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Solid-Phase Reactive Chromatography (SPRC): A New Methodology for Wittig and Horner–Emmons Reactions on a Column under Microwave Irradiation

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A new methodology named solid-phase reactive chromatography (SPRC), which combines reaction, separation, and purification into a single unit for the preparation of small samples, is described. This method was illustrated in the synthesis of some natural bioactive compounds, namely, methoxylated analogues of resveratrol, alkylresorcinols, and 5-aryl-2,4-pentadienoates, over a column of alumina-KF under microwave irradiation by using the Wittig and Horner–Emmons reactions. This approach permitted the preparation of the target olefins with high purity and good to excellent yields in short reaction times.

Introduction

The importance of chemical reactions using solid supports in organic synthesis has increased considerably, partly because the solid support provides an easy and simultaneous method to separate reaction products and also because an excess amount of the solid phase can lead to total consumption of starting materials. Recently, many catalyzed reactions performed in columns have been described;[1–4] such reactions include: (1) esterification reactions catalyzed by acidic ion-exchange resins[5] or by immobilized enzymes;[6] (2) etherification;[7] (3) (de)hydrogenation;[8–11] (4) ring-closing metathesis,[11] and (5) reactions involving sugars.[12] Typical examples for the adsorbents used are: zeolites, activated carbon, alumina, immobilized enzymes, ion-exchange resins,[13] immobilized palladium,[9,11] and immobilized gold.[14]

We describe herein a new synthetic methodology named solid-phase reactive chromatography (SPRC) that combines both the reaction and separation into a single unit. In this method, the substrates are adsorbed onto a reactive stationary phase that is already packed in a column. When the reaction reaches completion, the products can be eluted by using the appropriate solvent and passed over a second stationary phase (silica) located below the first, allowing the direct and simultaneous purification of the reaction products.

By this technique it is possible to prepare small samples of products by a series of reactions conducted in parallel with solid-phase extraction (SPE) equipment. This method provides flexible operating conditions and avoids long liquid–liquid extraction procedures. It is advantageous in the parallel synthesis of small samples of related structures for screening biologically active molecules or molecules having defined physical properties.

Results and Discussion

The feasibility of SPRC for the synthesis of some natural bioactive compounds, including (*E*)-stilbenes,[15] alkylresorcinols,[16] and 5-aryl-2,4-pentadienoates,[17] using the Wittig and Horner–Emmons reactions was investigated. The reactions were performed with use of the commercially available polypropylene SPE column (Varian Bond Elut, 6 mL). The column was packed with a strong base (alumina-KF), which served as the reactive stationary phase to permit the formation of the ylide or carbanion in the Wittig and Horner–Emmons reactions. The reactants were introduced into the column either without any solvent or with very small volumes of solvent (0.2 mL). A layer of silica under the reactive stationary phase allowed the purification of the formed olefin (Figure 1). The polar side-products of the Horner reaction (potassium phosphate) and the Wittig reaction (triphenylphosphane oxide) were retained on the column. The progress of the reaction was monitored by TLC. The automation of this method in parallel is envisaged.

Stilbene derivatives are an important class of naturally occurring compounds exhibiting a wide variety of biological activities.[15] For instance, resveratrol is known for

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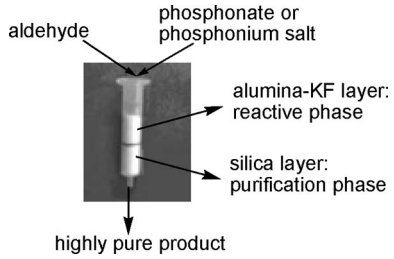


Figure 1. SPE column loaded with a layer of alumina-KF and a layer of silica.

its anti-inflammatory,[18] antioxidative,[19] vasodilator,[20] and anticancer chemopreventive properties.[21] In order to access methoxylated analogues of resveratrol, we prepared the phosphonate derivatives **2a** and **2b**. These phosphonates were synthesized via an Arbuzov reaction by heating the corresponding benzyl chlorides in triethylphosphite at 130 °C for 4 h.[22]

