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Chemoenzymatic Total Synthesis of a Naturally Occurring (5-5′)/(8′-*O*-4′′) Dehydrotrimer of Ferulic Acid

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The cross-linking of plant cell walls by ferulate dehydrodimerization reactions is well established. Recently, a (5-5′)/(8′-*O*-4′′) dehydrotrimer of ferulic acid (**A**) was isolated from alkali extracts of maize bran. Its structure was elucidated on the basis of an extensive structural analysis (UV, MS, 1D and 2D NMR). This first identified ferulic acid dehydrotrimer has revealed that parietal polysaccharide chains can be more extensively cross-linked than has been previously recognized. To produce the (5-5′)/(8′-*O*-4′′) dehydrotrimer (**A**) in sufficient high-purity quantities and allow the development of analytical methodologies (e.g., LC/GC, immunohistochemistry) to identify and quantify this peculiar trimer in plant extracts or samples, its first total convergent synthesis has been achieved in 10 steps and in 18 % yield starting from commercially available vanillin by horseradish peroxidase mediated enzymatic aryl–aryl coupling, aldolization/crotonization, and Wittig olefination reactions as the key steps.

Introduction

Ferulic acid (**1**) is one of the most abundant phenolic acids found in grasses. First isolated in the early 1900s, its biosynthesis is still obscure and remains under investigation. Nevertheless, some recent studies tend to prove that ferulic acid might be obtained from caffeic acid by the action of the enzyme *O*-methyl transferase.[1] Although present in seeds as the free acid and low-molecular-weight conjugates,[2] ferulic acid is found mostly as an ester-linked substituent of cell wall heteroxylans, especially in the brans. The cross-linking of plant cell walls by ferulate dehydrodimerization reactions is well established.[1–6] Ferulic acid acylates various polysaccharides, notably arabinoxylans in grasses,[3] particularly in the insoluble fiber fraction.[7,8] Ferulate dehydrodimerization is therefore a mechanism for linking two polysaccharide chains, providing structural integrity to the cell wall, but inhibiting fiber degradability.[9] As phenolic entities are involved in radical coupling reactions, ferulic acid may also be incorporated into lignin polymers as monomer or oligomer,[4,10] furthering the cross-linking of the cell wall biopolymers and thereby limiting the degradability of the polysaccharides.[11] The dehydrodimerization reaction is described as a combinatorial radical coupling reaction,[12] much like the radical coupling of monolignols in lignins.[13] A range of dehydrodiferulic acids can be found in a variety of materials,[12,14–18] as predicted and confirmed in 1994.[12] Dehydrodiferulic acids are characterized by the new bond formed in the coupling between the two ferulic acids (at their 4-*O*-, 5-, or 8-positions) as (5-5′), (8-8′), (8-5′), (8-5′ benzofuran), (8-*O*-4′), and (4-*O*-5′) dehydrodimers (Figure 1). More recently, new (5-5′)/(8′-*O*-4′′) dehydrotrimer **A** from ferulic acid was identified and isolated from maize bran extracts.[19,20]

A general issue for the development of analytical methodologies to identify ferulic acid dimers and trimers in complex mixtures resulting from biomass treatment is the availability of pure standard compounds allowing researchers to validate the methodologies used. Although efficient syntheses of ferulic acid dimers have been described,[12] none have been published for trimers. It became crucial to develop new convenient and straightforward synthetic routes to these trimers, not only to allow reliable quantification in plant extracts (e.g., LC/GC standards), but also to develop specific antibodies for their accurate localization in plant tissues using immunohistochemistry techniques. In addition, such compounds and their esters often exhibit potent biological properties and can prove themselves potential drug candidates.[21]

Herein we would like to report the first total synthesis of (5-5′)/(8′-*O*-4′′) dehydrotrimer **A** starting from commercially available vanillin (**2**) by a convergent synthetic pathway in which the aryl–aryl bond (5-5′), the two α,β-unsaturated carboxylic acids, and the internal α-phenoxy α,β-unsaturated carboxylic acid were formed by horseradish peroxidase (HRP) mediated enzymatic oxidative coupling, two

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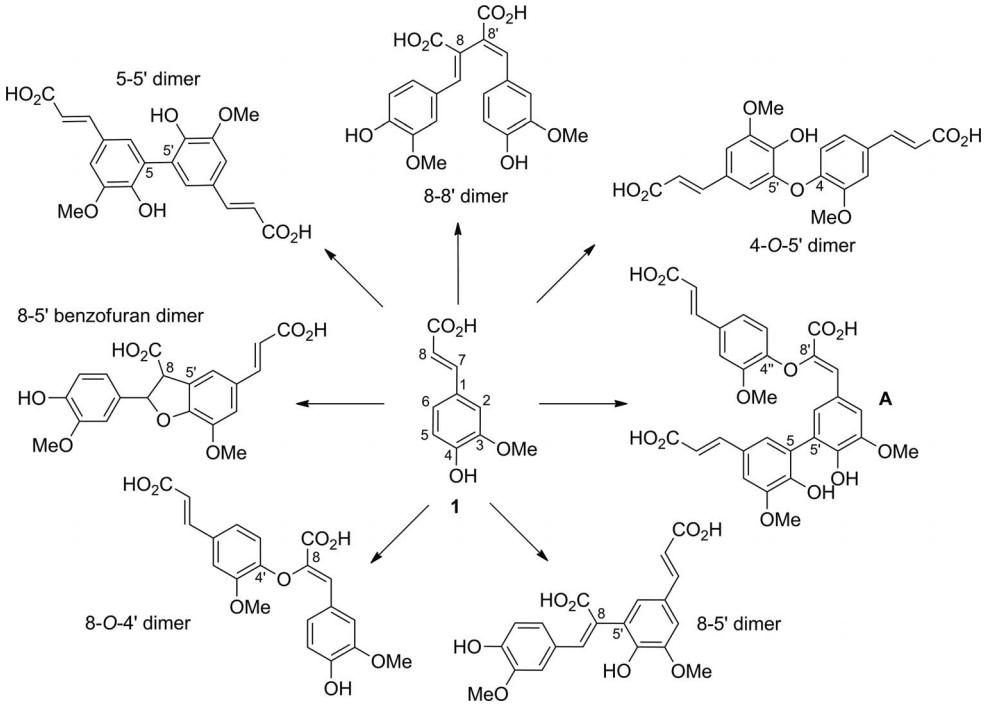
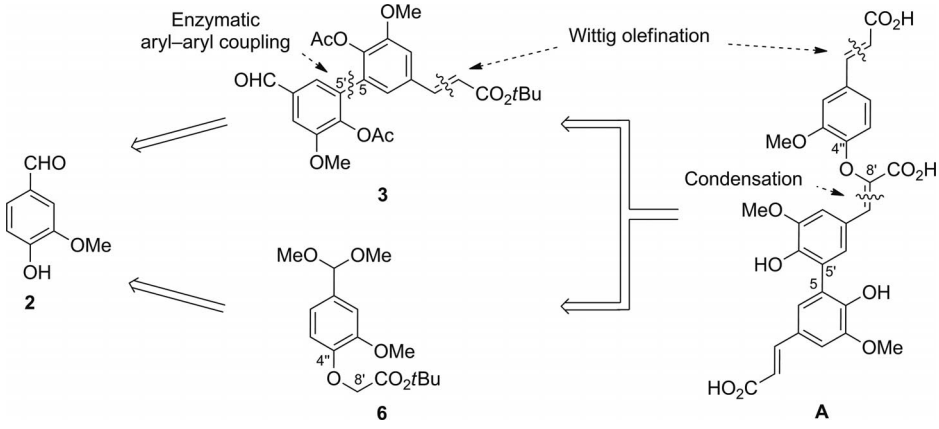


