Tetrahedron Letters,Vol.30,No.32,pp 4267-4270,1989   0040-4039/89 $3.00 + .00
Printed in Great Britain   Maxwell Pergamon Macmillan plc

A SELECTIVE ONE-CARBON RING EXPANSION REACTION OF 1-SILOXYCYCLOALKANECARBALDEHYDES CATALYZED BY A LEWIS ACID

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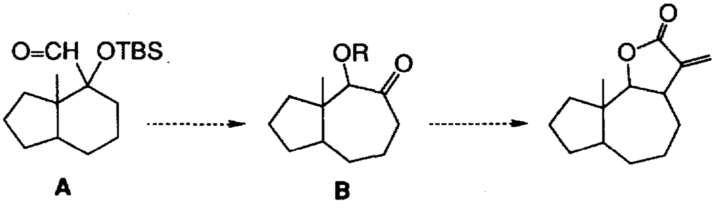
Abstract: Under the influence of a Lewis acid, 1-siloxycycloalkanecarbaldehydes undergo one-carbon ring enlargement reaction to afford the corresponding 2-siloxycycloalkanones in good yields. Regiochemistry of this rearrangement reaction has also been examined, and use of $FeCl_3$ greatly improves the selectivity to give the product arising from migration of a more-substituted site.

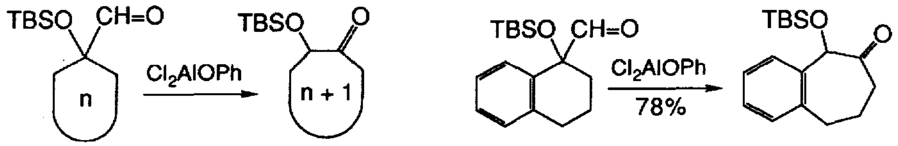
Bicyclo[5.3.0]decane carbon skeletons bearing butyrolactone moieties have been widely found in sesquiterpenoid natural products, and much attention has been attracted for construction of such carbon frameworks.1) In the previous paper, we described Lewis acid mediated one-carbon ring expansion reactions of 1-(trimethylsilylmethyl)cycloalkanecarbaldehydes which involves selective rearrangement of a more-substituted ring carbon to afford several types of compounds depending on the reaction conditions.2) A similar rearrangement reaction of α-hydroxyaldehydes was also reported,3) but regio-control of the reaction has been quite difficult to afford a mixture of several products. We have examined the reaction of 1-siloxycycloalkanecarbaldehydes to improve regio-control of the reaction. Our previous observations have suggested that the reaction of unsymmetrically substituted substrates such as **A** may lead to an exclusive formation of the product **B**, and such methodology may be quite useful for the natural product synthesis as depicted in Scheme 1. The requisite substrates **1** were easily prepared from the cyclic ketones by cyanosilylation4) followed by DIBAL reduction.



(Scheme 1)

Treatment of unsubstituted substrate **1a**-**1c** (n = 6, 8, and 12) or an aromatic one **1d** with Cl_2AlOPh (1 equiv) in methylene chloride cleanly gave the expected one-carbon ring expansion product in good yields (Eq 1).

However, different from the behavior of 1-(trimethylsilylmethyl)carbaldehydes, regiochemistry of this rearrangement reaction is not controlled so cleanly: 2-Methyl-1-(siloxy)cyclohexanecarbaldehyde **1e** gave a mixture of **2e** and **2e'** under similar reaction conditions. The Lewis acid used has a great influence on the ratio of **2e** and **2e'**. Thus, the reaction of **1e** (R = $^{i}Pr_3Si$) with Cl_2AlOPh gave a 1:1 mixture, whereas the use of $SnCl_4$ improved the ratio to 8:1. A dramatic change has been observed in the reaction of 2,2-disubstituted one **1f**, and the ratio was changed from 1:30 (with Cl_2AlOPh) to 7:1 (with $SnCl_4$) as shown in the Table.



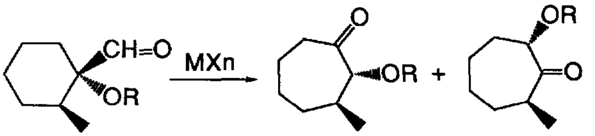
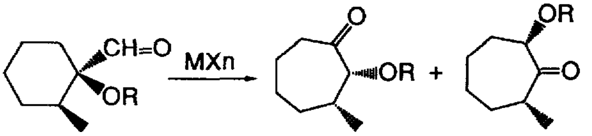
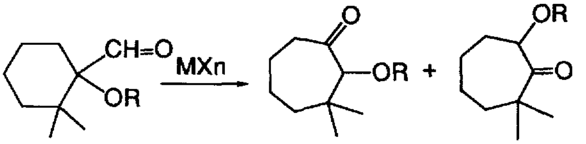
1a (n = 6) **2a** 76%
1b (n = 8) **2b** 83%
1c (n = 12) **2c** 96%

