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Synthetic Routes to Kaurene

by

James David Tauber

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Thesis Director's signature:

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June 1967
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jdt
I. INTRODUCTION

Following the total synthesis of dehydroabietic acid by Stork and Schulenberg in 1956,\textsuperscript{1} considerable interest has developed in stereospecific synthesis of polycyclic diterpenoid derivatives.\textsuperscript{2,3} Examples are found in the various synthetic routes devised for podocarpic acid,\textsuperscript{4,5,6} abietic acid,\textsuperscript{7} sclareol,\textsuperscript{8} nimbiol,\textsuperscript{9,10,11} and totarol,\textsuperscript{12,13} and the total synthesis of the \textit{Erytroleum} alkaloid, cassaine.\textsuperscript{14} More recent investigations have turn to the problem of diterpenes possessing bridge ring structures, of which phyllocladene (1) was to be the first to be obtained synthetically.\textsuperscript{15,16,17,18}

![Chemical structure](image)

(1)

Since the work described in this thesis was a direct outgrowth of the phyllocladene investigation, a general outline of the procedure developed for this substance is now presented (see Charts 1, 2, and 3).

The synthesis began with the commercially available 1,6-dihydroxynaphthalene (2) which was converted by methylation, reduction, and hydrolysis into 6-methoxy-
2-tetralone (3). The latter substance on methylation over the pyrrolidine enamine followed by Robinson annelation afforded the tricyclic conjugated ketone (5), which was methylated by the Woodward-Patchett procedure and hydrogenated over palladium to ketone (6). The carbonyl group of (6) was then removed by Clemmensen reduction, and the resulting product was demethylated with formation of the phenol (7). Certain improvements in this sequence which have been developed in connection with the present investigation are described in a later section. Catalytic hydrogenation of (7) yielded a mixture of epimeric alcohols, which was oxidized directly to the thermodynamically stable trans-anti-trans ketone (8). Condensation with furfuraldehyde and subsequent alkylation with allyl bromide then gave a substance shown to have structure (9).

At the time when this synthesis was undertaken the stereochemistry of the 2-carbon bridge in phyllocladene (1) was in doubt and, on the basis of certain biogenetic and mechanistic arguments,19 had been incorrectly assigned the opposite, αC, configuration. The αC-orientation of the allyl group in (9) therefore seemed appropriate for elaboration of the bridged D-ring of phyllocladene, and further synthetic work was designed to take advantage of this circumstance (Chart 2). Thus lithium aluminum hydride reduction of (9) followed by acetylation afforded compound (10), which on successive ozoniation, oxidation
Chart 2

(9)

(10)

(11)

(12)
with chromium trioxide, and treatment with acid furnished a well characterized keto-lactone (11). The latter substance was subjected to reductive ring opening and yielded keto-acid (12) from which the corresponding methyl ester was also obtained. Substances of this general formulation are known as degradation products of phyllolaudene, and the investigation had therefore reached the point where direct comparison of a synthetic material with its naturally derived counterpart was possible. Although the infrared spectra of appropriate samples measured in solution were very similar, there was no doubt but what the compounds in question were different. The simplest explanation for this discrepancy appeared to reside in the stereochemistry of the acetic acid chain which was \( \alpha \)-oriented in the synthetic series and hence probably \( \beta \)-oriented in the compounds of natural origin (13). It is of some interest to note that at this time the possibility of epimerization of the acetic acid chain under conditions of basic catalysis was recognized. Two mechanisms are

\[
\text{(13)} \quad \text{(14)} \quad \text{(15)}
\]

available for such an interconversion. One process could
involve equilibration via the reverse Michael intermediate (14), and the other equilibration over the bridged \( \beta \)-diketone (15). Unfortunately, insufficient amounts of synthetic keto-ester (12) were available to test this hypothesis, and treatment of the keto-ester of natural configuration\(^{17} \) with methoxide ion gave only the corresponding keto-acid, a phenomenon that was interpreted as an example of alkyl-oxygen fission of the Bunnett type.\(^{20} \) In retrospect it is unfortunate that this point was not pursued more vigorously, since in the present investigation it was established that the \( \beta \)-diketone (15), obtained by acid-catalyzed cyclization of keto-acid (13) is converted by treatment with sodium hydroxide into the keto-acid of the natural series (13). Since compound (15) is also the expected product of cyclization of the synthetic keto-acid (12), a pathway is clearly provided for the desired stereochemical transformation. A compound of structure (15)* has recently been obtained from the phyllocladene isomer, kaurene, by Hanson,\(^{21} \) who did not investigate the cleavage reaction. The problem has, however, been resolved by Briggs and his associates\(^{22} \) who showed that keto-acid (12), available through degradation of kaurene (see below), is indeed converted into keto-ester (13) by the action of sodium methoxide and methyl iodide.

* Melting point comparison: Hanson's structure (15) - 216-217.5\(^{\circ} \); this investigation's structure (15) - 218-220\(^{\circ} \).
The procedure for inverting stereochemistry at the asymmetric center in question that was ultimately adopted is outlined in Chart 3. Direct ozonolysis of the furfurylidene allyl ketone (9) afforded a triacid (16) which was converted by successive esterification, Dieckmann cyclization, hydrolysis and decarboxylation into a keto-ester (17), which proved to be identical with a known degradation product of phyllocladene. The further conversion of (17) into phyllocladene involved Refomatsky condensation to lactonic ester (18), base-catalyzed $\beta$-elimination to the unsaturated acid (19) which was converted into the 5-ring ketone (20) by calcium salt pyrolysis. Condensation of (20) with ethyl formate, formation of the acetal (21), lithium aluminum hydride reduction, and finally acid treatment afforded the unsaturated aldehyde (22). The latter substance had already been transformed into phyllocladene (1) by Wolff-Kishner reduction accompanied by the usual double bond migration.

The successful completion of the total synthesis of phyllocladene, coupled with the availability of intermediates epimeric at C.14 (cf. compound (12)) suggested that examination of methods for the synthesis of kaurene (23) might prove interesting.

Kaurene was first isolated from the leaf oil of the

# This substance was prepared in both d,l- and optically active modifications (see reference 16).
New Zealand kauri, *Agathis australis* Salisb., by Hosking. The substance has since been obtained from a variety of other sources, and both the dextro- and levorotatory antipodes occur naturally. In chemical behavior kaurene closely resembles phyllocladene so that a structural relationship between the two hydrocarbons was suspected at an early date.

(23)  
Kaurene has the molecular formula $C_{20}H_{32}$, possesses one double bond, and is therefore tetracyclic. Dehydrogenation affords pimanthrene but not retene, a product of the dehydrogenation of phyllocladene, and the only substance obtained on dehydrogenation of dihydrophyllocladene. However, dehydrogenation of dihydrokaurene and oxidation of the resulting mixture yields small amounts of retene quinone.

The double bond of kaurene is present as a methylene group (infrared and N.M.R.), and like phyllocladene double bond isomerization occurs in the presence of acid to yield isokaurene (24). Various oxidation procedures convert kaurene into kaurene norketone (25) (5-ring ketone);
while permanganate oxidation of isokaurene affords products (26) and (27), corresponding to those derived in a similar way from isophyllocladene.\textsuperscript{27,28} Baeyer-Villiger oxidation of (27) with trifluroperacetic acid and subsequent hydrolysis affords a mixture of the 5-ring lactone (28) and hydroxy-acid (29). The latter substance on esterification and oxidation with chromium trioxide yields the keto-ester (30).

\[(25)\quad (26)\quad (27)\]

\[(28)\quad (29)\quad (30)\]

Although a considerable body of further evidence could be cited in support of structure (23) for kaurene, the most critical argument relates to the correlation of kaurene and phyllocladene to which reference has already been made. Baeyer-Villiger oxidation of kaurene norketone yields a $\delta$-lactone (31) convertible into glycol (32) by reduction with
lithium aluminum hydride. On oxidation the glycol furnished a keto-acid in the form of the lactol (33), which yields a keto-ester (34) in the presence of potassium carbonate and methyl iodide, but is converted into (13), also obtained from phyllocladene, when the potassium carbonate is replaced by sodium methoxide. Since either or both of the centers of asymmetry at C.13 and C.14 could conceivably be inverted by base on assumption of a
reverse Michael mechanism and double bond equilibration in the intermediate (14), the evidence does not indicate the stereochemistry at those two centers. The skeletal structure and the stereochemistry at the A/B ring junction, however, are established, and the remaining uncertainties are resolved by synthesis.

During the course of the present investigation two syntheses of kaurene have appeared. The first of these is due to Bell, Ireland, and Partyka\textsuperscript{29} and follows a route outlined in Chart 4. The procedure suffers mainly from poor stereochemical and directional specificity at various key stages. The starting material was the tricyclic unsaturated ketone (35)\textsuperscript{30} which was reduced with lithium aluminum hydride to yield a mixture of epimeric alcohols of which (36) was carried forward to the vinyl ether (37). Claisen rearrangement of the latter substance, as suggested by Burgstahler,\textsuperscript{31} afforded the acetaldehyde derivative (38), which was converted into the corresponding acetal (39). Since (38) has been converted into the phyllocladene degradation product (17) by an unambiguous route, the stereochemistry (particularly that at C.13 and C.14) is rigorously established.

Hydroboration and oxidation of (39) yielded a mixture of keto-acetals from which compound (40) could be obtained in 26\% yield. Hydrolytic cleavage of the acetal function in the presence of dilute mineral acid was accompanied by
Chart 4

(35) \rightarrow (36)

(37) \rightarrow (38)

(39) \rightarrow (40)

(41) \rightarrow (42)

(43) \rightarrow (23)
internal aldol cyclization to the ketol (41), which was converted into kaurene by the standard procedures indicated.

The second kaurene syntheses appeared only very recently and involves an entirely different approach (Chart 5).

