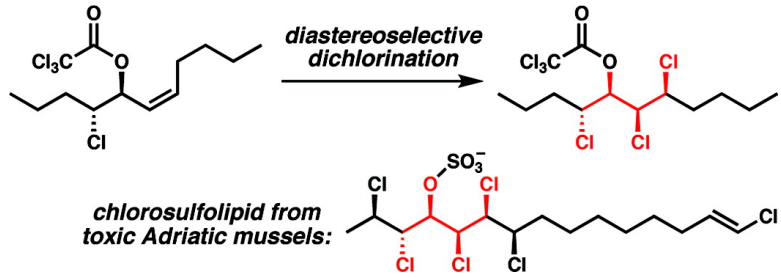
Article

Stereoselective Dichlorination of Allylic Alcohol Derivatives to Access Key Stereochemical Arrays of the Chlorosulfolipids

Grant M. Shibuya, Jacob S. Kanady, and Christopher D. Vanderwal

J. Am. Chem. Soc., **2008**, 130 (37), 12514-12518 • DOI: 10.1021/ja804167v • Publication Date (Web): 22 August 2008



More About This Article

Additional resources and features associated with this article are available within the HTML version:

- Supporting Information
- Access to high resolution figures
- Links to articles and content related to this article
- Copyright permission to reproduce figures and/or text from this article

View the Full Text HTML

J|A|C|S
ARTICLES

Published on Web 08/22/2008

Stereoselective Dichlorination of Allylic Alcohol Derivatives to Access Key Stereochemical Arrays of the Chlorosulfolipids

Grant M. Shibuya, Jacob S. Kanady, and Christopher D. Vanderwal*

Department of Chemistry, 1102 Natural Sciences II, The University of California, Irvine, California 92697-2025

Received June 2, 2008; E-mail: cdv@uci.edu

Abstract: Dichlorination of (*Z*)-allylic trichloroacetates efficiently and stereoselectively generates the syn,syn hydroxydichloride stereotriad that is prevalent in the understudied polychlorinated sulfolipid class of natural products. Further, the dichlorination of a (*Z*)-allylic chlorohydrin affords with high selectivity a stereotetrad present in one of the chlorosulfolipids.

Introduction

Over 2000 chlorine-containing natural products are currently known,[1] and many of these display potent antibiotic or cytotoxic properties. Therefore, it is noteworthy that the development of methods for the stereoselective introduction of chlorine into organic compounds significantly lags behind nearly all other aspects of stereoselective synthesis.[2−4] The lack of sophistication in this area, coupled with the broad range of important chlorinated natural and non-natural products, drives our laboratory to develop new methods for the stereoselective introduction of chlorine into organic scaffolds.

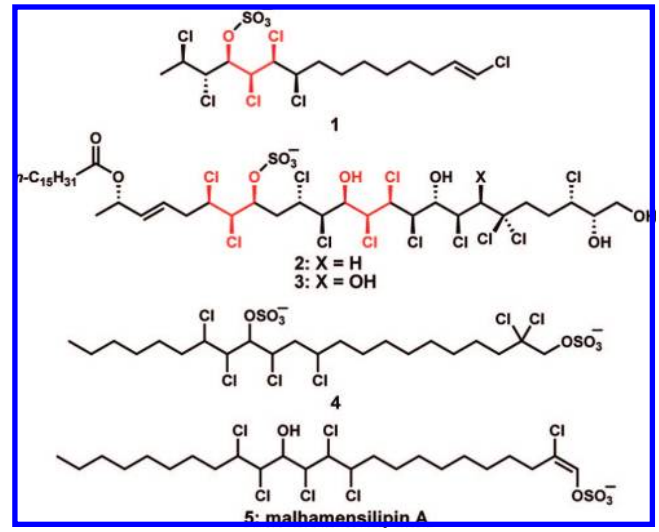


Figure 1. Unnamed chlorosulfolipids isolated from Adriatic mussels (**1**−**3**) and from freshwater algae (**4**) and algae-derived protein kinase inhibitor malhamensilipin A (**5**).

