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The application of a specific morphinan template to the synthesis of galanthamine

Naoshi Yamamoto [a], Takahiro Okada [b], Yukimasa Harada [c], Noriki Kutsumura [a], Satomi Imaide [c], Tsuyoshi Saitoh [a], Hideaki Fujii [c], Hiroshi Nagase [a, b, c, *]

[a] International Institute for Integrative Sleep Medicine (WPI-IIIS), University of Tsukuba, 1-1-1 Tennodai, Tsukuba, Ibaraki 305-8575, Japan
[b] Graduate School of Pure and Applied Sciences, University of Tsukuba, 1-1-1 Tennodai, Tsukuba, Ibaraki 305-8571, Japan
[c] Laboratory of Medicinal Chemistry, School of Pharmacy, Kitasato University, 5-9-1 Shirokane, Minato-ku, Tokyo 108-8641, Japan

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ABSTRACT

(−)-Galanthamine (**4**) was synthesized from naltrexone (**1**) in 18 steps with 3% total yield by overcoming many specific side reactions derived from the 4,5-epoxymorphinan skeleton. The key features are cleavage of the D-ring by the Hofmann elimination and the following the one-pot C9–C10 and C9–14 bond cleavages concomitant with the C9 removal by the OsO_4–$NaIO_4$ combination reaction. Then, the treatment with zinc powder in acetic acid led to not only removal of the 2,2,2-trichloroethoxycarbonyl (Troc) group, but also reductive amination of the resulting imine to give the desired 7-membered ring.

1. Introduction

Three types of opioid receptors (μ (MOR), *δ* (DOR), κ (KOR)) are well established not only by pharmacological studies but by molecular biological studies.[1] Narcotic addiction is believed to be derived from MOR type, and therefore KOR and DOR types are promising drug targets for analgesics without addiction.[2] To obtain ideal analgesics without addiction and other side effects derived from the MOR, we have synthesized various kinds of naltrexone derivatives by use of the specific reactivity of the morphinan template and have reported some selective ligands for the KOR[3] and DOR[4] receptors. One of our designed KOR selective agonists, nalfurafine hydrochloride (TRK-820, Scheme 1) prepared *via* 5 steps from the MOR antagonist, naltrexone (**1**),[5] was launched in Japan as an antipruritic for patients undergoing dialysis in 2009 and for patients with hepatic disease in 2015. On the other hand, other KOR agonists, aryl-acetamide derivatives such as U-50488H[6] and U-69593[7] were synthesized and developed (Fig. 1). However, all the aryl-acetamide derivatives were eliminated from clinical trials not only as analgesics, but also as antipruritics because of their serious side effects like psychotomimetic and aversive reactions.[8] Notably, nalfurafine has neither aversive nor addictive effects. We postulated that the absence of aversion may derive from the partial structure, the tyrosine moiety in nalfurafine, which is the N-terminal structure in the endogenous KOR agonist, dynorphin. The aforementioned aryl-acetamide derivatives have no tyrosine moiety. Focusing on the possible importance of the tyrosine moiety, we utilized naltrexone (**1**) as the starting material to synthesize the nalfurafine. Naltrexone (**1**) is also a medication that reverses the effects of opioids and is used primarily in the management of alcohol and opioid dependence in the USA.[5] The commercially available compound **1** has also been using as a readily available drug-like compound. Therefore, we have utilized **1** as a template to create many novel compounds.[9]

The specific structural features in naltrexone (**1**), the 4,5-epoxy ring, four sequential asymmetric centers, two hydroxy groups (14-OH and phenolic OH) and a basic nitrogen, have led to many intramolecular interactions resulting in unexpected complex rearrangement reactions. A noteworthy characteristic of the skeleton is the abnormal stability of the enol form of the 6-keto group in **2** (Fig. 2).[10] The stability is derived from the rigid and highly strained 4,5-epoxy morphinan skeleton (especially, the 4,5-epoxy ring which plays an important role). Furthermore, the 17-basic nitrogen

* Corresponding author. International Institute for Integrative Sleep Medicine (WPI-IIIS), University of Tsukuba, 1-1-1 Tennodai, Tsukuba, Ibaraki 305-8575, Japan.
E-mail address: nagase.hiroshi.gt@u.tsukuba.ac.jp (H. Nagase).

