

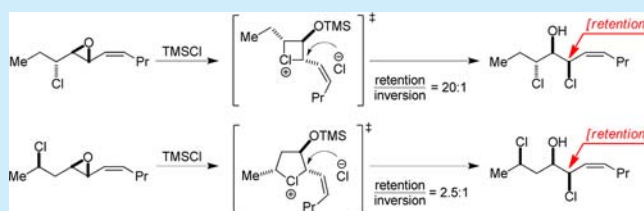
Stereochemical Studies of the Opening of Chloro Vinyl Epoxides: Cyclic Chloronium Ions as Intermediates

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S Supporting Information

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

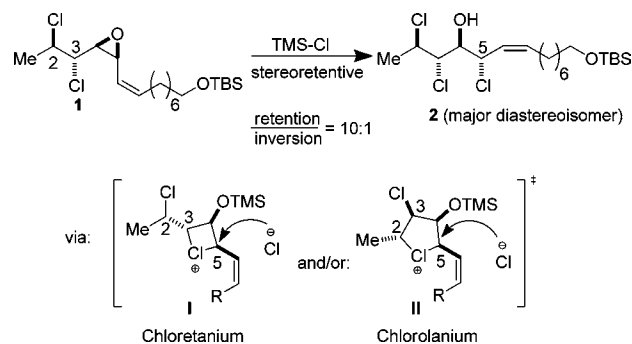


Organohalogens enjoy a wide distribution in nature.¹ The intriguing biosynthetic pathways through which they are assembled continue to be the subject of intense and rewarding investigations.² Likewise, the chemistry and syntheses of these compounds are at present receiving increased attention.^{3–7} 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-(chloretanium) 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.

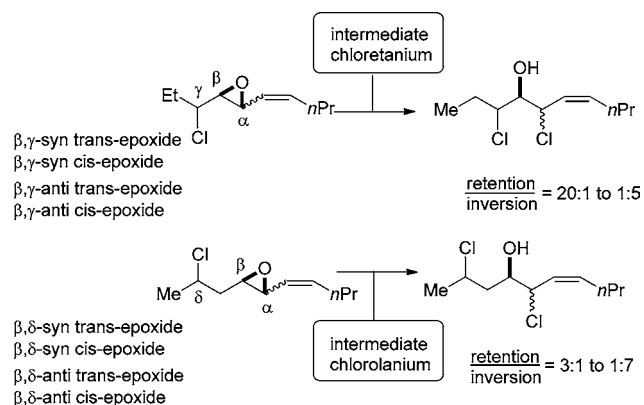
In our syntheses of hexachlorosulfolipids as well as the accompanying spectroscopic study of small chlorinated fragments, we noted the propensity of certain chlorinated epoxides

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 chloretanium **I** and chlorolanium **II** (Scheme 2).

Scheme 2. Epoxide Opening during Synthetic Studies of Hexachlorosulfolipid



Scheme 1. Stereochemical Studies Reported in This Study



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**.

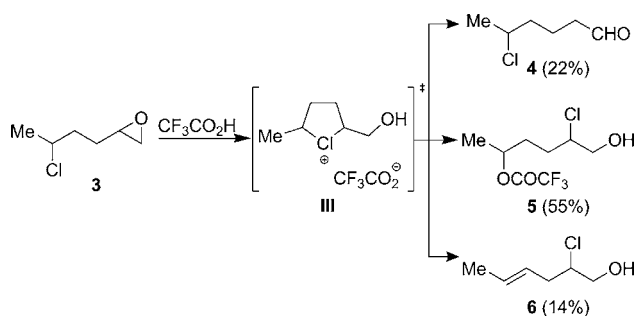
Early investigations of the solvolysis reactions of 5-chloro-1-pentene and activated chloroalcohols have implicated the presence of chlorolanium intermediates.⁸ This work was later extended to the study of 4-chlorobutene, wherein chloretanium intermediates were postulated.⁹ Data available from the literature for the solvolysis of 1-chloro-3-tosyloxy butane ($k = 4 \times 10^7 \text{ s}^{-1}$) versus 1-chloro-4-tosyloxy pentane ($k = 1800 \times 10^7 \text{ s}^{-1}$) suggest that five-membered chloronium ions are

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avored 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 co-workers and depicted in Scheme 3.¹⁰ Thus, it was shown that chloroepoxide

Scheme 3. Reported Example Showcasing Chlorine Participation in an Epoxide Opening Reaction



