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Catalyst-controlled oligomerization for the collective synthesis of polypyrroloindoline natural products

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In nature, many organisms generate large families of natural product metabolites that have related molecular structures as a means to increase functional diversity and gain an evolutionary advantage against competing systems within the same environment. One pathway commonly employed by living systems to generate these large classes of structurally related families is oligomerization, wherein a series of enzymatically catalysed reactions is employed to generate secondary metabolites by iteratively appending monomers to a growing serial oligomer chain. The polypyrroloindolines are an interesting class of oligomeric natural products that consist of multiple cyclotryptamine subunits. Herein we describe an iterative application of asymmetric copper catalysis towards the synthesis of six distinct oligomeric polypyrroloindoline natural products: hodgkinsine, hodgkinsine B, idiospermuline, quadrigemine H and isopsychotridine B and C. Given the customizable nature of the small-molecule catalysts employed, we demonstrate that this strategy is further amenable to the construction of quadrigemine H-type alkaloids not isolated previously from natural sources.

Primarily isolated from shrubs of the genera *Chimonanthus*, *Calycanthus*, *Psychotria* and *Hodgkinsonia*, the polypyrroloindolines are a family of alkaloid natural products that exhibits diverse therapeutic properties, which include analgesic, antibacterial, antifungal and antiviral activities in addition to promising *in vitro* cytotoxicity[1–14]. Polypyrroloindolines are defined by their oligomeric framework of repeating pyrroloindoline units that are connected via sterically congested and synthetically demanding quaternary stereocentres[15]. The biosynthesis of the polypyrroloindoline alkaloids has been postulated to proceed via the oxidative coupling of tryptamine monomers (Fig. 1)[15–17]. Accordingly, oligomers of varying chain lengths were isolated from the dimeric chimonanthine up to the octameric vatamidine (not shown). The higher-order members of this natural product class typically comprise a complex oligomeric chain of repeating pyrroloindolines joined by C3a–C7′ linkages, interrupted by a single C3a–C3a′ linked subunit, which can be located at the terminus of the oligomeric chain, as in hodgkinsine, quadrigemine H and isopsychotridine, or internally, as in quadrigemine C (Supplementary Section II gives a detailed discussion of the structural complexity in polypyrroloindolines).

Owing to their interesting biological properties and challenging structural complexity, a myriad of strategies have been employed towards the synthesis of specific members of this natural product family. However, only a handful of syntheses of higher-order ($n > 2$) polypyrroloindoline oligomers have been reported to date, because of the difficulty in constructing multiple monomer–monomer linkages in a controlled fashion[18–24]. Of particular note are Overman's syntheses of polypyrroloindolines, in which an asymmetric Heck reaction sets the key C3a–C7′ stereocentre[18–21], and Willis's synthesis of hodgkinsine B, wherein a substrate-controlled, diastereoselective palladium-catalysed enolate arylation sets the final monomer linkage[23,24]. However, these methods have not proved successful for the formation of successive C3a–C7′ linkages[25]. As a result, no polypyrroloindoline that contains more than four monomeric subunits or sequential C3a-C7′-linked subunits has been prepared successfully to date. In this context, the use of small-molecule chiral catalysts to control successive C3a–C7′ pyrroloindoline couplings with predictable stereochemical outcomes, and thus provide access to every possible stereoisomer in this family,

