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Asymmetric Total Synthesis of (+)-Hexachlorosulfolipid, a Cytotoxin Isolated from Adriatic Mussels

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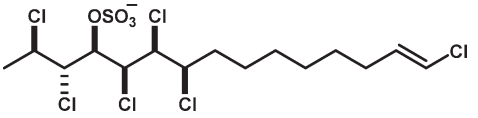

The enantioselective total synthesis of (+)-hexachlorosulfolipid, a cytotoxin found in the Adriatic mussel *Mytilus galloprovincialis*, is described. The unique chlorinated hydrocarbon motif of the lipid is successfully furnished by a series of dichlorination reactions of chiral epoxides with chlorophosphonium reagent generated in situ from Ph_3P/NCS. The present total synthesis has allowed the confirmation of the absolute configuration of the natural cytotoxic (+)-hexachlorosulfolipid originally proposed by Fattorusso, Ciminiello, and co-workers.

Introduction

Polychlorinated sulfolipids have recently emerged as attractive targets for biological investigations (Figure 1).[1] They are unique in featuring hydrocarbon motifs densely functionalized with polar chlorine atoms, which are rarely seen in other natural products. This unusual family of chlorine-rich lipids includes (+)-hexachlorosulfolipid **1**,[2a] undecachlorosulfolipid **2**,[2b] malhamensilipin A (**3**),[3a,d] and danicalipin A (**4**),[1b] all of which have drawn considerable attention as substances of toxicological concern. In the quest for deeper knowledge of their risks and effects on human health, massive efforts have been made to establish chemical access to chlorosulfolipids, which would allow the further evaluation of their biological properties and functions. However, the greatest difficulties in the chemical synthesis of chlorosulfolipids are those caused by the stereochemistry, which poses significant challenges in the artificial production of such molecules.

Vanderwal[4] and Carreira[5] have independently made significant contributions to this emerging field of organic synthesis, which have led to the successful total syntheses of the chlorosulfolipids. Carreira and co-workers were the first to establish a route to (±)-hexachlorosulfolipid **1** whose (+)-enantiomer is known as the causative substance of seafood

(1) For pioneering studies on this class of molecules, see: (a) Mayers, G. L.; Haines, T. H. *Biochemistry* **1967**, *6*, 1665–1671. (b) Elovson, J.; Vagelos, P. R. *Proc. Natl. Acad. Sci. U.S.A.* **1969**, *62*, 957–963. (c) Haines, T. H.; Pousada, M.; Stern, B.; Mayers, G. L. *Biochem. J.* **1969**, *113*, 565–566. (d) Elovson, J.; Vagelos, P. R. *Biochemistry* **1970**, *9*, 3110–3126. (e) Haines, T. H. In *Lipids and Biomembranes of Eukaryotic Microorganisms*; Erwin, J. A., Ed.; Academic Press: New York; 1973; pp 197−232. (f) Haines, T. H. *Annu. Rev. Microbiol.* **1973**, *27*, 403–412. (g) Hansen, J. A. *Physiol. Plant.* **1973**, *29*, 234–238. (h) Elovson, J. *Biochemistry* **1974**, *13*, 3483–3487. (i) Mercer, E. I.; Davies, C. L. *Phytochemistry* **1974**, *13*, 1607–1610. (j) Mercer, E. I.; Davies, C. L. *Phytochemistry* **1975**, *14*, 1545–1548. (k) Mercer, E. I.; Davies, C. L. *Phytochemistry* **1979**, *18*, 457–462.

(2) (a) Ciminiello, P.; Fattorusso, E.; Forino, M.; Di Rosa, M.; Ianaro, A.; Poletti, R. *J. Org. Chem.* **2001**, *66*, 578–582. (b) Ciminiello, P.; Dell'Aversano, C.; Fattorusso, E.; Forino, M.; Magno, S.; 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.; Di Meglio, P.; Ianaro, A.; Poletti, R. *Tetrahedron* **2004**, *60*, 7093–7098. For reviews, see: (d) Ciminiello, P.; Dell'Aversano, C.; Fattorusso, E.; Forino, M.; Magno, S. *Pure Appl. Chem.* **2003**, *75*, 325–336. (e) Ciminiello, P.; Fattorusso, E. *Eur. J. Org. Chem.* **2004**, 2533–2551.

(3) (a) 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. (b) Gerwick, W. H. *Biochim. Biophys. Acta* **1994**, *1211*, 243–255. (c) Gerwick, W. H.; Roberts, M. A.; Proteau, P. J.; Chen, J. L. *J. Appl. Phycol.* **1994**, *6*, 143–149. Recently, the revised structure of this natural compound has been reported: (d) Pereira, A. R.; Byrum, T.; Shibuya, G. M.; Vanderwal, C. D.; Gerwick, W. H. *J. Nat. Prod.* **2010**, *73*, 279–283.

(4) An elegant methodology was developed by this group: (a) Shibuya, G. M.; Kanady, J. S.; Vanderwal, C. D. *J. Am. Chem. Soc.* **2008**, *130*, 12514–12518. (b) Kanady, J. S.; Nguyen, J. D.; Ziller, J. W.; Vanderwal, C. D. *J. Org. Chem.* **2009**, *74*, 2175–2178. While the present paper was in review, asymmetric total synthesis of malhamensilipine A was reported: (c) Bedke, D. K.; Shibuya, G. M.; Pereira, A. R.; Gerwick, W. H.; Vanderwal, C. D. *J. Am. Chem. Soc.* **2010**, *132*, 2542–2543.

(5) For the total synthesis of (±)-hexachlorosulfolipid, see: (a) Nilewski, C.; Geisser, R. W.; Carreira, E. M. *Nature* **2009**, *457*, 573–576. For an account of this work, see: Bedke, D. K.; Vanderwal, C. D. *Nature* **2009**, *457*, 548–549. For related studies, see: (b) Nilewski, C.; Geisser, R. W.; Ebert, M.-O.; Carreira, E. M. *J. Am. Chem. Soc.* **2009**, *131*, 15866–15876.

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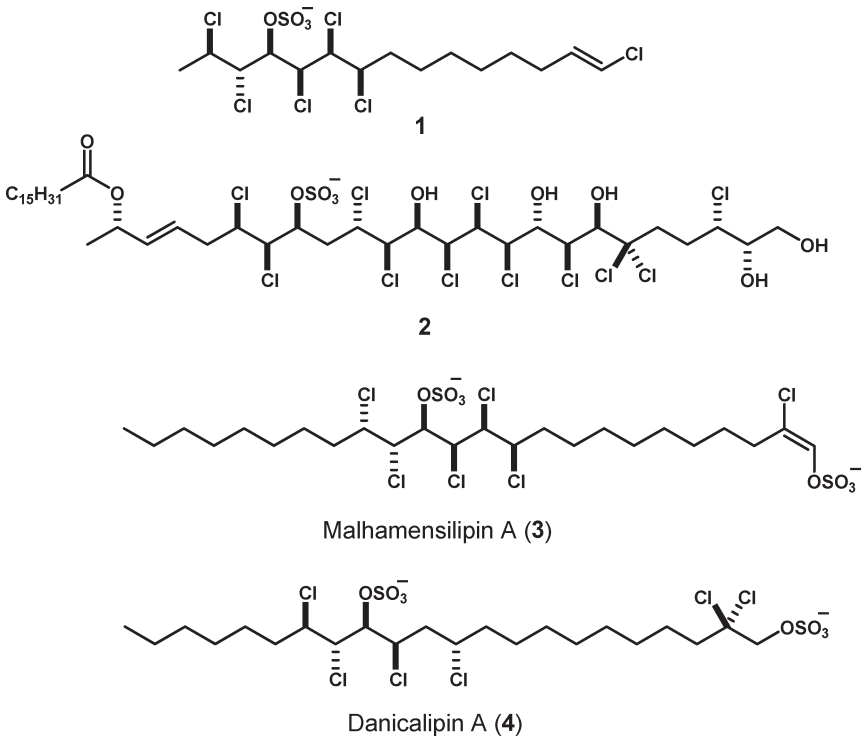


FIGURE 1. Natural polychlorosulfolipids.

poisoning in the Adriatic mussel *Mytilus galloprovincialis*.[2a] Carreira's synthesis of sulfolipid **1** elegantly demonstrates that the trimethylsilyl chloride-mediated ring opening of epoxides effects the construction of the chlorinated architecture and an anchimeric assistance of the distal chlorine atom takes place during another carbon−chlorine bond formation.[5a] Vanderwal and co-workers have also devised a general approach to multiply chlorinated hydrocarbon units by diastereoselective alkene dichlorinations in which the allylic strain ($A_{1,3}$) of the substrates directs the facial selectivity.[4a,b] In addition, their recent efforts culminated in the first stereoselective total syntheses of danicalipin A (**4**), a major chlorosulfolipid isolated from the freshwater alga *Ochromonas danica*,[6,7] and malhamensilipin A (**3**), a protein tyrosine kinase (PTK) inhibitor found in the cultured chrysophyte *Poterioochromonas malhamensis*.[4c]

We have also been engaged in the total synthesis of chlorosulfolipids as it would allow us to develop medicinal and toxicological research associated with this class of naturally occurring cytotoxins. Our avid interest in this area has been directed toward (+)-chlorosulfolipid **1** that exerts antiproliferative activity on several cancer cell lines, including WEHI 164 (murine fibrosarcoma) and P388 (murine leukemia).[2a] With a view to exploring further structure−activity relationship studies on (+)-hexachlorosulfolipid **1**, we initiated a research program aimed at establishing stereoselective access to natural lipid **1** and its stereoisomers.[8] In the present paper, we describe the asymmetric total synthesis of (+)-hexachlorosulfolipid **1** featuring the epoxide−chloride displacement strategy, which allowed us to confirm the absolute configuration of lipid (+)-**1**.

Results and Discussion

1. Key Transformations Leading to (+)-Hexachlorosulfolipid 1. Our approach to (+)-hexachlorosulfolipid **1** is retrosynthetically outlined in Scheme 1 and features the use of Ph_3P/NCS-mediated stereospecific dichlorinations of epoxides (Scheme 1).[8] In our approach, lipid (+)-**1** was traced back to the (*E*)-alkenyl chloro triad **5** that would serve as a suitable scaffold for alkene dichlorination and would be readily derived from the simple allylic hydroxylation of trichloride **6** followed by chain elongation. Prior to initiating our investigations, however, we had little appreciation of whether the dichlorination of an allylic double bond, which is generally directed by the conformational strain ($A_{1,3}$) of the substrate,[9] would provide the requisite configuration for natural product **1**: this is because the empirical rule might favor the opposite stereochemistry over that of our target,[10] and furthermore, in many cases, the degree of asymmetric induction for the (*E*)-allylic substrate is unpredictable and frequently low.[9] Nevertheless, it was our belief that the

(6) Bedke, D. K.; Shibuya, G. M.; Pereira, A. R.; Gerwick, W. H.; Haines, T. H.; Vanderwal, C. D. *J. Am. Chem. Soc.* **2009**, *131*, 7570–7572.

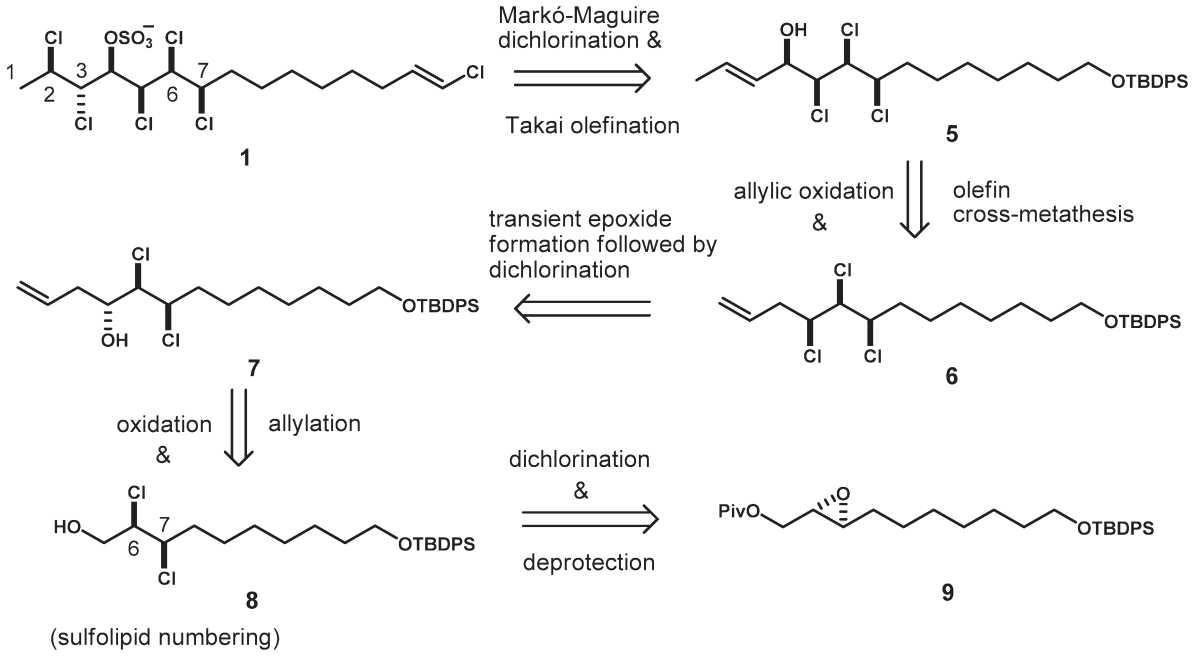
(7) Kawahara, T.; Kumaki, Y.; Kamada, T.; Ishii, T.; Okino, T. *J. Org. Chem.* **2009**, *74*, 6016–6024.

