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## Graphical Abstract

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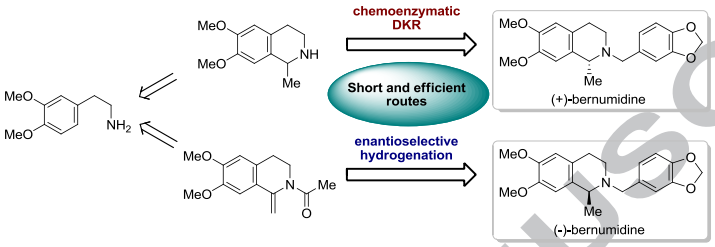

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# Total syntheses of (+)-bernumidine and its unnatural enantiomer

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ABSTRACT

Total syntheses of (+)-bernumidine and its unnatural enantiomer were accomplished through chemoenzymatic dynamic kinetic resolution and ruthenium(II)-catalyzed enantioselective hydrogenation, which provided (*R*)-salsolidine propyl carbamate and *N*-acetyl (*S*)-salsolidine in high yields and enantiomeric excesses, respectively. Both enantiomers of salsolidine were accessed and converted into (+)- and (-)-bernumidine *via* simple and efficient transformations.



(+)-Bernumidine (**1a**) is an benzylisoquinoline alkaloid isolated for the first time from leaves of *Berberis nummularia*[1] and (-)-bernumidine (**1b**) is its unnatural enantiomer.[2] Although plants of the genus *Berberis* have been employed for centuries throughout the world because of tonic, antimicrobial, and sedative properties,[2,3] to the best of our knowledge, no research concerning biological activities for (+)-bernumidine (**1a**) or even for (-)-bernumidine (**1b**) has been published until the present moment. Nevertheless, a recent study has disclosed that a racemic bernumidine derivative, i.e., where the piperonyl moiety was changed by 4-hydroxy-3,5-dimethylbenzyl group, was identified as a novel chemical scaffold with binding affinity to the μ opioid receptor (MOR) *in vitro*, combined with MOR antagonist properties. Moreover, *in vivo*, the same substance has been highly effective in antagonizing morphine-induced antinociception in mice.[4] Despite the important discoveries involving a bernumidine derivative in medicinal chemistry,[4] in preparative organic chemistry we realized a lack of synthetic routes to produce both enantiomers of bernumidine (**1a** and **1b**). In 2001, the synthesis of racemic bernumidine was reported by Vallée and coworkers through the alkylation of racemic salsolidine.[2] In that article, authors also resolved racemic salsolidine by precipitating one of the enantiomers with D-(-)-tartaric acid, further performing the alkylation of the entantiomer isolated to provide (+)-bernumidine (**1a**). However, there is no synthesis of (-)-bernumidine (**1b**) reported so far. Accordingly, enantioselective approaches for the syntheses of (+)-bernumidine (**1a**) and (-)-bernumidine (**1b**), which could be employed in the preparation of both enantiomers of a variety of bernumidine derivatives, would be of considerable importance. Thus, we examined the literature and found a practical, scalable, and efficient chemoenzymatic dynamic kinetic resolution (DKR) of secondary amines using an iridium-based amine racemization catalyst under significantly mild conditions, which was employed to the formation of (*R*)-salsolidine propyl carbamate in high yield and enantiomeric excess.[5] In addition, the operationally refined enantioselective hydrogenation of enamides catalyzed by BINAP-ruthenium(II) complexes was the method of choice to obtain *N*-acetyl (*S*)-salsolidine also in high yield and enantiomeric excess.[6]

In our retrosynthetic analysis (+)-bernumidine (**1a**) and its unnatural enantiomer (**1b**) are obtained from (*R*)-salsolidine (**2a**) and (*S*)-salsolidine (**2b**), which are produced from valuable approaches employing isoquinoline intermediates **5** and **6**, respectively, both obtained from 3,4-dimethoxyphenethylamine (**7**) (**Scheme 1**).

