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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 bioactive 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**) (Fig. 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}.[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]

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 Fig. 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.

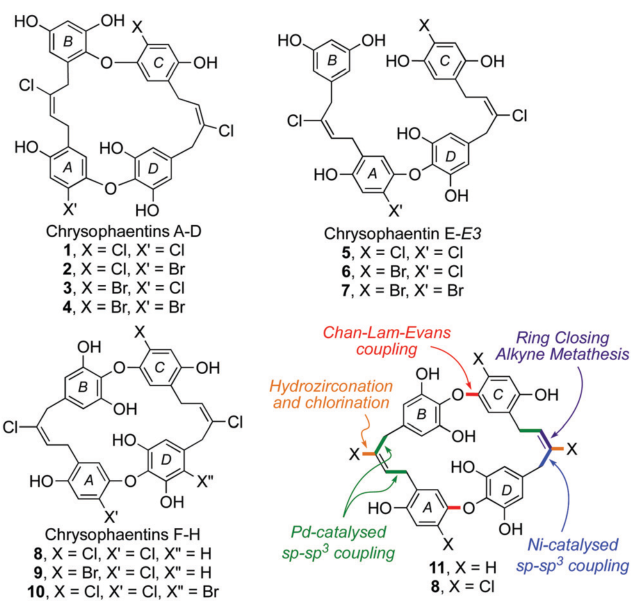

Fig. 1 The chrysophaentins and our approach to their total synthesis.

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

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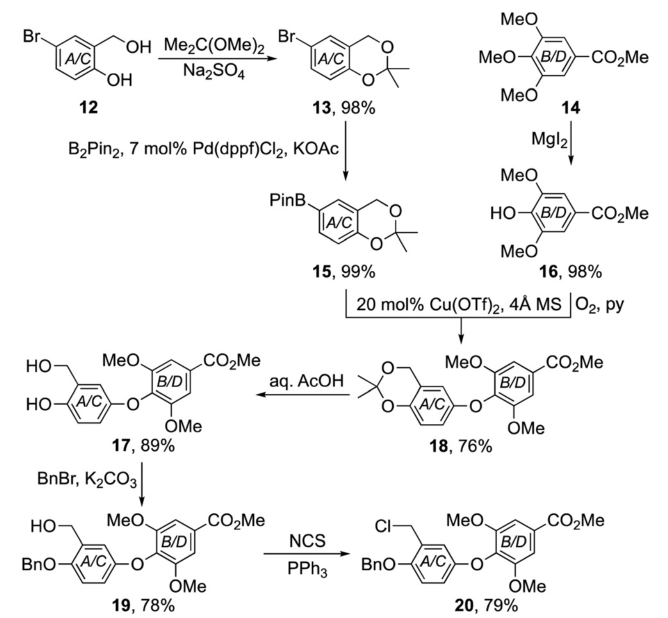
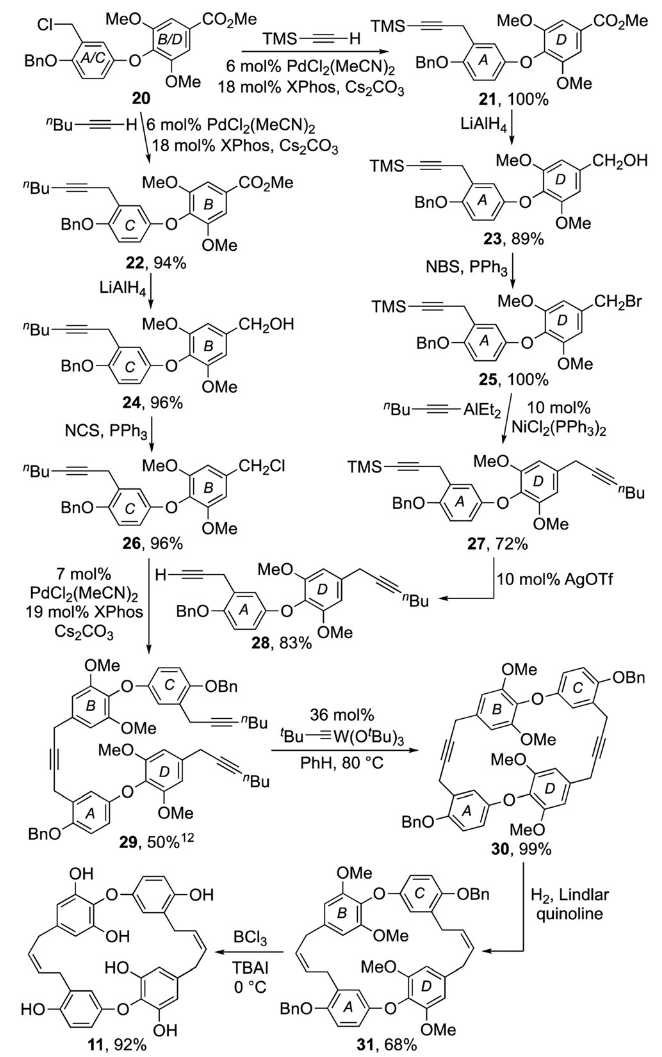


Scheme 1 Synthesis of the pivotal diaryl ether **20**.

of catalysts, solvents and reaction conditions, we found that it was best to employ $Cu(OTf)_2$ with 4 Å 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 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.

