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Article

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Total Synthesis of (±)-Brazilin

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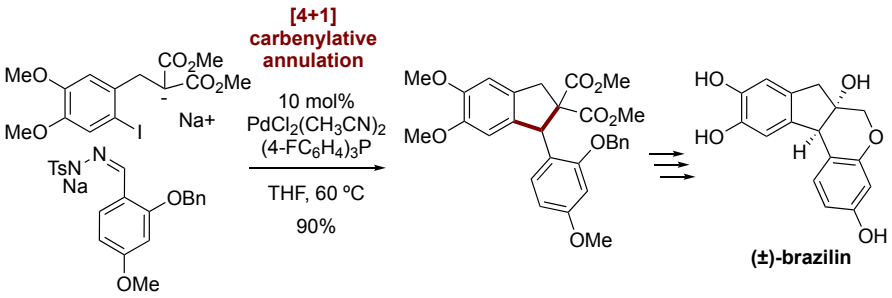


Abstract

Palladium-catalyzed carbene insertion was utilized in a formal synthesis of (±)-picropodophyllone and a total synthesis of (±)-brazilin. All prior syntheses of brazilin have involved a Friedel–Crafts alkylation in the key carbon-carbon bond forming events. The palladium-catalyzed [4+1] reaction generates a 1-arylindane with all of the functionality needed for formation of the indano[2,1-*c*]chroman ring system of brazilin. The synthesis of (±)-brazilin was achieved in 11 steps (longest linear sequence) with an overall 11% yield.

Introduction

Extracts from the heartwood of *Caesalpinia sappan* have been used as natural dyes for over two millennia.[1,2] The correct indano[2,1-*c*]chroman structure of brazilin, a major constituent of sappanwood extracts, was not determined until 1908 (Figure 1).[3] Under ambient conditions,

brazilin undergoes facile oxidation to the chromophore brazilein A. The related indano[2,1-*c*]chroman haematoxylin, is still used as a principal tissue stain, and undergoes a similar oxidation to hematein. Sappanwood extracts are used in traditional Asian medicine and have been the subject of continuous and extensive biological studies.[4] Brazilin has been studied for the treatment of diabetes,[5] arthritis,[6] and various cancer types.[7]

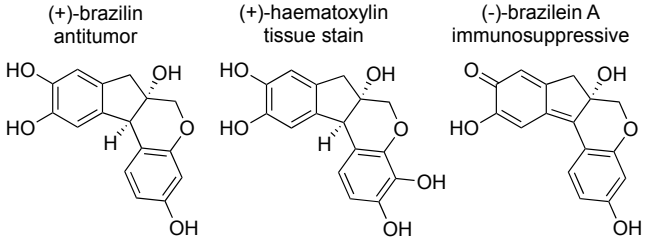


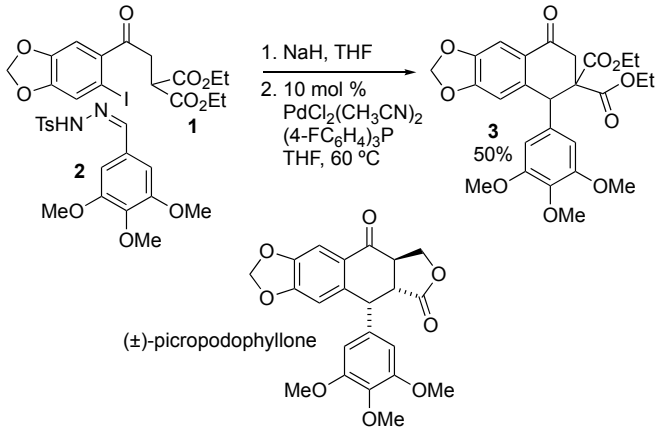
Figure 1. Brazilin and related bioactive indano[2,1-*c*]chromans.

Perkin and Robinson first reported the synthesis of the brazilin indano[2,1-*c*]chroman ring system using a biomimetic[4b,8] Friedel–Crafts cyclization[9,10,11] to form the five-membered indane[12,13,14] or the six-membered pyran ring.[15,16,17 18] Yadav and co-workers add the aryl ring to an indane core using an intermolecular Friedel–Crafts followed by cyclization to form the six-membered pyran.[19] Alternative synthetic strategies could broaden access to derivatives with improved activity so we were prompted to investigate an alternative synthesis of brazilin through a non-obvious disconnection. In 2014, we developed palladium-catalyzed [5+1] and [4+1] carbene insertions of aryl iodides and *N*-tosylhydrazones which gave access to the 1-aryltetralin and 1-arylindane cores present in natural products such as podophyllotoxin and brazilin, respectively.[20]

When the [5+1] palladium-catalyzed carbene insertion was applied to aryl iodide **1** and *N*-tosylhydrazone **2**, it generated 1-aryltetralin derivative **3** which is a key intermediate in the Kende syntheses of (±)-picropodophyllone and (±)-podophyllotoxin (Scheme 1).[21] Given the modest

yield for the [5+1] annulation reaction and the difficulty of removing azine side product, we set out to explore the applicability of the [4+1] palladium-catalyzed carbene insertion to a total synthesis of (±)-brazilin.

Scheme 1. Formal synthesis of (±)-picropodophyllone using a [5+1] palladium-catalyzed carbene insertion.



During our initial development of the palladium-catalyzed [4+1] carbenylative annulation we found that *ortho*-oxygenation on the *N*-tosylhydrazone was slightly detrimental to the yield, whereas oxygenation on the aryl iodide was slightly beneficial, as exemplified by previously published yields for arylindanes **6** and **7**, respectively (Figure 2).[20,22] These substituent effects appear to counter each other leading to useful yields of highly oxygenated 1-arylindanes **8aa–8ba** (Figure 2). Valdés and coworkers have successfully employed oxygenated *N*-tosylhydrazones in [4+1] carbenylative Heck reactions.[23] *N*-Tosylhydrazones with bromine substituents are well-tolerated in these reactions,[20] providing the opportunity for further late stage functionalizations.

Broadened peaks and a minor impurity were particularly apparent in the ^{1}H NMR spectra of 1-arylindanes **8ba** and **8bb** in spite of chromatographic homogeneity under all conditions tested. Counter to the expectations of $A_{1,3}$ strain, these hindered compounds, and some of the 1-arylindanes described later, appear to exist as two conformers based on the presence of two sets of

broadened peaks in the ^{1}H NMR spectra in a *ca* 5:1 ratio. For 1-arylindane **8bb**, the peaks converge at 110–120 °C and sharpen into well-resolved signals at 0 °C in DMF-d_7 (see supporting information). Two low energy conformers of **8bb** were identified with MMFF94 and shown to be different in energy by 0.78 kcal/mol at the b3lyp/6-31G(d) level of theory (supporting information). In the lowest energy conformer, $A_{1,3}$ strain is minimized by the syn orientation of the BnO group with the methine C–H,[24] but the aryl substituent ends up in a hindered pseudoaxial position. In the higher energy conformer, the aryl substituent is pseudoequatorial, but is not oriented to minimize $A_{1,3}$ strain. The requirement for a half-chair flip and rotation about the highly congested aryl-indanyl bond could result in an energy barrier significant enough to explain the broadening of peaks between 60 °C and 100 °C. In a 1-D gradient NOE experiment, irradiation of the *O*-benzyl methylene protons at 5.12 ppm in the major conformer of 1-arylindane **8bb** at 0 °C in $CDCl_3$, led to a reduction in signal of the *O*-benzyl methylene protons at 4.64 ppm in the minor conformer, consistent with conformational interconversion (see supporting information for spectra).[25]

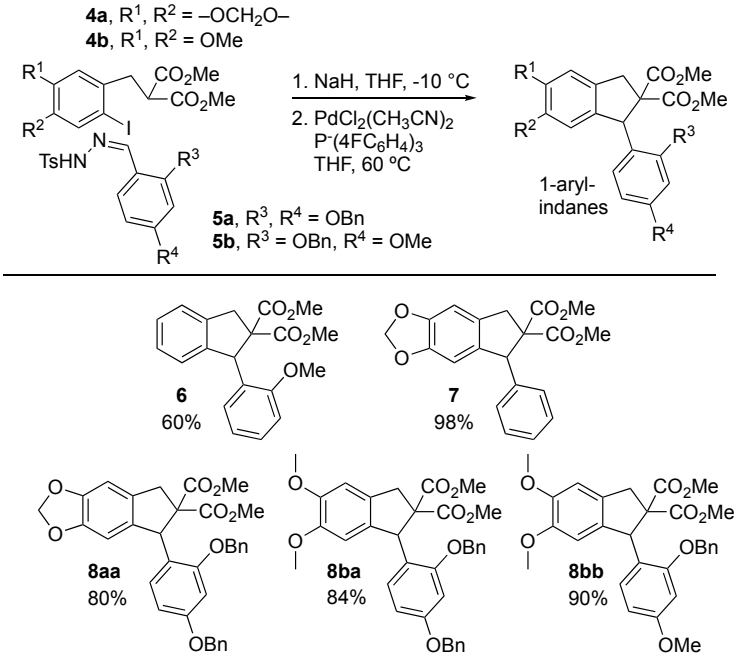
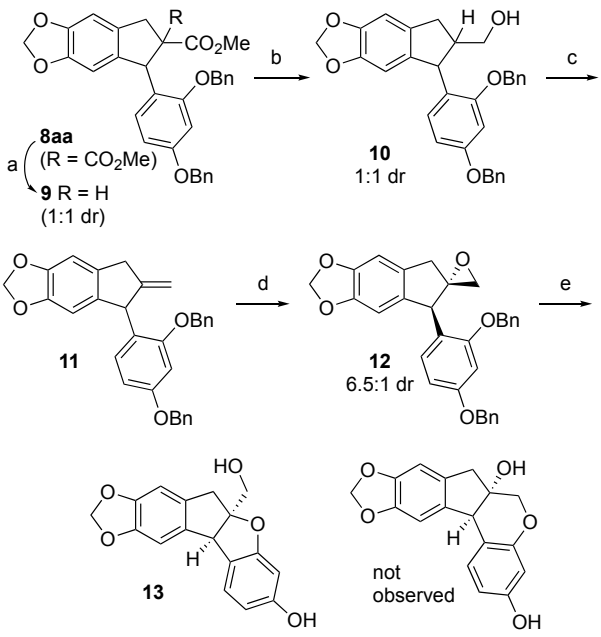


Figure 2. Palladium-catalyzed insertion of oxygenated aryl iodides and *N*-tosylhydrazones.

With access to a number of *O*-protected 1-arylindane intermediates we set out to remove the vestigial carboxymethyl group and close the dihydropyran ring (Scheme 2). Intramolecular cyclization under either neutral or basic conditions should favor 6-endo-*tet* cyclization[26] on the less substituted position of a 1,1-disubstituted epoxide. Krapcho decarboxylation of geminal diester **8aa** generated a 1:1 mixture of carboxymethyl epimers (**9**) that were reduced to primary alcohol **10** as a mixture of isomers. Initial attempts to eliminate the alcohol via the mesylate failed, but exocyclic alkene **11** was obtained through a selenoxide elimination. Treatment of alkene **11** with *m*-CPBA gave epoxide **12** as an inseparable 6.5:1 mixture of diastereomers, presumably from the face opposite the allylic arene substituent. Debenzylation was accompanied by spontaneous 5-exo-*tet* cyclization to produce the indano[2,1-*b*]benzofuran **13** containing the core of the kaempferiaosides A and B,[27,28] but not the desired indano[2,1-*c*]chroman ring system of brazilin. 5-Exo-*tet* cyclization on the more substituted position of the epoxide was favored even when the debenzylation was carried out in the presence of base.

Scheme 2. Initial synthetic strategy to brazilin involving late-stage formation of the dihydropyran.[a]

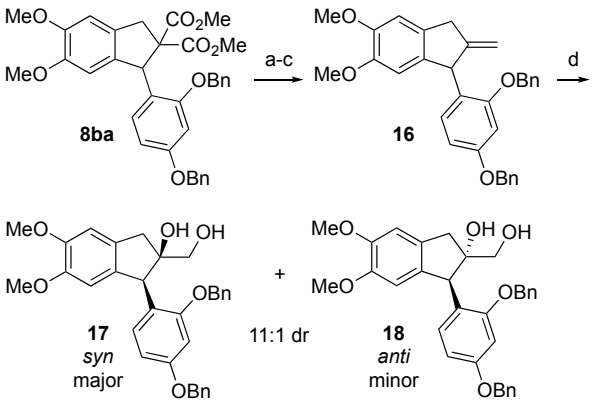


[a]Reagents and conditions: (a) NaI, $NaHCO_3$, DMF, 155 °C, 86%; (b) $LiAlH_4$, THF, 65 °C, 94%; (c) *o*-$O_2NC_6H_4SeCN$, PPh_3, THF, 23 °C, then 30% (w/w) H_2O_2, THF, 23 °C, 38%; (d) *m*-CPBA, $NaHCO_3$, DCM, 23 °C, 40%; (e) 49 mol % $Pd(OH)_2/C$, H_2, MeOH:THF (1:1), 23 °C, 49%.

We recognized the possibility of intercepting an exocyclic alkene **16** previously reported by both Zhang[28] and Yadav[19] and used by Yadav in a synthesis of brazilin. Bis-methoxy alkene **16** was prepared using the same sequence employed for synthesis of methylenedioxy alkene **11** in an overall yield of 48% (Scheme 3). Epoxidation of alkene **16** also generated a *ca* 7:1 mixture of diastereomeric epoxides corresponding to **12**, but the major isomer could be crystallized by vapor diffusion (CH_2Cl_2/hexane) and the epoxide oxygen was confirmed to be *anti* to the axial aryl substituent on the five-membered ring (see supporting information for **S12ba**). Following the dihydroxylation procedure of Zhang and co-workers, we obtained an 11:1 ratio of diastereomers **17** and **18** (Scheme 3). Surprisingly, the minor diastereomer **18** from dihydroxylation, and not the major diastereomer **17**, was found to match the diol prepared by Yadav through a different route, suggesting that the dihydroxylation proceeds from the same face as the hindered aryl substituent and that the dihydroxylation product had been previously mis-assigned. That structural mis-

assignment would explain the fact that the Yadav diol **18** was convertible to brazilin, whereas the Zhang diol **17** was not.

Scheme 3. Dihydroxylation gives the wrong diastereomer [a]



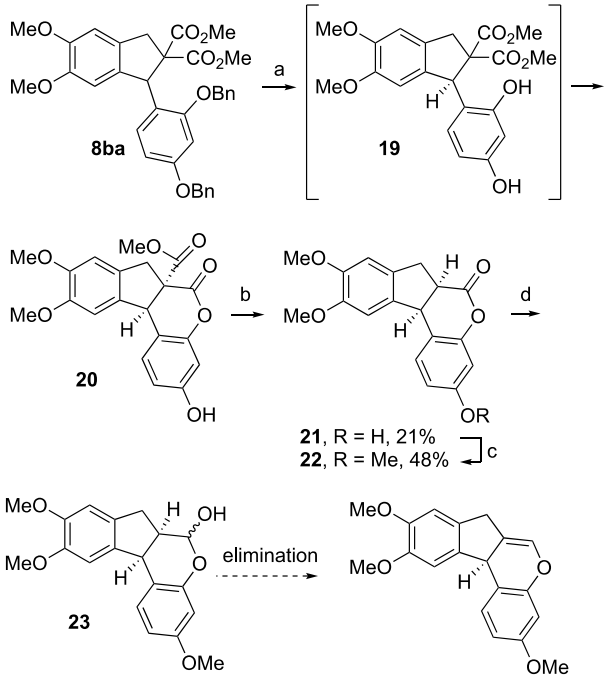
[a]Reagents and conditions:(a) NaI, $NaHCO_3$, DMF, 155 °C, 94%; (b) $LiAlH_4$, THF, 65 °C, 94%; (c) *o*-$O_2NC_6H_4SeCN$, PPh_3, THF, 23 °C, then 30% (w/w) H_2O_2, THF, 23 °C, 54%; (d) NMO/OsO_4, acetone:H_2O (9:1), 0 °C, 89%.

