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The synthetic preparation of naturally-occurring aromatase inhibitors, morachalcone A, isogemichalcone B, and isogemichalcone C

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ABSTRACT

A convergent synthesis applicable to the preparation of oxidized prenylchalcones is reported that relies on key Claisen–Schmidt, Mitsunobu, and vinyl/benzyl Stille coupling operations. The synthetic strategy was applied towards the preparation of the natural products morachalcone A and isogemichalcones B & C, allowing their preparation in less than 10 steps and 6–8% overall yield.

1. Introduction

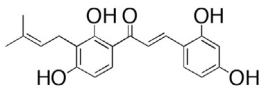
Aromatase represents a unique class of enzymes that catalyze a key oxidative transformation in the biosynthesis of the estrogens, estrone, and estradiol, through aromatization of their respective androgen precursors, androstenedione, and testosterone. Through a sequence of three cytochrome P_{450}-promoted steps, a pendant methyl (C_{19}) of the androgen A ring is cleaved, allowing for aromatization of the resulting enone, providing the phenol characteristic of the estrogens.[1]

The importance of the estrogens throughout development, being responsible for the regulation of metabolism, bone growth, the storage of fat tissue, and secondary sex characteristics, cannot be overestimated. However, in post-menopausal women, the unregulated production and storage of estrogen has been directly connected with breast cancer.[2] Therefore, the inhibition of aromatase, as a late focal point in aromatase production, has been used as attractive therapeutic strategy. Breast cancer treatments target the enzyme through the use of mechanism-based inactivators, such as Exemestane®, and competitive inhibitors, such as Anastrozole®.[3] As is often the case, natural products can serve as elegant templates for potential biological activity. As part of a natural product screening effort for aromatase activity, Kinghorn et al. determined that the natural products, morachalcone A, isogemichalcone B, and isogemichalcone C possessed moderate aromatase inhibitory activity with IC_{50} values of 4600, 500, and 7100 μM, respectively.[4] Morachalcone A, and isogemichalcones B and C are metabolites of *Maclura pomifera* (the Osage orange tree) and *Hypericum Geminiflorum*[5] and *Broussonetia papyrifera*.

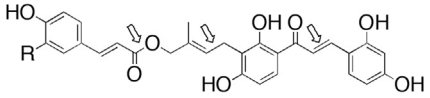
2. Results and discussion

The immediate purpose of this study is to prepare these three structurally-related naturally-occurring chalcones. The ultimate intent is to design a synthetic route that would be amenable to rapid analog preparation in order to effectively explore aromatase inhibition. In addressing the synthesis, the most readily apparent disconnections are located at the hydroxycinnamic ester, (for **2** and **3**), the aryl-prenyl bond, and the enone (Fig. 1).

Morachalcone A, (**1**), which does not possess the cinnamate ester, was prepared with the prenyl and enone disconnections in mind (Scheme 1). In a previously reported synthesis,[6] the phenols of commercially available β-resorcylaldehyde (**6**) were protected as MOM ethers in 82% yield, while resacetophenone **4** was more



1 Morachalcone A



2 R = H Isogemichalcone B
3 R = OCH_3 Isogemichalcone C

Fig. 1. Morachalcone A and isogemichalcones B and C.

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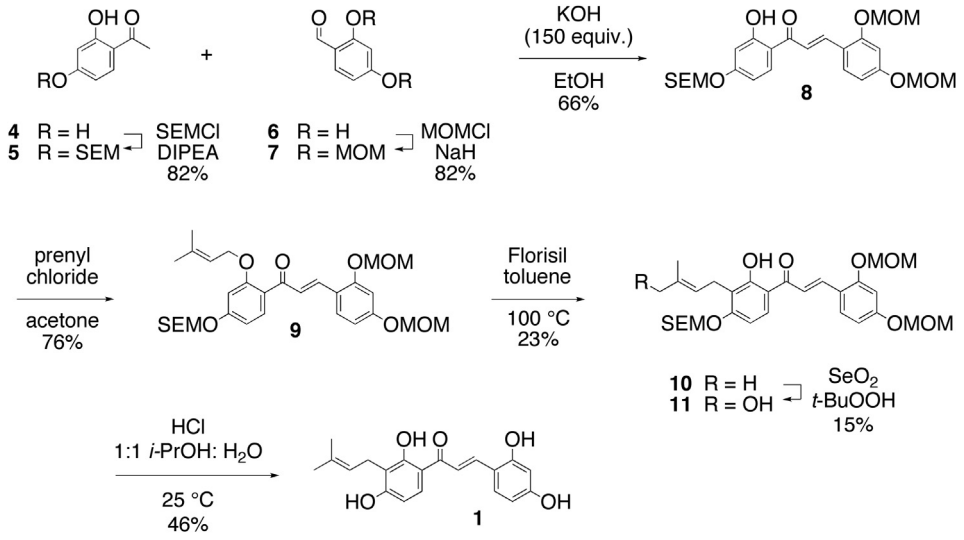


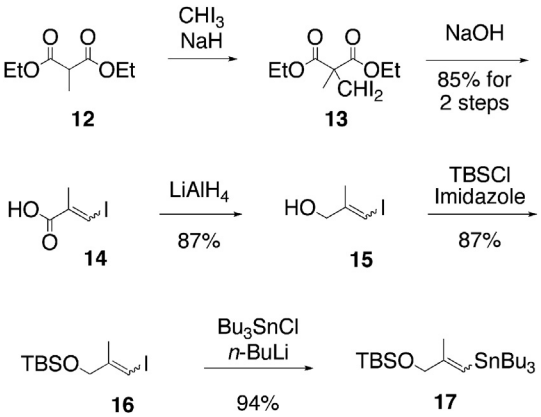
Scheme 1. The synthesis of Morachalcone A.

amenable to monoprotection as a SEM ether, also in 82% yield. That the *peri* phenol in the latter example did not readily sustain a protecting group was advantageous for later, selective prenylation. After some investigation, it was found that the chalcone core could be synthesized using a Claisen–Schmidt condensation of **5** and **7** in the presence of 150 equiv of ethanolic KOH at room temperature for 18 h.[7] Fewer equivalents gave poor conversion, while increased time or reaction temperatures led to decomposition of the protecting group. It would be observed repeatedly that only the thermodynamically preferred *E* enone, such as **8** was produced in good yield (66%), with recovered starting material composing the remainder of the reaction mixture. The simplicity and reliability of this method would make it a cornerstone of the synthetic strategy.

The free phenol of **8** was envisioned as a handle to install the prenyl group via a 1,3-prenyl rearrangement, as described by Talamas[8] and Dauben.[9] Accordingly, the prenyl ether was prepared by alkylation of **8** with prenyl chloride in refluxing acetone in 76% yield. Rearrangement of the *O*-prenyl ether (**9**), catalyzed by 10% w/w Florisil®, in a 100 °C toluene solution for 18 h provided the desired prenylated phenol **10** in a 23% yield that, though modest, was nevertheless sufficient for the task. Alkylation at the desired *ortho* position (**10**) predominated over the *para* (~2:1 ratio), with some accompanying deprenylated material (**8**). Deprotection of the MOM and SEM ethers under traditional acid catalysis (1 M HCl in 1:1 isopropanol–water solution) completed the synthesis of morachalcone A (**1**), in six steps in a 4% overall yield. The spectroscopic data were consistent with the isolated natural product.[10]

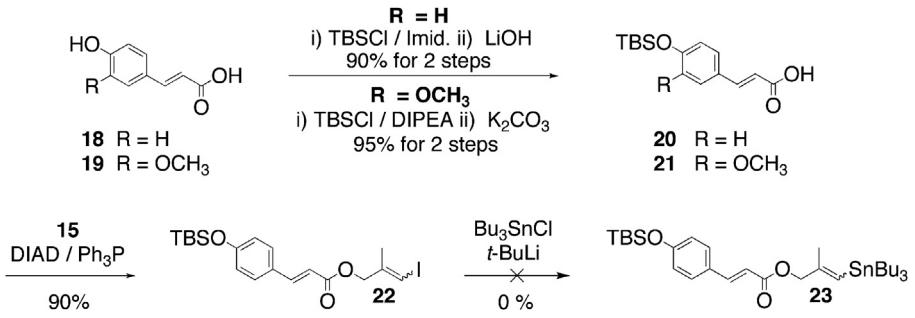
With the completion of morachalcone A (**1**), attention then turned to the preparation of isogemichalcones B and C (**2** & **3**), metabolites in which the prenyl group is oxidized on both, but differ from one another in substitution about the cinnamic ester. Unfortunately, it was quickly realized that oxidation of the prenyl of the protected morachalcone A (**10**) could not be accomplished efficiently. Though efforts to oxidize the prenyl of **10** using SeO_2 were regioselective for the desired *E*-allylic alcohol **11**, the reaction was sluggish, poor yielding, and generated equal amounts of over-oxidized aldehyde.