Chlorosulfolipids **1**−**5**[5,6] (Figure 1) represent a particularly daunting challenge for synthesis. Ciminiello, Fattorusso, and co-workers isolated compounds **1**−**3** from Adriatic mussels that caused diarrhetic shellfish poisoning upon ingestion;[5] these fascinating molecules were deemed to be the causative agents of this illness. The NMR method developed by Murata's group was used to arrive at the relative stereochemistry shown.[7] An efficient synthesis of these compounds would allow confirmation of their stereochemistry and, by extension, a validation of this NMR method in complex polychlorinated molecules. Related chlorosulfolipids have been isolated from freshwater algae,

(1) The status of organohalogen natural product isolation has been consistently monitored by Professor Gordon W. Gribble:(a) Gribble, G. W. *J. Chem. Educ.* **2004**, *81*, 1441–1449. (b) Gribble, G. W. *Am. Sci.* **2004**, *92*, 342–349. (c) Gribble, G. W. *Acc. Chem. Res.* **1998**, *31*, 141–152. (d) Gribble, G. W. *J. Nat. Prod.* **1992**, *55*, 1353–1395. (e) From 1995 through 2002, Professor Gribble frequently reviewed the literature pertaining to the isolation of organochlorine natural products. The results were published on the internet in a series of 18 "Natural Chlorine Updates". See: http://www.eurochlor.org/index.asp?page=84, accessed June 2, 2008.

(2) For several breakthrough examples of catalytic asymmetric α-chlorination of carbonyl compounds, see:(a) Hintermann, L.; Togni, A. *Helv. Chim. Acta* **2000**, *83*, 2425–2435. (b) Wack, H.; Taggi, A. E.; Hafez, A. M.; Drury, W. J.; Lectka, T. *J. Am. Chem. Soc.* **2001**, *123*, 1531–1532. (c) Hafez, A. M.; Taggi, A. E.; Wack, H.; Esterbrook, J.; Lectka, T. *Org. Lett.* **2001**, *3*, 2049–2051. (d) Brochu, M. P.; Brown, S. P.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2004**, *126*, 4108–4109. (e) Halland, N.; Braunton, A.; Bachmann, S.; Marigo, M.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2004**, *126*, 4790–4791.

(3) For representative chiral auxiliary- and reagent-based protocols for stereoselective introduction of chlorine, see:(a) Evans, D. A.; Sjogren, E. B.; Weber, A. E.; Conn, R. E. *Tetrahedron Lett.* **1987**, *28*, 39–42. (b) Evans, D. A.; Ellman, J. A.; Dorow, R. L. *Tetrahedron Lett.* **1987**, *28*, 1123–1126. (c) Hu, S.; Jayaraman, S.; Oehlschlager, A. C. *J. Org. Chem.* **1996**, *61*, 7513–7520. (d) Hu, S.; Jayaraman, S.; Oehlschlager, A. C. *J. Org. Chem.* **1998**, *63*, 8843–8849, and references therein.

(4) There have been innumerable reports of the introduction of single chloride-bearing stereogenic centers using alcohol to chloride conversion protocols.

(5) (a) Ciminiello, P.; Fattorusso, E.; Forino, M.; Magno, S.; Di Rosa, M.; Ianaro, A.; Poletti, R. *J. Org. Chem.* **2001**, *66*, 578–582. (b) Ciminiello, P.; Dell'Aversano, C.; Fattorusso, E.; Forino, M.; Di Rosa, M.; Ianaro, A.; Poletti, R. *J. Am. Chem. Soc.* **2002**, *124*, 13114–13120. (c) Ciminiello, P.; Dell'Aversano, C.; Fattorusso, E.; Forino, M.; Magno, S. *Pure Appl. Chem.* **2003**, *75*, 325–336. (d) Ciminiello, P.; Dell'Aversano, C.; Fattorusso, E.; Forino, M.; Magno, S.; Di Meglio, P.; Ianaro, A.; Poletti, R. *Tetrahedron* **2004**, *60*, 7093–7098. (e) Ciminiello, P.; Fattorusso, E. *Eur. J. Org. Chem.* **2004**, 2533–2551.

(6) (a) Elovson, J.; Vagelos, P. R. *Proc. Natl. Acad. Sci. U.S.A.* **1969**, *62*, 957–963. (b) Haines, T. H.; Pousada, M.; Stern, B.; Mayers, G. L. *Biochem. J.* **1969**, *113*, 565–566. (c) Elovson, J.; Vagelos, P. R. *Biochemistry* **1970**, *9*, 3110–3126. (d) Haines, T. H. In *Lipids and Biomembranes of Eukaryotic Microorganisms*; Erwin, J. A., Ed.; Academic Press: New York, 1973; pp 197−232. (e) Haines, T. H. *Annu. Rev. Microbiol.* **1973**, *27*, 403–412.

