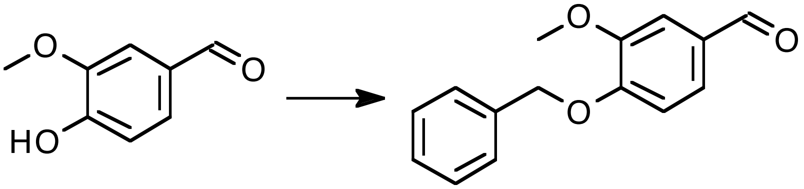
Electronic Supplementary Information

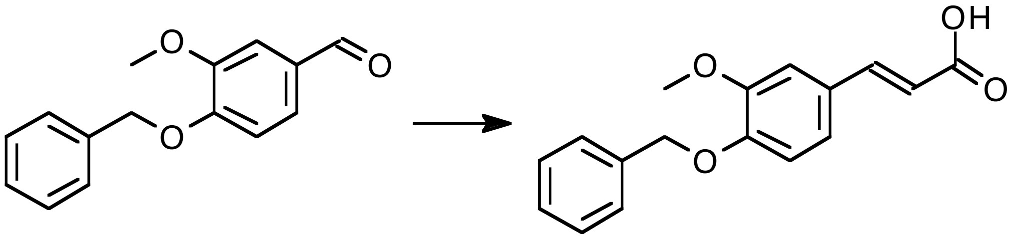
Synthetic Details, X-ray crystal structure of 4C2-Ac

A. Details of the Syntheses in Fig. 2

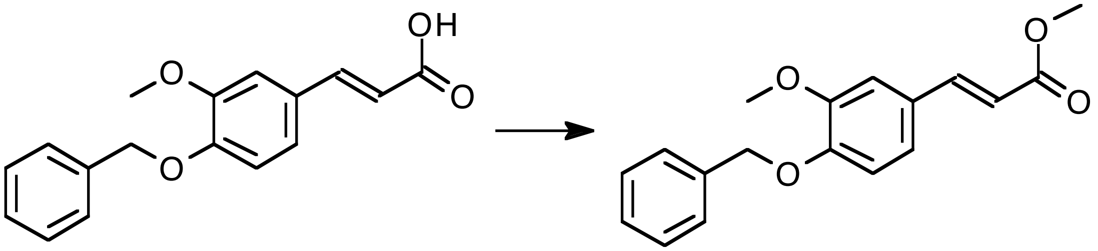
Compound numbering is in Fig. 2 in paper. The remainder of the synthesis (to compounds **13**, **4C2**, **4C2-Ac**, and **5C2**) are described in the paper.



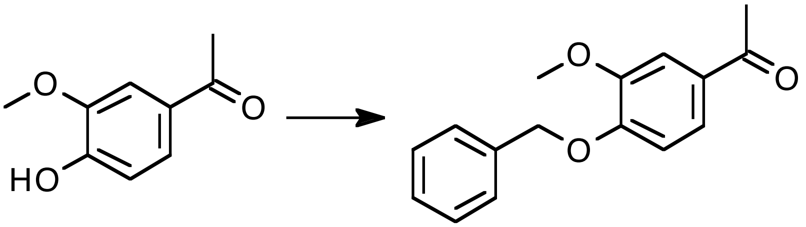
4-Benzyloxy-3-methoxybenzaldehyde **7** (step *i* in Fig. 2).[1] — Vanillin **6** (15.0 g, 98.7 mmol), potassium iodide (1.1 g, 6.8 mmol), potassium carbonate (22.1 g, 159.9 mmol), and 100 mL of anhydrous dimethyl formamide were placed into a 500 mL round-bottom flask equipped with a magnetic stirrer and a reflux condenser. The stirred mixture was heated to 80-90°C using a hot water bath. Benzyl chloride (16.8 g, 133.5 mmol) was added down the reflux condenser in small portions. The temperature of the mixture was maintained at 80-90°C for one hour. The mixture was allowed to cool to room temperature and then was poured onto approx. 150 g of ice. The mixture was stirred until all of the ice melted. The solid which formed was isolated by suction filtration and allowed to air dry. The isolated solid was 4-benzyloxy-3-methoxybenzaldehyde **7** (24.1 g, 100.7%). The unpurified solid had a melting point of 61-66°C, lit[2] mp 67°C. ^{1}H-NMR (d_6-acetone, 360 MHz) δ_H 3.89 (3H, s, OCH_3); 5.23 (2H, s, OCH_2Ph); 7.22 (1H, d, J = 8.29 Hz, H5); 7.33 (1H, br t, J = 6.8 Hz, benzyl H4); 7.40 (2H, br t, J = 7.1 Hz, benzyl H3 and H5); 7.44 (1H, d, J = 1.97 Hz, H2); 7.49 (1H, dd, J = 1.97, 8.29 Hz, H6); 7.50 (2H, br d, J = 7.1 Hz, benzyl H2 and benzyl H6); 9.85 (1H, s, aldehyde H). ^{13}C-NMR (d_6-acetone, 90 MHz) δ_C 56.16 (OCH_3); 71.24 (OCH_2Ph); 110.67 (C2); 113.55 (C5); 126.52 (C6); 128.54 (benzyl C2 and C6); 128.83 (benzyl C4); 129.31 (benzyl C3 and C5); 131.44 (C1); 137.62 (benzyl C1); 150.96 (C3); 154.60 (C4); 191.27 (C=O).



