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SYNTHESIS OF AN AZULENE LACTONE BY AN INTRAMOLECULAR [6+4] CYCLOADDITION

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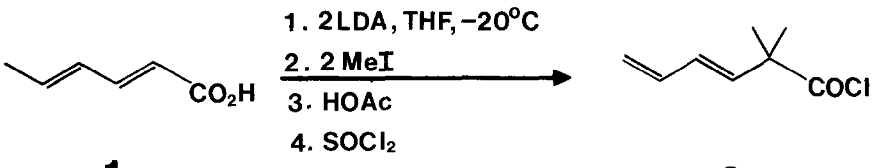
Summary: Intramolecular cycloadditions of 6-fulvenyl 2,2-dimethyl-3,5-hexadienoate produce both [6+4] and [4+2] adducts. The [6+4] adduct can be converted into an azulene lactone. Less highly substituted fulvenyl diene esters give analogous products in modest yields.

The hydroazulene lactone nucleus is present in many sesquiterpene natural products.[1] A variety of synthetic methods to these compounds have been developed.[2] We wish to report a new synthesis of hydroazulene lactones and a derived azulene lactone based upon the recently discovered intramolecular [6+4] cycloaddition.[3] The reactions reported here are not of general synthetic value, due to low stereoselectivity and competition between cycloaddition types. However, the incorporation of suitable activating substituents on the diene or fulvene[3] may lead to improved selectivity.



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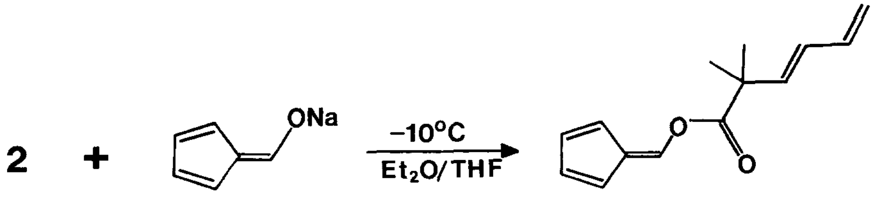

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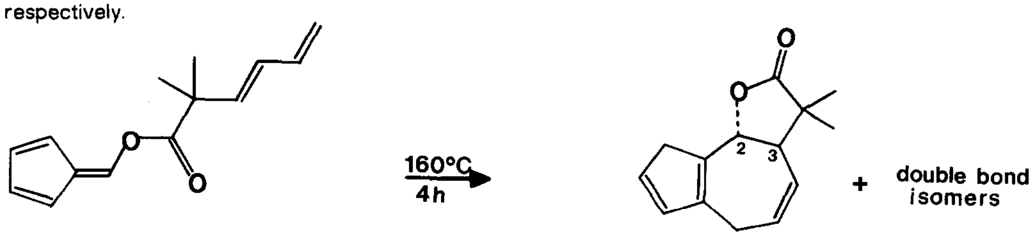
The 6-fulvenyl 2,2-dimethyl-3,5-hexadienoate, 3, was prepared in 29% overall yield from sorbic acid, 1, by the route shown above. The acid chloride, 2, was prepared by methylation of sorbic acid with LDA and methyl iodide, followed by reaction with thionyl chloride. The reaction of 2 with sodium formylcyclopentadienide[4] produces the light yellow fulvene, 3.

When a 1% solution of 3 was heated in toluene at 160°C for 4h, a mixture of cycloadducts was formed. These were separated by column chromatography to give 4 and 5 as colorless oils in 56% and 23% isolated yields, respectively.



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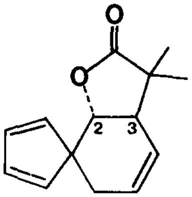

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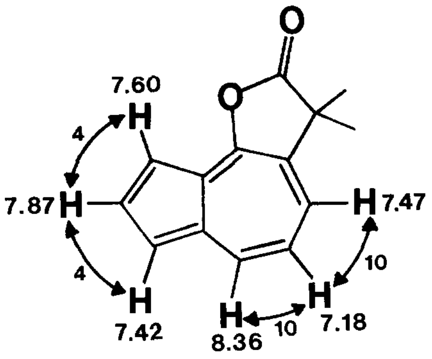
Adduct 4 is an inseparable mixture of rapidly interconverting cyclopentadiene isomers.[5] The nmr spectrum of this adduct has a singlet at δ1.26 for the two methyl groups, along with other less intense slightly offset singlets due to the cyclopentadiene isomers. The methine resonance at C-3 appears as a broad doublet at δ2.76. The C-2 methine is a doublet at δ4.99, $J_{2,3}$ = 10.7Hz, characteristic of a trans-fused lactone. Additional resonances indicate the presence of minor cyclopentadiene isomers, and possibly the presence of cis adducts as well.

