

Facile Synthesis of *cis*-2-Alkyl-3-trialkylsilyloxycycloalkanones via the Non-Aldol Aldol Rearrangement of 2,3-Epoxycycloalkanols

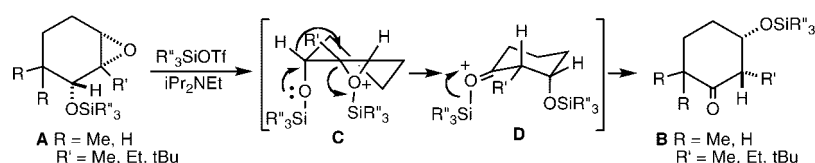
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ABSTRACT



Silyl triflate-promoted rearrangement of *cis*-2,3-epoxycycloalkanols **A**, prepared by epoxidation of the cyclic allylic alcohol and then silylation, afforded good yields (~70–75%) of the *cis*-2-alkyl-3-silyloxycycloalkanones **B**, presumably via the intermediates **C** and **D**, even with quite large α -substituents, e.g., *tert*-butyl. Finally, it has been shown that the stereochemistry of the epoxy alcohol is crucial as one would expect from the mechanism.

Functionalized carbocyclic rings are important synthons in organic synthesis. In particular, *cis*-2-alkyl-3-hydroxycycloalkanones are valuable intermediates that can be readily converted into a variety of motifs found in natural products. Unfortunately, no procedures currently exist for their synthesis. In acyclic systems, such β -hydroxy carbonyl compounds are usually made using the aldol condensation and asymmetric variants thereof. But few synthetic methods have been reported for the asymmetric intramolecular aldol to make α -alkyl β -hydroxy cyclic systems.

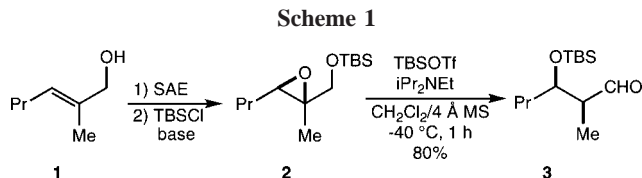
An alternative method to synthesize asymmetric β -hydroxyl carbonyl compounds is the Lewis acid promoted semipinacol rearrangement of optically active epoxy alcohols, obtained using methodology developed by Sharpless.¹ The activated epoxide is opened with inversion of stereochemistry via a concerted [1,2] migration, thereby transferring the stereochemical information from the starting material to the product. Much of this work has focused on phenyl, vinyl,

or alkyl migration in acyclic systems.² More recently, a few studies have been reported in cyclic systems in an effort to construct quaternary carbon centers. Several years ago, we reported a semipinacol rearrangement^{3a} involving not phenyl, vinyl, or alkyl migration, but rather hydride migration, and named the process the nonaldol aldol reaction^{3–5} (Scheme

(2) (a) Corey, E. J.; Guzman-Perez, A. *Angew. Chem., Int. Ed.* **1998**, *37*, 389. (b) Rickborn, B. In *Comprehensive Organic Synthesis; Carbon-Carbon σ -Bond Formation*; Patai, G., Ed.; Pergamon Press: Oxford, 1991; Vol. 3, Chapter 3.3. (c) Whalen, D. L. *Adv. Phys. Org. Chem.* **2005**, *40*, 247.