Treatment of 6-benzyloxy-1,2,3,4-tetrahydronaphthalene-2-carboxylic acid (44) successively with oxalyl chloride, diazomethane, and hydrobromic acid afforded the bromoketone (45). Reduction of (45) with sodium borohydride into epimeric bromohydrins, conversion into the tetrahydropyranyl ethers, and then hydrogenolysis with palladium on carbon yielded the corresponding phenols (46). Base treatment of (46) effected the cyclization of only one isomer to give a tetrahydropyranyl ether of the hyroxy-dienone (47). Catalytic hydrogenation of the benzoate from (47) afforded two isomeric tetrahydro compounds of which (48) was carboxymethoxylated with triphenylmethyl sodium and carbon dioxide and methylation to give the β-keto ester (49). Construction of ring A was accomplished by addition of ethyl vinyl ketone followed by cyclization. Exhaustive methylation of the tetrahydropyranyl ether and removal of the protective group afforded the dimethyl compound (50). Oxidation of (50) followed by catalytic hydrogenation and then Wolff-Kishner reduction on the monoketal provided the acid (51).

The corresponding ketal methyl ester (52) was reduced with lithium aluminum hydride to afford a hydroxy-ketal.
Chart 5

(44) → (45) → (46) → (47) → (48) → (49) → (50) → (51) $R = H$

(52) $R = CH_3$

(53) → (54)
which gave the ketal-aldehyde (53) on oxidation with chromic acid in pyridine. Compound (53) yielded the ketone (54) after being subjected to Wolff-Kishner reduction and acid hydrolysis. The racemate (54) was shown to be identical with kaurene norketone via infrared spectral comparison.

This completed the total synthesis of kaurene, since the norketone had previously been converted into kaurene.34
II. DISCUSSION

The availability of the tricyclic ketone (8), and demonstration of the fact that angular alkylation of this material affords a product (9) possessing stereochemistry appropriate to kaurene suggested that these substances might provide a convenient point of departure for the total synthesis of the latter product. Terminal stages of the Shaw synthesis of (8), however, involved transformations that appeared capable of some improvement, and

![Chemical structures](image)

(8)  (9)

initial work was therefore concentrated on this problem.

The first area of concern in the Shaw approach involved the conversion of the keto-methyl-ether (6) into phenol (7) by successive Clemmensen reduction and demethylation of the intermediate anisole derivative (55) with hydriodic acid. The Clemmensen reduction step proved troublesome and afforded only slightly better then 60% yield of the desired product (55) accompanied by considerable amounts of starting material, the separation of which was difficult. Direct Wolff-Kishner reduction of (6) appeared to be even less efficient. In the belief that Wolff-Kishner
reduction was probably accompanied by partial demethylation, the Shaw sequence was reversed and the demethylation reaction was carried out first. The phenolic ketone (56) was obtained in 77% yield as compared with 67% obtained by Shaw in demethylation of (55). Wolff-Kishner reduction of (56) then proceeded exceptionally smoothly and afforded phenol (7) in 93% yield.

The further conversion of (7) into (8) as carried out by Shaw also presented difficulties. High pressure hydrogenation of (7) over Raney nickel in the presence of hydroxide ion furnished a mixture of epimeric saturated alcohols in poor yield which could be separated only after chromatography, and direct oxidation of the reduction mixture provided only a marginally practicable route to the
difficultly crystallizable ketone (8).

An examination of the effect of various catalysts, including nickel, rhodium, ruthenium, and platinum, on the course of reduction was carried out. Although some variation in the extent of hydrogenolysis, depending upon the catalyst employed, was observed, no really significant improvement in yield could be obtained. However, the difficulties attending isolation and purification of (8) were circumvented in the following way. The total crude reduction mixture was filtered through Florisil to remove hydrogenolysis product, and the resulting, crystalline epimeric alcohols were oxidized to the ketone. The mother liquor from the crystallized ketone was re-reduced with sodium borohydride. This process furnishes predominately the equatorial alcohol,\(^{15}\) which was easily purified and reconverted into ketone (8), now free of contamination. Although platinum reduction at atmospheric pressure involves somewhat more hydrogenolysis than other procedures, it yields the cleanest product and is the method of choice. It should be noted, however, that the overall yield in the transformation of (7) into (8) could not be raised above about 45\%. Since hydrogenolysis accounts for only 33% of the starting material, hydrogen transfer to the \(\beta\)-face is presumed to compete with \(\alpha\)-hydrogenation.

Of the various approaches to the total synthesis of kaurene that were considered in the present investigation,
the only one that proved successful was based on Diana's observation\textsuperscript{35} that intramolecular aldol condensation provides a generally useful method for the preparation of bridged ring structures. Unfortunately completion of this investigation was anticipated by the appearance of Ireland's publication \textsuperscript{29} (see Chart 4), and the synthesis was therefore not carried forward to the final product, kaurene. The work, nevertheless, represents a somewhat more direct approach than that of Ireland, and possesses some points of interest which are noted below.

The fundamental requirement of the route in question was synthesis of allyl ketone (57), which was to be oxidized to the corresponding keto-aldehyde and cyclized to ketol (41). In proceeding from ketone (8) the use of a blocking group to direct alkylation into this angular

\[
\begin{align*}
\text{(57)} & \quad \text{(41)}
\end{align*}
\]

position appeared to be necessary, owing to the degree of steric hindrance developed in the angularly alkylated product. For the latter reason, also, the use of the methylanilinomethylene blocking group developed by Robinson\textsuperscript{36,37} was avoided, since attack on nitrogen could
conceivably compete favorably with hindered C-alkylation. However, removability of the blocking group was a necessary feature, and the applicability of the alkoxyethylene function was therefore investigated.

Condensation of ketone (8) with ethyl formate in the presence of sodium hydride proceeded smoothly and yielded the expected hydroxymethylene derivative (58a) in crystalline condition. Reaction of the latter substance

![Chemical Structure](image)

(58a) \( R = H \)
(58b) \( R = \text{isopropyl} \)

with potassium carbonate and isopropyl iodide\(^{38}\) on the one hand, or with isopropyl alcohol and acid\(^{39}\) on the other, furnished the corresponding isopropyl ether (58b). The reconversion of the isopropyl ether into ketone (8) by the action of sodium hydroxide by a presumed \( \beta \)-addition-\( \beta \)-elimination mechanism was demonstrated. This point was regarded as important in view of the fact that the usual acid hydrolysis on an allylated derivative might result in partial migration of the allyl double bond.

Alkylation of (58b) with allyl bromide and potassium \( t \)-butoxide under conditions that proved successful with the
corresponding furfurylidene ketone afforded an intractable oil. The presence of small amounts of alkylated material was detected by examination of the infrared spectrum, and direct base-catalyzed cleavage of the alkoxymethylenegroup afforded the desired allyl ketone (57) in poor yield (10 - 20%). Alkylation of (58b) is, therefore, much more difficult than the analogous alkylation of the furfurylidene ketone which affords compound (9) in pure form in 75% yield. (See Chart 3.)

Deactivation of the carbonyl group in alkoxymethylenederivatives of the type under discussion has been noted previously,40 and may be attributed to the fact that substances of this constitution are vinylogous esters. Ireland40 has reported on the use of thio-esters to suppress such deactivation, but investigation of this alternative led to no fruitful results.

The greater reactivity of phenyl esters as compared with alkyl esters is well-known. Thus hydrolysis of phenylacetate proceeds at a rate 13 times that of ethyl acetate. It seemed possible, therefore, that substitution of phenoxy for alkoxy in this blocking group (cf. 59) might enhance the reactivity of the carbonyl group. The hydroxymethyleneketone (58a) was accordingly treated in benzene with phenol in the presence of p-toluenesulfonic acid, and the desired phenoxy-methylenederivative (59) was obtained in good yield. This substance was in turn treated with allyl bromide and
potassium t-butoxide under the standard conditions, and the crude reaction product was submitted to chromatography. No crystalline material could be obtained, but infrared and N.M.R. analyses indicated that substantial alkylation had occurred. However, it was clear that the phenoxy group had given way to the t-butoxy function (cf. 60). It is

\[
\begin{align*}
(59) \\
(60)
\end{align*}
\]

assumed that alkylation precedes alkoxylation exchange, but this point has not been established. For reasons that are not clear in the absence of a definitive proof of structure, the amorphous alkylation product proved exceptionally resistant to hydrolytic cleavage with either acid or base. At this point developments in another line of attack appeared to offer greater promise, and the matter was not pursued further. It should be stated, however, that the potential of the phenoxymethylenne group as a blocking agent deserves additional future study.

Attention was now turned to the question of whether the furfurylidene group of the furfurylidene allyl ketone (9) might be cleaved by reversal of the aldol reaction employed for its introduction. Preliminary experiments had
been discouraging. On treatment with alkali under moderate conditions the starting material was recovered unchanged, and as the temperature of reaction was raised toward 180°, only resinous products resulted. Since stabilization of the system

(9)   (61)   (62)

by oxygen conjugation (see arrows, structure 9) was regarded as a possible contributing factor, the behavior of the corresponding benzylidene derivative (62), obtained in good yield from the benzylidene ketone (61), was examined. It may be noted parenthetically that a cumbersome procedure for removal of a benzylidene group (see formulas 63 through 67) was already on record. When compound (62) was treated with potassium hydroxide in ethanol at reflux temperature, material was obtained which afforded 35% of desired allyl ketone (57) on chromatography. In addition about 35% of starting material was recovered, making the ultimate yield of (57) well over 50%. Despite the success achieved in this particular case, the reaction does not appear to be general, since attempts to accomplish the transformation of (63) into (67) by this method did not give satisfactory results.
Ozonization of (57) proceeded smoothly, and treatment of the resulting crude product with either acid or base furnished the ketol (41). The melting point obtained for this product in the present investigation was 180 - 182° as contrasted to the melting point of 136 - 137° published by Ireland and his associates.\(^{29}\) Since complete details of the Ireland work have not yet appeared, it is not possible at this time to provide a definitive explanation for the discrepancy. Of the four obvious possibilities, (a) a misprint in the Ireland publication, (b) solvent of
crystallization, (c) dimorphism, and (d) a difference in the stereochemical orientation of the hydroxyl group, only the latter would have any chemical significance. In any event, oxidation of (41) furnishes the diketone (42), which possesses all of the properties ascribed to this substance by Ireland's group. The further conversion of (42) into d,l-kaurene has already been noted.

