Synthesis and Protein–Tyrosine Kinase Inhibitory Activity of Polyhydroxylated Stilbene Analogues of Piceatannol

Kshitij Thakkar, Robert L. Geahlen, and Mark Cushman*

Department of Medicinal Chemistry and Pharmacognosy, Purdue University, West Lafayette, Indiana 47907

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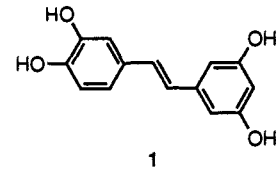
A series of hydroxylated *trans*-stilbenes related to the antileukemic natural product *trans*-3,3′,4,5′-tetrahydroxystilbene (piceatannol) (1) has been prepared and tested for inhibition of the lymphoid cell lineage-specific protein–tyrosine kinase p56^{lck}, which plays an important role in lymphocyte proliferation and immune function. A number of the analogues displayed enhanced enzyme inhibitory activity relative to the natural product. Reduction of the double bond bridging the two aromatic rings and benzylation of the phenolic hydroxyl groups was found to decrease activity significantly. The most potent compounds in the series proved to be *trans*-3,3′,5,5′-tetrahydroxystilbene, *trans*-3,3′,5-trihydroxystilbene, and *trans*-3,4,4′-trihydroxystilbene.

The pathways that regulate the proliferation of eukaryotic cells are stimulated by the interactions of extracellular ligands with cell surface receptors. The emerging biochemical knowledge concerning components of these signal transduction systems offers medicinal chemists new opportunities for the rational design of inhibitors to serve as chemotherapeutic agents for the treatment of neoplastic disease, modulators of immune function, and molecular probes for unraveling the mechanisms of signal transduction.[1,2] Protein–tyrosine kinases (PTK's), which catalyze the transfer of the terminal phosphate of ATP to tyrosine residues on substrate proteins, play key roles in these signal transduction pathways, and in many human malignancies, a specific PTK is activated or overexpressed. Examples include chromosomal translocation of *c-abl* in chronic myelogenous leukemia[3] and Ph^1-positive acute lymphocytic leukemia,[4] amplification of *c-erb-B-2* in human breast cancer,[5] activation of pp60$^{c\text{-}src}$ in colon carcinoma,[6] and overexpression of the epidermal growth factor (EGF) receptor in squamous cell carcinoma.[7,8] This situation has stimulated a great deal of interest in the development of PTK inhibitors as potential anticancer agents.[9-11]

We recently discovered that piceatannol (1), a known antileukemic principle in the seeds of *Euphorbia lagascae*, inhibits the PTK activities of p40 as well as p56^{lck} by binding to the substrate binding sites.[12] In view of the fact that virtually nothing has been reported on the structure–activity relationships for the PTK inhibitory activity of hydroxylated stilbenes related to piceatannol (1), we have undertaken a study of the effect of the number and placement of the phenolic hydroxyl groups on the *trans*-stilbene system on the inhibition p56^{lck}. The enzyme chosen for study, p56^{lck}, is a lymphoid cell lineage-specific PTK of the *src* family which is overexpressed in several lymphomas.[13-21] In addition, p56^{lck} is associated with both CD4 and CD8 surface glycoproteins in T-lymphocytes, where it exists as a link in the communication of CD4 and CD8 with the T-cell receptor (TCR) ξ chain,[22] and it is also involved as a critical signaling molecule downstream from the interleukin-2 receptor.[23] This evidence indicates that p56^{lck} also plays an important role in immune function.

Chemistry

Several syntheses of piceatannol (1) have been reported in which a tetramethoxystilbene precursor of piceatannol (1) is synthesized by the Wittig reaction, and the methyl protecting groups are then removed with pyridine hydrochloride[24] or boron tribromide.[25] Use of trimethylsilyl



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protecting groups has also been explored in a related sequence.[26] The original piceatannol (1) synthesis involved reaction of 3,5-dihydroxyphenyl acetate and 3,4-dihydroxybenzaldehyde in acetic anhydride, decarboxylation of the ensuing 3,3′,4,5′-tetraacetoxystilbene-α-carboxylic acid with copper and quinoline at high temperature, and hydrolysis of the resulting piceatannol tetraacetate with sodium hydroxide.[27] All of these routes are reported to proceed in moderate to low yields. The main problems with piceatannol (1) synthesis are caused by the instability of this polyphenolic stilbene toward oxidation, resulting in the formation of unstable radicals and quinones. The final isolation of the product has to therefore be carried out from black mixtures containing many components.

Our initial work on piceatannol (1) synthesis utilized Wittig chemistry to establish the stilbene skeleton of piceatannol (1) with the phenols in protected form. Several mono- and disubstituted [(*tert*-butyldimethylsilyl)oxy]stilbenes were synthesized at first, and these compounds were successfully deprotected with tetrabutylammonium fluoride. However, with increasing substitution the isolation of the desired deprotected products became much more difficult, if not impossible. Switching to methyl ethers to protect the phenols was not ideal, although a variety of deprotection methods were tried, including boron tribromide,[28] boron tribromide–dimethyl sulfide complex, boron trichloride–dimethyl sulfide complex,[29] and pyridine hydrochloride with a catalytic amount of quinoline at elevated temperatures.[30] In all of these cases, demethylation was always incomplete and the yields were disappointing.

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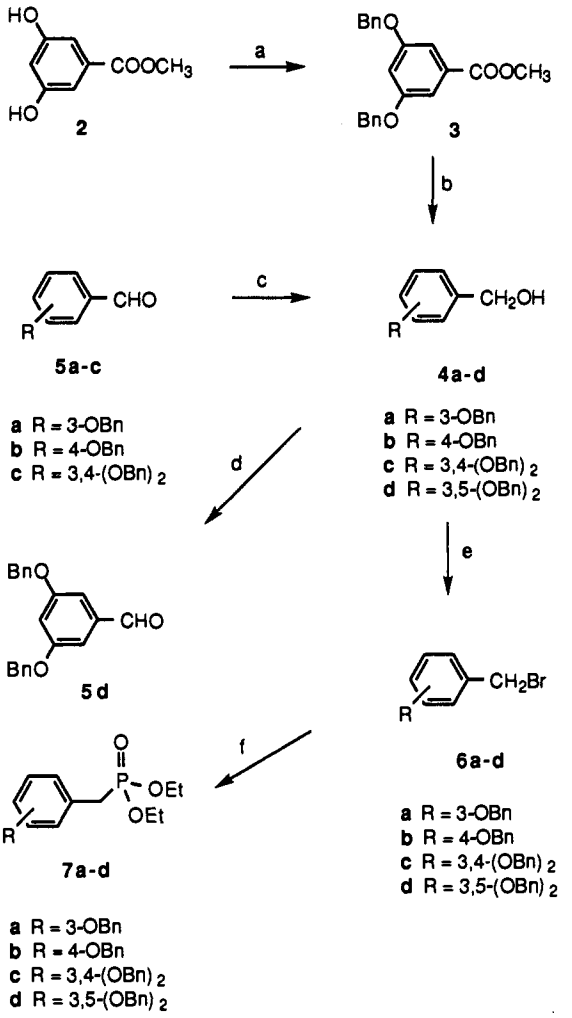
Scheme I[a]



