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Intermolecular Radical Cation Diels–Alder (RCDA) Reaction of Bicyclooctadienes: Biomimetic Formal Total Synthesis of Kingianin A and Total Syntheses of Kingianins D, F, H, and J

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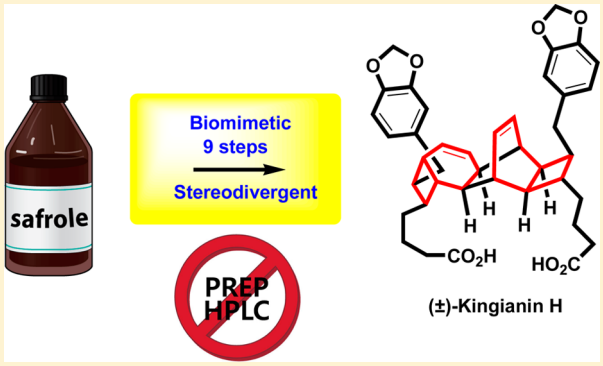
Supporting Information

ABSTRACT: Three endo bicyclooctadienol dimers corresponding to kingianins A and H, D, and F and J were obtained by the intermolecular radical cation Diels–Alder (RCDA) reaction. Each isomer was cleanly isolated without the aid of preparative HPLC. Kingianins D, F, H, and J were prepared by way of these intermediates from commercially available materials in 10, 13, 9, and 17 steps, respectively. Kingianin A has already been prepared from one of these compounds. Completion of the synthesis of kingianin H relied on Manchand's one-step, three-carbon homologation.



INTRODUCTION

The kingianins (e.g., kingianins **1A**, **1D**, **1F**, **1H**, and **1J**, Figure 1) are newly discovered racemic natural products from *Endiandra kingiana* Gamble; they are reported to be inhibitors of the antiapoptotic protein Bcl-xL.[1] Like the endiandric acids which are isolated from another *Endiandra* species,[2] the kingianins are thought to be the products of nonenzymatic cascades that proceed through bicyclooctadienes.[1]

While the last step in the biosynthesis of the endiandric acids is believed to be an intramolecular Diels–Alder reaction, that in the biosynthesis of the kingianins appears to be an *intermolecular* Diels–Alder dimerization. For example, kingianin A is the dimer of two enantiomerically identical molecules of prekingianin A (**2**), and kingianin D is the dimer of two enantiomeric molecules of prekingianin A (**2**) as suggested in Figure 1. On the other hand, kingianin F is the dimer of two enantiomerically identical molecules of the exo isomer of prekinginan A (**3**). Kingianin H corresponds to kingianin A in stereochemistry and kingianin J corresponds to kingianin F in stereochemistry.

A biomimetic approach to the kingianins is appealing but it has not been without its disappointments. Attempts by Moses et al. to prepare kingianin A by a thermal Diels–Alder dimerization of the presumed biogenetic precursor **2** were frustrated by the stability of the monomeric bicyclooctadiene structure with respect to the desired conversion.[3] We recognized that radical cation catalysis overcomes the reticence of cyclohexadienes to undergo the Diels–Alder dimerization reaction.[4] Furthermore, we postulated that the biosynthesis of the kingianins proceeds through a radical cation-mediated reaction, perhaps initiated by a photochemical event.[5] Pursuing this idea, we examined the bicyclooctadiene dimerization under radical cation initiating conditions. Our substrate was designed to control regiochemistry and stereochemistry in the cycloaddition of two bicyclooctadienes by linking them with a tether. This approach, applied to a mixture of the dimeric meso and racemic precursors, yielded two pentacyclic isomers. One, derived from the C-2 symmetric linked dimer (the endo Diels–Alder product), was converted to kingianin A by way of diol **6**. The structure of the second Diels–Alder product (exo product, from the meso linked dimer) did not correspond to that of any of the naturally occurring kingianins.

The intramolecular experiment established the radical cation Diels–Alder (RCDA) strategy as an entry to the kingianins and it provided an element of regiocontrol to this key reaction. However, the *intermolecular* RCDA has the potential to provide a stereodivergent synthesis,[6] affording up to four[7] pentacyclic scaffolds, three of which correspond to naturally occurring kingianins (A and its homologue H, D, and F and its homologue J).

As we have noted previously, a regio- and stereodivergent scheme can be considered practical only if the components of the final products or the components of an intermediate are readily separable.[5] Despite the description of sequential silica gel and HPLC chromatographies required for the separation of the natural products,[1a] we were encouraged to pursue the divergent intermolecular approach by the observation that diol **6** and its exo stereoisomer **7** (Figure 2) had slightly different R_f values on TLC. We postulated that regio- and stereoisomeric

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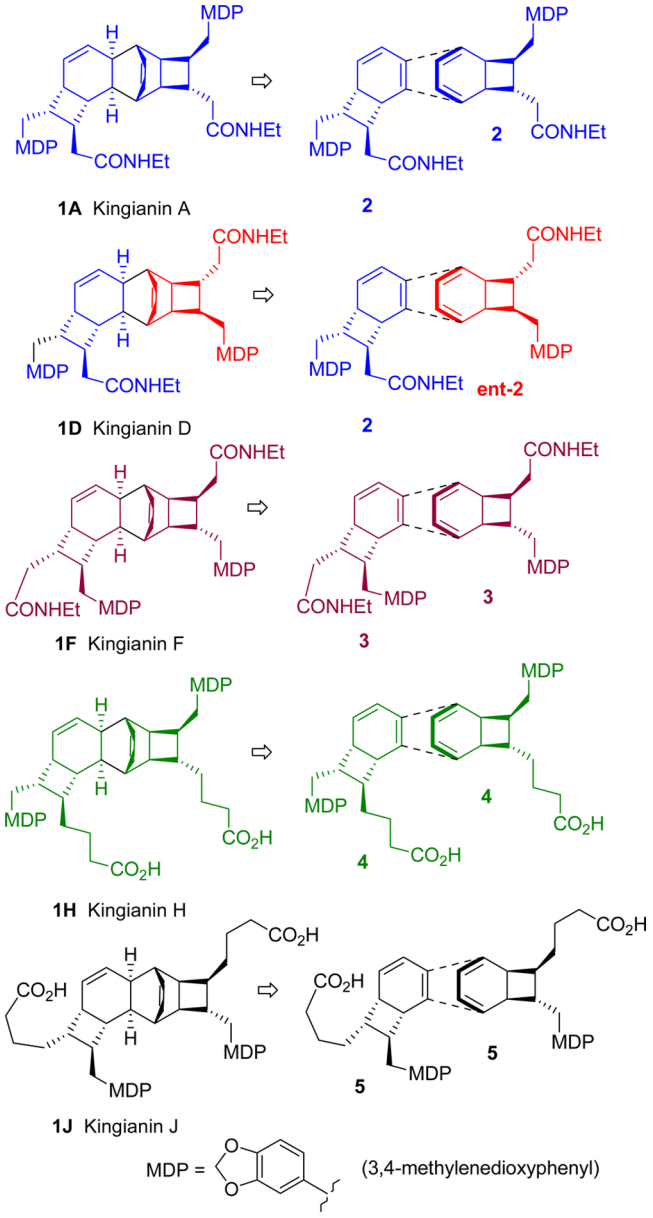


Figure 1. Kingianins A, D, F, H, and J and their corresponding monomers.

diols in the kingianin series might have usefully different chromatographic behaviors.

RESULTS AND DISCUSSION

Indeed, when endo cyclooctadienol **8** was subjected to RCDA conditions (5 mol % of the aminium salt catalyst for 1 h), a mixture of four separable compounds was obtained (Scheme 1). Known endo diol **6**[5] (37%), known exo diol **7**[5] (10%), a new endo dimeric diol **9** (18%, corresponding in structure to kingianin D), and alcohol **10** (7%, a non-Diels–Alder product) were easily separated by preparative TLC. Isolation of diol **6** comprises a formal total synthesis of kingianin A.

