JOC*Note*

Synthesis and Characterization of All Four Diastereomers of 3,4-Dichloro-2-pentanol, Motifs Relevant to the Chlorosulfolipids

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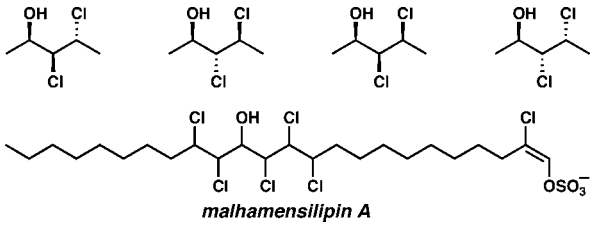

All four diastereomers of 3,4-dichloro-2-pentanol were synthesized by anti-dichlorination of the precursor allylic alcohols; their stereochemistry was elucidated by X-ray crystallographic analysis of tosylate derivatives. Complete NMR data is provided in the hope that this information will facilitate structural elucidation and synthesis studies on the chlorosulfolipid family of natural products, such as malhamensilipin A.

Databases of spectral information can be powerful tools for structural determination. For example, the Kishi group's NMR database for polyketide natural products[1] was developed by the independent synthesis of stereochemical motifs common to this important group and compilation of the NMR data for each. The advent of this data collection has enabled simplified protocols for the structure determination of newly discovered polyketides and synthetic fragments thereof.[2]

The chlorosulfolipids (**1**−**5**, Figure 1) are an unusual class of polychlorinated alkanes that represent particularly daunting challenges for chemical synthesis.[3] The obvious dearth of methodology for the stereocontrolled introduction of multiple chlorine atoms onto acyclic scaffolds poses a significant problem; however, the less obvious problem of stereochemical elucidation of these natural products and synthetic intermediates presents an equally important challenge. As part of our program targeting the chlorosulfolipids, we recently introduced a method for the stereoselective dichlorination of allylic alcohol derivatives to afford preferentially the *syn*,*syn* hydroxydichloride stereorelationship (**6** → **7**, eq 1).[4] Although the stereochemistry shown in Figure 1 for **1**−**3** had been elucidated using the powerful *J*-based configurational analysis of Murata,[3f,g,5] the accuracy of this method has not yet been validated in the context of polychlorinated compounds; therefore, we rigorously assigned the relative stereochemistry of our hydroxydichloride products by chemical manipulations that included epoxide- and pyran-forming schemes. To further solidify these and future stereochemical assignments, we describe in this Note the synthesis, spectroscopic characterization, and unambiguous structure determination by X-ray crystallography of the four diastereomeric hydroxychloride stereotriads on a minimal five-carbon chain. We hope that the data provided might enable stereochemical correlations by those who pursue the synthesis of the chlorosulfolipids. These data should certainly enable facile determination of the stereochemical outcomes of any allylic alcohol dichlorination reactions that are developed from this point on and could prove useful in the elucidation of the stereochemistry of chlorosulfolipids such as **4** and **5**.

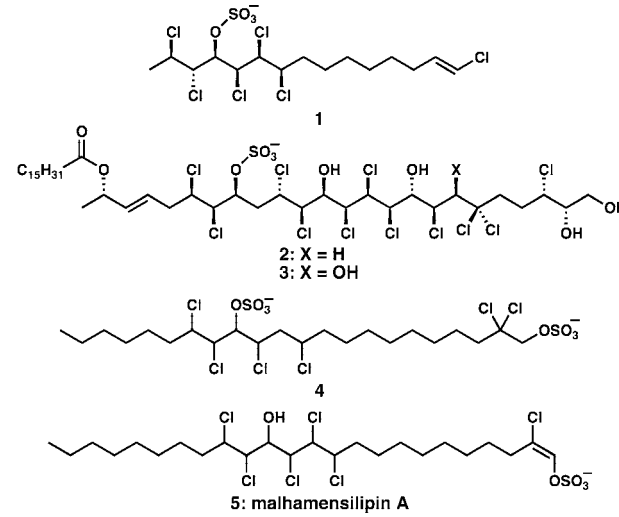

FIGURE 1. Unnamed chlorosulfolipids isolated from Adriatic mussels (**1**−**3**) and from freshwater algae (**4**) and algae-derived protein kinase inhibitor malhamensilipin A (**5**).

(1) (a) Kobayashi, Y.; Lee, J.; Tezuka, K.; Kishi, Y. *Org. Lett.* **1999**, *1*, 2177–2180. (b) Lee, J.; Kobayashi, Y.; Tezuka, K.; Kishi, Y. *Org. Lett.* **1999**, *1*, 2181–2184. (c) Kishi, Y. *Tetrahedron* **2002**, *58*, 6239–6258.

