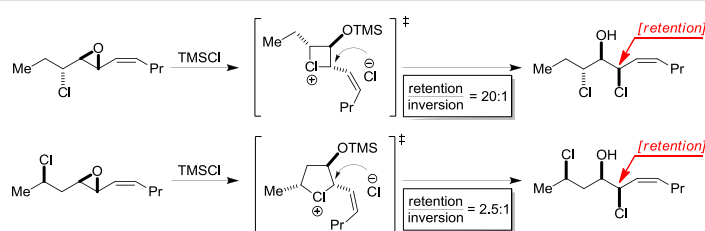


Stereochemical Studies of the Opening of Chloro Vinyl Epoxides: Cyclic Chloronium Ions as Intermediates

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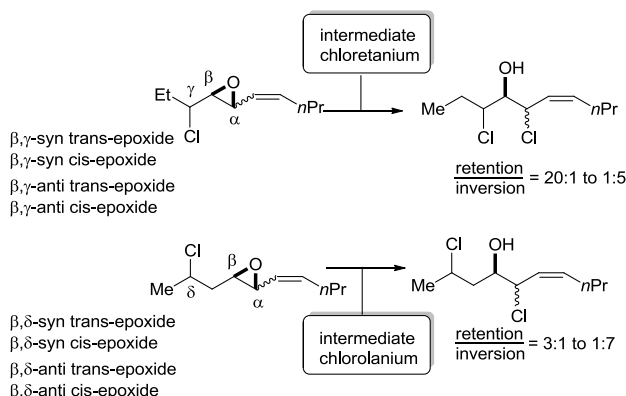
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ABSTRACT: We report a systematic study of the opening of a collection of chlorinated vinyl epoxides, which includes experiments that implicate both five- and four-membered chloronium ions as plausible intermediates in this type of epoxide opening reactions.

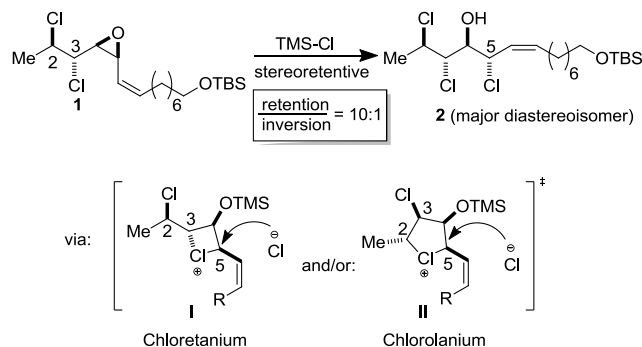
Organohalogens enjoy wide distribution in nature.¹ The intriguing biosynthetic pathways through which they are assembled continue to be the subject of intense and rewarding investigations.² Likewise, the chemistry and syntheses of these compounds is at present an area receiving increased attention.³⁻⁷ In the course of our interest in the synthesis of chlorinated natural products,⁷ we observed stereoretentive epoxide opening reactions that we attributed to the intervention of anchimeric assistance. The neighboring chlorides were suggested to lead to putative four- (chlorotanium) or five-(chlorolanium) membered ring ions. Considering the scarcity of reports that suggest the involvement of such intermediates,⁸ we decided to further explore this transformation. Herein, we report a systematic study of the opening of a collection of γ - and δ -chloro vinyl epoxides (Scheme 1), including results and observations that are consistent with both five- and four-membered chloronium ions as plausible intermediates.

Scheme 1. Stereochemical studies reported in this study.



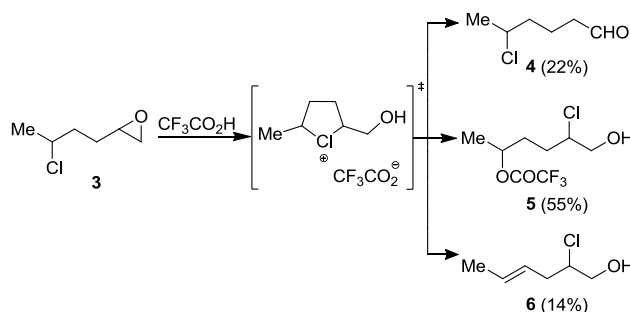
In our synthesis of hexachlorosulfolipid as well as the accompanying spectroscopic study of small chlorinated fragments, we noted the propensity of certain chlorinated epoxides to undergo stereoretentive ring opening reactions, a hallmark for the involvement of neighboring group participation. Thus, when vinyl epoxide **1** was treated with chlorotrimethylsilane, epoxide opening took place with retention of configuration, through intervention of putative cyclic chloronium intermediates, such as chlorotanium **I** and chlorolanium **II** (Scheme 2). We initially hypothesized that anchimeric participation of one of the chlorides at C2 and C3 is key to understanding the outcome. However, at that point we were unable to distinguish between the intervention of **I** versus **II**.

