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Syntheses of differentially protected isocoumarins

Andrew N. Lowell, Philip D. Wall, Stephen P. Waters, Marisa C. Kozlowski *

Department of Chemistry, Roy and Diana Vagelos Laboratories, University of Pennsylvania, 231 S. 34th St., Philadelphia, PA 19104-6323, United States

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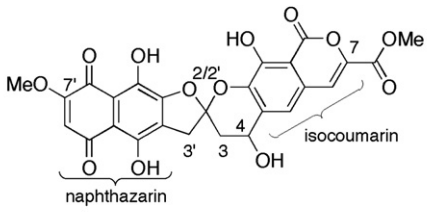
ABSTRACT

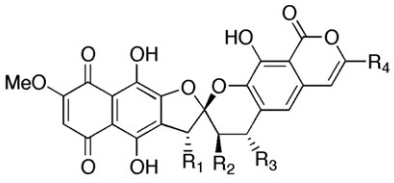
Syntheses of an isocoumarin subunit suitable for the completion of purpuromycin are outlined. Specifically, work targeting an orthogonally protected isocoumarin (eventually 12% yield over 12 steps) and an improved synthesis of a symmetrically protected isocoumarin (18% over 10 steps) are described. A new modification for selective catechol protection as mediated by potassium bicarbonate is also presented along with insights into oxidative and reductive functionalization of isocoumarins.

1. Introduction

The isocoumarin skeleton is a well known motif in natural products. Our group has maintained an interest in isocoumarins[1] as they represent one hemisphere of the rubromycin family of natural products (Fig. 1).[2] Our earlier work[1] and that of other groups[3,4] has demonstrated symmetric protection of the C7 and C8 positions (**2**, Fig. 2, this numbering will be used throughout the paper). To resolve issues associated with isocoumarin reactivity, we sought a synthesis that would allow a selectively functionalized 3,6,7,8-isocoumarin: an orthogonally protected species bearing a styrene at the C6 position (**3**). This product would be amenable to our desired coupling method[5] and avoid some of the problems we had encountered previously during spirocyclization attempts.[6] While methods exist to vinylate via an aromatic halogen[7] (Equation 1) and Reissig and co-workers have shown the ability of halide substituted isocoumarins to react in a Heck reaction to construct their orthogonally protected isocoumarin,[8,9] the complex reactivity of this system remonstrated against this newer methodology. Following are the two approaches undertaken toward a highly functionalized isocoumarin.

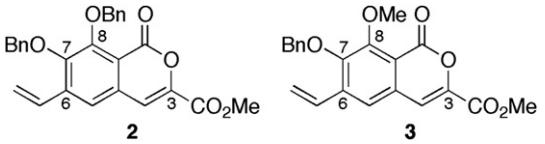


Purpuromycin 1



Compound	R_1	R_2	R_3	R_4
γ-Rubromycin	H	H	H	CO_2Me
Heliquinomycinone	OH	OH	H	CO_2Me
Griseorhodin C	OH	OH	OH	CH_3

Figure 1. The rubromycin family.



2 **3**

Figure 2. Symmetrically and unsymmetrically protected isocoumarins.

* Corresponding author. Tel.: +1 215 898 3048; fax: +1 215 573 2112; e-mail address: marisa@sas.upenn.edu (M.C. Kozlowski).

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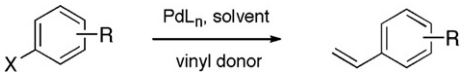
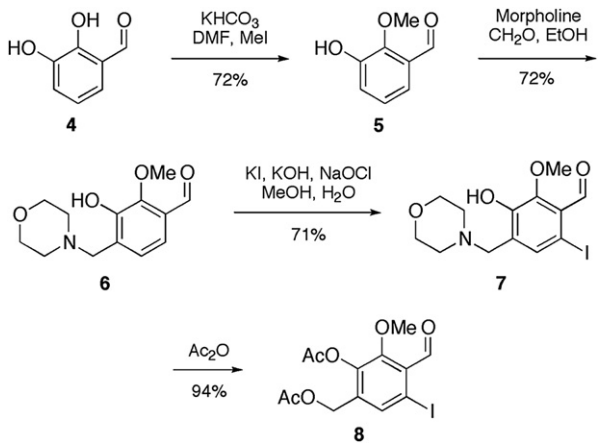


Equation 1. Vinylation of aromatic halides.

2. Results and discussion

2.1. Use of a modified Heck protocol to produce an orthogonally protected isocoumarin

Our first approach to an orthogonally protected isocoumarin (**3**) was an adaptation of our earlier methods[1] to make 7,8-symmetric isocoumarins. We hypothesized that after selective protection of a suitable precursor we could intercept the same general Heck coupling pathway to easily complete the isocoumarin. Initial efforts were directed toward aryl halide **8** as shown in Scheme 1.

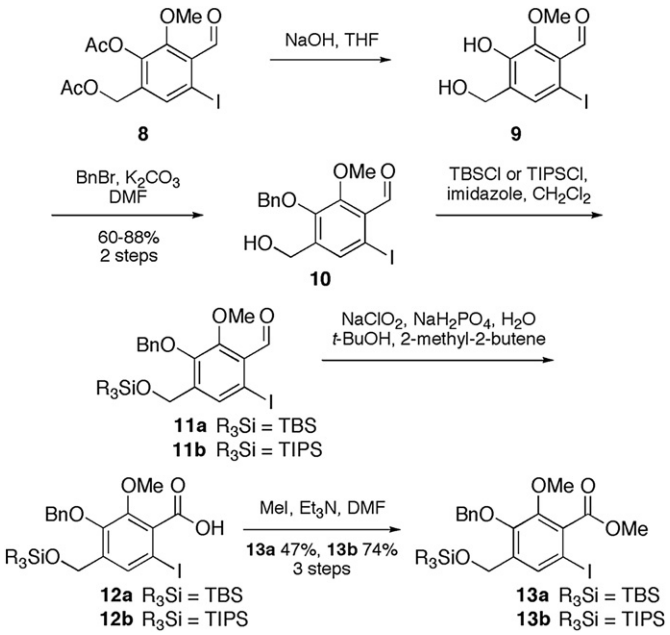


Scheme 1. Selective protection and functionalization of the core benzene ring.

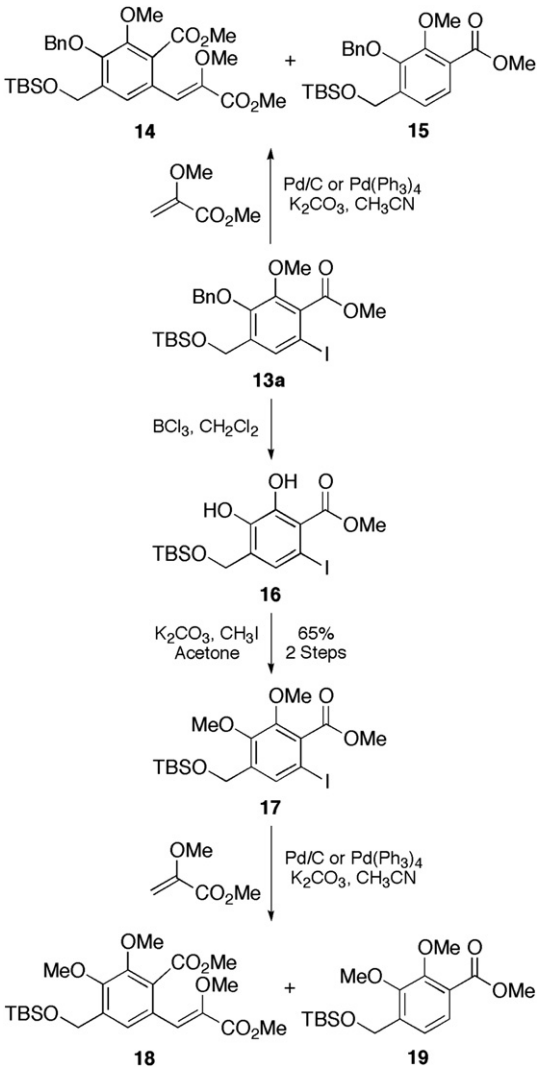
While there is precedent for the selective alkylation of 2,3-dihydroxybenzaldehyde (**4**)[10] as directed by the electronic effects of the conjugated carbonyl, we obtained superior yields for methylation (**5**) when using potassium bicarbonate, a mild, weakly coordinating base. Functionalization for the latent styrene chain by use of a Mannich reaction (**6**) and halide incorporation[11] (**7**) for the Heck reaction were both achieved using the free hydroxyl as a directing group. Notably, the order of these reactions could not be reversed; the aryl halide was reduced under the Mannich conditions giving **6**. Conversion of the morpholine and protection of the phenol as the diacetate proceeded smoothly (**8**).

Deprotection of the diacetate (**8**, Scheme 2) gave diol **9**, which was selectively benzylated (**10**) to establish the desired orthogonal protection. At this point it was unclear how robust of a protection group was needed to shield the primary alcohol. Both *tert*-butyldimethyl silyl (TBS) chloride and tri-*iso*-propyl silyl (TIPS) chloride were used as reagents giving their respective silyl ethers (**11**). Aldehyde **11** was converted via Pinnick oxidation to acid **12** and subsequently protected as the methyl ester **13** to better withstand the Heck reaction and react appropriately in the isocoumarin cyclization.

Difficulties were first encountered with this route in the initial trials of the Heck reaction (Scheme 3). An impurity, eventually determined to be dehalogenated material **15** was produced at significant levels. This type of competitive reaction has been reported[12] but its prevention has proven elusive. With the hope of gaining insight from our original system,[1] **13a** was deprotected using boron trichloride (**16**) and methylated to give **17**.



Scheme 2. Synthesis of silyl derivatives in preparation for Heck coupling.

