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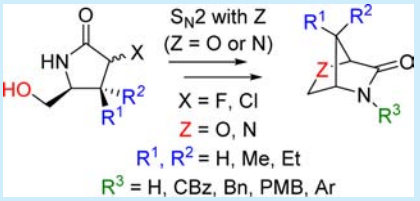
Synthesis of Chiral Azabicycles from Pyroglutaminols

Chulho Choi,*[,†] Philippe Nuhant,[†] James J. Mousseau,[†] Xiaojing Yang,[†] Brian S. Gerstenberger,[‡] Jessica M. Williams,[§] and Stephen W. Wright[†]

[†]Medicinal Chemistry, Medicine Design, Pfizer WorldWide R&D, 445 Eastern Point Road, Groton, Connecticut 06340, United States
[‡]Medicinal Chemistry, Medicine Design, Pfizer WorldWide R&D, 610 Main Street, Cambridge, Massachusetts 02139, United States
[§]Kutztown University of Pennsylvania, 15200 Kutztown Road, Kutztown, Pennsylvania 19530, United States

Supporting Information

ABSTRACT: The stereocontrolled synthesis of a range of substituted bicyclic morpholine and piperazine derivatives is reported from substituted pyroglutaminols via an intramolecular S_N2 cyclization as the key step. This enantiospecific approach toward chiral bicyclic morpholines and piperazines offers new opportunities to access these challenging ring systems, which are becoming increasingly common motifs in drug discovery.



Structurally constrained bicyclic morpholine and piperazine cores are key structural components of natural products such as loline[1] and also found in medicinally relevant motifs (Figure 1).[2] These strained ring systems have been

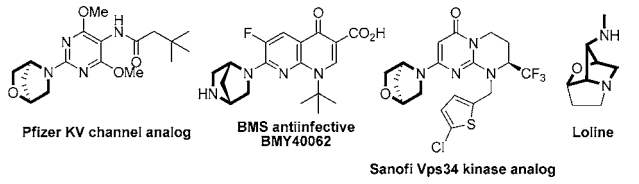


Figure 1. Selected compounds containing stereodefined bicyclic piperazines and morpholines.

incorporated, for example, as critical structural vectors for pharmacological activity in structure-guided drug discovery strategies.[3] Despite their desirability, current synthetic routes to access these structural motifs are generally lengthy and lack stereocontrol, requiring the separation and structure elucidation of multiple stereoisomers.[4] A stereocontrolled synthesis of these bicyclic structures would be a worthwhile addition to the synthetic chemist's toolbox.

As part of a recent medicinal chemistry program, we were interested in the stereocontrolled synthesis of chiral morpholinones such as **2a–f**. We noted the lack of literature precedent and envisioned a synthesis from pyroglutamic acid derivatives. Recently, we disclosed a methodology to access chiral pyroglutaminols[5] via a stereospecific conjugate addition strategy.[6] We reasoned that a suitably halogenated pyroglutaminol could be the key precursor in the synthesis of the target morpholinones (Figure 2) by an intramolecular S_N2 cyclization of the primary alcohol to the alkyl halide of **1a–f**.[7] Such a stereocontrolled transformation would allow access to the bicyclic systems of interest in an efficient manner.

To probe this synthetic hypothesis, we selected the α-chloropyroglutaminol **1a** as a candidate for the intramolecular

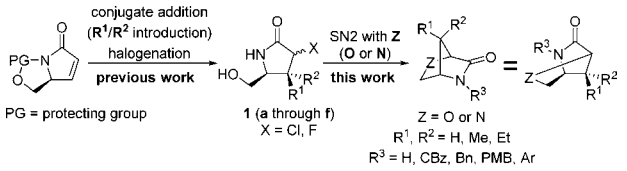
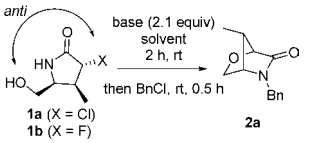
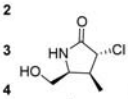
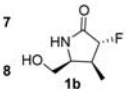


Figure 2. Stereocontrolled synthesis of morpholinones and piperazinones from enantiopure pyroglutaminols prepared by stereocontrolled cuprate conjugate addition.