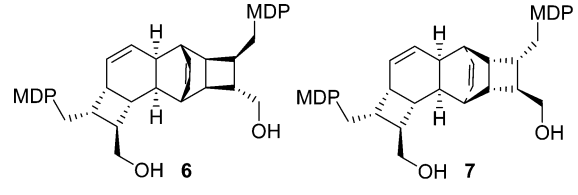
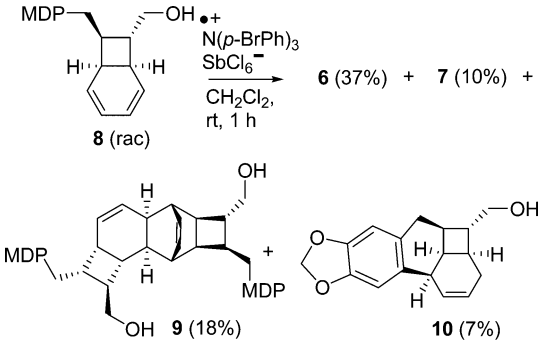


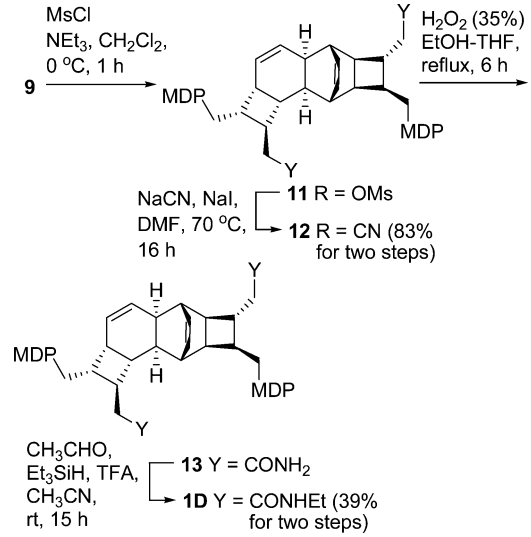
Figure 2. Endo diol **6** and exo diol **7**, obtained from a tether-mediated RCDA reaction of the bicyclooctadiene **8**.

Scheme 1. Intermolecular RCDA Dimerization of Racemic Endo Bicyclooctadiene 8



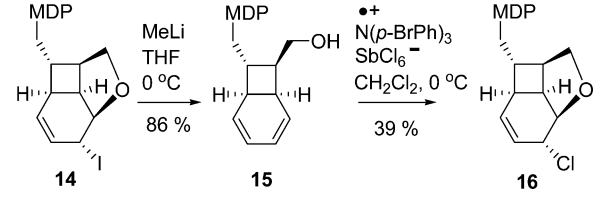
Diol **9** was converted to kingianin D in 32% yield (Scheme 2) by the four-step sequence employed previously in the synthesis of kingianin A.[5]

Scheme 2. Synthesis of Kingianin D



Having completed the syntheses of kingianins A and D from endo monomer **8**, we undertook the synthesis of kingianin F from the exo monomer **15**. This compound was prepared from the known ether **14**[5] by reductive elimination initiated by methyllithium (Scheme 3). However, it proved to be an unsatisfactory substrate in the RCDA reaction. When exo

Scheme 3. Preparation of Exo Substrate 15 and Its Radical Cation Reaction



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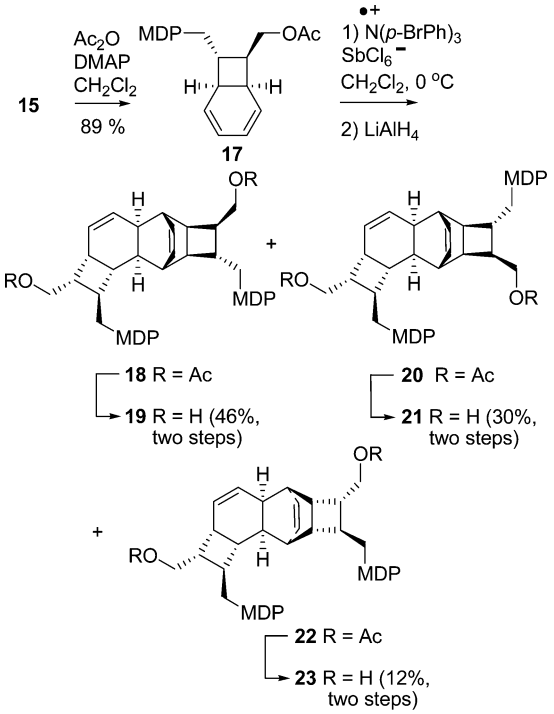
monomer **15** was subjected to the RCDA conditions, chloroether **16** was the only product isolated.

Therefore, the RCDA reaction was applied to acetate **17** (from alcohol **15**, Scheme 4). This reaction gave a mixture of

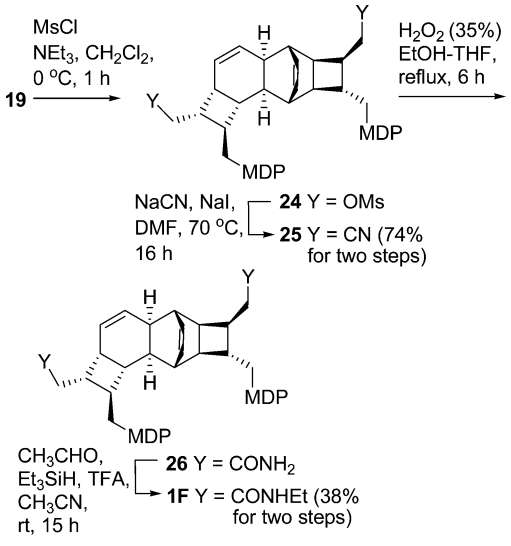
Scheme 4. Preparation of Exo Substrate 17 and Its RCDA Reaction



two major products, **18** and **20**, both derived from endo transition states, and a minor product **22**, derived from an exo transition state. These diacetates appeared to be inseparable; however, removal of the acetyl groups gave a mixture of three diols, **19**, **21**, and **23**, that were readily separated by preparative TLC.

Kingianin F was then prepared from diol **19** (Scheme 5) by the four-step homologation sequence used above (Scheme 2).

Scheme 5. Synthesis of Kingianin F



The structure of the second endo dimer, diol **21**, was established by X-ray crystallography (Figure 3, see the Supporting Information for the crystallographic data for diol **21**).

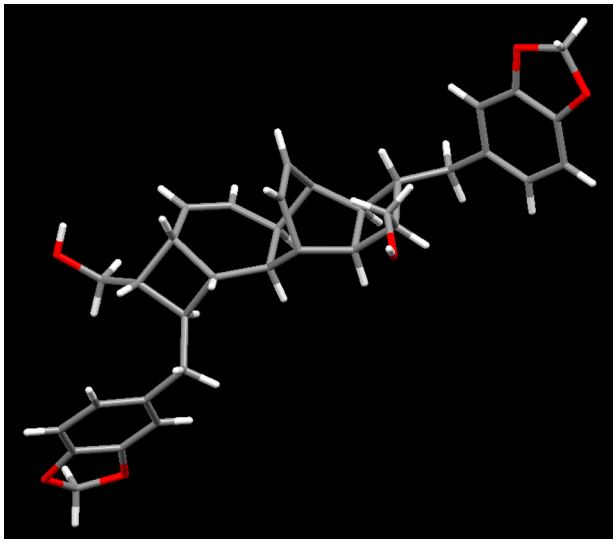


Figure 3. X-ray crystal structure of diol **21**.

In addition, the structure of exo diol **23** was firmly identified as the mixed exo RCDA product by a combination of COSY, NOESY, HMQC, and HMBC NMR experiments (see Tables 9−13 in the Supporting Information). The key correlations in the COSY and NOESY are depicted in Figure 4.

On the basis of the chemical shifts of the two more upfield olefinic signals (5.81 and 5.63, in the same range as H3 and H4 in the kingianins), we assigned the dienophilic western substructure of the pentacyclic core as being identical to that in diols **19** and **21**. This assumption was well supported by the crosspeaks of H3 (5.81) and H9 (3.28 and 3.46) in the NOESY. Also, the crosspeaks of H3/H2, H2/H1, H1/H10, H10/H7, H10/H8, H8/H6, and H6/H5 in the NOESY and the crosspeaks of H3/H4, H4/H5, H5/H6, H2/H1, H2/H7, H1/H8, H1/H9, H7/H8, and H8/H10 in the COSY confirmed that the connectivity and relative stereochemistry of the fused [4.2.0]bicyclooctene ring system in the western sector were the same as those in diols **19** and **21**.

With the H9 and H2 protons identified, we could assign the 2H signal at 3.32/3.50 ppm to the H9′ protons and 1H signal at 2.60 ppm to the H2′ proton. The crosspeaks of H9′/H1′, H1′/H2′, H2′/H7′, H7′/H10′, H10′/H8′, H3′/H4′, H5′/H6′, H5′/H8′ and H8′/H9′ in the NOESY and the crosspeaks of H1′/H2′, H2′/H7′, H7′/H8′, H8′/H10′, H4′/H5′, H4′/H3′, and H5′/H6′ in the COSY confirmed the connectivity and relative stereochemistry of the fused [4.2.0]-bicyclooctene ring system in the eastern sector.

