VIP Chlorosulfolipids

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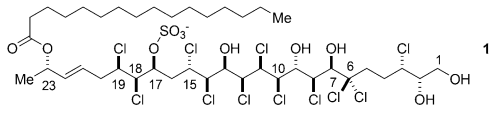
Synthesis of Undecachlorosulfolipid A: Re-evaluation of the Nominal Structure**

*Christian Nilewski, Nicholas R. Deprez, Thomas C. Fessard, Dong Bo Li, Roger W. Geisser, and Erick M. Carreira**

The chlorosulfolipids are an intriguing family of natural products initially isolated in 1969.[1] They originate from the phylogenetic class Chrysophyceae that includes golden algae. These structures are fascinating from a variety of perspectives and raise questions of relevance in chemistry, biology, toxicology, and pharmacology. This has led to a remarkable interest in these entities, as evidenced by numerous publications.[2–4] It is interesting to note that some of the more recently isolated chlorosulfolipids have been reported to be moderately cytotoxic and associated with seafood poisoning.

The chlorosulfolipids are chemically intriguing because of the complex stereochemical array of secondary chlorides and alcohols, some of which are O-sulfated. The structures have provided a forward stage for the development of novel tactics and strategies en route to their synthesis[5] as well as spectroscopic studies that enable configurational assignment.[3] The most complicated of the chlorosulfolipids known to date was isolated in 2002 from the Mediterranean mussels *M. galloprovincialis* in which microalgae accumulate, but knowledge of the organism that produces it remains elusive.[6] Herein, we document the first total synthesis of nominal undecachlorosulfolipid A (**1**), which not only led to the development of tactics and strategies to access this



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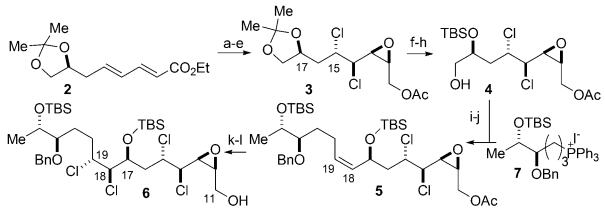
complex polychlorinated lipid, but it also revealed a structural misassignment of the natural product.

Our interest in this molecule arose from the unique synthetic challenges that this molecule presents. Examination of undecachlorosulfolipid A (**1**) reveals some structural homology to hexachlorosulfolipid[7] whose synthesis we have previously reported.[2] However, a collection of altogether different stereochemical patterns is embedded in undecachlorosulfolipid A (**1**), rendering it substantively more challenging. These include, for example, the dichloro alcohol along C17–C19, the congested array at C6–C8, which includes a vicinal chlorohydrin at C7–C8 juxtaposed to a geminal dichloride at C6. Finally, any synthesis route would have to contend with the sheer complexity of nine contiguous chlorinated or hydroxylated stereogenic centers and a target structure that is amphipathic, incorporating a charged sulfate and a palmitoyl ester side chain.

Our retrosynthetic analysis led to the disconnection of **1** into two fragments of comparable complexity, including the C11–C24 and the C1–C10 fragments. We commence the disclosure of our work with the preparation of the former (Scheme 1). Unsaturated ester **2** was prepared in a few steps



Scheme 1. Synthesis of the C11–C24 fragment. a) Et_4NCl_3, CH_2Cl_2, 0°C, 1.25 h, 66% (d.r. = 1.8:1); b) DIBAL-H, toluene, 0°C, 30 min, 43% (d.r. = 5:1); c) DMAP (cat.), Et_3N, AcCl, CH_2Cl_2, 0°C, 10 min, 81%; d) AD-Mix β, $MeSO_2NH_2$ (1.05 equiv), *t*BuOH/H_2O = 1:1, 74%; e) DABCO, $(F_3CSO_2)_2O$, CH_2Cl_2, −78°C to RT, 19 h, 50%; f) CSA (cat.), MeOH, RT, 2 h, 72%; g) 2,6-lutidine, TBDMSOTf, CH_2Cl_2, −78°C to −15°C, 1.75 h, 91%; h) HF/pyr/THF, 0°C to 4°C, 5 h, 40% **4**, 53% recovered starting material (after four cycles 79% overall yield, 86% brsm); i) DMP, RT, 45 min, 87%; j) **7** (1.3 equiv), $KN(SiMe_3)_2$, THF, 0°C, 20 min, then −78°C, RCHO (1.0 equiv), 30 min, 0°C, 30 min, 55%; k) Et_4NCl_3, CH_2Cl_2, −78°C, 71% (d.r. = 5:1); l) K_2CO_3, MeOH, 0°C, 10 min, 98%. Bn = benzyl, brsm = based on recovered starting material, CSA = camphorsulfonic acid, DABCO = 1,4-diazabicyclo[2.2.2]octane, DMAP = 4-dimethylaminopyridine, DMP = Dess–Martin periodinane, pyr = pyridine, TBS = *tert*-butyldimethylsilyl.

