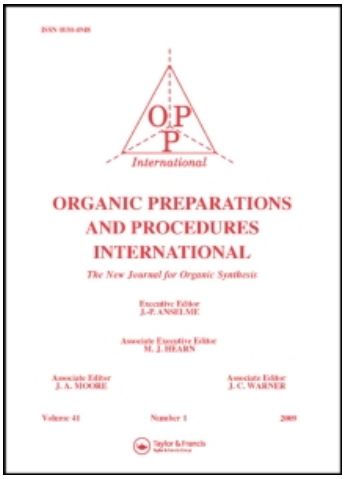

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A DIRECT APPROACH TOWARD THE SYNTHESIS OF ANALOGS OF ERBSTATIN

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A DIRECT APPROACH TOWARD THE SYNTHESIS OF ANALOGS OF ERBSTATIN

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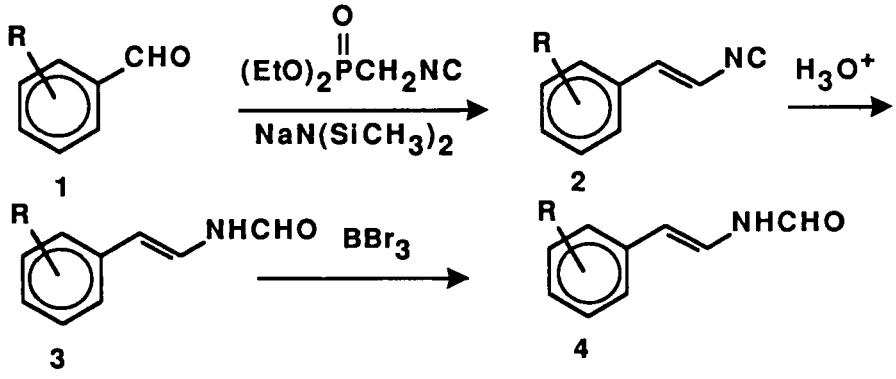
Tyrosine-specific protein kinases (TPK) constitute an important family of phosphoryl transfer enzymes which are critical to normal cellular growth and differentiation.[1] Aberrant expression of certain TPK's has been associated with a number of neoplastic diseases including skin, breast, renal, prostate and colon cancers. Currently TPK's are the object of intense study directed toward elucidation of their function and relationship to oncogenic states. Since its isolation by Umezawa in 1986,[2] the TPK-specific inhibitor erbstatin **4c** has proven to be a useful tool in these studies and has become a widely used standard of kinase inhibition.

To date seven syntheses of erbstatin have been described.[3] Six of these procedures,[4-9] while achieving satisfactory yields, require four or more steps each. The seventh procedure, which provided a very efficient two step synthesis of erbstatin,[10] utilized the reaction of

diethyl(isocyanomethyl)phosphonate with 2,5-dihydroxybenzaldehyde in the presence of sodium bis(trimethylsilyl)amide. Hydrolysis of the unisolated isocyanide **2c** provided erbstatin in 56% overall yield. In practice this latter procedure, while synthetically direct is disadvantageous in some regards. Conditions require a five fold excess of expensive phosphonate reagent. In addition, instability of the conjugated dihydroquinone system particularly under strongly basic conditions, results in substantial decomposition unless extreme care is exercised. Erbstatin itself is unstable, decomposing during chromatographic purification[4] and becoming colored within minutes when exposed to the air in solution. Considerable interest also exists in the synthesis of analogs of erbstatin to provide TPK inhibitors which are not available from natural sources. In this regard, a number of derivatives of erbstatin have been reported which differ in the pattern of aromatic hydroxyl substitution.[10,11] Herein is reported a general and facile synthesis of analogs of erbstatin starting from readily available methoxy benzaldehydes. Illustrative of the utility of this approach is the preparation of erbstatin itself and the 3,4-dihydroxy positional isomer **4d**.