Figure 1. Naturally occuring dehydrodimers and -trimer of ferulic acid.



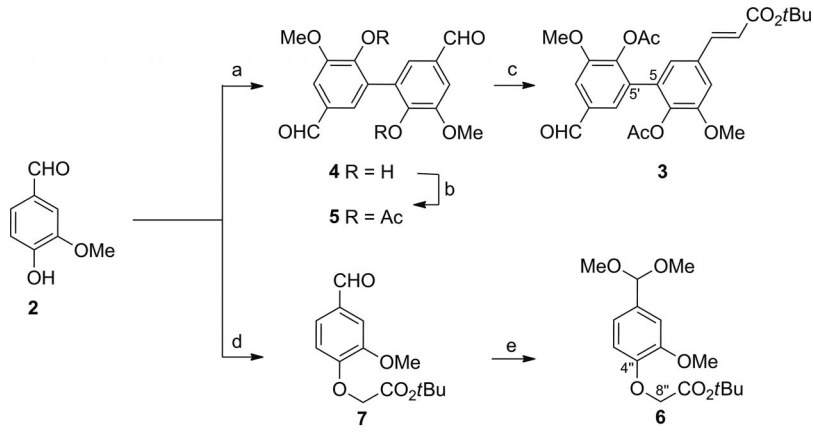
Scheme 1. Retrosynthetic strategy for the synthesis of (5-5′)/(8′-*O*-4′′) dehydrotrimer **A**.

Wittig olefination reactions, and a condensation reaction, respectively (Scheme 1).

Results and Discussion

Our efforts were first focused on the synthesis of the protected biaryl intermediate **3** featuring the 5-5′ interunit bonding pattern (Scheme 2). Oxidative C–C coupling of vanillin (**2**) in the presence of HRP and hydrogen peroxide at pH 4.2 in a buffered citrate/phosphate aqueous solution afforded bis-vanillin **4** in excellent yield (97%).[22] The free phenols were then acylated by using acetic anhydride in pyridine to give the symmetrical dialdehyde **5** in 86% yield. At this stage, a desymmetrization process had to be performed to selectively functionalize only one of the two aldehydes. This was successfully achieved through a classic Wittig olefination at 0 °C. In fact, dropwise addition of strictly 1 equiv. of (*tert*-butoxycarbonylmethylene)triphenylphosphorane ($Ph_3P{=}CHCO_2tBu$) to a diluted solution of **5** in dichloromethane provided the desired mono-α,β-unsaturated ester **3** in 60% yield (50% overall yield from **2**, three steps, *E*/*Z* ratio[23] 95:5) along with the corresponding bis-α,β-unsaturated ester **3-bis** (18%) and unreacted dialdehyde **5** (4%). The *tert*-butyl esters were chosen because of their selective, mild, and easy removal with trifluoroacetic acid (TFA) even in the presence of phenolic acetates.

The *tert*-butyl α-phenoxy acetate **6** was synthesized starting from the deprotonation of vanillin (**2**; K_2CO_3, anhydrous DMF), directly followed by the addition of *tert*-butyl bromoacetate ($BrCH_2CO_2tBu$) to provide key intermediate **7** in 95% yield. Subsequent protection of aldehyde **7** with methyl orthoformate in the presence of a catalytic amount

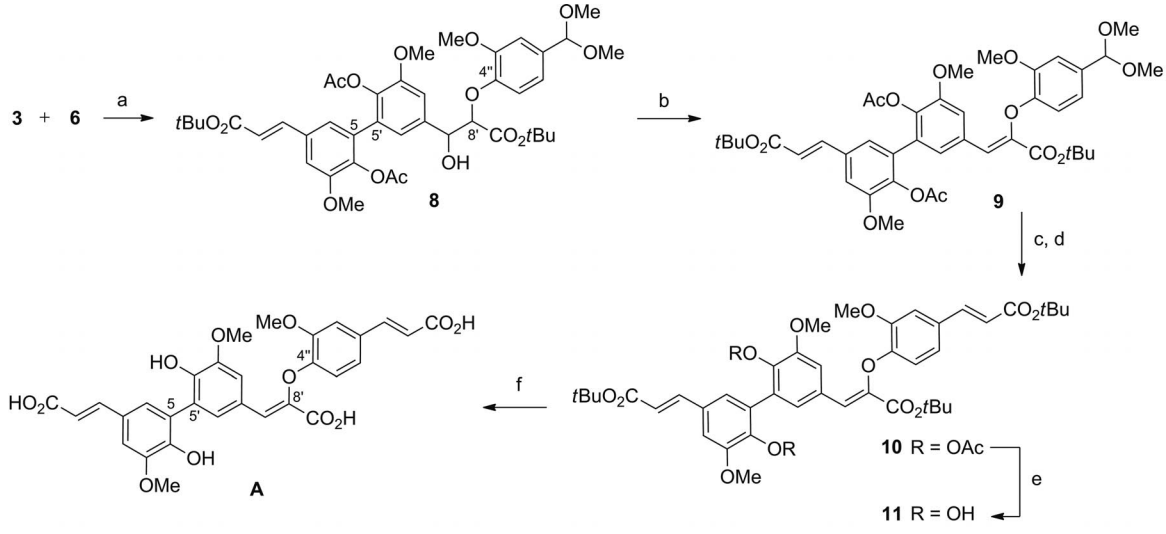


(a) HRP, H_2O_2, pH 4.2 buffer, 36 °C, 97%; (b) Ac_2O, pyridine, r.t., 86%; (c) $Ph_3P{=}CHCO_2tBu$, DCM, 0 °C, 60%; (d) $BrCH_2CO_2tBu$, K_2CO_3, DMF, r.t., 95%; (e) $HC(OMe)_3$, *p*TsOH, THF, r.t., 99%.

