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Enantiocontrolled Synthesis of Polychlorinated Hydrocarbon Motifs: A Nucleophilic Multiple Chlorination Process Revisited

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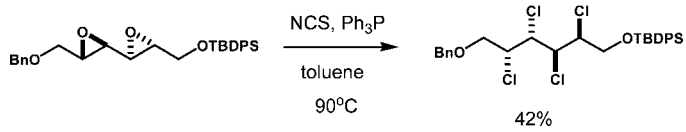

Polychlorinated hydrocarbon motifs have been synthesized in enantiomerically pure forms by means of nucleophilic multiple chlorinations of chiral epoxides, which stereospecifically incorporate halogen atoms into oxygenated molecular scaffolds. The present study demonstrates the scope of the *N*-chlorosuccinimide (NCS)/organophosphine reagent system that forms multiple sp^3C-Cl bonds in a regularly repeating pattern with proper stereochemical configurations and evaluates its applicability to various epoxides having elaborate structures. It is noteworthy that tetrachlorinated motifs are produced in one step from bisepoxides by using NCS/Ph_3P. Furthermore, Ph_2PCl used in combination with NCS has been found to serve as a potentially useful alternative to NCS/Ph_3P, especially for promoting dichlorination reactions of alkenyl-substituted epoxides.

Introduction

Naturally occurring polychlorinated hydrocarbons have recently been garnering considerable attention for their potential use as lead compounds for drug discovery as well as their unique toxicological profiles.[1,2] This class of bioactive molecules includes chlorosulfolipids, such as malhamensilipin A (**1**), a protein tyrosine kinase (PTK) inhibitor isolated in 1994 by Gerwick and Slate,[3] and cytotoxic polychlorosulfolipids **2** and **3** recently isolated from Adriatic mussels by Ciminiello, Fattorusso, and co-workers,[4] all of which possess chlorine-substituted multiple stereogenic centers as their structural feature (Figure 1).[5]

In addition to the difficulty of acquiring sufficient quantities of chiral polychlorides from natural resources, access to these compounds by chemical synthesis has been hampered because of the limited availability of methods capable of incorporating an array of chlorine atoms into hydrocarbon skeletons with correct absolute stereochemistries.[6,7] To address this problem, we initiated a research program aimed at establishing stereoselective approaches to polychlorinated hydrocarbons.[8,9]

(1) For pertinent reviews on natural halogenated compounds, see: (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. *Chemosphere* **2003**, *52*, 289–297. (d) Gribble, G. W. *Prog. Heterocycl. Chem.* **2003**, *15*, 58–74. (e) Gribble, G. W. *Acc. Chem. Res.* **1998**, *31*, 141–152. (f) Gribble, G. W. *J. Chem. Educ.* **1994**, *71*, 907–911. (g) Gribble, G. W. *J. Nat. Prod.* **1992**, *55*, 1353–1395.

(2) For synthetic studies on bioactive polyhalogenated natural compounds, see: (a) Jung, M. E.; Parker, M. H. *J. Org. Chem.* **1997**, *62*, 7094–7095. (b) Durow, A. C.; Long, G. C.; O'Connell, S. J.; Willis, C. L. *Org. Lett.* **2006**, *8*, 5401–5404. (c) Sotokawa, T.; Noda, T.; Pi, S.; Hirama, M. *Angew. Chem., Int. Ed.* **2000**, *39*, 3430–3432. (d) Schlama, T.; Baati, R.; Gouverneur, V.; Valleix, A.; Falck, J. R.; Mioskowski, C. *Angew. Chem., Int. Ed.* **1998**, *37*, 2085–2087. (e) Sheldrake, H. M.; Jamieson, C.; Burton, J. W. *Angew. Chem., Int. Ed.* **2006**, *45*, 7199–7202. (f) Frankie, M. S.; Curtis, N. R.; Payne, A. N.; Congreve, M. S.; Francis, C. L.; Burton, J. W.; Holmes, A. B. *Synthesis* **2005**, 3199–3201. (g) Grese, T. A.; Hutchinson, K. D.; Overman, L. E. *J. Org. Chem.* **1993**, *58*, 2468–2477. (h) Brown, M. J.; Harrison, T.; Overman, L. E. *J. Am. Chem. Soc.* **1991**, *113*, 5378–5384. (i) Williard, P. G.; De Laszlo, S. E. *J. Org. Chem.* **1985**, *50*, 3738–3749. Also see: Murai, A. In *Studies in Natural Products Chemistry*; Atta-ur-Rahman, Ed.; Elsevier Science B. V.: New York, 1997; Vol. 19, pp 411–461.

(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.

(4) (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. *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.

(5) For pioneering studies on this class of molecules, see: (a) Elovson, J.; Vagelos, P. R. *Biochemistry* **1970**, *9*, 3110–3126. (b) Haines, T. H. *Annu. Rev. Microbiol.* **1973**, *27*, 403–411. (c) Hansen, J. A. *Physiol. Plant.* **1973**, *29*, 234. (d) Mercer, E. I.; Davies, C. L. *Phytochemistry* **1974**, *13*, 1607–1610. (e) Mercer, E. I.; Davies, C. L. *Phytochemistry* **1975**, *14*, 1545–1548. (f) Mercer, E. I.; Davies, C. L. *Phytochemistry* **1979**, *18*, 457.

(6) For recent reviews on enantioselective halogenations, see: (a) Ibrahim, H.; Togni, A. *Chem. Commun.* **2004**, 1147–1155. (b) Guilena, G.; Ramon, D. J. *Tetrahedron: Asymmetry* **2006**, *17*, 1465–1492.