Given the challenges associated with stereoselective functionalization of the exocyclic alkene **16** and subsequent 5-exo-*tet* cyclization, we returned to the cyclic malonate **8ba** generated from the palladium-catalyzed [4+1] (Scheme 4), hoping to form the lactone with one of the ester groups. Hydrogenolysis of dibenzyl ether **8ba** gave the free resorcinol **19** and the desired lactone product **20** containing the tetracyclic ring system of brazilin. The remaining resorcinol **19** was driven to chromanone **20** by heating with *p*-toluenesulfonic acid. Krapcho decarboxylation of the methyl ester of **20** was accompanied by a competing methylation of the free phenolic group by the chloromethane byproduct to afford *O*-methyl ether **22** as the major product. Attempts to prevent the unwanted methylation were unsuccessful so the remaining phenol **21** was alkylated with dimethyl sulfate to afford the *O*-methyl ether **22** in 90%, for an overall yield of 67% for the decarboxylation/methylation process.

With chromanone **22** in hand, we proceeded to investigate the reduction,[29] dehydration,[30] and hydroboration-oxidation[31] sequence to access *O*-trimethylbrazilin. The lactone **22** was

reduced to lactol **23** in 48% yield (5.8:1 mixture of lactol isomers). Attempts to dehydrate the lactol were unsuccessful under E_1, E_2 and *syn*-elimination conditions possibly attributable to the incompatibility between oxocarbenium intermediates and electron-rich arenes or the sensitivity of the enol ether.

Scheme 4. Early-stage access to indano[2,1-*c*]chroman core through lactonization.[a]

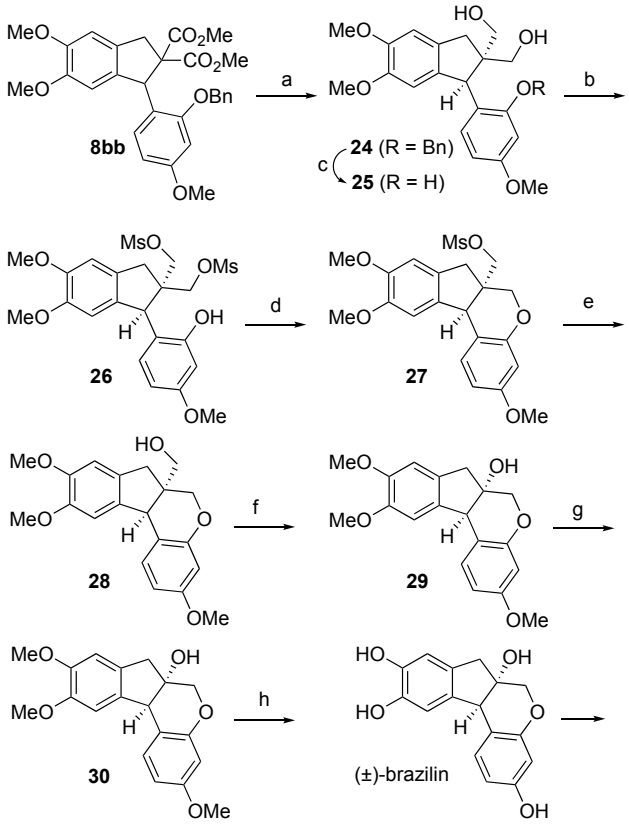


[a]Reagents and conditions: a) 24 mol % $Pd(OH)_2/C$, H_2, MeOH:THF (1:1), 23 °C; then 30 mol % *p*-TsOH•H_2O, toluene, 110 °C, 93%; (b) KCl, DMSO, 160 °C; (c) Me_2SO_4, K_2CO_3, acetone, 56 °C, 90%; (d) DIBAL-H, DCM, −78 °C, 48%.

The great facility of lactonizing one of the geminal carboxymethyl groups of malonate **8ba**, inspired a similar approach involving cyclization onto one of two geminal mesylates by one of the four phenolic groups protected as an *O*-benzyl ether (Scheme 5). This was easily accomplished by reducing the carboxymethyl groups of geminal ester **8bb** to afford the corresponding geminal alcohol **24** in 71% yield. Mesylation of the hydroxyl groups and hydrogenolysis of the benzylic protecting group generated the phenolic mesylate **26** in high yield. As described for 1-arylindane

8bb, geminal alcohol **24**, bis-mesylate **25**, and even bis-mesylate **26** (lacking an *O*-benzyl group) exhibited a second minor conformer evident in the ^{1}H NMR spectrum. Deprotonation of the phenolic group was followed by facile cyclization onto the *syn* mesylate to form the desired dihydropyran ring of indanochroman **27** in 81% yield. The extraneous mesylate was removed with lithium aluminum hydride to afford the neopentyl alcohol **28** which was oxidized to aldehyde **29** in 88% yield using Dess-Martin periodinane.

Scheme 5. Total synthesis of (±)-brazilin from bis-mesylate **26**.



[a]Reagents and conditions: (a) $LiAlH_4$, THF, 0 °C, 71%; (b) MsCl, NEt_3, 0 to 5 °C, 95%; (c) 24 mol % $Pd(OH)_2/C$, H_2, MeOH:THF (1:1), 23 °C, 99%; (d) NaH, THF, 0 °C, 81%; (e) $LiAlH_4$, THF, 65 °C, 90% (f) DMP, DCM, 0 to 5 °C, 86%; (g) NaOH, 30% (w/w) H_2O_2, MeOH, 65 °C, 42%; (h) BBr_3, DCM, 0 to 23 °C, 68%.

The aldehyde was subjected to Bayer-Villiger oxidation under nucleophilic conditions in order to minimize collateral oxidation of the electron-rich aromatic ring to afford *O*-

trimethylbrazilin, **30**, in 42% (>95% purity) yield upon treating aldehyde **29** with NaOH and 30% (w/w) H_2O_2. The methyl groups were removed with BBr_3, as previously reported, to afford (±)-brazilin in 68% (>95% purity); as noted by others,[32] the catechol brazilin is highly sensitive to oxidation.

Palladium-catalyzed [5+1] and [4+1] carbenylative annulation reactions with electron-rich aromatic rings have led to a formal synthesis of (±)-picropodophyllone and a total synthesis of (±)-brazilin. The [4+1] annulation reaction approach to (±)-brazilin varies dramatically from the Perkin-Robinson strategy first proposed over a century ago. The powerful palladium reaction brings in nearly all of the necessary functionality, but strategies to access the dihydropyran ring via epoxide ring opening or lactonization proved unworkable. Ultimately, a strategy involving construction of the dihydropyran ring through diastereotopic displacement of a mesylate paved the way for the synthesis of (±)-brazilin in 8 steps from the corresponding aryl iodide and in 12%, 11 steps in the longest linear sequence from commercial 3,4-dimethoxybenzyl alcohol (11% overall yield).

EXPERIMENTAL SECTION

GENERAL INFORMATION AND REAGENTS

All reactions were performed under an atmosphere of dry N_2 gas. Anhydrous solvents and reagents, where applicable, were transferred using Schlenk technique. Toluene, tetrahydrofuran (THF), diethyl ether (Et_2O), and dichloromethane (CH_2Cl_2) were dried by passage through alumina according to the procedure of Grubbs and co-workers.[33] All other solvents were purified according to reported procedures.[34] Unless otherwise noted, all reagents were commercially obtained and

used without prior purification. Where applicable, acetone Optima™ (Fisher), and 30% (w/w) H_2O_2 (Fisher) was used.

All reactions were monitored by thin-layer chromatography (TLC) and visualized by UV (254 nm) illumination and by $KMnO_4$ and *p*-anisaldehyde (*p*-anis) dip stains. The *p*-anis stain was prepared by adding 25 mL of concentrated sulfuric acid to a chilled solution of 95% ethanol (676 mL, made from 200 proof ethanol and de-ionized water). Glacial acetic acid (7.5 mL) and *p*-anisaldehyde (99%, 18.4 mL) were then added to afford a colorless solution. The stain was stored at 0 °C. Analytical TLC was performed using EMD Millipore 0.25 mm Silica gel 60 F_{254} 20 × 20 cm plates (EM1.05715.0001). "Flash" chromatography on silica gel was performed using Agela Technologies Flash Silica sorbent (40-63 μm) silica gel of 230-400 mesh (CS605025-P). Unless otherwise indicated, all reactions were heated using a silicon oil bath on a temperature-controlled heating-stirring plate.

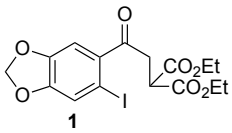
^1H and ^{13}C NMR spectral data were recorded at 23 °C using a Bruker Avance 500 or 600 MHz spectrometer equipped with a cryoprobe. All spectra were calibrated to tetramethylsilane (0.00 ppm) unless otherwise specified, in which case the reference peak will be reported as Shift (reference). In general, NMR spectra taken in $CDCl_3$ were calibrated to tetramethylsilane (0.00 ppm). ^1H and ^{13}C NMR spectra taken in CD_3OD were calibrated to 3.31 ppm and 49.15 ppm, respectively. ^1H and ^{13}C NMR spectra taken in $DCON(CD_3)_2$ were calibrated to 2.75 ppm, and 163.15 ppm, respectively. Variable temperature ^1H NMR stacked spectra taken in $DCON(CD_3)_2$ were calibrated to 8.03 ppm. ^1H and ^{13}C NMR spectra taken in $C_6D_5CD_3$ were calibrated to 2.09 ppm and 20.4 ppm, respectively.

The NMR data are reported as follows: chemical shift in ppm (δ), multiplicity (br = broad, app = apparent, s = singlet, d = doublet, t = triplet, q = quartet and m = multiplet), coupling

constants (Hz), and integration. NMR data was processed using Mestrelab Research MestReNova 11.0.2 software, using automatic baseline correction, automatic phasing, and the multiplet analysis function. Infrared spectroscopy data was acquired using a PerkinElmer Spectrum Two IR Spectrometer or a Thermo Scientific iD5 ATR (Nicolet iS5) Spectrometer. Mass spectra were obtained using a Waters (Micromass) LCT premier with a TOF analyzer using the ionization method indicated. Melting points were taken on a Thermo Scientific Electrothermal Mel-Temp® apparatus (Model No. 1001D) using a mercury thermometer. The reported melting point values are uncorrected. Chemical names found in the supporting information were generated using PerkinElmer ChemBioDraw Ultra 13.0 software.

SYNTHETIC PROCEDURES

Diethyl 2-(2-(6-iodobenzo[*d*][1,3]dioxol-5-yl)-2- oxoethyl)malonate, 1.



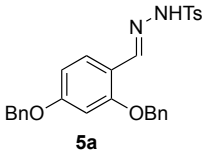
1

Malonate **1** was synthesized following a modified procedure from Ziegler and co-workers.[35] Briefly, a 25 mL 2-neck round-bottom flask was equipped with a stir bar, flame-dried, and charged with aryl iodide 1-(6- iodobenzo[*d*][1,3]dioxol-5-yl)ethan-1-one (0.300 g, 1.03 mmol). The round-bottom flask was evacuated and backfilled with N_2 (× 3) before being charged with DCM (6.1 mL) and TFA (0.04 mL, 0.52 mmol). To the yellow solution was added pyridinium tribromide (0.363 g, 1.14 mmol) in four portions over four hours. The flask was wrapped in aluminum foil during the reaction to exclude light. After 10 h, starting material was no longer detectable by TLC (100% toluene). The crude reaction mixture was quenched with saturated aqueous $NaHCO_3$ (6.0 mL) and stirred until gas ceased evolving. The crude reaction mixture was transferred to a separatory funnel and washed once with 6 mL of aqueous 1 N HCl. The aqueous layer was extracted with DCM (1 × 12 mL) and the combined organic phases were washed with brine (1 × 20 mL), dried (Na_2SO_4), and concentrated *in vacuo.* The resulting yellow

oil was immediately subjected to flash chromatography (10:90 hexanes:toluene) to afford the crude α-bromoketone as a clear oil (0.203 g) which was taken on to the alkylation step. R_f = 0.55 (100% toluene). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 (s, 1H), 7.02 (s, 1H), 6.07 (s, 2H), 4.40 (s, 2H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 193.5, 150.9, 148.3, 134.1, 120.5, 109.5, 102.6, 82.4, 32.7.

A flame-dried 25 mL, 2-necked round-bottom flask equipped with a short-stem vacuum adapter and rubber septum was charged with un-rinsed 60% NaH/mineral oil (0.066 g, 1.65 mmol), and a stir bar. The flask cooled was to –10 °C in a brine-ice bath, and charged with THF (4.5 mL). Diethyl malonate (0.272 g, 1.65 mmol) was added dropwise via syringe over 5 min resulting in a white slurry. After 25 min, a solution of α-bromoketone from the previous step (0.203 g, 0.55 mmol) in THF (1.0 mL) was added dropwise via syringe over 1 min. The reaction was removed from the brine-ice bath and warmed to 23 °C while stirring. After 4.5 h, α-bromoketone was no longer detectable by TLC (25:75 EtOAc:hexanes). The reaction mixture was quenched with 15 mL of saturated aqueous NH_4Cl and transferred to a separatory funnel. The mixture was extracted with Et_2O (3 × 20 mL) and the combined organic phases were dried (Na_2SO_4) and concentrated *in vacuo* to afford a clear oil. The oil was purified by flash chromatography (10:90 EtOAc:hexanes) to yield diethyl 2-(2-(6-iodobenzo[*d*][1,3]dioxol-5-yl)-2-oxoethyl)malonate **1** as a clear oil (0.153 g, 62%). R_f = 0.51 (20:80 EtOAc:hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 (s, 1H), 7.15 (s, 1H), 6.05 (s, 2H), 4.23 (qd, J = 7.1, 3.2 Hz, 4H), 4.06 (t, J = 7.2 Hz, 1H), 3.45 (d, J = 7.2 Hz, 2H), 1.29 (t, J = 7.1 Hz, 6H); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 198.5, 168.8, 150.6, 148.3, 135.6, 120.7, 109.2, 102.4, 81.5, 61.9, 47.5, 40.2, 14.1; HRMS (ESI): m / z calcd for $C_{16}H_{17}O_7INa$ $[M + Na]^+$ 470.9917, found 470.9906.

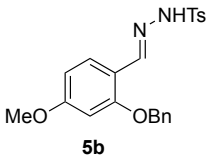
_N'_-(2,4-Bis(benzyloxy)benzylidene)-4-methylbenzenesulfonohydrazide, 5a.



5a

3,5-Dibenzyloxy-*N*-tosylhydrazone **5a** was synthesized as published by Aggarwal and co-workers with slight modification.[36] To a solution of *p*-toluenesulfonyl hydrazide (1.8 g, 9.5 mmol) in 5 mL of MeOH was added 2,4-dibenzyloxybenzaldehyde (3.0 g, 9.4 mmol) in three portions over 15 min. A thick yellow precipitate formed during the course of the reaction. Additional MeOH (25 mL) was added to ensure proper stirring. Upon complete consumption of the starting benzaldehyde (30 min), the reaction was cooled (0 °C) for 15 min. The yellow precipitate was filtered, washed with cold MeOH, and then purified by flash chromatography (0:100 – 20:80 EtOAc:hexanes) to yield *N*-tosylhydrazone **5a** as a pale yellow solid (3.8 g, 83%). R_f = 0.37 (30:70 EtOAc:hexanes). mp = 154–155 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.07 (s, 1H), 7.84 (dd, *J* = 8.4, 2.2 Hz, 2H), 7.78 (d, *J* = 8.8 Hz, 1H), 7.61 (s, 1H), 7.45 – 7.30 (m, 10H), 7.26 (d, *J* = 8.4 Hz, 2H), 6.57 (dd, *J* = 8.7, 2.3 Hz, 1H), 6.52 (d, *J* = 2.3 Hz, 1H), 5.04 (s, 2H), 4.97 (s, 2H), 2.38 (s, 3H); ^{13}C{^{1}H} (125 MHz, $CDCl_3$) δ 161.9, 158.3, 144.06, 144.04, 136.3, 136.1, 135.4, 129.6, 128.77, 128.75, 128.3, 128.2, 127.9, 127.8, 127.5, 115.2, 106.9, 100.1, 70.4, 70.2, 21.6; IR (ATR) 3201, 1601, 1164 cm^{-1}. HRMS (ESI): *m* / *z* calcd for $C_{28}H_{26}N_2O_4SNa$ [M + Na]$^+$ 509.1511, found 509.1499.

N'-(2-(Benzyloxy)-4-methoxybenzylidene)-4-methylbenzenesulfono-hydrazide, 5b.