(7) Matsumori, N.; Kaneno, D.; Murata, M.; Nakamura, H.; Tachibana, K. *J. Org. Chem.* **1999**, *64*, 866–876.

10.1021/ja804167v CCC: $40.75

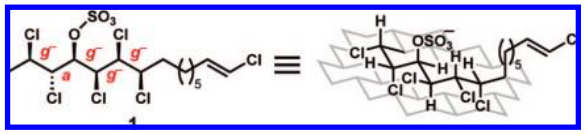


Figure 2. Probable conformational preference of chlorosulfolipid **1**. *g* = gauche, *a* = anti.

though their relative stereochemistry remains unknown.[6,8] In at least one species of freshwater algae, chlorosulfolipids such as **4**[6c] account for 15% of the total lipid content of the organism, and they are the primary lipids found in the cell membranes, *to the exclusion of phospholipids*.[6] The related algae-derived compound malhamensilipin A (**5**) was found to be a protein kinase inhibitor.[9,10]

These polychlorinated lipids may be viewed as electronically distinct isosteres of polyketide natural products. The enormous family of polyketides includes many important pharmaceutical agents, including antibiotic and antitumor compounds. Their complex stereochemical arrays confer substantial conformational organization to what appear to be very flexible molecules. The resulting preferred conformations, which dictate overall molecular shape, are critical to the biological activity of these compounds.[11] The chlorosulfolipids contain arrays of adjacent stereogenic carbon atoms that each bear an electronegative atom; in addition to the avoidance of *syn*-pentane-like interactions that is important in the context of polyketides, dipolar and stereoelectronic effects might be important. For example, the well-known stereoelectronic preference for mutual gauche orientations of electronegative substituents[12] might further limit the number of low-energy conformers of these molecules. Indeed, the $^3J_{H-H}$ coupling constants reported for **1**[5a] perfectly match the three-dimensional structure predicted simply on the basis of avoidance of *syn*-pentane-like interactions and maximization of relative gauche orientations (Figure 2).[13] Methodology that enables the synthesis of **1**−**5** and non-natural polychlorinated alkanes will enable study of the conformational aspects of these fascinating molecules and could eventually *provide opportunities for the control of molecular shape.*

As targets for synthesis, these complex lipids will necessarily elicit substantial methodology development for stereoselective polychlorination.[14] Given the nearly regular interspersion of hydroxyl (or sulfated hydroxyl) groups among the many chlorides of the chlorosulfolipids (see **2** and **3**, in particular) we reasoned that a method for the diastereoselective vicinal dichlorination of allylic alcohols would be both relevant and

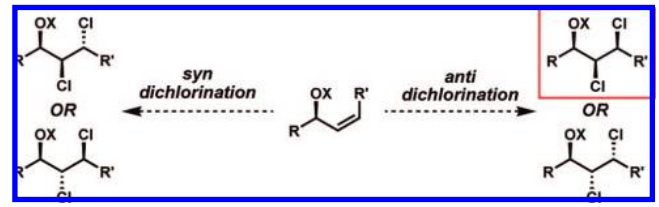


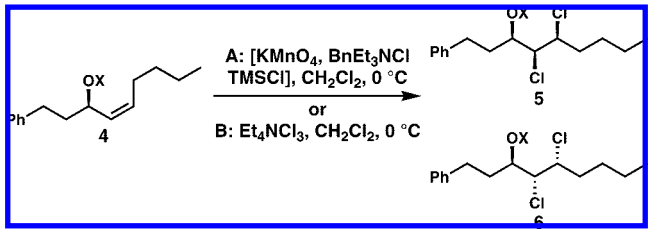
Figure 3. Possible stereochemical outcomes of the vicinal dichlorination of (*Z*)-allylic alcohol derivatives.

valuable. Ready access to enantiomerically enriched allylic alcohols of both *E* and *Z* geometry makes this approach appealing.[15−17] To our surprise, and to the best of our knowledge, a comprehensive study of the diastereoselective vicinal dichlorination of chiral acyclic alkenes has never been reported.[18,19] Progress toward this goal, in the form of the diastereoselective synthesis of syn,syn hydroxydichloride motifs from allylic alcohol derivatives, is reported here.