1d **2d**

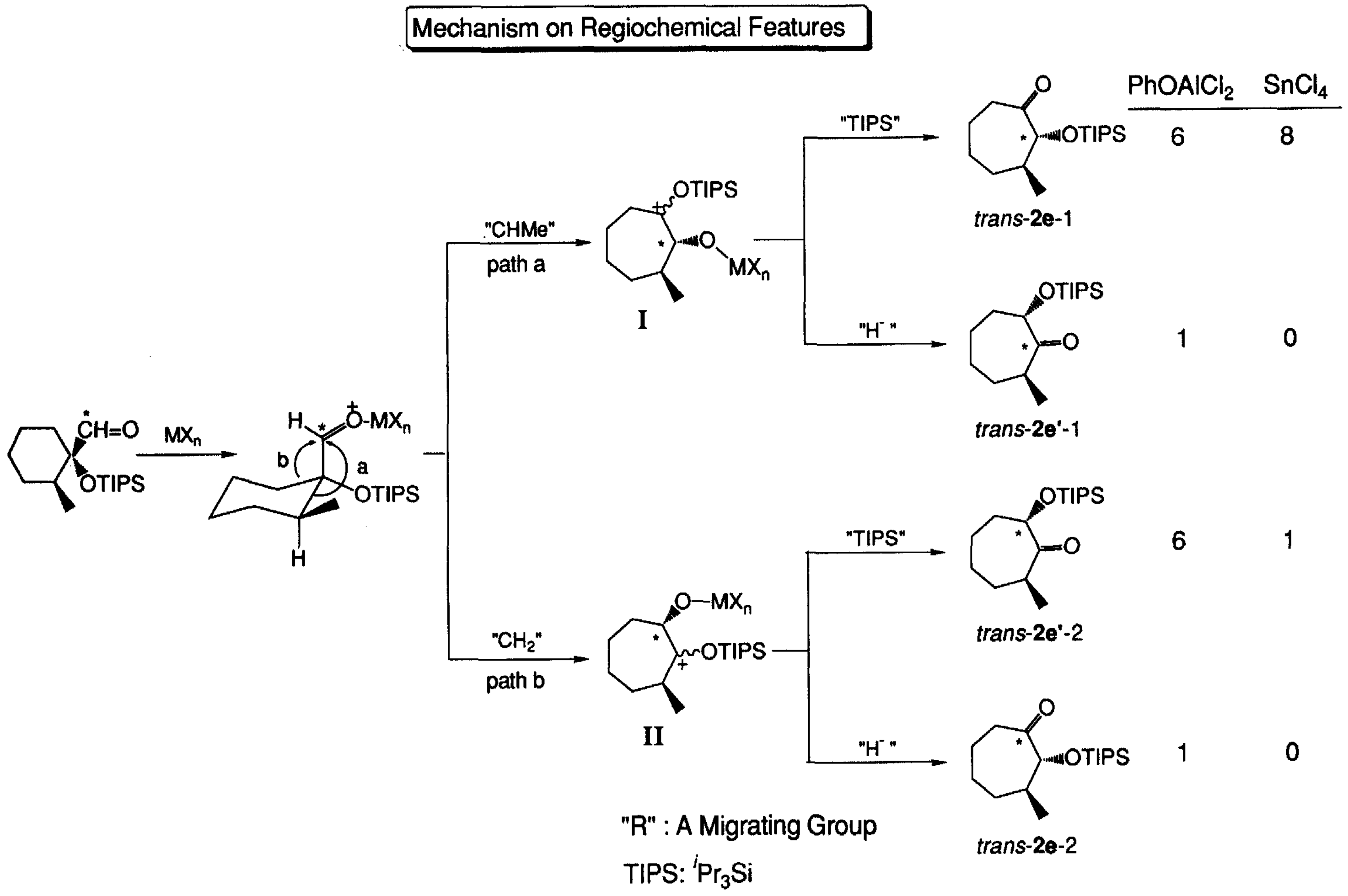
(Eq 1)

In contrast to low selectivity on regiochemical outcome, stereochemistry is completely controlled in the reactions of both *trans*- and *cis*-**1e**: The *trans*-**1e** gave *trans*-disubstituted cycloheptanones,[5] whereas a mixture of *cis*-disubstituted ketones[5] were obtained from the *cis*-**1e**.

Table. Rearrangement Reactions of 2-Substituted 1-Siloxycyclohexanecarbaldehydes

A **B**		Yield(%) (**A**:**B**)	
	R	Cl_2AlOPh	$SnCl_4$
 *trans*-**1e** *trans*-**2e** *trans*-**2e'**	$^tBu(Me)_2Si$	71%(2.2:1)	
	$^iPr_3Si$	99%(1:1)	80%(8:1)
 *cis*-**1e** *cis*-**2e** *cis*-**2e'**	$^tBu(Me)_2Si$	59%(1:1)	
 **1f** **2f** **2f'**	$^tBu(Me)_2Si$	70%(1:10)	
	$^iPr_3Si$	70%(1:30)	60%(7:1)

