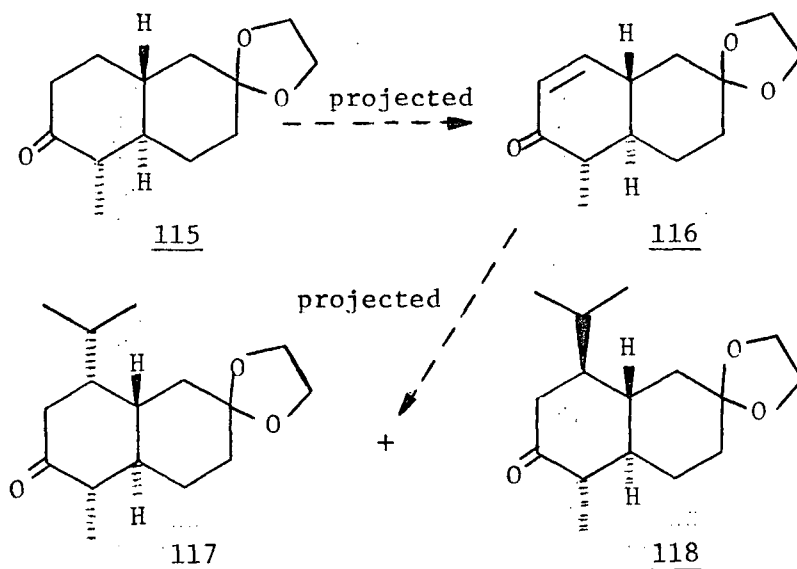
ketalization reactions were necessary to afford pure ketal diester 112. By this recyclization procedure an overall 44% yield of ketal diester 112 was realized. The spectral data of compound 112 were in complete accord with the assigned structure. In particular, the infrared spectrum of compound 112 exhibited a strong absorption at 5.78μ due to the two ester carbonyls. The n.m.r. spectrum of 112 displayed sharp singlets at τ 6.05 and τ 6.30 due to the ketal protons and methyl groups respectively.

Treatment of ketal diester 112 with sodium hydride in refluxing ether for five days afforded, in 80% yield, the Dieckmann condensation product 113. The fact that the desired transformation had indeed taken place was shown by the spectral data of the product 113. The infrared spectrum of 113 showed absorptions at 5.78, 5.81, 6.0 and 6.15μ while the n.m.r. spectrum exhibited a four-proton singlet at τ 6.01 and a three-proton singlet at τ 6.25 due to the ketal protons and the methyl group respectively.

Condensation of compound 113 with 1-diethylamino-3-pentanone methiodide in the presence of sodium methoxide for three days at room temperature, followed by treatment with aqueous potassium hydroxide afforded, in 64% yield, the desired octalone 114. The latter again exhibited the expected spectral properties. Of note was the appearance in the infrared spectrum of absorptions at 6.0μ and 6.2μ due to the α,β -unsaturated carbonyl group and the carbon-carbon double bond respectively. The ultraviolet spectrum exhibited a maximum at $245 m\mu$. The n.m.r. spectrum of 114 displayed singlets at τ 6.09 and τ 8.12 attributable to the ketal protons and the vinyl methyl group respectively.

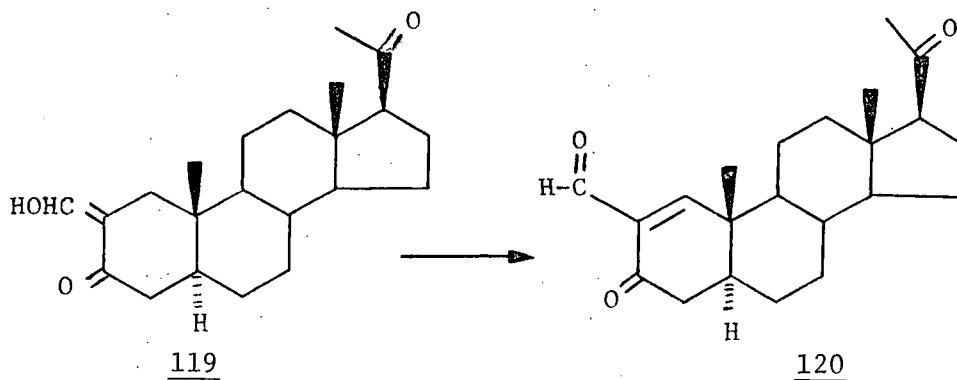
Thus having octalone 114 readily available, it was next planned to introduce the trans ring fusion by the well-documented lithium-liquid ammonia reduction (45,46,48). Therefore, compound 114 was subjected to Birch reduction conditions with lithium in liquid ammonia for two hours. The reaction was then quenched with ammonium chloride and, after appropriate work-up, afforded the corresponding trans-fused decalone 115, in 97% yield. The fact that the desired reduction had indeed taken place was clearly shown by the spectral data of compound 115. The infrared spectrum of 115 exhibited an absorption at $5.85\ \mu$ due to the saturated carbonyl. The n.m.r. spectrum exhibited a doublet at $\tau\ 8.96$ ($J = 6\ \text{Hz}$) due to the secondary methyl group and a singlet at $\tau\ 6.01$ due to the ketal protons.

The next steps in the projected synthesis involved introduction of the $\Delta^{3,4}$ -double bond into decalone 115, followed by cuprous ion catalyzed 1,4-conjugate addition of isopropylmagnesium halide to afford, presumably, a mixture of compounds of the cadinane (118) and bulgarane (117) skeletal types. However, introduction of the $\Delta^{3,4}$ -double bond

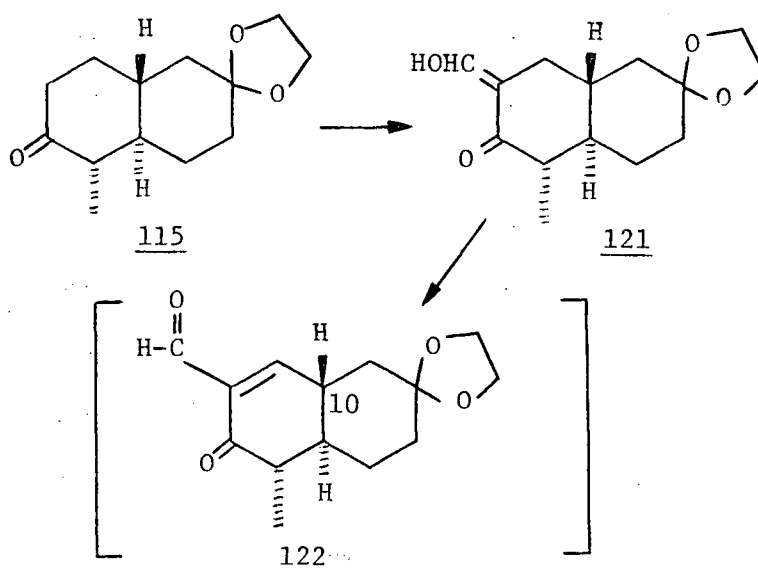


proved elusive. Standard bromination-dehydrohalogenation techniques, employing a wide variety of conditions, resulted in bad mixtures of products. A spectral examination of the crude bromination product indicated that under all of the reaction conditions tried, bromination was occurring not only on both sides of the keto group but also adjacent to the ketal functionality. Perhaps this observation is not entirely unexpected, since the bromination of ketals is a well-established phenomenon (53,54). Hence, this method was not satisfactory for the preparation of octalone 116. Therefore, an alternate method for introduction of the $\Delta^{3,4}$ -double bond was investigated.

Edwards and coworkers (55) had reported that α -formyl ketones could be readily dehydrogenated by high-potential quinones, such as 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ). Moreover, this reaction had been widely used in steroid chemistry. For example, α -formyl ketone 119 had been shown to undergo transformation to compound 120 upon treatment with one equivalent of DDQ in dry dioxane for 1 to 10 minutes at room temperature (56).

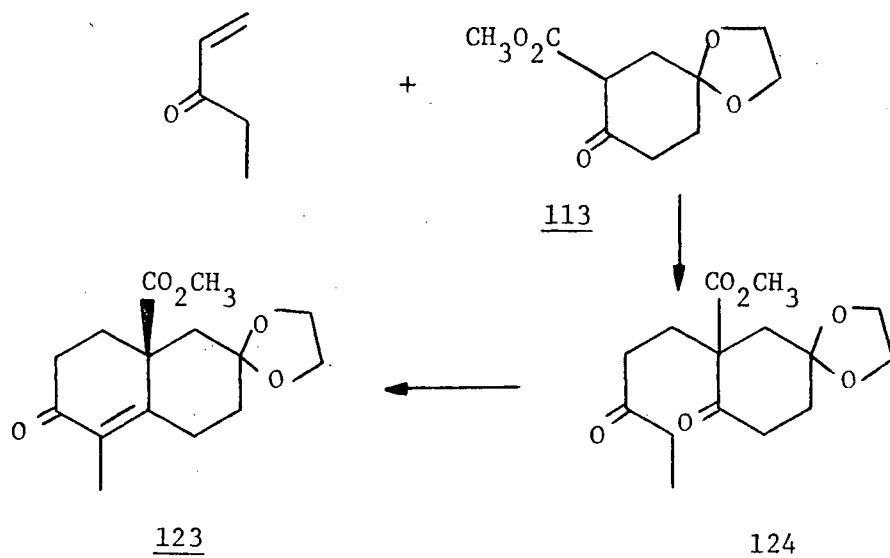


Therefore, it was decided to make use of a similar series of reactions. Treatment of decalone 115 with ethyl formate and sodium methoxide in dry benzene gave rise to the corresponding crystalline hydroxymethylene derivative 121, in 80% yield. However, dehydrogenation of 121 with DDQ under the above conditions failed to yield any of the desired product. This was not particularly surprising since the initially formed oxidation product 122 would also be susceptible to further oxidation with DDQ.



Hence, it was proposed that a substituent other than hydrogen would be required at the C_{10} position to prohibit further oxidation. Since the C_{10} position is unsubstituted in sesquiterpenes possessing the cadinane skeleton, it was essential to block the C_{10} position with a group which could be readily removed at a later stage in the synthesis. The starting material which was chosen for preparation of a suitable C_{10} substituted compound was the well-known octalone 123. This material

was prepared by condensation of the previously described keto ester 113 with ethyl vinyl ketone in the presence of a catalytic amount of triethylamine, to afford dione 124, in 84% yield (52). Sodium methoxide-

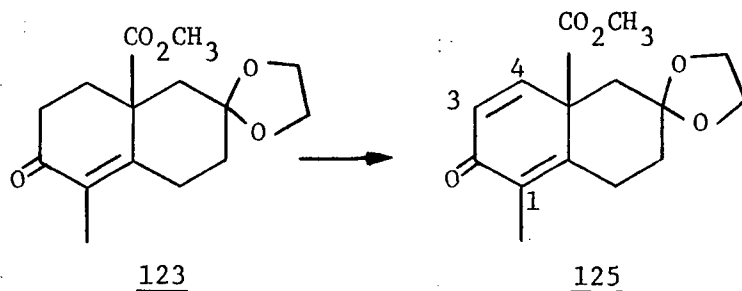


catalyzed ring closure of dione 124 afforded, in 97% yield, octalone 123. The latter exhibited the expected spectral properties. In particular, the ultraviolet spectrum exhibited a maximum at $245 \text{ m}\mu$. The infrared spectrum of 123 exhibited absorptions at 5.8μ (ester carbonyl), 6.0μ (unsaturated ketone) and at 6.2μ (carbon-carbon double bond). The n.m.r. spectrum of 123 exhibited assignable signals at τ 8.13 (singlet, vinyl methyl), τ 6.30 (singlet, methyl ester) and at τ 6.08 (singlet, ketal protons).

Octalone 123 appeared to be potentially well suited to the proposed reaction sequence. Firstly, it had been shown that octalones of this type directly underwent DDQ-promoted dehydrogenation to afford the corresponding cross-conjugated dienones in good yield (57).

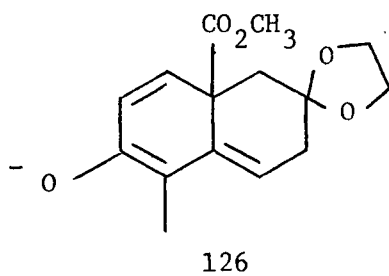
Moreover, direct conjugate alkylation at C_4 on the proposed dienone 125 should presumably yield the corresponding 4-alkyl- $\Delta^{1,9}$ -2-octalone. Retention of the $\Delta^{1,9}$ -double bond at this stage was mandatory to permit subsequent easy removal of the C_{10} carbomethoxy group by base-promoted hydrolysis and decarboxylation. Presumably this reaction would be accompanied by epimerization of the C_{10} proton in the resulting product. Furthermore, it was proposed from conformational analysis that this epimerization would furnish predominantly the compound with the required stereochemistry for the cadinene compounds.

Treatment of octalone 123 with one equivalent of DDQ (57) in the presence of glacial acetic acid in refluxing benzene for 36 h afforded, in 80% yield, dienone 125. The spectral properties of

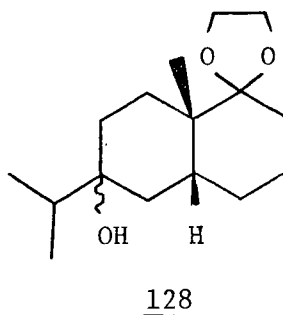
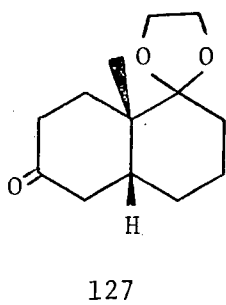


compound 125 were in complete accord with the assigned structure. Thus, the ultraviolet spectrum showed a maximum at 243 m μ , while the infrared spectrum showed absorptions at 5.82, 6.05, 6.15 and 6.25 μ . The n.m.r. spectrum of 125 displayed a typical AB pair of doublets at τ 3.72 and τ 3.28 ($J = 10$ Hz) for the protons at C_3 and C_4 respectively. In addition, there appeared a three-proton singlet at τ 8.04 attributable to the C_1 vinyl methyl, a three-proton singlet at τ 6.30 due to the methyl ester and a four-proton singlet at τ 6.02 due to the ketal protons.

The cuprous ion catalyzed 1,4-conjugate addition of isopropylmagnesium bromide to the cross-conjugated dienone 125 was attempted under a wide variety of conditions but only minor amounts of the desired product could be detected. In all cases, at least 90% of the starting dienone 125 was recovered unchanged. This fact, coupled with the observation that the reaction mixture was a deep red color indicated that the Grignard reagent was acting as a base, causing formation of the highly conjugated enolate anion 126. This anion would, of course, be inert with respect to the desired conjugate addition reaction.

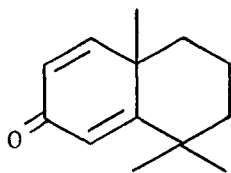


McMurry (58), in his paper on the synthesis of sativene, reported that addition of isopropylmagnesium bromide to decalone 127 resulted in the formation of only 5% of the desired tertiary alcohol 128. McMurry



proposed that enolate formation was responsible for the low yield. However, he found that this undesirable side reaction could be suppressed by carrying out the reaction at a lower temperature. Indeed, at a reaction temperature of -50° , it was possible to obtain 50% of the desired product. However, attempted application of this principle to our conjugate addition reaction proved fruitless, since varying the reaction temperature between 33° and -78° gave no significant change in the amount of product formed.

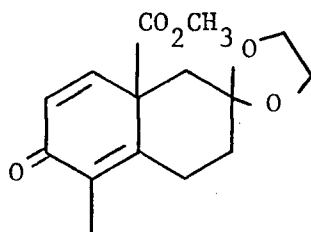
To gain supporting evidence for the proposed enolate formation, copper salt catalyzed 1,4-conjugate addition of isopropylmagnesium bromide to dienone 129¹ was investigated. Since both of the γ -positions



129

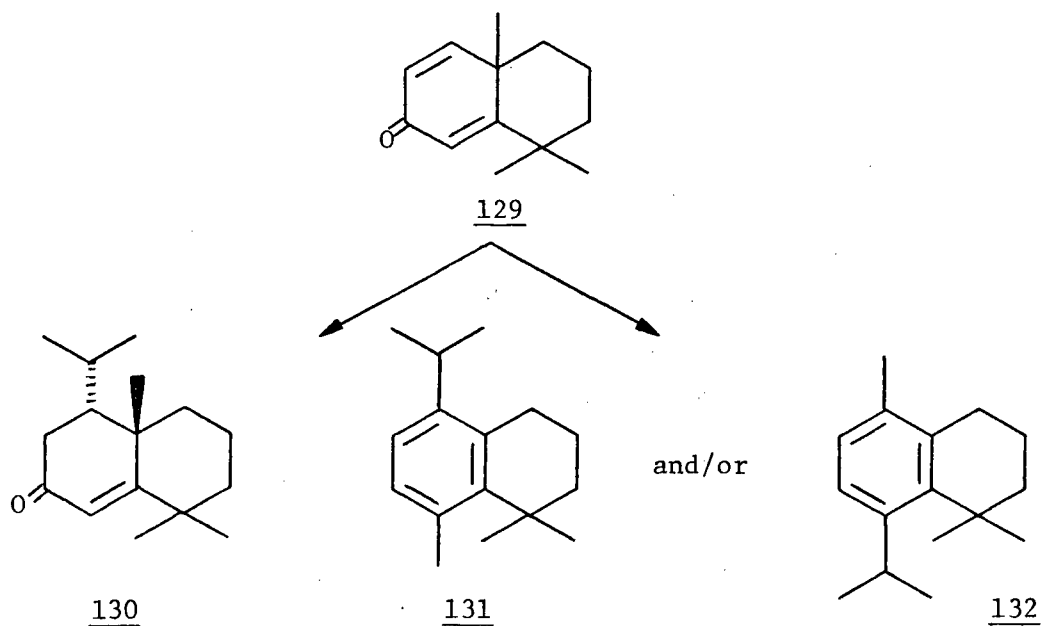
(with respect to the carbonyl group) in dienone 129 are fully substituted by alkyl groups, no enolate formation is possible. Indeed, treatment of dienone 129 with isopropylmagnesium bromide in the presence of cupric acetate resulted in the isolation of two products in the ratio of 3:2 respectively. In contrast to similar Grignard additions to dienone 125 no starting material was recovered.

¹ We thank Mr. Paul Worster for a sample of this compound.



125

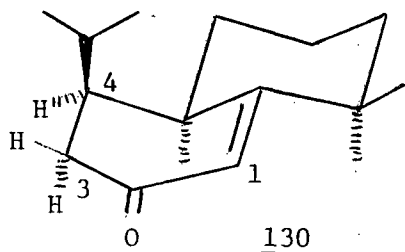
It was shown that the major product of the copper salt catalyzed 1,4-conjugate addition of isopropylmagnesium bromide to dienone 129 was compound 130, the 1,4-addition product. The minor product exhibited



spectral data in accord with either structure 131 or 132, presumably resulting from acid-catalyzed rearrangement (during work-up) of the initially formed 1,2-addition product (59).

Analytical samples of the major and minor products were collected

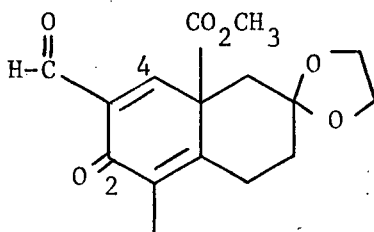
by preparative g.l.c. The spectral properties of compound 130 were in full accord with the proposed structure. Thus, the major product 130 gave an ultraviolet maximum at 240 m μ and a strong α,β -unsaturated carbonyl absorption at 6.0 μ and carbon-carbon double bond absorption at 6.25 μ in the infrared. The n.m.r. spectrum of compound 130 exhibited a pair of three-proton doublets at τ 9.35 and τ 9.08 (J = 7 Hz) due to the newly introduced isopropyl methyl groups, three three-proton singlets at τ 8.85, τ 8.82, and τ 8.61 due to the three tertiary methyl groups and a one-proton singlet at τ 4.04 due to the C_1 olefinic proton. The n.m.r. spectrum of 130 also provides evidence that



the newly introduced isopropyl group is in the axial orientation. The C_3 axial proton exhibited a pair of doublets at τ 7.39 and τ 7.21 due to the A part of an ABX system, with J_{AB} = 18 Hz and J_{AX} = 6 Hz, while the C_3 equatorial proton exhibited a pair of doublets at τ 7.46 and τ 7.65 due to the B part of the ABX system, with J_{AB} = 18 Hz and J_{BX} = 3 Hz (60). The small AX and BX coupling constants indicate that the C_4 proton must be equatorial. This is in agreement with the expected introduction of the isopropyl group from the side opposite to the angular methyl group. This point will be discussed later in more detail.

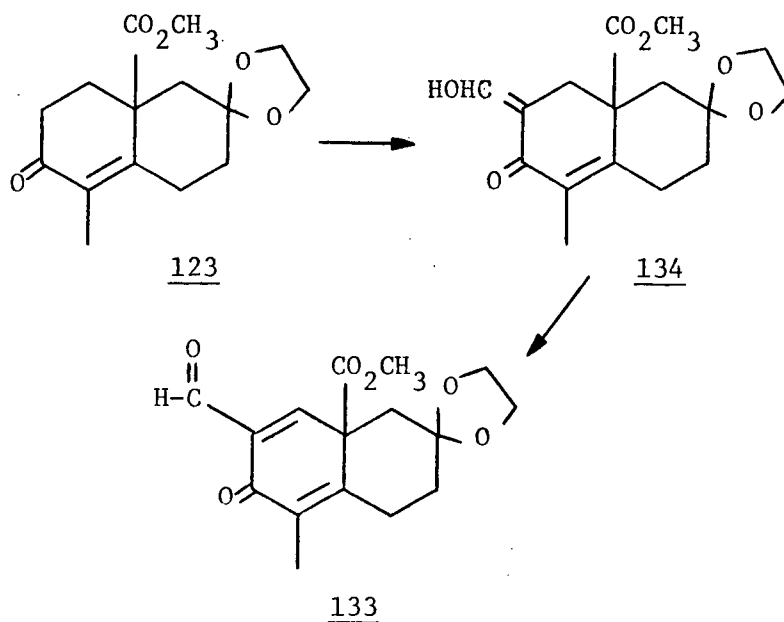
The minor product 131 or 132 exhibited two weak absorptions, at 6.25 and 6.4 μ in the infrared, typical of the stretching vibrations of an aromatic nucleus. The n.m.r. spectrum of the minor product exhibited a six-proton doublet at τ 8.80 ($J = 6.5$ Hz) due to the isopropyl methyl groups, a six-proton singlet at τ 8.75 due to the gem-dimethyl groups, a three-proton singlet at τ 7.84 due to the aromatic methyl group and two broad one-proton singlets at τ 3.20 and τ 3.00 due to the aromatic protons.

Since the copper salt catalyzed 1,4-conjugate addition of isopropylmagnesium bromide to dienone 129 was successful, it appeared even more likely that formation of enolate 126 was responsible for the failure of the analogous additions to dienone 125. In an attempt to circumvent this difficulty, additions to the corresponding dienone aldehyde 133 were proposed. It was felt that even if enolate formation involving the C_2 carbonyl occurred, the aldehyde carbonyl could still provide sufficient activation to make conjugate alkylation at C_4 possible. To this end, condensation of octalone 123 with ethyl formate



133

in the presence of sodium methoxide in benzene provided the 3-hydroxy-methylene derivative 134 in good yield.

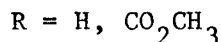
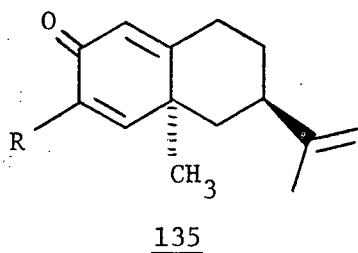


Dehydrogenation of the hydroxymethylene derivative 134 with DDQ (61) in dioxane for 3.5 min afforded the corresponding 3-formyl cross-conjugated dienone 133 in 43% yield. The spectral data were in complete agreement with the assigned structure. Of note was the appearance in the infrared spectrum of absorptions at 5.75, 5.9, 6.08, 6.15 and 6.25 μ due to the carbonyl groups and the carbon-carbon double bonds. In the n.m.r. spectrum of 133 there appeared one-proton singlets at τ -0.25 and at τ 2.55 due to the aldehydic proton and the C_4 olefinic proton respectively. Other pertinent n.m.r. signals for compound 133 appeared at τ 7.97 (singlet, vinyl methyl), τ 6.25 (singlet, methyl ester) and τ 5.98 (singlet, ketal protons). Compound 133 exhibited a maximum at 246 m μ in the ultraviolet spectrum.

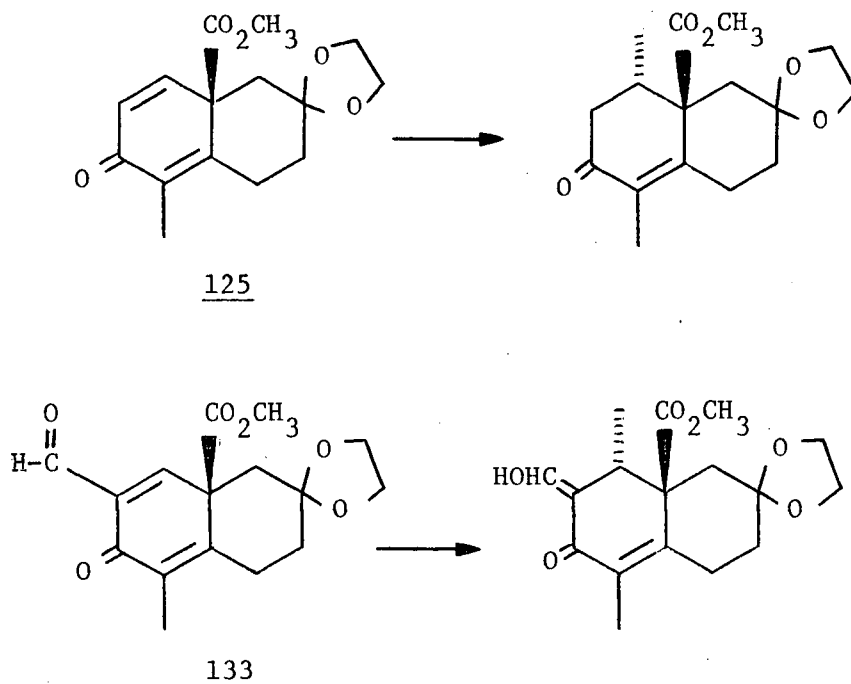
Unfortunately, copper salt catalyzed Grignard additions to 3-formyl

dienone 133 again failed to give synthetically useful yields of alkylated products. A spectral examination of the crude reaction mixture indicated that some conditions tried gave rise to bad mixtures of products while other conditions resulted in recovery of unchanged starting material.

In view of the failure of the copper salt catalyzed Grignard reagent to introduce the necessary isopropyl group via 1,4-conjugate addition to the above enone systems, the possibility of introducing the isopropyl group by means of lithium diisopropylcuprate was next investigated. At the time this work was undertaken, Schudel et al. (62) published a report concerning the synthesis of a naturally occurring sesquiterpenoid, nootkatone. One of the key steps in this synthesis involved the conjugate addition of a methyl group to cross-conjugated dienone 135, using lithium dimethylcuprate.



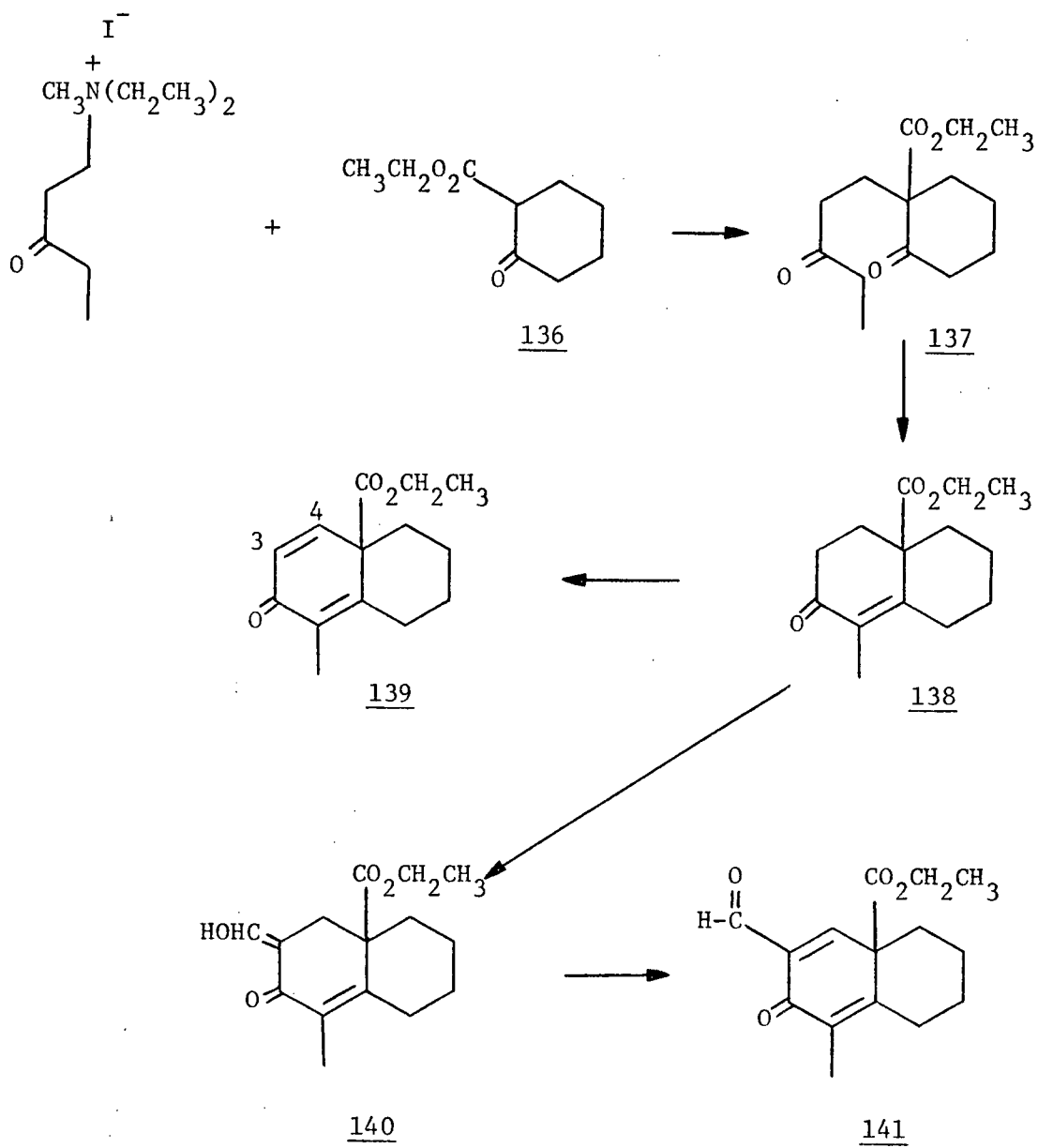
A series of preliminary reactions showed that lithium dimethylcuprate also added a methyl group to the C₄ position of dienones 125 and 133. These results were particularly encouraging and it was decided to study analogous reactions employing lithium diisopropylcuprate. However, cuprate addition reactions usually require quenching with acid. In order to study the reaction in some detail it was therefore



desirable to work with a more readily available model system (lacking the ketal group).

The sequence used for preparation of the model compounds is outlined in Chart XIV. Octalone 138 was prepared by the procedure of Meyer *et al.* (63). Thus, condensation of 1-diethylamino-3-pentanone methiodide with 2-carbethoxycyclohexanone (136) in ethanol in the presence of a catalytic amount of sodium ethoxide afforded, in 83% yield, dione 137. The latter compound exhibited the expected spectral data. In particular, the infrared spectrum exhibited a strong absorption at $5.8\ \mu$ due to the carbonyl groups. The n.m.r. spectrum of 137 displayed signals at τ 8.97 (triplet, $\text{CH}_3\text{CH}_2\overset{\text{O}}{\parallel}\text{C}-$, $J = 7\ \text{Hz}$), at τ 8.72 (triplet, $\text{CH}_3\text{CH}_2\text{O}-$, $J = 7\ \text{Hz}$), at τ 7.59 (quartet, $-\text{CH}_2-\overset{\text{O}}{\parallel}\text{C}-$, $J = 7\ \text{Hz}$) and at τ 5.8 (quartet, $-\text{CH}_2-\text{O}-$, $J = 7\ \text{Hz}$).

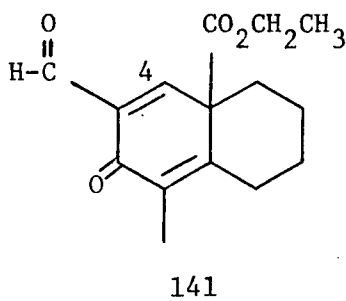
Chart XIV



Sodium ethoxide-catalyzed ring closure of dione 137 afforded octalone 138, in 96% yield. The fact that the expected ring closure had taken place was shown by the spectral data of product 138. Of note was the appearance in the infrared spectrum of absorptions at $5.8\ \mu$ (ester carbonyl), $6.0\ \mu$ (α,β -unsaturated ketone) and at $6.2\ \mu$ (carbon-carbon double bond). The ultraviolet spectrum exhibited a maximum at $247\ m\mu$. In the n.m.r. spectrum of 138 were signals due to the ethyl ester as a three-proton triplet at $\tau\ 8.72$ ($J = 7\ \text{Hz}$) and as a two-proton quartet at $\tau\ 5.72$ ($J = 7\ \text{Hz}$) and a signal due to the vinyl methyl group as a three-proton singlet at $\tau\ 8.12$.

Treatment of octalone 138 with DDQ (57) in the presence of glacial acetic acid in refluxing benzene for 70 h afforded dienone 139, in 76% yield. The fact that the expected dehydrogenation had taken place was shown by the spectral data of the product 139. In particular the infrared spectrum of 139 exhibited absorptions at 5.8, 6.05, 6.12 and $6.23\ \mu$. The n.m.r. spectrum of 139 displayed a typical AB pair of doublets at $\tau\ 3.77$ and $\tau\ 3.33$ ($J = 10\ \text{Hz}$) for the C_3 and C_4 olefinic protons, respectively. Other assignable signals in the n.m.r. spectrum appeared at $\tau\ 8.79$ (triplet, methyl of ester), $\tau\ 5.85$ (quartet, methylene of ester) and at $\tau\ 8.05$ (singlet, vinyl methyl).

Condensation of octalone 138 with ethyl formate in the presence of sodium methoxide afforded the corresponding 3-hydroxymethylene derivative 140, in 83% yield. Dehydrogenation of the hydroxymethylene derivative 140 with DDQ (61) in dioxane for 3.5 min afforded the corresponding 3-formyl cross-conjugated dienone 141 in 65% yield. The spectral data of dienone 141 were in complete accord with the assigned

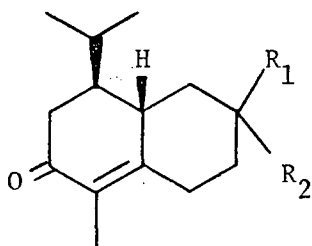



structure. Of note was the appearance in the n.m.r. spectrum of 141 of two one-proton singlets at τ -0.25 and at τ 2.55 due to the aldehydic proton and the C₄ olefinic proton, respectively. Other pertinent n.m.r. signals appeared at τ 8.75 (triplet, $-\text{CO}_2\text{CH}_2\text{CH}_3$, $J = 7$ Hz), at τ 7.97 (singlet, vinyl methyl) and at τ 5.82 (quartet, $-\text{CO}_2\text{CH}_2\text{CH}_3$, $J = 7$ Hz). The ultraviolet spectrum exhibited a maximum at 247 m μ . The infrared spectrum of 141 showed absorptions at 5.8, 5.9, 6.1, and 6.2 μ .

With the model compounds 139 and 141 readily available, the investigation of lithium diisopropylcuprate additions was carried out. The conjugate addition reactions were attempted under a wide variety of conditions including a wide temperature range, a variety of solvents, a variety of copper salts and a variety of additives similar to those used to enhance the nucleophilicity of Grignard reagents - amines, lithium halides and hexamethylphosphoramide (64,65,66). However, while all these conditions readily converted 2-cyclohexenone into 3-isopropylcyclohexanone, the material obtained from compounds 139 and 141 inexplicably showed no signs of the desired conjugate addition products.

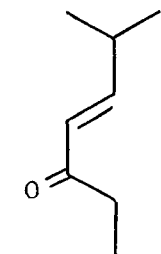
III. Condensation-Annellation Approach

In view of the failure of the approach involving introduction of the necessary isopropyl group via 1,4-conjugate addition to an enone system, an alternate method for the preparation of an intermediate of type 142 was investigated. The crucial proposed reaction in this new

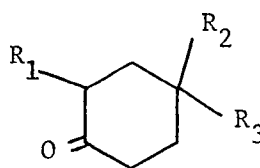


where $R_1 = \text{OH}, \text{OCC}_6\text{H}_5, \text{OCCH}_3$; $R_2 = \text{H}$; $R_1, R_2 = \text{}$ , H_2

approach was the Robinson annellation reaction of an appropriately substituted cyclohexanone of type 143 with a vinyl ketone such as 144.



144



143

$R_1 = \text{CHO}, \text{CO}_2\text{CH}_3, \text{H}$

$R_2 = \text{OH}, \text{OCC}_6\text{H}_5, \text{OCCH}_3$; $R_3 = \text{H}$

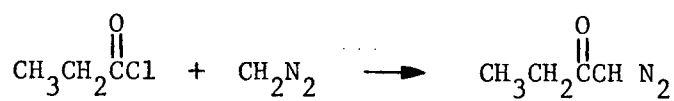
$R_2, R_3 = -\text{O}-\text{CH}_2-\text{CH}_2-\text{O}-, \text{H}_2$

Hence, the first synthetic objective was the preparation of vinyl ketone 144. Vinyl ketone 144 was prepared by two different routes which are outline in Chart XV.

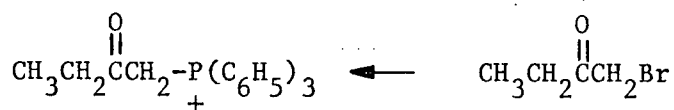
The general synthetic procedure used in the first route was analogous to that used by House and coworkers in the preparation of

Chart XV

Route I

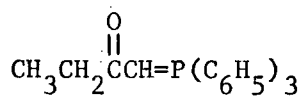


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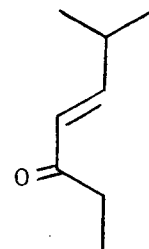
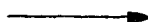


146

147

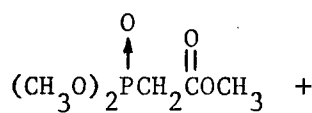


148

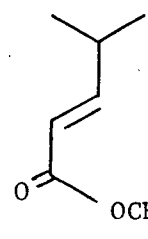
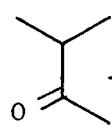


144

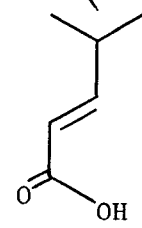
Route II



149

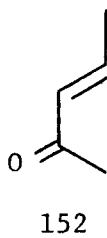


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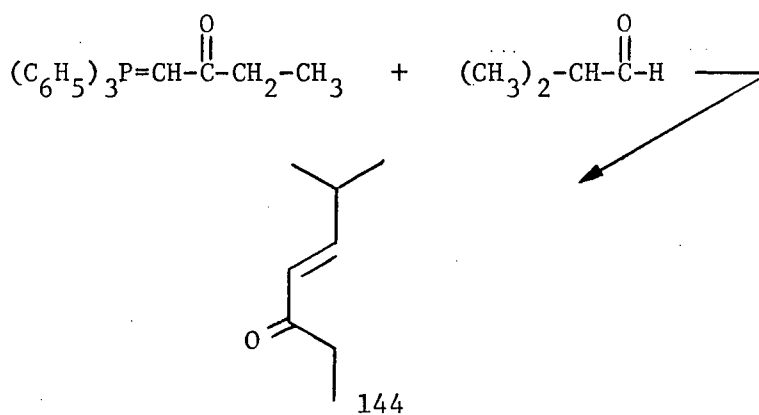


151

trans-3-penten-2-one (152) (67). This route involved the Wittig reaction



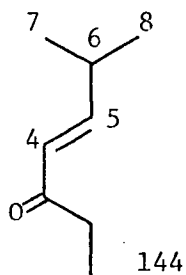
between a substituted phosphorane and an appropriate aldehyde or ketone. For the preparation of 144, the two necessary reactants would be the acylated phosphorane 148 and isobutyraldehyde.



The starting material used for the preparation of phosphorane 148, bromomethyl ethyl ketone (146), was prepared by a procedure analogous to that of Catch et al. (68). Thus, propionyl chloride was reacted with ethereal diazomethane at 0° for 30 min to yield diazomethyl ethyl ketone (145). The latter was not purified but was immediately converted, in 70% yield (from propionyl chloride), into bromomethyl ethyl ketone (146) by reaction with anhydrous hydrogen bromide at 0° for 30 minutes. Treatment of bromoketone 146 with triphenylphosphine in benzene afforded the corresponding acyl phosphonium bromide 147 in 85% yield. The latter, compound 147, was converted into

phosphorane 148 in 64% yield, by treatment with aqueous sodium hydroxide for 2 hours. An analytical sample of 148 exhibited spectral data in complete accord with the assigned structure. In particular, in the n.m.r. spectrum of 148, the olefinic proton was evident as a one-proton singlet at τ 1.0, the phenyl protons were present as an unresolved fifteen-proton multiplet at τ 2.50, while the ethyl group exhibited a two-proton quartet at τ 7.66 and a three-proton triplet at τ 8.85 ($J = 7$ Hz). The ultraviolet spectrum exhibited three maxima at 268, 275 and 288 m μ . The infrared spectrum of compound 148 exhibited absorptions at 6.60, 6.98, 7.16, and 9.07 μ .

