Total Syntheses of Strasseriolide A and B, Antimalarial Macrolide Natural Products

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Supporting Information Placeholder

ABSTRACT: We report the first total syntheses of strasseriolide A and B. Strasseriolide B shows potent activity against the wild-type malaria parasite *Plasmodium falciparum* and good activity against a chloroquine-resistant strain. A convergent strategy was envisioned with an aldehyde-acid fragment and a vinyl iodide-alcohol fragment. Both fragments were prepared using chiral pool starting materials. They were combined with a Yamaguchi esterification and cyclized with a Nozaki-Hiyama-Kishi reaction. Strasseriolide B was assembled in a 16-step LLS.

Malaria is a highly infectious disease whose mortality rates have reached epidemic proportions in the last century. According to the World Health Organization’s (WHO) annual malaria report, 2020 saw approximately 241 million individuals contract malaria, a 5% increase from 2019. This number is disproportionately concentrated in underdeveloped subtropical regions that lack the infrastructure to effectively combat the disease. What has become an even greater concern in the past decade is the emergence of strains of the parasite that are resistant to the current leading therapeutic treatments such as chloroquine and artemisinin (Figure 1). Through this effort, strasseriolide (1) was isolated, and its biological activity was evaluated against both drug-sensitive (3D7) and drug-resistant (Dd2) *P. falciparum* strains. Macrolide 1 demonstrated comparable potency to the leading antimalarials. However, the isolation chemists were only able to isolate milligram quantities of material from the natural source, an unnamed plant from a remote region in New Zealand, hampering efforts to determine the mechanism of action of 1.

The absolute configuration of strasseriolide B (1) was determined by X-ray crystallography. It contains two trisubstituted *E*-alkenes and a challenging *anti* 1,3-dimethyl array at C6 and C8. Further, while the mode of action is yet unknown, the presence of the hydroxyl group at C11 dramatically increases the macrolide’s bioactivity. Strasseriolide A (2), whose synthesis is also reported herein, contains a ketone in this position and demonstrates a significant decrease in bioactivity. Intrigued by its bioactivity and structural complexity, we decided to pursue the synthesis of strasseriolide B.

Figure 1. Structure and potency of strasseriolide natural products and other antimalarial compounds. *P. falciparum* 3D7 is the wild-type strain and Dd2 is a chloroquine-resistant strain.
aldehyde 3 and vinyl iodide 4, which would be coupled in a late-stage esterification. A Nozaki–Hiyama–Kishi (NHK) reaction would be employed as the key macrocyclization event. The NHK reaction has been shown to successfully close medium to large sized rings in a variety of total syntheses. We proposed a regio- and diastereoselective hydroiodination to set the E-alkene within the aldehyde fragment, and the eventual macro lactone acid was installed through a Negishi cross-coupling. The methyl stereocenter within alkyne 5 would arise from (R)-citronellic acid. Alcohol 6 can be mapped back through an Evan’s aldol addition to append the final carbons within the chain and set their relative configuration. The challenging anti-1,3-dimethyl array within alkyne 7 would arise from Feringa’s enantioselective conjugate addition chemistry, in which the precursor is easily accessible from (S)-citronellal.

Figure 2. Retrosynthetic analysis of strasseriolide B

Our synthesis began with the straightforward elaboration of (R)-citronellic acid to aldehyde 9 through a simple, high-yielding, 5 step sequence (Scheme 1). In order to install an alkyne between the carbonyl carbon and the adjacent methylene, a one-step elimination using tert-butylimino-tri(pyrrolidino)phosphorane (BTTP) and nonfluorobutanesulfonyl fluoride (NfF) was considered. However, the silyl protecting group is incompatible, and the preparation of BTTP requires large quantities of tert-butyl azide, which is a safety concern. A two-step dibromination, elimination procedure to afford terminal alkynes has been successful demonstrated in previous total syntheses and was implemented. The dibromination consistently afforded the desired geminal dibromide, along with the unexpected vinyl bromide diastereomers. Analogous vinyl bromide side products have not been described. Fortunately, this mixture could be funneled to the terminal alkyne upon exposure to LDA. In previous reports of this two-step sequence, the elimination was achieved using KO'Bu and 18-crown-6. However, when applied to our system, the rearranged allene isomer was often observed as a significant side-product. Various conditions were evaluated for the elimination of the geminal dibromide to the alkyne. We determined that treatment with LDA afforded the terminal alkyne without the generation of undesired allene side product. Presumably the lithiated alkyne intermediate is resistant to isomerization. Subsequent methylation of the terminal alkyne afforded terminal alkyne 10. A one step elimination-methylation was explored; however, higher yields were obtained in the two-step transformation.

Synthesis of the aldehyde 3 was completed using a palladium coupling. Regioselective and diastereoselective hydroiodination was achieved using Schwartz reagent (Cp2ZrHCl) and the resulting vinyl zirconium species captured with iodine. The vinyl iodide product was subjected to a Negishi cross-coupling with the zinc homoenolate reagent generated from ester 12 to afford E-alkene 11. Deprotection, oxidation, and hydrolysis completed the synthesis of the aldehyde fragment in 13 steps.

