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Synthesis of the diaryl ether cores common to chrysopaentins A, E and F

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Abstract

The synthesis of the diaryl ether subunits of the marine natural products chrysopaentin A, E and F is described. These natural products feature tetrasubstituted benzene rings with complex substitution patterns. The central strategy involves an S_NAr reaction between a complex phenol and a polysubstituted fluoronitrobenzene. Subsequent attempts to construct the unusual *E*-chloroalkene linkage through several different approaches are also disclosed.

Keywords

Natural Product Synthesis; Chrysopaentin; FtsZ; S_NAr ; Claisen

The chrysopaentins comprise a family of biosynthetically unique natural products with interesting antimicrobial activity. In 2010, Bewley and co-workers reported the isolation of eight related secondary metabolites from the marine chrysophyte (aka “golden algae”) *Chrysophaeum taylori*.¹ The structures of the chrysopaentins (Figure 1) were assigned by NMR spectroscopy and mass spectrometry. Each member of this family has two benzylic *E*-chloroalkene subunits that are asymmetrically macrocyclic (A–D) **1**, symmetrically macrocyclic (E) **2**, or acyclic (F–H) **3**. Although compound **4** has been prepared synthetically, it has not been isolated from the natural source, even though it would appear to be a biogenic precursor of several of the chrysopaentins.² Moreover, there are no similar natural products known and no biosynthetic hypothesis has been advanced to explain the origin of these unusual compounds. The only previous report of secondary metabolites from *C. taylori* does not describe any related chemical structures.³

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Supplementary Material

Experimental procedures and characterization data for synthetic intermediates associated with this article can be found, in the online version, at [http://dx.doi.org/\[link\]](http://dx.doi.org/[link]).

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The chrysopaentins exhibit antimicrobial activity that is consistent with inhibition of bacterial cell division.^{1,4} Several members exhibited low micromolar minimum inhibitory concentrations (MICs) against several Gram-positive organisms, including methicillin-resistant *Staphylococcus aureus* (MRSA). In addition, chrysopaentin A perturbed the polymerization of FtsZ, the central cell division protein in prokaryotes, and inhibited the GTPase activity of this protein. Preliminary NMR spectroscopy experiments paired with docking studies are also consistent with a direct interaction between chrysopaentin A and FtsZ.

Our research group has endeavored to synthesize and study natural products and other small molecules that perturb the function of FtsZ.^{5–8} This protein has emerged as a new potential target for antimicrobial chemotherapy designed to fight infections that are resistant to current drugs.^{9–14} Although small molecule inhibitors of FtsZ have been studied for two decades, there are still fundamental gaps in the basic understanding of the basic mechanisms by which inhibition occurs. To date, only a single X-ray crystal structure of a small molecule bound to FtsZ has been reported.^{15,16} The activity of certain inhibitors is often limited to a protein from a single strain of bacteria or has been difficult to reproduce outside of the laboratories from which the studies originate. Importantly, many inhibitors, including several for which docking models have been proposed, have been demonstrated to act unselectively through aggregation.¹⁷ Among the natural products that have been reported as FtsZ inhibitors, two have been demonstrated to act through aggregation, one has structural features make it a suspect for aggregation,¹⁸ and one has activity that can't be reproduced (viriditoxin).^{17,19} Aside from these phenolic natural products, the phenanthridine alkaloids berberine^{20–24} and sanguinarine²⁵ have also been reported as FtsZ inhibitor, but there is little evidence of a direct and selective interaction between these cationic alkaloids and the putative target. Collectively, these results demonstrate the stark difference between FtsZ and its eukaryotic homolog tubulin, for which three structurally unrelated natural products (*Vinca* alkaloids, colchicine, taxol) have all been demonstrated crystallographically to bind in distinct sites on the protein.^{26–28}

We have initiated a program to synthesize chrysopaentin A in order to better understand the origin of its activity. First, the structural novelty of the chrysopaentins paired with the complete lack of biosynthetic understanding suggests that independent assignment of their structures would be helpful. Although there is no reason to suspect that they have been misassigned, arguments about their molecular interactions with FtsZ would be best understood if the structures were unequivocally established by crystallography or total synthesis. Second, a synthetic route would establish methods for the preparation of photo-affinity reagents, analogs for structure-activity relationship (SAR) studies, and potentially enable access to larger quantities of the compound for co-crystallization. In this communication, we describe a synthetic route to the diaryl ether cores common to chrysopaentins A, E and F as well as preliminary findings on an approach to the unusual E-chloroalkene subunit of these natural products.