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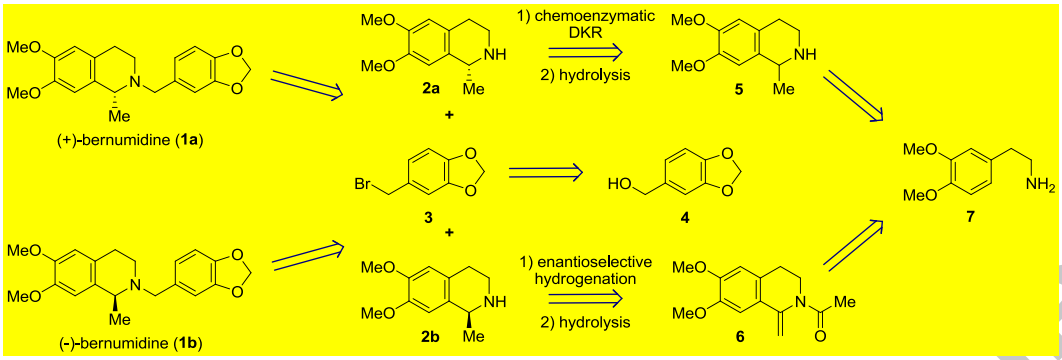
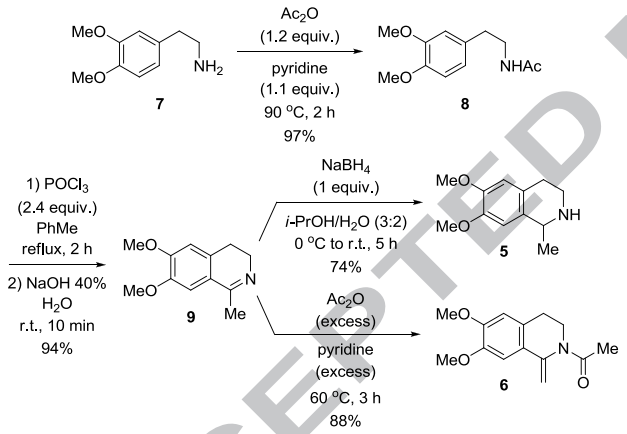


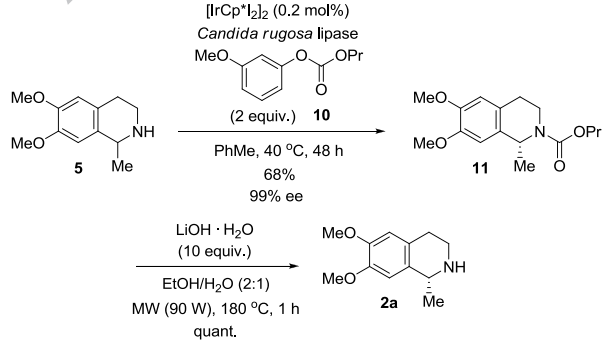

**Scheme 1.** Retrosynthetic analysis for (+)-bernumidine (**1a**) and its unnatural enantiomer (**1b**).

Intermediates **5** and **6** were prepared by minor modifications of well-established reactions.[7-10] Commercially available 3,4-dimethoxyphenethylamine (**7**) was treated with acetic anhydride in pyridine to produce corresponding *N*-(3,4-dimethoxyphenethyl)acetamide (**8**) in 97% yield.[7] Acetamide **8** was converted by Bischler-Napieralski reaction to heterocyclic compound **9** in 94% yield.[8] Intermediate **9** was reduced in the presence of $NaBH_4$ leading to 6,7-dimethoxy-1-methyl-1,2,3,4-tetrahydroisoquinoline (**5**) in 74% isolated yield.[9] Afterwards, intermediate **9** was also allowed to react with acetic anhydride in pyridine leading to the formation of 1-(6,7-dimethoxy-1-methylene-3,4-dihydroisoquinolin-2(1*H*)-yl)ethenone (**6**) in 88% isolated yield[10] (**Scheme 2**).