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 hexynylAlEt$_2$ 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]

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 (Fig. 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



Scheme 2 Synthesis of dehalogenated chrysophaentin **11**.

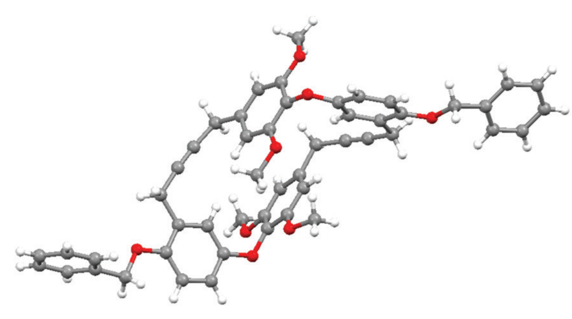
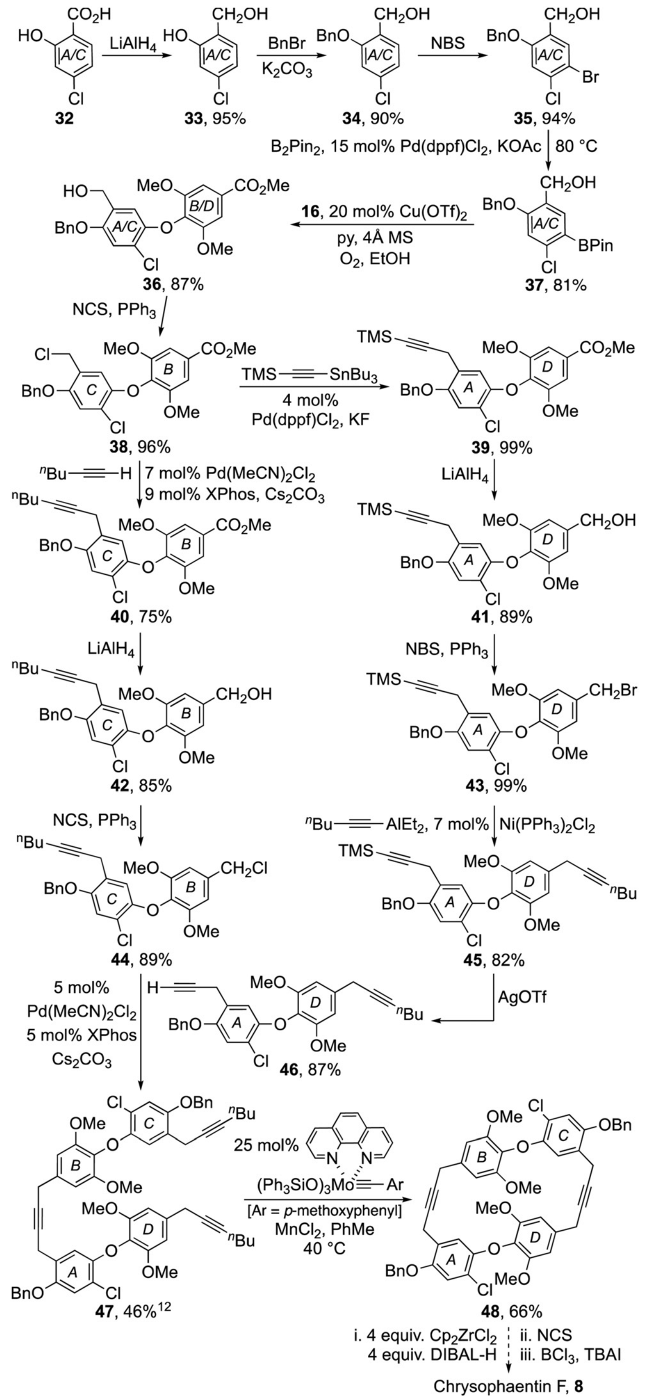


Fig. 2 X-ray crystal structure of macrocyclic diyne **30**.

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 in turn was



Scheme 3 A tentative synthesis of chrysophaentin F.

protected as its benzyl ether **34**. Arene bromination to **35** then facilitated a Miyaura borylation to **37** enabling its coupling 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 ESI† p. S124 and S125). 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 ESI† 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]

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Conflicts of interest

There are no conflicts to declare.

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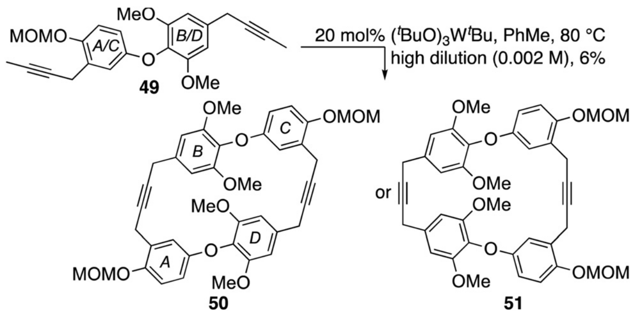
much optimization this gave a cyclodimer in 6% yield that could not be assigned unambiguously to either dimer **50** or its regioisomer **51** using the spectral data attained.



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