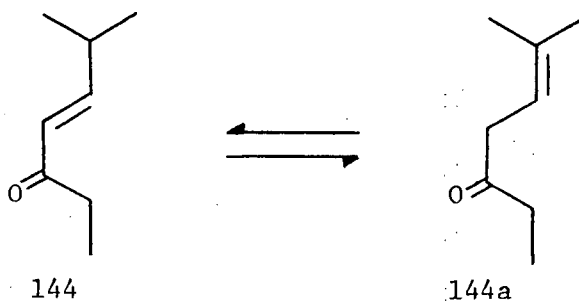
Wittig reaction of phosphorane 148 with isobutyraldehyde in refluxing methylene chloride for 12 h afforded, in 63% yield, trans-6-methyl-hept-4-en-3-one (144). Spectral data for this compound were in complete accord with the assigned structure. In particular, the infrared



spectrum exhibited absorptions at 5.98 and 6.14 μ due to the carbonyl group and carbon-carbon double bond, respectively. The n.m.r. spectrum of 144 exhibited a six-proton doublet at τ 8.90 ($J = 7$ Hz) for the C_7 and C_8 protons, a three-proton triplet at τ 8.95 and a two-proton quartet at τ 7.45 ($J = 7$ Hz) for the methyl and methylene protons of the ethyl group and two one-proton doublet of doublets at τ 3.98 and τ 3.20 for the C_4 and C_5 olefinic protons, respectively. The coupling constants

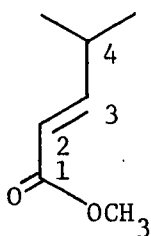
revealed a trans-olefinic coupling of 16 Hz for the C₄ and C₅ hydrogens, a coupling of 6 Hz for the C₅ and C₆ hydrogens and a long-range coupling of 1.5 Hz for the C₄ and C₆ hydrogens.

It is interesting to note that distillation of vinyl ketone 144 at temperatures above 75° resulted in a distillate which showed a n.m.r. spectrum quite different from that discussed above. This was due to the presence, in the distillate, of significant amounts of the corresponding β,γ-unsaturated ketone, 6-methylhept-5-en-3-one (144a).



Thus careful thermal control had to be maintained both in distillations and in the subsequent Robinson annelation reactions employing the vinyl ketone 144.

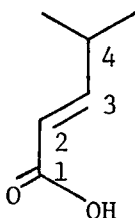
Since the overall yield of the above sequence was not particularly high (23%) and large scale preparation of anhydrous diazomethane proved very laborious, an alternate approach to the synthesis of 6-methylhept-4-en-3-one (144) was investigated (see Chart XV, Route II). This route involved an initial Wittig reaction, employing sodium hydride in DMSO, of isobutyraldehyde with trimethylphosphonoacetate (149) to afford, in 65% yield, the trans olefinic ester 150 (69). This compound exhibited the expected spectral properties. Of pertinence were the absorptions in the infrared spectrum, at 5.8 μ (carbonyl group) and at



150

6.05 μ (carbon-carbon double bond). The n.m.r. spectrum of 150 displayed a six-proton doublet at τ 8.95 ($J = 7$ Hz) for the secondary methyl groups, a three-proton singlet at τ 6.30 for the methyl ester group and two one-proton doublet of doublets at τ 4.25 and τ 3.05 for the C_3 and C_4 protons respectively. The trans-olefinic coupling constant for the C_2 and C_3 hydrogens was 16 Hz, while the coupling constant for the C_3 and C_4 protons was 7 Hz.

Hydrolysis of the olefinic ester 150 with potassium carbonate in aqueous methanol afforded, in 82% yield, the α,β -unsaturated acid 151. This compound exhibited the expected spectral characteristics.



151

Of note was the appearance, in the infrared spectrum, of the characteristic absorption bands for a carboxylic acid, at 3.1-4.0 μ and at 5.9 μ and a carbon-carbon double bond absorption at 6.05 μ . The n.m.r. spectrum of 151, which exhibited no signal due to the methyl ester,

exhibited a one-proton singlet at τ -2.15 for the acid proton, two one-proton doublet of doublets at τ 2.9 and τ 4.2 for the C_3 and C_4 protons respectively ($J_{2,3} = 15.5$ Hz, $J_{3,4} = 6.5$ Hz, $J_{2,4} = 1.5$ Hz) and a six-proton doublet at τ 8.95 ($J = 6.5$ Hz) for the secondary methyl groups.

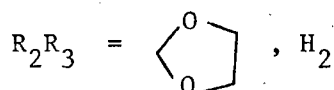
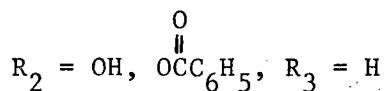
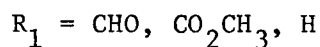
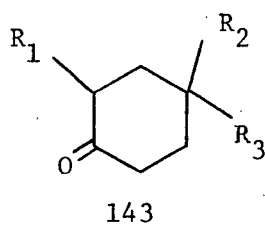
The next phase in the projected synthesis was to convert acid 151 into the corresponding acid chloride, followed by treatment with diethylcadmium. However, all attempts to prepare the acid chloride of 151 resulted in substantial isomerization of the carbon-carbon double bond to the β,γ -position. Due to this undesirable bond isomerization another approach was investigated. This approach involved treatment of carboxylic acid 151 with freshly prepared ethyllithium at -78° for 2 h, followed by rapid low temperature quenching with aqueous hydrochloric acid.

It should be noted that the success of this reaction depended, to a large extent, upon a judicious choice of reaction temperature, reactant concentration and reaction time. That is, use of reaction temperatures greater than -40° , or use of longer reaction times, resulted in the formation of a considerable amount of alcohol-containing product. On the other hand, milder reaction conditions (more dilute solutions, shorter reaction times) resulted in the recovery of fairly copious amounts of starting material. However, in order to eliminate the formation of alcohol-containing products, it was necessary to tolerate the recovery of some starting material. It was found that recycling the recovered starting material several times afforded, in 92% yield, trans-6-methylhept-4-en-3-one (144). The latter compound

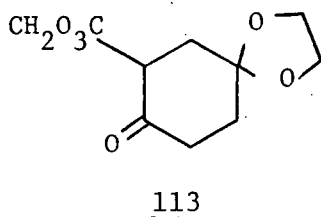
exhibited spectral properties which were identical in every respect with those of compound 144 previously prepared.

The above described synthesis has several advantages over the previous preparation of compound 144. The overall yield of the conversion of isobutyraldehyde into 144 via the route just described was 50%, obviously a considerable improvement over the first route (23%). Additionally, each of the steps was readily adaptable to relatively large scale, therefore allowing preparation of moderately large amounts of vinyl ketone 144.

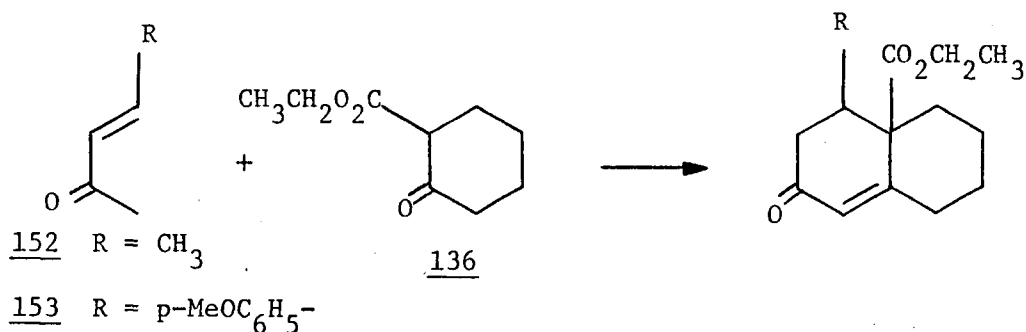
With the vinyl ketone 144 now readily available, it remained to synthesize the appropriate cyclohexanone compounds of type 143.



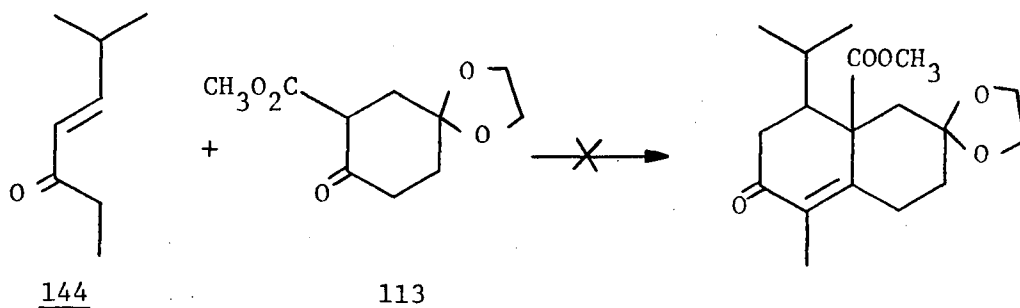
The keto ester 113 was readily available by the previously discussed synthetic method. It was therefore decided to employ this compound in the Robinson annelation reaction.



It is pertinent to note that Rapson (70) had reported good yields of base-catalyzed condensation products using the analogous 2-carboethoxycyclohexanone (136) and several vinyl ketones for example, ethylidene acetone (152) and *p*-methoxystyryl methyl ketone (153).



Thus, employing the reaction conditions described by Rapson (70) keto ester 113 was reacted with the vinyl ketone 144 in the presence of potassium ethoxide. However, none of the desired octalone could be

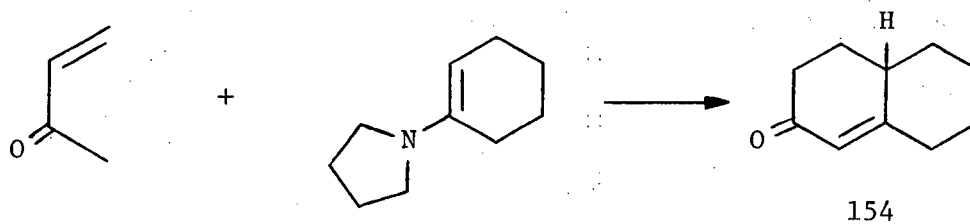


detected although a good recovery of starting material was realized. Keto ester 113 was then treated with vinyl ketone 144 employing a wide variety of base-catalyzed condensation conditions. Again only starting material could be isolated from the reaction mixtures.

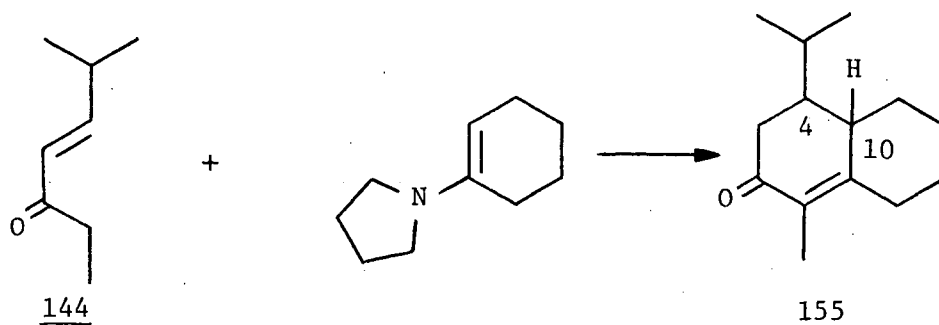
It was felt that the ketal functionality might be sterically hindering approach of vinyl ketone 144 to the carbanionic site of

the enolate anion derived from the keto ester 113. To test this possibility an unsubstituted cyclohexanone derivative was employed. Thus, the hydroxymethylene of cyclohexanone was prepared in the usual manner (sodium methoxide, ethyl formate) (71) and treated with the vinyl ketone 144 under a wide variety of base-catalyzed condensation conditions. Again no product could be isolated, and in each case a good recovery of starting material was realized.

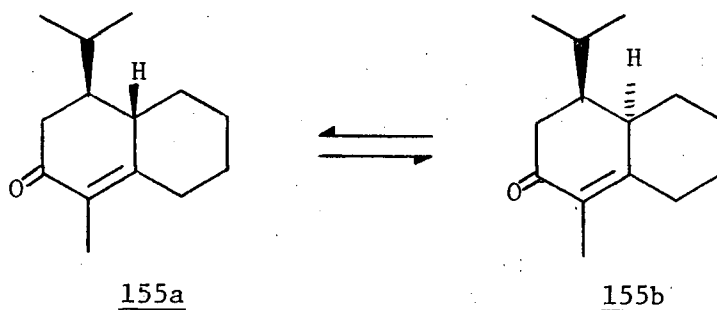
In view of the above failures of the base-promoted Robinson annelation reaction, another possible route was investigated. Stork *et al.* (72) had reported the facile condensation of the pyrrolidine enamine of cyclohexanone with methyl vinyl ketone to afford, in 83% yield, octalone 154. Hence, it was decided to attempt a similar condensation employing the vinyl ketone 144.



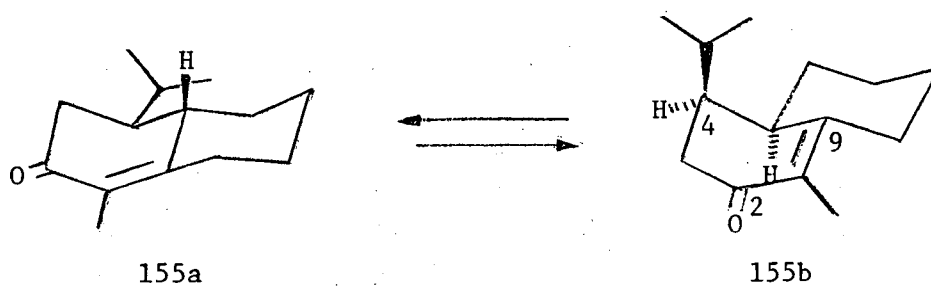
Thus, the pyrrolidine enamine of cyclohexanone and vinyl ketone 144 were stirred together at 60° for 40 h. Dry dioxane was then added and the solution refluxed for an additional 12 h. Subsequent hydrolysis of the crude reaction mixture with hot aqueous acetic acid-sodium acetate solution afforded, in 83% yield, octalone 155.



G.l.c. analysis of octalone 155 indicated the presence of two components in the ratio of 7:3, respectively. It was proposed that these two components were epimeric at C₁₀. Treatment of octalone 155 under base-catalyzed epimerization conditions (sodium methoxide, methanol) resulted in the recovery of the same two components, in the ratio of 3:1, respectively.



Upon examination of the non-bonded interactions present in 155a and 155b, it is evident that 155a is the more stable isomer. The two skew interactions between the isopropyl group and the C₂ and C₉ sp² centers, present in 155b, but absent in 155a, are mainly responsible for this relative stability. Hence, it was proposed that octalone 155a was the major component and octalone 155b was the minor component.



These compounds were isolated by preparative g.l.c. and showed the expected spectral properties. The major epimer exhibited, in the infrared spectrum, absorptions at $6.0\ \mu$ and $6.15\ \mu$ due to the carbonyl and carbon-carbon double bond respectively. In the n.m.r. spectrum (see Figure 1) the major epimer exhibited signals at $\tau\ 9.21$ and $\tau\ 9.11$ as three-proton doublets ($J = 7\ \text{Hz}$) due to the isopropyl methyl groups and at $\tau\ 8.26$ as a three-proton singlet due to the vinyl methyl group. Similarly the minor isomer exhibited, in the infrared spectrum, absorptions at 6.0 and $6.1\ \mu$ and in the n.m.r. spectrum (see Figure 2), signals at $\tau\ 9.11$ as a six-proton doublet ($J = 6\ \text{Hz}$) for the isopropyl methyl groups and at $\tau\ 8.26$ as a three-proton singlet for the vinyl methyl group. Both epimers exhibited a maximum in the ultraviolet spectrum at $249\ \text{m}\mu$.

Having realized incorporation of an isopropyl group into the C_4 position of a simple octalone, it was next planned to prepare a compound with functionality in the B ring which would allow elaboration to the cadinane skeleton. Thus, hydrolysis and decarboxylation of keto ester 113 employing aqueous potassium hydroxide, resulted in a 66% yield of 4-ethylenedioxycyclohexanone 156. This compound exhibited spectral

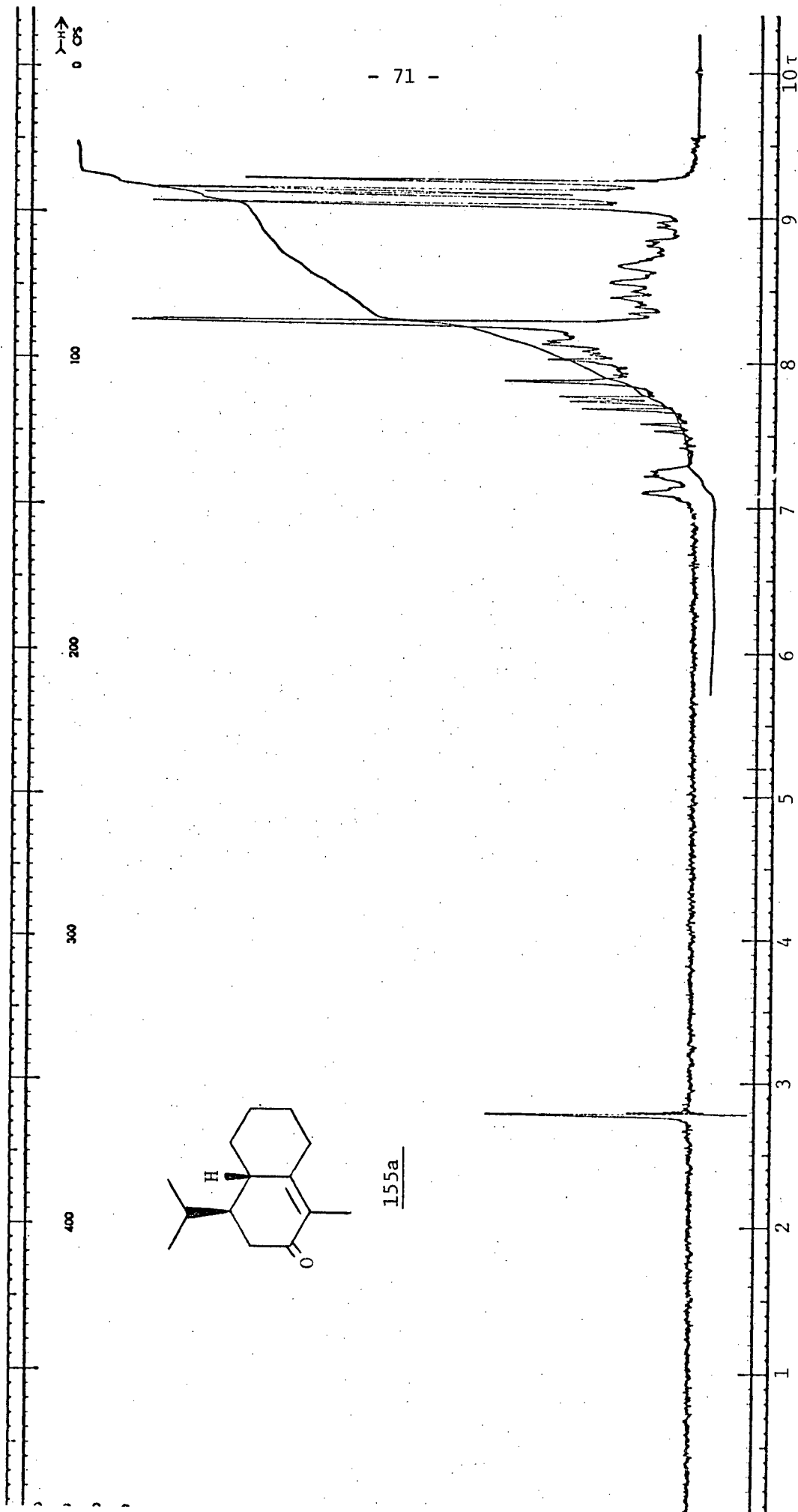


Figure 1. N.M.R. Spectrum of Octalone 155a.

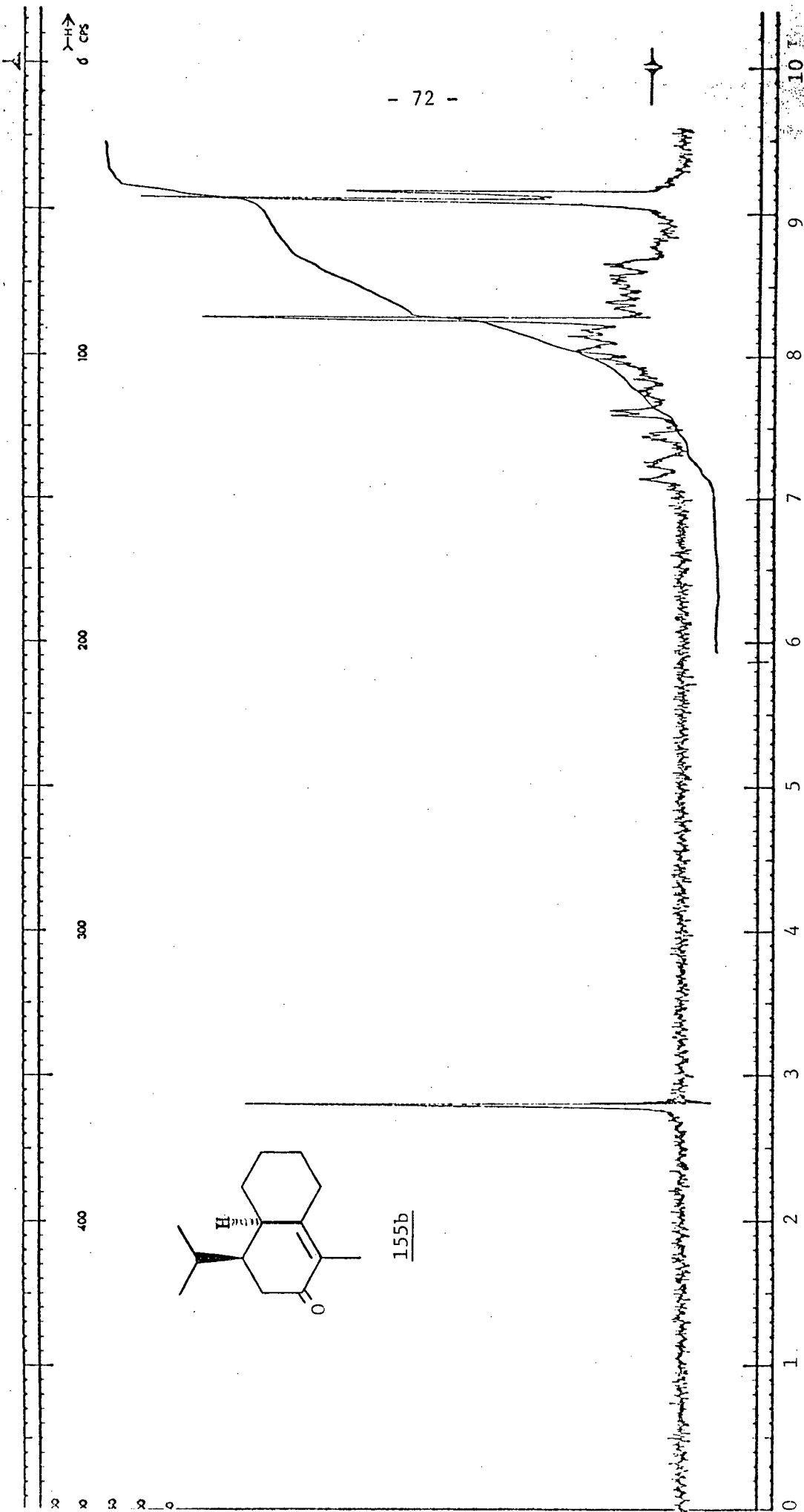
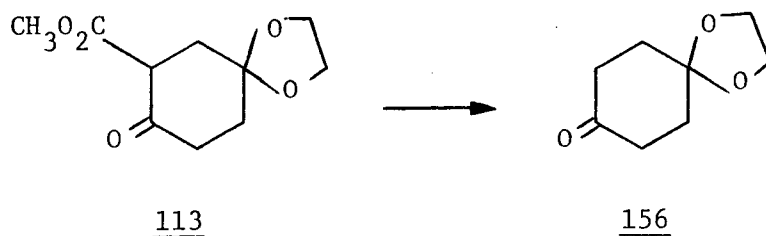
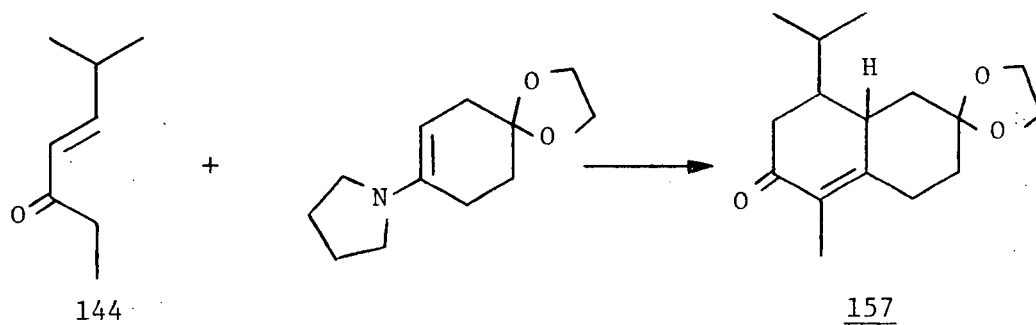


Figure 2. N.M.R. Spectrum of Octalone 155b.

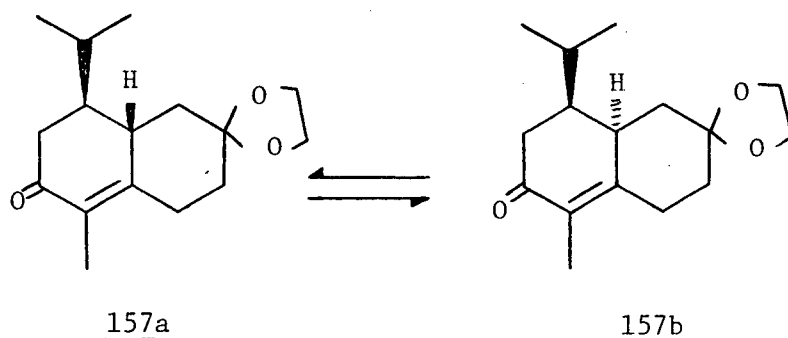


properties in complete accord with the assigned structure. Of note was the appearance in the infrared spectrum of a carbonyl absorption at $5.85\ \mu$ and the appearance, in the n.m.r. spectrum, of signals at $\tau\ 5.84$ (singlet, ketal protons) and at $\tau\ 7.17$ - 8.00 (unresolved multiplet, ring protons).

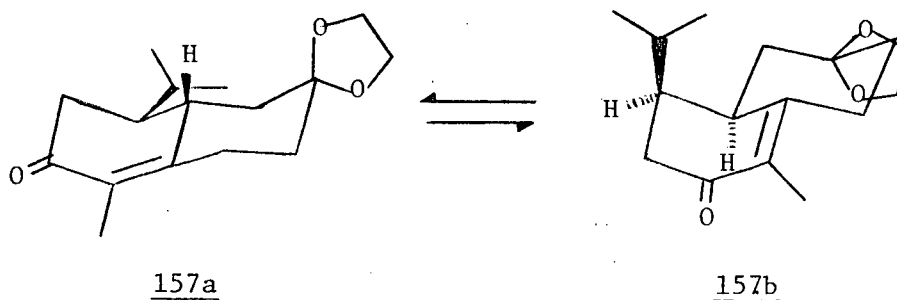
Treatment of the pyrrolidine enamine of ketone 156 with vinyl ketone 144 under the previously described conditions afforded, in only 8% yield, octalone 157. Attempts to improve the yield of this



reaction by varying the reaction conditions were unsuccessful. Octalone 157, after epimerization, was shown to be a mixture of octalones 157a and 157b in a ratio of 4:1 respectively.



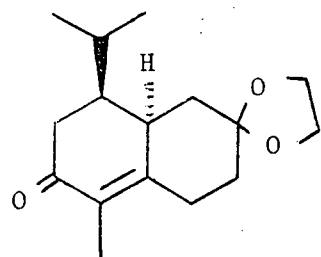
These compounds were isolated by preparative g.l.c. and exhibited the expected spectral properties. Using the same reasoning as above the major epimer was postulated to be 157a. The latter exhibited a strong



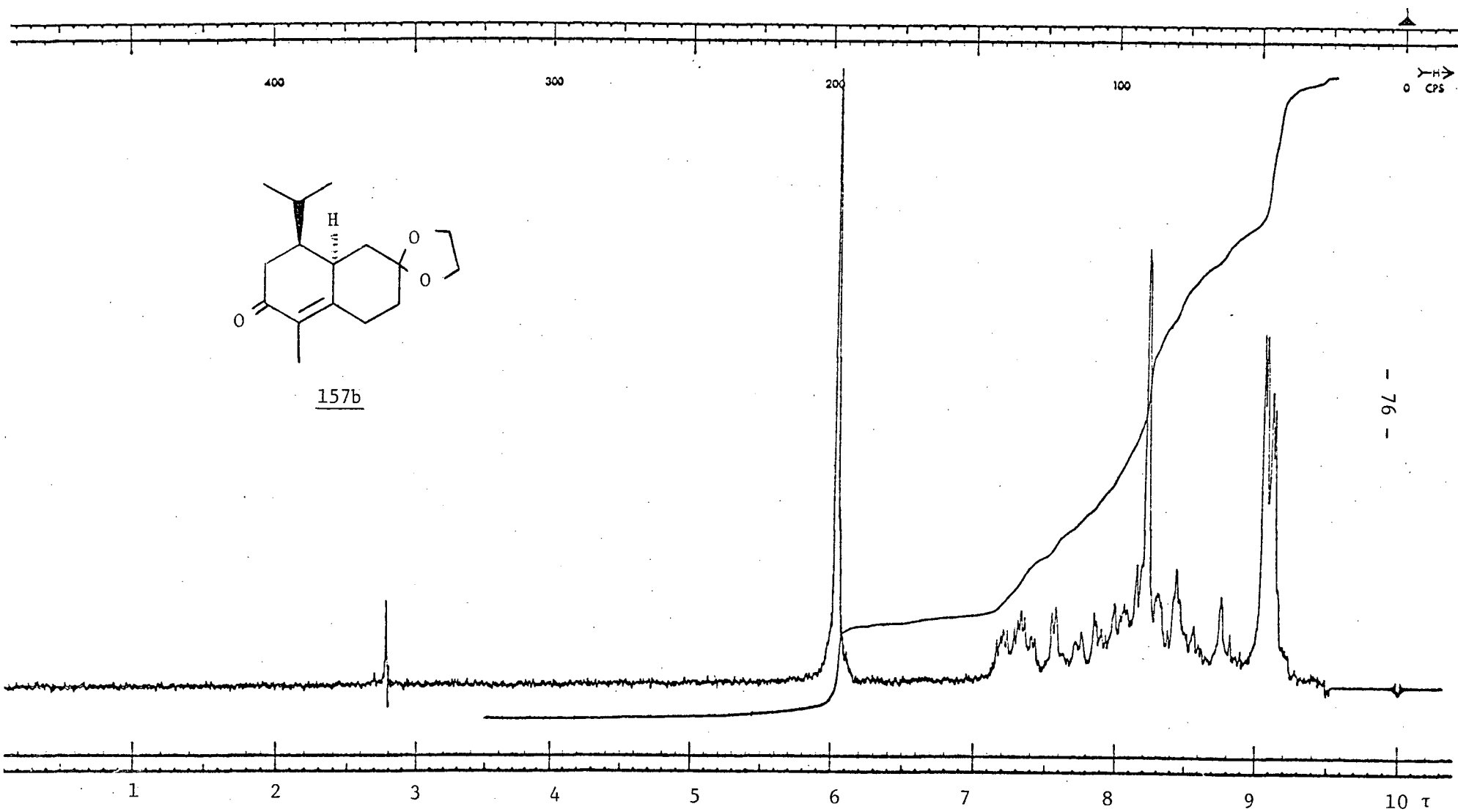
absorption at $6.05\ \mu$ in the infrared spectrum and signals in the n.m.r. spectrum (see Figure 3) at $\tau\ 9.18$ and $\tau\ 9.08$ (pair of doublets, isopropyl methyl groups, $J = 6.5\ \text{Hz}$), at $\tau\ 8.23$ (singlet, vinyl methyl group) and at $\tau\ 6.06$ (singlet, ketal protons). Similarly, the minor epimer exhibited a strong absorption at $6.01\ \mu$ (carbonyl) and a weak absorption at $6.15\ \mu$ (carbon-carbon double bond) in the infrared.

The n.m.r. spectrum of 157b (see Figure 4) exhibited signals at $\tau\ 9.08$ and $\tau\ 9.06$ (pair of doublets, isopropyl methyl groups, $J = 6.0\ \text{Hz}$), at $\tau\ 8.23$ (singlet, vinyl methyl) and at $\tau\ 6.06$ (singlet, ketal protons).

It was felt that the ketal functionality could be sterically



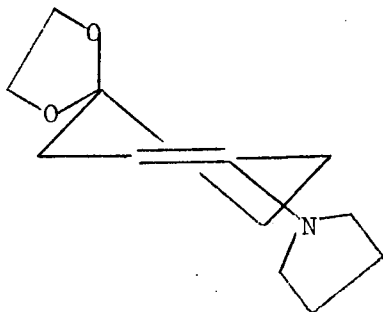
157b



- 76 -

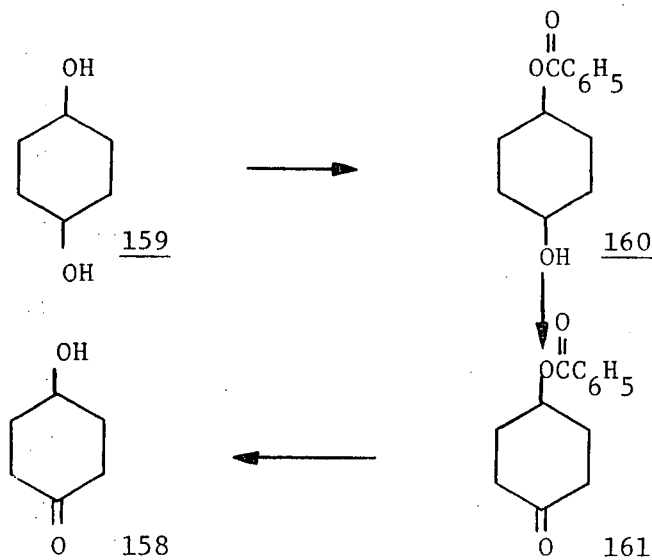
Figure 4. N.M.R. Spectrum of Octalone 157b.

hindering approach of the vinyl ketone 144 to the α -carbon of the enamine of 156, thus accounting for the low yield of octalone 157.



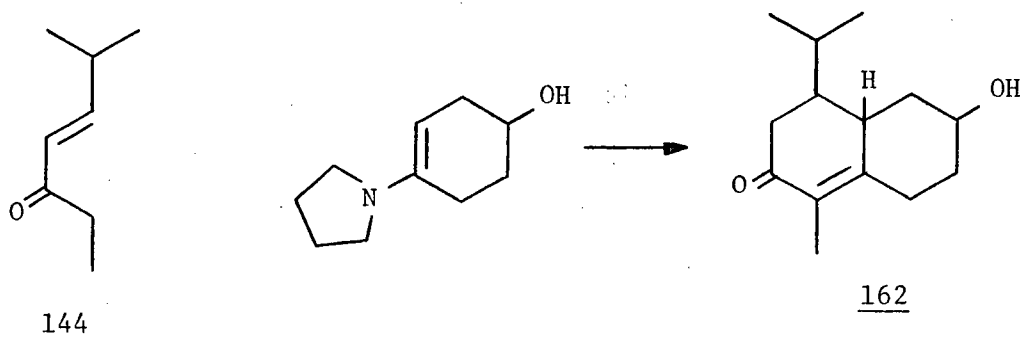
It was therefore decided to replace the ketal group by the sterically less demanding alcohol functionality. To this end, it was necessary to synthesize 4-hydroxycyclohexanone (158).

Quintol (159) was converted into keto alcohol 158 by a procedure similar to that described by Jones and Sondheimer (73). Thus, reaction of one equivalent of benzoyl chloride with quintol in a chloroform-pyridine solution afforded, in 62% yield, quintol mono-benzoate (160). Oxidation of 160 with chromium trioxide in glacial acetic acid afforded, in 87% yield, 4-benzoyloxycyclohexanone (161).

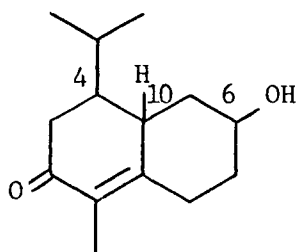


Transesterification of 161 with methanol in the presence of a catalytic amount of sodium methoxide afforded, in 74% yield 4-hydroxycyclohexanone (158).

Now with 4-hydroxycyclohexanone readily available it remained to investigate the crucial enamine-annulation reaction. Thus, condensation of the pyrrolidine enamine of 4-hydroxycyclohexanone with vinyl ketone 144 was attempted under a variety of conditions, with a 40% yield of octalone 162 finally realized. The optimum conditions found

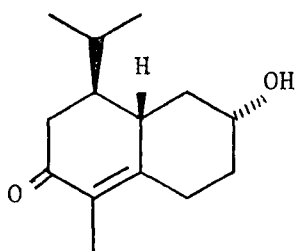


were as follows. The enamine of 158 was stirred with the vinyl ketone 144 for 36 h at 50°. Aliquot samples were taken at regular intervals and more vinyl ketone was added when the infrared spectrum of the material obtained from the aliquot showed the presence of enamine and saturated carbonyl compounds, but the absence of any α,β -unsaturated carbonyl-containing compounds. The crude reaction mixture was then hydrolyzed with hot acetic acid-sodium acetate solution to afford octalone 162.

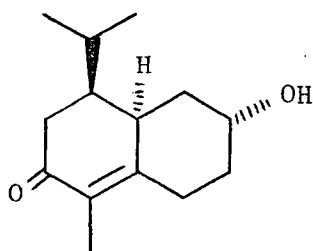


162

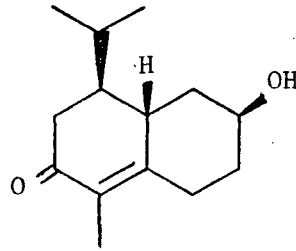
Since octalone 162 has three asymmetric centers (C_4 , C_{10} and C_6), the product obtained from the above condensation could consist of one or more of four different diastereomers. These, along with the corresponding conformational diagrams are listed below.



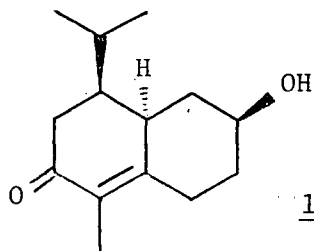
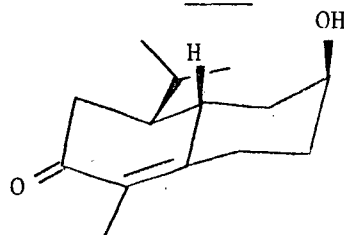
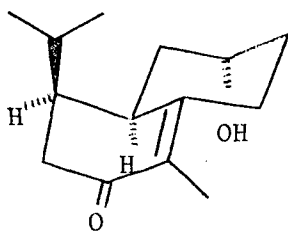
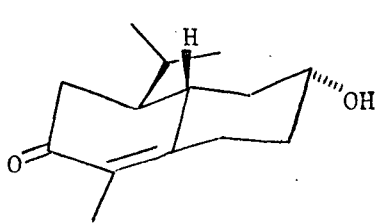
162a



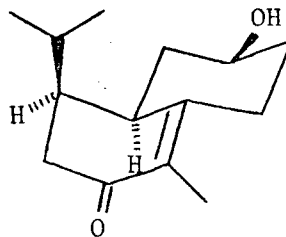
162b



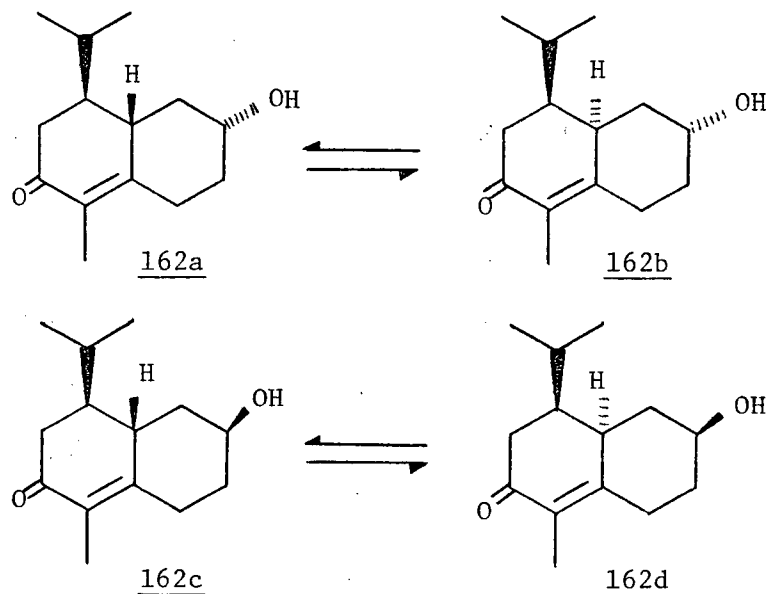
162c



162d



Analysis of the condensation product by a combination of g.l.c. and spectral methods revealed the presence of all four octalones 162a, 162b, 162c and 162d. Again it was felt that after base-catalyzed epimerization the octalones possessing an equatorial isopropyl group would predominate over the octalones possessing an axial isopropyl group. Octalone 162 was therefore subjected to epimerization conditions (sodium methoxide, methanol) to establish the following equilibria:



After this base-catalyzed epimerization of the crude octalone 162, g.l.c. analysis of the product exhibited two peaks in the ratio of 7:3, respectively. It was subsequently shown that the material giving rise to the major peak consisted of a mixture of products 162a and 162c, while the material giving rise to the minor peak consisted of a mixture of products 162b and 162d.²

² To avoid confusion in the subsequent discussion 162a plus 162c will be treated as one product and referred to as the major condensation product, while 162b plus 162d will be treated as one product and referred to as the minor condensation product.

