Example of a Stereoselective Synthesis in Industrial API Manufacture

Abstract
Stereochemistry is an important topic not only in academic research, but also in industrial manufacture. Herein, we present an example of a stereoselective transformation performed on multi-kilogram scale at CARBOGEN AMCIS AG for VenatoRx Pharmaceuticals.

Stereoselective Matteson Homologation using a Continuous Flow Process

Reaction Scheme:

Target:
Antibacterial agent, beta-lactamase inhibitor

Results from the Manufacturer:

<table>
<thead>
<tr>
<th>Entry</th>
<th>Input</th>
<th>Conversion</th>
<th>Yield</th>
<th>d.r.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Run I</td>
<td>8.00 kg</td>
<td>97 %</td>
<td>8.03 kg, 90 %</td>
<td>95.1 : 4.9</td>
</tr>
<tr>
<td>Run II</td>
<td>9.60 kg</td>
<td>96 %</td>
<td>9.51 kg, 88 %</td>
<td>97.3 : 2.7</td>
</tr>
<tr>
<td>Run III</td>
<td>13.33 kg</td>
<td>97 %</td>
<td>13.51 kg, 90 %</td>
<td>97.0 : 3.0</td>
</tr>
</tbody>
</table>

Flow Reactor Equipment:

Flow Process Parameters:
- Mixing of LDA / 2-Me-THF with Compound 3 / CH₂Cl₂ at -25°C
- Mixture pumped into ZnCl₂ suspension in collection tank at -15°C
- Flow rate: 200 g/min Compound 3 solution (50 g/min net)
- Residence time in flow reactor: approx. 30 s
- Aqueous work-up in batch mode

Advantages of Flow Process over Batch Process:
- Temperature: -25°C instead of -60°C to -100°C
- No need for large cryo reactors
- Higher purities, less by-products, higher selectivities

Conclusion
In conclusion, continuous flow technology was employed to perform a diastereoselective Matteson homologation using (+)-pinanediol as chiral diol on boron. The reaction was carried out on multi-kilogram scale, giving the product in high yields and with high diastereoselectivities. Most notably, in contrast to the batch process, the continuous flow process allows for much higher reaction temperatures without the need of cryogenic reactors on large scale.

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