Biomimetic Synthesis | Hot Paper

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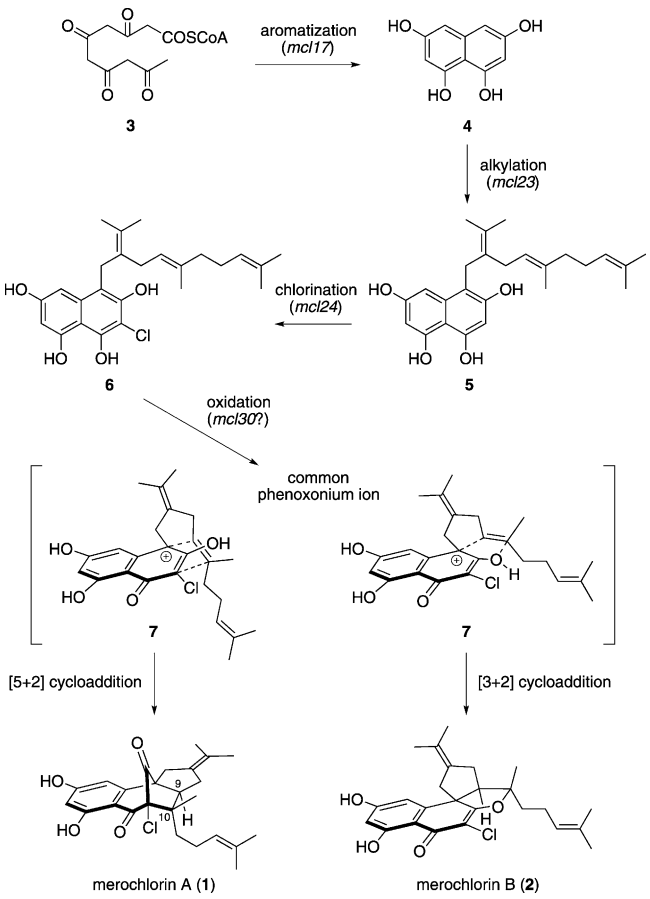
Biomimetic Total Synthesis of (±)-Merochlorin A**

*Henry P. Pepper and Jonathan H. George**

Dedicated to Professor Sir Jack E. Baldwin on the occasion of his 75th birthday

Merochlorins A (**1**) and B (**2**) are isomeric chlorinated meroterpenoids with unique polycyclic ring systems, and were recently isolated from the marine bacterium *Streptomyces* sp. strain CNH-189.[1] Merochlorin A has a compact bicyclo[3.2.1]octanone[2] core with four contiguous stereocenters, three of which are quaternary. The structure of **1** was initially elucidated using 2D NMR studies.[1b] However, later X-ray studies[1a] and our synthetic work indicate that its structure should be represented as shown in Scheme 1 (the configurations of the stereocenters at C9 and C10 of **1** were originally misassigned). Further to its structural interest, **1** is a potent antibiotic against *Clostridium difficile* (MIC = 0.15 μg mL^{-1}) and various multi-drug resistant *Staphylococcus aureus* strains (MIC = 2–4 μg mL^{-1}).[1b] It is therefore an excellent lead candidate for the development of novel antibiotics. However, the mechanism of action of **1** is unknown, and given its scarcity in nature a chemical synthesis is desirable.