On the assumption that allylic strain ($A_{1,3}$) might serve as a valuable stereocontrol element,[20] we opted to study the dichlorination of a series of (*Z*)-allylic alcohol derivatives (Figure 3). We surmised that the right combination of steric and electronic effects required for high diastereoselectivity might be unveiled by varying substituent groups on the allylic alcohol oxygen; the choice of reagents for either syn or anti dichlorination,

(8) A survey of the distribution of chlorosulfolipids among 30 species of algae has shown that these chlorosulfolipids are present in a significant number of freshwater algae. See:Mercer, E. I.; Davies, C. L. *Phytochemistry* **1979**, *18*, 457–462.
(9) Chen, J. L.; Proteau, P. J.; Roberts, M. A.; Gerwick, W. H.; Slate, D. L.; Lee, R. H. *J. Nat. Prod.* **1994**, *57*, 524–527.
(10) Increasingly common occurrences of halogenated fatty acids in a variety of organisms have prompted a review article on the subject: Dembitsky, V. M.; Srebnik, M. *Prog. Lipid Res.* **2002**, *41*, 315–367.
(11) Hoffmann, R. W. *Angew. Chem., Int. Ed.* **2000**, *39*, 2054–2070.
(12) For an excellent lead reference, see: Sonntag, L.-S.; Schweizer, S.; Ochsenfeld, C.; Wennemers, H. *J. Am. Chem. Soc.* **2006**, *128*, 14697–14703.
(13) O'Hagan and coworkers have pioneered the stereocontrolled synthesis of polyfluorinated alkanes with three or four adjacent fluorine-bearing stereogenic centers. For details, and a discussion of the conformations of these interesting polyfluorides, see: (a) Nicoletti, M.; O'Hagan, D.; Slawin, A. M. Z. *J. Am. Chem. Soc.* **2005**, *127*, 482–483. (b) Hunter, L.; O'Hagan, D.; Slawin, A. M. Z. *J. Am. Chem. Soc.* **2006**, *128*, 16422–16423. (c) Hunter, L.; Slawin, A. M. Z.; Kirsch, P.; O'Hagan, D. *Angew. Chem., Int. Ed.* **2007**, *46*, 7887–7890.
(14) In our work focusing on the chlorosulfolipids, we wish to avoid the potentially problematic conversion of acyclic polyols into the corresponding polychlorides; this procedure could suffer from serious issues of regiocontrol as targets **1**−**5** bear a mixture of chlorides and hydroxyl/sulfate groups, and potential problems of partial retention in the chlorination reactions would be devastating. In the context of hexapyranose sugars, some beautiful work for the conversion of multiple hydroxyl groups into chlorides, with inversion, has been reported:(a) Jennings, H. J.; Jones, J. K. N. *Can. J. Chem.* **1965**, *43*, 2372–2385. (b) Cottrell, A. G.; Buncel, E.; Jones, J. K. N. *Chem. Ind.* **1966**, 552.
(15) For state-of-the-art enantioselective syntheses of propargylic alcohols, which can be reduced to either the (*E*)- or (*Z*)-allylic alcohols, see:(a) Matsumura, K.; Hashiguchi, S.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1997**, *119*, 8738–8739. (b) Boyall, D.; Frantz, D. E.; Carreira, E. M. *Org. Lett.* **2002**, *4*, 2605–2606.
(16) For a seminal contribution in the area of direct enantioenriched (*E*)-allylic alcohol synthesis, see: Oppolzer, W.; Radinov, R. N. *Helv. Chim. Acta* **1992**, *75*, 170–173.
(17) For direct syntheses of enantioenriched (*Z*)-allylic alcohols, see: Salvi, L.; Jeon, S.-J.; Fisher, E. L.; Carroll, P. J.; Walsh, P. J. *J. Am. Chem. Soc.* **2007**, *129*, 16119–16125.
(18) Studies of related processes, including dibromination, haloetherification, halolactonization, and selenofunctionalization of alkenes have all been studied in some detail. For some representative examples, see:(a) Liotta, D.; Zima, G.; Saindane, M. *J. Org. Chem.* **1982**, *47*, 1258–1267. (b) Chamberlin, A. R.; Dezube, M.; Dussault, P.; McMills, M. C. *J. Am. Chem. Soc.* **1983**, *105*, 5819–5825. (c) Chamberlin, A. R.; Mulholland, R. L., Jr *Tetrahedron* **1984**, *40*, 2297–2302. (d) Bartlett, P. A. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press, Inc.: New York, 1984; Vol. 3, pp 411−454. (e) Kim, K. S.; Park, H. B.; Kim, J. Y.; Ahn, Y. H.; Jeong, I. H. *Tetrahedron Lett.* **1996**, *37*, 1249–1252.
(19) The significantly different behavior among the halides and related reagents means that previously studied stereoselective halogenation/halofunctionalization reactions of allylic alcohols do not necessarily translate to the corresponding dichlorination process. High selectivities in the selenofunctionalization of allylic alcohols are thought to derive from Se−O attractive interactions; analogous interactions are not likely to be operative in chlorination reactions. For an excellent study of the diastereoselective dibromination of chiral allylic alcohols, which resulted in high levels of selectivity in alcoholic solvents with an excess of added bromide ion, see:(a) Midland, M. M.; Halterman, R. L. *J. Org. Chem.* **1981**, *46*, 1227–1229. Attempts to adapt this procedure with the chlorine equivalent Et_4NCl_3 in alcoholic solvents, with added chloride, led to predominant chloroetherification and apparent low selectivity in the small amount of dichlorinated product observed.

