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AN ULLMANN ETHER REACTION INVOLVING AN ALKYNYL SUBSTRATE: A CONVERGENT ROUTE TO A COMBRETASTATIN INTERMEDIATE

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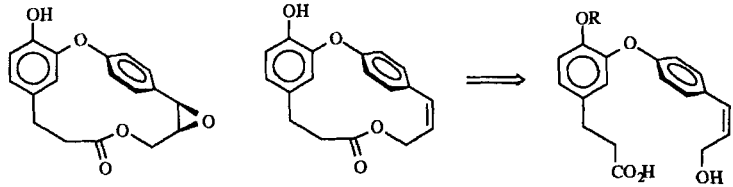
ABSTRACT: We found that we could employ a disubstituted alkynyl halide in an Ullmann ether reaction to produce the *cis*-alkene intermediate **3** of the combretastatin natural products.

In our synthetic investigations on the caffrane natural products, which include combretastatin D-1 (**1**) and combretastatin D-2 (**2**), the unusual 15-membered meta and paracyclophane lactones isolated from the South African tree, *Combretum caffrum*,[2,3] we wanted to develop a simple and efficient route to the bis aromatic ether **3** containing the *cis*-alkene moiety, characteristic of the caffrane skeleton.[4]



(-)-combretastatin D-1 **1** combretastatin D-2 **2** **3**

Several syntheses of **3** have been reported recently in the literature,[5] and in one report, this compound led directly to the total synthesis of combretastatin D-

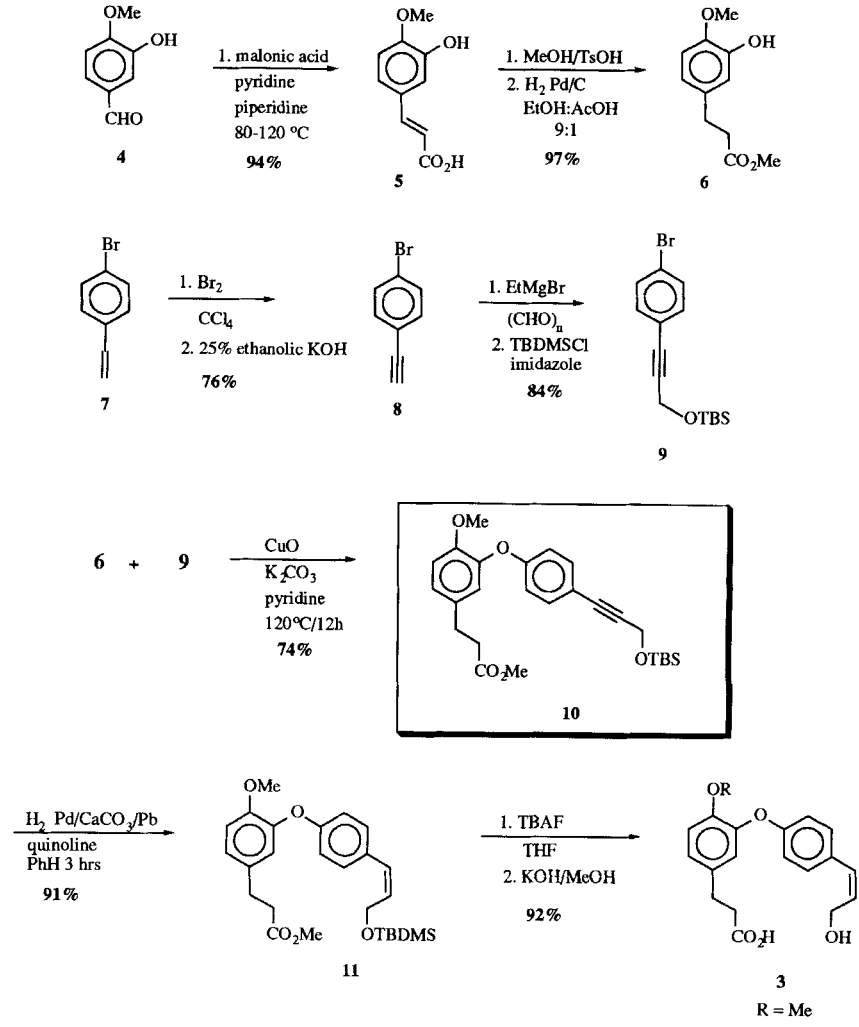
2.[5b] These syntheses involved the introduction of the *cis*-alkene carbons after the Ullmann ether coupling reaction. We wanted to investigate the possibility of using a disubstituted alkyne in order to introduce the entire carbon skeleton during the Ullmann ether coupling reaction and thus provide a highly convergent route to this intermediate. Standard Lindlar reduction of the triple bond could then yield the bis aromatic ether **3**. Interestingly, a search of the chemical literature showed that there appeared to be no synthetically useful examples of aromatic alkynyl halides employed as major components in the Ullmann ether reaction. Thus, we had several concerns about our investigation. One concern was that the aryloxycopper intermediate, proposed to be the reactive species in the Ullmann ether reaction mechanism,[6] would react with the alkyne, thus preventing formation of the desired product. Our second concern was that the alkynyl halide **9** did not possess any electron withdrawing groups on the aromatic nucleus, particularly *ortho* to the bromo substituent. Electron withdrawing groups are reported to have a marked activating effect on the aryl halide in the Ullmann ether reaction.[7] Despite these potential problems, we decided to investigate this reaction.