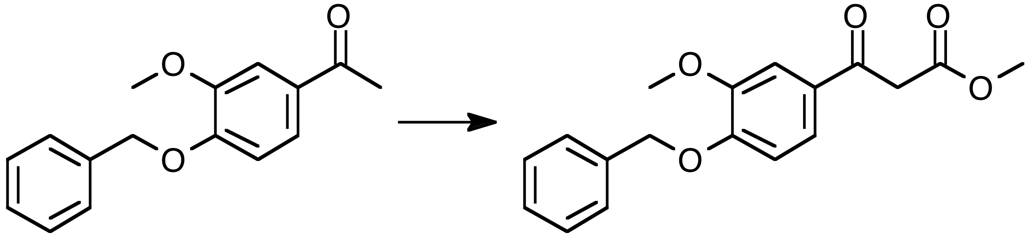
3-(4'-Benzyloxy-3'-methoxyphenyl)propenoic acid **8** (step *ii* in Fig. 2). — 4-Benzyloxy-3-methoxy-benzaldehyde **7** (2.43 g, 10 mmol), malonic acid (1.04 g, 10 mmol), and anhydrous ammonium acetate (0.81 g, 10.5 mmol)were intimately mixed and placed into a 50 mL Erlenmeyer flask. The mixture was irradiated in a microwave oven at high power for a total of 3 min. The irradiation was periodically interrupted to allow the foaming to subside. The irradiated mixture was allowed to cool, during which time the mixture solidified. The residue was broken up with a spatula and was stirred overnight with approx. 75 mL of 6N hydrochloric acid. The solid was isolated from the mixture by suction filtration. After air drying, the weight of the unpurified solid, 3-(4'-benzyloxy-3'-methoxyphenyl)propenoic acid **8**, was 2.60 g (91%), mp 186-191°C, lit[3]. mp 190-191°C. This material was used without further purification to prepare methyl 3-(4'-benzyloxy-3'-methoxyphenyl)propenoate **9**. ^{1}H-NMR (d_6-acetone, 360 MHz) δ_H 3.88 (3H, s, OCH_3); 5.16 (2H, s, OCH_2Ph); 6.40 (1H, d, J = 15.92 Hz, H8); 7.06 (1H, d, J = 8.29 Hz, H5); 7.16 (1H, dd, J = 1.97, 8.29 Hz, H6); 7.32 (1H, d, J = 1.97 Hz, H2); 7.32 (1H, br t, J = 7.0 Hz); 7.39 (2H, br t, J = 7.1 Hz, benzyl H3 and H5); 7.48 (2H, br d, J = 7.0 Hz, benzyl H2 and benzyl H6); 7.56 (1H, d J = 15.92 Hz, H7). ^{13}C-NMR (d_6-acetone, 90 MHz) δ_C 56.15 (OCH_3); 70.99 (OCH_2Ph); 111.42 (C2); 114.24 (C5); 117.66 (C8); 122.98 (C6); 128.37 (benzyl C2 and C6); 128.53 (C1); 128.70 (benzyl C4); 129.10 (benzyl C3 and C5); 137.93 (benzyl C1); 144.72 (C3); 150.72 (C7); 151.02 (C4); 168.58 (C=O).



