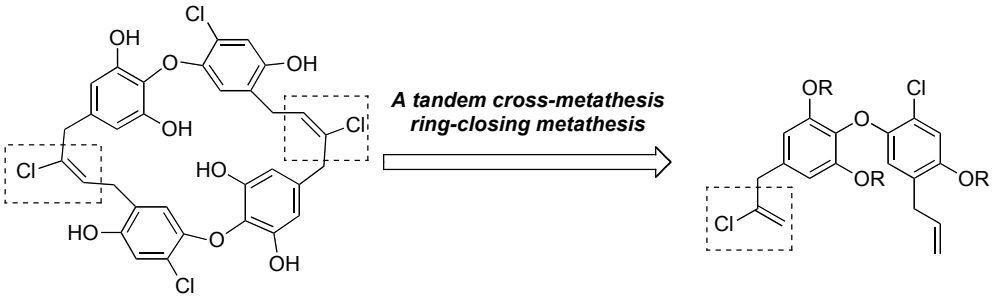
A p p e n d i x A

PROGRESS TOWARDS THE TOTAL SYNTHESIS OF CHRYSOPHAENTIN F

ABSTRACT

The progress towards the total synthesis of chrysophaentin F is herein reported. Chrysophaentin F is a recently isolated antimicrobial natural product from the chrysophyte alga *Chrysophaeum taylori* and has been shown to strongly inhibit the bacterial cell division protein FtsZ. The synthetic strategy involves a tandem cross-metathesis/ring-closing metathesis of the bisdiarylbutene macrocycles as the key step.



Chrysophaentin F

INTRODUCTION

One of the leading causes of death worldwide today is infectious diseases,[1,2] and in the United States it has been estimated that more people die due to methicillin-resistant *Staphylococcus aureus* (MRSA) bacterium than from HIV.[3] The increased amount of multidrug resistant bacteria results in more expensive treatments that can also be more uncertain and sometimes ineffective.[4] Therefore, there is clearly a need to identify new compounds with the potential to treat infections caused by multidrug resistant bacteria, as well as to find new ways to approach this growing problem.

The bacterial cell division protein FtsZ is a fairly new and attractive target in antimicrobial drug discovery, since it is both vital for cell division as well as highly conserved among most bacteria.[5] There are already some compounds that have been reported to inhibit the function of FtsZ. These compounds include the phenolic natural products totarol,[6] berberine,[7] viriditoxin,[8] and cinnamaldehyde.[9] Another potential source for new FtsZ inhibitors is marine natural products, because of their strong antimicrobial activities and unique structures.

Eight new antimicrobial natural products were recently isolated from the chrysophyte alga *Chrysophaeum taylori*, and they were termed chrysophaentin A-H.[10] The structure of these compounds (see **Figure A-1** for chrysophaentin A and F) was determined by thorough spectroscopic analysis, including mass spectrometry (MS) and nuclear magnetic resonance (NMR). Some of these compounds were found to strongly inhibit the growth of *S. aureus*, MRSA, *Enterococcus faecium*, and vancomycin-resistant *E. faecium*. Of these compounds, chrysophaentin A was the most potent antibiotic, and chrysophaentin F and H were found to be the next most potent compounds. Through studies of chrysophaentin A it was observed that it inhibited the GTPase activity and polymerization of FtsZ.[10]

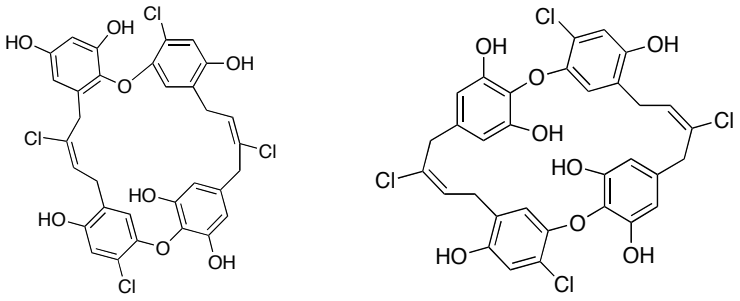
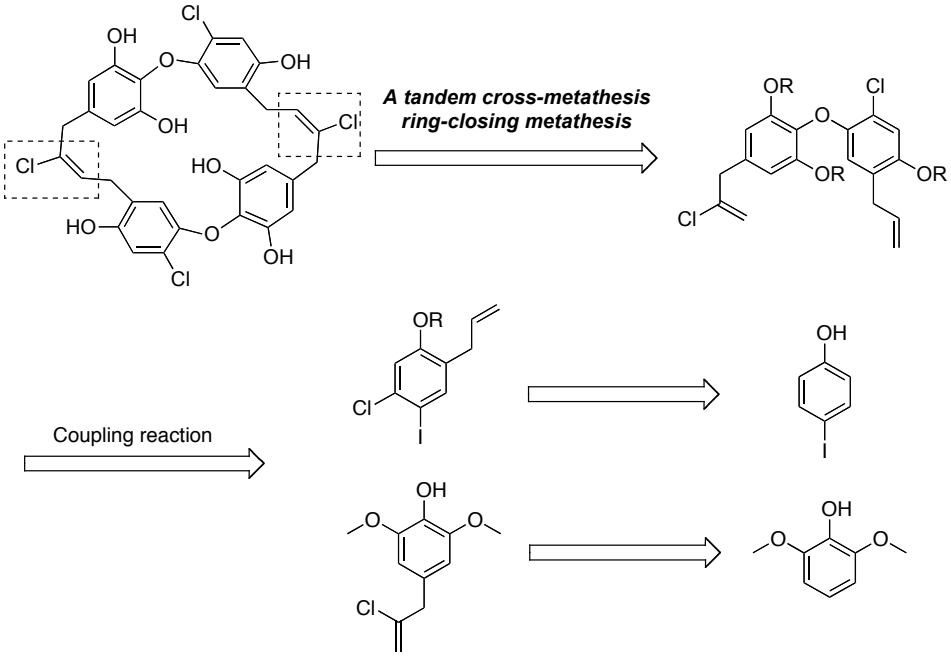


Figure A-1. The structures of Chrysophaentin A (left) and Chrysophaentin F (right).

