Antineoplastic Agents. 465. Structural Modification of Resveratrol: Sodium Resverastatin Phosphate[1]

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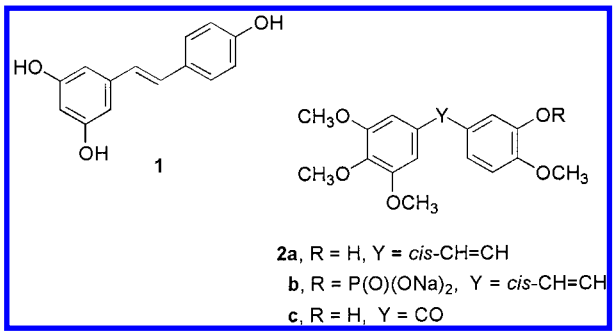
As an extension of structure/activity investigations of resveratrol (**1**), phenstatin (**2c**), and the cancer antiangiogenesis drug sodium combretastatin A-4 phosphate (**2b**), syntheses of certain related stilbenes (**14**) and benzophenones (**16**) were undertaken. The trimethyl ether derivative of (*Z*)-resveratrol (**4a**) exhibited the strongest activity (GI_{50} = 0.01−0.001 μg/mL) against a minipanel of human cancer cell lines. A monodemethylated derivative (**14c**) was converted to prodrug **14n** (sodium resverastatin phosphate) for further biological evaluation. The antitubulin and antimicrobial activities of selected compounds were also evaluated.

Resveratrol (**1**), 3,4′,5-trihydroxy-*trans*-stilbene, is a phytoalexin found in grapes[2] and certain other plants.[3] The compound exhibits a variety of useful biological properties[4] including antileukemic,[5] antibacterial,[6] antifungal,[7] antiplatelet aggregation,[8] and coronary vasodilator[9] activities. This triphenolic stilbene (**1**) also has strong antioxidative and antiinflammatory activities associated with chemopreventive properties.[10] Resveratrol (**1**) has been suggested as a possible cancer chemopreventive agent on the basis of inhibitory effects on tumor initiation, promotion, and progression.[11] In addition to antitumor-promoting activity, **1** has displayed cancer cell growth inhibition in vitro.[12] Importantly, resveratrol has recently been shown to induce apoptosis and decrease expression of Bcl-2 in the human leukemia HL-60 cell line.[13] Furthermore, the resveratrol tetramer vatdiospyridol[14] and resveratrol oligomers[15] recently isolated from Asian plants have shown significant inhibition of the growth of several cancer cell lines. Other biological properties of **1** include activities targeting cyclooxygenase,[11a] tyrosine kinase (PTK),[12c] and protein kinase C (PKC),[12c] as well as selective human cytochrome P450 1A1[12d] inhibition and microbiological transformation to resveratrol 3-*O*-β-D-glucoside.[16]

We have been exploring the antitumor properties of a series of structurally simple stilbenes derived from the South African bush willow *Combretum caffrum*.[17] These investigations eventually led to our isolation, structure determination, and synthesis[18] of the *cis*-stilbene combretastatin A-4 (**2a**) and its phosphate prodrug (**2b**).[19] The latter has been shown to selectively damage tumor neovasculature with induction of extensive blood flow shutdown in the metastatic tumor compared to normal tissues. For example, 6 h following treatment using the murine CaNT adenocarcinoma and a single ip injection of combretastatin A-4 prodrug (100 mg/kg), vascular function shutdown in the tumor was rapid, irreversible, and extensive.[19] In November 1998 four phase I human cancer trials were initiated, two in the United States and two in England. Current clinical trials[20] have been encouraging, and phase II human cancer clinical trials are soon to be initiated. Given these very encouraging results, we have been investigating related stilbenes, and the present study was directed at new resveratrol structural modifications as potential antineoplastic agents.



Materials and Methods

All solvents were redistilled. DIEA and proton sponge refer respectively to *N*,*N*-diisopropylethylamine and 1,8-bis(dimethylamino)naphthalene. Reactions were monitored by thin-layer chromatography using Analtech silica gel GHLF uniplates. All reactions were carried out under an inert atmosphere. Solvent extracts of aqueous solutions were dried over anhydrous sodium sulfate unless otherwise noted. Flash column chromatography was performed using silica gel (230−400 mesh ASTM).

Melting points were recorded employing an Electrothermal 9100 digital melting point apparatus and are uncorrected. The IR spectra were obtained using a Mattson FTIR model 2020 instrument. Low-resolution mass spectral data were collected using a Varian MAT 312 instrument (EIMS). The high-

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resolution FAB spectra were obtained employing a Kratos MS-50 spectrometer at the Midwest Center for Mass Spectrometry, University of Nebraska, Lincoln, NE. All ^{1}H and ^{13}C NMR spectra were determined using a Varian Gemini 300 MHz instrument with $CDC1_3$ (TMS internal reference) as solvent unless otherwise noted. The ^{31}P NMR spectra were measured in $CDC1_3$ with 85% H_3PO_4 as an external standard employing a Varian Unity 500 MHz instrument. Elemental analyses were determined by Galbraith Laboratories Inc., Knoxville, TN.

4-Methoxybenzyltriphenylphosphonium Bromide (3). To a solution of 4-methoxybenzyl bromide (22.4 g) in toluene (200 mL) was added triphenylphosphine (29.2 g). The solution was heated at reflux for 12 h under argon. The resulting precipitate was collected and recrystallized from ethanol as colorless crystals (44.0 g, 85.3%): mp 235−237 °C (lit.[19] mp 234 °C).

General Procedure for the Stilbene Syntheses. To the phosphonium bromide (1−35 mmol) in anhydrous tetrahydrofuran (5−200 mL) at −78 °C was added *n*-butyllithium (2.44 M, 1.0 equiv), and the resulting red solution was stirred under argon for 2−4 h. A solution of the aldehyde (1.0 equiv) in tetrahydrofuran was added dropwise over 30 min and the mixture stirred for 6−15 h. The resulting cream suspension was poured into water and extracted with dichloromethane. The organic phase was washed with water, and removal of the solvent in vacuo afforded a tan oil. The oil was separated by flash column chromatography (49:1 hexane/ethyl acetate). The *cis*-stilbene eluted first as a clear oil followed by the *trans* isomer as a colorless solid or oil (TBDMS-protected).

3,4′,5-Trimethoxystilbene (4a,b). Reaction of phosphonium bromide **3** (12.5 g) and 3,5-dimethoxybenzaldehyde (4.5 g) led to *cis*-stilbene **4a** as a clear oil (3.56 g) and the *trans* isomer **4b** as a colorless solid (3.08 g), 91% total yield. Data for (*Z*)-isomer **4a**: IR (neat, cm^{-1}) ν_{max} 3449, 2957, 2836, 1591, 1250, 1065, 640; ^{1}H NMR δ 7.22 (2H, dd, J = 2.4, 8.7 Hz), 6.77 (2H, dd, J = 2.4, 8.7 Hz), 6.53 (1H, d, J = 12.0 Hz), 6.45 (1H, d, J = 12.0 Hz), 6.44 (2H, d, J = 2.1 Hz), 6.32 (1H, t, J = 2.1 Hz), 3.78 (3H, s, OCH_3), 3.67 (6H, s, $OCH_3 \times 2$). Data for (*E*)-isomer **4b**: mp 57−58 °C (lit.[20] mp 55−56 °C).

Resveratrol (1). To stilbene **4b** (3.1 g) in anhydrous dichloromethane (150 mL) at −78 °C was added (dropwise) boron tribromide (1.0 M, 34.5 mL), and the resulting red solution was stirred under argon for 30 min. The solution was poured into water and extracted with dichloromethane. The organic phase was washed with water, and removal of the solvent in vacuo afforded a tan oil, which was separated by flash column chromatography (1:1 hexane/ethyl acetate) to afford a colorless solid (2.26 g, 86%): mp 260 °C (lit.[12c] mp 260 °C).

4-(*tert*-Butyldiphenylsilyloxy)benzaldehyde (5a). To a solution of 4-hydroxybenzaldehyde (3.2 g) in dimethylformamide (50 mL) was added imidazole (1.9 g, 1.1 equiv). The solution was stirred for 15 min, *tert*-butyldiphenylsilyl chloride (7.4 mL, 1.1 equiv) was added, and the light brown solution was stirred for 3 h. The reaction mixture was poured into water and extracted with ethyl acetate. Removal of the solvent in vacuo from the organic phase provided a brown oil. The oil was separated by flash column chromatography (1:0 → 19:1 hexane/ethyl acetate) to afford the aldehyde **5a** as a colorless solid (6.4 g, 68%): mp 103−105 °C; IR (neat, cm^{-1}) ν_{max} 3399, 2932, 2859, 1699, 1599, 1506, 1273, 1157, 910; ^{1}H NMR δ 9.80 (1H, s, CHO), 7.69 (4H, m, Ar-H), 7.64 (2H, d, J = 8.7 Hz), 7.40 (6H, m, Ar-H), 6.86 (2H, d, J = 8.7 Hz), 1.11 (9H, s, $C(CH_3)_3$).

4-(*tert*-Butyldiphenylsilyloxy)benzyl Alcohol (6). To a solution of aldehyde **5a** (4.7 g) in methanol (100 mL) at 0 °C was slowly added sodium borohydride (0.59 g, 1.2 equiv). After being stirred for 2 h, the reaction mixture was poured into water. The solvent was reduced to a minimum and extracted with ethyl acetate, and removal of the solvent in vacuo from the organic phase gave a clear oil (4.1 g, 88%): IR (neat, cm^{-1}) ν_{max} 3346, 2932, 2859, 1609, 1510, 1427, 1256, 1113, 918; ^{1}H NMR δ 7.72 (4H, m, Ar-H), 7.39 (6H, m, Ar-H), 7.10 (2H, d, J = 8.7 Hz), 6.76 (2H, d, J = 8.7 Hz), 4.55 (2H, s, CH_2), 1.11 (9H, s, $C(CH_3)_3$).

