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Total Synthesis of (±)-Kuwanol E

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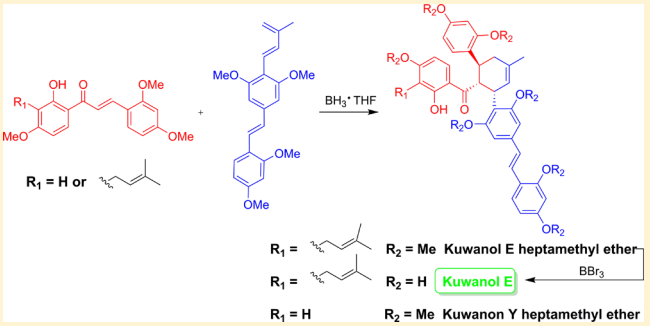
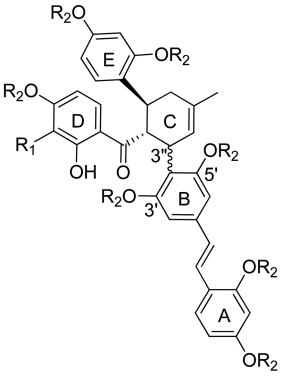
Supporting Information

ABSTRACT: The total synthesis of the Diels–Alder-type adducts (±)-kuwanol E and the heptamethyl ether derivative of (±)-kuwanon Y has been accomplished via a convergent strategy involving 2′-hydroxychalcone **6** or **9** and dehydroprenylstilbene **7**, in nine steps. The synthesis features, as a key step, a Lewis acid-mediated biomimetic intermolecular Diels–Alder [4+2] cycloaddition for the construction of the cyclohexene skeleton with three stereogenic centers. Notably, the *endo*/*exo* diastereoselectivity of the reaction proved to be temperature-controlled.



The use of plant-derived natural extracts as a powerful source of drugs to treat human diseases has a long history. Plants have always been the most important source of food and medical preparations in the treatment of several illnesses, with the earliest record dating back to 2600 B.C. The exploration of natural substances produced by the plants is a good strategy to discover new biologically active compounds with potential application in medicine.[1] In this context, the extracts of a tribe of plants belonging to the Moraceae family, namely the Moreae species, have found application in Traditional Chinese Medicine, with anti-inflammatory, diuretic, antitussive, and antipyretic purposes.[2] Chemical investigation of the constituents of the Moreae species[3] led to the identification of a class of polyphenolic compounds, known as Diels–Alder-type adducts, with promising biological activities. In fact, several types of Diels–Alder adducts have been shown to exhibit diuretic, blood sugar reducing, and blood pressure reducing effects, as well as activities against serious diseases[4,5] such as Alzheimer's, atherosclerosis, hyperlipidemia, and AIDS. We already showed that kuwanol E (**1**) (Figure 1) is the most potent naturally occurring inhibitor of *Mycobacterium tuberculosis* protein tyrosine phosphatase B reported so far (K_i = 1.6 ± 0.1 μM).[6] Kuwanol E is a polyphenolic secondary metabolite isolated from the roots of *Sorocea ilicifolia*[7] and from cell cultures of *Morus alba*[8] and *Morus nigra*.[9] In view of its biological activity, the total synthesis of kuwanol E (**1**) represents an attractive challenging task to provide sufficient amounts of pure product for biological assays.

Kuwanol E heptamethyl ether (**2**) (Figure 1) is the methylated derivative of **1**, and it represents a good precursor for the synthesis of **1** and other Diels–Alder adducts with promising biological activities. Kuwanol E (**1**) is the *endo*-adduct (*cis*–*trans*), with absolute configuration 3″*S*,4″*R*,5″*S*.[8,10] Compound **3** is the C3″ epimer of **2** (absolute configuration 3″*R*,4″*R*,5″*S*) and thus represents the *exo*-adduct (*trans*–*trans*). Kuwanon Y (**4**) is another secondary metabolite isolated from Moraceous plants,[11] and it is the deprenylated analogue of **1**; kuwanon Y heptamethyl ether (**5**) is the corresponding methylated derivative.



1: Kuwanol E	R_1= $CH_2CH=C(CH_3)_2$;	R_2= H; H3″β
2: Kuwanol E heptamethyl ether	R_1= $CH_2CH=C(CH_3)_2$;	R_2= Me; H3″β
3: *exo*-Kuwanol E heptamethyl ether	R_1= $CH_2CH=C(CH_3)_2$;	R_2= Me; H3″α
4: Kuwanon Y	R_1= H;	R_2= H; H3″β
5: Kuwanon Y heptamethyl ether	R_1= H;	R_2= Me; H3″β

Figure 1. Chemical structures of Diels–Alder-type adducts kuwanol E (**1**), kuwanol E heptamethyl ether (**2**), *exo*-kuwanol E heptamethyl ether (**3**), kuwanon Y (**4**), and kuwanon Y heptamethyl ether (**5**).

Herein, we report the first total synthesis of (±)-kuwanol E (**1**), (±)-kuwanol E heptamethyl ether (**2**), (±)-*exo*-kuwanol E heptamethyl ether (**3**), and (±)-kuwanon Y heptamethyl ether (**5**). The synthetic strategy features, as a key step, a biomimetic

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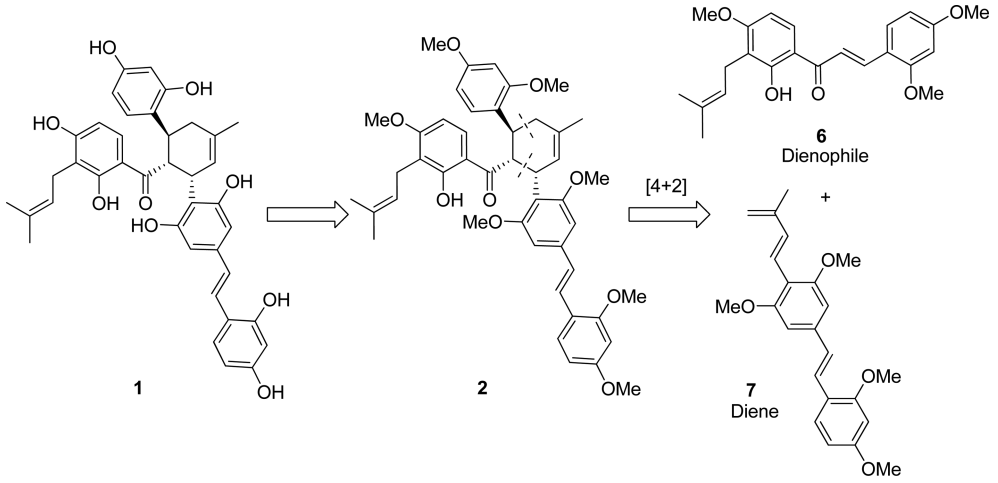
Scheme 1. Retrosynthetic Approach to Kuwanol E (1)

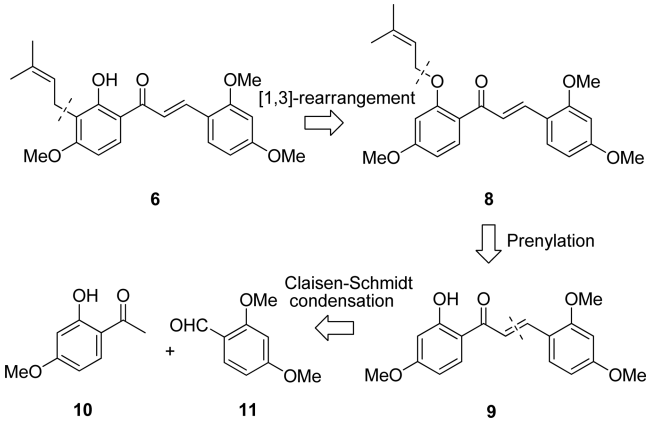


intermolecular Diels–Alder [4+2] cycloaddition for the construction of the cyclohexene skeleton with the appropriate stereochemistry. Such reaction, in fact, is known to proceed in a highly regioselective fashion, by affording only four stereoisomers.[12] The method paves the way to the preparation of a class of Diels–Alder-type adducts and establishes the strategy to design new analogues of **1**. During the compilation of this paper, a Chinese group reported the first enantioselective total synthesis of (+)-kuwanon Y (**4**), (−)-kuwanon X, and (+)-kuwanon A (structures not included in Figure 1) by using stereoselective Diels–Alder cycloaddition promoted by chiral Lewis acids.[13]

RESULTS AND DISCUSSION

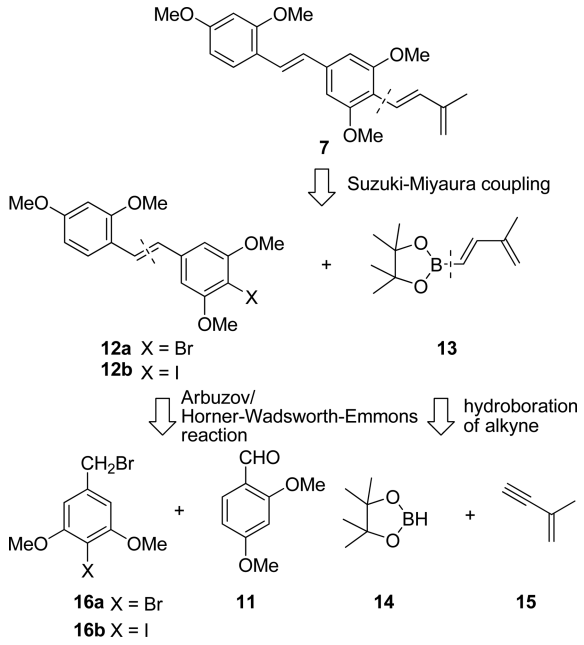
Retrosynthetic Analysis. Kuwanol E (**1**) could be obtained from kuwanol E heptamethyl ether (**2**) by cleavage of the *O*-methyl ether groups. The synthetic pathway to heptamethyl ether **2** is based on the retrosynthetic analyses depicted in Schemes 1–3. The first disconnection involves the

Scheme 2. Retrosynthetic Approach to Dienophile 6



cyclohexene ring (Scheme 1) and generates the two fragments for a Diels–Alder [4+2] cycloaddition, i.e., morachalcone A trimethyl ether (**6**) and stilbene tetramethyl ether (**7**), the dienophile and the diene, respectively. Compounds **6** and **7** can be synthesized individually and represent the coalescence of the convergent synthesis proposal.

