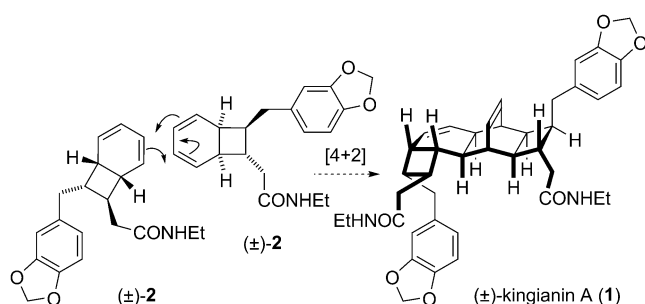


Total Synthesis of Kingianins A, D, and F**

Samuel L. Drew, Andrew L. Lawrence,* and Michael S. Sherburn*

In Memory of Rodney W. Rickards

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

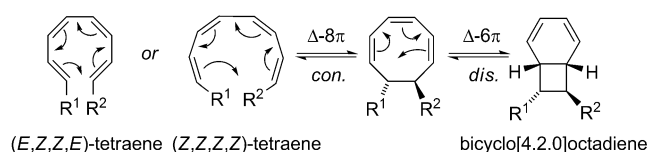


Scheme 1. Diels–Alder biosynthetic pathway to (±)-kingianin A (**1**), as proposed by Litaudon et al.^[1]

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.

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]



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

Black proposed that the bicyclo[4.2.0]octadiene structure was formed through a spontaneous 8 π –6 π domino electrocycloization 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 sp²–sp² 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 stereo-selective 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.

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 unsymmetrical tet-

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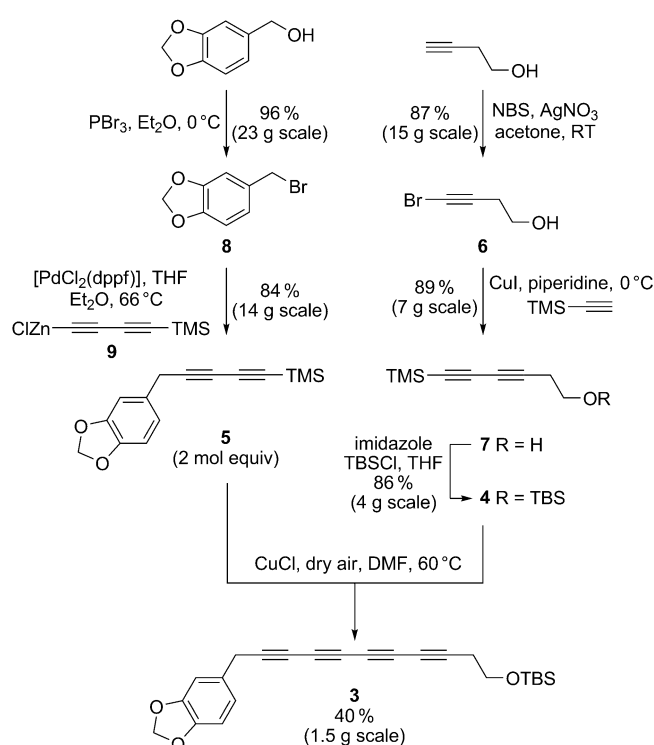
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raynes. It is well known that steric bulk can stabilize polyne structures.^[20] We took advantage of this fact by targeting TBS-protected (TBS = *tert*-butyldimethylsilyl) alcohol tetrayne **3**,^[21] using Mori–Hiyama conditions for TMS-alkyne (TMS = 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]

