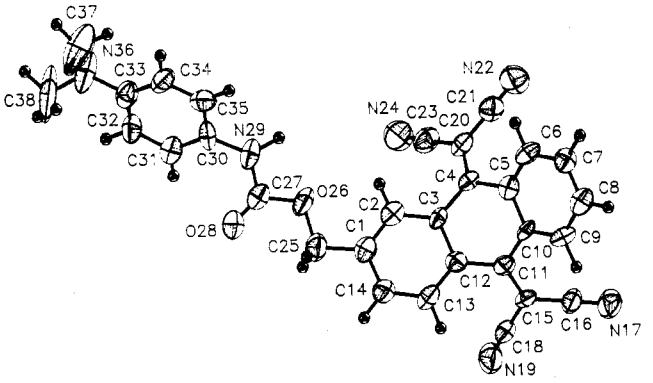

Figure 1. ORTEP plot of **4**.

pale yellow solid that separated was collected by filtration. This product, which appeared to be light-sensitive, was purified by silica gel chromatography (EtOAc/hexane, 5:95) to afford a pale yellow solid (**8**), 1.92 g (96%). This could be recrystallized from EtOAc–hexane: mp 119–120 °C; IR (KBr) 3040, 1655, 1115, 1090, 825 cm^{-1}. Anal. Calcd for $C_{31}H_{28}O_3Si$:C, 78.09; H, 5.92. Found: C, 78.14; H, 5.91.

2-(Hydroxymethyl)-11,11,12,12-tetracyanoanthraquinodimethane (2). Two solutions were prepared in a glovebox under an atmosphere of N_2. The first was made by the addition of 4.13 g (22 mmol) of $TiCl_4$ to a solution of 1.0 g (4 mmol) of **7** in 40 mL of dry $CHCl_3$. The second solution consisted of 8.01 g (121 mmol) of malononitrile, 2.19 g (24.6 mmol) of β-alanine, 3.75 mL of pyridine, and 50 mL of dry $CHCl_3$. The second solution was added to the first in three portions, and the resultant dark mixture was then heated to the reflux temperature for 4 h under N_2. It was stored at room temperature for 16 h before being poured into ice–water. The aqueous phase was extracted with $CHCl_3$ and then with EtOAc. The organic layers were combined, dried (anhydrous $MgSO_4$), and distilled under reduced pressure to yield 9.0 g of an oily product, which contained malononitrile. Silica gel column chromatography (acetone/hexane, 20:80) separated the product, **2**, which was recrystallized from EtOAc–hexane: 0.585 g (42%); mp 256–257 °C; IR (KBr) 3510, 2220, 1560, 1045, 830, 770 cm^{-1}. Anal. Calcd for $C_{21}H_{10}N_4O$: C, 75.44; H, 3.01; N, 16.76. Found: C, 75.12; H, 2.99; N, 16.51. A cyclic voltammogram was done at a Pt disk electrode on a 7.3 mM solution of **2** in CH_3CN that was 0.1 M in tetrabutylammonium hexafluorophosphate. The reduction peak potential was −0.372 V vs. SCE at 298 K. $E_{1/2}$ estimated from the average peak potentials was −0.333 V.

In some runs, especially those where β-alanine was omitted, a faster moving material was obtained by column chromatography which was also recrystallized from EtOAc–hexane: mp 204–206 °C; IR (KBr) 3300, 2220, 1675, 1060, 775, 700 cm^{-1}. Anal. Calcd for $(C_{18}H_{10}N_2O_2)_4H_2O$: C, 74.35; H, 3.64; N, 9.63. Found: C, 74.24; H, 3.95; N, 9.29. This was assumed to be a dicyano derivative, such as **10**.

