Enantiospecific Synthesis of All Four Diastereomers of 2-Methyl-3-((trialkylsilyl)oxy)alkanals: Facile Preparation of Aldols by Non-Aldol Chemistry

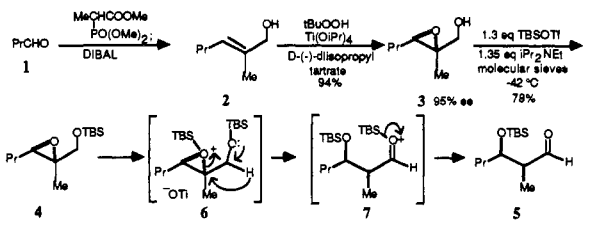
Michael E. Jung*,[1] and Derin C. D'Amico

Department of Chemistry and Biochemistry
University of California, Los Angeles, California 90024

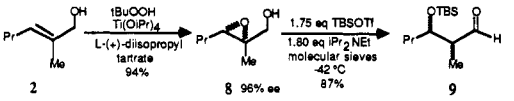
Received August 16, 1993

A large amount of excellent chemistry has been developed over the years to produce aldol products with high diastereomeric and enantiomeric control.[2,3] In general, the methods for enantiocontrol utilize an aldol reaction with well-designed chiral auxiliaries to produce the desired enantiomer with, at times, quite high selectivity. We now report a new method for synthesizing all four diastereomeric aldol products—3-alkoxy-2-methylalkanals—with high enantiocontrol by a unique non-aldol route. The absolute stereochemistry at both centers is introduced by a Sharpless asymmetric epoxidation reaction.[4] The key step involves the intramolecular hydride transfer from the methylene group of the silyl ether of the epoxy alcohol, which serves to open the epoxide regiospecifically with inversion of configuration to generate the desired 2-methyl-3-(silyloxy)alkanals, as described in detail below.

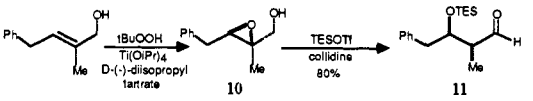
For example, the simple aldehyde butanal **1** was converted into (*E*)-2-methylhex-2-enol (**2**) by a straightforward route.[5] This allylic alcohol **2** was then converted into the optically active epoxy alcohol **3** in 94% yield and 95% enantiomeric excess (ee) using the D-(−)-diisopropyl tartrate [D-(−)-DIPT] as the chiral catalyst.



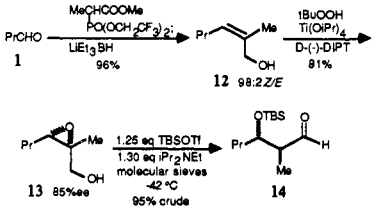
When the epoxy alcohol **3** was treated with *tert*-butyldimethylsilyl triflate (TBSOTf) at low temperature, optically active 3-((*tert*-butyldimethylsilyl)oxy)-2-methylhexanal (**5**), the syn aldol product, was formed readily in excellent yield.[6] We believe that the mechanism of this novel transformation involves activation of the epoxide oxygen with the silyl triflate followed by intramolecular hydride transfer as shown in **6** to generate the new stereochemical center at the methyl-substituted carbon in **7**, which then loses the trialkylsilyl group to give the product **5**. We can preform the silyl ether **4** under normal conditions (1.3 equiv of TBSCl, 1.5 equiv of Hunig's base, CH_2Cl_2, 12 h, heat, >90%)[7] and carry out the rearrangement with BF_3 etherate to also give **5**, the yields being only slightly lower than those for the one-step process.[8] The best conditions are direct treatment of the epoxy alcohol **3** with 1.3 equiv of TBSOTf and 1.35 equiv of Hunig's base in the presence of molecular sieves at −42 °C to afford the desired product **5** in 87% crude yield. Both capillary GC and NMR analyses show this compound to be a >50:1 mixture at the center α to the aldehyde;[9] after chromatography, we isolate a 96:4 mixture in 78% yield. In like manner, using the L-(+)-diisopropyl tartrate, compound **8**, the enantiomer of **3**, was prepared in 94% yield and 96% ee. Rearrangement using TBSOTf



as before afforded the enantiomer of **5**, namely the syn aldol product **9**, as a >99:1 mixture at the center α to the aldehyde[9] (isolated yield after chromatography 87% as a 92:8 ratio). Other silyl triflates work just as well. For example, the benzyl system was converted into the β-(triethylsilyl)oxy aldehyde **11** via the epoxy alcohol **10** in good overall yield and ee.



