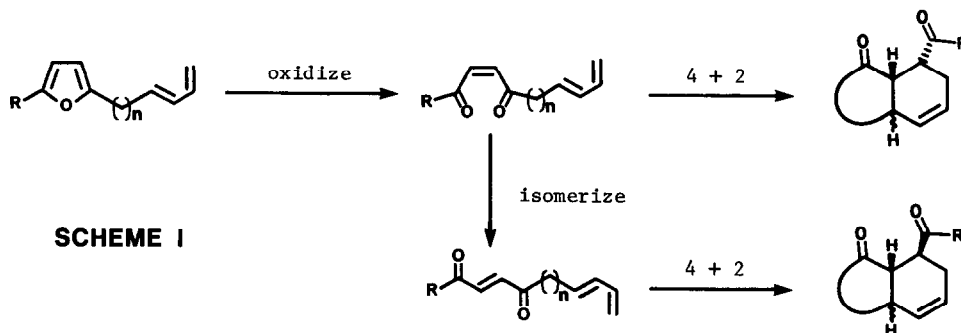


**OXIDATION OF FURANS II.
USE OF FURANS AS MASKED DIENOPHILES
IN THE INTRAMOLECULAR DIELS-ALDER REACTION**

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Summary: Chemoselective oxidation of alkadienylfurans using *m*-chloroperoxybenzoic acid gave trienes which underwent intramolecular Diels-Alder cycloaddition to hydrindenones.

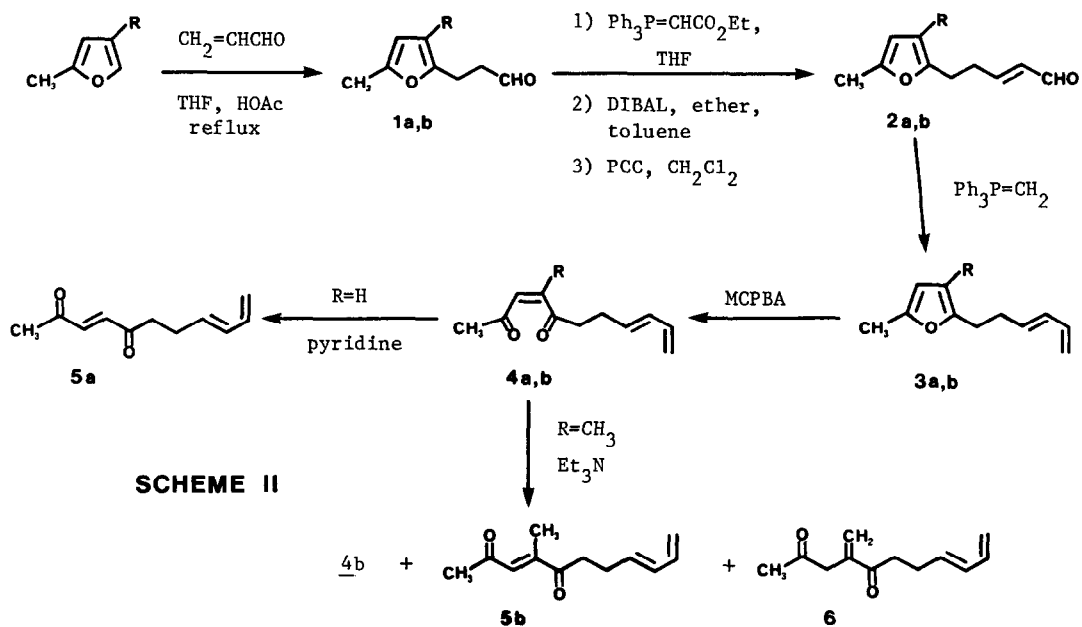
In a previous report we had demonstrated the efficacy of furan oxidation using *m*-chloroperoxybenzoic acid (MCPBA) by synthesizing a number of enedione-functionalized macrocycles from macrocyclic furan precursors.¹ With the advent of this mild, one-step procedure for the stereospecific conversion of 2,5-dialkylfurans to the corresponding *cis*-enediones,² we investigated other situations in which this transformation might be of preparative synthetic value. With the expectation that enediones should function well as dienophiles in the Diels-Alder reaction, attention was turned to the oxidation of alkadienylfurans (Scheme I). Chemoselective attack of the peracid at the electron-rich furan nucleus would give a triene which could then undergo intramolecular Diels-Alder cycloaddition.³ The synthetic utility of such a scheme might be further



enhanced by the possibilities for incorporation of additional substituents on the furan ring, and by control of the dienophile double bond geometry through isomerization of the kinetically produced *cis*-enedione. Herein we report implementation of this strategy for the synthesis of hydrindenones.⁴

Synthesis of the requisite hexadienylfurans **3a,b** (Scheme II) was accomplished in a straightforward manner using furylpropionaldehydes **1a,b**, which

