THE CONVERSION OF L-GLUTAMATE TO L-TYROSINE

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The Diels Alder reaction of a glutamate derived dienophile with trans-1-methoxy-3-trimethylsilyloxy-1,3-butadiene affords a spirodienone. This, upon treatment with aqueous base leads to N-CBz-tyrosine. Optical activity is substantially maintained throughout the process.

Recently we have begun some investigations into the possibility of the chemical interconversions of α-amino acids.1 Our long term objective in this activity is to learn to achieve such transformations within the context of a polypeptide, thus possibly modifying its biological function.

Our first success in the more limited area of interconversions of α-amino acids was the synthesis of γ-carboxyglutamate from L-glutamate via the intermediacy of pyroglutamate.2 Below we wish to describe a more complex type of transformation, i.e. the conversion of L-glutamate to L-tyrosine.

For this purpose, we started with the readily available L-benzyl-N-CBz-pyroglutamate (1). We have previously described2 the smooth reaction of 1 with the Bredereck reagent, bisdimethylamino-tert-butoxymethane, to afford a nearly quantitative yield of 2. Hydrolysis of 2 with aqueous 1N HCl-THF afforded the hydroxymethylene lactam a.3 The latter was converted to an E:Z mixture of α-thiophenylmethylenelactam isomers 43,4 through the action of tri-n-butyolphosphone and diphenyl disulfide (THF, rt, 68% yield).5

\[
\begin{array}{c}
\text{X} = \text{H}_2 \\
\text{X} = \text{C(H)N(Me)}_2 \\
\text{X} = \text{C(H)OH}
\end{array}
\]

Oxidation of 4 with m-chloroperoxybenzoic acid in chloroform at -23° for 2.5 hr provided a
60% yield of diastereometric sulfoxides \( \text{S}_1 \), \( \text{S}_2 \) which were not routinely separated for use in the next step. Diels Alder reaction of \( \text{S}_1 \) with diene \( \text{D}_1 \) was accomplished by heating the mixture in benzene at reflux for 22.5 hr. Hydrolysis of the crude adduct with 2.5% acetic acid in ethyl acetate afforded, after silica gel chromatography, a 57% yield of crystalline spirodienone \( \text{P}_1 \), mp 109.5-111\(^\circ\)C, \( \left[ \alpha \right]_D = -19.8^\circ \) (C = 1.0, chloroform).

Treatment of \( \text{P}_1 \) with 2N sodium hydroxide in tetrahydrofuran (2 mmol of hydroxide:mmol of \( \text{P}_1 \)) for 24 hr followed by acidification of the derived basic material with 1N aqueous hydrochloric acid produced a nearly quantitative yield of N-CBz-tyrosine \( \text{G}_8 \), mp 92.5-94\(^\circ\), \( \left[ \alpha \right]_D = +9.0 \) (C = 0.7, acetic acid); natural mp 94-98\(^\circ\) \( \left[ \alpha \right]_D = +9.8^\circ \) (C = 0.5, acetic acid).

Proof of the optical purity of the synthetically derived \( \text{G}_8 \) was provided by its conversion to optically pure L-tyrosine methyl ester. This was accomplished by treatment of \( \text{G}_8 \) with an ethereal solution of diazomethane in methanol at 0\(^\circ\) followed by catalytic transfer hydrogenolysis \( \text{II} \) (10% Pd/C, 2:1 methanol/cyclohexene) of the derived methyl ester. There was thus obtained the relatively unstable amino ester. Examination of its \(^1H\) NMR spectrum (CDCl\(_3\), 270 MHz) in the presence of the lanthanide shift reagent, tris [3-(trifluoromethylhydroxymethylene)-d-camphorato] europium (III) showed the L-tyrosine methyl ester to be >95% enantiomerically pure.\(^\text{12} \)

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References:

1. For some simple examples from the literature see: (a) H. Monteiro, Synthesis, 1974, 137.


3. The structure of this compound is in accord with its 'H NMR, 1R, and MS data.

4. Along with the desired vinyl sulfides $\mathcal{A}$, there was isolated a 15.6% yield of the bis-sulfide
   resulting from a 1,4 addition of the thiophenol to $\mathcal{A}$.


6. We are unsure as to whether the diastereomeric relationship between the two separable iso-
   mers is due to the double bond stereochemistry, the diastereomeric sulfur atom, or both.


10. Natural N-CBz-tyrosine was obtained from Sigma Chemical Company.


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