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# A New Entry to Oxacycles via Base-Catalyzed Endo Mode Cyclization of Allenyl Sulfoxides and Sulfones

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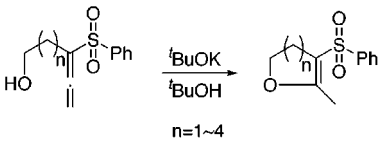
## ABSTRACT



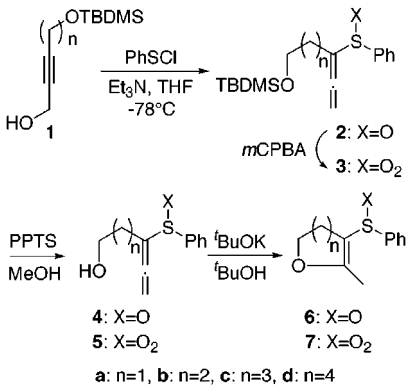

**Treatment of the allenyl sulfoxides and sulfones possessing a proper *δ*-hydroxy appendage at the C-1 position with potassium *tert*-butoxide effected endo mode ring closure at the sp-hybridized carbon center of the allenyl moiety to provide the five- to eight-membered oxacycles in high yields.**

Five- to nine-membered oxacycles are frequently found to be the major component of many biologically important natural products.[1] During the course of our studies on the development of an efficient method for the construction of oxacycles, we reported the highly stereoselective procedure[2,3] for the construction of the oxacycles by taking advantage of endo mode cyclization of the alkyne−cobalt complexes. To develop a simpler and more efficient procedure for the preparation of variously sized oxacycles, we paid significant attention to the allenyl compounds possessing an electron-withdrawing group such as a sulfinyl or sulfonyl group. These would be expected to undergo endo mode cyclization at the sp-hybridized carbon center, if these allenyl derivatives have a suitable *δ*-hydroxy appendage at the C-1 position.[4]

This Letter deals with our preliminary results on a novel and efficient method for construction of tetrahydrofuran to oxocane (five- to eight-membered oxacycles) frameworks via the endo mode cyclization process.[5−7]

The *O*-protected allenyl sulfoxides **2** (71−90%) were prepared from the corresponding propynyl alcohol derivatives **1** containing a suitable carbon chain by [2,3]-sigmatorpic reaction with benzenesulfenyl chloride (Scheme 1).[8] Oxidation of **2** with *m*CPBA under the standard conditions afforded the *O*-protected sulfonyl derivatives **3**. Treatment of **2** and

**Scheme 1**




(1) (a) Shimizu, Y. *Marine Natural Products*; Academic Press: New York, 1978, Vol. 1. (b) Moore, R. E. *Marine Natural Products: Chemical and Biological Perspectives*; Scheuer, P. J., Ed.; Academic Press: New York, 1978, Vol. 2. (c) Faulkner, D. J. *Nat. Prod. Rep.* **1986**, *3*, 1. (d) Yasumoto, T.; Murata, M. *Chem. Rev.* **1993**, *93*, 1897. (e) Faulkner, D. J. *Nat. Prod. Rep*. **1996**, *13*, 75.

(2) (a) Mukai, C.; Ikeda, Y.; Sugimoto, Y.; Hanaoka, M. *Tetrahedron Lett*. **1994**, *35*, 2179. (b) Mukai, C.; Sugimoto, Y. Ikeda, Y.; Hanaoka, M. *J. Chem. Soc., Chem. Commun*. **1994**, 1161. (c) Mukai, C.; Sugimoto, Y.; Ikeda, Y.; Hanaoka, N. *Tetrahedron* **1998**, *54*, 823. (d) Mukai, C.; Yamaguchi, S.; Sugimoto, Y.; Miyakoshi, N.; Kasamatsu, E.; Hanaoka, M. *J. Org. Chem*. **2000**, *65*, 6761. (e) Mukai, C.; Yamaguchi, S.; Kim, I. J.; Hanaoka, M. *Chem. Pharm. Bull*. **2001**, *49*, 613.

(3) Mukai, C.; Yamashita, H.; Ichiryu, T.; Hanaoka, M. *Tetrahedron* **2000**, *56*, 2203.

(4) Numbering was based on the allene skeleton for convenience.