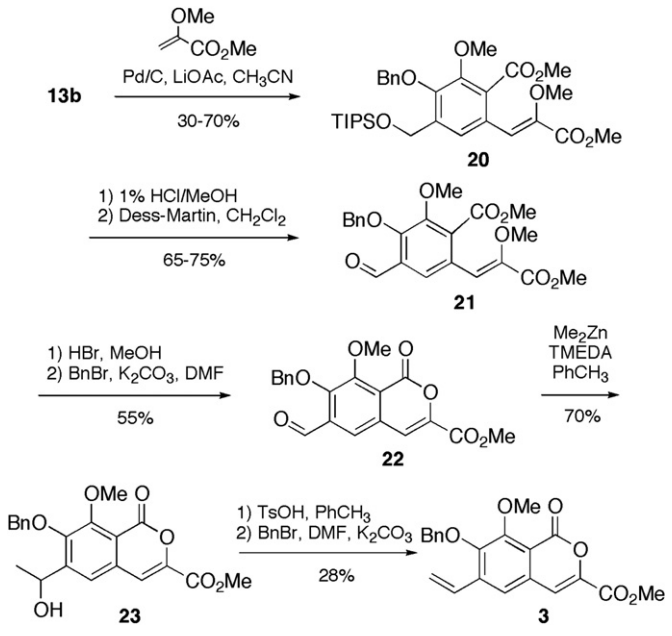


Scheme 3. Coupled and reductively dehalogenated products via the Heck reaction.

Unfortunately, the previously reported Heck coupling of dimethyl ether **17** to form **18**[1] was not reproducible and a mixture of product and dehalogenated starting material were observed. Optimization of catalyst, solvent, and base eventually resulted in improved yields, but dehalogenation continued to be problematic. The most compelling explanation of the competing dehalogenation reaction is the production of small, unsupported Pd-clusters in situ, which function as a surface on which catalytic dehalogenation can occur.[14]

Further confounding investigations into the Heck coupling were the coelution of starting material **13a** and **17** with their dehalogenated counterparts **15** and **19**, respectively. Additionally, the TBS ether was not sufficiently robust to withstand the coupling conditions adding desilylated compounds to the already complex mixture of product (**14**) and dehalogenated starting material (**15**). Use of the TIPS ether suppressed this problem. The best results in the Heck reaction were obtained when (1) a weaker base was used, such as bicarbonate in lieu of carbonate; (2) a smaller alkali metal was chosen as counterion to the base; (3) the concentration of the reaction was increased; (4) the alkene coupling partner[13] was recently prepared; (5) more null volume was allowed in the sealed tube.

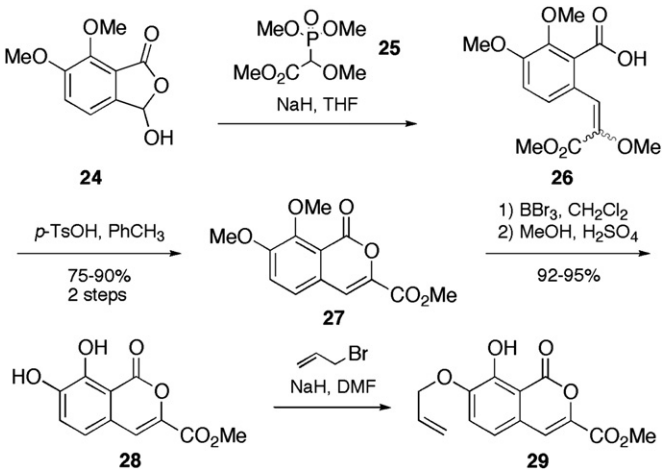
Having optimized for the formation of **20** (Scheme 4), desilylation and oxidation with Dess–Martin periodane (DMP) gave **21**. Treatment with methanolic hydrogen bromide effected cyclization to the complete isocoumarin skeleton at the expense of the benzyl ether, which could be readily reinstalled to produce **22**. This sequence gave superior results without intervening purifications. Treatment with dimethyl zinc incorporated the final carbon (**23**) of the desired isocoumarin. The strongly acidic conditions to eliminate alcohol **23** to the styrene caused additional debenzylation. This could again be rectified by subjecting the product mixture to benzylation conditions, but yields of **3** suffered. Due to the complications of competitive dehalogenation and the loss of the benzyl ether under strongly acidic conditions, an alternative route was investigated.



Scheme 4. Completion of the orthogonally protected isocoumarin via Heck coupling.

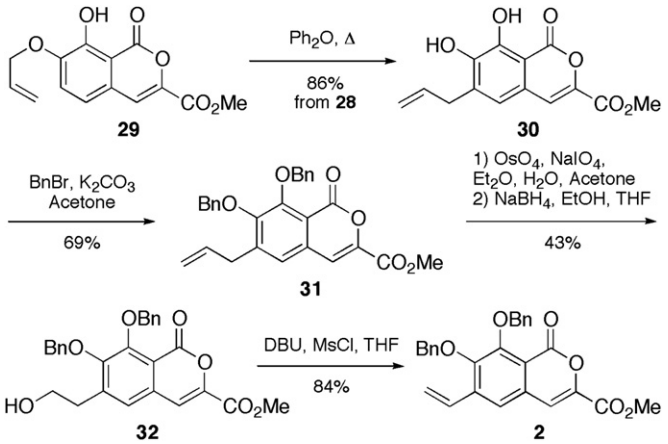
2.2. Using the Horner–Wadsworth–Emmons reaction to produce isocoumarins

Opianic acid (**24**, Scheme 5) could be purchased or produced from vanillin derivatives.[15,16] The Horner–Wadsworth–Emmons variation of the Witting olefination with **25**[17,18] gave a mixture of cis and trans isomers of acid **26**.[4] Under vigorous conditions, both isomers could be cyclized to give the complete isocoumarin skeleton (**27**) in high yield. Cleavage of the methyl ethers produced catechol **28**, which was selectively allylated furnishing phenol **29**.[3]



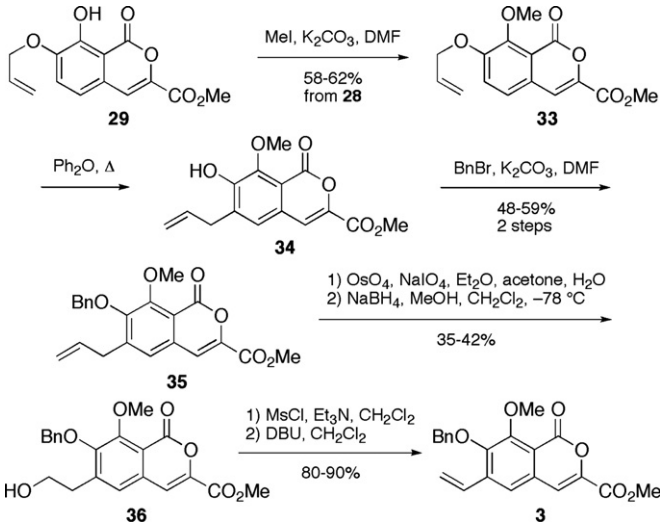
Scheme 5. Isocoumarin via the Horner–Wadsworth–Emmons reaction.

2.2.1. An improved route to a symmetrically protected isocoumarin. From phenol **29**, differentiation of the C7 and C8 positions was possible (see Section 2.2.2). Additionally, this intermediate allowed improved access to our original, dibenzylated isocoumarin (**2**, Scheme 6), a protecting group scheme we chose due to its orthogonality with the other functionality we were building into the molecule. Claisen rearrangement of **29** established the carbon functionality destined to become the vinyl chain (**30**).[3,4] The catechol was globally benzylated (**31**). A redox sequence[19] (see below for further discussion) reduced the carbon chain length by one unit (**32**). Alcohol **32** was then mesylated and eliminated to give target isocoumarin **2** in 18% yield over 10 steps from **24**.



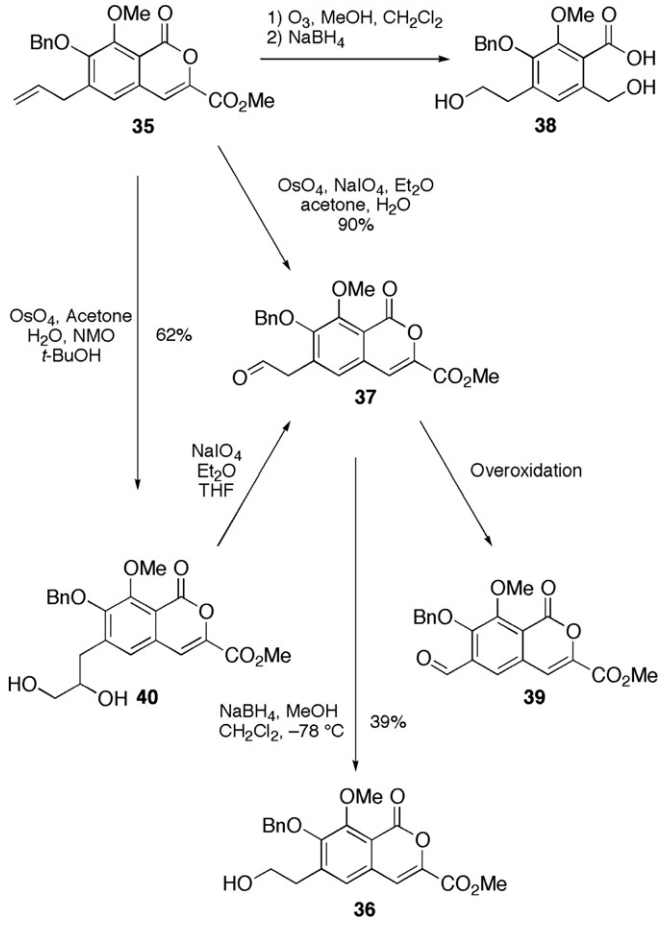
Scheme 6. Improved synthesis of the symmetrically protected isocoumarin.