Protection of the dihydroquinone as its bismethyl ether reduced the quantity of phosphonate required (1.1 versus 5 equivalents for the unprotected dihydroquinone) and resulted in significantly more stable reaction products which are amenable to purification by filtration through a silica gel pad. As previously noted for the dihydroquinone,[10] isolation was avoided. Since an extractive workup followed by stirring overnight with a biphasic 0.1 N HCl/ EtOAc system[10] proved unsatisfactory,[3] the crude reaction mixture was diluted with 3 molar equivalents of aqueous 1 N HCl at -78° and then stirred at room temperature until TLC



indicated no further reaction (approximately 1 hr). Finally, eluting with 2% EtOH in CH_2Cl_2 gave product **3a** as a light brown oil which was crystallized from CH_2Cl_2 : pet ether as white crystals (51% yield), mp 79-81° (lit.[9] mp 82-84°). Demethylation of **3a** was carried out as

previously reported,[9] yielding erbstatin **4c** in 37% yield. Melting point, ^{1}H-NMR and IR were consistent with literature[4] and chromatographic and spectral comparison with an authentic sample of erbstatin and further confirmed the structure. The utility of this approach was demonstrated in the preparation of the 3,4-dihydroxy analog of erbstatin (**4d**) which was obtained in 40% yield [mp 196-198° (dec.) lit.[10] mp 185-187°] by demethylation of the corresponding bismethyl ether **3b** (obtained in 43% yield from the corresponding aldehyde **1b**).

EXPERIMENTAL SECTION

(E)-N-[2-(2,5-Dimethoxyphenyl)ethenyl]formamide (**3a**).- To a solution of 2,5-dimethoxybenzaldehyde (1.66 g, 10 mmol) and diethyl(isocyanomethyl)phosphonate (1.76 mL, 11 mmol) in dry THF (75 mL, freshly distilled over Na) at -78° under argon was added sodium bis (trimethylsilyl)amide (2.20 g, 12 mmol) and the yellow solution stirred for 1 hr. At this point, TLC analysis (silica, CH_2Cl_2) showed product (Rf = 0.58, starting aldehyde Rf = 0.52) corresponding to isonitrile **2a**, which if isolated at this stage, proved to be an unstable crystalline solid having the expected NMR and IR. The mixture was acidified at -78° (15 mL of 1 N aqueous HCl), and allowed to warm up to RT (30 minutes); it was then partitioned between aqueous NaCl (150 mL) and EtOAc (4 x 50 mL). The combined organic extract was dried ($MgSO_4$), taken to dryness by rotary evaporation and passed through a silica pad (4 cm dia. x 3 cm high; 10 μ silica gel G) sequentially eluting with pet ether (bp 30-45°):CH_2Cl_2 (50:50), then (25:75) (this eluted an impurity running slightly faster than product). Elution with EtOH:CH_2Cl_2 (2:98) gave product **3a** (1.06 g, 51%) as white crystals from pet ether:CH_2Cl_2, mp 79-81°.

(E)-N-[2-(3,4-Dimethoxyphenyl)ethenyl]formamide (**3b**).- Reaction of 3,4-dimethoxybenzaldehyde (1.66 g, 10 mmol) under conditions identical to that described for **3a** yielded **3b** (898 mg, 43%) as white crystals mp 118-120° (from ether). ^{1}H NMR (DMSO-d_6) major rotamer: δ 3.70 (s, 3H, OCH_3); 3.75 (s, 3H, OCH_3); 6.15 (d, 1H, J = 14.7 Hz, H-2); 6.74-6.87 (m, 2H, ArH-5,6); 6.94 (s, 1H, ArH-2); 7.31 (dd, 1H, J = 14.7, 10.4 Hz, H-1); 8.07 (s, 1H, CHO); 10.20 (d, 1H, J = 10.4 Hz, NH). Minor rotamer: δ 3.70 (s, 3H, OCH_3); 3.75 (s, 3H, OCH_3); 5.93 (d, 1H, J = 14.4 Hz, H-2); 6.74-6.87 (m, 2H, ArH-5,6); 6.94 (s, 1H, ArH-2); 7.29 (dd, 1H, J = 14.4 , 10.7 Hz, H-1); 8.37 (d, 1H, J = 11.0 Hz, CHO); 10.12 (dd, 1H, J = 11.0, 10.7 Hz, NH). IR (KBr): 3262, 1656 cm^{-1}.

Anal. Calcd. for $C_{11}H_{13}NO_3$: C, 63.76; H, 6.32; N, 6.76. Found: C, 63.65; H, 6.36; N, 6.76

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AN IMPROVED SYNTHESIS OF 9-CHLORO-2-METHOXYACRIDINE

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Substituted chloroacridines are useful precursors for various important classes of biologically active molecules. The antiviral activity of acridine derivatives has been well documented.[1] Heterocyclic alkylating agents with unusual antitumor activity can be readily prepared from the chloroacridine skeleton.[2] Unique chromosomal staining derivatives have also been constructed from the chloroacridine precursor.[3] We report an improved synthesis of