(2) For a recent review that emphasizes the NMR Universal Database, see: Bifulco, G.; Dambruoso, P.; Gomez-Paloma, L.; Riccio, R. *Chem. Rev.* **2007**, *107*, 3744–3779.

(3) (a) Elovson, J.; Vagelos, P. R. *Proc. Natl. Acad. Sci. U.S.A.* **1969**, *62*, 957–963. (b) Haines, T. H.; Pousada, M.; Stern, B.; Mayers, G. L. *Biochem. J.* **1969**, *113*, 565–566. (c) Elovson, J.; Vagelos, P. R. *Biochemistry* **1970**, *9*, 3110–3126. (d) Haines, T. H. In *Lipids and Biomembranes of Eukaryotic Microorganisms*; Erwin, J. A., Ed.; Academic Press: New York; 1973; pp 197−232. (e) Haines, T. H. *Annu. Rev. Microbiol.* **1973**, *27*, 403–412. (f) 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. (g) Ciminiello, P.; Fattorusso, E.; Forino, M.; Magno, S.; Di Rosa, M.; Ianaro, A.; Poletti, R. *J. Org. Chem.* **2001**, *66*, 578–582. (h) Ciminiello, P.; Dell'Aversano, C.; Fattorusso, E.; Forino, M.; Di Rosa, M.; Ianaro, A.; Poletti, R. *J. Am. Chem. Soc.* **2002**, *124*, 13114–13120. (i) Ciminiello, P.; Dell'Aversano, C.; Fattorusso, E.; Forino, M.; Magno, S. *Pure Appl. Chem.* **2003**, *75*, 325–336. (j) Ciminiello, P.; Dell'Aversano, C.; Fattorusso, E.; Forino, M.; Magno, S.; Di Meglio, P.; Ianaro, A.; Poletti, R. *Tetrahedron* **2004**, *60*, 7093–7098. (k) Ciminiello, P.; Fattorusso, E. *Eur. J. Org. Chem.* **2004**, 2533–2551.

(4) Shibuya, G. M.; Kanady, J. S.; Vanderwal, C. D. *J. Am. Chem. Soc.* **2008**, *130*, 12514–12518.

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

10.1021/jo802390e CCC: $40.75
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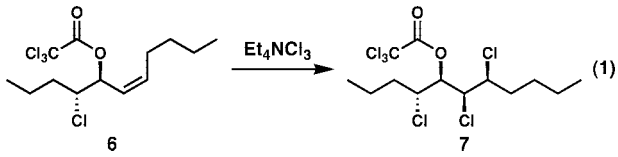
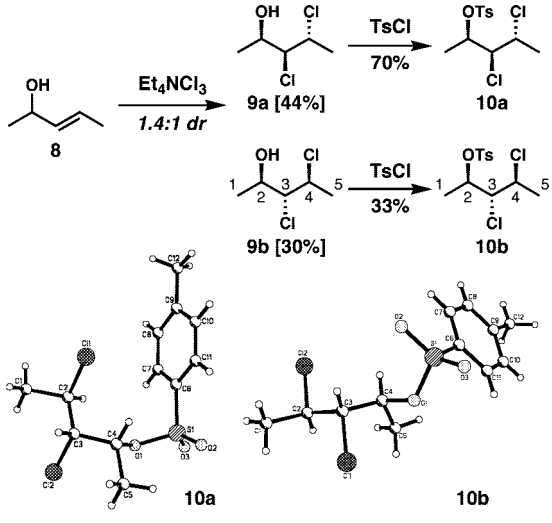


The chlorosulfolipids have never been crystallized, and di- and trichlorinated alkanes related to **7** are oils; these properties are likely the result of the long alkyl chains in each. We posited that the use of the minimal five-carbon chain (3,4-dichloropentan-2-ols) might best enable the generation of crystalline compounds. Derivatization of each diastereomer with groups known to impart crystallinity would then have the greatest chance of overriding any inherent lack of order of the hydroxydichloride-containing molecule. We were also inspired by a single report of the X-ray diffraction of the *p*-toluenesulfonate ester of one diastereomer of 3,4-dichloropentan-2-ol, though the crystal structure was not provided, nor were any characterization data.[6] That disclosure focused only on the vibrational spectra of one isomer of 2,3,4-trichloropentane, derived from the tosylate in question.