Retrosynthetic analysis of **3** leads to two major components: a substituted phenol **6** and an aromatic alkyne **9**. We first synthesized methyl 3-(3-hydroxy-4-methoxyphenyl) propionate[5a] (**6**) from the commercially available isovanillin in three steps, involving a Knoevenagel reaction with malonic acid, in the presence of pyridine and piperidine,[8] a standard Fisher esterification, and a palladium catalyzed hydrogenation. The propargyl alcohol **9** was synthesized in four steps from commercially available 4-bromostyrene, via a bromination, double-dehydrobromination,[9] and a formylation reaction.[10] Subsequent protection of the alcohol functionality as its *tert*-butyldimethylsilyl derivative under standard conditions led to **9** in 64% overall yield.

As illustrated in Scheme 1, we were able to perform this novel Ullmann ether coupling reaction involving **6** and **9**, following Evans procedure in refluxing pyridine,[11] to yield the bis aromatic ether **10** in 74% yield. This reaction is noteworthy in that the alkynyl functionality remained intact under these reaction conditions, and despite the absence of electron withdrawing substituents on the aryl bromide, we could accomplish this coupling reaction in an excellent yield. We saw very little decomposition of material despite the somewhat harsh conditions and we did not see any appreciable side products. Sonication[12] of the

reaction mixture, a technique often used to improve the yield of organometallic reactions, had no effect on this transformation. Lindlar reduction of the bis aromatic ether **10** in benzene led to the *cis*-olefin **11** in 91% yield. Subsequent deprotection of the silylated alcohol with tetrabutylammonium fluoride (TBAF) and saponification of the methyl ester with methanolic potassium hydroxide led to the known hydroxy acid **3**[5] in 92% overall yield for these two steps.

Scheme 1



Thus, this reaction sequence provided us with a highly efficient and convergent route to the combretastatin skeleton. At this point, we are investigating this Ullmann ether reaction with various alkynes to explore the general scope of this reaction.

Experimental

Proton and carbon NMR spectra were recorded on a Bruker ARX 300 MHz spectrometer in $CDCl_3$ with TMS as the internal standard unless otherwise indicated. Infrared spectra were recorded on a Nicolet 550 Magna spectrometer. Flash column chromatography was performed with Merck silica gel 60 (230-400 mesh). Thin layer chromatography (TLC) was done on EM Science Kieselgel 60 F-254 (1 mm) plates. All elemental analyses were performed by M-H-W Laboratories, Phoenix, Arizona. All reactions requiring anhydrous, anaerobic conditions were performed under an atmosphere of argon in flame-dried glassware. All solvents were distilled prior to use. THF was distilled over Na/benzophenone ketyl, pyridine, piperidine, CH_2Cl_2, and benzene were distilled over CaH_2, and methanol was distilled over Na metal. Quinoline was distilled over Zn dust, and DMF was dried over BaO and distilled.

