A New Cyclopentannulation Approach to Bicyclo[3.3.0]octenes Employing a Tandem Michael Addition–[3 + 2]-Anionic Cyclization Sequence

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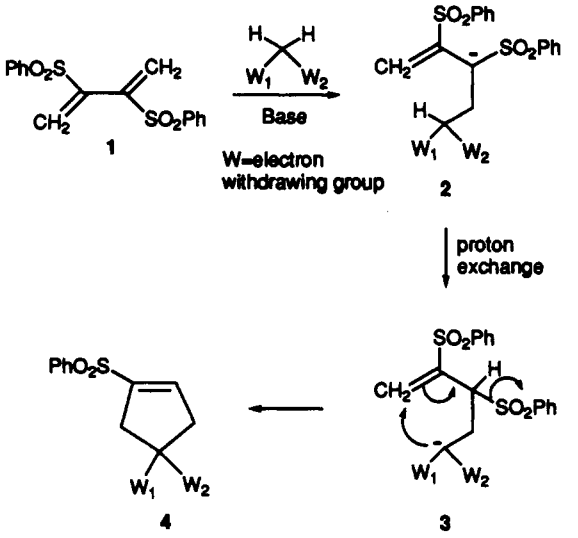
Summary: Treatment of 1-substituted dimethyl 1-pentenedioates with base in the presence of 2,3-bis(phenylsulfonyl)-1,3-butadiene results in the formation of bicyclo[3.3.0]octenes. The overall reaction involves a series of three sequential conjugate additions followed by phenyl sulfinate ion ejection.

Tandem or cascade processes occupy a central role in molecular construction, and new methods which lead to synthetically versatile arrays are particularly valuable.[1-3] The considerable importance of cyclopentanoid natural products has led to the development of a great number of new strategies for their construction.[4] While most of the cyclization methodologies typically involve the construction of a single carbon–carbon bond,[5,6] interest in new cyclopentannulation sequences by multiple bond constructions has intensified since these processes generate complex molecular frameworks in a single operation.[7-12]

In connection with our program dealing with the tandem annulation chemistry of unsaturated sulfones,[13] we have been exploring the chemical reactivity of 2,3-bis(phenylsulfonyl)-1,3-butadiene (1) as a versatile building block in organic synthesis.[14] In an earlier report, we described the reaction of diene 1 with various distabilized carbanions to produce cyclopentenyl sulfones.[15] The reaction involved a tandem *addition–proton exchange–addition* sequence. We now wish to describe the outcome of reactions of diene 1 with dimethyl 1-pentenedioates 5 containing electron-withdrawing substituents at the 1-position which lead to tetrahydro-1*H*-pentalenes 7 in high yield (74–95%). The overall reaction involves a series of three sequential conjugate additions[3] followed by phenylsulfinate ion ejection. The tandem cyclization sequence takes advantage of the usual role of the sulfonyl group as a carbanion



stabilizer[16] and also illustrates its utility as a leaving group under extremely mild conditions.[17] We first became interested in the reaction of 2-allyl substituted 1,3-dicarbonyl compounds with diene 1 in connection with the use of phenylsulfonyl-substituted allenes of type 8 as substrates for intramolecular [2 + 2]-cycloaddition chemistry.[18] The base-induced reaction of diene 1 with a series of allyl-substituted 1,3-dicarbonyl compounds (E = CO_2Me) proceeded by attack of the malonate anion onto the terminal position of the diene followed by elimination of $PhSO_2^-$ to give the phenylsulfonyl-substituted allene 8 (Scheme 1). A subsequent thermolysis (80–120 °C) resulted in a highly chemo- and stereospecific intramolecular [2 + 2]-cycloaddition producing cycloadduct 9.

