



## 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 methanolic extract of *Chrysophaeum taylori* alga during a screening study to identify promising new anti-infectives.<sup>1</sup> 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).<sup>2</sup> 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,<sup>3,4</sup> 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<sub>50</sub>) in the range of 0.8–9.5 μg mL<sup>-1</sup>.<sup>1</sup> 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.<sup>5</sup>

From a synthetic perspective the chrysophaentins have proven to be elusive targets. To date, all of the approaches



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

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.<sup>2,4–6</sup> 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 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.

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).<sup>7–9</sup> Their union to diaryl ether 18 was then achieved using a Chan–Lam–Evans coupling procedure.<sup>10</sup> After examining a range

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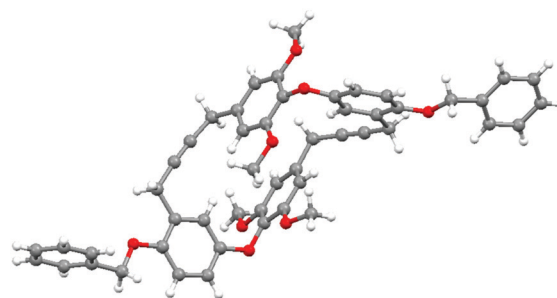
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Scheme 1 Synthesis of the pivotal diaryl ether **20**.

of catalysts, solvents and reaction conditions, we found that it was best to employ  $\text{Cu}(\text{OTf})_2$  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,<sup>11</sup> 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.*<sup>12</sup> 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  $\text{LiAlH}_4$  to facilitate their conversion to halides **25** and **26**.<sup>11</sup> Alas, attempts to effect the coupling of benzyl bromide **25** and 1-hexyne using the aforementioned Buchwald procedure also induced alkyne to allene isomerisation.<sup>12</sup> However, by switching to a nickel catalyzed coupling reaction developed by Gau *et al.*,<sup>13</sup> it was successfully coupled with hexynyl $\text{AlEt}_2$  to give diyne **28** in good yield after deprotection of the silyl acetylene **27** with catalytic silver triflate.<sup>14</sup> Pleasingly, the Buchwald procedure proved effective for the coupling of diaryl ether fragments **26** and **28** providing the macrocyclic precursor **29** in 50% yield.<sup>12</sup>

The stage was now set to enact our endgame strategy, which sought to use alkyne metathesis for the critical macrocyclization reaction.<sup>15,16</sup> 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.<sup>16</sup> 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 chrysosphaentin **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  $\text{BCl}_3$  and tetrabutylammonium iodide in DCM gave our target **11** in 92% yield (Scheme 2).<sup>17</sup>

The total synthesis of chrysosphaentin 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  $\text{LiAlH}_4$  to diol **33**, which in turn was



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. Saubern, 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. Bodlenner, J.-M. Weibel and P. Pale, *Tetrahedron Lett.*, 2005, **46**, 2259.  
 15 J. Heppekaussen, 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. Kostiuik, 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.