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Use of Hindered Silyl Ethers as Protecting Groups for the Non-aldol Aldol Process

Michael E. Jung,* Barbara Hoffmann, Bernhard Rausch, and Jean-Marie Contreras

Department of Chemistry and Biochemistry, University of California−Los Angeles, Los Angeles, California 90095-1569

jung@chem.ucla.edu

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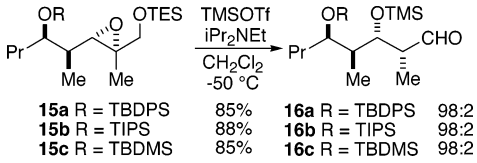
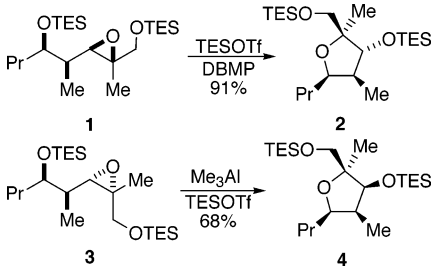
ABSTRACT



Bulky epoxy bis-silyl ethers, e.g., 15, derived from 5-trialkylsilyloxy-2-alken-1-ols by epoxidation and silylation were treated with TMSOTf to afford non-aldol aldol rearrangement products, the 3,5-bis(silyloxy)alkanals, e.g., 16, with little to none of the corresponding tetrahydrofurans.

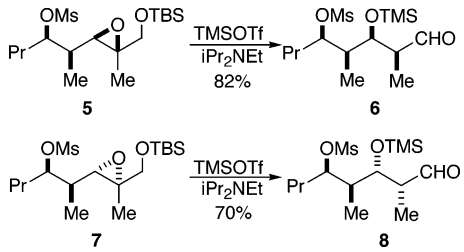
While investigating the iterative non-aldol aldol process,[1] we observed that simple silyl ethers were ineffective as protecting groups for the growing polypropionate chain. Treatment of the epoxy bis-silyl ethers **1** and **3** with silyl triflate in the presence of various bases, e.g., 2,6-di-*tert*-butyl-4-methylpyridine (DBMP) or trimethylaluminum, afforded mainly the product of cyclization of the silyl ether on to the developing tertiary carbocation to produce the fully substituted tetrahydrofurans in good yields (Scheme 1).[2]

Scheme 1



Consequently, we developed the mesylate group as a protecting group, which allowed the facile production of bis-propionates, e.g., **5** and **7** give **6** and **8**, respectively, in good yield (Scheme 2).[3] In our projected synthesis of erythromycin, we required a non-aldol aldol rearrangement to occur with a primary mesylate; however, since we encountered some problems handling this reactive substrate, we decided to revisit silyl ethers as protecting groups. Herein we report the first use of hindered silyl ethers for the rearrangement

Scheme 2



(1) Jung, M. E.; D'Amico, D. C. *J. Am. Chem. Soc.* **1993**, *115*, 12208−09.

(2) Jung, M. E.; D'Amico, D. C. *J. Am. Chem. Soc.* **1997**, *119*, 12150−58.

(3) Jung, M. E.; Lee, W. S.; Sun, D. *Org. Lett.* **1999**, *1*, 307−9.

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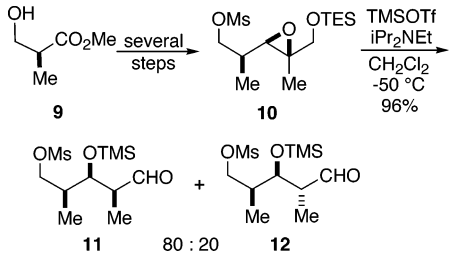
of epoxy bis-silyl ethers to give good yields of the polypropionate products.

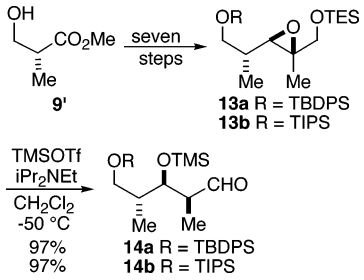
The commercially available β-hydroxy ester **9** was converted in several steps[2] to the epoxy mesylate **10**, which was treated under our normal conditions to give the desired rearrangement product **11**, along with about 20% of the C2-epimer, presumably formed via a Payne rearrangement mechanism,[4] e.g., a double-inversion process (Scheme 3).

