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SOLVOLYTIC HYDROPEROXIDE REARRANGEMENTS III. Stereoselective Rearrangements of Methylated Cyclopropyl Carbinols.

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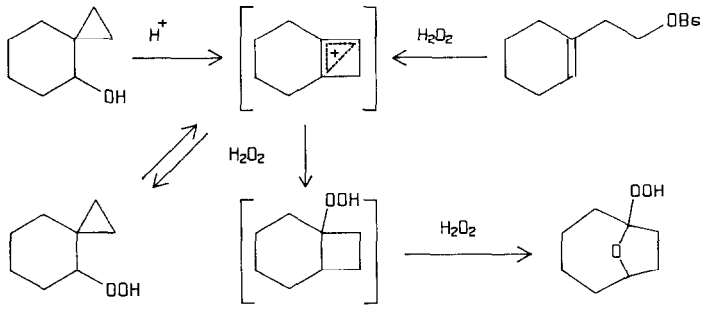
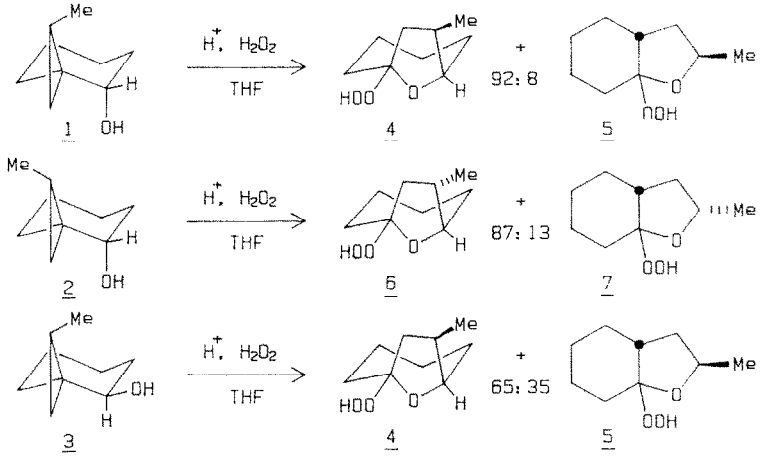
Abstract: Solvolysis of 1-methylspiro[5,2]octan-4-ols, **1-3**, in acidified THF-90% H_2O_2 through a combination of cyclopropylcarbinyl and Criegee rearrangements constitutes a new stereoselective synthesis of 3-alkyl-4-hydroxycyclooctanones.

We have recently shown that the reaction of certain cyclopropyl carbinols and homoallylic brosylates in THF-H_2O_2[1] results in the formation of 2-hydroperoxy tetrahydrofurans via capture of cyclopropylcarbinyl-bicyclobutonium ions followed by a Criegee rearrangement[2] of a cyclobutyl hydroperoxide intermediate.

