Tetrahedron Letters,Vol.30,No.32,pp 4211-4214,1989 0040-4039/89 $3.00 + .00
Printed in Great Britain Maxwell Pergamon Macmillan plc

FACILE CHEMICAL SYNTHESIS OF S,S-ISODITYROSINE, A NATURALLY-OCCURRING CROSS-LINKING AMINO ACID

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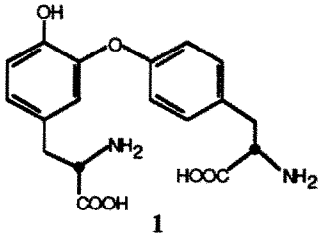
Abstract: Ullmann coupling of the two protected S-tyrosine derivatives **6** and **9** afforded the protected isodityrosine **10** which was converted into the natural bis-amino acid S,S-isodityrosine **1** in good yield.

In the early 1980's Fry[2] and Lamport[3] both isolated a new amino acid from plant cell wall glycoprotein (extensin), namely isodityrosine **1**.[2] This compound has been suggested to be the inter-polypeptide cross-link responsible for the insolubility of this glycoprotein. Later work by Fry has shown that the formation of isodityrosine **1** from tyrosine is a posttranslational event catalyzed by peroxidase isozymes.[4] The *o*-aryloxyphenol unit of isodityrosine and its derivatives (ring-halogenated, β-hydroxylated, etc.) appears in an ever-increasing



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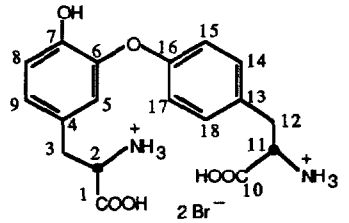
number of biologically active natural products,[5-10] including piperazinomycin,[5] bouvardin and deoxybouvardin,[6] K-13,[7] OF4949 I-IV,[8] RA I-VII,[9] and the large vancomycin class of antibiotics.[10] We report here a direct synthesis of S,S-isodityrosine **1** isolated as its bis-hydrobromide salt, and its spectral data.

Fry reported in 1984 that isodityrosine could be prepared in 1.8% yield by the oxidation of L-tyrosine in aqueous ammonia with potassium ferricyanide,[11] but offered no spectral data as proof of structure. This is still the only synthesis of isodityrosine although there has been a large amount of recent synthetic work on the more complex natural products derived from it. For example three groups have reported syntheses of some of these isodityrosine-derived natural products using as the key step the oxidation of 2,6-dibromo or -dichlorotyrosine with thallium trinitrate in methanol followed by zinc reduction.[12] In addition two other groups have reported syntheses in which the *o*-hydroxydiphenyl ether linkage was prepared by Ullmann-type chemistry.[13] We report herein a facile synthesis of S,S-isodityrosine **1** from S-tyrosine by a direct route utilizing an Ullmann diaryl ether synthesis.

