Total synthesis of zizaane sesquiterpenes: (−)-khusimone, (+)-zizanoic acid, and (−)-epizizanoic acid

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Three sesquiterpenes of the zizaane family, khusimone (**1**), epizizanoic acid (**3**), and zizanoic acid (**2**) have been synthesized in optically active form from the ammonium salt of (−)-*l*-10-camphorsulfonic acid in sixteen, nineteen, and twenty steps respectively.

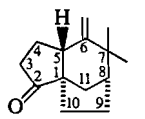
HSING-JANG LIU et WING HONG CHAN. Can. J. Chem. **60**, 1081 (1982).

Partant de l'acide (−)-*l*-camphresulfonique-10, on a synthétisé dans une forme optiquement active trois sesquiterpènes de la famille du zizaane soit la khusimone (**1**) et les acides zazinoïque (**2**) et épizazinoïque (**3**); ces synthèses requièrent respectivement seize, vingt et dix-neuf étapes.

[Traduit par le journal]

We wish to report a stereoselective total synthesis of khusimone (**1**) (1, 2), zizanoic acid (**2**) (3) (also known as khusenic acid (4)), and epizizanoic acid (**3**) (5), three tricyclic sesquiterpenes of the zizaane family which have been isolated from the essential oil of vetiver varieties. Zizaane sesquiterpenes have been the subject of considerable synthetic activity and several total syntheses have been accomplished during the last decade (6–13). A successful synthetic approach to this class of natural products must address three principal problems: (*i*) the construction of the tricyclo[6.2.1.$0^{1,5}$]-undecane ring system which is characteristic of the class, (*ii*) installation of an *exocyclic* methylene unit, and (*iii*) control of the stereochemistry, particularly the less stable *trans*-fused hydroindan ring junction. Although the tricyclic ring system has been assembled by a number of elegant approaches, simple solutions to the latter two problems are still in demand.

Khusimone (**1**)[1] was chosen as the primary target of our study because of its considerable importance to the perfume industry and for the possibility of its ready conversion to other members of the zizaane family. Our projected scheme (Scheme 1) would employ an intramolecular photochemical process (**4** → **5**) as a means to control the stereochemistry and facilitate the introduction of the *exocyclic* double bond. Not only does the stereochemistry of the resulting ketone **5** at C-1 and C-6 coincide with that of the two crucial centers, C-5 and C-8 respectively, of the natural products, but the replacement of the ketone carbonyl with a methylene unit (**5** → **7**) via the dehydration of alcohol **6** could



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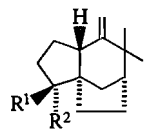
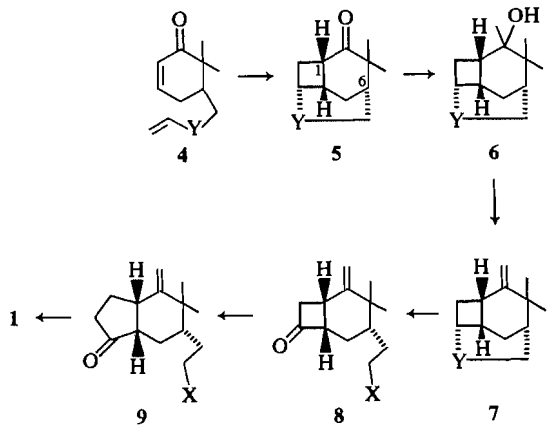


2 $R^1 = COOH$; $R^2 = H$
3 $R^1 = H$; $R^2 = COOH$

be expected to proceed without difficulty since the formation of an *endocyclic* double bond by dehydration of **6** would impose additional angular strain to the already strained cyclobutane ring. It was further anticipated that ring expansion of cyclobutanone **8** (derived from olefin **7**) to cyclopentanone **9** followed by cyclization would effectively complete the khusimone synthesis.

Towards this end, several 2-cyclohexenone derivatives of type **4** were prepared and their photochemistry was examined. (−)-α-Campholenic acid (**10**) possessing the same chirality as the natural khusimone (**1**) was obtained in 52% yield from the commercially available *l*-10-camphorsulfonic acid



4 **5** **6** **7** **8** **9** **1**

SCHEME 1

[1](±)-Khusimone has been synthesized previously by Büchi *et al.* (11). For a preliminary account of our work leading to (−)-khusimone, see ref. 14.

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ammonium salt by fusion with potassium hydroxide (15). Esterification of acid **10** with potassium carbonate and methyl iodide in refluxing acetone (16) gave a quantitative yield of ester **11** which was subjected to ozonolysis at −78°C in a solution of methylene chloride – methanol (1:1). Reductive work-up using triphenyl phosphine[2] (18) gave keto aldehyde **13** which, without purification,[3] was immediately treated with *p*-toluenesulfonic acid in refluxing benzene to give enone ester **14** (70% yield from **11**).

For the transformation of enone ester **14** to a tricyclic compound of type **5** via an intramolecular photocycloaddition reaction, vinyl ester **15** was an attractive intermediate. Apart from its anticipated ease of preparation from enone ester **14**, the cycloaddition of vinyl ester **15** was expected to proceed in a head-to-tail fashion, well precedented by the addition of vinyl acetate to 2-cyclohexenones by an intermolecular photochemical process,[4] to give product **16** with the desired orientation. The conversion of enone ester **14** into vinyl ester **15** was indeed straightforward. The latter compound was obtained in 60% yield when the former was hydrolyzed with sodium hydroxide and the resulting acid **17** was treated with vinyl acetate in the presence of a catalytic amount of mercuric acetate and concentrated sulfuric acid (22). The attempted photocycloaddition of vinyl ester **15** using a variety of conditions was, however, completely fruitless and resulted in recovery of the starting material. Although the observed unreactivity of vinyl ester **15** remains to be understood, we hoped that the photochemical reaction would take a different course by increasing or reducing its side chain by one atom. Thus, allyl ester **18** was prepared by esterification of acid **17** using allyl bromide and potassium carbonate. Disappointingly, allyl ester **18** was found to be equally unreactive. The photochemistry of enone acetate **19**, which has a shorter side chain than that of vinyl ester **15**, was also examined. This compound was prepared from enone ester **14** in four steps as follows. Enone ester **14** was first reduced to diol **20** (72% yield) by lithium aluminium hydride. Oxidation of **20** with four equiv. of pyridinium chlorochromate (23) afforded keto aldehyde **21** in 69% yield. Treatment of **21** with a slight excess of vinylmagnesium bromide at −78°C followed by acetylation of the resulting ketols **22** with acetic anhydride in pyridine gave an inseparable mixture of two epimeric keto acetates **19** (1:1) in 50% yield. Irradiation of a methanolic[5] solution of keto acetates **19** for 4 h caused the complete disappearance of the starting material. The product which was obtained in 43% yield showed in the ir spectrum the appearance of an absorption band at 1700 cm^{-1} and the absence of the 1675 cm^{-1} band previously observed for the conjugated enone system, suggesting that the photocycloaddition had taken place. This was confirmed by the mass spectrum displaying a molecular ion peak at 236.1419 and by the absence of low field signals for olefinic protons in the nmr spectrum. The nmr spectrum showing three sharp methyl singlets at δ 1.00, 1.21, and 1.95 further suggested that the product was a single compound which might have resulted from selective isomerization or destruction of one epimer of the starting material during the irradiation. The cycloaddition in principle can proceed in two different ways, head-to-tail and head-to-head, to give adducts **23** and **24** respectively. The available spectral data, however, did not permit unambiguous definition of the orientation of the isolated product. Nor did the examination of a Dreiding model reveal the preference of one orientation to the other. The conclusive evidence was provided by the following chemical transformations whereby the structure of the product was found to be as depicted in **24** with the undesired orientation. Hydrolysis of the acetate **24** with aqueous potassium carbonate in refluxing methanol gave the corresponding alcohol **25** which was oxidized with Jones reagent to diketone **26**. When treated with *m*-chloroperbenzoic acid in dichloromethane, diketone **26** underwent selective Baeyer–Villiger oxidation to give lactone **27**. Hydrolysis of **27** with aqueous potassium carbonate in refluxing methanol induced concomitant cyclobutane ring cleavage, apparently by a retro-aldol, giving rise to acid **28**,[6] the structure of which was further confirmed by esterification with diazomethane to give the corresponding methyl ester **30**.

