



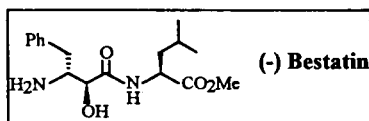
## Polyaniline Supported Cobalt Catalysed one pot Stereoselective Synthesis of the Structural Analogues of Aminopeptidase Inhibitor *Bestatin*.

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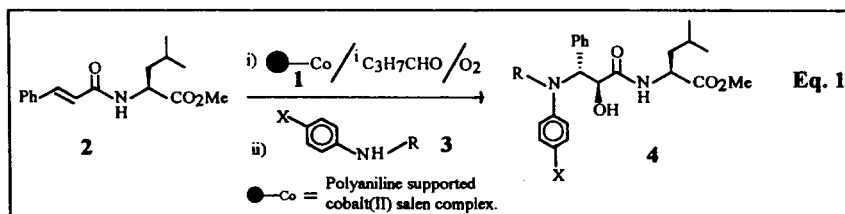
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**Abstract:** A one pot stereoselective conversion of cinnamoyl amide of L-leucine methyl ester to the corresponding structural analogues of bestatin was achieved by employing polyaniline supported cobalt(II) salen catalysed epoxidation followed by its opening with anilines at ambient conditions. © 1997 Elsevier Science Ltd.

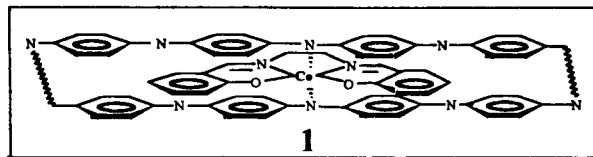
In continuation of our studies<sup>1</sup> on polyaniline supported cobalt catalysed epoxidation and its opening with anilines, we became interested in developing a general synthetic protocol for the structural analogues of the potent aminopeptidase inhibitor bestatin<sup>2</sup>. Bestatin has been shown to exhibit antitumor as well as antimicrobial activity and it is generally believed that this behavior is associated with its ability to inhibit<sup>3</sup> cell surface aminopeptidases. Apart from this, bestatin is also known to act as immune response modifiers<sup>4</sup> and analgesics by enkephalinase inhibition<sup>5</sup>. In order to probe the structural requirement for aminopeptidase inhibitor activity, Rayner and



coworkers<sup>6</sup> have developed a general synthetic route to  $\alpha$ -thiolbestatin as peptide isostere by a selective nucleophilic trapping of thiiranium ion intermediates with amino esters.


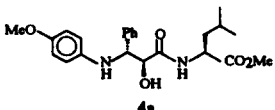

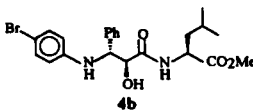
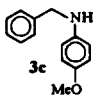
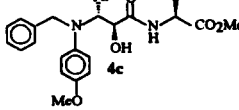
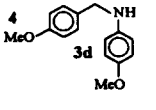
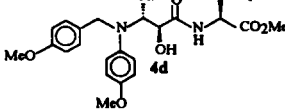
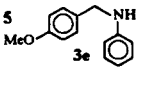
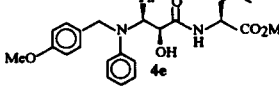
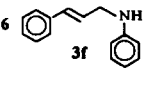
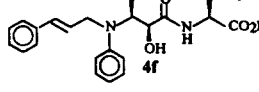


In an earlier study we have demonstrated<sup>1b</sup> a dual role of polyaniline supported cobalt (II) salen complex **1** during conversion of cinnamoyl amides to the corresponding  $\beta$  - phenylisoserine derivatives. We report herein a general route to the stereoselective synthesis of structural analogues of bestatin using polyaniline supported cobalt catalysed one pot conversion of cinnamoyl amide of L-leucine methyl ester **2** to the corresponding dipeptide derivatives **4** ( Eq.1).



