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A Synthetic Approach to Chrysophaentin F.

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The chrysophaentins are a newly discovered natural product family displaying promising anti-infective activity. Herein we describe an approach to chrysophaentin F that uses an array of metal catalysed coupling reactions (Cu, Ni, Pd, W, Mo) to form key bonds.

The chrysophaentins were discovered by Bewley *et al.* in the methanoic extract of *Chrysophaeum taylori* alga during a screening study to identify promising new anti-infectives.[1] Eight closely related bioactives macrocycles were identified in the extract, named chrysophaentins A-H (**1-5**, **8-10**), which were subsequently joined by the linear chrysophaentins E2 (**6**) and E3 (**7**) (Figure 1).[2] From a structural perspective they define a new class of marine natural products, the *bis*-diarylbutenes. Their core resembles that of the *bis*-bibenzyl family of natural products,[3,4] but with two additional carbon centres and unsaturation in each of the chains linking the diaryl ether units. In assays against *Staphylococcus aureus* (SA), methicillin-resistant SA (MRSA) and multidrug-resistant SA (MDR-SA), chrysophaentins A (**1**), F (**8**) and H (**10**) were found to have useful potency, with minimum inhibitory concentrations (MIC_{50}) in the range of 0.8-9.5 μg/mL.[1] By contrast, the acyclic chrysophaentin E **5**, and those with a bromide on arene A or arene C (**2**-**4** and **9**), showed greatly reduced activity. Chrysophaentin A (**1**) was also found to inhibit the bacterial cell division protein FtsZ, a popular target in antimicrobial drug discovery programmes.[5]

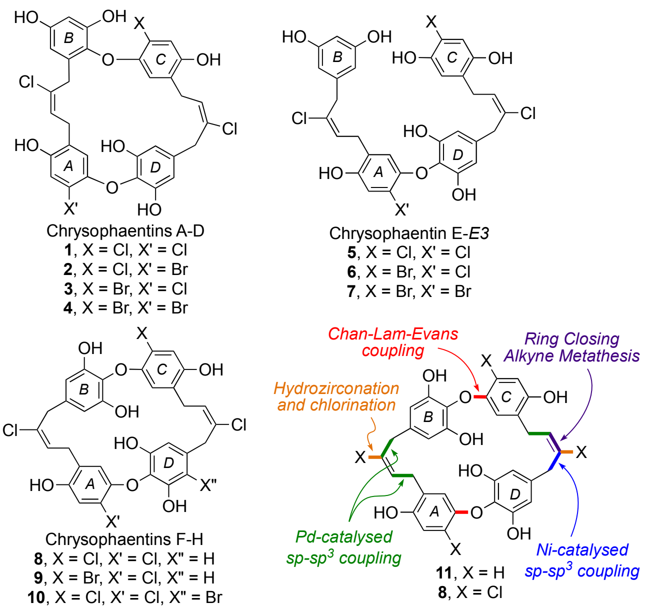

Figure 1 The chrysophaentins and our approach to their total synthesis

From a synthetic perspective the chrysophaentins have proven to be elusive targets. To date, all of the approaches described have sought to make one of the symmetrical chrysophaentins using a cyclodimerization strategy, yet none has succeeded in gaining access to the macrocyclic core.[2,4-6] Herein we describe our work on the development of a general synthetic approach to the natural product family, exemplified by syntheses of the dehalogentated core **11** and, tentatively, of chrysophaentin F (**8**) in impure form. Our approach, summarized in Figure 1, has both divergent and convergent phases and uses an array of metal catalyzed reactions (Cu, Ni, Pd, W and Mo) to construct key bonds.

To test the validity of our approach, we first targeted the chrysophaentin F-H core **11** lacking all halogen substituents. Our synthesis began with the preparation of benzo-1,3-dioxane **15** and phenol **16** using standard protocols (Scheme 1).[7-9] Their union to diaryl ether **18** was then achieved using a Chan-Lam-Evans coupling procedure.[10] After examining a range of catalysts, solvents and reaction conditions, we found that it was best to employ Cu(OTf)$_2$ with 4Å molecular sieves in ethanol under an oxygen atmosphere. In that way diaryl ether **18** could be formed reliably in 76% yield. Sequential hydrolysis of the

