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Process for the preparation of 2-(*S*)-piperazinecarboxylic acid by continuous resolution via diastereomeric salt pairs †

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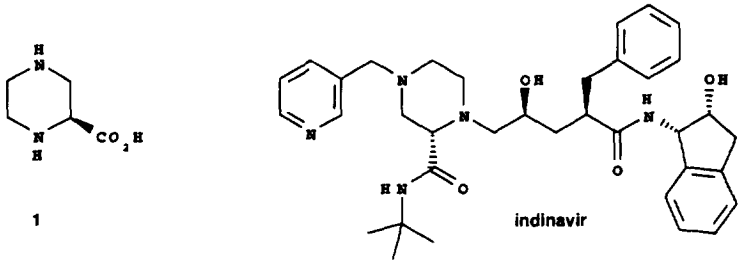
Abstract: Continuous resolution of 2-piperazinecarboxylic acid **2** with (*S*)-camphor-10-sulfonic acid as resolving and epimerisation agent affords 2-(*S*)-piperazinecarboxylic acid (*S*)-dicamphor-10-sulfonate **3** in 62% isolated yield and >99% ee. © 1997 Elsevier Science Ltd

Optically active amino acids and derivatives have generated widespread interest in various areas, especially in the agrochemicals (as herbicides, insecticides, fungicides), food (as peptide sweeteners), and pharmaceutical industries (as infusion solutions or therapeutic agents). During the last decade, non-proteinogenic amino acids, and derivatives thereof, have received particular attention in the synthesis of biologically active compounds. One example is 2-(*S*)-piperazinecarboxylic acid **1**, because its *N*-*tert*-butyl amide is an important intermediate in the preparation of Merck HIV protease inhibitor indinavir (Crixivan®)[1] (Scheme 1).



Scheme 1.

Simple resolution of the racemate **2** via formation of diastereomeric salt pairs has been reported by Felder[2] using (*S*)-camphorsulfonic acid [(*S*)-CSA] as the resolving agent.

However, the general disadvantage of this classical resolution technique is a maximum chemical yield of 50% and if the undesired enantiomer cannot be used elsewhere it is desirable to find a racemization method.

In the case of amino acids, racemization can be achieved by heating of an aqueous amino acid solution with catalytic amounts of carbonyl compounds,[3] aldehydes in the presence of metal ions under alkaline conditions,[4] as well as by heating in water under pressure,[5] in strong acids and bases[6] or with aliphatic carboxylic acids[7] (Scheme 2).

In this paper, we present a highly efficient method for a continuous preparation of 2-(*S*)-piperazinecarboxylic acid (*S*)-dicamphor-10-sulfonate **3** using (*S*)-camphor-10-sulfonic acid as both resolving and epimerising agent.

† Dedicated to Dr Herbert Tanner (Degussa AG, R&D) on the occasion of his 60th birthday.
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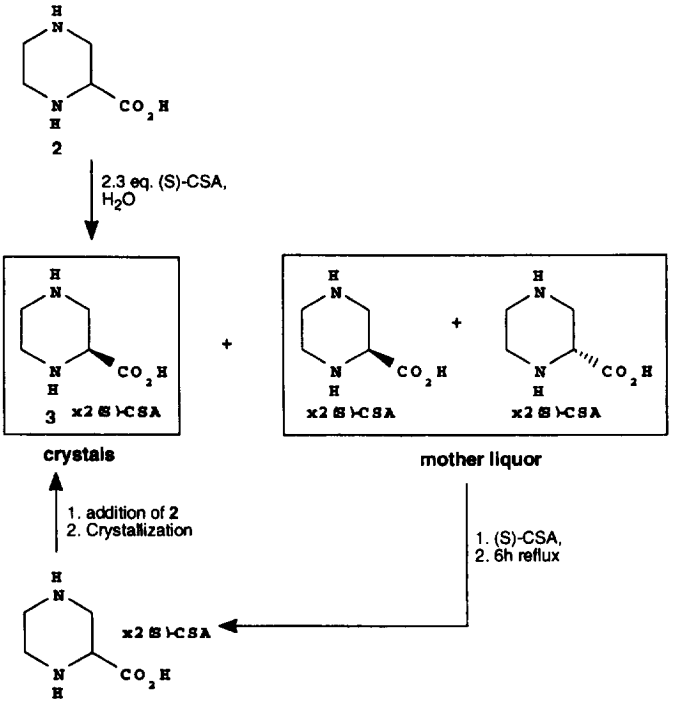

Scheme 2.

Table 1.

Epimerisation of (*R,S*)-3

reaction time [h] for epimerisation of the mother liquor	de* of (R,S)-3 in the mother liquor
0	32%
1	30%
2	22%
3	18%
4	14%
5	11%
6	8%

* de : diastereomeric excess[8]

For crystallization of the (*S,S*)-salt pair **3**, we used the method of Felder and coworkers.[2] The racemate **2** and the resolving agent (*S*)-CSA were dissolved in water at 70°C. After keeping the solution at room temperature for 16 h, we obtained the desired diastereomeric (*S,S*)-salt **3** as well-grown crystals in high diastereomeric excess (>99%) whereas, owing to its higher solubility, the 2-(*R*)-piperazinecarboxylic acid 2-(*S*)-CSA salt pair remained in the mother liquor. The same amount of (*S*)-CSA as was isolated as crystalline (*S,S*)-salt pair **3**, was added to the mother liquor. After heating the mother liquor for an additional 6 h at reflux temperature, we found almost essentially complete racemization of the 2-(*R*)-piperazinecarboxylic acid[8] (see Table 1). The enantiomeric purity of the resolving agent remained unchanged.

