



Cite this: *Chem. Commun.*, 2019, 55, 4837

Received 27th February 2019,
Accepted 1st April 2019

DOI: 10.1039/c9cc01666j

rsc.li/chemcomm

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

The chrysphaentins 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 chrysphaentins A–H (1–5, 8–10), which were subsequently joined by the linear chrysphaentins 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), chrysphaentins 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 $\mu\text{g mL}^{-1}$.¹ By contrast, the acyclic chrysphaentin E 5, and those with a bromide on arene A or arene C (2–4 and 9), showed greatly reduced activity. Chrysphaentin 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 chrysphaentins have proven to be elusive targets. To date, all of the approaches

A synthetic approach to chrysphaentin F†

Jean-Baptiste Vendeville,^{ab} Rebecca F. Matters,^a Anqi Chen,^b Mark E. Light,^a Graham J. Tizzard,^a Christina L. L. Chai ^{bc} and David C. Harrowven ^{ab*}

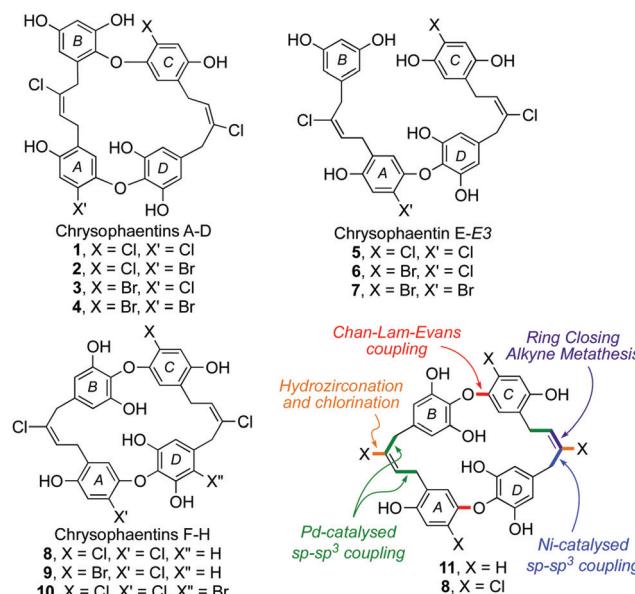


Fig. 1 The chrysphaentins and our approach to their total synthesis.

described have sought to make one of the symmetrical chrysphaentins 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 dehalogenated core 11 and, tentatively, of chrysphaentin 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.

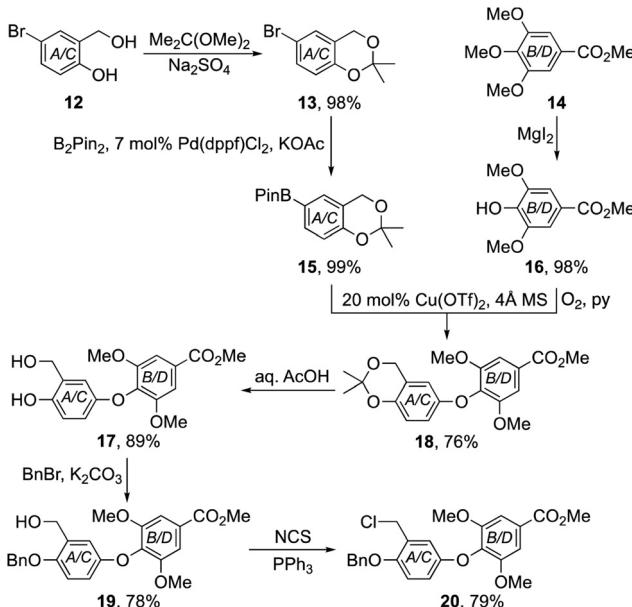
To test the validity of our approach, we first targeted the chrysphaentin F-H core 11 lacking all halogen substituents. Our synthesis began with the preparation of benzo-1,3-dioxane 15 and phenol 16 using standard protocols (Scheme 1).^{7–9} Their union to diaryl ether 18 was then achieved using a Chan-Lam–Evans coupling procedure.¹⁰ After examining a range

^a Chemistry, University of Southampton, Highfield, Southampton, SO17 1BJ, UK.
 E-mail: dch2@soton.ac.uk

^b Institute of Chemical and Engineering Sciences, Agency for Science, Technology and Research (A*STAR), 8 Biomedical Grove, Neuros, #07-01, 138665, Singapore

