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Application of the McMurry coupling reaction in the synthesis of tri- and tetra-arylethylene analogues as potential cancer chemotherapeutic agents

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ABSTRACT

Structural redesign of selected non-steroidal estrogen receptor binding compounds has previously been successful in the discovery of new inhibitors of tubulin assembly. Accordingly, tetra-substituted alkene analogues (**21**–**30**) were designed based in part on combinations of the structural and electronic components of tamoxifen and combretastatin A-4 (CA4). The McMurry coupling reaction was used as the key synthetic step in the preparation of these tri- and tetra-arylethylene analogues. The structural assignment of *E*, *Z* isomers was determined on the basis of 2D-NOESY experiments. The ability of these compounds to inhibit tubulin polymerization and cell growth in selected human cancer cell lines was evaluated. Although the compounds were found to be less potent than CA4, these analogues significantly advance the known structure–activity relationship associated with the colchicine binding site on β-tubulin.

1. Introduction

Structural diversity is an important theme describing the growing number of compounds that bind to the colchicine site on tubulin and inhibit tubulin assembly.[1] The diarylethylene moiety in both combretastatin A-4 (CA4)[2] and diethylstilbestrol (DES)[3] (Fig. 1) inspired us to modify the molecular templates found in certain non-steroidal antiestrogenic compounds to explore the interaction of the resulting new compounds with the tubulin–microtubule protein system. This molecular design strategy proved highly successful for the synthesis of new benzo[*b*]thiophene,[4] indole,[5] and dihydronaphthalene[6] analogues similar to raloxifene,[7] nafoxidine,[8] and trioxifene.[9] Tamoxifen[10] is a triarylethylene compound that has been widely used in the treatment of breast cancer, as well as hepatocellular, ovarian, colorectal, and pancreatic carcinomas.[11] In contrast to CA4, 2-methoxyestradiol (2ME), and DES,[12] tamoxifen does not have a significant effect on tubulin polymerization (IC_{50} >40 μM; Table 2). Tamoxifen and its metabolites are thought to act primarily through inhibition of the estrogen receptor, but other mechanisms have been documented[13] and include induction of apoptosis,[14] interference with the insulin-like growth factor I receptor,[15] and suppression of telomerase activity by inhibition of protein kinase C.[16] The pronounced biological activity of tamoxifen has inspired the synthesis of numerous structural congeners.[17]

Combretastatin A-4, a natural product found in the bush willow tree *Combretum caffrum*, is a potent inhibitor of tubulin assembly (IC_{50} = 1.2 μM)[18] and is also strongly cytotoxic against selected human cancer cell lines (e.g., GI_{50} = 2 nM against DU-145 prostate cancer cells).[19] A water soluble phosphate prodrug (CA4P, fosbretabulin, ZYBERSTAT™) is currently in human clinical trials as a vascular disrupting agent.[20]

It is instructive to note that a number of derivatives of estradiol are strong inhibitors of tubulin polymerization.[21] Interestingly, one of these derivatives, 2ME, is a natural metabolite of 17-β-estradiol in mammals (Fig. 2).[22]

The McMurry coupling reaction is an important methodology for the synthesis of highly-functionalized alkenes. This reaction, which has been used for the synthesis of tamoxifen and related compounds,[23] was employed to synthesize a series of tri- and tetra-arylethylene compounds **21**–**30** that mimic the structural core of tamoxifen while incorporating features of CA4 and colchicine. These compounds that each contains trimethoxyphenyl and *p*-methoxy-*m*-hydroxyphenyl rings were evaluated for their ability to inhibit tubulin polymerization and for their cytotoxicity against selected human cancer cell lines.

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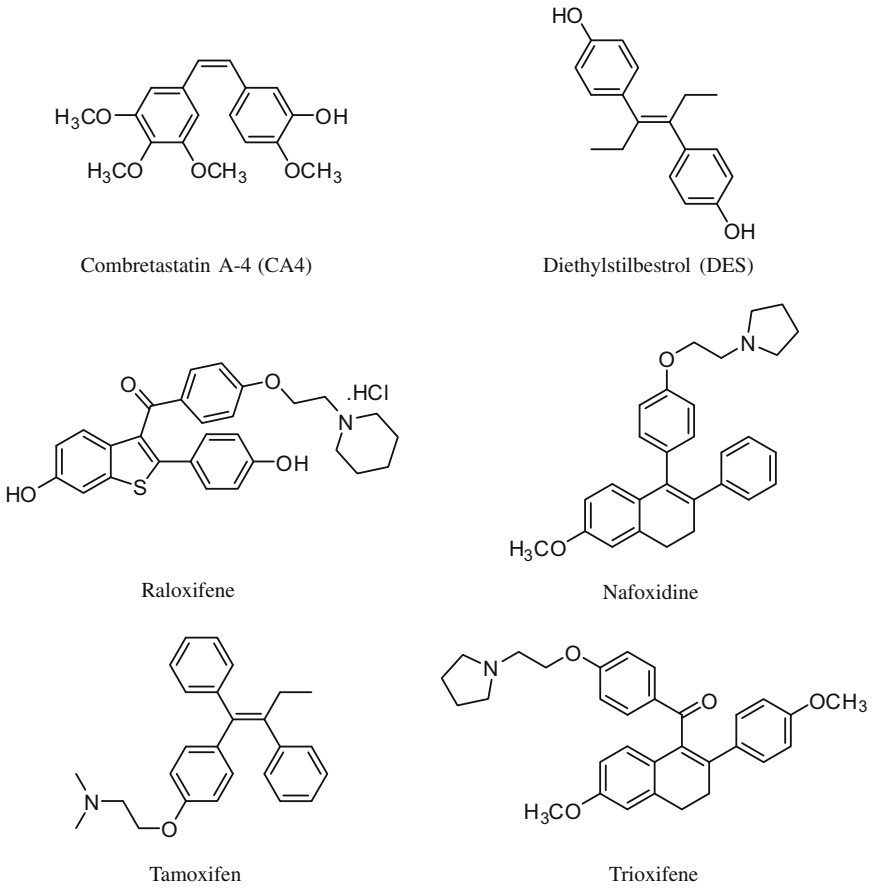


Figure 1. Combretastatin A-4 and selected non-steroidal antiestrogen compounds.

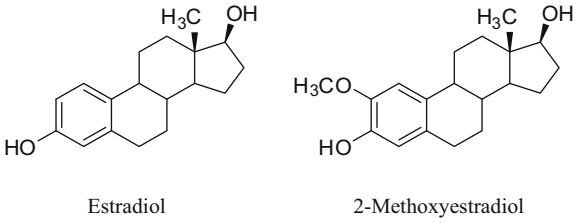


Figure 2. Estradiol and 2-methoxyestradiol.

