

## 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 [(1S)-(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. (c) 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.<sup>1</sup> This intermediate was initially synthesised from (S)-(+)-4-fluorophenylglycine by a two step process<sup>1,2</sup> 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,<sup>1,3,4</sup> or via a resolution process.<sup>5</sup>

In this communication we report an efficient crystallisation induced asymmetric transformation<sup>6</sup> 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.<sup>7</sup>

Racemic oxazinone (RS)-5 was prepared in 68% yield from 4-fluorobenzaldehyde 1 via a modified Strecker reaction,<sup>8</sup> hydrolysis<sup>9</sup> of the resultant aminonitrile 2, and subsequent alkylation with 1,2-dibromoethane<sup>2</sup> (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 [(1S)-(endo,anti)]-(-)-3-bromocamphor-8-sulfonic acid 6 ((-)-BCSA).<sup>10,11</sup> 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.<sup>12</sup> 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,<sup>13</sup> 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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results gave a 90% yield of (S)-(+)-oxazinone-(-)-BCSA salt 7 with 97.9% e.e.<sup>12</sup> 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.<sup>12</sup> 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.<sup>14,15</sup> 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.

(-)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*	89°C	3 days	90.0%	99.4% e.e.	
1.20 equivalents	89°C	2 days	90.4%	99.0% e.e.	

AMDIG I. I.COULDIGICUTION OI (I.D.) CHARMONIC	Table	1.	Resolution	racemisation	of	(RS)-ox	kazinone
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\* 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<sub>3</sub> 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  $\mu$ m, 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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