(*E*)-3-(3-hydroxy-4-methoxyphenyl)-2-propenic acid (5). To a mixture of isovanillin (25.0 g, 164.5 mmol) and malonic acid (34.0 g, 326.9 mmol) was added pyridine (65.0 mL) and the mixture was gently warmed to 50 °C until all the solids had dissolved. Piperidine (2.4 ml) was added to the resulting orange solution which then was heated to 80 °C for 0.5 hr and refluxed for an additional 3 hr. The solution was cooled to room temperature and transferred to a beaker containing 680 mL of cold water. The solution was acidified by the slow addition of concentrated HCl (80 mL) resulting in the formation of a thick white precipitate. The solid was collected by vacuum filtration, washed with cold water, and redissolved in an aqueous 10% NaOH solution (320 mL). The mixture was filtered to remove any undissolved materials and the filtrate was acidified with concentrated HCl (50 mL). The resulting white crystalline solid was collected by vacuum filtration, washed with cold water (3 x 20 mL) and dried under high vacuum at 60 °C for 2 days to yield 29.9 g (94%) of acid **5**: mp 232-233 °C (lit.

mp 233-234 °C[13]); ^{1}H NMR (DMSO-d_6, 300 MHz) 9.25 (br s, 1H, CO_2H), 7.49 (d, 1H, J = 15.9 Hz, C*H*=CHCO$_2$H), 7.13 (m, 2H, H2 and H5), 6.97 (1H, app d, J = 8.8, H6), 6.29 (d, 1H, J = 15.9 Hz, CH=C*H*CO$_2$H), 3.84 (s, 3H, OCH_3);[13] ^{13}C NMR (DMSO-d_6, 125 MHz) δ 168.0, 150.1, 146.9, 127.3 (quaternaries), 144.4, 121.2, 116.5, 114.3, 112.2 (CH), 55.8 (CH_3).

Methyl 3-(3-hydroxy-4-methoxyphenyl) propionate (6). To a solution of the propenic acid **5** (20.0 g, 103.1 mmol) and anhydrous MeOH (800 mL) was added p-TsOH (2.0 g, 10.5 mmol) and the reaction mixture was refluxed under an atmosphere of Ar for 24 hr. The solution was concentrated under reduced pressure and the residue was diluted with CH_2Cl_2 (250 mL). The organic layer was extracted with sat. $NaHCO_3$, brine, dried over $MgSO_4$, and concentrated to yield 21.2 g (97%) of methyl 3-hydroxy-4-methoxy-cinnamate as a white solid: mp 78-79 °C (lit. 78-79 °C[14]); ^{1}H NMR ($CDCl_3$, 300 MHz) 7.59 (d, 1H, J = 15.9 Hz, C*H*=CHCO$_2$Me), 7.13 (d, 1H, J = 1.8 Hz, H2), 7.00 (dd, J = 8.3, 1.8 Hz, H6), 6.81 (1H, d, J = 8.3 Hz, H5), 6.28 (d, 1H, J = 15.9 Hz, CH=C*H*CO$_2$Me), 6.03 (br s, 1H, OH), 3.84 (s, 3H, OCH_3), 3.78 (s, 3H, CO_2CH_3);[14] ^{13}C NMR ($CDCl_3$, 125 MHz) δ 167.7, 148.6, 145.8, 127.8 (quaternaries), 144.7, 121.7, 115.5, 112.9, 110.5 (CH), 55.8, 51.5 (CH_3).

A stirred solution of methyl 3-hydroxy-4-methoxy-cinnamate (3.5 g, 16.8 mmol) and 95% EtOH (150 mL) was evacuated and flushed with Ar several times. Palladium catalyst (10% Pd/C, 1.2 g) was added in one portion and the resulting slurry was evacuated and flushed with Ar several more times. After the last evacuation, the reaction mixture was placed under hydrogen gas at atmospheric pressure and stirred at room temperature overnight. The mixture was filtered through a pad of celite and the filtrate concentrated under reduced pressure to yield 3.5 g (100%) of ester **6** as a white solid which was recrystallized from 95% EtOH: mp 94-95 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) 6.75 (d, 1H, J = 8.0 Hz, H5), 6.74 (app s, 1H, H2), 6.64 (1H, dd, J = 8.0, 2.0 Hz, H6), 5.65 (br s, 1H, OH), 3.83 (s, 3H, OCH_3), 3.65 (s, 3H, CO_2CH_3), 2.83 (t, 2H, J = 8.1 Hz, C*H*$_2$CH$_2$CO$_2$Me), 2.57 (t, 2H, J = 8.1 Hz, CH$_2$C*H*$_2$CO$_2$Me); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 173.4, 145.5, 145.1, 133.8 (quaternaries), 119.6, 114.5, 110.7 (CH), 35.9, 30.3 (CH_2), 56.0, 51.6 (CH_3); MS (EI, *m/z*) 210 (M^+), 150, 137. Anal. Calcd for $C_{11}H_{14}O_4$ (210.23): C, 62.85; H, 6.71. Found: C, 62.85; H, 6.86. IR