Scheme 3. Retrosynthetic Approach to Diene 7



The retrosynthesis of **6** (Scheme 2) comprises a disconnection of the C–C bond between the prenyl moiety and the phenolic moiety, thus yielding fragment **8** as a potential intermediate for a [1,3]-rearrangement. Prenylated chalcone **8** may originate from 2′-hydroxychalcone **9**, which, in turn, may be synthesized from the commercially available **10** and **11**.

The diene intermediate **7** was disconnected (Scheme 3) at the C–C bond between the aromatic ring and the diene moiety. This operation generates the stilbene derivative **12a** or **12b** and alkenyl boronate **13**, as possible partners for a Suzuki–Miyaura coupling. Diene **13** would be available from pinacolborane **14** and alkyne **15**, which may be coupled by hydroboration. Stilbene derivative **12a** or **12b**, disconnected at the *trans*-double bond, would afford building blocks **11** and **16a** or **16b**, which could be employed in a one-pot Arbuzov/Horner–Wadsworth–Emmons reaction.

Finally, a sequence of functional group interconversions of benzyl bromide **16a** or benzyl iodide **16b** including nucleophilic substitution of benzylic alcohol **17a** or **17b**, reduction of the ethyl ester **18a** or **18b**, protection of the

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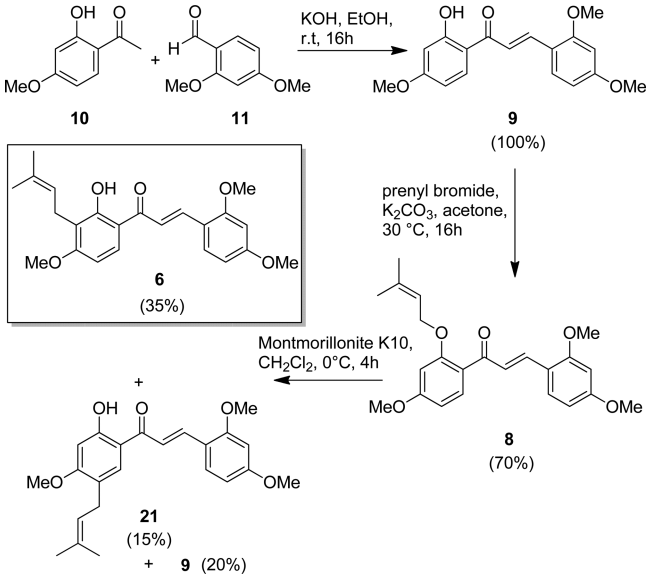
phenolic groups of **19**, and Fischer esterification led to commercially available 4-bromo-3,5-dihydroxybenzoic acid (**20**) as starting material.

Synthesis of Dienophile 6. The synthesis of morachalcone A trimethyl ether (**6**) as the building block for the biomimetic Diels–Alder cycloaddition proceeded via the classical reported conditions[12c] and is shown in Scheme 4.

Scheme 4. Synthesis of Dienophile 6

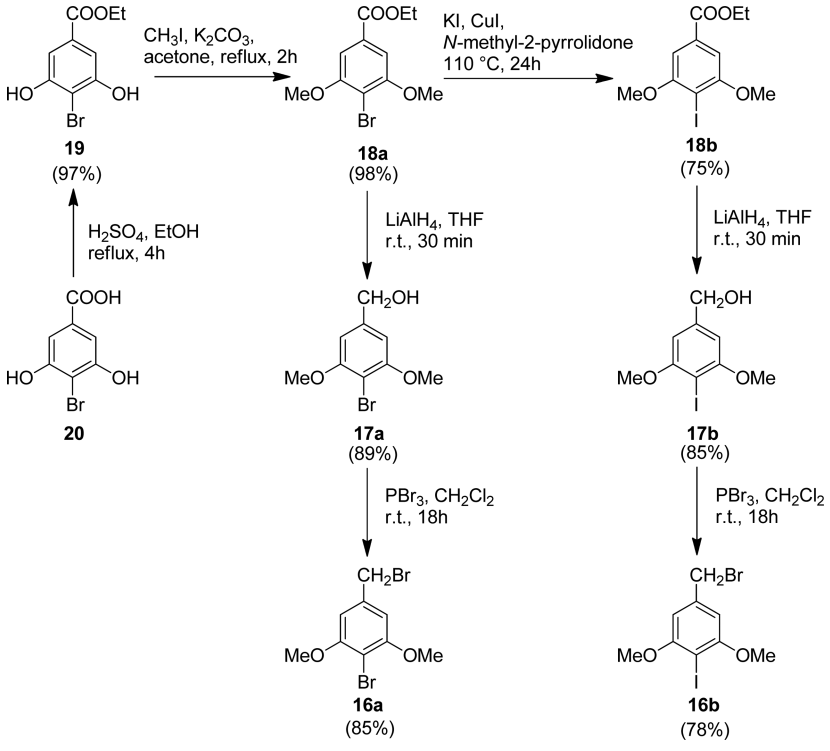


Briefly, dienophile **6** was obtained in three steps with an overall yield of 25%. Claisen–Schmidt condensation between commercially available acetophenone and benzaldehyde derivatives **10** and **11**, using KOH as the base, yields 2′-hydroxychalcone **9** in quantitative yield. The chalcone exhibited a sharp and strongly H-bonded phenolic deshielded resonance at δ = 13.71 in the ^{1}H NMR spectrum. The phenolic group of **9** was subsequently prenylated under standard conditions with prenyl bromide, affording the target prenyl ether **8** (70% yield), which was in turn subjected to a [1,3]-rearrangement in the presence of montmorillonite K10 in CH_2Cl_2.[14] The 3-prenyl isomer **6** was obtained in a 35% yield, while the [1,5]-shifted isomer **21** and chalcone **9** were isolated in 15% and 20% yields, respectively. Notably, a previous attempt to obtain dienophile **6** using Florisil in toluene at 100 °C[12c] afforded **21** (40%) and chalcone **9** (47%) as major products, whereas the target morachalcone derivative **6** was obtained in a low 7% yield.

Synthesis of Diene 7. The synthesis of the diene **7** began with commercially available 4-bromo-3,5-dihydroxybenzoic acid (**20**), which was converted into the corresponding ethyl ester **19** by Fischer esterification (Scheme 5) in 97% yield. Afterward, the phenolic groups were protected by treatment with methyl iodide, affording **18a** (98% yield), which was submitted to aromatic Finkelstein iodination[15] to give **18b** in 75% yield. The ester moiety of **18a** or **18b** was reduced with $LiAlH_4$, affording benzyl alcohol **17a** or **17b** (89% and 85% yields, respectively). The aromatic halides **17a** and **17b** were converted into benzyl bromides **16a** and **16b** using PBr_3 in 85% and 78% yields, respectively. These compounds served as the building blocks to stilbene halides **12a** and **12b** (Scheme 6), which were prepared through a one-pot Arbuzov and Horner–Wadsworth–Emmons[16] reactions with the commercially available 2,4-dimethoxybenzaldehyde (**11**).

