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A STEREOSELECTIVE SYNTHESIS OF BOTH ENANTIOMERS OF EMERIAMINE FROM A SINGLE PRECURSOR: L-ASPARTIC ACID

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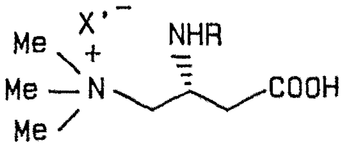
Abstract

A concise and stereoselective synthesis of both enantiomers of emeriamin **1**, through the key intermediate **3**, has been reported.

Emericidins A, B, C, chemically identified as the acyl derivatives of (3R)-3-amino-4-trimethylammonium butanoic acid hydrochloride, have been reported[1] as new inhibitors of long chain fatty acid oxidation, although their activity is very low. The deacylemericidine, designed as emeriamine or aminocarnitine for its structural analogy with carnitine[2], has shown powerful inhibitory activity of fatty acid oxidation, hypoglycemic and antiketogenic activity[1] in fasted rats after oral administration.



R = -H Emeriamine
R = $-COCH_3$ Emericidin A
R = $-COCH_2CH_3$ Emericidin B
R = $-COCH_2CH_2CH_3$ Emericidin C

Whereas several syntheses of the racemic emeriamine have been published, only one example of asymmetric synthesis has been proposed in the recent literature[3].

Due to the continuous interest for the development of simple and flexible synthetic methods of biologically active substances, we wish to report our approach to the synthesis of both enantiomers of emeriamine employing L-aspartic acid as common precursor.

The synthetic pathway involves the use of an intermediate **A** carrying different protecting groups for the two carboxylic functions and a compatible amine protecting group: so, it was possible to attain the target compounds through a suitable choice of R and R'.

Commercially available N-Cbz-L-aspartic acid 4-tert-butyl ester **2**[4] was transformed into the chiral diester **3** ($[\alpha]_D$ = -1.12, c = 3.5 in $CHCl_3$; Lit[5]: $[\alpha]_D$ = -1.15, c = 3.4 in $CHCl_3$) according to the Wakamiya method[6]: conversion of **2** to the correspondent α-diazoketone followed by Wolff rearrangement in the presence of silver benzoate in MeOH to give the key intermediate **3**, in 85% yield, which can be used without further purification. The crude product was then hydrogenated[7] (H_2, Pd/C, EtOH) to give the free amine diester **4** ($[\alpha]_D$ = +1.89, c = 1 in MeOH) in 90% yield; this last was converted immediately into the N-phthaloyl-β-amino diester **5** ($[\alpha]_D$ = +2.83, c = 1 in MeOH) in 65% yield, by using the Nefkens reagent[8].

The phthalimido-protecting group is necessary in order to avoid the formation of imidazolidin-2-one[9] during the insertion of the γ-amino group, performed by Curtius rearrangement. Acid treatment (CF_3COOH/CH_2Cl_2 1:2) of **5** affords, in almost quantitative yield, the N-phthalimido-amino acid **6** ($[\alpha]_D$ = -18.1, c = 1 in MeOH) which immediately undergoes the Curtius rearrangement: the acyl azide (i, EtOCOCl/Et_3N/AcOEt; ii, aqueous NaN_3 5M) was converted first into the corresponding isocianate in refluxing toluene and then, after addition of benzyl alcohol, into compound **7** ($[\alpha]_D$ = -4.93, c = 1 in MeOH) with an overall yield of 70%.

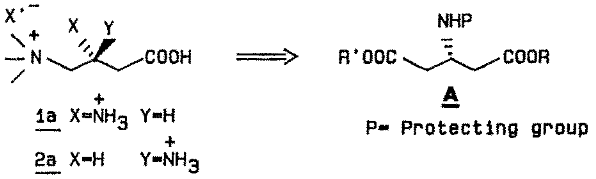
Attempts to hydrogenate (H_2, Pd/C) the Cbz group did not afford satisfactory results. Finally, the Cbz group was easily removed by treatment with a solution of HCOOH 4.4% (v/v) in MeOH in the presence of Pd black[10] to give **8** ($[\alpha]_D$ = +16.0, c = 1 in H_2O; mp = 229-230°C) as formate in 70% yield.

The trimethylammonium[11] salt **9** was obtained by methylation of the amine function (MeI, $NaHCO_3$), and immediately converted, by acid removal (HCl, 6N) of the protecting groups, into R-emeriamine hydrochloride**1a** ($[\alpha]_D$ = +7.0, c = 1 in H_2O, mp 221-223°C; Lit[3] $[\alpha]_D$ = +7.6, c = 1 in H_2O, mp 217-218°C) in 22% yield from **2**.

