Total syntheses of spirovetivanes and khusimone

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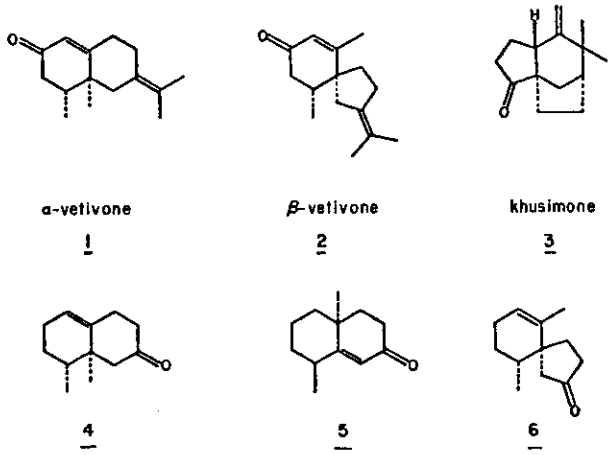
The essential oil of vetiver, Vetiveria zizanioides (L.) is one of the most important raw materials in modern perfumery. The grass is cultivated in many tropical and subtropical regions and the commercial oil is isolated by steam distillation of the roots. Traditionally Java, the Reunion Islands, and the Seychelles were the major producers but more recently a substantial portion of the total output comes from Haiti, Japan, Brazil, and India. Because of its commercial importance chemical analysis of this essential oil has been given much attention and over fifty compounds have thus far been isolated and identified.[1]

The majority of these substances belong to the sesquiterpene group of natural products. Among these α-vetivone (1), β-vetivone (2), the norsesquiterpene khusimone (3), and three biogenetically derived C_{12}-ketones (4, 5, and 6) provided the most exciting chemistry.[2,3] Since the spiroketone (6) and khusimone appear to play a significant role in the reconstitution of the essential oil,[4] we have developed total syntheses of these substances. In an earlier synthesis of the spiroketone, β-vetivone was utilized as starting material,[3] and more recently it has also been prepared by a photochemical route.[5] Among the many published syntheses of β-vetivone two deserve special mention because of their elegance and stereoselectivity.



Synthesis of the spiroketone

In the first of these syntheses an enolate of a β-diketone enol ether produced under kinetic control was alkylated with a dichloride to give intermediate (7) which in a second, this time intramolecular alkylation, afforded a single bicyclic ketone (9).[6] The stereoselectivity in the

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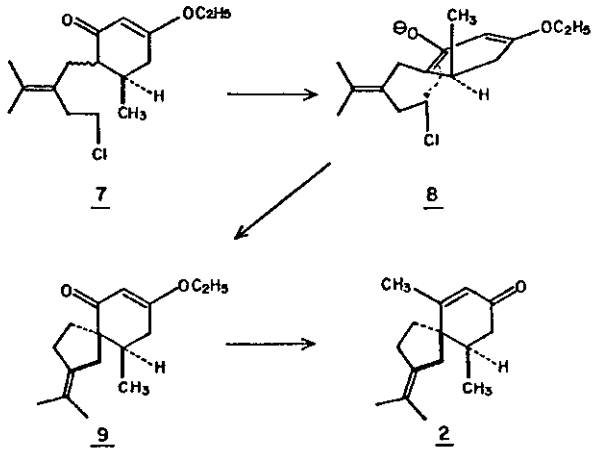
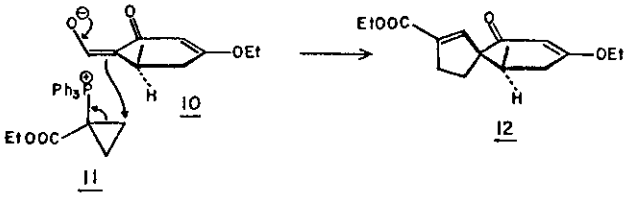
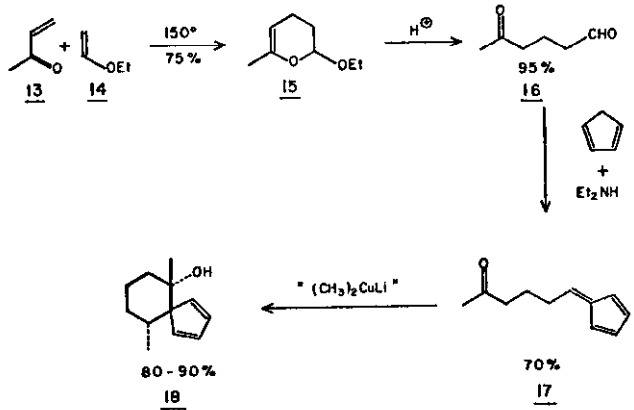
second alkylation can be rationalized if the critical enolate assumes conformation (8) with axially oriented methyl group. Standard transformations were used to convert intermediate 9 to β-vetivone.