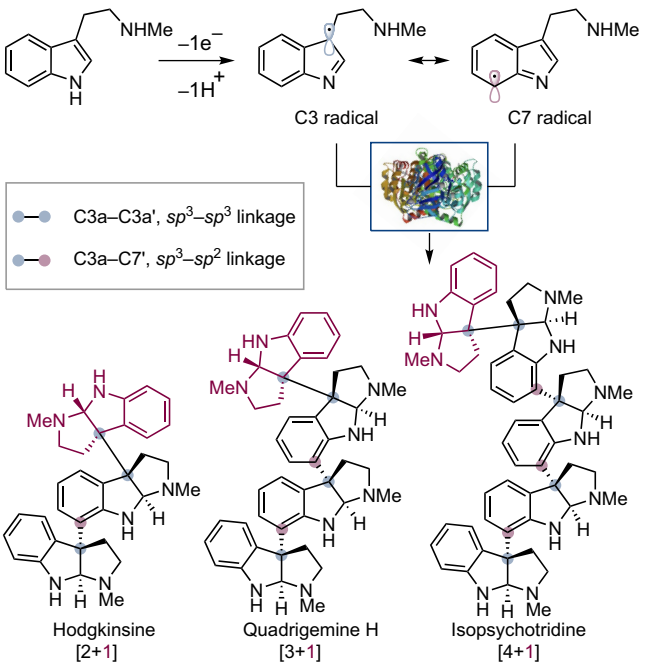

Figure 1 | Nature's method for the construction of polypyrroloindoline oligomers. Polypyrroloindoline biosynthesis is proposed to proceed through the enzymatic oxidation of two tryptamine monomers that selectively couple at either the C3 or C7 position. Iterative rounds of coupling build the complex architecture of this family of natural products, which include hodgkinsine, quadrigemine H and isopsychotridine.

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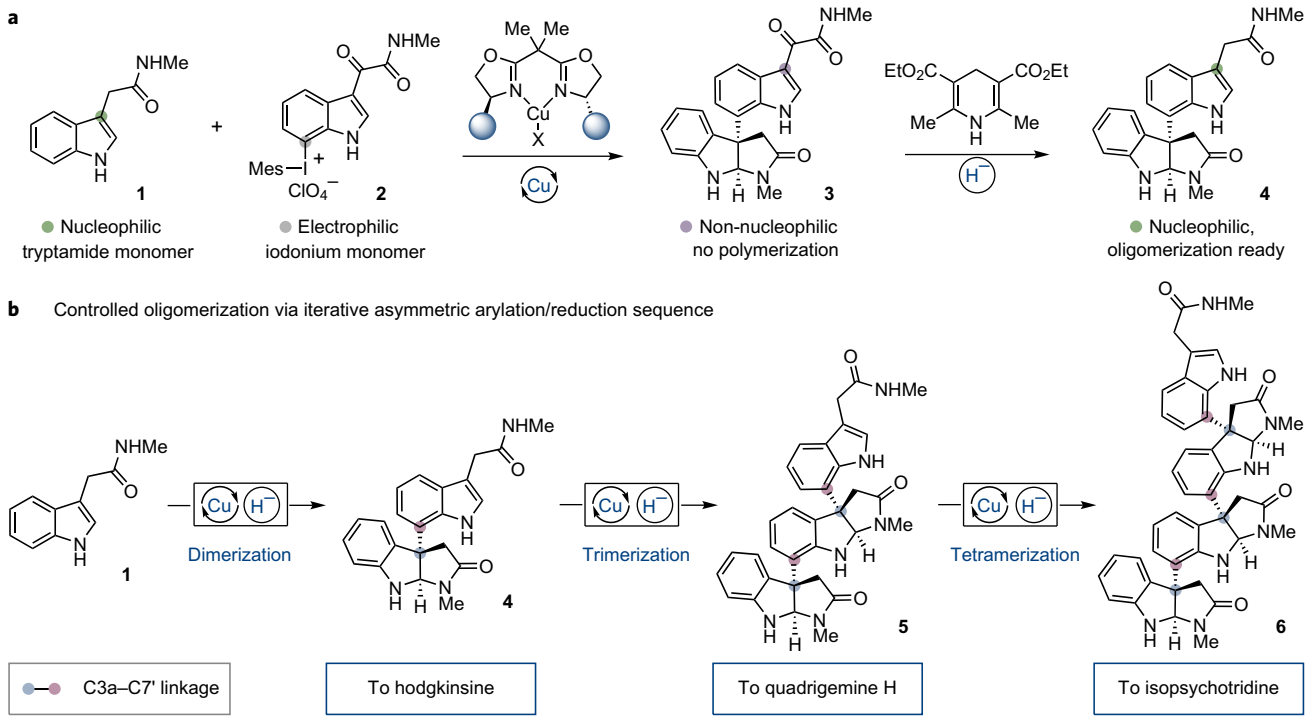