Next we needed to determine the stereochemistry of the connection of the eastern and western substructures. The key crosspeaks of H4/H2′ in the NOESY showed that the stereochemical relationship of the eastern and western sectors corresponds to that of an exo Diels−Alder product (COSY and NOE pictures).

The exo Diels−Alder structure was further supported by HMQC and HMBC assignments. Each carbon in the core pentacyclic structure was assigned to the attached protons by the crosspeaks in the HMQC. Indeed, the examination of the

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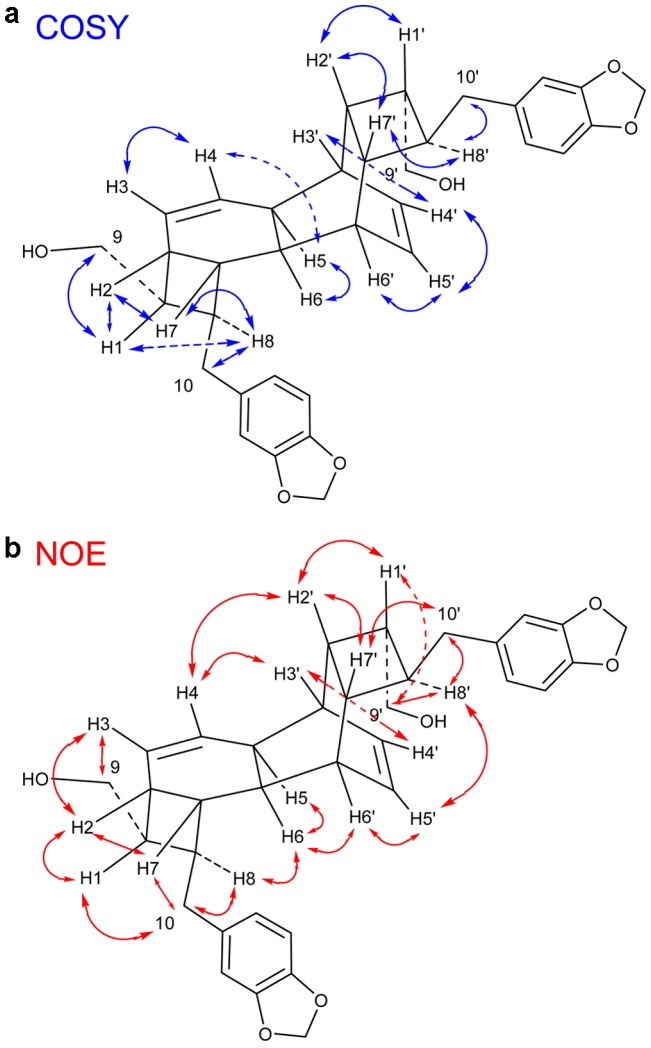


Figure 4. (a) COSY correlations in diol **23**. (b) NOE correlations in diol **23**.

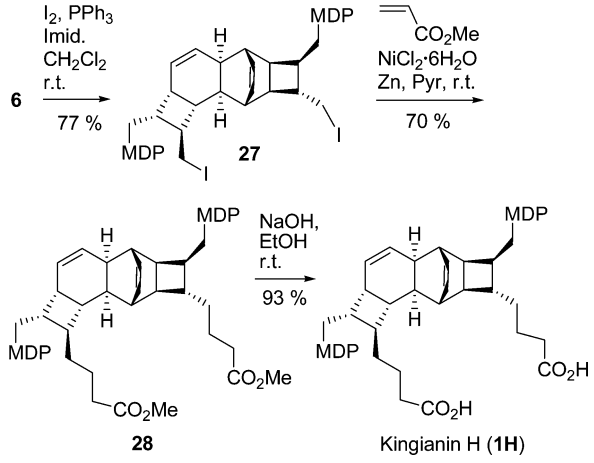
connectivity by HMBC analysis (the crosspeaks of selected carbon atoms and the corresponding protons) are consistent with the suggested structure in the COSY and NOE pictures.

Of the pseudosymmetric kingianins (i.e., those that are constructed from two identical or enantiomeric monomers, A–F, H, and J), kingianin H is reported to be the most active in the Bcl-xL inhibition assay.[1a] We considered therefore the synthesis of kingianin H from diol **6** which was in hand.

Conversion of diol **6** (previously converted to kingianin A) to kingianin H requires lengthening of the side chains. Short sequences that effect 3-carbon homologations are relatively rare. An attractive plan was the transition-metal-catalyzed conversion of primary iodides to 3-carbon homologated esters by the Ni(0)-catalyzed "formal conjugate addition" described by Manchand et al.[8,9] Accordingly, we prepared diiodide **27** and applied the chain-lengthening procedure, obtaining diester **28** in 70% yield. Hydrolysis then provided kingianin H (**1H**, Scheme 6).

Finally we turned to the synthesis of kingianin J (**1J**), the last of the naturally occurring pseudosymmetric dimers (Figure 1). Conversion of alcohol **19** to the corresponding diiodide was straightforward. However, when we applied the Manchand protocol or Cheng's Co(I)-mediated procedure[9a] to this substrate, we obtained a mixture of products; the NMR

Scheme 6. Synthesis of Kingianin H



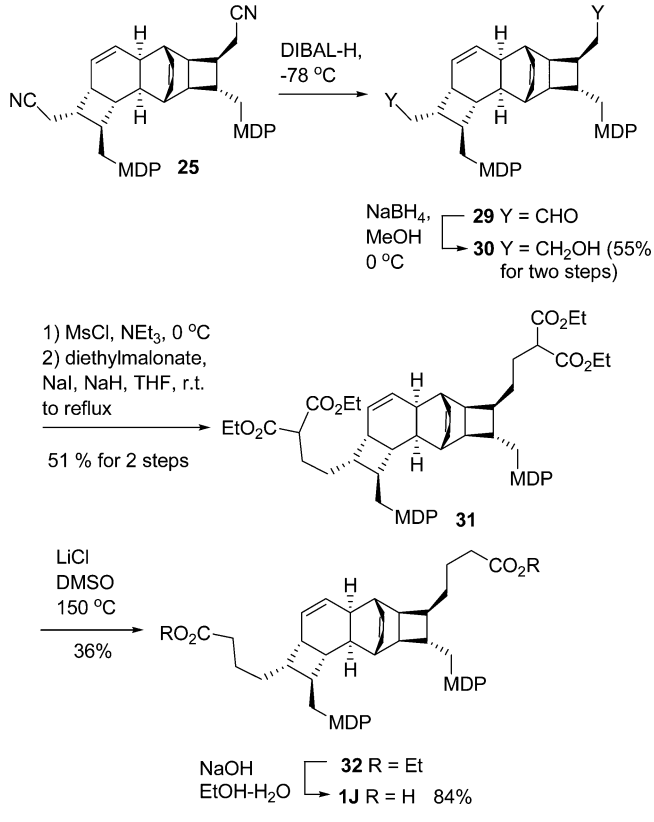
spectrum of neither crude product exhibited the olefinic protons of the western substructure.

These results led us to use a conventional homologation. DIBAL reduction of dinitrile **25** with hydrolysis of the diimine intermediate gave the dialdehyde **29**. Then reduction, mesylation, malonic ester homologation, chloride-induced decarboxylation, and hydrolysis gave the diacid natural product kingianin J (Scheme 7).

CONCLUSION

In summary, the intermolecular RCDA procedure, applied to the individual prekingianin structures **8** and **17**, gave key intermediates for kingianin synthesis. As expected,[10] the intermolecular RCDA reaction has a preference for an endo

Scheme 7. Synthesis of Kingianin J



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transition state in the RCDA reaction but this is not overwhelming. In both cases, the addition of the (+)-enantiomer to the (−)-enantiomer gives an exo Diels−Alder adduct as a minor product. Like the intramolecular case examined previously, both intermolecular RCDA reactions (Schemes 1 and 4) demonstrated additional regio- and stereoselective effects consistent with the structures of the isolated natural products. Thus, the C-5,6 double bond (proximal to the exo substituent on the cyclobutane ring) acts as the dienophile. It is attacked from the less hindered face by the diene component which reacts from its less hindered face.

Three of the major RCDA products were elaborated to four additional members of the kingianin family. The total syntheses of kingianins D, F, H, and J entailed 10, 13, 9, and 17 steps, respectively, from commercially available materials. None of the schemes required preparative HPLC separation of intermediates or products. These short syntheses appear to be scalable.

