

**A NEW ROUTE TO THE ZIZAANE SESQUITERPENES:
AN EFFICIENT SYNTHESIS OF (±)-ISOKHUSIMONE[‡]**

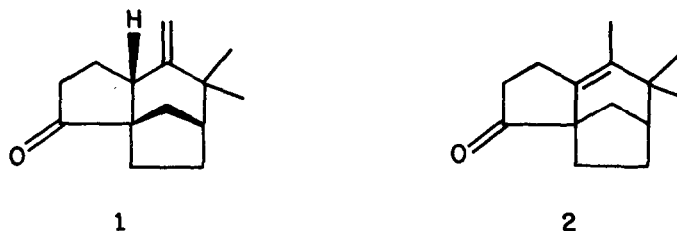
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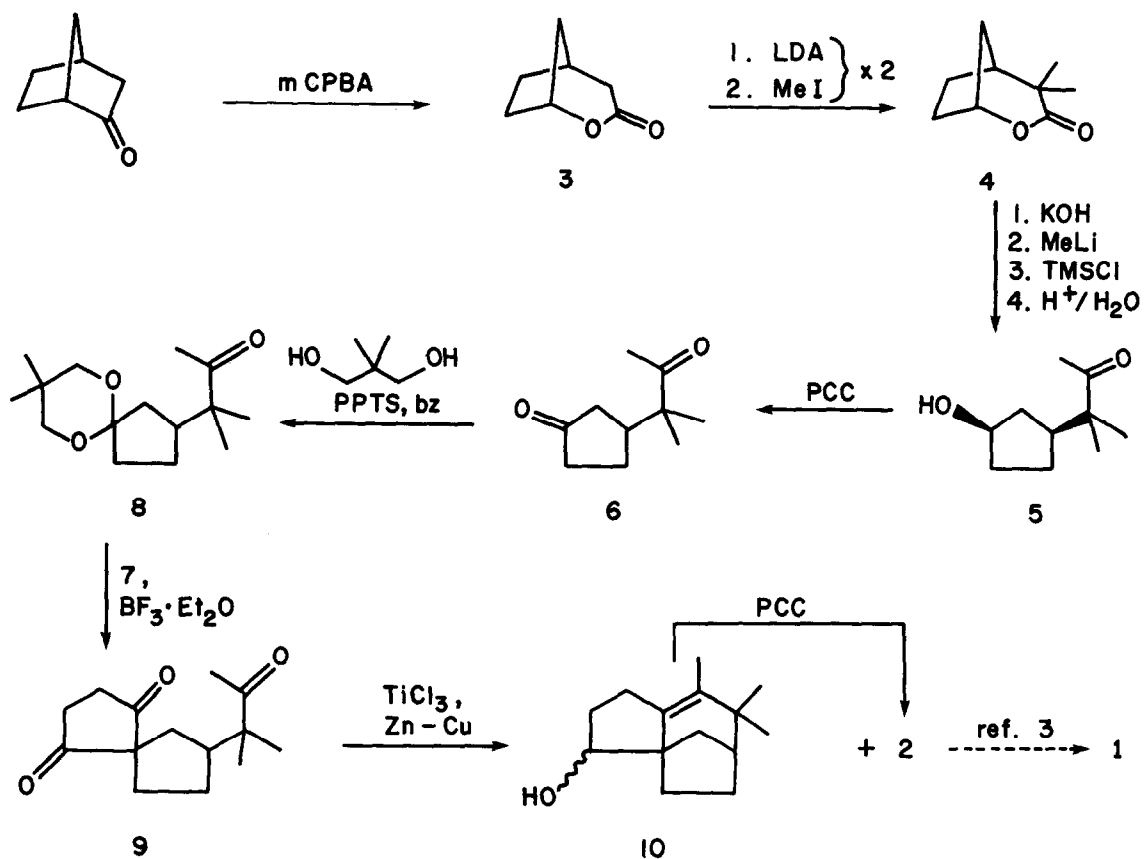
Abstract: A novel route to the zizaane sesquiterpene skeleton is demonstrated with a nine-step synthesis of (±)-isokhusimone (**2**) from norcamphor in an overall yield of 35%. This constitutes a formal synthesis of (±)khusimone (**1**).

