A new approach to combretastatin D_2†

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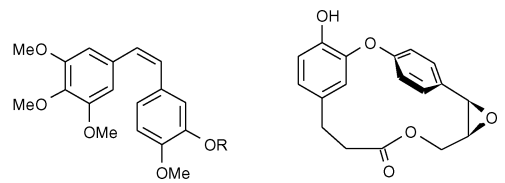
A concise and convergent route to combretastatin D_2 is described together with some preliminary biological data.

Introduction

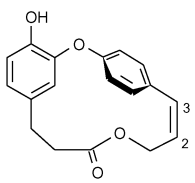
Shrubs and trees of the *Combretaceae* family are much used in Africa and India as a source of medicinal products, and the constituent combretastatins have been extensively studied as potential drugs.[1] Of these, combretastatin A_4 (**1a**) and its phosphate ester (**1b**) have shown particular promise as potential anti-cancer agents. The latter is currently undergoing phase II clinical trials as an inhibitor of angiogenesis.[2]

All of the combretastatins are acyclic with the exception of combretastatins D_1 (**2**) and D_2 (**3**) and the recently described combretastatins D_3 (**4**) and D_4 (**5**).[3] Several syntheses of D_1 and D_2 have been described[4] but none of the routes was efficient, and only one cytotoxicity study has been reported (using mouse leukaemia P388) which showed modest activity (ED_{50} 3–5 μg ml^{-1}) for these compounds.[5] Our interest in the design and synthesis of angiogenesis inhibitors prompted us to design a new, convergent route to this class of compounds with a view to further study of the biological properties of both the natural products and their analogues.

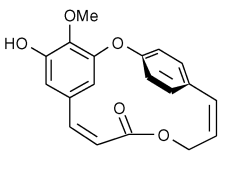


1a R=H Combretastatin A4
1b R=PO_3Na_2 Combretastatin A4 phosphate

2 Combretastatin D1



3 Combretastatin D2
5 2/3=alkane Combretastatin D4



4 Combretastatin D3

Structures of some combretastatins.

Results and discussion

Our synthetic route is shown in Scheme 1 and uses a copper-catalysed coupling of the phenol (**6**) and boronic acid (**7**) to provide the key ether linkage of combretastatin D_2. The phenol (**6**) was synthesised from 3-hydroxy-4-methoxybenzaldehyde by means of a Wittig reaction with carbomethoxymethylidene triphenylphosphorane, with subsequent catalytic transfer hydrogenation of the resultant alkene (85% overall). In a parallel synthesis, the ethylene ketal of 4-bromobenzaldehyde was converted into the aryl lithium and then reacted with triisopropyl borate followed by acid hydrolysis (70–75% overall). The coupling was accomplished using a modification of the method of Evans *et al.*[6] using copper(II) acetate to provide the required diaryl ether (**8**). This reaction was somewhat capricious with yields ranging from 32–81% but could be optimised to around 70% on the multigram scale. Transesterification using allyl alcohol and dibutyltin oxide[7] produced the allyl ester (**9**) in excellent yield (88–95%), and this was reduced to the alcohol (**10**) using $NaBH_4$ and then converted into the bromide (**11**) using CBr_4 and Ph_3P (overall yield 60%). Ozonolysis followed by cleavage of the ozonide (Me_2S) yielded aldehyde (**12**) (*ca.* 60–70% crude) which could be converted into the phosphonium salt (**13**) over a period of 2 days (quantitative yield). This participated in an intramolecular Wittig reaction following treatment with potassium carbonate in dichloromethane containing 18-crown-6. The yield of the methyl ether of combretastatin D_2 (**14**) was only 30% and has not yet been optimised, although a large number of other bases, solvents and reaction conditions have been investigated (Table 1). Stronger bases than potassium carbonate invariably caused hydrolysis of the ester group. Since compound (**14**) has been converted into combretastatin D_2 by Boger *et al.* (using BI_3 and dimethylaniline in benzene),[4] this constitutes a formal total synthesis of the natural product. However, our approach is both shorter and more efficient than the other published routes, and should allow access to a range of analogues for biological evaluation.

Interestingly, in the product mixture from the Wittig reaction the *trans*-alkene (**15**) could be seen, though this isomerised to the *cis*-alkene during silica chromatography (isomerisation was also effected using light). This isomer has never been reported before and both alkenes exhibited interesting ^1H NMR signals for the aryl hydrogen β to the methoxy group. For the *cis*-alkene this resonated at 5.11 ppm while for the *trans*-isomer it appeared at 4.59 ppm, providing evidence in both cases of significant diamagnetic shielding by the aromatic ring current

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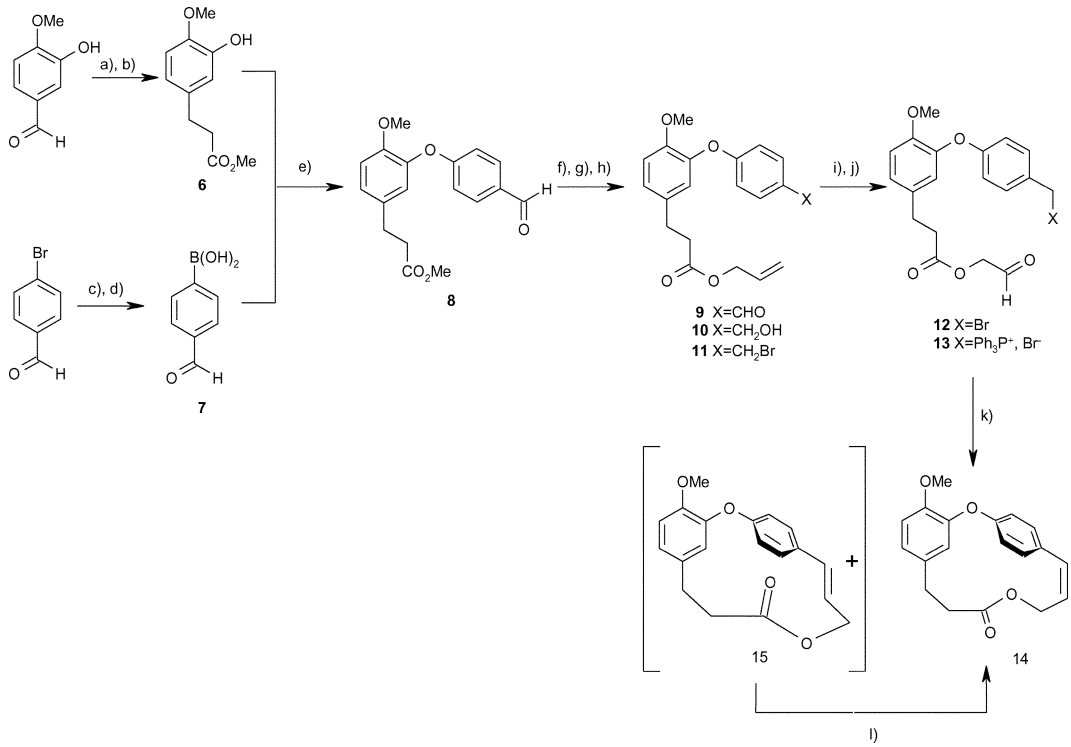
† This paper is dedicated to Professor Steve Ley on the occasion of his 60th birthday.

Table 1 Selected conditions screened for the intramolecular Wittig reactions

X	Solvent	Base	C/mM	T/°C	Yield (for 3 steps)
$O{=}P(OMe)_2$	DME	*t*BuOK	2	0 to 20	Decomp.
$O{=}P(OMe)_2$	DME	NaH	2	0 to 20	Decomp.
Ph_3P^+, Cl^-	DMF	*t*BuOK	2	0 to 20	<10%
Ph_3P^+, Br^-	DCM	K_2CO_3/18-C-6	2	20	31%[a]
Ph_3P^+, Br^-	DCM	K_2CO_3/18-C-6	5	20	29%[b]
Ph_3P^+, Br^-	DCM	K_2CO_3/18-C-6	10	20	26%[b]
Ph_3P^+, Br^-	DCM	DBU	2	0 to 20	<10%[a]
Ph_3P^+, Br^-	THF–DCM	NaHMDS	2.5	0 to 20	15%[a]
Ph_3P^+, Br^-	THF–DCM	Amberlite	2.5	20	17%[a]
Ph_3P^+, Br^-	DCM–H_2O	Sat. K_2CO_3	10	Reflux	0%

[a] After isomerisation on silica gel. [b] After irradiation.