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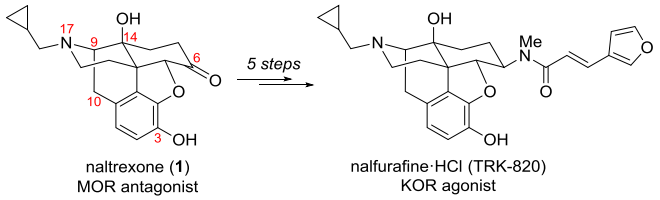


Scheme 1. Nalfurafine (KOR agonist) was synthesized from naltrexone (**1**, MOR antagonist).

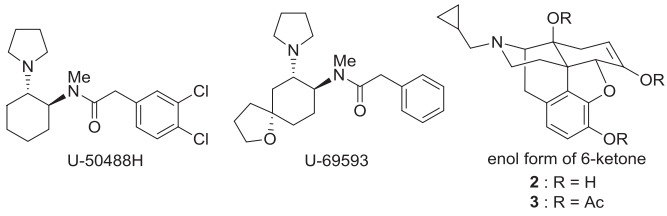


Fig. 1. Structures of U-50488H, U-69593, **2** and **3**.

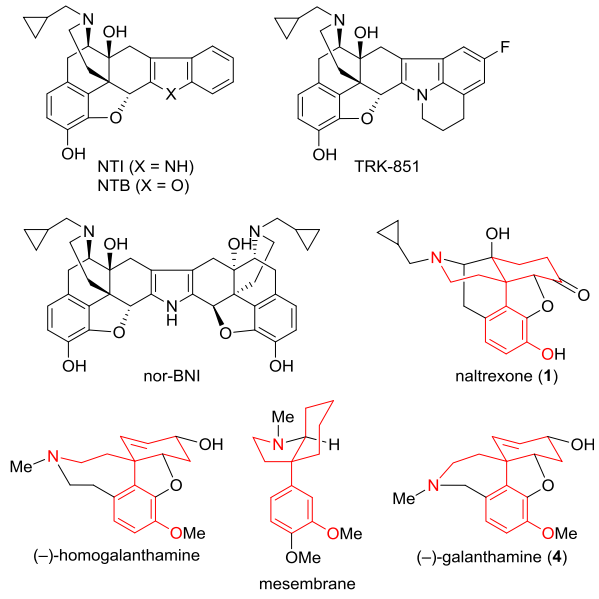


Fig. 2. Structures of NTI, NTB, TRK-851 and nor-BNI. The common features between naltrexone (**1**), (−)-homogalanthamine, mesembrane and (−)-galanthamine (**4**).

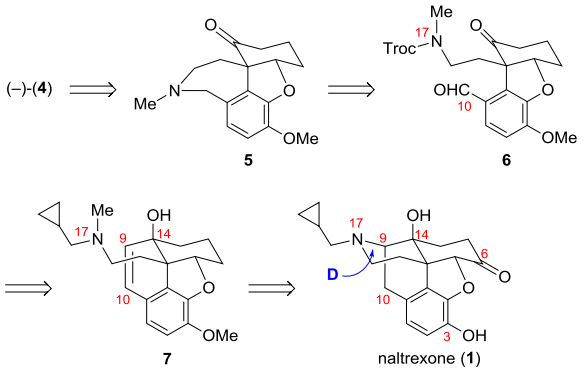
intramolecularly abstracts the hydrogen in 14-hydroxy group and the resulting hydroxide ion can drag away the 7-axial hydrogen to afford enol form **2**. The compound **2** was acetylated with acetic anhydride/pyridine at room temperature to give triacetates **3**.[10]