EXPERIMENTAL SECTION

General Methods. All air- and moisture-sensitive reactions were performed under argon in oven-dried or flame-dried glassware. Unless stated otherwise, commercially available reagents were used as supplied or distilled by short-path distillation. HPLC-grade hexane, EtOAc, CH_2Cl_2, and CH_3OH were used in chromatography. Tetrahydrofuran (THF) was distilled from sodium−benzophenone ketyl under argon. Dichloromethane was distilled from calcium hydride under nitrogen gas. All experiments were monitored by thin-layer chromatography (TLC) performed on Whatman precoated AL SIL G/UV 250 μm layer aluminum-supported flexible plates. Spots were visualized by exposure to ultraviolet (UV) light (254 nm) or by staining with 10% solution of phosphomolybdenic acid (PMA) in ethanol or $KMnO_4$ aq solution and then heating. Flash chromatography was carried out with Sorbent Technologies silica gel (porosity 60 Å, 230−400 mesh, surface area 500−600 m^2/g, bulk density 0.4 g/mL, pH range 6.5−7.5).

Infrared spectra were recorded with a Fourier transform (FT-IR) instrument. Samples were scanned as neat liquids or dissolved in CH_2Cl_2 on sodium chloride (NaCl) salt plates. Frequencies are reported in reciprocal centimeters (cm^{-1}). Nuclear magnetic resonance (NMR) spectra were recorded at 400 or 500 MHz for ^1H and at 100 or 126 MHz for ^{13}C spectra. Chemical shifts for proton NMR spectra are reported in parts per million (ppm) relative to the singlet at 7.260 ppm for chloroform-*d* and to the singlets at 8.74, 7.58, 7.22 ppm for pyridine-d_5. Chemical shifts for carbon NMR spectra are reported in ppm with the center line of the triplet for chloroform-*d* set at 77.000 ppm and the triplets for pyridine-d_5 set at 150.35, 135.91, 123.87 ppm. The COSY, NOESY, HMQC, and HMBC spectra were recorded with a 500 MHz spectrometer. High-resolution mass spectra were obtained on a Q-Tof spectrometer (ESI) and a 70-VSE spectrometer (EI).

Diols 6, 7, and 9 and Alcohol 10. To a stirred solution of the endo bicyclooctadienol **8** (100 mg, 0.37 mmol) in dry CH_2Cl_2 (2 mL) was added $SbCl_6{\cdot}N(p\text{-}BrPh)_3$ (15.1 mg, 0.019 mmol) at room temperature. The resulting deep blue solution was stirred for 1 h and quenched with wet NEt_3. After concentration of the reaction mixture, the residue was subjected to preparative TLC (hexane/Et_2O/CH_2Cl_2/MeOH = 1:1:1:0.02). Diols **6** (37 mg, 37%), **7** (10 mg, 10%), **9** (18 mg, 18%), and alcohol **10** (7 mg, 7%) were isolated.

Diol **9**: R_f 0.5 (Hex/EtOAc = 1:1); ^1H NMR (400 MHz, $CDCl_3$) δ 1.68 (d, J = 8.9 Hz, 1 H), 1.81 (m, 1 H), 1.95 (m, 1 H), 2.15 (m, 1 H), 2.22−2.36 (m, 3 H), 2.41−2.69 (m, 9 H), 3.30−3.40 (m, 4 H), 5.61 (br d, J = 10.3 Hz, 1 H), 5.68 (ddd, J = 10.4, 3.7, and 1.9 Hz, 1 H), 5.90 (s, 4 H), 6.11 (t, J = 7.3 Hz, 1 H), 6.32 (t, J = 7.3 Hz, 1 H), 6.55−6.71 (m, 6 H);. ^{13}C NMR (100 MHz, $CDCl_3$) δ 33.1, 35.5, 36.2, 37.2, 38.1, 39.2, 39.6, 40.2, 40.3, 40.6, 41.2, 41.4, 44.7, 48.2, 65.0, 67.0, 100.72, 100.74, 108.2, 108.81, 108.84, 120.98, 121.02, 124.8, 132.2, 133.1, 134.4, 135.0, 135.5, 145.5, 145.6, 147.57, 147.62.; IR (neat) ν_{max} 1039, 1246, 1441, 1448, 1502, 2915, 3373; HRMS[ES+] calcd for $C_{34}H_{36}O_6Na$ $[M + Na]^+$ 563.2410, found 563.2417.

Alcohol **10**: R_f 0.7 (Hex/EtOAc = 1:1); ^1H NMR (500 MHz, $CDCl_3$) δ 1.76 (m, 1 H), 1.93 (ddd, J = 16.7, 6.6, and 1.7 Hz, 1 H), 2.13 (m, 1 H), 2.24 (m, 1 H), 2.43 (dd, J = 14.2 and 9.7 Hz, 1 H), 2.50 (m, 1 H), 2.61 (dd, J = 17.7 and 9.7 Hz, 1 H), 2.71 (dd, J = 14.4 and 8.0 Hz, 1 H), 3.26 (m, 1 H), 3.72 (d, J = 7.0 Hz, 2 H), 5.67 (dt, J = 9.9 and 2.5 Hz, 1 H), 5.89 (s, 2 H), 5.97 (m, 1 H), 6.60 (s, 1 H), 6.69 (s, 1 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 27.0, 31.6, 32.0, 32.6, 33.2, 37.1, 49.4, 66.9, 100.5, 108.3, 108.5, 128.5, 131.6, 131.7, 135.1, 145.5, 145.7; IR (neat) ν_{max} 1039, 1233, 1481, 1501, 2921, 3356 cm^{-1}; HRMS[EI+] calcd for $C_{17}H_{18}O_3$ $[M]^+$ 270.1256, found 270.1249.

Dinitrile 12. *Step 1.* To a stirred solution of the diol **9** (18.0 mg, 33.3 μmol) in CH_2Cl_2 (1 mL) were added triethylamine (27.9 μL, 200 μmol) and methanesulfonyl chloride (7.70 μL, 99.8 μmol) at 0 °C under Ar. After 30 min, the reaction mixture was diluted with diethyl ether (20 mL), and the resulting mixture was washed with water, 5% HCl, and satd $NaHCO_3$ solution. The organic solution was then dried over $MgSO_4$ and concentrated. The crude product was directly used for the next step.

Dimesylate **11**: R_f 0.6 (Hex/EtOAc = 1:1); ^1H NMR (500 MHz, $CDCl_3$) δ 1.70 (d, J = 9.1 Hz, 1 H), 1.97 (m, 1 H), 2.04−2.60 (m, 15 H), 2.85 (s, 3 H), 2.87 (s, 3 H), 3.79−3.94 (m, 4 H), 5.60 (br d, J = 10.3 Hz, 1 H), 5.79 (ddd, J = 10.3, 3.8, and 1.9 Hz, 1 H), 5.9012 (s, 2 H), 5.9023 (s, 2 H), 6.11 (t, J = 7.3 Hz, 1 H), 6.34 (t, J = 7.3 Hz, 1 H), 6.53−6.70 (m, 6 H).

Step 2. To a stirred solution of the dimesylate **11** in DMF (1 mL) were added sodium iodide (2.5 mg, 17 μmol) and sodium cyanide (13.0 mg, 270 μmol) at rt. The solution was heated to 70 °C and stirred for 12 h. Then it was allowed to cool, diluted with ethyl acetate (20 mL), and washed with water (10 mL × 3). The organic layer was washed with brine, dried over $MgSO_4$, and concentrated. The residue was purified by column chromatography (Hex/EtOAc = 4:1) to afford dinitrile **12** (15.4 mg, 83% for two steps, colorless liquid).

Dinitrile **12**: R_f value 0.25 (Hex/EtOAc = 5:1); ^1H NMR (500 MHz, $CDCl_3$) δ 1.76 (d, J = 9.0 Hz, 1 H), 1.84 (m, 1 H), 1.95−2.07 (m, 5 H), 2.12−2.21 (m, 2 H), 2.31−2.39 (m, 3 H), 2.44 (dd, J = 14.0 and 8.5 Hz, 1 H), 2.50−2.69 (m, 7 H), 5.61 (br d, J = 10.3 Hz, 1 H), 5.79 (ddd, J = 10.3, 3.9, and 2.0 Hz, 1 H), 5.91 (s, 4 H), 6.12 (t, J = 7.3 Hz, 1 H), 6.36 (t, J = 7.3 Hz, 1 H), 6.52−6.71 (m, 6 H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 20.7, 22.8, 33.6, 34.9, 35.5, 36.7, 38.0, 38.9, 39.6, 40.3, 40.90, 40.96, 41.04, 41.5, 42.4, 43.6, 100.78, 100.81, 108.3, 108.6, 108.7, 118.5, 119.0, 120.95, 120.99, 124.3, 132.1, 133.3, 133.8, 134.2, 134.4, 145.7, 145.8, 147.6, 147.7; IR (neat) ν_{max} 1246, 1442, 1488, 1502, 2245, 2917 cm^{-1}; HRMS[ES+] calcd for $C_{36}H_{35}N_2O_4$ $[M + H]^+$ 559.2597, found 559.2609.

