Synthesis of intermediates useful for the preparation of Etripamil

V. Pagliari, G. Lucca, S. Saponaro, E. Bernardi, R. Rossi, S. Mantegazza

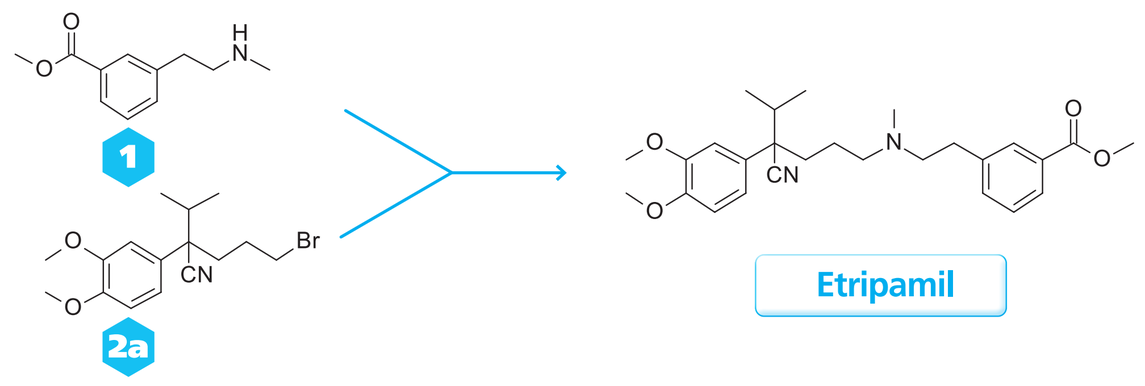
Introduction

Etripamil is a short-acting non-dihydropyridine L-type calcium-channel blocker and is currently in phase 3 clinical trial. The main advantage of **Etripamil** consists in **the innovative method of administration**: the intranasal application. It has been formulated as a **nasal spray for self-administration by patients** who experience paroxysmal supraventricular tachycardia (PSVT) recurrences with a rapid onset of action without hospitalization [1].

Etripamil, as described in the patent application WO 2016/165014 [2], is currently synthesized through a convergent synthesis which ultimately involves a **reaction between compound 2a and compound 1**.

This synthesis has several critical issues including:

- **the use of toxic gases** (KCN, Me_2SO_4) which can only be handled by authorized personnel;
- **the lack of control of the stereocenter** requiring a final resolution step (only the (S) enantiomer of Etripamil shows the desired pharmacological activity);
- **the need to purify some intermediates** with a chromatographic column.

