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Unexpected Syn Hydride Migration in the Non-aldol Aldol Reaction

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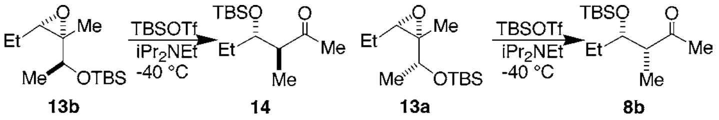
ABSTRACT

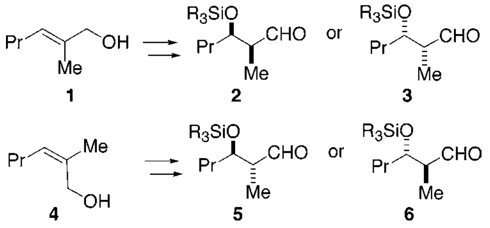


Non-aldol aldol rearrangement of the epoxy silyl ether 13b afforded the expected anti methyl ketone 14, while the diastereomeric epoxy silyl ether 13a afforded the syn methyl ketone 8b via an unprecedented syn hydride migration. Calculations suggest that this unusual reaction proceeds via the carbocation, which cannot easily rotate due to steric hindrance.

The products of the extensively studied aldol condensation can be obtained with both high diastereoselectivity and enantioselectivity. The non-aldol aldol reaction allows the formation of aldol products without using the aldol condensation[1] and involves the rearrangement of optically active tertiary epoxide silyl ethers derived from 2-methyl allylic alcohols in the presence of a hindered base and a silyl triflate. Chirality is introduced via a Sharpless asymmetric epoxidation.[2] Recently, we have shown that the chirality at the α center influences the diastereoselectivity as well as the chemoselectivity of the migrating group,[3] e.g., an α-methyl substituent selectively affords the syn methyl ketones, which are versatile intermediates in many natural product syntheses. During our study on the scope and limitations of the non-aldol aldol reaction of tertiary epoxide secondary silyl ethers, we discovered an unexpected and unprecedented rearrangement with retention of configuration at the tertiary epoxide carbon. We suggest a novel syn hydride migration to account for these results, the origin of which is explored by detailed theoretical calculations.

In 1993, we showed that both the syn **2** and **3** and the anti **5** and **6** aldol products could be obtained stereoselectively depending on the geometry and the chirality of the starting epoxides derived from (*E*)- and (*Z*)-allylic alcohols **1** and **4**, respectively (Scheme 1).[1] The mechanism involves a concerted anti hydride migration in the silylated epoxonium ion as shown for one diastereomeric epoxide **A** (Figure 1). We reported the expansion of this methodology to tertiary epoxide secondary silyl ethers to obtain the four possible

Scheme 1



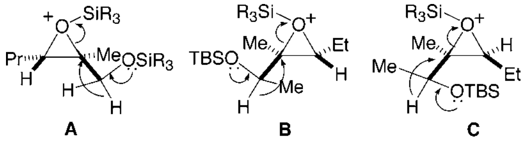


Figure 1.

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(1) Jung, M. E.; D'Amico, D. C. *J. Am. Chem. Soc.* **1993**, *115*, 12208−12209.

(2) For a review, see: Pfenninger, A. *Synthesis* **1986**, 89−116.

(3) Jung, M. E.; van den Heuvel, A. *Tetrahedron Lett.* **2002**, *43*, 8169−8172.

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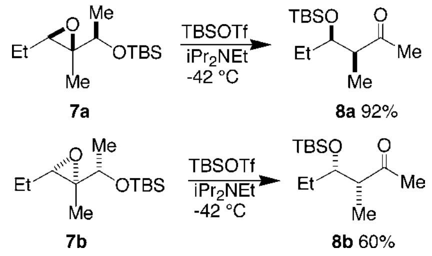
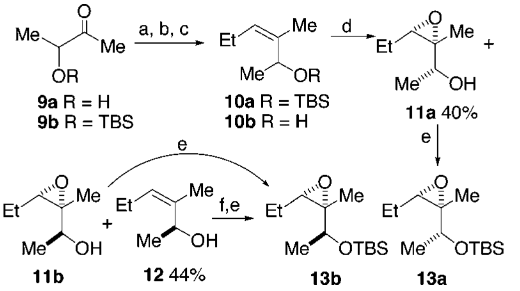
stereoisomers of the 3-methyl-4-silyloxy-2-alkanones. The non-aldol aldol reaction of the epoxy silyl ether **7a** afforded exclusively the syn aldol product **8a** with clean inversion of stereochemistry at the tertiary epoxide atom (Scheme 2). This reaction presumably proceeds via anti hydride migration in the silylated epoxonium ion **B** (Figure 1). Rearrangement of the enantiomer **7b** also gave the syn aldol product **8b**.[4]