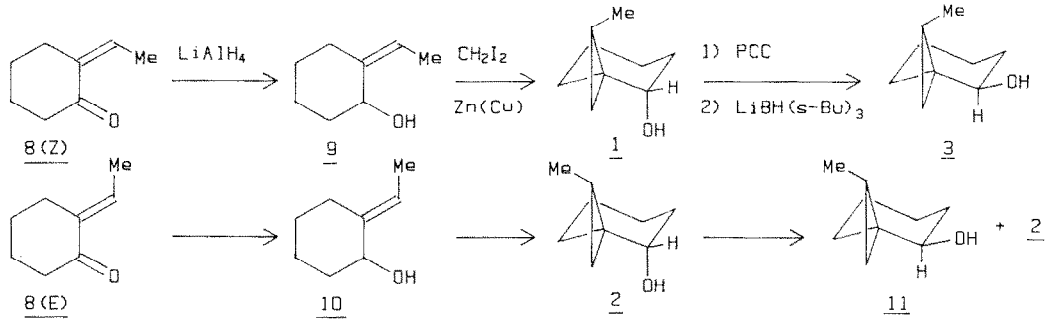


These peroxide mediated solvolytic rearrangements involve participation of the cyclopropane ring in formation of a bicyclobutonium ion which can subsequently be trapped with H_2O_2 to afford either a cyclopropylcarbinyl or cyclobutyl hydroperoxide. While the higher reactivity of the cyclopropylcarbinyl isomer toward re-ionization renders it solvolytically active in the system, the attenuated solvolytic activity of the cyclobutyl isomer, when coupled with its increased propensity to undergo an electron deficient oxygen migration, causes a bifurcation in the reaction pathway to make the formation of cyclobutyl hydroperoxides (and thus ring expansion products) appear to be essentially non-reversible. Thus, the initial 1,2-shift of one of the cyclopropane ring positions should be the primary determinant of stereoselection in these rearrangements. The subsequent steps in the rearrangement process would not be expected to affect significantly the overall diastereoselection of the reaction, except for the migratory selection in the Criegee rearrangement whereby bridged or fused furanoid products are generated. The Criegee reaction, like other electron deficient heteroatom rearrangements, occurs with retention of configuration of the migrating center[3].

Additional studies showed that axial cyclopropyl carbinols afforded ring expansion products with useful levels of stereochemical control[4]. Analysis of the various steps involved in the H_2O_2 mediated reaction of cyclopropyl carbinols suggested that the crucial event with respect to stereochemical control should be which of the cyclopropane ring carbons would be selected for migration in the formation of the bicyclobutonium cationic intermediate[5]. To assess the relative importance of the factors involved in the stereochemistry of these rearrangements we undertook an investigation of the reactions of the isomeric 1-methyl-spiro[5,2]octane-4-ols **1-3** in acidified H_2O_2-THF since such a study would provide useful information about migratory aptitudes and steric effects in the steps prior to the formation of the cyclobutyl hydroperoxide as well as the subsequent electron-deficient oxygen rearrangement.



To prepare substrates **1-3**, the E and Z isomers of 2-ethylidene cyclohexanone, **8**, (Wiley Organics) were separated by chomatography on silica gel. Reduction with $LiAlH_4$ afforded the *syn* and *anti*-2-ethylidene cyclohexanols, **9** and **10**. Simmons-Smith cyclopropanation with freshly made zinc-copper couple[6] yielded selectively *trans-syn*, **1**, and *trans-anti*, **2**, carbinols. The *cis-syn* carbinol, **3**, was obtained by oxidation of **1** with pyridinium chlorochromate followed by reduction with $LiHB(sec\text{-}Bu)_3$. Analogous treatment of **2** to prepare the *cis-anti* isomer, **11**, afforded only inseparable mixtures of **11** and *trans-anti* isomer, **2**. Thus, the *cis-anti* carbinol **11** was unavailable for these studies[7].



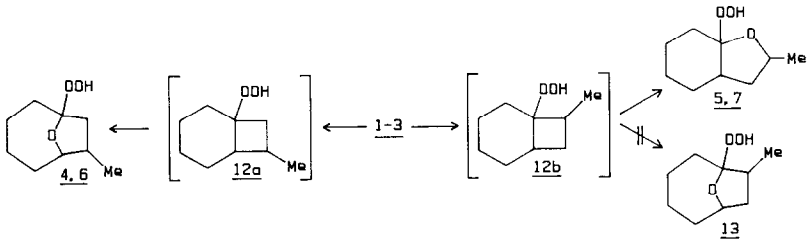
Substrates **1-3** in acidified THF-90% H_2O_2 afforded a mixture of ring expanded rearrangement products (60-80%) and minor amounts of cyclopropylcarbinyl hydro-

peroxide substitution products[8]. Initial experiments were carried out at room temperature in 1:1 THF-H_2O_2; under these conditions ring expansion products from both C-1(methine) and C-2(methylene) migrations were obtained. The selectivity for methine migration was greatly improved by decreasing both the temperature and proportion of H_2O_2. The best selectivities were obtained using a 4:1 THF-H_2O_2 mixture at 0 °C[9]. For example, solvolysis of **1** in 1:1 THF-H_2O_2 at 25 °C afforded a 80:20 mixture of **4** and **5**; in 4:1 THF-H_2O_2 at 0 °C a 92:8 ratio was obtained[10]. Similarly, the ratios of **6** to **7** from the solvolysis of **2** rose from 50:50 to 87:13. It is significant that there appeared to be no measurable cross-over in the solvolyses of the syn and anti precursors; that is, **4** was obtained only from **1** and **3** (*syn* substrates) and **6** was obtained only from **2** (*anti* substrate). This implies that the migration of the cyclopropane ring position to the cyclobutyl hydroperoxide occurs with retention of stereochemistry[11].