Scheme 1 Synthesis of combretastatin D_2 methyl ether *via* intramolecular Wittig reaction. (a) $Ph_3P{=}CHCO_2Me$, DCM, r.t., overnight, 95%, (b) HCO_2NH_4, 10% Pd/C, MeOH, reflux 3 h, 91%, (c) ethylene glycol, $PhCH_3$, *p*TsOH, 18 h, 75–89%, (d) i) *n*BuLi, THF, $B(OiPr)_3$, −78 °C to r.t. overnight, ii) 3 N HCl, THF, 2 h, r.t., 70–75% overall, (e) Et_3N, $Cu(OAc)_2$, DCM, 4A molecular sieves, r.t., 18 h, 55–70%, (f) allyl alcohol, Bu_2SnO, reflux, 20 h, 88–95%, (g) $NaBH_4$, MeOH, r.t., 3 h, 65%, (h) CBr_4, PPh_3, DCM, r.t, 3 h, 85–90%, (i) O_3, DCM, −78 °C, then Me_2S, DCM, −78 °C to r.t., 4 h, (j) PPh_3, MeCN, r.t., 2 d, (k) K_2CO_3–18-C-6, DCM, slow addition, 20 °C, overnight, 26–31% from **11**, (l) light, CCl_4–$CHCl_3$, overnight, quantitative.

(Figs. 1 and 2). An X-ray crystal structure of compound (**14**) confirmed the relationship of the β-hydrogen to the aromatic ring (Fig. 3)‡.

An alternative approach to (**14**) is shown in Scheme 2 and involved an attempted ring-closing metathesis reaction. The aldehydo-ester (**8**) was converted into the styrene (**16**) *via* a Wittig reaction (80–87%), and transesterification as before with allyl alcohol produced the diene (**17**) (85–95%). Attempted RCM reactions with Grubbs' catalyst I under a variety of conditions (Table 2) provided no products, while reaction with Grubbs' catalyst II yielded the dimeric product (**18**). The best conditions employed 20% of catalysts in toluene at 80 °C with a 75% conversion and 40% yield of the dimer. To date, other metathesis catalysts (*e.g.* Schrock catalyst) have not been tried.

‡ Crystal data for $C_{19}H_{18}O_4$: the crystals are small and show very weak diffraction and hence a low ratio of observed reflections (approx. 25%). However, we were able to establish the atomic connectivity from this crystal. $M = 310.33$, orthorhombic, space group *Pbca*, $a = 13.47(5)$ Å, $b = 10.86(4)$ Å, $c = 21.40(10)$ Å, $U = 3132(22)$ Å^3, $Z = 8$, $\mu = 0.092$ mm^{-1}. A total of 5614 reflections were measured for the angle range $2 < 2\theta < 45$ and 2022 independent reflections were used in the refinement. The final parameters were $wR2 = 0.2935$ and $R1 = 0.1041$ [$I > 2\sigma I$]. CCDC reference number 283472. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b513515j

Biological evaluation

Compound (**14**) was evaluated for antiproliferative activity against MCF-7 human breast carcinoma, RKO human colon carcinoma

Table 2 Selected conditions for the RCM

Solvent (%cat.)	C/mM	T/°C	t	Conversion (%)[a]
DCM (I, 6%)	5	50	20 h	0
DCM (I, 10% + 50% $Ti(OiPr)_4$)	5	50	3 d	80% (decomp.)
Toluene (I, 20% + 30% $Ti(OiPr)_4$)	5	80	3 d	45% (decomp.)
DCM (II, 5%)	5	50	2 d	0
DCE (II, 10%)	5	90	2 d	<10
Toluene (II, 10%)	5	80	3 d	60
Toluene (II, 20%)	5	80	2 d	75 (40% yield)[b]
Toluene (II, 10%)	0.5	110	1 h	0
Toluene (II, 10%)	2	80	2 d	<15
Toluene (II, 10%)	7.5	80	2 d	37
Toluene (II, 10%)	10	80	2 d	40

[a] Conversion determined by analysis of the NMR spectrum of the crude mixture. [b] Isolated yield.

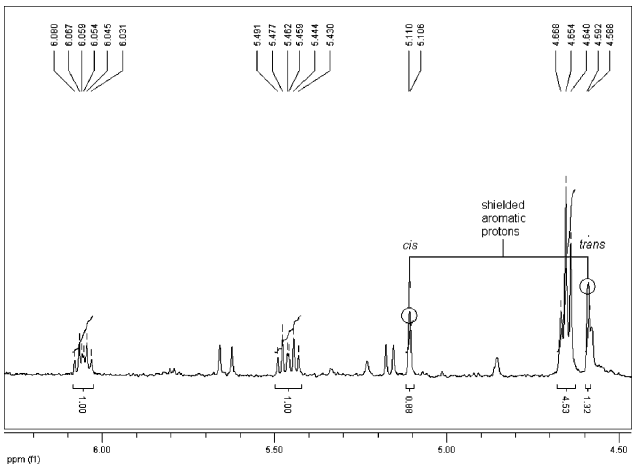


Fig. 1 NMR spectrum of the *cis–trans* mixture obtained after attempted isolation of the *trans*-isomer on neutralized silica gel.

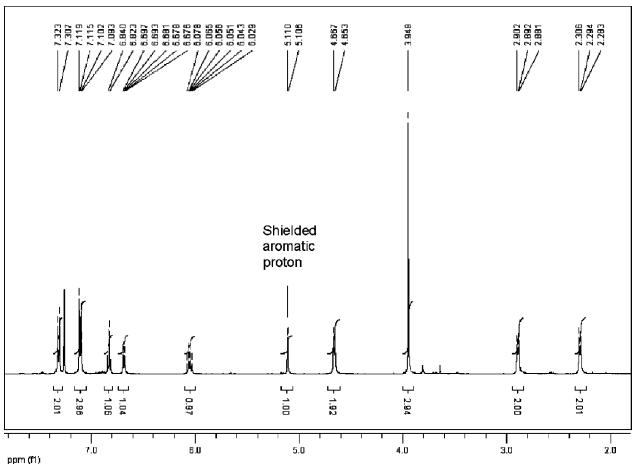


Fig. 2 NMR spectrum of combretastatin D_2 methyl ether.

and CRL 1730 human umbilical endothelial cells. It exhibited activity in all the cell lines at around 5–10 μM (IC_{50} values, see Figs. 4–6). No comparable data is available for (**14**) or combretastatin D_2 using these cell lines. The other products produced in this work have not yet been evaluated.

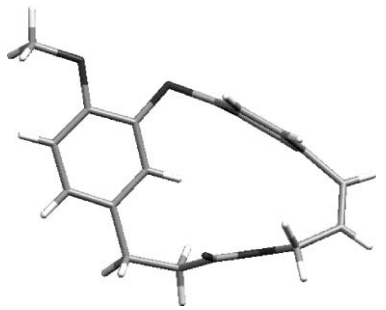
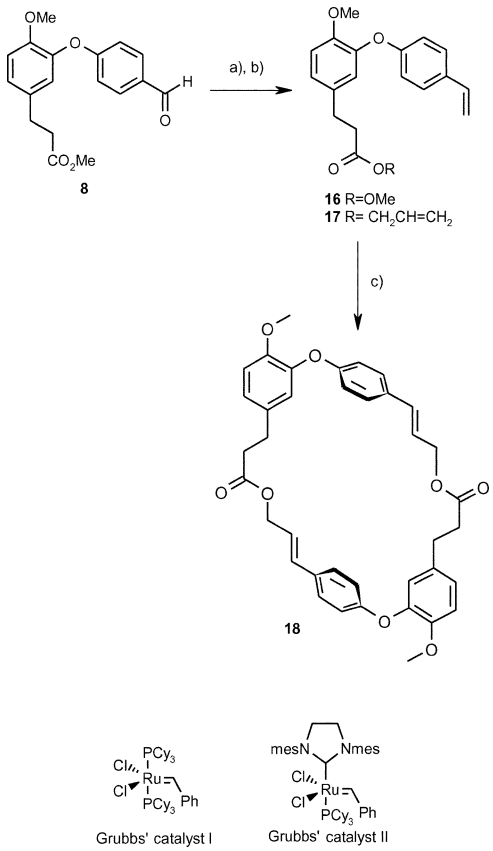


Fig. 3 X-Ray structure of combretastatin D_2 methyl ether.



Scheme 2 Attempted synthesis of combretastatin D_2 methyl ether *via* ring-closing metathesis. a) $Ph_3P^+CH_3$, Br^-, NaHMDS, THF, 0 °C to r.t., 20 h, 80–87%, b) allyl alcohol, Bu_2SnO, reflux, 20 h, 85–95%, c) Grubbs' catalyst II, toluene, 80 °C, 30–75% conversion, 30–40% yield.

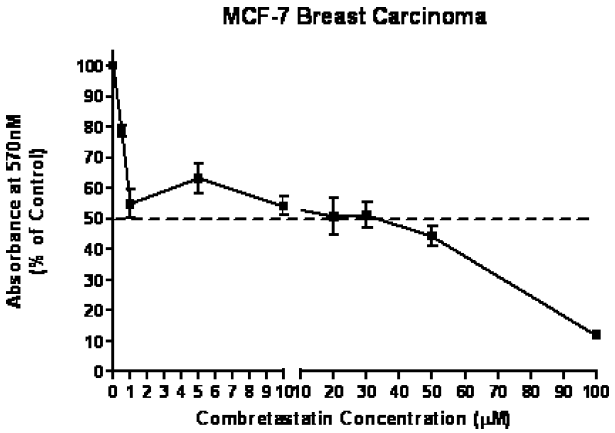


Fig. 4 Antiproliferative activity of combretastatin D_2 methyl ether against MCF-7 breast cancer cells.