4-(*tert*-Butyldiphenylsilyloxy)benzyl Bromide (7). Phosphorus tribromide (0.5 mL) was slowly added to a solution of alcohol **6** (4.0 g) in dichloromethane (75 mL) at 0 °C, and stirring was continued for 12 h. The reaction mixture was poured into aqueous sodium bicarbonate and extracted with dichloromethane. Removal of the solvent in vacuo from the organic phase afforded a colorless solid (4.3 g, 89%): EIMS m/z 426 [M(^{81}Br)$^+$], 424 [M(^{79}Br)$^+$], 390, 369, 367, 345, 289, 135; IR (neat, cm^{-1}) ν_{max} 3397, 3073, 2932, 2859, 1607, 1510, 1427, 1263, 1113, 918; ^{1}H NMR δ 7.72 (4H, m, Ar-H), 7.39 (6H, m, Ar-H), 7.13 (2H, d, J = 8.4 Hz) 6.72 (2H, d, J = 8.4 Hz), 4.42 (2H, s, CH_2), 1.11 (9H, s, $C(CH_3)_3$); ^{13}C NMR (75.5 MHz) δ 155.6, 135.4, 132.4, 130.1, 129.9, 127.7, 119.9, 34.0, 26.5, 19.5.

4-(*tert*-Butyldiphenylsilyloxy)benzyltriphenylphosphonium Bromide (8). To a solution of bromide **7** (4.3 g) in toluene (100 mL) was added triphenylphosphine (13.2 g). After being heated at 100 °C for 2 h, the reaction mixture was cooled to room temperature, and the product was collected and crystallized from ethanol in a colorless solid (6.1 g, 89%): mp 233 °C; FABMS m/z 607.2583 (M^+ − Br); IR (neat, cm^{-1}) ν_{max} 3385, 3054, 2934, 2859, 2787, 1607, 1512, 1437, 1273, 1111, 924; ^{1}H NMR δ 7.61 (19H, m, Ar-H), 7.30 (6H, m, Ar-H), 6.76 (2H, dd, J = 2.4, 8.7 Hz) 6.51 (2H, d, J = 8.7 Hz), 5.18 (2H, s, CH_2), 1.04 (9H, s, $C(CH_3)_3$); ^{13}C NMR (75.5 MHz) δ 155.7, 135.3, 134.7, 134.7, 134.3, 132.3, 132.3, 130.0, 129.8, 127.6, 120.2, 120.1, 118.9, 118.9, 118.1, 117.3, 30.5, 30.1, 26.5, 19.4.

3,5-Di(*tert*-butyldimethylsilyloxy)benzaldehyde (9a). DIEA (7.7 mL, 2 equiv) was added to a solution of 3,5-dihydroxybenzaldehyde (3.0 g) in dimethylformamide (30 mL), and the solution was stirred for 15 min. The silyl chloride (7.5 g) was added and the light brown solution stirred for 16 h. The mixture was poured into water and extracted with dichloromethane. Removal of the solvent in vacuo yielded a brown oil that was separated by flash column chromatography (9:1 hexane/ethyl acetate) to yield the disilyl ether as a tan oil (7.6 g, 94%): EIMS m/z 366 (M^+), 309, 267, 239, 133,73; IR (KBr, cm^{-1}) ν_{max} 2957, 2861, 2805, 2710, 1705, 1385, 831; ^{1}H NMR δ 9.85 (1H, s, CHO), 6.95 (2H, d, J = 2.1 Hz), 6.58 (1H, t, J = 2.1 Hz), 0.99 (18H, s, $C(CH_3)_3 \times 2$), 0.22 (12H, s, $Si(CH_3)_2 \times 2$).

***cis*-Resveratrol (10).** The Wittig reaction was performed as summarized above using 5 mmol of phosphonium salt, and the TBDPS-protected stilbene isomers were isolated as a mixture. The mixture was dissolved in tetrahydrofuran and treated with TBAF (3.0 equiv), being stirred for 1 h. The product was purified by gravity column chromatography (3:2 hexane/ethyl acetate) and yielded 0.21 g of the *cis* isomer as a colorless solid and 0.24 g of a mixture of isomers (95.1%): mp 172−174 °C (lit.[12c] mp 170−174 °C).

4-*tert*-Butyldimethylsilyloxybenzaldehyde (5b). To a solution of 4-hydroxybenzaldehyde (6.0 g) in dimethylformamide (50 mL) was added DIEA (17.2 mL, 2 equiv). The solution was stirred for 15 min. *tert*-Butyldimethylsilyl chloride (8.9 g) was added, and the light brown solution was stirred for 15 h. The reaction mixture was poured into water and extracted with dichloromethane. Removal of the solvent in vacuo afforded a brown oil that was separated by vacuum distillation to yield aldehyde **5b** as as a colorless oil (8.4 g, 73%): IR (neat, cm^{-1}) ν_{max} 3385, 2932, 2859, 1699, 1599, 1508, 1273, 1155, 909; ^{1}H NMR δ 9.88 (1H, s, CHO), 7.79 (2H, d, J = 8.4 Hz), 6.94 (2H, d, J = 8.4 Hz), 0.98 (9H, s, $C(CH_3)_3$), 0.25 (6H, s, $Si(CH_3)_2$).

3,5-Dimethoxybenzyltriphenylphosphonium Bromide (13). 3,5-Dimethoxybenzaldehyde (10 g) in methanol was reduced with sodium borohydride. The oily product **11** (9.6 g, 93% yield) was treated (0 °C, 12 h) with phosphorus tribromide (2.7 mL), and to its resulting bromide **12** (11.6 g, 89%) in toluene (200 mL) was added triphenylphosphine (13.2 g) (see the preparations of **6**−**8**). After being heated at reflux for 12 h, the mixture was cooled to room temperature. The product

was collected and recrystallized from ethanol in a colorless solid (22.8 g, 92%): mp 275 °C (lit.[12c] mp 266−268 °C).

4′-(*tert*-Butyldimethylsilyloxy)-3,5-dimethoxystilbene (14a,b). Phosphonium bromide **13** (6.9 g) in anhydrous tetrahydrofuran (40 mL) at −78 °C was treated with *n*-butyllithium (2.5 M, 5.6 mL) and aldehyde **5b** (3.3 g) in tetrahydrofuran (10 mL) according to the general Wittig procedure (see above). Data for (*Z*)-isomer **14a**: EIMS *m*/*z* 370 (M^+), 355, 313, 298, 157; IR (KBr, cm^{-1}) ν_{max} 2932, 2857, 1591, 1508, 1262, 1155, 914; ^1H NMR δ 7.14 (2H, d, J = 8.5 Hz), 6.70 (2H, d, J = 8.5 Hz), 6.51 (1H, d, J = 12.0 Hz), 6.43 (1H, d, J = 12.0 Hz), 6.42 (2H, d, J = 2.0 Hz), 6.31 (1H, t, J = 2.0 Hz), 3.65 (6H, s, $OCH_3 \times 2$), 0.96 (9H, s, $C(CH_3)_3$), 0.17 (6H, s, $Si(CH_3)_2$); ^{13}C NMR (75.5 MHz) δ 160.5, 154.9, 139.4, 130.3, 130.2, 128.8, 119.8, 106.6, 99.8, 55.2, 25.7, 18.2, −4.45. Data for (*E*)-isomer **14b**: EIMS *m*/*z* 370 (M^+), 355, 313, 255, 165, 73; IR (KBr, cm^{-1}) ν_{max} 2955, 2859, 1595, 1508, 1263, 1154, 914, 839; ^1H NMR δ 7.40 (2H, d, J = 8.5 Hz). 7.05 (1H, d, J = 16.0 Hz), 6.92 (1H, d, J = 16.0 Hz), 6.85 (2H, d, J = 8.5 Hz), 6.66 (2H, d, J = 2.5 Hz), 6.39 (1H, t, J = 2.5 Hz), 3.84 (6H, s, $OCH_3 \times 2$), 1.01 (9H, s, $C(CH_3)_3$), 0.23 (6H, s, $Si(CH_3)_2$); ^{13}C NMR (75.5 MHz) δ 160.9, 155.7, 139.7, 130.5, 128.8, 127.7, 126.7, 120.3, 104.3, 99.6, 55.3, 25.7, 18.2, −4.4.

(*Z*)- and (*E*)-3,5-Dimethoxy-4′-hydroxystilbene (14c,d) and General Silyloxy Deprotection Procedure. To a solution of the silyloxy-protected (*Z*)-stilbene **14a** (1.2 g) in anhydrous tetrahydrofuran (20 mL) was added tetrabutylammonium fluoride (1 M, 3.4 mL). The pale yellow solution was stirred for 45 min, poured into water, and extracted with dichloromethane, from which phase removal of the solvent in vacuo provided a tan oil. The oil was separated by gravity column chromatography (4:1 hexane/ethyl acetate) to afford *cis*-stilbene **14c** as a yellow oil (88%): IR (neat, cm^{-1}) ν_{max} 3385, 3005, 2940, 2837, 1591, 1512, 1456, 1152, 1065, 679; ^1H NMR δ 8.01 (1H, s, OH), 7.15 (2H, d, J = 8.7 Hz), 6.71 (2H, d, J = 8.7 Hz), 6.51 (1H, d, J = 12.6 Hz), 6.43 (2H, d, J = 2.5 Hz), 6.42 (1H, d, J = 12.6 Hz), 6.31 (2H, d, J = 2.5 Hz), 3.66 (6H s, $OCH_3 \times 2$).