2.2.2. A improved route to an orthogonally protected isocoumarin. As an ideal intermediate to intercept for orthogonal protection, phenol **29** (Scheme 7) was subjected to methylation (**33**). While the Claisen rearrangement of **33** was more sluggish than that of **29** (Scheme 6), **34** could be obtained efficiently and benzylation yielded allyl species **35**. The next step, a redox process to produce alcohol **36** (see also Scheme 6, above), was the most difficult transformation in this sequence. As depicted in Scheme 8, several



Scheme 7. Interception of **29** to orthogonally protect the isocoumarin.

methods of converting allyl **35** into alcohol **36** were examined. All pass through aldehyde intermediate **37**. The first attempt to convert **35** into **37** was via ozonolysis. This process cleaved both the external, allyl double bond and, surprisingly, the internal, isocoumarin double bond, the result of which was acid **38**. We next undertook another direct method to produce **37**. By using catalytic osmium tetroxide to convert the allyl into a diol and stoichiometric addition of sodium periodate to cleave the diol to the aldehyde and



Scheme 8. Redox investigations.

regenerate the osmium(VIII) species, we could produce **37** in up to 90% yield.[19] A danger of this route was over-oxidation to benzaldehyde **39**, a product we observed in trace amounts and which others have reported[4] as the major product in this type of reaction. Attempting to streamline the production of **37**, we also used a two-step protocol where diol **40** was isolated before conversion to aldehyde **37**. While successful, the yield of the first step in this sequence (**35**–**40**) precluded this pathway from being superior.

The reduction of **37** to produce alcohol **36** also proved problematic. At 0 °C, significant decomposition of the isocoumarin was observed as well as reduction of the aldehyde. Altering the reduction solvent (see Scheme 6 above) was one solution, but transesterification of the methyl ester frequently resulted. Eventually, we found that reducing the temperature to less than −60 °C in combination with portionwise addition of reductant afforded **36** in the best yields. With this material in hand, conversion to styrene **3** (Scheme 7) could easily be accomplished through a two-step mesylation/elimination protocol. This route allowed gram-scale production of the isocoumarin we desired as a coupling partner in yields of up to 12% over 12 steps.

3. Conclusions

The preceding report details our complete investigations toward the isocoumarin portion of the rubromycin family of compounds. The synthesis of our original, symmetrically protected isocoumarin styrene has improved to 18% yield over 10 steps from 9.5% yield over 15 steps.[1] It has been demonstrated that an orthogonally protected isocoumarin can be produced on scale; the Horner–Wadsworth–Emmons variation of the Wittig reaction proved superior to a Heck coupling/acid closure for the creation of the isocoumarin skeleton. The redox difficulties in these sequences highlight unexpectedly high reactivity of the isocoumarin moiety. Noteworthy was the observation that potassium bicarbonate is an excellent base for selective protection of electronically distinct catechols. This pathway also allowed synthesis on scale yielding over one gram of the orthogonal isocoumarin styrene (**3**) to be used with a suitable naphthalene portion in the investigations of spiroketalization toward synthetic purpuromycin.

4. Experimental

4.1. General information

Unless otherwise specified, all non-aqueous reactions were carried out under an atmosphere of dry nitrogen in dried glassware. Commercially available starting materials and reagents were used as received. When necessary, solvents and reagents were dried prior to use. Dichloromethane, diethyl ether, tetrahydrofuran, and toluene were dried and deoxygenated under N_2 using an Al_2O_3 solvent column purification system.[20] *N*,*N*-Dimethylformamide was distilled from magnesium sulfate under reduced pressure (50 Torr). Acetonitrile, dichloromethane, methanol, pyridine, and triethylamine were distilled from calcium hydride. Benzene and toluene were distilled from sodium. Tetrahydrofuran and diethyl ether was distilled from sodium with benzophenone as an indicator. House nitrogen was passed over Drierite (Ca_2SO_4) prior to use. Other gases were purchased from BOC gases and used without purification.

Analytical thin layer chromatography was performed on EM Reagents or Silicycle 0.25 mm silica gel 60-F plates. Visualization was accomplished by irradiation with a 254 nm UV lamp or by staining with an aqueous solution of ceric ammonium molybdate. Chromatography was performed using a forced flow[21] of the indicated solvent system on EM Reagents Silica Gel 60 (230–400 mesh).

^{1}H NMR spectra were recorded on a Bruker AM-500 (500 MHz) spectrometer. Chemical shifts are reported in parts per million from tetramethylsilane (0 ppm) using the solvent resonance as an internal standard ($CDCl_3$ 7.26 ppm). Data are reported as follows: chemical shift, multiplicity (s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, br=broad), coupling constants, and number of protons. Proton decoupled ^{13}C NMR were recorded on a Bruker AM-500 (125 MHz) spectrometer. Chemical shifts are reported in ppm from tetramethylsilane (0 ppm) using the solvent resonance as an internal standard ($CDCl_3$ 77.2 ppm). IR spectra were taken on an ASI ReactIR 1000 FT-IR spectrometer using a thin film. Melting points were obtained on a Thomas Scientific Unimelt and are uncorrected. High resolution mass spectra were obtained with an ionization mode of either CI or ES at the Mass Spectrometry Laboratories of the University of Pennsylvania.

4.2. Synthesis of 7-benzyloxy-8-methoxy-1-oxo-6-vinyl-1*H*-isochromene-3-carboxylic acid methyl ester (3) via Heck methodology

*4.2.1. 3-Hydroxy-2-methoxybenzaldehyde (**5**).* 2,3-Dihydroxybenzaldehyde (**4**) (20.0 g, 145 mmol) and $KHCO_3$ (58.0 g, 579 mmol) were combined in DMF (340 mL) and stirred for 0.5 h afterwhich CH_3I (37.0 mL, 594 mmol) was added in one portion. The mixture was stirred at rt for 28 h. Excess CH_3I was removed by evaporation under reduced pressure and the residual mixture was quenched by the addition of water (400 mL) and 1 N HCl (400 mL). After extraction with Et_2O (4×400 mL, 1×200 mL), the organic layers were combined, washed with saturated NH_4Cl (2×250 mL) and brine (500 mL), dried over $MgSO_4$, decolorized with charcoal, and concentrated to an amorphous orange solid. The residue was dissolved in Et_2O (500 mL) and extracted with 1 N NaOH (2×300 mL). The organic layer was dried (Na_2SO_4) and concentrated giving 2,3-dimethoxybenzaldehyde as a yellow oil. The aqueous layers were combined, acidified with concentrated HCl (~50 mL to pH 1), and extracted with CH_2Cl_2 (3×400 mL). The organic layers were combined, dried over $MgSO_4$, decolorized with charcoal, filtered, and concentrated to give (**5**) as an amorphous white-orange solid (15.9 g, 72%). Spectral data were in accord with those reported.[10]

*4.2.2. 3-Hydroxy-2-methoxy-4-morpholin-4-ylmethyl-benzaldehyde (**6**).* Morpholine (14.0 mL, 161 mmol) and formaldehyde (12.0 mL, 161 mmol) were combined in EtOH (20 mL) and stirred at rt for 25 h when they were added in one portion to **5** (15.9 g, 105 mmol) stirring in EtOH (65 mL). The mixture was heated to reflux (oil bath, 120–125 °C) and stirred for 2 days afterwhich it was cooled and concentrated. The impure product was eluted through a plug of SiO_2 (CH_2Cl_2) giving a pure and impure fraction. The impure portion was subjected to flash chromatography (EtOAc) and the products combined giving **6** as an orange oil (19.0 g, 72%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.39 (s, 1H), 7.26 (d, J=7.9 Hz, 1H), 6.82 (d, J=7.8 Hz, 1H), 4.03 (s, 3H), 3.77 (br s, 6H), 2.60 (br s, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 190.3, 151.3 (2), 129.4, 128.4, 124.0, 117.9, 66.8, 62.1, 62.0, 53.1; IR (film) 3466 (br), 2964, 2941, 2849, 1683, 1455 cm^{-1}; HRMS (CI) calcd for $C_{13}H_{18}NO_4$ (MH^+) 252.1236, found 252.1246.

*4.2.3. 3-Hydroxy-6-iodo-2-methoxy-4-morpholin-4-ylmethyl-benzaldehyde (**7**).* To a stirring solution of **6** (19.0 g, 75.6 mmol) in MeOH (475 mL) were added KOH (4.72 g, 84.1 mmol) and KI (13.25 g, 79.8 mmol). The mixture was cooled (ice bath) and 5% NaOCl (213 mL, 153 mmol) was added dropwise over 1.1 h. After 1 h the reaction was quenched by the addition of $Na_2S_2O_3$ (450 mL), neutralized with 1 N HCl (~180 mL to pH ~8), and the resulting solid filtered. Upon drying, **7** was a fine yellow powder (20.2 g, 71%): mp 126–128.5 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.13 (s, 1H), 7.35 (s, 1H), 3.96 (s, 3H), 3.75 (br s, 4H), 3.71 (br s, 2H), 2.59 (br s, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 191.7, 152.1, 151.3, 135.9, 129.5, 128.7, 80.5, 66.7, 62.1, 61.0, 53.1; IR (film) 3474 (br), 2941, 2849, 1695, 1455 cm^{-1}; HRMS (CI) calcd for $C_{13}H_{17}INO_4$ (MH^+) 378.0202, found 378.0204.