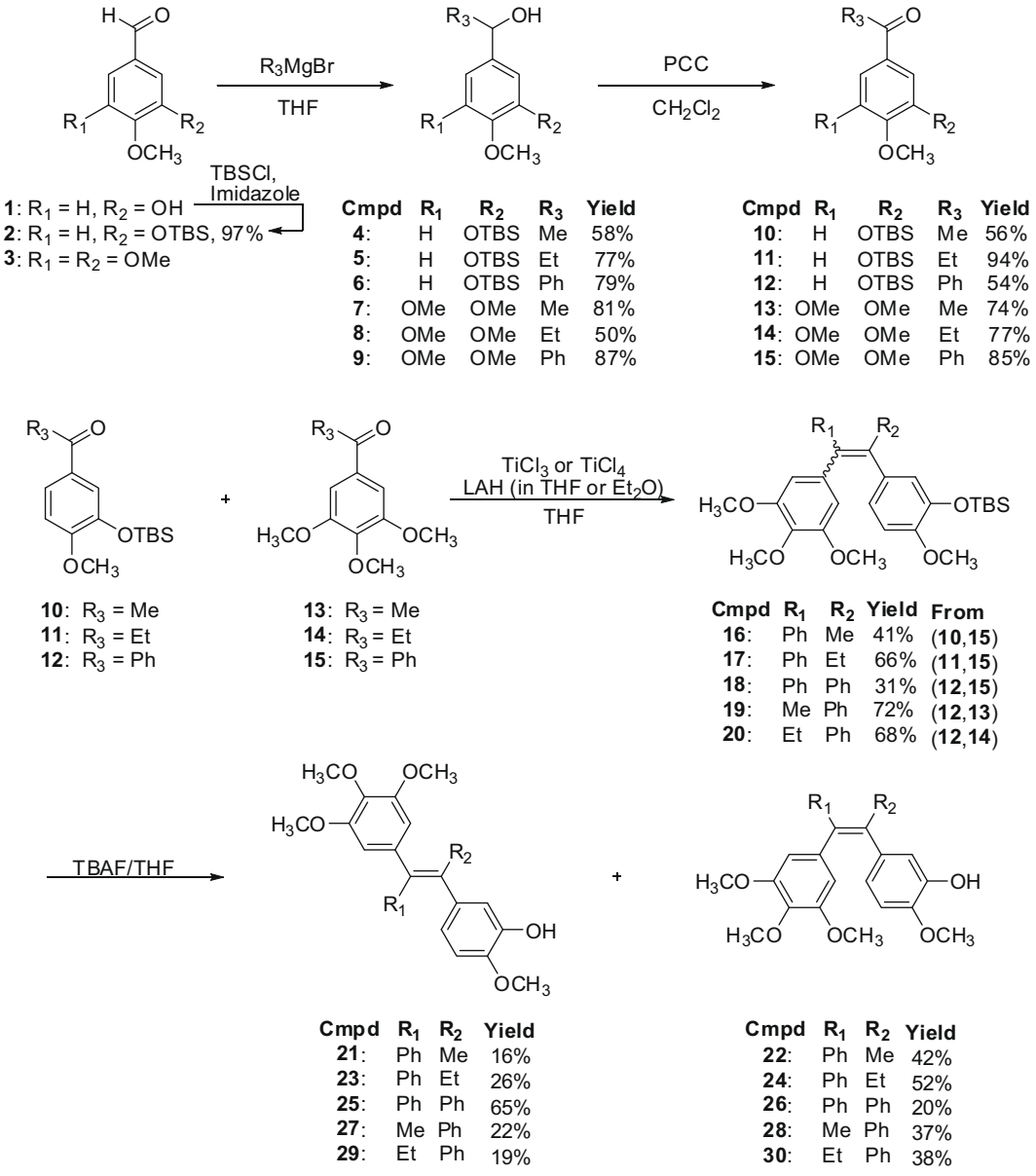
2. Results and discussion

2.1. Chemistry

The requisite ketones necessary for the McMurry coupling reaction were prepared as outlined in Scheme 1. In brief, the appropriate aldehyde, upon treatment with the indicated organometallic reagent, formed the anticipated secondary alcohols **4**–**9** that were oxidized upon treatment with pyridinium chlorochromate (PCC) to their corresponding ketones **10**–**15**. The low valent titanium (LVT) induced reductive deoxygenation of carbonyls to olefins (McMurry coupling) takes place in two successive steps: (i) reductive dimerization of the starting ketones to form a carbon–carbon bond and (ii) deoxygenation of the 1,2-diolate intermediate to give an alkene.[24] Careful addition of $LiAlH_4$ to the solution of $TiCl_3$ or $TiCl_4$ in THF followed by heating at reflux generated the LVT. The requisite ketones together with proton sponge as a solution in THF were heated at reflux to obtain **16**–**20**. The mixture of TBS protected *E*, *Z* isomers **16**–**20** proved difficult to separate by column chromatography. However upon deprotection, the resulting phenolic *E*, *Z* isomers **21**–**30** were readily separable. The stereochemical assignments of the *E*, *Z* isomers were determined primarily on the basis of 2D-NOESY experiments. For example, the stereochemistry of compound **21** was determined based on its 2D-NOESY spectrum (Supplementary data), obtained at 500 MHz. The methyl protons at 1.99 ppm demonstrate NOE cross peaks with protons at 6.50 ppm and 6.56 ppm of the 3′-hydroxy-4′-methoxyphenyl ring B as well as with the protons at 6.43 ppm on the 3,4,5-trimethoxyphenyl ring A. In addition, there is an absence of an NOE cross peak between the methyl protons and the protons at 6.91 ppm of the unsubstituted phenyl ring. Collectively, these NOE data establish the stereochemical assignment of compound **21** to be in the *E* configuration. Similarly, the stereochemistry of compound **22** was determined to be in the *Z* configuration based on its 2D-NOESY spectrum (Supplementary data), obtained at 360 MHz. The methyl protons at 1.97 ppm demonstrate NOE cross peaks with protons at 6.58 ppm and 6.59 ppm of the 3′-hydroxy-4′-methoxyphenyl ring B as well as with the protons at 7.22 ppm on the phenyl ring. In addition, there is an absence of an NOE cross peak between the methyl protons and the protons at 6.11 ppm of the 3,4,5-trimethoxyphenyl ring A. A similar strategy using 2D-NOESY data was employed for the stereochemical assignment of compounds **23**–**30** (Table 1). Single crystal X-ray diffraction of compounds **23** and **27** (each recrystallized from 20% EtOAc in hexanes) confirms the stereochemical assignment for these compounds (Supplementary data).[25]

2.2. Biology

This series of tri- and tetra-substituted stilbene derivatives were evaluated by an in vitro cytotoxicity assay, which was carried



Cmpd	R_1	R_2	R_3	Yield
4:	H	OTBS	Me	58%
5:	H	OTBS	Et	77%
6:	H	OTBS	Ph	79%
7:	OMe	OMe	Me	81%
8:	OMe	OMe	Et	50%
9:	OMe	OMe	Ph	87%

Cmpd	R_1	R_2	R_3	Yield
10:	H	OTBS	Me	56%
11:	H	OTBS	Et	94%
12:	H	OTBS	Ph	54%
13:	OMe	OMe	Me	74%
14:	OMe	OMe	Et	77%
15:	OMe	OMe	Ph	85%

10: R_3 = Me
11: R_3 = Et
12: R_3 = Ph

13: R_3 = Me
14: R_3 = Et
15: R_3 = Ph

Cmpd	R_1	R_2	Yield	From
16:	Ph	Me	41%	(**10**,**15**)
17:	Ph	Et	66%	(**11**,**15**)
18:	Ph	Ph	31%	(**12**,**15**)
19:	Me	Ph	72%	(**12**,**13**)
20:	Et	Ph	68%	(**12**,**14**)

Cmpd	R_1	R_2	Yield
21:	Ph	Me	16%
23:	Ph	Et	26%
25:	Ph	Ph	65%
27:	Me	Ph	22%
29:	Et	Ph	19%

Cmpd	R_1	R_2	Yield
22:	Ph	Me	42%
24:	Ph	Et	52%
26:	Ph	Ph	20%
28:	Me	Ph	37%
30:	Et	Ph	38%

Scheme 1. McMurry coupling to synthesize tri- and tetra-arylethylene analogues.

out with a panel of three human cancer cell lines comprised of prostate cancer (DU-145), ovarian cancer (SK-OV-3), and lung carcinoma (NCI-H460), using doxorubicin as a reference compound. The screening procedure was based on the standard sulforhodamine B (SRB) assay method.[6c,35] The GI_{50} values are shown in Table 2. A comparison of the triarylethylene analogues with R_1 = phenyl (**21**–**24**) showed enhanced activity for the *Z* isomers (**22** and **24**) in SK-OV-3 and NCI-H460 human cancer cell lines. The reverse trend was observed for the triarylethylene analogues (**27**–**30**) in which R_2 = phenyl. In this case, the *E* analogues (**27** and **29**) were more active in all three cancer cell lines. Collectively, compounds **27**–**30** were more active than compounds **21**–**24**. There were no significant differences in cytotoxicity between the *E* and *Z* tetra-arylethylene analogues **25** and **26**. Of this series of compounds, triarylethylene analogue **29** was the most cytotoxic across all three of the cell lines used in this study, and **29** was also more cytotoxic than tamoxifen against the three lines. It was especially active against SK-OV-3 cells (GI_{50} = 0.6 μM). Since the compounds in this study, like tamoxifen, did not significantly inhibit tubulin assembly (IC_{50} >40 μM), the cytotoxicity demonstrated by analogue **29** is presumed to result from a different mechanism.

