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Total Synthesis of Kingianins A, D, and F**‡

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[‡] In Memory of Rodney W. Rickards.

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Abstract

**A synthesis fit for a king:** The total synthesis of (±)-kingianins A, D, and F has been achieved in ten steps. Key features include the gram-scale synthesis and partial reduction of a conjugated tetrayne to a (Z,Z,Z,Z)-tetraene, the domino 8π–6π electrocyclic ring closure of a (Z,Z,Z,Z)-tetraene, and the radical-cation-catalyzed formal Diels–Alder dimerization of functionalized bicyclo[4.2.0]octadiene precursors.

Main text

The kingianin natural products are a unique group of complex racemic bicyclo[4.2.0]octadiene dimers, isolated from the bark of *Endiandra kingiana* (Lauraceae) by Litaudon and co-workers.[1] The first reported kingianin, (±)-kingianin A (1),[1a] formulates as a dimer of bicyclo[4.2.0]octadiene 2, and the Litaudon group proposed a biosynthesis involving spontaneous (non-enzyme-mediated) Diels–Alder dimerization (Scheme 1).[1] Several reports, however, describe the need for temperatures in excess of 150 °C for Diels–Alder dimerization of 1,3-cyclohexadiene.[2] The notion that a structural feature within compound 2 may lower the barrier to thermal Diels–Alder dimerization was investigated by Moses and co-workers in 2011.[3] An elegant synthesis of monomer 2 was achieved by the Moses group, but all attempts to induce thermal dimerization failed.[3] Inspired by the pioneering work of Bauld and co-workers,[4] we hypothesized that a radical cation Diels–Alder dimerization could explain the formation of the kingianins in nature.

![Scheme 1](image)

**Scheme 1.** Diels–Alder biosynthetic pathway to (±)-kingianin A (1), as proposed by Litaudon et al.[1]

The bicyclo[4.2.0]octadiene framework present within Litaudon’s proposed biosynthetic monomer 2 is a skeletal feature found in several natural products.[5–9] The endiandric acids, which were isolated in racemic form in the early 1980s by Black and colleagues, were the first reported examples.[5] Black proposed that the bicyclo[4.2.0]octadiene structure was formed through a spontaneous 8π–6π domino electrocyclization of either an (*E,Z,Z,E*)-tetraene or a (*Z,Z,Z,Z*)-tetraene (Scheme 2).[5b–f] Beautiful biomimetic syntheses of various
bicyclo[4.2.0]octadiene natural products by Nicolaou,\textsuperscript{[10]} Trauner,\textsuperscript{[11]} Baldwin,\textsuperscript{[12]} Parker,\textsuperscript{[13]} and Moses\textsuperscript{[14]} have successfully utilized the proposed \((E,Z,Z,E)\)-tetraene precursors. Evidently, the difficulty associated with preparing conjugated all-(Z)-polyenes has precluded their use in synthesis. In fact, \((2Z,4Z,6Z,8Z)\)-decatetraene is both the highest all-(Z)-conjugated polyene and the only \((Z,Z,Z,Z)\)-tetraene synthesized thus far.\textsuperscript{[15]}

Given the unprecedented structure and puzzling biosynthetic origin of the kingianin natural products,\textsuperscript{[11]} we decided to embark upon efforts towards their synthesis. The wealth of synthetic work in the literature utilizing \((E,Z,Z,E)\)-tetraene precursors to access bicyclo[4.2.0]octadiene structures\textsuperscript{[3,10–14]} convinced us that we should take this opportunity to investigate the alternative biosynthetic precursor, namely the \((Z,Z,Z,Z)\)-tetraene (Scheme 2).\textsuperscript{[5b–f]} Although initially drawn to the \(sp^2–sp^2\) cross-coupling strategy utilized by Negishi for the synthesis of \((Z,Z,Z)\)-triene,\textsuperscript{[16]} we elected instead to investigate the feasibility of a four-fold stereoselective partial reduction of a conjugated tetrayne. We anticipated that if this unprecedented\textsuperscript{[17]} and highly challenging\textsuperscript{[18]} synthetic transformation were realized then a remarkably short synthesis of the kingianins could be achieved.