This was shown as described below. The major and minor condensation products were isolated by preparative g.l.c. and exhibited spectral properties in complete accord with the assigned structures. The major condensation product (162a + 162c) exhibited absorptions in the infrared spectrum at 2.75 and 2.9 μ due to the alcohol functionality and at 6.05 μ due to the α,β -unsaturated carbonyl group. The n.m.r. spectrum of the major condensation product (see Figure 5) displayed signals at τ 9.16 and τ 9.07 as two three-proton doublets ($J = 6.5$ Hz) due to the isopropyl methyl groups, at τ 8.23 as a three-proton singlet due to the vinyl methyl group and at τ 6.15 and τ 5.82 as multiplets (totalling one proton) for the protons adjacent to the alcohol groups.³ The ultraviolet spectrum exhibited a maximum at 248 m μ .

The minor condensation product (162b plus 162d) exhibited absorptions, in the infrared spectrum, at 2.75 and 2.9 μ due to the alcohol functionality, at 6.05 μ due to the α,β -unsaturated carbonyl group and at 6.15 μ due to the carbon-carbon double bond. The n.m.r. spectrum of this material (see Figure 6) displayed two three-proton doublets at τ 9.07 and τ 9.04 due to the isopropyl methyl groups ($J = 6.5$ Hz), at τ 8.26 as a three-proton singlet due to the vinyl methyl group and at τ 6.10 and τ 5.78 as unresolved multiplets (totalling one proton) for the proton adjacent to the alcohol group.⁴ The ultraviolet spectrum exhibited a maximum at 247 m μ .

³ Integration of the n.m.r. spectrum indicated that the octalone 162c with an axial alcohol group and the octalone 162a with an equatorial alcohol group were present in the ratio of approximately 3:2, respectively.

⁴ Integration of the signals at τ 6.10 and τ 5.78 indicated that octalone 162b and 162d were present in a ratio of approximately 1:1.

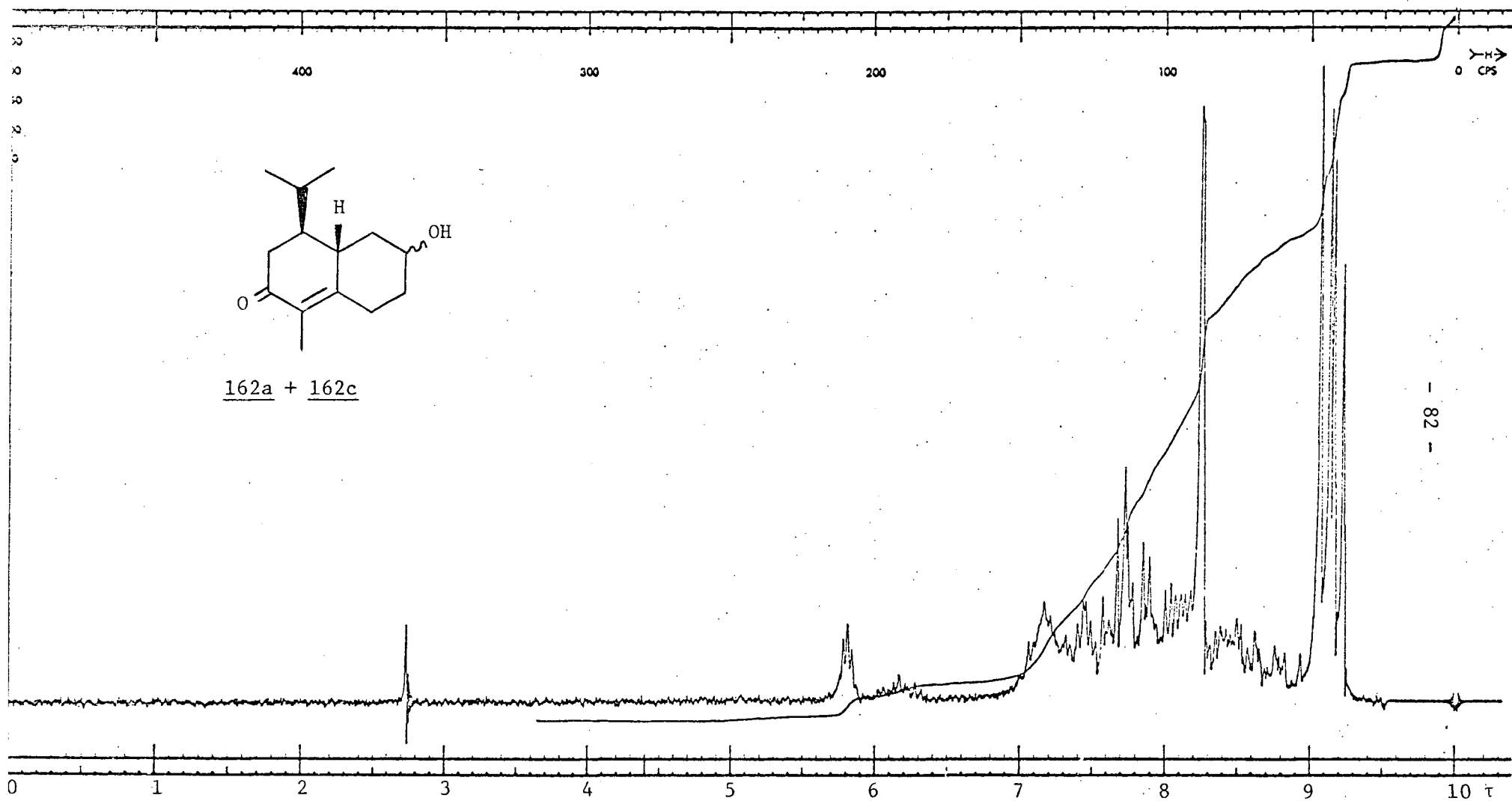


Figure 5. N.M.R. Spectrum of Octalones (162a + 162c).

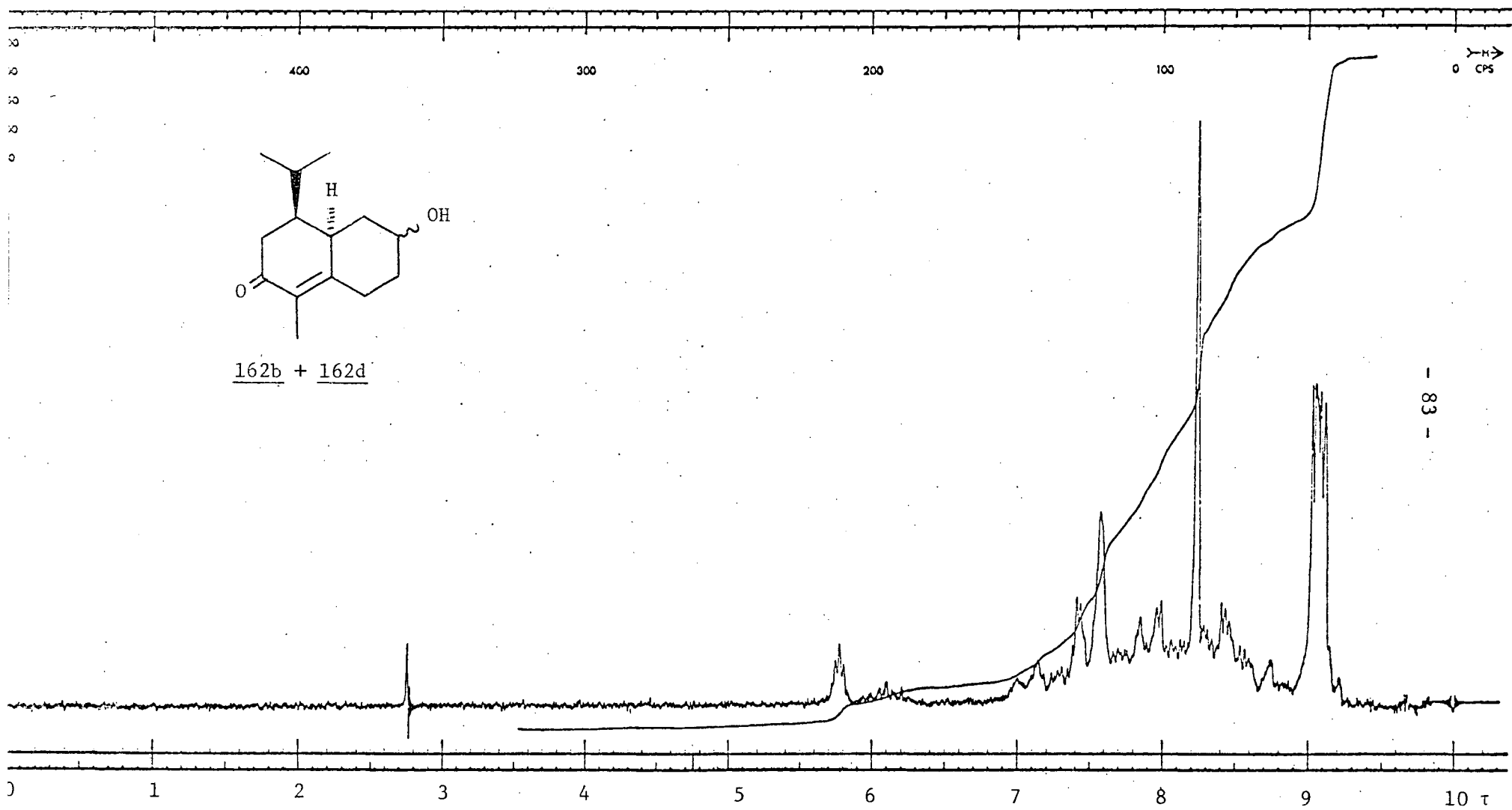
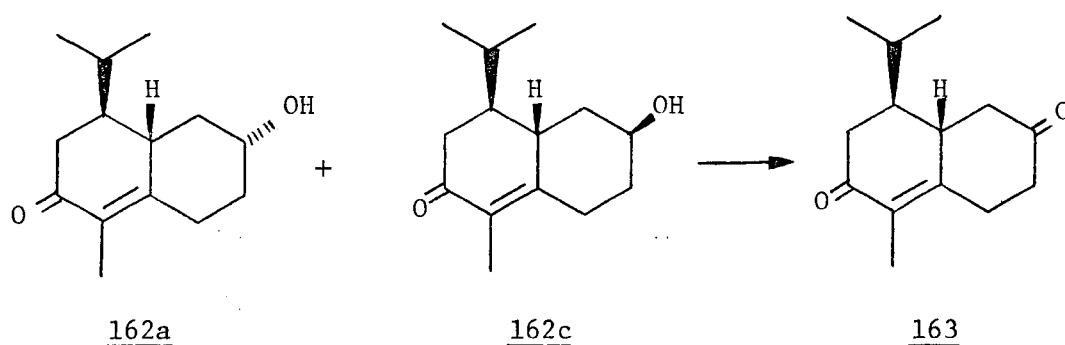


Figure 6. N.M.R. Spectrum of Octalones (162b + 162d).

Additional supporting evidence for the nature of the major condensation product was obtained as follows: a sample of the major condensation product was collected by preparative g.l.c. and subjected to Sarett oxidation (74). Thus, oxidation of the major condensation product (162a plus 162c) afforded, in 94% yield, compound 163 which was shown to be homogeneous by g.l.c. and spectral analysis. This demonstrated



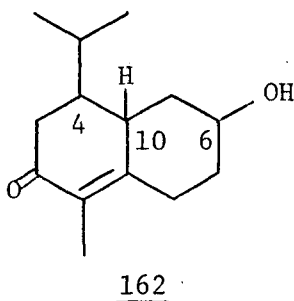
that the two components of the major condensation product did in fact differ only in the stereochemistry of the C₆-hydroxyl group.

The spectral properties of dione 163 were in complete accord with the assigned structure. The ultraviolet spectrum exhibited a maximum at λ_{max} 247 m μ . The infrared spectrum exhibited absorptions at 5.85 μ (saturated carbonyl group), at 6.05 μ (α, β -unsaturated carbonyl group) and at 6.15 μ (carbon-carbon double bond). The n.m.r. spectrum of 163 displayed two three-proton doublets at τ 9.20 and τ 9.07 due to the isopropyl methyl groups ($J = 6.5$ Hz) and a three-proton singlet at τ 8.12 due to the vinyl methyl group.

IV. Proof of the Stereochemistry of the Condensation Products

Having clearly shown that the proposed Stork enamine-annulation was a feasible process, it was necessary to unequivocally determine the

relative stereochemistry at C₄ and C₁₀ of the major and minor condensation products. In order to accomplish this objective, it was planned

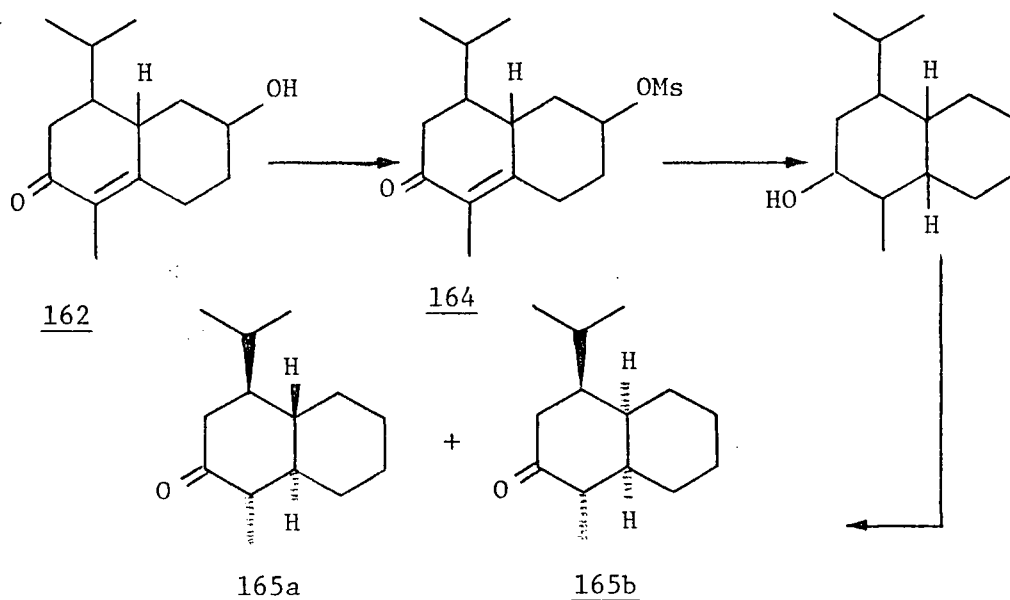


to convert octalones 162 into the corresponding simple decalone derivatives, unsubstituted at C₆. It was then hoped that careful spectral studies would unambiguously define the relative stereochemistry at C₄ and C₁₀. With this objective in mind, it was proposed that the next two necessary steps - namely removal of the C₆-hydroxyl group and saturation of the conjugated carbon-carbon double bond - could be conveniently carried out in one main operation.

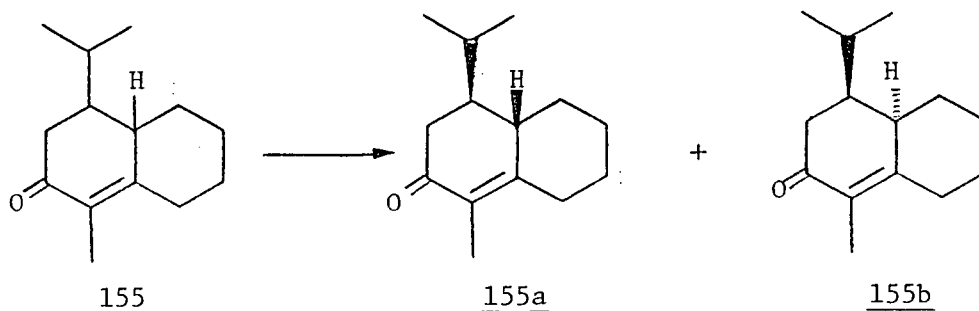
It has been well documented that α,β -unsaturated ketones undergo stereoselective lithium-ammonia reduction, affording the corresponding saturated ketones (45,46,48). Furthermore, it has been shown that mesylate groups can be hydrogenolyzed under lithium-ammonia reduction conditions (75). Hence, it appeared that Birch reduction would be the appropriate reaction for degrading octalone 162.

Treatment of octalone 162 with methanesulfonyl chloride in pyridine afforded, in 85% yield, the corresponding methanesulfonate derivative 164. Evidence that this transformation had indeed taken place was shown in the infrared spectrum of 164. It exhibited absorptions at 7.45 and 8.55 μ for the methanesulfonate group but no absorptions for the hydroxyl

group present in the starting material. Treatment of 164 with lithium in liquid ammonia, containing ethanol as co-solvent and proton source, followed by oxidation of the resulting crude alcohols with Jones reagent (76) afforded, in 85% yield, two epimeric decalones 165a and 165b⁵ in a ratio of 7:3, respectively.

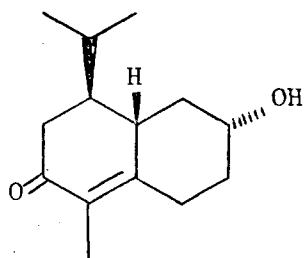


As previously described, base-catalyzed epimerization of octalone 155 afforded octalones 155a and 155b in the ratio of 3:1, respectively.

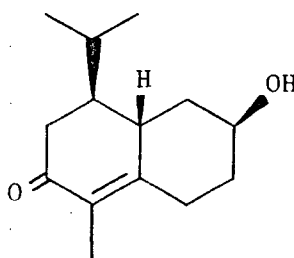


⁵ The fact that 165b did contain a cis ring junction was subsequently unambiguously shown (see p. 95).

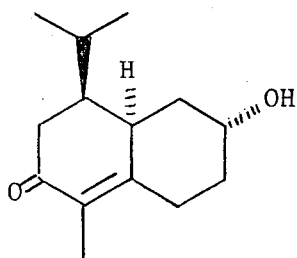
Birch reduction of this equilibrium mixture would be expected to yield decalones 165a and 165b in the ratio of 3:1 respectively. As expected Birch reduction of a 3:1 mixture of octalones 155a and 155b with lithium in liquid ammonia, followed by quenching with ammonium chloride afforded, in 78% yield, a mixture of decalones 165a and 165b in the ratio of 3:1 respectively. The spectral properties and g.l.c. retention times of the major and minor products formed from Birch reduction of octalone 155 were identical in every respect with those of the major and minor products formed from the reduction-oxidation of mesylate 164 (obtained from octalone 162). The above results provided confirmatory evidence that the major condensation product of octalone 162 did indeed consist of octalones 162a and 162c while the minor condensation product of octalone 162 consisted of octalones 162b and 162d.



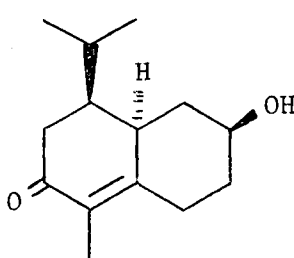
162a



162c

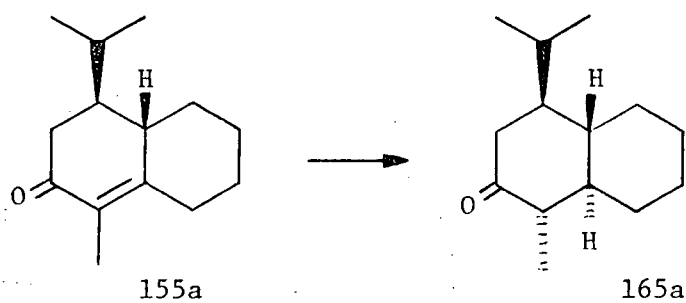


162b



162d

To ensure that no epimerization was taking place prior to reduction in the lithium-ammonia-ethanol conditions pure octalone 155a was isolated by preparative g.l.c. and subjected to these conditions. Reduction of octalone 155a with lithium in liquid ammonia containing ethanol as co-solvent and proton source, followed by Jones oxidation (76) of the crude product afforded, in 91% yield, only decalone 165a.



This control experiment demonstrated that the mesylate (164) of octalone 162 did not undergo epimerization prior to reduction. That is to say, the ratios of the reduction products, decalones 165a and 165b, did indeed reflect the original composition of octalone 162.

The spectral properties of the decalones 165a and 165b were in complete agreement with the assigned structures. Thus, the infrared spectrum of decalone 165a exhibited an absorption at 5.85μ due to the carbonyl group. In the n.m.r. spectrum of 165a (see Figure 7) signals were evident for the isopropyl methyl groups at τ 9.23 and τ 9.13 as two three-proton doublets ($J = 7$ Hz) and for the C_1 secondary methyl at τ 8.99 as a three-proton doublet ($J = 6.5$ Hz). Similarly, decalone 165b exhibited in the infrared spectrum, an absorption at 5.85μ (carbonyl group). The n.m.r. spectrum of 165b (see Figure 8) displayed two three-proton doublets at τ 9.13 and τ 9.09 attributable to the isopropyl methyl groups ($J = 6$ Hz) and a three-proton doublet at τ 9.02 for the C_1

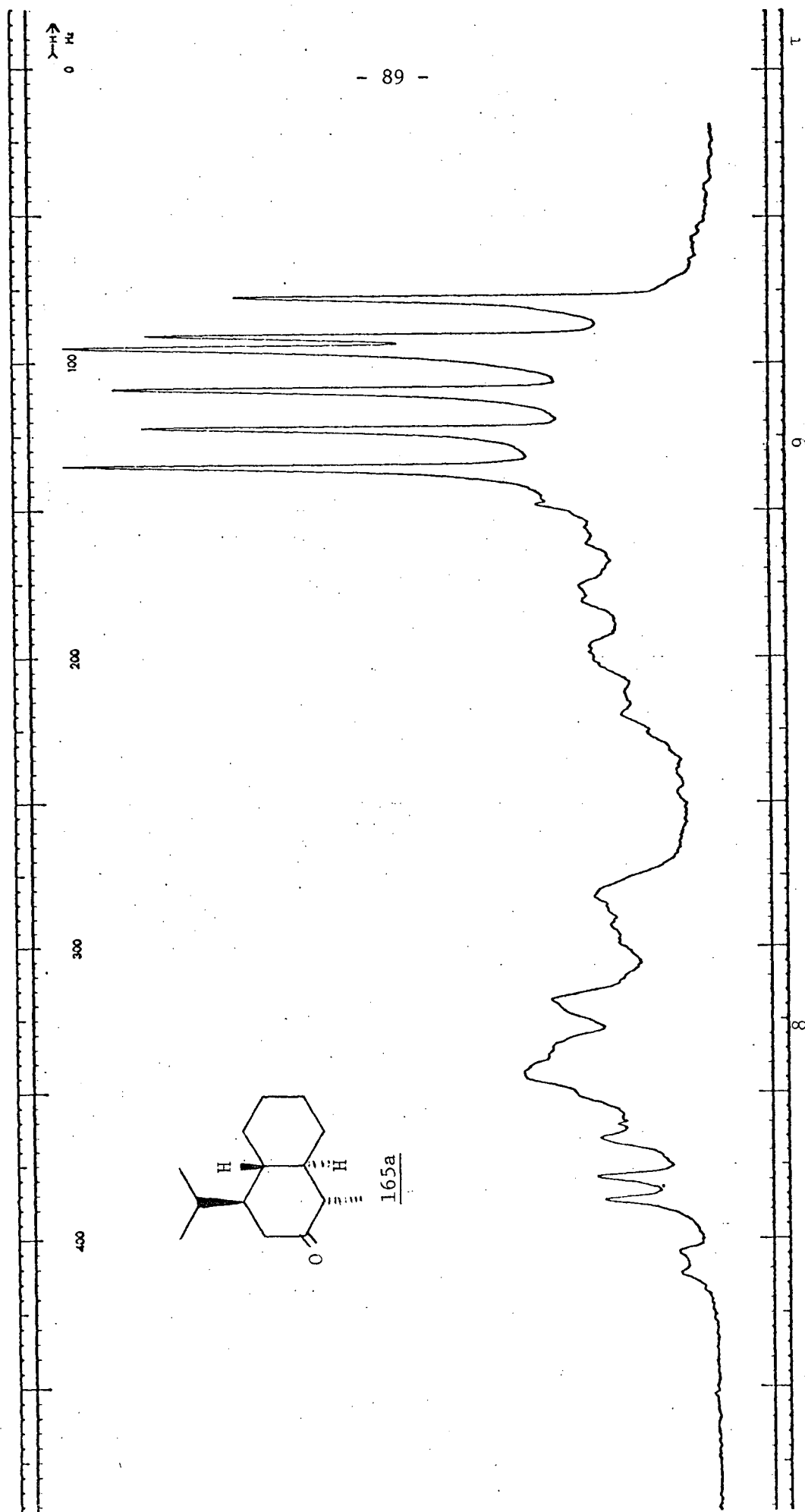


Figure 7. N.M.R. Spectrum of Decalone 165a.

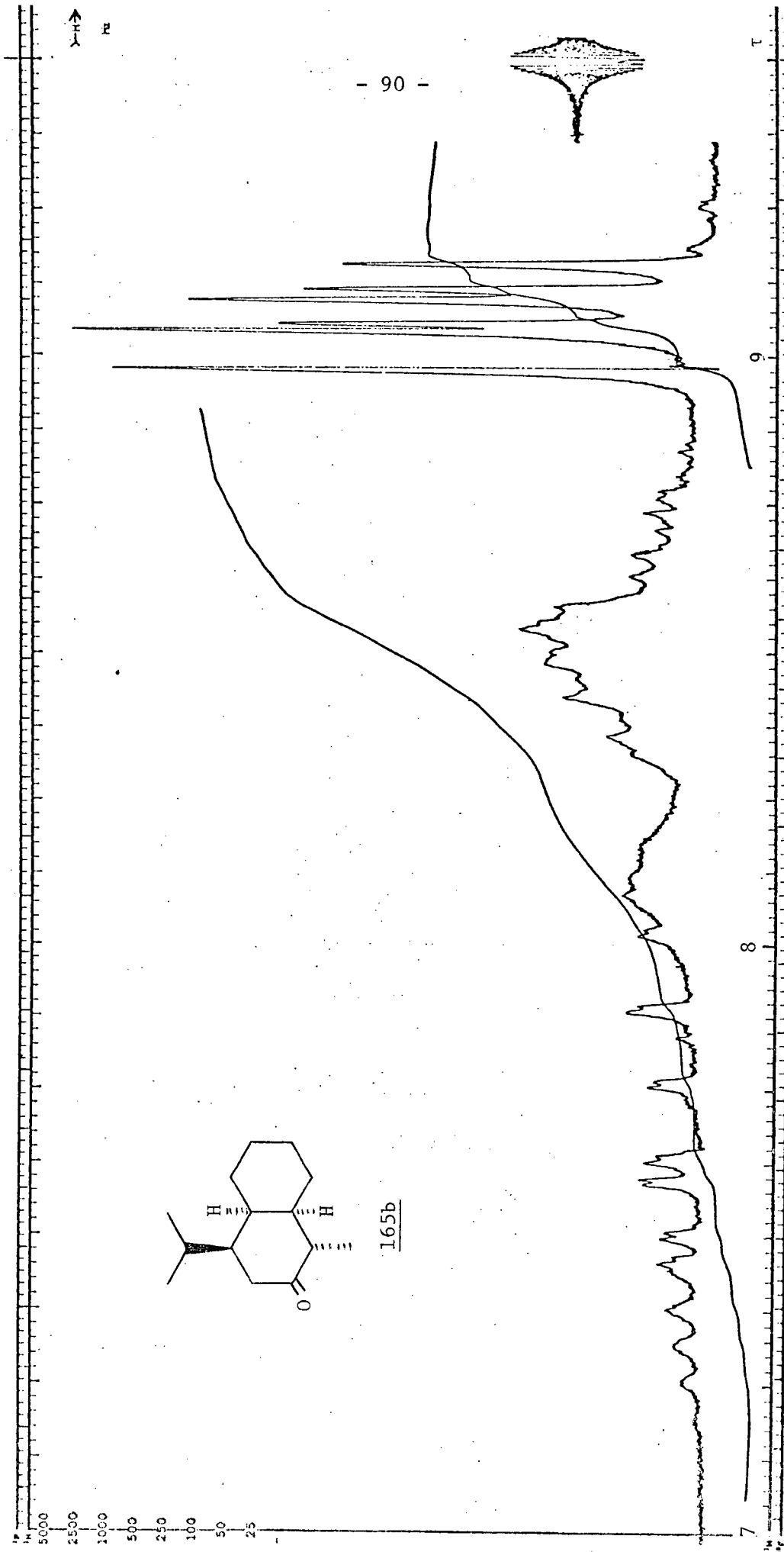
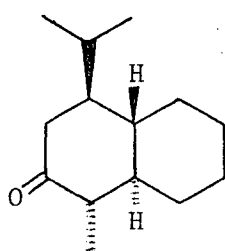


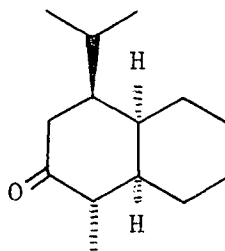
Figure 8. N.M.R. Spectrum of Decalone 165b.

methyl group ($J = 6.5$ Hz).

That the stereochemistry of the two decalones 165a and 165b was as shown below was subsequently confirmed by internuclear double resonance (INDOR) studies (77,78). Since the results obtained from the



165a



165b

INDOR experiments played a crucial role in the assignment of the stereochemistry of the two decalones 165a and 165b, it is pertinent to briefly discuss this technique. This experiment is performed using a perturbing energy beam of lower power than that used in either spin-decoupling (79) or spin-tickling experiments (80). The observing frequency is centered exactly on a single sharp spectral line. Then the perturbing energy beam is swept through the spectrum. This energy beam is just powerful enough to shift energy level populations.

In order to illustrate this technique, consider a two spin system for which a diagrammatic representation of the connected transitions is given in Figure 9. It should be emphasized that this is not meant to be a precise energy level diagram but is purely a convenient qualitative representation to aid in predicting results. Now if transition 1 is monitored and the perturbing energy beam coincides with the frequency of transition 4, level A will be depopulated and the intensity of the monitored signal will decrease. Conversely, when the perturbing

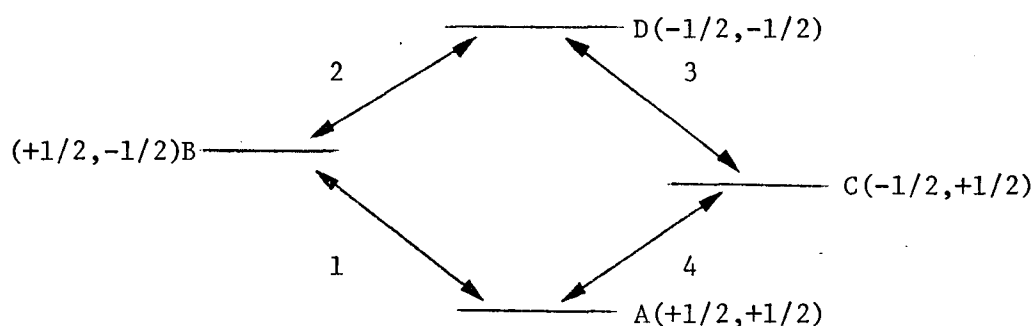


Figure 9

energy beam coincides with the frequency of transition 2, level B will be depopulated and the intensity of the monitored signal will increase. Hence, this technique gives rise to a spectrum possessing a flat baseline except when the perturbing frequency coincides with a transition connected to the transition being monitored. This technique therefore permits determination of the position and coupling constants of protons whose signals might otherwise be obscured by the methylene envelope.

This technique appeared particularly attractive because observation of a spectral line due to one of the protons at C_3 in decalones 165a and 165b would allow determination of the C_3 - C_4 proton coupling constants and thus provide information on the stereochemistry of the C_4 isopropyl group. The results obtained from the INDOR spectrums of decalone 165a and decalone 165b are shown in Table I and Table II respectively.

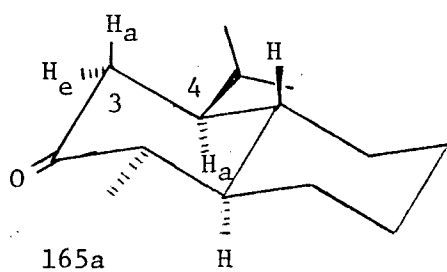
Table I. Chemical Shifts and Splittings for Decalone 165a

Proton	Measured Chemical Shift (in Hz from $CHCl_3$)	Protons	Measure Splittings (Hz)
H_{3e}	495.8	$H_{3e}-H_{3a}$	12.7
H_{3a}	523.2	$H_{3e}-H_{4a}$	3.8
H_4	580.4	$H_{3a}-H_{4a}$	12.7
H_1	517.5	$H_1-(CH_3)_1$	6.4

Table II. Chemical Shifts and Splittings for Decalone 165b

Proton	Measured Chemical Shift (in Hz from CHCl_3)	Protons	Measured Splittings (Hz)
H_{3e}	481.7	$\text{H}_{3e}-\text{H}_{3a}$	13.0
H_{3a}	515.7	$\text{H}_{3e}-\text{H}_{4a}$	3.9
H_1	463.1	$\text{H}_{3a}-\text{H}_{4a}$	13.0
		$\text{H}_1-(\text{CH}_3)_1$	6.4

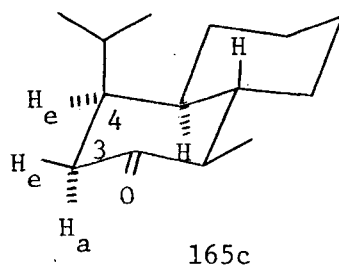
It should be noted that the observed splittings are not corrected for higher order effects but are almost certainly within experimental error of the true coupling constants. The observed splittings for decalone 165a are in complete accord with the stereochemistry as depicted in structure 165a.



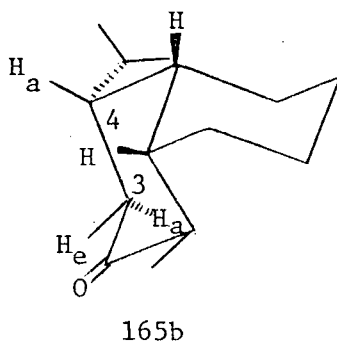
The splittings observed were 12.7 Hz due to the coupling between the geminal C_3 axial and C_3 equatorial protons, 12.7 Hz due to the diaxial coupling between the C_3 axial and C_4 axial protons and 3.8 Hz due to the coupling between the C_3 equatorial and the C_4 axial protons. These splittings are in accord with those predicted for compound 165a

from the Karplus curve (81). Hence, these splittings confirm that the isopropyl group at C_4 is indeed in the equatorial orientation as shown in 165a.

The splittings for the minor product of the Birch reduction of octalone 155 or mesylate 164, surprisingly paralleled those of the major product, decalone 165a, (discussed above). This indicated that contrary to all expectations the minor product obtained from these Birch reductions was not the trans-fused decalone 165c.

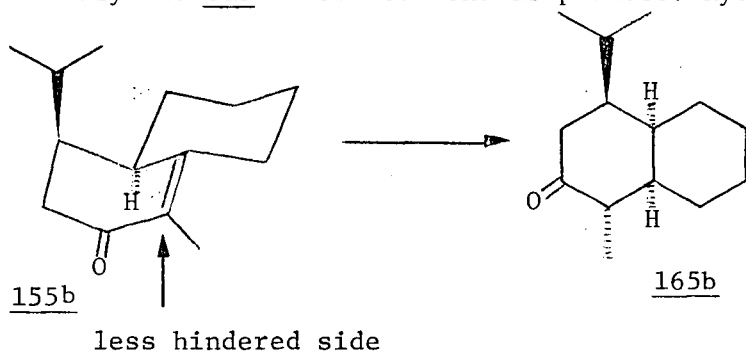


The INDOR spectrum of decalone 165c would be expected to reveal two small splittings - one for the diequatorial coupling between the C_3 equatorial and C_4 equatorial protons and one for the axial-equatorial coupling between the C_3 axial and C_4 equatorial protons. To explain the observed splittings it was necessary to postulate that the Birch reduction had proceeded anomalously to produce the cis-fused decalone 165b.



This compound would be expected to exhibit two large splittings - one due to the geminal coupling between the C₃ axial and C₃ equatorial protons and one due to the diaxial coupling between the C₃ axial and C₄ axial protons and one small splitting due to the coupling between the C₃ equatorial and C₄ axial protons. These predictions are in complete accord with the observed splittings of 13.0 Hz, 13.0 Hz and 3.9 Hz. This evidence combined with the following chemical evidence confirmed that the minor product from the Birch reduction of either octalone 155 or mesylate 164 possessed the stereochemistry depicted in structure 165b.

In order to obtain further chemical evidence that decalone 165b was the correct structure for the minor product obtained from the Birch reduction of mesylate 164 it was next planned to synthesize this decalone in another way. Examination of a molecular model of octalone 155b showed that the double bond was very hindered to attack from the β-side by the axial isopropyl group. Hence, hydrogenation of octalone 155b would be expected to yield only the cis-fused decalone as product. Hydrogenation of octalone 155b



in the presence of a catalytic amount of palladium on charcoal, followed by epimerization (sodium methoxide, methanol) of the α-methyl group in the product, afforded only decalone 165b. This decalone was identical in all respects with decalone 165b obtained from the

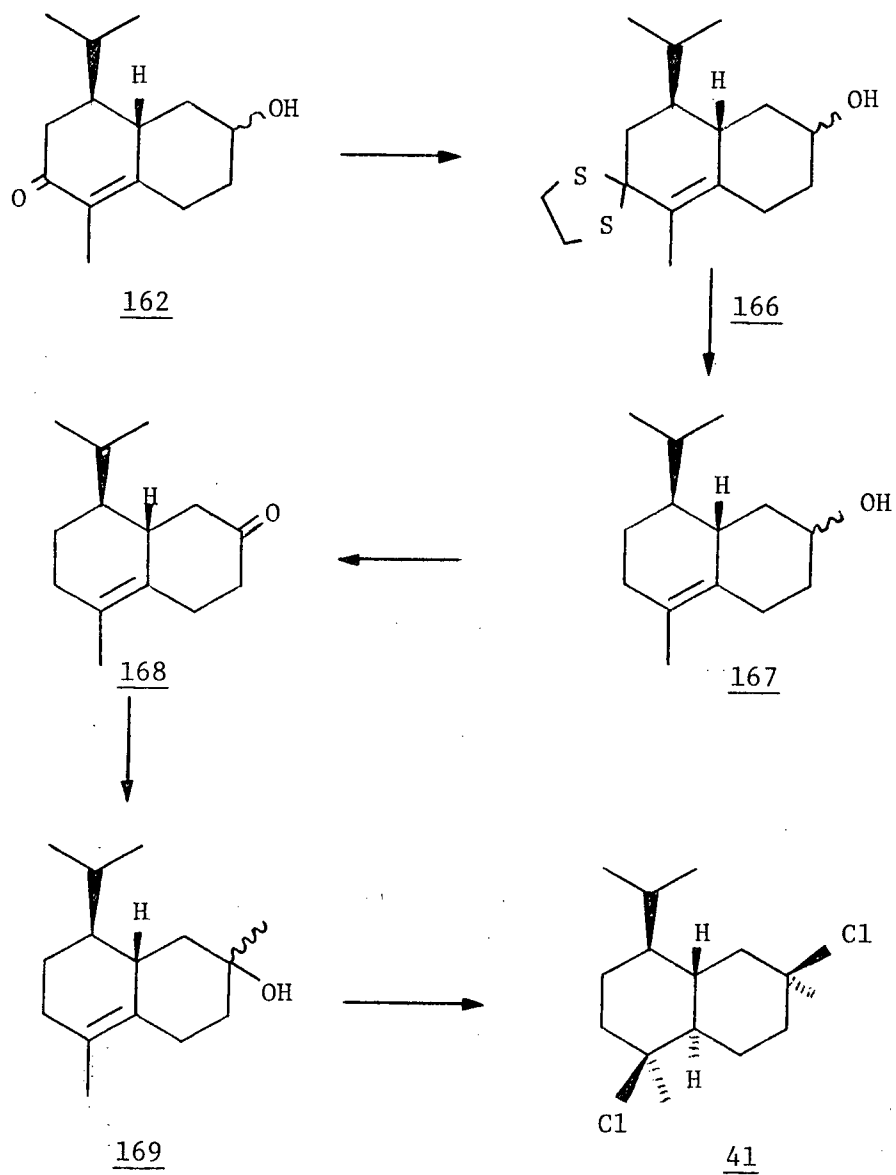
lithium-ammonia reduction of octalone 155b or mesylate 164. This confirms that the Birch reduction of octalone 155b and mesylate 164 had indeed proceeded to give the cis-fused decalone 165b. The Birch reduction results will be discussed in detail later in this thesis.

V. Synthesis of Cadinene Dihydrochloride

With confirmation that the relative stereochemistry at C₄ and C₁₀ of the major constituent of octalone 162 was that required for the cadinane skeleton, it was next planned to convert this octalone into cadinane derivatives.

The major constituents of octalone 162, octalones 162a plus 162c, were isolated by preparative g.l.c. and carried through the sequence outlined in Chart XVI. Thus, treatment of octalone 162a plus 162c with ethanedithiol in the presence of boron trifluoride etherate afforded, after recrystallization, a 66% yield of the corresponding thioketal 166. The fact that the desired transformation had indeed occurred was shown by the spectral data of compound 166. The infrared spectrum of compound 166 exhibited absorptions at 3.0 μ due to the alcohol functionality, 6.1 μ due to the carbon-carbon double bond but no absorption at 6.0 μ (carbonyl group). The n.m.r. spectrum of 166 exhibited two three-proton doublets at τ 9.21 and τ 9.02 attributable to the isopropyl methyl groups, a one-proton singlet at τ 8.57 due to the hydroxyl proton (exchanged on deuterium oxide addition), a three-proton singlet at τ 8.07 due to the vinyl methyl, a four-proton singlet at τ 6.67 due to the protons of the thioketal group and one multiplet (less than one proton) at τ 5.85 due to the equatorial proton adjacent to the hydroxyl group. Desulphurization of 166 with Raney nickel in

Chart XVI



refluxing ethanol afforded, in 77% yield, olefinic alcohol 167. The spectral data of compound 167 fully substantiated the assigned structure. In particular, the n.m.r. spectrum exhibited assignable signals at τ 9.23 and τ 9.09 (pair of doublets, isopropyl methyl groups, $J = 6.5$ Hz), at τ 8.40 (singlet, vinyl methyl) at τ 8.22 (singlet, hydroxyl proton, exchanged on addition of deuterium oxide) and at τ 6.36 and τ 5.85 (multiplets, CHOH) but no signal for the ketal group.