*4.2.4. 2-Acetoxy-4-formyl-5-iodo-3-methoxybenzyl acetate (**8**).* Phenol **7** (1.8 g, 4.77 mmol) was dissolved in Ac_2O (36.0 mL, 381 mmol) and stirred at reflux (heating mantle) for 5.25 h. The mixture was cooled and added to a stirring slurry of ice (700 mL), which was allowed to thaw (~2 h). The liquid was filtered away and the residual solid dissolved in CH_2Cl_2. This was dried over Na_2SO_4 and concentrated giving **8** as an amorphous yellow solid (1.753 g, 94%): mp 92–96 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.08 (s, 1H), 7.83 (s, 1H), 5.01 (s, 2H), 3.87 (s, 3H), 2.37 (s, 3H), 2.11 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 191.7, 170.4, 168.2, 154.7, 143.7, 136.8, 136.6, 130.4, 92.7, 63.7, 60.1, 20.9, 20.5; IR (film) 2945, 2856, 1776, 1745, 1698 cm^{-1}; HRMS (CI) calcd for $C_{13}H_{13}IO_6$ (M^+) 391.9757, found 391.9740.

*4.2.5. 3-Benzyloxy-4-hydroxymethyl-6-iodo-2-methoxy-benzaldehyde (**10**).* To a solution of **8** (1.6 g, 4.1 mmol) in THF (52 mL) was added 1 M NaOH (25 mL). The resulting mixture was stirred for 2 h, acidified with 10% HCl (25 mL, pH 1), and extracted with CH_2Cl_2 (3×25 mL). The combined organic layers were dried over $MgSO_4$ and concentrated affording **9** as a yellow oil, which was carried on without purification. Oil **9** was dissolved in DMF (55 mL) and K_2CO_3 (1 g, 11.4 mmol) and BnBr (1.4 mL, 11.7 mmol) were added. The resulting mixture was stirred for 16 h afterwhich the mixture was quenched by the addition of water (50 mL) and 10% HCl (50 mL) and extracted with Et_2O (3×50 mL). The combined organic layers were washed with saturated NH_4Cl (2×50 mL), brine (2×50 mL), dried over $MgSO_4$, and concentrated. The residue was purified by flash chromatography (33% EtOAc/hexanes, SiO_2) to give **10** (1.42 g, 88%) as a white solid mp: 80–81 °C, ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.15 (s, 1H), 7.77 (s, 1H), 7.37–7.42 (m, 5H), 5.10 (s, 2H), 4.51 (s, 2H), 3.97 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 192.0, 155.7, 150.0, 142.4, 136.4, 135.7, 128.7 (3), 128.6, 89.4, 75.3, 62.4, 60.1; IR (film) 2931, 2872, 1695, 1579, 1455, 1370, 1270, 1224, 1027 cm^{-1}; HRMS (ES) calcd for $C_{16}H_{15}IO_4Na$ (MNa^+) 420.9913, found 420.9913.

*4.2.6. 3-Benzyloxy-4-(tert-butyl-dimethyl-silanyloxymethyl)-6-iodo-2-methoxy-benzaldehyde (**11a**).* To a stirring solution of **10** (0.134 g, 0.329 mmol) in CH_2Cl_2 (3.5 mL) were added imidazole (0.093 g, 1.37 mmol) and TBSCl (0.116 g, 0.77 mmol). After 4 days, water (8 mL) and CH_2Cl_2 (4 mL) were added to the mixture, the layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (2×8 mL). The organic layers were combined, dried over Na_2SO_4, and concentrated. The residue was purified by flash chromatography (10% EtOAc/hexanes, SiO_2) giving **11a** as an oil (0.098 g, 58% from **8**): ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.15 (s, 1H), 7.85 (s, 1H), 7.35–7.40 (m, 5H), 5.06 (s, 2H), 4.56 (s, 2H), 3.95 (s, 3H), 0.93 (s, 9H), 0.05 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 192.4, 155.6, 149.3, 143.6, 136.9, 135.1, 129.1, 128.9, 128.8, 128.7, 89.9, 75.3, 62.6, 59.8, 26.1, 18.5, −5.2; IR (film) 3034, 2953, 2934, 2856, 1741, 1702, 1579, 1455 cm^{-1}; HRMS (ES) calcd for C_{22} $H_{29}IO_4SiNa$ (MNa^+) 535.0778, found 535.0779.

*4.2.7. 3-Benzyloxy-4-(tert-butyl-dimethyl-silanyloxymethyl)-6-iodo-2-methoxy-benzoic acid methyl ester (**13a**).* To a rapidly stirring biphasic solution of **11a** (0.462 g, 0.902 mmol) in *t*-BuOH (15 mL), water (15 mL), and 2-methyl-2-butene (10.3 mL, 96.8 mmol) was added NaH_2PO_4 (1.49 g, 12.4 mmol) followed by 80% $NaClO_2$ (1.92 g, 17.0 mmol). The resulting mixture was stirred vigorously for 0.5 h afterwhich it was acidified with 1 N HCl (pH ~4) and the layers

were separated. The aqueous layer was washed with CH_2Cl_2 (3×15 mL), the organic layers were combined, dried (Na_2SO_4), and concentrated giving **12a**, which was carried on without further purification.

To **12a** dissolved in DMF (25 mL) in an ice bath were added Et_3N (2.00 mL, 14.4 mmol) and CH_3I (0.90 mL, 14.5 mmol). The mixture was allowed to warm to rt stirring eventually for 71 h. The mixture was diluted first with water (50 mL) and then saturated NH_4Cl (50 mL), and extracted with Et_2O (4×50 mL). The organic layers were combined, dried over Na_2SO_4, and concentrated. The residue was purified by flash chromatography (10% EtOAc/hexanes, SiO_2) to give **13a** as a colorless oil (0.345 g, 71%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.63 (s, 1H), 7.37–7.38 (m, 5H), 5.01 (s, 2H), 4.54 (s, 2H), 3.98 (s, 3H), 3.90 (s, 3H), 0.91 (s, 9H), 0.03 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.7, 150.3, 148.5, 139.7, 137.0, 134.8, 133.0, 128.8, 128.6 (2), 84.7, 75.1, 62.0, 59.7, 53.0, 26.1, 18.5, −5.2; IR (film) 3034, 2953, 2934, 2856, 1737, 1397, 1270, 1042 cm^{-1}; HRMS (ES) calcd for $C_{23}H_{31}IO_5SiNa$ (MNa^+) 565.0883, found 565.0874.

*4.2.8. 3-Benzyloxy-6-iodo-2-methoxy-4-(triisopropyl-silanyloxy-methyl)-benzoic acid methyl ester (**13b**).* To a solution of **10** (3.57 g, 8.97 mmol) in CH_2Cl_2 (100 mL) were added imidazole (2.48 g, 36.4 mmol) and TIPSCl (4.9 mL, 22.9 mmol). After stirring for 16 h, the mixture was poured into water (100 mL) and the layers were separated. The aqueous layer was further extracted with CH_2Cl_2 (3×50 mL) and the combined organic layers were washed with saturated NH_4Cl (2×50 mL) and brine (100 mL), dried ($MgSO_4$), and concentrated affording **11b** as a yellow liquid, which was carried on without further purification.

Aldehyde **11b** was dissolved in 2-methyl-2-butene (113 mL) to which was added water (187 mL), *t*-BuOH (169 mL), $NaClO_2$ (19.1 g, 169 mmol), and NaH_2PO_4. After the biphasic mixture was stirred rapidly for 1.5 h, the layers were separated and the aqueous layer was further extracted with CH_2Cl_2 (3×100 mL). The combined organic layers were dried over $MgSO_4$ and concentrated yielding **12b** as an oily white solid, which was carried on without further purification.

To a solution of **12b** dissolved in DMF (268 mL) were added Et_3N (12.5 mL, 89.7 mmol) and CH_3I (5.6 mL, 89.7 mmol). The mixture was stirred for 16 h afterwhich it was diluted with water (100 mL) and saturated NH_4Cl (100 mL). After stirring for 1 h, the mixture was extracted with Et_2O (3×100 mL). The combined organic layers were dried over $MgSO_4$ and concentrated. Flash chromatography (10% EtOAc/hexanes, SiO_2) of the residue furnished **13b** (3.88 g, 74%) as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.72 (s, 1H), 7.34–7.39 (m, 5H), 5.02 (s, 2H), 4.61 (s, 2H), 3.98 (s, 3H), 3.90 (s, 3H), 1.03–1.12 (m, 21H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.5, 149.9, 148.0, 139.7, 136.8, 134.4, 132.5, 128.6, 128.5, 128.4, 84.5, 74.8, 61.7, 59.7, 52.8, 17.7, 11.8; IR (film) 2945, 2895, 2868, 1741, 1585, 1541, 1401, 1363, 1270, 1042 cm^{-1}; HRMS (ES) calcd for $C_{26}H_{37}IO_5SINa$ (MNa^+) 607.1353, found 607.1341.

*4.2.9. 4-(tert-Butyl-dimethyl-silanyloxymethyl)-6-iodo-2,3-dime-thoxy-benzoic acid methyl ester (**17**).* To a stirring solution of **13a** (0.056 g, 0.10 mmol) in CH_2Cl_2 (2.7 mL) in a dry ice bath was added BCl_3 in hexanes (0.48 mL, 0.48 mmol). Stirring was continued for 0.25 h afterwhich the reaction was quenched by the addition of 10% $NaHCO_3$ (2 mL) and warmed to rt. Water (~10 mL) was added and the mixture was extracted with CH_2Cl_2 (3×7 mL). The organic layers were combined, dried (Na_2SO_4), and concentrated.