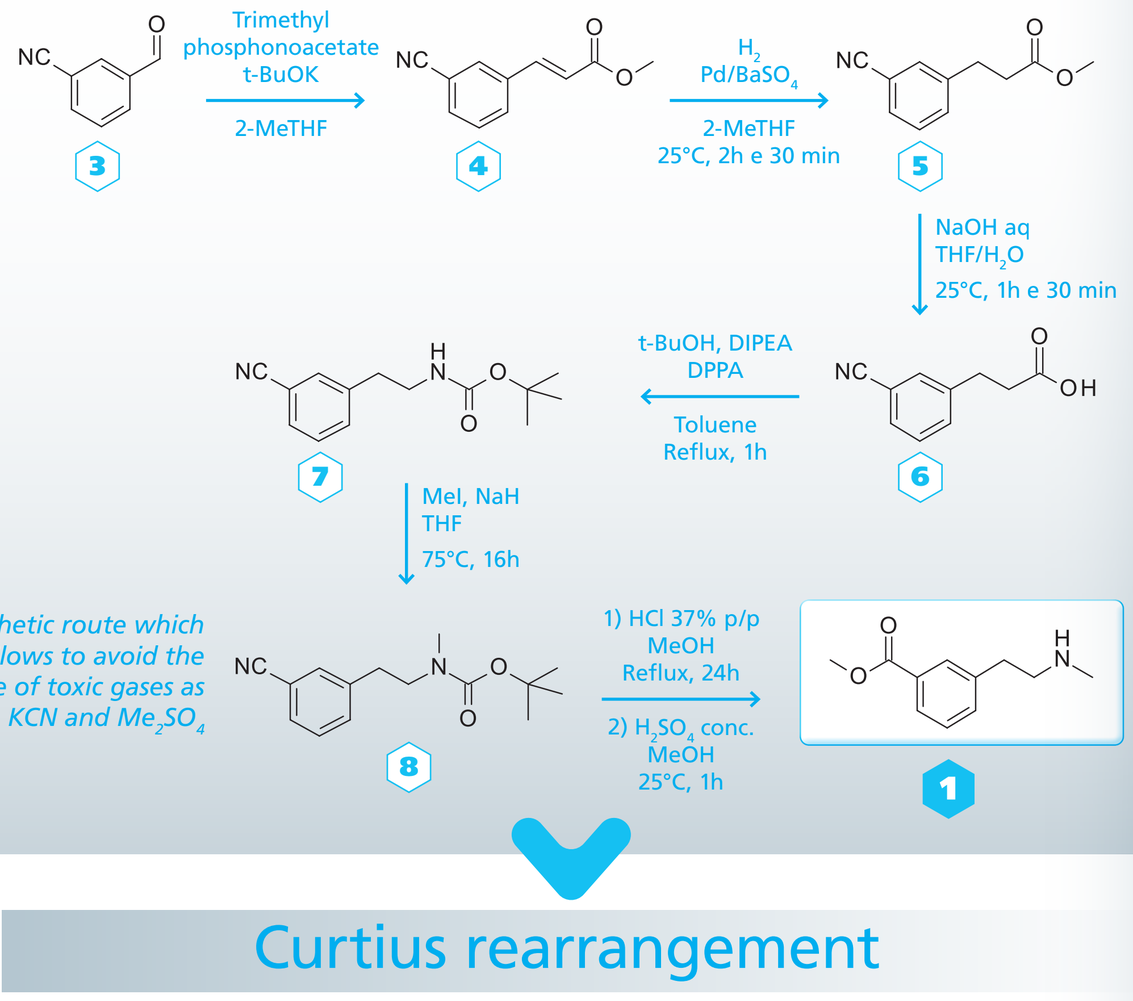


Aim of the work

In this work, possible synthetic alternatives were evaluated compared to that reported in the Milestone Pharmaceuticals patent (WO 2016/165014) to obtain synthon 1 and 2b. Subsequent coupling and reductive amination lead to the formation of **Etripamil**.