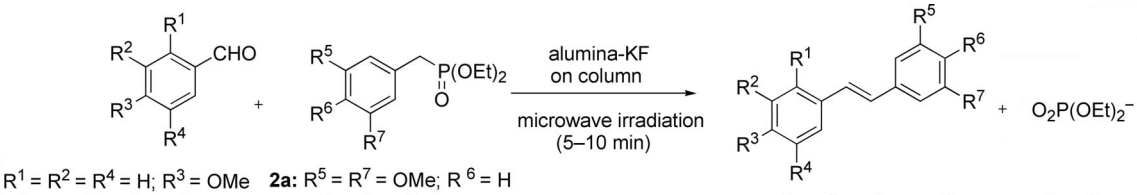
The experimental conditions used for the synthesis of the methoxylated (*E*)-stilbenes were optimized by using anisaldehyde and diethyl 3,5-dimethoxybenzylphosphonate (Table 1, entry 1). Initially, the reactants were introduced into the column containing alumina-KF without any solvent, and the reaction was allowed to proceed at room temperature. However, under these conditions, the starting aldehyde was only completely consumed after three days. When the column was heated at 80 °C for 17 h, stilbene **3a** was produced in 70% yield. Gratifyingly, our attempt to decrease the reaction time by using microwave irradiation (T = 100 °C, P = 120 W) was successful. Thus, under these conditions, the reaction was brought to completion in 5 min, furnishing the olefin in 85% yield.

These reaction conditions were applied to other aromatic aldehydes as summarized in Table 1. All the olefins were prepared with high purity and with good to excellent yields (57–85%). Compounds **3a**–**f** can be transformed into the corresponding polyhydroxystilbenes by using BBr_3 or $ISiMe_3$.[25]

Although yield of the reaction with aliphatic aldehydes was not as good as that with aromatic aldehydes, this method does provide a useful and easy synthetic route to alkylresorcinols **6a** and **b** (Scheme 1), in particular, the methoxylated analogue of olivetol **6a**.[26] The olefins were prepared in 41–43% yield and then reduced with Pd/C in methanol to generate the corresponding saturated compounds (80–86%).

Furthermore, because 5-aryl-2,4-pentadienoic acids and their derivatives exhibit a wide array of biological activities,[9] we investigated the synthesis of derivatives **8a**–**c** by using our methodology from the appropriate aldehyde and phosphonate **7a** or **7b**. The reaction was incomplete, and we

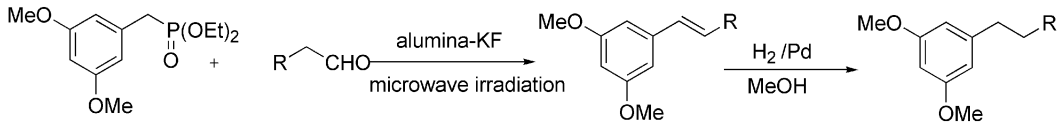
Table 1. Synthesis of methoxylated analogues of resveratrol over a column of alumina-KF under microwave irradiation.



$R^1 = R^2 = R^4 = H$; $R^3 = OMe$ **2a:** $R^5 = R^7 = OMe$; $R^6 = H$
$R^1 = H$; $R^2 = R^3 = R^4 = OMe$ **2b:** $R^5 = R^6 = R^7 = OMe$
$R^1 = R^4 = H$; R^2, $R^3 = OCH_2O$
$R^1 = OMe$, $R^2 = R^4 = H$; $R^3 = OMe$

3a: $R^1 = R^2 = R^4 = H$; $R^3 = OMe$; $R^5 = R^7 = OMe$; $R^6 = H$
3b: $R^1 = H$; $R^2 = R^3 = R^4 = OMe$; $R^5 = R^7 = OMe$; $R^6 = H$
3c: $R^1 = R^4 = H$; R^2, $R^3 = OCH_2O$; $R^5 = R^7 = OMe$; $R^6 = H$
3d: $R^1 = OMe$, $R^2 = R^4 = H$; $R^3 = OMe$; $R^5 = R^6 = R^7 = OMe$
3e: $R^1 = R^4 = H$; R^2, $R^3 = OCH_2O$; $R^5 = R^6 = R^7 = OMe$
3f: $R^1 = H$; $R^2 = R^3 = R^4 = OMe$; $R^5 = R^6 = R^7 = OMe$

Entry	1	2	Time [min]	3	Yield [%]	Ref.
1	**1a**	**2a**	5	**3a**	85	[23]
2	**1b**	**2a**	9	**3b**	75	[24]
3	**1c**	**2a**	10	**3c**	75	–
4	**1d**	**2b**	9	**3d**	60	–
5	**1c**	**2b**	9	**3e**	68	–
6	**1b**	**2b**	9	**3f**	57	[24]



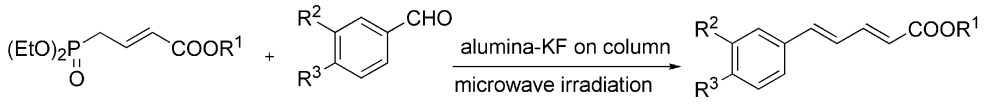
2a

4a: $R = C_2H_5$
4b: $R = C_5H_{10}$

5a:[27] $R = C_3H_7$, 41% yield **6a**: $R = C_3H_7$, 80% yield
5b: $R = C_6H_{13}$, 43% yield **6b**: $R = C_6H_{13}$, 86% yield

Scheme 1. Synthesis of methoxylated analogues of alkylresorcinols.