[a] Key: (a) $C_6H_5CH_2Br$, K_2CO_3, DMF, 23 °C (14 h); (b) $LiAlH_4$, Et_2O, 23 °C (4 h); (c) $NaBH_4$, THF, 23 °C (4 h); (d) $PyH^+ClCrO_3^-$, CH_2Cl_2, 0 °C (3.5 h); (e) PBr_3, CH_2Cl_2, 0 °C (2 h), 23 °C (1 h); (f) $P(OEt)_3$, $(n\text{-}Bu)_4N^+I^-$, 110–130 °C (10 h).

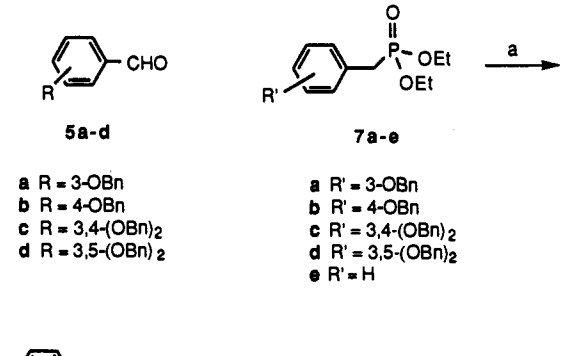
At this juncture, benzyl groups were tried to protect the phenols. A series of diethyl benzylphosphonates **7a-e** were prepared with benzyl protecting groups (Scheme I) and reacted with aldehydes **5a-d** containing benzyloxy groups to afford *trans*-stilbenes **8a-k** (Scheme II). A number of debenzylating reagents were then tried without much success, including iodotrimethylsilane,[31] chlorotrimethylsilane–sodium iodide,[32] boron tribromide,[33] boron trichloride,[33] boron trifluoride–ethanethiol,[34] boron tribromide–dimethylsulfide, and boron trichloride-dimethyl sulfide. Finally, the deprotection of the series **8a-k** was performed cleanly with a complex prepared from aluminum chloride (4 equiv) and *N,N*-dimethylaniline (3 equiv) in methylene chloride.[35] Oxidation of the products was minimized when the purification was performed rapidly with centrifugally accelerated TLC on silica gel under argon atmosphere.

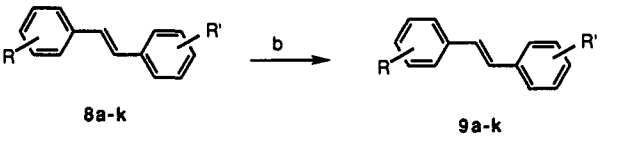
Dihydropiceatannol (**10j**) and the dihydropiceatannol analogue **10k** were prepared by treatment of **8j** and **8k** with hydrogen and palladium on charcoal as outlined in Scheme III.

Biological Results and Discussion

Several of the benzylated precursors were tested for inhibition of $p56^{lck}$, along with the deprotected polyphenols **9** and the dihydro compounds **10**. The IC_{50} values are listed in Table I. None of the benzylated compounds, including **8a**, **8b**, **8e**, **8f**, **8g**, and **8h**, were active as inhibitors

Scheme II[a]



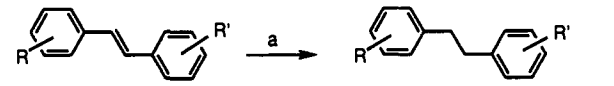


	R	R'
a	3,4-(OBn)2	H
b	3,5-(OBn)2	H
c	3-OBn	3-OBn
d	3-OH	4-OH
e	3,4-(OBn)2	3-OBn
f	3,4-(OBn)2	4-OBn
g	3,5-(OBn)2	3-OBn
h	3,5-(OBn)2	4-OBn
i	3,4-(OBn)2	3,4-(OBn)2
j	3,4-(OBn)2	3,5-(OBn)2
k	3,5-(OBn)2	3,5-(OBn)2

	R	R'
a	3,4-(OH)2	H
b	3,5-(OH)2	H
c	3-OH	3-OH
d	3-OBn	4-OBn
e	3,4-(OH)2	3-OH
f	3,4-(OH)2	4-OH
g	3,5-(OH)2	3-OH
h	3,5-(OH)2	4-OH
i	3,4-(OH)2	3,4-(OH)2
1	3,4-(OH)2	3,5-(OH)2
k	3,5-(OH)2	3,5-(OH)2

[a] Key: (a) NaH, THF, 23 °C (8–16 h); (b) $AlCl_3$, $(CH_{32}NC_6H_5$, CH_2Cl_2, 0 °C (2–8 h).

Scheme III[a]



	R	R'	R	R'
j	3,4-(OBn)2	3,5-(OBn)2	3,4-(OH)2	3,5-(OH)2
k	3,5-(OBn)2	3,5-(OBn)2	3,5-(OH)2	3,5-(OH)2

[a] Key: (a) H_2, Pd–C, 40 psi, EtOH (18–24 h).

Table I. Inhibition of Protein-Tyrosine Kinase $p56^{lck}$ Activity by Piceatannol Analogues

compd	IC_{50}[a] (μM)	compd	IC_{50}[a] (μM)
8a	>2030	**9e**	58
8b	>2030	**9f**	19
8e	>2030	**9g**	17
8f	>2030	**9h**	112
8g	>2030	**9i**	74
8h	>2030	**9k**	16
9a	203	**10j**	1560
9b	193	**10k**	487
9c	234	**1**	66
9d	36		

[a] The IC_{50} values are the averages of two determinations.

of the enzyme. In contrast, the debenzylated piceatannol analogues **9a-k** all displayed significant inhibitory activity. Five of these compounds, including **9d**, **9e**, **9f**, **9g**, and **9k**, were actually more potent than the natural product piceatannol (**1**), although the increase in activity was relatively moderate. The dihydro compounds, **10j** and **10k**, were much less active than their dehydrogenated counterparts piceatannol (**1**) and compound **9k**.

