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Conformational and Configurational Analysis in the Study and Synthesis of Chlorinated Natural Products

Christian Nilewski, Roger W. Geisser, Marc-Olivier Ebert, and Erick M. Carreira*

Laboratorium für Organische Chemie, ETH Zürich, CH-8093 Zürich, Switzerland

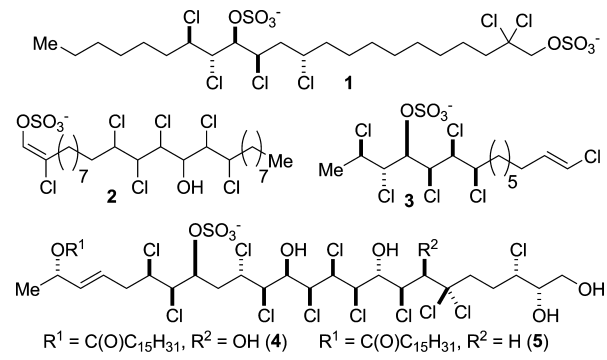
Received July 31, 2009; E-mail: carreira@org.chem.ethz.ch

Abstract: The first detailed study of the *J*-based configuration analysis method in chlorinated hydrocarbons and chlorohydrins is presented along with the development of a spectroscopic database that facilitates configurational assignment of these structures. The data are generated through the investigation of model structures in solution by NMR spectroscopic methods and in the solid state by X-ray crystallography. Consequently, complete conformational analysis of trichlorinated hexane-1,2- and -1,3-diols is presented. The investigations in chlorinated systems for the first time attest to the relevance, reliability, and accuracy of the spectroscopic approach in configurational assignment, which had been otherwise developed for polyketides. During the synthesis of the various molecules that constitute the database and exemplify the various possible stereochemical patterns, a number of observations were made that underscore the unique features of these chlorinated systems. Thus, certain diastereomeric subclasses of 4,5-dichloro-2,3-epoxyhexane-1-ols display a propensity to undergo ring-opening reactions at C-3 with concomitant inversion of configuration at the neighboring C−Cl at C4, implicating the intermediacy of chloronium ions. The observations of positional and stereochemical scrambling in polychlorinated hydrocarbons underscore the necessity of a spectroscopic database that enables rapid, reliable configurational assignment of chlorinated natural products and intermediates en route to these.

Introduction

Chlorosulfolipids represent an unusual class of natural products that were first isolated in the 1960s.[1] The structure of the most abundant of these novel lipids was identified later as disulfate **1** by chemical degradation and mass spectrometry, albeit devoid of stereochemical details.[2] Subsequently, chlorosulfolipids have been detected in numerous algae,[3,4] but only a few have been structurally characterized (e.g., **2**).[5] In the late 1990s and early 2000s, Ciminiello and Fattorusso were first to assign the absolute configuration of chlorosulfolipids isolated from digestive glands of contaminated shellfish *Mytilus galloprovincialis* along the Adriatic coast of Italy.[6−8] Lipids **3**−**5** display modest cytotoxic activity and are associated with seafood poisoning. For many others, such as **2**, the absolute and relative configuration remain unknown (Chart 1).

Chart 1. Docosane, Tetracosane, and Pentadecane Chlorosulfolipids that Originate from Microalgae



The difficulties with the structural characterization as well as the absence of methods and strategies to stereoselectively access acyclic polychlorinated arrays have likely hindered studies until recently. In this respect, a rather limited number of investigations of simple models for the construction of polychlorinated hydrocarbons have been reported,[9,10] and the first total synthesis of a member of this class of natural products was recently disclosed.[11] The applicability of the developed synthetic strategy[11] to other structurally similar chlorosulfolipids was demonstrated by Gerwick, Haines, and Vanderwal in the total synthesis of chlorosulfolipid **1**, which was given the name danicalipin A in the context of this work, referring to its origin from the microalga *Ochromonas danica*.[12] The absolute con-

(1) Elovson, J.; Vagelos, P. R. *Proc. Natl. Acad. Sci. U.S.A.* **1969**, *62*, 957.
(2) Elovson, J.; Vagelos, P. R. *Biochemistry* **1970**, *9*, 3110.
(3) Mercer, E. I.; Davies, C. L. *Phytochemistry* **1974**, *13*, 1607.
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(5) Chen, J. L.; Proteau, P. J.; Roberts, M. A.; Gerwick, W. H.; Slate, D. L.; Lee, R. H. *J. Nat. Prod.* **1994**, *57*, 524.
(6) Ciminiello, P.; Fattorusso, E.; Forino, M.; Di Rosa, M.; Ianaro, A.; Poletti, R. *J. Org. Chem.* **2001**, *66*, 578.
(7) 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.
(8) Ciminiello, P.; Dell'Aversano, C.; Fattorusso, E.; Forino, M.; Magno, S.; Di Meglio, P.; Ianaro, A.; Poletti, R. *Tetrahedron* **2004**, *60*, 7093.
(9) Shibuya, G. M.; Kanady, J. S.; Vanderwal, C. D. *J. Am. Chem. Soc.* **2008**, *130*, 12514.
(10) Yoshimitsu, T.; Fukumoto, N.; Tanaka, T. *J. Org. Chem.* **2009**, *74*, 696.
(11) Nilewski, C.; Geisser, R. W.; Carreira, E. M. *Nature* **2009**, *457*, 573.
(12) Bedke, D. K.; Shibuya, G. M.; Pereira, A.; Gerwick, W. H.; Haines, T. H.; Vanderwal, C. D. *J. Am. Chem. Soc.* **2009**, *131*, 7570.

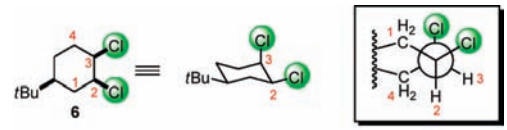
10.1021/ja906461h CCC: $40.75

figuration of chlorosulfolipid **1** was elucidated shortly after, using a modified Mosher's method after chemical degradation.[13]

Any study of the biology of chlorosulfolipids as well as their impact on marine ecology necessitates analytical methods for proper configurational assignment. Additionally, unexpected stereochemical outcomes in synthetic efforts toward chlorosulfolipids, i.e., the observation of anchimeric assistance in the course of nucleophilic opening of an epoxide with retention of configuration,[11] underscore the need for spectroscopic calibration data with which to secure the structure of intermediates in any synthesis route. Analysis of the $^3J(^1H,^1H)$ and NOE data alone, as frequently implemented for the assignment of the relative configuration of rigid cyclic systems, is usually insufficient for the unambiguous determination of the relative configuration of acyclic counterparts. Indeed, a recent study has underscored these shortcomings in analyses of diastereomeric 3,4-dichloro-2-pentanols.[14]

Investigators dealing with stereochemical issues associated with chlorosulfolipids have relied on implementation of Murata's database for oxygenated arrays. In this regard, Murata has investigated and documented a powerful spectroscopic approach for the configurational assignment of adjacent hydroxy/alkoxy-substituted methine carbons based on the analysis of homo- (^3J(H,H)) and heteronuclear (^2J(H,C), ^3J(H,C)) coupling constants as well as NOE or ROE data.[15−17] This method has been applied to the configurational characterization of chlorosulfolipids **1**[12,13] and **3**−**5**[6−8] as well as other simple chlorinated systems.[18] However, in this respect it is important to note that the method has never been independently validated in combination with X-ray structural analysis for polychlorinated compounds, and its accuracy and reliability have not been investigated in depth for such entities. The unambiguous determination of relative and absolute configuration often relies on chemical derivatization strategies, which can sometimes be laborious. Consequently, in order to properly apply Murata's method to chlorinated entities, calibration to reference values is strongly warranted.

Herein we report for the first time a database that enables configurational assignment of polychlorinated arrays using *J*-based analysis methods.[15−17] The data were obtained by detailed spectroscopic examination of a collection of crystalline diastereomeric trichlorinated hexane-1,2- and -1,3-diols. Its application is intended for the configurational assignment of vicinal dichloride and chlorohydrin intermediates in synthetic efforts toward chlorosulfolipids and other polychlorinated natural products. We hope that the data will facilitate structure elucidation in much the same way as Kishi's database for polyketides[19−21] has been instrumental. In this respect it is important to point out that Kishi's universal NMR database approach employing different types of profile descriptors (e.g., ^{1}H and ^{13}C shifts as well as ^3J(H,H) coupling constants)[19,20] and Murata's *J*-based configuration analysis method[15] are complementary to each other and together constitute state-of-the-art tools for the spectroscopic configurational assignment of acyclic entities.