3. Conclusions

The McMurry coupling reaction was applied successfully to the synthesis of a series of new tri- and tetra-arylethylene analogues **21**–**30**, which incorporate structural features of tamoxifen and CA4. In contrast to CA4, none of the compounds significantly inhibited tubulin assembly; however certain analogues (such as **27** and **29**) demonstrated significant cytotoxicity against human cancer cell lines, suggesting an alternate mechanism of action.

4. Experimental[27]

Chemical reagents used in the synthetic procedures were obtained from various chemical suppliers (Sigma Aldrich, Acros

Table 1
NOE correlations for compounds **21**–**30** in DMSO-d_6

Compound	Proton shift (δ_H ppm)	NOE correlation (δ_H ppm)		
		Ring A[a]	Ring B[b]	Phenyl ring(s)
21[c]	1.99 (s, 3H, CH_3)	6.43 (s, 2H)	6.50 (dd, 1H, J = 8.1 Hz, J = 2.0 Hz), 6.56 (d, 1H, J = 2.0 Hz)	
22[d]	1.97 (s, 3H, CH_3)		6.58 (dd, 1H, J = 8.0 Hz, J = 2.0 Hz), 6.59 (d, 1H, J = 2.0 Hz)	7.22 (d, 2H, J = 7.2 Hz)
23[d]	0.88 (t, 3H, J = 7.2 Hz, CH_2CH_3) and 2.33 (q, 2H, J = 7.2 Hz, CH_2CH_3)	6.45 (s, 2H)	6.50 (dd, 1H, J = 8.3 Hz, 2.2 Hz), 6.56 (d, 1H, J = 2.2 Hz)	
24[d]	0.87 (t, 3H, J = 7.2 Hz, CH_2CH_3) and 2.30 (q, 2H, J = 7.2 Hz, CH_2CH_3)		6.56 (dd, 1H, J = 7.9 Hz, 1.8 Hz), 6.57 (d, 1H, J = 1.8 Hz)	7.23 (d, 2H, J = 6.8 Hz)
25[d]	6.18 (s, 2H, Ar*H*)			7.02–7.16 (m, 10H)
26[d]	6.25 (s, 2H, Ar*H*)		6.54 (dd, 1H, J = 8.3 Hz, 2.1 Hz), 6.62 (d, 1H, J = 2.0 Hz)	7.00–7.12 (m, 10H)
27[c]	2.11 (s, 3H, CH_3)	6.37 (s, 2H)	6.59 (d, 1H, J = 2.0 Hz), 6.63 (dd, 1H, J = 8.2 Hz, 2.0 Hz)	
28[c]	2.03 (s, 3H, CH_3)	6.43 (s, 2H)		7.19 (m, 2H)
29[c]	0.92 (t, 3H, J = 7.4 Hz, CH_2CH_3) and 2.48 (q, 2H, J = 7.4 Hz, CH_2CH_3)	6.34 (s, 2H)	6.59 (d, 1H, J = 2.0 Hz), 6.63 (dd, 1H, J = 8.2 Hz, J = 2.0 Hz)	
30[c]	0.89 (t, 3H, J = 7.4 Hz, CH_2CH_3) and 2.37 (q, 2H, J = 7.4 Hz, CH_2CH_3)	6.40 (s, 2H)		7.18 (d, 2H, J = 7.0 Hz)

[a] 3,4,5-Trimethoxyphenyl ring.
[b] 3′-Hydroxy-4′-methoxyphenyl ring.
[c] Data determined at 500 MHz.
[d] Data determined at 360 MHz.

Chemical Co., Alfa Aesar, Fisher Scientific, EMD Chemicals, and VWR). The following solvents were either used in their anhydrous form as obtained from the chemical suppliers or freshly distilled prior to use: methylene chloride (CH_2Cl_2) over calcium hydride, tetrahydrofuran (THF) over potassium metal and benzophenone, and hexanes over calcium hydride. Anhydrous Et_2O or THF was used for organometallic reactions. Reactions were performed under an inert atmosphere using nitrogen gas unless specified. Thin layer chromatography (TLC) plates (pre-coated glass plates with Silica Gel 60 F_{254}, 0.25 mm thickness, EMD chemicals, VWR) were used to monitor reactions. Silica gel (200–400 mesh, 60 Å), used for column chromatography, was obtained from either Silicycle Inc. or VWR. Purification of intermediates and products was carried out using manual flash column chromatography with silica gel or a Biotage® Isolera™ flash purification system using Biotage® KP-Sil SNAP columns. Intermediates and products synthesized were characterized on the basis of ^{1}H NMR (Brüker DPX operating at 300 MHz or Brüker AMX operating at 360 MHz or Varian Inova operating at 500 MHz), and ^{13}C NMR (Brüker DPX operating at 75 MHz or Brüker AMX operating at 90 MHz or Varian Inova operating at 125 MHz). All the chemical shifts are expressed in ppm (δ), coupling constants (J) are presented in hertz, and peak patterns are reported as broad (br), singlet (s), doublet (d), triplet (t), quartet (q), and multiplet (m). Elemental analysis was performed by Atlantic Microlab, Norcross, GA. High-resolution mass spectra (HRMS) were obtained using Electron Impact (EI) ionization on a VG Prospec Micromass spectrometer or Electrospray Ionization (ESI) technique on a Thermo Scientific LTQ Orbitrap Discovery Mass spectrometer in the Baylor University Mass Spectrometry Core Facility. Melting points were determined on a Thomas Hoover capillary melting point apparatus and are uncorrected. Purity of the compounds was further analyzed at 25 °C using an Agilent Series 1200 high performance liquid chromatography (HPLC) system with a diode-array detector with a wavelength range of 190–400 nm, a Zorbax XDB-C18 HPLC column (4.6 mm × 150 mm, 5 μm) and a Zorbax reliance cartridge guard-column; eluents, solvent A, water; solvent B, acetonitrile; gradient, 90% A/10% B→0% A/100% B over 0–10 min; flow rate 0.5 mL/min; injection volume 20 μL; monitored at 254 nm wavelength).

Table 2
Cytotoxicity studies against human cancer cell lines DU-145, SK-OV-3, and NCI-H460, and assay for inhibition of tubulin polymerization

Compound	Inhibition of tubulin polymerization IC_{50} (μM)	GI_{50} (μM) SRB assay[a]		
		DU-145	SK-OV-3	NCI-H460
Tamoxifen	>40	6.07[b]	6.40[b]	4.48[b]
21	>40	28.0	24.1	23.4
22	>40	24.3	8.44	6.54
23	>40	20.9	27.4	34.1
24	>40	18.8	17.1	13.3
25	>40	21.9	13.8	37.2
26	>40	19.9	18.9	33.0
27	>40	4.25	2.72	5.37
28	>40	16.9	4.35	10.0
29	>40	2.58	0.576	3.41
30	>40	13.5	3.79	5.77

[a] These data are an average of a minimum three separate experiments.
[b] Ref. 26.