Merochlorin B has a 6-5-5-fused ring system with three contiguous stereocenters and an α-chloroenone motif. The unprecedented structures of **1** and **2** suggest an unusual biosynthesis. This was investigated by Moore et al.,[1a] who partially sequenced the genome of the CNH-189 bacterium to reveal a merochlorin gene cluster containing 41 genes (*mcl1-mcl41*). The key genes implicated in the biosynthesis of the merochlorins were found to encode a 1,3,6,8-tetrahydroxynaphthalene synthase (*mcl17*), an aromatic prenyl transferase (*mcl23*), a vanadium-dependent haloperoxidase[3] (VHPO; *mcl24*), and a protein containing an iron–sulfur cluster (*mcl30*). On the basis of their bioinformatic analysis, Moore and co-workers proposed a biosynthesis of **1** and **2** involving VHPO-dependent chlorination or oxidation of an alkene as the prelude to a cyclization cascade to form the polycyclic ring systems.[1a] However, their proposed cyclization mechanism is (by their own admission) highly speculative, and we herein propose an alternative biosynthetic mechanism (Scheme 1). In common with the biosynthesis described by Moore et al., we suggest that the starting point for the biosynthesis of **1** and **2** is the formation of 1,3,6,8-tetrahydroxynaphthalene (**4**) by aromatization of the acyclic polyketide **3**, catalyzed by the *mcl17* polyketide synthase. We then propose that **4** undergoes alkylation (*mcl23*) to give **5** and chlorination (*mcl24*) to give **6**. Oxidative dearomatization of **6** (perhaps catalyzed by the putative protein that contains the Fe–S cluster and is encoded by *mcl30*) would then generate phenoxonium ion **7** which could cyclize through a [5+2] cycloaddition to give **1** or a [3+2] cycloaddition to give **2**. These cycloadditions are presumably stepwise in mechanism. Previously, intramolecular [5+2] cycloadditions have been proposed to occur between *para*-quinones and alkenes in the biosynthesis of α- and β-pipitzol[4] and elisapterosin B,[5] which has inspired elegant biomimetic syntheses of these molecules.[6] However, we believe our suggested pathway to merochlorin A is the first proposal of a biosynthesis to involve an intramolecular [5+2] cycloaddition directly initiated by an oxidative dearomatization.



Scheme 1. Our proposed biosynthesis of merochlorins A and B. The key genes encoding the proteins responsible for a specific transformation are given in brackets.

[*] H. P. Pepper, Dr. J. H. George
School of Chemistry and Physics, University of Adelaide
Adelaide, SA 5005 (Australia)
E-mail: jonathan.george@adelaide.edu.au

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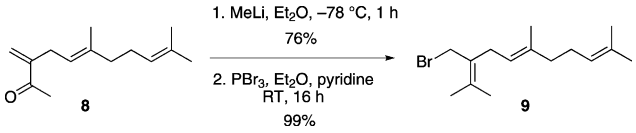
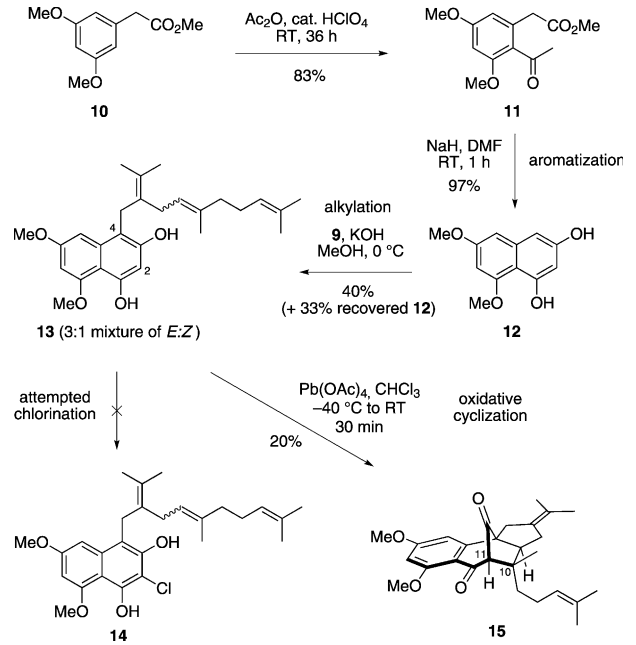
Our aim was to use this unprecedented biosynthetic pathway as the inspiration for a total synthesis of **1** that would involve a related sequence of aromatization, alkylation, chlorination, and oxidative cyclization reactions as the key steps. We have recently used a conceptually similar analysis of a biosynthesis to design short biomimetic syntheses of complex natural products.[7] This approach can inspire syntheses that rapidly install the molecular architecture of a natural product target with minimal protecting group operations and functional group interconversions.[8]