Although it would be of general interest to investigate the photochemistry of other suitable derivatives of keto ester **14** such as **31** and **32** in

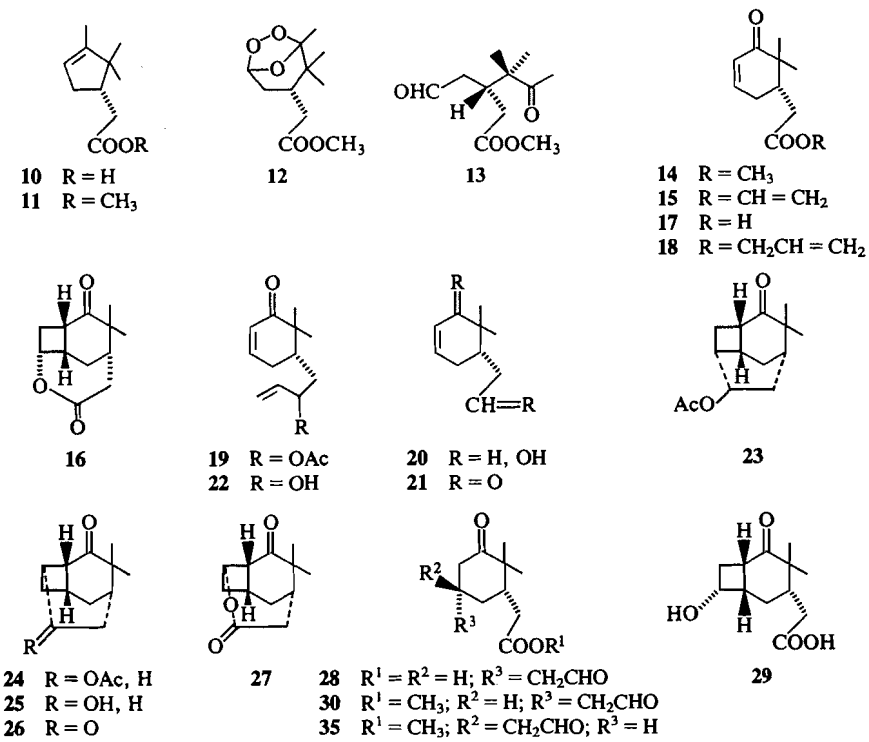
[2]Attempted reductive work-up using dimethyl sulfide (17) was proven to be ineffective and a single ozonide **12** (ir (neat): 1750 (C=O) cm^{-1}; nmr (CCl_4) δ: 5.62 (t, 1H, J = 1 Hz, —OCHO—), 3.58, 1.36, 1.12, and 0.93 (all s, 3H each, 4 × —CH_3)) was isolated in 42% yield.

[3]Keto aldehyde **13** was shown to be rather unstable. Attempted purification resulted in substantial loss of material.

[4]For reviews of photocycloaddition reactions, see refs. 19–21.

[5]Similar results were obtained using acetonitrile or benzene as a solvent.

[6]By the reaction sequence, the alternative photochemical product **23** should result in the formation of stable hydroxy acid **29**, and the isolation of acid **28** clearly defines the structures of its precursors as depicted.



particular, the large number of steps required for their synthesis as well as for the later modification preclude their efficient application to khusimone (**1**) synthesis. The subsequent studies were focussed on the addition, in a head-to-tail manner, of a latent ketene unit to the carbon–carbon double bond of keto ester **14** by an intermolecular photochemical process. We realized at the outset that such an approach would not allow profound stereochemical control as the addition could take place from both the α and the β face of the molecule and hence adjustment of stereochemistry at a suitable stage would be necessary. This drawback could, however, be compensated to a certain extent as enone **14** could be used directly without modifying its ester side chain.

Vinyl acetate was initially used as a ketene equivalent. Irradiation of enone **14** with a twenty-fold excess of vinyl acetate in benzene for 3 h at room temperature afforded a mixture of inseparable photoadducts in 77% yield. As shown by the subsequent transformation, both regioisomers **33** and **34** were formed in a ratio of approximately 4:1 with the desired isomer **33** predominating. On treatment with sodium methoxide in methanol at room temperature for 30 min, the mixture of photoadducts gave two products readily separable by column chromatography on silica gel. The minor component isolated in 16% yield was deduced to be a mixture of aldehyde **30** and its C-5 epimer **35** resulting, apparently, from the undesired photoadduct **34**. The major component, which was obtained in 67% yield, was shown to be a mixture of diastereomeric alcohols **36**[7] derived from the desired head-to-tail adducts **33**. Jones oxidation of this mixture gave two separable ketones **37** and **38** in a ratio of 5:6 and in a total yield of 67%. Although the ir and mass spectra of these ketones were very similar, distinct differences were observed in their nmr spectra. The geminal methyl groups of the major isomer appeared as a pair of singlets at δ 1.06 and 1.12 whereas the minor isomer showed two singlets at δ 0.97 and 1.21 for the corresponding methyls. The difference in Δδ (0.24 for the minor vs. 0.06 for the major) observed for the *gem*-dimethyl groups of these two compounds allowed us to tentatively assign their stereochemistry as follows. An examination of Dreiding models reveals that in the most stable contributive conformation of compound **37**, which could be represented by **37***a*, one methyl group lies within the deshielding zone of cyclohexanone carbonyl and the other within the shielding zone of cyclobutanone. On the other hand, in the case of compound **38**, whose stable conformation is depicted in formula **38***a*,

[7]Based on previous observations (24), a *cis* ring junction could be readily assigned to each diastereomer.

both methyls are distant from the cyclobutanone ring and thus devoid of any serious influence from its carbonyl. A larger $\Delta\delta$ for **37** and a smaller one for **38** are therefore expected and it follows that the minor isomer possesses structure **37** and the major structure **38**. These structural assignments were further supported by the optical rotatory dispersion analysis (25). The minor isomer displayed a positive anomalous single Cotton effect curve and the major showed a negative one. With the aid of models, the octant diagrams corresponding to the most stable conformations of the two diastereomers **37** and **38** are represented by Figs. 1 and 2 respectively. In the case of **37** (Fig. 1), since the large ester side chain occupies the positive octant at upper left position while the four-membered ring and the two methyl groups are more or less equally distributed among the positive and the negative octants, the octant rule predicts unambiguously a positive Cotton effect and indeed this was observed. In contrast, the Cotton effect of isomer **38** (Fig. 2) is less predictable, as the cyclobutanone ring and the ester chain are expected to exert opposing effects while two methyl substituents occupy two adjacent octants. It was especially gratifying to find that the major isomer showed a negative Cotton effect, eliminating its alternative structure of **37** (and thus confirming its structural assignment of **38**). The optical rotation dispersion properties of these two diastereomers are compiled in Table 1 which also summarizes the molecular amplitude of each compound. The observation that compound **37** showed a molecular amplitude far greater than that of **38** was in full support of the above analysis of substitution effect.

The transformation of enone ester **14** into diketones **37** and **38** was improved considerably when 1,1-diethoxyethene (26) was used as a ketene equivalent. Its photocycloaddition to **14** in benzene proceeded in a completely regioselective manner to give an inseparable mixture of at least two diastereomers (four sets of partially superimposed —OCH_2— quartets at the δ 3.39 region in the nmr spectrum) of the head-to-tail adduct **39** in near-quantitative yield. This mixture when treated with dilute hydrochloric acid in acetone gave, as the only products, diketones **37** and **38** (3:5) in a combined yield of 80%.

Of the two diketones **37** and **38**, only the former is synthetically useful. To enhance the efficiency of synthesis, it is highly desirable to invert the stereochemistry of both ring junction carbons of the latter compound. In principle, this could be directly accomplished by a process of double epimerization, since each of the chiral centers in question is α to a ketone carbonyl. In practice, it was found not to be the case; under a variety of reaction conditions the starting material was recovered intact. The unreactivity of the compound was, however, not totally surprising and could be attributed to its inability to undergo first-stage epimerization at either center to give the corresponding *trans*-fused compound, which is expected to be thermodynamically far less stable (24). An alternative approach which is conceivable for the conversion of diketone

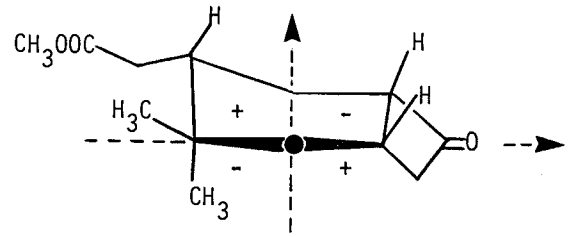


FIG. 1. Octant diagram of diketone **37**.

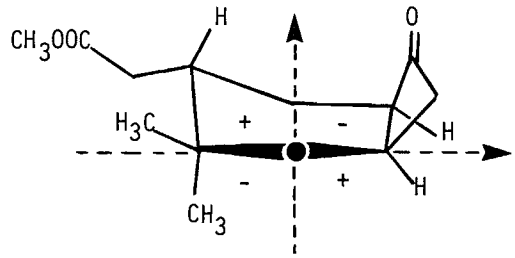
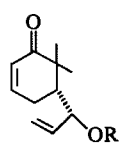


FIG. 2. Octant diagram of diketone **38**.



