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CATIONIC CYCLIZATION OF α,β-UNSATURATED KETONES. A FACILE SYNTHESIS OF 9-METHYLDECALIN-2-OL-5-ONE, AN INTERMEDIATE FOR SYNTHESIS OF EUDESMANE SESQUITERPENOIDS

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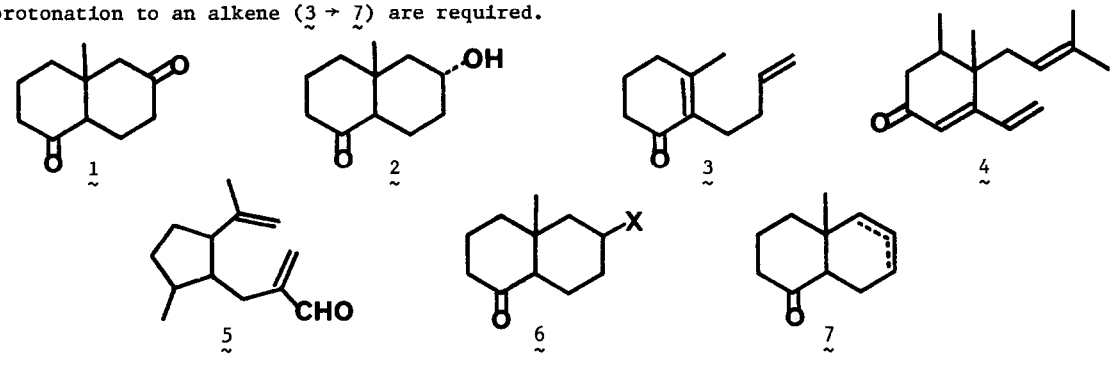
Derivatives of 9-methyldecalin-2,5-dione (1) have proven to be useful intermediates for the synthesis of several members of the eudesmane class of sesquiterpenoids.[1] We now report an efficient annellative synthesis of 9-methyldecalin-2-ol-5-one (2), a useful synthetic equivalent of dione 1. The procedure developed also illustrates the synthetic utility of α,β-unsaturated ketones for initiation of cationic olefin cyclizations.

As part of a continuing study on the synthetic and mechanistic aspects of cationic olefin cyclizations,[2] we attempted to develop procedures for direct cyclization of 2-(3-butenyl)-3-methyl-2-cyclohexenone (3).[3] Although acid-catalyzed cyclizations of trienone 4 and of α,β-unsaturated aldehyde 5 have been reported,[6] direct cation-olefin cyclizations of simple α,β-unsaturated ketones have not been exploited.[7,8] For this reaction to be generally useful, conditions which lead to nucleophilic capture of the bicyclic cationic intermediate (3 → 6) rather than deprotonation to an alkene (3 → 7) are required.



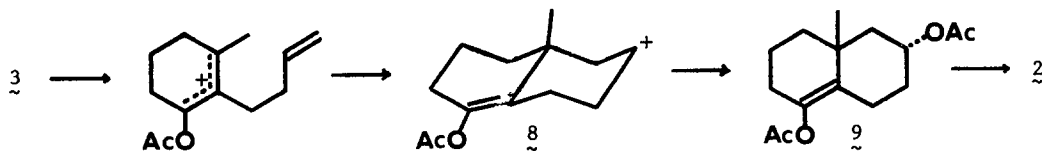
1 2 3 4 5 6 7

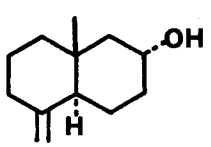
The known[4,5] ketone 3 was prepared in 85% yield, based on unrecovered starting material, by alkylation and decarbethoxylation of 4-carbethoxy-3-methylcyclohex-2-en-1-one following a procedure described by Johnson for a related alkylation.[10] Treatment of ketone 3 with a variety of protic and Lewis acids at room temperature (HCO_2H, CH_3CO_2H, CF_3CO_2H, $HClO_4$ in CH_3CO_2H, $SnCl_4$, $BF_3 \cdot Et_2O$ in CH_3CO_2H) all led to recovery of unchanged 3. The first indication that cyclization of ketone 3 was feasible was obtained upon attempted conversion to a ketal. Treatment with *p*-

toluenesulfonic acid and ethylene glycol in refluxing benzene gave a mixture of materials, but the nmr spectrum clearly showed a distinct singlet peak at δ=0.8 consistent with the absorption expected for an angular methyl group. This result led us to explore the reaction under conditions normally used to prepare enol acetates and used by Andersen for cyclization of aldehyde 5.[6b]

