A Short Stereoselective Synthesis of Erbstatin

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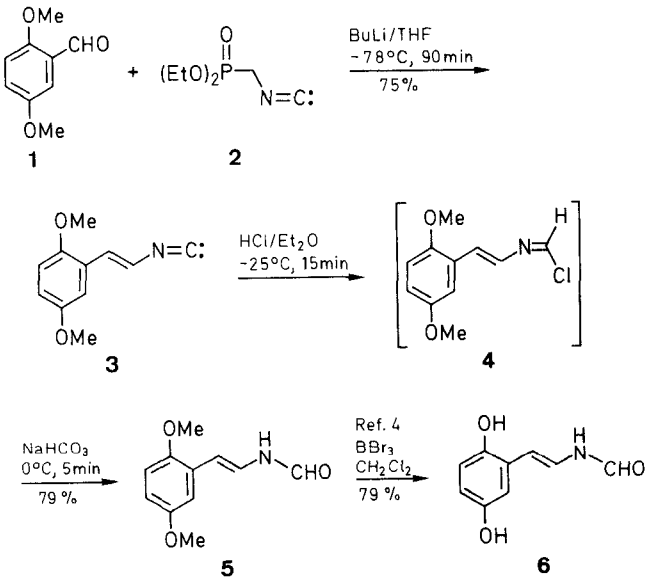
Reaction of diethyl (isocyanomethyl)phosphonate (**2**) with 2,5-dimethoxybenzaldehyde (**1**) in tetrahydrofuran in the presence of butyllithium affords 2-(2,5-dimethoxyphenyl)ethenyl isocyanide (**3**) with *E*-stereochemistry. Addition of hydrochloric acid at the isocyano carbon and hydrolysis of this adduct **4** yields (*E*)-*O,O*-dimethylerbstatin (**5**).

Erbstatin (**6**) is an antibiotically active fermentation product, which acts as an inhibitor of a membrane associated tyrosine-specific protein kinase. It has been shown to inhibit the growth of human epidermoid carcinoma cells (A-431) in tissue cultures.[1] Such inhibitors have the potential of providing leads to new classes of therapeutic agents for treatment of cancer. After the isolation from a strain of *Streptomyces*,[2] structure and biological activity of erbstatin have been reported,[1] and four syntheses of this natural product have been described in recent literature.[3-7]

We report here a new stereoselective three-step synthesis of erbstatin (**6**), the shortest so far, starting from commercially available 2,5-dimethoxybenzaldehyde (**1**).

(*E*)-Ethenyl isocyanide **3** was obtained in a butyllithium-induced Wittig–Horner-Emmons type condensation using diethyl (isocyanomethyl)phosphonate (**2**).[8,9] Compound **3** was formed in 75% yield together with some of the *Z*-isomer in an *E*/*Z* ratio of 10:1. Isolation of **3** was readily achieved by flash chromatography. In a less attractive alternative, using a butyllithium-induced Peterson olefination with trimethylsilylmethyl isocyanide[10] and aldehyde **1** (under conditions comparable to the Wittig–Horner–Emmons reaction), compound **3** was obtained in 60% yield with an *E*/*Z* ratio of 1:1. Compound **3**, not stable in air, darkens rapidly in neat form, however, it can be stored in diethyl ether solution at −25 °C under nitrogen. Acid hydration[11] of **3** provided *O,O*-dimethylerbstatin (**5**), which was previously demethylated in 84% to erbstatin (**6**) using boron tribromide.[4]



Initially, the hydration of **3** to **5** was a troublesome reaction. When the reaction was carried out with aqueous acid, the formation of **5** was accompanied with considerable amounts of 2,5-dimethoxyphenylacetaldehyde, as a result of subsequent hydrolysis of **5**. This problem was nicely overcome when an old method of controlled hydration was employed.[12] α-Addition of hydrochloric acid at the isocyano carbon of **3** under anhydrous conditions gave **4**, which *in situ* was hydrolyzed with aqueous sodium bicarbonate, to give the desired (*E*)-*O,O*-dimethylerbstatin (**5**) in 60–79% yield.