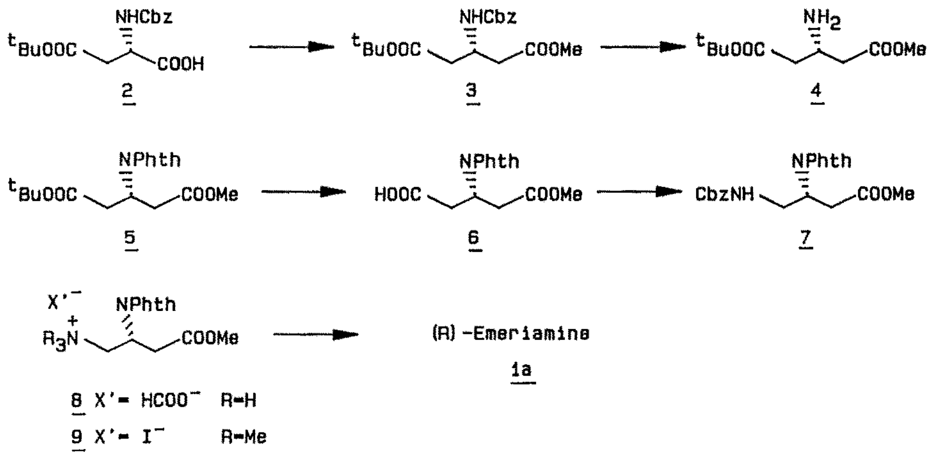
The enantiomeric purity of the final product was checked by HPLC analysis using O-phthalaldehyde and N-acetyl-L-cysteine as the chiral fluorescent derivatization reagent.[12] Chromatograms[13] show only a single peak corresponding to the (R)-enantiomer.

In order to prepare the (S)-isomer from the same starting material, we tried at first the basic hydrolysis of the methyl ester of **5** under different conditions, but unfortunately we obtained only a mixture of unidentified products.

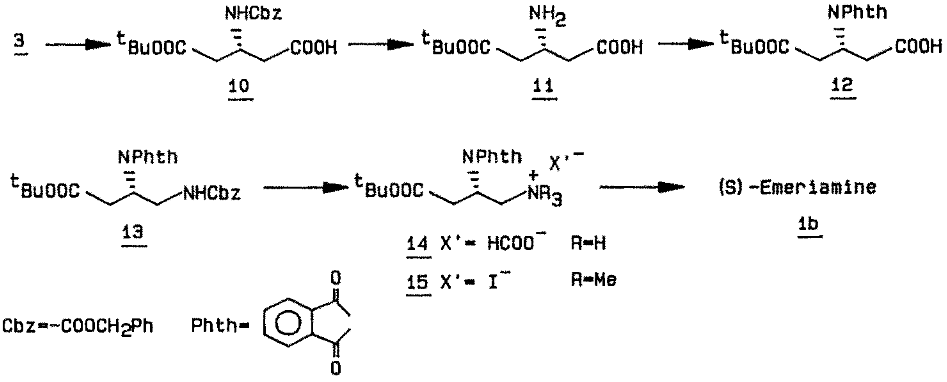
On the other hand, we succeeded by converting (NaOH 1N/MeOH, 0°C) **3** into the free acid **10** ($[\alpha]_D$ = -1.5, c = 5 in $CHCl_3$, mp 102- 103°C; Lit[14]: $[\alpha]_D$ = -1.3, c = 10 in $CHCl_3$, mp = 102-107°C) in 75% yield and then by hydrogenating **10** (H_2, Pd/C) to give **11** ($[\alpha]_D$ = +3.6, c = 1 in H_2O; Lit[14]: $[\alpha]_D$ = +3.3, c = 1 in H_2O) with a 80% yield. Compound **11** was then treated with the Nefkens reagent[9] and **12** ($[\alpha]_D$ = -4.65, c = 1 in MeOH) in 59% yield was achieved. So, when the monoacid **12** was subjected to the same reaction sequence utilized for the above (R)-enantiomer, compounds **13** ($[\alpha]_D$ = +11.3, c = 1 in MeOH), **14** ($[\alpha]_D$ = +17.1, c = 1 in H_2O, mp 226-227°C) and **15**,

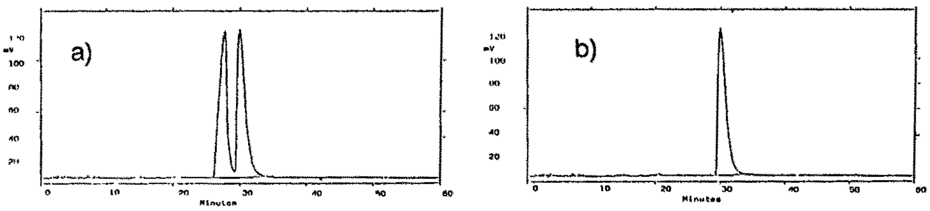


Scheme I



Scheme II





HPLC analysis of: a) R,S-emeriamine and b) R-emeriamine respectively, were prepared. Finally the (S)-enantiomer **1b** ($[\alpha]_D$ = -7.8, c = 1 in H_2O, mp 217-218°C; Lit[3]: $[\alpha]_D$ = -8.2, c = 1 in H_2O, mp = 214-216°C) was obtained in 25% overall yield by removing the protecting groups of the carboxylic and amino functions.

In conclusion, a stereoselective synthesis of both enantiomers of emeriamine has been elaborated through a judicious choose of the protecting groups and employing only the L-aspartic acid as starting materials.

Further applications of this strategy, for the synthesis of biologically active compounds are in progress.

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