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First enantioselective syntheses of the dopamine D1 and D2 receptor modulators, (+)- and (−)-govadine

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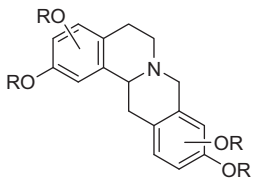
ABSTRACT

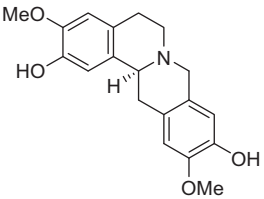
There is a pressing need to find and develop new antipsychotic agents for the treatment of schizophrenia. Current drugs primarily target dopamine D2 receptors and are only effective in the treatment of the positive symptoms of this indication. The tetrahydroprotoberberine natural product (±)-govadine has shown unique promise for the treatment of both the positive and negative symptoms of schizophrenia as it targets both dopamine D1 and D2 receptors. However, further clinical research has been hindered by the lack of availability of significant quantities of enantioenriched material. A new, enantioselective synthetic route has been developed that affords (−)-govadine in 39% overall yield over 5-steps from commercially available dopamine and homovanillic acid derivatives. Using only minor modifications in the synthetic route, (+)-govadine can be synthesized in comparable yields and enantioselectivities. The route is readily scalable as every intermediate was purified by crystallization and no flash column chromatography was necessary.

Schizophrenia is a chronic neuropathic disease for which there is currently no cure.[1] Studies suggest that the symptoms of schizophrenia are largely due to an excess of dopamine in the subcortex[2] and a deficiency of dopamine in the frontal cortex.[3] Current antipsychotic agents are primarily dopamine D2 receptor antagonists[2] and are only partial treatments of the imbalance of the dopaminergic system; these drugs are effective at treating the positive symptoms of schizophrenia, such as delusions and hallucinations, but have little effect on the cognitive deficits and negative symptoms, such as apathy. There is a pressing need to find and develop new pharmaceutical agents that effectively treat all symptoms of this debilitating disease. Recent studies have revealed that several tetrahydroprotoberberines (THPBs), a bioactive[4] class of tetracyclic alkaloids (Fig. 1),[5] exhibit unique pharmacological activities in their ability to elicit activities in both the D1 and D2 receptors in vitro and in vivo.[6] In a recent preclinical assessment of the THPB govadine,[7] in vitro and in vivo studies of the racemic compound indicate that it is a viable dopamine D1 agonist and dopamine D2 antagonist, and thus may be effective for treating both the positive and negative symptoms of schizophrenia.[8] Further testing of each enantiomer was restricted by access to each enantiomer.[9] As only racemic syntheses of govadine have been reported,[10] an efficient and scalable route to both (+)- and (−)-govadine was essential to continue its evaluation as an antipsychotic drug.

When designing an enantioselective synthesis of govadine, we wanted to minimize the need for flash column chromatography as this would significantly impede future production of either (+)- or (−)-govadine on a multi-gram scale. In addition, a convergent synthesis that minimized the total number of synthetic steps would facilitate future analog synthesis. Based on these requirements, we planned to synthesize govadine according to Scheme 1. Benzyl protective groups were to be used throughout the synthesis because they increase the crystallinity of each intermediate and they should be readily removed in the final step. We planned to set the stereocenter using an enantioselective reduction of dihydroisoquinoline **3**. If both enantiomers of the catalyst are readily available, then this route can be used to access either enantiomer of govadine. Intermediate **3** should be readily accessed from a Bischler–Napieralski cyclization of



tetrahydroprototperberine core structure



(–)-govadine (**1**)

Figure 1. Core structure of tetrahydroprotoberberines (THPB's) and (−)-govadine (**1**).