from commercially available (*S*)-1,2,4-butanetriol.[8] Dichlorination[9] of **2** gave the product displaying an *anti* relationship between C15 and C17 preferentially (d.r. = 1.8:1; Scheme 1). The relative configuration was unambiguously secured by *J*-based configuration analysis (JBCA)[3,10] following diastereomer separation and acetonide hydrolysis. On preparative scale it was more convenient to subject the mixture of diastereomers directly to reduction (DIBAL-H) and separate

[*] Dr. C. Nilewski, Dr. N. R. Deprez, Dr. T. C. Fessard, Dr. D. B. Li, Dr. R. W. Geisser, Prof. Dr. E. M. Carreira
ETH Zürich, HCI H335, 8093 Zürich (Switzerland)
E-mail: carreira@org.chem.ethz.ch
Homepage: http://www.carreira.ethz.ch

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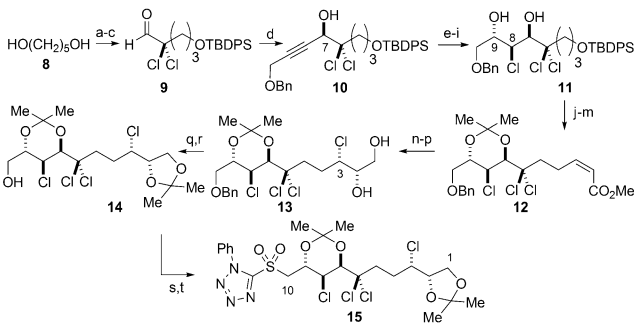
the resulting allylic alcohols. Acetylation (81% yield), Sharpless dihydroxylation[11] (74%), and subsequent cyclodehydration (50%)[2,3] furnished the protected epoxy alcohol **3**.[12] The vicinal ^{1}H,^{1}H coupling constant between H12 and H13 in **3** (J_{vic} = 4.0 Hz) is in agreement with a *cis* epoxide.[13,14]

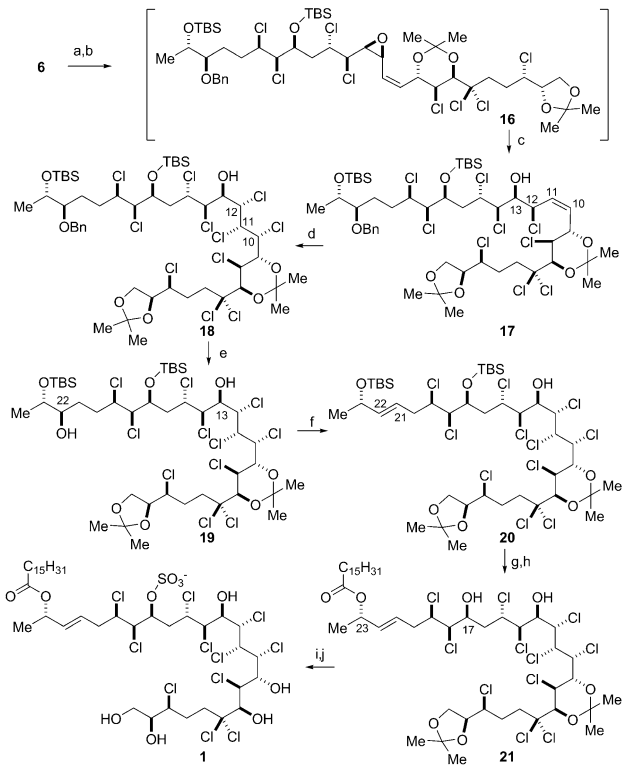
Intermediate acetonide **3** was then transformed into the primary alcohol **4** by a sequence involving acetonide cleavage (72%), silyl protection (91%), and selective deprotection (HF–pyr, 79% overall yield). Dess–Martin oxidation[15] of **4** led to an aldehyde that was allowed to react with the ylide derived from **7** to give (*Z*)-**5** in 55% yield. The configuration of the olefin was deduced from the NMR-spectroscopic fingerprint of H18 and H19 (J_{vic} = 11.0 Hz in C_6D_6). The synthesis of the C11–C24 fragment was then completed by treatment of **5** with Et_4NCl_3 (71%, d.r. = 5:1) followed by saponification (98%). The stereochemical outcome of the dichlorination at C18,C19 was confirmed by JBCA as well as chemical modification, that is, formation of a *cis* epoxide between C17 and C18 and stereoselective formation of an olefin along C18 and C19.[8]