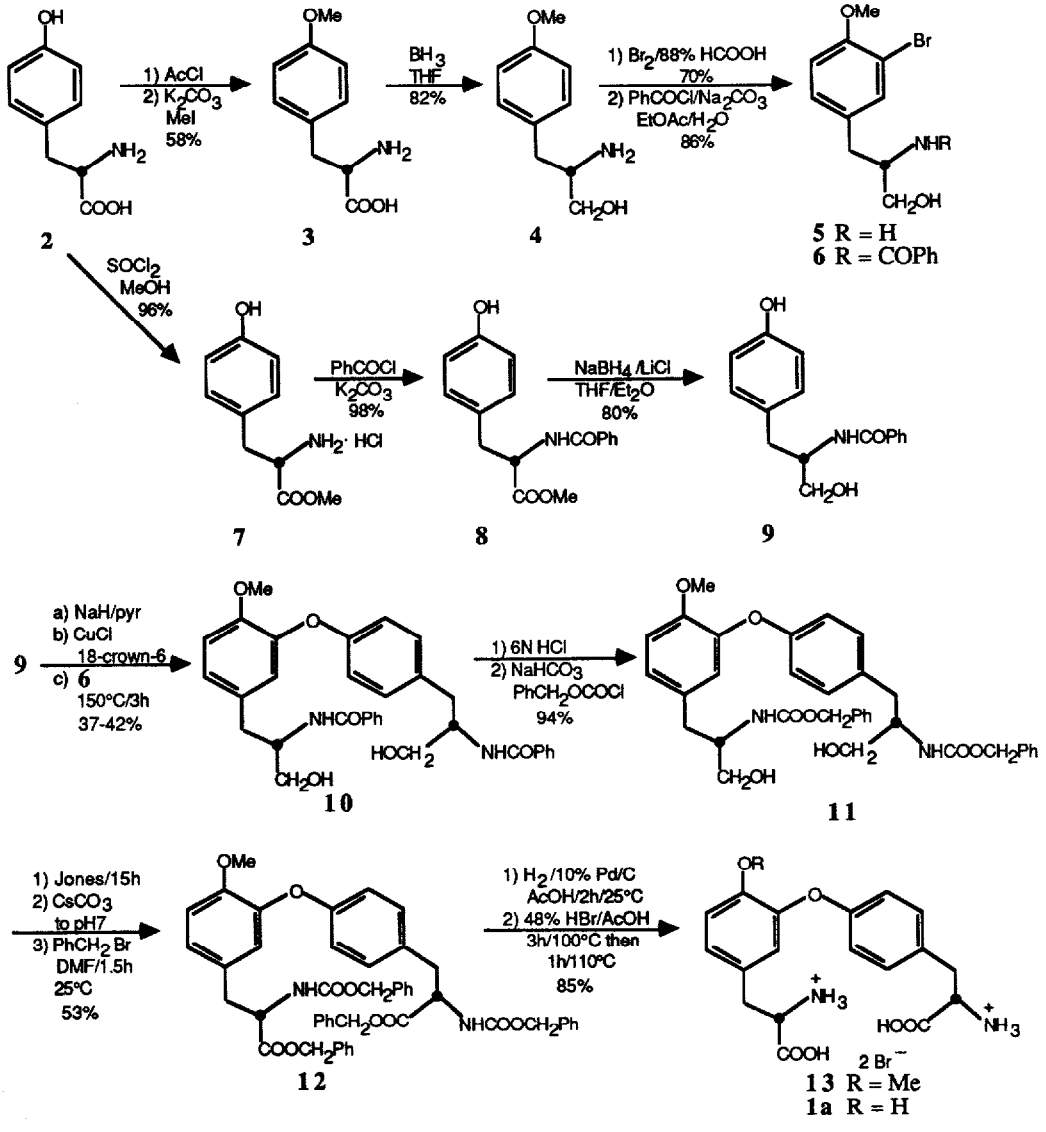
Conversion of S-tyrosine **2** into the two components for the Ullmann coupling, **6** and **9**, was straightforward. S-Tyrosine methyl ether **3** was prepared from **2** in two steps in 58% yield by the method of Clarke.[14] Reduction of the acid with borane in THF gave the crystalline amino alcohol **4** in 82% yield.

