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La(OTf)$_3$-Catalyzed 7-*Endo* and 8-*Endo* Selective Cyclizations of Hydroxy Epoxides

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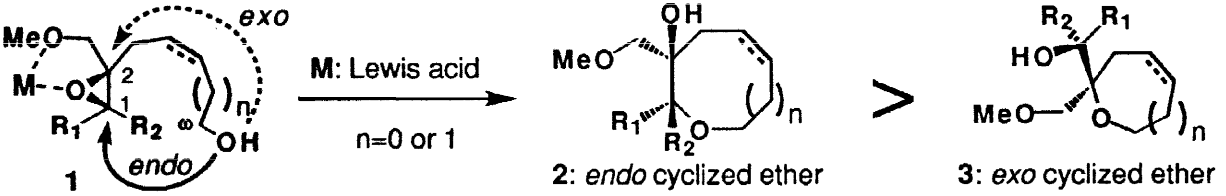
Abstract: *Endo* selective intramolecular cyclization has been achieved in 5, 6-epoxy-5-methoxymethyl-1-heptanol and 6, 7-epoxy-6-methoxymethyl-3-octen-1-ol systems by the chelation of La(OTf)$_3$ between the oxygen atoms of the epoxide and methoxymethyl groups, affording 3-hydroxyoxepane and 3-hydroxy-5-oxocene derivatives, respectively. © 1997 Elsevier Science Ltd. All rights reserved.

The *endo* selective cyclization of hydroxy epoxide, which can generate a new hydroxyl group stereospecifically on an ether ring, is the most attractive strategy for the straightforward synthesis of *cis*- and *trans*-fused polycyclic ethers.[1] Although many efficient methods which are capable of the 6-*endo* ring closure of hydroxy epoxide rather than the usually favored 5-*exo* mode[2] have been developed until now,[3,4] only a few general methods for the 7-*endo* selective cyclization[5] and none for the 8-*endo* mode have been reported. We recently developed a new method for 6-*endo* selective epoxide opening,[4] which was based on the 1-position selective activation in a 2-alkoxymethyl-1, 2-epoxide system by the chelation of Lewis acid between the oxygen atoms of the epoxide and alkoxymethyl groups.[6] In this context, we have been interested in the possibility of extension of our methodology to the 7-*endo* and 8-*endo* cyclization which provides a new entry to medium-sized cyclic ethers. We describe here our results on a search for an effective Lewis acid on *endo* selective cyclization in a 2-methoxymethyl-1, 2-epoxy-ω-ol system (**1**; ω=6 or 7) and the achievement of the 7-*endo* and the first 8-*endo* selective cyclizations by our methodology using La(OTf)$_3$ (Scheme1).



Scheme 1.

At first, *trans*- and *cis*-5, 6-epoxy-5-methoxymethylheptan-1-ols (**4a** and **4b**) were treated with each of the single-coordinating [camphor sulfonic acid (CSA) and BF$_3$•OEt$_2$] and multi-coordinating Lewis acids [TiCl$_4$, Sn(OTf)$_2$, Zn(OTf)$_2$, and La(OTf)$_3$] in CH$_2$Cl$_2$ under the conditions as shown in Table 1. When CSA was used, 6-*exo* cyclization predominated over 7-*endo* to produce oxanes **6a** and **6b** selectively from **4a** and **4b**, respectively (entries 1 and 8). Similar 6-*exo* selection was also observed in the reactions of BF$_3$•OEt$_2$ (entries 2 and 9). Treatment of **4a** with TiCl$_4$ gave only a chlorohydrin **7** in high yield (entry 3). In both the cases of Sn(OTf)$_2$ and Zn(OTf)$_2$ having a less nucleophilic ligand, **4a** and **4b** gave the respective oxanes mainly (entries 4, 5, 10, and 11), although some ligand addition reactions could be avoided. In the case of La(OTf)$_3$[7] under anhydrous conditions, the 7-*endo* cyclization of **4a** proceeded to give oxepane **5a** mainly