Adduct 5 is a spiro-[4+2] adduct. The two methyl groups appeared as a singlet at δ1.31 in the nmr spectrum. A multiplet for the methylene protons appeared at δ1.95-2.04, the C-3 methine resonance is a multiplet at δ2.95, and the C-2 methine resonance is doublet at δ4.51 with J_{23} = 10.3Hz, indicative of a trans-fused lactone. The two olefinic protons of the six-membered ring appear as a multiplet at δ5.72-5.91 and the cyclopentadiene ring olefinic protons appear as multiplets at δ6.29 (1H), 6.39 (2H), and 6.43 (1H).

The hydroazulene lactone, 4, was dehydrogenated to the azulene lactone, 6, mp. 121-122° in 20% yield by refluxing 4 with sulfur in triglyme. The brilliant blue azulene, 6,[6] has a lactone carbonyl stretch at 1810cm^{-1} in the ir spectrum.

The nmr spectrum of 6 is summarized and compared to that of azulene,[7] below.



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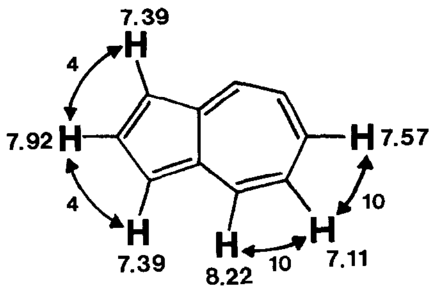
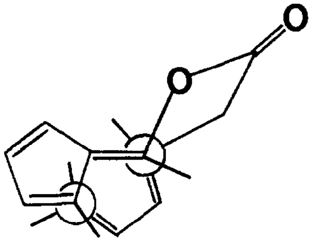


The formation of mainly the *trans* adducts of 4 is compatible with an *exo*-[6+4] transition state, 7, sketched below, as a double Newman projection along the forming bonds. This transition state requires that the ester adopt the unfavorable *anti* conformation. No exactly comparable Diels-Alder reactions are known.[8] The closest analogs have esters connected via attachment of the carbonyl group directly to a diene or a dienophile carbon. These generally give *cis*/*trans* mixtures, or upon suitable terminal activation of the dienophile, predominantly the *trans* product.[8,9] The reactions described are consistent with the *trans* preference expected for asynchronous transition states.[10]



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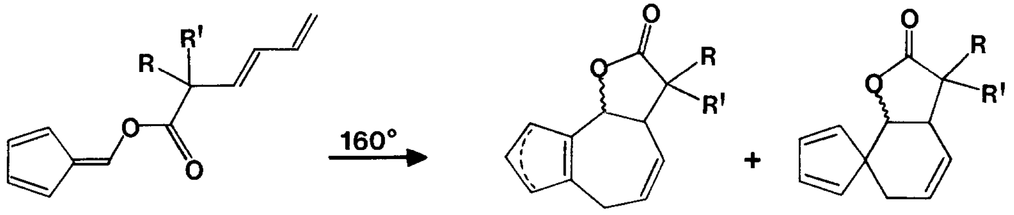
The unsubstituted and monomethyl analogs of 3 were prepared in an analogous fashion from sorbic acid and were pyrolyzed at 160°C. These reactions give complex mixtures which could not be adequately separated for complete characterization of adducts. The nmr spectra of the separated fractions indicate that the [6+4] adducts are formed as a mixture of cyclopentadiene isomers, as well as *cis* and *trans* isomers.

Data derived by comparisons of nmr spectra to those of 4 and 5, are given below.



R	R'		
H	H	52%	14%
Me	H	38%	17%
Me	Me	56%	23%

Studies of related reactions involving activated dienes, which should react faster and with greater selectivity, are in progress.

Acknowledgement. We are grateful to the National Institutes of Health for financial support of this research.

References and Notes

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