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A STEREOSELECTIVE TOTAL SYNTHESIS OF EPIGEIJERENE AND NEOGEIJERENE

by

© HENG-FOONG KOO

A THESIS

SUBMITTED TO THE FACULTY OF GRADUATE STUDIES AND RESEARCH IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF MASTER OF SCIENCE

DEPARTMENT OF CHEMISTRY

EDMONTON, ALBERTA

FALL, 1975

THE UNIVERSITY OF ALBERTA

FACULTY OF GRADUATE STUDIES AND RESEARCH

The undersigned certify that they have read, and recommend to the Faculty of Graduate Studies and Research, for acceptance, a thesis entitled

A STEREOSELECTIVE TOTAL SYNTHESIS OF
EPIGEIJERENE AND NEOGEIJERENE

submitted by HENG-FOONG KOO in partial fulfillment of the requirements for the degree of Master of Science.

.....
Supervisor

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Date: August 28, 1975

ABSTRACT

A stereoselective total synthesis of two hitherto unreported isomers of a naturally-occurring hydrocarbon geijerene (1), namely neogeijerene (14) and epigeijerene (15) has been achieved. In developing the synthesis, a new approach for constructing the elemene-type 1,5-diene system was introduced. Primarily, the method involved the addition of a latent isopropenyl group to the α-position of an α,β-unsaturated cyclohexenone *via* a photochemical route and subsequent addition of a vinyl group to the β-position using a vinyl ate complex.

Photocycloaddition of 3-methyl-2-cyclohexen-1-one and 1-propenyl acetate gave 7-acetoxy-6,8-dimethylbicyclo-[4.2.0]octan-2-one (16) which was then hydrolysed to the corresponding alcohol 17. Oxidative cleavage of 17 with ceric ammonium nitrate afforded 3-methyl-2-(1-methy-2-oxoethyl)-2-cyclohexen-1-one (18). Conjugate addition of a vinyl group to keto esters 29 and 43 which were obtained from 18 by selective reduction and esterification was accomplished by using vinyllithium-tetrakis[iodo(tri-*n*-butyl-phosphine)copper(I)] complex. Further modifications of the existing functionalities to double bonds completed the synthesis of neogeijerene (14) and epigeijerene (15).

ACKNOWLEDGEMENTS

The author wishes to thank the technical staff members of the Department of Chemistry, especially Mr. R. N. Swindlehurst and Dr. T. Nakashima and their associates for recording the nmr spectra, Dr. A. M. Hogg and his staff for running the mass spectra and Mrs. D. Marlow and Mrs. A. Dunn for determining the microanalyses.

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INTRODUCTION

Geijerene, a naturally-occurring hydrocarbon of molecular composition $C_{12}H_{18}$, was first isolated by Penfold[1] from the leaves of Geijera parviflora (lindley). In 1932, Penfold and Simonsen[2] reported their preliminary structural investigation, concluding that the hydrocarbon was an optically inactive monocyclic triene. Some three decades later, Sutherland[3,4] proposed the plane chemical structure of 3-isopropenyl-4-methyl-4-vinylcyclohexene for geijerene on the basis of his extensive degradative studies. Independently, the same conclusion was reached by Birch and his co-workers[5] using an array of physical methods. The stereochemistry of geijerene was not established until recently when its silver nitrate adduct ($C_{12}H_{18}.2AgNO_3$) was subjected to an X-ray examination[6] which confirmed the assigned structure and also revealed the trans-relationship of the two vinyl substituents as depicted in the structural formula 1.

Geijerene (1) is the simplest member of a class of commonly-occurring sesquiterpenoids[7] possessing elemene-skeleton. The elemenes are formally cyclohexane derivatives in which four carbon substituents are commonly observed as illustrated by elemol (2)[8], a representative member of the family. From both the biogenetic and the synthetic standpoints, elemene-type compounds are closely related to the

germacranolides[9] such as germacrone (3)[10]. The germacranolides constitute another class of sesquiterpenoids which are mostly cyclodeca-1,5-diene derivatives. The intimate relationship of these two classes of natural products is basically due to their capability to undergo interconversion. Biogenetically, germacranolides are believed to be the precursors of elemenes*. By this assumption, the "isoprene" origin of elemenes can be readily explained. In addition to the often observed co-existence of germacranolides and elemenes in nature [e.g. pregeijerene (4) and geijerene (1) from the leaves of G. parviflora (lindley)[12]], this hypothesis is further supported by the in vitro thermal rearrangement of the germacranolide-skeleton to the elemene-skeleton. The conversion of pregeijerene (4) to geijerene (1)[12] and germacrone (3) to β-elemenone (5)[13,14] are two of a vast number of reported examples**. It has also been noted that the biogenetic process is presumably parallel to the in vitro experiments involving thermal Cope rearrangement in a non-enzymatic fashion[3,4]; the total lack of optical activity of geijerene (1) with two chiral centres is rather unusual but can be readily accounted for by invoking such an assumption.

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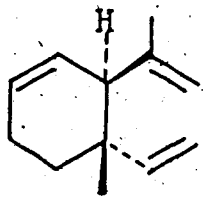
*For a recent review of sesquiterpenoid biogenesis, see ref. 11.

**For some other examples, see ref. 15-17.

Although the transformation of the elemene-skeleton to the germacranolide-skeleton by a "reverse" Cope rearrangement is to some extent conformationally dependent[18], many cases are known[18-21]. Whereas the direct formation of medium-sized rings is difficult experimentally, the construction of substituted cyclohexanes is relatively simple. The success of the "reverse" Cope rearrangement suggests the potential use of elemene-type compounds as intermediates in the construction of germacranolides. In fact, the first reported total synthesis of a germacranolide preisocalamendiol (6) using (-)-santonin (7) as a relay compound involves the thermal rearrangement of shyobunone (8) as a key step[19]. It is with this realization in mind that we initiated the current studies as part of our interest in exploring the synthetic chemistry of germacranolides. Our efforts have been concentrated on the development of a method, using geijerene (1) as a model, for the construction of an elemene-type 1,5-diene system necessary to proceed to the "reverse" Cope rearrangement. Existing methods towards this end are rather limited. The methods used by Kato, et al. for the synthesis of shyobunone (8)[19] and geijerene (1)[22] from (-)-santonin (7) required extensive degradation of the starting material and thus are limited in general applicability.

In view of the fact that 3-methyl-2-cyclohexen-1-ones are readily accessible (e.g. Birch reduction of the



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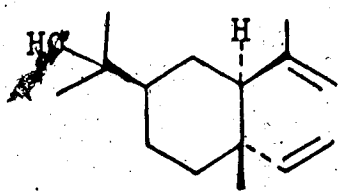

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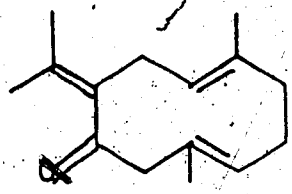

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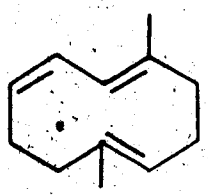

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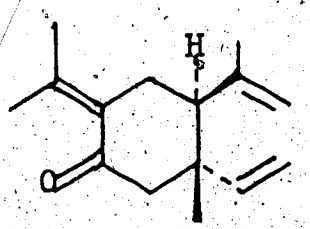

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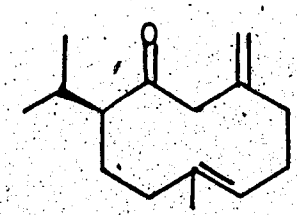

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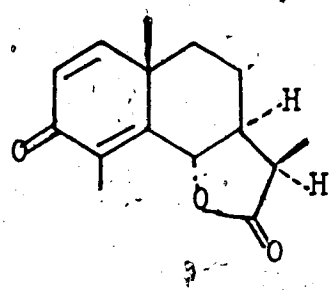
corresponding aromatics), a general approach to the 1,5-dienes could involve a sequential addition of a latent isopropenyl group and a vinyl group to the conjugated enone system as illustrated in Scheme I. Since a number of methods are available for the conjugate addition of a vinyl group to an α,β-unsaturated ketone [23-26], transformation of 10 to 11 should not present any difficulties. The feasibility of the scheme would therefore depend largely on the efficiency of the step 9→10. In this connection, the method developed by Valenta and his co-workers[27] for the introduction of a single 2-oxoalkyl chain specifically to the α-carbon of an α,β-unsaturated ketone is especially pertinent. Their method involves the photocycloaddition of a conjugated enone to vinyl acetate or its derivatives as an initial step. Subsequent oxidative cleavage of the resulting cyclobutane intermediate completes the overall process. For example, an efficient transformation of isophorone (12) to 3,5,5-trimethyl-2-(2-oxopropyl)-2-cyclohexen-1-one (13) was achieved by irradiation of a mixture of the former compound and isopropenyl acetate, followed by hydrolysis of the photoadduct with alkali and oxidation of the resulting alcohol with ceric ammonium nitrate (Scheme II)[28]. It is quite conceivable that the synthetic step in question (i.e. 9→10) could be implemented by a suitable choice of the two reactants involved in the initial photocycloaddition reaction.