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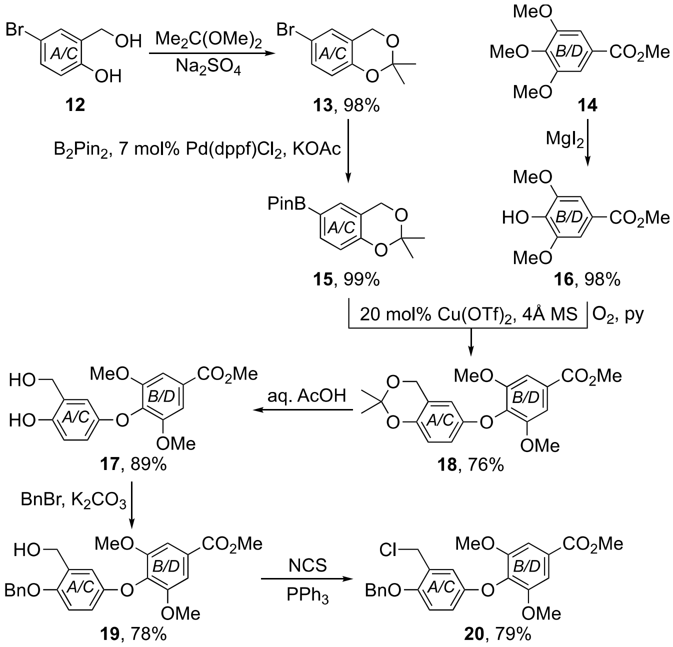
acetal to phenol **17**; protection as benzyl ether **19** and conversion of the benzylic alcohol to the corresponding chloride,[11] gave the pivotal diaryl ether **20** in high overall yield.



Scheme 1 Synthesis of the pivotal diaryl ether **20**

At this juncture our synthesis entered a divergent phase where diaryl ether **20** was advanced to both the B-*O*-C and A-*O*-D subunits, **26** and **28** respectively (Scheme 2). Thus, using a Pd-catalysed procedure developed by Buchwald *et al.*[12] diaryl ether **20** was coupled with TMS-acetylene and 1-hexyne respectively, to afford alkynes **21** and **22** in excellent yield. The esters in each of these products were then reduced with $LiAlH_4$ to facilitate their conversion to halides **25** and **26**.[11] Alas, attempts to effect the coupling of benzyl bromide **25** and 1-hexyne using the aforementioned Buchwald procedure also induced alkyne to allene isomerisation.[12] However, by switching to a nickel catalyzed coupling reaction developed by Gau *et al.*,[13] it was successfully coupled with hexynyl$AlEt_2$ to give diyne **28** in good yield after deprotection of the silyl acetylene **27** with catalytic silver triflate.[14] Pleasingly, the Buchwald procedure proved effective for the coupling of diaryl ether fragments **26** and **28** providing the macrocyclic precursor **29** in 50% yield.[12]

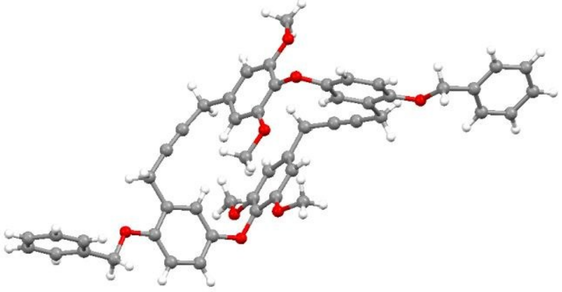
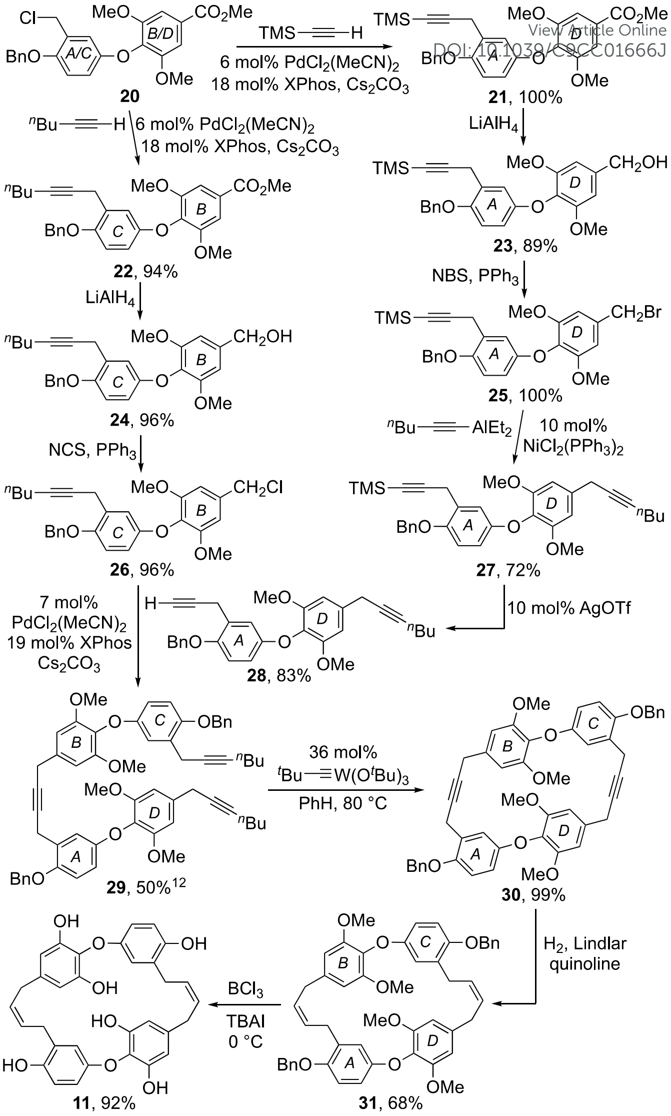