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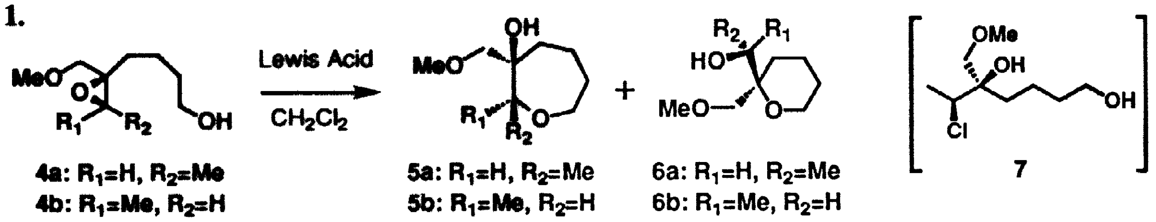
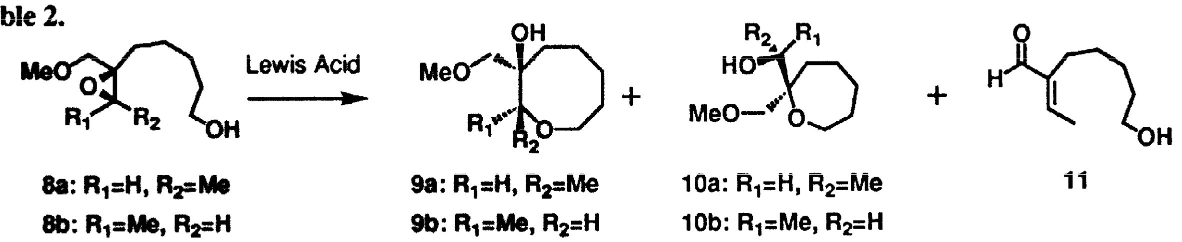
Table 1.



Entry	4	Conditions				Cyclic ethers		Recovery of 4/%
		Lewis acid (eq)	H_2O/eq	Temp./°C	Time	Yield/%	5 : 6[a]	
1	4a	CSA[b] (0.1)	0	20	24 h	90	5a:6a= 5 : 95	4a= 0
2		BF_3•OEt_2[c] (1.1)	0	20	1 h	61	3 : 97	0
3		$TiCl_4$[b] (1.1)	0	-78	1 h	0[f]	——	0
4		$Sn(OTf)_2$[b] (1.1)	0	20	1 h	64	5 : 95	0
5		$Zn(OTf)_2$[b] (1.1)	0	20	3 h	70	21 : 79	0
6		$La(OTf)_3$[d, e] (1.1)	0	20	3 days	73	81 : 19	21
7		$La(OTf)_3$[b, e] (1.1)	3.3	20	3 days	74	92 : 8	10
8	4b	CSA[b] (0.1)	0	20	3 h	82	5b:6b= 11 : 89	4b= 0
9		BF_3•OEt_2[b] (1.1)	0	20	1.5 h	73	3 : 97	0
10		$Sn(OTf)_2$[b] (1.1)	0	20	1 h	74	8 : 92	0
11		$Zn(OTf)_2$[b] (1.1)	0	20	2 h	81	8 : 92	0
12		$La(OTf)_3$[b, e] (1.1)	0	25	5 days	100	18 : 82	0
13		$La(OTf)_3$[b, e] (1.1)	3.3	25	5 days	46	86 : 14	34

a) Estimated by GLC. b) The concentration of substrate was 80 mM. c) The concentration of substrate was 50 mM. d) The concentration of substrate was 60 mM. e) La_2O_3 was contained [molar ratio La_2O_3:$La(OTf)_3$=1:4]. f) 82% production of 7.

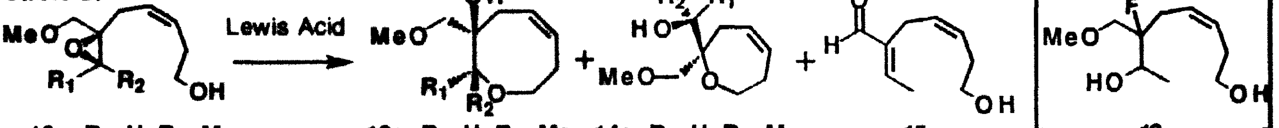
Table 2.



