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Stereochemical Revision, Total Synthesis and Solution State Conformation of the Complex Chlorosulfolipid Mytilipin B.

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Supporting Information Placeholder

ABSTRACT: Chlorosulfolipids constitute a structurally intriguing and synthetically challenging class of marine natural products that are isolated from mussels and freshwater algae. The most complex structure from this family of compounds is currently represented by Mytilipin B, isolated in 2002 from the culinary mussel *Mytilus galloprovincialis*, whose initially proposed structure was shown to be incorrect. In this study we present the synthesis of 4 diastereomers which allowed the reassignment of 8 stereocenters and stereochemical revision of Mytilipin B, along with the determination of the dominant solution state conformation.

Introduction

Chlorosulfolipids (CSL) are a fascinating class of marine membrane lipids that were first isolated by Elovson and Vagelos from the freshwater algae *Ochromonas danica* in 1969.[1] Numerous members of this family have been isolated since, mostly from the phylogenetic class Chrysophycae.[2] Their unusual structure raises interesting questions regarding their enigmatic role as lipids. CSLs have been linked to seafood poisoning and sparked significant research interest with regard to their toxicology, synthesis, and biological role.[3] Members of the family display antimicrobial and antiviral activity as well as protein kinase inhibition.[4] CSLs constitute 90% of the polar lipid content in the flagellar membrane of *O. Danica*, which otherwise lacks phospholipids.[5] Unlike many complex natural products, whose role are speculated to be defensive, CSL's are suggested to play a role integral to structure of the organism's membrane. This is noteworthy because cell compartmentalization is a requisite for the emergence of life[6] and fundamentally different membrane architectures are usually associated with different domains of life[7] or found in highly specialized organelles.[8]

To date the most complex CSL **1** (Figure 1, left) was isolated from the Italian region Emilia Romagna in 2002[9] when a routine check revealed a sample of the culinary mussel *Mytilus galloprovincialis* to be toxic in a mouse bioassay. The sample was subsequently shown to contain a lipid whose structure was proposed to be **1** (Figure 1). Although the primary producing organism remains elusive, it was hypothesized that the mussels accumulate this compound through their dietary intake and the similarity of **1** to other chlorosulfolipids that are produced by microalgae have led to the suggestion of a similar origin for **1**.

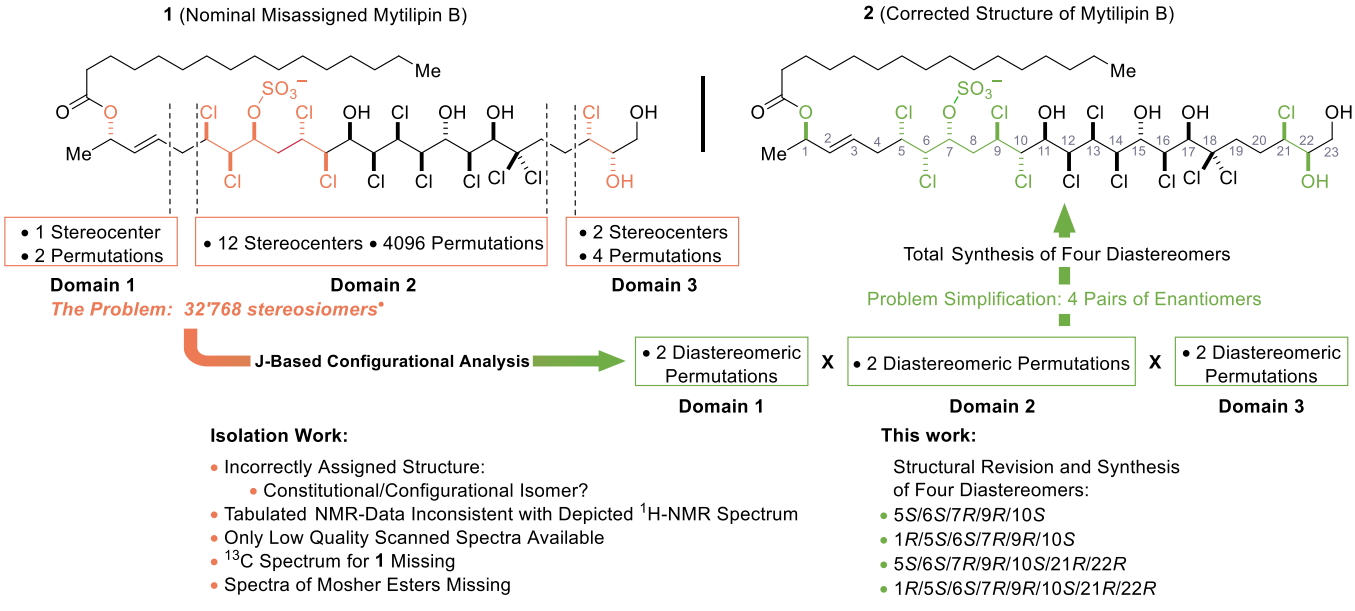


Figure 1. Originally proposed structure of Mytilipin B (**1**) and our strategy towards determining the revised structure of Mytilipin B (**2**).

This lack of knowledge impedes access to further material for chemical and biological study, currently rendering chemical synthesis the only potential supply source

In addition to missing provenance, there are additional complications concerning the natural product. A total synthesis of **1** from our group produced spectral data that was not in accordance with that published for natural Mytilipin B.[10] Confounding the problem, the raw isolation data of **1** (such as high-resolution NMR spectra or FIDs) are irrecoverable. Scanned spectra for ^{1}H, HMQC, and COSY as well as tabulated data from ^{1}H and ^{13}C-NMR, ESI-HRMS, and IR are the only available information for **1**. It is notable that a ^{13}C-NMR spectrum of **1** is missing from the collection. Additionally, there are inconsistencies with the published data for the peracetylated natural product (Figure 2, nominally **3**).

Our preliminary analysis suggested that the DEPT spectrum was accumulated in d_4-MeOD and not d_6-acetone as indicated. This discrepancy was also true for the HMQC of **1**, which was recorded in d_4-methanol and not d_6-acetone as well. Compounding the problem, spectra of three Mosher ester derivatives of the natural product, discussed by Ciminiello et. al. in the text for configurational assignment of C1, C11, C17 and C22, are absent in the published isolation report. On these terms we set out to revise the structure for Mytilipin B with the benefits of a broad outline of a synthesis route. This enabled access to a set of four diastereomers whose data proved critical for comparative purposes and reassignments of Mytilipin B as **2** (Figure 1, right).