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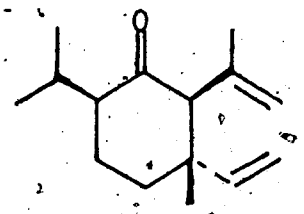

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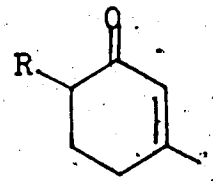
Scheme I



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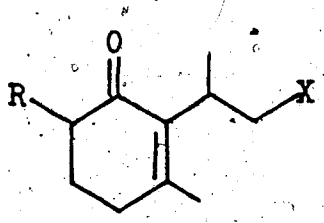

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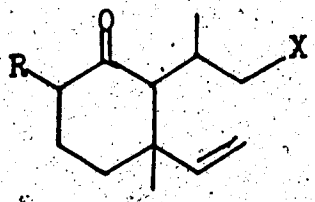

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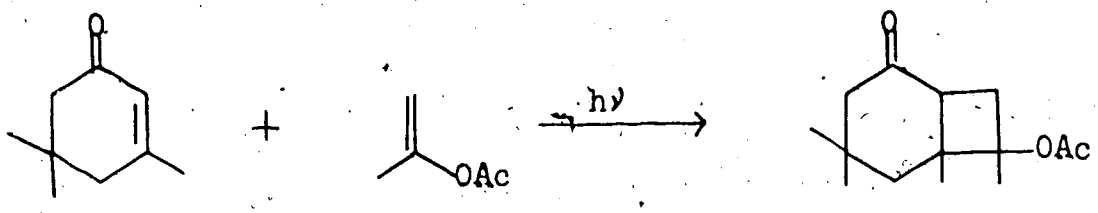
This thesis describes a stereoselective total synthesis of two hitherto unreported* isomers of geijerene (1), namely neogeijerene (14) and epigeijerene (15). Although the current approach fails to lead to geijerene (1) and further stereochemical control remains to be studied in order to attain this goal, this thesis clearly demonstrates a new method for constructing the elemene-type 1,5-diene system based on the general scheme I.

*Isogeijerene (3-isopropylidene-4-methyl-4-vinylcyclohexene) has been prepared by the treatment of geijerene (1) with potassium amide in liquid ammonia[5].

Scheme II



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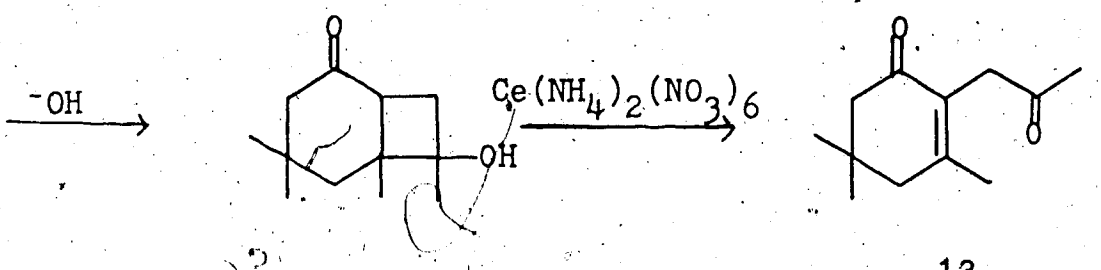

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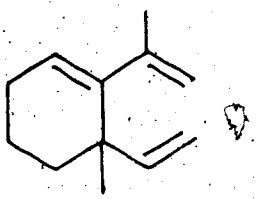

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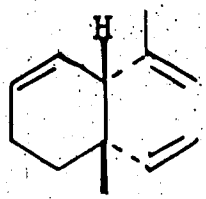

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RESULTS AND DISCUSSION

In order to incorporate a latent isopropenyl group to the α-position of a conjugated enone according to the procedure developed by Valenta et al.[27,28], 1-propenyl acetate was used in the initial photocycloaddition reaction. 3-Methyl-2-cyclohexen-1-one and a mixture of cis- and trans-1-propenyl acetate, readily prepared from propanal and acetic anhydride using a modified procedure of Curtin and Hurwitz[29] was irradiated in benzene for 20 hr and gave rise to an 80% yield of the head-to-tail photoadduct 16. The photoadduct thus obtained was shown to be a mixture consisting of at least three diastereomers by its nmr spectrum displaying three doublets at δ 4.84, 4.60 and 4.28 for a total of one methine proton adjacent to the acetoxy group. The ir spectrum showed the ester and ketone absorption bands at 1735 and 1697 cm^{-1} respectively. The appearance of the ketone carbonyl absorption at a frequency lower than the normally expected value is generally observed when the six-membered ring is fused with a four-membered one. The photocycloaddition reaction was found to be regiospecific; no detectable amount of the head-to-head photoadduct was obtained. The orientation of the photoadduct could be readily assigned on the basis of further transformations. Since three of the four asymmetric centres present in the molecule would be destroyed in the later stage, no attempt was made to separate the isomers of the photoadduct 16.

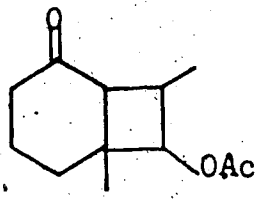
Subsequent treatment of 16 with aqueous potassium carbonate in methanol at reflux resulted in the hydrolysis of its acetoxy grouping to give quantitatively, the alcohol 17 as a mixture of diastereomers. In its ir spectrum, the hydroxy and ketone absorption bands appeared at 3420 and 1685 cm^{-1} respectively.

Alcohol 17 underwent oxidative fragmentation upon treatment with ceric ammonium nitrate in refluxing aqueous acetonitrile for a short period. In addition to the expected aldehyde 18 (40% yield), a ca. 30% yield of lactol 19 (contaminated by a small quantity of starting material) and a trace of aromatic compound 20 were also obtained. The structures of 18 and 20 followed clearly from their spectral data. The ir spectrum of 18 showed the characteristic absorption bands of the aldehyde group at 2820, 2710 and 1720 cm^{-1} and the ketone carbonyl absorption at 1655 cm^{-1}. In the nmr spectrum, the aldehydic proton appeared at δ 9.44 as a singlet. Another singlet at δ 1.97 and a doublet at δ 1.10 for the two methyls were also observed. Its mass spectrum further confirmed the structural assignment, showing a molecular ion peak at 166.0998. The nmr spectrum of 20 was in full agreement with the assigned structure, exhibiting signals at δ 6.95 (dd, 1H, J = J' = 7.5 Hz, aromatic), 6.57 (d, 1H, J = 7.5 Hz, aromatic), 6.52 (d, 1H, J = 7.5 Hz, aromatic), 5.40 (d, 1H, J = 5.0 Hz, -OCHOH), 3.09 (m, 1H, benzilic methine), 2.25 (s, 3H,

$=\dot{C}CH_3$) and 1.18 (d, 3H, J = 7.0 Hz, $-\dot{C}HCH_3$). The structure of lactol 19 was proven in correlation with aldehyde 18 as follows. Jones oxidation[30] of 18 followed by esterification of the resulting acid 21 with methyl iodide and potassium carbonate in acetone at room temperature afforded keto ester 22. Treatment of lactol 19 with Jones reagent resulted in the formation of lactone 23, which upon refluxing with potassium carbonate and methyl iodide in acetone[31] gave 22 identical in all respects with that previously obtained from aldehyde 18.

Compounds 19 and 20 were probably formed via aldehyde 18 involving hydration-cyclization and oxidation-aromatization-cyclization processes respectively. In principle, oxidative fragmentation of alcohol 17 could lead to the formation of either 18 or 24 or both, depending on whether the cleavage occurred at bond(s) a or/and b. The exclusive generation of 18 and its derivatives thereafter indicated that the cleavage of bond a took place specifically. This fragmentation pattern is consistent with all other cases so far studied[27,28] and appears to be general.

The three-step sequence, i.e. 3-methyl-2-cyclohexen-1-one → 16 → 17 → 18 thus completed the introduction of a latent isopropenyl group specifically to the α-position of an α,β-unsaturated ketone. The described route was found to be also applicable to substituted 3-methyl-2-cyclohexen-1-



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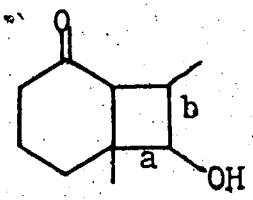

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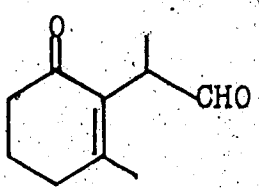

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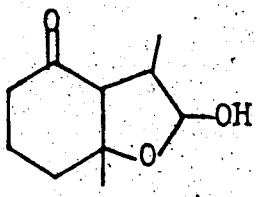

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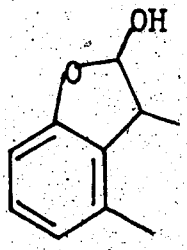

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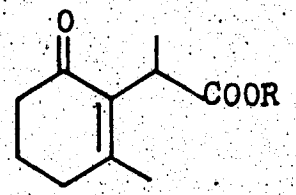

21 R = H

22 R = CH_3

ones. Under similar reaction conditions, photocycloaddition of 6-isopropyl-3-methyl-2-cyclohexen-1-one (25) to 1-propenyl acetate followed by hydrolysis of the resulting photoadduct 26 gave alcohol 27. Subsequent oxidative cleavage of 27 with ceric ammonium nitrate gave rise to keto aldehyde 28* in comparable yield.

