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Novel Conversion of 1,2-Disubstituted *cis*-Epoxides to One-Carbon Homologated Allylic Alcohols Using Dimethylsulfonium Methylide

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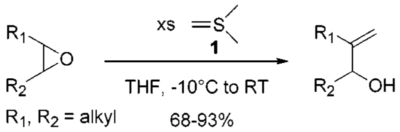
ABSTRACT



The treatment of *cis*-epoxides with an excess of dimethylsulfonium methylide affords one-carbon homologated allylic alcohols in good to excellent yields.

The well-established accessibility and versatility of epoxides have made them one of the key intermediates of modern organic synthesis.[1] Since Corey and Chaykovsky's report in 1965,[2] dimethylsulfonium methylide **1** has been the reagent of choice for the conversion of ketones and aldehydes to terminal epoxides.[3,4] More recently, Mioskowski et al. reported some useful and novel applications of **1** for the direct conversion of ketones to allylic alcohols,[5] the conversion of halides and mesylates to one-carbon homologated terminal alkenes,[6] and finally the conversion of epoxides to the corresponding homologated allylic alcohols.[7,8] In the latter case, transformation was originally thought to be limited to terminal or activated (allylic/benzylic) epoxides. However, the potential synthetic interest of compounds which would result from the opening of unactivated epoxides prompted us to reinvestigate the reaction. To our delight, we found that although the *trans*-epoxides remained inert under the reaction conditions, the *cis*-epoxides were smoothly converted to the desired homologated allylic alcohols (Scheme 1).[9]

We first studied the ring opening of symmetrical epoxides: the scope of which is summarized in Table 1.

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(1) For reviews, see: (a) Jacobsen, R. N. *Acc. Chem. Res.* **2000**, *33*, 421−431. (b) Padwa, A.; Murphree, S. *Prog. Heterocycl. Chem.* **1999**, *11*, 66−86. (c) Gorynski Smith, J. *Synthesis* **1984**, 629−656. (d) Paknikar, S. K.; Kirtane, J. G. *Tetrahedron* **1983**, *39*, 2323−2367.

(2) Corey, E. J.; Chaykovsky, M. *J. Am. Chem. Soc.* **1965**, *87*, 1353−1364.

(3) For example: (a) Fei, X.-S.; Verkade, J. G. *Heteroat. Chem.* **1999**, *10*, 538−540. (b) Deady, L. W.; Deneves, J. *Org. Prep. Proced. Int.* **1995**, *27*, 219−221. (c) Borredon, E.; Delmas, M.; Gaset, A. *Tetrahedron Lett.* **1982**, *23*, 5283−5286. (d) Merz, A.; Märkl, G. *Angew. Chem., Int. Ed. Engl.* **1973**, *12*, 845−846.

(4) Trost, B. M.; Melvin, L. S. *Sulfur Ylides, Emerging Synthetic Intermediates*; Academic Press: New York, 1975.

(5) Harnett, J. J.; Alcaraz, L.; Mioskowski, C.; Martel, J. P.; Le Gall, T.; Shin, D.-S.; Falck, J. R. *Tetrahedron Lett.* **1994**, *35*, 2009−2012.

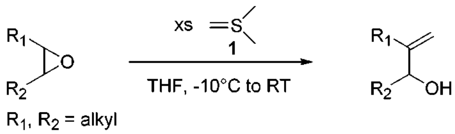
(6) (a) Alcaraz, L.; Harnett, J. J.; Mioskowski, C.; Martel, J. P.; Le Gall, T.; Shin, D.-S.; Falck, J. R. *Tetrahedron Lett.* **1994**, *35*, 5453−5456. For an example of synthetic use of the reaction, see: (b) Sylvain, C.; Wagner, A.; Mioskowski, C. *Tetrahedron Lett.* **1998**, *39*, 9679−9680. For related methodology using arsonium ylides see: (c) Seyer, A.; Alcaraz, L.; Mioskowski, C. *Tetrahedron Lett.* **1997**, *38*, 7871−7874.

(7) (a) Alcaraz, L.; Harnett, J. J.; Mioskowski, C.; Martel, J. P.; Le Gall, T.; Shin, D.-S.; Falck, J. R. *Tetrahedron Lett.* **1994**, *35*, 5449−5452. For an example of the synthetic use of the reaction, see: (b) Baylon, C.; Heck, M.-P.; Mioskowski, C. *J. Org. Chem.* **1999**, *64*, 3354−3360. See also: (c) Davoille, R. J.; Rutherford, D. T.; Christie, S. D. R. *Tetrahedron Lett.* **2000**, *41*, 1255−1259.

