Total Synthesis of Bromo- and Fluorodanicalipin A**

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Abstract: We disclose the total syntheses of (+)-bromodanicalipin A as well as (±)-fluorodanicalipin A. The relative configuration and ground-state conformation in solution of both molecules was secured by *J*-based configuration analysis which revealed that these are identical to danicalipin A. Furthermore, preliminary toxicological investigations suggest that the adverse effect of danicalipin A may be due to the lipophilicity of the halogens.

In 1969, the groups of Vagelos and Haines independently discovered the first chlorosulfolipids in extracts of the phytoflagellate *Ochromonas danica*.[1] In particular, the most complex constituent, danicalipin A (**2a**), captured the interest of researchers[2-4] even though it was not until 2009 when its relative and absolute configuration could be secured.[4] Since then, numerous total syntheses of chlorosulfolipids and accompanying biological studies have been published, albeit their biological function still remains unclear.[5] Herein, we report the total syntheses of the bromo and the fluoro analog, the determination of their ground-state conformation in solution as well as a preliminary assessment of their toxicology.

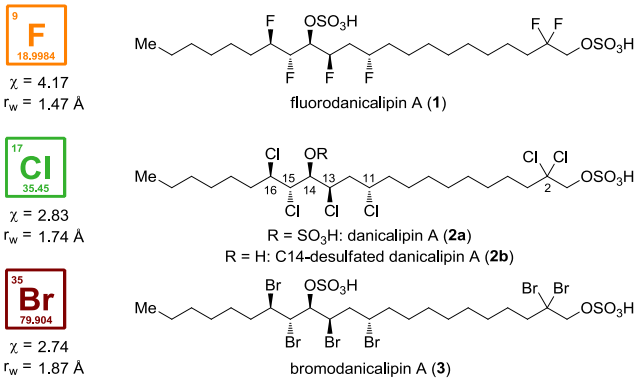
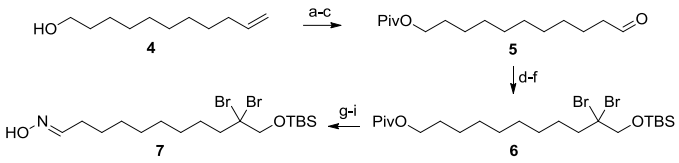


Figure 1. Fluorodanicalipin (**1**), danicalipin A (**2a**) and bromodanicalipin A (**3**). χ = electronegativity (Allred-Rochow), r_w = van der Waals radius.

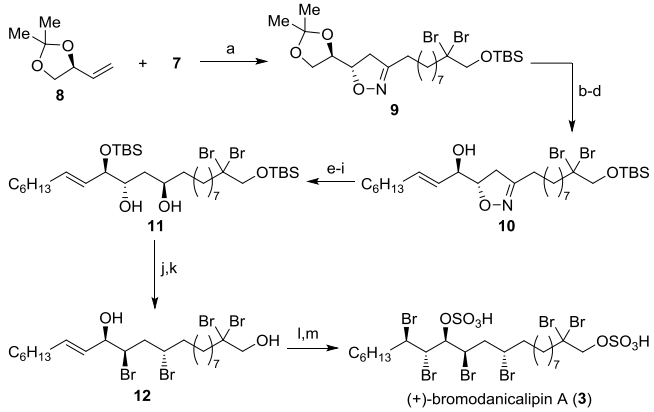
Chlorosulfolipids, which are biosynthetically derived from fatty acids through successive C14 oxygenation, sulfation and final (poly)chlorination,[2] account for about 10% of the total lipid and for up to 90% of the polar lipid content in the flagellar membrane of *O. danica*.[6] These astonishing amounts and the corresponding absence of phospholipids raise interesting questions about their function in these organisms. In addition, an intriguing observation was made when Haines replaced chloride in the growth media with bromide. Remarkably, under these conditions it was claimed that the corresponding set of bromosulfolipids was produced, presumably including bromodanicalipin A (**3**).[6]
As part of our ongoing studies towards an understanding of the biological relevance of danicalipin A (**2a**),[3h] we embarked on the syntheses of fluoro- (**1**)[7] and bromodanicalipin A (**3**). A comparative study of these congeners would potentially enable insight into the role of the halogens, analysis of their physicochemical and biological properties, understanding of their behavior in biomembranes as well as comparison of their conformations. Moreover, we were intrigued by the initial reports that underscored the instability of bromosulfolipids,[6a] a proposition which could be subjected to experimental verification by synthesis.