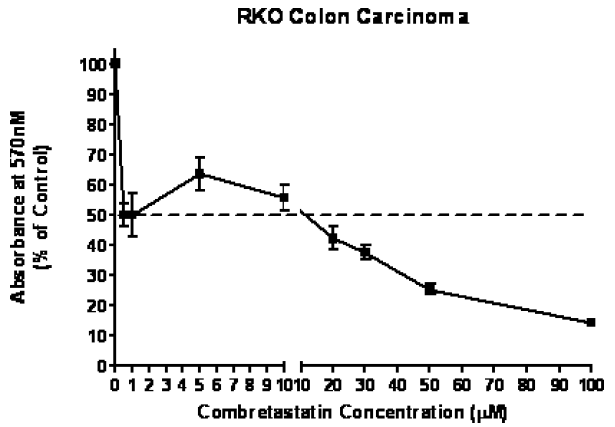


Fig. 5 Antiproliferative activity of combretastatin D_2 methyl ether against RKO colon cancer cells.

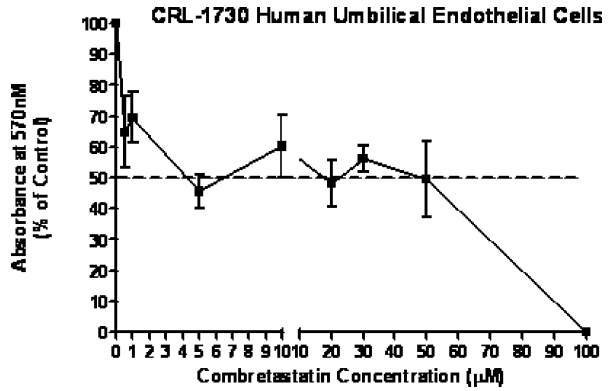


Fig. 6 Antiproliferative activity of combretastatin D_2 methyl ether against human endothelial cells.

Experimental

In vitro drug sensitivity as determined by MTT dye-exclusion assay

In vitro drug sensitivity was determined as previously described.[8] Combretastatin was dissolved in dimethyl sulfoxide (DMSO) to yield a stock solution of 10 mM. The fraction of viable cells remaining after drug treatment was determined by the ability of the cells to metabolise the water-soluble tetrazolium salt, 3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyltetrazolium bromide (MTT), into a water insoluble formazan precipitate. Exponentially growing cells (MCF-7 human breast carcinoma, RKO human colon carcinoma and CRL 1730 human umbilical endothelial cells) were seeded 24 hours prior to treatment into sterile flat-bottomed 96 well plates, at varied seeding densities determined by their growth characteristics. Cells were exposed to combretastatin (0.5–100 μM) for 96 hours. MTT (50 μl of a 2 mg ml^{-1} solution) was then added to each well. The plates were incubated for a further four hours and then the medium and any unconverted MTT was aspirated from the wells. The remaining formazan precipitate was dissolved in 100 μl DMSO and the absorbance read at 570 nm using a Molecular Devices plate reader. IC_{50} values (compound concentration that produces a 50% reduction in the growth of the cells) were determined from plots of absorbance *vs.* drug concentration.

General experimental procedures

All solvents were dried before use. Acetonitrile, dichloromethane and methanol were either distilled from calcium hydride under nitrogen or argon or used after drying on a high pressure alumina column device (MBRAUN). Tetrahydrofuran was either dried by distillation in the presence of sodium and benzophenone or used after drying on a high pressure alumina column device (MBRAUN). Dry DMF was purchased from Aldrich. Thin layer chromatography was used to monitor reactions using Polygram® SIL G/UV254 precoated plastic sheets with a 0.2 mm layer of silica gel containing fluorescent indicator UV254. Plates were visualised using a 254 nm UV lamp and potassium permanganate stain. Flash column chromatography was carried out using Sorbsil® (or Fluorochem®) C60 silica gel (40–60 mesh) with the eluent or the gradient of eluents reported. NMR spectra were recorded using Bruker Avance300 or Bruker DRX500 spectrometers. Samples were dissolved in $CDCl_3$ with tetramethylsilane as a reference. IR spectra were recorded using a Perkin-Elmer RXI FT-IR system spectrometer. Mass spectra were recorded on a VG Autospec spectrometer and were carried out by ASEP (Queen's University of Belfast). Elemental analyses were carried out by ASEP (Queen's University of Belfast). Melting points were recorded on a Stuart melting point apparatus and are uncorrected.

X-Ray crystallography

X-Ray crystallographic data for combretastatin D_2 methyl ether were collected using a Bruker SMART diffractometer with graphite monochromated Mo–K_α radiation. Data were collected at low temperature, *ca.* 153 K. Omega/phi scans were employed for data collection and absorption, Lorentz and polarisation corrections were applied.

The structure was solved by direct methods and ordered non-hydrogen atoms were refined with anisotropic atomic displacement parameters. Hydrogen-atom positions were added, and idealised positions and a riding model with fixed thermal parameters ($U_{ij} = 1.2U_{eq}$ for the atom to which they are bonded (1.5 for CH_3)), was used for subsequent refinements. The function minimised for $wR2$ was $\Sigma[w(|F_o|^2 - |F_c|^2)]$ with reflection weights $w^{-1} = [\sigma^2 |F_o|^2 + (g_1P)^2 + g_2P]$ where $P = [\max |F_o|^2 + 2|F_c|^2]/3$ for all F^2 and the function minimised for $R1$ was $\Sigma[w(|F_o| - |F_c|)]$. The

SAINT[9] and SHELXTL[10] packages were used for data collection, reduction, structure solution and refinement. Additional material available from the Cambridge Structural Database includes atomic co-ordinates, thermal parameters, remaining bond lengths and angles, and structure factors (CCDC no. 283472)‡.

Synthesis of 3-(3-hydroxy-4-methoxyphenyl)-acrylic acid methyl ester *cis* and *trans*. Carbomethoxymethylidene triphenylphosphorane (12.09 g, 36.1 mmol, 1.1 eq.) was added to a solution of isovanillin (5 g, 32.9 mmol) in DCM (110 mL) under argon, and the mixture was stirred at room temperature for 20 h, then refluxed for 2 h. The solvent was removed under vacuum and the crude product was purified by flash chromatography (EtOAc–P.E., 4 : 6). The *cis*- and *trans*-isomers were not separated and 6.94 g (quantitative) of a pale yellow solid were obtained. *R*f: 0.62 (*trans*), 0.73 (*cis*) (EtOAc–P.E., 4 : 6); ν_{max}/cm^{-1}: 3420 (OH), 1700 (C=O), 1511 (C=C), 1267 (C–O–C), 1162 (C–O–C); mp: 74–76 °C (lit.[11] 72.4 °C); ^{1}H NMR δ_H ($CDCl_3$): 3.68 (0.82H, s, OMe-*cis*), 3.79 (3H, s, OMe-*trans*), 3.91 (0.82H, s, OMe-*cis*), 3.92 (3H, s, OMe-*trans*), 5.63 (0.28H, s, OH-*cis*), 5.72 (1H, s, OH), 5.26–5.32 (d, 2H, $H_{3'}$, $J_{trans} = 18$ Hz), 5.79–5.86 (1.61H, dm, $H_{5'}$-*trans* + Ar-*cis* + H_2-*cis*, $J_o = 9$ Hz), 7.01–7.04 (1H, dd, $H_{6'}$, $J = 2.1$ Hz, $J_o = 9$ Hz), 7.13–7.14 (1H, d, $H_{2'}$, $J_m = 2.1$), 7.22–7.25 (dd, Ar-*cis*), 7.32 (0.28, d, $J_m = 1.8$), 7.57–7.63 (1H, d, H_2, $J_{trans} = 18$ Hz); ^{13}C NMR δ_C ($CDCl_3$): 168 (C=O), 149 ($C_{4'}$), 146 (C_3), 145 ($C_{3'}$), 129 ($C_{1'}$), 122 ($C_{6'}$), 116 (C_2), 113 ($C_{2'}$), 111 ($C_{5'}$), 56 (OMe), 52 (CO_2Me); *m*/*z* (EIMS): 208 (M^+, 100), 193 (13), 177 (52), 149 (11), 133 (20), 117 (11), 105 (12), 89 (17), 78 (14); mass found 208.073877, $C_{11}H_{12}O_4$ requires 208.073559; found: C: 63.98, H: 5.66, $C_{11}H_{12}O_4$ requires C: 63.45, H: 5.81, O: 30.74%.