(8) After this submission, E. Carreira reported an elegant synthesis of epothilones in which an improved version of this methodology was employed: Bode, J. B.; Carreira, E. M. *J. Org. Chem.* **2001**, *66*, 6410−6424. The authors found that in their case replacement of THF by diethyl ether and of iodide by a nonnucleophilic sulfonium counterion such as triflate led to an increase in the reaction yield.

10.1021/ol016782y CCC: $20.00

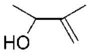
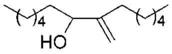
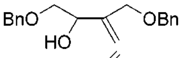
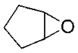
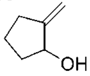
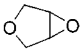
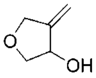
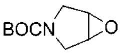
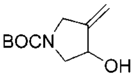
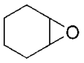
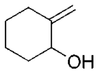
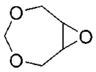
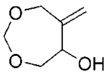
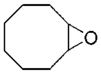
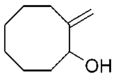
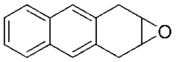
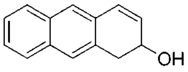
Scheme 1



Exposure of acyclic *cis*-epoxides to an excess of **1** at −10 °C in THF resulted in a high yield of the corresponding one-carbon homologated allylic alcohols (entries 1, 2, and 3). In the case of cyclic epoxides (entries 4 to 9), both five- to seven-membered carbocyclic (entries 4 and 7) and heterocyclic (entries 5, 6, and 8) substrates reacted smoothly, affording the desired products in excellent yields. Interestingly, cyclooctene oxide was recovered intact (entry 9). Base-sensitive substrate 2,3-epoxyanthracene (entry 10) underwent β-elimination and represents a limitation of the methodology.

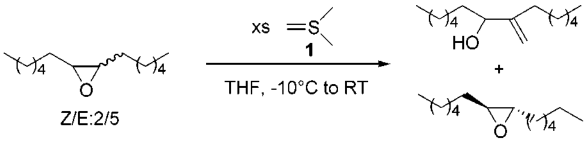
The chemoselectivity of the reaction is illustrated in Scheme 2. Treatment of an isomeric mixture of tetradec-7-ene oxide (*Z*/*E* 2/5) with ylide **1** led to a selective conversion of the *cis*-isomer to the corresponding allylic alcohol while the *trans*-isomer was left unreacted. The starting *Z*/*E* mixture was barely separable by classical column chromatography; this could also represent a simple and clean way of selectively removing the unwanted *cis*-isomer in situations where the *trans*-isomer is the compound of interest.

Table 1. Ring Opening of Symmetrical *cis*-Epoxides[10]

entry	substrate	product	yield (%)[a]
1			91%
2			88%
3			90%
4			91%
5			92%
6			93%
7			86%
8			81%
9			0%[b]
10			75%

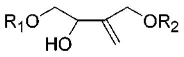
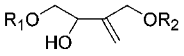
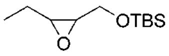
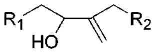
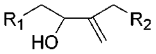
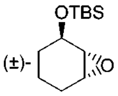
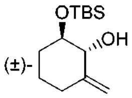
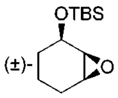
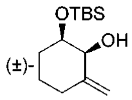
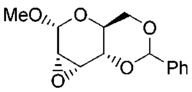
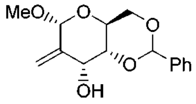
[a] Isolated yield. [b] Recovered starting material.[11]

Scheme 2



This novel transformation[12] is an alternative way of introducing the 1,2-disubstituted propenol moiety present in numerous natural products as well as a quick and simple route to versatile synthetic intermediates. To illustrate these points, we then turned our interest to unsymmetrical 1,2-disubstituted epoxides. The results are reported in Table 2.

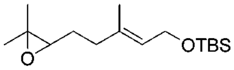
Table 2. Ring Opening of Asymmetrical *cis*-Epoxides[10]

entry	substrate	products (Ratio)[a]	yield (%)[b]
1		 R_1=Bn;R_2=H: 7 R_1=H;R_2=Bn: 3	85%[c]
2		 R_1=Bn;R_2=Tr: 1 R_1=Tr;R_2=Bn: 5	68%
3		 R_1=Me;R_2=OTBS: 1 R_1=OTBS;R_2=Me: 2	77%
4		 R_1=Me;R_2=OTr: 1 R_1=OTr;R_2=Me: 3	72%
5			80%
6			71%[d]
7			91%

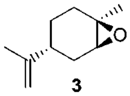
[a] Determined by crude ^{1}H NMR. [b] Combined isolated yield. [c] Inseparable by chromatography; 5% of Payne rearranged/ring opened compound was also isolated. [d] 5−10% of TBS migration was observed.