^{1}H-NMR spectra were obtained using a 300 MHz Varian VTR-300 apparatus. IR spectra were recorded on a Perkin-Elmer 257 spectrophotometer. Melting points were taken using a Mettler FP1 melting point apparatus and are uncorrected.

(*E*)-[2-(2,5-Dimethoxyphenyl) ethenyl] Isocyanide (3):
To a cold (−78 °C) solution of diethyl (isocyanomethyl)phosphonate (**2**; 0.89 g, 5.0 mmol) in anhydrous THF (20 mL, distilled from Na) under N_2 is added dropwise a 1.6 M hexane solution of BuLi (3.4 mL, 5.5 mmol). The mixture is stirred at −78 °C for 15 min, then a solution of 2,5-dimethoxybenzaldehyde (**1**; 0.67 g, 5.0 mmol) in THF (5 mL) is added dropwise. Stirring is continued for 90 min at −78 °C, and the temperature is allowed to rise to −25 °C. The mixture is poured into a sat. solution of NH_4Cl and extracted with Et_2O (2 × 25 mL). The combined extracts are washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure using a water bath at 18 °C. The oily residue is flash chromatographed on a short column of silica gel (60, Merck), using EtOAc/toluene (1:1) as eluent to afford **3** as a yellow, foul smelling oil, which darkens on standing at r.t.; yield: 0.71 g (75%); R_f = 0.64.

The yield of **3** can be increased by using LiN(*i*-Pr)$_2$ or LiN(SiMe$_3$)$_2$, however, at the expense of stereoselectivity [with LiN(*i*-Pr)$_2$ in THF at −78 °C the yield is 80% (*E*/*Z* 4:1), and with LiN(SiMe$_3$)$_2$ the yield is 92% (*E*/*Z*, 3:2)].

IR (film): ν = 2940, 2830, 2120, 1615, 1490, 1030 cm^{-1}.

^{1}H-NMR (300 MHz, $CDCl_3$/TMS): δ = 3.68, 3.73 (2 s, 3 H each, 2OCH$_3$), 6.42 (d, 1 H, J = 13.9 Hz, =CHAr), 6.70–6.77 (m, 3 H$_{arom}$), 6.97 (d, 1 H, J = 14.7 Hz, =CHNC).

No microanalysis was performed due to the low stability of **3**.

(*E*)-*N*-[2-(2,5-Dimethoxyphenyl)ethenyl]formamide (*O,O*-Dimethylerbstatin, 5):
To a cold (−25 °C) solution of ethenyl isocyanide **3** (0.59 g, 3.12 mmol) in anhydrous Et_2O (10 mL, distilled from P_2O_5) under N_2 is added dropwise a freshly prepared[13] sat. solution of HCl in Et_2O (4 mL). Immediately a greenish-brown precipitate of compound **4** appears, and stirring is continued for 15 min at −25 °C. To this suspension is added a sat. solution of $NaHCO_3$ (25 mL), and after stirring for 5 min at 0 °C, the solution is extracted with EtOAc (2 × 25 mL). The organic layer is washed with water (25 mL), brine (25 mL), dried (Na_2SO_4), and concentrated at reduced pressure. The residue, a slowly solidifying orange oil, is purified by flash chromatography on silica gel (60, Merck) using EtOAc/toluene (1:3) as eluent. It is necessary to carry out the purification rapidly, since compound **5** decomposes on standing on silica gel, as described for **6**.[3] The second fraction (R_f = 0.20) is crystallized from Et_2O to give *O,O*-dimethylerbstatin (**5**) as pale yellow crystals; yield: 0.51 g (79% based on **3**); mp 83–85 °C (Lit.[3] mp 82–84 °C).

Received: 15 January 1990

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(13) When aged HCl/Et_2O solutions are used, the yield of **5** may drop considerably.