^3J(H2,H3)	+2.9 Hz	small
^3J(H2,C4)	+0.8 Hz	small
^3J(H3,C1)	+4.7 Hz	large
^2J(H2,C3)	+3.6 Hz	small
^2J(H3,C2)	-4.5 Hz	large

Figure 1. Coupling constants for model system **6**. The use of "small" or "large" follows that of Murata et al. for the corresponding conformation of a dioxygenated system.[15]

Results

In order to apply the *J*-based configuration analysis method to chlorinated systems, it is key to determine reference values for all relevant homo- and heteronuclear coupling constants for *gauche*- and *anti*-conformers. We therefore commenced our investigation with the preparation and NMR spectroscopic study of a simple conformationally rigid model system, namely, *cis*-1,2-dichloro-4-*tert*-butylcyclohexane (**6**), which could be obtained by *cis*-dichlorination of 4-*tert*-butylcyclohexene (Figure 1).[22] The *tert*-butyl group in **6** functions as a "conformational anchor"; that is, the high energetic cost of an axial *tert*-butyl group (A_{value} = 4.7−4.9) leads to the conformation in which the *tert*-butyl group is oriented equatorially. In addition, the 1,3-*cis*-relationship of the *tert*-butyl group and one of the chloride substituents further destabilizes the other possible chair conformer. Hence, dichloride **6** is expected to be found as a single conformer in solution with an equatorial *tert*-butyl group. The potential differences in the coupling constants compared to the oxygenated counterparts, which compound **6** was anticipated to reveal, are therefore expected to have electronic reasons.

The heteronuclear coupling constants were extracted from an HSQC-HECADE-spectrum (*he*teronuclear *c*ouplings from *A*SSCI-*d*omain experiments with *E*.COSY-type cross-peaks).[23,24]

Although the experimental data displayed similar trends to those reported by Murata for 1,2-dioxygenated systems, the absolute values differ in two aspects. First, the magnitude of ^2J(H2,C3) for the synclinal dichloride array (+3.6 Hz) is larger than that reported for the dioxygenated system (0−2 Hz). Second, the magnitude of ^3J(H3,C1) in **6** (+4.7 Hz) is smaller than of the corresponding dioxygenated array, for which 5−7 Hz is reported (Figure 1).[15]

A salient feature of the work we describe herein is the preparation and full characterization of a family of configurationally defined polychlorinated acyclic molecules that we expected to allow retrieval of information about the ranges of the variability of the relevant coupling constants. We had noted early in our synthetic studies that the ring-opening products of

(13) Kawahara, T.; Kumaki, Y.; Kamada, T.; Ishii, T.; Okino, T. *J. Org. Chem.* **2009**, *74*, 6016.
(14) Kanady, J. S.; Nguyen, J. D.; Ziller, J. W.; Vanderwal, C. D. *J. Org. Chem.* **2009**, *74*, 2175.
(15) Matsumori, N.; Kaneno, D.; Murata, M.; Nakamura, H.; Tachibana, K. *J. Org. Chem.* **1999**, *64*, 866.
(16) Matsumori, N.; Murata, M.; Tachibana, K. *Tetrahedron* **1995**, *51*, 12229.
(17) Bifulco, G.; Dambruoso, P.; Gomez-Paloma, L.; Riccio, R. *Chem. Rev.* **2007**, *107*, 3744.
(18) Kaluzna, I. A.; Feske, B. D.; Wittayanan, W.; Ghiviriga, I.; Stewart, J. D. *J. Org. Chem.* **2005**, *70*, 342.
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(20) Seike, H.; Ghosh, I.; Kishi, Y. *Org. Lett.* **2006**, *8*, 3861.
(21) For a recent application of Kishi's NMR universal database approach, see: Seike, H; Ghosh, I.; Kishi, Y. *Org. Lett.* **2006**, *8*, 3865.
(22) Nugent, W. A. *Tetrahedron Lett.* **1978**, *19*, 3427.
(23) Kozminski, W.; Nanz, D. *J. Magn. Reson.* **1997**, *124*, 383.
(24) Kozminski, W.; Nanz, D. *J. Magn. Reson.* **2000**, *142*, 294.

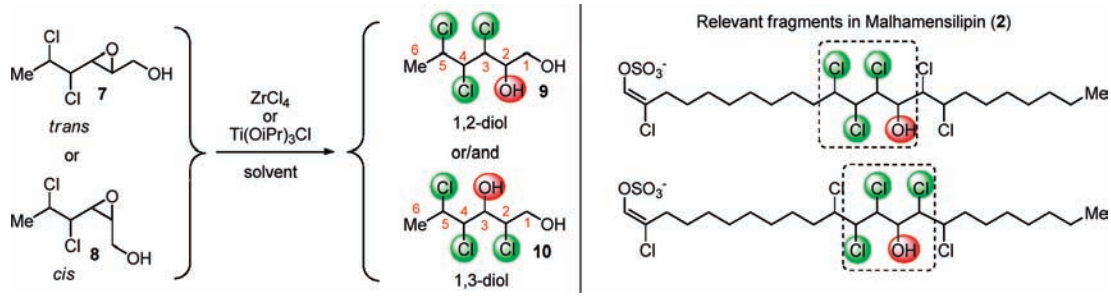
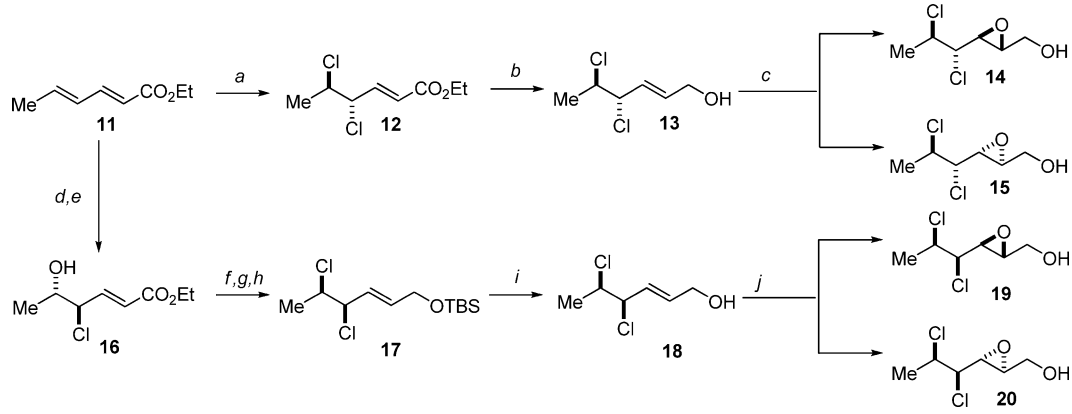


Figure 2. Epoxide-opening reactions of diastereomeric 4,5-dichloro-2-epoxyhexane-1-ols. The diols obtained include substitution patterns commonly found in the chlorosulfolipids, as exemplified by two highlighted fragments of the configurationally unassigned chlorosulfolipid malhamensilipin (**2**).

Scheme 1. Synthesis of All Diastereomeric 4,5-Dichloro-2-*trans*-epoxyhexane-1-ols[a]



[a] Reagents and conditions: (a) Et_4NCl_3, DCM, 0 °C, 45 min, 68%, (b) DIBAL (2.3 equiv), toluene, 0 °C, 10 min, 72%, (c) *m*-CPBA (2.5 equiv), DCM, 0 °C to rt, 20 h, dr(crude product) = 1/1, overall 75%, (d) *m*-CPBA (1.25 equiv), DCM, 0−4 °C, 67 h, 99%, (e) TMS-Cl (2.5 equiv), DMAP (0.05 equiv), EtOAc, rt−60 °C, 5 d, then citric acid hydrate (0.06 equiv), EtOH, rt, 16 h, 82%, (f) PPh_3 (2.2 equiv), CCl_4, reflux, 26 h, (g) DIBAL (2.5 equiv), toluene, 0 °C, 10 min, (h) TBS-Cl (1.1 equiv), imidazole (1.5 equiv), DCM, rt, 14 h, 27% over three steps, (i) CSA (0.1 equiv), MeOH, rt, 16 h, 96%, (j) *m*-CPBA (3.3 equiv), DCM, 0 °C to rt, 21 h, dr(crude product) = 2.3/1, 58% **20**, 33% **19**.

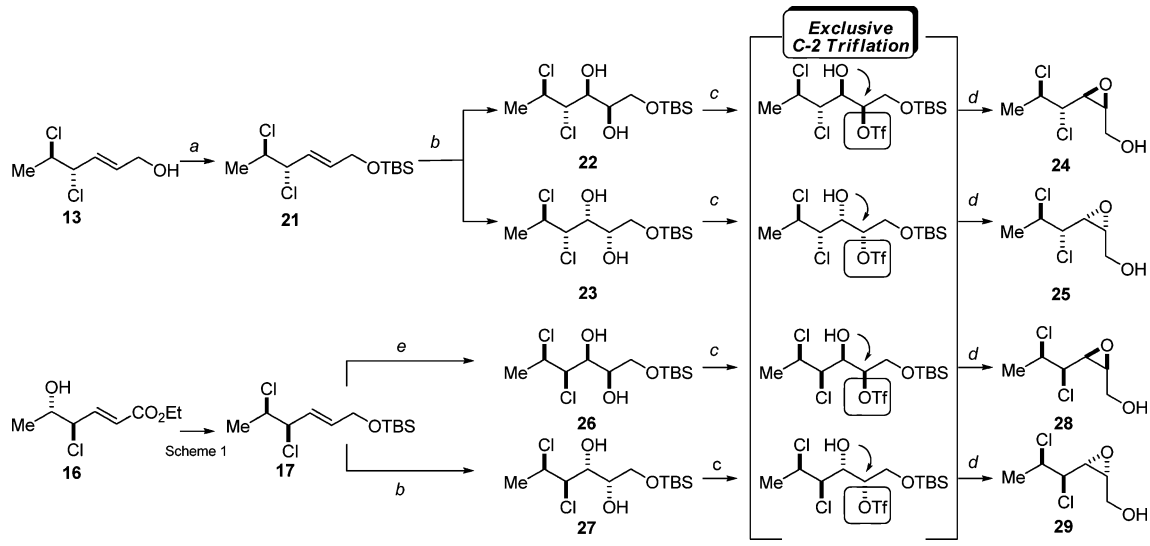
4,5-dichloro-2-epoxyhexane-1-ols with chloride are usually crystalline compounds. Therefore, we envisioned a study of ring-openings of diastereomeric 4,5-dichloro-2-epoxyhexane-1-ols (**7**, **8**) that provide a number of trichlorinated hexane-1,2- and -1,3-diols (**9**, **10**) (Figure 2) and expected to obtain valuable insight into the various patterns of homo- and heteronuclear coupling constants by subsequent analysis of NMR in combination with X-ray crystallographic data. Thus, it was anticipated that the various patterns found in naturally occurring chlorosulfolipids as well as non-natural permutations would be represented in the database (Figure 2).