Scheme 2. Epoxide opening during synthetic studies of hexachlorosulfolipid.



Early investigations of the solvolysis reactions of 5-chloro-1-pentene and activated chloroalcohols have implicated the presence of chlorolanium intermediates.⁸ This work was later extended to the study of 4-chlorobutene, wherein chloretanium intermediates were postulated.⁹ Data available from the literature for the solvolysis of 1-chloro-3-tosyloxy butane ($k = 4 \times 10^7 \text{ sec}^{-1}$) versus 1-chloro-4-tosyloxy pentane ($k = 1800 \times 10^7 \text{ sec}^{-1}$) suggests that five-membered chloronium ions are favored over the corresponding four-membered chloronium ions.⁹ To the best of our knowledge, there is only one report of anchimeric assistance by a chloride substituent in epoxide opening reactions, as described by Peterson and coworkers and depicted in Scheme 3.¹⁰ Thus, it was shown that chloroepoxide **3** undergoes solvolysis in TFA to furnish a mixture of products consisting of aldehyde **4**, chlorohydrins **5**, and **6**. The results strongly implicate five-membered chlorolanium ion **III**, as a consequence of the extensive amount of products in which 1,4-chlorine transposition had occurred.

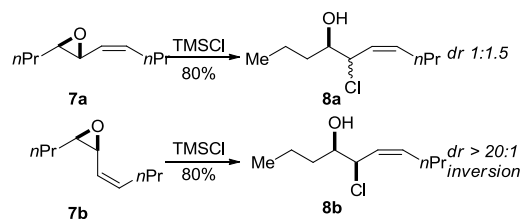
Scheme 3. Reported example showcasing chlorine participation in an epoxide opening reaction.



The various chloroepoxides examined en route to chlorosulfolipid natural products and the attendant spectroscopic studies are considerably more complex than **3**. In the absence of additional data for more elaborate, relevant systems, it was difficult to distinguish between the intermediacy of chloretanium versus chlorolanium in the opening reactions of allylic epoxides such as **1** (Scheme 1).¹¹ In order to shed light on the role of anchimeric assistance by chloride in epoxide opening reactions and the concomitant formation of 4- or 5- ring chloronium intermediates, a collection of stereochemically diverse monochlorinated vinyl epoxides were prepared and examined (Schemes 4-5).¹² We had previously noted that the configurational pattern of the dichlorinated epoxides influenced the stereochemical course of the reaction, leading to substrate dependent products from both stereoretentive and stereoinvertive C-O cleavage.^{7b} Consequently, all diastereoisomers of each test compound were synthesized. Epoxide opening reactions were uniformly conducted using identical reaction conditions, namely, 2.0 equiv Me_3SiCl in $\text{CH}_2\text{Cl}_2/\text{EtOAc}$ at 0°C for 3 hours, as reported previously for the preparation of trichloroalcohol **2**. Each product was fully characterized by NMR spectroscopy; and X-ray crystallographic data was collected for derivatives of products, **9b**, **9c**, **11a**, and **11c**.

We commenced our studies with a control experiment in which vinyl epoxides **7a** and **7b** were subjected to ring opening, as shown in Scheme 4. The chlorohydrin products of ring opening of **7a** were obtained as 1:1.5 mixture of diastereomers. Remarkably, the opening of cis-epoxide **7b** under otherwise identical conditions led to **8b** as a single diastereomer, resulting from invertive opening. These observations strongly suggest that in the displacement reaction of **7a** competing $\text{S}_{\text{N}}2$ and $\text{S}_{\text{N}}1$ pathways are operative, whereas the reaction of **7b** is strictly $\text{S}_{\text{N}}2$.^{13,14}