Although lactol 19 could also be a useful synthetic intermediate (e.g. via keto ester 22), this possibility remains to be examined. The present work was continued with aldehyde 18.

In order to complete the carbon-skeleton of geijerene (1) from 18, a vinyl group remains to be incorporated into the β-position of its conjugated enone moiety. To avoid possible complications, the reactive aldehyde carbonyl was first modified. Treatment of 18 with lithium tri-t-butoxyaluminum hydride in tetrahydrofuran at 0° for 3 hr followed by addition of a large excess of acetyl chloride resulted in selective reduction of its aldehyde and acetylation of the intermediate alkoxy ion to give keto acetate 29 in 90% yield. Initial attempts to isolate the intermediate alcohol 30 were unsuccessful, due to its rapid isomerization to hemiketal 31. In the ir spectrum of 29,

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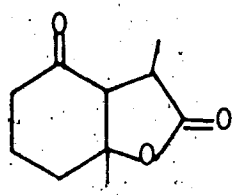
*The possible use of this compound in shyobunone (8) - preisocalamendiol (6) synthesis is being studied in this laboratory.



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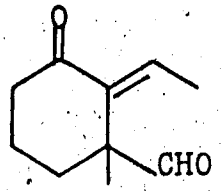

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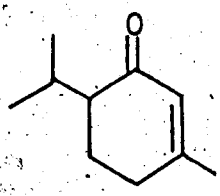

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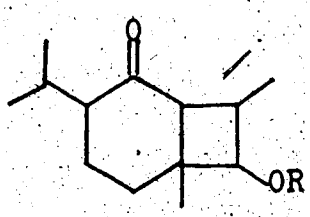
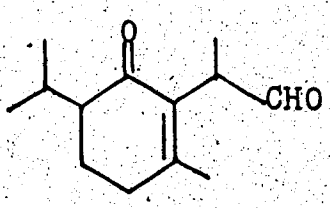


26 R = Ac

27 R = H



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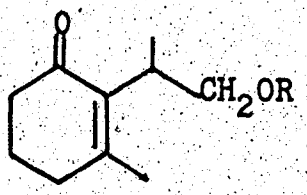


29 R = Ac

30 R = H

absorptions occurred at 1733 and 1657 cm^{-1} for the ester and unsaturated ketone carbonyls whereas its nmr spectrum showed a doublet at δ 4.10 for the two methylene protons adjacent to the acetoxy group and a singlet at δ 1.89 for a total of six acetyl and allylic methyl hydrogen atoms. The mass spectrum displayed a molecular ion peak at 210.1264, confirming the assigned structure.

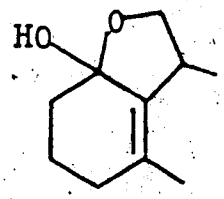
Subsequently, efforts were made to transform 29 to 32 directly by 1,4-addition of a vinyl complex. The method reported by Corey et al.[24] using vinyllithium-cuprous iodide-isopropenyl sulphide complex was attempted initially, but without success. Under various reaction conditions, it only resulted in the recovery of starting material. On the other hand, treatment of 29 with vinyllithium-tetrakis-[iodo(tri-n-butylphosphine)copper(I)] complex according to the described procedure[23] afforded the desired ketone 32 albeit in poor yield (less than 15%), presumably due to the concomitant formation of hemiketal 33. Although the latter compound was found to be inseparable from the vast amount of phosphorus-containing material by either column chromatography or distillation and thus could not be positively identified, its possible presence in the crude product was indicated by the fact that hydrolysis of ketone 32 with alkali gave exclusively 33 showing the same tlc behaviour as that of the phosphorus-containing material. Most importantly, a satisfactory yield (64%) of the desired ketone 32

could be obtained by allowing the crude addition product to react with acetic anhydride in pyridine prior to its isolation. The stereochemistry of 32 could not be established unambiguously at this stage on the basis of the available information although its tlc behaviour coupled with the fact that the nmr spectrum showed only one set of characteristic signals [δ 5.87 (dd, 1H, J = 18.0 Hz, J' = 10.0 Hz, $-C\underline{H}=CH_2$), 5.02 (dd, 1H, J = 10.0 Hz, J' ~ 1.0 Hz, $H\diagup C=C\diagdown^{H}_{\underline{H}}$), 4.98 (dd, 1H, J = 18.0 Hz, J' ~ 1.0 Hz, $H\diagup C=C\diagdown^{H}_{\underline{H}}$), 3.89 (d, 2H, J = 7.0 Hz, $-C\underline{H}_2OAc$), 1.98 (s, 3H, $-OCOCH_3$), 1.09 (s, 3H, methyl) and 1.03 (d, 3H, J = 7.5 Hz, $-CHC\underline{H}_3$)] were suggestive of the homogeneity of the two introduced side chains in their relative stereochemistry. Partial stereochemistry of 32 could be assigned as depicted as a consequence of the later findings that its further transformation under conditions whereby complete isomerization was extremely unlikely resulted in only epigeijerene (15) and no detectable amount of geijerene (1). Up to this stage, the feasibility of the outlined general scheme (Scheme I) was clearly demonstrated.

To complete the synthesis of geijerene (1) and/or its analog, it was necessary to incorporate the two additional double bonds using the existing functionalities. Towards this end, our original plan was to carry out a Bamford-Stevens reaction[32-35] on ketone 32 to generate first the endocyclic double bond. There have been isolated cases which showed that the application of this reaction to

unsymmetrically substituted ketones gave rise to the less substituted olefins preferentially. For example, 3-methylcyclohexene was obtained in greater than 98% yield from 2-methylcyclohexanone upon treatment of its tosylhydrazone derivative with alkyllithium[33]. Hence, by adopting this reaction, it would enable us to place the double bond specifically at the desired position. Experimentally however, ketone 32 proved to be totally unreactive towards tosylhydrazine. Despite numerous attempts using different solvent systems such as methanol, ethanol, benzene and tetrahydrofuran even at elevated temperature, no reaction occurred. Consequently, the following method was chosen as an alternative. We realized however, that this method would be considerably less selective and could theoretically lead to two double-bond isomers which hopefully, could be separated at a convenient stage.

Reduction of ketone 32 with sodium borohydride in methanol at 0° furnished a 67% yield of hydroxy acetate 34 as a mixture of diastereomers which were indistinguishable on tlc. The diastereomeric nature of the product was however, indicated by its nmr spectrum showing overlapping signals at δ 5.13-4.75 (-CH=C$\underline{H}_2$), 4.55-3.67 (-C$\underline{H}_2$OAc and -C$\underline{H}$OH) and 1.34-0.93 (methyls). The ir spectrum displayed, in addition to the hydroxy absorption band at 3505 cm^{-1}, two ester maxima at 1735 and 1720 cm^{-1} thereby further supporting this fact.



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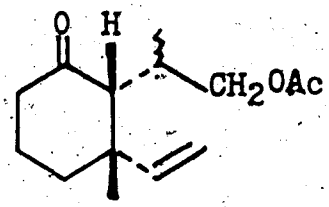
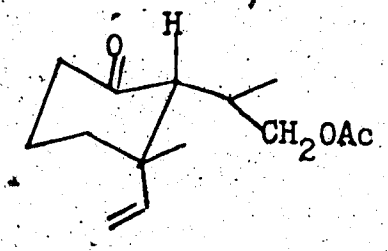
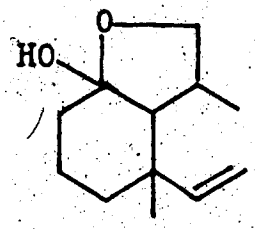


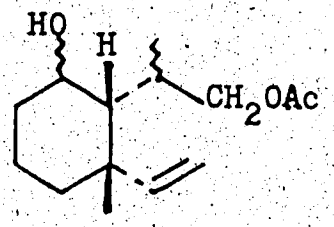
32



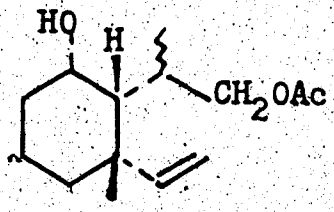
32a



33



34



34a

The mixture of hydroxy acetate 34 underwent dehydration smoothly when it was subjected to phosphorus oxychloride-pyridine treatment to give a mixture of olefins 35 and 36 in 77% yield. Attempted separation of these two compounds by column chromatography was unsuccessful. However, from the relative intensities of the nmr methyl signals as well as those corresponding to the vinyl protons on the newly formed double bonds, the ratio of 35 to 36 could be deduced to be approximately 1:2. The predominant formation of 36 from a mixture of hydroxy acetates 34 by a trans-dehydration process further indicated that the mixture was enriched with the stereoisomer 34a.

The introduction of the remaining double bond was achieved by a sequence of rather trivial reactions. Hydrolysis of the mixture of 35 and 36 was effected by aqueous potassium carbonate in methanol at reflux for two hours. The alcohols 37 and 38 thus obtained (94% yield) were again found to be inseparable by column chromatography. The ir spectrum of the mixture showed a hydroxy band at 3330 cm^{-1} and the absence of any carbonyl absorptions.