^c Department of Pharmacy, National University of Singapore, 18 Science Drive 4, 117543, Singapore. E-mail: phacllc@nus.edu.sg

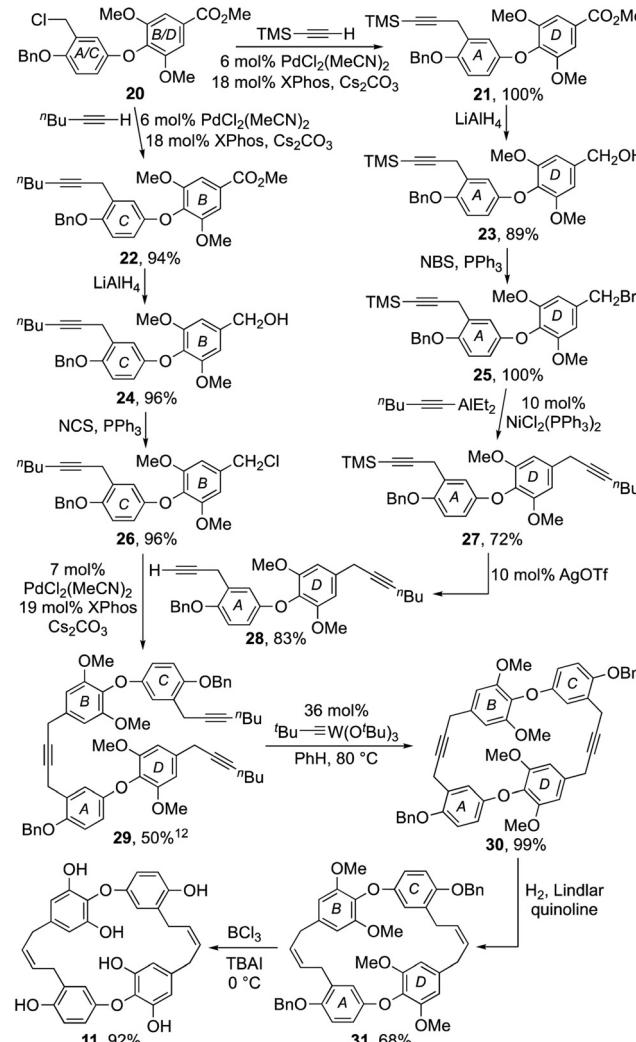
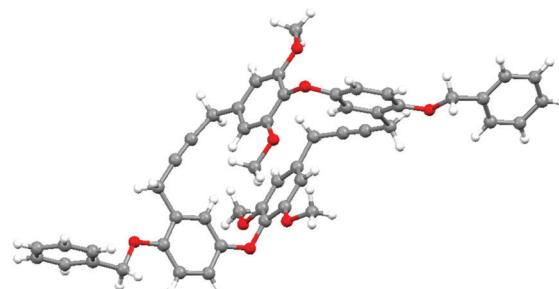
† Electronic supplementary information (ESI) available: Experimental accounts with spectral details and copies of NMR spectra. CCDC 1899398 and 1898679. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c9cc01666j

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

of catalysts, solvents and reaction conditions, we found that it was best to employ $\text{Cu}(\text{OTf})_2$ 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.

