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A crystallization-induced asymmetric transformation to prepare (*R*)-4-chlorophenylalanine methyl ester

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Abstract

A second order asymmetric transformation of racemic 4-chlorophenylalanine methyl ester was achieved via salt formation with (2*S*,3*S*)-(−)-tartaric acid in the presence of salicylaldehyde to afford the desired (*R*)-enantiomer of 4-chlorophenylalanine methyl ester in good yield and high enantiomeric purity.

1. Introduction

p-Chlorophenylalanine is of considerable pharmacological interest, particularly in regards to its ability to inhibit serotonin formation in the tissue of laboratory animals.[1–3] The (*R*)- and (*S*)-enantiomers are used in synthesizing biologically active compounds that often achieve important antagonistic effects.[4–7]

Over recent years, numerous syntheses of 4-chlorophenylalanine and its derivatives have been reported. These diverse approaches exemplify the advances in asymmetric synthesis prompted by the need for single enantiomers of unnatural and unusual amino acids.[8] In particular, 4-chlorophenylalanine was synthesized by O'Donnell using enantiomeric phase transfer catalyzed alkylation of a glycine imine.[9]

Another well-executed approach is the asymmetric reduction of the appropriate dehydroamino acid derivative.[10] When a source of the racemic compound is readily available, as is the case for 4-chlorophenylalanine, enzyme-based kinetic resolution is an attractive alternative for generation of gram to multi-gram quantities of the optically active amino acid derivative. Indeed, workers have used both carboxypeptidase A mediated *N*-deacylation[11,12] and α-chymotrypsin mediated hydrolysis of esters[13,14] to gain access to both enantiomers of 4-chlorophenylalanine. A disadvantage of resolutions, of course, is the maximal yield of 50% unless a suitable method for racemization of the undesired enantiomer is also developed.

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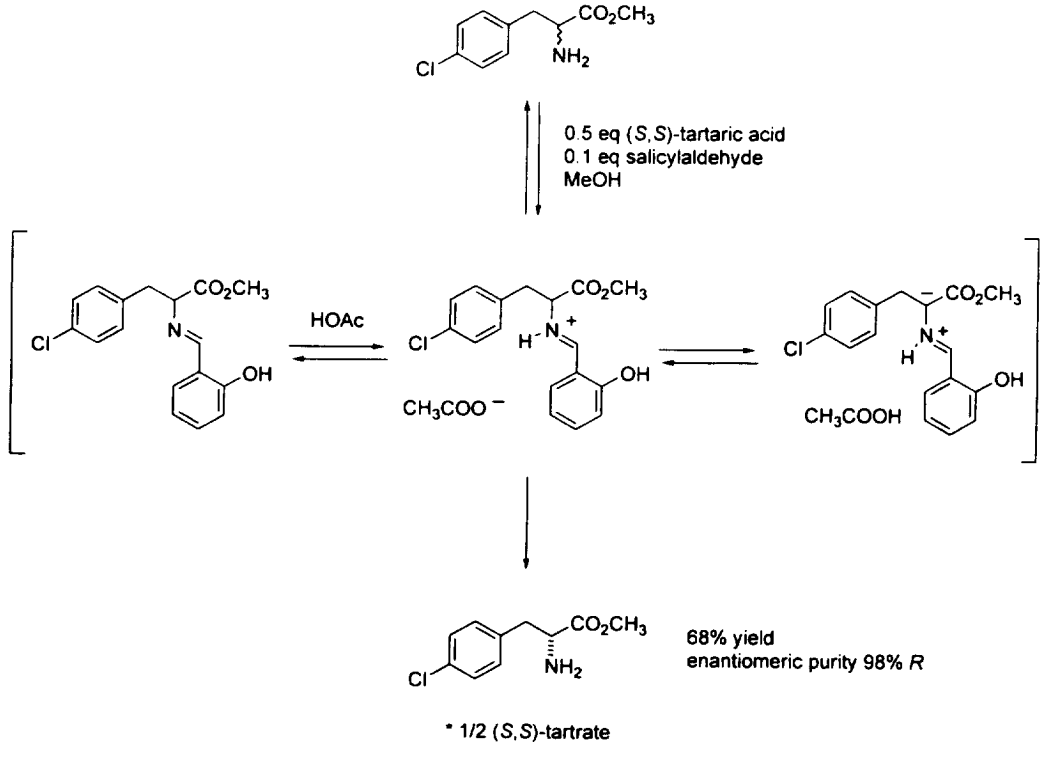
Faced with the need to synthesize a pseudo peptide target containing the *R*-enantiomer of 4-chlorophenylalanine as one 'residue', and given the ready synthetic availability of 4-chlorophenylalanine methyl ester, we elected to examine a classical resolution through a diastereomeric salt as a first approach. Then, with a suitable classical resolution identified, a means for recycling (through racemization) the undesired (*S*)-enantiomer was developed. Eventually, (*R*)-4-chlorophenylalanine methyl ester was synthesized via a one-pot resolution–racemization sequence, to give what is termed a crystallization-induced asymmetric transformation.[15,16]

2. Results and discussion

Resolution of (*RS*)-4-chlorophenylalanine methyl ester (free base) using (−)-tartaric acid afforded the diastereomeric (*R*)-4-chlorophenylalanine methyl ester (−)-tartrate salt (the ratio of free base:tartaric acid in the salt was 2:1) in 32% yield and in 94.0% ee. Although diastereomeric resolution provides a route to (*R*)-4-chlorophenylalanine methyl ester, the inherent loss of the undesired enantiomer is a significant drawback. This limitation was overcome by incorporating an in situ racemization with a classical resolution. Thus reacting (*RS*)-4-chlorophenylalanine methyl ester with one equivalent of (−)-tartaric acid and a catalytic amount of salicylaldehyde in refluxing methanol effected resolution, providing the (*R*)-amine methyl ester (−)-tartrate (2:1) in 68% yield (98% ee).