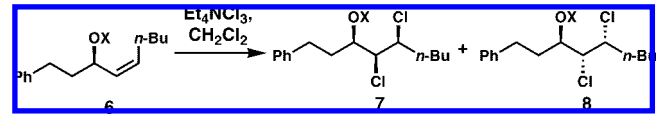
Table 1. Comparison of the Markó−Maguire and Mioskowski Reagents for Diastereoselective Vicinal Dichlorination of Allylic Alcohol Derivatives (TBS = *tert*-Butyldimethylsilyl, Piv = Pivaloate)



X	method	dr (**5**:**6**)[a]
H	A	1.2:1
H	B	1.1:1
TBS	A	1.2:1
TBS	B	1.5:1
Piv	A	2.5:1
Piv	B	2.4:1

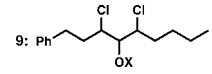
[a] Diastereomeric ratio (dr) determined by ^{1}H NMR analysis of crude reaction mixtures.

Table 2. Evaluation of the Optimal O-Substituent for Dichlorination Diastereoselectivity (TBS = *tert*-Butyldimethylsilyl, Boc = *tert*-Butoxycarbonyl, Ac = Acetate, Piv = Pivaloate)



X	temp (°C)	dr (**7**:**8**)[a]	X	temp (°C)	dr (**7**:**8**)[a]
H	−78	1.0:1	Piv	−78	7.5:1[b]
Me	−78	2.0:1	Piv	−90	7.7:1[b]
TBS	−78	2.0:1	Cl_3CCO	−78	5.0:1
CO_2Me	−78	5.0:1[b]	**Cl_3CCO**	**−90**	**6.5:1**
Boc	−78	5.0:1[b]	F_3CCO	−78	6.0:1
Ac	−78	5.0:1[b]	**F_3CCO**	**−90**	**7.0:1**

[a] Diastereomeric ratio (dr) determined by ^{1}H NMR analysis of crude reaction mixtures. [b] In addition to **7** and **8**, rearranged products such as **9** were produced with unconfirmed stereochemistry in varying quantities; all other reactions proceeded cleanly to complete conversion.



combined with diastereofacial selectivity, might eventually enable access to all four stereotriads shown. In particular, stereoselective access to the syn,syn isomer by anti dichlorination would be directly relevant to targets **1**−**3** (see highlighted substructures in Figure 1).