(8) Yoshimitsu, T.; Fukumoto, N.; Tanaka, T. *J. Org. Chem.* **2009**, *74*, 696–702.

(9) For a pertinent review on the chemistry of allylic 1,3-strain, see: Hoffmann, R. W. *Chem. Rev.* **1989**, *89*, 1841–1860.

(10) Chamberlin and co-workers (ref 10a) have reported that 2-iodo-1,3-*anti*-diols are stereo- and regioselectively produced from 1,2-disubstituted allylic alcohols via an intermediacy of cyclic iodonium ions generated preferentially *syn* to the allylic hydroxyl group in the 1,3-allylic strain model, followed by their nucleophilic hydration at the sterically more accessible position. This observation suggested that dichlorination of our allylic alcohol substrate **5** would favor the production of undesired (2*S*,3*R*)-pentachloride **21**. (a) Chamberlin, A. R.; Mulholland, R. L., Jr. *Tetrahedron* **1984**, *40*, 2297–2302. (b) Chamberlin, A. R.; Dezube, M.; Dussault, P.; McMills, M. C. *J. Am. Chem. Soc.* **1983**, *105*, 5819–5825. Other related studies on the diastereoselective halogenation of allylic alcohols, for instance: (c) Midland, M. M.; Halterman, R. L. *J. Org. Chem.* **1981**, *46*, 1227–1229. (d) Liotta, D.; Zima, G.; Saindane, M. *J. Org. Chem.* **1982**, *47*, 1258–1267. (e) Bartlett, P. A. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press, Inc.: New York, 1984; Vol. 3, pp 411−454. (f) Kim, K. S.; Park, H. B.; Kim, J. Y.; Ahn, Y. H.; Jeong, I. H. *Tetrahedron Lett.* **1996**, *37*, 1249–1252.

SCHEME 1. Retrosynthesis of (+)-Hexachlorosulfolipid 1



stereochemistry would be changeable and tunable to some extent by modifying either the structural features of the substrate or the reaction conditions. The present study demonstrates that our prospect was indeed the case and that the free hydroxyl group significantly altered the stereochemical outcome of the alkene dichlorination, leading to the desired polychloro motif. Then, we expected that trichloride **6** would be synthesized from simple starting material **9** by epoxide−chloride displacement: the two chlorine atoms at the C6/C7 positions (sulfolipid numbering) of target (+)-**1** would be readily installed by the dichlorination of enantiomerically pure epoxide **9** with the Ph_3P/NCS reagent system to deliver dichloro alcohol **8**. This compound **8**, in turn, would be transformed, upon oxidation followed by stereoselective allylation, into alcohol **7** that would serve as a suitable precursor of trichloride **6**. As described in detail in the following section, initial attempts to simply chlorinate the hydroxyl group of **7** were unsuccessful. However, the Ph_3P/NCS-mediated dichlorination of an epoxide derived from **7** provided an efficient access to the chlorinated motif, again showing the power of the epoxide−chloride displacement strategy for the stereoselective construction of polychlorinated scaffolds.

2. Synthesis of Alcohol 5 and Trichloroacetate 14. The starting enantiomerically pure epoxide **9** (>98% ee) was prepared from 10-*tert*-butyldiphenylsilyloxydec-2-en-1-ol[11] via a two-step sequence comprising Sharpless asymmetric epoxidation[12] followed by protection of the hydroxyl group as pivalic ester (Scheme 2). Installation of the vicinal dichloro functionality into epoxide **9** was successfully achieved using NCS/Ph_3P in toluene at 90 °C to afford dichloride **11** in 85% yield as a single isomer.[13] Removal of the pivalic group of **11** with DIBAL efficiently took place, and the resultant alcohol **8** was then oxidized with Dess−Martin periodinane under buffered conditions to deliver dichloroaldehyde **i** (shown in brackets). As we had anticipated, this aldehyde **i** was easily decomposed upon thin-layer silica gel chromatography, showing its propensity for β-elimination of the chlorine atom. Therefore, the crude aldehyde **i** was immediately reacted with allyltrimethylsilane in the presence of $BF_3 \cdot OEt_2$ to afford *anti*-chlorohydrin **7** along with the *syn*-diastereomer in an *anti*/*syn* ratio of ds = 3.8:1 (72% in two steps from **8**).[14] The *anti* selectivity observed in the present case can be rationalized

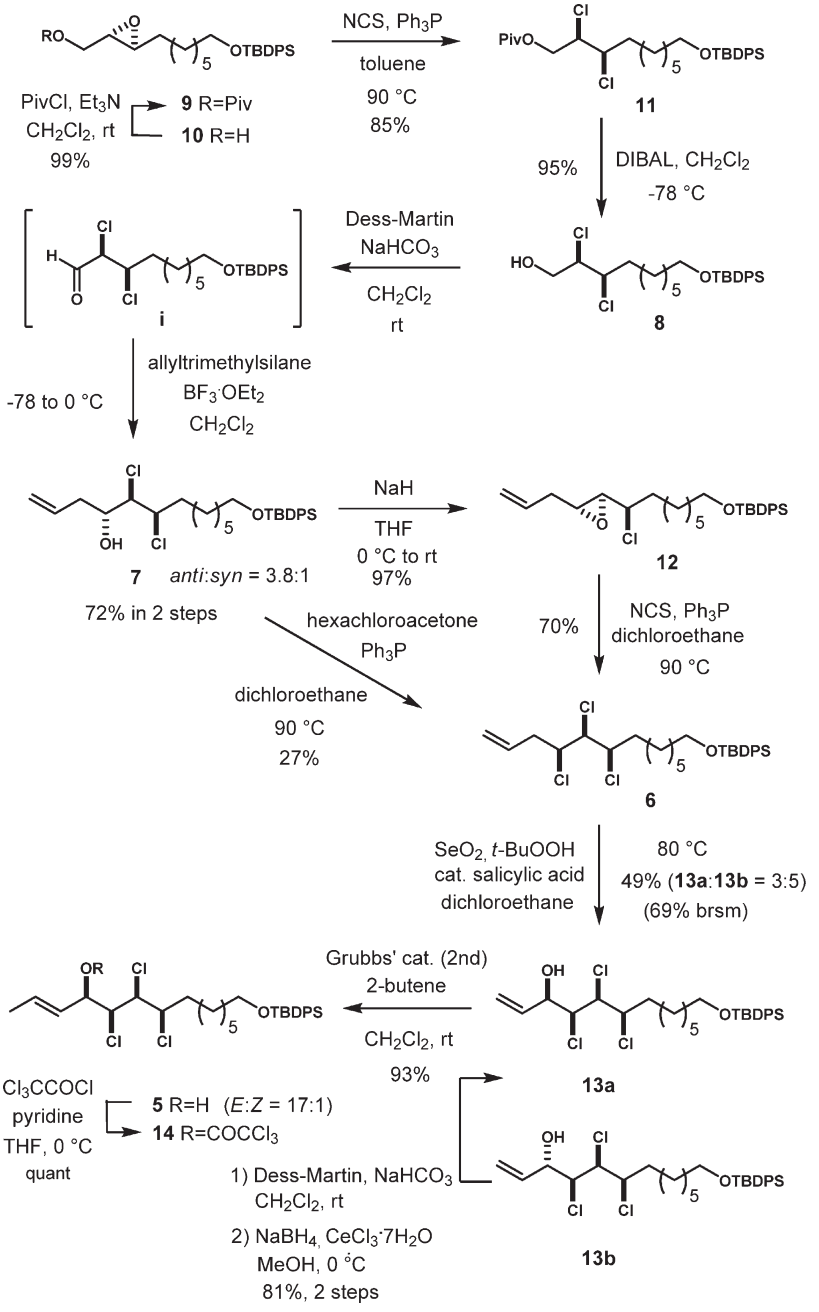
(11) Allylic alcohol **10** was prepared by a four-step protocol similar to the known method; see: Lu, K.; Huang, M.; Xiang, Z.; Liu, Y.; Chen, J.; Yang, Z. *Org. Lett.* **2006**, *8*, 1193–1196.

(12) Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 5974–5976. For reviews, see: (a) Finn, M. G.; Sharpless, K. B. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: Orlando, 1985; Vol. 5, p 247−308. (b) Rossiter, B. E. *Chem. Ind.* **1985**, *22*, 295–308. (c) Pfenninger, A. *Synthesis* **1986**, 89–116. (d) Johnson, R. A.; Sharpless, K. B. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 7, pp 389−436. (e) Hoeft, E. *Top. Curr. Chem.* **1993**, *164*, 63–77. (f) Schinzer, D. In *Organic Synthesis Highlights II*; Herbert, W., Ed.; VCH: Weinheim, 1995; pp 3−8. (g) Katsuki, T.; Victor, M. *Org. React.* **1996**, *48*, 1–299. (h) Stephenson, G. R. *Adv. Asymmetric Synth.* **1996**, 367–391. (i) Shum, W. P.; Cannarsa, M. J. *Chirality Ind. II* **1997**, 363–380. (j) Katsuki, T. *Transition Met. Org. Synth.* **1998**, *2*, 261–271. (k) Kagan, H. B. *Compr. Asymmetric Catal. I−III* **1999**, *1*, 9–30. (l) Katsuki, T. *Compr. Asymmetric Catal. I−III* **1999**, *2*, 621–648. (m) Mahrwald, R. *J. Prakt. Chem.* **1999**, *341*, 191–194. (n) Johnson, R. A.; Sharpless, K. B. *Catal. Asymmetric Synth.* (*2nd Ed.*) **2000**, 231–280. (o) Liu, M. *Rodd's Chem. Carbon Compd.* (*2nd Ed.*) **2001**, *5*, 1–32. (p) Martin, V. S. *Asymmetric Oxid. React.* **2001**, 50–69. (q) Bonini, C.; Righi, G. A. *Tetrahedron* **2002**, *58*, 4981–5021. (r) Sharpless, K. B. *Angew. Chem., Int. Ed.* **2002**, *41*, 2024–2032.

(13) The stereochemistry of dichloride **11** was established by its transformation into (*E*)-olefin by means of the known reductive olefination protocol. Sonnet, P. E.; Oliver, J. E. *J. Org. Chem.* **1976**, *41*, 3284–3286. For details, see the Supporting Information.

(14) Hosomi, A.; Sakurai, H. *Tetrahedron Lett.* **1976**, *16*, 1295. Selected reviews for Hosomi−Sakurai reactions: (a) Biamonte, M. A. In *Name Reactions for Homologations*; Li, J. J., Ed.; John Wiley & Sons: Hoboken, NJ, 2009; Part 1, pp 539−575. (b) Hosomi, A.; Miura, K. In *Acid Catalysis in Modern Organic Synthesis*; Yamamoto, H., Ishihara, K., Eds.; Wiley-VCH Verlag GmbH & Co. KGaA: Weinhem, 2008; Vol. 1, pp 469−516. (c) Hosomi, A.; Miura, K. *Bull. Chem. Soc. Jpn.* **2004**, *77*, 835–851. (d) Fleming, I. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; vol. 6, pp 563−593. (e) Fleming, I.; Dunogues, J.; Smithers, R. *Org. React.* **1989**, *37*, 57. (f) Hosomi, A. *Acc. Chem. Res.* **1988**, *21*, 200–206. (g) Schinzer, D. *Synthesis* **1988**, 263–273. (h) Sakurai, H. *Pure Appl. Chem.* **1982**, *54*, 1–22.

SCHEME 2. Preparation of Alcohol 5 and Trichloroacetate 14



by considering either the Cornforth or the polar Felkin−Anh transition-state model that preferentially undergoes allylation reaction with allyltrimethylsilane to provide *anti*-alcohol **7** (Figure 2).[15]

The next process necessary for producing the chlorinated skeleton was to displace the hydroxyl group of dichloro alcohol **7** with a chloride ion at the position α to the bulky vicinal dichloro motif. Contrary to our expectation, this seemingly simple chlorination was difficult, and all our efforts to deliver this *all-syn* chloro triad **6** were unfruitful due to the concomitant occurrence of elimination reactions. Hexachloroacetone/Ph_3P was among the most effective, but the yield of trichloride **6** was still only 27%. The disappointing

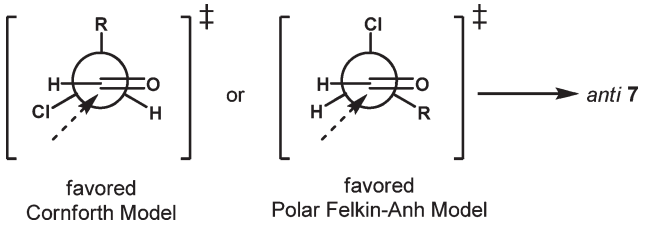
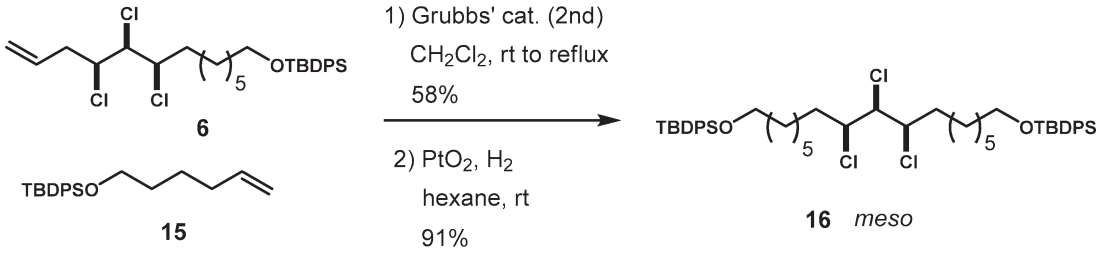


FIGURE 2. Rationale for *anti* selectivity of allylation of dichloroaldehyde **i**.