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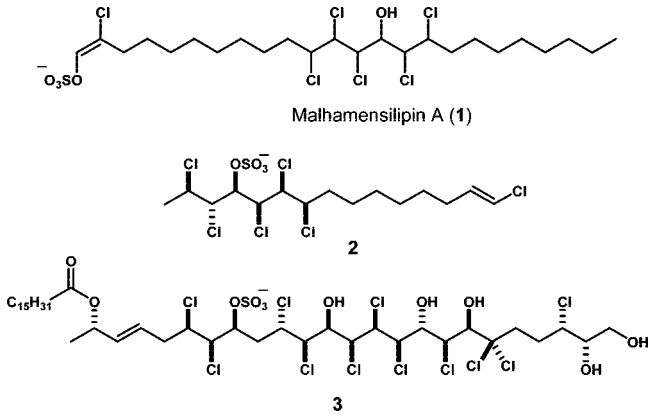


FIGURE 1. Natural bioactive polychlorides.

Isaacs and Kirkpatrick have demonstrated a potential direct approach to chiral vicinal dichlorides from epoxides in a stereospecific manner using organophosphonium chlorides prepared in situ from Ph_3P/CCl_4.[9a,b] Recently, Iranpoor et al. have also reported that NCS/Ph_3P promotes dichlorination of terminal epoxides as well as cyclohexene oxide.[9g] However, little is known about the general scope of the dichlorination reactions of structurally complex internal epoxides. Consequently, some questions occurred to us: do stereospecific dichlorinations take place with internal epoxides carrying various functional groups that might affect stereospecificity and reactivity? Is it possible to install more than two chlorine atoms stereospecifically into consecutive epoxy groups in a similar manner? In the present study, new insights to these questions were provided through the evaluations of several *N*-chlorosuccinimide (NCS)/organophosphine reagents that form sp^3C-Cl bonds in terms of selectivity and reactivity, and attempts were made to apply the multiple chlorination method to various internal epoxides.[10] We also explored new reagent systems for the dichlorination of epoxides and found that NCS/Ph_2PCl,[11] a highly reactive chlorinating reagent, was suitable for this purpose in some cases.

Results and Discussion

Evaluation of Reagent Scope and Reaction Conditions. We initially evaluated the reagent scope and reaction conditions for the dichlorination of simple alkyl-substituted epoxides. As a first set of experiments, racemic *trans*- and *cis*-epoxides **4a** and **4b** were subjected to nucleophilic substitution reactions using various chlorinating agents (Tables 1 and 2). Tables 1 and 2 indicate that NCS/Ph_3P was best suited for the dichlorination of each epoxide in terms of reaction time and product yield.

In general, dichloride **5a** or **5b** was produced in moderate to good yield, together with small amounts of olefins.[12] Commercially available Cl_2PPh_3 also promoted the dichlorination reaction;[9c,d] however, this reagent showed somewhat limited utility because of low reproducibility that possibly stems from its susceptibility to hydrolytic decomposition upon exposure to moisture (Table 1, entry 1, and Table 2, entry 1). The use of $(c\text{-Hex})_3P$ or $n\text{-Bu}_3P$ in combination with NCS also gave dichloride **5a** or **5b** but required longer reaction times, and when *trans*-epoxide **4a** was used as substrate, the yield of dichloride **5a** decreased (Table 1, entries 4 and 5, and Table 2, entries 4 and 5). Interestingly, dichlorination of epoxides **4a** and **4b** with NCS/$t\text{-Bu}_3P$ gave chlorohydrins **7/8** and **9/10** rather than the desired dichlorides **5a** and **5b**, respectively (Table 1, entry 6, and Table 2, entry 6). The reason for the preferential production of the chlorohydrins in these particular cases is currently unclear; however, the severe steric demand of bulky *tert*-butylphosphonium intermediates (vide infra) that retarded subsequent nucleophilic substitution may be responsible for their formation. Reagent amount also affected product yield (Table 1, entry 3): a small reagent amount (NCS 2.5 equiv/Ph_3P 2.5 equiv) led to poor yield. The reaction rate decreased at low temperature (i.e., 7 h at 45 °C vs 1 h at 90 °C) (Table 2, entry 3). Use of the Isaacs reagent system, Ph_3P/CCl_4,[9a] efficiently transformed *cis*-epoxide **4b** into dichloride **5b**, but it was less effective for *trans*-epoxide **4a** (Table 1, entry 7, and Table 2, entry 7). An attempted dichlorination of epoxide **4a** using PCl_5 under buffered conditions resulted in significant decomposition of the starting epoxide (Table 1, entry 8).

Reaction Mechanism. The dichlorination by NCS/organophosphine is reasonably assumed to involve sequential substitution reactions as proposed by Iranpoor et al. (Scheme 1).[9g] The stereospecific displacement of epoxide oxygen atoms with a chloride ion begins with the activation of the epoxide via coordination of phosphonium salt **i** generated from the chlorination of R_3P with NCS (**i** → **ii**). The initial nucleophilic attack of a chloride ion that comes from 1 equiv of phosphonium salt **i** provides oxyphosphonium intermediate **iii** (**ii** → **iii**). Then, another chloride ion reacts with intermediate **iii** via the S_N2 pathway, giving rise to dichloride **iv** along with organophosphine oxide and its derivative **v**. If the phosphonium intermediate **iii** undergoes E2 elimination, chloroalkene **vi** is stereospecifically produced (**iii** → **vi**).

Dichlorination of 1,4-Dioxygenated 2,3-Epoxides. Then, the dichlorination of chiral epoxides **4c**−**h** possessing oxygen functionalities at 1,4-positions was examined under NCS/Ph_3P conditions (Table 3). The reaction of *trans*-epoxide **4c** and *cis*-epoxide **4d** with NCS/Ph_3P afforded corresponding dichlorides *syn*-**5c** and *anti*-**5d** in good yields along with olefins **6c/6c′** and **6d/6d′**, respectively (Table 3, entries 1 and 2). The reaction times were significantly shortened at 90 °C, as expected, and the dichloride/olefin ratio showed a slight decrease at this

(7) For a pertinent review on the use of epoxides as precusor for chiral halohydrins, see: Bonini, C.; Righi, G. *Synthesis* **1994**, 225–238.

