

Supporting Information

Electron Transfer-Initiated Diels-Alder Cycloadditions of 2'-Hydroxychalcones

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I. General Information

A. Instrumentation and methods

¹H NMR spectra were recorded at 400 MHz at ambient temperature with CDCl₃ (Cambridge Isotope Laboratories, Inc.) as the solvent unless otherwise stated. ¹³C NMR spectra were recorded at 100.0 MHz at ambient temperature with CDCl₃ as the solvent unless otherwise stated. Chemical shifts are reported in parts per million relative to CDCl₃ (¹H, δ 7.24; ¹³C, δ 77.0). Data for ¹H NMR are reported as follows: chemical shift, integration, multiplicity (app = apparent, br = broad, par obsc = partially obscure, ovrlp = overlapping, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet) and coupling constants. All ¹³C NMR spectra were recorded with complete proton decoupling. Infrared spectra were recorded on a Nicolet Nexus 670 FT-IR spectrophotometer. High-resolution mass spectra were obtained in the Boston University Chemical Instrumentation Center using a Waters Q-TOF mass spectrometer. Melting points were recorded on a Mel-temp (Laboratory Devices). Analytical thin layer chromatography was performed using 0.25 mm silica gel 60-F plates. Flash chromatography was performed using 200-400 mesh silica gel (Sorbent Technologies, Inc.). Preparative TLC was conducted with glass backed 1000μm silica gel 60-F plates (Silicycle, Inc.) Yields refer to chromatographically and spectroscopically pure compounds, unless otherwise stated. Diels-Alder reactions at 40°C were conducted in heavy wall pressure vessels with Teflon[®] screw caps (Chemglass CG-1880, 15 mL) to minimize solvent evaporation. All other reactions were carried out in oven-dried glassware under an argon atmosphere unless otherwise noted. Analytical and preparative HPLC were performed on a Waters FractionLynx System with a Waters 600 HPLC pump, MicroMass ZQ 2000 mass spectrometer, Waters 996 diode array, and Sedere Sedex 75 ELS detector. A Sunfire[™] 4.6 x 50 mm C18 column was used for analytical HPLC and a Sunfire[™] 19 x 50 mm C18 column was used for preparative HPLC. The Arthur[™] Suite Reaction Planner (Symyx Technologies, Inc.) was used for experimental procedure planning.

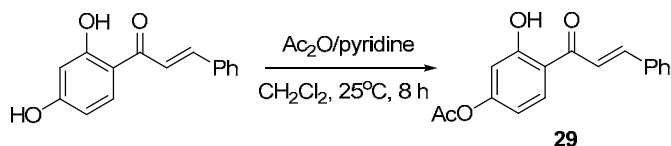
B. Reagents and solvents

HPLC grade tetrahydrofuran, methylene chloride, diethyl ether, toluene, acetonitrile, and benzene were purchased from Fisher and VWR and were purified and dried by passing through a PURE SOLV[®] solvent purification system (Innovative Technology, Inc.). Methylene chloride used for Diels-Alder cycloadditions was further purged with argon for 30 min prior to use. Anhydrous cobalt iodide and zinc iodide were purchased from Strem Chemicals. Bu₄NBH₄ was purchased from Aldrich. All other reagents were purchased from Acros, TCI America, Indofine, and Alfa Aesar, and were used as received.

II. Experimental Procedures and Compound Characterization

A. Preparation of substrates

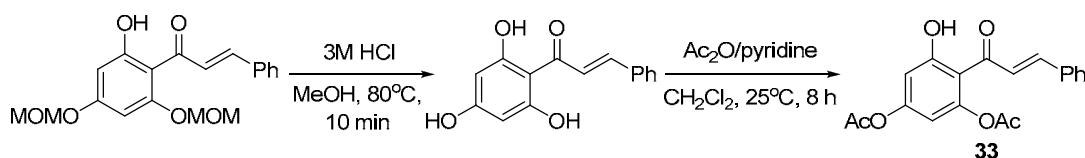
Diene **21** was synthesized according to a literature procedure.^{S1} *O*-Methylated chalcones were either purchased from commercial suppliers or synthesized *via* Claisen condensation between corresponding acetophenones and the appropriate aldehydes under basic conditions.^{S2} *O*-Acetylated chalcones were synthesized by acetylation^{S3} of the corresponding polyhydroxy chalcones.^{S4}



Acetylated chalcone 29. To a yellow solution of 2',4'-dihydroxychalcone^{S4} (94.8 mg, 0.39 mmol, 1.0 equiv.) and pyridine (100 μ L, 1.2 mmol, 3.2 equiv.) in CH_2Cl_2 (2.0 mL) was slowly added acetic anhydride (37.0 μ L, 0.39 mmol, 1.0 equiv.) at 0°C. The reaction mixture was kept at 0°C for 1 h before being warmed to room temperature (25°C) and stirred for 8 h. The reaction mixture was concentrated *in vacuo*. Purification on silica gel (10% EtOAc in hexane) afforded **29** (91.2 mg, 82%) as a yellow solid.

mp: 124-126°C; R_f : 0.25 (20% EtOAc in hexane);

^1H NMR (400 MHz, CDCl_3) δ 13.02 (1H, s), 7.92 (1H, d, $J = 8.4$ Hz), 7.91 (1H, d, $J = 15.6$ Hz), 7.64 (2H, m), 7.58 (1H, d, $J = 15.6$ Hz), 7.43 (3H, m), 6.77 (1H, d, $J = 2.0$ Hz), 6.71 (1H, dd, $J = 8.8$ Hz, 2.0 Hz), 2.30 (1H, s); ^{13}C NMR (100.0 MHz, CDCl_3) δ 192.7, 168.5, 165.1, 156.6, 145.7, 134.4, 131.0, 130.9, 129.0, 128.7, 119.9, 117.9, 112.8, 111.3, 21.2; IR ν_{max} (film): 2920, 1767, 1639, 1586, 1574, 1500, 1197 cm^{-1} ; HRMS (ESI+) m/z calculated for $\text{C}_{17}\text{H}_{15}\text{O}_4$ ($\text{M} + \text{H}^+$) 283.0970, found 283.0974.



^{S1} Baudin, J. B.; Hareau, G.; Julia, S. A.; Lorne, R.; Ruel, O. *Bull. Soc. Chim. Fr.* **1993**, 130, 856-878.

^{S2} Singh, Om V.; Muthukrishnan, M.; Sunderavivelu, M. *Indian J. Chem., Sect B* **2005**, 44, 2575-2581.

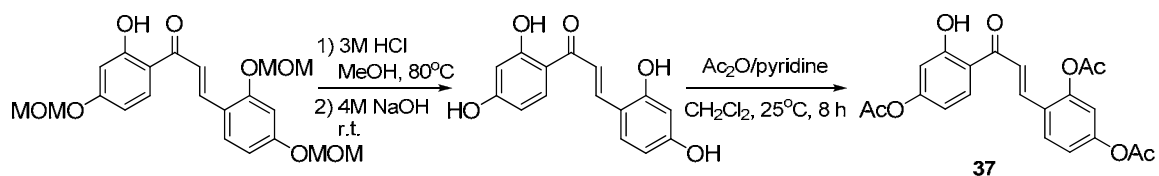
^{S3} Tian, X.; Rychnovsky, S. D. *Org. Lett.* **2007**, 9, 4955-4958.

^{S4} Jun, N.; Hong, G.; Jun, K. *Bioorg. Med. Chem.* **2007**, 15, 2396-2402.

Acetylated chalcone 33. To a stirred solution of 2'-hydroxy-4',6'-di(methoxymethoxy) chalcone^{S4} (280.5 mg, 0.81 mmol, 1.0 equiv.) in MeOH (12 mL) was slowly added 3 M HCl (8 mL) at room temperature (25°C). The resulting orange solution was refluxed at 80°C for 10 min, diluted with water, and extracted with ethyl acetate. The organic layer was successively washed with water, brine, dried over anhydrous Na₂SO₄, and evaporated under reduced pressure. The residue was dissolved in pyridine (260 μL, 3.2 mmol, 3.9 equiv.) and CH₂Cl₂ (7.0 mL). To the resulting orange solution was slowly added acetic anhydride (150 μL, 1.6 mmol, 2.0 equiv.) at 0°C. The reaction mixture was kept at 0°C for 1 h before being warmed to room temperature (25°C) and stirred for 8 h. The reaction mixture was concentrated *in vacuo*. Purification on silica gel (15% EtOAc in hexane) afforded **33** (68.0 mg, 25%) as a yellow oil.

R_f: 0.15 (20% EtOAc in hexane);

¹H NMR (400 MHz, CDCl₃) δ 12.36 (1H, s), 7.74 (1H, d, *J* = 15.6 Hz), 7.59 (2H, m), 7.46 (1H, d, *J* = 15.6 Hz), 7.41 (3H, m), 6.70 (1H, d, *J* = 2.4 Hz), 6.50 (1H, d, *J* = 2.0 Hz), 2.28 (3H, s), 2.16 (3H,s); ¹³C NMR (100.0 MHz, CDCl₃) δ 192.7, 168.3, 168.1, 164.3, 155.4, 151.3, 144.4, 134.3, 131.0, 129.2, 128.4, 125.2, 113.4, 108.8, 108.2, 21.1, 21.0; IR ν_{max} (film): 2920, 1777, 1637, 1585, 1369, 1179, 1132 cm⁻¹; HRMS (ESI+) *m/z* calculated for C₁₉H₁₇O₆ (M + H⁺) 341.1025, found 341.1010.