The second synthesis also owes its success to a stereoselective alkylation. In this case conformation (10) of the formyl ketone caused combination with the cyclopropylphosphonium salt (11) to occur from the α-side of the molecule.[7] The resulting phosphorane then undergoes an intramolecular Wittig olefin synthesis and the spirocompound (12) served for the synthesis of all known spiro [4.5] decane sesquiterpenes.

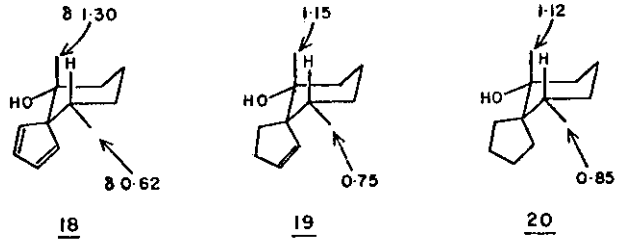


Our synthesis of the spiroketone started with the known acetal (15) prepared by cycloaddition of ethyl vinyl ether (14) and methyl vinyl ketone (13).[8] Hydrolysis of 15 gave 5-oxohexanal (16) which produced the fulvene (17) on condensation with cyclopentadiene in the presence of a catalytic amount of diethylamine. Secondary amines were superior to tertiary amines, suggesting that an iminium salt rather than starting aldehyde undergoes the actual condensation

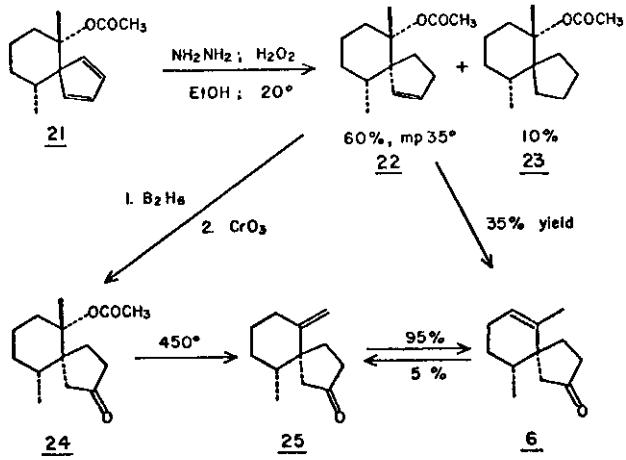


with cyclopentadiene.[9] The transformation of the fulvene to the bicyclic carbinol (18) represents the critical and novel step in our synthesis. We reasoned that lithium dimethylcuprate should add to this fulvene to produce the derived lithium cyclopentadienide, which should combine with the proximate carbonyl group to form a cyclohexanol in preference to a cycloheptanol. In practice a single cyclohexanol (18) was formed and its configuration is based on an NMR argument and its chemical behavior.

The chemical shift of the protons attached to the secondary methyl group depends on the presence or absence of double bonds in the cyclopentane ring. The decrease in shielding observed in the sequence 18, 19, 20 agrees with an equatorial orientation of this methyl group. On the other hand the chemical shift of the methyl carbinol protons remains constant through the series, suggesting an axially oriented methyl group.

