EFFECTIVE SYNTHESIS OF ERBSTATIN AND ITS ANALOGS

Sir:

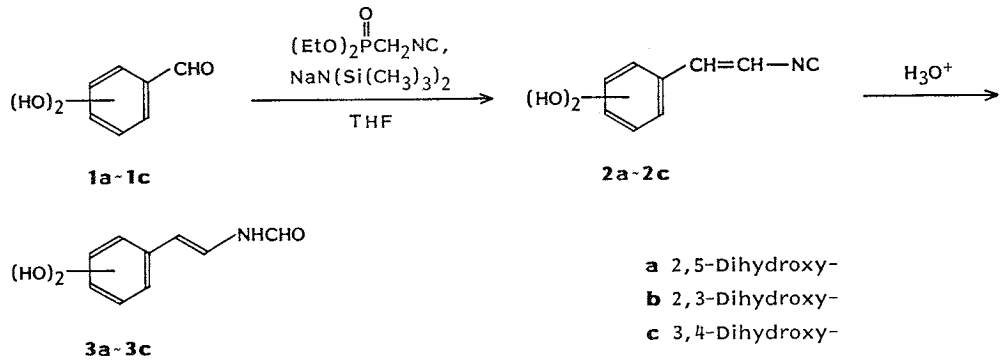
Recently, in our laboratory, erbstatin (**3a**)[1], a new potent inhibitor for tyrosine protein kinase (TPK), was isolated from the broth of *Streptomyces* sp. (MH435-hF3) and the structure was determined by X-ray crystallographic analysis[2] as illustrated in Fig. 1. Erbstatin (**3a**) and its analogs are expected to be useful for the studies of the functions of oncogenes (tumor inducing genes), and may have therapeutic activity for the treatment of cancer. We now present a facile synthesis of erbstatin (**3a**) and related compounds (**3b** and **3c**)[3,4] in two steps with 52% ~ 58% overall yields through the α,β-unsaturated isocyanides (**2a** ~ **2c**) from the corresponding aldehydes. While we were developing more useful analogs[3] than the natural product by the present procedure, researchers at Merck reported a 6-step synthesis[5] of erbstatin, that was less appropriate for the preparation of many kinds of analogs. Our synthesis mainly consists of the reaction of diethyl(isocyanomethyl)phosphonate with dihydroxybenzaldehydes (**1a** ~ **1c**) by a modified SCHÖLLKOPF's procedure[6,7].

Reaction of 2,5-dihydroxybenzaldehyde (20.7 mg) with diethyl(isocyanomethyl)phosphonate (132.8 mg, 5 eq) in the presence of sodium bis-(trimethylsilyl)amide (137.3 mg, 5 eq) in absolute THF (4 ml) at −78°C gave the *E*-isomer of 2-(2,5-dihydroxyphenyl)vinylisocyanide (**2a**) as a main product in 62% yield: IR ν_{max}^{KBr} cm^{-1} 3280, 2140 (NC), 1590, 1505; ^{1}H NMR ($CDCl_3$ - CD_3OD, 10:1) δ 6.60 (1H, d, J=14 Hz), 6.70 (2H, s), 7.08 (1H, d, J=14 Hz), 7.36 (1H, s). The isocyanide (**2a**) was hydrolyzed with 0.1 N HCl (5 ml) in EtOAc (5 ml) with vigorous stirring at room temp for 24 hours to give crystalline erbstatin (**3a**) in 68% yield after silica gel column chromatography (toluene - Me_2CO, 3:1). The physico-chemical and biological properties (Rf values, IR, ^{1}H NMR, UV and TPK inhibiting activity) of **3a** were identical with those of erbstatin[1,2]. Melting point of **3a** was 156 ~ 157°C (literature 1 78 ~ 82°C, the value was the softening point[5] and natural erbstatin melted at exactly 156 ~ 157°C).

Without isolation of the isocyanide (**2a**), the overall yield was improved to 56% as follows. After the reaction of the phosphonate with **1a**, the resulting mixture was extracted with EtOAc. The combined extracts were washed with 0.1 M phosphate buffer (pH 7.0) and concentrated to about 5 ml. The solution was stirred with 0.1 N HCl (5 ml) at room temp to give erbstatin (**3a**) in 56% overall yield. Similarly, *E*-2-(2,3-dihydroxyphenyl)vinylformamide (**3b**) and *E*-2-(3,4-dihydroxyphenyl)vinylformamide (**3c**) were obtained in 52% and 58% overall yields from **1b** and **1c**, respectively [**3b**: MP 164 ~ 165°C; UV ν_{max}^{MeOH} nm (ε) 282 (18,600), 225 (14,500), 207 (12,000); IR ν_{max}^{KBr} cm^{-1} 3350, 1670, 1655, 1484, 1390, 1290; ^{1}H NMR (acetone-d_6) δ 6.51 (1H, d, J=15 Hz), 6.6 ~ 7.0 (3H, m), 7.70 (1H, dd, J=15 and 10.5 Hz), 8.22 (1H, s), 7.60 (1H, br), 8.50 (1H, br), 9.25 (1H, br), **3c**: MP 185 ~ 187°C; IR ν_{max}^{KBr} cm^{-1} 3340, 1670, 1640, 1500, 1390, 1280; ^{1}H NMR (acetone-d_6 - CD_3OD, 10:1) δ 6.20 (1H, d, J=15 Hz), 6.7 ~ 6.9 (3H, m), 7.35 (1H, d, J=15 Hz), 8.19 (1H, s)].

Thus, we have synthesized erbstatin and its analogs in two step reactions. This method will be applicable for the preparation of other erbstatin analogs in multigram quantities from

Fig. 1. Synthetic process to erbstatin and its analogs.



mono-, di- and tri-hydroxybenzaldehydes.

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