Figure 2 | Design of orthogonal monomers and catalyst-controlled oligomerization. a, Selective coupling of the nucleophilic tryptamide monomer **1** with the electrophilic monomer **2** under the control of a chiral copper catalyst provides the non-nucleophilic pyrroloindoline dimer **3**, which is inert to further reaction with **2**. Selective reduction of **3** regenerates C3 nucleophilicity in tryptamide **4**, which is capable of undergoing a subsequent round of coupling with monomer **2**. **b**, Iterative rounds of asymmetric copper-catalysed arylation followed by reduction facilitate a controlled tryptamide arylation to construct the complex C3a–C7′ chain of the polypyrroloindoline natural products. Mes, mesityl.

would represent an ideal strategy[26,27]. Moreover, such an approach lends itself to extremely concise syntheses of a range of natural products that have remained largely recalcitrant to total synthesis. Herein we present the successful execution of these ideals and the collective total synthesis of a diverse, representative set of polypyrroloindoline alkaloids (including non-natural members) via the iterative, copper-catalyst-controlled installation of tryptamine-based subunits with high levels of stereocontrol.

Design plan

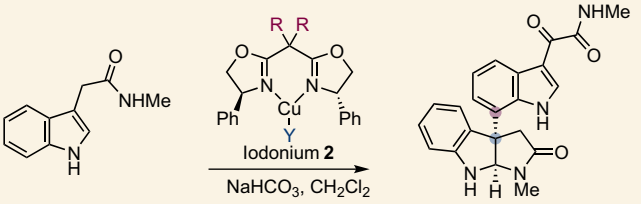
As described in Fig. 2, we envisioned adapting our recently reported asymmetric copper-catalysed tryptamide arylation[28] to exploit the orthogonal reactivity of two distinct monomeric units—one nucleophilic at the C3 position (tryptamide **1**) and one electrophilic at the C7 position (iodonium **2**)—to forge the required C3a–C7′ linkage found in dimer **3**. By utilizing a chiral copper catalyst, we anticipated that this arylation would proceed with exquisite regio- and enantioselectivity, as we observed previously for simple iodonium electrophiles.

Central to this iterative monomer-addition strategy is the prevention of uncontrolled polymerization via the incorporation of an electron-withdrawing ketoamide at the C3 position of iodonium monomer **2**. This strategy ensures that selective monoarylation can be achieved through attenuation of the π nucleophilicity of the resulting pyrroloindoline–indole dimer **3**. Further, selective reduction of this dimeric adduct **3** with a mild hydride source (Supplementary Section V gives a proposed mechanism) would then re-establish an electron-rich tryptamide (**4**) poised to undergo a subsequent round of arylation with iodonium **2**. Thereafter, iterative rounds of tryptamide addition–hydride reduction should rapidly build the complex C3a–C7′ carbon backbones of the polypyrroloindolines to deliver dimers, trimers and tetramers (for example, **4**–**6**) from the simple monomers **1** and **2**. Finally, C3a–C3a′ bond formation of the oligomer chain using a head-to-head tryptamine dimerization, with a concomitant vicinal quaternary carbon stereocentre formation, would furnish the corresponding oligomeric pyrroloindoline natural products[29–32]. Importantly, we envisioned that access to every possible permutation of the C3a–C7′ stereoisomers in this complex alkaloid series could be achieved selectively via the use of an asymmetric catalyst control.

Optimization of copper-catalysed arylation

First, we investigated the critical enantioselective coupling of the nucleophilic tryptamide monomer **1** and the electrophilic iodonium monomer **2** (Table 1). We were pleased to observe promising levels

Table 1 | Optimization of enantioselective arylation of tryptamide.



Entry*	Concentration (M)	2 (equiv.)	[Cu]-Y	*R,R*	Yield	e.e.
1	0.1	1.3	OTf	Me,Me	12%	80%
2	0.01	1.3	OTf	Me,Me	52%	76%
3	0.01	2	OTf	Me,Me	77%	76%
4†	0.01	2	ClO_4	Me,Me	85%	84%
5‡	0.02	2	ClO_4	CMe_2	98%	86%

The asymmetric copper-controlled coupling of tryptamide **1** and iodonium **2** generates the dimeric scaffold **3**. Counterions of both iodonium and the copper catalyst are critical to the efficacy and asymmetry of the transformation. *5 mg scale, 1 equiv. **1**, 20 mol% catalyst. Yield by NMR analysis of the crude mixture against an internal standard, e.e. by HPLC. †500 mg scale, isolated yield. ‡1 g scale, 30 mol% catalyst, isolated yield.