Treatment of ketone 3 (100 mg) with a mixture of 70% perchloric acid (150 mg) and acetic acid (5 ml) in ethyl acetate (8 ml) for 10 min at room temperature led to complete disappearance of starting ketone and formation of a cyclic enol acetate. Upon basic hydrolysis and evaporative distillation (1 mm/100°), ketone 7 was isolated in 50% overall yield: ir (neat) 1715 (C=O), 3100 and 1640 cm^{-1} (C=C); ms Calcd for $C_{11}H_{16}O$ 164.1201, Found 164.1206. The nmr spectrum indicated that this material was an approximately equal mixture of *cis* and *trans* isomers with both double bonds present[11] [major $-CH_3$ absorptions at δ 1.12 (cis) and 0.78 (trans) with minor absorptions at δ=1.08 (cis) and 0.84 (trans)]. Thus cyclization had been effected, but under these conditions the bicyclic cation was deprotonating in the absence of a nucleophile. This problem was reduced by inclusion of additional acetic acid into the medium.

Treatment of 640 mg of ketone 3 with a mixture of 70 ml of acetic anhydride, 90 ml of acetic acid and 1.2 g of 70% perchloric acid for 1.5 hr at rt followed by basic hydrolysis and column chromatography to remove ketone 7 (12% yield) gave, after evaporative distillation (0.2 mm/120°), ketoalcohol 2 in 50% overall yield: ir (neat) 3400 (OH) and 1715 cm^{-1} (C=O); ms Calcd for $C_{11}H_{18}O_2$ 182.1307, Found 182.1312; *Anal.* Calcd C 72.49, H 9.95, Found C 72.26, H 9.74. The nmr spectrum of this keto alcohol showed two angular methyl absorptions at δ 0.80 (major) and 1.14. On the basis of both the ^1H and ^{13}C spectra and the gas chromatogram this product is considered to be a mixture of *cis*-2 and *trans*-2 with the trans isomer amounting to about 80% of the mixture. On the basis of mechanistic considerations (see Scheme below) the enol acetate precursor of ketoalcohol 2 would be expected to have the stereochemistry shown by structure 9 as a result of equatorial attack on the conformationally rigid cation 8.[4,12] The same stereochemistry is predicted if the mechanism of cyclization involves concerted attack of acetate rather than the bicyclic cation 8. As required by this argument the diacetate 9 was shown to be essentially homogeneous by gc and nmr: nmr (CCl_4) δ 1.22 (angular CH_3), 1.95 and 2.07 (CH_3CO-) and 4.5-5.4 (-CH-O); ms Calcd for $C_{15}H_{22}O_4$ 266.1518, Found 266.1513. The mixture of *cis*-2 and *trans*-2 then results from the basic hydrolysis of the enol acetate.





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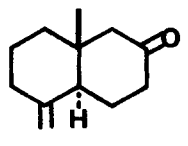

11

As a demonstration of the synthetic utility of this cyclization and as further proof of structure, ketoalcohol 2 was converted to the known[1] ketone 11. Treatment of ketoalcohol 6 with methylene triphenylphosphorane in DMSO at rt for 24 hrs gave, after evaporative distillation (0.25 mm/110°), the *trans*-alcohol 10 in 67% yield:[13] ir (neat) 3350 (OH), 1650 and 880 cm^{-1} ($C=CH_2$); nmr (CCl_4) δ 0.74 ppm (s, 3H, angular CH_3), 4.0-3.6 (m, 1H, -CHO-), 4.44 (m, 1H, vinyl proton) and 4.69 (m, 1H, vinyl proton); ms Calcd for $C_{12}H_{20}O$ 180.1514, Found 180.1513; *Anal.* Calcd for $C_{12}H_{20}O$ C 79.94, H 11.18, Found C 79.65, H 11.37. The nmr spectrum indicated that no more than a few percent of the *cis* isomer could be present. Alcohol 10 was oxidized with Collin's reagent to give, after evaporative distillation (0.25 mm/90°), ketoolefin 11 in 89% yield: ir (neat) 1715 (C=O), 3100, 1650, and 880 cm^{-1} ($C=CH_2$); nmr (CCl_4) δ 0.72 (s, 3H, angular CH_3), 4.52 (m, 1H, vinyl proton) and 4.81 (m, 1H, vinyl proton). The ir and nmr spectra of ketone 11 were essentially identical with the corresponding spectra of an authentic sample of this ketone.[1a,14] The synthesis of ketone 11 constitutes a formal total synthesis of β-eudesmol, atractylon, and isoalantolactone,[1] and demonstrates the utility of this type of cyclization in synthesis.