(8) Recently, Vanderwal and co-workers established the stereoselective dichlorination-based access to this class of polychlorinated natural products: Shibuya, G. M.; Kanady, J. S.; Vanderwal, C. D *J. Am. Chem. Soc.* **2008**, *130*, 12514–12518.

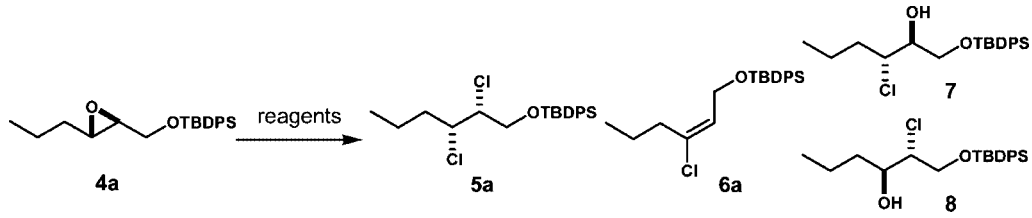
(9) For the stereospecific dichlorination of epoxides, see: (a) Isaacs, N. S.; Kirkpatrick, D. *Tetrahedron Lett.* **1972**, *13*, 3869–3870. (b) Croft, A. P.; Bartsch, R. A. *J. Org. Chem.* **1983**, *48*, 3353–3354. (c) Oliver, J. E.; Sonnet, P. E. *Org. Synth.* **1978**, *58*, 64–67. (d) Sonnet, P. E.; Oliver, J. E. *J. Org. Chem.* **1976**, *41*, 3279–3283. (e) Echigo, Y.; Watanabe, Y.; Mukaiyama, T. *Chem. Lett.* **1977**, 1013–1014. (f) Iranpoor, N.; Firouzabadi, H.; Aghapour, G.; Nahid, A. *Bull. Chem. Soc. Jpn.* **2004**, *77*, 1885–1891. (g) Iranpoor, N.; Firouzabadi, H.; Azadi, R.; Ebrahimzadeh, F *Can. J. Chem.* **2006**, *84*, 69–75.

(10) O'Hagan and co-workers have reported an enantioselective synthesis of polyfluorinated motifs by means of nucleophilic displacement of oxygen functionalities: (a) Hunter, L.; Slawin, A. M. Z.; Kirsch, P.; O'Hagan, D. *Angew. Chem., Int. Ed.* **2007**, *46*, 7887–7890. (b) Hunter, L.; O'Hagan, D.; Slawin, A. M. Z. *J. Am. Chem. Soc.* **2006**, *128*, 16422–16423. (c) Nicoletti, M.; O'Hagan, D.; Slawin, A. M. Z. *J. Am. Chem. Soc.* **2005**, *127*, 482–483.

(11) Ph_2PCl itself is known to serve as a chlorinating reagent for alcohols; see: (a) Hiebel, M.; Pelotier, B.; Piva, O. *Tetrahedron* **2007**, *63*, 7874–7878. (b) Hayashi, T.; Konishi, M.; Okamoto, Y.; Kabeta, K.; Kumada, M. *J. Org. Chem.* **1986**, *51*, 3772–3781.

(12) The stereochemistry of each chloroalkene (**6a** and **6b**) was unambiguously confirmed by NOE experiments. The selective production of 3-chloro-substituted alkene is presumably attributed to the preferential attack of a chloride ion at the less hindered site where interaction with the bulky *tert*-butyldiphenylsilyl substituent is avoidable.

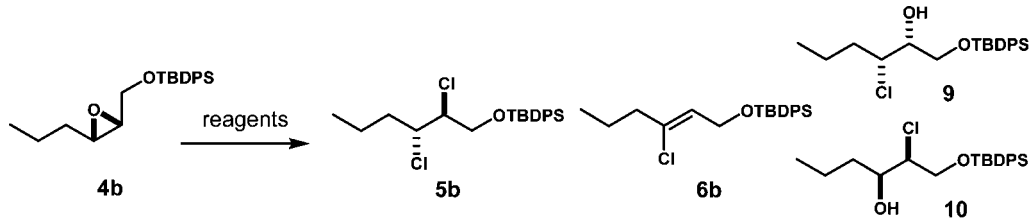
TABLE 1. Dichlorination of *trans*-Epoxide 4a with Various Chlorinating Reagents



entry	reagents (equiv)	solvent	*T* (°C)	time (h)	products[a,b] (%)
1	Cl_2PPh_3 (4)	toluene	80	0.5	**5a** (79), **6a** (18)
2	NCS/Ph_3P (3/3)	toluene[c]	90	0.7	**5a** (76), **6a** (17)
3	NCS/Ph_3P (2.5/2.5)	toluene	90	13	**5a** (69), **6a** (19), **7** (9)
4	NCS/(c-Hex)$_3$P (3/3)	toluene	90	6	**5a** (65), **6a** (11), **7** (4), **8** (2)
5	NCS/*n*-Bu_3P (3/3)	toluene	90	6	**5a** (66), **6a** (11), **7** (19)
6	NCS/*t*-Bu_3P (3/3)	toluene	90	22	**7** (65), **8** (32)
7	Ph_3P (3)	CCl_4	reflux	7	**7** (47), **8** (10) [d]
8	PCl_5 (3), $NaHCO_3$	CH_2Cl_2	rt	1	complex mixture

[a] Isolated yield. [b] Ratio determined by ^{1}H NMR analysis. [c] When MeCN was used as solvent, **5a** (65%) and **6a** (24%) were produced. [d] Unreacted **4a** (43%) was recovered.