In connection with the work described above various subsidiary experiments were carried out. Attempts to convert the allyl ketone (57) into the corresponding epoxide (68) in the hope that cyclization to (69) might be accomplished failed to yield the desired product when perbenzoic acid or monoperphthalic acid were employed as oxidizing agents. This observation is perhaps not surprising in view of the recent report that 2-allylcyclohexanone undergoes the Baeyer-Villiger reaction instead of epoxidation when treated with peracetic acid. The use of benzonitrile and hydrogen peroxide which converts 2-allylcyclohexanone into corresponding epoxide was not examined in the present case.
Direct alkylation of tricyclic ketone (8) with 2-bromo-3-pentene* affords a crystalline product to which structure (70) was assigned. This material was then oxidized to keto-aldehyde (71), which proved to be amorphous. It was hoped that (71) could be placed in equilibrium by internal aldol condensation with products (72a) and (72b), which might then be further transformed into kaurene and/or phyllocoadene. Unfortunately, treatment of (71) with acid furnished uncharacterizable material with only residual carbonyl in the infrared, while reaction with base afforded hydroxy-acid (73a) by internal hydride transfer. Oxidation of (73a) yielded what is proposed to be the lactol (74) in crystalline form. Attempted cyclization to (75) in the presence of p-toluenesulfonic acid.

* The use of this reagent was dictated by the circumstance that the products of $S_{N2}$ and $S_{N2}'$ substitution are identical.
acid,\textsuperscript{44} hoping to take advantage of an equilibrium established between lactol and keto-acid, gave neutral, oily material which showed an infrared absorption band developing at 5.56 \textsuperscript{45} \textsuperscript{46}, consistent with the enol-lactone structure (76).

\begin{align*}
(73a) & R = H. \\
(73b) & R = \text{CH}_3.
\end{align*}

In the synthetic approach described above a single carbonyl group provided entry at the two positions required for attachment of the bridged D-ring. An alternative possibility of providing individual activation for each of these centers has also been explored. Transformations that were carried out in this connection are outlined in Chart 6.

The known tricyclic, conjugated ketone (77)\textsuperscript{45} was methylated by the Woodward-Patchett procedure\textsuperscript{46} and afforded the dimethyl ketone (78), which would not be
induced to crystallize. However, direct reduction of the crude methylation product with sodium borohydride furnished a crystalline alcohol (79), and purification was therefore accomplished at this stage. In an attempt to obtain the ketone (78) in crystalline condition, a purified sample of (79) was oxidized with chromium trioxide and pyridine. Although this reagent does not normally attack allylic or benzylic positions, in the present instance conversion into diketone (86) was observed. It may be assumed that double activation is responsible for this phenomenon, and since

![Chemical structures](image)

standard allylic (or benzylic) oxidation by chromium trioxide-acetic acid is a poor procedure at best, an improved method for introduction of the B-ring keto group was thereby made available. Diones (87) and (88) were also prepared by this route. (See ref. 3.)

Birch reduction of compound (79) proceeded uneventfully to give the amorphous dihydro derivative (80a), which was characterized as the crystalline acetate (80b). Cleavage of the enol-ether function in (80a) with aqueous ethanolic oxalic acid yielded the \( \beta, \gamma \)-unsaturated
ketone (81), which was transformed by sodium borohydride reduction into the diene diol (82a). This substance, although crystalline, showed a tendency to become oily on standing, and it was therefore acetylated to the amorphous diacetate (82b), which was in turn oxidized directly with chromium trioxide and pyridine (see above) to the dienone (83). Although the latter product melted reasonably sharply (115 - 117°) and showed a single spot on thin layer chromatography, both it and its precursors (82a) and (82b) appear to be mixtures of epimers arising in the borohydride reduction or of double bond isomers. Subsequent reactions carried out on material melting at 115 - 117° gave poor yields of characterizable products, and recrystallization of the dienone afforded a substance melting at 152.5 - 163.5° with considerable attendant loss of material. Although methods other than reduction and acetylation can be imagined for masking the ring C keto group in the critical alkylation step involving (85), sufficient material could be obtained by the present route to test the feasibility of this key transformation. Moreover, it should be noted that ketal formation, which would avoid the stereochemical problem, involves acid catalysis and the accompanying danger of double bond migration.

Partial hydrogenation of (83) over palladized charcoal afforded a dihydro derivative to which structure (84) is assigned on the basis of ultraviolet absorption
measurements. Hydrogenation with two molar equivalents of hydrogen furnished the tetrahydro derivative (85). The reduction products appear to be homogeneous, but as noted previously the yields are poor and do not exceed 30% of theoretical. The stereochemistry proposed for the A/B ring fusion of (84) and (85) and for the B/C ring fusion of the latter compound is supported by ample analogy.\textsuperscript{15}

In considering the mode of alkylation of ketone (85), it will be observed that approach of the alkylation agent to carbon atom 10 from either the \( \mathbf{P} \)- or the \( \mathbf{S} \)-side is strongly hindered. In the first case two axially oriented methyl groups at C.1 and C.12 effectively block normal axial approach\textsuperscript{49} to C.10, while the equatorial methyl group at C.1 similarly interferes with equatorial attack on the \( \mathbf{S} \)-side of carbon 10. On the other hand, approach by the alkylation agent to the \( \mathbf{S} \)-side of C.14 should be relatively unencumbered, and it will be recalled that alkylation of the benzylidene ketone (61) proceeds smoothly and in good yield. The prospects for stereospecific allylation at C.14 in (85) therefore appeared good, and the expected product (86) is presumably capable of transformation in a series of routine operations into the bridged ketol (87). However, despite repeated attempts carried out under a variety of conditions, allylation of (85) could not be accomplished. The methods employed included potassium \( t \)-butoxide in \( t \)-butanol-benzene,\textsuperscript{15} potassium \( t \)-butoxide in benzene,\textsuperscript{1}
potassium t-butoxide in dimethylsulfoxide,\textsuperscript{50} and sodium hydride in benzene. With the failure of the key step in this approach, the procedure was reluctantly abandoned.

![](image)

and attention was turned to other matters.

Since phyllocladene had already been synthesized, any conversion of this substance into the stereoisomer, kaurene, would constitute a total synthesis of the latter substance. An interesting possibility for accomplishing such a conversion was suggested by the well-known Demjanov rearrangement, of which a pertinent example is the transformation of bornyl amine (88) into camphene (89) and its hydrate (90).\textsuperscript{51}

![](image)

(88)  (89)  (90)

For this purpose phyllocladene norketone was converted into the corresponding oxime (91), and this substance was
reduced with sodium and alcohol. There was obtained in this way a single amine (92), which was characterized as the hydrochloride and as the N-acetyl derivative. Since reductions of this type are expected to yield the thermodynamically more stable product,\textsuperscript{52,52} and since the \( \alpha \)-orientation of bridge substituents is favored over the alternate \( \beta \)-arrangement,\textsuperscript{54,55} the \( \alpha \)-configuration is assigned to the amine (92). A three-dimensional representation of this structure is indicated in formula (93). It will be observed that this stereochemistry is appropriate to concerted deamination-rearrangement and that solvent attack will then lead to a derivative (94) that possesses kaurene stereochemistry. The behavior of amine (93) in the presence of nitrous acid was accordingly investigated.
Aqueous acetic acid was chosen as a suitable solvent, and sodium nitrite was added to a solution of the amine in a reaction vessel connected to a buret system to permit measurement of nitrogen evolution. In the first experiment carried out under these conditions gas \textit{absorption}, instead of gas evolution, was observed. This remarkable result was traced to oxidation of the nitrous acid by atmospheric oxygen, and subsequent experiments were conducted in an inert atmosphere where nitrogen evolution was rapid and complete. Although it is inconceivable that this phenomenon has not been encountered previously, none of the experimental procedures that are readily accessible in the literature makes any mention of this difficulty. Indeed, the fact that standard methods employ prolonged reaction times and repeated addition of nitrite, frequently with heating, suggest ignorance of this possibility on the part of many investigators.

An infrared scan of the total deamination product indicated the presence of both alcohol and acetate. For this reason, and to avoid complications introduced by lack of stereoselectivity in solvent attack,\textsuperscript{56} the crude material was subjected to ester cleavage with lithium aluminum hydride and direct oxidation with chromium trioxide. The resulting product (37.5 mg.) was then chromatographed on alumina. Elution with petroleum ether afforded 4.7 mg. of compound that was identified as unrearranged olefin (95).
by infrared comparison with an authentic sample. Further processing with benzene-petroleum ether mixtures yielded 15.5 mg. of phyllocladene norketone (96), 5.7 mg. of the known isomeric ketone (20), and 6.7 mg. of an unidentified substance (mp. 125 - 127°), which showed 6-ring ketone absorption in the infrared and may arise by hydride transfer in an intermediate carbonium ion. Hydride transfer may also explain the appearance of compound (20), although chromic acid attack on the olefin (95) represents an alternative possibility. No kaurene norketone could be detected, and the amounts of this substance, if present, must have been extremely small. It is clear, therefore, that in this case deamination proceeds for the most part without skeletal rearrangement. This observation, of course, does not distinguish between a classical carbonium ion intermediate and a bridged ion of type (97), which may persist in collapse to unrearranged products.

The question of the precise nature of positively charged species produced in deamination reactions and in various solvolytic processes has involved an extended controversy
which only recently has appeared to approach a satisfactory resolution.\textsuperscript{57} In connection with the present problem, the

\begin{equation}
\text{(97)}
\end{equation}

suggestion of Corey and his associates\textsuperscript{58} that deamination of \textit{exo}- and \textit{endo}-norbornylamine produces a classical carbonium ion, but that a symmetrical bridged ion is obtained by solvolysis of \textit{exo}-norbornyl arenesulfonates, is of special interest. Rationalization for this phenomenon rests on the notion that the inferior characteristics of the arenesulfonate anion \textit{vis à vis} nitrogen as a leaving group require a greater degree of assistance (\textit{eg}., carbon participation) for heterolysis in the former than in the latter case. Hence, the likelihood of rearrangement may be greater in the solvolysis than in the deamination reaction.