Methyl 3-(4'-benzyloxy-3'-methoxyphenyl)propenoate **9** (step *iii* in Fig. 2). — 3-(4'-Benzyloxy-3'-methoxyphenyl)propenoic acid **8** (3.96 g, 13.9 mmol), anhydrous potassium carbonate (2.95 g, 21.4 mmol), and 20 mL of dimethyl formamide were placed into a 100 mL round-bottom flask equipped with a reflux condenser. The stirred mixture was heated with a hot water bath and iodomethane (2.74 g, 19.3 mmol) was added in small portions down the condenser. The stirred mixture was heated at 80-90°C for one hour. The mixture was poured into 100 mL of cold water and stirred. A white solid formed and this was isolated by suction filtration. After air drying overnight, the solid, methyl 3-(4'-benzyloxy-3'-methoxyphenyl)propenoate **9**, weighed 4.00 g (96%), mp 95-97°C, lit[4]. mp 98.5-99.5°C. ^{1}H-NMR (d$_6$-acetone, 360 MHz) δ_H 3.72 (3H, s, CO$_2$CH$_3$); 3.89 (3H, s, OCH$_3$); 5.17 (2H, s, OCH$_2$Ph); 6.43 (1H, d, J = 15.92 Hz, H8); 7.06 (1H, d, J = 8.29 Hz, H5); 7.17 (1H, dd, J = 1.97 Hz, 8.29 Hz, H6); 7.32 (1H, br t, J = 7.4 Hz, benzyl H4); 7.34 (1H, d, J = 1.97, H2); 7.39 (2H, br t, J = 7.4 Hz, benzyl H3 and H5); 7.49 (2H, br d, J = 7.2 Hz, benzyl H2 and benzyl H6); 7.60 (1H, d J = 15.92 Hz, H7). ^{13}C-NMR (d$_6$-acetone, 90 MHz) δ 51.52 (OCH$_3$); 56.25 (OCH$_3$); 71.27 (OCH$_2$Ph); 111.61 (C2); 114.42 (C5); 116.41 (C8); 123.32 (C6); 128.48 (benzyl C2 and C6); 128.56 (C1); 128.88 (benzyl C4); 129.25 (benzyl C3 and C5); 138.12 (benzyl C1); 145.37 (C7); 151.03 (C3); 151.52 (C4); 167.73 (C=O). A small sample was recrystallized from 95% ethanol.



4-Benzyloxy-3-methoxyacetophenone **11** (step *iv* in Fig. 2).[5] – Acetovanillone **10** (16.4 g, 98.8 mmol), potassium iodide (1.08 g, 7 mmol), potassium carbonate (22.1 g, 160 mmol), and 100 mL of anhydrous dimethyl formamide were placed into a 250 mL round-bottom flask equipped with a magnetic stirrer and a reflux condenser. The stirred mixture was heated to 90°C. Benzyl chloride (17.0 g, 133 mmol) was added down the reflux condenser in small portions. The temperature of the mixture was maintained at 80-90°C for one hour. The mixture was allowed to cool to room temperature and then was poured onto approximately 150 g of ice. The mixture was stirred until all of the ice had melted. The solid which formed was isolated by suction filtration and allowed to air dry. The isolated solid was 4-benzyloxy-3-methoxyacetophenone (25.9 g, 102%). The unpurified solid melted from 85-86.5°C, lit[6]. mp 88°C. ^{1}H-NMR (d$_6$-acetone, 360 MHz) δ_H 2.50 (3H, s, $CH_3C{=}O$); 3.87 (3H, s, OCH_3); 5.21 (2H, s, OCH_2Ph); 7.10 (1H, d, J = 8.42 Hz, H5); 7.33 (1H, br t, J = 7.2 Hz, benzyl H4); 7.39 (2H, br t, J = 7.2 Hz, benzyl H3 and H5); 7.49 (2H, br d, J = 7.4 Hz, benzyl H2 and benzyl H6); 7.53 (1H, d, J = 2.10 Hz, H2); 7.59 (1H, dd, J = 2.10, 8.42 Hz, H6). ^{13}C-NMR (d$_6$-acetone, 90 MHz) δ_C 26.28 (CH_3); 56.16 (OCH_3); 71.16 (OCH_2Ph); 111.68 (C2); 113.27 (C5); 123.63 (C6); 128.49 (benzyl C2 and C6); 128.76 (benzyl C4); 129.29 (benzyl C3 and C5); 131.68 (C1); 137.87 (benzyl C1); 150.48 (C3); 153.46 (C4); 196.38 (C7, C=O).