TABLE 2. Dichlorination of *cis*-Epoxide 4b with Various Chlorinating Reagents



entry	reagents (equiv)	solvent	*T* (°C)	time (h)	products[a,b] (%)
1	Cl_2PPh_3 (4)	toluene	80	0.5	**5b** (82), **6b** (17)
2	NCS/Ph_3P (3/3)	toluene	90	1	**5b** (88), **6b** (9)
3	NCS/Ph_3P (3/3)	toluene	45	7	**5b** (90), **6b** (6)
4	NCS/(c-Hex)$_3$P (3/3)	toluene	90	4.5	**5b** (86), **6b** (7)
5	NCS/*n*-Bu_3P (3/3)	toluene	90	6	**5b** (82), **6b** (7)
6	NCS/*t*-Bu_3P (3/3)	toluene	90	22	**9** (72), **10** (17)
7	Ph_3P (3)	CCl_4	reflux	7	**5b** (81), **6b** (7)

[a] Isolated yield. [b] Ratio determined by ^{1}H NMR analysis.

reaction temperature compared to that at 45 °C. It was revealed that *tert*-butyldimethylsilyl and pivaloyl substituents were compatible with the present conditions, without accompanying undesired deprotection (Table 3, entries 3 and 4).

Epoxides **4g** and **4h**, both having a ketal group, were moderately transformed with Ph_3P/NCS into dichlorides **5g** and **5h** (Table 3, entries 5 and 6). In those cases, however, the yields of alkenes **6g** and **6g′** slightly increased, reflecting that the steric hindrance of the ketal oxygen adjacent to the epoxide retarded the second nucleophilic substitution and led to E2 elimination of the oxyphosphonium intermediates. Thus, epoxide **4g** underwent dichlorination with NCS/Ph_3P to afford dichloride **5g** in moderate yield (56%) along with regioisomeric alkenes **6g**/**6g′** (Table 3, entry 5). The selective production of alkene **6g′** over **6g** indicated the occurrence of an exclusive C2 attack with a chloride ion rather than a nucleophilic displacement at C3-position. Interestingly, under the same conditions, epoxide **4h** gave dichloride **5h** (42%) as a stereoisomeric mixture (*syn:anti* = 3:1), suggesting that the participation of the neighboring ketal oxygen occurred (Table 3, entry 6). Thus, *anti*-**5h** was probably produced through the double inversion at the C3 center, which led to net configurational retention of the stereogenic center (Scheme 2).

Dichlorination of Aryl Epoxides 4i and 4j. Further applications of the present method to various epoxides revealed that subtle differences in the structures of epoxides significantly affected yields and selectivities (Table 4). When phenyl-substituted epoxide **4i** was subjected to dichlorination using NCS/Ph_3P in toluene at 90 °C, desired dichloride **5i** was produced in 57% yield (*syn*:*anti* = 1:50), together with olefin **6i** (38%) (Table 4, entry 1). The reaction of *trans*-epoxide **4j** under the same conditions, however, produced olefin **6j** as the major product (68%) and dichloride **5j** in low yield (19%; *syn*:*anti* = 14:1) (Table 4, entry 2). The preferential formation of the undesired olefin from epoxide **4j**, which markedly contrasts the result obtained with *cis*-epoxide **4i**, could be rationalized by considering the steric hindrance of the initially introduced chlorine atom as well as the stability of the product; the bulky chlorine atom installed at the benzylic position covered the α-face of the staggered alkyl chain to disrupt the second nucleophilic attack of another chloride ion at the same face of the intermediate, favoring an elimination reaction to give stable conjugated olefins.

NCS/Ph_2PCl, a New Dichlorinating Reagent for Alkenyl Epoxides. A marked difference in product ratios of *cis*- and *trans*-epoxides was also observed for alkenyl epoxides **4k**−**m**

