neuland

Process optimization and scaling up of a 17-step API route

Case Study

Key outcomes

Optimisation of a 17-step synthesis for a process scale, including 7 isolated intermediates over a total of three different synthetic sequences

Preparation of over 101 kg of API material using GMP processes

Preparation of two 5 kg batches of API under cGMP conditions

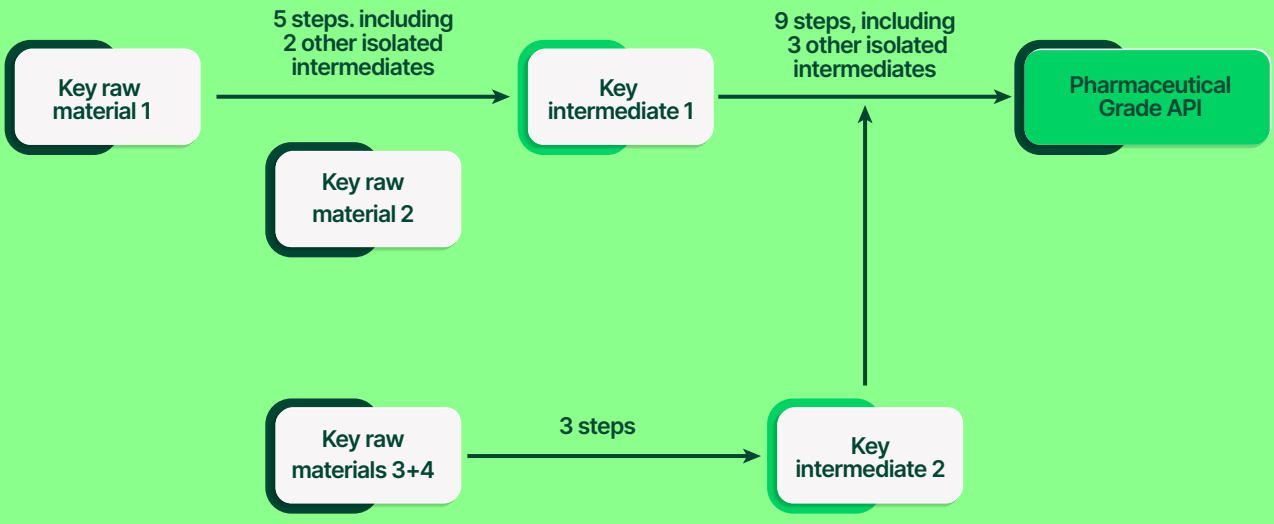
Control of oxidation and cyclisation reactions to substantially minimise by-product formation

Large-scale asymmetric chlorination with excellent stereoselectivity

Controlled crystallisation of final API to meeting stringent guidelines on polymorph formation and particle size

About the client

Our client was a large Japanese company that specialises in healthcare solutions. The project was for process optimisation and scale-up of an API that was in Phase II trials for treatment of bone diseases. Manufacture of the API required 17 discrete steps, with seven isolated intermediates, Scheme 1.



Scheme 1: General overview of API preparation

Client objectives

The client had the following objectives for Neuland:

1. To undertake process optimisation for scale-up of API material
2. To prepare 2 × 5 g batches of the API from 2 × 10 g batches of the key intermediates 1 and 2 under non-GMP conditions
3. To prepare 101 kg of the API material under GMP conditions
4. Develop analytical methods for monitoring product purity

