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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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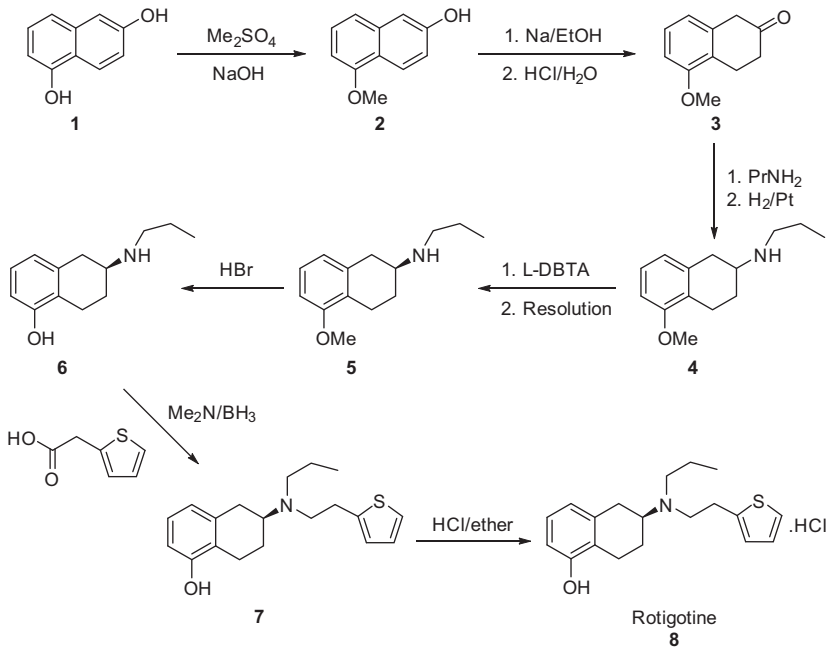
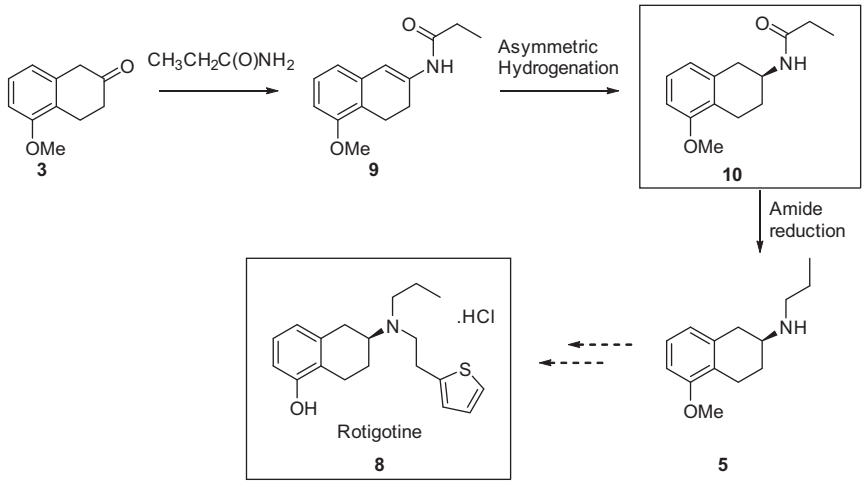


Scheme 1. Synthesis of rotigotine via classical resolution.[1,2]

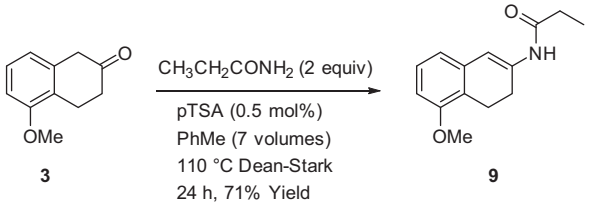


Scheme 2. Catalytic, enantioselective synthesis of rotigotine.

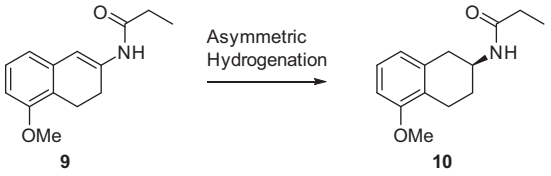
high enantioselectivity; leaving promising scope for process development and optimization (entry 5). Increasing both pressure and temperature for precatalyst $[RuCl_2((R)\text{-BINAP})]_2{\cdot}NEt_3$ had a beneficial effect in terms of conversion but with a concomitant reduction in enantioselectivity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

Table 1
Asymmetric hydrogenation[a] screening results

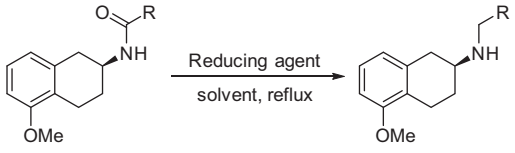
Entry	Precatalyst	*P* (bar)	*T* (°C)	Conv. (%)	ee (%)
1	[(*R,R*)-Ph-BPE Rh(cod)]BF_4	10	20	89	28 (*S*)
2	[(*R*)-PhanePhos Rh(cod)]BF_4	10	20	98	42 (*S*)
3	[(*R,R*)-Et-DuPhos Rh(cod)]BF_4	10	20	17	8 (*S*)
4	[(*S,S*)-Et-FerroTane Rh(cod)]BF_4	10	20	43	4 (*S*)
5	[$RuCl_2$((*R*)-BINAP)]$_2$·NEt_3	10	30	13	>99 (*S*)
6	[$RuCl_2$((*R*)-BINAP)]$_2$·NEt_3	25	30	51	>99 (*S*)
7	[$RuCl_2$((*R*)-BINAP)]$_2$·NEt_3	25	40	>99	87 (*S*)
8	[RuCl((*R*)-BINAP)$_2$(μ-Cl)$_3$][NH_2Me_2]	25	30	92	87 (*S*)
9	[RuCl((*R*)-T-BINAP)$_2$(μ-Cl)$_3$][NH_2Me_2]	25	30	99	89 (*S*)
10	[RuCl((*R*)-DM-BINAP)$_2$(μ-Cl)$_3$][NH_2Me_2]	25	50	99	85 (*S*)
11	[Ru((*R*)-DM-BINAP)($OAc)_2$]	25	30	93	84 (*S*)
12	[Ru((*R,R*)-Et-DuPhos)($TFA)_2$]	10	30	99	90 (*S*)
13	[Ru((*R*)-MeO-BIPHEP)($TFA)_2$]	10	30	99	88 (*S*)