SCHEME 1. Plausible Mechanism of Dichlorination

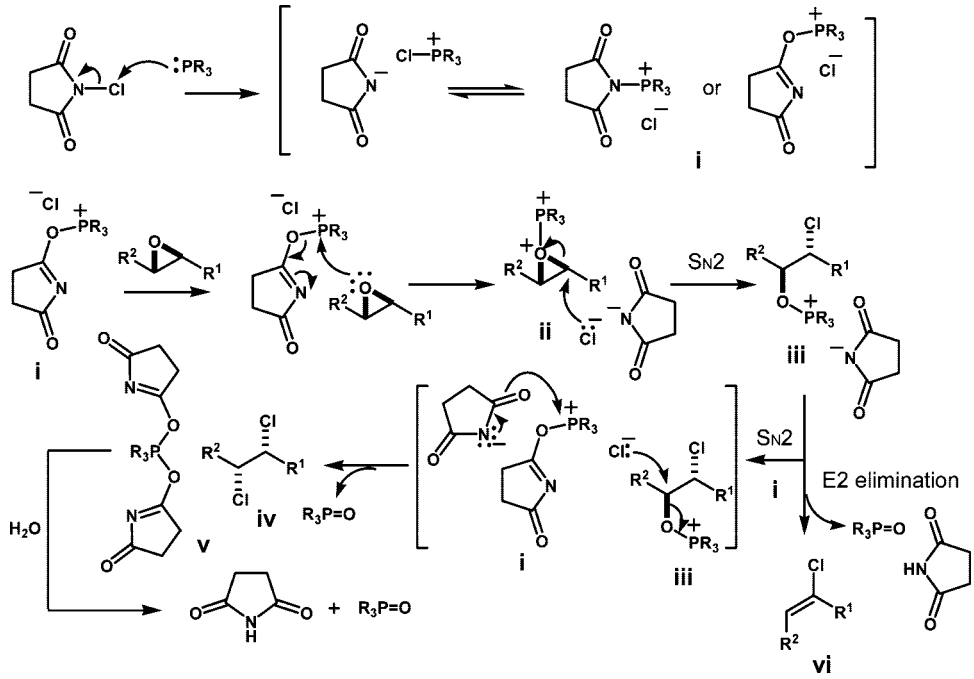
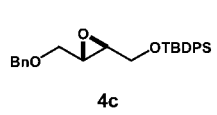
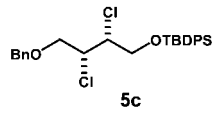
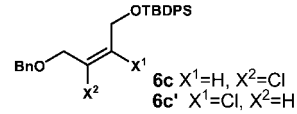
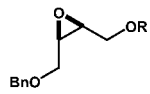
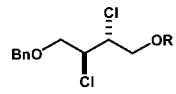
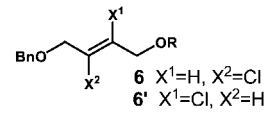
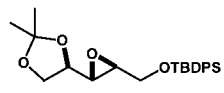
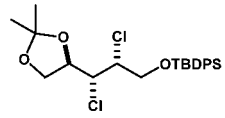
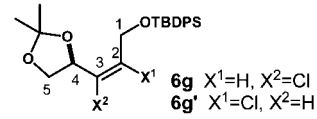
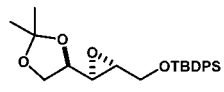
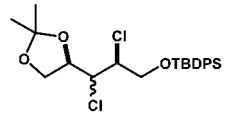
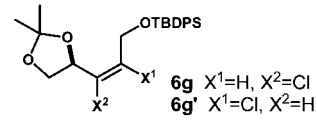


TABLE 3. Dichlorination of 1,4-Dioxygenated 2,3-Epoxides 4c−h

entry	substrate[a]	temp (°C)	products[b,c]	time (h)
1	 **4c**	90	 **5c** 82 %	3.4
		45	80 %	22
		90	 14 % (**6c**:**6c'**=4:1)	3.4
		45	8 % (**6c**:**6c'**=3:1)	22
				
			 **6** X^1=H, X^2=Cl **6'** X^1=Cl, X^2=H	
2	**4d** R=TBDPS	90	**5d** 79 %	2.7
		45	**5d** 84 %	48
		90	20 % (**6d**:**6d'**=6:1)	2.7
		45	14 % (**6d**:**6d'**=1:0)	48
3	**4e** R=TBS	90	**5e** 69 %	1
			18 % (**6e**:**6e'**=5:2)	1
4	**4f** R=Piv	90	**5f** 82 %	1.5
			12 % (**6f**:**6f'**=3:2)	1.5
5	 **4g**	90	 **5g** 56 %	1
			 **6g** X^1=H, X^2=Cl **6g'** X^1=Cl, X^2=H	1
			28 % (**6g**:**6g'**=1:27)[d]	1
6	 **4h**	90	 **5h** 42% (*syn*:*anti* = 3:1)	2.7
			 **6g** X^1=H, X^2=Cl **6g'** X^1=Cl, X^2=H	2.7
			33 % (**6g**:**6g'**=3:4)[d]	2.7

[a] All reactions were carried out using NCS (3 equiv) and PPh_3 (3 equiv) in toluene. [b] Isolated yield. [c] Ratio determined by ^{1}H NMR analysis. [d] Accompanied by small amounts of deprotected compounds (1−6%).

(Table 4, entries 3−5). Alkenyl *cis*-epoxide **4k** was transformed into dichloride **5k** in 58% yield, together with diene **6k** in 34% yield (entry 3). In contrast, *trans*-epoxide **4l** predominantly underwent S_N2' substitution reaction to give dichloride **6l** (52%) and desired dichloride **5l** was produced in only 33% yield (entry 4). This was also the case for *trans*-epoxide **4m** having a simple alkyl substituent (entry 5). To our delight, however, byproduct formation could be circumvented to some extent by using NCS/

SCHEME 2. Rationale for Configurational Retention at the C3 Position

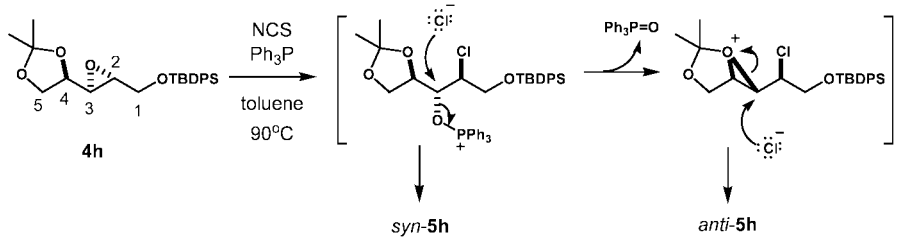
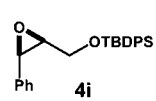
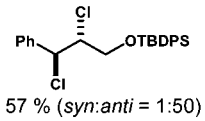
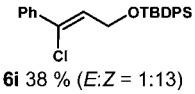
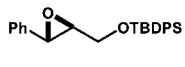
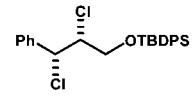
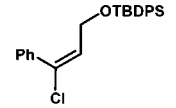
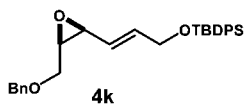
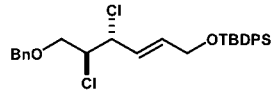
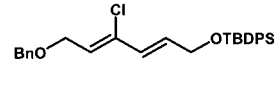
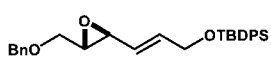
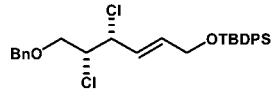
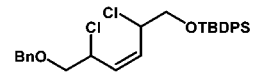
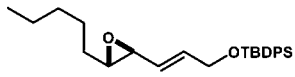
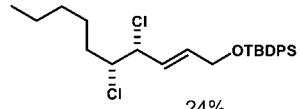
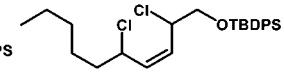
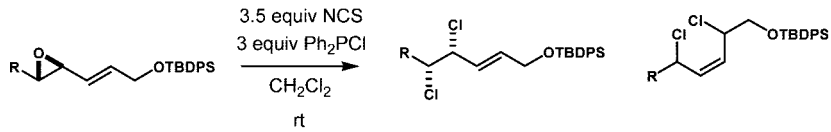