The *p*-(*N*,*N*-Dimethylamino)phenylcarbamate of 2-(Hydroxymethyl)-11,11,12,12-tetracyanoanthraquinodimethane (4). To a solution of 117 mg (0.34 mmol) of **2** and 56 mg (0.35 mmol) of *p*-(*N*,*N*-dimethylamino)phenyl isocyanate[8] in 15 mL of dry CH_3CN was added 25 μL of dibutyltin dilaurate, and the resultant mixture was stirred at room temperature for 2.5 h and at 45 °C for 17.5 h, all under an N_2 atmosphere. The solvent was removed by distillation in vacuo, and the brown-black residue was purified by silica gel column chromatography (EtOAc/hexane, 60:40) and then by recrystallization from EtOAc to afford almost black crystals (**4**): 89 mg (51%); mp 243–245 °C; IR (KBr) 3430, 2240, 1725, 1215, 1065, 820, 770 cm^{-1}. Anal. Calcd for $C_{30}H_{20}N_6O_2$: C, 72.57; H, 4.06; N, 16.93. Found: C, 72.28; H, 3.91; N, 16.72.

The 1-Pyrenylcarbamate of 2-(Hydroxymethyl)-11,11,12,12-tetracyanoanthraquinodimethane (3). Dibutyltin dilaurate (50 μL) was added to a mixture of 105 mg (0.31 mmol) of **2**, 78 mg (0.32 mmol) of 1-pyrenyl isocyanate,[8] and 10 mL of dry THF, and the result was stirred at room temperature for 15 h under an atmosphere of N_2. After removal of the solvent by distillation in vacuo, the brown oily residue was chromatographed on a silica gel column (EtOAc/hexane, 35:65), and the purified fraction was recrystallized from EtOAc/hexane, yielding dark crystals of **3**: 69 mg (28%); mp 251.5–253.0 °C; IR (KBr) 3380, 2220, 1730, 1210, 1075, 835, 780 cm^{-1}. Anal. Calcd for $C_{38}H_{19}N_5O_2$: C, 79.02; H, 3.32; N, 12.12. Found: C, 79.02; H, 3.20; N, 11.87.

(8) Prepared from the carboxylic acid via the acid chloride and the acid azide.

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Synthesis of Erbstatin, a Naturally Occurring Inhibitor of Tyrosine-Specific Protein Kinase

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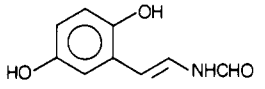
Retroviral oncogenes encode a group of proteins known as transforming growth factors (TGFs) that induce a reversible malignant transformation of cells.[1] One type of TGF binds to the epidermal growth factor (EGF) receptor and activates the receptor-associated tyrosine-specific protein kinase. This leads to phosphorylation of the EGF receptor and induction of anchorage-independent cell growth. The human oncogene *erb*-B encodes an abnormal EGF receptor that cannot bind EGF but that continuously activates the protein kinase. Thus, normal growth control is lost in a cell with an aberrant EGF receptor or a cell that produces TGF and a receptor for the TGF. One possible way to control this growth is to regulate the activity of the protein kinase.

In this paper we report the synthesis of erbstatin (**1**). Erbstatin (**1**) inhibits tyrosine-specific protein kinase and inhibits the phosphorylation of the epidermal growth factor receptor.[2] Erbstatin has also been shown to inhibit the



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growth of human epidermoid carcinoma (A-431 cells) and IMC-carcinoma cells in tissue culture.[2] The compound is an antibiotic produced by a strain of *Streptomyces* (MH435-hF3) related to *Streptomyces viridosporus* and was isolated as part of a screening program for inhibitors of tyrosine-specific protein kinase derived from the membrane fraction of human epidermoid carcinoma cell line A-431.[2,3]

The synthesis (Scheme I) begins with the treatment of the readily available 2,5-dimethoxybenzaldehyde with nitromethane in methanol–sodium hydroxide (0 → 20 °C) followed by dehydration (60 °C) in a modification of a

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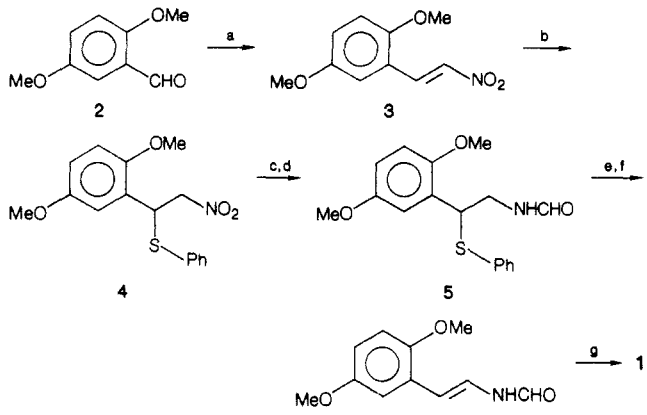
Scheme I[a]