4.1. Chemistry

4.1.1. 1-{3-[(*tert*-Butyldimethylsilyl)oxy]-4-methoxyphenyl}-1-ethanol (4)[28]

To a solution of 3-[(*tert*-butyldimethylsilyl)oxy]-4-methoxybenzaldehyde **2** (5.47 g, 20.5 mmol) in Et_2O (anhydrous, 25 mL), cooled to 0 °C, MeMgBr (10.3 mL, 3.0 M soln in Et_2O) was added dropwise and stirred under N_2. The reaction mixture was allowed to warm to room temperature and monitored for completion by TLC. After 8 h, the reaction mixture was quenched with water (25 mL) and extracted with EtOAc (2 × 100 mL). The organic layer was separated, washed with brine, dried over anhydrous $MgSO_4$, and concentrated in vacuo. Purification by flash chromatography (silica gel, 20:80, EtOAc/hexanes) afforded alcohol **4** (3.39 g, 12.0 mmol, 58%) as a colorless liquid.

^{1}H NMR ($CDCl_3$, 500 MHz): δ 6.75 (dd, 1H, J = 8.0 Hz, J = 2.0 Hz, Ar*H*), 6.72 (d, 1H, J = 2.0 Hz, Ar*H*), 6.65 (d, 1H, J = 8.0 Hz, Ar*H*), 4.63 (dq, 1H, J = 6.5 Hz, J = 3.0 Hz, C*H*OH), 3.63 (s, 3H, OCH_3), 1.29 (d, 3H, J = 6.5 Hz, CHCH_3), 0.84 (s, 9H, C(CH_3)$_3$), 0.00 (s, 6H, Si(CH_3)$_2$).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 150.3, 145.0, 138.6, 118.5, 118.3, 112.0, 67.0, 55.6, 25.7, 25.0, 18.5, −4.6.

HRMS (ESI^+) *m/z*: 305.1545 (Calcd for $C_{15}H_{26}O_3SiNa^+$—305.1543).

4.1.2. 1-{3-[(*tert*-Butyldimethylsilyl)oxy]-4-methoxyphenyl}-1-propanol (5)

To a solution of 3-[(*tert*-butyldimethylsilyl)oxy]-4-methoxybenzaldehyde **2** (5.46 g, 20.5 mmol) in THF (anhydrous, 25 mL) cooled to 0 °C, EtMgBr (10.5 mL, 2.8 M soln in Et_2O) was added dropwise and stirred under N_2. The reaction mixture was allowed to warm to room temperature and monitored for completion by TLC. After 8 h, the reaction mixture was quenched with water (25 mL) and extracted with EtOAc (2 × 100 mL). The organic layer was separated, washed with brine, dried over anhydrous $MgSO_4$, and concentrated in vacuo. Purification by flash chromatography (silica gel, 20:80, EtOAc/hexanes) afforded alcohol **5** (4.67 g, 15.8 mmol, 77%) as a colorless liquid.

^{1}H NMR ($CDCl_3$, 500 MHz): δ 6.78 (dd, 1H, *J* = 8.0 Hz, *J* = 3.0 Hz, Ar*H*), 6.75 (d, 1H, *J* = 3.0 Hz, Ar*H*), 6.72 (d, 1H, *J* = 8.0 Hz, Ar*H*), 4.38 (t, 1H, *J* = 6.5 Hz, C*H*OH), 3.70 (s, 3H, OCH_3), 1.59–1.69 (m, 2H, *J* = 6.5 Hz, CH_2CH$_3$), 0.90 (s, 9H, C(CH_3)$_3$), 0.78 (t, 3H, *J* = 6.5 Hz, CH$_2$CH_3), 0.06 (s, 6H, Si(CH_3)$_2$).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 150.4, 145.0, 137.3, 119.2, 118.8, 111.9, 75.6, 55.5, 31.7, 25.74, 18.5, 10.2, −4.6.

HRMS (ESI^+) *m/z*: 319.1702 (Calcd for $C_{16}H_{28}O_3SiNa^+$—319.1700).

4.1.3. 1-{3-[(*tert*-Butyldimethylsilyl)oxy]-4-methoxyphenyl} benzyl alcohol (6)

To a solution of 3-[(*tert*-butyldimethylsilyl)oxy]-4-methoxybenzaldehyde **2** (5.35 g, 20.1 mmol) in Et_2O (anhydrous, 25 mL) cooled to 0 °C, PhMgBr (10.8 mL, 2.8 M soln in Et_2O) was added dropwise and stirred under N_2. The reaction was left to warm to room temperature and monitored for completion by TLC. After 8 h, the reaction mixture was quenched with water (25 mL) and extracted with EtOAc (2 × 100 mL). The organic layer was separated, washed with brine, dried over anhydrous $MgSO_4$, and concentrated in vacuo. Purification by flash chromatography (silica gel, 20:80, EtOAc/hexanes) afforded alcohol **6** (5.48 g, 15.9 mmol, 79%) as a colorless liquid.

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.21–7.27 (m, 4H, Ph*H*), 7.14–7.17 (m, 1H, Ph*H*), 6.80 (dd, 1H, *J* = 8.0 Hz, *J* = 2.0 Hz, Ar*H*), 6.76 (d, 1H, *J* = 2.0 Hz, Ar*H*), 6.70 (d, 1H, *J* = 8.0 Hz, Ar*H*), 5.65 (d, 1H, *J* = 3.0 Hz, C*H*OH), 3.68 (s, 3H, OCH_3), 2.16 (d, 1H, O*H*), 0.87 (s, 9H, C(CH_3)$_3$), 0.02 (s, 6H, Si(CH_3)$_2$).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 150.4, 145.0, 144.0, 136.7, 128.4, 127.4, 126.4, 119.9, 119.6, 112.0, 75.7, 55.6, 25.7, 18.5, −4.7.

HRMS (ESI^+) *m/z*: 367.1704 (Calcd for $C_{20}H_{28}O_3SiNa^+$—367.1700).

4.1.4. Phenyl-(3,4,5-trimethoxyphenyl)-methanol (9)[29]

To a solution of 3,4,5-trimethoxybenzaldehyde **3** (6.04 g, 30.8 mmol) in THF (anhydrous, 25 mL) cooled to 0 °C, PhMgBr (16.5 mL, 2.8 M soln in Et_2O) was added dropwise with stirring. The reaction mixture was allowed to warm to room temperature and monitored for completion by TLC. After 8 h, the reaction mixture was quenched with water (50 mL) and extracted with EtOAc (2 × 100 mL). The organic layer was separated, washed with brine, dried over anhydrous $MgSO_4$, and concentrated in vacuo. Purification by flash chromatography (silica gel, 20:80, EtOAc/hexanes) afforded alcohol **9** (7.31 g, 26.6 mmol, 87%) as a white solid.

Melting point: **9** (110–112 °C).

^{1}H NMR ($CDCl_3$, 360 MHz): δ 7.27–7.40 (m, 5H, Ph*H*), 6.62 (s, 2H, Ar*H*), 5.78 (s, 1H, C*H*OH), 3.83 (s, 9H, OCH_3), 2.44 (s, 1H, O*H*).

^{13}C NMR ($CDCl_3$, 90 MHz): δ 153.3, 143.6, 139.4, 137.4, 128.5, 127.7, 126.5, 103.7, 76.4, 60.8, 56.1.

HRMS (ESI^+) *m/z*: 297.1099 (Calcd for $C_{16}H_{18}O_4Na^+$—297.1097).

4.1.5. A typical experimental procedure for the oxidation of alcohols 4–9 to ketones 10–15 using PCC

To a solution of the appropriate alcohol in CH_2Cl_2, at 0 °C, PCC was added in small portions under N_2 with vigorous stirring. The reaction was monitored for completion by TLC. After the reaction was completed, water was added. The reaction mixture was extracted with CH_2Cl_2, washed with brine, dried over anhydrous $MgSO_4$, and concentrated in vacuo. Additional details for these syntheses are found in the Supplementary data.

4.1.5.1. 1-{3-[(*tert*-Butyldimethylsilyl)oxy]-4-methoxyphenyl}-propan-1-one (11). Purification by flash chromatography (silica gel, 20:80, EtOAc/hexanes) afforded ketone **11** (0.57 g, 1.9 mmol, 96%) as a white solid.