Kingianin D (1D). *Step 1.* To a stirred solution of dinitrile **12** (13.0 mg, 23.2 μmol) in EtOH−THF (2.5 mL/0.5 mL) was added aq NaOH solution (0.05 mL, 7 M) and then, dropwise, H_2O_2 solution (0.6 mL, 35% in water) at 0 °C. The mixture was warmed to room temperature, stirred for 30 min, and stirred at reflux for an additional 4 h. The reaction mixture was cooled, diluted with brine, and extracted with CH_2Cl_2 (15 mL × 5). The combined organic solution was washed with brine, dried over Na_2SO_4, filtered, and concentrated. The residue was used for the next step.

Step 2. The residue from step 1 was placed in a 3 mL vial and flushed with Ar for 10 min. To the stirred clear solution of the crude product in CH_3CN (1.5 mL) were added acetaldehyde (7.7 μL, 139 μmol), triethylsilane (22.2 μL, 139 μmol), and trifluoroacetic acid (9.8 μL, 128 μmol) in that order. Then, the vial was capped and sealed with parafilm. After being stirred for 15 h, the reaction mixture was diluted with CH_2Cl_2 (30 mL), washed with satd $NaHCO_3$ solution and brine, dried over Na_2SO_4, and concentrated. The residue was subjected to preparative TLC (hexane/EtOAc = 1:2) to afford kingianin D (5.9 mg, 39%: white solid; mp = 86−91 °C, lit.[1a] mp not reported); R_f 0.2 (hexane/EtOAc = 1:2); for ^1H NMR (500 MHz, $CDCl_3$) and ^{13}C NMR (126 MHz, $CDCl_3$), see Tables 1 and 2 in the Supporting Information; IR (neat) ν_{max} 1040, 1246, 1442, 1488, 1503, 1555, 1639, 2924, 3287 cm^{-1}.

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Exo Alcohol 15. To a stirred solution of iodo ether **14** (92.0 mg, 0.232 mmol) in THF (5 mL) was added MeLi (1.6 M in THF, 0.24 mL, 1.2 mmol) at 0 °C under Ar. After 10 min, the reaction was quenched with satd NH_4Cl solution, and the resulting mixture was extracted with diethyl ether (10 mL × 3). The combined organic solution was washed with satd $Na_2S_2O_3$ solution and brine, dried over $MgSO_4$, and concentrated. The residue was subjected to column chromatography (Hex/EtOAc = 5:1) to afford the exo alcohol **15** (66 mg, 86%) as a colorless oil; R_f value 0.3 (Hex/EtOAc = 4:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.55−2.75 (m, 5 H), 3.23 (m, 1 H), 3.57 (dd, J = 10.8 and 5.7 Hz, 1 H), 3.71 (dd, J = 10.8 and 8.4 Hz, 1 H), 5.44 (dd, J = 9.6 and 5.4 Hz, 1 H), 5.59 (dd, J = 9.8 and 3.8 Hz, 1 H), 5.62 (dd, J = 9.7 and 5.4 Hz, 1 H), 5.85 (ddd, J = 9.8, 5.5, and 1.6 Hz, 1 H), 5.92 (s, 2 H), 6.61 (dd, J = 7.9 and 1.6 Hz, 1H), 6.65 (d, J = 1.6 Hz, 1 H), 6.72 (d, J = 7.9 Hz, 1 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 32.5, 36.1, 41.6, 50.4, 51.7, 63.3, 100.8, 108.2, 109.1, 121.4, 121.5, 124.4, 125.3, 127.2, 134.3, 145.8, 147.6.; IR (neat) ν_{max} 1040, 1246, 1442, 1488, 1502, 2916, 3356 cm^{-1}; HRMS[ES+] calcd for $C_{17}H_{18}O_3$ $[M + Na]^+$ 293.1154, found 293.1150.

Chloro Ether 16. To a stirred solution of alcohol **15** (7.0 mg, 25.9 μmol) in CH_2Cl_2 (1.0 mL) was added $SbCl_6{\cdot}N(p\text{-BrPh})_3$ (1.1 mg, 1.3 μmol) at room temperature. After 1 min, the reaction mixture became yellow in color. To ensure complete conversion, more catalyst (29.6 mg, 36.3 μmol) was added in portions until a blue color was maintained. The deep blue solution was stirred for 1 h and quenched with wet NEt_3. After concentration of the reaction mixture, the residue was subjected to column chromatography (Hex/EtOAc = 20:1−10:1) to afford chloro ether **16** (3.1 mg, 39%, colorless oil): R_f 0.8 (Hex/EtOAc = 5:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.91 (m, 1 H), 2.54 (m, 1 H), 2.62 (dt, J = 6.4 and 3.8 Hz, 1 H), 2.74 (d, J = 6.6 Hz, 2 H), 3.10 (m, 1 H), 3.53 (dd, J = 7.4 and 3.7 Hz, 1 H), 3.68 (d, J = 7.4 Hz, 1 H), 4.09 (dd, J = 4.8 and 1.7 Hz, 1 H), 4.62 (dd, J = 4.6 and 1.8 Hz, 1H), 5.62 (dd, J = 8.0 and 3.4 Hz, 1 H), 5.82 (m, 1 H), 5.92 (s, 2 H), 6.60 (dd, J = 6.3 and 1.2 Hz, 1H), 6.63 (d, J = 1.2 Hz, 1 H), 6.72 (d, J = 6.3 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 31.7, 32.9, 41.4, 41.8, 47.5, 50.3, 73.1, 78.9, 100.8, 108.2, 108.9, 121.4, 122.3, 131.9, 133.4, 145.9, 147.6.; IR (neat) ν_{max} 1248, 1440, 1489, 1504, 2920 cm^{-1}; HRMS[EI +] calcd for $C_{17}H_{17}O_3Cl$ $[M]^+$ 304.0866, found 304.0869.

Acetate 17. To a stirred solution of exo alcohol **15** (114 mg, 0.422 mmol) and DMAP (10.3 mg, 0.0843 mmol) in CH_2Cl_2 (2 mL) was added acetic anhydride (59.7 μL, 0.632 mmol) at room temperature. After 1 h, the reaction mixture was diluted with CH_2Cl_2 (10 mL), washed with satd $NaHCO_3$ solution and brine, dried over $MgSO_4$, and concentrated. The residue was subjected to column chromatography (Hex/EtOAc = 5:1) to afford the acetate **17** (117 mg, 89%) as a colorless oil: R_f 0.6 (Hex/EtOAc = 5:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.00 (s, 3 H), 2.56−2.80 (m, 5 H), 3.23 (m, 1 H), 4.04 (dd, J = 11.0 and 6.4 Hz, 1 H), 4.13 (dd, J = 11.0 and 9.1 Hz, 1 H), 5.38 (dd, J = 9.6 and 5.4 Hz), 5.50 (dd, J = 9.9 and 3.7 Hz, 1 H), 5.61 (dd, J = 9.7 and 5.5 Hz, 1 H), 5.84 (ddd, J = 9.8, 5.5, and 1.6 Hz, 1 H), 5.92 (s, 2 H), 6.60 (dd, J = 7.9 and 1.6 Hz, 1H), 6.64 (d, J = 1.6 Hz), 6.71 (d, J = 7.9 Hz, 1 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 21.0, 32.7, 36.2, 41.4, 47.7, 50.4, 64.7, 100.8, 108.1, 109.1, 121.4, 121.6, 124.6, 124.8, 126.8, 134.1, 145.8, 147.5, 171.0.; IR (neat) ν_{max} 1239, 1364, 1442, 1489, 1502, 1738, 2917 cm^{-1}; HRMS[ES+] calcd for $C_{19}H_{20}O_4Na$ $[M + Na]^+$ 335.1259, found 335.1253.

Diols 19, 21, and 23. *Step 1.* To a stirred solution of acetate **17** (115 mg, 0.369 mmol) in CH_2Cl_2 (2 mL) was added $SbCl_6{\cdot}N(p\text{-BrPh})_3$ (9.0 mg, 0.011 mmol) at 0 °C. The resulting deep blue solution was stirred for 1 h and quenched with wet NEt_3. After concentration of the reaction mixture, the residue was subjected to column chromatography. The fractions containing mixtures of diacetates were combined and concentrated. The crude product mixture was directly used for the next step.

