

Versatile Diastereoselectivity in Formal [3,3]-Sigmatropic Shifts of Substituted 1-Alkenyl-3-alkylidenecyclobutanols and Their Silyl Ethers

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Received March 15, 2005; E-mail: jung@chem.ucla.edu

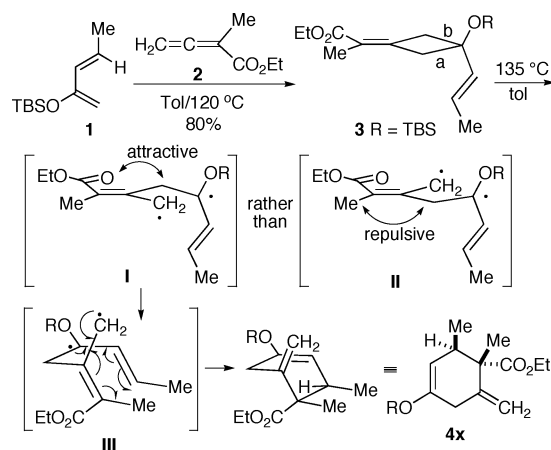
We recently reported the formal [3,3]-sigmatropic shift of 1-alkenyl-3-alkylidenecyclobutyl silyl ethers to give various 2-methylenecyclohex-4-enecarboxylates and the application of this methodology to the total synthesis of the antitumor agent dysidiolide in its correct enantiomeric form.¹ We proposed a mechanism to account for the unusual exo selectivity of this thermal process. We now report the rearrangement of more substituted systems to include unsymmetric 2,2-dialkylethenyl derivatives, which have caused us to revise this original mechanism. In addition, we report herein the base-catalyzed rearrangement of the corresponding cyclobutanols, which proceeds at very low temperatures and affords the opposite diastereoselectivity. This work now permits the formation of very hindered substituted cyclohexene systems.

Heating the cyclobutyl silyl ether **3**, prepared by the [2 + 2] cycloaddition of the silyloxybutadiene **1** and the 2-methylallene-carboxylate **2**, gave only the exo cyclohexene **4x** (Scheme 1). We believe that this rearrangement occurs via a diradical mechanism, as proposed by Dolbier,² in which bond **a** of the cyclobutane is selectively cleaved over bond **b** since the electron-deficient methylene radical in **I** would be expected to be more stable cis to the electron-donating methyl group rather than cis to the electron-withdrawing ester. This seems to be due to two factors: a repulsive steric interaction between the methyl and the sp³ carbon in **II** and a slight attractive interaction of the carbonyl oxygen and protons on the sp³ methylene group in **I**. Rotation and electronic reorganization, as shown in **III**, would give the observed exo product **4x**.³

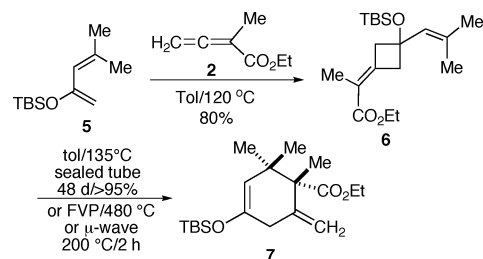
Because it is often extremely difficult to prepare very hindered cyclohexene systems by cycloadditions, for example, compounds with contiguous quaternary centers, we studied the rearrangement of the 2,2-dialkylethenyl systems. Thus, cycloaddition of the silyloxydiene **5** prepared from mesityl oxide and the allenecarboxylate **2** gave the cyclobutane **6**, which could be cleanly rearranged to the hindered cyclohexene **7** on heating in a sealed tube at 135 °C for 48 days or by flash vacuum pyrolysis⁴ or microwave heating⁵ (Scheme 2). We also prepared the unsymmetrical 2,2-disubstituted alkenyl systems, namely, the three aryl alkenes, **9a–c**, via cycloaddition of the analogous *E*-arylbutadienes **8** and the allenecarboxylate **2**. Heating of these cyclobutanones gave the desired cyclohexenes but with poor diastereoselectivity (roughly 2:1) (Scheme 3).