Table 2. Synthesis of 5-aryl-2,4-pentadienoates on a column of alumina-KF.



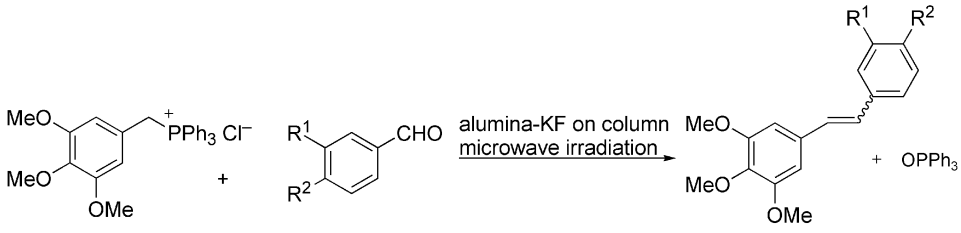
7a:[17] R^1 = Me
7b:[28] R^1 = Et

1a: R^2 = H, R^3 = OMe
1c: R^2, R^3 = OCH_2O

8a: R^1 = Et, R^2, R^3 = OCH_2O
8b: R^1 = Me, R^2, R^3 = OCH_2O
8c: R^1 = Me, R^2 = H, R^3 = OMe

Entry	Aldehyde	7	Time [min]	8	Conversion [%]	Ref.
7	**1c**	**7b**	8	**8a**	40	[29]
8	**1c**	**7a**	15	**8b**	65	[29]
9	**1a**	**7a**	18	**8c**	66	[30]

Table 3. Synthesis of (*E*)-stilbenes by the Wittig reaction on a column of alumina-KF.



9

1c: R^1, R^2 = OCH_2O
1e : R^1 = OTHP; R^2 = OMe

3e: R^1, R^2 = OCH_2O
10b: R^1 = OTHP; R^2 = OMe

Entry	Aldehyde	9	Time [min]	Product	Yield [%]	*E*/*Z* Ratio
10	**1c**	**9**	3	**3e**	75	100:0
11	**1e**	**9**	3	**10b**	68	70:30

obtained 40–66% conversion of the aldehyde (Table 2). The reduced conversion and yield were attributed to hydrolysis of the ester group of the phosphonates employed.

In the context of synthesizing bioactive molecules by using our method, we investigated the synthesis of combrestatine A-4[16,31] using isovanillin and 3,4,5-trimethoxybenzylphosphonium chloride (**9**); the latter being prepared by refluxing 3,4,5-trimethoxybenzyl chloride with triphenylphosphane in toluene for 8 h. The hydroxy group of isovanillin was protected by using dihydropyran in the presence of catalytic amounts of pyridinium-*p*-toluenesulfonic acid in dichloromethane. The reaction of the protected isovanillin (**1e**) with phosphonium salt **9** was complete in 3 min and afforded the corresponding olefin **10b** in 68% yield as a mixture of *E* and *Z* isomers (7:3). On the other hand, the reaction of piperonal (**1c**) with phosphonium salt **9** under the same conditions gave only the *E* isomer **3e** in 75% yield (Table 3).

Conclusions

We have used SPRC to prepare some natural bioactive compounds by the Wittig and Horner–Emmons reactions on a column of alumina-KF. SPRC integrated both the reaction and separation into a single unit and permitted the preparation of the target olefins with high purity in short reaction times under microwave irradiation, thus avoiding long liquid–liquid extraction procedures and purification protocols. This method might be interesting for cascade reactions and for the parallel synthesis of sets of small samples of compounds.

