THE CONVERSION OF L-GLUTAMATE TO L-TYROSINE

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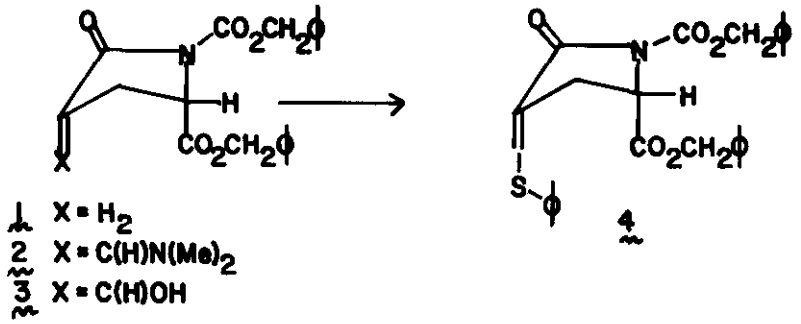
The Diels Alder reaction of a glutamate derived dienophile with trans-1-methoxy-3-trimethylsilyloxy-1,3-butadiene affords a spirodienone. This, upon treatment with aqueous base leads to N-CBz-tyrosine. Optical activity is substantially maintained throughout the process.

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 described[2] 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 hydroxymethylenelactam 3.[3] The latter was converted to an E:Z mixture of α-thiophenylmethylenelactam isomers 4[3,4] through the action of tri-n-butylphosphine and diphenyl disulfide (THF, rt, 68% yield).[5]



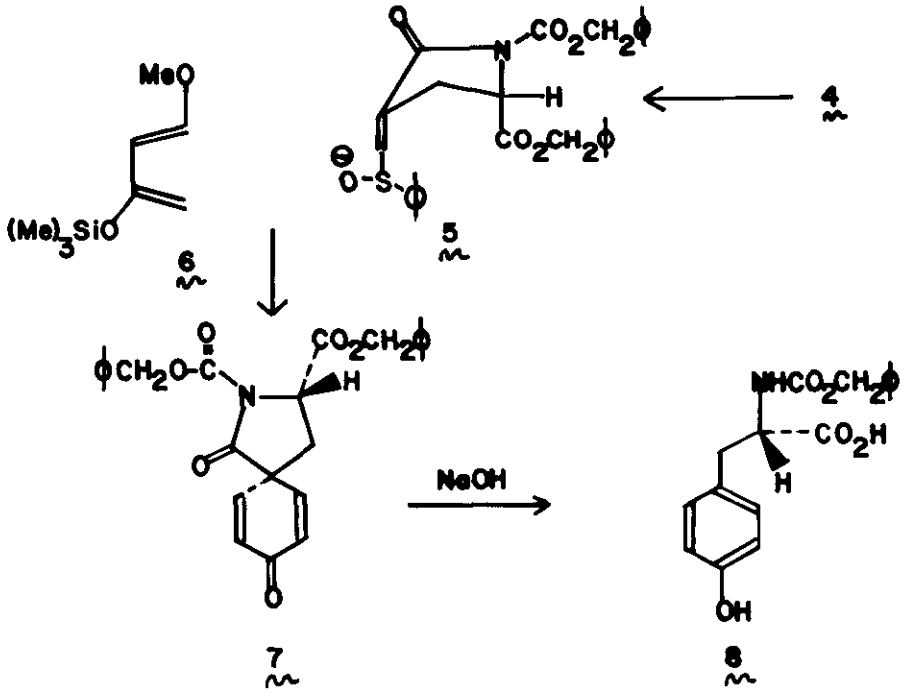
1 X = H_2
2 X = C(H)N(Me)$_2$
3 X = C(H)OH

4

Oxidation of 4 with m-chloroperoxybenzoic acid in chloroform at -23° for 2.5 hr provided a

60% yield of diastereometric sulfoxides 5,[3,6] which were not routinely separated for use in the next step. Diels Alder reaction of 5 with diene 6[7,8,9] 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 7,[3] mp 109.5-111°, $[\alpha]_D$ = -19.8° (C = 1.0, chloroform).

Treatment of 7 with 2N sodium hydroxide in tetrahydrofuran (2 mmol of hydroxide/mmol of 7) 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 8, mp 92.5-94°, $[\alpha]_D$ = $^{+}$9.0 (C = 0.7, acetic acid); natural[10] mp 94-98° $[\alpha]_D$ = $^{+}$9.8° (C = 0.5, acetic acid).



Proof of the optical purity of the synthetically derived 8 was provided by its conversion to optically pure L-tyrosine methyl ester. This was accomplished by treatment of 8 with an ethereal solution of diazomethane in methanol at 0° followed by catalytic transfer hydrogenolysis[11] (10% Pd/C, 2:1 methanol/cyclohexene) of the derived methyl ester. There was thus obtained the relatively unstable amino ester. Examination of its ^{1}H 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.[12]

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References:

1. For some simple examples from the literature see: (a) H. Monteiro, Synthesis, 1974, 137. (b) S. Yoshifuji, H. Matsumoto, K. Tanaka, Y. Nitta, Tetrahedron Lett. 1980, 2963.
2. S. Danishefsky, E. Berman, L.A. Clizbe, M. Hirama, J. Am. Chem, Soc. 1979, 101, 4385.
3. The structure of this compound is in accord with its 'H NMR, IR, and MS data.
4. Along with the desired vinyl sulfides 4, there was isolated a 15.6% yield of the bis-sulfide resulting from a 1,4 addition of the thiophenol to 4.
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6. We are unsure as to whether the diastereomeric relationship between the two separable isomers is due to the double bond stereochemistry, the diastereomeric sulfur atom, or both.
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10. Natural N-CBz-tyrosine was obtained from Sigma Chemical Company.
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