Attempts to promote the rearrangement using TBAF to prepare the alkoxide in situ failed due to elimination of the tertiary allylic silyl ether by the basic fluoride ion.⁶ To try to improve the diastereoselectivity of this process, we decided to prepare the diastereoselectivity of this process, we decided to prepare the trimethylsilyl ether rather than the corresponding *tert*-butyldimethylsilyl ether. Thus, the TMS enol ether **11** was prepared from mesityl oxide and reacted with the allenecarboxylate **2** to give the desired silyl ether **12** in 58% yield (Scheme 4). Hydrolysis of the silyl ether in acidic ethanol furnished the cyclobutanol **13** in 45% yield. After several failed attempts to rearrange the alcohol with sodium bases (with and without metal additives), we found that

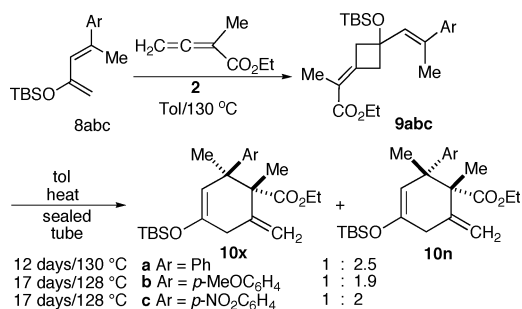
Scheme 1



Scheme 2



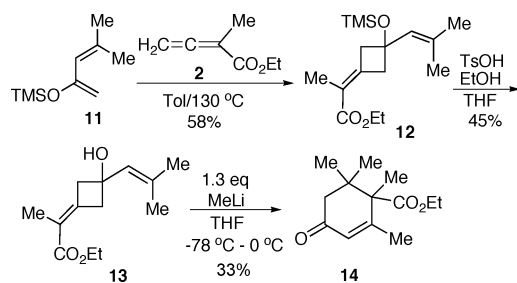
Scheme 3



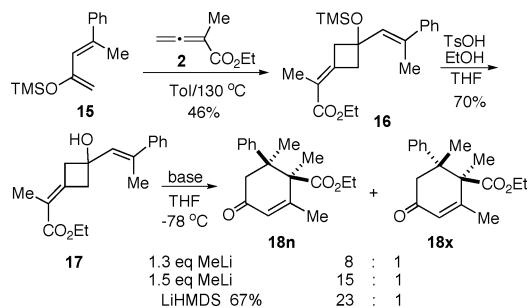
treatment of **13** with methyl lithium at -78 °C gave the desired rearrangement product **14** in 33% yield along with 10% of recovered **13** and some of the tertiary alcohol from addition of methyl lithium to the ester. Thus, as hoped, the anion of the alcohol rearranged at low temperatures to give the enone ester.

Now that we had developed a method for the rearrangement of these systems at low temperature, we decided to reexamine the unsymmetrical 2,2-disubstituted alkenyl systems. The diene **15** (prepared from the *E*-enone) reacted with **2** to give the silyl ether **16**, which was hydrolyzed to give the alcohol **17** in 70% yield. Treatment of this alcohol with lithium bases afforded the cyclo-

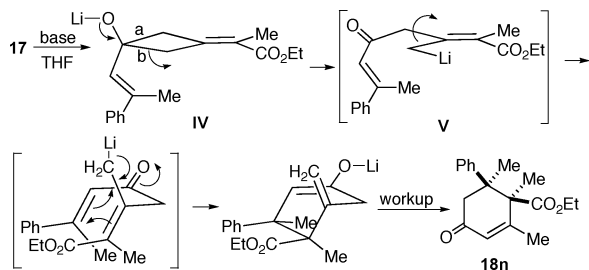
Scheme 4



Scheme 5



Scheme 6

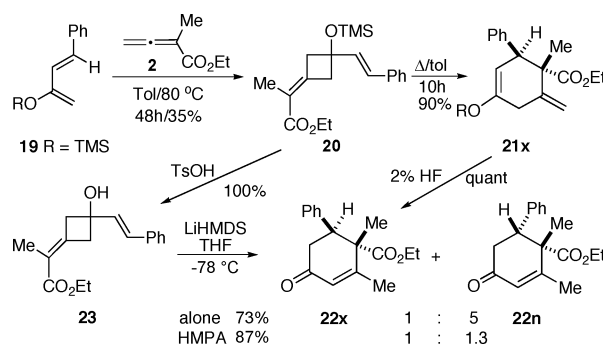


hexenone products with a great preference for the endo isomer, for example, LiHMDS afforded a 67% yield of **18n** with only a trace of **18x** (23:1).⁷ Thus, we have developed a method for the low temperature conversion of such cyclobutanols into cyclohexenones but with a complete inversion of the stereochemical preference.