The residue (**16**) was dissolved in acetone (10 mL) and K_2CO_3 (0.286 g, 2.07 mmol) and CH_3I (3.0 mL, 48.2 mmol) were added. The mixture was heated to reflux (oil bath, 65 °C) and stirred for 5.5 h afterwhich it was cooled, filtered through a plug of Celite, and concentrated. The residue was eluted through a pad of SiO_2 (CH_2Cl_2, then 25% EtOAc/hexanes) to give **17** (0.031 g, 65%) as an oil. Spectral data were in accord with those reported.[1]

*4.2.10. A typical procedure for the preparation of 7-benzyloxy-6-formyl-8-methoxy-1-oxo-1H-isochromene-3-carboxylic acid methyl ester (**22**).* Aryl iodide **13b** (1.88 g, 16.2 mmol), CH_3CN (14.7 mL), freshly prepared 2-methoxy-acrylic acid methyl ester[13] (1.88 g, 16.2 mmol), LiOAc (0.968 g, 14.7 mmol), and 10% Pd/C (1.99 g, 1.87 mmol) were combined and sealed in a pressure tube. The mixture was placed behind a blast shield, heated to 140 °C (oil bath) and stirred for 88 h. The mixture was cooled, filtered through a plug of Celite (CH_2Cl_2) and further purified by flash chromatography (17% EtOAc/hexanes, SiO_2). Compounds **14** and **15** were produced using the Heck protocol from **13a** and were characterized. 3-Benzyloxy-4-(*tert*-butyl-dimethyl-silanyloxymethyl)-2-methoxy-6-(2-methoxy-2-methoxycarbonyl-vinyl)-benzoic acid methyl ester (**14**) as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.00 (s, 1H), 7.35–7.42 (m, 5H), 6.88 (s, 1H), 5.06 (s, 2H), 4.64 (s, 2H), 3.97 (s, 3H), 3.91 (s, 3H), 3.83 (s, 3H), 3.73 (s, 3H), 0.92 (s, 9H), 0.07 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.8, 164.8, 149.7, 148.7, 146.3, 138.0, 137.3, 129.0, 128.8, 128.59, 128.56, 126.9, 124.6, 119.4, 75.2, 61.9, 60.3, 59.7, 52.8, 52.5, 26.1, 18.6, −5.2; IR (film) 3035, 2935, 2858, 1730, 1637, 1452, 1282, 1251, 1112, 1066 cm^{-1}; HRMS (ES) calcd for $C_{28}H_{39}O_8Si$, (MH^+) 531.2414, found 531.2408. 3-Benzyloxy-4-(*tert*-butyl-dimethyl-silanyloxymethyl)-2-methoxy-benzoic acid methyl ester (**15**) as a yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.59 (d, J=8.0 Hz, 1H), 7.34–7.42 (m, 5H), 7.26 (d, J=8.0 Hz, 1H), 5.06 (s, 2H), 4.64 (s, 2H), 3.94 (s, 3H), 3.93 (s, 3H), 0.92 (s, 9H), 0.05 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.6, 153.1, 149.2, 141.3, 137.5, 128.8, 128.6, 128.5, 126.4, 124.5, 122.0, 75.2, 61.9, 60.4, 52.4, 26.1, 18.6, −5.2; IR (film) 3035, 1935, 2858, 1730, 1460, 1413, 1274, 1120, 1043 cm^{-1}; HRMS (ES) calcd for $C_{23}H_{32}O_5SiNa$ (MNa^+) 439.1917, found 439.1905.

The residue (**20**) was dissolved in MeOH (100 mL) and concentrated HCl (1 mL) was added. After stirring for 16 h, the mixture was diluted with water (75 mL) and extracted with CH_2Cl_2 (3×75 mL). The combined organic layers were dried over $MgSO_4$ and concentrated. The resulting colorless oil was dissolved in CH_2Cl_2 (27 mL) and Dess–Martin periodinane (1.06 g, 2.50 mmol) was added to the mixture. After stirring for 3 h the mixture was concentrated and purified by flash chromatography (33% EtOAc/hexanes, SiO_2) giving **21** as a yellow solid, which was carried on without further purification.

Aldehyde **21** was dissolved in MeOH (11 mL) and 48% HBr (11 mL), heated to reflux, and stirred for 21 h afterwhich the mixture was concentrated. The residue was dissolved in DMF (22 mL) and K_2CO_3 (1.13 g, 8.15 mmol) was added portionwise over 1.5 h resulting in a red mixture. BnBr (1.02 mL, 8.54 mmol) was added and the mixture was stirred for 20 h afterwhich it was acidified with 10% HCl (60 mL, pH 1) and extracted with Et_2O (3×60 mL). The combined organic layers were washed with saturated NH_4Cl (2×60 mL), brine (60 mL), dried over $MgSO_4$, and concentrated. The residue was purified by flash chromatography (33% EtOAc/hexanes, SiO_2) affording **22** (0.308 g, 23 %) as a yellow solid: mp 146–148 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.20 (s, 1H), 7.69 (s, 1H), 7.40 (s, 1H), 7.33–7.37 (m, 5H), 5.34 (s, 2H), 4.08 (s, 3H), 3.95 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 188.6, 160.4, 156.7, 156.4, 155.5, 142.9, 135.3, 135.2, 132.1, 129.1, 128.9 (2), 121.9, 120.9, 111.8, 77.3, 62.3, 53.0; IR (film) 2953, 2876, 1742, 1741, 1695, 1455, 1413, 1355, 1324, 1278, 1116 cm^{-1}; HRMS (ES) calcd for $C_{20}H_{16}O_7Na$ (MNa^+) 391.0794, found 391.0809.

*4.2.11. 7-Benzyloxy-8-methoxy-1-oxo-6-vinyl-1H-isochromene-3-carboxylic acid methyl ester (**3**).* A solution of Me_2Zn in $PhCH_3$ (3.1 mL, 6.2 mmol) was added dropwise to a solution of **22** (0.260 g, 0.706 mmol) and TMEDA (0.077 g, 0.66 mmol) in toluene (28 mL). After stirring for 28 h, the mixture was cooled in an ice bath and quenched by the addition of saturated NH_4Cl (30 mL). The mixture was further diluted with water (30 mL) and extracted with CH_2Cl_2

(3×30 mL). The combined organic layers were washed with 10% HCl (2×15 mL), brine (15 mL), dried over $MgSO_4$, and concentrated. Flash chromatography (50% EtOAc/hexanes, SiO_2) afforded starting material **22** (0.039 g, 15%) and **23** (0.191 g, 70%). 7-Benzyloxy-6-(1-hydroxy-ethyl)-8-methoxy-1-oxo-1*H*-isochromene-3-carboxylic acid methyl ester (**23**): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44 (s, 1H), 7.39 (s, 1H), 7..36–7.42 (m, 5H), 5.26 (d, J=13.7, 1H), 5.24 (d, J=13.7 Hz, 1H), 5.09 (dq, J=4.1 Hz, 6.5 Hz, 1H), 4.01 (s, 3H), 3.95 (s, 3H), 1.94 (d, J=4.1 Hz, 1H), 1.43 (d, J=6.5 Hz, 3H).

A portion of **23** (0.019 g, 0.049 mmol) was dissolved in $PhCH_3$ (5 mL), combined with TsOH (0.011 g, 0.064 mmol), and heated to reflux. After stirring for 1 h, the mixture was concentrated and dissolved in DMF (2 mL). K_2CO_3 (0.050 g, 0.36 mmol) and BnBr (0.033 mL, 0.28 mmol) was added to the mixture, which was stirred for 16 h. The mixture was acidified with 10% HCl (pH 1) and extracted with Et_2O (3×5 mL). The organic layers were combined, washed with saturated NH_4Cl (2×5 mL), dried over $MgSO_4$, and concentrated. Flash chromatography (25% EtOAc/hexanes, SiO_2) of the residue resulted in **3** (0.005 g, 28%) identical to that produced using the Horner–Wadsworth–Emmons condensation pathway describe below.

4.3. Synthesis of divergent intermediate 7-Allyloxy-8-hydroxy-1-oxo-1*H*-isochromene-3-carboxylic acid methyl ester (29) via Horner–Wadsworth–Emmons methodology

*4.3.1. 3-Hydroxy-6,7-dimethoxy-3H-isobenzofuran-1-one (**24**)*[16]. To a stirring solution of 3,4-dimethoxybenzaldehyde (50.0 g, 301 mmol) in MeOH (150 mL) were added $HC(OMe)_3$ (98.0 mL, 896 mmol) and TFA (2.5 mL, 33.7 mmol). The mixture was stirred at rt for 1 day afterwhich it was concentrated by vacuum pump to a purple liquid. The residue was purified by distillation from K_2CO_3 (0.1 Torr, distillation temperature 115–125 °C) to give 4-dimethoxymethyl-1,2-dimethoxy-benzene (48.7 g, 76%) as a faintly yellow liquid. Spectral data were in accord with those reported.[15]

To a clear, faintly yellow solution of 4-dimethoxymethyl-1,2-dimethoxy-benzene (2.31 g, 10.9 mmol) dissolved in Et_2O (55 mL) in an ice bath was added *n*-BuLi (9.5 mL, 15.2 mmol) dropwise over 5 min. The resulting opaque, light orange colored mixture was stirred for 1 h when the ice bath was replaced with a dry ice bath. An excess of solid CO_2 (~7 g) was added to the mixture and the cooling bath was removed. After the opaque white mixture had reached rt, water (50 mL) was added until two homogenous layers were obtained. The layers were separated and the aqueous layer was washed with Et_2O (50 mL). The aqueous layer was acidified with 5 N HCl (~2 mL, pH 1) and heated causing a yellow substance to oil out. Upon standing, the oil solidified into a yellow crystalline solid. Further cooling in an ice water bath, resulted in a white crystalline material precipitating out of solution. The mixture was filtered and dried over $CaSO_4$ under reduced pressure giving a mixture of **24** and its tautomer (1.73 g, 78%) as white and yellow crystals. Spectral data were in accord with those reported.[22]

