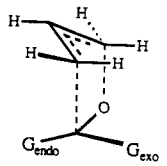
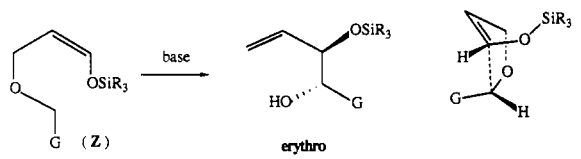
Table I. Relative Energies (kcal/mol) of Endo and Exo Substitutions Estimated by Single Point Calculations on the 3-21G Transition Structure with a Standard Substituent Replacing H_6 or H_7



G	E_{rel}(endo)	E_{rel}(exo)
C≡CH	0.9	0.0
C≡N	0.5	0.0
CHO	0.0	2.8
SiH_3	0.0	0.0
CH_3	1.5	0.0

Scheme II



mol.[19] The electronic interactions between the Li cation and the carbonyl oxygen of the formyl group could contribute somewhat to this endo preference, since the Li–O distance is 2.91 Å in the endo structure while it is 3.1 Å in the exo structure. However, the inherent endo preference of the group is clear.

When the substituents SiH_3 and CH_3 were calculated, they were arranged in the staggered conformation with respect to the C_1–C_3 bond. While SiH_3 gives no preference, CH_3 gives an exo preference of 1.5 kcal/mol. While there is no obvious steric reason for this, we can rationalize it by electrostatic arguments. Overall, methyl is negatively charged and SiH_3 is positively charged, according to Mulliken population analyses. Therefore, electronically SiH_3 should be favorable for the endo position.

Although optimizations and higher level basis sets are necessary to give a more accurate account of the steric and electronic effects, these initial simple calculations do suggest that while there is a general exo preference for G, good π-acceptors like the carbonyl group and electropositive groups like SiR_3 tend to favor the endo position. By applying these qualitative features, we can explain not only the general trends of the stereoselectivities but also the exception that carbonyl substituents lead to opposite sense of stereoselectivity. We also explain the exceptional anti selectivity for *Z*-siloxy allylic system observed by Nakai et al.[2f] (Scheme II) by the electrostatic argument. Namely, G tends to avoid a syn orientation to $OSiR_3$ because the lone pairs on O cause a significant destabilizing interaction with G.

Further studies on quantitative aspects of the steric and electronic effects of various substituents and molecular modeling of stereoselectivities have been undertaken[20] and will be reported in the near future.

Acknowledgment. We are grateful to the National Science Foundation and the National Institutes of Health for financial support of this research, to Professor Mark Midland for helpful comments, and to Dr. David Spellmeyer for preliminary calculations.

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(20) See also: Midland, M. M.; Gabriel, J. *J. Org. Chem.* **1985**, *50*, 1144. Midland, M. M.; Kwon, Y. C. *Tetrahedron Lett.* **1985**, *26*, 5013, 5017.

Methodology for the Enantioselective Synthesis of Aldols and Other 1,3-Dioxygenated Systems[1]

Robert E. Ireland,* Peter Wipf, Wolfgang Miltz, and Benoit Vanasse

Department of Chemistry, McCormick Road, University of Virginia, Charlottesville, Virginia 22901

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Summary: The enantioselective synthesis of the spiroenones **3**, **4** from (*S*)-glycidol-*O*-benzyl ether and lithiated furan derivatives is described. After conjugate addition of lithium dimethyl cuprate or lithium divinyl cuprate and conversion of the resulting saturated ketones to their respective iodides **7** and **8**, fragmentation of these halides leads to the formation of acyclic aldol-containing carbon skeletons.

The plethora of natural products that arise from the polyacetate biosynthetic pathways has in recent years stimulated many elegant and efficient synthetic methods[2] for the construction of complex 1,3-dioxygenated carbon frameworks. While 1,3-diols can be used directly or after suitable blocking in further synthetic work, aldol systems are seldom used as intermediates in extended synthetic plans due to their susceptibility to dehydration and/or reverse reaction. In addition to the aldol unit's intrinsic value for the synthesis of molecules like erythromycin and FK-506, recent work[3] on directed reduction procedures that form 1,3-diols of predetermined stereochemistry make an aldol unit an attractive intermediate for the synthesis of complex polyoxygenated compounds. For this to be feasible it is necessary that the aldol unit be masked during the intermediate synthetic operations.