In view of these results, several generalizations may be offered. The inactivity of the benzylated precursors **8** in comparison to the polyphenols in the **9** series indicates

that free phenolic hydroxyl groups may be required for enzyme inhibitory activity. Within the series of polyphenols **9**, there is a general correlation of the inhibitory activity with the number of phenolic hydroxyl groups. The three least active compounds, **9a** (IC_{50} 203 μM), **9b** (IC_{50} 193 μM), and **9c** (IC_{50} 234 μM), are diphenols, the exception being diphenol **9d** (IC_{50} 36 μM), which is more potent than piceatannol (IC_{50} 66 μM). Of the three most potent compounds, **9f** (IC_{50} 19 μM) and **9g** (IC_{50} 17 μM) are both triphenols and **9k** (IC_{50} 16 μM) is a tetraphenol. A minimum of three hydroxyl groups seems to be required for optimal activity. With regard to the placement of the hydroxyl groups in the tetraphenols, comparison of the activity of piceatannol (**1**, IC_{50} 66 μM) vs **9k** (IC_{50} 16 μM) and **10j** (IC_{50} 1560 μM) vs **10k** (IC_{50} 487 μM) reveals that moving the phenol para to the bridge over one carbon to the open meta position results in an increase in activity. Similarly, within the series of triphenols, movement of the *p*-phenol in **9e** (IC_{50} 58 μM) to the adjacent open meta position gave the more active **9g** (IC_{50} 17 μM). However, a similar relocation in **9f** (IC_{50} 19 μM) to yield **9h** (IC_{50} 112 μM) resulted in a decrease in activity, demonstrating that this effect on activity in the triphenol series is influenced by the placement of the phenol in the other benzene ring bearing only one hydroxyl group. The additional conformational mobility conferred on reduction of the central double bonds of piceatannol (**1**) and **9k** to form **10j** and **10k**, respectively, resulted in a decrease in activity, indicating that a dihedral angle of 180° of the bonds to the two phenyl rings may be important in binding to the enzyme.

In summary, it may be concluded that the arrangement of the phenolic hydroxyl groups on the *trans*-stilbene framework in the natural product piceatannol (**1**) is not optimal for inhibition of the protein–tyrosine kinase $p56^{lck}$, as several tri- and tetraphenols were prepared having enhanced activity. The IC_{50}'s of the most potent hydroxystilbenes reported here are not as low as those recently reported by Burke *et al.* for certain 7,8-dihydroxyisoquinolines against $p56^{lck}$, although the values are not strictly comparable because of differences in the assay conditions.[36] The methodology utilized here for the preparation of polyhydroxylated stilbenes should prove to be of general use for the preparation of this class of compounds, which are of interest not only because of their PTK inhibitory activity but also because they possess antifungal[37-39] and nematocidal[40] activity, as well as coronary vasodilator activity,[41] hypotensive activity,[41] and inhibitory activity against mitochondrial ATPase[42] and histamine release.[43]

Experimental Section

Melting points were determined in capillary tubes on a Mel-Temp apparatus and are uncorrected. Spectra were obtained as follows: CI mass spectra on a Finnegan 4000 spectrometer, high-resolution EIMS and high-resolution CIMS on a Kratos MS 50 spectrometer, and ^{1}H NMR spectra on Chemagnetics A-200, Varian VXR-500S, and Varian XL-200 spectrometers with TMS as the internal standard in $CDCl_3$ or $(CD_3)_2CO$. Microanalyses were performed at the Purdue University microanalysis laboratory, and all the values were within ±0.4% of the calculated compositions. THF was distilled from sodium metal and benzophenone under argon to remove moisture and oxygen. DMF was vacuum distilled from calcium hydride under anhydrous argon atmosphere. Methylene chloride was distilled from calcium hydride. Analytical thin-layer chromatography was done on Whatman silica 60 K6F and Merck silica 60 F_{254} glass coated plates. Silica gel column chromatography was performed using Sigma 70–230 mesh silica gel, and flash chromatography was carried out with 230–400 mesh silica gel. All compounds possessed analytical data consistent with the proposed structure.

Methyl 3,5-Bis(benzyloxy)benzoate (3). Finely powdered anhydrous potassium carbonate (23.49 g, 170 mmol) was added to a well-stirred solution of methyl 3,5-dihydroxybenzoate(**2**)(6.125 g, 36.46 mmol) dissolved in DMF (100 mL) under argon atmosphere. After 2 h, benzyl bromide (9.33 g, 1.5 equiv, 54.6 mmol) was added dropwise over a period of 45 min, and the reaction was allowed to proceed for 14 h. The reaction mixture was poured on ice–water (100 mL) and extracted with chloroform (5 × 85 mL). The organic fractions were combined and washed with a saturated solution of sodium chloride (200 mL) and dried over anhydrous magnesium sulfate. Evaporation of the solvent gave the product, which was crystallized from hexane–ether to give the protected ester **3**: yield 10.26 g (82%), mp 67–68 °C (lit.[44] mp 77–79 °C); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 3.81 (s, 3 H), 5.03 (s, 4 H), 6.76 (t, J = 2.1 Hz, 1 H), 6.83 (d, J = 2.1 Hz, 2 H), 7.40 (m, 10 H).

General Procedure for the Preparation of Benzyl Alcohols 4a-c. A solution of benzaldehydes **5a-c** (10 mmol) in THF (25 mL) was added dropwise to a well-stirred suspension of sodium borohydride (0.378 g, 10 mmol) in THF (50 mL). The reaction mixture was stirred at room temperature for 4 h and then quenched by the dropwise addition of water (10 mL). The resulting reaction mixture was passed through a Celite pad. The filtrate was dried over anhydrous magnesium sulfate, and the solvent was evaporated to give the corresponding alcohols **4a-c**.

3-(Benzyloxy)benzyl alcohol (4a): yield 2.09 g (98%), white needles, mp 47–48 °C (lit.[45] mp 47–49 °C); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.35 (br s, OH, exchangeable with D_2O), 4.51 (s, 2 H), 5.00 (s, 2 H), 6.83 (d, J = 2.0 Hz, 1 H), 6.88 (dt, J = 8.0, 2.0 Hz, 1 H), 6.95 (t, J = 8.0 Hz, 1 H), 7.40 (m, 6 H).

4-(Benzyloxy)benzyl alcohol (4b): yield 1.96 g (92%), white needles, mp 89–90 °C (lit.[45] mp 86–89 °C); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.70 (br s, OH), 4.49 (s, 2 H), 5.03 (s, 2 H), 6.92 (AA', J_{AB} = 8.3, 2.1 Hz, 2 H), 7.20 (BB', J_{AB} = 8.3 Hz, 2 H), 7.40 (m, 5 H).

3,4-Bis(benzyloxy)benzyl alcohol (4c): yield 2.97 g (93%), pale white needles, mp 65–67 °C (lit.[46] mp 66–68 °C); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 4.51 (s, 2 H), 5.15 (s, 2 H), 5.18 (s, 2 H), 6.86 (dd, J = 8.1, 1.7 Hz, 1 H), 6.93 (d, J = 8.1 Hz, 1 H), 6.93 (d, J = 1.7 Hz, 1 H), 7.43 (m, 10 H).