The synthesis of bromodanicalipin A (**3**) commenced with the preparation of the C1-C11 fragment from 10-undecen-1-ol (**4**) (Scheme 1). After protection of the 1° alcohol, the alkene was converted into **5** *via* hydroboration and subsequent Swern oxidation. Treatment of **5** with Br_2 led to the geminal dibromide.[8] The resulting unpurified product was directly reduced and protected to give **6**. A three step sequence consisting of pivalate cleavage, oxidation of the liberated alcohol and aldoxime formation afforded fragment **7**.



Scheme 1. Reagents and conditions: a) PivCl (1.1 equiv), Et_3N (1.4 equiv), DMAP (0.1 equiv), CH_2Cl_2; b) BH_3·THF (0.5 equiv), THF, 0 °C to RT, then $NaOH/H_2O_2$; c) $(COCl)_2$ (1.2 equiv), Me_2SO (2.2 equiv), Et_3N (5.3 equiv), CH_2Cl_2, −78 °C to RT, 84% over 3 steps; d) Br_2 (5.5 equiv), HBr (33% in AcOH, 14 mol%), CH_2Cl_2, 0 °C to RT; e) $NaBH_4$ (1.8 equiv), EtOH, 0 °C to RT; f) TBSCl (1.8 equiv), imidazole (1.9 equiv), DMAP (10 mol%), DMF, RT, 73% over 3 steps; g) $(i\text{Bu})_2$AlH (2.2 equiv), CH_2Cl_2, −78 °C; h) $(COCl)_2$ (1.2 equiv), Me_2SO (2.2 equiv), Et_3N (5.3 equiv), CH_2Cl_2, −78 °C to RT; i) $HONH_2$·HCl (1.2 equiv), Et_3N (1.4 equiv), EtOH, RT, 97% over 3 steps. DMAP = 4-dimethylaminopyridine, Piv = pivaloyl, TBS = *tert*-butyldimethylsilyl.

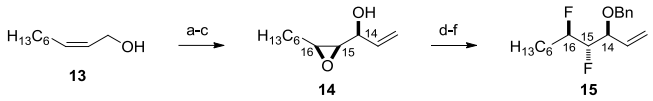
Diastereoselective nitrile oxide cycloaddition involving aldoxime **7** and olefin **8**[9] furnished isoxazoline **9** in good yield and *dr* = 79:21.[10] The *anti* and *syn* diastereomers were identified on the basis of their characteristic chemical shifts and coupling constants.[11] Chemoselective hydrolysis of the 1,3-dioxolane without concomitant loss of the TBS group was possible with phosphotungstic acid hydrate.[12] Subsequent glycol cleavage afforded a highly unstable formyl isoxazoline, which set the stage for nucleophilic addition.[13] When this aldehyde was allowed to react with the vinyl zinc species[14] obtained from 1-octyne (hydrozirconation followed by transmetallation with Me_2Zn), allylic alcohol **10** was obtained in 85% yield and *dr* = 76:24. Mosher ester analysis[15] and NMR spectroscopy studies[11] revealed *anti*-**10** to be the major product. Additionally, the *ee* could be unambiguously determined as 95% by HPLC analysis.



Scheme 2. Reagents and conditions: a) **8** (1.4 equiv), NaOCl (13% in H_2O, 3.7 equiv), CH_2Cl_2, 0 °C to RT, 89%, *dr* = 79:21; b) $H_3[P(W_3O_{10})_4]\cdot(H_2O)_{24}$ (3 mol%), $MeCN/H_2O$ (10:1), RT; c) $NaIO_4$ (1.3 equiv), THF/pH 7 buffer (1:1), 0 °C to RT, 75% over 2 steps; d) oct-1-yne (1.5 equiv), $Cp_2Zr(H)Cl$ (1.2 equiv), Me_2Zn (1.2 equiv), CH_2Cl_2, −78 °C to RT, 85%, *dr* = 76:24, 95% *ee*; e) TBSOTf (1.3 equiv), Et_3N (1.5 equiv), CH_2Cl_2, 0 °C; f) $Mo(CO)_8$ (1.2 equiv), $MeCN/H_2O$ (10:1), 90 °C; g) *i*PrCHO (11 equiv), SmI_2 (0.09 M in THF, 30 mol%), THF, −30 °C; h) $(i\text{Bu})_2$AlH (3.0 equiv), CH_2Cl_2, −78 °C, 67% over 4 steps; j) CBr_4 (4.9 equiv), PPh_3 (5.4 equiv), pyridine (13 equiv), CH_2Cl_2, RT, 45%; k) HF·pyridine (33 equiv), THF, 0 °C to RT, 99%; l) $PhNMe_3Br_3$ (1.4 equiv), CH_2Cl_2, 0 °C to RT, 99%, *dr* = 90:10; SO_3·pyridine (4.1 equiv), THF, RT, 99%. Cp = cyclopentadienyl, TBS = *tert*-butyldimethylsilyl, Tf = trifluoromethanesulfonyl.