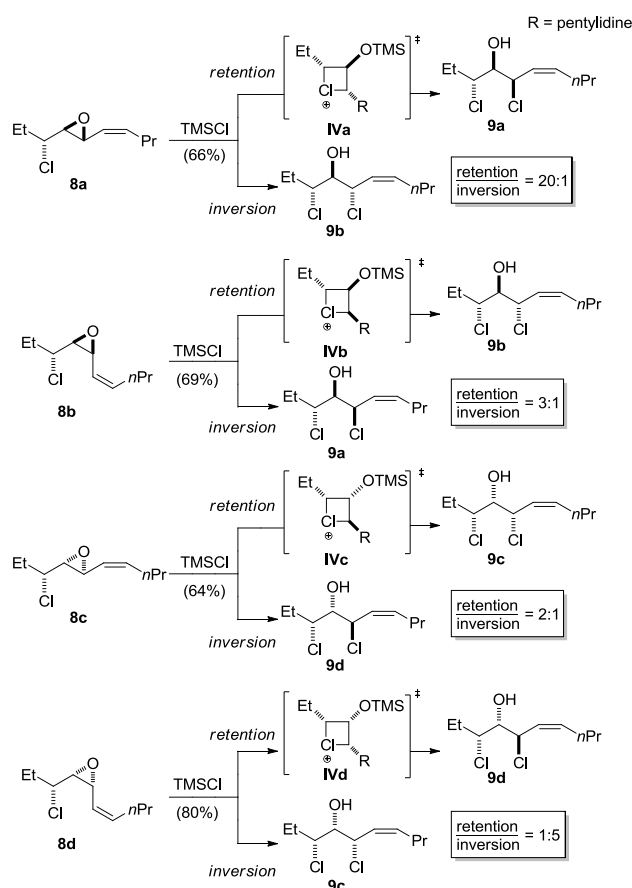
Scheme 4. Control Substrates in epoxide opening by Me_3SiCl .



A second set of substrates **8a–8d** incorporating γ -chloride (trishomoallylic) substitution were then examined as a means to probe for the formation of chloretanium ions **IVa–d** (Scheme 5). In the experiments, the isomeric ratio of products formed was determined by ^1H NMR spectroscopic analysis of the unpurified products. Importantly, no products resulting from 1,3-chlorine shift were observed. In addition, increasing reaction times or subjecting diastereomerically pure products to the reaction conditions had no impact on the stereochemical outcome.

The results of experiments of epoxide opening reactions of **8a–8d** display a surprisingly wide range of values for the ratio of retentive/invertive ring opening products, as shown in Scheme 5. Intriguingly, only the ring opening of **8a** afforded products with a high degree of stereospecificity (20:1 retention/inversion). As such, the observation of product **9a**, resulting predominantly from retention of configuration in the epoxide opening reaction, provides clear evidence of the intervention of a chloretanium ion. The observations of modest bias favoring retentive openings for **8b** and **8c** are also consistent with the intermediacy of chloretanium intermediates. The reaction of cis-substituted **8d** afforded **9c** and displayed the highest degree of inversion of configuration in the epoxide opening reaction (1:5 retention/inversion). In light of the high degree of invertive opening observed for **7b** (20:1), the results for the corresponding cis-substituted epoxides **8b** and **8d** are noteworthy and suggestive of the intermediacy of a chloretanium ion. Although the intervention of a competing $\text{S}_{\text{N}}1$ pathway cannot be excluded, we speculate it is unlikely for **8d**. The fact that **7b** shows no appreciable competing $\text{S}_{\text{N}}1$ opening makes it unlikely that **8d**, which is substituted with an electron withdrawing chloride, would be more susceptible to reaction via a carbocation.

Scheme 5. Investigation of bishomoallylic chloroepoxides.