Scheme 2. Synthesis of protected 5-5′ biaryl moiety **3** and key intermediate **6**.

of *p*TsOH afforded dimethyl acetal **6** in 99% yield (94%, two steps; Scheme 2).[24] With both key intermediates **3** and **6** in hand, we were able to proceed to the creation of the remaining 8′-*O*-4′′ interunit bond by the formation of β-hydroxy ester **8**.

As depicted in Scheme 3, *tert*-butyl α-phenoxy acetate **6** was deprotonated with lithium diisopropylamide (LDA) in freshly distilled THF at –78 °C and the corresponding ester enolate was subsequently treated with aldehyde **3** to give aldol **8** in 80% yield as an *erythro*/*threo* mixture (3:2).[23,25,26] β-Hydroxy ester **8** was then immediately mesylated (MsCl, TEA) and transformed, through DBU-mediated dehydration, to the desired *Z*-unsaturated ester **9** (77% yield, 58% overall yield from **6**, 95:5 *Z*/*E* ratio).[27] Selective acid-mediated deprotection of the dimethyl acetal moiety by treatment of a solution of **9** in ethyl acetate with a saturated aqueous ammonium chloride solution provided the corresponding aldehyde in quantitative yield. Subsequent Wittig olefination with (*tert*-butoxycarbonylmethylene)triphenylphosphorane in 1,2-dimethoxyethane (1,2-DME)[28] at reflux afforded compound **10** in 88% yield and with a 97:3 *E*/*Z* ratio.[23] At this stage, two options were offered to achieve desired trimer **A**: Both acetates and *tert*-butyl esters could be removed simultaneously by a classic saponification reaction, or the *tert*-butyl esters or acetates could be selectively deprotected for subsequent regioselective functionalization. To demonstrate this concept, we chose a two-step deprotection process for the clean and mild sequential removal of the acetate and *tert*-butyl protecting groups. In this manner, treatment of **10** with NaOMe in MeOH provided bis-phenol **11** in 71% yield. The *tert*-butyl esters were then efficiently cleaved in the presence of TFA to afford (5-5′)/(8′-*O*-4′′) dehydrotrimer **A** in 99% yield (18% overall yield, 10 steps from vanillin). The analytical and spectro-



(a) LDA, THF, –78 °C, 80%; (b) i. MsCl, TEA, DCM, r.t., ii. DBU, THF, r.t., 77%; (c) sat. NH_4Cl aq., r.t., quantitative; (d) $Ph_3P{=}CHCO_2tBu$, 1,2-DME, reflux, 88%; (e) NaOMe, MeOH, r.t., 71%; (f) TFA, DCM, r.t., 99%.

Scheme 3. Aldolization, crotonization, and the final steps of the synthesis of (5-5′)/(8′-*O*-4′′)-dehydrotrimer **A**.

scopic data of **A** are in good agreement with those reported in the literature.[19a] Note, this sequence can also be inverted if one wants to saponify the *tert*-butyl esters first.

Conclusions

The first total convergent synthesis of the naturally occurring (5-5′)/(8′-*O*-4′′) dehydrotrimer of ferulic acid (**A**) has been successfully achieved in 10 steps and in 18% overall yield starting from commercially available vanillin by HRP-mediated enzymatic aryl–aryl coupling, aldol-like condensation/crotonization, Wittig olefination reactions, and desymmetrization as the key steps. The use of orthogonal protecting groups such as *tert*-butyl esters and acetates offers great flexibility and demonstrates the high potential of this synthetic route in terms of the scope of the targets (e.g., polyacids, polyols, polyesters) and their applications (e.g., chromatographic samples, antibodies, bioactive compounds). As part of a collaborative research project aiming at the localization and quantification of this trimer in grass tissues (e.g., wheat, maize and miscanthus) by immunohistochemistry, we are currently applying this synthesis to the production of specific antibodies. This work will be reported in due course.

Experimental Section

General: CH_2Cl_2 (stabilized with amylene) was purified by distillation from CaH_2 under N_2 immediately before use. THF and Et_2O were purified by distillation from sodium/benzoquinone under N_2. Moisture- and O_2-sensitive reactions were carried out in flame-dried glassware under Ar. Evaporations were conducted under reduced pressure at temperatures below 35 °C unless otherwise noted. Column chromatography (CC) was carried out with an automated flash chromatography PuriFlash system and pre-packed INTERCHIM PF-30SI-HP (30 μm silica gel) columns. ^{1}H NMR spectra of samples in the indicated solvent were recorded at 300 MHz at 20 °C [^{1}H NMR: $CDCl_3$ residual signal at δ = 7.26 ppm, [D_6]DMSO residual signal at δ = 2.50 ppm, and $(CD_3)_2$-CO residual signal at δ = 2.05 ppm]. ^{13}C NMR spectra of samples in the indicated solvent were recorded at 75 MHz at 20 °C [^{13}C NMR: $CDCl_3$ residual signal at δ = 77.16 ppm, [D_6]DMSO residual signal at δ = 39.5 ppm, and $(CD_3)_2CO$ residual signal at δ = 29.84 ppm]. The atomic labeling used in the assignment of NMR signals is presented in the Supporting Information. All reported yields are uncorrected and refer to purified products. Low- and high-resolution mass spectra (HRMS) were obtained by the Small Molecule Mass Spectrometry platform of IMAGIF (CNRS-Gif-sur-Yvette, France). All reagents were purchased from Sigma–Aldrich and used without further purification.