Melting point: **11** (50–52 °C).

^{1}H NMR ($CDCl_3$, 360 MHz): δ 7.59 (dd, 1H, *J* = 8.5 Hz, *J* = 2.2 Hz, Ar*H*), 7.48 (d, 1H, *J* = 2.2 Hz, Ar*H*), 6.86 (d, 1H, *J* = 8.5 Hz, Ar*H*), 3.86 (s, 3H, OCH_3), 2.92 (q, 2H, *J* = 7.2 Hz, CH_2CH$_3$), 1.20 (t, *J* = 7.2 Hz, CH$_2$CH_3), 1.00 (s, 9H, C(CH_3)$_3$), 0.16 (s, 6H, Si(CH_3)$_2$).

^{13}C NMR ($CDCl_3$, 90 MHz): δ 199.4, 155.1, 144.9, 130.3, 122.9, 120.4, 110.9, 55.5, 31.4, 25.7, 18.4, 8.4, −4.6.

HRMS (ESI^+) *m/z*: 317.1546 (Calcd for $C_{16}H_{26}O_3SiNa^+$—317.1543).

4.1.5.2. {3-[(*tert*-Butyldimethylsilyl)oxy]-4-methoxyphenyl}-phenyl-methanone (12). Purification by flash chromatography (silica gel, 20:80, EtOAc/hexanes) afforded ketone **12** (1.79 g, 5.23 mmol, 55%) as a pale yellow liquid.

^{1}H NMR ($CDCl_3$, 360 MHz): δ 7.76 (dd, 2H, *J* = 9.8 Hz, *J* = 1.6 Hz, Ar*H*), 7.38–7.49 (m, 5H, Ph*H*), 6.89 (d, 1H, Ar*H*), 3.88 (s, 3H, OCH_3), 1.00 (s, 9H, C(CH_3)$_3$), 0.18 (s, 6H, Si(CH_3)$_2$).

^{13}C NMR ($CDCl_3$, 90 MHz): δ 195.4, 155.1, 144.7, 138.3, 131.8, 130.4, 129.7, 128.1, 125.5, 122.4, 110.7, 55.5, 25.6, 18.4, −4.6.

HRMS (ESI^+) *m/z*: 365.1544 (Calcd for $C_{20}H_{26}O_3SiNa^+$—365.1543).

4.1.5.3. 1-(3,4,5-Trimethoxyphenyl)-1-ethanone (13)[30]. Purification by flash chromatography (silica gel, 20:80, EtOAc/hexanes) afforded ketone **13** (7.56 g, 36.0 mmol, 74%) as a yellow solid.

Melting point: **13** (76–78 °C).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.22 (s, 2H, Ar*H*), 3.93 (s, 6H, OCH_3), 3.92 (s, 3H, OCH_3), 2.59 (s, 3H, CH_3).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 196.9, 153.0, 143.0, 132.5, 105.9, 61.0, 56.3, 26.4.

HRMS (ESI^+) *m/z*: 233.0785 (Calcd for $C_{11}H_{14}O_4Na^+$—233.0784).

4.1.5.4. 1-(3,4,5-Trimethoxyphenyl)-1-propanone (14)[31]. Purification by flash chromatography (silica gel, 20:80, EtOAc/hexanes) afforded ketone **14** (8.2 g, 37 mmol, 77%) as a yellow solid.

Melting point: **14** (49–50 °C).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.22 (s, 2H, Ar*H*), 3.93 (s, 6H, OCH_3), 3.92 (s, 3H, OCH_3), 2.98 (q, 2H, *J* = 7.5 Hz, CH_2CH$_3$), 1.23 (t, 3H, *J* = 7.5 Hz, CH$_2$CH_3).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 199.6, 153.0, 142.4, 132.2, 105.5, 60.9, 56.3, 31.6, 8.4.

HRMS (ESI^+) *m/z*: 247.0941 (Calcd for $C_{12}H_{16}O_4Na^+$—247.0941).

4.1.5.5. Phenyl-(3,4,5-trimethoxyphenyl)-methanone (15)[32]. Purification by flash chromatography (silica gel, 20:80, EtOAc/hexanes) afforded ketone **15** (6.42 g, 23.6 mmol, 85%) as a yellow solid.

Melting point: **15** (74–76 °C).

^{1}H NMR ($CDCl_3$, 360 MHz): δ 7.82 (dd, J = 7.4 Hz, 2H, Ar*H*), 7.58 (t, J = 7.4 Hz, 1H, Ph*H*), 7.50 (t, J = 7.4 Hz, 2H, Ph*H*), 7.08 (s, 2H, Ph*H*), 3.95 (s, 3H, OCH_3), 3.88 (s, 6H, OCH_3).

^{13}C NMR ($CDCl_3$, 90 MHz): δ 195.7, 152.9, 142.2, 137.9, 132.6, 132.2, 129.8, 128.2, 107.9, 61.0, 56.3.

HRMS (ESI$^+$) *m/z*: 295.0942 (Calcd for $C_{16}H_{16}O_4Na^+$—295.0941).

4.1.6. A typical experimental procedure for the McMurry coupling reaction using $TiCl_4$ to form compounds 16–18

To a solution of titanium tetrachloride (1.7 g, 9.2 mmol, 1.0 mL) in anhydrous THF (50 mL) under N_2 atmosphere, $LiAlH_4$ (1.0 M soln in ether) (0.17 g, 4.6 mL) was added dropwise. The solution was heated at reflux for 20 min, at which point a premixed solution of the ketone **15** (0.50 g, 1.8 mmol), and the appropriate ketone **10**–**12** (1.8 mmol), and 1,8-bis(dimethylamino)naphthalene (0.40 g, 1.8 mmol) in THF (10 mL) was added dropwise to the reaction mixture. Reflux was continued for an additional 5 h. The reaction mixture was returned to room temperature, and a potassium carbonate solution (20% aqueous) was added dropwise until no further bubble formation was observed. The mixture was filtered, and the filtrate was extracted with Et_2O (2 × 25 mL). The organic layer was separated, washed with water followed by brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo.

4.1.6.1. (*E*/*Z*) 2-{[3′-(*tert*-Butyldimethylsilyl)oxy]-4′-methoxyphenyl}-1-phenyl-1-(3″,4″,5″-trimethoxyphenyl)-prop-1-ene (16). Purification by flash chromatography (silica gel, 20:80, EtOAc/hexanes) afforded alkene **16** (0.40 g, 0.77 mmol, 42%) as a colorless, viscous oil, containing the *E* and *Z* isomers. The isomers could not be readily separated at this stage by chromatography and were carried on to the next step as a mixture.

4.1.6.2. (*E*/*Z*) 2-{[3′-(*tert*-Butyldimethylsilyl)oxy]-4′-methoxyphenyl}-1-phenyl-1-(3″,4″,5″-trimethoxyphenyl)-but-1-ene (17). Purification by flash chromatography (silica gel, 20:80, EtOAc/hexanes) afforded alkene **17** (0.64 g, 1.2 mmol, 65%) as a colorless, viscous oil, containing the *E* and *Z* isomers. The isomers could not be readily separated at this stage by chromatography and were carried on to the next step as a mixture.

4.1.6.3. (*E*/*Z*) 2-{[3′-(*tert*-Butyldimethylsilyl)oxy]-4′-methoxyphenyl}-1,2-bis-phenyl-1-(3″,4″,5″-trimethoxyphenyl)-ethylene (18). Purification by flash chromatography (silica gel, 20:80, EtOAc/hexanes) afforded alkene **18** (0.27 g, 0.46 mmol, 25%) as a colorless, viscous oil, containing the *E* and *Z* isomers. The isomers could not be readily separated at this stage by chromatography and were carried on to the next step as a mixture.