[a] (a) CH_3NO_2, $NaOH/H_2O$, CH_3OH; (b) PhSH, DMAP, THF, reflux; (c) LAH, ether/THF (2:1), reflux; (d) HCO_2COCH_3 (AFA), THF, −15 °C; (e) $NaIO_4$, methanol; (f) toluene, reflux; (g) BBr_3, CH_2Cl_2, −78 °C to room temperature.

literature procedure[4] to give reproducible recrystallized yields (81–85%, absolute ethanol) of yellow needles of the dimethoxy-β-nitrostyrene **3**.

Conjugate addition of thiophenol[5] to **3** (DMAP, THF, reflux) gave the thioether **4** in quantitative yield. Conversion of **4** to **5** was accomplished by lithium aluminum hydride ($LiAlH_4$) reduction[6] of the nitro group in an ether/THF solvent mixture under reflux conditions, the resulting primary amine (76%) was N-formylated with acetic formic anhydride (AFA)[7] in THF at −15 °C to give crystalline (ethyl acetate–hexane) **5** in 91% yield. Compound **5** was readily converted to the enamide **6** by a sulfenylation/dehydrosulfenylation elimination process.[5,8] Thus, sodium metaperiodate oxidation[9] of **5** to the sulfoxide followed by thermolysis (in refluxing toluene for 6 h, in the presence of sodium carbonate) gave the enamide **6** in 94% yield.

Cleavage of the methyl ethers was effected by treatment of **6** with boron tribromide[10] (3 equiv) in anhydrous dichloromethane under a nitrogen atmosphere (−78 °C for 1 h, −78 → 24 °C over 1 h, then 24 °C for 2.5 h). The reaction mixture was quenched by the slow (10 min) dropwise addition of water (at −10 °C, then warmed to 24 °C over 10 min) and extracted with ethyl acetate.[11] The extract was concentrated to dryness at *ambient temperature* in vacuo under a nitrogen purge and the residue was crystallized from methanol–chloroform to give crystalline erbstatin as the 1:1 methanol solvate (79% yield.[12] The solvate was heated at 78 °C for 2 h in vacuo to remove the methanol.

The IR, UV, ^1H NMR, and ^{13}C NMR data obtained for synthetic erbstatin were identical with those reported for the natural product[2,3] with one exception. The signal for H7 in the published report[3] was erroneously given[14] as 6.64 whereas we found the signal at 6.47.[15] Irradiation of the H8 signal (7.65) caused the doublet at 6.47 to collapse to a singlet.

In conclusion, this synthesis can be carried out in large scale and is suited for the production of quantities of this important new "lead" compound for further in vitro and in vivo studies. The overall yield of erbstatin was 44%. Further, the flexible approach can be used to synthesize congeners of erbstatin for structure–activity relationship studies.

Experimental Section

Melting points were obtained on a Thomas-Hoover Unimelt apparatus and are uncorrected. ^1H nuclear magnetic resonance spectra were recorded on a Varian Model EM390 or a Brucker 360-MHz spectrometer for acetone-d_6 solutions (unless otherwise noted), using Me_4Si as internal reference. ^{13}C NMR spectra were determined for acetone-d_6 solutions containing Me_4Si as internal standard on a Brucker 360-MHz NMR. Infrared spectra were obtained for KBr pellets with a Nicolet 7000 series FT-IR. Ultraviolet spectra were obtained with a Cary Model 118 spectrophotometer. Elemental analyses were performed by Atlantic Microlabs, Inc., Atlanta, GA. Analtech GF silica gel plates (250 μm) were used for TLC analysis. Baker Analyzed silica gel (60–200 mesh) from J. T. Baker Chemical Co. was used for column chromatography. Reagents and starting materials were purchased from Aldrich Chemical Co.

