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Discovery of fused azetidines as novel selective α4β2 neuronal nicotinic receptor (NNR) agonists*

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Abstract: An efficient synthesis of (1*R*,5*S*)-6-(5-cyano-3-pyridinyl)-3,6-diaza-bicyclo[3.2.0]heptane **A-366833**, a novel potent selective neuronal nicotinic receptor (NNR) agonist, is described. The enantiomerically pure pharmacophore benzyl (*1S*,5*S*)-3,6-diaza-bicyclo[3.2.0]heptane-3-carbamate was successfully constructed from benzyl *N*-allyl-*N*-(2-hydroxyimino-ethyl)-carbamate through a convenient approach including an intramolecular [1,3]-dipolar cycloaddition, reductive ring-opening reaction, chiral resolution, and intramolecular cyclization. Subsequent *N*-arylation of the pharmacophore with 3-bromo-5-cyano-pyridine and *N*-Cbz deprotection with trifluoroacetic acid furnished **A-366833**.

Keywords: Fused azetidines; neuronal nicotinic receptors; NNR agonists; antinociceptive; NNR-based analgesics.

In the search for novel therapeutic compounds to safely treat both acute and chronic pain, a number of novel approaches to pain relief are currently under investigation. One of the most promising approaches is the use of selective neuronal nicotinic receptor (NNR) agonists as analgesics [1]. A diversity of NNR subtypes are widely distributed throughout the central and peripheral nervous systems. The centrally expressed α4β2 subtype is understood to be an important target involved in mediating the analgesic response elicited by NNR agonists [2]. The discovery of epibatidine, an NNR agonist with extremely potent analgesic activity [3], fueled great interest in research directed toward identifying safe and efficacious analgesics acting through an NNR-mediated mechanism. At Abbott Laboratories, **ABT-594** was discovered to possess broad-spectrum antinociceptive activity in preclinical assays of acute and chronic pain and was advanced to clinical development [4]. To further understand the NNR subtypes that mediate analgesia vs. adverse events, and to develop a second-generation NNR-based analgesic, a series of enantiopure-fused azetidines have been prepared. **A-366833** was found to be a selective α4β2 agonist with broad-spectrum analgesic activity and an improved safety profile relative to **ABT-594** [5]. Here, we disclose the synthesis of enantiomerically pure benzyl (1*S*,5*S*)-3,6-diaza-bicyclo[3.2.0]heptane-3-carbamate and its further application in the efficient synthesis of **A-366833**.

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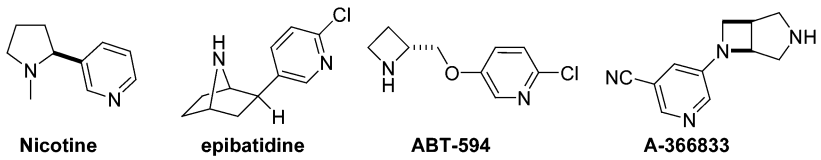
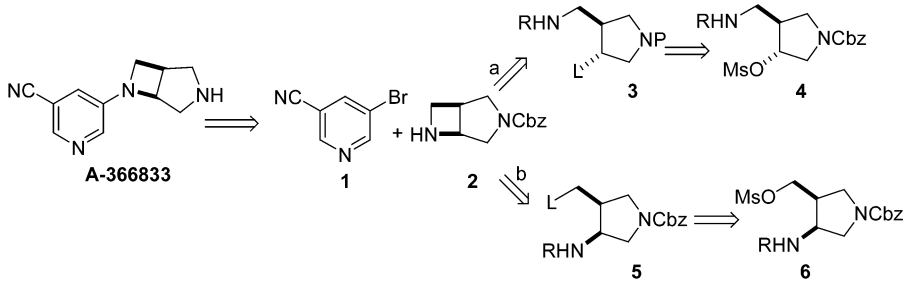


