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DIASTEREOSELECTIVE EPOXIDATION OF ALPHA'-ALKOXY SUBSTITUTED CYCLOHEXENYL KETONES

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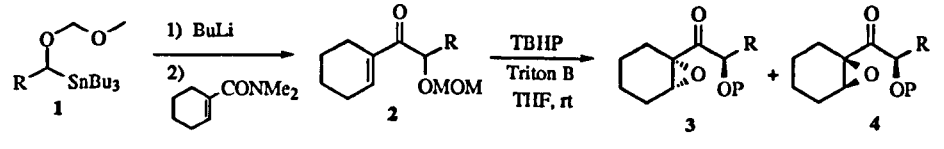
Abstract The stereochemistry of nucleophilic epoxidation of α,β–unsaturated–α'-alkoxy substituted ketones with *t*-butylhydroperoxide in the presence of Triton B is determined by the α'-alkoxy substituent via a Felkin-Ahn type transition state.

Oxygenated hexahydrobenzofuran-3-ones are present in a number of natural products including the hypocholesterolemic breynins [1] and have served as precursors in the synthesis of the avermectins. [2] The synthesis of this ring system has been achieved by a variety of methods; [3] however, construction of the furanone portion of the molecule by intramolecular epoxide ring opening is an uncommon approach. We previously reported a single example of the synthesis of a hexahydrobenzofuranone system by acid catalyzed furanone ring closure via an intermediate epoxide. [4] In this communication, we wish to detail the novel diastereoselectivity of nucleophilic epoxidation of the enone precursor which is controlled by the stereochemistry of the α'-alkoxy substituent. Although there are many examples of substrate directed epoxidation and nucleophilic addition reactions, there appear to be no examples of stereoselective nucleophilic epoxidation of unsaturated acyloin derivatives in the literature. [5]

Several α'-alkoxy enones **2** were readily prepared by condensation of N,N-dimethyl cyclohexene-carboxamide with the corresponding α-alkoxylithio species. [6] Nucleophilic epoxidation of **2a** using t-butylhydroperoxide (TBHP) and Triton B(benzyltrimethylammonium hydroxide) [7] at room temperature



1 2 3 4

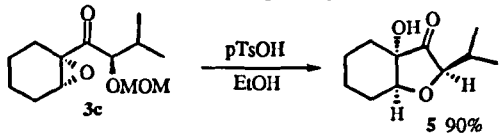
provided a 5.5:1 ratio of epoxides **3a**:**4a** in very good yield. Additional examples are listed in Table 1. For the MOM protected alcohol, little variation in the diastereoselectivity of the epoxidation reaction was observed. In each case, the diastereoselectivity ranged from 4-5:1. There also was little temperature dependence for the selectivity of the reaction. For example, epoxidation of **2d** at 0°C, 25°C, and 45°C provided **3d**:**4d** in 5.2:1, 4.9:1, and 4.5:1, respectively. The reaction required a much longer time to go to completion at 0°C relative to

Table 1 Diastereoselective Nucleophilic Epoxidation

Entry	Enone	R=	Yield,%[a]	3:4[b]
1	**2a**	-C_5H_{11}	87	5.5:1
2	**2b**	-$(CH_2)_2$	75	3.8:1
3	**2c**	-iPr	95	4.5:1
4	**2d**	-$(CH_2)_4$OTBS	79	5.0:1

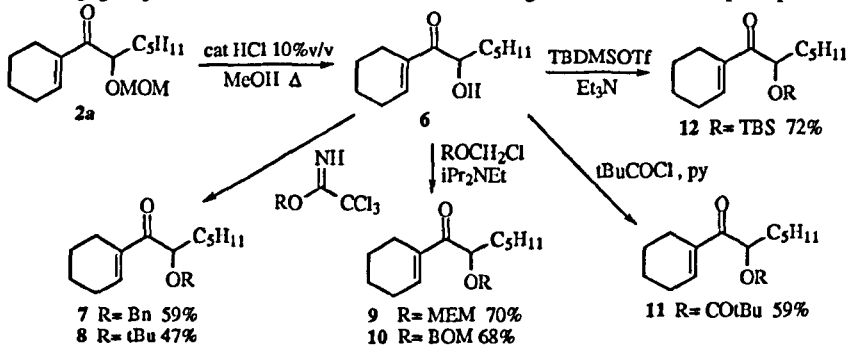
[a]Isolated yield after chromatography. [b]Diastereoselectivity of crude reaction mixture as determined by GC. P= MOM.

room temperature (>6 hours vs <1 hour). The relative stereochemistry of the epoxide major isomer was established by conversion of **3c** to the sensitive hexahydrobenzofuranone **5** by treatment of the epoxide with acid. An X-ray crystal structure of the furanone **5** unambiguously established the stereochemical assignment as



that shown. Epimerization of the iPr group during the ring closure seems unlikely given the fact that the furanone isolated bears the iPr group on the concave face of the molecule. Since the epoxides **3** and **4** are readily separable by chromatography, this approach can lead to single enantiomers of the derived furanone. Use of an enantiomerically enriched α-alkoxystannane **1a** [6a,8] in formation of the enone ultimately provides either isomer of the epoxide. For example, (R)-**1** (98% ee) resulted in epoxide (+)**3a** with [α] +1.88, while (S)-**1** (92%ee) provided (-)**3a** with [α] -1.72. Epimerization during the epoxidation reaction does not seem to occur.