3,5-Bis(benzyloxy)benzyl alcohol (4d). A solution of methyl 3,5-bis(benzyloxy)benzoate (**3**) (10.26 g, 30 mmol) in anhydrous ether (75 mL) was added to a cold suspension of lithium aluminum hydride (1.449 g, 39.7 mmol) in anhydrous ether (200 mL) over the period of 40 min. The reaction mixture was stirred for 4 h. The excess lithium aluminum hydride was decomposed by the successive dropwise addition of methanol (5 mL), water (10 mL), and 10% sodium hydroxide (10 mL). The organic layer was then passed through a Celite filter pad, and the filtrate was dried over anhydrous sodium sulfate. The solvent was evaporated under vacuum to afford the alcohol **4d**: yield 8.568 g (88%), white needles, mp 85–86 °C (lit.[47] mp 86 °C); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 4.63 (s, 2 H), 5.03 (s, 4 H), 6.56 (t, J = 2.0 Hz, 1 H), 6.63 (d, J = 2.0 Hz, 2 H), 7.40 (m, 10 H).

3,5-Bis(benzyloxy)benzaldehyde (5d). Pyridinium chlorochromate (3.22 g, 15 mmol) was suspended in methylene chloride (25 mL), and 3,5-bis(benzyloxy)benzyl alcohol (**4d**) (3.08 g, 0.62 mmol) was rapidly added at 0 °C. The solution became briefly homogeneous before depositing the black insoluble reduced reagent. The reaction mixture was then allowed to stir for 3.5 h. The black reaction mixture was diluted with anhydrous ether (10 mL) and filtered through a layer of Celite on top of a layer of silica gel in a Buchner funnel. The aldehyde **5d** (2.98 g, 96%) was obtained as white needles after evaporation of solvent from the filtrate: mp 77–80 °C. (lit.[47] mp 78 °C); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 5.09 (s, 4 H), 7.11 (t, J = 2.0 Hz, 1 H), 7.87 (d, J = 2.0 Hz, 2 H), 7.40 (m, 10 H), 9.90 (s, 1 H).

General Procedure for the Preparation of Benzyl Bromides 6a-d. Phosphorous tribromide (2.71 g, 10 mmol) was added to a well-stirred solution of benzyl alcohols **4a-d** (10 mmol) in dry methylene chloride (45 mL) at 0 °C under argon. The stirring was continued for 2 h at 0 °C and at room temperature for 1 h. The reaction mixture was poured onto ice–water (200 mL), warmed, and extracted with diethyl ether (5 × 50 mL). The

ether layers were combined and dried over anhydrous magnesium sulfate. Evaporation of the solvent gave the respective bromides **6a-d**.

3-(Benzyloxy)benzyl bromide (6a): yield 2.34 g (85%), pale white needles, mp 52–55 °C (lit.[45] mp 55–56 °C); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 4.44 (s, 2 H), 5.05 (s, 2 H), 6.79 (d, J = 2.0 Hz, 1 H), 6.93 (tt, J = 8.0, 2.0 Hz, 1 H), 7.23 (t, J = 8.0 Hz, 1 H), 7.40 (m, 6 H).

4-(Benzyloxy)benzyl bromide (6b): yield 2.54 g (92%), white needles, mp 84–87 °C (lit.[46] mp 85–86 °C); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 4.49 (s, 2 H), 5.06 (s, 2 H), 6.95 (AA′, J_{AB} = 8.3 Hz, 2 H), 7.37 (BB′, J_{AB} = 8.3 Hz, 2 H), 7.40 (m, 5 H).

3,4-Bis(benzyloxy)benzyl bromide (6c): yield 3.10 g (78%), mp 72–75 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 4.53 (s, 2 H), 5.15 (s, 2 H), 5.17 (s, 2 H), 6.83 (dd, J = 8.1, 1.8 Hz, 1 H), 6.90 (d, J = 8.1 Hz, 1 H), 6.99 (d, J = 1.8 Hz, 1 H), 7.52 (m, 10 H).

3,5-Bis(benzyloxy)benzyl bromide (6d): yield 3.23 g (83%), mp 87–89 °C (lit.[47] mp 92–93 °C); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 4.41 (s, 2 H), 5.02 (s, 4 H), 6.55 (t, J = 2.0 Hz, 1 H), 6.63 (d, J = 2.0 Hz, 2 H), 7.40 (m, 10 H).

General Procedure for the Preparation of Diethyl Benzylphosphonate Esters 7a-d. Freshly distilled triethyl phosphite (2.49 g, 15 mmol) was added to the benzyl bromides **6a-d** (10 mmol) containing a catalytic amount of tetrabutylammonium iodide, and the resulting mixture was heated at 110–130 °C for 10 h. Excess triethyl phosphite was removed by heating for 3 h at 55 °C under vacuum (0.5 mmHg) to yield the resulting phosphonate esters **7a-d**.

Diethyl [3-(benzyloxy)benzyl]phosphonate (7a): yield 2.83 g (85%), light yellow oil; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.23 (t, J = 7.4 Hz, 6 H), 3.10 (d, J_{PCH_2} = 21.6 Hz, 2 H), 4.02 (quint, J = 7.4 Hz, 4 H), 5.05 (s, 2 H), 6.83 (d, J = 2.0 Hz, 1 H), 6.95 (dt, J = 8.0 Hz, 2.0 Hz, 1 H), 7.05 (t, J = 8.0 Hz, 1 H), 7.40 (m, 6 H); low-resolution CIMS (isobutane) m/e 335 (MH^+, 100). Anal. ($C_{18}H_{23}O_4P$) C, H, P.

Diethyl [4-(benzyloxy)benzyl]phosphonate (7b): yield 3.12 g (94%), yellow oil; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.26 (t, J = 7.4 Hz, 6 H), 3.08 (d, J_{PCH_2} = 21.6 Hz, 2 H), 3.99 (quint, J = 7.4 Hz, 4 H), 5.02 (s, 2 H), 6.89 (AA′, J_{AB} = 8.3 Hz, 2 H), 7.41 (BB′, J_{AB} = 8.3 Hz, 2 H), 7.5 (m, 5 H); low-resolution CIMS (isobutane) m/e 335 (MH^+, 100). Anal. ($C_{18}H_{23}O_4P$) C, H, P.