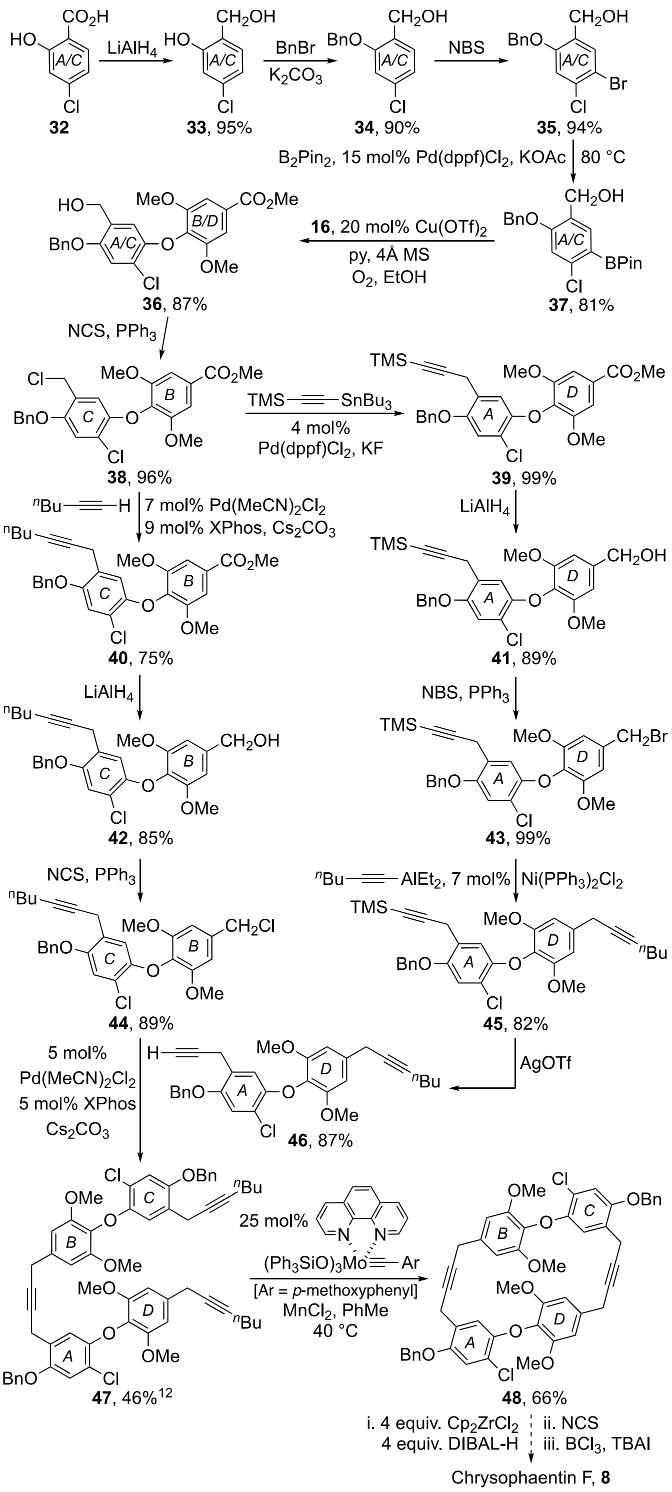
Figure 2 X-ray crystal structure of macrocyclic diyne **30**



