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Stereoselective syntheses of 3-dehydroxynaltrexamines and *N*-methyl-3-dehydroxynaltrexamines

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ABSTRACT

Methodology is presented for the synthesis of 6α/β-3-dehydroxynaltrexamines and 6α/β-*N*-methyl-3-dehydroxynaltrexamines. A stereoselective route is provided for each target compound while a novel one-pot method for the synthesis of 6α/β-*N*-methyl-3-dehydroxynaltrexamines is also explored. These results enable the versatile and efficient preparation of key epoxymorphinan intermediates to facilitate future selective opioid ligand discovery and development.

Introduction

6α- and 6β-Naltrexamines (NTA, Fig. 1) are crucial epoxymorphinan intermediates used for the synthesis of opioid receptor ligands [1–6]. Based on *in vitro* and *in vivo* studies, many synthetic NTA derivatives with selective kappa opioid receptor (KOR) binding profiles have exhibited potential therapeutic effects for a wide variety of diseases such as alcohol addiction, cocaine addiction, pruritus, and anagelsia [1–8]. Many KOR ligands have also shown high affinity for the mu opioid receptor (MOR) making them MOR/KOR dual-selective ligands, e.g. nalfurafine (Fig. 1). Recent structural biology studies [9–12] have provided insight into opioid receptor subtype selective molecular design. For example, the 3-hydroxy group in the epoxymorphinan skeleton may be essential for MOR binding but not for KOR binding, as exemplified by 42B (Fig. 1). It is therefore conceivable that the corresponding 3-dehydroxy counterparts of NTA will be of cardinal significance in the preparation of KOR-selective molecules. Nonetheless, no preparatory method for either 6α- or 6β-3-dehydroxynaltrexamine has been reported, nor their *N*-methyl derivatives.

Herein we present, for the first time, stereoselective synthetic strategies for 3-dehydroxynaltrexamines and *N*-methyl-3-dehydroxynaltrexamines as essential building blocks for the preparation of opioid ligands [12,13].

Results and discussion

As shown in Scheme 1, novel target compounds **4** and **7** were successfully prepared *via* asymmetric synthesis. Previously, similar stereoselective methods have been applied to prepare α/β-naltrexamines [14,15]. In detail, the starting material 3-dehydroxynaltrexone **1** was first prepared from naltrexone (Scheme S1). Then, the iminium ion intermediate **2** was formed by the azeotropic removal of water to allow nucleophilic addition. Without any purification process, the *N*-dibenzyl protected 6β-3-dehydroxyamine **3** was obtained through reductive amination of intermediate **2**. As previously reported [14], the cyclohexyl C ring in **2** may shift from the more stable chair conformation to a higher energy boat conformation due to the strain between the epoxy ether oxygen and the benzyl group in the chair conformation (Fig. 2). Thus, the reducing agent would mostly approach the C ring from the more sterically accessible α-face to yield a β-amine after hydride transfer, therefore achieving stereoselectivity. The fact that 6α-epimer products were not observed further supports this mechanism. Additionally, we believe the repulsion between the epoxy ether oxygen and the iminium ion is also an important driving force in the chair-to-boat conformation change. Following this critical step, debenzylation of intermediate **3** gave the desired 6β-3-dehydroxynaltrexamine **4** as its hydrochloride salt in acceptable yield.

Meanwhile, the key intermediate **6** used to prepare 6α-3-dehydroxynaltrexamine was obtained through imine formation and stereoselective reduction, followed by catalytic hydrogenation to give **7**. Of note, intermediate **6** was an imine rather than an iminium ion due to the less acidic conditions (absence of benzoic