Diethyl [3,4-bis(benzyloxy)benzyl]phosphonate (7c): yield 3.86 g (88%), light yellow oil; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.26 (t, J = 7.4 Hz, 6 H), 3.13 (d, J_{PCH_2} = 21.6 Hz, 2 H), 3.99 (quint, J = 7.4 Hz, 4 H), 5.02 (s, 2 H), 5.04 (s, 2 H), 6.78 (dt, J = 8.0, 2.0 Hz, 1 H), 6.86 (d, 8.0 Hz, 1 H), 6.94 (d, J = 2.0 Hz, 1 H), 7.40 (m, 10 H); low-resolution CIMS (isobutane) m/e 441 (MH^+, 100). Anal. ($C_{25}H_{29}O_5P$) C, H, P.

Diethyl [3,5-bis(benzyloxy)benzyl]phosphonate (7d): yield 4.18 g (95%), yellow oil; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.22 (t, J = 7.4 Hz, 6 H), 3.10 (d, J_{PCH_2} = 21.6 Hz, 2 H), 3.95 (quint, J = 7.4 Hz, 4 H), 5.05 (s, 4 H), 6.54 (t, J = 2.1 Hz, 1 H), 6.57 (d, J = 2.1 Hz, 2 H), 7.38 (m, 10 H); low-resolution CIMS (isobutane) m/e 441 (MH^+, 100). Anal. ($C_{25}H_{29}O_5P$) C, H, P.

General Procedure for the Preparation of Stilbenes 8a-k. Sodium hydride (0.2 g, 4 mmol) was added to a well-stirred suspension of the phosphonate esters **7a-d** (2 mmol) in dry THF (10 mL) at −5 °C under argon. After 30 min, the aldehydes **5a-d** (2 mmol) in THF (15 mL) were added dropwise, and the reaction mixture was allowed to stir at room temperature for 8–16 h. The mixture was then cooled to 0 °C, and the excess sodium hydride was quenched with distilled water (5 mL). The reaction mixture was then poured on ice, followed by addition of 2 M HCl (5 mL), and the products were extracted with ethyl acetate (4 × 50 mL). The organic layers were combined and were washed with a saturated solution of sodium chloride (1 × 30 mL). The ethyl acetate layer was dried over anhydrous magnesium sulfate and evaporated. The purification of the crude product was done by flash chromatography (ethyl acetate–hexane, gradient elution of 0–50%, silica gel 230–400 mesh) which gave Z and E isomers in the pure form. Only the E isomer was isolated and characterized.

(*E*)-1-[3,4-Bis(benzyloxy)phenyl]-2-phenylethene (8a): yield 0.62 g (79%), mp 119–121 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.17 (s, 2 H), 5.21 (s, 2 H), 6.91 (d, J = 15.48 Hz, 1 H), 6.93 (d, J = 8.2 Hz, 1 H), 7.01 (d, J = 15.48 Hz, 1 H), 7.03 (dd, J = 8.2, 2.1 Hz, 1 H), 7.13 (d, J = 2.1 Hz, 1 H), 7.22 (m, 2 H), 7.30 (m, 2 H), 7.42 (m, 3 H), 7.50 (m, 8 H); low-resolution CIMS (isobutane) m/e 393 (MH^+, 100). Anal. ($C_{28}H_{24}O_2$) C, H.

(*E*)-1-[3,5-Bis(benzyloxy)phenyl]-2-phenylethene (8b): yield 0.59 g (75%), mp 113–115 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.07 (s, 4 H), 6.57 (t, J = 2.2 Hz, 1 H), 6.77 (d, J = 2.2 Hz, 2 H), 7.02 (d, J = 16.1 Hz, 1 H), 7.08 (d, J = 16.1 Hz, 1 H), 7.24 (m, 2 H), 7.33 (m, 2 H), 7.48 (m, 3 H), 7.55 (m, 8 H); low-resolution CIMS (isobutane) m/e 393 (MH^+, 100). Anal. ($C_{28}H_{24}O_2$) C, H.

(*E*)-1-[3-(Benzyloxy)phenyl]-2-[3-(benzyloxy)phenyl]ethene (8c): yield 0.53 g (67%), mp 140–142 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.10 (s, 4 H), 6.88 (ddd, J = 8.5, 2.4, 1.9 Hz, 2 H), 7.05 (s, olefin, 2 H), 7.12 (dd, J = 8.5, 2.4 Hz, 2 H), 7.26 (t, J = 8.5 Hz, 2 H), 7.26 (t, J = 8.1 Hz, 2 H), 7.35 (m, 2 H), 7.40 (m, 4 H), 7.46 (m, 4 H); low-resolution CIMS (isobutane) m/e 393 (MH^+, 100). Anal. ($C_{28}H_{24}O_2$) C, H.

(*E*)-1-[3-(Benzyloxy)phenyl]-2-[4-(benzyloxy)phenyl]ethene (8d): yield 0.55 g (70%), mp 138–139 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.08 (s, 2 H), 5.09 (s, 2 H), 6.86 (ddd, J = 8.1, 2.2, 2.2 Hz, 1 H), 6.94 (d, J = 16.3 Hz, 1 H), 6.97 (AA′, J_{AB} = 8.3 Hz, 2 H), 7.04 (d, J = 16.3 Hz, 1 H), 7.09 (d, J = 8.3 Hz, 2 H), 7.12 (d, J = 2.2 Hz, 1 H), 7.26 (t, J = 8.1 Hz, 1 H), 7.40 (m, 10 H); low-resolution CIMS (isobutane) m/e 393 (MH^+, 100). Anal. ($C_{28}H_{24}O_2$) C, H.

(*E*)-1-[3-(Benzyloxy)phenyl]-2-[3,4-bis(benzyloxy)phenyl]ethene (8e): yield 0.79 g (79%), mp 130–132 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.10 (s, 2 H), 5.18 (s, 2 H), 5.21 (s, 2 H), 6.87 (dd, J = 2.2, 2.0 Hz, 2 H), 6.90 (d, J = 16.0 Hz, 1 H), 6.92 (d, J = 8.0 Hz, 1 H), 6.98 (d, J = 16.0 Hz, 1 H), 7.02 (dd, J = 8.0, 2.0 Hz, 1 H), 7.08 (dd, J = 8.0, 2.0 Hz, 1 H), 7.10 (d, J = 2.0 Hz, 1 H), 7.14 (d, J = 2 Hz, 1 H), 7.40 (m, 15 H); low-resolution CIMS (isobutane) m/e 499 (MH^+, 100). Anal. ($C_{35}H_{30}O_3$) C, H.

(*E*)-1-[4-(Benzyloxy)phenyl]-2-[3,4-bis(benzyloxy)phenyl]ethene (8f): yield 0.74 g (74%), mp 178–179 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.06 (s, 2 H), 5.16 (s, 2 H), 5.19 (s, 2 H), 6.84 (s, olefin, 2 H), 6.88 (d, J = 8.3 Hz, 1 H), 6.93 (AA′, J_{AB} = 8.5 Hz, 2 H), 6.97 (dd, J = 8.3, 1.9 Hz, 1 H), 7.10 (d, J = 1 Hz, 1 H), 7.40 (m, 17 H); CIMS (isobutane) m/e 499 (MH^+, 100). Anal. ($C_{35}H_{30}O_3$) C, H.