It was hoped that the Stille coupling would serve as a more selective, efficient alternative to install the prenyl group. Rather than attempt a conventional aryl/prenyl coupling, initial efforts focused on generating the prenyl group via construction of the benzyl/vinyl bond. A precedented means to prepare a vinyl stannane suitable for a Stille reaction was then identified (Scheme 2).[11] In this preparation, diethyl methylmalonate (**12**) was alkylated with iodoform to yield a diiodomethyl derivative **13** that was not isolated, but rather treated with excess NaOH to promote concomitant elimination, saponification, and decarboxylation. The resultant vinyl iodide (**14**) was produced exclusively as the *E* isomer in 85% yield from the malonate (**12**). The carboxylic acid was reduced with $LiAlH_4$ to alcohol **15** that was subsequently protected as a TBS ether affording iodide **16**, both steps proceeding in 87% yield.[12] In this instance, transmetalation of the iodide with *n*-BuLi, followed by tributylstannylchloride quench was readily accomplished to give stannane **17** in 94% yield.[13]



Scheme 2. Preparation of vinyl stannane (**17**) and its subsequent use in a Stille coupling.

With protocols for each of the major pieces of the puzzle now assembled, the next objective was to optimize the order in which each major fragment (hydroxycinnamate ester, prenyl, resorcinone, and resorcylaldehyde) was to be installed. Ideally, the synthesis could be made more convergent by a Stille reaction with an esterified vinyl stannane **23** (Scheme 3) and bromomethylchalcone **27**. To this end, *p*-coumaric acid (**18**) was protected in a two-step, one-pot procedure beginning with exhaustive TBS protection followed by LiOH-promoted saponification of the resulting TBS-ester to give



Scheme 3. Protection of cinnamates (**20** & **21**) and an unsuccessful Stille coupling.

silylated coumaric acid (**20**) in 90% yield.[14] Subsequent attempts to couple coumarate **20** with iodide **15** under DCC conditions provided no product, nor was any reaction noted with the corresponding acyl halide or Yamaguchi anhydride. However, Mitsunobu conditions using a twofold excess of coumarate were successfully employed to generate the desired ester (**22**) in 90% yield.[15] Predictably perhaps, the metalation conditions needed to prepare stannane (**23**) were shown to be incompatible with the newly formed ester. Though a method to esterify the coumarate had been identified, it was determined that the Stille coupling must precede esterification.

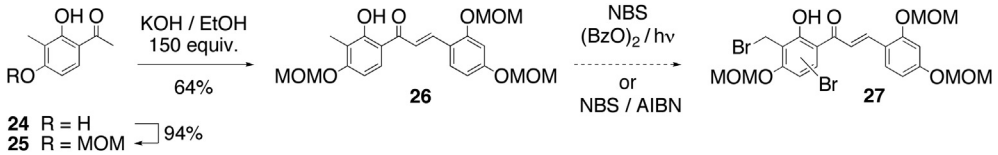
The preparation of benzyl halide **27** necessary for Stille coupling was also unexpectedly problematic (Scheme 4). Selective MOM protection of a methyl-substituted acetophenone **24** to give **25** was straightforward in 94% yield. The earlier success of the Claisen–Schmidt condensation was reproduced when **25** was coupled with benzaldehyde **7** to generate chalcone **26** in good yield (64%) as the sole stereoisomer. Unfortunately, the normally trustworthy NBS-promoted radical bromination, using either AIBN in refluxing CCl_4 or benzoyl peroxide initiated by light provided a complex mixture of halogenated products, in which both the benzylic position and the acetophenone ring were affected. Having determined that the assembled chalcone could not be present during the halogenation step, the Claisen–Schmidt condensation was slotted to follow the Stille coupling.

Finally, to individually establish the two natural products, the TBS protecting group was efficiently removed with TBAF to provide alcohol **31** in 80% yield. The treatment of this alcohol **31** with coumarate **20** under Mitsunobu conditions was successful in providing ester **32** in 66% yield. Simultaneous deprotection of the phenolic TBS and three MOM ethers using 5% HCl in THF proceeded sluggishly but effectively to provide isogemichalcone B (**2**) in 52% yield. Further, there was no evidence of competing isomerization of the olefin or of cyclization into a flavonoid.

Similarly, ferulic acid (**19**) was protected using the earlier two-step exhaustive TBS silylation/saponification strategy to provide the TBS ether in 95% yield (refer Scheme 3).[17] Likewise, the protected ferulic acid (**21**) was smoothly converted to the ester (**33**) under the same Mitsunobu conditions in 56% yield. The final deprotection using 5% HCl in THF was selective for the TBS and MOM ethers, providing isogemichalcone C (**3**) in high yield (91%), again without evidence of isomerization or methyl ether removal.

3. Conclusion

Isogemichalcone B (**2**) was synthesized in 6% overall yield in 10 steps by its longest linear route while isogemichalcone C was prepared in 8% overall yield in as many steps. Perhaps more importantly, the synthetic approach is convergent and highly amenable to substitution, theoretically providing access to a diverse



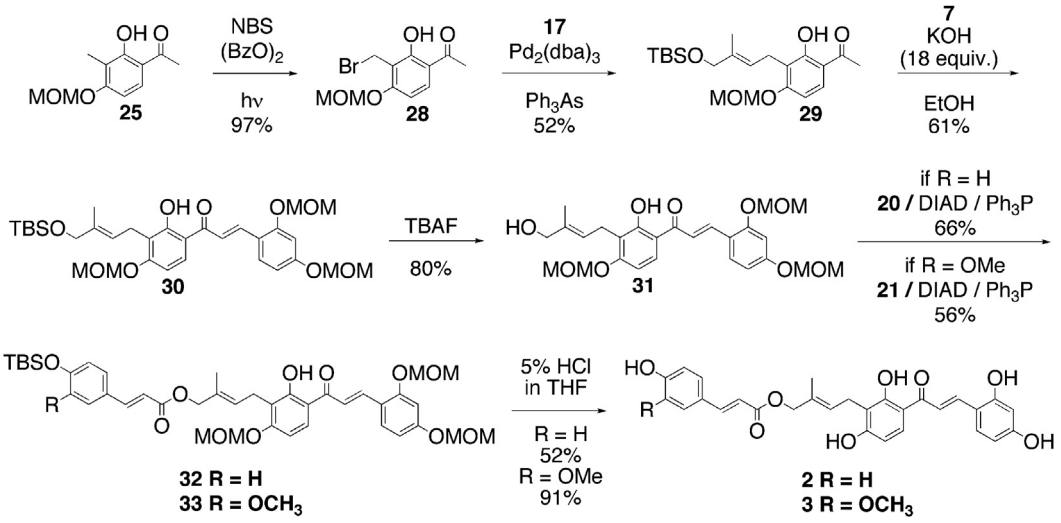
Scheme 4. Attempted formation of bromomethylchalcone (**27**).

Therefore, the optimal ordering of the steps should lead with Stille coupling to provide the central prenylated acetophenone (**29**) to be followed by the Claisen–Schmidt condensation and finally the Mitsunobu esterification (Scheme 5). With this in mind, acetophenone **25** was brominated without complication using NBS and benzoyl peroxide in 97% yield to give the desired benzyl bromide **28**. Using a protocol by Peter,[16] the pivotal Stille coupling of the unpurified bromide (**28**) with vinyl stannane **17** in the presence of $Pd_2(dba)_3$ and AsPh as a co-catalyst successfully generated the prenylated acetophenone **29** in 52% yield. With the oxidized prenyl group in place, the Claisen–Schmidt condensation with MOM-protected benzaldehyde **7** (requiring in this instance only 15 equiv of KOH) readily provided the desired chalcone **30** in a respectable 61% yield.

collection of Isogemichalcone B and C analogs. Further, the three key reactions (Stille, Claisen–Schmidt, and Mitsunobu) are compatible with a wide range of functional groups. The electronic and steric requirements of Isogemichalcone B and C can now be probed by facile modifications to the aryl substituents. Efforts to replace the phenols of resorcylaldehyde **7** and ferulate **21** with such functionality as –H, $-CH_3$, –*t*-butyl, $-CF_3$, –F, and –CN has begun in the hopes of creating a small library of analogs that can be used to explore the structure activity relationships of aromatase inhibition.

4. Materials and methods

Anhydrous reactions were conducted in flame-dried vessels under inert atmosphere, using magnetic stirring, and heating



Scheme 5. Completed syntheses of isogemichalcones B and C (**2** & **3**).

mantles/oil baths, when necessary. Moisture-sensitive reagents and solvents were added to reaction vessels using oven-dried syringes through rubber septa. Cited reaction temperatures refer to sand bath temperatures, not internal reaction temperatures. Unless otherwise noted, commercially available reagents and solvents from Aldrich, Acros, Fluka, and Lancaster were used without further purification. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian NMR spectrophotometer at 300 MHz and 75 MHz, respectively, or a Varian INOVA spectrometer at 400 MHz and 100 MHz, respectively. $CDCl_3$ was used as an internal reference (7.26 ppm or 77.0 ppm) unless otherwise indicated. Coupling constants are measured in Hertz. Infrared spectra were recorded on a Perkin–Elmer RX1 spectrophotometer. Thin layer chromatography analyses were conducted on aluminum-backed Kieselgel 60 F_{254} plates, and were visualized by ultraviolet light at 254 nm, or by treatment with alkaline aq $KMnO_4$, phosphomolybdic acid, or Hanessian solution. Chromatography was carried out using Baker 60–200 mesh silica gel for columns, silica gel with gypsum on 1, 2, 4, and 6 mm rotors for radial chromatography, an Isco Sg100 using 12, 40 or 120 g prepacked RediSep silica gel cartridges or a Biotage Horizon HPFC system using 20, 40, 50, 100, or 350 g prepacked silica gel cartridges.