(15) For a theoretical investigation of the nucleophilic addition to α-chloroaldehydes, see: Cee, V. J.; Cramer, C. J.; Evans, D. A. *J. Am. Chem. Soc.* **2006**, *128*, 2920–2930. For a recent example, see: Kang, B.; Britton, R. *Org. Lett.* **2007**, *9*, 5083–5086. and references cited therein.

SCHEME 3. Determination of Stereochemistry of Trichloride 6

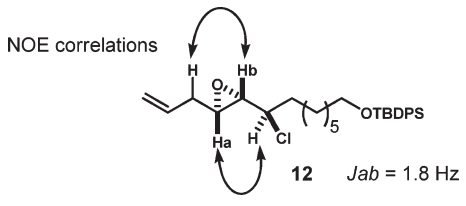


results prompted us to devise an alternative pathway to produce chloro triad **6**, and again, the epoxide−dichlorination method was found to be suitable for this process. Thus, dichloro alcohol **7** was first transformed into *trans*-epoxide **12** by treatment with NaH,[16] which, in turn, was subjected to dichlorination under Ph_3P/NCS conditions[17,18] to furnish trichloride **6** in 70% yield. This two-step protocol (**7** → **12** → **6**) could deliver triad **6** in a satisfactory overall yield, indicating that the epoxide−dichlorination method serves as a powerful means for the stereoselective construction of polychloro motifs. The *all-syn* configuration of triad **6** was unambiguously confirmed by its transformation into achiral *meso*-symmetrical trichloride **16** (Scheme 3). Thus, trichloride **6** was initially subjected to a cross-olefin metathesis with TBDPS-protected alkene **15**[19] in the presence of Grubbs' second-generation catalyst, giving rise to an olefin (structure not indicated) in 58% yield. Hydrogenation of the olefin under PtO_2 conditions afforded symmetrical *meso*-trichloride **16** in 91% yield, thereby unambiguously establishing the *all-syn* arrangement of the chlorine atoms embedded in trichloride **6**.

The stereoselective introduction of the allylic hydroxyl group to compound **6** was achieved by selenium oxidation. Numerous attempts to effect this transformation eventually led to the discovery that the use of excess selenium dioxide and *tert*-butyl hydroperoxide (TBHP) in the presence of catalytic salicylic acid[20] provided the highest product yield. In this allylic oxidation, although the formation of unwanted α-alcohol **13b** was more pronounced with moderate diastereoselectivity (ca. **13a**/**13b** = 3:5), each isomer was separable by simple silica gel column chromatography, and furthermore, α-alcohol **13b** could be isomerized to *β*-alcohol **13a**.[21] Thus, Dess−Martin oxidation of α-alcohol **13b** was followed by the reduction of the resultant ketone with $NaBH_4$ in the presence of $CeCl_3 \cdot 7H_2O$ to yield *β*-alcohol **13a** in 81% overall yield. Alcohol **13a** was then assembled with 2-butene in the presence of Grubbs' second-generation catalyst to efficiently deliver (*E*)-alkene **5** (*E*/*Z* = ca. 17:1) that bears an internal unsaturated three-carbon unit suitable for the production of a chloro pentad motif.

3. Synthesis of Chloro Pentad by Diastereoselective Dichlorination of Alkenes. As we approached even closer to the target polychlorinated scaffold, the next task was to install two more vicinal chlorine atoms at the 2/3 positions of allylic alcohol **5**, which allowed us to access pentad **20** that corresponds to the C_1−C_{14} portion of (+)-hexachlorosulfolipid **1** (Table 1). As we mentioned earlier in this paper, it has been well delineated that an asymmetric induction adjacent to allylic substituents is predictable on the basis of allylic strain ($A_{1,3}$), particularly when the substrates possess a substituent on the double bond *Z* to the allylic center.[9] This is exactly exemplified by Vanderwal's work in which (*Z*)-allylic trichloroacetates exert high levels of diastereoselectivity in alkene dichlorination.[4a] Vanderwal's work has also revealed that the degree of selectivity depends on the allylic hydroxyl protecting group. Accordingly, it was reasonably assumed that, by considering such conformational strain, dichlorination of the alkene in the present case would favor the undesired configuration rather than the desired one corresponding to that of the natural product.[10] However, we expected that (*E*)-allylic substrates would possibly undergo dichlorination to provide pentachloride with the desired configuration since our (*E*)-allylic substrates might be less sensitive to the allylic strain. In addition to this prospect, we also envisioned that the alteration of the hydroxyl protecting group would significantly change the facial selectivity in the initial chloronium formation as shown in Vaderwal's work, hopefully furnishing the natural configuration. In this context, Vanderwal's work has suggested that the dichlorination of substrates with a free hydroxyl group proceeds less selectively than that of protected variants[4a] and shows a slight preference for chloronium formation that occurs from *anti* to the hydroxyl group, which would lead to the stereochemistry relevant to our target natural product (+)-**1**.

(16) The relative stereochemistry of epoxide **12** was unambiguously determined by analyzing both NOEs and the coupling constants between the protons Ha and Hb (*J* = 1.8 Hz) in the ^{1}H NMR spectra.



(17) The dichlorination of epoxide **12** with Ph_3P/hexachloroacetone similarly gave desired trichloride **6** in 74% yield. However, partly because side reactions occurred under this condition, the yields varied when the reactions were performed on a large scale.

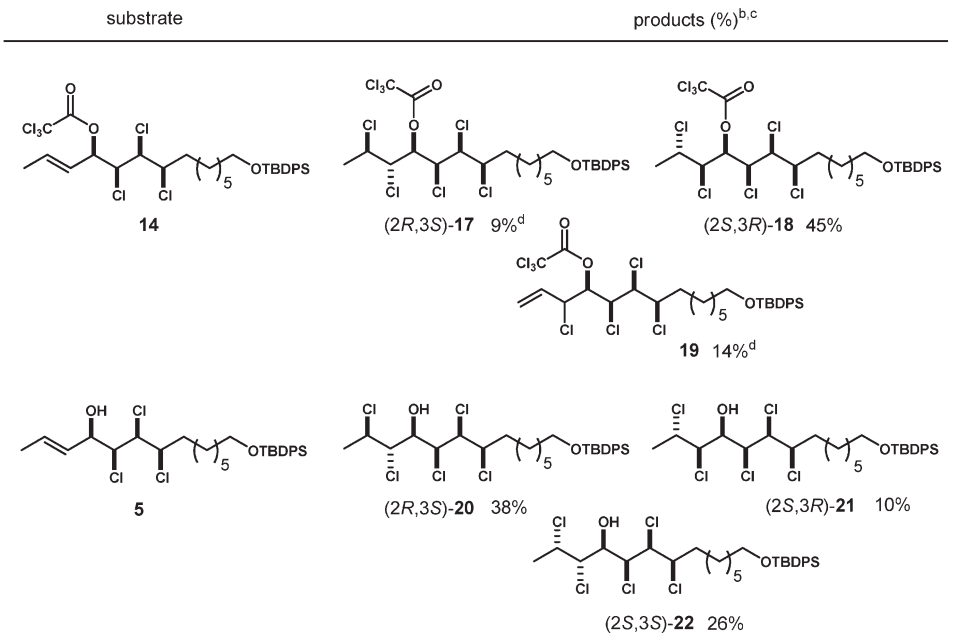
(18) In this case, dichloroethane was used as solvent because of the higher solubility of the reagents and substrate. Dichlorination of epoxide **12** in toluene, however, afforded trichloride **6** in a comparable yield (68%) to that in dichloroethane.

(19) This material was readily prepared by silylating 5-hexen-1-ol with TBDPSCl in the presence of imidazole in DMF (95% yield).

(20) Winkler, J. D.; Rouse, M. B.; Greaney, M. F.; Harrison, S. J.; Jeon, Y. T. *J. Am. Chem. Soc.* **2002**, *124*, 9726–9728.

(21) The stereochemistry of *β*-alcohol **13a** and α-alcohol **13b** was determined by their transformation into the corresponding *cis*- and *trans*-epoxides, respectively. For details, see the Supporting Information.

TABLE 1. Dichlorination of Trichloroacetate 14 and Alcohol 5 under Markó's Conditions[a]



[a]The reaction was performed with $KMnO_4$ (1.2 equiv), $BnEt_3NCl$ (1.2 equiv), and TMSCl (7.4 equiv for trichloroacetate **14**; 5.2 equiv for alcohol **5**) in CH_2Cl_2 at −78 to −10 °C. [b]The stereochemistry of dichlorinated C2/C3 positions of chlorides **17**, **18**, and **20**−**22** was determined by chemical correlations including epoxide formation. For details, see the Supporting Information. [c]The rest of the materials were unidentified products whose structures were difficult to elucidate. [d]The yield of the material was determined after removal of the trichloroacetyl group.

The reagent that we chose for the dichlorination process was the Markó−Maguire ($KMnO_4$/$BnEt_3NCl$/TMSCl) chlorination system (Table 1).[22] Considering Vanderwal's observation that trichloroacetates are superior to other allylic congeners in terms of yield and selectivity, we initially examined the dichlorination of trichloroacetate **14** under Markó's conditions. The reaction of trichloroacetate **14** prepared by the reported procedure[4a] took place by gradually warming from −78 to −10 °C to provide a mixture of (2*R*,3*S*)-pentachloride **17** (9%) and (2*S*,3*R*)-pentachloride **18** (45%) along with tetrachloride **19** (14%).[23] The observed stereochemical preference is in line with the prediction stemming from the consideration of the allylic strain ($A_{1,3}$) of substrate **14** and suggests that chloronium formation preferentially occurred *syn* to the trichloroacetyl substituent that avoids steric repulsion caused by the bulky chlorinated backbone, followed by attacking of a chloride ion at the sterically more accessible 2 position (Scheme 4). Conformational analysis on a chlorinated hydrocarbon model that possesses a shorter backbone with the requisite stereochemistry using Gaussian 03 program [B3LYP/6-31G(d)][24] suggested that the most energetically favorable conformer of trichloroacetate was in good agreement with the allylic strain model as proposed.

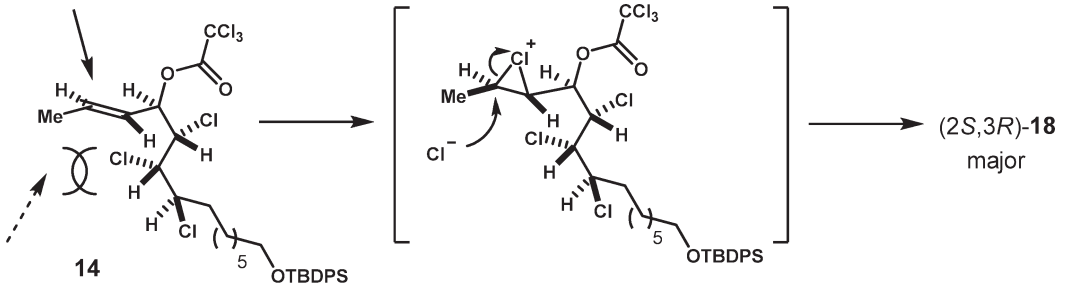
We then expected that the free hydroxyl group of the allylic substrate would considerably change the stereochemical course of the dichlorination. Therefore, we evaluated alcohol **5** as the substrate with a view to giving rise to the desired pentachloro motif. Gratifyingly, the dichlorination occurred under the same conditions to yield desired (2*R*,3*S*)-pentachloride **20** (38%) as the major product together with (2*S*,3*R*)-pentachloride **21** (10%) as well as (2*S*,3*S*)-pentachloride **22** (26%). Although further studies are necessary for elucidating the origin of this moderate yet obvious change in diastereoselectivity, it can be assumed that the lack of streic demands of the protection-free (*E*)-allylic alcohol system allows the greater conformational flexibility, leading to the opposite facial selectivity. In this context, the conformational analysis of the simple model of alcohol **5**

(22) It has been proposed that both Markó−Maguire ($KMnO_4$/$BnEt_3NCl$/TMSCl) and Mioskowski (Et_4NCl_3) reagents involve similar reactive chlorinating species as exemplified by R_4NCl_3. In fact, Vanderwal's work has demonstrated that both Markó−Maguire ($KMnO_4$/$BnEt_3NCl$/TMSCl) and Mioskowski (Et_4NCl_3) dichlorination protocols have nearly identical levels of efficiency and selectivity. However, we assume that there may be some differences in the Lewis acidities of the two reagent systems, which possibly arise from the chemical species generated in the reaction mixtures. (a) Markó, I. E.; Richardson, P. R.; Bailey, M.; Maguire, A. R.; Coughlan, N. *Tetrahedron Lett*. **1997**, *38*, 2339–2342. (b) Schlama, T.; Gabriel, K.; Gouverneur, V.; Mioskowski, C. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2342–2344.

(23) Compound **19** was possibly produced by the neighboring participation of the trichloroacetyl group followed by the elimination. Its stereochemistry at the 3 position has, however, yet to be determined.