One such masked system is the Δ^2-isoxazoline grouping[4] which has been used in many successful syntheses[5] but in

(1) No reprints of this paper are available.

(2) For a review of synthetic methodology in the context of the aldol reaction, see: (a) Heathcock, C. H. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1984; Vol. 3, p 111. (b) Evans, D. A.; Nelson, J. V.; Taber, T. R. *Top. Stereochem.* **1982**, *13*, 1. (c) Braun, M. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 24.

(3) For anti diols, see inter alia: Evans, D. A.; Chapman, K. T.; Carreira, E. M. *J. Am. Chem. Soc.* **1988**, *110*, 3560. For syn diols, see, inter alia: Nakata, T.; Tani, Y.; Hatozaki, M.; Oishi, T. *Chem. Pharm. Bull.* **1984**, *32*, 1411.

(4) For leading references, see: (a) Torssell, K. *Nitrile oxides, Nitrones, and Nitronates in Organic Synthesis: Novel Strategies in Synthesis*; VCH: New York, 1988. (b) Curran, D. P. *Advances in Cycloaddition*; Curran, D. P., Ed.; JAI Press: New York, 1988; Vol. 1, p 129. (c) Kozikowski, A. P. *Acc. Chem. Res.* **1984**, *17*, 410.

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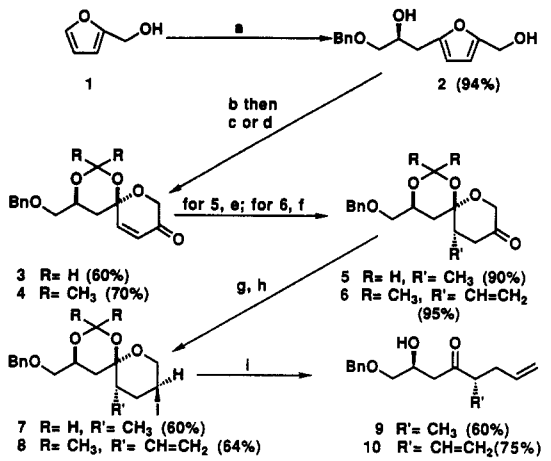
Scheme I. Spiroenone as a Masked Aldol Subunit[a]



[a] (a) 2 equiv of *n*-BuLi, THF; (*S*)-benzylglycidol, LiCl, DME; (b) MCPBA, CH_2Cl_2; (c) $(CH_2O)_x$, H_2SO_4; (d) $CH_2{=}C(OCH_3)CH_3$, HCl; (e) $LiCuMe_2$, $(C_2H_5)_2O$; (f) $LiCu(CH{=}CH_2)_2$, $(C_2H_5)_2O$; (g) L-Selectride; (h) *n*-Bu_3P, I_2; (i) C_8K/Ag/Zn.

the acyclic series the cycloaddition of chiral nitrile oxides with alkenes lacks stereochemical control.[6] A suitably substituted spiroketal[7] would also serve this purpose if means were developed for its facile synthesis in enantiomerically pure form and then fragmentation to the desired acyclic 1,3-dioxygenated skeleton. The construction and some transformations of a member of this class that leads stereoselectively to substituted aldol units are reported here.

Conceptually the spiroenones **3**, **4** are β-alkoxy ketals and by the union of these functionalities through the acetal/ketal grouping, the possibility for simultaneous cleavage of these blocking groups to free the parent aldol system is presented. An enantioselective synthesis of these spiroenones **3**, **4** is of crucial importance and such a process appeared possible by an extension of some of the work of DeShong and others[8] on the construction of spiroketals from substituted furans.

