ORGANIC LETTERS

2006
Vol. 8, No. 9
1889−1891

Epoxysilane Rearrangement Induced by a Carbanion Generated by Conjugate Addition of Enolates of Chloroacetate and α-Chloroacetamides: Formation of Functionalized Cyclopropane Derivatives

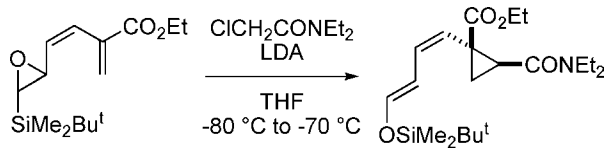
Noriko Okamoto,[†] Michiko Sasaki,[†] Masatoshi Kawahata,[‡] Kentaro Yamaguchi,[‡] and Kei Takeda*,[†]

Department of Synthetic Organic Chemistry, Graduate School of Medical Sciences, Hiroshima University, 1-2-3 Kasumi, Minami-Ku, Hiroshima 734-8553, Japan, and Tokushima Bunri University, Shido, Sanuki, Kagawa, 769-2193 Japan

takedak@hiroshima-u.ac.jp

Received February 23, 2006

ABSTRACT



Reaction of an enoate bearing an epoxysilane moiety at the α-position with lithium enolate of 2-chloroacetamide afforded highly functionalized cyclopropane derivatives via a tandem process that involves Michael addition, ring opening of the epoxide, Brook rearrangement, and intramolecular alkylation.

We have previously reported results of studies on anion-induced epoxysilane rearrangement involving the formation of a *β*-siloxy allylic anion from a *β*-silyl-α,*β*-epoxy carbanion via Brook rearrangement.[1,2] The methods we have used for generating the carbanion in the process are a base-induced deprotonation[1a−c,e] and reaction of acylsilanes with a nucleophile followed by Brook rearrangement.[1d,f] Herein, we report the evolution of our studies based on the generation of a carbanion by a conjugate addition of a nucleophile to an enoate system bearing an epoxysilane moiety at the α-position and the resulting formation of functionalized cyclopropane derivatives.[3,4] Our initial approach involves Michael addition[5] of a carbanion **2** bearing a leaving group in the α-position to enoate **1** followed by an intramolecular

[†] Hiroshima University.
[‡] Tokushima Bunri University.

(1) (a) Takeda, K.; Kawanishi, E.; Sasaki, M.; Takahashi, Y.; Yamaguchi, K. *Org. Lett.* **2002**, *4*, 1511−1514. (b) Sasaki, M.; Kawanishi, E.; Nakai, Y.; Matsumoto, T.; Yamaguchi, K.; Takeda, K. *J. Org. Chem.* **2003**, *68*, 9330−9339. (c) Matsumoto, T.; Masu, H.; Yamaguchi, K.; Takeda, K. *Org. Lett.* **2004**, *6*, 4367−4369. (d) Tanaka, K.; Takeda, K. *Tetrahedron Lett.* **2004**, *45*, 7859−7861. (e) Sasaki, M.; Takeda, K. *Org. Lett.* **2004**, *6*, 4849−4851. (f) Tanaka, K.; Masu, H.; Yamaguchi, K.; Takeda, K. *Tetrahedron Lett.* **2005**, *46*, 6429−6432.

(2) For reviews on Brook rearrangement, see: (a) Brook, M. A. *Silicon in Organic, Organometallic, and Polymer Chemistry*; John Wiley & Sons: New York, 2000. (b) Brook, A. G.; Bassindale, A. R. In *Rearrangements in Ground and Excited States*; de Mayo, P., Ed.; Academic Press: New York, 1980; pp 149−221. (c) Brook, A. G. *Acc. Chem. Res.* **1974**, *7*, 77−84. For the use of Brook rearrangement in tandem bond formation strategies, see: (d) Moser, W. H. *Tetrahedron* **2001**, *57*, 2065−2084. Also, see: (e) Ricci, A.; Degl'Innocenti, A. *Synthesis* **1989**, 647−660. (f) Page, P. C. B.; Klair, S. S.; Rosenthal, S. *Chem. Soc. Rev.* **1990**, *19*, 147−195. (g) Qi, H.; Curran, D. P. In *Comprehensive Organic Functional Group Transformations*; Katritzky, A. R., Meth-Cohn, O., Rees, C. W., Moody, C. J., Eds.; Pergamon: Oxford, 1995; pp 409−431. (h) Cirillo, P. F.; Panek, J. S. *Org. Prep. Proc. Int.* **1992**, *24*, 553−582. (i) Patrocinio, A. F.; Moran, P. J. S. *J. Braz. Chem. Soc.* **2001**, *12*, 7−31.