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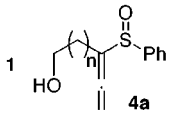
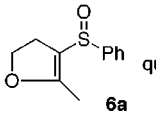
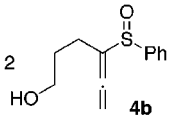
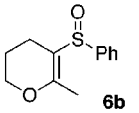
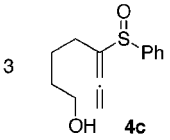
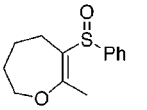
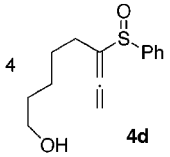
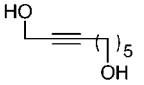
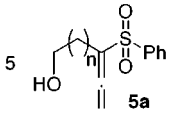
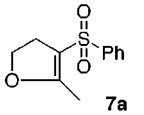
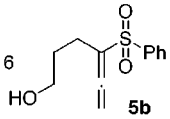
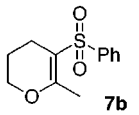
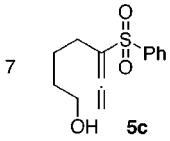
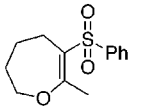
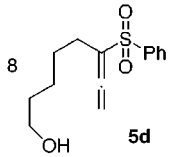
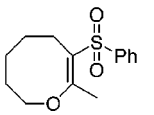
**3** with PPTS in MeOH gave the $\delta$-hydroxy compounds **4** (78−92%) and **5** (80−93%), respectively, which were then reacted under ring closure conditions. For initial evaluation of the endo mode cyclization of allenyl derivatives **4** and **5**, the sulfoxide **4a**, producing the formation of the furan derivative, was chosen. Upon exposure to $^t$BuOK in $^t$BuOH[9] at room temperature, the sulfoxide **4a** unexpectedly underwent a rapid ring closure (within 5 min) to provide furan derivative **6a**[10] in a quantitative yield (Table 1, entry1).

**Table 1.** Ring Closure of Allenes **4** and **5**

| entry | allene | product | yield (%) |
|---|---|---|---|
| 1 |  **4a** |  **6a** | quant. |
| 2 |  **4b** |  **6b** | 79 |
| 3 |  **4c** |  **6c** | 81 |
| 4 |  **4d** |  | 74[a] |
| 5 |  **5a** |  **7a** | 78 |
| 6 |  **5b** |  **7b** | 90 |
| 7 |  **5c** |  **7c** | 85 |
| 8 |  **5d** |  **7d** | 79 |

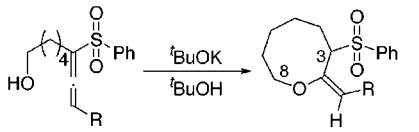
[a] 2-Octyne-1,8-diol was obtained.

Similar treatment of the carbon chain elongated analogue **4b** produced the pyran derivative **6b**[10] in 79% yield (entry 2). Oxepane formation was also realized when **4c** was treated with the base to furnish **6c**[9] in 81% yield (entry 3).

The next phase of this program was to determine whether the construction of medium-sized oxacycles would be realized. Thus, sulfoxide **4d** was exposed to the standard basic conditions at room temperature, anticipating the formation of the medium-sized oxacycle **6d**. However, nothing happened and the starting **4d** was recovered completely intact. When the reaction temperature was raised to 60 °C, consecutive retro [2,3]-sigmatropic rearrangement and desulfenylation occurred, leading to the exclusive production of 2-octyne-1,8-diol (desilylated **1d**) in 74% yield (entry 4). These results are summarized in Table 1.

This ring closure might tentatively be rationalized in terms of the endo mode Michael-type reaction initiated by the attack of the terminal hydroxy anion at the electron-deficient sp-hybridized carbon of the allenyl functionality, followed by double bond migration. Therefore, conversion of the sulfinyl group of **4** into the sulfonyl one would increase the reactivity of the allenyl moiety as a formal Michael acceptor. On the basis of the above hypothesis, we investigated the ring closure of the sulfonyl derivative **5**. Exposure of **5a**−**c** to the basic conditions described for **4** effected efficient ring closure to give **7a**−**c**[10] in 78−90% yield (see Table 1, entries 5−7). The eight-membered ring formation that could not be attained using **4** was next investigated. Upon treatment with $^t$BuOK in $^t$BuOH at room temperature, **5d** underwent ring closure in a manner similar to that of the sulfonyl derivatives **5a**−**c**, resulting in the exclusive formation of oxocane **7d**[10] in 79% yield (entry 8). To evaluate this procedure for the oxocane skeleton formation, two additional allenyl sulfones, **8** and **9**,[11] were examined. Sulfone **8** was reacted under standard basic conditions at room temperature, giving rise to the easy endo mode cyclization as expected and produced oxocane **10** with the (*E*)-ethylidene moiety[12] in 74% yield as the sole product (Scheme 2).[13] A similar result was

**Scheme 2**




**8**: R=Me
**9**: R=Ph

**10**: R=Me (74%)
**11**: R=Ph (78%)

observed when **9** was treated with base, affording **11**[13,14] in 78% yield.

