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Biomimetic Synthesis of (±)-Merochlorin B

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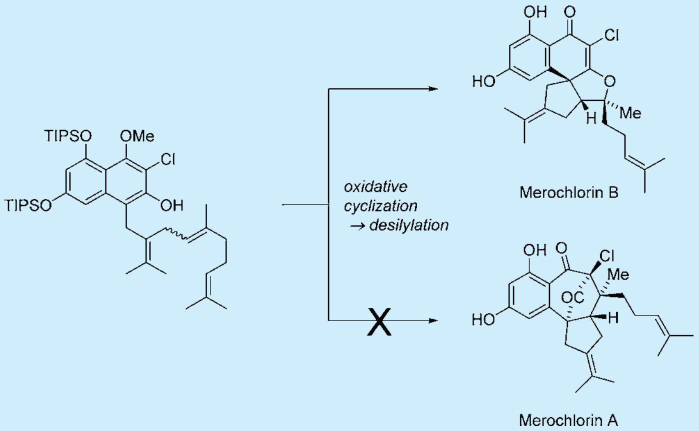
Supporting Information



ABSTRACT: A short total synthesis, guided by biosynthetic considerations, of racemic merochlorin B is presented. The formation of its isomer, merochlorin A, was not observed under the conditions. Key steps include a directed *ortho*-metalation (DoM), a selective demethylation, an *ortho*-allylation, and an oxidative [3 + 2]-cycloaddition mediated by an iodine(III) reagent.

The merochlorins, **1**–**4**, are a small family of meroterpenoids recently isolated from the sediment bacterium *Streptomyces spectrabilis* strain CNH 189 (Figure 1).[1] Merochlorins A, **1**, and B, **2**, have attracted considerable attention due to their unusual structures and their high activity against methicillin-resistant strains of *Staphylococcus aureus.*[1]

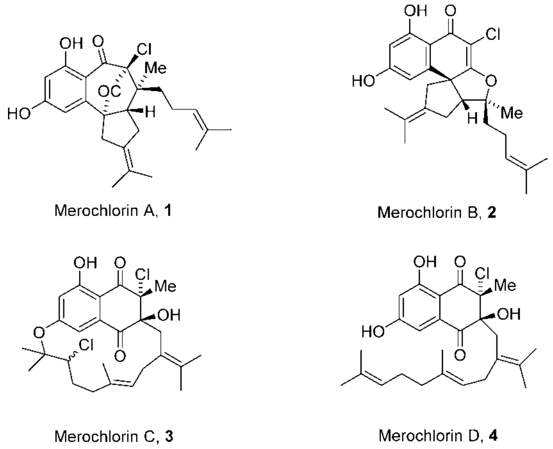


Figure 1. Merochlorins A–D, **1**–**4**, isolated from *Streptomyces spectrabilis* strain CNH-189.

Merochlorin A, **1**, features a tetracarbocyclic ring system with four contiguous stereocenters, two of which are quaternary. Its isomer, merochlorin B, **2**, possesses a ring system that incorporates a heterocycle, a chlorinated vinylogous ester, and, like merochlorin A, **1**, a propan-2-ylidenecyclopentane. Furthermore, **2** features three contiguous stereocenters, one of which is quaternary.

Biosynthetically, all members of the merochlorin family have been proposed to derive from a common chlorinated tetrahydroxynaphthalene (THN) derivative **5** (Scheme 1).[1,2] Moore and co-workers identified the biosynthetic gene cluster associated with **5** and proposed that a THN synthase, a polyprenyl synthase, a prenyltransferase, and a vanadium-dependent haloperoxidase are involved in its formation.[1b] Its subsequent cyclization to merochlorin A, **1**, and B, **2**, would proceed via epoxidation or chlorination of the central double bond.

This proposal was modified by George and co-workers who recently disclosed a biomimetic synthesis of merochlorin A, **1**.[2] They assumed that oxidation of the electron-rich aromatic core of **5**, possibly by an enzyme that contains an iron–sulfur cluster, would give rise to phenoxonium ion **6**. This reactive intermediate would then cyclize to merochlorin A, **1**, or B, **2**, via a [5 + 2]- or [3 + 2]-cycloaddition depending on the orientation of the terpenoid side chain (Scheme 1).

