

# NOVEL OXEPANE FORMATION BY REDUCTIVE CLEAVAGE OF 1-METHOXYMETHYL-6,8-DIOXABICYCLO[3.2.1]OCTANES<sup>†</sup>

Kenshu Fujiwara,\* Arika Amano, Tetsuo Tokiwano, and Akio Murai\*

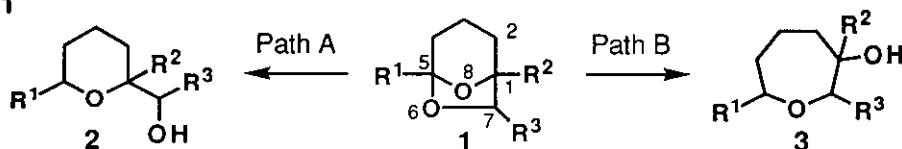
Division of Chemistry, Graduate School of Science, Hokkaido University,  
Sapporo 060, Japan

<sup>†</sup> Dedicated to Professor Koji Nakanishi on the occasion of his 75th birthday.

**Abstract**—The introduction of a methoxymethyl group at the C1 position in the 6,8-dioxabicyclo[3.2.1]octane system enabled novel formation of oxepane in reductive cleavage induced by triethylsilane and titanium(IV) chloride.

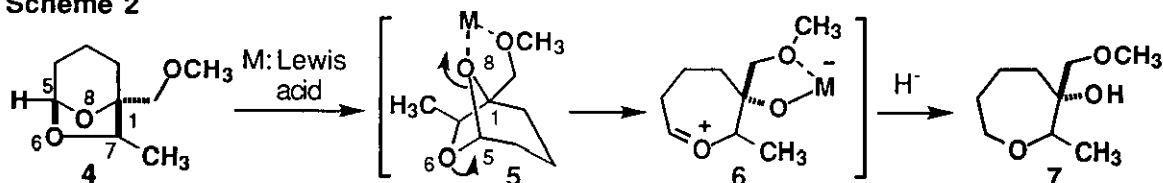
In the reductive cleavage of bicyclic acetal, which is one of the most attractive methods for the synthesis of natural cyclic ethers,<sup>1,2</sup> the C-O bond cleavage is directed to production of smaller ring ethers. For example, the 6,8-dioxabicyclo[3.2.1]octane system (**1**) has produced exclusively oxane (**2**) (path A) but not oxepane (**3**) (path B) under two conditions using DIBALH or combination of triethylsilane (Et<sub>3</sub>SiH) with a Lewis acid (Scheme 1).<sup>2,3</sup> In this paper, we describe a method which enables the selective reductive cleavage to the larger ring in the system.

**Scheme 1**



As outlined in Scheme 2, we planned the fixation of a Lewis acid on O8 to enhance the cleaving ability of the C5-O8 bond rather than the C5-O6 bond by chelation of the Lewis acid between O8 and the oxygen of the methoxymethyl function at C1. Thus, bicyclic acetals (**4a**) and (**4b**) having a methoxy-methyl group at C1 and a methyl group at C7 were examined under some reducing conditions (Table).

**Scheme 2**



At first, DIBALH was used for reductive cleavage in CH<sub>2</sub>Cl<sub>2</sub>. The reactions of **4a** and **4b** required 3 or 2 days for completion even at 20 °C and produced only oxanes (**8a**) and (**8b**) in high yields, respectively (Entries 1 and 4). It was thought that mono-coordinating DIBALH could not chelate between the oxygen atoms of the acetal and the methoxymethyl group and showed a normal<sup>1-3</sup> oxane selectivity. Next, the combination of Et<sub>3</sub>SiH and bis-coordinating titanium(IV) chloride (TiCl<sub>4</sub>) was examined in CH<sub>2</sub>Cl<sub>2</sub> at -78

