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New catalytic route for the synthesis of an optically active tetralone-derived amine for rotigotine

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ABSTRACT

Rotigotine is a launched drug for the treatment of Parkinson's disease and restless legs syndrome. The key steps of an alternative route for the synthesis of rotigotine have been demonstrated. Formation of a prochiral enamide, asymmetric hydrogenation of the enamide with high enantioselectivity, and reduction of the resulting amide to an amine have been proved to work successfully. The best conditions screened to date for the asymmetric hydrogenation of enamide **9** to amide **10** were with [(RuCl((*R*)-T-BINAP))$_2$(μ-Cl)$_3$][NH_2Me_2] at 25 bar H_2 and 30 °C (500:1 S/C ratio, 99% conversion, 91% ee *S*). Reduction of amide **10** to amine **5** was best achieved with Red-Al giving 95% conversion.

Introduction

Rotigotine is a launched drug of the non-ergoline class of medications that acts as a dopamine agonist for the treatment of Parkinson's disease and restless legs syndrome. It was developed by Aderis Pharmaceuticals and licensed by UCB S.A. and it has been in use in Europe since 2006.[1] Currently, the majority of reported syntheses of the chiral amine intermediates used in the preparation of this drug involve the classical resolution of racemic amines[1,2] (and hence a maximum theoretical yield of 50%) as shown in Scheme 1.

The development of an efficient asymmetric synthesis would lead to obvious cost and yield benefits. One approach, reported in a recent publication, is the synthesis of a chiral tetralone primary amine as a key intermediate via a multi-enzymatic approach of ene-reductases (ERs) and alcohol dehydrogenases (ADHs).[3] A different strategy that has been patented is a chiral auxiliary based route using α-methylbenzylamine.[4] Herein, we report the preparation of a prochiral enamide (**9**), from the appropriately substituted tetralone (**3**) and propionamide, followed by asymmetric hydrogenation which gives access to a chiral amide (**10**) in high yield and enantioselectivity. Subsequent reduction of this chiral amide yields the necessary secondary amine intermediate (**5**) in a highly efficient and selective fashion (Scheme 2). The remaining downstream steps to rotigotine, as shown in Scheme 1, have been previously reported.[5]

The key elements of the overall alternative process are a highly selective asymmetric hydrogenation reaction that uses a directing group of relevance to the downstream product of interest, a concise overall route where each step is high yielding with an efficient amide reduction as the final step, minimising any loss of enantioselectivity.

Results and discussion

The reaction between a substituted β-tetralone and a primary amide to yield the corresponding enamide has been widely reported.[6] In this case, the specific combination shown in Scheme 3 is required.[2b,7]

Enamide **9** was prepared on a 16 g scale showing quantitative conversion by ^{1}H NMR spectroscopy. Water was removed under Dean–Stark conditions using pTSA as an acidic catalyst. Recrystallization was achieved from the reaction solvent in an unoptimized 80% isolated yield.

The asymmetric hydrogenation of tetralone-derived enamides has been reported in recent years.[8] However, the reduction of the preferred enamide **9** leading to rotigotine (**8**) had not been reported prior to this work[7] (Scheme 4).

A screen of Rh and Ru catalyst was undertaken (Table 1 shows representative results of a total of 4 Rh and 26 Ru precatalysts). Hydrogenation of **9** with Rh complexes such as [((*R*,*R*)-Ph-BPE)Rh(cod)]BF_4 and [((*R*)-PhanePhos)Rh(cod)]BF_4 showed good conversion, albeit at a low enantioselectivity (entries 1 and 2). On the other hand, the hydrogenation carried out with Ru dimer species showed a low conversion at 10 bar hydrogen pressure, but a very