Oxidation of 167 with chromium trioxide in pyridine afforded, in 89% yield, the corresponding ketone 168. Confirmation that the expected oxidation had in fact taken place was given by the absorption in the infrared spectrum of 168 at 5.85μ due to a saturated carbonyl but no absorption characteristic of a hydroxyl group. The n.m.r. spectrum of 168 displayed signals at τ 9.21 and τ 9.05 (pair of doublets, isopropyl methyl groups, $J = 6.5$ Hz), and at τ 8.36 (singlet, vinyl methyl).

Treatment of ketone 168 with methyllithium resulted in the formation of alcohol 169 in 91% yield. An analytical sample of alcohol 169 was isolated by preparative g.l.c. The spectral data were in complete agreement with the assigned structure. In particular, the infrared exhibited absorptions at 3.0μ (hydroxyl group) and at 6.1μ (carbon-carbon double bond). The n.m.r. spectrum of 169 exhibited assignable signals at τ 9.21 and τ 9.07 (pair of doublets, isopropyl methyl groups, $J = 6.5$ Hz), at τ 8.81 (singlet, tertiary methyl group) and at τ 8.37 (singlet, vinyl methyl group).

Alcohol 169 was converted into (+)-cadinene dihydrochloride (41) in 80% yield, by treatment with anhydrous hydrogen chloride in anhydrous

ether at 0°. The recrystallized material exhibited an infrared spectrum which was identical with that of authentic (+)-cadinene dihydrochloride.⁶ The melting point of the synthetic material showed no depression on admixture with the authentic material. Since the stereochemistry of a cadinene dihydrohalide derivative had been unambiguously shown by X-ray structural determination (18) this conversion of alcohol 169 into cadinene dihydrochloride confirmed that all of the previously described stereochemical work was correct. That is to say, the major condensation product, after epimerization, of the enamine-annulation reactions did indeed possess the stereochemistry necessary for the synthesis of the cadinane sesquiterpenes.

Hence, the enamine-annulation approach is particularly attractive, since in one step it yields a compound possessing all the skeletal features required for elaboration to the cadinane compounds. This permits the synthetic sequence to be kept relatively simple and short. However, this sequence does possess several disadvantages. One serious complication is the production of closely related epimeric products, requiring preparative g.l.c. purification at the initial stages of the sequence. In addition, this approach does not make allowance for the regioselective introduction of the required double bond into the B ring. This latter disadvantage coupled with the fact that authentic samples of the cadinene hydrocarbons were not available hindered attempts to obtain and identify ω - and δ -cadinene, (52) and (8) respectively, by dehydration of alcohol 169. However, if the above mentioned disadvantages could be

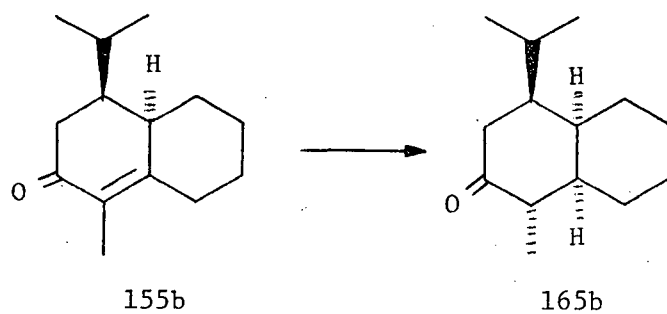
⁶ We thank M.D. Sutherland for a generous sample of (+)-cadinene dihydrochloride.

effectively overcome, this synthetic sequence would provide an efficient entry into the cadinane type of sesquiterpenes.

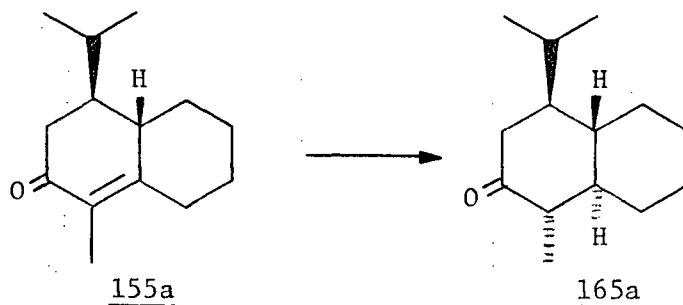
VI. Studies on the Birch Reductions of $\Delta^{1,9}$ -2-Octalone Systems

A. General

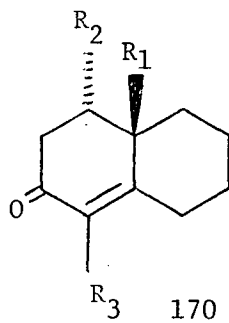
Although a number of theories have been proposed to explain the stereochemistry of the products of Birch reduction of $\Delta^{1,9}$ -2-octalone systems, research to date has failed to adequately explain the product selectivity observed in these reductions (48). Generally, lithium-ammonia reductions of $\Delta^{1,9}$ -2-octalones proceed to yield a high proportion (~98%) of the corresponding trans-fused decalone. As previously discussed, lithium-ammonia reduction of octalone 155b proceeded anomalously to afford stereoselectively, the cis-fused decalone 165b; while similar



reduction of the corresponding C_4 equatorially substituted octalone 155a proceeded normally to afford the trans-fused decalone 165a.



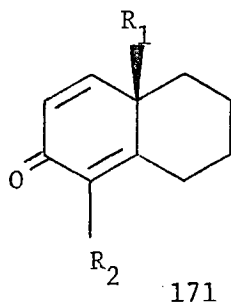
Since an explanation for the anomalous result obtained in the Birch reduction of octalone 155b was not obvious, it was decided to extend the investigation to include lithium-ammonia reductions of analogous octalone systems of type 170. It was thus hoped that these



results would assist in clarifying some of the factors governing the stereochemical outcome of Birch reductions of this type of octalone.

B. Synthesis of $\Delta^{1,9}$ -2-Octalone Systems

The first objective was, therefore, to synthesize octalones of type 170. It was decided that of the number of possible routes which might be employed in the construction of these octalones, the scheme involving 1,4-conjugate addition of lithium dialkylcuprates to cross-conjugated dienones of type 171 was both attractive and general.



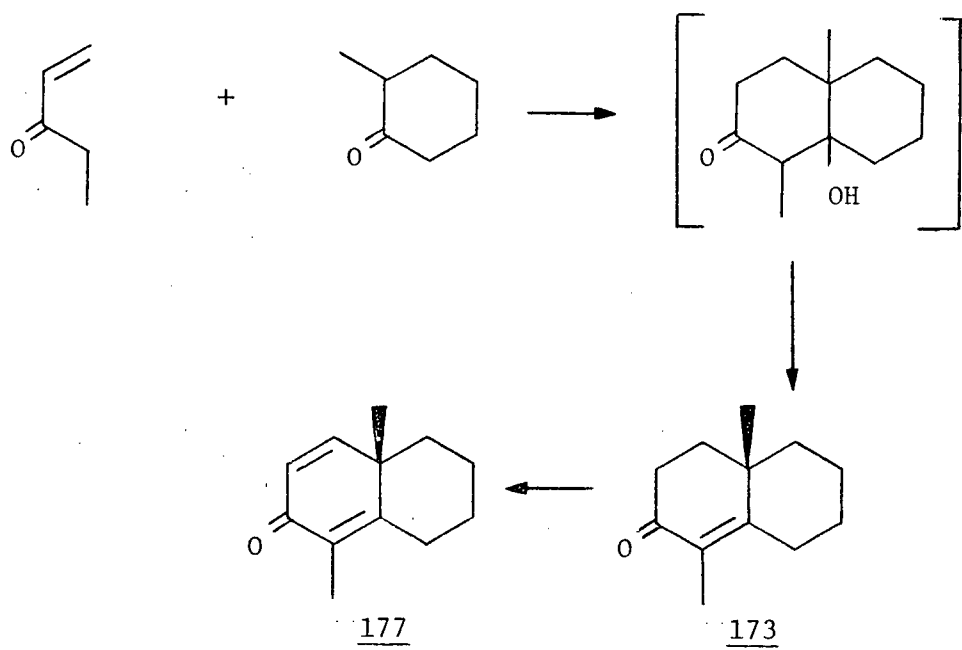
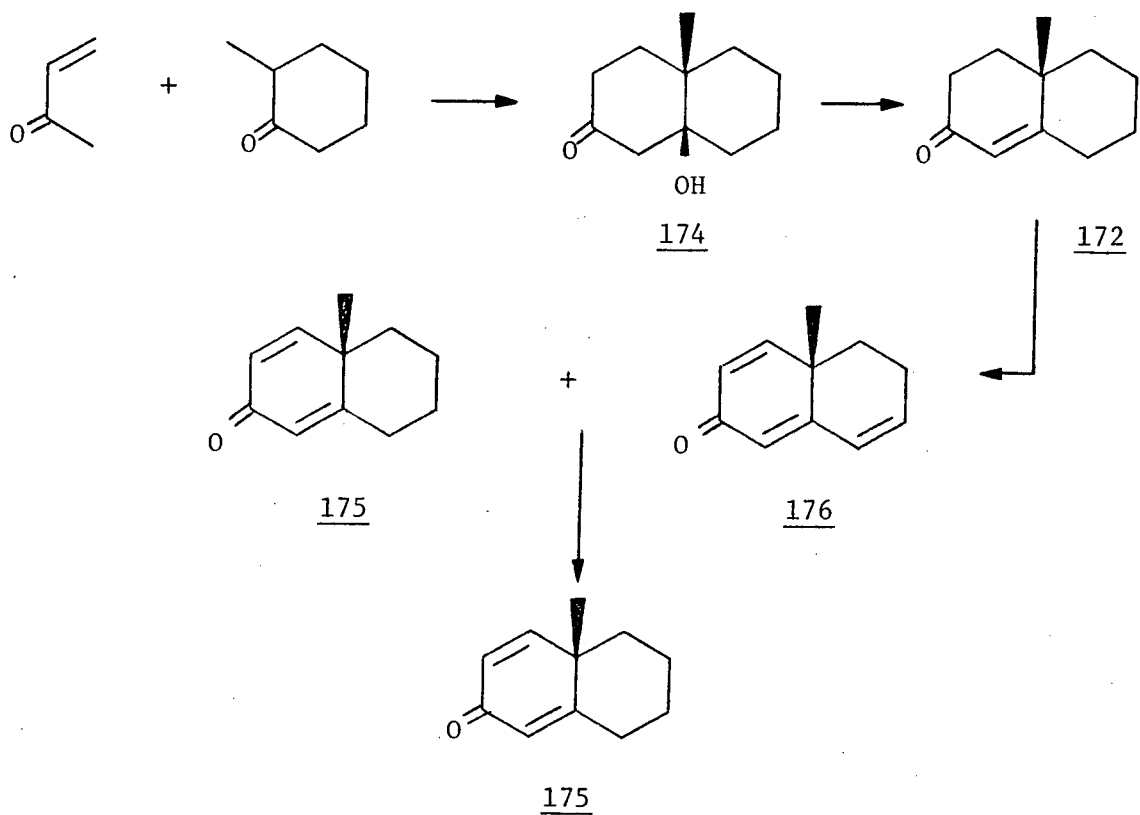
It is obvious that in dienones of type 171, R_1 can not be hydrogen. Furthermore syntheses of octalones of type 170 with $R_1 = H$ generally are ambiguous with respect to the relative stereochemistry at C_4 and C_{10} . For these reasons a methyl group was chosen as the C_{10} bridgehead substituent in contrast to the hydrogen substituent present in the compound originally studied, octalone 155b.

The starting materials which were chosen for the synthesis of octalones of type 170 were the two well-known octalones 172 and 173 (see Chart XVII). These octalones were prepared by the literature procedure of Marshall and Fanta (82). Thus, condensation of 2-methylcyclohexanone with methyl vinyl ketone at -10° in the presence of a catalytic amount of sodium ethoxide afforded the cis-ketol 174. The latter was subjected to potassium hydroxide-catalyzed dehydration to afford, in 48% yield, 10-methyl- $\Delta^{1,9}$ -2-octalone (172). Similarly, condensation of 2-methylcyclohexanone with ethyl vinyl ketone, followed by base-catalyzed dehydration of the intermediate ketol afforded, in 60% yield, 1,10-dimethyl- $\Delta^{1,9}$ -2-octalone (173) (83).

Treatment of octalone 172 with DDQ (84) in the presence of benzoic acid in refluxing anhydrous benzene for 48 h afforded a mixture of the desired cross-conjugated dienone 175 plus trienone 176, in a ratio of 88:12 respectively. Hydrogenation of this mixture (175 + 176) under carefully controlled basic conditions in the presence of a catalytic amount of palladium on charcoal afforded, in 70% yield (from octalone 172), cross-conjugated dienone 175 (85).

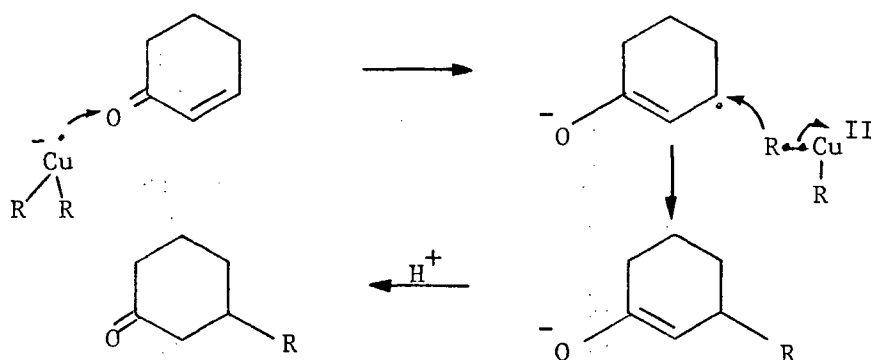
Dehydrogenation of octalone 173 with DDQ in the presence of glacial acetic acid in refluxing anhydrous benzene for 60 h afforded, in 84% yield, the corresponding cross-conjugated dienone 177 (57). The

Chart XVII



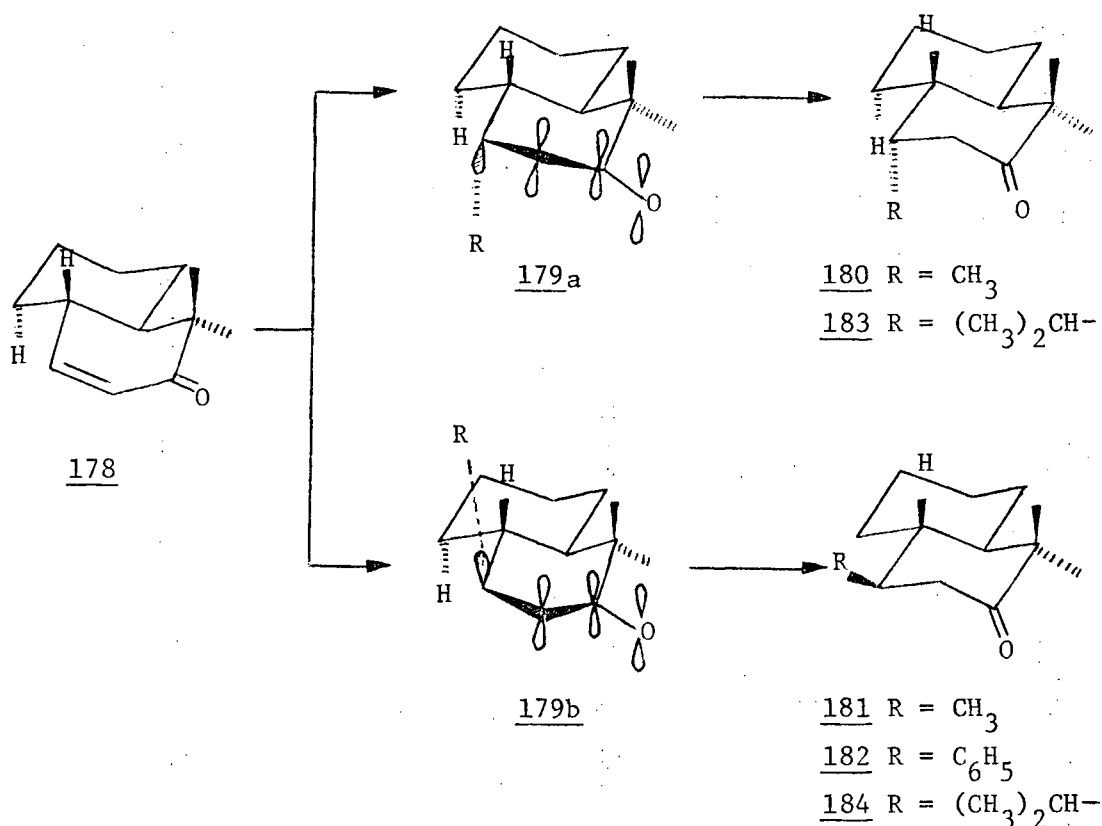
spectral data of dienone 177 fully corroborated the structural assignment. In particular the infrared spectrum exhibited absorptions at 6.01, 6.12 and 6.21 μ . The n.m.r. spectrum of 177 displayed a typical AB pair of doublets at τ 3.80 and τ 3.31 ($J = 10$ Hz) due to the C_3 and C_4 olefinic protons. Other assignable signals in the n.m.r. spectrum appeared at τ 8.78 (singlet, tertiary methyl) and at τ 8.12 (singlet, vinyl methyl). The ultraviolet spectrum exhibited a maximum at 240 $m\mu$.

It was next planned to investigate the 1,4-conjugate additions of the appropriate lithium dialkylcuprate reagents to the now readily available cross-conjugated dienones 175 and 177. Since the conjugate addition of lithium dialkylcuprate reagents is crucial to the remaining synthesis, it would be advantageous to digress to consider the nature of the pathway of 1,4-conjugate additions of cuprate reagents to enone systems. The proposed mechanism (65,67,86) for 1,4-conjugate addition of lithium dialkylcuprate reagents is as follows:



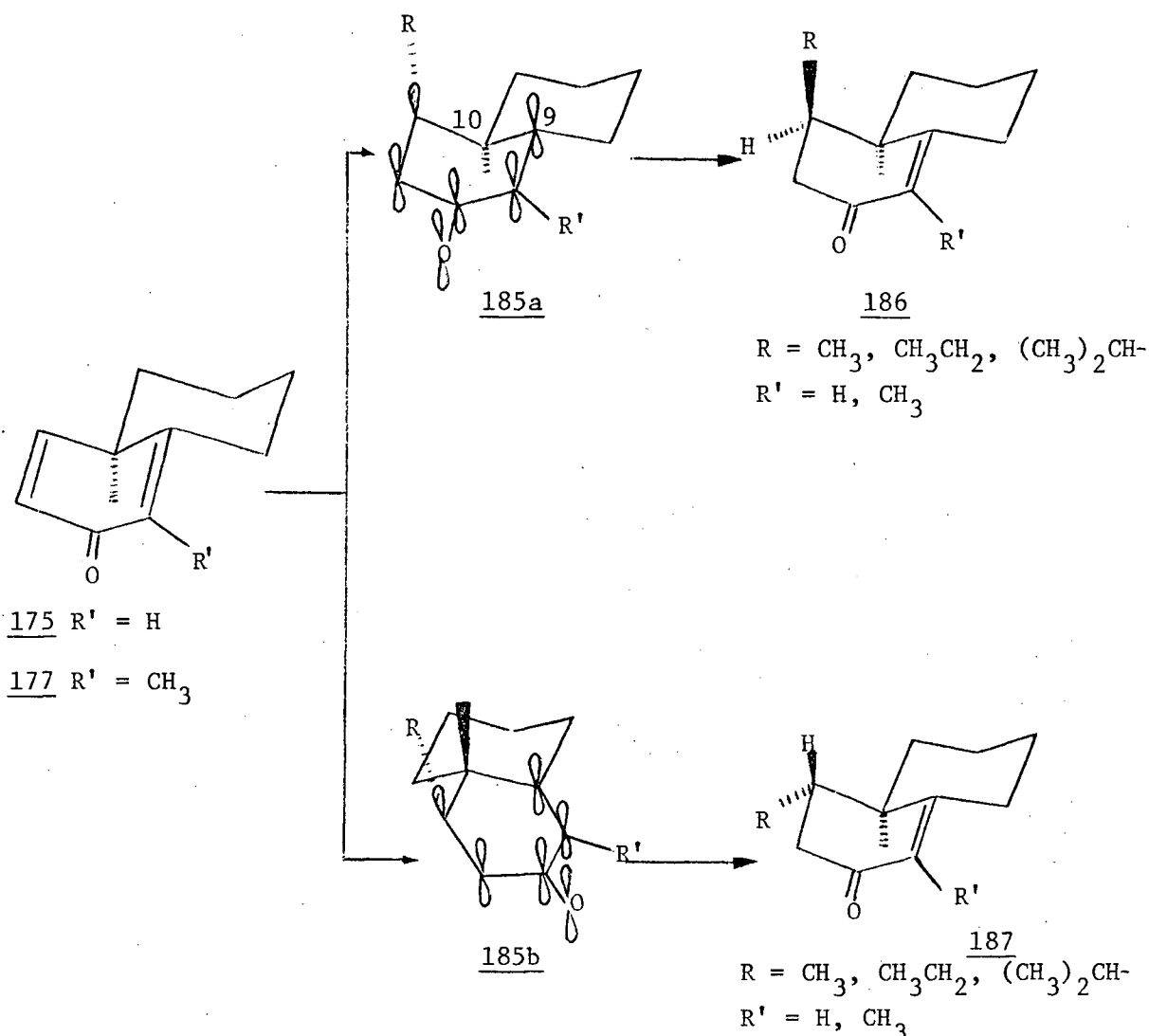
While extrapolations of the stereochemical results obtained in cuprous ion catalyzed 1,4-conjugate addition of Grignard reagents to enone systems, to the product stereochemistry of the analogous lithium

dialkylcuprate reactions must be done with caution, there are many analogies in the literature where conjugate alkylation by a copper salt catalyzed Grignard reagent and the analogous cuprate reagent proceed to yield products with the same stereochemistry. With this precaution in mind, it is pertinent to discuss the elegant work of Marshall and Andersen (87) who studied the cuprous ion catalyzed conjugate addition of several Grignard reagents to 1,1-dimethyl-trans-3-octal-2-one (178). Briefly, these workers proposed that the conjugate addition of an alkyl group, by means of cuprous ion catalyzed Grignard reagents, to an octalone of type 178 must, for stereoelectronic reasons, take place via the chair-like transition state 179a and/or the boat-like transition state 179b. Marshall and Andersen's experiments showed that, in the



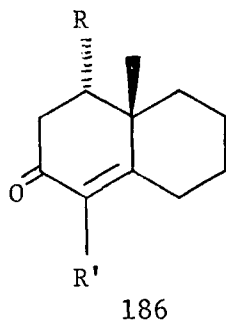
absence of large steric factors the former transition state 179a was favored over the latter transition state 179b. Hence, the addition of methylmagnesium iodide to octalone 178 produced decalone 180 as the major conjugate addition product, while decalone 181 was formed in minor amounts. However, as the bulk of the Grignard reagent was increased, steric hindrance to axial attack via transition state 179a also increased. When phenylmagnesium bromide was employed as the Grignard reagent the only product formed was 182 (attack via transition state 179b). Finally, in the case of isopropylmagnesium bromide steric hindrance to axial approach intrinsic in transition state 179a was approximately balanced by the unfavorable nature of the boat-like transition state 179b. Consequently the two products 183 and 184 were formed in approximately equal amounts.

If one now considers the conjugate addition of lithium dialkylcuprate reagents to dienones 175 and 177, by analogy with the above principles transition states 185a and 185b can be proposed. It is immediately obvious that the important factors in these transition states 185a and 185b are the presence of the angular methyl group at C₁₀ and the absence of the C₉ hydrogen (removing one syn-axial R-H interaction in transition state 185a).



Molecular models indicate that if stereoelectronic control is to be maintained in transition state 185b, then the incoming alkyl group must approach the molecule in such a way that it is nearly eclipsed with the C_{10} angular methyl group. The resulting steric and torsional strain (88,89) should be the dominant factor and should ensure that transition state 185a is favored over transition state 185b. Hence, it was fully expected that the introduction of an alkyl group in the lithium dialkylcuprate conjugate addition reactions would be highly

stereoselective and furthermore it was predicted that the product should contain the stereochemistry depicted in 186 . In all cases studied



the lithium dialkylcuprate additions were highly stereoselective as analysis by a combination of g.l.c. and spectral methods of the reaction product revealed the presence of only one of the two possible epimeric compounds.

It should be noted that in the previously discussed systematic study of conjugate additions of lithium dialkylcuprate reagents to cross-conjugated dienone systems several important experimental requirements were worked out. It should be pointed out that House and coworkers (65,67) had done a detailed study of the properties of lithium dimethylcuprate but at the time this work was underway no analogous information was available for lithium divinyl- or lithium diisopropylcuprate. Initially a procedure analogous to that used by House et al. (65) for the preparation of lithium dimethylcuprate was employed in the preparation of lithium divinyl- or lithium diisopropylcuprate. Thus, two equivalents of the alkylolithium reagent were added to one equivalent of cuprous iodide in ether at 0°. It was found that addition of cross-conjugated dienones of type 171 to solutions of lithium divinylcuprate or lithium diisopropylcuprate, prepared in the

above manner gave rise to only poor yields of conjugate addition products in the former case and only recovered starting material or polymeric material in the latter case. In an attempt to enhance the reactivity to 1,4-conjugate addition of lithium diisopropylcuprate solutions, reactions were tried in the presence of various additives. Indeed fair yields of conjugate addition products could be realized if anhydrous lithium bromide was present in the reaction mixture.

Repetition of the reactions at various temperatures revealed that better yields of conjugate addition products were obtained if these reactions were run at -78° . However, yields obtained in these reactions were only moderate when compared with the yields obtained in the analogous lithium dimethylcuprate reactions (62).

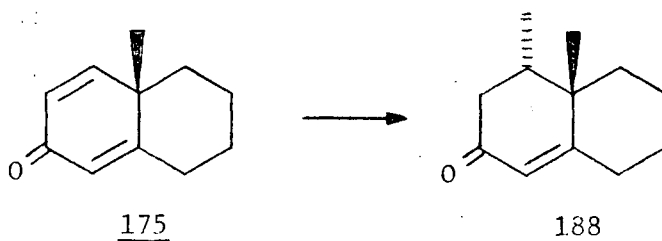
Hence, another method of preparing the cuprate reagents was investigated. In this approach the ether-soluble copper (I) iodide-tri-*n*-butylphosphine complex prepared by the method of Kaufman et al. (90) was employed instead of cuprous iodide. The resulting organocopper I solutions were homogeneous in contrast to the colloidal appearance of those previously prepared. Lithium diisopropylcuprate prepared with the phosphine complex again required the addition of anhydrous lithium bromide before 1,4-conjugate addition to cross-conjugated dienones would occur. While use of the phosphine complex in preparation of these reagents gave rise to better yields of 1,4-conjugate addition products it also complicated the isolation procedures. It was found that fractional distillations of the crude reaction mixtures, followed by chromatography of the low boiling fractions on silica gel allowed isolation of the desired product. This purification procedure was

used in all the following reactions employing lithium divinylcuprate and lithium diisopropylcuprate.

In an attempt to optimize the yields of conjugate addition products, the variable parameters of reaction time, temperature, concentration, and quenching procedures were next investigated. Again it was found that use of low temperatures (-78°) improved the yields.

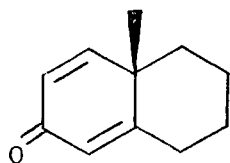
Yields obtained upon varying the reaction time from 4 h to 36 h appeared to be invariant although use of reaction times shorter than 4 h generally resulted in some recovered starting material. The reactions were quenched by dropwise addition of the reaction mixture to a rapidly stirred solution of aqueous acid. The product yields were found to be substantially lower if this quenching procedure was not employed. After attempting the additions under a variety of concentrations it was found that optimum yields were obtained when the solution was between 0.01 and 0.005 molar in the organocopper I reagent.

The lithium dialkylcuprate conjugate addition reactions were next attempted employing the optimum conditions listed above. Thus, an ethereal solution of dienone 175 was added to a solution of lithium dimethylcuprate and stirred at 0° for 2 h. After the appropriate workup the crude product was purified by distillation, followed by chromatography of the distillate on silica gel, to afford, in 82% yield, octalone 188. That the desired transformation had taken place was shown clearly

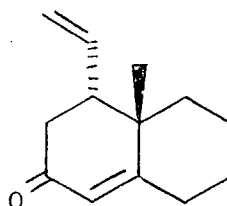


by the spectral data of compound 188 (91). In particular the infrared spectrum of octalone 188 showed a carbonyl absorption at $6.0\ \mu$ and a carbon-carbon double bond absorption at $6.15\ \mu$. The n.m.r. spectrum of 188 exhibited a three-proton doublet at $\tau\ 9.02$ ($J = 7\ \text{Hz}$) attributable to the newly introduced methyl group, a three-proton singlet at $\tau\ 8.74$ due to the tertiary methyl group and a one-proton singlet at $\tau\ 4.30$ due to the C_1 vinyl hydrogen. There were no signals due to the C_3 and C_4 olefinic protons present in the starting material. The ultraviolet spectrum of 188 exhibited a maximum at $239\ \text{m}\mu$.

Treatment of dienone 175 with lithium divinylcuprate for 4 h at -78° , followed by appropriate workup and purification, afforded octalone 194 in 73% yield. That the vinyl group had been introduced at the C_4



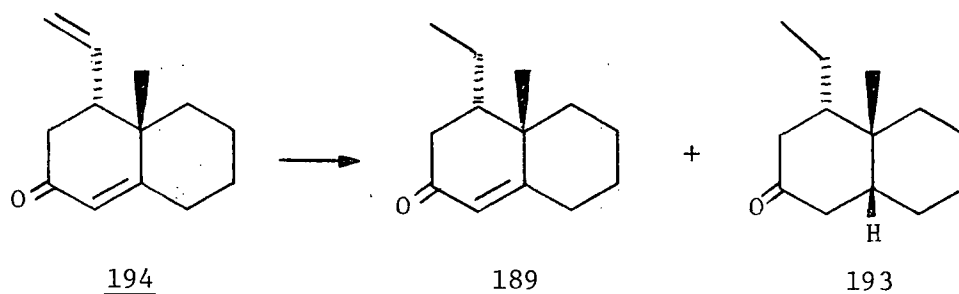
175



194

position of dienone 175 was clearly shown by the spectral data of the product. The n.m.r. spectrum of 194 displayed signals due to the vinyl group as an unresolved multiplet ($\tau\ 3.89-5.13$), a signal due to the tertiary methyl group as a three-proton singlet at $\tau\ 8.72$ and a signal due to the vinyl proton at C-1 as a one-proton singlet at $\tau\ 4.25$. The infrared spectrum of 194 exhibited absorptions at $6.0\ \mu$ and $10.9\ \mu$ due to the α,β -unsaturated carbonyl group and the vinyl group respectively. Octalone 194 proved to be quite unstable and hence the vinyl group was

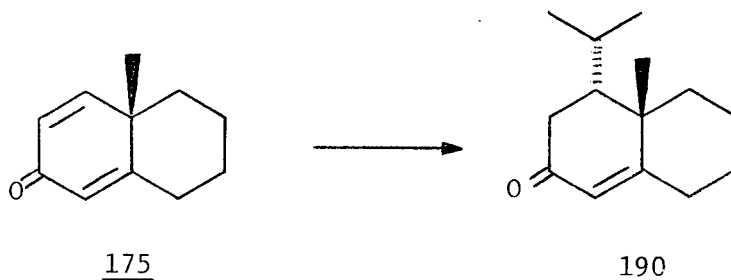
immediately transformed to the desired ethyl group. Since it was feared that standard hydrogenation procedures might result in considerable reduction of the endocyclic double bond tris (triphenylphosphine) chlororhodium (92), a selective catalyst for hydrogenation of unhindered double bonds, was employed. Hydrogenation of octalone 194 at atmospheric pressure and room temperature, employing the above catalyst afforded as the major product octalone 189, with a minor amount of the fully saturated cis-decalone 193 also being formed. The minor component was



readily separated from the octalone by chromatography on silica gel. The fact that the simple hydrogenation had indeed taken place was shown by the spectral data of octalone 189. In particular, the infrared spectrum while still exhibiting an absorption at $6.0\ \mu$ for the α,β -unsaturated carbonyl, no longer exhibited an absorption at $10.9\ \mu$ for the vinyl group. Octalone 189 exhibited a maximum in the ultraviolet spectrum at $239\ m\mu$. The n.m.r. spectrum of octalone 189 no longer exhibited the complex signals for the protons of the vinyl group but exhibited a three-proton triplet at $\tau\ 9.07$ ($J = 6.5\ \text{Hz}$) for the primary methyl group, a three-proton singlet at $\tau\ 8.75$ for the tertiary methyl group and a one-proton singlet at $\tau\ 4.21$ for the C_1 olefinic proton. The spectral data for the cis-fused decalone 193 will be

discussed later.

Treatment of dienone 175 with lithium diisopropylcuprate for 5.75 h at -78° , followed by the appropriate workup and purification afforded octalone 190 in 95% yield. The fact that the addition of an



isopropyl group to C_4 of dienone 175 had indeed taken place was shown by the spectral data of octalone 190. The ultraviolet spectrum exhibited a maximum at 240 m μ . The infrared spectrum exhibited sharp absorptions at 6.0 μ (carbonyl) and at 6.16 μ (carbon-carbon double bond). The n.m.r. spectrum of octalone 190 (see Figure 10) displayed two three-proton doublets at τ 9.20 and τ 9.05 ($J = 6.5$ Hz), due to the newly introduced secondary methyl groups, a three-proton singlet at τ 8.74, due to the tertiary methyl group and a one-proton singlet at τ 4.22, due to the C_1 olefinic hydrogen.

The synthesis of the desired octalones was then continued by 1,4-conjugate additions of organocopper (I) reagents to the dimethyl dienone 177. Hence, treatment of dienone 177 with lithium dimethylcuprate for 1 h at 0° , followed by quenching with dilute hydrochloric acid, afforded octalone 191 in 92% yield. An analytical sample of octalone 191 exhibited the expected spectral properties. In the infrared spectrum of 191 two sharp absorptions appeared at 6.0 and 6.2 μ due to the carbonyl group and the carbon-carbon double bond.

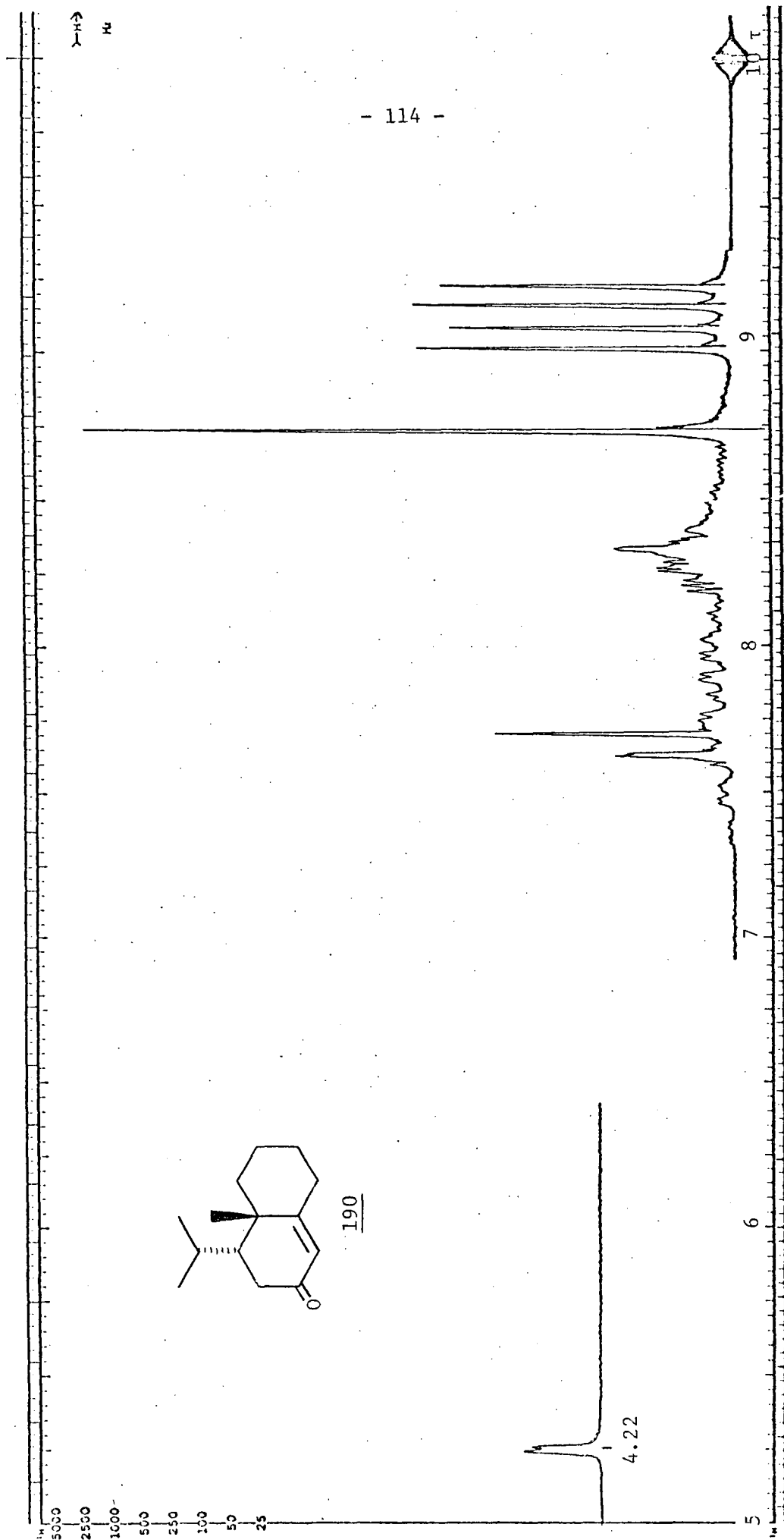
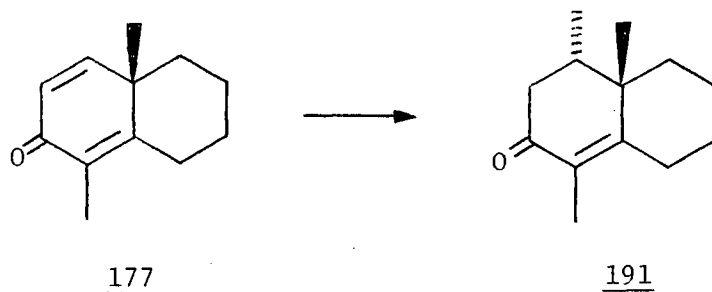
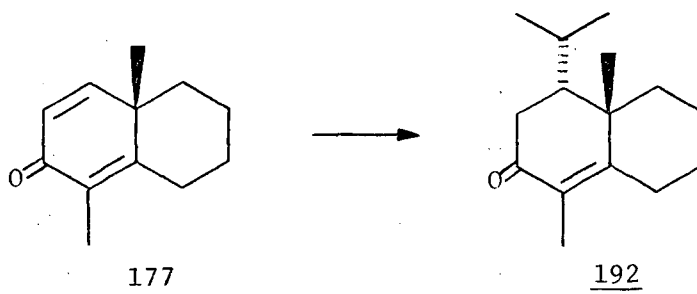


Figure 10. N.M.R. Spectrum of Octalone 190.



respectively. The n.m.r. spectrum of 191 exhibited signals at τ 9.04 as a three-proton doublet ($J = 6.5$ Hz) due to the newly introduced secondary methyl group. Other assignable signals in the n.m.r. spectrum appeared at τ 8.74 and τ 8.25 as two three-proton singlets attributable to the tertiary methyl group and the vinyl methyl group respectively. Octalone 191 exhibited a maximum at 249 m μ in the ultraviolet spectrum.

Treatment of dienone 177 with excess lithium diisopropylcuprate at -78° afforded, after purification, octalone 192 in 95% yield.