(5) Denmark reported intramolecular reaction of allenyl sulfones with alkoxides: Denmark, S, E.; Harmata, M. A.; White, K. S. *J. Org. Chem.* **1987**, *52*, 4031.

(6) Parsons noted that exo mode ring closure of allenyl sulfoxide derivatives possessing a carbon side chain at the C-3 position[4] under basic conditions resulted in the formation of the five- and six-membered oxacycles (benzofuran and pyran derivatives, respectively): (a) Pairaudeau, G.; Parsons, P. J.; Underwood, J. M. *J. Chem. Soc., Chem. Commun.* **1987**, 1718. (b) Gray, M.; Parsons, P. J.; Neary, A. P. *Synlett* **1992**, 597.

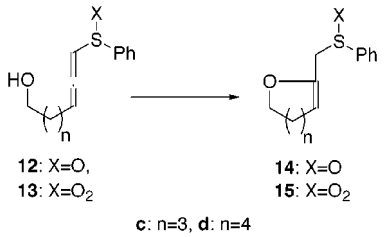
(7) Dai described an exo mode cyclization of the allenyl sulfone derivatives leading to compounds having a furan framework: Dai, W.-M.; Lee, Y. H. *Tetrahedron* **1998**, *54*, 12497.

(8) Horner, L.; Binder, V. *Ann. Chem.* **1972**, *37*, 757.

Our interest was then direct toward comparing the reactivity of the exo mode Michael-type reaction of the allenyl sulfoxides as well as sulfones having a $\delta$-hydroxy group at the C-3 position[4] as reported by Parsons[6] and Dai[7] with the reactivity of the endo mode reaction we developed. Thus, treatment of sulfoxide **12c**[15] with $^t$BuOK afforded oxepane derivatives **14c** in a rather lower yield (21%).

When **12d** was exposed to the standard basic conditions, no isolatable products were obtained. In addition, the sulfonyl derivatives **13c**,**d**[15] unexpectedly gave an intractable mixture. The seven- and eight-membered oxacycles **15c**,**d** could not be detected in the reaction mixture (Scheme 3). These experiments might suggest that the endo mode process would intrinsically be much easier than that of the exo mode process. Studies on the scope and limitation of the endo mode cyclization of various kinds of 1-substituted 1-sulfonyl allene derivatives are now in progress.

**Scheme 3**




**Supporting Information Available:** Experimental procedures for ring closure and preparation of compounds **2d**, **4d**, and **5d** and spectral data and $^1$H and $^{13}$C NMR spectra for **2d**, **4d**, **5d**, **6a**−**c**, **7a**−**d**, **10**, **11**, and **14c**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(9) After screening several conditions, we found that $^t$BuOK in $^t$BuOH was by far the most effective condition for this cyclization. For example, no reaction took place when tertiary amines such as $Et_3N$ and $^i Pr_2EtN$ were employed. In the cases of NaH and KH, the cyclized products were obtained, but their yields were rather low compared to those with $^t$BuOK.

(10) The corresponding exo methylene derivative could not be detected in the reaction mixture.

(11) The sulfonyl derivatives, **8** and **9**, were synthesized according to the procedure described for the preparation of **5**.

(12) The stereochemistry of **10** was determined on the basis of an NOE experiment. Irradiation of H-3 diagnostically showed 6.0% enhancement of the methyl protons and no enhancement of the vinyl proton. On the other hand, 8.8% enhancement of the methyl protons was confirmed, while no enhancement of H-3 could be detected upon irradiation of the vinyl proton.

(13) No endo methylene derivatives could be isolated. It should be mentioned that no isomerization was observed when **7d**, **10**, and **11** were independently exposed to the standard basic conditions and the staring materials were completely recovered intact.

(14) The fact that irradiation of the benzylidene proton produced 6.3% enhancement of H-8 while no enhancement of H-3 could be detected in its NOE experiment strongly supported the (*E*)-structure of **11**.

(15) The starting **12** and **13** were prepared from the corresponding propynyl alcohol derivatives according to the procedure described for the preparation of **4** and **5**.