Synthesis of 6,6′-Dihydroxy-5,5′-dimethoxy-[1,1′-biphenyl]-3,3′-dicarbaldehyde (4)

HRP-Mediated Procedure:[22b] Vanillin (**2**; 5.0 g, 33 mmol) was dissolved at 36.5 °C in a minimum volume of citrate/phosphate buffer (pH 4.2, ca. 500 mL). Horseradish peroxidase (2025 units) was then poured into the clear solution and the mixture was stirred for an extra 2 min. Hydrogen peroxide (35% w/v, 2.8 mL) was then added dropwise over a 5 min period and the reaction was stirred at 36.5 °C overnight. The precipitate was filtered and washed with water and then chloroform to give the dialdehyde **4** (4.4 g, 97%).

Iron(III)-Mediated Procedure:[22c] $FeSO_4$ (0.4 g, 1.4 mmol) was added to vanillin (**2**; 10.64 g, 70 mmol) in water (700 mL) whilst stirring. After heating for 10 min at 50 °C, $Na_2S_2O_8$ (8.93 g, 37.5 mmol) was added and the reaction mixture was stirred at 50 °C for 5 d. The brown precipitate formed was removed by filtration. The solid was then dissolved in NaOH (2 M) solution. HCl (2 M) was added to precipitate dialdehyde **4**, which was isolated by filtration (10.0 g, 95%), m.p. 315–316 °C. IR (neat): $\tilde{\nu}$ = 3250, 1671 cm^{-1}. ^{1}H NMR ([D_6]DMSO, 300 MHz): δ = 9.81 (s, 2 H, 7-H, 2 CHO), 7.43 (s, 4 H, 2-H, 6-H), 3.93 (s, 6 H, 8-H, OCH_3) ppm. ^{13}C NMR ([D_6]DMSO, 75 MHz): δ = 191.0 (d, C-7, 2 CHO), 150.9 (s, C-4), 148.3 (s, C-3), 128.1 (d, C-1), 127.6 (s, C-6), 124.7 (s, C-5), 109.1 (d, C-2), 56.0 (s, C-8, O*C*H$_3$) ppm. MS (EI, 50 eV): *m*/*z* (%) = 301 (100) [M – H]$^+$, 151 (5). HRMS (EI): calcd. for $C_{16}H_{13}O_6$ [M – H]$^+$ 301.0712; found 301.0716.

5,5′-Diformyl-3,3′-dimethoxy-[1,1′-biphenyl]-2,2′-diyl Diacetate (5): A solution of **4** (2.00 g, 6.62 mmol) in acetic anhydride (4.73 g, 4.38 mL, 46.31 mmol) and pyridine (2 mL) was stirred at room temperature for 6 h. The mixture was then poured into an ice/water mixture (30 mL), which was stirred for 1 h. The solid was then filtered and dried to provide pure **5** (2.2 g, 86%), m.p. 125–130 °C. IR (neat): $\tilde{\nu}$ = 1770, 1695, 1196 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.98 (s, 2 H, 7-H, 2 CHO), 7.63 (s, 2 H, 6-H), 7.46 (s, 2 H, 2-H), 3.94 (s, 6 H, 8-H, 2 OCH_3), 2.05 (s, 6 H, 10-H, 2 Ac) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 190.7 (d, C-7, CHO), 167.8 (s, C-9), 152.5 (s, C-3), 142.9 (s, C-4), 134.8 (s, C-1), 131.4 (s, C-5), 126.5 (d, C-6), 110.5 (d, C-2), 56.4 (q, C-8), 20.4 (q, C-10) ppm. MS (EI$^+$, 50 eV): *m*/*z* (%) = 404 (100) [M + NH_4]$^+$, 401 (62), 387 (42), 359 (16), 345 (5), 295 (9). HRMS (EI): calcd. for $C_{20}H_{19}O_8$ [M + H]$^+$ 301.1080; found 387.1085.

(*E*)-5-[3-(*tert*-Butoxy)-3-oxoprop-1-en-1-yl]-5′-formyl-3,3′-dimethoxy-[1,1′-biphenyl]-2,2′-diyl Diacetate (3): A solution of (*tert*-butoxycarbonylmethylene)triphenylphosphorane (487 mg, 1.29 mmol) in DCM (26 mL) was added dropwise to a solution of **5** (500 mg, 1.29 mmol) in freshly distilled DCM (26 mL) at 0 °C over a 1 h period through a syringe pump. The mixture was quenched with H_2O (30 mL) and the aqueous layer was extracted with AcOEt (3 × 30 mL). The combined organic extracts were dried with anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The crude product was then purified by flash chromatography (cyclohexane/AcOEt, 8:2) to give pure compound **3** (95:5 *E*/*Z* ratio) as a white solid (376 mg, 60%). The pure corresponding diester **3-bis** was also recovered in 18% yield. ***Important note:*** To scale up the reaction to "$n \times 1.29$" mmol of **5**, one must add the phosphorane solution over a period of "n" hours.

Major Product 3: M.p. 87–89 °C. IR (neat): $\tilde{\nu}$ = 1769, 1698, 1189 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.94 (s, 1 H, 7′-H, CHO), 7.54 (d, *J* = 15.9 Hz, 1 H, 8-H), 7.53 (s, 1 H, 6′-H), 7.38 (s, 1 H, 6-H), 7.14 (s, 1 H, 2′-H), 7.02 (s, 1 H, 2-H), 6.32 (d, *J* = 15.9 Hz, 1 H, 7-H), 3.93 (s, 3 H, 10-H or 10′-H), 3.89 (s, 3 H, 10′-H or 10-H), 2.13 (s, 3 H, 12-H or 12′-H), 2.10 (s, 3 H, 12′-H or 12-H), 1.53 (s, 9 H, 14-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 190.7 (d, C-7′, CHO), 168.1 (s, C-11 or C-11′), 167.7 (s, C-11′ or C-11), 165.8 (s, C-9), 152.3 (s, C-3′), 151.7 (s, C-3), 142.3 (s, C-4, C-4′), 134.6 (s, C-1′), 133.2 (s, C-5′), 131.9 (s, C-5), 130.9 (s, C-1), 126.6 (d, C-7), 122.6 (d, C-6, C-6′), 121.0 (d, C-8), 110.9 (d, C-2 or C-2′), 110.0 (d, C-2′ or C-2), 80.6 [s, C-13, *C*(CH$_3$)$_3$], 56.3 (q, C-10 or C-10′, OCH_3), 56.1 (q, C-10′ or C-10, OCH_3), 28.1 [q, C-14, C(*C*H$_3$)], 20.3 (q, C-12, C-12′) ppm. MS (EI$^+$, 50 eV): *m*/*z* (%) = 507 (40) [M + Na]$^+$, 502 (100) [M + NH_4]$^+$, 499 (2), 249 (7).

