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HIGHLY ANTI SELECTIVE S_N2' ADDITIONS OF $LiMe_2Cu$ TO CHIRAL ACYCLIC VINYLOXIRANES

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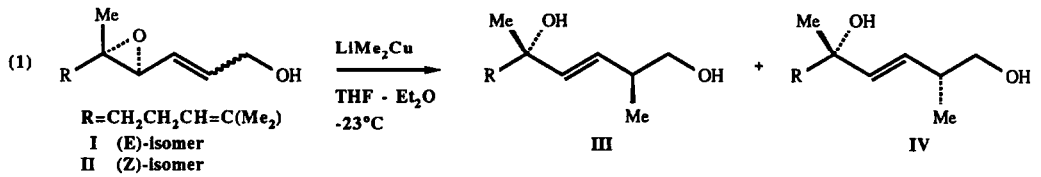
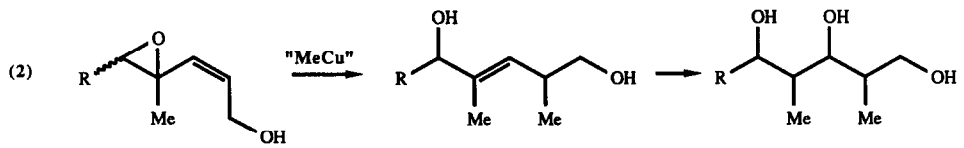
Summary: Additions of $LiMe_2Cu$ to the *trans* and *cis-Z* vinyloxiranes **8** and **10** proceed with virtually 100% anti diastereoface selectivity to afford the *syn-Z* diol **12** and the *anti-E* diol **13** as the major products.

In some feasibility studies pertaining to directed S_N2' additions of organocopper reagents to homochiral acyclic vinyloxiranes, we examined additions of $LiMe_2Cu$ to I and II (eq. 1).[1]



R=$CH_2CH_2CH=C(Me_2)$
I (E)-isomer
II (Z)-isomer

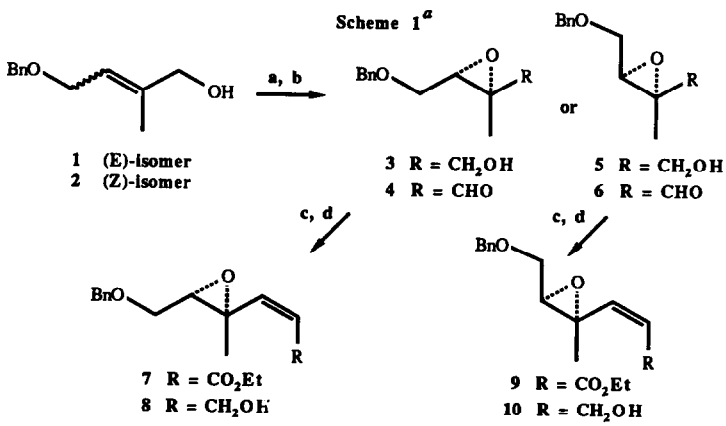
Both isomers reacted exclusively via their s-trans conformers and both showed a preference for anti addition, as indicated by the predominance of III (84:16) from the (*E*)-vinyloxirane and IV (97:3) from the (*Z*)-vinyloxirane. We have now extended these studies to vinyloxiranes such as V with a view toward the synthesis of homochiral subunits of polypropionate natural products (eq. 2).[2]



V VI VII

Prototype substrates were prepared as shown in Scheme 1 starting from 2-benzyloxyethanol.[3] Swern oxidation[4] and Wittig condensation of the resulting aldehyde with α-triphenylphosphonium propionate[4] or α-trifluoroethylphosphonopropionate[5] afforded the (*E*) and (*Z*)-conjugated esters. These

Scheme 1[a]



1 (E)-isomer
2 (Z)-isomer

3 R = CH_2OH
4 R = CHO

5 R = CH_2OH
6 R = CHO

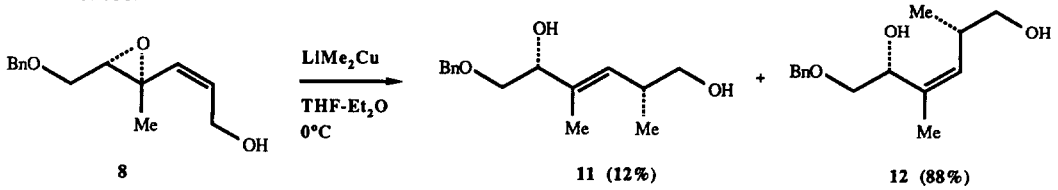
7 R = CO_2Et
8 R = CH_2OH

9 R = CO_2Et
10 R = CH_2OH

[a] (a) *L*-(+)-DET, TBHP, TIP, CH_2Cl_2; (b) DMSO, $(COCl)_2$, CH_2Cl_2, Et_3N; (c) $(CF_3CH_2O)_2POCH(Me)CO_2Et$, KHMDS, 18-crown-6, THF; (d) DIBAH, hexane.

were reduced with DIBAH[6] to the allylic alcohols **1** and **2**, respectively. Each of these allylic alcohols was epoxidized with the reagent derived from *L*-(+)-diethyl tartrate[7] affording the epoxy alcohols **3** and **5** of 80-90% ee, according to ^{1}H NMR analysis of the O-methyl mandelic esters.[8] The foregoing Swern-oxidation, Still-Horner-Emmons-condensation, DIBAH-reduction sequence was repeated with each of the epoxy alcohols to yield the vinyloxiranes of interest **8** and **10**.

