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THE ACID-CATALYZED REARRANGEMENT OF A CYCLOPROPYL KETONE RELATED TO 10-EPIEUDESMANE[1]

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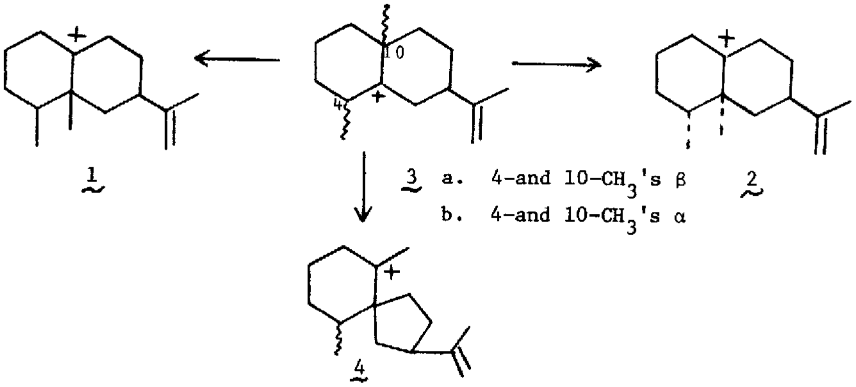
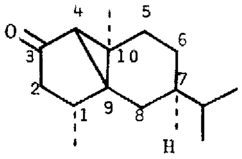
The currently accepted scheme for the biosynthesis of eremophilanes (1) and nootkatanes (2) involves a 1,2-shift of an angular methyl group in a eudesmane (3a) or a 10-epieudesmane (3b) precursor.[2] Migration of a methylene group in species such as 3 may also yield compounds with a spirovetivane skeleton (4).[2] In the past few years there has been a considerable amount of interest in the duplication of reactions such as these in the laboratory.[3]



The cyclopropyl ketone 5 may be considered as a 10-epieudesmane derivative. Cleavage of the internal (4,9) bond of the cyclopropane ring of 5 toward the carbonyl group would yield a carbonium ion related to 3b. Recent studies on the acid-catalyzed opening of the cyclopropane ring of bicyclohexanones in aprotic solvents have shown that concerted olefin or aryl participation may be involved in the process.[4] Also, it has been found that steroidal bicyclohexanones related to 5 undergo preferential cleavage of the internal bond of the three-membered ring upon treatment with electrophilic reagents.[5] These results suggested that treatment of 5 with Lewis acids in aprotic solvents might lead to products of the type 2 and/or 4 which formally could be considered to arise via methyl and/or methylene migration in a species related to 3b. In this Communication we wish to report the synthesis of 5 and its reaction with boron trifluoride in methylene chloride.



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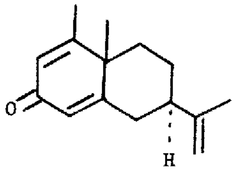

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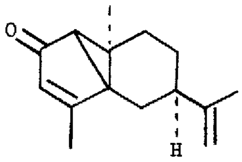

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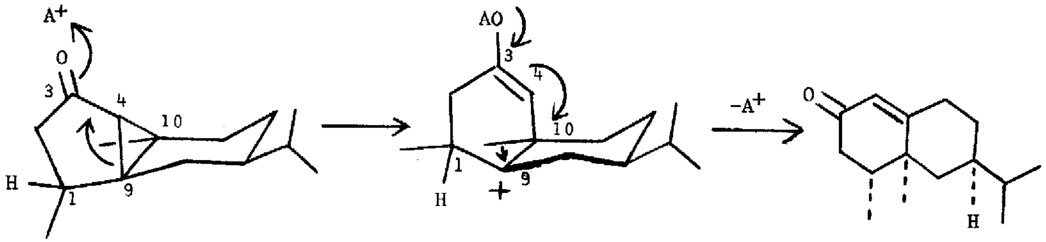
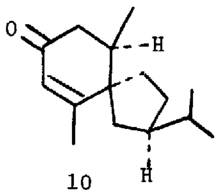
The known cross-conjugated dienone 6[6] was the starting material for the synthesis of 5. Irradiation of a 1% solution of this compound in anhydrous dioxane at 2537Å for 6 hr. followed by chromatography of the photolysis mixture on silica gel gave the bicyclohexenone derivative 7 [bp 120-130°/0.05 mm; ir(CCl_4) 1689 and 1607 cm^{-1}; NMR(CCl_4) δ 1.15 (s, 3H, 10-CH_3), 1.70 (s, 3H, $C(CH_3)=CH_2$), 2.02 (d, J = 1.5 Hz, 3H, 1-CH_3), 4.70 (br s, 2H, $=CH_2$), and 5.55 (br s, 1H, =CH); Anal Calcd for $C_{15}H_{20}O$: C, 83.28; H, 9.32. Found: C, 83.14; H, 9.34] in 65% yield. Catalytic hydrogenation of 7 using 5% palladium on carbon in 95% ethanol gave 5 [bp 120-130°/0.1 mm; ir(CCl_4) 1719 cm^{-1}; NMR(CCl_4) δ 0.87 (mult., 6H, $-CH(CH_3)_2$) 1.14 (d, J = 7 Hz, 3H, 1-CH_3), and 1.32 (s, 3H, 5-CH_3); Anal Calcd for $C_{15}H_{24}O$: C, 81.76; H, 10.98. Found: C, 81.70, H, 10.99] in 90% yield. Examination of a model of 7 clearly showed that the addition of hydrogen would be expected to occur from the β side of the 1,2 double bond to produce a saturated product having a cis relationship of the 1- and 10-methyl groups as shown in 5.