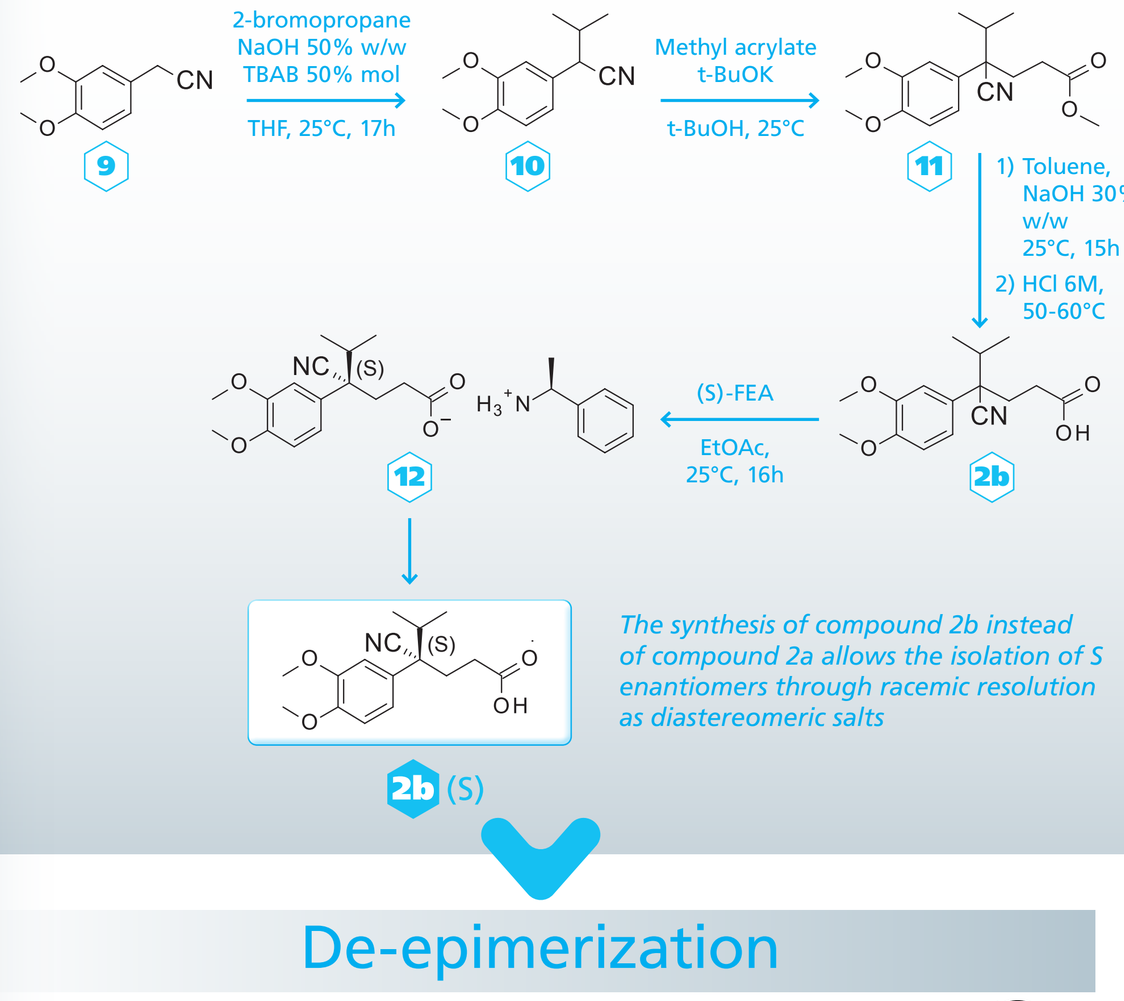
The final aim was to produce a generic drug of Etripamil, through an **economical, non-infringing and industrially scalable process**, which **avoids the use of toxic substances** such as KCN and Me_2SO_4 and with a control of the stereocenter.