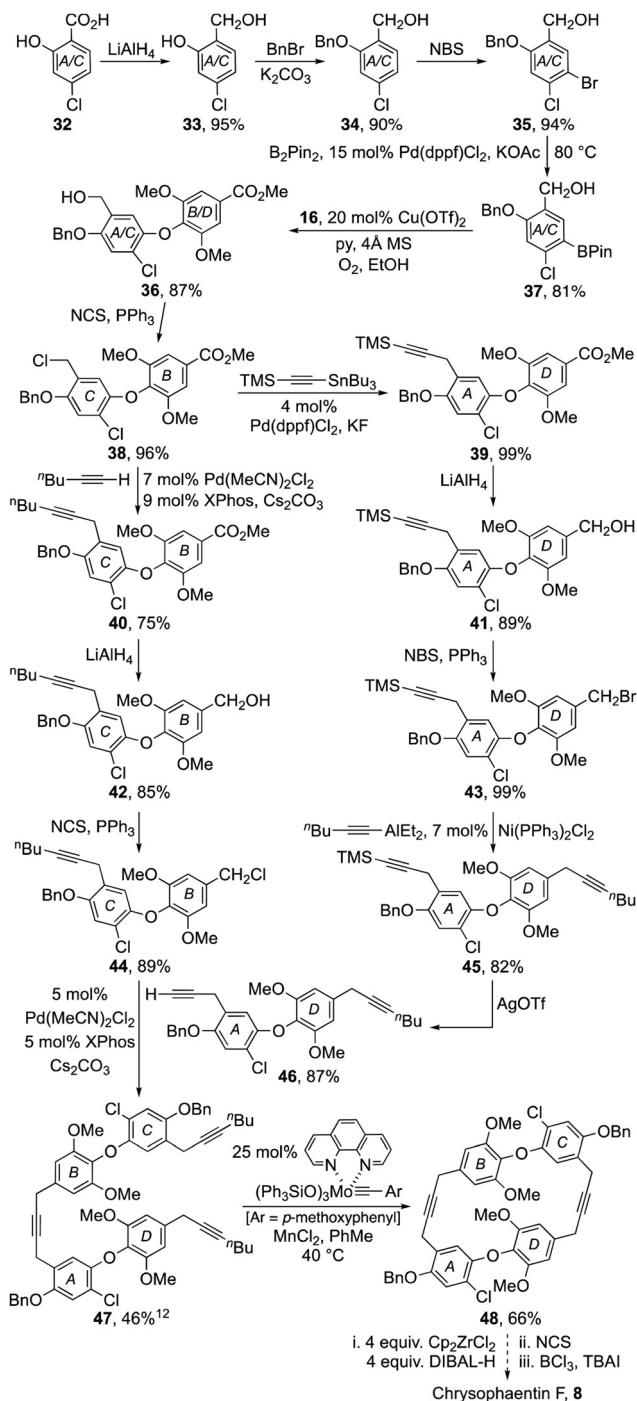
At this juncture our synthesis entered a divergent phase where diaryl ether **20** was advanced to both the B–O–C and A–O–D subunits, **26** and **28** respectively (Scheme 2). Thus, using a Pd-catalysed procedure developed by Buchwald *et al.*¹² diaryl ether **20** was coupled with TMS-acetylene and 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 hexynylAlEt₂ 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 chrysophaeantin **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 chrysophaeantin **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 chrysophaeantin 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 dehalochrysophaeantin **11** was now applied to the synthesis of chrysophaeantin 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 chrysophaeantin F **8** in an impure state (see ESI† for LRMS, ^1H 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 chrysophaeantin 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 $\text{sp}-\text{sp}^3$ coupling reactions between alkynes and benzyl halides;^{12,13} and (iii) Fürstner's alkylidene pre-catalyst for macrocyclisation through ring-closing alkyne metathesis.^{15,16}

We thank Prof. A. Fürstner for his kind donation of the molybdenum-phenanthroline pre-catalyst. The University of Southampton VC Scholarship Scheme, the A*STAR ARAP Scheme, the ERDF (LabFact: InterReg V project 121) and the EPSRC [EP/K039466/1, EP/P013341/1 and EP/L003325/1] are thanked for their financial support.

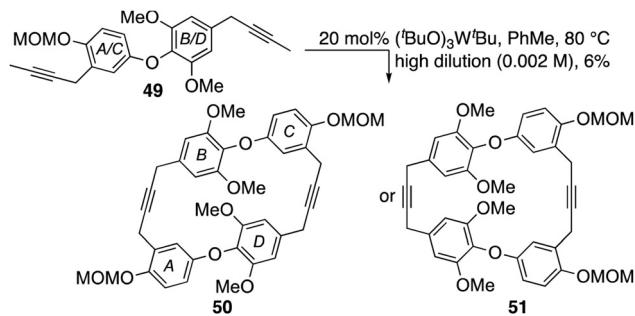
Conflicts of interest

There are no conflicts to declare.