(KBr) ν_{max}: 3420, 2930, 2860, 1740, 1605, 1520, 1440, 1260, 1095, 1010, 810 cm^{-1}.

4-Bromo-1-ethynylbenzene (8). To a solution of 4-bromostyrene (10.0 g, 54.6 mmol) in CCl_4 (100 mL) was added dropwise slowly freshly distilled Br_2 (9.1 g, 57.3 mmol). After the addition was complete, the reaction mixture was washed with 5% $NaHSO_3$, and brine. The organic layer was dried over $MgSO_4$ and concentrated to yield 18.6 g (100%) of 1-(1,2-dibromoethyl)-4-bromobenzene as a pale yellow solid which was used without further purification: mp 59-60 °C (lit. mp 60-61 °C[9]).

To 1-(1,2-dibromoethyl)-4-bromobenzene (18.6 g, 54.5 mmol) was added 25% ethanolic KOH solution (95 g) and the reaction mixture was heated to reflux for 2.5 hr. The mixture was cooled to room temperature, diluted with ethyl acetate and the organic layer was washed with 1N HCl, brine, dried over $NaSO_4$ and concentrated to yield a crude yellow oil. Kugelrohr distillation of the crude product (bp 58-62 °C at 0.25 torr) afforded 7.5 g (76%) of alkyne **8** as a colorless solid: mp 64-65 °C (lit. mp 65 °C[9]); ^1H NMR ($CDCl_3$, 300 MHz) 7.47 (d, 2H, J = 8.6 Hz, H3), 7.35 (d, 2H, J = 8.6 Hz, H2), 3.12 (s, 1H).[9]

3-(4-Bromophenyl)-2-propyn-1-*t*-butyldimethylsilyl ether (9). 4-bromo-1-ethynylbenzene **8** (8.7 g, 48.1 mmol) was dissolved in anhydrous THF (190 mL) and EtMgBr (3.0 M in ether, 64.0 mL, 192.0 mmol) was added dropwise slowly. The resulting red solution was gently warmed to 45 °C and the reaction mixture maintained at that temperature for 1 hr. Formaldehyde gas, formed by heating anhydrous solid paraformaldehyde (13.0 g) to 180°C in a separate vessel, was bubbled through the reaction mixture under a vigorous flow of Ar. After the addition was complete the reddish brown mixture was stirred at 45 °C for an additional hr, cooled to 0 °C and quenched by the addition of 4 N HCl. The mixture was diluted with ethyl acetate (200 mL) and the organic layer was washed with sat. $NaHCO_3$, brine, dried over Na_2SO_4 and concentrated under reduced pressure. Purification by flash chromatography on silica gel eluting with hexane/ethyl acetate (9:1) led to 8.6 g (85%) of 3-(4-bromophenyl)-2-propyn-1-ol as a colorless solid: mp 79-80 °C (lit mp 80.5-81.5 °C[15]); ^1H NMR ($CDCl_3$, 300 MHz) δ 7.39 (d, 2H, J = 8.5 Hz, H3), 7.25 (d, 2H, J = 8.5 Hz, H2), 4.49 (s, 2H,

CH_2OH), 1.81(br s, 1H, OH);[15] ^{13}C NMR ($CDCl_3$, 125 MHz) δ 122.8, 121.4, 88.3, 84.6 (quaternaries), 133.1, 131.6 (CH, double signal), 51.6 (CH_2).