The antibiotic potential of these compounds made them ideal synthetic targets and thus, it was decided to pursue the total synthesis of the symmetrical chrysophaentin F using metathesis as the key step to form the macrocycle.

SYNTHETIC STRATEGY

The synthetic strategy for this target was organized towards using a tandem olefin cross-metathesis/ ring-closing metathesis as the key step to combine two fragments of biaryl ether symmetrically. The following retrosynthetic analysis was aimed at making the biaryl ether with a coupling reaction between an aryl halide and a phenol, which could each be synthesized from readily available starting materials (**Scheme A-1**).



Scheme A-1. Retrosynthetic analysis of Chrysophaentin F, leading to readily available starting materials.

For the forward synthesis of the aryl halide it was required that we find a way to introduce the chlorine to the meta-position and an allyl group to the ortho-position of the molecule, as well as protect the hydroxyl group. We decided to start with a Williamson ether synthesis,[11–13] followed by a Claisen rearrangement[11–15] in a microwave reactor,[11,16] to insert the allyl group to the desired position. To prepare the molecule for the chlorination, we decided to protect the ortho/para-directing hydroxyl group as an acetyl.[17–19] Since iodine is an ortho/para-directing group[20] and the

allyl group is ortho/para-directing as well, we believed that even though phenyl acetate is also ortho/para-directing on its own,[21] the combined effect would yield the desired chlorinated product in some amount.[22,23]

The forward synthesis of the phenol was based on an analogous approach starting with a Williamson ether synthesis[11–13] and followed by a Claisen rearrangement, resulting in the 2-chloroallyl group at the para-position since both ortho-positions were occupied.[24,25]

With both A and B synthesized the next step would be a coupling reaction. The conditions of the Ullmann biaryl ether synthesis seemed suitable for the reactants.[26–28] Since there would only be one available hydroxyl group and the reactivity trend of the halides follows I > Br > Cl >>F,[29] this reaction was expected to give the appropriate biaryl ether.

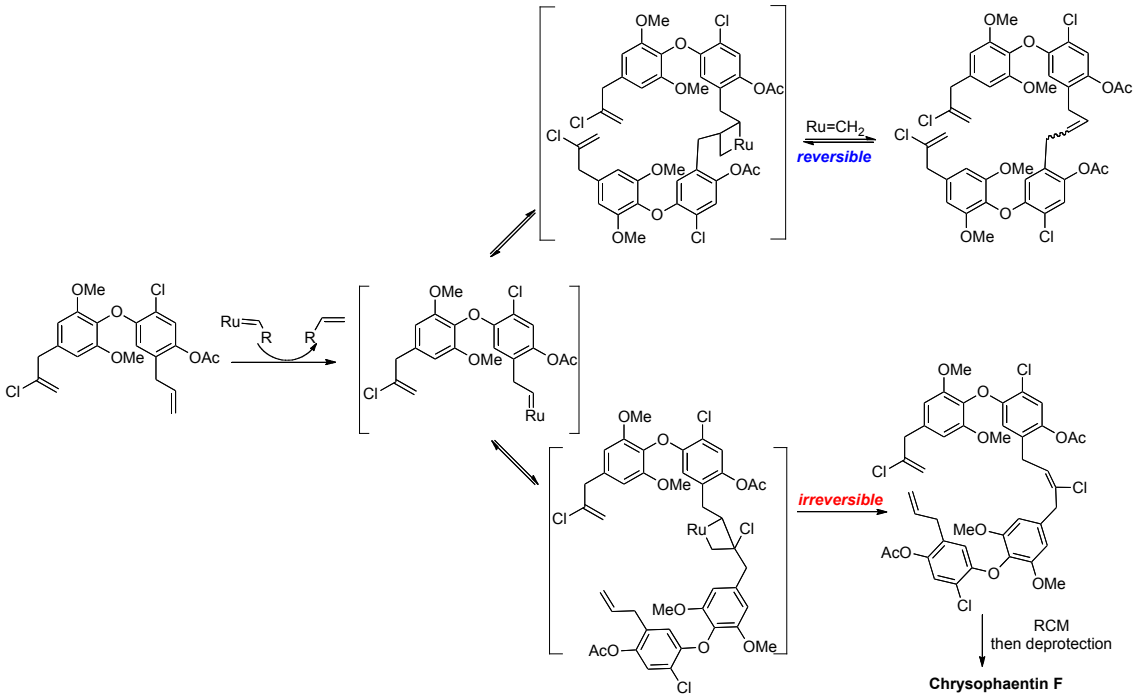
Inspired by the progress made in metathesis of vinyl halides in the past decade, its application in the synthesis of chrysophaentin F was appealing. Recent reports have shown that vinyl halides can undergo both ring-closing metathesis[30–32] and cross-metathesis[33,34] with appropriate catalysts. Since metathesis has also been used to close macrocycles[35,36] it was deemed desirable to accomplish a ring-closing metathesis of a macrocycle through a vinyl halide.