(*E*)-1-[3-(Benzyloxy)phenyl]-2-[3,5-bis(benzyloxy)phenyl]ethene (8g): yield 0.67 g (67%), mp 137–138 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 5.07 (s, 4 H), 5.10 (s, 2 H), 6.58 (t, J = 2.0 Hz, 1 H), 6.77 (d, J = 2.0 Hz, 2 H), 6.90 (ddd, J = 8.0, 8.0, 1.3 Hz, 1 H), 6.99 (d, J = 16.29 Hz, 1 H), 7.03 (d, J = 16.29 Hz, 1 H), 7.04 (dd, J = 8.0, 1.3 Hz, 1 H), 7.05 (d, J = 8.0 Hz, 1 H), 7.17 (t, J = 7.8 Hz, 1 H), 7.45 (m, 15 H); low-resolution CIMS (isobutane) m/e 499 (MH^+, 100). Anal. ($C_{35}H_{30}O_3$) C, H.

(*E*)-1-[4-(Benzyloxy)phenyl]-2-[3,5-bis(benzyloxy)phenyl]ethene (8h): yield 0.76 g (76%), mp 156–158 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.05 (s, 4 H), 5.07 (s, 2 H), 6.54 (t, J = 2.0 Hz, 1 H), 6.73 (d, J = 2.0 Hz, 2 H), 6.89 (d, J = 16.0 Hz, 1 H), 6.95 (AA′, J_{AB} = 8.5 Hz, 2 H), 7.03 (d, J = 16.0 Hz, 1 H), 7.40 (m, 17 H); low-resolution CIMS (isobutane) m/e 499 (MH^+, 100). Anal. ($C_{35}H_{30}O_3$) C, H.

(*E*)-1-[3,4-Bis(benzyloxy)phenyl]-2-[3,4-bis(benzyloxy)phenyl]ethene (8i): yield 1.02 g (83%), mp 181–182 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.17 (s, 4 H), 5.20 (s, 4 H), 6.81 (s, olefin, 2 H), 6.92 (d, J = 7.8 Hz, 2 H), 6.98 (dd, J = 7.8, 1.9 Hz, 2 H), 7.10 (d, J = 1.9 Hz, 2 H), 7.40 (m, 20 H); low-resolution CIMS (isobutane) m/e 605 (MH^+, 100). Anal. ($C_{42}H_{36}O_4$) C, H.

(*E*)-1-[3,4-Bis(benzyloxy)phenyl]-2-[3,5-bis(benzyloxy)phenyl]ethene (8j): yield 0.92 g (76%), mp 158–161 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.06 (s, 4 H), 5.18 (s, 2 H), 5.20 (s, 2 H), 6.36 (d, J = 16.1 Hz, 1 H), 6.53 (t, J = 2.2 Hz, 1 H), 6.72 (d, J = 2.2 Hz, 2 H), 6.90 (d, J = 7.8 Hz, 1 H), 6.94 (d, J = 16.1 Hz, 1 H), 7.00 (dd, J = 7.8, 2.2 Hz, 1 H), 7.12 (d, J = 2.2 Hz, 1 H), 7.42 (m, 20 H); low-resolution CIMS (isobutane) m/e 605 (MH^+, 100). Anal. ($C_{42}H_{36}O_4$) C, H.

(*E*)-1-[3,5-Bis(benzyloxy)phenyl]-2-[3,5-bis(benzyloxy)phenyl]ethene (8k): yield 0.94 g (78%), mp 187–188 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.02 (s, 8 H), 6.48 (t, J = 2.2 Hz, 2 H), 6.72 (d, J = 2.2 Hz, 4 H), 6.96 (s, olefin, 2 H), 7.35 (m, 20 H); low-resolution CIMS (isobutane) m/e 605 (MH^+, 100). Anal. ($C_{42}H_{36}O_4$) C, H.

(*E*)-1-(4-Methoxyphenyl)-2-[3,4-bis(benzyloxy)phenyl]ethene (8l): yield 0.66 g (78%), mp 128–131 °C; ^{1}H NMR (acetone-d_6, 500 MHz) δ 3.82 (s, 3 H), 5.17 (s, 2 H), 5.22 (s, 2 H),

6.91 (AA', J_{AB} = 8.5 Hz, 2 H), 7.00 (d, J = 16.4 Hz, 1 H), 7.04 (d, J = 2.5 Hz, 1 H), 7.07 (d, J = 16.4 Hz, 1 H), 7.07 (dd, J = 8.0, 2.0 Hz, 1 H), 7.35 (m, 3 H), 7.40 (m, 5 H), 7.55 (m, 5 H); low-resolution CIMS (isobutane) m/e 423 (MH^+, 100). Anal. ($C_{29}H_{26}O_3$) C, H.

(*E*)-1-(4-Methoxyphenyl)-2-(3,4-dihydroxyphenyl)ethene (9l). Stilbene 8l (0.321 g, 0.76 mmol) was dissolved in anhydrous methylene chloride (25 mL) under argon. BBr_3·$(Me)_2S$ (1 M, 3 mL) in methylene chloride (75 mL) was added. The reaction mixture was allowed to stir for 38 h at room temperature under argon atmosphere. The reaction mixture was poured on ice–water, and 2 M HCl (10 mL) was added to yield 9l (0.07 g, 42%): ^{1}H NMR (acetone-d_6, 500 MHz) δ 6.79 (d, J = 8.1 Hz, 1 H), 6.81 (AA', J_{AB} = 8.5 Hz, 2 H), 6.87 (dd, J = 8.1, 2.0 Hz, 1H), 6.89 (s, olefin, 2 H), 7.05 (d, J = 2.1 Hz, 1 H), 7.37 (BB', J_{AB} = 8.5 Hz, 2 H), 8.19 (br s, exchangeable with D_2O), 8.35 (br s, exchangeable with D_2O); low-resolution CIMS (isobutane) m/e 243 (MH^+, 100).

