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Asymmetric Amino Acid Synthesis: Preparation of the β Anion derived from Aspartic Acid

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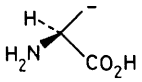
(*S*)-1-t-Butyl 4-methyl *N*-benzyloxycarbonylaspartate (**5a**), and (*S*)-1-t-butyl 4-allyl *N*-benzyloxycarbonylaspartate (**5b**) have been synthesized from (*S*)-aspartic acid (**2**), and can be readily alkylated and hydroxyalkylated at the β-carbon for asymmetric amino acid synthesis.

The non-proteinogenic α-amino acids are an important group of natural and unnatural products.[1] Their use in the determination of enzyme mechanisms,[2,3] and their biological properties,[2] have prompted many stereospecific syntheses.[4–6] Amongst these, the bis-lactim ether method of Schollkopf,[6] has already found applicability in the synthesis of a wide range of amino acids.

We recently reported a synthesis of γ,δ-unsaturated amino acids,[7] which proceeded from the γ-anion derived from (*S*)-glutamic acid.[8] In this paper, we report the preparation and reactions of a β-anion synthon (**1**) from (*S*)-aspartic acid.



(**1**)

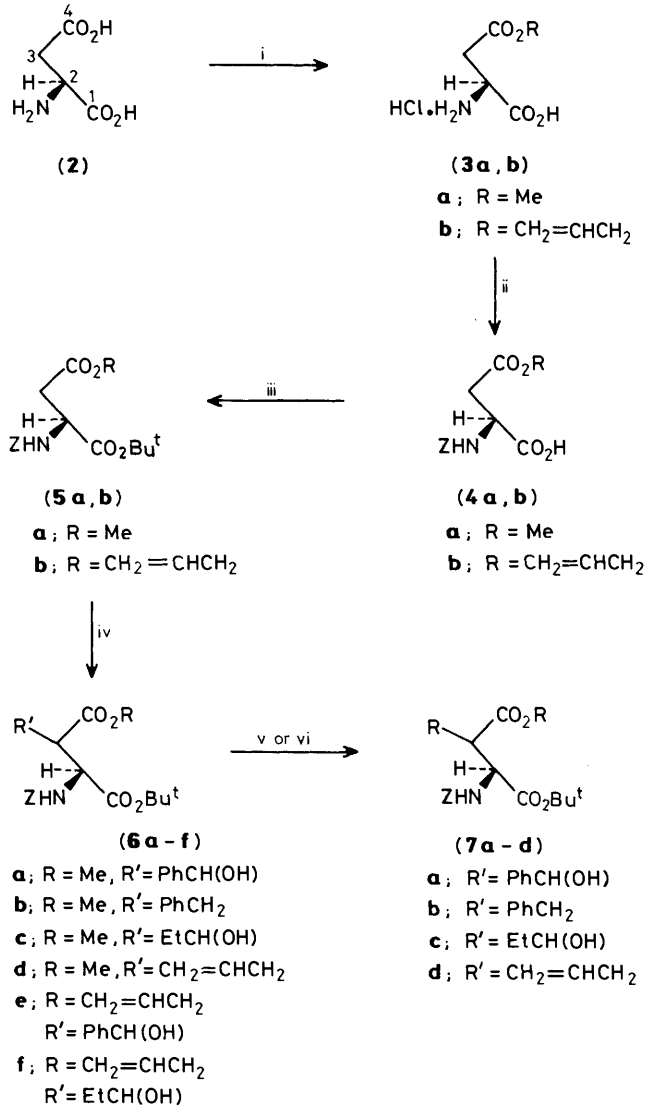
Two difficulties needed to be addressed in the preparation of this anion. These were β-elimination of the amine group,[9] and α-deprotonation.[10] Literature precedent[10,11] suggested that use of an amide or urethane group to protect the amine would prevent any β-elimination. It was hoped that the use of sterically hindered protecting groups and base would prevent α-deprotonation, as we had observed with the corresponding γ-anion from glutamic acid.[8]

The 4-methyl ester (**3a**), prepared from (*S*)-aspartic acid (**2**) in 95% yield by the method of Coleman,[12] was converted into the *N*-benzyloxycarbonyl derivative (**4a**) (benzyl chloroformate–potassium carbonate, 90%),[12] and thence into the 1-t-butyl ester (**5a**) (2-methylpropene–concentrated sulphuric acid),[13] in 80% overall yield (Scheme 1).

Treatment of aspartate (**5a**) with 2.2 equiv. of lithium diisopropylamide (LDA), or lithium hexamethyldisilazide (LHMDS) at −78 °C, warming to −30 °C, and recooling to −78 °C, followed by a range of electrophiles in tetrahydrofuran (THF) as solvent, gave the β-substituted adducts (**6a—d**)* in good yield (Table).