Experimental Section

General Methods: All commercial reagents were purchased from Acros, Aldrich, or Sigma and were used as received without further purification. Reaction times were monitored by TLC until no starting material remained. TLC was performed by using Silica gel 60 F_{254} precoated aluminum sheets. Column chromatography was performed by using Silica gel Si 60 (40–63 μm). Microwave irradiation was performed with a microwave mono-mode Prolabo Synthewave 402 cavity. ^{1}H, ^{31}P, and ^{13}C NMR spectra were recorded with a Bruker AC 250 or Bruker AC 400 spectrometer. Chemical shifts (δ) are expressed in parts per million (ppm) and are referenced to the internal deuterated solvents with tetramethylsilane as the internal standard. Data are reported as follows: multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublet, dt = doublet of triplet, m = multiplet, br. = broad), coupling constants [expressed in Hertz (Hz)], integral, and assignment. Mass spectra were recorded with a QTOF Micro (Waters) spectrometer with electrospray ionization (ESI, positive mode), lockspray orthophospho-

ric acid, infusion introduction at 10 μL/min, a source temperature of 80 °C and desolvation temperature of 120 °C.

General Procedure for the Synthesis of (*E*)-Stilbenes Using the Horner–Emmons Reaction on-Column: A polypropylene SPE column (Varian Bond Elut®, 6 mL), equipped with a frit at its lower end, was charged with silica (1.5 g). Above the layer of silica, a second layer of alumina-KF (1.8 g) was introduced. An equimolar mixture of the appropriate aldehyde (**1a**–**d** or **4a**,**b**) and a suitable phosphonate (**2a**,**b** or **7a**,**b**) in tetrahydrofuran (0.2 mL) was then adsorbed over the alumina-KF in the column. The column was then placed in a quartz reactor and exposed to microwave irradiation (120 W, T_{max} = 100 °C) in a resonate cavity for 1.5 min and then cooled to room temperature (10 min). This process was repeated until full consumption of the starting materials was observed. The formed olefin was eluted from the column with dichloromethane (20 mL), and the solvent was evaporated in vacuo to afford the corresponding olefin.

General Procedure for the Synthesis of (*E*)-Stilbenes Using the Wittig Reaction on-Column: The same procedure described above was employed, except that the phosphonates were replaced by phosphonium salt **9** and the column was irradiated for 3 min. Also, a mixture of cyclohexane/ethyl acetate (80:20) was used as eluent instead of dichloromethane.

4-Methoxy-3-(tetrahydro-2*H*-pyran-2-yloxy)benzaldehyde (1e): To a well stirred solution of isovanillin (1.52 g, 10 mmol) in anhydrous dichloromethane (40 mL) was added dihydropyran (6.5 g, 7.7 mmol) and pyridinium-*p*-toluenesulfonate (0.1 g). The reaction mixture was stirred overnight at room temperature under a nitrogen atmosphere, then saturated sodium hydrogen carbonate (50 mL) was added, and the mixture was extracted with dichloromethane (3 × 100 mL). The combined organic layers were dried with magnesium sulfate, and the solvent was removed in vacuo to afford the protected isovanillin as a colorless thick liquid in 75% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.84 (s, 1 H, HC=O), 7.63 (d, J = 2.0 Hz, 1 H, ArH), 7.52 (dd, J = 2.0, 8.4 Hz, 1 H, ArH), 6.99 (d, J = 8.4 Hz, 1 H, ArH), 5.47 (t, J = 3.6 Hz, 1 H, OCHO), 3.98–3.95 (m, 1 H, CH_2O), 3.93 (s, 3 H, OCH_3), 3.65–3.60 (m, 1 H, CH_2O), 2.04–1.87 (m, 2 H, CH_2), 1.72–1.58 (m, 4 H, CH_2) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 190.9, 155.6, 146.6, 130.1, 126.6, 116.7, 111.3, 79.5, 62.4, 56.2, 30.2, 25.1, 18.8 ppm. HRMS: calcd. for $C_{13}H_{17}O_4$ $[M + H]^+$ 237.1127; found 237.1131.

5-(3,5-Dimethoxystyryl)benzo[*d*][1,3]dioxole (3c): Prepared by reaction of piperonal (0.16 g, 1.1 mmol) and diethyl 3,5-dimethoxybenzylphosphonate (0.31 g, 1.1 mmol) as a white solid in 75% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.06 (d, J = 1.8 Hz, 1 H, ArH), 7.00 (d, J = 16.3 Hz, 1 H, CH=CH), 6.93 (dd, J = 1.8, 8.3 Hz, 1 H, ArH), 6.86 (d, J = 16.3 Hz, 1 H, CH=CH), 6.79 (d, J = 8.0 Hz, 1 H, ArH), 6.64 (d, J = 2.3 Hz, 2 H, ArH), 6.38 (t, J = 2.3 Hz, 1 H, ArH), 5.98 (s, 2 H, OCH_2O), 3.84 (s, 6 H, OCH_3) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 160.9 (2 C), 148.2, 147.4, 139.4, 131.7, 128.9, 126.9, 121.6, 108.4, 105.6, 104.4 (2 C), 101.1, 99.8, 55.4 (2 C) ppm. HRMS: calcd. for $C_{17}H_{17}O_4$ $[M + H]^+$ 285.1127; found 285.1130.