To access the *syn*,*anti* and *anti*,*anti* stereotriads, commercially available (*E*)-3-penten-2-ol (**8**) was dichlorinated (Scheme 1) with *anti* stereospecificity using the reagent pioneered by Mioskowski, Et_4NCl_3,[7] which serves as a bench-stable equivalent to chlorine. The resulting dichloroalcohol diastereomers **9a** and **9b** were separated by careful flash chromatography, and the individual isomers were converted into their corresponding tosylates, *p*-bromobenzoates, and *p*-nitrobenzoates. The tosylates (**10a** and **10b**) of both isomers readily provided crystals appropriate for X-ray diffraction analysis, and the resulting structures are shown in the scheme. The tosylate derived from the first eluting hydroxydichloride isomer (pentane/Et_2O on SiO_2) had *syn*,*anti* stereochemistry (**10a**), and that derived from the slower eluting isomer had *anti*,*anti* stereochemistry (**10b**).

SCHEME 1. Synthesis of *syn*,*anti* and *anti*,*anti* Dichlorotosylates



We knew from previous studies in our group that the separation of *syn*,*syn* and *anti*,*syn* hydroxydichloride diastereomers by silica gel chromatography was typically challenging but that the resulting TBS ethers were easily separable. Racemic (*Z*)-2-*tert*-butyldimethylsilyloxy-3-pentene (**11**) was prepared according to known protocols by addition of 1-propynylmagnesium bromide to acetaldehyde, followed by alkyne semireduction and silylation. As anticipated, the diastereomeric products of anti-dichlorination (**12a** and **12b**, Scheme 2) were readily isolated in stereoisomerically pure form following flash chromatography. No great effort was made to optimize silyl ether cleavage, which proceeded in low yield; nonetheless, significant quantities of each hydroxydichloride isomer were available for derivatization and crystallization studies. The tosylate **14a** of the slower eluting hydroxydichloride isomer **13a** was crystallized and shown to have *syn*,*syn* stereochemistry; several derivatives of the other isomer (**13b**) including the tosylate proved difficult to crystallize. However, by process of elimination, we had now secured the relative configurations of all of the diastereomers of 3,4-dichloropentan-2-ol. The complete proton and carbon NMR assignments can be found in Table 1.

SCHEME 2. Synthesis of *syn*,*syn* and *anti*,*syn* Dichlorotosylates

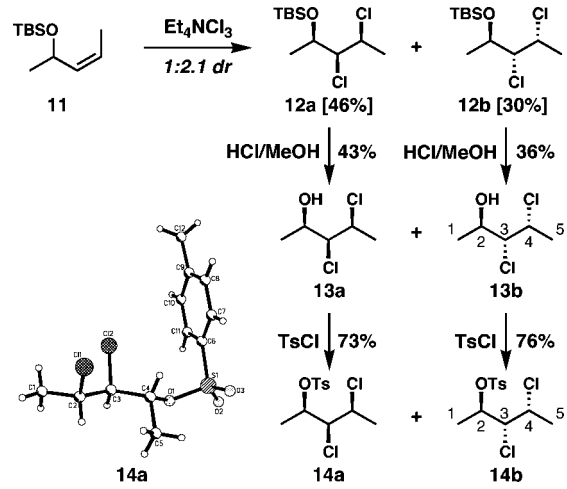


TABLE 1. ^1H and ^{13}C NMR Assignments for All Hydroxydichloride Stereotriads[a]

	H1 [C1]	H2 [C2]	H3 [C3]	H4 [C4]	H5 [C5]
9a	1.33 (d) *J* = 6.4 [21.2]	4.46 (m) [66.4]	3.82 (dd) *J* = 9.2, 2.0 [72.7]	4.29 (dq) *J* = 9.2, 6.6 [56.8]	1.70 (d) *J* = 6.6 [22.9]
9b	1.31 (d) *J* = 6.2 [17.8]	4.29 (m) [68.1]	4.09 (dd) *J* = 8.0, 4.7 [72.4]	4.16 (dq) *J* = 8.0, 6.4 [56.6]	1.68 (d) *J* = 6.4 [22.4]
13a	1.32 (d) *J* = 6.4 [20.0]	4.11 (m) [68.8]	3.86 (dd) *J* = 5.7, 3.7 [73.5]	4.31 (dq) *J* = 6.7, 3.7 [57.9]	1.65 (d) *J* = 6.8 [22.8]
13b	1.42 (d) *J* = 6.2 [20.8]	4.00 (m) [69.3]	3.71 (dd) *J* = 8.5, 2.4 [70.4]	4.69 (dq) *J* = 6.7, 2.4 [56.9]	1.62 (d) *J* = 6.7 [22.8]

[a] From COSY and HMQC experiments, $CDC1_3$, 500 MHz.

