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SOLVOLYTIC HYDROPEROXIDE REARRANGEMENTS IV.

Selective Rearrangement of Spiro[5,2]octan-4-ol.

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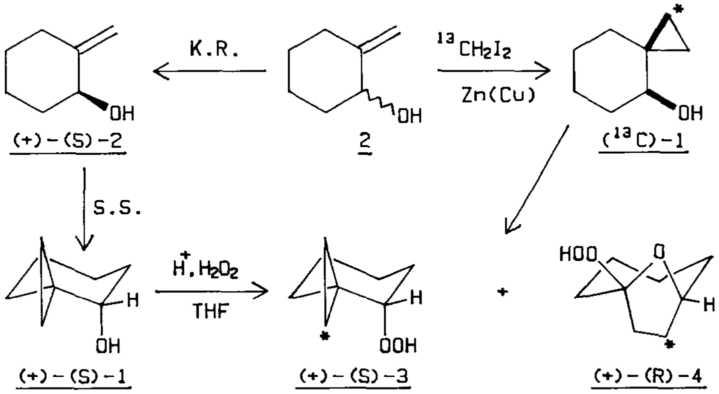
Abstract: Rearrangement of spiro[5,2]octan-4-ol, 1, in acidified THF-H_2O_2 *is a selective process in which substitution occurs with retention of configuration and ring-expansion with inversion of the carbinyl center.*

Recently, we reported that rearrangements of certain cyclopropyl carbinols in acidified 90% H_2O_2-THF occur stereoselectively to afford ring-expansion products with defined stereochemistry[1,2]. In this study we now show that these reactions are inherently asymmetric and that the preferred mode of reaction, in the absence of modifying substituents, is an unexpected frontside migration of a cyclopropane methylene group resulting in formation of ring expansion products with overall inversion of configuration at the carbinyl center[3]. Analysis of the substitution and ring-expansion products strongly suggests that these arise from a common, asymmetric, ionic precursor which is trapped by nucleophilic H_2O_2. Asymmetric cyclopropylcarbinyl-bicyclobutonium cations have previously been postulated in the solvolysis of certain cyclopropylcarbinyl systems[4].

This investigation was prompted by an nmr study on 1 which showed that axial conformers are stereoelectronically favored in solution[5]. Since some of our recent work has shown that selective peroxide mediated ring expansions occur most readily for axial carbinols[1,2], this nmr evidence suggested that a study to probe mechanistic details of these H_2O_2 mediated rearrangements, using isotopically labelled, and or, optically active 1, might be feasible.



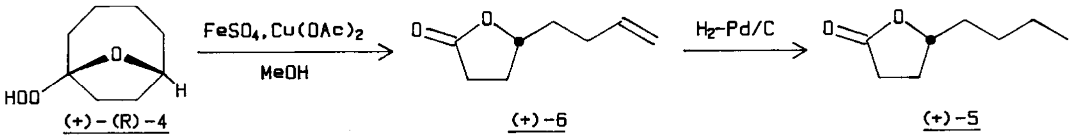
The substrates for this study were readily prepared from racemic 2-methylenecyclohexanol[6], 2. The optically active substrate, (+)-(S)-1, was obtained by kinetic resolution of 2 followed by cyclopropanation. Catalytic Sharpless epoxidation/resolution[7] of 2 was achieved using 0.17 eq (-)-DIPT[8], 0.13 eq $Ti(OPr)_4$ with 4A molecular sieves[9] in CH_2Cl_2 aged at -25 °C for 1h before the addition of 0.67eq of TBHP in toluene. After 20h at -25 °C the mixture was worked up by quenching with 10% aq NaOH in saturated brine, filtration, and rapid chromatography on silica gel (eluted with Et_2O-light petroleum). A 46% yield of (+)-(S)-2, $[\alpha]^{25}_D$ +6.7° ($CHCl_3$), was obtained[10], and shown by Mosher ester analysis to be 80% ee. The epoxy alcohols from this reaction were obtained as a mixture of diastereoisomers which were hydrolytically quite reactive and not processed further[11]. Simmons-Smith cyclopropanation of (+)-2 afforded (+)-1, which upon standing for a few days, crystallized in long flat needles. Re-crystallization from pentane to constant rotation gave material, $[\alpha]^{20}_D$ +67° ($CHCl_3$), mp 46-48 °C. The ^{19}F nmr spectrum of the Mosher ester had only a single peak at δ -71.51[12].

Isotopically labeled (^{13}C)-1 was obtained by Simmons-Smith cyclo-propanation of racemic 2 using $^{13}CH_2I_2$ in pentane. As in the epoxidation above, the stereoselectivity of the cyclopropanation was modest, and only a 6:1 syn/anti ratio was obtained[13]. When the reaction was run in Et_2O the syn/anti ratio was 1:1.