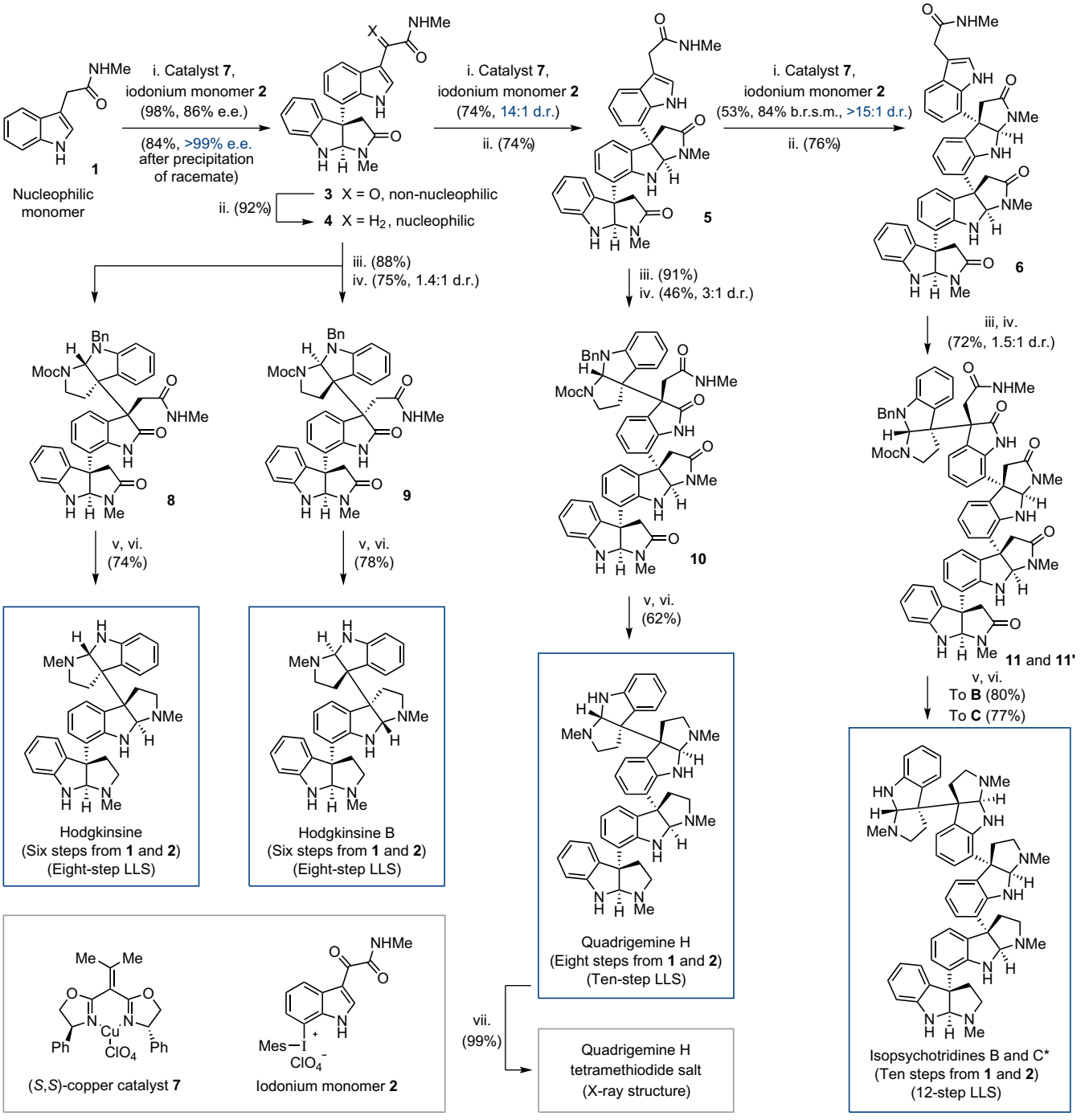


Figure 3 | Synthesis of hodgkinsine and hodgkinsine B, quadrigemine H and isopsychotridine B and C. A modular, iterative strategy allows for the catalyst-controlled synthesis of oligomeric polypyrroloindoline natural products. Critically, catalyst **7** allows for the highly stereoselective dimerization, trimerization and tetramerization to provide **3**, **5** and **6** from the coupling of iodonium **2** with **1**, **4** and **5**, respectively. The formation of the C3a–C3a′ linkage is accomplished by an inverse-electron-demand Diels–Alder reaction between a tryptamide nucleophile and an *in situ*-generated indol-2-one to provide the full carbon skeleton of [2+1], [3+1] and [4+1] polypyrroloindolines. Reagents and conditions are as follows: i, **7** (30 mol%), **2**, $NaHCO_3$, CH_2Cl_2, 23 °C; ii, Hantzsch ester, $BF_3{\cdot}OEt_2$, CH_3CN, 23 °C; iii, *N*-chlorophthalimide (NCP), DMF, H_2O, −5 °C; iv, *N*1-Bn-*N*-Moc-tryptamine, Na_3PO_4, Na_2CO_3 or Cs_2CO_3, CH_2Cl_2; v, Red-Al, 1,4-dioxane, 75 °C; vi, Na, NH_3, THF, −78 °C. vii, MeI, 0 °C. *Owing to the high levels of conformational heterogeneity, the absolute stereochemistry of the pseudo-*meso* caps of isopsychotridine B and C could not be assigned. As such, a single pseudo-*meso* diastereomer as arbitrarily drawn here. Bn, benzyl; Moc, methoxycarbonyl; b.r.s.m., based on recovered starting material.

of efficiency and asymmetric induction for this coupling using commercially available CuOTf·PhMe (OTf, OSO_2CF_3) as the copper source and (*S*,*S*)-PhBOX (BOX, bis(oxazoline)) as the ligand (Table 1, entry 1). The efficiency could be improved drastically by diluting the heterogeneous reaction mixture and utilizing greater equivalents of **2** (entries 2 and 3, Table 1). Finally, utilizing a more-reliable $CuClO_4$ pre-catalyst improved both the efficiency and selectivity of the coupling, to yield a synthetically useful transformation of scale (entry 4, Table 1). Finally, we observed that a BOX ligand with an unsaturated backbone, (*S*,*S*)-Ph-IsButBOX (ref. 33), delivered the coupled product in nearly quantitative yield and excellent stereoselectivity (98% yield, 86% e.e. (entry 5, Table 1)). As we