Seeing that vinyl halides are less reactive than monosubstituted alkenes, it was expected that the cross metathesis of the monosubstituted alkenes would be observed first. Since this step would be reversible in a closed system, that would be acceptable. In addition, it would also be unlikely that the two remaining vinyl halides would undergo metathesis to close the macrocycle due to their relatively low reactivity.

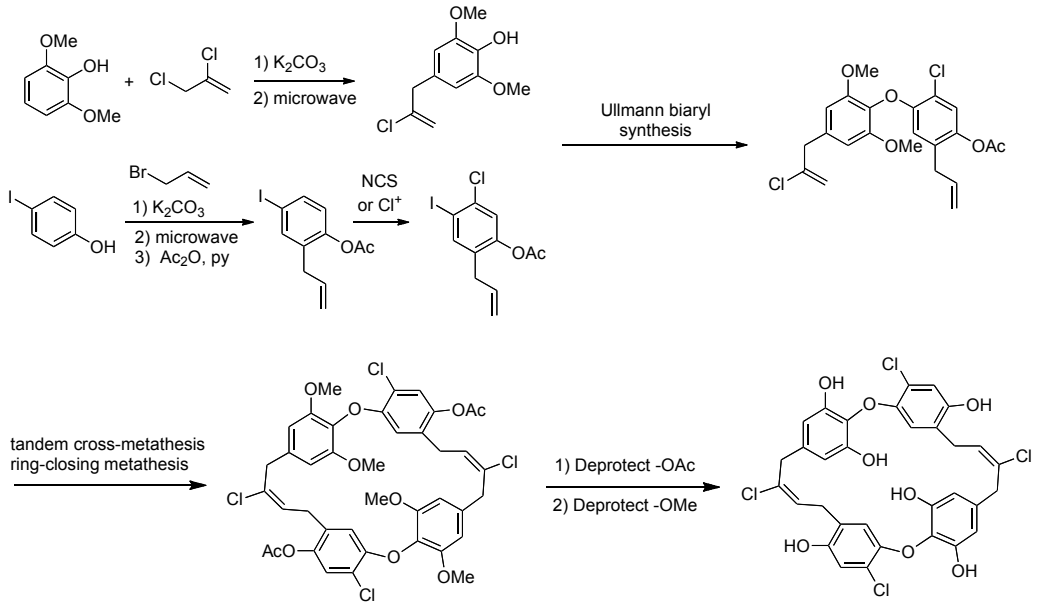
It was presumed that some cross metathesis of the vinyl halide with the monosubstituted alkene would eventually be observed, and that step would be irreversible due to the lack of metathesis reactivity expected of the product formed. The metathesis of the remaining alkenes in the newly formed molecule would lead to a ring-closing of the macrocycles, and thus give the desired product (**Scheme A-2**).

When the metathesis step would be completed, all that would remain would be to deprotect the acetyl groups[37] as well as the methyl ether groups.[38] The success of this synthetic strategy would

lead to an effective route to synthesize chrysophaentin F from commercially available starting materials in 10 steps, where the longest linear sequence would include 7 steps (**Scheme A-3**).



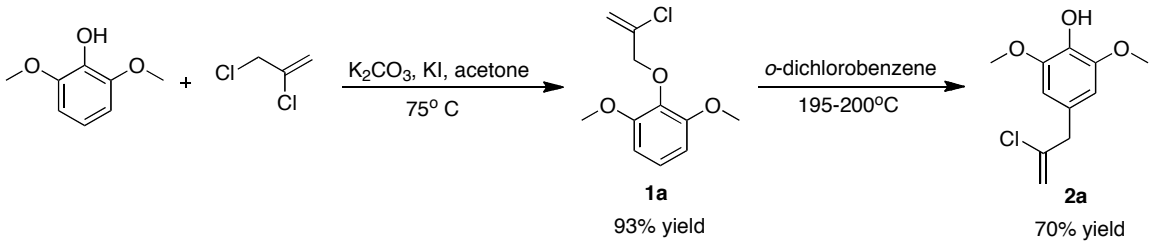
Scheme A-2. The expected route of the tandem cross-metathesis/ring-closing metathesis step.



Scheme A-3. The synthetic strategy from available starting material to Chrysophaentin F.

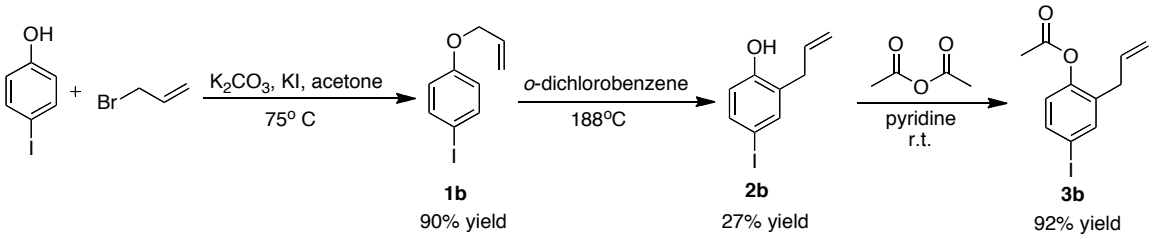
RESULTS AND DISCUSSION

The synthesis commenced with a simple substitution reaction to introduce the chloro-substituted allyl group to the 2,6-dimethoxy-phenol. This reaction was followed by a Claisen rearrangement to advance the allyl group to the desired para position. These two steps worked well and gave 93% and 70% yields, respectively (**Scheme A-4**).