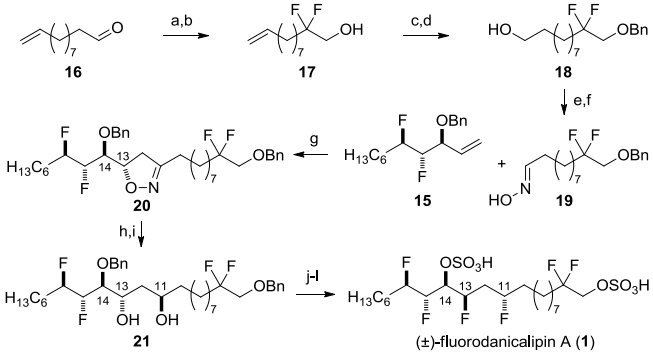
Subsequent protection of the 2° hydroxyl and opening of the isoxazoline[16] afforded a *β*-hydroxy ketone, which was subjected to an Evans–Tishchenko reduction[17] to furnish 1,3-*anti*-diol **11** (*dr* > 20:1) in 2 steps.
Double Appel substitution of the 1,3-diol in **11** gave the desired tetrabrominated compound as a single diastereomer.[18] Removal of both TBS ethers then afforded diol **12**, which was subjected to bromination with $PhNMe_3Br_3$ to deliver the desired product with *dr* = 9:1. The relative configuration of the hexabromodiol[19] was unambiguously corroborated by JBCA[20] (see supporting information). Finally, sulfation afforded (+)-bromodanicalipin A (**3**) in 99% yield.

The synthesis of fluorodanicalipin A (**1**) commenced with the preparation of olefin **15** from (*Z*)-non-2-en-1-ol (**13**) (Scheme 3). Allylic oxidation with MnO_2 afforded the unstable (*Z*)-enal which was directly subjected to the action of (vinyl)MgCl, providing the corresponding double-allylic alcohol in 92% yield. Treatment with *m*CPBA then led to the regioselective formation of an oxirane at C15/C16 and the desired *threo*-epoxy-alcohol **14** could be isolated in 84% yield and *dr* = 96:4, as identified by NMR analysis.[21]



Scheme 3. Reagents and conditions: a) MnO_2 (25 equiv), CH_2Cl_2, RT, 30 min, 97%, *Z*/*E* = 97:3; b) (vinyl)MgCl (1.3 equiv), THF, 0 °C, 2 h, 95%; c) *m*CPBA (1.2 equiv), Na_2HPO_4 (2.0 equiv), CH_2Cl_2, 0 °C, 3 h, 84%, *dr* = 96:4; d) BnBr (1.5 equiv), NaH (2.5 equiv), *n*Bu_4NI (10 mol%), THF, −78 °C to RT, 90%; e) $Et_3N{\cdot}(HF)_3$ (4 equiv), 150 °C, 8 h, 81%; f) $F_9C_4SO_2F$ (4.0 equiv), $Et_3N{\cdot}(HF)_3$ (2.0 equiv), DBU (3.0 equiv), THF, RT, 10 h, 38%. Bn = benzyl, *m*CPBA = *meta*-chloroperbenzoic acid, DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene.

Protection of the 2° alcohol set the stage for the introduction of the first fluorine. To this end, the benzyloxy epoxide was mixed with $Et_3N{\cdot}(HF)_3$ and the solution heated to 150 °C,[22] affording the (C16–F)-fluorohydrin in 81% as a single regio- and diastereomer. The introduction of the second fluoride at C15 was more challenging. After extensive experimentation, it was found that treatment with a mixture of $F_9C_4SO_2F$, $Et_3N{\cdot}(HF)_3$ and DBU in THF for 10 h provided difluoride **15** in 38% yield as a single diastereomer.[23] The synthesis of the nitrile oxide precursor **19** was addressed next. Undec-10-enal (**16**) was subjected to *α*-difluorination (Scheme 4),[24] and the difluoroaldehyde produced was isolated and directly treated with $NaBH_4$ to furnish difluoroalcohol **17** in 86% yield (2 steps).



