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A synthetic approach to kingianin A based on biosynthetic speculation†

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A synthetic approach towards the structurally complex dimer, kingianin A is reported. The strategy involved a cascade of complexity generating reactions, inspired through biosynthetic speculation. A concise protecting group free synthesis of the proposed monomeric precursor pre-kingianin A has been achieved using a tandem Stille cross-coupling reaction and electrocyclisation process. However, preliminary studies of the key dimerisation reaction have been conducted, which indicate that the process is not spontaneous, raising questions as to the origin of this complex natural product.

The isolation of natural products not only provides a foundation for new biologically active compounds and drug candidates,[1,2] but also a feedstock of complex and unique molecular architectures to challenge and inspire synthetic chemists.[3,4]

Recently, Litaudon *et al.*, reported the isolation and characterisation of the novel natural product kingianin A (**1**), from the bark of the Malaysian *Endiandra kingiana* Gamble.[5] The structure of **1** was verified by X-ray crystallography and comprises an unusual pseudo-symmetrical pentacyclic skeletal core with amide and benzodioxole appendages. A plausible biosynthetic proposal to **1** was put forward by Litaudon and co-workers, which involves a key *endo*-Diels–Alder (DA) dimerisation reaction of the homochiral bicyclo[4.2.0]octa-2,4-diene **2** (Scheme 1). The bicyclooctadiene **2** was assumed to arise *via* an electrocyclisation reaction cascade starting from the corresponding (*Z*,*Z*,*Z*,*Z*)-tetraene **3**.[6–8] Thus, thermal conrotatory 8π electrocyclisation in the tetraene **3** is predicted to lead to the corresponding cyclooctatriene **4**, which then undergoes a diastereoselective disrotatory 6π electrocyclisation reaction producing **2**.

This complexity-generating electrocyclisation cascade has similarities with that established in the better known endiandric acids,[9] isolated from a related genus of Endiandra.[10–13] It is significant that both the endiandric acids and kingianin A (**1**) were isolated as racemates, implying the absence of enzymatic catalysis in the latter stages of their biosynthesis, and raising questions about whether these compounds are true natural products or artefacts of isolation procedures. For example, the dimerisation of 1,3-cyclohexadiene requires very forcing and undesirable reaction conditions,[14] and we were particularly intrigued by the speculation of Litaudon *et al.*, that the DA dimerisation of **2** could be spontaneous, since we considered this unlikely for electronically unactivated reactants. This is consistent with our own[15] and others[6,8,16] synthetic experience with related bicyclo[4.2.0]octadiene natural products, which are not reported to undergo spontaneous dimerisation.

Nevertheless, the intriguing biosynthetic proposal summarised in Scheme 1 offered a potential expedient route to the novel molecular entity **1**, and we were compelled to investigate the biogenetic hypothesis experimentally. Rather than target the more synthetically demanding all *Z*-tetraene **3**, we considered the (*E*,*Z*,*Z*,*E*)-tetraene **5** to be a more convenient target with regards to a stereocontrolled synthesis. In terms of the initial 8π electrocyclisation to the cyclooctatriene **4**, both **3** and **5** would be expected to lead to the same bicyclooctadiene products. We elected to use a convergent Stille cross-coupling reaction to access **5**, given the success of this approach in related systems.[7,16] Thus, retrosynthetic disconnection of the tetraene **5** revealed the vinyl bromide **6** and the stannane **7** as key precursors (Scheme 1).

Our synthesis of **6** began from the known conjugated ester **8**, itself readily available from safrole *via* a one pot oxidative cleavage,[17] and Wittig olefination.[18] DIBAL-H mediated reduction of **8** gave the allylic alcohol **9**, which underwent smooth oxidation with Dess–Martin periodinane leading to the corresponding aldehyde **10**. Finally, elaboration of **10** to the corresponding 1,1-dibromo diene,[19] followed by selective reduction using $HSnBu_3$ and tetrakis(triphenylphosphine)-palladium (0) gave the vinyl bromide **6** in good overall yield (Scheme 2).[20] The bromide **6** was found to be stable at ambient temperature with no sign of isomerisation of the double bonds into conjugation with the aromatic ring. The *E*,*Z*-double bond geometry in **6** was elucidated by NMR spectroscopy and NOESY analyses.