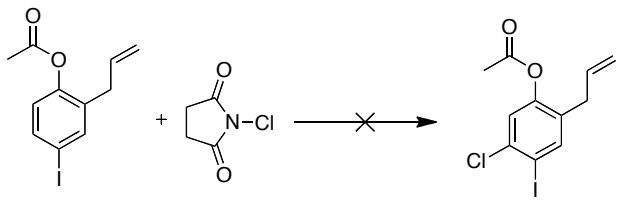
Scheme A-4. Synthesis of intermediat **2a**, 4-(2-chloroallyl)-2,6-dimethoxyphenol.

The next steps were analogous with a 4-iodophenol to introduce a non-substituted allyl group via a substitution reaction, followed by a Claisen rearrangement to shift the allyl group to the desired ortho position. The Claisen rearrangement did not give good yields since it was not allowed to run to full conversion, and thus a lot of the starting material was recovered. Then the phenol was reacted with acetic anhydride in pyridine at room temperature to protect the hydroxyl group as an acetate before attempting to chlorinate the compound (**Scheme A-5**).



Scheme A-5. Synthesis of intermediat **3b**, 2-allyl-4-iodophenyl acetate.

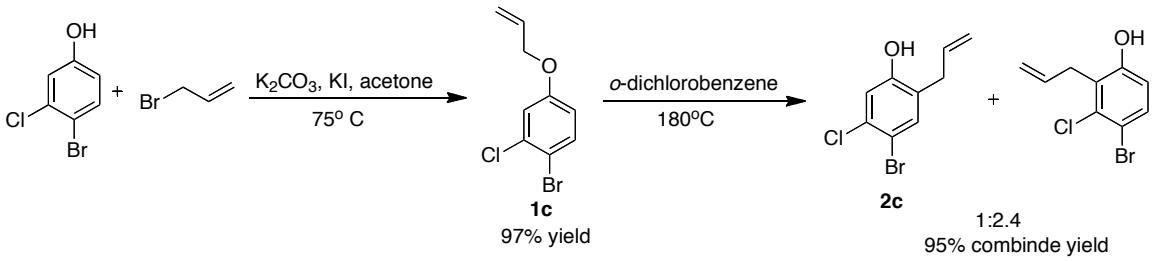
The following step was to chlorinate the 2-allyl-4-iodophenyl acetate. That was first attempted utilizing the chlorinating agent N-chlorosuccinimide (NCS). These attempts were unsuccessful, and either resulted in the degradation of the essential allyl group (possibly through chlorination of the alkene) or no apparent reaction, depending on the reaction conditions (**Scheme A-6**).



Scheme A-6. The unsuccessful synthesis of 2-allyl-5-chloro-4-iodophenyl acetate. Attempted conditions were a) dichloromethane, r.t.; b) methanol, 55° C; c) acetic acid, acetonitrile; d) acetic acid, acetonitrile, $FeCl_3$.

While searching for other appropriate reaction conditions and chlorinating agents, it was discovered that 4-bromo-3-chlorophenol was commercially available and therefore it was decided to pursue the synthesis using that compound as the starting material instead. That was done to evade the chlorination step, which could have required stronger and more dangerous chlorinating agents.

Thus, the same approach was executed using the new starting material (**Scheme A-7**). The substitution reaction gave excellent yields while the Claisen rearrangement did not, but instead showed an inclination towards the non-desired isomer product.



Scheme A-7. Synthesis of 2-allyl-4-bromo-5-chlorophenol.

A short study was done on the solvent effect on the regioselectivity of the Claisen rearrangement. Approximately 40 mg of the allyloxy compound were dissolved in 0.5 mL of solvent, followed by 2-3 freeze-pump-thaw cycles to degas the solvents. The mixture was subsequently heated under argon in a microwave reactor at 170°C for 90 minutes. Due to the small conversion of the reaction, the NMR results may have been somewhat inaccurate, but still gave a rough aspect on the solvent effect (**Table A-1**).

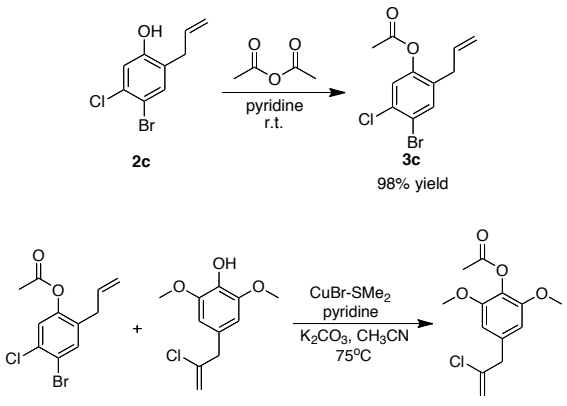
Table A-1. Effect of solvent on the ratio between products of the Claisen rearrangement of 4-(allyloxy)-1-bromo-2-chlorobenzene.

Solvent	2-allyl-4-bromo-5-chlorophenol	2-allyl-4-bromo-3-chlorophenol
o-dichlorobenzene	1	2.4
Pyridine	1	2.7
Acetonitrile	1	2.2
DMF	1	2.3
Water	1	2.3
No solvent	1	2.8

The results showed some effect where more polar solvents seemed to favor the desired product. The greatest improvement observed was roughly 20% between acetonitrile and no solvent.