4.1. 1-(2-Hydroxy-4-{[2-(trimethylsilyl)ethoxy]methoxy}phenyl)ethanone (5)

A solution of 2,4-dihydroxyacetophenone **4** (3.45 g, 22.7 mmol), and SEMCl (4.54 g, 27.2 mmol) in 22.7 mL of CH_2Cl_2 was cooled to 0 °C, then treated with diisopropylethylamine (7.03 g, 54.4 mmol). The solution was warmed to 25 °C and stirred for 18 h. The reaction mixture was diluted with dichloromethane before being washed twice with 5% HCl. The organic layer was washed with satd $NaHCO_3$ then dried with brine and Na_2SO_4. The resulting colorless oil was purified by silica gel chromatography (gradient elution: 5–20% EtOAc in hexanes) providing **5** as a white solid (5.24 g, 18.6 mmol, 82.0% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.61 (s, 1H, OH), 7.64 (d, J=8.9 Hz, 1H, H-6), 6.59 (d, J=2.4 Hz, 1H, H-3), 6.54 (dd, J=8.9, 2.4 Hz, 1H, H-5), 5.24 (s, 2H, OCH_2O), 3.75 (t, J=8.2 Hz, 2H, CH_2), 2.56 (s, 2H, $COCH_3$), 0.95 (t, J=8.2 Hz, 2H, CH_2), 0.01 (s, 9H, $Si(CH_3)_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ 202.9, 165.0, 164.0, 132.6, 114.8, 108.4, 103.9, 92.7, 67.0, 26.5, 18.2, −1.3; HRMS (ESI) m/z calcd for $C_{14}H_{23}O_4Si$ [$(M+H)^+$] 283.1365, found 283.1360.

4.2. 2,4-Bis(methoxymethoxy)benzaldehyde (7)

A solution of 2,4-dihydroxybenzaldehyde **6** (10.0 g, 72.4 mmol) in 25 mL THF was cooled to 0 °C, then treated with a 60% sodium hydride suspension in mineral oil (8.7 g, 217 mmol). After 5 min, methoxymethyl chloride (17.5 g, 217 mmol) was added and the mixture was allowed to stir at 65 °C for 18 h. The reaction mixture was poured onto water, then extracted with EtOAc. The organic layer was washed with brine and dried over $MgSO_4$. The resulting orange oil was purified by silica gel chromatography, eluting with CH_2Cl_2. Pooled fractions containing product were evaporated to give **7** as an orange oil that solidified upon standing (13.4 g, 59.2 mmol, 81.8% yield). Structural data was identical to literature precedents.[18] ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.35 (s, 1H, CHO), 7.82 (d, J=8.8 Hz, 1H, H-6), 6.83 (d, J=1.8 Hz, 1H, H-3), 6.76 (dd, J=8.7, 1.8 Hz, 1H, H-5), 5.28 (s, 2H, OCH_2O), 5.22 (s, 2H, OCH_2O), 3.53 (s, 3H, OCH_3), 3.49 (s, 3H, OCH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 188.3, 163.6, 161.3, 130.3, 120.4, 109.6, 102.8, 94.8, 94.3, 56.5, 56.4; HRMS (ESI) m/z calcd for $C_{11}H_{14}O_5Na$ [$(M+Na)^+$] 249.0739, found 249.0733.

4.3. (2*E*)-3-(2′,4′-Bis(methoxymethoxyphenyl))-1-(2″-hydroxy-4″-{[2-(trimethylsilyl)ethoxy]methoxy}phenyl)prop-2-en-1-one (8)

To a solution of aldehyde **7** (3.93 g, 17.4 mmol) and ketone **5** (2.45 g, 8.68 mmol) in 125 mL ethanol was added KOH (73.0 g, 1.30 mol). The resulting mixture was stirred at 25 °C for 18 h, giving a deep red solution. The reaction mixture was poured onto water and EtOAc. The organic layer was separated, dried over $MgSO_4$ and concentrated. The resulting oil was purified by silica gel chromatography, eluting with CH_2Cl_2, providing **8** as an orange oil (2.81 g, 5.73 mmol, 66.0% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 13.46 (s, 1 H, OH), 8.20 (d, J=15.5 Hz, 1H, H-2), 7.83 (d, J=9.1 Hz, 1H, H-6′), 7.61 (d, J=9.0 Hz, 1H, H-6″), 7.58 (d, J=15.5 Hz, 1H, H-3), 6.87 (d, J=2.3 Hz, 1H, H-3′), 6.75 (dd, J=8.7, 2.3 Hz, 1H, H-5′), 6.64 (d, J=2.3 Hz, 1H, H-3″), 6.59 (dd, J=8.7, 2.3 Hz, 1H, H-5″), 5.29 (s, 2H, OCH_2O), 5.27 (s, 2H, OCH_2O), 5.21 (s, 2H, OCH_2O), 3.77 (t, J=8.4 Hz, 2H, CH_2), 3.53 (s, 3H, OCH_3), 3.50 (s, 3H, OCH_3), 0.97 (t, J=8.4 Hz, 2H, CH_2), 0.01 (s, 9H, $Si(CH_3)_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ 192.6, 166.4, 163.8, 160.8, 158.1, 139.9, 131.4, 130.2, 118.9, 118.6, 115.2, 109.6, 108.2, 104.1, 103.5, 94.9, 94.5, 92.7, 67.0, 56.6, 56.4, 18.2, −1.2; HRMS (ESI) m/z calcd for

$C_{25}H_{34}O_8Si$ [$(M+H)^+$] 491.2085, found 491.2096; Anal. Calcd for $C_{25}H_{34}O_8Si$: C, 61.20; H, 6.99, found C, 60.82; H, 6.92.

4.4. (2*E*)-3-[2′,4′-Bis(methoxymethoxy)phenyl]-1-(2″-[(3-methylbut-2-en-1-yl)oxy]-4″-{[2-(trimethylsilyl)ethoxy]methoxy}phenyl)prop-2-en-1-one (9)

To a suspension of enone **8** (0.22 g, 0.45 mmol) and potassium carbonate (0.14 g, 1.0 mmol) in 10 mL acetone was added prenyl chloride (0.13 g, 1.3 mmol). The reaction mixture was refluxed for 18 h then concentrated to an orange oil. The product was partitioned between EtOAc and water. The organic layer was separated, dried over $MgSO_4$ and concentrated. The resulting oil was purified by silica gel chromatography (gradient elution: 5–30% EtOAc in hexanes) to provide **9** as a yellow oil (0.190 g, 0.34 mmol, 76% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.04 (d, J=15.9 Hz, 1H, H-2), 7.74 (d, J=8.6 Hz, 1H, H-6′), 7.58 (d, J=15.9 Hz, 1H, H-3), 7.56 (d, J=8.7 Hz, 1H, H-6″), 6.84 (d, J=2.4 Hz, 1H, H-3′), 6.70 (dd, J=8.7, 2.2 Hz, 1H, H-5′), 6.64 (m, J=2H, H-3″, 5″), 5.52 (t, J=6.6 Hz, 1H, =CH), 5.26 (s, 2H, OCH_2O), 5.23 (s, 2H, OCH_2O), 5.19 (s, 2H, OCH_2O), 4.59 (d, J=6.6 Hz, 2H, OCH_2), 3.77 (t, J=8.3 Hz, 2H, CH_2), 3.49 (s, 3H, OCH_3), 3.49 (s, 3H, OCH_3), 1.78 (s, 3H, CH_3), 1.74 (s, 3H, CH_3) 0.97 (t, J=8.3 Hz, 2H, CH_2), 0.01 (s, 9H, $Si(CH_3)_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ 190.7, 161.9, 160.1, 159.9, 157.7, 138.6, 136.5, 132.9, 128.8. 126.2, 123.6, 119.6, 119.5, 108.6, 108.2, 103.6, 101.4, 94.9, 94.5, 93.0, 66.8, 65.9, 56.5, 56.4, 25.9, 18.5, 18.3, −1.2; HRMS (ESI) m/z calcd for $C_{30}H_{43}O_8Si$ [$(M+H)^+$] 559.2713, found 559.2722; Anal. Calcd for $C_{30}H_{42}O_8Si$: C, 64.49; H, 7.58, found C, 64.14; H, 7.20.