(24) Conformational analysis on simple hydrocarbon models having a shorter backbone was carried out using the Gaussian 03 program [B3LYP/6-31G(d)]. For experimental details, see the Supporting Information. Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, J. A.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada.; M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; Pople, J. A. *Gaussian 03, Revision E.01*; Gaussian, Inc.: Wallingford, CT, 2004.

SCHEME 4. Rationale for the Stereochemical Outcome of Dichlorination of Trichloroacetate 14 Based on the Calculated Models



suggested that there was essentially no difference in energies between the two favorable conformers **a** and **b** (~ca. 0.5 kcal/mol) (Figure 3).[25] The dichlorination reaction of conformer **b** was reasonably assumed to take place via an α-configurational cyclic chloronium intermediate that avoids the severe steric interaction with the bulky polychlorinated backbone, giving rise to (2*R*,3*S*)-pentachloride **20** as a major product, whereas it is difficult to rationalize preferential production of (2*R*,3*S*)-**20** from conformer **a** (Scheme 5).[26] The production of (2*S*,3*S*)-*syn*-pentachloride **22** may also indicate an intermediacy of the α-configurational chloronium species that possibly underwent the double inversion at the 2 or 3 position through anchimeric assistance of the distal chlorine atom.[5]

4. Completion of the Asymmetric Total Synthesis of (+)-Hexachlorosulfolipid 1. To complete the total synthesis of (+)-hexachlorosulfolipid **1**, pentachloride **20** possessing requisite functionalities with the correct stereochemistry was initially converted into acetate **23** quantitatively (Scheme 6). The TBDPS group of pentachloride **23** was then removed by HF−pyridine to provide primary alcohol **24** in 94% yield. Dess−Martin oxidation of primary alcohol **24** afforded aldehyde **25** (98%), which was subjected to $CrCl_2$-mediated chloroalkenylation[27] to deliver alkenyl chloride **26** in 75% yield. Deacetylation of alkenyl chloride **26** was successfully carried out by DIBAL-mediated reduction to provide alcohol **27** in 96% yield. The final task necessary to yield target molecule (+)-**1** was the sulfation of the hydroxyl group of alcohol **27**, which was successfully accomplished by conventional protocol using $SO_3 \cdot Py$ in DMF at room temperature to furnish (+)-hexachlorosulfolipid **1** in 75% yield. The spectroscopic and analytical data were in good agreement with those reported in the literature.[2a,5] The optical rotation of our synthetic material **1** was $[\alpha]^{24}_D$ +49 (*c* 0.59, MeOH) [lit.[2a] $[\alpha]^{25}_D$ +20.4 (*c* 0.0015, MeOH)], indicating that the absolute configuration of natural sulfolipid was as proposed by Ciminiello and Fattorusso.

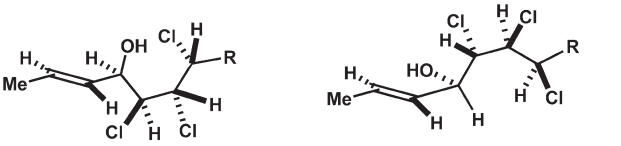


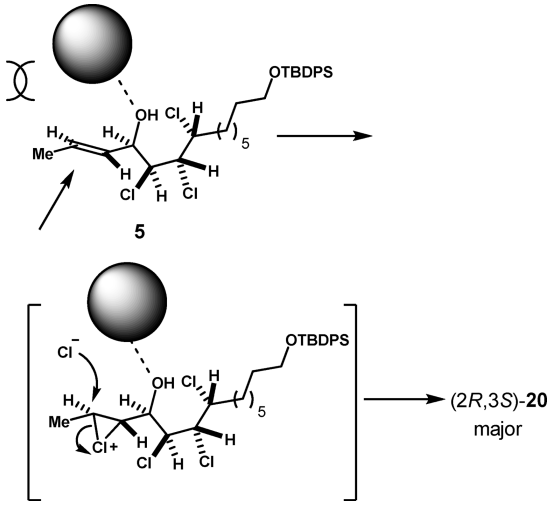
FIGURE 3. Energetically favorable conformers of model compound of alcohol **5**.

Conclusions

We have accomplished the asymmetric total synthesis of cytotoxic (+)-hexachlorosulfolipid **1** isolated from the Adriatic mussel *Mytilus galloprovincialis* and successfully confirmed the absolute stereochemistry as proposed by Fattorusso, Ciminiello, and co-workers. In the present study, we established a general method for the preparation of a polychloro array, a structural feature commonly found in many classes of natural chlorosulfolipids, and used it to synthesize (+)-hexachlorosulfolipid **1**, one of the typical members of the family. We are currently undertaking avid research to establish a polychlorinated sulfolipid library that will open up further structure−activity relationship studies on this class of natural compounds.

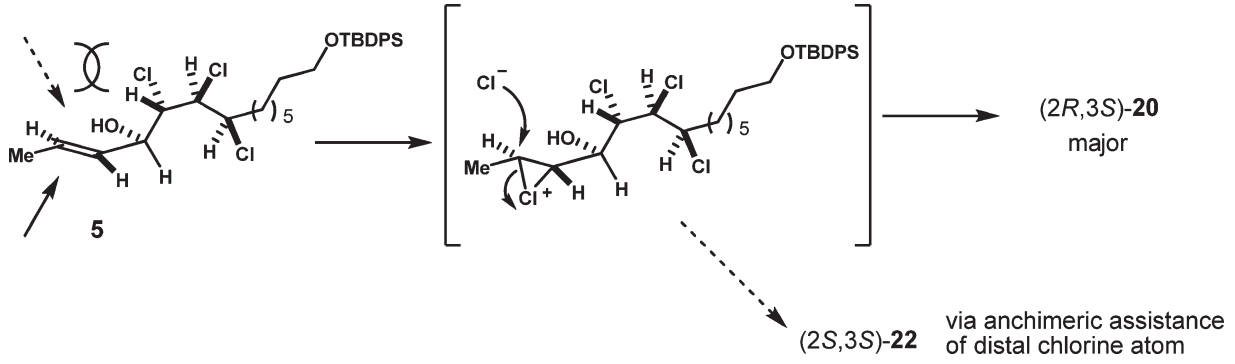
(25) We currently assume that the low energy gap observed between the two conformers **a** and **b** may arise from the relative instability of conformer **a** that suffers from steric interaction between the hydrogen atom at C3 position and the chlorine atom at C5. The interaction increases the relative energy of conformer **a**, leading to the proximity in the conformational energy gap of the two possible conformers.

(26) In this case, however, the observed stereochemical outcome may possibly indicate an intermediacy of the coordination of a Lewis acidic reagent to the hydroxyl group, such as the trimethylsilylated manganese complex,[22] which prevents substrate **5** from forming a β-chloronium intermediate as in the case of substrate **14**, eventually leading to (2*R*,3*S*)-pentachloride **20** as the major product. We are currently making further efforts to elucidate the origin of this stereochemical preference.

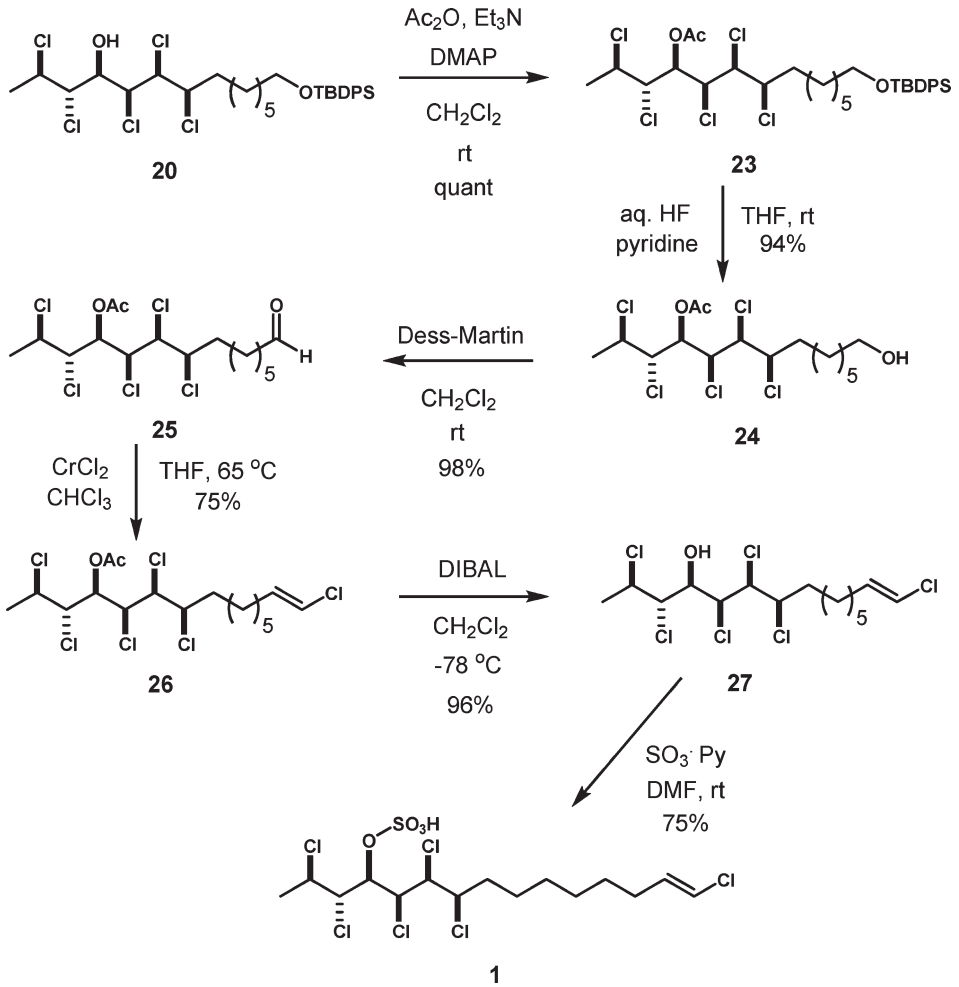


(27) Takai, K.; Nitta, K.; Utimoto, K. *J. Am. Chem. Soc.* **1986**, *108*, 7408–7410. Also see ref 5a.

SCHEME 5. Rationale for the Opposite Stereoselection Observed in Dichlorination of Alcohol 5 Based on the Calculated Models



SCHEME 6. Completion of Asymmetric Total Synthesis of (+)-Hexachlorosulfolipid 1



Experimental Section

[(2*S*,3*S*)-3-[7-[(*tert*-Butyldiphenylsilyl)oxy]heptyl]oxiran-2-yl]-methanol (10). To a magnetically stirred suspension of 4A MS (1.3 g) in CH_2Cl_2 (65 mL) at −25 °C were added L-diethyl tartrate (0.12 mL, 0.70 mmol) and Ti(O-*i*-Pr)$_4$ (0.13 mL, 0.44 mmol). After 15 min, TBHP (5.5 M in decane, 3.1 mL, 17.1 mmol) was added, and stirring was continued for an additional 1 h. To the mixture was added a solution of (*E*)-10-[(*tert*-butyldiphenylsilyl)-oxy]dec-2-en-1-ol (3.52 g, 8.59 mmol) in CH_2Cl_2 (15 mL), and the mixture was stirred at −25 °C for further 10 h. Following addition of 10% NaOH and brine, the stirred mixture was allowed to warm to room temperature. After 1 h, Celite and $MgSO_4$ were added, and stirring was continued for 15 min. The mixture was filtered through a Celite pad, and the filtrate was concentrated by rotary evaporation. The residue was purified by silica gel column chromatography (EtOAc/*n*-hexane 1:3) to give epoxide **10** (3.52 g, 96%) as a colorless oil. The enantiomeric purity of this material was determined by the Mosher method to be >98% ee. Epoxide **10**: colorless oil; $[\alpha]^{25}_D$ −13.4 (*c* 1.03, $CHCl_3$); IR (neat) ν 3420, 2930, 2857, 1427, 1111, 702 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.72−7.63 (m, 4H), 7.46−7.33 (m,

6H), 3.91 (ddd, 1H, J = 12.7, 5.5, 2.4 Hz), 3.65 (t, 2H, J = 6.6 Hz), 3.66−3.55 (m, 1H), 2.99−2.88 (m, 2H), 1.99 (t, 1H, J = 6.3 Hz), 1.61−1.51 (m, 4H), 1.47−1.26 (m, 8H), 1.05 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.5, 134.1, 129.4, 127.5, 63.9, 61.7, 58.4, 55.9, 32.5, 31.5, 29.3, 29.2, 26.8, 25.8, 25.6, 19.2; MS m/z 427 (MH^+), 199 (100); HRMS (FAB) calcd for $C_{26}H_{39}O_3Si$ (MH^+) 427.2668, found 427.2644.