The preparation of the C1–C10 fragment starts with diol **8** which was converted into aldehyde **9** in three steps and 83% overall yield (Scheme 2). The stereogenic center at C7 was then envisioned to be installed by enantioselective Zn-acetylide addition to a dichloro aldehyde.[16] The addition was found to proceed in 70% yield to give propargylic alcohol **10** in 92% *ee* as judged by ^{1}H NMR spectroscopic analysis of the corresponding Mosher ester derivatives. This transformation represents the first example of an asymmetric Zn-acetylide addition to an α,α-dichlorinated aldehyde. Conversion of the propargylic alcohol into diol **11** commenced with alkyne semireduction (Red-Al) and subsequent vanadium-catalyzed epoxidation. We were unable to identify conditions for the efficient regioselective opening of the isolated epoxide to the corresponding chlorohydrin. However, oxidation of the intermediate secondary epoxyalcohol to the ketone enabled the subsequent chloride introduction at C8 with $ZrCl_4$. In order to minimize epimerization at Cα, the resulting chloroketone was reduced without purification, which provided diol **11** in 34% yield over the three steps. The configuration of **11** was confirmed by JBCA combined with evaluation of the NMR spectra of the two diastereomeric Mosher ester derivatives at the C9-OH group.[8] Acetonide protection of the diol (93% yield) was followed by removal of the TBDPS group (95% yield), Dess–Martin oxidation of the resulting primary alcohol, and subsequent Still–Gennari olefination,[17] leading to *cis* ester **12** in 68% yield. The intermediate *cis* allylic alcohol resulting from DIBAL reduction of **12** was subjected to diastereoselective epoxidation (d.r. = 9:1)[18] in 92% yield. Subsequently, the chloride at C3 was introduced with $TiCl(OiPr)_3$ (40%).[19] In order to establish the regiochemical outcome, we treated the major product of the reaction with $NaIO_4$,[8] which led to an aldehyde, consistent with the formation of a 1,2-diol in the preceding step. Formation of the C2,C3 *cis* epoxide from a mono-TBS-protected derivative of **13** established the invertive epoxide opening.[8] The synthesis of the C1–C10 fragment was then completed following acetonide formation, benzyl ether cleavage, and Mitsunobu displacement of the resulting primary alcohol with phenyltetrazolylsulfide followed by oxidation to the corresponding sulfone (40% yield over four steps).