TABLE 4. Dichlorination of Aryl Epoxides 4i/4j and Alkenyl Epoxides 4k−m

entry	substrate[a]	products[b,c]	time (h)
1	 **4i**	 **5i** 57 % (*syn*:*anti* = 1:50)  **6i** 38 % (*E*:*Z* = 1:13)	1.5
2	 **4j**[d]	 **5j** 19 % (*syn*:*anti* = 14:1)  **6j** 68 % (*E*:*Z* = 19:1)	1.5
3	 **4k**	 **5k** 58%  **6k** 34%	0.7
4	 **4l**	 **5l** 33% 53%[e]  **6l** 52%[f] 7%[e,f]	0.5
5	 **4m**	 **5m** 24% 58%[e]  **6m** 60%[f] 27%[e,f]	1.2

[a] All reactions were carried out using NCS (3 equiv) and PPh_3 (3 equiv) in toluene at 90 °C. [b] Isolated yield. [c] Ratio determined by ^1H NMR analysis. [d] The use of MeCN as solvent gave similar yields: 16% of **5j** (*syn*/*anti* = 25:1) and 76% of **6j** (*E*/*Z* = 12:1). [e] NCS/Ph_2PCl was used (see Scheme 3). [f] Stereochemistry has yet to be determined.

SCHEME 3. Dichlorination of Alkenyl Epoxides 4l and 4m with NCS/Ph_2PCl



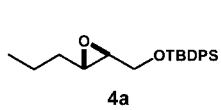
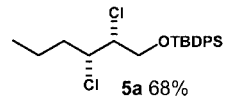
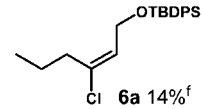
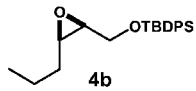
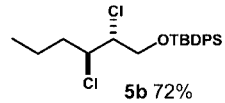
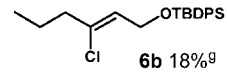
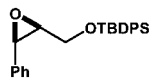
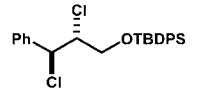
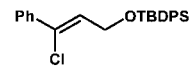
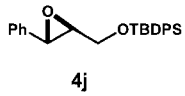
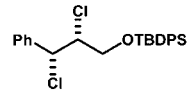
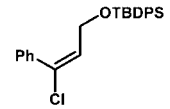
4l R=$BnOCH_2$ **5l** R=$BnOCH_2$ 53% **6l** R=$BnOCH_2$ 7%
4m R=*n*-C_5H_{11} **5m** R=*n*-C_5H_{11} 58% **6m** R=*n*-C_5H_{11} 27%

Ph_2PCl, a new chlorinating reagent that promoted the reaction efficiently at room temperature (Scheme 3). Thus, a solution of epoxide **4l** or **4m** in CH_2Cl_2 at room temperature was added slowly over 5 min to the chlorinating reagent that was prepared by premixing NCS (3.5 equiv) and Ph_2PCl (3.0 equiv) in CH_2Cl_2, and the mixture was stirred for an additional 5 min to furnish desired dichloride **5l** in 53% yield or **5m** in 58% yield (entries 4 and 5). We also evaluated the applicability of this new reagent system to substrates **4a**, **4b**, **4i**, and **4j** and found that the reactions with NCS/Ph_2PCl showed unique substrate scope (Table 5). Dichlorination of alkyl-substituted epoxides **4a** and **4b** smoothly took place at room temperature to give dichlorides **5a** and **5b** in acceptable yields along with alkenes **6a** and **6b**, respectively (Table 5: entries 1 and 2), whereas the reactions with phenyl-substituted epoxides **4i** and **4j** led to only moderate yields of dichlorides **5i** and **5j** (Table 5, entries 3 and 4).

Tetrachlorination of Bisepoxides. As an extension of our multiple chlorination strategy, we then applied the NCS/Ph_3P

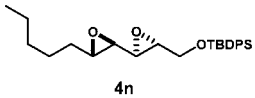
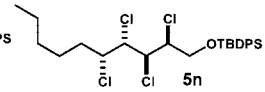
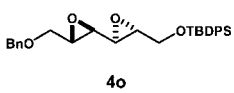
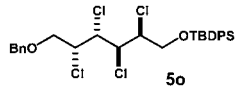
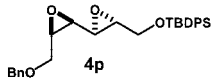
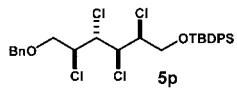
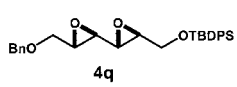
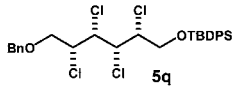
(13) The stereochemistry of each compound **5n** and **5p** was tentatively assigned on the basis of the stereochemical outcomes obtained for other substrates.