The Arbuzov reaction was performed by heating benzyl bromide **16a** or **16b** at 150 °C in pure $P(OEt)_3$. On the basis of the classical Horner–Wadsworth–Emmons conditions, aldehyde **11** was introduced *in situ* to give **12a** or **12b** in 62% and 30% yields, respectively. Suzuki–Miyaura coupling[12c,17] of **12a**

Scheme 5. Synthesis of Benzyl Bromides 16a and 16b



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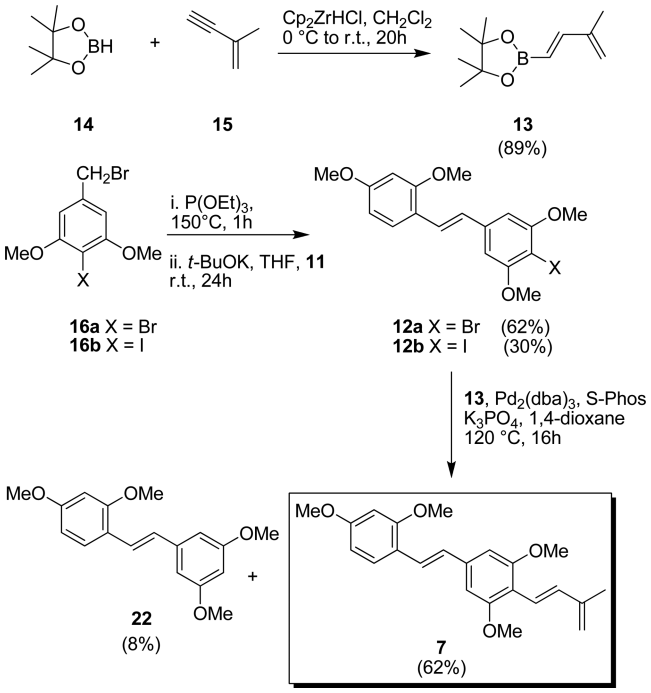
Scheme 6. Synthesis of Diene 7



or **12b** with boronate **13** was performed using $Pd_2(dba)_3$ and S-Phos as the catalysts. Diene **13** was previously obtained by hydroboration[18] starting from 4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**14**) and 2-methylbut-1-en-3-yne (**15**), both commercially available, using a catalytic amount of the Schwartz reagent.[18] Diene **7** was obtained in comparable yields of 62% and 60% from **12a** and **12b**, respectively, together with the formation of the reduced compound **22** as byproduct (8%). A key to achieving success in the Suzuki–Miyaura coupling step proved to be the use of S-Phos as a bulky and electron-rich ligand.[19] In fact, traditional ligands, such as PPh_3 or $AsPh_3$, gave **7** in very low yield and byproduct **22** as the major compound (data not shown). The synthesis of diene **7** was achieved with an overall yield of 28%.

Synthesis of the Diels–Alder-Type Adduct (±)-Kuwanol E Heptamethyl Ether (2). A first attempt to perform the Diels–Alder cycloaddition of dienophile **6** and diene **7** in dry *o*-xylene at 160 °C proved to be unsuccessful (see Table 1).

Table 1. Optimization of the Diels–Alder Reaction of Dienophile 6 with Diene 7 in Dry *o*-Xylene

entry	temp (°C)	Lewis acid[a]	**2** (% yield)	**3** (% yield)	time	*endo*/*exo*[b]
1	160	–	0	0	5 days	
2	25	BH_3·THF	0	0	24 h	
3	50	BH_3·THF	0	0	24 h	
4	100	BH_3·THF	40	12	60 h	4:1
5	160	BH_3·THF	14	42	24 h	1:4

[a]0.05 equiv. [b]Based on HPLC areas ratio.

Thus, BH_3·THF was added as catalyst, which is known[13a] to enhance the reactivity of 2′-hydroxychalcones by coordinating the carbonyl and phenolic groups in **6**. The reaction mixture was monitored by analytical HPLC (Experimental Section). Since no reactivity was observed at room temperature, the temperature was progressively increased to 100 °C. At this temperature, the reaction gave a mixture of two Diels–Alder adduct diastereoisomers with an *endo*/*exo* = 4:1 ratio (Scheme 7). The *endo*- and *exo*- adducts (i.e., *cis*–*trans* **2** and *trans*–*trans* **3**) were separated by preparative MPLC. Notably, a further increase of the temperature to 160 °C yielded the two diastereoisomers in the opposite ratio, i.e., 1:4 (Table 1). Thus, the synthesis of the *exo*-isomer **3** was carried out at 160 °C. The assignment of the relative configuration for each adduct was done by comparison of key ^{1}H NMR data with reported data for similar adducts,[20] and by direct comparison with an authentic sample of hepta-*O*-methylkuwanol E (**2**). Typically, in the *endo*-isomer **2**, one signal was observed for the 3′- and 5′-OMe groups that appeared a broad six-proton singlet at δ 3.47, as well as the two-proton signal of H-2′ and H-6′ at δ 6.50. On the contrary, in the *exo*-isomer **3**, two different singlets of the 3′- and 5′-OMe groups were observed, namely, at δ 3.93 (3H) and 3.53 (3H). The H-2′ and H-6′ signals resonated as a doublet at δ 6.31 (1H, J = 2.0 Hz) and a broad singlet at δ 6.60 (1H), respectively, due to the hindered rotation around the C-3″–C-4′ bond.[12c]

A further catalytic system for the Diels–Alder reaction, namely, AgOTf/Bu_4NBH_4,[12f] was screened in order to improve the reaction yield. However, this catalyst led to the formation of diastereoisomers **2** and **3** in lower yield.

In conclusion, a stereoselective synthesis of both the *endo*-**2** and *exo*-**3** adducts of the kuwanol E heptamethyl ethers was achieved by temperature control, with an overall yield of 11% from 4-bromo-3,5-dihydroxybenzoic acid. The heptamethyl ethers **2** and **3** have been prepared for the first time as precursors of natural kuwanol E and of the *exo*-adduct of kuwanol E, respectively. Notably, the latter has not yet been isolated from plants.

Synthesis of (+)-Kuwanol E Heptamethyl Ether (2). An authentic sample of (+)-kuwanol E (**1**), isolated from the methanol extract of *Morus nigra* cell cultures, was purified by semipreparative HPLC and successively methylated in order to obtain a product directly comparable with that synthesized according to the above-mentioned procedure. The reaction was performed using $(CH_3)_2SO_4$ as methylating agent (Scheme 8). Compound (+)-**2** was isolated by semipreparative HPLC in 33% yield. The ^{1}H NMR spectra of methylated kuwanol E and synthetic **2** were superimposable.

Synthesis of the Target Compound (±)-Kuwanol E (1). (±)-Kuwanol E (**1**) was obtained by cleavage of the methoxy groups of the *endo*-isomer **2** with BBr_3 in CH_2Cl_2[21] at −78 °C for 120 h (Scheme 9). (±)-Kuwanol E (**1**) was isolated by semipreparative HPLC in 20% yield. The NMR spectroscopic data for synthetic and naturally occurring **1** were coincident and in agreement with those reported.[8]

Synthesis of Diels–Alder-Type Adduct (±)-Kuwanon Y Heptamethyl Ether (5). 2′-Hydroxychalcone **9** (Scheme 4) was subjected to the aforementioned cycloaddition with diene **7**, in order to get direct access to another Diels–Alder-type adduct, namely, kuwanon Y (**4**), which lacks the prenyl moiety. The reaction was carried at 100 °C in the presence of BH_3·THF as the catalyst (Scheme 10) and monitored by analytical HPLC. Under these conditions, kuwanon Y heptamethyl ether (**5**) was formed as the major product (40% yield). The presence of the corresponding *exo*-adduct, kuwanon X heptamethyl ether, could not be confirmed. The demethylation of compound **5** was not attempted since a standard of the target compound **4** (Figure 1) was not available and because of the published total synthesis of kuwanol Y.[13c]

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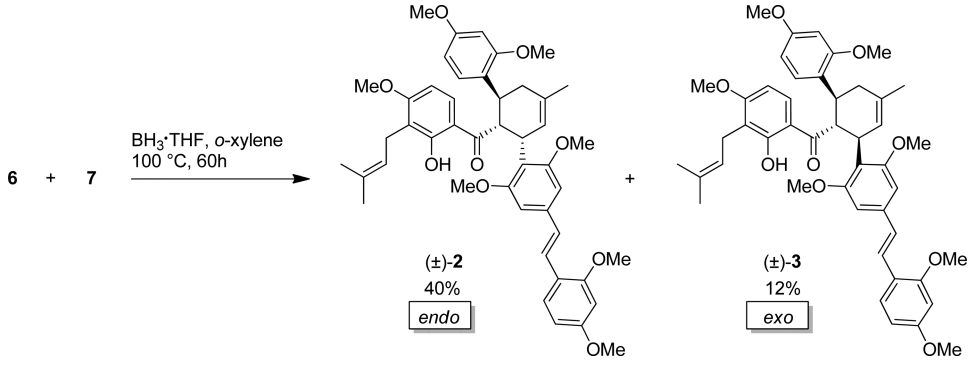
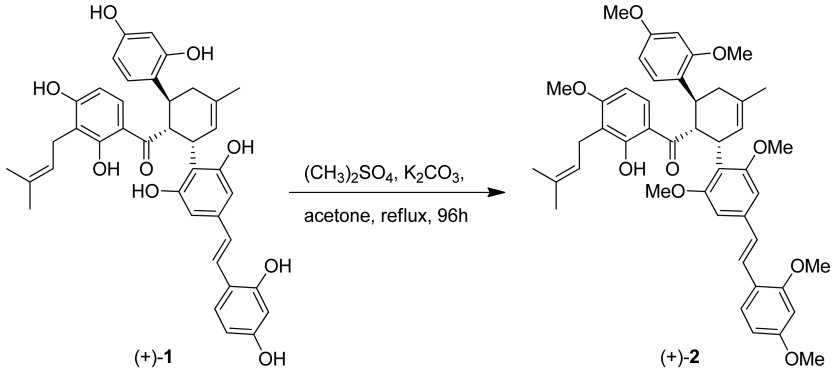
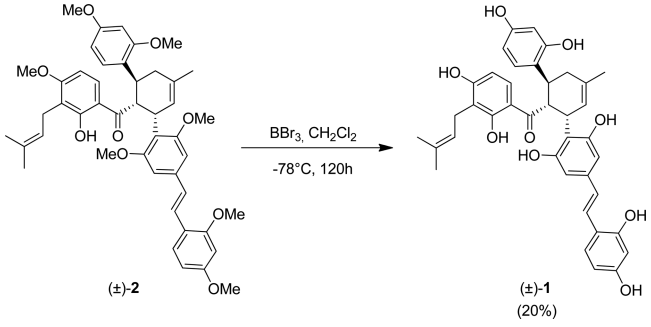
Scheme 7. Synthesis of (±)-Kuwanol E Heptamethyl Ether (2)