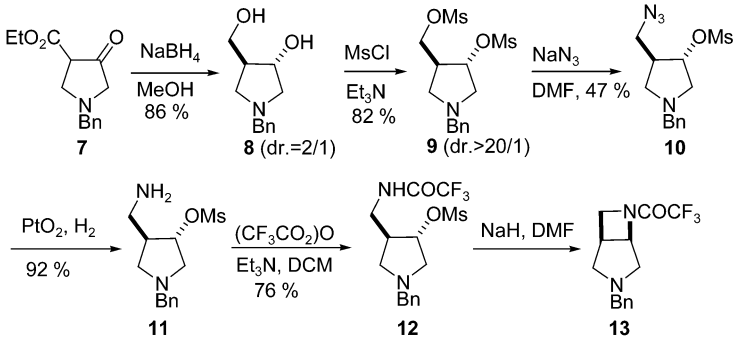
Scheme 1

From a retrosynthetic point of view, **A-366833** is straightforwardly disconnected at the C–N bond between the aromatic pyridine and fused azetidine. Upon this disconnection, the enantiomerically pure pharmacophore (1*S*,5*S*)-3,6-diaza-bicyclo[3.2.0]heptane **2** becomes the key precursor (Scheme 2). Of the many possible synthetic routes toward **2** [7], two different approaches were initially chosen for further investigation: (a) a *trans*-pyrrolidine approach, constructing the azetidine ring from the *trans*-3,4-disubstituted pyrrolidine (**4**) originally reported by Jacquet et al [6]; (b) a *cis*-pyrrolidine approach, assembling azetidine ring from the *cis*-3,4-disubstituted pyrrolidine (**6**).



Scheme 2

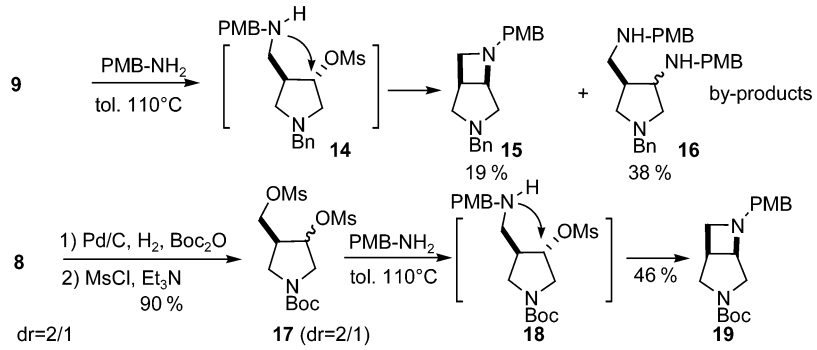
Jacquet et al. reported a racemic synthesis of 3,6-diazabicyclo[3.2.0]heptane (**13**) via an intramolecular cyclization of 3,4-disubstituted *N*-benzyl pyrrolidine (**12**) (Scheme 3) [6]. This synthesis involved a multistep sequence toward the preparation of *trans*-3,4-disubstituted pyrrolidine (**12**) and required a key ring construction step via C–N bond formation through substitution of the secondary mesylate with the primary amino group. We therefore investigated this synthetic route. The mixture of *trans*- and *cis*-*N*-benzyl-4-hydroxymethyl-pyrrolidin-3-ol (d.r. ~2/1) (**8**) was prepared by the reduction of 4-oxo-pyrrolidine **7** with $NaBH_4$ [7]. Treatment of **8** with methanesulfonyl chloride in the presence of Et_3N afforded *trans*-dimesylate **9** in 82 % yield. Displacement of the primary mesylate in **9** with NaN_3 gave azide **10**. Hydrogenation of azide **11** using PtO_2 as catalyst followed by protection of the amino group in **11** with trifluoroacetic anhydride gave key intermediate **12**. However, the cyclization of



Scheme 3

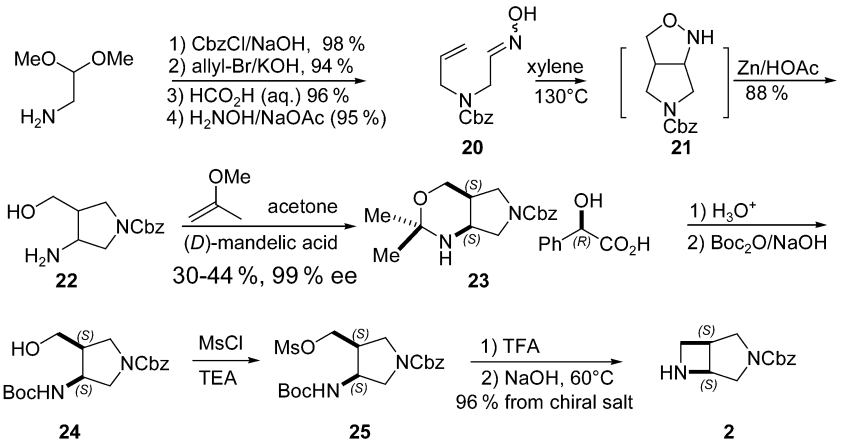
12 with NaH in DMF provided **13** in low to moderate chemical yield. Elimination of the secondary mesylate in **12** was the major side reaction limiting the conversion to **13** (Scheme 3).