The first synthetic target was a highly functionalized tetrahydroxynaphthalene derivative similar to **6**, which is composed of terpene and polyketide fragments. Synthesis of the terpene fragment in the form of alkyl bromide **9** was achieved according to Scheme 2. Addition of methyllithium to the known ketone **8**[9] gave an allylic alcohol in 76% yield, which was then brominated to give the unstable alkyl bromide **9**[10] in near-quantitative yield.[11]



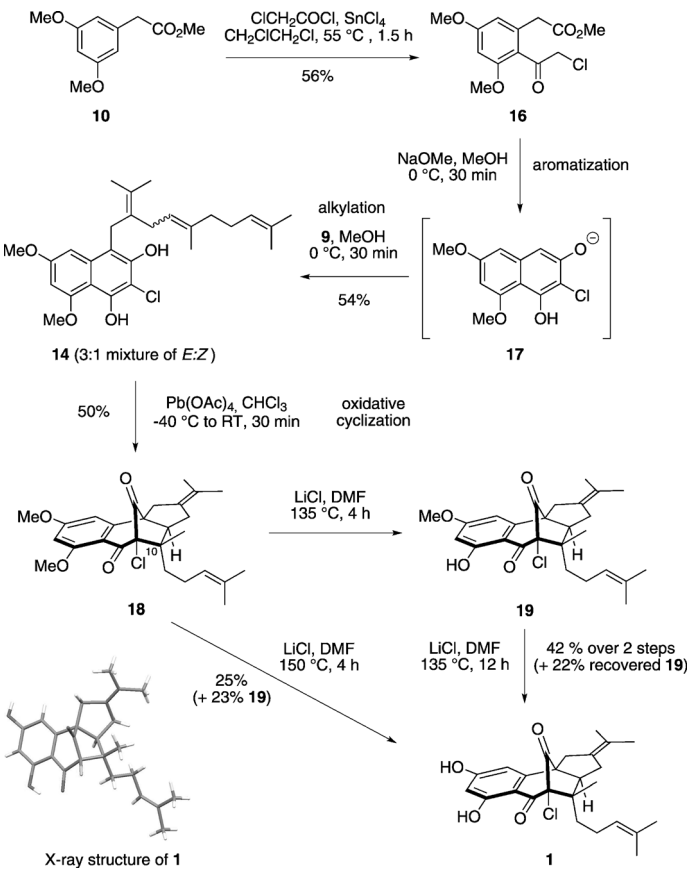
Scheme 2. Synthesis of alkyl bromide **9**.

Synthesis of the polyketide fragment began with Friedel–Crafts acylation of methyl 3,5-dimethoxyphenyl acetate **10**[12] to give **11**[13] (Scheme 3). Ketone **11** was then aromatized under basic conditions to give 1,3-dihydroxy-6,8-dimethoxynaphthalene (**12**)[14] in high yield. We were pleased to find that **12** could be selectively alkylated at C4 with alkyl bromide **9** to give **13** in 40% yield (with 33% recovered starting material), although efforts to drive the reaction further to completion led to undesired alkylation at C2. NMR analysis indicated that **13** had been formed as an inseparable 3:1 mixture of *E* and *Z* alkenes because of an unusual partial isomerization of the terpene side chain. Unfortunately, all attempts to selectively chlorinate **13** at the nucleophilic C2 position failed to generate **14**. However, after screening a variety of oxidants, we were encouraged to observe that oxidative dearomatization[15,16] of **13** with $Pb(OAc)_4$[17] gave merochlorin A analogue **15** through an intramolecular [5+2] cycloaddition,[18] albeit in modest yield. The relative configuration of **15** was established by analysis of 2D NMR spectra,[19] which were very similar to the published data for merochlorin A.



Scheme 3. Synthesis of merochlorin analogue **15**. DMF = *N*,*N*-dimethylformamide.

