

Synthesis of Diastereomerically and Enantiomerically Pure 2,3-Disubstituted Tetrahydrofurans Using a Sulfoxonium Ylide

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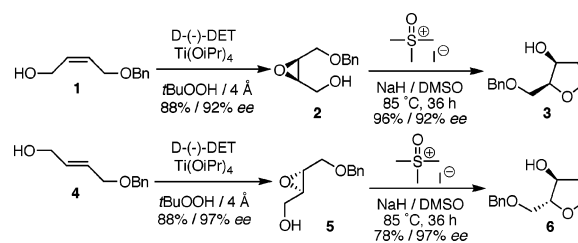
Nucleophilic substitution reactions of 2,3-epoxy alcohols, easily accessed via Sharpless asymmetric epoxidation, are a useful method for the preparation of many types of enantiomerically enriched compounds.^{1–10} We were interested in transferring the chirality of an epoxy alcohol to a tetrahydrofuran (THF) via a ring expansion reaction. It was envisioned that this could be accomplished by attacking the epoxide with a carbon-based nucleophile containing within itself a good leaving group.

A common reaction illustrating the use of such a nucleophile is the Wittig olefination.^{11,12} Preliminary screening of phosphonium, ammonium, arsenium, and sulfur-based ylides prompted the use of dimethylsulfoxonium methylyde, an ylide useful for the preparation of oxetanes from epoxides.^{13,14} The heat stability, reactivity, and easy preparation of this ylide¹⁵ allows convenient access to 2,3-disubstituted THF rings in a highly diastereoselective and enantioselective fashion. The overall strategy is depicted in Scheme 1. Asymmetric epoxidation of allylic alcohols such as **1** and **4** yields epoxides **2** and **5**, respectively. The reaction of **2** and **5** with the ylide generated from trimethylsulfoxonium iodide affords the 2,3-disubstituted THF rings **3** and **6** in good yields with complete control of stereochemistry.¹⁶ Thus, a *cis* epoxide yields the corresponding *cis*-disubstituted THF ring while the *trans* epoxide gives the *trans*-disubstituted THF ring.

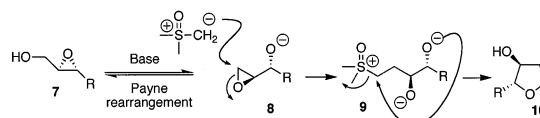
Regiochemical control afforded during the epoxide opening by the nucleophilic ylide is paramount to the success of this reaction. The Payne rearrangement reaction^{17,18} has been aptly demonstrated by both Sharpless⁸ and Ganem¹⁹ to be an effective means of favoring selective C1 attack of 2,3-epoxy alcohols. Sharpless in particular has had great success in using sulfur nucleophiles to access several acyclic diols with good control of regioselectivity.⁸ We have also found the Payne rearrangement to be useful for controlling the regioselectivity in dimethylsulfoxonium ylide attack on the epoxy alcohol. As illustrated in Scheme 2, the transformation begins with the Payne rearrangement of the enantiomerically pure 2,3-epoxy alcohol **7** leading to the more sterically accessible terminal epoxide **8**. Nucleophilic epoxide opening with the ylide at C1 leads to the generation of the bis-alkoxide **9**, which can undergo 5-*exo-tet* ring closure to yield the desired 2,3-disubstituted THF ring **10** with complete stereochemical fidelity. There was no evidence of oxetane formation via the 4-*exo-tet* closure.

A series of epoxy alcohols were synthesized using standard methodologies. Table 1 lists the conversion of these substrates to THF rings. In most cases, an excess of ylide greatly increased the yield, perhaps due to decreased ylide stability at the elevated reaction temperatures. Concentration was also crucial for the success of the reaction in that concentrations greater than approximately 0.1 M in epoxy alcohol tend to give allylic alcohols via elimination^{20,21} rather than THFs via cyclization. The optical purities of several of the epoxy alcohols and the corresponding products were

Scheme 1



Scheme 2



checked by preparing the MPA esters in order to ensure that racemization was not taking place under the prescribed reaction conditions.

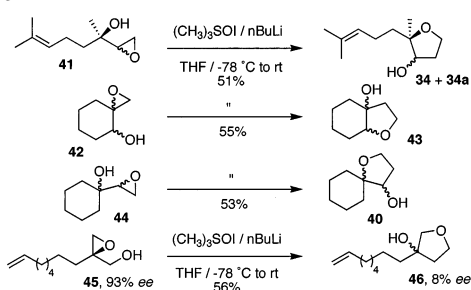
Compounds containing an oxygen substituent at C4 of the epoxy alcohol were good substrates for the Payne rearrangement/ring-opening/cyclization sequence (Scheme 1 and Table 1, entry 1).⁸ In the case of *trans* epoxy alcohols, products arising from attack at carbons other than C1 were seen, although in most cases, these impurities could be easily separated from the desired product. Presumably, the Payne equilibrium strongly favors the initial 2,3-epoxy alcohol for *trans* epoxy alcohols, while the composition of isomeric epoxy alcohols for *cis* substrates tends to be more evenly distributed due to steric interaction between substituents at C1 and C4 of the *cis*-2,3-epoxy alcohol.¹⁷ Epoxy alcohols containing an oxygen at C5 or even at C6 were successfully transformed to the desired THF rings (entries 2–5), although the yields dropped with increasing carbons in the side chain. Compounds containing simple alkyl substituents (entries 9–10) gave poor yields due to lack of good selectivity during the nucleophilic attack by the ylide (C3 attack as a major product). Slow addition of the nucleophile to the equilibrating mixture of epoxy alcohols has been reported to partially solve the regioselectivity problem⁸ but was not particularly successful in our system.