With this in mind the preparation of a pttoluene-sulfooxy derivative of appropriate stereochemistry was next undertaken. Both epimeric alcohols (98) and (99) are known,\textsuperscript{55} but the reported synthesis of the desired product (98) is indirect and not suited to a situation in which limited amounts of starting material are available.

Phyllocladene norketone (96) was, therefore, reduced
with sodium and ethyl alcohol in the expectation that the thermodynamically more stable alcohol (98) would be obtained as the major, if not the exclusive, product. Chromatography of the reaction mixture afforded both epimers in pure condition. However, the fact that epimer (99) predominated in a ratio of 3 to 1 was surprising. Isolated reports of non-equilibrium reduction of ketones by metal-alcohol combinations have appeared in the literature, but the phenomenon is clearly not a general one. Equilibration of the epimeric products was accomplished by refluxing with sodium n-butoxide in butanol, and the composition of the equilibrium mixture was found to be $63\%$ of (98) and $37\%$ of (99). Recycling provided a method for satisfactory conversion of compound (99) into the required epimer (98).

It should be noted that these results cast considerable doubt on the stereochemistry assigned to amine (92), also obtained by metal-alcohol reduction. If deamination involves direct formation of a carbonium ion, the stereochemistry is not especially relevant. On the other hand, the arrangement shown in (92) is the only one that can suffer
concerted deamination and rearrangement.

Treatment of alcohol (98) with p-toluenesulfonyl chloride in pyridine furnished the corresponding tosylate, which could not be induced to crystallize. Solvolysis of this material in acetic acid, containing small amounts of acetic anhydride and added sodium acetate to prevent acid-catalyzed ionization of product acetate,\textsuperscript{61} yields a mixture that appeared to consist mainly of unrearranged olefin (95). Small amounts of starting tosylate were recovered, but only traces of acetate could be detected. It was therefore evident that additional driving force was required if rearrangement were to be achieved.

In this connection utilization of the pinacol rearrangement (100) to (25), or pinacolic deamination, offered the most obvious solution to the problem. Confirmation of the validity of this view has very recently appeared in the form of a communication from Japanese investigators,\textsuperscript{62} who have employed this device in connection with a total synthesis of the diterpene alkaloids garryine and veatchine.
For preparation of the requisite glycol (100), a study of the acyloin condensation of keto-ester (13) was undertaken. Treatment of this substance with sodium in toluene afforded approximately 30% of a crystalline product, mp. 151 - 153°, which showed hydroxyl absorption in the infrared and a carbonyl band at 5.73 μ consistent with structure (101). However, the substance shows other characteristics which suggest that it is a mixture, possibly involving (101) and the hydroxy-ester (102). For example, treatment with sodium borohydride reduces the intensity of

\[
\begin{align*}
\text{(13)} & \quad \text{(101)} & \quad \text{(102)} \\
\end{align*}
\]

the carbonyl band in the infrared, but only to about half of its original value. Acetylation with acetic anhydride and pyridine at room temperature yields material possessing an intense band at 8.02 μ characteristic of the carbon-oxygen stretching frequency of an acetate ester. The most definitive evidence is derived from the proton magnetic resonance spectrum which shows a band at 3.68 ppm ascribable to the -OCH₃ group, but with about 1/3 the intensity of the starting keto-ester. That this absorption is not due to hydroxyl function is demonstrated by the absence
of any shift in the position of the band in the presence of acid.

The acyloin reaction of keto-ester (13) was also carried out under the Sheehan conditions with sodium and liquid ammonia. There was obtained in good yield an extremely insoluble, high melting product (mp. 268 - 270°) showing hydroxyl but no carbonyl absorption in the infrared. This substance is tentatively regarded as the glycol (100), but caution must be exercised in this judgment. Jones oxidation affords neutral material that shows two carbonyl bands in the infrared in the 5- and 6-ring ketone regions respectively. Reaction with BF₃-acetic acid gives rise to acetate (I.R.), and treatment with sulfuric acid abolishes hydroxyl absorption introducing instead carbonyl bands at
$5.75\mu$ and $5.84\mu$. Unfortunately, lack of time and material has prevented further investigation of these observations. It is possible that acid treatment of the acyloin product has indeed furnished some kaurene norketone, but future study will be required to establish this point with certainty.

Mention should finally be made of certain fragmentary experiments that were carried out along other lines that possess elements of chemical interest. It will be observed that if protonation of the tetracyclic olefin (103) proceeded in the sense indicated in (104), rearrangement to carbonium ion (105) could occur, and isokaurene (24) would be predicted as the ultimate product. The recent report\(^6\) that treatment of (+)-stachene (hibaene), a naturally occurring product possessing structure (103), with hydrogen chloride in benzene at room temperature affords (-)-kaurene and (-)-isokaurene confirms this prediction. Alternatively, acid-catalyzed cyclization of diene (106) and hydride transfer in species (107) might lead to the same overall result.

A direct synthesis of (106) can be formulated starting
with keto-ester (17), a known degradation product of phyllocladene. Lithium aluminum hydride reduction of this substance yields glycol (108), which—may in turn be oxidized with chromium trioxide-pyridine to the crystalline keto-aldehyde (109). Reaction of the latter compound with triphenylphosphine methide in a double Wittig transformation gives an amorphous product which could not be induced to crystallize. However, infrared and proton magnetic resonance spectra are in complete agreement with structure (106). When this substance was subjected to the action of acid, an intractable mixture was produced. The result proved discouraging, as there was no similarity with isophyllocladene via infrared comparison.
III. EXPERIMENTAL

Acid-Catalyzed Cyclization of Keto-acid (13). Thirty three milligrams of keto-acid (13; mp. 156 - 157°C) from natural series was dissolved in 20 cc. of benzene, and the volume of the solution was reduced to 10 cc. by distillation. p-Toluenesulfonic acid (9 mg.) was then added. The reaction mixture was heated under reflux in a dry nitrogen atmosphere for 17 hours and was then poured into cold water and made basic with cold 2N sodium hydroxide solution. The product was extracted with ether. The organic layer was washed with cold water and saturated sodium chloride solution. After drying over magnesium sulfate, the organic layer was concentrated to dryness yielding 31 mg. of material. Recrystallization from methylene chloride - petroleum ether yielded 27 mg. of (15) melting at 215 - 217°C. Further recrystallization gave material melting at 218 - 220°C. The infrared spectrum showed two carbonyl peaks (5.71 μ and 5.80 μ) in carbon disulfide solution.

Cleavage of Diketone (15). To a refluxing solution of 21 mg. of compound 15 (mp. 215 - 217°C) in 4.5 cc. of methanol 0.5 cc. of aqueous potassium hydroxide solution (containing 250 mg. of potassium hydroxide) was added. The reaction mixture was allowed to reflux for 2 hours under a nitrogen atmosphere. The bulk of the methanol was removed under reduced pressure. The residue was diluted with water and extracted with several portions of methylene chloride. The
aqueous layer was made acidic and extracted with ether. The ether layer was washed with water and saturated sodium chloride solution. The resulting solution was then dried and evaporated to yield 16 mg. of material. This was dissolved in a small amount of ether and was treated with ethereal diazomethane solution. After 15 minutes in an ice bath and 15 minutes at room temperature, the solvent was removed under a stream of nitrogen yielding 18 mg. of material. Recrystallization from methanol gave material melting at 175 - 177° (keto-ester from natural series of phyllocladene has mp. 179 - 180°), which had infrared absorption identical with that of the authentic naturally derived substance.

Preparation of trans-1,2,3,4,9,10,11,12-Octahydro-8-hydroxy-1,1,12-trimethyl-2-oxophenanthrene (56). A solution of 5.5 g. of keto methyl ester (6) in 200 cc. of refluxing acetic acid was treated with 15.5 cc. of 49% hydriodic acid under nitrogen atmosphere. After heating for one hour, the reaction mixture was quickly cooled and was poured into 300 cc. of ice-water mixture containing 5 g. of sodium bisulfite. Ether was added, and the organic phase was washed with water, saturated sodium chloride solution, dried over magnesium sulfate, and evaporated. Crystallization of the residue from methanol gave 4.1 g. of (56), mp. 211 - 216°. (cf. reference 15.)

Preparation of trans-1,2,3,4,9,10,11,12-Octahydro-8-hydroxy-1,1,12-trimethylphenanthrene (7). The apparatus
for this experiment consisted of a three-necked, round-bottomed flask, reflux condenser, and a gas inlet tube which extended to just above the bottom of the flask. (Throughout the entire experiment nitrogen was introduced via the gas inlet tube.) Into the flask was put 1.48 g. of keto-phenol (56) and 75 cc. of diethylene glycol which was then treated with 11.3 g. of 99% hydrazine hydrate and 2.3 g. of potassium hydroxide. The solution was heated to 120° for 6 hours in a metal bath. The condenser was then removed, and the solution was heated to 195°. After this temperature was reached, the reflux condenser was replaced, and the reaction was allowed to continue at that temperature for 6 hours longer. The solution was cooled and 2N hydrochloric acid was added (pH approximately 2). The product was isolated by extraction with ether. The ether layer was washed with water, saturated salt solution, dried, and evaporated to yield crude crystalline material. Recrystallization of the product from ether - petroleum ether gave 1.32 g. of (7), mp. 136 - 146°. Further recrystallizations furnished material melting at 146 - 148°. The product was identical with that obtained by Shaw (cf. reference 15).

Preparation of the Epimeric Podocarpan-8-ols. To 1.63 g. of phenol (7) in 25 cc. of acetic acid was added 2 g. of 5% platinum-on-charcoal. The reaction mixture was hydrogenated at room temperature and atmospheric pressure. The catalyst was removed by filtration, and after addition
of ether, the organic layer was washed with cold 2N sodium hydroxide solution, water, saturated sodium chloride solution, dried and evaporated; yield 1.65 g. of clear oil. This material was filtered on 60 g. of Florisil. Elution with petroleum ether (200 cc.) gave 400 mg. of hydrocarbon; with benzene (200 cc.), 500 mg. of a crystalline alcohol; 10% ether - benzene yielded 750 mg. of a second crystalline alcohol. Recrystallization of the two alcohols from methanol furnished material melting at 99.5 -100° and at 119.5 - 121°, respectively. The alcohols had been previously encountered by Shaw. Both alcohols afford podocarpan-8-one (8) on oxidation with Jones' reagent.

