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Synthesis of *N*-benzyl-3-(*S*)-(+)-(4-fluorophenyl)-1,4-oxazin-2-one via a crystallisation induced asymmetric transformation

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Abstract: The simple and efficient preparation of enantiomerically pure *N*-benzyl-3-(*S*)-(+)-(4-fluorophenyl)-1,4-oxazin-2-one by a crystallisation induced asymmetric transformation of its racemate is reported. A key feature of this process is the use of [(1*S*)-(endo,anti)]-(−)-3-bromocamphor-8-sulfonic acid as both resolving agent for the pure (*S*)-enantiomer, and *in situ* racemising agent of the unwanted enantiomer, affording the title compound in high yield. © 1997 Elsevier Science Ltd. All rights reserved.

We recently required *N*-benzyl-3-(*S*)-(+)-(4-fluorophenyl)-1,4-oxazin-2-one (*S*)-**5** as a key intermediate in the synthesis of Substance P (neurokinin-1) receptor antagonists.[1] This intermediate was initially synthesised from (*S*)-(+)-4-fluorophenylglycine by a two step process[1,2] which required strict control of the process parameters to prevent racemisation. In addition, the process suffered from the fact that (*S*)-(+)-4-fluorophenylglycine was not readily available, being prepared either by multi-step asymmetric syntheses,[1,3,4] or via a resolution process.[5]

In this communication we report an efficient crystallisation induced asymmetric transformation[6] of the racemic oxazinone (*RS*)-**5** affording enantiomerically pure *N*-benzyl-3-(*S*)-(+)-(4-fluorophenyl)-1,4-oxazin-2-one (*S*)-**5** in high yield.[7]

Racemic oxazinone (*RS*)-**5** was prepared in 68% yield from 4-fluorobenzaldehyde **1** via a modified Strecker reaction,[8] hydrolysis[9] of the resultant aminonitrile **2**, and subsequent alkylation with 1,2-dibromoethane[2] (Scheme 1). Resolution at this point has the advantage that optical purity is introduced at the last stage of the synthesis, after the cyclisation step. *In situ* resolution-racemisation would also offer the potential of a 100% conversion to the (*S*)-(+)-oxazinone.

Resolution was achieved with [(1*S*)-(endo,anti)]-(−)-3-bromocamphor-8-sulfonic acid **6** ((−)-BCSA).[10,11] Treatment of racemic oxazinone with 1.3 equivalents of (−)-BCSA at ambient temperature resulted in a 27% yield of (*S*)-(+)-oxazinone-(−)-BCSA salt with 88% e.e.[12] Recrystallisation from dimethylformamide/*iso*-propyl acetate gave material of 99% e.e. in 88% recovery.

Combination of the resolution process with *in situ* racemisation of the undesired enantiomer (*R*)-**5** would give a dynamic *in situ* resolution-racemisation process,[13] and realise our goal of an efficient synthesis of (*S*)-**5**. (*S*)-(+)-Oxazinone had been observed to be susceptible to racemisation under acidic conditions, and complete racemisation of the (*S*)-(+)-oxazinone was achieved in glacial acetic acid after one hour at 50°C. It proved more difficult to obtain an ideal combination of a fast racemisation rate in a reaction medium in which the (*S*)-**5**-(−)-BCSA salt had low solubility. For example, a 1:4 mixture of acetic acid:*iso*-propyl acetate at 50°C afforded (*S*)-(+)-oxazinone-(−)-BCSA salt with 96% e.e. in only 25% yield, whilst 3 vol% trifluoroacetic acid in *iso*-propyl acetate required 5–7 days to reach a 90% yield and 98% e.e. The most promising results were achieved using an excess of (−)-BCSA itself as the racemising agent in an *in situ* resolution/racemisation process (Scheme 2). Initial

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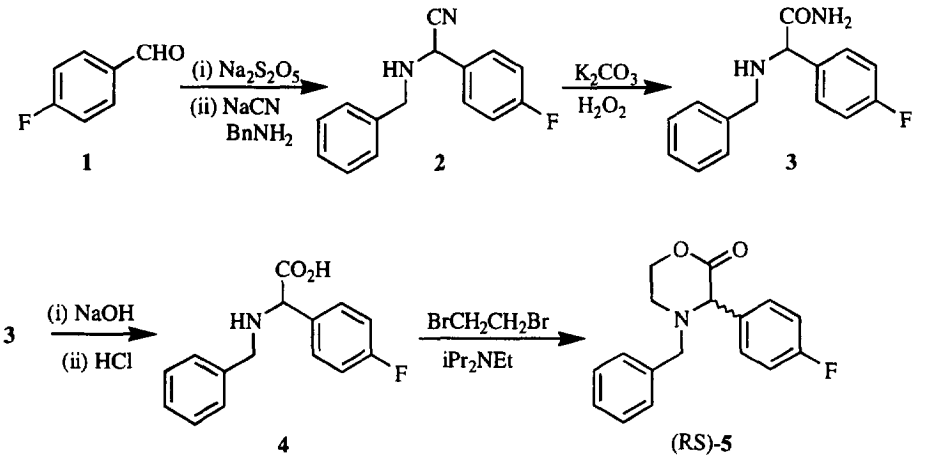


Scheme 1.

results gave a 90% yield of (*S*)-(+)-oxazinone-(−)-BCSA salt **7** with 97.9% e.e.[12] after 7–9 days. The initially formed (*S*)-(+)-oxazinone-(−)-BCSA salt was of 76% e.e., and its low solubility in the reaction mixture resulted in the slow turnover to material with high e.e. Increasing the reaction temperature and the (−)-BCSA charge, markedly increased the rate of the reaction (Table 1), giving initial crystals with 87% e.e. Further progress was made, where slow addition of the (−)-BCSA reagent **6** to a reaction mixture seeded with **7** ensured that the diastereomeric salt crystallised with >97% e.e.[12] This reduced the turnover time, and afforded a 90% yield of (*S*)-(+)-oxazinone-(−)-BCSA salt **7** with 99% e.e. in 48 hours.

