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Total Synthesis of Naphterpin and Marinone Natural Products

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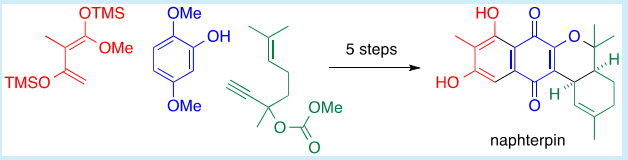
Supporting Information

ABSTRACT: A concise and divergent strategy for the synthesis of the naphterpin and marinone meroterpenoid families has been developed. The approach features a succession of pericyclic reactions—an aromatic Claisen rearrangement, a retro-6π-electrocyclization, and two Diels–Alder reactions—which facilitated the first total synthesis of naphterpin itself in five steps from 2,5-dimethoxyphenol, alongside similar syntheses of 7-demethylnaphterpin and debromomarinone. Late-stage oxidation and bromination reactions were also investigated, leading to the first total syntheses of naphterpins B and C and isomarinone.



Marine and terrestrial strains of *Streptomyces* bacteria have been an excellent source of new natural products with novel structures and potent bioactivity,[1] including naphthoquinone meroterpenoids such as the naphterpins (Figure 1a),

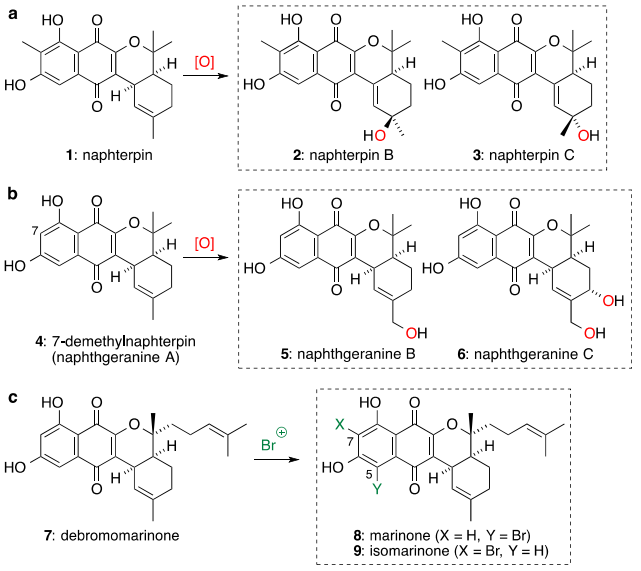
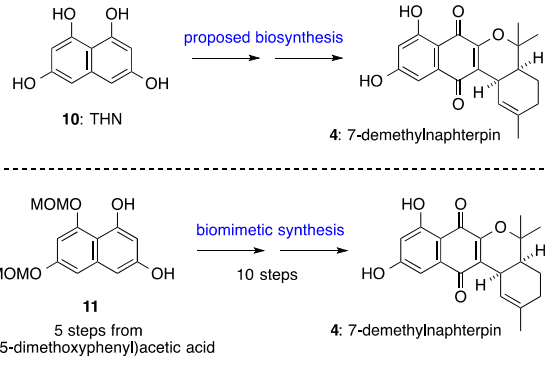


Figure 1. THN meroterpenoids of interest in this work: (a) the naphterpins, (b) the naphthgeranines, (c) the marinones.

the naphthgeranines (Figure 1b), and the marinones (Figure 1c). Naphterpin (**1**) was the first natural product discovered in this family, isolated by Seto et al. in 1990 from *Streptomyces* sp. CL-190 that was collected in Ishigaki Island, Okinawa.[2] The isolation of the oxidized derivatives naphterpin B (**2**) and naphterpin C (**3**) from the same microbial source was reported later in 2005.[3] Naphthgeranine A (**4**, also independently reported as 7-demethylnaphterpin[4]) was isolated alongside several oxidized derivatives such as naphthgeranine B (**5**) and naphthgeranine C (**6**) by Zeeck in 1991.[5] Debromomarinone (**7**) and marinone (**8**) were isolated by Fenical and coworkers from an actinomycete derived from marine sediment in 1992,[6] with isomarinone (**9**) reported in 2000.[7]

Previous ^{13}C labeling studies by Seto et al.[8] and Moore et al.[9] have indicated that the naphterpins and marinones are biosynthetically derived from 1,3,6,8-tetrahydroxynaphthalene (THN, **10**) and either geranyl or farnesyl diphosphate, respectively, although the precise biosynthesis was not immediately obvious (Scheme 1). We recently proposed a