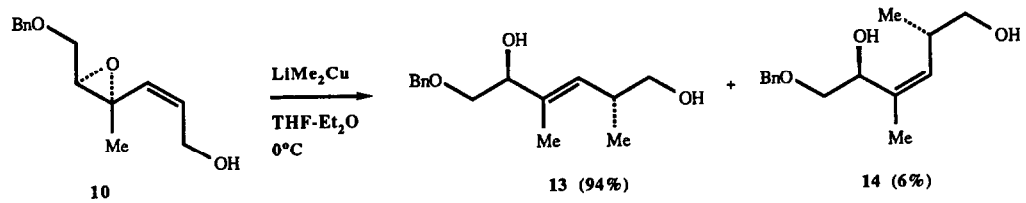
Addition of $LiMe_2Cu$ to the *trans-Z* vinyloxirane **8** proceeded in 88% yield and gave only two products, the *syn-E* and the *syn-Z* diols **11** and **12**, a 12:88 mixture according to capillary gc analysis of the diacetates.[9]



8 **11 (12%)** **12 (88%)**

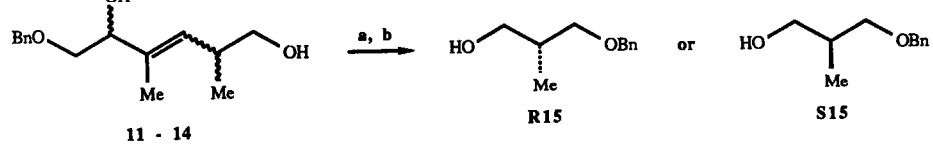
Both **11** and **12** derive from anti S_N2' addition, the former via the *s-trans* and the latter via the *s-cis* conformer of vinyloxirane **8**.

The *cis-Z* vinyloxirane **10** under comparable conditions afforded a 94:6 mixture of the *anti-E* and *anti-Z* diols **13** and **14** in 72% yield.



10 **13 (94%)** **14 (6%)**

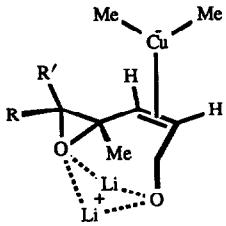
Again, S_N2' addition has occurred exclusively anti, but in this case, the reaction proceeds mainly by way of the *s-trans* conformer. In both of the foregoing examples the *E* and *Z* isomers are readily separated by flash column chromatography[10] thus permitting pure samples of the diols to be easily obtained. Furthermore, the diacetates of all four diols **11**, **12**, **13**, and **14** are differentiable by capillary gc so that isomer ratios can be accurately measured. The configuration of the newly introduced stereogenic center was deduced through ozonolysis/reduction[11] of the *tris*-benzyl ethers[12] of **11-14**. (*R*)-3-Benzyloxy-2-methyl-1-propanol (**R15**) was obtained from the benzyl ether of diols **11** and **13** whereas the ethers from diols **12** and **14** afforded the enantiomeric (*S*)-alcohol **S15**.[4b] In all cases the optical purity of **R15** or **S15** compared favorably with that of its vinyloxirane progenitor **8** or **10**.



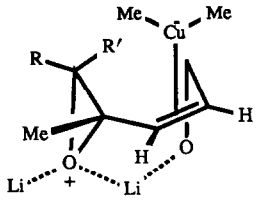
11 - 14 **R15** **S15**

(a) $(MeOCH_2CH_2OCH_2CH_2)_3N$, KOH, C_6H_6, BnBr;[12] (b) O_3, CH_2Cl_2; Me_2S, LiAl-[$OC(Et)_3$]H, THF.[11]

The foregoing additions show remarkably high diastereoface selectivity (≥99:1) suggestive of a chelation controlled process. Two possibilities can be envisioned, one involving the s-trans conformer VIII and the other the s-cis conformer IX.[13]



VIII (s-trans)

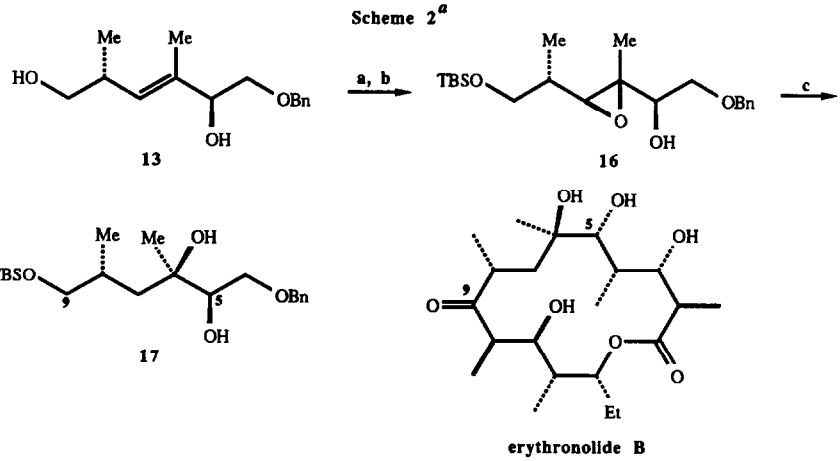


IX (s-cis)