Discussion

Connectivity of published structure. Our analysis began with careful examination of reported ^{1}H-NMR for the verification of the proposed connectivity in **1**. Comparison of the isolation team's ^{1}H-NMR spectrum and their tabulated ^{1}H-NMR data of **1** recorded in d_6-acetone revealed discrepancies between the two. For example, one of the most pronounced deviations is seen in the methylene signal corresponding to the primary alcohol, which appears at δ 3.60 as a broad multiplet in the spectrum but is tabulated at δ 4.26 and δ 4.01 ppm. Accordingly, ^{1}H-NMR data for **1** was judged unreliable. This was further complicated by the fact that the respective HMQC of **1** appeared to be recorded in d_4-methanol, as suggested by the strong residual solvent peak at δ ≈ 3.31 ppm (^{1}H)/49.0 ppm (^{13}C), with the other spectra of **1** having been recorded in d_6-acetone. Consequently, we turned to the spectral data of nominal pentaacetate **3**[11] (Figure 2). Close inspection of the published ^{1}H-NMR and ^{13}C-NMR along with 2D NMR COSY, HSQC, and HMBC spectra lead to the conclusion that no revision of the connectivity was necessary.

Absolute configuration assignment at C11/C17/C22 by isolation group. Mosher ester analysis employing Kakisawa's modified protocol[12] was conducted by the isolation team following preparation of the (*R*)- and (*S*)-Mosher-triester derivatives acylated at C11, C17, and C22 (Figure 2, alcohols indicated with a green line).[13] It should be noted that selected

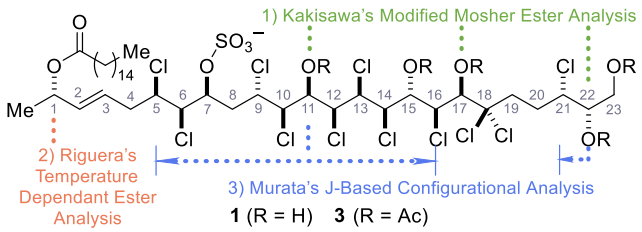


Figure 2. Strategy for the configurational assignment of **1** by Ciminiello and co-workers.

^{1}H-NMR shifts for the Mosher esters are provided in the text of the manuscript only, and there is otherwise a lack of spectra in SI. Nonetheless, our own analysis using the data provided for these three centers was in accordance with the assignment of configuration by Ciminiello as C11(*R*), C17(*R*), and C22(*S*). This influenced our decision to look to reassignment at other stereogenic centers of **1**.

Configuration assignment at remote stereocenter C1. The configuration at C1 was determined by Ciminiello after reductive cleavage of the palmitoyl ester and esterification with (*R*)-Mosher's acid chloride, following a temperature-dependent protocol modelled after that devised by Riguera.[14] However, it is important to note this NMR-experiment was originally developed for methoxy-phenylacetic acid esters; and in an earlier study, Riguera had noted that Mosher esters can only provide limited information, as they are subject to more complex conformational equilibria.[15] Accordingly, we hypothesized that the C1 stereocenter might be subject to revision.

*Analysis of Published Configurational Assignment of **1***. Ciminiello and co-workers employed Murata's *J*-based configurational analysis (JBCA)[16] with data supplied for nominal pentaacetate **3** for the determination of relative configuration. Given the limited quality of the supplied spectra (as exemplified by Figure 3), we could only extract some of the coupling constants, and still, most proved difficult to determine accurately. Consequently, we depended on the published table of coupling constants and not the spectra themselves, which led to no corrections. Murata has pointed out that two conformations A3 and B3 (Figure 3) cannot be differentiated purely on the basis of homo- and heteronuclear coupling constants. Thus, Ciminiello and co-workers recorded ROE (Rotating frame nuclear Overhauser Effect) experiments, of which a portion is shown in Figure 3. Our analysis concurs with that of Ciminiello that the conformation about C14–C15 appears to correspond to B3, which results in assigning the relative configuration as *anti* because no ROE signal can be observed between protons H13 and H16 (Figure 3, green circles). Additionally, the conformation about C12 and C13 is judged to be A3, because an ROE signal can be clearly identified for protons H11 and H14 (orange circles, Figure 3). The authors state in the text that the ROE interaction between H9 and H12 is consistent with conformation A3. Inspection of the ROESY spectrum reveals that there is no such interaction (blue circles and boxes, Figure 3).