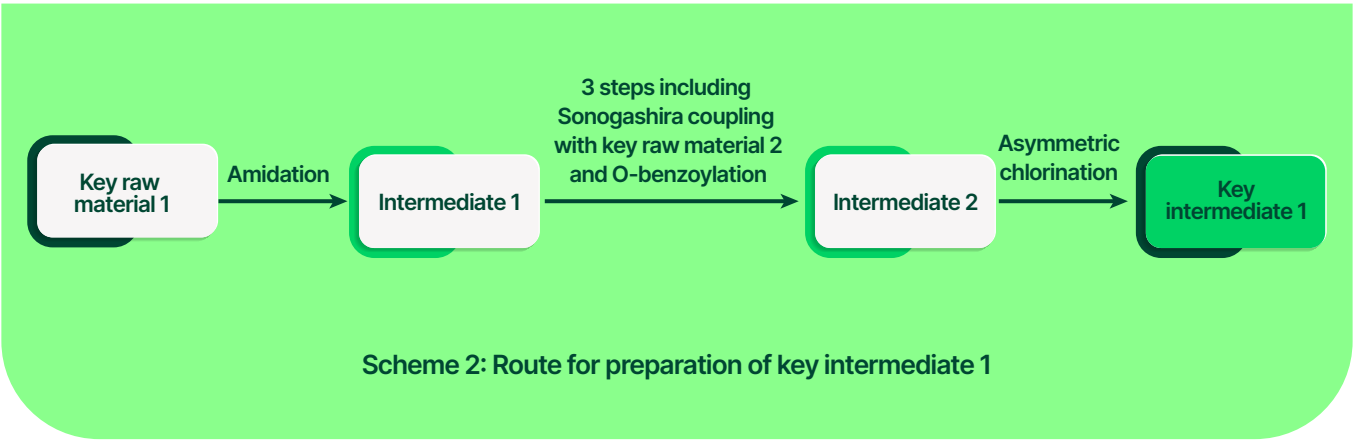
Key challenges

The Neuland team broke the synthesis down into three smaller processes to address the challenges efficiently.

The first synthetic sequence focussed upon preparation of key intermediate 1 and comprised of five discrete processes and two isolated intermediates, Scheme 2.

Challenges included:

- **Air and moisture sensitive reactions**
- **Hazards relating to large-scale use of butyn-2-ol in the Sonogashira coupling**
- **Formation of an N-benzoylated by-product**
- **Poor stereoselectivity during asymmetric chlorination**

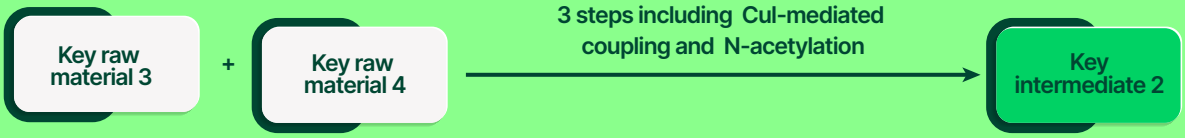


Scheme 2: Route for preparation of key intermediate 1

The second process, although shorter, was far from straightforward, Scheme 3.

Challenges in this sequence included:

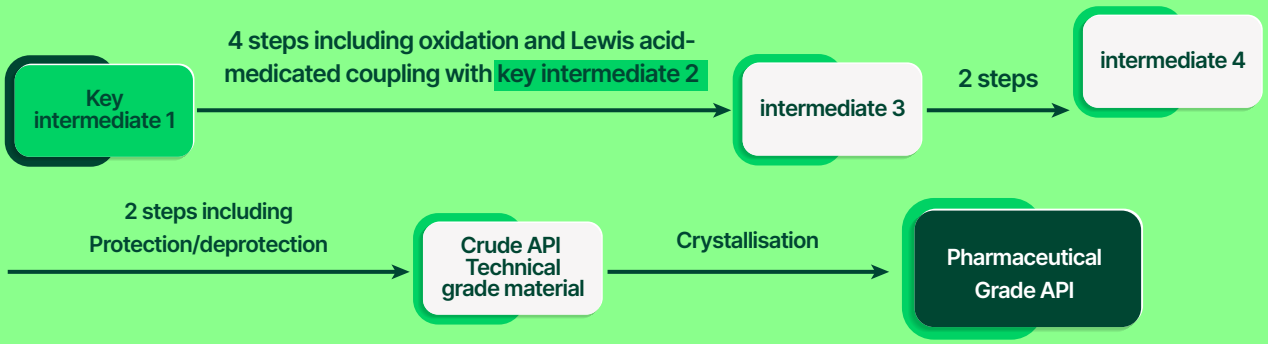
- **Difficulties during separation of the organic phase after copper-mediated coupling due to emulsion formation**
- **Unacceptable copper contamination of key intermediate 2**
- **Air and moisture sensitive N-acetylation; water resulted in decomposition of a key intermediate**



Scheme 3: Route for preparation of key intermediate 2

The final process focused upon coupling key intermediates 1 and 2, as well as isolation of pure API material. This was by far the longest linear sequence, with a total of nine operations and three isolated intermediates, Scheme 4. Within this sequence, issues included:

- **Over-oxidation to the sulfone**
- **A highly air and moisture-sensitive coupling reaction**
- **Stringent requirements for API form and particle size**



Scheme 4: Route for preparation of the final API

Neuland's approach: Use smaller pieces to make the bigger picture

Dividing the overall process into three sub-processes enabled the Neuland team to focus on overcoming difficulties one at a time. In addition, the convergent nature of the route meant that several teams were able to work on the issues at once, reducing the time required for optimisation and delivery to the client.