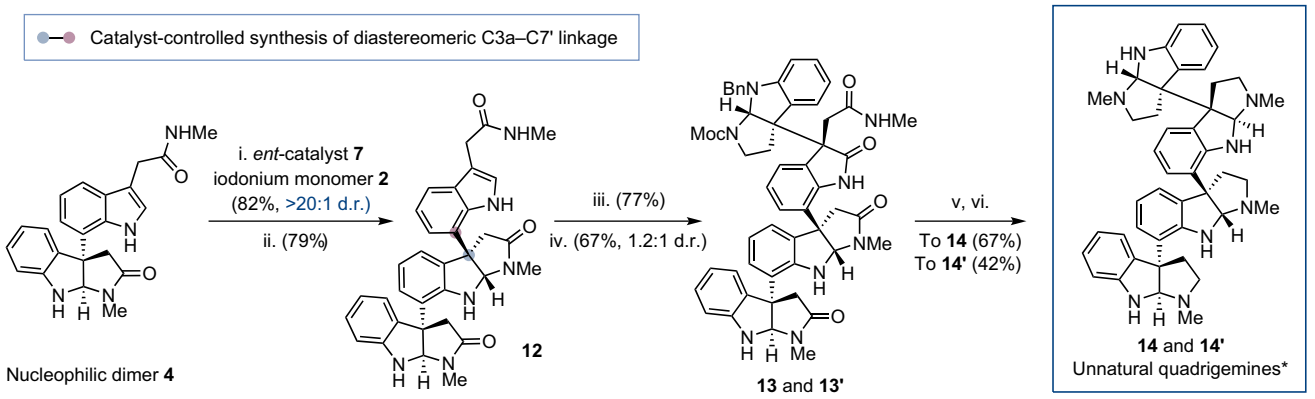


Figure 4 | Synthesis of two putatively unnatural quadrigemines. Using the (*R,R*)-enantiomer of the ligand in the trimerization step allows for the synthesis of the diastereomeric scaffold **12** with an excellent stereocontrol. This modular approach can be used for the synthesis of putatively unnatural scaffolds, such as **14**. Reagents and conditions are as follows: i, *ent*-**7** (30 mol%), **2**, $NaHCO_3$, CH_2Cl_2, 23 °C; ii, Hantzsch ester, $BF_3{\cdot}OEt_2$, CH_3CN, 23 °C; iii, NCP, DMF, H_2O, −5 °C; iv, *N*1-Bn-*N*-Moc-tryptamine, Cs_2CO_3, CH_2Cl_2; v, Red-Al, 1,4-dioxane, 75 °C; vi, Na, NH_3, THF, −78 °C. *Owing to the high levels of conformational heterogeneity, the absolute stereochemistry of the pseudo-*meso* caps of the unnatural quadrigemines **14** and **14′** could not be assigned. As such, a single pseudo-*meso* diastereomer is arbitrarily drawn here.

expected, the electrophile **2** and the resulting α-ketoamide **3** are not sufficiently π nucleophilic to undergo uncontrolled polymerization in the presence of a copper catalyst. A full discussion of the iodonium development and optimization is given in Supplementary Section III.

Hodgkinsines: [2+1] trimers

With the optimized conditions to produce the dimeric scaffold **3** in hand, we first applied this controlled oligomerization strategy towards the synthesis of the [2+1] polypyrroloindolines hodgkinsine and hodgkinsine B (Fig. 3)[2–4]. Importantly, fully enantioenriched **3** can be acquired through the precipitation of the racemate, which allows for the isolation of an 84% yield of **3** as a single enantiomer. Selective reduction of **3** with a Hantzsch ester produced dimeric tryptamide **4** in a 92% yield and re-established the required nucleophilicity at the indole 3 position in preparation for installation of the C3a–C3a′ dimeric cap or further copper-catalysed oligomerization. To install the C3a–C3a′ vicinal quaternary centres of the pseudo-*meso* cap, we drew inspiration from Funk's elegant synthesis of the non-pyrroloindoline natural product perophoramidine[34]. First, chlorination of **4** was accomplished to give the intermediate chlorooxindole in an 88% yield as an inconsequential mixture of diastereomers (3.4:1 d.r.)