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SOLVOLYTIC HYDROPEROXIDE REARRANGEMENTS V.
A Stereoselective Synthesis of *trans*-Fused Butyrolactones.

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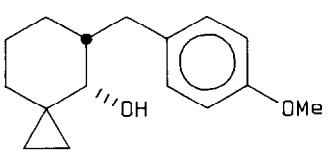
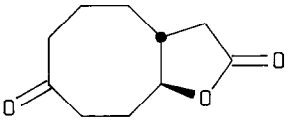
Abstract: Stereoselective rearrangement of cis-5-(4-methoxybenzyl)-spiro[5,2]-octan-4-ol cis-1 in acidified THF-90% H_2O_2 affords 9-oxabicyclo[6.2.1]nonyl hydroperoxides 7 and 8 which are converted to medium-ring, keto-butyrolactones 2 and 3.

In the previous paper we have described a stereoselective rearrangement of spiro[5,2]octan-4-ol in high strength H_2O_2 which resulted in ring- expansion with overall inversion of configuration at the carbinyl center[1]. We report herein how this rearrangement may be exploited in a short and efficient synthesis of keto-lactones 2 and 3. Our strategy for lactone synthesis introduces the acetic acid residue of the lactone in masked form as a 5-alkyl group in the spiro[5,2]-octan-4-ol, **cis-1**. When this side chain (which at a later stage is oxidatively unmasked to elaborate the carboxy-methyl of the lactone) has a *cis* relationship with the cyclopropyl carbinol it also serves as a conformational anchor to maximize the amount of axial hydroxyl which is favorable for ring expansion[2]. For the 5-alkyl substituent we selected the *p*-anisyl group which can be introduced via alkyl-ation of spiro[5,2]octan-4-one, 4 (a ketone readily available in one step from cyclo-hexanone[3]), and converted to a carboxymethyl group by oxidation. Peroxide mediated ring expansion of the carbinol accompanied by inversion generated a *trans* relationship between the C-4 and C-5 groups which formed the lactone ring after ozonolysis. Since a large number of natural systems have *trans* lactonic structures fused to rings of various sizes the methodology presented herein should be quite useful.



cis-1



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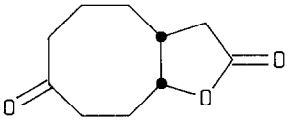
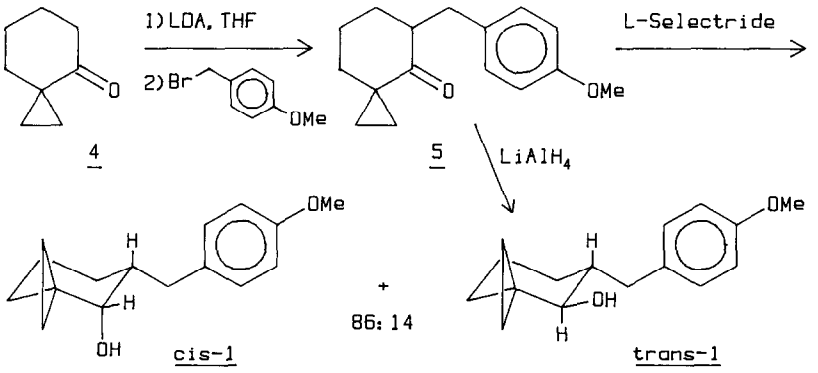


3

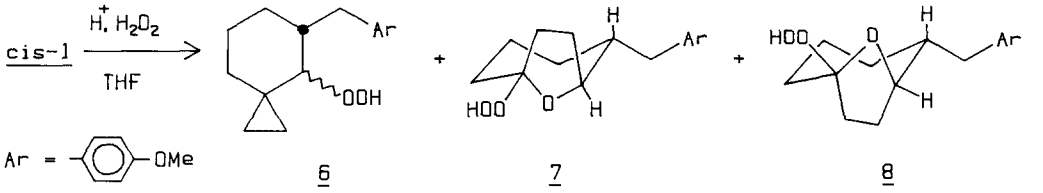
Alkylation of the lithium enolate (LDA, THF, 0 °C) of 4 with 4-methoxy benzyl bromide[4] (excess halide, inverse addition, 0 °C, THF) afforded the monoalkyl ketone, 5, in 58% yield after chromatography on silica gel (5% Et_2O-light petroleum)(mp 41-43 °C, from pentane)[5]. The oily, more mobile, dialkylated ketone (20-40%) was easily removed by this chromatography.