Synthesis of Diastereomeric 4,5-Dichloro-2-epoxyhexane-1-ols. Diastereomeric epoxides **14** and **15** were synthesized according to a published procedure[11] starting from commercially available ethyl sorbate (**11**) (Scheme 1), involving dichlorination, DIBAL reduction, and subsequent epoxidation of the resulting allylic alcohol **13**. Epoxides **19** and **20**, possessing a *syn* relative configuration between the vicinal dichlorides, were prepared in an overall similar fashion, starting with the selective epoxidation of ethyl sorbate (**11**) with *m*-CPBA (96% yield). Subsequent epoxide opening with TMS-Cl[25] in the allylic position led to chlorohydrins **16** in 82% yield. Displacement of the alcohol under Appel conditions (PPh_3, CCl_4) led to the corresponding dichloroester together with the eliminated $\alpha,\beta,\gamma,\delta$-unsaturated ester as the major byproduct. The purification was significantly simplified by reduction of this intermediate with DIBAL and subsequent protection of the resulting allylic alcohol as a TBS ether. Through the implementation of this strategy, TBS-ether **17** could be obtained in 27% yield over three steps, starting from chlorohydrins **16**. Deprotection with CSA in MeOH gave allylic alcohol **18** in 96% yield; subsequent epoxidation with *m*-CPBA furnished epoxides **19** and **20** in 33% and 58% yield, respectively.

The *cis*-epoxy alcohols **24**, **25**, **28**, and **29** were prepared from TBS-ethers **21** and **17** employing a sequence involving dihydroxylation and cyclodehydration. Thus, treatment of the starting diols with triflic anhydride and DABCO led to the formation of the TBS-protected *cis*-epoxy alcohols, and subsequent acidic methanolysis (Scheme 2) afforded the targeted epoxides. It is interesting to note that for the cases we have examined triflate formation occurs exclusively at the C-2 alcohol, farthest removed from the chlorides, leading to the formation of a single epoxide by in situ cyclization. Preparation of **24** was achieved following this strategy according to a published procedure;[11] **25** could be obtained accordingly, starting from the minor diastereomer of the dihydroxylation of **21**. In a similar fashion, **29** could be isolated from **17** in a three-step sequence, employing dihydroxylation (OsO_4 and NMO) and subsequent epoxide formation (Tf_2O, DABCO) and deprotection (MeOH, cat. CSA). Unfortunately, a dr of 7/1 in the dihydroxylation of **17** in favor of **27** precluded the isolation of sufficient amounts of diasteromer **26** at this point. However, Sharpless dihydroxylation conditions employing ADMix β led to a diastereomeric ratio of 1.8/1 (**27**/**26**), which enabled the isolation of the enantiomerically enriched diol **26** as well. Transformation of **26** into **28** was achieved in

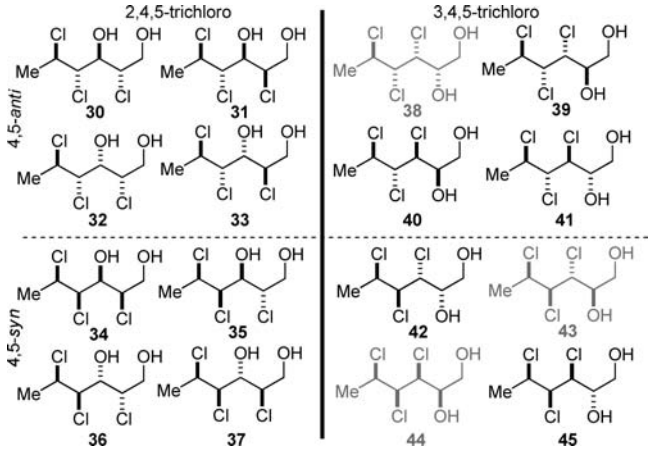
(25) Daviu, N.; Delgado, A.; Llebaria, A. *Synlett* **1999**, *8*, 1243.

Scheme 2. Synthesis of Diastereomeric 4,5-Dichloro-2-*cis*-epoxyhexane-1-ols[a]



[a] Reagents and conditions: (a) TBS-Cl (1.2 equiv), imide (1.4 equiv), DCM, rt, 30 min, 87%, (b) OsO_4 (0.05 equiv), NMO (1.1 equiv), aq acetone (2/1), 0 °C to rt, 19 h; dihydroxylation of **21**: dr = 5.6/1, 68% **22**, 13% **23**; dihydroxylation of **17**: dr = 7/1, 64% **27**, (c) DABCO (3 equiv), Tf_2O (1.0 equiv), DCM, −78 °C to rt, for **22**: 75% (21% **22** recovered); for **23**: 77% (13% **23** recovered); for **26**: 77% (9% **26** recovered), for **27**: 69% (26% **27** recovered), (d) CSA (0.1 equiv), MeOH, rt, 98% **24**, 91% **25**, 83% **28**, 72% **29**, (e) AD-Mix β, $MeSO_2NH_2$ (1.0 equiv), 4 °C, 52.5 h, dr(**27**/**26**) = 1.8/1, 89% overall.

Chart 2. Fragments Prepared (Black) and Spectroscopically Examined in This Study



a similar manner to that previously discussed for the preparation of *cis*-epoxides.

Lewis-Acid-Mediated Epoxide Opening Reactions. A collection of trichloro-1,3-diols **30**−**37** as well as trichloro-1,2-diols **38**−**45**, displaying diverse stereochemical permutations, were prepared by treatment of epoxides **14/15**, **19/20**, **24/25**, and **28/29** with $ZrCl_4$[26] or $TiCl(OiPr)_4$.[27] Fortuitously the diol products proved in large part to be crystalline (Chart 2).[28] An overview of the structures generated in the course of the epoxide-opening reactions is given in Table 1.

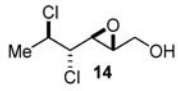
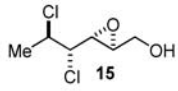
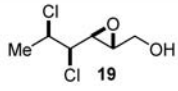
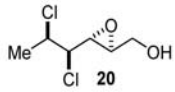
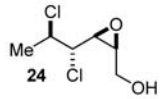
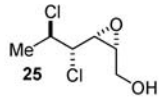
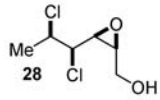
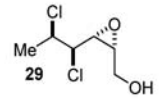
Several features of the ring-opening reactions are worth noting, as they collectively underscore some of the unique aspects of chlorosulfolipid chemistry. First, the regioselective opening of 4,5-dichloro-2-epoxyhexane-1-ols with $TiCl(OiPr)_3$ to give generally and preferentially 1,3-diol products stands in contrast to the observations with nonchlorinated epoxy alcohols.[27] Second, in a few cases analysis of the product revealed a surprising result (Scheme 3). For example, the use of 4,5-*syn* dichloride starting material **20** gives 1,2-diol **41**, displaying a 4,5-*anti* relative configuration. We speculate that anchimeric participation of chloride at C4 is responsible for this result. The manifestation of this effect was also observed during the preparation of diols **31/42** and **36/40** (Scheme 3). This finding as well as the previously reported retentive epoxide opening[11] has to be given careful consideration in future synthetic endeavors. It is interesting to note that the substrates that are observed to suffer chloride scrambling include both *trans*- and *cis*-substituted epoxides, as shown for **20**, **24**, and **29**. However, in order to account for the stereochemical observations, both epoxide types would lead to a putative epichloronium ion that is *trans*-substituted as shown for **46** (and not *cis*). Thus, the ability to access the *trans*-substituted ionic intermediate appears to be a necessary condition for the manifestation of anchimeric assistance by chloride. However, why it is that only a subset of *trans*-substituted epoxides undergoes such scrambling remains unclear.

NMR Spectroscopic Analysis. All epoxide-opening products were spectroscopically analyzed using HSQC-HECADE,[23,24] refocused phase-sensitive HMBC[16,29,30] and NOESY experiments. An overview of the extracted data for all compounds is found in Table 2.