Step 2. To a stirred solution of the diacetates in dry THF (3 mL) was added lithium aluminum hydride (56 mg, 1.5 mmol) at 0 °C under Ar. After 1 h, the reaction mixture was quenched with water and with satd NaOH solution. After being stirred for 2 h, the mixture was extracted with diethyl ether (10 × 5 mL). The combined organic solution was washed with brine, dried over $MgSO_4$, and concentrated. The residue was subjected to preparative TLC (hexane/Et_2O/CH_2Cl_2/MeOH = 1:1:1:0.04) to afford the diols **19** (52.9 mg, 46%, colorless oil), **21** (34.5 mg, 30%, white solid, mp = 179−181 °C), and **23** (13.8 mg, 12%, colorless oil).

Diol **19**: R_f 0.4 (hexane/Et_2O/CH_2Cl_2/MeOH = 1:1:1:0.04); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.39 (d, J = 8.9 Hz, 1 H), 1.79 (m, 1 H), 1.87−1.94 (m, 2 H), 2.00 (m, 1 H), 2.12−2.28 (m, 4 H), 2.44−2.70 (m, 7 H), 3.24 (dd, J = 10.9 and 5.6 Hz, 1 H), 3.31 (dd, J = 10.6 and 7.3 Hz, 1 H), 3.40 (dd, J = 10.9 and 8.3 Hz, 1 H), 3.52 (dd, J = 10.6 and 8.2 Hz, 1 H), 5.56 (br d, J = 10.4 Hz, 1 H), 5.64 (br d, J = 10.4 Hz, 1 H), 5,92 (m, 4 H), 6.00 (t, J = 7.3 Hz, 1 H), 6.10 (t, J = 7.3 Hz, 1 H), 6.56−6.74 (m, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 31.4, 37.3, 38.0, 38.2, 40.8, 41.5117, 41.5410, 42.2, 42.5, 43.6, 44.1, 44.2, 44.7, 62.5, 63.0, 100.8, 108.1, 109.0, 109.2, 121.2, 121.4, 124.9, 131.9, 132.1, 134.5, 134.7, 134.8, 145.6, 145.7, 147.5, 147.5; IR (neat) ν_{max} 1040, 1243, 1441, 1488, 1502, 2919, 3354 cm^{-1}; HRMS[ES+] calcd for $C_{34}H_{37}O_6$ $[M + H]^+$ 541.2590, found 541.2578.

Diol **21**: R_f value: 0.55 (hexane/Et_2O/CH_2Cl_2/MeOH = 1:1:1:0.04); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.40 (d, J = 9.1 Hz, 1 H), 1.78 (m, 1 H), 1.86−1.93 (m, 2 H), 1.99 (m, 1 H), 2.13−2.27 (m, 3 H), 2.35−2.56 (m, 6 H), 2.63−2.68 (m, 2 H), 3.25 (dd, J = 10.9 and 5.6 Hz, 1 H), 3.34 (dd, J = 10.6 and 7.4 Hz, 1 H), 3.41 (dd, J = 10.9 and 8.3 Hz, 1 H), 3.55 (dd, J = 10.6 and 8.0 Hz, 1 H), 5.55 (br d, J = 10.3 Hz, 1 H), 5.67 (ddd, J = 10.3, 3.8, and 1.9 Hz, 1 H), 5,91 (d, J = 1.4 Hz, 2 H), 5.92 (d, J = 1.4 Hz, 2 H), 5.98 (t, J = 7.3 Hz, 1 H), 6.17 (t, J = 7.3 Hz, 1 H), 6.55−6.72 (m, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 31.7, 36.9, 38.3, 39.6, 40.0, 40.7, 41.2, 41.6, 42.16, 42.25, 42.3, 43.8, 44.4, 45.3, 62.7, 63.0, 100.7, 100.8, 108.1, 108.2, 108.9, 109.2, 121.2, 121.4, 124.5, 132.2, 132.9, 134.2, 134.4, 134.7, 145.6, 145.7, 147.5, 147.5; IR (neat) ν_{max} 1040, 1245, 1441, 1488, 1502, 2918, 3356 cm^{-1}; HRMS[ES+] calcd for $C_{34}H_{37}O_6$ $[M + H]^+$ 541.2590, found 541.2582.

Diol **23**: R_f 0.35 (hexane/Et_2O/CH_2Cl_2/MeOH = 1:1:1:0.04); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.29 (dd, J = 10.9 and 2.4 Hz, 1 H), 1.83 (m, 1 H), 1.89 (m, 1 H), 1.92 (m, 1 H), 2.10 (m, 1 H), 2.12 (m, 1 H), 2.14 (m, 1 H), 2.21 (dd, J = 9.6 and 8.0 Hz, 1 H), 2.24 (m, 1 H), 2.44 (m, 1 H), 2.47 (m, 1 H), 2.49 (m, 1 H), 2.60 (br td, J = 9.5 and 2.7 Hz, 1 H), 2.65 (br d, J = 6.5, 1 H), 2.68 (br d, J = 6.6 Hz, 1 H), 2.76 (br t, J = 6.9 Hz, 1 H), 3.28 (dd, J = 10.9 and 5.7 Hz, 1H), 3.32 (dd, J = 10.6 and 7.7 Hz, 1 H), 3.46 (dd, J = 10.9 and 8.8 Hz, 1 H), 3.50 (dd, J = 10.6 and 7.9 Hz, 1 H), 5.63 (br d, J = 10.4 Hz, 1 H), 5.81 (br d, J = 10.4 Hz, 1 H), 5.91 (s, 2 H), 5.92 (s, 2 H), 6.24 (t, J = 7.3 Hz, 1 H), 6.41 (t, J = 7.3 Hz, 1 H), 6.55−6.72 (m, 6 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 32.0, 32.9, 33.2, 33.7, 36.1, 37.6, 40.3, 40.5, 42.0, 42.4, 43.1, 44.2, 44.8, 45.6, 62.8, 62.9, 100.8, 108.1, 108.9, 109.2, 121.2, 121.5, 126.0, 131.5, 134.2, 134.8, 135.0, 135.5, 145.66, 145.72, 147.5, 147.6; IR (neat) ν_{max} 1040, 1244, 1441, 1488, 1502, 2917, 3351 cm^{-1}; HRMS[ES+] calcd for $C_{34}H_{37}O_6$ $[M + H]^+$ 541.2590, found 541.2585.

Dinitrile 25. *Step 1.* To a stirred solution of the diol **19** (16.5 mg, 30.5 μmol) in CH_2Cl_2 (0.5 mL) were added triethylamine (25.5 μL, 183 μmol) and methanesulfonyl chloride (7.1 μL, 91.5 μmol) at 0 °C under Ar. After 30 min, the reaction mixture was diluted with diethyl ether (20 mL), and the resulting mixture was washed with water, 5% HCl, and satd $NaHCO_3$ solution. The organic solution was then dried over $MgSO_4$ and concentrated. The crude product was directly used for the next step.

Dimesylate **24**: R_f 0.7 (Hex/EtOAc = 1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.35 (d, J = 9.1 Hz, 1 H), 1.77 (m, 1 H), 1.91 (m, 2H), 2.13−2.24 (m, 4 H), 2.43−2.67 (m, 8 H), 2.89 (s, 3 H), 2.90 (s, 3 H), 3.74 (dd, J = 9.8 and 5.6 Hz, 1 H), 3.80 (dd, J = 9.7 and 6.4 Hz, 1 H), 3.97 (t, J = 9.7 Hz, 1 H), 4.17 (t, J = 9.1 Hz, 1 H), 5.55 (br d, J = 10.4 Hz, 1 H), 5.67 (br d, J = 10.4 Hz, 1 H), 5,93 (m, 4 H), 6.04 (t, J = 7.2 Hz, 1 H), 6.14 (t, J = 7.2 Hz, 1 H), 6.54−6.74 (m, 6 H).

Step 2. To a stirred solution of the dimesylate **24** in DMF (1 mL) were added sodium iodide (2.3 mg, 15 μmol) and sodium cyanide (12.0 mg, 244 μmol). The resulting suspension was heated to 70 °C and stirred for 16 h. Then it was cooled, diluted with ethyl acetate (20 mL), and washed with water (10 mL × 3). The organic layer was washed with brine, dried over $MgSO_4$, and concentrated. The residue

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was purified by column chromatography (Hex/EtOAc = 4:1) to afford dinitrile **25** (12.6 mg, 74% in two steps, colorless liquid).

