



## Cyclization of hydroxy epoxides promoted by $(\text{Bu}_3\text{Sn})_2\text{O}$ /Lewis acid: efficient synthesis of oxepanes

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### Abstract

Cyclization of hydroxy epoxides mediated by a  $(\text{Bu}_3\text{Sn})_2\text{O}$ /Lewis acid system proceeded via an  $\text{S}_{\text{N}}2$  process and *exo* mode to provide the corresponding seven-membered cyclic ethers in high yield. © 2000 Elsevier Science Ltd. All rights reserved.

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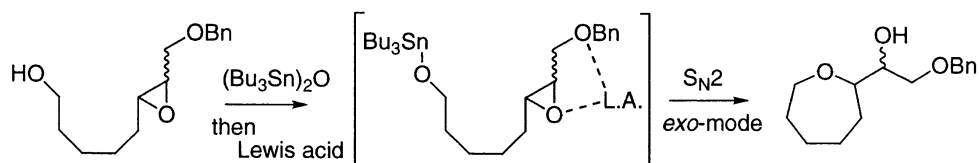
The wide occurrence of medium-sized cyclic ethers in a variety of *Laurencia* species and in the organisms which feed on these algae has become a feature of marine natural products.<sup>1</sup> In recent years, considerable synthetic activity has been centered around this group.<sup>2</sup> However, most of the reported methods lacked general flexibility and versatility for the construction of these systems with the desired ring junction stereochemistry.

The most straightforward access to the stereoselective construction of cyclic ethers would be the regio- and stereoselective cyclization of the corresponding hydroxy epoxides. In fact, this approach is often being used for the synthesis of tetrahydropyran, tetrahydrofuran and other related systems.<sup>3</sup> In these cases, the reactions are generally carried out either by the activation of an epoxide under acid catalysis or a hydroxyl group by a base. In the case of epoxy substrates, the nucleophilic attack by the hydroxyl group is expected to provide the products corresponding to those afforded by the  $\text{S}_{\text{N}}2$  reaction and *exo* mode process.<sup>4</sup> However, depending on the substituent adjacent to the epoxide and the geometry of the epoxide, the reaction gave products derived from a competing *endo* mode process.<sup>5,6</sup> In contrast, very few applications<sup>5a,c-e,6a,d</sup> of these methodologies toward the synthesis of medium-sized cyclic ethers have been pursued mainly due to entropic disfavor, angle deformations, bond opposition forces

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and transannular interactions.<sup>7</sup> Thus, it is evident that a flexible and ingenious reaction design is lacking to achieve this purpose. In an effort to overcome the said limitation, we initiated some work in this area and in the present paper we describe our preliminary results on the stereoselective construction of seven-membered cyclic ethers popularly known as oxepanes by intramolecular opening of hydroxy epoxides promoted by a  $(\text{Bu}_3\text{Sn})_2\text{O}$ /Lewis acid system.

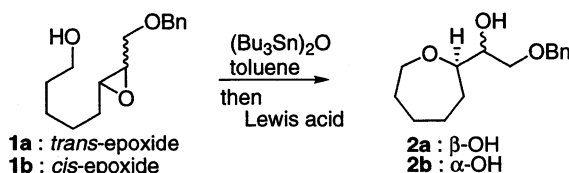
The Moulines group reported the synthesis of tetrahydrofurans and tetrahydropyrans utilizing  $\text{Bu}_2\text{SnOMe}$  as a reagent.<sup>8</sup> It is of interest to note that the said reagent serves the dual purpose of enhancing the nucleophilicity of the hydroxy function and also acting as a Lewis acid through coordination with the epoxide moiety. Encouraged by this report, we conceived a reaction plan in which activation of both groups, namely the hydroxyl moiety via formation of tin ether and the epoxide group by coordination with a suitable Lewis acid, would provide stereospecifically the corresponding oxepanes via an  $\text{S}_{\text{N}}2$  process (Scheme 1). The presence of an oxygenated substituent adjacent to the epoxide is expected to enhance the substrate reactivity and the *exo* mode selectivity through coordination of the Lewis acid with the epoxide to form a rigid five-membered chelate structure.<sup>9</sup>



Scheme 1.

Accordingly, model compound **1a** was subjected to the above investigation in an effort to explore the generality of the reaction conditions, and the results obtained are summarized in Table 1. The tin ether prepared by the treatment of epoxy alcohol **1a** with  $(\text{Bu}_3\text{Sn})_2\text{O}$  in toluene was refluxed for several hours<sup>10</sup> in the absence of any added Lewis acid. Under these conditions,

Table 1  
Cyclization of **1a** and **1b** promoted by  $(\text{Bu}_3\text{Sn})_2\text{O}$ /Lewis acid