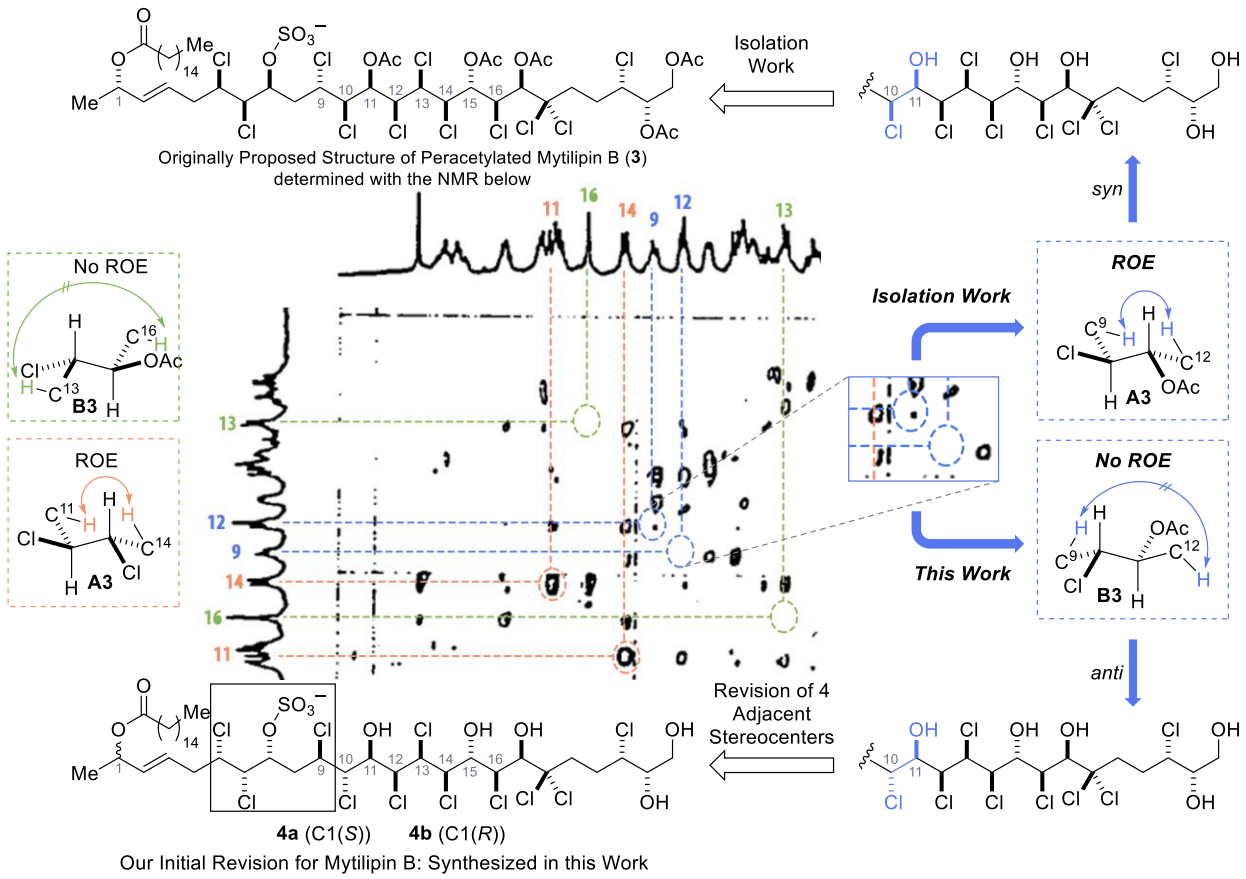
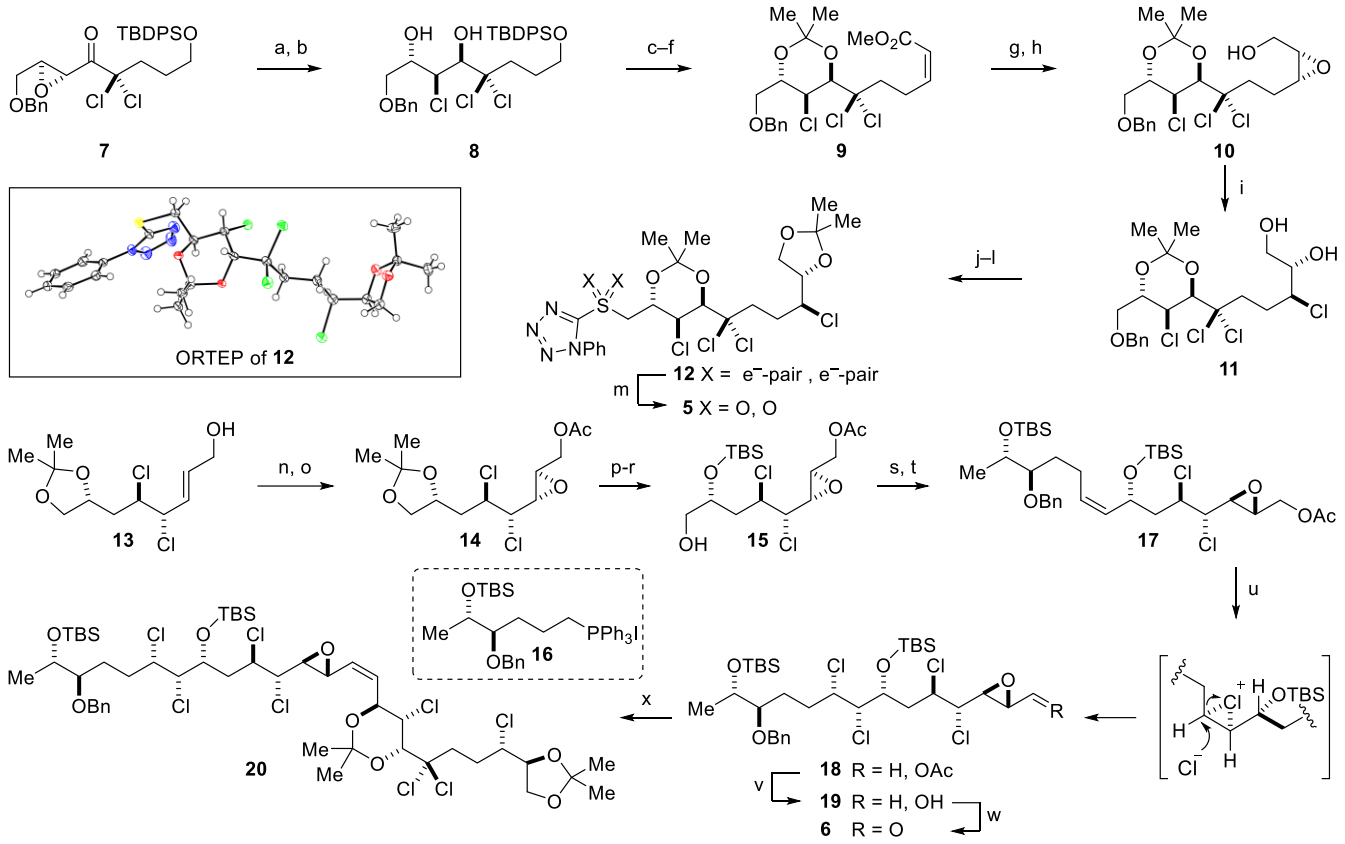


Figure 3. Analysis of the ROESY spectrum of **3** and the accordance with its proposed structure. For conformations A3 and B3 all five significant coupling constants are of similar size: $^{3}J_{1H\text{-}1H'}$: large, $^{2}J_{13C'\text{-}1H}$: large, $^{2}J_{1H'\text{-}13C}$: large, $^{3}J_{13C''\text{-}1H}$: small $^{3}J_{1H'\text{-}13C'''}$: small.

This is especially noteworthy given that the spectrum is missing the expected twinned, cognate signal. Accordingly, we conclude that the data is consistent with B3 as the dominant conformation and assign relative *anti*-configuration for C10–C11. Our assignment of configuration at C10 necessitates revision of the original assignment at C5–C7 (*S*,*S*,*R*) and C9–C10 (*R*,*S*) with five inverted stereocenters (C5–C7 (*R*,*R*,*S*) and C9–C10 (*S*,*R*)) as their configurations were determined relative to that at C11. When combined with the uncertainty at C1, this leads to a pair of C1 epimers **4a** and **4b** (Figure 3), which would need to be prepared and studied to potentially identify the correct configuration of natural Mytilipin B.

*Synthesis and Analysis of **4a-b***. The route to the originally published structure **1** reported by our group was designed to address the specific, proposed configurational relationship in the C5-C10 domain. Accordingly, a new stereochemically-driven retrosynthetic analysis targeting **4a** was necessary. This led to two fragments of similar complexity: sulfone **5** and aldehyde **6**, which in the synthetic direction would be joined by implementation of the Julia-Kociensky olefination reaction (Scheme 1).[17] Sulfone fragment **5** was prepared from epoxide **7**, itself available in seven steps from 1,5-pentane-diol.[10] The use of $ZrCl_4$ for epoxide opening of **7** did not scale well, consequently, we looked to a different method for generation of the chlorohydrin. Denmark's method for epoxide openings with $SiCl_4$ and HMPA[18] proved reliable on large scale and cleanly delivered a chlorohydrin, which without purification was converted to 1,3-*anti* diol **8** with $NaBH(OAc)_3$ in 92% yield as a single diastereomer. A sequence of reactions which included acetonide formation (73%), silyl ether cleavage (quant.), DMP oxidation of the primary alcohol (97%), followed by Still–Gennari olefination (72%) provided *cis*-enoate **9**. 1,2-Reduction with DIBAL followed by Sharpless epoxidation then provided unstable *cis*-2,3-epoxyalcohol **10**. Opening of the epoxide at C3 with a chloride source proved to be troublesome, as reported methods led to either no desired reactivity (PPh_3Cl_2, TMSCl) or mixtures of regioisomers ranging from 1:1 to 1.5:1 ($Ti(OiPr)_4/NH_4Cl$, $TiCl(OiPr)_3$, $CeCl_3$).[19] Screening of a wide variety of metal chlorides led to the identification of $MgCl_2$ as a novel reagent for the selective chlorolysis of *cis*-2,3-epoxy alcohols, providing the desired 1,2-diol **11** in high yield and regioselectivity in refluxing ethyl acetate (86% 1,2-diol, 13% 1,3-diol).[20] Interestingly, the reaction showed little regioselectivity when run at room temperature (1,2:1,3 diol ~ 1:1). Following 1,3-dioxolane formation (79%) and hydrogenolysis of the benzyl ether in 95% yield, the primary alcohol was subjected to a Mitsunobu reaction to give **12** in quantitative yield, and subsequent oxidation delivered sulfone **5** in 84% yield. The synthesis of aldehyde fragment **6** containing the five reassigned stereocenters commenced from **13**, which is accessible in seven steps from D(+)-malic acid.[21] Allylic alcohol **13** underwent Sharpless epoxidation to give 4,5-dichloro-2,3-epoxy alcohol **14** (72%, Scheme 1). Esterification followed by dioxolane hydrolysis provided the 1,2-diol (76%) of which both hydroxyl groups were TBS-protected (77%). Selective cleavage of the primary silyl ether to **15** (77%, 2 cycles), and Dess–Martin oxidation delivered an unstable aldehyde that was directly subjected to conditions