\[\textbf{Scheme 2.} \text{The } 8\pi–6\pi \text{ biosynthesis of bicyclo[4.2.0]octadiene structures, as proposed by Black et al.}^{[5b–f]}\]

The application of previously reported methods\textsuperscript{[19]} for the synthesis of unsymmetrical tetryynes was met with great difficulties. The instability of the requisite intermediates and problems associated with scaling up these approaches led us to develop a new scalable synthesis of unsymmetrical tetryynes. It is well known that steric bulk can stabilize polyyne structures.\textsuperscript{[20]} We took advantage of this fact by targeting TBS-protected (TBS=\textit{tert}-butyldimethylsilyl) alcohol tetryne 3,\textsuperscript{[21]} using Mori–Hiyama conditions for TMS-alkyne (TMS=trimethylsilyl) dimerization,\textsuperscript{[22]} thereby avoiding unstable halogenated and terminal polyyynes. The two requisite diynes 4 and 5 were successfully prepared in three and two steps, respectively, on a multi-gram scale (Scheme 3). Thus, an Alami modified\textsuperscript{[23]} Cadiot–Chodkiewicz coupling of known bromobutynol 6\textsuperscript{[24]} with ethynyltrimethylsilane afforded TMS-diyne 7, which was converted into TBS-ether 4 under standard conditions.\textsuperscript{[25]} Meanwhile, known benzyl bromide 8\textsuperscript{[26]} was employed in a Negishi reaction\textsuperscript{[27]} with organozinc reagent 9,\textsuperscript{[28]} which was derived from 1,4-bis(trimethylsilyl)buta-1,3-diyne.\textsuperscript{[20]} Following extensive optimization, tetryne 3 was isolated in 40 % yield on a gram scale.\textsuperscript{[20]} This is the first reported crossed Mori–Hiyama coupling reaction\textsuperscript{[22]} and the first gram-scale synthesis of an unsymmetrical tetryne.\textsuperscript{[19]}
With significant quantities of tetrayne 3 now available, investigation into the daunting four-fold reduction could begin.\textsuperscript{[17, 18]} Following extensive experimentation, it was found that Rieke zinc in ethanol afforded (Z,Z,Z,Z)-tetraene 10 in a completely chemoselective and highly diastereoselective manner (Scheme 4).\textsuperscript{[17, 31]} A solution of tetraene 10 in toluene was immediately heated to 100 °C, which triggered the domino 8π–6π electrocyclization sequence.\textsuperscript{[32]} Following deprotection, the two diastereomeric alcohols 11 and 12 were isolated in a combined yield of 21 % from tetrayne 3 (Scheme 4).

\textbf{Scheme 3.} Gram-scale synthesis of unsymmetrical tetrayne 3. dppf=1,1′-bis(diphenylphosphino)ferrocene, NBS=N-bromosuccinimide, TBS=tert-butyldimethylsilyl, TMS=trimethylsilyl.

We were delighted to find that both alcohols 11 and 12 underwent fast radical cation Diels–Alder dimerizations using catalytic quantities of the Ledwith–Weitz aminium salt, (p-BrC₆H₄),N-SbCl₆ (13; Scheme 4).\textsuperscript{[33]} Amide 2, the proposed biosynthetic precursor to (±)-kingianin A (1),\textsuperscript{[1a]} failed to dimerize under these reaction conditions (Scheme 4).
Scheme 4. Completion of the total synthesis of (±)-kingianins A, D, and F. EDC=1-ethyl-3-(3-dimethylaminopropyl) carbodiimide, HOBT=hydroxybenzotriazole, NMO=N-methylmorpholine-N-oxide, TBAF=tetrabutylammonium fluoride, TPAP=tetrapropylammonium perruthenate.

