

ENANTIOSPECIFIC SYNTHESIS OF AMINO ACIDS: PREPARATION OF (*R*)- AND (*S*)- α -
METHYLASPARTIC ACID FROM (*S*)-TRYPTOPHAN

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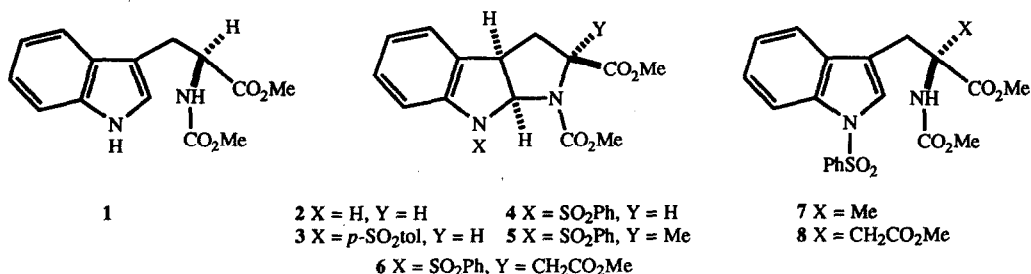
Summary: The enantiospecific synthesis of both antipodes of α -methylaspartic acid from (*S*)-tryptophan is described with the key steps being alkylation of the hexahydropyrroloindole **4**, oxidative degradation of indoles and, for the preparation of the (*R*)-isomer, Barton reductive decarboxylation.

The asymmetric synthesis of natural and unnatural non-proteinogenic amino acids is an area of considerable interest at the present time.¹ The α -disubstituted amino acids, in particular, are of interest owing to the increased lipophilicity² and increased resistance to exo- and endo-peptidases and to chemical hydrolysis³ that they confer on peptides into which they are included. α -Disubstituted amino acids are also known to stabilise helical domains in peptides⁴ and have found extensive use as enzyme inhibitors.⁵ In this laboratory we have developed an enantiospecific synthesis of α -substituted tryptophan derivatives from (*S*)-tryptophan. The underlying principle of our method is the alkylation, with clean retention of configuration, of the derived hexahydropyrrolo[2,3-b]indole **3**.^{6, 7} We report here on the extension of this tryptophan based methodology to the preparation of α -substituted aspartic acid derivatives as exemplified by the enantiospecific synthesis of both (*R*)- and (*S*)- α -methylaspartic acids, of interest owing to their ability to competitively inhibit aspartate amino transferase.⁸

As previously described, the (*S*)-tryptophan derivative **1** was converted in high yield to its cyclic tautomer (**2**).^{6, 9} by dissolution in 85% phosphoric acid at room temperature. Sulfonylation with benzenesulfonyl

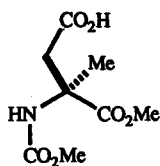
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chloride in pyridine then gave the sulfonamide **4**, as a single diastereoisomer, in 69% yield. The benzenesulfonamide (**4**) is preferred over the *p*-toluenesulfonamide (**3**), employed in our initial work, owing to its high degree of crystallinity which enables preparation of 50g batches without recourse to chromatography.^{10, 11} Deprotonation of **4** with lithium diisopropylamide in tetrahydrofuran under an inert atmosphere at -78 °C followed by treatment of the so-formed yellow enolate with methyl iodide gave the crystalline 2-methyl derivative (**5**) in 95% yield as a single diastereoisomer. Similarly, quenching of the enolate with methyl bromoacetate gave **6**, again as a single, crystalline, diastereoisomer in essentially quantitative yield. The assignment of relative configuration in **5** and **6** is greatly facilitated by the typical⁶ ¹H-nmr chemical shift of δ 3.05 for a C-2 CO₂Me on the *endo*-face of the diazabicyclooctane system, where it is shielded by the aromatic ring current. Stirring of **5** and **6** in trifluoroacetic acid at room temperature for 1h gave the corresponding tryptophan derivatives (**7**) and (**8**) quantitatively.

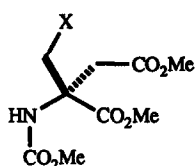


Oxidative cleavage of **7** was achieved, essentially as described for tryptophan containing dipeptides by Ranganathan,¹² by heating to reflux in aqueous acetonitrile with a 20 molar excess of sodium metaperiodate and 2 mole% of ruthenium trichloride trihydrate. After silica gel chromatography the (*S*)-aspartic acid derivative **9** was isolated in 64% yield. Application of the same procedure to **8** gave **10**, chiral simply by virtue of its differentially protected side chains, in 68% yield. The byproduct from this oxidative cleavage process was the sulfonamide **12**. We view this oxidation as proceeding via the kynurenine derivatives **13** with subsequent Baeyer-Villiger type cleavage of the aryl ketone, and hydrolysis of the so-formed aryl ester and formamide groups. We also wish to stress that the oxidation was operative on the *N*-sulfonylindoles, in contrast to the oxidations described by Ranganathan¹² in which the indoles were unprotected.

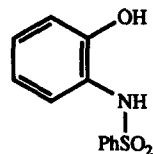
The acid **10** was decarboxylated, according to the Barton *O*-acyl thiohydroxamate protocol,¹³ by stirring in dichloromethane with triethylamine and reagent **14** followed by immediate *in situ* white light photolysis in the presence *t*-butyl mercaptan to give the (*R*)-aspartic acid derivative **11** in 83% yield.



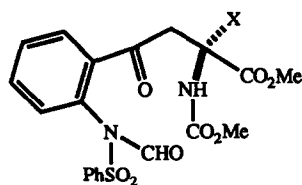
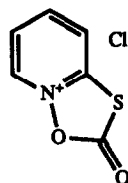
9



10 X = CO₂H
11 X = H

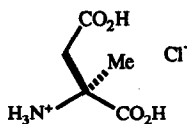


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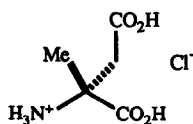
13 X = Me or CH₂CO₂Me

14

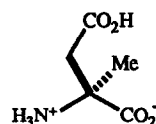
Finally, deprotection of **9** and **11** was achieved by heating to reflux for 1h in 6M hydrochloric acid giving the enantiomeric (*S*)- and (*R*)- α -methylaspartic acids (**15**) $\{[\alpha]_D = +33.5^0, (c = 1.54, \text{MeOH})\}$, and (**16**) $\{[\alpha]_D = -35.13^0, (c = 1.27, \text{MeOH})\}$ respectively in the form of their hygroscopic hydrochloride salts in excellent yield. The enantiomeric purity of **15** and **16** follows from the extreme propensity of **4** to undergo alkylation on its *exo*-face. For the purpose of comparison with literature data **15** was converted to the corresponding zwitterion (**17**) by ion exchange chromatography. The measured optical rotation of **17** $\{[\alpha]_D = +52.2, c = 0.45, \text{H}_2\text{O}\}$ corresponds well with literature values for samples obtained by asymmetric synthesis $\{[\alpha]_D = +55.3^0 (c = 0.67, \text{H}_2\text{O})\}$ for **17**¹⁴ and by partial synthesis from resolved material $\{[\alpha]_D = -52.9^0 (c = 0.68, \text{H}_2\text{O})\}$ for the enantiomer.¹⁵ The minor variations observed in optical rotations between samples are, almost certainly, a function of the difficulty in removing all traces of water from these somewhat hygroscopic substances.



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The methodology described in this communication makes possible the enantiospecific synthesis of many α -substituted aspartic acid derivatives from commercially available **4** and thence, by manipulation of the side chain

acid, of a wide range of α -disubstituted amino acids.

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