[(2*S*,3*S*)-3-[7-[(*tert*-Butyldiphenylsilyl)oxy]heptyl]oxiran-2-yl]-methyl 2,2-dimethylpropanoate (9). To a stirred solution of epoxide **10** (3.58 g, 8.39 mmol) in CH_2Cl_2 (40 mL) at room temperature were added Et_3N (1.8 mL, 12.9 mmol) and pivaloyl chloride (1.4 mL, 11.1 mmol). After 2.5 h, DMAP (90 mg, 0.74 mmol) was added, and stirring was continued for an additional 0.5 h. Following addition of satd $NaHCO_3$, the mixture was poured into a separatory funnel and extracted with EtOAc. The organic phase was separated, dried over $MgSO_4$, filtered, and concentrated. Purification of the residue by silica gel column chromatography (EtOAc/*n*-hexane 1:20) gave epoxide **9** (4.24 g, 99%) as a colorless oil. **Epoxide 9**: colorless oil; $[\alpha]^{25}_D$ −14.8 (*c* 1.12, $CHCl_3$); IR (neat) ν 2957, 2932, 2857, 1732, 1153, 1111, 702 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.72−7.64 (m, 4H), 7.44−7.34 (m, 6H), 4.34 (dd, 1H, J = 12.2, 3.4 Hz), 3.93 (dd, 1H, J = 12.2, 6.0 Hz), 3.65 (t, 2H, J = 6.4 Hz), 2.96 (ddd, 1H, J = 6.0, 3.4, 2.3 Hz), 2.84 (ddd, 1H, J = 5.5, 5.5, 2.3 Hz), 1.61−1.50 (m, 4H), 1.38−1.18 (m, 17H), 1.05 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.2, 135.5, 134.1, 129.4, 127.5, 64.6, 63.8, 56.4, 55.4, 38.8, 32.5, 31.5, 29.2, 27.1, 26.8, 26.5, 25.8, 25.6, 19.2; MS m/z 511 (MH^+), 57 (100); HRMS (FAB) calcd for $C_{31}H_{47}O_4Si$ (MH^+) 511.3244, found 511.3231.

(2*R*,3*R*)-10-[(*tert*-Butyldiphenylsilyl)oxy]-2,3-dichlorodecyl 2,2-dimethylpropanoate (11). To a stirred solution of epoxide **9** (4.14 g, 8.11 mmol) in toluene (80 mL) at room temperature were added Ph_3P (6.38 g, 24.3 mmol) and NCS (3.25 g, 24.3 mmol), and the mixture was heated at 90 °C for 4.3 h. Additional amounts of Ph_3P (1.10 g, 4.05 mmol) and NCS (0.54 g, 4.06 mmol) were added, and stirring was continued for a further 1 h. The mixture was quenched with satd $NaHCO_3$, poured into a separatory funnel, and extracted with EtOAc. The organic phase was separated, dried over $MgSO_4$, filtered, and concentrated. *The following procedure was applied to ensure the removal of inseparable olefin byproducts:* The residue obtained by the above-mentioned protocol was again dissolved in CH_2Cl_2 (40 mL), and solid $NaHCO_3$ was added to the solution. An outlet stream containing O_3 and O_2 from an ozonizer was introduced into the mixture at −78 °C for 30 min to oxidize chloroalkene that was produced as a byproduct in the above-mentioned process. After being quenched with Me_2S, the mixture was allowed to warm to room temperature and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (EtOAc/*n*-hexane 1:30) to give dichloride **11** (3.91 g, 85%) as a colorless oil. **Dichloride 11**: colorless oil; $[\alpha]^{25}_D$ +18.3 (*c* 0.67, $CHCl_3$); IR (neat) ν 2932, 2859, 1738, 1148, 1111, 702 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.72−7.65 (m, 4H), 7.46−7.35 (m, 6H), 4.41−4.35 (m, 2H), 4.27 (ddd, 1H, J = 7.2, 6.0, 2.4 Hz), 4.18−4.10 (m, 1H), 3.66 (t, 2H, J = 6.4 Hz), 1.93−1.82 (m, 2H), 1.61−1.51 (m, 3H), 1.42−1.21 (m, 16H), 1.06 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.8, 135.5, 134.1, 129.5, 127.5, 64.9, 63.8, 61.8, 60.9, 38.8, 35.0, 32.4, 29.1, 28.8, 27.1, 26.8, 26.5, 25.6, 19.2; MS m/z 565 (MH^+), 57 (100); HRMS (FAB) calcd for $C_{31}H_{47}O_3{}^{35}Cl_2Si$ (MH^+) 565.2672, found 565.2662.

(2*R*,3*R*)-10-[(*tert*-Butyldiphenylsilyl)oxy]-2,3-dichlorodecan-1-ol (8). To a stirred solution of dichloride **11** (3.87 g, 6.86 mmol) in CH_2Cl_2 (54 mL) at −78 °C was added DIBAL (0.98 M in *n*-hexane, 15.4 mL, 15.1 mmol), and the mixture was stirred for 20 min. Following addition of satd NH_4Cl, the whole mixture was stirred at room temperature for 30 min. Celite was added to the solution, and the mixture was stirred for further 30 min and then filtered through a Celite pad. The filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (EtOAc/*n*-hexane 1:8) to give alcohol **8** (3.13 g, 95%) as a colorless oil. **Alcohol 8**: colorless oil; $[\alpha]^{25}_D$ +13.9 (*c* 0.27, $CHCl_3$); IR (neat) ν 3383, 2932, 2857, 1427, 1111, 702 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.73−7.63 (m, 4H), 7.47−7.33 (m, 6H), 4.28−4.13 (m, 2H), 3.96 (dd, 1H, J = 11.7, 5.7 Hz), 3.88 (dd, 1H, J = 11.7, 7.0 Hz), 3.66 (t, 2H, J = 6.4 Hz), 1.92−1.82 (m, 2H), 1.65−1.47 (m, 2H), 1.43−1.23 (m, 8H), 1.05 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.5, 134.1, 129.5, 127.5, 65.4, 64.5, 63.9, 62.0, 35.2, 32.4, 29.1, 28.9, 26.8, 26.5, 25.6, 19.2; MS m/z 481 (MH^+), 135 (100); HRMS (FAB) calcd for $C_{26}H_{39}O_2{}^{35}Cl_2Si$ (MH^+) 481.2096, found 481.2074.

(4*R*,5*R*,6*R*)-13-[(*tert*-Butyldiphenylsilyl)oxy]-5,6-dichlorotridec-1-en-4-ol (7) and (4*S*,5*R*,6*R*)-13-[(*tert*-Butyldiphenylsilyl)oxy]-5,6-dichlorotridec-1-en-4-ol (*syn*-7). To a stirred solution of alcohol **8** (5.13 g, 10.7 mmol) in CH_2Cl_2 (100 mL) were added $NaHCO_3$ (8.96 g, 106.7 mmol) and Dess−Martin periodinane (6.71 g, 15.8 mmol) at room temperature. The mixture was stirred for 20 min and then treated with satd $NaHCO_3$ and satd $Na_2S_2O_3$. The mixture was poured into a separatory funnel where it was extracted with Et_2O. The organic phase was separated, dried over $MgSO_4$, filtered, and concentrated. The residue was dissolved in CH_2Cl_2 (100 mL) and was subjected to the next allylation reaction without further purification. To this solution were added allyltrimethylsilane (2.2 mL, 13.8 mmol) and $BF_3\cdot OEt_2$ (1.6 mL, 13.8 mmol) at −78 °C, and the mixture was stirred for 30 min. Following addition of additional amounts of allyltrimethylsilane (0.8 mL, 5.0 mmol) and $BF_3\cdot OEt_2$ (0.4 mL, 3.5 mmol) at the same temperature, the mixture was stirred for 15 min and then allowed to warm to 0 °C. After 15 min of stirring, the reaction was quenched with water. The mitxture was poured into a separatory funnel where it was partitioned between satd $NaHCO_3$ and EtOAc. The organic phase was separated, dried over $MgSO_4$, filtered, and concentrated. TLC analysis of the residue indicated that a trace of α,β-unsaturated aldehyde was produced by β-elimination of dichloroaldehyde **i**. Therefore, the crude residue was immediately dissolved in MeOH−CH_2Cl_2 (5:3 v/v, 80 mL) without further purification and was subjected to reduction with $NaBH_4$ (100 mg, 2.64 mmol) at 0 °C. After being stirred for 10 min, the solution was concentrated under reduced pressure. The residue was poured into a separatory funnel where it was partitioned between satd NH_4Cl and EtOAc. The organic phase was separated, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by silica gel column chromatography (CH_2Cl_2/*n*-hexane 1:2) to give less polar *anti*-alcohol **7** (3.18 g, 57%) as a colorless oil and more polar *syn*-alcohol ***syn*-7** (0.82 g, 15%) as a colorless oil. ***anti*-Alcohol 7**: colorless oil; $[\alpha]^{26}_D$ +10.0 (*c* 0.51, $CHCl_3$); IR (neat) ν 3447, 2932, 2857, 1427, 1111, 702 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.72−7.65 (m, 4H), 7.47−7.35 (m, 6H), 5.96−5.79 (m, 1H), 5.31−5.19 (m, 2H), 4.54 (ddd, 1H, J = 9.0, 5.3, 1.8 Hz), 4.02−3.91 (m, 1H), 3.79 (dd, 1H, J = 9.2, 1.7 Hz), 3.66 (t, 2H, J = 6.5 Hz), 2.82−2.70 (m, 1H), 2.38−2.24 (m, 1H), 2.13 (d, 1H, J = 4.9 Hz), 2.05−1.90 (m, 1H), 1.85−1.70 (m, 1H), 1.64−1.48 (m, 3H), 1.44−1.24 (m, 7H), 1.06 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.5, 134.1, 133.3, 129.5, 127.5, 119.7, 71.2, 66.5, 63.9, 61.9, 38.4, 36.3, 32.5, 29.1, 29.0, 26.8, 26.4, 25.6, 19.2; MS m/z 543 (MNa^+), 135 (100); HRMS (FAB) calcd for $C_{29}H_{42}O_2{}^{35}Cl_2SiNa$ (MNa^+) 543.2229, found 543.2221. ***syn*-7**: colorless oil; $[\alpha]^{24}_D$ +13.8 (*c* 1.02, $CHCl_3$); IR (neat) ν 3447, 2932, 2857, 1427, 1111, 702 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70−7.65 (m, 4H), 7.46−7.34 (m, 6H), 5.94−5.77 (m, 1H), 5.24−5.13 (m, 2H), 4.14 (ddd, 1H, J = 8.1, 5.4, 3.3 Hz), 4.09−4.00 (m, 2H), 3.65 (t, 2H, J = 6.5 Hz), 2.55−2.42 (m, 1H), 2.42−2.28 (m, 1H), 2.22 (d, 1H, J = 2.9 Hz), 1.97−1.77 (m, 2H), 1.61−1.47 (m, 4H), 1.40−1.24 (m, 6H), 1.05 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.5, 134.1, 133.1, 129.5,

127.5, 118.7, 71.3, 69.9, 63.9, 63.1, 38.4, 35.5, 32.5, 29.1, 28.9, 26.8, 26.3, 25.6, 19.2; MS *m*/*z* 543 (MNa^+), 135 (100); HRMS (FAB) calcd for $C_{29}H_{42}O_2{}^{35}Cl_2SiNa$ (MNa^+) 543.2229, found 543.2229.

***tert*-Butyl[[(8*R*)-8-chloro-8-[(2*S*,3*R*)-3-(prop-2-en-1-yl)oxiran-2-yl]octyl]oxy]diphenylsilane (12).** To a solution of alcohol **7** (3.04 g, 5.84 mmol) in THF (58 mL) at 0 °C was added NaH (60% in oil, 467 mg, 11.7 mmol). The mixture was stirred at room temperature for 12.3 h. The mixture was poured into a separatory funnel where it was partitioned between satd NH_4Cl and Et_2O. The organic phase was separated, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by silica gel column chromatography (Et_2O/*n*-hexane 1:30) to give epoxide **12** (2.74 g, 97%) as a colorless oil. **Epoxide 12**: colorless oil; $[\alpha]^{22}{}_D$ +5.4 (*c* 0.55, $CHCl_3$); IR (neat) ν 2932, 2857, 1427, 1111, 702 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.71−7.61 (m, 4H), 7.45−7.33 (m, 6H), 5.82 (ddt, 1H, *J* = 17.2, 10.3, 6.6 Hz), 5.20 (dd, 1H, *J* = 17.2, 1.6 Hz), 5.13 (dd, 1H, *J* = 10.3, 1.4 Hz), 3.65 (t, 2H, *J* = 6.3 Hz), 3.46 (ddd, 1H, *J* = 8.4, 8.0, 4.5 Hz), 2.96 (dt, 1H, *J* = 5.4, 1.8 Hz), 2.88 (dd, 1H, *J* = 8.0, 1.8 Hz), 2.44−2.27 (m, 2H), 2.01−1.86 (m, 1H), 1.85−1.70 (m, 1H), 1.61−1.23 (m, 10H), 1.05 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.6, 134.1, 132.5, 129.5, 127.6, 117.9, 63.9, 62.0, 60.3, 57.7, 35.9, 35.5, 32.5, 29.1, 29.0, 26.9, 25.8, 25.6, 19.2; MS *m*/*z* 507 (MNa^+), 135 (100); HRMS (FAB) calcd for $C_{29}H_{41}O_2{}^{35}ClSiNa$ (MNa^+) 507.2462, found 507.2480.