Scheme 2. Synthesis of the C1–C10 fragment. a) *t*BuPh$_2$SiCl, imidazole, DMF, 0°C to RT, 16 h, 96%; b) TEMPO, KBr, NaOCl, CH_2Cl_2, 0°C, 2 h, 93%; c) *t*BuNH$_2$, NCS, CCl_4, 0°C to RT, 12 h, then HCl, RT, 2 h, 96%; d) BnOCH$_2$CCH, (−)-*N*-methylephedrine, Zn(OTf)$_2$, Et$_3$N, toluene, 24 h, RT, 70% (92% *ee*); e) NaAlH$_2$(OCH$_2$CH$_2$OMe)$_2$, THF, −78°C to RT, 2 h, 92%; f) VO(acac)$_2$, *t*BuO$_2$H, CH_2Cl_2, 0°C to RT, 19 h, 62%; g) DMP, CH_2Cl_2, 0°C to RT, 1.5 h, 95%; h) $ZrCl_4$, CH_2Cl_2, 0°C to RT, 20 min; i) $NaBH_4$, MeOH, −78°C, 20 min, 36% over two steps; j) MeCH(OMe)CH$_2$, PPTS, CH_2Cl_2, 0°C to RT, 18 h, 93%; k) Bu$_3$NF, AcOH, DMF, RT, 24 h, 95%; l) DMP, CH_2Cl_2, 0°C to RT, 1 h; m) (CF$_3$CH$_2$O)$_2$P(O)CH$_2$CO$_2$Me, KN(SiMe$_3$)$_2$, THF, −78°C, 0.5 h, 68% (2 steps); n) *i*Bu$_2$AlH, THF, −78°C, 4 h, 88%; o) Ti(O*i*Pr)$_4$, *t*BuO$_2$H, (+)-diethyl L-tartrate, CH_2Cl_2, −20°C, 18 h, 92% (d.r. = 9:1); p) TiCl(O*i*Pr)$_3$, C_6H_6, RT, 1 h, 40%; q) $CuSO_4$, TsOH, acetone, RT, 20 h, 83%; r) Pd/C, H_2, EtOAc, RT, 3 h, 94%; s) 1-phenyl-1*H*-tetrazole-5-thiol, (*i*PrO$_2$C)N$_2$, PPh$_3$, THF, 0°C to RT, 1 h, 85%; t) *m*CPBA, 0°C to 40°C, 22 h, 61%. *m*CPBA = *meta*-chloroperbenzoic acid, NCS = *N*-chlorosuccinimide, PPTS = pyridinium *p*-toluenesulfonate, TBDPS = *tert*-butyldiphenylsilyl, TEMPO = 2,2,6,6-tetramethylpiperidine *N*-oxyl.

With the completion of both key fragments, the stage was set to examine the crucial fragment coupling (Scheme 3). Dess–Martin oxidation of primary alcohol **6** gave the corresponding aldehyde that was conveniently used directly in the next step. Addition of freshly prepared NaHMDS solution to a cold (−78°C) solution of **15** and the epoxyaldehyde derived from **6** followed by slow warming to room temperature gave the coupled product **16** as a 3:1 *Z*/*E* mixture.[20] Chromatographic separation of the diastereomers proved troublesome; however, epoxide opening with Ph_3PCl_2[21] led to the corresponding chlorohydrins, which could be separated easily to afford **17** in 64% yield. As a result of our observation that epoxide openings in related systems can occur with retention of configuration,[2] the stereochemical outcome of this transformation was investigated by subsequent based-induced ring closure, leading to the starting C12,C13 *cis* epoxide, supporting the C12–C13 *syn* arrangement in **17**. Further evidence for the configurational assignment was secured at a later stage of the synthesis (cf. **18**).[8] Subsequent dichlorination of the C11–C10 double bond using Et_4NCl_3 provided **18** as the major diastereomer in 70% yield.[22] The stereochemical outcome of the dichlorination was established by application of JBCA. In particular, combined analysis of the ^{1}H NMR, ^{13}C NMR, COSY, HSQC, PS-HMBC, HSQC-HECADE, and ROESY spectra of **18** revealed coupling constant patterns along C11–C12 that



Scheme 3. Fragment coupling and completion of the synthesis. a) DMP, CH_2Cl_2, 0 °C to RT, 95%; b) **15** (1.2 equiv), toluene, −78 °C, then $NaN(SiMe_3)_2$, −78 °C to RT, 67% ($Z/E = 3:1$); c) Ph_3PCl_2, CH_2Cl_2, 0 °C, 64%; d) Et_4NCl_3, CH_2Cl_2, 0 °C to 4 °C, 70%; e) H_2 (1 atm), Pd/C (20 mol%), EtOAc, 1.5 h, RT, 79%; f) Martin sulfurane, C_6H_6, RT, 2 h, 50%; g) HF–pyr, pyr, MeCN, 0 °C to RT to 40 °C, 92 h, quant.; h) palmitoyl chloride, pyr, CH_2Cl_2, −78 °C to −40 °C, then, −78 °C, MeOH, −78 °C to RT; 60%; i) DMF–SO_3 (excess), $NaSO_4$, DMF/pyr, 0 °C to RT to 45 °C, 5 h 20 min, 60%; j) F_3CCO_2H/H_2O (1:1), 4 h, 0 °C to RT.

are, in combination with the observed ROESY correlation between H10 and H13, typical of a *syn* arrangement.