Acetylated chalcone 37. To a stirred solution of 2'-hydroxy-2,4,4'-tri(methoxymethoxy) chalcone^{S4} (282 mg, 0.70 mmol, 1.0 equiv.) in MeOH (6 mL) was slowly added 3 M HCl (3 mL) and the reaction was refluxed at 80°C for 10 min. To the resulting orange solution was slowly added 4 M NaOH (5 mL) at 0°C and the reaction was stirred at room temperature (25°C) for 2 h. The reaction mixture was diluted with saturated aqueous NH₄Cl, adjusted to pH 4 by adding 1 M HCl, and extracted with ethyl acetate. The organic layer was successively washed with water, brine, dried over anhydrous Na₂SO₄, and evaporated under reduced pressure. The red residue was dissolved in pyridine (200 μL, 2.5 mmol, 3.5 equiv.) and CH₂Cl₂ (5.0 mL). To the resulting orange solution was slowly added acetic anhydride (200 μL, 2.1 mmol, 3.0 equiv.) at 0°C. The reaction mixture was kept at 0°C for 1 h before being warmed to room temperature (25°C) and stirred for 8 h. The reaction mixture was

concentrated *in vacuo*. Purification on silica gel (20% EtOAc in hexane) afforded **37** (80.2 mg, 29%) as a yellow solid.

mp: 111-114°C; R_f: 0.23 (40% EtOAc in hexane);

¹H NMR (400 MHz, CDCl₃) δ 12.91 (1H, s), 7.91 (1H, d, *J* = 15.2 Hz), 7.86 (1H, d, *J* = 8.8 Hz), 7.74 (1H, d, *J* = 8.8 Hz), 7.52 (1H, d, *J* = 15.6 Hz), 7.06 (1H, dd, *J* = 8.8 Hz, 2.4 Hz), 7.02 (1H, d, *J* = 2.0 Hz), 6.76 (1H, d, *J* = 2.0 Hz), 6.69 (1H, dd, *J* = 8.8 Hz, 2.4 Hz), 2.37 (3H, s), 2.29 (3H, s), 2.28 (3H, s); ¹³C NMR (100.0 MHz, CDCl₃) δ 192.3, 168.6, 168.5, 168.4, 165.1, 156.7, 152.7, 150.2, 137.9, 130.8, 128.2, 124.8, 121.7, 119.7, 117.8, 116.8, 112.8, 111.3, 21.12, 21.06, 20.9; IR ν_{max} (film): 2926, 1766, 1641, 1584, 1500, 1369, 1190 cm⁻¹; HRMS (ESI+) *m/z* calculated for C₂₁H₁₈O₈Na (M + Na⁺) 421.0899, found 421.0879.

B. Experimental procedures for [4+2] cycloadditions

With Cobalt:

General procedure A1: To a 10 mL round-bottom flask equipped with a stirbar were added CoI₂ (6.3 mg, 0.02 mmol, 0.1 equiv) and 1,10-phenanthroline (3.6 mg, 0.02 mmol, 0.1 equiv) in a dry box. The flask was capped with a septum and removed from the dry box. Anhydrous methanol (0.5 mL) was added to the flask under an atmosphere of dry Ar. The resulting mixture was sonicated for 10 seconds and stirred vigorously at room temperature for 2 h. The methanol was removed under vacuum before the flask containing the dark brown cobalt complex was transferred into dry box. ZnI₂ (38.4 mg, 0.12 mmol, 0.6 equiv), Bu₄NBH₄ (5.1 mg, 0.02 mmol, 0.1 equiv) and CH₂Cl₂ (1.3 mL) were added consecutively to the flask. To the resulting black suspension were added 2'-hydroxychalcone derivative (0.2 mmol, 1.0 equiv) and 2,3-dimethylbutadiene **6** (250 μL, 2.2 mmol, 11 equiv). The flask was capped, sealed with Parafilm[®], and removed from the dry box. The reaction flask was sonicated for 10 seconds and stirred at room temperature (25°C) for 36 h. The reaction mixture was filtered through a short Celite[®] pad with the aid of ethyl acetate. The resulting solution was concentrated *in vacuo*. Purification using silica gel or preparative TLC (hexane: ethyl acetate) afforded the cycloaddition product.

General procedure A2: To a 10 mL round-bottom flask equipped with a stirbar were added CoI₂ (6.3 mg, 0.02 mmol, 0.1 equiv) and 1,10-phenanthroline (3.6 mg, 0.02 mmol, 0.1 equiv) in a dry box. The flask was capped with a septum and removed from the dry box. Anhydrous methanol (0.5 mL) was added to the flask under an atmosphere of dry Ar. The resulting mixture was sonicated for 10 seconds and stirred vigorously at room temperature for 2 h. The

methanol was removed under vacuum before the flask containing the dark brown cobalt complex was transferred into dry box. A 15 mL pressure vessel was charged with ZnI₂ (38.4 mg, 0.12 mmol, 0.6 equiv) and Bu₄NBH₄ (5.1 mg, 0.02 mmol, 0.1 equiv). The cobalt complex (including the stirbar in the flask) was then transferred to the pressure vessel with the aid of CH₂Cl₂ (1.3 mL) and a spatula. To the resulting black suspension were added 2'-hydroxychalcone derivative (0.2 mmol, 1.0 equiv) and diene (3.5-13 equiv.). The pressure vessel was capped, removed from the dry box, sonicated for 10 seconds, and stirred at 40°C for 36 h. The reaction mixture was filtered through a short Celite[®] pad with the aid of ethyl acetate. The resulting solution was concentrated *in vacuo*. Purification using silica gel or preparative TLC (hexane: ethyl acetate) afforded the cycloaddition product.

General procedure A3: To a 10 mL round-bottom flask equipped with a stirbar were added CoI₂ (12.6 mg, 0.04 mmol, 0.2 equiv) and 1,10-phenanthroline (14.4 mg, 0.08 mmol, 0.4 equiv) in a dry box. The flask was capped with a septum and removed from the dry box. Anhydrous methanol (0.5 mL) was added to the flask under an atmosphere of dry Ar. The resulting mixture was sonicated for 10 seconds and stirred vigorously at room temperature for 2 h. The methanol was removed under vacuum before the flask containing the light brown cobalt complex was transferred into dry box. A 15 mL pressure vessel was charged with ZnI₂ (76.8 mg, 0.24 mmol, 1.2 equiv) and Bu₄NBH₄ (10.2 mg, 0.04 mmol, 0.2 equiv). The cobalt complex (including the stirbar in the flask) was then transferred to the pressure vessel with the aid of CH₂Cl₂ (1.3 mL) and a spatula. To the resulting black suspension were added 2'-hydroxychalcone derivative (0.2 mmol, 1.0 equiv) and 2,3-dimethylbutadiene **6** (250 μL, 2.2 mmol, 11 equiv). The pressure vessel was capped, removed from the dry box, sonicated for 10 seconds, and stirred at 40°C for 36 h. The reaction mixture was filtered through a short Celite[®] pad with the aid of ethyl acetate. The resulting solution was concentrated *in vacuo*. Purification using silica gel or preparative TLC (hexane: ethyl acetate) afforded the cycloaddition product.

Without Cobalt:

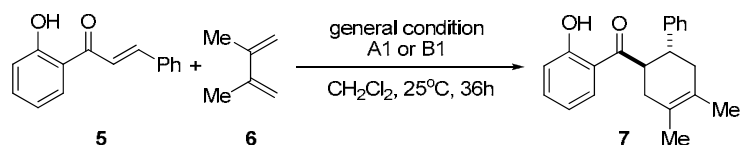
General procedure B1: To a 10 mL round-bottom flask equipped with a stirbar were added ZnI₂ (38.4 mg, 0.12 mmol, 0.6 equiv), Bu₄NBH₄ (5.1 mg, 0.02 mmol, 0.1 equiv), and CH₂Cl₂ (1.3 mL) consecutively in a dry box. To the resulting colorless suspension were added 2'-hydroxychalcone derivative (0.2 mmol, 1.0 equiv) and 2,3-dimethylbutadiene **6** (250 μL, 2.2 mmol, 11 equiv). The flask was capped with a septum, sealed with Parafilm[®], and removed from the dry box. The reaction flask was sonicated for 10 seconds and stirred at room temperature (25°C) for 36 h. The reaction mixture was filtered through a short Celite[®] pad

with the aid of ethyl acetate. The resulting solution was concentrated *in vacuo*. Purification using silica gel or preparative TLC (hexane: ethyl acetate) afforded the cycloaddition product.

General procedure B2: To a 15 mL pressure vessel equipped with a stirbar were added ZnI₂ (38.4 mg, 0.12 mmol, 0.6 equiv), Bu₄NBH₄ (5.1 mg, 0.02 mmol, 0.1 equiv), and CH₂Cl₂ (1.3 mL) consecutively in a dry box. To the resulting colorless suspension were added 2'-hydroxychalcone derivative (0.2 mmol, 1.0 equiv) and diene (3.5-13 equiv.). The pressure vessel was capped, removed from the dry box, sonicated for 10 seconds, and stirred at 40°C for 36 h. The reaction mixture was filtered through a short Celite[®] pad with the aid of ethyl acetate. The resulting solution was concentrated *in vacuo*. Purification using silica gel or preparative TLC (hexane: ethyl acetate) afforded the cycloaddition product.

General procedure B3: To a 15 mL pressure vessel equipped with a stirbar were added ZnI₂ (76.8 mg, 0.24 mmol, 1.2 equiv), Bu₄NBH₄ (10.2 mg, 0.04 mmol, 0.2 equiv), and CH₂Cl₂ (1.3 mL) consecutively in a dry box. To the resulting colorless suspension were added 2'-hydroxychalcone derivative (0.2 mmol, 1.0 equiv) and 2,3-dimethylbutadiene **6** (250 μL, 2.2 mmol, 11 equiv). The pressure vessel was capped, removed from the dry box, sonicated for 10 seconds, and stirred at 40°C for 36 h. The reaction mixture was filtered through a short Celite[®] pad with the aid of ethyl acetate. The resulting solution was concentrated *in vacuo*. Purification using silica gel or preparative TLC (hexane: ethyl acetate) afforded the cycloaddition product.