S_N2 cyclization reaction (Table 1). The cyclized intermediate was trapped in situ with benzyl chloride in order to facilitate both reaction monitoring and the isolation of the morpholi-

Table 1. Screening of Conditions for S_N2 Cyclization



entry	substrate	base	solvent	yield[a] (%)
1		NaH	THF	0
2		NaH	dioxane	0
3		KHMDS	THF	0
4		NaHMDS	DMF	42
5		KHMDS	DMF	87
6		KtOBu	DMF	91
7		KHMDS	DMF	87
8		KtOBu	DMF	85

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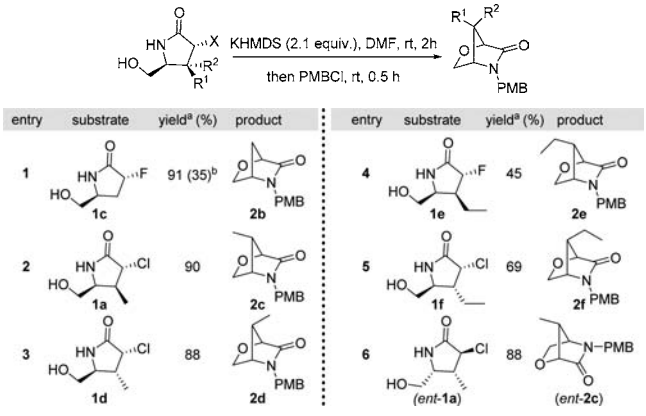
none product **2a**. Initial screening of reaction conditions revealed that both NaH and KHMDS in ethereal solvents were ineffective (entries 1−3). Precipitates were observed in these ethereal solvents that presumably resulted in poor reactivity. Screening in DMF revealed that NaHMDS gave a moderate yield (42%, entry 4), and KHMDS (entry 5) or *t*-BuOK (entry 6) gave the best results (87% and 91%, respectively). The intermediate alkoxide was significantly more soluble in DMF, as no precipitate formation was observed when DMF was used as solvent. Interestingly, fluoride was also found to be an excellent leaving group. Starting from the α-fluoropyroglutamic lactam **1b**, KHMDS (entry 7) or *t*-BuOK (entry 8) in DMF gave similar yields (85% and 87%, respectively). The structure of **2a** was confirmed through small-molecule X-ray crystallography (see the Supporting Information).

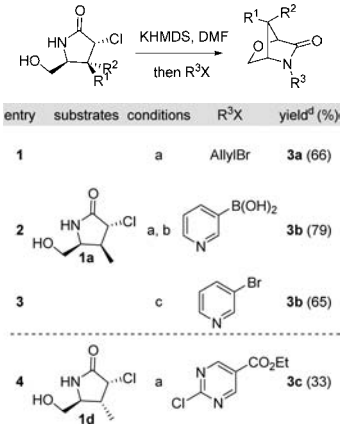
Having identified productive conditions for the cyclization, we next investigated the influence of size and configuration of the lactam β-substituent during the cyclization (Table 2, entries 1−6). In substrates lacking a substituent (e.g., **1c**), the reaction performed well to afford **2b** (entry 1, 91%). Interestingly a 1:1 mixture of the *syn* and *anti* α-F epimers of **1c** led to the cyclization of only one epimer, presumably **1c**, in which fluorine is *trans* relative to the alcohol (entry 1, 35%).[8] Substrates with a β-methyl substituent cyclized in very good yield (entry 2 and 3, 90% and 88% respectively). Steric effects were observed with a β-alkyl group larger than a methyl group. A change from a *syn* β-methyl group (**1a**) to a *syn* β-ethyl group (**1e**) led to a decrease in yield from 87% (Table 1, entry 7) to 45% (Table 2, entry 4), presumably as a result of steric crowding of the transition state by the ethyl group. As expected, the *anti* β-ethyl substrate **1f** was more easily cyclized under the same conditions (69%, entry 5). Enantiomers could also be easily accessed (88%, entry 6).