[35]. Then, an elimination–cycloaddition–fragmentation–cyclization cascade allowed for the selective formation of the requisite C3a–C3a′ stereocentres in a 75% yield and exclusively as the desired pseudo-*meso* capped diastereomers **8** and **9** (1.4:1 ratio), with no detectable C_2-capped isomer formation (Supplementary Section V gives the mechanism and stereochemical rationale)[36]. Subsequent hydride reduction followed by a Birch reduction (74 and 78% yields over two steps, respectively) completed the total synthesis of hodgkinsine and hodgkinsine B in six steps from **1** and **2** (longest linear sequence (LLS) of eight steps). This scalable route allowed for the production of >450 mg of hodgkinsine in a single pass. The synthetic hodgkinsines were identical to those previously reported in all respects[19]. Additionally, a similar strategy was employed for the synthesis of the [2+1] polypyrroloindoline alkaloid idiospermuline[12] in four steps from monomeric starting materials (LLS of six steps (Supplementary Section IV)).

Quadrigemine H: [3+1] tetramer

The synthesis of the [3+1] polypyrroloindoline quadrigemine H proceeded from the common dimeric tryptamide **4** via C3 arylation/cyclization with iodonium **2**. At this stage, it was discovered that (*S,S*)-Ph-IsButBOX was uniquely competent for this diastereoselective arylation (74% yield, 14:1 d.r.), whereas (*S,S*)-Ph-BOX delivered the C3a-aryl product in just 16% yield, favouring the undesired diastereomer (1:8 d.r. (discussed in Supplementary Section III). Selective reduction of the resulting trimer yielded **5** in a 74% yield. Subsequent chlorination (91% yield) followed by implementation of the pseudo-*meso* capping strategy outlined above yielded the corresponding C3a–C3a′ vicinal quaternary centres of oxindole **10** in a 46% yield (3:1 d.r.). Global reduction of **10** with Red-Al followed by Birch reduction (62% yield over two steps) completed the first synthesis of quadrigemine H in eight steps from monomeric subunits **1** and **2** (LLS of ten steps). The synthetic material matched both isolation reports and an authentic sample from *Psychotria muscosa*[7]. Treatment of the synthetically prepared natural product with iodomethane produced the crystalline tetramethiodide salt, whose structure was unambiguously assigned by X-ray crystallographic analysis.