Bromination *ortho* to the methoxy group of **4** with bromine in 88% formic acid produced in 70% yield the crystalline bromo compound **5** which was benzoylated on the nitrogen under standard conditions to give the crystalline bromo hydroxy amide **6**. The other component **9** was prepared from **2** in three high-yielding steps, namely esterification to give the known methyl ester hydrochloride **7** (96%), N-benzoylation to afford **8** (98%), and finally lithium borohydride reduction to give the crystalline amido alcohol, N-benzoyl S-tyrosinol **9**. The crucial Ullmann coupling of these two components was carried out as follows: to the dried sodium phenoxide, prepared from **9** by treatment with sodium hydride in pyridine was added cuprous chloride, 18-crown-6, and dry pyridine; to this was added the aryl bromide **6** and the mixture heated in a 150°C oil bath for 3 h. Workup produced the crystalline diaryl ether **10** in yields ranging from 37-42%. Exchange of the benzoyl protecting groups for carbobenzoyloxy (CBZ) groups proceeded smoothly over two steps to give **11** in 94% yield. Jones oxidation of the primary alcohols to acids followed by esterification with benzyl bromide furnished the crystalline dibenzyl ester **12** in 53% yield. The final transformations in the synthesis of **1** were carried out without full purification of the intermediate bis amino acid. Hydrogenation over 10% palladium on charcoal in acetic acid at 25°C produced in good yield the completely debenzylated material **13**, which was isolated by filtration and evaporation and not purified further. This crude material was then subjected to demethylation with 48% hydrobromic acid in acetic acid for 3h at 100°C and 1h at reflux to give the dihydrobromide of isodityrosine **1a** in a yield of 85% for the last two steps. The spectroscopic data for **1a** is in full agreement with the assigned structure. 500 MHz proton NMR (D_2O): δ: 7.12 (2H, d, J=8.4 Hz, $H_{14, 18}$), 6.90 (2H, s, $H_{8, 9}$), 6.82 (2H, d, J=8.4 Hz, $H_{15, 17}$), 6.79 (1H, s, H_5), 4.11 (1H, dd, J=7.3, 5.5 Hz, H_2 or H_{11}), 4.05 (1H, dd, J=7.3, 5.5 Hz, H_2 or H_{11}), 3.15 (1H, dd, J=14.6, 5.5 Hz, H_3, $H_{3'}$, H_{12}, or $H_{12'}$), 3.05 (1H, dd, J=14.6, 7.3 Hz, H_3, $H_{3'}$, H_{12}, or $H_{12'}$), 3.03 (1H, dd, J=14.6, 5.5 Hz, H_3, $H_{3'}$, H_{12}, or $H_{12'}$), and 2.96 (1H, dd, J=14.6, 7.3 Hz, H_3, $H_{3'}$, H_{12}, or $H_{12'}$). 90 MHz carbon NMR (D_2O): δ: 182.2 (2), 157.9, 148.0, 144.4, 131.9 (2), 129.5, 127.9, 127.7, 123.3, 118.7, 118.3 (2), 56.1 (2), 35.8 (2). IR: 3100, 1740, 1600 cm^{-1}.



1a

In order to ascertain whether any racemization had occurred during the synthesis, we prepared the N-(S)-phenethyl urea of RS-tyrosine methyl ester and observed a reasonable splitting of the two methyl esters peaks at δ δ 3.64 and 3.58 in the 500 MHz proton NMR (the downfield peak is assigned to the urea from S-tyrosine methyl ester by its independent preparation and measurement). We then worked out conditions for the clean formation of the corresponding bis-urea from the bis-methyl ester of **1a** (prepared by treatment of **1a** with thionyl chloride and then methanol), namely treatment with S-phenethyl isocyanate and 1 eq of DMAP in acetonitrile. The 500 MHz proton NMR of this bis-urea showed only two peaks for the two methyl esters at δ 3.64 and 3.57, thus making it very unlikely that there was any racemization during the synthesis and therefore lending strong support that **1a** is optically pure.[15]



We have completed a direct total synthesis of S, S-isodityrosine dihydrobromide **1a** in 7 steps from the two tyrosinol derivatives **6** and **9** in an overall yield of approximately 18%. Further work on other biaryl couplings and on the synthesis of more complex natural products having isodityrosine units is underway.

Acknowledgement. We thank the National Institutes of Health (GM-31349) and Rhône-Poulenc for their generous support of this work.

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15. To guarantee that there was not accidental equivalence of both methyl esters peaks in the high-field NMR of the bis-urea, one would have to prepare the same derivative from the unavailable racemic isomer of **1a**. However, since racemization at either center would produce different diastereomers (and not enantiomers) and it is very unlikely that the shifts would be identical in all four diastereomers, we believe that this is strong evidence, but not proof, of the enantiomeric purity of **1a**.

(Received in USA 19 April 1989)