



Crystallisation Induced Resolution of 4-Fluorophenylglycine

Jonathan D. Moseley, Brian J. Williams,* Simon N. Owen and Hugh M. Verrier

Merck Sharp and Dohme Research Laboratories, Neuroscience Research Centre,

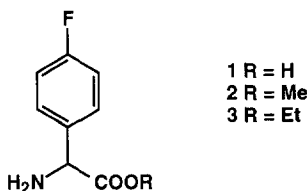
Terlings Park, Eastwick Road, Harlow, Essex, CM20 2QR. United Kingdom

Abstract: 4-Fluorophenylglycine **1** is resolved to 99.0% e.e. and 65% overall yield *via* its methyl ester **2** using a crystallisation induced resolution.

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Whilst working on our Substance P project we required large quantities of enantiomerically pure (*S*)-(+)-4-fluorophenylglycine **1** as a key intermediate.¹ Although both the racemate and the (*R*)-(-) enantiomer were commercially available the (*S*)-(+)-enantiomer was not, and so we decided to investigate methods suitable for a large scale resolution.

Persistent attempts to resolve **1** with camphor sulfonic acid (CSA), tartaric acid (TA) and dibenzoyl tartaric acid (DBT) gave only racemic salt mixtures. However, asymmetric syntheses *via* Strecker² or Evans oxazolidinone³ methodology did provide the initial material required for the project, but not in sufficient quantities to be synthetically useful. Both methods relied on multistep syntheses and inefficient separation of diastereomers by chromatography, and so were not amenable to scale-up. In the case of the Strecker synthesis, the valuable chiral auxiliary (phenyl glycinol) was also destroyed. We therefore investigated a crystallisation induced asymmetric transformation⁴ relying on the relative solubilities of the diastereomeric salt pairs to effect the resolution.



Attempts to resolve **1** by a crystallisation induced asymmetric transformation using (+) or (-)-CSA in propionic acid failed.⁵ Earlier work on the resolution of phenylglycinate esters⁶ indicated that the more readily racemised esters could be crystallised in the presence of TA to obtain enantiomeric enrichment. Under these conditions, addition of (+)-TA or (+)-DBT to methyl 4-fluorophenylglycine **2** in 1:1 ratio yielded only the racemate. However, slow addition of 0.25 equivalents of (+)-DBT⁷ to (\pm)-**2** in ethanol:water (7:1) to give a final concentration of 1.8-2.2 M yielded the hemi-DBT salt of (*S*)-**2** on cooling

to 5 °C in typically 94-96% e.e.⁸ The mother liquors enriched in the (*R*) enantiomer could then be racemised by heating to 40 °C with 10 mol. % benzaldehyde. Following filtration to remove traces of **1** that had formed, further (+)-DBT was added to achieve a final ratio of 4:1 **2**:(+)-DBT as determined by HPLC,⁹ and a second crop obtained on cooling. In this way, four to six crops¹⁰ of (*S*)-**2** could be obtained in 92-96% e.e. and up to 73% yield (~80% allowing for the recycling by hydrolysis of partially resolved **2** back to (±)-**1**).¹¹ The chiral auxiliary was readily recovered by ethereal extraction from 5.5 N HCl in quantitative yield with its stereochemical integrity intact. Ester (*S*)-**2** was hydrolysed by refluxing in 5.5 N HCl to yield (*S*)-**1** on cooling as its HCl salt in 99.0% e.e. and 85-93% yield.¹²

In summary, we report an efficient, large scale resolution of (*S*)-**1**.HCl¹³ to typically 99.0% e.e and in 65% overall chemical yield from (±)-**1**. This resolution relies on an *in situ* racemisation using benzaldehyde with the most technically demanding part of the resolution requiring only careful monitoring of the stoichiometry of the resolving agent and substrate by HPLC. Furthermore, the commercially available resolving agent can be recovered quantitatively at the end of each batch.

References and Notes

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8. All e.e.s were determined by chiral HPLC using a Crownpak CR(+) column, 150 mm x 4.0 mm i.d., 5 µm, eluting with 5% methanol in aqueous HClO₄ (pH 2) at 1.5 mL min⁻¹, oven temperature 40 °C, UV detection at 200 nm. Retention times for **1**, 2.0 and 4.7 mins. and for **2**, 5.3 and 11.2 mins. High R_s values (> 4.0) represent a high degree of enantioselectivity.
9. By integration of peak area, normalised for the UV chromophores using a PRP-1 C₈ column eluting with 5-95% acetonitrile in water at 1.0 mL min⁻¹, UV detection at 254 nm.
10. Formation of ethyl ester (**3**) by transesterification and racemic amino acid **1** by hydrolysis precluded further racemisation cycles.
11. Material of less than 90% e.e. could not be recrystallised to higher e.e.s and had to be recycled by acidic hydrolysis back to the racemic amino acid **1**.
12. Satisfactory spectroscopic (nmr, m/z) and physical analyses (HPLC, elemental analysis, m.p.) were obtained on all intermediates.
13. Zwitterionic (*S*)-**1** could be precipitated from an aqueous solution by neutralisation with concentrated ammonia in effectively quantitative yield and with a further enhanced e.e. of 99.9%.⁸