Ethers and Epoxides; Thiols and Sulfides

Klein, D. (2012). Ethers and Epoxides; Thiols and Sulfides. *En Organic Chemistry* (pp. 636-639). USA: Wiley.

The reaction is slow, but old bottles of ether will invariably contain a small concentration of hydroperoxides, rendering the solvent very dangerous to use. Hydroperoxides are unstable and decompose violently when heated. Many laboratory explosions have been caused by distillation of ethers that were contaminated with hydroperoxides. Ethers used in the laboratory must be frequently tested for the presence of hydroperoxides and purified prior to use.

14.7 Nomenclature of Epoxides

Cyclic ethers are compounds that contain an oxygen atom incorporated in a ring. Special parent names are used to indicate the ring size.

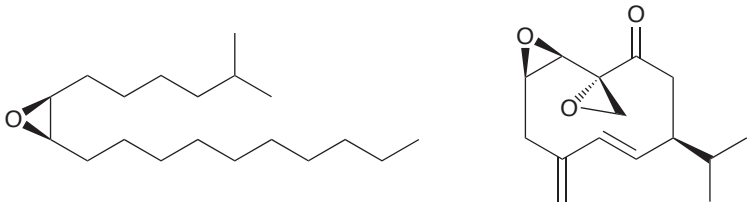
Oxirane ring system | **Oxetane ring system** | **Oxolane ring system** | **Oxane ring system**

BY THE WAY
The common name "ethylene oxide" denotes the fact that it is produced from ethylene.

For our current discussion, we will focus on **oxiranes,** cyclic ethers containing a three-membered ring system. This ring system is more reactive than other ethers because it has significant ring strain. Substituted oxiranes, which are also called **epoxides**, can have up to four R groups. The simplest epoxide (no R groups) is often called by its common name, ethylene oxide.

A substituted oxirane (an epoxide) | **Ethylene oxide** (the simplest epoxide)

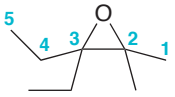
Epoxides, although strained, are commonly found in nature. The following are two examples.



Disparlure
Sex pheromone of the female gypsy moth

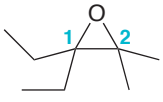
Periplanone B
Sex pheromone of the female American cockroach

There are two methods for naming epoxides. In the first method, the oxygen atom is considered to be a substituent on the parent chain, and the exact location of the epoxide moiety is identified with two numbers followed by the term "epoxy."



3-Ethyl-2-methyl-2,3-epoxypentane

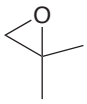
In the second method, the parent is considered to be the epoxide (parent = oxirane), and any groups connected to the epoxide are listed as substituents.

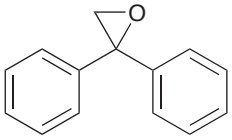


1,1-Diethyl-2,2-dimethyloxirane

CONCEPTUAL CHECKPOINT

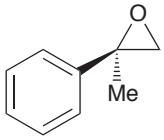
14.12 Assign a name for each of the following compounds.

(a) 

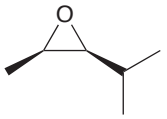
(b) 

(c) 

14.13 Assign a name for each of the following compounds. Be sure to assign the configuration of each chirality center and indicate the configuration(s) at the beginning of the name.

(a) 

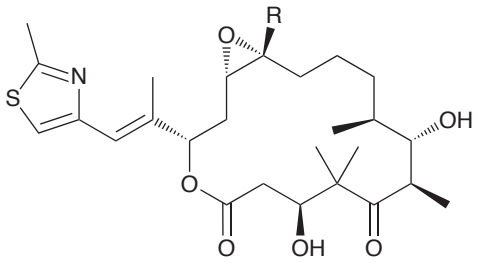
(b) 

(c) 

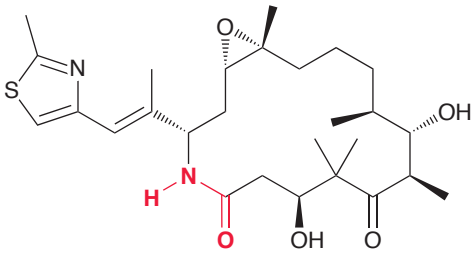
MEDICALLYSPEAKING

Epothilones as Novel Anticancer Agents

Epothilones are a class of novel compounds first isolated from the bacterium *Sorangium cellulosum* in Southern Africa.



Epothilone A (R = H)
Epothilone B (R = Me)



Ixabepilone

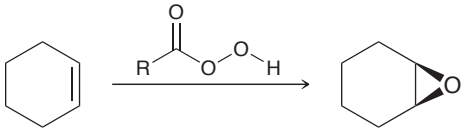
The discovery of the antitumor behavior of these naturally occurring epoxides led to a search for related compounds that might exhibit enhanced potency and selectivity. In October 2007, the FDA approved one such derivative, called ixabepilone, for treatment of advanced breast cancer. Ixabepilone is an analog of epothilone B, in which the ester linkage is replaced with an amide linkage, highlighted in red.

Ixabepilone is currently being marketed by Bristol-Myers Squibb under the trade name Ixempra. Several other analogs of the epothilones are currently undergoing clinical trials for treatment of many different forms of cancer. The next decade is likely to witness several epothilone analogs emerge as new anticancer agents.