Scheme 4. Reagents and conditions: a) *DL*-(±)-proline (2.0 equiv), $(PhSO_2)_2NF$ (2.5 equiv), THF, RT, 48 h; b) $NaBH_4$ (3.0 equiv), CH_2Cl_2/EtOH (3:2), RT, 2 h, 86% for 2 steps; c) BnBr (1.5 equiv), NaH (1.5 equiv), *n*Bu_4NI (10 mol%), THF, −15 °C to RT, 2.5 h, 84%; d) $BH_3{\cdot}$THF (0.5 equiv), THF, 0 °C to RT, 5 h; then 3.0 M aq. NaOH (1.1 equiv), H_2O_2 (3.1 equiv), 0 °C to RT, 1.5 h, 99%; e) DMP (1.9 equiv), *t*BuOH (1.9 equiv), CH_2Cl_2, RT, 0.5 h, 71%; f) Et_3N (1.2 equiv), MeOH, RT; then $HONH_2{\cdot}$HCl (1.1 equiv), 20 min, 99%, *E*/*Z* = 6:4; g) **15** (1.0 equiv), NaOCl, 13% in H_2O (3.0 equiv), CH_2Cl_2, syringe pump addition of **19** (1.2 equiv) over 24 h; RT; then RT, 16 h, 62%, *dr* > 95:5; h) $Mo(CO)_6$ (1.3 equiv), MeCN/H_2O (10:1), 90 °C, 1.5 h, 84%; i) $Me_4NBH(OAc)_3$ (10 equiv), MeCN/AcOH/CH_2Cl_2 (5.5:2.5:1), 0 °C, 2 h, 88%, *dr* = 87:13; j) $(MeOCH_2CH_2)_2NSF_3$ (6 equiv), CH_2Cl_2, 0 °C, 1 h; then RT, 24 h; k) Pd/C (15 mol%), H_2 (1 atm), MeOH, RT, 6 h, 42% for 2 steps; l) $SO_3{\cdot}$pyridine (4.0 equiv), THF, RT, 1.5 h, 93%. DMP = Dess−Martin periodinane.

Following protection of difluoroalcohol **17** attention was turned towards the elaboration of the terminal olefin into a suitable nitrile oxide precursor. Consequently, hydroboration of the olefin and subsequent *in situ* oxidation delivered primary alcohol **18** in 99% yield. Aldoxime **19** could be readily accessed in 70% yield and 2 steps by means of Dess–Martin oxidation[25] followed by condensation of the aldehyde produced with $HONH_2{\cdot}$HCl. The 1,3-dipolar cycloaddition between olefin **15** and the nitrile oxide derived from aldoxime **19** was found to proceed relatively slowly and therefore it became necessary to add the latter component by syringe pump over 24 h in order to prevent extensive dimerization of the nitrile oxide.[10] After an additional 16 h, isoxazoline **20** was isolated as a 84:16 mixture of diastereomers in favor of the desired C13/C14 *anti*-product (^3J = 3.4 Hz).[11] Separation of these by column chromatography proved simple, leading to **20** in 62% yield as a single diastereomer. Reductive opening of the isoxazoline with $Mo(CO)_6$ at 90 °C[16] followed by *anti*-selective reduction[26] of the intermediate *β*-hydroxy ketone furnished 1,3-diol **21** in 74% yield and *dr* = 87:13 in favor of the expected C11/C13 *anti*-product. The stereochemical relationship of the 1,3-diol was unambiguously secured by means of the ^{13}C NMR chemical shifts of the corresponding 1,3-acetonide[27] while the overall relative configuration could be corroborated on the basis of JBCA[20] (see supporting information). Treatment of 1,3-diol **21** with 6 equiv of $(MeOCH_2CH_2)_2NSF_3$ for 24 h afforded an inseparable mixture of the desired difluorinated compound and two tetrahydrofuran by-products.[28] Hydrogenolytic cleavage of the benzyl ether (15 mol% Pd/C, H_2) allowed clean separation of the three products, and the targeted hexafluorodiol was obtained in 42% yield over 2 steps.[29] Finally, sulfation with $SO_3{\cdot}$pyridine afforded (±)-fluorodanicalipin A (**1**) in 93% yield.