The conjugate addition product gave an ultraviolet maximum at 249 m μ , and a strong carbonyl absorption at 6.0 μ and carbon-carbon double bond absorption at 6.2 μ in the infrared. The n.m.r. spectrum of 192 (see Figure 11) showed two three-proton doublets at τ 9.23 and τ 9.04

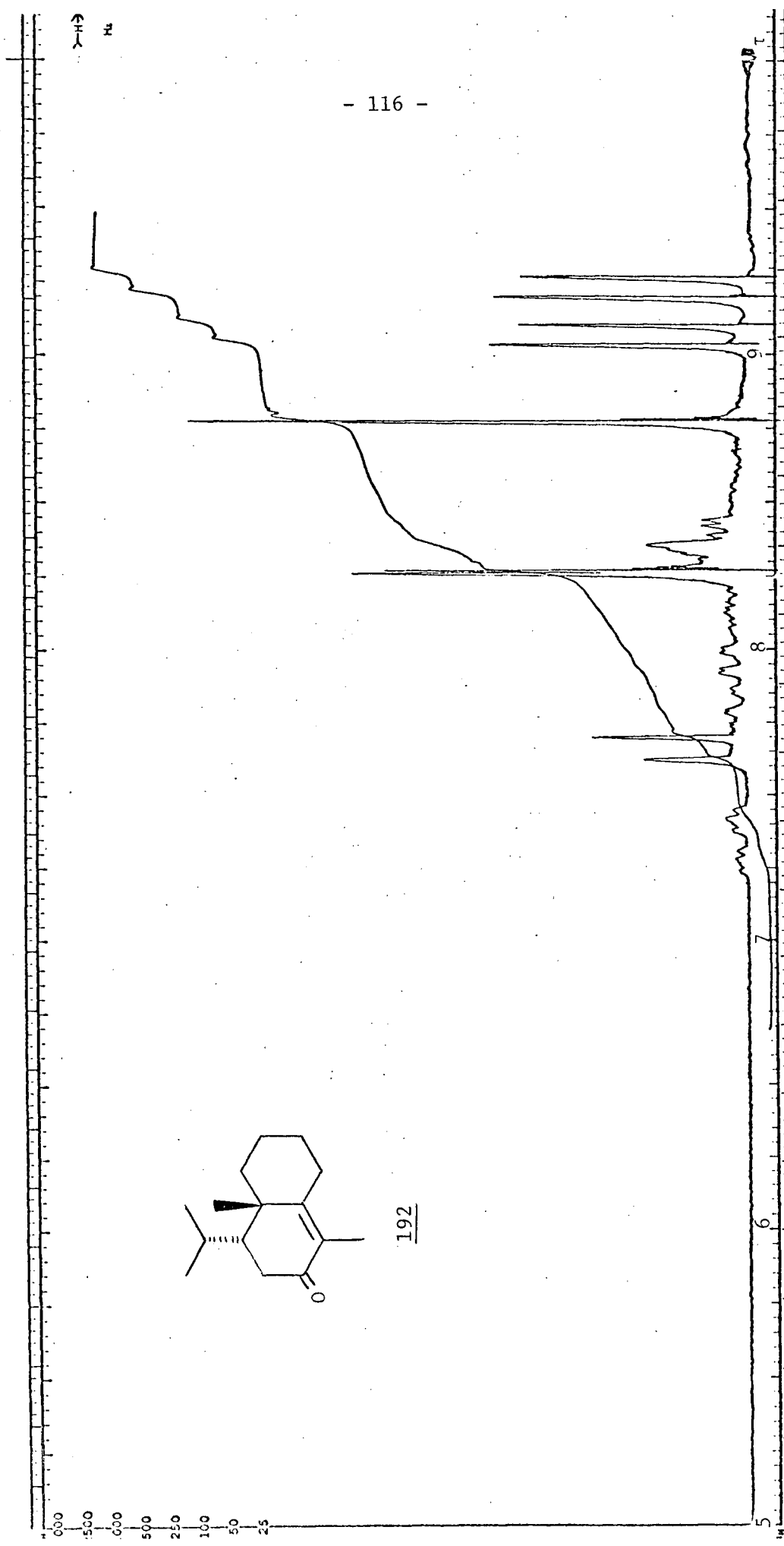
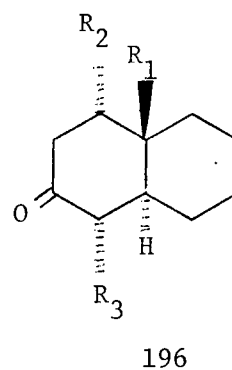
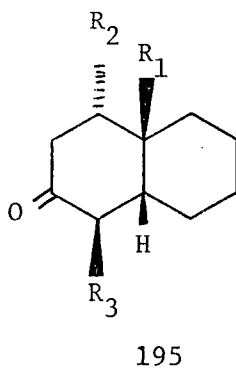
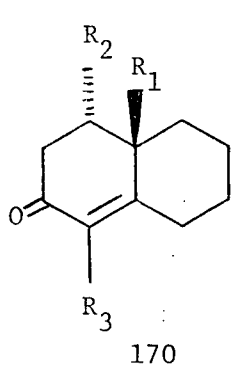


Figure 11. N.M.R. Spectrum of Octalone 192.

($J = 7$ Hz) for the isopropyl methyl groups, a three-proton singlet at τ 8.73 for the tertiary methyl group and a three-proton singlet at τ 8.22 for the vinyl methyl group.

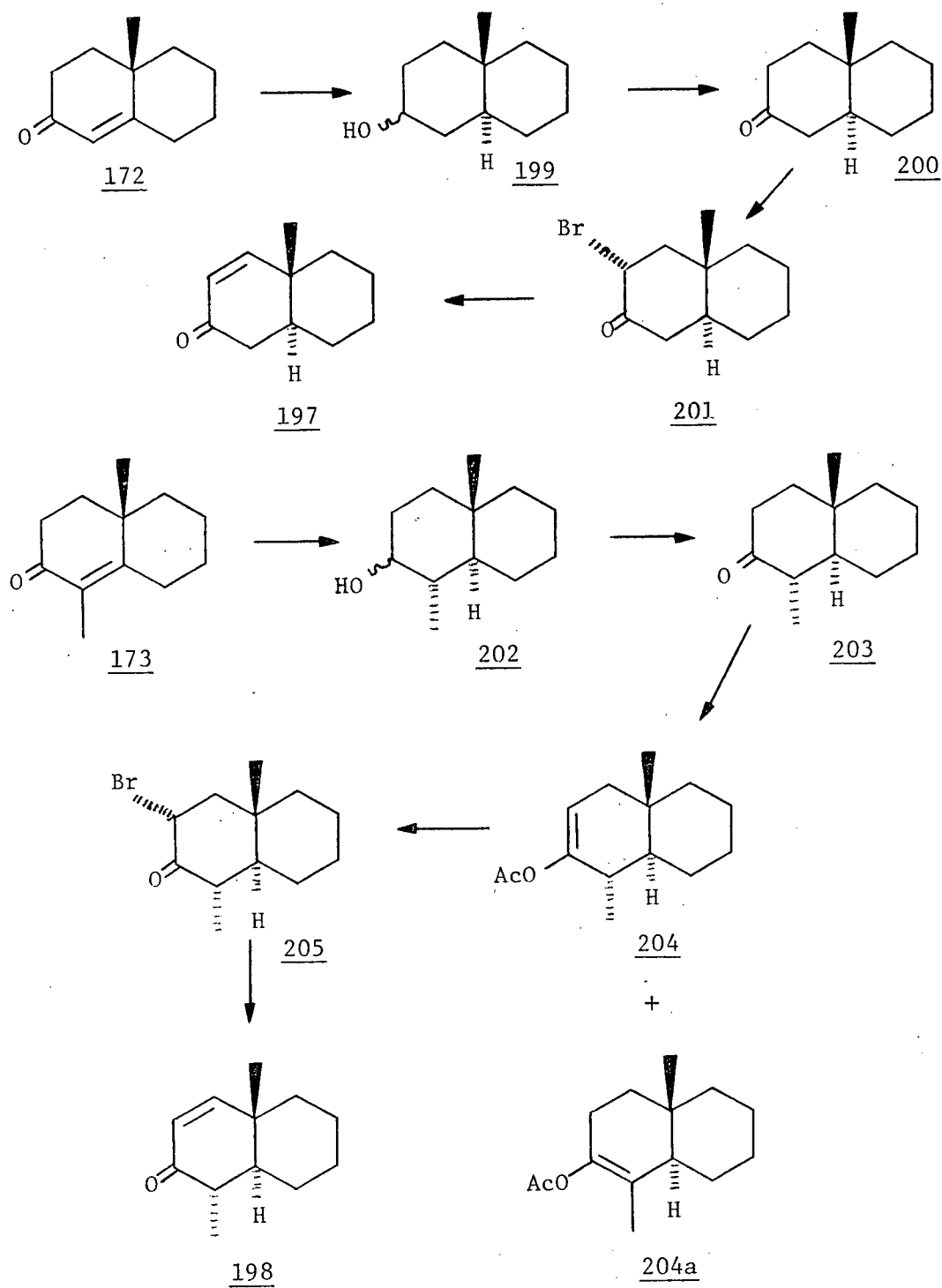
C. Synthesis of *trans*-Fused Decalones

Having realized efficient synthesis of the desired octalones of type 170, it was next planned to unambiguously synthesize the corresponding *cis*- and *trans*-fused decalones of type 195 and 196 respectively. These decalones would then serve as authentic samples for direct comparison with the products expected from the Birch reduction of octalones 188 to 192.



The key intermediates in the proposed syntheses of the *trans*-fused decalones of type 196 were envisaged as octalones 197 and 198 (see Chart XVIII). It was proposed that these octalones could be readily elaborated to the desired *trans*-fused decalones of type 196 by 1,4-conjugate addition of the appropriate organocopper (I) species to the α,β -unsaturated carbonyl system. Using the same reasoning as before (see p. 107) the alkyl group would be expected to be introduced *trans* to the angular methyl group to give the stereochemistry depicted in structure 196.

Chart XVIII



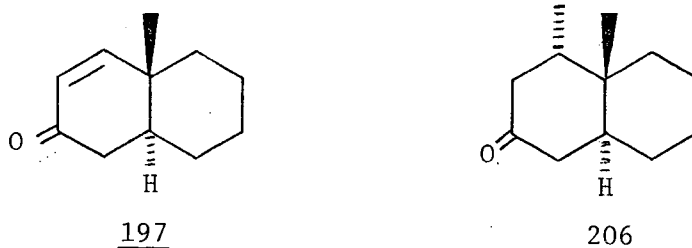
The starting materials chosen for the synthesis of octalones 197 and 198 were the previously discussed octalones 172 and 173. It is well documented (45,46,48) that lithium-ammonia reductions of simple octalones such as 172 and 173 stereoselectively yield the trans-fused decalones as products, with less than 2% of the corresponding cis isomer being detected. Thus, lithium-ammonia reduction of octalone 172 with ethanol (93) as co-solvent and proton source, followed by Jones oxidation (76) of the resulting mixture of alcohols 199, gave, in 62% yield, the known decalone 200 (93,94). Treatment of the latter with bromine in glacial acetic acid afforded, after recrystallization, a 60% yield of bromo-ketone 201 (93). Dehydrohalogenation of bromoketone 201 with anhydrous lithium bromide in hot hexamethylphosphoramide, afforded, in a 76% yield, the desired octalone 197 (95).

Similarly lithium-ammonia reduction of octalone 173 in the presence of ethanol, followed by Jones oxidation (76) of the resulting alcohols 202, afforded in 70% yield decalone 203 (84). As expected this decalone exhibited a strong carbonyl absorption at 5.85μ in the infrared. Direct bromination of decalone 203 by a procedure similar to that described above afforded an inseparable mixture of the two possible mono-bromoketones. In an attempt to circumvent this difficulty decalone 203 was treated with isopropenyl acetate in the presence of a catalytic amount of concentrated sulphuric acid to afford a mixture of enol acetates 204 and 204a in the ratio of 85:15 respectively. The crude enol acetates were purified by chromatography on Activity III neutral alumina. The purified material exhibited the expected spectral properties. In particular, the infrared spectrum exhibited absorptions

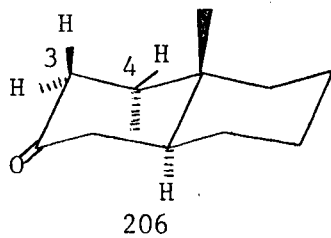
at 5.7 and 5.95 μ due to the acetate carbonyl and the carbon-carbon double bond respectively. Treatment of a mixture of enol acetates 204 and 204a with a sodium acetate buffered solution of bromine in glacial acetic acid for 1 h afforded, after several recrystallizations, the highly crystalline bromoketone 205 in 84% yield. This compound exhibited the expected spectral data. Of note was the carbonyl absorption in the infrared spectrum at 5.8 μ and the signals in the n.m.r. spectrum of 205 due to the proton adjacent to the bromine at τ 5.13 as the X portion of an ABX system with the observed splittings of 14 Hz and 6 Hz. Other assignable signals in the n.m.r. spectrum appeared at τ 8.99 as a three-proton doublet ($J = 6.5$ Hz) due to the secondary methyl group and at τ 8.84 as a three-proton singlet due to the tertiary methyl group. Bromoketone 205, when dehydrobrominated by treatment with a mixture of anhydrous lithium bromide in hot hexamethylphosphoramide, afforded the desired octalone 198 in 76% yield. The latter compound, which was isolated by chromatography on silica gel, exhibited a maximum at 229 $m\mu$ in the ultraviolet spectrum. The other spectral properties also corroborated the assigned structure. Of note was the appearance in the infrared spectrum of absorptions at 6.0 μ (α,β -unsaturated carbonyl) and at 6.15 μ (carbon-carbon double bond). The n.m.r. spectrum of 198 exhibited signals at τ 8.93 as a three-proton singlet for the tertiary methyl group, at τ 8.92 as a three-proton doublet ($J = 7$ Hz) for the secondary methyl group, and at τ 4.19 and τ 3.35 as two one-proton doublets ($J = 9$ Hz) for the C_3 and C_4 olefinic protons respectively.

Having achieved the synthesis of the two required intermediates 197

and 198, it was next planned to investigate the 1,4-conjugate addition reactions of the appropriate organocopper I species to these intermediates. Thus, treatment of octalone 197 with lithium dimethylcuprate at 0° for 2 h afforded, in 98% yield, the known dimethyl decalone 206 (96). It was shown by INDOR studies that the stereochemistry of this conjugate addition product was as depicted by structure 206. The



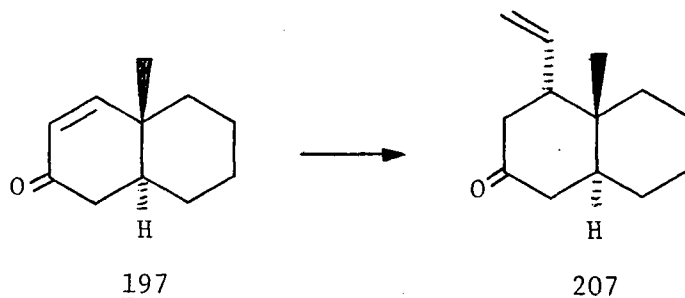
splittings that were observed for compound 206 are listed below. It should be noted that these splittings are not corrected for higher order effects but are almost certainly very close in value to the true coupling constants. Thus $J_{3a,3e} = 14.5$ Hz, $J_{3a,4e} = 6.2$ Hz, $J_{3e,4e} = 1.4$ Hz, $J_{3a,(CH_3)_{4a}} = 0.5$ Hz and $J_{4e,(CH_3)_{4a}} = 7.3$ Hz. These observed



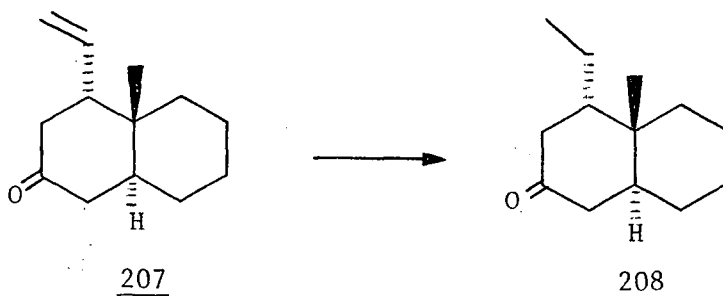
splittings are those expected for a compound possessing an axial methyl group at C₄.

Treatment of octalone 197 with lithium divinylcuprate at -78° for

4 h followed by the usual workup and purification, afforded decalone 207 in 73% yield. Compound 207 exhibited the expected spectral



properties. Of pertinence were the absorptions in the infrared spectrum at $5.85\ \mu$ (carbonyl) and $6.15, 10.9\ \mu$ (vinyl group). The n.m.r. spectrum of 207 exhibited signals due to the vinyl protons (τ 4.0-5.2) as an unresolved multiplet and a signal due to the tertiary methyl group at τ 8.88. Hydrogenation of decalone 207 in the presence of a catalytic amount of palladium on charcoal afforded, in 98% yield, the corresponding saturated decalone 208. Absence of signals in the



infrared and n.m.r. spectra due to the vinyl group confirmed that the expected transformation had taken place.

Treatment of octalone 197 with lithium diisopropylcuprate at -78° for 4 h afforded, in 72% yield, the crystalline decalone 209.



210



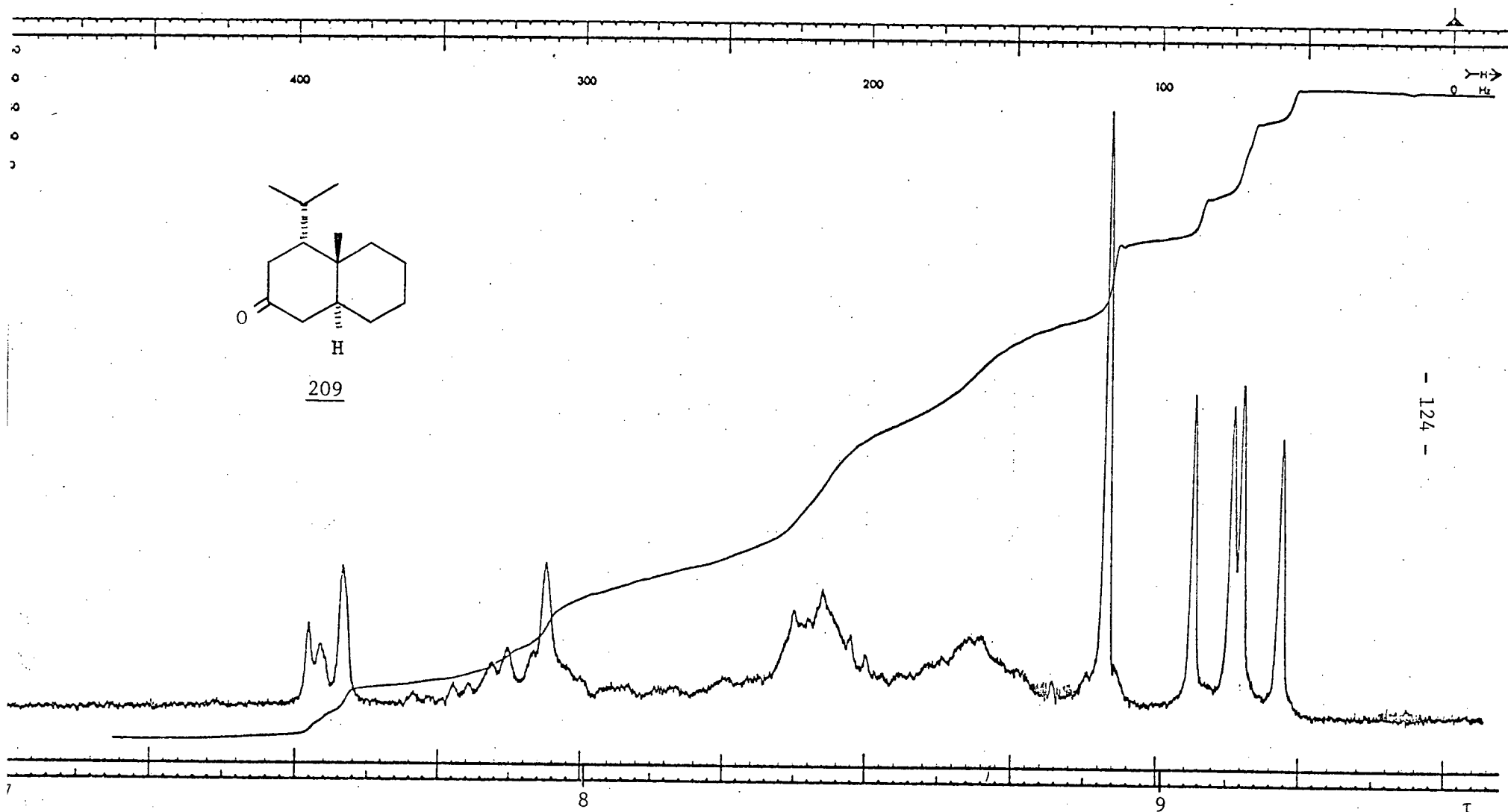
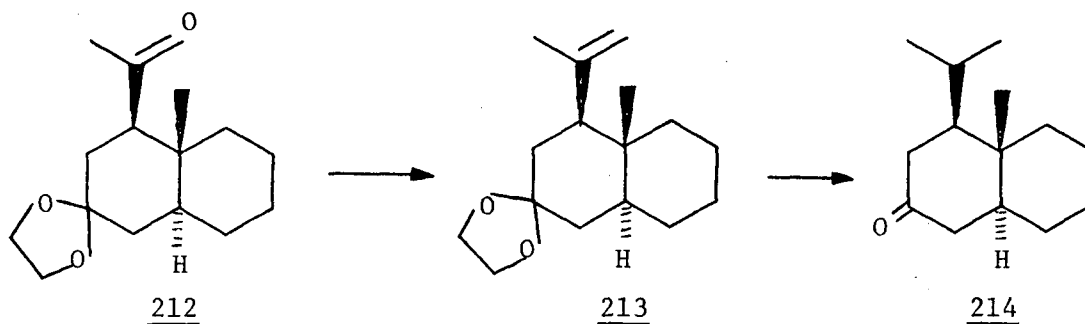
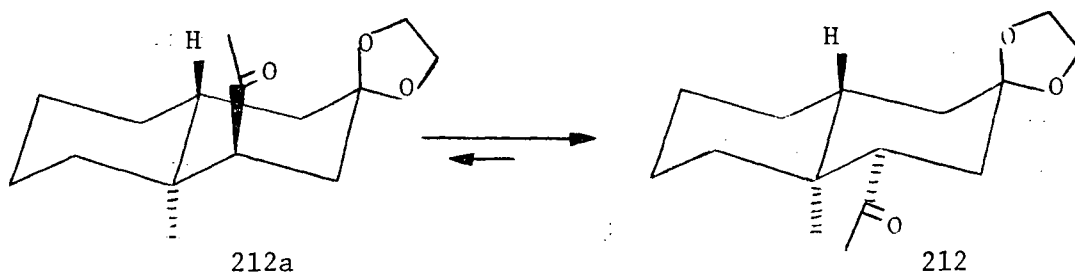


Figure 12. N.M.R. Spectrum of trans-Fused Decalone 209.



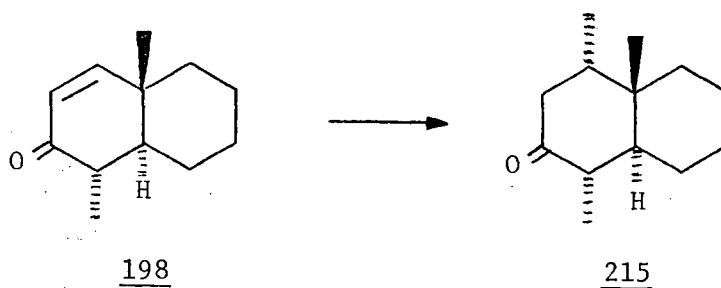
Briefly, decalone 210 (formed by cuprous ion catalyzed 1,4-conjugate addition of isopropenylmagnesium bromide to octalone 197) was hydrogenated to afford decalone 209. Ketalization of decalone 210, followed by ozonolysis of the isopropenyl double bond and chromatography (alumina) of the resulting product, afforded a mixture of dione 211 and keto ketal 212. The latter compound remained unchanged when subjected to epimerization conditions. From examination of molecular models of 212 and 212a the more stable epimer and hence the one expected to predominate after epimerization was predicted to be 212. This



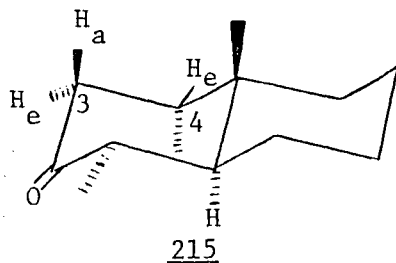
prediction was based on the relief of the 1,3-diaxial interaction between the acetyl group and the axial oxygen of the ketal group in going from compound 212a to the equatorial epimer 212. Reaction of 212 with methylenetriphenylphosphorane, followed by successive hydrolysis and

hydrogenation of the resulting product 213 afforded decalone 214. The latter compound was distinctly different from decalone 209. The stereochemistry of decalone 209 was therefore completely defined.

Treatment of octalone 198 with lithium dimethylcuprate at 0° for 2 h afforded, in 93% yield decalone 215. The spectral properties of the latter, were in complete accord with the assigned structure and stereochemistry. Of note was the appearance in the infrared spectrum

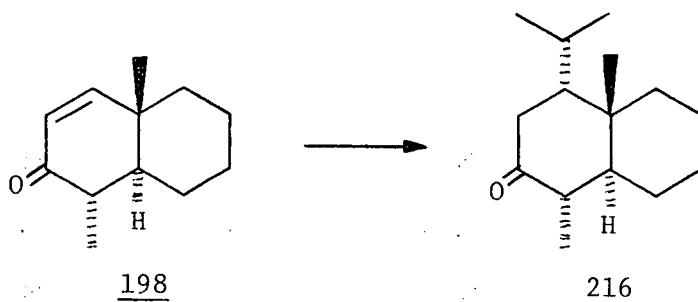


of 215 of a strong carbonyl absorption at 5.87 μ . The n.m.r. spectrum of 215 exhibited signals at τ 9.18 and τ 9.12 as two three-proton doublets ($J = 6.5$ Hz) due to the secondary methyl groups, at τ 8.89 as a three-proton singlet due to the tertiary methyl group, and at τ 7.97 and τ 7.21 as two one-proton doublet of doublets due to the C₃ equatorial and C₃ axial protons respectively ($J_{3a,3e} = 14$ Hz). The coupling constants confirm the assigned stereochemistry. The C₃ equatorial proton



coupled with the C₄ equatorial proton with a coupling constant of 2.2 Hz, while the C₃ axial proton coupled with the C₄ equatorial proton with a coupling constant of 6 Hz. These coupling constants together with the absence of a large diaxial coupling constant ($J \approx 14$ Hz) confirmed the axial orientation of the newly introduced methyl group at C₄.

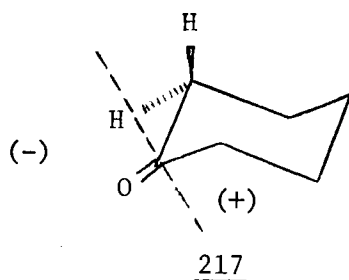
Treatment of octalone 198 with lithium diisopropylcuprate at -78° for 4 h afforded, in 84% yield, the trans-fused decalone 216. The



spectral data of the latter compound confirmed the assigned structure and stereochemistry. Of particular importance was the absorption at 5.85μ in the infrared spectrum due to the saturated carbonyl and signals in the n.m.r. spectrum at τ 9.21, and τ 9.09 as two three-proton doublets ($J = 6.5$ Hz) due to the isopropyl methyl groups, at τ 9.00 as a three-proton doublet ($J = 6$ Hz) due to the C₁ secondary methyl group and at τ 8.87 as a three-proton singlet due to the tertiary methyl group.

A well-known technique used in n.m.r. spectroscopy to separate otherwise indistinguishable signals is solvent-induced chemical shifts (99,100). Connolly and McCrindle (101) have proposed an empirical rule to predict the effect of solvent change on the chemical shift of the protons adjacent to the carbonyl group in cyclic ketones. This

rule stated that when a plane is drawn through the carbonyl carbon at right angles to the bonds, the protons in front of the plane are shifted downfield relative to the protons behind the plane, when the n.m.r. solvent is changed from deuteriochloroform to benzene (see structure 217). Indeed, for compound 216, changing the n.m.r. solvent from



deuteriochloroform to benzene resulted in a simplification of the n.m.r. spectrum (see Figure 13) in the region τ 7.40 to τ 7.90. Application of the above rule allowed assignment of the downfield doublet of doublets at τ 7.56 to the C_3 equatorial proton and the doublet of doublets at τ 7.74 to the axial C_3 proton $J_{3a,3e} = 15.5$ Hz. The coupling constants thus obtained confirmed the assigned stereochemistry of C_4 . The coupling constant between the C_3 axial proton and the C_4 equatorial proton was 7.6 Hz while the coupling constant between the C_3 equatorial and the C_4 equatorial proton was 2.4 Hz. Both these values are predicted for compound 216 from examination of the Karplus curve (81).

D. Synthesis of cis-Fused Decalones

Having realized the efficient synthesis of the required authentic trans-fused decalones, it was next planned to unambiguously synthesize

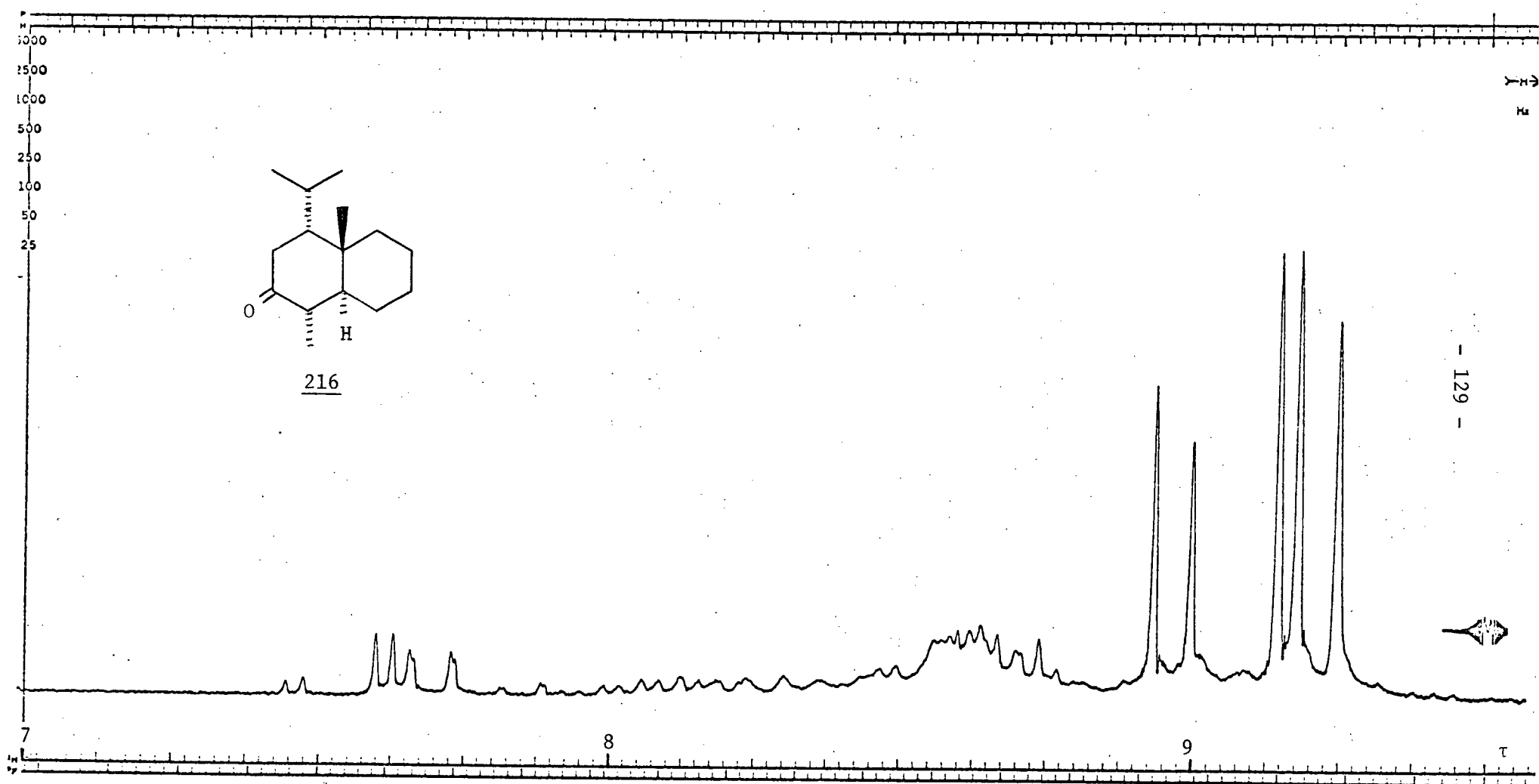
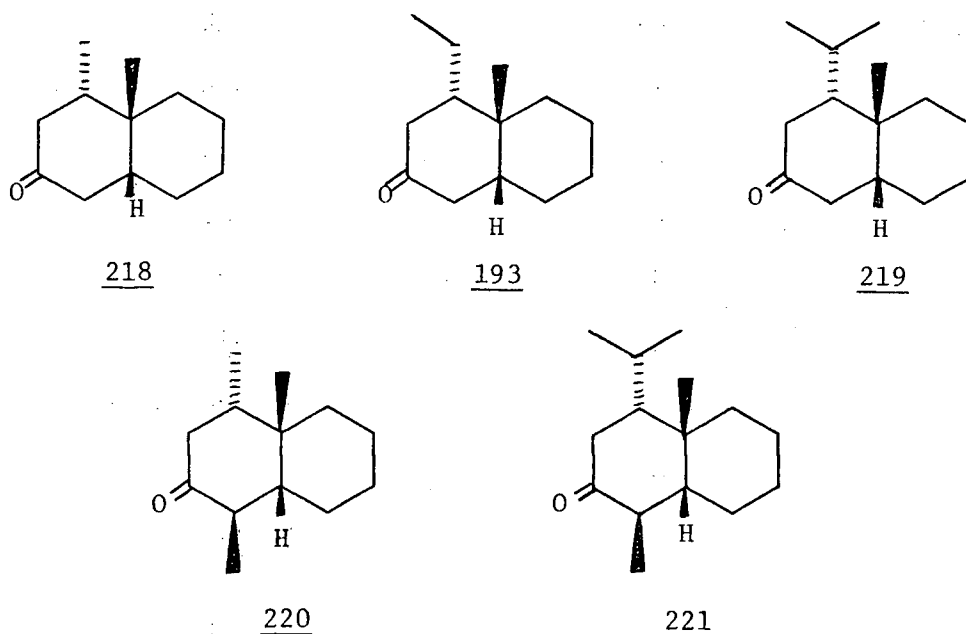


Figure 13. N.M.R. Spectrum of trans-Fused Decalone 216.

the corresponding cis-fused decalones. Lowenthal (102) demonstrated that the hydrogenation of Δ^4 -3-keto steroids and related materials in basic media produced almost exclusively the cis A/B ring-fused product. Since octalones 188 to 192 were readily available it was felt that hydrogenation under basic conditions of these octalones should furnish the required cis-fused decalones. Thus octalones 188 to 192 were hydrogenated at atmospheric pressure and room temperature in the presence of 0.3 N ethanolic potassium hydroxide to yield the corresponding cis-fused decalones shown below.



These hydrogenations all proceeded in better than 95% yield. In all cases, g.l.c. analysis of the product revealed the presence of a maximum of 6% of a minor component, which in each case, was shown by g.l.c. retention times to be the corresponding trans-fused decalone. Analytical samples of the major products, the cis-fused decalones 193, 218-221, were isolated by preparative g.l.c. The spectral data of all

these compounds were in complete accord with the proposed structures. In each case, the infrared spectrum exhibited an absorption at 5.85μ due to the saturated carbonyl group.

The n.m.r. spectrum of decalone 218 displayed a three-proton doublet at τ 9.10 ($J = 6.5$ Hz) attributable to the secondary methyl group and a three-proton singlet at τ 8.95 due to the tertiary methyl group.

The only assignable signal in the n.m.r. spectrum of decalone 193 appeared at τ 8.90 (singlet, tertiary methyl).

The n.m.r. spectrum of decalone 219 (see Figure 14) displayed signals at τ 9.19 and τ 9.10 as two three-proton doublets ($J = 6.5$ Hz) due to the secondary methyl groups and at τ 8.88 as a three-proton singlet due to the tertiary methyl group.

The n.m.r. spectrum of decalone 220 exhibited signals at τ 9.08 and τ 9.01 as two three-proton overlapping doublets ($J = 6.5$ Hz) due to the secondary methyl groups, at τ 8.92 as a three-proton singlet due to the tertiary methyl group, at τ 7.35 as a one-proton sextet due to the C_1 proton ($J_{1a, (CH_3)_{1e}} = 6$ Hz, $J_{1a, 9a} = 13$ Hz), at τ 7.85 as the B portion of an ABX system due to the C_3 equatorial proton and at τ 7.64 as the A portion of an ABX system due to the C_3 axial proton ($J_{3a, 3e} = 13$ Hz). The coupling constants derived from the multiplets at τ 7.85 and τ 7.64 allowed confirmation of the stereochemistry at C_4 . The coupling constant for the C_3 axial- C_4 axial protons was 14.4 Hz, while the coupling constant for the C_3 equatorial- C_4 axial protons was 3.6 Hz. These values corroborate the assigned stereochemistry for cis-decalone 220.

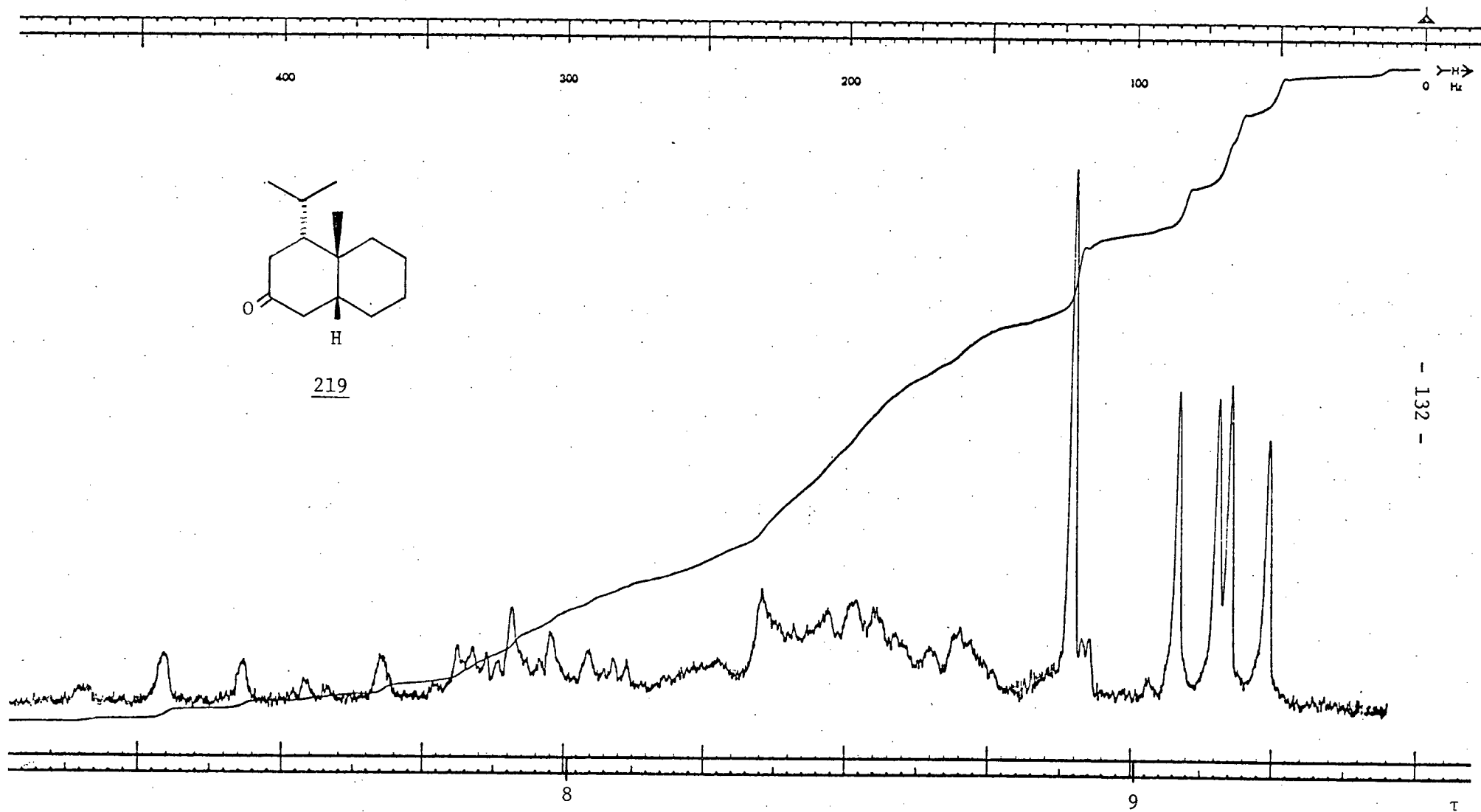
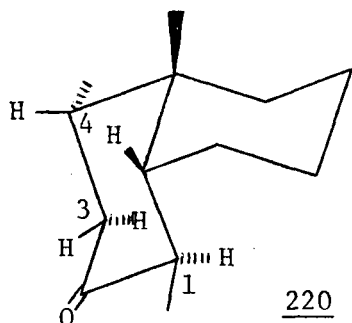
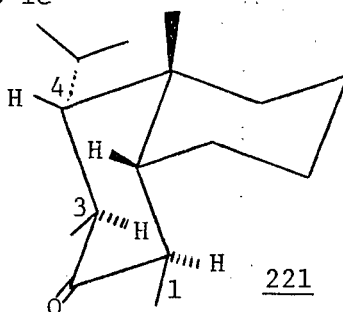


Figure 14. N.M.R. Spectrum of cis-Fused Decalone 219.



The n.m.r. spectrum for the cis-fused decalone 221 (see Figure 15) exhibited signals at τ 9.19 and τ 9.11 as two three-proton doublets ($J = 6.5$ Hz) due to the isopropyl methyl groups, at τ 9.01 as a three-proton doublet ($J = 6$ Hz) due to the C_1 secondary methyl group, at τ 8.89 as a three-proton singlet due to the tertiary methyl group, at τ 7.86 as the B portion of an ABX system due to the C_3 equatorial proton ($J_{3a,3e} = 14$ Hz, $J_{3e,4a} = 3.6$ Hz), at τ 7.63 as the A portion of an ABX system due to the C_3 axial proton ($J_{3a,4a} = 14.3$ Hz) and at τ 7.30 as a one-proton sextet due to the C_1 proton ($J_{1a,9a} = 13$ Hz, $J_{1a(CH_3)_{1e}} = 6$ Hz). The coupling constants revealed



by the signals for the axial and equatorial C_3 protons and the signals for the C_1 proton confirm that the stereochemistry is as depicted in structure 221.