Dinitrile **25**: R_f 0.7 (Hex/EtOAc = 2:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.36 (d, J = 9.1 Hz, 1 H), 1.75 (m, 1 H), 1.82−1.99 (m, 4 H), 2.04−2.22 (m, 5 H), 2.29−2.42 (m, 2 H), 2.52−2.71 (m, 7 H), 5.55 (br d, J = 10.3 Hz, 1 H), 5.72 (ddd, J = 10.3, 3.4, and 2.1 Hz, 1 H), 5.94 (m, 4 H), 6.07 (t, J = 7.2 Hz, 1 H), 6.36 (t, J = 7.2 Hz, 1 H), 6.55−6.74 (m, 6 H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 16.9, 17.8, 31.9, 37.5, 37.6, 37.8, 37.9, 38.0, 39.9, 41.2, 41.3, 42.5, 43.6, 43.9, 47.1, 100.8, 100.9, 108.20, 108.24, 108.8, 109.1, 119.0, 119.4, 121.2, 121.5, 123.5, 133.0, 133.3, 133.5, 133.7, 134.0, 145.8, 145.9, 147.58, 147.65; IR (neat) ν_{max} 1039, 1240, 1441, 1488, 1502, 2242, 2920; HRMS[ES +] calcd for $C_{36}H_{35}N_2O_4$ $[M + H]^+$ 559.2597, found 559.2591 cm^{-1}.

Kingianin F (1F). *Step 1.* To a stirred solution of dinitrile **25** (14.1 mg, 25.2 μmol) in EtOH−THF (2.5 mL−0.5 mL) was added aq NaOH solution (0.05 mL, 7 M) and then, dropwise, H_2O_2 solution (0.6 mL, 35% in water) at 0 °C. The mixture was warmed to room temperature, stirred for 30 min, and heated to reflux. After 3 h, the same amounts of NaOH and H_2O_2 solutions were added to the mixture. After being stirred for an additional 3 h, the reaction mixture was diluted with brine and then extracted with CH_2Cl_2 (15 mL × 5). The combined organic solution was washed with brine, dried over Na_2SO_4, filtered, and concentrated. The residue was used for the next step.

Step 2. The residue from step 1 was placed in a 3 mL vial, and the vial was flushed with Ar for 10 min. Addition of CH_3CN (1.5 mL) gave a clear solution which was stirred and to which acetaldehyde (8.4 μL, 151 μmol), triethylsilane (24.3 μL, 151 μmol), and trifluoroacetic acid (10.6 μL, 139 μmol) were added in that order. Then, the vial was capped and sealed with parafilm. After being stirred for 15 h, the reaction mixture was diluted with CH_2Cl_2 (30 mL). The resulting solution waswashed with satd $NaHCO_3$ solution and brine, dried over Na_2SO_4, and concentrated. The residue was subjected to preparative TLC (hexane/EtOAc = 1:2) to afford kingianin F (6.2 mg, 38%, white solid, mp =86−91 °C, lit.[1a] 90−95 °C): R_f 0.2 (hexane/EtOAc = 1:2); for ^{1}H NMR (500 MHz, pyridine-d_5) and ^{13}C NMR (126 MHz, pyridine-d_5), see Tables 3 and 4 in the Supporting Information; IR (neat) ν_{max} 1039, 1244, 1441, 1488, 1502, 1548, 1641, 2922, 3292 cm^{-1}.

Diiodide 27. To a stirred solution of triphenylphosphine (58 mg, 0.22 mmol) and imidazole (25 mg, 0.37 mmol) in CH_2Cl_2 (1.5 mL) was added iodine (55.8 mg, 0.22 mmol) at 0 °C under Ar. The mixture was stirred for 20 min and treated dropwise with a solution of the diol **6** (20 mg, 0.037 mmol) in CH_2Cl_2 (0.5 mL). The resulting mixture was allowed to warm to room temperature over 1 h, and then the suspension was filtered. The filtrate was diluted with ethyl ether (10 mL) and washed twice with satd $Na_2S_2O_3$ solution. The combined aqueous solution was extracted with CH_2Cl_2 (5 mL × 3). The combined organic solution was washed with brine, dried over $MgSO_4$, and concentrated. The residue was subjected to column chromatography (Hex/EtOAc = 20:1) to afford the diiodide **27** (21.7 mg, 77%) as a colorless oil: R_f 0.5 (Hex/EtOAc = 10:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.83−1.92 (m, 2 H), 1.99 (d, J = 8.9 Hz, 1 H), 2.07−2.27 (m, 5 H), 2.49 (m, 2 H), 2.56−2.67 (m, 6 H), 2.93−3.03 (m, 4 H), 5.59 (br d, J = 10.4 Hz, 1 H), 5.68 (ddd, J = 10.4, 3.1, and 2.0 Hz, 1 H), 5.91 (s, 2 H), 5.92 (s, 2 H), 6.11 (t, J = 7.3 Hz, 1 H), 6.23 (t, J = 7.3 Hz, 1 H), 6.56−6.72 (m, 6 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 11.6, 13.5, 32.1, 34.8, 35.5, 37.58, 37.61, 38.1, 38.2, 42.2, 43.5, 44.6, 45.2, 45.3, 45.8, 46.8, 100.7, 108.1, 108.2, 108.7, 108.8, 120.96, 120.97, 125.1, 132.1, 132.3, 134.4, 134.82, 134.84, 145.5, 145.6, 147.5; IR (neat) ν_{max} 938, 1039, 1247, 1442, 1488, 1501, 2919 cm^{-1}.

Diester 28. The procedure of Manchand et al. was adapted.[8a] A mixture of $NiCl_2{\cdot}6H_2O$ (32.8 mg, 138 μmol), Zn (45.1 mg, 690 μmol), and methyl acrylate (57.5 μL, 634 μmol) in pyridine (0.5 mL) was stirred at 60 °C for 30 min under Ar. The resulting reddish brown heterogeneous suspension was cooled to room temperature and treated with a solution of diiodide **27** (21.0 mg, 27.6 μmol) in pyridine (0.5 mL). After 4 h, the reaction mixture was filtered through a pad of Celite, and the Celite was washed through with EtOAc. The filtrate was diluted with EtOAc (15 mL), and this solution was washed with 5% HCl (10 mL × 2), satd $NaHCO_3$ solution, and brine, dried over $MgSO_4$, and concentrated. The residue was subjected to column chromatography (Hex/EtOAc = 5:1) to afford diester **28** (13.1 mg, 70%) as a colorless oil: R_f 0.5 (Hex/EtOAc = 1:2); ^{1}H NMR (MHz, $CDCl_3$) δ 1.12−1.71 (m, 11 H), 1.79 (m, 1 H), 2.00 (m, 1 H), 2.11 (m, 1 H), 2.16−2.25 (m, 6 H), 2.33 (m, 1 H), 2.45−2.66 (m, 7 H), 3.65 (s, 3 H), 3.66 (m, 3 H), 5.56 (br d, J = 10.4 Hz, 1 H), 5.64 (ddd, J = 10.4, 3.0, and 2.0 Hz, 1 H), 5.89 (s, 2 H), 5.91 (s, 2 H), 6.06 (t, J = 7.3 Hz, 1 H), 6.20 (t, J = 7.3 Hz, 1 H), 6.55−6.70 (m, 6 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 22.7, 23.2, 32.6, 34.1, 34.5, 34.7, 35.5, 36.15, 36.24, 38.2, 38.5, 39.1, 39.3, 41.7, 42.6, 43.35, 43.42, 43.9, 44.4, 45.1, 51.40, 51.43, 100.6, 108.0, 108.76, 108.82, 120.9, 121.0, 125.4, 132.0, 132.2, 134.8, 135.4, 135.8, 145.30, 145.31, 147.40, 147.44, 174.1, 174.2; IR (neat) ν_{max} 1246, 1440, 1488, 1503, 1737, 2914 cm^{-1}; HRMS[ES+] calcd for $C_{42}H_{49}O_8$ $[M + H]^+$ 681.3427, found 681.3425.

Kingianin H (1H). To a stirred solution of diester **28** (12.5 mg, 18.3 μmol) in EtOH−H_2O (2 mL/0.2 mL) was added NaOH (7.30 mg, 180 μmol) at room temperature. The mixture was stirred overnight and concentrated. The residue was dissolved in water, and this solution was acidified with 1 N aq HCl. The resulting mixture was extracted with CH_2Cl_2 (20 mL × 3), and the combined organic solution was washed with water and brine, dried over $MgSO_4$, and concentrated to afford kingianin H (11.2 mg, 93%, white solid, mp = 59−63 °C, lit.[1a] mp not reported): R_f 0.5 (Hex/EtOAc = 1:1); ^{1}H NMR (400 MHz, $CDCl_3$) and ^{13}C NMR (100 MHz, $CDCl_3$) δ see Tables 5 and 6 in the Supporting Information; IR (neat) ν_{max} 924, 1039, 1186, 1245, 1442, 1488, 1503, 1704, 2913 cm^{-1}.