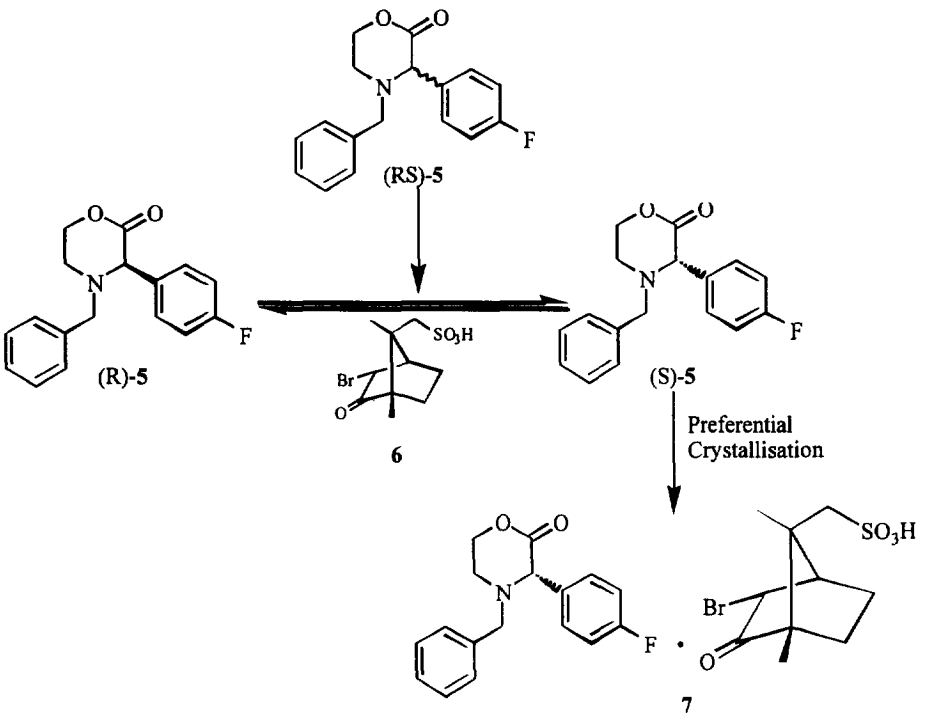
The experimental procedure is as follows. To a solution of racemic oxazinone (*RS*)-**5** (5.0 g, 17.5 mmol) in *iso*-propyl acetate (47.0 ml) was added (*S*)-(+)-oxazinone-(−)-BCSA salt **7** as seed (0.5 g, 99% e.e.), and the thin slurry heated to reflux temperature (89°C). A 0.91 M solution of (−)-BCSA **6** in *iso*-propyl acetate (23.0 ml=6.5 g, 21.0 mmol) was then added via a syringe pump over a period of 3 hours, and the resultant slurry stirred at 89°C for 48 hours. The slurry was cooled to 0–5°C, and aged for 1 hour. Filtration, and washing with *iso*-propyl acetate (10.0 ml), afforded the (*S*)-(+)-oxazinone-(−)-BCSA salt **7** (9.4 g excluding seed) in 90% yield and 99% e.e. in a single crop.[14,15] The free (*S*)-(+)-oxazinone base was recovered in quantitative yield by partitioning the (*S*)-(+)-oxazinone-(−)-BCSA salt **7** between ammonium hydroxide solution and a suitable organic solvent e.g. ethyl acetate or toluene. The procedure described has been demonstrated on a multi-kilo scale.

In conclusion, an efficient resolution of *N*-benzyl-3-(*S*)-(+)-(4-fluorophenyl)-1,4-oxazin-2-one (*S*)-**5** from the racemate (*RS*)-**5** has been realised in 90% yield and 99% e.e. by a crystallisation induced asymmetric transformation.

Table 1. Resolution/racemisation of (*RS*)-oxazinone

(-)BCSA Charge	Temperature	Time	Yield (7)	Final e.e.[12]
1.05 equivalents	75°C	7-9 days	90.0%	97.9% e.e.
1.20 equivalents	89°C	3 days	93.2%	98.1% e.e.
1.05 equivalents[a]	89°C	3 days	90.0%	99.4% e.e.
1.20 equivalents[a]	89°C	2 days	90.4%	99.0% e.e.

[a] slow addition over 3 hours to reaction mixture containing (S)-(+)-oxazinone-(-)-BCSA seed (10 wt% w.r.t. oxazinone)



Scheme 2.

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12. Enantiomeric excesses were obtained on the oxazinone free base by partitioning the oxazinone-(−)-BCSA salt between ethyl acetate and a saturated solution of $NaHCO_3$ and using chiral HPLC analysis; Chiral DNBPG (covalent) column (available from J. T. Baker B.V., Holland) 250 mm ×

4.6 mm i.d., 5 μm, eluting with 1% ethanol in hexane at 1 ml/min, oven temperature 30°C, UV detection at 210 nm; (*R*)-oxazinone RT=16.0 min, (*S*)-oxazinone RT=16.9 min.
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14. Satisfactory physical and analytical data were obtained.
15. HPLC assay confirmed that the reaction mother liquors contained the remaining 10% of the oxazinone. Enantiomer ratio (*S*):(*R*)=1:5.

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