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TOTAL SYNTHESIS OF ERBSTATIN

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Summary: The total synthesis of erbstatin in six steps and 38% overall yield from commercially available lactone **1** is presented.

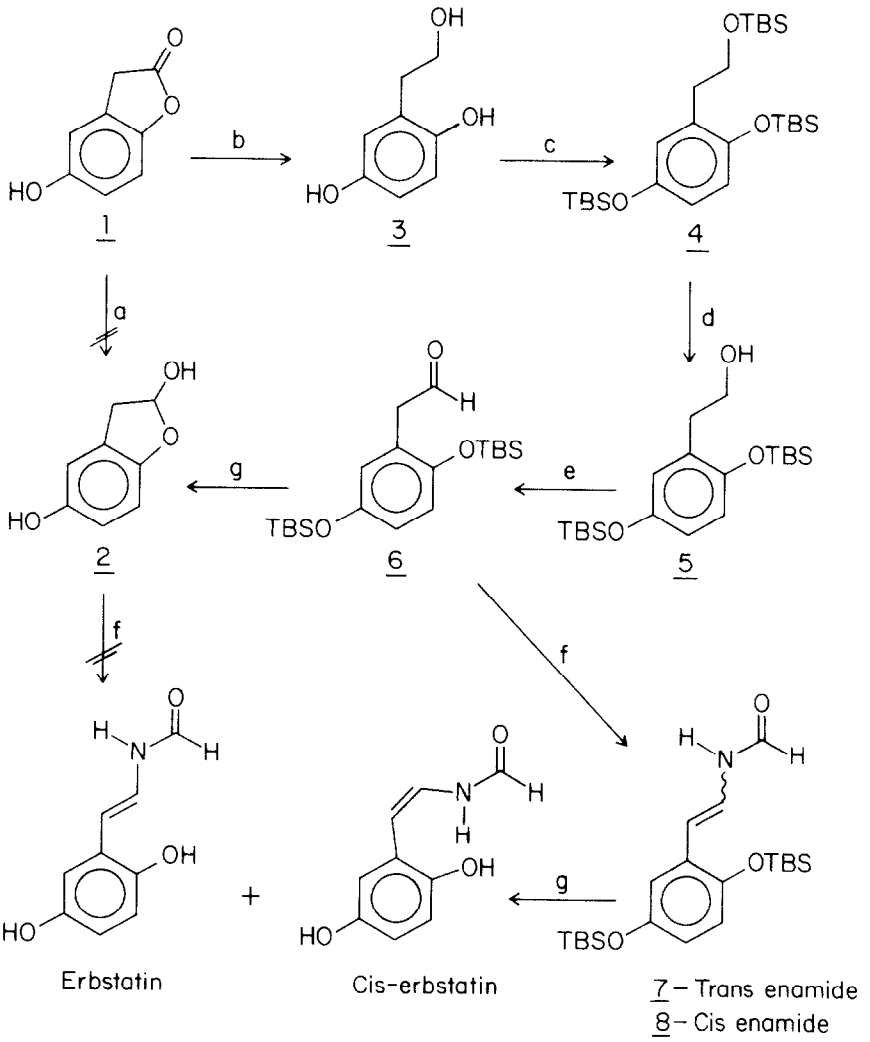
Over the last decade a number of growth factor receptors and proteins produced by cancer causing genes (oncogenes)[1] have been identified as enzymes (tyrosine kinases) capable of phosphorylating tyrosine residues. Inhibitors of these enzymes will be extremely useful for further elucidating the role of tyrosine kinases in cell growth, proliferation and metabolism. Tyrosine kinase inhibitors have the longer range potential of providing a new class of therapeutic agents for the treatment of cancer. Recently, erbstatin (Scheme) was isolated by Umezawa and co-workers and shown to be a novel inhibitor of the epidermal growth factor receptor tyrosine kinase.[2] This natural product has the unusual structural feature of a hydroquinone conjugated with an enamide. We now report a practical total synthesis of erbstatin which proceeds in high overall yield.