The availability of glycidol[9] in either enantiomeric form[10] and the ease with which it may be converted to its benzyl ether appeared to be a ready source of the desired chirality. Initially, epoxide opening by lithiated furan and then Vilsmeier condensation and reduction to introduce the hydroxymethylene portion served as a useful means for the formation of the diol **2**. However, after some experimentation, it was shown that the entire transformation could be accomplished in one operation and in excellent yield with lithiated furfuryl alcohol **1** in the presence of LiCl or $BF_3{\cdot}Et_2O$.

The chirality of the diol **2** thus assured, acetal/ketal formation was explored. After oxidation with MCPBA, the use of paraformaldehyde and sulfuric acid catalysis afforded, rather erratically, an adequate yield of the desired spiroenone **3**. A more reliable procedure that leads to the spiroenone **4** is one that employs 2-methoxypropene and HCl catalysis. In each case only one stereoisomer of the spiroenone system is formed as a result of the acid-catalyzed equilibration of the spiroketal center. Since ultimate aldol liberation will remove the acetal/ketal portion, the latter transformation is much to be preferred.

This spiroenone system represents a masked aldol unit that is a template upon which numerous structural changes may be made. An obviously important step is the utilization of the α,β-unsaturated ketone functionality for the introduction of disparate substituents. Toward this end the conjugate addition of cuprate reagents was explored. Lithium dimethyl cuprate added in high yield to the spiroenone **3** and gave exclusively the ketone **5** from expected axial attack.[11,12] With the spiroenone **4** the product **6** of lithium divinyl cuprate addition also formed a single stereoisomer in excellent yield. The transformations demonstrate the use of the spiroenone system as a synthetic platform for highly stereoselective reactions. Once the necessary functionality is introduced, the masked aldol system can be unravelled by a fragmentation process. Toward this end the spiroketones **5** and **6** were transformed through their respective intermediate axially oriented alcohols to their iodides **7** and **8**, which are clear candidates for metal initiated fragmentation.

The recent development[13] of the use of zinc/silver–graphite combination prepared by the reduction of the metal salts with C_8K served this purpose well. The fragmentation of each spiroketone **7** and **8** led in good yield to the acyclic aldol units **9** and **10**, and no structural or stereoisomerization was encountered. The mild conditions of this fragmentation procedure are an essential feature of this process.

It is clear that the spiroenone system **3**, **4** is of value for the construction of other acyclic aldol arrays and some of these are under active investigation. Coupled with previously described procedures for the controlled asymmetric reduction of the carbonyl group in the final aldol product, the spiroenone system will be of value in the stereoselective synthesis of aldol based polyhydroxylated natural products.

Acknowledgment. The authors thank the University of Virginia for support of this work and Dr. Wipf thanks the Swiss National Science Foundation for a fellowship.

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(7) For reviews on the chemistry of spiroketals, see: (a) Kluge, A. F. *Heterocycles* **1986**, *24*, 1699. (b) Boivin, T. L. B. *Tetrahedron* **1987**, *43*, 3309. (c) Perron, F.; Albizati, K. F. *Chem. Rev.* **1989**, *89*, 1617.

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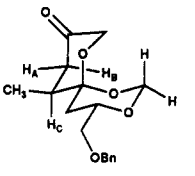
(11) (a) Corey, E. J.; Boaz, N. W. *Tetrahedron Lett.* **1984**, *25*, 3063; **1985**, *26*, 6015. (b) For a general discussion of nucleophilic attack on enones, including cuprates, see: Duval, D.; Geribaldi, S. In *The Chemistry of Enones*; Patai, S., Rapoport, Z., Eds.; John Wiley and Sons: New York, 1989.

(12) The relative stereochemistry of the cuprate addition was determined by examination of the coupling constants. A diaxial coupling constant for H_B–H_C would be in the range of 12–13 Hz, based on MM2 calculations.



J_{AC} = 2.1 Hz (eq.-eq.)
J_{BC} = 4.2 Hz (ax.-eq.)
$J(H_C\text{-}CH_3)$ = 7.2 Hz

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