In order for this method to be generally useful, it must not only work well for the syn diastereomers but also be applicable for the preparation of the anti diastereomers. Therefore, we next examined the (*Z*)-allylic alcohols, which should give rise to the anti diastereomers by an application of this route. Thus butanal **1** was treated with the bis(trifluoroethoxy)phosphonate reagent of Still[10] to give the (*Z*)-α,β-unsaturated ester which was not isolated but directly reduced with Super-Hydride (Aldrich) in a one-pot procedure to give the (*Z*)-allylic alcohol **12** in 96% yield as the major component of a 98:2 *Z*/*E* mixture. Sharpless



epoxidation of **12** with D-(−)-DIPT gave the desired epoxy alcohol **13** in 81% yield and 85% ee, which was rearranged by treatment with TBSOTf and Hunig's base to the desired anti aldol product **14**, as a >50:1 crude mixture (more than 20:1 after column chromatography). In like manner, using L-(+)-DIPT, the alcohol **12** was converted into the anti aldehyde **16** via the epoxy alcohol

(1) UCLA McCoy Award recipient, 1991-92; UCLA Hanson-Dow Teaching Award recipient, 1992.

(2) For reviews, see: (a) Heathcock, C. H. The Aldol Addition Reaction. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1984; Vol. 3, Chapter 2, pp 111–212. (b) Braun, M. Recent Developments in Stereoselective Aldol Reactions. In *Advances in Carbanion Chemistry*; Snieckus, V., Ed.; JAI Press: Greenwich, CT, 1992; Vol. 1, Chapter 4. (c) Togni, A.; Pastor, S. D. *Chirality* **1991**, *3*, 331. (d) Evans, D. A.; Nelson, J. V.; Taber, T. R. *Top. Stereochem.* **1982**, *13*, 1. (e) Masamune, S.; Choy, W. *Aldrichim. Acta* **1982**, *15*, 47.

(3) For some recent specific examples, see: (a) Paterson, I.; Lister, M. A.; McClure, C. K. *Tetrahedron Lett.* **1986**, *27*, 4787 and references therein. (b) Reetz, M. T.; Kunisch, F.; Heitman, P. *Tetrahedron Lett.* **1986**, *27*, 4721.

(4) (a) Finn, M. G.; Sharpless, K. B. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1985; Vol. 5, Chapter 8, pp 247–308. (b) Martin, V. S.; Woodard, S. S.; Katsuki, T.; Yamada, Y.; Ikeda, M.; Sharpless, K. B. *J. Am. Chem. Soc.* **1981**, *103*, 6237. (c) Rossiter, B. E.; Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1981**, *103*, 464. (d) Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 5974.

(5) A better way to make large quantities of the allylic alcohol is via a modified Bayliss–Hillman procedure using ethyl acrylate and DABCO, followed by acetylation and reduction with an ethoxyaluminum hydride reagent. See: Basavaiah, D.; Sarma, P. K. S. *J. Chem. Soc., Chem. Commun.* **1992**, 955.

(6) The relative stereochemistries of both the syn and anti products were confirmed by ^1H NMR analysis of the corresponding acetonides (prepared by reduction of the aldehyde to the primary alcohol, fluoride removal of the TBS group, and acetonide formation). The coupling constants observed for the protons α to the oxygen atoms were those expected for the structures drawn.

(7) These conditions produce an 88:12 mixture of the epoxy alcohol **4** and the rearranged silyloxy aldehyde **5**.

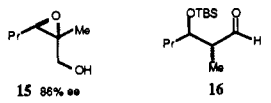
(8) We assume that the BF_3 complexes with the epoxide and that internal hydride transfer occurs as with the silyl triflate to give the analogue of **7**, which then internally transfers the silyl group from the oxonium salt to the $ROBF_3$ group (with loss of BF_3) to give the observed product **5**.

