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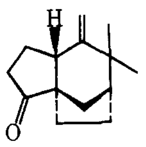
The Synthesis of Khusimone

Summary: A biogenetically patterned synthesis of khusimone (1), a norsesquiterpene with zizaene skeleton, proceeds through the two epimeric tricyclic ketones 14 and 15, prepared by intramolecular Diels–Alder cyclization of the trienone ketal 13. Acid-catalyzed isomerization of 15 gives exclusively isokhusimone (17), while isomerization of epimer 14 yields norcedrenone (16) and isokhusimone (17) in a ratio of 2:1. To convert isokhusimone (17) to the less stable racemic khusimone (1), the allylic alcohol 21 produced on photooxygenation of 17 is reduced with zinc and hydrogen chloride in ether.

Sir: Vetiver oil [*Vetiveria zizanioides* (L.) Nash] is one of the important raw materials for the composition of refined fragrances. The characteristic scent of the essence is partly due to khusimone (1), a tricyclic norsesquiterpene ketone.[1] Oxidative decarboxylation of *natural* zizanoic acid (2) with lead tetraacetate, followed by oxidation of the resulting secondary alcohol, has been utilized[2] to produce quantities of khusimone (1), but the two published *total* syntheses[3] of zizanoic acid (2) are unfortunately not practicable.

We describe a total synthesis of khusimone (1), which in its critical stages mimics the most likely biogenetic pathway.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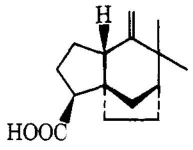
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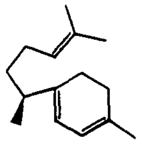
Yoshikoshi[4] was the first to suggest that zizaenes might biogenetically be derived from γ-curcumene (3) via the ion 4, followed by two Wagner–Meerwein rearrangements. The subsequent discovery of prezizaene (5),[5] its acid-catalyzed isomerization to, among other products, isozizaene (6), and the very inefficient dehydration of allocedrol (secondary alcohol derived from 4) to *enantio*-prezizaene[6] provided indirect evidence in support of this biogenetic scheme.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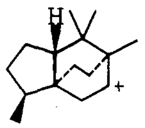
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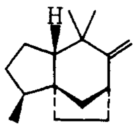
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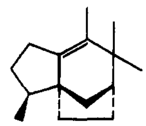
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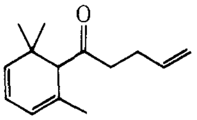
Our plan to construct the critical tricyclic olefin 14 or 15 by an intramolecular Diels–Alder reaction was based on the previously observed thermal cyclization of 7 to 9 (70% yield), which seems to proceed via the hypothetical intermediate 8, the product resulting from a 1,5-hydride shift.[7]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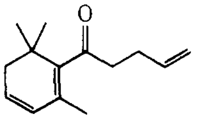
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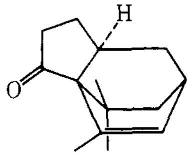
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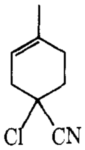
Addition of isoprene to α-chloroacrylonitrile[8] in the presence of some 2,5-di-*tert*-butylhydroquinone (15 h, 100 °C) gave the adduct 10 accompanied by 30% of its isomer. In preparative runs these were not separated, and the mixture was treated with 1,5-diazabicyclo[3.4.0]non-5-ene in tetrahydrofuran at 0–5 °C. Fractional distillation afforded the pure nitrile 11, UV max (95% EtOH) 295 nm (ϵ 9950), in 55% overall yield. Condensation of 11 with 5-lithio-2-methylpent-2-ene, prepared from the corresponding bromide[9] and lithium con-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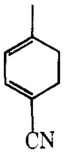
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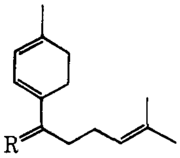
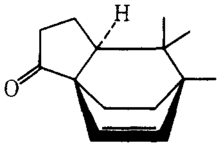