(3) For a review on the synthesis of cyclopropane-containing natural products, see: Donaldson, W. A. *Tetrahedron* **2001**, *57*, 8589−8627.

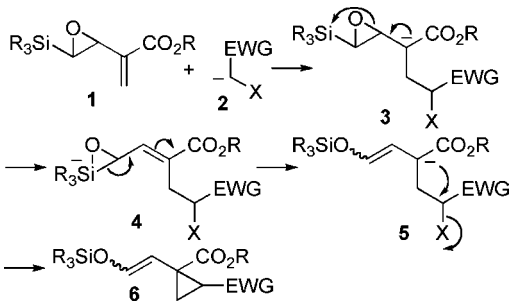
(4) For reviews on the synthesis of cyclopropane derivatives, see: (a) Reissig, H.-U.; Zimmer, R. *Chem. Rev.* **2003**, *103*, 1151−1196. (b) Label, H.; Marcoux, J.-F.; Molinaro, C.; Charette, A. B. *Chem. Rev.* **2003**, *103*, 977−1050.

(5) Chapdelaine, M. J.; Hulce, M. *Org. React.* **1990**, *38*, 225−653.

10.1021/ol060469k CCC: $33.50
Published on Web 04/01/2006

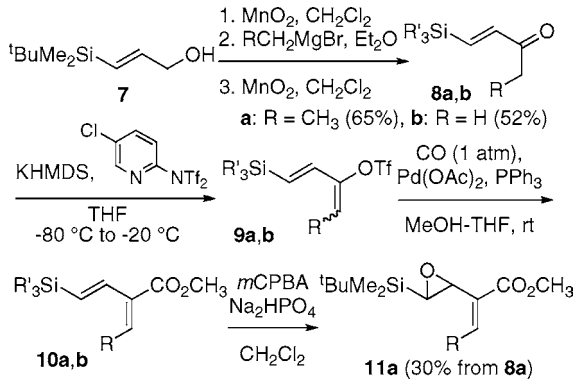
displacement of a carbanion **5** generated via anion-induced epoxysilane rearrangement (**3** → **4** → **5**) in the adduct **3** (Scheme 1).

Scheme 1



Although attempted synthesis of **11b** starting from **7**[6] resulted in the Diels−Alder self-dimerization of **10b** in the stage of palladium-catalyzed carbonylation[7] of enol triflate **9b**,[8] introduction of a methyl group at the β-position of an enoate was found to suppress the dimerization to give **11a** after epoxidation (Scheme 2).

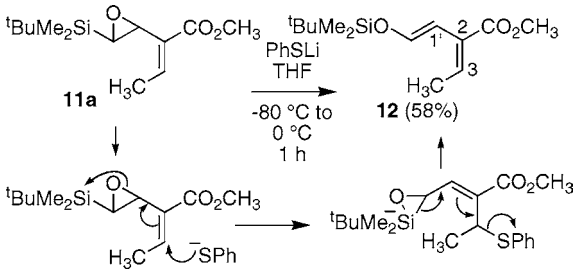
Scheme 2. Preparation of **11a**



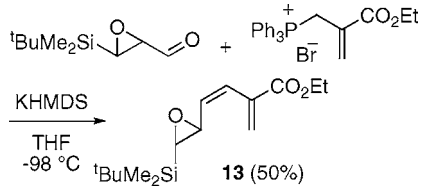
To test the feasibility of the Michael addition and subsequent epoxysilane rearrangement, we first conducted the reaction of **11a** with lithium thiophenoxide, which is a nucleophile that can function as a leaving group after addition to the enoate moiety. Treatment of **11a** with PhSLi afforded the corresponding tandem reaction product **12** in 58% yield (Scheme 3). The geometry of the C2−C3 double bond was determined on the basis of NOESY correlation between H-3 and H-1′.

