The First General Synthesis of 1,5-Dioxaspiro[3.2]hexanes

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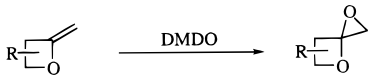
From the chemist's perspective, strained ring systems present a unique combination of challenge and opportunity. The challenge undoubtedly arises from the fact that their inherent instability means any successful syntheses must employ reagents and conditions compatible with their preparation and isolation. Conversely, the high reactivity of mono- and bicyclic small rings under mild conditions, particularly with respect to rearrangement reactions,[1] means that they can be invaluable for circumventing or minimizing what would otherwise be long or tedious synthetic strategies. In addition, the relative rigidity of small rings tends to confer in them a potential for high chirality transfer such that a single chiral center can be used to direct subsequent stereoselective transformations. Examples of these features can be found in the chemical literature.[1,2] Among heteroatom-containing small rings, oxiranes and, to a lesser extent, oxetanes have proved useful as synthetic intermediates because of their accessibility and multiplicity of reactions.[3]

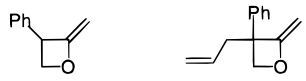
1,5-Dioxaspiro[3.2]hexanes **1** combine oxetane and oxirane ring systems in a single entity. A survey of the literature, however, indicates that only two examples have been reported as unexpected outcomes of unrelated experiments, one from the oxidation of a cumulene[4] and the other from the dimerization of a pyrilium salt.[5] Thus, they are a class of compounds that has not been accessible by any generally applicable synthetic methodology. The unique structure of this ring system suggests a number of promising areas of study, including an investigation of their ring opening and rearrangement reactions. In this paper, we describe the first general method for the synthesis, isolation, and characterization of **1**.

The most direct route to **1** would seemingly involve the epoxidation of 2-methyleneoxetanes **2**, a ring system for which we have recently described the first general synthesis.[6] Given the likely susceptibility of **1** to even mildly acidic or basic conditions, this would appear to be a particularly demanding transformation for which few of the commonly used epoxidation reagents are appropriate. Dimethyldioxirane (DMDO) has been widely used for the oxidation of alkenes to epoxides. It can be used under neutral conditions, produces only inert byproducts, and allows even sensitive epoxides such as those derived from enol ethers, enol silanes, and enol esters to be prepared successfully.[7] Crandall and co-workers also described its use for the epoxidation of allenes to α-hydroxyketones via allene oxides.[8] We now wish to report the successful oxidation of 2-methyleneoxetanes **2** to give 1,5-dioxaspiro[3.2]hexanes **1**.



2 **1**

Our initial study of the epoxidation reaction was conducted with 2-methyleneoxetane **2a**. DMDO prepared in acetone[9] gave inconsistent results with yields varying between successive runs. This was attributed to the reactivity of the products and the difficulty in obtaining rigorously dry acetone. More successful, however, was the use of the recently reported anhydrous, "acetone free" DMDO.[10] Under these conditions, epoxidation was essentially quantitative as can be seen from Table 1. The reactivity of the enol ether exceeded that of a monosubstituted alkene as evidenced by the regioselective oxidation of **2c** to **1c**. However, the addition of more DMDO caused further oxidation of the terminal alkene to give the bis-epoxide **1d** also in quantitative yield. The formation of the parent 1,5-dioxaspiro[3.2]-hexane **1f** was obvious from the proton NMR spectrum of the crude reaction mixture, but its enhanced volatility and decreased stability have, thus far, precluded its isolation. As expected, TBDPS (**1e**) and TBDMS (**1g**) ethers survive the reaction conditions, and this will facilitate the selective manipulation of the three hydroxy groups obtained from hydrolysis of these two compounds (vide infra). The presence of a BOC group, a carbamate NH, and an allyl residue in compounds **1h** and **1i** was also well tolerated.



2a **2c**

The diastereoselectivities of the epoxidation reactions were deduced from the proton NMR spectra. Excellent diastereoselectivities were observed for a single substituent at C3 (**1a**, **1h**, and **1i**). When a second group was introduced at the same position, diastereoselectivity was highest when there was a disparate size between the two groups (cf. compounds **1b** vs **1c** and **1d**). These effects were compromised, however, by additional substituents. For example, both **1e**, which has a single substituent at C3 but a geminal dimethyl group at C4, and **1g**, having a trans 3,4-disubstitution pattern, exhibited little diastereoselectivity. It should be noted at this point that hydrolysis of **1** to give α,β′-dihydroxy ketones does not result in a chiral center at either of the two positions arising from the epoxide (ketone and primary alcohol, respectively), and thus, the issue of diastereoselectivity is less important than it might appear.

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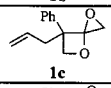
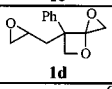
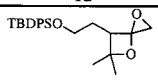
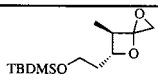
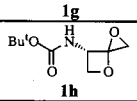
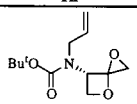
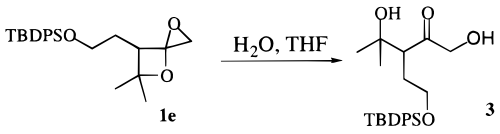
Table 1

Product	Isolated Yield	Diastereomer ratio
 **1a**	99	14:1
 **1b**	100	6:1
 **1c**	97	3:1
 **1d**	100	2:2:1:1
 **1e**	100	1.1:1
 **1f**	see text	-
 **1g**	93	1.5:1
 **1h**	100	6:1
 **1i**	90	>19:1

These data are best explained if epoxidation occurred from the face of the alkene oriented trans to the single substituent at C3 in compounds **2a**, **2h**, and **2i**, as additional substituents decrease stereoselectivity.

The internal acetal unit found in the 1,5-dioxaspiro[3.2]-hexanes **1** should make them particularly susceptible to ring-opening reactions. For hydrolysis, this appears to be indeed the case. For example, treatment of **1e** with a water/THF mixture in the absence of any acid gives **3** in 97% yield.



1e **3**

In conclusion, we have reported what we believe to be the first general synthesis of the 1,5-dioxaspiro[3.2]hexane framework, demonstrating tolerance of a number of functional groups. We are currently evaluating the reactivity of these systems and will disclose the results shortly.

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Supporting Information Available: Experimental procedures and characterization data for all new compounds, as well as proton NMR for compounds **1a,b,d,i** (14 pages).

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