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Efficient, Stereoselective Synthesis of *trans*-2,5-Disubstituted Morpholines

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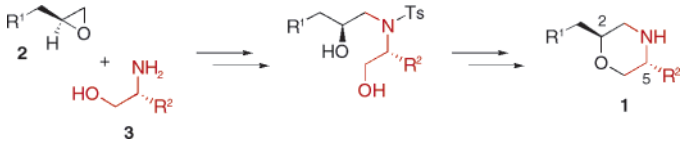
ABSTRACT



Enantio- and diastereoselective syntheses of *trans*-2,5-disubstituted morpholine derivatives are described. The routes are initiated by the reaction of enantiopure epoxides (2) with amino alcohols (3) and address the problem of regioselective hydroxyl activation–ring closure of the resulting amino diol adducts for (amino alcohol-derived) alkyl substituents of different steric demands.

In the course of research directed toward the solid-phase synthesis of a library of saframycin analogues,[1] we had need of gram quantities of several *trans*-2,5-disubstituted morpholine derivatives (**1**). These were required to function as dual linkers,[2] providing both a point for attachment to the solid support (via the 2-substituent of the morpholine ring) and a site for linkage to various α-amino aldehydes that we employed as synthetic precursors (by amino nitrile formation with the nitrogen atom of the morpholine ring). It was desirable that the latter transformation be diastereoselective, for which purpose the 5-substituent of the morpholine ring played a critical role.[3]

Despite the fact that *trans*-2,5-disubstituted morpholine derivatives are widely represented among pharmacologically active substances (Figure 1), there are no commercial sources

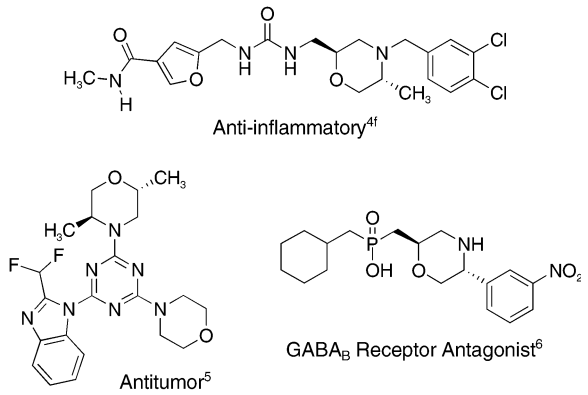


Figure 1. Examples of biologically active *trans*-2,5-disubstituted morpholine derivatives.

of such compounds of which we are aware, and existing protocols for their synthesis lead to diastereomeric mixtures of products.[4] Although retrosynthetic analysis of this general target structure is not difficult (a component-based approach

(1) Myers, A. G.; Lanman, B. A. *J. Am. Chem. Soc.* **2002**, *124*, 12969−12971.

(2) (a) Tam, J. P.; Tjoeng, F. S.; Merrifield, R. B. *Tetrahedron Lett.* **1979**, *20*, 4935−4938. (b) Tam, J. P.; Tjoeng, F. S.; Merrifield, R. B. *J. Am. Chem. Soc.* **1980**, *102*, 6117−6127.

(3) Lanman, B. A.; Myers, A. G. Manuscript in preparation.

(4) (a) Berlin, A. Y.; Sycheva, T. P. *Zh. Obshch. Khim.* **1950**, *20*, 640−647. (b) Dobrev, A.; Perie, J. J.; Lattes, A. *Tetrahedron Lett.* **1972**, *13*, 4013−4016. (c) Uozumi, Y.; Tanahashi, A.; Hayashi, T. *J Org. Chem.* **1993**, *58*, 6826−6832. (d) Sun, G.; Savle, P. S.; Gandour, R. D.; Bhaírd, N. N. a′; Ramsay, R. R.; Fronczek, F. R. *J. Org. Chem.* **1995**, *60*, 6688−6695. (e) Take, K.; Konishi, N.; Shigenaga, S.; Kayakiri, N.; Azami, H.; Eikyu, Y.; Nakai, K.; Ishida, J.; Morita, M. Preparation of Piperazines for Treating or Preventing Tachykinin-Mediated Diseases. PCT Int. Appl. WO 00035915, Jun 22, 2000. (f) Ancliff, R. A.; Cook, C. M.; Eldred, C. D.; Gore, P. M.; Harrison, L. A.; Hayes, M. A.; Hodgson, S. T.; Judd, D. B.; Keeling, S. E.; Lewell, X. Q.; Mills, G.; Robertson, G. M.; Swanson, S.; Walker, A. J.; Wilkinson, M. Preparation of Morpholinylmethylureas as CCR-3 Antagonists. PCT Int. Appl. WO 03082861, Oct 9, 2003.