Synthesis of 3-(3-hydroxy-4-methoxyphenyl)-propionic acid methyl ester (6). Pd/C (200 mg, 10% of the weight of the olefin) and ammonium formate (6.06 g, 96 mmol, 10 eq.) were added to a solution of the alkene (2 g, 9.61 mmol) in methanol (50 mL). The mixture was refluxed under nitrogen for 3 h. The cooled reaction mixture was filtered over Celite and the methanol was removed under vacuum. Chloroform (20 mL) was added to precipitate the excess of ammonium formate, which was removed by filtration. After removal of the solvent and short purification by flash chromatography (EtOAc–P.E., 4 : 6), 1.81 g (90%) of a white crystalline solid were obtained. *R*f: 0.47 (EtOAc–P.E., 3 : 7); ν_{max}/cm^{-1}: 1733 (C=O), 1506 (Ar), 1127 (C–O–C); mp: 96–97 °C (lit.[12]: 94–95 °C); ^{1}H NMR δ_H ($CDCl_3$): 2.57–2.62 (t, 2H, H_3, $J =$ 8.1 Hz), 2.83–2.89 (t, 2H, H_2, $J = 8.1$), 3.67 (s, 3H, OMe), 3.86 (s, 3H, OMe), 5.58 (s, 1H, OH), 6.66–6.69 (dd, 1H, $H_{6'}$, $J_m = 1.9$ $J_o = 8.2$), 6.76–6.78 (m, 2H, $H_{2'}$ and $H_{5'}$); ^{13}C NMR δ_C ($CDCl_3$): 174 (C=O), 146 ($C_{4'}$), 145 ($C_{3'}$), 134 ($C_{1'}$), 120 ($C_{6'}$), 115 ($C_{5'}$), 111 ($C_{2'}$), 56 (OMe), 52 (OMe), 36 (C_2), 31 (C_3); *m*/*z* (EIMS): 211 ($M^+ + H^+$, 11), 210 (M^+, 63), 179 (9), 150 (34), 137 (100), 135 (20), 122 (9), 107 (14), 94 (9), 91 (14), 79 (11), 77 (13), 65 (10); mass found 210.088452, $C_{11}H_{14}O_4$ requires 210.089209; found C: 63.09, H: 6.62, $C_{11}H_{14}O_4$ requires C: 62.85, H: 6.71, O: 30.44%.

Synthesis of 2-(4-bromophenyl)-1,3-dioxolane. Ethylene glycol (1.2 mL, 21.6 mmol, 2eq.) and *p*-toluenesulfonic acid (catalytic amount) were dissolved in dry toluene (20 mL) under nitrogen in a Dean Stark apparatus. The mixture was vigorously refluxed for 1.5 h to remove the water from the ethylene glycol. Bromobenzaldehyde (2 g, 10.8 mmol) dissolved in toluene (10 mL) was added and the mixture was refluxed for 20 h. The cooled reaction mixture was quenched with saturated $NaHCO_3$ and the product was extracted with EtOAc (3 × 40 mL). The combined organic layers were washed with brine and dried with $MgSO_4$. The crude product was purified by flash chromatography (Et_2O–P.E., 1 : 9) and 2.209 g (89%) of a pale yellow solid were obtained. *R*f: 0.38 (P.E.–Et_2O, 9 : 1); mp: 37–38 °C (lit.[13]: 39–40 °C); ν_{max}/cm^{-1}: 2886 (C–H), 1595 (Ar), 1082 (C–O–C); ^{1}H NMR δ_H ($CDCl_3$): 4.00–4.03 (m, 2H, H_4 or H_5), 4.07–4.10 (2H, m, H_4 or H_5), 5.76 (s, 1H, H_2), 7.33–7.36 (d, 2H, $H_{2'}$ and $H_{6'}$, $J_o = 8.4$ Hz), 7.49–7.52 (dd, 2H, $H_{3'}$ and $H_{5'}$, $J_o = 8.4$ Hz, $J_m = 1.5$ Hz); ^{13}C NMR δ_C ($CDCl_3$): 137 ($C_{1'}$), 132 ($C_{3'}$ and $C_{5'}$), 129 ($C_{2'}$ and $C_{6'}$), 124 ($C_{4'}$), 103 (C_2), 66 (C_4 and C_5); *m*/*z* (EIMS): 229 (M^+(^{81}Br), 12), 227 (M^+(^{79}Br), 12), 203 (48), 201 (48), 185 (96), 183 (97), 157 (37), 155 (37), 76 (40), 74 (18); mass found 227.978709, $C_9H_9O_2Br$ requires 227.978591.

Synthesis of 4-formyl phenyl boronic acid (7). 2-(4-Bromophenyl)-1,3-dioxolane (3.89 g, 16.9 mmol) was dissolved in dry THF (55 mL) under nitrogen and cooled to −78 °C with a dry ice–acetone bath. *n*-Butyllithium (2.5 M in hexanes, 10.1 mL, 25.3 mmol, 1.5eq.) was added dropwise and the mixture was stirred at −78 °C for 45 min. Triisopropyl borate (11.7 mL, 50.6 mmol, 3eq.) was added dropwise and the mixture was allowed to heat slowly to room temperature and was stirred overnight. The reaction was quenched with 3 N HCl and was stirred at room temperature for 2 h. The crude product was extracted with ethyl acetate and the combined organic layers were washed with brine then dried with $MgSO_4$. The crude product was purified by flash chromatography (EtOAc–P.E., 5 : 5, then MeOH) and 1.63 g (64%) of a white solid were obtained. *R*f: 0.63 (EtOAc–P.E., 6 : 4); mp: 235–237 °C (lit.: 240[14] and 252 °C[15]); ν_{max}/cm^{-1}: 3210–3411 (OH), 2927–2846 (CHO), 1670 (CHO), 1507 (Ar), 1343 (B–O); ^{1}H NMR δ_H (DMSO): 7.92–7.94 (d, 2H, H_2 and H_6, $J_o = 7.8$ Hz), 8.03–8.06 (d, 2H, H_3 and H_5, $J_o = 7.8$ Hz), 8.40 (s, 2H, $B(OH)_2$), 10.09 (s, 1H, CHO); ^{13}C NMR δ_C (DMSO): 194 (C=O), 137 (C_4), 135 (C_3 and C_5), 129 (C_2 and C_6), 116 (C_1); *m*/*z* (EIMS): 150 (M^+, 25), 149 ($M^+ - H^+$, 64), 121 ($M^+ - H^+ - CO$, 100), 105 ($M^+ - B(OH)_2$, 16); mass found: 150.048187, $C_7H_7BO_3$ requires 150.048824; found C: 55.41, H: 4.68, $C_7H_7BO_3$ requires C: 56.07, H: 4.71, B: 7.21, O: 32.01%.

Synthesis of 3-[3-(4-formylphenoxy)-4-methoxyphenyl]-propionic acid methyl ester (8). The phenol (**6**) (984 mg, 4.68 mmol) was dissolved in dry DCM (25 mL) and powdered molecular sieves (6 g) were added. The boronic acid (**7**) (1.75 g, 11.7 mmol, 2.5 eq.), copper(II) acetate (935 mg, 5.15 mmol, 1.1 eq.) and triethylamine (3.26 mL, 23.4 mmol, 5 eq.) were successively added. The mixture was vigorously stirred at room temperature for 24 h under ambient atmosphere. The mixture was filtered over Celite and 5% Na_2EDTA was added. The organic layer was separated and washed with 1 N HCl. The aqueous layer was extracted with DCM. The combined organic layers were washed with brine and dried with $MgSO_4$. The crude product was purified by flash chromatography and 1.005 g (68%) of a pale cream solid were obtained. *R*f: 0.39 (EtOAc–P.E., 2 : 8); mp: 52–54 °C; ν_{max}/cm^{-1}: 2839–2852 (CHO), 1735 (CO_2Me), 1691 (CHO), 1512 (Ar), 1273–1230–1126 (C–O–C); ^{1}H NMR δ_H ($CDCl_3$): 2.59–2.64 (t, 2H, H_3, $J = 7.8$ Hz), 2.86–2.91 (t, 2H, H_2, $J = 7.8$ Hz), 3.66 (s, 3H, OMe), 3.76 (s, 3H, OMe), 6.94–6.99 (m, 4H, $H_{6'}$, $H_{2''}$, $H_{6''}$ and $H_{2'}$), 7.05–7.09 (dd, 1H, $H_{5'}$, $J_m = 2.1$ Hz, $J_o = 8.4$ Hz), 7.80–7.83 (dd, 2H,

$H_{3''}$ and $H_{5''}$, $J_m = 2.1$, $J_o = 7.2$ Hz), 9.90 (s, 1H, CHO); ^{13}C NMR δ_C ($CDCl_3$): 191 (CHO), 174 (C=O), 164 ($C_{1''}$), 150 ($C_{3'}$), 143 ($C_{4'}$), 134 ($C_{1'}$), 132 ($C_{3''}$ and $C_{5''}$), 131 ($C_{4''}$), 126 ($C_{5'}$), 123 ($C_{6'}$), 117 ($C_{2''}$ and $C_{6''}$), 113 ($C_{2'}$), 61 (OMe), 52 (OMe), 36 (C_2), 30 (C_3); *m/z* (CIMS): 333 ($M^+ + H^+ + NH_4^+$), 332 ($M^+ + NH_4^+$), 315 ($M^+ + H^+$), 314 (M^+), 241, 228, 210; mass found: 314.116638, $C_{18}H_{18}O_5$ requires 314.115424; found C: 68.47, H: 5.83, $C_{18}H_{18}O_5$ requires C: 68.78, H: 5.77, O: 25.45%.