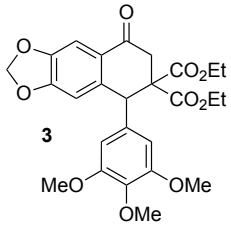


5b

To a cooled (0 °C) solution of *p*-toluenesulfonyl hydrazide (11.7 g, 62.7 mmol) in THF (105 mL) was added 2-benzyloxy-4-methoxybenzaldehyde (11.9 g, 52.3 mmol).[37] After stirring for 30 min, the reaction mixture was warmed to 23 °C. A thick yellow precipitate formed during the course of the reaction. Upon consumption of the aldehyde (1 h 45 min), the reaction was concentrated *in vacuo* and recrystallized from MeOH to afford product **5b** as an off-white solid (15.6 g, 73%). The filtrate was further recrystallized to afford additional *N*-tosylhydrazone **5b** as an off-white solid (2.78 g, 13%). The identical samples

were combined to afford *N*-tosylhydrazone **5b** in 86% yield. R_f = 0.44 (40:60 EtOAc:hexanes, stains orange by *p*-anis dip stain). mp = 162–163 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.09 (s, 1H), 7.84 (d, *J* = 8.3 Hz, 2H), 7.79 (d, *J* = 8.6 Hz, 1H), 7.40 – 7.31 (m, 5H), 7.28 – 7.26 (m, 2H), 6.50 (dd, *J* = 8.7, 2.3 Hz, 1H), 6.44 (d, *J* = 2.3 Hz, 1H), 5.00 (s, 2H), 3.79 (s, 3H), 2.38 (s, 3H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 162.8, 158.4, 144.1, 144.0, 136.2, 135.5, 129.6, 128.7, 128.3, 128.0, 127.9, 127.5, 115.1, 106.1, 99.2, 70.5, 55.5, 21.6; IR (ATR) 3193, 3066, 3035, 2862, 2840, 1606, 1506, 1442, 1279, 1155, 1022, 822 cm^{-1}. HRMS (ESI) *m* / *z* calcd for $C_{22}H_{22}N_2O_4SH$ $[M + H]^+$ 411.1378, found 411.1378.

Diethyl 8-oxo-5-(3,4,5-trimethoxyphenyl)-7,8-dihydronaphtho[2,3-*d*][1,3]dioxole-6,6(5*H*)-dicarboxylate, 3.



A flame-dried 5 mL, pear-shaped flask was charged with $PdCl_2(MeCN)_2$ (2.6 mg, 0.01 mmol), tris(4-fluorophenyl)phosphine (12.6 mg, 0.04 mmol), and a stir bar. The flask was purged and backfilled with nitrogen three times and then fitted with a rubber septum. THF (0.3 mL) was then added and the mixture was stirred for 10 min, resulting in a clear yellow solution.

A separate flame-dried 5 mL, pear-shaped flask containing malonate **1** (44.5 mg, 0.10 mmol), *N*-tosylhydrazone **2** (72.9 mg, 0.20 mmol), and a stir bar was purged and backfilled with nitrogen three times and fitted with a rubber septum. THF (0.3 mL) was added and the mixture was stirred for 10 min resulting in a clear solution.

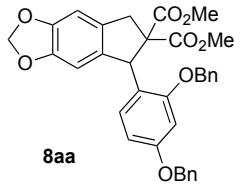
A separate flame-dried 15 mL, round-bottom flask was equipped with a short-stem vacuum adapter and charged with un-rinsed 60% NaH/mineral oil (14.4 mg, 0.36 mmol) and a stir bar. The flask was purged and backfilled with nitrogen three times and fitted with a rubber septum. THF (0.8 mL) was added and the suspension was cooled to –10 °C in a brine-ice bath. The solution of

aryl iodide **1** and *N*-tosylhydrazone **2** in THF was then added dropwise via syringe over 5 min to the 15 mL flask containing a stirring NaH suspension. During the course of addition, a white solid precipitated out of solution. The flask containing aryl iodide **1** and *N*-tosylhydrazone **2** was washed with THF (2 × 0.3 mL) and the washes were added to the 15 mL flask.

The flask was then warmed to 23 °C and stirred for 20 min. Under a stream of nitrogen, the yellow catalyst solution was added to the reaction. The flask containing catalyst solution was washed with THF (2 × 0.3 mL) and the washes were added to the reaction. The reaction mixture was heated at 60 °C. After 1.5 h, aryl iodide **1** was no longer detectable by TLC.

The reaction mixture was cooled to 23 °C, diluted with 15 mL of Et_2O, and passed through a plug of silica. The plug of silica was washed with Et_2O (3 × 100 mL) and the filtrate was concentrated *in vacuo*. The product was purified by flash chromatography on silica gel (25:75 EtOAc:hexanes) to afford a mixture of tetralone **3** and azine (9:1 tetralone **3**:azine) as a yellow solid. (24.5 mg, 50%). R_f = 0.20 (10:90 EtOAc:toluene). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47 (s, 1H), 6.64 (s, 1H), 6.23 (s, 2H), 6.02 (s, 2H), 5.05 (s, 1H), 4.19 – 3.98 (m, 4H), 3.80 (s, 3H), 3.73 (s, 6H), 3.28 (d, *J* = 18.1 Hz, 1H), 3.21 (d, *J* = 18.0 Hz, 1H), 1.18 (t, *J* = 7.2 Hz, 3H), 1.14 (t, *J* = 7.1 Hz, 3H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 193.1, 169.4, 168.0, 153.4, 153.1, 147.9, 140.5, 137.6, 132.9, 129.5, 128.8, 126.3, 108.8, 107.9, 106.7, 105.4, 103.4, 102.0, 62.4, 62.0, 60.8, 59.9, 56.1, 49.8, 38.4, 13.9, 13.8. HRMS (ESI) *m* / *z* calcd for $C_{26}H_{28}O_{10}Na$ $[M + Na]^+$ 523.1580, found 523.1570.

Dimethyl 5-(2,4-bis(benzyloxy)phenyl)-5,7-dihydro-6*H*-indeno[5,6-*d*][1,3]dioxole-6,6-dicarboxylate, 8aa.



8aa

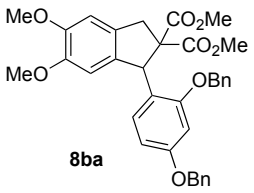
Arylindane **8aa** was synthesized using the same carbenylative annulation procedure for tetralone **3** above. To a stirring, chilled (–10 °C) solution of un-

rinsed 60% NaH/mineral oil (184 mg, 4.59 mmol) in THF (21.3 mL) was added a pre-stirred solution of malonate **4a** (0.500 g, 1.28 mmol) and *N*-tosylhydrazone **5a** (1.24 g, 2.55 mmol), in THF (7.1 mL). Additional THF (2 × 7.1 mL) was used to transfer any remaining reagent solution. After 15 min, the stirring, cooled, heterogeneous solution was warmed to 23 °C, and stirred an additional 20 min. A pre-stirred solution of $PdCl_2(CH_3CN)_2$ (33.1 mg, 0.128 mmol) and P(4-$FC_6H_5)_3$ (161 mg, 0.510 mmol) in THF (7.1 mL) was then added. Additional THF (2 × 7.1 mL) was used to transfer any remaining catalyst solution. The reaction was heated (60 °C) and monitored for the consumption of malonate **4a** and *N*-tosylhydrazone **5a** starting material. After 2 h, neither was detectable by TLC. The mixture was cooled to 23 °C, diluted with Et_2O (25 mL), and then passed through a pad of silica gel. The pad was rinsed with Et_2O (3 × 15 mL) and the filtrate concentrated *in vacuo* to afford a crude red-brown oil. The oil was purified by two rounds of flash chromatography (0:100 – 10:90 EtOAc:hexanes; then 1:99 EtOAc:toluene) to yield arylindane **8aa** as a yellow solid (574 mg, 80%).R_f = 0.30 (20:80 EtOAc:hexanes, stains mahogany by *p*-anis dip stain). mp = 48–58 °C. ^{1}H NMR (500 MHz, $CDCl_3$, 298.0 K) δ 7.54 (s, 2H), 7.43 – 7.29 (m, 6H), 6.68 (s, 0.7H), 6.57 (s, 0.6H), 6.50 (s, 0.3H), 6.41 (s, 1H), 5.89 (s, 4H), 5.08 (s, 2H), 5.03 – 4.92 (m, 2H), 3.97 (d, *J* = 16.7 Hz, 0.6H), 3.71 (s, 3H), 3.30 (d, *J* = 16.1 Hz, 0.4H), 3.20 (s, 3H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$, 298.0 K) δ 172.3, 170.0, 158.8, 157.0, 147.4, 137.2, 136.8, 132.5, 130.4, 128.6, 128.5, 128.0, 127.7, 127.6, 127.0, 122.1, 105.5, 104.3, 101.0, 100.3, 70.2, 70.0, 66.3, 52.9, 52.0, 47.9, 39.9; IR (ATR) 2950, 1732, 1233, 1166, 1036 cm^{-1}; HRMS (ESI) *m* / *z* calcd for $C_{34}H_{30}O_8Na$ $[M + Na]^+$ 589.1838, found 589.1836.

Broadened peaks are apparent in the ^{1}H NMR, suggesting rotamers. Additional ^{1}H NMR data is reported below. The corresponding ^{1}H NMR spectra can be found in the supporting information. ^{1}H NMR (500 MHz, $CDCl_3$, 253.0 K) δ 7.60 – 7.52 (m, 2H), 7.49 – 7.33 (m, 8H),

6.73 (s, 1H), 6.60 (d, J = 2.3 Hz, 1H), 6.52 – 6.49 (m, 1H), 6.46 (s, 1H), 6.43 (dd, J = 8.5, 2.3 Hz, 1H), 5.95 – 5.93 (m, 2H), 5.91 (s, 1H), 5.17 – 5.04 (m, 2H), 5.05 – 4.90 (m, 2H), 4.00 (d, J = 16.8 Hz, 1H), 3.76 (d, J = 1.1 Hz, 3H), 3.34 (d, J = 16.8 Hz, 1H), 3.25 (s, 3H); ^{1}H NMR (600 MHz, $CDCl_3$, 328.0 K) δ 7.75 – 7.25 (m, 9H), 6.88 – 6.20 (m, 4H), 5.98 – 5.74 (m, 2H), 5.19 – 4.87 (m, 4H), 3.94 (d, J = 16.6 Hz, 1H), 3.69 (s, 3H), 3.39 – 3.02 (m, 5H); ^{1}H NMR (600 MHz, $C_6D_5CD_3$, 372.5 K) δ 7.33 (s, 2H), 7.26 – 7.13 (m, 4H), 7.11 – 7.02 (m, 4H), 6.99 – 6.96 (m, 1H), 6.78 (s, 1H), 6.55 (d, J = 2.4 Hz, 1H), 6.44 (s, 1H), 6.38 (d, J = 5.1 Hz, 1H), 6.33 (dd, J = 8.4, 2.4 Hz, 1H), 6.02 (s, 1H), 5.38 (d, J = 7.4 Hz, 1H), 4.78 (s, 2H), 4.75 (s, 2H), 4.10 (d, J = 16.5 Hz, 1H), 3.39 (d, J = 1.3 Hz, 3H), 3.27 (d, J = 16.5 Hz, 1H), 3.03 (d, J = 1.3 Hz, 3H).

Dimethyl 1-(2,4-bis(benzyloxy)phenyl)-5,6-dimethoxy-1,3-dihydro-2*H*-indene-2,2-dicarboxylate, 8ba.

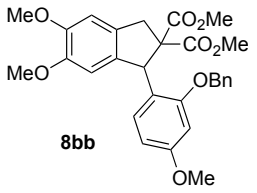


8ba

Arylindane **8ba** was synthesized using the same carbenylative annulation procedure for tetralone **3**. Reaction of malonate **4b** (2.00 g, 4.89 mmol), *N*-tosylhydrazone **5a** (3.75 g, 7.34 mmol), un-rinsed 60% NaH/mineral oil (607 mg, 15.2 mmol), $PdCl_2(CH_3CN)_2$ (127 mg, 0.489 mmol), and P(4-$FC_6H_5)_3$ (620 mg, 1.95 mmol) in THF (245 mL) for 2 hr at 60 °C afforded a crude golden-brown solid that was subjected to three rounds of flash chromatography (25:75 – 30:70 EtOAc:hexanes (× 2); then 1:99 EtOAc:toluene) to afford a solid mixture of arylindane **8ba** and *N*-tosylhydrazone **5a**. Upon diluting the mixture with Et_2O, a white solid remained insoluble. The mixture was cooled (–78 °C) for 20 min and then filtered. The white solid was washed with cold Et_2O to yield arylindane **8ba** (2.38 g, 84%). R_f = 0.28 (30:70 EtOAc:hexanes, stains red by *p*-anis dip stain). mp = 124–126 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.57 (d, J = 7.5 Hz, 2H), 7.45 – 7.28 (m, 8H), 6.75 (s, 1H), 6.60 (s, 1H), 6.49 (s, 1H), 6.48 – 6.37 (m, 2H), 5.96 (s, 1H), 5.09 (s, 2H), 5.04 – 4.93 (m, 2H), 4.03 (d, J = 16.6 Hz, 1H),

3.87 (s, 3H), 3.73 (s, 3H), 3.71 (s, 3H), 3.35 (d, J = 16.6 Hz, 1H), 3.20 (s, 3H); $^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$) δ 172.4, 170.1, 158.8, 157.1, 148.9, 148.8, 137.1, 136.8, 135.9, 131.5, 130.5, 128.6, 128.5, 128.0, 127.7, 127.6, 127.1, 122.2, 107.7, 106.7, 105.5, 100.2, 70.2, 70.0, 66.4, 55.9, 52.9, 52.0, 48.3, 40.1; IR (ATR) 2948, 1731, 1502, 1215, 1170, 1151, 1097 cm^{-1}; HRMS (ESI) m / z calcd for $C_{35}H_{34}O_8Na$ $[M + Na]^+$ 605.2151, found 605.2137.

Dimethyl 1-(2-(benzyloxy)-4-methoxyphenyl)-5,6-dimethoxy-1,3-dihydro-2*H*-indene-2,2-dicarboxylate, 8bb.



8bb

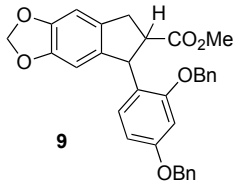
Arylindane **8bb** was synthesized using the same carbenylative annulation procedure for tetralone **3**. To a stirring solution of 60% NaH/mineral oil (705 mg, 17.6 mmol) in THF (27.0 mL) at –10 °C was added a pre-stirred solution of malonate **4b** (2.0 g, 4.89 mmol) and *N*-tosylhydrazone **5b** (4.00 g, 9.79 mmol) in THF (27.0 mL). Additional THF (2 × 27.0 mL) was used to transfer the remaining reagent solution. After 15 min, the stirring, cooled, heterogeneous solution was warmed to 23 °C, and stirred an additional 20 min. A pre-stirred solution of $PdCl_2(CH_3CN)_2$ (127 mg, 0.489 mmol) and $(4\text{-}FC_6H_4)_3P$ (620 mg, 1.95 mmol) in THF (27.0 mL) was then added. Additional THF (2 × 27.0 mL) was used to transfer any remaining catalyst solution. The reaction was then heated (60 °C) and monitored by TLC for the consumption of malonate **4b** and *N*-tosylhydrazone **5b**. After 1.5 h, neither was detectable by TLC. The mixture was cooled to 23 °C, diluted with Et_2O (25 mL), and then passed through a pad of silica gel. The pad was rinsed with Et_2O (3 × 60 mL), and the filtrate concentrated *in vacuo* to afford a crude green fluff. The solid was purified by flash chromatography to afford mixed fractions of product and co-eluting impurities. Successive purifications yielded product **8bb** as a yellow fluff that was crushed into a solid (2.23 g, 90%). Column eluent conditions: four column volumes of 15:85 EtOAc:hexanes, followed by two column volumes of 20:80

DCM:toluene, followed by 25:85 – 30:70 EtOAc:hexanes. Mixed fractions were then subjected to 5:95 – 8:92 EtOAc:toluene, followed by 5:95 – 15:85 EtOAc hexanes. R_f = 0.08 (25:75 EtOAc:hexanes, stains pink by *p*-anis dip stain). R_f = 0.08 (20:80 acetone:hexanes). mp = 144–146 °C. ^{1}H NMR (600 MHz, $CDCl_3$, 298.0 K) δ 7.64 – 7.51 (broad m, 2H), 7.46 – 7.36 (broad m, 2H), 7.36 – 7.26 (broad m, 1H), 6.93 (s, 0.4H), 6.75 (broad s, 1H), 6.52 (broad s, 1H), 6.48 (s, 1H), 6.32 (broad d, J = 8.6 Hz, 1H), 5.96 (broad s, 1H), 5.33 – 4.90 (broad m, 2H), 4.69 (s, 0.2H), 4.59 (s, 0.2H), 4.03 (broad d, J = 16.6 Hz, 1H), 3.87 (broad s, 3H), 3.74 (s, 3H and s, 1H), 3.73 (s, 3H), 3.71 (s, 3H), 3.35 (d, J = 16.7 Hz, 1H), 3.23 (s, 3H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$, 298.0 K) δ 172.4, 170.1, 159.7, 157.1, 149.0, 148.8, 137.2, 136.0, 131.5, 130.6, 128.5, 127.7, 127.1, 122.0, 107.8, 106.7, 104.4, 99.4, 70.2, 66.4, 55.93, 55.91, 55.2, 52.9, 52.0, 48.3, 40.1; IR (ATR) 1731, 1504, 1218, 1158, 1098 cm^{-1}; HRMS (ESI) m / z calcd for $C_{29}H_{30}O_8Na$ $[M + Na]^+$ 529.1838, found 529.1812.