Reduction of 5 with L-selectride in THF at 0 °C afforded a quantitative yield of the alcohols, **cis-1** and **trans-1**, in an 86:14 ratio by HPLC (silica, 1% THF-CH_2Cl_2). Reduction of 5 with $LiAlH_4$ afforded **trans-1** (mp 89-90 °C, from CH_2Cl_2-iPr_2O). Separation of the desired

cis-1 from trans-1 was accomplished by low temperature recrystallization (-25 °C, pentane) after seeding with a small amount of trans-1; oily cis-1 (97% cis by HPLC) was retained in the mother liquors. The trans-1 recovered from this separation was 98% *trans* by HPLC.



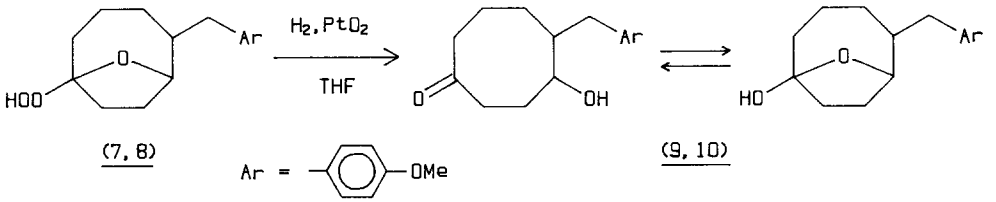
The carbinol isomers were easily distinguished by ^{1}H-nmr; the carbinyl proton of cis-1 was a broadened singlet at δ 2.67 and the cyclopropane protons were a broadened multiplet centered around δ 0.26. In contrast, the carbinyl proton of trans-1 appeared as a doublet of doublets at δ 3.29 (J_a=8Hz, J_b=5Hz), and the cyclopropanes were split into two multiplets at δ 0.20 and δ 0.58 which each integrated for two protons. The unusually high resonance of the equatorial carbinyl proton of cis-1 is probably due to shielding by the flanking cyclopropane ring and perhaps by the aromatic ring.



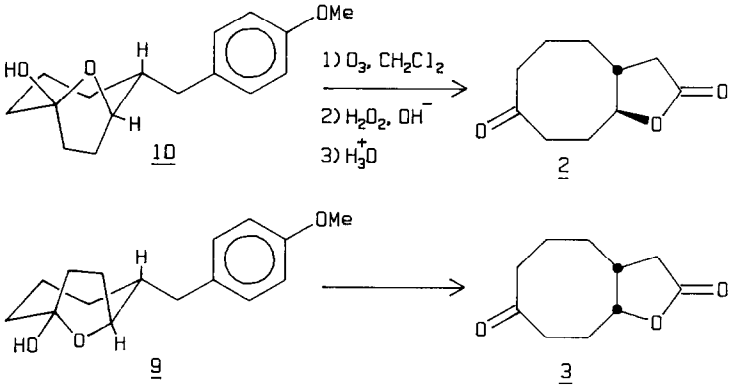
Peroxide mediated rearrangement of cis-1 occurred readily in acidified THF-H_2O_2, even at temperatures as low as -25 °C[6], to afford mixtures of sub-stitution and ring expansion products 6-8. In a typical procedure, cis-1 (330mg, 1.34 mmole)[97% *cis* by HPLC] was dissolved in THF (4 mL), cooled to 0 °C, and 90% H_2O_2 (4 mL) was carefully added[7]. The mixture was then placed in a 25 °C bath and TsOH·H_2O (25mg) was added. After 30 min the reaction mixture was quenched with H_2O and submitted to normal aqueous workup to yield 434 mg of crude, oily product which was chromatographed on silica gel (200g, eluted with a mixture of 25% ether-light petroleum), and separated into three main fractions. The most mobile fraction, 6, (TLC R_f 0.6), 67mg, was shown to be a mixture of cis and trans cyclopropyl carbinyl hydro-peroxides by reduction to a mixture (≈1:1) of cis- and trans-1. The second fraction, 7, (TLC R_f 0.4), 37mg (9.9%), mp 90-92.5 °C (from hexane) was the *cis* ring expansion product. The main fraction, 8, (TLC R_f 0.3), 293mg (79%), mp 77-78 °C (from iPr_2O), was the *trans* ring expansion product. The carbinyl proton of 8 was a broadened triplet at δ 4.39 (J=5Hz); for the *cis* isomer 7 this proton was a doublet at δ 4.25 (J=9Hz). The rearrangement of trans-1 was unselective. Under the conditions above, approximately a 1:1:1 mixture of 6, 7, and 8 was obtained.

