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Diastereoselective Synthesis of Tetrahydrofurans via Reaction of γ,δ-Epoxycarbanions with Aldehydes†

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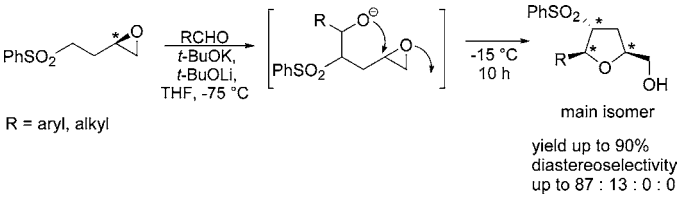
ABSTRACT



Hydroxymethyl-substituted tetrahydrofurans were prepared with high diastereoselectivity by reaction of the carbanion derived from 3,4-epoxybutyl phenyl sulfone with aldehydes in the presence of a mixture of lithium and potassium *tert*-butoxides. Initial formation of aldol-type adducts is a nondiastereoselective but reversible process; thus, subsequent formation of one main diastereoisomer is controlled by the relative rates of cyclization. The configuration of the carbon stereocenter at the oxirane ring is inverted in the course of the S_N2 process, and two new centers are created diastereoselectively.

Many natural and synthetic biologically active compounds contain tetrahydrofuran rings; thus, methods of synthesis of substituted tetrahydrofurans are of great interest.[1] One of the valuable synthetic methods for the constructing tetrahydrofurans is cyclization of epoxyalcohols.[2] Both γ,δ-[3] and δ,ϵ-epoxyalcohols can be exploited in this reaction depending on the preferred mode of the cyclization. For example, δ,ϵ-epoxyalcohols cyclize predominantly in a 5-*exo* mode, leading to tetrahydrofurans,[4] but intensive effort has successfully forced an 6-*endo* process, yielding tetrahydropyrane derivatives.[5−7]

Recently, we reported reaction of simple γ-halocarbanion precursors with aldehydes leading to formation of 2,3-disubstituted tetrahydrofurans in a one-pot addition−alkylation process.[8] Despite the fast cyclization of γ-halocarbanions, deprotonation of γ-chlorobutyronitrile, γ-chloropropyl phenyl sulfone in the presence of the aldehydes allows trapping of these carbanions to produce aldol-type anions. Subsequent intramolecular 1,5-substitution of the halogen in these O-anions results in the formation of substituted tetrahydrofurans. The major obstacle for wide use of this valuable reaction is a high rate of the intramolecular reaction of γ-halocarbanions, which limits the intermolecular process to active electrophiles such as aromatic aldehydes.

An attractive extension of this concept therefore would be use of carbanions containing less active leaving groups in the γ-position such as γ,δ-epoxycarbanions, where the intramolecular oxirane ring opening is anticipated be a rather

† Part of this work is the subject of the M.S. Thesis of D. Krajewski at Faculty of Chemistry, Warsaw University of Technology.

(1) See for example: Faul, M. M.; Huff, B. E. *Chem. Rev.* **2000**, *100*, 2407.

(2) Heffron, T. P.; Jamison, T. F. *Org. Lett.* **2003**, *5*, 2339.

(3) Karikomi, M.; Watanabe, S.; Kimura, Y.; Uyehara, T. *Tetrahedron Lett.* **2002**, *43*, 1495.

(4) Coxon, J. M.; Hartshorn, M. P.; Swallow, W. H. *Aust. J. Chem.* **1973**, *26*, 2521.

(5) Nicolaou, K. C.; Duggan, M. E.; Kwang, C.-K.; Somers, P. K. *J. Chem. Soc., Chem. Commun.* **1985**, 1359.

(6) Wu, M. H.; Hansen, K. B.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **1999**, *38*, 2012.

(7) Janda, K. D.; Shevlin, C. G.; Lerner, R. A. *Science* **1993**, *259*, 490.