It can be seen that the CH_2OLi grouping interacts unfavorably with the oxirane methyl substituent in the *s-trans* conformer VIII or the R' substituent in the *s-cis* conformer IX. When R' is H, as for vinyloxirane **8**, the *s-cis* conformer is favored.[14,15] When the oxirane methyl is replaced by H and R' is larger than H, S_N2' addition proceeds exclusively via the *s-trans* conformer (eq. 1).[1] Likewise, an R' grouping larger than H favors the *s-trans* mode of addition, even in the presence of the oxirane methyl substituent (**10** → **13**).[14]

To illustrate a potential application of the foregoing methodology we converted diol **13** to the differentially diprotected tetrol **17**, a C4-C9 subunit of erythronolide B (Scheme 2).[16,17]

Scheme 2[a]



erythronolide B

[a](a) TBSCl, DMAP, Et_3N; (b) MCPBA, CH_2Cl_2, -20°C; (c) $LiAlH_4$, Et_2O.

These findings demonstrate that properly designed acyclic vinyloxiranes, readily available in high optical purity and known configuration, undergo S_N2' additions with predictable stereochemistry and excellent diastereoface selectivity. Our studies with vinyloxiranes **8** and **10** are particularly relevant to the current interest in polypropionate natural product synthesis.[2] Additional work along these lines is in progress.

Acknowledgement. Support from the National Science Foundation (CHE-8615569 and CHE-8411172) is gratefully acknowledged.

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1. Marshall, J. A.; Trometer, J. D. *Tetrahedron Lett.* **1987**, *28*, 4985.

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3. 2-Benzyloxyethanol was prepared by monobenzylation (BnBr, NaH, THF) of ethylene glycol.

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6. Abbreviations: Bn = $PhCH_2$, DET = diethyl tartrate, DIBAH = $(i\text{-Bu})_2AlH$, DMAP = 4-(*N*,*N*-dimethylamino)pyridine, KHMDS = $(Me_3Si)_2NK$, MCPBA = $m\text{-}ClC_6H_4CO_3H$, TBHP = *t*-BuOOH, TBSCl = $t\text{-Bu(Me)}_2SiCl$, TIP = $Ti(O\text{-}i\text{-Pr})_4$.

7. *Cf.* Hanson, R. M.; Sharpless, K. B. *J. Org. Chem.* **1986**, *51*, 1922.

8. Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1968**, *90*, 3732.

9. The analysis was performed with a 25 m x 0.25 mm Alltech Superox Column coated with Carbowax 20M.

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11. Krishnamurthy, S. *J. Org. Chem.* **1981**, *46*, 4628.

12. Soula, G. *J. Org. Chem.* **1985**, *50*, 3717. We are indebted to Dr. O. Campopiano for suggesting the use of this phase-transfer catalyst for benzylations.

13. For a mechanistic interpretation of S_N2' displacements of allylic carboxylates with organocuprates, see: Goering, H. L.; Kantner, S. D.; Sietz, E. P., Jr. *J. Org. Chem.* **1985**, *50*, 5495. For recent work on diastereoselective S_N2' displacements of allylic mesylates, see Ibuka, T.; Nakao, T.; Nishii, S.; Yamamoto, Y. *J. Am. Chem. Soc.* **1986**, *108*, 7420.

14. These conclusions are supported by molecular mechanics calculations performed with W. C. Still's MacroModel program on the vinyloxiranes **8** and **10** constrained to transition state like conformations.

15. Replacement of the OH grouping in vinyloxirane **8** with OTIPS led to a predominance (2.3:1) of the (*E*)-allylic alcohol products with the product of anti addition (**11**) favored over the product of syn addition (enantiomer of **13**) by 3.3:1. This addition involves a preferred *s-trans* conformer of the vinyloxirane in accord with predictions based on molecular modeling. For these calculations the vinyloxirane grouping was constrained to coplanarity but the allylic OR grouping was allowed to rotate.[14] The TIPS derivative of vinyloxirane **10** gave only elimination products[1] upon treatment with $LiMe_2Cu$.

16. For the first total synthesis, see Corey, E. J.; Kim, S.; Yoo, S.; Nicolaou, K. C.; Melvin, L. S., Jr.; Brunelle, D. J.; Falck, J. R.; Trybulski, E. J.; Lett, R.; Sheldrake, P. W. *J. Am. Chem. Soc.* **1978**, *100*, 4620.

17. For close analogies to step b, see Johnson, M. R.; Kishi, Y. *Tetrahedron Lett.* **1979**, 4347. Isobe, M.; Kitamura, M.; Mio, S.; Goto, T. *Tetrahedron Lett.* **1982**, *23*, 221.

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