Methyl 4-benzyloxy-3-methoxybenzoylacetate **12** (step *v* in Fig. 2). – Anhydrous tetrahydrofuran (40 mL), dimethylcarbonate (3.75 g, 42 mmol), and 1.35 g (56 mmol) of sodium hydride powder were placed in a 250 mL three-neck round-bottom flask fitted with a dropping funnel and a reflux condenser. The third neck of the flask was fitted with a glass stopper. The condenser was capped with a bubbler containing oil which was used to monitor the evolution of gas during the course of the reaction. The mixture was stirred with a magnetic stir bar and heated to reflux. A solution of 4-benzyloxy-3-methoxy-acetophenone **11** (5.01 g, 19 mmol) in 20 mL of anhydrous tetrahydrofuran was placed in the dropping funnel and was then added dropwise to the refluxing mixture. After all of the solution was added, heating was continued until no gas evolution could be detected with the bubbler. The mixture was allowed to cool to room temperature and 5 mL of acetic acid was added. A gelatinous solid formed. Ice-cold water (20 mL) was added and the solid dissolved. The mixture was acidified to pH 3 with concentrated hydrochloric acid. The aqueous mixture was extracted three times with 25 mL portions of ethyl acetate. The combined ethyl acetate extracts were washed with three 50 mL portions of ice-cold water and one 50 mL portion of brine. After drying over anhydrous magnesium sulfate, the ethyl acetate was removed with a rotary evaporator leaving a brown residue which crystallized on standing. The brown residue was dissolved in 100 mL of ethyl acetate and stirred with activated charcoal. After filtration, the solvent was removed with a rotary evaporator leaving 4.88 g (80%) of methyl 4-benzyloxy-3-methoxy-benzoylacetate **12** as a light yellow solid. Recrystallization of a sample from methanol afforded light yellow needles melting at 71.5-72.5°C, lit.[8] 66-68°C. ^{1}H-NMR (d_6-acetone, 360 MHz) δ_H 3.67 (3H, s, CO_2CH_3); 3.88 (3H, s, OCH_3); 4.04 (2H, s, H8); 5.23 (2H, s, OCH_2Ph); 7.14 (1H, d, J = 8.42 Hz, H5); 7.33 (1H, br t, J = 7.4 Hz, benzyl H4); 7.40 (2H, br t, J = 7.4 Hz, benzyl H3 and H5); 7.50 (2H, br d, J = 7.4 Hz, benzyl H2 and benzyl H6); 7.54 (1H, d, J = 2.10 Hz, H2); 7.61 (1H, dd, J = 2.10, 8.42 Hz, H6). ^{13}C-NMR (d_6-acetone, 90 MHz) δ_C 45.81 (C8); 52.23 (OCH_3); 56.21 (OCH_3); 71.21 (OCH_2Ph); 111.87 (C2); 113.28 (C5); 124.06 (C6); 128.54 (benzyl C2 and C6); 128.83 (benzyl C4); 129.32 (benzyl C3 and C5); 130.48 (C1); 137.74 (benzyl C1); 150.60 (C3); 154.05 (C4); 168.92 (C9); 191.79 (C7).