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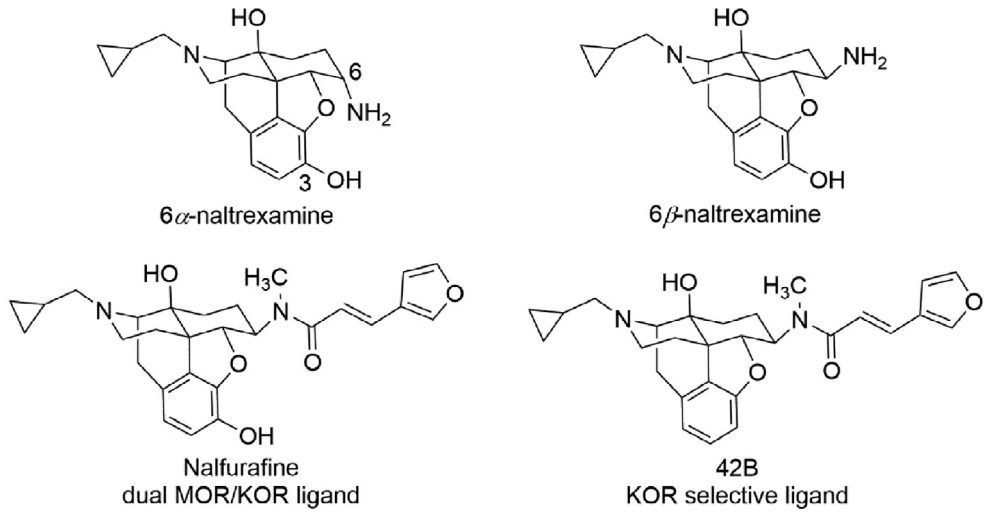
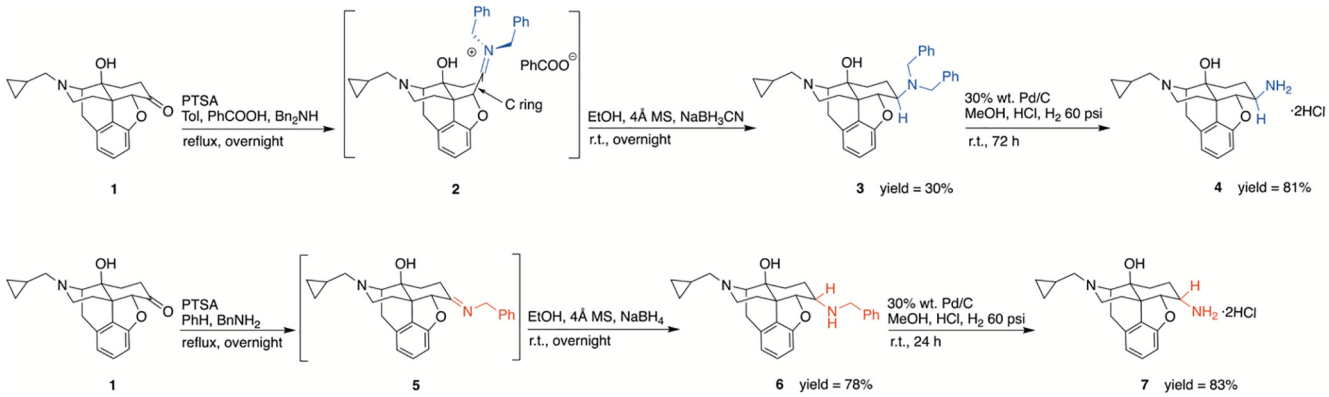


Fig. 1. 6α- and 6β-Naltrexamines and examples of opioid selective ligands [8,13].



Scheme 1. Stereoselective syntheses of 6α- and 6β-3-dehydroxynaltrexamines.

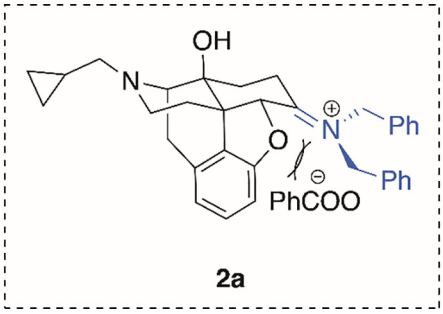


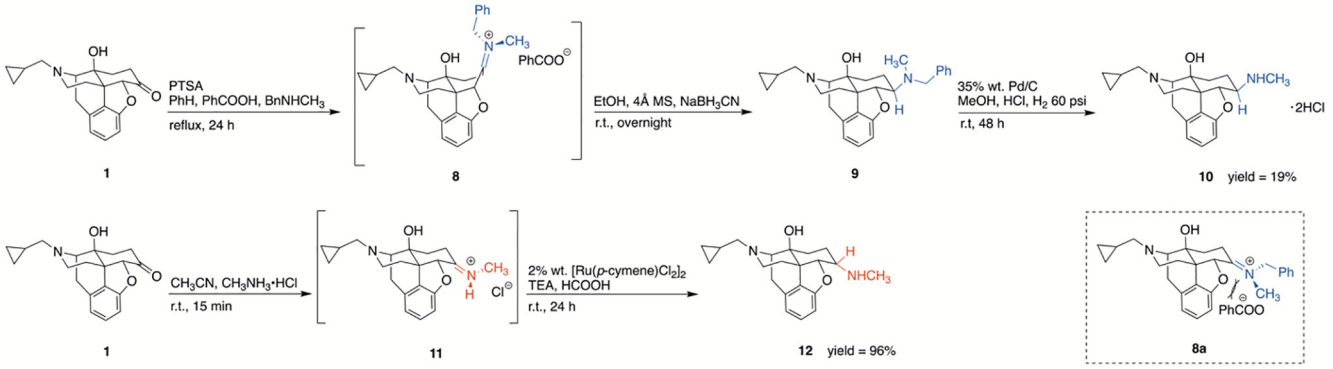
Fig 2. Demonstration of the strained chair conformation of **2a**.

