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STEREOCONTROL IN THE FORMATION OF 2,3,4-TRISUBSTITUTED TETRAHYDROFURANS

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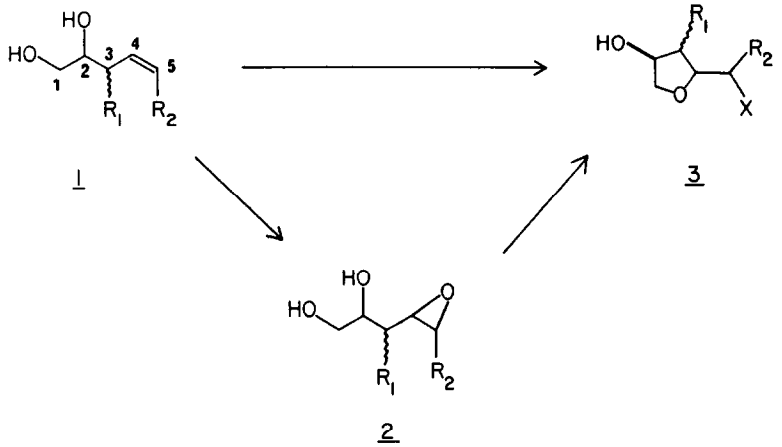
Summary: Investigations have defined the stereochemical outcome of ring-forming reactions in a series of highly substituted tetrahydrofurans. Two complementary processes are discussed.

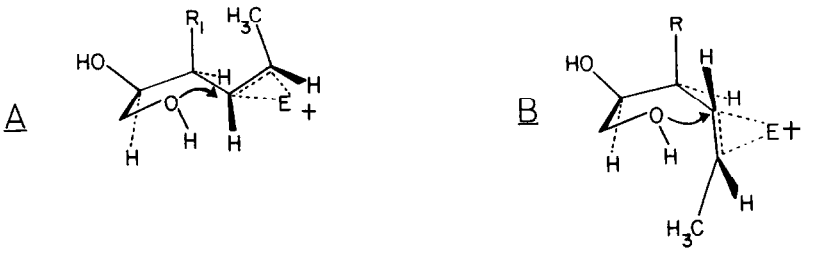
Previous reports from our laboratories have focused on the stereochemical consequences of novel strategies for preparation of highly substituted tetrahydrofurans.[2,3] While the literature reports numerous examples of the formation of tetrahydrofurans induced by electrophilic attack on γ,δ-unsaturated alcohols, circumstances which effect stereocontrol are quite rare.[4] Herein we communicate our efforts resulting in the stereocontrolled formation of 2,3,4-trisubstituted tetrahydrofurans.

As illustrated below, two differing modes for electrophilic cyclization of the homoallylic glycols 1 have been examined. Direct ring closure by iodoetherification (I_2, CH_3CN, 0°C, solid $NaHCO_3$) or selenoetherification (PhSeCl, CH_2Cl_2, -78°C) gave similar results, which were compared to the tetrahydrofurans 3 obtained in a two step sequence from oxiranes 2 with subsequent boron trifluoride-induced cyclization.



All direct cyclizations displayed complete regiocontrol regardless of the chosen conditions with exclusive participation of the primary alcohol of 1 in C-O bond formation and ring closure in the five-exo-trigonal manner.[5] Oxetanes and tetrahydropyrans were not observed as reaction products.[6] Likewise, cyclization of the epoxy diols 2 demonstrated similar regiospecificity.

Examples are shown in Table I.[7] Our direct cyclizations of 1 using iodine or phenylselenenyl chloride indicate facial selectivity in the ring closure process which will minimize unfavorable steric repulsions with substituents at the 3-position (R_1). This is most acutely illustrated in the cyclizations of Z-disubstituted alkenes as diagrammed below.

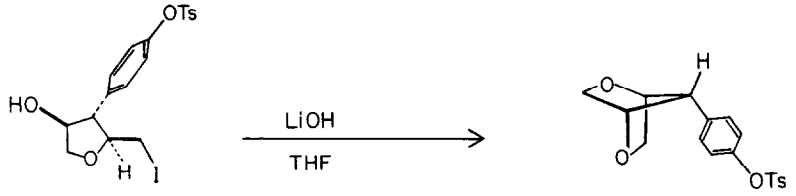


These situations afford complete stereoselectivity along pathway B to yield only tetrahydrofurans 3cd. Thus, substituents (R_1) at the 3-position appear to determine stereochemistry at C-2 of the ring with all major products demonstrating *trans*-orientations.

This preference is reversed by utilizing the epoxides 2 as intermediates for tetrahydrofuran formation. Vanadium-catalyzed epoxidations of alkenes 1 proceeded with high stereoselectivity providing substrates 2a-2e.[8] Our evidence suggest only involvement of the secondary homoallylic alcohol in these oxidations since the corresponding benzyl and *tert*-butyldiphenylsilyl ethers of primary hydroxyls of 1a and 1c gave results which paralleled the parent diols, as illustrated by the preparation of epoxide 2d.[9]

Treatment with boron trifluoride etherate in dry tetrahydrofuran or methylene chloride gave rapid ring closure by intramolecular epoxide opening with inversion of configuration at the site of hydroxyl attack.[10] We have noted that 2c undergoes cyclization strictly with inversion in spite of unfavorable steric interactions (see intermediate A). However, attempts with 2e failed to afford ring closures under these more forcing conditions. Five-endo processes did not occur even in situations with benzyl ether protection of the primary alcohol.[11] Example 2d demonstrated participation of the silyl ether oxygen in ring formation, and specific intramolecular silyl transfer through a five-membered transition state from the intermediate oxonium ion, thus allowing selective differentiation of the two secondary hydroxyls of 3h.[12]