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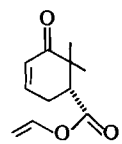
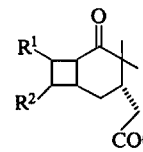
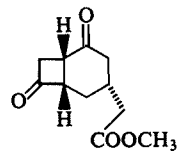


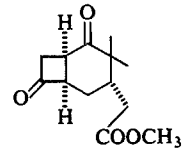
32



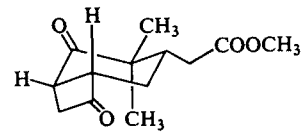
33 $R^1 = H$; $R^2 = OAc$
34 $R^1 = OAc$; $R^2 = H$
36 $R^1 = H$; $R^2 = OH$



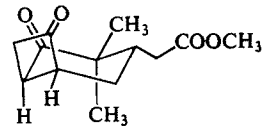
37



38



37a



38a

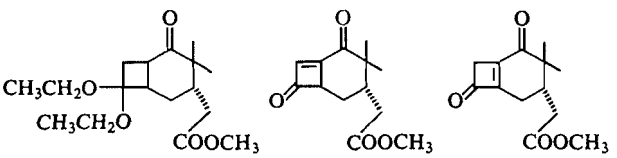
TABLE 1. Optical rotation dispersion properties of diketones **37** and **38**

Compound	Specific rotation $[\alpha]_D^{25}$	Molecular rotation $[\phi]_{320}$	$[\phi]_{278}$	Molecular amplitude $([\phi]_{320} - [\phi]_{278})/100$
37	+119.5°	+17024°	−15679°	+327
38	−126.4°	−4164°	+2959°	−71

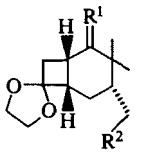
38 to its diastereomer **37** involves a two-step sequence, dehydrogenation and hydrogenation. This was successfully applied. Although initial attempts to oxidize diketone **38** with standard oxidizing agents such as dichlorodicyanoquinone and selenium dioxide were fruitless, its treatment with pyridinium bromide perbromide in acetic acid induced consecutive bromination and dehydrobromination to give an inseparable mixture of enediones **40** and **41** (ca. 7:1; 66% yield). Reduction of this mixture with zinc dust in acetic acid at room temperature afforded a 3:2 ratio of diketones **37** and **38** in 65% yield.

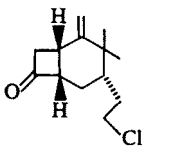
Before the incorporation of the required *exo*-methylene group into diketone **37**, its cyclobutanone carbonyl was protected. Although standard ketalization conditions ($(CH_2OH)_2$ and *p*-TsOH in refluxing benzene) showed little selectivity, transketalization of diketone **37** with 2-ethyl-2-methyl-1,3-dioxolane at 95°C in the presence of a catalytic amount of *p*-toluenesulfonic acid (27) resulted in the formation of the desired ketal ester **42** in 84% yield. Hydrolysis of **42**[8] with aqueous sodium hydroxide in refluxing methanol followed by treatment of the resulting acid **43** sequentially with sodium hydride[9] (1 equiv.) and methylmagnesium bromide (5 equiv.) at room temperature gave hydroxy acid **45**, which was immediately converted by diazomethane to the corresponding methyl ester **46** (78% yield from **42**). When **46** was exposed to thionyl chloride and pyridine in benzene, it underwent dehydration giving an 89% yield of olefin **47**. The reaction was found to be completely regioselective; no detectable amount of the corresponding endocyclic olefin was produced via the alternative mode of dehydration.

Olefin **47** was subsequently reduced with lithium aluminum hydride in tetrahydrofuran at room temperature to give alcohol **48**. Treatment of this alcohol with phosphorus oxychloride in pyridine afforded chloride **49**, which was hydrolysed with



39 **40** **41**





50

42 $R^1 = O$; $R^2 = COOCH_3$
43 $R^1 = O$; $R^2 = COOH$
44 $R^1 = CH_3$, OH; $R^2 = C(CH_3)_2OH$
45 $R^1 = CH_3$, OH; $R^2 = COOH$
46 $R^1 = CH_3$, OH; $R^2 = COOCH_3$
47 $R^1 = CH_2$; $R^2 = COOCH_3$
48 $R^1 = CH_2$; $R^2 = CH_2OH$
49 $R^1 = CH_2$; $R^2 = CH_2Cl$

aqueous hydrochloric acid in acetone to give keto chloride **50** in 75% yield over three steps.

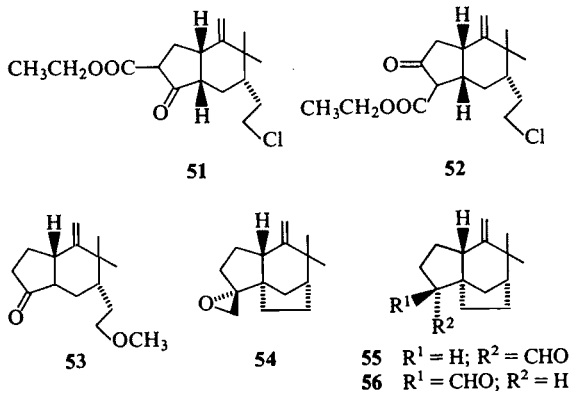
The transformation of keto chloride **50** to (−)-khusimone (**1**) requires two primary operations: homologation of the cyclobutanone ring and cyclization. Each was accomplished by a single step. Keto chloride **50** was subjected to one-carbon ring expansion with ethyl diazoacetate and boron trifluoride etherate in ether (28, 29). The reaction was found to be complete after 1 h at 0°C and 4 h at room temperature and two isomeric products were obtained in a ratio of 2:1 and a total yield of 86%. Tentative assignment of structure **51** to the major isomer and **52** to the minor[10] was made on the basis of previous findings (29, 30) that the boron trifluoride catalyzed homologation of cycloalkanone with ethyl diazoacetate proceeded, without a single exception, via the preferential migration of the less substituted carbon α to the carbonyl group. When heated at reflux with aqueous sodium hydroxide in refluxing methanol[11] for 40 min, the major isomer

[8]As previously observed for similar systems (6, 8), ketal ester **42** failed to undergo Wittig reaction with methylenetriphenylphosphorane. Its ketone carbonyl also failed to react preferentially with methylmagnesium bromide and methyllithium.

[9]Direct treatment of acid **43** with methylmagnesium bromide produced a substantial quantity of diol **44**.

[10]These assignments were substantiated by the following transformation of the major isomer to (−)-khusimone (**1**).

[11]It was necessary to bring the solution into reflux rapidly using a preheated oil bath. Otherwise a substantial amount of keto ether **53** was formed.



51[12] underwent concomitant decarbethoxylation and cyclization to give a 70% yield (−)-khusimone (**1**). The totally synthetic material was shown to be identical in all respects with the natural product.

Following the completion of the (−)-khusimone synthesis, our efforts were directed towards its extension to the synthesis of other zizaane sesquiterpenes possessing the normal fifteen-carbon skeleton. A scheme leading to (+)-zizanoic acid (**2**) and its (−)-epimer **3**[13] was successfully explored as follows.

The synthetic (−)-khusimone was treated with an excess of dimethylsulfonium methylide (31) in tetrahydrofuran. The addition of the ylide occurred exclusively from the sterically less hindered β face of the molecule to give a single epoxide **54** in 52% yield. Upon brief treatment with boron trifluoride etherate in ether at 0°C, epoxide **54** underwent rearrangement with inversion of stereochemistry (32) to give aldehyde **55** in quantitative yield. Jones oxidation of this compound afforded a 77% yield of (−)-epizizanoic acid (**3**). The ir and nmr spectra of the synthetic material were shown to be identical with those of the natural product.

Aldehyde **55** underwent epimerization on treatment with aqueous sodium hydroxide in methanol at room temperature. After 9 h, an equilibrium mixture consisting of five parts of α-epimer **55** and seven parts of β-epimer **56** (47% combined yield) was established. The latter compound was oxidized to (+)-zizanoic acid (**2**) in 86% yield when treated with Jones reagent. The identity of the synthetic and the naturally occurring material was established by comparison of their ir and nmr spectra.

[12]Under the same conditions, the minor ring expansion product gave rise to a complex mixture in which (−)-khusimone (**1**) was absent. These results were in agreement with its structural assignment.

[13]For existing syntheses of these two compounds, see refs. 6–8.

Experimental

General

Melting points were determined on a Kofler hot stage apparatus and are uncorrected. Optical rotations were measured by a Perkin–Elmer 141 polarimeter. The ir spectra were obtained by using a Perkin–Elmer model 457, 337 spectrophotometer and Nicolet 7199 Fourier transform spectrophotometer. Unless otherwise stated, ir samples were run as thin films. The nmr spectra were recorded on Varian A-60, HR-100, and 90 MHz Perkin–Elmer 32 spectrometers. Unless otherwise stated, carbon tetrachloride was used as solvent and tetramethylsilane as internal standard. Mass spectra (ms) were recorded on an AEI MS-50 mass spectrometer. Elemental analyses were performed by the microanalytical laboratory of this department. Jasco ORD/UV-5-SS-20-2 was used to measure optical rotatory dispersion.

Materials

Acetone was treated with potassium permanganate, dried over anhydrous potassium carbonate, and distilled. Dichloromethane used for reactions was distilled from phosphorus pentoxide. Methanol was dried over magnesium turnings at elevated temperature for 2 h and distilled. Ether, tetrahydrofuran, 1,2-dimethoxyethane, and benzene were freshly distilled from lithium aluminium hydride. Ozone was generated with a Welsbach ozonator. Ammonium salt of (−)-*l*-10-camphorsulfonic acid was obtained from Aldrich Chemical Company. Silica gel, 0.15–0.33 mm granulation, was used as adsorbent for column chromatography. Thin-layer chromatography was carried out using Merck silica gel G (type 60).