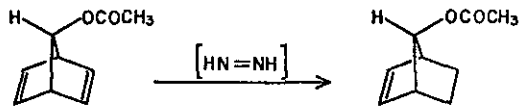


Considerable time and effort was expended to find a method that would specifically attack only one of the two double bonds present in 18 or the corresponding acetate (21). Attempts to regioselectively reduce these two dienes over a wide variety of catalysts failed. Similarly, monoepoxides obtained by various means, although exhibiting fascinating transformations, turned out to be mixtures of isomers. Surprisingly, reduction of the acetate with diimide gave a single, crystalline dihydro derivative (22) accompanied by some tetrahydroacetate (23). Transformation of acetate 22 to the spiroketone was accomplished in two ways. Treatment of the acetate with diborane followed by oxidation



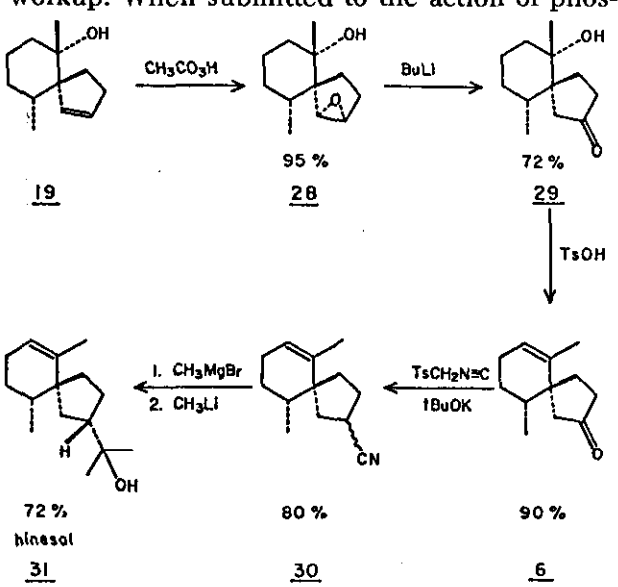
with sodium dichromate gave the acetoxyketone (24). Pyrolysis, followed by equilibration of exo- and endocyclic olefin (25 and 6 respectively) with p-toluenesulfonic acid in boiling benzene yielded the more stable endo-isomer (6) contaminated by less than 10% of exo-isomer (25). Spectral and chromatographic properties of racemic ketone 6 agreed with those of optically active material.*

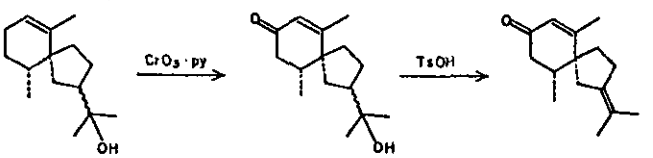
Before leaving this phase of the work it should be emphasized that we do not even have a hypothesis to rationalize the regioselective reduction of the cyclopentadiene 21 by diimide. Preferential reduction of the syn-double bond in 7-acetoxynorbornadiene (26) to give 27 has been attributed to an interaction of diimide and acetoxy group.[10] The much more subtle effect causing a rate enhancement in the reduction of only one of the two double bonds in the diene (21) will only be explained after the acetoxy-diimide interaction has been specified in precise structural terms.



26 27

An alternate synthesis of the C_{12}-ketone (6) starts with alcohol (19) available by saponification of the corresponding acetate. Epoxidation with peracetic acid furnished epoxide (28), assumed to have the α-configuration. Butyl lithium in ether at room temperature caused isomerization to the cyclopentanone (29) not via an allylic alcohol but by deprotonation of the epoxide followed by C-O bond heterolysis and enolate-ketone transformation during aqueous workup. When submitted to the action of phosphorous oxychloride or thionyl chloride in pyridine carbinol, 29 and others in this series were dehydrated mainly to exocyclic olefins, thus providing chemical evidence for the presence of methyl cyclohexanols with equatorial hydroxy groups. Dehydration of 29 with p-toluenesulfonic acid in boiling benzene leads to the more stable olefin (6). To complete the synthesis of C_{15}-spirovetivanes, ketone 6 was converted to the epimeric nitriles (30) with p-toluenesulfonylmethyl isocyanide. Condensation with methylmagnesium bromide provided the ketones which on treatment with methyllithium gave a 3:2 mixture of epimeric carbinols. Spectra of the acetate derived from the major epimer were identical with those of authentic hinesol (31) acetate.**





β-Vetivone was synthesized from the alcohols (31) by oxidation with chromium trioxide followed by acid catalyzed dehydration of intermediates (32).