Scheme 3



The opposite ester enantiomer **9′** was converted in seven steps into the diastereomeric epoxy bis-silyl ethers **13a**,**b**, which were treated with TMSOTf to afford 97% yield of the desired aldehydes **14a**,**b** in a diastereomeric ratio of 98:2 (Scheme 4). This is the first reported example of a simple

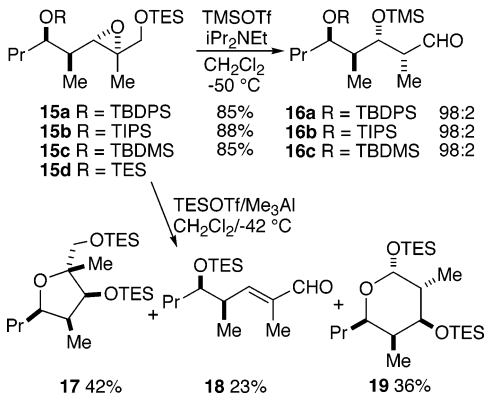
Scheme 4



silyl ether affording the protected bis-propionate chain and opens up many more possibilities for the use of this process in synthesis. We also showed that TESOTf produced the more stable TES ethers analogous to **14a**,**b** in similar yield and purity (96%, 98:2 de).[5]

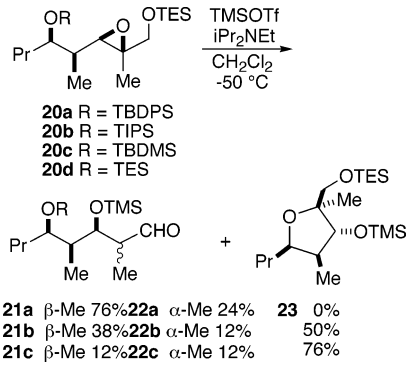
We decided to test the generality of this process for the more useful secondary ethers as a possible replacement method for simple polypropionate chains. A series of anti epoxy bis-silyl ethers **15a**−**c** were prepared by peracid epoxidation of the corresponding allylic alcohol followed by triethylsilylation. Treatment with TMSOTf and base afforded the desired bis-propionate bis-silyl ethers **16a**−**c** in excellent yield and extremely high diastereoselectivity (Scheme 5). It is clear that a quite bulky silyl ether is required since

Scheme 5



treatment of the triethylsilyl ether **15d** under similar conditions gave the tetrahydrofuran **17** as well as the two products derived from the non-aldol aldol rearrangement **18** and **19**.[5] However, not all diastereomers work well under these conditions. In particular, treatment of the syn epoxy bis-silyl ethers **20a**−**c** (prepared by titanium-promoted hydroperoxide epoxidation of the allylic alcohol and triethylsilylation) with TMSOTf afforded mixtures of products **21**−**23** (Scheme 6).

Scheme 6



The epoxide protected with the largest silyl ether **20a** gave the best results, namely, a 3:1 mixture of the desired bis-propionate **21a** and its C-2 epimer **22a** with none of the THF **23**. The other two substrates gave increasing amounts of the THF **23** and poorer mixtures of the bis-propionates **21bc** and **22bc**. The corresponding TES ether **20d** gave only the THF **23** in excellent yield.[5]

The difference in reactivity of the anti and syn epoxy bis-silyl ethers **15** and **20**, respectively, seems to involve the stability of the transition state for cyclization of the silylated epoxonium ion to the tetrahydrofuran product. In the case of the anti epoxides **A**, there is significant steric interaction between the side chain methyl group and the methyl group on the epoxide, while with the syn epoxides **B**, this

(4) Jung, M. E.; van den Heuvel, A. *Tetrahedron Lett.* **2002**, *43*, 8169−72.

(5) Structures of the products were proven by analysis of the coupling constants and NOEs of the appropriate protons of the acetonides made by hydride reduction of the aldehyde, removal of the secondary silyl ether, and ketal formation with dimethoxypropane.

interaction is absent or very small (Figure 1). Therefore, in the anti case **A**, the semipinacol rearrangement to give the non-aldol aldol product is favored, while in the syn case **B**, cyclization to give the THF is preferred.

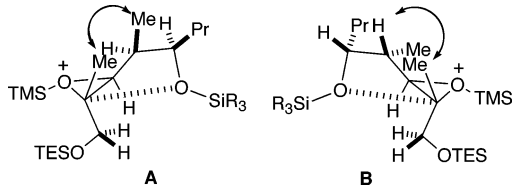


Figure 1.

In summary, we have developed the first rearrangement of epoxy bis-silyl ethers in both primary and secondary cases to give the differentially protected bis-silyloxy alkanals (bis-propionates) in high yield and excellent diastereoselectivity. Further work on this process and its application to the synthesis of erythromycin is currently in progress.

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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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