Diol 30. *Step 1.* To a stirred solution of the dinitrile **25** (17.8 mg, 31.9 μmol) in CH_2Cl_2 (1.5 mL) was added dropwise DIBAL (1.0 M in hexane, 70.0 μL, 70.0 μmol) at −78 °C. The mixture was stirred for 4 h at the same temperature, quenched with satd NH_4Cl solution, and treated with 10% potassium sodium tartrate. The resulting mixture was stirred for 1 h and extracted with CH_2Cl_2 (5 mL × 5). The organic solution was dried over $MgSO_4$, concentrated, and directly used for the next step.

Step 2. To a stirred solution the dialdehyde **29** in MeOH (1.0 mL) was slowly added $NaBH_4$ (3.6 mg, 95.6 μmol) at 0 °C. The mixture was stirred for 30 min, quenched with satd NH_4Cl solution, and extracted with ethyl acetate (5 mL × 3). The combined organic solution was dried over $MgSO_4$ and concentrated. The residue was subjected to silica gel column chromatography (Hex/ EtOAc = 2:1) to afford the diol **30** (9.9 mg, 55%) as a colorless oil: R_f 0.6 (Hex/EtOAc = 1:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.30 (m, 1 H), 1.42 (m, 1 H), 1.49−1.62 (m, 3 H), 1.72 (m, 1 H), 1.80−1.87 (m, 3 H), 2.04−2.12 (m, 4 H), 2.7 (m, 2 H), 2.50 (m, 1 H), 2.56 (m, 4 H), 3.33 (m, 2 H), 3.47 (m, 2 H), 5.53 (br d, J = 10.4 Hz, 1 H), 5.62 (br d, J = 10.4 Hz, 1 H), 5.92 (s, 2 H), 5.94 (s, 2 H), 5.97 (t, J = 6.8 Hz, 1 H), 6.11 (t, J = 6.8 Hz, 1 H), 6.55−6.74 (m, 6 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 32.3, 32.9, 33.4, 38.0, 38.2, 38.6, 38.9, 39.0, 41.0, 42.0, 42.6, 42.7, 43.8, 44.3, 47.2, 61.8, 61.9, 100.7, 108.0, 109.0, 109.3, 121.2, 121.5, 125.3, 131.99, 132.03, 134.6, 134.8, 135.1, 145.5, 145.6, 147.4; IR (neat) ν_{max} 1040, 1243, 1441, 1488, 1502, 2917, 3347 cm^{-1}; HRMS[ES+] calcd for $C_{36}H_{41}O_6$ $[M + H]^+$ 569.2903, found 569.2911.

Dimalonate 31. *Step 1.* To a stirred solution of the diol **30** (6.1 mg, 10.7 μmol) in CH_2Cl_2 (1.0 mL) were added triethylamine (9.0 μL, 64 μmol) and methanesulfonyl chloride (2.5 μL, 32 μmol) at 0 °C under Ar. After 30 min, the reaction mixture was diluted with diethyl ether (10 mL), and the resulting mixture was washed with water, 5% HCl, and satd $NaHCO_3$ solution. The organic solution was then dried over $MgSO_4$ and concentrated. The crude product was directly used for the next step.

Step 2. To a stirred solution of NaH (60% dispersion in oil, 7.70 mg, 193 μmol) in THF (3.0 mL)−DMF (0.3 mL) was added diethyl malonate (32.5 μL, 214 μmol) at rt. After 30 min, the mixture was treated with mesylate (from the above procedure) and NaI (0.8 mg, 5.4 μmol) in THF (0.2 mL). The reaction mixture was then heated to reflux and stirred for 18 h. The resulting mixture was cooled to rt, quenched with satd NH_4Cl solution, and extracted with diethyl ether (10 mL × 3). The combined organic solution was dried over $MgSO_4$, concentrated, and subjected to silica gel column chromatography

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(Hex/EtOAc = 5:1) to afford the dimalonate **31** (4.7 mg, 51%) as a colorless oil: R_f 0.5 (Hex/EtOAc = 5:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.24 (m, 17 H), 1.54 (m, 1 H), 1.61−1.83 (m, 7 H), 1.95−1.2.08 (m, 4 H), 2.36 (m, 2 H), 2.52 (m, 5 H), 3.18 (m, 2 H), 4.17 (m, 8 H), 5.50 (br d, J = 10.4 Hz, 1 H), 5.59 (br d, J = 10.4 Hz, 1 H), 5.91−5.94 (m, 5 H), 6.03 (t, J = 7.2 Hz, 1 H), 6.52−6.73 (m, 6 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 14.06, 14.08, 27.2, 27.4, 27.5, 28.0, 32.1, 38.05, 38.08, 38.3, 38.9, 40.9, 41.7, 42.0, 42.2, 42.5, 42.7, 43.6, 44.0, 47.2, 52.1, 52.2, 61.2, 100.7, 108.0, 109.0, 109.2, 121.2, 121.5, 124.9, 131.9, 132.1, 134.6, 134.8, 135.1, 145.45, 145.52, 147.4, 169.4, 169.5, 169.5; IR (neat) ν_{max} 1036, 1146, 1324, 1375, 1463, 1742, 2922 cm^{-1}; HRMS[ES+] calcd for $C_{50}H_{61}O_{12}$ $[M + H]^+$ 853.4163, found 853.4150.

Diester 32. To a stirred solution of the dimalonate **31** (10.0 mg, 11.7 μmol) in wet DMSO (1.0 mL) was added LiCl (4.9 mg, 117.0 μmol) at room temperature. The resulting suspension was heated to 150 °C and stirred for 4 h. Then, the reaction mixture was diluted with 2 N HCl solution and extracted with diethyl ether (10 mL × 3). The combined organic solution was washed with water and brine, dried over $MgSO_4$, and concentrated. Silica gel column chromatography (Hex/EtOAc = 5:1) afforded the diester **32** (3.0 mg, 36%) as a colorless oil: R_f 0.7 (Hex/EtOAc = 5:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.19−1.50 (m, 15 H), 1.61−1.72 (m, 2 H), 1.76−1.84 (m, 2 H), 1.93−2.02 (m, 3 H), 2.08 (m, 1 H), 2.17−2.22 (m, 4 H), 2.32−2.37 (m, 2 H), 2.49−2.60 (m, 5 H), 4.097 (q, J = 7.2 Hz, 2 H), 4.103 (q, J = 7.1 Hz, 2 H), 5.50 (d, J = 10.5 Hz, 1 H), 5.59 (d, J = 10.5 Hz, 1 H), 5.91−5.94 (m, 5 H), 6.06 (t, J = 6.9 Hz, 1 H), 6.53−6.60 (m, 4 H), 6.69−6.74 (m, 2 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 14.2, 14.3, 23.5, 23.8, 29.2, 29.7, 32.3, 34.5, 34.6, 38.1, 38.2, 38.4, 39.0, 41.0, 41.7, 42.1, 42.3, 42.6, 42.7, 43.7, 44.0, 47.3, 60.2, 100.7, 108.0, 109.0, 109.3, 121.3, 121.5, 125.2, 129.7, 131.9, 132.0, 134.8, 134.77, 134.83, 135.2, 145.4, 145.5, 147.4, 173.7, 173.8; IR (neat) ν_{max} 1039, 1246, 1371, 1442, 1488, 1503, 1731, 2923 cm^{-1}; HRMS[ES+] calcd for $C_{44}H_{53}O_8$ $[M + H]^+$ 709.3740, found 709.3727.

Kingianin J (1J). To a stirred solution of diester **32** (3.0 mg, 4.2 μmol) in EtOH−H_2O (2 mL/0.2 mL) was added NaOH (3.0 mg, 74.0 μmol) at room temperature. The mixture was stirred overnight and concentrated. The residue was dissolved in water and acidified with 1 N aq HCl solution. The resulting mixture was extracted with ethyl acetate (20 mL × 3). The combined organic solution was then washed with water and brine, dried over $MgSO_4$, and concentrated to afford kingianin J (2.3 mg, 84%, colorless oil): R_f 0.4 (Hex/EtOAc = 2:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ and ^{13}C NMR (126 MHz, $CDCl_3$) δ see Tables 7 and 8 in the Supporting Information; IR (neat) ν_{max} 1040, 1097, 1243, 1442, 1488, 1503, 1707, 2922 cm^{-1}.

■ ASSOCIATED CONTENT

Supporting Information

Comparison of NMR data for natural and synthetic kingianins, tabulated crosspeaks for COSY, NOESY, HMQC, and HMBC spectra of diol **23**, summary of assigned ^{1}H and ^{13}C signals for the pentacyclic core of diol **23**. ^{1}H and ^{13}C spectra for synthetic kingianins D, F, H, and J and for all stable, isolated intermediates, COSY, NOESY, HMQC, and HMBC spectra of diol **23**, X-ray crystallographic data for compound **21**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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