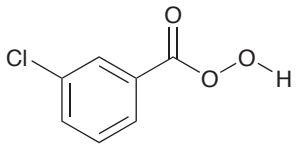
14.8 Preparation of Epoxides

Preparation with Peroxy Acids

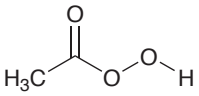
Recall from Section 9.9 that alkenes can be converted into epoxides upon treatment with peroxy acids (see Mechanism 9.6).



Any peroxy acid can be used, although MCPBA and peroxyacetic acid are the most common:

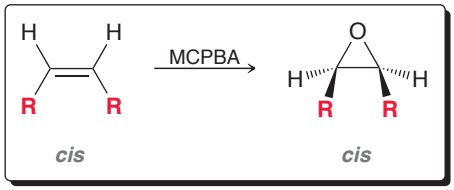


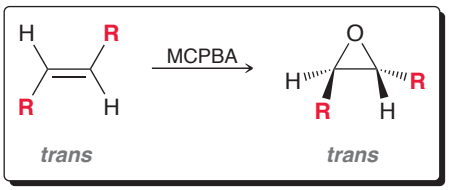
***meta*-Chloroperoxybenzoic acid (MCPBA)**



Peroxyacetic acid

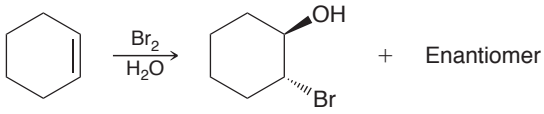
The process is stereospecific. Specifically, substituents that are *cis* to each other in the starting alkene remain *cis* to each other in the epoxide, and substituents that are *trans* to each other in the starting alkene remain *trans* to each other in the epoxide:



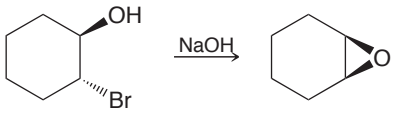


Preparation from Halohydrins

Recall from Section 9.8 that alkenes can be converted into halohydrins when treated with a halogen in the presence of water (see Mechanism 9.5).

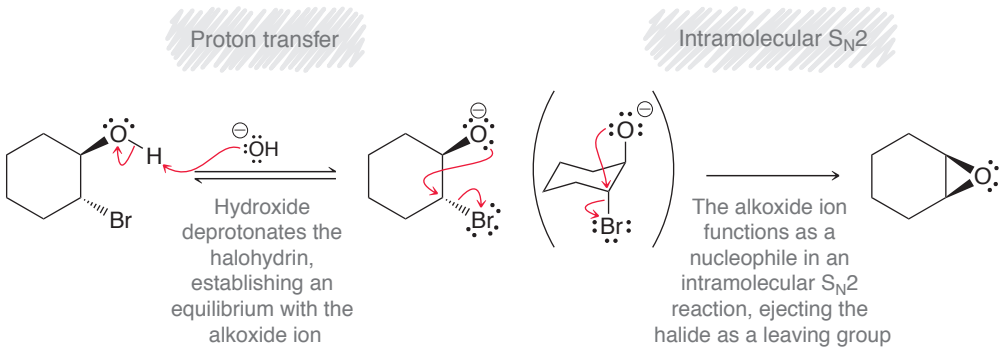


Halohydrins can be converted into epoxides upon treatment with a strong base:

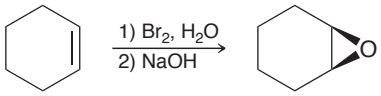


The process is achieved via an intramolecular Williamson ether synthesis. An alkoxide ion is formed, which then functions as a nucleophile in an intramolecular S_N2-like process (Mechanism 14.4).

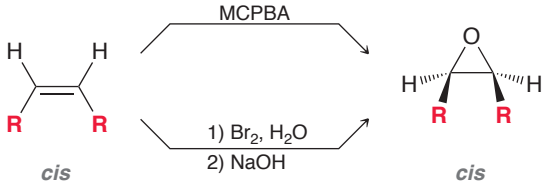
MECHANISM 14.4 EPOXIDE FORMATION FROM HALOHYDRINS



This provides us with another way of forming an epoxide from an alkene.



The overall stereochemical outcome is the same as direct epoxidation with MCPBA. That is, substituents that are *cis* to each other in the starting alkene remain *cis* to each other in the epoxide, and substituents that are *trans* to each other in the starting alkene remain *trans* to each other in the epoxide.

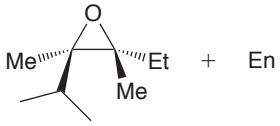


SKILLBUILDER

14.3 PREPARING EPOXIDES

LEARN the skill

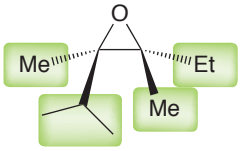
Show what reagents you would use to prepare the following epoxide.



SOLUTION

Begin by analyzing all four groups connected to the epoxide.

STEP 1 Identify the four groups attached to the epoxide.



STEP 2 Identify the relative configuration of the four groups in the starting alkene.

The starting alkene must contain these four groups. Look carefully at the relative configuration of these groups. The methyl groups are *trans* to each other in the epoxide, which means that they must have been *trans* to each other in the starting alkene. To convert this alkene into the epoxide, we can use either of the following acceptable methods.

STEP 3 Use either of the following two methods to prepare the epoxide from the starting alkene.