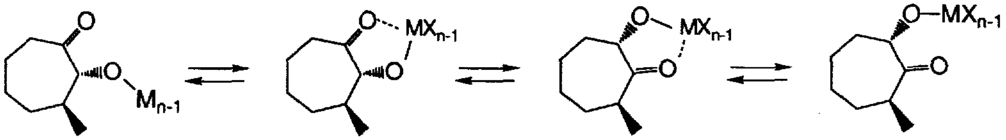
Two mechanistic rationales may be conceivable on the formation of these products: One involves non-selective migration of methyne (path a) and methylene (path b) groups, and in the other case, a more-substituted group undergoes migration selectively (path a), but a subsequent migration of hydride and a silyl group may take place concomitantly to afford a mixture of two regio-isomers. In order to clarify the mechanistic feature, the reaction was performed by using C-13 (C*) labeled aldehyde, and the ratio of each product was determined.[6] Results including two interesting aspects are shown in Scheme 2.


Mechanism on Regiochemical Features
CH=O
OTIPS
MXn
H
O-MXn
b
a
OTIPS
H
"CHMe"
path a
"CH2"
path b
OTIPS
O
MXn
I
O—MXn
OTIPS
II
"TIPS"
"H- "
"TIPS"
"H- "
O
OTIPS
trans-2e-1
OTIPS
O
trans-2e'-1
OTIPS
O
trans-2e'-2
O
OTIPS
trans-2e-2
PhOAlCl2
SnCl4
6
8
1
0
6
1
1
0
"R" : A Migrating Group
TIPS: iPr3Si

(Scheme 2)

First, the reaction involving a hydride shift takes places as a minor process on using an Al catalyst, whereas it can be excluded in the $SnCl_4$ mediated reaction. Second, a migratory aptitude of a substituent is highly dependent on the Lewis acid, and use of $SnCl_4$ is preferable for selective migration of a more-substituted ring carbon.

Sometimes, α-hydroxy ketones were also formed. However, ratio (almost 1:1) of two regio-isomers was very different from that of siloxy ketones **2e** and **2e'**. Thus, these hydroxy compounds may not be derived from **2es** by hydrolysis, but are formed from removal of a silyl group from a cationic species **I** or **II** and a subsequent equilibration shown in Eq 2. Consequently, it seems to be important to use a readily unremovable silyl group to achieve a good regio-selection.



(Eq 2)

Based on these observations, several Lewis acids were further examined, and $FeCl_3$ has been found to be most satisfactory both on chemical yield and regio-control. Thus, on treating with $FeCl_3$ (0.5 equiv) in dichloroethane at -23°C for 30 min, *trans*-**1e** (R = $^iPr_3Si$) gave the corresponding products (**2e**: **2e'** = 14:1) in 89% yield. Similarly, **1f** (R = $^iPr_3Si$) could be converted to the ring enlargement products (**2f**:**2f'** = 26:1) in 82% yield by performing the reaction for 2 h under similar conditions.

We are currently studying on application of these reactions for natural product synthesis.

Acknowledgement. This work was partially supported by Grants from the Ministry of Education, Science, and Culture of the Japanese Government.

References

1) See for example, C. H. Heathcock, S. L. Graham, M. C. Pirrung, F. Plavac, and C. T. White, "The Total Synthesis of Natural Products", Ed by J. ApSimon, Vol 5, Chapter 5 (1983).

2) K. Tanino, T. Katoh, and I. Kuwajima, *Tetrahedron Lett.*, **29**, 1815 (1988). T. Katoh, K. Tanino, and I. Kuwajima, *ibid.*, **29**, 1819 (1988).

3) On rearrangement reaction of 1-hydroxyaldehydes, see: C. J. Collins and J. F. Eastham, "The Chemistry of the Carbonyl Group", Ed by S. Patai, Vol. 1, Chapter 15, Interscience, New York (1966). On discussion about non-regioselectivity of such reactions: Elphimoff-Felkin, *Bull. Soc. Chim. France,* **1956**, 1845. Non-regiocontrolled feature observed in these reactions is also attributable to the equilibration described in the text.

4) For example, 2-methyl-1-(tri-*i*-propylsiloxy)cyclohexanecarbonitrile was obtained almost quantitatively by heating 2-methylcyclohexanone with tri-*i*-propylsilyl chloride (1.0 equiv), KCN (1.3 equiv) and 18-crown-6 (0.3 equiv) in dichloromethane for 9 h.

5) Chemical shifts (ppm) of C<u>H</u>-OTBS: *trans*-**2e**; 3.90 (d, J = 6.7 Hz). *trans*-**2e'**; 4.27 (m). *cis*-**2e**; 4.01 (almost s). *cis*-**2e'**; 4.32 (dd, J = 5.4 and 3.6 Hz).

6) Ratio was determined based on the integration of C-13 NMR. Chemical shift (ppm) of a C-13 portion of each isomer: *trans*-**2e**-1; 84.47. *trans*-**2e'**-1; 215.70. *trans*-**2e'**-2; 78.69. *trans*-**2e**-2; 213.25.

(Received in Japan 26 May 1989)