HRMS (EI): calcd. for $C_{26}H_{28}O_9Na$ [M + Na]$^+$ 507.1631; found 507.1646.

Minor Product 3-bis: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.56 (d, J = 15.6 Hz, 1 H, 8-H), 7.14 (s, 1 H, 6-H), 7.03 (s, 1 H, 2-H), 6.35 (d, J = 15.9 Hz, 1 H, 7-H), 3.91 (s, 6 H, 10-H), 2.13 (s, 6 H, 12-H), 1.55 (s, 18 H, 14-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 168.3 (s, C-11), 166.1 (s, C-9), 151.7 (s, C-3), 142.6 (s, C-4), 139.1 (s, C-1), 133.1 (s, C-5), 131.5 (s, C-7), 122.9 (d, C-6), 120.9 (d, C-8), 110.7 (d, C-2), 80.7 [s, C-13, $C(CH_3)_3$], 56.2 (q, C-10, OCH_3), 28.3 [q, C-14, C(CH_3)], 20.3 (q, C-12) ppm.

***tert*-Butyl 2-(4-Formyl-2-methoxyphenoxy)acetate (7):** Anhydrous K_2CO_3 (13.6 g, 98.4 mmol) was added to a solution of vanillin (**2**; 10.0 g, 65.6 mmol) in anhydrous DMF (133 mL) and the mixture was stirred at room temperature for 30 min. The mixture was then cooled to 0 °C and *tert*-butyl bromoacetate (14.5 mL, 98.4 mmol) was added dropwise. The ice bath was then removed and the reaction was stirred at room temperature overnight. The mixture was then quenched with H_2O (200 mL) and the aqueous layer extracted with AcOEt (3 × 200 mL). The combined organic extracts were dried with anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The crude product was dissolved in a minimum volume of dichloromethane, reprecipitated in hexanes, and then filtered to give pure compound **7** as a white solid (16.6 g, 95%), m.p. 95–96 °C. IR (neat): $\tilde{\nu}$ = 1743, 1667, 1155 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.65 (s, 1 H, 7-H, CHO), 7.23 (br. s, 2 H, 2-H, 6-H), 6.69 (d, J = 8.4 Hz, 1 H, 5-H), 4.51 (s, 2 H, 9-H), 3.73 (s, 3 H, 8-H), 1.29 [s, 9 H, 12-H, C(CH_3)$_3$] ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 190.9 (d, C-7, CHO), 167.1 (s, C-10, CO_2tBu), 152.8 (s, C-4), 150.0 (s, C-3), 131.0 (s, C-1), 126.2 (d, C-6), 112.2 (d, C-2), 110.0 (d, C-5), 83.0 [s, C-11, $C(CH_3)_3$], 66.2 (t, C-9), 56.2 (q, C-8), 28.1 [q, C-12, C(CH_3)$_3$] ppm. MS (EI$^+$, 50 eV): m/z (%) = 330 (40) [M + Na + CH_3CN]$^+$, 308 (14), 289 (23), 284 (34) [M + NH_4]$^+$, 267 (20), 252 (12), 211 (10). HRMS (EI): calcd. for $C_{14}H_{19}O_5$ [M + H]$^+$ 267.1232; found 267.1241.

***tert*-Butyl 2-[4-(Dimethoxymethyl)-2-methoxyphenoxy]acetate (6):** Trimethyl orthoformate (13.8 mL, 126 mmol) and *p*-toluenesulfonic acid (36 mg, 0.21 mmol) were added to a solution of **7** (3.0 g, 12.6 mmol) in anhydrous methanol (25 mL) at room temperature. The mixture was stirred at room temperature for 30 min, quenched with solid $NaHCO_3$ (100 mg), filtered, and the solid was washed with AcOEt (50 mL). The combined organic extracts were washed with brine, dried with anhydrous $MgSO_4$, filtered, and concentrated in vacuo to give pure compound **6** as an oil (3.55 g, 99%). IR (neat): $\tilde{\nu}$ = 1754, 1259 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.83 (s, 1 H, 2-H), 6.76 (d, J = 8.1 Hz, 1 H, 6-H), 6.59 (d, J = 8.1 Hz, 1 H, 5-H), 5.15 (s, 1 H, 7-H), 4.41 (s, 2 H, 10-H), 3.72 (s, 3 H, 8-H), 3.14 (s, 6 H, 9-H), 1.29 [s, 9 H, 13-H, C(CH_3)$_3$] ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 168.0 (s, C-11, CO_2tBu), 149.5 (s, C-3), 147.6 (s, C-4), 132.2 (s, C-1), 119.1 (d, C-6), 113.4 (d, C-2), 110.5 (d, C-5), 103.1 (d, C-7), 82.2 [s, C-12, $C(CH_3)_3$], 66.7 (t, C-10), 56.0 (q, C-8), 52.7 (q, C-9), 28.1 [q, C-13, C(CH_3)$_3$] ppm. MS (EI$^+$, 50 eV): m/z (%) = 335 (49) [M + Na]$^+$, 308 (17), 281 (100), 267 (29), 225 (16), 211 (9). HRMS (EI): calcd. for $C_{16}H_{24}O_6Na$ [M + Na]$^+$ 335.1471; found 335.1473.

(*E*)-5-{3-(*tert*-Butoxy)-2-[4-(dimethoxymethyl)-2-methoxyphenoxy]-1-hydroxy-3-oxopropyl}-5′-[3-(*tert*-butoxy)-3-oxoprop-1-en-1-yl]-3,3′-dimethoxy-[1,1′-biphenyl]-2,2′-diyl Diacetate (8): LDA preparation: A solution of *n*-butyllithium (2 mL, c = 1.6 M in hexanes, 3.20 mmol) was added dropwise to a solution of redistilled diisopropylamine (0.45 mL, 3.20 mmol) in anhydrous THF (3.60 mL) at 0 °C over a 15 min period through a syringe pump. Once the reaction mixture had turned yellow, the temperature was gradually cooled to –78 °C.