Table 2. Effect of the Lactam β-Substituents R^1 and R^2 on the S_N2 Cyclization Reaction



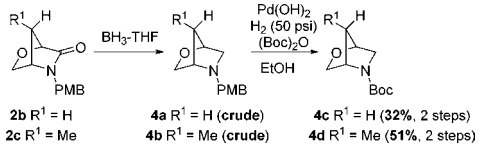
With successful cyclization outcomes in hand for a variety of pyroglutaminol substrates, we were next interested in trapping the cyclized intermediate with a panel of electrophiles (Table 3). Pleasingly, allyl bromide performed well under the reaction conditions (66%, entry 1). S_NAr trapping reactions of the cyclized morpholinone intermediate with heterocyclic halide such as ethyl 2-chloropyrimidine-5-carboxylate proceeded in moderate yields (33%, entry 4). Likewise, an in situ copper-mediated Chan−Lam coupling of the cyclized morpholinone intermediate could be effected to afford the 3-aminopyridine derivative **3b** (79%, entry 2).[9] Interestingly, exposure of the pyroglutaminol precursor **1a** to typical palladium-mediated N-arylation conditions with 3-bromopyridine resulted in concomitant cyclization and N-arylation to afford the same product **3b** (65%, entry 3).[10] These results demonstrate the usefulness of these intermediates for derivatization without need for isolation.

Table 3. Tandem Synthesis and in Situ Derivitization of Substituted Bicyclic Morpholinones



Further elaboration of these versatile bicyclic morpholinones could be accomplished by reduction to bicyclic morpholines. Bicyclic morpholinones **2b** and **2c** were readily reduced with borane−THF to provide the corresponding bicyclic PMB-protected morpholines (**4a** and **4b**), which were carried forward without purification in a one-pot hydrogenation/Boc protection sequence to afford the Boc morpholines **4c** and **4d** in 32% and 51% overall yields from **2b** and **2c**, respectively (Scheme 1).

Scheme 1. Preparation of Bicyclic Morpholines by Reduction and Protecting Group Exchange



With the stereocontrolled synthesis of substituted bicyclic morpholines established, we next turned our attention to the stereocontrolled synthesis of substituted bicyclic piperazines by replacing the primary alcohol group in the pyroglutaminol starting material with a primary amine. Efforts to install a primary amine via reductive amination techniques resulted in disappointingly low isolated yields (<20%). We developed a successful stepwise process in which the masked amine could be installed via an azide displacement of a primary *O*-tosylpyroglutaminol **5** with $TBAN_3$.[11] Staudinger reduction of the azide **6** with PPh_3 led to the desired amine, which spontaneously underwent cyclization in the presence of base to afford the bicyclic piperazinone **7** (Scheme 2). Subsequent protection of the amine with CbzCl, reduction of the lactam with BH_3−THF, and protection with Boc_2O yielded the differentially protected bicyclic piperazine **9** as a single stereoisomer.

Previous work had shown that halogenation of the protected pyroglutaminols **I** and **II** gave mixtures of halogen diastereomers which could often be separated by column chromatog-

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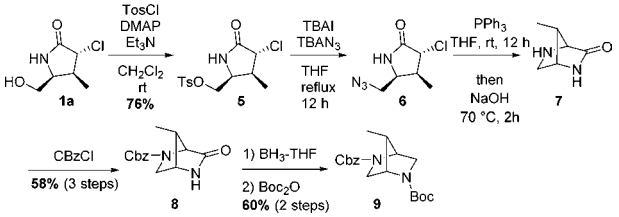
Scheme 2. Preparation of a Differentially Protected Bicyclic Piperazine from Pyroglutaminol 1a



raphy (Figure 3).[12] Depending on the R^1 substituent and the specific halogenation reaction conditions, the diastereoselectivities varied from 2:1 to 10:1 in favor of the diastereomer in which the halogen is *anti* to the R^1 substituent. The major product of the halogenation of lactam **I** is the diastereomer **Iα** in which the halogen is placed *anti* to both the R^1 substituent and the latent CH_2OH group. This diastereomer undergoes the cyclization reaction readily (eq 1). On the other hand, halogenation of lactam **II** affords primarily diastereomer **IIβ**, in which the halogen is *anti* to the R^1 substituent as expected but is unfortunately *syn* to the latent CH_2OH group. This diastereomer is resistant to cyclization as may be expected, and we viewed this as a potential limitation of the utility of this chemistry.