acid). In this scenario, the decreased bulkiness of the *N*-benzyl substitution paired with the absence of the benzoate ion helped maintain the C ring of intermediate **5** in the more stable chair conformation. As a result, the hydride would approach from the less sterically hindered β-face, leading to the desired 6α stereochemistry for intermediate **6** and final compound **7** as its hydrochloride salt. Utilizing this approach, no 6-hydroxy reduction product was observed from either synthetic route (Scheme 1). Therefore, the above asymmetric syntheses serve as stereoselective as well as chemoselective approaches to prepare 6α- and 6β-3-dehydroxynaltrexamines.

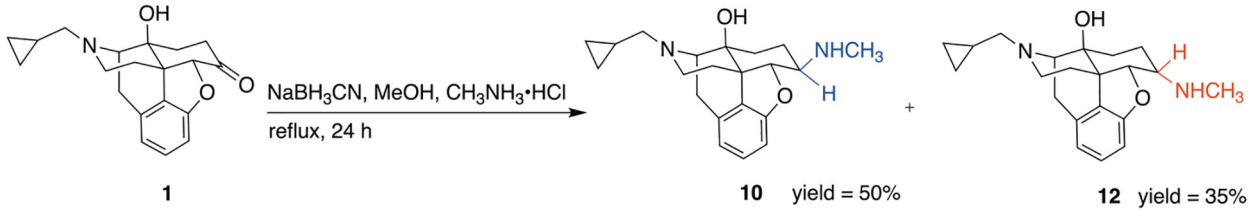
Next, we explored the preparation of two *N*-methyl-3-dehydroxynaltrexamines **10** and **12**, respectively [13,16,17] (Scheme 2), because they are also key intermediates to prepare many opioid ligands, e.g. nalfurafine (Fig. 1). First, the same stereoselective strategy used to prepare **4** was applied to obtain 6β-*N*-methyl-3-dehydroxynaltrexamine **10** wherein benzylmethylamine was used for the formation of the iminium ion instead of dibenzylamine. Of note, it is very likely that steric repulsion between the ether oxygen and the negatively charged benzoate ion is the primary driving force for the C ring to adopt the boat conformation to achieve the desired stereoselectivity (Scheme 2, **8a**). The target product **10** was obtained in moderate yield over three steps.

For the preparation of 6α-*N*-methyl-3-dehydroxynaltrexamine **12**, a Noyori ruthenium catalyst, $[Ru(II)(p\text{-cymene})Cl_2]_2$, was utilized to induce the stereoselectivity, while formic acid in the presence of triethylamine provided the hydrogen source. Intriguingly, no chiral ligand was required due to the unique "T shape" of the epoxymorphinan skeleton providing significant steric hindrance to the α-face to only allow the hydride bearing bulky Noyori catalyst to approach from the β-face; this ultimately resulted in the α-product in high yield. Of note, the less bulky borohydride reagents did not give satisfactory results.

Furthermore, we explored a one-pot method to prepare the epimeric *N*-methyl-3-dehydroxynaltrexamines. To the best of our knowledge, this is the first application of such a method to generate amines **10** and **12** which can then be separated by column



Scheme 2. Stereoselective syntheses of 6α- and 6β-*N*-methyl-3-dehydroxynaltrexamines.



Scheme 3. One-pot method to prepare *N*-methyl-3-dehydroxynaltrexamines.

chromatography. This one-pot method, although not stereoselective, appears to be the most time-efficient way to access the *N*-methyl-3-dehydroxynaltrexamine building blocks on potentially large scales (Scheme 3). One convenience of this reaction is obtaining both epimers in a much shorter period of time, one day, compared to nearly a weeks' time necessitated by stereoselective methods. In addition, the one-pot method significantly improves atom economy in the scenario that both epimers are desired. A final merit of this method is the avoidance of carcinogenic reagents, i.e. benzene, in the preparation of 6β-*N*-methyl-3-dehydroxynaltrexamine **10** and ruthenium for 6α-*N*-methyl-3-dehydroxynaltrexamine **12**.

Conclusion

In summary, stereoselective reductive amination protocols have been developed for four important building blocks of epoxymorphinan derivatives, 6α/β-3-dehydroxynaltrexamines and 6α/β-*N*-methyl-3-dehydroxynaltrexamines. Also, an efficient one-pot reductive amination method to prepare 6α/β-*N*-methyl-3-dehydroxynaltrexamines is a reasonable alternative to consider. We believe this effort will facilitate the preparation of novel opioid selective ligands.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2020.152379.

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