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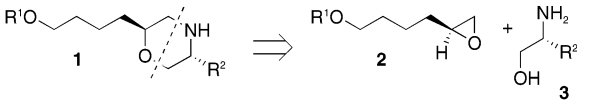


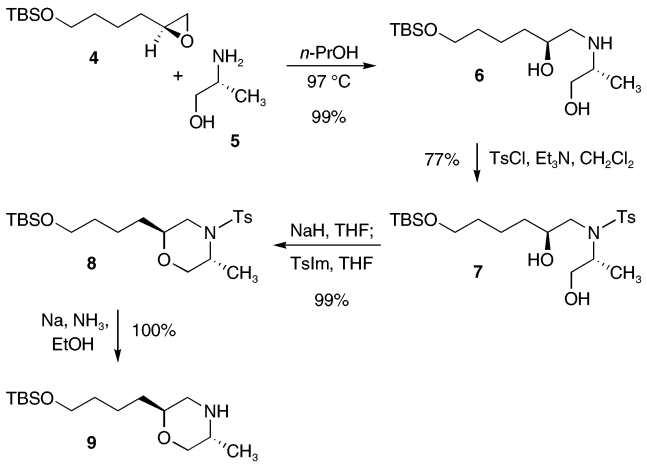
Figure 2. Identification of readily available chiral starting materials for the enantio- and diastereoselective synthesis of *trans*-2,5-disubstituted morpholines.

involving enantiopure epoxides **2** and amino alcohols **3** as starting materials is readily derived; see Figure 2), we found that implementation of this approach was not completely straightforward. In light of the value of *trans*-2,5-disubstituted morpholines in different contexts, we outline here two synthetic solutions for their preparation, optimized for 5-substituents with different steric requirements.

The chiral building blocks **2** and **3** in the proposed component-based route (Figure 2) were selected in part because they were readily available, the former by the Jacobsen hydrolytic kinetic resolution procedure[7] and the latter from amino acids (and widely available from commercial sources). The general sequence by which we envisioned that these starting materials would be transformed into the desired morpholines involved epoxide (**2**) opening by the amino group of the amino alcohol (**3**), N-protection of the resultant adduct, then selective hydroxyl activation, ring closure, and N-deprotection. It proved necessary to develop two variations on this scheme in order to access *trans*-2,5-disubstituted morpholines with 5-substituents of differing steric requirements (see Schemes 1 and 2). These are discussed in sequence, beginning with a description of the route to 2,5-disubstituted morpholine derivatives with less hindered 5-substituents (illustrated with a 5-methyl group; compound **9**, Scheme 1).

Synthesis of the *trans*-2,5-disubstituted morpholine derivative **9** began with the reaction of the enantiopure epoxide (*S*)-**4**[1] with a 4-fold excess of enantiopure D-alaninol (**5**) in *n*-propanol at reflux, providing exclusively the product of monoalkylation (**6**), with the amino group bonding to the less-hindered carbon atom of the epoxide ring (99%). Exposure of the resultant amino diol (**6**) to tosyl chloride (1.1 equiv) in the presence of triethylamine (2.0 equiv) in dichloromethane at 0 °C provided selectively the *N*-tosylated diol **7** (77%). This product was then cyclized by a method that we had previously reported, without specific discussion in that context, that allows for simultaneous hydroxyl activation−ring closure of suitably substituted 1,5-diols.[1] This one-step procedure involved deprotonation of **7** with excess sodium hydride (2.5 equiv) in THF (0 → 23 °C), followed

Scheme 1. Synthesis of Morpholine **9**



by the addition of 1 equiv of *p*-toluenesulfonyl imidazole at 0 °C, and afforded the *N*-tosyl morpholine derivative **8** in 99% yield. The stereoisomeric product that would have arisen from activation of the secondary hydroxyl group was not detected. Cleavage of the *N*-protective group proceeded in quantitative yield when the sulfonamide **8** was subjected to treatment with excess sodium in ethanolic ammonia at −78 °C followed by warming to ambient temperature. Extractive isolation then provided the desired morpholine derivative **9** in pure form (100% yield).

