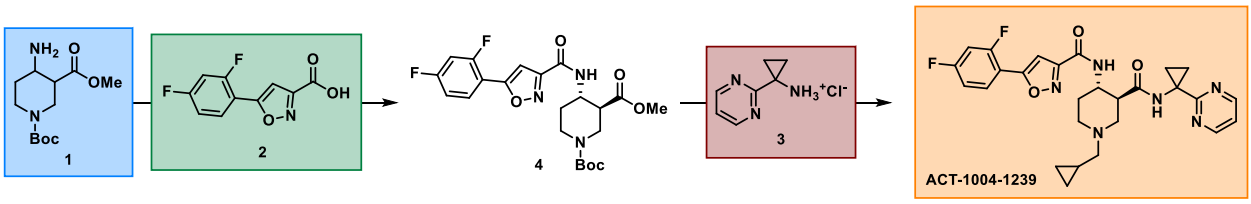
Development of a Stereoselective Route for CXCR7-Antagonist ACT-1004-1239

Gabriel Schäfer,* Tony Fleischer, Muhamed Ahmetovic, Stefan Abele

*Director, Group Leader Chemistry Process R&D, Idorsia Pharmaceuticals

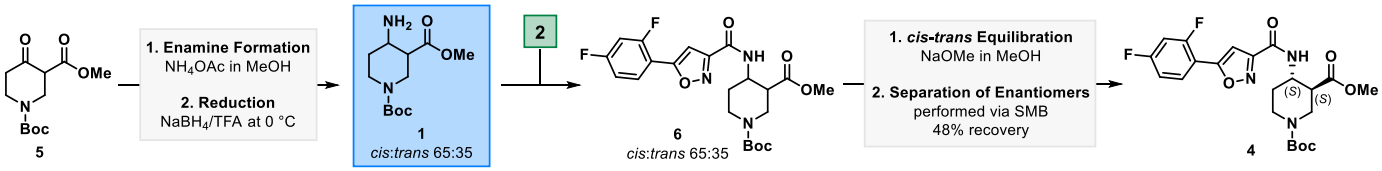
The chemokine receptor CXCR7 is involved in various pathologies such as neurological diseases, autoimmune diseases and cancers. Therefore, CXCR7-antagonists could be used as potential treatment for the afore mentioned diseases. Idorsia recently reported the discovery of **ACT-1004-1239** - a potent, selective, and orally available CXCR7-antagonist.[1]

From a retrosynthetic point of view, **ACT-1004-1239** can be divided into three main building blocks: Boc-protected piperidine **1** (blue), isoxazole **2** (green) and aminocyclopropyl pyrimidine **3** (red).

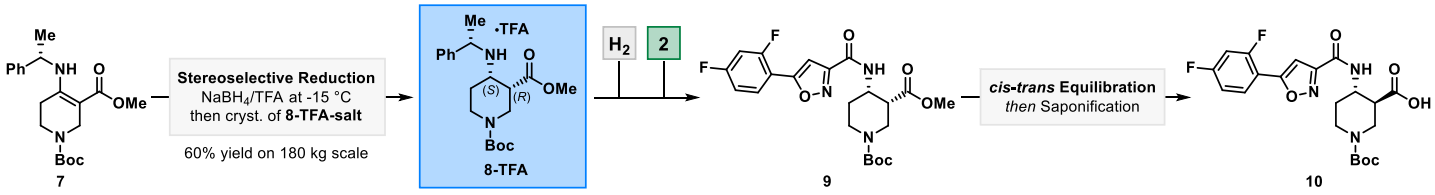


For **2** and **3**, robust and scalable syntheses were rapidly developed in-house and delivered multi-kg amounts of both building blocks.[2] For the central piperidine core **1**, we were faced with a major decision at the outset of the project: 1) synthesizing **1** racemically and separating the enantiomers on an intermediate stage via chromatography to deliver the first API batches as soon as possible, or 2) delaying the first API batches and investing time in the exploration of stereoselective approaches to gain access to enantiopure **1**. Due to the high time-pressure on the project, delaying the deliveries of the initial API batches was out of question. Therefore, the 1st non-GMP batch for toxicological studies and the 1st GMP-batch for Phase 1 clinical studies were delivered by using the "racemic route".

"**Racemic route**": The racemic Boc-protected piperidine **1** was synthesized in two steps from commercially available piperidone **5** via a sequence of enamine formation and subsequent reduction. Crude racemic **1** (*cis-trans* ratio: 65:35) was a viscous yellow oil and therefore directly telescoped into the subsequent amide-coupling with isoxazole **2**. The resulting amide **6** was equilibrated with NaOMe in MeOH to isolate the racemic *trans*-isomer as a crystalline solid in excellent purity. At this stage, the separation of the enantiomers via SMB chromatography[3] was performed to recover the desired *trans*-(3*S*,4*S*)-isomer **4** in pure form. The final sequence to **ACT-1004-1239** consisted of saponification of **4**, amide formation with **3**, Boc-deprotection and reductive amination with cyclopropanecarboxaldehyde (not depicted). Using this "racemic route", several multihundred-gram API batches were produced to support the preclinical toxicology program, as well as a 5.5 kg GMP-API batch for Phase 1 clinical studies.



"**Stereoselective Route**": For Phase 2 API-resupply, the separation via SMB would have needed to be performed on at least 50 kg *trans*-racemate scale. However, due to the projected high price (>500k CHF) and long duration (>2 months) of this chiral separation, using the "racemic route" was not a viable option anymore. Therefore, a stereoselective approach towards **ACT-1004-1239** was developed. After exploring multiple options, we found that the reduction of enamine **7** - prepared from the inexpensive chiral auxiliary (*S*)-1-phenylethylamine (<15 CHF/kg) and **5** - worked well and with good selectivity for the *cis*-(3*R*,4*S*)-isomer **8**. In addition, we were able to selectively crystallize the pure *cis*-(3*R*,4*S*)-isomer from TBME as its TFA-salt **8-TFA** (60% yield on 180 kg scale). After cleavage of the ethylbenzene-group via hydrogenation and subsequent amide coupling with isoxazole **2**, *cis*-(3*R*,4*S*)-amide **9** was isolated with high chemical and enantiomeric purity (er: 99.6:0.4). In order to install the desired *trans*-(3*S*,4*S*)-configuration as in **ACT-1004-1239**, **9** was directly converted into carboxylic acid **10** via a modified *cis-trans* equilibration/saponification sequence.



The final steps from **10** to **ACT-1004-1239** were adopted from the "racemic route", as they worked well on scale and ensured the new API batch for Phase 2 to have a similar impurity profile as the batch used for Phase 1. In total, 32 kg of **ACT-1004-1239** were produced with the novel "stereoselective route". The implementation of the "stereoselective route" led to a distinct price reduction per kg/API of more than 75% in comparison to the "racemic route" - or in other words - 4-times more API could be produced for the same total price.

---

[1] S. Richard-Bildstein, H. Aissaoui, J. Pothier, G. Schäfer, C. Gnerre, E. Lindenberg, F. Lehembre, L. Pouzol, P. Guerry, *J. Med. Chem.* **2020**, *63*, 15864–15882.

[2] G. Schäfer, T. Fleischer, M. Ahmetovic, S. Abele, *Org. Process Res. Dev.* **2020**, *24*, 1735–1742.

[3] SMB: simulated moving bed. See: https://www.knauer.net/en/Systems-Solutions/SMB