Among the components of vetiver oil are the zizaane sesquiterpenes including the fragrant norsesquiterpene khusimone (**1**).¹ Construction of the zizaane tricyclo[6.2.1.0^{1,5}]undecane skeleton² and the synthesis of khusimone itself^{3,4} have been the subject of considerable interest. In this report we present a novel and efficient route from norcamphor to isokhusimone (**2**), which has been converted to khusimone by Büchi *et al.*³ and which may serve as a common intermediate for the preparation of all the zizaane sesquiterpenes.



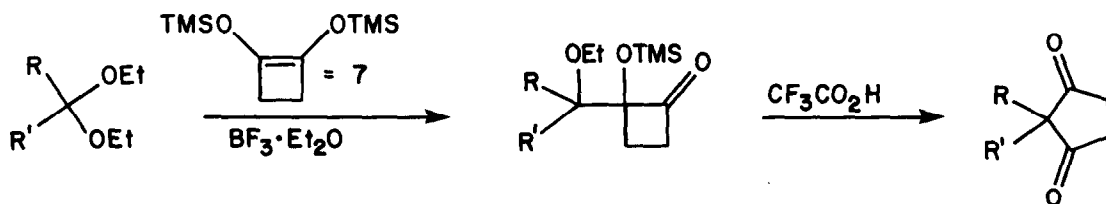
Baeyer-Villiger oxidation of norcamphor with *m*-chloroperoxybenzoic acid (CHCl₃ solution, 2 days at room temperature) provided the lactone **3** in 86% yield.⁵ Double treatment of **3** in THF at -78 °C with LDA then iodomethane gave the dimethyl lactone **4** (82%). Although a number of methods for the direct

[‡]This paper is dedicated to Professor Zdenek Valenta on the occasion of his 60th birthday.



conversion of esters/lactones to methyl ketones are known, in this instance we found that we obtained superior results by initial hydrolysis of the lactone (KOH in ethanol-water, reflux) then treatment of the hydroxy-acid with 15 equivalents of methyl lithium followed by 20 equivalents of chlorotrimethylsilane.⁶ Aqueous work-up provided **5** in a yield of 85%. Oxidation to the diketone **6** was nearly quantitative with pyridinium chlorochromate (PCC). The ¹H nmr (300 MHz) spectrum of **6** showed singlets at δ 2.14, 1.17, and 1.14, and the carbonyl signals in the ¹³C nmr spectrum were apparent at δ 218.2 and 212.9. The ir spectrum included absorptions at 1745 and 1705 cm^{-1} .

For the introduction of a 1,3-cyclopentanedione moiety we planned on using the method of Kuwajima and coworkers,⁷ involving the Lewis acid-catalysed reaction of a dimethyl or diethyl ketal (but not a ketone) with 1,2-bis(trimethylsiloxy)cyclobutene (**7**)⁸ followed by rearrangement of the resulting cyclobutanone with trifluoroacetic acid:



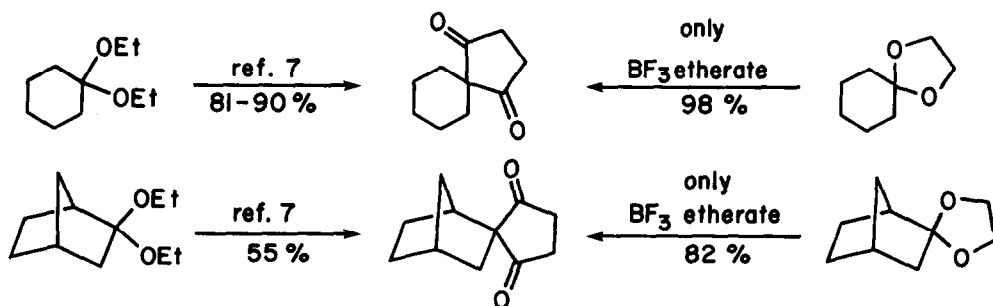
We required the monoketal of **6**, but in order to achieve acceptable selectivity in the monoketalization we had to resort to the ketal **8** derived from 2,2-dimethyl-1,3-propanediol (89% in 40 min with a catalytic amount of pyridinium *p*-toluenesulfonate with 1.5 equivalents of the diol in refluxing benzene). The ^1H nmr spectrum of **8** now had singlets at δ 2.13, 1.08, 1.07, 0.96 and 0.95. The ^{13}C nmr spectrum had one carbonyl signal at δ 213.3 (ir: 1710 cm^{-1}) and a ketal resonance at δ 108.3. In simple systems we had found this type of ketal will react readily with **7** and that the highest yields of 1,3-cyclopentanedione derivatives are realized in a modified one-pot procedure that uses excess BF_3 etherate to effect the rearrangement also.⁹ Consequently, a CH_2Cl_2 solution of **8** was stirred with 3 equivalents of **7** and 15 equivalents of BF_3 etherate (6 hours at -78°C) to afford the triketone **9** in a yield of 85% after purification.¹⁰ (Much of the remainder of the material was recovered as the diketone **6**.) The ^1H nmr of **9** included singlets at δ 2.14, 1.14, and 1.10 as well as a 4H multiplet centered at δ 2.79; the ^{13}C nmr now had three carbonyl resonances at δ 215.7, 215.3, and 213.0. The ir spectrum showed strong absorptions at 1725 and 1710 cm^{-1} .

Initial attempts following McMurry's procedure¹¹ for titanium-induced carbonyl coupling to close the six-membered ring gave very low yields of the desired product with significant amounts of very nonpolar material and approximately 30% recovered **9**. However, very much slower addition of **9** to the low-valent titanium greatly improved this reaction. Thus, a DME solution of **9** was added over 51 hours (using a syringe pump) to a stirred slurry formed from TiCl_3 (8 equivalents) and Zn-Cu couple (21 equivalents) in a large volume of boiling DME; then the mixture was heated for a further 4 days. Flash chromatography of the product afforded isokhusimone **2** (57%) and 1:1 mixture of the epimeric alcohols **10** (21%). Oxidation of **10** to **2** with PCC was essentially quantitative, providing **2** in a total yield of 78% from **9**, hence 35% from norcamphor. Singlets at δ 1.54, 1.04, and 1.02 appeared in the ^1H nmr spectrum of **2**, and in its ^{13}C nmr there was a single carbonyl resonance at δ 222.7 (ir: 1748 cm^{-1}) and olefinic signals at δ 136.3 and 130.6.¹² As Büchi *et al.*³ have transformed **2** to khusimone (**1**) in two steps, this constitutes, in a formal sense, a synthesis of khusimone itself.

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5. The structures of all synthetic products were consistent with their ir, nmr (^1H and ^{13}C , including 2-D) and mass spectra as well as with their elemental analyses.
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9. Prolonged treatment of a variety of ketals with **7** in the presence of many equivalents of BF_3 etherate, gave better yields of the 1,3-cyclopentanedione derivative than did the procedure that used trifluoroacetic acid to effect the rearrangement. (Cleaner products were obtained in longer experiments at lower temperatures.) Typically, the reactants were stirred at -78°C for about 6 hours, then the mixture was allowed to attain room temperature overnight before work-up. The following are some representative yields with simpler systems:



10. The crude product appeared to be almost 100% **9** by GC-MS; however when flash chromatography was used to remove the yellow color of the crude product about 15% of the mass was lost.
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12. The ir, ^1H nmr, and mass spectra of **2** were completely in accord with spectra of isokhusimone kindly provided by Professor George Büchi.

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