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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 lipophilicity[2] and increased resistance to exo- and endo-peptidases and to chemical hydrolysis[3] that they confer on peptides into which they are included. α-Disubstituted amino acids are also known to stabilise helical domains in peptides[4] 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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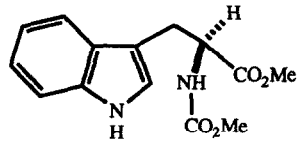
chloride in pyridine then gave the sulfonamide **4**, as a single diastereoisomer, in 69% yield. The benzenesulfonamide (**4**) is preferred over the *p*-toluenesulfonamide (**3**), employed in our initial work, owing to its high degree of crystallinity which enables preparation of 50g batches without recourse to chromatography.[10, 11] Deprotonation of **4** with lithium diisopropylamide in tetrahydrofuran under an inert atmosphere at -78 ^{0}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 typical[6] ^{1}H-nmr chemical shift of δ3.05 for a *C*-2 CO_2Me 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.



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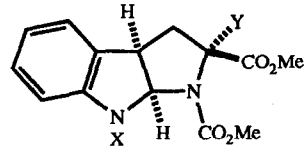
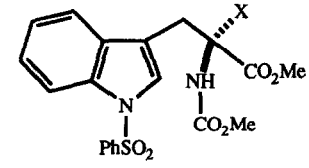


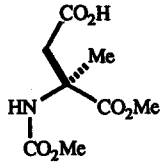
2 X = H, Y = H
3 X = *p*-SO_2tol, Y = H
4 X = SO_2Ph, Y = H
5 X = SO_2Ph, Y = Me
6 X = SO_2Ph, Y = CH_2CO_2Me



7 X = Me
8 X = CH_2CO_2Me

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 Ranganathan[12] 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.



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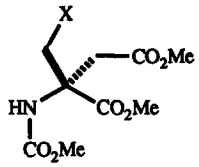
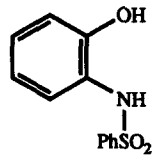


10 X = CO_2H
11 X = H



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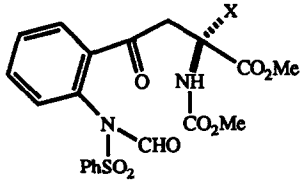
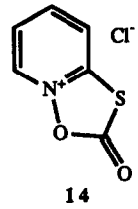


13 X = Me or CH_2CO_2Me



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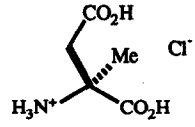
Finally, deprotection of **9** and **11** was achieved by heating to reflux for 1h in 6M hydrochloric acid giving the enantiomeric (*S*)- and (*R*)-α-methylaspartic acids (**15**) {$[\alpha]_D$ = +33.5^0, (c = 1.54, MeOH)}, and (**16**) {$[\alpha]_D$ = -35.13^0, (c = 1.27, MeOH)} respectively in the 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, H_2O) corresponds well with literature values for samples obtained by asymmetric synthesis {$[\alpha]_D$ = + 55.3^0 (c = 0.67, H_2O)} for **17**[14] and by partial synthesis from resolved material {$[\alpha]_D$ = - 52.9^0 (c = 0.68, H_2O)} 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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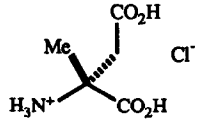

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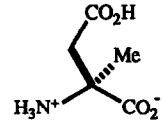

17

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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