Technical Note

Approaches to chiral products: Racemic resolution

Abstract

A number of chiral myths exist related to pharmaceutical products. Although nobody denies the importance of enantioselective synthesis, sometimes there is no real need for such advanced methods. Moreover, often the old-fashioned racemic resolution of a chiral compound is not only a good option, but an essential step in the development of a New Chemical Entity.

In this case study, we present an example of a project involving the racemic resolution of a promising candidate.

GalChimia

The human body is highly chiral responsive, and more often than not the isomers of chiral drugs present very different biological properties. Unfortunately, the process for obtaining enantiopure compounds can be very expensive, which becomes a significant issue during drug development.

Different approaches can be considered to obtain the desired enantiomer of a drug (Fig. 1),[1] all of them with advantages and drawbacks depending on the nature and properties of the parent species. In the case of natural products, one can go to the natural source and proceed to extract it. This approach is usually impractical at large scale, plus it is not applicable in the case of synthetic molecules.

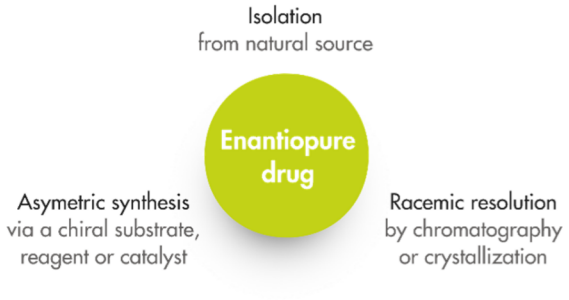

Figure 1 Main approaches to enantiopure drugs.

The synthesis of enantiopure compounds can be achieved via asymmetric methods, where selectivity may be enforced through the use of a chiral substrate, reagent or catalyst. These methods however are not universal and present a series of limitations, that is, enantiomeric excess (ee) values that cannot be increased any further.

The final main option is racemic resolution, where a mixture of enantiomers is enriched progressively in the desired isomer by generating the corresponding diastereomers and exploiting their different physicochemical properties.[2,3] An example of the latter methodology is described here.

Case Study

One of our clients approached us with a request to develop a racemic resolution method for a promising pre-clinical candidate. The main features of the compound are an aryl group introduced via organometallic coupling and a dimethylamino moiety introduced by means of aminative reduction of a ketone. The compound presents a chiral center in that position and initial assays showed that the *S*-enantiomer presented better activity than the *R*-isomer. Chirality was therefore a critical issue.

We were provided with the details of a straightforward route in two steps, considering that the needed building block for the coupling was also supplied. A method for the enantioselective synthesis of the compound was being developed, but to cover intellectual property claims and allow for faster supplying of bigger batches of the enantiomerically pure candidate for the upcoming trials, a classic racemic resolution procedure was required.

We considered three possible approaches to the problem: first, resolution of the final compound; second, resolution of the intermediate dimethylamine generated before the coupling reaction; and third, resolution of another intermediate amine suitable for the preparation of the desired compound (Fig. 2).