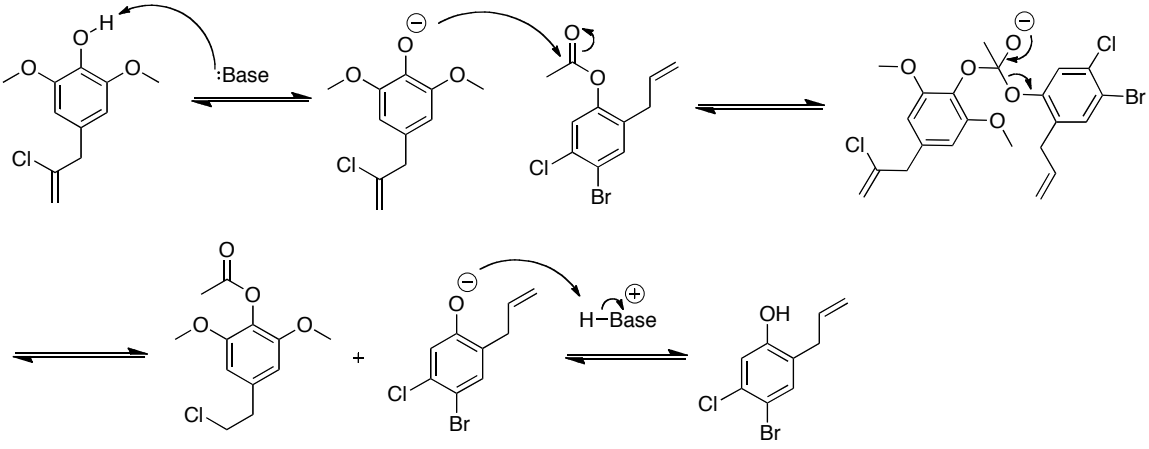
It was also observed in this short study that the conversion of the reaction differed greatly depending on whether solvent was used or not. In all the cases when solvent was used the observed conversion was less than 5% after 90 minutes, while when the reaction was run neat the conversion was 45% after the same amount of time. This unexpected result might be due to some concentration effect, but still it was not expected to have any effect for this reaction, which is generally unimolecular.

After isolation of the desired Claisen product, it was protected with an acetyl group and then reacted with **2a** using Ullmann biaryl ether synthesis conditions.[26] Unfortunately, this reaction did not give the desired biaryl product. Instead it seems that the hydroxyl group of **2a** reacted with the acetyl group of **3c**, giving 4-(2-chloroallyl)-2,6-dimethoxyphenyl acetate. (**Scheme A-8**).



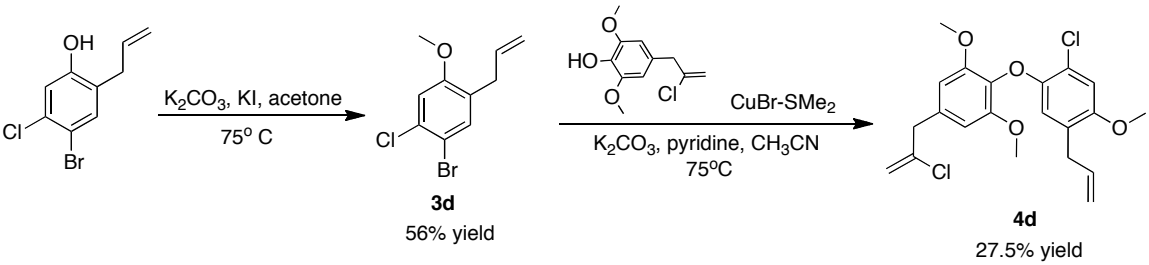
Scheme A-8. The acetyl protection of **2c** (top). The result of the attempted Ullman biaryl ether synthesis (bottom).

The observed reaction can be explained by the proposed mechanism shown in **Scheme A-9** where a base deprotonates the phenol, enabling it to attack the acetyl group and eventually relocate it.



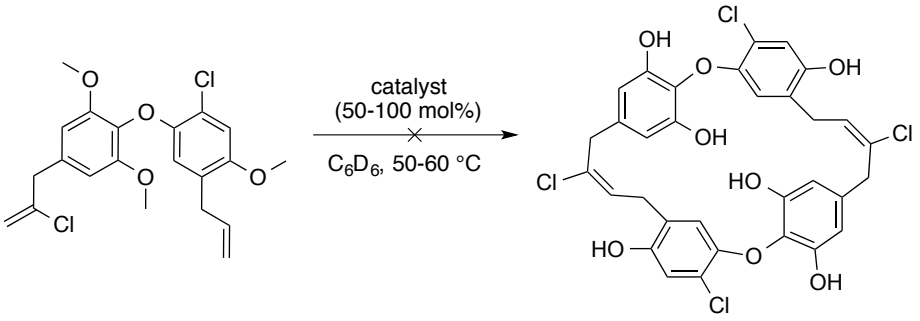
Scheme A-9. Proposed mechanism for the acyl relocation.

To overcome the coupling obstacle, it was decided to use a methyl ether protecting group instead of acetyl, especially since the 4-(2-chloroallyl)-2,6-dimethoxyphenol already had methoxy protecting groups. That way, only one deprotection step would be required at the end of the synthesis, rather than two. This approach was successful in giving the desired biaryl ether compound (**Scheme A-10**), although current yields are low.



Scheme A-10. Synthesis of the biaryl ether intermediate, **4d**.

Attempts were made at the tandem cross metathesis/ring-closing metathesis reaction with the second generation Grubbs catalyst, but to no avail (**Scheme A-11**).



Scheme A-11. Attempts at the tandem cross-metathesis/ring-closing metathesis step have been unsuccessful with the 2nd generation Grubbs catalyst.

CONCLUSION AND FUTURE DIRECTIONS

Further efforts were not made towards finishing the total synthesis of *Chrysophaentin F* at this point in time. The next steps would be to test out other catalyst for the key reaction. A few potential candidates have been identified and are shown in **Figure A-2**.