(9) This ratio was determined both by ^1H NMR integration of the relevant peaks in **5** and **9** and their C_2 epimers (compounds **14** and **16**, respectively) and by capillary GC analysis.

(10) Still, W. C.; Gennari, C. *Tetrahedron Lett.* **1983**, *24*, 4405.

0002-7863/93/1515-12208$04.00/0

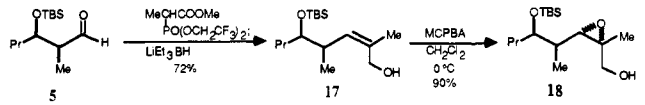
15 in comparable yield and stereochemical purity. Thus the (*E*)-



allylic alcohols give the syn aldol products, while the (*Z*)-allylic alcohols afford the anti aldol products. Therefore, by a three-step process—Wittig, and reduction, epoxidation, and rearrangement—we can prepare all four diastereomers of the 2-methyl-3-(silyloxy)alkanals in high yield and excellent enantioselectivity.

The closest literature precedent to this rearrangement is in the work of Yamamoto and Tsuchihashi. In a series of papers, Yamamoto[11] has shown that hindered aluminum-based Lewis acids can promote rearrangements of epoxy silyl ethers to produce various products including both erythro and threo aldols. But in all cases, the group being transferred (hydrogen or alkyl) is originally attached to the epoxide carbon and not at the adjacent carbon as it is here. Tsuchihashi[12] observed transfer of alkyl groups from adjacent carbons to tertiary epoxide centers to generate quaternary carbons α to ketones but reported the preparation of neither tertiary centers nor aldehydes by that approach. In a joint paper,[12a] the two authors reported the migration of phenyl and vinyl groups in the presence of $TiCl_4$ and Et_3SiH to produce primary alcohols. Thus we are the first to observe hydride migration and to prepare aldehydes by this type of chemistry.

One of the major advantages of this approach for the synthesis of polypropionates is that the product of the key rearrangement is already a protected aldehyde, so the next sequence can be carried out directly. In most of the other known aldol procedures, one must protect the β-hydroxy group and convert the acyl unit into an aldehyde to continue the process. We report here one example of such a second process. Conversion of the aldehyde **5** into the (*Z*)-allylic alcohol **17** was accomplished in 72% yield.



Epoxidation with peracid afforded the epoxy alcohol **18** as the major isomer of a 12:1 stereochemical mixture.[13] We are currently examining the preparation of all four of the diastereomeric epoxides corresponding to **18** and their rearrangements to aldol products.

Thus we have shown that simple methyl-substituted epoxy alcohols can be easily transformed into 2-methyl-3-((trialkylsilyl)-oxy)alkanals with high enantiocontrol.

Acknowledgment. We thank the National Institutes of Health (GM 31349) for generous financial support.

(11) (a) Maruoka, K.; Sato, J.; Yamamoto, H. *Tetrahedron* **1992**, *48*, 3749. (b) Maruoka, K.; Ooi, T.; Yamamoto, H. *J. Am. Chem. Soc.* **1989**, *111*, 6431. (c) Maruoka, K.; Ooi, T.; Nagahara, S.; Yamamoto, H. *Tetrahedron* **1991**, *47*, 6983.

(12) (a) Maruoka, K.; Hagesawa, M.; Yamamoto, H.; Suzuki, K.; Shimazaki, M.; Tsuchihashi, G. *J. Am. Chem. Soc.* **1986**, *108*, 3827. (b) Suzuki, K.; Miyazawa, M.; Tsuchihashi, G. *Tetrahedron Lett.* **1987**, *28*, 3515. (c) Shimazaki, M.; Hara, H.; Suzuki, K.; Tsuchihashi, G. *Tetrahedron Lett.* **1987**, *28*, 5891.

(13) Epoxidation of chiral allylic alcohols is often more stereoselective when using the resident chirality present in the alkene and simple peracid or metal-catalyzed epoxidation than when using external sources of chirality as in reactions such as the Sharpless epoxidation. For an excellent review of such substrate-directed reactions, see: Hoveyda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev.* **1993**, *93*, 1307.