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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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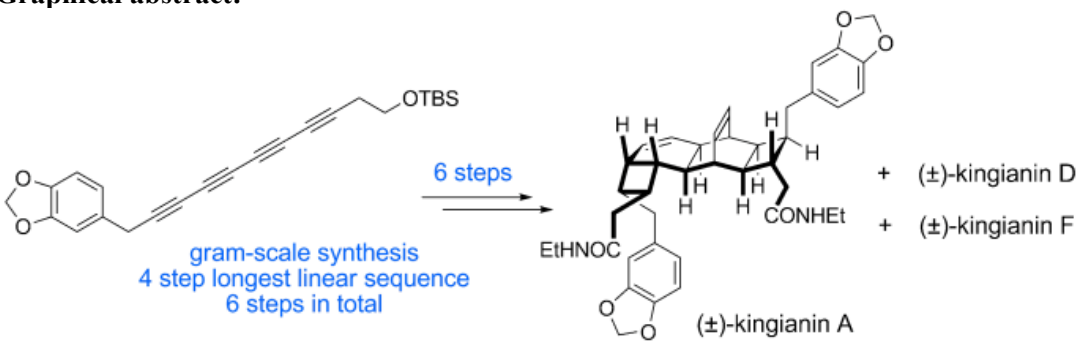
Graphical abstract:



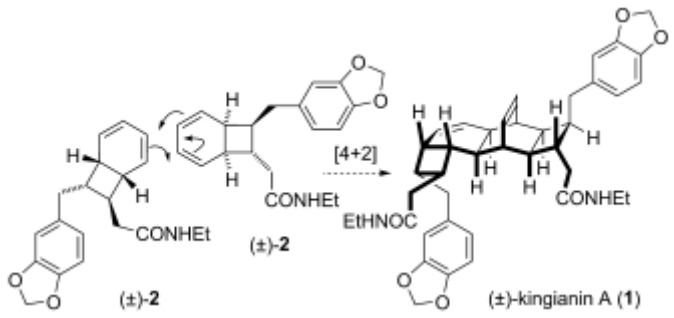
Keywords:
biomimetic synthesis; domino reactions; natural products; polyynes; radical cations

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. 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

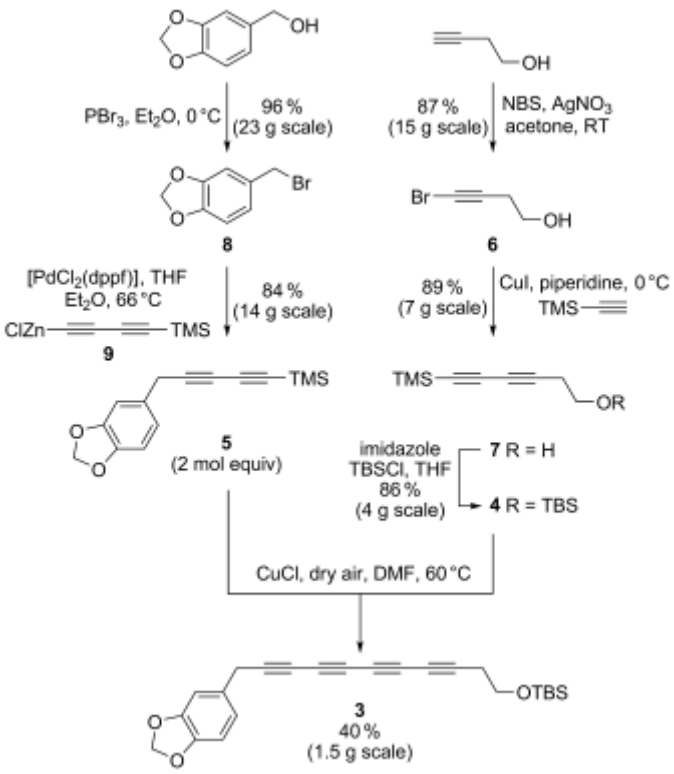
bicyclo[4.2.0]octadiene natural products by Nicolaou,[10] Trauner,[11] Baldwin,[12] Parker,[13] and Moses[14] have successfully utilized the proposed (*E*,*Z*,*Z*,*E*)-tetraene precursors. Evidently, the difficulty associated with preparing conjugated all-(*Z*)-polyenes has precluded their use in synthesis. In fact, (2*Z*,4*Z*,6*Z*,8*Z*)-decatetraene is both the highest all-(*Z*)-conjugated polyene and the only (*Z*,*Z*,*Z*,*Z*)-tetraene synthesized thus far.[15]

Given the unprecedented structure and puzzling biosynthetic origin of the kingianin natural products,[1] 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[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).[5b–f] Although initially drawn to the sp^2–sp^2 cross-coupling strategy utilized by Negishi for the synthesis of (*Z*,*Z*,*Z*)-trienes,[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[17] and highly challenging[18] synthetic transformation were realized then a remarkably short synthesis of the kingianins could be achieved.