Entry	8	Conditions				Cyclic ethers		Yield of 11/%
		Lewis acid (eq)	Solvent[a]	Temp./°C	Time	Yield/%	9 : 10[b]	
1	8a	$Zn(OTf)_2$ (1.1)	CH_2Cl_2	25	5 days	trace	9a:10a= 33 : 66	25
2		$La(OTf)_3$[c] (1.1)	CH_3CH_2CN	55	3 days	2	63 : 37	0
3		$La(OTf)_3$[c] (1.1)	$(CH_2Cl)_2$	55	6 days	7	56 : 44	8
4	8b	$Zn(OTf)_2$ (1.0)	CH_2Cl_2	20	7 days	14	9b:10b= 7 : 93	6
5		$La(OTf)_3$[c] (1.1)	CH_3CH_2CN	60	6 days	23	43 : 57	7
6		$La(OTf)_3$[c] (1.1)	$(CH_2Cl)_2$	55	6 days	10	47 : 53	24

a) The concentration of substrate was 50 mM. b) Estimated by 300 MHz ^1H NMR. c) La_2O_3 was contained [molar ratio La_2O_3:$La(OTf)_3$=1:4].

Table 3.



12a: R_1=H, R_2=Me
12b: R_1=Me, R_2=H
13a: R_1=H, R_2=Me
13b: R_1=Me, R_2=H
14a: R_1=H, R_2=Me
14b: R_1=Me, R_2=H
15
16

Entry	12	Conditions				Cyclic ethers		Yield of 15/%	Recovery of 12/%
		Lewis acid (eq)	Solvent	Temp./°C	Time	Yield/%	13 : 14[a)]		
1	**12a**	CSA (0.1)	CH_2Cl_2[d)]	25	11 days	4	**13a**:**14a**= 44 : 56	trace	**12a**= 79
2		BF_3•OEt_2 (1.1)	CH_2Cl_2[e)]	5	17 h	56	22 : 78	8	0
3		$Zn(OTf)_2$ (1.1)	CH_2Cl_2[d)]	20	3 days	49	84 : 16	1	0
4		$La(OTf)_3$[b)] (1.1)	CH_2Cl_2[f)]	25	6 days	42	96 : 4	0	15
5		$La(OTf)_3$[b, c)] (1.1)	CH_2Cl_2[f)]	25	8 days	3	91 : 9	0	24
6		$La(OTf)_3$[b)] (1.1)	CH_3CN[f)]	25	7 days	40	98 : 2	0	0
7	**12b**	CSA (0.1)	CH_2Cl_2[d)]	25	5 days	8	**13b**:**14b**=89 : 11	4	**12b**= 54
8		BF_3•OEt_2 (1.1)	CH_2Cl_2[e)]	5	6 h	27[g)]	83 : 17	8	0
9		$Zn(OTf)_2$ (1.1)	CH_2Cl_2[d)]	20	23 h	12	50 : 50	19	0
10		$La(OTf)_3$[b)] (1.1)	CH_2Cl_2[f)]	25	8 days	55	100 : 0	0	0
11		$La(OTf)_3$[b)] (1.1)	$(CH_2Cl)_2$[f)]	50	6 days	56	99 : 1	0	2
12		$La(OTf)_3$[b)] (1.1)	CH_3CN[f)]	25	8 days	69	98 : 2	0	0
13		$La(OTf)_3$[b)] (1.1)	CH_3CN[f)]	45	3 days	71	98 : 2	0	0

a) Estimated by 300 MHz and 400 MHz ^{1}H-NMR. b) La_2O_3 was contained [molar ratio $La(OTf)_3$:$La(OTf)_3$=1:4]. c) H_2O (3.3 eq) was contained. d) The concentration of substrate was 25 mM. e) The concentration of substrate was 4 mM. f) The concentration of substrate was 50 mM. g) Fluoride **16** was also given (28%).

(entry 6, **5a**:**6a**=81:19) in contrast to the 6-*exo* selective cyclization of **4b** (entry 12, **5b**:**6b**=18:82). The addition of 3 eq of H_2O to $La(OTf)_3$ improved the 7-*endo* opening of epoxide in both the cases of **4a** and **4b** (**5a**:**6a**=92:8; entry 7 and **5b**:**6b**=86:14; entry 13),[4,8] while the reaction rate in **4b** slowed down.

Secondly, we examined the cyclization of *trans*- and *cis*-6, 7-epoxy-6-methoxymethyloctan-1-ols (**8a** and **8b**, Table 2). After several attempts, only $Zn(OTf)_2$ and $La(OTf)_3$ gave cyclic ethers (**9** and **10**) along with aldehyde **11** albeit in low yields under the conditions shown in Table 2.[9] While $Zn(OTf)_2$ gave oxepane predominantly (entries 1 and 4), $La(OTf)_3$ effected 8-*endo* cyclization comparably to the 7-*exo* mode (entries 2, 3, 5, and 6).