The synthesis of (±)-kingianins A (1) and D (14) was eventually optimized to a sequence involving oxidation of alcohol 11 using the tetrapropylammonium perruthenate/ N-methylmorpholine-N-oxide (TPAP/NMO) conditions of Stark et al.,\(^\text{[34]}\) with the product directly subjected to radical cation Diels–Alder dimerization using the Ledwith–Weitz salt (13; 5 mol %).\(^\text{[4, 33]}\) The resultant mixture of diastereomeric diacids was directly converted into the corresponding diamides. Column chromatography afforded a mixture of three dimeric diamides in 17 % yield over the three steps from alcohol 11. Reverse-phase preparative HPLC allowed the isolation of analytically pure samples of (±)-kingianin A (1), (±)-kingianin D (14) and a third, as yet undetermined, structure.\(^\text{[1]}\) This radical cation Diels–Alder dimerization is a remarkably selective reaction, with only three of the potential thirty-two isomeric products isolated. Both (±)-kingianin A (1), a homochiral dimer, and (±)-kingianin D (14), a heterochiral dimer, are the result of endo-selective formal Diels–Alder reactions occurring at the convex faces of both diene and dienophile. Previous studies have shown that the radical cation Diels–Alder dimerization of 1,3-cyclohexadiene is endo selective,\(^\text{[4]}\) however, a full explanation of the site and orientational regioselectivity observed in the present study will require further investigation. The natural product (±)-kingianin F (15) was similarly obtained by dimerization of the other bicyclo[4.2.0]octadiene diastereomer 12, followed by double oxidation and diamide formation.\(^\text{[35]}\)
In summary, our highly divergent biomimetic strategy has resulted in the total synthesis of (±)-kingianins A (1), D (14) and F (15), in a longest linear sequence of ten steps. The noteworthy synthetic aspects of our successful approach include the gram-scale preparation of an unsymmetrical tetryne, the unprecedented reduction of a conjugated tetryne to a (Z,Z,Z,Z)-tetraene, and radical cation Diels–Alder dimerization of functionalized bicyclo[4.2.0]octadienes. From these studies, we conclude that the kingianins are not formed through spontaneous Diels–Alder dimerization. Instead, we propose that nature uses a SET-mediated cycloaddition analogous to the approach described herein. Our results, in conjunction with previous biomimetic syntheses, demonstrate that (E,Z,Z,E)-tetraenes, and not their all-(Z) congeners, are the likely biosynthetic precursors to bicyclo[4.2.0]octadiene natural products.
Notes and references


[3] P. Sharma, D. J. Ritson, J. Burnley, J. E. Moses, *Chem. Commun.* 2011, **47**, 10605. No spontaneous dimerization of compounds2, **11**, **12** (or the corresponding oxidation products) was observed during the present study (see the Supporting Information for details), nor has any spontaneous dimerization of any bicyclo[4.2.0]octadiene ever been reported.


[21] The free-alcohol congener of 3 was significantly less stable.


[30] The more readily accessible TMS-diyne 5 was used in excess to increase the yield of the cross-coupled product. A 1:1 ratio of TMS-diynes 4 and 5 typically afforded unsymmetrical tetrayne 3 in yields of 25–30%.


[32] We believe that the 100 °C temperature required for the electrocyclization of 10 discounts the all-(Z) isomer as a likely biosynthetic precursor. The previously reported 8π–6π electrocyclization of (2Z,4Z,6Z,8Z)-decatetraene required 14 h at 65 °C to go to completion, see: R. Huisgen, A. Dahmen, H. Huber, *J. Am. Chem. Soc.* 1967, 89, 7130.


[35] The three-step sequence to produce (±)-kingianin F proved higher yielding when the radical cation Diels–Alder dimerization was carried out first, followed by double oxidation, and diamide formation.

[36] To the best of our knowledge, this constitutes only the second reported example of a biomimetic radical cation Diels–Alder reaction; see: S. Lin, M. A. Ischay, C. G. Fry, T. P. Yoon, *J. Am. Chem. Soc.* 2011, **133**, 19350.

[37] While this manuscript was under review, Parker and Lim published an article detailing the total synthesis of (±)-kingianin A, by a tether-mediated intramolecular radical cation Diels–Alder strategy; see: H. N. Lim, K. A. Parker, *Org. Lett.* 2013, **15**, 398.

[38] Although, it should be noted that enzyme participation in the kingianin biosynthesis cannot be ruled out.