*(−)-α-Campholenic acid (**10**)*

To the fused potassium hydroxide (120 g, 2.14 mol) in a porcelain casserole, was added slowly with stirring the ammonium salt of (−)-*l*-10-camphorsulfonic acid (100 g, 0.40 mol). After the completion of the addition (ca. 25 min), the molten mass was heated for an additional period of 15 min. Upon cooling, the mass was dissolved with water (800 mL). After extraction with ether (200 mL) and dichloromethane (400 mL), the aqueous solution was acidified with ice-cold dilute hydrochloric acid and extracted with ether (300 mL) and dichloromethane (2 × 300 mL). The organic solution was dried ($MgSO_4$) and filtered. After most of the solvent was removed under the reduced pressure, the viscous residue was distilled to give pure acid **10** (35.4 g, 52% yield); bp 97°C/0.65 Torr; $[\alpha]_D^{25}$ −9.0° (*c* 1.1, $CHCl_3$); ir: 3200–2500 and 1708 (acid) cm^{-1}; nmr δ: 11.48 (br s, 1H, —COOH), 5.20 (br s, 1H, —HC=), 1.60 (br s, 3H, CH_3—CH=), 0.98 (s, 3H, —CH_3), and 0.79 (s, 3H, —CH_3); ms M^+ 168.1142 (calcd. for $C_{10}H_{16}O_2$: 168.1150).

*Methyl α-campholenate (**11**)*

A mixture of α-campholenic acid (**10**) (2.02 g, 12 mmol) and potassium carbonate (4.14 g, 30 mmol) in acetone (20 mL) was stirred at room temperature for 2 h. Methyl iodide (37 mL, 60 mmol) was introduced by syringe and the reaction mixture was refluxed overnight. After most of the solvent was evaporated under the reduced pressure, water was added and the organic product extracted with dichloromethane. The combined organic extracts were dried ($MgSO_4$), filtered, and evaporated to dryness. Bulb-to-bulb distillation (100°C/2 Torr) of the residue gave methyl ester **11** (2.17 g, 100% yield); ir: 1745 (ester) cm^{-1}; nmr δ: 5.20 (br s, 1H, —CH=), 1.58 (br s, 3H, CH_3C=). 0.98 (s, 3H, —CH_3), and 0.75 (s, 3H, —CH_3); ms M^+ 182.1308 (calcd. for $C_{11}H_{18}O_2$: 182.1306). *Anal.* calcd. for $C_{11}H_{18}O_2$: C 72.49, H 9.95; found: C 72.46, H 10.12.

*5-Carbomethoxymethyl-6,6-dimethyl-2-cyclohexenone (**14**)*

At −78°C, ozone (condition: E = 80 V, air inlet = 8 psi, ozone

outlet = 0.06 psi) was allowed to pass through a solution of ester **11** (23.58 g, 0.13 mol) in dichloromethane (65 mL) and methanol (60 mL) until a light blue color was retained. The mixture was warmed up gradually to about −25°C under a nitrogen atmosphere and triphenylphosphine (34 g, 0.13 mol) was added. After removal of the solvent, the crude keto aldehyde **13** (ir: 2840, 2740 (aldehyde), 1735 (ester), and 1705 (ketone and aldehyde) cm^{-1}; nmr δ: 9.52 (t, 1H, J = 1.5 Hz, —CHO), 3.59 (s, 3H, $—COOCH_3$), 2.11 (s, 3H, $—COCH_3$), 1.07 (s, 6H, 2 × $—CH_3$); ms M^+ 198.1250 (calcd. for $C_{11}H_{18}O_3$: 198.1255)) without purification was dissolved in 100 mL of benzene. To this solution *p*-toluenesulfonic acid (2.58 g, 15 mmol) was added. The resulting mixture was refluxed for 5 h with continuous removal of water using a Dean–Stark water separator. After the solvent was removed *in vacuo* ether was introduced to precipitate triphenylphosphine oxide. Filtration and concentration gave a residue which was subjected to bulb-to-bulb distillation at 100°C/2 Torr. Enone ester **14** (15.6 g, 70% yield) thus obtained showed the following physical data: $[\alpha]_D^{25}$ −65.1° (*c* 2.6, $CHCl_3$); ir: 1675 (α,β-unsaturated ketone), 1735 (ester), 1380 and 1368 (geminal methyls) cm^{-1}; nmr δ: 6.75 (m, 1H, —COCH=C*H*—), 5.86 (dt, J = 10, J' = 2 Hz, 1H, —COC*H*—CH—), 3.61 (s, 3H, $—COOCH_3$), 1.11 (s, 3H, $—CH_3$), and 0.94 (s, 3H, $—CH_3$); ms M^+ 196.1095 (calcd. for $C_{11}H_{16}O_3$: 196.1100). *Anal.* calcd. for $C_{11}H_{16}O_3$: C 67.32, H 8.22; found: C 67.19, H 8.40.

*5-Carboxymethyl-6,6-dimethyl-2-cyclohexenone (**17**)*

Keto ester **14** (2.94 g, 15 mmol) was dissolved in methanol (60 mL) and 2 *N* aqueous sodium hydroxide (30 mL) was added. The mixture was refluxed for 1.5 h. After cooling to room temperature, it was diluted with water and washed with dichloromethane to remove the nonacidic material. Ice-cold hydrochloric acid was introduced to adjust the acidity of the solution to ca. pH 1. The resulting aqueous solution was extracted with dichloromethane. Combined extracts were dried ($MgSO_4$), filtered, and concentrated to give acid **17** (2.73 g, 100% yield) as an oil; $[\alpha]_D^{25}$ −38.7° (*c* 0.9, $CHCl_3$); ir ($CHCl_3$): 3200–2500, 1708 (acid), and 1673 (α,β-unsaturated ketone) cm^{-1}; nmr ($CDCl_3$) δ: 10.65 (br s, 1H, —COOH), 6.82 (m, 1H, —COCH=C*H*—), 5.88 (m, 1H, —COC*H*=CH—), 1.21 (s, 3H, $—CH_3$), and 1.04 (s, 3H, $—CH_3$); ms M^+ 182.0945 (calcd. for $C_{10}H_{14}O_3$: 182.0943).

*Vinyl (6,6-dimethyl-5-oxo-3-cyclohexenyl)acetate (**15**)*

Acid **17** (900 mg, 4.94 mmol) was dissolved in vinyl acetate (8 mL) and the solution was stirred for 30 min under a nitrogen atmosphere. Mercuric acetate (20 mg) and concentrated sulfuric acid (3 μL) were added. The reaction mixture was refluxed for 4 h. Ice-cold aqueous sodium bicarbonate solution was added and the organic material extracted with dichloromethane. The combined organic extracts were dried over magnesium sulfate. Filtration and concentration yielded 819 mg of crude product which was chromatographed on silica gel (50 g). Elution with pentane–benzene (1:4) afforded pure ester **15** (610 mg, 60% yield) as an oil; ir: 3080, 1642 (olefins), 1748 (ester), 1670 (α,β-unsaturated ketone), 1390 and 1370 (geminal methyls) cm^{-1}; nmr δ: 7.28 (dd, J = 14, J' = 6 Hz, 1H, —OC*H*=CH_2), 6.80 (m, 1H, —COCH=C*H*—), 5.89 (dt, J = 10, J' = 2 Hz, 1H, —COC*H*=CH—), 4.83 (dd, J = 14, J' = 2 Hz, 1H, —OCH=C*H*H), 4.55 (dd, J = 6, J' = 2 Hz, 1H, —OCH=C*H*H), 1.12 (s, 3H, $—CH_3$), and 0.96 (s, 3H, $—CH_3$); ms M^+ 208.1109 (calcd. for $C_{12}H_{16}O_3$: 208.1100). *Anal.* calcd. for $C_{12}H_{16}O_3$: C 69.21, H 7.74; found: C 69.41, H 7.94.

*Allyl (2,2-dimethyl-3-oxo-4-cyclohexenyl)acetate (**18**)*

Acid **17** (346 mg, 1.9 mmol) was dissolved in acetone (8 mL). To this solution, anhydrous potassium carbonate (690 mg, 5 mmol) was added. The resulting mixture was stirred at room temperature for 2 h before allyl bromide (0.87 mL, 10 mmol) was introduced. After heating at reflux for 5 h, the reaction mixture was poured into water and extracted with dichloromethane. Drying ($MgSO_4$), filtration, and concentration gave the crude product which was purified by column chromatography on silica gel (30 g). Elution with benzene gave the allyl ester **18** (331 mg, 79% yield); ir: 3030, 3010, 1660 (olefins), 1675 (α,β-unsaturated ketone), and 1735 (ester) cm^{-1}; nmr δ: 6.86 (m, 1H, —COCH=C*H*—), 5.95 (m, 1H, —COC*H*=CH—), 5.75 (m, 1H, —C*H*=CH_2), 5.35 (m, 1H, —CH=C*H*H), 5.15 (m, 1H, —CH=C*H*H), 4.50 (m, 2H, $—OCH_2CH=CH_2$), 1.12 (s, 3H, $—CH_3$), and 0.95 (s, 3H, $—CH_3$); ms M^+ 222.1261 (calcd. for $C_{13}H_{18}O_3$: 222.1256).