TABLE 5. Dichlorination of Epoxides 4a, 4b, 4i, and 4j with NCS/Ph_2PCl

entry	substrate	time (min)	products[d,e]	
1[a,b]	 **4a**	25	 **5a** 68%	 **6a** 14%[f]
2[a,b]	 **4b**	10	 **5b** 72%	 **6b** 18%[g]
3[c]	 **4i**	25	 **5i** 37% (*syn*:*anti* = 1:14)	 **6i** 56% (*E*:*Z* = 1:25)[h]
4[c]	 **4j**	25	 **5j** 36% (*syn*:*anti* = 3.6:1)	 **6j** 52% (*E*:*Z* = 6:1)[i]

[a] The reaction was carried out using NCS (3 equiv) and Ph_2PCl (2 equiv) in CH_2Cl_2 at rt. [b] Racemic substrate was used. [c] The reaction was carried out using NCS (3 equiv) and Ph_2PCl (3 equiv) in CH_2Cl_2 at rt. [d] Isolated yield. [e] Ratio determined by ^1H NMR analysis. [f] Phosphinate (14%) was also produced. For the details, see the Supporting Information. [g] Phosphinate (5%) was produced. [h] No phosphinate was produced. [i] Phosphinate (6%) was produced.

TABLE 6. Tetrachlorination of Bisepoxides 4n−q with NCS/Ph_3P

entry	substrate	product[d]	yield (%)[e]
1[a]	 **4n**	 **5n**	40[f]
2[b]	 **4o**	 **5o**	42
3[c]	 **4p**	 **5p**	30[f]
4[b]	 **4q**	 **5q**	10

[a] The reaction was carried out using NCS (6 equiv) and PPh_3 (6 equiv) in toluene at 90 °C. [b] NCS (10 equiv) and PPh_3 (10 equiv) were used. [c] The reaction mixture was initially heated at 45 °C for 1.3 h then at 90 °C for 3.7 h. [d] Accompanied by olefin byproducts. [e] Isolated yield. [f] Stereochemistry has yet to be determined.

system to tetrachlorination, which would provide a novel short access to the structural motifs of polychlorosulfolipids. To our delight, despite the limited substrate scope at the present time, tetrachlorination of bisepoxides **4n** and **4o** under NCS/Ph_3P conditions provided chiral tetrachlorides **5n** and **5o**, respectively (Table 6, entries 1 and 2).[13] Bisepoxide **4n** was transformed with NCS/Ph_3P into tetrachloride **5n** in 40% yield as a single diastereomer. Benzyloxy derivative **4o** was also stereospecifically chlorinated under the same conditions, giving compound **5o** in 42% yield. Bisepoxide **4p** possessing *cis*/*trans* configuration was moderately transformed into tetrachloride **5p** (Table 6, entry 3).[13] Although bisepoxide **4q** was found to be a poor substrate (Table 6: entry 4),[14] the present one-step tetrachlorination of bisepoxides potentially serves as a useful methodology for synthesizing chiral polychlorinated hydrocarbons.

Determination of Stereochemistry of Chiral Polychlorides. The stereochemistry of the products was unambiguously confirmed by chemical correlations with known compounds as well as NMR analysis (Scheme 4). *syn*-Dichloride **5c** was converted into chiral C_2-symmetric diol **11c** ($[\alpha]^{21}_D$ +6.6 (*c* 0.54, MeOH)) in 96% yield over two steps by sequential removal of TBDPS and benzyl groups.[15] Similar conversion of *anti*-isomer **5d** afforded *meso*-diol **11d** in 90% yield, thereby establishing its relative configuration. Tetrachloride **5o** was converted into *meso*-acetate **11o** in 58% overall yield, while by deprotection and subsequent acetylation, tetrachloride **5q** gave chiral C_2-symmetric acetate **11q** ($[\alpha]^{24}_D$ +8.8 (*c* 0.16, MeOH)). Stereochemical assignments of all other dichlorides were deduced from NMR analyses of olefins that were stereospecifically prepared with known olefination procedures using NaI in refluxing HMPA (for details, see the Supporting Information).

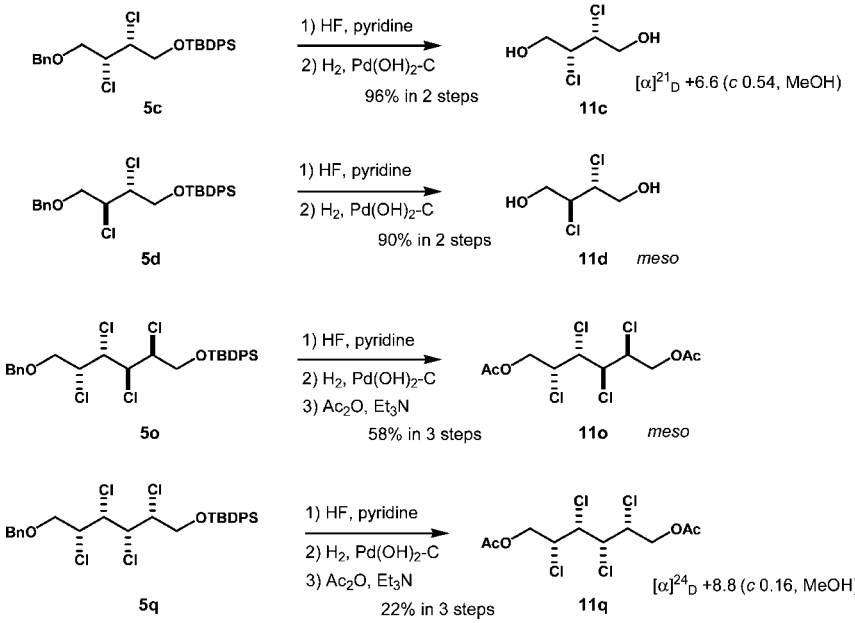
Conclusions

We have demonstrated that chiral polychlorides were accessible stereospecifically by nucleophilic multiple chlorination reactions of internal epoxides using NCS/organophosphine. The fact that various chiral epoxides are readily obtainable by asymmetric epoxidation reactions of alkenes is evidence that the organochlorination process disclosed here provides significant opportunities for preparing an array of chiral chlorinated stereocenters. Further applications of the present technique to

(14) The rest of the material was a complex mixture of many products, including alkenes and dichlorides, and was difficult to analyze.