Broadened peaks are apparent in the ^{1}HNMR. Using the method of Ley and co-workers, the broadened peaks are determined to be of rotamers.[25] The difference spectrum for the 1D gradient NOE is provided in the supporting information. Peaks sharpen into well-resolved signals at temperatures below 23 °C. Additional ^{1}H NMR data is reported below. The corresponding ^{1}H NMR spectra can be found in the supporting information.^{1}H NMR (600 MHz, $CDCl_3$, 274.2 K) δ 7.60 (d, J = 7.5 Hz, 2H), 7.43 (t, J = 7.6 Hz, 2H), 7.35 (t, J = 7.4 Hz, 1H), 6.93 (d, J = 7.1 Hz, 0.4H), 6.77 (s, 1H), 6.52 (d, J = 2.4 Hz, 1H), 6.50 (s, 1H), 6.48 (d, J = 8.6 Hz, 1H), 6.37 (s, 0.2H), 6.32 (dd, J = 8.5, 2.4 Hz, 1H), 6.30 (s, 0.2H), 5.96 (s, 1H), 5.19 (s, 0.2H), 5.16 – 5.05 (m, 2H), 4.69 (d, J = 10.9 Hz, 0.2H), 4.59 (d, J = 11.0 Hz, 0.2H), 4.05 (d, J = 16.6 Hz, 1H), 3.89 (s, 3H), 3.81 (s, 0.5H), 3.78 (s, 0.3H), 3.75 (s, 4H), 3.74 (s, 7H), 3.73 (s, 3H), 3.71 (s, 0.6H), 3.36 (d, J = 16.6 Hz, 1H), 3.24 (s, 4H), 3.01 (d, J = 16.2 Hz, 0.2H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$, 274.2

K) δ 172.4, 170.2, 159.5, 156.8, 148.6, 148.5, 137.0, 135.7, 131.2, 130.5, 128.5, 127.7, 126.9, 121.6, 107.3, 106.3, 104.0, 99.2, 69.9, 66.2, 55.82, 55.76, 55.2, 53.0, 52.1, 48.0, 39.9; ^{1}H NMR (600 MHz, DMF-d_7, 298 K) δ 7.68 (d, J = 7.6 Hz, 2H), 7.47 (t, J = 7.8 Hz, 2H), 7.38 (t, J = 7.4 Hz, 1H), 6.98 (s, 1H), 6.75 (s, 1H), 6.59 (s, 1H), 6.42 (s, 2H), 5.95 (s, 1H), 5.30 (d, J = 12.2 Hz, 1H), 5.21 (d, J = 12.2 Hz, 1H), 4.02 (d, J = 16.7 Hz, 1H), 3.83 (s, 3H), 3.78 (s, 3H), 3.75 (s, 3H), 3.67 (s, 3H), 3.34 (d, J = 16.7 Hz, 1H), 3.26 (s, 3H). ^{13}C{^{1}H} NMR (151 MHz, DMF-d_7, 298 K) δ 172.6, 170.0, 160.2, 157.5, 149.8, 149.6, 138.1, 136.7, 131.8, 130.5, 128.7, 128.0, 127.6, 121.9, 108.2, 107.9, 105.3, 99.7, 70.3, 66.5, 55.8, 55.7, 55.2, 52.9, 51.9, 48.2, 40.0; ^{1}H NMR (600 MHz, DMF-d_7, 274.2 K) δ 7.69 (d, J = 7.5 Hz, 2H), 7.49 (t, J = 7.5 Hz, 2H), 7.39 (t, J = 7.4 Hz, 1H), 7.33 – 7.24 (m, 0.1H), 7.00 (s, 1H), 6.93 (s, 0.1H), 6.76 (d, J = 2.1 Hz, 1H), 6.61 (s, 1H), 6.45 – 6.39 (m, 2H), 5.95 (s, 1H), 5.31 (d, J = 12.2 Hz, 1H), 5.21 (d, J = 12.3 Hz, 1H), 4.86 (d, J = 11.8 Hz, 0.1H), 4.79 (d, J = 12.0 Hz, 0.1H), 4.03 (d, J = 16.6 Hz, 1H), 3.83 (s, 3H), 3.78 (s, 3H), 3.77 (s, 3H), 3.68 (s, 3H), 3.35 (d, J = 16.7 Hz, 1H), 3.27 (s, 3H). ^{13}C{^{1}H} NMR (151 MHz, DMF-d_7, 274.2 K) δ 172.7, 170.0, 160.2, 157.4, 149.6, 149.5, 138.2, 136.5, 131.6, 130.6, 128.8, 128.1, 127.6, 121.7, 107.8, 107.6, 105.2, 99.5, 70.2, 66.5, 55.6, 55.57, 55.2, 53.0, 52.1, 48.2, 40.0.

Methyl 5-(2,4-bis(benzyloxy)phenyl)-6,7-dihydro-5*H*-indeno[5,6-*d*][1,3]dioxole-6-carboxylate, 9 (1:1 *syn*/*anti*).

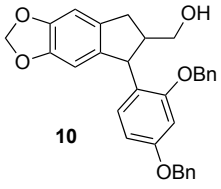


9

A round-bottom flask containing arylindane **8aa** (0.559 g, 0.988 mmol), anhydrous NaI (0.454 g, 3.06 mmol), and $NaHCO_3$ (0.339 g, 4.04 mmol), was evacuated and backfilled with N_2 (× 3). Anhydrous DMF (8.0 mL) was then added. The flask was connected to a water jacketed condenser, and then submerged in an oil bath (160 °C). The reaction was stirred and monitored for the consumption of arylindane (6 h). The mixture was cooled to 23 °C. Then, H_2O (80 mL) was added while stirring, and the resulting

solution extracted with Et_2O (4 × 50 mL). The combined organic layers were washed with H_2O (× 3) and with brine (× 1). The organic solution was then dried ($MgSO_4$), and concentrated *in vacuo*. The resulting crude yellow oil was purified by flash chromatography (10:90 EtOAc:hexanes) to afford methyl ester **9** as an inseparable 1:1 mixture of diastereomers as a white foam (0.433 g, 86%). R_f = 0.43 (20:80 EtOAc:hexanes). mp = 40–58 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.50 – 7.27 (m, 16.1H), 7.20 (d, *J* = 7.3 Hz, 2.1H), 6.94 (d, *J* = 8.4 Hz, 1.1H), 6.77 – 6.68 (m, 1.7H), 6.66 (s, 1.1H), 6.63 (d, *J* = 2.4 Hz, 1.2H), 6.59 (d, *J* = 2.4 Hz, 0.9H), 6.51 (dd, *J* = 8.4, 2.4 Hz, 1.2H), 6.47 (s, 0.9H), 6.44 (dd, *J* = 8.5, 2.4 Hz, 1H), 6.38 (s, 1H), 5.92 – 5.89 (m, 2.9H), 5.89 – 5.87 (m, 1.1H), 5.18 (d, *J* = 10.0 Hz, 0.9H), 5.09 – 4.93 (m, 7.3H), 4.89 (d, *J* = 7.6 Hz, 1H), 3.75 (td, *J* = 8.9, 6.4 Hz, 0.9H), 3.54 (s, 3.1H), 3.48 – 3.36 (m, 1.5H), 3.35 (d, *J* = 6.5 Hz, 0.5H), 3.19 (s, 2.7H), 3.12 (d, *J* = 8.4 Hz, 2.1H), 2.99 (dd, *J* = 15.9, 8.6 Hz, 0.9H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 175.5, 173.9, 159.0, 158.7, 157.4, 157.3, 147.0, 146.9, 146.8, 137.8, 137.1, 136.9, 136.79, 136.77, 135.5, 134.1, 130.0, 129.7, 128.6, 128.57, 128.5, 128.4, 128.04, 127.98, 127.87, 127.7, 127.6, 127.3, 127.1, 124.3, 122.5, 105.44, 105.40, 105.3, 105.1, 104.7, 104.6, 101.0, 100.9, 100.7, 100.2, 70.2, 70.16, 70.0, 69.9, 52.1, 51.7, 51.1, 49.4, 35.5, 34.3; IR (ATR) 2916, 1732, 1609, 1584, 1502, 1474, 1248, 1167, 1036, 735 cm^{-1}; HRMS (ESI) *m* / *z* calcd for $C_{32}H_{28}O_6Na$ $[M + Na]^+$ 531.1783, found 531.1788.

(5-(2,4-Bis(benzyloxy)phenyl)-6,7-dihydro-5*H*-indeno[5,6-*d*][1,3]dioxol-6-yl)methanol, 10 (1:1 *syn*/*anti*).

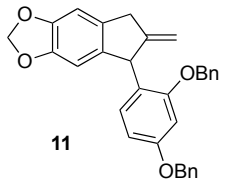


10

To a cooled (0 °C) solution of methyl ester **9** (1:1 *syn*/*anti*, 0.420 g, 0.826 mmol) in THF (69.0 mL) was added $LiAlH_4$ (62.7 mg, 1.65 mmol) portion wise over 5 minutes, with vigorous stirring. The reaction mixture was warmed to 23 °C and then heated at reflux. Upon consumption of the methyl ester (1 h), the mixture was cooled

to 23 °C. After, aqueous 0.4 M NaOH (25 mL)was added and the mixture stirred for 5 min. H_2O (50 mL) was added to help solubilize the aluminum salts. The resulting mixture was then filtered through tightly packed Celite, and the pad was rinsed with EtOAc (3 × 50 mL). The biphasic mixture was poured into a separatory funnel and the organic layer removed. The aqueous layer was extracted with EtOAc (3 × 50 mL). The combined organic layers were dried ($MgSO_4$), and concentrated *in vacuo*. The resulting crude peach solid was purified by flash chromatography (20:80 EtOAc:hexanes) to afford alcohol **10** as an inseparable 1:1 mixture of diastereomers as a white solid (0.375 g, 94%). R_f = 0.19 (20:80 EtOAc:hexanes, stains purple by *p*-anis dip stain). mp = 118–120 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.49 – 7.29 (m, 17H), 6.85 (d, *J* = 8.4 Hz, 1H), 6.73 (s, 1H), 6.70 (s, 2H), 6.69 (s, 1H), 6.68 (d, *J* = 2.4 Hz, 1H), 6.52 (dd, *J* = 8.4, 2.4 Hz, 1H), 6.49 (s, 1H), 6.46 (d, *J* = 8.0 Hz, 1H), 6.43 (s, 1H), 6.40 (d, *J* = 8.4 Hz, 0.5H), 5.93 – 5.90 (m, 3H), 5.89 (d, *J* = 1.4 Hz, 1H), 5.19 – 5.06 (m, 1H), 5.05 (s, 2H), 5.03 (s, 2H), 5.00 (s, 2H), 4.81 (d, *J* = 7.9 Hz, 1H), 4.45 (d, *J* = 7.1 Hz, 1H), 3.69 – 3.56 (m, 1H), 3.37 (s, 1H), 3.23 (t, *J* = 10.1 Hz, 1H), 3.03 – 2.98 (m, 0.4H), 2.95 (dd, *J* = 15.6, 8.1 Hz, 2H), 2.79 (dd, *J* = 15.4, 7.8 Hz, 1H), 2.66 (dd, *J* = 15.5, 7.3 Hz, 1H), 2.58 (dd, *J* = 15.4, 9.6 Hz, 1H), 2.51 (h, *J* = 7.0 Hz, 1H), 2.26 (d, *J* = 9.1 Hz, 1H), 1.68 (t, *J* = 6.2 Hz, 1H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 158.5, 157.1, 156.5, 146.8, 146.72, 146.66, 146.55, 138.8, 138.2, 136.9, 136.8, 136.3, 136.13, 136.12, 135.9, 130.3, 129.3, 128.8, 128.7, 128.6, 128.4, 128.3, 128.1, 128.0, 127.78, 127.75, 127.58, 127.57, 125.6, 122.2, 106.4, 106.0, 105.8, 105.6, 104.9, 104.8, 100.93, 100.90, 100.8, 100.5, 71.0, 70.6, 70.20, 70.18, 65.2, 63.9, 52.6, 48.2, 46.1, 44.0, 34.4, 33.7; IR (ATR) 3390, 2922, 1607, 1583, 1500, 1472, 1166, 1035 cm^{-1}; HRMS (ESI) *m* / *z* calcd for $C_{31}H_{28}O_5Na$ $[M + Na]^+$ 503.1834, found 503.1830.

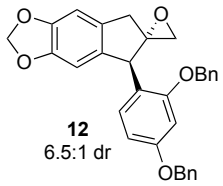
5-(2,4-Bis(benzyloxy)phenyl)-6-methylene-6,7-dihydro-5*H*-indeno[5,6-*d*][1,3]dioxole, 11.



11

A flame-dried flask was charged with alcohol **10** (0.302 g, 0.625 mmol), 2-nitrophenyl selenocyanate (0.865 g, 3.12 mmol.) and THF (2.0 mL). The heterogeneous solution was stirred briefly prior to adding P(*n*-Bu)$_3$ (0.77 mL, 3.12 mmol) dropwise over 30 min via syringe pump. Upon addition, the heterogeneous solution turned red in color. At 30 min, additional THF (1.0 mL) was added to ensure proper stirring of the slurry. The mixture was stirred at 23 °C and monitored by TLC. At 1 h 15 min, the mixture was concentrated *in vacuo* and subjected to flash chromatography (30:70 – 40:60 ether:hexanes) to afford a yellow oil that was carried on to the next step without further purification. The yellow oil was dissolved in THF (2.0 mL) and then cooled (0 °C) and stirred. Then, degassed 30% (w/w) H_2O_2 (146 μL, 6.25 mmol) was added dropwise. Upon completion (3.5 h), the cooled mixture was quenched with saturated aqueous $Na_2S_2O_3$ (0.15 mL) and stirred vigorously for 5 min. The mixture was partitioned between H_2O (30 mL) and EtOAc (15 mL). The layers were separated and the aqueous extracted with EtOAc (2 × 15 mL), ether (1 × 15 mL), and EtOAc (1 × 15 mL) in sequence. The combined organic layers were washed with saturated $NaHCO_3$ (1 × 50 mL), brine (1 × 50 mL), dried (Na_2SO_4), and concentrated *in vacuo*. The crude oil was purified by flash chromatography (2.5:0:97.5 – 2.5:8:89.5 NEt_3:EtOAc:hexanes) to afford alkene **11** as a yellow oil (0.109 g, 38%). R_f = 0.65 (20:80 EtOAc:hexanes, stains blue by *p*-anis dip stain). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47 – 7.24 (m, 10H), 6.88 (d, *J* = 8.3 Hz, 1H), 6.64 (s, 2H), 6.49 (d, *J* = 8.5 Hz, 1H), 6.45 (s, 1H), 5.86 (s, 2H), 5.24 (s, 1H), 5.12 – 4.90 (m, 4H and s, 1H), 4.87 (s, 1H), 3.62 (s, 2H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 158.6, 157.2, 154.1, 146.7, 139.0, 137.0, 136.9, 134.3, 130.1, 128.6, 128.4, 128.0, 127.8, 127.6, 127.3, 126.4, 108.3, 105.7, 105.3, 104.6, 100.74, 100.70, 70.19, 70.15, 49.5, 38.8. IR (ATR) 3064, 3032, 1721, 1608, 1036, 939, 735, 696 cm-1; HRMS (ESI) *m* / *z* calcd for $C_{31}H_{26}O_4Na$ $[M + Na]^+$ 485.1729, found 485.1752.