General Procedure for the Cleavage of the Benzyloxy Groups To Afford Piceatannol (1) and Compounds 9a-k. Freshly distilled *N*,*N*-dimethylaniline (3 mmol) was added to a well-stirred solution of stilbene 8a (1 mmol) in dry methylene chloride (10 mL) under argon atmosphere at 0 °C. After 5 min, anhydrous $AlCl_3$ (4 mmol) was added to the reaction mixture. After 2–8 h the reaction mixture was quenched with water at 0 °C. The reaction mixture was poured into a 1.0 M solution of HCl (15 mL). The resulting mixture was extracted with ethyl acetate (4 × 50 mL), and the combined extracts were washed with a saturated solution of sodium chloride (25 mL). Evaporation of ethyl acetate from the dried (Na_2SO_4) solution gave the crude hydroxystilbene, which was purified by centrifugally accelerated thin layer chromatography under argon atmosphere (ethyl acetate–hexane gradient elution of 0%–75%, silica gel 60 PF_{254} with gypsum, 2 mm and 4 mm coated silica plate) which afforded the pure corresponding hydroxy stilbenes 1 and 9a-k.

(*E*)-1-(3,4-Dihydroxyphenyl)-2-phenylethene (9a): yield 79%, mp 137–139 °C (lit.[40] mp 132–135 °C); ^{1}H NMR (CD_3OD, 200 MHz) δ 6.77 (d, J = 8.0 Hz, 1 H), 6.72 (dd, J = 8.0, 2.1 Hz, 1 H), 6.87 (d, J = 16.2 Hz, 1 H), 7.04 (d, J = 16.2 Hz, 1 H), 7.10 (d, J = 2.1 Hz, 1 H), 7.25 (tt, J = 8.2, 2.0 Hz, 1 H), 7.36 (d, J = 8.0 Hz, 2 H), 7.43 (d, J = 8 Hz, 2 H); low-resolution CIMS (isobutane) m/e 213 (MH^+, 100). Anal. ($C_{14}H_{12}O_2$) C, H.

(*E*)-1-(3,5-Dihydroxyphenyl)-2-phenylethene (9b): yield 58%, mp 153–156 °C (lit.[40] mp 157–158 °C); ^{1}H NMR (CD_3OD, 200 MHz) δ 6.29 (t, J = 2.0 Hz, 1 H), 6.60 (d, J = 2.1 Hz, 2 H), 6.97 (d, J = 16.8 Hz, 1 H), 7.09 (d, J = 16.8 Hz, 1 H), 7.10 (d, J = 2.1 Hz, 1 H), 7.22 (tt, J = 8.2, 2.0 Hz, 1 H), 7.39 (td, J = 8.0, 2.0 Hz, 2 H), 7.53 (d, J = 8.2 Hz, 1 H); CIMS (isobutane) m/e 213 (MH^+, 100). Anal. ($C_{14}H_{12}O_2$) C, H.

(*E*)-1-(3-Hydroxyphenyl)-2-(3-hydroxyphenyl)ethene (9c): yield 59%, mp 148–150 °C (lit.[40] mp 152–153 °C); ^{1}H NMR (acetone-d_6, 500 MHz) δ 6.75 (ddd, J = 8.1, 2.2 Hz, 1.8 Hz, 2 H), 7.05 (m, 4 H), 7.09 (s, olefin, 2 H), 7.17 (t, J = 8.1 Hz, 2 H), 8.40 (br s, exchangeable with D_2O); low-resolution CIMS (isobutane) m/e 213 (MH^+, 100); high-resolution EIMS m/e 212.0837 (M^+) ($C_{14}H_{12}O_2$ requires 212.0837). Anal. ($C_{14}H_{12}O_2$) C, H.

(*E*)-1-(3-Hydroxyphenyl)-2-(4-hydroxyphenyl)ethene (9d): yield 62%, mp 210–213 °C (lit.[40] mp 216–218 °C); ^{1}H NMR (acetone-d_6, 500 MHz) δ 6.70 (ddd, J = 8.1, 2.2 Hz, 1.8 Hz, 1 H), 6.78 (AA', J_{AB} = 8.3, 2.1 Hz, 2 H), 6.87 (d, J = 16.3 Hz, 1 H), 6.95 (d, J = 1.8 Hz, 1 H), 6.98 (d, J = 2.2 Hz, 1 H), 7.03 (d, J = 16.3 Hz, 1 H), 7.15 (t, J = 8.1 Hz, 1 H), 7.37 (BB', J_{AB} = 8.3, 2.1 Hz, 2 H); low-resolution CIMS (isobutane) m/e 213 (MH^+, 100); high-resolution EIMS m/e 212.0838 (M^+) ($C_{14}H_{12}O_2$ requires 212.0837). Anal. ($C_{14}H_{12}O_2$) C, H.

(*E*)-1-(3-Hydroxyphenyl)-2-(3,4-dihydroxyphenyl)ethene (9e): yield 61%; ^{1}H NMR (acetone-d_6, 500 MHz) δ 6.69 (ddd, J = 8.1, 2.0, 1.9 Hz, 1 H), 6.80 (d, J = 8.1 Hz, 1 H), 6.89 (dd, J = 8.1, 2.0 Hz, 1 H), 6.92 (d, J = 16.5 Hz, 1 H), 6.95 (d, J = 8.1 Hz, 1 H), 6.98 (d, J = 1.9 Hz, 1 H), 7.00 (d, J = 16.5 Hz, 1 H), 7.10 (d, J = 2.0 Hz, 1 H), 7.14 (d, J = 8.1 Hz, 1 H), 8.25 (br s, exchangeable with D_2O); low-resolution CIMS (isobutane) m/e 229 (MH^+, 100); high-resolution EIMS m/e 228.0788 (M^+) ($C_{14}H_{12}O_3$ requires 228.0786). Anal. ($C_{14}H_{12}O_3$) C, H.

(*E*)-1-(4-Hydroxyphenyl)-2-(3,4-dihydroxyphenyl)ethene (9f): yield 70%, mp 242–243 °C; ^{1}H NMR (acetone-d_6, 500 MHz) δ 6.79 (d, J = 8.1 Hz, 1 H), 6.81 (AA', J_{AB} = 8.5 Hz, 2 H), 6.87 (dd, J = 8.1, 2.0 Hz, 1 H), 6.89 (s, olefin, 2 H), 7.05 (d, J = 2.1 Hz, 1 H), 7.37 (BB', J_{AB} = 8.5 Hz, 2 H), 8.19 (br s, exchangeable with D_2O), 8.35 (br s, exchangeable with D_2O); low-resolution CIMS (isobutane) m/e 229 (M^+, 100); high-resolution EIMS m/e 228.0793 (M^+) ($C_{14}H_{12}O_3$ requires 228.0786). Anal. ($C_{14}H_{12}O_3$) C, H.