For most 1,2- and 1,3-diols, the data were interpreted as the existence of one predominating conformer in solution. Frequently, this is already evident from the ^3J(H,H) coupling constants, which are either small (1−3.5 Hz), indicating a *gauche*-conformation, or large (7.5−10.5 Hz), indicating an *anti*-conformation. A graphical overview of the coupling constant

(26) Sarabia, F.; Sánchez-Ruiz, A. *Tetrahedron Lett.* **2005**, *46*, 1131.
(27) Raifeld, Y. E.; Nikitenko, A. A.; Arshava, B. M. *Tetrahedron: Asymmetry* **1991**, *2*, 1083.
(28) CCDC 725274−725284 contain the supplementary crystallographic data (11 structures) for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. Two additional X-ray structures were previously reported by us; see ref 11.
(29) Zhu, G.; Bax, A. *J. Magn. Reson.* **1993**, *104A*, 353.
(30) The applied sequence is a modified version of the one described in: Cicero, D. O.; Barbato, G.; Bazzo, R. *J. Magn. Reson.* **2001**, *148*, 209.

Table 1. Overview of the Products Obtained by Epoxide Opening

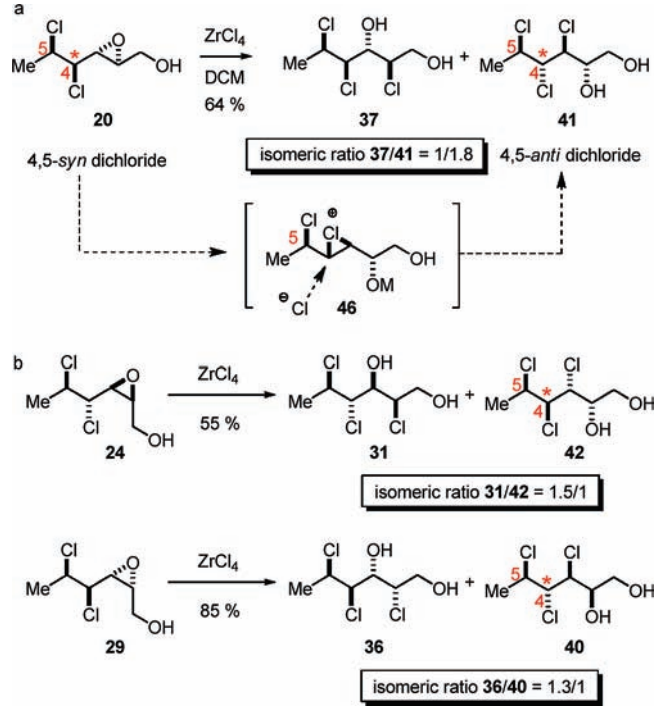
Substrate	Lewis Acid [a]	1,3-diol (%) [b]	1,2-diol (%) [b]
 **14**	$TiCl(OiPr)_3$	63 % (**30**)	12 % (**39**)
	$ZrCl_4$	18 % (**30**)	50 % (**39**)
 **15**	$TiCl(OiPr)_3$	87 % (**33**)	-
	$ZrCl_4$	75 % (**33**) [c]	12 % (**41**) [c]
 **19**	$TiCl(OiPr)_3$	90 % (**35**)	-
	$ZrCl_4$	70 % (**35**)	9 %, 2 % [d]
 **20**	$TiCl(OiPr)_3$	82 % (**37**)	13 % (**45**)
	$ZrCl_4$	23 % (**37**)	41 % (**41**)
 **24**	$TiCl(OiPr)_3$	38 % (**31**) [c,e]	[e]
	$ZrCl_4$	29 % (**31**) [c]	26 % (**42**)
 **25**	$TiCl(OiPr)_3$	76 % (**32**)	-
	$ZrCl_4$	73 % (**32**)	-
 **28**	$TiCl(OiPr)_3$ [f]	70 % (**34**) [c]	-
	$ZrCl_4$ [f]	78 % (**34**)	-
 **29**	$TiCl(OiPr)_3$	70 % (**36**) [g]	-
	$ZrCl_4$	48 % (**36**)	37 % (**40**) [c]

[a] Conditions: $ZrCl_4$ (1.2 equiv), CH_2Cl_2, 0 °C to rt, or $TiCl(OiPr)_3$ (1.5−2.0 equiv), C_6H_6, rt. [b] Isolated yields, unless stated otherwise. [c] Determined by ^1H NMR after chromatographic purification of the crude product. See Supporting Information for details. [d] Two 1,2-diols in 2% and 9% yield isolated. [e] The 1,3-diol was obtained as a mixture with another isomer (ratio 1.4/1, 65% overall yield). Another 9% of an inseparable isomeric mixture was obtained. [f] Diastereomeric purity of the starting material: dr(**28**/**29**) = 8/1. [g] Another 13% of a 1,3-diol resulting from epoxide opening with isopropoxide was isolated. See Supporting Information for details.

patterns of Table 2 for these trichlorohexanediols together with the conformers that can be correlated with them is given in Figure 3. Interestingly, for *syn*-configured stereogenic centers, only one of the two possible *gauche*-conformations was observed (see Figure 3, *threo I*). However, a detailed analysis of the coupling constant patterns (Table 2) suggests that in a few cases the data are best interpreted to arise from the presence of conformational equilibria along specific bond axes interconnecting two stereogenic centers,[15] such as, C2−C3 in diol **30**, C4−C5 in diol **35**, and C3−C4 as well as C4−C5 in diol **41**.

In diol **30**, the medium-sized value of ^3J(H3,H4) (+4.3 Hz) together with the small value of ^3J(H2,C4) (+1.4 Hz) and medium-sized value of ^2J(H3,C2) (−1.8 Hz) indicates an equilibrium between *erythro II* and *erythro III*. Similar consid-

Scheme 3. Inversion at C4 during Epoxide Opening with $ZrCl_4$: (a) Mechanistic Proposal for the Opening of Epoxide **20**; (b) Opening of Epoxides **24** and **29** [a]

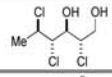
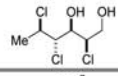
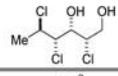
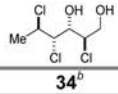
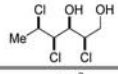
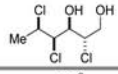
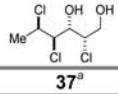
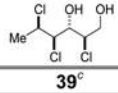
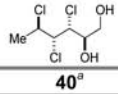
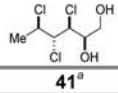
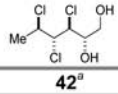
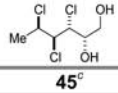
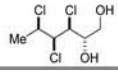


[a] Reagents and conditions: $ZrCl_4$ (1.2 equiv), DCM, 0 °C to rt. Yields of **31** and **40** determined by ^1H NMR.

erations for the coupling constant pattern between C4 and C5 in diol **35** led to the conclusion that the medium-sized value of ^3J(H4,H5) (+5.8 Hz) in combination with the relevant ^3J(H,C) coupling constants of 2.8 Hz (small) and 3.2 Hz (small/medium) and ^2J(H,C) coupling constants of −3.6 Hz (medium/large) and −2.9 Hz (medium) can be interpreted as an equilibrium between conformers *threo I* and *threo II*. The data obtained for diol **41** are interpreted in the same way. Although the conformation along the C2−C3 axis seems to be predominantly *erythro III* (a more detailed analysis of the coupling constant pattern might suggest the presence of conformer *erythro II* as a minor equilibrium component), the existence of a conformational equilibrium along the C3−C4 bond seems likely, as evident when considering the medium-sized ^3J(H3,H4) coupling constant (+4.3 Hz). The pattern of this homonuclear coupling constant in combination with the ^3J(H3,C5) and ^3J(H4,C2) values (+2.2 Hz, small, and +3.0 Hz, small/medium, respectively) and the medium-sized and large ^2J(H3,C4) and ^2J(H4,C3) values (−1.1 and −4.2 Hz, respectively) would follow from conformational equilibrium between conformers *erythro II* (major) and *erythro III* (minor). Finally, a conformer that orients the two protons of C4 and C5 in an antiperiplanar arrangement seems to prevail in solution, as indicated by the large value of ^3J(H3,H4) (8.0 Hz), corresponding to conformation *erythro III*. However, the medium-sized value for the heteronuclear coupling between H5 and C4 (−2.4 Hz) seems to be somewhat unusual for this conformation. In combination with the medium-sized value of ^3J(H4,C6) (+3.3 Hz), we therefore conclude that these data could indicate an equilibrium between *erythro III* (major) and *erythro I* (minor).