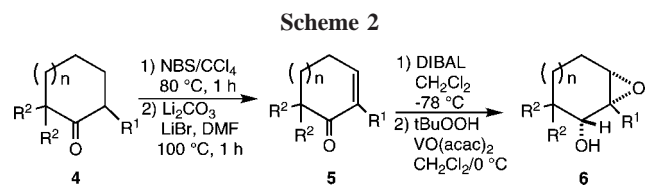
(3) (a) Jung, M. E.; D'Amico, D. C. *J. Am. Chem. Soc.* **1993**, *115*, 12208. (b) Jung, M. E.; D'Amico, D. C. *J. Am. Chem. Soc.* **1995**, *117*, 7379. (c) Jung, M. E.; D'Amico, D. C. *J. Am. Chem. Soc.* **1997**, *119*, 12150. (d) Jung, M. E.; Marquez, R. *Tetrahedron Lett.* **1999**, *40*, 3129. (e) Jung, M. E.; Lee, W. S.; Sun, D. *Org. Lett.* **1999**, *1*, 307. (f) Jung, M. E.; Sun, D. *Tetrahedron Lett.* **1999**, *40*, 8343. (g) Jung, M. E.; Marquez, R. *Org. Lett.* **2000**, *2*, 1669. (h) Jung, M. E.; Lee, C. P. *Tetrahedron Lett.* **2000**, *41*, 9719. (i) Jung, M. E.; Lee, C. P. *Org. Lett.* **2001**, *3*, 333. (j) Jung, M. E.; van den Heuvel, A. *Tetrahedron Lett.* **2002**, *43*, 8169. (k) Jung, M. E.; Hoffmann, B.; Rausch, B.; Contreras, J.-M. *Org. Lett.* **2003**, *5*, 3159. (l) Jung, M. E.; van den Heuvel, A.; Leach, A. G.; Houk, K. N. *Org. Lett.* **2003**, *5*, 3375. (m) Jung, M. E.; van den Heuvel, A. *Org. Lett.* **2003**, *5*, 4705. (n) Jung, M. E.; Yoo, D. *Org. Lett.* **2007**, *9*, 3543. (o) Jung, M. E.; Zhang, T. *Org. Lett.* **2008**, *10*, 137. (p) Jung, M. E.; Yoo, D. *Tetrahedron Lett.* **2008**, *49*, 816.

(1) (a) Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 5974. (b) Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765.



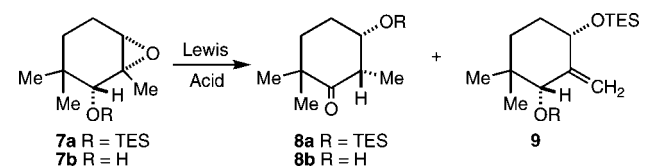
1). Good yields of **3** were obtained from the epoxide **2** using a silyl triflate in combination with a hindered base as a unique Lewis acid system to promote hydride migration, a process that requires more rigorous conditions than phenyl or vinyl migration. However, these studies were mostly confined to acyclic systems. We report herein the use of the nonaldol reaction in cyclic systems for the preparation of *cis*- α -alkyl β -silyloxy cycloalkanones from α -alkyl epoxy alcohols.

The α -alkyl epoxy alcohols **6** were prepared in four steps from the corresponding cycloalkanones **4** (Scheme 2).



Bromination with NBS followed by elimination gave the cycloalkenones **5**. DIBAL reduction and hydroxyl-directed epoxidation gave the desired *cis*-epoxy alcohols **6**. The results of the treatment of either the free epoxy alcohol or the derived silyl ether of the dimethyl-substituted cyclohexane system are shown in Table 1. Treatment of the triethylsilyl

Table 1. Rearrangement of Epoxy Alcohols and Silyl Ethers

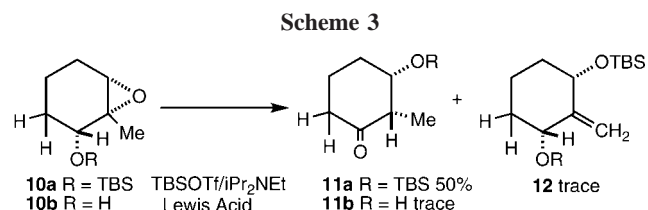


compd	R	Lewis acid	additive	T (°C)	yield of 8 (%)	yield of 9 (%)
7a	TES	TESOTf	<i>i</i> Pr ₂ NEt	0	74	10
7b	H	TiCl ₄	none	-78	47	
7b	H	SnCl ₄	none	-78	65	
7b	H	BF ₃ -OEt ₂	none	-78	64	
7b	H	LiBF ₄	none	23	32	

ether **7a**⁶ with TESOTf and Hünig's base gave the nonaldol aldol product **8a** as the only detectable diastereomer in 74% yield. In addition, the readily separable ether **9** was formed, presumably via an E2-like elimination of the epoxide with

base.⁷ The epoxy alcohol **7b** was treated with various Lewis acids, e.g., TiCl₄, SnCl₄, BF₃·OEt₂, and LiBF₄, to induce the rearrangement, but they afforded the β -hydroxy ketone **8b** in lower yields (32–65%). Thus, this is the first example of the formation of *cis*- α -alkyl β -silyloxy cycloalkanones from such epoxy ethers.