Subsequent treatment of the alcohols 37 and 38 with p-toluenesulphonyl chloride in pyridine at 0^{o} gave rise to a 94% yield of the corresponding tosylates 39 and 40 homogeneous on tlc. An attempted elimination reaction on this mixture with 1,5-diazabicyclo[5.4.0]undec-5-ene (DBU)

at 90° resulted in total recovery of the starting material. Consequently, the tosylates 39 and 40 were converted to the corresponding iodides 41 and 42* (combined yield 72%) by boiling the former mixture with a fifteen-fold excess of sodium iodide in acetone. In spite of the fact that the isomeric iodides 41 and 42 showed two overlapping spots on tlc, no attempt was made to separate them as they were found to be quite unstable.

Subsequently, heating the mixture of 41 and 42 with DBU at 90° over a period of 8 hr brought about their dehydroiodination to give a mixture of two isomeric compounds (88% yield) in ca. 3:2 ratio. These two isomers were readily separable by preparative tlc. The mass spectra of these two compounds displayed identical molecular ion peaks at 162.1411 and thus verified their isomeric nature as well as their molecular composition of $C_{12}H_{18}$. The structure of the major isomer could be readily assigned as neogeijerene (14) on the basis of spectral data. In the ultraviolet (uv) spectrum, a maximum appeared at 229 nm (ϵ = 5560) being indicative of a conjugated diene system. Its nmr spectrum showed three doublets of doublets at δ 5.84 ($-C\underline{H}=CH_2$), 4.98 ($_{H}>C=C<^{H}_{\underline{H}}$) and 4.93 ($_{H}>C=C<^{H}_{\underline{H}}$), a triplet at δ 5.67 ($=C\underline{H}CH_2-$) and a broad singlet at δ 4.75 ($-\dot{C}=CH_2$) clearly defining the

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*It is interesting to note that the mixture possesses lachrymal properties.

six vinylic protons present in the molecule. In addition, the appearance of two methyl signals at δ 1.78 (narrowly split doublet) and δ 1.18 (singlet) was also in agreement with the structural assignment. The minor product was indistinguishable with an authentic sample of geijerene (1) in glc and tlc. Their ir and nmr spectra however, were found to be similar but not identical; particularly in the nmr spectra, in contrast to geijerene (1) which showed a singlet at δ 0.91 ($-\overset{|}{C}CH_3$), the synthetic product displayed a singlet at δ 1.11. These findings led logically to the structural assignment of epigeijerene (15) to the minor isomer.

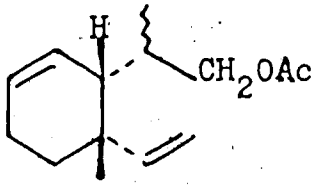
After the completion of the total synthesis of 14 and 15 it became interesting to modify the synthetic scheme in such a way that the incorporation of the disubstituted ring double bond could be attended preferentially. As discussed earlier, the fact that the dehydration of the diastereomeric mixture 34 with phosphorus oxychloride-pyridine gave olefin 36 as the major product required isomer 34a to be predominant in the mixture. This suggested that the preceeding sodium borohydride reduction of ketone 32 proceeded stereoselectively with preferential formation of 34a.

Substitution effects on metal hydride reductions of cyclohexanones have been studied extensively[36]. It has been well established that the metal hydride reduction of cyclohexanone possessing an axial substituent at C-3 gives

the thermodynamically less stable alcohol as the major product as a consequence of preferential attack of hydride ion from the less hindered equatorial side. On the other hand, the reduction of 2-alkylcyclohexanone favours the formation of trans-2-alkylcyclohexanol as a result of axial attack by the hydride ion leading to the more stable (having less torsional strain) transition state.

In examining ketone 32 whose stable conformation can be represented as shown in 32a, it was expected that the axial vinyl group at C-3 and the equatorial side chain at C-2 would exert opposite effects as to the stereochemical outcome of the sodium borohydride reduction of its ketone carbonyl. The fact that its reduction afforded predominantly isomer 34a indicated that the axial vinyl group played a more important role. It is quite conceivable that this observed effect could be offset by increasing the size of the C-2 side chain. Consequently, it would enhance the axial attack of the carbonyl by the hydride ion and the product thus obtained would favourably lead to the formation of the disubstituted double bond by a trans-dehydration process.

Based on these considerations, the alkoxide intermediate from the reduction of aldehyde 18 was quenched with isobutyryl bromide. The use of a larger ester protecting group (also a less reactive one) would require only a minimal change of our original synthetic scheme.



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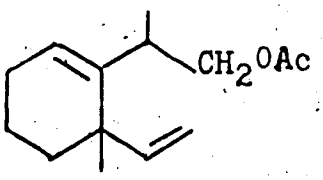

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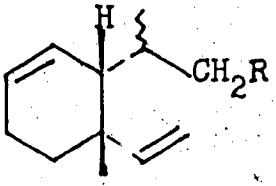
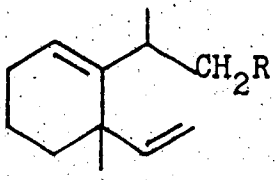


37 R = OH

39 R = OTs

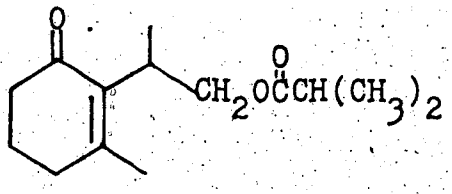
41 R = I



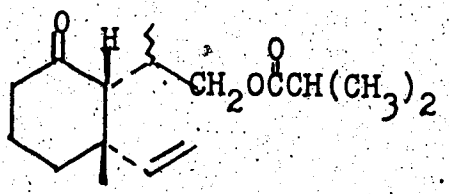
38 R = OH

40 R = OTs

42 R = I



43



44

Treatment of the resulting ester 43 with vinyllithium - tetrakis[iodo(tri-n-butylphosphine)copper(I)] complex gave directly* the keto ester 44 in 50% yield. Although it was hoped that the change in the size of the protecting group might alter the stereochemical outcome of the vinyl addition, this was not found to be the case. The fact that subsequent transformation of 44 gave a mixture of neogeijerene (14) and epigeijerene (15) but not geijerene (1) indicated that the relative stereochemistry of its vinyl group and its ester side chain was again cis.

The completion of the synthesis from keto ester 44 followed closely to that described for ketone 32. Sodium borohydride reduction of 44 gave a 90% yield of hydroxy ester 45 as a diastereomeric mixture containing mainly isomer 45a. This was evident from the fact that dehydration of the mixture with phosphorus oxychloride in pyridine gave rise to a mixture of two olefins 46 and 47 in a ratio of ca. 2:1 based on its nmr spectrum. Further transformation of this olefinic mixture by the same sequence as previously described for the mixture 35 and 36 gave epigeijerene (15) and neogeijerene (14) in 2:1 ratio and a total yield of 66%.

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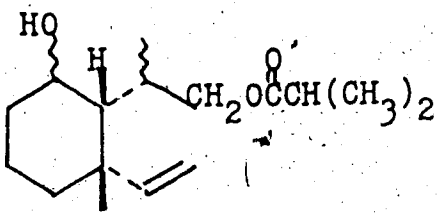
*As expected, the use of the less reactive ester group prevented its hydrolysis in contrast to the case of keto acetate (29).

The development of a new-elemene-type 1,5-diene synthesis leading to neogeijerene (14) and epigeijerene (15) represents the current advance in our synthetic studies on elemene-germacranolide sesquiterpenoids. In order to obtain geijerene (1), it is necessary to further modify the approach so that the relative stereochemistry of the substituents can be rectified. Towards this end, efforts are currently being made to explore the possibility of using lactone 48 as a synthetic intermediate.



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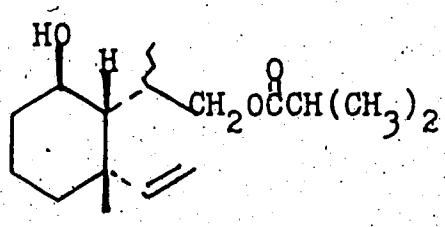
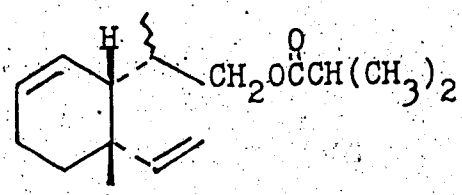


45a



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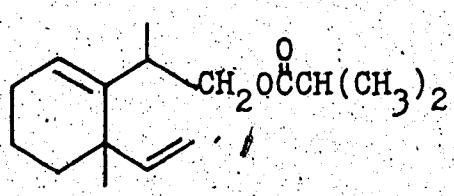

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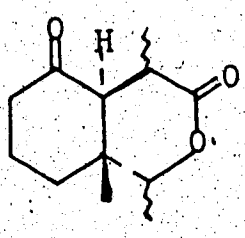

48

EXPERIMENTAL

General

Mass spectra were recorded on AEI MS-9 and MS-2 mass spectrometers. Infrared (ir) spectra were obtained using a Perkin-Elmer Model 457 spectrophotometer and samples were run as liquid films. Nuclear magnetic resonance (nmr) spectra were recorded on Varian A-60 and Varian HR-100 spectrometers using carbon tetrachloride as solvent and tetramethylsilane as internal standard. The following abbreviations are used in the text: s = singlet, d = doublet, t = triplet, q = quartet and m = multiplet. Ultraviolet (uv) spectra were recorded on Perkin-Elmer Model 202 spectrophotometer. Elemental analyses were performed by the microanalytical laboratory of this department. Gas chromatographic (glc) analyses were performed on an Aerograph A-90 - P-3 with a column of 15% SE 30 on Chromosorb W.

