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Stereospecific synthesis of eight- and nine-membered cyclic ethers by Eu(fod)$_3$-mediated cyclization of hydroxy epoxides

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Abstract—An efficient and versatile method for the stereospecific construction of α,ω-*cis*- and α,ω-*trans*-disubstituted eight- and nine-membered cyclic ethers was developed. Cyclization of the hydroxy epoxides promoted by Eu(fod)$_3$ proceeded via an S$_N$2 process and *exo* mode to provide the corresponding cyclic ethers in excellent yields. © 2003 Elsevier Science Ltd. All rights reserved.

Red algae of the genus *Laurencia* produce medium-sized cyclic ethers as distinctive members of marine natural products.[1] In recent years, considerable synthetic efforts[2] have been made towards these systems in view of certain problems incurred in assembling medium-sized cyclic ethers[3] as well as the stereoselective introduction of alkyl substituents into the α- and ω-positions of a cyclic ether with *cis*- or *trans*-orientation.

In the course of our synthetic efforts towards the *Laurencia* metabolites, we have developed an efficient methodology for the stereospecific construction of α,ω-*cis*- and α,ω-*trans*-seven-membered cyclic ethers by cyclization of hydroxy epoxides promoted by a (Bu$_3$Sn)$_2$O/Zn(OTf)$_2$ system.[4] The methodology has a potential advantage in that stereochemistry at the α- and ω-positions could be controlled stereospecifically since the reaction proceeds via an S$_N$2 process and *exo* mode selectivity regardless of the configuration of the hydroxyl and epoxide groups. In order to establish the methodology as a general approach towards *Laurencia* metabolites, an extension to synthesis of eight- and nine-membered cyclic ether systems, that are abundant in *Laurencia* metabolites, was required.

At the outset, model compound **1b** was subjected to the (Bu$_3$Sn)$_2$O/Zn(OTf)$_2$ conditions[4] employed for the formation of seven-membered cyclic ethers in an effort to examine the capability for the formation of eight-membered cyclic ethers (Table 1). Reaction was quite sluggish and a large excess of Zn(OTf)$_2$ (4.4 equiv.) was required to complete the reaction, and the corresponding cyclic ether **2b** was obtained in 51% yield (entry 2). The unsatisfactory result led us to survey suitable Lewis acids for use in combination with (Bu$_3$Sn)$_2$O for the reaction. As the result, it was proved that Eu(fod)$_3$ and Pr(fod)$_3$ were superior Lewis acids[5] for this purpose to afford **2b** in 79 and 77% yields, respectively (entries 3 and 4). Moreover, it was revealed that use of Eu(fod)$_3$ in itself exhibited higher activity to promote the cyclization.[6] The reaction proceeded cleanly and its yield improved up to 85% (entry 5). An attempt at using a catalytic amount of Eu(fod)$_3$ in this reaction resulted in drastic decrease in the reaction rate (entry 6). This result showed that a stoichiometric amount of Eu(fod)$_3$, though it was not essential for the reaction to proceed, was required to obtain the practical reaction rate. The improved method could be applied to *cis*-epoxide **1c**, and the corresponding cyclic product **2c** was obtained selectively in high yield regardless of the geometry of the epoxy group (entry 7).

Similarly, successful results were obtained in the formation of nine-membered cyclic ethers under identical reaction conditions. Although the presence of a *cis*-double bond in acyclic precursors was essential, the reaction of **1e** and **1f** proceeded smoothly to afford the corresponding products **2e** (82%) and **2f** (86%), respectively (entries 9 and 10). It should be noted that the excellent yields in the formation of eight- and nine-membered cyclic ethers were comparable to that of the

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Keywords: cyclization; hydroxy epoxides; oxocenes; oxonenes; regioselection.

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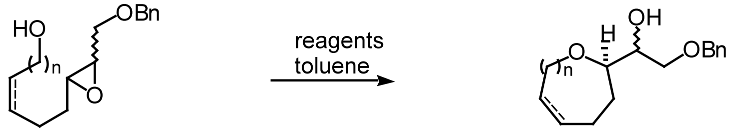
ring-closing metathesis method[1,2k,7] popularly employed for the synthesis of these systems.