C. Counter ion Effect of Zinc Source:



ZnX₂ was used under otherwise same conditions as outlined in general procedures A1 or B1. Conversions are based on ¹H NMR integrations of H^a and H^b in **5** (δ 7.91, overlapping) and H^c in **7** (δ 7.83). The same method applies to the conversions reported in Table 1 of the paper.

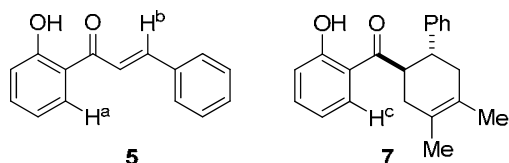


Table S1. Counter Ion Effect of Zinc Source

zinc source	condition	conversion ^a
ZnF ₂	A1	<2% ^b
	B1	<2% ^b
ZnCl ₂	A1	36%
	B1	45%
ZnBr ₂	A1	93%
	B1	43%
ZnI ₂	A1	95%
	B1	85%
Zn(OAc) ₂	A1	<2% ^b
	B1	<2% ^b
Zn(OTf) ₂	A1	5%
	B1	8%

^aBased on ¹H NMR integrations. ^bNot observed

D. Preliminary Cyclic Voltammetry Studies

All electrochemical measurements were performed using a Princeton Applied Systems Model 273 potentiostat/galvanostat in an inert atmosphere box.^{S5} All measurements were carried out in dry, distilled methylene chloride with a glassy carbon disc working electrode, a Pt wire counter electrode, and a silver wire pseudo-reference electrode.^{S6} Tetrabutylammonium tetrafluoroborate (0.5 M) was used as a supporting electrolyte. Ferrocene (0.47 V *vs.* SCE in CH₂Cl₂)^{S7} was used as an internal reference. The sample of 2'-hydroxychalcone/ZnI₂ (1:1 molar ratio) was prepared by the following procedure. To a 10 mL round bottom flask with a stirbar was added 2'-hydroxychalcone (11.6 mg, 1.0 equiv.), ZnI₂ (16.6 mg, 1.0 equiv.), and 1 mL of anhydrous CH₂Cl₂ under argon. The flask was capped with a septum, sonicated for 10 seconds, and stirred for 2 hours at room temperature (25 °C) before solvent was evaporated under vacuum. The flask containing the yellow residue was transferred to the dry box. The 2'-hydroxychalcone/ZnI₂ sample was

^{S5} The experimental setup (all samples, solutions, electrochemical cell, and electrodes) was contained within a nitrogen-filled inert atmosphere glove box. The potentiostat is located outside the glove box and is connected to the electrode leads inside the box through an 8-pin cable.

^{S6} The silver wire pseudo-reference electrode, also known as a quasi-reference electrode is a common element in non-aqueous electrochemical setups and avoids the need to carefully re-measure reference potentials when the chemical environment changes. The silver wire is coated with a thin layer of AgCl that mimics the properties of a Ag/AgCl electrode, but is not standardized, and exhibits a varying potential depending on the environment. Instead, we use the IUPAC recommended (*Pure Appl. Chem.* **1984**, 56, 461.) reference couple for non-aqueous electrochemistry, the Fe^{II}/Fe^{III} couple in ferrocene, which is well studied in a variety of solvents and whose potential been measured versus the common standard reference electrodes. All data measured were converted and reported in reference to SCE.

^{S7} Connelly, N. G.; Geiger, W. E. *Chem. Rev.* **1996**, 96, 877.

dissolved in CH_2Cl_2 and filtered through a short pad of glass wool to form a homogeneous solution that was directly used in electrochemical measurements.

Figure S1. Cyclic Voltammogram of 5 mM 2'-Hydroxychalcone in CH_2Cl_2 at 250 mV/s. (vs. SCE)

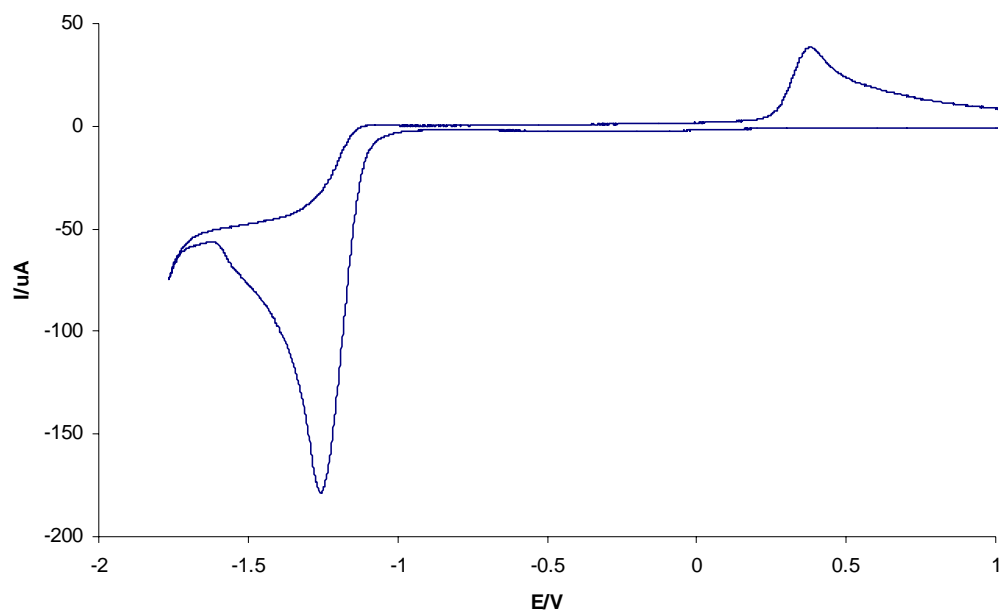


Figure S2. Cyclic Voltammogram of 5 mM 2'-Hydroxychalcone/ ZnI_2 (1:1 molar ratio) in CH_2Cl_2 at 250 mV/s. (vs. SCE)

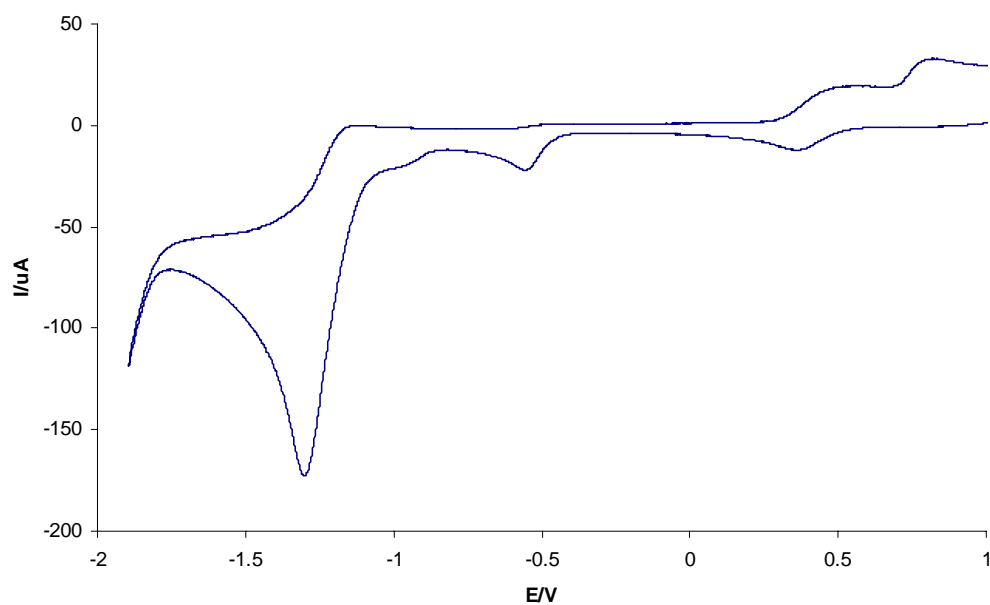
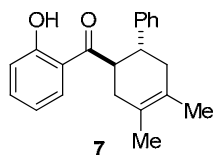


Table S2. Cyclic Voltammetry Parameters

(0.5 M Bu₄NBF₄, CH₂Cl₂, 250 mV/s, vs. SCE, average of two parallel experiments)

Condition	E _{p,c} (V)
4 mM 2'-hydroxychalcone	-1.25
4 mM 2'-hydroxychalcone/ZnI ₂ (1:1 molar ratio)	0.36, -0.59, -1.28

E. Compound Characterization



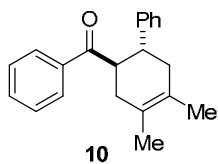
Diels-Alder adduct 7. *With cobalt:* Prepared using general procedure A1 employing 44.6 mg (0.20 mmol, 1.0 equiv.) of chalcone **5** and 250 μ L (2.2 mmol, 11 equiv.) of diene **6**. After chromatography on silica gel (5% EtOAc in hexane), the desired compound **7** (58.1 mg, 95%) was

isolated as a light yellow oil. *Without cobalt:* Prepared using general procedure B1 employing 45.0 mg (0.20 mmol, 1.0 equiv.) of chalcone **5** and 250 μ L (2.2 mmol, 11 equiv.) of diene **6**. After purification by preparative TLC (5% EtOAc in hexane), the desired compound **7** (50.6 mg, 82%) was isolated as a light yellow oil.