Scheme 1. Construction of Sulfone 5, Aldehyde 6 and Key Julia Olefination.



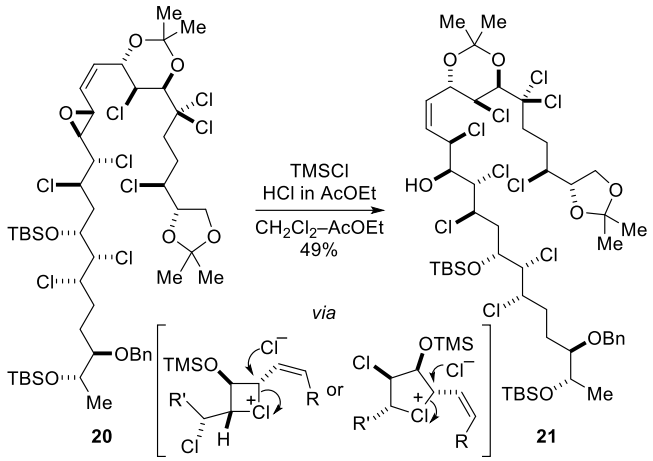
Reagents and conditions: Synthesis of sulfone fragment **5**: a) $SiCl_4$, HMPA, CH_2Cl_2, 96 h, 91%; b) $NaBH(OAc)_3$, AcOH-MeCN, 0 °C, 92%; c) $MeCH(OMe)CH_2$, PPTS, CH_2Cl_2, 23 °C, 73%; d) nBu_4NF, AcOH, DMF, 23 °C, quant.; e) DMP, CH_2Cl_2, 23 °C, 97%; f) $(CF_3CH_2O)_2P(O)CH_2CO_2Me$, $KN(SiMe_3)_2$, THF, –78 °C, 72%; g) *i*-Bu_2AlH, THF, –78 °C, 4 h, 96%; h) $Ti(Oi\text{-}Pr)_4$, *t*-BuO_2H, (+)-diethyl L-tartrate, CH_2Cl_2, –20 °C, 83% (dr = 4:1); i) $MgCl_2$, AcOEt, 80 °C, 86%; j) $CuSO_4$, *p*-TsOH, acetone, 79%; k) Pd/C, H_2, EtOAc, 23 °C, 90 min, 95%; l) 1-phenyl-1*H*-tetrazole-5-thiol, $(i\text{-}PrO_2C)N_2$, PPh_3, THF, 0 °C to 23 °C, quant.; m) $(NH_4)_6Mo_7O_{24}{\bullet}4H_2O$, H_2O_2, THF–EtOH 60 °C, 84%. Synthesis of aldehyde fragment **6** and Julia-olefination: n) $Ti(Oi\text{-}Pr)_4$, (–)-diethyl D-tartrate, *t*-BuOOH, 4Å MS, CH_2Cl_2, 72%; o) AcCl, pyridine, CH_2Cl_2, 76%; p) CSA, MeOH, 80%; q) TBSOTf, 2,6-lutidine, CH_2Cl_2, 77%; r) HF•py, py, THF, 77% (2 cycles); s) DMP, *t*-BuOH, CH_2Cl_2, quant.; t) **16**, KHMDS, THF, 93%; u) Et_4NCl_3, CH_2Cl_2, –78 °C, 92%, dr 5:1; v) K_2CO_3, MeOH, 0 °C, 95%; w) DMP, CH_2Cl_2; x) **5** (1.2 equiv.), NaHMDS, PhMe, –78 °C to rt, 49% (2 steps), *E:Z* = 3:1. DMP = Dess–Martin periodinane, PPTS = pyridinium *para*-toluenesulfonate, *p*TsOH = *para*-toluenesulfonic acid.

for Wittig olefination with ylide **16**[10] to give *cis*-olefin **17**. Inverse addition of the starting aldehyde to the phosphonium ylide was crucial to obtain a high yield of **17** (93%, 2 steps). The olefin was then subjected to dichlorination employing Mioskowki's reagent (Et_4NCl_3) to give **18**. The stereochemical outcome of the chlorination reaction was in accordance with Vanderwal's report that *cis*-allylic alcohol derivatives provide the corresponding *syn-syn* dichloride.[22] Initial attempts in executing this reaction (0.05M in CH_2Cl_2, addition of Et_4NCl_3 to the olefin at –78 °C) gave low yields due to competing formation of a furan, derived from intramolecular attack of the proximal benzyl ether on the intermediate epichloronium ion with subsequent loss of benzyl chloride. A related mode of anchimeric attack was previously observed by Burns en route to (−)-Danicalipin.[23]

Whilst intramolecular opening of the chloronium ion can be expected to follow a first order rate law, the desired chloride addition to the chloronium ion may also depend on chloride concentration. Consequently, inverse addition of the alkene **17** to a saturated solution of Et_4NCl_3 in CH_2Cl_2 at –78 °C was employed, yielding product **18** in high yield and good diastereoselectivity, as determined by NMR (92%, dr = 5:1).[24] Hydrolysis of the ester in **18** delivered **19** (95%), and DMP oxidation of the primary alcohol afforded unstable aldehyde **6**, which was coupled with sulfone **5** in toluene in the presence of NaHMDS to obtain the desired *cis*-olefin **20** (49% over 2 steps, dr = 3:1 as determined by NMR).[25] In this reaction the base was added last to a solution of the sulfone and the aldehyde at –78 °C to avoid $E1_{cb}$ elimination of the deprotonated sulfone.

Next, we attempted opening of *trans*-epoxide in **20** with retention of configuration at the allylic sterecoenter (Scheme 2) in order to obtain the desired *cis*-chlorohydrin. Lewis acids such as $SiCl_4$, $MgCl_2$, or Ph_3PCl_2 did not lead to any product formation. Although TMSCl in methylene chloride effected the conversion of **20** in 2 h to the corresponding chlorohydrin in 51% yield, analysis of the product indicated that inversion of configuration had occurred at the allylic carbon.[26] When **20** was subjected to TMSCl in a 1:1 mixture of ethyl acetate and methylene chloride the desired *syn*-chlorohydrin **21** was obtained after long reaction times (5 days). In accordance with results previously reported by our group,[26] addition of ethyl acetate as a

Scheme 2. Stereoretentive Epoxide Opening with Anchimeric Assistance.