Presumably, the selective formation of the endo isomer **18n** from **17** proceeds via the mechanism outlined in Scheme 6. The metal alkoxide **IV** formed by deprotonation of the alcohol **17** would open bond **b** cis to the ester group in great preference to **a** since Weiler and Harris have shown that the cis anion is formed in complete preference to the trans in similar systems.⁸ Rotation in **V** followed by an intramolecular Michael addition as shown would then afford **18n**. Thus, the reaction proceeds via two distinct mechanisms depending on conditions.

The consequences of this mechanistic dichotomy imply that either diastereomer can be made from the same substrate by choice of conditions. We have now shown that to be the case (Scheme 7). [2 + 2] Cycloaddition of the diene **19** with **2** gave the cyclobutyl silyl ether **20** in 35% yield (along with some of the [4 + 2] product **21x**).⁹ Thermolysis of **20** in toluene afforded only the exo product **21x** in 90% yield, which was desilylated to give the exo cyclohexenone **22x** as the sole product. To access the opposite diastereomer, the silyl ether **20** was hydrolyzed in acid to the alcohol **23** in quantitative yield. Treatment of **23** with LHMDS in THF at -78 °C afforded a 73% yield of a 5:1 mixture in which the endo

Scheme 7



diastereomer **22n** predominated. Thus, either the endo or the exo diastereomer can be prepared as the major product of the rearrangement of **20**. It is interesting to note that when HMPA is added to the solution to help dissociate the lithium ion, the selectivity decreases to only 1.3:1. Therefore, a tight metal alkoxide bond is required for high stereoselectivity, presumably because it is necessary for the selective cleavage of bond **b** in Scheme 6.

In summary, we have developed a route to very hindered cyclohexene systems via a thermal [3,3]-sigmatropic rearrangement of cyclobutyl silyl ethers and the base-promoted cyclobutanone opening—intramolecular Michael cyclization to give either diastereomer of the desired product. Further work on the application of these rearrangements in synthesis is underway and will be reported in due course.

Acknowledgment. We thank the National Science Foundation (CHE0314591) for generous support of this work.

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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- (2) (a) Dolbier, W. R., Jr.; Mancini, G. J. *Tetrahedron Lett.* **1975**, 2141. (b) Dolbier, W. R., Jr.; Piedrahita, C. A.; Al-Sader, B. H. *Tetrahedron Lett.* **1979**, 2957. (c) Spitzner, D. *Angew. Chem.* **1982**, *94*, 639. (d) Kozhushkov, S. I.; Kuznetsova, T. S.; Zefirov, N. S. *Dokl. Akad. Nauk SSSR* **1988**, *299*, 1395–1399. (e) Spitzner, D.; Klein, I. *Liebigs Ann. Chem.* **1990**, 63.
- (3) These conclusions are drawn from an extensive theoretical study of the mechanism of this reaction, which is currently underway. Houk, K. N.; Zhao, Y. L. Unpublished results. The mechanism proposed here is different than the one proposed earlier by us for this process.^{1a}
- (4) For a review of flash vacuum pyrolysis, see: Trahanovsky, W. S.; Lee, S. K. *Synthesis* **1996**, 1085–1086 and references therein.
- (5) The use of various solvents for this process showed that moderately polar solvents, such as chlorobenzene, 1,2-dichlorobenzene, THF, etc., accelerated the rearrangement by a factor of about 4–5, whereas very polar solvents, such as DMF and DMSO, gave the two triene products (approximately 1:1 mixture) via solvolysis of the tertiary silyl ether.
- (6) This produced the same approximately 1:1 mixture of triene esters as did heating in DMSO or DMF.
- (7) Although hexa-1,5-dien-3-olates are well-known to rearrange to enones (e.g., anionic oxy-Cope), there are no examples of this process with an 3-methylene-1-alkenylcyclobutan-1-ol system such as these.
- (8) (a) Harris, F. L.; Weiler, L. *Tetrahedron Lett.* **1985**, *26*, 1939. (b) Harris, F. L.; Weiler, L. *Tetrahedron Lett.* **1984**, *25*, 1333. Deprotonation of stereospecifically deuterated 3-methylcrotonate was carried out with LDA in the presence of HMPA, so that it is not clear whether an association of the lithium base with the carbonyl was the determining factor in the stereochemical course of the reaction (syn deprotonation).
- (9) The yield of the [2 + 2] product **20** is somewhat low because the aryl group in monoaryl substituted systems accelerates the rearrangement to give the exo products (e.g., **21x**) during the heating required to prepare the cyclobutane. This is not the case for monoalkyl substituted systems (e.g., **3**), where the yield is generally 80% or so.

JA051663P