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ALKYLATIVE EPOXIDE REARRANGEMENT. APPLICATION TO STEREOSELECTIVE SYNTHESIS OF CHIRAL PHEROMONE EPOXIDES.

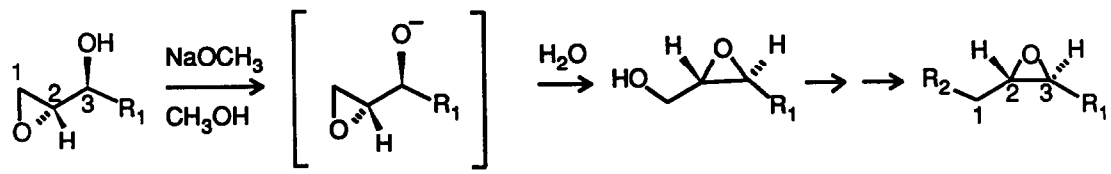
Thomas W. Bell* and James A. Ciaccio

Department of Chemistry, State University of New York at Stony Brook,
Stony Brook, New York 11794-3400.

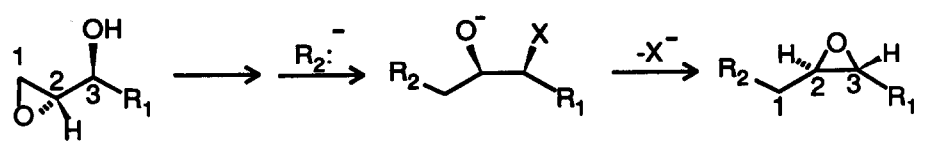
Abstract: An approach is described for the stereospecific conversion of threo and erythro 1,2-epoxy-3-alkanol tosylates to cis and trans internal epoxides, respectively. The method is illustrated by the synthesis of chiral epoxides, including insect pheromones.

Synthetic chemists face a major challenge in the preparation of chiral compounds having very high optical purity. The need for pure enantiomers is particularly apparent in the field of pheromone chemistry, since insect chemoreception can be highly stereoselective.[1,2] Optically active 2,3-epoxy-1-alkanols are common intermediates in the preparation of insect pheromones[3] and may be obtained by asymmetric epoxidation of allylic alcohols or through the Payne rearrangement[4] of readily available 1,2-epoxy-3-alkanols.[5] We report an alternative synthesis of internal epoxides from 1,2-epoxy-3-alkanols via an "alkylative rearrangement" of the corresponding *p*-toluenesulphonate esters. This new route is shorter than the approach using the Payne rearrangement and produces epoxides having the opposite absolute configuration, as indicated below.

Payne Rearrangement:



Alkylative Epoxide Rearrangement:



In the Payne rearrangement, the C-3 alkoxy group intramolecularly attacks the epoxide ring at C-2, leading to inversion of configuration at this center. Our method utilizes the proclivity of terminal epoxides towards nucleophilic attack at C-1, which is also the basis of a stereoselective approach to vicinal diols by regioselective cleavage of 1,2-epoxy-3-alkanols.[6] In our approach, the hydroxyl at C-3 is converted into a leaving group (e.g. X = tosylate) prior to nucleophilic attack at C-1. The ring-opened intermediate could be isolated, if possible, or recyclized *in situ* to directly afford the desired product. The proposed alkylative epoxide rearrangement differs from the Payne rearrangement in the configurations at C-2 and C-3.[7] Hence; the same optically active 1,2-epoxy-3-alkanol gives opposite enantiomers.[8]

As a test reactant for the proposed alkylative rearrangement, epoxy tosylate **1** was synthesized from (R)-glyceraldehyde acetonide, as shown in Figure 1. When **1** was treated with 1-lithio-1-heptyne and boron trifluoride-diethyl etherate,[9] followed by potassium carbonate in methanol, (2R,3R)-2-(2-octynyl)-3-undecyloxirane (**2**, $[\alpha]_D^{23}$ = -4.2±0.2) was obtained in 52% yield. This glyceraldehyde-derived trans epoxy alkyne had a more intense rotation than its optical antipode ($[\alpha]_D^{23}$ = +2.5±0.1 ; 66% ee[10]) which we prepared via asymmetric epoxidation of E-5-undecyn-2-en-1-ol,[11] followed by alkylation of the corresponding iodomethyloxirane.[12] The high optical purity of the product proves that the alkylative rearrangement step is stereoselective, as expected.

