

# Production of (*R*)-2-Bromo-5-phthalimidopentanoic Acid via a Diazotisation Process from (*R*)-Ornithine

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## Abstract:

A scaleable “one-pot” preparation of (*R*)-2-bromo-5-phthalimidopentanoic acid from (*R*)-ornithine is described. The use of this chirality pool method allowed for rapid development of the process. Acetic acid was found to be an efficient antifoaming agent during the diazotisation reaction. The use of an extractive workup procedure has the benefit of reducing operator exposure to the corrosive reaction mixture and minimised manual handling operations.

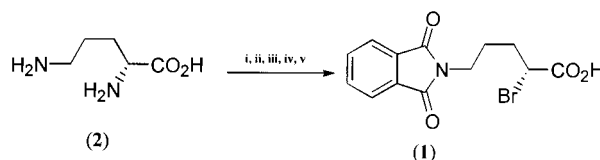
## Introduction

The (*R*)- $\alpha$ -bromo acid (**1**) is a key intermediate in the synthesis of potential inhibitors of matrix metalloproteinase (MMP) enzymes for use in the treatment of inflammatory disorders.<sup>1,2</sup> The preparation of (**1**) from (*R*)-ornithine (**2**) has previously been described.<sup>3</sup> This aqueous-based process involved the selective protection of the  $\alpha$ -amino group as a copper salt and reaction of the  $\epsilon$ -amino group with *N*-carboethoxyphthalimide (CEP). Cleavage of the copper salt with aqueous hydrobromic acid and diazotisation of the amino acid furnished the (*R*)- $\alpha$ -bromo acid (**1**) (Scheme 1). The stereochemical course of this reaction is well established and proceeds with overall retention of configuration. Mechanistically, a double inversion of the amino acid (**3**) takes place by way of an  $\alpha$ -lactone intermediate (**4**) (Scheme 2). In this paper, we discuss the translation of this process to the pilot plant and the modifications required to make an efficient large-scale process.

## Aqueous Process

During our kilogram laboratory work, a number of critical issues became apparent. The first of these was control of pH during the reaction of the (*R*)-ornithine copper complex with the CEP. If the reaction mixture was allowed to become too basic partial hydrolysis of the phthalimido group gave rise to an impure product. The control of pH had previously been achieved by the use of an autotitrator, whereas the pilot-

## Scheme 1



i) CuSO<sub>4</sub>; ii) KOH; iii) CEP; iv) aq. HBr; v) NaNO<sub>2</sub>/KBr

plant work would rely on manual adjustments using a pH probe in an external recirculation loop. The second issue was the control of the foam produced during the diazotisation stage of the reaction. The addition of PPG2025 had been found essential to control this problem; it was not clear how this would manifest itself in the pilot plant. The final issue related to product isolation which had previously been accomplished simply by direct filtration from the reaction mixture. The highly acidic nature (pH < 1) of this mixture necessitated isolation of the crude product on a fibre-glass filter and a mild base slurry was introduced prior to drying in a stainless steel drier.

The preparation of the first pilot-plant batch (17.4 kg input) revealed that pH control was relatively easy. As had been observed during the laboratory work, the uptake of base was most rapid over the first 3–5 h, with smaller additions being required during an overnight work-out. Disappointingly, however, we found that the foaming issue became worse, giving a nitrite feed time of ~34 h as opposed to the expected 4–6 h. Furthermore, we found that additional amounts of PPG failed to reduce the level of the foam.<sup>4</sup> Although a reduction in the batch size (11.5 kg input) was initially promising, giving a feed time of 12.5 h for two batches, a third batch required a 21 h feed. Nevertheless, a total of 52.1 kg of (*R*)-ornithine was processed, giving a crude yield of 60.65 kg (*R*)-**1** (70% assay; 42.5 kg active).