The diaryl ether subunits of the chrysopaentins present a significant challenge due to the positioning of substituents on the benzene rings. The two isomeric subunits required for chrysopaentins A, E and F (**1–3**) are highlighted in blue and red, respectively, in Figure 1.

A para relationship between carbon and Oxygen **5** is required for the D-rings of **1** and **3** as well as the B/B' rings of **2** (Figure 2). The isomeric ortho relationship **6** is required for the C-ring of **1**. We envisioned that each of these cores could arrive from similar synthetic routes, specifically either a Chan-Lam coupling^{29,30} (as adapted by Evans³¹ for aryl ethers) or from an S_NAr reaction. The Chan-Lam route could arise from two possible combinations of a phenol and a boronic acid. Although two analogous S_NAr disconnections are possible, the combination shown would minimize the subsequent manipulations required and would avoid use of an aromatic electrophile that would be deactivated by two ortho substituents, one of which would be highly electron donating.

We first explored the Chan-Lam route, which would enable the most direct access to the requisite diaryl ethers. Initial results with model substrates were disappointing. The reaction of **10** with **11** under a variety of conditions yielded no detectable product **12** formation. Control experiments indicated that the presence of three ortho substituents was deleterious to this process. *o*-Chlorophenyl boronic acid **10** underwent smooth conversion to the corresponding ether **14** when combined with *p*-methoxyphenol **13** under standard conditions. Similar efficiency was observed with 2,6-dimethoxyphenol (**11**) when combined with phenyl-boronic acid **15** (Scheme 1).

Pursuit of the S_NAr route commenced with the synthesis of the two requisite phenol isomers with the general structure of **5** and **6** (Figure 2). The choice of carbon substituent was important for the synthetic route to the phenol and for the subsequent manipulations that would eventually install the *E*-chloroalkene subunits of the targets. We settled on an allyl group in order to enable access to a variety of potential coupling partners with an eye toward employing an olefination with concomitant installation of the chloride. 2,4-Dihydroxybenzaldehyde **17** was isopropylated³² in high yield and then converted to phenol **19** using magnesium monoperoxyphthalate (MMPP) to effect a Dakin oxidation.³³ This intermediate could be allylated³³ and then heated to induce Claisen rearrangement to phenol **21** (Scheme 2). This robust route was routinely executed on large (>25g) scale. The para-substituted isomer was prepared by a similar route starting with resorcinol **22**. After isopropylation,³⁴ a sequence of ortho-metallation, borylation and oxidation installed the requisite central hydroxyl group of **24**. Allylation and tandem Claisen and Cope rearrangements^{35,36} proceeded (with similar efficiency as seen with **19**) to yield phenol **26** in 81% yield over two steps (Scheme 2).

The requisite electrophile for the S_NAr reaction required extensive exploration and optimization. The 1,2,4,5 substitution pattern defies many traditional sequences of benzene functionalization. We initially explored several routes that would install the carbon substituent in a regioselective manner, i.e. para to the chlorine. These included Claisen rearrangements and the lesser-known vicarious S_NAr substitution reaction,^{37,38} which installs enolate-like nucleophiles ortho to nitro groups (not shown). The failure of these routes prompted us to explore substrates with carbon installed first, which ultimately lead to nitration of a suitable precursor. Although fluorine is mildly deactivating for electrophilic aromatic substitutions, this halogen is known to induce high levels of para selectivity.^{39–43} Benzyl bromide **27** was treated with cyanide and hydrolyzed to phenylacetic acid **29** (Scheme 3). This intermediate could be nitrated in high yield with high para selectivity,

provided fuming HNO₃ was employed. Reduction and protection as the TBS ether provided fluoronitrobenzene **31**. This five-step sequence could be completed on multigram scale in 63% overall yield with a single chromatographic separation. Treatment of **31** with phenol **21** or **26** and potassium carbonate produced diaryl ethers **32** and **33** in 78% and 75% yields, respectively (Scheme 3).