To a solution of 3-(4-bromophenyl)-2-propyn-1-ol (7.0 g, 33. 2 mmol), DMF (25.0 mL) and imidazole (11.3 g, 166.0 mmol) was added *t*-butyldimethylsilyl chloride (10.0 g, 66.4 mmol) and the resulting reaction mixture was stirred at room temperature for 24 hr after which time it was concentrated under reduced pressure to remove the DMF. The residue was diluted with CH_2Cl_2 (200 mL) and the organic layer was washed with sat. $NaHCO_3$, brine, dried over $MgSO_4$ and concentrated. Purification by flash chromatography on silica gel eluting with hexane/ethyl acetate (9:1) afforded 10.7 g (99%) of the silyl ether **9** as a colorless solid: mp 25-26 °C; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.42 (d, 2H, J = 8.8 Hz, H3), 7.25 (d, 2H, J = 8.8 Hz, H2), 4.50 (s, 2H, CH_2OSi), 0.93 (s, 9H, $(CH_3)_3C$), 0.16 (s, 6H, $2CH_3$); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 122.4, 121.8, 89.0, 83.7, 18.2 (quaternaries), 132.9, 131.5 (CH, double signal), 52.1 (CH_2), -5.1 (CH_3, double signal), 25.8 (CH_3, triple signal); MS (EI, *m/z*) 269, 267 (M^+-57), 239, 237. Anal. Calcd for $C_{15}H_{21}BrOSi$ (325.32): C, 55.38; H, 6.51. Found: C, 55.32; H, 6.67. IR (thin film) ν_{max}: 2959, 2930, 2860, 2240, 1489, 1472, 1368, 1250, 1095, 1010, 838, 821 cm^{-1}.

Methyl-3-{3-[4-(3-*t*-butyldimethylsilylether-1-propynyl)phenoxy]-4-methoxyphenyl} propionate (10). A 3-neck round bottom flask equipped with a reflux condenser and stir bar was vigorously flushed with Ar for 5 min and alkyne **9** (3.22 g, 9.90 mmol), hydroxy ester **6** (1.73 g, 8.22 mmol), pyridine (20.0 mL) and anhydrous potassium carbonate (2.39 g, 17.33 mmol) were combined. CuO (1.64 g, 20.62 mmol) was added in one portion to the mixture, the reaction again was flushed with Ar, and the resulting black slurry was heated to reflux in a sand bath (135 °C) with vigorous stirring under a positive flow of Ar for 12 hr. After this time, the brown residue was diluted with CH_2Cl_2 (150 mL) and filtered through a pad of celite. The solid material was washed repeatedly with CH_2Cl_2 (4 x 50 mL) and the combined filtrates were extracted with 1N HCl, brine, dried over $MgSO_4$ and concentrated to yield a brown oil. Purification by flash chromatography eluting with hexane/ethyl acetate (85:15) led to the isolation of 2.59 g (74%) biaryl ether **10** as a colorless viscous oil: ^1H NMR ($CDCl_3$, 300 MHz) δ 7.33 (d, 2H, J = 8.8 Hz, C3'-H and C5'-H), 6.94 (dd, 1H, J = 8.3, 2.1 Hz,

C5-H), 6.88 (d, 1H, J = 8.3 Hz, C6-H), 6.82 (d, 1H, J = 2.1 Hz, C3-H), 6.79 (d, 2H, J = 8.8 Hz, C2' and C6'-H), 4.50 (s, 2H, CH_2OSi), 3.74 (s, 3H, OCH_3), 3.61 (s, 3H, CO_2CH_3), 2.83 (t, 2H, J = 7.8 Hz, $ArCH_2$), 2.54 (t, 3H, J = 7.8 Hz, CH_2CO_2Me), 0.91(s, 9H, $C(CH_3)_3$), 0.14 (s, 6H, $Si(CH_3)_2$); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 173.0, 158.1, 149.9, 143.8, 133.5, 116.6, 86.8, 84.4, 18.2 (quaternaries), 124.9, 121.5, 112.9 (CH), 132.9, 116.4 (CH, double signal), 52.2, 35.6, 29.9, (CH_2), 55.9, 51.5 (CH_3), -5.1 (CH_3, double signal), 25.8 (CH_3, triple signal); MS (EI, m/z) 454 (M^+), 397, 355, 323. Anal. Calcd for $C_{26}H_{34}O_5Si$ (454.64): C, 68.69; H, 7.54. Found: C, 68.58; H, 7.57. IR (thin film) ν_{max}: 2960, 2940, 2860, 2260(C≡C), 1735, 1610, 1585, 1515, 1510, 1270, 1230, 1090, 835, 780 cm^{-1}.