We had originally envisioned a two step synthesis for erbstatin beginning from lactone **1**.[3] The first step involved a partial reduction to lactol **2** followed by condensation with formamide. An attempted partial reduction with 2.5 eq. of diisobutylaluminum hydride (DIBAL-H) in toluene/tetrahydrofuran at -78°C for 1.5 hours afforded only the water soluble overreduced material **3**[4,10] in 60% chromatographed yield and recovered starting material in 23% yield. Apparently the hydroquinone moiety is a good enough leaving group to cause breakdown of the lactol-diisobutylaluminum complex resulting in an unmasked aldehyde which consumes the remaining DIBAL-H more rapidly than lactone **1**. Consequently, the reduction was driven to completion using 3.5 eq. of DIBAL-H in toluene/tetrahydrofuran at -78°C for 3 hours. After work-up, the triol **3** was isolated in quantitative yield by elution from a short silica gel column with 5% methanol/ethyl acetate.

The triol **3** was fully protected by treatment with 3.5 eq. of t-butyldimethylsilyl chloride in dimethylformamide containing 4.5 eq. of triethylamine and 0.3 eq. of 4-dimethylaminopyridine at 0°C to room temperature for 25 hours. The trisilylether **4**[4] was isolated in 84% yield by elution from a short silica gel column with 100/5-hexanes/ethyl acetate. Selective cleavage of the aliphatic silyl ether group[5] was achieved in 87% yield by subjecting **4** to 2 eq. of 50% aqueous HF at room temperature for 1.8 hours in an acetonitrile/methylene chloride (2/1) solution. The alcohol **5**[4] was purified by silica gel MPLC using 10% ethyl acetate/hexanes. Oxidation of **5** to aldehyde **6**[4] using 1.5 eq. of pyridinium chlorochromate in methylene chloride proceeded in only 50% isolated (by chromatography) yield. The yield was increased to 97% (no chromatography needed) with a Swern oxidation[6] run using 1.2 eq. of oxalyl chloride and 2.4 eq. of dimethylsulfoxide in methylene chloride at -60°C to -10°C over 45 minutes.

Condensation of **6** with 1.8 eq. of formamide in refluxing benzene containing a catalytic amount of p-toluenesulfonic acid for 47 hours gave an 84/16 ratio of the trans/cis enamides **7**[4] and **8**.[4] The enamides were purified and completely separated by silica gel MPLC using 15% ethyl

Scheme



Reagents for Scheme

(a) 2.5 eq. DIBAL-H, Toluene/THF, −78°, 1.5 h. (b) 3.5 eq. DIBAL-H, Toluene/THF, −78°, 3 h. (c) 3.5 eq. t-$BuMe_2SiCl$, 4.5 eq. TEA, 0.3 eq. DMAP, DMF, 0°–25°, 25 h. (d) 2 eq. 50% HF/H_2O, CH_3CN, CH_2Cl_2, 25°, 18 h. (e) 1.2 eq. ClCOCOCl, 2.4 eq. DMSO, CH_2Cl_2, −60° → −10°, 45 m. (f) 1.8 eq. H_2NCOH, Catalytic p-TSA, C_6H_6, reflux, 47 h. (g) 2 eq. Bu_4NF, THF, 0°, 15 m.

acetate/hexanes. Aldehyde **6** was also recovered resulting in a 73% yield of enamides **7** and **8** at 57% conversion. The condensation reaction appears (by TLC) to have reached equilibrium within 22 hours. The 1.8 eq. of formamide used is not completely soluble in refluxing benzene. An attempt was made to drive the condensation completely to the enamides by using dimethoxyethane as the solvent and 50 eq. of formamide (completely soluble) in the presence of a catalytic amount of p-toluenesulfonic acid and powdered 3A sieves at 75°C for 23 hours. Only unidentified byproducts were formed and some aldehyde **6** remained.

Removal of the t-butyldimethylsilyl protecting groups from the trans enamide **7** was accomplished by treatment with 2 eq. of 1 M tetrabutylammonium fluoride in tetrahydrofuran at 0°C for 15 minutes followed by 2.5 eq. of acetic acid. The addition of acetic acid appeared to be helpful in minimizing the facile air oxidation of the hydroquinone moiety during subsequent handling. Interestingly, the basic deprotection conditions caused a small amount (i.e. 7%) of isomerization of the trans enamide to cis enamide. Erbstatin was isolated as a mixture with the 7% "cis-erbstatin" by silica gel MPLC using 5% methanol/ethyl acetate in 88% yield. Analytically pure erbstatin (free of cis-erbstatin) was obtained as light brown crystals by crystallization from 1/1/1-methanol/chloroform/hexanes at 5°C. The 300 MHz ^{1}H NMR of synthetic erbstatin in acetone-d_6 (internal TMS reference) was in agreement with the spectrum reported[2b] for the natural product.[7] A satisfactory combustion analysis for a 1/1 complex with methanol and a strong molecular ion at m/e 179 in the EI mass spectrum was obtained. Synthetic erbstatin softens at about 80°C and gives off gas bubbles (MeOH) at ca. 88-91°C then melts sharply at 150.5-152.0°C.[8] The reported[2a] melting point for the natural product is 78-82°C. However, since the natural product was also isolated as light brown crystals, and as a 1/1 complex with methanol, it seems likely that the 78-82°C reported melting point may in fact be the softening point as observed for synthetic erbstatin.