The use of the *p*-toluenesulfonamide protective group in the sequence outlined in Scheme 1 was critical; when a related sequence was attempted using instead an *N*-benzyl protective group, cyclization, as above,[1] led to a 1.5:1 mixture of *trans*-2,5- and *cis*-2,6-disubstituted morpholine derivatives.[8] Similarly, the use of an *N*-carbamoyl protective group proved to be problematic, in this case due to oxazolidinone formation between the primary hydroxyl group and the N-protective group. In contrast, the use of the *N*-tosyl group, as outlined in Scheme 1, provided the desired morpholine derivative **9** as a single diastereomer in four steps (75% yield) and required only one chromatographic purification (to separate excess tosyl chloride from the intermediate **7**).[9] This represents a marked improvement over related syntheses that were previously reported[4] and has proven effective for the preparation of **9** on a 20-g scale.[10]

Although the sequence summarized in Scheme 1 was highly effective for the application illustrated, when we

(5) Kawashima, S.; Matsuno, T.; Yaguchi, S.; Sasahara, H.; Watanabe, T. Preparation of Heterocyclic Compounds as Antitumor Agents. PCT Int. Appl. WO 02088112, Nov 7, 2002.

(6) (a) Ong, J.; Kerr, D. I. B.; Bittiger, H.; Waldmeier, P. C.; Baumann, P. A.; Cooke, N. G.; Mickel, S. J.; Froestl, W. *Eur. J. Pharmacol.* **1998**, *362*, 27−34. (b) Kuo, S.-C.; Blythin, D. J.; Kreutner, W. 2-Substituted Morpholine and Thiomorpholine Derivatives as GABA-B Antagonists. U.S. Patent 5,929,236, Jul 27, 1999.

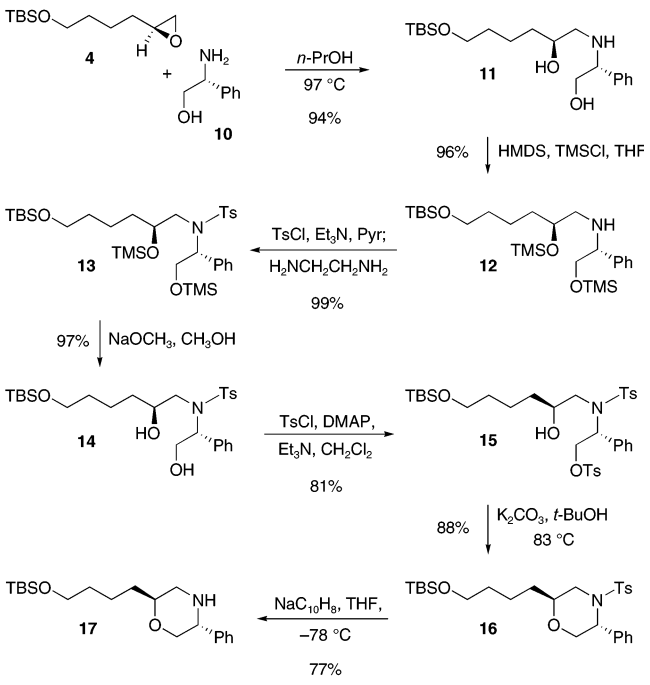
(7) Tokunaga, M.; Larrow, J. F.; Kakiuchi, F.; Jacobsen, E. N. *Science* **1997**, *277*, 936−938.

(8) The undesired *cis*-2,6-disubstituted morpholine is presumed to have arisen by a sequence involving reversible aziridinium ion formation. Tosylate-mediated opening of the aziridinium ion at the more substituted terminus followed by ring closure would proceed with net retention of configuration at the methyl-bearing center while effecting its transfer from the 5- to the 6-position of the cyclic product.

(9) The 2-nitrobenzenesulfonamide (nosyl) protective group (Fukuyama, T.; Jow, C.-K.; Cheung, M. *Tetrahedron Lett.* **1995**, *36*, 6373−6374) was found not to be a viable substitute for the *N*-tosyl protective group in the synthesis of **9**, as it was not stable toward the conditions of attempted cyclization (cf. **7** → **8**, Scheme 1; nosyl cleavage occurred, forming a mixture of 2-nitrophenyl ethers as products).

(10) We acknowledge Dr. Jonathan White for conducting the synthesis of **9** on a 20-g scale.