We now report the total synthesis of (±)-merochlorin B, **2**, that was guided by similar biosynthetic considerations. Interestingly, the formation of merochlorin A, **1**, was not observed under our conditions, whereas George and co-workers did not observe the

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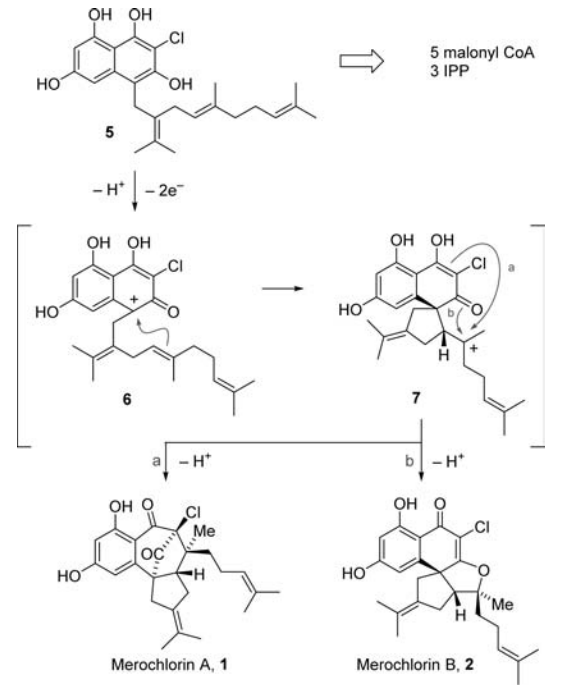
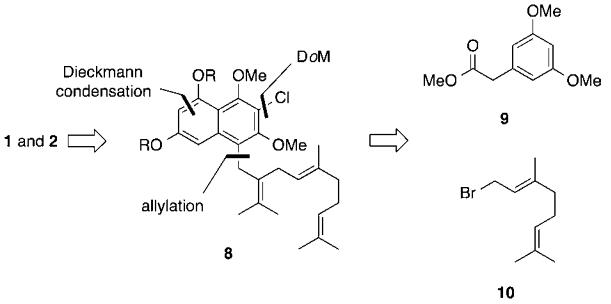
Scheme 1. Presumed Biosynthetic Origin of Merochlorin A, 1, and B, 2[2]



formation of merochlorin B, 2, under theirs. As such, our work provides another example for a subtle variation of a substrate that results in a markedly different outcome of a cascade reaction.

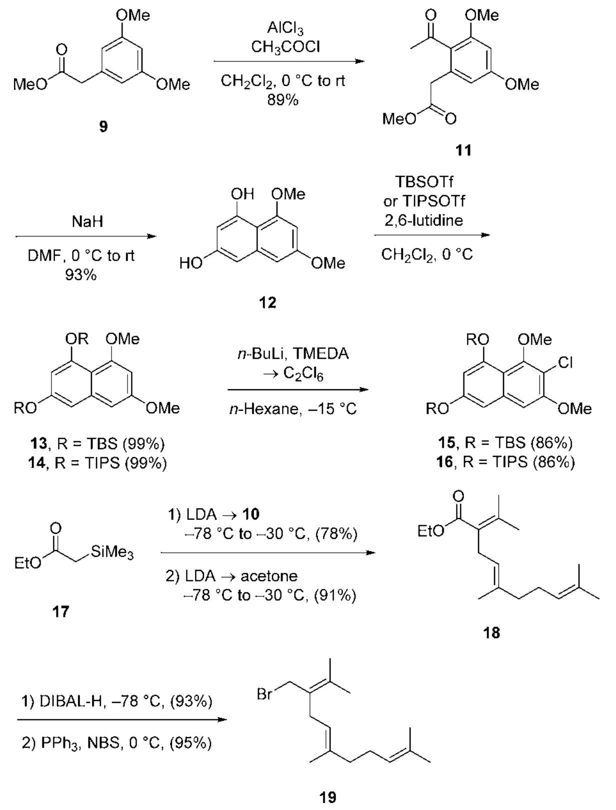
Retrosynthetically, we envisioned that 1 and 2 could be obtained from naphthalene 8, which is a protected version of 5 (Scheme 2).[3] Compound 8 could be accessed by a late stage allylation with a terpenoid side chain ultimately derived from commercially available geranyl bromide, 10. Furthermore, the incorporation of the chlorine atom could be achieved by a directed *ortho*-metalation (D*o*M) of a protected dimethoxynaphthalene derivative which in turn could be accessed via Dieckmann condensation starting from phenylacetic acid methyl ester 9.

Scheme 2. Retrosynthetic Analysis of Merochlorins A, 1, and B, 2



Accordingly, our synthesis commenced with the preparation of 6,8-dihydroxy-1,3-dimethoxynaphthalene, 12, from phenylacetic acid 9 using a modification of a known procedure (Scheme 3).[4] Friedel–Crafts acylation of 9 then afforded acetophenone 11 which underwent Dieckmann cyclization in excellent yield upon treatment with sodium hydride.[5,6] Protection of both phenolic hydroxyl groups with TBS or TIPS triflate afforded naphthalenes 13 and 14. The use of the more reactive triflate reagents was necessary at this point to achieve the protection of the sterically more hindered hydroxyl group in the *peri*-position of the naphthalene core 12.

