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ADDITION INITIATED RING CLOSURE
SUBSTITUTED SPIRO[4,2]HEPTA-1,3-DIENES via FULVENE INTERMEDIATES

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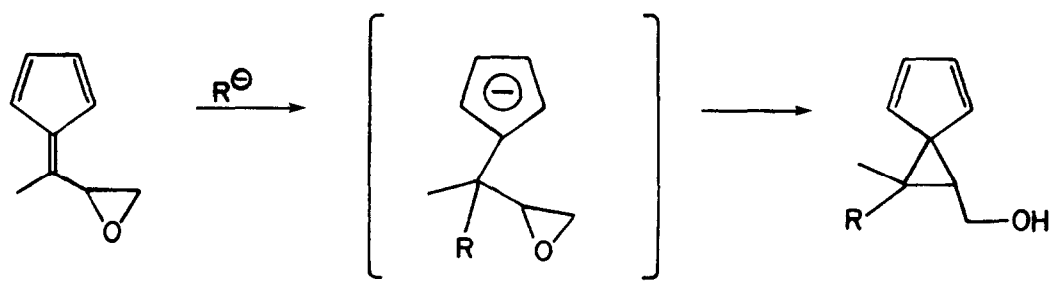
Abstract: The reactivity of the epoxy-fulvene **1** with various nucleophiles has been examined. It is a versatile intermediate for the preparation of spiro[4.2]hepta-1,3-diene synthons via nucleophilic addition to the C_6 position followed by intramolecular cyclization of the substituted cyclopentadiene anion generated *in situ*.

Synthetic routes involving sequential nucleophilic addition with the generation of a new nucleophilic centre that can react intramolecularly with another electrophile have particular appeal. These schemes require intermediates bearing several electrophilic sites and in principle, offer rapid synthetic access to an array of bridged, fused, conjoint, and spiro ring systems. This strategy, which is currently receiving considerable attention, is frequently initiated by a Michael addition (Michael initiated ring closure)[1-4].



1 **2** **3**

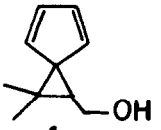
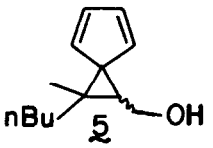
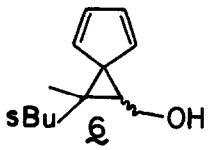
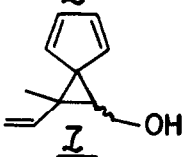
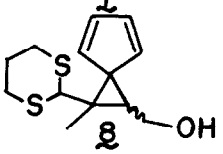
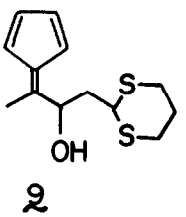
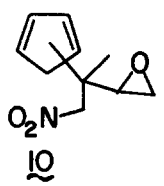
The use of substituted cyclopentadienes in natural product synthesis has frequently been complicated by the facile 1,5-sigmatropic rearrangements which these species undergo. One solution we have developed is to block the rearrangement with a cyclopropyl unit which may serve as a source of latent functionality[5,6]. We wish to report a general route to spiro[4.2]hepta-1,3-dienes ("blocked cyclopentadienes") from fulvene intermediates via *in situ* generation of substituted cyclopentadiene anions as illustrated.

It is well established that the exocyclic double bond in fulvenes is polarized and of similar reactivity to a carbonyl group[7]. Thus fulvenes have served as a source of substituted cyclopentadienes by both hydride reduction[8,9] and nucleophilic addition[10]. However with the exception of the preparation of β-vetivone by Buchi and co-workers[11] they have been underutilized in total synthesis.