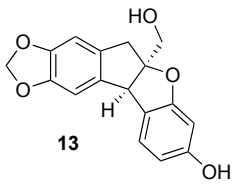
5-(2,4-Bis(benzyloxy)phenyl)-5,7-dihydrospiro[indeno[5,6-*d*][1,3]dioxole-6,2'-oxirane], 12.



12
6.5:1 dr

To a flame-dried flask was added a solution of alkene **11** (0.205 g, 0.443 mmol) in DCM (1.1 mL). The solution was stirred briefly before adding $NaHCO_3$ (49.4 mg, 0.589 mmol) and *m*-CPBA (112 mg, 0.456 mmol, 70%). The reaction was monitored by TLC for the consumption of alkene **11**. The reaction was forced to completion by adding *m*-CPBA (0.443 mmol) and DCM (0.3 mL) within 1 h, and adding *m*-CPBA (0.310 mmol), $NaHCO_3$ (0.443 mmol) and DCM (1.0 mL) at 2 h. At 3 h, the reaction was quenched with aqueous 10% (w/w) Na_2SO_3 (5 mL) and stirred vigorously for 10 min. The layers were separated and the aqueous layer was extracted with DCM (3 × 10 mL). The combined organic layers were washed with aqueous 5% (w/w) $NaHCO_3$ (1 × 30 mL), dried ($MgSO_4$), and concentrated *in vacuo*. The crude oil was purified by flash chromatography (15:85 EtOAc:hexanes) to yield epoxide **12** as an inseparable 6.5:1 mixture of diastereomers as a yellow oil (87.7 mg) containing a small amount (18 mol %, 4 wt.% by ^{1}H NMR) of EtOAc (40% yield of **12**). The major diastereomer is reported below. R_f = 0.36 (20:80 EtOAc:hexanes, stains purple by *p*-anis dip stain). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45 – 7.28 (m, 10H), 7.23 – 7.17 (m, 2H), 6.85 (d, *J* = 8.4 Hz, 1H), 6.63 (s, 1H), 6.60 (d, *J* = 2.4 Hz, 1H), 6.48 (dd, *J* = 8.5, 2.5 Hz, 1H), 6.45 (s, 1H), 5.90 (q, *J* = 1.5 Hz, 2H), 5.01 (s, 2H), 4.92 (d, *J* = 3.3 Hz, 2H), 4.54 (s, 1H), 3.19 (d, *J* = 17.2 Hz, 1H), 2.91 (d, *J* = 17.2 Hz, 1H), 2.73 (d, *J* = 4.7 Hz, 1H), 2.69 (d, *J* = 4.8 Hz, 1H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 159.2, 157.3, 147.04, 146.99, 137.5, 137.0, 136.7, 133.1, 130.6, 128.8, 128.6, 128.2, 128.0, 127.7, 127.5, 122.9, 105.5, 105.3, 104.8, 101.0, 100.9, 70.3, 70.2, 68.6, 52.1, 51.2, 38.9; HRMS (ESI) *m* / *z* calcd for $C_{31}H_{26}O_5Na$ $[M + Na]^+$ 501.1678, found 501.1678.

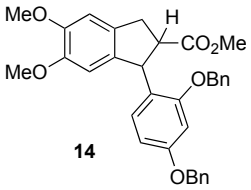
5a-(Hydroxymethyl)-5a,10b-dihydro-5*H*-[1,3]dioxolo[4',5':5,6]indeno[2,1-*b*]benzofuran-8-ol, 13.



13

A portion of the above isolated epoxide **12** (28.2 mg, 0.0589 mmol) was dissolved in 1:1 MeOH/THF (1.0 mL) and stirred at 23 °C prior to adding Pearlman's catalyst, 20 wt. % $Pd(OH)_2/C$ (20.6 mg, 0.0294 mmol). The contents of the flask were evacuated and backfilled with H_2 (× 3). Upon consumption of epoxide **12** (30 min)**,** the flask was evacuated and backfilled with N_2. The mixture was then diluted with EtOAc (3 mL) and filtered through tightly packed Celite pad. The pad was rinsed with EtOAc (3 × 10 mL), and the organic fraction purged with N_2, and concentrated *in vacuo* to afford a pink oil. The oil was purified by flash chromatography with degassed solvents (40:60 EtOAc:hexanes) to yield indano[2,1-*b*]benzofuran **13** as an off-white oil (9.0 mg) containing a small amount (5 mol %, 1.7 wt. % and 6 mol %, 1.6 wt. % by ^{1}H NMR) of EtOAc and benzene, respectively (49% yield of **13**). Benzofuran **13** was isolated as an inseparable 10:1 mixture with a structurally similar compound not matching the desired indano[2,1-*c*]chroman. This sample was stored in benzene at –20 °C. R_f = 0.47 (50:50 EtOAc:hexanes, stains pink by *p*-anis dip stain).^{1}H NMR (600 MHz, CD_3OD) δ 7.15 (d, *J* = 8.0 Hz, 1H), 6.83 (s, 1H), 6.64 (s, 1H), 6.29 (dd, *J* = 8.1, 2.2 Hz, 1H), 6.18 (d, *J* = 2.2 Hz, 1H), 5.88 (d, *J* = 1.4 Hz, 1H), 5.85 (d, *J* = 1.5 Hz, 1H), 4.51 (s, 1H), 3.76 (d, *J* = 11.8 Hz, 1H), 3.70 (d, *J* = 11.7 Hz, 1H), 3.25 (d, *J* = 17.2 Hz, 1H), 3.13 (d, *J* = 17.3 Hz, 1H). ^{13}C{^{1}H} NMR (151 MHz, CD_3OD) δ 161.6 (C), 159.2 (C), 148.9 (C), 148.7 (C), 137.7 (C), 133.9 (C), 125.3 (CH), 122.0 (C), 108.5 (CH), 106.0 (CH), 105.3 (CH), 102.3 (CH_2), 101.4 (C), 98.4 (CH), 66.3 (CH_2), 54.8 (CH), 42.5 (CH_2). IR (ATR) 3321, 1620, 1473, 1144, 1035, 963, 734 cm^{-1}. HRMS (ESI) *m / z* calcd for $C_{17}H_{14}O_5Na$ $[M + Na]^+$ 321.0739, found 321.0739.

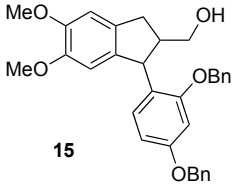
Methyl 1-(2,4-bis(benzyloxy)phenyl)-5,6-dimethoxy-2,3-dihydro-1*H*-indene-2-carboxylate, 14.



14

A round-bottom flask containing arylindane **8ba** (0.357 g, 0.608 mmol), anhydrous NaI (0.274 g, 1.83 mmol), and $NaHCO_3$ (0.205 g, 2.43 mmol) was evacuated and backfilled with N_2 (× 3). Anhydrous DMF (4.9 mL) was then added. The flask was connected to a water jacketed condenser, and then submerged in an oil bath (160 °C). The reaction was stirred and monitored for the consumption of arylindane (6 h). The mixture was cooled to 23 °C. Then, H_2O (50 mL) was added and stirred vigorously. The resulting solution was extracted with Et_2O (4 × 50 mL). The combined organic layers were washed with H_2O (× 3) and with brine (× 1). The organic solution was then dried ($MgSO_4$), and concentrated *in vacuo*. The crude peach solid was purified by flash chromatography (15:85 EtOAc:hexanes) to afford methyl ester **14** as an inseparable 1.1:1 mixture of diastereomers as a white solid (0.299 g, 94%). R_f = 0.25 (20:80 EtOAc:hexanes, stains violet by *p*-anis dip stain). mp = 39–46 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.48 (s, 2H), 7.45 – 7.26 (m, 18H), 7.22 (d, *J* = 7.4 Hz, 2H), 6.92 (d, *J* = 8.3 Hz, 1H), 6.79 (s, 1H), 6.74 (s, 1H), 6.73 – 6.69 (m, 1H), 6.64 (d, *J* = 2.4 Hz, 1H), 6.60 (d, *J* = 2.4 Hz, 1H), 6.54 (s, 1H), 6.51 (dd, *J* = 8.4, 2.4 Hz, 1H), 6.47 (s, 1H), 6.44 (dd, *J* = 8.5, 2.4 Hz, 1H), 5.25 (s, 1H), 5.07 (s, 2H), 5.03 (s, 2H), 5.02 – 4.93 (m, 5H), 3.88 (s, 4H), 3.88 (s, 3H), 3.76 (dd, *J* = 8.9, 6.5 Hz, 1H), 3.74 (s, 3H), 3.73 (s, 3H), 3.53 (s, 3H), 3.42 (dd, *J* = 15.8, 6.5 Hz, 1H), 3.35 (q, *J* = 7.8 Hz, 1H), 3.19 (s, 3H), 3.17 (d, *J* = 8.1 Hz, 2H), 3.04 (dd, *J* = 15.8, 8.5 Hz, 1H); ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 175.7, 174.0, 158.9, 158.7, 157.5, 157.4, 148.6, 148.5, 148.46, 148.4, 137.1, 136.9, 136.8, 136.4, 135.6, 134.4, 133.2, 129.9, 129.85, 128.6, 128.57, 128.5, 128.4, 128.05, 127.99, 127.9, 127.7, 127.6, 127.3, 127.1, 124.7, 122.7, 108.0, 107.7, 107.22, 107.17, 105.4, 105.3, 100.6, 100.2, 70.2, 70.17, 70.05, 69.95, 56.1, 56.03, 56.02, 56.0, 52.2, 51.7, 51.1, 49.3, 35.6, 34.4; IR (ATR) 2946, 1730, 1606, 1583, 1502, 1164, 1092, 1025, 735 cm^{-1}; HRMS (ESI) *m* / *z* calcd for $C_{33}H_{32}O_6Na$ $[M + Na]^+$ 547.2097, found 547.2084.

(1-(2,4-Bis(benzyloxy)phenyl)-5,6-dimethoxy-2,3-dihydro-1*H*-inden-2-yl)methanol, 15.

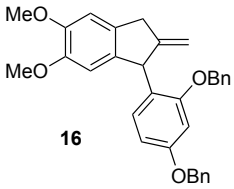


15

To a cooled (0 °C) solution of methyl ester **14** (1.1:1 mixture of diastereomers 0.277 g, 0.528 mmol) in THF (40.0 mL) was added $LiAlH_4$ (40.0 mg, 1.06 mmol) portion wise over 5 minutes, with vigorous stirring. The reaction mixture was warmed to 23 °C and then heated at reflux. Upon consumption of the methyl ester (1 h), the mixture was cooled to 23 °C. After, aqueous 0.4 M NaOH (40 mL) was added and the mixture stirred for 5 min. H_2O (80 mL) was added to help solubilize the aluminum salts. The resulting mixture was then filtered through tightly packed Celite, and the pad was rinsed with EtOAc (3 × 50 mL). The biphasic mixture was poured into a separatory funnel, and the aqueous phase extracted with EtOAc (3 x 50 mL). The combined organic fractions were dried ($MgSO_4$), and concentrated *in vacuo*. The resulting crude yellow solid was purified by flash chromatography (20:80 – 40:60 EtOAc:hexanes) to afford alcohol **15** an inseparable 1:1 mixture of diastereomers as a white solid (0.246 g, 94%). R_f = 0.28 (40:60 EtOAc:hexanes, stains bluish-purple by *p*-anis dip stain). mp = 48–55 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.52 – 7.30 (m, 19H), 6.82 (d, *J* = 8.5 Hz, 1H), 6.81 (s, 1H), 6.77 (s, 1H), 6.72 (s, 1H), 6.69 (d, *J* = 2.4 Hz, 1H), 6.57 (s, 1H), 6.52 (dd, *J* = 8.6, 2.6 Hz, 1H), 6.51 (s, 1H), 6.48 – 6.42 (m, 1H), 6.37 (d, *J* = 8.5 Hz, 1H), 5.19 – 5.05 (m, 4H), 5.03 (s, 2H), 5.01 (s, 2H), 4.86 (d, *J* = 8.0 Hz, 1H), 4.51 (d, *J* = 6.7 Hz, 1H), 3.89 (s, 3H), 3.88 (s, 3H), 3.77 (s, 3H), 3.75 (s, 3H), 3.63 (q, *J* = 5.5 Hz, 2H), 3.38 (s, 1H), 3.24 (t, *J* = 10.0 Hz, 1H), 3.00 (dt, *J* = 14.8, 7.5 Hz, 2H), 2.84 (dd, *J* = 15.3, 7.8 Hz, 1H), 2.69 (dd, *J* = 15.5, 7.0 Hz, 1H), 2.63 (dd, *J* = 15.3, 9.5 Hz, 1H), 2.49 (h, *J* = 6.5 Hz, 1H), 2.27 (d, *J* = 9.5 Hz, 1H), 1.73 (s, 1H); The absence of 1H from the 7.52 – 7.30 region is likely due to differences in relaxation delay times. With longer relaxation delay (d1 = 15 s), the integration for the 7.52 – 7.30 region is 20H. ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 158.56, 158.52, 157.1, 156.6, 148.37, 148.35, 148.29, 148.23,

137.7, 136.9, 136.85, 136.83, 136.4, 136.2, 135.0, 134.9, 130.4, 129.2, 128.8, 128.7, 128.6, 128.4, 128.3, 128.08, 128.06, 127.8, 127.6, 125.9, 122.5, 108.3, 107.6, 107.3, 106.4, 106.0, 100.9, 100.4, 71.0, 70.6, 70.22, 70.20, 65.4, 64.0, 56.1, 56.01, 56.00, 52.6, 48.2, 46.3, 44.3, 34.5, 33.9; IR (ATR) 3513, 2932, 1605, 1582, 1500, 1292, 1248, 1216, 1165, 1090, 1024, 735 cm^{-1}; HRMS (ESI) *m* / *z* calcd for $C_{32}H_{32}O_5Na$ $[M + Na]^+$ 519.2147, found 519.2148.

1-(2,4-Bis(benzyloxy)phenyl)-5,6-dimethoxy-2-methylene-2,3-dihydro-1*H*-indene, 16.



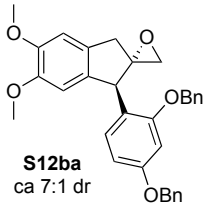
16

A flame-dried flask was charged with alcohol **15** (0.300 g, 0.604 mmol), 2-nitrophenyl selenocyanate (0.837 g, 3.02 mmol.) and THF (2.0 mL). The heterogeneous solution was stirred briefly prior to adding P(*n*-Bu)$_3$ (0.75 mL, 3.02 mmol) dropwise over 30 min via syringe pump. Upon addition, the heterogeneous solution turned red in color. At 30 min, additional THF (1.0 mL) was added to ensure proper stirring of the slurry. The mixture was stirred at 23 °C and monitored by TLC. At 3.5 h, the mixture was concentrated *in vacuo* and subjected to flash chromatography (15:85 – 40:60 EtOAc:hexanes) to afford a yellow oil that was carried on to the next step without further purification. The yellow oil was dissolved in THF (2.0 mL) and then cooled (0 °C) and stirred. Degassed 30% (w/w) H_2O_2 (142 μL, 6.04 mmol) was then added dropwise. Upon completion (5.5 h), the cooled mixture was quenched with saturated aqueous $Na_2S_2O_3$ (0.15 mL) and stirred vigorously for 5 min. The mixture was partitioned between H_2O (20 mL) and EtOAc (20 mL). The layers were separated and the aqueous extracted with EtOAc (2 × 15 mL), and ether (1 × 15 mL). The combined organic layers were washed with saturated $NaHCO_3$ (1 × 50 mL), brine (1 × 50 mL), dried (Na_2SO_4), and concentrated *in vacuo*. The crude oil was purified by flash chromatography (2.5:0:97.5 – 2.5:8:89.5 NEt_3:EtOAc:hexanes) to yield alkene **16** as a yellow oil (0.161 g) containing a small amount (4 mol %, 4 wt. %, by ^1H NMR) of bis(*o*-nitrophenyl) diselenide (54% yield of **16**). R_f = 0.28 (20:80

EtOAc:hexanes, stains blue by *p*-anis dip stain). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.45 – 7.40 (m, 2H), 7.41 – 7.36 (m, 2H), 7.37 – 7.27 (m, 6H), 6.87 (d, *J* = 8.4 Hz, 1H), 6.73 (s, 1H), 6.66 (d, *J* = 2.4 Hz, 1H), 6.53 (s, 1H), 6.50 (dd, *J* = 8.4, 2.4 Hz, 1H), 5.30 (s, 1H), 5.04 (d, *J* = 3.8 Hz, 3H), 5.02 (s, 2H), 4.90 (q, *J* = 2.4 Hz, 1H), 3.87 (s, 3H), 3.72 (s, 3H), 3.67 (d, *J* = 2.8 Hz, 2H); ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 158.5, 157.2, 154.3, 148.4, 148.3, 137.7, 137.02, 136.98, 133.4, 130.0, 128.6, 128.4, 128.0, 127.8, 127.6, 127.3, 126.6, 108.3, 107.8, 107.2, 105.7, 100.7, 70.17, 70.15, 56.01, 55.98, 49.6, 38.8. IR (ATR) 3064, 3031, 1710, 1656, 1606, 1501, 1168, 1026, 735, 697 cm^{-1}; HRMS (ESI) *m* / *z* calcd for $C_{32}H_{30}O_4Na$ $[M + Na]^+$ 501.2042, found 501.2034.