Scheme 2



The epoxides derived from the (*Z*)-alkenes were then prepared starting from 3-hydroxy-2-butanone **9a** (Scheme 3). A (*Z*)-selective Wittig reaction[5] of the TBS ether **9b** gave the (*Z*)-allylic ether, **10a**, which was deprotected. The resulting allylic alcohol **10b** was subjected to the Sharpless asymmetric epoxidation under kinetic resolution conditions to afford the epoxide **11a** and the alkene **12**. The other diastereomer **11b** was obtained in variable yield from the epoxidation but could be prepared via a Mitsunobu reaction on **11a** followed by hydrolysis.[6] Silylation of **11ab** proceeded smoothly to give the two diastereomeric silyl ethers **13ab**.

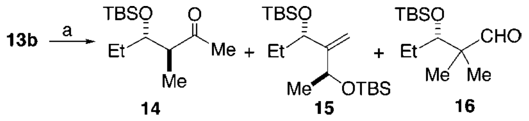
Scheme 3 [a]



[a] Reaction conditions: (a) TBSCl, ImH, CH_2Cl_2, 0 °C, 90 min, 94%. (b) $PrPPh_3Br$, KHMDS, THF, 23 to −78 °C, **9b**, −78 to 23 °C, 85%. (c) TBAF, THF, 0 to 23 °C, quant. (d) ${}^tBuOOH$, $Ti(OiPr)_4$, D-(−)-DET, CH_2Cl_2, −15 °C, 24 h. (e) TBSCl, ImH, DMF, 23 °C, 1 h. (f) PPh_3, DEAD, p-$NO_2C_6H_4CO_2H$, Et_3N; K_2CO_3, MeOH.

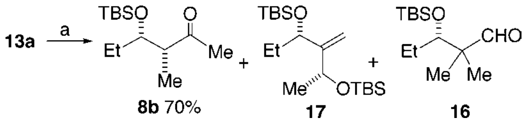
Non-aldol aldol rearrangement of **13b** occurred as expected to give the anti product **14** along with some elimination product **15** and the methyl migration product **16** (Scheme 4). The major product **14** is formed via the intermediate **C** (Figure 1), which suffers from some nonbonded interaction, e.g., the methyl−methyl interaction and the steric crowding of the two large groups oriented cis on the epoxide. Consequently, considerable amounts of the elimination product **15** and the product of the methyl migration **16** are obtained. When the diastereomeric epoxy silyl ether **13a** was subjected to the rearrangement (Scheme 5), the expected anti product **14** did not result but rather the syn aldol product **8b**, with high selectivity. This is a very unusual result and requires a new mechanistic picture to account for the retention (and not inversion) of stereochemistry at the tertiary epoxide carbon. We propose that upon activation of the epoxide **13a** with TBSOTf to give the intermediate **D**, the opening of the epoxide occurs to generate the tertiary carbocation **E**, and subsequent migration of the hydride to form **8b** is much faster than rotation around the bond (Figure 2). The conformation that would lead to the expected anti migration **F** (Figure 2) is presumably too hindered to be formed in large amounts perhaps due to the severe non-bonded interaction between the ethyl and methyl groups as shown.

Scheme 4 [a]



[a] Reaction conditions: (a) TBSOTf, iPr2NEt, CH_2Cl_2, 4 Å MS, −40 °C; **14**:**15**:**16** = 1:0.8:0.25.

Scheme 5 [a]



[a] Reaction conditions: (a) TBSOTf, iPr2NEt, CH_2Cl_2, 4 Å MS, −40 °C; **12b**:**17**:**16** = 1:0.1:trace.

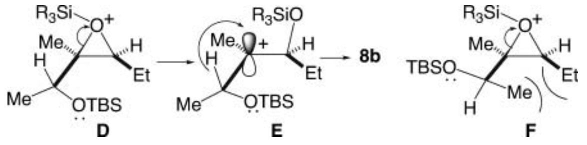


Figure 2.

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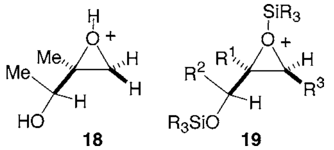
(4) Compounds **8a**, **8b**, and **15** were desilylated, and the NMRs of the resulting keto alcohols matched those in the literature: Hoffmann, R. W.; Ditrich, K.; Fröch, S. *Liebigs Ann. Chem.* **1987**, 977−985.

(5) (a) Sreekumar, C.; Darst, K. P.; Still, W. C. *J. Org. Chem.* **1980**, *45*, 5, 4260−4262. (b) Jung, M. E.; Fahr, B. T.; D'Amico, D. C. *J. Org. Chem.* **1998**, *63*, 2982−2987.