***tert*-Butyldiphenyl[[(8*R*,9*S*,10*S*)-8,9,10-trichlorotridec-12-enyl]-oxy]silane (6).** To a stirred solution of epoxide **12** (1.05 g, 2.17 mmol) in dichloroethane (22 mL) at room temperature were added Ph_3P (1.36 g, 5.20 mmol) and NCS (694 mg, 5.20 mmol), and the mixture was heated at 90 °C for 1 h. The mixture was treated with satd $NaHCO_3$, poured into a separatory funnel, and extracted with CH_2Cl_2. The organic phase was separated, dried over $MgSO_4$, filtered, and concentrated. The residue was filtered through a pad of silica gel (CH_2Cl_2/*n*-hexane 1:4), which allowed the removal of triphenylphosphine oxide to give a material (1.17 g) comprising trichloride **6** and unidentified olefin as a colorless oil. Further purification of the mixture using flash silica gel column chromatography (CH_2Cl_2/*n*-hexane 1:40) furnished trichloride **6** (825 mg, 70%) as a colorless oil. **Trichloride 6**: colorless oil; $[\alpha]^{26}{}_D$ +9.6 (*c* 1.05, $CHCl_3$); IR (neat) ν 2930, 2857, 1427, 1111, 702 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.72−7.62 (m, 4H), 7.48−7.33 (m, 6H), 5.84 (ddt, 1H, *J* = 17.1, 10.0, 7.2 Hz), 5.29−5.17 (m, 2H), 4.30−4.10 (m, 3H), 3.65 (t, 2H, *J* = 6.5 Hz), 2.82−2.57 (m, 2H), 1.97−1.71 (m, 2H), 1.71−1.20 (m, 10H), 1.05 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.5, 134.1, 132.4, 129.5, 127.5, 119.5, 68.1, 63.8, 63.5, 62.0, 39.8, 35.2, 32.4, 29.0, 28.8, 26.8, 26.1, 25.6, 19.2; MS *m*/*z* 541 (MH^+), 154 (100%); HRMS (FAB) calcd for $C_{29}H_{42}O^{35}Cl_2{}^{37}ClSi$ (MH^+) 541.2041, found 541.2055.

Determination of Stereochemistry of Trichloride 6. To a stirred solution of trichloride **6** (6 mg, 11 μmol) in CH_2Cl_2 (1 mL) at room temperature were added olefin **15** (0.02 mL, 57 μmol) and second-generation Grubbs catalyst (1.5 mg, 1.8 μmol). After being heated at reflux for 2 h, the mixture was concentrated under reduced pressure. The residue was purified by flash silica gel column chromatography (CH_2Cl_2/*n*-hexane 1:10) to give unreacted trichloride **6** (2.5 mg, 42%) as a colorless oil, and further elution with CH_2Cl_2/*n*-hexane (1:3 v/v) afforded alkenyl trichloride (5.5 mg, 58%) as a colorless oil. The alkenyl trichloride (5.5 mg, 6.5 μmol) was dissolved in *n*-hexane (1 mL), and Pt_2O (1.5 mg) was added to the solution. The mixture was stirred at room temperature under hydrogen atmosphere for 10 min and filtered through a pad of Celite to give *meso*-trichloride **16** (5 mg, 91%) as a colorless oil.

(12*R*,13*R*,14*S*)-12,13,14-Trichloro-2,2,24,24-tetramethyl-3,3,23,23-tetraphenyl-4,22-dioxa-3,23-disilapentacosan (16): colorless oil; $[\alpha]^{24}{}_D$ ~0 (*c* 0.23, $CHCl_3$); IR (neat) ν 2930, 2857, 1427, 1111, 702 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.71−7.62 (m, 8H), 7.47−7.33 (m, 12H), 4.22−4.13 (m, 2H), 4.10 (dd, 1H, *J* = 4.8 Hz), 3.65 (t, 4H, *J* = 6.6 Hz), 1.98−1.74 (m, 4H), 1.63−1.49 (m, 4H), 1.39−1.22 (m, 16H), 1.04 (s, 18H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.6, 134.1, 129.5, 127.6, 69.1, 63.9, 63.7, 35.3, 32.5, 29.1, 28.9, 26.9, 26.3, 25.6, 19.2; MS *m*/*z* 853 (MH^+), 154 (100); HRMS (FAB) calcd for $C_{49}H_{70}O_2{}^{35}Cl_3Si_2$ (MH^+) 853.3980, found 853.3972.

(3*R*,4*S*,5*S*,6*R*)-13-[(*tert*-Butyldiphenylsilyl)oxy]-4,5,6-trichlorotridec-1-en-3-ol (13a) and (3*S*,4*S*,5*S*,6*R*)-13-[(*tert*-Butyldiphenylsilyl)oxy]-4,5,6-trichlorotridec-1-en-3-ol (13b). To a stirred solution of trichloride **6** (459 mg, 0.85 mmol) in dichloroethane (14 mL) at room temperature were added SeO_2 (379 mg, 3.42 mmol), TBHP (5.5 M TBHP in decane, 0.9 mL, 4.95 mmol), and salicylic acid (46 mg, 0.33 mmol). The mixture was heated at 80 °C for 4 h and then cooled to room temperature. The mitxture was poured into a separatory funnel, washed with satd $NaHCO_3$ and satd $Na_2S_2O_3$, and extracted with Et_2O. The organic phase was separated, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by silica gel column chromatography (CH_2Cl_2/*n*-hexane 2:3) to give unreacted trichloride **6** (133 mg, 29%) as a colorless oil and *syn*-alcohol **13a** (89 mg, 19%). Further elusion with CH_2Cl_2/*n*-hexane (1:1 v/v) afforded *anti*-alcohol **13b** (143 mg, 30%) as a colorless oil. ***syn*-Alcohol 13a**: colorless oil; $[\alpha]^{22}{}_D$ +15.3 (*c* 0.49, $CHCl_3$); IR (neat) ν 3414, 2930, 2857, 1427, 1111, 702 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.70−7.64 (m, 4H), 7.46−7.34 (m, 6H), 5.91 (ddd, 1H, *J* = 17.3, 10.6, 5.5 Hz), 5.43 (d, 1H, *J* = 17.3 Hz), 5.35 (d, 1H, *J* = 10.6 Hz), 4.62−4.49 (m, 1H), 4.34−4.19 (m, 3H), 3.65 (t, 2H, *J* = 6.4 Hz), 2.15 (d, 1H, *J* = 7.9 Hz), 1.96−1.83 (m, 2H), 1.62−1.45 (m, 4H), 1.39−1.22 (m, 6H), 1.05 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.3, 135.5, 134.1, 129.5, 127.5, 118.3, 72.3, 69.1, 67.1, 63.8, 62.8, 35.9, 32.4, 29.0, 28.8, 26.8, 26.1, 25.6, 19.2; MS *m*/*z* 579 (MNa^+), 135 (100); HRMS (FAB) calcd for $C_{29}H_{41}O_2{}^{35}Cl_2{}^{37}ClSiNa$ (MNa^+) 579.1810, found 579.1799. ***anti*-Alcohol 13b**: colorless oil; $[\alpha]^{22}{}_D$ +4.0 (*c* 0.79, $CHCl_3$); IR (neat) ν 3410, 2930, 2857, 1427, 1111, 702 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.71−7.63 (m, 4H), 7.45−7.34 (m, 6H), 6.01 (ddd, 1H, *J* = 17.2, 10.3, 6.4 Hz), 5.45 (d, 1H, *J* = 17.2 Hz), 5.35 (d, 1H, *J* = 10.3 Hz), 4.53 (dd, 1H, *J* = 6.6, 3.7 Hz), 4.48−4.36 (m, 1H), 4.20−4.07 (m, 2H), 3.65 (t, 2H, *J* = 6.4 Hz), 2.25 (brs, 1H), 2.01−1.86 (m, 1H), 1.84−1.68 (m, 1H), 1.60−1.21 (m, 10H), 1.05 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.9, 135.5, 134.1, 129.5, 127.5, 119.2, 73.4, 65.5, 64.6, 64.2, 63.8, 34.3, 32.4, 29.0, 28.8, 26.8, 26.1, 25.6, 19.2; MS *m*/*z* 579 (MNa^+), 135 (100); HRMS (FAB) calcd for $C_{29}H_{41}O_2{}^{35}Cl_2{}^{37}ClSiNa$ (MNa^+) 579.1810, found 579.1823. The stereochemistry of *syn*-alcohol **13a** and *anti*-alcohol **13b** was determined by their transformation into the corresponding epoxides (see the Supporting Information).

(4*R*,5*S*,6*S*,7*R*,*E*)-14-[(*tert*-Butyldiphenylsilyl)oxy]-5,6,7-trichlorotetradec-2-en-4-ol (5). A round-bottomed flask equipped with rubber balloon filled with 2-butene was charged with *syn*-alcohol **13a** (268 mg, 0.48 mmol), CH_2Cl_2 (10 mL), and second-generation Grubbs catalyst (12 mg, 0.015 mmol) at room temperature. The mixture was stirred at the same temperature for 1 h and concentrated under reduced pressure. The residue was purified by flash silica gel column chromatography (Et_2O/*n*-hexane 1:10) to give less polar (*E*)-olefin **5** (241 mg, 88%) as a colorless oil and the more polar (*Z*)-isomer of **5** (14 mg, 5%) as a colorless oil. (***E*)-5**: colorless oil; $[\alpha]^{21}{}_D$ +8.6 (*c* 1.01, $CHCl_3$); IR (neat) ν 3447, 2932, 2857, 1427, 1111, 702 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.69−7.64 (m, 4H), 7.46−7.34 (m, 6H), 5.88 (ddq, 1H, *J* = 15.4, 6.6, 0.7 Hz), 5.55 (ddq, 1H, *J* = 15.4, 6.6, 1.3 Hz), 4.52−4.42 (m, 1H), 4.31−4.22 (m, 2H), 4.16 (dd, 1H, *J* = 6.2, 4.4 Hz), 3.65 (t, 2H, *J* = 6.2 Hz), 2.08 (d, 1H, *J* = 5.9 Hz), 1.94−1.83 (m, 2H), 1.76 (dd, 3H, *J* = 6.6, 1.3 Hz), 1.61−1.23 (m, 11H), 1.05 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.5, 134.1, 130.9, 129.5, 129.0, 127.5, 72.6, 69.4, 67.1, 63.8, 63.1, 35.6, 32.4, 29.0, 28.8, 26.8, 26.1, 25.6, 19.2, 17.8; MS *m*/*z*: 571 (MH^+), 135 (100); HRMS (FAB) calcd for $C_{30}H_{44}O_2{}^{35}Cl_2{}^{37}ClSi$ (MH^+) 571.2147, found 571.2146.

(*Z*)-**Isomer of 5**: colorless oil; $[\alpha]^{20}_{D}$ +2.0 (*c* 0.30, $CHCl_3$); IR (neat) ν 3412, 2930, 2857, 1427, 1111, 702 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.69−7.64 (m, 4H), 7.45−7.34 (m, 6H), 5.78 (dq, 1H, J = 10.8, 7.0 Hz), 5.48 (ddq, 1H, J = 10.8, 8.2, 1.7 Hz), 4.86 (dd, 1H, J = 8.2, 4.4 Hz), 4.34−4.24 (m, 2H), 4.17 (dd, 1H, J = 5.9, 4.2 Hz), 3.65 (t, 2H, J = 6.4 Hz), 1.96−1.84 (m, 2H), 1.77 (dd, 3H, J = 7.0, 1.7 Hz), 1.61−1.25 (m, 11H), 1.05 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.6, 134.1, 130.4, 129.5, 128.4, 127.6, 69.5, 67.5, 67.0, 63.9, 63.3, 35.7, 32.5, 29.1, 28.9, 26.9, 26.2, 25.6, 19.2, 13.8; MS *m*/*z* 571 (MH^+), 154 (100); HRMS (FAB) calcd for $C_{30}H_{44}O_2{}^{35}Cl_2{}^{37}ClSi$ (MH^+) 571.2147, found 571.2152.

(4*R*,5*S*,6*S*,7*R*,*E*)-14-[(*tert*-Butyldiphenylsilyl)oxy]-5,6,7-trichlorotetradec-2-en-4-yl 2,2,2-Trichloroacetate (14). To a stirred solution of alcohol **5** (8 mg, 0.014 mmol) in THF (1 mL) were added pyridine (20 μL, 0.25 mmol) and trichloroacetyl chloride (10 μL, 0.09 mmol) at 0 °C. After being stirred for 15 min, the mixture was poured into a separatory funnel where it was partitioned between satd $NaHCO_3$ and Et_2O. The organic phase was separated, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by silica gel column chromatography (EtOAc/*n*-hexane 1:20) to give trichloroacetate **14** (10 mg, quant) as a colorless oil. **Trichloroacetate 14**: colorless oil; $[\alpha]^{19}_{D}$ +7.8 (*c* 1.58, $CHCl_3$); IR (neat) ν 2931, 2857, 1771, 1427, 1231, 1111, 824, 702, 683 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.70−7.63 (m, 4H), 7.45−7.34 (m, 6H), 6.17 (dq, 1H, J = 15.0, 6.6 Hz), 5.62 (dd, 1H, J = 8.1, 6.7 Hz), 5.51 (ddq, 1H, J = 15.0, 8.2, 1.6 Hz), 4.37 (dd, 1H, J = 6.6, 4.0 Hz), 4.19 (dd, 1H, J = 5.9, 4.1 Hz), 4.18−4.06 (m, 1H), 3.65 (t, 2H, J = 6.4 Hz), 2.01−1.87 (m, 1H), 1.81 (dd, 3H, J = 6.7, 1.5 Hz), 1.81−1.70 (m, 1H), 1.64−1.46 (m, 2H), 1.41−1.23 (m, 8H), 1.05 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.5, 137.1, 135.6, 134.1, 129.5, 127.6, 122.5, 89.7, 80.8, 65.4, 63.92, 63.86, 62.8, 34.5, 32.4, 29.0, 28.8, 26.9, 26.3, 25.6, 19.2, 18.1; MS *m*/*z* 715 (MH^+), 154 (100); HRMS (FAB) calcd for $C_{32}H_{43}O_3{}^{35}Cl_5{}^{37}ClSi$ (MH^+) 715.1083, found 715.1068.

