A Simple Synthesis of Erbstatin and Its *cis*-Isomer

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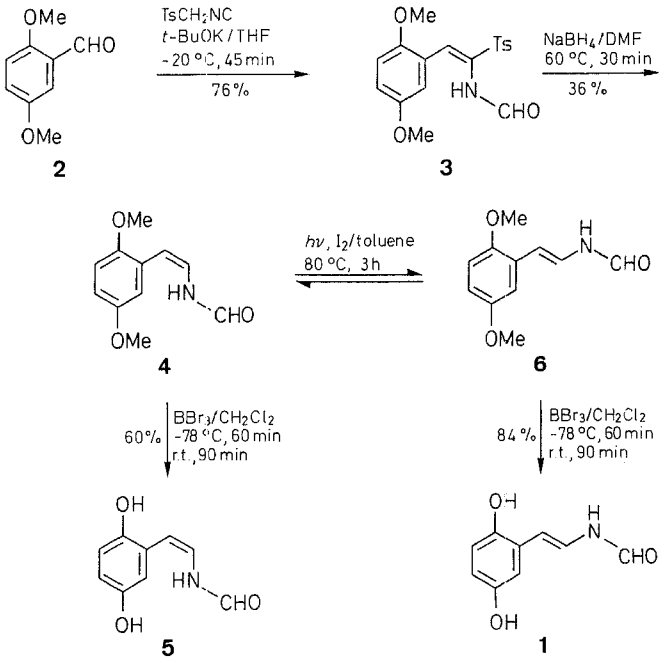
Reaction of 2,5-dimethoxybenzaldehyde with tosylmethyl isocyanide in tetrahydrofuran in the presence of potassium *tert*-butoxide affords *N*-[2-(2,5-dimethoxyphenyl)-1-tosylethenyl]formamide with assumed *E*-stereochemistry. Reductive detosylation of this compound with sodium borohydride in dimethylformamide and *O*-demethylation of the resultant (*Z*)-*N*-[2-(2,5-dimethoxyphenyl)ethenyl]formamide with boron tribromide in dichloromethane yields *cis*-erbstatin whereas equilibration of (*Z*)-*N*-[2-(2,5-dimethoxyphenyl)ethenyl]formamide by irradiation in toluene in the presence of iodine, isolation of the *E*-isomer from the *Z*/*E* mixture thus formed, and *O*-demethylation with boron tribromide in dichloromethane yields (*trans*-)erbstatin.

Erbstatin (**1**) has recently attracted interest as an inhibitor of tyrosine-specific protein kinase that appears to be involved in the process of uncontrolled cell proliferation. Since its isolation from a strain of *Streptomyces*[1] and its structural elucidation,[2] three routes have been reported for the synthesis of erbstatin.[3–5] We here describe a new, short synthesis by which erbstatin, starting from 2,5-dimethoxybenzaldehyde (**2**), is prepared in four steps. This procedure also allows the preparation of *cis*-erbstatin (**5**) which has not been isolated before in isomerically pure form.[4] The yields given in the Scheme have not been optimized. Reaction of 2,5-dimethoxybenzaldehyde (**2**) with tosylmethyl isocyanide in the presence of excess potassium *tert*-butoxide gave the substituted *N*-styrylformamide **3**. Although the stereochemistry of **3** could not be established unambiguously, we assume *E*-stereochemistry for reasons analogous to those used for the assignment of stereochemistry for the corresponding 3,4-dimethoxy isomer.[6,7]

Reductive detosylation of **3** with sodium borohydride in dimethylformamide at 60 °C[6] occurred in a remarkably stereoselective fashion but with only moderate yield due to the formation of reduction by-products. The crude reaction product, obtained after the usual aqueous work-up, contains *cis*-enamide **4** and *trans*-enamide **6** in a ratio of 94:6 according to the ratio of the vinyl proton signals in the ^{1}H-NMR spectrum. After chromatographic separation, compound **4** was obtained as the pure *cis*-isomer. Besides some starting material **3**, only small amounts of *N*-[2-(2,5-dimethoxyphenyl)ethyl]formamide resulting from reduction of the double bond of **4** were isolated as one of the reduction by-products. The ^{1}H-NMR spectrum of **4** revealed a 2:1 ratio of conformational isomers due to restricted rotation around the amide bond. *O*-Demethylation was achieved by treatment with boron tribromide in dichloromethane under conditions described previously[3] to afford pure *cis*-erbstatin (**5**). Irradiation of a toluene solution of *cis*-enamide **4** with a 500-W daylight lamp at 80 °C for 15 h in the presence of catalytic traces of iodine led to an equilibrium mixture consisting of *cis*-enamide **4** and *trans*-enamide **6**. Chromatography on silica gel with toluene/ethyl acetate gave *trans*-enamide **6** (39%) along with *cis*-enamide **4** (57%). In solution, *trans-enamide* **6** slowly isomerizes to the *cis*-isomer **4** as evidenced by TLC. Cleavage of the methoxy groups of *trans*-enamide **6** with boron tribromide[3] and crystallization from methanol/chloroform/hexane afforded erbstatin (**1**) as methanol solvate in 84% yield (mp 147–149 °C).