Preparation of Podocarpan-8-one (8). One of the previous epimeric alcohols (198 mg.; mp. 99 - 99.5°) was dissolved in 15 cc. of acetone. The solution was flushed with nitrogen by bubbling the gas through the solution. (The gas flow was allowed to continue throughout the entire experiment.) To the flushed solution was added 0.29 cc. of standard Jones' reagent. Two minutes after the addition the reaction mixture was diluted with water, and the acetone was removed under reduced pressure. Ether and water were then added and the aqueous layer was reextracted with a small amount of ether. After combining of the organic layers, they were washed with water and sodium chloride solution, dried over magnesium sulfate, and evaporated to yield 183 mg. of crystalline material. Recrystallization from petroleum
ether furnished material (145 mg.) melting at 65 – 68°.

As a result of losses encountered in the recrystallization of this ketone, it proved desirable to reduce the mother liquors obtained after two crystallizations with sodium borohydride to the corresponding epimeric alcohols. Material obtained in this way may be combined with any oily or crudely crystalline alcohols from the previous filtration and resubmitted to the same sequence, i.e., filtration on Florisil, crystallization of alcohols, oxidation of the crystalline alcohols, and crystallization of the ketone (8).

Preparation of Hydroxymethylene Derivative (58a) of Podocarpan-8-one (8). To a solution of 112 mg. of podocarpan-8-one (8) in 30 cc. of anhydrous benzene was added two cc. of freshly distilled ethyl formate and 300 mg. of sodium hydride. The mixture was stirred at room temperature under nitrogen for 8 hours. After cautious addition of methanol to destroy excess hydride, 25 cc. of ice water and 30 cc. of ether were added. The ether layer was extracted with cold 2N sodium hydroxide solution. The combined aqueous layers were kept cold, and were made acid by adding cold 2N sulfuric acid solution. The resulting white, cloudy aqueous solution was then extracted with ether. The organic phase was dried and evaporated to yield 123 mg. of crystalline product. Since the product was rather sensitive toward decomposition, no purification was attempted.
This material showed infrared absorption at $\lambda_{max}^{CHCl_3}$ 6.13$\mu$ (broad).

**Preparation of Enol-ether (58b) with Potassium Carbonate and Isopropyl Iodide.** A solution of 46 mg. of hydroxymethylene derivative (58a) in 7cc. of dry acetone was refluxed for one day with 300 mg. of ignited potassium carbonate and 1.25 cc. of isopropyl iodide. The solvent was removed under reduced pressure. Water and ether were added, and the ether layer was separated and was washed with cold dilute potassium hydroxide solution. After drying over anhydrous potassium carbonate, the ether was removed to yield 20 mg. of crystalline material which showed carbonyl absorption at $\lambda_{max}^{CHCl_3}$ 6.01$\mu$. No purification was attempted.

**Enol-ether (58b) Formation Using Isopropyl Alcohol and Acid.** Ninety milligrams of hydroxymethylene derivative (58a), 20 cc. of anhydrous benzene, 5 cc. of isopropyl alcohol, and 5 mg. of p-toluenesulfonic acid were refluxed for 20 hours using a water separator. After cooling, the reaction mixture was added to cold, saturated sodium bicarbonate solution and extracted with ether. The ether solution was washed three times with cold dilute sodium hydroxide solution and finally with water. The solvent was removed yielding 93 mg. of crystalline material whose infrared spectrum was essentially identical with that of material derived via isopropyl iodide and potassium carbonate.

**Treatment of Enol-ether (58b) with Potassium Hydroxide**
Solution. To 200 mg. of potassium hydroxide in 2 cc. of water and 8 cc. of methanol was added 33 mg. of enol-ether (58b). The solution was refluxed for 18 hours under a nitrogen atmosphere. Removal of solvent under reduced pressure and addition of 10 cc. of cold water and 30 cc. of ether gave an organic phase which was washed, dried, and concentrated to dryness furnishing 19 mg. of light oil. Chromatography on 1.5 g. of Florisil yielded 15.4 mg. of crystalline material. This product was shown to be identical with podocarpan-8-one (8) by infrared spectra comparison.

Alkylation and Cleavage of Enol-ether (58b). Alkylation was accomplished by adding 2 cc. of potassium t-butoxide solution (containing 100 mg. of potassium) to a solution of 70 mg. of compound (58b) in 3 cc. of dry benzene. To the stirred resultant red solution was added 0.8 cc. of freshly distilled allyl bromide. The reaction mixture was stirred for 4 hours at room temperature under nitrogen. At the end of the allotted time, the mixture was neutralized with acetic acid, water and ether added, and the organic phase was separated. The ether layer was washed thoroughly, filtered through anhydrous sodium sulfate, and evaporated yielding 67 mg. of an oil; $\lambda_{\text{max}}^{\text{CS}_2} = 3.25, 5.98, 10.92 \mu$.

The product of the alkylation procedure (67 mg.) was then subjected to cleavage. The material was dissolved in
8 cc. of methanol and 2 cc. of water containing 250 mg. of potassium hydroxide. After refluxing for 62 hours under a nitrogen atmosphere, the reaction mixture was cooled, and most of the methanol was removed under reduced pressure. Following general "work-up" procedure, 44 mg. of oil was obtained which was chromatographed on 2 g. of Florisil. Processing with benzene - petroleum ether furnished 21.5 mg. of oil which failed to crystallize, \( \lambda_{\text{max}}^{\text{CS}_2} 3.26, 5.87, 10.92 \mu \).

A procedure developed later for the preparation of the desired allyl ketone gave material with similar infrared absorption.

**Preparation of Phenoxy-compound (59).** To a solution of 161 mg. of hydroxymethylene derivative (58a) in dry benzene was added 5 cc. of purified phenol and a few milligrams of p-toluenesulfonic acid. After refluxing for 40 hours under a nitrogen atmosphere, the cooled reaction mixture was poured into cold 2N sodium hydroxide solution. Ether extraction followed. The organic layer was thoroughly washed, dried, and evaporated to yield 190 mg. of oil which crystallized upon scratching. Several recrystallization from petroleum ether yielded 45 mg. of product (59) melting at 114 - 115°. Combination of the mother liquors and chromatography on 6 g. of Florisil furnished 60 mg. additional material.

The analytical sample melted at 114 - 115°, \( \lambda_{\text{max}}^{\text{EtOH}} \)
275.5 m\(\mu\) (e 13,300), \(\lambda_{\text{max}}^{\text{CS}_2} = 5.93, 13.28, 14.54\mu\).

Anal. Calcd. for C\(_{24}\)H\(_{32}\)O\(_2\): C, 81.77; H, 9.15.
Found: C, 81.46; H, 9.09.

Alkylation and Attempted Cleavage of the Phenoxy-compound (59). A solution of potassium t-butoxide prepared from 45 mg. of potassium and 2 cc. of dry t-butyl alcohol was added to a stirred solution of 45 mg. of phenoxy-ether (59) in 5 cc. of anhydrous benzene. Freshly distilled allyl bromide (1 cc.) was then added, and the reaction mixture was stirred at room temperature under nitrogen for 4 hours. The product was isolated by the usual procedure and furnished 48 mg. of oily material. From the N.M.R. analysis no aromatic proton absorption was observed, but a strong peak corresponding to the t-butyl function appeared. The infrared spectrum showed \(\lambda_{\text{max}}^{\text{CS}_2} = 3.25, 5.97, 10.92\mu\).

Attempted hydrolytic cleavage of the alkylated material proved fruitless. Two examples are (1) by refluxing in aqueous methanolic potassium hydroxide solution for 12 hours and (2) treatment with oxalic acid in refluxing ethanol for 6 hours. The conjugated carbonyl absorption persisted.

Reaction of Podocarpan-8-one (8) with Benzaldehyde. A solution of 100 mg. of podocarpan-8-one (8) in 2 cc. of methanol was treated with 1 cc. of freshly distilled benzaldehyde and 1 cc. of 33% aqueous sodium hydroxide solution. The mixture was placed in the dark at room
temperature (nitrogen atmosphere) for 12 hours. After cooling, the reaction mixture was filtered, and the remaining crystalline material was washed with 50% aqueous menthol. Three recrystallizations from methanol furnished material melting at 128 - 129°.

The analytical sample melted at 128.5 - 129.5°C.
\[ \lambda_{\text{max}}^{\text{EtOH}} = 221 \, \text{m} \mu, \quad (\varepsilon = 8,600), \quad \lambda_{\text{max}}^{\text{EtOH}} = 285.5 \, \text{m} \mu, \]
\[ (\varepsilon = 17,200); \quad \lambda_{\text{max}}^{\text{CS}_2} = 5.94, 13.30, 14.35 \, \text{(broad)} \, \mu. \]


Found: C, 85.71; H, 9.62.

Alkylation of the Benzylidene Ketone (61) with Allyl Bromide. A solution of potassium t-butoxide prepared from 100 mg. of potassium and 2.5 cc. of t-buty alcohol was added to a stirred solution of 90 mg. of benzylidene ketone (61) in 1 cc. of dry ether. After stirring for 5 minutes, 1 cc. of freshly distilled allyl bromide was added. The reaction mixture was then stirred at room temperature under nitrogen atmosphere for 4 hours. Water and ether were added, and the organic layer separated. After thorough washing of the organic phase, it was filtered through anhydrous magnesium sulfate and concentrated to dryness furnishing 82 mg. of material. Crystallization from methanol gave 41 mg. of product (62; mp. 68 - 71°C). The mother liquor was chromatographed on Florisil to yield 20 mg. additional crystalline material.

The analytical sample melted at 72 - 73°C, \[ \lambda_{\text{max}}^{\text{EtOH}} = 220 \, \text{m} \mu. \]
(ε 7.400), λ_{max}^{EtOH} 284 μm, (ε 15.700), \lambda_{max}^{CS_2} 3.26, 
5.93, 10.91, 13.19, 14.43 μm.