Scheme 1. Proposed Biosynthesis and Previous Biomimetic Synthesis of the Naphterpins and Marinones



biosynthetic pathway to the naphterpins and marinones in which the THN ring system undergoes oxidation via "cryptic chlorination" catalyzed by vanadium-dependent haloperoxidases (VHPOs), despite the absence of chlorine in these natural products.[10] This biosynthetic speculation was originally based on analogies to the merochlorin[11] and napyradiomycin[12] families of marine *Streptomyces* meroterpenoids, which we have previously shown to be biosynthesized via the VHPO-catalyzed dearomatization of THN derivatives. On the basis of our

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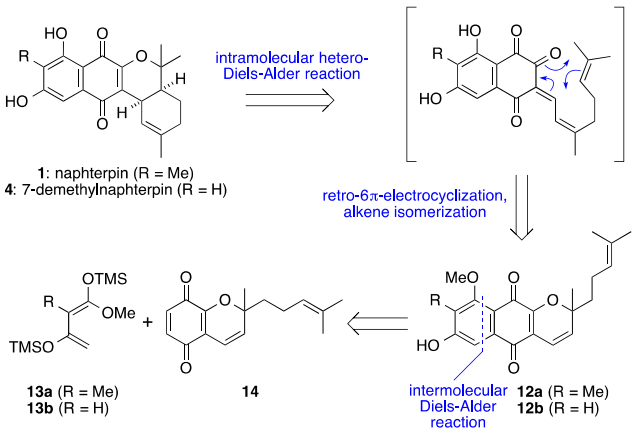
biosynthetic studies, we achieved a biomimetic synthesis of 7-demethylnaphterpin (**4**) and debromomarinone (**7**) from the protected THN derivative **11**.[10] We also synthesized several proposed biosynthetic intermediates, which were used to decipher the reactivity of two VHPO enzymes from the putative marinone gene cluster that chlorinate and dearomatize prenylated THN derivatives. However, because of the complexity of the biosynthetic pathway, our biomimetic route to 7-demethylnaphterpin (**4**) and debromomarinone (**7**) was 15 steps from commercially available (3,5-dimethoxyphenyl)acetic acid (Scheme 1). The biomimetic strategy was too long and too linear to allow the synthesis of further oxidized or brominated members of the naphterpin/marinone family.

We have therefore devised a simpler, nonbiomimetic retrosynthetic analysis of the naphterpins that is not constrained by the use of a THN building block (Scheme 2). We

Scheme 2. Retrosynthetic Analysis of the Naphterpins



envisaged that the cis-fused cyclohexane and pyran rings of **1** and **4** could be formed by an intramolecular hetero-Diels–Alder reaction of a reactive enone, which is unveiled via a late-stage retro-6π-electrocyclization (and alkene isomerization) of naphthoquinones **12a/b**. This endgame was also used in our previous synthesis.[10] However, the disconnection of **12a/b** from the simple Brassard dienes[13] **13a/b** and quinone **14** via an intermolecular Diels–Alder reaction[14] (and aerobic oxidation) had the potential to significantly shorten our previous biomimetic synthesis and therefore allow divergent access to oxidized and brominated family members. A related intermolecular Diels–Alder reaction was used in Nakata's total synthesis of the napyradiomycin A80915G[12a] and also in Tapia's synthetic study toward the naphterpins (but no naphterpin total syntheses were achieved by this route).[15]

As shown in Scheme 3, our synthesis of the naphterpin family began with the commercially available 2,5-dimethoxyphenol (**15**),[16] which was coupled to propargylic carbonate **16**[17] in the presence of DBU and copper(II) chloride[18] to give **17**. The thermal rearrangement of **17** gave chromene **18** in high yield via a sequence of aromatic Claisen rearrangement to give an *o*-allenyl phenol, followed by a 1,5-hydrogen shift to give an *o*-quinone methide and a final oxa-6π-electrocyclization.[19] Chromene **18** was then oxidized to give quinone **14** using $PhI(O_2CCF_3)_2$.[20] A regioselective intermolecular Diels–Alder reaction between **14** and diene **13a**[21] proceeded spontaneously at room temperature to give naphthoquinone **12a** (presumably via the aerobic oxidation of an intermediate hydroquinone). Heating **12a** with $MgBr_2$ in MeCN induced a retro-6π-electrocyclization and alkene isomerization to give a reactive enone, which then underwent an intramolecular Diels–Alder reaction to form naphterpin (**1**). The labile C-8 methyl ether was also cleaved under these mild conditions. The epoxidation of naphterpin with *m*-CPBA gave a separable 3:1 mixture of epoxides **19** and **20**. Unexpectedly, the major epoxide diastereomer **19** results from the electrophilic attack on the concave face of the $\Delta^{12,13}$ alkene of **1**. However, Brase et al. observed a similar ratio of endo and exo epoxide products in the epoxidation of a related meroterpenoid system.[22] The relative configuration of **19** was unambiguously assigned via single-crystal X-ray crystallography, whereas **20** was assigned using nuclear Overhauser effect (NOE) data and a comparison of key ^3J coupling constants with computational predictions.[23] The ring opening of epoxides **19** and **20** with lithium diisopropylamide (LDA) then gave naphterpin B (**2**) and naphterpin C (**3**), respectively, presumably by an E1cB mechanism that involves an intermediate *o*-quinone methide enolate, with the retention of the stereochemistry at C-13. The relative configuration of naphterpin C was originally assigned by Seto via a rotating frame Overhauser enhancement spectroscopy (ROESY) correlation between Me-20 and Me-18. Replacing diene **13a** with **13b**[24] in the intermolecular Diels–Alder reaction with quinone **14** allowed the synthesis of **12b**, followed by 7-demethylnaphterpin (**4**) upon Lewis-acid-catalyzed rearrangement. To date, we have been unable to convert **4** into more oxidized members of the naphthgeranine family, such as naphthgeranines B and C (**5** and **6**), via allylic oxidations.