As in the case of *trans*-enamide **6**, erbstatin (**1**) slowly isomerizes in solution. On recrystallization, however, due to its higher solubility the *cis*-isomer **5** remains in the mother liquor.

Table. Compounds **3**, **4**, **6**, *cis*-Erbstatin (**5**), and Erbstatin (**1**) Prepared

Product	Yield (%)	mp (°C)[a] (solvent)	Molecular Formula[b] or Lit. mp (°C)	MS (70 eV)[c] *m/z* (%)	IR (KBr)[d] ν (cm^{-1})	^{1}H-NMR (solvent/TMS)[e] δ, *J* (Hz)
3	76	142–145 (EtOAc)	$C_{18}H_{19}NO_5S$ (361.4)	361 (M^+, 21), 177 (94), 162 (100), 151 (67), 91 (67), 65 (58)	3700–2800, 1690, 1500, 1320, 1300, 1225, 1150	DMSO-d_6: 2.4[f] (s, 3H, OCH_3); 3.65[f] (s, 3H, OCH_3); 3.83 (s, 3H, OCH_3); 6.9–8.0 (m, 9H, $6H_{arom}$, CH=, CHO); 10.05 (s, NH)[g]; 9.78 (br s, NH)[h] (1H)
4	36	70–72 (hexane)	$C_{11}H_{13}NO_3$ (207.2)	207 (M^+, 100), 164 (14), 137 (34), 136 (20), 40 (14)	3225, 1650, 1510, 1475, 1255, 1220, 1195	$CDCl_3$: A[g]: 3.78 (s, 3H, OCH_3); 3.84 (s, 3H, OCH_3); 5.73 (d, 1H, *J* = 9.8, H-7); 6.7–7.05 (m, 4H, $3H_{arom}$, H-8); 8.18 (s, 1H, CHO); 8.0–8.4 (br, 1H, NH) B[h]: 3.78 (s, 3H, OCH_3); 3.84 (s, 3H, OCH_3); 5.60 (d, 1H, *J* = 9.7, H-7); 6.47 (dd, 1H, *J* = 9.7, 11.3, H-8); 6.7–7.05 (m, $3H_{arom}$); 8.18 (s, 1H, CHO); 8.35 (d, 1H, *J* = 11.3, NH)
6[3]	39	82–84 (*i*-Pr_2O)	87–88[3]	207 (M^+, 100), 164 (25), 137 (55), 136 (44), 109 (28), 57 (41), 43 (55)	3280, 1700, 1670, 1650, 1525, 1500, 1220, 1040	DMSO-d_6: A[g]: 3.7 (s, 3H, OCH_3); 3.75 (s, 3H, OCH_3); 6.4 (d, 1H, *J* = 14.8, H-7); 6.65–7.0 (m, $3H_{arom}$); 7.48 (dd, 1H, *J* = 10.6, 14.8, H-8); 8.10 (s, 1H, CHO); 10.23 (br d, 1H, *J* = 10.6, NH) B[h]: 3.7 (s, 3H, OCH_3); 3.75 (s, 3H, OCH_3); 6.23 (d, 1H, *J* = 14.4, H-7); 6.65–7.0 (m, $3H_{arom}$); 7.41 (dd, 1H, *J* = 10.7, 14.4, H-8); 8.4 (d, 1H, *J* = 10.8, CHO); 10.13 (br ps-t, 1H, $J_1 \approx J_2 \approx 11$, NH)
5 (*cis*-erbstatin)[4]	60	>150 (dec) (*i*-Pr_2O/EtOAc)	$C_9H_9NO_3 \cdot 0.25H_2O$ (183.7)	179 (M^+, 19), 134 (100), 124 (26), 123 (31), 55 (52), 39 (59)	3700–2500, 1635, 1495, 1435, 1375, 1200	acetone-d_6: A[g]: 5.70 (d, 1H, *J* = 10, H-7); 6.5–7.0 (m, 4H, $3H_{arom}$, H-8); 7.75 (s, 1H, OH); 8.15 (s, 1H, OH); 8.24 (s, 1H, CHO); 9.0–9.4 (br, 1H, NH) B[h]: 5.49 (d, 1H, *J* = 10, H-7); 6.5–7.0 (m, 4H, $3H_{arom}$, H-8); 8.41 (d, 1H, *J* = 11, CHO)
1 (erbstatin)[2–5]	84	147–149 ($CHCl_3$/MeOH/hexane)	149–151[3] 150.5–152[4] 146–148[5]	179 (M^+, 25), 134 (100), 124 (16), 123 (19), 44 (42), 39 (59)	3700–2500, 1675, 1650, 1460, 1210, 945	acetone-d_6: A[g]: 6.45 (d, 1H, *J* = 14.8, H-7); 6.52 (dd, *J* = 8.6, 2.9, H-4); 6.69 (d, 1H, *J* = 8.6, H-3); 6.81 (d, 1H, *J* = 2.9, H-6); 7.63 (dd, 1H, *J* = 14.8, 10.8, H-8); 7.7 (br s, 1H, OH); 8.0 (br s, 1H, OH); 8.18 (s, 1H, CHO); 9.25 (br, 1H, NH) B[h]: 6.34 (d, 1H, *J* = 14.4, H-7); 6.51 (dd, partially obscured, H-4); 6.68 (d, 1H, *J* = 8.6, H-3); 6.79 (d, 1H, *J* = 2.9, H-6); 7.41 (dd, 1H, *J* = 14.4, 10.9, H-8); 7.68 (br s, 1H, OH); 7.96 (br s, 1H, OH); 8.46 (d, 1H, *J* = 11, CHO); 9.05 (br, 1H, NH)