*6,6-Dimethyl-5-(2-hydroxyethyl)-2-cyclohexen-1-ol (**20**)*

At 0°C, to a suspension of lithium aluminum hydride (228 mg, 6 mmol) in tetrahydrofuran (10 mL), was added a solution of enone ester **14** (413 mg, 2.1 mmol) in tetrahydrofuran (2 mL). After 15 min the reaction mixture was allowed to warm up to room temperature and stirred for 5 h. The mixture was treated successively with 0.2 mL of water, 0.2 mL of 3 *N* aqueous sodium hydroxide solution, and again with 0.6 mL of water. The inorganic salt was removed by filtration. Concentration of the filtrate gave diol **20** (257 mg, 72% yield); ir ($CHCl_3$): 3340 (alcohol), 3020 and 1660 (olefin) cm^{-1}; nmr ($CDCl_3$) δ: 5.58 (m, 2H, —CH=CH—), 3.83 (br s, 1H, —C*H*OH), 3.60 (m, 2H, $—CH_2OH$), 2.55 (br s, 2H, 2 × —OH), 1.00 (s, 3H, $—CH_3$), and 0.70 (s, 3H, $—CH_3$); ms M^+ 170.1307 (calcd. for $C_{10}H_{18}O_2$: 170.1307.

*6,6-Dimethyl-5-(2-oxoethyl)-2-cyclohexenone (**21**)*

To a suspension of pyridinium chlorochromate (2.37 g, 11 mmol) in dichloromethane (26 mL), a solution of diol **20** (470 mg, 2.8 mmol) in dichloromethane (4 mL) was introduced in one portion. The mixture was stirred at room temperature for 2 h and diluted with ether (50 mL). The resulting mixture was passed through a short pad of Florisil. Removal of the solvent under reduced pressure gave keto aldehyde **21** (315 mg, 69% yield); ir: 2730, 1735 (aldehyde), and 1680 (α,β-unsaturated ketone) cm^{-1}; nmr δ: 9.70 (m, 1H, —CHO), 6.70 (m, 1H, —COCH=C*H*—), 5.83 (dt, J = 10, J' = 2 Hz, 1H, —COC*H*=CH—), 1.12 (s, 3H, $—CH_3$), and 0.96 (s, 3H, $—CH_3$); ms M^+ 166.0997 (calcd. for $C_{10}H_{14}O_2$: 166.0994).

*5-(2-Acetoxy-3-butenyl)-6,6-dimethyl-2-cyclohexenone (**19**)*

At −78°C, to a stirred solution of keto aldehyde **21** (181 mg, 1.1 mmol) in tetrahydrofuran (5 mL) under a nitrogen atmosphere, was added a 1.2 *M* solution of vinylmagnesium bromide in tetrahydrofuran (1 mL, 1.2 mmol). After stirring for 30 min, ice-cold aqueous ammonium chloride solution was added. The resulting solution was extracted with ether. The etherate solution was dried ($MgSO_4$) filtered, and evaporated to dryness to give crude keto alcohol **22** (200 mg) which was dissolved in pyridine (2 mL). To this solution, acetic anhydride (0.5 mL) was added. After stirring at room temperature for 16 h the reaction mixture was concentrated. The residue was chromatographed on silica gel (10 g). Elution with a solution of 2% ether in benzene afforded keto acetates **19** (126 mg, 50% yield from **21**); ir: 1735 (ester), 1675 (α,β-unsaturated ketone), 1395 and 1375 (geminal methyls) cm^{-1}; nmr δ: 6.68 (m, 1H, —COCH=C*H*—), 5.80 (dt, J = 10, J' = 3Hz, 1H, —COC*H*=CH—), 5.58 (m, 1H, —C*H*=CH_2), 5.20 (m, 2H, —CH=C*H*$_2$), 5.16 (m, 1H, —CHO—), 2.00, 1.98 (both s, total 3H, CH_3COO—), 1.11, 1.08, and 0.94 (all s, total 6H, 2 × $—CH_3$); ms M^+ 236.1408 (calcd. for $C_{14}H_{20}O_3$: 236.1413).

3-Acetoxy-9,9-dimethyltricyclo[4.3.1.0^{4,7}]decan-8-one (24)

Keto acetates **19** (94 mg, 0.4 mmol) were dissolved in 10 mL of methanol. The solution was placed in a Pyrex tube and irradiated at room temperature using a 450 W Hanovia high-pressure quartz mercury vapor lamp for 4 h. The solution was concentrated and the residue chromatographed on silica gel (9 g). Elution with a solution of 2% ether in benzene gave keto acetate **24** (40 mg, 43% yield) as a colorless liquid; ir: 1735 (ester), 1700 (ketone), 1390 and 1372 (geminal methyls) cm^{-1}; nmr δ: 4.84 (m, 1H, —CHO—), 1.95 (s, 3H, CH_3COO—), 1.21 (s, 3H, —CH_3), and 1.00 (s, 3H, —CH_3); ms M$^+$ 236.1419 (calcd. for $C_{14}H_{20}O_3$: 236.1412).

3-Hydroxy-9,9-dimethyltricyclo[4.3.1.0^{4,7}]decan-8-one (25)

Keto acetate **24** (170 mg, 0.72 mmol) was dissolved in methanol (6 mL) and saturated aqueous potassium carbonate (3 mL) was added. The reaction mixture was refluxed for 1.5 h, poured into water, and extracted with dichloromethane. The extracts were dried ($MgSO_4$), filtered, and concentrated to yield an oily product (120 mg) which was chromatographed on silica gel (10 g). Elution with ether–benzene (3:2) gave keto alcohol **25** (91 mg, 65% yield); ir: 3400 (alcohol) and 1695 (ketone) cm^{-1}; nmr δ: 3.78 (m, 1H, —CHO—), 1.12 (s, 3H, —CH_3), and 0.98 (s, 3H, —CH_3).

9,9-Dimethyltricyclo[4.3.1.0^{4,7}]decane-3,8-dione (26)

At 0°C, to a solution of keto alcohol **25** (91 mg, 0.46 mmol) in acetone (5 mL) was added 8 *N* Jones reagent (0.3 mL) (33). After stirring at room temperature for 10 min, the mixture was diluted with water and extracted with ether. The organic solution was dried ($MgSO_4$), filtered, and evaporated to dryness. The crude product was chromatographed on silica gel (6 g). Elution with a solution of 2% ether in benzene gave diketone **26** (70 mg, 80% yield); ir: 1695 and 1710 (ketone) cm^{-1}; nmr δ: 2.96 (d, J = 2.5 Hz, 2H, —$COCH_2$—), 1.13 (s, 3H, —CH_3), and 1.08 (s, 3H, —CH_3).

10,10-Dimethyl-4-oxatricyclo[5.3.1.0^{5,8}]decane-3,9-dione (27)

A mixture of the diketone **26** (80 mg, 0.4 mmol), *m*-chloroperbenzoic acid (259 mg, 1.2 mmol), and sodium bicarbonate (200 mg, 2.0 mmol) in dichloromethane (4 mL) was stirred for three days. A 10% aqueous sodium sulfite solution (5 mL) was added and the resulting solution was extracted with dichloromethane. The combined extracts were washed with aqueous sodium bicarbonate solution. Concentration gave an oil which was chromatographed on silica gel (5 g). Elution with a solution of 10% ether in benzene gave keto lactone **27** (50 mg, 60% yield); ir: 1730 (lactone) and 1705 (ketone) cm^{-1}; nmr δ: 5.04 (m, 1H, —CHO—), 1.21 (s, 3H, —CH_3), and 1.11 (s, 3H, —CH_3); ms M$^+$ 208.1105 (calcd. for $C_{12}H_{16}O_3$: 208.1100).

cis-*3-Carbomethoxymethyl-2,2-dimethyl-5-(2-oxoethyl)cyclohexanone (30)*

Lactone **27** (20 mg, 0.1 mmol) was dissolved in methanol (6 mL). To this solution, saturated aqueous potassium carbonate (3 mL) was added. The reaction mixture was refluxed for 30 min under a nitrogen atmosphere. After cooling to room temperature, it was poured into water and extracted with dichloromethane to remove the nonacidic material. The aqueous solution was acidified with hydrochloric acid and extracted with dichloromethane. Drying ($MgSO_4$), filtration, and concentration yielded acid **28** (10 mg, 45% yield); ir ($CHCl_3$): 3200–2500 (acid), 2730 (aldehyde) and 1705 (carbonyls) cm^{-1}; nmr ($CDCl_3$) δ: 11.8 (br s, 1H, —COOH), 9.76 (br s, 1H, —CHO), 1.11 (s, 3H, —CH_3), and 1.01 (s, 3H, —CH_3); ms M$^+$ 226.1207 (calcd. for $C_{12}H_{18}O_4$: 226.1205).

Acid **28** (10 mg) was dissolved in ether (4 mL). At 0°C, to this solution, diazomethane in ether was added dropwise until the light yellow color was retained. Removal of the solvent gave ester **30** (10 mg, 95% yield); ir: 2730 (aldehyde), 1735 (ester), and 1710 (ketone and aldehyde) cm^{-1}; nmr δ: 9.72 (s, 1H, —CHO), 3.62 (s, 3H, —$COOCH_3$), 1.15 (s, 3H, —CH_3), and 0.98 (s, 3H, —CH_3); ms M$^+$ 240.1362 (calcd. for $C_{13}H_{20}O_4$: 240.1362).