The synthetic strategy was also applicable to the marinone family by replacing the prenyl propargylic carbonate **16** with geranyl propargylic carbonate **21**,[25] which was coupled to **15** to give **22** (Scheme 4). The thermal aromatic Claisen rearrangement of **22**, followed by oxidation gave quinone **23**, which underwent a facile intermolecular Diels–Alder reaction with **13b** to give naphthoquinone **24**. The conversion of **24** to debromomarinone (**7**) was then achieved via the now familiar $MgBr_2$-catalyzed cascade of retro-6π-electrocyclization and the intramolecular hetero-Diels–Alder reaction. Finally, debromomarinone was brominated using 1.5 equiv *N*-bromosuccinimide (NBS) in CH_2Cl_2 at 0 °C. Under these conditions, we observed the exclusive bromination of **7** at C-7 to give isomarinone (**9**) in 38% isolated yield. We observed no bromination at C-5 and therefore no formation of marinone (**8**). Heteronuclear multiple bond correlation (HMBC) correlations confirmed the original assignment of the isomarinone bromination pattern. In nature, the selective bromination of **7** at C-5 to give marinone (**8**) might occur under the control of a vanadium-dependent haloperoxidase enzyme, or it could occur at an earlier point in the biosynthetic pathway.

While searching online databases for further members of the naphterpin family of meroterpenoids, we found a report of "naphthoquinone C" (**25**), isolated from a marine-derived *Penicillium* sp. (Figure 2).[26] Given the likely biosynthetic origin of **25** from THN and geranyl diphosphate, we thought that its structure was probably misassigned. Indeed, the comparison of the ^{1}H NMR spectrum of **25** recorded in CD_3OD showed an excellent match with the corresponding data for the previously reported naphthgeranine C (**6**).[5a,27] Unfortunately, the ^{13}C NMR spectra of the two natural products were recorded in different solvents; nevertheless, we suggest that naphthoqui-