Scheme 8. Synthesis of (+)-Kuwanol E Heptamethyl Ether (2)

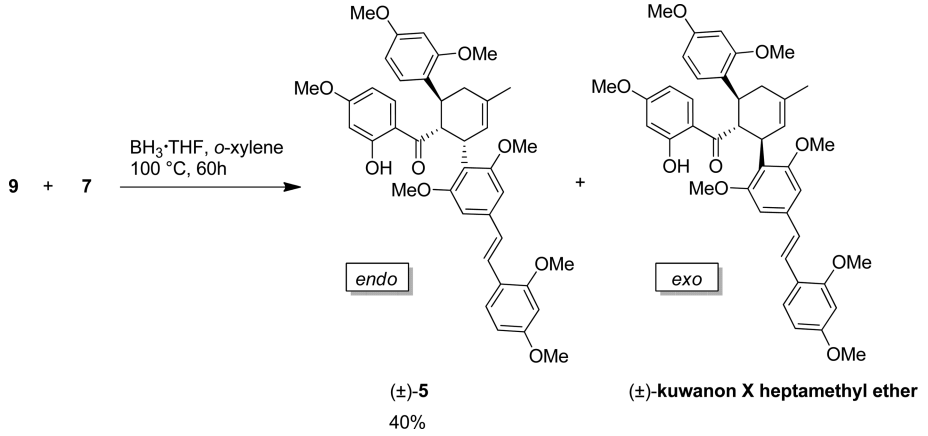


Scheme 9. Synthesis of (±)-Kuwanol E (1)



In conclusion, the total synthesis of (±)-kuwanol E (**1**), (±)-kuwanol E heptamethyl ether (**2**), *exo*-(±)-kuwanol E heptamethyl ether (**3**), and (±)-kuwanon Y heptamethyl ether (**5**) was achieved in 2−11% overall yields from 4-bromo-3,5-dihydroxybenzoic acid, by a convergent synthesis involving, as a key step, a biomimetic Diels−Alder reaction between dienophiles **6** or **9** (overall yields 25% and 100%, respectively) and diene **7** (overall yield 28%). Morachalcone derivative **6** and stilbene derivative **7** were obtained in three and seven steps, respectively. While a synthesis of **6** has been published,[12c] the construction of the diene moiety was a daunting task. Moreover, the Diels−Alder cycloaddition between dienophile **6** and diene **7** was tested under different conditions and proved

Scheme 10. Synthesis of (±)-Kuwanon Y Heptamethyl Ether (5)



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to need a Lewis acid catalysis to proceed. The synthetic method described here provides an efficient access to this class of Diels–Alder adducts.

EXPERIMENTAL SECTION

General Experimental Procedures. Melting points were recorded with a Büchi melting point B-545 and are not corrected. Optical rotations were measured with a Jasco P-1030 polarimeter. ^{1}H and ^{13}C NMR spectra have been acquired with a Bruker Avance 400 spectrometer operating at 400.13 and 100.6 MHz, respectively, at 300 K in $CDCl_3$, acetone-d_6, or DMSO-d_6, using 5 mm diameter glass tubes. Chemical shifts were expressed in ppm, and coupling constants (J) in hertz (Hz), approximated to 0.1 Hz. The residual solvent peak was used as an internal reference for ^{1}H and ^{13}C NMR spectra. Data for ^{1}H NMR are reported as follows: chemical shift, multiplicity (br = broad, ovrlp = overlapped, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = double doublet), coupling constant, integral. Spectra were processed with the program MestReNova version 6.0.2-5475, FT and zero filling at 64K. Mass spectra were obtained using a Thermo Finnigan LCQ Deca XP Plus mass spectrometer equipped with an electrospray ionization (ESI) source and a Fleet ion-trap analyzer: capillary temperature 275 °C, spray voltage 5.0 kV (positive mode), sheath gas (N_2) 25 arbitrary units, capillary voltage 40 V, tube lens 15 V. High-resolution (HR) mass spectra were obtained using a Thermo Fischer Exactive mass spectrometer equipped with an ESI source and an Orbitrap analyzer: capillary temperature 275 °C, spray voltage 3.5 kV, sheath gas (N_2) 10 arbitrary units, capillary voltage 65 V, tube lens 125 V. Compounds **2**, **3**, **5**, and **7** were purified by MPLC, using axially compressed columns, packed with 25–40 μm silica gel (Macherey-Nagel, Düren, Germany), connected to a solvent delivery system, equipped with a refractive index (RI) detector, and eluted with *n*-hexane/EtOAc mixtures at flow rates of 20–35 mL/min. Semipreparative purification of a crude MeOH extract of cell cultures from *Morus nigra* was performed using an HPLC system equipped with a UV detector (280 nm). The column used was a reversed-phase Thermo Fisher Scientific Hypersil ODS column, 5 μm (250 × 10 mm i.d., Waltham, MA, USA). Eluent: MeCN/H_2O = 50:50 (v/v). Flow rate: 3.0 mL/min. The purity of (+)-kuwanol E (**1**) was checked by analytical HPLC. Column: Phenomenex Luna C_{18} (250 × 4.6 mm i.d., Torrance, CA, USA). Mobile phases A: H_2O/MeCN = 90:10 (v/v); B: MeCN. Gradient elution: at 30% B for 5 min; to 100% B in 15 min (linear); at 100% B for 5 min; to 30% B in 5 min. Flow rate: 1.0 mL/min. PDA detection at 280 nm. Semipreparative purification of (+)-kuwanol E heptamethyl ether (**2**) was performed using an HPLC system equipped with an RI detector. The column used was a Macherey-Nagel Nucleosil column (250 × 10 mm i.d.). Eluent: *n*-hexane/EtOAc = 80:20 (v/v). Flow rate: 5.0 mL/min. Analytical liquid chromatography was performed using a Waters 1525 HPLC system equipped with a 2996 PDA detector (200–400 nm). The column used was a reversed-phase Phenomenex Luna C_{18} column (250 × 4.6 mm i.d.), operating in isocratic mode with mobile phases consisting of MeCN/H_2O mixtures, delivered at a flow rate of 1.00 mL/min. Analytical TLC was performed using 0.25 mm Fluka F_{254} silica gel. The compounds on TLC were revealed by quenching fluorescence (at 254 and 365 nm) using a 4 W UV lamp. Otherwise, plates were stained with a 10% EtOH solution of phosphomolybdic acid and heated (T = 120 °C). The product mixture purifications were carried out with silica column chromatography using Fluka 60 Å silica gel (0063–0200 mm, 70–230 mesh). Flash chromatography was performed using 200–400 mesh silica gel.

Commercially available reagents were supplied by Sigma-Aldrich and used without further purification. Dry solvents were purchased from Sigma-Aldrich or dried by distillation as follows: THF from sodium/benzophenone, CH_2Cl_2 from CaH_2. Yields of compounds synthesized are referred to chromatographically and spectroscopically pure compounds, unless otherwise stated.

(*E*)-3-(2,4-Dimethoxyphenyl)-1-(2-hydroxy-4-methoxyphenyl)prop-2-en-1-one (9). To a yellow solution of 2-hydroxy-4-methoxyacetophenone **10** (3.808 g, 22.92 mmol) and 2,4-dimethoxybenzaldehyde **11** (4.190 g, 25.21 mmol) in EtOH (70 mL) was added KOH (25.26 g, 458.40 mmol) at room temperature and under magnetic stirring. The mixture turned orange-reddish within a few minutes, and stirring was continued for 16 h. After the addition of H_2O (150 mL), the mixture was neutralized with concentrated HCl and the precipitate was filtered and washed with cold H_2O. The orange solid obtained in quantitative yield (7.20 g, 22.90 mmol) is the pure product. **9**: orange, microcrystalline solid; mp 154.7–155.4 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 13.71 (s, 1H), 8.13 (d, J = 15.3 Hz, 1H), 7.82 (d, J = 8.8 Hz, 1H), 7.62 (d, J = 15.3 Hz, 1H), 7.58 (d, J = 8.4 Hz, 1H), 6.54 (br d, J = 8.4 Hz, 1H), 6.48 (d, J = 8.0 Hz, 3H), 3.92 (s, 3H), 3.87 (s, 3H), 3.86 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 192.5, 166.5, 165.8, 163.2, 160.6, 140.2, 131.3, 131.1, 118.4, 117.1, 114.3, 107.4, 105.5, 101.0, 98.5, 55.6, 55.5, 55.5; ESIMS (+) m/z 315.3 $[M + H]^+$, 337.1 $[M + Na]^+$, 650.9 $[2M + Na]^+$.