In asymmetric acyclic systems, although the reactions took place in good yields (entries 1−4), total regioselectivity was not observed. Attempts to improve this by lowering the initial reaction temperature to −78 or −50 °C (for entries 3 and 4) did not significantly alter the mixture ratios. This is probably a consequence of the lack of reactivity of **1** below −10 °C.[13] However, these preliminary results did show that a degree of regioselectivity can be achieved by varying steric bulk around the epoxide. The highest ratios have been obtained using trityl as a protective group (entries 2 (5/1) and 4 (3/1)). In contrast, introduction of conformational constraints and steric hindrance in cyclic systems led to total regioselectivity of the epoxide ring opening and afforded potentially synthetically very interesting allylic alcohols in high yields (entries 5−7). It is worth noting that as exemplified in a cyclic system (entry 7) the use of acyclic chiral epoxides (e.g., via Sharpless asymmetric epoxidation) would afford the corresponding chiral allylic alcohols.

Finally, consistent with the finding that *trans*-isomers do not react under these experimental conditions, both trisubstituted acyclic **2** and cyclic **3** epoxides remained inert when exposed to an excess of **1**.



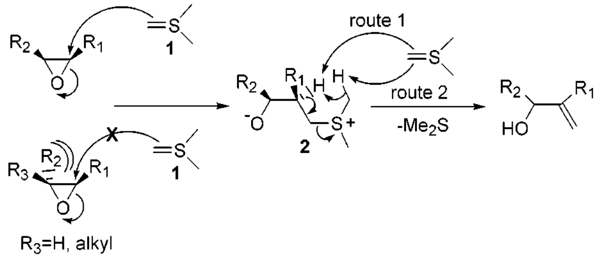
2



3

The mechanism we propose for the reaction is similar to the one reported for related homologations[5−7] and is outlined in Scheme 3: nucleophilic addition of the ylide **1** on the epoxide yields the betaine intermediate **2** and is followed by β-elimination of dimethyl sulfide via an intermolecular (route 1) or intramolecular process (route 2). As suggested by previous studies[6,7] and the present work (Table 2), we postulate that the interesting reactivity difference between *cis*-epoxides and *trans* or trisubstituted epoxides results from sensitivity to steric bulk.

Scheme 3



In summary, we have developed a general new application of dimethylsulfonium methylide which leads to synthetically valuable intermediates from readily accessible *cis*-epoxides. The use of chiral sulfonium methylides for the desymmetrization of *meso cis*-epoxides and modified conditions for the reaction of *trans* and trisubstituted epoxides are currently under investigation.

Acknowledgment. We thank Dr. Mark Furber, Prof. Steve Clark, and Prof. Nigel Simpkins for helpful discussions. We are also grateful to Dr. Mark Dixon and Dr. Richard Lewis and Hema Pancholi for their expert assistance in NMR and for MS studies, respectively.

Supporting Information Available: ^{1}H and ^{13}C NMR data and literature references for the products illustrated in Tables 1 and 2. This material is available free of charge via the Internet at http://pubs.acs.org.

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(9) **General procedure:** To a −10 °C suspension of trimethylsulfonium iodide (4.0 equiv, 4.00 mmol, 816 mg) in THF (15 mL) was added *n*-BuLi (3.7 equiv, 3.70 mmol, 1.50 mL of 2.5 M hexane solution). After 30 min, epoxide (1.0 equiv, 1.00 mmol) in THF (3 mL) was introduced and the reaction slowly allowed to warm to 0 °C over 1 h; the mixture was then stirred at ambient temperature for 2 h. The reaction was quenched with water and extracted with diethyl ether or ethyl acetate. The combined extracts were washed with brine, dried over magnesium sulfate, filtered, and concentrated under vacuum. The residues were purified on silica gel using pentane/ether to give the desired allylic alcohol.

(10) All compounds have been satisfactorily characterized spectroscopically, and structures have been assigned unambiguously by COSY and NOE experiments.

(11) A first attempt at switching the solvent for diethyl ether[8] did not produce the desired allylic alcohol.

(12) To the best of our knowledge, only one example of a related transformation has been previously reported: Schakel, M.; Luitjes, H.; Dewever, F. L. M.; Scheele, J.; Klumpp, G. W. *Chem. Commun.* **1995**, 513−514. The reaction proceeds in moderate yields (42% in the case of cyclohexene oxide) and presents severe limitations due to the carbenoid nature of the intermediates involved.

(13) Monitoring the progression of the reactions by TLC showed that they did not proceed at these low temperatures and only began when warmed to approximately −30 °C. The optimal range is −10 to 0 °C owing to the instability of the ylide at ambient temperature.