Data for bis(o-nitrophenyl) diselenide for comparison. Peaks present in ^{1}H and ^{13}C NMR of alkene **16** corresponding to diselenide: ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.36 (dd, *J* = 8.2, 1.4 Hz, 2H), 7.91 (dd, *J* = 8.2, 1.3 Hz, 2H), 7.50 (ddd, *J* = 8.3, 7.1, 1.5 Hz, 2H), 7.46 – 7.41 (m, 2H of impurity and overlapping m, 50 H of **16**). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 134.8, 131.6, 128.8, 127.6, 126.4. Previously reported data[38]: ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.37 (d, 2H, *J* = 4 Hz), 7.92 (d, 2H, *J* = 8 Hz), 7.50–7.52 (m, 2H), 7.42–7.46 (m, 2H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 134.8, 131.6, 128.8, 127.6, 126.4.

1-(2,4-Bis(benzyloxy)phenyl)-5,6-dimethoxy-1,3-dihydrospiro[indene-2,2'-oxirane], S12ba.

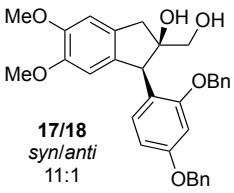


S12ba
ca 7:1 dr

A sample of alkene **16** (0.1037g, 0.287 mmol) was dissolved in DCM (0.72 mL) at 23 °C. Purified *m*-CPBA (51.0 mg, 0.296 mmol) was added in one portion. The reaction was driven to completion by adding *m*-CPBA (0.296 mmol) at 1 h 15 min, and again at 2.5 h. Additional DCM (0.70 mL) was added at 2.5 h to ensure proper stirring. At 3.5 h, the reaction was quenched with aqueous10% (w/w) Na_2SO_3 (3 mL). The mixture was stirred vigorously for 5 min and then partitioned between H_2O (10 mL) and DCM (10 mL). The layers were separated and the aqueous extracted with DCM (2 × 10 mL). The combined organic

layers were washed with 5% (w/w) $NaHCO_3$ (1 × 25 mL), dried (Na_2SO_4), purged with N_2 for 20 min, and then concentrated *in vacuo* to afford a yellow brown oil. The oil was purified by flash chromatography (10:90 – 20:80 EtOAc:hexanes) to yield epoxide **S12ba** as an inseparable 7.6:1 mixture of diastereomers as a yellow oil (42.2 mg) containing a small amount (8 mol %, 2 wt. % by ^{1}H NMR) of EtOAc (29% yield of **S12ba**). Crystals suitable for X-ray diffraction were obtained through vapor diffusion of hexane into a solution of S12ba in dichloromethane. R_f = 0.21 (20:80 EtOAc:hexanes, stains purple by *p*-anis dip stain). Major diastereomer: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.44 – 7.26 (m, 10H), 7.20 (d, *J* = 7.2 Hz, 2H), 6.83 (d, *J* = 8.3 Hz, 1H), 6.70 (s, 1H), 6.61 (d, *J* = 2.4 Hz, 1H), 6.52 (s, 1H), 6.48 (dd, *J* = 8.4, 2.4 Hz, 1H), 5.01 (s, 3H), 4.98 – 4.88 (m, 2H), 4.60 (s, 1H), 3.88 (s, 3H), 3.72 (s, 3H), 3.28 (dd, *J* = 17.0, 3.9 Hz, 1H), 2.94 (d, *J* = 17.1 Hz, 1H), 2.75 (d, *J* = 4.8 Hz, 1H), 2.72 (d, *J* = 4.8 Hz, 1H); ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 159.0, 157.2, 148.6, 148.5, 136.9, 136.6, 136.3, 132.1, 130.4, 128.6, 128.4, 128.1, 127.9, 127.6, 127.3, 123.1, 107.7, 107.2, 105.4, 100.8, 70.2, 70.1, 68.6, 56.0, 55.97, 51.8, 51.2, 38.8. IR (ATR) 3065, 3028, 3010, 2991, 2960, 2908, 2863, 2834, 1608, 1582, 1501, 1172, 1084, 1028, 739, 692 cm $^{-1}$; HRMS (ESI) *m* / *z* calcd for $C_{32}H_{30}O_5Na$ $[M + Na]^+$ 517.1991, found 517.1999.

1-(2,4-Bis(benzyloxy)phenyl)-2-(hydroxymethyl)-5,6-dimethoxy-2,3-dihydro-1*H*-inden-2-ol, 17/18 (11:1 *syn*/*anti*).

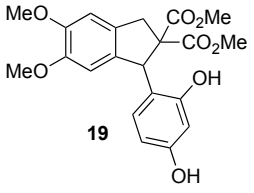


17/18
syn/*anti*
11:1

To a cooled (0 °C) solution of alkene **16** (9.0 mg, 18.8 μmol) and NMO (6.6 mg, 56.4 μmol) in DCM (0.22 mL) was added OsO_4 (6.0 μL, 0.94 μmol, 4 wt. % in H_2O). The mixture was stirred at 0 °C for 5 h, and then warmed to 23 °C to stir for an additional 14 h. After, the mixture was quenched with 5 wt. % $NaHSO_3$ (4.0 mL) and stirred for 15 min. The layers were separated and the aqueous extracted with DCM (3 × 10 mL). The combined organic layers were dried ($MgSO_4$), and concentrated *in vacuo* to afford a crude

orange solid. The solid was purified by flash chromatography (20:80 – 40:60 EtOAc:hexanes) to afford diols *syn*-**17** and *anti*-**18** as an inseparable 11:1 mixture of diastereomers as a white solid (8.5 mg, 89%). R_f = 0.15 (50:50 EtOAc/hexanes; stains pink by *p*-anis dip stain). The *anti*-**18** diol has been previously characterized.[19] Peaks for the major *syn*-**17** diol are reported. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.52 – 7.31 (m, 10H and m, 1 H), 6.82 (s, 1H), 6.74 (s, 1H), 6.59 (s, 1H), 6.48 (s, 2H), 5.19 (d, *J* = 11.2 Hz, 1H), 5.09 (d, *J* = 11.4 Hz, 1H), 5.06 (s, 1H), 5.02 (s, 2H), 4.82 (s, 0.09H, *anti*), 4.74 (s, 1H, *syn*), 3.89 (s, 3H), 3.78 (s, 3H), 3.31 (d, *J* = 11.5 Hz, 1H), 3.25 (d, *J* = 11.7 Hz, 1H), 3.13 (s, 1H), 3.06 (d, *J* = 16.0 Hz, 1H), 2.83 (d, *J* = 16.0 Hz, 1H), 2.43 (s, 1H); ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 158.8, 156.8, 148.7, 148.6, 136.7, 135.8, 135.4, 133.2, 129.6, 128.9, 128.7, 128.6, 128.1, 127.9, 127.6, 127.6, 121.7, 108.7, 107.9, 106.7, 101.2, 85.5, 71.3, 70.3, 70.3, 66.6, 56.0, 53.9, 41.4. IR (ATR) 3350, 2938, 2921, 2851, 1608, 1584, 1504, 1215, 1175, 1094 cm^{-1}; HRMS (ESI) *m / z* calcd for $C_{32}H_{32}O_6Na$ $[M + Na]^+$ 535.2097, found 535.2098. Stereochemical assignment of major (17) and minor (18) diols by correlation with ^{13}C NMR data is available in the supporting information.

Dimethyl 1-(2,4-dihydroxyphenyl)-5,6-dimethoxy-1,3-dihydro-2*H*-indene-2,2-dicarboxylate, 19.

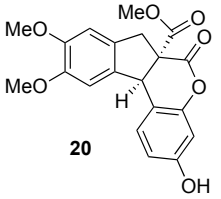


19

A reaction mixture containing arylindane **8ba** (1.5 g, 2.57 mmol) and 20 wt.% $Pd(OH)_2$/C (442 mg, 0.629 mmol) in a solution of 1:1 MeOH/THF (88.0 mL) was evacuated and backfilled with H_2 (× 3). Arylindane **8ba** was consumed within 30 min. The flask was evacuated and backfilled with N_2 (× 3), and the reaction mixture diluted with EtOAc (40 mL). The heterogenous mixture was filtered through tightly packed Celite and the pad washed with EtOAc (3 × 50 mL). The organic was concentrated *in vacuo* to afford a black solid. The solid was purified by flash chromatography (45:55 EtOAc:hexanes) to

yield resorcinol **19** and chromanone **20** (1.08 g) as an inseparable 2.1:1 mixture. This mixture was used in the next step without further purification. In a different run, an analytical sample of resorcinol **19** was obtained by chromatography. R_f = 0.18 (50:50 EtOAc:hexanes). mp = 138–142 °C (shrinkage begins at 80 °C; sharp melt at 138–142 °C). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.38 (s, 1H), 6.78 (s, 1H), 6.61 (d, *J* = 8.5 Hz, 1H), 6.50 (d, *J* = 2.6 Hz, 1H), 6.42 (s, 1H), 6.29 (dd, *J* = 8.5, 2.6 Hz, 1H), 5.41 (s, 1H), 5.15 (s, 1H), 3.89 (s, 3H), 3.86 (s, 3H), 3.80 (d, *J* = 16.3 Hz, 1H), 3.73 (s, 3H), 3.30 (d, *J* = 16.3 Hz, 1H), 3.19 (s, 3H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 175.9, 170.0, 157.1, 156.4, 149.1, 148.7, 133.1, 132.2, 130.2, 117.6, 108.2, 107.6, 106.7, 104.2, 67.2, 56.1, 56.0, 53.9, 52.4, 50.3, 39.6; IR (ATR) 3418, 2953, 1713, 1621, 1505, 1454, 1262, 1216, 1112, 1087, 1055, 975 cm^{-1}; HRMS (ESI) *m / z* calcd for $C_{21}H_{22}O_8Na$ $[M + Na]^+$ 425.1212, found 425.1212.

Methyl 3-hydroxy-9,10-dimethoxy-6-oxo-7,11b-dihydroindeno[2,1-*c*]chromene-6a(6*H*)-carboxylate, 20.

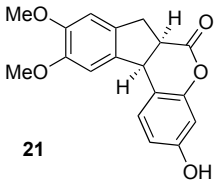


20

A solution of the 2.1:1 mixture of resorcinol **19** and chromanone **20** (1.08 g) described above, and *p*-toluenesulfonic acid hexahydrate (133 mg, 0.772 mmol) in toluene (103 mL) was heated at reflux. When resorcinol **19** was no longer detected by TLC (1 h), the mixture was cooled to 23 °C and partitioned between EtOAc (50 mL) and saturated aqueous $NaHCO_3$ (100 mL). The layers were separated and the organic layer washed sequentially with H_2O and brine. The organic was then dried ($MgSO_4$) and concentrated *in vacuo* to afford a peach solid that was purified by flash chromatography (40:60 – 60:40 EtOAc:hexanes) to afford chromanone **20** as a peach solid (0.889 g, 93% over two steps). R_f = 0.14 (40:60 EtOAc:hexanes). mp = 188–190 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.27 (d, *J* = 2.0 Hz, 1H), 6.79 (s, 1H), 6.75 (dd, *J* = 8.2, 2.5 Hz, 1H), 6.65 (d, *J* = 2.5 Hz, 1H), 6.42 (s, 1H), 5.95 (s, 1H), 4.72 (s, 1H), 3.92 (d, *J* = 15.2 Hz, 1H), 3.85 (s, 3H), 3.75 (s, 3H), 3.72 (s, 3H), 3.64 (d, *J* = 15.2 Hz, 1H);

$^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$) δ 169.8, 167.4, 156.7, 151.0, 149.5, 149.0, 132.2, 130.7, 129.8, 112.4, 112.2, 107.7, 106.5, 104.6, 61.3, 56.10, 56.09, 53.5, 50.5, 40.5; IR (ATR) 3432, 2953, 1737, 1629, 1503, 1457, 1306, 1244, 1160 cm^{-1}; HRMS (ESI) *m / z* calcd for $C_{20}H_{18}O_7Na$ $[M + Na]^+$ 393.0950, found 393.0944.

3-hydroxy-9,10-dimethoxy-7,11b-dihydroindeno[2,1-*c*]chromen-6(6a*H*)-one, 21.



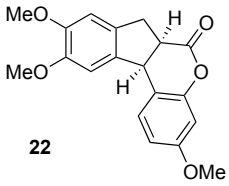
21

All glassware was oven-dried or flame-dried. A 5 mL round-bottom flask half-filled with KCl was placed under vacuum, and flame-dried until the salt no longer adhered to the flask wall. All materials were kept under N_2. DMSO was stored over 3 Å molecular sieves in a Schlenk flask. Chromanone **20** (50 mg, 0.135 mmol) and KCl (106 mg, 1.42 mmol) were quickly added to a 10 mL round-bottom flask. The flask was connected to a condenser. The set-up was evacuated, backfilled with N_2 and capped tightly with a rubber septum. A steady stream of N_2 was added through the top of the condenser. Anhydrous DMSO (2.7 mL) was then added through the top of the condenser. The mixture was heated at 160 °C and stirred for 2 h 40 min. At 2 h 40 min, the reaction was removed from the oil bath and cooled to 23 °C while stirring. Then, brine (4.0 mL) was added, causing a precipitate to form. Additional brine (1.0 mL) was added if no precipitate formed. The mixture was briefly stirred and then poured into a separatory funnel containing brine (15 mL). The aqueous layer was extracted with EtOAc (3 × 15 mL) and the combined organic layers then washed with water (3 × 50 mL). The organic layer was dried (Na_2SO_4), and concentrated *in vacuo*.

This reaction was performed six times in parallel to bring up material as scaling the reaction led to lower yields, on average. Combining reactions producing identical ^{1}H NMR led to fraction A and fraction B. These were purified separately by flash chromatography (25:75 – 40:60 EtOAc:hexanes). Fraction A and B afforded phenol **21** as a yellow solid (45 mg, 18%) and (18

mg, 7%) respectively. The phenol, **21**, from fraction A and B were triturated, separately, with distilled hexanes to afford analytical samples for characterization (38 mg, 15%) and (15 mg, 6%) respectively, for a combined yield of 53 mg (21%). ^{1}H and ^{13}C{^{1}H} NMR for both samples were identical. R_f = 0.08 (30:70 EtOAc:hexanes). R_f = 0.23 (40:60 EtOAc:hexanes). ^{1}H NMR (499 MHz, $CDCl_3$) δ 7.26 (s, 1H), 6.82 (s, 1H), 6.72 (d, *J* = 8.3 Hz, 1H), 6.63 (s, 1H), 6.60 (s, 1H), 6.08 (s, 1H), 4.41 (d, *J* = 7.3 Hz, 1H), 3.85 (s, 3H), 3.79 (s, 3H), 3.63 – 3.52 (m, 2H), 3.25 (dd, *J* = 15.3, 7.0 Hz, 1H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 170.6, 156.4, 151.3, 149.1, 148.7, 134.3, 132.6, 129.7, 113.3, 112.2, 108.0, 107.0, 104.4, 56.2, 56.1, 44.7, 44.3, 35.5; IR (ATR) 3402, 2947, 1720, 1634, 1601, 1503, 1449, 1348, 1297, 1227, 1160, 1081, 852 cm^{-1}; HRMS (ESI) *m / z* calcd for $C_{18}H_{16}O_5Na$ $[M + Na]^+$ 335.0895, found 335.0898; ^{1}H NMR data of same sample, at a different time, with resolved peaks. ^{1}H NMR (499 MHz, $CDCl_3$) δ 7.26 (s, 1H), 6.82 (s, 1H), 6.72 (dd, *J* = 8.3, 2.5 Hz, 1H), 6.63 (d, *J* = 2.5 Hz, 1H), 6.60 (s, 1H), 5.55 (s, 1H), 4.41 (d, *J* = 7.3 Hz, 1H), 3.85 (s, 3H), 3.79 (s, 3H), 3.58 (dd, *J* = 15.3, 2.7 Hz, 1H), 3.51 (td, *J* = 7.2, 2.7 Hz, 1H), 3.25 (dd, *J* = 15.2, 7.0 Hz, 1H). The main byproduct results from in-situ methylation of phenol **21** to afford chromanone **22** (127 mg, 48%).