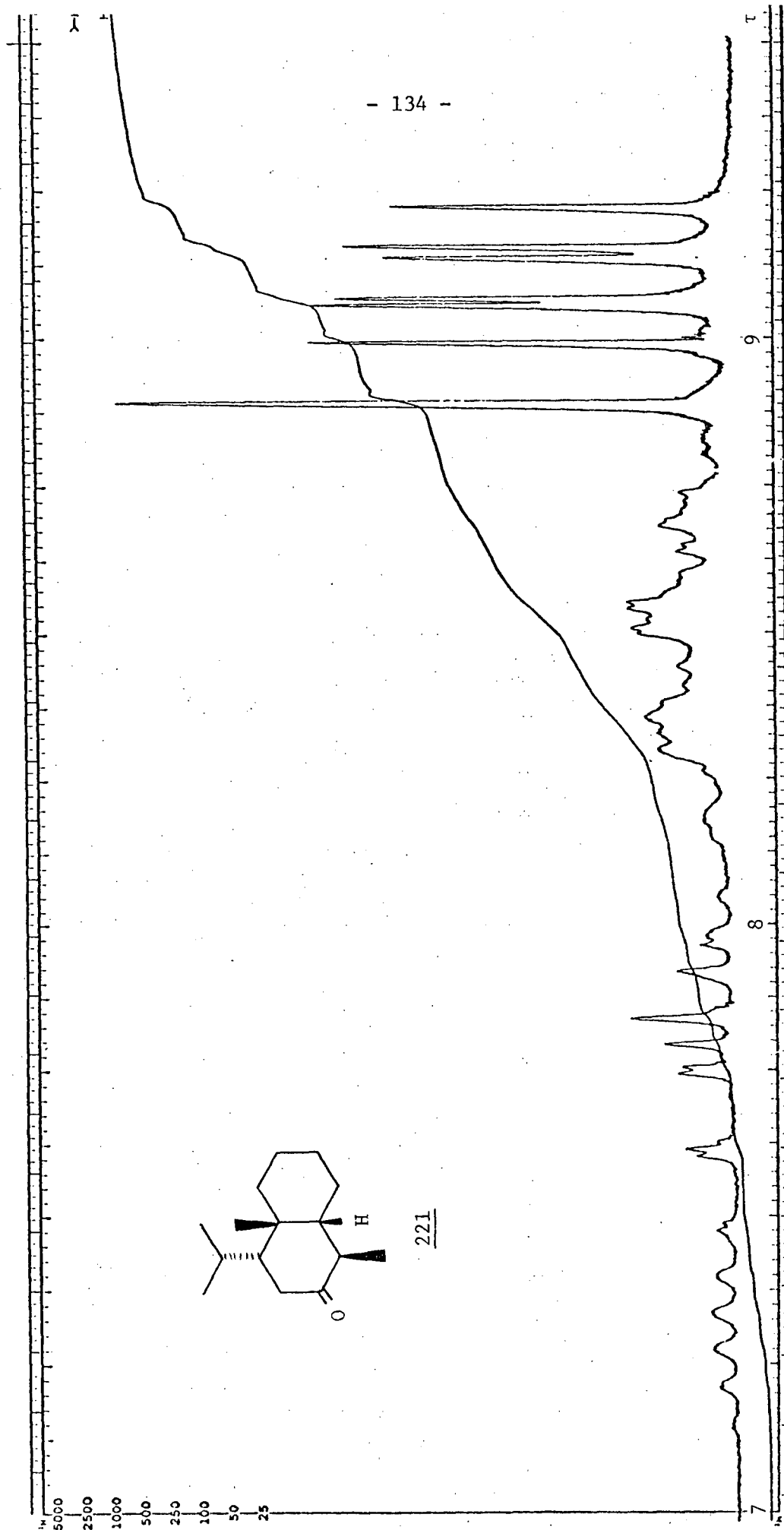
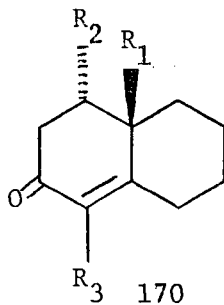


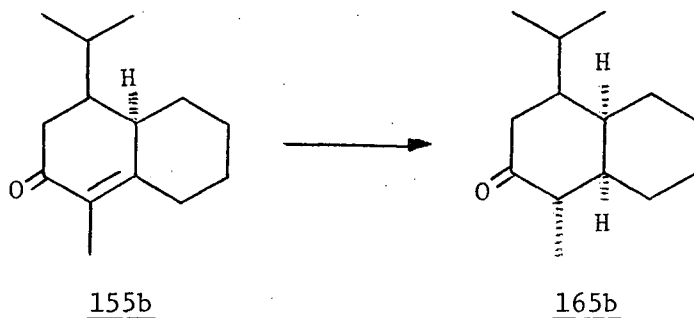
Figure 15. N.M.R. Spectrum of cis-Fused Decalone 221.

E. Lithium-Ammonia Reduction Studies

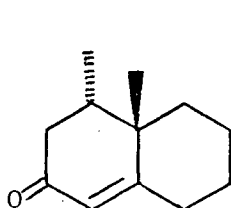
As previously discussed, a study of the lithium-liquid ammonia reactions of octalones of type 170 was undertaken because of the analogy of these compounds to octalone 155b, which under lithium-liquid ammonia reduction conditions proceeded stereoselectively to afford



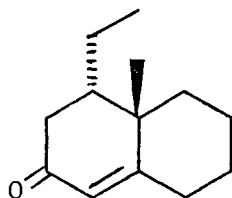
the cis-fused decalone 165b. It was hoped that the additional information



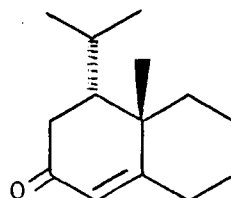
obtained from the Birch reductions of octalones of type 170 would aid in clarifying some of the factors affecting the stereochemical outcome of the Birch reduction of $\Delta^{1,9}$ -2-octalone systems in general. As mentioned earlier octalones 188 to 192 had been synthesized and had been shown to be homogeneous by g.l.c. In addition, the authentic cis- and trans-fused decalones corresponding to the above octalones were now readily available (by the syntheses described above) for comparison with the products obtained from the Birch reductions of octalones 188 to 192. In each case, gas-liquid chromatographic conditions were found



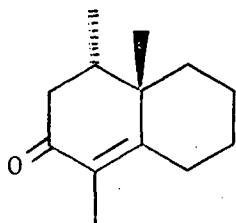
188



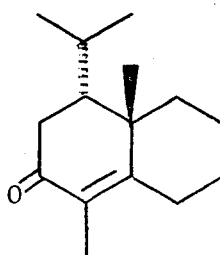
189



190



191



192

in which the octalone, the corresponding cis-fused decalone and the corresponding trans-fused decalone exhibited distinct retention times on g.l.c. co-injection. Hence, it was anticipated that the product mixtures from Birch reduction of octalones 188 to 192 would be readily analyzable by g.l.c.

As previously noted by other workers (49) lithium-liquid ammonia reductions, in the absence of proton donors, generally lead to the recovery of some starting material. Presumably this is because some of the unreduced enone acts as a proton source and reacts with a base (e.g. amide ion) to form the corresponding enolate anion, which is then inert to the described reduction (49). However, in the present case recovered starting material posed no problem to the analysis of the product mixtures. Furthermore, the yields of the Birch reduction

products were higher when the additional oxidation step could be omitted. Hence, the following conditions were chosen for the Birch reductions.

Octalones 188 to 192 were reacted with lithium in anhydrous liquid ammonia for 2 h , and the reactions were quenched by addition of ammonium chloride as the proton source. Each reduction was repeated at least twice while the majority of the reductions were performed five times. The results (yields and product composition) for the lithium-liquid ammonia reductions were averaged over the various runs and are recorded in Table III.⁷

In each case, g.l.c. analysis of the crude reduction product revealed some recovered octalone, along with the corresponding trans- and cis-fused decalones. The trans- and cis-fused decalones were isolated by preparative g.l.c. and shown to be identical (infrared and n.m.r. spectra, g.l.c. retention times) with the corresponding authentic trans- and cis-fused decalones previously prepared.

The percent composition of the crude reduction product was determined by integration (disc integrator) of the g.l.c. trace of the product mixture. It was found that the molar response factor was the same for each pair of cis- and trans-fused decalones. This is expected as molecules of similar molecular complexity generally have identical response factors (103). This factor was determined by weighing samples of the authentic cis- and trans-fused decalones and combining them so

⁷ The percent composition results were found to be reproducible to within $\pm 2\%$ for each of the cis- and trans-fused decalones listed in Table III.

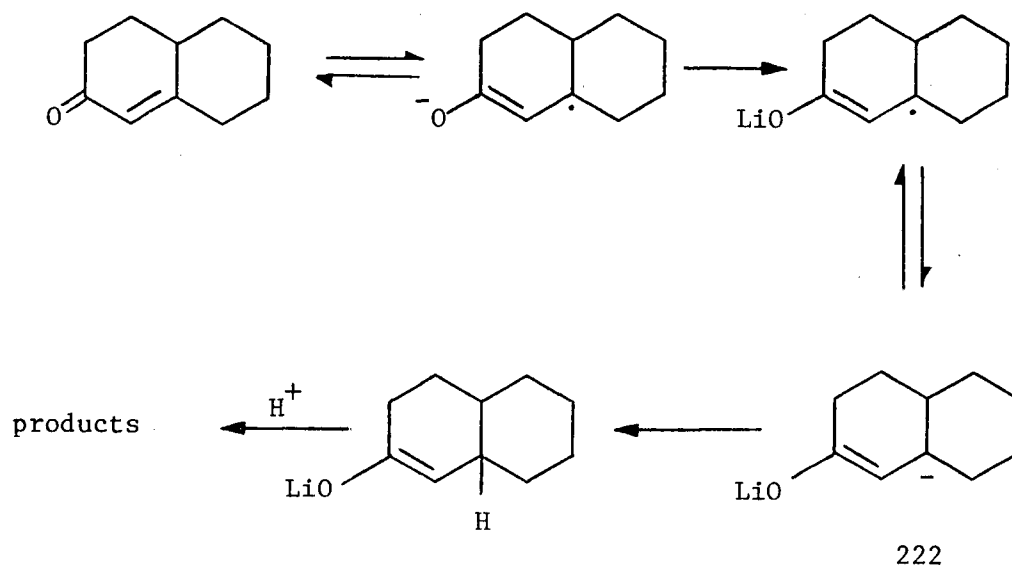
that the ratio represented by their admixture would be very similar to the observed ratio in the Birch reduction product. The mixture of known composition was then injected into the g.l.c. The ratio of cis- to trans-fused decalone was then calculated by integration of the g.l.c. trace and found to be within experimental error of the known ratio.

Table III. Results Obtained from the Birch Reduction of Octalones 188 to 192

Octalone	% Yield	<u>trans</u> : <u>cis</u> ratio	% Recovered starting material	Observed stereoselectivity -RT ln <u>cis</u> / <u>trans</u> decalone Kcal/mole
<u>188</u>	93	87:13	2	0.91
<u>189</u>	94	75:25	13	0.52
<u>190</u>	98	69:31	14	0.38
<u>191</u>	90	82:18	8	0.72
<u>192</u>	98	65:35	7	0.29

Before discussing the results of the Birch reductions of octalones 188 to 192 it would be advantageous to digress to consider the nature of the pathway of lithium-liquid ammonia reductions of $\Delta^{1,9}$ -2-octalone systems. The mechanism recently proposed by House et al. (49) for dissolving metal reductions is summarized in Chart XIX. This mechanism involves an initial rapid reversible addition of an electron to the unreduced enone, followed by subsequent formation of a tight ion pair

Chart XIX



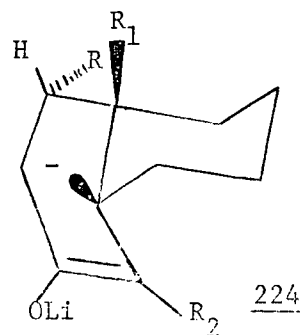
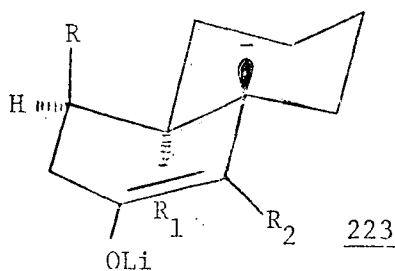
with the lithium cation (or of the corresponding enol by protonation in the presence of a proton source). The second electron is then added in a reversible step followed by a non-reversible product determining protonation. The transition state for protonation can, therefore, be assumed to lie between the intermediate 222 and the final protonated product, that is, in the present case, the corresponding lithium enolate of the decalone.

As previously discussed the nature of the geometry of the β -carbon atom in the transition state for protonation in lithium-ammonia reductions is uncertain. Various workers have proposed that the geometry of the β -carbon atom in the transition state for protonation could be trigonal (sp^2 hybridized), pyramidal (sp^3 hybridized) or a

geometry somewhere between these two extremes. In the absence of any experimental data to distinguish between the various geometries of the β -carbon atom, this discussion will consider several of the possibilities.

An examination of the results in Table III revealed that as the bulk of the C_4 alkyl group increased, the percentage of cis-fused decalone product was increased. Furthermore, the results for octalone 192 (listed in Table III) compared with the results for octalone 155b revealed that the C_{10} angular methyl group had a large effect on the stereochemical outcome of the lithium-ammonia reduction of octalone 192.

As previously discussed in the introduction, many workers (44,45,50) have proposed a pyramidal configuration for the geometry of the β -carbon atom in the transition state for protonation. This proposal has been modified to include a stereoelectronic requirement (45). Bearing in mind this stereoelectronic requirement, the product determining protonation of the intermediate carbanion 222 could theoretically proceed through one or both of two possible transition states, one resembling the pyramidal carbanion intermediate 223, which would give rise to the trans-fused decalone product and the other resembling the

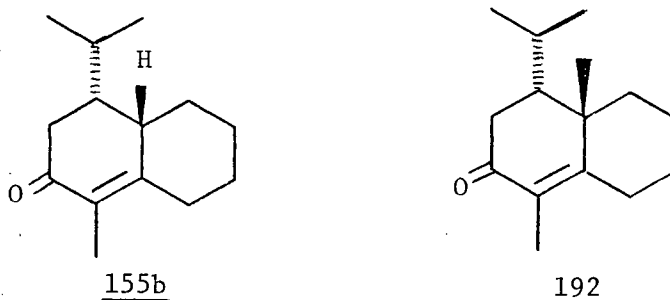


pyramidal carbanion intermediate 224, which would give rise to a cis-fused decalone product. Generally a transition state for protonation resembling 223 is favored as it is of lower energy than 224, thus accounting for the general predominance of the trans-fused products. However, the lithium-ammonia reductions of octalones 188 to 192 should be exceptional as the stereoelectronically allowed transition states leading to the trans- and cis-fused decalones are essentially equivalent in energy or that leading to the cis product is slightly favored. At the present time experimental conformational energy values are not available for the conformations of Δ^1 -octalin derivatives. Hence, only rather qualitative estimates for the relative energies of 223 and 224 can be made by conventional conformational analysis. A qualitative examination of the non-bonded interactions present in 223 and 224 revealed that these two intermediates should be of approximately the same energy. That is, the unfavorable nature of the cis-like transition state plus the skew R-CH₃ interaction present in 224 are approximately comparable with the skew R-sp² interaction plus the developing syn axial R-H interaction between the incoming proton and the axial R group in the transition state for protonation resembling 223. Thus on the basis of a pyramidal transition state for protonation, an approximately 50:50 mixture of products would be expected.

An examination of the results in Table III revealed a stereoselectivity higher than would be expected by the above qualitative energy approximations on the transition states resembling 223 and 224. However, this trend seems to be in line with the empirical trend that the cis/trans product ratio is generally less than would be expected on the

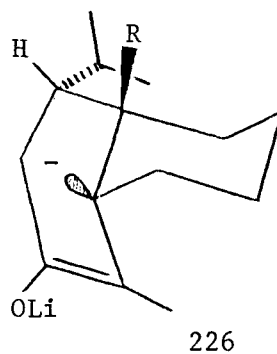
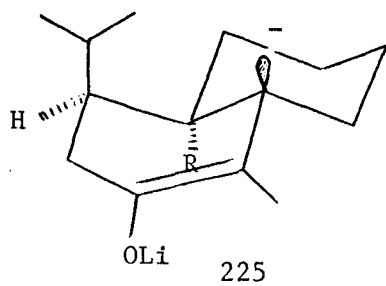
basis of the conformational energies involved (46). Since immediate explanations for the effect of the bulk of the C₄ alkyl group and for the effect of the angular methyl group on the cis/trans product ratios are not obvious, the following discussion will examine several plausible factors which might be directing the reaction pathway.

Firstly the effect of the angular methyl group on the stereochemical outcome of the lithium-ammonia reductions will be discussed in terms of a pyramidal transition state. As mentioned above, a striking difference in product stereoselectivity was evident on comparison of the products obtained from the Birch reduction of octalones 155b and 192.

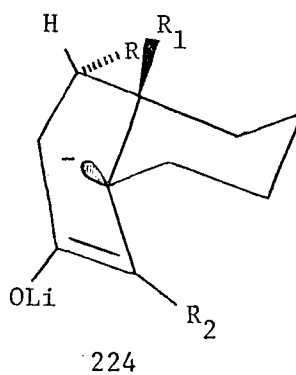
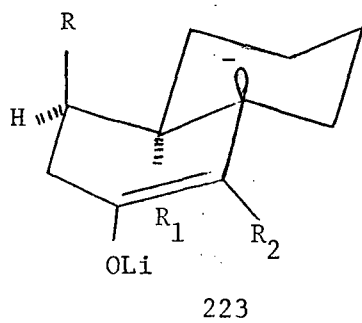


Changing the C₁₀ substituent from a hydrogen to a methyl group effected a change from the stereoselective production of the cis-fused decalone product in the case of octalone 155b, to the production of a 35:65 ratio of cis-fused to trans-fused decalone products in the case of octalone 192.

Examination of molecular models of the possible pyramidal carbanion intermediates - 225, protonation of which would lead to the trans-fused decalone, and 226, protonation of which would lead to the cis-fused decalone - revealed the introduction of one serious interaction in 226 when R was changed from a hydrogen to a methyl group. (That is,

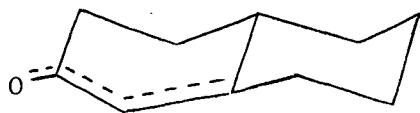


when R in 226 is a methyl group, a gauche interaction between the angular methyl substituent and the C₄ isopropyl group is present, whereas when R in 226 is a hydrogen, this gauche interaction is absent.) This gauche interaction would, therefore, make the transition state resembling the intermediate carbanion 226 less favorable when R is a methyl group than when R is a hydrogen. There is also the added possibility that the C₁₀ methyl group in 226 (R = CH₃) might be affording a small amount of steric hindrance to the incoming protonating species in the transition state leading to the cis product which would be absent when R (in 226) is a hydrogen. It follows that less cis-fused decalone should be formed on lithium-ammonia reduction of octalone 192 than on reduction of octalone 155b. As reported above this was found to be the case. As the bulk of the C₄ alkyl substituent increases the

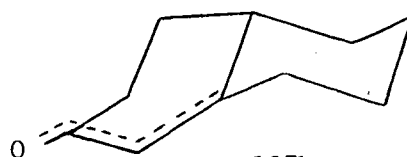


non-bonded interaction in 223 between the C_4 alkyl group and the C_2 sp^2 center and the C_4 alkyl group and the incoming protonating species would be expected to increasingly make conformation 224, in which the C_4 alkyl group is equatorial, more favorable relative to conformation 223. This could partially account for the increase in the amount of cis-fused product as the bulk of the C_4 alkyl group increases.

As discussed previously, Robinson proposed that the β -carbon atom was trigonal, or very nearly trigonal, in the transition state for protonation. In addition he proposed that the reduction could proceed via one or both of two possible transition states, 107a which would lead predominantly to the trans-fused decalone and 107b which would give rise predominantly to the cis-fused decalone. Other possible transition states were also considered but were predicted to be of very high energy and therefore were not considered further (46). Robinson stated



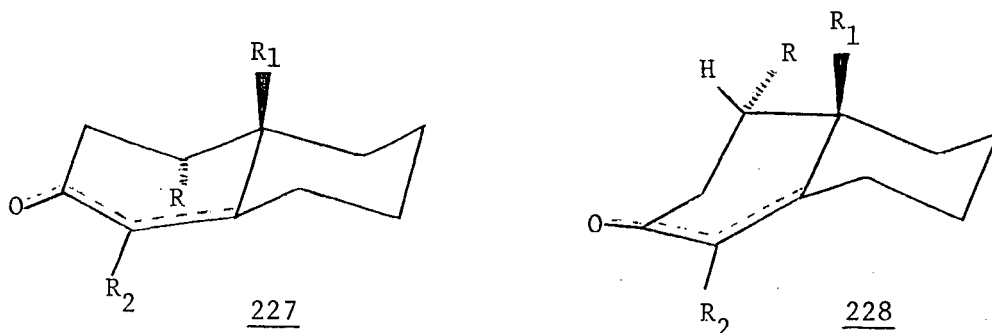
107a



107b

that there would be less angle and torsional strain involved in a transition state resembling 107a than there would be in one resembling 107b. If we consider octalones 155b and 188 to 192, it is possible that the stability gained by changing the C_4 alkyl group from an axial orientation in 227 (analogous to 107a) to an "equatorial-like" orientation in 228

(analogous to 107b) would at least partially offset the angle and



torsional strain intrinsic in conformation 228. This would result in a lowering of the energy of the transition state resembling 228 relative to that resembling 227. Robinson's theory would thus predict a higher proportion of cis-fused decalone in the present examples relative to that normally found. However, in contrast to octalone 155b, octalones 188 to 192 possess an added destabilizing interaction in conformation 228. In the case of octalones 188 to 192 the stabilization arising from changing the alkyl group from the axial orientation to the "equatorial-like" orientation (227 → 228) would thus be partially offset by the increasing skew interaction between the equatorial C₄ alkyl group and the C₁₀ methyl group (in 228). Hence, in these octalones 188 to 192 the amount of cis-fused decalone formed on lithium-ammonia reduction would be predicted to be less than in the case of octalone 155b where there is no developing interaction between the C₁₀ hydrogen and C₄ alkyl group.

As the bulk of the C₄ alkyl group increases it is probable that the stabilization arising from changing the alkyl group from the axial orientation to the "equatorial-like" orientation would also increase. This increased stabilization would make the transition state resembling

228 increasingly more favored, and could thus account for the observed fact that as the C₄ alkyl group increases in size, the amount of cis-decalone obtained in the reduction also increases.

It is also possible that in the transition state leading to the trans-fused decalone there is an increasing degree of steric hindrance to protonation as the bulk of the C₄ substituent increases. This would make protonation of 228 more likely as the bulk of the C₄ substituent increases. The effect of the C₄ alkyl substituent on the stereochemistry of lithium-ammonia reductions has both practical and theoretical interest. The Birch reduction of octalones 188 to 192 revealed a higher percentage of cis-fused decalone product than normally obtain in other substituted $\Delta^{1,9}$ -2-octalone systems. Although use of a transition state model possessing a pyramidal β -carbon atom along with crude estimates of conformational energies would predict a higher percentage of cis-fused decalone than observed, use of a transition state model possessing a trigonal β -carbon atom would give rise to qualitative predictions in accord with the observed results. The magnitude of the effect of changing the C₁₀ substituent from a hydrogen to a methyl group was not expected a priori. However, in retrospect the results can at least qualitatively be accounted for (see above).

Finally the fact that the reduction of octalone 155b led stereoselectively to a cis-fused decalone has obvious synthetic applications. For example, use of this observation could provide a synthetic entry into the amorphane class of sesquiterpenes.

EXPERIMENTAL

General

Melting points, which were determined on a Fisher-Johns melting point apparatus, and boiling points are uncorrected. Routine infrared spectra were recorded on a Perkin-Elmer Infracord model 137 or a Perkin-Elmer Infrared Spectrophotometer model 710, while comparison spectra were recorded on Perkin-Elmer spectrophotometers model 421 or model 457. Ultraviolet spectra were, unless otherwise noted, measured in methanol solution on a Unicam, SP. 800, spectrophotometer. N.m.r. spectra were, unless otherwise noted, recorded in deuteriochloroform solution on Varian Associates spectrometers, models A-60, T-60 and/or HA-100, XL-100. Line positions are given in the Tiers τ scale, with tetramethylsilane as internal standard; the multiplicity, integrated peak areas and proton assignments are indicated in parentheses. Gas-liquid chromatography (g.l.c.) was carried out on either an Aerograph Autoprep, model 700 or a Varian Aerograph, model 90-P. The following columns (10 ft x 1/4 in unless otherwise noted) were employed, with the inert supporting material being 60/80 mesh Chromosorb W (unless otherwise noted): column A, 3% SE-30; column B, 15% QF-1; column C, (10 ft x 3/8 in) 20% SE-30; column D, 20% FFAP; column E, 8% FFAP (60/80 mesh Chromosorb G); column F, 20% Carbowax 20 M; column G (10 ft x 3/8 in) 30% Carbowax 20 M; column H, 20% SE-30. The

specific column used, along with the column temperature and carrier gas (helium) flow-rate (in ml/min) are indicated in parentheses. High resolution mass spectra were recorded on an AEI, type MS-9, mass spectrometer. Microanalyses were performed by Mr. P. Borda, Microanalytical Laboratory, University of British Columbia, Vancouver.

Preparation of Dimethyl α -ketopimelate (111)

The procedure used was that of Lukes, Poos and Sarett (51).

Through a solution of 100 g (0.725 mole) of commercial furylacrylic acid (110) in 400 ml of methanol was passed hydrogen chloride until the solution reached the boiling point. The gas flow was reduced and the solution was maintained at the boiling point for 4 h. Then the solution was concentrated on the rotary evaporator to one-fourth the volume. One litre of benzene was added to the residue and distillation continued at atmospheric pressure until the vapour temperature reached 80°. Then the remaining benzene was removed under reduced pressure. To the residue was added 350 ml of methanol and one-third ml of 95% sulphuric acid and the mixture refluxed overnight. The methanol was then removed under reduced pressure and the residue dissolved in 650 ml of benzene. The benzene solution was washed successively with water, 1 N sodium carbonate solution (until basic), water and brine and dried over anhydrous magnesium sulfate. The concentrated benzene extract was distilled in vacuo, b.p. 110-115° at 0.65 mm; lit. (51) b.p. 90-93° at 0.1 mm, to afford 122 g (84%) of dimethyl α -ketopimelate (111), m.p. 49-50°; lit. (51) m.p. 49-50°. Infrared (CHCl_3), λ_{max} 5.8, 6.97, 8.5 μ ; n.m.r., τ 7.29 (multiplet, 8 H, $-\text{CH}_2-\text{CH}_2-$), 6.33 (singlet, 6 H, CO_2CH_3).

Preparation of Dimethyl- γ -ethylenedioxy pimelate (112)

The procedure used was analogous to that of Lukes, Poos and Sarett (51).

In a 1.0 l flask, equipped with a Dean-Stark water separator, was placed 120 g (0.59 mole) of keto diester 111, 41.5 g (0.64 mole) of ethylene glycol and 220 mg of *p*-toluenesulfonic acid in 600 ml of dry benzene. The mixture was refluxed until the calculated amount of water had been collected. The cooled solution was washed successively with saturated sodium bicarbonate solution, water and brine, and dried over anhydrous magnesium sulfate. The concentrated residue was distilled through a Vigreux column several times to afford 34 g (23%) of dimethyl- γ -ethylenedioxy pimelate (112), which was greater than 97% pure by g.l.c. (column A, 220°, 85), b.p. 115-120° at 0.6 mm; lit. (51) b.p. 96-98° at 0.08 mm, n_D^{20} 1.4504; lit. (51) n_D^{25} 1.4501. Infrared (film), λ_{\max} 5.77, 7.0 μ ; n.m.r., τ 6.30 (singlet, 6 H, CO₂CH₃), 6.04 (singlet, 4 H, ketal protons). It should be noted that after distillation a substantial amount of high boiling material was recovered. This material was subjected to methanol-sulfuric acid treatment which regenerated keto diester 111. It was therefore felt that this material had transesterified under the ketalization conditions. Recycling of recovered keto diester 111 several times raised the overall yield of this reaction to 44%.

Preparation of Keto Ester 113

The procedure employed was that of Lukes, Poos and Sarett (51).

A solution of 58 g (0.24 mole) of ketal diester 112 and 5.7 g (0.24 mole) of sodium hydride in 350 ml dry ether was refluxed with efficient stirring for 5 days under a nitrogen atmosphere. At the end of this time 20 ml of glacial acetic acid and 20 ml of water were added successively. The ether layer was washed with 1 N sodium carbonate solution, water and brine and dried over anhydrous magnesium sulfate. The ether layer was concentrated and the residue distilled to afford a colorless oil which crystallized on standing, b.p. 124° at 0.35 mm. Recrystallization from methanol afforded 40.5 g (80%) of keto ester 113, m.p. 60-61°; lit. (51) m.p. 60-61°. Infrared (CHCl_3), λ_{max} 5.75, 5.85, 6.03, 6.20 μ ; n.m.r., τ 6.23 (singlet, 3H, CO_2CH_3), 5.97 (singlet, 4H, ketal protons).

Preparation of Octalone 114

The procedure used was similar to that of Ireland et al. (52).

A solution of 14.6 g (68 mmoles) of keto ester 113 and 4.0 g (73 mmoles) of sodium methoxide in 120 ml of anhydrous methanol was stirred at room temperature under a nitrogen atmosphere. To this solution was added 30.8 g (102 mmoles) of 1-diethylamino-3-pentanone methiodide in 80 ml of anhydrous methanol and the reaction allowed to stir for 3 days. At the end of this period, the methanol was removed in vacuo and 1 g of potassium hydroxide in 200 ml of water was added. An additional 9 g of potassium hydroxide in 150 ml of water was added dropwise over 3 h and the solution refluxed for an additional 5 h. The cooled reaction mixture was thoroughly extracted with ether and the combined ether extracts were washed with water and brine and dried over

anhydrous sodium sulfate. The ether extract was concentrated and distilled, b.p. 117-120° at 0.1 mm, to afford a colorless oil which crystallized on standing. Recrystallization from petroleum ether (30-60°) afforded 9.5 g (64%) of the desired octalone 114, m.p. 61-62°; lit. (52) m.p. 61-63°. Ultraviolet, λ_{max} 245 m μ (ϵ = 14,400); infrared (nujol), λ_{max} 6.03, 6.24 μ ; n.m.r., τ 8.13 (singlet, 3H, vinyl methyl), 6.08 (singlet, 4H, ketal protons).

Reduction of Octalone 114

To 150 ml of liquid ammonia (freshly distilled from sodium metal) was added 108 mg of finely cut lithium wire. After all the lithium had dissolved 500 mg (2.24 mmoles) of octalone 114 dissolved in 25 ml of dry ether was added dropwise over 0.5 h. The solution was allowed to stir for an additional 2 h and then the blue color was discharged by addition of ammonium chloride. The liquid ammonia was allowed to evaporate and the residue diluted with water. The aqueous solution was thoroughly extracted with ether. The combined ether extracts were washed with water and brine and dried over anhydrous sodium sulfate. The ether extract was concentrated and the residue distilled (b.p. 120° at 2 mm) to afford 491 mg (97%) of the desired decalone 115. G.l.c. analysis of the reaction product (column B, 195°, 85) revealed approximately 10% of recovered starting material plus the desired decalone 115. An analytical sample of the latter was collected by preparative g.l.c. (column C, 200°, 110) and exhibited the following spectral data: n_D^{25} 1.4954; infrared (film), λ_{max} 5.85 μ ; n.m.r., τ 8.96 (doublet, 3H, secondary methyl group, J = 6 Hz), 6.01 (singlet, 4H, ketal protons).

Mol. Wt. Calcd. for $C_{13}H_{20}O_3$: 224.141. Found (high resolution mass spectrometry): 224.138.

Preparation of Hydroxymethylene Derivative 121

To an ice-cold solution of 4 g (18 mmoles) of decalone 115, 1.95 g of sodium methoxide in 20 ml of dry benzene was added 3 ml of ethyl formate. The reaction mixture was allowed to stir at room temperature under nitrogen for 14 h. At the end of this time ice water was added and the benzene layer separated. The aqueous layer was acidified with glacial acetic acid and thoroughly extracted with ether. The combined ether extracts were washed with water and brine and dried over anhydrous sodium sulfate. The ether extract was concentrated to afford 3.7 g (80%) of the desired hydroxymethylene derivative 121. Infrared (film), λ_{\max} 6.1, 6.4 μ . Due to the instability of this compound it was oxidized immediately without further characterization.

Preparation of Dione 124

This compound was prepared by the procedure of Ireland *et al.* (52).

A solution containing 25 g (0.127 mole) of keto ester 113, 16.8 g (0.2 mole) of ethyl vinyl ketone, 5 ml of triethylamine in 250 ml of methanol was allowed to stand for 48 h at room temperature under an atmosphere of nitrogen. The methanol was then removed *in vacuo*. The residue crystallized on standing. Recrystallization from methanol afforded 29.1 g (84%) of dione 124, m.p. 83-85°; lit. (52) m.p. 83-85°. Dione 124 exhibited the following spectral properties. Infrared (nujol), λ_{\max} 5.85 μ ; n.m.r., τ 8.97 (triplet, 3H, $\text{CH}_3\text{CH}_2\overset{\text{O}}{\underset{\text{||}}{\text{C}}}-$, $J = 7$ Hz), 6.30 (singlet,

3H, methyl ester), 6.08 (singlet, 4H, ketal protons).

Preparation of Octalone 123

The procedure used to prepare this compound was that of Ireland et al. (52).

A suspension of 10 g (0.034 mole) of dione 124 in 75 ml of absolute methanol containing 1 g of sodium metal was warmed in a nitrogen atmosphere at 40° for 1 h. This solution was then refluxed for 2 h. At the end of this time 3.1 g (0.05 mole) of glacial acetic acid was added slowly at 15°. The reaction mixture was then filtered. The filtrate was concentrated under reduced pressure. The residue was extracted with benzene. The benzene extract was then washed with water, sodium bicarbonate solution (until neutral), water and brine and dried over anhydrous sodium sulfate. The benzene extract was concentrated and the residue crystallized on standing. These crystals were combined with those obtained from the first filtration. Recrystallization of octalone 123 from methanol-water afforded 9.02 g (97%), m.p. 102-103°; lit. (52) m.p. 101.5-103°. Infrared (CHCl₃), λ_{max} 5.8, 6.0, 6.2 μ ; n.m.r., τ 8.13 (singlet, 3H, vinyl methyl), 6.30 (singlet, 3H, methyl ester), 6.08 (singlet, 4H, ketal protons); ultraviolet, λ_{max} 247 m μ (ϵ = 13,000).

Preparation of Dienone 125

A solution of 5 g (18 mmoles) of octalone 114, 4.4 g (19 mmoles) of DDQ, 6.2 ml of glacial acetic acid in 100 ml of anhydrous benzene was refluxed for 36 h under nitrogen. At the end of this time, the cooled

reaction mixture was filtered and concentrated in vacuo. The residue was taken up in ether and washed with water, saturated sodium bicarbonate solution, water and brine and dried over anhydrous magnesium sulfate. The dried extract was concentrated to afford 4 g (80%) of a white crystalline solid. An analytical sample was prepared by recrystallization from ethyl acetate-petroleum ether (30-60°) to afford white needles, m.p. 143-144°. This sample exhibited ultraviolet, λ_{\max} 243 m μ (ϵ = 10,300); infrared (nujol), λ_{\max} 5.82, 6.05, 6.15, 6.25 μ ; n.m.r., τ 8.04 (singlet, 3H, vinyl methyl), 6.30 (singlet, 3H, CO₂CH₃), 6.02 (singlet, 4H, ketal protons), 3.72, 3.28 (pair of doublets, 2H, C₃ and C₄ protons respectively, J = 10 Hz).

Anal. Calcd. for C₁₅H₁₈O₅: C, 64.74; H, 6.52. Found: C, 64.84; H, 6.49.

Isopropylmagnesium Bromide Addition to Dienone 129

To an ice-cold suspension of 326 mg of magnesium filings in 12 ml anhydrous tetrahydrofuran (THF) was added 1.55 ml of isopropyl bromide. After all the magnesium had reacted 12 mg of cuprous chloride was added and the solution placed in an external ice bath. To this solution 190 mg of dienone 129 in 4 ml of anhydrous ether was added dropwise over 15 min and the solution allowed to stir for an additional 2 h. The reaction mixture was poured into a rapidly stirred 1 N hydrochloric acid solution. The ether layer was separated and washed with water and brine and dried over anhydrous magnesium sulfate. The ether extract was concentrated in vacuo to afford 207 mg of a yellow oil. Analysis of the product by g.l.c. revealed two major products in the

ratio of 2:3 respectively, (column B, 180°, 85). The minor product (131 or 132) exhibited infrared (film), λ_{\max} 3.45, 6.25 (w), 6.4 (w) μ ; n.m.r., τ 8.80 (doublet, 3H, secondary methyls, $J = 6.5$ Hz), 8.75 (singlet, 6H, tertiary methyls), 7.84 (singlet, 3H, vinyl methyl), 3.20, 3.00 (broad singlets, 2H, phenyl protons).

Anal. Calcd. for $C_{16}H_{24}$: C, 88.82; H, 11.18. Found: C, 88.70; H, 11.07.

The major product exhibited infrared (film), λ_{\max} 6.0, 6.25 μ ; ultraviolet, λ_{\max} 240 m μ ($\epsilon=13,000$); n.m.r., τ 9.35, 9.08 (pair of doublets, 6H, secondary methyls, $J = 7$ Hz), 8.85, 8.82 (singlets, 6H, gem-dimethyl groups), 8.61 (singlet, 3H, C_{10} tertiary methyl), 7.39, 7.21 (pair of doublets, 1H, C_{3a} proton, $J_{3a,3e} = 18$ Hz, $J_{3a,4e} = 6$ Hz), 7.46, 7.65 (pair of doublets, 1H, C_{3e} proton, $J_{3e,3a} = 18$ Hz, $J_{3e,4e} = 3$ Hz), 4.04 (singlet, 1H, C_1 proton).

Anal. Calcd. for $C_{16}H_{26}O$: C, 81.99; H, 11.18. Found: C, 81.89; H, 11.09.

Preparation of Hydroxymethylene Derivative 134

To an ice-cold solution of 1.75 g (6.25 mmoles) of octalone 123, 0.756 g of sodium methoxide in 17.5 ml of dry benzene was added 463 mg of ethyl formate. The reaction mixture was allowed to stir at room temperature under nitrogen for 14 h. At the end of this time ice water was added and the benzene layer separated. The aqueous layer was acidified with glacial acetic acid and thoroughly extracted with ether. The combined ether extracts were washed with water and brine and dried over anhydrous sodium sulfate. The ether extract was concentrated to

afford 1.34 g (70%) of the desired hydroxymethylene derivative 134.

Infrared (film), λ_{\max} 5.8, 6.1, 6.4 μ . Due to the instability of this compound it was oxidized immediately without further characterization.

Dehydrogenation of Hydroxymethylene Derivative 134

To 700 mg (2.26 mmoles) of hydroxymethylene derivative 134 dissolved in 10 ml of anhydrous dioxane was added 570 mg (2.5 mmoles) of DDQ in 10 ml of anhydrous dioxane. The reaction was allowed to stir rapidly for 3.5 min. At the end of this time, methylene chloride was added to quench the reaction. The solution was filtered and the filtrate washed with water, 2% sodium hydroxide solution (until basic), water (until neutral) and brine and dried over anhydrous sodium sulfate. The organic extract was then concentrated and the residue crystallized on standing. Recrystallization from *n*-hexane-ether afforded 292 mg (43%) of pale yellow crystals, m.p. 142-144°. Infrared (nujol), λ_{\max} 5.75, 5.9, 6.08, 6.15, 6.25 μ ; n.m.r., τ 7.97 (singlet, 3H, vinyl methyl), 6.25 (singlet, 3H, CO₂CH₃), 5.98 (singlet, 4H, ketal protons), 2.55 (singlet, 1H, C₄ vinyl proton), -0.25 (singlet, 1H, aldehydic H); ultraviolet, λ_{\max} 246 m μ (ϵ =14,700).

Anal. Calcd. for C₁₆H₁₈O₆: C, 62.74; H, 5.92. Found: C, 62.81; H, 5.97.

Preparation of Dione 137

To a solution of 60 g of 1-N,N-diethylamino-3-pentanone in 250 ml of dry benzene at 0° was added over 2 h 60 g of freshly distilled methyl iodide. The resulting solution was allowed to stir at 0° for an

additional 15 h. At the end of this time the benzene and excess methyl iodide were removed in vacuo and 200 ml of anhydrous ethanol were added. A solution of 60 g of 2-carbethoxycyclohexanone and 20 g of sodium ethoxide in 900 ml of anhydrous ethanol was cooled to 0°. To this solution was added dropwise over 2 h the above 1-diethylamino-3-pentanone methiodide solution. The reaction mixture was allowed to stir for an additional 4 h at 0° and refluxed for 0.5 h. At the end of this period, most of the ethanol was removed on the rotary evaporator and the residue diluted with water. The aqueous layer was thoroughly extracted with ether. The combined ether extracts were washed with water, dilute hydrochloric acid, water and brine and dried over anhydrous sodium sulfate. The ether extract was concentrated and the residue distilled to afford 64.8 g (83%) of a pale yellow oil, b.p. 130-135° at 0.9 mm. G.l.c. analysis (column D, 200°, 75) exhibited one peak only. Infrared (film), λ_{\max} 5.8 μ ; n.m.r., τ 8.97 (triplet, 3H, $\text{CH}_3\text{CH}_2\overset{\text{O}}{\underset{\text{O}}{\text{C}}}$, J = 7 Hz), 8.72 (triplet, 3H, $\text{CH}_3\text{CH}_2\text{-O}$, J = 7 Hz), 7.59 (quartet, 2H, $\text{CH}_2\overset{\text{O}}{\underset{\text{O}}{\text{C}}}$, J = 7 Hz), 5.8 (quartet, 2H, $\text{-CH}_2\text{-O-}$, J = 7 Hz).

