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Complete List of Authors:	Moses, John; Unversity of Nottingham, Department of Chemisty Sharma, Pallavi; University of Lincoln, Chemistry Moore, Jonathan; University of Nottingham, School of Chemistry Walsh, Darren; University of Nottingham, School of Chemistry Davies, Edward; University of Nottingham, The School of Chemistry

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Formal Synthesis of Kingianin A Based Upon a Novel Electrochemically-Induced Radical Cation Diels-Alder Reaction†

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Jonathan C. Moore,[a] E. Stephen Davies,[a] Darren W. Walsh,[a] Pallavi Sharma,[a,b] and John E. Moses*[a]

The application of electrochemical reactions in natural product synthesis has burgeoned in recent years. We herein report a formal synthesis of the complex and dimeric natural product kingianin A, which employs an electrochemically-mediated radical cation Diels-Alder cycloaddition as the key step.

The kingianin family of natural products (A-N) isolated by Leverrier *et al.*,[1,2] from the bark of the Malaysian *Endiandra kingiana* Gamble, characteristically comprise a unique, complex and stereochemically rich pentacyclic core framework (Fig S1, SI).

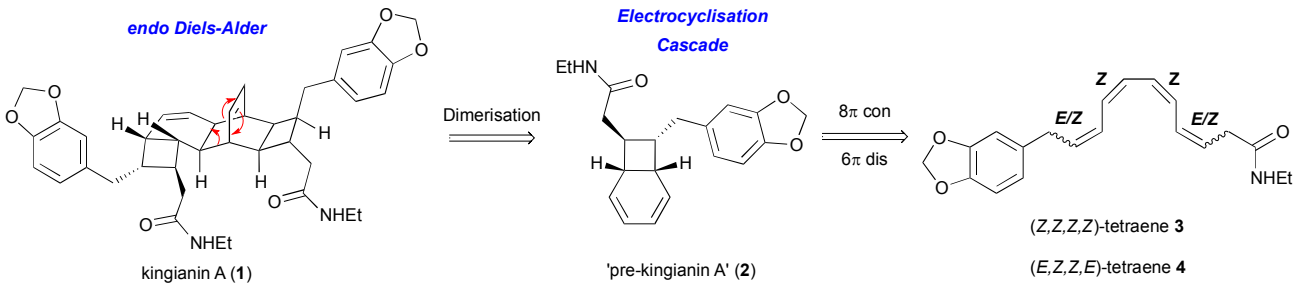
A plausible biogenesis of kingianin A (**1**), involving a key Diels-Alder dimerisation of the bicyclo[4.2.0]octadiene monomer pre-kingianin A (**2**) was proposed by the isolation group (Scheme 1).[1] Pre-kingianin A (**2**), *in vivo*, is most likely formed *via* a tandem 8π/6π thermal electrocyclisation sequence from the tetraene **3** (or **4**) (Scheme 1); a sequence closely resembling the endiandric acid electrocyclisation cascade.[3] Interestingly, like the endiandric acids, the kingianin metabolites are all isolated as racemates, thereby questioning the involvement of enzymatic-mediation in the later stages of their biosynthesis.

We recently reported the biomimetic synthesis of the monomer **2** based on the electrocyclisation strategy described above.[4] Contrary to speculation,[1] the monomer **2** was not susceptible to spontaneous dimerisation to **1**, which raised some interesting questions about the likely origins of these naturally occurring compounds.[5]

A total synthesis of kingianin A (**1**) was first reported by Parker *et al.*, in 2013.[6] Their synthetic approach centred on a novel intramolecular radical cation activated Diels-Alder (RCDA)[7] cycloaddition of a tethered bicyclo[4.2.0]octadienyl monomer.[8] Shortly thereafter Sherburn *et al.* reported total syntheses of the kingianins A (**1**), D and F (Fig S1, SI) employing, for the first time, an elegant intermolecular[8] RCDA approach of a bicyclo[4.2.0]octadienyl monomer.[9,10] Both groups employed the stable radical cation Ledwith-Weitz salt (tris(4-bromophenyl)aminium hexachloroantimonate) to initiate the electron transfer reaction.

We herein report a formal synthesis of kingianin A (**1**), whereby an electrochemically mediated RCDA cycloaddition was employed as the key synthetic step. In spite of the fact that they offer a powerful and sustainable alternative to reagent-controlled syntheses, electrochemical transformations are not widely used in organic synthesis.[11,12]

Encouraged by the report of Nigenda *et al.*, on the electrochemically initiated RCDA dimerisation of 1,3-cyclohexadiene (CHD),[13] we designed a similar approach to the synthesis of the kingianin core *via* dimerisation of a suitable bicyclo[4.2.0]octadienyl monomer (Scheme 2).