A variety of bases have been employed for fulvene preparation[7] from carbonyl compounds. The mildest and most efficient tend to be amines[12]. In these studies a significant improvement in yield was achieved by using pyrrolidine as the catalyst. Thus condensation of cyclopentadiene with the epoxide derived from 3-butenone (30% H_2O_2, CH_3OH, 71%) in the presence of pyrrolidine (0°C, 2 h) afforded the epoxy-fulvene **1** in 86% yield (^1H nmr (CCl_4) δ: 1.91 (s, 3H, CH_3), 2.82 (m, 2H, CH_2-O), 3.90 (dd, 1H, J=1.5, 1 Hz, CH-O), 6.35 (m, 4H, HC=)). As anticipated, in spite of the presence of three major electrophilic sites, nucleophilic addition occurred preferentially at the C_6 fulvene centre to generate the cyclopentadiene intermediate **2** which cyclized to form the the cyclopropyl unit by *exo* cleavage of the epoxide as summarized for a variety of nucleophiles in the Table. The alternative cyclization to form a cyclobutane requires an *endo-tet* ring opening which is disfavoured[13-16]. The ^1H nmr spectrum of **4** is typical and displayed methyl singlets at δ 1.38 and 1.40, a triplet (J = 7 Hz) at 2.22 due to the cyclopropyl hydrogen, a doublet (J = 7 Hz) for the methylene protons at 3.71, and two overlapping multiplets at 6.30 representing the cyclopentadienyl hydrogens. The vinyl protons in fulvene **9** appeared as a four proton singlet at 6.52, the vinyl methyl as a three proton singlet at 2.18, the thianyl methine hydrogen at 4.15 (dd, J=6, 8 Hz), and the allylic methine proton at 5.23 (m).

The additions were conducted at 0°C in tetrahydrofuran and the products purified by flash chromatography. Yields based on consumed fulvene were 10-15% higher than listed, since in all cases unreacted fulvene was recovered even with excess nucleophile. Lithium reagents were the most efficient although their use is influenced by their steric bulk. These results were consistent with related studies on Michael initiated ring closure of methyl 4-bromocrotonate[3], where it was also found that the better nucleophiles afforded the best yields of cyclopropanes. In contrast to the results for methyllithium, methyl Grignard and related reagents were unreactive towards both the fulvene and the epoxide. Apparently as a consequence of its size t-butyllithium was also unreactive. Sodium methyl malonate did not add to the fulvene but after prolonged reflux (3 h) a low yield (<10%) of alcohols was obtained. In contrast, 2-lithio-1,3-dithiane occupied an intermediate position since it reacted at both the fulvene terminus to give **8** and at the primary epoxide centre to generate the secondary alcohol **9**. Some control over the relative amounts of these

Table

Entry	Nucleophile	Product	Yield	
a	MeLi	 **4**	55%	
b	*n*BuLi	 **5**	52%(1:1)	
c	*s*BuLi	 **6**	40%(1:3)	
d	VinylLi	 **7**	46%	
e	DithianylLi	 **8**	31%(1:2) (-60°C, 10 min) (22°C, 2 h)	25%(2:3) (-60°C, 2.5 h) (22°C, 40 min)
		 **9**	16% (-60°C, 10 min) (22°C, 2 h)	26% (-60°C, 2.5 h) (22°C, 40 min)
f	KCH_2NO_2	 **10**	41%	

were separated by chromatography. The potassium anion of nitromethane was generated with potassium hydride but addition to fulvene occurred only in the presence of 18-crown-6 ether. However, unlike the examples above, the reaction stopped at the cyclopentadiene stage and subsequent base treatment of the isolated cyclopentadiene **10** failed to produce any of the corresponding spiro compound.

In summary, these bicyclic synthons are of general synthetic utility for subsequent Diels-

Alder reactions, as synthetic equivalents for 5,5-disubstituted cyclopentadienes[17], and in cases where the cyclopropane contains olefinic substituents for subsequent vinyl cyclopropane type rearrangements to diverse ring systems. We intend to ultimately prepare the fulvene-epoxide **1** in chiral form for use in the asymmetric total synthesis of sesquiterpenes and are extending these investigations to other fulvenes bearing electrophilic centres for the preparation of various spiro and fused rings.

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