R_f: 0.60 (20% EtOAc in hexane);

¹H NMR (400 MHz, CDCl₃) δ 12.35 (1H, s), 7.83 (1H, dd, J = 8.0 Hz, 1.2 Hz), 7.39 (1H, ddd, J = 8.0 Hz, 8.0 Hz, 1.6 Hz), 7.16 (4H, m), 7.07 (1H, m), 6.86 (1H, d, J = 7.2 Hz), 6.85 (1H, ddd, J = 8.0 Hz, 8.0 Hz, 1.2 Hz), 4.03 (1H, ddd, J = 10.8 Hz, 10.8 Hz, 5.6 Hz), 3.29 (1H, ddd, J = 11.2 Hz, 8.4 Hz, 8.4 Hz), 2.26-2.34 (4H, m), 1.67 (6H, s); ¹³C NMR (100.0 MHz, CDCl₃) δ 209.3, 162.8, 144.3, 136.3, 129.7, 128.4, 127.1, 126.3, 125.8, 123.9, 119.2, 118.7, 118.5, 46.4, 42.5, 40.9, 37.4, 18.7, 18.6; IR ν_{max} (film): 2914, 1634, 1487, 1446, 1306, 1157, 754 cm⁻¹; HRMS (ESI+) m/z calculated for C₂₁H₂₃O₂ (M + H⁺) 307.1698, found 307.1725.

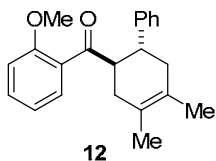
Compound **7** was also synthesized under thermal Diels-Alder conditions (neat): To a 15 mL pressure vessel equipped with a stirbar were added 110.2 mg (0.49 mmol, 1.0 equiv.) chalcone **5** and 1.0 mL (8.8 mmol, 18 equiv.) of diene **6** under argon. The pressure vessel was capped and stirred at 70°C for 5 days. The reaction mixture was concentrated *in vacuo*. Purification using silica gel (2% EtOAc in hexane) afforded the cycloadduct **7** (126.6 mg, 84%) as a light yellow oil. Characterization data for **7** synthesized under thermal Diels-Alder conditions were identical to the data reported above, therefore confirming the *trans* stereochemistry of **7** under catalyzed conditions.



Diels-Alder adduct 10. *With cobalt:* Prepared using general procedure A1 employing 42.5 mg (0.20 mmol, 1.0 equiv.) of chalcone **9** and 250 μ L (2.2 mmol, 11 equiv.) of diene **6**. After purification on preparative TLC (5% EtOAc in hexane), the desired compound **10** (22.5 mg, 38%) was isolated as a colorless solid. *Without cobalt:* Prepared using general procedure B1 employing 42.3 mg (0.20 mmol, 1.0 equiv.) of chalcone **9** and 250 μ L (2.2 mmol, 11 equiv.) of diene **6**. After purification by preparative TLC (5% EtOAc in hexane), the desired compound **10** (16.8 mg, 28%) was isolated as a colorless solid.

mp: 64-67°C; R_f : 0.60 (20% EtOAc in hexane);

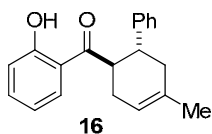
^1H NMR (400 MHz, CDCl_3) δ 7.80 (2H, dd, $J = 7.2$ Hz, 1.2 Hz), 7.46 (1H, dd, $J = 7.2$ Hz, 7.2 Hz), 7.35 (2H, m), 7.16 (4H, m), 7.04 (1H, m), 3.99 (1H, ddd, $J = 10.8$ Hz, 10.8 Hz, 5.6 Hz), 3.27 (1H, ddd, $J = 10.8$ Hz, 9.2 Hz, 7.2 Hz), 2.22-2.35 (4H, m), 1.66 (6H, s); ^{13}C NMR (100.0 MHz, CDCl_3) δ 203.5, 144.6, 137.3, 132.7, 128.4, 128.3, 128.0, 127.4, 126.1, 125.7, 124.1, 47.4, 43.0, 40.7, 36.9, 18.72, 18.65; IR ν_{max} (film): 3059, 2919, 1678, 1597, 1580, 1494, 1447 cm^{-1} ; HRMS (ESI+) m/z calculated for $\text{C}_{21}\text{H}_{22}\text{ONa}$ ($\text{M} + \text{Na}^+$) 313.1568, found 313.1594.



Diels-Alder adduct 12. *With cobalt:* Prepared using general procedure A1 employing 49.0 mg (0.21 mmol, 1.0 equiv.) of chalcone **11** and 250 μ L (2.2 mmol, 11 equiv.) of diene **6**. After purification on preparative TLC (5% EtOAc in hexane), the desired compound **12** (36.4 mg, 55%) was isolated as a colorless solid. *Without cobalt:* Prepared using general procedure B1 employing 45.7 mg (0.19 mmol, 1.0 equiv.) of chalcone **11** and 250 μ L (2.2 mmol, 11 equiv.) of diene **6**. After purification by preparative TLC (5% EtOAc in hexane), the desired compound **12** (30.9 mg, 50%) was isolated as a colorless solid.

mp: 84-85°C; R_f : 0.50 (20% EtOAc in hexane);

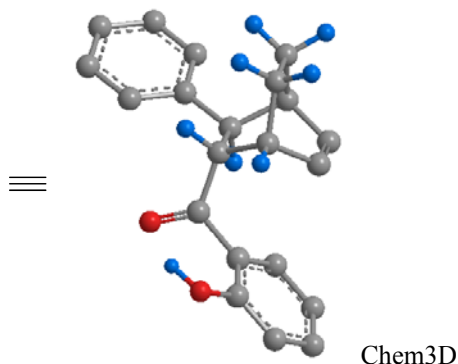
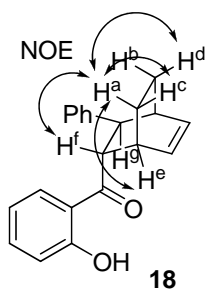
^1H NMR (400 MHz, CDCl_3) δ 7.28 (1H, dd, $J = 8.0$ Hz, 8.0 Hz), 7.11 (4H, m), 7.06 (1H, m), 6.82 (2H, m), 6.72 (1H, dd, $J = 7.2$ Hz, 7.2 Hz), 3.84 (1H, ddd, $J = 10.0$ Hz, 10.0 Hz, 6.4 Hz), 3.83 (3H, s), 3.13 (1H, ddd, $J = 10.0$ Hz, 10.0 Hz, 6.4 Hz), 2.19-2.39 (4H, m), 1.67 (3H, s), 1.64 (3H, s); ^{13}C NMR (100.0 MHz, CDCl_3) δ 207.8, 157.3, 144.5, 132.2, 130.7, 129.3, 128.0, 127.8, 126.0, 125.0, 124.6, 120.4, 110.8, 55.5, 52.5, 44.0, 40.3, 35.4, 18.8, 18.7; IR ν_{max} (film): 2910, 2837, 1676, 1598, 1485, 1436, 1244 cm^{-1} ; HRMS (ESI+) m/z calculated for $\text{C}_{22}\text{H}_{25}\text{O}_2$ ($\text{M} + \text{H}^+$) 321.1855, found 321.1828.



Diels-Alder adduct 16. *With cobalt:* Prepared using general procedure A2 employing 44.4 mg (0.20 mmol, 1.0 equiv.) of chalcone **5** and 250 μ L (2.5 mmol, 13 equiv.) of diene **15**. After chromatography on silica gel (1% EtOAc in hexane), the desired compound **16** (56.2 mg, 97%) was isolated as a light yellow solid and as a single regioisomer. *Without cobalt:* Prepared using general procedure B2 employing 45.2 mg (0.20 mmol, 1.0 equiv.) of chalcone **5** and 250 μ L (2.5 mmol, 13 equiv.) of diene **15**. After purification on preparative TLC (5% EtOAc in hexane), the desired compound **16** (39.5 mg, 67%) was isolated as a light yellow solid and as a single regioisomer. (see Part III page S27 for HMBC and HMQC NMR spectra)

mp: 95-97°C; R_f : 0.58 (20% EtOAc in hexane);

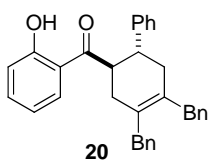
^1H NMR (400 MHz, CDCl_3) δ 12.35 (1H, s), 7.82 (1H, dd, $J = 8.0$ Hz, 1.6 Hz), 7.39 (1H, dd, $J = 7.2$ Hz, 7.2 Hz, 1.6 Hz), 7.17 (4H, m), 7.08 (1H, m), 6.86 (1H, dd, $J = 8.4$ Hz, 0.8 Hz), 6.85 (1H, ddd, $J = 7.2$ Hz, 7.2 Hz, 1.2 Hz), 5.50 (1H, br, d, $J = 2.4$ Hz), 3.97 (1H, ddd, $J = 10.4$ Hz, 10.4 Hz, 5.6 Hz), 3.34 (1H, ddd, $J = 10.4$ Hz, 10.4 Hz, 6.4 Hz), 2.22-2.44 (4H, m), 1.73 (3H, s); ^{13}C NMR (100.0 MHz, CDCl_3) δ 209.5, 162.8, 144.3, 136.2, 134.2, 129.7, 128.4, 127.2, 126.3, 119.2, 119.0, 118.7, 118.5, 45.6, 42.4, 39.1, 31.3, 23.1; IR ν_{max} (film): 2912, 1635, 1487, 1446, 1157, 753, 699 cm^{-1} ; HRMS (ESI+) m/z calculated for $\text{C}_{20}\text{H}_{20}\text{O}_2\text{Na}$ ($\text{M} + \text{Na}^+$) 315.1329, found 315.1361.