The NMR-spectroscopic data obtained (Table 2, Figure 3) can be correlated with the predominant conformation of the trichlorinated diols in solution and compared with their solid

Table 2. Homo- and Heteronuclear Coupling Constants for Diols **30**−**37**, **39**−**42**, and **45**

Compound	Relative Configuration/ Relevant Coupling Constants	C2-C3 (x=2, y=3)	C3-C4 (x=3, y=4)	C4-C5 (x=4, y=5)
30[a]	Relative Configuration	*erythro*	*erythro*	*erythro*
	$^3J(H_x,H_y)$	+4.3	+8.1	+3.8
	$^3J(H_x,C_{(y+1)})$ / $^3J(H_y, C_{(x-1)})$	+1.4 / *nd*	*nd* / +2.0	+4.1 / +1.5
	$^2J(H_x,C_y)$ / $^2J(H_y,C_x)$	-1.8 / *nd*	-3.1 / -3.6	-4.7 / 0.0
31[a]	Relative Configuration	*threo*	*erythro*	*erythro*
	$^3J(H_x,H_y)$	*nd*	9.9[f]	+2.6
	$^3J(H_x,C_{(y+1)})$ / $^3J(H_y, C_{(x-1)})$	1.3[d] / *nd*	*nd* / 3.1[d]	+4.6 / +1.8
	$^2J(H_x,C_y)$ / $^2J(H_y,C_x)$	-0.6 / *nd*	*nd* / -4.7	-4.2 / 1.8[d]
32[a]	Relative Configuration	*threo*	*threo*	*erythro*
	$^3J(H_x,H_y)$	+ 7.7[e]	+2.2	+9.1
	$^3J(H_x,C_{(y+1)})$ / $^3J(H_y, C_{(x-1)})$	2.2[d] / +1.6	1.9[d] / +1.0	+2.9 / +1.8
	$^2J(H_x,C_y)$ / $^2J(H_y,C_x)$	-4.1 / -4.0	1.5[d] / +0.6	-5.2 / -3.6
33[a]	Relative Configuration	*erythro*	*threo*	*erythro*
	$^3J(H_x,H_y)$	+9.4	+1.2	+10.0
	$^3J(H_x,C_{(y+1)})$ / $^3J(H_y, C_{(x-1)})$	2.0[d] / +2.5	1.9[d] / 1.0[d]	+2.3 / 2.4[d]
	$^2J(H_x,C_y)$ / $^2J(H_y,C_x)$	-4.5 / -4.5	4.1[d] / 2.3[d]	4.2[d] / -6.0
34[b]	Relative Configuration	*threo*	*threo*	*threo*
	$^3J(H_x,H_y)$	+2.8	+7.0[e]	+3.1
	$^3J(H_x,C_{(y+1)})$ / $^3J(H_y, C_{(x-1)})$	1.6[d] / *nd*	0.0[d] / 1.7[d]	+1.9 / +1.3
	$^2J(H_x,C_y)$ / $^2J(H_y,C_x)$	0.0 / *nd*	-4.5 / -5.0	+0.8 / 0.9[d]
35[a]	Relative Configuration	*erythro*	*threo*	*threo*
	$^3J(H_x,H_y)$	+8.9[g]	+1.4	+5.8
	$^3J(H_x,C_{(y+1)})$ / $^3J(H_y, C_{(x-1)})$	2.1[d] / *nd*	*nd* / 1.4[d]	+2.8 / 3.2[d]
	$^2J(H_x,C_y)$ / $^2J(H_y,C_x)$	-3.8 / *nd*	*nd* / +0.7	-3.6 / -2.9
36[c]	Relative Configuration	*threo*	*erythro*	*threo*
	$^3J(H_x,H_y)$	+1.2	+9.5[f]	+1.6
	$^3J(H_x,C_{(y+1)})$ / $^3J(H_y, C_{(x-1)})$	+1.0 / 2.0[d]	1.9[d] / 2.4[d]	+1.5 / +0.4
	$^2J(H_x,C_y)$ / $^2J(H_y,C_x)$	+0.7 / +2.6	4.5[d] / 5.3[d]	+3.4 / +2.0
37[a]	Relative Configuration	*erythro*	*erythro*	*threo*
	$^3J(H_x,H_y)$	+2.8	+9.6	+1.8
	$^3J(H_x,C_{(y+1)})$ / $^3J(H_y, C_{(x-1)})$	+1.1 / +3.9	*nd* / 2.1[d]	+1.5 / +1.3
	$^2J(H_x,C_y)$ / $^2J(H_y,C_x)$	-0.9 / -3.9	-4.2 / -3.9	+2.9 / +1.7
39[c]	Relative Configuration	*erythro*	*threo*	*erythro*
	$^3J(H_x,H_y)$	+9.2[h]	+1.6	+10.3
	$^3J(H_x,C_{(y+1)})$ / $^3J(H_y, C_{(x-1)})$	*nd* / +3.1	0.0[d] / 1.4[d]	+2.5 / 2.3[d]
	$^2J(H_x,C_y)$ / $^2J(H_y,C_x)$	*nd* / -5.1	2.5[d] / +2.0	-4.6 / -5.2
40[a]	Relative Configuration	*threo*	*erythro*	*erythro*
	$^3J(H_x,H_y)$	+1.5	+10.4	+2.8
	$^3J(H_x,C_{(y+1)})$ / $^3J(H_y, C_{(x-1)})$	*nd* / 1.6[d]	2.0[d] / 2.6[d]	+4.5 / +1.2
	$^2J(H_x,C_y)$ / $^2J(H_y,C_x)$	*nd* / 0.0	-4.5 / -5.1	-4.8 / +1.5
41[a]	Relative Configuration	*erythro*	*erythro*	*erythro*
	$^3J(H_x,H_y)$	+7.7	+4.3	+8.0
	$^3J(H_x,C_{(y+1)})$ / $^3J(H_y, C_{(x-1)})$	*nd* / +3.6	2.2[d] / +3.0	+3.3 / +2.0
	$^2J(H_x,C_y)$ / $^2J(H_y,C_x)$	-3.3 / -4.3	-1.1 / -4.2	-5.4 / -2.4
42[a]	Relative Configuration	*threo*	*erythro*	*threo*
	$^3J(H_x,H_y)$	+1.0	+10.3	+1.4
	$^3J(H_x,C_{(y+1)})$ / $^3J(H_y, C_{(x-1)})$	<2[i] / <2[i]	*nd* / *nd*	+1.2 / <1.5[d]
	$^2J(H_x,C_y)$ / $^2J(H_y,C_x)$	nd / 3.5[d]	-6.4 / -6.7	1.5[d] / *nd*
45[c]	Relative Configuration	*erythro*	*threo*	*threo*
	$^3J(H_x,H_y)$	+8.7[h]	+2.2	+8.3[e]
	$^3J(H_x,C_{(y+1)})$ / $^3J(H_y, C_{(x-1)})$	2.4[d] / +2.6	3.6[d] / +1.2	+1.9 / 1.5[d]
	$^2J(H_x,C_y)$ / $^2J(H_y,C_x)$	-4.0 / -5.2	2.0[d] / 1.9[d]	-4.5 / -4.8

[a] In $CDCl_3$. [b] In d_6-acetone. [c] In d_8-THF. [d] Determined by refocused PS-HMBC using a suitable coupling constant from the HSQC-HECADE spectrum as a reference value; sign of the coupling constant not determined. [e] NOESY cross-peak between H(x−1) and H(y+1). [f] NOESY cross-peak between H5 and H7. [g] NOESY cross-peak between H1 and H7. [h] No analysis of the NOESY possible due to signal overlap. [i] No HMBC cross-peak observed. Coupling constants (Hz) determined by HSQC-HECADE, unless otherwise noted. No relevant NOE for configurational assignment was observed unless stated. For numbering, see Figure 2. *nd* = not determined due to signal overlap or weak intensity of cross-peaks.

state conformation (Chart 3). Interestingly, in all but two cases, diols **32** and **41**, the solid-state conformation is identical to that observed in solution.

It is possible that the conformational discrepancy for diol **41** in the solid state and solution ($CDCl_3$) arises from the dependency of conformational equilibrium on the solvent used to acquire spectral data.[31] Hence, a full analysis of the homo- and heteronuclear coupling constants in CD_3OD and $(CD_3)_2SO$ was carried out for **41**. The data are summarized in Table 3 along with the measured coupling constants in $CDCl_3$.

Comparison of the data in different solvents is revealing. First, in the solvents examined, diol **41** exists as a mixture of