A solution of **6** (1.03 g, 2.13 mmol) in anhydrous THF (5.7 mL) was added dropwise to a solution of LDA (3.19 mmol) prepared in situ at –78 °C over a 20 min period through a syringe pump. The mixture was stirred for 1 h at this temperature and a solution of **3** (664 mg, 2.13 mmol) in anhydrous THF (5.7 mL) was then added dropwise over a 20 min period through a syringe pump. The mixture was stirred for 2 h at –78 °C, quenched with H_2O (10 mL), and then the aqueous layer was extracted with AcOEt (3 × 10 mL). The combined organic extracts were dried with anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The crude product was then purified by flash chromatography. Starting with 8:2 cyclohexane/AcOEt as eluent, unreacted **3** and **6** were obtained, and then changing the eluent to 5:5 cyclohexane/AcOEt afforded compound **8** (3:2 *erythro*/*threo* mixture) as a white solid (1.35 g, 80%), m.p. 85–90 °C. IR (neat): $\tilde{\nu}$ = 1767, 1706, 1591, 1270, 1193 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.50 (d, J = 16.2 Hz, 1 H, 7-H), 7.26 (s, 1 H, 6-H), 7.10 (m, 1 H, 6′-H), 7.03–6.86 (m, 5 H, 2-H, 2′-H, 2′′-H, 5′′-H, 6′′-H), 6.30 (d, J = 15.9 Hz, 1 H, 8-H), 5.32 (s, 1 H, 7′′-H), 5.18 (m, 0.6 H, 7′-H), 5.05 (d, J = 6.0 Hz, 0.4 H, 7′-H), 4.68 (d, J = 3.9 Hz, 0.6 H, 8′-H), 4.43 (d, J = 6.6 Hz, 0.4 H, 8′-H), 3.87 (s, 9 H, 10-H, 10′-H, 10′′-H), 3.31 (s, 6 H, 8′′-H), 2.08 (s, 6 H, 12-H, 12′-H), 1.53 (s, 9 H, 14-H or 14′-H), 1.31 (s, 9 H, 14′-H or 14-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 168.5 (s, C-11 or C-11′), 168.3 (s, C-11′ or C-11), 168.0 (s, C-9′), 166.1 (s, C-9), 151.8 (s, C-3 or C-3′), 151.4 (s, C-3′ or C-3), 151.3 (s, C-3 or C-3′), 150.6 (s, C-4′′), 150.4 (s, C-4′′), 147.4 (s, C-3′′), 147.2 (s, C-3′′), 142.8 (s, C-7), 139.3 (s, C-4 or C-4′), 137.6 (s, C-5 or C-5′), 136.9 (s, C-4′ or C-4), 134.0 (s, C-1 or C-1′), 133.9 (s, C-1 or C-1′), 132.9 (C-5 or C-5′), 132.1 (s, C-1′ or C-1), 131.9 (s, C-1′ or C-1), 130.9 (s, C-1′′), 130.6 (s, C-1′′), 123.3 (d, C-7), 123.2 (d, C-7), 121.6 (d, C-6 or C-6′), 121.2 (d, C-6′ or C-6), 120.8 (d, C-6′′), 119.5 (d, C-2′′), 117.9 (d, C-8), 117.6 (d, C-8), 111.6 (s, C-5′′), 111.2 (s, C-5′′), 110.8 (d, C-2 or C-2′), 110.7 (d, C-2 or C-2′), 110.5 (d, C-2′ or C-2), 103.1 (d, C-7′′), 103.0 (d, C-7′′), 85.1 (d, C-8′), 83.4 (d, C-8′), 82.7 (s, C-13 or C-13′), 80.7 (C-13′ or C-13), 74.9 (d, C-7′), 73.7 (d, C-7′), 56.2 (q, C-10, C-10′), 56.0 (q, C-10′′), 52.8 (q, C-8′′), 28.3 (q, C-14, C-14′), 27.9 (q, C-14, C-14′), 20.5 (q, C-12, C-12′) ppm. MS (EI$^+$, 50 eV): m/z (%) = 819 (100) [M + Na]$^+$, 814 (93), 765 (15). HRMS (EI): calcd. for $C_{42}H_{52}O_{15}Na$ [M + Na]$^+$ 819.3204; found 819.3218.

5-{(*Z*)-3-(*tert*-Butoxy)-2-[4-(dimethoxymethyl)-2-methoxyphenoxy]-3-oxoprop-1-en-1-yl}-5′-[(*E*)-3-(*tert*-butoxy)-3-oxoprop-1-en-1-yl]-3,3′-dimethoxy-[1,1′-biphenyl]-2,2′-diyl Diacetate (9): NEt_3 (0.11 mL, 0.76 mmol) and methanesulfonyl chloride (0.06 mL, 0.82 mmol) was added to a solution of **8** (500 mg, 0.63 mmol) in anhydrous DCM (1.89 mL) at 0 °C. The mixture was stirred overnight, quenched with a satd. aq. $NaHCO_3$ solution (10 mL), and the aqueous layer extracted with DCM (3 × 10 mL). The combined organic extracts were dried with anhydrous $MgSO_4$ filtered, and concentrated in vacuo.

The crude mesylate was dissolved in anhydrous THF (1.26 mL) at room temperature and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU; 0.29 mL, 1.89 mmol) was then added. The mixture was stirred until TLC indicated complete consumption of the starting material. The reaction was then quenched with H_2O (10 mL) and the aqueous layer extracted with DCM (3 × 10 mL). The combined organic extracts were dried with anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The crude product was then purified by flash chromatography (cyclohexane/AcOEt, 75:25) to give pure compound **9** (95:5 *E*/*Z* ratio) as a white solid (750 mg, 77%), m.p. 99–