Diels-Alder adduct 18. *With cobalt:* Prepared using general procedure A2 employing 45.6 mg (0.20 mmol, 1.0 equiv.) of chalcone **5** and 250 μ L (2.5 mmol, 13 equiv.) of diene **17**. After chromatography on silica gel (2% EtOAc in hexane), the desired compound **18** (60.1 mg, 97%) was isolated as a light yellow solid and as a single *endo*-isomer. *Without cobalt:* Prepared using general procedure B2 employing 44.5 mg (0.20 mmol, 1.0 equiv.) of chalcone **5** and 250 μ L (2.5 mmol, 13 equiv.) of diene **17**. After purification on preparative TLC (5% EtOAc in hexane), the desired compound **18** (39.3 mg, 65%) was isolated as a light yellow solid and as a single *endo*-isomer.

mp: 135-138°C; R_f: 0.60 (20% EtOAc in hexane);

¹H NMR (400 MHz, CDCl₃) δ 12.39 (1H, s), 7.71 (1H, dd, *J* = 8.0 Hz, 1.6 Hz), 7.39 (1H, ddd, *J* = 7.2 Hz, 7.2 Hz, 1.6 Hz), 7.29 (4H, m), 7.20 (1H, m), 6.95 (1H, dd, *J* = 8.0 Hz, 0.8 Hz), 6.82 (1H, ddd, *J* = 7.2 Hz, 7.2 Hz, 1.2 Hz), 6.59 (1H, dd, *J* = 7.6 Hz, 7.6 Hz), 6.12 (1H, dd, *J* = 7.2 Hz, 7.2 Hz), 3.86 (1H, dd, *J* = 6.8 Hz, 1.2 Hz), 3.48 (1H, dd, *J* = 6.8 Hz, 2.0 Hz), 2.97 (1H, m), 2.70 (1H, m), 1.91 (1H, m), 1.83 (1H, m), 1.49 (1H, dddd, *J* = 12.0 Hz, 12.0 Hz, 3.6 Hz, 3.6 Hz), 1.13 (1H, m); NOED (400 MHz, CDCl₃) Irradiation at δ 1.91 (H^a): 9.1% enhancement at H^c, 2.6% enhancement at H^d, 1.5% enhancement at H^e, 2.4% enhancement at H^f; ¹³C NMR (100.0 MHz, CDCl₃) δ 206.8, 163.1, 142.3, 136.3, 136.1, 130.4, 129.7, 128.5, 128.0, 126.3, 118.74, 118.73, 118.4, 50.3, 44.5, 36.3, 35.5, 26.7, 18.2; IR ν_{max} (film): 2946, 1636, 1487, 1446, 1276, 1154, 755 cm⁻¹; HRMS (ESI+) *m/z* calculated for C₂₁H₂₁O₂ (M + H⁺) 305.1542, found 305.1570.

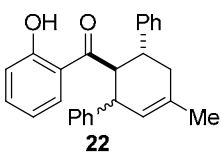


Diels-Alder adduct 20. Prepared using general procedure A2 employing 44.6 mg (0.20 mmol, 1.0 equiv.) of chalcone **5** and 188.8 mg (0.91 mmol, 4.5 equiv.) of diene **19**. After chromatography on silica gel (2% EtOAc in hexane), the desired compound **20** (90.1 mg, 99%) was isolated as a light yellow solid.

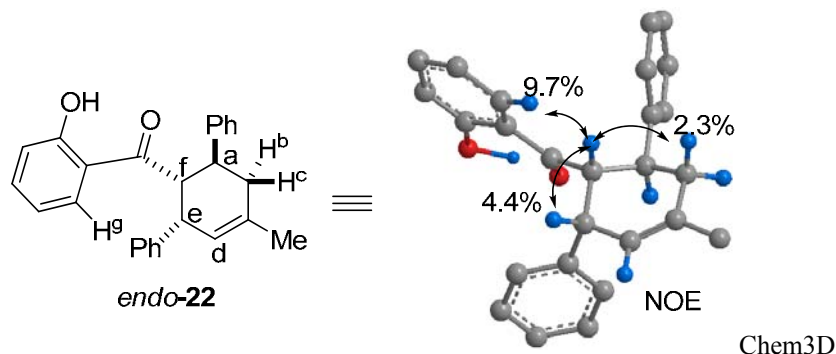
mp: 69-72°C; R_f: 0.48 (20% EtOAc in hexane);

¹H NMR (400 MHz, CDCl₃) δ 12.27 (1H, s), 7.66 (1H, dd, *J* = 8.0 Hz, 1.6 Hz), 7.33 (1H, ddd, *J* = 7.2 Hz, 7.2 Hz, 1.6 Hz), 7.28 (4H, m), 7.18 (6H, m), 7.10 (4H, m), 7.02 (1H, m), 6.81 (1H, dd, *J* = 8.0 Hz, 0.8 Hz), 6.76 (1H, ddd, *J* = 7.2 Hz, 7.2 Hz, 1.2 Hz), 3.96 (1H, ddd, *J* = 10.4 Hz, 10.4 Hz, 6.4 Hz), 3.49-3.66 (4H, m), 3.27 (1H, ddd, *J* = 10.8 Hz, 10.8 Hz, 5.6 Hz), 2.26-2.42 (4H, m); ¹³C NMR (100.0 MHz, CDCl₃) δ 209.0, 162.8, 143.8, 139.7, 139.6, 136.3, 130.8, 129.7, 129.0, 128.52, 128.50, 128.45, 128.36, 127.2, 126.3, 126.15, 126.09, 119.2, 118.7, 118.4, 46.3, 42.6, 38.8, 38.7, 38.5, 35.2; IR ν_{max} (film): 3026, 2919, 1634, 1493, 1446, 1306, 1157 cm⁻¹; HRMS (ESI+) *m/z* calculated for C₃₃H₃₀O₂Na (M + Na⁺) 481.2144, found 481.2101.

Diels-Alder adduct 22. Prepared using general procedure A2 employing 47.6 mg (0.21 mmol, 1.0 equiv.) of chalcone **5** and 106.2 mg (0.74 mmol, 3.5 equiv.) of diene **21**. After chromatography on silica gel (2% EtOAc in hexane), the desired compound **22** (75.8 mg, 97%) was isolated as a white solid which was shown to be single regioisomer and 1:1.5 mixture of *endo/exo* diastereomers (determined by ¹H NMR integration). Pure sample of each

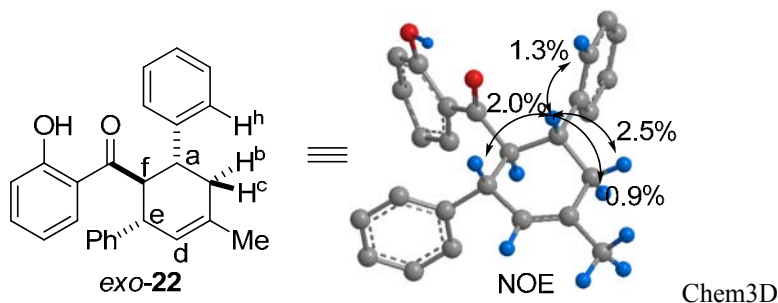


diastereomer was obtained by further separation using preparative HPLC (Sunfire™ 19 x 50 mm C18 column, gradient from 90% H₂O/9% CH₃CN/1% HCOOH to 1% H₂O/98% CH₃CN/1% HCOOH over 17 min, held to 27 min). Retention time: *endo*- isomer 14.4 min, *exo*- isomer 14.9 min.



endo-**22**: white solid. mp: 130-133°C; R_f: 0.54 (20% EtOAc in hexane);

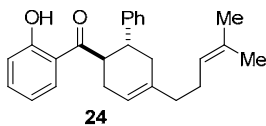
¹H NMR (400 MHz, CDCl₃) δ 11.77 (1H, s), 8.01 (1H, d, *J* = 8.0 Hz), 7.45 (1H, dd, *J* = 7.6 Hz, 7.6 Hz), 7.14-7.19 (7H, m), 7.07 (1H, m), 6.96 (1H, dd, *J* = 7.6 Hz, 7.6 Hz), 6.88 (3H, m), 5.57 (1H, br, d, *J* = 4.0 Hz), 4.43 (1H, dd, *J* = 11.2 Hz, 5.6 Hz), 3.99 (1H, br, m), 3.44 (1H, ddd, *J* = 11.6 Hz, 11.6 Hz, 6.0 Hz), 2.48 (1H, dd, *J* = 18.0 Hz, 18.0 Hz, 6.0 Hz), 2.25 (1H, dd, *J* = 18.0 Hz, 18.0 Hz, 11.2 Hz), 1.84 (3H, s); NOED (400 MHz, CDCl₃) Irradiation at δ 4.43 (H^f): 2.3% enhancement at H^c, 4.4% enhancement at H^e, 9.7% enhancement at H^g; ¹³C NMR (100.0 MHz, CDCl₃) δ 206.2, 162.5, 145.1, 139.7, 136.1, 135.1, 129.19, 129.15, 128.4, 128.0, 127.14, 127.10, 126.1, 122.1, 120.2, 118.9, 118.8, 50.5, 45.7, 40.0, 36.6, 23.2; IR ν_{max} (film): 3027, 2908, 1638, 1488, 1446, 1273, 1158 cm⁻¹; HRMS (ESI+) *m/z* calculated for C₂₆H₂₄O₂Na (M + Na⁺) 391.1674, found 391.1688.



exo-**22**: white solid. mp: 159-161°C; R_f: 0.54 (20% EtOAc in hexane);

