



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

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ARTICLE INFO

Article history:

Received 12 July 2018

Revised 14 August 2018

Accepted 22 August 2018

Available online 23 August 2018

Keywords:

(+)-Bernumidine

Bernumidine enantiomer

MOR ligands

Chemoenzymatic DKR

Enantioselective hydrogenation

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.

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(+)-Bernumidine (**1a**) is an benzyloquinoline 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 enantiomer 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

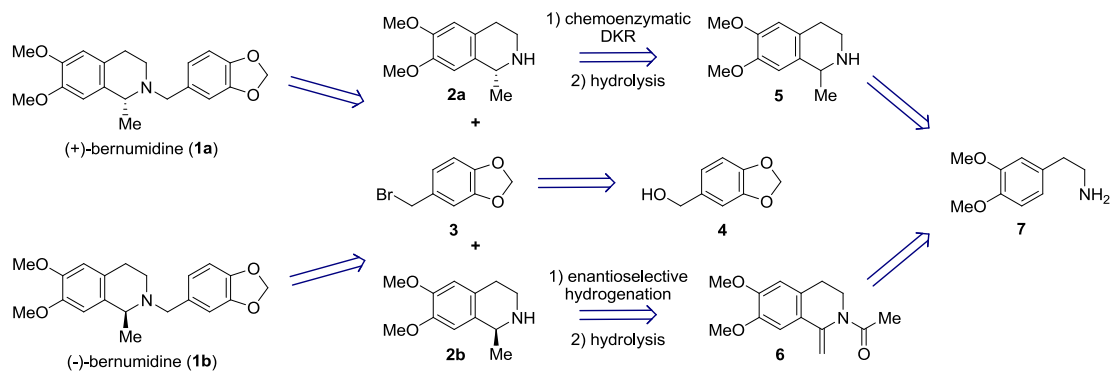
employed in the preparation of both enantiomers of a variety of bernumidine derivatives, would be of considerable importance. Thus, we examined the literature and found a practical, scalable, and efficient chemoenzymatic dynamic kinetic resolution (DKR) of secondary amines using an iridium-based amine 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).

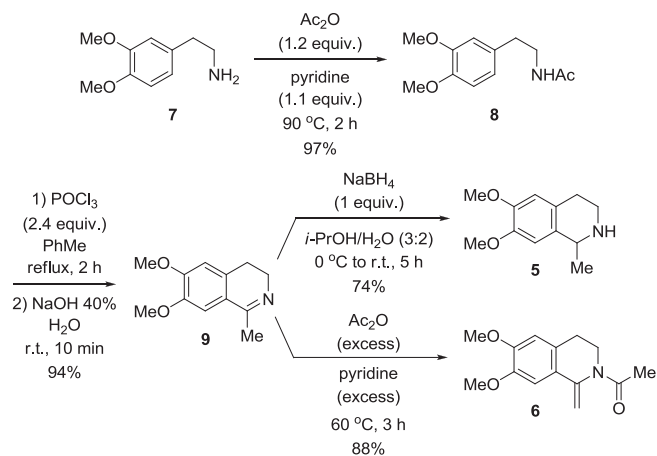
Intermediates **5** and **6** were prepared by minor modifications of well-established reactions [7–10]. Commercially available 3,4-dimethoxyphenethylamine (**7**) was treated with acetic anhydride in pyridine to produce corresponding *N*-(3,4-dimethoxyphenethyl)acetamide (**8**) in 97% yield [7]. Acetamide **8** was converted by Bischler-Napieralski reaction to heterocyclic compound **9** in 94% yield [8]. Intermediate **9** was reduced in the presence of NaBH₄ 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).

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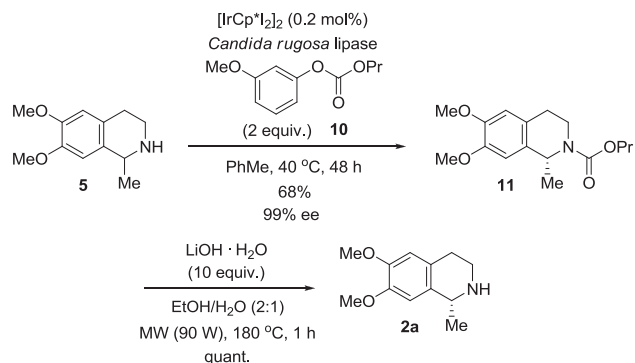
Scheme 1. Retrosynthetic analysis for (+)-bernumidine (**1a**) and its unnatural enantiomer (**1b**).