Consequently, selective crystallization of the (*S,S*)-isomer **3** and racemization of the undesired (*R*)-

Table 2. Yield and de of **3** from six consecutive crystallisation–epimerisation sequences

Sequence 1-6	Chemical yield [%] of 3	de* of 3 [%]
1	24	>99.0
2	21	99.0
3	20	99.0
4	24	>99.0
5	21	>99.0
6	21	>98.5

*de: diastereomeric excess[8]

enantiomer of the amino acid can be performed in one pot with the same reagent. This is particularly favorable for a large scale application.

In continuation of our process, racemate **2** was added to the epimerized mother liquor at 70°C. After cooling the solution, we obtained a second crop of diastereomerically pure product **3**. This process, i.e. crystallization, epimerization, and repeated crystallization was performed six times (Table 2).

During these sequences, no significant decrease in chemical yield or diastereomeric excess of salt **3** was observed. Overall chemical yield of **3** in runs 1–6 was 62%.[9]

Recovery of the resolving agent (97% yield) and isolation of the enantiomerically pure 2-(*S*)-piperazine carboxylic acid **1** (97% yield, >99% ee) can easily be done by ion exchange chromatography.[10]

In summary, we have developed an efficient process for the synthesis of the enantiomerically pure 2-(*S*)-piperazinecarboxylic acid **1**.[11] The key step of the procedure is a continuous resolution of the corresponding racemate **2** using (*S*)-CSA as resolving and epimerization agent. This method provides a practical route for the economical production of 2-(*S*)-piperazinecarboxylic acid **1**. Further optimization is in progress.

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8. The diastereomeric excess (de) of **3** was determined by chiral HPLC; column: chiral-Si-100 L-Pro-Cu; Serva, Heidelberg, No. Z 42306; eluent: 10 mmol $CuSO_4$/100 mL H_2O.
9. *Typical experimental procedure:* To a stirred solution of racemate **2** (29.3 g, 225 mmol) in 170 mL of water 2.3 eq. of (*S*)-camphor-10-sulfonic acid (120.3 g, 518 mmol) were dissolved at 70°C. This solution was kept at room temperature, seeded with crystals of (*S*)-piperazine carboxylic acid (*S*)-dicamphorsulfonate **3** and gently stirred for 16 h. The first crop of crystals was quickly collected by filtration, washed with 20 mL of ethanol (important: do not combine the mother liquor with the washing ethanol), and dried to give **3** (32.7 g, 24%), >99% de (see ref. 8). 25.6 g (*S*)-CSA were dissolved in the aqueous mother liquor and refluxed for 6 h. Subsequently, additional 7.15 g

of racemate **2** were dissolved at 70°C and the solution cooled down to room temperature. Within 16 h a second crop of crystals [27.8 g (21%), >99% de] was isolated in the same way. This cycle, i.e. racemization and crystallization, has been repeated an additional four times: 3rd crop: 27.0 g (20%), >99% de; 4th crop: 32.5 g (24%), >99% de; 5th crop: 27.8 g (21%), >99% de; 6th crop: 27.8 g (21%), >98.5% de. After these six cycles, the overall yield of **3** was 62%. Spectral data for **3**: ^{1}H-NMR (500 MHz, d_6-DMSO) δ=0.78 (s, 6H), 1.03 (s, 6H), 1.27–1.39 (m, 4H), 1.81–1.92 (m, 4H), 1.97 (m, 2H), 2.22–2.28 (m, 2H), 2.47–2.52 (m, 4H), 2.58–2.63 (m, 2H), 2.95 (d, 2H), 3.17–3.37 (m, 3H), 3.51–3.58 (m, 2H), 3.74 (dd, 1H), 4.41 (dd, 1H), 9.52 (m, 5H).

10. *A typical experimental procedure*: A solution of **3** (71.4 g, 120 mmol) in 300 mL of water was passed over a cation exchange resin (Amberlite IR 120®, 480 mL). After neutral washing of the exchanger, the combined eluates were evaporated to dryness. The residual was collected, washed with a small amount of ice water, dried (54.1 g, 97%) and analyzed as optically pure (*S*)-CSA, $[\alpha]^{20}_D$=20.4 (c=10, H_2O). Subsequently, the resin was washed with diluted aqueous ammonia and water. The combined eluates were evaporated to dryness, the residual solid dissolved in a small amount of water and crystallized by adding ethanol to the stirred solution at 5°C. The precipitated crystals were collected by filtration and dried at 60°C to yield 15.14 g (97%) of enantiomerically pure **1** (>99% ee, see ref. 8).
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