(6) Mitsunobu, O. *Synthesis* **1981**, 1−28.

Theoretical calculations on model systems provide evidence that support this hypothesis. Calculations (B3LYP/6-31G*) on the simple model compound, the protonated epoxy alcohol **18** (Figure 3), indicate that of the three possible reactions, two (the anti hydride migration (anti H-migration) and the Payne-type rearrangement (PR)) are concerted processes, while the third, the syn hydride migration (syn H-migration), takes place through a transition state that resembles a tertiary carbocation. The energetics of the transition states (TS) for the three competing rearrangements of **18** are: anti H-migration, 2.1 kcal/mol; PR, 2.6 kcal/mol; syn H-migration, 4.0 kcal/mol. The most notable feature of the energetics is the closeness of the three processes, suggesting that appropriate sets of substituents should be able to cause each of the pathways to be the favored one. From a detailed examination of the calculations on the reactions of the simple model **18**, we suggest that in the general case of **19** (Figure 3), (a) substrates with large alkyl groups on silicon should disfavor the PR because both silyloxy groups are required to be in a position approaching the central carbon atom in that transition state; (b) R^2 and R^3 are close to each other in the TS for the anti H-migration so that increasing the size of those groups should disfavor this reaction; and (c) R^1 and R^2 are close to each other in the TS for the PR and the syn H-migration via the cation and thus increasing their size should disfavor those reactions. The first hypothesis has been borne out in our earlier research on the PR;[3] namely, the PR is much slower with OTBS groups than with OTMS or OTES groups. On the basis of these results with the simple model, we decided to carry out calculations of the larger model, the bis-trimethylsilyl analogue, **20**, of the real system. A conformational energy profile of the rotamers of **20** is given in Figure 4. This analysis lends evidence to the hypothesis that the normally favored anti H-migration, which must proceed via rotamer **20e**, is disfavored in this particular case: steric interactions cause **20e** to be the least stable of the three fully staggered rotamers. As mentioned above, the large silyl groups (TBS), not included in these calculations, would disfavor the PR via rotamer **20a**. Also, the transition states for rotation among the rotamers are relatively large and would be expected to be even larger for the bis-OTBS derivative **13a**. It is interesting to note that the calculations imply that the silylated epoxide oxygen is somewhat distorted from a tetrahedral geometry, with the calculated displacement from coplanarity being 36°. Thus, the TBS group on this oxygen would have a significant interaction with the groups on the substituted carbon.



18 **19**

Figure 3.

Three transition states for rearrangement were also located (Figure 5). Transition state **G** is for the concerted PR, while transition state **H** is highly dissociative and leads to the product **21** corresponding to syn H-migration. Transition state