(*E*)-3,5-Dimethoxy-4′-hydroxystilbene (14d) was similarly prepared from stilbene **14b** (0.5 g) and tetrabutylammonium fluoride (1M, 1.3 mL) in anhydrous tetrahydrofuran (10 mL), to yield 0.8 g of yellow oil (90%): IR (neat, cm^{-1}) ν_{max} 3385, 3005, 2940, 2837, 1591, 1512, 1456, 1152, 1065, 961; ^1H NMR δ 8.01 (1H, s, OH), 7.44 (2H, d, J = 8.7 Hz), 7.18 (1H, d, J = 16.5 Hz), 6.98 (1H, d, J = 16.5 Hz), 6.85 (2H, d, J = 8.7 Hz), 6.73 (2H, d, J = 2.1 Hz), 6.38 (1H, t, J = 2.1 Hz), 5.25 (1H, br s, OH), 3.81 (6H, s, $OCH_3 \times 2$).

Unless otherwise noted, the following intermediates and stilbene objectives were prepared by the preceding general methods for silyloxy protection, Wittig reaction, and deprotection.

3-(*tert*-Butyldimethylsilyloxy)-5-hydroxybenzaldehyde (9b). 3,5-Dihydroxybenzaldehyde (1.1 g) in dimethylformamide (10 mL) was monosilylated using DIEA (1.9 mL, 1.4 equiv) and the silyl chloride (1.2 g) with stirring for 3 h. The oily product was separated by flash column chromatography (9:1 hexane/ethyl acetate) to afford some disilylated product (0.7 g) and the desired monosilylated product as a colorless oil (0.8 g, 38.5%) that crystallized from ethanol: mp 79.6−80 °C; EIMS *m*/*z* 252 (M^+), 195, 167, 58, 45; IR (KBr, cm^{-1}) ν_{max} 3211, 2930, 2859, 1672, 1591, 1332, 841; ^1H NMR δ 9.84 (1H, s, CHO), 6.99 (1H, dd, J = 2.0, 1.0 Hz), 6.91 (1H, dd, J = 2.0, 1.0 Hz), 6.64 (1H, t, J = 2.0 Hz), 6.00 (1H, br s, OH), 0.97 (9H, s, $C(CH_3)_3$), 0.21 (6H, s, $Si(CH_3)_2$); ^{13}C NMR (75.5 MHz) δ 192.4, 157.6, 157.4, 138.3, 114.4, 114.0, 109.1, 25.6, 18.2, −4.47.

3-(*tert*-Butyldimethylsilyloxy)-5-methoxybenzaldehyde (9c). To a solution of phenol **9b** (0.7 g) in dichloromethane (10 mL) was added molecular sieves (4 Å, 0.8 g), proton sponge (1.6 g, 2.5 equiv), and trimethyloxonium tetrafluoroborate (1.1 g, 2.5 equiv), and the solution was stirred for 15 h. The solution was filtered, the sieves were rinsed with ethyl acetate, and the solvent was removed from the combined filtrate in vacuo to yield a yellow oil. The oil was purified by flash column chromatography (10:1 hexane/ethyl acetate), yielding a colorless oil (0.6 g, 79%): EIMS *m*/*z* 266 (M^+), 209, 181, 166, 89, 58, IR (KBr, cm^{-1}) ν_{max} 2932, 2859, 1703, 1593, 1468, 1337, 1059, 839; ^1H NMR δ 9.86 (1H, s, CHO), 7.00 (1H, d, J = 2.0 Hz), 6.92 (1H, d, J = 2.0 Hz), 6.63 (1H, t, J = 2.0 Hz), 3.81 (3H, s, OCH_3), 0.97 (9H, s, $C(CH_3)_3$), 0.21 (6H, $Si(CH_3)_2$); ^{13}C NMR (75.5 MHz) δ 191.8, 161.2, 157.3, 138.4, 114.5, 113.0, 106.6, 55.5, 25.6, 18.2, −4.5.

3-(*tert*-Butyldimethylsilyloxy)-4′,5-dimethoxystilbene (14e,f). Reaction of phosphonium bromide **3** (1.71 g) with aldehyde **9c** (1.0 g) led to stilbenes **14e,f** (0.75 g, 55% total yield). Data for (*Z*)-isomer **14e**: EIMS *m*/*z* 370 (M^+), 313, 298, 156, 89; IR (KBr, cm^{-1}) ν_{max} 2955, 2859, 1588, 1510, 1433, 1252, 1159, 1034, 839, 679; ^1H NMR δ 7.21 (2H, d, J = 9.0 Hz), 6.77 (2H, d, J = 9.0 Hz), 6.52 (1H, d, J = 12.0 Hz), 6.45 (1H, s) 6.43 (1H, d, J = 12.0 Hz), 6.36 (1H, d, J = 2.1 Hz), 6.27 (1H, t, J = 2.1 Hz), 3.78 (3H, s, OCH_3), 3.67 (3H, s, OCH_3), 0.95 (9H, s, $C(CH_3)_3$), 0.11 (6H, s, $Si(CH_3)_2$); ^{13}C NMR (75.5 MHz) δ 160.6, 158.8, 156.7, 139.4, 130.3, 128.8, 127.5, 126.3, 113.6, 110.9, 105.4, 55.2, 25.3, 14.1, −4.5. Anal.: C, 71.36; H, 8.08. Data for (*E*)-isomer **14f**: EIMS *m*/*z* 370 (M^+), 313, 298, 156, 89; IR (KBr, cm^{-1}) ν_{max} 2955, 2859, 1588, 1510, 1433, 1252, 1159, 1034, 941, 839; ^1H NMR δ 7.45 (2H, d, J = 8.7 Hz), 7.01 (1H, d, J = 15.9 Hz), 6.90 (2H, d, J = 8.7 Hz), 6.87 (1H, d, J = 15.9 Hz), 6.66 (1H, s), 6.58 (1H, s), 6.31 (1H, t, J = 2.1 Hz), 3.83 (3H, s, OCH_3), 3.81 (3H, s, OCH_3), 1.00 (9H, s, $C(CH_3)_3$), 0.23 (6H, s, $Si(CH_3)_2$); ^{13}C NMR (75.5 MHz) δ 160.8, 159.4, 156.9, 139.6, 130.0, 128.5, 127.8, 126.6, 114.1, 110.9, 104.8, 55.3, 25.7, 14.1, −4.4.

3-Hydroxy-4′,5-dimethoxystilbene (14g,h). The preceding stilbene (0.75 g) isomeric mixture was deprotected, and the products were separated by gravity column chromatography (9:1 hexane/ethyl acetate). As usual the *cis*-stilbene (0.25 g) eluted first followed by the *trans* isomer (0.26 g, 99% total yield). Data for (*Z*)-isomer **14g**: EIMS *m*/*z* 256 (M^+), 225, 181, 152, 115; IR (KBr, cm^{-1}) ν_{max} 3407, 3005, 2938, 2837, 1607, 1511, 1456, 1300, 1254, 1154, 1057; ^1H NMR δ 7.20 (2H, d, J = 9.0 Hz), 6.77 (2H, d, J = 9.0 Hz), 6.52 (1H, d, J = 12.0 Hz), 6.42 (1H, s), 6.40 (1H d, J = 12.0 Hz), 6.33 (1H, d, J = 2.1 Hz), 6.27 (1H, t, J = 2.1 Hz), 3.79 (3H, s, OCH_3), 3.67 (3H, s, OCH_3). Data for (*E*)-isomer **14h**: EIMS *m*/*z* 256 (M^+), 225, 181, 152, 115; IR (KBr, cm^{-1}) ν_{max} 3405, 2936, 2837, 1593, 1510, 1456, 1252, 1150, 1057; ^1H NMR δ 7.44 (2H, d, J = 8.7 Hz), 7.02 (1H, d, J = 15.9 Hz), 6.90 (2H, d, J = 8.7 Hz), 6.86 (1H, d, J = 15.9 Hz), 6.63 (1H, t, J = 2.1 Hz), 6.58 (1H, t, J = 2.1 Hz), 6.31 (1H, t, J = 2.1 Hz), 3.83 (3H, s, OCH_3) 3.82 (3H, s, OCH_3).

3,5-Di(*tert*-Butyldimethylsilyloxy)-4′-methoxystilbene (14i,j). Intermediate **9a** and **3** served as starting materials for preparing stilbenes **14i** (1.73 g) and **14j** (0.19 g). Data for (*Z*)-isomer **14i**: EIMS *m*/*z* 470 (M^+), 455, 413, 147, 73; IR (KBr, cm^{-1}) ν_{max} 2955, 2859, 1582, 1510, 1437, 1331, 1254, 1165, 1031, 678; ^1H NMR δ 7.17 (2H, d, J = 8.1 Hz), 6.75 (2H, d, J = 8.1 Hz), 6.49 (1H, d, J = 12.0 Hz), 6.39 (1H, d, J = 12.0 Hz), 6.35 (2H, d, J = 2.4 Hz), 6.19 (1H, t, J = 2.4 Hz), 3.77 (3H, s, OCH_3), 0.93 (18H, s, $C(CH_3)_3 \times 2$), 0.10 (12H, s, $Si(CH_3)_2 \times 2$). Data for (*E*)-isomer **14j**: EIMS *m*/*z* 470 (M^+), 455, 413, 147, 73; IR (KBr, cm^{-1}) ν_{max} 2955, 2859, 1582, 1510, 1437, 1331, 1254, 1165, 1031, 980; ^1H NMR δ 7.44 (2H, d, J = 8.1 Hz), 6.97 (1H, d, J = 16.2 Hz), 6.89 (2H, d, J = 8.1 Hz), 6.83 (1H, d, J = 16.2 Hz), 6.59 (2H, d, J = 2.1 Hz), 6.24 (1H, t, J = 2.1 Hz), 3.83 (3H, s, OCH_3), 1.00 (18H, s, $C(CH_3)_3 \times 2$), 0.22 (12H, s, $Si(CH_3)_3 \times 2$).