Photocycloaddition of enone 14 to vinyl acetate

To a photochemical reaction vessel (34) containing enone ester **14** (2.15 g, 11 mmol) in benzene (50 mL) was added freshly distilled vinyl acetate (21 mL, 0.22 mol). The mixture was irradiated using a 450 W Hanovia high-pressure quartz mercury vapor lamp and a Pyrex filter for 1.5 h. The solution was concentrated and the residue chromatographed on silica gel (300 g) with benzene elution to give 2.37 g (77% yield) of photoadducts **33** and **34**; ir: 1735 (ester) and 1698 (ketone) cm^{-1}; nmr δ: 3.61 (s, 3H, —$COOCH_3$), 1.95, 1.96 (both s, total 3H, CH_3COO—), and 0.9–1.1 (complex, 6H, 2 × —CH_3); ms M$^+$ 282.1462 (calcd. for $C_{15}H_{22}O_5$: 282.1467).

4-Carbomethoxymethyl-7-hydroxy-3,3-dimethylbicyclo[4.2.0]-octan-2-one (36), cis-(30) and trans-3-carbomethoxymethyl-2,2-dimethyl-5-(2-oxoethyl)cyclohexanone (35)

At 0°C, sodium (690 mg, 30 g-atom) was added to methanol (35 mL). After all sodium reacted, a mixture of photoadducts **33** and **34** (3.07 g, 10.87 mmol) was added. The resulting mixture, after stirring at room temperature for 45 min, was carefully poured into ice-cold 3 *N* hydrochloric acid (100 mL) and extracted with dichloromethane. The extracts were dried ($MgSO_4$), filtered, and concentrated to give an oily residue which was chromatographed on silica gel (120 g). Elution with a solution of 50% ether–pentane gave keto aldehydes **30** and **35** (0.42 g, 16% yield); ir: 2730, (aldehyde), 1735 (ester), and 1710 (aldehyde and ketone) cm^{-1}; ms M$^+$ 240.1355 (calcd. for $C_{13}H_{20}O_4$: 240.1362). The nmr spectrum of the mixture showed, in addition to one set of signals corresponding to keto aldehyde **30** (*vide supra*), the following signals for compound **35**: δ: 9.72 (s, 1H, —CHO), 3.62 (s, 3H, —$COOCH_3$), 1.03 (s, 3H, —CH_3), and 0.98 (s, 3H, —CH_3).

Further elution with a solution of ether–pentane (4:1) gave a mixture of diastereomeric alcohols **36** (1.75 g, 67% yield); ir: 3450 (alcohol), 1738 (ester), and 1702 (ketone) cm^{-1}; nmr δ: 3.60 (s, 3H, —$COOCH_3$), 3.76 (m, 1H, —CHO—), and 0.90–1.21 (six s, total 6H, 2 × —CH_3); ms M$^+$ 240.1355 (calcd. for $C_{13}H_{20}O_4$: 240.1362).

4-Carbomethoxymethyl-3,3-dimethylbicyclo[4.2.0]octane-2,7-diones (37 and 38)

At 0°C, to a solution of alcohols **36** (3.2 g, 13.3 mmol) in acetone (30 mL), 8 *N* Jones reagent (ca. 5 mL) was introduced dropwise until the brown color persisted for more than 30 s. The mixture was stirred at room temperature for 30 min. After most of the solvent was removed under reduced pressure, water was added. The resulting aqueous solution was extracted with chloroform. The extracts were washed successively with aqueous sodium bicarbonate solution and aqueous sodium chloride solution and dried ($MgSO_4$). Filtration and concentration yielded 2.6 g of crude product which showed two partially overlapping spots on silica gel thin-layer chromatography. Column chromatography on silica gel (150 g), eluting with a solution of 40% ether in pentane, gave diketone **37** (850 mg, 27% yield); $[\alpha]_D^{25}$ +119.5° (*c* 2.0, $CHCl_3$); ir: 1785 (four-membered ketone), 1738 (ester), and 1710 (ketone) cm^{-1}; nmr δ: 3.61 (s, 3H, —$COOCH_3$), 1.21 (s, 3H, —CH_3), and 0.97 (s, 3H, —CH_3); ms M$^+$ 238.1204 (calcd. for $C_{13}H_{18}O_4$: 238.1205). *Anal.* calcd. for $C_{13}H_{18}O_4$: C 65.53, H 7.61; found: C 65.20, H 7.28.

Further elution with the same solvent system gave a mixture of **37** and **38** (ca. 1:1; 234 mg, 7% yield). This was followed by pure ketone **38** (1.055 g, 33% yield) as a white solid; mp 127–128°C (ether); $[\alpha]_D^{25}$ −126.4° (*c* 1.4, $CHCl_3$); ir ($CHCl_3$): 1785 (four-membered ketone), 1738 (ester), and 1708 (ketone) cm^{-1}; nmr δ: 3.67 (s, 3H, —$COOCH_3$), 1.12 (s, 3H, —CH_3), and 1.06 (s, 3H, —CH_3); ms M^+ 238.1205 (calcd. for $C_{13}H_{18}O_4$: 238.1205). *Anal.* calcd. for $C_{13}H_{18}O_4$: C 65.53, H 7.61; found: C 65.79, H 7.80.

*4-Carbomethoxymethyl-7,7-diethoxy-3,3-dimethylbicyclo-[4.2.0]octan-2-one (**39**)*

To a Pyrex tube containing a solution of enone ester **14** (500 mg, 2.5 mmol) in benzene (12 mL), 1,1-diethoxyethene (4.35 g, 37.5 mmol) was added. The reaction mixture was irradiated at room temperature with a 450 W Hanovia high-pressure quartz mercury vapor lamp for 3 h. The solvent and excess reagent were removed under the reduced pressure. The residue was chromatographed on silica gel (40 g). Elution with a solution of 20% ether in pentane gave a diastereomeric mixture of adducts **39** (750 mg, 96% yield); ir: 1735 (ester) and 1700 (ketone) cm^{-1}; nmr δ: 3.61 (s, 3H, —$COOCH_3$), 3.31, 3.33, 3.37, 3.39 (all q, J = 7 Hz each, total 4H, —OCH_2CH_3), and ~1.10 (complex, total 12H, 4 × —CH_3); ms M^+ 312.1943 (calcd. for $C_{17}H_{28}O_5$: 312.1937).

*Diketones **37** and **38** from ketal **39***

Ketal **39** (680 mg, 2.2 mmol) was dissolved in 8 mL of acetone and 2 *N* aqueous hydrochloric acid (4 mL) was added. After stirring at room temperature for 3 h, the solution was diluted with water and extracted with dichloromethane. The combined extracts were dried ($MgSO_4$), filtered, and evaporated to dryness. The crude product was chromatographed on silica gel (40 g). Elution with a solution of 40% ether in pentane gave pure diketones **37** (160 mg, 30% yield) and **38** (260 mg, 50% yield).

*Mixture of $\Delta^{1,8}$- (**40**) and $\Delta^{1,6}$-4-carbomethoxymethyl-3,3-dimethylbicyclo[4.2.0]octene-2,7-dione (**41**)*

To a solution of the diketone **38** (100 mg, 0.42 mmol), in glacial acetic acid (4 mL), pyridinium bromide perbromide (268 mg, 0.84 mmol) was added. The reaction mixture was stirred at room temperature for 16 h. It was cautiously made basic with ice-cold saturated aqueous sodium bicarbonate solution. Extraction with dichloromethane followed by the usual work-up of the extracts gave a thick oil which was chromatographed on silica gel (6 g). Elution with a solution of 25% ether in pentane gave enediones **40** and **41** (65 mg, 66% yield); ir: 1785 (four-membered ketone), 1740 (ester), and 1695 (six-membered ketone) cm^{-1}; nmr δ: 5.44 (br s, 0.88 H, —CH=C(—)—), 3.65 (s, 3H, —$COOCH_3$), 3.42 (m, 0.24 H, —$COCH_2$C(=)—), 1.22, 1.28 (both s, total 3H, —CH_3), and 1.08 (s, 3H, —CH_3); ms M^+ 236.1048 (calcd. for $C_{13}H_{16}O_4$: 236.1049).

*Reduction of enediones **40** and **41***

Zinc dust (1 g, 0.015 g-atom) was added to a solution of enediones **40** and **41** (523 mg, 2.21 mmol) in glacial acetic acid (8 mL). The resulting mixture was stirred at room temperature for 5 h. It was then cautiously made basic with ice-cold saturated aqueous sodium bicarbonate solution. Extraction with dichloromethane followed by concentration of the organic solution gave an oily product which was chromatographed on silica gel (30 g). Elution with a solution of 40% ether in pentane afforded diketones **37** (192 mg, 39% yield) and **38** (135 mg, 26% yield).