Synthesis of allyl 3-[3-(4-formylphenoxy)-4-methoxyphenyl]-propanoate (9). The ester (**8**) (150 mg, 0.48 mmol) was dissolved in allyl alcohol (4 mL), and dibutyltin oxide (24 mg, 0.096 mmol, 0.2 eq.) was added. The mixture was refluxed for 20 h. Saturated Na_2CO_3 was added to the cooled reaction mixture and the aqueous layer was extracted with EtOAc. The combined organic layers were filtered over Celite and dried with $MgSO_4$. The solvents were evaporated under vacuum and the crude product was purified by flash chromatography (EtOAc–P.E., 3 : 7) to give 143 mg of a yellow oil. ν_{max}/cm^{-1}: 2832 (CHO), 1732 (CO_2Me), 1694 (CHO), 1600–1580 (C=C), 1512 (Ar), 1273–1230–1126 (C–O–C); ^{1}H NMR δ_H ($CDCl_3$): 2.59–2.64 (t, 2H, H_3, $J = 8.0$ Hz), 2.85–2.94 (t, 2H, H_2, $J = 7.9$ Hz), 3.77 (s, 3H, OMe), 4.55–4.60 (d, 2H, $CH_2C{=}C$, $J = 4.6$ Hz), 5.19–5.30 (m, 2H, $C{=}CH_2$), 5.83–5.87 (ddt, 1H, CH=C, $J_{cis} = 11.0$ Hz, $J_{trans} = 17.6$ Hz, $J = 4.6$ Hz), 6.94–7.06 (m, 5H, $H_{6'}$, $H_{2''}$, $H_{6''}$, $H_{2'}$ and $H_{5'}$), 7.80–7.84 (dd, 2H, $H_{3''}$ and $H_{5''}$), 9.93 (CHO); ^{13}C NMR δ_C ($CDCl_3$): 191 (CHO), 174 (C=O), 164 ($C_{1''}$), 150 ($C_{3'}$), 144 ($C_{4'}$), 134 ($C_{1'}$ and CH=C), 132 ($C_{3''}$ and $C_{5''}$), 131 ($C_{4''}$), 126 ($C_{5'}$), 123 ($C_{6'}$), 119 ($C{=}CH_2$), 117 ($C_{2''}$ and $C_{6''}$), 113 ($C_{2'}$), 66 ($CH_2C{=}C$), 56 (OMe), 36 (C_2), 30 (C_3); *m/z* (CIMS): 359 ($M^+ + H^+ + NH_4^+$, 22), 358 ($M^+ + NH_4^+$, 100), 342 (27), 341 ($M^+ + H^+$, 96); mass (calculated for $M + H^+$) found: 341.140213, $C_{20}H_{21}O_5$ requires 341.138899.

Synthesis of allyl 3-{3-[4-(hydroxymethyl)phenoxy]-4-methoxyphenyl}propanoate (10). Sodium borohydride (60 mg, 1.58 mmol, 2 eq.) was added to a solution of the aldehyde (**9**) (268 mg, 0.79 mmol) in MeOH (2.5 mL) at 0 °C and the resulting mixture was stirred at this temperature for 1.5 h. The reaction was quenched with 2 N HCl and the crude product was extracted with EtOAc. The combined organic extracts were washed with brine and dried over $MgSO_4$. The crude product was purified by flash chromatography (EtOAc–P.E., 4 : 6) and 106 mg (65% from ester **8**) of a colourless oil were obtained. *R*f: 0.42 (EtOAc–P.E., 4 : 6); ν_{max}/cm^{-1}: 3444 (br, OH), 1734 (CO_2Me), 1609 (C=C), 1507 (Ar), 1270–1225–1126 (C–O–C); ^{1}H NMR δ_H ($CDCl_3$): 2.60–2.65 (t, 2H, H_3, $J = 7.7$ Hz), 2.87–2.92 (t, 2H, H_2, $J = 7.7$ Hz), 3.84 (s, 3H, OMe), 4.57–4.59 (d, 2H, $CH_2C{=}C$, $J = 5.7$ Hz), 4.67 (s, 2H, CH_2OH), 5.22–5.33 (m, 2H, $C{=}CH_2$), 5.84–5.97 (ddt, 1H, CH=C, $J_{cis} = 11$ Hz, $J_{trans} = 17$ Hz, $J = 5.7$ Hz), 6.84 (d, 2H, $H_{2'}$, $J_m = 1.7$ Hz), 6.93–6.99 (m, 4H, $H_{6'}$, $H_{5'}$, $H_{2''}$, $H_{6''}$), 7.31–7.34 (d, 2H, $H_{3''}$ and $H_{5''}$, $J_o = 8.4$ Hz); ^{13}C NMR δ_C ($CDCl_3$): 173 (C=O), 158 ($C_{1''}$), 150 ($C_{3'}$), 145 ($C_{4'}$), 135 ($C_{1'}$), 134 ($C_{4''}$), 133 (CH=C), 129 ($C_{3''}$ and $C_{5''}$), 125 ($C_{5'}$), 121 ($C_{6'}$), 119 ($C{=}CH_2$), 118 ($C_{2''}$ and $C_{6''}$), 113 ($C_{2'}$), 66 (CH_2OH), 65 ($CH_2C{=}C$), 56 (OMe), 36 (C_2), 30 (C_3); *m/z* (EIMS): 342 (M^+, 100), 256 (15), 243 ($M^+ - CH_2{=}CHCH_2 - CO_2$, 58), 239 (39), 197 (11), 153 (14), 137 (26), 134 (17), 121 (13), 105 (17), 77 (25); mass found: 342.146004, $C_{20}H_{22}O_5$ requires 342.146724; found C: 69.56, H: 6.50, $C_{20}H_{22}O_5$ requires C: 70.16, H: 6.48, O: 23.36%.

Synthesis of allyl 3-{3-[4-(bromomethyl)phenoxy]-4-methoxyphenyl}propanoate (11). Triphenylphosphine (91 mg, 0.35 mmol, 1.2 eq.) was added in small portions to a solution of the benzylic alcohol (**10**) (100 mg, 0.29 mmol) and carbon tetrabromide (194 mg, 0.58 mmol, 2 eq.) in DCM (1.5 mL) at room temperature. The resulting mixture was stirred at room temperature for 2 h and the reaction was quenched with a saturated solution of $NaHCO_3$. The crude product was extracted with DCM and the combined organic extracts were washed with brine, then dried with $MgSO_4$. After evaporation of the solvent, the crude product was purified by flash chromatography (EtOAc–P.E., 3 : 7), and 147 mg (91%) of the bromide (**11**) were obtained. *R*f: 0.76 (EtOAc–P.E., 3 : 7); ν_{max}/cm^{-1}: 1735 (CO_2Me), 1607 (C=C), 1506 (Ar), 1272–1226–1168–1126 (C–O–C); ^{1}H NMR δ_H ($CDCl_3$): 2.61–2.67 (t, 2H, H_3, $J = 7.7$ Hz), 2.89–2.94 (t, 2H, H_2, $J = 7.7$ Hz), 3.83 (s, 3H, OMe), 4.53 (s, 2H, CH_2Br), 4.58–4.60 (d, 2H, $CH_2C{=}C$, $J = 5.8$ Hz), 5.23–5.33 (m, 2H, $C{=}CH_2$), 5.84–5.97 (ddt, 1H, CH=C, $J_{cis} = 11.0$ Hz, $J_{trans} = 17.0$ Hz, $J = 5.7$ Hz), 6.88–7.04 (m, 5H, $H_{2'}$, $H_{6'}$, $H_{5'}$, $H_{2''}$, $H_{6''}$), 7.33–7.36 (d, 2H, $H_{3''}$ and $H_{5''}$, $J_o = 8.54$ Hz); ^{13}C NMR δ_C ($CDCl_3$): 173 (C=O), 159 ($C_{1''}$), 150 ($C_{3'}$), 145 ($C_{4'}$), 134 ($C_{1'}$), 133 ($C_{4''}$), 132 (CH=C), 131 ($C_{3''}$ and $C_{5''}$), 125 ($C_{5'}$), 122 ($C_{6'}$), 119 ($C{=}CH_2$), 117 ($C_{2''}$ and $C_{6''}$), 114 ($C_{2'}$), 66 ($CH_2C{=}C$), 57 (OMe), 36 (C_2), 34 (C_3), 30 (CH_2Br); *m/z* (EIMS): 406 ($M^+(^{81}Br)$, 8), 404 ($M^+(^{79}Br)$, 8), 336 ($M^+(^{81}Br) - CO_2CH_2CH{=}CH_2$, 9), 334 ($M^+(^{79}Br) - CO_2CH_2CH{=}CH_2$, 9), 325 ($M^+ - Br$, 76), 299 (26), 253 (98), 251 ($M^+ - Br - CO_2CH_2CH{=}CH_2$, 100), 249 (36), 211 (14), 172 (26), 149 (18), 91 (44), 79 (38); mass found: 404.060319, $C_{20}H_{21}BrO_4$ requires 404.062320.