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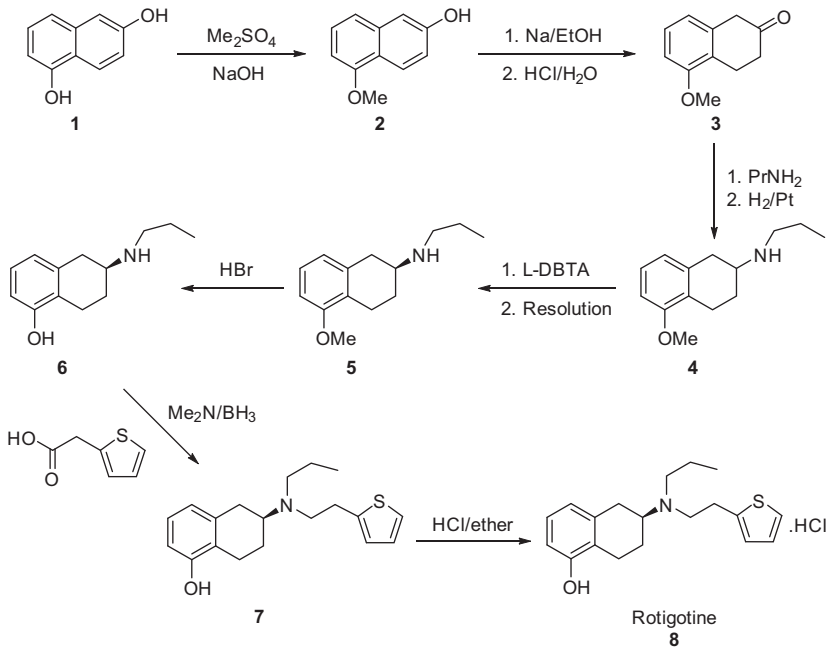
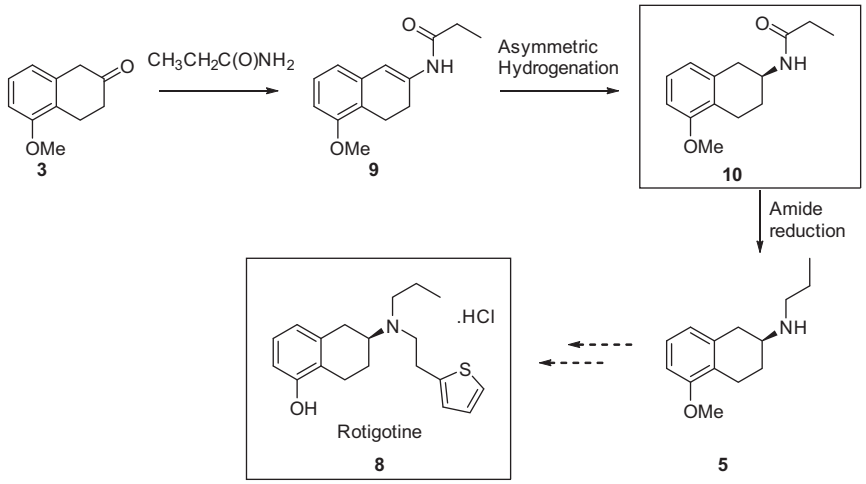


Scheme 1. Synthesis of rotigotine via classical resolution.[1,2]

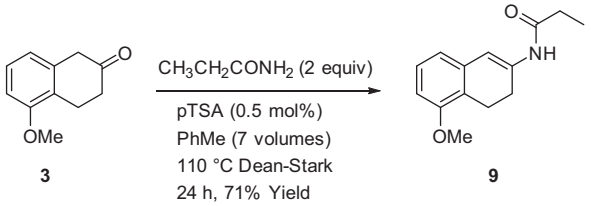


Scheme 2. Catalytic, enantioselective synthesis of rotigotine.

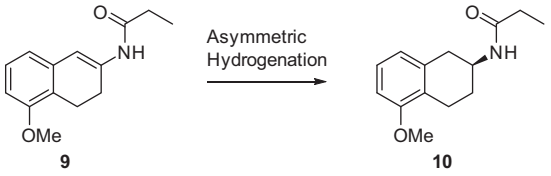
high enantioselectivity; leaving promising scope for process development and optimization (entry 5). Increasing both pressure and temperature for precatalyst $[RuCl_2((R)\text{-BINAP})]_2{\cdot}NEt_3$ had a beneficial effect in terms of conversion but with a concomitant reduction in enantioselectivity (cf. entries 5 and 6 and entries 6 and 7).

Different Ru precursors and BINAP derivatives were tried giving good conversions and ees of up to 99%.

Similar results were obtained with BINAP derived ligands (entries 8, 9, 12, and 13) and ligands such as DuPhos and BIPHEP (Fig. 1). This, in addition to the economic attractiveness of BINAP derivatives relative to these other ligand families, precatalyst



Scheme 3.



Scheme 4.