The stereochemical details of our tetrahydrofuranyl products were unambiguously confirmed upon conversion of iodide 3a into the novel bicyclic[2.2.1] ether 4, which was confirmed by subsequent X-ray crystallographic analysis.[13,14]

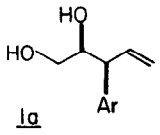
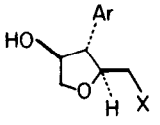
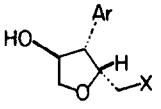
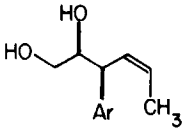
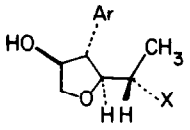
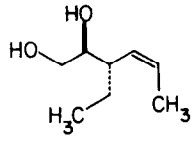
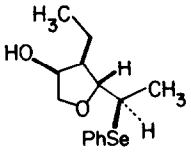
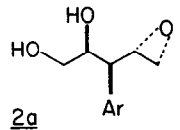
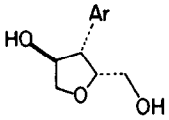
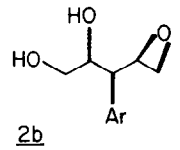
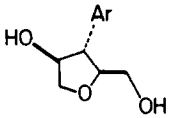
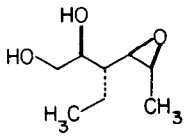
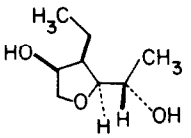


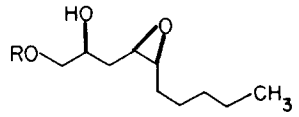
3a 4 (92%)

In summary, two complementary strategies have been studied to afford development of three contiguous asymmetric carbons in the formation of 2,3,4-trisubstituted tetrahydrofurans. Further investigations for natural product total synthesis are underway.

Acknowledgement: We thank the National Institutes of Health (AI-17674) for their generous support, and the National Science Foundation (CHE-81-05004) for purchase of 360 MHz NMR instrumentation.

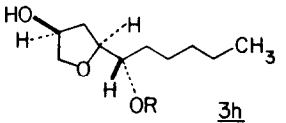
TABLE I.

Substrate	Conditions	Product		Yield
 1a	A, B		3a major	X = I 80% ratio 2.2:1
			3b minor	X = PhSe 80% ratio 1.7:1
 1b	A, B		3c	80% (X=I) 88% (X = PhSe)
 1c	B		3d	94%
 2a	C		3e	89%
 2b	C(a)		3f	81%
 2c	C(b)		3g	73%



2d R = Si^tBuPh_2

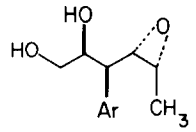
C



3h

R = Si^tBuPh_2

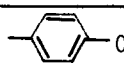
40%



2e

C[(b)]

———

Ar = 

A Iodine (1.1 equivs) in acetonitrile with solid $NaHCO_3$ at 0°C

B PhSeCl (1.1 equivs) in methylene chloride at -78°C

C Freshly distilled boron trifluoride etherate (1.0 equiv) was added to a solution of the epoxide in methylene chloride or anhydrous tetrahydrofuran at -10°C with stirring for 10 minutes.
(a) Allowed to warm to 22°C over 40 mins.
(b) Remained at 0°C for 3 hours, then 22°C for 1 hour.

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4. S.D. Rychnovsky and P.A. Bartlett, *J. Am. Chem. Soc., 103*, 3963 (1981). More extensive listings of preparations of tetrahydrofurans have been provided in references 2, 3 and 6.
5. J.E. Baldwin, *Chem. Commun.* 734 and 736 (1976).
6. P.C. Ting and P.A. Bartlett, *J. Am. Chem. Soc., 106*, 2668 (1984).
7. All yields are reported for purified samples, characterized by infrared, nuclear magnetic resonance (360 MHz) and mass spectral data. Complete details will be provided in a full account of this work.
8. E.D. Mihelich, K. Daniels and D.J. Eickhoff, *J. Am. Chem. Soc., 103*, 7690 (1981). The literature conditions were employed yielding epoxides 2c (90%), 2d (82%), 2e (92%) and 2ab (50% in a 1.5:1.0 ratio). We have noted that buffered MCPBA gave a similar ratio of 2ab in 85% yield.
9. Note that bishomoallylic alcohols have also been reported to allow directed epoxidations: T. Fukuyama, B. Vranesic, D.P. Negri, and Y. Kishi, *Tetrahedron Letters*, 2741 (1978).
10. For a detailed study: J.M. Coxon, M.P. Hartshorn, and W.H. Swallow, *Aust. J. Chem., 26*, 2521 (1973).
11. These substrates continued to produce tetrahydrofurans 3 with concomittant debenzylation, albeit in low yields.
12. This silyl transfer process could not be generalized for substrates with greater (R_1) substitution.
13. Diol 3f was also converted into ether 4, and the iodide 3c cyclized readily to provide the corresponding methyl derivative of 4.
14. Complete X-ray crystallographic data are available from the Indiana University Chemistry Library. Request Molecular Structure Center Report 83063.

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