Results and Discussion

Consideration of stereospecific processes for the anti dichlorination of alkenes led us to two seemingly distinct procedures, in addition to the less appealing direct use of molecular chlorine. Markó, Maguire, and co-workers reported the use of an uncharacterized reagent generated by premixing a tetraalkylammonium permanganate with TMSCl; this reagent effectively dichlorinates a range of alkenes with quite reasonable functional group tolerance and apparent anti stereospecificity.[21,22] Mioskowski's group pioneered the use of tetraethylammonium trichloride, an easily prepared, bench-stable solid for vicinal anti dichlorinations of both alkenes and alkynes, which also demonstrates good functional group compatibility.[23] We were hopeful that the reagent of Markó and Maguire, which might proceed via some sort of chloromanganese reagent,[22b] could coordinate to an allylic alcohol or a Lewis basic derivative (ether, ester, carbonate, etc.) to afford useful levels of stereocontrol based on a substrate-directed mechanism.[24] To our surprise, we found nearly identical levels of efficiency and diastereoselectivity with both reagents, using several different allylic alcohol derivatives (three examples shown, Table 1). As a result, we considered that the reagent made in situ by the Markó−Maguire procedure might simply be a Mioskowski-type reagent; the soluble permanganate salt could oxidize chloride ion, generating molecular chlorine, and thence a tetraalkylammonium trichloride reagent.[25,26] Although our evidence is at best circumstantial, we feel that this is a plausible explanation for the reactivity of the Markó−Maguire reagent.[27]

Screening of a variety of groups of differing steric and electronic nature on the allylic hydroxyl (Table 2) indicated that the steric bulk of the substituent had little impact on selectivity. However, electron-deficient (acyl-type) groups led to reasonable margins of selectivity. In particular, pivaloyl, trichloroacetyl, and trifluoroacetyl groups showed significant diastereoselectivities, with best results at −90 °C. However, dichlorinations of the less electron-deficient acyl groups, including pivaloyl, suffered from substantial side product formation resulting from ester carbonyl participation/rearrangement to afford compounds tentatively assigned as **9**. The good selectivity and clean reactivity of the allylic trihaloacetates is particularly noteworthy given the ease of introduction and removal of these acyl groups. As a result of the lability of trifluoroacetate esters to chromatographic purification, the more stable trichloroacetate group was deemed optimal, despite the slightly diminished selectivities. A screen of solvents (not shown) demonstrated that the use of dichloromethane at −90 °C was optimal for both clean conversion and diastereoselectivity.

The results in Table 3 indicate that, after some further optimization, the reaction affords usable selectivities (from 4.6:1 to 10.9:1 diastereomeric ratio (dr) for crude reaction mixtures) across a range of structurally different substrates and is tolerant of a variety of functional groups (see also Table 2 and ref 23 for further compatibility of the reagent). There appears to be little effect from steric modulation in

(20) For an excellent review, see:(a) Hoffmann, R. W. *Chem. Rev* **1989**, *89*, 1841–1860. For seminal applications of $A_{1,3}$-strain minimization for acyclic stereocontrol in natural product synthesis, see the first synthesis of monensin by Kishi and coworkers: (b) Schmid, G.; Fukuyama, T.; Akasaka, K.; Kishi, Y. *J. Am. Chem. Soc.* **1979**, *101*, 259–260.

(21) Markó, I. E.; Richardson, P. R.; Bailey, M.; Maguire, A. R.; Coughlan, N. *Tetrahedron Lett.* **1997**, *38*, 2339–2342.

(22) An earlier variant of this protocol used oxalyl chloride as a chlorine source and generated a thermally unstable reagent of unknown structure that lost chlorination activity above −35 °C: (a) Markó, I. E.; Richardson, P. F. *Tetrahedron Lett.* **1991**, *32*, 1831–1834. (b) Richardson, P. F.; Markó, I. E. *Synlett* **1991**, 733–736.

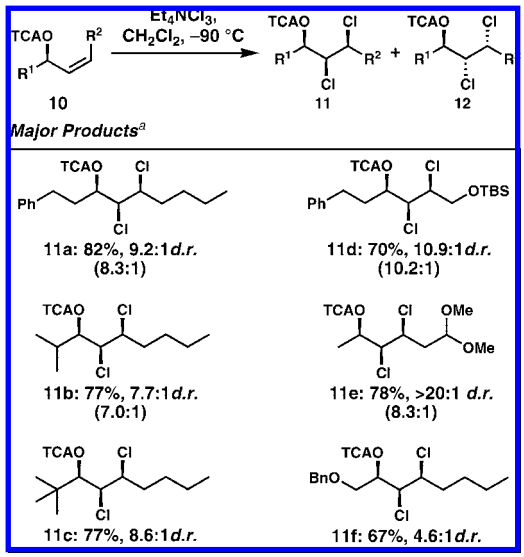
(23) Schlama, T.; Gabriel, K.; Gouverneur, V.; Mioskowski, C. *Angew. Chem., Int. Ed.* **1997**, *36*, 2341–2344.