**Scheme 2.** Syntheses of intermediates **5** and **6**.

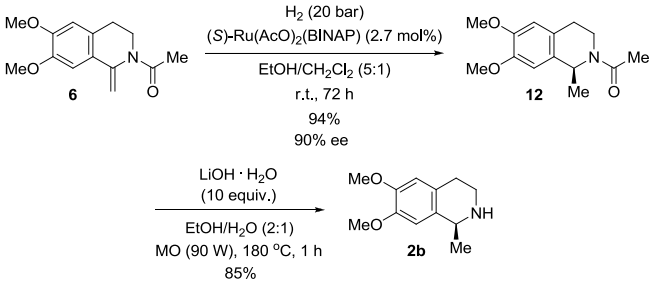
Intermediate **5** was treated with 3-methoxyphenylpropyl carbonate (**10**)[5b] employing $[IrCp^*I_2]_2$[5b,c] (0.2 mol%) and *Candida rugosa* lipase (1117 U/mg) as catalysts in toluene saturated with water at 40 °C for 48 h to produce (*R*)-salsolidine propyl carbamate (**11**) in 68% isolated yield and with 99% ee[5] (**Scheme 3**).




**Scheme 3.** Chemoenzymatic DKR and base hydrolysis providing (*R*)-salsolidine (**2a**).

Chemoenzymatic DKR of intermediate **5** was performed through an experimentally simple protocol on a 0.2 g scale. According to the literature,[5] when the same transformation was carried out on a 3 g scale, compound **11** was obtained in 82% yield and with 96% ee. Afterwards, (*R*)-salsolidine propyl carbamate (**11**) was subjected to a base hydrolysis using $LiOH{\cdot}H_2O$ in a mixture of ethanol/water (2:1) under microwave heating (90 W) at 180 °C for 1 h,[11] leading to (*R*)-salsolidine (**2a**) in quantitative yield (**Scheme 3**).

Intermediate **6** was asymmetrically reduced employing hydrogen (20 atm) and (*S*)-Ru(AcO)$_2$(BINAP) (2.7 mol%) as catalyst in ethanol/dichloromethane (5:1) at room temperature for 72 h to produce (*S*)-salsolidine acetate (**12**) in 94% isolated yield and with 90% ee[6] (**Scheme 4**).