Synthesis of compound **1**



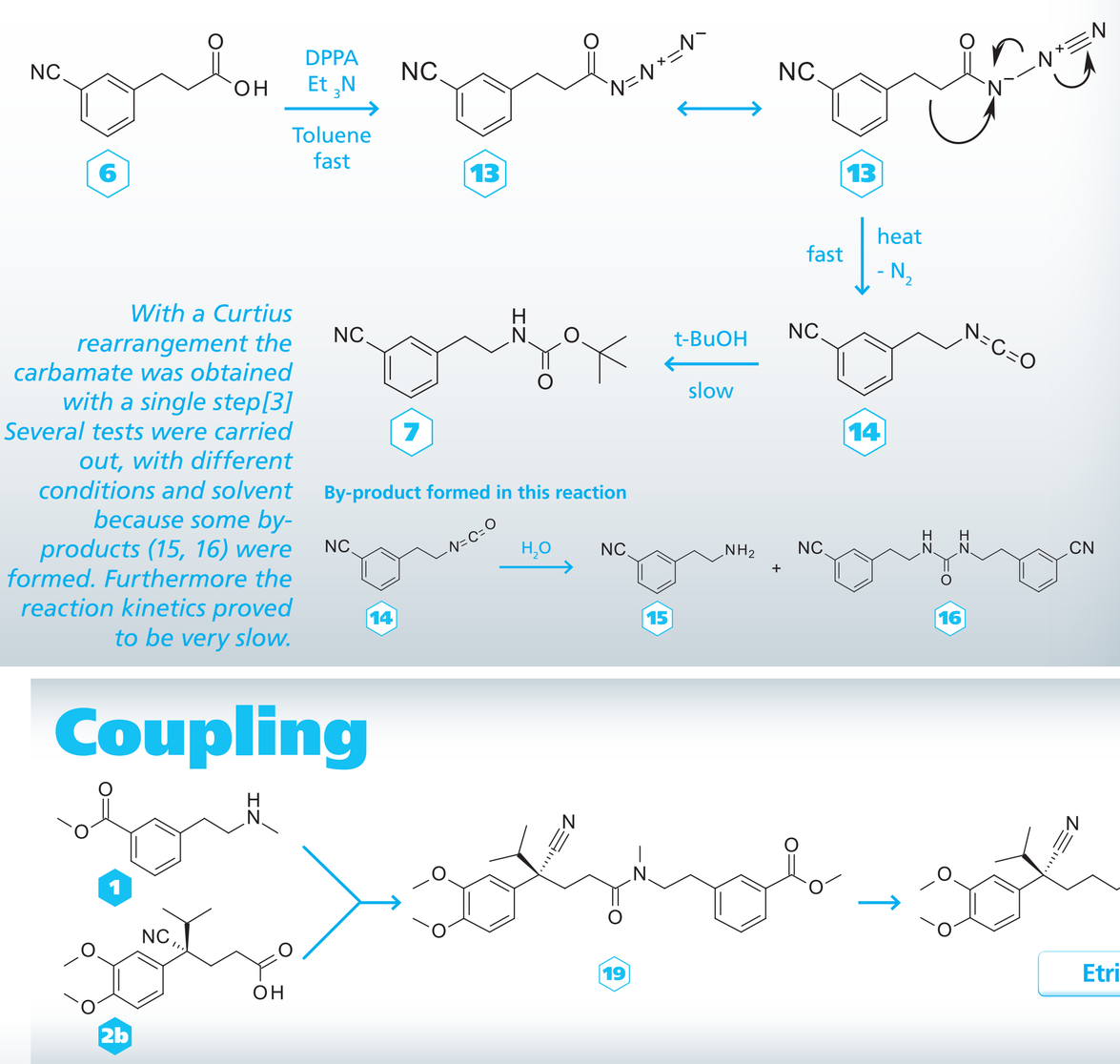
Synthetic route which allows to avoid the use of toxic gases as KCN and Me_2SO_4

Synthesis of compound **2b**



The synthesis of compound 2b instead of compound 2a allows the isolation of S enantiomers through racemic resolution as diastereomeric salts