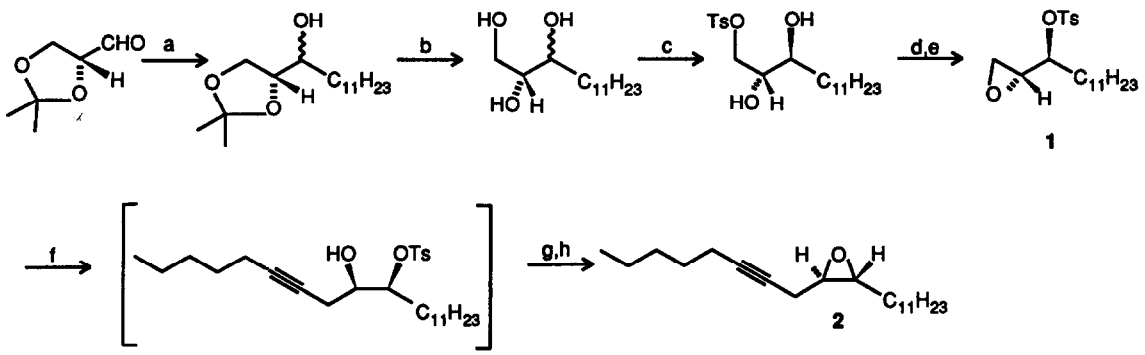


Figure 1. Synthesis of Epoxide **2** in High Optical Purity via Alkylative Rearrangement of **1**: (a) $C_{11}H_{23}MgBr$, Et_2O (erythro:threo = 3:1); (b) 1:1 1N HCl:THF, 5 h, recryst. from EtOAc (erythro:threo = 4:1); (c) TsCl, Py, 0° C, flash chrom.; (d) K_2CO_3, CH_3OH; (e) TsCl, Py, $CHCl_3$; (f) $C_5H_{11}C{\equiv}C$-Li, BF_3:OEt_2, -78° C, THF, 5 h; (g) K_2CO_3, CH_3OH; (h) 52 % from **1**.

We have also used this new alkylative epoxide rearrangement to prepare *cis*- and *trans*-(+/-)-(Z,Z)-2-(2,5-octadienyl)-3-undecyloxirane (**8** and **9**)[2b,c] and *cis*-(+/-)-(Z)-2-(2-octenyl)-3-undecyloxirane (**10**)[13] from racemic, diastereomerically pure erythro and threo epoxy alcohols, as described in Figure 2. Dodecanal was treated with ethenylmagnesium bromide in anhydrous THF to afford 1-tetradecen-3-ol (**3**). Epoxidation of **3** with MCPBA in CH_2Cl_2 gave a 3:2 ratio of threo to erythro 1,2-epoxy-3-alkanols. The diastereomers could be separated by large-scale HPLC at this stage or converted to the threo (**4**) and erythro (**5**) 1,2-epoxy-3-alkanol tosylates, which were separable by flash chromatography on silica gel. Treatment of **4** with 2.75 equivalents each of 1-

lithio-1,4-heptadiyne and boron trifluoride-diethyl etherate in anhydrous THF at -78° C afforded *threo*-10-tosyloxy-3,6-heneicosadiyn-9-ol (**6**) This intermediate could be isolated or recyclized *in situ* by treatment with approx. 2 equivalents of potassium carbonate in anhydrous methanol, affording *cis*-2-(2-octadiynyl)-3-undecyloxirane (**7**) in 56% from **4**. Catalytic hydrogenation of **7** gave cis epoxy diene **8**, which was spectroscopically and chromatographically identical to the natural epoxide, isolated from female sex glands of *C. gangis*.[2b,c] In a similar manner, trans epoxy diene **9** was prepared from **5** and cis epoxy alkene **10**, a recently identified sex pheromone component of the ruby tiger moth, *P. fuliginosa*,[13] was prepared from **4**.