Scheme 2. Synthesis of 2,5-Disubstitued Morpholines with Larger 5-Substituents

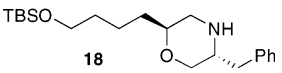


attempted to use the same sequence to prepare morpholine derivatives with larger 5-substituents (phenyl, benzyl; see compounds **17** and **18**) selective *O*-tosylation occurred during attempted N-protection, apparently as a result of increased steric hindrance about the amino group. Thus, the sequence outlined in Scheme 2 was developed.

As illustrated (Scheme 2), this sequence began in the same way as that of Scheme 1, by the selective coupling of the epoxide **4** with an amino alcohol, in this case enantiopure (*R*)-(−)-2-phenylglycinol (**10**). To achieve *N*-tosylation in this series, however, we found it necessary to transiently protect the hydroxyl groups of the amino diol product (**11**) using hexamethyldisilazane (2.04 equiv) in the presence of trimethylsilyl chloride (0.4 equiv) in THF at 0 °C. The bis-trimethylsilyl ether that was formed (**12**, 96%) was then *N*-tosylated upon treatment with *p*-toluenesulfonyl chloride (4.0 equiv) in pyridine containing triethylamine. The latter additive was necessary to avoid premature cleavage of the trimethylsilyl ether protective groups during this relatively slow *N*-tosylation reaction (15 h required for complete reaction). Excess *p*-toluenesulfonyl chloride was scavenged by the addition of ethylenediamine, greatly facilitating the isolation of the sulfonamide **13** (chromatography on silica gel, 99%). The trimethylsilyl ether groups within **13** were then readily cleaved upon treatment with sodium methoxide in methanol, affording the cyclization precursor, diol **14** (97%).

Attempted cyclodehydration of **14** using the prior one-step protocol[1] (cf. **7** → **8**, Scheme 1) was not successful, but led instead to *O*-tosylation−elimination (forming an *N*-tosyl enamine), necessitating the development of an alternative procedure. Although Mitsunobu-based cyclodehydration protocols were promising in preliminary experiments, the imperfect regioselectivity (primary vs secondary hydroxyl activation) that we observed in these experiments led us to develop an alternative two-step activation-closure sequence that allowed for the preparation of a single regioisomer. Thus, reaction of **14** with *p*-toluenesulfonyl chloride (1.25 equiv), 4-(dimethylamino)pyridine (0.4 equiv), and triethylamine (3.7 equiv) afforded a 4.4:1 mixture of the primary tosylate (**15**) and the corresponding 1,5-bis-*O*-tosylate. When this mixture was heated at reflux in a solution of potassium carbonate in *tert*-butyl alcohol, the N-protected morpholine derivative **16** was formed in 71% yield (from **14**, two steps).[11] Interestingly, the use of stronger bases or aprotic solvents in this transformation afforded predominantly the product of elimination of the *O*-tosyl group.[12]

Completion of the synthesis of the *trans*-2,5-disubstituted morpholine **17** was achieved by the deprotection of **16** using sodium naphthalenide in tetrahydrofuran.[13] The *trans*-2,5-disubstituted morpholine **17** was obtained as a single diastereomer, in 77% yield (48% overall yield; seven steps). We have used this method to prepare gram quantities of **17**. The protocol of Scheme 2 also proved to be directly applicable to the synthesis of diastereomerically pure 5-benzyl morpholine derivative **18** (40% yield; seven steps).



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In summary, we have described two efficient, highly stereoselective methods for the preparation of gram quantities of *trans*-2,5-disubstituted morpholine derivatives, starting from readily available, enantiomerically pure starting materials. These complementary protocols allow for the preparation of *trans*-2,5-disubstituted morpholine derivatives bearing both large and small 5-substituents. We believe that these protocols may be of value in a range of applications.

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Supporting Information Available: Experimental procedures and spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) The 1,5-bis-*O*-tosylate formed during the synthesis of **15** did not react under the cyclization conditions; it was readily separated from **16** by flash column chromatography on silica gel.

(12) Cooper, K. A.; Dhar, M. L.; Hughes, E. D.; Ingold, C. K.; MacNulty, B. J.; Woolf, L. I. *J. Chem. Soc.* **1948**, 2043−2049.

(13) Sodium naphthalenide/tetrahydrofuran was used in lieu of sodium/ammonia in order to avoid competing Birch reduction of the aromatic ring.