Conversion of the nitro group to a protected hydroxyl group proved to be a significant challenge. Direct hydrolysis with base was unsuccessful. The nitro group of **32a** was reduced to the corresponding aniline **32b** in high yield under various conditions (Scheme 4). Although Sandmeyer reactions *via* the diazonium intermediate to either an ether or phenol **34a** or **34b** were also fruitless, conversion to the iodide **32c** occurred in high yield. Under aqueous conditions, the TBS ether remained intact and under the anhydrous conditions of Knochel,⁴⁴ the TBS ether was cleaved. Many attempts were made at conversion of the iodide to the isopropoxy and methyl ethers under copper-mediated conditions. In the case of **32c**, cyclization to benzodihydrofuran **35** was observed. Although this intermediate could not easily be converted to the required acyclic structure, we were prompted to oxidize **32c** to the corresponding acid **36** to explore lactone formation. Unfortunately a variety of conditions failed to convert **36** into lactone **37** (Scheme 4).

Ultimately the iodide intermediate was employed in a successful nitro-to-hydroxyl conversion sequence. Iodide **32c** was re-silylated and then metallated using recently-reported conditions that employ the lithium chloride complex of isopropylmagnesium chloride, aka “turbo-Grignard.”^{45,46} Trapping of the organomagnesium intermediate with tri-isopropylborate and subsequent oxidation yielded phenol **34a** in high yield in this one-pot process (Scheme 5). Protection of the phenol as the isopropyl ether once again removed the silyl group, which was subsequently re-installed to give ether **34b**. An analogous sequence converted **33a** to **33d** with similar efficiency. Although this route provides access to the required intermediates with high levels of efficiency for the individual steps, it suffers from significant repetitive changes in oxidation state.

With reliable routes to the diaryl ether fragments in hand, we turned our attention to the construction of the *E*-chloroalkene **38a**. Although the synthesis of alkenes with similar substitution patterns have been reported,⁴⁷ *E*-configured chloroalkenes with two benzylic carbons are unknown in the literature outside of the chrysopaentins. In addition, the quasi-symmetry, i.e. similar steric demands of the two benzylic substituents, suggests that hydrometallation reactions employing boranes⁴⁸ or Schwartz’s reagent⁴⁹ would not be regioselective. Alkene cross-metathesis in the synthesis of chloroalkenes is limited to vinyl chloride.⁵⁰ With these limitations in mind, we considered several approaches involving olefination of an aldehyde precursor. The most straightforward approach would involve a chloro-substituted phosphorous ylide **38b**, for which there was precedent.^{51,52} This approach is complicated by the high enol content of phenyl acetaldehydes **38c**, which makes these substrates particularly troublesome for olefination reactions (Figure 3). The combined basicity and steric bulk of **38c** led to degradation of the aldehyde, presumably through aldol addition and condensation reactions. As such we investigated two possible alternatives to reduce steric bulk and basicity in the olefination component. First, we investigated a Wittig reaction,⁵³ which would use a stabilized anion **40** with reduced basicity. The product of this

reaction could later be converted to the E-chloroalkene by the Hunsdiecker decarboxylation-halogenation reaction⁵⁴ or related processes reported by Barton.⁵⁵ Second, we explored Schlosser's one-pot approach to trisubstituted alkenes by the SCOOPY sequence,⁵⁶ which employs an unsubstituted Wittig reagent **41**.