(15) Werner, F. P. DE Patent 10933345, 1960.

SCHEME 4. Determination of Structure of Polychlorides



the synthesis of natural bioactive polychlorides are currently being evaluated in this laboratory.

Experimental Section

Representative Procedure for Dichlorination of Epoxides with NCS/Ph_3P. To a magnetically stirred solution of epoxide **4c** (204 mg, 0.47 mmol) in toluene (5 mL) at room temperature were added Ph_3P (367 mg, 1.40 mmol) and NCS (190 mg, 1.39 mmol), and the mixture was heated at 90 °C for 3.4 h. The mixture was then poured into a separatory funnel and 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 (CH_2Cl_2/hexane 1:8) to give dichloride **5c** (188 mg, 82%) as a colorless oil and an inseparable mixture of alkenes **6c**/**6c′** (29 mg, 14%; **6c**:**6c′** = 4:1 determined by ^1H analysis) as a colorless oil. The stereo- and regiochemistry of each olefin were determined by NOE experiments. We sometimes encountered difficulties in separating dichlorides from Ph_3P remaining in the crude reaction mixture. In such cases, treatment of the reaction mixture with satd $NaHCO_3$ and *t*-BuOOH (80 μL; ca. 1.5 equiv; 80% solution in di-*tert*-butyl peroxide) prior to workup oxidized the remaining Ph_3P to give $Ph_3P{=}O$ that was easily removable. [(2*R*,3*R*)-4-(Benzyloxy)-2,3-dichlorobutoxy](*tert*-butyl)diphenylsilane (**5c**): colorless oil; $[\alpha]^{22}_D$ −4.6 (*c* 3.10, $CHCl_3$); IR (neat) ν 2931, 1589, 1471, 1113, 700 cm^{-1}; ^1H (300 MHz, $CDCl_3$) δ 7.63−7.53 (m, 4H), 7.40−7.20 (m, 11H), 4.67 (ddd, 1H, J = 8.2, 6.0, 2.0 Hz), 4.62 (d, 1H, J = 12.1 Hz), 4.58 (d, 1H, J = 12.3 Hz), 4.42 (ddd, 1H, J = 8.8, 5.7, 2.0 Hz), 3.93 (dd, 1H, J = 10.2, 8.9 Hz), 3.88−3.70 (m, 3H), 0.98 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.5, 135.6, 135.5, 132.8, 132.6, 129.9, 128.5, 127.9, 127.8, 127.7, 73.4, 70.9, 64.3, 59.9, 58.0, 26.8, 19.2; MS *m*/*z* 487 (MH^+), 91 (100); HRMS (FAB) calcd for $C_{27}H_{33}O_2{}^{35}Cl_2Si$ (MH^+) 487.1627, found 487.1634. Due to the difficulty of separation of alkenes **6c**/**6c′**, the structures were elucidated by their transformation into the corresponding aldehydes (for details, see the Supporting Information).

Representative Procedure for Dichlorination of Epoxides with NCS/Ph_2PCl. Ph_2PCl (27 μL, 0.15 mmol) was added to a magnetically stirred solution of NCS (24 mg, 0.18 mmol) in CH_2Cl_2 (0.4 mL) at room temperature, followed by a solution of alkenyl epoxide **4m** (21 mg, 0.05 mmol) in CH_2Cl_2 (0.6 mL) over 5 min. The mixture was stirred for an additional 5 min and then transferred to a separatory funnel where it was neutralized with satd $NaHCO_3$ and extracted with EtOAc. The organic phase was separated, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by silica gel column chromatography (hexane) to give dichloride **5m** (14 mg, 58%) as a colorless oil and olefin **6m** (6.3 mg, 27%) as a colorless oil. *tert*-Butyl({[(*E*,4*R*,5*R*)-4,5-dichlorodec-2-en-1-yl]oxy})diphenylsilane (**5m**): colorless oil; $[\alpha]^{24}_D$ +20.1 (*c* 0.86, $CHCl_3$); IR (neat) ν 1957, 1892, 1822, 1464, 1113 cm^{-1}; ^1H (300 MHz, $CDCl_3$) δ 7.71−7.62 (m, 4H), 7.50−7.33 (m, 6H), 6.02 (ddt, 1H, J = 15.1, 8.2, 1.5 Hz), 5.89 (dt, 1H, J = 15.2, 3.8 Hz), 4.62 (dd, 1H, J = 8.2, 3.8 Hz), 4.25 (dd, 2H, J = 3.8, 1.5 Hz), 4.04 (dt, 1H, J = 9.7, 3.7 Hz), 2.03−1.84 (m, 1H), 1.78−1.63 (m, 1H), 1.50−1.24 (m, 6H) 1.07 (s, 9H), 0.91 (t, 3H, J = 6.7 Hz); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 135.4, 134.3, 133.3, 129.6, 127.6, 125.6, 65.5, 64.9, 63.2, 33.9, 31.2, 26.9, 26.2, 22.5, 19.3, 14.1; MS *m*/*z* 485 (MNa^+), 135 (100); HRMS (FAB) calcd for $C_{26}H_{36}O^{35}Cl_2SiNa$ (MNa^+) 485.1810, found: 485.1819.

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

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