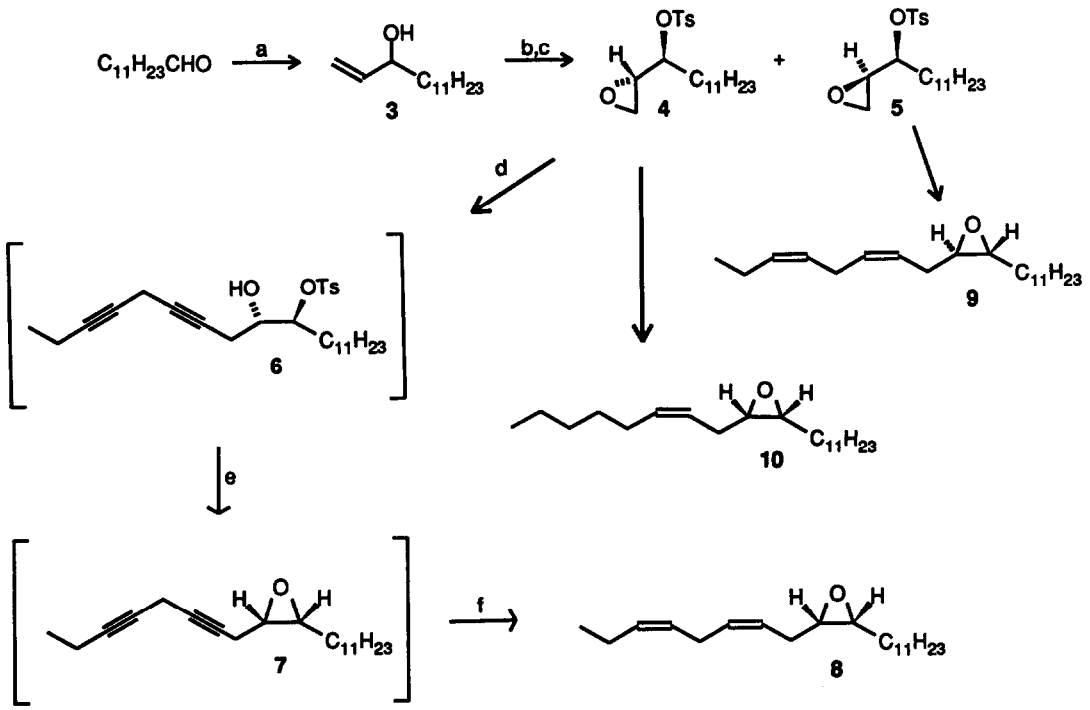


Figure 2. Diastereospecific Synthesis of Pheromone Epoxides: (a) $H_2C{=}CHMgBr$, Et_2O; (b) MCPBA, CH_2Cl_2 (threo:erythro = 3:2); (c) TsCl, Py; (d) $CH_3CH_2C{\equiv}CCH_2C{\equiv}C\text{-}Li$, $BF_3{:}OEt_2$, THF, -78° C; (e) K_2CO_3, CH_3OH; (f) H_2, Pd-$BaSO_4$, quinoline, C_5H_{12}, 23° C (**8**, 53 % from **4**; **9**, 45 % from **5**; **10**, 50 % from **4**).

In summary, we have shown that alkylative epoxide rearrangement may be used to prepare cis and trans epoxides in high optical purity and in good yield from corresponding 1,2-epoxy-3-alkanols. This approach is complementary to existing methods for the stereoselective synthesis of epoxides, such as the Payne rearrangement and Sharpless epoxidation.[14,15,16,17]

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7) A complication arises in the case of hydroxymethyloxirane when the hydroxyl is converted to a leaving group. It has been shown (McClure, D.E.; Arison, B.H.; Baldwin, J.J. *J. Am. Chem. Soc.* **1979**, *101*, 3666-3668) that there is significant competition between the two possible modes of nucleophilic attack by phenoxide: (1) direct displacement of the leaving group and (2) initial cleavage at C-1, followed by extrusion of the leaving group to form the new epoxide ring. In such a case, the use of a chiral epoxide leads to racemization. More recently, Russel and Pabon[14b] have obtained 1,2-epoxy-4-decyne in only 76% optical purity by treatment of (S)-epichlorohydrin with heptynyllithium in liquid ammonia.

8) The fundamental reactivity of the epoxide ring is different in each case. In Payne rearrangement, the epoxide functions solely as an electrophile, whereas in alkylative epoxide rearrangement it possesses latent nucleophilic character that is revealed upon nucleophilic attack at C-1.

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17) The reported optical rotations were measured in CCl_4 (c = 5.2).

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