The necessary aldehyde and phosphorous ylide components were prepared from **34b** and **33d**, respectively. Hydroboration/oxidation of **34b** produced alcohol **42**, which was carried through to the analogous *tert*-butyl ester **43** by a three-step oxidation and esterification sequence. Cleavage of the TBS ether and oxidation yielded aldehyde **44** (Scheme 6). A similar sequence was initially pursued for the ylide in which the ester would be halogenated and displaced with triphenylphosphine. The failure of the requisite α -halogenation led us to a route based on alkylation of a pre-formed ylide. The allyl group of **33d** was isomerized with palladium(II) chloride, unexpectedly cleaving the silyl ether, which had to be re-installed. One-pot oxidative cleavage of alkene **45** to the aldehyde was followed up with reduction to produce benzylic alcohol **46**. Conversion of this intermediate to the iodide proceeded smoothly. Alkylation of the iodide with the phosphonium ylide **47** yielded coupling partner **48**, which was used without purification after a quick work-up to remove the base. Unfortunately, treatment of this ylide with aldehyde **44** produced none of the desired alkene product **49**. As was the case with unstabilized ylides, complete destruction of the aldehyde was observed, presumably by the aforementioned self-aldol processes for which phenylacetaldehydes are notorious (Scheme 7). This sequence demonstrated that reducing the basicity of the ylide partner was not sufficient to suppress aldehyde decomposition.

Our final attempt to install the E-chloro alkene subunit involved exploration of Schlosser's SCOOPY method.⁵⁶ This process relies on deprotonation of the betaine intermediate in a Wittig reaction and allowing this anion to react with an electrophile before the final elimination that results in alkene formation. In order to enable thorough exploration of this route, we prepared substrates to serve as model system. Chlorohydroquinone **50** was isopropylated and formylated to benzaldehyde **51**.^{57,58} Two-step homologation provided aldehyde **54**.⁵⁹ This material proved to difficult to store and handle and was in later runs, reduced to the alcohol **53** and oxidized with DMP as needed (Scheme 8). The ylide partner was prepared from Claisen-Cope product **26** by protection as the ethoxymethyl (EOM) ether, oxidative cleavage, reduction and bromination. Subsequent displacement with triphenylphosphine provided the triphenylphosphonium salt **56** in modest yield. This intermediate was deprotonated with phenyllithium (PhLi), treated with aldehyde **54**, then deprotonated again with PhLi and treated with electrophilic chlorine reagents. In no case was any of the desired haloalkene observed and, as with previous attempts at olefination, the aldehyde decomposed (Scheme 8). Although we had hoped that addition to the aldehyde at lower temperature by the ylide of **56** would be fast enough to avoid aldehyde decomposition, it appears that the enolization problem represents a fundamental flaw in our synthetic plan.

In summary, we have successfully assembled the diaryl ether subunits common to chrysopaentins A, E and F. The routes are high-yielding and easily scaled up to multigram quantities, in spite of a cumbersome nitro-to-hydroxyl conversion that relies on a long sequence of atom-transfer reactions. We have also thoroughly explored three olefination

routes to the E-chloroalkene subunit of these unique natural products. In each case, the enolizability of the required phenylacetaldehyde prevented alkene formation. We are continuing to explore more efficient diaryl ether assembly sequences as well as alternate E-chloroalkene-forming processes that eschew the problematic olefination reactions of phenylacetaldehydes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
Structures of chrysopaentins A, E and F and "hemi-chrysopaentin," synthetic subunit (not a natural product).

Figure 2.
Retrosynthetic analysis of the diaryl ether fragments of chrysophaentin A, E and F.

Figure 3.
Retrosynthetic analysis of *E*-chloroalkene subunit.

Scheme 1.
Attempted Chan-Lam coupling reactions.

Scheme 2.
Synthesis of phenols **21** and **26**.

Scheme 3.
Synthesis of S_NAr substrate **31** and reactions with **21** and **26**.

Scheme 4.
 Attempted nitro-to-hydroxyl conversion.

Scheme 5.

Nitro-to-hydroxyl conversion to prepare fragments **34b** and **33d**.

Scheme 6.
Synthesis of aldehyde **44** for olefination.

Scheme 7.
Synthesis of ylide **48** for olefination.

Scheme 8.
Attempted SCOOPY route to E-chloroalkene **57**.