Preparation of Octalone 138

To a solution of 530 mg of sodium dissolved in 35 ml of dry ethanol was added 5 g of dione 137. This solution was allowed to stir at 40° for 2 h, under a nitrogen atmosphere. At the end of this period, the ethanol was removed in vacuo and the residue diluted with water. The aqueous solution was thoroughly extracted with ether. The ether layer was washed with water and brine and dried over anhydrous magnesium sulfate. The ether extract was concentrated and the residue distilled to afford 4.2 g (96%) of the desired octalone 138, b.p. 135° at 0.2 mm;

lit. (105) b.p. 135-136° at 0.2 mm. Ultraviolet, λ_{\max} 247 m μ (ϵ 13,000); infrared (film), λ_{\max} 5.8, 6.0, 6.2 μ ; n.m.r., τ 8.72 (triplet, 3H, $\text{CH}_3\text{CH}_2\text{-O}$, $J = 7$ Hz), 8.12 (singlet, 3H, vinyl methyl), 5.72 (quartet, 2H, $\text{CH}_3\text{-CH}_2\text{-O}$, $J = 7$ Hz).

Dehydrogenation of Octalone 138

A solution of 3.2 g (13.6 mmoles) of octalone 138, 4.8 g (21 mmoles) of DDQ, 6.4 ml of glacial acetic acid in 128 ml of anhydrous benzene was refluxed under nitrogen for 70 h. At the end of this time the cooled reaction mixture was filtered, and concentrated in vacuo. The residue was taken up in ether and washed thrice with water, with saturated sodium bicarbonate solution, with water and with brine and dried over anhydrous magnesium sulfate. The concentrated extract was distilled, b.p. 120° at 0.2 mm, to afford 2.4 g (76%) of dienone 139, which crystallized on standing, m.p. 55-57°. Ultraviolet, λ_{\max} 245 m μ ($\epsilon = 9,680$), sh 265 m μ ($\epsilon = 6,700$); infrared (CHCl_3), λ_{\max} 5.8, 6.05, 6.12, 6.23 μ ; n.m.r., τ 8.79 (triplet, 3H, $\text{CO}_2\text{CH}_2\text{CH}_3$, $J = 7$ Hz), 8.05 (singlet, 3H, vinyl methyl), 5.85 (quartet, 2H, $-\text{CH}_2\text{-O}$, $J = 7$ Hz), 3.77, 3.33 (pair of doublets, 2H, C_3 and C_4 protons respectively, $J = 10$ Hz).

Anal. Calcd. for $\text{C}_{14}\text{H}_{18}\text{O}_3$: C, 71.77; H, 7.74. Found: C, 71.61; H, 7.91.

Preparation of Hydroxymethylene Derivative 140

To a solution of 4 g (17.1 mmoles) of octalone 138 and 1.84 g (34.1 mmoles) of sodium methoxide dissolved in 20 ml of dry benzene,

at 0°, was added 3.15 ml (39 mmoles) of ethyl formate. The reaction vessel was then put under a nitrogen atmosphere and stirring continued at room temperature for 24 h. At the end of this time, ice water was added and the benzene layer separated. The aqueous layer was neutralized with dilute hydrochloric acid and the solution thoroughly extracted with ether. The combined ether extracts were washed with water and brine and dried over anhydrous sodium sulfate. The ether layer was concentrated in vacuo to afford 3.7 g (83%) of an orange colored oil. Infrared (film), λ_{\max} 5.8, 6.1, 6.4 μ ; n.m.r., τ 8.82 (triplet, 3H, $\text{CH}_3\text{CH}_2\text{O}_2\text{C}$, $J = 7$ Hz), 8.09 (singlet, 3H, vinyl methyl), 5.89 (quartet, 2H, $\text{CH}_2\text{-O}$, $J = 7$ Hz), 2.65 (singlet, 1H, $=\text{CHOH}$).

Preparation of 3-Formyl Dienone 141

To a solution of 2.6 g (0.01 mole) of hydroxymethylene derivative 140 in 20 ml of dry dioxane was added 2.3 g (0.01 mole) of DDQ in 20 ml of dry dioxane. The solution was allowed to stir with a rapid flow of nitrogen passing through the solution for 3.5 min. The reaction mixture was then diluted with methylene chloride and filtered through a column of neutral alumina. The filtrate was concentrated and distilled, b.p. 200° at 0.1 mm, to afford 1.68 g (65%) of a liquid which crystallized on standing. Recrystallization from n-hexane-ether afforded an analytical sample, m.p. 46-48°, which gave the following spectral data: ultraviolet, λ_{\max} 247 $m\mu$ ($\epsilon = 8,270$); infrared (nujol), λ_{\max} 5.8, 5.9, 6.1, 6.2 μ ; n.m.r., τ 8.75 (triplet, 3H, $\text{CO}_2\text{CH}_2\text{CH}_3$, $J = 7$ Hz), 7.97 (singlet, 3H, vinyl methyl), 5.82 (quartet, 2H, $-\text{CH}_2\text{-O}$, $J = 7$ Hz), 2.55 (singlet, 1H, C_4 vinyl hydrogen), -0.25 (singlet, 1H, aldehydic H).

Anal. Calcd. for $C_{15}H_{18}O_4$: C, 68.69; H, 6.92. Found: C, 68.52; H, 7.09.

Preparation of Bromomethyl ethyl Ketone (146)

A procedure similar to that of Catch et al. was used (68).

To an ice-cold ethereal solution of 12 g (0.3 mole) of anhydrous diazomethane was added 14 g (0.15 mole) of freshly distilled propionyl chloride. This solution was allowed to stir for 30 min at 0°. Then anhydrous hydrogen bromide was bubbled through the solution and the solution maintained at 0° for an additional 30 min. The ethereal solution was then washed with water, 5% sodium bicarbonate solution and brine and dried over anhydrous magnesium sulfate. Removal of the solvent and distillation of the oily residue under reduced pressure afforded 15.8 g (70%) of bromomethyl ethyl ketone (146), b.p. 48° at 10 mm; lit. (68) b.p. 154-155°; n_D^{20} 1.4673. Infrared (film), λ_{\max} 5.85 μ ; n.m.r., τ 8.88 (triplet, 3H, CH_3- , $J = 6.5$ Hz), 7.27 (quartet, 2H, CH_3-CH_2- , $J = 6.5$ Hz), 6.06 (singlet, 2H, $-CH_2-Br$).

Preparation of Acyl Phosphonium Salt 147

To a solution of 20 g of triphenylphosphine in 20 ml anhydrous benzene was added 15 g of bromomethyl ethyl ketone. The reaction mixture was allowed to stand overnight at room temperature. The precipitated phosphonium salt (147) was then collected by suction filtration. Recrystallization from methanol gave 33.6 g (82%) of white needles, m.p. 253-255°. An analytical sample gave infrared (nujol), λ_{\max} 5.85, 6.90, 7.00, 9.05 μ ; n.m.r., τ 9.08 (triplet, 3H, CH_3- , $J =$

6.5 Hz), 6.97 (quartet, 2H, $-\text{CH}_2-\overset{\text{O}}{\underset{\text{||}}{\text{C}}}$, $J = 6.5$ Hz), 4.03 (doublet, 2H, $-\text{CH}_2-\text{P}$, $J = 11$ Hz), 2.30 (unresolved multiplet, 15H, $(\text{C}_6\text{H}_5)_3$).

Anal. Calcd. for $\text{C}_{22}\text{H}_{22}\text{OPBr}$: C, 63.93; H, 5.37; Br, 19.33.

Found: C, 63.65; H, 5.61; Br, 19.21.

Preparation of Acyl Phosphorane 148

To a solution of 34 g of sodium hydroxide in 330 ml of water was added 33.5 g of the acyl phosphonium salt 147 and allowed to stir for 2 h. The product was collected by suction filtration, air-dried and recrystallized from ethyl acetate-petroleum ether (30-60°) to afford 17.3 g (64%) of the acyl phosphorane 148, m.p. 224-226°. Infrared (CHCl_3), λ_{max} 6.60, 6.98, 7.16, 9.07 μ ; n.m.r., τ 8.85 (triplet, 3H, CH_3 , $J = 7$ Hz), 7.66 (quartet, 2H, $-\text{CH}_2-\overset{\text{O}}{\underset{\text{||}}{\text{C}}}$, $J = 7$ Hz), 2.50 (unresolved multiplet, 15 H, phenyl protons), 1.0 (singlet, 1H, $=\text{CH}-\overset{\text{O}}{\underset{\text{||}}{\text{C}}}$); ultraviolet, λ_{max} 268 m μ ($\epsilon = 6,600$), 275 m μ ($\epsilon = 6,200$), 288 m μ ($\epsilon = 5,500$).

Anal. Calcd. for $\text{C}_{22}\text{H}_{21}\text{PO}$: C, 79.49; H, 6.37. Found: C, 79.22; H, 6.38.

Preparation of trans-6-methylhept-4-en-3-one (144)

To a solution consisting of 11.3 g (0.034 mole) of acyl phosphorane 148 in 50 ml of methylene chloride was added 7 ml (0.085 mole) of isobutyraldehyde and the solution refluxed overnight. The solvent was removed by careful distillation through a Vigreux column and the residue diluted with 40 ml of *n*-pentane. The solution was filtered to collect the triphenylphosphine oxide and the filtrate concentrated as above. The concentrated filtrate was then fractionally distilled

to afford 4.28 g (63%) of a colorless oil, b.p. 54° at 10 mm; lit. (104) b.p. 55-58° at 10 mm. An analytical sample of the unsaturated ketone was collected by preparative g.l.c. (column D, 200°, 100). Infrared (film), λ_{\max} 5.98, 6.14 μ ; n.m.r., τ 8.90 (doublet, 6H, $\overset{\text{CH}_3}{\text{C}}\text{-CH}_3$, $J = 7$ Hz), 8.95 (triplet, 3H, $\text{CH}_3\text{-CH}_2$, $J = 7$ Hz), 7.45 (quartet, 2H, $-\text{CH}_2\text{-}\overset{\text{O}}{\underset{\text{||}}{\text{C}}}$, $J = 7$ Hz), 3.98 (doublet of doublets, 1H, C_4 proton, $J_{4,5} = 16$ Hz, $J_{4,6} = 1.5$ Hz), 3.20 (doublet of doublets, 1H, C_5 proton, $J_{4,5} = 16$ Hz, $J_{5,6} = 6$ Hz); ultraviolet, λ_{\max} 221 m μ (since it was not possible to obtain vinyl ketone 144 without its β,γ -isomer a quantitative ultraviolet spectrum was not run), n_D^{25} 1.4425.

Anal. Calcd. for $\text{C}_8\text{H}_{14}\text{O}$: C, 76.19; H, 11.11. Found: C, 76.10; H, 11.12.

Preparation of Olefinic Ester 150

A stirred suspension of 4.3 g of a 56% sodium hydride dispersion in mineral oil in 50 ml of dimethyl sulphoxide (DMSO) was slowly heated under a nitrogen atmosphere to 75° and maintained at that temperature until all frothing had ceased (\sim 45 min). The solution was cooled to room temperature and a solution of 18.2 g of trimethylphosphonoacetate (149) in 30 ml of DMSO was added. The solution was allowed to stir for 10 min and then dropwise addition of 5.76 g of isobutyraldehyde in 30 ml of DMSO was begun. The reaction was very exothermic. After the addition was complete the reaction mixture was allowed to stir for an additional hour. Water was added to the cooled reaction mixture and it was thoroughly extracted with petroleum ether (30-60°). The

combined petroleum ether extracts were washed thrice with water, brine and dried over anhydrous magnesium sulfate. The solvent was removed at atmospheric pressure and the residual oil distilled at aspirator pressure (10 mm) to afford 6.5 g (65%) of a clear colorless oil, b.p. 65° at 10 mm; lit. (106) b.p. 145-148° at 640 mm; n_D^{25} 1.4309; lit. (106) n_D^{25} 1.4302. This product exhibited infrared (film), λ_{\max} 5.8, 6.05 μ ; n.m.r., τ 8.95 (doublet, 6H, gem-dimethyl groups, $J = 7$ Hz), 7.50 (multiplet, 1H, $\begin{array}{c} \text{CH}_3 \quad \text{CH}_3 \\ \diagdown \quad \diagup \\ -\text{C}-\text{H} \end{array}$), 6.30 (singlet, 3H, methyl ester), 4.25 (doublet of doublets, 1H, C_2 proton, $J_{2,3} = 16$ Hz, $J_{2,4} = 1$ Hz), 3.05 (doublet of doublets, 1H, C_3 proton, $J_{2,3} = 16$ Hz, $J_{3,4} = 7$ Hz); ultraviolet, λ_{\max} 227 $m\mu$ ($\epsilon = 5,600$).

Preparation of Olefinic Acid 151

To a stirred solution of 34 g of potassium carbonate dissolved in 200 ml of methanol-water was added 23 g of unsaturated ester 150. The reaction mixture was stirred at reflux for 3 h. Most of the methanol was then removed under reduced pressure and water added to the residue. This aqueous solution was thoroughly extracted with ether. The ethereal layer was washed with water and with brine and dried over anhydrous magnesium sulfate. The concentrated extract afforded 2 g of starting ester 150. The aqueous layer was acidified with dilute hydrochloric acid and thoroughly extracted with ether. The ether extract was washed with water and brine and dried over anhydrous magnesium sulfate. Removal of the solvent and vacuum distillation afforded 15 g (82%) of a colorless oil, b.p. 75° at 0.6 mm; lit. (106) b.p. 99-110°

at 10 mm; n_D^{27} 1.4454. This unsaturated acid 151 exhibited infrared (film), λ_{\max} 3.1-4.0, 5.9, 6.1 μ ; n.m.r., τ 8.95 (doublet, 6H, gem-dimethyl groups, $J = 6.5$ Hz), 7.25-7.8 (multiplet, 1H, C_4 proton), 4.2 (doublet of doublets, 1H, C_2 proton, $J_{2,3} = 15.5$ Hz, $J_{2,4} = 1.5$ Hz), 2.9 (doublet of doublets, 1H, C_3 proton, $J_{2,3} = 15.5$ Hz, $J_{3,4} = 6.5$ Hz), -2.15 (singlet, 1H, CO_2H); ultraviolet, λ_{\max} 217 m μ ($\epsilon = 3634$).

Anal. Calcd. for $C_6H_{10}O_2$: C, 63.14; H, 8.83. Found: C, 62.85; H, 8.76.

Preparation of Ethyllithium

To 600 ml of anhydrous ether under nitrogen was added 25.8 g of finely cut lithium wire. To the stirred mixture was added dropwise a solution of 120 ml of ethyl bromide (distilled from calcium hydride) in 300 ml of anhydrous ether. During the addition the reaction mixture was kept at -10° by an external dry ice-acetone cooling bath. After the addition was complete the solution was warmed to 0° for 1 h, filtered and used immediately.

Preparation of *trans*-6-methylhept-4-ene-3-one (144)

A solution of 32 g of unsaturated acid 151 in 540 ml of anhydrous ether was cooled to -78° by an external dry ice-acetone bath. To this solution 600 ml of the previously prepared ethyllithium solution was added dropwise. After the addition was complete, the resulting white slurry was allowed to stir for an additional hour. Then the cooling bath was removed and the stirring continued until a clear solution resulted.

It was then poured into a stirred and cooled 1 N hydrochloric acid solution. The resulting solution was thoroughly extracted with ether. The ether layer was washed with dilute ammonium hydroxide, water and brine and dried over anhydrous magnesium sulfate. The solvent was then carefully removed by distillation through a Vigreux column at atmospheric pressure. The residue was fractionally distilled to give 17 g (92%, based on recovered starting material) of unsaturated ketone b.p. 54° at 10 mm. This product gave infrared, n.m.r. and ultraviolet spectra which were superimposable with those obtained for trans-6-methylhept-4-ene-3-one (144) by the previous preparation.

Preparation of Octalone 155

The enamine of cyclohexanone was prepared by the method of Stork et al. (66).

A solution of 6 g of freshly distilled cyclohexanone and 9 g of pyrrolidine in 20 ml of benzene were refluxed under a Dean-Stark water separator until no further separation of water occurred (approximately 3 h). The excess pyrrolidine and benzene were removed on a rotary evaporator and the residue distilled under vacuum to afford 6 g (79%) of the pyrrolidine enamine of cyclohexanone, b.p. 60-70° at 0.6 mm; lit. (66) b.p. 105-107° at 13 mm. Infrared (film), λ_{\max} 6.1 μ .

A solution of 6 g (0.02 mole) of the pyrrolidine enamine of cyclohexanone and 2.6 g (0.02 mole) of trans-6-methylhept-4-en-3-one (144) were stirred together under nitrogen at 60° for 40 h. Then 12 ml of anhydrous dioxane was added and the reaction mixture refluxed

overnight. To the reaction mixture was added 1 ml glacial acetic acid, 2 ml water and 0.5 g anhydrous sodium acetate and reflux maintained for 4 h. The cooled reaction mixture was diluted with water and the resulting solution thoroughly extracted with ether. The combined ether extracts were washed with water, dilute hydrochloric acid, water and brine before being dried over anhydrous magnesium sulfate. The solvent was removed and the residue distilled under vacuum to afford 3.5 g (83%) of a pale yellow oil, b.p. 100° at 0.2 mm. This was shown by g.l.c. to contain a 70:30 mixture of octalone 155a and 155b, respectively. Analytical samples of these two components were collected by preparative g.l.c. (column E, 200°, 86) and exhibited the following spectral properties:

Major epimer: Infrared (film), λ_{\max} 6.0, 6.15 μ ; n.m.r., τ 9.21, 9.11 (pair of doublets, 6H, isopropyl methyl groups, $J = 7$ Hz), 8.26 (singlet, 3H, vinyl methyl); ultraviolet, λ_{\max} 249 m μ ($\epsilon = 13,600$).

Mol. Wt. Calcd. for C₁₄H₂₂O: 206.167. Found (high resolution mass spectrometry): 206.166.

Minor epimer: Infrared (film), λ_{\max} 6.0, 6.1 μ ; n.m.r., τ 9.11 (doublet, 6H, isopropyl methyl groups, $J = 6$ Hz), 8.26 (singlet, 3H, vinyl methyl); ultraviolet λ_{\max} 249 m μ ($\epsilon = 13,400$).

Mol. Wt. Calcd. for C₁₄H₂₂O: 206.167. Found (high resolution mass spectrometry): 206.166.

Preparation of 4-ethylenedioxycyclohexanone (156)

A solution of 3 g (14 mmoles) of keto ester 113, 1.5 g of potassium hydroxide and 30 ml of 1:1 methanol-water was refluxed for

4 h. At the end of this time the methanol was removed in vacuo. The aqueous layer was acidified with glacial acetic acid and thoroughly extracted with ether. The combined ether extracts were washed with water, saturated sodium bicarbonate solution, water and brine and dried over anhydrous magnesium sulfate. The ether layer was concentrated and the residue crystallized on standing. Recrystallization from n-hexane afforded 1.5 g (66%) of white plates, m.p. 69-70°. Infrared (nujol), λ_{\max} 3.45, 5.85 μ ; n.m.r., τ 7.17-8.00 (unresolved multiplet, 8H, ring protons), 5.84 (singlet, 4H, ketal protons).

Preparation of Octalone 157

The enamine of keto ketal 156 was prepared by the method of Stork et al. (66).

A solution of 1 g of keto ketal 156 and 0.5 g of freshly distilled pyrrolidine in 10 ml of anhydrous benzene were refluxed under a Dean-Stark water separator until no further separation of water occurred. The excess pyrrolidine and benzene were removed on the rotary evaporator and the residue distilled under vacuum to yield 1 g (86%) of a colorless oil, b.p. 128-138° at 0.3 mm; lit. (66) b.p. 110-120° at 0.1-0.15 mm. Infrared (film), λ_{\max} 6.1 μ .

A solution of 1 g of the previously prepared pyrrolidine enamine of 156, 500 mg of vinyl ketone 144 in 4 ml of dry dioxane were refluxed together for 48 h. Then 1.1 ml of the following solution was added: 1 ml acetic acid, 2 ml water and 0.5 g sodium acetate. These reagents were refluxed together for 1.5 h. The cooled reaction mixture was then diluted with water and thoroughly extracted with ether.

The combined ether extracts were washed with water, sodium carbonate solution, water and brine and dried over anhydrous magnesium sulfate.

The concentrated ether extract was distilled to afford 121 mg (8%) b.p. 150° at 0.1 mm, of a viscous oil. G.l.c. analysis (column E, 180°, 85) revealed two components in the ratio 1:4 respectively.

Analytical samples were collected by preparative g.l.c. using the above conditions. The minor isomer, octalone 157a, exhibited the following spectra: ultraviolet, λ_{\max} 243 m μ (ϵ = 13,000); infrared (film), λ_{\max} 6.05 μ ; n.m.r., τ 9.18, 9.08 (pair of doublets, 6H, isopropyl methyl groups, J = 6.5 Hz), 8.23 (singlet, 3H, vinyl methyl), 6.06 (singlet, 4H, ketal protons).

Mol. Wt. Calcd. for $C_{16}H_{24}O_3$: 264.172. Found (high resolution mass spectrometry): 264.172.

The major isomer, octalone 157b, exhibited the following spectra: ultraviolet, λ_{\max} 243 m μ (ϵ = 18,900); infrared (film), λ_{\max} 6.01, 6.15 μ ; n.m.r., τ 9.08, 9.06 (pair of doublets, 6H, isopropyl methyl groups, J = 6.0 Hz), 8.23 (singlet, 3H, vinyl methyl), 6.06 (singlet, 4H, ketal protons).

Mol. Wt. Calcd. for $C_{16}H_{24}O_3$: 264.172. Found (high resolution mass spectrometry): 264.172.

Preparation of Quintol Monobenzoate (160)

This compound was prepared using the procedure of Jones and Sondheimer (73).

To a solution of 125 g (1.0 mole) of quintol (159) dissolved in a mixture of 355 ml of anhydrous chloroform and 292 ml of anhydrous

pyridine, was added dropwise over 5 h 148 g (1.04 mole) of benzoyl chloride in 307 ml of anhydrous chloroform. The temperature was kept at 0° during the addition by an external ice bath. After standing at room temperature for 2 days, the chloroform solution was thoroughly washed with water, dilute sulphuric acid, water and brine and dried over anhydrous magnesium sulfate. After removal of the solvent the oily residue was fractionally distilled to afford 140 g (62%) of quintol monobenzoate 160, b.p. 160-165° at 0.3 mm; lit. (73) b.p. 175-178° at 0.2 mm. The product exhibited infrared (film), λ_{max} 2.93, 5.85, 6.3, 6.35 μ ; n.m.r., τ 1.95-2.55 (unresolved multiplet, 5H, phenyl protons), 4.95 (broad singlet, 1H, $-\text{CH}-\overset{\text{O}}{\parallel}\text{C}_6\text{H}_5$), 6.25 (broad singlet, 1H, $-\text{CH}-\text{OH}$), 6.64 (singlet, 1H, exchangeable, OH), 8.20 (multiplet, 8H, remaining ring protons).

Preparation of 4-Benzoyloxycyclohexanone (161)

To a cooled and stirred solution of 50 g of quintol monobenzoate (160) in 85 ml of glacial acetic acid was added 22 g of chromium trioxide in 12.5 ml of water and 50 ml of glacial acetic acid. The temperature was maintained below 35° during the addition and then at room temperature for an additional 12 h. After this period ether was added and the solution thoroughly washed with water, dilute sodium hydroxide solution, water and brine and dried over anhydrous magnesium sulfate. Removal of the solvent afforded 48 g of a white crystalline product. Recrystallization from ether-petroleum ether (30-60°) gave 42 g (87%) of the keto ester 161 m.p. 59-61°; lit. (73) m.p., 62°. The keto ester 161 exhibited infrared (nujol), λ_{max} 5.85, 6.25, 6.3 μ ;

n.m.r., τ 1.95-2.55 (unresolved multiplet, 5H, phenyl protons), 4.55 (broad singlet, 1H, $\text{CH}-\text{O}-\overset{\text{O}}{\parallel}\text{C}_6\text{H}_5$), 7.50 (unresolved multiplet, 8H, remaining ring protons).

Preparation of 4-Hydroxycyclohexanone (158)

This compound was prepared by a procedure analogous to Jones and Sondheimer (73).

A solution of 80 g of 4-benzoyloxycyclohexanone (161) in 320 ml of dry methanol, containing 0.8 g of sodium metal, was refluxed for 18 h. To the cooled reaction mixture water and dry ice were added. After the solution became homogeneous, the methanol was removed on the rotary evaporator. To this viscous solution, water and ether were added. The solution was thoroughly extracted with ether to remove the methyl benzoate. The aqueous layer was then carefully distilled to give 30.6 g (74%) of a clear colorless oil, b.p. 92° at 1.1 mm; lit. (73), b.p. 83-85 at 0.6 mm. The product was shown to be homogeneous by g.l.c. analysis (column F, 180°, 85). The alcohol exhibited infrared (film), λ_{max} 2.95, 5.85 μ ; n.m.r., τ 5.85 (multiplet, 1H, $\text{C} \begin{array}{l} \nearrow \text{OH} \\ \searrow \text{H} \end{array}$), 6.25 (singlet, 1H, exchangeable on D_2O addition, OH).

Preparation of Octalone 162

A solution of 18 g (0.16 mole) of 4-hydroxycyclohexanone (158) and 20.7 ml of pyrrolidine in 234 ml of benzene were refluxed under a Dean-Stark water separator until no further separation of water occurred (approximately 3 h). The benzene and excess pyrrolidine were removed under vacuum (0.1 mm) to yield a white crystalline enamine.

Infrared (nujol), λ_{\max} 3.0, 6.1 μ . To the above enamine under nitrogen was added 13.5 g (0.1 mole) of trans-6-methylhept-4-en-3-one (144). These reagents were stirred together at 50° for 17 h. At this time the infrared spectrum of the enamine mixture exhibited absorptions for the starting enamine, the enamine of the octalone 162 but no vinyl ketone. Hence, an additional 5 g of vinyl ketone 144 was added and stirring continued for an additional 19 h. Dry dioxane was then added and the solution refluxed for 16 h. To this reaction mixture was added the hydrolysis solution, consisting of 5 g anhydrous sodium acetate, 10 ml glacial acetic acid and 20 ml of water and the solution refluxed for 4 h. The cooled reaction mixture was then diluted with water and thoroughly extracted with ether. The combined ether extracts were washed successively with water, dilute hydrochloric acid, water and brine and dried over anhydrous magnesium sulfate. The ether was removed under reduced pressure and the oily residue distilled to afford 14 g (40%) of the desired octalone 162, b.p. 200° at 0.1 mm. This was shown by g.l.c. analysis (column G, 215°, 170) to be a 3:2 mixture of octalone (162a plus 162c) and octalone (162b plus 162d), respectively. These two components were isolated by g.l.c. and then distilled to give the following spectral data: Major epimer octalones 162a + 162c: Infrared (CHCl_3), λ_{\max} 2.75, 2.9, 6.05 μ ; n.m.r., τ 9.16, 9.07 (pair of doublets, 6H, isopropyl methyl groups, $J = 6.5$ Hz), 8.23 (singlet, 3H, vinyl methyl), 6.15, 5.82 (unresolved multiplets, 1H, $\text{C} \begin{smallmatrix} \text{OH} \\ \text{H} \end{smallmatrix}$); ultraviolet, λ_{\max} 248 m μ ($\epsilon = 10,900$).

Mol. Wt. Calcd. for $\text{C}_{14}\text{H}_{22}\text{O}_2$: 222.162. Found (high resolution

mass spectrometry): 222.162.

Minor epimer octalones 162b + 162d: Infrared (CHCl_3), λ_{max} 2.75, 2.9, 6.05, 6.15 μ ; n.m.r., τ 9.07, 9.04 (pair of doublets, 6H, isopropyl methyl groups, $J = 6$ Hz), 8.26 (singlet, 3H, vinyl methyl group), 6.10, 5.78 (unresolved multiplet, 1H, $\text{C} \begin{array}{l} \text{OH} \\ \diagup \\ \text{H} \end{array}$); ultraviolet, λ_{max} 247 $\text{m}\mu$ ($\epsilon = 9,272$).

Mol. Wt. Calcd. for $\text{C}_{14}\text{H}_{22}\text{O}_2$: 222.162. Found (high resolution mass spectrometry): 222.162.

Epimerization of Octalone 162

To a solution of 100 mg of sodium metal dissolved in 20 ml of methanol was added 2 g of the 3:2 epimeric mixture of octalones 162. The solution was refluxed under nitrogen for 12 h. Then most of the methanol was removed at aspirator pressure and water added. The resulting solution was thoroughly extracted with ether. The combined ether extracts were washed with water, dilute hydrochloric acid, water and brine and dried over anhydrous magnesium sulfate. The dried ethereal extract was concentrated and distilled under vacuum to afford 1.8 g (90%) of a pale yellow oil, b.p. 200° at 0.1 mm. G.l.c. analysis (column G, 215° , 170) showed the epimers to now be in the ratio of 7:3. These two components were isolated by g.l.c. and exhibited g.l.c. retention times, infrared, n.m.r. and ultraviolet spectra identical with the two starting epimers.

Preparation of Dione 163

A solution of 60 mg of chromium trioxide in 1.5 ml of methylene chloride containing 0.09 ml pyridine was allowed to stir at room temperature for 15 min. To this solution was added 30 mg of octalones 162a + 162c in 0.5 ml methylene chloride and the solution allowed to stir for 25 min at room temperature. At the end of this time the reaction mixture was diluted with 8 ml of ether. The ether layer was washed twice with water and brine and dried over anhydrous magnesium sulfate. The concentrated residue afforded 28 mg (94%) of dione 163, m.p. 108-110°. This compound exhibited one peak on g.l.c. analysis (column E, 180°, 86); infrared (CHCl₃), λ_{\max} 5.85, 6.05, 6.15 μ ; n.m.r., τ 9.20, 9.07 (pair of doublets, 6H, isopropyl methyl groups, J = 6.5 Hz), 8.12 (singlet, 3H, vinyl methyl); ultraviolet, λ_{\max} 247 m μ (ϵ = 13,000).

Anal. Calcd. for C₁₄H₂₀O₂: C, 76.33; H, 9.15. Found: C, 76.28; H, 9.18.

Preparation of Methanesulfonate Derivative 164

To a solution of 200 mg of octalone 162 in 5 ml of dry pyridine, at 0°, was added 0.1 ml of methanesulfonyl chloride. The reaction mixture was then allowed to stir at room temperature for 3.5 h. Ice was added and the solution allowed to stir for an additional 10 min. The solution was then thoroughly extracted with ether. The combined ether extracts were washed with water, dilute sulfuric acid (until acidic), aqueous sodium bicarbonate (until neutral), and brine and dried over anhydrous magnesium sulfate. Removal of the solvent in vacuo

afforded 250 mg (85%) of an oily methanesulfonate derivative 164.

Infrared (film), λ_{\max} 6.0, 7.45, 8.55 μ .

Reduction of Octalone 155

To 150 ml of liquid ammonia (distilled from sodium metal) was added 200 mg of finely cut lithium wire. After the lithium had dissolved, 450 mg of octalone 155 dissolved in 25 ml of anhydrous ether was added dropwise over 0.5 h. The reaction mixture was allowed to stir for an additional 1.5 h, and then ammonium chloride added to discharge the blue color. After all the ammonia had evaporated water was added and this aqueous solution thoroughly extracted with ether. The combined ether extracts were washed successively with water, dilute hydrochloric acid, water and brine and dried over anhydrous magnesium sulfate. The ether was removed in vacuo and the oily residue vacuum distilled to afford 350 mg (78%) of a pale yellow oil, b.p. 125° at 0.6 mm. This exhibited two components in a 3:1 ratio on g.l.c. analysis (column F, 215°, 110). Analytical samples of these two components were collected by g.l.c. and exhibited the following spectral properties:

Major component (decalone 165a): Infrared (film), λ_{\max} 3.42, 3.51, 5.85 μ ; n.m.r., τ 9.23, 9.13 (pair of doublets, 6H, isopropyl methyl groups, $J = 7$ Hz), 8.99 (doublet, 3H, secondary methyl, $J = 6.5$ Hz).

Anal. Calcd. for $C_{14}H_{24}O$: C, 80.71; H, 11.61. Found: C, 80.48; H, 11.31.

Minor component (decalone 165b): Infrared (film), λ_{\max} 3.45, 5.85 μ ; n.m.r., τ 9.13, 9.09 (pair of doublets, 6H, isopropyl methyl groups, $J = 6$ Hz), 9.02 (doublet, 3H, secondary methyl, $J = 6.5$ Hz).

Mol. Wt. Calcd. for $C_{14}H_{24}O$: 208.183. Found (high resolution mass spectrometry): 208.182.

Reduction of Methanesulfonate Derivative 164

A solution of 280 mg of the methanesulfonate derivative 164 in 1.8 ml of absolute ethanol was added dropwise to a solution of 1.35 g of lithium dissolved in 50 ml of liquid ammonia (distilled from sodium metal) at -78° . The mixture was stirred at -78° for 1 h then for 1.5 h at -33° . The reaction was quenched by careful addition of ethanol. The liquid ammonia was then allowed to evaporate and water added. This aqueous solution was thoroughly extracted with ether. The combined ether extracts were washed with water and brine and dried over anhydrous magnesium sulfate. The solvent was removed in vacuo and the residue vacuum distilled to afford 160 mg (98%) of a mixture of alcohol-containing products, b.p. 120° at 0.25 mm. Infrared (film), λ_{\max} 3.0 μ . This product was immediately dissolved in 12 ml of acetone (distilled from potassium permanganate) and 0.8 ml of a standard chromic acid solution (76) was added dropwise until the orange color persisted. The orange color was then discharged by addition of isopropanol and most of the acetone removed on the rotary evaporator. The residue was then diluted with water and the solution thoroughly extracted with ether. The combined ether extracts were washed with water and brine and dried over anhydrous magnesium sulfate. The solvent was removed in vacuo and vacuum distillation of the residue afforded 136 mg (85%) of the decalones 165a and 165b, b.p. 125° at 0.6 mm. Decalones 165a and 165b were shown by g.l.c. analysis (column F, 215° , 110) to be in the ratio

of 70:30. Analytical samples of these two products were collected and shown to have identical g.l.c. retention times, infrared and n.m.r. spectra with the two products from the Birch reduction of octalones 155a and 155b.

Birch Reduction of Octalone 155a

To a solution of 35 mg of lithium metal in 100 ml of liquid ammonia (freshly distilled from sodium metal) was added over 15 min 103 mg (0.5 mmole) of octalone 155a in 5 ml of anhydrous ether containing 0.094 ml of anhydrous ethanol. The reaction mixture was allowed to stir for 2 h. The reaction was then quenched by careful addition of excess ethanol, and the ammonia allowed to evaporate. The residual material was diluted with saturated brine and extracted three times with ether. The ether was removed at aspirator pressure and the crude material oxidized by Jones reagent as described above. This procedure afforded 94.6 mg (91%) of decalone 165a. Analysis of the product by g.l.c. (column F, 215°, 110) revealed the presence of only one component. The spectral data of this product (n.m.r., i.r., g.l.c. retention time) were identical with those of decalone 165a previously prepared.

Hydrogenation of Octalone 155b

A solution of 100 mg of octalone 155b [isolated by preparative g.l.c. (column F, 180°, 110)] dissolved in 10 ml of freshly distilled ethyl acetate was hydrogenated at atmospheric pressure and room temperature over 10 mg of 10% palladium on charcoal. After filtration

and removal of the solvent the residue was vacuum distilled to afford 96 mg (92%) of a colorless oil, b.p. 125° at 0.6 mm. This material was subjected to the previously described sodium methoxide epimerization conditions to epimerize the α -methyl group. The resulting product was shown to contain 98% of one component by g.l.c. analysis (column F, 180°, 100). An analytical sample gave infrared and n.m.r. spectra that were superimposable with those of the minor isomer of the Birch reduction of octalone 155 or mesylate 164.

Preparation of Thioketal 166

The major epimer of octalone 162 was collected by preparative g.l.c. (column G, 230°, 110). To a 3.6 g sample of octalones 162a and 162c was added 3.0 ml of ethanedithiol. This solution was cooled to 0° and 1.4 ml of boron trifluoride etherate was added. The solution was allowed to warm to room temperature and allowed to stir for 1 h. The solution was then diluted with water and thoroughly extracted with chloroform. The chloroform extracts were combined and washed with water and brine and dried over anhydrous magnesium sulfate. The concentrated extract gave 5.2 g of crude thioketal. This material was then filtered through a 20 g bed of Woelm activity I neutral alumina. The concentrated filtrate crystallized on standing. It was recrystallized from ether to afford 3.2 g (66%) of white rectangular crystals, m.p. 109-110°. An analytical sample exhibited the following spectral properties: infrared (nujol), λ_{\max} 3.0, 6.1 μ ; n.m.r., τ 9.21, 9.02 (pair of doublets, 6H, isopropyl methyl groups, $J = 7$ Hz), 8.57 (singlet, 1H, exchanges on D₂O addition, C-OH), 8.07 (singlet, 3H, vinyl methyl),

6.67 (singlet, 4H, thioketal protons), 5.86 (unresolved multiplet, 1H, CHOH (equatorial)).

Mol. Wt. Calcd. for $C_{16}H_{26}OS_2$: 298.142. Found (high resolution mass spectrometry): 298.144.

Preparation of Alcohol 167

To a solution of 700 mg (1.44 mmoles) of thioketal 166 in 100 ml of absolute ethanol was added 10 g of commercial Raney nickel. The solution was refluxed for 5 h. The solution was then cooled and the Raney nickel removed by suction filtration through a bed of Celite. The filtrate was concentrated and the residual oil vacuum distilled to afford 350 mg (77%) of a viscous colorless alcohol 167, b.p. 120° at 0.25 mm. On g.l.c. analysis (column F, 215° , 110) this product exhibited one major peak along with trace amounts of unidentified components. An analytical sample of the major component was collected by preparative g.l.c. (column G, 215° , 110) and exhibited infrared (film), λ_{\max} 3.0, 6.0 μ ; n.m.r., τ 9.23, 9.09 (pair of doublets, 6H, isopropyl methyl groups, $J = 6.5$ Hz), 8.40 (singlet, 3H, vinyl methyl), 7.52 (singlet, 1H, exchanges on D_2O addition, hydroxyl proton), 6.36, 5.85 (unresolved multiplets, totalling 1H, CHOH).

Mol. Wt. Calcd. for $C_{14}H_{24}O$: 208.183. Found (high resolution mass spectrometry): 208.183.

Preparation of Octalone 168

To an ice-cold solution of 720 mg of chromium trioxide dissolved in 18 ml of anhydrous pyridine was added 350 mg of alcohol 167 in 9 ml

of anhydrous pyridine. The solution was allowed to stir at room temperature for 40 h. The reaction mixture was then poured into stirred anhydrous ether. Celite was then added and the mixture filtered. The filtrate was thoroughly washed with water and brine and dried over anhydrous magnesium sulfate. After removal of the solvent the oily residue was distilled under vacuum to yield 307 mg (89%) of a colorless oil, b.p. 130° at 0.35 mm. This product was shown to be homogeneous by g.l.c. (column F, 180°, 85). An analytical sample exhibited infrared (film), λ_{\max} 5.85 μ ; n.m.r., τ 9.21, 9.05 (pair of doublets, 6H, isopropyl methyl groups, $J = 6.5$ Hz), 8.36 (singlet, 3H, vinyl methyl).

Mol. Wt. Calcd. for $C_{14}H_{22}O$: 206.167. Found (high resolution mass spectrometry): 206.168.

Preparation of Alcohol 169

A solution of 230 mg (1.06 mmoles) of octalone 168 dissolved in 30 ml of anhydrous ether was cooled to 0°. To this solution was added, dropwise, 2 ml of 2.16 M methyllithium (4.32 mmoles). After the addition was complete the solution was allowed to stir for 2 h at room temperature. It was then poured onto a mixture of ice and water. The ether layer was separated and washed with water and brine and dried over anhydrous magnesium sulfate. The solvent was removed at aspirator pressure and the oily residue vacuum distilled to afford 224 mg (91%) of a viscous oil, b.p. 130° at 0.25 mm. This oil was shown to contain one major component along with trace amounts of unidentified material on g.l.c. analysis (column G, 200°, 110). The major component was g.l.c. isolated and shown to be a white crystalline

substance, m.p. 79-80°. Infrared (nujol), λ_{\max} 3.0, 6.1 μ ; n.m.r., τ 9.21, 9.07 (pair of doublets, 6H, isopropyl methyl groups, $J = 6.5$ Hz), 8.81 (singlet, 3H, tertiary methyl group), 8.37 (singlet, 3H, vinyl methyl).

Mol. Wt. Calcd. for $C_{15}H_{26}O$: 222.198. Found (high resolution mass spectrometry): 222.198.

Preparation of Cadinene Dihydrochloride 41

A solution of 100 mg of crystalline g.l.c. isolated alcohol 169 in 10 ml of anhydrous ether was cooled to 0° and dry hydrogen chloride gas passed in. At the end of 15 min, the gas flow was stopped and the solution stirred for an additional hour. The ether was then removed under vacuum and the residue crystallized to afford 100 mg (80%) of compound 41. An analytical sample was recrystallized from n-hexane-methanol to afford white crystals, m.p. 104.5-106°. This sample showed no depression of melting point on admixture with an authentic sample of cadinene dihydrochloride and its infrared spectrum was superimposable with that of the authentic sample. Infrared (nujol), λ_{\max} 3.45, 6.95, 8.75, 11.75 μ .

Anal. Calcd. for $C_{15}H_{26}Cl_2$: C, 65.01; H, 9.39. Found: C, 64.75; H, 9.52.

Preparation of Octalone 172

This compound was prepared by the procedure of Marshall and Fanta (82).