Compound 4C2-Ac, Acetylation of 4C2 (step *viii* in Fig. 2).
Tetrahydrofuran **4C2** (0.494 g, 1.1 mmol) was dissolved in 10 mL of anhydrous pyridine. The mixture was cooled in an ice/water bath. Acetyl chloride (0.534 g. 6.8 mmol) was added dropwise to the cooled and stirred mixture. The mixture was stirred for 1 hour while being cooled in the ice/water bath. The cooling bath was removed and the mixture was then stirred for 1 hour at ambient temperature. The reaction was worked up by pouring the mixture onto 50 mL of icy water. After the ice melted, the mixture was extracted with ethyl acetate (3 x 50 mL). The combined organic extracts were washed with saturated ammonium chloride solution (1 x 50 mL) and with saturated sodium chloride solution (1 x 50 mL) and then dried over anhydrous magnesium sulfate. Evaporation of the volatiles on a rotary evaporator left a solid (0.450 g, 0.9 mmol, 79%).
Recrystallization from methanol afforded colorless crystals of **4C2-Ac** (0.381 g, m.p. 137-140°C).

References:

1. P. F. Schatz, Laboratory Research Notebook A, page 13.
2. Martin and Pierre, *Helv. Chim. Acta*, **1989**, *72*, 1554.
3. Alok Kumar Mitra, Aparna De and Nilay Karchaudhuri, *Syn. Comm.*, **1999**, *29*, 573-581.
4. J. W. Bode, M. P. Doyle, M. N. Protopopova, and Q-L. Zhou, *J. Org. Chem.* **1998**, *28*, 3693-3700.
5. P. F. Schatz, Laboratory Research Notebook A, page 15.
6. Buu-Hoi et al.; *J.Org.Chem.*; **1953**; *18*; 121.

B. Compound 4C2-Ac Crystallographic Experimental Section

Data Collection

A colorless crystal with approximate dimensions 0.43 x 0.32 x 0.26 mm^3 was selected under oil under ambient conditions and attached to the tip of a glass capillary. The crystal was mounted in a stream of cold nitrogen at 100(2) K and centered in the X-ray beam by using a video camera.

The crystal evaluation and data collection were performed on a Bruker CCD-1000 diffractometer with Mo K_α (λ = 0.71073 Å) radiation and the diffractometer to crystal distance of 4.9 cm.

The initial cell constants were obtained from three series of ω scans at different starting angles. Each series consisted of 20 frames collected at intervals of 0.3° in a 6° range about ω with the exposure time of 10 seconds per frame. A total of 144 reflections was obtained. The reflections were successfully indexed by an automated indexing routine built in the SMART program. The final cell constants were calculated from a set of 16169 strong reflections from the actual data collection.

The data were collected by using the hemisphere data collection routine. The reciprocal space was surveyed to the extent of a full sphere to a resolution of 0.80 Å. A total of 39503 data were harvested by collecting three sets of frames with 0.3° scans in ω with an exposure time 20 sec per frame. These highly redundant datasets were corrected for Lorentz and polarization effects. The absorption correction was based on fitting a function to the empirical transmission surface as sampled by multiple equivalent measurements. [1]

Structure Solution and Refinement

The systematic absences in the diffraction data were uniquely consistent for the space group *Pbca* that yielded chemically reasonable and computationally stable results of refinement [2].

A successful solution by the direct methods provided most non-hydrogen atoms from the *E*-map. The remaining non-hydrogen atoms were located in an alternating series of least-squares cycles and difference Fourier maps. All non-hydrogen atoms were refined with anisotropic displacement coefficients. All hydrogen atoms were included in the structure factor calculation at idealized positions and were allowed to ride on the neighboring atoms with relative isotropic displacement coefficients.

The final least-squares refinement of 335 parameters against 5229 data resulted in residuals *R* (based on F^2 for $I \geq 2\sigma$) and *wR* (based on F^2 for all data) of 0.0453 and 0.1280, respectively.

The ORTEP diagram is drawn with 50% probability ellipsoids.

References

[1] Blessing, R.H. *Acta Cryst.* **1995**, *A51*, 33-38.

[2] All software and sources of the scattering factors are contained in the SHELXTL (version 5.1) program library (G. Sheldrick, Bruker Analytical X-Ray Systems, Madison, WI).