Synthesis of 2-oxoethyl-3-{3-[4-(bromomethyl)phenoxy]-4-methoxyphenyl}propanoate (12). Ozone was bubbled through a solution of the benzylic bromide (**11**) (100 mg, 0.25 mmol) in DCM (15 mL) at −78 °C for 2 min. Nitrogen was bubbled through the resulting blue solution until the colour faded, and dimethyl sulfide (130 μL, 2.5 mmol, 10 eq.) was added. The mixture was stirred at −78 °C for 1 h, then at room temperature for 4 h. The volatiles were removed under vacuum and the aldehyde (**12**) (120 mg, 116% (DMSO)) was used without further purification for the next step. ν_{max}/cm^{-1}: 2919 (ArH), 1737 (CO_2Me + CHO), 1507 (Ar), 1272–1226–1168–1126–1027 (C–O–C); ^{1}H NMR δ_H ($CDCl_3$): 2.70–2.73 (t, 2H, H_3, $J = 7.6$ Hz), 2.90–2.93 (t, 2H, H_2, $J = 7.6$ Hz), 3.79 (s, 3H, OMe), 4.49 (s, 2H, CH_2Br), 4.63 (s, 2H, CH_2CHO), 6.85–6.87 (m, 3H, $H_{2'}$, $H_{2''}$, $H_{6''}$, $J = 8.5$ Hz), 6.89–6.93 (d, 1H, $H_{5'}$, $J = 8.3$ Hz), 6.99–7.00 (dd, 1H, $H_{6'}$, $J_o = 8.3$ Hz, $J_m = 1.94$ Hz), 7.30–7.31 (d, 2H, $H_{3''}$ and $H_{5''}$, $J_o = 8.5$ Hz), 9.54 (s, 1H, CHO); ^{13}C NMR δ_C ($CDCl_3$): 196 (CHO), 172 (C=O), 159 ($C_{1''}$), 151 ($C_{3'}$), 145 ($C_{4'}$), 134 ($C_{1'}$), 132 ($C_{4''}$), 131 ($C_{3''}$ and $C_{5''}$), 125 ($C_{5'}$), 122 ($C_{6'}$), 117 ($C_{2''}$ and $C_{6''}$), 113 ($C_{2'}$), 69 (CH_2CHO), 56 (OMe), 36 (C_2), 34 (CH_2Br), 30 (C_3); *m/z* (EIMS): 407 ($M^+(^{81}Br)$, 22), 406 ($M^+(^{81}Br) - H^+$, 98), 405 ($M^+(^{79}Br)$, 22), 404 ($M^+(^{79}Br) - H^+$, 98), 391 (39), 380 ($M^+(^{81}Br) - H^+ - CO$, 46), 378 ($M^+(^{79}Br) - H^+ - CO$, 46), 370 (37), 366 ($M^+(^{81}Br) - CH_2CHO$, 43), 364 ($M^+(^{79}Br) - CH_2CHO$), 360 (58), 333 (10), 325 (14), 299 (14), 241 (13), 185 (17), 167 (16), 149 (54), 78 (58); mass found: 405.033638, $C_{19}H_{19}BrO_5$ requires 405.033760.

Synthesis of (4-{2-methoxy-5-[2-(2-oxoethoxycarbonyl)-ethyl]-phenoxy}-benzyl)-triphenylphosphonium bromide (13). Triphenylphosphine (312 mg, 1.19 mmol, 1 eq.) was added to a solution of

the bromide (**12**) (485 mg, 1.19 mmol) in acetonitrile (6 mL), and the mixture was stirred for 2 days when a TLC of the crude mixture showed completion of the reaction. The solvents were removed under vacuum. A small amount of Et_2O was added, and the crude product was dried under high vacuum to remove the DMSO, present in the crude starting material. A pale cream hygroscopic crystalline compound was obtained (800 mg, quantitative). ν_{max}/cm^{-1}: 2924.4 (ArH), 1734.7 (CO + CHO), 1506.3 (Ar), 1438.5 (PPh), 1272–1194.8, 1112.4–1058.2 (C–O–C); mp: 81–83 °C; ^{1}H NMR δ_H ($CDCl_3$): 2.66–2.71 (t, 2H, H_3, $J = 7.4$ Hz), 2.85–2.90 (t, 2H, H_2, $J = 7.4$ Hz), 3.77 (s, 3H, OMe), 4.64 (s, 2H, CH_2CHO), 5.34–5.38 (d, 2H, CH_2P^+, $^2J_{PH} = 14$ Hz), 6.68–6.71 (d, 2H, $H_{2''}$, $H_{6''}$, $J = 8.69$ Hz), 6.75–6.76 (d, 1H, $H_{2'}$, $J = 1.8$ Hz), 6.87–6.90 (d, 1H, $H_{5'}$, $J = 8.3$ Hz), 6.93–6.97 (dd, 1H, $H_{6'}$, $J_o = 8.3$ Hz, $J_m = 1.8$ Hz), 7.00–7.05 (dd, 2H, $H_{3''}$ and $H_{5''}$, $J_o = 8.69$ Hz, $^4J_{PH} = 2.56$ Hz), 7.62–7.76 (m, 15H, PPh_3), 9.55 (s, 1H, CHO); ^{13}C NMR δ_C ($CDCl_3$): 196 (CHO), 172 (C=O), 159 ($C_{1''}$), 150 ($C_{3'}$), 145 ($C_{4'}$), 135, (s, P^+Ph_{3p}), 134.8–134.9 (d, P^+Ph_{3o}, $^2J_{PC} = 9.7$ Hz), 134 ($C_{1'}$), 132 ($C_{4''}$), 132 (d, $C_{3''}$ and $C_{5''}$, $^3J_{PC} = 9.84$ Hz), 130.5–130.6 (d, P^+Ph_{3m}, $^3J_{PC} = 12.6$ Hz), 128 (P^+Ph_{3i}, $^1J_{PC} = 34$ Hz), 126 ($C_{6'}$), 117 ($C_{2''}$ and $C_{6''}$), 117 ($C_{2'}$), 114 ($C_{5'}$), 69 (CH_2CHO), 56 (OMe), 36 (C_3), 30.5–30.9 (d, CH_2P^+, $^1J_{PC} = 50.3$ Hz), 30 (C_3); *m/z* (FAB$^+$): 607 ($M^+ + H_2O$, 17), 589 (M^+, 52), 561 (31), 547 (33), 503 (14), 455 (15), 369 (56), 293 (28), 279 (100), 262 (52), 183 (33), 154 (49), 136 (41); mass found: 589.214401, $C_{37}H_{34}O_5P^+$ requires 589.214388.

Synthesis of allyl 3-{3-[4-(chloromethyl)phenoxy]-4-methoxyphenyl}propanoate. Thionyl chloride (44 μL, 0.60 mmol, 2eq.) was added dropwise to a solution of the alcohol (**10**) (100 mg, 0.29 mmol) in DCM (1.5 mL) at 0 °C. The resulting mixture was stirred at this temperature for 2 h. The volatile compounds were removed under vacuum to yield the pure chloride (94 mg, 90%) as a pale yellow oil, which was used without further purification. *R*f: 0.39 (EtOAc–P.E., 2 : 8); ν_{max}/cm^{-1}: 1735 (CO_2Me), 1609 (C=C), 1507 (Ar), 1270–1225–1126 (C–O–C); ^{1}H NMR δ_H ($CDCl_3$): 2.62–2.67 (t, 2H, H_3, $J = 7.8$ Hz), 2.89–2.94 (t, 2H, H_2, $J = 7.8$ Hz), 3.83 (s, 3H, OMe), 4.58–4.60 (d, 2H, $CH_2C{=}C$, $J = 5.8$ Hz), 4.61 (s, 2H, CH_2Cl), 5.23–5.33 (m, 2H, $C{=}CH_2$), 5.85–5.98 (ddt, 1H, CH=C, $J_{cis} = 10.5$ Hz, $J_{trans} = 16.5$ Hz, $J = 5.8$ Hz), 6.88–7.04 (m, 5H, $H_{2'}$, $H_{6'}$, $H_{5'}$, $H_{2''}$, $H_{6''}$), 7.32–7.35 (d, 2H, $H_{3''}$ and $H_{5''}$, $J_o = 7.34$ Hz); ^{13}C NMR δ_C ($CDCl_3$): 173 (C=O), 159 ($C_{1''}$), 150 ($C_{3'}$), 145 ($C_{4'}$), 134 ($C_{1'}$), 133 ($C_{4''}$), 132 (CH=C), 130 ($C_{3''}$ and $C_{5''}$), 125 ($C_{5'}$), 122 ($C_{6'}$), 119 ($C{=}CH_2$), 117 ($C_{2''}$ and $C_{6''}$), 113 ($C_{2'}$), 66 ($CH_2C{=}C$), 56 (OMe), 46 (CH_2Cl), 36 (C_2), 30 (C_3); *m/z* (EIMS): 362 (M^+(^{37}Cl), 36), 360 (M^+(^{35}Cl), 100), 325 (M^+, 35), 319 (M^+, 15), 261 (40), 241 (26), 136 (32), 215 (27), 153 (32), 137 (43), 113 (20), 91 (22); mass found: 360.112236, $C_{20}H_{21}ClO_4$ requires 360.112837; found C: 65.58, H: 5.72, $C_{20}H_{21}ClO_4$ requires C: 66.57, H: 5.87, O: 17.73, Cl: 9.83%.