*4-Carbomethoxymethyl-7,7-ethylenedioxy-3,3-dimethylbicyclo[4.2.0]octan-2-one (**42**)*

Diketone **37** (655 mg, 2.76 mmol) was dissolved in 2-methyl-2-ethyl-1,3-dioxalane (8 mL) and *p*-toluenesulfonic acid (40 mg, 0.26 mmol) was added. The mixture was heated at 95°C (oil bath temperature) for 12 h. After cooling to 0°C, aqueous sodium bicarbonate solution was added. Extraction with dichloromethane followed by the usual work-up of the extracts gave the crude product which was chromatographed on silica gel (30 g). Elution with a solution of 40% ether in benzene gave ketal **42** (650 mg, 84% yield); $[\alpha]_D^{25}$ +71.8° (*c* 1.5, $CHCl_3$); ir: 1735 (ester) and 1715 (ketone) cm^{-1}; nmr δ: 3.75 (m, 4H, —OCH_2CH_2O—), 3.72 (s, 3H, —$COOCH_3$), 1.06 (s, 3H, —CH_3), and 0.96 (s, 3H, —CH_3); ms M^+ 282.1471 (calcd. for $C_{15}H_{22}O_5$: 282.1467).

*4-Carbomethoxymethyl-7,7-ethylenedioxy-2-hydroxy-2,3,3-trimethylbicyclo[4.2.0]octane (**46**)*

To a solution of ketal **42** (209 mg, 0.74 mmol) in methanol (6 mL) was added 2 *N* aqueous sodium hydroxide (3 mL). The resulting mixture was refluxed for 1 h. After cooling to room temperature, the mixture was poured into ice-cold dilute hydrochloric acid and extracted with dichloromethane. The usual work-up of the extracts gave crude acid **43**. The crude acid was then dissolved in 1,2-dimethoxyethane (10 mL) and cooled to 0°C. Sodium hydride (36 mg, 50% oil dispersion, 0.75 mmol) was added. After the evolution of gas ceased, a 2 *M* solution of methylmagnesium bromide in ether (1.8 mL, 3.6 mmol) was slowly introduced. The mixture was allowed to warm up to room temperature and stirred for 20 h under a nitrogen atmosphere. Saturated aqueous ammonium chloride solution was added and the resulting mixture was extracted with dichloromethane. The combined extracts were dried ($MgSO_4$), filtered, and concentrated to give a mixture of acids **43** and **45** as a light yellow liquid. This acidic material was dissolved in ether (6 mL) and a slight excess of ethereal diazomethane was introduced. The residue obtained upon concentration was chromatographed on silica gel (20 g). Elution with a solution of 40% ether in pentane gave the starting ketal **42** (39 mg, 19% recovery). Further elution with a solution of 50% ether in pentane afforded alcohol **46** (140 mg, 78% yield based on consumed **42**); ir: 3520 (alcohol) and 1735 (ester) cm^{-1}; nmr δ: 3.81 (br s, 4H, —OCH_2CH_2O—), 3.63 (s, 3H, —$COOCH_3$), 1.10 (s, 3H, —CH_3), 0.96 (s, 3H, —CH_3), and 0.92 (s, 3H, —CH_3); ms M^+ 298.1777 (calcd. for $C_{16}H_{26}O_5$: 298.1780). *Anal.* calcd. for $C_{16}H_{26}O_5$: C 64.41, H 8.78; found: C 64.19, H 8.68.

*4-Carbomethoxymethyl-7,7-ethylenedioxy-3,3-dimethyl-2-methylidenebicyclo[4.2.0]octane (**47**)*

To a solution of alcohol **46** (1.5 g, 5.0 mmol) and pyridine (4 mL), in benzene (50 mL), was added a solution of thionyl chloride (1 mL) in benzene (5 mL). The reaction mixture was stirred at room temperature under an atmosphere of nitrogen for 30 min. It was acidified with ice-cold 2 *N* aqueous hydrochloric acid and extracted with dichloromethane. The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated. Column chromatography of the residue on silica gel (80 g), eluting with a solution of 20% ether in pentane, gave olefin **47** (1.176 g, 89% yield); $[\alpha]_D^{25}$ +41.4° (*c* 1.0, $CHCl_3$); ir: 3100, 1630, 890 (olefin), and 1740 (ester) cm^{-1}; nmr δ: 4.96 (br s, 1H, —C(—)=C*H*H), 4.78 (br s, 1H, —C(—)=C*H*H), 3.75 (br s, 4H, —OCH_2CH_2O—), 3.60 (s, 3H, —$COOCH_3$), 1.10 (s, 3H, —CH_3), and 1.03 (s, 3H, —CH_3); ms M^+ 280.1674 (calcd. for $C_{16}H_{24}O_4$: 280.1674). *Anal.* calcd. for $C_{16}H_{24}O_4$: C 68.55, H 8.63; found: C 68.80, H 8.69.

*7,7-Ethylenedioxy-4-(2-hydroxyethyl)-3,3-dimethyl-2-methylidenebicyclo[4.2.0]octane (**48**)*

To a suspension of lithium aluminium hydride (200 mg, 5.3 mmol) in tetrahydrofuran (20 mL) at 0°C, a solution of ester **47** (1.176 g, 4.2 mmol) in tetrahydrofuran (2 mL) was added. The

reaction mixture was stirred at room temperature under a nitrogen atmosphere for 16 h. Water (0.2 mL), 3 *N* sodium hydroxide (0.2 mL), and again water (0.6 mL) were successively added. Filtration followed by concentration of the filtrate gave alcohol **48** (1.05 g, 99% yield); $[\alpha]_D^{25}$ +39.2° (*c* 1.3, $CHCl_3$); ir: 3420 (alcohol), 3100 and 1630 (olefin) cm^{-1}; nmr δ: 4.91 (s, 1H, —C(=)C*H*H), 4.27 (s, 1H, —C(=)C*H*H), 3.74 (br s, 4H, —OCH_2CH_2O—), 1.06 (s, 3H, —CH_3), and 1.03 (s, 3H, —CH_3); ms M^+ 252.1730 (calcd. for $C_{15}H_{24}O_3$: 252.1725). *Anal.* calcd. for $C_{15}H_{24}O_3$: C 71.39, H 9.59; found: C 71.70, H 9.66.

*4-(2-Chloroethyl)-7,7-ethylenedioxy-3,3-dimethyl-2-methylidenebicyclo[4.2.0]octane (**49**)*

Alcohol **48** (190 mg, 0.75 mmol) was dissolved in pyridine (2 mL) and cooled to 0°C. Phosphorus oxychloride (0.5 mL) was introduced. The mixture was stirred at room temperature under a nitrogen atmosphere for 16 h and poured into ice-cold water. The resulting mixture was extracted with dichloromethane. The organic solution was dried ($MgSO_4$), filtered, and concentrated to give an oily residue which was chromatographed on silica gel (15 g). Elution with a solution of 10% ether in pentane yielded chloride **49** (150 mg, 75% yield); $[\alpha]_D^{25}$ +29.7° (*c* 0.7, $CHCl_3$); ir: 1630 (olefin) cm^{-1}; nmr δ: 4.92 (s, 1H, —C(=)C*H*H), 4.75 (s, 1H, —C(=)C*H*H), 4.74 (br s, 4H, —OCH_2CH_2O—), 3.50 (m, 2H, —CH_2Cl), 1.07 (s, 3H, —CH_3), and 1.03 (s, 3H, —CH_3); ms M^+ 270.1380 and 272.1362 (calcd. for $C_{15}H_{23}OCl$: 270.1386 and 272.1357).

*4-(2-Chloroethyl)-3,3-dimethyl-2-methylidenebicyclo[4.2.0]-octan-7-one (**50**)*

Chloride **49** (120 mg, 0.44 mmol) was dissolved in acetone (4 mL) and 2 *N* aqueous hydrochloric acid (2 mL) was added. After stirring at room temperature for 8 h, the mixture was poured into water and extracted with dichloromethane. Drying ($MgSO_4$), filtration, and concentration gave ketone **50** (100 mg, quantitative yield; $[\alpha]_D^{25}$ +48.6° (*c* 1.3, $CHCl_3$); ir: 1785 (ketone) and 1640 (olefin) cm^{-1}; nmr δ: 5.04 (d, *J* = 2 Hz, 1H, —C(=)C*H*H), 4.91 (d, *J* = 2 Hz, —C(=)C*H*H), 3.50 (m, 2H, —CH_2Cl), 1.16 (s, 3H, —CH_3), and 1.11 (s, 3H, —CH_3); ms M^+ 226.1124 and 228.1090 (calcd. for $C_{13}H_{19}OCl$: 226.1124 and 228.1095).