Reagents and conditions: TMSCl (30 equiv.), HCl in AcOEt (1M, 7-9 equiv.), CH_2Cl_2–AcOEt (1:1), 49%.

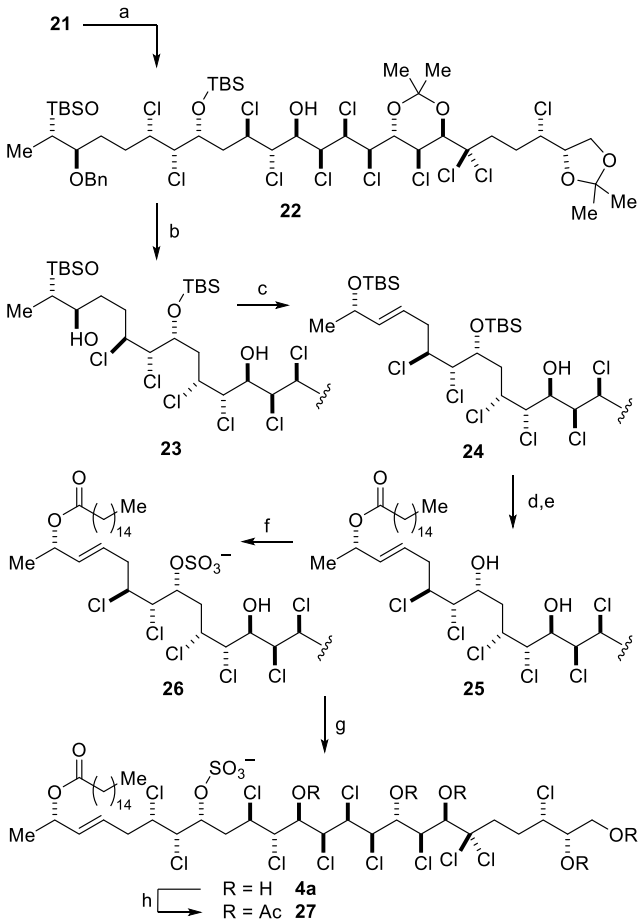
more polar solvent is thought to promote anchimeric assistance through formation of polar chloretanium and chlorolanium ions (Scheme 2). Unfortunately, this method proved to be even slower and unreliable on large scale, producing complex mixtures of polar by-products. In attempts to understand the lack of scalability, we focussed on TMSCl and hypothesized that it served two functions. First, its reaction with adventitious water on small scale would generate HCl, which would in turn effect rapid epoxide opening. Second, its reaction with water also preserves a strictly anhydrous reaction medium, thereby precluding hydrolysis of the various labile protecting groups. Accordingly, we found that slow addition of HCl in ethyl acetate in the presence of TMSCl led to rapid (2 h) formation of **21** (49%), which proved to be highly sensitive to alkaline conditions.[27]

Subsequently, **21** underwent smooth dichlorination in 67% yield with Et_4NCl_3 in CH_2Cl_2 when warmed to room temperature to give undecachloride **22** (Scheme 3) as the desired stereoisomer as determined by NMR.[28] Debenzylation of **22** proved surprisingly challenging, as standard conditions (Pd/C and H_2 in AcOEt) failed to provide product. Fortunately, screening a wide variety of palladium sources revealed Degussa type NE/W Pd/C as suitable, delivering alcohol **23** (65%) within a few minutes at 35 °C in a 1:1 mixture of MeOH–THF. Stepwise addition of Martin's sulfurane in small portions of 0.12 equivalents proved vital to selective dehydration of **23** to access **24** (52%). The *trans*-configuration of the olefin was established on the basis of the large vinylic C–H coupling ($^3J_{H-H}$ = 15.4 Hz). Subsequent silyl ether cleavage delivered the corresponding triol that was selectively acylated at the allylic alcohol to give **25** (67%).[29] Subsequently, *O*-sulfation with DMF•SO_3[30] gave monosulfate **26** in 80% yield. Hydrolysis of the acetals then delivered the target structure **4a** (72%), without transposition or cleavage of either the ester or the sulfate groups. Unfortunately, the ^{1}H and ^{13}C-NMR spectra we acquired for **4a** in d_6-acetone differed substantially from ^{1}H-NMR spectra and the tabulated ^{1}H and ^{13}C-NMR data reported by Ciminiello for natural Mytilipin B in d_6-acetone. In the original isolation and structural determination work, as a consequence of multiply overlapping ^{1}H-NMR signals for the natural product (nominally **1**), Ciminiello synthesized the corresponding nominal pentaacetate **3**. We made use of this strategy by preparing the pentaacetate of synthetic **4a** (Scheme 3) by treatment with Ac_2O and pyridine over 3 days to give **27**. Although there were now considerable similarities between the ^{1}H-NMR spectra of Ciminiello's pentaacetate (500 MHz) and **27** (400 MHz), there were notable differences extracted from the spectral data for the shifts of various protons, for example the methylene protons at C19 δ 2.55 (nominal **3**) versus δ 2.65/2.48 (**27**). These results suggest H-bonding effects in the natural product pose a potential complication when conducting spectral comparisons and strongly imply that spectral comparisons should include the peracetylated derivatives.

Taking into account our observations involving **27** together with our reservations concerning the assignment of the configuration at C1, we decided to prepare the C1-epimer of compound **4a** (C1-epi **4a**), or **4b**. We identified bis-TBS ether **24** as a suitable late stage entry point (Scheme 4 A).