¹H NMR (400 MHz, CDCl₃) δ 12.20 (1H, s), 6.95-7.23 (12H, m), 6.60 (1H, dd, *J* = 8.4 Hz, 0.8 Hz), 6.40 (1H, dd, *J* = 7.6 Hz, 7.6 Hz), 5.53 (1H, s), 3.89 (1H, m); 3.85 (1H, dd, *J* = 10.4 Hz, 10.4 Hz), 3.45 (1H, ddd, *J* = 10.8 Hz, 10.8 Hz, 5.2 Hz), 2.47 (1H, dd, *J* = 17.6 Hz, 11.6 Hz), 2.34 (1H, dd, *J* = 17.6 Hz, 5.2 Hz), 1.82 (3H, s); NOED (400 MHz, CDCl₃) Irradiation at δ 3.45 (H^a): 0.9% enhancement at H^b, 2.5% enhancement at H^c, 2.0% enhancement at H^e, 1.3% enhancement at H^h; ¹³C NMR (100.0 MHz, CDCl₃) δ; 210.3, 161.7, 143.4, 142.7,

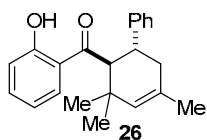
135.7, 134.3, 129.9, 128.4, 128.3, 127.7, 127.5, 126.7, 126.6, 124.5, 120.9, 118.0, 117.5, 54.2, 48.4, 44.9, 38.8, 23.2; IR ν_{\max} (film): 3024, 2907, 1630, 1621, 1490, 1443, 1157 cm^{-1} ; HRMS (ESI+) m/z calculated for $\text{C}_{26}\text{H}_{25}\text{O}_2$ ($\text{M} + \text{H}^+$) 369.1855, found 369.1834.



Diels-Alder adduct 24. Prepared using general procedure A2 employing 45.3 mg (0.20 mmol, 1.0 equiv.) of chalcone **5** and 300 μL (1.7 mmol, 8.7 equiv.) of diene **23**. After chromatography on silica gel (2% EtOAc in hexane), the desired compound **24** (70.2 mg, 96%) was isolated as a light yellow oil and as a single regioisomer. (see Part III page S33 for HMBC and HMQC NMR spectra)

R_f : 0.62 (20% EtOAc in hexane);

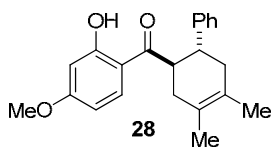
^1H NMR (400 MHz, CDCl_3) δ 12.36 (1H, s), 7.83 (1H, dd, $J = 8.0$ Hz, 1.6 Hz), 7.40 (1H, ddd, $J = 8.0$ Hz, 8.0 Hz, 1.6 Hz), 7.18 (4H, m), 7.09 (1H, m), 6.86 (2H, m), 5.52 (1H, br, d, $J = 2.8$ Hz), 5.13 (1H, dd, $J = 6.8$ Hz, 6.8 Hz), 3.99 (1H, ddd, $J = 10.8$ Hz, 10.8 Hz, 5.2 Hz), 3.33 (1H, ddd, $J = 10.8$ Hz, 10.8 Hz, 5.6 Hz), 2.27-2.48 (4H, m), 2.02-2.13 (4H, m), 1.71 (3H, s), 1.62 (3H, s); ^{13}C NMR (100.0 MHz, CDCl_3) δ 209.4, 162.8, 144.4, 137.9, 136.3, 131.7, 129.7, 128.4, 127.2, 126.3, 123.9, 119.2, 118.7, 118.54, 118.49, 45.8, 42.4, 37.6, 37.2, 31.3, 26.3, 25.7, 17.7; IR ν_{\max} (film): 3028, 2912, 1634, 1486, 1445, 1156, 752 cm^{-1} ; HRMS (ESI+) m/z calculated for $\text{C}_{25}\text{H}_{28}\text{O}_2\text{Na}$ ($\text{M} + \text{Na}^+$) 383.1987, found 383.1962.



Diels-Alder adduct 26. Prepared using general procedure A2 employing 44.7 mg (0.20 mmol, 1.0 equiv.) of chalcone **5** and 250 μL (1.9 mmol, 9.8 equiv.) of diene **25**. After purification by preparative TLC (5% EtOAc in hexane), the desired compound **26** (34.9 mg, 55%) was isolated as a white solid and as single regioisomer.

mp: 128-130 $^\circ\text{C}$; R_f : 0.65 (20% EtOAc in hexane);

^1H NMR (400 MHz, CDCl_3) δ 12.49 (1H, s), 7.86 (1H, dd, $J = 8.0$ Hz, 1.6 Hz), 7.37 (1H, ddd, $J = 8.0$ Hz, 8.0 Hz, 1.6 Hz), 7.14 (4H, m), 7.04 (1H, m), 6.83 (2H, m), 5.21 (1H, s), 3.98 (1H, d, $J = 11.6$ Hz), 3.43 (1H, ddd, $J = 11.6$ Hz, 11.6 Hz, 6.0 Hz), 2.13-2.28 (2H, m), 1.68 (3H, s), 1.04 (3H, s), 1.03 (3H, s); ^{13}C NMR (100.0 MHz, CDCl_3) δ 209.3, 162.4, 144.3, 136.1, 132.4, 130.6, 130.6, 128.3, 127.4, 126.3, 121.8, 118.5, 118.4, 54.2, 40.8, 40.0, 37.1, 31.2, 25.3, 23.0; IR ν_{\max} (film): 2960, 2925, 1734, 1632, 1487, 1445, 1277 cm^{-1} ; HRMS (ESI+) m/z calculated for $\text{C}_{22}\text{H}_{25}\text{O}_2$ ($\text{M} + \text{H}^+$) 321.1855, found 321.1854.

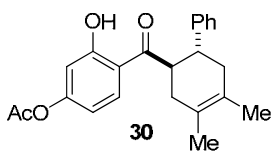


Diels-Alder adduct 28. *With cobalt:* Prepared using general procedure A3 employing 50.2 mg (0.20 mmol, 1.0 equiv.) of chalcone **27** and 250 μ L (2.2 mmol, 11 equiv.) of diene **6**. After purification on preparative TLC (12% EtOAc in hexane), the desired compound **28** (44.9 mg, 68%) was isolated as a yellow oil.

Without cobalt: Prepared using general procedure B3 employing 50.7 mg (0.20 mmol, 1.0 equiv.) of chalcone **27** and 250 μ L (2.2 mmol, 11 equiv.) of diene **6**. After purification by preparative TLC (10% EtOAc in hexane), the desired compound **28** (23.9 mg, 36%) was isolated as a yellow oil.

R_f: 0.50 (20% EtOAc in hexane);

¹H NMR (400 MHz, CDCl₃) δ 12.89 (1H, s), 7.72 (1H, d, J = 9.2 Hz), 7.16 (4H, m), 7.07 (1H, m), 6.38 (1H, dd, J = 8.8 Hz, 2.8 Hz), 6.30 (1H, d, J = 2.8 Hz), 3.90 (ddd, 1H, J = 11.2 Hz, 11.2 Hz, 5.2 Hz), 3.78 (3H, s), 3.27 (ddd, 1H, J = 10.8 Hz, 8.4 Hz, 8.4 Hz), 2.20-2.40 (4H, m), 1.66 (6H, s); ¹³C NMR (100.0 MHz, CDCl₃) δ 207.2, 165.9, 165.8, 144.4, 131.3, 128.4, 127.2, 126.2, 125.8, 124.0, 113.5, 107.5, 100.9, 55.5, 46.2, 42.6, 40.9, 37.4, 18.7, 18.6; IR ν_{max} (film): 2919, 1624, 1508, 1442, 1376, 1239, 1209 cm⁻¹; HRMS (ESI+) m/z calculated for C₂₂H₂₅O₃ (M + H⁺) 337.1804, found 337.1800.



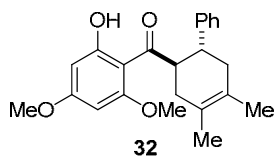
Diels-Alder adduct 30. *With cobalt:* Prepared using general procedure A3 employing 56.7 mg (0.20 mmol, 1.0 equiv.) of chalcone **29** and 250 μ L (2.2 mmol, 11 equiv.) of diene **6**. After chromatography on silica gel (5% EtOAc in hexane), the desired compound **30** (61.8 mg, 84%) was isolated as a colorless oil.

Without cobalt: Prepared using general procedure B3 employing 53.1 mg (0.19 mmol, 1.0 equiv.) of chalcone **29** and 250 μ L (2.2 mmol, 11 equiv.) of diene **6**. After purification by preparative TLC (15% EtOAc in hexane), the desired compound **30** (37.2 mg, 54%) was isolated as a colorless oil.

R_f: 0.40 (20% EtOAc in hexane);

¹H NMR (400 MHz, CDCl₃) δ 12.53 (1H, s), 7.82 (1H, d, J = 8.4 Hz), 7.15 (4H, m), 7.07 (1H, m), 6.61 (2H, m), 3.94 (ddd, 1H, J = 10.8 Hz, 10.8 Hz, 5.6 Hz), 3.27 (ddd, 1H, J = 11.2 Hz, 8.4 Hz, 8.4 Hz), 2.26 (3H, s), 2.22-2.36 (4H, m), 1.65 (6H, s); ¹³C NMR (100.0 MHz, CDCl₃) δ 208.3, 168.5, 164.4, 156.4, 144.2, 131.0, 128.5, 127.1, 126.3, 125.9, 123.8, 117.2, 112.6, 111.1, 46.7, 42.5, 40.8, 37.4, 21.2, 18.7, 18.6; IR ν_{max} (film): 3027, 2911, 1764, 1633, 1495, 1368, 1184 cm⁻¹; HRMS (ESI+) m/z calculated for C₂₃H₂₄O₄Na (M + Na⁺) 387.1572,

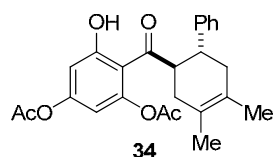
found 387.1554.