[a] Reaction conditions: 0.14 M in MeOH, S/C ratio 200:1, 18 h.

Table 2
Asymmetric hydrogenation results at different catalyst loadings and conditions

Precatalyst	S/C	*P* (bar)	*T* (°C)	Conv. (%)	ee (%)
[RuCl((*R*)-T-BINAP)$_2$ (μ-Cl)$_3$][NH_2Me_2]	500[a]	25	30	99	91 (*S*)
	500[b]	100	30	98	91 (*S*)
	1000[b]	25	50	99	85 (*S*)
	5000[c]	100	50	69	88 (*S*)

[a] Reaction condition: 0.43 M in MeOH, 41 h.
[b] Reaction condition: 0.22 M in MeOH, 22 h.
[c] Reaction condition: 0.22 M in MeOH, 18 h.



10 **5**

Scheme 5.

Table 3
Conversion results for the reduction of amide **10** to amine **5**

Reducing agent	Conversion (%)
Red-Al	95
$LiAlH_4$	89
BH_3·THF	67
DIBAL-H	78
BH_3·NEt_3	No reaction

Reaction conditions: see ESI details

[RuCl((*R*)-T-BINAP)$_2$(μ-Cl)$_3$][NH_2Me_2] was chosen to conduct a further study increasing the pressure and molar substrate to catalyst (S/C) ratio (Table 2). Increasing pressure had a positive effect on the rate of hydrogenation of enamide **9**; the reaction at 25 bar at 500 S/C ratio reached completion in 41 h, whereas the reaction at 100 bar using the same catalyst loading proceeded to 98% conversion in only 18 h. The reaction proceeded to full conversion with a high ee at 1000 S/C and 50 °C. At 5000 S/C, the conversion only reached 69%.

A hot recrystallization of **10** from ethyl acetate increased the enantioselectivity from 91% to 98% with an unoptimized recovery of 28%.

The downstream reduction of amide to amine (Scheme 5) has been published for a range of tetrahydronaphthalen-2-amides with a variety of reducing agents (including BH_3·THF, BH_3·SMe_2, Zn/silane, $LiAlH_4$, DIBAL-H, and Red-Al).[9]

Reduction of amide **10** (R = Et) with 4 different reducing agents was demonstrated. Reaction of **10** with Red-Al, $LiAlH_4$, BH_3·THF, and DIBAL-H resulted in the formation of **5** (R = Et) in 67–95% conversion. The reaction with BH_3·NEt_3 was not successful, with only starting material observed (Table 3).

Amine **5** was isolated as the hydrochloric salt **5**·HCl in 98.56% ee concluding that the loss of enantioselectivity did not occur in the downstream chemistry.

Conclusions

The key steps of an alternative route for the synthesis of an achiral amine intermediate for rotigotine have been demonstrated. The formation of a prochiral enamide, its asymmetric hydrogenation with good enantioselectivity, and the 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*). When the S/C ratio was lowered to

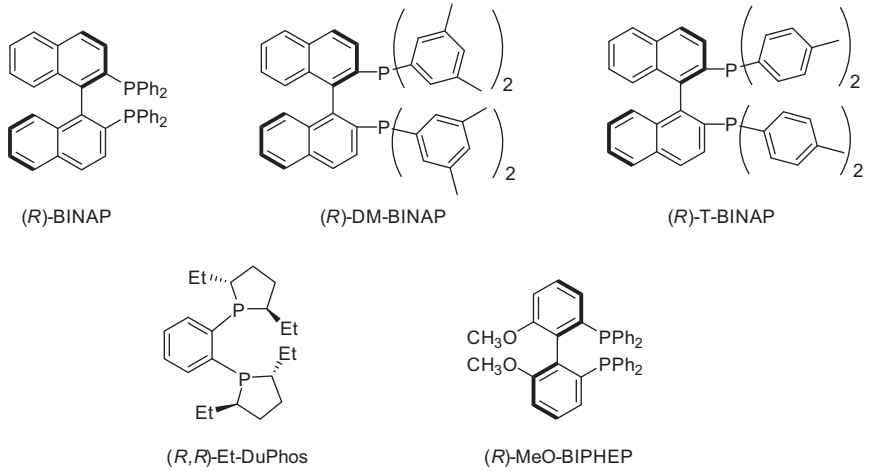


Figure 1.

1000:1 at 25 bar H_2 and 50 °C, the conversion remained high but the enantioselectivity dropped to 85%. Reduction of amide 10 to amine 5 was best achieved with Red-Al giving 95% conversion.

Experimental

Please refer to E.S.I. for experimental details.

Acknowledgement

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2016.01.060.

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