4.5. (2*E*)-3-[2′,4′-Bis(methoxymethoxy)phenyl]-1-(2″-hydroxy-3″-(3-methylbut-2-en-1-yl)-4″-{[2-(trimethylsilyl)ethoxy]methoxy}phenyl)prop-2-en-1-one (10)

To a solution of enone **9** (1.90 g, 3.40 mmol) in 20 mL toluene was added 60–100 mesh Florisil® (4.50 g). The reaction mixture was heated at 100 °C for 8 h, then filtered. The filtrate was evaporated then purified by silica gel chromatography (3:1 dichloromethane–hexanes) to give **10** as an orange oil (0.43 g, 0.77 mmol, 23% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 13.55 (s, 1H, OH), 8.17 (d, J=15.5 Hz, 1H, H-β), 7.75 (d, J=9.1 Hz, 1H, H-6), 7.61 (d, J=15.2 Hz, 1H, H-α), 7.60 (d, J=9.1 Hz, 1H, H-6′), 6.86 (d, J=2.3 Hz, 1H, H-3), 6.75 (dd, J=8.6, 2.3 Hz, 1H, H-5), 6.70 (d, J=9.1 Hz, 1H, H-5′), 5.32 (s, 2H, OCH_2O), 5.28 (s, 2H, OCH_2O), 5.21 (t, J=7.2 Hz, 1H, H-8′), 5.21 (s, 2H, OCH_2O), 3.76 (t, J=8.3 Hz, 2H, CH_2), 3.52 (s, 3H, OCH_3), 3.49 (s, 3H, OCH_3), 3.41 (d, J=6.8 Hz, 2H, H-7′), 1.81 (s, 3H, CH_3), 1.67 (s, 3H, CH_3), 0.98 (t, J=8.3 Hz 2H, CH_2), 0.00 (s, 9H, $Si(CH_3)_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ 193.0, 163.4, 161.0, 160.7, 158.1, 139.6, 131.8, 130.2, 128.9, 122.4, 119.3, 118.8, 118.5, 115.3, 109.6, 105.0, 103.5, 94.9, 94.5, 92.5, 66.8, 56.6, 56.5, 26.0, 22.2, 18.3, 18.0, −1.2; HRMS (ESI) m/z calcd for $C_{30}H_{43}O_8Si$ [$(M+H)^+$] 559.2710, found 559.2722.

4.6. Morachalcone A, (2*E*)-1-[2″,4″-dihydroxy-3″-(3-methylbut-2-en-1-yl)phenyl]-3-(2′,4′-dihydroxyphenyl)prop-2-en-1-one (1)

The protected chalcone **10** (40 mg, 0.070 mmol) was dissolved in 5 mL of a 1:1 THF–*i*-PrOH solution. Concentrated HCl (0.5 mL) was added to the solution before stirring for 18 h at 25 °C. EtOAc and water (15 mL each) were added, the organic layer was separated, dried over Na_2SO_4 and concentrated to a red oil. The crude oil was purified by silica gel chromatography (gradient elution: 2.5–5% MeOH in CH_2Cl_2) to provide morachalcone A (**1**) as an orange powder (11 mg, 0.032 mmol, 46% yield). Structural data was identical to literature precedent.[4] ^{1}H NMR (400 MHz, CD_3OD): δ 8.07 (d, J=15.6 Hz, 1H, H-β), 7.75 (d, J=9.0 Hz, 1H, H-6), 7.71 (d, J=15.4 Hz, 1H, H-α), 7.50 (d, J=8.2 Hz, 1H, H-6′), 6.40 (d, J=9.0 Hz, 1H, H-5′), 6.36 (dd, J=8.2, 2.2 Hz, 1H, H-5′), 6.34 (d, J=2.0 Hz, 1H, H-3), 5.23 (t, J=7.2 Hz, 1H, H-8′), 3.30 (d, J=7.2 Hz, 1H, H-7′), 1.78 (s, 3H, H-10′), 1.66 (s, 3H, H-11′); ^{13}C NMR (100 MHz, CD_3OD): δ 193.2, 163.8, 162.1, 161.5, 159.5, 140.5, 131.1, 130.6, 128.9, 122.5, 116.7, 115.3, 114.4, 107.8, 106.8, 104.6, 102.3, 24.7, 21.3, 16.7; HRMS (ESI) m/z calcd for $C_{20}H_{20}O_5SiNa$ [$(M+Na)^+$] 363.1238, found 363.1203.

4.7. (2*E*)-3-[2′,4′-Bis(methoxymethoxy)phenyl]-1-(2″-hydroxy-3″-[(2*E*)-4-hydroxy-3-methylbut-2-en-1-yl]-4″-{[2-(trimethylsilyl)ethoxy]methoxy}phenyl)prop-2-en-1-one (11)

Chalcone **10** (20 mg, 0.036 mmol) was dissolved in 1 mL of THF. A catalytic amount of SeO_2 (0.40 mg, 0.004 mmol) and *tert*-butyl hydroperoxide (6.5 mg, 0.070 mmol, 5.5 M in decane) was added. The reaction mixture as then stirred for 6 h at 25 °C. After filtration, the crude reaction mixture was purified by reverse phase HPLC (2:5 to 95:5 MeCN in 0.15% aqueous TFA, 50×20 mm Phenomenex Luna C_{18} column) to afford **11** as a yellow oil (3.0 mg, 15% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 13.59 (s, 1H, OH), 8.17 (d, J=15.4 Hz, 1H, H-β), 7.76 (d, J=9.1 Hz, 1H, H-6), 7.61 (d, J=15.4 Hz, 1H, H-α), 7.60 (d, J=9.1 Hz, 1H, H-6′), 6.86 (d, J=2.3 Hz, 1H, H-3), 6.75 (dd, J=8.5, 2.3 Hz, 1H, H-5), 6.71 (d, J=9.1 Hz, 1H, H-5′), 5.53 (t, J=6.8 Hz, 1H, H-8′), 5.32 (s, 2H, OCH_2O), 5.28 (s, 2H, OCH_2O), 5.21 (s, 2H, OCH_2O), 3.99 (s, 2H, H-10′), 3.76 (t, J=8.3 Hz, 2H, CH_2), 3.52 (s, 3H, OCH_3), 3.50 (s, 3H, OCH_3), 3.46 (d, J=6.8 Hz, 2H, H-7′), 1.87 (s, 3H, CH_3), 0.01 (s, 9H, $Si(CH_3)_3$); HRMS (ESI) m/z calcd for $C_{30}H_{43}O_9Si$ [$(M+H)^+$] 575.2702, found 575.2671.

4.8. Diethyl 2-(diiodomethyl)-2-methylmalonate (13)[19]

A dispersion of 60% NaH in mineral oil (w/w) (9.21 g, 0.230 mol) was introduced to a flame-dried round bottom flask under inert gas. Diethyl ether (120 mL) was added to create a suspension. Diethyl methylmalonate (33.2 g, 0.185 mol) was added slowly over 30 min via syringe, causing gas evolution. After the addition, the solution was refluxed for 4 h, then cooled to room temperature. Iodoform (75.0 g, 0.190 mol) was added to the cooled solution. After the addition, the solution was again refluxed for 36 h. The reaction mixture was cooled to 0 °C, before 10% aqueous HCl (120 mL) was added slowly over 20 min. The aqueous layer was extracted three times with diethyl ether (60 mL). The organic fractions were combined, dried over $MgSO_4$, filtered and concentrated. The iodide (**13**), as a dark brown oil, was used in the next reaction without purification. ^{1}H NMR spectral data was consistent with that found in the literature.[20] ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.77 (s, 1H, CHI_2), 4.22 (q, J=8.0 Hz, 4H, CH_2), 1.80 (s, 3H, CH_3), 1.29 (t, J=8.1 Hz, 6H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.9, 62.5 (2), 62.0, 20.2, 13.9 (2), −26.0; HRMS (EI) (m/z): [M^+] calcd for $C_9H_{14}O_4I_2$ 439.8982, found, 439.8988.

4.9. (*E*)-3-Iodo-2-methylacrylic acid (14)[19,20]

Iodide (**13**) was dissolved in EtOH–H_2O (3:1) (520 mL) then treated with KOH (28.1 g, 0.500 mol). The solution was refluxed for 24 h, cooled to room temperature, then concentrated to give a red oil. The oil was treated with 10% aqueous K_2CO_3 (300 mL) to induce the precipitation of residual iodoform. The resulting yellow solid was rinsed with DCM (2×50 mL) then removed by vacuum filtration. The filtrate was acidified with concd HCl (130 mL) before being exhaustively extracted with DCM (5×35 mL). The combined organic layers were dried over $MgSO_4$ and concentrated. The crude product was purified by Biotage flash column chromatography, eluting with 10% EtOAc–Hexanes to afford carboxylic acid (**14**) (33.5 g, 0.158 mol) as a white solid. The total yield through two steps was 85.4%. NMR spectral data was consistent with that found in the literature.[12,21] mp=49.0–50.0 °C; ^{1}H NMR (300 MHz, $CDCl_3$):

δ 8.03 (s, 1H, H-3), 2.06 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.2, 139.0, 102.0, 19.8; HRMS (EI) (*m*/*z*): [M^+] calcd for C_4H_7OI 197.9542, found, 197.9545.