(8) (a) Mąkosza, M.; Judka, M. *Chem. Eur. J.* **2002**, *8*, 4234. (b) Mąkosza, M.; Przyborowski, J.; Klain, R.; Kwast, A. *Synlett* **2000**, 1773. (c) Fleming, F. F.; Gudipati, V.; Steward, O. W. *J. Org. Chem.* **2003**, *68*, 3943. For an analogous process with Michael acceptors, see: Mąkosza, M.; Judka, M. *Synlett* **2004**, 717.

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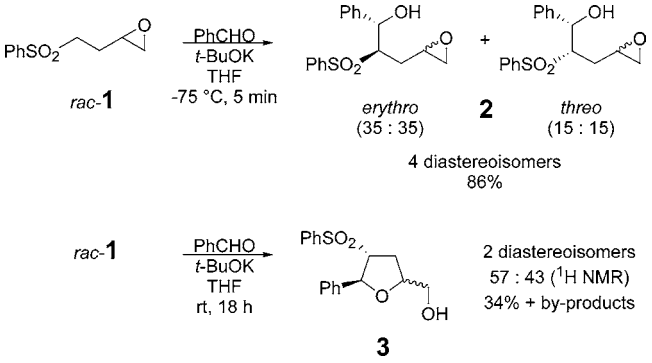
slow process.[9] Trapping the γ,δ-epoxycarbanion with an aldehyde[10] should produce an intermediate epoxyalkoxide that will subsequently cyclize to tetrahydrofuran in a preferred 5-*exo* mode.

Probing this potential strategy, we employed 3,4-epoxybutyl phenyl sulfone **1**. In our first experiments, we observed that cyclization of $\mathbf{1}^-$ via intramolecular oxirane ring opening does not proceed without Lewis acids and that addition of this carbanion to benzaldehyde is a fast but nonstereoselective process. Thus, **1** in the presence of *t*-BuOK in THF at −75 °C gave a mixture of four diastereoisomers of the epoxyalcohols in high yield upon protonation at low temperature.[11] When the mixture was kept at room temperature for 18 h, the expected hydroxymethyl tetrahydrofuran was formed in a moderate yield (34%) as a mixture of two diastereoisomers (Scheme 1).

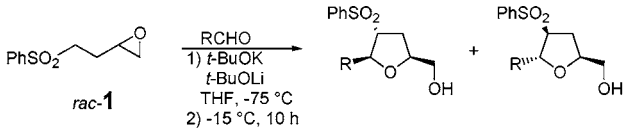
Scheme 1. Reactions of Epoxycarbanions with Aldehydes

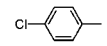
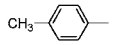
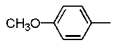


Since efficient cyclization of epoxyalkoxides requires activation of the oxirane ring by Lewis acids, we tested of a number of additives (LiBr, LiCl, $LiClO_4$, $CeCl_3$, $BF_3{\cdot}OEt_2$, Ti(*i*-OPr)$_4$, $ZnCl_2$, CuOTf, Cu(OTf)$_2$, Sc(OTf)$_3$) and observed lithium cations to be the most effective. Lithium bromide, used in excess, promoted the cyclization but with poor diastereoselectivity. After some variations, we found that a mixture of lithium and potassium *tert*-butoxides provided good yield and diastereoselectivity of the products.

Under the optimized conditions,[12] a series of reactions of aldehydes with **1** were performed, giving substituted hydroxymethyl tetrahydrofurans (Table 1). Aromatic aldehydes reacted with **1** in good yields and diastereoselectivity (Table 1, entries 1−5). Only in the case of furfural were the yield and diastereoselectivity reduced, probably due to the presence

Table 1. Synthesis of Tetrahydrofurans under Optimized Conditions



entry	R =	yield	diastereoselectivity (^{1}H NMR)
1		75%	82:18:0:0
2		87%	77:23:0:0
3		87%	82:18:0:0
4		90%	87:13:0:0
5		61%	81:19:0:0
6		41%	63:37:0:0
7	*t*-Bu	74%	53:47:0:0
8	*i*-Pr	36%	55:45:0:0
9	Me	0%	-

of the complexing oxygen atom affecting the transition state geometry (entry 6). Reactions of aliphatic aldehydes (entries 7, 8) were unselective, and low yields were obtained with isobutyraldehyde (entry 8) and acetaldehyde (entry 9) probably because of aldol condensation.