The excellent results of the preliminary experiments led us to proceed with the stereospecific cyclization protocol leading to the α,ω-*cis*- and α,ω-*trans*-cyclic ethers. The *cis*-double bond in the substrates proved necessary for cyclization to occur in all cases. Model compound **3a** having a *cis*-epoxide group was reacted under identical conditions. As expected, the corresponding eight-membered cyclic ether **4a** possessing alkyl substituents at the α- and ω-positions with *cis*-orientation was obtained in 97% yield, arising from cyclization via the selective S_N2 process and *exo* mode (Table 2, entry 1). Similarly, cyclization of the isomer **3b** leading to the α,ω-*trans*-derivative proceeded stereospecifically to afford the corresponding product **4b** in 76% yield (entry 2). Furthermore, the present method was applicable to the stereospecific synthesis of α,ω-*cis*- and α,ω-*trans*-nine-membered cyclic ethers. The substrates **3c** and **3d** having the *cis*-epoxide afforded the corresponding cyclic ethers **4c** and **4d**, respectively, without any decrease in chemical yields (entries 3 and 4). It was noteworthy that no regio- and stereoisomeric products were detected in all reactions.

Interestingly, it was found that the relative configuration generated at the α,ω-positions had an influence on the regioselectivity in the cyclization from the results employing a series of *trans*-epoxide substrates (Table

Table 1. Cyclization of hydroxy epoxides leading to eight- and nine-membered cyclic ethers[a]



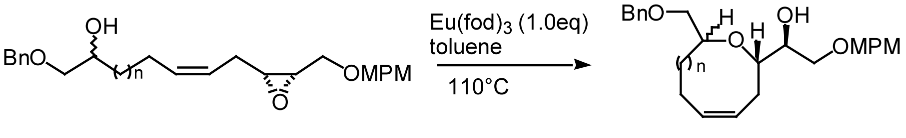
1a : n=1, *trans*-epoxide
1b : n=2, *trans*-epoxide
1c : n=2, *cis*-epoxide
1d : n=3, *trans*-epoxide
1e : n=3, Δ^4, *trans*-epoxide
1f : n=3, Δ^4, *cis*-epoxide

2a : β-OH
2b : β-OH
2c : α-OH
2d : β-OH
2e : β-OH
2f : α-OH

Entry	Substrate	Reagents (equiv.)	Temp. (°C)	Time (h)	Product	Yield (%)
1	**1a**	$(Bu_3Sn)_2O$ (0.6)/$Zn(OTf)_2$ (0.4)	90	12	**2a**	99[b]
2	**1b**	$(Bu_3Sn)_2O$ (0.6)/$Zn(OTf)_2$ (4.4)[c]	90	80	**2b**	51
3	**1b**	$(Bu_3Sn)_2O$ (0.6)/$Eu(fod)_2$ (1.0)	110	15	**2b**	79
4	**1b**	$(Bu_3Sn)_2O$ (0.6)/$Pr(fod)_2$ (1.0)	110	23	**2b**	77
5	**1b**	$Eu(fod)_3$ (1.0)	110	16	**2b**	85
6	**1b**	$Eu(fod)_3$ (0.2)	110	16	**2b**	35 (**1b**, 55)
7	**1c**	$Eu(fod)_3$ (1.0)	110	18	**2c**	81
8	**1d**	$Eu(fod)_3$ (1.0)	110	24	**2d**	– (**1d**, 96)
9	**1e**	$Eu(fod)_3$ (1.0)	110	24	**2e**	82
10	**1f**	$Eu(fod)_3$ (1.0)	110	24	**2f**	86

[a] All reactions were carried out in 0.005 M solution.
[b] Ref. 4a.
[c] Each 1.1 equiv. of $Zn(OTf)_2$ was added at 20 h intervals.