Diels-Alder adduct 32. Prepared using general procedure A3 employing 58.5 mg (0.21 mmol, 1.0 equiv.) of chalcone **31** and 250 μ L (2.2 mmol, 11 equiv.) of diene **6**. After purification by preparative TLC (15% EtOAc in hexane), the desired compound **32** (25.0 mg, 33%) was isolated as a yellow solid.

mp: 119-120°C; R_f : 0.42 (20% EtOAc in hexane);

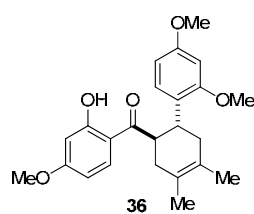
^1H NMR (400 MHz, CDCl_3) δ 13.70 (1H, s), 7.14 (4H, m), 7.06 (1H, m), 5.92 (1H, d, $J = 2.4$ Hz), 5.88 (1H, d, $J = 2.4$ Hz), 4.30 (1H, ddd, $J = 10.8$ Hz, 10.8 Hz, 5.6 Hz), 3.88 (3H, s), 3.75 (3H, s), 3.24 (1H, ddd, $J = 10.8$ Hz, 10.8 Hz, 6.4 Hz), 2.17-2.34 (4H, m), 1.66 (3H, s), 1.64 (3H, s); ^{13}C NMR (100.0 MHz, CDCl_3) δ 208.5, 167.5, 165.6, 162.2, 145.3, 128.2, 127.2, 125.9, 125.2, 124.5, 106.4, 93.5, 90.9, 55.7, 55.5, 50.9, 43.1, 41.3, 36.6, 18.74, 18.69; IR ν_{max} (film): 2917, 1618, 1582, 1416, 1208, 1159, 1114 cm^{-1} ; HRMS (ESI+) m/z calculated for $\text{C}_{23}\text{H}_{26}\text{O}_4\text{Na}$ ($\text{M} + \text{Na}^+$) 389.1729, found 389.1691.



Diels-Alder adduct 34. Prepared using general procedure A3 employing 46.1 mg (0.14 mmol, 1.0 equiv.) of chalcone **33** and 250 μ L (2.2 mmol, 16 equiv.) of diene **6**. After purification by preparative TLC (20% EtOAc in hexane), the desired compound **34** (41.0 mg, 72%) was isolated as a colorless oil.

R_f : 0.25 (20% EtOAc in hexane);

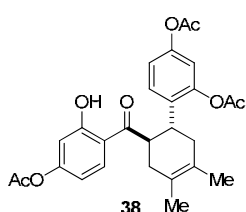
^1H NMR (400 MHz, CDCl_3) δ 12.26 (1H, s), 7.15 (2H, m), 7.07 (3H, m), 6.48 (1H, d, $J = 2.4$ Hz), 6.46 (1H, d, $J = 2.4$ Hz), 3.90 (1H, ddd, $J = 10.8$ Hz, 10.8 Hz, 4.8 Hz), 3.20 (1H, ddd, $J = 10.8$ Hz, 10.8 Hz, 6.0 Hz), 2.32 (3H, s), 2.24 (3H, s), 2.19-2.37 (4H, m), 1.68 (3H, s), 1.64 (3H, s); ^{13}C NMR (100.0 MHz, CDCl_3) δ 208.3, 168.2, 168.0, 164.3, 154.9, 151.0, 143.9, 128.4, 127.0, 126.3, 126.0, 123.7, 112.8, 108.6, 108.2, 51.9, 43.9, 41.3, 36.4, 21.2, 18.7, 18.6; IR ν_{max} (film): 2917, 1777, 1632, 1419, 1370, 1174, 1133 cm^{-1} ; HRMS (ESI+) m/z calculated for $\text{C}_{25}\text{H}_{26}\text{O}_6\text{Na}$ ($\text{M} + \text{H}^+$) 445.1627, found 445.1636.



Diels-Alder adduct 36. Prepared using general procedure A3 employing 61.6 mg (0.20 mmol, 1.0 equiv.) of chalcone **35** and 250 μ L (2.2 mmol, 11 equiv.) of diene **6**. After purification by preparative TLC (15% EtOAc in hexane), the desired compound **36** (14.3 mg, 18%) was isolated as a yellow oil.

R_f: 0.52 (40% EtOAc in hexane);

¹H NMR (400 MHz, CDCl₃) δ 12.99 (1H, s), 7.83 (1H, d, *J* = 9.2 Hz), 6.93 (1H, d, *J* = 8.4 Hz), 6.39 (1H, dd, *J* = 9.2 Hz, 2.8 Hz), 6.32 (2H, d, *J* = 2.4 Hz), 6.28 (1H, dd, *J* = 8.4 Hz, 2.8 Hz), 4.11 (1H, ddd, *J* = 10.4 Hz, 10.4 Hz, 5.2 Hz), 3.78 (3H, s), 3.75 (3H, s), 3.70 (3H, s), 3.47 (1H, ddd, *J* = 10.4 Hz, 10.4 Hz, 5.6 Hz), 2.28 (2H, m), 2.17 (2H, m), 1.64 (6H, s); ¹³C NMR (100.0 MHz, CDCl₃) δ 207.9, 165.8, 165.7, 159.0, 158.0, 131.5, 128.5, 125.9, 124.7, 124.0, 113.6, 107.3, 104.1, 100.8, 98.8, 55.5, 55.3, 55.2, 44.8, 38.5, 37.8, 37.0, 18.71, 18.67; IR ν_{max} (film): 2911, 1615, 1586, 1506, 1239, 1208, 1156 cm⁻¹; HRMS (ESI+) *m/z* calculated for C₂₄H₂₈O₅Na (M + H⁺) 419.1834, found 419.1838.

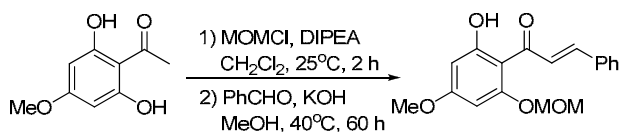


Diels-Alder adduct 38. Prepared using general procedure A3 employing 72.1 mg (0.18 mmol, 1.0 equiv.) of chalcone **37** and 250 μL (2.2 mmol, 12 equiv.) of diene **6**. After purification on preparative TLC (25% EtOAc in hexane), the desired compound **38** (52.7 mg, 61%) was isolated as a colorless oil.

R_f: 0.28 (40% EtOAc in hexane);

¹H NMR (400 MHz, CDCl₃) δ 12.40 (1H, s), 7.81 (1H, d, *J* = 9.2 Hz), 7.12 (1H, d, *J* = 8.4 Hz), 6.84 (2H, m), 6.63 (2H, m), 3.94 (1H, ddd, *J* = 10.8 Hz, 8.0 Hz, 8.0 Hz), 3.20 (1H, ddd, *J* = 10.8 Hz, 10.8 Hz, 5.6 Hz), 2.35 (3H, s), 2.27 (3H, s), 2.20 (3H, s), 2.10-2.32 (4H, m, overlapping), 1.64 (6H, s); ¹³C NMR (100.0 MHz, CDCl₃) δ 207.4, 169.1, 168.8, 168.5, 164.5, 156.5, 148.8, 148.5, 133.5, 130.8, 127.0, 125.9, 123.7, 119.3, 117.0, 116.2, 112.7, 111.3, 46.3, 39.3, 37.3, 34.8, 21.12, 21.11, 21.07, 18.62, 18.60; IR ν_{max} (film): 2915, 1763, 1634, 1499, 1369, 1190 cm⁻¹; HRMS (ESI+) *m/z* calculated for C₂₇H₂₈O₈Na (M + H⁺) 503.1682, found 503.1642.

F. Total synthesis of nicolaioidesin C

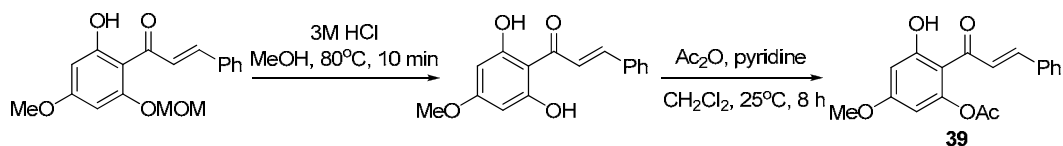


2'-Hydroxy-4'-methoxy-6'-methoxymethoxychalcone. To a stirred solution of 2',6'-dihydroxy-4'-methoxyacetophenone (94.5 mg, 0.52 mmol, 1.0 equiv.) in CH₂Cl₂ (2.0 mL) was added *N,N*-diisopropylethylamine (220 μL, 1.26 mmol, 2.4 equiv.) at 0°C. The resulting

light yellow mixture was stirred for 10 min before MOMCl (60.0 μ L, 0.79 mmol, 1.5 equiv.) was added dropwise. The reaction was kept at 0°C for 10 min, warmed to room temperature (25°C), and stirred for 2 hours. The reaction was quenched by addition of saturated aqueous NH₄Cl, extracted with EtOAc, washed with brine, dried over Na₂SO₄ and concentrated *in vacuo*. To the pale yellow residue was added MeOH (3.0 mL) and benzaldehyde (80.0 mL, 0.79 mmol, 1.5 equiv.), followed by slow addition of a KOH solution (305 mg KOH dissolved in 0.5 mL H₂O). The resulting yellow solution was stirred at 40°C for 3 days. The reaction was diluted with saturated aqueous NH₄Cl, adjusted to pH 4 by adding 1 M HCl, extracted with EtOAc, washed with brine, dried over Na₂SO₄ and concentrated *in vacuo*. Purification on silica gel (10% EtOAc in hexane) afforded the title compound (144.9 mg, 89% for two steps) as an orange solid.