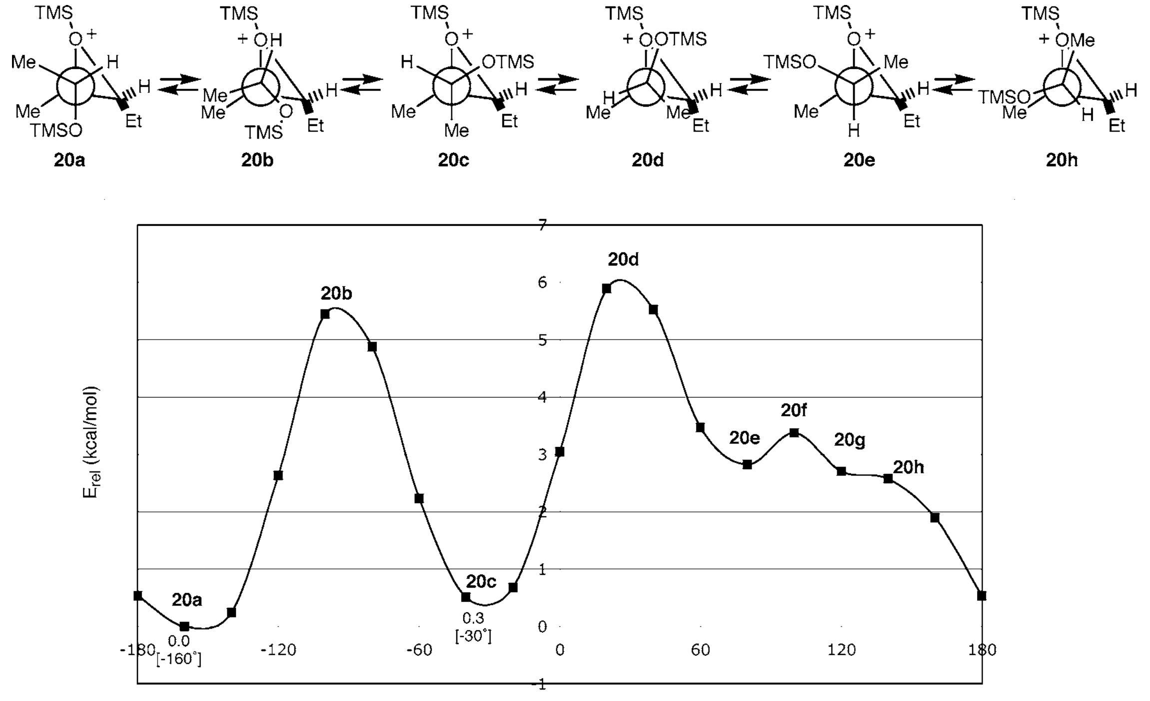


Figure 4. Conformational analysis of **20**, relative energies in kcal/mol (including vibrational corrections).

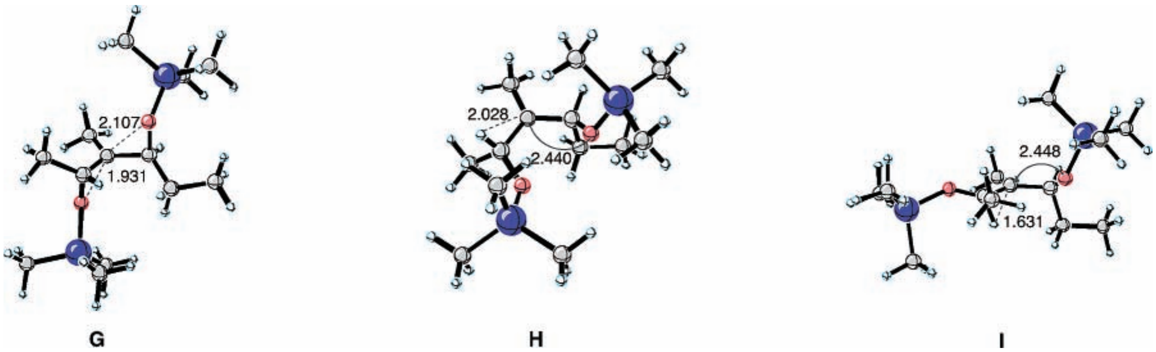
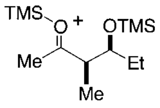
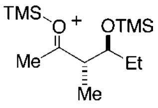


Figure 5. Three transition states for rearrangement of **20**. Transition state **G** is for the Payne rearrangement; **H** is for an H-migration in the syn stereochemistry (which would lead to **21** and then **8b**), and **I** is for an H-migration in the anti stereochemistry (which would lead to **22** and then **14**). Distances are given in Å.

I leads to the product **22** corresponding to anti H-migration. Neither a carbocation intermediate nor a transition state linking such an intermediate to **20** could be located. Of the three rearrangement transition states, the lowest in energy is **H**, the syn migration transition state, which is at 6.1 kcal/mol relative to **20a**. Transition states **G** and **I** are at 6.6 and 6.7 kcal/mol, respectively. The syn H-migration is calculated to be the favored rearrangement path. Thus, we suggest that the rearrangement of **13a** occurs by opening of the strained silylated epoxonium ion via low-energy rotamers **20c** and/or **20a** through a transition state that closely resembles the corresponding carbocation but does not have a barrier to H-migration. Therefore, H-migration occurs rather than the rapid rotation about the single bond to the side chain. The transfer of the hydride occurs on the same face of the carbocation (the top face as drawn in **20**) since it is on that side of the molecule in both rotamers **20c** and **20a**. The calculated barriers suggest a borderline Curtin–Hammett situation, with rearrangement occurring competitively with conformational interconversion of reactants. A somewhat similar argument involving rotation of a substituted alkyl group α to a carbocation has been used to account for the preferential alkyl group migration over hydride migration.[7]



21



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Thus, we have shown that while the non-aldol aldol rearrangement of one diastereomer of the (*Z*)-epoxy silyl ether **13b** proceeds normally to give the anti ketone **14**, the other diastereomer **13a** unexpectedly provides the syn ketone **8b** by a novel syn hydride migration. Calculations suggest that this unusual reaction proceeds via the carbocation, which cannot easily rotate due to steric hindrance. Further work in this area is underway.

Acknowledgment. We thank the National Institutes of Health (CA-72684) for generous support and the National Science Foundation for support under equipment grant CHE-9974928. A.G.L. thanks the Fulbright Commission and Astra-Zeneca for a fellowship and the National Computational Science Alliance and the UCLA Academic Technology Service for allocations of computer time.

Supporting Information Available: General experimental procedure for the non-aldol aldol rearrangements and proton and carbon NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(7) Jung, M. E.; D'Amico, D. C. *J. Am. Chem. Soc.* **1995**, *117*, 7379–7380.