Anal. Calc. for C_{27}H_{36}: C, 86.12; H, 9.62.
Found: C, 86.06; H, 9.71.

Preparation of Allyl Ketone (57) by Reverse Aldol. To 2 cc. of water in which 2 g. of potassium hydroxide was dissolved there was added 75 mg. of alkylated benzylidene ketone (62) in ethanol. Enough ethanol was added to make reaction mixture homogenous, and then the solution was heated under reflux for 48 hours with nitrogen bubbler. The reaction mixture was cooled and diluted with water. Extraction with ether followed. The organic layer was washed, dried, and evaporated to yield 70 mg. of crude oil.

The above material was chromatographed on 6 g. of Florisil. The first eight fractions of this chromatogram were combined and rechromatographed on 5 g. of Florisil to yield 37 mg. of crystalline material (57).

The analytical sample melted at 61 - 62°. \lambda_{max}^{CS_2} 3.27, 5.87, 10.94 μm.

Anal. Calcd. for C_{20}H_{32}O: C, 83.27; H, 11.18.
Found: C, 83.22; H, 11.06.

Ozonization of Allyl Ketone (57). Twenty one milligrams of crudely crystalline allyl ketone (57) in 3 cc. of methylene chloride cooled in dry ice-acetone bath was treated with a small stream of ozone for one minute. The reaction mixture was allowed to stand in the cooling bath for 15
minutes and was transferred to an ice-salt bath for an additional 15 minutes. A small portion of zinc dust and 1 cc. of acetic acid were added, and the reaction mixture was stirred for 20 minutes at ice-salt bath temperature. The mixture was filtered, and the filtrate was diluted with water. Extraction with ether followed. The organic phase was washed, dried, and concentrated to dryness to yield 19 mg. of crystalline material.

*Cyclization of Keto-aldehyde to Ketol (41)*. The 19 mg. of keto-aldehyde obtained in the previous experiment was treated with 2.5 cc. of methanol, 2 drops of water and 3 drops of concentrated hydrochloric acid. The reaction mixture was refluxed for 2.5 hours under a nitrogen atmosphere. After most of the methanol was removed under reduced pressure, the residue was diluted with water. Upon addition of ether, the organic layer was separated, washed, dried and evaporated to furnish 17.5 mg. of crystalline material (41). Several recrystallizations from ether - petroleum ether yielded material melting at 180 - 182°.

**Preparation of Diketone (42).** To 15 mg. of crystalline ketol (41) in 5 cc. of acetone (flushed with nitrogen) was added 5 drops of standard Jones' reagent. The mixture was stirred for 2 minutes, and then water and ether were added. The ether layer was washed, dried and concentrated to dryness furnishing 15 mg. of crystalline product (42).
After recrystallization four times from ether - petroleum ether, the product melted at 199 - 200\(^\circ\)C, \(\lambda_{\text{max}}^{\text{CS}_2} 5.65, 5.76\mu\).

**Direct Alkylation of Podocarpan-8-one (8) with 4-Bromo-2-pentene.** A solution of potassium t-butoxide prepared from 313 mg. of potassium and 8 cc. of dry t-butyl alcohol was added to a stirred solution of 299 mg. of ketone (8) in 10 cc. of dry benzene. Freshly prepared 4-bromo-2-pentene was then added, and the reaction mixture was stirred at room temperature over night. At the end of this time water and ether were added. The organic phase was thoroughly washed, dried and evaporated to yield 380 mg. of clear oil.

The crude material was placed on 11 g. of Florisil and chromatographed. Elution with petroleum ether and further development with benzene - petroleum ether mixtures furnished the following fractions: 1) 229 mg. of clear oil, 2) 102 mg. of crystalline material, and 3) 16 mg. of crystalline podocarpan-8-one (8). Although the oil and the crystalline material had identical infrared spectra, the oil could not be induced to crystallize even with seeding. Recrystallization of the intermediate material from petroleum ether gave material melting at 118 - 123\(^\circ\).

The analytical sample melted at 122.5 - 125\(^\circ\), \(\lambda_{\text{max}}^{\text{CS}_2} 5.87, 10.33\mu\).

**Anal.** Calcd. for C\(_{22}\)H\(_{36}\)O: C, 83.48; H, 11.47.

Found: C, 83.80; H, 11.49.
Ozonization of Alkylated Ketone (70). A solution of 206 mg. of (70) in 5 cc. of methylene chloride cooled to dry ice-acetone bath temperature was treated with a small stream of ozone for 3 minutes. Allowed to remain at this temperature for 15 minutes; then transferred to ice-salt bath for an additionally 15 minutes. To the reaction mixture was added 2 cc. of acetic acid and zinc dust. The mixture was stirred at ice-salt bath temperature for 30 minutes. The zinc dust was filtered off and washed thoroughly with ether - methylene chloride solution. Water was added to the filtrate, and the organic layer was washed, dried and concentrated to yield 206 mg. of oil, $\lambda_{\text{max}}^{\text{CS}_2} 3.71, 5.85 \mu$.

Base Treatment of Keto-aldehyde (71). After treatment of 66 mg. of keto-aldehyde (71) in 2 cc. of methanol with 2 drops of concentrated sodium hydroxide solution under nitrogen atmosphere, the reaction mixture was allowed to stand 17 hours at room temperature. Removal of the methanol under reduced pressure and dilution with water then followed. Extraction with ether achieved separation of the neutral material (8 mg.). The aqueous layer was made acidic and was extracted with ether - methylene chloride. The organic layer was washed, dried and evaporated furnishing 47 mg. of crystalline material which upon recrystallization from methanol yielded material (73) melting at 212 - 215°.
The analytical sample melted at 219 - 220\(^\circ\)C, \(\lambda_{\text{max}}^{KBr} = 5.80\ \mu\).

**Anal.** Calcd. for \(C_{20}H_{34}O_3\): C, 75.42; H, 7.60. Found: C, 75.35; H, 7.64.

**Oxidation of Hydroxy-acid (73).** A solution of 38 mg. of (73) in 5 cc. of acetone flushed with nitrogen was treated with 3 drops of standard Jones' reagent. After 3 minutes stirring, water was added, and the acetone was removed under reduced pressure. Final extraction with ether-methylene chloride solution yielded, after washing, drying and evaporating, 39 mg. of crystalline material. Recrystallization from methylene chloride - petroleum ether furnished 30 mg. of compound (74) melting at 176 - 181\(^\circ\), \(\lambda_{\text{max}}^{KBr} = 2.97, 5.73\ \mu\).

**Attempted Cyclization to Diketone (75).** A solution of 5 mg. of material from the oxidation of hydroxy-acid (73) and a crystal of \(p\)-toluenesulfonic acid in 2 cc. of benzene was allowed to reflux under nitrogen for 12 hours. The reaction mixture was then cooled. Ether and water were added. The organic phase was separated, washed, dried and concentrated to dryness furnishing oily neutral material which showed infrared absorption at 5.56 \(\mu\) in carbon disulfide solution.

**Preparation of 7-Methoxy-2-tetralone.** A 100 g. sample of 2,7-dimethoxynaphthalene was reduced with sodium and alcohol by the procedure of Cornforth and Robinson,\(^{69}\) and the resulting enol-ether was hydrolyzed with aqueous acid.
The crude product was distilled and furnished 70 g. of crystalline 7-methoxy-2-tetralone, bp. 116 - 120°/0.2mm.

**Preparation of 1-Methyl-7-methoxy-2-tetralone.** A solution of 70 g. of 7-methoxy-2-tetralone in 500 cc. of dry benzene was treated with 154 cc. of freshly distilled pyrrolidine, and the mixture was heated under reflux for 1.5 hours in a nitrogen atmosphere. Water was removed continuously by means of a water separator: 11 cc. was collected during the reflux period. The solvent was then removed under reduced pressure at room temperature, and the residue was taken up in 500 cc. of dry methanol. The solution was refluxed for 30 minutes after the addition of 36 cc. of methyl iodide. An additional 73 cc. of methyl iodide was then added, and heating was continued for 1 hour.

The excess methyl iodide was removed by distillation, and 74 cc. of glacial acetic acid and 74 g. of sodium acetate in 150 cc. of water were added. After heating under reflux for 45 minutes, the bulk of the solvent was evaporated under reduced pressure. The residue was taken up in ether and water. The organic layer was separated, washed thoroughly, dried and concentrated to dryness. The product was distilled under reduced pressure: yield 43.3 g., bp. 115 - 122°/0.1mm.

**Preparation of 2,3,4,9,10,12-Hexahydro-6-methoxy-12-methyl-2-oxophenanthrene.** A solution of 36.5 g. of 1-methyl-
7-methoxy-2-tetralone in 200 cc. of dry benzene was treated with diethylaminobutanone methiodide (from 27.4 g. of diethylaminobutanone)\textsuperscript{71} and a solution of 7 g. of sodium in 140 cc. of ethanol according to the procedure of Cornforth and Robinson.\textsuperscript{69} The crude product crystallized upon addition of ether.\textsuperscript{45} The mother liquor was distilled, and the fraction boiling from 150 - 180\textdegree C/0.1 mm. could be induced to crystallize upon ether addition.

**Preparation of trans-1,2,3,4,9,12-Hexahydro-6-methoxy-1,1,12-trimethyl-2-oxophenanthrene (78).** Methylation of the tricyclic ketone (77) was carried out according to the Woodward-Patchett procedure.\textsuperscript{46} Four hundred milligrams of (77) was dissolved in 5 cc. of anhydrous \textit{t}-butyl alcohol, and a solution of 200 mg. of potassium in 20 cc. of \textit{t}-butyl alcohol was added under a nitrogen atmosphere. An immediate addition of 1.4 cc. of methyl iodide followed. The mixture was stirred for 2 hours at room temperature; at the end of which time enough aqueous sulfuric acid was added to render the mixture acidic. Ether and water were then added. After separation of layers, the ether phase was washed with dilute sodium hydroxide solution, water, saturated sodium chloride solution and dried over anhydrous sodium sulfate. The solvent was removed, and a futile crystallization attempt was made. The crude red oil (494 mg.) was filtered through Florisil column to yield 387 mg. of clear oil, $\lambda_{\text{max}}^{CS_2} 5.84 \mu$, which would
not be induced to crystallize.