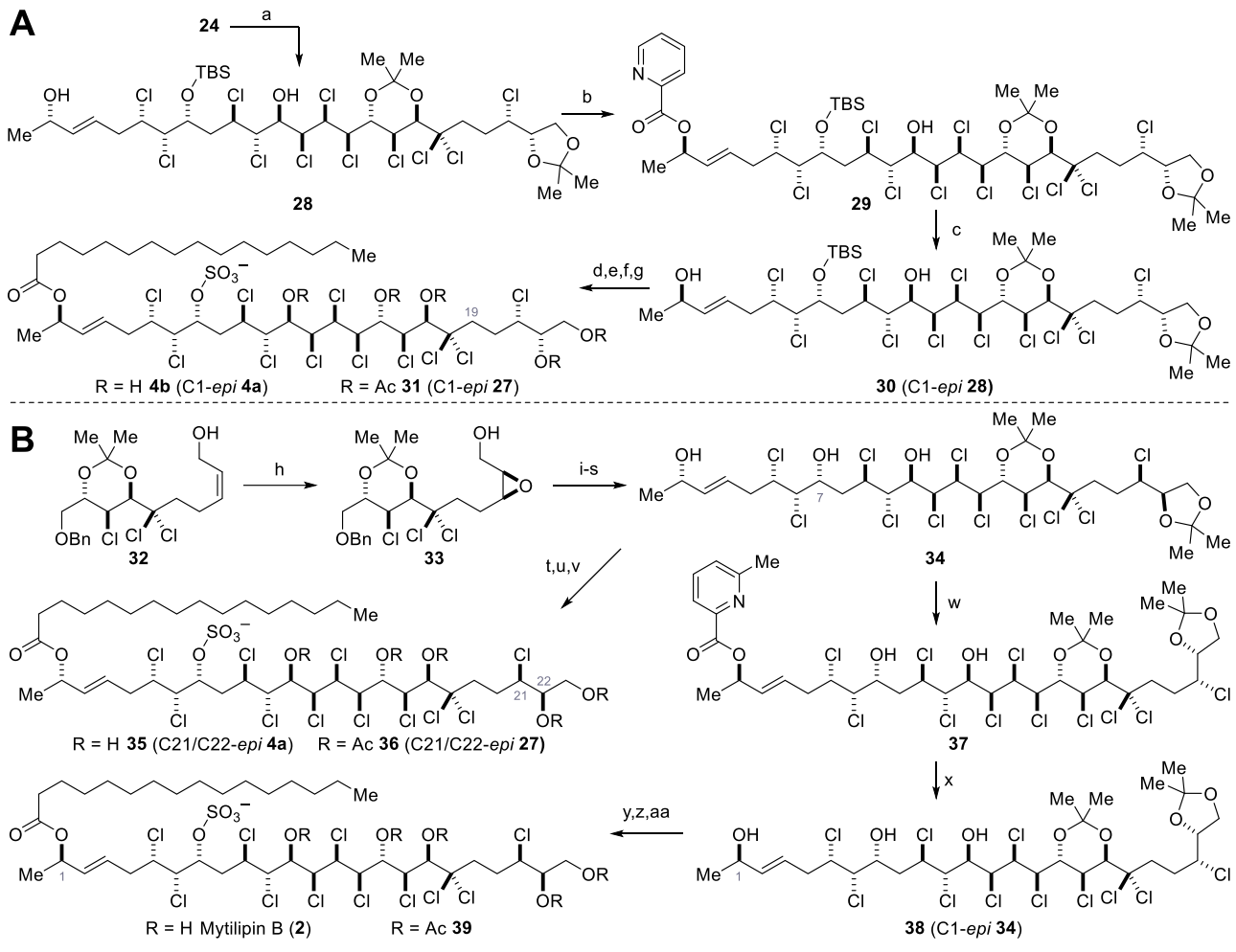
Monodeprotection of the less hindered TBS ether at 0 °C delivered **28** (50%), which is poised for inversion at the allylic C1 by implementation of a Mitsunobu reaction (Scheme 4 A).

Scheme 3. Synthesis of Diastereomer 4a and Peracetylation.



Reagents and conditions: a) Et_4NCl_3, CH_2Cl_2, 57%; b) H_2, Pd/C, THF–MeOH, 35 °C, 65%; c) *Martin's sulfurane*, PhMe, 58%; d) HF•py, py, MeCN, 95%; e) palmitoyl chloride, py, CH_2Cl_2, –78 °C to –40 °C 67%; f) DMF•SO_3, Na_2SO_4, DMF–py, 80%; g) F_3CCO_2H–H_2O (1:1), 72%, h) Ac_2O, py. *Martin's sulfurane* = $[PhC(CF_3)_2O]_2SPh_2$, py = pyridine.

Scheme 4. Synthesis and Peracetylation of Key Diastereomers 4b, 35 and the Natural Product Mytilipin B (2).



Reagents and conditions: a) HF•py, py, MeCN, 23 °C to 0 °C, 50% **28**, 35% **24**; b) 2-picolinic acid, (*i*-PrO_2C)N_2, PPh_3, THF, -20 °C to 0 °C, 18%; c) $Cu(OAc)_2$, MeOH, $CHCl_3$, 100%; d) HF•py, py, MeCN, 73%; e) $C_{15}H_{31}COCl$, py, CH_2Cl_2, –78 °C to –40 °C 75%; f) DMF•SO_3, Na_2SO_4, DMF–py, 83%; g) F_3CCO_2H–H_2O (1:1), 72%; h) Ti(O*i*-Pr)$_4$, *t*-BuO_2H, (–)-diethyl D-tartrate, CH_2Cl_2, –20 °C, 77% (dr=4:1);); i) $MgCl_2$, AcOEt, 80 °C, 77%; j) $CuSO_4$, *p*-TsOH, acetone, 81%; k) Pd/C, H_2, EtOAc, 23 °C, 90 min, 95%; l) 1-phenyl-1*H*-tetrazole-5-thiol, (*i*-PrO_2C)N_2, PPh_3, THF, 0 °C to 23 °C, 91%; m) $(NH_4)_6Mo_7O_{24}$•$4H_2O$, H_2O_2, THF–EtOH 60 °C, 70%, n) **6**, NaHMDS, PhMe, –78 °C to rt, 66% (2 steps), *E*:*Z* = 3:1; o) HCl in AcOEt (1M), AcOEt–CH_2Cl_2 (1:1), 55%; p) Et_4NCl_3, CH_2Cl_2, 66%; q) H_2, Pd/C, THF–MeOH, 35 °C, 61%; r) *Martin's sulfurane*, PhMe, 60%; s) HF•py, py, MeCN, 66%; t) $C_{15}H_{31}COCl$, py, CH_2Cl_2, –78 °C to –40 °C 76%; u) DMF•SO_3, Na_2SO_4, DMF–py, 84%; v) F_3CCO_2H–H_2O (1:1), 72%; w) 6-Me-2-picolinic acid, (*i*-PrO_2C)N_2, PPh_3, THF, -20 °C to 0 °C, 42%; x) $Cu(OAc)_2$, MeOH–$CHCl_3$ (1:1), 85%; y) palmitoyl chloride, py, CH_2Cl_2, –78 °C to –40 °C 71%; z) DMF•SO_3, Na_2SO_4, DMF–py, 90%; aa) F_3CCO_2H–H_2O (1:1), 79%. py = pyridine, DMF = *N*,*N*-dimethylformamide, *Martin's sulfurane* = $[PhC(CF_3)_2O]_2SPh_2$.

The use of standard conditions involving *p*-nitrobenzoic acid proved to be unsuitable, because conditions for the subsequent hydrolysis were incompatible with the base-sensitive chlorohydrins. Accordingly, picolinic acid was examined as nucleophile, as it has been reported to undergo hydrolysis under neutral conditions with $Zn(OAc)_2$ or $Cu(OAc)_2$ in methanol.[31] Fortunately, we were able to obtain ester **29** inverted at C1, albeit in only 18% yield. Subsequently, hydrolysis of **29** to **30** occurred in quantitative fashion (3.8 equivalents $Cu(OAc)_2$, 100 equivalents MeOH in $CHCl_3$),and silyl ether cleavage with HF/pyridine delivered the triol (73%). The previously established acylation-sulfation-acetal hydrolysis sequence gave access to **4b** (3 steps, 45%). Pentaol **4b** was subjected to peracetylation to give **31**. We then compared the data from ^1H and ^{13}C-NMR spectra for **31** to the Ciminiello data for the peracetate of the natural product. For **31** the methylene protons at C19 once again showed the largest deviation, with Ciminiello tabulating a multiplet at δ 2.60 for **3** while synthetic material **31** displayed resonances at δ 2.63 and δ 2.48 ppm.

