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TOTAL SYNTHESIS OF ERBSTATIN.

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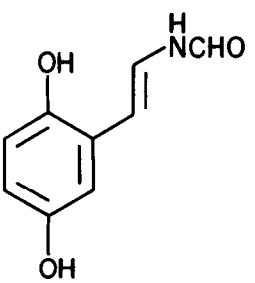
Abstract: Synthesis of the protein tyrosine kinase inhibitor, erbstatin (1), in 36% overall yield from commercially available 2,5-dihydroxycinnamic acid is described.

Tyrosine-specific protein kinases have been implicated as mediators in triggering normal cellular proliferation.[1] Additionally, tyrosine kinase activity is associated with the protein products of retroviruses.[2] As part of a screening program directed towards identifying inhibitors of tyrosine kinases, Umezawa and coworkers have recently[3] discovered a fermentation product which inhibits the membrane associated tyrosine kinase activity of the human epidermoid carcinoma cell line A-431. The structure of this inhibitor, termed erbstatin (1), has been confirmed by X-ray crystallographic analysis.[4] Based on the potential applications of erbstatin as a biological probe, we undertook a total synthesis of this product.



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Erbstatin is structurally related via the N-styrylformamide functionality to tuberin, an antitubular antibiotic.[5] Our approach is based on methodologies developed for the total synthesis of tuberin.[6] This synthesis is based on the conversion of a cinnamic acid into a N-styrylformamide, employing a highly selective reduction[6a] of the corresponding isocyanate intermediate. Since the appropriately substituted cinnamic acid is readily available, this approach to the synthesis of erbstatin is highly efficient.

The synthesis of erbstatin was initiated by the acetylation of commercially available 2,5-dihydroxycinnamic acid[7] to afford **3** (mp 152-153°C; lit.[8] mp 157-158°C) in 80% yield (see Scheme).[9] The use of acetate protecting groups during the course of this synthesis is based on their known[6b,10] ease of introduction and removal, the latter being a key point due to the presence of the chemically-sensitive[5] N-styrylformamide functionality. Formation of acyl azide **4** (mp 93-94°C) via the corresponding acid chloride was accomplished in an overall yield of 86%. Thermally induced rearrangement of **4** generated the isocyanate (**5**), which was isolated by concentration of the toluene solution in vacuo. Reduction to the formamide functionality was accomplished employing lithium tri-tert-butoxyaluminohydride, according to the procedure of Massey and Harrison.[6a] In this manner, diacetoxyerbstatin **6** (mp 146-148°C) was isolated in a 74% overall yield from **4**. As reported for erbstatin,[4] ^{1}H NMR spectroscopy of **6** in acetone-d_6 exhibits a doubling of signals (approximately a 3:1 mixture) due to restricted rotation around the amide (N-C) bond. Finally, erbstatin was obtained as a light-brown colored solid (70% yield) after treatment of a methanolic solution of **6** with aqueous sodium bicarbonate[10] and purification by flash chromatography. Synthetic erbstatin had spectral properties (^{1}H, ^{13}C, IR, HRMS, and UV) identical with those reported for the natural product.[3,4] However, a sample obtained from methanol:chloroform recrystallization, underwent only slight crystal deformation at the reported[3] melting point (78-82°C) and melted at 146-148°C.[11] There was no alteration in the spectral properties of synthetic erbstatin upon recrystallization.

In summary, a versatile and stereoselective synthesis of the protein tyrosine kinase inhibitor, erbstatin, has been accomplished in a 36% overall yield (six steps) from commercially available 2,5-dihydroxycinnamic acid.

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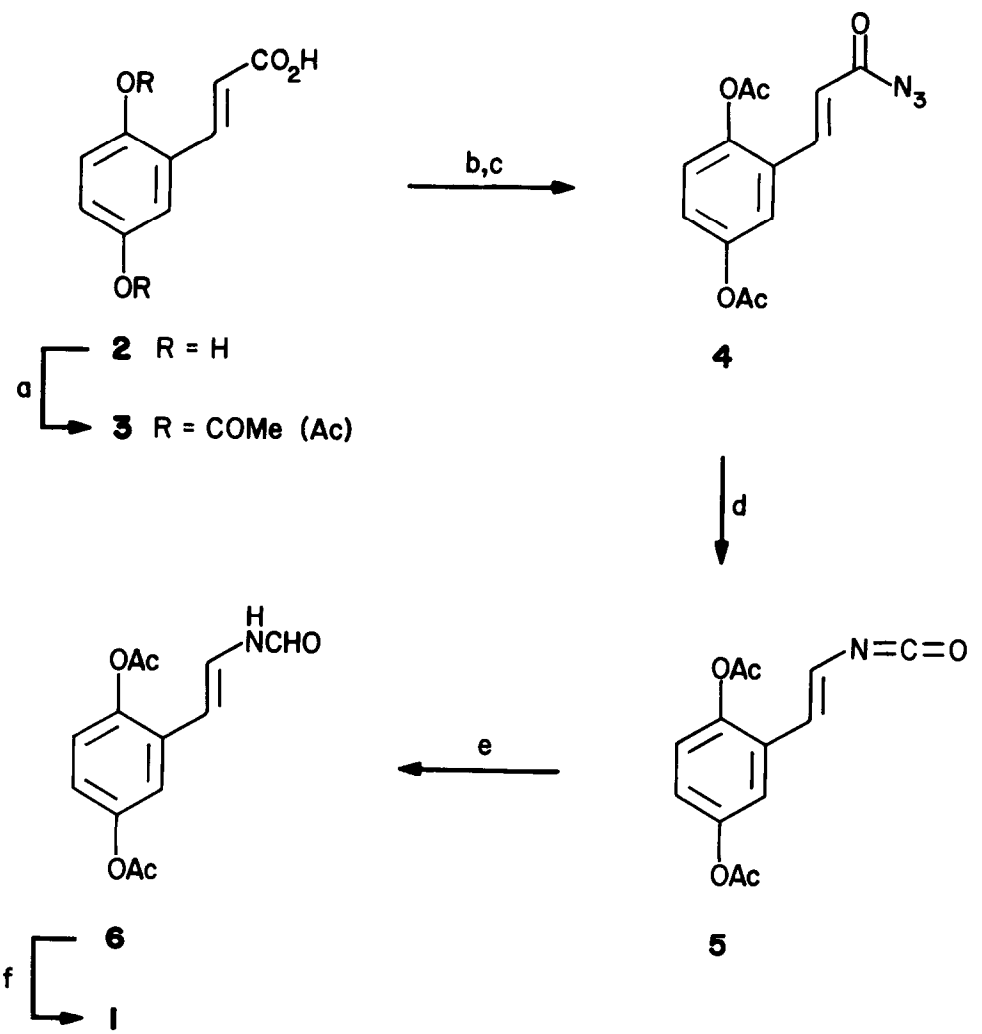
Scheme



(a) $(MeCO)_2O$, NaOH, H_2O; (b) $(ClCO)_2$, CH_2Cl_2; (c) NaN_3, Me_2CO, H_2O; (d) PhMe, 100°; (e) $Li(t\text{-}BuO)_3AlH$, THF; (f) $NaHCO_3$, H_2O, MeOH.

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11. While this publication was in the review process an alternative synthesis of erbstatin was reported: Hangauer, D.G. Tetrahedron Lett. **1986**, 27, 5799. This author noted similar melting point characteristics for synthetic erbstatin.

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