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Asymmetric Epoxy Cyclohexenyl Sulfones: Readily Accessible Progenitors of Stereodefined Six-Carbon Arrays[1]

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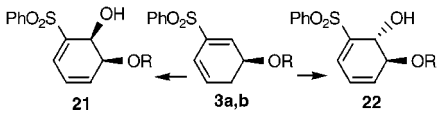
ABSTRACT



Enantiopure epoxy vinyl sulfones serve as highly effective substrates for a variety of stereo- and regiospecific oxidation and nucleophilic functionalization reactions. These materials can be easily transformed to cyclic and acyclic six-carbon segments. Nucleophilic epoxidation of 3a,b followed by palladium[0] catalysis enables access to differentially protected arene diols 21 and 22.

An unambiguous method for creation of multiple contiguous stereocenters is a long-standing goal of the synthetic community. Some of the state-of-the-art methods include the highly effective iterative aldol strategy and desymmetrization tactics involving Pd[0] catalysis, chiral bases, or enzymatic resolution.[2] While each of these methods has its own unique profile of attributes, a truly general solution remains tantalizingly out of reach.

In a pair of recent publications[3] which derived inspiration from the seminal contributions of Johnson, Lautens, and Hudlicky,[2b,d,e] we discussed utilization of enantiopure epoxyvinyltriflates as progenitors of enantiopure cyclic and acyclic targets. While these findings provided useful information, stability difficulties were observed with several of the compounds. Since vinyl sulfones exhibit superb stability, we elected to exploit the outstanding enantioselectivities obtained in the epoxidation of 2-sulfonyl-1,3-cycloalkadienes using Jacobsen conditions.[4]

2-Phenylsulfonyl-1,3-cyclohexadiene **1** is available in one operation from 1,3-cyclohexadiene[5] and is regularly prepared in our laboratories in 100-g lots. Enantiopure epoxide **2**, which has become the "workhorse" of our strategy, has been prepared in 15-g quantities (72% yield, >96% ee), and this crystalline white solid (mp 97−99 °C) has excellent handling properties and stability. Bäckvall has elegantly demonstrated the synthetic versatility of dienyl sulfones,[6] and his observations coupled with our own have provided an impetus for further research.

Treatment of epoxide **2**[7] with LiHMDS generates cross-

(1) Syntheses via Vinyl Sulfones 81; Chiral Carbon Catalog 4.

(2) (a) Evans, D. A. *Aldrichim. Acta* **1982**, *15*, 23. Evans, D. A.; Ng, H. H.; Clark, J. S.; Rieger, D. L. *Tetrahedron* **1992**, *48*, 2127. (b) Hudlicky, T.; Thorpe, A. J. *Chem. Commun.* **1996**, 1993. (c) Trost, B. M. *Pure. Appl. Chem.* **1996**, *68*, 779. (d) Trost, B. M.; Van Vranken, D. L. *Chem. Rev.* **1996**, *96*, 395. (e) Johnson, C. R. *Acc. Chem. Res.* **1998**, *31*, 333. Johnson, C. R.; Golebiowski, A.; Steensma, D. H. *J. Am. Chem. Soc.* **1992**, *114*, 9414. (f) Lautens, M.; Ren, Y.; Delanghe, P.; Chiu, P.; Ma, S.; Colucci, J. *Can. J. Chem.* **1995**, *73*, 1251 and references cited therein.

(3) (a) Hentemann, M.; Fuchs, P. L.*Tetrahedron Lett.* **1999**, *40*, 2699−2702. (b) Evarts, J. B., Jr.; Fuchs, P. L. *Tetrahedron Lett.* **1999**, *40*, 2703−2706.

(4) Hentemann, M. F., Fuchs, P. L. *Tetrahedron Lett.* **1997**, *38*, 5615.

(5) Bäckvall, J. E.; Juntunen, S. K.; Andell, O. S. *Org. Synth.* **1990**, *68*, 148. The 1,3-cyclohexadiene can be prepared very affordably from cyclohexene by dibromination and double elimination (*Org. Synth.* **1973**, Coll. Vol. *5*, 285). A more "environmentally friendly" approach to **1** has also been developed in four steps (∼60% overall) starting from cyclohexanone (Evarts, J., unpublished results).