A solution of 56 g (0.5 mole) of 2-methylcyclohexanone and 3 ml of 3 N ethanolic sodium ethoxide were placed under nitrogen in a flame-dried flask equipped with a dropping funnel and mechanical stirrer. The reaction vessel and contents were then cooled to -10° by a thermostatically controlled constant temperature bath. To the reaction mixture was added 35 g (0.5 mole) of methyl vinyl ketone over a 6 h period. The reaction mixture was then allowed to stir for an additional 6 h. The intermediate ketol 174 was then dehydrated by the addition of 400 ml of 15% potassium hydroxide and the resulting octalone 172 removed from the reaction mixture by continuous steam distillation. The steam distillate was saturated with sodium chloride and extracted with ether. The ether extracts were dried over anhydrous magnesium sulfate and then concentrated. The residue was distilled under reduced pressure to afford 39.3 g (48%) of octalone 172, b.p. 73° at 0.4 mm; lit. (82) b.p. $82-83^{\circ}$ at 0.7 mm. An analytical sample collected by g.l.c. (column H, 200° , 85), exhibited n_D^{20} 1.5249; lit. (82) n_D^{25} 1.5230. Ultraviolet, λ_{\max} 239 m μ (ϵ = 14,400); infrared (film), λ_{\max} 5.96, 6.17 μ ; n.m.r., τ 8.74 (singlet, 3H, tertiary methyl), 4.29 (singlet, 1H, vinyl proton).

Preparation of Dienone 175

To a solution of 20.4 g (90 mmoles) of 2,3-dichloro-5,6-dicyano-benzoquinone and 1 g of benzoic acid in 150 ml dry benzene was added 10 g (61 mmoles) of octalone 172. This solution was refluxed under

nitrogen for a 48 h period. To the cooled reaction mixture was added with stirring 150 ml of methylene chloride and Celite. After filtration, the solution was passed through a 100 g bed of Woelm activity III neutral alumina. An additional 400 ml of methylene chloride was passed through the alumina and the combined elutants flask evaporated and vacuum distilled to yield 7.1 g (72%) of a yellow oil, b.p. 110-115° at 0.5 mm; lit. (84) b.p. 129° at 4 mm. The distilled product was subjected to g.l.c. analysis (column H, 200°, 85) and showed 88% dienone and 12% trienone. An analytical sample of dienone was collected by preparative g.l.c. (column C, 200°, 110) which exhibited n_D^{21} 1.5470; infrared (film), λ_{\max} 6.0, 6.15, 6.2 μ ; n.m.r., τ 8.74 (singlet, 3H, tertiary methyl), 3.94 (singlet, 1H, C₁ proton), 3.31, 3.84 (pair of doublets, 2H, C₄ and C₃ protons respectively, J = 9 Hz); ultraviolet, λ_{\max} 240 m μ (ϵ = 10,500).

Hydrogenation of Dienones 175 + 176

A suspension of 300 mg of 5% palladium on charcoal in 200 ml of 0.005 N ethanolic potassium hydroxide was placed in an atmospheric pressure hydrogenation apparatus at room temperature and allowed to equilibrate for 1.5 h. A solution of dienones 175 + 176 was then introduced by syringe. After 45 min the required amount of hydrogen had been absorbed. The reaction mixture was filtered through a bed of Celite and the filtrate concentrated in vacuo. The residue was chromatogrammed on 1 kg of Woelm activity III neutral alumina. The fractions eluted with 90% benzene-petroleum ether (30-60°) afforded 14.3 g (70%) of the desired dienone 175. G.l.c. analysis (column C,

200°, 110) revealed the presence of up to 3% impurities.

Preparation of Octalone 173

This compound was prepared by the procedure of Marshall and Fanta (82).

To a flame-dried flask under nitrogen was added 56 g of 2-methylcyclohexanone and 3 ml of 3 N ethanolic sodium ethoxide. The resulting yellow solution was cooled to -10°. Over a period of 6 h, 42 g of ethyl vinyl ketone was added. The viscous reaction mixture was allowed to stir for an additional 6 h. At the end of this period, 400 ml of 15% potassium hydroxide was added and the solution subjected to continuous steam distillation. The 4 l. of steam distillate collected, were thoroughly extracted with ether. The combined ethereal extracts were washed with brine and dried over anhydrous magnesium sulfate. The ether was removed at aspirator pressure and the residue distilled under vacuum to afford two distinct fractions. The first fraction contained 11 g of starting material, 2-methylcyclohexanone, b.p. 36-42° at 2.5 mm, while the second fraction contained 53 g (60%) of the desired octalone 173, b.p. 96-100° at 0.6 mm; lit. (57) b.p. 74-78° at 0.4 mm. An analytical sample was collected by preparative g.l.c. (column H, 200°, 85) and exhibited n_D^{22} 1.5439, infrared (film), λ_{\max} 6.0, 6.2 μ ; n.m.r., τ 8.77 (singlet, 3H, tertiary methyl), 8.22 (singlet, 3H, vinyl methyl); ultraviolet, λ_{\max} 246 m μ (ϵ = 15,500).

Preparation of Dienone 177

This compound was prepared by a procedure similar to that used by Kropp (57).

To a solution of 7.7 g (33 mmoles) of 2,3-dichloro-5,6-dicyano-benzoquinone and 25 ml glacial acetic acid in 250 ml anhydrous benzene was added 4 g (22 mmoles) of octalone 173. This solution was allowed to reflux for 60 h under nitrogen. Then the reaction mixture was cooled, filtered, concentrated and ether added. The ethereal layer was washed successively with water, 10% sodium bicarbonate solution, water and saturated brine and dried over anhydrous magnesium sulfate. The concentrated extract was distilled at 154° at 0.2 mm to afford 6.5 g (84%) of a pale yellow oil; n_D^{25} 1.5234. The product was greater than 95% pure by g.l.c. analysis (column B, 180°, 80). The dienone exhibited ultraviolet, λ_{\max} 240 m μ (ϵ = 10,500); infrared (film), λ_{\max} 6.0, 6.15, 6.2 μ ; n.m.r., τ 8.78 (singlet, 3H, tertiary methyl), 8.12 (singlet, 3H, vinyl methyl), 3.80, 3.31 (AB quartet, 2H, C₃ and C₄ protons respectively, J = 10 Hz).

Preparation of Tri-n-butylphosphine Copper I Iodide

The procedure employed is that of Kaufman et al. (90).

A suspension of 13.15 g of cuprous iodide, 130 g of potassium iodide, 10.15 g of tri-n-butylphosphine and 100 ml of water were shaken together until the initially formed greasy precipitate became crystalline. The precipitate was filtered and recrystallized from isopropanol-ethanol to afford 17.6 g (89%) of white crystalline complex, m.p. 74.5-75.5°; lit. (90) m.p. 75°.

Preparation of Octalone 188

To an ice-cold slurry of 6.84 g of cuprous iodide in 150 ml of anhydrous ether was added 34.3 ml of 2.1 M methyllithium in ether solution. To the resulting clear solution was added, dropwise over 1 h, 1 g (6.2 mmoles) of dienone 175. The resulting thick yellow solution was immediately quenched by addition to a saturated ammonium chloride solution. The ammonium chloride solution was thoroughly extracted with ether. The ether extract was washed with water, dilute ammonium hydroxide, water and brine and dried over anhydrous magnesium sulfate. The ether extract was concentrated and distilled (b.p. 124° at 0.3 mm). The distillate was chromatogrammed on 40 g of MN silica gel and the fractions eluted with 15% ether-petroleum ether (30-60°) afforded 900 mg (82%) of a clear colorless oil. This oil showed a single peak on analysis by g.l.c. (column E, 190°, 86). The product exhibited infrared (film), λ_{\max} 6.0, 6.15 μ ; n.m.r., τ 9.02 (doublet, 3H, secondary methyl, $J = 7$ Hz), 8.74 (singlet, 3H, tertiary methyl), 4.30 (singlet, 1H, vinyl H); ultraviolet, λ_{\max} 239 m μ ($\epsilon = 14,000$).

Preparation of Octalone 191

The cross-conjugate addition to dienone 177 by lithium dimethylcuprate was carried out by a procedure identical to the above. From 1 g of dienone 177 after distillation, b.p. 125° at 0.3 mm, was obtained 1 g (92%) of octalone 191. This product was shown to be homogeneous by g.l.c. (column E, 200°, 86). Infrared (film), λ_{\max} 6.0, 6.2 μ ; n.m.r., τ 9.04 (doublet, 3H, secondary methyl, $J = 6.5$ Hz),

8.74 (singlet, 3H, tertiary methyl), 8.25 (doublet, 3H, vinyl methyl, $J = 1$ Hz); ultraviolet, λ_{\max} 249 m μ ($\epsilon = 13,800$).

This compound was further characterized as a red 2,4-dinitrophenyl-hydrazone, recrystallized from ethanol, m.p. 174-175°.

Anal. Calcd. for $C_{19}H_{24}N_4O_4$: C, 61.28; H, 6.50; N, 15.04. Found: C, 60.98; H, 6.42; N, 15.11.

Preparation of Octalone 194

A solution of 15 g of tri-n-butylphosphine copper (I) iodide in 150 ml of anhydrous ether was cooled to -78° by an external dry ice-acetone bath. To this colorless solution was added by syringe 22.8 ml of 3.2 M vinylolithium in tetrahydrofuran. To the resulting pale green solution was added over 1 h, 1 g (6.1 mmoles) of dienone 175 in 50 ml of anhydrous ether. The resulting thick yellow solution was allowed to stir for an additional 4 h. At the end of this time the reaction mixture was allowed to warm to room temperature and was quenched by pouring onto 250 ml of 10% hydrochloric acid. The aqueous solution was thoroughly extracted with ether. The combined ether extracts were washed with water, dilute ammonium hydroxide, water and brine and dried over anhydrous magnesium sulfate. After removal of the solvent, the product was roughly separated from the high boiling material by collecting all material with a boiling point less than 130° at 0.2 mm. The distillate was then chromatogrammed on 100 g of MN silica gel. The fractions eluted with 10% ether-petroleum ether (30-60°) afforded 870 mg (73%) of octalone 194. On analysis by g.l.c. this material exhibited only one peak (column E, 195°, 100). All

traces of solvent were removed on the vacuum pump (~ 0.1 mm) to afford an analytical sample. Infrared (film), λ_{max} 6.0, 6.2, 10.9 μ ; n.m.r., τ 8.72 (singlet, 3H, tertiary methyl), 3.89-5.13 (unresolved multiplet, 3H, vinyl protons), 4.25 (singlet, 1H, vinyl proton). Due to its instability this compound was not characterized further but immediately hydrogenated.

Hydrogenation of Octalone 194

The hydrogenation of octalone 194 was carried out in benzene (50 ml) at room temperature and atmospheric pressure using tris(triphenylphosphine)chlororhodium (120 mg) as catalyst. At the end of the hydrogen uptake the reaction mixture was filtered through a column of Woelm activity III neutral alumina (20 g) and eluted with an additional 100 ml of benzene. From 708 mg (3.73 mmoles) of octalone 194 was obtained after distillation 650 mg of a clear colorless oil. Analysis of this product by g.l.c. (column E, 180°, 100) showed that it consisted of 10% decalone 193 and 90% octalone 189. The mixture was chromatogrammed on a 50 g MN silica gel column. The fractions eluted with 8% ether-petroleum ether (30-60°) contained 57 mg of cis-decalone 193. The fractions eluted with 15% ether-petroleum ether (30-60°) contained 413 mg (58%) of the desired octalone 189. An analytical sample of octalone 189 exhibited the following spectral properties: infrared (film), λ_{max} 6.0, 6.2 μ ; n.m.r., τ 9.07 (triplet, 3H, CH_2CH_3 , $J = 4$ Hz), 8.73 (singlet, 3H, tertiary methyl), 4.21 (broad singlet, 1H, vinyl H); ultraviolet, λ_{max} 239 m μ ($\epsilon = 11,000$).

This compound was further characterized as a red 2,4-dinitrophenyl-

hydrazone derivative, recrystallized from ethanol, m.p. 118-120°.

Anal. Calcd. for $C_{19}H_{24}N_4O_4$: C, 61.28; H, 6.50; N, 15.04. Found: C, 61.07; H, 6.42; N, 15.05.

Preparation of Octalone 190

A solution of 15 g (38 mmoles) of tri-n-butylphosphine copper (I) iodide, 0.5 g anhydrous lithium bromide in 150 ml of anhydrous ether was cooled to -78° with an external dry ice-acetone bath. Then 39 ml (73 mmoles) of 1.86 M isopropylolithium in n-pentane was added, forming first a dark red and then a pale aqua solution. To this complex was added 1 g (6.1 mmoles) of dienone 175 in 50 ml of anhydrous ether over a 0.75 h period. The dark red reaction mixture was allowed to stir for an additional 5 h period. The reaction was then allowed to slowly warm to room temperature. This resulted in the formation of a copper mirror on the walls of the reaction vessel. The reaction mixture was transferred under nitrogen to a dropping funnel and slowly added to a rapidly stirred solution of 10% hydrochloric acid. The aqueous layer was separated and twice extracted with ether. The combined ethereal extracts were washed successively with water, dilute ammonium hydroxide, water and saturated brine and dried over anhydrous magnesium sulfate. After removal of the solvent, the residue was distilled and the distillate chromatogrammed on 25 g of MN silica gel. The fractions eluted with 20% ether-petroleum ether (30-60°) afforded 395 mg (95%) of octalone 190. This sample exhibited one component by g.l.c. (column E, 180°, 86). Infrared (film), λ_{\max} 6.0, 6.15 μ ; n.m.r., τ 9.2, 9.05 (pair of doublets, 6H, isopropyl methyl groups,

$J = 6.5$ Hz), 8.74 (singlet, 3H, tertiary methyl), 4.22 (broad singlet, 1H, vinyl H); ultraviolet, λ_{\max} 240 m μ ($\epsilon = 9,370$).

This compound was characterized as its 2,4-dinitrophenylhydrazone derivative, recrystallized from ethanol, m.p. 153-155°.

Anal. Calcd. for $C_{20}H_{26}N_4O_4$: C, 62.16; H, 6.78; N, 14.50. Found: C, 62.01; H, 6.80; N, 14.40.

Preparation of Octalone 192

The cross-conjugate addition to dienone 177 by lithium diisopropylcuprate was carried out by a procedure identical to that described above.

From 2 g of dienone 177, after chromatography on 140 g of MN silica gel, the fractions eluted with 15% ether-petroleum ether (30-60°) afforded 2.38 g (95%) of octalone 192. All traces of solvent were removed on the vacuum pump (0.1 mm) to afford an analytical sample which exhibited the following spectral properties: one component on g.l.c. (column E, 190°, 86); infrared (film), λ_{\max} 6.0, 6.2 μ ; n.m.r., τ 9.23, 9.04 (pair of doublets, 6H, isopropyl methyl groups, $J = 7$ Hz), 8.73 (singlet, 3H, tertiary methyl), 8.22 (singlet, 3H, vinyl methyl); ultraviolet λ_{\max} 249 m μ ($\epsilon = 14,000$).

This compound was further characterized as a red 2,4-dinitrophenylhydrazone derivative, recrystallized from ethanol, m.p. 134-135°.

Anal. Calcd. for $C_{21}H_{28}N_4O_4$: C, 62.98; H, 7.05; N, 13.99. Found: C, 63.13; H, 6.90; N, 13.76.

Preparation of Decalone 200

To 800 ml of liquid ammonia, which had been distilled from sodium metal, was added 4 g of lithium. After the lithium had dissolved 10 g (61 mmoles) of octalone 172 in 80 ml of anhydrous ether was added dropwise. After 1 h, 11 ml of anhydrous ethanol was added and the reaction mixture was allowed to stir for an additional 1.5 h. The reaction was quenched with excess ethanol and the liquid ammonia was allowed to evaporate. After removal of most of the ethanol, brine was added and the resulting solution thoroughly extracted with ether. The combined ether extracts were washed with water and brine and dried over anhydrous magnesium sulfate. The ether was removed at aspirator pressure and the resulting material crystallized to afford 7.7 g of decalol. The crude decalol was immediately oxidized to the desired decalone 200.

To a solution of 7.7 g (46 mmoles) of decalol in 177 ml acetone at 0° was added dropwise a standard solution of chromic acid (76) until the orange color persisted. Isopropanol was then added to destroy the excess oxidizing agent and the solvent was removed under reduced pressure. Water was added to the residue and it was thoroughly extracted with ether. The combined ether extracts were washed with water and brine and dried over anhydrous magnesium sulfate and concentrated in vacuo. Vacuum distillation of the oily residue afforded 6.5 g (88%) of the desired decalone 200, b.p. 80-82° at 0.8 mm; lit. (93) b.p. 69° at 0.1 mm; n_D^{20} 1.4943. The decalone 200 exhibited infrared (film), λ_{max} 5.85 μ ; n.m.r., τ 8.95 (singlet, 3H, tertiary methyl).

Bromination of Decalone 200

To a solution of 8.7 g (0.052 mole) of trans-fused decalone 200 dissolved in 100 ml of glacial acetic acid was added, dropwise over 1 h, 8.4 g (0.052 mole) of bromine in 100 ml glacial acetic acid. After the addition was complete, the reaction was allowed to stir for an additional 15 min and then ice was added. The major part of the water and glacial acetic acid was then removed at aspirator pressure. The residue was dissolved in ether and washed twice with water, twice with 5% sodium bicarbonate solution, once with water and brine and dried over anhydrous magnesium sulfate. The solvent was removed to afford 13.1 g of a crystalline bromoketone 201. This material was recrystallized from petroleum ether (65-110°) to afford 7.7 g (60%) of a white crystalline bromoketone, m.p. 100-102°; lit. (93) m.p., 101-102°.

The bromoketone 201 exhibited infrared (KBr), λ_{\max} 5.78 μ ; n.m.r., τ 8.86 (singlet, 3H, tertiary CH_3), 5.32 (X portion of an ABX system, 1H, $-\overset{\text{O}}{\text{C}}\text{CHBr}$, $J_{\text{AX}} = 12 \text{ Hz}$, $J_{\text{BX}} = 6 \text{ Hz}$).

Dehydrohalogenation of Bromoketone 201

A solution of 7.7 g of bromoketone 201 and 3 g of anhydrous lithium bromide dissolved in 75 ml of hexamethylphosphoramide was heated at 120° for 3 h under nitrogen. The cooled reaction mixture was diluted with water and thoroughly extracted with ether. The combined ethereal extracts were washed thrice with water, once with brine and dried over anhydrous magnesium sulfate. After removal of the ether the residue was chromatogrammed on 100 g of MN silica gel. The

fractions eluted with 10% ether-benzene afforded 3.9 g of octalone 197 (76%) which exhibited one peak only on g.l.c. (column E, 180°, 86). The compound was placed on the vacuum pump (~ 0.1 mm) to remove any traces of solvent to afford an analytical sample. This sample gave the following spectral data: infrared (film), λ_{\max} 5.95, 6.15 μ ; n.m.r., τ 8.96 (singlet, 3H, tertiary methyl), 4.24, 3.33 (pair of doublets, 2H, $\overset{\text{O}}{\parallel}\text{CCH}=\text{CH}$ and $\overset{\text{O}}{\parallel}\text{CCH}=\text{CH}$ respectively, $J = 9.8$ Hz); ultraviolet, λ_{\max} 229 m μ ($\epsilon = 9,200$); n_{D}^{20} 1.5088.

Birch Reduction of Octalone 173

To a solution of 4 g of lithium metal dissolved in 1 litre liquid ammonia (distilled from sodium metal) was added, dropwise over 0.75 h, 10 g (0.056 mole) of octalone 173 dissolved in 80 ml of anhydrous ether. The reaction was allowed to stir for 1 h after addition was complete. Then 11 ml of anhydrous ethanol was added and stirring continued for an additional hour. The reaction was then quenched by careful addition of excess ethanol and the liquid ammonia allowed to evaporate. The residual material was neutralized with 10% hydrochloric acid and extracted thrice with ether. The combined ether extracts were then washed with water, 5% sodium bicarbonate solution and saturated brine and dried over anhydrous magnesium sulfate. The ether was removed at aspirator pressure to afford 8.9 g of crude decalol. Without further purification the crude decalol was oxidized with a standard chromic acid solution (76).

To a solution of 8.9 g (56 mmoles) of decalol in 150 ml acetone at 0° was added dropwise a standard solution of chromic acid until the

orange color persisted. Isopropanol was then added to destroy the excess oxidizing agent and the solvent was removed under reduced pressure. Water was added to the residue and it was thoroughly extracted with ether. The combined ether extracts were washed with water and brine and dried over anhydrous magnesium sulfate and concentrated in vacuo. Vacuum distillation of the oily residue afforded 7.1 g (81%) of decalone 203, b.p. 89° at 1.5 mm; lit. (84) 99° at 3 mm. The decalone exhibited infrared (film), λ_{\max} 5.85 μ ; n.m.r., τ 8.98 (doublet, 3H, secondary methyl, J = 6.5 Hz), 8.84 (singlet, 3H, tertiary methyl).

Preparation of Enol Acetate 204

To a solution of 7.9 g (44 mmoles) of decalone 203 dissolved in 50 ml of isopropenyl acetate was added 0.1 ml of 98% sulfuric acid. This mixture was refluxed for 2.5 h under a nitrogen atmosphere. At the end of this time most of the isopropenyl acetate was removed on the rotary evaporator. The residue was dissolved in ether and washed successively with water, 5% sodium bicarbonate solution, water and saturated brine and dried over anhydrous magnesium sulfate. After removal of the ether the product was chromatogrammed on 150 g of Woelm activity III neutral alumina. The fractions eluted with benzene gave 9.5 g of an 85:15 mixture of enol acetates, with enol acetate 204 predominating. The mixture exhibited infrared (film), λ_{\max} 5.7, 5.95 μ .

Preparation of Bromoketone 205

To a solution of 9.5 g of enol acetates 204 and 204a and 10 g of anhydrous sodium acetate dissolved in 100 ml of glacial acetic acid was

added during 1 h, 7.2 g of bromine in 50 ml of glacial acetic acid. After the addition was complete, the reaction was allowed to stir for an additional 15 min. The glacial acetic acid was then removed in vacuo and the residue dissolved in water and thoroughly extracted with ether. The combined ethereal extracts were washed successively with water, thrice with 5% sodium bicarbonate solution, water and brine and dried over anhydrous magnesium sulfate. After removal of the solvent the residue crystallized and was recrystallized from petroleum ether (30-60°) to afford 4.7 g of a white crystalline bromoketone 205, m.p. 67-69°. Concentration of the mother liquors gave an additional 4.5 g (84%) crystalline bromoketone, m.p. 69-70°.

The crystalline bromoketone 205 exhibited infrared (CHCl_3), λ_{max} 5.8 μ ; n.m.r., τ 8.99 (doublet, 3H, secondary methyl, $J = 6.5$ Hz), 8.84 (singlet, 3H, tertiary methyl), 5.13 (X portion of ABX system, 1H, $\overset{\text{O}}{\text{CCH Br}}$, $J_{\text{AX}} = 14$ Hz, $J_{\text{BX}} = 6$ Hz).

Anal. Calcd. for $\text{C}_{12}\text{H}_{19}\text{OBr}$: C, 55.60; H, 7.34; Br, 30.89. Found: C, 55.59; H, 7.26; Br, 30.86.

Preparation of Octalone 198

A solution of 4 g (15 mmols) of crystalline bromoketone 205 and 1.5 g of anhydrous lithium bromide dissolved in 35 ml of hexamethylphosphoramide was heated to 120° for 3 h under nitrogen. At the end of this time the solution was diluted with water and thoroughly extracted with ether. The combined ether extracts were washed thrice with water and once with saturated brine and dried over anhydrous magnesium sulfate. The solvent was removed at aspirator pressure to

yield the crude octalone 198. The latter was chromatogrammed on 100 g of silica gel to afford, with benzene as elutant, 2.1 g of octalone 198 (76%). This was shown to be a mixture of octalone 198 and octalone 173 by g.l.c. (column E, 185°, 86). The mixture of octalones (4 g) was separated on 150 g of MN silica gel. The fractions eluted with 3% ether-benzene gave 3.8 g of octalone 198 while the fractions eluted with 5% ether-benzene gave 100 mg of octalone 173. An analytical sample of the major product was collected by preparative g.l.c. (column E, 185°, 86) and exhibited: infrared (film), λ_{\max} 6.0, 6.15 μ ; n.m.r., τ 8.93 (singlet, 3H, tertiary methyl), 8.92 (doublet, 3H, secondary methyl, J = 7 Hz), 4.19, 3.35 (pair of doublets, 2H, $\overset{\text{O}}{\text{C}}\text{CH}=\text{CH}$ and $\overset{\text{O}}{\text{C}}\text{CH}=\text{CH}$ respectively, J = 9 Hz); ultraviolet, λ_{\max} 229 m μ (ϵ = 9,200).

This compound was further characterized as a red 2,4-dinitro-phenylhydrazone derivative, recrystallized from ethanol, m.p. 198-199°.

Anal. Calcd. for $\text{C}_{18}\text{H}_{22}\text{N}_4\text{O}_4$: C, 60.32; H, 6.19; N, 15.63. Found: C, 60.51; H, 6.11; N, 15.73.

Preparation of Decalone 206

To an ice-cold slurry of 2.3 g cuprous iodide in 67 ml anhydrous ether under nitrogen, was added 11.4 ml of 2.1 N methyllithium solution. To the resulting clear solution was added, dropwise over 0.5 h, 328 mg (2 mmoles) of octalone 197 in 40 ml of anhydrous ether. The reaction was allowed to stir for an additional 1.5 h. Then it was poured slowly into a stirred 10% aqueous hydrochloric acid solution. The layers were separated and the aqueous layer extracted twice with ether. The combined ethereal extracts were washed with water and brine and

dried over anhydrous magnesium sulfate. The concentrated ethereal extract was distilled b.p. 110° at 0.2 mm; lit. (96) b.p. 133-137° at 9 mm to afford 345 mg (98%) of a clear oil. This oil exhibited, one peak on g.l.c. (column E, 190°, 100); infrared (film), λ_{\max} 3.45, 5.85 μ ; n.m.r., τ 9.08 (doublet, 3H, secondary methyl, $J = 6.5$ Hz), 8.87 (singlet, 3H, tertiary methyl).

Preparation of Decalone 207

A solution of tri-n-butylphosphine copper (I) iodide (4 g) in anhydrous ether (50 ml) was cooled to -78° by an external dry ice-acetone cooling bath. A solution of 3.1 M vinylolithium in tetrahydrofuran (6.4 ml) was added dropwise until the initially formed red solution became colorless. To this solution was added, dropwise over 0.5 h, 328 mg (2 mmoles) of octalone 197 in 50 ml anhydrous ether. The resulting brown solution was allowed to stir for an additional 5 h at -78° and then allowed to warm slowly to room temperature. The reaction mixture was then added dropwise with stirring to 100 ml of 10% hydrochloric acid. The layers were separated and the aqueous layer extracted twice with ether. The combined ethereal extracts were washed with dilute ammonium hydroxide, water and brine and dried over anhydrous magnesium sulfate. The ether was removed at aspirator pressure to afford 4.6 g of a viscous yellow oil. This material was subjected to column chromatography on 50 g of MN silica gel. The fractions eluted with 15% ether-petroleum ether (30-60°) contained 280 mg (73%) of the desired decalone 207. This material was distilled, b.p.

130° at 0.15 mm, to afford an oil which exhibited one peak only on g.l.c. analysis (column E, 190°, 100). An analytical sample of this material exhibited the following spectral properties: infrared (film), λ_{max} 5.85, 6.1, 10.9 μ ; n.m.r., τ 8.88 (singlet, 3H, tertiary methyl), 4.0-5.2 (unresolved multiplet, 3H, vinyl group). This compound was further characterized as a dark red 2,4-dinitrophenylhydrazone derivative, m.p. 186°, recrystallized from ethanol.

Anal. Calcd. for $\text{C}_{19}\text{H}_{24}\text{N}_4\text{O}_4$: C, 61.28; H, 6.50; N, 15.04. Found: C, 60.98; H, 6.41; N, 14.94.

Hydrogenation of Decalone 207

The hydrogenation of the vinyl substituted decalone 207 was done at atmospheric pressure and room temperature using 10% palladium on charcoal as catalyst and absolute ethanol as solvent. From 675 mg (3.5 mmoles) of decalone 207 was obtained 670 mg (98%) of ethyl substituted decalone 208. The product exhibited one component by g.l.c. (column E, 180°, 86). Infrared (film), λ_{max} 5.85 μ ; n.m.r., τ 8.88 (singlet, 3H, tertiary methyl). This compound was further characterized as a pale orange 2,4-dinitrophenylhydrazone derivative, recrystallized from ethanol, m.p. 192-193°.

Anal. Calcd. for $\text{C}_{19}\text{H}_{26}\text{N}_4\text{O}_4$: C, 60.95; H, 7.00; N, 14.96. Found: C, 60.74; H, 6.89; N, 14.92.

Preparation of Decalone 209

To a solution of 4 g of tri-n-butylphosphine copper (I) iodide in

60 ml of anhydrous ether at -78° was added 11 ml of 1.86 M isopropyl-lithium in *n*-pentane. To the resulting aqua solution was added, dropwise over 0.5 h, 328 mg (2 mmoles) of octalone 197 in 10 ml of anhydrous ether. After the addition was complete the dark red reaction mixture was allowed to stir for an additional 3 h and then quenched by dropwise addition to 50 ml of 10% hydrochloric acid solution. The resulting solution was thoroughly extracted with ether. The combined ether extracts were washed with water, dilute ammonium hydroxide, water and brine and dried over anhydrous magnesium sulfate. The concentrated ether extract was distilled under vacuum (~ 0.1 mm) and all material boiling at less than 150° was collected. The distillate was chromatogrammed on 35 g of MN silica gel. The fractions eluted with 20% ether-petroleum ether ($30-60^{\circ}$) afforded 297 mg of trans-decalone 209 (72%). Analysis of the product by g.l.c. demonstrated the presence of only one component. The decalone 209 crystallized on standing. Recrystallization from *n*-hexane gave an analytical sample, m.p. $49-50^{\circ}$; lit. (97,98) m.p. $49-50^{\circ}$. This compound gave the following spectral properties: infrared (CHCl_3), λ_{max} 5.87μ ; n.m.r., τ 9.08, 9.17 (pair of doublets, 6H, secondary methyls, $J = 6.8$ Hz), 8.89 (singlet, 3H, tertiary methyl).

Preparation of Decalone 215

To an ice-cold slurry of 1.36 g (7.3 mmoles) of cuprous iodide in 15 ml anhydrous ether was added 6.8 ml (14 mmoles) of 2.1 M methyllithium solution in ether. To this clear solution was added, dropwise over 1 h, 200 mg (1.2 mmoles) of octalone 198 in 10 ml of anhydrous ether. After

the addition was complete, the yellow reaction mixture was allowed to stir for an additional 1.5 h and then quenched by addition to 30 ml of 5% hydrochloric acid solution. The resulting mixture was then thoroughly extracted with ether. The combined ether extracts were washed with water, dilute ammonium hydroxide and water and dried over anhydrous magnesium sulfate. After removal of the ether, the residue was chromatogrammed on 20 g of MN silica gel. The fractions eluted with 5% ether-petroleum ether (30-60°) afforded 189 mg (93%) of trans-decalone 215. The product exhibited on g.l.c. (column E, 220°, 86), one major product with ~3% of a shorter retention time impurity. An analytical sample collected by preparative g.l.c. (column E, 190°, 86) exhibited: infrared (film), λ_{max} 5.85 μ ; n.m.r., τ 9.1, 9.02 (pair of doublets, 6H, secondary methyls, $J = 7$ Hz), 8.77 (singlet, 3H, tertiary methyl), 7.97 (doublet of doublets, 1H, H_{3e} , $J_{3e,4e} = 2.2$ Hz, $J_{3a,3e} = 14$ Hz), 7.21 (doublet of doublets, 1H, H_{3a} , $J_{3a,3e} = 14$ Hz, $J_{3a,4e} = 6$ Hz). This compound was further characterized as an orange 2,4-dinitrophenylhydrazone derivative, recrystallized from ethanol, m.p. 167-168°.

Anal. Calcd. for $C_{19}H_{26}N_4O_4$: C, 60.95; H, 7.00; N, 14.96. Found: C, 60.66; H, 6.87; N, 15.06.

Preparation of Decalone 216

To a stirred solution of 4 g (10.1 mmol) of tri-n-butylphosphine copper (I) iodide in 50 ml anhydrous ether at -78° was added 11 ml of 1.86 M (20.2 mmol) of isopropyl lithium in n-pentane. To the resulting

blue solution was added, dropwise over 0.5 h, 356 mg (2.1 mmoles) of octalone 198 in 20 ml anhydrous ether. The solution was allowed to stir for an additional 3 h and then quenched by dropwise addition to 100 ml of 10% hydrochloric acid. The resulting solution was then thoroughly extracted with ether. The combined ether extracts were washed with water, dilute ammonium hydroxide, water and brine and dried over anhydrous magnesium sulfate. The residue after concentration was hot-box distilled (b.p. 120° at 0.3 mm) and the distillate chromatogrammed on 20 g of MN silica gel. The third and fourth fractions eluted with benzene afforded 262 mg (84%) of trans-decalone 216. This product exhibited one peak by g.l.c. (column E, 198°, 86). The product gave infrared (film), λ_{\max} 5.85 μ ; n.m.r., τ 9.21, 9.09 (pair of doublets, 6H, isopropyl methyls, $J = 6.5$ Hz), 9.00 (doublet, 3H, secondary methyl, $J = 6$ Hz), 8.87 (singlet, 3H, tertiary methyl); n.m.r., (benzene), 7.74 (doublet of doublets, 1H, H_{3a} , $J_{3a,3e} = 15.5$ Hz, $J_{3a,4e} = 7.6$ Hz), 7.56 (doublet of doublets, 1H, H_{3e} , $J_{3a,3e} = 15.5$ Hz, $J_{3e,4e} = 2.4$ Hz). The product was further characterized as a yellow 2,4-dinitrophenylhydrazone derivative, recrystallized from ethanol, m.p. 145-146°.

Anal. Calcd. for $C_{21}H_{30}N_4O_4$: C, 62.67; H, 7.51; N, 13.92. Found: C, 62.55; H, 7.50; N, 13.73.

Hydrogenation of Octalone 188

A suspension of 20 mg of 10% palladium on charcoal in 15 ml of 0.3 N ethanolic sodium hydroxide solution was equilibrated for 1 h in an atmospheric pressure hydrogenation apparatus at room temperature.

After this period 122 mg (0.68 mmole) of octalone 188 in 10 ml ethanol was added by syringe. After the calculated amount of hydrogen had been absorbed, the mixture was filtered and the filtrate concentrated. The residue was diluted with water and then thoroughly extracted with ether. The combined ether extracts were washed successively with 5% hydrochloric acid, 5% sodium bicarbonate solution, water and brine and dried over anhydrous magnesium sulfate. The residue, after removal of the solvent, was distilled, b.p. 110° at 0.2 mm, to afford 119 mg (97%) of cis-fused decalone 218. This sample was shown to be homogeneous by g.l.c. (column E, 190°, 86). Decalone 218 exhibited infrared (film), λ_{\max} 5.85 μ ; n.m.r., τ 9.10 (doublet, 3H, secondary methyl, J = 7 Hz), 8.95 (singlet, 3H, tertiary methyl). This compound was further characterized as a yellow 2,4-dinitrophenylhydrazone derivative, recrystallized from ethanol, m.p. 161-162°.

Anal. Calcd. for $C_{18}H_{24}N_4O_4$: C, 59.99; H, 6.71; N, 15.55. Found: C, 59.99; H, 6.80; N, 15.46.

Hydrogenation of Octalone 189

The hydrogenation was carried out as above. From 100 mg of octalone 189 was obtained 96 mg of cis-decalone 193. The product exhibited one major peak by g.l.c. with approximately 3% of a shorter retention time impurity (column E, 180°, 86). An analytical sample was collected by preparative g.l.c. and exhibited: infrared (film), λ_{\max} 5.85 μ ; n.m.r., τ 8.90 (singlet, 1H, tertiary methyl). This compound was further characterized as a yellow 2,4-dinitrophenylhydrazone derivative, recrystallized from ethanol, m.p. 174°.

Anal. Calcd. for $C_{19}H_{26}N_4O_4$: C, 60.95; H, 7.00; N, 14.96. Found: C, 60.81; H, 6.85; N, 14.88.

Hydrogenation of Octalone 190

The octalone 190 was hydrogenated as above. From 100 mg of octalone 190 was obtained 96 mg of cis-decalone 219 (96%). The decalone exhibited one major peak on g.l.c. (column E, 190° , 86) with a 5% impurity of identical retention time to the trans-decalone 209. An analytical sample of cis-decalone 219 was collected by preparative g.l.c. (column E, 190° , 86). Infrared (film), λ_{\max} 5.85 μ ; n.m.r., τ 9.19, 9.10 (pair of doublets, 6H, isopropyl methyls, $J = 6.5$ Hz), 8.88 (singlet, 3H, tertiary methyl). This compound was further characterized as an orange 2,4-dinitrophenylhydrazone derivative, recrystallized from ethanol, m.p. $180-181^\circ$.

Anal. Calcd. for $C_{20}H_{28}N_4O_4$: C, 61.84; H, 7.27; N, 14.42. Found: C, 61.86; H, 7.35; N, 14.30.

Hydrogenation of Octalone 191

The material was hydrogenated by a procedure identical to that described above. From 130 mg of octalone 191 was obtained 125 mg (95%) of a colorless oil, b.p. 115° at 0.2 mm. This product exhibited one peak by g.l.c. (column E, 180° , 86). Infrared (film), λ_{\max} 5.85 μ ; n.m.r., τ 9.08, 9.01 (pair of doublets, 6H, secondary methyls, $J = 6.5$ Hz), 8.92 (singlet, 3H, tertiary methyl), 7.85 (doublet of doublets, 1H, H_{3e} , $J_{3e,3a} = 13$ Hz, $J_{3e,4a} = 3.6$ Hz), 7.64 (doublet of doublets, 1H, H_{3a} , $J_{3a,3e} = 13$ Hz, $J_{3a,4a} = 14.4$ Hz), 7.35 (sextet, 1H, H_{1a} , $J_{1a,9a} = 13$ Hz,

$J_{H_{1a},(CH_3)_{1e}} = 6 \text{ Hz}$). The decalone 220 was further characterized as its 2,4-dinitrophenylhydrazone derivative, recrystallized from ethanol, m.p., 213-214°.

Anal. Calcd. for $C_{19}H_{26}N_4O_4$: C, 60.95; H, 7.00; N, 14.96. Found: C, 60.85; H, 7.08; N, 14.93.

Hydrogenation of Octalone 192

Octalone 192 was hydrogenated by a procedure identical to that used for octalone 188.

From 100 mg (0.45 mmoles) of octalone 192 was obtained 96 mg (95%) of cis-decalone 221. This product exhibited one component on g.l.c. (column E, 180°, 86). Infrared (film), λ_{max} 5.85 μ ; n.m.r., τ 9.19, 9.11 (pair of doublets, 6H, isopropyl methyls, $J = 6.5 \text{ Hz}$), 9.01 (doublet, 3H, secondary methyl, $J = 6 \text{ Hz}$), 8.89 (singlet, 3H, tertiary methyl), 7.86 (multiplet, 1H, H_{3e} , $J_{3e,3a} = 14 \text{ Hz}$, $J_{3e,4a} = 3.6 \text{ Hz}$), 7.63 (multiplet, 1H, H_{3a} , $J_{3a,3e} = 14 \text{ Hz}$, $J_{3a,4a} = 14.3 \text{ Hz}$), 8.30 (multiplet, 1H, H_{1a} , $J_{1a,9a} = 13 \text{ Hz}$, $J_{H_{1a},(CH_3)_{1e}} = 6 \text{ Hz}$). This cis-decalone was characterized further as its 2,4-dinitrophenylhydrazone derivative, m.p. 188-189° from ethanol.

Anal. Calcd. for $C_{21}H_{30}N_4O_4$: C, 62.67; H, 7.51; N, 13.92. Found: C, 62.46; H, 7.28; N, 14.01.

Birch Reductions

General:

Each Birch reduction was repeated at least twice while the majority of the reductions were performed five times. The results (yields and

product composition) are listed in Table III. These results are the average of the various runs. In each case, gas-liquid chromatographic

Table III. Results Obtained from the Birch Reduction of Octalones
188 to 192.

Octalone	% Yield	<u>trans</u> : <u>cis</u> Ratio	% Recovered starting material
<u>188</u>	93	87:13	2
<u>189</u>	94	75:25	13
<u>190</u>	98	69:31	14
<u>191</u>	90	82:18	8
<u>192</u>	98	65:35	7

conditions were found in which the octalone, the corresponding cis-fused decalone and the corresponding trans-fused decalone exhibited distinct retention times on g.l.c. co-injection, (column E, 160-190°, 86). In each case, the cis-fused and trans-fused decalones were collected by preparative g.l.c. and the infrared and n.m.r. spectra were identical with those of the authentic cis-fused and trans-fused decalones previously prepared.

Sample Procedure: Reduction of Octalone 188

To 60 ml of liquid ammonia (freshly distilled from sodium metal) was added 55 mg of finely cut lithium wire. After all the lithium had dissolved, 100 mg of octalone 188 in 10 ml of anhydrous ether was added

dropwise over 0.5 h to the blue ammonia solution. After the addition was complete, the reaction mixture was allowed to stir for an additional 2 h. The blue color was then discharged by careful addition of ammonium chloride. After the liquid ammonia had evaporated dilute hydrochloric acid was added until the solution became neutral. This solution was diluted with water and thoroughly extracted with ether. The combined ether extracts were washed with water and brine and dried over anhydrous magnesium sulfate. After removal of the ether, the residue was vacuum distilled, b.p. 110° at 0.2 mm, to afford 94 mg (93%) of cis- and trans-fused decalones and starting material. The product proved to be an 87:13 mixture of trans:cis decalone by g.l.c. analysis (column E, 180°, 86). The percent composition was determined by integration (disc integrator) of the g.l.c. trace of the crude reduction product. Samples of cis-fused decalone 218 and trans-fused decalone 206 were then weighed out and combined to afford an authentic mixture of known composition approximating that observed in the Birch reduction of octalone 188. Injection of this authentic mixture into the g.l.c. (column E, 180°, 86) followed by integration of the g.l.c. trace confirmed that no compensation was required (i.e. the molar response factors of decalones 218 and 206 were identical).

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