Scheme 2 Synthesis of dehalogenated chrysophaentin **11**

The stage was now set to enact our endgame strategy, which sought to use alkyne metathesis for the critical macrocyclization reaction.[15,16] Pleasingly, this proved remarkably efficient as, after some optimization, triyne **29** was transformed into macrocyclic diyne **30** in near quantitative yield using Schrock's alkylidyne catalyst in toluene at 80 °C for 12 h under high dilution.[16] Success was confirmed by X-ray crystallographic analysis (Figure 2). Selective hydrogenation of **30** using Lindlar's catalyst in the presence of quinoline next provided *bis-cis*-alkene **31**, leaving us the task of unmasking the six phenol residues. Although the double bonds in **31** proved sensitive to an array of standard deprotection protocols, a combination of BCl_3 and tetrabutylammonium iodide in DCM gave our target **11** in 92% yield (Scheme 2).[17]

The total synthesis of chrysophaentin F **8** became our next target with the preparation of the keystone diaryl ether **38** becoming the immediate goal (Scheme 3). To that end, benzoic acid **32** was reduced with $LiAlH_4$ to diol **33**, which was in turn was protected as its benzyl ether **34**. Arene bromination to **35** then facilitated a Miyaura borylation to **37** enabling it's coupling



Scheme 3 A tentative synthesis of chrysophaentin F

to phenol **16** using a Chan-Lam-Evans procedure. Finally, conversion of the resulting benzyl alcohol **36** to the corresponding chloride **38** delivered the required diaryl ether.

The divergent strategy used to prepare dehalochrysophaentin **11** was now applied to the synthesis of chrysophaentin F **8**. While most of the steps were easy to replicate, it proved advantageous to use a Stille coupling to advance chloride **38** to alkyne **39** as it proceeded reliably in near quantitative yield.[18] All other steps in the sequence mirrored those demonstrated previously, readily providing the B-*O*-C and A-*O*-D diaryl ether subunits **44** and **46** (Scheme 3). These were coupled using the Buchwald procedure to give triyne **47**, setting the stage for our end-game strategy.

Pleasingly, after some optimization, triyne **47** was transformed into macrocyclic diyne **48** in modest yield using Fürstner's molybdenum·phenanthroline pre-catalyst in toluene at 40 °C for 12 h.[15] Hydrozirconation of **48** with Schwartz reagent (generated *in situ* by reduction of Cp_2ZrCl_2) followed by chlorination with NCS gave a complex mixture of products,[19,20] that was partially separated by column chromatography (see Supplementary Information p S124-5). The main fractions were then combined and treated with BCl_3 and tetrabutylammonium iodide to unmask the phenolic residues. Purification of the product mixture by column chromatography gave a major fraction exhibiting spectral characteristics consistent with the formation of chrysophaentin F **8** in an impure state (see Supplementary Information for LRMS, ^{1}H and ^{13}C NMR data).[1] Alas, attempts to purify the natural product further by preparative TLC and HPLC proved unrewarding with material losses putting paid to further endeavours.

In summary, we have developed a synthetic approach to chrysophaentin F **8** with the flexibility to allow all members of this family to be targeted. The approach demonstrates the value of i) Chan-Lam-Evans coupling reactions for the preparation of diaryl ethers with high steric demand;[10] ii) Buchwald's, Gau's and Stille's procedures for effecting sp-sp^3 coupling reactions between alkynes and benzyl halides;[12,13] and iii) Fürtsner's alkylidyne pre-catalyst for macrocyclisation through ring-closing alkyne metathesis.[15,16]

Conflicts of interest

There are no conflicts to declare.

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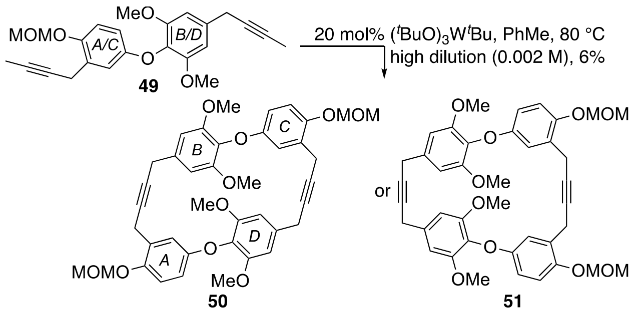
6 In common with others, our first approach to chrysophaentin F was based on a cyclodimerization strategy, *e.g.* **49** → **50**. Indeed, after much optimization~~,~~ this gave a cyclodimer in 6% yield that could not be assigned unambiguously to either dimer **50** or its regioisomer **51** using the spectral data attained.



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