Typically, cinnamoyl amide **2** ( 5 mmol ) was dissolved in acetonitrile ( 25 ml ) and 2 - methylpropanal ( 15 mmol ) was added to it and the resulting mixture was stirred in the presence of catalytic amount of polyaniline supported cobalt ( II ) salen complex **1** ( ~ 25 mg ) under dioxxygen balloon at ambient temperature for 16 to 20 h. The progress of reaction was monitored by TLC and as soon as the starting cinnamoyl amide disappeared the oxygen balloon was removed and aniline derivative **3** ( 5 mmol ) and catalyst **1** ( ~ 10 mg ) was added to the reaction mixture. After an additional stirring for 12 to 15 h at 25<sup>0</sup>c the solvent was removed and the residue columned over silica gel ( EtOAc - hexane ) to afford the corresponding  $\beta$  - phenylisoserine L - leucine derivatives **4** as a solid in >95% purity ( HPLC ) ( Table 1 ).The generality of these reactions was demonstrated by converting the cinnamoyl amide of L-leucine methylester **2** with several primary and secondary amines **3**, derived from anilines, to the corresponding dipeptide **4** ( Table 1, entry 1-6 ).Thus the reaction of amide **2** with p-anisidine **3a** afforded a mixture of two diastereomers in equal amounts and on separation by column chromatography, the anti diastereomer **4a** was obtained in high chemical ( 97.3%, HPLC ) and optical (  $[\alpha]_D = -20^0$  ) purity ( Table 1, entry 1 ). Similarly p-bromoaniline **3b** also afforded an equal amount of two diastereomers from which **4d** was isolated in good chemical and optical purity ( Table 1, entry 2 ) after the column chromatography. The reaction of amide **2** with secondary amines **3c-3f** afforded the corresponding products **4c-4f** mainly as one diastereomer in high chemical and optical purity ( Table 1, entry 3-6 ). Interestingly, the reaction mixture was found to contain only a trace amount of the other diastereomer and as discussed in the preceding<sup>7</sup> paper, the secondary amine with a p - methoxy group of the benzene ring ( **3c** and **3d** ) directly attached to nitrogen, afforded the corresponding *anti* diastereomer **4c** and **4d** respectively as the major product<sup>8</sup> in high chemical purity ( Table 1, Entry 3-4 ). On the other hand, the secondary

**Table 1: Polyaniline supported cobalt(II) salen complex 1 catalysed one pot conversion of 2 to dipeptide derivatives 4.**

| Entry | Amine   | Product <sup>b</sup>  | Yield(%) <sup>a</sup> | Melting Point(°C) | Purity(%) <sup>d</sup> (HPLC) | $[\alpha]_{D}^{25}$ °C |
|-------|---|---|-----------------------|-------------------|-------------------------------|------------------------|
| 1     |    |    | 31 <sup>c</sup>       | 140               | 97.3                          | -20 <sup>0</sup>       |
| 2     |    |    | 28 <sup>c</sup>       | 164               | 84.5                          | -14 <sup>0</sup>       |
| 3     |    |    | 35                    | 148               | 98.6                          | -15 <sup>0</sup>       |
| 4     |    |    | 39                    | 88                | 98                            | -23 <sup>0</sup>       |
| 5     |   |   | 41                    | 137               | 99                            | -40 <sup>0</sup>       |
| 6     |  |  | 49                    | 156               | 98.3                          | -51 <sup>0</sup>       |

a) Isolated yield based on **2**. b) Only the relative stereochemistry for products **4** is shown. c) An equal mixture of diastereomers were obtained in these reactions and only the *anti* diastereomer **4a-b** gave high chemical and optical purity. d) Optical rotation was measured in CHCl<sub>3</sub> (c = 0.01)

amine **3e** and **3f**, with an unsubstituted benzene ring directly attached to the nitrogen, opened the epoxide to afford the corresponding *syn* diastereomer **4e** and **4f** respectively as the major product in very high chemical purity (Table 1, Entry 5-6). The high chemical purity and optical rotation of these diastereomers indicate them to be optically pure enantiomers. Although the relative stereochemistry of the diastereomer has been assigned based on the X - ray data of the related

structure<sup>7</sup>, an unambiguous assignment of the absolute stereochemistry for them can only be done by single crystal X - ray analysis.

The high optical and chemical purity of dipeptide **4** indicates that the intermediate epoxide is formed in a highly enantioselective manner. This enantiomerically pure epoxide thus opens up additional possibility where it can be opened with other nucleophiles to give variety of chiral intermediates.

In conclusion, polyaniline supported cobalt(II) salen complex **1** is an efficient catalyst for a one pot conversion of cinnamoyl amide of L-leucine methylester to the corresponding structural analogues of bestatin by a combined use of epoxidation and ring opening sequence. We are further exploring this methodology for the synthesis of other potential aminopeptidase inhibitors.

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7. Preceding Communication.
8. <sup>1</sup>H NMR: **4d**: ( 200 MHz, CDCl<sub>3</sub> ): 6.69-7.45 (m, 13H), 4.85 (d, J=2.2Hz, 1H), 4.4 (d, J=2.2Hz, 2H), 4.15 (d, J=20Hz, 1H), 3.95 (d, J=20Hz, 1H), 3.73 (s, 6H), 3.55 (s, 3H), 3.3-3.2 (br. s, 1H), 1.25-1.52 (m, 4H), 0.87 (d, J=2.6Hz, 3H), 0.82 (d, J=5.8, 3H). **4e**: 6.7-7.4 (m, 14H), 5.47 (d, J=3.02Hz, 1H), 4.3-4.65 (m, 4H), 3.75 (s, 3H), 3.64 (s, 3H), 2.9 (d, J=4Hz, 1H), 1.13-1.16 (m, 4H), 0.80 (br. s, 6H).

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