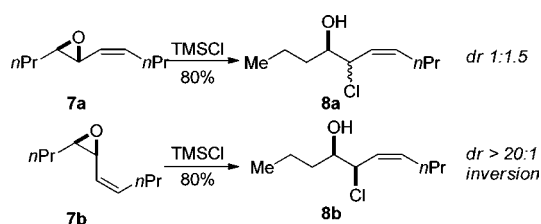
3 undergoes solvolysis in TFA to furnish a mixture of products consisting of aldehyde 4, chlorohydrins 5, and 6. The results strongly implicate five-membered chlorolanium ion III, as a consequence of the extensive amount of products in which 1,4-chlorine transposition had occurred.

The various chloroepoxides examined en route to chloro-olfolipid 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 chloroetanium 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 5 and 6).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 of Me₃SiCl in CH₂Cl₂/EtOAc at 0 °C for 3 h, as reported previously for the preparation of trichloroalcohol 2. Each product was fully characterized by NMR spectroscopy; X-ray crystallographic data were collected for derivatives of products, 10b, 10c, 12a, and 12c.

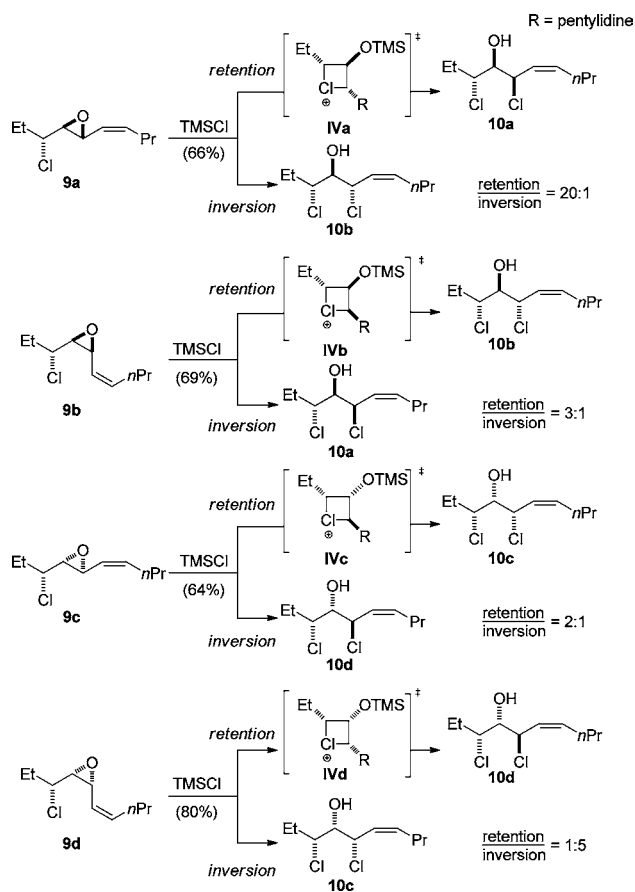
We commenced our studies with a control experiment in which vinyl epoxides 7a and 7b were subjected to ring opening, as shown in Scheme 4. The chlorohydrin products of ring opening of 7a were obtained as a 1:1.5 mixture of diastereomers. Remarkably, the opening of cis-epoxide 7b under otherwise identical conditions led to 8b as a single diastereomer, resulting from invertive opening. These observations strongly suggest that in the displacement reaction of 7a competing S_N2 and S_N1 pathways are operative, whereas the reaction of 7b is strictly S_N2.^{13,14}

A second set of substrates 9a–9d incorporating γ -chloride (bishomoallylic) substitution were then examined as a means to probe for the formation of chloroetanium ions IVa–d (Scheme 5). In the experiments, the isomeric ratio of products formed

Scheme 4. Control Substrates in Epoxide Opening by Me₃SiCl



Scheme 5. Investigation of Bishomoallylic Chloroepoxides



was determined by ¹H NMR spectroscopic analysis of the unpurified products. Importantly, no products resulting from the 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.