Methyl (*Z*)-3-{3-[4-(3-*t*-butyldimethylsilyloxy-1-propenyl)phenoxy]-4-methoxyphenyl} propionate (11). A stirred solution of alkyne **10** (0.60 g, 1.32 mmol), PhH (10.80 mL), and quinoline (0.25 mL) was evacuated and flushed with Ar several times. Lindlar catalyst (0.11 g) was added in one portion and the resulting slurry was evacuated and flushed with Ar several more times. After the last evacuation, the reaction mixture was placed under hydrogen gas at atmospheric pressure and stirred at room temperature for 3 hr. The mixture was filtered through a pad of celite and the filtrate concentrated under reduced pressure to yield a yellow oil. Flash chromatography on silica gel eluting with hexane/ethyl acetate (85:15) afforded 0.54 g (91%) of *cis*--alkene **11** as a colorless oil : ^1H NMR ($CDCl_3$, 300 MHz) δ 7.12 (d, 2H, J = 8.8 Hz, C3'-H and C5'-H), 6.94 (dd, 1H, J = 8.3, 2.1 Hz, C5-H), 6.88 (d, 1H, J = 8.3 Hz, C6-H), 6.82 (d, 1H, J = 2.1 Hz, C3-H), 6.79 (d, 2H, J = 8.8 Hz, C2' and C6'-H), 6.43 (d, 1H, J = 11.8 Hz, CH=$CHCH_2OH$), 5.76 (dt, 1H, J = 11.8, 6.1, CH=$CHCH_2OH$)), 4.44 (dd, 2H, J = 6.1, 1.5 Hz, CH_2OSi), 3.79 (s, 3H, OCH_3), 3.63 (s, 3H, CO_2CH_3), 2.86 (t, 2H, J = 7.8 Hz, $ArCH_2$), 2.57 (t, 3H, J = 7.8 Hz, CH_2CO_2Me), 0.90(s, 9H, $C(CH_3)_3$), 0.06 (s, 6H, $Si(CH_3)_2$); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 173.0, 157.0, 149.8, 144.6, 133.5, 131.2, 18.2 (quaternaries), 131.4, 128.9, 124.5, 121.1, 112.9 (CH), 130.0, 116.6 (CH, double signal), 60.3, 35.7, 30.0, (CH_2), 56.0, 51.5 (CH_3), -5.2 (CH_3, double signal), 25.9 (CH_3, triple signal); MS (EI, m/z) 456 (M^+), 399, 251. Anal. Calcd for $C_{26}H_{36}O_5Si$ (456.65): C, 68.39; H, 7.95. Found: C, 68.15; H, 7.87. IR (thin film) ν_{max}: 2953, 2930, 2856, 1740, 1604, 1581, 1463, 1440, 1361, 1294, 1032, 841, 814 cm^{-1}.