mp: 71-74°C; R_f: 0.30 (20% EtOAc in hexane);

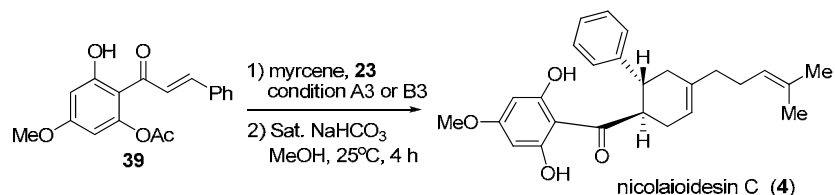
¹H NMR (400 MHz, CDCl₃) δ 14.04 (1H, s), 7.92 (1H, d, *J* = 16.0 Hz), 7.77 (1H, d, *J* = 15.6 Hz), 7.59 (2H, m), 7.38 (3H, m), 6.14 (2H, s), 5.27 (2H, s), 3.81 (3H, s), 3.51 (3H, s); ¹³C NMR (100.0 MHz, CDCl₃) δ 192.7, 167.9, 166.0, 159.8, 142.4, 135.4, 130.2, 128.9, 128.3, 127.3, 106.8, 95.0, 94.8, 94.0, 56.8, 55.6; IR ν_{max} (film): 2940, 1617, 1561, 1340, 1212, 1154 cm⁻¹; HRMS (ESI+) *m/z* calculated for C₁₈H₁₉O₅ (M + H⁺) 315.1232, found 315.1221.



Acetylated chalcone 39. To a suspension of 2'-hydroxy-4'-methoxy-6'-methoxymethoxy chalcone (196.6 mg, 0.63 mmol, 1.0 equiv.) in 10 mL MeOH was added 3M HCl (4 mL) dropwise. The resulting orange suspension was refluxed at 80°C for 10 min. The reaction mixture was cooled to ambient temperature, diluted with water, extracted with EtOAc, washed with brine, dried over Na₂SO₄ and concentrated *in vacuo*. To the orange residue was added CH₂Cl₂ (5.0 mL) and pyridine (55.0 μ L, 0.68 mmol, 1.1 equiv.), then acetic anhydride (59.0 μ L, 0.63 mmol, 1.0 equiv.) was added dropwise at 0°C. The resulting orange solution was kept at 0°C for 1 h, warmed to room temperature (25°C) and stirred overnight (8 h). The reaction mixture was concentrated *in vacuo*. Purification on silica gel (15% EtOAc in hexane) afforded the acetylated chalcone **39** (162.4 mg, 83% for two steps) as a yellow solid.

mp: 119-121°C; R_f: 0.22 (20% EtOAc in hexane);

^1H NMR (400 MHz, CDCl_3) δ 13.07 (1H, s), 7.70 (1H, d, $J = 15.6$ Hz), 7.58 (2H, m), 7.50 (1H, d, $J = 15.6$ Hz), 7.40 (3H, m), 6.37 (1H, d, $J = 2.4$ Hz), 6.18 (1H, d, $J = 2.4$ Hz), 3.81 (3H, s), 2.16 (3H, s); ^{13}C NMR (100.0 MHz, CDCl_3) δ 192.1, 168.6, 166.3, 165.2, 152.1, 143.4, 134.6, 130.6, 129.1, 128.2, 125.5, 109.4, 103.0, 99.2, 55.7, 21.1; IR ν_{max} (film): 2941, 1770, 1621, 1564, 1343, 1149 cm^{-1} ; HRMS (ESI+) m/z calculated for $\text{C}_{18}\text{H}_{16}\text{O}_5\text{Na}$ ($\text{M} + \text{Na}^+$) 335.0895, found 335.0896.



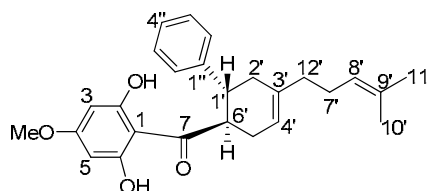
Nicolaioidesin C (4). *With Cobalt:* Using general procedure A3 employing 62.6 mg (0.20 mmol, 1.0 equiv.) of chalcone **39** and 300 μL (1.7 mmol, 8.7 equiv.) of diene **23**. After stirred at 40°C for 36 h, the reaction mixture was filtered through a short Celite[®] pad with the aid of ethyl acetate. The solvents were removed *in vacuo*. To the brown residue was added 2 mL of MeOH and 2 mL of saturated aqueous NaHCO_3 . The resulting pale yellow suspension was stirred at room temperature (25°C) for 4 h. The reaction mixture was adjusted to pH 4 by adding 1 M HCl, extracted with EtOAc, washed with brine, dried over Na_2SO_4 , and concentrated *in vacuo*. Purification on preparative TLC (15% EtOAc in hexane) afforded **4** (42.5 mg, 52% for two steps) as a light yellow solid.

Without Cobalt: Using general procedure B3 employing 64.4 mg (0.20 mmol, 1.0 equiv.) of chalcone **39** and 300 μL (1.7 mmol, 8.7 equiv.) of diene **23**. After stirred at 40°C for 36 h, the reaction mixture was filtered through a short Celite[®] pad with the aid of ethyl acetate. The solvents were removed *in vacuo*. To the dark yellow residue was added 2 mL of MeOH and 2 mL of saturated aqueous NaHCO_3 . The resulting pale yellow suspension was stirred at room temperature (25°C) for 4 h. The reaction mixture was adjusted to pH 4 by adding 1 M HCl, extracted with EtOAc, washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. Purification on preparative TLC (15% EtOAc in hexane) afforded **4** (12.6 mg, 15% for two steps) as a light yellow solid.

mp: 104-108°C; R_f : 0.18 (20% EtOAc in hexane);

IR ν_{max} (film): 3277 (br), 2913, 1624, 1581, 1424, 1205, 1159 cm^{-1} ; HRMS (ESI+) m/z calculated for $\text{C}_{26}\text{H}_{31}\text{O}_4$ ($\text{M} + \text{H}^+$) 407.2222, found 407.2239.

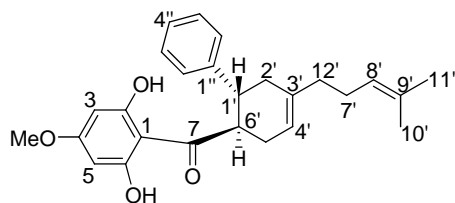
Table S3. ^1H NMR for Synthetic Nicolaoidesin C Compared with Literature Data^{S8}



Position	δ ($J_{\text{H-H}}$ in Hz)	
	literature (500 MHz, CDCl_3)	synthetic (400 MHz, CDCl_3)
3/5	5.84 (s)	5.83 (s)
1'	3.30 (ddd, $J = 11, 11, 6.1$)	3.29 (ddd, $J = 11.2, 11.2, 5.6$)
2'	2.27, 2.17 (overlapping)	2.15-2.28 (overlapping)
4'	5.51 (br, s)	5.49 (br, d, $J = 4.0$)
5'a	2.24 (overlapping)	2.15-2.28 (overlapping)
5'b	2.55 (dt, $J = 17, 5.2$)	2.56 (ddd, $J = 16.8, 4.8, 4.8$)
6'	4.41 (ddd, $J = 11, 11, 4.8$)	4.48 (ddd, $J = 10.8, 10.8, 5.2$)
7'	2.01, 2.09 (overlapping)	1.99, 2.07 (overlapping)
8'	5.11 (t, $J = 6.8$)	5.09 (dd, $J = 6.8, 6.8$)
10'	1.61 (s)	1.58 (s)
11'	1.69 (s)	1.67 (s)
12'	2.01, 2.09 (overlapping)	1.99, 2.07 (overlapping)
2''/6''	7.18-7.26 (overlapping)	7.15-7.22 (overlapping)
3''/5''	7.18-7.26 (overlapping)	7.15-7.22 (overlapping)
4''	7.09 (m)	7.08 (m)
OMe-4	3.75 (s)	3.71 (s)
OH-2	---	not detected
OH-6	---	not detected

^{S8}Gu, J-Q; Park, E. J.; Vigo, J. S.; Graham, J. G.; Fong, H. H. S.; Pezzuto, J. M.; Kinghorn, A. D. *J. Nat. Prod.* **2002**, 65, 1616-1620.

Table S4. ^{13}C NMR for Synthetic Nicolaoidesin C Compared with Literature Data^{S6}



Position	δ	
	literature (125 MHz, CDCl_3)	synthetic (100 MHz, CDCl_3)
1	107.5	105.3
2	not detected	163.0 (weak signal)
3/5	94.5	94.4
4	165.3	165.4
6	not detected	163.2 (weak signal)
7	208.5	208.8
1'	42.7	42.7
2'	38.2	38.2
3'	137.6	137.5
4'	119.2	119.2
5'	30.7	30.7
6'	50.1	50.0
7'	37.3	37.3
8'	124.2	124.1
9'	131.6	131.6
10'	17.7	17.7
11'	25.7	25.7
12'	26.4	26.4
1''	145.2	145.5
2''/6''	127.3	127.2
3''/5''	128.3	128.3
4''	126.0	126.0
OMe-4	55.5	55.4

III. Select NMR Spectra