Scheme 2. The 8π–6π biosynthesis of bicyclo[4.2.0]octadiene structures, as proposed by Black et al.[5b–f]

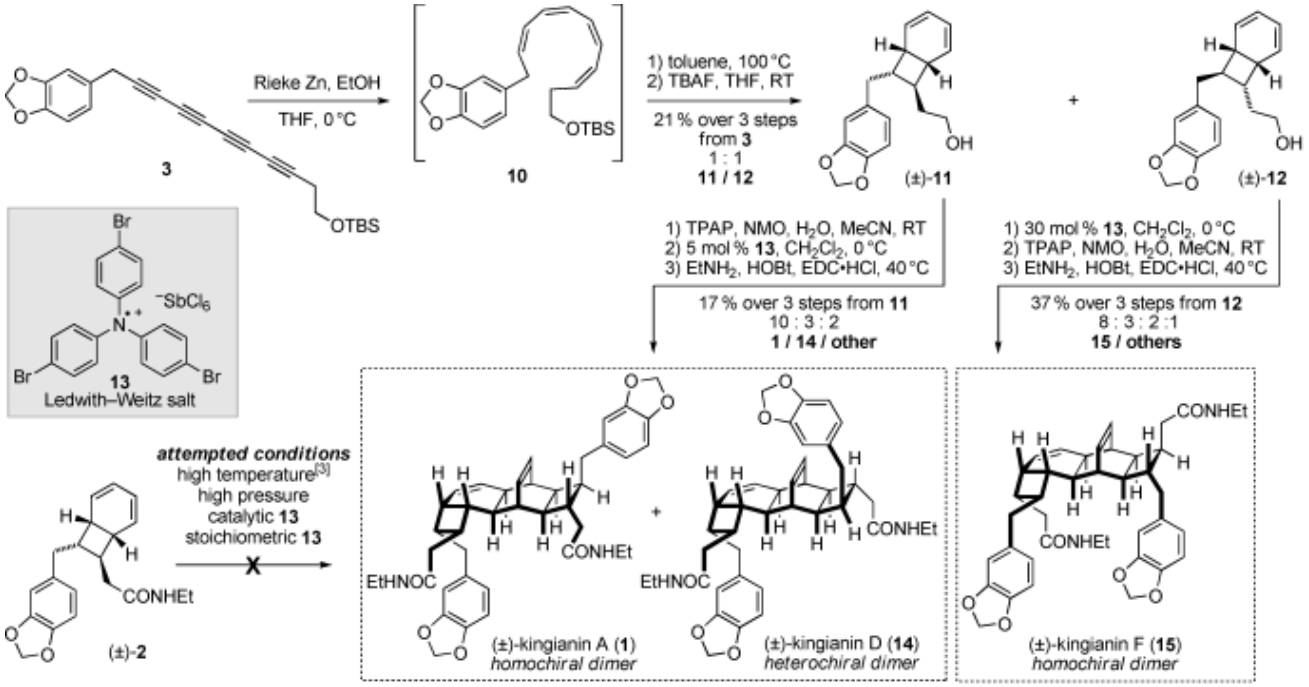
The application of previously reported methods[19] for the synthesis of unsymmetrical tetraynes was met with great difficulties. The instability of the requisite intermediates and problems associated with scaling up these approaches led us to develop a new scalable synthesis of unsymmerical tetraynes. It is well known that steric bulk can stabilize polyyne structures.[20] We took advantage of this fact by targeting TBS-protected (TBS=*tert*-butyldimethylsilyl) alcohol tetrayne **3**,[21] using Mori–Hiyama conditions for TMS-alkyne (TMS=trimethylsilyl) dimerization,[22] thereby avoiding unstable halogenated and terminal polyynes. 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[23] Cadiot–Chodkiewicz coupling of known bromobutynol **6**[24] with ethynyltrimethylsilane afforded TMS-diyne **7**, which was converted into TBS-ether **4**under standard conditions.[25] Meanwhile, known benzyl bromide **8**[26] was employed in a Negishi reaction[27] with organozinc reagent **9**,[28]which was derived from 1,4-bis(trimethylsilyl)buta-1,3-diyne.[29] Following extensive optimization, tetrayne **3** was isolated in 40 % yield on a gram scale.[30] This is the first reported crossed Mori–Hiyama coupling reaction[22] and the first gram-scale synthesis of an unsymmetrical tetrayne.[19]

With significant quantities of tetrayne **3** now available, investigation into the daunting four-fold reduction could begin.[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).[17, 31] A solution of tetraene **10** in toluene was immediately heated to 100 °C, which triggered the domino 8π–6π electrocyclization sequence.[32] Following deprotection, the two diastereomeric alcohols **11** and **12** were isolated in a combined yield of 21 % from tetrayne **3** (Scheme 4).



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-$BrC_6H_4)_3N{\cdot}SbCl_6$ (**13**; Scheme 4).[33] Amide **2**, the proposed biosynthetic precursor to (±)-kingianin A (**1**),[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.,[34] with the product directly subjected to radical cation Diels–Alder dimerization using the Ledwith–Weitz salt (**13**; 5 mol %).[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.[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,[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.[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 tetrayne, the unprecedented reduction of a conjugated tetrayne 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.[36, 37] Our results, in conjunction with previous biomimetic syntheses,[3, 10–14] demonstrate that (*E*,*Z*,*Z*,*E*)-tetraenes, and not their all-(*Z*) congeners,[32] are the likely biosynthetic precursors to bicyclo[4.2.0]octadiene natural products.[38]

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