Entry	Substrate	Lewis acid (equiv.)	Temp. (°C)	Time (h)	Product	Yield (%)
1	<b>1a</b>	none	110	20	— <sup>a</sup>	—
2	<b>1a</b>	$\text{Zn}(\text{OTf})_2$ (1.1)	50	18	<b>2a</b>	73
3	<b>1a</b>	$\text{Zn}(\text{OTf})_2$ (0.4)	90	12	<b>2a</b>	99
4	<b>1a</b>	$\text{Sn}(\text{OTf})_2$ (0.4)	90	16	<b>2a</b>	83
5	<b>1a</b>	$\text{Yb}(\text{OTf})_3$ (0.4)	90	15	<b>2a</b>	96
6	<b>1a</b>	$\text{La}(\text{OTf})_3$ (0.6)	90	23	<b>2a</b>	90
7	<b>1a</b>	$\text{Eu}(\text{OTf})_3$ (0.4)	90	16	<b>2a</b>	95
8	<b>1b</b>	$\text{Zn}(\text{OTf})_2$ (0.4)	90	10	<b>2b</b>	90

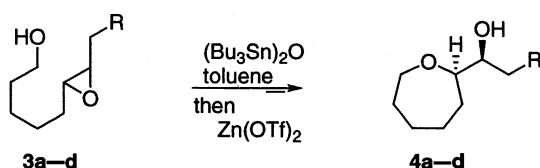
<sup>a</sup> Almost starting material was recovered.

the cyclization did not proceed and the starting material was recovered unchanged (entry 1). However, addition of the Lewis acid  $\text{Zn}(\text{OTf})_2$  allowed the reaction to proceed smoothly to afford the corresponding oxepane derivative **2a** as the sole cyclization product in 73% yield (entry 2). The yield of the product could be further improved up to 99% by using a catalytic quantity of  $\text{Zn}(\text{OTf})_2$  (entry 3). Other Lewis acids, namely,  $\text{Sn}(\text{OTf})_2$ ,  $\text{Yb}(\text{OTf})_3$ ,  $\text{La}(\text{OTf})_3$  and  $\text{Eu}(\text{OTf})_3$  were also found to be useful catalysts to promote the cyclization reaction. The cyclization reaction proceeded well regardless of the geometry of the epoxy group, and in the case of *cis*-epoxide **1b**, the corresponding cyclized product **2b** was obtained in high yield (entry 9). It may be noted that in all cases, no regio- and stereoisomeric products were detected during the cyclization reaction.

In order to demonstrate the superiority of tin ether as a substrate for the cyclization reaction, the epoxy alcohol itself was directly treated with the Lewis acid  $\text{Zn}(\text{OTf})_2$  under the reaction conditions previously employed. Interestingly enough, the cyclization did proceed to provide **2a** (73%) and **2b** (10%) as a mixture of products. It is obvious that the minor product **2b** is formed as a result of a competing  $\text{S}_{\text{N}}1$  reaction. Thus, it is evident that the tin ether plays a crucial role during the stereoselective cyclization to the corresponding oxepanes in high yield.

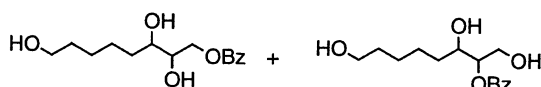
In an effort to investigate the effect of various substituents adjacent to the epoxide moiety, the cyclization of a variety of substrates from **3a–d** were studied under the same reaction conditions (Table 2). Accordingly, compound **3a** ( $\text{R}=\text{OMEM}$ , entry 1), which is capable of forming a five-membered chelated structure through coordination with the Lewis acid, gave the cyclization product **4a** in high yield. Similarly, **3b** ( $\text{R}=\text{OTBS}$ , entry 2) underwent cyclization with the same efficiency by keeping the labile TBS group intact. On the other hand, the presence of an alkyl substituent as in the case of **3c** ( $\text{R}=\text{Pr}$ , entry 4) caused the rate of cyclization to drop. In contrast, the substrate possessing an acyloxy substituent **3d** ( $\text{R}=\text{OBz}$ , entry 5) gave mainly the product derived from an intramolecular opening of the epoxy group by means of neighboring group participation.<sup>11</sup> These results clearly demonstrated that although the rigid coordination of a Lewis acid with the epoxy oxygen and the substituent accelerates the cyclization reaction, this coordination is not an essential factor for the cyclization to take place.

Table 2  
Substituent effect adjacent to the epoxide



Entry	Substrate	R	Time (h)	Yield (%)
1	<b>3a</b>	OMEM	12	81
2	<b>3b</b>	OTBS	16	82
3	<b>3c</b>	Pr	30	75
4	<b>3d</b>	OBz	45	13 <sup>a</sup>

<sup>a</sup> By-products: ca 60%.



In conclusion, the cyclization of various hydroxy epoxides promoted by a  $(\text{Bu}_3\text{Sn})_2\text{O}$ /Lewis acid system provided efficiently the corresponding oxepanes in high yield. The reaction proceeded in the *exo* mode and by an  $\text{S}_{\text{N}}2$  process regardless of the geometry of the epoxy group and without the formation of regio- and stereoisomers. The application of this methodology towards the synthesis of  $\alpha,\omega$ -*cis*- or  $\alpha,\omega$ -*trans*-disubstituted oxepanes, the fundamental skeleton of many marine natural products, will be reported in subsequent communications.

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