Given the difficulty of selectively chlorinating **13**, we elected to introduce the chlorine atom at an earlier point in the synthesis (Scheme 4). Thus, Friedel–Crafts reaction between methyl 3,5-dimethoxyphenyl acetate (**10**) and chloroacetyl chloride in the presence of $SnCl_4$ gave the chloroketone **16** in 56% yield. We then used a one-pot aromatization–alkylation sequence to convert **16** directly into **14** (again formed as an inseparable 3:1 mixture of *E* and *Z* alkenes) in 54% yield by sequential treatment with NaOMe in MeOH followed by alkyl bromide **9**. This reaction formed two key carbon–carbon bonds in one step, presumably via the phenolate anion **17**, and is a concise method for the synthesis of highly functionalized naphthalene derivatives.



Scheme 4. Total synthesis of merochlorin A.

Treatment of **14** with $Pb(OAc)_4$ rapidly formed **18** as a single diastereomer, generating the bicyclo[3.2.1]octanone ring system of **1** in 50% yield. This cascade reaction formed two carbon–carbon bonds, two rings, and four contiguous stereocenters (two of which are all-carbon quaternary centers) by a mechanism that perhaps mirrors the biosynthesis of **1**. The formation of a single diastereomer of **18** from a 3:1 mixture of *E* and *Z* isomers of **14** suggests that the key [5+2] cyclization is nonconcerted, and instead proceeds via a tertiary carbocation intermediate that preferentially cyclizes to give the most stable diastereomer, that is, the diastereomer that minimizes steric interactions between the alkyl chain at C10 and the adjacent cyclopentene ring. Although there are a few other examples of biomimetic intramolecular [5+2] cycloadditions in natural product synthesis,[6] we believe this is the first example that is directly initiated by oxidative dearomatization. It was interesting to note that cyclization of the chlorinated naphthalene derivative **14** was significantly higher yielding than cyclization of the nonchlorinated derivative **13**, which perhaps lends weight to our biomimetic proposal. Products containing the ring system of **2** were not observed in this reaction, indicating that cyclization of phenoxonium ion **7** is predisposed to form **1** under non-enzymatic conditions.

Conversion of **18** to (±)-merochlorin A was challenging, as it was unstable toward Lewis acids (e.g. BBr_3) commonly used for the demethylation of aryl methyl ethers.[20] However, we eventually found that heating **18** at 150 °C for 4 hours with LiCl in DMF[21] gave **1** in 25% yield, along with the monodemethylated analogue **19** in 23% yield. Presumably the second demethylation was hindered by the presence of a neighboring phenolate anion, so we reasoned that the yield could be improved by conducting two successive monodemethylations. Thus, treatment of **18** with LiCl in DMF at 135 °C for 4 hours gave **19**, which was re-subjected to identical reaction conditions for 12 hours immediately after a work-up to give **1** in 42% yield over the two steps. Analytical data for **1** fully matched the published data of Moore et al.,[1a] and the structure was confirmed by X-ray crystallography.[22] Importantly, our overall synthetic strategy will be amenable to the rapid generation of diverse merochlorin analogues to allow structure–activity relationships of this potent antibiotic to be investigated, primarily through systematic variation of a) the alkyl chain at C10, b) the halogen substituent at C11, and c) the substitution pattern of the aromatic ring. The synthesis is also scalable, with over 1 gram of **1** prepared by this route to date.

In summary, we have completed the first total synthesis of the highly active antibiotic (±)-merochlorin A in four linear steps from 3,5-dimethoxyphenyl acetate (**10**). The overall synthetic strategy is based on our proposed biosynthesis, including a sequence of aromatization, alkylation, and oxidative cyclization reactions. We believe our synthesis gives insight into the biosynthesis of merochlorin A, strongly suggesting its formation through a stepwise [5+2] cyclization initiated by oxidative dearomatization. Finally, the rapid formation of the molecular framework of the natural product with minimal protecting-group operations fully vindicates a biomimetic approach to synthesis in this case.[23]

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