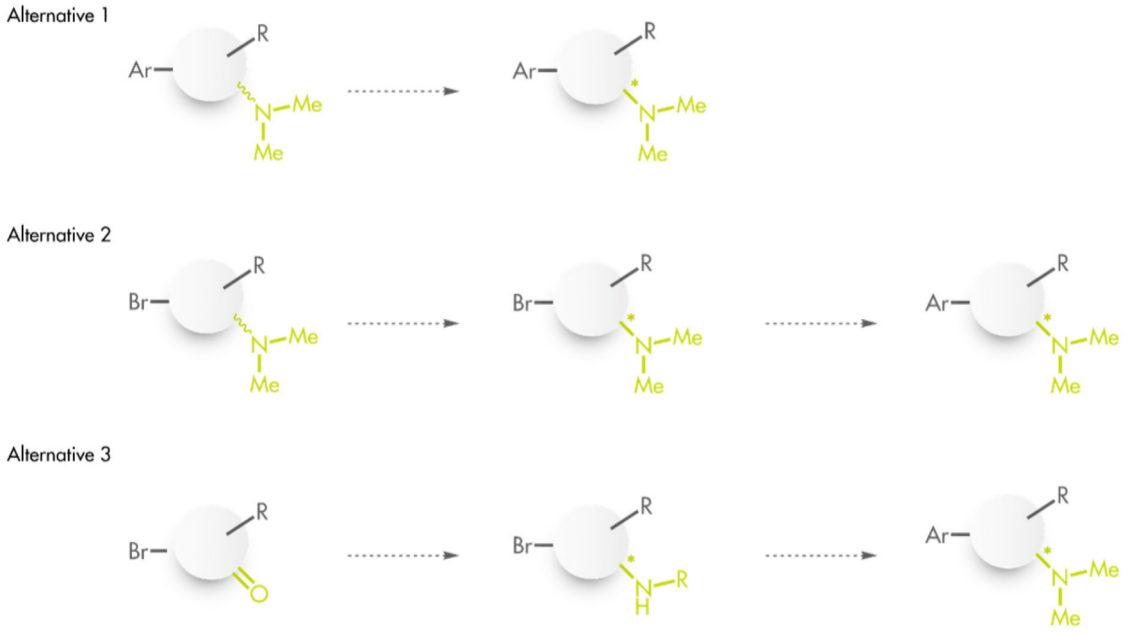

Figure 2 The different alternatives considered in this project.

Each alternative had advantages and disadvantages. Alternative 1 would be faster because the route was already established and a chiral HPLC method for ee determination had been developed by our client. On the other hand, alternatives 2 and 3 would allow the introduction of an expensive building block at a later stage, thus reducing costs, but the synthetic steps had to be tested and chiral HPLC methods had to be developed.

We started exploring alternative 1. First, fast optimization of the coupling reaction was carried out while increasing the scale to grams. The subsequent aminative reduction worked finely to provide us with the final compound in enough quantities for our study. Applying the usual DoE principles, a short screening was designed using three solvents and five common and cheap resolution reagents under standard conditions (Fig. 3).

Of the fifteen parallel experiments, nine showed no crystals. In the remaining six experiments, crystals were isolated from the solution, and they were assayed using a chiral HPLC method. One result was promising, with 73% ee. Although such ee value was far from excellent, it offered a good starting point. Further crystallization of the enriched mixture allowed us to obtain the compound with an ee higher than 99%. A comparison between the isolated enantiomer and some samples obtained by preparative chiral HPLC showed us that we had separated the incorrect enantiomer. We reproduced the experiment with the enantiomer of the resolution agent, and the conditions, results, ee values, and identity of the obtained product were all successfully validated.

Although these results were excellent and they were obtained in just a few weeks, we pursued the other two alternatives bearing in mind a reduction in costs and mass employed in the resolution.

Alternatives 2 and 3 involved swapping the synthetic steps, with the aminative reduction being placed first. The aminative reduction of the starting material with dimethylamine was troublesome. The reaction was not complete, required harsh conditions and long reaction times. We turned then to microwave conditions in order to expedite the reaction and provide product enough for the screening. However, development of the chiral HPLC method was also troublesome and, when the samples of a screening study were assayed, the results were disappointing. Alternative 2 was obviously pushed to the back of our to-do list.

We were simultaneously working in alternative 3. This involved an aminative reduction with a protected amine to yield a product amenable to resolution. The reductive amination was carried out without problems at multigram scale with excellent yield and purity to provide the desired compound. A chiral HPLC method was promptly developed, and the protected amine was subjected to a screening study. Taking in account the results obtained in alternative 1, only one solvent was chosen, while the pool of chiral reagents was expanded to eight.

Of the eight parallel experiments, only two did not afford crystals. The remaining six crystals were isolated from the solution and analyzed by chiral HPLC, but only one result was promising, with 94% ee. Further crystallization of the enriched mixture allowed us to get the compound with an ee value higher than 99%. The pure enantiomeric product was subjected to a sequence of four reactions to give the final product in 25% yield and >99% ee.