(6) (a) Bäckvall, J.-E.; Chinchilla, R.; Nájera, C.; Yus, M. *Chem. Rev.* **1998**, *98*, 2291 and references cited therein.

(7) By using vigorous mechanical stirring, **2** can be prepared using 1.5 mol % of the Jacobsen catalyst, and 6 mol % of the additive 4-phenylpropyl pyridine *N*-oxide and 1.5 equiv of commercial bleach after 15 min at 4 °C. We have found that the ee % shows some decline with decreasing amounts of catalyst, with 2−4% being optimal for yield and >96% ee. Results of a systematic study will be presented in a later publication. ee % determined by HPLC using Daicel ChiralPak AD column.

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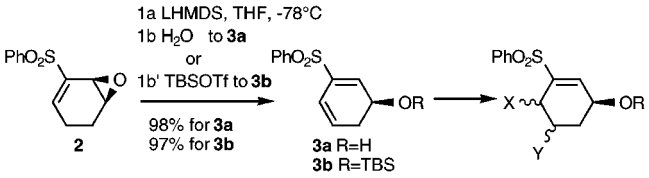
conjugated dienyl sulfones **3a,b** (functionalized "benzene hydrates") almost quantitatively after addition of water or TBSOTf, respectively (Scheme 1). Compounds **3a,b** serve as central pivots, enabling increased chemical diversity to be expressed through a second olefin functionalization step.[8] We envisioned that subsequent chemospecific derivatization of the electron-rich olefin would create an effective stereochemical scaffold for further transformations.

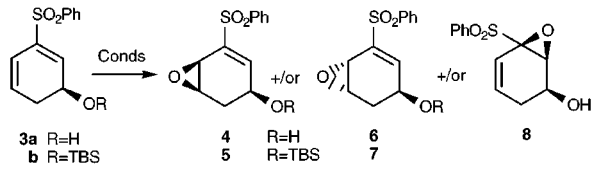
Scheme 1. Use of Sulfones in Functionalization Strategy[a]



[a] The other enantiomeric series is also available but not shown; absolute configuration of epoxide **2** is *S,S* when using the *R,R* Jacobsen catalyst.[8]

The first approach that was considered was the directed epoxidation of dienyl alcohol **3a**; an undertaking that was complicated by competitive conjugate epoxidation of the vinyl sulfone moiety (Table 1). This difficulty was alleviated using buffered trifluoroperacetic acid which provided epoxy alcohol **5** with improved stereoselectivity relative to mCPBA.

Table 1. Epoxidation Results

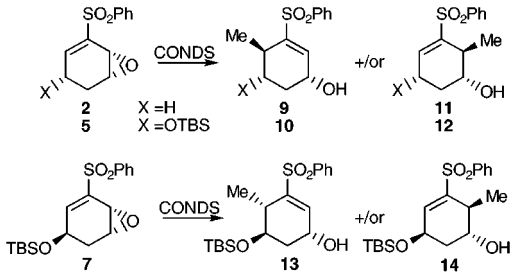


SM	reagents	prod	% yield
3a	1.1 equiv of mCPBA, 2.5 equiv of $NaHCO_3$, CH_2Cl_2	8	68 17 (**4**+**6**)
3a	1.2 equiv of mCPBA, no buffer, CH_2Cl_2	4	72 (5:1 **4**:**6**)
3a	oxone, cat. trifluoroacetone	6	88 (4:1 **6**:**4**)
3a	1.5 equiv of CF_3CO_3H, 5 equiv of $NaHCO_3$, CH_2Cl_2, −78 °C	4	83 (15:1 **4**:**6**)
3a	0.025% methyl trioxorhenium, H_2O_2	4	74 (3:1 **4**:**6**)
3b	oxone, cat. trifluoroacetone	7	94
3b	*R,R* Jacobsen Catalyst, NaOCl	-	no reaction
3b	*S,S* Jacobsen Catalyst, NaOCl	7	84

Compound **7** is readily prepared from **3b** using either in situ generated trifluoromethyldioxirane or a second application of the Jacobsen conditions.[7] Interestingly, use of the *S,S* catalyst cleanly gave **7** in 84% yield, while treatment with the *R,R* catalyst gave no reaction in a striking example of mismatched double stereoselection.[10] Not surprisingly, Jacobsen epoxidation of free alcohol **3a** gives only the aromatization product, diphenyl sulfone, regardless of catalyst choice or reaction conditions.