3,5-Dihydroxy-4′-methoxystilbene (14k,l). The preceding silyloxy-protected stilbene isomers **14i,j** were deprotected to yield 0.60 and 0.05 g, respectively. Data for (*Z*)-isomer **14k**: EIMS *m*/*z* 242 (M^+), 226, 211, 194, 181, 152, 137; IR (KBr, cm^{-1}) ν_{max} 3356, 3009, 2971, 2837, 1605, 1510, 1254, 1154, 1005, 677; ^1H NMR δ 7.20 (2H, d, J = 8.7), 6.77 (2H, d, J = 8.7 Hz), 6.50 (1H, d, J = 12.0 Hz) 6.36 (1H, d, J = 12.0 Hz), 6.32 (2H, d, J = 2.1 Hz), 6.22 (1H, t, J = 2.1 Hz), 4.89 (2H, br s, OH × 2), 3.77 (3H, s, OCH_3). Data for (*E*)-isomer **14l**: EIMS *m*/*z* 242 (M^+), 226, 211, 194, 181, 152, 137; IR (KBr, cm^{-1}) ν_{max} 3356, 3009, 2971, 2837, 1605, 1510, 1254, 1154, 1005, 974; ^1H NMR δ 7.43 (2H, d, J = 8.1 Hz), 7.01, (1H, d, J = 15.9 Hz),

6.90 (2H, d, J = 8.1 Hz), 6.83 (1H, d, J = 15.9 Hz), 6.56 (2H, d, J = 2.4 Hz), 6.25 (1H, t, J = 2.4 Hz), 4.70 (2H, br s, OH × 2), 3.83 (3H, s, OCH_3).

(*Z*)-3,5-Dimethoxy-4′-[*O*-bis(benzyl)phosphoryl]stilbene (14m). A mixture of phenol **14c** (3.9 g) and *N*,*N*-(dimethylamino)pyridine (0.2 g) in anhydrous acetonitrile (30 mL) was cooled to −10 °C, and carbon tetrachloride (7.3 mL, 5 equiv) and DIEA (5.5 mL, 2.1 equiv) were added. The mixture was stirred at −10 °C for 30 min under argon, dibenzyl phosphite (5.0 mL, 1.5 equiv) was added, and the solution was stirred for 12 h and then poured into 0.5 M monobasic potassium phosphate. The mixture was extracted with ethyl acetate, and removal of solvent in vacuo from the organic phase yielded a tan oil. This was subjected to flash column chromatography (4:1 hexane/ethyl acetate), and the phosphate ester was recovered as a tan oil (6.6 g, 85%): EIMS m/z 516 (M^+), 425, 334, 319, 255, 227, 91; IR (KBr, cm^{-1}) ν_{max} 3443, 3007, 2959, 2837, 1591, 1505, 1456, 1289, 1208, 1155, 1015, 953; ^{1}H NMR δ 7.32 (10H, m, AR−H), 7.19 (2H, d, J = 8.4 Hz), 7.01 (2H, d, J = 8.4 Hz), 6.52 (2H, s, $H_{1a,1'a}$), 6.36 (2H, d, J = 2.0 Hz), 6.31 (1H, t, J = 2.0 Hz), 5.11 (2H, s, Bn), 5.08 (2H, s, Bn), 3.62 (6H, s, OCH_3 × 2); ^{13}C NMR (75.5 MHz) δ 160.6, 149.5, 149.5, 138.8, 135.4, 135.4, 134.2, 130.4, 130.3, 129.4, 128.6, 128.6, 128.0, 127.0, 119.8, 119.7, 106.6, 99.8, 70.0, 69.9, 55.2. Anal.: C, 69.84; H, 5.97; P, 5.84.

Sodium Resverastatin Phosphate (14n). To a solution of the dibenzyl phosphate **14m** (2.62 g) in anhydrous dichloromethane (15 mL) at 0 °C was added bromotrimethylsilane (1.40 mL, 2.1 equiv), and the mixture was stirred for 2 h. Water (10 mL) was added, the solution was stirred for 1 h and washed with ethyl acetate, and the aqueous phase was freeze-dried to a white solid. To a solution of the solid in ethanol (30 mL) was added sodium methoxide (0.57 g), and the suspension was stirred for 12 h. Solvent was removed in vacuo, and the resulting tan oil was dissolved in water. The solution was washed with ethyl acetate and then freeze-dried to afford 1.88 g of colorless solid (98%): HRFAB MS m/z; IR (KBr, cm^{-1}) ν_{max} 3385, 2999, 2938, 2834, 1601, 1508, 1366, 1155, 1063, 683; ^{1}H NMR δ 6.93 (2H, d, J = 8.4 Hz), 6.85 (2H, d, J = 8.4 Hz), 6.29 (1H, d, J = 12.4 Hz), 6.17 (2H, s, $H_{2,6}$), 6.15 (1H, d, J = 12.4 Hz), 6.09 (1H, s, H_4), 3.34 (6H, s, OCH_3 × 2); ^{13}C NMR (75.5 MHz) δ 171.1, 160.1, 139.9, 131.8, 130.8, 130.0, 129.0, 120.3, 107.3, 99.7, 55.6.

General Procedure for Benzhydrol Formation. To the bromide (1−10 mmol) in anhydrous tetrahydrofuran (5−35 mL) at −78 °C was added *n*-butyllithium (2.5 M, 1.1 equiv), and the resulting solution was stirred under argon for 15 min. A solution of aldehyde (1.0 equiv) in tetrahydrofuran was added dropwise over 30 min and the mixture stirred for 6 h. The solution was poured into water and extracted with ethyl acetate. The organic phase was washed with water, and removal of the solvent in vacuo afforded an oil that was purified by flash column chromatography (9:1 hexane/ethyl acetate).

3,4′,5-Trimethoxybenzhydrol (15a). 4-Bromoanisole (2.3 g) and 3,5-dimethoxybenzaldehyde (2.1 g) led to **15a** (2.7 g, 80.9%) as a colorless oil: EIMS m/z 274 (M^+) 257, 243, 227, 165, 139, 135, 109, 77; IR (KBr, cm^{-1}) ν_{max} 3451, 3001, 2940, 2837, 1597, 1248, 1172, 1034; ^{1}H NMR δ 7.28 (2H, d, J = 8.8 Hz), 6.85 (2H, d, J = 8.8 Hz), 6.53 (2H, d, J = 2.0 Hz), 6.35 (1H, t, J = 2.0 Hz), 5.72 (1H, d, J = 2.8 Hz), 3.78 (3H, s, OCH_3), 3.76 (3H, s, OCH_3); ^{13}C NMR (75.5 MHz) δ 160.9, 159.1, 146.5, 135.9, 127.9, 113.9, 104.4, 99.3, 75.8, 55.3, 55.3.

General Procedure for Benzophenone Formation. To a solution of the benzhydrol (1−10 mmol) in dichloromethane (5−35 mL) was added pyridinium dichromate (2.0 equiv) and molecular sieves (4 Å activated powder, same weight as PDC), and the resulting suspension was stirred under argon for 24 h. The reaction mixture was filtered through Celite and the solvent removed in vacuo to yield a brown oil. The oil was subjected to gravity column chromatography (4:1 hexanes−ethyl acetate) to yield the desired product in 75−90% yield.

3,4′,5-Trimethoxybenzophenone (16a). Alcohol **15a** (1.1 g) provided a solid (0.8 g, 77.7%) that recrystallized from methanol in colorless needles: mp 90.3−91.6 °C (lit.[21] mp 97−98 °C); EIMS m/z 272 (M^+), 257, 241, 229, 165, 135, 92, 77; IR (KBr, cm^{-1}) ν_{max} 3071, 2967, 2841, 1645, 1588, 1263, 1065; ^{1}H NMR δ 7.84 (2H, d, J = 9.0 Hz), 6.95 (2H, d, J = 9.0 Hz), 6.87 (2H, d, J = 2.0 Hz), 6.65 (1H, t, J = 2.0 Hz), 3.88 (3H, s, OCH_3), 3.82 (3H, s, OCH_3); ^{13}C NMR (75.5 MHz) δ 195.2, 163.3, 160.5, 140.2, 132.6, 130.1, 113.6, 107.6, 104.2, 55.6, 55.5.

1-Bromo-4-*O*-(*tert*-butyldimethylsilyloxy)benzene (17). 4-Bromophenol (4.15 g) was dissolved in anhydrous dichloromethane (40 mL), and imidazole (1.63 g) and *tert*-butyldimethylsilyl chloride (3.61 g) were added. The cream suspension was stirred under argon for 12 h, and the reaction was terminated with addition of water. The mixture was extracted with ethyl acetate. The organic phase was washed with water, and the solvent was removed in vacuo to afford a yellow oil that was subjected to flash column chromatography (9:1 hexane/ethyl acetate) to yield a colorless oil (87%, 6.0 g): EIMS m/z 274 (M^+), 257, 243, 227, 165, 139, 135, 109, 77; IR (KBr, cm^{-1}) ν_{max} 2957, 2859, 1588, 1487, 1458, 910, 839; ^{1}H NMR δ 7.32 (2H, d, J = 8.7 Hz), 6.71 (2H, d, J = 8.7 Hz), 0.97 (9H, s, $C(CH_3)_3$), 0.18 (6H, s, $Si(CH_3)_2$).

4′-(*tert*-Butyldimethylsilyloxy)-3,5-dimethoxybenzhydrol (15b). Protected bromophenol **17** (3.2 g) and 3,5-dimethoxybenzaldehyde (1.8 g) afforded **15b** as a colorless oil (3.4 g, 83%): EIMS m/z 374 (M^+), 317, 167, 151, 139; IR (KBr, cm^{-1} ν_{max} 3420, 2957, 2859, 1607, 1260, 1155, 1063, 839; ^{1}H NMR δ 7.21 (2H, d, J = 8.4 Hz), 6.80 (2H, d, J = 8.4 Hz), 6.53 (2H, d, J = 2.0 Hz), 6.36 (1H, t, J = 2.0 Hz), 5.67 (1H, s), 3.75 (6H, s, OCH_3· 2), 0.99 (9H, s, $C(CH_3)_3$), 0.20 (6H, s, $Si(CH_3)_2$); ^{13}C NMR (75.5 MHz) δ 160.7, 155.0, 146.5, 136.4, 127.8, 119.9, 104.4, 99.2, 75.7, 55.2, 25.6, 18.1, −4.5.