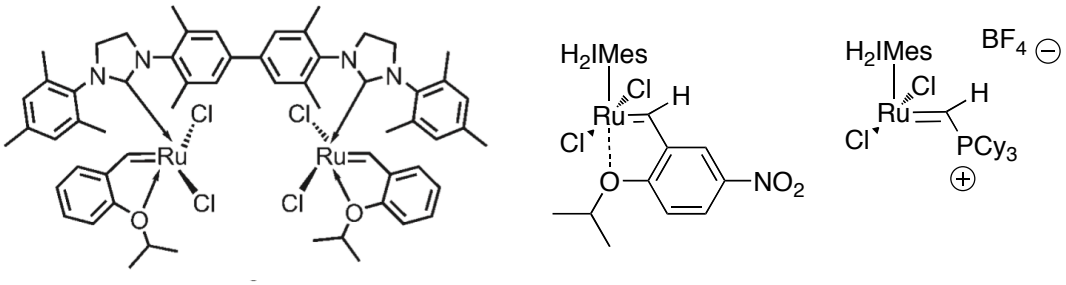


Figure A-2. Examples of ruthenium catalysts yet to be screened.

Alternatively, it would be possible to reverse the order of the cross metathesis reaction and the Ullmann biaryl ether coupling reaction in order to attempt finishing the synthesis. The cross-metathesis step would still be expected to be the main challenge, and it is expected that the yields for that step would be low due to the competing homometathesis reaction.

EXPERIMENTAL SECTION

General information

NMR spectra were recorded on a Varian Inova 500 (at 500 MHz). The NMR spectra were analyzed on MestReNova software and are reported relative to CDCl3 (δ 7.26). High-resolution mass spectra were provided by the California Institute of Technology Mass Spectrometry Facility. IR spectra were recorded on a Perkin Elmer Paragon 1000 Spectrometer and are reported in frequency of absorption (cm-1). Microwave reactions were conducted in a Biotage Initiator Microwave Synthesizer. NMR abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, bs = broad singlet, bd = broad doublet, dd = doublet of doublets, dt = doublet of triplet, dq = doublet of quartet, ddt = doublet of doublet of triplet.

Materials

All solvents were purchased from EMD Chemicals and Sigma-Aldrich. 4-iodophenol was bought from Acros chemicals, 4-bromo-3-chlorophenol was purchased from Alfa Aesar, sodium sulfate was acquired from Mallinckrodt, and potassium iodide and potassium carbonate were purchased from EM Science. Other chemicals were purchased from Sigma-Aldrich. All solvents and chemicals were used without further purification.

2-((2-chloroallyl)oxy)-1,3-dimethoxybenzene (**1a**)

0.6286 g of 2,6 dimethoxy-phenol (4.104 mmol) was dissolved in 46 mL of acetone in a 100 mL round bottom flask. 1.3392g of K_2CO_3 (9.69 mmol) and 75.4 mg of KI (0.45 mmol) were added to the solution as well as 0.491 g of 2,3-dichloroprop-1-ene (4.425 mmol). This mixture was allowed to reflux for 17 hours. The solution was filtered through celite and the solvent evaporated off. The product was dissolved in ethyl acetate (25 mL) and washed with a solution of KH_2PO_4 (10 mL), Na_2CO_3 (10 mL), and water (10 mL). Then it was dried over sodium sulfate and filtered, and the solvent evaporated off. Finally, the product was dried under high-vacuum and the product obtained as a red-brown oil in 93% yield. (872.9 mg, 3.83 mmol). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.00 (t, J = 8.4 Hz, 1H), 6.58 (d, J = 8.4 Hz, 2H), 5.73 (q, J =1.4 Hz, 1H), 5.39 (m, 1H), 4.57 (dd, J = 1.3, 0.9 Hz 2H), 3.85 (s, 6H). ^{13}C NMR (500 MHz, $CDCl_3$): δ 153.36, 137.44, 136.48, 123.98, 113.67, 105.33, 74.76, 56.13. IR (Thin Film, NaCl): 3002, 2939, 2838, 1637, 1598, 1495, 1479, 1379, 1298,

1254, 1215, 1185, 1173, 1113, 1031, 895, 839, 775, 733, 718 cm^{-1}. HRMS (EI+) m/z calculated for $C_{11}H_{13}O_3Cl$ $[M+H]^+$: 228.0553, found 228.0552.

4-(2-chloroallyl)-2,6-dimethoxyphenol (**2a**)

314 mg of **1a** (1.38 mmol) was added to a 2 mL microwave vial and dissolved in 1.3 mL of 1,2-dichlorobenzene. This solution was heated in a microwave reactor at 200°C for 30 minutes and at 195°C for an additional 40 minutes. The product was purified by silica gel chromatography (10:90 ethyl acetate:hexanes, R_f = 0.23) and isolated as a dark red oil in 70 % yield (221 mg, 0.97 mmol). ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.46 (s, 2H), 5.44 (s, 1H), 5.26 (m, 1H), 5.14 (q, J = 1.2 Hz, 1H), 3.88 (s, 6H), 3.56-3.55 (m, 2H). ^{13}C NMR (500 MHz, $CDCl_3$): δ 147.0, 141.8, 133.7, 127.8, 113.5, 105.7, 56.3, 45.6. IR (Thin Film, NaCl): 3514, 2938, 2840, 1615, 1518, 1461, 1429, 1366, 1330, 1242, 1216, 1115, 1039, 976, 889, 832, 803, 723 cm^{-1}. HRMS (EI+) m/z calculated for $C_{11}H_{13}O_3Cl$ $[M+H]^+$: 228.0553, found 228.0554.