Scheme 1.

The mechanism of racemization of amino acids and derivatives under the influence of aldehydes is generally known to involve formation of an imine (Schiff base)[17,18] followed by a reversible 1,2-proton shift, generating a 1,3-dipolar species as shown in Scheme 1. The presence of (−)-tartaric acid provides

a crystalline salt that is essentially removed from the system by virtue of its insolubility, driving the equilibrium.

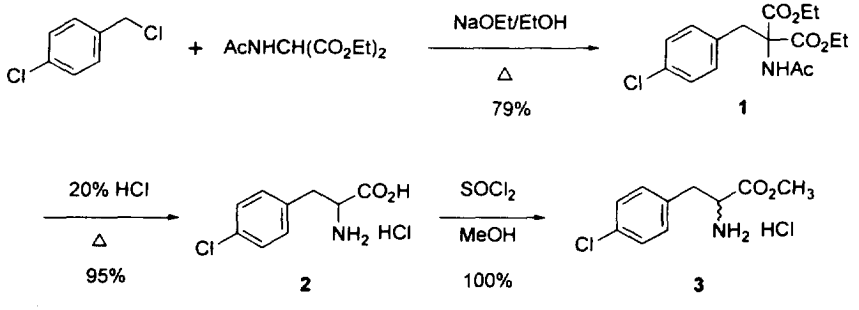
3. Conclusion

In conclusion, a crystallization-induced asymmetric transformation of racemic 4-chlorophenylalanine methyl ester was developed to provide a convenient and practical route to enantiomerically enriched (*R*)-4-chlorophenylalanine methyl ester via a (−)-tartaric acid mediated classical resolution and a salicylaldehyde catalyzed racemization.

4. Experimental

4.1. General

Racemic 4-chlorophenylalanine methyl ester hydrochloride was prepared from 4-chlorobenzyl chloride using the acetamidomalonate route reported by Porter et al.[12] followed by conversion to the methyl ester with thionyl chloride/methanol[13] (Scheme 2).



Scheme 2.

Enantiomeric purity of 4-chlorophenylalanine methyl ester was determined as the *N*-trifluoroacetyl derivative by GC using a Hewlett Packard 5890 gas chromatograph fitted with a Chirasil-L-Val (Chrompack) column 25 m×0.25 mm; helium carrier gas at 140 kPa; temperature isothermal @ 160°C; injection 1 μl of a 2 mg/mL EtOAc solution; temperature 200°C; FID detection at 230°C; retention time: (*R*)-enantiomer 3.90 min, (*S*)-enantiomer 4.09 min.

Preparation of *N*-trifluoroacetyl-4-chlorophenylalanine methyl ester (for analysis by enantiomeric GC). To a mixture of 1 mL of diethyl ether and 1 mL of 50% aqueous K_2CO_3 was added 3 mg of 4-chlorophenylalanine methyl ester tartrate. After shaking and separating the layers, the organic layer was evaporated in a stream of nitrogen and 1 mL of trifluoroacetic anhydride was added. Stirring was continued for 10 min, followed by evaporation in a stream of nitrogen. The residue was dissolved in EtOAc (1.5 mL).

4.2. Classical resolution of (RS)-4-chlorophenylalanine methyl ester from methanol

(*RS*)-4-Chlorophenylalanine methyl ester hydrochloride (10.0 g, 40.0 mmol) was dissolved in water (30 mL), to which was added K_2CO_3 (10.0 g, 72.0 mmol). The solution was extracted with diethyl ether (2×50 mL). The organic layer was separated and dried with K_2CO_3, then the solvent was removed

in vacuo. The resulting free base residue (7.28 g, 34.1 mmol) was dissolved in methanol (50 mL) and a solution of (2*S*,3*S*)-(−)-tartaric acid (5.11 g, 34.0 mmol) in warm methanol (ca. 50°C, 50 mL) was added. The mixture was cooled to ambient temperature, filtered and washed with methanol (2×30 mL), then air dried to give 3.94 g (32%) of (*R*)-4-chlorophenylalanine methyl ester (−)-tartrate (2:1), enantiomeric purity 94%.

4.3. Crystallization-induced asymmetric transformation of (RS)*-4-chlorophenylalanine methyl ester*

(*RS*)-4-Chlorophenylalanine methyl ester (20.0 g, 96.0 mmol, prepared from the hydrochloride as described above) was combined with (2*S*,3*S*)-(−)-tartaric acid (7.20 g, 48.0 mmol), salicylaldehyde (1.17 g, 10 mmol) and methanol (300 mL). The mixture was refluxed overnight and allowed to cool to ambient temperature. The resulting solid was filtered, washed with methanol (2×30 mL) and air dried to give 18.82 g (68%) of (*R*)-4-chlorophenylalanine methyl ester (−)-tartrate (2:1), enantiomeric purity 98%.

4.4. (R)*-4-Chlorophenylalanine methyl ester*

To a solution of potassium carbonate (3.0 g, 10 mmol) in distilled water was added (*R*)-4-chlorophenylalanine methyl ester (−)-tartrate (2:1), enantiomeric purity 96% (prepared as described above) followed by the addition of dichloroethane (25 mL). After complete solution the layers were separated and the aqueous layer was extracted with dichloroethane (3×25 mL). The combined organic layer was dried over potassium carbonate, filtered and concentrated under reduced pressure to give 2.14 g (96%) of the free base, (*R*)-4-chlorophenylalanine methyl ester, as a colorless oil.

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