3,9,10-Trimethoxy-7,11b-dihydroindeno[2,1-*c*]chromen-6(6a*H*)-one, 22.

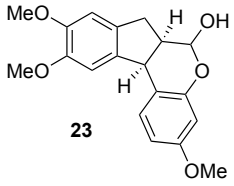


22

A partial sample of phenol **21** (47 mg, 0.15 mmol), described above, anhydrous K_2CO_3 (63 mg, 0.45 mmol), and dimethyl sulfate (43 μL, 0.45 mmol) in acetone (7.5 mL) were heated at reflux and monitored for consumption of phenol **21**. At 2 h, additional dimethyl sulfate (0.45 mmol) was added. At 5 h, additional K_2CO_3 (0.45 mmol) was added. Within 9 h, phenol **21** was consumed as determined by TLC. After the reaction was cooled to 23 °C, the solvent was removed *in vacuo*. The residue was partitioned between H_2O (10 mL) and EtOAc (10 mL). The layers were separated and the aqueous extracted

with EtOAc (2 × 10 mL). The combined organic layers were dried ($MgSO_4$), and concentrated *in vacuo* to afford a mixture that was purified by flash chromatography (25:75 EtOAc: hexanes) to yield chromanone **22** as a pale yellow solid (44 mg, 90%). R_f = 0.23 (30:70 EtOAc:hexanes). R_f = 0.35 (40:60 EtOAc:hexanes). mp = 145–149 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.30 (d, *J* = 8.4 Hz, 1H), 6.82 (s, 1H), 6.78 (dd, *J* = 8.4, 2.6 Hz, 1H), 6.61 (d, *J* = 2.6 Hz, 1H), 6.60 (s, 1H), 4.42 (d, *J* = 7.3 Hz, 1H), 3.85 (s, 3H), 3.81 (s, 3H), 3.80 (s, 3H), 3.58 (dd, *J* = 15.3, 2.8 Hz, 1H), 3.51 (td, *J* = 7.2, 2.8 Hz, 1H), 3.25 (dd, *J* = 15.1, 7.2 Hz, 1H); ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 170.1, 160.0, 151.4, 149.1, 148.7, 134.2, 132.5, 129.4, 113.4, 111.0, 107.9, 106.9, 102.5, 56.14, 56.07, 55.5, 44.8, 44.3, 35.5; IR (ATR) 1754, 1626, 1588, 1504, 1154, 1103, 1080, 829 cm^{-1}; HRMS (ESI) *m / z* calcd for $C_{19}H_{18}O_5Na$ $[M + Na]^+$ 349.1052, found 349.1049.

3,9,10-Trimethoxy-6,6a,7,11b-tetrahydroindeno[2,1-*c*]chromen-6-ol, 23.

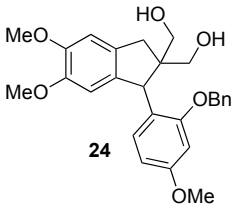


23

To a cooled (–78 °C) solution of chromanone **22** (40.0 mg, 0.123 mmol) in DCM (0.82 mL) was added DIBAL–H (0.13 mL, 0.129 mmol, 1M in THF) dropwise over three minutes. Stirring continued at –78 °C until chromanone **22** was no longer detected by TLC. Within 15 min, a light-yellow solid appeared. At 1 h, additional DCM (1.0 mL) was added to solubilize the yellow solid. The mixture was warmed to 23 °C at 3 h when no reaction progress was detected. Stirring at 23 °C for 1 h did not result in any observable effect by TLC. At 4 h and 6 h, the flask was briefly cooled (–78 °C) and DIBAL–H (0.123 mmol) added dropwise over five minutes. By 7 h, there was approximately 5% chromanone **22** remaining and the reaction was briefly cooled (–78 °C), quenched with H_2O (3.0 mL), and warmed to 23 °C. The mixture was extracted with Et_2O (3 ×15 mL) and the combined organic layers washed with brine (1 × 15 mL), dried (Na_2SO_4), and concentrated *in vacuo* to afford a crude white solid. The crude mixture was purified by flash chromatography (25:75 EtOAc:hexanes) to yield lactol **23** as

an inseparable 5.8:1 mixture of diastereomers as a white solid (19.4 mg, 48%). The major side-products resulted from over-reduction. The $^{13}C\{^1H\}$ NMR was obtained using lactol **23** from a different run. R_f = 0.10 (25:75 EtOAc:hexanes). R_f = 0.15 (30:70 EtOAc:hexanes). R_f = 0.24 (40:60 EtOAc:hexanes). ^1H NMR (500 MHz, $CDCl_3$) δ 7.30 (d, *J* = 8.6 Hz, 1H), 6.90 (s, 1H), 6.77 (s, 1H), 6.61 (dd, *J* = 8.5, 2.5 Hz, 1H), 6.45 (d, *J* = 2.5 Hz, 1H), 5.11 (t, *J* = 5.9 Hz, 1H), 4.33 (d, *J* = 7.1 Hz, 1H), 3.87 (s, 3H), 3.85 (s, 3H), 3.77 (s, 3H), 3.12 (dd, *J* = 15.6, 7.3 Hz, 1H), 3.08 – 2.97 (m, 2H), 2.85 – 2.74 (m, 1H); $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$) δ 159.3, 152.4, 148.6, 148.3, 137.0, 132.4, 129.8, 115.6, 108.6, 108.2, 107.7, 102.3, 94.2, 56.2, 56.1, 55.3, 44.1, 42.4, 33.6; IR (ATR) 3446, 2930, 2850, 1617, 1582, 1501, 1302, 1258, 1222, 1198, 1158, 1125, 1031, 843, 734 cm^{-1}. HRMS (ESI) *m / z* calcd for $C_{19}H_{20}O_5Na$ $[M + Na]^+$ 351.1208, found 351.1208. ^1H NMR data of same sample containing resolved peaks of major diastereomer: ^1H NMR (500 MHz, $CDCl_3$) δ 7.30 (d, *J* = 8.5 Hz, 1H), 6.90 (s, 1H), 6.77 (s, 1H), 6.61 (dd, *J* = 8.5, 2.6 Hz, 1H), 6.45 (d, *J* = 2.6 Hz, 1H), 5.11 (t, *J* = 6.0 Hz, 1H), 4.33 (d, *J* = 7.2 Hz, 1H), 3.87 (s, 3H), 3.84 (s, 3H), 3.77 (s, 3H), 3.12 (dd, *J* = 15.7, 7.3 Hz, 1H), 3.03 (dd, *J* = 15.7, 4.7 Hz, 1H), 2.98 (d, *J* = 5.8 Hz, 1H), 2.79 (dt, *J* = 12.0, 7.0 Hz, 1H).

(1-(2-(Benzyloxy)-4-methoxyphenyl)-5,6-dimethoxy-2,3-dihydro-1*H*-indene-2,2-diyl)dimethanol, 24.

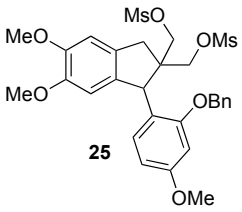


24

In one portion, $LiAlH_4$ (300 mg, 7.89 mmol) was added to a stirring, chilled (0 °C) solution of arylindane **8bb** (1.00 g, 1.97 mmol) in THF (22.0 mL). Additional THF (14.0 mL) was added to rinse the $LiAlH_4$ off the walls of the flask. The reaction was stirred (23 °C) and quenched with saturated aqueous potassium sodium tartrate solution (65.0 mL) upon consumption of arylindane **8bb** (1 h 10 min). The mixture was stirred vigorously for 15 min and then extracted with EtOAc (3 × 75 mL). The combined organic

layers were dried (Na_2SO_4) and concentrated *in vacuo* to afford a peach solid. The solid was dissolved in minimal EtOAc with light heating. After cooling to 23 °C, the solution was chilled (0 °C) and room temperature hexanes was added slowly, until a cloudy suspension remained in the solution while swirling. The persistent cloudy suspension was kept cool (0 °C) until the amount of precipitate forming remained unchanged. The resulting suspension was filtered to yield geminal alcohol **24** as a white solid (635 mg, 71%). The additional peaks in the ^{1}H NMR are determined to be of rotamers and not impurities. This was the assignment based on the 1D NOE data obtained for arylindane **8bb**. R_f = 0.19 (50:50 EtOAc:hexanes, stains purple by *p*-anis dip stain). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.49 (d, *J* = 7.0 Hz, 2H), 7.43 (t, *J* = 7.4 Hz, 2H), 7.39 – 7.33 (m, 1H), 6.77 (s, 1H), 6.65 (d, *J* = 2.4 Hz, 1H), 6.51 – 6.48 (m, 2H), 6.41 (dd, *J* = 8.5, 2.4 Hz, 1H), 5.18 (d, *J* = 11.1 Hz, 1H), 5.09 (d, *J* = 11.1 Hz, 1H), 4.65 (s, 1H), 3.88 (s, 3H), 3.79 (s, 3H), 3.75 (s, 3H), 3.73 (d, *J* = 4.4 Hz, 1H), 3.65 (dd, *J* = 11.0, 4.6 Hz, 1H), 3.41 – 3.37 (m, 2H), 2.73 (s, 2H), 2.60 (d, *J* = 6.2 Hz, 1H), 2.33 (t, *J* = 6.1 Hz, 1H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 159.5, 156.6, 148.45, 148.36, 136.8, 135.9, 133.6, 130.7, 128.8, 128.5, 127.9, 122.2, 108.5, 107.6, 105.6, 100.1, 71.1, 68.7, 67.0, 56.0, 55.4, 54.3, 46.9, 37.0; IR (ATR) 3230, 2933, 1606, 1584, 1503, 1216, 1162, 1093, 1043 cm^{-1}; HRMS (ESI) *m / z* calcd for $C_{27}H_{30}O_6Na$ [M + Na]$^+$ 473.1940, found 473.1929.

(1-(2-(Benzyloxy)-4-methoxyphenyl)-5,6-dimethoxy-2,3-dihydro-1*H*-indene-2,2-diyl)bis(methylene) dimethanesulfonate, 25.



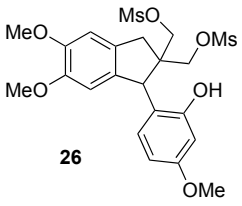
25

To a stirring, chilled (0 °C) solution of a separate batch of alcohol **24** (0.976 g, 2.16 mmol) in DCM (15.5 mL) was added NEt_3 (0.700 mL, 5.05 mmol) and mesyl chloride (0.391 mL, 5.05 mmol). NEt_3 and mesyl chloride were purified prior to use. The yellow reaction mixture was kept chilled for the duration of the reaction. At 1.5 h, mesyl chloride (0.100 mL, 1.29 mmol) was added and at 2 h, NEt_3 (0.200 mL, 1.43 mmol)

was added to drive complete consumption of starting alcohol. At 2.5 h, the starting alcohol was no longer detectable by TLC. The mixture was then diluted with DCM (15 mL) and washed with chilled portions of H_2O (1 × 30 mL) and aqueous 5% HCl (1 × 30 mL). Then, the organic was washed with saturated aqueous $NaHCO_3$ (1 × 30 mL) and brine (1 × 30 mL). The organic layer was dried ($MgSO_4$), and concentrated *in vacuo* to afford a crude pink solid that was purified by flash chromatography (10:90 to 30:70 EtOAc:toluene) to yield bis(mesylate) **25** as a fluffy white solid (1.29 g, 95%). The additional peaks in the ^{1}HNMR are determined to be due to rotamers using the method of Ley and co-workers.[25] Major peaks for bis(mesylate) **25** and minor peaks of rotamer, are reported below. Major peaks: R_f = 0.39 (30:70 EtOAc:toluene, stains pink by *p*-anis dip stain). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.53 (d, *J* = 7.4 Hz, 2H), 7.44 (t, *J* = 7.2 Hz, 2H), 7.36 (t, *J* = 7.4 Hz, 1H), 6.76 (s, 1H), 6.60 (d, *J* = 3.1 Hz, 1H), 6.50 (s, 2H), 6.37 (dd, *J* = 7.6, 3.8 Hz, 1H), 5.15 (d, *J* = 11.3 Hz, 1H), 5.09 (d, *J* = 11.3 Hz, 1H), 4.81 (s, 1H), 4.23 (s, 2H), 4.08 (d, *J* = 9.7 Hz, 1H), 3.89 (d, *J* = 2.6 Hz, 4H), 3.78 – 3.77 (m, 3H), 3.77 – 3.75 (m, 3H), 2.99 (d, *J* = 16.4 Hz, 1H), 2.87 (d, *J* = 16.5 Hz, 1H), 2.79 – 2.76 (m, 3H), 2.74 – 2.70 (m, 3H); ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 160.0, 157.4, 149.1, 149.0, 136.7, 135.3, 131.9, 130.4, 128.8, 128.3, 128.0, 120.0, 108.4, 107.4, 104.9, 99.7, 71.2, 70.6, 70.2, 56.05, 56.02, 55.4, 50.8, 47.0, 38.0, 36.9, 36.8; Minor peaks of rotamer: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.35 (s, 1H), 7.25 – 7.18 (m, 3H), 6.87 (d, *J* = 7.2 Hz, 2H), 6.48 (s, 4H), 6.41 (s, 1H), 4.78 (d, *J* = 11.1 Hz, 1H), 4.54 (d, *J* = 10.9 Hz, 1H), 4.19 (d, *J* = 8.6 Hz, 2H), 4.00 (d, *J* = 9.2 Hz, 1H), 3.90 (s, 2H), 3.83 (s, 3H), 3.79 (d, *J* = 2.3 Hz, 4H), 3.74 (s, 3H), 3.05 – 3.02 (m, 3H), 2.64 (d, *J* = 2.3 Hz, 4H); ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 160.7, 157.9, 148.6, 148.5, 135.6, 134.9, 133.5, 131.7, 128.3, 128.2, 128.1, 120.5, 107.3, 104.7, 100.6, 71.5, 70.5, 70.3, 60.4, 56.1, 55.9, 55.7, 55.4, 49.3, 39.0, 37.3, 36.3; IR (ATR) 3026, 2937, 2836,

1607, 1504, 1352, 1253, 1171, 1038, 949, 826 cm^{-1}; HRMS (ESI) *m / z* calcd for $C_{29}H_{34}O_{10}S_2Na$ $[M + Na]^+$ 629.1491, found 629.1509.

(1-(2-Hydroxy-4-methoxyphenyl)-5,6-dimethoxy-2,3-dihydro-1*H*-indene-2,2-diyl)bis(methylene) dimethanesulfonate, 26.