(24) Hoveyda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev.* **1993**, *93*, 1307–1370.

(25) In ref 21, the Markó−Maguire reagent is also reported to open epoxides to the corresponding chlorohydrins and oxidize sufides to sulfoxides. We have not evaluated the reactivity of the Mioskowski reagent in these transformations, as the presence of manganese salt byproducts in the former procedure might well be critical.

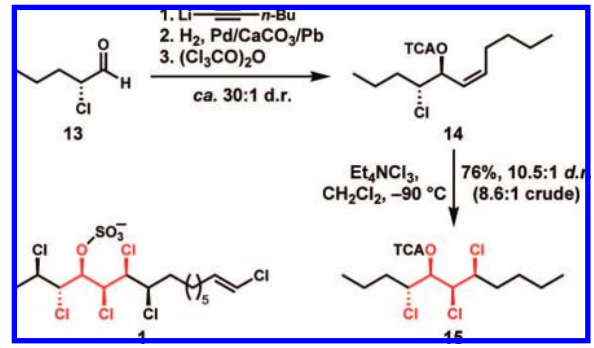
(26) As an important historical note, Scheele's discovery of molecular chlorine resulted from the oxidation of chloride ion by manganese oxides. See: Weeks, M. E. *Discovery of the Elements*, 3rd ed.; Journal of Chemical Education: Easton, PA, 1935; pp 253−257.

Table 3. Scope of the Stereoselective Dichlorination Reaction (TCA = Trichloroacetate, TBS = *tert*-Butyldimethylsilyl, Bn = Benzyl)

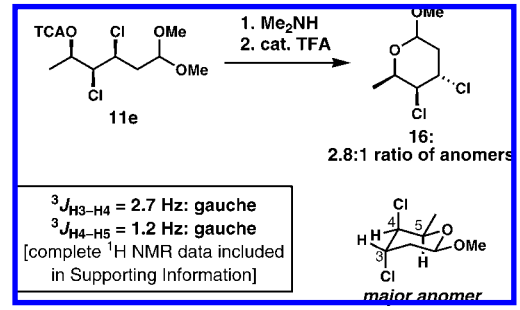


[a] Yield refers to isolated yield of indicated diastereomeric composition. Diastereomeric ratios (*d.r.*) determined by integration using ^{1}H NMR; *d.r.* in parentheses refers to crude product when different from purified product.

Scheme 1. Diastereoselective Synthesis of a Stereotetrad Relevant to Chlorosulfolipid **1** (TCA = Trichloroacetate)



Scheme 2. Synthesis of Pyran **16** to Confirm the Relative Stereochemistry of Dichlorination



the vicinity of the trichloroacetate group (see **11a**−**11c**), and useful functional group handles were tolerated at the other terminus (see **11d** and **11e**). These two examples provide means for chain extension for applications to complex polychlorinated targets. Product **11f**, formed in a 4.6:1 dr, demonstrates that synthetically useful heteroatom functional groups are tolerated at the trichloroacetate terminus. Removal of the trichloroacetyl group, which is necessary for stereocontrol, occurs in nearly quantitative yield without disruption of the chlorides (NH_3 in MeOH/Et_2O) to afford product of sufficient purity to obviate chromatography.[28] In several cases we have run the three-step sequence of acylation, dichlorination, and deacylation and obtained diastereoselectivities identical to those shown in Table 3 in good overall yields.[28]

We were aware that this methodology would need to be applied in even more complex contexts, so we generated racemic trichloroacetylated allylic chlorohydrin **14** as shown in Scheme 1. According to the method of Kang and Britton,[29] acetylide addition to α-chloroaldehyde **13** provided anti chlorohydrin in up to 30:1 dr, consistent with the polar Felkin−Anh model;[30] semihydrogenation and trichloroacetylation completed the simple, unoptimized sequence. Fortunately, the extra chlorine-bearing stereogenic center had little effect on selectivity, as stereotetrad **15** was produced in 10.5:1 dr in 76% yield. The relative stereorelationships in **15** match perfectly the central stereotetrad of chlorosulfolipid **1**.