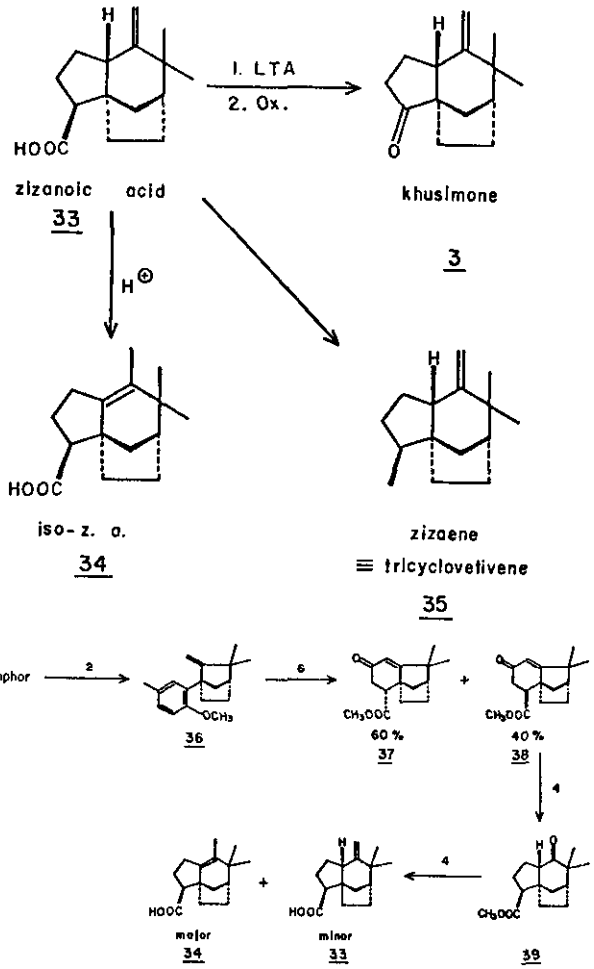
Synthesis of khusimone

The second part of this discussion will be concerned with a total synthesis of khusimone (3). This important vetiver constituent has been prepared by oxidative decarboxylation of natural zizanoic acid (33), followed by oxidation of the resulting secondary alcohol to the ketone. Some

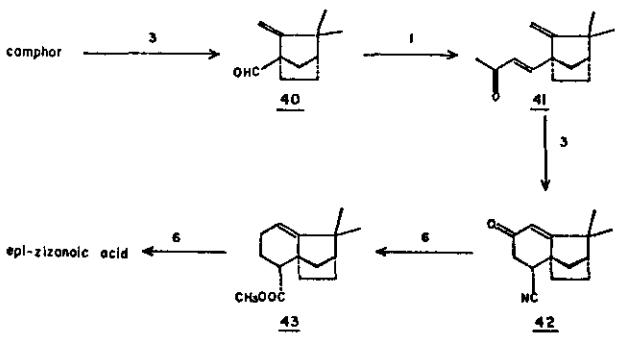
*Kindly supplied by Drs. Maurer and Ohloff, Firmenich SA.