*8-Carboethoxy-4-(2-chloroethyl)-3,3-dimethyl-2-methylidenebicyclo[4.3.0]nonan-7-one (**51**) and 7-carboethoxy-4-(2-chloroethyl)-3,3-dimethyl-2-methylidenebicyclo-[4.3.0]nonan-8-one (**52**)*

At 0°C, to a solution of ketone **50** (100 mg, 0.46 mmol) in ether (8 mL), was added boron trifluoride etherate (0.12 mL, 1 mmol). After stirring at 0°C for 15 min, ethyl diazoacetate (0.1 mL, 1 mmol) was introduced. The mixture was stirred under a nitrogen atmosphere at 0°C for 1 h and at room temperature for 4 h. Ice-cold saturated aqueous sodium bicarbonate solution was added dropwise. Extraction with dichloromethane followed by the usual work-up of the organic solution gave an oily product which showed two spots in thin-layer chromatography. Their separation was effected by column chromatography on silica gel (10 g). Elution with a solution of 8% ether in pentane afforded keto ester **51** (82 mg, 57% yield); $[\alpha]_D^{25}$ +31.9° (*c* 0.6, $CHCl_3$); ir: 1760 (ketone), 1735 (ester), and 1650 (olefin) cm^{-1}; nmr δ: 4.90 (br s, 2H, —C(=)CH_2), 4.12 (q, *J* = 7 Hz, 2H, —$COOCH_2CH_3$), 3.54 (m, 2H, —CH_2Cl), 1.24 (s, 3H, —CH_3), 1.23 (t, *J* = 7 Hz, 3H, —$COOCH_2CH_3$), and 1.06 (s, 3H, —CH_3); ms M^+ 312.1490 and 314.1445 (calcd. for $C_{17}H_{25}O_3Cl$: 312.1492 and 314.1462).

Further elution with the same solvent system gave keto ester **52** (42 mg, 29% yield); ir: 1750 (ketone), 1730 (ester), and 1635 (olefin) cm^{-1}; nmr δ: 4.98 (s, 1H, —C(=)C*H*H), 4.72 (s, 1H, —C(=)C*H*H), 4.14 (q, *J* = 7 Hz, 2H, —$COOCH_2CH_3$), 3.52 (m, 2H, —CH_2Cl), 1.25 (t, *J* = 7 Hz, 3H, —$COOCH_2CH_3$), 1.15 (s, 3H, —CH_3), and 1.01 (s, 3H, —CH_3); ms M^+ 312.1488 and 314.1466 (calcd. for $C_{17}H_{25}O_3Cl$: 312.1492 and 314.1463).

*(−)-Khusimone (**1**)*

To a solution of the keto ester **51** (122 mg, 0.39, mmol) in methanol (3 mL) under a nitrogen atmosphere, was added 2 *N* aqueous sodium hydroxide solution (1.5 mL). The resulting solution was immediately brought into reflux using a preheated oil bath. After 40 min, ice-cold water was added. Extraction with dichloromethane, drying ($MgSO_4$), filtration, and concentration gave a solid which was recrystallized from petroleum ether to give (−)-khusimone (**1**) (56 mg, 70% yield); mp 78°C; $[\alpha]_D^{25}$ −108.7° (*c* 2.0, $CHCl_3$); ir ($CHCl_3$): 3140, 1640 (olefin), 1728 (ketone), 1395 and 1360 (geminal methyls) cm^{-1}; nmr ($CDCl_3$) δ: 4.84 (br s, 1H, —C(=)C*H*H), 4.68 (br s, 1H, —C(=)C*H*H), and 1.06 (s, 6H, 2 × —CH_3); ms M^+ 204.1514 (calcd. for $C_{14}H_{20}O$: 204.1512).

*2,12-Epoxyzizaene (**54**)*

At 0°C, to a suspension of trimethylsulfonium iodide (100 mg, 0.5 mmol) in tetrahydrofuran (6 mL) under a nitrogen atmosphere, was added a solution of 2 *M* butyllithium in ether (0.16 mL, 0.32 mmol). After stirring at room temperature for 1 h, the mixture was again cooled to 0°C and a solution of (−)-khusimone (**1**) (40 mg, 0.2 mmol) in tetrahydrofuran (4 mL) was added. The resulting mixture was stirred at room temperature for 2.5 h. Water was added and the aqueous solution extracted with dichloromethane. The usual work-up of the extracts gave an oil which was chromatographed on silica gel (6 g). Elution with a solution of 2% ether in pentane gave epoxide **54** (15 mg, 52% based on consumed starting material); ir: 3110 and 1645 (olefin), 1385 and 1365 (geminal methyls) cm^{-1}; nmr δ: 4.77 (m 1H, —C(=)C*H*H), 4.58 (br s, 1H, —C(=)C*H*H), 2.67 (d, *J* = 12 Hz, 1H, —OC*H*H), 2.53 (d, *J* = 12 Hz, 1H, —OC*H*H), and 1.06 (s, 6H, 2 × —CH_3); ms M^+ 218.1674 (calcd. for $C_{15}H_{22}O$: 218.1670).

Further elution with a solution of 5% ether in pentane afforded 13 mg of the starting material.

*12-Oxoepizizaene (**55**)*

Epoxide **54** (17.5 mg, 0.08 mmol) was dissolved in ether (4 mL) and cooled to 0°C. Boron trifluoride etherate (0.05 mL, 0.41 mmol) was introduced. The mixture was stirred under a nitrogen atmosphere at 0°C for 1 h, and then at room temperature for 30 min. It was made basic with saturated sodium bicarbonate and extracted with ether. The organic solution was dried ($MgSO_4$), filtered, and concentrated to give aldehyde **55** (17.5 mg, quantitative yield); ir: 2710, 1720 (aldehyde), 1640 (olefin), 1380 and 1360 (geminal methyls) cm^{-1}; nmr δ: 9.73 (d, *J* = 2 Hz, 1H, —CHO), 4.80 (s, 1H, —C(=)C*H*H), 4.60 (s, 1H, —C(=)C*H*H), 1.10 (s, 3H, —CH_3), and 1.06 (s, 3H, —CH_3); ms M^+ 218.1670 (calcd. for $C_{15}H_{22}O$: 218.1670).

*(−)-Epizizanoic acid (**3**)*

At 0°C, to a solution of the aldehyde **55** (16 mg, 0.073 mmol) in acetone (3 mL), was slowly added 8 *N* Jones reagent until a brown color persisted. The mixture was stirred for 5 min, added to ice-cold aqueous sodium chloride solution (50 mL), and extracted with dichloromethane. The usual work-up of the extracts gave the crude product which was taken up in ether and extracted with saturated sodium bicarbonate. The extracts were

combined and acidified with hydrochloric acid. This was followed by extraction with dichloromethane. Drying ($MgSO_4$), filtration, and concentration gave (−)-epizizanoic acid (14) (13 mg, 77% yield); mp 110°C (petroleum ether); $[\alpha]_D^{25}$ −1.0° (*c* 1.2, $CHCl_3$); ir ($CHCl_3$): 3200–2500, 1691 (acid), 1638 (olefin), 1380 and 1360 (geminal methyls) cm^{-1}; nmr δ: 11.7 (s, 1H, —COOH), 4.75 (s, 1H, —C(=)C*H*H), 4.56 (s, 1H, —C(=)C*H*H), 1.08 (s, 3H, —CH_3), and 1.05 (s, 3H, —CH_3); ms M^+ 234.1626 (calcd. for $C_{15}H_{22}O_2$: 234.1619).

Epimerization of aldehyde 55

To a solution of aldehyde **55** (13 mg, 0.06 mmol) in methanol (4 mL), was added 2 *N* aqueous sodium hydroxide solution (1 mL). The reaction mixture was stirred at room temperature under a nitrogen atmosphere for 9 h. Saturated aqueous sodium chloride solution was added. The resulting solution was extracted with dichloromethane. Drying ($MgSO_4$), filtration, and concentration gave a mixture of epimeric aldehydes **55** and **56** which was separated by column chromatography on silica gel (5 g). Elution with a solution of *5%* ether in petroleum ether gave pure β-aldehyde **56** (2.5 mg), a mixture of α- and β-epimers (1:1; 2 mg), followed by pure α-aldehyde **55** (1.6 mg). β-Aldehyde **56** showed the following spectral data; ir: 2720, 1720 (aldehyde), 1640 (olefin), 1380 and 1360 (geminal methyls) cm^{-1}; nmr δ: 9.80 (d, J = 2 Hz, 1H, —CHO), 4.78 (dd, $J = J'$ = 2 Hz, 1H, —C(=)C*H*H), 4.63 (dd, $J = J'$ = 2 Hz, 1H, —C(=)C*H*H), and 1.07 (s, 6H, 2 × —CH_3); ms M^+ 218.1667 (calcd. for $C_{15}H_{22}O$: 218.1670).

(+)-Zizanoic acid (2)

At 0°C, to a solution of aldehyde **56** (2.5 mg, 0.011 mmol) in 2 mL of acetone, was added 8 *N* Jones reagent until a brown color persisted. After stirring at room temperature for 15 min, the reaction mixture was added to water and extracted with dichloromethane. The usual work-up of the extracts gave (+)-zizanoic acid (**2**) (2.3 mg, 86% yield); $[\alpha]_D^{25}$ +22.2° (*c* 0.23, $CHCl_3$); ir ($CHCl_3$): 3200–2600, 1701 (acid), 1639 and 891 (olefin) cm^{-1}; nmr δ: 4.77 (dd, $J = J'$ = 1.5 Hz, 1H, —C(=)C*H*H), 4.63 (dd, $J = J'$ = 1.5 Hz, 1H, —C(=)C*H*H), 2.68 (m, 1H, —C*H*COOH), 1.10 (s, 3H, —CH_3), and 1.07 (s, 3H, —CH_3); ms M^+ 234.1621 (calcd. for $C_{15}H_{22}O_2$: 234.1620).

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