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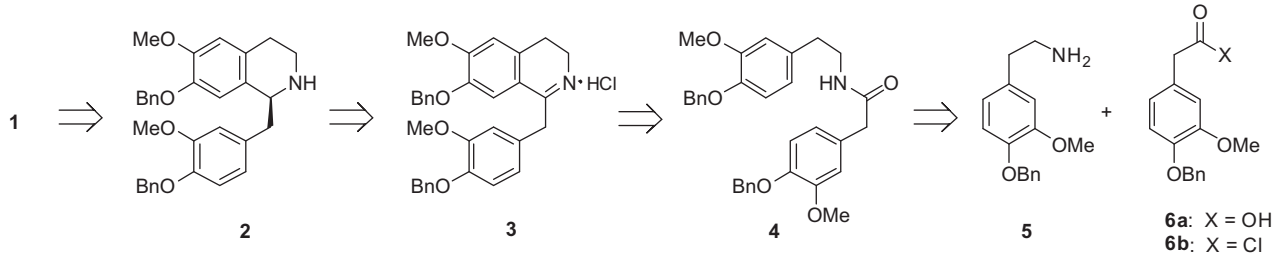
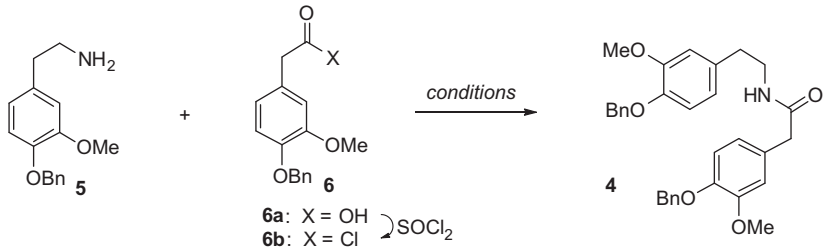


Scheme 1. Retrosynthetic analysis of (−)-govadine.

Table 1
Optimization of the peptide coupling between dopamine derivative **5** and homovanillic acid derivative **6**



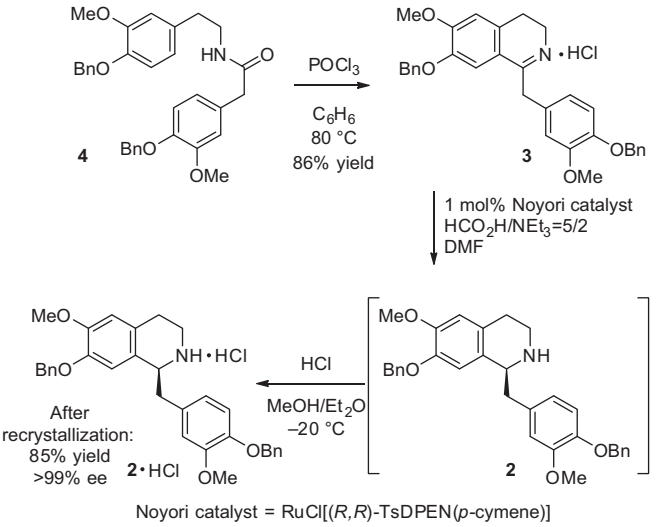
Entry	Homovanillic acid derivative	Conditions	Yield (%)
1	**6b**	NEt_3, DCM	59[a]
2	**6a**	DCC, *N*-hydroxysuccinimide, DCM	46[a]
3	**6a**	Neat, 180 °C	90[b]
4	**6a**	μw, 170 °C, DMSO	nd

[a] Yield after column chromatography.
[b] Yield after recrystallization.

4.[11] Compound **4**, in turn, can be prepared from the coupling of dopamine derivative **5** and homovanillic acid (**6a**), both of which are commercially available.

The synthesis of (−)-govadine began with an investigation of the known peptide couplings between dopamine derivative **5** and homovanillic acid derivative **6** to determine which conditions provided the highest yields and which could be purified by crystallization (Table 1). We first explored conversion of carboxylic acid **6a** to the corresponding acid chloride (**6b**) using thionyl chloride, followed by coupling with amine **5** (entry 1).[12] This protocol only afforded modest yields (50–60%) of amide **4** and the reaction was not clean, thus necessitating purification by flash column chromatography. Peptide coupling using DCC and hydroxysuccinimide provided **5** in a slightly lower yield (40–50%),[13] but the product could still not be isolated cleanly by crystallization (entry 2). We next explored a thermal peptide coupling between amine **5** and acid **6a** (entry 3). Although these conditions have never been explored with either **5** or **6a**, they have been demonstrated to be successful when coupling comparable dopamine and homovanillic acid derivatives.[14] Gratifyingly, heating the two species neat at 180 °C provided clean conversion to the desired coupled product, which could readily be purified by recrystallization. Thermal peptide couplings were also attempted using a microwave reactor, but there was significant decomposition (entry 4).