Further experiments on the scope and mechanism of cation-olefin cyclizations of α,β-unsaturated ketones are in progress.

Acknowledgements.

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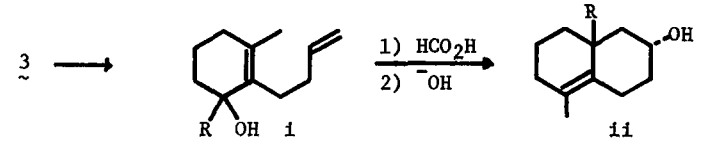
2. For the previous paper in this series see K. E. Harding and W. D. Nash, *Synth. Commun.*, *7*, 19 (1977).
3. Previous conversions of ketone 3 to synthetically useful bicyclic intermediates have involved conversion to an allylic alcohol followed by formic acid cyclization (3 → i → ii).[4,5]



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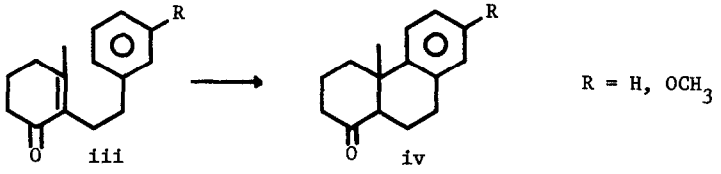
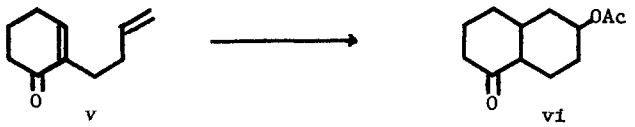


8. Subsequent to our initial investigations in this area we learned that R. Wightman and W. S. Johnson[9] effected the cyclization of dienone v to keto acetate vi in good yield by treatment at room temperature with boron trifluoride etherate in acetic acid, but found (as we have confirmed) that dienone 3 was unreactive under the same conditions.



9. R. Wightman, Research Report to W. S. Johnson, Stanford University, 1965. We thank Professor Johnson for communicating these results to us.
10. W. S. Johnson, M. I. Dawson, and B. E. Ratcliffe, *J. Org. Chem.*, *42*, 153 (1977).
11. These assignments are based on analogy to the assignments for the octolones vii and viii. A. van der Gen, K. Wiedhaup, J. J. Swoboda, H. C. Dunathan and W. S. Johnson, *J. Amer. Chem. Soc.*, *95*, 2656 (1973). See also footnote 17 in the above paper.

12. W. S. Johnson, W. H. Lunn and K. Fitzi, *J. Amer. Chem. Soc.*, *86*, 1972 (1964).
13. For other examples of Wittig reactions with epimerizable 1-decalones giving the *trans*-fused olefin see: F. E. Ziegler and J. A. Kloek, *Tetrahedron*, *33*, 373 (1977); J. A. Marshall, W. F. Huffman and J. A. Ruth, *J. Amer. Chem. Soc.*, *94*, 4691 (1972); J. A. Huffman, *J. Org. Chem.*, *37*, 13 (1972); C. H. Heathcock and R. Ratcliffe, *J. Amer. Chem. Soc.*, *93*, 1746 (1971); J. A. Marshall, M. T. Pike and R. D. Carrol, *J. Org. Chem.*, *31*, 2933 (1966).
14. We thank Prof. R. B. Miller for kindly supplying us with spectra and an authentic sample of ketone 11.