Having found the tandem sequence triggered by Michael addition to proceed as expected, we attempted to prepare **11b** by several routes without success. On the basis of our previous experience[1] with the epoxysilane rearrangement, we next focused on a vinylogous variant **13** that does not have a β-substituent and could be prepared by the sequence shown in Scheme 4.

Scheme 3. Reaction of **11a** with PhSLi



Scheme 4. Preparation of **13**

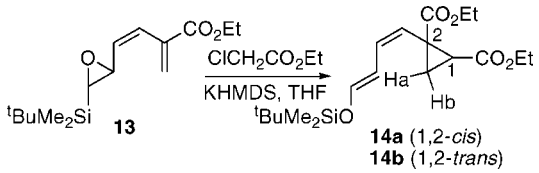


Attempted reactions of **13** with a variety of nucleophiles, including thiophenoxide, a malonate anion, and a benzyl cyanide anion, resulted in extensive decomposition. This failure was attributed to the existence of several electrophilic sites in **13** and/or to decomposition of the ester enolate generated by the epoxysilane rearrangement. The latter possibility prompted us to trap the enolate by an electrophile. After extensive examination using a variety of external electrophiles such as alkyl halides and internal nucleophile−electrophiles such as ketone enolate, we found that the reaction with the enolate of chloroacetate gave the best results. Treatment of **13** with the potassium enolate[9] of ethyl chloroacetate in THF at −80° to −60 °C afforded cyclopropanediolate derivatives **14a** and **14b** with predominant formation of a cis isomer (Table 1). The relative stereochemistries were assigned on the basis of the fact that a larger difference in the chemical shift between H_a and H_b in **14a** (1.23 and 1.96 ppm) than in **14b** (1.56 and 1.77 ppm) was observed[10] and were finally determined by X-ray analysis of the corresponding bis(*p*-bromobenzoate) after conversion of **14a** into the 1,2-bis(hydroxymethyl) derivative by LAH reduction. Lowering of the reaction temperature to −98 °C improved both the selectivity and the yield.

The more favorable formation of the cis isomer can be explained as being a consequence of chelation in which the two ester groups are involved because addition of HMPA

(6) Yamamoto, K.; Heathcock, C. H. *Org. Lett.* **2000**, *2*, 1709−1712.
(7) (a) Cacchi, S.; Morera, E.; Ortar, G. *Tetrahedron Lett.* **1985**, *26*, 1109−1112. (b) Yamamoto, K.; Heathcock, C. H. *Org. Lett.* **2000**, *2*, 1709−1712.
(8) Comins, D. L.; Dehghani, A.; Foti, C. J.; Joseph, S. P *Org. Synth.* **1997**, *74*, 77−83.
(9) The use of lithium and sodium enolates resulted in recovery of the starting material and a lower yield of **14**, respectively.
(10) Chen, C.; Xi, C.; Jiang, Y.; Hong, X. *Tetrahedron Lett.* **2004**, *45*, 6067−6069.

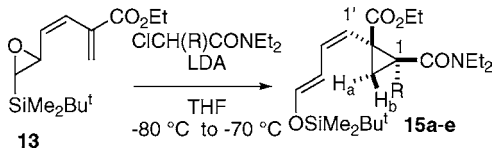
Table 1. Reaction of **13** with the Potassium Enolate of Ethyl Chloroacetate



conditions	yield (%) (**14a/14b**)
−80 °C to −60 °C	75 (1.0:0.5)
−98 °C	85 (1.0:0.2)
HMPA (10%), −80 °C to −60 °C	76 (0.7:1.0)

resulted in a reversal of selectivity. We considered that stabilization of the chelation structure would enhance the selectivity, and we focused on the use of lithium enolate of chloroacetamides from the point of view that the higher reactivity of the enolates and the stronger chelating ability of the amide function and the lithium cation are sufficient to compensate for the lower reactivity of lithium enolates relative to potassium enolates. When **13** was treated with the lithium enolate of *N*,*N*-diethylchloroacetamide, the corresponding cyclopropane derivative **15a** was obtained as a single diastereomer in an excellent yield (Table 2). Similar