4.10. (*E*)-3-Iodo-2-methylprop-2-en-1-ol (15)[12]

Carboxylic acid (**14**) (25.0 g, 118 mmol) was dissolved in diethyl ether (236 mL, 0.50 M) to produce a pale yellow solution. The solution was cooled to 0 °C. $LiAlH_4$ (4.47 g, 118 mmol) was added in small portions over 15 min accompanied by hydrogen gas evolution. The solution was allowed to stir for 4 h at room temperature. Approximately 0.45 g of additional $LiAlH_4$ (11.8 mmol) was added and allowed to stir for an additional 30 min to ensure complete reduction. The mixture was then cooled to 0 °C in an ice/water bath then quenched by the slow addition of 2 M H_2SO_4. The aqueous layer was separated and extracted with DCM (3×75 mL). The organics were pooled then washed with 10% aqueous K_2CO_3 (100 mL). The washes were back-extracted with DCM (3×50 mL). The combined organics were dried over $MgSO_4$ and concentrated. Vinyl alcohol (**15**) (20.3 g, 103 mmol, 87%) was isolated as a clear oil without the need for purification. Structural data was identical to literature precedent.[12] ^1H NMR (300 MHz, $CDCl_3$): δ 6.29 (br s, 1H, H-3), 4.14 (br d, 2H, H-1), 1.85 (br s, 3H, CH_3); ^{13}C NMR (300 MHz, $CDCl_3$) δ 147.2, 77.3, 67.1, 21.3; HRMS (EI) (*m*/*z*): [M^+] calcd for $C_4H_5O_2I$ 211.9335, found, 211.9338.

4.11. (*E*)-1-(*tert*-Butyldimethylsiloxy)-3-iodo-2-methyl-2-propene (16)

A solution of alcohol (**15**) (5.00 g, 25.3 mmol) in DCM (85.0 mL, 0.30 M) was cooled to 0 °C in an ice/water bath then treated with TBSCl (4.18 g, 27.7 mmol). DIPEA (8.80 mL, 50.5 mmol) was then added slowly over 5 min. The solution was warmed to room temperature then stirred for 18 h. The resulting red solution was transferred to a separatory funnel and washed with 5% aqueous HCl (2×100 mL), $NaHCO_3$ and brine, then dried over $MgSO_4$ and concentrated. The crude product was purified by Biotage flash column chromatography, eluting with 10% Et_2O–Hexanes to afford silyl ether (**16**) (6.90 g, 22.1 mmol, 87%) as a clear yellow oil. ^1H NMR spectral data was identical to that found in the literature.[13] ^1H NMR (300 MHz, $CDCl_3$): δ 6.20 (s, 1H, H-3), 4.14 (br s, 2H, H-1), 1.78 (s, 3H, CH_3), δ 0.95 (s, 9H, $SiC(CH_3)_3$), 0.10 (s, 6H, $Si(CH_3)_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.0, 76.3, 67.1, 29.9, 26.1, 21.4, −5.2; HRMS (EI) (*m*/*z*): [M^+] calcd for $C_{10}H_{21}OISi$ 312.0407, found, 312.0412.

4.12. (*E*)-1-(*tert*-Butyldimethylsiloxy)-2-methyl-3-(tributylstannyl)-2-propene (17)

TBS-protected vinyl iodide (**16**) (3.5 g, 11 mmol) dissolved in diethyl ether (56.0 mL, 0.20 M) was cooled to −78 °C. To the cooled solution, 2.5 M *n*-BuLi in hexanes (7.18 mL, 17.9 mmol) was added, followed immediately by addition of tributyltin chloride (4.87 mL, 17.9 mmol). After 3 h of stirring at low temperature, the solution was gradually warmed to room temperature over 1 h. The solution was quenched with H_2O (8.00 mL). The organic layer was partitioned, washed once with $NaHCO_3$, and brine, then dried over $MgSO_4$ and concentrated. The crude product was purified by column chromatography, eluting with 20% EtOAc–Hexanes to afford vinyl stannane (**17**) (5.00 g, 10.5 mmol, 94%) as a clear oil. ^1H NMR spectral data was identical to that found in the literature.[13] ^1H NMR (300 MHz, $CDCl_3$): δ 5.82 (s, 1H, H-3), 4.11 (s, 2H, H-1), 1.70 (s, 3H, CH_3), 1.50 (m, 18H, $Sn(CH_2)_9$), 1.35 (m, 9H, CH_3), 0.95 (s, 9H, $SiC(CH_3)_3$), 0.10 (s, 6H, $Si(CH_3)_2$) ^{13}C NMR (75 MHz, $CDCl_3$): δ 152.8, 120.3, 69.0, 29.2, 27.3, 26.2, 21.0, 18.4, 13.7, 10.1, −5.3.

4.13. (*E*)-3-(4′-((*tert*-Butyldimethylsilyl)oxy)phenyl)acrylic acid (20)[14]

A solution of *p*-coumaric acid (4.00 g, 24.4 mmol) (**18**) and imidazole (6.64 g, 97.5 mmol) in DCM (48.0 mL, 0.51 M) was prepared and cooled to 0 °C then treated with TBSCl (9.12 g, 61.0 mmol). The solution was allowed to stir for 24 h then quenched with brine (20.5 mL). The aqueous layer was extracted with EtOAc (2×25 mL). The organic fractions were pooled and dried over $MgSO_4$.

The clear concentrate was dissolved in THF–H_2O (80 mL/20 mL) then saponified with LiOH (1.02 g, 24.4 mmol). After stirring for 10 min, the reaction was quenched with 20 mL of 0.1 M HCl. The solution was extracted with EtOAc (45 mL). The organic layer was washed with brine, dried over $MgSO_4$ and concentrated. The crude product was purified by Biotage flash column chromatography, eluting with 33% EtOAc–Hexanes to afford (**20**) (6.10 g, 21.9 mmol, 90%) as a white solid. ^1H NMR spectral data was identical to literature precedent.[14] mp=128.5–130 °C; ^1H NMR (300 MHz, $CDCl_3$): δ 7.75 (d, *J*=16.1 Hz, 1H, H-2), 7.46 (dt, *J*=8.8, 2.5 Hz, 2H, H-2′,6′), 6.86 (dt, *J*=8.8, 2.2 Hz, 2H, H-3′,5′), 6.32 (d, *J*=16.1 Hz, 1H, H-3), 0.99 (s, 9H, $SiC(CH_3)_3$), 0.23 (s, 6H, $Si(CH_3)_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.5, 158.3, 146.8, 130.0, 127.4, 120.6, 114.9, 25.6, 18.2, −4.4; HRMS (EI) (*m*/*z*) [M^+] calcd for $C_{15}H_{22}O_3Si$ 278.1338, found 278.1336.

4.14. (*E*)-3-(4′-((*tert*-Butyldimethylsilyl)oxy)-3′-methoxyphenyl)acrylic acid (21)[17]

A solution of ferulic acid (3.00 g, 15.5 mmol) (**19**) in DCM (20.0 mL, 0.77 M) was cooled to 0 °C. DIPEA (8.07 mL, 46.3 mmol) followed by TBSCl (5.82 g, 38.6 mmol) were added to the solution. After stirring for 24 h, the solution was diluted with EtOAc (60.0 mL) then quenched with water (15.0 mL). The layers were separated then the organic layer was washed with 1 M HCl (2×30 mL), brine (30.0 mL), then dried over $MgSO_4$ and concentrated. The residue was dissolved in THF–H_2O (15 mL/5 mL) then saponified with solid K_2CO_3 (2.12 g, 15.4 mmol). After 2 h of stirring, the solution was quenched with 0.1 M HCl (20.0 mL). The solution was diluted with EtOAc (60.0 mL) then washed with water (15.0 mL), 1 M HCl (30.0 mL), brine (30.0 mL), then dried over $MgSO_4$ and concentrated. The crude product was purified by Biotage flash column chromatography, eluting with 40% EtOAc–Hexanes to provide (**21**) (4.54 g, 14.7 mmol, 95.0%) as a white solid. Mp=150–152 °C; ^1H NMR spectral data was identical to that found in the literature.[17] ^1H NMR (300 MHz, $CDCl_3$): δ 7.73 (d, *J*=16.0 Hz, 1H, H-2), 7.06 (dd, *J*=8.0, 2.0 Hz, 1H, H-6′), 7.05 (d, *J*=1.9 Hz, 1H, H-2′), 6.86 (d, *J*=8.7 Hz, 1H, H-5′), 6.32 (d, *J*=16.1 Hz, 1H, H-3), 3.85 (s, 3H, OCH_3), 1.00 (s, 9H, $SiC(CH_3)_3$), 0.18 (s, 6H, $Si(CH_3)_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.6, 151.2, 148.0, 147.2, 127.9, 122.7, 121.1, 114.9, 110.9, 55.4, 25.6, 18.5, −4.6; HRMS (EI) (*m*/*z*) [M^+] calcd for $C_{16}H_{24}O_4Si$ 308.1444, found 308.1438.