(2*S*,3*R*,4*R*,5*S*,6*S*,7*R*)-14-[(*tert*-Butyldiphenylsilyl)oxy]-2,3,5,6,7-pentachlorotetradecan-4-yl 2,2,2-Trichloroacetate (18) and (4*R*,5*S*,6*S*,7*R*)-14-[(*tert*-Butyldiphenylsilyl)oxy]-3,5,6,7-tetrachlorotetradec-1-en-4-yl 2,2,2-Trichloroacetate (19). To a stirred suspension of $KMnO_4$ (4 mg, 0.025 mmol) in CH_2Cl_2 (0.8 mL) was added $BnEt_3NCl$ (6 mg, 0.026 mmol) at room temperature. After being stirred for 30 min, the mixture was allowed to cool to 0 °C, and TMSCl (20 μL, 0.16 mmol) was added. After 5 min, the mixture was allowed to cool to −78 °C, and a solution of trichloroacetate **14** (15 mg, 0.021 mmol) in CH_2Cl_2 (1.2 mL) was added. The mixture was stirred for further 2.8 h at −78 °C and for 1.5 h during which time the mixture was allowed to gradually warm to −10 °C. Then the mixture was stirred at the same temperature for an additional 1 h and treated with satd $NaHCO_3$ and satd $Na_2S_2O_3$. The whole mixture was poured into a separatory funnel where it was partitioned between Et_2O and H_2O. The organic phase was separated, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by flash silica gel column chromatography (CH_2Cl_2/*n*-hexane 1:5) to give an inseparable mixture of less polar pentachloride **17** and olefin **19** (4.5 mg) as a colorless oil, and more polar pentachloride **18** (7.5 mg, 45%) as a colorless oil. Separation of compound **17** from compound **19** was quite difficult; therefore, the structure of compound **17** has been elucidated after removal of the trichloroacetyl group (for details, see the Supporting Information). The data of compound **19** given below are those obtained for the material that could be partially separated. **Pentachloride 18**: colorless oil; $[\alpha]^{22}_{D}$ −1.0 (*c* 0.73, MeOH); IR (neat) ν 2932, 2857, 1786, 1427, 1220, 1111, 824, 702, 677 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.70−7.62 (m, 4H), 7.46−7.33 (m, 6H), 6.09 (dd, 1H, J = 7.7, 2.0 Hz), 4.60 (d, 1H, J = 7.5 Hz), 4.30−4.15 (m, 3H), 4.14−4.00 (m, 1H), 3.65 (t, 2H, J = 6.4 Hz), 2.01−1.84 (m, 1H), 1.83−1.66 (m, 1H), 1.74 (d, 3H, J = 6.2 Hz), 1.63−1.46 (m, 4H), 1.42−1.23 (m, 6H), 1.05 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.1, 135.6, 134.1, 129.5, 127.6, 77.7, 64.6, 64.4, 63.9, 63.7, 61.9, 54.8, 33.8, 32.4, 29.1, 28.7, 26.9, 25.7, 25.6, 22.8, 19.2; MS *m*/*z* 785 (MH^+), 135 (100); HRMS (FAB) calcd for $C_{32}H_{43}O_3{}^{35}Cl_7{}^{37}ClSi$ (MH^+) 785.0460, found 785.0445. **Olefin 19**: colorless oil; $[\alpha]^{23}_{D}$ +34.6 (*c* 0.23, $CHCl_3$); IR (neat) ν 2930, 2857, 1773, 1427, 1225, 1111, 824, 702, 679 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.68−7.63 (m, 4H), 7.44−7.35 (m, 6H), 5.86 (ddd, 1H J = 17.1, 9.8, 9.2 Hz), 5.48 (d, 1H, J = 17.1 Hz), 5.43 (dd, 1H, J = 8.5, 2.4 Hz), 5.37 (d, 1H, J = 9.8 Hz), 4.88 (dd, 1H, J = 7.9, 2.4 Hz), 4.71 (dd, 1H, J = 8.5, 9.2 Hz), 4.15 (dd, 1H, J = 7.9, 3.1 Hz), 4.04 (ddd, 1H, J = 7.9, 4.9, 3.1 Hz), 3.64 (t, 2H, J = 6.4 Hz), 1.96−1.78 (m, 2H), 1.58−1.50 (m, 2H), 1.38−1.21 (m, 8H), 1.04 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.9, 135.6, 134.1, 132.4, 129.5, 127.6, 122.4, 77.3, 66.2, 63.9, 62.5, 61.2, 59.6, 36.1, 32.4, 29.0, 28.7, 26.9, 26.1, 25.6, 19.2; MS *m*/*z* 749 (MH^+), 135 (100%); HRMS (FAB) calcd for $C_{32}H_{42}O_3{}^{35}Cl_6{}^{37}ClSi$ (MH^+) 749.0693, found 749.0668.

(2*R*,3*S*,4*R*,5*S*,6*S*,7*R*)-14-[(*tert*-Butyldiphenylsilyl)oxy]-2,3,5,6,7-pentachlorotetradecan-4-ol (20), (2*S*,3*R*,4*R*,5*S*,6*S*,7*R*)-14-[(*tert*-Butyldiphenylsilyl)oxy]-2,3,5,6,7-pentachlorotetradecan-4-ol (21), and (2*S*,3*S*,4*R*,5*S*,6*S*,7*R*)-14-[(*tert*-Butyldiphenylsilyl)oxy]-2,3,5,6,7-pentachlorotetradecan-4-ol (22). To a stirred suspension of $KMnO_4$ (17 mg, 0.108 mmol) in CH_2Cl_2 (1.4 mL) was added $BnEt_3NCl$ (25 mg, 0.108 mmol) at room temperature. After being stirred for 30 min, the mixture was allowed to cool to 0 °C, and TMSCl (60 μL, 0.47 mmol) was added. After 40 min, the mixture was allowed to cool to −78 °C, and a solution of alcohol **5** (51 mg, 0.090 mmol) in CH_2Cl_2 (2.6 mL) was added. The mixture was stirred for further 20 min at −78 °C and for an additional 2.5 h during which time the mixture was allowed to gradually warm to −10 °C. Then the mixture was stirred at −10 °C for an additional 30 min and treated with satd $NaHCO_3$ and satd $Na_2S_2O_3$. The whole mixture was poured into a separatory funnel, where it was partitioned between Et_2O and H_2O. The organic phase was separated, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by flash silica gel column chromatography (Et_2O/*n*-hexane 1:20) to give less polar pentachloride **21** (6 mg, 10%) as a colorless oil, pentachloride **20** (22 mg, 38%) as a colorless oil, and more polar pentachloride **22** (15 mg, 26%) as a pale yellow oil. **Pentachloride 20**: colorless oil; $[\alpha]^{24}_{D}$ +12.5 (*c* 0.23, $CHCl_3$); IR (neat) ν 3524, 2930, 2857, 1427, 1111, 702 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.69−7.64 (m, 4H), 7.46−7.34 (m, 6H), 4.85 (d, 1H, J = 8.4 Hz), 4.66 (dq, 1H, J = 6.5, 2.6 Hz), 4.31 (dd, 1H, J = 9.5, 2.6 Hz), 4.26 (dd, 1H, J = 8.4, 2.2 Hz), 4.18 (ddd, 1H, J = 7.9, 5.7, 2.2 Hz), 4.01 (d, 1H, J = 9.5 Hz), 3.65 (t, 2H, J = 6.4 Hz), 2.28 (brs, 1H), 2.03−1.80 (m, 2H), 1.60 (d, 3H, J = 6.5 Hz), 1.63−1.50 (m, 2H), 1.41−1.24 (m, 8H), 1.04 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.5, 134.1, 129.5, 127.5, 71.9, 67.7, 67.5, 66.5, 63.8, 61.2, 56.1, 36.4, 32.4, 29.0, 28.9, 26.8, 26.2, 25.5, 19.2, 19.0; MS *m*/*z* 641 (MH^+), 135 (100); HRMS (FAB) calcd for $C_{30}H_{44}O_2{}^{35}Cl_4{}^{37}ClSi$ (MH^+) 641.1524, found 641.1528. **Pentachloride 21**: colorless oil; $[\alpha]^{23}_{D}$ +6.4 (*c* 0.35, $CHCl_3$); IR (neat) ν 3441, 2930, 2857, 1427, 1231, 1111, 702 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.70−7.63 (m, 4H), 7.46−7.34 (m, 6H), 4.52 (dd, 1H, J = 6.4, 3.3 Hz), 4.42−4.29 (m, 2H), 4.27−4.18 (m, 2H), 4.11 (dd, 1H, J = 8.1, 3.3 Hz), 3.65 (t, 2H, J = 6.4 Hz), 1.99−1.85 (m, 1H), 1.84−1.72 (m, 1H), 1.69 (d, 3H, J = 6.6 Hz), 1.63−1.44 (m, 2H), 1.40−1.23 (m, 8H), 1.05 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.6, 134.1, 129.5, 127.6, 72.4, 66.8, 65.8, 65.3, 64.4, 63.9, 55.6, 34.4, 32.4, 29.1, 28.8, 26.9, 25.65, 25.60, 22.0, 19.2; MS *m*/*z* 641 (MH^+), 135 (100); HRMS (FAB) calcd for $C_{30}H_{44}O_3{}^{35}Cl_4{}^{37}ClSi$ (MH^+) 641.1524, found 641.1527. **Pentachloride 22**: pale yellow oil; $[\alpha]^{22}_{D}$ +9.9 (*c* 0.70, $CHCl_3$); IR (neat) ν 3524, 2932, 2857, 1427, 1111, 702 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.71−7.63 (m, 4H), 7.46−7.34 (m, 6H), 4.87 (dd, 1H, J = 9.6, 1.3 Hz), 4.71 (dq, 1H, J = 6.7, 1.7 Hz), 4.31 (dd, 1H, J = 8.6, 2.2 Hz), 4.30−4.18 (m, 2H), 4.07 (dd, 1H,

J = 9.5, 1.8 Hz), 3.65 (t, 2H, J = 6.4 Hz), 2.05−1.80 (m, 2H), 1.66 (d, 3H, J = 6.7 Hz), 1.61−1.44 (m, 2H), 1.42−1.22 (m, 8H), 1.05 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.5, 134.1, 129.5, 127.6, 71.9, 67.6, 67.4, 65.6, 63.8, 61.2, 55.9, 36.5, 32.4, 29.0, 28.9, 26.9, 26.2, 25.6, 22.7, 19.2; MS m/z 641 (MH^+), 135 (100); HRMS (FAB) calcd for $C_{30}H_{44}O_2{}^{35}Cl_4{}^{37}ClSi$ (MH^+) 641.1524, found 641.1519. The stereochemistry of pentachlorides **18** and **20**−**22** was determined by their chemical correlations. For details, see the Supporting Information.

(2*R*,3*S*,4*R*,5*S*,6*S*,7*R*)-14-[(*tert*-Butyldiphenylsilyl)oxy]-2,3,5,6,7-pentachlorotetradecan-4-yl Acetate (23). To a stirred solution of pentachloride **20** (54 mg, 0.085 mmol) in CH_2Cl_2 (1.6 mL) were added Et_3N (0.03 mL, 0.22 mmol), Ac_2O (0.015 mL, 0.16 mmol), and DMAP (1 mg, 0.008 mmol). After 10 min, the mixture was poured into a separatory funnel where it was partitioned between H_2O and EtOAc. The organic phase was separated, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by silica gel column chromatography (EtOAc/*n*-hexane 1:6) to give acetate **23** (57.5 mg, quant) as a pale yellow oil. **Acetate 23**: pale yellow oil; $[\alpha]^{24}{}_D$ +33.5 (*c* 0.18, $CHCl_3$); IR (neat) ν 2932, 2859, 1751, 1427, 1213, 1111, 702 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.69−7.64 (m, 4H), 7.46−7.34 (m, 6H), 5.29 (dd, 1H, J = 9.6, 1.5 Hz), 4.96 (dd, 1H, J = 7.6, 1.5 Hz), 4.54 (dd, 1H, J = 9.6, 2.7 Hz), 4.28 (ddd, 1H, J = 8.0, 5.7, 2.7 Hz), 4.23 (dq, 1H, J = 6.6, 2.7 Hz), 4.07 (dd, 1H, J = 7.6, 2.7 Hz), 3.65 (t, 2H, J = 6.6 Hz), 2.17 (s, 3H), 1.94−1.82 (m, 2H), 1.68−1.51 (m, 2H), 1.56 (d, 3H, J = 6.6 Hz), 1.42−1.22 (m, 8H), 1.05 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.8, 135.5, 134.1, 129.5, 127.5, 72.1, 66.2, 64.8, 63.8, 63.0, 61.7, 55.3, 35.8, 32.4, 29.0, 28.8, 26.8, 26.2, 25.6, 20.7, 19.3, 19.2; MS m/z 705 (MNa^+), 135 (100); HRMS (FAB) calcd for $C_{32}H_{45}O_3{}^{35}Cl_4{}^{37}ClSiNa$ (MNa^+) 705.1449, found 705.1451.

