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Development of a scalable synthetic route towards a 2,2,6-trisubstituted chiral morpholine *via* stereoselective hydroalkoxylation

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ABSTRACT

A scalable synthetic route towards a chiral 2,2,6-trisubstituted chiral morpholine, which is a known opioid antagonist, was developed. The synthetic route involves incorporating an aryl group *via* Suzuki-Miyaura coupling and stereoselective hydroalkoxylation catalyzed by trifluoromethanesulfonic acid. Late stage incorporation of both the aryl and *N*-alkyl groups make this route suitable for further SAR studies on this molecule.

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Introduction

C-Substituted chiral morpholines are an sp^3-rich structural motif commonly found in pharmacologically active molecules.[1] Significant attention has been paid to morpholine because of its ability to participate in a donor-acceptor interaction through its oxygen atom and the decreased basicity of the nitrogen atom which can have a beneficial impact on ADME and safety properties.[1a,2] Representative examples of pharmaceutical agents which incorporate a substituted morpholine: reboxetine (antidepressant), aprepitant (antiemetic), finafloxacin (antibiotic), and fenpropimorph (fungicide) are highlighted in Fig. 1.

During our search for a μ-opioid receptor antagonist as a potential analgesic, we discovered trisubstituted morpholine compound **1a**, which had previously been prepared by Wyeth pharmaceuticals (Fig. 2). Closely analogous compounds including **1b** have been reported as opiate antagonists.[3] When we initiated the synthesis of **1b** for further biological studies, we focused on two aspects. First, we intended to efficiently resynthesize **1b** with reasonable stereoselectivity and scalability. Second, and more importantly, we intended to develop a route that allows late stage incorporation of C2-aryl and *N*-alkyl groups, which are two important vectors for further SAR studies.

In seeking to identify a synthetic route to resynthesize **1a**, several literature examples of di-substituted morpholines (e.g. 2,6-, 2,5-, 3,5-) indicated that they have been synthesized by using one of two approaches: combination of two chiral fragments (Scheme 1A)[4] or diastereoselective cyclization with a pre-existing chiral center (Scheme 1B).[5a-f,2,5g,6] Due to the complexity of the molecule, a diastereoselective cyclization to form **1a** was preferred. However, there are only few examples regarding the synthesis of challenging tri-substituted chiral morpholines with a quaternary center as in **1a** *via* diastereoselective cyclization.[5a,b,6]

Results and discussion

Kozlowski and co-workers previously reported the synthesis of a closely related compound **1b**, which provided us initial access to **1a** (Scheme 2).[5a] The synthesis begins with the early stage introduction of the quaternary stereogenic center-bearing chiral amino-alcohol **5**. This was achieved by the stereoselective addition of diethyl zinc to α-ketoester **2**, catalyzed by a titanium complex with a non-commercial salen ligand **3**. The resulting chiral quaternary alcohol **4** was obtained with a modest enantioselectivity of 80% ee, and the major enantiomer separated by chiral HPLC. A two-step functional group conversion of **4** to **5**, followed by acylation with 2-chlorobutanoyl chloride, and then KOH-promoted etherification provided morpholine **6** as a 1:1 mixture of diastereomers, which were again separated by HPLC to isolate the desired (2*S*,6*R*)-**6**.

Although Kozlowski's method provided the desired tri-substituted morpholine **1a**, we sought to improve upon several limitations. The modest enantioselectivity in the generation of chiral alcohol **4**, use of a non-commercial salen ligand, scalability concerns regarding the use of pyrophoric diethyl zinc under cryogenic

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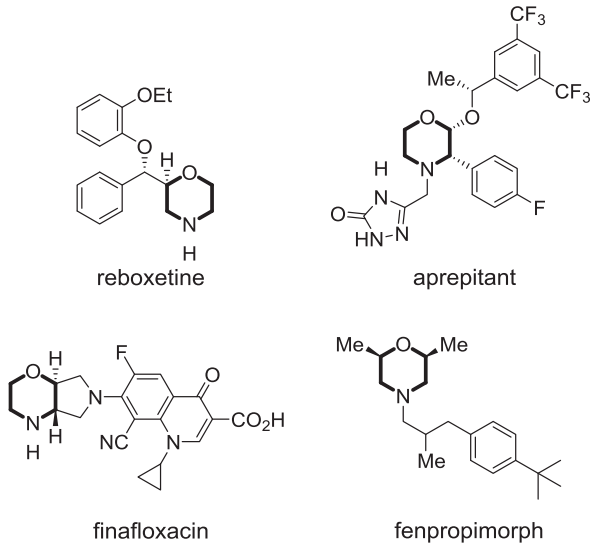


Fig. 1. *C*-substituted chiral morpholine drugs.

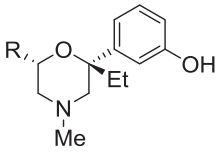
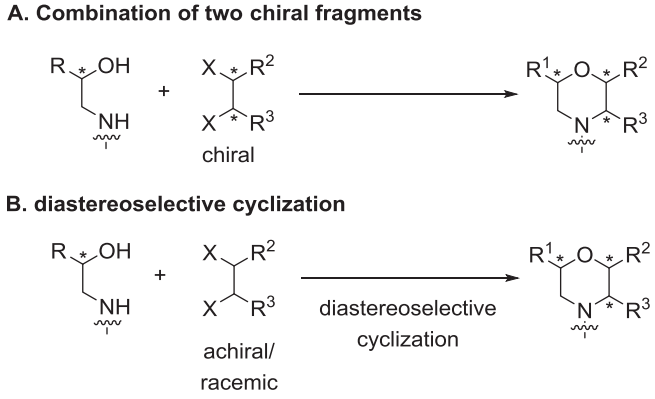


Fig. 2. Trisubstituted morpholines with μ-opioid antagonistic activity.