Scheme 1. A general proposal for the biosynthesis of kingianin A (**1**).

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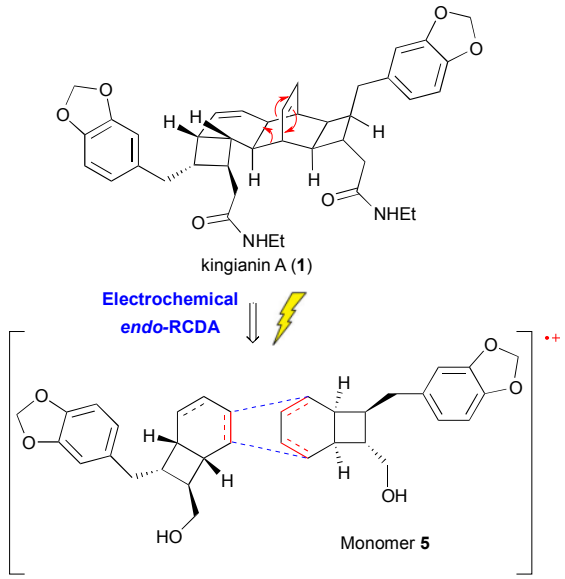
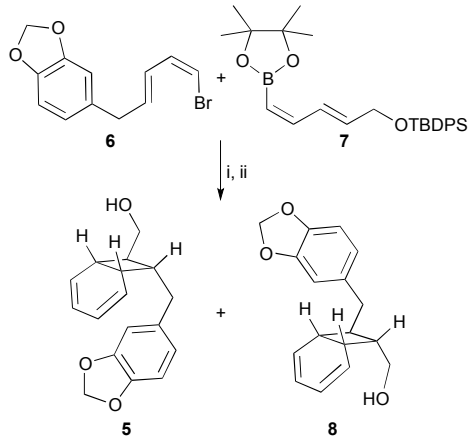


Scheme 2. Retrosynthetic analysis of kingianin A (**1**) based upon an electrochemical RCDA dimerisation of **5**.

The alcohol **5** was selected for our electrochemical studies, since it had previously been demonstrated as a suitable substrate for chemically induced RCDA (*cf.* pre-kingianin A (**2**)).[8, 10]
Scheme 3 outlines our synthetic approach towards the monomer



Scheme 3. Synthesis of the bicyclo[4.2.0]octadienyl monomers **5** and **8**. *Reagents and Conditions:* (i) $Pd(PPh_3)_4$, TlOEt, THF:H_2O (3:1), 90 °C, 2 h. (ii) TBAF•$3H_2O$, THF, 0 °C to rt, 4 h, 83% (over 2 steps) (**5**:**8**::3:2).

5, which employed a thallium ethoxide-mediated Suzuki cross coupling[14] between the dienyl bromide **6** and the boronic ester **7**,[6] followed by deprotection of the TBDPS group with tetrabutylammonium fluoride trihydrate.

The tetraene intermediate resulting from the coupling was not observed. It instead underwent *in situ* transformation to yield an inseparable mixture of the bicyclo[4.2.0]octadienyl monomers **5** and **8** (3:2) in 83% yield over two steps (Scheme 3).[6]

We next performed our preliminary electrochemical investigations with **5** and **8**. The voltammetric studies of 1,3-cyclohexadiene in CH_2Cl_2/$^nBu_4NBF_4$ reported by Nigenda *et al.* demonstrated that a potential of 1.1 V (E1, vs. Ag/Ag^+) was required to instigate oxidation.[13,15] Thus, cyclic voltammetry of the bicyclo[4.2.0]octadienyl monomers **5** and **8** was carried out at a platinum disk electrode using an Autolab PGSTAT20 potentiostat. The cyclic voltammogram in Figure 1 clearly shows an oxidation wave with an onset potential of 1.1 V, without evidence of a reduction in the return sweep. The oxidation current reached a diffusion-limited peak current of 5 μA at a peak potential of 1.45 V.