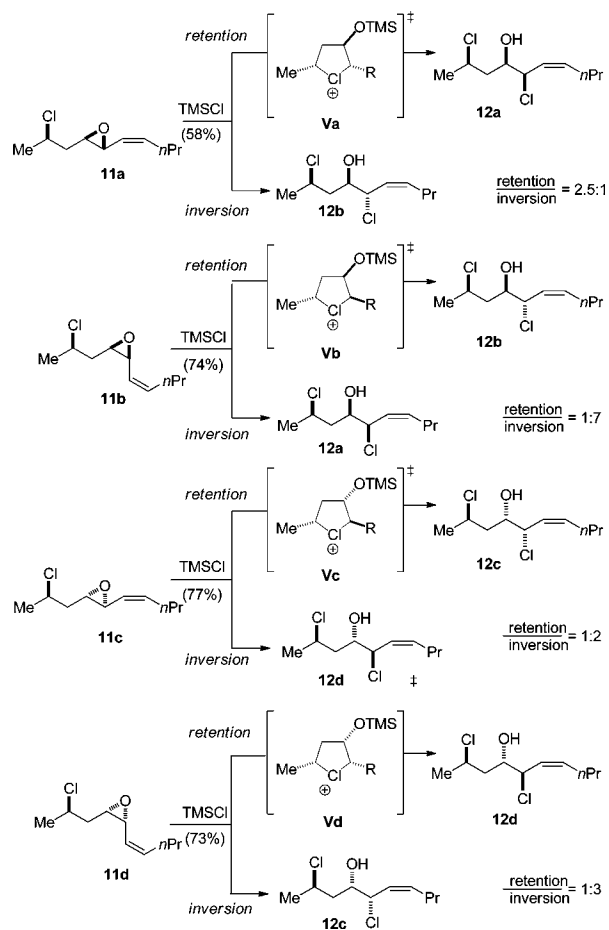
The results of experiments of epoxide opening reactions of 9a–9d display a surprisingly wide range of values for the ratio of retentive/invertive ring opening products, as shown in Scheme 5. Intriguingly, only the ring opening of 9a afforded products with a high degree of stereospecificity (20:1 retention/inversion). As such, the observation of product 10a, resulting predominantly from retention of configuration in the epoxide opening reaction, provides clear evidence of the intervention of a chloroetanium ion. The observations of modest bias favoring retentive openings for 9b and 9c are also consistent with the intermediacy of chloroetanium intermediates. The reaction of cis-substituted 9d afforded 10c 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 **9b** and **9d** are noteworthy and suggestive of the intermediacy of a chlorotanium ion. Although the intervention of a competing S_N1 pathway cannot be excluded, we speculate it is unlikely for **9d**. The fact that **7b** shows no appreciable competing S_N1 opening makes it unlikely that **9d**, which is substituted with an electron withdrawing chloride, would be more susceptible to reaction through a carbocation.

Analysis of the results in Scheme 5 for **9a–d** leads to a follow-up question: Why is it that only **9a** participates in a highly stereospecific transformation? The results can be rationalized by examination of the chlorotanium 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 chlorotanium intermediate and leads to a high degree of retentive opening. In the intermediate cases **9b** and **9c**, unfavorable interactions from the *cis*-arrangement between the substituents are 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 **9b**.

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.

Scheme 6. Investigation of Trishomoallylic Chloroepoxides



Chloroepoxide **11a** furnished **12a** with a modest preference for the product resulting from retentive opening (2.5:1). Importantly, only chloroepoxide **11b** gave an opening with a reasonable level of stereospecificity (1:7) with inversion of configuration predominating. By contrast, **11c** and **11d** afforded products with a modest preference for invertive opening. It is only the results with **11a** 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 **12b** and **12d** suggests that these also may be partially formed through putative five-membered chlorolanium ions **Vb** and **Vd**, given 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 **11b** and **11d** 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 **11a**.

Our work involving the total synthesis of the hexachloro-*osulfolipid* described in Scheme 2 led to the study we have described herein. In light of the results with **9a–9b** and **11a–11d** 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 **9a** and **11a** that favor epoxide opening with retention through either chlorotanium or chlorolanium intermediates. However, the high degree of configurational inversion in the reaction of **1** is consistent with the intervention of a four-membered ring chloronium ion.

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 amounts of products formed by stereoretentive ring opening are consistent with the intervention of chlorotanium and chlorolanium ions. Furthermore, comparative analysis of the results suggests the intervention of chlorotanium intermediates is favored over that of the chlorolanium ion. The data we have gathered are 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.

■ ASSOCIATED CONTENT

📄 Supporting Information

Experimental procedures and full spectroscopic data for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Notes

The authors declare no competing financial interest.

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- (12) For stereoselective preparation of all substrates, see Supporting Information.
- (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 chlorotanium intermediate is suggestive of a highly unsymmetrical ring that results from significant stabilization of the allylic over a secondary carbocation.