*4.3.2. (Dimethoxy-phosphoryl)-methoxy-acetic acid methyl ester (**25**)*[18]. *CAUTION*! This radical reaction can be vigorous and possibly become self sustaining, especially on scales larger than the following. The authors recommend using a high capacity condenser cooled with dry ice/acetone. Carbon tetrachloride is highly toxic and should be handled with care. Methyl methoxyacetate (40.1 g, 385 mmol), NBS (68.6 g, 385 mmol), and benzoyl peroxide (0.191 g, 0.789 mmol) were combined in CCl_4 (200 mL) and slowly heated to reflux (oil bath, 95 °C), which was maintained for 1.5 days. The mixture was cooled, filtered through Celite (CCl_4), and concentrated to an orange liquid. The residue was purified by distillation under vacuum (10 Torr, 75 °C) to give bromo-methoxy-acetic acid methyl ester (60.6 g, 86%) as a colorless liquid. Spectral data were in accord with those reported.[17]

Trimethyl phosphite (28.0 mL, 237 mmol) was added dropwise over 45 min to stirring bromo-methoxy-acetic acid methyl ester (41.5 g, 227 mmol). The mixture was then heated to reflux (oil bath, 180–200 °C) for 3.5 h, then cooled to rt for 15 h, and again heated to reflux (oil bath, 180–200 °C) for 1.5 h. Upon cooling, the resulting clear yellow liquid was purified by distillation under reduced pressure (165 °C oil bath, 2 Torr, 125–130 °C distillation temperature) to give **25** (43.3 g, 90%) as a clear and colorless liquid. Spectral data were in accord with those reported.[18]

*4.3.3. 2,3-Dimethoxy-6-(2-methoxy-2-methoxycarbonyl-vinyl)-benzoic acid (**26**)*[4]. To a stirring suspension of sodium hydride (1.76 g, 27.8 mmol) in THF (150 mL) in an ice bath was added the clear and colorless phospho ester **25** (14.57 g, 68.7 mmol). The mixture was stirred for 1.75 h when **24** (5.84 g, 27.8 mmol) dissolved in THF (100 mL) was added dropwise. The mixture was warmed to rt and stirred for 2.5 h afterwhich it was poured into 1 N HCl (500 mL) and extracted with CH_2Cl_2 (3×400 mL). The organic layers were combined, dried over Na_2SO_4, and concentrated to give **26** as a slightly yellow oil, which was carried on without further purification.

*4.3.4. 7,8-Dimethoxy-1-oxo-1H-isochromene-3-carboxylic acid methyl ester (**27**)*[3,4]. Unpurified **26** (8.23 g, 27.8 mmol) and *p*-TsOH (5.43 g, 28.5 mmol) were combined in $PhCH_3$ (200 mL), stirred, and heated to reflux (oil bath, 130–140 °C) for 21 h. The mixture was cooled in a freezer and **27** crystallized out of solution. The $PhCH_3$ was decanted away and the residue sonicated with MeOH (100 mL) for 1 h. The mixture was cooled in a freezer and then filtered to give upon drying in a vacuum desiccator ($CaSO_4$) **27** (6.6 g, 90%) as a white crystalline solid: mp: 170.5–173.5 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 (d, J=9.0 Hz, 1H), 7.35 (s, 1H), 7.30 (d, J=8.5 Hz, 1H), 3.97 (s, 3H), 3.96 (s, 3H), 3.92 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.1, 157.3, 155.2, 151.5, 141.5, 129.1, 124.1, 119.5, 117.1, 112.6, 61.9, 56.7, 52.9; IR (film) 3090, 2989, 2950, 2850, 1730, 1498, 1437, 1290, 1251, 1120 cm^{-1}; HRMS (ES) calcd for $C_{13}H_{12}O_6Na$ (MNa^+) 287.0532, found 287.0538.

*4.3.5. 7,8-Dihydroxy-1-oxo-1H-isochromene-3-carboxylic acid methyl ester (**28**)*[3,4]. To an opaque, off-white stirring solution of **27** (6.4 g, 24.2 mmol) in CH_2Cl_2 (165 mL) in an ice bath was added BBr_3 (10 mL, 106 mmol). The mixture turned opaque yellow and was stirred for 1 h. The mixture was diluted with CH_2Cl_2 (250 mL) and quenched by the addition of water (500 mL). The layers were separated and the aqueous layer was washed with EtOAc (3×350 mL). The organic layers were combined, washed with water (2×300 mL) and brine (300 mL), dried over Na_2SO_4, and concentrated to afford **28** as a yellow powder contaminated with its hydrolyzed counterpart.

The mixture of **28** and its acid was taken up in MeOH (120 mL) and combined with concentrated H_2SO_4 (5.5 mL). The mixture was stirred and heated to reflux (oil bath, 90–95 °C) for 12 h. After cooling and concentrating, the slightly yellow solid was diluted with water (200 mL) and extracted with EtOAc (3×200 mL). The organic layers were combined, washed with brine (250 mL), dried (Na_2SO_4), and concentrated to afford **28** as an amorphous white solid (5.4 g, 95%): mp: 210–213.5 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.91 (s, 1H), 7.49 (s, 1H), 7.39 (d, J=8.0 Hz, 1H), 7.09 (d, J=8.0 Hz, 1H), 5.93 (s, 1H), 3.96 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.2, 160.7, 148.0, 146.3, 140.9, 126.9, 123.2, 119.5, 114.3, 107.9, 53.1; IR (film) 3414, 3090, 2958, 2927, 2858, 1730, 1684, 1460, 1282, 1213, 1128 cm^{-1}; HRMS (ES) calcd for $C_{11}H_9O_6$ (MH^+) 237.0399 found 237.0394.

*4.3.6. 7-Allyloxy-8-hydroxy-1-oxo-1H-isochromene-3-carboxylic acid methyl ester (**29**)*[3]. To a stirring solution of NaH (0.0316 g,

1.39 mmol) in DMF (7.0 mL) at −20 °C was added **28** (0.112 g, 0.474 mmol) in DMF (6.0 mL). The new mixture turned yellow and was stirred at −20 °C for 2 h afterwhich the orange solution was cooled to −45 °C.[23] Allyl bromide (0.55 mL, 6.46 mmol) was added and the mixture was stirred at −45 °C for 17 h afterwhich the reaction was quenched with saturated NH_4Cl (5 mL) and warmed to rt. The mixture was further diluted with 1 N HCl (25 mL) and extracted with EtOAc (3×25 mL). The organic layers were combined, washed with saturated NH_4Cl (2×25 mL) and brine (1×25 mL), dried over Na_2SO_4, and concentrated to give **29** as an amorphous yellow solid (0.123 g, 94%), which was carried on without purification: ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.12 (s, 1H), 7.47 (s, 1H), 7.32 (d, J=8.4 Hz, 1H), 7.06 (d, J=8.4 Hz, 1H), 6.04–6.10 (m, 1H), 5.43–5.47 (m, 1H), 5.33–5.36 (m, 1H), 4.72–4.74 (m, 1H), 3.95 (s, 3H).

4.4. An improved synthesis of 7,8-dibenzyloxy-1-oxo-6-vinyl-1*H*-isochromene-3-carboxylic acid methyl ester (2)

*4.4.1. 6-Allyl-7,8-dihydroxy-1-oxo-1H-isochromene-3-carboxylic acid methyl ester (**30**)*[3,4]. Phenol **29** (0.106 g, 0.384 mmol) and Ph_2O (12 mL) were combined and heated to reflux (heating mantle) and stirred for 3 h. The mixture was cooled, diluted with hexanes (~50 mL) and filtered through a plug of SiO_2 (hexanes then CH_2Cl_2 then EtOAc). The filtrate from the EtOAc fraction was concentrated to afford **30** (0.093 g, 88%) as a brown solid: mp: 181.5–185 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.83 (s, 1H), 7.45 (s, 1H), 6.96 (s, 1H), 6.08 (s, 1H), 5.94–6.02 (m, 1H), 5.16–5.17 (m, 1H), 5.13–5.15 (m, 1H), 3.94 (s, 3H), 3.51–3.53 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.1, 160.8, 147.3, 144.1, 140.9, 136.3, 134.6, 126.3, 119.8, 117.5, 114.3, 106.2, 53.0, 34.4; IR (film) 3468, 3090, 3005, 2958, 2927, 2858, 1722, 1676, 1637, 1452, 1328, 1251, 1213, 1151, 1097, 1020 cm^{-1}; HRMS (ES) calcd for $C_{14}H_{13}O_6$ (MH^+) 277.0712, found 277.0717.

*4.4.2. 6-Allyl-7,8-dibenzyloxy-1-oxo-1H-isochromene-3-carboxylic acid methyl ester (**31**).* To **30** (0.093 g, 0.337 mmol) in acetone (13 mL) were added K_2CO_3 (0.276 g, 2.00 mmol) and BnBr (0.14 mL, 1.18 mmol). The mixture was heated (60–65 °C, oil bath) and stirred for 14 h afterwhich it was cooled, filtered through Celite (acetone), and concentrated. The resultant brown solid was purified by flash chromatography (20% acetone/hexanes) to give **31** (0.106 g, 69%) as a white powder: mp 135–137 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.58–7.60 (m, 2H), 7.34–7.38 (m, 8H), 7.36 (s, 1H), 7.17 (s, 1H), 5.88 (tdd, J=6.6, 10.1, 16.9 Hz, 1H), 5.14 (dm, J=10.4 Hz, 1H), 5.133 (s, 2H), 5.132 (s, 2H), 5.07 (dm, J=17.0 Hz, 2H), 3.95 (s, 3H), 3.43 (dm, J=6.6 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.0, 157.4, 154.1, 152.9, 144.0, 142.6, 136.9, 136.4, 135.1, 132.5, 129.6, 128.69, 128.65, 128.63, 128.61, 128.5, 124.6, 117.8, 116.0, 112.3, 76.8, 75.8, 53.0, 34.7; IR (film) 3088, 3065, 3034, 2957, 2887, 1749, 1725, 1644, 1598, 1444 cm^{-1}; HRMS (ES) calcd for $C_{28}H_{25}O_6$ (MH^+) 457.1651, found 457.1667.