Table

	4a: R <sup>1</sup> =H, R <sup>2</sup> =CH <sub>3</sub>		7a: R <sup>1</sup> =H, R <sup>2</sup> =CH <sub>3</sub>		8a: R <sup>1</sup> =H, R <sup>2</sup> =CH <sub>3</sub>	
	4b: R <sup>1</sup> =CH <sub>3</sub> , R <sup>2</sup> =H		7b: R <sup>1</sup> =CH <sub>3</sub> , R <sup>2</sup> =H		8b: R <sup>1</sup> =CH <sub>3</sub> , R <sup>2</sup> =H	
Entry	Substrate	Reagent (eq.)	Temp.	Time	Yield <sup>a</sup>	7 : 8 <sup>b</sup>
1	4a	DIBALH (4)	20 °C	3 days	77%	7a:8a= 0 : 100
2		Et <sub>3</sub> SiH (8) TiCl <sub>4</sub> (2.4)	-78 °C	1 h	98%	99 : 1
3		Et <sub>3</sub> SiH (8) SnCl <sub>4</sub> (2.4)	-78 °C 0 °C	1.5 h 0.5 h	60%	0 : 100
4	4b	DIBALH (4)	20 °C	2 days	100%	7b:8b= 0 : 100
5		Et <sub>3</sub> SiH (8) TiCl <sub>4</sub> (2.4)	-78 °C	1 h	74%	74 : 26
6		Et <sub>3</sub> SiH (12) SnCl <sub>4</sub> (3.6)	-78 °C	5.5 h	43%	0 : 100

a) isolated yield. b) determined by GC.

°C. Under the conditions, the major product was oxepane (7a) (7a:8a=99:1, 98% yield) from 4a and 7b (7b:8b=74:26, 74% yield) from 4b (Entries 2 and 5). Interestingly, when tin(IV) chloride (SnCl<sub>4</sub>), a bis-coordinating Lewis acid similar to TiCl<sub>4</sub>, was used in reductive cleavage, an oxane was produced exclusively (Entries 3 and 6). At present, we can only speculate on the reason for the difference. The selectivity of the acetal cleavage is thought to depend strongly on Lewis acidity which controls the abilities of cleavage of the acetalic C5-O8 bond and the chelation between O8 and the oxygen of the methoxymethyl group. From the fact that the SnCl<sub>4</sub> catalyzed reductive cleavage proceeded more slowly than with TiCl<sub>4</sub>, SnCl<sub>4</sub> apparently lacked sufficient Lewis acidity<sup>4</sup> to produce oxepane.

In conclusion, introduction of the methoxymethyl group at the C1 position in the 6,8-dioxabicyclo[3.2.1]octane system enabled novel formation of oxepane in reductive cleavage induced by Et<sub>3</sub>SiH and TiCl<sub>4</sub>. Further application of this methodology toward natural cyclic ethers is in progress.

## REFERENCES AND NOTES

1. Y. Kim and B. P. Mundy, *J. Org. Chem.*, 1982, **47**, 3556; Y. Masaki, Y. Serizawa, K. Nagata, and K. Kaji, *Chem. Lett.*, 1983, 1601.
2. H. Kotsuki, Y. Ushio, I. Kadota, and M. Ochi, *Chem. Lett.*, 1988, 927; H. Kotsuki, Y. Ushio, I. Kadota, and M. Ochi, *J. Org. Chem.*, 1989, **54**, 5153; H. Kotsuki, *Synlett*, 1992, 97.
3. K. Ishihara, A. Mori, and H. Yamamoto, *Tetrahedron Lett.*, 1987, **28**, 6613; K. Ishihara, A. Mori, and H. Yamamoto, *Tetrahedron*, 1990, **46**, 4595.
4. For the Lewis acidity strengths of Ti<sup>4+</sup> and Sn<sup>4+</sup>, see: Y. Zhang, *Inorg. Chem.*, 1982, **21**, 3889.

Received, 28th April, 1997