Table 2. Reaction of **13** with the Potassium Enolate of 2-Chloro-*N*,*N*-diethylacetamide



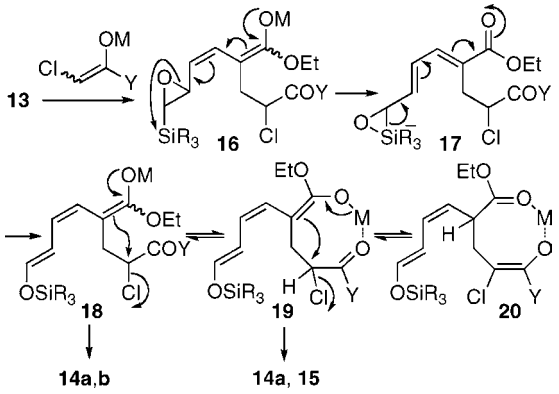
	R	yield (%)
a	H	100
b	Me	82
c	*n*-Bu	67
d	Ph	74
e	Cl	86

results were obtained with other amides. The relative stereochemistry was assigned by analogy to **14** with the difference in the chemical shift between H_a and H_b (1.26 and 2.18 ppm for **15a**) and on the basis of the observed NOESY correlations between H_a and both CH_3-1 and H-1′ in **15b**.

A plausible reaction pathway that accounts for the stereochemical outcome of the reaction of **13** is outlined in Scheme 5. The fact that the reaction of **13** with bromoacetamide afforded cyclopropane derivatives **21**[11] as the major products (Scheme 6) suggests that a concerted pathway from **13** to silicate intermediate **17** that involves Michael addition

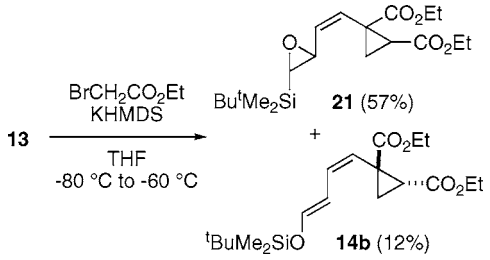
(11) The relative stereochemistry was not determined.

Scheme 5. Plausible Reaction Pathway



followed by ring opening of the epoxide is unlikely. The exclusive formation of the internal (*Z*)-olefin in the reactions of both ester and amide enolates can be understood by assuming that silicate intermediate **17** reacts in an *s*-cis diene conformation and is faster than the change in the conformation of the diene moiety in **17** to give **18**. The enolate **18** can undergo either or both of two reaction pathways, intramolecular alkylation to give **14a** and **14b** and formation of the chelation structures **19** and **20**, depending on the stability of the chelation structures.

Scheme 6. Reaction of **13** with the Potassium Enolate of Ethyl Bromoacetate



In summary, we demonstrated that the generation of a carbanion by a conjugate addition of an amide enolate to an enoate system bearing an epoxysilane moiety at the α-position can induce epoxysilane rearrangement to afford highly functionalized cyclopropane derivatives.

Acknowledgment. This research was partially supported by a Grant-in-Aid for Scientific Research (B) 15390006 and a Grant-in-Aid for Scientific Research on Priority Areas 17035054 from the Ministry of Education, Culture, Sports, Science and Technology (MEXT). We thank the Research Center for Molecular Medicine, Faculty of Medicine, Hiroshima University, and N-BARD, Hiroshima University, for the use of their facilities.

Supporting Information Available: Full experimental details and spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

OL060469K