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Preparation of enantiomerically enriched aromatic β-amino acids via enzymatic resolution

Susan J. Faulconbridge,[a] Karen E. Holt,[b] Luis Garcia Sevillano,[b] Christopher J. Lock,[a,*] Peter D. Tiffin,[a,†] Neil Tremayne [a] and Stephen Winter [b]

[a] *Celltech Chiroscience Ltd, Cambridge Science Park, Milton Road, Cambridge, CB4 0WG, UK*
[b] *Chirotech Technology Ltd, Cambridge Science Park, Milton Road, Cambridge, CB4 0WG, UK*

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Abstract

A range of enantiomerically enriched aromatic β-amino acids with high e.e. have been prepared via enzymatic resolution of ethyl ester derivatives. © 2000 Elsevier Science Ltd. All rights reserved.

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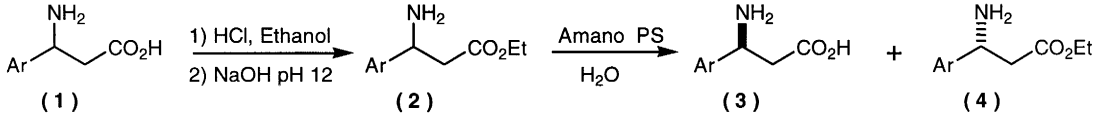
The preparation of enantiomerically pure β-amino acids for incorporation into medicinal chemistry programmes is an area of intense activity.[1] Given the facile synthesis of racemic compounds of type **1**[2] from the corresponding aromatic aldehyde we sought to develop an efficient biocatalytic resolution process based on a simple ester derivative **2** (Scheme 1).[3] Indeed, such an approach formed the basis of the first resolution of β-phenylalanine wherein the *N*-acetyl ethyl ester was resolved with α-chymotrypsin.[4] The slow rate (25% hydrolysis after 90 h), however, renders this process impractical.



Scheme 1.

In this letter we disclose the first simple resolution of aromatic β-amino esters, wherein the nitrogen atom is not protected.[5] Racemic amino acids **1** were readily converted into their ethyl ester hydrochloride salts by standard Fisher esterification. After basification to pH 12, the ester **2** was subjected to the action of a range of commercially available enzymes from which lipase Amano PS emerged as the most promising.

* Corresponding author.
† Present address: Chemical Synthesis Department, Roche Discovery Welwyn, Broadwater Road, Welwyn Garden City, Herts, AL7 3AY, UK.

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The influence of pH was found to have a pronounced effect on selectivity; with pH 8 being preferred. Thus, for example, racemic β-phenylalanine ethyl ester gave 73% e.e. amino acid at pH 7 and 99% e.e. amino acid at pH 8 at the same conversion. The stereochemical outcome of the reaction was determined by correlation of the $[\alpha]_D$ of the isolated β-phenylalanine with that reported in the literature.[6] Thus, the (*S*)-ester is preferentially hydrolysed.

This scaleable procedure is volume efficient (200 g/l) and allows access to both enantiomers of the amino acid in high e.e. and yield.[7]

We believe that the facile hydrolysis of the recovered starting material is an advantageous feature of the processes. The scope of the reaction was examined with respect to the tolerance of substituents in the aromatic ring and the results, at 50% conversion are summarised in Table 1.

Table 1

Ar	% Yield Acid (3)	e.e./% (i)	% Yield Ester (4)	e.e./% (i)
Ph	44	99	36 (ii)	98
2-BrPh	43	99	41	96
3-BrPh (iii)	44	77	42	74
4-BrPh	46	99	18 (ii)	99
4-FPh	13	91	46	90
1-Naphthyl	34	98	39	99

Notes: (i) By chiral HPLC or GC[8]; (ii) yield of amino acid after saponification and (iii) reaction performed on HCl salt.

In conclusion we have demonstrated the first simple bioresolution of aromatic β-amino esters using a commercially available lipase without the need for a nitrogen protecting group. From Table 1 it is apparent that the reaction is broadly applicable and allows easy access to both isomers.

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7. Typical procedure: Amano PS 18 g was added to a suspension of 3-amino-3-phenylpropionic acid ethyl ester 358 g (1.85 mol) in 50 mM KH_2PO_4 adjusted to pH 8.2 and the mixture stirred for 15 h. The resulting white precipitate was filtered and washed with acetone to yield (*S*)-3-amino-3-phenylpropionic acid 136 g (44% yield, 99% ee). The aqueous filtrate was basified to pH 9.5 and extracted with ethyl acetate. Evaporation gave (*R*)-3-amino-3-phenylpropionic acid ethyl ester which was saponified with sodium hydroxide to yield (*R*)-3-amino-3-phenylpropionic acid 109 g (36%, 98% ee).

8.

Compound/ Ar	Analytical method	Retention Times/min
Amino acids		
Ph	HPLC using Penicillamine: Methanol / 2mMCuSO$_4$ (5/95) 1ml/min	58.1, 69.1
2-BrPh	HPLC using chiralpak WH 5mM CuSO$_4$ at pH4.5 1ml/min	5.1, 7.4
3-BrPh	HPLC using chiralpak WH 5mM CuSO$_4$ at pH4.5 1ml/min	3.8, 5.8
4-BrPh	HPLC using Penicillamine: Methanol / 2mMCuSO$_4$ (5/95) 1ml/min	50.1, 58.6
4-FPh	Re-esterified then analysed by ester method below	10.8, 11.2
1-Naphthyl	Re-esterified then analysed by ester method below	24.05, 24.81
Amino esters		
Ph	Derivatised as trifluoroacetate GC using CP Chirasil L-valine: 100°C 10min then 10°C/min until 200°C 20psi	17.8, 18.0
2-BrPh	Saponified to amino acid	5.1, 7.4
3-BrPh	HPLC using Chiracel OJ: heptane/isopropanol/diethylamine (98/1.9/0.1) 1ml/min	
4-BrPh	Derivatised as trifluoroacetate GC using CP Chirasil L-valine: 100°C 10min then 10°C/min until 200°C 20psi	22.2, 22.4
4-FPh	Derivatised as acetate GC using CP Chirasil L-valine: 170°C 20psi	10.8, 11.2
1-Naphthyl	Derivatised as acetate GC using CP Chirasil L-valine: 200°C 20psi	24.05, 24.81