Initial exploration focussed on laboratory-scale experimentation. Once this was completed to a satisfactory level, pilot-batches were prepared where material was synthesized under non-GMP conditions. Finally, cGMP processes were followed for preparation of pharmaceutical grade API used in trials. This stepwise approach to scale enabled issues to be identified early, as well as isolation and characterisation of impurities.

In addition, due to the team's extensive synthetic knowledge and experience, pinch-points were identified ahead of time and mitigating approaches used where necessary. For example, across several steps protection of the reaction mass from oxygen and moisture through use of an inert atmosphere immediately solved issues, for example, eliminating homo-coupling of the alkyne during the Sonogashira step, a previously troublesome side-reaction. In other cases, scrutiny of by-products formed, both organic and inorganic, enabled the team to control both reaction conditions and work-up such that purification was optimised, reducing losses and improving purity overall.

Outcomes: One step at a time

- Throughout the laboratory scale processes and scale-up, an inert atmosphere was used to protect the reactions from oxygen and moisture, which enhanced yield and purity across several synthetic steps.
- Several N-protecting groups were trialled to assess impact on yield, colour, purity and side-reactions. Use of several protecting groups gave orthogonality, so synthetic control was easier. During protection steps side-product formation was monitored, such as N- protection rather than O-protection, with reagents added in aliquots where necessary to improve selectivity.

Key improvements in process I

- A cyclisation in the first process was optimised, where the impurity profile (organic and inorganic) was improved from 15% using the original procedure, to <1%.
- Chlorination resulted in the desired R-isomer in 99% ee. Adjusting the temperature and solvents used during this process ensured desired isomer formation, and reduced time required for purification.

Key improvements in process II

- Formation of an emulsion at the organic-water interface resulted in unacceptable copper contamination of the intermediate. Use of aqueous ammonium chloride and brine during work-up facilitated phase separation, and ensured copper impurities were substantially below the stringent requirements.

Key improvements in process III

- Formation of a sulfone impurity was controlled through stepwise addition of the oxidant, precise control of the reaction internal temperature and mixing, as well as through washing with aqueous sodium thiosulfate.
- Coupling of key intermediates 1 and 2 required Al(Oi-Pr)3, which was highly oxygen and water sensitive. Suspending the Lewis acid in toluene and addition of the resultant slurry to the reaction mass mitigated this issue.
- Care during isolation of the API technical grade material, as well as during recrystallisation to give the pharmaceutical grade API, ensured that both the polymorph formed and particle sizes were within the client's specification.

Conclusion: 17-step process-scale synthesis - not for the faint-hearted

Across the whole 17-step process, impurities were limited to below 0.5% w/w and at each stage a yield of at least 50% yield was achieved. Key to success was carefully monitoring the reaction mixtures for impurities (organic and inorganic), identifying why or how they were formed, then adjusting the reaction conditions to minimise their formation. Using this approach, over 101 kg of the API material was prepared under GMP conditions, and two batches of 5 kg of the final API were prepared under cGMP conditions. This achievement is testament to the Neuland team's experience within complex synthesis and their care and attention to detail.

About Neuland

A global CDMO, Neuland delivers success for biotechnology and pharmaceutical clients seeking complex APIs and intermediates at all phases of the product life cycle. Their strength lies in overcoming complex chemistry challenges to advance drugs to market, having completed more than 150 NCE projects for custom APIs and developed more than 300 API processes. In business for more than 40 years, with 500+ clients in more than 80 countries, Neuland boasts an impeccable record of quality standards.

Make Neuland your strategic partner for improved process efficiency, quality, and ultimately, faster time-to-market for your drug product.

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