*4.4.3. 7,8-Dibenzyloxy-6-(2-hydroxy-ethyl)-1-oxo-1H-isochromene-3-carboxylic acid methyl ester (**32**).* To a stirring suspension of **31** (1.0 g, 2.19 mmol) in Et_2O (100 mL) was added OsO_4 (0.121 g, 0.476 mmol) in acetone (20 mL).[19] The mixture was stirred for 10 min. Water (100 mL) was added followed by $NaIO_4$ (4.74 g, 22.2 mmol) in five portions over a 4 h period. Stirring was continued after the final addition for 1.5 h afterwhich the reaction was quenched by the addition of 10% $Na_2S_2O_3$ (400 mL). The mixture was extracted with CH_2Cl_2 (3×300 mL), the organic layers were combined, dried over Na_2SO_4, and concentrated to afford aldehyde **32ald** as a light brown solid. A small amount of **32ald** was purified by flash chromatography (SiO_2) for characterization purposes: 7,8-*Dibenzyloxy*-1-*oxo*-6-(2-*oxo-ethyl*)-1*H*-*isochromene*-3-*carboxylic acid methyl ester*, a white powder: mp 158.5–160 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.58 (t, J=1.3 Hz, 1H), 7.58–7.59 (m, 2H), 7.33–7.37 (m, 6H), 7.34 (s, 1H), 7.26–7.27 (m, 2H), 7.13 (s, 1H), 5.16 (s, 2H), 5.15 (s, 2H), 3.95 (s, 3H), 3.67 (d, J=0.9 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 197.3, 160.8, 157.1, 154.1, 153.0, 142.9, 136.5, 136.3, 136.2, 132.6, 129.6, 128.8, 128.80, 128.76 (2), 128.7, 125.7, 117.2, 112.0, 77.0, 75.9, 53.1, 45.7; IR (film) 3092, 3065, 3034, 3011, 2953, 2880, 2853, 2733, 1725, 1648, 1598, 1498, 1471, 1440 cm^{-1}; HRMS (ES) calcd for $C_{27}H_{23}O_7$ (MH^+) 459.1444, found 459.1462.

Sodium borohydride (0.120 g, 3.17 mmol) was combined with EtOH (20 mL) and stirred together at rt for 1 h. This was added dropwise to **32ald** in dry THF (100 mL). The reaction was completed by as judge TLC after about one quarter of the reducing agent had been added. The reaction mixture was poured into 1 N HCl (200 mL) and extracted with CH_2Cl_2 (1×200 mL, 2×150 mL). The organic layers were combined, dried over Na_2SO_4, and concentrated. The resultant brown-white solid was subjected to flash chromatography (33% acetone/hexanes) to give **32** (0.438 g, 43%) as a white powder: mp 101–106 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.56–7.58 (m, 2H), 7.31–7.37 (m, 8H), 7.34 (s, 1H), 7.23 (s, 1H), 5.15 (s, 2H), 5.12 (s, 2H), 3.94 (s, 3H), 3.82 (t, J=6.3 Hz, 2H), 2.91 (t, J=6.3 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.9, 157.4, 154.0, 153.2, 142.9, 142.6, 136.8, 136.3, 132.4, 129.6, 128.73, 128.66, 128.64, 128.59 (2), 125.3, 116.2, 112.3, 76.9, 75.9, 62.3, 53.0, 34.2; IR (film) 3524 (br), 3065, 3034, 2953, 2883, 1722, 1598, 1444 cm^{-1}; HRMS (ES) calcd for $C_{27}H_{24}O_7Na$ (MNa^+) 461.1600, found 461.1601.

*4.4.4. 7,8-Dibenzyloxy-1-oxo-6-vinyl-1H-isochromene-3-carboxylic acid methyl ester (**2**).* Alcohol **32** (0.438 g, 0.278 mmol) and DBU (1.8 mL, 12.0 mmol) were combined in THF (34 mL) and cooled in an ice bath. Methanesulfonyl chloride (0.32 mL, 4.93 mmol) in THF (2 mL) was added dropwise to the cold solution for 0.5 h. After the addition was completed the mixture was stirred at rt for 3 h afterwhich the mixture was filtered through Celite (Et_2O). The filtrate was washed with 1 N HCl (3×100 mL) and brine (2×100 mL), dried over Na_2SO_4, and concentrated. The resultant yellow solid was subjected to flash chromatography (20% acetone/hexanes, CH_2Cl_2) to give **2** (0.362 g, 84%) as a white or light yellow powder: mp 170.5–173 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.59–7.61 (m, 2H), 7.46 (s, 1H), 7.39 (s, 1H), 7.34–7.38 (m, 8H), 7.04 (dd, J=11.1, 17.8 Hz, 1H), 5.92 (d, J=17.7 Hz, 1H), 5.51 (d, J=11.1 Hz, 1H), 5.14 (s, 2H), 5.08 (s, 2H), 3.95 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.0, 157.2, 154.8, 152.1, 142.8, 140.3, 136.6, 136.5, 132.5, 130.3, 129.6, 128.8, 128.7, 128.6 (3), 120.6, 119.9, 116.6, 112.4, 76.9, 76.3, 53.0; IR (film) 3088, 3069, 3034, 2961, 2937, 2883, 1749, 1722, 1594, 1444 cm^{-1}; HRMS (ES) calcd for $C_{27}H_{22}O_6Na$ (MNa^+) 465.1314, found 465.1293.

4.5. An improved synthesis of 7-Benzyloxy-8-methoxy-1-oxo-6-vinyl-1*H*-isochromene-3-carboxylic acid methyl ester (3)

*4.5.1. 7-Allyloxy-8-methoxy-1-oxo-1H-isochromene-3-carboxylic acid methyl ester (**33**).* Phenol **29** (5.03 g, 18.2 mmol), K_2CO_3 (25.3 g, 183 mmol), and CH_3I (11.5 mL, 185 mmol) were combined in DMF (300 mL) and stirred at rt for 20 h. The mixture was diluted with EtOAc (500 mL) and eluted through a plug of Celite (EtOAc). The eluant was partitioned between 1 N HCl (1 L) and EtOAc (500 mL). The aqueous layer was washed with additional EtOAc (2×250 mL). The combined organic layers were washed with saturated NH_4Cl (2×250 mL) and brine (500 mL), dried over Na_2SO_4, and concentrated to an oily brown solid. This residue was purified by flash chromatography (33–50% EtOAc/hexanes, SiO_2) to give the dimethyl isocoumarin **27** (0.4 g, 8%) and **33** (3.3 g, 62%) as an off-white solid: mp 120–122 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 (d, J=8.6 Hz, 1H), 7.33 (s, 1H), 7.26 (d, J=8.5 Hz, 1H), 6.04 (tdd, J=5.2, 10.6, 17.2 Hz, 1H), 5.43 (dd, J=1.4, 17.3 Hz, 1H), 5.31 (dd, J=1.3, 10.5 Hz, 1H), 4.67 (td, J=1.4, 5.1 Hz, 2H), 3.97 (s, 3H), 3.91 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.0, 157.3, 154.1, 151.9, 141.5, 132.4, 129.4, 123.9, 121.5, 118.5, 117.1, 112.5, 70.3, 61.8, 52.9; IR (film) 3092, 2999,

2941, 2845, 1725, 1637, 1594, 1490 cm^{-1}; HRMS (CI) calcd for $C_{15}H_{14}O_6$ (M^+) 290.0790, found 290.0782.

*4.5.2. 6-Allyl-7-benzyloxy-8-methoxy-1-oxo-1H-isochromene-3-carboxylic acid methyl ester (**35**).* Allyl ether **33** (3.3 g, 11.4 mmol) and diphenyl ether (500 mL) were combined, heated to reflux (heating mantle), and stirred for 1.5 h. The mixture was cooled, poured into hexanes (750 mL), and filtered through a plug of SiO_2 (hexanes then CH_2Cl_2 then EtOAc). The fractions were concentrated, the EtOAc fraction yielding **34** as a dark yellow solid. A small amount of **34** was purified by flash chromatography (SiO_2) for characterization purposes: 6-*Allyl*-7-*hydroxy*-8-*methoxy*-1-*oxo*-1*H*-*isochromene*-3-*carboxylic acid methyl ester*, an off-white solid: mp 188–190.5 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37 (s, 1H), 7.16 (s, 1H), 6.54 (s, 1H), 6.00 (tdd, *J*=6.8, 10.1, 16.9 Hz, 1H), 5.18 (dm, *J*=10.1 Hz, 1H), 5.16 (dm, *J*=16.9 Hz, 1H), 4.03 (s, 3H), 3.93 (s, 3H), 3.53 (d, *J*=6.7 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.0, 157.6, 149.8, 147.3, 141.5, 136.2, 134.4, 128.8, 124.7, 117.8, 113.9, 113.0, 63.1, 53.0, 34.5; IR (film) 3405 (br), 3084, 3007, 2957, 2853, 1722, 1644, 1606, 1482, 1455 cm^{-1}; HRMS (CI) calcd for $C_{15}H_{14}O_6$ (M^+) 290.0790, found 290.0780.