4′-Hydroxy-3,5-dimethoxybenzhydrol (15c). Alcohol **15b** (0.12 g) was deprotected with TBAF as for the stilbenes above to provide **15c** as a colorless oil (0.03 g, 42%): EIMS m/z 260 (M^+), 243, 165, 139, 121, 95; IR (KBr, cm^{-1}) ν_{max} 3362, 2932, 2859, 1599, 1256, 1155, 1067; ^{1}H NMR δ 7.16 (2H, d, J = 8.4 Hz), 6.72 (2H, d, J = 8.4 Hz), 6.52 (2H, d, J = 2.4 Hz), 6.34 (1H, t, J = 2.4 Hz), 5.66 (1H, s), 3.73 (6H, s, OCH_3 × 2); ^{13}C NMR (75.5 MHz) δ 160.6, 155.4, 146.3, 135.3, 128.0, 115.3, 104.4, 99.2, 75.8, 55.3.

4′-(*tert*-Butyldimethylsilyloxy)-3,5-dimethoxybenzophenone (16b). Alcohol **15b** (0.58 g) led to **16b** as a colorless oil (0.46 g, 80%): EIMS m/z 372 (M^+), 315, 165, 157, 137, 28; IR (KBr, cm^{-1}) ν_{max} 2957, 2859, 1657, 1260, 1067, 910, 841; ^{1}H NMR δ 7.78 (2H, d, J = 9.2 Hz), 6.89 (2H, d, J = 9.2 Hz), 6.87 (2H, t, J = 2.0 Hz), 6.63 (1H, t, J = 2.0 Hz), 3.80 (6H, s, OCH_3 × 2), 0.98 (9H, s, $C(CH_3)_3$), 0.23 (6H, s, $Si(CH_3)_2$); ^{13}C NMR (75.5 MHz) δ 195.0, 160.3, 159.8, 140.0, 132.3, 130.5, 119.6, 107.5, 104.1, 55.5, 25.6, 18.3, −4.3.

General Procedure for Benzophenone Deprotection with TBAF. To a solution of the protected phenol (0.3−3.5 mmol) in anhydrous tetrahydrofuran (5−25 mL) was added tetrabutylammonium fluoride (1 M, 1.0 equiv per TBDMS), and the pale yellow solution was stirred for 45 min. The mixture was poured into water and extracted with ethyl acetate. Removal of the solvent in vacuo from the organic phase afforded a tan oil that was subjected to gravity column chromatography (9:1 hexane/ethyl acetate) to afford the product (70−93% yield).

4′-Hydroxy-3,5-dimethoxybenzophenone (16c). Protected benzophenone **16b** (0.71 g) led to **16c** as a white solid (0.35 g, 72%): EIMS m/z 258 (M^+), 243, 227, 199, 165, 121, 45; IR (KBr, cm^{-1}) ν_{max} 3424, 2940, 1640, 1591, 1454, 1206, 1157, 1065; ^{1}H NMR δ 7.68 (2H, d, J = 8.8 Hz), 6.80 (2H, d, J = 8.8 Hz), 6.75 (2H, d, J = 2.0 Hz), 6.53 (1H, t, J = 2.0 Hz), 3.70 (6H, s, OCH_3 × 2); ^{13}C NMR (75.5 MHz) δ 196.0, 162.3, 160.4, 140.2, 133.1, 128.6, 115.6, 107.5, 104.2, 55.5.

3,5-Di(*tert*-butyldimethylsilyloxy)-4′-methoxybenzhydrol (15d). 4-Bromoanisole (0.43 g) and aldehyde **9a** (0.76 g) provided **15d** as a faint yellow oil (0.80 g, 82%): EIMS m/z 474 (M^+), 459, 417, 361, 343, 73; IR (KBr, cm^{-1}) ν_{max} 3420, 2932, 2859, 2361, 1591, 1451, 1252, 1163, 1026, 833; ^{1}H NMR δ 7.29 (2H, d, J = 9.04 Hz), 6.89 (2H, d, J = 9.0 Hz), 6.52 (2H, d, J = 2.0 Hz), 6.28 (1H, t, J = 2.0 Hz), 5.70 (1H, s), 3.83 (3H,

s, OCH_3), 1.00 (18H, s, $C(CH_3)_3 \times 2$), 0.20 (12H, s, $Si(CH_3)_2 \times 2$); ^{13}C NMR (75.5 MHz) δ 159.0, 156.5, 146.1, 136.0, 127.9, 113.7, 111.5, 111.0, 75.5, 55.3, 25.7, 18.2, −4.4.

3,5-Di(*tert*-butyldimethylsilyloxy)-4′-methoxybenzophenone (16d). Alcohol **15d** (0.72 g) provided **16d** as a colorless oil (0.64 g, 90%): EIMS *m/z* 472 (M^+), 457, 415, 359, 135, 73; IR (KBr, cm^{-1}) ν_{max} 2957, 2932, 2859, 1657, 1586, 1437, 1339, 1254, 1169, 831; ^1H NMR δ 7.82 (2H, d, J = 9.0 Hz), 6.94 (2H, d, J = 9.0 Hz), 6.80 (2H, d, J = 1.5 Hz), 6.52 (1H, t, J = 1.5 Hz), 3.88 (3H, s, OCH_3), 0.97 (18H, s, $C(CH_3)_3 \times 2$), 0.19 (12H, s, $Si(CH_3)_2 \times 2$); ^{13}C NMR (75.5 MHz) δ 195.0, 163.2, 156.3, 140.1, 132.5, 130.2, 115.6, 114.7, 113.5, 55.5, 25.7, 18.2, −4.4.

3,5-Dihydroxy-4′-methoxybenzophenone (16e). Protected benzophenone **16d** (0.54 g) led to **16e** as a white solid (0.36 g, 93%): EIMS *m/z* 244 (M^+), 227, 135, 107, 92; IR (KBr, cm^{-1}) ν_{max} 3300, 2972, 2841, 2361, 1692, 1591, 1451, 1350, 1263, 1171, 1030; ^1H NMR δ 8.60 (2H, br s, OH × 2), 7.80 (2H, d, J = 9.0 Hz), 7.06 (2H, d, J = 9.0 Hz), 6.69 (2H, d, J = 2.5 Hz), 6.59 (1H, t, J = 2.5 Hz), 3.91 (3H, s, OCH_3); ^{13}C NMR (75.5 MHz) δ 195.4, 164.6, 159.7, 141.8, 133.4, 131.5, 114.8, 109.3, 107.2, 56.4.

3,4′,5-Tris(*tert*-butyldimethylsilyloxy)benzhydrol (15e). Protected bromophenol **17** (0.49 g) and aldehyde **9a** (0.62 g) afforded **15e** as a faint yellow oil (0.76 g, 78%): EIMS *m/z* 574 (M^+), 559, 517, 461, 443, 73; IR (KBr, cm^{-1}) ν_{max} 3420, 2932, 2859, 2361, 1591, 1451, 1252, 1163, 1026, 833; ^1H NMR δ 7.18 (2H, d, J = 8.5 Hz), 6.79 (2H, d, J = 8.5 Hz), 6.48 (2H, d, J = 2.0 Hz), 6.25 (1H, t, J = 2.0 Hz), 5.63 (1H, s, CH), 0.99 (9H, s, $C(CH_3)_3$), 0.97 (18H, s, $C(CH_3)_3 \times 2$), 0.19 (6H, s, $Si(CH_3)_2$), 0.17 (12H, s, $Si(CH_3)_2 \times 2$); ^{13}C NMR (75.5 MHz) δ 156.4, 155.0, 146.2, 136.7, 127.8, 119.9, 111.6, 111.0, 75.4, 25.7, 18.2, −4.4, −4.5.

3,4′,5-Tris(*tert*-butyldimethylsilyloxy)benzophenone (16f). Alcohol **15e** (0.50 g) led to **16f** as a colorless oil (0.44 g, 89%): EIMS *m/z* 572 (M^+), 515, 459, 323, 193, 73; IR (KBr, cm^{-1}) ν_{max} 2932, 2861, 1661, 1589, 1437, 1339, 1256, 1167, 831; ^1H NMR δ 7.74 (2H, d, J = 8.5 Hz), 6.88 (2H, d, J = 8.5 Hz), 6.80 (2H, d, J = 2.5 Hz), 6.52 (1H, t, J = 2.5 Hz), 0.99 (9H, s, $C(CH_3)_3$), 0.97 (18H, s, $C(CH_3)_3 \times 2$), 0.24 (6H, s, $Si(CH_3)_2$), 0.19 (12H, s, $Si(CH_3)_2 \times 2$); ^{13}C NMR (75.5 MHz) δ 195.2, 159.9, 156.3, 140.0, 132.4, 130.7, 119.7,115.7, 114.7, 25.7, 25.6, 18.3, 18.2, −4.4.

3,4′,5-Trihydroxybenzophenone (16g). Protected benzophenone **16f** (0.42 g) led to **16g** as a white solid (0.12 g, 73%): EIMS *m/z* 230 (M^+), 137, 121, 93, 65, 28; IR (KBr, cm^{-1}) ν_{max} 3300, 2974, 1692, 1593, 1346, 1260, 1167; ^1H NMR δ 7.73 (2H, d, J = 8.5 Hz), 6.95 (2H, d, J = 8.5 Hz), 6.68 (2H, d, J = 2.0 Hz), 6.57 (1H, t, J = 2.0 Hz); ^{13}C NMR (75.5 MHz) δ 195.0, 162.4, 159.2, 141.6, 133.3, 130.2, 115.9, 108.8, 106.7.