Reactions of **1** with other electrophilic partners such as ketones, imines, and Michael acceptors carried out under the optimized conditions failed to give the expected products, whereas **1** was partially recovered.

We assume that under these conditions, aldol-type addition of carbanion of **1** to aldehydes is a *reversible process* since the diastereoselectivity of tetrahydrofurans does not correspond to the ratio of initially formed aldol adducts obtained after protonation of the mixture at low temperature (Scheme 2). ^{1}H NMR analysis of **2** showed that addition is not selective, as pairs of *erythro* and *threo* diastereoisomers were *equimolar* mixtures of products differing by the configuration at the oxirane ring. Since the configuration of the stereogenic center at the benzylic position in intermediate adducts can change only by the dissociation−addition mechanism, cyclization of this mixture should lead to an equimolar mixture of **3**, as opening of the oxirane ring proceeds stereospecifically with inversion of configuration.[13]

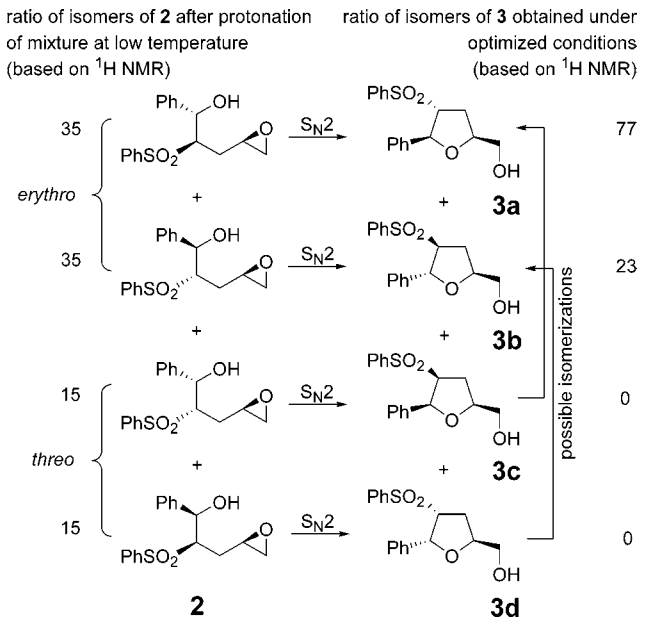
(9) Conversion of **1** into 1-phenylsulfonyl-2-hydroxymethyl-cyclopropane requires activation with Lewis acids such as Li^+: Corbel, B.; Decesare, J. M.; Durst, T. *Can. J. Chem.* **1978**, *56*, 505.

(10) For other reactions of epoxycarbanions, see: (a) Reference 9. (b) Najera, C.; Yus, M. *J. Org. Chem.* **1989**, *54*, 1491. (c) Cere, V.; et al. *J. Org. Chem.* **1991**, *56*, 4513.

(11) Mixture of four diastereoisomers was separated chromatographically into two pairs, namely, *erythro* and *threo*, having different configurations of stereogenic centers of the oxirane ring within the pair. Providing that this center is inverted in a S_N2-type cyclization process, they should cyclize to mixtures of 2,3-trans (**3a**, **3b**) and 2,3-cis (**3c**, **3d**) tetrahydrofurans, respectively (Scheme 2).