1-(allyloxy)-4-iodobenzene (**1b**)

1.3064 g of 4-iodophenol (5.94 mmol) was dissolved in 75 mL of acetone in a 100 mL round bottom flask. 1.8327g of K_2CO_3 (13.3 mmol) and 132 mg of KI (0.80 mmol) were added to the solution as well as 1.3 mL of allyl bromide (15.0 mmol). This mixture was refluxed for 3 hours. After that the solution was filtered through celite and the solvent evaporated off. The product was dissolved in ethyl acetate (30 mL) and washed with a solution of KH_2PO_4 (15 mL), Na_2CO_3 (15 mL), and water (15 mL). Then it was dried over sodium sulfate and filtered, and solvent evaporated off. Finally, the product was dried under high-vacuum and the product obtained as a light yellow oil in 90 % yield. (1.3862 g, 5.33 mmol). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.55 (d, J = 9.0 Hz, 2H), 6.69 (d, J = 9.0 Hz, 2H), 6.03 (ddt, J = 17.3, 10.5, 5.3 Hz, 1H), 5.40 (dq, J = 17.3, 1.6 Hz, 1H), 5.29 (dq, J = 10.5, 1.4 Hz, 1H), 4.50 (dt, J = 5.3, 1.5 Hz, 2H). ^{13}C NMR (500 MHz, $CDCl_3$): δ 158.4, 138.2, 132.8, 117.9, 117.2, 82.9, 68.8.

2-allyl-4-iodophenol (**2b**)

515.5 mg of **1b** (1.98 mmol) was dissolved in 1.4 mL of o-dichlorobenzene in a 2 mL microwave. This solution was heated in a microwave reactor at 188°C for 4.5 hours. The product was purified by silica gel chromatography (1:9 → 2:8 ethyl acetate:hexanes, R_f = 0.42 in 2:8 ethyl

acetate:hexanes) and isolated as a light yellow oil in 27% yield (141.3 mg, 0.54 mmol). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.42-7.40 (m, 2H), 6.59 (d, J = 8.9 Hz, 1H), 5.96 (ddt, J = 16.6, 10.3, 6.4 Hz, 1H), 5.20-5.14 (m, 2H), 4.98 (s, 1H), 3.35 (dt, J = 6.3, 1.4 Hz, 2H). ^{13}C NMR (500 MHz, $CDCl_3$): δ 154.0, 138.9, 136.6, 135.5, 128.1, 118.1, 117.2, 82.9, 34.7.

2-allyl-4-iodophenyl acetate (**3b**)

22.5 mg of **2b** (0.087 mmol) was dissolved in a 0.4 mL of pyridine in a small vial. 0.4 mL of acetic anhydride (4.2 mmol) was added to the vial and the solution allowed to stir at room temperature for 18 hours. The solvent was evaporated off under high vacuum and the product purified by silica gel chromatography (1:9 ethyl acetate:hexanes) and isolated as a clear oil in 92% yield (24 mg, 0.079 mmol). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.57-7.54 (m, 2H), 6.80 (d, J = 8.3 Hz, 1H), 5.85 (ddt, J = 16.8, 10.1, 6.6 Hz, 1H), 5.12-5.05 (m, 2H), 3.24 (bd, J = 6.6 Hz, 2H), 2.29 (s, 3H). ^{13}C NMR (500 MHz, $CDCl_3$): δ 169.0, 148.8, 139.2, 136.4, 134.9, 134.5, 124.4, 117.0, 90.4, 34.3, 20.9.

4-(allyloxy)-1-bromo-2-chlorobenzene (**1c**)

1.04 g of 4-bromo-3-chloro-phenol (5.01 mmol) was dissolved in 30 mL of acetone in a 100 mL round bottom flask. 1.1232g of K_2CO_3 (8.13 mmol) and 71.4 mg of KI (0.43 mmol) were added to the solution as well as 0.65 mL of allyl bromide (7.51 mmol). This mixture was refluxed for 3.5 hours, cooled to room temperature, filtered through celite, and purified by silica gel chromatography (10:90 ethyl acetate:hexanes, R_f = 0.66). The product was isolated as clear oil in 97 % yield (1.2079 g, 4.88 mmol). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.47 (d, J = 8.9 Hz, 1H), 7.02 (d, J = 2.9 Hz, 1H), 6.71 (dd, J = 8.9, 2.9 Hz, 1H), 6.05-5.97 (m, 1H), 5.43-5.38 (m, 1H), 5.33-5.30 (m, 1H), 4.52-4.50 (m, 2H). ^{13}C NMR (500 MHz, $CDCl_3$): δ 158.3, 134.8, 133.8, 132.4, 118.2, 116.7, 115.2, 113.0, 69.2. IR (Thin Film, NaCl): 3085, 2867, 1588, 1566, 1469, 1424, 1381, 1362, 1295, 1282, 1263, 1223, 1110, 1025, 1012, 999, 929, 902, 861, 839, 800 cm^{-1}. HRMS (EI+) m/z calculated for $C_9H_8OBr^{37}Cl$ [M+H]+: 247.9418, found 247.9420.

2-allyl-4-bromo-5-chlorophenol (**2c**)

1.4545 g of **1c** (5.9 mmol) was added to a 5 mL microwave vial and dissolved in 3 mL of dichlorobenzene. This solution was put under three vacuum-argon cycles and then heated in a microwave reactor at 180°C for 24 hours. The reaction produced the desired product along with its

isomer, 2-allyl-4-bromo-3-chlorophenol in a ratio of 1:2.4. The product was purified by silica gel chromatography (0:100 → 20:80 ethyl acetate:hexanes, R_f = 0.47 in 10:90 ethyl acetate: hexanes) and obtained as a light yellow oil after drying under high-vacuum. This reaction gave 28% yield of the desired product (0.41 g, 1.64mmol). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.32 (s, 1H), 6.94 (s, 1H), 5.99-5.91 (m, 1H), 5.42 (s, 1H), 5.20-5.14 (m, 1H), 5.18-5.17 (m, 1H), 3.36-3.33 (m, 2H). ^{13}C NMR (500 MHz, $CDCl_3$): δ 153.8, 135.1, 134.5, 132.6, 126.4, 117.6, 117.4, 112.8, 34.2. IR (Thin Film, NaCl): 3500, 3081, 2918, 1639, 1595, 1575, 1562, 1481, 1464, 1431, 1381, 1267, 1246, 1201, 1123, 997, 923, 879, 843, 798 cm^{-1}. HRMS (EI+) m/z calculated for $C_9H_8OBr^{37}Cl$ $[M+H]_+$: 247.9418, found 247.9414.