**Kindly provided by Prof. James Marshall.

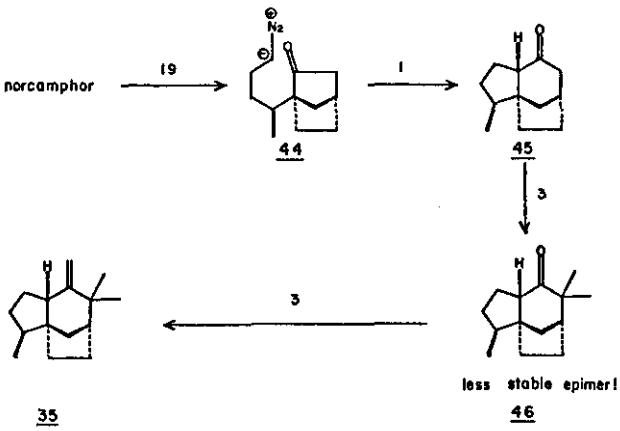
vetiver oils also contain iso-zizanoic acid (34)[12] and the basic sesquiterpene hydrocarbon zizaene (35). These substances are available from natural zizanoic acid by standard chemical transformations.



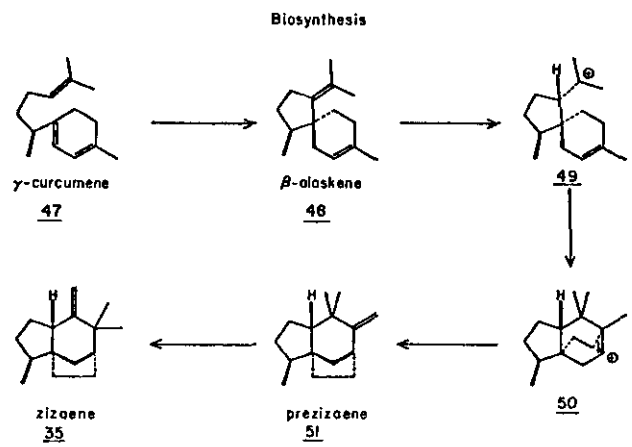
The total synthesis of the zizaene sesquiterpenes has caught the attention of several research groups, and three syntheses were published within a short time. Ramage's synthesis of zizanoic acid starts with camphor, which was converted to the substituted camphene (36) in two steps.[13] Further transformations to a norketone, Birch reduction, olefin isomerization, ozonization, Jones oxidation and aldol type cyclization led to a mixture of epimeric cyclohexenones (37 and 38). The next phase of the synthesis was concerned with the transformation of the minor isomer (38) to the ketoester (39), the critical step being a pinacol type rearrangement. Difficulties were encountered in the conversion of the cyclohexanone to the methylenecyclohexane because the carbonyl group is exceedingly hindered and gives very little olefin with Wittig reagents. A mixture of epimeric methylcarbinols prepared by Grignard addition on dehydration, even under kinetic control, led mostly to isozizanoic acid (34) rather than zizanoic acid.



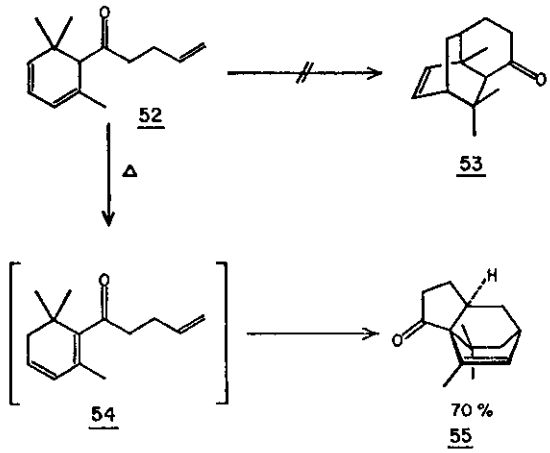
In Yoshikoshi's synthesis the zizaene skeleton was again created by a Wagner-Meerwein type rearrangement of a glycol derived from olefin (43) which in turn was available from camphor in thirteen steps via 40, 41, and 43.[14] This synthesis afforded epi-zizanoic acid which in the course of structural studies had already been converted to zizanoic acid by an equilibration procedure.