Recrystallisation from toluene caused some darkening of the product but gave a good mass recovery (40.1 kg; 95%). However, chiral analysis<sup>5</sup> of the product revealed that some racemisation of the product had occurred (ca. 80% ee) presumably through contamination of the crude cake with bromide ion.<sup>6</sup> Furthermore, the product was contaminated with phthalimide (7.3%). Both of these issues needed to be

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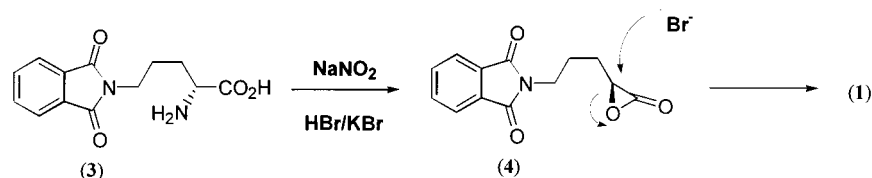
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(4) A screen of 20 different commercially available surfactants failed to reveal a superior alternative. We thank Mr S. J. Hepworth of Hickson and Welch for this information.

(5) Enantiomeric excess (ee) assay for **1**: Chiralpak AD, eluant heptane:IPA:TFA (80:20:1), flow rate 1 mL/min, 254 nm (*R*)-**1** 10 min, (*S*)-**1** 12 min.

(6) The racemisation of  $\alpha$ -bromo acids by excess bromide ion is well established.

## Scheme 2



addressed before we could proceed further. We felt that a recrystallisation would solve both problems simultaneously in a simple manner and from a solvent screen ethyl acetate emerged as the solvent of choice. The process was transferred to the pilot plant, giving 23.9 kg of pure product (95% assay; 99% ee; 0.07% phthalimide). Thus, the first batch of (*R*)-1 was successfully prepared, although at the expense of some yield loss [25% from (*R*)-ornithine]. The origin of the phthalimide was traced back to the CEP input, and this problem was rectified for subsequent batches by the purchase of higher grade material.

### Solvent Process

We felt that the main problem with the aqueous process was the precipitation of the product during the reaction which then inhibits the escape of gases from the reaction mixture and gives rise to the excess foam and variable reaction times. A potential solution was to add a cosolvent which would solubilise the product and acetic acid was chosen for initial development.<sup>7</sup> Trial reactions were carried out in a 10 L vessel in order that we could clearly see the foam. We were greatly encouraged to find that the addition of 3 volumes of acetic acid had a dramatic effect. Thus, although there was an expansion in the volume of the reaction mixture this clearly died down when the nitrite feed was suspended. The rate of addition was now governed by the exotherm of the reaction and the cooling capabilities of the reaction vessel.<sup>8</sup>

Having identified an improved reaction protocol, we now needed to address the issue of product isolation. The crude product was readily extracted into dichloromethane (DCM), and simple evaporation to dryness gave a product contaminated with urethane (ethyl carbamate,  $\text{H}_2\text{NCO}_2\text{Et}$ ). This byproduct, from the reaction with CEP, was not detected in the crude product from the aqueous process. When the crude product was slurried with toluene the level of urethane was reduced to acceptable levels by  $^1\text{H}$  NMR analysis. Toluene proved superior to ethyl acetate in this instance. The product isolation thus simply involved solvent exchange from DCM to toluene and filtration of the crystalline product. An advantage of the solvent-based process was that the crude product could now be isolated directly in the stainless steel filter/drier, thus avoiding the need to dig out the crude cake from the box filter.

This process was successfully transferred to the pilot plant where four batches (17.4 kg input) were completed with

sodium nitrite feed times of 5–7 h. The yield of crude product was 75.0 kg, 56% yield (92% assay, 94% ee). Recrystallisation from ethyl acetate afforded 55.0 kg, 74% yield (41% overall yield, 96% assay, >99% ee); the main impurity (2%) being the  $\alpha$ -hydroxy analogue.<sup>9</sup>

### Conclusions

In conclusion we have identified a scaleable route to (*R*)-1 utilising a chirality pool approach which allowed for rapid development. The addition of acetic acid to the aqueous-based diazotisation process circumvented the problems associated with excessive foaming during the reaction. This may be a generally useful feature for aqueous-based diazotisation procedures where product precipitation causes problems. A change in the product isolation procedure also had additional benefits of reducing operator exposure to the corrosive reaction mixture and minimising manual handling operations.