Next, *trans*- and *cis*-6, 7-epoxy-6-methoxymethyl-3-octen-1-ols (**12a** and **12b**) were investigated (Table 3). Treatment of **12** with CSA at 25 °C for several days produced only a small amount of cyclic ethers along with the recovery of the majority of the starting epoxides. Surprisingly, **12b** gave 8-*endo* cyclized ether mainly under the conditions (**13b**:**14b**=89:11, entry 7), while **12a** afforded a 44:56 mixture of **13a** and **14a** (entry 1). The preferential production of the oxocene from **12b** was also observed in the case of BF_3•OEt_2 under highly diluted conditions (**13b**:**14b**=83:17, entry 8), although the yield of cyclization was modest (27%) with concomitant production of **16**. On the other hand, the reaction of **12a** under the same conditions gave a mixture of **13a** and **14a** in moderate yield (56%) in the ratio of 22:78, respectively (entry 2). The use of $Sn(OTf)_2$ gave only complex by-products (data not shown), probably due to its strong Lewis acidity. When $Zn(OTf)_2$ was used, the 8-*endo* selective cyclization of **12a** was observed to give an 84:16 mixture of **13a** and **14a** in 49% yield (entry 3). Even under the same conditions, **12b** afforded cyclic ethers only in low yield and

selectivity (entry 9). In both the reactions of 12a and 12b with $La(OTf)_3$, exclusive 8-*endo* cyclization **was effected, although prolonged reaction time needed** for consumption of the starting material in each case **(entries 4 and 11). The addition of** H_2O^4 **lowered the** activity of the catalyst and 8-*endo* selectivity (entry 5). **Acetonitrile as a solvent was also useful in the** reaction of 12a and heightened the yield of the oxocene from **12b** (entries 6 and 12). Heating was effective for increase of the reaction rate without reduction of the *endo* selectivity (entries 11 and 13).

The yield of cyclization products and the rate of the reaction decreased with increasing distance between the hydroxyl and epoxide groups of the substrate in the order of 4<12<8. In the cases of **12** and **8**, unfavorable side reactions, such as rearrangement of the epoxide moiety, led to the formation of enals (**11** and **15**) and other undesirable products, and such formation increased as the strength of Lewis acidity increased. The success with $La(OTf)_3$ might be attributed to not only its ability to chelate rigidly between the oxygen atoms of the epoxide and methoxymethyl groups but also its Lewis acidity which is adequate for the cyclization but not so high as to induce such side reactions.

In summary, the use of $La(OTf)_3$ achieved the 7-*endo* and 8-*endo* selective cyclizations of **4** and **12**, respectively. Even in the case of **8**, $La(OTf)_3$ rather than other Lewis acids increased the 8-*endo* cyclization. Addition of H_2O in the reactions of **4** raised the 7-*endo* selectivity. Further mechanistic studies and synthetic applications of these reactions are now in progress in our laboratory.

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7. $La(OTf)_3$ was prepared by the following method and used without pre-drying: La_2O_3 was treated with 4 eq of TfOH in H_2O (the same volume as TfOH) at 120 °C for 1 h. Then, the reaction mixture was dried at 230 °C (keep below 250 °C) *in vacuo* for 6 h without removal of leaving La_2O_3. The absence of La_2O_3 and high temperature during the removal of H_2O from the catalyst impaired the reproducibility of the *endo* cyclization. The use of commercial $La(OTf)_3$ gave only unsatisfactory results. For preparation of $La(OTf)_3$, see: Forsberg, J. H.; Spasiano, V. T.; Balasubramanian, T. M.; Liu, G. K.; Kinsley, S. A.; Duckworth, C. A.; Poteruca, J. J.; Brown, P. S.; Miller, J. L. *J. Org. Chem.* 1987, *52*, 1017.
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9. In the case of CSA, the majority of the starting epoxides were recovered at 25 °C after 1 month. Other Lewis acids [$Sn(OTf)_2$ and $BF_3{\cdot}OEt_2$] gave complex by-products even under highly diluted conditions. The addition of H_2O to $La(OTf)_3$ did not effect in yield and selectivity.