Preparation of trans-1,2,3,4,9,12-Hexahydro-6-methoxy-1,1,12-trimethyl-2-hydroxyphenanthrene (79). To 2.8 g. of ketone (78) in 30 cc. of ethanol was added (slowly and with cooling) 2.8 g. of sodium borohydride. After addition the reaction was stirred at room temperature for 8 hours. Aqueous sulfuric acid was added, and the resulting solution was extracted with ether. The ether layer was washed with water and saturated sodium chloride solution. Drying, evaporation of solvent, and crystallization from methanol yielded 1.5 g. of material (79). The sample for analysis melted at 122.5 - 123.5°, \( \lambda_{\text{max}}^{\text{CS}_2} = 2.78 \mu \).


Treatment of (79) with acetic anhydride and pyridine gave the corresponding acetyl derivative, mp. 134 - 135° (methylene chloride - petroleum ether), \( \lambda_{\text{max}}^{\text{CS}_2} = 5.76 \mu \).

**Anal.** Calcd. for C\(_{20}\)H\(_{26}\)O\(_3\): C, 76.40; H, 8.33. Found: C, 76.42; H, 8.35.

**Oxidation of Hydroxy-anisole Derivative (79).** A solution of 50 mg. of (79) in 2 cc. of dry pyridine was added to chromium trioxide - pyridine complex prepared from 200 mg. of chromium trioxide and 3 cc. of dry pyridine. The resulting mixture was allowed to stand at room temperature over night. The reaction was stopped by addition of ice, cold 2N aqueous sulfuric acid, and methylene chloride.
When the mixture was acidic, it was filtered through "Celite." The filtrate was transferred to a separatory funnel. The organic layer was 'floated' by addition of ether. After washing thoroughly and drying over magnesium sulfate, the organic phase was evaporated to furnish 43 mg. of crystalline material. Recrystallization from ether-petroleum ether yielded 30 mg. of material melting at 156 - 160°. The analytical sample melted at 161 - 163°, $\lambda_{\text{max}}^{\text{EtOH}}$ 238 m$\mu$, ($\epsilon$ 17,900); 302 m$\mu$, ($\epsilon$ 14,000); $\lambda_{\text{max}}^{\text{CH}_2\text{Cl}_2}$ 5.83, 6.05 m$\mu$.

**Anal.** Calcd. for C$_{18}$H$_{20}$O$_3$: C, 76.03; H, 7.09. Found: C, 75.88; H, 7.17.

Similar results were obtained from oxidations performed on the analogous 6-methoxy- and 7-methoxy-compounds.

**Birch Reduction of Hydroxy-anisole Derivative (79).**

Small pieces of lithium wire (390 mg. in all) were added over a period of 15 minutes to a stirred solution of 100 mg. of (79) in 2 cc. of absolute ethanol and 50 cc. of liquid ammonia. After stirring for 45 minutes, the ammonia was allowed to evaporate, and water was added followed by ether. The organic phase was washed thoroughly, dried and evaporated to yield 100 mg. of clear oil, $\lambda_{\text{max}}^{\text{CS}_2}$ 2.78, 5.85, 5.97 m$\mu$.

Treatment of (80a) with acetic anhydride and pyridine gave the corresponding acetyl derivative (80b), mp. 141.5 - 143.5° (methylene chloride - petroleum ether), $\lambda_{\text{max}}^{\text{CS}_2}$ 5.77.
5.87, 5.98 µ.

**Anal.** Calcd. for C_{20}H_{28}O_{3}: C, 75.91; H, 8.92.
Found: C, 75.80; H, 8.84.

**Hydrolysis of Birch Reduction Product (80a).** To 500 mg. of (80a) in 10 cc. of ethanol was added 1 g. of oxalic acid and 1 cc. of water. The mixture was stirred at room temperature for 1.5 hours and was then cooled and treated with ice and water. The mixture was then extracted with ether. The organic layer was washed with water, cold dilute sodium hydroxide solution, water and saturated sodium chloride solution. Drying and evaporating followed to yield 440 mg. of crystalline material (mp. 123 - 131°). Recrystallization from methylene chloride - petroleum ether yielded 349 mg. of material melting at 137 - 143°. The analytical sample (ether - petroleum ether) furnished material melting at 150 - 154°. λ_{max}^{CH_{2}Cl_{2}} 2.81, 5.85 µ.

**Anal.** Calcd. for C_{17}H_{24}O_{2}: C, 78.42; H, 9.29.
Found: C, 78.43; H, 9.05.

**Preparation of Diol (82a).** To a solution of 263 mg. of ketol (81) in 15 cc. of ethanol was added 263 mg. of sodium borohydride. The mixture was stirred at room temperature for 6 hours. Using standard "work-up" procedure 255 mg. of crystalline material was obtained (mp. 154 - 162°). Thin layer chromatography (t.l.c.) showed only one peak (aluminum oxide - ethyl acetate).

**Preparation of Diacetate (82b).** Treatment of the
unpurified diol (82a) with acetic anhydride and pyridine furnished an oil ($\lambda_{\text{max}}^{\text{CS}_2} 5.77, 8.05\mu$) which t.l.c. showed to be made up of at least two components. No purification was attempted.

Oxidation of Diacetate (82b). To chromium trioxide - pyridine complex (2 cc. of pyridine - 100 mg. of chromium trioxide) was added 54 mg. of diacetate (82b) in 2 cc. of pyridine. The mixture was allowed to stand at room temperature for 16 hours. General "work-up" procedure yielded 40 mg. of oil which was chromatographed on Florisil. Crystalline material (33 mg.) was obtained after elution development had reached the 100% benzene stage. Recrystallization from methylene chloride - petroleum ether yielded 24 mg., mp. 114 - 117°. After repeated recrystallization, the analytical sample melted at 162.5 - 163.5°, $\lambda_{\text{max}}^{\text{EtOH}} 246\mu$ (\$ 15,300); $\lambda_{\text{max}}^{\text{CH}_2\text{Cl}_2} 5.79, 6.04, 6.12\mu$.

Anal. Calcd. for C_{21}H_{28}O:  C, 69.98;  H, 7.83. Found:  C, 69.86;  H, 7.94.

Hydrogenation of Dienone (83). A mixture of 65 mg. of (83), 5 cc. of acetic acid, and 75 mg. of 10% palladium-on-charcoal catalyst was hydrogenated at room temperature and atmospheric pressure for 24 hours. The product was isolated in the usual way and furnished 65 mg. of clear oil which crystallized on addition of petroleum ether and seeding. The analytical sample (85) melted at 158.5 - 160°, $\lambda_{\text{max}}^{\text{CS}_2} 5.76, 5.82, 8.04\mu$. 
Anal. Calcd. for C$_{21}$H$_{32}$O$_{5}$: C, 69.20; H, 8.85.
Found: C, 68.87; H, 8.76.

If the catalyst is not very active or hydrogenation is allowed to proceed for a shorter length of time, the dienone (83) furnishes (84) as a crystalline compound. The analytical sample melted at 116.5 - 117.5° (ether-petroleum ether), $\lambda_{\text{max}}$ 251 m$\mu$, ($\epsilon$ 5,800); $\lambda_{\text{max}}^{\text{CS}}$ 5.74, 5.99, 8.07 m$\mu$.

Anal. Calcd. for C$_{21}$H$_{30}$O$_{5}$: C, 69.58; H, 8.35.
Found: C, 69.75; H, 8.39.

**Preparation of Oxime (92) from Phyllocladene Norketone.**
To a solution of 98 mg. of norketone in 5 cc. of ethanol and 5 cc. of pyridine was added 150 mg. of hydroxylamine hydrochloride. The reaction mixture was allowed to reflux for six hours. Water and ether were added. The organic layer was washed, dried and evaporated to yield crystalline material. Recrystallization from methanol several times furnished needles melting at 176 - 178°.

**Reduction of Oxime (92).** Small pieces of sodium metal were added to a solution of 46 mg. of oxime (92) in 7 cc. of refluxing isopropyl alcohol. The reaction mixture was heated under reflux for three hours. Ethanol was added to destroy excess sodium. After cooling, water was added to layer the alcohols. Ether added and organic layer separated. The ether layer was washed with cold 2N sodium hydroxide solution, water and saturated sodium chloride solution.
The organic layer was dried by filtration through magnesium sulfate and removal of the solvent yielded 40 mg. of crude amine, isolated as the hydrochloride by dissolving crude amine in ethanol and adding three drops of concentrated hydrochloric acid. Crystalline material was filtered and washed with cold ether.

Preparation of Acetamide Derivative. Acetic anhydride (1 cc.) was added to 24 mg. of crude amine in 2 cc. of ether, and the reaction mixture was allowed to stand at room temperature for 9 hours. At the end of that time the solution was cooled, poured into iced 2N sodium hydroxide solution and extracted with ether. The ether layer was washed with water and saturated sodium chloride solution, dried over magnesium sulfate and evaporated to yield 24 mg. of crystalline material. Recrystallization from benzene yielded 19 mg. of material melting at 217 - 218°, \( \lambda_{\text{max}}^\text{CS2} 5.98 \mu \).

Anal. Calcd. for \( \text{C}_2\text{H}_3\text{N} \): C, 79.44; H, 11.11; N, 4.41. Found: C, 79.68; H, 11.11; N, 4.10.