102 °C. IR (neat): ṽ = 1768, 1709, 1640, 1589, 1269, 1192 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.64 (s, 1 H, 6-H), 7.50 (d, J = 16.2 Hz, 1 H, 7-H), 7.17 (s, 1 H, 2′-H), 7.08–6.97 (m, 4 H, 2-H, 2′′-H, 6′-H, 7′-H), 6.90 (d, J = 8.1 Hz, 1 H, 6′′-H), 6.76 (d, J = 7.8 Hz, 1 H, 5′′-H), 6.30 (d, J = 15.9 Hz, 1 H, 8-H), 5.34 (s, 1 H, 7′′-H), 3.91 (s, 3 H, 10-H or 10′-H), 3.87 (s, 3 H, 10′-H or 10-H), 3.71 (s, 3 H, 10′′-H), 3.31 (s, 6 H, 8′′-H), 2.06 (s, 6 H, 12-H, 12′-H), 1.53 (s, 9 H, 14-H or 14′-H), 1.36 (s, 9 H, 14′-H or 14-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 168.4 (s, C-11 or C-11′), 168.3 (s, C-11′ or C-11), 166.1 (s, C-9), 162.3 (s, C-9′), 151.8 (s, C-3 or C-3′), 151.4 (s, C-3′ or C-3), 149.1 (s, C-4′′), 146.1 (s, C-3′′), 142.7 (d, C-7), 142.0 (s, C-4 or C-4′), 139.3 (s, C-4′ or C-4), 138.5 (s, C-8′), 133.2 (s, C-5 or C-5′), 133.1 (s, C-5′ or C-5), 131.8 (s, C-1 or C-1′), 131.3 (s, C-1′′), 131.0 (s, C-1′ or C-1), 125.5 (d, C-7′), 124.5 (d, C-6 or C-6′), 123.1 (d, C-6′ or C-6), 120.9 (d, C-6′′), 119.3 (d, C-2′′), 114.3 (d, C-8), 113.2 (d, C-5′′), 110.9 (d, C-2 or C-2′), 110.7 (d, C-2′ or C-2), 103.0 (d, C-7′′), 82.3 (s, C-13′), 80.7 (s, C-13), 56.3 (q, C-10, C-10′), 56.0 (q, C-10′′), 52.8 (q, C-8′′), 28.2 (q, C-14′, C-14), 20.5 (q, C-12, C-12′) ppm. MS (EI$^+$, 50 eV): m/z (%) = 801 (100) [M + Na]$^+$, 796 (93), 747 (88), 733 (32), 677 (10), 517 (29). HRMS (EI): calcd. for $C_{42}H_{50}O_{14}Na$ [M + Na]$^+$ 801.3098; found 801.3126.

5-[(*Z*)-3-(*tert*-Butoxy)-2-{4-[(*E*)-3-(*tert*-butoxy)-3-oxoprop-1-en-1-yl]-2-methoxyphenoxy}-3-oxoprop-1-en-1-yl]-5′-[(*E*)-3-(*tert*-butoxy)-3-oxoprop-1-en-1-yl]-3,3′-dimethoxy-[1,1′-biphenyl]-2,2′-diyl Diacetate (10): A satd. aq. NH_4Cl solution (50 mL) was added to a solution of **9** (400 mg, 0.51 mmol) in AcOEt (15 mL) at room temperature. The mixture was then stirred over a 2 h period. The aqueous layer was then extracted with AcOEt (3 × 50 mL) and the combined organic extracts were dried with anhydrous $MgSO_4$, filtered, and concentrated in vacuo to give the corresponding aldehyde, which was used without further purification.

A solution of (*tert*-butoxycarbonylmethylene)triphenylphosphorane (308 mg, 0.82 mmol) in 1,2-dimethoxyethane (5.3 mL) was added to a solution of the crude aldehyde in anhydrous 1,2-dimethoxyethane (5.3 mL) at room temperature and the mixture was heated at reflux for 3 h.[28] Water (30 mL) was then added and the solution was extracted with AcOEt (3 × 30 mL). The combined organic extracts were dried with anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The crude product was then purified by flash chromatography (cyclohexane/AcOEt, 8:2) to give pure compound **10** as a white solid (400 mg, 88%), m.p. 143–147 °C. IR (neat): ṽ = 1769, 1706, 1636, 1589, 1259, 1193 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.58–7.48 (m, 3 H, 7-H, 7′′-H, 6-H), 7.25–6.82 (m, 7 H, 2-H, 2′-H, 2′′-H, 5′′-H, 6-H, 6′-H, 6′′-H), 6.31 (d, J = 15.3 Hz, 1 H, 8-H or 8′′-H), 6.29 (d, J = 15.3 Hz, 1 H, 8′′-H or 8-H), 3.91 (s, 3 H, 10-H or 10′-H), 3.87 (s, 3 H, 10′-H or 10-H), 3.72 (s, 3 H, 10′′-H), 2.05 (s, 6 H, 12-H, 12′-H), 1.52 (s, 18 H, 14-H, 14′′-H), 1.36 (s, 9 H, 14′-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 168.3 (s, C-11, C-11′), 166.5 (s, C-9′′), 166.1 (s, C-9), 162.1 (s, C-9′), 151.8 (s, C-3 or C-3′), 151.5 (s, C-3 or C-3′), 149.4 (s, C-4′′), 147.5 (s, C-3′′), 143.2 (d, C-7′′), 142.7 (d, C-7), 141.6 (s, C-4 or C-4′), 139.3 (s, C-4′ or C-4), 138.7 (s, C-8′), 133.1 (s, C-5 or C-5′), 131.7 (s, C-5′ or C-5), 131.2 (s, C-1 or C-1′), 131.0 (s, C-1′ or C-1), 130.0 (s, C-1′′), 125.6 (d, C-7′), 124.5 (d, C-6 or C-6′), 123.1 (s, C-6′ or C-6), 121.9 (s, C-8′′), 120.9 (s, C-6′′), 119.1 (d, C-2′′), 114.9 (d, C-8), 113.2 (s, C-5′′), 111.3 (s, C-2 or C-2′), 110.7 (s, C-2′ or C-2), 82.5 (s, C-13′), 80.8 (s, C-13 or C-13′′), 80.5 (s, C-13′′ or C-13), 56.2 (q, C-10, C-10′ or C-10′′), 55.9 (q, C-10, C-10′ or C-10′′), 28.3 (q, C-14, C-14′ or C-14′′), 28.0 (q, C-14, C-14′ or C-14′′), 20.5 (q, C-12, C-12′) ppm. MS (EI$^+$, 50 eV): m/z (%) = 853 (93) [M + Na]$^+$, 848 (100) [M + NH_4]$^+$, 831 (56), 775 (16), 719 (13), 663 (13). HRMS (EI): calcd. for $C_{46}H_{55}O_{14}$ [M + H]$^+$ 831.3592; found 831.3558.

