



Route scouting and optimisation for high-complexity, low-yield APIs



PROJECT OVERVIEW

In pharmaceutical development, routes established during early discovery are often prioritised for speed rather than scalability. As processes progress, these legacy pathways, frequently characterised by long synthetic sequences and reliance on chiral resolution, can become significant barriers to commercial viability.

At scale, these inefficiencies translate into extended timelines, elevated costs and substantial product loss.

At this stage, organisations must determine whether existing chemistry can support a viable manufacturing process. One organisation that saw product losses exceeding 50% turned to Sterling for a more scalable solution.

Leveraging extensive expertise in route scouting and process optimisation, Sterling's Newcastle Biosphere team evaluated and redesigned synthetic pathways to reduce step count, improve material efficiency and enable scalable production.

AT-A-GLANCE



Key challenge

Efficiency and stereochemical control for multi-step synthesis



Legacy route

20+ step synthesis, chiral resolution, low yield



Optimised route

Reduced to 14 steps, chiral pool-derived starting material, stereocontrolled synthesis



Key results

Fewer process steps, reduced cycle times, increased yield, reduced costs

The Sterling solution

Navigating high-loss legacy routes

Legacy synthetic routes are often lengthy and inefficient, particularly when they rely on chiral resolution. In this case, the legacy route exceeded 20 steps and depended heavily on resolution techniques. Since every additional step in a process can introduce added costs, risks and variability, the customer sought a more efficient and effective route.

Furthermore, the organisation relied on the same intermediate across multiple programmes, intensifying the need for a more optimal approach.



The Newcastle Biosphere team evaluated multiple synthetic pathways in parallel, combining literature precedent, model system validation and rapid screening of key transformations to identify the most viable route. After working through this iterative process, the team found a solution that reduced step count by 33%, saving weeks of cycle time. Further efficiency gains were achieved through process intensification strategies, including telescoping steps to minimise intermediate isolations and streamline the overall process.

Maintaining control without chiral resolution

Transitioning away from chiral resolution introduces a different layer of process complexity. While stereocontrolled synthesis provides a more efficient and scalable pathway, it requires precise management of stereochemical outcomes at each step of the route.

As even minor deviations in reaction conditions can compromise stereochemical integrity, ensuring confidence in stereochemical outcomes at each step was crucial to ensure downstream success.



To eliminate inefficiencies associated with chiral resolution, Sterling applied its expertise in developing stereospecific routes using readily available chiral starting materials.

By introducing stereochemistry early and maintaining control throughout the process, the team eliminated the need for resolution. This resulted in higher overall yield, reduced waste, reduced step count and lowered production costs.

Identifying a practical, scalable route

Route scouting is rarely a straightforward process. It involves evaluating multiple potential pathways, each with its own advantages and limitations, as well as conducting thorough literature reviews, using model compounds to test feasibility and rapidly screening key reaction steps.

In this case, several viable routes emerged, each requiring careful assessment of chemical feasibility alongside practical considerations like scalability and costs.



Sterling combined chemical expertise with practical process considerations to identify the most viable route. The team conducted rapid screening of key steps and used model compounds to test feasibility, ensuring that selected pathways were not only chemically sound but also scalable and economically viable. This integrated evaluation enabled confident selection of a route suitable for development and manufacturing.

Ensuring stereochemical integrity and process understanding

Maintaining stereochemical integrity across a multi-step synthesis requires robust analytical methods.

Standard techniques are not always sufficient to accurately monitor chirality or detect subtle deviations. Without this insight, inconsistencies can go unnoticed and impact downstream performance.



To ensure stereochemical integrity, Sterling's integrated analytical team developed tailored analytical methods to monitor chirality at key stages of synthesis. This included chiral HPLC method development and reference standard synthesis to support peak assessment and verify purity.

At the same time, the team conducted ongoing mechanistic studies to investigate unexpected results and gain deeper insight into reaction behaviour that allowed us Sterling to identify further potential optimisations.

By aligning practical route design with process and analytical considerations, Sterling transformed a complex, low-yield synthesis into a robust and scalable process for manufacturing. This approach saved time and reduced inefficiency while ensuring control, consistency and performance at scale.

Ready to learn how we can optimise your complex synthetic route?

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