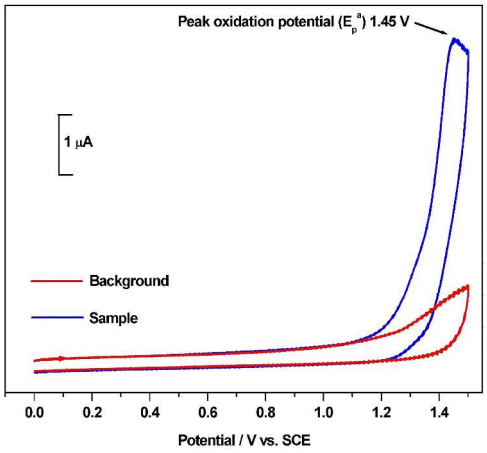
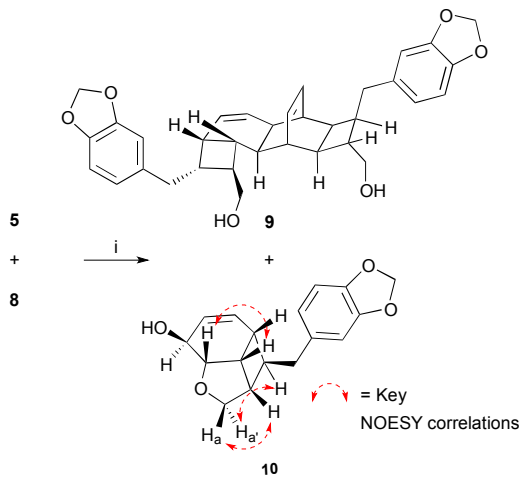


Figure 1. Cyclic voltammogram recorded on a glassy carbon disc electrode (3 mm) for **5** and **8** (3:2) (0.04 mmol) (blue line) and the background (red line) in CH_2Cl_2 containing $^nBu_4NBF_4$ (0.4M) at ambient temperature and at a scan rate of 0.1 Vs^{-1}.

In some instances, the absence of a reduction peak during the return sweep of a cyclic voltammogram can be attributed to chemical reactions that follow electron transfer into the electrode. Examples include the so-called EC and ECC reactions, where E represents the electron-transfer reaction and C a following chemical reaction.[16] If on the timescale of the reaction an EC process had occurred, and the product of the chemical reaction was itself electrochemically inactive, no return peak would be observed.
The work by Nigenda et al. indicated that RCDA dimerisation had occurred after electron transfer from 1,3-cyclohexadiene into the electrode.[13] We were therefore optimistic that a corresponding process could have occurred in our system and could be used in a synthesis of the kingianins.
To test this hypothesis, a solution of a 3:2 mixture of the bicyclo[4.2.0]octadienyl monomers **5** and **8** in 0.4M $^nBu_4NBF_4$ in CH_2Cl_2, was electrolysed at 1.5 V using a reticulated vitreous

carbon electrode. The polycyclic compounds **9** (13%) and **10** (16%) were isolated as the major reaction products and fully characterised using extensive spectroscopic techniques including NOESY 2D NMR (Scheme 4).

The occurrence of compound **9**[6,8] was significant and through convergence with the work of Parker,[6] constitutes a formal synthesis of kingianin A (**1**). The formation of compound **10** can be explained by anodic oxidation followed by intramolecular etherification from the diastereoisomer **8**, whereby the close proximity of the *endo*-alcohol functionality and the cyclohexadiene core is sufficient to allow nucleophilic attack on the activated diene.



Scheme 4. The electrochemical oxidation of **5** and **8**. *Reagents and Conditions:* (i) Anodic oxidation, 1.5 V, $^{n}Bu_4NBF_4$, CH_2Cl_2, **9** (13%) and **10** (16%).

The same is not possible for the diastereoisomer **5** in which case the Diels-Alder dimerisation to yield **9** is free to occur. The practical outcome of this phenomenon is that when the diastereoisomers **5** and **8** were subjected to anodic oxidation, no cross-dimerisation was observed.

Conclusions

A formal synthesis of kingianin A has been accomplished *via* a novel, electrochemically-initiated radical cation Diels-Alder cycloaddition. The electrolysis was performed on a mixture of diastereoisomers without the complication of forming mixed dimeric species. This was possible due to an intramolecular cyclisation of the diastereoisomer **8**. The current study further demonstrates the potential for electrochemical transformations in organic chemistry and provides the first example of an electrochemically induced Diels-Alder dimerisation applied to a natural product synthesis.

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Notes and references

[a] School of Chemistry, University of Nottingham, University Park, Nottingham, NG7 1RD, UK.
E-mail: john.moses@nottingham.ac.uk;
Fax: ++44 (0)115 951 3564; Tel: ++44 (0)115 951 3533
[b] School of Chemistry, University of Lincoln, LN6 7TS, UK.

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