3,4′-Di(*tert*-butyldimethylsilyloxy)-5-methoxybenzhydrol (15f). Protected bromophenol **17** (1.07 g) and aldehyde **9c** (0.99 g) provided **15f** as a faint yellow oil (1.19 g, 67%): EIMS *m/z* 474 (M^+), 459, 417, 361, 343, 73; IR (KBr, cm^{-1}) ν_{max} 3397, 2932, 2859, 1595, 1508, 1256, 1159, 839; ^1H NMR δ 7.19 (2H, d, J = 8.4 Hz), 6.78 (2H, d, J = 8.4 Hz), 6.55 (1H, s), 6.42 (1H, s), 6.29 (1H, s), 5.67 (1H, s, CH), 3.74 (3H, s, OCH_3), 0.96 (9H, s, $C(CH_3)_3$), 0.95 (9H, s, $C(CH_3)_3$), 0.17 (6H, s, $Si(CH_3)_2$), 0.15 (6H, s, $Si(CH_3)_2$); ^{13}C NMR (75.5 MHz) δ 160.5, 156.6, 155.0, 146.2, 136.4, 127.8, 119.9, 110.8, 105.1, 105.0, 75.7, 55.3, 25.7, 18.3, −4.3.

3,4′-Di(*tert*-butyldimethylsilyloxy)-5-methoxybenzophenone (16h). Alcohol **15f** (0.91 g) led to **16h** as a colorless oil (0.71 g, 78%): EIMS *m/z* 472 (M^+), 415, 373, 223, 193, 179, 73; IR (KBr, cm^{-1}) ν_{max} 2932, 2859, 1659, 1595, 1507, 1258, 1163, 839; ^1H NMR δ 7.76 (2H, d, J = 8.8 Hz), 6.90 (1H, t, J = 2.4 Hz), 6.88 (2H, d, J = 8.8 Hz), 6.77 (1H, t, J = 2.4 Hz), 6.58 (1H, t, J = 2.4 Hz), 3.80 (3H, s, OCH_3), 0.99 (9H, s, $C(CH_3)_3$), 0.97 (9H, s, $C(CH_3)_3$), 0.24 (6H, s, $Si(CH_3)_2$), 0.20 (6H, s, $Si(CH_3)_2$); ^{13}C NMR (75.5 MHz) δ 195.0, 160.3, 159.8, 156.3, 140.0, 132.3, 130.6, 119.6, 114.2, 110.1, 107.6, 55.5, 25.7, 25.7, 18.3, 18.3, −4.3.

3,4′-Dihydroxy-5-methoxybenzophenone (16i). Protected benzophenone **16h** (0.61 g) led to **16i** as a white solid (0.26 g, 82%): mp 179−180 °C; EIMS *m/z* 244 (M^+), 229, 213, 151, 121, 93; IR (KBr, cm^{-1}) ν_{max} 3333, 2961, 2841, 1690, 1589, 1435, 1346, 1165, 1059, 849; ^1H NMR δ 9.21 (1H, br s, OH), 8.66 (1H, br s, OH), 7.75 (2H, d, J = 9.0 Hz), 6.96 (2H, d, J = 9.0 Hz), 6.77 (2H, t, J = 2.0 Hz), 6.74 (1H, t, J = 2.0 Hz), 6.63 (1H, t, J = 2.0 Hz), 3.80 (3H, s, OCH_3); ^{13}C NMR (75.5 MHz) δ 195.0, 162.6, 161.8, 159.2, 141.6, 133.4, 130.1, 116.0, 109.9, 107.0, 105.50, 55.8.

3-(*tert*-Butyldimethylsilyloxy)-4′,5-dimethoxybenzhydrol (15g). 4-Bromoanisole (0.59 g) and aldehyde **9c** (0.82 g) provided **15g** as a faint yellow oil (0,59 g, 52%): EIMS *m/z* 374 (M^+), 359, 317, 299, 243, 75; IR (KBr, cm^{-1}) ν_{max} 3418, 2932, 2859, 1595, 1462, 1250, 1157, 1036, 837; ^1H NMR δ 7.30 (2H, d, J = 8.4 Hz), 6.89 (2H, d, J = 8.4 Hz), 6.58 (1H, s), 6.49 (1H, s), 6.32 (1H, s), 5.72 (1H, s, CH), 3.82 (3H, s, OCH_3), 3.77 (3H, s, OCH_3), 0.99 (9H, s, $C(CH_3)_3$), 0.20 (6H, s, $Si(CH_3)_2$); ^{13}C NMR (75.5 MHz) δ 160.5, 158.9, 156.6, 146.2, 135.9, 127.8, 113.8, 110.7, 105.1, 104.9, 75.6, 55.3, 25.8, 18.3, −4.3.

3-(*tert*-Butyldimethylsilyloxy)-4′,5-dimethoxybenzophenone (16j). Alcohol **15g** (0.54 g) led to **16j** as a colorless oil (0.41 g, 76%): EIMS *m/z* 372 (M^+), 315, 272, 135; IR (KBr, cm^{-1}) ν_{max} 2932, 2859, 1657, 1593, 1454, 1429, 1339, 1254, 1161, 1034, 839; ^1H NMR δ 7.83 (2H, d, J = 8.8 Hz), 6.95 (2H, d, J = 8.8 Hz), 6.89 (1H, t, J = 1.2 Hz), 6.77 (1H, t, J = 1.6 Hz), 6.58 (1H, t, J = 2.2 Hz), 3.88 (3H, s, OCH_3), 3.80 (3H, s, OCH_3), 0.97 (9H, s, $C(CH_3)_3$), 0.20 (6H, s, $Si(CH_3)_2$); ^{13}C NMR (75.5 MHz) δ 194.9, 163.1, 160.4, 156.3, 140.1, 132.5, 130.0, 114.2, 113.4, 110.1, 107.6, 55.6, 55.5, 25.7, 18.1, −4.3.

4′,5-Dimethoxy-3-hydroxybenzophenone (16k). Protected benzophenone **16j** (0.37 g) led to **16k** as a colorless solid (0.18 g, 70%): EIMS *m/z* 258 (M^+), 227, 135, 92, 77; IR (KBr, cm^{-1}) ν_{max} 3354, 3005, 2938, 2841, 1692, 1636, 1593, 1433, 1346, 1256, 1171, 1030; ^1H NMR δ 8.67 (1H, br s, OH), 7.80 (2H, dd, J = 6.8, 2.0 Hz), 7.05 (2H, dd, J = 6.8, 2.0 Hz), 6.77 (1H, dd, J = 2.0, 1.6 Hz), 6.74 (1H, dd, J = 2.4, 1.2 Hz), 6.64 (1H, t, J = 2.4 Hz), 3.90 (3H, s, OCH_3), 3.80 (3H, s, OCH_3); ^{13}C NMR (75.5 MHz) δ 194.6, 164.0, 161.5, 159.0, 141.1, 132.8, 130.8, 114.3, 109.7, 106.9, 105.4, 55.9, 55.7.

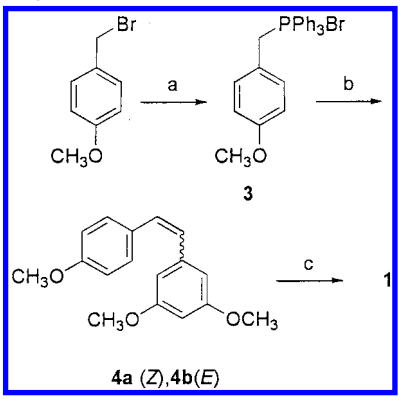
Cancer Cell Line Procedure. Inhibition of human cancer cell growth was assessed using the National Cancer Institute's standard sulforhodamine B assay as previously described.[22] Briefly, cells in 5% fetal bovine serum/RPMI1640 were inoculated in 96-well plates and incubated for 24 h, and dilutions of the compounds were added. After 48 h, the plates were fixed with trichloroacetic acid, washed, stained with sulforhodamine B, and read with an automated microplate reader. Growth inhibition of 50% (GI_{50} or the drug concentration causing a 50% reduction in the net protein increase) was calculated from optical density data with Immunosoft software. Inhibition of the mouse leukemia P388 cells was assessed in 10% horse serum/Fisher media, with incubation for 24 h and dilutions of the compounds added. After 48 h, cell growth inhibition (ED_{50}) was calculated using a Z1 Coulter particle counter.

Antimicrobial Susceptibility Methods. Compounds were screened against the bacteria *Stenotrophomonas maltophilia*, *Micrococcus luteus*, *Staphylococcus aureus*, *Escherichia coli*, *Enterobacter cloacae*, *Enterococcus faecalis*, *Streptococcus pneumoniae*, and *Neisseria gonorrhoeae* and the fungi *Candida albicans* and *Cryptococcus neoformans*, according to established broth microdilution susceptibility assays.[23a,b] The minimum inhibitory concentration was defined as the lowest concentration of compound that inhibited all visible growth of the test organism (optically clear). Assays were repeated on separate days.