Peroxide mediated rearrangement[14] of (+)-1 (198 mg, 1.57 mmoles) at 21 °C in 2:1 THF-90% H_2O_2 (4.5 mL) catalyzed by $TsOH\text{-}H_2O$ (24.5 mg, 0.13 mmoles, added as a solution in 0.5 mL THF) gave a 3:1 mixture of substitution and ring-expansion products when the reaction was quenched as soon as the carbinol had all reacted (≃30 min). Rapid chromatography of the crude product on silica gel (eluted with 20% Et_2O-light petroleum) afforded the cyclopropyl-carbinyl hydroperoxide, (+)-3, (159 mg, 71%), $[\alpha]^{22}_D$ +40° (c = 2.75 $CHCl_3$) and the oxa-bicyclo hydroperoxide, (+)-4, (65 mg, 26%), $[\alpha]^{22}_D$ +32° (c = 1.99 $CHCl_3$). This corresponds to 39% ee in the formation of (+)-4, *vida infra*. Reduction of 3 with $LiAlH_4$ followed by kugelrohr distillation at 80 °C (0.05mm) afforded a sample of 1 $[\alpha]^{25}_D$ +28° (c = 2.40 $CHCl_3$)(40% ee). This corresponds to 70% retention in the formation of (+)-3.

In a separate experiment using 55.6 mg of (+)-1 in 1:1 THF-H_2O_2 at 23-25 °C a 2.5:1 mixture of (+)-3 $[\alpha]^{22}_D$ +32.7° (c = 1.42 $CHCl_3$), and (+)-4 $[\alpha]^{22}_D$ + 27.3° (c = 0.63 $CHCl_3$) was obtained in 64% overall yield. Reduction of the (+)-3 with $LiAlH_4$ and conversion to the Mosher ester gave material that had ^{19}F nmr signals at δ -71.51 and -71.41 in a ratio of 66.4 : 33.6. Hydrogenation of the (+)-4 with Adam's catalyst and conversion of the hydroxyketone product to the Mosher ester gave material with ^{19}F nmr signals at δ -71.47 and -71.37 in a ratio of 66.4 : 33.6[15]. The fact that both 3 and 4 were formed with essentially the same enantiomeric excess is strongly suggestive that both originate from a common, asymmetric, ionic precursor.

While the optical rotations and Mosher ester chemical shifts clearly support retention in the formation of 3, these methods do not provide information about the stereochemistry of the ring-expansion product 4. The configuration of (+)-4 was determined by conversion to optically active 4-butyl-butyrolactone, (+)-5. Radical-induced, reductive cleavage of (+)-4 (65 mg, α = +32°) with $Cu(OAc)_2$ and $FeSO_4$ in methanol[16] resulted in formation of the butenyl-butanolide (+)-6[17], 27 mg, bp 75 °C (0.01mm), $[\alpha]^{23}_D$ +22° (c = 1.17 MeOH). Hydrogenation (H_2-Pd/C, 20 psi) afforded the saturated lactone (+)-5, 23 mg, bp 75 °C (0.05mm), $[\alpha]^{25}_D$ +19° (c = 0.965 MeOH). All of the reported, dextrorotatory, saturated 5-alkyl-2(3H)-dihydrofuranones have been shown to have the R configuration[18]. Thus, (+)-5 and (+)-4 must have the same configuration, R, and (+)-(R)-4 must be formed from (+)-(S)-1 with inversion of configuration at the carbinyl center. This also implies that the inversion is accomplished by a very unusual frontside, or *syn* migration, in formation of the ion that leads to the putative cyclobutyl hydroperoxide that undergoes the Criegee migration.



The frontside migration in the formation of 4 was confirmed using (^{13}C)-1. Rearrangement in THF-H_2O_2 afforded (^{13}C)-4 with enhanced carbon signals at δ 30.46 and 32.66 with an intensity ratio of 74:26, respectively[19]. The selective enhancement of the C_7 resonance in (^{13}C)-4 can only be accommodated if frontside, or *syn*, migration of the cyclopropane methylene occurs in the formation of the crucial ionic intermediate that leads to the Criegee rearrangement product. *Syn* migration of the cyclopropane methylene group ultimately leads to overall inversion in the ring expansion product.

While the selectivities observed in the rearrangement of 1 are only modest, this work provides important mechanistic insights into these reactions which are applicable to more complex systems. These studies show that the preferred mode of peroxide mediated ring expansion for spiro[5,2]-octan-4-ols involves *syn* migration of the cyclopropane (inversion) followed by Criegee rearrangement with retention resulting in overall inversion of configuration. When additional substituents are present which produce a substantial conformational bias, significantly higher levels of selectivity can be obtained[20]. We are currently investigating similar rearrangements in other larger ring systems.

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References and Notes.

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2) Ronald, R. C.; Lillie, T. S. *Tetrahedron Lett.* in press.