Scheme 3. Synthesis of the Naphthalene Building Blocks 15 and 16 and of Allylic Bromide 19

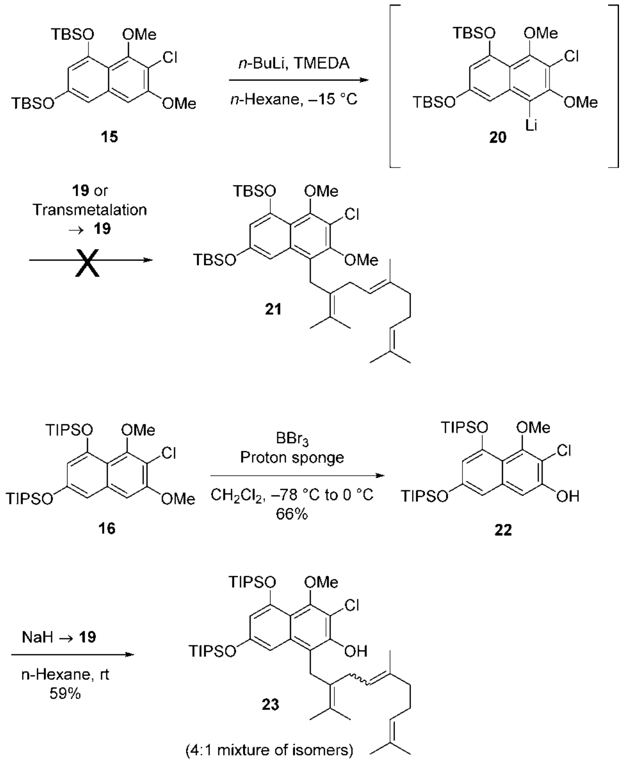


The ability of methoxy groups to direct the metalation of aromatic systems is well described in the literature.[7] In our case, the cooperative interaction of the two methoxy groups led to a completely regioselective metalation. Treatment of naphthalene 13 or 14 with *n*-BuLi and TMEDA formed the corresponding lithiated species, which was quenched with hexachloroethane (C_2Cl_6) to form the chlorinated naphthalene cores 15 and 16, respectively, in high yield. The advantages of C_2Cl_6 over other Cl^+-sources have been documented in the literature.[8]

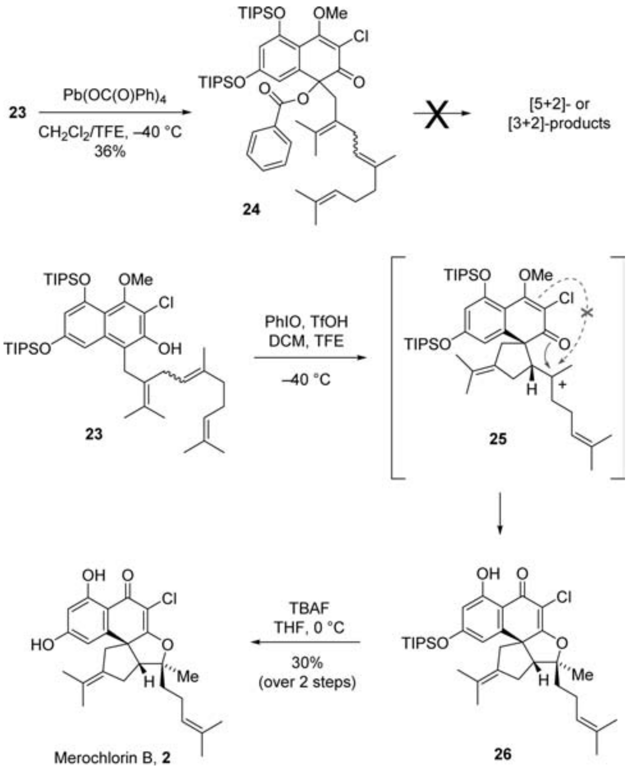
Initial experiments to access the terpenoid side chain using a Horner–Wadsworth–Emmons strategy[9] did not lead to acceptable results in our case. We therefore took recourse to a Peterson olefination[10] starting from commercially available silyl acetate 17 which was alkylated with geranyl bromide, 10, in good yield (Scheme 3).[11] Subsequent treatment with LDA followed by the addition of acetone gave *α*,*β*-unsaturated ester 18.[12] Reduction followed by Appel reaction then provided the sensitive bromide 19 in good yield.