(*E*)-3-(2,4-Dimethoxyphenyl)-1-(4-methoxy-2-[(3-methylbut-2-en-1-yl)oxy]phenyl)prop-2-en-1-one (8). To a solution of **9** (4.00 g, 12.72 mmol) in acetone (150 mL) were added K_2CO_3 (14.00 g, 101.29 mmol) and 1-bromo-3-methylbut-2-ene (6.6 mL, 8.53 g, 57.24 mmol, d = 1.29 g/mL). The reaction mixture was kept at 30 °C under magnetic stirring for 16 h. The acetone was removed *in vacuo*, and the residue was diluted with H_2O and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, and evaporated *in vacuo*. The crude residue was crystallized from CH_2Cl_2/*n*-hexane to give pure **8** as yellow crystals (3.405 g, 8.90 mmol, 70% yield). **8**: yellow crystals; mp 96.7–97.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (d, J = 16.0 Hz, 1H), 7.79 (d, J = 8.8 Hz, 1H), 7.58 (d, J = 16.0 Hz, 1H), 7.53 (d, J = 8.4 Hz, 1H), 6.55 (dd, J = 8.8, 2.4 Hz, 1H), 6.50–6.48 (m, 2H), 6.45 (m, 1H), 5.52 (t, J = 6.0 Hz, 1H), 4.59 (d, J = 6.4 Hz, 2H), 3.85 (s, 6H), 3.84 (s, 3H), 1.77 (s, 3H), 1.73 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 190.8, 163.7, 162.5, 160.0, 159.7, 138.1, 137.0, 132.9, 129.6, 125.6, 123.0, 119.4, 117.8, 105.4, 105.3, 99.9, 98.2, 65.7, 55.5, 55.5, 55.4, 25.7, 18.3; ESIMS (+) m/z 405.2 $[M + Na]^+$, 786.7 $[2M + Na]^+$.

(*E*)-3-(2,4-Dimethoxyphenyl)-1-[2-hydroxy-4-methoxy-3-(3-methylbut-2-en-1-yl)phenyl]prop-2-en-1-one (6). To a cooled (T = 0 °C) solution of **8** (1.179 g, 3.08 mmol) in dry CH_2Cl_2 (10 mL) was added montmorillonite K10 (1.18 g), and the reaction mixture was stirred for 4 h. The mixture was filtered on a gooch and washed with CH_2Cl_2, the solution was dried over Na_2SO_4, and the solvent was removed *in vacuo*. The yellow residue was purified by flash chromatography (*n*-hexane/EtOAc = 85:15) to obtain **6** (0.413 g, 1.08 mmol, 35% yield) and **21** (0.177 g, 0.46 mmol, 15% yield) as yellow solids. **6**: yellow, microcrystalline solid; mp 105.9–106.7 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 13.61 (s, 1H); 8.11 (d, J = 15.4 Hz, 1H), 7.79 (d, J = 9.2 Hz, 1H), 7.64 (d, J = 15.4 Hz, 1H), 7.57 (d, J = 8.8 Hz, 1H), 6.54 (dd, J = 8.8, 2.6 Hz, 1H), 6.50–6.48 (m, 2H), 5.24 (t, J = 7.2 Hz, 1H), 3.92 (s, 3H), 3.90 (s, 3H), 3.86 (s, 3H), 3.39 (d, J = 7.2 Hz, 2H), 1.80 (s, 3H), 1.68 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 192.9, 163.1, 163.0, 162.9, 160.5, 139.9, 131.8, 131.1, 129.1, 122.1, 118.7, 117.4, 117.1, 114.8, 105.4, 101.9, 98.4, 55.7, 55.6, 55.5, 25.8, 21.7, 17.8; ESIMS (+) m/z 383.3 $[M + H]^+$, 786.9 $[2M + Na]^+$. **21**: yellow, microcrystalline solid; mp 109.4–110.9 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 13.66 (s, 1H), 8.09 (d, J = 15.6 Hz, 1H), 7.63 (d, J = 15.6 Hz, 1H), 7.60 (s, 1H), 7.56 (d, J = 8.4 Hz, 1H), 6.55 (dd, J = 8.4, 2.0 Hz, 1H), 6.49 (d, J = 2.0 Hz, 1H), 6.43 (s, 1H), 5.31 (t, J = 7.2 Hz, 1H), 3.92 (s, 3H), 3.87 (s, 3H), 3.87 (s, 3H), 3.25 (d, J = 7.2 Hz, 2H), 1.78 (s, 3H), 1.73 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 192.5, 165.2, 163.8, 163.0, 160.5, 139.9, 132.9, 131.5, 129.6, 122.2, 121.2, 118.7, 117.2, 113.5, 105.5, 99.2, 98.5, 55.6, 55.5, 55.5, 27.8, 25.8, 17.8; ESIMS (+) m/z 383.3 $[M + H]^+$, 786.9 $[2M + Na]^+$.

Ethyl 4-Bromo-3,5-dihydroxybenzoate (19). In a two-neck round-bottom flask a solution of 4-bromo-3,5-dihydroxybenzoic acid **20** (10.00 g, 42.92 mmol) in EtOH (540 mL) containing concentrated H_2SO_4 (22.4 mL) was heated to reflux for 4 h. A saturated solution of $NaHCO_3$ was slowly added until pH = 7, and the organic solvent was removed *in vacuo*. The aqueous solution was extracted with EtOAc (3 × 50 mL), and the organic layers were collected, dried over Na_2SO_4, and evaporated *in vacuo*. The crude residue was crystallized from *n*-

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hexane to give **19** as white crystals (10.87 g, 41.63 mmol, 97% yield). **19**: white crystals; mp 134.7−136.6 °C; ^{1}H NMR (400 MHz, acetone-d_6) δ 9.07 (s, 2H), 7.17 (s, 2H), 4.29 (q, J = 7.1 Hz, 2H), 1.33 (t, J = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, acetone-d_6) δ 166.1, 156.2, 156.2, 131.5, 108.7, 108.7, 104.4, 61.6, 14.5.

Ethyl 4-Bromo-3,5-dimethoxybenzoate (18a). To a solution of **19** (3.00 g, 11.49 mmol) in acetone (120 mL) was added K_2CO_3 (6.351 g, 45.96 mmol), and the reaction mixture was heated to reflux. Then, CH_3I (4.3 mL, 9.78 g, 68.94 mmol, d = 2.28 g/mL) was added, and the heating was continued for 2 h. After the addition of a 1 N HCl solution, the acetone was removed *in vacuo* and the aqueous layer was extracted with $CHCl_3$ (3 × 30 mL). The organic layers were collected, washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The crude residue was crystallized from $CHCl_3$, giving **18a** (3.255 g, 11.26 mmol, 98% yield) as white crystals. **18a**: white crystals; mp 117.6−118.4 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 (s, 2H), 4.39 (q, J = 7.2 Hz, 2H), 3.94 (s, 6H), 1.40 (t, J = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.9, 156.9, 156.9, 130.5, 106.5, 105.4, 105.4, 61.4, 56.6, 56.6 14.3.

Ethyl 4-Iodo-3,5-dimethoxybenzoate (18b). To a solution of **18a** (3.00 g, 10.37 mmol) in dry *N*-methyl-2-pyrrolidone (10 mL) were added KI (3.44 g, 20.74 mmol) and CuI (0.987 g, 5.18 mmol) under an argon atmosphere. The reaction mixture was heated at 110 °C and kept under magnetic stirring for 24 h, quenched with 30% NH_4OH (5 mL), and diluted with H_2O. The solution was extracted with CH_2Cl_2 (3 × 30 mL), and the organic layers were collected, washed with brine, dried over Na_2SO_4, and evaporated *in vacuo*. The pale yellow solid obtained as a residue is the pure compound **18b** (2.61 g, 7.78 mmol, 75% yield). **18b**: pale yellow, microcrystalline solid; mp 104.3−105.4 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (s, 2H), 4.39 (q, J = 7.1 Hz, 2H), 3.96 (s, 6H), 1.41 (t, J = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.0, 157.0, 157.0, 130.5, 106.5, 105.5, 105.5, 61.5, 56.6, 56.6, 14.3; anal. found C, 39.29; H, 3.91; I, 37.73; calcd for $C_{11}H_{13}IO_4$, C, 39.31; H, 3.90; I, 37.76.