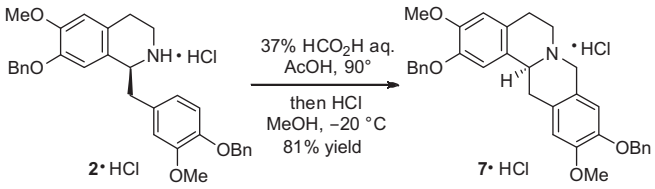
Treatment of coupled product **4** with phosphoryl chloride induced a Bischler–Napieralski cyclization affording dihydroisoquinoline hydrochloride **3** in 86% yield (Scheme 2). We then began our investigations into the key enantioselective reduction step with a Noyori transfer hydrogenation (Scheme 2).[15] Noyori transfer hydrogenations are powerful methods for the hydrogenation of imines and have been demonstrated to enantioselectively hydrogenate dihydroisoquinolines with excellent selectivities (93–95% ee).[16,17]



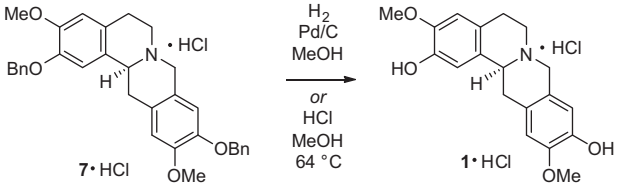
Scheme 2. Synthesis of tetrahydroisoquinoline derivative **2**·HCl from amide **4**.

Hydrogenation of dihydroisoquinoline **3** under the standard conditions described by Noyori et al. cleanly provided the desired tetrahydroisoquinoline **2**. Tetrahydroisoquinoline **2** was unstable at room temperature,[18] so it was converted to the corresponding HCl salt and crystallized in 85% overall yield and >99% ee. While the yield can be improved by carrying crude material through to the next step, later intermediates could not be efficiently enantioenriched through recrystallization.

Mannich-type cyclization of tetrahydroisoquinoline **2**·HCl using aqueous formaldehyde and acetic acid afforded only the desired



Scheme 3. Mannich-type cyclization of tetrahydroisoquinoline **2**.



Scheme 4. Completion of the synthesis of (−)-govadine (**1**).

govadine regioisomer **7** (Scheme 3). To complete the synthesis, the benzyl group was removed through hydrogenation, and the product was crystallized as the HCl salt to afforded the desired govadine salt in 92% yield (Scheme 4). While it has been noted that racemization has been observed during benzyl hydrogenolysis of other THPB analogs, no loss of enantioselectivity in the final product was observed when the reaction was performed on small scale. However, racemization was observed during scale-up (79% ee) due to increased reaction times.[19] To avoid racemization, the benzyl groups can be deprotected using HCl to afford govadine hydrochloride in 73% yield. Using the opposite enantiomer of the Noyori catalyst, the same route was utilized for the synthesis of (+)-govadine.

Preliminary in vitro testing of both enantiomers of govadine obtained from this synthetic route provided different antagonist properties towards the dopamine D1 and D2 receptors.[8] (−)-Govadine was found to be a nanomolar dopamine D1 antagonist ($EC_{50} = 5.6 \times 10^{-9}$) and moderate D2 antagonist properties ($EC_{50} = 5.6 \times 10^{-5}$). In contrast, (+)-govadine displayed weak antagonist properties at both D1 ($EC_{50} > 1.0 \times 10^{-4}$) and D2 ($EC_{50} = 1.4 \times 10^{-5}$). Current in vivo studies on each enantiomer of govadine are currently underway.

Overall, we have developed an efficient 5-step synthesis of the potential antipsychotic (+)-govadine and (−)-govadine in 39% overall yield from commercially available materials. This marks the first enantioselective synthesis of govadine and the one of the most efficient enantioselective synthesis of any THPB. Furthermore, every intermediate was purified by crystallization and no flash column chromatography was necessary. Testing of both (+)- and (−)-govadine as pharmaceutical agents in the treatment of schizophrenia and other neuropathic diseases is currently underway.

Acknowledgments

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Supplementary data

Supplementary data (all of the full procedures and chemical compound information) associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2012.01.005.

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