Material

Practical grade propanal was dried over magnesium sulphate and distilled (bp 48-9°/700 mm) prior to use. 3-Methyl-2-cyclohexen-1-one was purchased from Aldrich Chemical Company. Tetrahydrofuran (THF) was freshly distilled from lithium aluminum hydride. Kieselgel was used as adsorbant for column chromatography.

cis- and trans-1-Propenyl acetate

The method of Curtin and Hurwitz[29] was adopted, with some modifications. Freshly distilled propanal (634.2 g, 13.50 mol) and acetic anhydride (3058.6 g, 29.50 mol) were added to oven-dried potassium acetate (134.0 g, 1.37 mol). The mixture was refluxed for 18 hr under a nitrogen atmosphere. At the end of this period, it was distilled and the fraction boiling below 127° (atm pressure) was collected (ca. 1000 ml). Acetic acid and acetic anhydride in the distillate were destroyed by the addition of 4 N aqueous sodium hydroxide solution to pH 5 and saturated aqueous sodium carbonate solution to pH 9. The organic phase was separated, dried over magnesium sulphate, filtered and distilled under atmospheric pressure (bp 99-106°) giving 327.5 g (30% yield) of a mixture of cis- and trans-1-propenyl acetate; ir: 1755 (ester) and 1675 cm^{-1} (C=C); nmr: δ 7.17-6.92 (m, 1H, =CHOAc), 5.33, 4.83 (both m, total 1H, =CHMe, 2.08, 2.02 (both s, total 3H, $OCOCH_3$) and 1.67, 1.54 (both d, total 3H, J = 1.5 Hz each, $=CHCH_3$).

7-Acetoxy-6,8-dimethylbicyclo[4.2.0]octan-2-one (16)

The apparatus used for the photocycloaddition reaction is shown diagramatically in Fig. 1. 3-Methyl-2-cyclohexen-1-one (25.7 g, 0.23 mol) and a mixture of cis- and trans-1-propenyl acetate (327.5 g, 3.28 mol) were

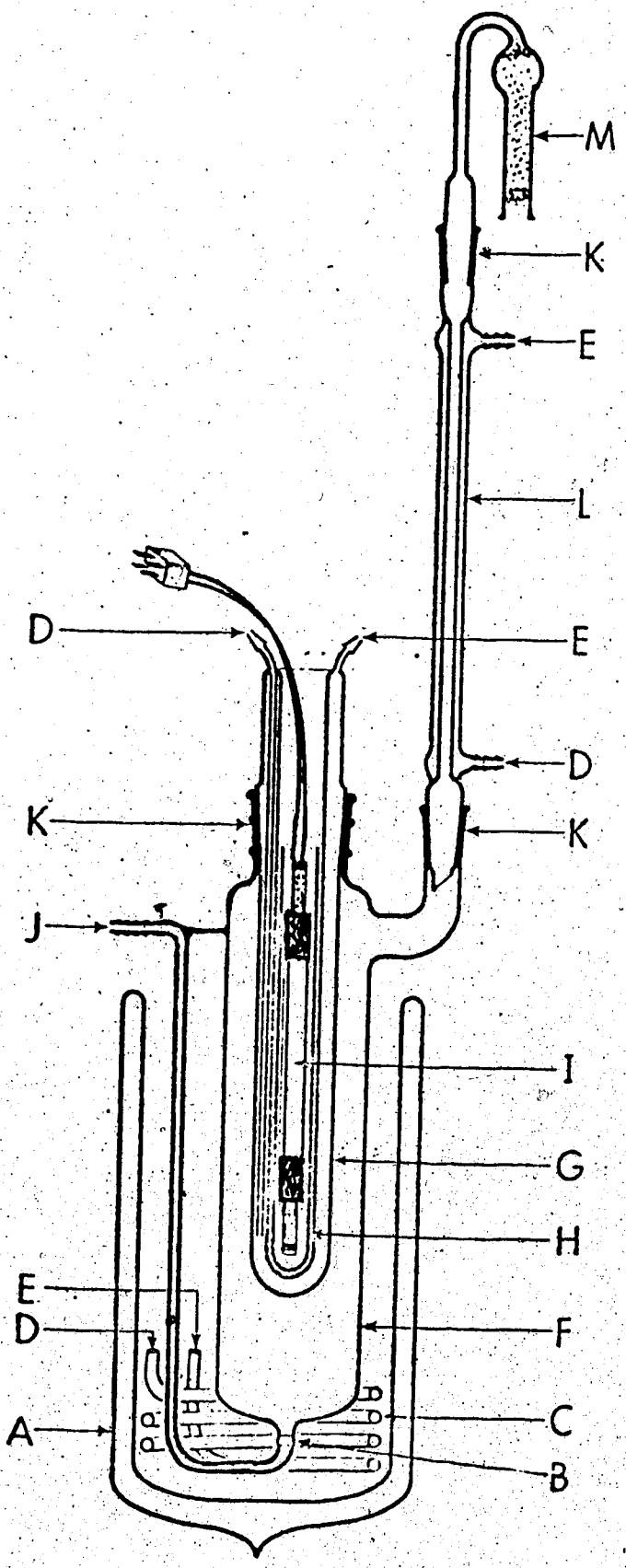

Fig. 1. A. Dewar flask; B. sintered glass filter; C. metal cooling coil; D. water inlet; E. water outlet; F. reaction vessel; G. quartz immersion well; H. pyrex filter; I. lamp; J. nitrogen gas inlet; K. ground glass joint; L. condenser; M. calcium chloride drying tube.

placed in the reaction vessel. The solution was diluted with 650 ml of benzene and a constant flow of dry nitrogen was maintained to agitate the solution throughout the reaction period. The dewar flask was filled with crushed ice and water and the reaction mixture was irradiated with a 450-watt Hanovia high pressure quartz mercury-vapour lamp using a pyrex filter. After 20 hr, all the enone was consumed (reaction monitored by glc) and irradiation was discontinued. The solvent and excess enol acetate were removed by distillation under reduced pressure (water aspirator). Further distillation of the residue gave a diastereomeric mixture of photoadduct 16 (42.5 g, 87% yield): bp 96-102°/0.5 mm; ir: 1735 (ester) and 1697 cm^{-1} (ketone); nmr: δ 4.84, 4.60, 4.28 (all d, total 1H, J = 7.0 Hz, -CHOAc), 2.05, 2.01 (both s, total 3H, $-OCOCH_3$); mass spectrum: M^+ 210.1252 (calcd for $C_{12}H_{18}O_3$, 210.1256).

Anal. Calcd for $C_{12}H_{18}O_3$: C, 68.55; H, 8.63. Found: C, 68.51; H, 8.84.

7-Hydroxy-6,8-dimethylbicyclo[4.2.0]octan-2-one (17)

Potassium carbonate (35.2 g, 0.25 mol) was added, with stirring, to a solution of the photoadduct 16 (40.0 g, 0.19 mol) in 50% aqueous methanol (400 ml). After refluxing for 1 hr, the resulting solution was extracted with chloroform (4 X 200 ml). The organic extracts were combined and washed with saturated sodium chloride (200 ml), dried

with magnesium sulphate and filtered. After removal of the solvent under reduced pressure, the keto alcohol 17 was obtained as a pale-yellow, viscous oil (32.0 g, quantitative yield). An analytical sample purified by chromatography using a solution of 5% ether in benzene showed the following spectral data: ir: 3420 (alcohol) and 1685 cm^{-1} (ketone); nmr: δ 3.92, 3.65, 3.24 (all d, 1H, J ~ 7.0 Hz, -CHOH) and 1.17-0.90 (methyls); mass spectrum: M^+ 168.1146 (calcd for $C_{10}H_{16}O_2$, 168.1150).

Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.54. Found: C, 71.71; H, 9.83.

Oxidative Cleavage of 17

Ceric ammonium nitrate (72.36 g, 130 mmol) was added in one portion to a solution of the keto alcohol 17 (10.0 g, 60 mmol) in 50% aqueous acetonitrile (500 ml). The mixture was stirred at room temperature for 20 min during which time the colour changed from deep-red to pale-yellow. The reaction mixture was then refluxed for 15 min. After cooling to room temperature the solution was extracted with chloroform (3 X 200 ml). The organic solution was washed with saturated sodium chloride, dried ($MgSO_4$) and filtered. Upon concentration, a brown oil (9.0 g) was obtained. Column chromatography of the oil, using a solution of 2% ether in benzene afforded a trace amount of 20 (0.5 g, 5% yield). nmr: δ 6.95 (dd, 1H, J = J' = 7.5 Hz, aromatic),

6.57 (d, 1H, J = 7.5 Hz, aromatic), 6.52 (d, 1H, J = 7.5 Hz, aromatic), 5.40 (d, 1H, J = 5.0 Hz, -OC<u>H</u>OH), 3.09 (m, 1H, benzylic methine), 2.25 (s, 3H, =CC<u>H</u>$_3$) and 1.18 (d, 3H, J = 7.0 Hz, -CHC<u>H</u>$_3$).