(4-Bromo-3,5-dimethoxyphenyl)methanol (17a) and (4-Iodo-3,5-dimethoxyphenyl)methanol (17b). A solution of **18a** (3.00 g, 10.38 mmol) or **18b** (3.00 g, 8.92 mmol) in dry THF (18 mL) was added dropwise to a stirred solution of $LiAlH_4$ (10.38 mmol) in dry THF (0.48 mL), under an argon atmosphere. The mixture was stirred for 30 min at room temperature, and H_2O (18 mL) and 15% NaOH (18 mL) were added in sequence. The organic solvent was removed *in vacuo*, and the aqueous solution was extracted with CH_2Cl_2 (3 × 30 mL). Pure compounds **17a** (2.282 g, 9.24 mmol, 89% yield) and **17b** (2.229 g, 7.58 mmol, 85% yield) were obtained as white solids. **17a**: white, microcrystalline solid; mp 90.8−93.0 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.59 (s, 2H), 4.67 (s, 2H), 3.90 (s, 6H), 1.88 (br s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.9, 154.9, 141.8, 107.7, 107.7, 95.1, 64.9, 56.4, 56.4; ESIMS (+) m/z 739.1 $[3M + H]^+$. **17b**: white, microcrystalline solid; mp 91.6−92.3 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.59 (s, 2H), 4.67 (s, 2H), 3.90 (s, 6H), 1.75 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.1, 157.1, 141.7, 104.5, 104.5, 99.6, 65.1, 56.4, 56.4; ESIMS (+) m/z 296.0 $[M + H]^+$.

2-Bromo-5-(bromomethyl)-1,3-dimethoxybenzene (16a) and 5-(Bromomethyl)-2-iodo-1,3-dimethoxybenzene (16b). Phosphorus tribromide (3.48 mL, 10.037 g, 37.08 mmol, d = 2.88 g/mL) was slowly added to a solution of **17a** (2.292 g, 9.27 mmol) or **17b** (2.229 g, 7.56 mmol) in CH_2Cl_2 (40 mL) at 0 °C, and the solution was stirred for 18 h at room temperature. The reaction mixture was poured into aqueous $NaHCO_3$ and extracted with CH_2Cl_2 (3 × 30 mL). The organic layers were collected, dried over Na_2SO_4, and concentrated *in vacuo*. Pure compounds **16a** (2.442 g, 7.88 mmol, 85% yield) and **16b** (2.105 g, 5.90 mmol, 78% yield) were obtained as white solids. **16a**: white, microcrystalline solid; mp 46.8−48.2 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.60 (s, 2H), 4.45 (s, 2H), 3.91 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.2, 157.2, 138.2, 105.4, 105.4, 101.1, 56.5, 56.5, 33.3; ESIMS (+) m/z 229.3 $[M - Br]^+$. **16b**: white, microcrystalline solid; mp 84.5−86.0 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.60 (s, 2H), 4.45 (s, 2H), 3.91 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.1, 157.1, 138.2, 105.4, 105.4, 101.1, 56.5, 56.5, 33.3; anal. found C, 30.29; H, 2.80; Br, 22.36; I, 35.56; calcd for $C_9H_{10}BrIO_2$, C, 30.28; H, 2.82; Br, 22.38; I, 35.55.

2-Bromo-5-[(*E*)-2-(2,4-dimethoxyphenyl)ethenyl]-1,3-dimethoxybenzene (12a) and 2-Iodo-5-[(*E*)-2-(2,4-dimethoxyphenyl)ethenyl]-1,3-dimethoxybenzene (12b). A solution of **16a** (1.50 g, 4.83 mmol) or **16b** (1.50 g, 4.20 mmol) and $P(OEt)_3$ (1.66 mL, 1.605 g, 9.66 mmol, d = 0.969 g/mL) was heated at 150 °C and stirred for 1 h. A solution of *t*-BuOK (1.626 g, 14.49 mmol) in THF (5 mL) was added, and the reaction mixture was stirred for 10 min. 2,4-Dimethoxybenzaldehyde **11** (0.803 g, 4.83 mmol) was slowly added, and stirring continued at room temperature for 24 h. The reaction mixture was poured into a flask with ice and water, and the yellow precipitate obtained was left stirring for 15 min. Pure compounds **12a** (1.137 g, 2.99 mmol, 62% yield) and **12b** (0.537 g, 1.26 mmol, 30% yield) were obtained as white crystals. **12a**: white crystals; mp 117.0−117.8 °C; ^{1}H NMR (400 MHz, acetone-d_6) δ 7.55 (d, J = 8.4 Hz, 1H), 7.46 (d, J = 16.4 Hz, 1H), 7.10 (d, J = 16.4 Hz, 1H), 6.89 (s, 2H), 6.60 (d, J = 2.4 Hz, 1H), 6.57 (dd, J = 8.4, 2.4 Hz, 1H), 3.93 (s, 6H), 3.90 (s, 3H), 3.83 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 160.5, 157.9, 157.9, 156.6, 138.7, 127.9, 126.4, 124.3, 118.1, 105.6, 102.7, 102.7, 98.4, 98.2, 56.3, 56.3, 55.5, 55.3; ESIMS (+) m/z 379.2 $[M + H]^+$; anal. found C, 57.04; H, 5.03; Br, 21.05; calcd for $C_{18}H_{19}BrO_4$, C, 57.01; H, 5.05; Br, 21.07. **12b**: white crystals; mp 141.5−142.4 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (d, J = 8.4 Hz, 1H), 7.37 (d, J = 16.4 Hz, 1H), 6.96 (d, J = 16.4 Hz, 1H), 6.71 (s, 2H), 6.53 (dd, J = 8.4, 2.4 Hz, 1H), 6.48 (d, J = 2.4 Hz, 1H), 3.95 (s, 6H), 3.89 (s, 3H), 3.84 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.8, 158.1, 158.1, 157.0, 138.8, 127.5, 126.6, 124.2, 119.0, 105.0, 102.8, 102.8, 99.5, 98.5, 56.5, 56.5, 55.5, 55.4; ESIMS (+) m/z 427.0 $[M + H]^+$; anal. found C, 50.69; H, 4.51; I, 29.75; calcd for $C_{18}H_{19}IO_4$, C, 50.72; H, 4.49; I, 29.77.

4,4,5,5-Tetramethyl-2-[(*E*)-3-methylbuta-1,3-dienyl]-1,3,2-dioxaborolane (13). 4,4,5,5-Tetramethyl-1,3,2-dioxaborolane **14** (0.7 mL, 4.82 mmol, d = 0.882 g/mL), 2-methylbut-1-en-3-yne **15** (0.4 mL, 4.2 mmol, d = 0.695 g/mL), bis(cyclopentadienyl)zirconium chloride hydride (Cp_2ZrHCl, 0.055 g, 0.21 mmol), and dry CH_2Cl_2 (4.5 mL) were introduced into a Schlenk tube cooled at T = 0 °C, under an argon atmosphere. The reaction mixture was stirred in the dark for 20 h at room temperature. The solution was diluted with brine and extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layers were dried over Na_2SO_4, and evaporated *in vacuo*. The crude residue was purified by flash chromatography using *n*-hexane as eluent, to give pure **13** (0.247 g, 3.74 mmol; 89% yield) as a colorless oil. **13**: colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.11 (d, J = 18.2 Hz, 1H), 5.53 (d, J = 18.2 Hz, 1H), 5.13 (s, 2H), 1.83 (s, 3H), 1.26 (s, 12H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 152.2, 143.0, 120.0, 100.0, 83.2, 83.2, 24.7, 24.7, 24.7, 24.7, 17.7.

5-[(*E*)-2-(2,4-Dimethoxyphenyl)ethenyl]-1,3-dimethoxy-2-[(*E*)-3-methylbuta-1,3-dienyl]benzene (7). In a sealed tube under an inert atmosphere were introduced 5% $Pd_2(dba)_3$ (0.017 g, 0.0195 mmol), 10% S-Phos (0.016 g, 0.039 mmol), K_3PO_4 (0.248 g, 1.17 mmol), **12a** (0.150 g, 0.39 mmol) or **12b** (0.150 g, 0.35 mmol), **13** (0.227 g, 1.17 mmol), and 1,4-dioxane (2 mL). The solution was heated at 120 °C for 16 h, and the reaction was monitored by analytical HPLC (eluent: MeCN/H_2O = 80/20). The solvent was removed *in vacuo*, and the crude residue was poured into brine and extracted with EtOAc (3 × 20 mL). The organic layers were collected, dried over Na_2SO_4, and concentrated. The crude residue was purified by preparative MPLC (eluent: *n*-hexane/EtOAc = 90:10) to give diene **7** (0.089 g, 0.24 mmol, 62% yield, from **12a**; 0.077 g, 0.21 mmol, 60% yield, from **12b**) as a yellow solid and **22** (0.009 g, 0.031 mmol, 8% yield) as a white solid. **7**: yellow, microcrystalline solid; mp 128.4−129.3 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (d, J = 8.4 Hz, 1H), 7.38 (d, J = 4.0 Hz, 1H), 7.34 (d, J = 4.0 Hz, 1H), 6.97 (d, J = 16.4 Hz, 1H), 6.87 (d, J = 16.4 Hz, 1H), 6.71 (s, 2H), 6.52 (dd, J = 8.4, 2.4 Hz, 1H), 6.48 (d, J = 2.4 Hz, 1H), 5.07 (s, 1H), 5.02 (s, 1H), 3.92 (s, 6H), 3.89 (s, 3H), 3.84 (s, 3H), 2.00 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.6, 158.5, 158.5, 158.1, 143.9, 138.1, 135.1, 127.4, 127.3, 123.3, 119.9, 119.4, 116.2, 114.0, 105.0, 102.2, 102.2, 98.5, 55.8, 55.8, 55.5, 55.4, 18.4; ESIMS (+) m/z 367.3 $[M + H]^+$; HRMS (ESI Orbitrap)