4.1.7. (*E*/*Z*) 1-{[3′-(*tert*-Butyldimethylsilyl)oxy]-4′-methoxyphenyl}-1-phenyl-2-(3″,4″,5″-trimethoxyphenyl)-prop-1-ene (19)

To a solution of titanium trichloride (1.97 g, 12.8 mmol) in anhydrous THF (50 mL) under a N_2 atmosphere, $LiAlH_4$ (2.5 M soln in THF) (0.25 g, 2.6 mL) was added dropwise. The solution was heated at reflux for 20 min, at which point a premixed solution of ketone **13** (0.385 g, 1.83 mmol), ketone **12** (0.628 g, 1.83 mmol), and 1,8-bis(dimethylamino)naphthalene (0.398 g, 1.83 mmol) in THF (10 mL) was added dropwise to the reaction mixture. Reflux was continued for an additional 5 h. The reaction mixture was returned to room temperature, at which point a potassium carbonate solution (20% aqueous) was added dropwise until no further bubble formation was observed. The solution was filtered, and the filtrate was extracted with Et_2O (3 × 25 mL). The organic layer was washed with water followed by brine, dried over anhydrous $MgSO_4$, and concentrated in vacuo. Purification by flash chromatography (silica gel, 20:80, EtOAc/hexanes) afforded alkene **19** (0.687 g, 1.32 mmol, 72%) as a colorless, viscous oil, containing the *E* and *Z* isomers. The isomers could not be readily separated at this stage by chromatography and were carried on to the next step as a mixture.

4.1.8. (*E*/*Z*) 1-{[3′-(*tert*-Butyldimethylsilyl)oxy]-4′-methoxyphenyl}-1-phenyl-2-(3″,4″,5″-trimethoxyphenyl)-but-1-ene (20)

To a solution of titanium trichloride (2.26 g, 14.7 mmol) in anhydrous THF (50 mL) under a N_2 atmosphere, $LiAlH_4$ (2.5 M soln in THF) (0.28 g, 3.0 mL) was added dropwise. The solution was heated at reflux for 20 min, at which point a premixed solution of ketone **14** (0.537 g, 2.39 mmol), ketone **12** (0.82 g, 2.4 mmol), and 1,8-bis(dimethylamino)naphthalene (0.398 g, 1.83 mmol) in THF (10 mL) was added dropwise to the reaction mixture. Reflux was continued for an additional 5 h. The reaction mixture was returned to room temperature, at which point a potassium carbonate solution (20% aqueous) was added dropwise until no further bubble formation was observed. The solution was filtered, and the filtrate was extracted with Et_2O (3 × 25 mL). The organic layer was washed with water followed by brine, dried over anhydrous $MgSO_4$, and concentrated in vacuo. Purification by flash chromatography (silica gel, 20:80, EtOAc/hexanes) afforded alkene **20** (0.868 g, 1.62 mmol, 68%) as a colorless, viscous oil, containing the *E* and *Z* isomers. The isomers could not be readily separated at this stage by chromatography and were carried on to the next step as a mixture.

4.1.9. A typical experimental procedure for the deprotection of TBS ether derivatives to form compounds 21–30

To a solution of the appropriate alkene **16**–**20** in CH_2Cl_2 at 0 °C under N_2, tetrabutylammonium fluoride was added slowly. The reaction mixture was stirred for 1 h (0 °C to rt). The reaction was quenched with water and extracted with CH_2Cl_2. The organic layer was separated, washed with brine, dried over $MgSO_4$, and concentrated in vacuo.

4.1.9.1. 2-{3′-Hydroxy-4′-methoxyphenyl}-1-phenyl-1-(3″,4″,5″-trimethoxyphenyl)-prop-1-ene (*E* = 21, *Z* = 22). Purification by flash chromatography (silica gel, 5:95, EtOAc/hexanes) afforded **21** (0.047 g, 0.12 mmol 16%, *E*-isomer) and **22** (0.130 g, 0.320 mmol, 42%, *Z*-isomer) as white solids.

Melting point: **21** (159–160 °C), **22** (151–152 °C).

21 *E*-isomer: ^{1}H NMR (DMSO-d_6, 360 MHz): δ 8.72 (s, 1H, O*H*), 6.98–7.1 (m, 3H, Ph*H*), 6.91 (d, 2H, J = 7.4 Hz, Ph*H*), 6.68 (d, 1H, J = 8.2 Hz, Ar*H*), 6.56 (d, 1H, J = 2.0 Hz, Ar*H*), 6.50 (dd, 1H, J = 8.1 Hz, J = 2.0 Hz, Ar*H*), 6.43 (s, 2H, Ar*H*), 3.71 (s, 6H, OCH_3), 3.68 (s, 3H, OCH_3), 3.66 (s, 3H, OCH_3), 1.99 (s, 3H, CH_3).

^{13}C NMR (DMSO-d_6, 90 MHz): δ 152.7, 146.0, 145.7, 142.7, 139.0, 137.8, 136.1, 136.0, 134.9, 130.0, 127.5, 125.8, 120.0, 116.4, 111.4, 106.7, 60.0, 55.9, 55.4, 23.4.

21 *E*-isomer: HRMS (EI$^+$) *m/z*: 406.1787 (Calcd for $C_{25}H_{26}O_5$—406.1780).

22 *Z*-isomer: ^{1}H NMR (DMSO-d_6, 360 MHz): δ 8.79 (s, 1H, O*H*), 7.38 (m, 2H, Ph*H*), 7.28 (m, 1H, Ph*H*), 7.22 (d, 2H, J = 7.2 Hz, Ph*H*), 6.77 (d, 1H, J = 8.0 Hz, Ar*H*), 6.59 (d, 1H, J = 2.0 Hz, Ar*H*), 6.58 (dd, 1H, J = 8.0 Hz, J = 2.0 Hz, Ar*H*), 6.11 (s, 2H, Ar*H*), 3.84 (s, 3H, OCH_3), 3.55 (s, 3H, OCH_3), 3.43 (s, 6H, OCH_3), 1.97 (s, 3H, CH_3).

^{13}C NMR (DMSO-d_6, 90 MHz): δ 151.8, 146.2, 146.0, 142.8, 138.2, 137.7, 136.5, 135.6, 135.0, 129.6, 128.2, 126.7, 119.5, 116.1, 116.0, 111.8, 108.0, 59.9, 55.6, 55.5, 23.3.

Anal. Calcd for $C_{25}H_{26}O_5$ **22** *Z*: C, 73.87, H, 6.45. Found: C, 73.57, H, 6.50.

22 *Z*-isomer: HRMS (EI$^+$) *m/z*: 406.1766 (Calcd for $C_{25}H_{26}O_5$—406.1780).

4.1.9.2. 2-{3′-Hydroxy-4′-methoxyphenyl}-1-phenyl-1-(3″,4″,5″-trimethoxyphenyl)-but-1-ene (*E* = 23, *Z* = 24). Purification by flash chromatography (silica gel, 5:95, EtOAc/hexanes) afforded **23** (0.13 g, 0.31 mmol, 26%, *E*-isomer) and **24** (0.26 g, 0.62 mmol, 52 %, *Z*-isomer) as white solids.

Melting point: **23** (150–151 °C), **24** (126–127 °C).

23 *E*-isomer: ^{1}H NMR (DMSO-d_6, 360 MHz): δ 8.75 (s, 1H, O*H*), 6.99–7.10 (m, 3H, Ph*H*), 6.91–6.94 (m, 2H, Ph*H*), 6.72 (d, 1H, *J* = 8.6 Hz, Ar*H*), 6.56 (d, 1H, *J* = 2.2 Hz, Ar*H*), 6.50 (dd, 1H, *J* = 8.3 Hz, *J* = 2.2 Hz, Ar*H*), 6.45 (s, 2H, Ar*H*), 3.74 (s, 6H, OCH_3), 3.70 (s, 3H, OCH_3), 3.68 (s, 3H, OCH_3), 2.33 (q, 2H, *J* = 7.2 Hz CH_2CH$_3$), 0.88 (t, 3H, *J* = 7.2 Hz, CH$_2$CH_3).