The synthesis of the stannane fragment **7** for the proposed Stille coupling with **6** began from the known diene ester **11**, which itself was available in 3 steps from propargyl alcohol.[21–23]

DIBAL-H reduction of **11** then afforded the alcohol **12** in 65% yield. The stereochemistry of the diene unit in **12** was established from the magnitude of the appropriate vicinal couplings between olefinic protons in the ^{1}H NMR, and corroborated by NOESY analysis. Finally, conversion of the alcohol functionality in **12** using acetone cyanohydrin in a modified Mitsunobu protocol, gave the nitrile stannane **7** (Scheme 2).[24,25]

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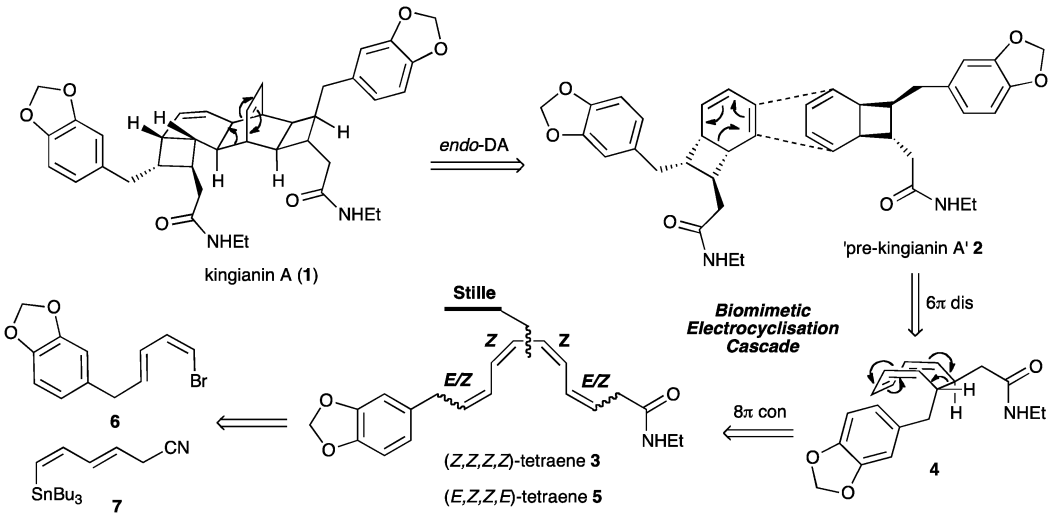
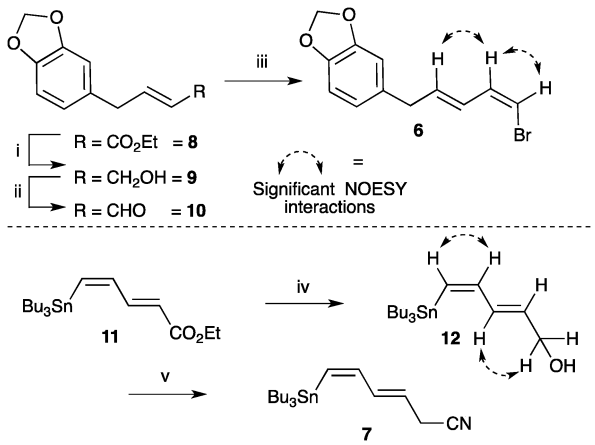


Scheme 1 Biosynthetic proposal for the formation of kingianin A (**1**) and retrosynthetic analysis of tetraene **5**.

