# FACILE SYNTHESIS OF OPTICALLY ACTIVE 2-HYDROXYMETHYL-4-METHYLENE-CYCLOHEXANOL. DE NOVO SYNTHESIS OF DIDEOXYCARBOCYCLIC SUGARS[1]

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Summary: Treatment of the olefinic epoxy alcohol **4** with diethylaluminum fluoride gives the hydroxymethyl methylenecyclohexanol **5** in yields of 60-75% rather than the other possible epoxide opening product **6** presumably due to a geometrical constraint similar to that in Baldwin's rules for ring closure.

Synthetic chemists have been extremely successful in developing methods for the production of cyclic chiral materials in high optical purity, particularly when the stereogenic center has a heteroatom directly attached. For example, there are many methods for the preparation of optically active alcohols, amines, etc., via enantioselective reductions, additions, and the like.[3] However, there are fewer methods for the easy preparation of non-heteroatomic systems in high optical purity, although several useful methods have recently been developed which involve enantio-selective cycloadditions[4] and asymmetric alkylations.[5] One possible solution for the preparation of stereogenic centers bearing only carbon and hydrogen in high purity would be to convert heteroatom asymmetry into carbon asymmetry. The most notable example of this process is the Ireland ester enolate Claisen reaction.[6] However, the ready availability of chiral epoxy alcohols in nearly complete optical purity via Sharpless-Katsuki asymmetric epoxidation[7] led us to examine the potential use of them for the production of cyclic stereogenic centers in high optical purity. Indeed Kishi and Sharpless have shown that strong nucleophiles such as dialkylcuprates could be used to open acyclic epoxy alcohols to give good yields of optically active diols.[8] In particular we wished to see if more modest nucleophiles such as simple alkenes or vinyl- or allylsilanes could be used as the nucleophiles in a cyclic version of the epoxy alcohol opening. Herein we report the successful cyclization of olefinic epoxy alcohols under mild conditions to produce cyclic diols in good yield and high optical purity.

The known trimethylsilyl methallyl alcohol[9] **1** (prepared in high yield from methallyl alcohol) was converted in 77% yield by the normal procedure into the vinyl ether which was thermolyzed to give the aldehyde **2** in 66% yield (Scheme 1). Horner-Emmons reaction followed by hydride reduction afforded the allylic alcohol **3** in 83% overall yield. Epoxidation of this allylic alcohol under Sharpless' catalytic conditions produced the desired optically active

epoxy alcohol **4** in 89% yield (analysis by ^{1}H NMR using chiral shift reagents showed that this material was of 95% ee).[10] Treatment of **4** with a variety of Lewis acids gave poor results with many products being produced. However the use of the mild Lewis acid, diethylaluminum fluoride, Et$_2$AlF, was successful.[11] Treatment of **4** in methylene chloride with slightly more than two equivalents of a solution of Et$_2$AlF in hexane furnished 2-hydroxymethyl-4-methylenecyclohexanol **5** in a yield of 75%. It is interesting to note than none of the product of the alternative opening to give the 5-membered ring, namely **6**, was observed. Thus in only six steps from the readily available alcohol **1**, one can prepare a carbocyclic 2,3-dideoxy-D-glucopyranose derivative in good yield and high optical purity.
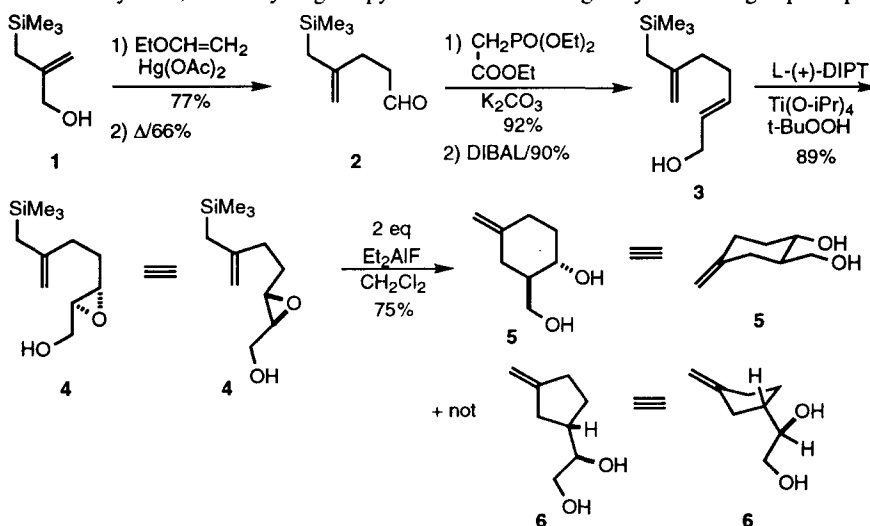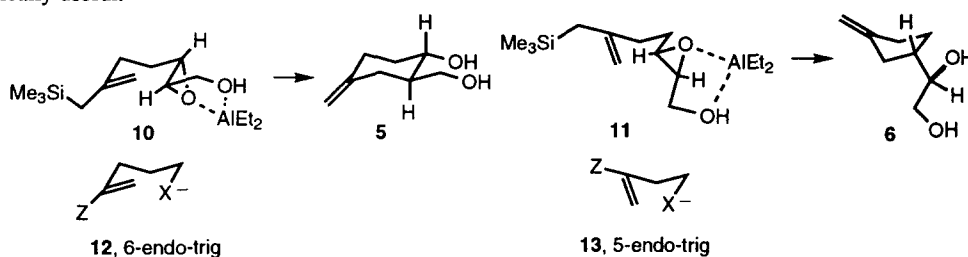