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m/z 367.1830 [M + H]$^+$ (calcd for $C_{23}H_{27}O_4$, 367.1909), 389.1730 [M + Na]$^+$ (calcd for $C_{23}H_{26}O_4Na$, 389.1729). **22**: white, microcrystalline solid; mp 129.5−131.1 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (d, J = 8.4 Hz, 1H), 7.36 (d, J = 16.4 Hz, 1H), 6.94 (d, J = 16.4 Hz, 1H), 6.67 (d, J = 2.2 Hz, 2H), 6.52 (dd, J = 8.4, 2.4 Hz, 1H), 6.47 (d, J = 2.4 Hz, 1H), 6.36 (t, J = 2.2 Hz, 1H), 3.87 (s, 3H), 3.84 (s, 3H), 3.83 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.9, 160.9, 160.6, 158.1, 140.4, 127.4, 127.0, 123.9, 119.3, 105.0, 104.4, 104.4, 99.4, 98.5, 55.5, 55.40, 55.35, 55.35; ESIMS (+) *m/z* 301.1 [M + H]$^+$.

(±)-Kuwanol E Heptamethyl Ether (2). Diene **7** (0.050 g, 0.136 mmol), dienophile **6** (0.052 g, 0.136 mmol), dry *o*-xylene (2 mL), and 1 M BH_3·THF (0.6 μL, 0.006 mmol, d = 0.87 g/mL) were introduced into a sealed tube. The mixture was heated at 100 °C for 60 h under an inert atmosphere, and the reaction was monitored by analytical HPLC (eluent: MeCN/H_2O = 70/30). After the complete disappearance of the starting materials, the reaction mixture was cooled and concentrated *in vacuo*, and the crude residue was purified by preparative MPLC (eluent: *n*-hexane/EtOAc = 80:20) to give the target *endo*-isomer **2** (0.040 g, 5.44 mmol, 40% yield) and the *exo*-isomer **3** (0.012 g, 0.016 mmol, 12% yield) as white solids. **2**: white, microcrystalline solid; mp 96.2−97.8 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.60 (s, 1H), 7.76 (d, J = 9.2 Hz, 1H), 7.47 (d, J = 8.8 Hz, 1H), 7.24 (d, J = 16.4 Hz, 1H), 6.98 (d, J = 8.0 Hz, 1H), 6.88 (d, J = 16.4 Hz, 1H), 6.54−6.48 (m, 1H), 6.50 (br ovrlp s, 2H), 6.46 (d, J = 2.4 Hz, 1H), 6.39−6.34 (m, 2H), 6.31 (dd, J = 8.4, 2.4 Hz, 1H), 5.47 (s, 1H), 5.12 (t, J = 7.2 Hz, 1H), 4.46 (br s, 2H), 4.15−4.05 (m, 1H), 3.86 (s, 3H), 3.85 (s, 3H), 3.83 (s, 3H), 3.75 (s, 3H), 3.72 (s, 3H), 3.47 (s, 6H), 3.24 (d, J = 7.2 Hz, 2H), 2.47 (dd, J = 17.8, 5.8 Hz, 1H), 2.30−2.16 (m, 1H), 1.79 (s, 3H), 1.71 (s, 3H), 1.64 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 206.2, 161.9, 161.4, 160.4, 159.2, 159.2, 158.7, 158.1, 158.0, 138.1, 132.9, 131.3, 129.2, 127.6, 127.3, 126.9, 126.9, 122.8, 122.4, 122.3, 119.6, 116.8, 116.6, 115.7, 104.9, 104.1, 102.4, 102.4, 101.0, 98.9, 98.5, 55.6, 55.49, 55.45, 55.4, 55.22, 55.22, 55.17, 48.5, 37.5, 35.1, 31.6, 25.8, 23.4, 21.5, 17.7; HRMS (ESI-Orbitrap) *m/z* 771.3482 [M + Na]$^+$ (calcd for $C_{46}H_{52}O_9Na$, 771.3509), 787.3217 [M + K]$^+$ (calcd for $C_{46}H_{52}O_9K$, 787.3243).

(±)-*exo*-Kuwanol E Heptamethyl Ether (3). Diene **7** (0.050 g, 0.136 mmol), dienophile **6** (0.052 g, 0.136 mmol), dry *o*-xylene (2 mL), and 1 M BH_3·THF (0.6 μL, 0.006 mmol, d = 0.87 g/mL) were introduced into a sealed tube. The mixture was heated at 160 °C for 24 h under an inert atmosphere, and the reaction was monitored by analytical HPLC (eluent: MeCN/H_2O = 70/30). After the complete disappearance of the starting materials, the reaction mixture was cooled and concentrated *in vacuo*, and the crude residue was purified by preparative MPLC (eluent: *n*-hexane/EtOAc = 80:20) to give the target *exo*-isomer **3** (0.043 g, 0.057 mmol, 42% yield) and the *endo*-isomer **2** (0.014 g, 0.019 mmol, 14% yield) as white solids. **3**: white, microcrystalline solid; mp 96.9−98.2 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.96 (s, 1H), 7.45 (d, J = 8.4 Hz, 1H), 7.20 (d, J = 9.6 Hz, 1H), 7.19 (d, J = 16.4 Hz, 1H), 7.00 (d, J = 8.4 Hz, 1H), 6.82 (d, J = 16.4 Hz, 1H), 6.60 (br s, 1H), 6.50 (dd, J = 8.4, 2.4 Hz, 1H), 6.46 (d, J = 2.0 Hz, 1H), 6.31 (d, J = 2.0 Hz, 1H), 6.27 (d, J = 2.0 Hz, 1H), 6.26 (dd, J = 8.4, 2.4 Hz, 1H), 5.97 (d, J = 9.2 Hz, 1H), 5.30 (s, 1H), 5.27 (br s, 1H), 5.07 (t, J = 7.2 Hz, 1H), 4.61 (br s, 1H), 4.36 (d, J = 10 Hz, 1H), 3.93 (br s, 3H), 3.87 (s, 3H), 3.83 (s, 3H), 3.80 (s, 3H), 3.69 (s, 3H), 3.67 (s, 3H), 3.53 (br s, 3H), 3.16 (d, J = 6.4 Hz, 2H), 2.40 (br s, 1H), 2.21 (br d, J = 13.2 Hz, 1H), 1.73 (s, 3H), 1.69 (s, 3H), 1.62 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 209.0, 162.3, 161.1, 160.4, 159.3, 159.3 158.8, 158.1, 157.9, 137.8, 131.2, 131.1, 129.6, 127.4, 127.2, 124.4, 122.7, 122.5, 119.5, 119.4, 115.9, 115.7, 104.9, 104.2, 103.3, 103.3, 102.2, 102.2, 100.9, 98.8, 98.4, 56.2, 55.6, 55.44, 55.39, 55.2, 53.4, 53.4, 46.8, 38.1, 37.3, 31.6, 25.7, 23.2, 21.5, 17.7; HRMS (ESI-Orbitrap) *m/z* 771.3490 [M + Na]$^+$ (calcd for $C_{46}H_{52}O_9Na$, 771.3509), 787.3224 [M + K]$^+$ (calcd for $C_{46}H_{52}O_9K$, 787.3243).

Purification of Naturally Occurring (+)-Kuwanol E (1). A crude MeOH extract of cell cultures from *Morus nigra* (100 mg) was purified by semipreparative reversed-phase HPLC (for conditions, see the General Experimental Procedures) to afford (+)-**1** as a white solid. Recovery: 8 mg (94% purity, checked by analytical HPLC, see the Supporting Information). (+)-**1**: white, amorphous solid; $[\alpha]^{20}_D$ +168 (*c* 0.1, MeOH); ^{1}H NMR (400 MHz, acetone-d_6) δ 13.00 (s, 1H), 8.42 (d, J = 9.1 Hz, 1H), 7.34 (d, J = 8.5 Hz, 1H), 7.21 (d, J = 16.4 Hz, 1H), 6.99 (d, J = 8.4 Hz, 1H), 6.76 (d, J = 16.4 Hz, 1H), 6.50 (d, J = 2.3 Hz, 1H), 6.46−6.41 (m, 3H), 6.40 (d, J = 2.3 Hz, 1H), 6.34 (dd, J = 8.5, 2.3 Hz, 1H), 6.30 (dd, J = 8.4, 2.3 Hz, 1H), 5.76 (s, 1H), 5.21−5.14 (m, 1H), 4.63−4.59 (m, 1H), 4.10−4.05 (m, 1H), 3.75−3.70 (m, 1H), 3.27 (d, J = 7.2 Hz, 2H), 2.49 (br d, J = 17.4 Hz, 1H), 2.16 (d, J = 18.1 Hz, 1H), 1.92 (s, 3H), 1.72 (s, 3H), 1.58 (s, 3H); ^{13}C NMR (101 MHz, acetone-d_6) δ 209.8, 164.7, 163.7, 159.0, 157.9, 157.5, 157.5, 156.8, 156.4, 139.1, 133.4, 132.2, 131.4, 128.7, 128.2, 126.0, 124.9, 123.8, 123.3, 122.0, 117.4, 115.8, 115.1, 113.3, 108.4, 108.3, 107.4, 106.6, 106.6, 103.6, 103.5, 47.8, 36.5, 33.1, 32.2, 25.8, 23.9, 22.2, 17.9; HRMS (ESI-Orbitrap) *m/z* 649.2460 [M − H]$^-$ (calcd for $C_{39}H_{37}O_9$, 649.2446).