We proceeded to conduct configurational studies of **4b** by JBCA. The derived couplings in the C5–C16 and C21–C22 arrays were in accordance with Ciminiello's observations within these regions for peracetylated Mytilipin B (**3**) (see SI for details). With this in mind, we reasoned that the remaining spectral discrepancies could only be explained by incorrect relative configuration between the two spin systems C1-Me–C17 and C19–C23. This leads to compounds **35** and **2** as targets of

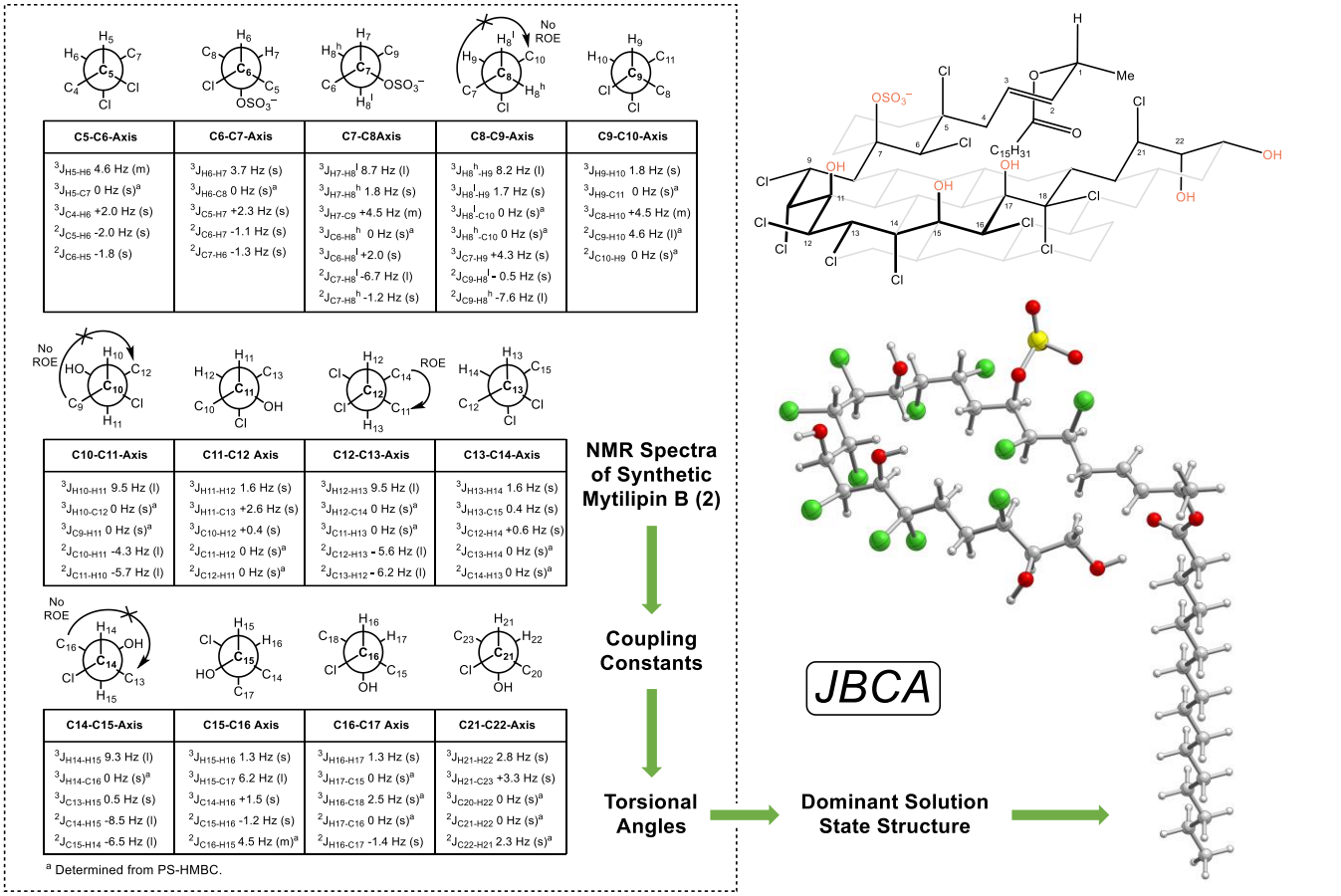


Figure 4. Observed coupling constants in d_6-acetone and the resulting dominant solution-state conformation of Mytilipin B (**2**) determined for C5–C17 and C21–C22 by *J*-based configurational analysis.

interest (Scheme 4 B). The stereochemical problem presented by the new targets necessitated restarting the synthetic sequence with allylic alcohol **32** (1 step from **9**). Using D(–)-diethyl tartrate instead of L(+)-diethyl tartrate, Sharpless epoxidation of **32** delivered epoxide **33**[32] (77%, dr = 4:1). Elaboration to **34** was conducted as previously presented in Schemes 2 and 3 for the respective C21-*epi*/C22-*epi* compounds. Palmitoylation (76%), *O*-sulfation (84%), and acetonide hydrolysis (72%) delivered **35**. Additionally, pentaol **35** was subjected to peracetylation, as previously described for **27,** to give **36**.

The HSQC-spectrum of pentaol **35** in d_4-methanol matched the HMQC reported by Ciminiello for the natural product Mytilipin B. However, comparing the spectra obtained for **36** to the peracetylated natural product, a significantly different peak shape of the two vinylic resonances at δ 5.69 and δ 5.79 ppm was observed. We thus set out to synthesize the C1-inverted compound **2** (Scheme 4 B). Given the small amount of material available and the necessity to prepare both C1 diastereomers, we were forced to improve the Mitsunobu inversion to gain access to sufficient material. While changing the nucleophile from picolinic acid to chloroacetic acid vastly improved the yield of the inverted product (62%), we were unable to find hydrolytic conditions that left the sensitive chlorohydrin intact.[33] Further experimentation revealed that the use of the less nucleophilic 6-methyl-2-picolinic acid delivered **37** in a significantly improved yield of 42% (vs. 18% for synthesis of **29** as shown in Scheme 4 A). Subsequent hydrolysis of the more hindered 6-methyl picolinate **37** to **38** was achieved through the use of higher amounts of both methanol ($CHCl_3$–MeOH 1:1) and $Cu(OAc)_2$ (10 equivalents) without any observable chlorohydrin reactions despite three potential sites for oxirane formation (85%, Scheme 4 B). It is interesting to note that unlike the sequence from **28** to **30**, the inversion sequence of **34** to **38** was conducted with the free alcohol at C7, obviating the need for a second silyl deprotection step in the reaction sequence. Elaboration of **38** was conducted as previously described for **35** through palmitoylation (71%), *O*-sulfation (90%), and acetonide deprotection (79%) (Scheme 4 B). Acylation with Ac_2O and pyridine delivered **39**. Comparing the recorded spectra of the four synthetic diastereomeric pentaacetates **27**, **31**, **36**, and **39,** the spectra of **39** optically matched with those published by Ciminiello for the peracetylated natural product (nominal **3**).[34] In addition the HSQC of synthetic pentaol **2** in d_4-methanol also matched the HMQC of the natural product (nominally **1**). The ^{13}C-NMR spectrum of synthetic pentaol **2** in d_4-methanol matched the DEPT spectrum provided for the peracetylated natural product (nominally pentaacetate **3** and nominally recorded in d_6-acetone), suggesting the DEPT spectrum provided by Ciminiello was recorded of the natural product in d_4-methanol and incorrectly labeled.[35] Thus, we conclude that **2**, inverted at the eight stereocenters C1/C5/C6/C7/C9/C10/C21/C22 relative to the originally proposed structure **1**, represents the structure of Mytilipin B. Additionally, these results may suggest that the related natural product Mytilipin C lacking the C17-hydroxyl group is likely