Scheme 1

The structure of the product was indicated by its ^{1}H NMR data and that of its derivatives. For example the diacetate of **5** showed absorptions corresponding to an axial proton α to an acetoxy group at δ 4.80 (td, $J = 9.7, 4.1$ Hz, 1H) and the diastereotopic methylene protons α to the primary acetate at δ 4.07 (dd, $J = 11.1, 5.8$ Hz, 1H) and δ 4.02 (dd, $J = 11.1, 4.2$ Hz, 1H). The correctness of the relative and absolute configuration was shown by the conversion of the olefinic diol **5** into the known diol **8** via ozonolysis to the cyclohexanone **7** and Clemmensen reduction. The optical rotation of our synthetic **8** ($[\alpha]_D^{25} = +27.2$ °) matched that reported for the (1S, 2R)-2-hydroxy-methylcyclohexanol ($[\alpha]_D^{25} = +28$ °),[12] which had been prepared by resolution of the 2-hydroxycarboxylic acid, and demonstrated that our material was nearly optically pure (97% pure). Other derivatives of **5** also confirmed the relative stereochemistry as well as afforded compounds for potential use in the de novo synthesis of deoxy carbocyclic sugars. Thus benzylidenation of **5** using α,α-dimethoxytoluene and PPTS gave in 80% yield the expected acetal which was
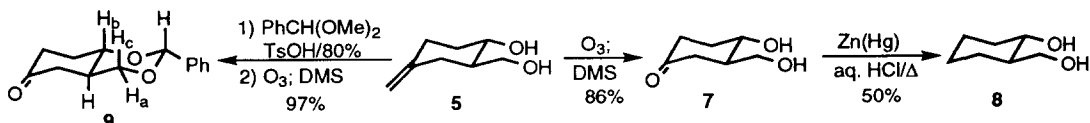
ozonolyzed in 97% yield to give the ketone **9**, a protected form of carbocyclic 2,3-dideoxy-1-keto-D-glucopyranose. Again ^{1}H NMR confirmed the assigned structure of **9** [δ 4.15 (dd, J = 11.0, 4.1 Hz, H_a), 3.89 (ddd, J = 11.3, 9.4, 4.1 Hz, H_b), 3.68 (t, J = 11.0 Hz, H_c)].

The mechanism of formation of the cyclohexanol **5** from **4** involves the simple opening of the epoxy alcohol activated by coordination of the epoxide oxygen with the non-nucleophilic Lewis acid diethylaluminum fluoride at C2 of the epoxy alcohol (Scheme 2). This is in contrast to the normal nucleophilic opening of epoxy alcohols described by Sharpless[13] in which C3 is preferentially attacked. Several examples of cyclizations of epoxy allylsilanes are also known which produce good yields of olefinic alcohols (and diols).[14] However in these cases,[14] the major product formed from allylsilane epoxyalcohols again all involve attack at C3 of the epoxy alcohol.[15] Obviously in the cyclization of **4**, other conformational forces outweigh the normal preference for C3 attack. Examination of molecular models shows that there is good overlap of the C-O bond at C2 of the epoxy alcohol with the π-orbital of the allylsilane as shown in **10** thereby leading easily to **5**. However, there is very poor overlap of the C-O bond at C3 of the epoxy alcohol with the π-orbital of the allylsilane as shown in **11** which would then lead to **6**. In particular this can be viewed as an example of Baldwin's rules for ring closure,[16] since the preferred cyclization via **10** resembles a 6-endo-trig cyclization **12** (but with the polarity inverted) and the disfavored transition state **11** resembles the disfavored 5-endo-trig cyclization **13** (again with the polarity inverted). It should be pointed out that when the olefin is exo to the ring being formed, then cyclization to the 5-membered product via a 5-exo-trig cyclization is quite good and can be synthetically useful.[17]

12, 6-endo-trig   **13, 5-endo-trig**

Scheme 2

This preference for C2 attack is so strong that even when C2 is substituted with a more electron-withdrawing group, cyclization still gives preferentially the cyclohexanol product. Thus treatment of the tosylate **14** (prepared in 87% yield by tosylation of **5**) with Et$_2$AlF gave 50% yield of the monotosylate **15**.

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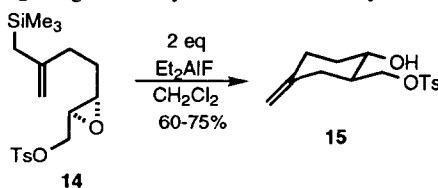
In summary we have shown that Lewis acid catalyzed cyclizations of olefinic epoxy alcohols afford preferentially 2-hydroxymethylcyclohexanols via a 6-endo-trig process in good yield and high optical purity. The utility of this process for carbocyclic sugar synthesis, e.g., for the production of compounds such as the β-glucosidase inhibitor cyclophellitol, is currently under investigation.