The selectivities can be rationalized on the basis of a combination of conformational and migratory preference factors. In substrates **1** and **2**, favorable *trans* geometry for migration of the methine is extant when these substrates have diaxial conformations for the hydroxyl and the cyclopropane methine[12]. Such conformations are favored owing to relief of steric interactions of the cyclopropyl methyl group in a manner similar to the A-strain of allylic alcohols. An axial cyclopropyl carbinol should also be favored electronically as well; overlap of the C-O σ^* with orbitals of the cyclopropane stabilizes conformations in which the hydroxyl is axial[13]. This effect would be enhanced by protonation of the hydroxyl, and by solvents of decreased polarity. We do observe increased selectivity in solvent mixtures containing a larger fraction of THF.

The lower level of selectivity observed in the rearrangement of **3** is possibly conformational in origin. A-strain between the *cis-syn* methyl and the hydroxyl group favors conformers in which the hydroxyl is equatorial[14]. The orbitals of the equatorial hydroxyl are not well positioned to overlap with the cyclopropane ring so that ionization can lead directly to either a bisected-cyclopropylcarbinyl cation[15] or a bicyclobutonium ion. This could be critical in the migration of the methine center; either the rearrangement is taking place from an ion that might best be described as a cyclopropylcarbinyl cation, or else a rather disturbing frontside migration of the methine needs to be invoked to explain the large proportion of **4** obtained in the rearrangement of **3**.

These rearrangements also shed some light on the migrational selectivities of the Criegee rearrangement. It is interesting that the choice between similar groups results in preferential migration to form fused rather than bridged products. Thus, Criegee rearrangement of the putative cyclobutyl hydroperoxide **12b** results only in the formation of **5** and not the bridged product **13**; whereas in the isomeric hydroperoxide **12a** the choice between fused, **5**, and bridged, **4**, products is made upon the basis of migratory preferences between methine and methylene groups and results in only bridgehead migration.



Thus, in the peroxide mediated rearrangement of these spirooctanols, the more substituted cyclopropane center will be expected to migrate preferentially, especially if the ionic precursors (hydronium ions) arise from axial hydroxyl. The rearrangement will occur with retention of the stereochemistry of the migrating terminus. Ring-expansion of the cyclobutyl hydroperoxide will afford fused bicyclic products in the absense of factors such as differential migratory aptitudes which would favor the bridged-bicyclic product. When these conditions can be met, these reactions constitute a novel route to stereoselectively substituted 3-alkyl-4-hydroxy-cyclooctanone derivatives.

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7) Satisfactory spectral and analytical data were obtained for all compounds.

8) After purification by chromatography, structural assignments of rearrangement products were made spectroscopically, followed by reduction (H_2/Pt) to hydroxyketones which were analyzed separately.

9) In a typical procedure, a solution of **2** (237mg, 1.69mmole) was dissolved in THF (16mL) and chilled to 0 °C. To this was carefully added 90% H_2O_2 [FMC Corp.] (4mL, 144mmole H_2O_2) followed by TsOH·H_2O (4mg, 0.02mmole). The flask was closed with a wad of cotton (to prevent the entry of particulates which could catalyze the decomposition of the H_2O_2) and stirred at 0 °C for 18h to afford a 87:13 mixture of **8** and **9** in 60% yield after aqueous work-up and chromatography on silica gel (5% Et_2O–light petroleum).

10) Isomer ratios were determined by integration of the characteristic OO-H resonances which are typically δ8-10 in $CDCl_3$. The ratios were subsequently confirmed by preparative TLC.

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14) The calculated difference (MM2) between axial and equatorial hydroxyls in **1** is 0.9 kcal/mole in favor of the axial conformer; for **3** the conformer with an equatorial hydroxyl appeared favored by 0.5 kcal/mole.

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