Notes and references

- A. Plaza, J. Keffer, G. Bifulco, J. Lloyd and C. Bewley, *J. Am. Chem. Soc.*, 2010, **132**, 9069; J. R. Davison and C. Bewley, *J. Nat. Prod.*, 2019, **82**, 148.
- J. L. Keffer, J. T. Hammill, J. R. Lloyd, A. Plaza, P. Wipf and C. A. Bewley, *Mar. Drugs*, 2012, **10**, 1103.
- D. C. Harrowven and S. L. Kostik, *Nat. Prod. Rep.*, 2012, **29**, 223. For our work on macrocyclic bis-benzyl total synthesis see: F. A. Almaliki and D. C. Harrowven, *Eur. J. Org. Chem.*, 2016, 5738; S. L. Kostik, T. Woodcock, L. F. Dudin, P. D. Howes and D. C. Harrowven, *Chem. – Eur. J.*, 2011, **17**, 10906; D. C. Harrowven, T. Woodcock and P. D. Howes, *Angew. Chem., Int. Ed.*, 2005, **44**, 3899.
- H. P. Erikson, *Cell*, 1995, **80**, 367; M. H. Foss, Y.-J. Eun and D. B. Weibel, *Biochemistry*, 2011, **50**, 7719.
- A. Brockway, C. Grove, M. Mahoney and J. Shaw, *Tetrahedron Lett.*, 2015, **56**, 3396.
- In common with others, our first approach to chrysophaeantin 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.



7 N. Gisch, J. Ballzarini and C. Meier, *J. Med. Chem.*, 2007, **50**, 1658.
 8 T. Ishiyama, M. Murata and N. Miyaura, *J. Org. Chem.*, 1995, **60**, 7508.
 9 K. Bao, A. Fan, Y. Dai, L. Zhang, W. Zhang, M. Cheng and X. Yao, *Org. Biomol. Chem.*, 2009, **7**, 5084.
 10 D. Chan, K. Monaco, R. Wang and M. Winters, *Tetrahedron Lett.*, 1998, **39**, 2933; D. Evans, J. Katz and T. West, *Tetrahedron Lett.*, 1998, **39**, 2937; P. Lam, C. Clark, S. Sauborn, J. Adams, M. Winters, D. Chan and A. Combs, *Tetrahedron Lett.*, 1998, **39**, 2941. See also S. V. Ley and A. W. Thomas, *Angew. Chem., Int. Ed.*, 2003, **42**, 5400.
 11 R. Appel, *Angew. Chem., Int. Ed. Engl.*, 1975, **14**, 801.
 12 C. H. Larsen, K. W. Anderson, R. E. Tundel and S. L. Buchwald, *Synlett*, 2006, 2941. The optimised procedure reported used the alkyne in slight excess (1.3 equiv.) and was adopted for advancing benzyl chloride **20** to alkynes **21** and **22**. However, it was not deemed appropriate to use alkynes **28** and **46** in excess in their respective couplings with benzyl chlorides **26** and **44**, as each was prepared by multi-step sequences. When using equimolar quantities of each component, some benzyl chloride was usually recovered (~25%) but no alkyne. The known isomerisation of the alkyne product to an allene was also observed as a side reaction in many cases.
 13 D. Biradar and H. Gau, *Chem. Commun.*, 2011, **47**, 10467.
 14 A. Orsini, A. Viterisi, A. Bodenner, J.-M. Weibel and P. Pale, *Tetrahedron Lett.*, 2005, **46**, 2259.
 15 J. Heppenhausen, R. Stade, R. Goddard and A. Fürstner, *J. Am. Chem. Soc.*, 2010, **132**, 11045; A. Fürstner, *Chem. Commun.*, 2011, **47**, 6505; A. Fürstner and P. W. Davies, *Chem. Commun.*, 2005, 2307.
 16 M. L. Listemann and R. R. Schrock, *Organometallics*, 1985, **4**, 74.
 17 P. R. Brooks, M. C. Wirtz, M. G. Vetelino, D. M. Rescek, G. F. Woodworth, B. P. Morgan and J. W. Coe, *J. Org. Chem.*, 1999, **64**, 9719.
 18 R. R. Singidi and T. V. RajanBabu, *Org. Lett.*, 2008, **10**, 3351; D. C. Harrowven, D. P. Curran, S. L. Kostiuk, I. L. Wallis-Guy, S. Whiting, K. J. Stenning, B. Tang, E. Packard and L. Nanson, *Chem. Commun.*, 2010, **46**, 6335; D. C. Harrowven and I. L. Guy, *Chem. Commun.*, 2004, 1968.
 19 Z. Huang and E. Negishi, *Org. Lett.*, 2006, **8**, 3675.
 20 D. W. Hart and J. Schwartz, *J. Am. Chem. Soc.*, 1974, **96**, 8115; D. W. Hart, T. F. Blackburn and J. Schwartz, *J. Am. Chem. Soc.*, 1975, **97**, 679; J. Schwartz and J. A. Labinger, *Angew. Chem., Int. Ed. Engl.*, 1976, **15**, 333.