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

Intermediate **5** was treated with 3-methoxyphenylpropyl carbonate (**10**) [5b] employing [IrCp^{*}]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).

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·H₂O in a mixture of ethanol/water (2:1) under microwave heating



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

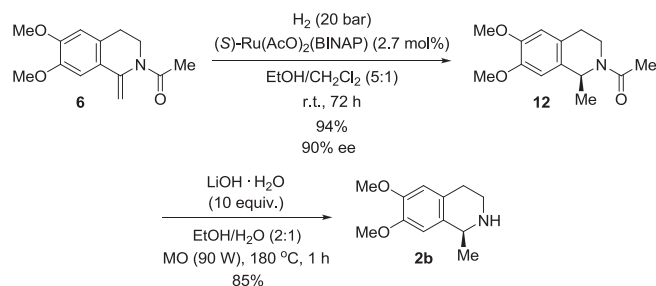
(90 W) at 180 °C for 1 h [11], leading to (*R*)-salsolidine (**2a**) in quantitative yield (Scheme 3).

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*)-salsidine acetate (**12**) in 94% isolated yield and with 90% ee [6] (Scheme 4).

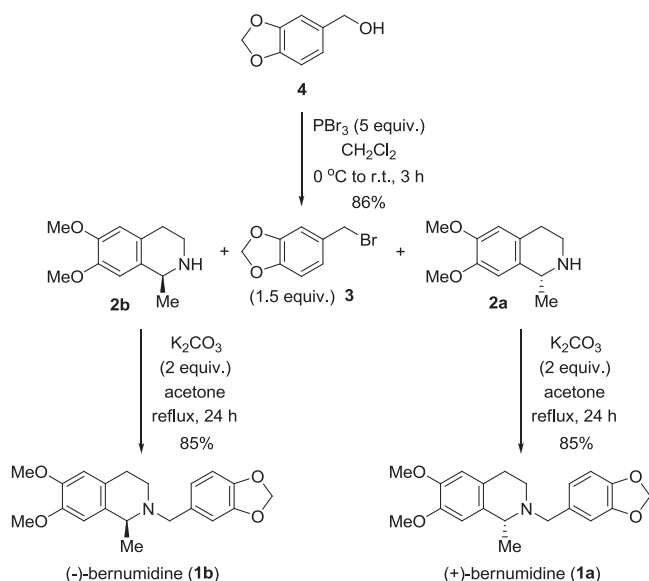
Asymmetric reduction of intermediate **6** provided (S)-salsolidine acetate (**12**) employing 20 atm pressure of hydrogen for 72 h under strictly inert atmosphere and anhydrous conditions. According to previous report [6], the reduction of intermediate **6** gave (S)-salsolidine acetate (**12**) in 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·H₂O 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 PBr₃ in 86% yield [12]. Then, (*R*)-salsolidine (**2a**) and (*S*)-salsolidine (**2b**) were allowed to react with piperonyl bromide (**3**) in the presence of K₂CO₃, 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 4. Enantioselective hydrogenation and base hydrolysis providing (S)-salsolidine (**2b**).



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

(+)-Benumidine (**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 $\geq 90\%$.

The structures of compounds **2a,b** and **3–12** were assigned according to their LRMS, IR, ^1H , 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, ^1H , ^{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

We are grateful to São Paulo Research Foundation (FAPESP) (Grant Number: 2017/21990-0) and to National Council for Scientific and Technological Development (CNPq) for financial support. B.K.C. and T.R.C.S. thank Coordination of Improvement of Higher Level Personnel (CAPES) for the fellowships.

Appendix A. Supplementary data

Supplementary data (experimental procedures, characterization data, and NMR spectra) associated with this article can be found, in the online version, at <https://doi.org/10.1016/j.tetlet.2018.08.046>.

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