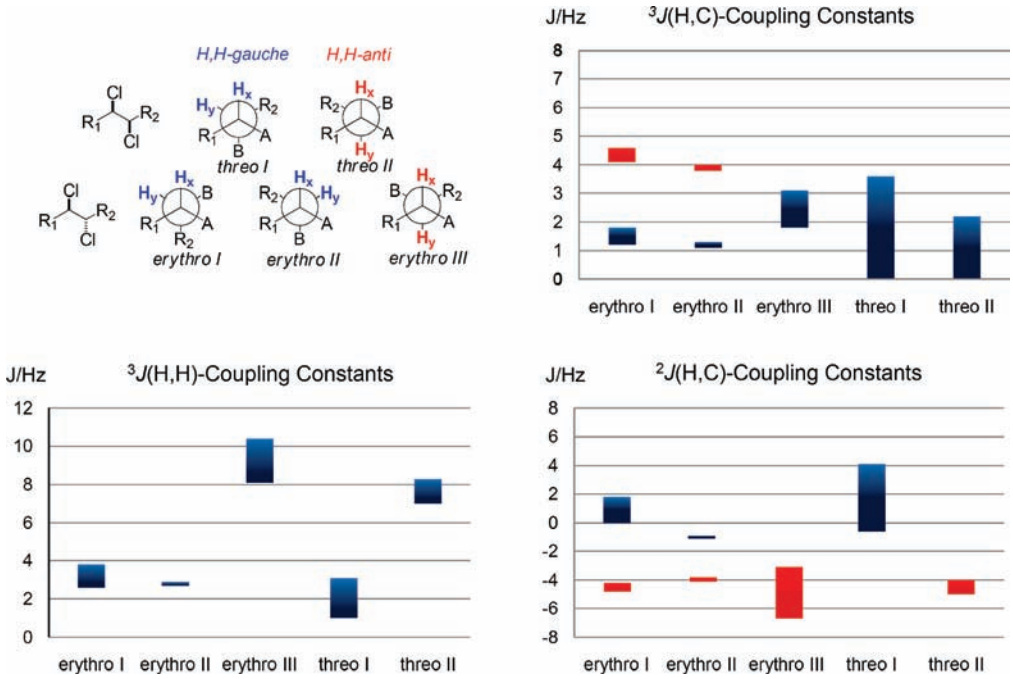


Figure 3. Overview of the *J* ranges as a function of conformation. For the heteronuclear (C,H) coupling constants, the blue and red bars represent the range for small and large *J*'s, respectively. A, B = Cl, Cl or Cl, OH. Conformational equilibria (diol **30**, C2−C3; diol **35**, C4−C5; and diol **41**) were not considered in the presentation of the data; however, for a thorough discussion see text.

conformers in equilibrium, with the contributing conformers the same in all solvents, i.e., *erythro II*/*erythro III* for C2−C3 as well as C3−C4 and *erythro I*/*erythro III* for C4−C5. Second, the ^3J(H,H) coupling constants were observed to be different in $CDCl_3$, CD_3OD, and $(CD_3)_2SO$. For instance, while for C4−C5 *erythro III*, with an antiperiplanar H,H arrangement seems to be favored in $CDCl_3$, the ratio of *erythro I* (gauche H,H arrangement)/*erythro III* (antiperiplanar H,H arrangement) is increased in both deuterated methanol and DMSO. This indicates that the extent of participation by a given conformer in the corresponding equilibrium is solvent dependent. The solvent dependency of dipole interactions in chlorinated hydrocarbons that might be responsible for the latter observation is discussed below.

Discussion

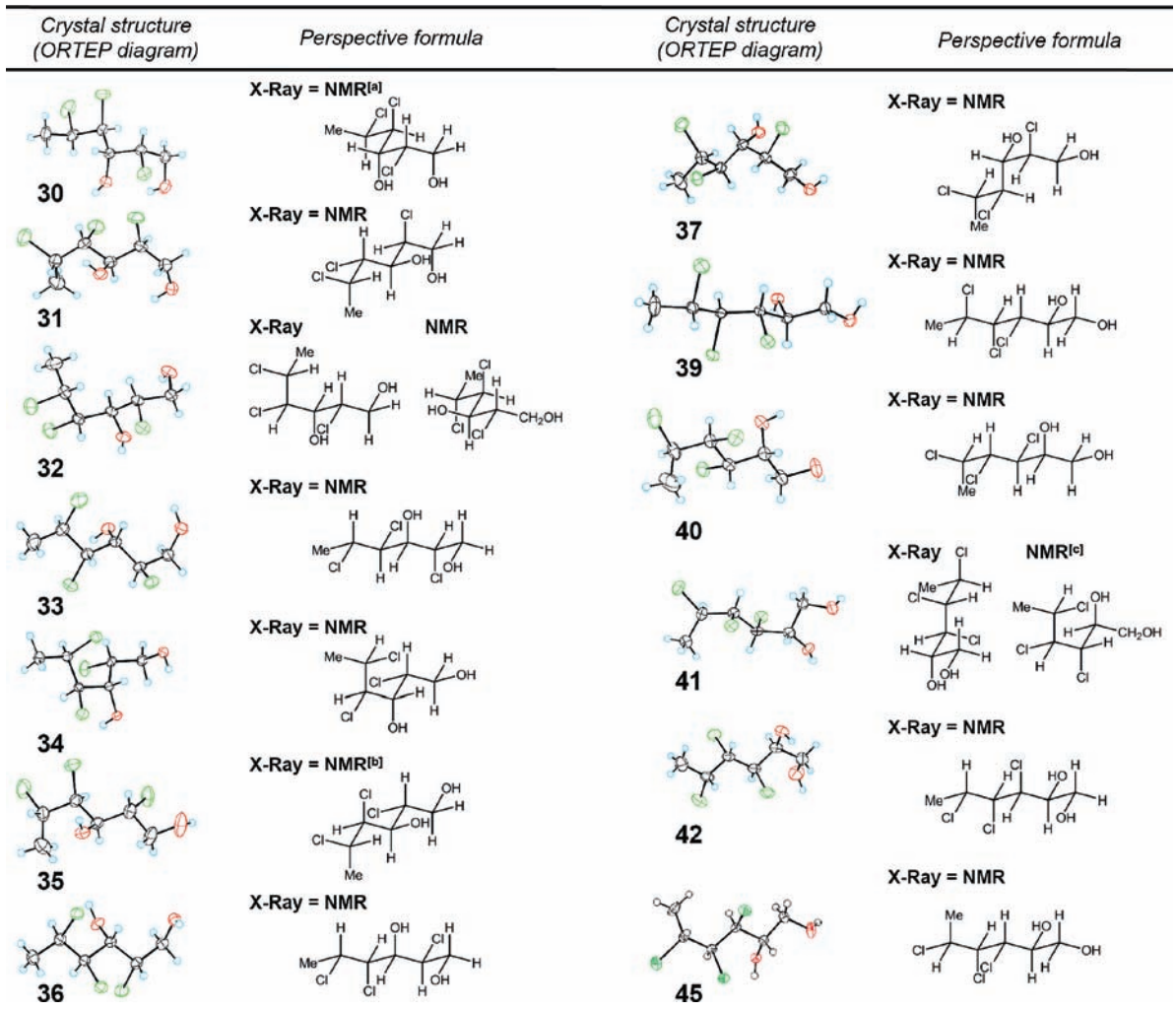
Validation of the *J*-Based-Configuration Analysis Method for Polychlorinated Systems. Collectively the results support the notion that *J*-based configuration analysis can be applied to 1,2-dichlorinated systems and chlorohydrins, although the ranges of the coupling constants have to be adjusted from those for dioxygenated counterparts. The generalized ranges for the relevant homo- and heteronuclear coupling constants are given in Figure 4. Nonetheless, the ^2J(H,C) coupling constants that are classified as "small" in Murata's terminology[15] are in general found in a range −0.5 to +4.0 Hz for the chlorinated arrays. This highlights that the sign of the ^2J(H,C) coupling constant might be of greater importance for 1,2-dichlorinated than for the corresponding dioxygenated systems, because the corresponding "large" coupling constants for polychlorinated systems can have values of similar magnitude but opposite sign. Additionally, the ^3J(H,C) coupling constants for a H,C *anti*-conformation (+4.0 to +5.0 Hz) are below the range that is reported for dioxygenated systems (+5 to +7 Hz).[15] Consequently, the difference in value between a "small" and a "large" ^3J(H,C) coupling constant can actually be rather minuscule. It is therefore important to point out that although for some cases any one ^3J(H,C) coupling constant used alone may be insufficient for unambiguous assignment of *gauche* or *anti* H,C arrangement, collectively the overall pattern of all relevant homo- and heteronuclear coupling constants is unambiguous.

It is noteworthy that the *J*-based configuration analysis method relies on NOEs to distinguish the *anti*-conformations of *erythro*- and *threo*-configured vicinal stereocenters. In the case of *erythro*-configured stereogenic centers C_x and C_y, two key observations may be expected: (1) the absence of an NOE between H_{x-1} and H_{y+1} and (2) an NOE between H_{x-1} or H_{y+1} and the OH at C_y or C_x, respectively.[15] In our experiments (Table 2), we noticed that the latter NOEs are sometimes weak or even absent.

As one example, analysis of 1,3-diol **36** showcases the utility of the data (Table 2). All coupling constants relevant to the configuration at C2 and C3 for **36** are small. This is in agreement with conformer *threo I* in Figure 3 and thus indicates a *syn*-relationship. For elucidation of the relative configuration at C3 and C4, additional NOE data are required because both *threo* II and *erythro* III display large ^3J(H,H) and ^2J(H,C) coupling constants, and both relevant ^3J(H,C) coupling constants are small. In the experiments, the absence of an NOE between H2 and H5 in combination with the observed NOE between H5 and H7 imply a C3−C4 *anti*-configuration. This corresponds to conformer *erythro III* (Figure 3). Finally, the coupling constant pattern for the C4−C5 axis resembles the one discussed above for the C2−C3 axis and hence can be interpreted as

(31) In this respect, it is worth noting that the data for **41** in Table 2 were collected in a halogenated solvent ($CDCl_3$). This raises the intriguing possibility that intermolecular halogen interactions with the solvent might influence the conformational profile in solution. Consequently, spectral measurements in various non-chlorinated solvents were collected for comparison purposes. We are grateful to a referee for this suggestion.