Methyl (Z)-3-{3-[4-(3-hydroxy-1-propenyl)phenoxy]-4-methoxyphenyl} propionate (12). To a solution of the silyl ether **11** (1.15 g, 2.52 mmol) in THF (3 mL) at 0 °C was added TBAF (2.03 g, 7.75 mmol) and the reaction mixture was stirred at 0 °C for 5 min. The reaction was allowed to warm to room temperature and stirred at ambient temperature for 2 hr after which time it was diluted with CH_2Cl_2 (150 mL) and the organic layer was washed with H_2O, 1N HCl, brine, dried over Na_2SO_4 and concentrated. Purification by flash chromatography on silica gel eluting with hexane/ethyl acetate (1:1) yielded 0.81 g (94%) alcohol **12** as a colorless oil: ^1H NMR ($CDCl_3$, 300 MHz) δ 7.12 (d, 2H, J = 8.8 Hz, C3'-H and C5'-H), 6.94 (dd, 1H, J = 8.3, 2.1 Hz, C5-H), 6.88 (d, 1H, J = 8.3 Hz, C6-H), 6.82 (d, 1H, J = 2.1 Hz, C3-H), 6.81 (d, 2H, J = 8.8 Hz, C2' and C6'-H), 6.47 (d, 1H, J = 11.8 Hz, C*H*=CHCH$_2$OH), 5.78 (dt, 1H, J = 11.8, 6.1 Hz, CH=C*H*CH$_2$OH), 4.40 (app d, 2H, J = 6.1 Hz, C*H*$_2$OH), 3.78 (s, 3H, OC*H*$_3$), 3.62 (s, 3H, CO_2CH_3), 2.86 (t, 2H, J = 7.8 Hz, ArC*H*$_2$), 2.57 (t, 3H, J = 7.8 Hz, C*H*$_2$CO$_2$Me), 2.21 (br s, 1H, CH$_2$O*H*); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 173.1, 157.1, 149.8, 144.4, 133.5, 130.8, (quaternaries), 130.2, 130.0, 124.5, 121.1, 112.9 (CH), 129.95, 116.6 (CH, double signal), 59.5, 35.6, 29.9 (CH_2), 56.0, 51.5 (CH_3); Anal. Calcd for $C_{20}H_{22}O_5$ (342.391): C, 70.16; H, 6.48. Found: C, 69.98; H, 6.22. IR (thin film) ν_{max}: 3440, 3022, 2951, 1735, 1603, 1581, 1440, 1365, 1169, 1028, 841, 814 cm^{-1}.

(Z)-3-{3-[4-(3-hydroxy-1-propenyl)phenoxy]-4-methoxyphenyl} propanoic acid (3). To a solution of the methyl ester **12** (0.79 g, 2.31 mmol) in MeOH (7.0 mL) and H_2O (4.0 mL) at 0 °C was added solid KOH (2.80 g, 49.90 mmol) and the resulting colorless solution was stirred at 0 °C for 10 min and at room temperature for an additional 0.5 h. The reaction mixture was then cooled in an ice bath, diluted with H_2O (10 mL) and acidified to pH 2 by the dropwise addition of concentrated HCl. The aqueous phase was extracted with CH_2Cl_2 (2 x 100 mL) and the combined organic extracts were washed with sat. NaCl, dried over Na_2SO_4 and concentrated under reduced pressure to yield 0.74 g (98%) of pure hydroxy acid **3** as colorless solid: mp 95 °C (dec); ^1H NMR ($CDCl_3$, 300 MHz) δ 7.15 (d, 2H, J = 8.8 Hz, C3'- Hand C5'-H), 6.94 (dd, 1H, J = 8.3, 2.1 Hz, C5-H), 6.88 (d, 1H, J = 8.3 Hz, C6-H), 6.82 (d, 1H, J = 2.1 Hz, C3-H), 6.81 (d, 2H, J = 8.8 Hz, C2' and C6'-H), 6.52 (d, 1H J = 11.8 Hz, C*H*=C*H*CH$_2$OH), 5.78 (dt, 1H, J = 11.8, 6.1 Hz, CH=C*H*CH$_2$OH), 4.43 (dd, 2H, J = 6.1, 1.6 Hz, C*H*$_2$OH), 3.81 (s,

3H, OCH_3), 2.86 (t, 2H, J = 7.8 Hz, $ArCH_2$), 2.61 (t, 3H, J = 7.8 Hz, CH_2CO_2H); ^{13}C NMR (CDCl3 125 MHz) δ 174.6, 157.2, 149.5, 142.9, 135.7, 130.6, (quaternaries), 132.6, 127.9, 125.4, 122.0, 113.4 (CH), 130.2, 115.6 (CH, double signal), 58.3, 38.5, 30.7 (CH_2), 55.8 (CH_3). Anal. Calcd for $C_{19}H_{20}O_5$ (328.364): C, 69.50; H, 6.14. Found: C, 69.57; H, 5.98. IR (KBr) ν_{max}: 3306 (br), 2932, 2860, 1610, 1602, 1569, 1585, 1515, 1440, 1273, 1222, 1169, 1124, 125, 840, 819 cm^{-1}.

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