Substitution of the primary mesylate in **9** with a slight excess of *p*-methoxybenzylamine in toluene at 110 °C was also tried (Scheme 4). The reaction gave the fused azetidine **15** in 19 % yield, along with a mixture of *cis/trans* of disubstituted acyclic by-products **16** (38 % isolated yield). The yield for the formation of fused azetidine was improved to 46 % by the replacement of the *N*-benzyl protecting group in **9** with the *N*-Boc group (**17**). However, due to the limited potential of achieving a chiral synthesis of optically pure **2**, further optimization of this approach was not pursued.



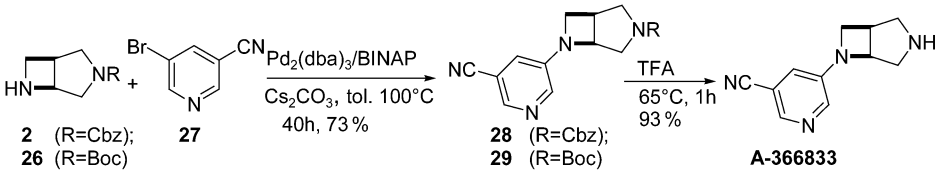
Scheme 4

Our inability to achieve efficient intramolecular displacement of the secondary mesylate with either an amide anion (Scheme 3) or amine (Scheme 4) nucleophile led us to consider translocation of the reacting groups, so that ring closure involves more facile displacement of the primary mesylate by the secondary amine. This, in turn, required access to the *cis*-disubstituted pyrrolidine, and we specifically targeted enantiomerically pure (3*S*,4*S*)-3-amino-4-hydroxymethylpyrrolidines like **24** [8]. Ohta et al. reported that racemic benzyl 3-amino-4-hydroxymethylpyrrolidinyl carbamate could be resolved by formation of optically pure chiral salt with either (D)- or (L)-mandelic acid [8c]. To examine this protocol, racemic benzyl 3-amino-4-hydroxymethylpyrrolidinyl carbamate (**22**) was prepared through a two-step/one-pot sequence involving the intramolecular 1,3-dipolar cycloaddition [9] of oxime **20**, followed by the reductive cleavage of isoxazolidine **21** with Zn/HOAc in overall 88 % chemical yield (Scheme 5). According to the procedures reported by Ohta, racemic amino-alcohol **22** was then treated with 1 equiv of D-mandelic acid in dry acetone at –20 °C for 48 h, and chiral salt **23** was isolated in <10 % recovery with >99 % ee. The recovery can be improved up to 30–44 % by simply pretreating **22** with excess of 2-methoxypropene. This modification also allows the chiral resolution proceed at ambient temperature without sacrificing either optical purity or chemical recovery. Hydrolysis of **23** under acidic conditions, followed by *N*-Boc protection under basic conditions afforded **24** in quantitative yield. Reaction of **24** with methanesulfonylchloride gave mesylate **25.** As expected, the primary mesylate **25** was smoothly transformed to **2** by removal of the Boc protecting group under acidic conditions, followed by basification to liberate the nucleophilic amine, which cyclized at 60 °C to provide **2** in 96 % overall yield from **23.**



Scheme 5

As shown in Scheme 6, **2** was then coupled with 3-bromo-5-cyanopyridine under the catalysis of $Pd_2(dba)_3$/BINAP [10]. Under conventional reaction conditions using 1.5 equiv of ^{t}BuONa as base, the reaction proceeds over 10 h to provide the desired product **28** in 47 % yield, accompanied by its *tert*-butoxide exchange product **29** (22 % yield). This problem could be avoided by switching to the *N*-Boc protected amine **26**, which affords **29** in 79 % yield under these conditions, but the conversion of **2** to **29** requires several steps. A better alternative is the use of Cs_2CO_3 as the base in the amination reaction, whereupon **2** is coupled with **27** over 40 h to furnish **28** in 73 % isolated yield. Removal of the Cbz protecting group under the usual hydrogenation conditions proved problematic, as it was difficult to avoid partial reduction of the nitrile. Fortunately, we found that **28** was cleanly deprotected by heating in trifluoroacetic acid at 65 °C for 1 h, to provide **A-366833** in 93 % yield.



Scheme 6

In conclusion, the work described herein provides an efficient synthetic process for the enantiomerically pure benzyl (1*S*,5*S*)-3,6-diaza-bicyclo[3.2.0]heptane-3-carbamate. The 12-step synthetic route incorporates chiral resolution of a key intermediate with readily available (D)-mandelic acid, requires no chromatography and gives 25 % overall yield. The diazabicyclic core was successfully coupled with 3-bromo-5-cyanopyridine furnishing a practical 14-step synthesis of novel α4β2 NNR agonist **A-366833** in overall 17 % yield. **A-366833** has broad-spectrum analgesic activities in animal models and shows significantly improved preclinical safety profiles compared to **ABT-594**. The efficient synthesis of **A-366833** also allows for large-scale preparations required for development purposes.

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