Chart 3. Comparison of the X-ray Structures of Diols **30**−**37**, **39**−**42**, and **45** with the Predominant Conformation in Solution Determined by *J*-Based Configuration Analysis



For diols **37** and **42**, two structures were found in the asymmetric unit, which do not significantly differ in the conformation between the stereogenic centers, and only one is depicted in each case. See Supporting Information for details. Solvents for the NMR analysis are given in Table 2. [a]Conformational equilibrium between C2 and C3, *erythro II*/*erythro III*, observed in solution. [b]Conformational equilibrium between C4 and C5, *threo I*/*threo II*, observed in solution. [c]Conformational equilibrium in solution observed, and only the major conformer is drawn. For a discussion of the conformations of diol **41**, see text.

Table 3. Homo- and Heteronuclear Coupling Constants for Diol **41** in $CDCl_3$, CD_3OD, and $(CD_3)_2SO$[a]

solvent	relevant coupling constants	C2−C3 (x=2, y=3)	C3−C4 (x=3, y=4)	C4−C5 (x=4, y=5)
$CDCl_3$	$^3J(H_x,H_y)$	+7.7	+4.3	+8.0
	$^3J(H_x,C_{(y+1)})/^3J(H_y,C_{(x-1)})$	*nd*/+3.6	2.2[b]/+3.0	+3.3/+2.0
	$^2J(H_x,C_y)/^2J(H_y,C_x)$	−3.3/−4.3	−1.1/−4.2	−5.4/−2.4
CD_3OD	$^3J(H_x,H_y)$	+6.6	+5.5	+6.4
	$^3J(H_x,C_{(y+1)})/^3J(H_y,C_{(x-1)})$	+1.6/+3.5	+3.0/+3.1	+3.3/+1.5
	$^2J(H_x,C_y)/^2J(H_y,C_x)$	−2.2/−4.5	−2.6/−4.3	−5.5/−1.2
$(CD_3)_2SO$	$^3J(H_x,H_y)$	+6.1	+6.1	+5.1
	$^3J(H_x,C_{(y+1)})/^3J(H_y,C_{(x-1)})$	+2.4/+3.8	+3.1/+2.9	+3.9/*nd*
	$^2J(H_x,C_y)/^2J(H_y,C_x)$	−1.1/−4.4	−3.0/−3.6	−4.0/*nd*

[a] Coupling constants (Hz) determined by HSQC-HECADE, unless otherwise noted. *nd* = not determined due to signal overlap or weak intensity of cross-peaks. [b] Determined by refocused PS-HMBC using a suitable coupling constant from the HSQC-HECADE spectrum as a reference value; sign of the coupling constant not determined.

arising from a *syn*-configuration. In Figure 3, conformer *threo I* would be in agreement with these data.[15]

There are a few cases where the magnitude of coupling constants is medium sized (see Table 2 and Chart 3), e.g., diol **35**, C4−C5, implicating a conformational equilibrium. In most cases it is possible to recognize these by the ^3J(H,H) value in the range 4−7 Hz. However, as shown by Murata[15] for dioxygenated systems, if the equilibrium consists of only two major conformers, the *J*-based configuration analysis method can still be applied; the coupling patterns in these cases then result from a weighted average of the coupling constants of the conformers involved in the equilibrium. This holds true for chlorinated systems as well, and the coupling constant pattern for the C4−C5 axis in diol **35** can be interpreted as an equilibrium between the conformers *threo I* and *threo II*.

Comparison of the Universal Database Approach and the *J*-Based Configuration Analysis Method. It is important to differentiate between and contrast the configurational analysis method described herein based on Murata's approach and the complementary one involving a universal database of vicinal H−H coupling constants.[19−21] One ^3J-coupling constant be-

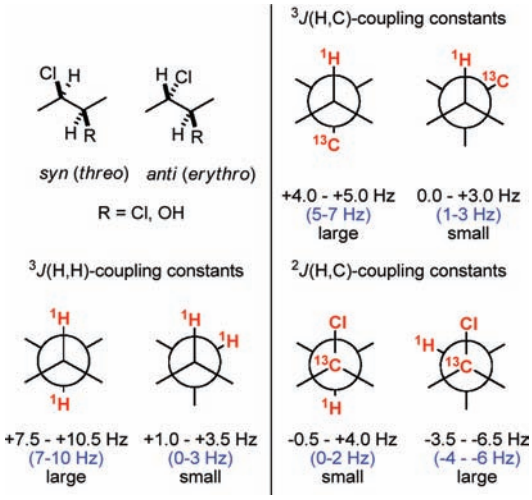


Figure 4. Generalized homo- and heteronuclear coupling constants for vicinal dichlorides and chlorohydrins as a function of the dihedral angle. The values in parentheses constitute the ranges for dioxygenated systems reported by Murata.[15]

tween protons located at neighboring stereogenic centers per se provides no information about the relative configuration at the proton-bearing carbons (for example compare in Figure 3 *threo I* and *erythro I*). The power of Kishi's insightful approach relies on the configuration-dependent conformational propensity of a chain of carbon atoms in a specific class of natural products, such as polyketides, defined by a set of juxtaposed functional groups. Accordingly, the members of the database have to sample the configuration-dependent conformational characteristics of a given class of molecules. In Murata's method the relative configuration is determined directly by making use of the conformation-dependence of homo- and heteronuclear coupling constants in combination with NOEs. Consequently, in Murata's approach the knowledge of typical coupling constants for staggered conformations of a given vicinal array of functional groups is essential for calibration purposes (cf. Figure 1).

It is straightforward to create coupling constant profiles with the data from Table 2. However, it is important to note that in such a case immediate use of ^3J (H,H) coupling constant profiles following a universal database approach[19,20] requires caution, because hexanediols with a methyl group and hydroxymethyl group at the ends of the backbone might not necessarily represent the conformational characteristics of similar compounds terminated by longer hydrocarbon chains. By contrast, even if a configurationally unassigned unknown chlorinated compound adopts a conformation different from a chosen trichlorinated hexane-1,2- and -1,3-diol model system, the *J*-based configuration analysis method is still expected to reveal the predominant conformation or a conformational equilibrium unambiguously, allowing the facile determination of relative configuration. Consequently the *J*-based configurational analysis is expected to be a general and reliable method for the determination of relative configuration in acyclic polychlorinated and -oxygenated systems.

Conformational Analysis of Trichlorohexanediols. Examination of the solution and solid-state structures we have collected reveals that the dominant determinant of the preferred conformation is the minimization of unfavorable double *gauche*-

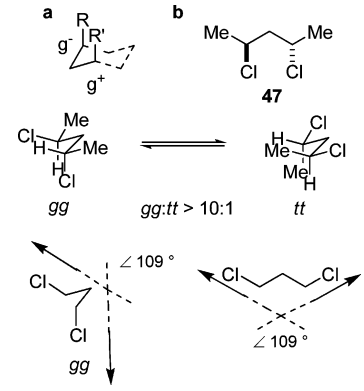


Figure 5. (a) Unfavorable *syn*-pentane interactions in acyclic systems. (b) Preferred conformation of (*RS*,*RS*)-2,4-dichloropentane (**47**) at room temperature in solution.[34]

pentane (*syn*-pentane) interactions.[32−34] It was noted by Hoffmann that the avoidance of *syn*-pentane interactions of methyl groups along a hydrocarbon chain seems to be one of the two major principles that nature uses to destabilize undesired conformations.[32] In this regard, Hoffmann has discussed the conformational preferences of (*RS*,*RS*)-2,4-dichloropentane (**47**). In solution, it was observed by NMR to largely adopt two conformations, *gg* and *tt* (see Figure 5), in both of which *syn*-pentane Me ↔ Me and Cl ↔ Cl interactions are absent altogether. The preference of the *gg* over the *tt* conformer (*gg*/*tt* > 10/1) had been ascribed earlier to 1,3-dipole−dipole interactions.[35] However, it is noteworthy that straightforward calculation of the dipole[36] does not reveal any significant difference in the overall dipole itself for the two conformers: 3.2 D for the *gg* and 3.1 D for the *tt* conformer, respectively. This can be readily appreciated by considering the individual C−Cl dipole vectors and their relative orientation in each structure. Thus, the angle subtended by the C−Cl vectors in each molecule is identical (109°); the minuscule difference in the dipole moment arises from the fact that the sum of the other remaining vectors is not identical. It is likely that the energetic difference between the two conformers arises from the minimization of steric interactions in the *gg* conformer relative to the *tt* counterpart. This is best understood by considering the relative sizes of methyl and chloride groups, as manifest in their *A* values: Cl ($A_{value} = 0.6$) and Me ($A_{value} = 1.7$). Thus, although the van der Waals radius of chloride (1.8 Å)[37] is only slightly smaller than that of a methyl group (2.0 Å),[37] the longer C−Cl bond (1.8 Å) in comparison to the C−C bond (1.5 Å) results in a reduction of the effective size of chloride. The conformational data we have accumulated indicate that this effect, i.e. the avoidance of *syn*-pentane interactions, is also manifest in the more highly substituted systems that constitute the database. The preferences are surely relevant in any understanding of the conformation profile of chlorosulfolipids as it relates to their biology.