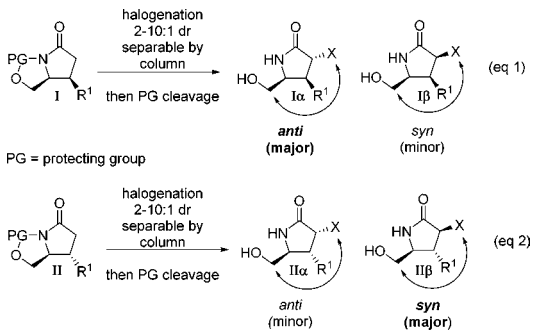
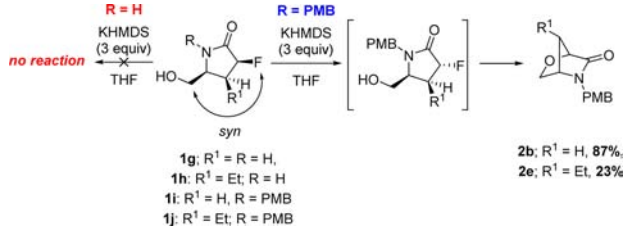


Figure 3. Influence of R^1 relative stereochemistry on the halogenation reaction.

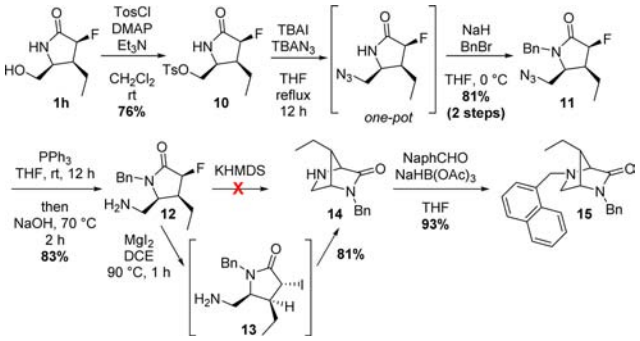
In order to overcome this limitation, we reasoned that it should be possible to epimerize the halogenated stereocenter during the course of the cyclization reaction. Such an epimerization would lead to the formation of the *anti* halogen isomer and subsequent cyclization. Initially, when the *α*-fluoro pyroglutaminol **1g** was used, epimerization did not occur. Presumably, deprotonation of the secondary lactam makes epimerization difficult by the establishment of a negative charge adjacent to the carbon atom of interest. Accordingly, the PMB-protected lactam **1i** was prepared. This was readily epimerized in situ under the cyclization reaction conditions, leading to the desired bicyclic morpholinone **2b**. In the same manner, pyroglutaminol **1j** was similarly epimerized and converted to morpholinone **2e** (Scheme 3).

We applied a similar sequence of reactions to the preparation of bicyclic piperazinones from *syn* halo intermediates. Thus, the primary amine **12** was prepared in four steps from the pyroglutaminol **1h** (Scheme 4). Surprisingly, base-mediated epimerization and cyclization did not proceed under the same conditions employed previously, despite N-protection of the lactam with a benzyl group. As an alternative, we considered a double-inversion strategy in which the *syn* fluoro lactam **12** would be exchanged to the *anti* iodo lactam **13**, which should cyclize under the reaction conditions. Given the high reactivity of MgI_2 for this purpose,[13] we applied this reagent in a Finkelstein reaction. Gratifyingly, the desired bicyclic piperazinone **14** was obtained in 81% yield. This substance was subsequently derivatized by reductive amination to afford **15** in excellent yield.

Scheme 3. In Situ Epimerization/Cyclization Sequence of *syn*-Halopyroglutaminols to Bicyclic Morpholinones



Scheme 4. Conversion of *syn*-Halopyroglutaminols to Bicyclic Piperazinones



In conclusion, we have demonstrated that novel bicyclic morpholine and piperazine derivatives can be synthesized with full stereocontrol from halogenated pyroglutaminols by means of an intramolecular S_N2 cyclization reaction. The products are readily functionalized by subsequent alkylation, S_NAr reaction, Chan−Lam coupling, and palladium-mediated arylation. Further, we have demonstrated that *syn*-halogenated pyroglutaminols could also be productively used in this chemistry via epimerization under the reaction conditions or by a double-displacement strategy.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b03024.

Experimental procedures and characterization data for all new compounds; ORTEP drawing and crystallographic data for **2a**, **3b**, and **4c** (PDF)
NMR spectra for all new compounds (PDF)
Crystallgraphic data for **2a** (CIF)
Crystallgraphic data for **3b** (CIF)
Crystallgraphic data for **4c** (CIF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: chulho.choi@pfizer.com.

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Notes

The authors declare no competing financial interest.

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