5-(2,4-Dimethoxystyryl)-1,2,3-trimethoxybenzene (3d): Prepared by reaction of 2,4-dimethoxybenzaldehyde (0.15 g, 0.89 mmol) and diethyl 3,4,5-trimethoxybenzylphosphonate (0.28 g, 0.89 mmol) as a white solid in 60% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.49 (d, J = 8.4 Hz, 1 H, ArH), 7.27 (d, J = 16.4 Hz, 1 H, CH=CH), 6.94 (d, J = 16.4 Hz, 1 H, CH=CH), 6.73 (s, 2 H, ArH), 6.53 (dd, J = 2.4, J = 8.4 Hz, 1 H, ArH), 6.48 (d, J = 2.4 Hz, 1 H, ArH), 3.91 (s, 6 H, OCH_3), 3.88 (s, 3 H, OCH_3), 3.86 (s, 3 H, OCH_3), 3.84 (s, 3 H, OCH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.5, 158.0, 153.3 (2 C), 137.5, 134.1, 127.3, 127.1, 122.9, 119.4, 105.0, 103.4 (2 C), 98.5, 61.0, 56.1 (2 C), 55.5, 55.4 ppm. HRMS: calcd. for $C_{19}H_{23}O_5$ $[M + H]^+$ 331.1545; found 331.1561.

5-(3,4,5-Trimethoxystyryl)benzo[*d*][1,3]dioxole (3e): Prepared either by reaction of piperonal (0.23 g, 0.85 mmol) and diethyl 3,4,5-trimethoxybenzylphosphonate (0.27 g, 0.85 mmol) in 68% yield as a white solid or by the reaction of piperonal (0.08 g, 0.5 mmol), and 3,4,5-trimethoxybenzylphosphonium chloride (0.24 g, 0.5 mmol) in 75% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.05 (d, J = 1.6 Hz, 1 H, ArH), 6.94 (d, J = 16.0 Hz, 1 H, CH=CH), 6.93 (dd, J = 2.0, J = 8.4 Hz, 1 H, ArH), 6.86 (d, J = 16.0 Hz, 1 H, CH=CH), 6.79 (d, J = 8.0 Hz, 1 H, ArH), 6.70 (s, 2 H, ArH), 3.91 (s, 6 H, OMe), 3.86 (s, 3 H, OMe) ppm. ^{13}C NMR (100.61 MHz, $CDCl_3$): δ = 153.4 (2 C), 148.2, 147.3, 137.8, 133.2, 131.8, 127.9, 127.0, 121.4, 108.4, 105.5, 103.4 (2 C), 101.2, 61.0, 56.1 (2 C) ppm. HRMS: calcd. for $C_{18}H_{19}O_5$ $[M + H]^+$ 315.1232; found 315.1225.

1,3-Dimethoxy-5-[(*E*)-oct-1-enyl]benzene (5b): Prepared by reaction of heptanal (0.2 g, 1.8 mmol) and diethyl 3,5-dimethoxybenzylphosphonate (0.30 g, 1.0 mmol) in 43% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.51 (d, J = 2.4 Hz, 2 H, ArH), 6.33 (t, J = 2.4 Hz, 1 H, ArH), 6.31 (d, J = 16 Hz, 1 H, CH=CH), 6.25–6.18 (td, J = 6.8, 15.6 Hz, 1 H, CH=CH), 3.79 (s, 3 H, OCH_3), 2.22–2.18 (m, 2 H, CH_2), 1.40–1.29 (m, 8 H, CH_2), 0.91–0.86 (m, 3 H, CH_3) ppm. ^{13}C NMR (100.61 MHz, $CDCl_3$): δ = 160.9 (2 C), 140.1, 131.8, 129.7, 104.0 (2 C), 99.1, 55.3 (2 C), 32.9, 31.7, 29.3, 28.9, 22.6, 14.1 ppm. HRMS: calcd. for $C_{16}H_{25}O_2$ $[M + H]^+$ 249.1855; found 249.1867.