To unpurified **34** (3.3 g, 11.4 mmol) in DMF (230 mL) were added K_2CO_3 (7.87 g, 56.9 mmol) and BnBr (1.4 mL, 11.8 mmol). The mixture was stirred at rt for 20 h afterwhich it was diluted with EtOAc and filtered through a plug of Celite (EtOAc). The mixture was washed with 1 N HCl (500 mL) and the aqueous layer was extracted once with EtOAc (250 mL). The combined organic layers were washed with saturated NH_4Cl (2×200 mL) and brine (400 mL), dried over Na_2SO_4, and concentrated to a brown solid. The residue was purified by flash chromatography (33–50% EtOAc/hexanes, SiO_2) to give **35** as a yellow solid. The column was flushed with 10% MeOH/CH_2Cl_2 to dissolve product residue from the top of the column yielding two fractions. The latter was dissolved in EtOAc (200 mL), washed successively with saturated NH_4Cl (2×200 mL) and brine (250 mL), dried over $MgSO_4$, decolorized with activated carbon, and concentrated to give **35** as yellow solid. The impure fractions were combined and resubjected to flash chromatography (33% EtOAc/hexanes, SiO_2) to give **35** as an off-white solid. The combined purifications yielded deallylated **35** (0.758 g, 20%) and **35** (2.537 g, 59%): mp 155–156.5 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36–7.45 (m, 5H), 7.35 (s, 1H), 7.15 (s, 1H), 5.87 (tdd, *J*=6.7, 10.2, 16.9 Hz, 1H), 5.16 (s, 2H), 5.14 (dm, *J*=10.2 Hz, 1H), 5.07 (dm, *J*=17.1 Hz, 1H), 4.00 (s, 3H), 3.94 (s, 3H), 3.43 (dm, *J*=6.6 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.0, 157.4, 155.5, 152.6, 144.0, 142.6, 137.0, 135.2, 132.4, 128.8, 128.63, 128.60, 124.4, 117.8, 115.7, 112.4, 75.7, 62.1, 53.0, 34.8; IR (film) 3048, 3034, 3007, 2980, 2953, 2849, 1737, 1644, 1598, 1552, 1451 cm^{-1}; HRMS (ES) calcd for $C_{22}H_{20}O_6Na$ (MNa^+) 403.1158, found 403.1145.

*4.5.3. 7-Benzyloxy-6-(2-hydroxy-ethyl)-8-methoxy-1-oxo-1H-isochromene-3-carboxylic acid methyl ester (**36**).* To a stirring suspension of **35** (1.023 g, 2.69 mmol) in Et_2O (150 mL) was added OsO_4 (0.143 g, 0.562 mmol) in acetone (30 mL).[19] After stirring for 10 min, water (150 mL) was added followed by $NaIO_4$ (5.77 g, 27.0 mmol) in five portions over a 4 h period. Stirring was continued after the final addition for 2.5 h. The layers were separated and the aqueous layer was extracted with EtOAc (2×75 mL). The combined organic layers were washed with 10% $Na_2S_2O_3$ (250 mL) and this aqueous layer was further washed with EtOAc (2×75 mL). The combined organic layers were dried over Na_2SO_4 and concentrated. The resulting solid was immediately dissolved in CH_2Cl_2 and eluted through a plug of SiO_2 (33% Et_2O/CH_2Cl_2) to give **37** as a yellow-brown solid. A small amount of **37** was purified for characterization purposes: 7-*Benzyloxy*-8-*methoxy*-1-*oxo*-6-(2-*oxo*-*ethyl*)-1*H*-*isochromene*-3-*carboxylic acid methyl ester*, a yellow solid: mp 121.5–126 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.60 (t, *J*=1.3 Hz, 1H), 7.35–7.37, (m, 5H), 7.34 (s, 1H), 7.12 (s, 1H), 5.19 (s, 2H), 4.01 (s, 3H), 3.94 (s, 3H), 3.69, (d, *J*=1.2 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 197.3, 160.8, 157.1, 155.4, 152.6, 142.8, 136.6, 136.3, 132.5, 128.9, 128.8 (2), 125.6, 116.9, 112.0, 75.8, 62.2, 53.1, 45.7; IR (film) 3092, 3069, 3034, 3007, 2949, 2876, 2849, 2733, 1722, 1648, 1598, 1552, 1498, 1451 cm^{-1}; HRMS (ES) calcd for $C_{21}H_{18}O_7Na$ (MNa^+) 405.0950, found 405.0938.

Unpurified **37** was dissolved in CH_2Cl_2 (42 mL) and MeOH (35 mL) and cooled to −65 to −55 °C (cryocool). $NaBH_4$ (0.483 g, 12.8 mmol) dissolved in MeOH (12 mL) was added. After stirring 42 h, the mixture was quenched by the addition of 1 N HCl (20 mL) and warmed to rt. The mixture was further diluted with 1 N HCl (150 mL) and extracted with CH_2Cl_2 (3×150 mL). The combined organic layers were dried over Na_2SO_4 and concentrated to a light brown solid. The residue was purified by flash chromatography (25% Et_2O/CH_2Cl_2, SiO_2) to give **37** (0.122 g), **35** (0.118 g) and **36** (0.403 g, 39%) as a white powder: mp 153–158.5 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36–7.44 (m, 5H), 7.35 (s, 1H), 7.22 (s, 1H), 5.19 (s, 2H), 4.00 (s, 3H), 3.94 (s, 3H), 3.83 (t, *J*=6.3 Hz, 2H), 2.91 (t, *J*=6.3 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.0, 157.3, 155.4, 152.9, 142.8, 142.6, 137.0, 132.4, 128.8, 128.7, 128.6, 125.1, 115.9, 112.3, 75.9, 62.3, 62.1, 53.0, 34.2; IR (film) 3509 (br), 3092, 3034, 2953, 2876, 1722, 1648, 1598, 1552, 1498, 1455 cm^{-1}; HRMS (ES) calcd for $C_{21}H_{20}O_7Na$ (MNa^+) 407.1107, found 407.1088.

*4.5.4. 7-Benzyloxy-6-(2,3-dihydroxy-propyl)-8-methoxy-1-oxo-1H-isochromene-3-carboxylic acid methyl ester (**40**).* To a stirring yellow suspension of **35** (0.0490 g, 0.129 mmol) in acetone (1.5 mL) and water (1.3 mL) was added OsO_4 (0.0034 g, 0.017 mmol) in acetone (0.5 mL) turning the mixture light brown followed by *N*-methylmorpholine oxide (0.0303 g, 0.224 mmol). After stirring at rt for 2 d, the mixture was quenched by the addition of $NaHSO_3$ and stirred for 0.5 h. The mixture was filtered through a plug of Celite (EtOAc). The filtrate was diluted with EtOAc (10 mL), washed with water (10 mL) and brine (10 mL), dried over Na_2SO_4, and concentrated. The residue was purified by flash chromatography (5% MeOH/CH_2Cl_2) to give **40** (0.0330 g, 62%) as a faintly black to colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37–7.44 (m, 5H), 7.34 (s, 1H), 7.24 (s, 1H), 5.21 (d, *J*=11.0 Hz, 1H), 5.18 (d, *J*=11.0 Hz, 1H), 4.00 (s, 3H), 3.94 (s, 3H), 3.86–3.90 (m, 1H), 3.59 (dd, *J*=3.5, 11.2 Hz, 1H), 3.44 (dd, *J*=6.2, 11.2 Hz, 1H), 2.84 (dd, *J*=4.9, 13.6 Hz, 1H), 2.78 (dd, *J*=7.9 Hz, 13.6 Hz, 1H), 2.42 (s, 1H), 2.01 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.9, 157.3, 155.4, 152.8, 142.7, 142.0, 136.8, 132.4, 128.94, 128.86, 128.7, 125.7, 116.0, 112.3, 76.1, 72.0, 66.2, 62.2, 53.1, 34.9; IR (film) 3460, 3090, 3035, 2943, 2881, 1730, 1599, 1452, 1259, 1112 cm^{-1}; HRMS (ES) calcd for $C_{22}H_{23}O_8$ (MH^+) 415.1393, found 415.1375.

*4.5.5. 7-Benzyloxy-8-methoxy-1-oxo-6-vinyl-1H-isochromene-3-carboxylic acid methyl ester (**3**).* To **36** (0.403 g, 1.05 mmol) dissolved in CH_2Cl_2 (30 mL) and cooled in an ice bath were added Et_3N (0.29 mL, 2.08 mmol) and MsCl (0.080 mL, 1.2 mmol). The mixture was stirred cold for 15 min afterwhich it was partitioned between 1 N HCl (100 mL) and CH_2Cl_2 (100 mL). The organic layer was washed with brine (75 mL), dried over Na_2SO_4, and concentrated to give the mesylate as a faintly yellow oil.

To a stirring solution of the mesylate in CH_2Cl_2 (40 mL) in an ice bath was added DBU (0.32 mL, 1.2 mmol). The mixture was warmed to rt and stirred for 16 h afterwhich it was partitioned between CH_2Cl_2 (100 mL) and 1 N HCl (150 mL). The organic layer was dried over Na_2SO_4 and concentrated to a light yellow solid. The residue was eluted through a plug of SiO_2 (20% Et_2O/CH_2Cl_2) to give **3** (0.346 g, 90%) as a white powder: mp 136–139 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37–7.46 (m, 5H), 7.43 (s, 1H), 7.38 (s, 1H), 7.02 (dd, *J*=11.1, 17.7 Hz, 1H), 5.91 (d, *J*=17.7 Hz, 1H), 5.50 (d, *J*=11.2 Hz, 1H), 5.11 (s, 2H), 4.02 (s, 3H), 3.95 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.0, 157.2, 156.1, 151.8, 142.7, 140.3, 136.8, 132.4, 130.4, 128.8, 128.72, 128.66, 120.4, 119.9, 116.2, 112.4, 76.2, 62.2, 53.1; IR

(film) 3092, 3065, 3034, 3011, 2949, 2876, 2853, 1745, 1722, 1594, 1455 cm^{-1}; HRMS (ES) calcd for $C_{21}H_{18}O_6Na$ (MNa^+) 389.1001, found 389.1016.

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Supplementary data

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