Scheme 1. Synthesis of the carboxylic acid fragment

Scheme 2. Synthesis of the vinyl iodide fragment
Synthesis of the vinyl iodide coupling partner 16 began with a Wittig homologation between the commercially available (S)-citronellal (8) and the previously reported phosphorous ylide 18 (Scheme 2). The addition proceeded smoothly to afford a 15:1 diastereomeric mixture favoring the desired E-alkene. During optimization of the sequence, the E- and Z-isomers were separated by chromatography to improve yields and diastereoselectivity in the conjugate addition. With the α,β-unsaturated thioester in hand, we were poised for a conjugate addition to assemble the anti-1,3-dimethyl array. Biosynthetically, the skipped methyl substitution patterns are installed via PKS I enzymes. However, achieving this outcome diastereoselectively in the laboratory has been a long standing challenge. The Feringa group reported a copper-catalyzed conjugate addition methodology that alkylates α,β-unsaturated thioesters with high levels of enantioselectivity. Treatment of the unsaturated thioester with CuBr-DMS, MeMgBr and (R,S)-Josiphos furnished thioester 13 as a single diastereomer with yields up to 88%. Isomerization of the reactive E-alkene starting material to traces of the unreactive Z-alkene during the reaction process was noted, but the product and Z-alkene compounds were separable, albeit with some difficulty. Furthermore, this sequence was performed on a preparatory scale of 25 mmol, the largest scale reported to date for a Feringa enantioselective cuprate addition.

Ozonolysis of the remaining alkene, followed by treatment with NaBH4 gave the desired alcohol along with trace amounts of the partially reduced thioester. Protection of the alcohol and Fukuyama reduction of the thioester afforded the expected aldehyde. Exposure of the aldehyde to bromine and triphenylphosphite gave the geminal dibromide 14 as well as a small amounts of the E- and Z-vinyl bromides as an inconsequential mixture (as observed in the synthesis of alkyne 10). The previously developed two-step elimination-alkylation afforded the internal alkynyl, which, when exposed to the hydroazirination conditions, smoothly furnished vinyl iodide 15 in a 54% yield over three steps.

We next directed our attention to the TBDPS ether of compound 15, where deprotection and oxidation afforded the aldehyde needed for the proposed aldol addition. Exposure of the aldehyde to the boron enolate of oxazolidinone 17 under standard Evansaldol conditions furnished alcohol 16 in modest yields as a single diastereomer. The vinyl iodide 16 was assembled in 12 steps from commercially available (S)-citronellal.

With both fragments in hand, we turned our attention to the planned coupling and macrocyclization sequence. In theory, either esterification or the NHK reaction could be used to close the macrocyclic ring, but to circumvent chemoselectivity issues, we chose to first pursue the esterification as an intermolecular reaction. Many unsuccessful esterification methods were explored (Shiina, EDCI, DCC, PyBOP, HBTU); ultimately, we saw the best yields, although still modest, through a Yamaguchi esterification (39%). Closure of the macroclide was achieved via an intramolecular NHK cyclization to afford a 1.1:1 mixture of diastereomers at the C11 alcohol. The diastereomers were separated by chromatography and carried on separately. Lithium hydroxide/hydrogen peroxide hydrolysis cleaved the auxiliary from the more polar alcohol diastereomer 20 to afford strasseriolide B (1), which confirmed the C11 configuration of 20. The (S)-alcohol 21 from the NHK reaction was oxidized with DMP and subsequently hydrolyzed to produce strasseriolide A (2). The spectral data for both natural products matched those reported (vide infra) and the optical rotations were consistent with the assigned absolute configurations.

Initial evaluation of synthetic samples of strasseriolide A and B were odd—they were missing several peaks in their respective carbon spectrum. The carbon NMR spectra of strasseriolide A was investigated in detail, as shown in Table 1. In a dilute CD3OD solution, the 13C peaks for C1 and C2 were missing, and the chemical shifts for C3 and C20 were slightly off. The C2 peak was observed in the HSQC spectrum in the appropriate region, which suggested that the peaks were shifted and broadened by an exchange process. All the discrepancies were localized around the free carboxylic acid (C1). If the effect arose from a monomer-dimer exchange of the carboxylic acid, it would be very sensitive to acid concentration. We added acetic acid-d4 and found that it progressively returned the carbon spectrum expected for the natural product, Table 1. Presumably we are generating a mixed carboxylic acid dimer and increasing...
the exchange rate between different forms. The spectra reported for the natural products also showed reduced intensity at C2, suggesting that line broadening was also observed in the isolation chemist’s spectra. Similar to alkaloids spectra being very sensitive to conditions and concentrations, it appears that carboxylic acids also show some sensitivity to concentration and that their spectra can be stabilized with added acetic acid-d₄.

Table 1. Unusual NMR behavior of strasseriolide A and the effect of added acetic acid-d₄

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<th>carbon #</th>
<th>lit. carbon chemical shift</th>
<th>no AcOH</th>
<th>5 equiv AcOH</th>
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<td>absent</td>
<td>177.5</td>
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<tr>
<td>2</td>
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<td>13.7</td>
<td>14.3</td>
<td>13.7</td>
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</tr>
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*Carbon NMR spectra acquired in CD₃OD at 151 MHz. Concentration of strasseriolide A was 10 mM.

We report the first total syntheses of strasseriolide A and B. Strasseriolide B shows potent activity against the wild-type malaria parasite *Plasmodium falciparum* and good activity against a chloroquine-resistant strain. It was prepared in a convergent synthetic sequence with a longest linear sequence of 16 steps from (R)-citronelllic acid. Synthetic access to the natural product will allow us to confirm its *P. falciparum* activity and to design and prepare probes to investigate its mode of action. Malaria is a worldwide epidemic, and strasseriolide B is a promising starting point for a new therapeutic agent.

ASSOCIATED CONTENT

Supporting Information
Full experimental details; compound characterization; ¹H and ¹³C spectra are provided (pdf). FAIR Data is available as Supporting Information for Publication and includes the primary NMR FID files for compounds: 1, 2, 3, 9, 10, 11, 13, 14, 15, 16, 20, 21, S3, S4, S5, S7-S14 and S16-S20.

The Supporting Information is available free of charge on the ACS Publications website.

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Notes
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