Nitrosation and Rearrangement of Amine (93). After the reaction vessel was flushed completely with nitrogen, 52 mg. of sodium nitrite was added to 93 mg. of amine hydrochloride in 3 cc. of water and 3 cc. of acetic acid. The evolution of nitrogen was followed. The mixture was stirred for 14 hours at which time 26 mg. more of sodium nitrite was added. Allowed to stir one hour longer; the
reaction mixture was distilled under vacuum with trapping of solvent in dry ice - acetone trap. The bath temperature was never allowed to rise above 25°. After approximately one half of the solvent was removed, more water was added and distillation was continued. The reaction mixture was diluted with water after one half of this solvent volume had been removed. The cloudy mixture was repeatedly extracted with ether. The organic layer was washed with water, cold 2N sodium hydroxide solution, water and saturated sodium chloride solution. Drying and evaporation of the ether layer gave 76 mg. of oily material showing hydroxyl and carbonyl absorption in the infrared.

**Reductive Cleavage of Rearranged Material.** To a solution of the crude mixture from the previous reaction in 10 cc. of anhydrous ether was added 100 mg. of lithium aluminium hydride. The reaction mixture was stirred at room temperature for 3 hours. The excess hydride was destroyed with wet ether. The mixture was made acidic and was extracted with ether - methylene chloride. The organic phase was washed, dried and evaporated to furnish 40 mg. of partially crystalline material showing no absorption in the carbonyl region of its infrared spectrum.

**Oxidation and Identification of Mixture from Rearranged Amine (93).** The 40 mg. of material from previous experiment in 3 cc. of acetone was treated with 0.25 cc. of Jones' reagent. The reaction mixture was allowed to stand for
2.5 minutes and was then diluted with water and distilled under reduced pressure (not allowing the bath temperature to exceed 25°C). After most of the acetone was removed, the mixture was extracted with ether - methylene chloride. The organic layer was washed, dried and evaporated to yield 37.5 mg. of crystalline material. This sample was placed on 6 g. of alumina. Elution with 100% petroleum ether yielded 4.7 mg. of partially crystalline material which compared favorably with hydrocarbon (95) via infrared analysis. Further development with benzene - petroleum ether mixtures yielded 5.7 mg. of ketone (20), mp. 129.5 - 131°C, 15.5 mg. of phyllocladene norketone (96), mp. 100 - 101°C, and an unidentified substance, mp. 125 - 127°C, λ_max CS² 5.81 μ.

Sodium - Alcohol Reduction of Phyllocladene Norketone (96). Approximately 850 mg. of sodium metal in small pieces was added to a refluxing solution of 85 mg. of norketone (96) in 10 cc. of ethanol over a period of 24 minutes (nitrogen atmosphere). Then 3 cc. of ethanol was distilled from the reaction mixture; to the mixture was added now ice-water mixture and ether. The organic layer was washed, dried and evaporated to yield 83 mg. of crystalline material.

The 83 mg. of material was subjected to column chromatography on 8 g. of Florisil. Processing with benzene - petroleum ether mixtures furnished 58.5 mg. of
alcohol (99), mp. 152°, and 17.5 mg. of epimeric alcohol (98), mp. 157°.

**Equilibration of Alcohols (98) and (99).** To 7 cc. of purified \textit{n}-butyl alcohol\textsuperscript{60} at reflux temperature under nitrogen atmosphere was added 550 mg. of sodium metal. After the sodium disappeared, 55 mg. of alcohol (99) was introduced in 3 cc. of \textit{n}-butyl alcohol. The reaction mixture was stirred at 140° (oil bath temperature) for 45 hours, after which time the solution was cooled, diluted with water and extracted with ether. The organic layer was washed, dried and evaporated to furnish 55 mg. of crystalline material.

Standard chromatography on 8 g. of Florisil yielded 19 mg. of alcohol (99) and 32 mg. of epimeric alcohol (98), \textit{i.e.}, 37\% and 63\% respectively.

The results of reduced equilibration times were as follows — starting with 100\% (99):

<table>
<thead>
<tr>
<th>Hours of Reflux</th>
<th>% Alcohol (99)</th>
<th>% Alcohol (98)</th>
</tr>
</thead>
<tbody>
<tr>
<td>23</td>
<td>65</td>
<td>35</td>
</tr>
<tr>
<td>33</td>
<td>54.5</td>
<td>45.5</td>
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**Tosylate Preparation.** To 1 cc. of dry \textit{p}-rtyidine containing 60 mg. of alcohol (98) was added 120 mg. of \textit{p}-toluenesulfonyl chloride. After standing for four days under a nitrogen atmosphere, the reaction mixture was diluted with a mixture of ice and water. Ether was added after the diluted reaction mixture was allowed to stand five minutes. The ether layer was washed, dried and evaporated
to furnish 90 mg. of clear oil. No attempt was made to crystallize the material.

**Acetolysis of Tosylate.** The 90 mg. of tosylate from the previous reaction was dissolved in 2 cc. of acetic acid which was 0.1M in sodium acetate and 0.01M in acetic anhydride. The reaction vessel was sealed under nitrogen. The flask was immersed in an oil bath at 49° and was allowed to remain at this temperature for 48 hours. After cooling, the reaction mixture was poured into an ice-water-ether mixture. The ether layer was washed, dried and evaporated to furnish 66 mg. of material with negligible absorption in the carbonyl region of its infrared spectrum.

A few drops of n-hexane were added, and 20 mg. of crystalline material was recovered. From N.M.R. the material appeared to be unreacted tosylate. The only identifiable material from the mother liquor was olefinic material, mainly hydrocarbon (95) as deduced from infrared analysis.

**Sodium - Xylene Acyloin on Keto-ester (13).** A heated solution (120°) of 82 mg. of keto-ester (13) in 15 cc. of dry xylene was treated with 20 mg. of sodium. The mixture was stirred vigorously under a nitrogen atmosphere at 120° for 4 hours. Cooled and sodium destroyed carefully. Separation of the product into acid and neutral fractions followed. The acidic material (30 mg.) was shown to be convertible into starting keto-ester (13) by treatment with diazomethane. The neutral material (48 mg.) which was
partially crystalline furnished 9 mg. of material on crystallization from methanol. The 9 mg. of material was shown to be starting keto-ester (13). Chromatography of the mother liquor on 6 g. of Florisil yielded 27 mg. of crystalline product. Recrystallization several times from methanol furnished 13 mg. of material melting at 151 - 153°, $\lambda_{\text{max}}^\text{CS}_2 2.83, 5.73 \mu$. The infrared spectrum was consistent with structure (101); however, from N.M.R. the possibility of a mixture involving (101) and hydroxy-ester (102) was indicated.

**Sodium - Ammonia Cyclization of Keto-ester (13).** To a solution of 30 cc. of dry ether, 45 cc. of liquid ammonia, and 210 mg. of sodium was added drop-wise 101 mg. of keto-ester (13) in 30 cc. of dry ether. The addition was completed in 90 minutes. Ten minutes after this addition was completed, the blue color of the liquid layer had disappeared. The ammonia and most of the ether were removed in a stream of nitrogen. Water and ether - methylene chloride were added. The organic phase was washed with cold water. The aqueous layers were combined and acidified yielding, after extraction with ether - methylene chloride, 8 mg. of acidic material.

Washing of the neutral organic layer with sodium chloride solution, drying over magnesium sulfate, and evaporation furnished 86 mg. of crudely crystalline material. Recrystallization from ethyl acetate yielded 25 mg.
of material (mp. 260 - 262°) which showed no carbonyl absorption in infrared analysis.

Further crystallization yielded material melting at 268 - 270°.

Anal. Calcd. for C₁₉H₃₂O₂:  C, 78.03;  H, 11.03. 
Found:  C, 77.39;  H, 10.79.

Preparation of Glycol (108). To a solution of 100 mg. of keto-ester (17) derived from phyllocladene in 10 cc. of dry ether under nitrogen was added 200 mg. of lithium aluminum hydride. The mixture was stirred for 7 hours, and the excess lithium aluminum hydride was then decomposed by careful addition of water. A portion of 2N aqueous sulfuric acid was cautiously added. Ether was then added, and the organic layer was washed, dried and evaporated to yield 89 mg. of crystalline material. No attempt was made to purify the glycol (108).

Preparation of Keto-aldehyde (109). The chromium trioxide - pyridine complex was prepared using 300 mg. of chromium trioxide and 2 cc. of dry pyridine. To the cooled complex was added 89 mg. of diol in 1 cc. of pyridine. The resulting mixture was allowed to stand at room temperature for 9 hours. The reaction was stopped by addition of ice, cold 2N aqueous sulfuric acid, and methylene chloride. When the mixture was slightly acidic, it was filtered through "Celite." The filtrate was transferred to a separatory funnel. The organic layer was 'floated' by addition of
ether and was washed, dried and concentrated to dryness yielding 85 mg. of crystalline material. Recrystallization from ether - petroleum ether yielded 42 mg. of material melting at 127 - 129°, \( \lambda_{\text{max}}^{\text{CS}_2} \) 3.69, 5.79 μ.

**Preparation of Diene (106).** A solution of 35 mg. of keto-aldehyde (109) in 2 cc. of dry ether was added under a nitrogen atmosphere to a mixture of 565 mg. of methyl triphenylphosphonium bromide and 165 mg. of powdered potassium t-butoxide in 15 cc. of petroleum ether. After stirring 10 hours at room temperature, the reaction mixture was diluted with water and ether. The organic layer washed with water, dried and evaporated to yield 85 mg. of material.

The crude material was put on 6 g. of Florisil in a small amount of benzene. The first fraction eluted with petroleum ether contained 29 mg. of an oil. Infrared and N.M.R. analysis showed characteristic vinylidene absorption, \( \lambda_{\text{max}}^{\text{CS}_2} \) 3.25, 11.00, 11.24 μ; (N.M.R. taken in carbon disulfide with t.m.s. as external standard) 4.6, 5.1, 6.1 ppm; \( R_f = 0.076 \) (tlc on alumina eluted with chloroform).

**Attempted Acid - Catalyzed Cyclization of Diene (106).** Refluxing under nitrogen atmosphere was continued for three days on 31 mg. of diene (106) in 4 cc. of 98 - 100% formic acid. After this time the reaction solution was cooled and diluted with water and ether. The ether layer was washed thoroughly, dried and evaporated to yield 25.5 mg. of oil. This was filtered directly through Florisil to
furnish 20 mg. of oil via petroleum ether elution. No vinyl protons were detected either by infrared or N.M.R. studies.

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