***tert*-Butyl (*Z*)-3-{5′-[(*E*)-3-(*tert*-Butoxy)-3-oxoprop-1-en-1-yl]-2′,6-dihydroxy-3′,5-dimethoxy-(1,1′-biphenyl)-3-yl}-2-{4-[(*E*)-3-(*tert*-butoxy)-3-oxoprop-1-en-1-yl]-2-methoxyphenoxy}acrylate (11):** Sodium methoxide (60 mg, 0.98 mmol) was added to a solution of **10** (500 mg, 0.60 mmol) in anhydrous methanol (3.5 mL) at room temperature. The mixture was stirred overnight, treated with Amberlyst IR 120, filtered, and concentrated in vacuo. The crude product was then purified by flash chromatography (cyclohexane/AcOEt, 6:4) to give pure compound **11** as a white solid (333 mg, 71%), m.p. 125–127 °C. IR (neat): ṽ = 1702, 1634, 1596, 1257 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.54–7.49 (m, 3 H, 7-H, 7′′-H, 6′-H), 7.19 (s, 1 H, 6-H), 7.11–6.61 (m, 5 H, 2-H, 2′-H, 2′′-H, 6′′-H, 7′-H), 6.27–6.18 (m, 3 H, 8-H, 8′′-H, 5′′-H), 3.94 (s, 6 H, 10-H, 10′-H), 3.80 (s, 3 H, 10′′-H), 1.52 (s, 18 H, 12-H, 12′′-H), 1.36 (s, 9 H, 12′-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.6 (s, C-9 or C-9′′), 166.5 (s, C-9′′ or C-9), 162.5 (s, C-9′), 149.3 (s, C-4′′), 147.9 (s, C-3′ or C-3), 147.4 (s, C-3′′), 147.1 (s, C-3′ or C-3), 145.0 (s, C-4 or C-4′), 144.5 (s, C-4′ or C-4), 143.6 (d, C-7′′), 143.3 (d, C-7), 139.6 (s, C-8′), 129.7 (s, C-1 or C-1′), 127.3 (d, C-1′ or C-1), 127.1 (s, C-1′′), 126.4 (d, C-7′), 125.0 (s, C-6 or C-6′), 124.9 (d, C-6′ or C-6), 124.0 (s, C-5 or C-5′), 123.5 (s, C-5 or C-5′), 122.0 (d, C-8′′), 118.9 (d, C-6′′), 118.3 (d, C-2′′), 114.5 (d, C-8), 111.5 (d, C-5′′), 111.2 (d, C-2 or C-2′′), 108.9 (d, C-2′ or C-2), 82.1 (s, C-11′), 80.5 (s, C-11 or C-11′′), 80.4 (s, C-11 or C-11′′), 56.4 (q, C-10, C-10′ or C-10′′), 56.3 (q, C-10, C-10′ or C-10′′), 56.0 (q, C-10, C-10′ or C-10′′), 28.4 (q, C-12, C-12′ or C-12′′), 28.0 (q, C-12, C-12′ or C-12′′) ppm. MS (EI$^+$, 50 eV): m/z (%) = 769 (100) [M + Na]$^+$, 747 (77) [M – H]$^+$, 691 (23), 635 (12), 579 (24). HRMS (EI): calcd. for $C_{42}H_{51}O_{12}$ [M + H]$^+$ 747.3381; found 747.3389.

(*Z*)-3-{5′-[(*E*)-2-Carboxyvinyl]-2′,6-dihydroxy-3′,5-dimethoxy-(1,1′-biphenyl)-3-yl}-2-{4-[(*E*)-2-carboxyvinyl]-2-methoxyphenoxy}acrylic Acid (A): Trifluoroacetic acid (0.51 mL, 6.72 mmol) was added to a solution of **11** (251 mg, 0.34 mmol) in anhydrous DCM (3.40 mL) at room temperature. The mixture was stirred overnight, concentrated in vacuo, redissolved in toluene (5 mL), and concentrated in vacuo (azeotropic removal of TFA) to give pure compound **A** as a white solid (195 mg, 99%). The analytical and spectroscopic data of synthetic **A** are in good agreement with those reported in the literature,[19a] m.p. 215–220 °C. IR (neat): ṽ = 2996, 2836, 1694, 1629, 1596 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.08 (m, 2 H, OH), 7.62 (d, J = 15.9 Hz, 1 H, 7′′-H), 7.62–7.57 (m, 2 H, 7-H, 2′-H), 7.49 (s, 1 H, 7′-H), 7.44 (s, 1 H, 2′′-H), 7.35 (s, 2 H, 2-H, 6′-H), 7.14 (d, J = 7.8 Hz, 1 H, 6′′-H), 7.10 (s, 1 H, 6-H), 6.85 (d, J = 8.1 Hz, 1 H, 5′′-H), 6.44 (d, J = 15.6 Hz, 1 H, 8′′-H), 6.41 (d, J = 15.6 Hz, 1 H, 8-H), 3.96 (s, 3 H, 10-H, 10′-H or 10′′-H), 3.90 (s, 3 H, 10-H, 10′-H or 10′′-H), 3.79 (s, 3 H, 10-H, 10′-H or 10′′-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 168.3 (s, C-9), 168.1 (s, C-9′), 164.6 (s, C-9′′), 150.3 (s, C-4′′), 149.0 (d, C-3′), 148.6 (s, C-3′′), 147.5 (s, C-7), 147.1 (s, C-3), 146.1 (s, C-4 and C-4′), 145.4 (d, C-7′′), 138.6 (s, C-8′), 130.1 (s, C-1′′), 128.7 (d, C-6 or C-6′), 128.4 (d, C-6′ or C-6), 126.7 (s, C-1′), 126.1 (d, C-7′), 125.8 (s, C-5 or C-5′), 125.7 (s, C-5′ or C-5), 124.7 (s, C-1), 123.0 (d, C-6′′), 117.6 (d, C-8′′), 116.3 (d, C-8), 113.8 (d, C-5′′), 112.7 (d, C-2′), 112.5 (d, 2′′), 110.1 (d, C-2), 56.6 (q, C-10, C-10′ or C-10′′), 56.4 (q, C-10, C-10′ or C-10′′), 56.3 (q, C-10, C-10′ or C-10′′) ppm. MS (EI, 50 eV): m/z (%) = 577 (100) [M + Na]$^+$, 288 (33). HRMS (EI): calcd. for $C_{30}H_{25}O_{12}$ [M + H]$^+$ 577.1346; found 577.1350.

Supporting Information (see footnote on the first page of this article): ^{1}H and ^{13}C NMR spectra and the numbering of the carbon atoms in each compound for NMR assignments.

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