When an electron-withdrawing substituent was situated on the double bond, an entirely different transformation occurred. Thus, treatment of **5a** with NaH in THF at 0 °C followed by the addition of diene 1 afforded bicyclo[3.3.0]octene **7a** in 74% yield. When these conditions were applied to the other alkenes investigated, the corresponding bicyclic compounds were obtained with the yields indicated in Scheme 1. Another aspect of the cycloaddition worth noting is the complete stereospecificity

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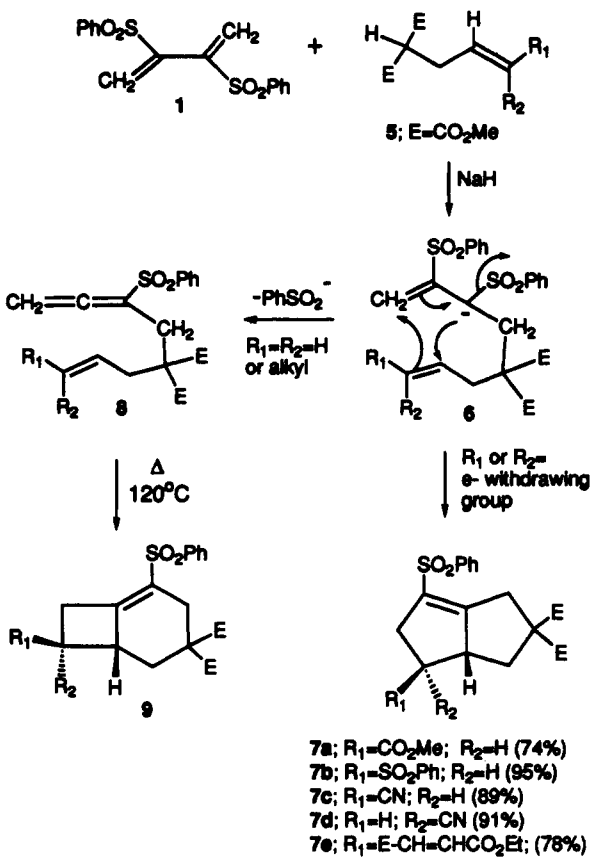
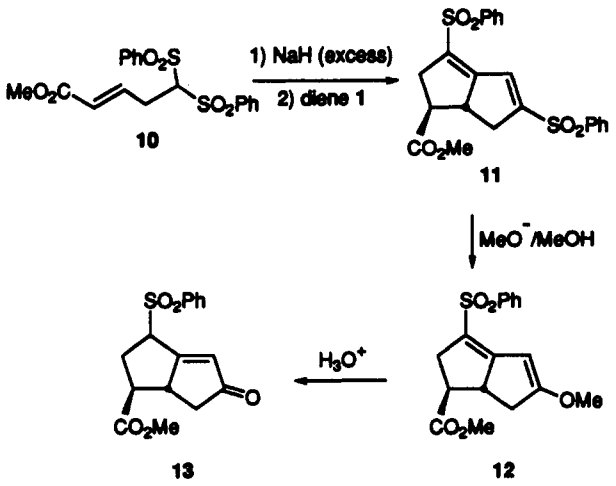
Scheme 1



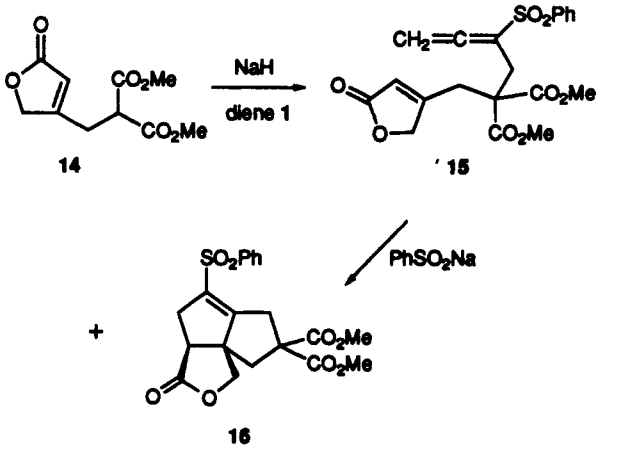
of the process. For example, subjecting isomerically pure (*E*)-alkenes **5a**–**5c** and **5e** to the tandem cyclization process produced only the *trans*-cycloadducts. Likewise, (*Z*)-nitrile **5d** afforded *cis*-adduct **7d** with no detectable signs of **7c**.

The functional tolerance and control of stereochemistry displayed by this process make it useful for the synthesis of natural products containing fused bis(cyclopentanes).[19] An interesting application of the method involves the preparation of bicyclo[3.3.0]octenone **13**. Bis(sulfone) **10** was prepared and studied as a tandem Michael substrate. The phenylsulfonyl groups permit ready activation of C_5 as a Michael donor and then, following cyclization, allow for the removal of the cumbersome functionality. Indeed, the reaction of **10** with excess NaH using diene **1** afforded **11** in 58% yield. This compound is derived by elimination of phenyl sulfinate from the initially formed cycloadduct. Further treatment of **11** with sodium methoxide in MeOH gave enol ether **12** which, on aqueous hydrolysis, produced the synthetically useful bicyclo[3.3.0]octenone **13** as a 2:1 mixture of diastereomers.