3) We previously reported retention during ring expansion of 6-*tert*-butylspiro-[5,2]octan-4-ol, see ref. 1. In light of the results of the present study, that stereochemical assignment, made on the basis of ^1H nmr spectra, is questionable. We are currently attempting to resolve this ambiguity by X-ray crystallography.

4) Poulter, C. D.; Spillner, C. J.; *J. Am. Chem. Soc.* **1974**, *96*, 7591-7593. For reviews on cyclopropylcarbinyl rearrangements see: P. D. Bartlett, *Nonclassical Ions*, W. A. Benjamin, Menlo Park, Calif., 1965; M. Hanack and H.-J. Schneider, *Angew. Chem., Intl. Ed. Engl.* **1967**, *6*, 666; G. A. Olah and P. v.R. Schleyer, Ed., *Carbonium Ions*, Vol III, J. Wiley, New York, 1972; H. C. Brown, *The Nonclassical Ion Problem*, Plenum, New York, 1972.

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7) Martin, V.; Woodard, S.; Katsuki, T.; Yamada, Y.; Sharpless, K. B.; *J. Am. Chem. Soc.* **1983**, *103*, 6237-6240.

8) (-)-Diisopropyl tartrate. The model in ref. 5 predicts that the unreacted allylic alcohol should be enriched in the (S)-enantiomer.

9) R. M. Hanson and K. B. Sharpless, unpublished results.

10) The calculated rotation of pure (+)-(S)-2 is +8.3°. The (S) configuration predicted by ref. 5 was confirmed by ozonolysis of a sample of (+)-2 (70% ee) at -78 °C, Me_2S workup, and conversion of the resulting 2-hydroxycyclohexanone to the phenylhydrazone, $[\alpha]^{20}_{D}$ +64° (c = 1.78 EtOH). The phenylhydrazone of (R)-2-hydroxycyclohexanone (69% ee) is reported to have a rotation of -57° (EtOH); Posternak, T.; Reymond, D.; Friedli, H., *Helv. Chim. Acta*. **1955**, *38*, 205.

11). We obtained very poor material balance in isolation of the epoxy alcohols. These appeared to be very sensitive to hydrolysis as shown by their almost total destruction upon treatment with aq. NaOH that was not saturated with brine.

12) Dale, J.; Dull, D.; Mosher, H. S.; *J. Org. Chem*. **1969**, *34*, 2543-2549. Chemical shifts for ^{19}F were assigned using external CF_3Cl. All Mosher esters reported herein were prepared from the (+)-(R)-acid chloride $[\alpha]^{25}_{D}$ +134.7° (c = 5.46 CCl_4) using DMAP as a base.

13) Enhancements of C_2 and C_3 in the ^{13}C nmr: δ 9.25 and 10.08, intensity ratio 84:16. These are assigned the *syn* and *anti* stereochemistry, respectively, based on the directive effects of the hydroxyl group in the cyclopropanation of allylic alcohols. See: Simmons, H.; Cairns, T.; Vladuchick, S.; Hoiness, C.; *Org. React*. **1973**, *20*, 1-131.

14) Consult ref. 1 for procedures for the safe handling of high strength H_2O_2 mixtures with organic solvents.

15) From these results the calculated rotation for (+)-3 is +99.7° ,and for (+)-4 is +83.2°.

16) Schreiber, S. L.; *J. Am. Chem. Soc*. **1980**, *103*, 6163-6165.

17) Satisfactory spectral and analytical data were obtained for new compounds.

18) Tuynenburg-Muys, G.; van der Ven, B.; Jorge, A.; *Applied Microbiology* **1963**, *11*, 389-93; Mori, K.; *Tetrahedron* **1975**, *31*, 1381; Uzi, R.; Silverstein, R.; Smith, L.; *Tetrahedron* **1978**, *34*, 1449-1452.

19) A combination of heteronuclear decoupling and deuterium labelling experiments have enabled us to make assignments of the ^{13}C nmr spectra of 1 and 4. For **1**: δ 21.46 (C_1); 9.25 (C_2); 10.08 (C_3); 72.94 (C_4). For 4: δ 115.45 (C_1); 35.83 (C_2); 22.94, 24.11 (C_3, C_4); 36.60 (C_5); 77.44 (C_6); 30.40 (C_7); 32.57 (C_8). The critical assignment of the C_7 and C_8 resonances was made by reduction (H_2-PtO_2) of 4 to the hydroxyketone followed by deuteration (D_2O-THF, 3:1, catalytic K_2CO_3, 24h). Reformation of 4 [THF-H_2O_2 (1:1), TsOH] afforded material that was deuterated at C_2 and C_8. The proton decoupled ^{13}C spectrum of this material showed only residual signals at δ 35.83 and 32.57, thus allowing the distinction between C_2 and C_5, and C_7 and C_8 to be made unambiguously.

20) Please see the following article in this issue.

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