The focus was next set on the introduction of the C21–C22 double bond. Hydrogenolytic deprotection of the benzylether provided **19** in 79% yield and subsequent treatment with Martin sulfurane[23] gave the *E* olefin **20** in 50% yield. The latter transformation is noteworthy because of the chemoselectivity in the hydroxyl activation step (C22-OH vs. C13-OH) as well as the regioselectivity in the subsequent elimination. The final steps of the route were then examined. The TBS groups in **20** were cleaved by reaction with HF–pyridine. Subsequent treatment of the resulting triol with palmitoyl chloride and pyridine at low temperature allowed for the selective esterification of the C23-OH group to give **21** in 60% yield over the last two steps. The chemoselectivity in the esterification step was deduced from the spectroscopic fingerprint of H23, which experiences a downfield shift from $\delta = 4.23$ to 5.30 ppm in $[D_6]$acetone upon esterification, as supported by COSY experiments. Selective mono-sulfation of C17-OH in **21** was effected with DMF–SO_3 in pyridine and proceeded in 60% yield; however, hydrolysis of the acetonides proved difficult. The dioxolane is rapidly hydrolyzed within minutes (TFA/H_2O 1:1) while the 1,3-dioxane was surprisingly stable under these conditions. Removal of the latter required prolonged stirring (4 h) at room temperature. Initially, the product was identified by HR ESIMS and purified by MS-guided HPLC techniques. Subsequent acquisition of ^1H NMR as well as COSY and HSQC spectra then provided spectral data for the synthetic material. Surprisingly, there were discrepancies in the characteristic region 4–6 ppm, which includes the protons of the chlorinated and hydroxylated stereogenic centers as well as the olefin protons. This result compelled us to re-examine the published spectral data for the natural product.

Careful reconsideration of the data available in the report of the isolation of **1**[6] led to concerns about the assignment of the configuration at C23, which is based on a temperature-dependent change of chemical shifts of the neighboring protons upon esterification of C23-OH with (*R*)-MTPA chloride. In the original disclosure of this method by Riguera et al., methoxy phenylacetic acid (MPA) derivatives were employed.[24] It is known that the shielding and deshielding effects of MTPA esters are the result of a complex conformational equilibrium and typically lead to opposite changes in the chemical shifts of the neighboring protons compared to those of MPA derivatives of the same configuration.[25] Consequently, the implementation of this method without modification is suspect. In this regard, careful scrutiny of the data reveals that the original assignment was based on an erroneous assumption concerning the conformational preferences of MTPA esters. We thus suggest that the configuration at C23 may be *R* instead of *S*. Some other features of the described data were intriguing. In this context, we note with surprise the report that esterification of **1** with Mosher's acid chloride leads to a product with the free primary hydroxy group at C1, while the secondary hydroxy group at C2 formed the corresponding esters. Unless this results from selective hydrolysis of the less hindered ester during workup (K_2CO_3, H_2O), such reactivity would stand in stark contrast to what is typical.[26] Additionally, we noted that analysis of the coupling constants provided by the authors lead to a conformation including a *syn*-pentane interaction between the C19-chloride and the C17-sulfate groups. Although such a conformation cannot be dismissed, the assignment does suggest some caution. Regretfully, the original spectra in electronic form were not available, which hampers a more detailed re-examination at this time.

In summary, we have developed a route to the nominal structure for undecachlorosulfolipid A (**1**), the most complex of the chlorosulfolipids isolated to date. As a result of our studies we note that the configuration of the natural product is misassigned. In addition to this important result some salient synthetic features are documented. These features include: the first example of an alkyne addition to an α,α-dichloro aldehyde with excellent enantiocontrol, the use of a *Z*-selective Julia–Kocienski olefination for the coupling of two stereochemically complex chlorinated fragments, a strategy for the introduction of the C21–C22 olefin that allows for regioselective introduction of the requisite double bond by controlled elimination with the Martin sulfurane reagent. Given the chemical, biological, and toxicological interest in these structures, the work we delineate collectively is of importance for ongoing efforts to understand these fascinat-

ing natural products. Moreover, the route described delineates a roadmap in the form of strategy and tactics for the synthesis of the most complex chlorosulfolipid. The configurational uncertainty provides an additional challenge to researchers in the field, which will likely be resolved only through chemical synthesis.[27]

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