We easily synthesized the representative δ and κ receptor selective antagonists (NTI,[11] NTB,[12] TRK-851[13] and nor-BNI[14]) using the stable enol formation (Fig. 2). On the other hand, the abnormally strained structure accelerated the undesired cleavage reaction of 4,5-epoxy ring to disturb the reductive removal of the 6-keto-group of **1** in the synthesis of (−)-homogalanthamine.[15] Thus, the abnormal reactivity needed to be effectively controlled to utilize the antagonist as a template. The above-mentioned knowledge of many specific and abnormal reactions derived from the skeleton should help investigators utilize the naltrexone (**1**) as a template. Recently, we have considered the common features between the partial structures of naltrexone (**1**) and the target molecules, (−)-homogalanthamine, mesembrane, and (−)-galanthamine (**4**) (red part of the structures, Fig. 2).

(−)-Galanthamine (**4**),[16] an alkaloid isolated from the Caucasian snowdrop *Galanthus woronowii*, and also from another species of the Amaryllidaceae family, *Lycoris radiata*, is a prescription drug for the treatment of Alzheimer's disease in Europe, the United States and Japan.[17] The mechanism of the anti-Alzheimer's disease effect is derived from the dual action on the cholinergic system, not only inhibiting acetylcholinesterase (AChE) activity but also allosterically modulating the nicotinic acetylcholine receptor.[18] Many reports have described the synthesis of **4**[19] and its derivatives.[20] We were also interested in efficient synthesis of **4** maximizing the similarities with the partial structure of naltrexone (**1**). However, at that time, the lack of a method to remove the carbon (C9) from **1** inevitably led us to synthesize (−)-homogalanthamine[15] instead of (−)-**4**. After reporting the synthesis of (−)-homogalanthamine, we discovered that the C9 removal method cited in the synthesis of mesembrane[21] was applicable to the synthesis of (−)-**4**. In consideration of the key step, we proposed a retrosynthetic pathway of (−)-**4** that differed from that of (−)-homogalanthamine in Scheme 2. The D-ring in **1** can be cleaved by the Hofmann elimination to give an allyl alcohol **7**. A keto-aldehyde **6** would be transformed from **7**, and then, deprotection of the 2,2,2-trichloroethoxycarbonyl (Troc) group of **6** and reductive amination of the resulting imine would lead to ketone **5** with a 7-membered ring. Finally, the ketone group would be converted to the desired allyl alcohol moiety to accomplish synthesis of (−)-**4**. However, again, we encountered the formidable side reactions derived from the reactivity of the naltrexone in the synthesis of (−)-**4** from **1**. We overcame these side reactions and attained the synthesis of (−)-**4**. Herein, we report the two synthetic methods for (−)-**4** from **1**.

2. Results and discussion

Naltrexone (**1**) was converted to the methyl ether **8** with methyl iodide. It was our bitter experience that the direct removal of the ketone group by either the Clemmensen-type[22] or the Wolff–Kishner reductions[23] led to the cleavage reaction of the 4,5-epoxy ring. Therefore, we applied the longer indirect method as follows: (1) reduction of the ketone with sodium triacetoxy borohydride, (2) mesylation of the resulting α-hydroxy compound with mesyl chloride, and (3) treatment of the mesylate **9** with sodium iodide followed by treatment with DBU to give the isomeric mixtures of double bond **10** and **11**. The obtained mixtures were reduced with Wilkinson's catalyst in benzene to afford a saturated single compound **12** in 73% yield over six steps (Hydrogenation of compound **10** with heterogeneous catalysts like PtO_2 or Pd/C led to the 4,5-epoxy ring opening).[15]



Scheme 2. Retrosynthesis of (−)-**4** from naltrexone (**1**).