(+)-Kuwanol E Heptamethyl Ether (2). A purified sample of naturally occurring (+)-kuwanol E (**1**) (4 mg, 6.15 μmol) was dissolved in acetone (1.5 mL) in a round-bottom flask containing K_2CO_3 (16.54 mg, 0.12 mmol) and $(CH_3)_2SO_4$ (0.0058 mL, 0.061 mmol, d = 1.33 g/mL). The mixture was heated at reflux for 96 h. The solvent was removed under reduced pressure, and H_2O was added. The aqueous solution was extracted with EtOAc (6 × 2 mL). The organic layers were collected, dried over Na_2SO_4, and evaporated *in vacuo*. The crude residue was purified by semipreparative HPLC (eluent: *n*-hexane/EtOAc = 80/20) to give (+)-**2** as a white solid (1.5 mg, 0.002 mmol, 33% yield). (+)-**2**: white, amorphous solid; $[\alpha]^{20}_D$ +23 (*c* 0.1, EtOH), +30 (*c* 0.1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.60 (s, 1H), 7.76 (d, J = 9.1 Hz, 1H), 7.46 (d, J = 8.4 Hz, 1H), 7.24 (d, J = 16.4 Hz, 1H), 6.98 (d, J = 8.4 Hz, 1H), 6.88 (d, J = 16.4 Hz, 1H), 6.53−6.47 (m, 1H), 6.49 (br ovrlp s, 2H), 6.46 (d, J = 2.4 Hz, 1H), 6.38−6.34 (m, 2H), 6.30 (dd, J = 8.4, 2.4 Hz, 1H), 5.46 (s, 1H), 5.11 (t, J = 7.2 Hz, 1H), 4.46 (s, 2H), 4.15−4.05 (m, 1H), 3.86 (s, 3H), 3.85 (s, 3H), 3.83 (s, 3H), 3.75 (s, 3H), 3.72 (s, 3H), 3.47 (s, 6H), 3.24 (d, J = 6.7 Hz, 2H), 2.47 (dd, J = 17.2, 6.3 Hz, 1H), 2.23 (s, 1H), 1.79 (s, 3H), 1.71 (s, 3H), 1.63 (s, 3H); HRMS (ESI-Orbitrap) *m/z* 749.3671 [M + H]$^+$ (calcd for $C_{46}H_{53}O_9$, 749.3689), 771.3489 [M + Na]$^+$ (calcd for $C_{46}H_{52}O_9Na$, 771.3509), 787.3217 [M + K]$^+$ (calcd for $C_{46}H_{52}O_9K$, 787.3243).

(±)-Kuwanol E (1). Compound **2** (20 mg, 0.027 mmol), dry CH_2Cl_2 (1.8 mL), and 1 M BBr_3 in CH_2Cl_2 (0.094 g, 0.376 mmol, d = 1.467 g/mL) were introduced into a sealed tube. The mixture was stirred at −78 °C for 120 h under an inert atmosphere. The reaction was quenched with H_2O (1 mL), extracted with EtOAc (3 × 5 mL), dried over $MgSO_4$, filtered, and concentrated. The resultant dark red solid was purified by semipreparative reversed-phase HPLC (same conditions used for (+)-**1**) to afford **1** as a white solid (3.51 mg, 0.0054 mmol, 20% yield). (±)-**1**: white, amorphous solid; ^{1}H NMR (400 MHz, acetone-d_6) δ 13.00 (s, 1H), 8.42 (d, J = 9.1 Hz, 1H), 7.34 (d, J = 8.5 Hz, 1H), 7.21 (d, J = 16.4 Hz, 1H), 6.99 (d, J = 8.5 Hz, 1H), 6.76 (d, J = 16.4 Hz, 1H), 6.50 (d, J = 2.6 Hz, 1H), 6.46−6.41 (m, 3H), 6.40 (d, J = 2.6 Hz, 1H), 6.34 (dd, J = 8.5, 2.6 Hz, 1H), 6.30 (dd, J = 8.4, 2.6 Hz, 1H), 5.76 (s, 1H), 5.22−5.13 (m, 1H), 4.64−4.58 (m, 1H), 4.05 (d, J = 7.2 Hz, 1H), 3.76−3.69 (m, 1H), 3.27 (d, J = 7.2 Hz, 2H), 2.59−2.45 (m, 1H), 2.16 (d, J = 17.5 Hz, 1H), 1.92 (s, 3H), 1.72 (s, 3H), 1.58 (s, 3H); ^{13}C NMR (101 MHz, acetone-d_6) δ 209.8, 164.7, 163.7, 159.0, 157.9, 157.5, 157.5, 156.8, 156.4, 139.1, 133.4, 132.2, 131.4, 128.7, 128.2, 126.0, 124.9, 123.8, 123.3, 122.0, 117.4, 115.8, 115.1, 113.3, 108.4, 108.3, 107.4, 106.6, 106.6, 103.6, 103.5, 47.8, 36.5, 33.1, 32.2, 25.8, 23.9, 22.2, 17.9; HRMS (ESI-Orbitrap) *m/z* 649.2443 [M − H]$^-$ (calcd for $C_{39}H_{37}O_9$, 649.2446), 1299.4952 [2M − H]$^-$ (calcd for $C_{78}H_{75}O_{18}$, 1299.4953).

(±)-Kuwanon Y Heptamethyl Ether (5). Diene **7** (0.050 g, 0.136 mmol), dienophile **9** (0.043 g, 0.136 mmol), dry *o*-xylene (2 mL), and 1 M BH_3·THF (0.6 μL, 0.006 mmol, d = 0.87 g/mL) were introduced into a sealed tube. The mixture was kept at 100 °C for 72 h under an inert atmosphere, and the reaction progress was monitored by analytical HPLC (eluent: MeCN/H_2O = 70/30). After the complete disappearance of the starting materials, the reaction mixture was cooled and concentrated *in vacuo*, and the crude residue was purified by preparative MPLC (eluent: *n*-hexane/EtOAc = 80:20) to give the *endo*-isomer **5** as a pale yellow solid (0.039 g, 0.054 mmol, 40% yield).

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5: pale yellow, amorphous solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.71 (s, 1H), 7.86 (d, J = 9.0 Hz, 1H), 7.47 (d, J = 8.5 Hz, 1H), 7.25 (d, J = 16.4 Hz, 1H), 6.97 (d, J = 8.4 Hz, 1H), 6.88 (d, J = 16.4 Hz, 1H), 6.53 (s, 2H), 6.50 (dd, J = 8.5, 2.4 Hz, 1H), 6.46 (d, J = 2.3 Hz, 1H), 6.40 (dd, J = 8.5, 2.4 Hz, 1H), 6.35 (d, J = 2.3 Hz, 1H), 6.30 (dd, J = 8.5, 2.4 Hz, 1H), 6.27 (d, J = 2.3 Hz, 1H), 5.48 (br s, 1H), 4.56−4.46 (m, 2H), 4.12 (br s, 1H), 3.86 (s, 3H), 3.83 (s, 3H), 3.79 (s, 3H), 3.74 (s, 3H), 3.72 (s, 3H), 3.52 (s, 6H), 2.43 (dd, J = 17.5, 5.6 Hz, 1H), 2.30−2.20 (m, 1H), 1.80 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 206.0, 164.83, 164.80, 160.4, 159.1, 159,1, 158.7, 158.1, 158.0, 138.2, 132.8, 131.6, 127.6, 127.3, 126.7, 126.7, 122.9, 122.3, 119.6, 116.8, 115.2, 106.3, 105.0, 104.1, 102.5, 102.5, 100.5, 98.9, 98.5, 55.5, 55.41, 55.36, 55.36, 55.26, 55.26, 55.1, 48.7, 37.5, 35.0, 31.6, 23.4; HRMS (ESI-Orbitrap) m/z 703.2878 $[M + Na]^+$ (calcd for $C_{41}H_{44}O_9Na$, 703.2859), 719.2596 $[M + K]^+$ (calcd for $C_{41}H_{44}O_9K$, 719.2622).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.jnatprod.6b00350.

1D NMR spectra of all synthesized compounds and 2D NMR spectra for compounds **2**, **3**, **5**, and **7**; HPLC chromatograms of (+)-**1** (PDF)

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Notes

The authors declare no competing financial interest.

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