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References and Notes

1. Presented at the 33rd GECO Conference, Corsica, France, September 1992.
2. American Chemical Society Arthur C. Cope Scholar, 1995.
3. For excellent reviews, see: a) Nishizawa, M.; Noyori, R. "Reduction of C=X to CHXH by Chirally Modified Hydride Reagents," Chapter 1.7 in *Comprehensive Organic Synthesis*, Trost, B. M., Ed.; Pergamon; Oxford, 1991; Vol. 8, pp. 159-182. b) Jones, B. J. "Reduction of C=X to CHXH Using Enzymes and Microorganisms," Chapter 1.8 in *Comprehensive Organic Synthesis*, Trost, B. M., Ed.; Pergamon; Oxford, 1991; Vol. 8, pp. 183-210 and references in both of the above.
4. a) For a review of enantioselective cyclopropanation see: Helquist, P. "Methylene and Nonfunctionalized Alkylidene Transfer to Form Cyclopropanes," Chapter 4.6 in *Comprehensive Organic Synthesis*, Trost, B. M., Ed.; Pergamon; Oxford, 1991; Vol. 4, pp. 951-997. b) For a review of Diels-Alder reactions, see: Oppolzer, W. "Intermolecular Diels-Alder Reactions," Chapter 4.1 in *Comprehensive Organic Synthesis*, Trost, B. M., Ed.; Pergamon; Oxford, 1991; Vol. 5, pp. 315-399.
5. For a review of enantioselective alkylations, see: Caine, D. "Alkylations of Enols and Enolates," Chapter 1.1 in *Comprehensive Organic Synthesis*, Trost, B. M., Ed.; Pergamon; Oxford, 1991; Vol. 3, pp. 1-63.
6. For a review of ester enolate Claisen rearrangements, see: Altenbach, H.-J. "Functional Group Transformations via Allyl Rearrangement," Chapter 4.5 in *Comprehensive Organic Synthesis*, Trost, B. M., Ed.; Pergamon; Oxford, 1991; Vol. 6, pp. 829-871.
7. a) Finn, M. G.; Sharpless, K. B. in *Asymmetric Synthesis*; Morrison, J. D. , Ed.; Academic Press: New York, 1985; Vol. 5, Ch. 8, pp 247-308. b) Hanson, R. M.; Sharpless, K. B. *J. Org. Chem.* **1986**, *51*, 1922. c) Martin, V. S.; Woodard, S. S.; Katsuki, T.; Yamada, Y.; Ikeda, M.; Sharpless, K. B. *J. Am. Chem. Soc.* **1981**, *103*, 6237. d) Rossiter, B. E.; Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1981**, *103*, 464. e) Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 5974.
8. a) Johnson, M. R.; Nakata, T.; Kishi, Y. *Tetrahedron Lett.* **1979**, 4343. b) Behrens, C. H.; Sharpless, K. B. *Aldrichim. Acta* **1983**, *16*, 67.
9. Trost, B. M.; Chan, D. M. T.; Nanninga, T. N. *Org. Synth.* **1984**, *62*, 58; *Organic Syntheses*; Wiley: New York, 1990; Collect. Vol. VII, p. 266.
10. Jung, M. E.; Jung, Y. H. *Tetrahedron Lett.* **1989**, *30*, 6637.
11. For examples of the use of this reagent for epoxide openings, see: a) Jung, M. E.; Gardiner, J. M. *J. Org. Chem.* **1991**, *56*, 2614; b) Maruoka, K.; Sano, H.; Yamamoto, H. *Chem. Lett.* **1985**, 599.
12. Nohira, H.; Ehara, K.; Miyashita, A. *Bull. Chem. Soc. Jpn.* **1970**, *43*, 2230.
13. Sharpless, K. B.; Caron, M. *J. Org. Chem.* **1985**, *50*, 1557. For a cyclic example where attack at C3 is again favored over attack at C2, see: Morgans, D. J., Jr.; Sharpless, K. B.; Traynor, S. G. *J. Am. Chem. Soc.* **1981**, *103*, 462.
14. a) Molander, G. A.; Andrews, S. W. *J. Org. Chem.* **1989**, *54*, 3114. b) Proctor, G.; Russell, A. T.; Murphy, P. J.; Tan. T. S.; Mather, A. N. *Tetrahedron* **1988**, *44*, 3953. c) Petterson, L.; Frejd, T.; Magnusson, G. *Tetrahedron Lett.* **1987**, *28*, 2753.
15. Procter[14b] reports the formation of products of both C2 and C3 attack but couldn't isolate them, prove the structures, or determine a yield.
16. Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 734.
17. For examples of 5-endo-trig cyclizations of allylsilanes on aldehydes, see: a) Lee, T. V.; Roden, F. S. *Tetrahedron Lett.* **1990**, *31*, 2067. b) Sarkar, T. K.; Andersen, N. H. *Tetrahedron Lett.* **1978**, 3513.

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