Synthesis of 3-{3-[4-(dimethoxyphosphorylmethyl)-phenoxy]-4-methoxyphenyl}-propionic acid allyl ester. A solution of the chloride (94 mg, 0.26 mmol) in trimethyl phosphite (484 mg, 3.9 mmol, 15 eq.) was refluxed for 20 h. The excess of trimethyl phosphite was co-evaporated with toluene under vacuum, and 103 mg of a yellow oil (91%) were obtained. The crude product was used without further purification for the next step. ν_{max}/cm^{-1}: 2954 (Ar), 1734.7 (C=O), 1506.5 (Ar), 1270.8–1227.3–1171.0–1127.2 (C–O–C, P=O and P–O); ^{1}H NMR δ_H ($CDCl_3$): 2.60–2.65 (t, 2H, H_3, $J = 7.8$ Hz), 2.87–2.92 (t, 2H, H_2, $J = 7.8$ Hz), 3.12–3.19 (d, 2H, CH_2P, $^2J_{PH} = 21.3$ Hz), 3.68–3.72 (d, 6H, $P(OMe)_2$, $^3J_{PH} = 10.8$ Hz), 3.82 (s, 3H, OMe), 4.57–4.58 (d, 2H, $CH_2C{=}C$, $J = 5.6$ Hz), 5.22–5.32 (m, 2H, $C{=}CH_2$), 5.83–5.96 (ddt, 1H, CH=C, $J_{cis} = 10.7$ Hz, $J_{trans} = 17$ Hz, $J = 5.6$ Hz), 6.84 (d, 1H, $H_{2'}$, $J_m = 1.7$ Hz), 6.88–7.00 (m, 4H, $H_{6'}$, $H_{5'}$, $H_{2''}$, $H_{6''}$), 7.22–7.26 (dd, 2H, $H_{3''}$ and $H_{5''}$, $J_o = 8.54$ Hz, $J_m = 2.20$ Hz); ^{13}C NMR δ_C ($CDCl_3$): 173 (C=O), 158 ($C_{1''}$), 150 ($C_{3'}$), 145 ($C_{4'}$), 134 ($C_{1'}$), 133 (CH=C), 131 (d, $C_{3''}$ and $C_{5''}$, $^3J_{PC} = 6.6$ Hz), 130 ($C_{4''}$), 125 ($C_{5'}$), 122 ($C_{6'}$), 119 ($C{=}CH_2$), 118 (d, $C_{2''}$ and $C_{6''}$, $^4J_{PC} = 2.8$ Hz), 113 ($C_{2'}$), 66 ($CH_2C{=}C$), 56 (OMe), 53 ($P(OMe)_2$, $^2J_{PC} = 6.9$ Hz), 36 (C_2), 32–33 (CH_2P, $^1J_{PC} = 139$ Hz), 30 (C_3); *m/z* (EIMS): 434 (M^+, 8), 360 (10), 348 (6), 325 (7), 261 (8), 239 (18), 211 (15), 134 (15), 109 (100), 89 (27), 78 (33); mass found: 434.149195, $C_{22}H_{27}O_7P$ requires: 434.149442.

Synthesis of 3-{3-[4-(dimethoxyphosphorylmethyl)-phenoxy]-4-methoxyphenyl}-propionic acid 2-oxoethyl ester. Ozone was bubbled through a solution of the phosphonate (85 mg, 0.20 mmol) in DCM (15 mL) at −78 °C for 2 min. Nitrogen was bubbled through the resulting blue solution until the colour faded, and dimethyl sulfide (300 μL, 4 mmol, 20 eq.) was added. The mixture was stirred at −78 °C for 1 h, then at room temperature for 4 h. The volatiles were removed under vacuum and the product (85 mg, 98%) was used without further purification for the next step. ν_{max}/cm^{-1}: 2957 (Ar), 1734.4 (C=O), 1507.8 (Ar), 1271–1226–1171–1127 (C–O–C); ^{1}H NMR δ_H ($CDCl_3$): 2.70–2.76 (t, 2H, H_3, $J = 7.6$ Hz), 2.88–2.95 (t, 2H, H_2, $J = 7.6$ Hz), 3.12–3.19 (d, 2H, CH_2P, $^2J_{PH} = 21.3$ Hz), 3.68–3.71 (d, 6H, $P(OMe)_2$, $^3J_{PH} = 10.8$ Hz), 3.82 (s, 3H, OMe), 4.66 (s, 2H, CH_2CHO), 6.85–7.00 (m, 5H, $H_{2'}$, $H_{6'}$, $H_{5'}$, $H_{2''}$, $H_{6''}$), 7.22–7.24 (dd, 2H, $H_{3''}$ and $H_{5''}$, $J_o = 8.54$ Hz, $J_m = 2.20$ Hz), 9.56 (CHO); ^{13}C NMR δ_C ($CDCl_3$): 196 (CHO), 172 (C=O), 158 ($C_{1''}$), 150 ($C_{3'}$), 145 ($C_{4'}$), 134 ($C_{1'}$), 131 (d, $C_{3''}$ and $C_{5''}$, $^3J_{PC} = 6.6$ Hz), 130 ($C_{4''}$), 125 ($C_{5'}$), 122 ($C_{6'}$), 118 (d, $C_{2''}$ and $C_{6''}$, $^4J_{PC} = 3.0$ Hz), 113 ($C_{2'}$), 69 (CH_2CHO), 56 (OMe), 53 ($P(OMe)_2$, $^2J_{PC} = 6.9$ Hz), 36 (C_2), 32–33 (CH_2P, $^1J_{PC} = 139$ Hz), 30 (C_3); *m/z* (EIMS): 436 (M^+, 10), 408 (27), 394 (28), 348 (46), 334 (23), 327 (17), 299 (46), 285 (62), 261 (30), 239 (47), 216 (100), 211 (75); mass found: 436.129509, $C_{21}H_{25}O_8P$ requires 436.128707.

Synthesis of combretastatin D_2 methyl ether (14).

Procedure with tBuOK–DMF. Potassium *t*-butoxide was added at 0 °C to a dilute solution of the phosphonium salt (**13**) in DMF. The resulting yellow solution was allowed to warm to room temperature and was stirred overnight. The reaction was quenched with saturated NH_4Cl and the aqueous layer was extracted with EtOAc. The combined organic extracts were washed several times with brine, then dried with $MgSO_4$.

General procedure for intramolecular Wittig reactions with K_2CO_3–18-C-6. A slurry of potassium carbonate (4 eq.) and 18-crown-6 (4 eq.) in DCM (15 mL mmol^{-1}) was stirred at room temperature for 3 h before the slow addition of a solution of the phosphonium salt (**13**) *via* a syringe pump (3 mL h^{-1}). The resulting yellow solution was stirred overnight and the mixture was concentrated under vacuum. The reaction was quenched with saturated NH_4Cl, and the aqueous layer was extracted with DCM. The combined organic extracts were washed with brine, then dried with $MgSO_4$. The crude product was purified by flash chromatography (EtOAc–hexane, 2 : 8).

(The same procedure was used for the intramolecular Wittig reactions with the other bases listed in Table 1.)

Combretastatin D_2 methyl ether data:

white powder; *R*f: 0.43 (EtOAc–hexane, 2 : 8); ν_{max}/cm^{-1}: 2925 (ArH), 1732 (C=O), 1586, 1519, 1502, 1265–1219–1149–1128 (C–O–C); mp: 130–131 °C (lit.[4]: 130–132), ^{1}H NMR δ_H ($CDCl_3$): 2.28–2.30 (t, 2H, H_{16}, $J = 5.4$ Hz), 2.88–2.90 (t, 2H, H_{15}, $J = 5.4$ Hz), 3.95 (s, 3H, OMe), 4.65–4.67 (d, 2H, H_2, $J = 6.68$ Hz), 5.12 (d, 1H, H_{20}, $J = 1.99$ Hz), 6.03–6.08 (dt, 1H, H_3, $J_1 = 11.1$ Hz, $J_2 = 6.68$ Hz), 6.67–6.69 (dd, 1H, H_{13}, $J_1 = 8.2$ Hz, $J_2 = 1.99$ Hz), 6.82–6.84 (d, 1H, H_{12}, $J = 8.2$ Hz), 7.09–7.12 (m, 3H, H_4 H_7 H_{19}), 7.31–7.32 (d, 2H, H_6 H_{18}, $J = 8.2$ Hz); ^{13}C NMR δ_C ($CDCl_3$): 173 (C_{17}), 156 (C_8), 151 (C_{10}), 146 (C_{11}), 138 (C_3), 135 (C_4), 133 (C_5), 129 (C_6/C_{14}), 125 (C_{18}), 121 (C_7/C_{19}), 122 (C_{13}), 113 (C_{12}), 112 (C_{20}), 59 (C_2), 56 (OMe), 31 (C_{16}), 27 (C_{15}); *m*/*z* (EIMS): 310 (M^+, 100), 253 (16), 239 (35), 183 (37), 149 (39), 123 (44), 115 (36), 112 (21), 97 (23), 91 (20), 83 (26), 71 (37), 57 (65); mass found: 310.120979, $C_{19}H_{18}O_4$ requires 310.120509.