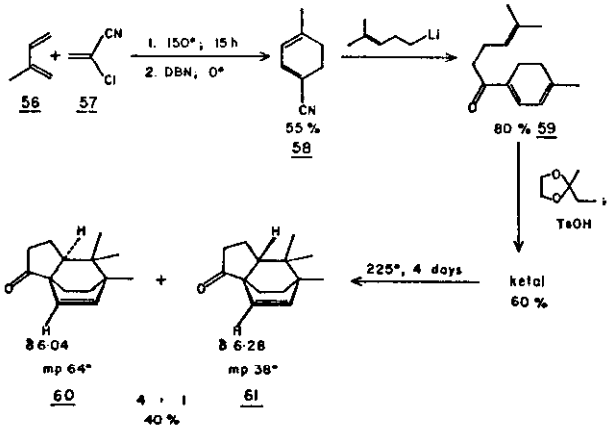
The intramolecular addition of the diazo group to the carbonyl function within 44 probably represents the most elegant step in Coates' synthesis of zizaene.[15] It not only created the third ring but also brought about rearrangement to the ketone (45) with correct stereochemistry. In the final transformation a new method for geminal dimethylation of ketones and a new olefin synthesis were employed successfully.



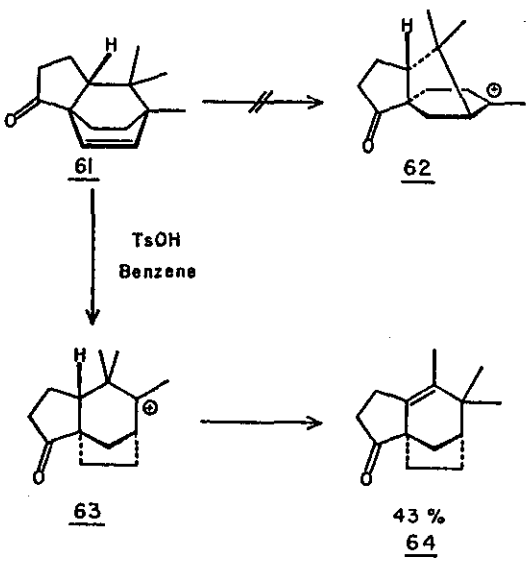
While contemplating a total synthesis of khusimone we examined biogenetic schemes that had been proposed for the zizaene type sesquiterpenes. The pathway (47-35) first proposed by Yoshikoshi and later refined by Anderson[16] accomodates the various structural types handsomely, but there is very little experimental evidence in its favor available as of now. The postulated Wagner-Meerwein rearrangements, however, have been realized in the laboratory. Thus treatment of prezizaene (51) and zizaene (35) with hot formic acid afforded the same mixture of isomeric zizaenes,[17] and solvolysis of the p-bromobenzenesulfonate of allo-cedrol, a secondary alcohol derived from cation 50 gave small amounts of enantio-prezizaene (51).[18] It occurred to us that the tricyclic olefin derived from ion 50 by loss of a proton might be prepared in a simple manner utilizing intramolecular Diels-Alder reaction, and we already had performed such a cyclization in connection with other work.



Thermolysis of the trienone (52) related to α-damascenone did not yield the anticipated cycloadduct (53) with patchoulane skeleton but a single isomer (55) derived from the hypothetical 54 which in turn resulted from the starting material (52) by a [1-5]-hydride shift.[19] The methyl groups in 55 are not placed properly for a khusimone precursor and the correct intermediate was prepared as follows.