(*E*)-1-(2,5-Dimethoxyphenyl)-2-nitroethene (3). A mixture of 2,5-dimethoxybenzaldehyde (**2**) (1.97 g, 11.8 mmol) and nitromethane (0.72 g, 11.8 mmol) in methanol (200 mL) was stirred at room temperature until the solids dissolved. The solution was cooled to 0 °C and a 10.5 M NaOH solution (2 mL) was added dropwise over 20 min. The alkaline solution was added slowly to a 40% HCl solution (200 mL) maintained at 60 °C. The pale yellow amorphous solid that formed was filtered and washed with water (200 mL). The crude product was recrystallized from absolute ethanol to give yellow needles (2.11 g, 85%): mp 121–123 °C; IR 3100, 1620, 1500, 1351 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.9 (dd, J = 14 Hz, 2 H), 6.88 (d, J = 3 Hz, 3 H), 3.85 (s, 3 H), and 3.75 (s, 3 H). Anal. Calcd for $C_{10}H_{11}NO_4$: C, 57.41; H, 5.30; N, 6.69. Found: C, 57.49; H, 5.32; N, 6.68.

1-(2,5-Dimethoxyphenyl)-1-(phenylthio)-2-nitroethane (4). A mixture of **3** (0.5 g, 2.39 mmol) and thiophenol (0.52 g, 4.7 mmol) and a catalytic amount (ca. 10 crystals) of 4-(dimethylamino)-pyridine (DMAP) in dry THF (30 mL) was heated at reflux for 6 h. The solvent was removed in vacuo and the residue was dissolved in ether. The ether extract was washed successively with dilute NaOH solution (100 mL) (to remove unreacted thiophenol) and dilute HCl solution (100 mL) (to remove DMAP). The ethereal layer was dried (Na_2SO_4) and concentrated in vacuo to give an oil (0.765 g, 100%) that was homogeneous on TLC (methanol–chloroform): ^1H NMR ($CDCl_3$) δ 7.30 (m, 5 H), 6.70 (m, 3 H), 5.22 (t, J = 6 Hz, 1 H), 4.75 (dd, J = 3 Hz, 2 H), 3.62 (s, 3 H), 3.70 (s, 3 H).

1-(2,5-Dimethoxyphenyl)-1-(phenylthio)-2-aminoethane. A solution of **4** (7.11 g, 22.2 mmol) in a mixed solution of anhydrous ether and THF (2:1) was added dropwise to a vigorously

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(11) Excessive decomposition of erbstatin resulted on attempted chromatography of the product using either silica gel or alumina.
(12) The methanol solvate was reported (ref 2 and 3) to have mp 78–82 °C; the product we obtained softened at ca. 80 °C (open capillary) but did not melt until 150 °C.
(13) NMR spectra of erbstatin show it to exist as a mixture of syn and anti isomers. The minor isomer had the following: ^1H NMR δ 9.10 (br, NH; exchangeable with D_2O) 8.48 [d, J = 11 Hz, CHO (became a singlet after D_2O treatment)], 7.42 [dd, J = 11 Hz, J = 15 Hz, H8 (became a d, J = 15 Hz, after D_2O treatment)], 6.80 (d, J = 3 Hz, H6), 6.69 (d, J = 9 Hz, H3), 6.51 (partially obscured multiplet, H4), 6.36 (d, J = 15 Hz, H7); ^{13}C NMR 126.2, 117.1, 114.6, 108.6.
(14) Dr. M. Imoto kindly supplied us with an NMR spectrum of natural erbstatin, the signal for H7 was at 6.46 not 6.64 as reported.[3]
(15) ^1H NMR and ^{13}C NMR data for the erbstatin methanol solvate and the dried methanol-free sample were identical.