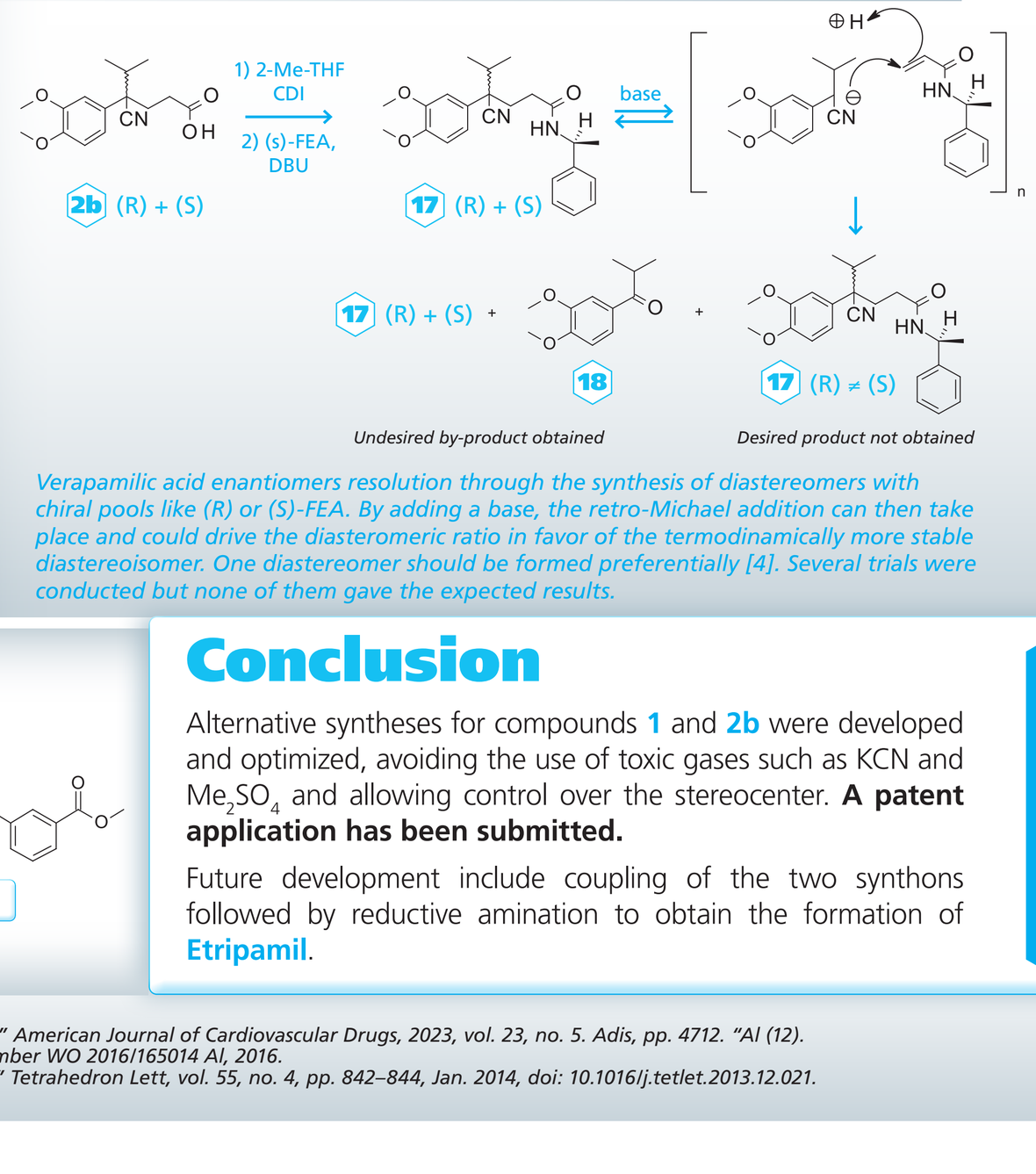
Curtius rearrangement



With a Curtius rearrangement the carbamate was obtained with a single step[3] Several tests were carried out, with different conditions and solvent because some by-products (15, 16) were formed. Furthermore the reaction kinetics proved to be very slow.

By-product formed in this reaction

De-epimerization



Undesired by-product obtained

Desired product not obtained

Verapamilic acid enantiomers resolution through the synthesis of diastereomers with chiral pools like (R) or (S)-FEA. By adding a base, the retro-Michael addition can then take place and could drive the diasteromeric ratio in favor of the termodinamically more stable diastereoisomer. One diastereomer should be formed preferentially [4]. Several trials were conducted but none of them gave the expected results.

Coupling

Conclusion

Alternative syntheses for compounds **1** and **2b** were developed and optimized, avoiding the use of toxic gases such as KCN and Me_2SO_4 and allowing control over the stereocenter. **A patent application has been submitted.**

Future development include coupling of the two synthons followed by reductive amination to obtain the formation of **Etripamil**.

REFERENCES

1. J. Huston et al., "Etripamil Nasal Spray: Therapeutic Potential for Treating Paroxysmal Supraventricular Tachycardia," American Journal of Cardiovascular Drugs, 2023, vol. 23, no. 5. Adis, pp. 4712. "Al (12).
2. "Al (12) international application published under the patent cooperation treaty (pct) International Publication Number WO 2016/165014 Al, 2016.
3. X. Sun, et al "Boc-protected 1-(3-oxocycloalkyl)ureas via a one-step Curtius rearrangement: Mechanism and scope," Tetrahedron Lett, vol. 55, no. 4, pp. 842–844, Jan. 2014, doi: 10.1016/j.tetlet.2013.12.021.
4. Racemisation of quaternary chiral centers, WO1997029080 A1, 10 Feb. 1997.

Since 1949 Dipharma

veronica.pagliari@dipharma.com