

Synthesis of Four Diastereomeric 3,5-Dialkoxy-2,4-dimethylalkanals by a Simple Extension of the Non-Aldol Aldol Process to Bis(propionates)

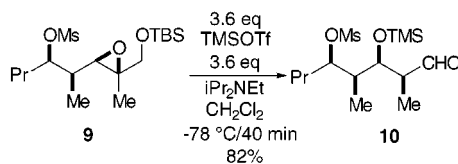
Michael E. Jung,* Woo Song Lee, and Daqing Sun

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

jung@chem.ucla.edu

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ABSTRACT



The synthesis of all four diastereomers of bis(propionates), 3,5-dialkoxy-2,4-dimethylalkanals, by non-aldol aldol chemistry is described. The epoxy alcohols (**3**, **4**) were converted into the mesylates (**9**, **11**) which were cleanly rearranged to the desired 3,5-bis(oxygenated)-2,4-dimethylalkanals (**10**, **12**) in high yield. The epoxy mesylates (**13**, **16**) gave the desired products (**14**, **17**) in good yield on treatment with TMSOTf and a hindered base.

During the past several years, a large amount of excellent chemistry has been developed to produce aldol products with high stereocontrol.^{1,2} Many of the methods for enantiocontrol utilize an aldol reaction with well-designed chiral auxiliaries

or, more recently, chiral catalysts, to produce the desired enantiomer with, at times, quite high selectivity. Several years ago we reported an alternative method for the preparation of all four diastereomeric aldol products—3-alkoxy-2-methylalkanals—with high enantiocontrol by a unique non-aldol route.³ The key step of this new method involved the intramolecular hydride transfer from the methylene group of either an epoxy alcohol (prepared with high enantioselectivity by a Sharpless asymmetric epoxidation reaction)⁴ or its silyl ether **1** which opened the epoxide regioselectively with inversion of configuration to generate the desired 2-methyl-3-silyloxyalkanals **2**. We now report herein the extension of this method for the preparation of bis(propio-

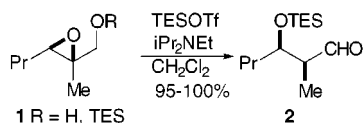
(1) For reviews of the aldol reaction, see: (a) Mukaiyama, T.; Kobayashi, S. *Org. React.* **1995**, *46*, 1. (b) Franklin, A. S.; Paterson, I. *Contemp. Org. Synth.* **1994**, *1*, 317. (c) Heathcock, C. H. The Aldol Addition Reaction. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1984; Vol. 3, Chapter 2, pp 111–212. (d) 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. (e) Togni, A.; Pastor, S. D. *Chirality* **1991**, *3*, 331. (f) Evans, D. A.; Nelson, J. V.; Taber, T. R. *Top. Stereochem.* **1982**, *13*, 1. (g) Masamune, S.; Choy, W. *Aldrichimica Acta* **1982**, *15*, 47.

(2) For some recent examples, see: (a) Paterson, I.; Cowden, C. J.; Woodrow, M. D. *Tetrahedron Lett.* **1998**, *39*, 6037. (b) Paterson, I.; Woodrow, M. D.; Cowden, C. J. *Tetrahedron Lett.* **1998**, *39*, 6041. (c) Evans, D. A.; Kim, A. S.; Metternich, R.; Novack, V. J. *J. Am. Chem. Soc.* **1998**, *120*, 5921. (d) Corey, E. J.; Lee, D.-H.; Choi, S. *Tetrahedron Lett.* **1992**, *33*, 6735. (e) Corey, E. J.; Lee, D.-H. *Tetrahedron Lett.* **1993**, *34*, 1737. (f) Corey, E. J.; Kim, S. S. *J. Am. Chem. Soc.* **1990**, *112*, 4976. (g) Duthaler, R. O.; Herold, P.; Wyler-Helfer, S.; Riediker, M. *Helv. Chim. Acta* **1990**, *73*, 659. (h) Singer, R. A.; Carreira, E. M. *Tetrahedron Lett.* **1997**, *38*, 927. (i) Carreira, E. M.; Singer, R. A.; Lee, W. S. *J. Am. Chem. Soc.* **1994**, *116*, 8837.

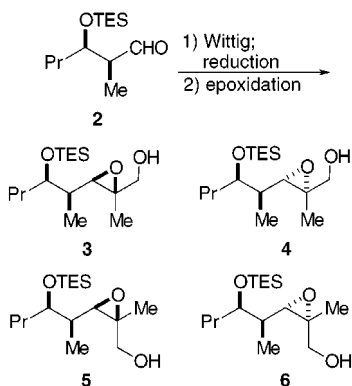
(3) Jung, M. E.; D'Amico, D. C. *J. Am. Chem. Soc.* **1993**, *115*, 12208.