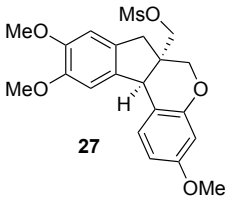


26

To a 40 mL amber vial containing 20% wt. $Pd(OH)_2/C$ (316 mg, 0.45 mmol) was added a solution of bis-mesylate **25** (1.12 g, 1.83 mmol) in THF (3.2 mL). Methanol was dried (Na_2SO_4) briefly, and then added (3.2 mL) to the mixture. The reaction vessel was evacuated and backfilled with H_2 (× 3). After debenzylation was complete (1.5 h), the mixture was filtered through a tightly packed Celite pad. The pad was rinsed with EtOAc (3 × 25 mL) and the organic concentrated *in vacuo*. The crude pink solid was purified by flash chromatography (60:40 EtOAc:hexanes) to yield phenol **26** as a white solid (940 mg, 99%) which was used without any further purification in the next step. Rotamers are present in the ^{1}HNMR as determined by the published method of Ley and co-workers.[25] ^{1}H and ^{13}C NMR in two different solvents at two different temperatures results in peak resolution and splitting. R_f = 0.21 (60:40 EtOAc:hexanes, stains red by *p*-anis dip stain). ^{1}H NMR (600 MHz, $CDCl_3$) (20:80 mixture of rotamers) δ 7.26 (s, 1H), 7.14 (d, *J* = 8.3 Hz, 0.2H), 6.77 (s, 1H), 6.58 (s, 0.2H), 6.55 – 6.52 (m, 1H), 6.45 (apparent d, *J* = 7.8 Hz, 0.8H), 6.43 – 6.40 (m, 0.9H), 6.39 – 6.34 (m, 0.8H), 6.31 (apparent s, 0.2H), 5.59 (br s, 0.8H), 4.73 (apparent s, 0.8H), 4.68 (s, 0.2H), 4.39 – 4.31 (m, 1.6H), 4.30 – 4.21 (m, 0.6H), 4.16 (apparent d, *J* = 9.4 Hz, 0.2H), 4.08 (apparent d, *J* = 9.5 Hz, 0.8H), 4.02 (apparent d, *J* = 8.8 Hz, 0.2H), 3.93 (apparent d, *J* = 9.6 Hz, 0.9H), 3.91 – 3.87 (m, 3H), 3.78 – 3.72 (m, 6H), 3.22 (apparent d, *J* = 16.6 Hz, 0.2H), 3.07 (s, 3H), 3.02 (apparent d, *J* = 16.3 Hz, 0.8H), 2.95 (apparent d, *J* = 16.6 Hz, 0.2H), 2.90 (overlapping d, 0.8H), 2.87 (s, 2.8H), 2.76 (s, 0.5H); ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) (20:80 mixture of rotamers) δ 160.8, 159.7, 155.8, 154.6,

149.9, 149.7, 149.1, 149.1, 135.0, 133.4, 132.7, 131.6, 131.2, 130.6, 128.3, 117.8, 117.0, 108.4, 107.8, 107.6, 107.4, 106.9, 106.5, 103.5, 102.2, 71.4, 71.0, 70.5, 70.2, 56.1, 56.0, 55.4, 55.3, 54.8, 50.9, 49.7, 47.1, 38.9, 37.8, 37.4, 37.0, 36.6; $^{13}C\{^{1}H\}$ NMR major peaks: δ 159.7, 154.6, 149.15, 149.12, 135.0, 131.6, 130.6, 128.3, 117.8, 108.4, 107.4, 106.5, 102.2, 71.4, 70.5, 56.1, 56.0, 55.3, 50.9, 47.1, 37.8, 37.4, 37.0. $^{13}C\{^{1}H\}$ NMR minor peaks: δ 160.8, 155.8, 149.9, 149.7, 133.4, 132.7, 131.2, 117.0, 107.8, 107.6, 106.9, 103.5, 71.0, 70.2, 55.4, 54.8, 49.7, 38.9, 36.6; IR (ATR) 3429, 2936, 1614, 1505, 1351, 1172, 957, 835 cm^{-1}; HRMS (ESI) *m / z* calcd for $C_{22}H_{28}O_{10}S_2Na$ $[M + Na]^+$ 539.1022, found 539.1005.

(3,9,10-trimethoxy-7,11b-dihydroindeno[2,1-*c*]chromen-6a(6*H*)-yl)methyl methanesulfonate, 27.

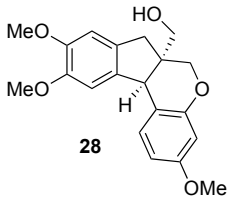


27

To a stirring solution of phenol **26** (0.900 g, 1.74 mmol) in THF (22.0 mL) at 0 °C was added un-rinsed 60% NaH/mineral oil (73.0 mg, 1.83 mmol) in one portion. Upon consumption of phenol **26** (2 h), the reaction was quenched with 20 mL of H_2O. The resulting mixture was extracted with EtOAc (3 × 50 mL) and the combined organic layers dried ($MgSO_4$) and concentrated *in vacuo* to afford a fluffy pink solid. Purification by two rounds of flash chromatography (40:60 EtOAc:hexanes; then, 4:96 – 30:70 EtOAc:toluene) yielded partially purified mesyl chromane product **27** as a white fluffy solid (660 mg) containing (34 mol %, 10 wt. % by ^{1}H NMR) of toluene (81% yield of **27**). Upon standing under vacuum, this compound turns pink in color. This sample was carried on to the next step without further purification. R_f = 0.35 (50:50 EtOAc:hexanes, stains pink by *p*-anis dip stain). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29 (d, *J* = 8.5 Hz, 1H), 6.79 (s, 1H), 6.74 (s, 1H), 6.64 (dd, *J* = 8.4, 2.6 Hz, 1H), 6.45 (d, *J* = 2.6 Hz, 1H), 4.42 (d, *J* = 9.9 Hz, 1H), 4.33 (d, *J* = 9.9 Hz, 1H), 4.12 (dd, *J* = 11.4, 1.3 Hz, 1H), 4.03 (s, 1H), 3.85 (s, 3H), 3.83 (s, 3H), 3.78 (s, 3H), 3.70 (d, *J* = 11.3 Hz, 1H), 3.20 (d, *J* =

16.0 Hz, 1H), 3.03 (s, 3H), 2.66 (d, J = 16.0 Hz, 1H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 159.5, 154.5, 148.8, 148.5, 136.1, 130.9, 130.8, 129.0 (toluene), 128.2 (toluene), 125.3 (toluene), 113.9, 108.7, 108.4, 107.6, 102.0, 71.4, 66.4, 56.1, 56.08, 55.3, 45.4, 45.0, 38.0, 37.1; IR (ATR) 2925, 2852, 1503, 1355, 1174, 957, 845, 730 cm^{-1}; HRMS (ESI) m/z calcd for $C_{21}H_{24}O_7SNa$ $[M + Na]^+$ 443.1140, found 443.1143.

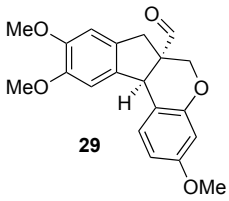
(3,9,10-Trimethoxy-7,11b-dihydroindeno[2,1-*c*]chromen-6a(6*H*)-yl)methanol, 28.



28

To a cooled (0 °C) solution of mesyl chromane **27** containing (34 mol %, 10 wt. % by ^1H NMR) of toluene (660 mg, 90% wt/wt, 1.41 mmol of **27**) in THF (32 mL), described above, was added $LiAlH_4$ (238 mg, 6.27 mmol) in one portion. The solution warmed to 23 °C and then heated at reflux. Upon consumption of mesyl chromane **27** (2 h), the reaction was cooled (0 °C) and slowly quenched with 20 mL of saturated aqueous potassium sodium tartrate. The solution was stirred at 23 °C for 15 min and then extracted with EtOAc (3 × 50 mL). The combined organic layers were dried (Na_2SO_4), concentrated *in vacuo*, and purified by flash chromatography (30:70 – 50:50 EtOAc:hexanes) to yield alcohol **28** as a beige fluffy solid (440 mg, 90%). R_f = 0.30 (50:50 EtOAc:hexanes; stains pink by *p*-anis dip stain). ^1H NMR (600 MHz, $CDCl_3$) δ 7.29 (dd, J = 8.5, 0.8 Hz, 1H), 6.81 (d, J = 0.9 Hz, 1H), 6.74 (s, 1H), 6.61 (dd, J = 8.4, 2.6 Hz, 1H), 6.43 (d, J = 2.6 Hz, 1H), 4.16 (dd, J = 11.1, 1.3 Hz, 1H), 3.98 (s, 1H), 3.86 (d, J = 10.9 Hz, 1H), 3.84 (s, 3H), 3.83 (s, 3H), 3.77 (s, 3H), 3.74 (d, J = 10.8 Hz, 1H), 3.68 (d, J = 11.1 Hz, 1H), 3.13 (d, J = 15.8 Hz, 1H), 2.61 (d, J = 15.9 Hz, 1H); $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$) δ 159.3, 154.9, 148.5, 148.3, 137.2, 131.7, 130.9, 115.1, 108.5, 108.2, 107.8, 101.8, 67.2, 65.2, 56.1, 56.07, 55.3, 46.9, 45.3, 37.8; IR (ATR) 3502, 2931, 2833, 1502, 1160, 1134, 1125, 1086, 1034, 846, 730 cm^{-1}; HRMS (ESI) m/z calcd for $C_{20}H_{22}O_5Na$ $[M + Na]^+$ 365.1365, found 365.1371.

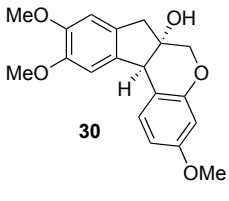
3,9,10-Trimethoxy-7,11b-dihydroindeno[2,1-*c*]chromene-6a(6*H*)-carbaldehyde, 29.



29

Dess–Martin periodinane (105 mg, 0.24 mmol, 98%) was added in one portion to a solution of alcohol **28** (76 mg, 0.22 mmol) in DCM (1.1 mL) at 0 °C. The reaction was stirred at 23 °C until alcohol was no longer observed by TLC (45 min). The reaction was quenched with saturated aqueous $Na_2S_2O_3$ (3.0 mL) and stirred vigorously for 15 min. The solution was purged with N_2 gas (1.5 h) and extracted with degassed EtOAc (3 × 15 mL). The combined organic layers were dried (Na_2SO_4), concentrated *in vacuo*, and purified by flash chromatography (30:70 EtOAc:hexanes). The fractions containing product were collected and purged with N_2 before concentrating *in vacuo* to afford aldehyde **29** as an amorphous, fluffy red solid (67 mg) containing a small amount (13 mol %, 4 wt. % by ^{1}H NMR) of EtOAc (86% yield of **29**). R_f = 0.25 (40:60 EtOAc:hexanes; stains pink-orange by *p*-anis dip stain). ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.86 (s, 1H), 7.34 (d, *J* = 8.5 Hz, 1H), 6.85 (s, 1H), 6.74 (s, 1H), 6.63 (dd, *J* = 8.5, 2.6 Hz, 1H), 6.44 (d, *J* = 2.5 Hz, 1H), 4.56 (s, 1H), 4.45 (dd, *J* = 11.4, 1.2 Hz, 1H), 3.84 (s, 6H), 3.82 (d, *J* = 11.3 Hz, 1H), 3.76 (s, 3H), 3.31 (d, *J* = 15.9 Hz, 1H), 2.71 (d, *J* = 15.9 Hz, 1H); ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 201.9, 159.5, 154.8, 148.9, 148.8, 135.9, 130.4, 129.7, 114.0, 108.8, 108.2, 107.7, 102.0, 65.8, 56.6, 56.10, 56.07, 55.3, 44.1, 35.7; IR (ATR) 2924, 2834, 1725, 1286, 1269, 1086, 1034, 908, 731, 698 cm^{-1}; HRMS (ESI) *m / z* calcd for $C_{20}H_{20}O_5Na$ $[M + Na]^+$ 363.1208, found 363.1201.

***O*-Trimethylbrazilin (3,9,10-trimethoxy-7,11b-dihydroindeno[2,1-*c*]chromen-6a(6*H*)-ol), 30.**

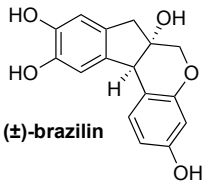


30

To a stirring solution of aldehyde **29** (78 mg, 0.23 mmol) in anhydrous MeOH (3.3 mL) was added solid NaOH (42 mg, 1.06 mmol) in one portion. Then, degassed aqueous 30% (w/w) H_2O_2 (152 μL, 1.49 mmol) was added. The yellow, cloudy reaction mixture was then heated and stirred at 65 °C until aldehyde **29** was no

longer observed by TLC. Upon completion, the reaction was cooled (23°C) and then concentrated *in vacuo*. The residue was partitioned between DCM (15 mL) and H_2O (15 mL) (both degassed). The layers were separated and the aqueous was extracted with DCM (3 × 15 mL). The combined organic layers were washed with brine (1 × 20 mL), dried ($MgSO_4$), and purged with N_2 (45 min). The solution was then concentrated and purified by flash chromatography using degassed solvents (40:60 EtOAc:hexanes) to yield *O*-trimethylbrazilin **30** as a beige fluffy solid (31.9 mg, 42%, >95% purity). R_f = 0.19 (40:60 EtOAc:hexanes; stains pink by *p*-anis dip stain). R_f = 0.28 (50:50 EtOAc:hexanes; stains pink by *p*-anis dip stain). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.29 (d, *J* = 8.3 Hz, 1H), 6.78 (s, 1H), 6.73 (s, 1H), 6.65 (dd, *J* = 8.6, 1.9 Hz, 1H), 6.48 (d, *J* = 2.0 Hz, 1H), 4.11 (s, 1H), 4.02 (dd, *J* = 11.2, 1.8 Hz, 1H), 3.84 (s, 3H), 3.83 – 3.79 (s, 3H and d, *J* = 11.4 Hz, 1H), 3.77 (s, 3H), 3.24 (d, *J* = 15.7 Hz, 1H), 2.87 (d, *J* = 15.7 Hz, 1H); ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 159.4, 154.4, 148.7, 148.4, 136.1, 131.1, 130.6, 114.4, 108.9, 108.4, 107.7, 102.0, 77.5, 70.3, 56.10, 56.06, 55.3, 50.5, 41.4; IR (ATR) 3309, 2917, 1619, 1579, 1503, 1157, 1034, 763 cm^{-1}; HRMS (ESI) *m / z* calcd for $C_{19}H_{20}O_5Na$ [M + Na]$^+$ 351.1208, found 351.1208.

(±)-Brazilin (7,11b-dihydroindeno[2,1-*c*]chromene-3,6a,9,10(6*H*)-tetraol).



(±)-brazilin

A solution of BBr_3 (0.49 mL, 0.49 mmol, 1 M in DCM) was added dropwise via syringe pump over 10 min to a cooled (–78 °C) solution of *O*-trimethylbrazilin (31.9 mg, 0.097 mmol) in DCM (3.04 mL). The resulting bright red solution was stirred at –78 °C for 2 h and then 18 h at 23 °C. The reaction was quenched with degassed H_2O (3.0 mL) and stirred vigorously for 5–10 min. The biphasic mixture was then partitioned between degassed H_2O (30 mL) and degassed EtOAc (15 mL). The layers were separated and the aqueous extracted with degassed EtOAc (2 × 15 mL) and degassed DCM (1 × 20 mL). The

combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo* to afford red oil. The red oil was purified by flash chromatography (50:50 EtOAc:hexanes) to afford **(±)-brazilin** as a red oil (18.8 mg, 68%, >95% purity) that solidifies upon standing. R_f = 0.09 (50:50 EtOAc:hexanes, stains pink by *p*-anis dip stain). R_f = 0.36 (80:20 EtOAc:hexanes, stains pink by *p*-anis dip stain). R_f = 0.38 (10:90 MeOH/$CHCl_3$, stains pink by *p*-anis dip stain). ^{1}H NMR (600 MHz, CD_3OD) δ 7.18 (d, *J* = 8.3 Hz, 1H), 6.71 (s, 1H), 6.60 (s, 1H), 6.47 (dd, *J* = 8.3, 2.5 Hz, 1H), 6.29 (d, *J* = 2.4 Hz, 1H), 3.96 (s, 1H), 3.93 (d, *J* = 11.4 Hz, 1H), 3.69 (d, *J* = 11.3 Hz, 1H), 3.02 (d, *J* = 15.5 Hz, 1H), 2.77 (d, *J* = 15.6 Hz, 1H); ^{13}C{^{1}H} NMR (151 MHz, CD_3OD) δ 157.9, 155.7, 145.6, 145.3, 137.4, 132.2, 131.3, 115.5, 112.9, 112.4, 109.9, 104.3, 78.1, 70.8, 51.0, 49.0 (CD_3OD), 42.9; IR (ATR) 3275, 2922, 1620, 1598, 1505, 1462, 1298, 1156, 1116, 1036, 844 cm^{-1}; HRMS (ESI) *m / z* calcd for $C_{16}H_{13}O_5$ $[M - H]^-$ 285.0763, found 285.0758.

ASSOCIATED CONTENT

Supporting Information:

• X-ray crystallography data for **S12ba** and NMR spectra

• CIF File for **S12ba**

The Supporting Information is available free of charge.

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