With the two analogs in hand, we conducted a preliminary evaluation of the toxicology of **1** and **3** in a standardized brine shrimp (*Artemia salina*) assay.[30] Thereby, bromodanicalipin A (**3**) (LC_{50} = 4.7 μM) exerted similar toxicity towards brine shrimp

as did danicalipin A (**2a**) (LC_{50} = 5.3 µM), whereas fluorodanicalipin A (**1**) was found to be 15-times less effective and hence comparable to docosane 1,14-disulfate (Table 1). It is noteworthy that these values are within the range of various infamous chlorinated environmental toxins such as DDT (LC_{50} = 46 µM) or toxaphene (LC_{50} = 0.77 µM).[31] In combination with previously reported data,[3h,4a] our preliminary comparative study suggests that the toxicity of the sulfolipids is highly dependent on the ability of the C11-C16 segment to counterbalance the polar character of the C14 sulfate.[32] This would, furthermore, be consistent with the finding of Okino that C14-desulfated danicalipin A (**2b**) is one order of magnitude more toxic (LC_{50} = 0.43 µM) than the natural product.[3b]

Table 1. Brine Shrimp Assay.

Entry	Compounds	LC_{50}[a]
1	Docosane 1,14-disulfate	63.8[b]
2	Danicalipin A (**2a**)	5.3[b]
3	Bromodanicalipin A (**3**)	4.7
4	Fluorodanicalipin A (**1**)	72.2

[a] LC_{50}: the median lethal concentration against brine shrimp is reported in units of µM. All experiments were performed at least in triplicate [b] Literature value (Ref. [3h]).

With ample quantities of the two synthetic halologs in hand, we set out to determine their ground-state conformation in solution using JBCA for bromodanicalipin A (**3**) and a modified version thereof for fluorodanicalipin A (**1**).[29,33] As shown in Figure 2 for X = F, Cl, and Br, the three congeners were spectroscopically indistinguishable. This structural similarity coupled with the differences in biological activity (Table 1) suggest that conformation, or shape, alone is unlikely to influence significantly the toxicity.

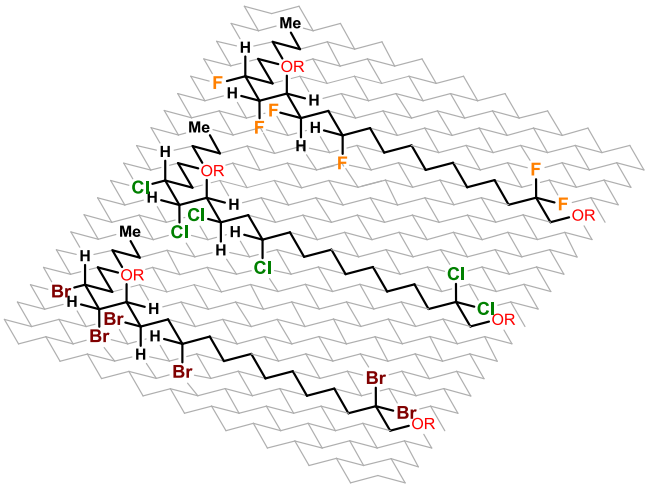


Figure 2. Ground-state conformation in solution for R = H determined for C11 to C16 by *J*-Based Configuration Analysis (for numbering see Fig. 1).

In conclusion, we reported the first asymmetric total synthesis of (+)-bromodanicalipin A (**3**), which is much more stable than previously suggested, as well as an efficient total synthesis of (±)-fluorodanicalipin A (**1**). The conformations of **1** and **3** in solution were determined by extensive NMR studies and unveiled to be identical to danicalipin A (**2a**). A preliminary brine shrimp assay was conducted which indicated that the observed adverse effect towards such aquatic organisms is most likely dependent on the lipophilicity of the halogens. With fully characterized bromodanicalipin A (**3**) in hand, we are currently seeking to confirm the results of Haines while fluorodanicalipin A (**1**) developed into a benchmark for future comparative studies. Given

that no experimental details have been provided for the production of bromolipids in *O. danica*, investigations are currently ongoing and results will be reported in due course.

Keywords: natural products • total synthesis • chlorosulfolipids • bromine • fluorine • conformational analysis

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[29] The relative configuration and ground-state conformation in solution were determined by a modified JBCA, including $^{3}J(^{1}H,^{19}F)$ analysis of coupling patterns, see supporting information.

[30] M. Lieberman, *J. Chem. Ed.* **1999,** *76*, 1689; For previous uses of this assay, see: Ref. [3e,3h,4a].

[31] See ECOTOX database of the US Environmental Protection Agency, http://cfpub.epa.gov/ecotox.

[32] K. Naumann, *J. Prakt. Chem.* **1999**, *341*, 417.

[33] The NMR experiments for the comparative study were conducted with the alcohols (R = H) in $CDCl_3$. Under these conditions we obtained sufficiently resolved spectra. In our experience derivatization of the hydroxyl groups does not impact on the ground-state conformation in solution, see also Ref. [4a].