stirring suspension of lithium aluminum hydride (LAH) in anhydrous ether–THF (2:1) solvent mixture (150 mL). The reaction mixture was heated at reflux for 24 h and then cooled to 0 °C. Ether (100 mL) was added and the excess LAH was quenched by the cautious successive addition of water (4 mL), 15% NaOH solution (4 mL), and water (12 mL). The aluminum salts were filtered and the organic layer was concentrated in vacuo to give an oil. The oil was dissolved in ether (150 mL) and extracted with 10% HCl solution. The aqueous acidic layer was basified to pH 9 and extracted with ether. The dried (Na_2SO_4) ethereal layer was concentrated to dryness in vacuo to give an oil (4.9 g, 76%) that was homogeneous on TLC (MeOH–EtOAc): ^1H NMR ($CDCl_3$) δ 7.25 (m, 5 H), 6.80 (m, 3 H), 4.65 (t, J = 6 Hz, 1 H), 3.65 (s, 3 H), 3.70 (s, 3 H), 3.2 (d, J = 6 Hz, 2 H), 1.60 (br, 2 H; exchangeable with D_2O).

***N*-[2-(Phenylthio)-2-(2,5-dimethoxyphenyl)ethyl]formamide (5).** A solution of 1-(2,5-dimethoxyphenyl)-1-(phenylthio)-2-aminoethane (0.218 g, 0.75 mmol) in THF (10 mL) was added dropwise to a solution of acetic formic anhydride (prepared by a literature procedure) at −15 °C. The reaction mixture was allowed to warm to room temperature and the volatiles were removed in vacuo. The residue was dissolved in ether and washed successively with water (50 mL), saturated $NaHCO_3$ solution and dried over anhydrous K_2CO_3. The ether was removed in vacuo to yield an oil that was triturated with an ethyl acetate–hexane mixture to give a crystalline colorless solid (0.21 g, 91%): mp 84–86 °C; IR 3244, 1648, 1500 cm^{-1}; ^1H NMR δ 8.0 (s, 1 H), 7.25 (m, 5 H), 7.03 (br, 1 H; exchangeable with D_2O), 6.80 (m, 3 H), 4.85 (t, J = 7.5 Hz, 1 H), 3.80 (br, 2 H) 3.75 (s, 3 H), and 3.70 (s, 3 H). Anal. Calcd for $C_{17}H_{19}NO_3S$: C, 64.33; H, 6.03; N, 4.41; S, 10.10. Found: C, 64.43; H, 6.08; N, 4.40; S, 10.00.

***N*-[2-(Phenylsulfinyl)-2-(2,5-dimethoxyphenyl)ethyl]formamide.** A solution of sodium metaperiodate (0.14 g, 0.66 mmol) in a minimal amount of water was added dropwise to a solution of **5** (0.21 g, 0.66 mmol) in 10 mL of methanol cooled to 0 °C. The reaction was then stirred at room temperature for 24 h. The solids were filtered and the precipitate washed several times with ethyl acetate (100 mL). The combined filtrate and washings were concentrated in vacuo to give an oil (0.23 g, 100%). The sulfoxide was used in the next step without further purification.

(*E*)-*N*-[2-(2,5-Dimethoxyphenyl)ethenyl]formamide (6). Sodium carbonate (1.59 g, 15.07 mmol) was added to a solution of *N*-[2-(phenylsulfinyl)-2-(2,5-dimethoxyphenyl)ethyl]formamide (5.025 g, 15.07 mmol) in toluene (100 mL). The reaction mixture was heated at reflux for 6 h and then cooled and filtered. The filtrate was concentrated in vacuo and the residue was subjected to column chromatography over silica gel. Elution with chloroform yielded a solid that was recrystallized from ethyl acetate to give colorless crystals (2.9 g, 94%): mp 87–88 °C; IR 3279, 1669, 1521 cm^{-1}; NMR δ 9.20 (br, 1 H; exchangeable with D_2O), 8.15 (s, 1 H), 7.60 (dd, J = 12 Hz, J = 15 Hz, 1 H), 6.95 (d, J = 3 Hz, 1 H), 6.75 (dd, J = 9 Hz, J = 3 Hz, 2 H), 6.47 (d, J = 15 Hz, 1 H), 3.75 (s, 3 H), 3.70 (s, 3 H). Anal. Calcd for $C_{11}H_{13}NO_3$: C, 63.76; H, 6.32; N, 6.76. Found: C, 63.82; H, 6.33; N, 6.69.