Treatment of 5 with a saturated solution of boron trifluoride in methylene chloride for 24 hr. at room temperature followed by GLC analysis[7] of the reaction mixture revealed that essentially all the starting material had been consumed and one major product which made up greater than 65% of the volatile components had been formed. The mixture also contained four minor products but none of these amounted to as much as 10% of the total volatile material. The yield of the major product was 46% by GLC analysis[7] using an internal standard. This compound was isolated by chromatography on silica gel and found to have identical spectral properties and GLC retention time[7] with an authentic sample of 11,12-dihydronootkatone (8) which was prepared by selective hydrogenation of natural nootkatone[8] using tris(triphenylphosphine)rhodium chloride in benzene.[3c] Because the minor products of the reaction of 5 were produced in very low yields, they have not been isolated in pure form and characterized at this time.

The formation of **8** from **5** involves cleavage of the 4,9 bond of the cyclopropane ring and migration of the 10-methyl group to C-9. While it is quite possible that this entire process is concerted, it may be represented formally as involving a bicyclic carbonium ion intermediate. In cyclopropyl ketones of the type **5** the external (4,10) bond of the cyclopropane overlaps more favorably than the internal bond with the Π orbital of the carbonyl function. However, **5** would be expected to prefer a steroid-like conformation (**5A**) with the bulky isopropyl group equatorial to the six-membered ring. In **5A** cleavage of the 4,9 bond can occur in a diaxial manner leading to a bicyclic carbonium ion in the conformation **9** in which the enolized carbonyl function is axial with respect to the B ring.^{5a} Conformation **9** may well be preferred for the bicyclic intermediate on thermodynamic as well as kinetic grounds since it provides the possibility for relatively efficient overlap of the Π electrons of the 3,4 double bond with the electron deficient center at C-9. In **9** a transition state which would allow for maximum orbital overlap during bond migration to C-9 appears to be much more easily achieved by the methyl group than the methylene group. Methyl migration would also relieve the 1,3-diaxial interaction between the 10- and the 1-methyl groups which is present in **9**. This latter factor may be an important driving force for the rearrangement. The relief of steric crowding seems to have been an important factor in other systems in which methyl migrations have been observed.^{3b,d} If methylene migration accompanied opening of the 4,9 bond, the spiro enone **10** would be expected to be formed. However, examination of the spectral properties of the crude reaction mixture or of some of the partially purified minor components from the reaction of **5** provided no evidence for this type of system. The minor products from the reaction may be formed by proton transfer rather than rearrangement of **9**, or, possibly by pathways involving cleavage of the 4,10 bond.



5A **9** **8**



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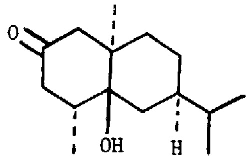

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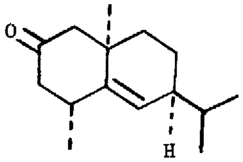

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It is of interest to note that the ketol 11 which would be expected to give a carbonium ion of the type 3b yielded only the simple dehydration product 12 and related double bond isomers on treatment with boron trifluoride etherate in acetic acid or other dehydrating agents.[3c] In the boron trifluoride-catalyzed cleavage of 5 the enolized carbonyl function and the electron deficient center at C-9 are generated simultaneously and methyl migration may lead directly to the conjugated enone system in 8. This may account for the relatively large amount of skeletal rearrangement which was observed in the reaction of 5.

We are investigating the reaction of 5 with other electrophilic reagents. The biosynthetic-like methyl migration process which has been observed here may be of value in the synthesis of various other nootkatane derivatives.

References and Notes

1. This investigation was supported by Grant Number CA 12193, awarded by the National Cancer Institute, DHEW.

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6. a) Dienone 6 may be obtained by photochemical rearrangement of lumidehydronootkatone[6b] or by oxidation of the minor product of annelation of (+)-dihydrocarvone with *trans*-3-penten-2-one[6c] with 2,3-dichloro-5,6-dicyanobenzoquinone;[6b,d] b) D. Caine and C. Y. Chu, Tetrahedron Lett., 703(1974); c) T. J. Leitereg, ibid., 2617(1972); d) We have developed a more convenient route to 6 which will be reported in detail in a full paper.

7. A 0.125 in. x 6.0 ft. column containing carbowax K-20 M on chromosorb W/HMDS was employed for the analysis.

8. We are grateful to Dr. Ben Clark of the Coca-Cola Company for a pure sample of (+)-nootkatone.