4.15. (*E*)-(*E*)-3″-Iodo-2″-methylallyl 3-(4′-((*tert*-butyldimethylsilyl)oxy)phenyl)acrylate (22)[16]

DIAD (0.20 mL, 1.0 mmol) was suspended in THF (3.0 mL) and stirred. Separately, vinyl alcohol (**15**) (0.10 g, 0.51 mmol), protected *p*-coumaric acid (**20**) (0.28 g, 1.0 mmol), and PPh_3 (0.26 g, 1.0 mmol) were dissolved in THF (7.00 mL). The latter solution was stirred until all solids were dissolved. The coumarate solution was transferred to the suspension of DIAD in THF, then stirred at room temperature. After 70 h, the solution was diluted in EtOAc and washed with brine. The organic layer was dried over $MgSO_4$ and concentrated. Purification though silica gel, eluting with 30% EtOAc–Hexanes afforded (**22**) as a yellow oil, 0.21 g (0.46 mmol, 90% yield). ^1H NMR (300 MHz, $CDCl_3$): δ 7.66 (d, *J*=15.4 Hz, 1H, H-2), 7.43 (d, *J*=8.8 Hz, 2H, H-2′,6′), 6.84 (d, *J*=8.8 Hz, 2H, H-3′,5′), 6.38 (br

s, 1H, H-3″), 6.31 (d, *J*=16.1 Hz, 1H, H-3), 4.69 (s, 2H, H-1″), 1.90 (s, 3H, CH_3), 0.98 (s, 9H, $Si(CH_3)_3$), 0.22 (s, 6H, $Si(CH_3)_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.6, 158.1, 145.2, 142.7, 129.8, 127.6, 120.6, 115.1, 79.8, 67.2, 25.6, 21.7, 18.2, −4.4; IR (neat, cm^{-1}): 2954, 2929, 2857, 1713, 1633, 1599, 1508, 1253, 906, 833; HRMS (EI) (*m*/*z*) [$(M+H)^+$] calcd for $C_{19}H_{27}IO_3Si$ 458.0775, found 458.0781.

4.16. 1-(2-Hydroxy-4-(methoxymethoxy))-3-methylacetophenone (25)

1-(2,4-Dihydroxy-3-methylphenyl)ethanone (6.00 g, 36.1 mmol) (**24**) was dissolved in DCM (110 mL, 0.330 M) to give an orange solution. DIPEA (15.9 mL, 95.5 mmol) was added causing the solution to turn a deep red color. Technical grade MOMCl (5.50 mL) was added, at, which time the solution turned yellow. The solution was allowed to stir at RT for 18 h before being quenched with H_2O. The aqueous layer was extracted with DCM (2×30 mL). The organic fractions were washed once each with $NaHCO_3$, brine, then dried over $MgSO_4$ and concentrated. The crude product was purified by Biotage flash column chromatography, eluting with 30% EtOAc–Hexanes on a 100 g cartridge to afford (**25**) (7.14 g, 34.0 mmol, 94%) as white needles. Mp 47.5–49.5 °C; ^1H NMR (300 MHz, $CDCl_3$): δ 7.57 (d, *J*=9.1 Hz, 1H, H-6), 6.65 (d, *J*=9.1 Hz, 1H, H-5), 5.26 (s, 2H, OCH_2), 3.48 (s, 3H, OCH_3), 2.57 (s, 3H, $COCH_3$), 2.13 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.2, 162.5, 161.3, 129.6, 114.8, 105.0, 105.0, 94.2, 56.4, 26.4, 7.8; IR (neat, cm^{-1}): 2969.0, 2918.4, 1607.0, 1254.8, 1069.5, 798.9; Anal. Calcd for $C_{11}H_{14}O_4$: C, 62.85; H, 6.71, found: C, 62.81; H, 6.81; HRMS (EI) (*m*/*z*): [$(M+H)^+$] calcd for $C_{11}H_{14}O_4$ 210.0892, found, 210.0897.

4.17. (*E*)-3-(2′,4′-Bis(methoxymethoxy)phenyl)-1-(2″-hydroxy-4″-(methoxymethoxy)-3″-methylphenyl)prop-2-en-1-one (26)

Aldehyde (**7**) (1.0 g, 4.4 mmol) and the protected acetophenone (**25**) (1.02 g, 4.85 mmol) were dissolved in EtOH (65.0 mL, 0.070 M). KOH (4.10 g, 72.9 mmol) was then added to the solution as solid pellets. As the solution was stirred, the solution color turns to a deep red color. After 36 h, the reaction mixture was quenched with 10% aqueous AcOH (60.0 mL) at which time the solution turned bright yellow. The organic layer was removed, then washed with $NaHCO_3$ and dried over $MgSO_4$. The residue was crystallized with Et_2O–hexanes to afford 1.18 g (2.82 mmol) of chalcone (**26**) as a yellow solid, (64% yield). Mp=94.5–96.5 °C; ^1H NMR (300 MHz, $CDCl_3$): δ 8.19 (d, *J*=15.7 Hz, 1H, H-2), 7.75 (d, *J*=9.1 Hz, 1H, H-6′), 7.62 (d, *J*=15.4 Hz, 1H, H-3), 7.61 (d, *J*=9.1 Hz, 1H, H-6″), 6.87 (d, *J*=2.2 Hz, 1H, H-3′), 6.75 (dd, *J*=8.8, 2.2 Hz, 1H, H-5′), 6.69 (d, *J*=9.1 Hz, 1H, H-5″), 5.29 (s, 4H, OCH_2), 5.21 (s, 2H, OCH_2), 3.52 (s, 3H, OCH_3), 3.50 (s, 3H, OCH_3), 3.50 (s, 3H, OCH_3), 2.17 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 192.7, 163.4, 160.8, 160.4, 157.8, 139.4, 130.0, 128.2, 118.8, 118.4, 114.9, 114.6, 109.3, 104.6, 103.1, 94.6, 94.2, 93.9, 56.4, 56.2, 56.2, 7.8; IR (neat, cm^{-1}) 2956, 2853, 1630, 1603, 1554, 1490, 1259, 1155; Anal. Calcd for $C_{22}H_{26}O_8$: C, 63.15; H, 6.26, found: C, 63.14; H, 6.29; HRMS (EI) (*m*/*z*): [$(M+H)^+$] calcd for $C_{22}H_{26}O_8$ 418.1628, found, 418.1625.

4.18. 1-(3-(Bromomethyl))-2-hydroxy-4-(methoxymethoxy) acetophenone (28)

A solution of acetophenone (**25**) (6.00 g, 28.5 mmol) in CCl_4 (190 mL, 0.15 M) was placed round bottomed flask fitted with a reflux condenser. The solution was treated with NBS (5.10 g, 28.7 mmol) and benzoyl peroxide (0.700 g, 2.89 mmol) to form a yellow solution. The solution was irradiated from a tungsten lamp, causing the solvent to reflux. After 4 h, the cloudy white suspension was placed in an ice/water bath to precipitate the spent solid succinimides. The mixture was filtered and the filtrate was dried over $MgSO_4$ then concentrated to afford 8.0 g of **28** (28 mmol, 97%) as a yellow oil. ^1H NMR (300 MHz, $CDCl_3$): δ 7.68 (d, *J*=9.1 Hz, 1H, H-6), 6.66 (d, *J*=9.1 Hz, 1H, H-5), 5.35 (s, 2H, OCH_2), 4.82 (s, 2H, CH_2Br), 3.50 (s, 3H, OCH_3), 2.60 (s, 3H, $COCH_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 203.1, 162.3, 160.9, 134.3, 130.1, 114.7, 104.8, 93.6, 56.6, 26.3, 21.9; IR (neat, cm^{-1}) 2960.5, 1763.9, 1720.9, 1629.5, 1497.2, 1261.0, 1045.5, 798.1; HRMS (EI) (*m*/*z*): [(M^+)] calcd for $C_{11}H_{13}O_4Br$, 287.9997, found 287.9999.

4.19. 1-{3-[(2*E*)-4′-[(*tert*-Butyldimethylsilyl)oxy]-3′-methylbut-2′-en-1′-yl]-2-hydroxy-4-(methoxymethoxy)acetophenone (29)[16]

$Pd_2(dba)_3$ (0.635 g, 0.677 mmol) was suspended in anhydrous THF (7.00 mL, 0.10 M). The subsequent addition of $AsPh_3$ (0.265 g, 0.865 mmol), as a co-catalyst caused the mixture to turn a green color. After 15 min of stirring, benzyl bromide (**28**) (2.00 g, 6.92 mmol) was added, followed soon thereafter by a solution of the vinyl stannane (**17**) (3.97 g, 8.33 mmol) in THF (1.00 mL) via syringe. The resulting solution was brought to reflux and stirred for 20 h. The solution was washed with brine (50 mL), satd $NaHCO_3$, (50 mL), 10% aqueous KF (50 mL) and brine again (50 mL). The organic solution was passed through a Celite/charcoal pad (1:1 v/v) that was rinsed with 15% EtOAc–hexanes. The eluent was concentrated and purified by silica gel chromatography again using 15% EtOAc–hexanes to afford the Stille product (**29**) (1.41 g, 3.58 mmol, 52%) as a clear oil. ^1H NMR (300 MHz, $CDCl_3$): δ 12.75 (s, 1H, OH), 7.56 (d, *J*=8.3 Hz, 1H, H-6), 6.63 (d, *J*=9.4 Hz, 1H, H-5), 5.49 (tqt, *J*=7.3, 1.8 Hz, 1H, H-2′), 5.24 (s, 2H, OCH_2), 3.98 (s, 2H, H-4′), 3.46 (s, 3H, OCH_3), 3.42 (d, *J*=7.6 Hz, 2H, H-1′), 2.55 (s, 3H, $COCH_3$), 1.78 (s, 3H, CH_3), 0.86 (s, 9H, $SiC(CH_3)_3$), 0.01 (s, 6H, $Si(CH_3)_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.0, 162.1, 160.9, 134.7, 129.9, 122.3, 117.8, 114.9, 104.9, 93.9, 68.9, 56.2, 26.3, 25.9, 21.4, 18.4, 13.5, −5.3; IR (neat, cm^{-1}) 2955.4, 2929.3, 2855.8, 1628.5, 1256.7, 1046.1, 833.7, 774.9; HRMS (EI) (*m*/*z*): [$(M+H)^+$] calcd for $C_{21}H_{34}O_5Si$, 395.2254, found 395.2252; Anal. Calcd for $C_{21}H_{34}O_5Si$: C, 63.92; H, 8.69, found C, 63.50; H, 8.69.