Discussion and Results

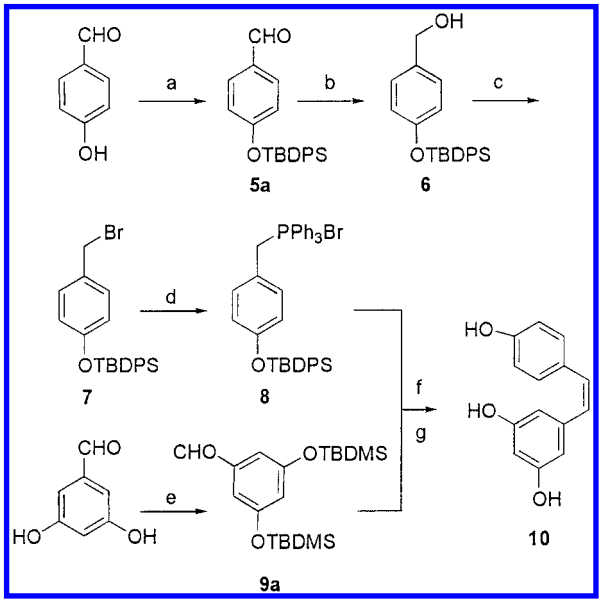
Because of the interesting biological properties of resveratrol (**1**), combined with the remarkable[19] in vivo anticancer activity of combretastatin A-4 (**2a**) and its sodium phosphate prodrug (**2b**), we elected to investigate a series of resveratrol structural modifications as an extension of our combretastatin and phenstatin (**2c**) structure/activity relationship (SAR) research. Suitable application of the experimental procedures already

Scheme 1. Synthesis of **1**[a]



[a] Reagents and conditions: (a) PPh_3, toluene, reflux, 85%. (b) *n*-BuLi, THF, −78 °C, 3,5-dimethoxybenzaldehyde, 91%. (c) (i) chromatography; (ii) BBr_3, CH_2Cl_2, 86%.

Scheme 2. Synthesis of **10**[a]

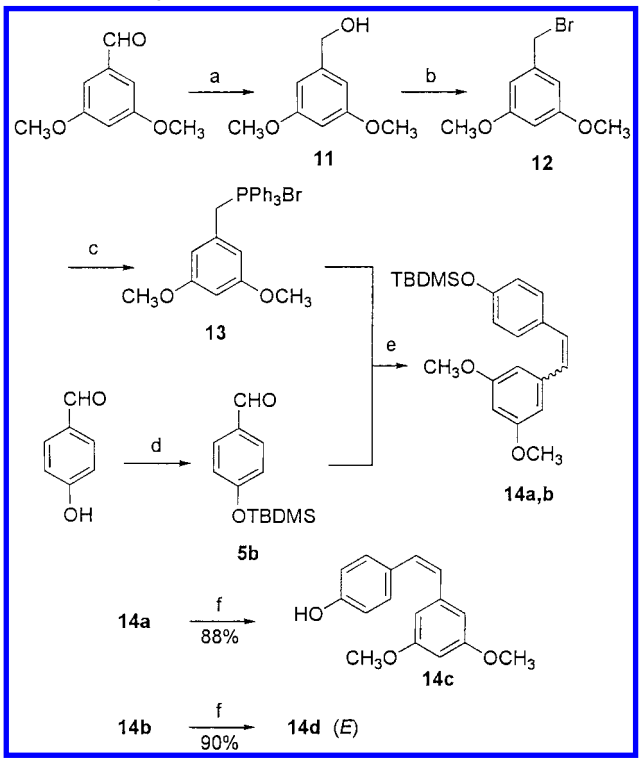


[a] Reagents and conditions: (a) *t*-Bu$(C_6H_5)_2$SiCl, imidazole, DMF, 68%. (b) $NaBH_4$, CH_3OH, 0 °C, 88%. (c) PBr_3, CH_2Cl_2, 0 °C, 89%. (d) PPh_3, toluene, reflux, 89%. (e) *t*-Bu$(CH_3)_2$SiCl, DIEA, DMF, 94%. (f) *n*-BuLi, THF, −78 °C. (g) (i) Bu_4NF, THF, 95%; (ii) chromatography.

developed for synthesis[18b] of combretastatin A-4 and its prodrug derivatives was extended to obtaining the *cis*- and *trans*-stilbenes as well as the benzophenones (Schemes 1−7).[24]

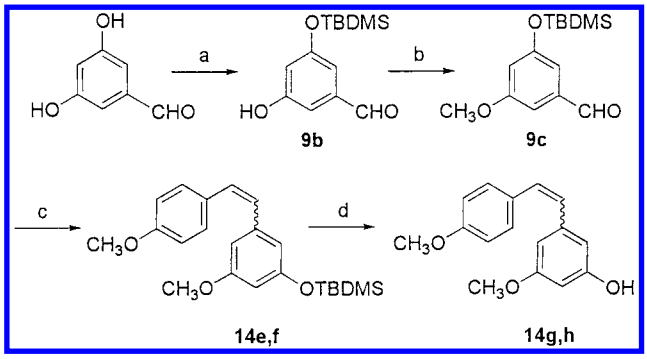
The cancer cell growth evaluations resulting from the resveratrol stilbenes are summarized in Table 1. The *cis* isomer of resveratrol (**10**) exhibited slightly less inhibitory effects on the cancer cell lines tested than did the *trans* isomer. Thus far, this is the only example that our research group has observed in which the *trans*-stilbene had greater cytotoxic activity than the *cis* isomer. The trimethoxystilbenes **4a,b** are from 10- to 100-fold more active against tumor cell lines than the parent compound **1**, with compound **4a** (the *cis*-stilbene) far more active than **4b**. Demethylation at any position yielded compounds much less cytotoxic than **4a**, but the *cis*-stilbenes **14c**, **14g**, and **14k** all retained anticancer activity comparable to that of resveratrol. The corresponding *trans* isomers **14d**, **14h**, and **14l** were all slightly less active than their *cis* counterparts.

Scheme 3. Synthesis of **14c,d**[a]



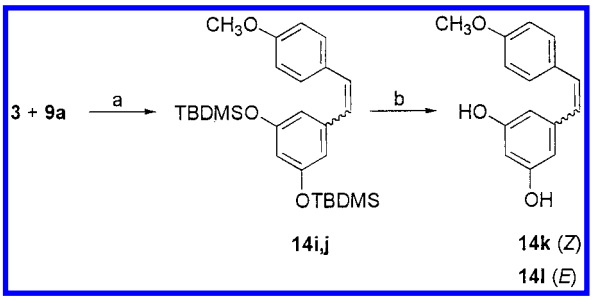
[a] Reagents and conditions: (a) $NaBH_4$, CH_3OH, 0 °C, 93%; (b) PBr_3, CH_2Cl_2, 0 °C, 89%. (c) PPh_3, toluene, reflux, 92%. (d) *t*-Bu$(CH_3)_2$SiCl, DIEA, DMF, 73%. (e) (i) *n*-BuLi, THF, −78 °C, 73%; (ii) chromatography. (f) Bu_4NF, THF, 88%.

Scheme 4. Synthesis of **14g,h**[a]



[a] Reagents and conditions: (a) *t*-Bu$(CH_3)_2$SiCl, DIEA, DMF, 39%. (b) $BF_4O(CH_3)_3$, proton sponge, CH_2Cl_2, 4 Å sieves, 79%. (c) **3**, *n*-BuLi, THF, −78 °C, 55%. (d) (i) Bu_4NF, THF, 99%; (ii) chromatography.

Scheme 5. Synthesis of **14k,l**[a]



[a] Reagents and conditions: (a) *n*-BuLi, THF, −78 °C, 63%. (b) (i) chromatography; (ii) Bu_4NF, THF, 99%.

In our earlier work[25] we had found that **2c** retained most of the cytotoxic properties of **2a**, and this led us to prepare **16a**, as well as additional benzophenones. While

Table 1. Cancer Cell Growth Inhibition Results for **1**, **2a**, **14c**, the Disodium Resverastatin Prodrug **14n**, and Related Stilbenes

	ED_{50} (μg/mL)	GI_{50} (μg/mL)					
compd	leukemia P388	pancreas BXPC-3	breast MCF-7	CNS SF-268	lung-NSC NCI-H460	colon KM20L2	prostate DU-145
1	4.49	3.3	3.9	4.1	3.6	13.1	3.5
10	24.4	15.5	14.8	5.0	13.2	22.0	10.2
2a	3.0×10^{-4}	0.39		$>1.0 \times 10^{-2}$	6.0×10^{-4}	0.34	8.0×10^{-4}
4a	2.62×10^{-2}	3.4×10^{-3}		4.4×10^{-3}	2.8×10^{-3}		5.4×10^{-3}
4b	2.77	3.5×10^{-1}		5.6×10^{-1}	6.2×10^{-1}		1.5
14c	2.95	12.6	3.0	2.2	2.8	11.9	2.3
14d	4.87	6.5	2.3	4.3	2.7	3.4	2.7
14g	3.82	3.3		1.5	7.2×10^{-1}	2.6	2.5
14h	31.5	12.7		10.3	11.2	13.1	6.0
14k	2.75	14.1	12.7	15.6	6.4	17.7	10.6
14l	28.9	6.3	3.4	3.1	6.8	3.8	2.7
14m	4.45	5.4	9.0	38.5	10.7	24.7	35.6
14n	2.81	6.6	7.3×10^{-1}	1.9	3.6	11.8	3.7

Table 2. Cancer Cell Growth Inhibition Comparison for **1**, **2c**, and Related Benzophenones and Benzhydrols

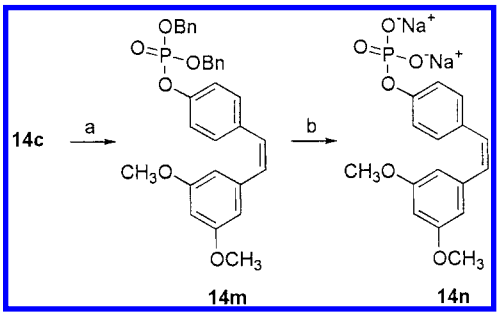
	ED_{50} (μg/mL)	GI_{50} (μg/mL)					
compd	leukemia P388	pancreas BXPC-3	breast MCF-7	CNS SF-268	lung-NSC NCI-H460	colon KM20L2	prostate DU-145
1	4.49	3.3	3.9	4.1	3.6	13.1	3.5
2c	3.3×10^{-3}			5.2×10^{-2}	5.7×10^{-3}	4.0×10^{-2}	ND
15a	20.2	16.1		23.3	21.7	21.0	23.2
16a	1.23	4.2×10^{-1}		8.6×10^{-1}	5.3×10^{-1}	4.2×10^{-1}	1.2
15c	>10	1.3	2.0	6.5×10^{-1}	2.3	5.3	5.8
16c	24.8	4.0	2.2	3.8	3.0	3.6	4.1
16e	17.8	21.2	21.7	24.5	16.6	24.5	15.1
16g	>100	20.5	30.6	22.3	25.0	24.5	15.0
16i	26.2	21.7	26.8	26.4	12.1	31.6	16.5
16k	13.4	15.0	14.2	13.9	10.3	16.2	12.6