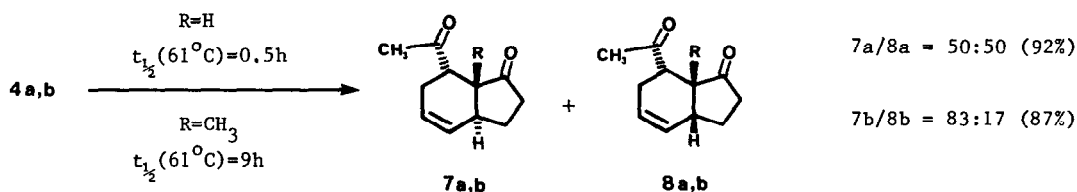
are readily prepared in multigram quantities by acid-catalyzed addition⁵ of 2-methylfuran or 2,4-dimethylfuran⁶ to acrolein. Homologation to the unsaturated aldehydes **2a,b** was brought about by Wittig olefination (97-99%), reduction to the allylic alcohol (92-96%), and oxidation (2 eq. PCC, CH₂Cl₂, 0°C to r.t., 2h, 58-68%). In this last operation it is noteworthy that there is selective oxidation of the allylic alcohol, as it is known that alkylfurans are oxidized by PCC to give trans-enediones.⁷ Methylenation (81-88%) provided **3a,b** exclusively as their E-isomers as judged by 250 MHz ¹H NMR.⁸



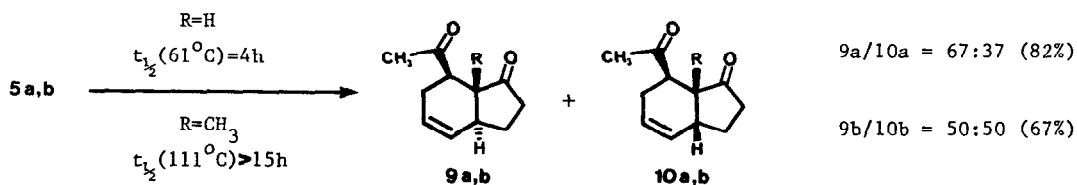
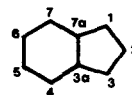
The oxidation chemoselectivity of these substrates using MCPBA was then examined. Treatment of **3a** with a slight deficiency of peracid (0.9 eq. MCPBA, CH₂Cl₂, -10°C to r.t., 2h) gave triene **4a** in 61% isolated yield (70% yield based on 13% recovered starting material). Diene oxidation had occurred only to the extent of 8% (the isolated yield of a mixture of internal and terminal allylic epoxides). Oxidation of **3b** using similar reaction conditions produced triene **4b** in 87% isolated yield (96% yield based on 10% recovered starting material), with diene oxidation being undetectable! This latter result no doubt stems from the electronic effect of increased alkyl substitution on the furan ring which renders it even more susceptible to electrophilic attack by the peracid. Secondary Baeyer-Villiger products, which form very rapidly during the MCPBA oxidation of certain tri- and tetrasubstituted furans,^{9,10} were not observed with **3b**.

Previous experience with the isomerization of cis-enediones¹¹ suggested that **4a** might be converted to **5a** upon exposure to pyridine. In the event

(excess pyridine, CH_2Cl_2 , r.t., 18h), trans-enedione **5a** was obtained in 40% yield, with intramolecular Diels-Alder products derived from **4a** accounting for the remainder of the mass balance. Similar conditions with **4b** using pyridine or 4-(*N,N*-dimethylamino)pyridine gave no reaction. Triethylamine however, gave an equilibrium mixture of **4b**, **5b**, and deconjugated isomer **6** in a ratio of 1:1.2:1.8. The trans isomer **5b** was easily separated by column chromatography, and the remaining two components could be recycled to give more **5b**.



SCHEME III

a series, $\text{R}=\text{H}$ b series, $\text{R}=\text{CH}_3$ 

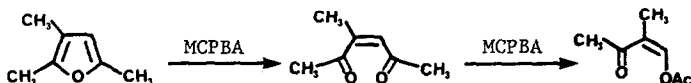
The Diels-Alder chemistry of the four trienes was then studied, and the results are summarized in Scheme III.¹² As indicated above, cis-enedione **4a** cyclized even at room temperature, giving equal amounts of the trans- and cis-fused hydrindenones **7a** ($J_{7a-3a}=13.6\text{Hz}$) and **8a** ($J_{7a-3a}=7.7\text{Hz}$). The trans-fused product **7a** was easily epimerized to the more stable cis-fused hydrindenone **10a** ($J_{7a-3a}=7.3\text{Hz}$) by weak acid or base.¹³ The trans-enedione **5a** cyclized more slowly¹⁴ to give a mixture favoring to a small extent the trans-fused product **9a** (J_{7a-3a} obscured). Not unexpectedly, methyl substitution on the dienophile slowed the rate of cyclization. Cis-enedione **4b**, however, exhibited the best selectivity, giving predominantly the trans-fused product (**7b**: $\delta\text{CH}_3-7a=0.89\text{ppm}^{4a}$; **8b**: $\delta\text{CH}_3-7a=1.14\text{ppm}^{4a}$). Trans-enedione **5b** cyclized at a much slower rate, even at higher temperature (111°C , toluene), giving equal amounts of trans- and cis-fused products. For preparative purposes, cyclization of **5b** was conducted at higher temperatures (195°C , sealed tube, toluene, 8h). The results of this study indicate that dienophile 1,2-diactivation, while having a favorable effect upon the rate of cyclization relative to other monoactivated systems, **4a,b,e-g** does not divert to a great extent the established preference^{4a-d,g} for exo cyclization of substrates possessing terminal dienophile activation.

During this study, a spectroscopic feature which aided in differentiating the *cis*- and *trans*-fused hydrindenones emerged from the ^{13}C NMR spectra: for each pair of products, the *trans*-fused isomer exhibited a C-1 chemical shift which was 4-5 ppm upfield of the corresponding resonance for the *cis*-fused isomer.¹⁵

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