The less substituted epoxy ether **10a** reacted similarly with the silyl triflate and base to afford the β -silyloxy ketone **11a** in 50% yield along with some allylic ether **12** (Scheme 3).



In this case, the reaction went to completion at -40 °C while the rearrangement of **7a** required warming to 0 °C. However, treatment of **10b** with various Lewis acids—TiCl₄, SnCl₄, BF₃·OEt₂, and LiBF₄—led mainly to decomposition, and only small amounts of **11b** were obtained. Thus, the mild silyl triflate/Hünig's base conditions are superior for less hindered compounds where the products are more prone to side reactions. Overall, the silyl triflate/Hünig's base protocol gave the highest yields.

The stereochemistry of the products were assigned by comparison of the coupling constants, especially J_{23} , to the same J values in analogous literature compounds. Thus, the J_{23} value for the *trans* isomer is 8–9 Hz for similar 3-hydroxy- or 3-alkoxy-2-alkylcyclohexanones, while the J_{23} value for the *cis* isomer is 3 Hz.⁸ In compounds **8a**, **8b**, and **11a**, J_{23} was 2.4, 3.1, and 2.1 Hz, respectively. In addition, the proton and carbon NMR data of the *cis* isomer **8b** do not match those reported for the known *trans* compound.^{8c} Thus, the structures of **8** and **11** were assigned by this coupling constant and literature comparison.

The effect of the epoxy substituent and the ring size on the rearrangement was also tested by treating a number of analogues with TBSOTf and Hünig's base (Scheme 4). The ethyl analogue **13a** afforded the expected product **14a** in 77% yield, and the 5-membered methyl analogue **13d** also worked

(4) For an excellent review of semi-pinacol rearrangements, see: Snape, T. J. *Chem. Soc. Rev.* **2007**, *36*, 1823.

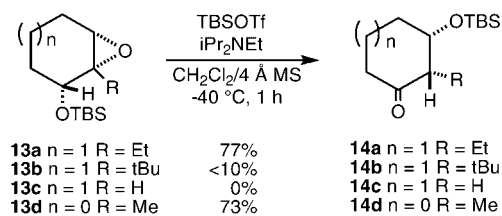
(5) (a) For recent uses of the non-aldol process, see: Mitton-Fry, M. J.; Cullen, A. J.; Sammakia, T. *Angew. Chem. Int. Ed.* **2007**, *46*, 1066. (b) Fenster, M. D. B.; Dake, G. R. *Chem. Eur. J.* **2005**, *11*, 639. (c) Dake, G. R.; Fenster, M. D. B.; Fleury, M.; Patrick, B. O. *J. Org. Chem.* **2004**, *69*, 5676. (d) Angle, S. R.; White, S. L. *Tetrahedron Lett.* **2000**, *41*, 8059.

(6) The alcohol **7b** was too hindered to allow formation of the TBS ether, so the TES ether **7a** was used instead.

(7) This byproduct **9** is seen whenever there is a methyl substituent α to the epoxide and the rearrangement is relatively slow.^{3f}

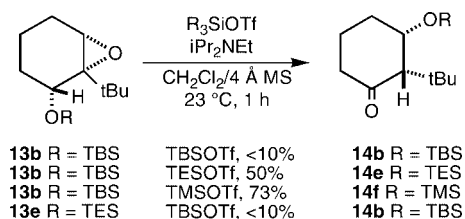
(8) (a) *trans*-3-Hydroxy-2-methylcyclohexanone: Corey, E. J.; Melvin, L. S., Jr.; Haslanger, M. F. *Tetrahedron Lett.* **1975**, *16*, 3117. (b) *trans*-3-Hydroxy- and 3-silyloxy-2-butylcyclohexanone: Tanner, D.; Sellen, M.; Baekvall, J. E. *J. Org. Chem.* **1989**, *54*, 3374. (c) *cis*-3-Silyloxy-2,6,6-trimethylcyclohexanone: Keränen, M. D.; Kot, K.; Hollmann, C.; Eilbracht, P. *Org. Biomol. Chem.* **2004**, *2*, 3379.