Further elution with the same solvent system gave 3-methyl-2-(1-methyl-2-oxoethyl)-2-cyclohexen-1-one (<u>18</u>) (4.0 g, 40% yield): ir: 2820, 2710 (C-H, aldehyde), 1720 (C=O, aldehyde) and 1655 cm^{-1} (ketone); nmr: δ 9.44 (s, 1H, -CHO), 3.20 (q, 1H, J = 7.0 Hz, -C<u>H</u>CHO), 1.97 (s, 3H, =CHC<u>H</u>$_3$), 1.10 (d, 3H, J = 7.0 Hz, -CHC<u>H</u>$_3$); mass spectrum: M$^+$ 166.0998 (calcd for $C_{10}H_{14}O_2$, 166.0994).

<u>Anal</u>. Calcd for $C_{10}H_{14}O_2$: C, 72.26; H, 8.49. Found: C, 72.15; H, 8.26.

Final elution with ether afforded 8-hydroxy-6,9-di[illegible]abicyclo[4.3.0]nonan-2-one (<u>19</u>) (3.0 g, 30% yie[illegible]inated by a small quantity of starting material.

Trans[illegible]tion of <u>18</u> to 2-(1-carbethoxyethyl)-3-methyl-2-cycloh[illegible]-1-one (<u>22</u>)

To a solution of 2.0 g (12 mmol) of <u>18</u> in 50 ml of acetone at 0° was added dropwise, Jones reagent[37] (2.1 ml) until a orange-green colour was retained. The excess oxidizing agent was then destroyed by the addition of 2-propanol (0.5 ml). Extraction with methylene chloride

followed by the usual work-up of the organic solution afforded the crude acid 21 which was dissolved in acetone (50 ml). To this solution, potassium carbonate (4.0 g) and methyl iodide (4.0 ml) were added and the mixture was refluxed under an atmosphere of nitrogen for 24 hr. The resulting mixture was then poured into water and extracted with methylene chloride. Work-up of the methylene chloride solution in the usual manner gave an oil which was subjected to column chromatography. Elution with benzene gave 1.06 g (45% from 18) of 22: ir: 1742 (ester), 1670 (unsaturated ketone) and 1632 cm^{-1} (C=C); nmr δ 3.52 (s, 3H, $-COOCH_3$), 1.93 (s, 3H, $=CCH_3$), and 1.17 (d, 3H, J = 8.0 Hz, $-CHCH_3$); mass spectrum: M^+ 196.

Transformation of 19 to 22

Lactol 19 (360 mg) was dissolved in 5 ml of acetone and 8 N Jones reagent (1 ml) was added. After stirring at 0° for 20 min, the reaction mixture was poured into water and extracted with methylene chloride. After the usual work-up, the organic solution gave an oily product which, without purification was dissolved in acetone (10 ml). To this solution, were added potassium carbonate (500 mg) and methyl iodide (1 ml). The resulting mixture was refluxed for 5 days (at the end of each 24 hr period, an additional 0.5 ml of methyl iodide was added). Work-up of the mixture in the same manner as described in the preceeding

experiment gave 310 mg (81% yield) of 22.

7-Acetoxy-3-isopropyl-6,8-dimethylbicyclo[4.2.0]octan-2-one (26)

A solution of 6-isopropyl-3-methyl-2-cyclohexen-1-one (25) (31.4 g, 0.21 mol) and 1-propenyl acetate (310.0 g, 3.1 mol) in benzene (650 ml) was irradiated under the same conditions as described previously for the preparation of 16. After removal of the solvent and the excess enol acetate under reduced pressure, the residue was distilled, giving 43.7 g (84% yield) of 26: bp 102-5°/0.2 mm; ir: 1740 (ester) and 1695 cm^{-1} (ketone); nmr: δ 2.00 (s, 3H, $-OCOCH_3$); mass spectrum: M^+ 252.

Anal: Calcd for $C_{15}H_{24}O_3$: C, 71.39; H, 9.59. Found: C, 71.62; H, 9.76.

7-Hydroxy-3-isopropyl-6,8-dimethylbicyclo[4.2.0]octan-2-one (27)

A solution of the photoadduct 26 (5.0 g, 19.8 mmol) and potassium carbonate (8.23 g, 59.4 mmol) in 50% aqueous methanol (100 ml) was refluxed for 1 hr. Work-up of the reaction in the usual manner and purification of the resulting crude product by column chromatography using 5% ether in benzene as eluent gave 3.0 g (72% yield) of alcohol (27) as a mixture of diastereomer. ir: 3450 (alcohol) and 1700 cm^{-1} (ketone); mass spectrum: M^+ 210.

Anal. Calcd for $C_{13}H_{22}O_2$: C, 74.24; H, 10.54. Found: C, 74.02; H, 10.68.

6-Isopropyl-3-methyl-2-(1-methyl-2-oxoethyl)-2-cyclohexen-1-one (28)

The same procedure as described previously for the transformation 17→18 was applied, using 22.6 g (108 mmol) of keto alcohol 27, 132.8 g (242 mmol) of ceric ammonium nitrate and 1000 ml of 50% aqueous acetonitrile. After work-up and purification, 7.37 g (33% yield) of aldehyde 28 were obtained. Its spectra showed the following features: ir: 2820, 2710, 1720 (aldehyde), 1655 (unsaturated ketone) and 1630 cm^{-1} (C=C); nmr: δ 9.41 (s, 1H, -CHO), 3.18 (q, 1H, J = 7.0 Hz, -CHCHO), 1.97 (s, 6H, $-OCOCH_3$ and $=CCH_3$), 1.11 (d, 3H, J = 7.0 Hz, $-CHCH_3$), 0.91 [d, 3H, J = 5.0 Hz, $-CH(CH_3)CH_3$] and 0.80 [d, 3H, J = 5.0 Hz, $-CH(CH_3)CH_3$].

Anal. Calcd for $C_{13}H_{20}O_3$: C, 74.91; H, 9.68. Found: C, 74.80; H, 9.71.

2-(2-Acetoxy-1-methylethyl)-3-methyl-2-cyclohexen-1-one (29)

The aldehyde 18 (1.65 g, 10 mmol) was dissolved, with stirring in THF (30 ml) at 0°. Lithium tri-t-butoxy-aluminum hydride (3.75 g, 15 mmol) was added and stirring was continued for 3 hr after which time an excess of acetyl chloride (4.0 ml, 56 mmol) was introduced. After stirring

for another 3 hr at room temperature, the reaction mixture was poured into a mixture of ice and water and extracted with chloroform (3 X 100 ml). The organic extract was washed with saturated aqueous sodium bicarbonate solution and saturated sodium chloride solution, dried ($MgSO_4$) and filtered. Concentration of the filtrate furnished a yellow oil which was purified by column chromatography. Elution with benzene gave keto acetate (29) (1.89 g, 90%): ir: 1733 (ester), 1657 (unsaturated ketone) and 1613 cm^{-1} (C=C); nmr δ 4.10 (d, 2H, J = 7.5 Hz, $-CH_2OAc$), 2.97 (m, 1H, J = 7.5 Hz, $-\underline{C}HCH_2OAc$), 1.89 (s, 6H, $-OCOC\underline{H}_3$ and $=CC\underline{H}_3$) and 1.08 (d, 3H, J = 7.5 Hz, $-CHC\underline{H}_3$); mass spectrum: M^+ 210.1264 (calcd for $C_{12}H_{18}O_3$, 210.1256).

Anal. Calcd for $C_{12}H_{18}O_3$: C, 68.55; H, 8.63. Found: C, 68.44; H, 8.50.

2-(2-Acetoxy-1-methylethyl)-3-methyl-3-vinylcyclohexanone (32)

Tetrakis[iodo(tri-n-butylphosphine)copper(I)] was prepared according to the method of Kauffman and Teter[38]. The crude complex was recrystallized twice from a mixture of ethanol and 2-propanol (23:15 by volume) and dried in vacuo (drying pistol with phosphorus pentoxide as drying agent) until a constant melting point of 75° was attained.

A solution of the above complex (9.56 g, 24 mmol)

in dry THF (30 ml) was prepared at -78° (Dry Ice-acetone bath) under nitrogen. A solution of 2.2 M vinyllithium in THF (20.0 ml) was added dropwise over a period of 15 min and the resulting brown solution was stirred at -78° for an additional 20 min. Subsequently, a solution of keto acetate 29 (1.61 g, 7.7 mmol) in THF (10.0 ml) was added dropwise over a period of 15 min and stirring was continued for an additional 20 min. The mixture was then allowed to warm to 0° (ice bath). After 3 hr it was poured into saturated aqueous ammonium chloride solution buffered with ammonium hydroxide (pH 8) and extracted continuously with ether (200 ml) for 24 hr. Drying ($MgSO_4$), filtration and concentration gave an oily mixture which without purification, was dissolved in acetic anhydride (6 ml) and pyridine (12 ml). After stirring at room temperature for 12 hr, the resulting mixture was poured into water and extracted with chloroform. The chloroform solution was washed twice with 2 N hydrochloric acid, dried ($MgSO_4$), filtered and evaporated to dryness and the residue was subjected to column chromatography. After the removal of a large quantity of phosphorus-containing compounds by petroleum ether, the column was eluted with benzene to give 1.7 g (64% yield) of ketone 32: ir: 1733 (ester), 1705 (ketone) and 1632 cm^{-1} (C=C); nmr δ 5.87 (dd, 1H, J = 18.0, J' = 10.0 Hz, $-C\underline{H}=CH_2$), 5.02 (dd, 1H, J = 10.0, J' ~ 1.0 Hz, $H\!>\!C=C\!<^{H}_{\underline{H}}$), 4.98 (dd, 1H, J = 18.0, J' ~ 1.0 Hz, $H\!>\!C=C\!<^{H}_{\underline{H}}$), 3.89 (d, 2H, J = 7.0 Hz, $-CH_2OAc$), 1.98 (s, 3H, $-OCOCH_3$), 1.09 (s, 3H, methyl) and 1.03 (d, 3H,

J = 7.5 Hz, -CHC$\underline{H}_3$); mass spectrum: M^+ 238. 1578 (calcd for $C_{14}H_{22}O_3$, 238.1569).