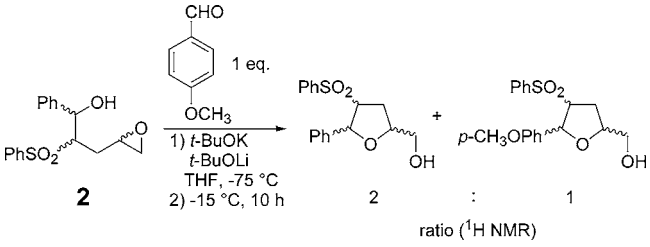
(12) **General Procedure** (Table 1). To a solution of **1** (212 mg, 1 mmol) and aldehyde (1.25 mmol) in THF (4 mL) at −75 °C under argon were added consecutively solutions of *t*-BuOK (1 mL, 1 M in THF) and *t*-BuOLi (1 mL, 1 M in THF, Aldrich) . The flask was left at between −20 and −15 °C for 10 h; then, aqueous NH_4Cl was added, and the mixture was extracted with ethyl acetate, washed with brine, and dried with $MgSO_4$. Chromatographic separation with hexane/ethyl acetate (3:1) mixture gave 2-substituted 3-phenylsulfonyl-5-hydroxymethyltetrahydrofuran as a mixture of diastereoisomers. See Supporting Information for details.

Scheme 2. Cyclization of Diastereoisomers of Adducts According to a S_N2 Pathway



To prove that under the reaction conditions there is equilibration between diastereoisomeric adducts via a dissociation−addition process, an exchange experiment was carried out. The mixture of diastereoisomers of the aldol products from the reaction of **1** with benzaldehyde and *p*-methoxybenzaldehyde was subjected to the standard conditions. Isolated tetrahydrofurans contained phenyl and *p*-methoxyphenyl substituents, confirming our hypothesis (Scheme 3).

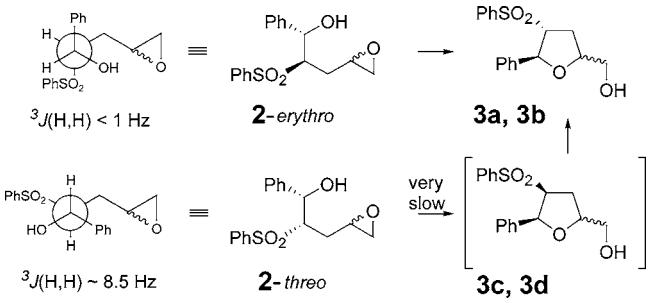
Scheme 3. Reaction of Aldol Adducts of Benzaldehyde with **1** and *p*-Methoxybenzaldehyde under Optimized Reaction Conditions



Thus, the preferred formation of one tetrahydrofuran diastereoisomer indicated that the final composition of the product is controlled by rates of cyclization of the isomeric adducts being in equilibrium, according to the Curtin−Hammett postulate (**1** ⇆ **2** → **3**).

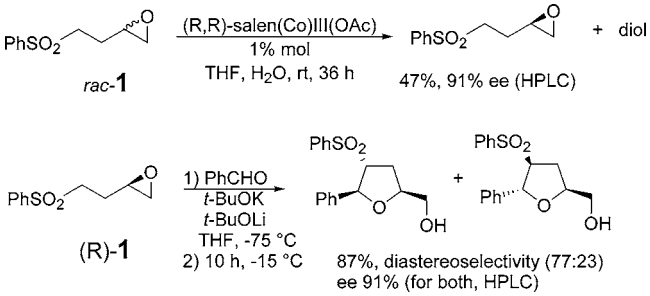
Additionally, we can assume that only *erythro* adducts cyclize directly to 2,3-*trans*-tetrahydrofurans **3a** and **3b**. However, there is also the possibility of cyclization of the *threo* adducts to 2,3-cis products (**3c**, **3d**)[14] and subsequent epimerization at the carbon bearing a $PhSO_2$ group to the 2,3-trans configuration, but this pathway is probably not realized. ^{1}H NMR studies based on ^3J(H,H) coupling constants revealed that the preferred conformations of the intermediate epoxyalkoxides favor the anti orientation of sterically demanding phenyl and phenylsulfonyl groups.[15] While in *erythro* adducts reacting centers are synclinal, the antiperiplanar orientation in *threo* adducts precludes cyclization to a five-membered ring (Scheme 4, see Supporting Information for details).[16]