### Experimental Section

**Preparation of (*R*)-2-Bromo-5-phthalimidopentanoic Acid.** Demineralised water (87.0 kg) was charged to the vessel followed by (*R*)-ornithine (17.4 kg, 103 mol), and the mixture was stirred for 15 min. Copper(II) sulfate pentahydrate (12.9 kg, 51 mol) was added via the manway, and the mixture was worked out for 15 min. The mixture was pumped through a recirculation loop to a pH meter and the pH adjusted to 8.3–9.0 by the addition of a solution of aqueous potassium hydroxide (14.6 kg, 260 mol in 31.0 kg of demineralised water). CEP (22.6 kg, 103 mol) was added via the manway, and the mixture was stirred at 20–25 °C whilst additional aqueous potassium hydroxide was added to maintain the pH between 8.3 and 9.0. After ca. 5 h, the uptake of potassium hydroxide slowed markedly. The mixture was stirred overnight at 15–25 °C. Additional potassium hydroxide was added as required to maintain the pH between 8.3 and 8.7. The mixture was cooled to 10–20 °C, and glacial acetic acid (55.0 kg) was added, followed by 48% aqueous hydrobromic acid (114.0 kg). Solid potassium bromide (12.2 kg, 103 mol) was added via the manway, and the mixture was cooled to ca. 5 °C. A solution of aqueous sodium nitrite (13.8 kg, 200 mol in 30 kg demineralised water) was added over 5–7 h, keeping the temperature below 10 °C. The charge pot was rinsed with demineralised water (12 kg), and the mixture was stirred for 1 h. Dichloromethane (238.0 kg) was added, and the mixture was worked out for 15 min and allowed to separate. The lower DCM phase was separated. The aqueous phase was

(7) Acetic acid has been used in the preparation of (*S*)-2-hydroxy-4-phthalimidobutyric acid: Horiuchi, Y.; Akita, E.; Ito, T. *Agric. Biol. Chem.* **1976**, *40*, 1649.

(8) The adiabatic temperature rise was calculated at 19 °C for the addition of the sodium nitrite solution. The heat output was found to decline rapidly when the addition was stopped. We thank Dr. John O'Rourke of Chiroscience for this result.

(9) We thank Dr. Steven Lloyd and Miss Katie Tam of Chiroscience for the isolation of this impurity by preparative HPLC.

re-extracted with DCM ( $2 \times 116.0$  kg). The acidic aqueous phase containing copper residues was drummed off for disposal. The vessel, including the recirculation line, was rinsed with demineralised water (30.0 kg). Demineralised water (174.0 kg) was charged to the vessel, followed by potassium hydroxide (235 g). After a 15 min work out, the DCM extracts were returned to the vessel. The lower DCM layer was separated and the aqueous phase run off to drums. The DCM extracts were returned to the vessel and distilled at atmospheric pressure. When the bulk of the DCM had been removed the vessel was cooled and toluene (116.0 kg) was charged. The mixture was distilled under vacuum to a constant still-head temperature and then allowed to slowly cool. The mixture was aged out overnight and filtered in a Rosemund filter/drier. The damp cake was slurry washed with toluene ( $2 \times 35.0$  kg) and dried.

Yield = 75.0 kg (*R*)-**1** (92% assay; 94% ee, 56% from ornithine) for 4 batches.

**Recrystallisation.** Crude (*R*)-**1** (74.2 kg) was charged to the vessel, followed by ethyl acetate (201.0 kg), and the mixture was heated to reflux. The mixture was maintained at reflux for 30 min and then allowed to cool slowly over 4–5 h. The mixture was aged out overnight and filtered. The damp cake was washed with ethyl acetate ( $2 \times 39.0$  kg) and dried to constant weight.

Yield = 55.0 kg (*R*)-**1** (96% assay, 99% ee, 41% overall from ornithine).

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