As with the standard Michael process, the success of the current method is dependent on the electrophilicity of the proximal π-bond. For example, when lactone **14** was subjected to the usual conditions, a mixture of allene **15** (48%) and the tricyclic adduct **16** (42%) was obtained. In this case, elimination of the phenyl sulfinate group from the initially formed sulfone-stabilized anion **6** is competitive with the intramolecular [3 + 2]-annulation process. Further treatment of **15** with sodium benzenesulfinate in THF at 25 °C results in its quantitative conversion to **16**. Under these conditions, addition of phenylsulfinate anion



onto the activated allene sets up an equilibrium process that produces the sulfone-stabilized anion (*i.e.*, **6**) which subsequently undergoes intramolecular cyclization.



As a logical extension of this methodology, we also investigated the base-induced reaction of dimethyl 2-(methoxycarbonyl)-2-pentenedioate (**17**) with diene **1**. Even though the position of the acceptor moiety on the π-bond has been altered, the tandem Michael reaction sequence still occurs. The major products obtained correspond to bicyclo[3.3.0]octene **19** (48%) as well as allene **18** (43%). The formation of **18** and **19** can be attributed to intermolecular conjugate addition of the anion derived from **17** onto diene **1** generating the sulfonyl-stabilized carbanion **20**. This transient species ejects $PhSO_2^-$ anion producing **18** and also undergoes the intramolecular [3 + 2]-annulation reaction. That the cyclized carbanion **21** does not induce elimination of the adjacent phenylsulfonyl group as was observed with **6a** is quite surprising. The absence of this pathway may be related to the fact that sulfonyl carbanion **21** cannot adopt the antiperiplanar orientation necessary for β-elimination[20] since, in this conformation, the three bulky substituents would lie on the same side of the five-membered ring. One conceivable route by which carbanion **21** is converted to cycloadduct **19** involves protonation followed by a subsequent base-induced elimination. It should be noted, however, that the base-induced elimination of unactivated sulfones is usually an inefficient reaction requiring drastic conditions unless the new double bond is conjugated with some unsaturated group already

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present in the molecule.[21] It is for this reason that we propose the alternate path shown in Scheme 2 which involves α-elimination of phenyl sulfinate from carbanion **21** followed by a rapid 1,2-hydrogen shift of the resulting carbene **22**. Further work is clearly necessary before this route can be unequivocally established.[22]

In conclusion, the results presented herein demonstrate the potential of using the tandem Michael addition-[3 + 2]-anionic cyclization sequence of unsaturated sulfones for the formation of five-membered rings. We are currently investigating the generality of this process for the construction of other ring systems and its application in target-oriented synthesis.

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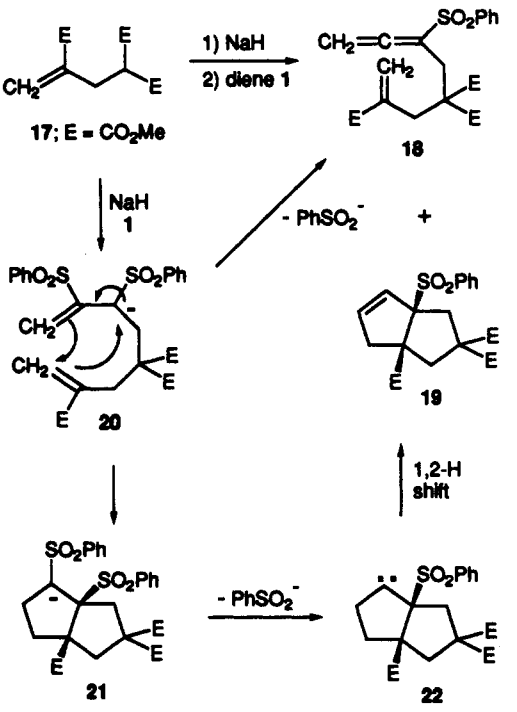
Supplementary Material Available: Experimental details for the preparation as well as spectroscopic data for all new compounds (10 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

Scheme 2



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