Not surprisingly, nucleophilic addition at the benzylic position was favored due to electronic stabilization of the transition state when an aryl group was substituted at C3 of the epoxy alcohol (entry 11) and the desired 2,3-substituted THF was obtained only as a minor product (major product was **30**). THF as the solvent gave exclusively the 3,4-disubstituted product **30** (entry 12) as the result of C3 attack in 51% yield. It was hoped that more highly substituted epoxides (entries 14–17) might deter ylide attack at C3; however, the tendency to favor the 2,3-epoxy alcohol in the Payne equilibrium led to poor results except when the epoxide was contained in a ring (entry 8) where the quaternary asymmetric center could be effectively generated.

Table 1. Conversion of 2,3-Epoxy Alcohols to 2,3-Disubstituted THF Rings^a

entry	starting epoxy alcohol	product	yield	entry	starting epoxy alcohol	product	yield	entry	starting epoxy alcohol	product	yield
1			86	7			61	12 ^b			51
2			91					13 ^b			33
3			85	8			90	14			14
4			66	9			17	15			20
5			68	10			38	16			33
6			55	11			20	17			21

^a Typical reaction conditions (3.0–10.0 equiv trimethylsulfoxonium iodide, NaH, 0.1 M epoxy alcohol in DMSO, 80 °C, 36 h). ^b In THF with *n*BuLi as the base.

Scheme 3

Utilization of the Payne rearrangement for regiochemical control was initially invoked since optically enriched 2,3-epoxy alcohols can be generated with ease; however, in theory, any epoxide containing a neighboring free hydroxyl available for cyclization can be used provided the regiochemistry of ylide attack can be controlled by steric or electronic factors. The substrates in Scheme 3 were prepared to circumvent the problems encountered with alkyl-substituted epoxy alcohols such as **33** (Table 1, entry 14) in the Payne rearrangement approach. The reaction could be performed in either DMSO using ylide generated from trimethylsulfoxonium iodide and NaH or in THF using ylide generated with *n*BuLi as the base. It is known that THF retards Payne rearrangement and thus is a good medium to promote direct attack of the epoxide with ylide generated in situ.²² Thus, reaction of **41** (Payne rearranged equivalent of **33**, 2:1 mixture of diastereomers) yielded **34** and **34a** (epimeric at the hydroxyl bearing carbon) in better yields as compared to the reaction of **33**, which would require in situ Payne rearrangement.

In some cases, such as **42**, the choice of solvent is not important (55% with THF, 56% with DMSO) but, more often than not, can be crucial to the success of the reaction. For example, **44** was treated with dimethylsulfoxonium methylide in both DMSO and tetrahydrofuran as solvents. In DMSO, the desired **40** (diastereomeric mixture) was obtained in 18% yield and the elimination product in 27% yield, results similar to entry 17 in Table 1. However, when the reaction was performed in THF as the solvent, **40** was obtained in 53% yield (mixture of diastereoisomers) with no evidence of elimination products. Racemization was a problem with epoxide **45**, since the enantiomeric compounds resulting from Payne rearrangement both undergo indiscriminate attack by the ylide.

In conclusion, we have developed a new method for the synthesis of 2,3-substituted THF rings. The stereochemistry that is set by the asymmetric epoxidation is translated fully to the final product.

Since it is relatively simple to obtain 2,3-epoxy-alcohols in high enantiomeric excess via the Sharpless asymmetric epoxidation, this can be a powerful methodology in gaining entry into the synthesis of THF rings with stereodefined substituents. Future work is focused on methods to control regioselectivity of ylide attack, to increase the extent of substitution by varying groups on the epoxide and ylide, and to use this approach to synthesize larger rings.

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Supporting Information Available: Experimental procedures and spectral data for compounds **3–45** (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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- Possible counterion influence in the conversion of **2** to **3** was investigated with Li, Na, and K salts. The isolated yields of **3** LiHMDS, NaHMDS, and KHMDS as bases were 59%, 92%, and 82%, respectively. Per the suggestion of the reviewer, microwave-assisted conversion of **2** to **3** with NaHMDS as the base in DMSO greatly reduced the reaction time (30 pulses, 15 s/pulse) while maintaining a high yield of product (see Supporting Information for details).
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