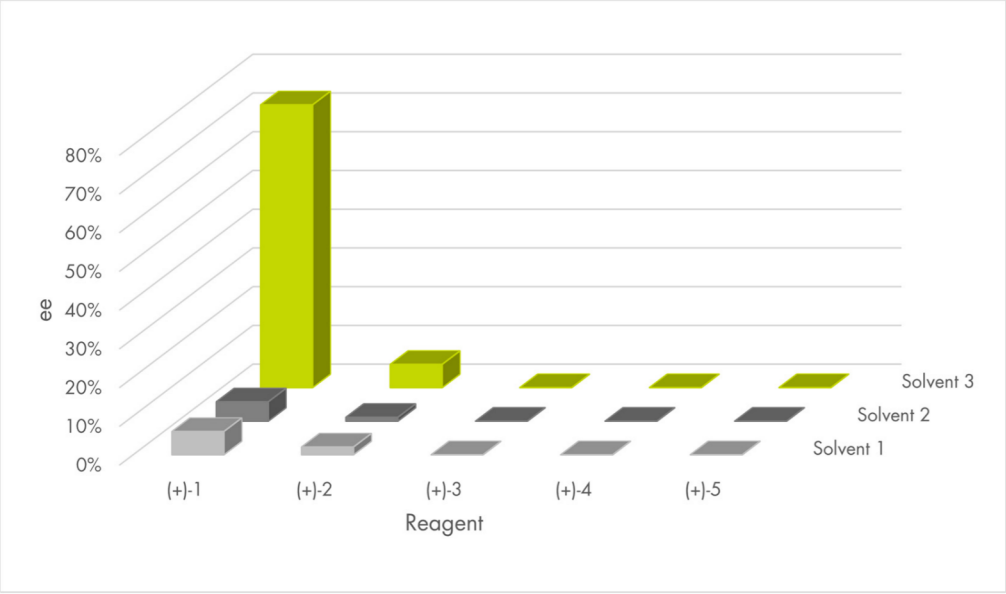

Figure 3 Screening of crystallization conditions explored in Alternative 1.

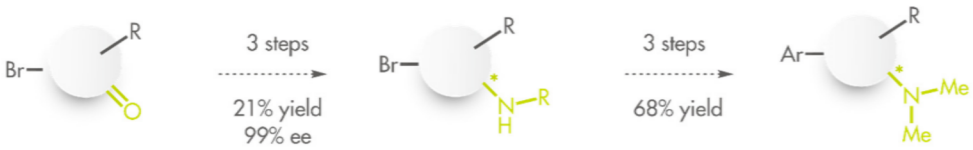

Figure 4 Optimized process for the synthesis of the chiral target.

However, since the sequence of reactions needed to reach the final compound from the resolved amine was too long, we introduced a small change in the protocol, which allowed us to reduce one step and obtain the final compound in 68% yield and >99% ee (Fig. 4).

In conclusion, in the present case study, we applied DoE principles, parallelization techniques, and analytical skills and were able to offer our client not one but two solutions, with a broad range of conditions for them to choose from. Moreover, the development of classic resolution methods would cover important intellectual property issues once the product entered regulatory phases, thus barring possible challenges from competitors.

References

1. Mane, S. Anal. Methods, 2016, 8, 7567.
2. Ferreira, F.C.; Ghazali, N.F.; Cocchini, U.; Livingston, A.G. Tetrahedron: Asymmetry, 2006, 17(9), 1337.
3. Marchand, P.; Loi¨c Lefèbvre, L.; Querniard, F.; Cardinaël, P.; Perez, G.; Counioux, J.-J.; Coquerel, G. Tetrahedron: Asymmetry, 2004, 15 (16), 2455.

Authors

- Iria Perez, R&D Chemist
- Ana Caamaño, Project Manager
- Monica Carreira, Scientific Innovation Officer
- Jacobo Cruces, Chief Scientific Officer

About GalChimia

GalChimia is a contract research organization offering specialized services in Discovery, Process, and Analytical Chemistry for the pharma, biotech, and agrochemical industries. We strongly believe that continuous training and innovation is key to provide the best service to our customers. By investing in new technologies and keeping our chemists updated on the state of the art, we are able to push the boundaries of organic synthesis for the benefit of your project.

GalChimia owns a range of high efficiency synthesis equipment:
> Automated microwave reactor with robotic arm
> Parallel chemistry stations
> High pressure reactors
> Continuous flow reactor

For more information, please visit our website www.galchimia.com or contact us at hello@galchimia.com.