Process Development and Scale Up – Challenging Chemistry

Introduction and Background

A large Pharma client had previously contracted with an overseas CDMO company to create a scalable process for the production of a small molecule API. This molecule presented many production challenges due to its chirality and substituents being attached in a diastereoselective manner. After more than a year of effort, a scalable process was still unavailable. As a result, the client requested that Olon USA create a scalable production process and produce a 2 kg and 10 kg batch in the pilot plant.

Challenge

The desired API has multiple stereocenters with one of them being easily racemized. Many of the intermediates in the process were not able to be isolated, minimizing the available purification possibilities. The process from the overseas CDMO company required 12 linear steps with one chiral SFC and two prep-HPLCs purifications.

Due to delays at the previous CDMO, the client was in urgent need of material within seven months. At the time of writing the proposal, Olon USA determined that the 2 kg batch could be available within that time frame even though the timeline was extremely tight.

Approach and Execution

During the initial project evaluation, Olon USA proposed evaluating an enzymatic resolution approach in synthesizing the compound due to the difficulties encountered at the previous CDMO company. When that proposal did not work as desired, alternate solutions were quickly developed for each step. The alternate solutions implemented in the process include the following:

- Using a chiral starting material and then controlling all downstream conditions to prevent racemization or epimerization of that chiral center. This eliminated the need for resolution (chromatographic, chemical, or enzymatic) in later steps and doubled the theoretical production output.
- Alternate materials and coupling conditions were found to remove the need for expensive and potentially explosive HOBt. This also mitigated the risk of racemization.
- Processing steps were telescoped when possible and purification strategies were implemented at the processing stages most conducive for purification. This allowed for maximum purification with minimal effort and product loss. Purification strategies included acid/base extraction and formation of salts to create solids that could be isolated.
- A new chiral ligand was developed for an asymmetric borohydride reduction, which improved the diastereo-selectivity ratio (dr) from 86:14 to 96:4, thus eliminating the need for prep-HPLC purification.

The critical timing of the project added urgency to the chemical development process to ensure that all critical processing problems were resolved before the pilot plant production began. Any problems in production would directly have an impact on the tight timeline for the client. To minimize the risk of any unforeseen issues, the chemistry and engineering department worked very

closely together as the process was developed in the lab so that the final process could be seamlessly scaled in the pilot plant facility.

Results

Overall, the number of linear steps were reduced from the original 12 to 10. Five of the linear steps were telescoped and all column purifications were eliminated. In addition to solving many difficult processing challenges, the overall yield of the process was increased from about 4% to more than 18%.

The processing of the 2 kg batch was completed in about 9 weeks with no significant process related delays or problems encountered. As a result, the client timeline was met and the resulting toxicology study could be completed on time. The 10 kg batch was produced as planned and two additional production campaigns were completed over the next year (up to a 30 kg scale) with no significant processing problems or delays encountered in any of the production campaigns.