[a] Uncorrected, measured with a Reichert hot stage microscope.
[b] Satisfactory microanalyses obtained: C, H, N, S ±0.3.
[c] Recorded on a Finnigan 4500 mass spectrometer.
[d] Recorded on a Perkin-Elmer 599B.
[e] Obtained on a Bruker AM 300.
[f] Two singlets due to the presence of rotamers.
[g] Major rotamer.
[h] Minor rotamer.

(*E*)-*N*-[2-(2,5-Dimethoxyphenyl)-1-(4-methylphenylsulfonyl)ethenyl]-formamide (3):

A solution of tosylmethyl isocyanide (10.0 g, 51 mmol, Aldrich Chemical Co.) in dry THF (50 mL, N_2 atmosphere, all solutions degassed) is added with stirring to *t*-BuOK (30 g, 267 mmol) in THF (500 mL). The mixture is immediately cooled to −20 °C and after 5 min a solution of 2,5-dimethoxybenzaldehyde (8.2 g, 49 mmol) in THF (50 mL) is added dropwise and stirring is continued at −20 °C for 45 min. Acetic acid (20 mL) and then H_2O (50 mL) are added dropwise, and the mixture is allowed to warm to room temperature. The THF is evaporated and the residue is partitioned between CH_2Cl_2 (200 mL) and H_2O (200 mL). The organic layer is dried (Na_2SO_4) and evaporated, and the residue is chromatographed on silica gel (CH_2Cl_2/MeOH, 99:1 as eluent). Recrystallization of the isolated fraction (R_f 0.3) from EtOAc (80 mL) gives product **3** (12.3 g) as yellow crystals. Concentration of the filtrate to 15 mL gives an additional crop of pure material (1.1 g); total yield: 13.4 g (76%).

According to ^{1}H-NMR (DMSO-d_6) spectrometry, compound **3** is obtained in solution as a 3:2 mixture of rotational isomers.

(*Z*)-*N*-[2-(2,5-Dimethoxyphenyl)ethenyl]formamide (4):

Compound **3** (4.0 g, 11.1 mmol) and $NaBH_4$ (1.9 g, 50.2 mmol) in dry DMF (100 mL) are heated to 60 °C for 30 min. Then, H_2O (15 mL) is added, and the mixture is evaporated at reduced pressure. After addition of H_2O (500 mL), the product is extracted with CH_2Cl_2 (4×200 mL). The organic layer is dried (Na_2SO_4) and evaporated and the oily residue is dissolved in Et_2O (250 mL) and this solution washed with H_2O (2×100 mL) for complete removal of DMF. The Et_2O solution is dried (Na_2SO_4) and evaporated. According to integration of the H-7 vinyl protons (see Table) of **4** and **6** in the ^{1}H-NMR spectrum (300 MHz, DMSO-d_6), the crude product contains *cis*-**4** and *trans*-**6** in a ratio of 96:4 along with by-products. The residue is chromatographed on silica gel (toluene/EtOAc, 3:1). The main fraction (~950 mg, R_f 0.3) is crystallized from hexane to give product **4** as pale yellow crystals (see Table); yield: 825 mg (36%).

From the more polar fractions, the starting material **3** (R_f 0.2, toluene/EtOAc 3:1) [yield: 152 mg (4%)] and *trans*-enamide **6** (R_f 0.15, toluene/EtOAc 3:1) [yield: 70 mg (3%)] are obtained as semi-solids after evaporation at reduced pressure.