4.20. (*E*)-3-(2′,4′-Bis(methoxymethoxy)phenyl)-1-(3″-((*E*)-10″-((*tert*-butyldimethylsilyl)oxy)-9″-methylbut-8″-en-7″-yl)-2″-hydroxy-4″-(methoxymethoxy)phenyl)prop-2-en-1-one (30)

Acetophenone (**29**) (4.74 g, 12.0 mmol) and aldehyde (**7**) (2.72 g, 12.0 mmol) were dissolved in EtOH (60 mL, 0.20 M). The resulting solution was treated with KOH (10.1 g, 180 mmol) at which time the solution turned a dark brown color. After 60 h, the solution was treated with 10% AcOH until the solution turned bright yellow in color. The phases were separated and the aqueous phase was extracted with DCM (3×20 mL). The pooled organics were washed with $NaHCO_3$, brine, then dried over $MgSO_4$ and concentrated. The crude product was purified by Biotage flash column chromatography twice, eluting with 5% MeOH–DCM to afford (**30**) (4.42 g, 7.33 mmol, 61%) as a yellow oil. ^1H NMR (300 MHz, $CDCl_3$): δ 13.2 (s, 1H, OH), 8.17 (d, *J*=15.8 Hz, 1H, H-3), 7.75 (d, *J*=9.4 Hz, 1H, H-6″), 7.61 (d, *J*=15.5 Hz, 1H, H-2), 7.60 (d, *J*=8.8 Hz, 1H, H-6′), 6.86 (d, *J*=2.4 Hz, 1H, H-3′), 6.75 (dd, *J*=8.6, 2.2 Hz, 1H, H-5′), 6.68 (d, *J*=9.1 Hz, 1H, H-5″) 5.52 (br t, 1H, *J*=8.1 Hz, H-8″), 5.28 (s, 2H, OCH_2), 5.27 (s, 2H, OCH_2), 5.21 (s, 2H, OCH_2), 4.00 (br s, 2H, H-10″), 3.52 (s, 3H, OCH_3), 3.50 (s, 6H, OCH_3), 3.48 (d, 2H, H-7″), 1.80 (s, 3H, H-11″), 0.87 (s, 9H, $Si(CH_3)_3$), 0.02 (s, 6H, $Si(CH_3)_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 192.8, 163.3, 160.6, 160.5, 157.9, 139.5, 134.6, 130.1, 128.8, 122.5, 119.1, 118.5, 117.9, 115.2, 109.4, 104.6, 103.3, 94.7, 94.3, 93.8, 68.9, 56.5, 56.3, 56.3, 25.9, 21.4, 18.4, 13.5, −5.3; HRMS (EI) (*m*/*z*): [$(M+H)^+$] calcd for $C_{32}H_{47}O_9Si$ 603.2989, found 603.2983; IR (neat, cm^{-1}) 2951.3, 2927.5, 2853.9, 1631.3, 1608.0, 1562.0, 1492.9, 1255.6, 1236.4, 1044.8, 995.4, 834.0; UV (MeCN) (λ_{max}, nm) 202, 210, 242,

370; Anal. Calcd for $C_{32}H_{46}O_9Si$: C, 63.76; H, 7.69, found: C, 63.67; H, 7.47.

4.21. (*E*)-3-(2′,4′-Bis(methoxymethoxy)phenyl)-1-(2″-hydroxy-3″-((*E*)-10″-hydroxy-9″-methylbut-8″-en-7″-yl)-4″-(methoxymethoxy)phenyl)prop-2-en-1-one (31)

Chalcone (**30**) (1.31 g, 2.17 mmol) was dissolved in THF (4.45 mL, 0.49 M) producing a yellow solution. The solution was treated with 1.0 M TBAF in THF (2.60 mL, 2.6 mmol) causing the solution to turn deep red in color. The solution was stirred for 18 h, then quenched with H_2O. The aqueous phase was extracted with DCM (3×10 mL). The organic fractions were pooled then washed with $NaHCO_3$, brine, then dried over $MgSO_4$ and concentrated. The crude product was purified by Biotage flash column chromatography, eluting with 50% EtOAc–Hexanes on a 50 g cartridge to afford alcohol **31** (0.85 g, 1.7 mmol, 80%) as a yellow solid. Mp=90.5–91.5 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.18 (d, J=15.8 Hz, 1H, H-3), 7.76 (d, J=9.2 Hz, 1H, H-6″), 7.60 (d, J=15.8 Hz, 1H, H-2), 7.60 (d, J=8.8 Hz, 1H, H-6′), 6.86 (d, J=2.6 Hz, 1H, H-3′), 6.75 (dd, J=8.8, 2.6 Hz, 1H, H-5′), 6.68 (d, J=9.2 Hz, 1H, H-5″) 5.54 (br t, J=6.6 Hz, 1H, H-8″), 5.28 (s, 4H, OCH_2), 5.21 (s, 2H, OCH_2), 4.00 (d, J=5.3 Hz, 2H, H-10″), 3.52 (s, 3H, OCH_3), 3.49 (s, 3H, OCH_3), 3.49 (s, 3H, OCH_3), 3.47 (d, 2H, H-7″), 1.87 (s, 3H, H-11″); ^{13}C NMR (75 MHz, $CDCl_3$): δ 192.8, 163.3, 160.5, 160.5, 157.9, 139.7, 135.0, 130.1, 128.9, 123.8, 118.9, 118.4, 117.5, 115.2, 109.4, 104.7, 103.3, 94.6, 94.2, 93.8, 69.0, 56.5, 56.3, 56.3, 21.5, 13.8; IR (neat, cm^{-1}) 3327.6, 2971.1, 2907.5, 2826.6, 1630.4, 1605.7, 1563.6, 1492.1, 1272.7, 1234.9, 1154.0, 991.7, 976.2; HRMS (EI) (m/z): [(M+H)$^+$] calcd for $C_{26}H_{33}O_9$489.2125, found 489.2113; UV ($CHCl_3$) (λ_{max}, nm) 248, 292.

4.22. (*E*)-(*E*)-1-(3-((*E*)-β-(2,4-Bis(methoxymethoxy)phenyl) acryloyl)-2′-hydroxy-4′-(methoxymethoxy)phenyl)-3′-methylbut-9′-en-8′-yl-(11′-(4″-((*tert*-butyldimethylsilyl)oxy)phenyl)) acrylate (32)

Chalcone (**31**) (0.600 g, 1.23 mmol), protected *p*-coumaric acid (**20**) (0.684 g, 2.46 mmol), and PPh_3 (0.645 g, 2.46 mmol) were stirred in THF (12.3 mL) until all the solids dissolved to give a yellow solution. This mixture was added to a solution of DIAD (0.485 mL, 0.498 g, 2.46 mmol) in THF (0.50 mL) before being allowed to stir at room temperature. After 72 h, the solution was diluted in EtOAc (5 mL) then quenched with brine. The organic layer was dried over $MgSO_4$ and concentrated. The crude product was purified by Biotage flash column chromatography, eluting with 40% EtOAc–Hexanes on a 50 g cartridge to provide ester **32** (0.61 g, 0.81 mmol, 66%) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.18 (d, J=15.4 Hz, 1H, H-β), 7.78 (d, J=9.5 Hz, 1H, H-6′), 7.62 (d, J=16.1 Hz, 1H, H-α), 7.61 (d, J=16.1 Hz, 1H, H-8″), 7.60 (d, J=8.8 Hz, 1H, H-6), 7.40 (d, J=8.1 Hz, 2H, H-2″, 6″), 6.86 (d, J=2.2 Hz, 1H, H-3), 6.83 (d, J=8.1 Hz, 2H, H-3″, 5″), 6.74 (dd, J=8.8, 2.2 Hz, 1H, H-5), 6.69 (d, J=8.8 Hz, 1H, H-5′), 6.30 (d, J=15.4 Hz, 1H, H-7″), 5.64 (br t, J=7.3 Hz, 1H, H-8′), 5.29 (s, 4H, OCH_2O), 5.21 (s, 2H, OCH_2O), 4.57 (s, 2H, H-11′), 3.52 (s, 3H, OCH_3), 3.49 (s, 3H, OCH_3), 3.48 (s, 3H, OCH_3), 3.46 (d, J=6.6 Hz, 2H, H-7′), 1.90 (s, 3H, H-10′), 0.98 (s, 9H, $SiC(CH_3)_3$) 0.21 (s, 6H, $Si(CH_3)_2$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 192.9, 167.1, 163.3, 160.7, 160.6, 158.0, 157.8, 144.4, 139.7, 130.5, 130.2, 129.6, 129.0, 127.1, 120.5, 119.2, 118, 116.0, 115.4, 109.6, 104.7, 103.5, 94.8, 94.4, 93.9, 77.2, 76.0, 70.1, 56.5, 56.3, 56.3, 25.6, 21.8, 18.2, 14.1, −4.4; IR (neat, cm^{-1}) 2955, 2930, 2857, 1709, 1630, 1601, 1563, 1509, 1258, 1080, 1004; Anal. Calcd for $C_{41}H_{52}O_{11}Si$: C, 65.75; H, 7.00, found: C, 65.56; H, 6.96; HRMS (EI) (m/z) [(M+H)$^+$] calcd for $C_{41}H_{53}O_{11}Si$ 749.3357, found, 749.3347.