Table 2. Cyclization of hydroxy *cis*-epoxides leading to α,ω-*cis*- and α,ω-*trans*-cyclic ethers[a]



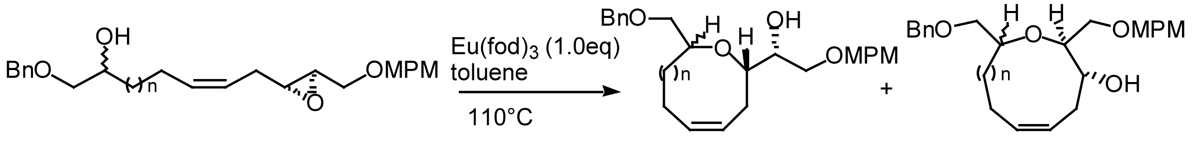
3a–d

4a–d

Entry	Substrate	Time (h)	Product[b]	Yield (%)
1	**3a**: $n=1$, α-OH	44	**4a**: α,ω-*cis*	97
2	**3b**: $n=1$, β-OH	55	**4b**: α,ω-*trans*	76
3	**3c**: $n=2$, α-OH	94	**4c**: α,ω-*cis*	87
4	**3d**: $n=2$, β-OH	74	**4d**: α,ω-*trans*	85

[a] All reactions were carried out in 0.01 M solution.
[b] Relative stereochemistry at α,ω-positions was determined by NOE experiments.

Table 3. Cyclization of hydroxy *trans*-epoxides leading to α,ω-*cis*- and α,ω-*trans*-cyclic ethers[a]



5a–d **6a–d** **7a–d**

Entry	Substrate	Time (h)	Product[b] yield (%)	
1	**5a**: $n=1$, α-OH	51	**6a**: α,ω-*cis* (88)	**7a**: α,ω-*trans* (–)[c]
2	**5b**: $n=1$, β-OH	48	**6b**: α,ω-*trans* (43)	**7b**: α,ω-*cis* (43)
3	**5c**: $n=2$, α-OH	94	**6c**: α,ω-*cis* (64)	**7c**: α,ω-*trans* (–)[c]
4	**5d**: $n=2$, β-OH	94	**6d**: α,ω-*trans* (35)	**7d**: α,ω-*cis* (8)

[a] All reactions were carried out in 0.01 M solution.

[b] Relative stereochemistry at α,ω-positions was determined by NOE experiments.

[c] Not detected.

3). While compound **5a** gave the α,ω-*cis*-orientated cyclic ether **6a** exclusively via an 8-*exo* mode (entry 1), the reaction of its isomer **5b** resulted in competitive 9-*endo* cyclization to afford α,ω-*cis*-oriented **7b** accompanied with α,ω-*trans*-oriented **6b** via 8-*exo* cyclization (entry 2). Similarly, competitive 10-*endo* cyclization was observed in the reaction of **5d** in contrast to the exclusive 9-*exo* cyclization of the isomer **5c**. These results suggested that cyclization in all cases proceeded via the S_N2 process and *exo* mode except the substrates such as **5b** and **5d** which led to the α,ω-*trans*-orientation via *exo* mode, and, on the other hand, α,ω-*cis*-orientation via *endo* mode. The exceptional *endo* cyclization was a minor problem in view of the stereospecific synthesis of α,ω-*cis*- and α,ω-*trans*-cyclic ethers, since all stereoisomers with regard to these positions could be stereospecifically derived from the corresponding substrates possessing the *cis*-epoxide group via the convincing S_N2 and *exo* cyclization.

In conclusion, we have developed a highly efficient methodology for the stereospecific construction of eight- and nine-membered cyclic ether systems possessing alkyl substituents at the α,ω-positions with *cis*- and *trans*-orientation by cyclization of hydroxy epoxides promoted by Eu(fod)$_3$. In fact, cyclic ethers synthesized in this paper inherited the requisite carbon skeleton for the synthesis of a variety of natural products, e.g. laurencin,[8] *cis*-dihydrorhodophytin,[9] 12,13-*epi*-obtusenyne,[10] obtusenyne,[11] etc. found in *Laurencia* metabolites. Therefore, the present method provides an extremely useful tool for the synthetic study of these natural products.

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