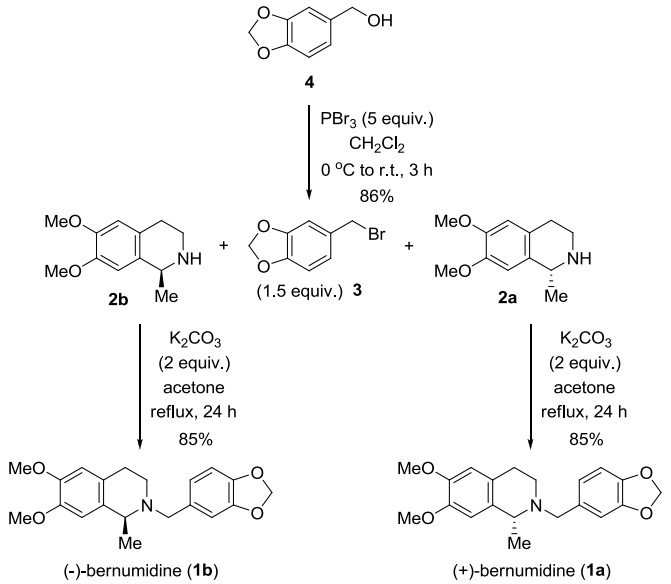



**Scheme 4.** Enantioselective hydrogenation and base hydrolysis providing (*S*)-salsolidine (**2b**).

Asymmetric reduction of intermediate **6** provided (*S*)-salsolidine acetate (**12**) employing 20 atm pressure of hydrogen for 72 h under strictly inert atmosphere and anhydrous conditions. According to previous report,[6] the reduction of intermediate **6** gave (*S*)-salsolidine acetate (**12**) in 100% conversion and with 96% ee employing 4 atm pressure of hydrogen for 48 h also under strictly inert atmosphere and anhydrous conditions. Subsequently, (*S*)-salsolidine acetate (**12**) was hydrolyzed using $LiOH{\cdot}H_2O$ in a mixture of ethanol/water (2:1) under microwave heating (90 W) at 180 °C for 1 h,[11] affording (*S*)-salsolidine (**2b**) in 85% (**Scheme 4**).

Although chemoenzymatic DKR represents a practical, scalable, and efficient transformation to produce (*R*)-salsolidine propyl carbamate (**11**) only this enantiomer can be accessed through this approach.[5] In spite of the ruthenium(II)-catalyzed enantioselective hydrogenation may be considered operationally laborious, this method can be used to produce (*S*)-salsolidine acetate (**12**) and also its enantiomer just by changing the chiral BINAP ligand employed.[6]

Piperonyl alcohol (**4**) was converted to piperonyl bromide (**3**) using $PBr_3$ in 86% yield.[12] Then, (*R*)-salsolidine (**2a**) and (*S*)-salsolidine (**2b**) were allowed to react with piperonyl bromide (**3**) in the presence of $K_2CO_3$, under extensively optimized conditions, which were achieved performing the transformation in different temperatures and times, using conventional and microwave heating, leading to (+)-bernumidine (**1a**) and (-)-bernumidine (**1b**), respectively, both in an isolated yield of 85% (**Scheme 5**).




**Scheme 5.** Transformations to achieve (+)-bernumidine (**1a**) and (-)-bernumidine (**1b**).

(+)-Bernumidine (**1a**) and (-)-bernumidine (**1b**) were obtained after 6 steps with overall yields of 39% and 54%, respectively. Furthermore, both enantiomers of bernumidine (**1a** and **1b**) were achieved through short and efficient routes with enantiomeric excesses ≥ 90%.

The structures of compounds **2a,b** and **3-12** were assigned according to their LRMS, IR, $^1$H, and $^{13}$C NMR spectra. DEPT 135, COSY, and HSQC NMR spectra were obtained to confirm the structure of compound **11**. The structures of compounds **1a,b** were assigned according to their LRMS, IR, $^1$H, $^{13}$C, DEPT 135, COSY, and HSQC NMR spectra. Compound **1b** provided HRMS that is in agreement with the proposed structure. The optical rotation of compound **1a** matched the one reported for the natural bernumidine[1] (Supporting Information).

In summary, total syntheses of (+)-bernumidine and its unnatural enantiomer were accomplished through chemoenzymatic dynamic kinetic resolution and ruthenium(II)-catalyzed enantioselective hydrogenation, respectively. Chemoenzymatic DKR represents a practical, scalable, and efficient transformation to produce (*R*)-salsolidine propyl carbamate, however, only this enantiomer can be accessed through this method. Although ruthenium(II)-catalyzed enantioselective hydrogenation may be considered operationally laborious, this approach can be used to produce (*S*)-salsolidine acetate (**12**) and also its enantiomer. Short and efficient routes were developed for both enantiomers of bernumidine (**1a** and **1b**) and we expect that these routes may be employed for the preparation of bernumidine derivatives with application in medicinal chemistry.

## Acknowledgments

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## Supplementary Material

Supplementary data (experimental procedures, characterization data, and RMN spectra) associated with this article can be found, in the online version, at http://dx.doi.org/XXX.

**Highlights**

- Synthetic routes were developed for (+)-bernumidine and its unnatural enantiomer.
- Total synthesis of (+)-bernumidine was accomplished through chemoenzymatic DKR.
- Bernumidine unnatural enantiomer was achieved via enantioselective hydrogenation.