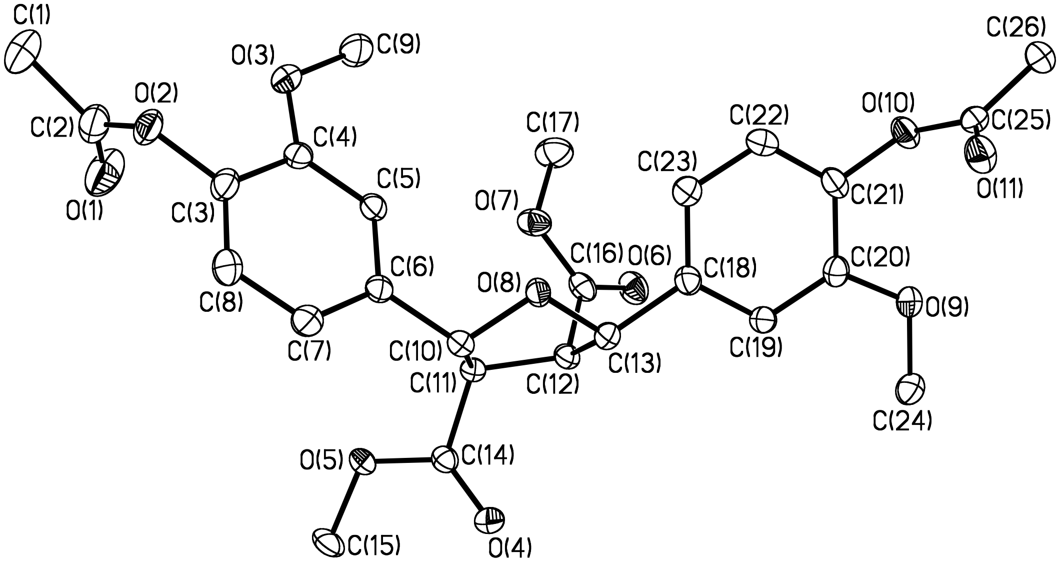


Table 1. Crystal data and structure refinement for **4C2-Ac**.

Identification code	ral01	
Empirical formula	$C_{26} H_{28} O_{11}$	
Formula weight	516.48	
Temperature	173(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	Pbca	
Unit cell dimensions	a = 7.3722(6) Å	α= 90°.
	b = 25.899(2) Å	β= 90°.
	c = 26.760(2) Å	γ = 90°.
Volume	5109.4(7) $Å^3$	
Z	8	
Density (calculated)	1.343 Mg/m^3	
Absorption coefficient	0.106 mm^{-1}	
F(000)	2176	
Crystal size	0.43 x 0.32 x 0.26 mm^3	
Theta range for data collection	2.77 to 26.40°.	
Index ranges	$-9<=h<=9$, $-32<=k<=32$, $-33<=l<=33$	
Reflections collected	39503	
Independent reflections	5229 [R(int) = 0.0350]	
Completeness to theta = 26.40°	99.6 %	
Absorption correction	Empirical with SADABS	
Max. and min. transmission	0.9731 and 0.9560	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	5229 / 0 / 335	
Goodness-of-fit on F^2	1.046	
Final R indices [I>2sigma(I)]	R1 = 0.0453, wR2 = 0.1220	
R indices (all data)	R1 = 0.0514, wR2 = 0.1280	
Largest diff. peak and hole	1.231 and -0.208 e.$Å^{-3}$	

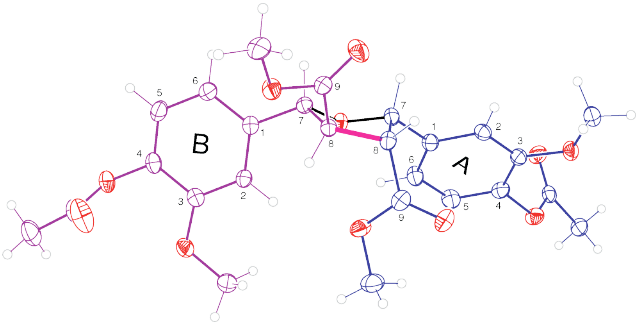


Fig. 4 (In color, to more easily track the two ferulate precursors). 3D structure of compound **4C2-Ac** (Fig. 2) from the X-ray crystal structure, demonstrating the assigned *cis-trans-trans*-stereochemistry. The 8–8-bond formed (*in planta*) via the radical coupling step is colored magenta and bolded; the two original ferulates are color-differentiated. The structure is numbered to be consistent with the structures in Fig. 2; full numbering for the crystal structure coordinates is provided above.