also correctly depicted with our revised stereochemical assignment at the respective eight stereocenters given the similarities that have been pointed out for Mytilipin B and C.[36]

In addition, the dominant solution state structure of Mytilipin B (**2**) was modeled based on the determined conformations (Figure 4). Intriguingly the C5–C17 carbon chain adopts a rigid conformation in which the chlorinated region appears U-shaped. The sulfate and the core hydroxyl groups form the polar face of Mytilipin B (**2**). The opposing face is dominated by the large palmitoate sidechain along with numerous chloride substituents. However, it should be noted that regions C1–C4 and C18–C20 are likely to have increased degree of rotational flexibility in solution. Conventional phospholipids usually consist of a polar, relatively small phosphate headgroup and a long nonpolar fatty acid chain. In contrast, chlorosulfolipids often contain a broad distribution of polar groups throughout the molecule. Given the observed dominant solution state conformation of Mytilipin B (**2**) we propose that this discrepancy may be resolved for **2** when considering its folded secondary structure.

Intriguingly, comparative analysis of the stereohexade C9–C14 of Mytilipin B relative to other known chlorosulfolipids reveals partially conserved stereochemical sequences. As shown in Figure 5 alignment of the aliphatic array of Mytilipin A and B, Danicalipin A as well as Malhamensilipin A reveals homologies. The complete stereohexade of Mytilipin A[2c] is conserved in the revised structure of Mytilipin B (**2**). Malhamensilipin A[37] and Danicalipin A[38] share a sequence of five and four stereocenters with **2**. This may hint to a common biosynthetic pathway or lipid function and raises the question what structural role this highly conserved sequence fulfills. Comparison of the solution state structure of our Mytilipin B, Mytilipin A (both in d_6-acetone),[2c] Danicalipin A (in d_4-MeOD), as well as desulfated Fluoro- and Bromodanicalipin (in $CDCl_3$)[39] and a reduced, desulfated derivative of Malhamensilipin A (in C_6D_6)[37a] displays similar conformations within conserved sequences.

In conclusion, we followed a strategy prioritizing changes in configuration likely to have the largest impact on the spectral signatures. This guided us through incremental, stepwise correction for Mytilipin B. Subsequently, we synthesized a total of four diastereomers, culminating in the reassignment of 8 out of 15 stereocenters. The distance between stereochemical arrays

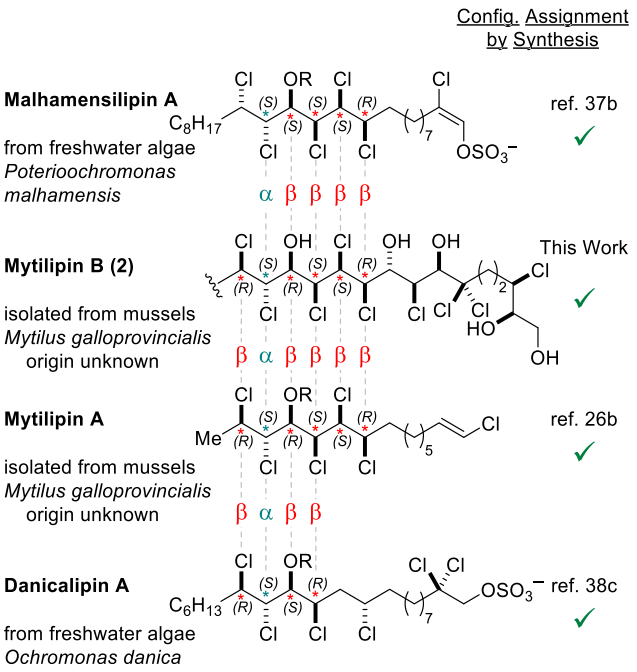


Figure 5. Comparison of conserved stereoarray patterns throughout a selection of different chlorosulfolipids. α/green denotes a substituent pointing inwards, β/red outwards. Some conserved stereocenters are formally inverted in the CIP nomenclature. R = SO_3^-.

results in subtle spectral differences among the diastereomers. However, the synthesis of four key diastereomers **2**, **4a**, **4b** and **35**, enables direct comparison and identification of **2** as the most likely structure of the natural product, illustrating the power of *J*-based configurational analysis. Moreover, we conducted conformational analysis of the solution state structure of **2**. This may explain for the ability of chlorosulfolipids to form or insert into lipid bilayers by taking into account the secondary structure. It is intriguing to speculate how Mytilipin B (**2**), in light of its solution state structure, impacts the mechano-physical properties of the membrane in terms of density, rigidity, chemical stability, curvature or permeability. Further biophysical studies are required to provide insight into the phenomena.

ASSOCIATED CONTENT

The Supporting Information is available free of charge via the Internet at http://pubs.acs.org."

General methods; detailed experimental procedures; spectral data; comparison of synthetic and natural Mytilipin B; X-ray crystallographic data; and references

X-ray crystallographic data

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[34] The natural product provided d_6-acetone spectra that were highly dependent on concentration, water content and counterion. The closest match withthe ^{1}H-NMR spectrum of **1** was observed with a Na^+ counterion (prepared by dissolving **2** in aq. $NaHCO_3$ and subsequent lyophilization). Our group has previously established a sulfolipid to be protonated after silica column chromatography through elemental analysis of bromodanicalipin: Dissertation Stefan Fischer, Diss. ETH Nr. 24978, Zürich 2018. This irreproducibility was less pronounced in protic solvents and consequently the HMQC of natural Mytilipin B matches the HSQC of synthetic **2** in d_4-MeOD very well. See also: Sigala, P. A.; Ruben, E. A.; Liu, C. W.; Piccoli, P. M. B.; Hohenstein, E. G.; Martinez, T. J.; Schultz, A. J.; Herzschlag, D. Determination of Hydrogen Bond Structure in Water versus Aprotic Environments To Test the Relationship Between Length and Stability. *J. Am. Chem. Soc*. **2015**, *137*, 5730-5740.

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