(*E*)-1-(3-Hydroxyphenyl)-2-(3,5-dihydroxyphenyl)ethene (9g): yield 58%, mp 228–231 °C; ^{1}H NMR (acetone-d_6, 200 MHz) δ 6.29 (t, J = 2.0 Hz, 1 H), 6.56 (d, J = 2.0 Hz, 2 H), 6.74 (ddd, J = 8.0, 2.0, 1.9 Hz, 1 H), 7.02 (d, J = 16.5 Hz, 1 H), 7.03 (d, J = 16.5 Hz, 1 H), 7.06 (ddd, J = 8.0, 2.0, 1.9 Hz, 2 H), 7.17 (t, J = 8.0 Hz, 1 H), 8.25 (br s, exchangeable with D_2O), 8.35 (br s, exchangeable with D_2O); low-resolution CIMS (isobutane) m/e 229 (MH^+, 100); high-resolution EIMS m/e 228.0783 (M^+) ($C_{14}H_{12}O_3$ requires 228.0786).

(*E*)-1-(4-Hydroxyphenyl)-2-(3,5-dihydroxyphenyl)ethene (9h): yield 69%, mp 256–259 °C (lit.[40] mp 256–258 °C); ^{1}H NMR (acetone-d_6, 500 MHz) δ 6.30 (t, J = 2.0 Hz, 1 H), 6.57 (d, J = 2.0 Hz, 2 H), 6.82 (AA', J_{AB} = 8.5 Hz, 2 H), 6.88 (d, J = 16.6 Hz, 1 H), 7.01 (d, J = 16.6 Hz, 1 H), 7.41 (BB', J_{AB} = 8.5 Hz, 2 H), 8.19 (br s, exchangeable with D_2O), 8.45 (br s, exchangeable with D_2O); low-resolution CIMS (isobutane) m/e 229 (MH^+, 100); high-resolution EIMS m/e 228.0790 (M^+) ($C_{14}H_{12}O_3$ requires 228.0786).

(*E*)-1-(3,4-Dihydroxyphenyl)-2-(3,4-dihydroxyphenyl)ethene (9i): yield 35%, mp 241 °C dec; ^{1}H NMR (acetone-d_6, 500 MHz) δ 6.79 (d, J = 8.1 Hz, 2 H), 6.85 (dd, J = 2.0, 2.0 Hz, 2 H), 6.91 (s, olefin, 2 H), 7.04 (d, J = 2.0 Hz, 2 H), 8.35 (br s, exchangeable with D_2O); low-resolution CIMS (isobutane) m/e 245 (MH^+, 100); high-resolution CIMS (isobutane) m/e 245.0809 (MH^+) ($C_{14}H_{12}O_4$ requires 245.0814). Anal. ($C_{14}H_{12}O_4$) C, H.

(*E*)-1-(3,4-Dihydroxyphenyl)-2-(3,5-dihydroxyphenyl)ethene (1): yield 63%, mp 223–228 °C dec (lit.[46] mp 228–229 °C); ^{1}H NMR (acetone-d_6, 500 MHz) δ 6.25 (dd, J = 2.1, 1.0 Hz, 1 H), 6.52 (dd, J = 2.1, 1.0 Hz, 2 H), 6.80 (d, J = 8.1 Hz, 1 H), 6.82 (d, J = 16.18 Hz, 1 H), 6.90 (dd, J = 8.1, 2.1 Hz, 1 H), 6.95 (d, J = 16.18 Hz, 1 H), 7.07 (d, J = 2.1 Hz, 1 H), 8.20 (br s, exchangeable with D_2O), 8.5 (br s, exchangeable with D_2O); low-resolution CIMS (isobutane) m/e 245 (MH^+, 100).

(*E*)-1-(3,5-Dihydroxyphenyl)-2-(3,5-dihydroxyphenyl)ethene (9k): yield 58%, mp >300 °C dec (lit.[40] mp 320–323 °C); ^{1}H NMR (acetone-d_6, 500 MHz) δ 6.28 (t, J = 2.0 Hz, 2 H), 6.53 (d, J = 2.0 Hz, 4 H), 6.92 (s, olefin, 2 H), 8.20 (br s, exchangeable with D_2O); low-resolution CIMS (isobutane) m/e 245 (MH^+, 100); high-resolution CIMS (isobutane) m/e 245.0813 (MH^+) ($C_{14}H_{12}O_4$ requires 245.0814). Anal. ($C_{14}H_{12}O_4$) C, H.

General Procedure for the Preparation of Dihydrostilbenes 10j,k. A mixture of (*E*)- and (*Z*)-stilbenes 8j,k (0.606 g, 1 mmol) in ethanol (120 mL) was hydrogenated at 40 psi in the presence of 10% palladium on charcoal (60 mg) for 18–24 h. The catalyst was removed by filtration through a Celite pad, and the solvent was evaporated from the filtrate to afford dihydrostilbene derivatives.

(*E*)-1-(3,4-Dihydroxyphenyl)-2-(3,5-dihydroxyphenyl)ethane (10j): yield 0.160 g (65%); ^{1}H NMR (acetone-d_6, 500 MHz) δ 2.69 (m, 4 H), 6.17 (t, J = 2.1 Hz, 2 H), 6.20 (d, J = 2.1 Hz, 2 H), 6.80 (dd, J = 8.1, 2.0 Hz, 1 H), 6.69 (d, J = 2.0 Hz, 1 H), 6.90 (d, J = 8.1 Hz, 1 H), 7.64 (br s, exchangeable with D_2O), 7.68 (br s, exchangeable with D_2O), 8.05 (br s, exchangeable with D_2O); low-resolution CIMS (isobutane) m/e 247 (MH^+, 100).

(*E*)-1-(3,5-Dihydroxyphenyl)-2-(3,5-dihydroxyphenyl)ethane (10k): yield 0.200 g (82%); ^{1}H NMR (acetone-d_6, 500 MHz) δ 2.70 (s, 4 H), 6.19 (t, J = 2.0 Hz, 2 H), 6.23 (d, J = 2.0 Hz, 4 H), 8.09 (br s, exchangeable with D_2O); low-resolution CIMS (isobutane) m/e 247 (MH^+, 100).

Enzyme Inhibition Studies. The assays were performed as previously described.[49] In vitro assays of protein–tyrosine kinase activity were carried out using angiotensin I (1.2 mM) and [γ-^{32}P]ATP (50 μM) as described previously for the routine assay of the p40 protein–tyrosine kinase[50] except that reactions contained 8% DMSO, which was used as a carrier for the inhibitors. Control reactions run in the absence of inhibitor also contained 8% DMSO. Angiotensin I was prepared by the Purdue Peptide Synthesis Facility. p56^{lck} was partially purified from bovine thymus by sequential chromatography on columns of DEAE-cellulose, heparin–agarose, and butyl–agarose.[51] Analogs were screened for inhibition of p56^{lck} at seven concentrations

ranging from 0.8 to 800 μg/mL. IC_{50} values were determined graphically and represented the concentration of inhibitor that gives half-maximal inhibition as compared to control assays carried out in the absense of inhibitor, but in the presence of DMSO carrier.

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