^{13}C NMR (DMSO-d_6, 90 MHz): δ 152.7, 146.0, 145.7, 142.5, 141.2, 138.9, 137.4, 136.1, 133.9, 129.9, 127.5, 125.7, 120.4, 116.6, 111.4, 106.2, 60.0, 55.8, 55.3, 28.9, 13.4.

23 *E*-isomer: HRMS (EI$^+$) *m/z*: 420.1940 (Calcd for $C_{26}H_{28}O_5$—420.1937).

24 *Z*-isomer: ^{1}H NMR (DMSO-d_6, 360 MHz): δ 8.79 (s, 1H, O*H*), 7.37–7.42 (m, 2H, Ph*H*), 7.28–7.32 (m, 1H, Ph*H*), 7.23 (d, 2H, *J* = 6.8 Hz, Ph*H*), 6.79 (d, 1H, *J* = 7.9 Hz, Ar*H*), 6.57 (d, 1H, *J* = 1.8 Hz, Ar*H*), 6.56 (dd, 1H, *J* = 7.9 Hz, *J* = 1.8 Hz, Ar*H*), 6.11 (s, 2H, Ar*H*), 3.72 (s, 3H, OCH_3), 3.56 (s, 3H, OCH_3), 3.44 (s, 6H, OCH_3), 2.30 (q, 2H, *J* = 7.2 Hz, CH_2CH$_3$), 0.87 (t, 3H, *J* = 7.2 Hz, CH$_2$CH_3).

^{13}C NMR (DMSO-d_6, 90 MHz): δ 151.7, 146.1, 145.9, 142.7, 141.3, 138.0, 137.3, 135.4, 134.4, 128.9, 128.2, 126.6, 119.8, 116.4, 111.7, 107.9, 59.8, 55.45, 55.36, 28.6, 13.3.

Anal. Calcd for $C_{26}H_{28}O_5$ **24** *Z*: C, 74.26, H, 6.71. Found: C, 74.09, H, 6.79.

24 *Z*-isomer: HRMS (EI$^+$) *m/z*: 420.1939 (Calcd for $C_{26}H_{28}O_5$—420.1937).

4.1.9.3. 2-{3′-Hydroxy-4′-methoxyphenyl}-1,2-bis-phenyl-1-(3″,4″,5″-trimethoxyphenyl)-ethylene (*E* = 25, *Z* = 26).

Purification by flash chromatography (silica gel, 5:95, EtOAc/hexanes) afforded **25** (0.14 g, 0.30 mmol, 65%, *E*-isomer) and **26** (0.04 g, 0.09 mmol, 20%, *Z*-isomer) as white solids.

Melting point: **25** (198–199 °C), **26** (184–186 °C).

25 *E*-isomer: ^{1}H NMR (CDCl$_3$, 500 MHz): δ 7.02–7.16 (m, 10H, Ph*H*), 6.59 (d, 1H, *J* = 2.0 Hz, Ar*H*), 6.57 (d, 1H, *J* = 8.4 Hz, Ar*H*), 6.50 (dd, 1H, *J* = 8.4 Hz, *J* = 2.0 Hz, Ar*H*), 6.18 (s, 2H, Ar*H*), 5.37 (s, 1H, O*H*), 3.81 (s, 3H, OCH_3), 3.79 (s, 3H, OCH_3), 3.49 (s, 6H, OCH_3).

^{13}C NMR (DMSO-d_6, 90 MHz): δ 151.9, 146.2, 145.6, 144.0, 143.0, 140.2, 139.2, 138.6, 135.9, 135.6, 130.6, 130.2, 127.7, 126.4, 126.2, 121.9, 117.9, 111.2, 108.5, 59.9, 55.4, 55.2.

Anal. Calcd for $C_{30}H_{28}O_5$ **25** *E*: C, 76.90, H, 6.02. Found: C, 76.55, H, 6.05.

25 *E*-isomer: HRMS (EI$^+$) *m/z* 468.1928 (Calcd for $C_{30}H_{28}O_5$—468.1937).

26 *Z*-isomer: ^{1}H NMR (CDCl$_3$, 500 MHz): δ 7.00–7.12 (m, 10H, Ph*H*), 6.62 (d, 1H, *J* = 2.0 Hz, Ar*H*), 6.61 (d, 1H, *J* = 8.2 Hz, Ar*H*), 6.54 (dd, 1H, *J* = 8.3 Hz, 2.1 Hz, Ar*H*), 6.25 (s, 2H, Ar*H*), 5.40 (s, 1H, O*H*), 3.83 (s, 3H, OCH_3), 3.81 (s, 3H, OCH_3), 3.55 (s, 6H, OCH_3).

^{13}C NMR (DMSO-d_6, 90 MHz): δ 151.9, 146.3, 145.8, 143.4, 142.8, 140.2, 139.2, 138.6, 136.2, 136.1, 130.7, 130.5, 127.61, 127.56, 126.4, 126.2, 121.4, 117.6, 111.6, 108.4, 59.9, 55.5.

Anal. Calcd for $C_{30}H_{28}O_5$ **26** *Z*: C, 76.90, H, 6.02. Found: C, 76.38, H, 6.07.

26 *Z*-isomer: HRMS (EI$^+$) *m/z* 468.1934 (Calcd for $C_{30}H_{28}O_5$—468.1937).

4.1.9.4. 1-{3′-Hydroxy-4′-methoxyphenyl}-1-phenyl-2-(3″,4″,5″-trimethoxyphenyl)-prop-1-ene (*E* = 27, *Z* = 28).

Purification by flash chromatography (silica gel, 5:95, EtOAc/hexanes) afforded **27** (0.116 g, 0.285 mmol 22%, *E*-isomer) and **28** (0.200 g, 0.492 mmol, 37%, *Z*-isomer) as white solids.

Melting point: **27** (134–135 °C), **28** (167–168 °C).

27 *E*-isomer: ^{1}H NMR (DMSO-d_6, 500 MHz): δ 8.93 (s, 1H, O*H*), 7.09 (t, 2H, *J* = 7.0 Hz, Ph*H*), 7.03 (t, 1H, *J* = 7.2 Hz, Ph*H*), 6.90 (d, 1H, *J* = 8.2 Hz, Ar*H*), 6.88 (d, 1H, *J* = 7.3 Hz, Ph*H*), 6.63 (dd, 1H, *J* = 8.2 Hz, *J* = 2.0 Hz, Ar*H*), 6.59 (d, 1H, *J* = 2.0 Hz, Ar*H*), 6.37 (s, 2H, Ar*H*), 3.77 (s, 3H, OCH_3), 3.57 (s, 3H, OCH_3), 3.51 (s, 6H, OCH_3), 2.11 (s, 3H, CH_3).

^{13}C NMR (CDCl$_3$, 125 MHz): δ 152.5, 145.3, 145.2, 143.5, 139.2, 139.0, 136.9, 136.4, 134.9, 130.4, 127.5, 125.8, 121.8, 116.3, 110.2, 106.9, 60.9, 55.92, 55.9, 22.8.

Anal. Calcd for $C_{25}H_{26}O_5$ **27** *E*: C, 73.87, H, 6.45. Found: C, 73.78, H, 6.36.

27 *E*-isomer: HRMS (EI$^+$) *m/z*: 406.1769 (Calcd for $C_{25}H_{26}O_5$—406.1780).