On elution with toluene/EtOAc (1:1) and crystallization from hexane, colorless crystals of *N-[2-(2,5-dimethoxyphenyl)ethenyl]formamide* are obtained; yield: 140 mg (6%); mp 60–61 °C.

$C_{11}H_{15}NO_3$ (209.2)	calc.	C 63.14	H 7.23	N 6.69
	found	63.04	7.29	6.59

MS (70 eV): *m/z* = 209 (M^+, 26); 164 (100); 121 (53).

IR (KBr): ν = 3290; 1650; 1220 cm^{-1}.

^{1}H-NMR (300 MHz, DMSO-d_6): δ = 2.67 (t, 2H, J = 7.3, CH_2); 3.26 (dt, 2H, $J \approx 7$, $J \approx 7$, CH_2); 3.68, 3.72 (2 s, 3H each, 2 OCH_3); 6.73 (s, 1H, H_{arom}); 6.74 (d, 1H, J = 8, H_{arom}); 6.87 (d, 1H, J = 8, H_{arom}); 7.97 (d, 1H, J = 1.3, CHO); 8.0 (br, 1H, NH).

***(Z)*-*N*-[2-(2,5-Dihydroxyphenyl)ethenyl]formamide (5, *cis*-Erbstatin):**
To a stirred, cold (−78 °C) solution of the *cis*-formamide **4** (1.0 g, 4.83 mmol) in dry CH_2Cl_2 (50 mL) under N_2 is added dropwise boron tribromide (1.4 mL, 14.8 mmol) in CH_2Cl_2 (10 mL). Stirring is continued at −78 °C for 60 min. After warming to ambient temperature, the mixture is stirred for 90 min, cooled again to −10 °C, and quenched by the dropwise addition of H_2O (50 mL). The cooling bath is removed and the mixture is extracted with EtOAc (600 mL). The organic layer is washed with H_2O (50 mL), dried (Na_2SO_4), and evaporated at reduced pressure without heating. The residue is crystallized from *i*-Pr_2O/EtOAc (9:1) to give *cis*-erbstatin **(5)** as a nearly colorless crystalline solid; yield: 517 mg (60%, see Table). Attempted chromatography of *cis*-erbstatin on silica gel led to excessive decomposition as described for erbstatin.[3] According to ^{1}H-NMR analysis (acetone-d_6), *cis*-erbstatin is obtained in solution as a 5:1 mixture of rotamers.

***(E)*-*N*-[2-(2,5-Dimethoxyphenyl)ethenyl]formamide (6):**
To a solution of the *cis*-formamide **4** (4.07 g, 19.6 mmol) in toluene (230 mL) is added a saturated solution (3 drops) of iodine in toluene. Irradiation of the solution with a 500 W day-light lamp for 3 h at 80 °C affords an equilibrium mixture of *cis*-**4** and *trans*-**6** (TLC, toluene/EtOAc, 3:1). (When the reaction time is prolonged up to 15 h, there is no obvious change in the ratio of the isomers according to TLC). The solution is evaporated at reduced pressure, and the residue is chromatographed on silica gel (toluene/EtOAc, 3:1). The first eluted product (R_f 0.3) is unchanged starting material **4**; yield: 2.33 g (57%).

The second fraction (R_f 0.15) is recrystallized from *i*-Pr_2O to give the *trans*-formamide **6** as colorless crystals; yield: 1.57 g (39%, see Table and Lit.[3]). According to ^{1}H-NMR (DMSO-d_6), the enamide **6** is obtained in solution as a 3:1 mixture of rotational isomers.

***(E)*-*N*-[2-(2,5-Dihydroxyphenyl)ethenyl]formamide (1, Erbstatin):**
As described previously,[3] a stirred, cold (−78 °C) solution of *trans*-formamide **6** (400 mg, 1.93 mmol) in dry CH_2Cl_2 (20 mL) under N_2 is treated dropwise with boron tribromide (0.55 mL, 5.8 mmol) in CH_2Cl_2 (5 mL). Stirring is continued at −78 °C for 60 min. After warming to ambient temperature, the mixture is stirred for 90 min, cooled again to −30 °C, and quenched by the dropwise addition of H_2O (20 mL). The cooling bath is removed and the mixture is diluted with EtOAc (100 mL). The organic layer is washed with H_2O (2 × 50 mL), dried (Na_2SO_4), and evaporated at reduced pressure without heating. The oily residue is dissolved in a small amount of MeOH/$CHCl_3$ (9:1), hexane is added dropwise to faint turbidity, and the mixture is stirred for 3 h at 0 °C to give colorless crystals of erbstatin **(1)** as MeOH solvate; yield: 342 mg (84%).

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