Selected ^1H NMR data for each tosylate are provided in Table 2. It is noteworthy that the coupling constants between the methine protons do not change dramatically upon introduction of the tosyl group onto the dichloroalcohols. It

(6) Chough, S. H.; Krimm, S. *Spectrochim. Acta* **1990**, *46A*, 1405–1418.
(7) Schlama, T.; Gabriel, K.; Gouverneur, V.; Mioskowski, C. *Angew. Chem., Int. Ed.* **1997**, *36*, 2341–2344.

TABLE 2. Selected ^{1}H NMR Data for Dichlorotosylates 10a, 10b, 14a, and 14b, Including Methine Methine Coupling Constants

	H2	H3	H4
10a	5.36 (dq) $J_{H2-H3} = 1.8$	3.73 (dd) $J_{H3-H4} = 9.7$	4.00 (dq)
10b	5.10 (dq) $J_{H2-H3} = 4.5$	4.07 (dd) $J_{H3-H4} = 8.3$	3.98 (dq)
14a	4.88 (dq) $J_{H2-H3} = 6.4$	3.89 (dd) $J_{H3-H4} = 3.6$	4.26 (dq)
14b	4.84 (dq) $J_{H2-H3} = 8.5$	3.86 (dd) $J_{H3-H4} = 1.5$	4.32 (dq)

is apparent from analysis of the coupling constant data that the solution conformations of these stereochemically rich small molecules are not all strongly biased toward single, low-energy conformations. While the coupling constants observed for **10a** and **14b** suggest the predominant population of a single low energy conformer for each molecule, the intermediate coupling constant values observed for **10b** and **14a** point to the absence of a single preferred conformation. From the perspective of using these stereotriads for prediction of stereochemistry of the chlorosulfolipids, this result is both surprising and unfortunate. For chlorosulfolipid **1**, coupling constants of the vicinal protons throughout the C9−C14 region are either very large (ca. 10 Hz) or very small (≤1.5 Hz),[3g] indicating a strong conformational preference for anti or gauche disposition of these protons, respectively (Figure 2). The stereotriads **14a** and **10b** that correspond to the C10−C12 and C12−C14 regions of chlorosulfolipid **1** (with the tosylate group representing a sulfate surrogate), respectively, are the ones for which the coupling constants are indicative of multiple low energy conformations; therefore, any hope of performing stereochemical elucidations of lipids **4** and **5** using this small database is unlikely. On the other hand, we have learned that *the high degree of conformational order that characterizes the chlorosulfolipids might only be possible when more than three contiguous stereogenic centers are present and working in concert.*

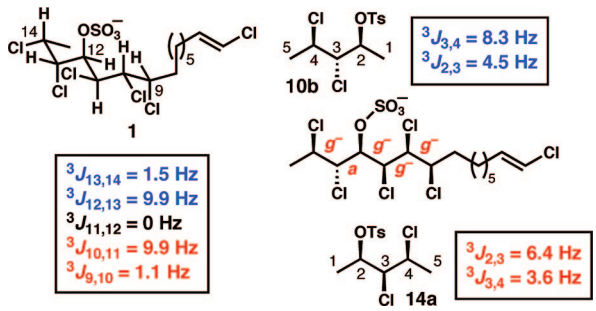
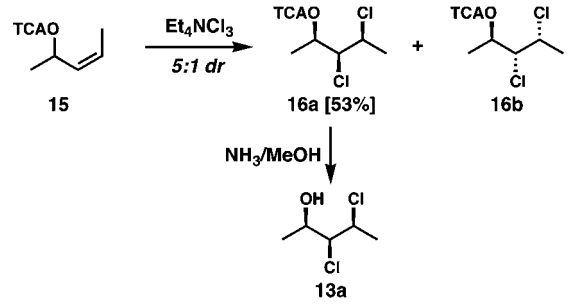


FIGURE 2. Comparison of the C10−C12 and C12−C14 regions of **1** with **10b** and **14a**, respectively. The simple stereotriads do not share the conformational characteristics of the complete lipid.