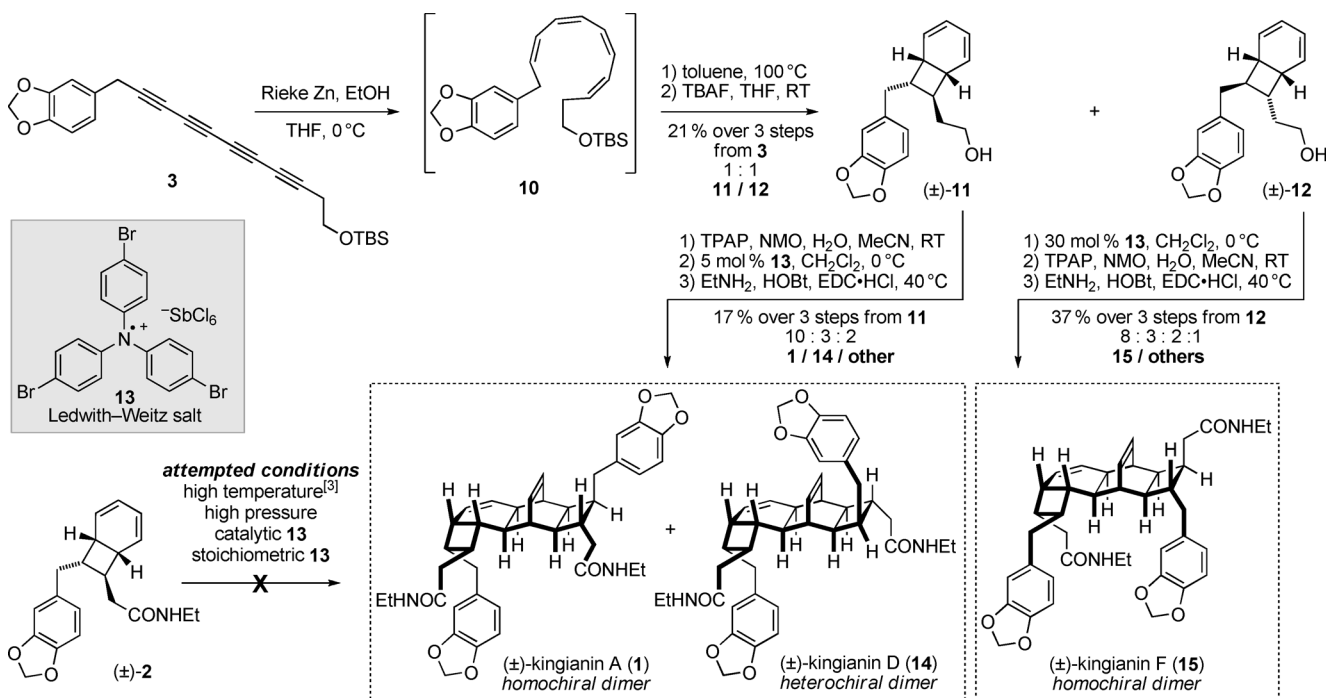
With significant quantities of tetrayne **3** now available, investigation into the daunting four-fold reduction could begin.^[17,18] Following extensive experimentation, it was found that Rieke zinc in ethanol afforded (*Z,Z,Z,Z*)-tetraene **10** in a completely chemoselective and highly diastereoselective manner (Scheme 4).^[17,31] A solution of tetraene **10** in toluene was immediately heated to 100 °C, which triggered the domino 8 π –6 π 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).

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



Scheme 3. Gram-scale synthesis of unsymmetrical tetrayne **3**. dppf = 1,1'-bis(diphenylphosphino)ferrocene, NBS = *N*-bromosuccinimide, TBS = *tert*-butyldimethylsilyl, TMS = trimethylsilyl.

salt, (*p*-BrC₆H₄)₃N⁺·SbCl₆[−] (**13**; Scheme 4).^[33] Amide **2**, the proposed biosynthetic precursor to (±)-kingianin A (**1**),^[1a]



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.

failed to dimerize under these reaction conditions (Scheme 4).

The synthesis of ($\pm$)-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 ($\pm$)-kingianin A (**1**), ($\pm$)-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 ($\pm$)-kingianin A (**1**), a homochiral dimer, and ($\pm$)-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 ($\pm$)-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 ($\pm$)-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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