The cis enamide **8** was desilylated by exposure to 2 eq. of 1 M tetrabutylammonium fluoride in tetrahydrofuran at 0°C for 15 minutes followed by quenching with 2.5 eq. of acetic acid. As with the trans enamide **7**, the desilylation conditions resulted in a small amount of isomerization to the opposite enamide olefin geometry. In this case about 9% of erbstatin was produced as a "byproduct". Cis-erbstatin[9] was isolated as a mixture with the 9% erbstatin by silica gel chromatography in 88% yield using 5% methanol/ethyl acetate. The observed isomerization of cis-erbstatin to erbstatin during the desilylation opens the possibility of improving the overall yield of erbstatin by subjecting cis-erbstatin to more vigorous isomerization conditions.

In order to test the second step of our originally proposed two step synthesis, we subjected aldehyde **6** to the same desilylation conditions described above. Lactol **2**[4] was obtained in quantitative yield after preparative TLC (silica gel) using 5% methanol/ethyl acetate. Unfortunately, lactol **2** was largely insoluble in benzene, even at reflux. An attempted condensation of **2** with 1.8 eq. of formamide in refluxing benzene containing a catalytic amount of p-toluenesulfonic acid for 19 hours gave no reaction. Consequently, dimethylformamide was added to make the reaction homogeneous and refluxing continued for 24 hours, but starting material still remained. The benzene was distilled from the reaction and the reaction temperature raised to 150°C for 2.5 hours. Even under these vigorous conditions starting material remained and no detectable erbstatin was produced.

The judicious choice of a protection/selective deprotection scheme utilizing the t-butyldimethylsilyl protecting group was critical to the success and practicality of our synthesis for the following reasons: 1)This protecting group allowed selective unmasking of the aliphatic alcohol in

excellent yield and prevented oxidation of the hydroquinone during the subsequent step and while handling the various intermediates. 2)The t-butyldimethylsilyl groups provided the necessary solubility in organic solvents for the Swern oxidation, the condensation with formamide and convenient work-ups. 3)The protecting groups facilitated a clean separation of the cis **8** and trans **7** enamides by silica gel chromatography . Finally, our observation of cis enamide isomerization to erbstatin during desilylation offers the possibility of increasing the overall yield of erbstatin.

REFERENCES AND NOTES

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3. Aldrich Chemical Co., Milwaukee, Wisconsin, USA.
4. All new compounds were isolated in good purity and gave a fully consistent 300 MHz ^{1}H NMR and EI mass spectrum including a strong molecular ion.
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7. A UV spectrum in methanol was also in agreement with the reported spectrum.
8. If one emerses a new sample of synthetic erbstatin into the oil bath at 140°C the crystals immediately melt and bump up the capillary tube presumably due to a rapid vaporization of the methanol.
9. The 300 MHz ^{1}H NMR (TMS internal reference) of cis-erbstatin in acetone-d_6 showed a 4.5/1 ratio of conformational isomers due to a restricted rotation around the N-C bond of the amide. The major rotational isomer shows one of the olefinic protons at 5.70ppm (d,J=10.3 Hz) and the minor isomer shows the same proton at 5.49ppm (d,J=10.3 Hz). The formyl proton of the major isomer is a singlet at 8.24ppm and of the minor a singlet at 8.41ppm. The aromatic protons and the remaining olefinic proton form a complex pattern in the 6.4-7.1ppm region. The EI mass spectrum gave a strong molecular ion and a fragmentation pattern similar to erbstatin.
10. Triol **3** can be recovered from the water layer by several ethyl acetate extractions.

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