Conversion of the rearrangement products 7 and 8 to keto-lactones 2 and 3 was accomplished by reduction of the hydroperoxy group followed by oxidative degradation of the

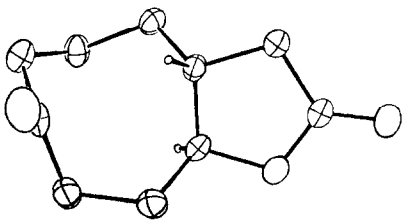
aromatic ring. Hydrogenation over PtO_2 in THF occurred rapidly when the catalyst was pre-reduced before the peroxy substrate was added. The oily reduction products 9 and 10 were each obtained as a mixture (as shown by IR spectroscopy) of bicyclic hemiketal and hydroxy-ketone forms. These were considerably more polar chromatographically than the parent hydro-peroxides. The reduction products 9 and 10, obtained from 7 and 8, respectively, were not distinguishable by TLC.



Oxidative degradation of the crude hydroxy-ketones to the keto-lactones was accomplished by a three stage, one-pot procedure. Exhaustive ozonolysis in CH_2Cl_2 at room temperature followed by decomposition of the ozonides with basic H_2O_2 served to "burn away" the methoxy-phenyl substituent to a carboxyl group. Upon acidification the keto-lactones were isolated directly. Thus, saturation at -78 °C of a solution of 10 (45 mg) in CH_2Cl_2 (2 mL) with ozone (ozonized oxygen) followed by removal of the cooling bath and continued ozonolysis at room temperature for 2h resulted in complete reaction of the starting material. The ozonides were decomposed by addition of 30% H_2O_2 (1 mL) and 10% aq. NaOH (1 mL); after 2h the mixture was acidified and extracted with CH_2Cl_2, washed with aq. $NaHCO_3$, and concentrated to afford lactone 2 in 77% yield. After chromatography on silica gel (25% Et_2O-CH_2Cl_2) crystalline *trans*-keto-lactone, 2, mp 102-103 °C (from $iPrO_2$), was obtained. Similarly, the oily *cis*-keto-lactone 3 was obtained from 9[8].



We obtained X-ray confirmation of the structure of the crystalline keto-lactone 2 which clearly showed the *trans* fusion of the lactone ring[9].



ORTEP plot of X-ray structure of the *trans*-keto-lactone 2.

Since *trans* fused lactones are typically more difficult to obtain synthetically, this simple, six step procedure constitutes a significant new route to these structures fused to medium to large rings[10]. We are currently investigating these ring-expansion lactonizations in other ring systems.

ACKNOWLEDGEMENTS. We thank the NIH (GM33034) for primary support of this work. The gift of the BOEING Co. of a Nicolet Technology Inc. 200 MHz NMR spectrometer to the Department of Chemistry is gratefully acknowledged.

References and Notes.

1) Please see the preceding article in this issue.

2) Lillie, T. S.; Ronald, R. C.; *J. Org. Chem.* **1985**, *50*, 5084-5088.

3) Ruder, S. M; Ronald, R. C.; *Tetrahedron Lett.* **1984**, *25*, 5501-5504. The reagent for this transformation, 2-chloroethyl dimethyl sulfonium iodide is now available from Aldrich Chemical Co.

4) This highly reactive bromide is readily prepared by shaking an Et_2O solution of 4-methoxy benzyl alcohol with concentrated HBr (aq.), washing with satd. aq. NaBr, drying with anhyd. K_2CO_3, and concentrating. The crude material so obtained is satisfactory for alkylation of enolate anions. It should be stored in the freezer as it will polymerize within a few days at room temperature.

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

6) For reasons of safety low temperatures are recommended for any large scale work. For example, we have rearranged 2.00g **cis-1** in 18 mL of 1:1 THF-H_2O_2 at -25 to-30 °C (freezer). The reaction required about seven days for completion and afforded a 1:10 ratio of **7** to **8**. From this reaction crystalline **8** was obtained in 63% yield, and the substitution product **6** was obtained in 20% yield.

7) For information on the safe handling of H_2O_2 in these rearrangements see: Ronald, R. C.; Lillie, T. S.; *J. Am. Chem. Soc.* **1983**, *105*, 5709-10.

8) The isomeric *cis* and *trans*-lactones were separable on a 25m SE-30 glass WCOT column at 200 °C: **3**, 5.12min; **2**, 5.35min; **2** and **3** were indistinguishable by TLC and LC on silica gel. No cross-over in the formation of the keto-lactones from the hydroperoxy-hemiketals could be detected; that is **7** produced only **3** and **8** afforded only **2**.

9) We thank P. Carroll of the Department of Chemistry, University of Pennsylvania for obtaining the X-ray structure of **2**.

10) For a recent review on the chemistry and biology of naturally occurring butyrolactones see: Hoffman, H. M. R.; Rabe, J.; *Angew. Chem. Int. Ed. Engl.* **1985**, *24*, 94-110.

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