NOVEL OXEPANE FORMATION BY REDUCTIVE CLEAVAGE OF 1-METHOXYMETHYL-6,8-DIOXA-BICYCLO[3.2.1]OCTANES[†]

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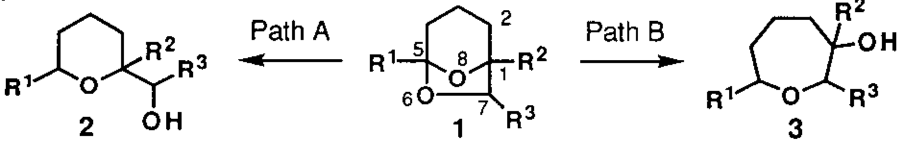
† Dedicated to Professor Koji Nakanishi on the occasion of his 75th birthday.

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.

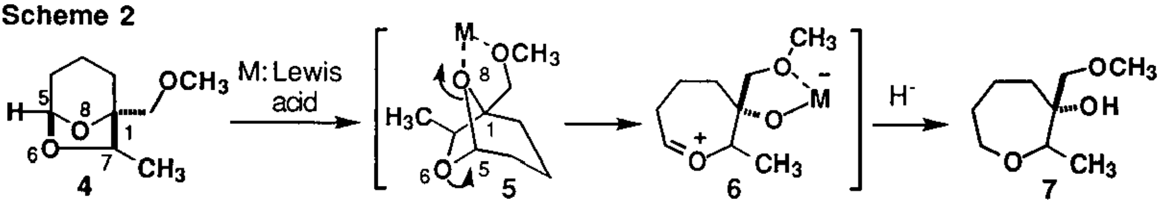
In the reductive cleavage of bicyclic acetal, which is one of the most attractive methods for the synthesis of natural cyclic ethers,[1,2] the C-O bond cleavage is directed to production of smaller ring ethers. For example, the 6,8-dioxabicyclo[3.2.1]octane system (1) has produced exclusively oxane (2) (path A) but not oxepane (3) (path B) under two conditions using DIBALH or combination of triethylsilane (Et_3SiH) with a Lewis acid (Scheme 1).[2,3] In this paper, we describe a method which enables the selective reductive cleavage to the larger ring in the system.

Scheme 1



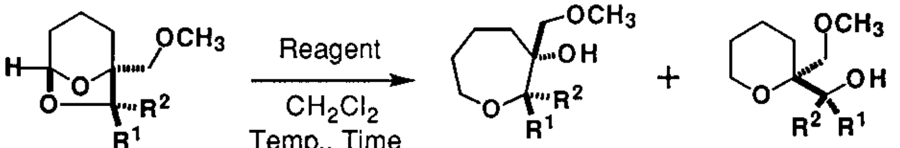
As outlined in Scheme 2, we planned the fixation of a Lewis acid on O8 to enhance the cleaving ability of the C5-O8 bond rather than the C5-O6 bond by chelation of the Lewis acid between O8 and the oxygen of the methoxymethyl function at C1. Thus, bicyclic acetals (4a) and (4b) having a methoxy-methyl 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_2Cl_2. 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[1-3] oxane selectivity. Next, the combination of Et_3SiH and bis-coordinating titanium(IV) chloride ($TiCl_4$) was examined in CH_2Cl_2 at -78

Table



4a: R^1=H, R^2=CH_3
4b: R^1=CH_3, R^2=H

7a: R^1=H, R^2=CH_3
7b: R^1=CH_3, R^2=H

8a: R^1=H, R^2=CH_3
8b: R^1=CH_3, R^2=H

Entry	Substrate	Reagent (eq.)	Temp.	Time	Yield[a]	**7** : **8**[b]
1	**4a**	DIBALH (4)	20 °C	3 days	77%	**7a**:**8a**= 0 : 100
2		Et_3SiH (8) $TiCl_4$ (2.4)	-78 °C	1 h	98%	99 : 1
3		Et_3SiH (8) $SnCl_4$ (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_3SiH (8) $TiCl_4$ (2.4)	-78 °C	1 h	74%	74 : 26
6		Et_3SiH (12) $SnCl_4$ (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 ($SnCl_4$), a bis-coordinating Lewis acid similar to $TiCl_4$, 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 $SnCl_4$ catalyzed reductive cleavage proceeded more slowly than with $TiCl_4$, $SnCl_4$ apparently lacked sufficient Lewis acidity[4] 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_3SiH and $TiCl_4$. Further application of this methodology toward natural cyclic ethers is in progress.

REFERENCES AND NOTES

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