Anal. Calcd for $C_{14}H_{22}O_3$: C, 70.56; H, 9.30. Found: C, 70.44; H, 9.18.

2-(2-Acetoxy-1-methylethyl)-3-methyl-3-vinylcyclohexanol (34)

Sodium borohydride (460 mg, 12 mmol) was added to a solution of ketone 32 (966 mg, 4 mmol) in methanol (25 ml) at 0°. After stirring for 30 min the reaction mixture was poured into ammonium chloride solution (75 ml) and the crude product was extracted with three 30 ml portions of chloroform. The combined organic phase was dried over magnesium sulphate and filtered. On concentration of the filtrate, a pale-yellow oil was obtained. Purification by column chromatography using 5% ether in benzene as eluent afforded the hydroxy acetate 34 (650 mg, 67% yield) as a diastereomeric mixture: ir: 3505 (alcohol), 1735, 1720 (esters) and 1630 cm^{-1} (C=C); nmr δ 5.95-5.48, 5.13-4.75 (both m, total 3H, olefinic), 4.55-3.67 (m, 3H, $-CH_2OAc$ and -CHOH), 1.99 (s, 3H, $-OCOCH_3$) and 1.34-0.93 (m, 6H, methyls); mass spectrum: M^+ 240.1733 (calcd for $C_{14}H_{24}O_3$, 240.1726).

Anal. Calcd for $C_{14}H_{24}O_3$: C, 69.96; H, 10.06. Found: C, 69.80; H, 9.87.

3-(2-Acetoxy-1-methylethyl)-4-methyl-4-vinylcyclohexene (35) and 2-(2-Acetoxy-1-methylethyl)-3-methyl-3-vinylcyclohexene (36)

Phosphorus oxychloride (1.0 ml, 10.9 mmol) was added to a stirred solution of hydroxy acetate 34 (650 mg, 2.7 mmol) in pyridine (3.0 ml) maintained at 0° under an atmosphere of nitrogen. Stirring was continued for 3 hr after which time the mixture was carefully poured into ice-cold 2 N hydrochloric acid (60 ml), extracted with methylene chloride (3 X 20 ml) and washed with saturated aqueous sodium bicarbonate and water. After drying ($MgSO_4$) and concentration, the crude product was purified by column chromatography. Elution with benzene gave 463 mg (77% yield) of a mixture of 35 and 36 (~ 1:2): ir: 1738 (ester) and 1638 cm^{-1} (C=C); nmr: δ 5.90-5.58 (m, ~1.7H, $-C\underline{H}=CH_2$ and $-\underline{H}C=C\underline{H}-$), 5.52 (t, ~0.7H, J = 4.0 Hz, $-CH=\overset{|}{C}-$), 5.05-4.85 (m, 2H, $-CH=C\underline{H}_2$), 4.05-3.63 (m, 2H, $-CH_2OAc$), 2.26 [m, 1H, -CH(Me)-], 1.91 (s, 3H, $-OCOCH_3$), 1.14 (s, ~1H, $-\overset{|}{C}CH_3$), 1.12 (s, 2H, $-\overset{|}{C}CH_3$), 1.00 (d, ~2H, J = 7.0 Hz, $-\overset{|}{C}H\underline{C}H_3$) and 0.97 (d, ~1H, J = 7.0 Hz, $-\overset{|}{C}H\underline{C}H_3$); mass spectrum: M^+ 222.1625 (calcd for $C_{14}H_{22}O_2$, 222.1620).

Anal. Calcd for $C_{14}H_{22}O_2$: C, 75.63; H, 9.97. Found: C, 75.48; H, 9.83.

3-(2-Hydroxy-1-methylethyl)-4-methyl-4-vinylcyclohexene (37) and 2-(2-Hydroxy-1-methylethyl)-3-methyl-3-vinylcyclohexene (38)

A solution of 35 and 36 (463 mg, 2 mmol) and potassium carbonate (1.44 g, 10 mmol) in 50% aqueous methanol (30 ml) was refluxed for 2 hr. After it was cooled to room temperature, the reaction mixture was extracted with chloroform (3 X 20 ml). Drying ($MgSO_4$), filtration and concentration gave the oily crude product which was purified by column chromatography using benzene as eluent. The isomeric alcohols 37 and 38 thus obtained (352 mg, 94% yield) were indistinguishable on tlc. The mixture showed the following spectral data: ir: 3330 (alcohol) and 1630 cm^{-1} (C=C); nmr: δ 5.88-5.40 (m, ~2.3H, -CH=C-, -CH=CH- and -CH=CH_2), 5.05-4.83 (m, 2H, -CH=CH_2), 1.15 (s, 3H, -CCH_3) and 1.01 (d, 3H, J = 7.0 Hz, -$CHCH_3$); mass spectrum: M^+ 180.1510 (calcd for $C_{12}H_{20}O$, 180.1514).

Anal. Calcd for $C_{12}H_{20}O$: C, 79.94; H, 11.18. Found: C, 80.04; H, 11.37.

4-Methyl-3-(1-methyl-2-p-toluenesulphonoxyethyl)-4-vinylcyclohexene (39) and 3-Methyl-2-(1-methyl-2-p-toluenesulphonoxyethyl)-3-vinylcyclohexene (40)

Recrystallized p-toluenesulphonyl chloride (400 mg, 2.1 mol) was added to a solution of isomeric alcohols

37 and 38 (350 mg, 1.9 mmol) in pyridine (4.0 ml) at 0° under nitrogen atmosphere. After stirring for 3 hr, water (50 ml) was added and the resulting mixture was extracted with chloroform (3 X 25 ml). The combined organic solution was washed with 2 N hydrochloric acid, saturated sodium bicarbonate solution and water (50 ml each), dried ($MgSO_4$) and concentrated to give a mixture of 39 and 40 (612 mg, 94% yield) indistinguishable on tlc. The isomers were found to be rather unstable and hence they were used directly in the subsequent reaction without further purification. Their ir spectrum showed absorption bands at 1630 (double bond), 1593 (aromatic), 1360 and 1175 cm^{-1} (tosylate).

3-(2-Iodo-1-methylethyl)-4-methyl-4-vinylcyclohexene (41) and 2-(2-iodo-1-methylethyl)-3-methyl-3-vinylcyclohexene (42)

A solution of tosylates 39 and 40 (150 mg, 1.7 mmol) and sodium iodide (3.78 g, 25.2 mmol) in acetone (50 ml) was refluxed for 12 hr under an atmosphere of nitrogen. After cooling to room temperature, the mixture was poured into saturated sodium chloride solution (50 ml) and extracted with methylene chloride (3 X 20 ml). The combined organic solution was washed with 2 N sodium carbonate solution and water (50 ml each). Upon drying ($MgSO_4$) and concentration, the crude product was percolated rapidly through a column packed with florisil, using n-pentane as eluent to give 41 and 42 (350 mg, 72% yield). Although

these two isomers showed two overlapping spots on tlc, their separation was not attempted because they were found to be unstable as indicated by their colour change (colourless to violet) on standing. The following spectral data were obtained: ir: 1629 cm^{-1} (C=C); nmr δ 6.03-5.43 (m, 2-3H, vinylic), 5.14-4.63 (m, 2H, -CH=C$\underline{H}_2$) and 1.12 (s, 3H, -C$\underline{CH}_3$); mass spectrum: M^+ 290.0527 (calcd for $C_{12}H_{19}I^{127}$, 290.0532).

Neogeijerene (14) and Epigeijerene (15)

A solution of the iodides 41 and 42 (350 mg, 1.2 mmol) in 1,5-diazabicyclo[5.4.0]undec-5-ene (2.0 ml) was heated at 90° under a nitrogen atmosphere for 8 hr with stirring. At the end of this period, the dark solution was poured into 2 N hydrochloric acid (60 ml) and extracted with n-pentane (3 X 15 ml). The organic solution was washed with water (50 ml), dried over magnesium sulphate and filtered. After removal of the solvent, 172 mg (88% yield) of the mixture of 14 and 15 were obtained. The two components showed two spots on fluorescent tlc plates (observed under uv light) and were separated by preparative tlc (Merck silica gel PF - 254 + 366, n-pentane as eluent). From 97 mg of the mixture, 57 mg of neogeijerene (14) (faster moving) and 35 mg of epigeijerene (15) (slower moving) were isolated. Ratio of 14 to 15 was about 1.6:1.0 and the total recovery of material was 94%. Epigeijerene (15) was indistinguishable from naturally-occurring geijerene (1) in both glc and

tlc. The following spectral data were obtained for geijerene (1), neogeijerene (14) and epigeijerene (15):

Geijerene (1)

ir: 1640 and 900 cm^{-1} (C=C); nmr: δ 6.00-5.35 (m, 3H, olefinic), 5.00-4.63 (m, 4H, olefinic), 1.70 (d, 3H, J ~ 1.0 Hz, $=\overset{|}{C}CH_3$) and 0.91 (s, 3H, $-\overset{|}{C}CH_3$); mass spectrum: M^+ 162.1411.