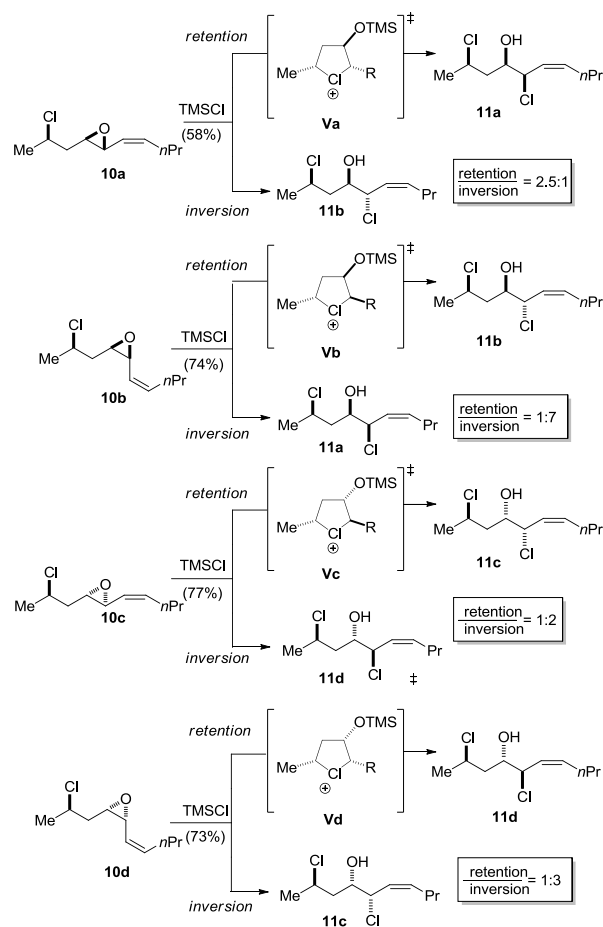
Analysis of the results in Scheme 5 for **8a–d** leads to a follow-up question: Why is it that only **8a** participates in a highly stereospecific transformation? The results can be rationalized by examination of the chloretanium ions **IVa–Vd** involved in the stereoretentive pathways. Accordingly, minimization of steric interactions among the all-trans positioned substituents on the four-membered ring in **Va** favors the formation of the corresponding chloretanium intermediate and leads to high degree of retentive opening. In the intermediate cases **8b** and **8c**, unfavorable interactions from the cis-arrangement between the substituents is unavoidable. Nonetheless, it is noteworthy that the observed bias for some degree of retention of configuration in the opening reactions, which is contrary to the expectation based on the control experiments, supports the action of anchimeric assistance, especially for **8b**.

We next examined a series of compounds to evaluate potential participation of chloride substituents via a chlorolanium (five-membered) intermediate as shown in Scheme 6. Chloroepoxide **10a** furnished **11a** with a modest preference for the product resulting from retentive opening (2.5:1). Importantly, only chloroepoxide **10b** gave opening with a reasonable level of stereospecificity (1:7) with inversion of configuration predominating. By contrast, **10c** and **10d** afforded products with a modest preference for in-

vertive opening. It is only the results with **10a** in which the partial intervention of a chlorolanium intermediate **Va** is clearly implicated, when compared to the results with **7a** (Scheme 4). The partial erosion of stereoinvertive ring opening that leads to the formation of **11b** and **11d** suggests that these also may be partially formed through putative five-membered chlorolanium ions **Vb** and **Vd**, given that the strong preference for invertive opening of the parent cis-substituted epoxide **7b**. Moreover, as a consequence of the inductive effects of chloride substitution, it is unlikely that **10b** and **10d** undergo opening through partially competing S_N1 pathways. However, such a scenario cannot be completely ruled out. In analogy to the results in Scheme 5, inspection of **Va-Vd** suggests that a stereoretentive pathway is significantly manifest for the cyclic chlorolanium intermediate when all of the substituents are positioned in an all trans-arrangement as is the case for **10a**.

Our work involving the total synthesis of hexachlorosulfolipid described in Scheme 2 led to the study we have described herein. In light of the results with **8a-8d** and **10a-10d** the earlier observations can now be re-examined. In this respect, it is interesting to note that cis-epoxide **1** bears the stereochemical features observed for **8a** and **10a** that favor epoxide opening with retention through either chloretanium or chlorolanium intermediates. However, the high degree of configurational inversion in the reaction of **1** is consistent with the intervention of a 4-membered ring chloronium ion.

Scheme 6. Investigation of trishomoallylic chloroepoxides.



In summary, we have prepared a series of chloro vinyl epoxides and examined the corresponding ring-opening reactions at the allylic position. Observations of significant amount of products formed by stereoretentive ring opening are consistent with the intervention of chloretanium and chlorolanium ions. Furthermore, comparative analysis of the results suggests the intervention of chloretanium intermediates is favored over that of the chlorolanium ion. The data we have gathered is critical knowledge for the synthesis of acyclic polychlorinated natural products. Additional investigations, as well as mechanistic and computational studies, are ongoing and will be reported as results become available.

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 - (13) The distinct behavior of the two diastereomeric epoxides may reflect conformational differences about the allylic C-C bond for each. In this regard, in the trans-epoxide C=C can orient itself in a manner that interaction with epoxide ($\pi \rightarrow \sigma^*_{C-O}$) renders C-O more labile and lowers the barrier of the S_N1 pathway. By contrast the cis-arrangement of the epoxide precludes a conformation in **7b** that would stabilize an allylic cation. Accordingly, the S_N1 pathway experiences an energetic penalty.
 - (14) The observation of products resulting exclusively from opening at the allylic end of the chloretanium intermediate is suggestive of a highly unsymmetrical ring that results from significant stabilization of the allylic over a secondary carbocation.
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