Isopsychotridines: [4+1] pentamers

Our controlled oligomerization protocol was further applied to the synthesis of the [4+1] polypyrroloindoline oligomers isopsychotridine B and C. Exposure of pyrroloindoline–indole **5** to the copper-catalysed arylation–cyclization conditions yielded the corresponding C3a–C7′-coupled tetramer intermediate in a 53% yield of the major diastereomer (>15:1 d.r.). A Hantzsch ester reduction provided the tetrameric tryptamide **6** in a 76% yield, and installation of the pseudo-*meso* cap provided the corresponding pentameric oxindole **11** in a 72% yield over two steps with a 1.5:1 d.r. Global reduction of each diastereomer of **11** followed by a Birch reduction (80 and 77% yield over two steps to isopsychotridine B and C, respectively) completed the syntheses of two pseudo-*meso* capped isopsychotridines, the largest polypyrroloindolines synthesized to date, in just ten steps from the monomeric tryptamide **1** and iodonium **2** (LLS of 12 steps). Based on a comparison of these two synthetic [4+1] diastereomers to the limited available literature data for isopsychotridine A to E, we propose that these two isomers are consistent with isopsychotridine B and C (Supplementary Section VII gives a comparison of synthetic ^{13}C data to literature isolation reports). The predictable stereochemical control of the chiral copper catalyst, coupled with the known pseudo-*meso* diastereoselective preference of the capping protocol, constitutes strong evidence for our assignment of the relative and absolute stereochemistries of the pair of isopsychotridines synthesized herein (Supplementary Section V).

Unnatural quadrigemines: [3+1] tetramers

Finally, we demonstrated that this strategy is amenable to the synthesis of putatively unnatural stereoisomers of quadrigemine H (Fig. 4).

Using the (*R*,*R*)-enantiomer of catalyst **7** (the antipode of the catalyst used in the natural series), the tryptamide dimer **4** underwent copper-catalysed C3a–C7′ coupling to form the diastereomeric trimer in a 82% yield, with a >20:1 d.r. Selective reduction yielded tryptamide **12** in a 79% yield. Subsequent chlorination and capping successfully produced oxindole **13** in a 52% yield (over two steps) as a 1.2:1 mixture of the pseudo-*meso* diastereomers. Reduction and debenzylation of each diastereomer of **13** (67 and 42% yields over two steps, respectively) provided the unnatural quadrigemine stereoisomer **14** and its complementary pseudo-*meso* diastereomer **14′**.

Conclusion

In brief, we developed and implemented a controlled oligomerization strategy for the total synthesis of six oligomeric polypyrroloindoline natural products. The key C3a–C7′ stereochemical monomer linkages found throughout this class of natural products was controlled via the asymmetric copper-catalysed arylation/cyclization of nucleophilic tryptamides. The syntheses of hodgkinsine and hodgkinsine B were executed in six steps from monomers **1** and **2**, respectively, and the first syntheses of the higher-order polypyrroloindoline alkaloids quadrigemine H and isopsychotridine B and C were accomplished in eight and ten linear steps from monomeric subunits **1** and **2**, respectively. The iterative stepwise technology described herein also allows access to unnatural polypyrroloindoline scaffolds, such as **14**. In principle, this strategy could be used to access a large range of known or previously unknown oligomers of the pyrroloindoline alkaloid family.

Data availability. Crystallographic data are deposited at the Cambridge Crystallographic Date Centre (CCDC) as CCDC 1550111 (**2**) and CCDC 1550112 (quadrigemine H tetramethiodide salt). All of the data supporting the findings of this study are available within the article and its Supplementary Information, or from the corresponding author on reasonable request.

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Author contributions

C.R.J., J.J.B., J.M.L. and R.J.C. performed and analysed the experiments. C.R.J., J.J.B., J.M.L., R.J.C. and D.W.C.M. designed the experiments. C.R.J., J.J.B., J.M.L. and D.W.C.M. prepared this manuscript.

Additional information

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Competing financial interests

The authors declare no competing financial interests.