28 *Z*-isomer: ^{1}H NMR (DMSO-d_6, 500 MHz): δ 8.68 (s, 1H, O*H*), 7.36 (t, 2H, *J* = 7.4 Hz, Ph*H*), 7.25 (t, 1H, *J* = 7.4 Hz, Ph*H*), 7.19 (m, 2H, Ph*H*), 6.65 (d, 1H, *J* = 8.4 Hz, Ar*H*), 6.43 (s, 2H, Ar*H*), 6.34 (d, 1H, *J* = 2.1 Hz, Ar*H*), 6.29 (dd, 2H, *J* = 8.3 Hz, *J* = 2.2 Hz, Ar*H*), 3.65 (s, 3H, OCH_3), 3.60 (s, 3H, OCH_3), 3.56 (s, 6H, OCH_3), 2.03 (s, 3H, CH_3).

^{13}C NMR (CDCl$_3$, 125 MHz): δ 152.5, 144.8, 144.7, 143.5, 139.4, 139.0, 136.8, 136.4, 134.7, 129.8, 128.1, 126.5, 122.5, 116.7, 109.8, 106.7, 60.9, 56.0, 55.8, 22.9.

Anal. Calcd for $C_{25}H_{26}O_5$ **28** *Z*: C, 73.87, H, 6.45. Found: C, 73.44, H, 6.44.

28 *Z*-isomer: HRMS (EI$^+$) *m/z*: 406.1763 (Calcd for $C_{25}H_{26}O_5$—406.1780).

4.1.9.5. 1-{3′-Hydroxy-4′-methoxyphenyl}-1-phenyl-2-(3″,4″,5″-trimethoxyphenyl)-but-1-ene (*E* = 29, *Z* = 30).

Purification by flash chromatography (silica gel, 5:95, EtOAc/hexanes) afforded **29** (0.130 g, 0.309 mmol, 19%, *E*-isomer) and **30** (0.262 g, 0.623 mmol, 38%, *Z*-isomer) as white solids.

Melting point: **29** (140–142 °C), **30** (165–166 °C).

29 *E*-isomer: ^{1}H NMR (DMSO-d_6, 500 MHz): δ 8.95 (s, 1H, O*H*), 7.07 (t, 2H, *J* = 7.3 Hz, Ph*H*), 7.01 (t, 1H, *J* = 7.3 Hz, Ph*H*), 6.90 (d, 1H, *J* = 8.3 Hz, Ar*H*), 6.86 (d, 2H, *J* = 7.1 Hz, Ar*H*), 6.63 (dd, 1H, *J* = 8.2 Hz, *J* = 2.0 Hz, Ar*H*), 6.59 (d, 1H, *J* = 2.0 Hz, Ar*H*), 6.34 (s, 2H, Ar*H*), 3.77 (s, 3H, OCH_3), 3.58 (s, 3H, OCH_3), 3.52 (s, 6H, OCH_3), 2.48 (q, 2H, *J* = 7.4 Hz, CH_2CH$_3$), 0.92 (t, 3H, *J* = 7.4 Hz, CH$_2$CH_3).

^{13}C NMR (CDCl$_3$, 125 MHz): δ 152.5, 145.3, 145.2, 143.5, 141.6, 138.4, 137.4, 136.9, 136.4, 130.3, 127.4, 125.7, 121.1, 115.8, 110.2, 107.2, 60.9, 56.0, 55.9, 28.5, 13.8.

Anal. Calcd for $C_{26}H_{28}O_5$ **29** *E*: C, 74.26, H, 6.71, O, 19.02. Found: C, 74.14, H, 6.53, O, 18.85.

29 *E*-isomer: HRMS (EI$^+$) *m/z* 420.1933 (Calcd for $C_{26}H_{28}O_5$—420.1937).

30 *Z*-isomer: ^{1}H NMR (DMSO-d_6, 500 MHz): δ 8.65 (s, 1H, O*H*), 7.36 (t, 2H, *J* = 7.5 Hz, Ph*H*), 7.26 (m, 1H, *J* = 7.5 Hz, Ph*H*), 7.18 (d, 2H, *J* = 7.0 Hz, Ar*H*), 6.62 (d, 1H, *J* = 8.4 Hz, Ar*H*), 6.40 (s, 2H, Ar*H*), 6.32 (d, 1H, *J* = 2.1 Hz, Ar*H*), 6.27 (dd, 1H, *J* = 8.3 Hz, *J* = 2.1 Hz, Ar*H*), 3.63 (s, 3H, OCH_3), 3.61 (s, 3H, OCH_3), 3.57 (s, 6H, OCH_3), 2.37 (q, 2H, *J* = 7.4 Hz, CH_2CH$_3$), 0.89 (t, 3H, *J* = 7.4 Hz, CH$_2$CH_3).

^{13}C NMR (CDCl$_3$, 125 MHz): δ 152.6, 144.66, 144.65, 143.5, 141.3, 138.4, 137.6, 136.8, 136.4, 129.3, 128.1, 126.5, 122.4, 116.6, 109.7, 107.0, 60.9, 56.0, 55.8, 28.6, 13.7.

Anal. Calcd for $C_{26}H_{28}O_5$ **30** *Z*: C, 74.26, H, 6.71. Found: C, 74.34, H, 6.67.

30 *Z*-isomer: HRMS (EI$^+$) *m/z* 420.1936 (Calcd for $C_{26}H_{28}O_5$—420.1937).

4.2. Biology

4.2.1. Effects on tubulin polymerization

Bovine brain tubulin was purified as described previously.[33] To evaluate the effect of the compounds on tubulin assembly in vitro, varying concentrations were preincubated with 10 μM tubulin (1.0 μg/mL) in glutamate buffer at 30 °C and then cooled to 0 °C. After the addition of GTP, the mixtures were transferred to 0 °C cuvettes in a recording spectrophotometer and warmed to 30 °C.

The assembly of tubulin was observed turbidimetrically.[34] The IC_{50} was defined as the compound concentration that inhibited the extent of assembly by 50% after a 20 min incubation.

4.2.2. Cell lines

All cell lines were maintained and grown on 60 cm^2 dishes at 37 °C in a humidified atmosphere containing 5% CO_2. The DU-145 prostate cancer and the SK-OV-3 ovarian cancer cell lines were cultured in Dulbecco's modified Eagle's medium (DMEM) cell culture medium (Biowhittaker®, Cat# 12–614F) containing final concentrations of the following ingredients: 10% fetal bovine serum (Gibco One Shot™, Cat# 16000-077), 2 mM L-glutamine (Glutamax®, Gibco, Cat# 35050-061), 100 IU/mL penicillin, and 100 μg/mL streptomycin. The NCI-H460 lung cancer cell line was cultured in RPMI-1640 culture medium (ATCC®, Cat# 30-2001) containing 5% fetal calf serum, 100 IU/mL penicillin, and 100 μg/mL streptomycin.

During the SRB assay, cells were plated in media containing the same serum, glutamine, and penicillin/streptomycin concentrations as described above and allowed to grow for 24 h before addition of compounds to be assayed. Compounds to be assayed were added as serial dilutions in media appropriate to the cell line, containing 5% fetal bovine serum, 2 mM L-glutamine, 100 μg/mL penicillin, and 100 μg/mL streptomycin.

4.2.3. SRB assay (cell growth inhibition assay)

Inhibition of human cancer growth was assessed using the National Cancer Institute's standard SRB assay, as previously described.[35] Briefly, cells were distributed into 96-well plates (Costar®, Corning Inc., New York) in 100 μL of medium at a final concentration of 1×10^4 cells/well and incubated for 24 h, followed by treatment with study compounds and doxorubicin as a control at concentrations between 0.000005 and 50.0 μg/mL at 37 °C for 48 h. A growth inhibition of 50% in comparison to untreated controls (GI_{50} or the drug concentration causing a 50% reduction in net protein increase) was calculated by nonlinear regression analysis.

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Supplementary data

Supplementary data (details regarding structural characterization of final compounds (**21**–**30**) including ^1H NMR, ^{13}C NMR, 2D-NOESY, and HRMS spectra along with the thermal ellipsoid plots at 50% probability for compounds **23** and **27**) associated with this article can be found, in the online version, at doi:10.1016/j.bmc.2009.08.011.

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