With compounds 15, 16, and 19 in hand we investigated the formation of cyclization precursor 21 (Scheme 4). Our initial plan was to incorporate the side chain by a second directed *ortho*-metalation of the aromatic core 15 followed by reaction of the resulting organolithium compound 20 with the bromide 19.[13] Although the regioselective formation of 20 could be proven by D_2O quench, it was impossible to connect side chain 19 in that manner. The transmetalation of 20 with various metals (Cu, Mg, Zn, $SnMe_3$) and addition of 19 with and without palladium catalysis did not lead to the desired coupling product 21 either. As a consequence, we changed the order of events and

Scheme 4. Synthesis of Cyclization Precursor 23



Scheme 5. Synthesis of Merochlorin B, 2



investigated demethylation of the chlorinated naphthalenes **15** and **16**. After extensive optimization, compound **16** could be selectively deprotected by boron tribromide in good yield. The addition of proton sponge and use of the TIPS protected core **16** was found to be essential for a fast and clean conversion to naphthol **22** in the presence of silyl protecting groups.[14] Importantly, double demethylation was not observed under these conditions.

Gratifyingly, naphthol **22** underwent clean *ortho*-allylation by treatment with sodium hydride and subsequent trapping with allylic bromide **19**.[15] The resulting prenylated naphthol **23** was obtained in good yield as an inseparable 4:1 mixture of isomers, presumably due to an isomerization at the double bond indicated in Scheme 4. An analogous isomerization was observed by George and co-workers in their synthesis of merochlorin A, **1**.[2]

In an attempt to synthesize both merochlorin A, **1**, and B, **2**, we treated **23** with lead(IV) tetraacetate (LTA). These conditions, also used by George and co-workers,[2] resulted in a complex mixture of products. Based on ^{1}H NMR and mass spectroscopy data, we determined that the major component of this mixture resulted from Wessely oxidation (not shown).[16] A much cleaner reaction was observed by changing the oxidant to lead(IV) tetrabenzoate, which can be prepared from LTA via ligand exchange,[17] and use of a mixture of dichloromethane and trifluoroethanol (TFE) as a solvent (Scheme 5). Under these conditions, the Wessely oxidation product **24** could be isolated in moderate yield. Inspired by the work of Horne et al.,[3d] we tried to use **24** as a precursor of the requisite phenoxonium ion. However, when **24** was treated with a variety of Brønsted and Lewis acids, no [5 + 2]- or [3 + 2]-cycloaddition products could be observed.

We next turned to iodine(III) reagents[18] as oxidants. After extensive screening, we found that a variant of Koser's reagent [PhI(OH)OTs],[19] generated *in situ*, gave a desired product. Mixing iodosobenzene (PhIO) with trifluoromethanesulfonic acid,[20] followed by addition to naphthol **23**, afforded merochlorin B derivative **26**, which still contained one of the two silyl ethers of the starting material (Scheme 5). Subsequent deprotection afforded merochlorin B, **2**, as a single diastereomer and in 30% overall yield from **23**. The spectral data of our synthetic compound are in accordance with those reported by Moore et al.,[1b] and Prof. Moore agrees with this analysis (see Supporting Information).[21]

Interestingly, we did not observe the formation of merochlorin A, **1**, under our oxidative conditions. We believe that this is not due to a variation in the oxidant but rather due to the presence of a methyl ether in intermediate **25**. In the case of George's merochlorin A, **1**, synthesis,[2] the corresponding cyclization precursor bears a free hydroxyl group at the C-1 position, which can be deprotonated, rendering the resultant enolate highly nucleophilic. Presumably, the methyl substituent in intermediate **25** increases the relative nucleophilicity of the carbonyl, thus favoring the [3 + 2]-pathway. The resulting oxocarbenium ion is either directly demethylated by nucleophilic attack or forms a labile acetal that is lost upon aqueous workup.

In conclusion, we have achieved the first total synthesis of (±)-merochlorin B, **2**, a biologically active chlorinated meroterpenoid, by a longest linear sequence of eight steps starting from commercially available phenylacetic acid methyl ester **9**. Key steps include a directed *ortho*-metalation (DoM), a chemoselective demethylation of a naphthalene, and a biosynthetically inspired oxidative [3 + 2]-cycloaddition using an iodine(III) reagent generated *in situ*. Attempts to achieve asymmetric syntheses of the merochlorins are currently underway in our laboratories and will be reported in due course.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental details as well as spectroscopic and analytical data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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