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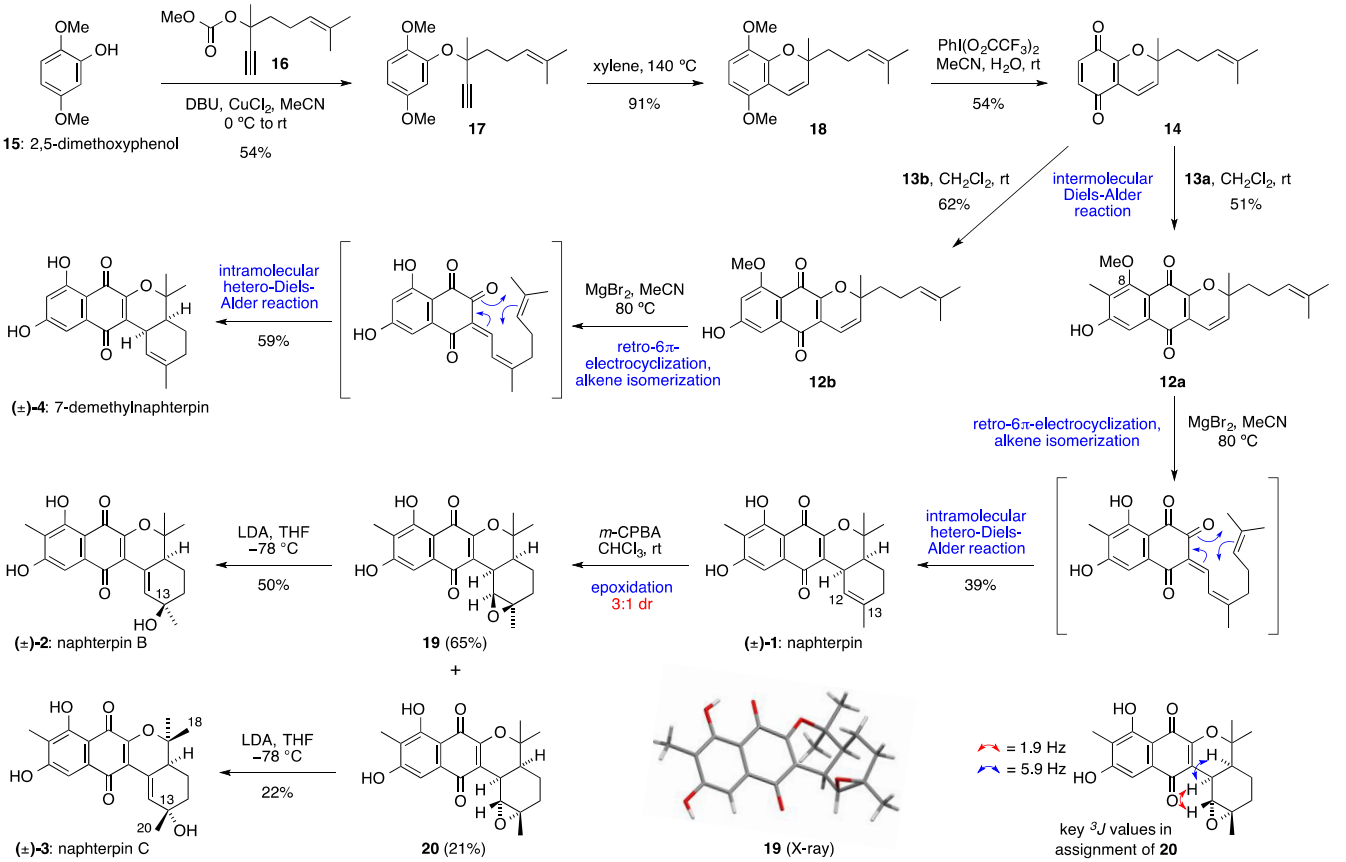
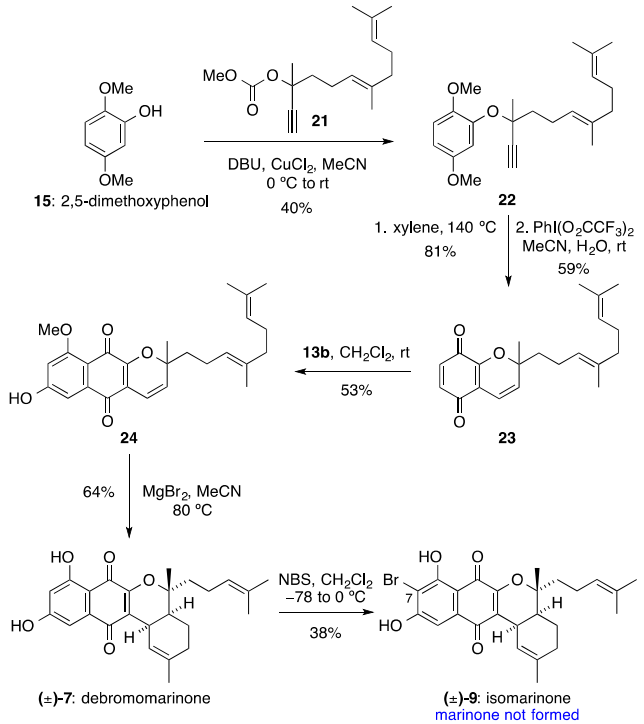
Scheme 3. Divergent Total Synthesis of Naphterpin, Naphterpin B, Naphterpin C, and 7-Demethylnaphterpin



Scheme 4. Total Synthesis of Debromomarinone and Isomarinone



none C has been incorrectly assigned, and that it is probably reisolated naphthgeranine C.[28] This proposal is supported by the computational prediction of the ^{13}C NMR spectra of structures **6** and **25** and the comparison to the natural product data.[23]

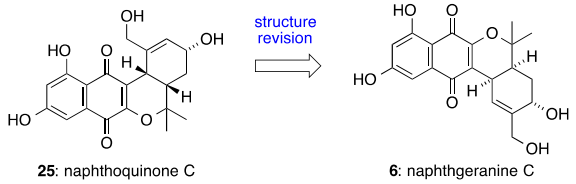


Figure 2. Suggested structure revision of naphthoquinone C.

In conclusion, we have developed a concise, modular strategy for the synthesis of the naphterpin and marinone families of marine merotepenoids. This has resulted in the divergent synthesis of six natural products, with naphterpin, naphterpin B, naphterpin C, and isomarinone all synthesized for the first time. The synthetic strategy features a sigmatropic rearrangement, an electrocyclization and two Diels–Alder reactions, thus showcasing the power of pericyclic reactions in the construction of complex natural products.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b03095.

Experimental procedures and analytical data for all new compounds (PDF)

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Accession Codes

CCDC 1944007 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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