(*E*)-*N*-[2-(2,5-Dihydroxyphenyl)ethenyl]formamide (1) (Erbstatin). A stirred, cold (−78 °C) solution of **6** (100 mg, 0.483 mmol) in anhydrous methylene chloride (5 mL) under nitrogen was treated, over a period of 7 min, with a 1.0 M solution of boron tribromide in methylene chloride [1.45 mL (1.45 mmol, 3 equiv)]. The resulting white mixture was stirred at −78 °C for 1 h under nitrogen and then allowed to warm to ambient temperature over a 1-h period. The reaction was stirred for 1.5 h at ambient temperature and the nitrogen atmosphere removed. The reaction mixture was cooled to −10 °C (2-propanol–ice bath) and quenched by the dropwise addition of water (5 mL) over a 10-min period. The cooling bath was removed and the mixture was stirred for 10 min (while warming to ambient temperature) and diluted with ethyl acetate (120 mL). This mixture was stirred for 20 min. The organic layer was washed with water (10 mL), dried (Na_2SO_4), and filtered, and the filtrate was reduced in vacuo (without heating) to dryness, venting with nitrogen. The residue was dissolved in 10% methanol in chloroform (20 mL) and reduced in vacuo (without heating), venting with nitrogen. The oil was dissolved in 10% methanol in chloroform (4 mL) and this solution was diluted with chloroform to faint turbidity (3 mL); the mixture was cooled (4 °C) for 6 h to give 80.2 mg (79% yield) of a white crystalline solid: mp (after drying at −78 °C in vacuo, 2 h) 149–151 °C; TLC (10% methanol in methylene chloride, 250 μm thick, Analtech GF silica gel plates) R_f 0.18 (R_f dimethylerbstatin is 0.62); UV (methanol) 278 (λ_{max}), 286 (shoulder), 331 nm; IR (after drying at 78 °C in vacuo, 2 h) 3352 (br), 1639, 1505, 1393, 1259, 1195, 949, and 780 cm^{-1}; ^1H NMR (360 MHz) δ 9.30–9.02 (br s, 1 H, N*H*; exchanges with D_2O), 8.19 (s, 1 H, CHO), 7.99–7.55 (s br, 2 H, OH; exchanges with D_2O), 7.65 [dd, J = 11 Hz, J = 15 Hz, 1 H, H-8, collapses to d (J = 15 Hz) with D_2O], 6.83 (d, J = 3 Hz, H-6), 6.71 (d, J = 9 Hz, H-3), 6.53 (dd, J = 9 Hz, J = 3 Hz, H-4), 6.47 (d, J = 15 Hz, H-7); ^{13}C NMR δ 159.3, 151.3, 148.2, 124.7, 122.5, 117.2, 115.1, 113.3, and 110.4.

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A Novel Synthesis of 3-Alkyl-Substituted Isoprenylsilanes

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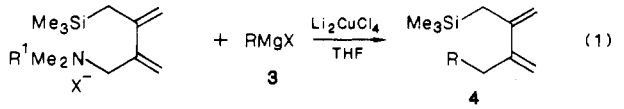
We have previously reported that 2-[(trimethylsilyl)methyl]-1,3-butadiene (isoprenylsilane) and related compounds are important reagents not only for the nucleophilic isoprenylation as allylsilanes but also for the building blocks of terpene synthesis as regioselective Diels–Alder dienes.[1] Moreover, we have recently found that 2-[(dimethylamino)methyl]-3-[(trimethylsilyl)methyl]-1,3-butadiene (**1**) is a synthon of the 2,2′-biallyl diradical.[2] In an extension of the studies on the application of **1** to organic synthesis, we now report a novel method for preparing 3-alkyl-substituted isoprenylsilanes **4** by the cross-coupling reaction between the ammonium salt **2** of **1** and the Grignard reagent **3** in the presence of dilithium tetrachlorocuprate as a catalyst (eq 1). The results are summarized in Table I.



2a: R^1 = Me, X = I
b: R^1 = *n*-Bu, X = I
c: R^1 = $PhCH_2$, X = Cl

For the purpose of coupling reactions between **2** and *n*-butylmagnesium bromide (**3a**), a copper salt,[3] in par-

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