Table 3. Interactions of Stilbenes and Benzophenones with Tubulin[a]

		inhibition of colchicine binding, % inhibition	
compd	inhibition of tubulin polymerization, IC_{50} (μM) ± SD	2 μM inhibitor	5 μM inhibitor
1	>40		
2a	2.0 ± 0.2	91 ± 3	98 ± 1
2c	1.1 ± 0.1	73 ± 1	85 ± 2
4a	1.8 ± 0.3	88 ± 1	95 ± 1
14c	29 ± 9		
16a	2.6 ± 0.3	47 ± 0.3	69 ± 0.3

[a] The tubulin polymerization assay was performed as previously described.[24] The tubulin concentration was 10 μM, with varying drug concentrations, as required, to obtain IC_{50} values. The extent of assembly after 20 min at 30 °C was the parameter measured. The colchicine binding assay was performed as reported earlier.[27] The tubulin concentration was 1.0 μM, the [^{3}H]colchicine concentration was 5.0 μM, and the potential inhibitor concentrations were as indicated. Binding of colchicine was measured following a 10 min incubation at 37 °C.

Scheme 6. Synthesis of Resverastatin Prodrug **14n**[a]



[a] Reagents and conditions: (a) $(C_6H_5CH_2O)_2P(O)H$, CH_3CN, CCl_4, DMAP, DIEA, −10 °C, 85%. (b) (i) $Si(CH_3)_3Br$, CH_2Cl_2; (ii) $NaOCH_3$, CH_3OH, 97.5%.

the cytotoxic properties of most of these compounds were quite similar to those of the stilbene derivatives of resveratrol (Table 2), the trimethoxy derivative was again the most potent of the series. However, it was 10−100-fold less active than compound **4a**, the analogous *cis*-stilbene.

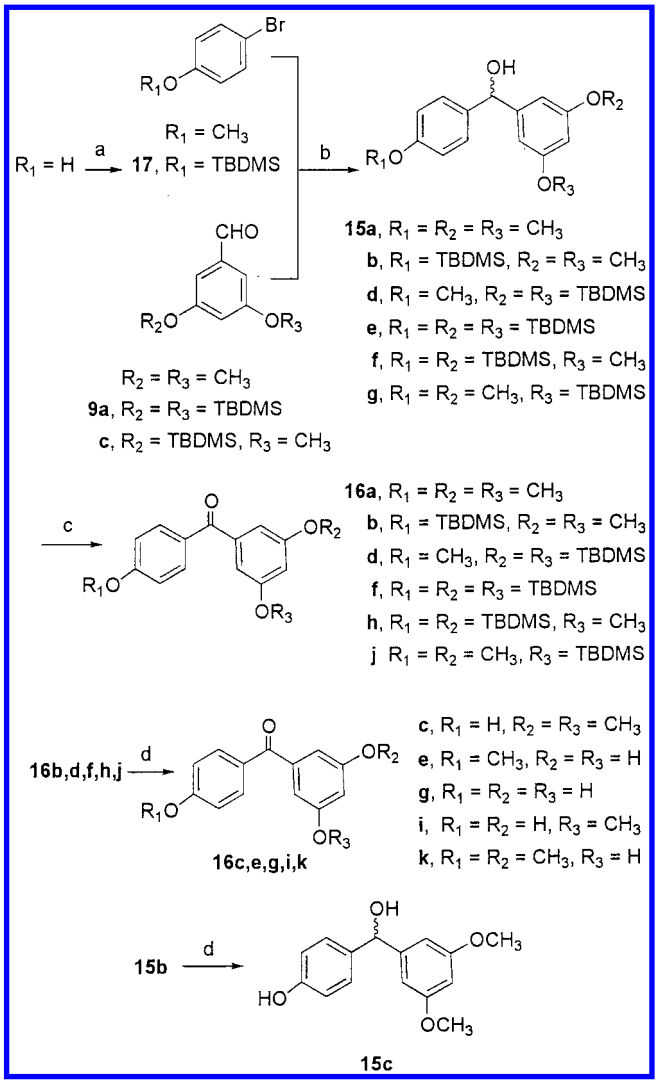
General conclusions arising from the SAR study of resveratrol based on cytotoxic effects on P-388 and human tumor cell lines can be summarized as 3,4′,5-OCH_3 ≫ resveratrol, 4′-OH, prodrug, 3-OH > 3,5-OH,

Table 4. Antimicrobial Evaluations of **1** and Related Stilbenes and Benzophenones

	min inhibitory concn (ug/mL)												
microorganism	**1**	**4a**	**14c**	**14h**	**14k**	**14n**	**15c**	**16a**	**16c**	**16e**	**16g**	**16i**	**16k**
C. neoformans	*	*	16	16	*	64	*	*	*	*	*	*	64
C. albicans	*	*	64	*	*	*	*	*	*	*	*	*	*
S. aureus	*	*	32	*	*	*	*	*	*	*	*	*	*
S. pneumoniae	*	*	16	*	*	*	16	*	64	*	64	64	32−64
E. faecalis	*	*	32−64	*	*	*	*	*	*	*	*	*	*
M. luteus	*	*	8	16−64	*	32−64	*	*	*	*	*	*	*
E. coli	*	*	*	*	*	*	*	*	*	*	*	*	*
E. faecalis	*	*	*	*	*	*	*	*	*	*	*	*	*
E. cloacae	*	*	*	*	*	*	*	*	*	*	*	*	*
S. maltophilia	*	*	*	*	*	*	*	*	*	*	*	*	*
N. gonorrhoeae	16−32	*	8	8	16	8−32	2−4	32	32−64	*	*	32	16−32

[a] The asterisks indicate no inhibition at 64 μg/mL.

Scheme 7. General Synthesis of the Benzophenones **16**[a]



[a] Reagents and conditions: (a) *t*-Bu(CH_3)$_2$SiCl, imidazole, CH_2Cl_2, 87%. (b) *n*-BuLi, THF, −78 °C, 52−83%. (c) PDC, CH_2Cl_2, 75−90%. (d) Bu_4NF, THF, 70−93%.

3,4′-OH ≫ 3,4′,5-OH. The trimethoxy derivatives **4a,b** and **16a** were all superior in activity to **1** as well as the remaining variations. Resveratrol (**1**), however, was comparable in activity to several of the other *cis*-stilbenes described here, including the 4′-hydroxy (**14c**, herein named resverastatin) and the 3-hydroxy (**14g**) *cis* derivatives. For this reason we decided to synthesize the prodrug of the 4′-hydroxystilbene **14c**. The synthesized prodrug **14n** was essentially identical to **14c** in its effects on the growth of cancer cells.

From the known antimitotic activity of **2a** and **2c** and their potent interactions with tubulin, it seemed likely that the most cytotoxic compounds prepared in the current series would also inhibit this important cellular protein. Several of the newly synthesized compounds were therefore examined for inhibitory effects on tubulin assembly, in a direct comparison with **2a** and **2c** (Table 3). Compound **4a** proved to be more inhibitory than **2a** (IC_{50} values of 1.8 and 2.0 μM, respectively), while, in contrast, **16a** was somewhat less potent than **2c** (IC_{50} values of 2.6 and 1.1 μM, respectively). These values are qualitatively parallel to the differences observed in relative cytotoxic effects with the four compounds. Resveratrol (**1**) was inactive as an inhibitor of tubulin assembly. Compound **14c**, representing demethylation at position 4′ of **4a**, was 16-fold less active (IC_{50} = 29 μM) than **4a**.

Combretastatin A-4 (**2a**) binds in the colchicine site of tubulin and is exceptionally potent as an inhibitor of the binding of radiolabeled colchicine to tubulin.[26] We compared the two active compounds **4a** and **16a** to **2a** and **2c** for their effects on colchicine binding to tubulin (Table 3). Combretastatin A-4 (**2a**) displayed its usual potency, inhibiting colchicine binding by 98% when the two drugs were present in equimolar (5 μM) concentrations and by 91% when **2a** was present at 2 μM (the tubulin concentration in these experiments was 1.0 μM). Compound **4a** was essentially equivalent to **2a** as an inhibitor of colchicine binding. Phenstatin, **2c**, despite its greater inhibition of polymerization, was less potent than **2a** as an inhibitor of colchicine binding, while **16a** had the least activity in both assays. The reasons for these discrepancies are at present unknown but do not appear to derive from salt or temperature differences in the reaction conditions.

Resveratrol (**1**) contained in the roots of *Polygonum cuspidatum* has apparently been used in Chinese and Japanese traditional medicine as a treatment for gonorrhea.[6] In the present study, its activity against the etiologic agent of gonorrhea, *N. gonorrhoeae*, was demonstrated in broth microdilution assays (Table 4). Stilbene production has been correlated with the resistance of grape leaves to fungal infection.[7c] Stilbenes **14c**, **14h**, and **14n** and benzophenone **16k** exhibited marginal antifungal activity (Table 4). The dimethyl derivative of *cis*-resveratrol (**14c**), with both antibacterial and antifungal activities, was the most active of the stilbenes and benzophenones tested. Further biological evaluation of such resveratrol structural modifications should include chemopreventive potential and effects on targets such as COX-1 and COX-2, and as nicely pointed out by a reviewer, "lack of cytotoxic potential can be viewed as an advantage" in these areas.

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