We have observed that a large variety of nucleophiles[11] can be added to vinyl epoxides **2**, **5**, and **7**, in a regiospecific fashion to give a rich array of stereodefined products. Extension of this strategy into the crucial domain of nucleophilic methylation has been extremely successful, providing selective 1,2- or 1,4-addition products in good yield. This was of crucial importance because of the prevalence of polypropionate systems in natural products.[12] A previous study had revealed that treatment of *dl*-epoxyvinyl sulfone **2** with trimethylaluminum in the presence of catalytic methyl copper afforded *trans*-1,4-adduct **9**, while trimethylaluminum by itself provided the *trans*-1,2-adduct **11**.[13] Application of hydrous trimethylaluminum[14] to the enantiopure substrates **2**, **5**, and **7** has improved the yield and stereospecificity as shown (Table 2).

Table 2. Nucleophilic Methylation Experiments



SM	reagent and solvent	major product, % yield	1,4:1,2 ratio
2	MeCu(cat.), 1.2 equiv of Me_3Al, THF	**9**; 74	8:1
2	10 equiv of Me_3Al, H_2O, CH_2Cl_2	**11**; 76	1:>20
5	MeCu(cat.), 1.2 equiv of Me_3Al, THF	**13**; 91	>20:1
5	10 equiv of Me_3Al, H_2O, CH_2Cl_2	**14**; 76	1:8
7	MeCu(cat.), 1.2 equiv of Me_3Al, THF	**10**; 93	>20:1
7	10 equiv of Me_3Al, H_2O, CH_2Cl_2	**12**; 64	10:1

Transfer of the newly created array of contiguous stereocenters to the acyclic domain requires oxidative cleavage of the vinyl sulfone moiety. In this instance ozonolysis[3] proved expedient for production of the termini-differentiated six-carbon segments **16** and **18** (Scheme 2).

(8) Such directable reactions include cyclopropanation, dihydroxylation, aminohydroxylation, nucleophilic additions, etc. See: Hoveyda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev.* **1993**, *93*, 1307.

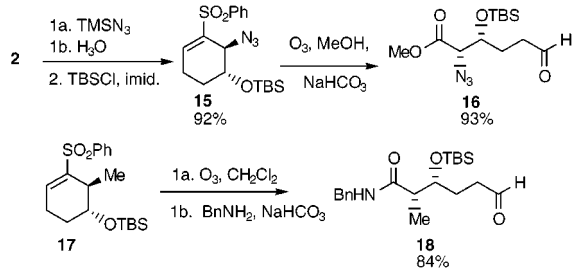
(9) Absolute stereochemistry was determined by opening the epoxide to form the corresponding bromohydrin and obtaining crystallographic data.

(10) (a) Masamune, S.; Choy, W.; Petersen, J. S.; Sita, L. R. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 1. (b) Jain, N. F.; Takenaka, N.; Panek, J. S. *J. Am. Chem. Soc.* **1996**, *118*, 12475. (c) Doyle, M. P.; Kalinin, A. V.; Ene, D. G. *J. Am. Chem. Soc.* **1996**, *118*, 8837. (d) Evans, D. A.; Dart, M. J.; Duffy, J. L.; Rieger, D. L. *J. Am. Chem. Soc.* **1995**, *117*, 9073.

(11) Carbon, nitrogen, and halogen nucleophiles add in good yield in either a 1,2- or 1,4-sense (manuscript in preparation).

(12) Paterson, I. *Pure. Appl. Chem.* **1992**, *64*, 1821.