Scheme 4



very well to give the cyclopentanone **14d** in 73% yield.⁹ Not unexpectedly, the unsubstituted epoxy ether **13c** produced no product, presumably because, as we had shown earlier, an alkyl-stabilizing group is required to direct cleavage of the oxirane ring at C2 (a tertiary carbocation is required). Finally treatment of the 6-membered *tert*-butyl analogue **13b** with TBSOTf, even on heating to 40 °C for more than 12 h, resulted in less than 10% conversion to the desired product **14b**. The low conversion for this analogue is probably due to steric hindrance of the coordination of the hindered epoxide to the hindered silyl triflate, although we could not a priori rule out some unusual stereoelectronic effect due to the *tert*-butyl group, namely that the ring could no longer adopt a conformation such that the hydride could align with the σ^* orbital of the epoxide. We could distinguish between these two effects and carry out the rearrangement by changing the Lewis acid from the bulky TBSOTf to the less bulky TESOTf or TMSOTf (Scheme 5). Treatment of

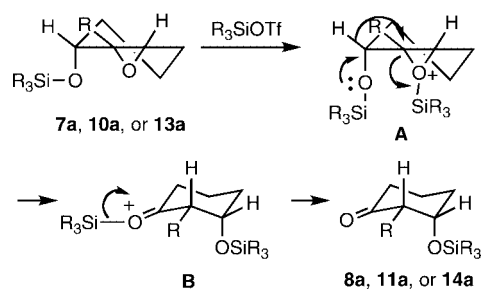
Scheme 5



the *tert*-butyl substrate **13b** with the smaller TESOTf afforded the TES ether **14e** in 50% yield. The yield could be improved by using the less hindered TMSOTf to give the TMS ether **14f** in 73% yield. We showed that the silyl ether present in the substrate had little effect since treatment of the less hindered TES ether analogue **13e** with the hindered TBSOTf afforded a low yield (<10%) of the expected product **14b**.

We presume that the mechanism of this cyclic nonaldol aldol process is similar to the acyclic version, namely the pathway shown in Scheme 6. Complexation of the basic epoxide oxygen to the silyl triflate Lewis acid would afford the silylated epoxide **A**, which would undergo concerted 1,2-hydride migration promoted by the lone pair of electrons on

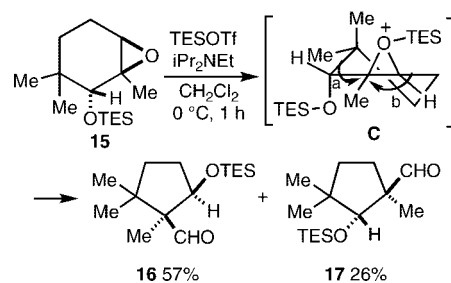
Scheme 6



the oxygen of the silyl ether to give the oxonium ion **B** in which inversion of configuration has occurred. Final loss of the silyl group would then furnish the observed ketone products.

Evidence in support of this mechanism was obtained by the attempted rearrangement of the anti epoxy silyl ether **15** (Scheme 7). Treatment of **15** with TESOTf afforded a

Scheme 7



mixture of the two diastereomeric aldehydes **16** and **17** in 57% and 26% yields, respectively. The structures were assigned based on extensive proton NMR analysis and NOE experiments.¹⁰ Since the normally favored anti 1,2-hydride migration is disfavored due to poor orbital overlap, the normally less favored ring contraction via alkyl migration is observed, with pathway a being favored over pathway b in intermediate **C**.

In summary, we describe the first example of the nonaldol aldol rearrangement of cyclic α -alkyl epoxy silyl ethers to afford α -alkyl β -silyloxy cycloalkanones. The process works for nearly all α -alkyl substituents as long as the hydrogen is anti to the epoxide oxygen. Further work on this rearrangement and its use in synthesis will be reported in due course.

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Supporting Information Available: Experimental procedures and proton and carbon NMR data for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(9) The stereochemistry of these compounds were assigned by analogy to the earlier analogues **8** and **11**.

(10) There was a strong NOE between the proton α to the OTES group and the aldehyde in **17** which was absent from **16**.