(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.

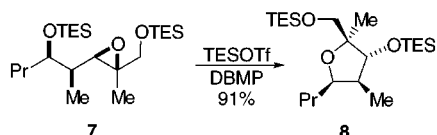
onates), namely, the double aldol products—3,5-dialkoxy-2,4-dimethylalkanal.



The process of converting an aldehyde into a 3-alkoxy-2-methylalkanal required only three steps, Wittig reaction and in situ reduction of the ester, epoxidation, and then silylation—rearrangement. Since the product of this process is itself an aldehyde, we realized that iteration of the sequence would afford a second propionate unit and, after several iterations, a polypropionate. We now describe conditions to carry out this sequence. The conversion of the substituted aldehydes, e.g., **2**, into all four of the required elongated epoxy alcohols, e.g., **3–6**, was straightforward, requiring



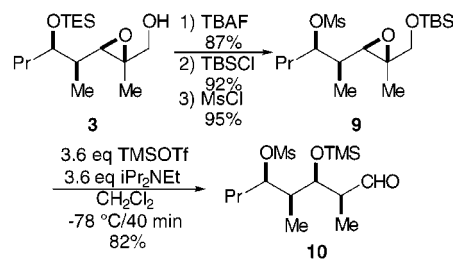
only two steps, namely, an *E*- or *Z*-selective Wittig reaction and in situ reduction to the allylic alcohol and then diastereoselective epoxidation.⁶ However, the normal conditions for rearrangement—silylation, triethylsilyl triflate and a base [2,6-di-*tert*-butyl-4-methylpyridine (DBMP)], did not afford the desired products but instead gave good yields of the corresponding tetrahydrofurans, e.g., the epoxide **7** gave **8** in 91% yield.⁵ Several attempts to effect the desired rearrangement, e.g., treatment of the 4-methoxybenzyl ether analogue of **7** with CAN and use of stronger Lewis acids such as BF_3 etherate with triethylsilane as an in situ reducing agent,⁶ etc., met with little success. The two key issues were



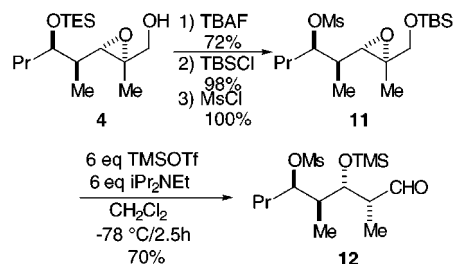
to use a protecting group on oxygen that was less electron-rich and therefore less likely to participate in trapping the tertiary cation and a less-hindered electrophilic reagent since the epoxides **3–6** were quite hindered. Although some success was found using trifluoroacetate as the protecting group,⁷ the best set of conditions utilizes a mesylate as the

protecting group and trimethylsilyl triflate (TMSOTf) as the silyl electrophile.⁸

Conversion of the epoxy alcohol **3** (prepared in two steps and high yield from **2**) in three steps gave the mesylate **9** in 76% overall yield. Treatment of this compound with excess



TMSOTf and base at -78 °C for 40 min afforded the desired bis(propionate) **10** in 82% yield.⁹ In an analogous process, the epoxy alcohol **4** was converted in 70% yield into **11** which was rearranged with excess TMSOTf and base to give the bis(propionate) **12** in 70% yield. The mesylates analogous

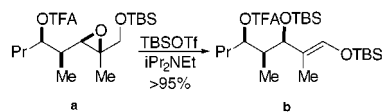


to **9** and **11**, derived from the epoxy alcohols having the opposite stereochemistry about the epoxide (**5** and **6**), did not react under these conditions, giving back mostly starting materials. However, treatment of the mesylate alcohol **13** (prepared from **5** in four steps and 61% overall yield) with TEBSCl followed by TMSOTf and the hindered base 2,6-di-*tert*-butylpyridine gave the desired anti aldehyde **14** in 58% yield along with 14% of the allylic silyl ether **15** produced

(5) Jung, M. E.; D'Amico, D. C. *J. Am. Chem. Soc.* **1997**, *119*, 12150. Epoxidation of chiral allylic alcohols is often more stereoselective under substrate control using peracid or metal-catalyzed epoxidation than by reagent control 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.

(6) (a) Jung, M. E.; Anderson, K. L. *Tetrahedron Lett.* **1997**, *38*, 2605. (b) Maruoka, K.; Hasegawa, M.; Yamamoto, H.; Suzuki, K.; Shimazaki, M.; Tsuchihashi, G. *J. Am. Chem. Soc.* **1986**, *108*, 3827.