Scheme 2



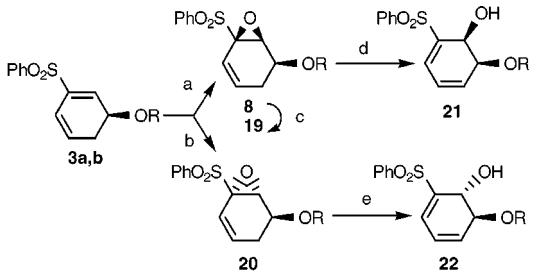
Azidation of **2** using Yb catalysis followed by methanolic ozonolysis in the presence of bicarbonate gives ester−aldehyde **16** after reductive quench. The intermediate acyl sulfone[15] can also be trapped by stoichiometric amine to give the corresponding amide. Ozonolysis of **17** followed by dimethyl sulfide quench and addition of benzylamine gives amide−ester **18** after simple workup.

Another very attractive feature of the epoxyvinyl sulfones is their ability to selectively undergo *nucleophilic reaction* at the electron-deficient olefin. This concept has been superbly demonstrated by Bäckvall on racemic sulfones,[6b] so we sought an extension of his findings by exploiting the allylic oxygen substituent to control the stereochemistry of nucleophilic addition. As seen in Table 3, the free hydroxyl group in **3a** effectively directs the epoxidation, exclusively giving the *syn* epoxy-alcohol **8** in excellent yield. Similarly, epoxidation of silyl ether **3b** solely afforded the *anti* product **20**. With each of these protected epoxy alcohols it was envisioned that we could utilize our LHMDS ring-opening reaction (Scheme 1) to generate enantiopure arene diols. Unfortunately, our initial attempts met with failure, so we had to employ an alternate approach.

The route adopted again advanced the findings of Bäckvall with Pd[0]-catalyzed conversion of vinyl epoxides to dienes.[6a]

(13) Saddler, J. C.; Fuchs, P. L. *J. Am. Chem. Soc.* **1981**, *103*, 2112.
(14) Miyashita, M.; Hoshino, M.; Yoshikoshi, A. *J. Org. Chem.* **1991**, *56*, 6483.
(15) (a) Schank, K.; Werner, F. *Liebigs Ann. Chem.* **1979**, 1977. (b) Adam, W.; Hadjiarapoglou, L. *Tetrahedron Lett.* **1992**, *33*, 469. (c) Claes, M. G.; Löfström, A. M.; Ericsson, L. B.; Juntunen, S. K.; Bäckvall, J. E. *J. Org. Chem.* **1995**, *60*, 3586.

Table 3. Nucleophilic Epoxidation Scheme



rxn[a]	R	reagents	prod	% yield
a	H	TBHP, cat Triton B, CH_2Cl_2	**10**	92
b	TBS	TBHP, cat Triton B, CH_2Cl_2	**23**	95
c	H	TBSCl, imidazole, CH_2Cl_2	**22**	97
d	TBS	5% $Pd(PPh_3)_4$, THF	**24**	86
e	TBS	5% $Pd(PPh_3)_4$, THF	**25**	84

[a] The other enantiomeric series is also available but not shown.

This route was particularly attractive because it conformed to an approach which employs catalytic reagents.[3] Treatment of both **19** and **20** with catalytic palladium[0] in THF cleanly provided dienylic diols **21** and **22** under very mild conditions (Table 3). Compounds **21** and **22** bear a strong resemblance to the arene diols developed by Hudlicky[16] and provide a point of commonality between the two strategies. While the Hudlicky aryl halide enzyme oxidation strategy has the advantage of brevity, our approach is able to substantially extend the scope of these materials by making readily available both stereoisomers in either enantiomeric configuration with differentiable hydroxyl functionality, thereby enabling a wealth of stereochemical permutations.

Acknowledgment. We acknowledge Arlene Rothwell and Karl Wood for mass spectral data and the NIH for partial support of this project (GM 32693). Dr. Douglas Lantrip is thanked for assistance in manuscript preparation.

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(16) (a)Hudlicky, T.; Luna, H.; Barbieri, G., Kwart, L. D. *J. Am. Chem. Soc.* **1988**, *110*, 4735. (b) Hudlicky, T.; Price, J. D., Rulin, F.; Tsunoda, T. *J. Am. Chem. Soc.* **1990**, *112*, 9439. (c) Hudlicky, T.; Rouden, J.; Luna, H. *J. Org. Chem.* **1993**, *58*, 985.