It is noteworthy that in vicinal dichloride systems stereoelectronic effects, i.e., the *gauche*-effect, is potentially an important

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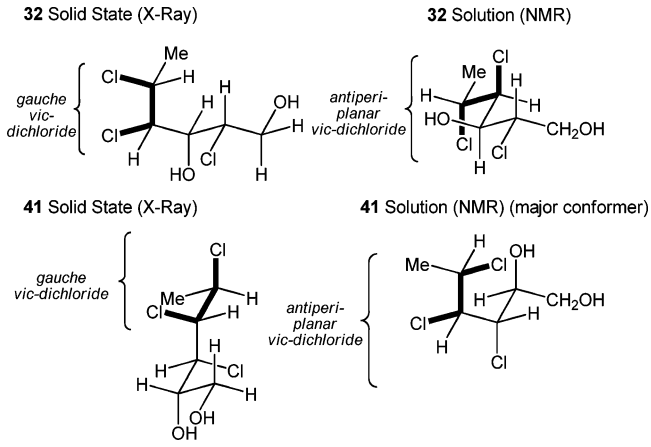


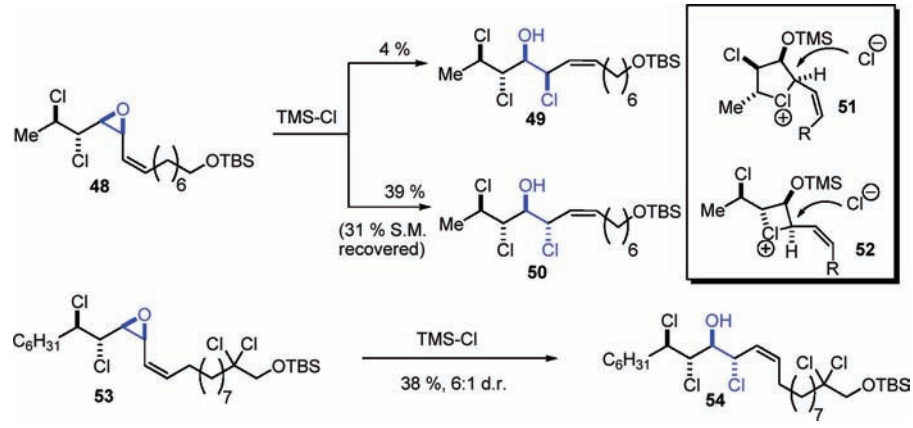
Figure 6. Comparison of the solid-state and solution structures ($CDCl_3$) of diols **32** and **41**.

consideration.[38] The *gauche*-effect has been defined as the tendency of acyclic systems vicinally substituted with electron-withdrawing substituents to adopt that structure which has the maximum number of *gauche*-interactions between the polar bonds.[38] Additionally, it is known that $\sigma_{C-H}-\sigma^*_{C-X}$ interactions can play an important role in conformations of chlorinated hydrocarbons.[39] For 1,2-dihalosubstituted ethanes the preferred conformations have been well studied, wherein it has been shown that *gauche*-conformations become increasingly favored along the series I < Br < Cl < F.[40] In 1,2-difluoroethane the *gauche*-conformation is preferred over the *anti*-conformation by about 0.6 kcal/mol.[41] However, in the case of 1,2-dichloroethane, the *anti*-conformer is preferred over the *gauche*-conformer by about 1.1 kcal/mol (gas phase),[42] which is a larger energy difference than in *n*-butane, with an *anti*/*gauche* energy difference along the C2−C3 bond of about 0.89 kcal/mol (gas phase).[43] The difference has been attributed to strong dipole−dipole repulsion of the C−Cl dipoles present in the *gauche*-conformer.[44] In solution, the importance of these dipole effects in $ClCH_2CH_2Cl$ decreases with increasing polarity of solvents, which is accompanied by an increase of the *gauche*/*anti* ratio in the conformational equilibrium.[44]

It is interesting to note that in the collection of trichlorodiols that were accessed and studied in the solid state and in solution in only two cases was a discrepancy observed, namely, **32** and **41** (Chart 2). Comparison of the solution and solid-state structure of **32** reveals some interesting features (Figure 6). The X-ray crystal structure for **32** displays $+g$ and $-g$ conformations about the C(4)−C(5) and C(3)−C(4) bond axes, respectively (Cl−C−C−Cl and Cl−C−C−OH dihedral angles = +60° and −60°). The corresponding solution structures differ in that the chlorides are antiperiplanar along the C(4)−C(5) (*t* conformation, Cl−C−C−Cl dihedral angle = 180°) and $+g$ about C(3)−C(4). Neither conformer possesses overriding unfavorable double *gauche*-pentane interactions, and thus both represent energy minima in the conformational profile. It is interesting that the solution structure actually prefers to minimize dipole interactions at the expense of any stereoelectronic gains, i.e., the *gauche*-effect. The discrepancy that arises between solution and solid-state conformations for **41** is difficult to rationalize. The solid-state structure clearly is a minimum that is lacking any obvious energetic penalty. The analysis of coupling constants for **41** reveals an unusual circumstance in which a conformational equilibrium seems to appear in solution. The major conformer in this equilibrium is shown in Figure 6. It appears to incorporate the same conformational feature observed for **32**, in which the dipolar interactions are at a minimum for the *vic*-dichloride.

Significance of this Study for the Synthesis and Investigation of Polychlorinated Arrays. The value of the database developed can be appreciated when considering that anchimeric assistance by chloride can lead to unexpected stereochemical outcomes in various displacement reactions. In this regard, in the context of our reported synthesis of a chlorosulfolipid, we recently observed an intriguing epoxide-opening reaction that occurs with retention of configuration[11] (Scheme 4). Given the lack of a spectroscopic database for reliable configuration analysis of chlorinated systems at the time of the discovery, we became aware only after inadvertently preparing a diastereomer of the natural product **3**. Consequently, the fact that stereochemical scrambling had taken place only became clear after completion of the synthesis of an unnatural diastereomer. In the course of acquiring the database, we have noted additional examples wherein putative chloronium ion intermediates can interfere in the reaction pathway, leading to unexpected inversion of configuration in C−Cl moieties adjacent to the site undergoing substitution (Scheme 3). Had the database we document herein been available at that time, we would have had an immediate indication that the course of the epoxide-opening reactions had not proceeded with inversion by analysis of the signature coupling constants. For instance, comparison of the coupling constants (Table 2) between C4 and C5 of the two products obtained by opening of epoxy alcohol **29** (see Scheme 3) is clear. For **36** the pattern shows the typical signature of conformation *threo I* (Figure 3), i.e., *syn*-arrangement of the

Scheme 4. Examples of Anchimeric Assistance by Chloride Substitutents, Leading to Unexpected Stereochemical Outcomes[11,12]



two chloride substituents, while in the case of 1,2-diol **40** the coupling constants show all characteristics of conformation *erythro I* (Figure 3), consistent with the *anti*-arrangement of the two *vic*-chlorides. Altogether, the problems we encountered can now be safely circumvented in ongoing endeavors involving chlorosulfolipids by employing *J*-based configuration analysis afforded by the database. Thus, the database will prove critical in additional studies of this fascinating class of natural products.

Conclusion

In conclusion, we presented the first thorough investigation of *J*-based configuration analysis of chlorinated systems. During our studies we noted that some diastereomers of 4,5-dichloro-2,3-epoxyhexan-1-ols undergo opening ($ZrCl_4$) with inversion of configuration at C4−Cl adjacent to the center that itself undergoes nucleophilic attack. This is yet another unexpected result, which suggests that the intervention of three-membered chloronium ions may be common in these systems. Consequently, the observation of anchimeric participation in various displacement reactions underscores the need for the spectroscopic database in order to secure stereochemical assignment.

On the basis of our data it is now finally possible to verify the applicability of *J*-based configuration analysis to chlorinated systems and therefore, retrospectively, support the proposed configurations of chlorosulfolipids **1**,[12,13] **3**,[6] **4**,[7] and **5**.[8] The detailed set of reference values provided will also be of significance for further studies of acyclic polychlorinated natural products, as it now substantively allows the reliable spectroscopic determination of the relative configuration of acyclic chlorinated intermediates. Our results expand the NMR database for coupling constants and thus fill a previously existing gap.

Additionally, a detailed conformational analysis of various trichlorinated hexanediols was undertaken to further understand the conformational preferences of acyclic chlorinated entities. In this respect, the avoidance of unfavorable *syn*-pentane interactions was found to be the major conformation-determining factor. By far most of the model compounds we have prepared and analyzed display well-defined conformational energetic minima with only a few exceptions discussed above. Consequently, they would seem to be ideal candidates as templates at room temperature for conformational design.[32] Indeed it is likely the case that the conformation of the unusual chlorosulfolipids is correlated to their biological activity in the membrane. Hence, we anticipate that the database we have generated will be useful in understanding the conformational preferences of polychlorinated molecules and any further investigations concerning their mode of action.

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Supporting Information Available: Experimental procedures and characterization data (^{1}H NMR, ^{13}C NMR, IR, HRMS, melting points), ^{1}H and ^{13}C NMR spectra of all new compounds, *J*-based configuration analysis of **6**, and all crystallographic data are available free of charge via the Internet at http://pubs.acs.org.

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