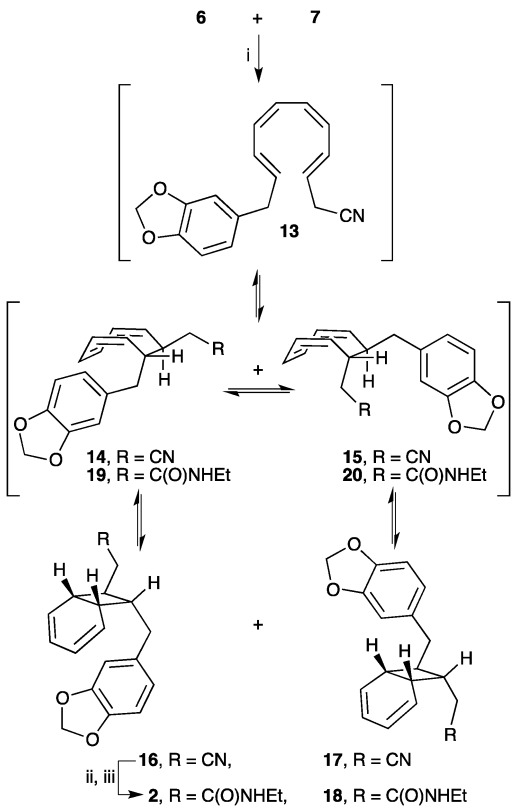


Scheme 2 Synthesis of fragments **6** & **7**. (i) DIBAL-H, DCM, −78 °C to rt, 40 min, 71%; (ii) DMP, DCM, 0 °C, 30 min, 96%; (iii) (a) CBr_4, PPh_3, Et_3N, DCM, rt, 15 min (b) $HSnBu_3$, $Pd(PPh_3)_4$, toluene, rt, 1 h, 67% (over 2 steps); (iv) DIBAL-H, DCM, −78 °C to rt, 16 h, 65%; (v) Acetone cyanohydrin, THF, 0 °C, 15 min, 55%.

With the alkenyl bromide **6** and alkenyl stannane **7** fragments in hand, the Stille cross-coupling reaction towards the tetraene **13** was first examined using $Pd_2(dba)_3$, tri-2-furylphosphine (TFP) at 100 °C.[26] To our initial surprise however, under these reaction conditions the tetraene **13** could not be isolated, and instead a mixture of diastereoisomers of the bicyclo[4.2.0]octa-2,4-diene **2**, *viz* **16** and **17** was obtained in 60% combined yield. The formation of the bicyclooctadienes **16** and **17** can be explained as arising through rapid 6π-electrocyclisation of the equilibrating cyclooctatriene conformers **14** and **15** respectively, produced from 8π electrocyclisation of the initially produced tetraene **13**. Interestingly, both **16** and **17** were stable and were not observed to undergo dimerisation.

Hydrolysis of the nitrile functionality in the mixture of diastereoisomers gave the corresponding amides,[27] which underwent successful reductive *N*-alkylation[28] to give a separable mixture of the isomeric bicyclooctadienes **2** and **18** in 62% yield. The structures of **2** and **18** were established by spectroscopic analyses including NOESY (Scheme 3).

In our hands the putative biosynthetic precursor **2** to kingianin A (**1**) was found to be stable at room temperature over several weeks, and showed no sign of dimerisation to **1**. Heating solutions of both of the bicyclooctadienes **2** and **18** up to 195 °C (See T1, SI), provided no evidence for the formation of **1**. However, under the given reaction conditions, compounds **2** and **18** underwent inter-conversion, presumably *via* retro-6π electrocyclisation to the corresponding cyclooctatriene conformers **19** and **20** respectively. Heating a solution of **18**



Scheme 3 Tandem coupling-electrocyclisation reaction sequence to **2**. (i) $Pd_2(dba)_3$, TFP, toluene, 100 °C, 10 h, 60%; (ii) KOH, EtOH, 5 h; (iii) CH_3CHO, toluene, Et_3SiH, TFA, 120 °C, 1 h, 62% (over 2 steps).

over several hours established an equilibrium mixture of **2** and **18** with an approximate 1 : 1 ratio. Further attempts to promote [4 + 2] Diels–Alder dimerisation of **2**/**18** using Grieco's conditions[29] *i.e.* 5M $LiClO_4$ solution, were also unsuccessful, with only inter-conversion between isomeric cyclooctatrienes **2** and **18** being observed.

In summary, although we have developed the first synthesis of the bicyclo[4.2.0]octadiene pre-kingianin A (**2**) (and the corresponding isomer **18**), which is believed to be the penultimate precursor to kingianin A (**1**), studies of the biomimetic dimerisation of **2** into **1** have been inconclusive. It is clear however that the process is not spontaneous, implying that **1** is not a simple artefact of isolation. We believe therefore that the process involved in the proposed dimerisation of pre-kingianin A (**2**) into **1** *in vivo* may be subtler than hitherto expected . This is consistent with the chemistry of cyclohexadienes, which do not undergo Diels–Alder dimerisation readily. Further studies to delineate the requirements of this intriguing dimerisation of **2**/**18** to kingianin A (**1**) are now in progress in our laboratory and will be reported in due course.

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