Nonetheless, this study had a second purpose, for which it is still useful. Syntheses of the chlorosulfolipids are likely to rely, at least in part, on stereoselective dichlorination reactions of allylic alcohols. Our database can be used to determine the stereochemical outcome of dichlorination reactions of chiral allylic alcohols by correlation. This idea is illustrated using our previously described method for stereoselective dichlorination of (*Z*)-allylic trichloroacetates,

SCHEME 3. Synthesis of 13a by Diastereoselective Dichlorination of (*Z*)-Allylic Trichloroacetate 15 (Unoptimized)



which was applied to five-carbon substrate **15** (Scheme 3). The major product of the 5:1 ratio that resulted, after cleavage of the trichloroacetate ester, was found to be identical with *syn*,*syn*-diastereomer **13a**, as expected on the basis of our previous studies.[4]

We hope that these data will enable correlation in the event that new methods for the stereoselective dichlorination of allylic alcohols are developed and that they will prove useful to other researchers engaged in studies toward the chlorosulfolipids.[8]

Experimental Section

(2*R,3*S**,4*R**)-3,4-Dichloropentan-2-ol (9a).** To a solution of (*E*)-3-penten-2-ol (1.5 g, 17 mmol) in CH_2Cl_2 (58 mL), was added Et_4NCl_3 (5.7 g, 24 mmol) at −78 °C. The mixture was stirred for 1.5 h as the temperature warmed to −40 °C. The reaction was quenched with a 1:1 solution of 10% aqueous $Na_2S_2O_3$/saturated aqueous $NaHCO_3$ (50 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 80 mL). The combined organic extracts were washed with brine (50 mL), dried with $MgSO_4$, and concentrated. ^{1}H NMR spectroscopic analysis revealed a 1.4:1 (**9a**:**9b**) ratio of diastereomers. The diastereomers were separated by flash chromatography (SiO_2, 9:1 pentane/Et_2O) to yield **9a** (1.2 g, 44%) and **9b** (0.83 g, 30%) as yellow oils. **9a**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.33 (d, J = 6.4, 3H), 1.70 (d, J = 6.6, 3H), 1.75 (d, J = 9.4, 1H), 3.82 (dd, J = 9.2, 2.0, 1H), 4.29 (dq, J = 9.2, 6.6, 1H), 4.46 (m, 1H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 21.2, 22.9, 56.8, 66.4, 72.7; IR (neat) 3402, 2984, 2936, 1453, 1380, 1122, 755, 668; HRMS (CI/CH_2Cl_2) *m*/*z* calcd for $C_5H_{10}OCl_2$ $(M + Na)^+$ 179.0006, found 179.0005.

(2*R,3*S**,4*R**)-3,4-Dichloropentan-2-yl 4-Methylbenzene-sulfonate (10a).** To a solution of **9a** (54 mg, 0.34 mmol) in CH_2Cl_2 (2.1 mL) were added triethylamine (0.17 mL, 1.2 mmol), 4-dimethylaminopyridine (83 mg, 0.68 mmol), and tosyl chloride (0.23 g, 1.2 mmol) at room temperature. The reaction mixture was stirred at room temperature for 22 h and monitored by TLC. The remaining tosyl chloride was quenched with 1,3-propanediol (0.12 mL, 1.7 mmol). The crude product was diluted with Et_2O and filtered through cotton. The organic phase was washed with 0.5 M $CuSO_4$ (3 × 5 mL), saturated aqueous $NaHCO_3$ (3 × 5 mL), and brine (5 mL) and dried with Na_2SO_4. The crude product was purified by flash chromatography (SiO_2, 9:1 hexanes/ethyl acetate) to yield **10a** as a viscous yellow oil (75 mg, 70%), which could be crystallized as small rods from 5:1 hexanes/acetone using a hexane exchange chamber: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.46 (d, J = 6.4, 3H), 1.64 (d, J = 6.5, 3H), 2.45 (s, 3H), 3.73 (dd, J = 9.7, 1.8, 1H),

(8) While this manuscript was in review, an excellent study of the conversion of epoxides into dichlorides with inversion of configuration at both centers appeared. This method has clear relevance to the chlorosulfolipids: Yoshimitsu, T.; Fukumoto, N.; Tanaka, T. *J. Org. Chem.* **2009**, *74*, 696–702.

4.00 (dq, $J = 9.7, 6.5$ 1H), 5.36 (dq, $J = 1.8, 6.4$, 1H), 7.35 (d, $J = 8.0$, 2H), 7.83 (dd, $J = 6.7, 1.6$, 2H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 19.2, 21.6, 23.1, 55.9, 68.5, 76.1, 127.8, 129.8, 133.9, 144.9; IR (neat) 2992, 2936, 1599, 1453, 1360, 1176, 1096, 810; HRMS (CI/CH_2Cl_2) *m*/*z* calcd for $C_{12}H_{16}O_3Cl_2S$ $(M + Na)^+$ 333.0095, found 333.0104.

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Supporting Information Available: General experimental details, synthesis procedures and characterization data for all new compounds, including copies of ^{1}H and ^{13}C NMR spectra, and crystallographic information files in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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