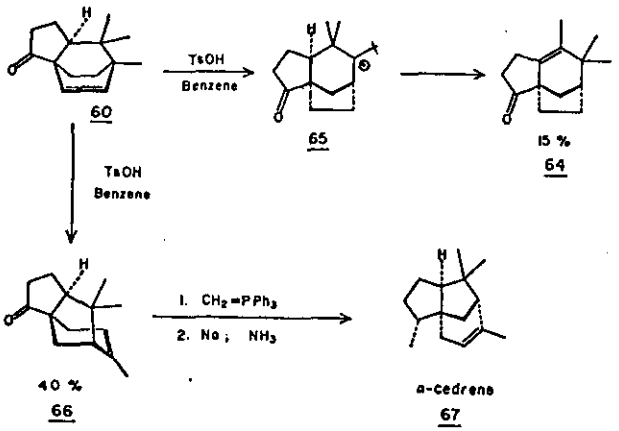


Condensation of isoprene 56 with α-chloroacrylonitrile (57) gave an adduct which lost hydrochloric acid on exposure to 1,5-diazabicyclo [4.3.0] nonene-5. Diene 58 was separated from small amounts of its 1,3-disubstituted isomer by fractional distillation. The critical trienone (59) was easily prepared by condensation of the nitrile with the appropriate lithium reagent but attempts to cyclize it thermally were disappointing. Since aromatization prior to cyclization could not be avoided we prepared the corresponding ketal and found that it does cyclize, although only slowly to give, after hydrolysis, a 4 : 1 mixture of isomeric ketones (60 and 61). The chemical shifts of the low field vinyl protons differed in the two isomers and these were used to assign the configurations indicated. The two consecutive Wagner-Meerwein rearrangements were first studied using individual epimers.

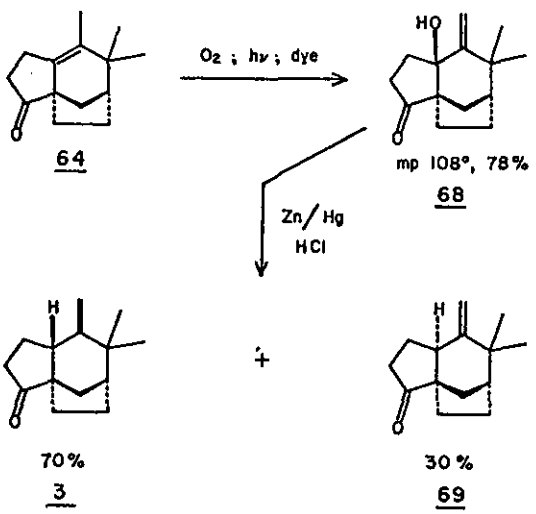


Heating diastereomer 61 with natural (khusimone-like) configuration in refluxing benzene in the presence of toluenesulfonic acid caused isomerization to isokhusimone (64) presumably via cation 63 with prezizaene skeleton. The selectivity observed in this reaction is remarkable but it was anticipated. Protonation of the double bond in 61 could lead to two carbonium ions. That located β- to the carbonyl group is not likely to rearrange because 1,2-alkyl shifts would lead to either an electron deficiency α- to the carbonyl group or a bridgehead carbonium ion. Methyl migration within the other cation would again create a bridgehead ion. Migration of the most substituted carbon atom would give a highly strained trans-bicyclo [3,3,0] -octane(62). Of the six statistically possible rearrangements five are thus eliminated on theoretical grounds and, in fact, not observed.

The isomeric ketone (60) with unnatural configuration behaved somewhat differently when submitted to the action of the same acid catalyst.



Isokhusimone derived from ion 65 is now the minor and ketone (66) containing a cis-[3,3,0] -octane framework the major product. The structure of the later isomer was ascertained by transformation to α-cedrene (67). The final conversion of isokhusimone to khusimone represents a contrathermodynamic isomerization. Very few methods have been developed to achieve such transformations. One of these, namely hydrozirconation, had to be eliminated from consideration because it fails with tetrasubstituted olefins. We did attempt to utilize the borane isomerization but isokhusimone ketal did not combine with diborane.



We eventually prepared the allylic alcohol (68) by oxidation with singlet oxygen. Reduction with zinc and hydrochloric acid in ether gave almost exclusively the less substituted olefins, khusimone, and some of its epimer (69).[20] Racemic khusimone was identical with natural material*, except for optical rotation.

Acknowledgement

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* Kindly supplied by Dr. G. Ohloff.

syntheses of the spirovetivones. A. Hauser and J. Limacher succeeded in synthesizing khusimone. I wish to acknowledge my gratitude to these able and hard working collaborators. This work was supported generously by Firmenich SA Geneva and I am grateful to the management of this firm and particularly Dr. G. Ohloff, its Director of Research, for help and encouragement.

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