Scheme 1. Strategies for constructing morpholine derivatives with multiple chiral centers.

conditions, and the lack of diastereoselectivity during introduction of the second stereocenter to form **6** were major issues. In addition, difficulties in the diversification of both the aryl group and *N*-alkyl group due to their early incorporation in the sequence (9 and 7 steps, respectively, from the final analogs) reduce the utility of this route in further SAR studies. Alternatively, we attempted to generate chiral aminoalcohol **5** utilizing chiral auxiliary methods (Scheme 3)[7] Substrate **7** was prepared as described in the literature.[7] Grignard addition to chiral ketone **7** at low temperature proceeded smoothly. However, chiral aldehyde **8** was isolated in only 24% yield after acidic hydrolysis of the auxiliary, along with the formation of numerous unidentified side-products.

Next, we tested the possibility of Shi epoxidation on the known compound **9**.[8] The resulting epoxide **10** can be converted to amines *via* desilylation and epoxide opening, which was previously developed by Shi and co-workers.[9] Although the chiral epoxide **10** could be synthesized with high yield and enantioselectivity (99% clean crude, ee >98%), the epoxidation conditions required high loading of expensive D-epoxone catalyst. Literature conditions required 0.65 equivalents of D-epoxone. However, in our hands, up to 1.5 equivalents of the catalyst was required to ensure complete reaction. Due to the problems described, these two approaches were eventually discarded.

During our search for an alternative method of ring construction, a boron trifluoride-mediated hydroalkoxylation emerged as a potential solution to obtain our tri-substituted morpholine target (Scheme 4).[6] The reported examples indicated alcohol **11** could be cyclized to form tri-substituted morpholine **12** as a single diastereomer. However, it was unclear if this methodology could be extended to highly hindered, tri-substituted internal olefins such as **13** with reasonable reactivity and diastereoselectivity.

To test the feasibility of this stereoselective hydroalkoxylation, and more importantly to utilize it as SAR-amenable and scalable route for further biological studies, a synthetic route to access olefin **17** was needed (Scheme 5). Therefore, chiral *N*-tosylaminoalcohol **15** was synthesized by opening the chiral epoxide (*S*)-(-)-butylene oxide with *N*-tosylamide following the known procedure using TEBAC (benzyltriethylammonium chloride) as a phase transfer catalyst.[4f,10] This was treated with 2-bromoallylbromide under basic conditions to form *N*-(2-bromoallyl)-*N*-tosylamide **16**. The resulting vinyl bromide **16** and 3-methoxyphenylboronic acid were coupled under typical $Pd(PPh_3)_4$ catalyzed Suzuki-Miyaura conditions. The resulting 2-aryl-allylamide **17** was treated with boron trifluoride diethyl etherate (1.2 equiv.) at room temperature for 5 h, following Saikia and co-workers protocol.[6] The cyclized product **18** was obtained in 84% yield as a mixture of diastereomers (dr = 4.6:1). 1D NOE experiments confirmed the relative stereochemistry of the major product. The success of this route provided us the ability to replace the aryl group and *N*-alkyl group at relatively late stages of the synthesis for further SAR studies.

With confidence in the reproducibility of this methodology with reasonable stereoselectivity, it was extended to the tri-substituted internal olefin substrate **21** (Scheme 6). (*Z*)-1-Bromo-2-iodobut-2-ene (**19**) was easily synthesized from crotonaldehyde following a known three-step sequence in high yield and purity without the need for purification.[11] *N*-Tosylaminoalcohol **15** was combined with **19** under basic conditions to afford vinyl iodide **20** in 93% yield without the necessity for column purification. This was then coupled with 3-methoxyphenylboronic acid under the same Suzuki-Miyaura coupling conditions to obtain **21** in 83% yield.

With the internal olefin substrate **21** in hand, the hydroalkoxylation reaction was attempted (Table 1). The initial attempt at room temperature with boron trifluoride resulted in no reaction (Entry 1). Even at reflux, the reaction was slow, resulting in the formation of **22** in 49% yield with 3.3:1 dr, which is still reasonable for the formation of a highly crowded quaternary stereogenic center (Entry 2). The reaction was attempted at a higher temperature (60 °C) using DCE as a solvent for 6 h. The desired morpholine product **22** was formed in 62% isolated yield as a mixture of diastereomers with 2.2:1 dr (Entry 3). In an attempt to further optimize yield and diastereoselectivity, several Brønsted acids as well as a gold catalyst were screened.[12] Trifluoromethanesulfonic acid[13] emerged as the best option for scale-up, promoting the reaction with only catalytic acid (10 mol%) at 60 °C with 76% isolated yield and 2.0:1 dr (Entry 5). These conditions allowed for a scaled-up synthesis with a short reaction time, high yield, and use of catalytic

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