4.23. (*E*)-(*E*)-1-(3-((*E*)-β-(2,4-Bis(methoxymethoxy)phenyl) acryloyl)-(2′-hydroxy-4′-(methoxymethoxy)phenyl)-3′-methylbut-9′-en-8′-yl-(11′-(4″-(*tert*-butyldimethylsilyl)oxy)-3″-methoxyphenyl)acrylate (33)

Chalcone (**31**) (0.200 g, 0.409 mmol), protected ferulic acid (**21**) (0.252 g, 0.817 mmol), and PPh_3 (0.215 g, 0.820 mmol) were dissolved in THF (5.0 mL) providing a yellow solution. The chalcone solution was then added to a DIAD (0.16 g, 0.16 mL, 0.81 mmol) solution in THF (2.0 mL). The resulting solution was allowed to stir at room temperature for 72 h, at which time the solution was diluted in EtOAc (5 mL) and quenched with brine. The organic layer was dried over $MgSO_4$ and concentrated. The crude product was purified by Biotage flash column chromatography, eluting with 40% EtOAc–Hexanes on a 50 g cartridge to provide ferulate ester **33** (0.18 g, 0.23 mmol, 56%) as an orange solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.18 (d, J=15.4 Hz, 1H, H-β), 7.77 (d, J=8.8 Hz, 1H, H-6′), 7.60 (d, J=8.8 Hz, 1H, H-6), 7.60 (d, J=15.4 Hz, 1H, H-α), 7.60 (d, J=16.1 Hz, 1H, H-7″), 7.00 (m, 2H, H-2″, H-6″), 6.86 (d, J=2.2 Hz, 1H, H-3), 6.83 (d, J=8.8 Hz, 1H, H-5″), 6.75 (dd, J=8.1, 2.2 Hz, 1H, H-5), 6.69 (d, J=8.8 Hz, 1H, H-5′), 6.30 (d, J=15.4 Hz, 1H, H-8″), 5.65 (br t, J=6.6 Hz, 1H, H-8′), 5.29 (s, 4H, OCH_2), 5.21 (s, 2H, OCH_2), 4.58 (s, 2H, H-11′), 3.83 (s, 3H, OCH_3), 3.52–3.47 (m, 11H, H-7′& 3×OCH_3), 1.90 (s, 3H, H-10′), 0.99 (s, 9H, $SiC(CH_3)_3$), 0.16 (s, 6H, $Si(CH_3)_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 192.9, 167.1, 163.3, 160.7, 160.6, 158.0, 151.2, 147.5, 144.7, 139.7, 130.4, 130.2, 129.0, 128.4, 127.2, 122.2, 121.1, 119.1, 118.6, 117.3, 116.0, 115.3, 110.9, 109.5, 104.7, 103.4, 94.8, 94.4, 93.9, 70.2, 56.5, 56.3, 56.3, 55.5, 25.7, 21.7, 18.5, 14.1, −4.6; IR (neat, cm^{-1}): 3328, 2929, 2855, 1720, 1605, 1505, 156, 1232, 995; Anal. Calcd for $C_{42}H_{54}O_{12}Si$: C, 64.76; H, 6.99, found: C, 65.22; H, 6.90; HRMS (EI) (m/z): [(M+H)$^+$] calcd for $C_{42}H_{55}O_{12}Si$ 779.3463, found, 779.3448.

4.24. Isogemichalcone B (2)

Protected isogemichalcone B (**32**) (0.17 g, 0.23 mmol) was dissolved in 1.5 mL of a 5% HCl/THF (1:1 v/v) solution. The solution was brought to reflux. After 8 h, the solution was cooled to room temperature and diluted with EtOAc. The organic fractions were washed with $NaHCO_3$, brine, then dried over $MgSO_4$ and concentrated. When the reaction was found to be incomplete, the reaction mixture was reintroduced to the same conditions for an additional 3 h, then worked up in the same manner. The crude product was purified by flash column chromatography, eluting with 100% EtOAc on a 40 g cartridge to afford (**2**) (0.06 g, 0.12 mmol, 52%) as an orange solid. Structural data was identical to that of the isolated natural product reported in the literature.[5] δ ^{1}H NMR (300 MHz, acetone-d_6): δ 8.22 (d, J=15.4 Hz, 1H, H-β), 7.92 (d, J=9.5 Hz, 1H, H-6′), 7.79 (d, J=15.4 Hz, 1H, H-α), 7.69 (d, J=8.8 Hz, 1H, H-6), 7.59 (d, J=15.4 Hz, 1H, H-7″), 7.55 (d, J=8.8 Hz, 2H, H-2″, H-6″), 6.87 (d, J=8.8 Hz, 2H, H-3″, H-5″), 6.53 (d, J=8.7 Hz, 1H, H-5′), 6.51 (d, J=2.2 Hz, 1H, H-3), 6.45 (dd, J=8.8, 2.2 Hz, 1H, H-5), 6.35 (d, J=16.1 Hz, 1H, H-8″), 5.67 (br t, J=7.0 Hz, 1H, H-9′), 4.54 (s, 2H, H-11′), 3.46 (d, J=7.1 Hz, 2H, H-7′), 1.86 (s, 3H, H-10′); ^{13}C NMR (75 MHz, $CDCl_3$) δ 193.6, 167.3, 165.2, 162.5, 162.3, 160.6, 160.0, 145.3, 141.0, 131.8, 131.2, 130.9, 130.9, 130.2, 127.7, 127.1, 117.7, 116.7, 116.7, 115.8, 115.5, 115.2, 114.9, 109.3, 108.0, 103.6, 70.2, 22.1, 14.2; HRMS (EI) (m/z): [(M+H)$^+$] calcd for $C_{29}H_{27}O_8$ 503.1706, found, 503.1707.

4.25. Isogemichalcone C (3)

Protected isogemichalcone C (**33**) (0.18 g, 0.23 mmol) was dissolved in a 1.5 mL of a 5% HCl/THF (1:1 v/v) solution. The solution was brought to reflux. After 8 h, the solution was cooled to room temperature and diluted with EtOAc. The organic layer was washed with $NaHCO_3$, brine, then dried over $MgSO_4$ and concentrated. The crude product was purified by Biotage flash column

chromatography, eluting with 100% EtOAc on a 20 g cartridge to afford (**3**) (0.11 g, 0.21 mmol, 91%) as an orange solid. ^{1}H NMR spectral data was identical to that of the isolated natural product.[4a] ^{1}H NMR (300 MHz, acetone-d_6): δ 8.21 (d, J=15.4 Hz, 1H, H-β), 7.94 (d, J=8.9 Hz, 1H, H-6′), 7.80 (d, J=15.4 Hz, 1H, H-α), 7.70 (d, J=8.5 Hz, 1H, H-6), 7.60 (d, J=16.0 Hz, 1H, H-7″), 7.35 (d, J=2.3 Hz, 1H, H-2″), 7.15 (d, J=8.7 Hz, 1H, H-6″), 6.86 (d, J=8.5 Hz, 1H, H-5″), 6.54 (d, J=15.8 Hz, 1H, H-5′), 6.52 (br s, 1H, H-3), 6.44 (d, J=8.4 Hz, 1H, H-5), 6.45 (br d, J=8.2 Hz, 1H, H-5), 6.35 (d, J=16.0 Hz, 1H, H-8″), 5.70 (br t, J=7.0 Hz, 1H, H-8′), 4.55 (s, 2H, H-11′), 3.99 (s, 3H, OCH_3), 3.48 (d, J=7.1 Hz, 2H, H-7′), 1.91 (s, 3H, H-10′); ^{13}C NMR (75 MHz, $CDCl_3$) δ 193.6, 167.3, 165.2, 162.5, 162.3, 159.9, 150.1, 148.8, 145.6, 141.0, 131.8, 131.3, 130.2, 127.8, 127.6, 124.0, 117.8, 116.1, 116.1, 115.5, 115.2, 114.7, 111.5, 109.3, 108.0, 103.8, 70.3, 56.5, 22.1, 14.2; HRMS (ESI) (m/z): [$(M+H)^+$] calcd for $C_{30}H_{29}O_9$ 533.1812, found, 503.1799.

Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2013.09.068.

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