12,R = O

13,R = O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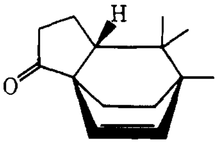
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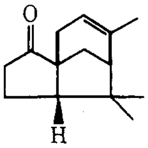
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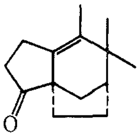
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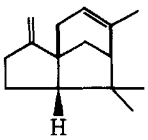
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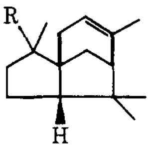
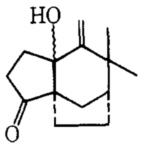

19,R = α-H
20,R = β-H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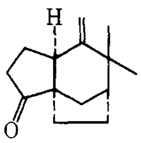
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taining 1% sodium in ether at −10 °C, followed by hydrolysis of the ketimine with 1 N aqueous hydrochloric acid–ether, gave the trienone **12**, bp 94–95 °C (0.02 mm), UV max (95% EtOH) 315 nm (ϵ 11 700) (75%). Experiments to effect the Diels–Alder condensation within this intermediate were discouraging and produced mainly the aromatic ketone derived from **12**. Ketal **13**, prepared with 1,2-propanediol (91% yield) in benzene with a trace of 85% phosphoric acid (Dean–Stark trap, 60 h), when heated in a sealed tube in mesitylene solution at 250 °C for 24 h, followed by hydrolysis of the crude product with perchloric acid in aqueous tetrahydrofuran, furnished a mixture of two epimeric ketones, **14** and **15**, in 55% yield. Chromatography of the ketals on silica gel and hydrolysis afforded pure isomers **14** [75%; mp 64–65 °C; IR ($CHCl_3$) 1735 cm^{-1}; NMR (CCl_4) δ 6.04 (1 H, d, $J = 8$ Hz)] and **15** [25%, mp 38–39 °C; IR ($CHCl_3$) 1735 cm^{-1}; NMR (CCl_4) δ 6.28 (1 H, d, $J = 8$ Hz). The configurations already assigned are based on the relative chemical shifts of the vinyl protons in the β position to the carbonyl group.

Heating epimer **15** with *p*-toluenesulfonic acid in benzene caused isomerization to racemic isokhusimone (**17**) (80%), identical with (−)-isokhusimone prepared by acid-catalyzed isomerization of (−)-khusimone (**1**).[11] The selectivity observed in this isomerization came as no surprise. Protonation of the double bond in **15** 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 forbidden carbonium ion, while migration of the most substituted carbon atom would give a strained *trans*-bicyclo[3.3.0]octane. Of the six possible 1,2-migrations, five are thus highly unlikely and were in fact not observed.

Isomerization of epimer **14** gave two products separable, as of now, only with loss of material. Isokhusimone (**17**) (15% of pure material) is now the minor and norcedrenone (**16**) [40% of pure material; mp 57–59 °C; IR ($CHCl_3$) 1730 cm^{-1}], a substituted *cis*-bicyclo[3.3.0]octane, the major product. Condensation of the new ketone **16** with methylenetriphenylphosphorane produced the liquid diene **18**, which on reduction with diimide (N_2H_4, H_2O_2) gave a mixture of α-cedrene (**19**) and *epi*-2α-cedrene (**20**).[12]

The contrathermodynamic isomerization of isokhusimone (**17**) to khusimone (**1**) caused difficulties, but was eventually accomplished as follows. Photosensitized oxygenation (Rose Bengal, EtOH–H_2O, 90 min, 25 °C), followed by workup with triethyl phosphite (20 °C, 8 h), yielded the allylic alcohols **21**, mp 107–110 °C (77%), which could be reduced with zinc and hydrogen chloride[13] in 75% yield to a mixture of epikhusimone (**22**) (30%) and racemic khusimone (**1**), mp 72–72.5 °C (70%). Identity with natural material was established by comparison of IR and NMR spectra, as well as chromatographic behavior.

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