Synthesis of 3-[4-methoxy-3-(4-vinylphenoxy)phenyl] propionic acid methyl ester (16). A 2 M solution of NaHMDS in THF (600 μL, 1.2 mmol, 2.5 eq.) was added to a suspension of methyltriphosphonium bromide (429 mg, 1.2 mmol) in THF (1.5 mL) under nitrogen at 0 °C. After stirring for 1 h at this temperature, a solution of the aldehyde (**8**) (150 mg, 0.48 mmol) in THF (1.5 mL) was added dropwise and the mixture was stirred for 20 h. The reaction was quenched with water and the crude product was extracted with EtOAc. The combined organic layers were washed with brine then dried with $MgSO_4$. After evaporation of the solvents, the crude product was purified by flash chromatography (EtOAc–P.E., 2 : 8) and 130 mg (87%) of a yellow oil were obtained. *R*f: 0.65 (EtOAc–P.E., 2 : 8); ν_{max}/cm^{-1}: 2849–2954 (C–H), 1734 (CO_2Me), 1605 (C=C), 1506 (Ar), 1227–1270–1127 (C–O–C); ^{1}H NMR δ_H ($CDCl_3$): 2.47–2.54 (t, 2H, H_3, $J = 7.5$ Hz), 2.76–2.81 (t, 2H, H_2, $J = 7.5$ Hz), 3.57 (s, 3H, OMe), 3.74 (s, 3H, OMe), 5.07–5.11 (d, 1H, C=CH_2, $J_{cis} = 10.9$ Hz), 5.55–5.60 (d, 1H, C=CH_2, $J_{trans} = 17.6$ Hz), 6.55–6.65 (dd, 1H, CH=C, $J_{cis} = 10.9$ Hz, $J_{trans} = 17.6$ Hz), 6.74–6.91 (m, 5H, $H_{6'}$, $H_{5'}$, $H_{2'}$, $H_{3''}$ and $H_{5''}$), 7.26–7.28 (dd, 2H, $H_{2''}$ and $H_{6''}$, $J_m = 1.9$ Hz, $J_o = 6.8$ Hz); ^{13}C NMR δ_C ($CDCl_3$): 172 (C=O), 157 ($C_{1''}$), 149 ($C_{3'}$), 144 ($C_{4'}$), 135 (ArC=C), 132 ($C_{1'}$), 131 ($C_{4''}$), 127 ($C_{3''}$ and $C_{5''}$), 123 ($C_{5'}$), 120 ($C_{6'}$), 116 ($C_{2''}$ and $C_{6''}$), 112 (ArCH=CH_2), 111 ($C_{2'}$) 55 (OMe), 51 (CO_2Me), 35 (C_2), 29 (C_3); *m*/*z* (CIMS): 313 ($M^+ + H^+$), 281 ($M^+ + H^+ -$ OMe); mass (calculated for $M + H^+$) found: 313.143349, $C_{19}H_{21}O_4$ requires 313.143984.

Synthesis of 3-[4-methoxy-3-(4-vinylphenoxy)phenyl] propionic acid allyl ester (17). The ester (**16**) (190 mg, 0.61 mmol) was dissolved in allyl alcohol (5 mL), and dibutyltin oxide (15 mg, 0.06 mmol, 0.1 eq.) was added. The mixture was refluxed for 20 h. Saturated Na_2CO_3 was added to the cooled reaction mixture and the crude product was extracted with EtOAc. The combined organic layers were filtered over Celite and dried with $MgSO_4$. The solvents were evaporated under vacuum and the crude product was purified by flash chromatography (EtOAc–P.E., 2 : 8) to yield 143 mg (71%) of a yellow oil. *R*f: 0.36 (EtOAc–P.E., 1 : 8); ν_{max}/cm^{-1}: 2918 (C–H), 1734 (CO_2Me), 1605 (C=C), 1506 (Ar), 1227–1270–1127 (C–O–C); ^{1}H NMR δ_H ($CDCl_3$): 2.50–2.55 (t, 2H, H_3, $J = 7.9$ Hz), 2.77–2.82 (t, 2H, H_2, $J = 7.9$ Hz), 3.73 (s, 3H, OMe), 4.46–4.48 (d, 2H, CH_2–C=C, $J = 4.6$ Hz), 5.07–5.11 (d, 1H, ArC=CH_2, $J_{cis} = 11.0$ Hz), 5.15–5.22 (m, 2H, CH=CH_2), 5.53–5.59 (d, 1H, ArC=CH_2, $J_{trans} = 17.6$ Hz), 5.79–5.85 (ddt, 1H, CH=C, $J_{cis} = 11.0$ Hz, $J_{trans} = 17.6$ Hz, $J = 4.6$ Hz), 6.55–6.65 (dd, 1H, ArCH=C, J_{cis} 10.9 Hz, $J_{trans} = 17.6$ Hz), 6.75–6.91 (m, 5H, $H_{2'}$, $H_{5'}$, $H_{6'}$, $H_{2''}$ and $H_{6''}$), 7.20–7.28 (dd, 2H, $H_{3''}$ and $H_{5''}$, $J_m = 2.0$ Hz, $J_o = 6.9$ Hz); ^{13}C NMR δ_C ($CDCl_3$): 171 (C=O), 156 ($C_{1''}$), 149 ($C_{3'}$), 144 ($C_{4'}$), 135 (ArC=C), 132 ($C_{1'}$), 131 ($C_{4''}$ and CH=C), 126 ($C_{3''}$ and $C_{5''}$), 123 ($C_{5'}$), 120 ($C_{6'}$), 117 (C=CH_2), 116 ($C_{2''}$ and $C_{6''}$), 112 (ArCH=CH_2), 111 ($C_{2'}$), 64 (CH_2C=C), 55 (OMe), 35 (C_2), 29 (C_3); *m*/*z* (CIMS): 339 ($M^+ + H^+$); mass (calculated for $M + H^+$) found: 339.160606, $C_{21}H_{23}O_4$ requires: 339.159634; found C: 74.12, H: 7.02, $C_{21}H_{22}O_4$ requires: C: 74.54, H: 6.55, O: 18.91%.

Synthesis of the dimer (18). Representative procedure: a solution of the Grubbs' catalyst 2nd generation (10 mol%) in toluene (0.003 M) was added to a solution of the diene (**17**) in toluene at 80 °C. The resulting brown/pink solution was stirred at 80 °C for 2 days and the solvent was removed under vacuum. The crude product was purified by flash chromatography (EtOAc–P.E., 3 : 7). ν_{max}/cm^{-1}: 2925.6, 1729.9 (CO_2Me), 1602.7 (C=C), 1515.6 (Ar), 1506.4 (Ar), 1269.0–1230.2–1123.0 (C–O–C); mp: 216–217 °C; ^{1}H NMR δ_H ($CDCl_3$): 2.49–2.54 (t, 2H, H_{16}, $J = 8.8$ Hz), 2.78–2.84 (t, 2H, H_{15}, $J = 8.8$ Hz), 3.88 (s, 3H, OMe), 4.65–4.67 (dd, 2H, H_2, $J_1 = 6.9$ Hz, $J_2 = 0.9$ Hz), 6.07–6.17 (dt, 1H, H_3, $J_{trans} = 15.9$ Hz), 6.58–6.61 (d, 1H, H_4, $J = 15.9$ Hz), 6.59 (d, 1H, H_{20}, $J_m = 1.8$ Hz), 6.89–6.91 (dd, 1H, H_{13}, $J_o = 8.3$ Hz, $J_m = 1.8$ Hz), 6.92–6.93 (d, 1H, H_{12}, $J_o = 8.3$ Hz), 6.94–6.97 (dd, 2H, H_7, H_{19}, $J_o = 8.7$ Hz, $J_m = 2.0$ Hz), 7.30–7.32 (dd, 2H, H_6 and H_{18}, $J_o = 8.7$ Hz, $J_m = 2.0$ Hz); ^{13}C NMR δ_C ($CDCl_3$): 29.3 (C_{15}), 35.3 (C_{16}), 55.1 (OMe), 64.3 (C_2), 112 (C_{13}), 117 (C_{20}), 118 (C_7 and C_{19}), 121 (C_3), 123 (C_{12}), 127 (C_6 and C_{18}), 130 (C_5), 132 (C_{14}), 134 (C_4), 145 (C_{11}), 148 (C_{10}), 156 (C_8), 171 (C_{17}); *m*/*z* (FAB): 621 (M^+, 36), 391 (6), 311 (23), 307 (16), 251 (34), 195 (17), 176 (14), 154 (100), 136 (85), 131 (46), 121 (33); mass found: 620.241592, $C_{38}H_{36}O_8$ requires 620.241019.

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