2-allyl-4-bromo-3-chlorophenyl acetate (**3c**)

85.1 mg of **2c** (0.344 mmol) was dissolved in a 0.5 mL of pyridine in a small vial. 0.5 mL of acetic anhydride (5.3 mmol) was added and the solution allowed to stir at room temperature for 22 hours. The solvent was evaporated off under high vacuum and the product purified by silica gel chromatography (1:9 ethyl acetate:hexanes) and isolated as a clear oil in 98% yield (96.4 mg, 0.333 mmol). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.48 (s, 1H), 7.19 (s, 1H), 5.87-5.79 (m, 1H), 5.14-5.11 (m, 1H), 5.10-5.06 (m, 1H), 3.24 (bd, J = 6.6 Hz, 2H), 2.29 (s, 3H).

1-allyl-5-bromo-4-chloro-2-methoxybenzene (**3d**)

49.9 mg of **2c** (0.202 mmol) was dissolved in 2.5 mL of acetone in a round bottom flask. Then 67.6 mg of K_2CO_3 (0.489 mmol) and 6.5 mg of KI (0.04 mmol) were added to the solution as well as 31 μL of iodomethane (0.50 mmol). This mixture was refluxed overnight, cooled to room temperature, filtered, and concentrated *in vacuo*, followed by purification by silica gel chromatography (10:90 ethyl acetate:hexanes). The product was isolated as clear oil in 56% yield (29.5 mg, 0.11 mmol). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.32 (s, 1H), 6.92 (s, 1H), 5.95-5.87 (m, 1H), 5.09-5.04 (m, 1H), 5.08-5.07 (m, 1H), 3.81 (s, 3H), 3.31-3.29 (m, 2H). ^{13}C NMR (500 MHz, $CDCl_3$): δ 156.9, 135.5, 133.8, 132.3, 129.4, 116.4, 112.5, 112.4, 55.8, 33.4.

2-(5-allyl-2-chloro-4-methoxyphenoxy)-5-(2-chloroallyl)-1,3-dimethoxy-benzene (**4d**)

16.7 mg of **3d** (63.9 μmol) was added to a small vial along with 15.2 mg of CuBr•SMe_2 (74 μmol) and 14.9 mg of K_2CO_3 (108 μmol). The vial was closed and put under three vacuum-argon cycles. 15.3 mg of **2a** (66.9 μmol) was dissolved seperately in 0.15 mL of pyridine and 0.30 mL of acetonitrile, and that solution was added to the small vial under a constant flow of argon via syringe. The reaction mixture was allowed to stir in a pre-heated oil bath at 75°C for 45 hours. The product was purified by silica gel chromatography (0:10 → 2:8 ethyl acetate:hexanes, R_f, product = 0.62 in 2:8 ethyl acetate:hexanes). The product was isolated as a white solid in 27.5% yield (7.2 mg, 17.6 μmol). ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.89 (s, 1H), 6.51 (s, 2H), 6.35 (s, 1H), 5.85-5.77 (m, 1H), 5.30 (d, J = 0.8 Hz, 1H), 5.17 (dd, J = 2.1, 0.8 Hz, 1H), 4.94-4.87 (m, 1H), 4.92-4.91 (m, 1H), 3.78 (s, 3H), 3.76 (s, 6H), 3.62 (s, 2H), 3.20 (m, 2H). ^{13}C NMR (500 MHz, $CDCl_3$): δ 153.2, 152.0, 147.8, 141.3, 136.4, 134.3, 131.8, 127.6, 119.6, 116.1, 115.4, 113.8, 112.6, 106.5, 56.4, 56.1, 45.8, 33.7. HRMS (EI+) m/z calculated for $C_9H_8OBr^{37}Cl$ $[M+H]^+$: 408.0895, found 408.0888.

Attempted synthesis of 2-allyl-5-chloro-4-(4-(2-chloroallyl)-2,6-dimethoxyphenoxy)-phenyl acetate (**4c**) *that gave 4-(2-chloroallyl)-2,6-dimethoxyphenyl acetate*

30 mg of **3c** (0.104 mmol) was added to a small vial, along with 23.0 mg of CuBr•SMe_2 (0.112 mmol) and 20.8 mg of K_2CO_3 (0.15 mmol). The vial was then closed and put under three vacuum-argon cycles. 24.2 mg of **2a** (0.105 mmol) was dissolved seperately in 0.23 mL of pyridine and 0.46 mL of acetonitrile, and that solution was added to the small vial under a constant flow of Ar. The reaction mixture was allowed to stir in a pre-heated oil bath at 75°C for 48 hours. None of the desired product was isolated, but instead some 4-(2-chloroallyl)-2,6-dimethoxyphenyl acetate was observed by NMR. ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.48 (s, 2H), 5.29 (bs, 1H), 5.19-5.18 (m, 1H), 3.81 (s, 6H), 3.59 (bs, 2.20), 2.33 (s, 3H).

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