(2*R*,3*S*,4*R*,5*S*,6*S*,7*R*)-2,3,5,6,7-Pentachloro-14-hydroxytetradecan-4-yl Acetate (24). To a solution of pentachloride **23** (46 mg, 0.068 mmol) in THF (1.0 mL) at room temperature were added pyridine (0.16 mL, 1.98 mmol) and 48% aq HF (0.05 mL, 1.38 mmol). After 25 h, the mixture was poured into a separatory funnel where it was partitioned between satd $NaHCO_3$ and Et_2O. The organic phase was separated, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by silica gel column chromatography (EtOAc/*n*-hexane 1:2) to give alcohol **24** (28 mg, 94%) as a pale yellow oil. **Alcohol 24**: pale yellow oil; $[\alpha]^{23}{}_D$ +57.8 (*c* 0.38, $CHCl_3$); IR (neat) ν 3368, 2932, 2859, 1749, 1373, 1213, 1055, 1022 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.29 (dd, 1H, J = 9.5, 1.5 Hz), 4.96 (dd, 1H, J = 7.6, 1.5 Hz), 4.54 (dd, 1H, J = 9.5, 2.6 Hz), 4.30 (ddd, 1H, J = 8.1, 5.5, 2.8 Hz), 4.24 (dq, 1H, J = 6.6, 2.6 Hz), 4.08 (dd, 1H, J = 7.6, 2.8 Hz), 3.65 (t, 2H, J = 6.6 Hz), 2.19 (s, 3H), 1.97−1.82 (m, 2H), 1.64−1.51 (m, 2H), 1.56 (d, 3H, J = 6.6 Hz), 1.48−1.31 (m, 8H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.9, 72.1, 66.2, 64.8, 63.0, 62.9, 61.7, 55.3, 35.7, 32.6, 29.0, 28.7, 26.2, 25.5, 20.8, 19.3; MS m/z 445 (MH^+), 154 (100); HRMS (FAB) calcd for $C_{16}H_{28}O_3{}^{35}Cl_4{}^{37}Cl$ (MH^+) 445.0452, found 445.0456.

(2*R*,3*S*,4*R*,5*S*,6*S*,7*R*)-2,3,5,6,7-Pentachloro-14-oxotetradecan-4-yl Acetate (25). To a stirred solution of alcohol **24** (25 mg, 0.057 mmol) in CH_2Cl_2 (1 mL) were added $NaHCO_3$ (10 mg, 0.12 mmol) and Dess−Martin periodinane (36 mg, 0.085 mmol) at room temperature. The mixture was stirred for 30 min and then treated with satd $NaHCO_3$ and satd $Na_2S_2O_3$. The mixture was poured into a separatory funnel where it was partitioned between satd $NaHCO_3$ and EtOAc. The organic phase was separated, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by silica gel column chromatography (EtOAc/*n*-hexane 1:3) to give aldehyde **25** (25 mg, 98%) as a pale yellow oil. **Aldehyde 25**: pale yellow oil; $[\alpha]^{23}{}_D$ +46.2 (*c* 0.35, $CHCl_3$); IR (neat) ν 2934, 1751, 1722, 1211 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.77 (t, 1H, J = 1.7 Hz), 5.28 (dd, 1H, J = 9.6, 1.5 Hz), 4.96 (dd, 1H, J = 7.5, 1.5 Hz), 4.54 (dd, 1H, J = 9.6, 2.6 Hz), 4.30 (ddd, 1H, J = 8.2, 5.4, 2.8 Hz), 4.24 (dq, 1H, J = 6.6, 2.6 Hz), 4.07 (dd, 1H, J = 7.5, 2.8 Hz), 2.45 (dt, 2H, J = 7.3, 1.6 Hz), 2.20 (s, 3H), 1.97−1.77 (m, 2H), 1.73−1.56 (m, 2H), 1.55 (d, 3H, J = 6.6 Hz), 1.46−1.17 (m, 8H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 202.6, 169.9, 72.1, 66.2, 64.8, 63.0, 61.7, 55.3, 43.8, 35.7, 28.8, 28.5, 26.1, 21.8, 20.8, 19.3; MS m/z 443 (MH^+), 154 (100); HRMS (FAB) calcd for $C_{16}H_{26}O_3{}^{35}Cl_4{}^{37}Cl$ (MH^+) 443.0295, found 443.0294.

(2*R*,3*S*,4*R*,5*S*,6*S*,7*R*,*E*)-2,3,5,6,7,15-Hexachloropentadec-14-en-4-yl Acetate (26). To a stirred suspension of $CrCl_2$ (35 mg, 0.27 mmol) in THF (0.8 mL) at room temperature was added a premixed solution of aldehyde **25** (20 mg, 0.046 mmol) and $CHCl_3$ (0.01 mL, 0.13 mmol) in THF (1.7 mL). The mixture was heated at 65 °C for 1.7 h and poured into a separatory funnel where it was partitioned between H_2O and Et_2O. The organic phase was separated, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by silica gel column chromatography (Et_2O/*n*-hexane 1:20) to give olefin **26** (16 mg, 75%) as a colorless oil. **Olefin 26**: colorless oil; $[\alpha]^{24}{}_D$ +48.1 (*c* 0.24, $CHCl_3$); IR (neat) ν 2930, 1749, 1211 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.95 (d, 1H, J = 13.4 Hz), 5.88 (dt, 1H, J = 13.4, 6.6 Hz), 5.29 (dd, 1H, J = 9.7, 1.5 Hz), 4.96 (dd, 1H, J = 7.6, 1.5 Hz), 4.55 (dd, 1H, 9.7, 2.7 Hz), 4.30 (ddd, 1H, J = 8.2, 5.5, 2.7 Hz), 4.24 (dq, 1H, J = 6.6, 2.7 Hz), 4.07 (dd, 1H, J = 7.6, 2.7 Hz), 2.19 (s, 3H), 2.05 (dt, 2H, J = 6.8, 6.6 Hz), 1.94−1.79 (m, 2H), 1.55 (d, 3H, J = 6.6 Hz), 1.45−1.23 (m, 8H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.9, 133.8, 116.8, 72.1, 66.2, 64.8, 63.0, 61.7, 55.3, 35.7, 30.8, 28.7, 28.6, 28.5, 26.2, 20.8, 19.3; MS m/z 475 (MH^+), 154 (100); HRMS (FAB) calcd for $C_{17}H_{27}O_2{}^{35}Cl_5{}^{37}Cl$ (MH^+) 475.0113, found 475.0096.

(2*R*,3*S*,4*R*,5*S*,6*S*,7*R*,*E*)-2,3,5,6,7,15-Hexachloropentadec-14-en-4-ol (27). To a solution of acetate **26** (25 mg, 0.053 mmol) in CH_2Cl_2 (1 mL) at −78 °C was added DIBAL (0.98 M in *n*-hexane, 0.14 mL, 0.14 mmol). After 10 min, satd NH_4Cl was added, and the mixture was allowed to warm to room temperature. After 20 min, Celite was added, and the whole mixture was stirred for an additional 50 min. After filtration of the mixture through a Celite pad followed by concentration of the filtrate under reduced pressure, the residue was purified by flash silica gel column chromatography (EtOAc/hexane 1:10) to give alcohol **27** (22 mg, 96%) as a colorless oil. **Alcohol 27**: colorless oil; $[\alpha]^{25}{}_D$ +27.4 (*c* 0.42, $CHCl_3$); IR (neat) ν 3526, 2930, 2857, 1265, 1092 cm^{-1}; ^{1}H NMR (500 MHz, CD_3OD) δ 6.04 (dd, 1H, J = 13.4, 1.2 Hz), 5.89 (dt, 1H, J = 13.4, 7.3 Hz), 4.71 (dq, 1H, J = 6.7, 2.4 Hz), 4.60 (dd, 1H, J = 9.2, 1.8 Hz), 4.42−4.34 (m, 3H), 3.99 (dd, 1H, J = 9.8, 1.2 Hz), 2.07 (dt, 2H, J = 7.3, 1.2 Hz), 2.01−1.85 (m, 2H), 1.54 (d, 3H, J = 6.7 Hz), 1.46−1.26 (m, 8H); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.94 (d, 1H, J = 13.2 Hz), 5.88 (dt, 1H, J = 13.2, 6.4 Hz), 4.85 (dd, 1H, J = 8.4, 1.1 Hz), 4.67 (dq, 1H, J = 6.6, 2.6 Hz), 4.32 (dd, 1H, J = 9.6, 2.6 Hz), 4.27 (dd, 1H, J = 8.4, 2.4 Hz), 4.19 (ddd, 1H, J = 8.1, 5.6, 2.4 Hz), 4.07−3.96 (m, 1H), 2.34 (d, 1H, J = 11.2 Hz), 2.09−1.82 (m, 4H), 1.61 (d, 3H, J = 6.6 Hz), 1.57−1.22 (m, 8H); ^{13}C NMR (125 MHz, CD_3OD) δ 135.12, 118.00, 71.99, 69.39, 69.12, 68.59, 62.56, 57.39, 38.08, 31.67, 29.89, 29.81, 29.78, 27.27, 18.88; ^{13}C NMR (75 MHz, $CDCl_3$) δ 133.81, 116.84, 71.94, 67.67, 67.50, 66.44, 61.19, 56.11, 36.41, 30.76, 28.69, 28.654, 28.646, 26.20, 19.07; MS m/z 455 (MNa^+), 176 (100); HRMS (FAB) calcd for $C_{15}H_{24}O^{35}Cl_5{}^{37}ClNa$ (MNa^+) 454.9826, found 454.9840.

(2*R*,3*S*,4*R*,5*S*,6*S*,7*R*,*E*)-2,3,5,6,7,15-Hexachloropentadec-14-en-4-ylhydrogen Sulfate (1). To a solution of alcohol **27** (9 mg, 0.021 mmol) in DMF (1 mL) at room temperature was added SO_3·Py (50% active SO_3, 67 mg, 0.21 mmol). After 1 h, MeOH was added, and the mixture was concentrated under reduced pressure. The residue was poured into a separatory funnel where it was partitioned between H_2O and Et_2O. The organic phase was separated, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by silica gel column chromatography (AcOH/EtOAc 1:30) to give alcohol **27** (2 mg, 22%) as a colorless

oil and hexachlorosulfolipid **1** (8 mg, 75%) as a pale yellow oil. TLC analysis clearly indicated that sulfation of alcohol **27** took place quantitatively to afford sulfolipid **1**, which was, however, somewhat unstable toward hydrolysis to again produce alcohol **27** during the workup. **Hexachlorosulfolipid** (+)**-1**: pale yellow oil; $[\alpha]^{24}_{D}$ +49.0 (*c* 0.59, MeOH) (lit. $[\alpha]^{25}_{D}$ +20.4 (*c* 0.0015, MeOH); IR (neat) ν 3472, 2928, 2857, 1269, 1040, 937 cm^{-1}; ^1H NMR (500 MHz, acetone-d_6) δ 6.13 (d, 1H, J = 13.4 Hz), 5.94 (dt, 1H, J = 13.4, 7.3 Hz), 5.16 (ddd, 1H, J = 8.5, 4.3, 1.8 Hz), 5.09 (dq, 1H, J = 6.1, 1.8 Hz), 4.79 (dd, 1H, J = 9.8, 1.2 Hz), 4.73 (dd, 1H, J = 9.8, 1.8 Hz), 4.71 (dd, 1H, J = 9.8, 1.2 Hz), 4.43 (dd, 1H, J = 9.8, 1.8 Hz), 2.13−2.06 (m, 1H), 1.94−1.82 (m, 2H), 1.66−1.53 (m, 2H), 1.61 (d, 3H, J = 6.1 Hz), 1.45−1.27 (m, 7H); ^{13}C NMR (125 MHz, acetone-d_6) δ 135.11, 117.46, 75.62, 69.14, 68.92, 67.93, 63.19, 57.16, 37.80, 31.22, 29.44, 29.39, 29.24, 26.64, 19.25; MS (negative ion mode) m/z 511 ($M - H^+$), 153 (100); HRMS (FAB) calcd for $C_{15}H_{23}O_4{}^{35}Cl_5{}^{37}ClS$ ($M - H^+$) 510.9419, found 510.9421. The spectroscopic data of synthetic (+)-hexachlorosulfolipid **1** were in good agreement with those reported in the literature.[2a,5a] However, it was found that there was a significant change in the shape of the ^1H NMR spectra depending on the concentration of the material. The concentration dependence of the spectra was particularly found in the area of 4.6−4.7 ppm. (The spectra are provided in the Supporting Information.) At lower concentrations of sulfolipid, the spectra showed good agreement with those of natural product. For details, see the Supporting Information.

Computational Methods

The fully optimized geometries calculated by the PM3 method using the Spartan Pro program (Wavefunction, Inc., Irvine, CA, 2000) were used as starting geometries for DFT calculations. DFT calculations were carried out using the Gaussian 03 program. The geometries were fully optimized in vacuo by using the B3LYP method with the standard 6-31G(d) basis set. Frequency calculations were carried out at the B3LYP/6-31G(d) level of theory and performed on all of the species to confirm convergence to appropriate local minima on the energy surface. For details, see the Supporting Information.

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Supporting Information Available: Experimental details for the structural determination and copies of the $^1H/^{13}C$ NMR spectra of products. Cartesian coordinates, total energies, and zero-point vibrational energies of the energetically favorable conformers of model compounds of alcohol **5** and trichloroacetate **14**. This material is available free of charge via the Internet at http://pubs.acs.org.