The optical integrity of C-2 in the alkylated products (**6**) was demonstrated by conversion of (**6a,b**) into the derived Mosher amides (**8a,b**). Thus hydrogenolysis of (**6a,b**) (5% Pd/C, 1 atm, EtOH, 2 h) gave the corresponding amines, which when treated with (*R*)-3,3,3-trifluoro-2-methoxy-2-phenylpropionyl chloride[14] and pyridine in $CDCl_3$ gave the amides (**8a,b**) (see Scheme 2). The corresponding racemic amides (**9a,b**) were also prepared from (*RS*)-aspartic acid as described for amides (**8a,b**).

The ^{19}F n.m.r. spectra of amides (**9a,b**) showed four peaks corresponding to the four epimers at C-2 and C-3. The ^{19}F n.m.r. spectra of amides (**8a,b**), which had been prepared using



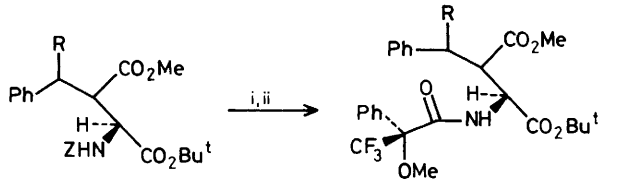
Scheme 1. *Reagents and conditions:* i, ROH–HCl; ii, $PhCH_2OCOCl$–K_2CO_3; iii, $CH_2{=}CMe_2/H_2SO_4$; iv, a LHMDS, b electrophile; v, LiOH–MeOH–H_2O; vi, $Pd(PPh_3)_4$–pyrrolidine

LDA as the base, also showed four peaks, and the enantiomeric excess was calculated as 80%. However, in the case of (**8a,b**) which had been prepared using LHMDS as the

Table. Products* and yields from the reaction of the aspartates (**5a,b**) with electrophiles

Diester	Electrophile	Product	Yield (%)	Diastereoisomeric ratio
(**5a**)	PhCHO	(**6a**)	50	1:1:0:0
(**5a**)	$PhCH_2Br$	(**6b**)	50	5:1
(**5a**)	EtCHO	(**6c**)	55	1:1:0:0
(**5a**)	CH_2=$CHCH_2Br$	(**6d**)	45	3:1
(**5b**)	PhCHO	(**6e**)	52	1:1:0:0
(**5b**)	EtCHO	(**6f**)	54	1:1:0:0

* All new compounds gave satisfactory analytical and spectroscopic data.



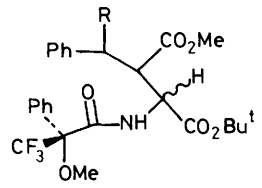
(**6a,b**) (**8a,b**)

a; R = OH **a**; R = OH

b; R = H **b**; R = H

Scheme 2. *Reagents and conditions:* i, 5% Pd/C, 1 atm H_2/EtOH; ii, (*R*)-Mosher's acid chloride–pyridine

base, only two peaks could be detected, one for each epimer at C-3. On this basis, it was concluded that using LHMDS as the base, no racemisation occurred in the synthesis of compounds (**6a**—**d**). The optical purity of adducts (**6a**—**d**) having been shown, an attempt was made to saponify selectively the 4-methyl ester. Whilst this was possible for the alkylated adducts (**6b,d**) (LiOH–MeOH–H_2O), the hydroxyalkylated adducts (**6a,c**) did not give the expected hydroxy acids (**7a,c**). Attempted cleavage of the methyl ester of (**6a,c**) under S_N2 conditions[15] (*e.g.* NaI–pyridine, or NaCN–HMPA) resulted only in cleavage of the benzyloxycarbonyl protecting group.



(**9a,b**)

a; R = OH

b; R = H

In order to avoid these problems, the differentially protected aspartic acid derivative (**5b**) was prepared. The allyl ester group was chosen both because of its chemical stability under the required reaction conditions,[16] and because it could be selectively cleaved by tetrakis(triphenylphosphine)palladium(0) and pyrrolidine.[17] The ester (**3b**)[18] was prepared in 95% yield by stirring (*S*)-aspartic acid (**2**) with allyl alcohol containing 1 equiv. of anhydrous HCl at room temperature for 18 h, and converted into the diester (**5b**) (Scheme 1). The aspartate diester (**5b**) could be hydroxyalkylated as described for the corresponding 4-methyl ester, giving the adducts (**6e,f**) (Table). Selective cleavage of the 4-allyl ester was achieved by treatment with tetrakis(triphenylphosphine)palladium(0), and pyrrolidine, giving the hydroxy acids (**7a,c**) in 70—80% yield.

The use of the aspartates (**5a,b**) in the synthesis of non-proteinogenic α-amino acids is currently under investigation and will be reported shortly.

Acknowledgements

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