1,3-Dimethoxy-5-octylbenzene (6b): A solution of 1,3-dimethoxy-5-[(*E*)-oct-1-enyl]benzene (**5b**; 0.26 g, 1 mmol) in methanol (10 mL) was placed in a 250 mL glass Parr hydrogenation flask containing 5% Pd/C catalyst, and the mixture was shaken for 18 h under 20 psi of hydrogen gas. The solution was then filtered through Celite to remove the catalyst. The solvent was removed under reduced pressure to afford the corresponding saturated product in 83% yield. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.7 (2 C), 145.4, 106.5 (2 C), 97.6, 55.2 (2 C), 36.3, 31.9, 31.3, 29.5, 29.4, 29.3, 22.7, 14.1 ppm.

3,4,5-Trimethoxybenzylphosphonium Chloride (9): Triphenylphosphane (4.58 g, 17.4 mmol) was added to a well stirred solution of 3,4,5-trimethoxybenzyl chloride (1.89 g, 8.7 mmol) in toluene (20 mL). The reaction mixture was then refluxed for 24 h under a nitrogen atmosphere. The corresponding phosphonium salt precipitated during the reaction and was collected at the end of the reaction by suction filtration as a white solid in 89% yield. ^{1}H NMR (400 MHz, D_2O): δ = 7.87–7.83 (m, 3 H, ArH), 7.68–7.59 (m, 12 H, ArH), 6.20 (d, J = 2.4 Hz, 2 H, ArH), 4.64 (d, J = 14.0 Hz, 2 H, CH_2P), 3.71 (s, 3 H, OCH_3), 3.44 (s, 6 H, OCH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 152.4 (2 C), 135.2, 134.0 (6 C), 129.8 (9 C), 123.6, 117.5 (3 C), 108.5 (2 C), 61.0, 55.8 (2 C), 30.2 ppm. ^{31}P NMR (400 MHz, D_2O): δ = 22.93 ppm. HRMS: calcd. for $C_{28}H_{28}O_3P$ $[M + H]^+$ 443.1776; found 443.1764.

2-[4-(3,4,5-Trimethoxystyryl)-2-methoxyphenoxy]tetrahydro-2*H*-pyran (10b): Prepared by using 3,4,5-trimethoxybenzylphosphonium chloride (**9**; 0.24 g, 0.5 mmol) and protected isovanillin (**1e**; 0.12 g, 0.5 mmol) to afford the product as a white solid in 68% yield as a mixture of *E* and *Z* isomers (7:3). ***E* Isomer**: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.33 (d, J = 2 Hz, 1 H, ArH), 7.12 (dd, J = 2.0, 8.5 Hz, 1 H, ArH), 6.94 (d, J = 16.0 Hz, 1 H, CH=CH), 6.88 (d, J = 16 Hz, 1 H, CH=CH), 6.88 (d, J = 8.5 Hz, 1 H, ArH), 6.71 (s, 2 H, ArH), 5.48 (t, J = 3.0 Hz, 1 H, OCHO), 4.05–4.01 (m, 1 H, OCH_2), 3.91 (s, 6 H, OCH_3), 3.88 (s, 3 H, OCH_3), 3.86 (s, 3 H, OCH_3), 3.67–3.64 (m, 1 H, OCH_2), 2.08–1.90 (m, 2 H, CH_2), 1.75–1.62 (m, 4 H, CH_2) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ

= (ppm) 153.4 (2 C), 150.1, 146.5, 137.6, 133.4, 130.5, 127.9, 126.8, 121.1, 115.4, 112.4, 103.3 (2 C), 97.5, 62.1, 61.0, 56.2, 56.1 (2 C), 30.4, 25.3, 18.7. HRMS: calcd. for $C_{23}H_{29}O_6$ $[M + H]^+$ 401.1964; found 401.1953. ***Z* Isomer**: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.07 (d, J = 2 Hz, 1 H, ArH), 6.91 (br. s, 1 H, ArH), 6.78 (d, J = 8 Hz, 1 H, ArH), 6.51 (s, 2 H, ArH), 6.48 (d, J = 12 Hz, 1 H, CH=CH), 6.42 (d, J = 12 Hz, 1 H, CH=CH), 5.17 (t, J = 3.6 Hz, 1 H, OCHO), 3.85 (m, 1 H, OCH_2), 3.83 (s, 6 H, OCH_3), 3.70 (s, 6 H, OCH_3), 3.46–3.40 (m, 1 H, OCH_2), 2.03–1.58 (m, 6 H, CH_2) ppm.

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