Although the Mioskowski reagent is known to effect stereospecific anti dichlorination reactions,[23] we clearly needed to unambiguously assign the relative stereochemistry of our products. Unfortunately, the majority of our dichlorinated products were oils, and preliminary screens of derivatives did not lead to promising candidates for X-ray crystallographic analysis. In principle, the NMR method developed by Murata's group,[7] which was used to assign the relative stereochemistry of lipids **1**−**3**, could be used; however, we desired independent means of stereochemical analysis to be certain of our assignments. To elucidate the stereorelationship between the trichloroacetoxy-bearing carbon and the newly formed chlorine-bearing centers, we turned to the stereospecific epoxidation reaction of chlorohydrins; differentiation of cis- and trans-epoxides is readily accomplished on the basis of coupling constant analysis and nuclear Overhauser effect (nOe) experiments.[31] The conversion of product **11a** and its anti,syn-diastereomer to the corresponding cis- and trans-epoxides, respectively, supported our assignment of the syn,syn stereochemistry of the major reaction products.[28] To further solidify our assignment, we converted product **11e** into dichloropyran **16** (Scheme 2); coupling constant analysis on the six-membered ring scaffold clearly supported our analysis.[28]

(27) Et_4NCl_3 effects smooth anti dichlorination of alkynes (ref 23). We have found that the Markó−Maguire reagent performs the same transformation. This is also consistent with these reagents being similar in nature and argues against a possible mechanism involving syn chloromanganation of the π-system, followed by invertive S_N2 displacement of manganese by chloride (see reference 22a); in the case of alkyne substrates, S_N2 displacement on an sp^2 carbon would need to be invoked.

(28) Please see the Supporting Information for details.

(29) For a recent account of highly stereoselective alkynyllithium additions to α-chloroaldehydes, see: Kang, B.; Britton, R. *Org. Lett.* **2007**, *9*, 5083–5086.

(30) The addition of organometallic nucleophiles to α-chloroaldehydes generally proceeds to afford the anti product, consistent with the polar Felkin−Anh model (hyperconjugative stabilization of the transition state/steric control), though the Cornforth model (dipole minimization/steric control) also accounts for the stereochemistry of the products. For an excellent discussion and lead reference, see: Cee, V. J.; Cramer, C. J.; Evans, D. A. *J. Am. Chem. Soc.* **2006**, *128*, 2920–2930.

(31) For one example of the determination of halohydrin relative stereochemistry by stereospecific conversion to the corresponding epoxides, see:(a) Besse, P.; Sokoltchik, T.; Veschambre, H. *Tetrahedron: Asymmetry* **1998**, *9*, 4441–4457. See also refs 3c,d, and 29.

Inspired by polychlorinated sulfolipids **1**−**5**, we have outlined a direct solution to the synthesis of syn,syn hydroxydichloride stereotriads by the dichlorination of allylic alcohol derivatives using tetraethylammonium trichloride. Readily available (*Z*)-allylic trichloroacetates have demonstrated high levels of diastereocontrol across a range of substrates; the ease of deprotection without interference of the chlorides is noteworthy. We are currently studying the extent to which (*Z*)-allylic trichloroacetates are competent substrates for the stereoselective additions of other reagents that react via anti addition processes. We have also synthesized a stereotetrad relevant to chlorosulfolipid **1** using our methodology, and we have firmly established the relative stereochemistry of our products. Further methods for the stereoselective introduction of chlorine into carbon scaffolds, application of these methods to the synthesis of the chlorosulfolipids, and studies on the conformational aspects and membrane behaviors of polychlorinated alkanes will be the subjects of future disclosures.

Acknowledgment. The authors thank the School of Physical Sciences of University of California, Irvine for generous startup funding. New Faculty Awards from Amgen and Eli Lilly are also gratefully acknowledged. J.S.K. thanks Pfizer for a 2007 Summer Undergraduate Research Fellowship and The Camille & Henry Dreyfus Foundation for a 2008 Jean Dreyfus Boissevain Undergraduate Scholarship for Excellence in Chemistry.

Supporting Information Available: Complete experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

JA804167V