Neogeijerene (14)

ir: 1635 and 898 cm^{-1} (C=C); nmr: δ 5.84 (dd, 1H, J = 16.0, J' = 11.0 Hz, $-C\underline{H}=CH_2$), 5.67 (t, 1H, J = 3.0 Hz, $=C\underline{H}CH_2-$), 4.98 (dd, 1H, J = 11.0, J' = 2.0 Hz, $H\diagup C=C\diagdown^{H}_{\underline{H}}$), 4.93 (dd, 1H, J = 16.0, J' = 2.0 Hz, $H\diagup C=C\diagdown^{H}_{\underline{H}}$), 4.75 (broad s, 2H, $-\overset{|}{C}=CH_2$), 1.78 (d, 3H, J ~ 1 Hz, $=\overset{|}{C}CH_3$) and 1.18 (s, 3H, $-\overset{|}{C}CH_3$); uv: λ_{max}(MeOH) 229 nm (ε = 5560); mass spectrum: M^+ 162.1411 (calcd for $C_{12}H_{18}$, 162.1409).

Epigeijerene (15)

ir: 1627 and 910 cm^{-1} (C=C); nmr: δ 5.98-4.74 (m, 7H, olefinic), 1.67 (d, 3H, J = 4.0 Hz, $=\overset{|}{C}CH_3$) and 1.11 (s, 3H, $-\overset{|}{C}CH_3$), mass spectrum: M^+ 162.1414.

2-(2-Isobutyroxy-1-methylethyl)-3-methyl-2-cyclohexen-1-one (43)

Lithium tri-t-butoxyaluminum hydride (9.1 g, 36 mmol) was added to a solution of aldehyde 18 (4.0 g, 24 mmol) in THF (50 ml) at 0°. After stirring for 3 hr, isobutyryl bromide (12.9 ml, 120 mmol) was introduced and stirring was continued for another 3 hr. The mixture was then poured into ice-cold water (150 ml) and extracted with chloroform (3 X 100 ml). The combined organic phase was washed with saturated sodium bicarbonate solution and water (150 ml each), dried ($MgSO_4$) and filtered. Removal of the solvent under reduced pressure followed by elution of the residue with benzene gave keto ester 43 (3.06 g, 87% yield): ir: 1737 (ester), 1670 (unsaturated ketone) and 1622 cm^{-1} (C=C); nmr: δ 4.18 (d, 2H, J = 7.5 Hz, $-C\underline{H}_2OCOC_3H_7$), 3.01 (m, 1H, $-C\underline{H}CH_3$), 1.93 (s, 3H, $=CCH_3$), 1.12, 1.05 [both d, total 6H, J = 7.0 Hz each, $-OCOCH(C\underline{H}_3)_2$] and 1.10 (d, 3H, J = 7.5 Hz, $-CHC\underline{H}_3$); mass spectrum: M^+ 238.1561 (calcd for $C_{14}H_{22}O_3$, 238.1569).

Anal. Calcd for $C_{14}H_{22}O_3$: C, 70.33; H, 9.58. Found: C, 70.56; H, 9.30.

2-(2-Isobutyroxy-1-methylethyl)-3-methyl-3-vinylcyclohexanone (44)

The same procedure as described for the preparation

of 32 was applied. Keto ester 43 (690 mg, 2.9 mmol), tetrakis[iodo(tri-n-butylphosphine)copper(I)] (3.64 g, 9.3 mmol), 2.2 M vinyllithium in THF (7.9 ml, 17.4 mmol) and THF (25 ml) were used. At the end of the reaction, a solution of ammonium chloride and ammonium hydroxide (150 ml) was added and the mixture was continuously extracted with ether (150 ml) for 24 hr. The ethereal solution was dried ($MgSO_4$), filtered and concentrated, leaving an oily, yellow liquid. Column chromatography of the oil using benzene as eluent gave ketone 44 (347 mg, 50% yield): ir: 1735 (ester), 1774 (ketone) and 1640 cm^{-1} (C=C); nmr δ 6.23-5.63 (m, 1H, $-CH=CH_2$), 5.21-4.83 (m, 2H, $-CH=CH_2$), 4.16-3.84 (m, 2H, $-CH_2OCOR$) and 1.19-0.99 (complex m, 12H, methyls); mass spectrum: M^+ 266.1872 (calcd for $C_{16}H_{26}O_3$, 266.1882).

Anal. Calcd for $C_{16}H_{26}O_3$: C, 72.14; H, 9.84. Found: C, 72.01; H, 9.67.

2-(2-Isobutyroxy-1-methylethyl)-3-methyl-3-vinylcyclohexanol (45)

To a solution of ketone 44 (480 mg, 1.8 mmol) in methanol (20 ml), sodium borohydride (204 mg, 5.4 mmol) was added. After stirring at 0° for 30 min, the reaction mixture was poured into saturated ammonium chloride solution (50 ml) and extracted with chloroform (3 X 20 ml). Work-up of the chloroform solution in the usual manner gave the crude alcohol which was purified by column chromatography.

Elution with 2% ether in benzene afforded alcohol 45 as a diastereomeric mixture: ir: 3500 (alcohol) and 1735 cm^{-1} (ester); nmr: δ 5.84-5.55, 4.98-4.65 (both m, total 3H, olefinic) [illegible].75 (m, 3H, $-CH_2OCOR$ and $-\underline{C}HOH$), 1.30 (s, 3H, $-\overset{|}{C}CH_3$ [illegible], 6H, J = 7.0 Hz, $-CH(C\underline{H}_3)_2$] and 1.08 (d, 3H, J [illegible] $-\overset{|}{C}H\underline{C}H_3$); mass spectrum: M^+ 268.2071 (cal[illegible]or [illegible]O_3, 268.2039).

Anal. Calcd for $C_{16}H_{28}O_3$: C, 71.60; H, 10.51. Found: [illegible], 68; H, 10.64.

3-(2-Is[illegible]yroxy-1-methylethyl)-4-methyl-4-vinylcyclohexene (46) and [illegible](2-Isobutyroxy-1-methylethyl)-3-methyl-3-vinylcycl[illegible]xene (47)

Phosphorus oxychloride (0.4 ml, 4.4 mmol) was added to a s[illegible]ution of alcohol 45 (252 mg, 1.0 mmol) in pyridine ([illegible]). After stirring at 0° under an atmosphere of nitroge[illegible]or 5 hr, the mixture was poured into an ice-water mixture (50 ml) and extracted with chloroform (3 x 15 ml). The combined organic solution was washed with 2 N hydrochloric acid and water (30 ml each), dried ($MgSO_4$) and filtered. The crude product obtained on evaporation of the solvent was chromatographed, using benzene as eluent, affording 192 mg (82% yield) of an isomeric mixture of olefins 46 and 47 indistinguishable on tlc. The mixture gave the following spectral data: ir: 1735 (ester) and 1630 cm^{-1} (C=C); nmr: δ 5.90-5.41 (m, ~2.7H, $-C\underline{H}=CH_2$,

2/3-HC=CH- and 1/3-C=CH-), 5.05-4.86 (m, 2H, -CH=CH$_2$), 4.03-3.63 (m, 2H, -CH$_2$OCO-), 1.16 (s, 3H, -CCH$_3$), 1.14 [d, 6H, J = 7.0 Hz, -CH(CH$_3$)$_2$] and 1.03 (d, 3H, J = 7.0 Hz, -CHCH$_3$); mass spectrum: M^+ 250.1932 (calcd for $C_{16}H_{26}O_2$, 250.1933).

Anal. Calcd for $C_{16}H_{26}O_2$: C, 76.75; H, 10.47. Found: C, 76.78; H, 10.24.

Transformation of olefins 46 and 47 to Epigeijerene (15) and Neogeijerene (14)

A solution of the mixture of olefins 46 and 47 (106 mg, 0.4 mmol) and potassium carbonate (274 mg, 2.0 mmol) in 50% aqueous methanol (15 ml) was refluxed for 5 hr. After cooling, the mixture was poured into water (50 ml) and extracted with methylene chloride (4 X 10 ml). Work-up of the organic solution in the usual manner and purification of the crude product by column chromatography with benzene as eluent gave 74 mg (97% yield) of the mixture of 37 and 38. This mixture was converted into iodides 41 and 42 under the same reaction conditions described previously. From 114 mg of the mixture, 157 mg (86% yield over two steps) of the mixture of 41 and 42 were obtained. The spectra of these mixtures were similar (with the exception of relative intensities) to those obtained previously. The mixture of 41 and 42 (157 mg) was subsequently heated with DBU at 90° for 8 hr. Work-up of the reaction mixture in the same manner as described previously gave 69 mg (78% yield) of a

mixture of neogeijerene (14) and epigeijerene (15). Preparative tlc on this mixture resulted in the isolation of 14 mg of neogeijerene (14) and 27 mg of epigeijerene (15) (ratio of 14:15 ~ 1:2).

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