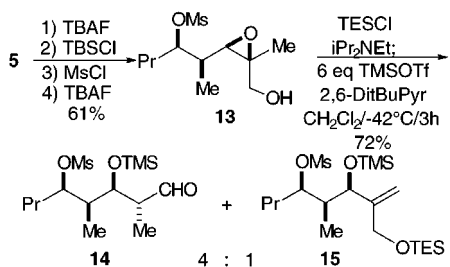
(7) For example, treatment of the trifluoroacetate **a** furnished the *E*-enol silyl ether **b** in excellent yield. We thank Susumu Harashima for this experiment and others in this area



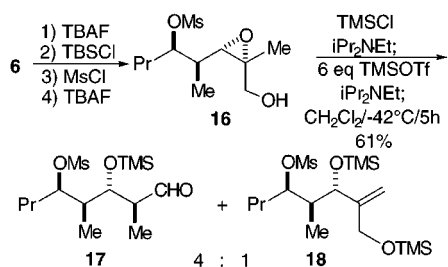
(8) We had earlier shown that trimethylsilyl triflate was an excellent promoter of the desired rearrangement but chose to use the ethyl analogue instead because of the greater stability of the triethylsilyl ethers. D'Amico, D. C. Ph.D. Thesis, UCLA, 1994.

(9) The structures of all of the bis(propionate) products were proven by ^1H NMR studies (coupling constants and NOE studies) of the cyclic carbonates or acetonides formed from the corresponding diols.

by deprotonation of the methyl group in an E2-type elimination. In similar fashion the fourth diastereomeric epoxide,

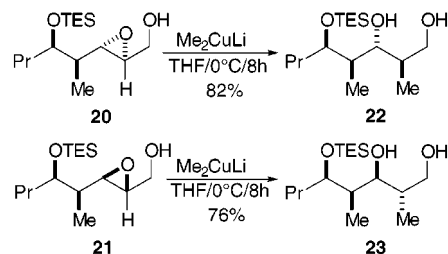


16 (prepared from **6**), was converted into the desired aldehyde **17** and the allylic ether **18** in similar yield and selectivity, in this case using Hünig's base. Thus, all four of the possible isomers of the bis(propionates) derived from the syn aldol **2**—compounds **10**, **12**, **14**, and **17**—can be prepared in a simple iterative process.

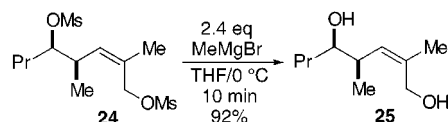


Of course, there are other known methods for the formation of anti aldol isomers that can also be applied to these systems. For example, the method of Kishi¹⁰ worked very well, namely, first preparation of the two disubstituted epoxy alcohols **20** and **21** by highly stereoselective epoxidation of the *E*-allylic alcohol **19**. Addition of lithium dimethylcuprate

to either epoxy alcohol gave high yields of the desired anti diols **22** and **23**.



Finally we tested the conditions for removal of the mesylate protecting groups in similar systems. For example, treatment of the dimesylate **24** with 2.4 equiv of methylmagnesium bromide in THF at 0 °C for 10 min afforded the desired diol **25** in 92% yield.¹¹

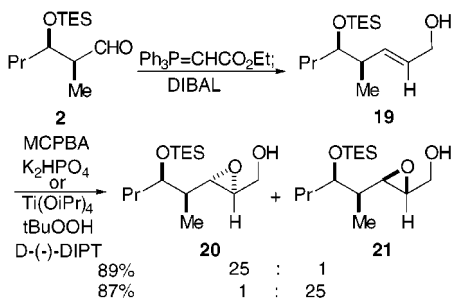


Thus we have shown that the “non-aldol aldol” process can be extended to the preparation of bis(propionates) with good diastereocontrol. The application of this chemistry to the synthesis of polypropionate natural products such as tedanolide¹² and 13-deoxytedanolide¹³ is currently underway in our laboratories.¹⁴

Acknowledgment. We thank the National Institutes of Health (CA72684) for generous financial support.

Supporting Information Available: Typical experimental procedures for the formation of both syn and anti aldol products 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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(10) Kishi, Y.; Nagaoka, H. *Tetrahedron* **1981**, *23*, 3873.

(11) For an example of these conditions, see: Cossy, J.; Ranaivosata, J. L.; Bellosta, V.; Wietzke, R. *Synth. Commun.* **1995**, *25*, 3109.

(12) Schmitz, F. J.; Gunasekera, S. P.; Yalamanchili, G.; Hossain, M. B.; van der Helm, D. *J. Am. Chem. Soc.* **1984**, *106*, 7251.

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(14) For further studies on the use of this process in the synthesis of the tedanolides, see: Jung, M. E.; Marquez, R. *Tetrahedron Lett.* **1999**, *40*, 3129. Jung, M. E.; Marquez, R.; Karama, U. *J. Org. Chem.* **1999**, *64*, 993.