The effect of the protecting group on the diastereoselectivity was then examined by conversion of the MOM protecting group of **2a** to a number of other protecting groups. The MOM group was conveniently removed with dilute aqueous acid to provide the acyloin **6**. Protection of the alcohol was then achieved with a variety of protecting groups as illustrated below. It is interesting to note that attempted protection of the



acyloin **6** with benzyl bromide under basic conditions resulted in C alkylation at the enone γ-position on the cyclohexene ring, whereas acid catalyzed reaction with the imidate provided the benzyl ether cleanly. [9] The results of the epoxidation reactions of the protected enones **7** to **12** are given in Table 2. The diastereoselectivity remains in the range of 5-7:1 for acetal and ether protecting groups with the exception that the tert-butyl ether **8** resulted in a relatively poor diastereoselectivity of 1.7:1. The best result was obtained with the benzyloxymethylether **10**, resulting in a 6.8:1 (average value for several trials ranging from 6.3 to 7.4:1) ratio

of epoxide diastereomers. The pivaloate derivative **11** provided the epoxide with good stereoselectivity, but in a low yield. The TBDMS ether **12** suffered decomposition and failed to provide any epoxide under the reaction

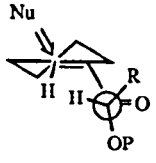
Table 2 Effect of Protecting Group

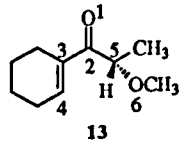
Entry	Enone	P=	3:4	Yield,%[a]
1	**2a**	MOM	5.2:1	87
2	**6**	H	--	--[b]
3	**7**	Bn	5.2:1	73
4	**8**	tBu	1.7:1	82
5	**9**	MEM	6.3:1	79
6	**10**	BOM	6.8:1	65
7	**11**	COtBu	6.3:1	59
8	**12**	TBS	--	--

[a]Isolated yield after chromatography. [b]Epoxide not obtained.

conditions. Surprisingly, the unprotected alcohol **6** was unreactive under the nucleophilic epoxidation reaction conditions. An attempt to effect a metal catalyzed electrophilic epoxidation of the enone **12** using VO(acac)/TBHP resulted in oxidation of the alcohol to form a dione in 64% yield. Stereoselective epoxidation of enones bearing an allylic alcohol have been reported using VO(acac). [10]

There are extensive studies of nucleophilic addition reactions of γ-alkoxy substituted enones, [11] but few examples of attack on an α'-alkoxy substituted system. Smith and co-workers demonstrated that high diastereoselectivity could be realized in cuprate addition reactions to 5-methoxy cyclopentenone, [12] while Corey and co-workers demonstrated a chelation controlled approach for cuprate addition to an acyclic α'-alkoxy enone. [13] In the present case, one must assume that nucleophilic attack of the hydroperoxide anion establishes the stereochemistry at the β-position of the enone followed by a rapid intramolecular alkylation of the enolate to form the epoxide. The observed relative stereochemistry of the epoxide and the α'-alkoxy group indicates that the epoxide may be formed by preferential approach of the nucleophile to an enone conformation which disposes the α'-alkoxy group *anti* to the incoming nucleophile. This conformation, resembling a Felkin-Anh transition state argument, would provide a favorable stereoelectronic effect as well as minimize steric interactions of the α'-substituents with the enone β-hydrogen. We have examined the reaction by modeling the approach of the nucleophile to enone **13** by AM1 computational methods. The enone **13** slightly favors the *s-trans* isomer over the *s-cis* and further calculations were carried out using the *s-trans* enone. A methoxide anion





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was placed orthogonal to the plane of the *s-trans* enone system and allowed to approach along an axial trajectory. Full geometry optimization was carried out for each 10° incremental rotation about the C2-C5 bond (0° to 360°) for methoxide distances of 3.0, 2.5, 2.0, and 1.5 angstroms from the enone β-carbon. Plots of conformational energy versus dihedral angle were produced for each set of calculations. A well defined energy minima was observed when the methoxide anion was 2.0 angstroms from the enone β-carbon with a dihedral angle (atoms 1,2,5,6) of 80°. A second minima at 140° was also noted. Interestingly, no well defined minima was noted in calculations carried out without the approaching nucleophile. Epoxidation of the *s-cis* isomer would have ultimately resulted in a furanone with the opposite relative stereochemistry at C2 assuming the

nucleophile approached the enone *anti* to the alkoxy substituent. Yet, the possibility remains that the reaction proceeds through a directed epoxidation (same face delivery of the peroxide as the alkoxy group) via the *s-cis* enone configuration. A directed epoxidation mechanism may provide an explanation for the lack of stereoselectivity observed in the epoxidation of the t-butyl ether **8**. Nevertheless, the computational and experimental results lend support to the assertion that diastereoselective epoxidation of enones such as **2** is established by the stereochemistry of the α'-carbon.

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