Scheme 4. Preferred Conformations of Intermediate Epoxyalkoxides **2** and Their Reactivity



The stereoselectivity is effectively controlled by the epoxide stereochemistry. Formation of one predominant diastereoisomer in high yield without racemization of the stereogenic center at the oxirane ring could result in the formation of valuable 2,3,5-trisubstituted tetrahydrofurans in optically pure form in a one-pot procedure. Hydrolysis of racemic **1** with Jacobsen catalyst under kinetic resolution conditions provided (*R*)-**1** with an enantiomeric excess as high as 91% (HPLC).[17] Under the standard conditions, reaction of this oxirane with benzaldehyde gave two diastereomeric tetrahydrofurans with enantiomeric purities equal to purity of the starting oxirane (Scheme 5).

Scheme 5. Synthesis of Optically Enriched **1** and Its Reaction with Benzaldehyde under Optimized Conditions



The absolute configuration of the products was established by X-ray analyses of the (−)-ω-camphanic acid[18] ester derivatives and confirms the S_N2 inversion of configuration in the course of the ring-opening process (Figure 1).

(13) Ratio of diastereoisomers of **3** obtained after cyclization mixture of **2** according to S_N2 mechanism should be 35:35:15:15. Subsequent isomerization of tetrahydrofurans could lead to a (35 + 15):(35 + 15) = 50:50 mixture.

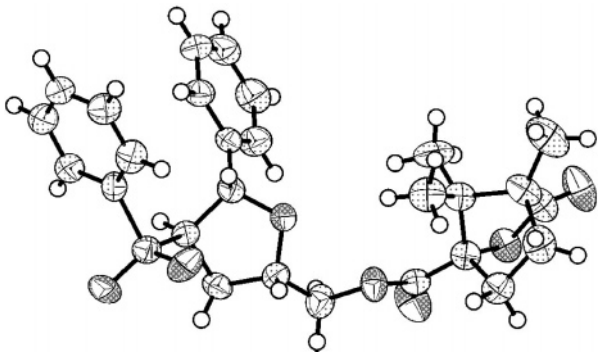


Figure 1. X-ray structure of the main diastereoisomer of tetrahydrofuran obtained from chiral epoxide precursor **1** and benzaldehyde as an ester with (−)-ω-camphanic acid.

The cyclization stereochemistry and the crossover experiment leads to the following mechanistic conclusions. The first step of the reaction, aldol-type addition of the sulfonyl carbanion to the carbonyl group, is a relatively fast and nondiastereoselective but reversible process. Subsequent cyclization is faster for one diastereoisomer, and an equilibrium process operates until conversion of all the substrates in a favored manner is complete.

(14) Diastereoisomers **3c** and **3d** were isolated only during the optimization process. Under optimized conditions, no traces of **3c** or **3d** were detected (see Supporting Information for details).

In conclusion, we have developed a novel, high-yield, chemo-, regio-, and diastereoselective method of synthesizing 2-substituted 3-phenylsulfonyl-5-hydroxymethyltetrahydrofurans. The potential of these products and the simplicity of the procedure will make this tandem addition−cyclization strategy useful in natural product synthesis.

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Supporting Information Available: Experimental procedures, characterization data for all new compounds with reprints of some NMR spectra, and additional X-ray information (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(16) For analogous literature precedence, see: Hassner, A.; Usak, D.; Kumareswaran, R.; Friedman, O. *Eur. J. Org. Chem.* **2004**, 2421.
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