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Practical Synthesis of 1-Aryl-6-(hydroxymethyl)-2-ketopiperazines via a 6-*exo* Amide–Epoxide Cyclization

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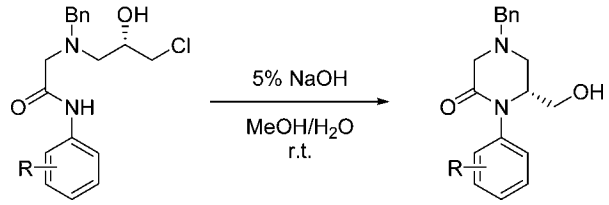
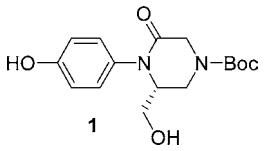
ABSTRACT



Chiral 1-aryl-6-(hydroxymethyl)-2-ketopiperazines can be prepared via an operationally simple, 6-*exo* epoxide ring-opening cyclization to form the ketopiperazine C6–N1 bond in high yields and with excellent enantiomeric purity.

Ketopiperazines are valuable motifs that have found widespread use as conformationally constrained peptidomimetics, as well as synthetic intermediates for the construction of biologically active molecules in total synthesis and the pharmaceutical industry.[1] During a recent medicinal chemistry program, we became interested in developing a synthesis towards the chiral 1-aryl-6-hydroxymethyl-2-oxopiperazine **1** for use as a central scaffold for further manipulation.



1

In the early stages of the program, we were able to prepare gram quantities of **1** via a Buchwald amidation coupling reaction[2] between ketopiperazine **6** and 4-benzyloxy-1-iodobenzene **7** (Scheme 1). This route utilized serine derivatives as the source of the C6 chiral center. DIBAl-H reduction of the commercially available ester **2** provided Garner's aldehyde **3**.[3] Reductive amination of the crude aldehyde **3** with ethyl *N*-benzylglycine afforded the tertiary amine **4** in good overall yield. Removal of the *N*-Boc protecting group and cyclization to the ketopiperazine were accomplished in one pot by treatment with aqueous HCl in refluxing MeOH to provide the chiral 6-hydroxymethyl-2-ketopiperazine **5** in excellent yield. The *N*-benzyl protecting group was converted to a *N*-Boc carbamate by hydrogenolysis in the presence of Boc_2O to afford ketopiperazine **6**. The coupling of **6** and 4-benzyloxy-1-iodobenzene **7** was accomplished by treatment with 5 mol % CuI and 10 mol % *N*,*N*′-dimethylethylenediamine,[2] giving **8** in good yield. The phenolic benzyl group was deprotected by hydrogenolysis to give **1** in excellent yield.

Although the above synthesis satisfied our needs during the early stages of the project, the starting materials proved

(1) Dinsmore, C. J.; Beshore, D. C. *Org. Prep. Proc. Int.* **2002**, *34*, 367−404.

(2) Klapars, A.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 7421−7428.

(3) Garner, P., Park, J. M. *Org. Synth., Collect. Vol. IX* **1998**, 300−305.

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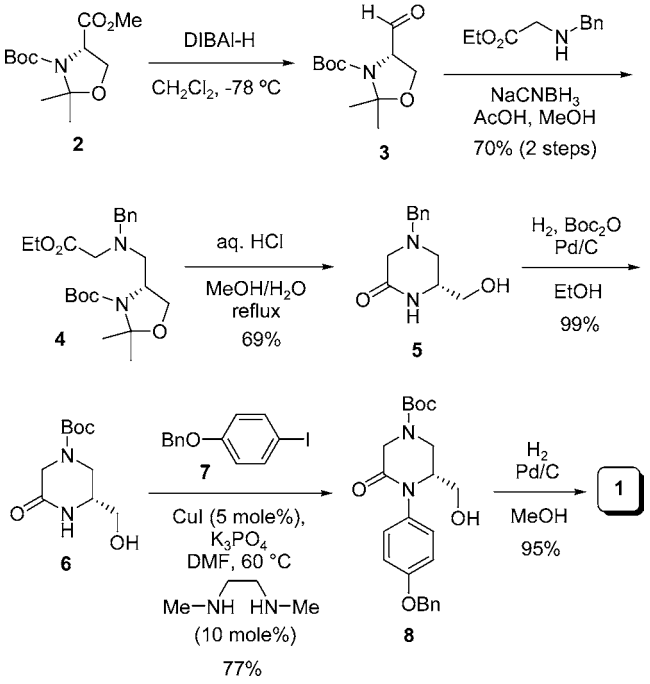
Scheme 1



to be cost prohibitive and of low atom efficiency for synthesis of multigram quantities of **1**. To achieve a more practical synthesis, we chose to investigate an alternative retrosynthesis that formed the ketopiperazine ring at the N1−C6 bond through an intramolecular 6-*exo* cyclization of amide−epoxide **9** (Figure 1). Further retrosynthetic cleavage of the

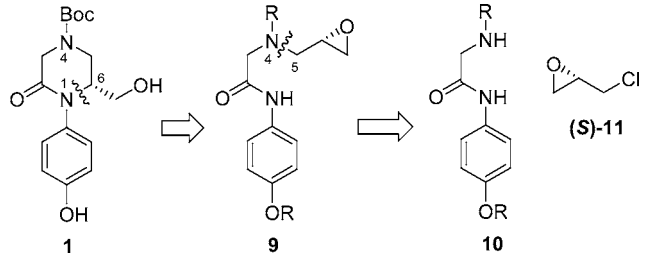


Figure 1. Revised retrosynthesis.

N4−C5 bond revealed the α-aminoacetamide **10** and (*S*)-epichlorohydrin **11** as the source of the C6 chiral center. The intermolecular nucleophilic opening of epoxides by amides is well precedented in the literature; however, fewer examples of intramolecular ring-opening reactions of unactivated epoxides with amides exist. A synthesis of heteronorbornanes via a 5-*exo* amide−epoxide cyclization was reported by Spurlock and co-workers, as well as an example of a conformationally constrained 6-*exo* cyclization to form an azaadamantanol.[4] Kibayashi and co-workers have also reported a 5-*exo* example to form a fused bicyclic pyrrolidinone ring, although formation of the 6-*endo* product competed with the desired 5-*exo* pathway.[5] Although all of the above examples utilized conformationally constrained bicyclic cyclization precursors, we were encouraged to investigate this route toward the ketopiperazine ring structure.

Our revised synthesis began with the acylation of 4-benzyloxyaniline **12** with chloroacetyl chloride to provide the chloroacetamide **13** in excellent yield (Scheme 2). The use of an inorganic base allowed for the simple filtration and precipitation of **13**. Alkylation of $BnNH_2$ with **13** provided the secondary amine **10** in 93% yield. Condensation of amine **10** with (*S*)-epichlorohydrin **11** in the presence of $MgSO_4$ afforded the desired chlorohydrin **14** in quantitative crude yield.[6] Attempts to purify the crude chlorohydrin by chromatography on silica gel gave variable yields of pure **14**. The crude product was therefore used without purification and briefly treated with cold 5% aqueous NaOH for 20 min to initiate formation of the terminal epoxide **9**. Treatment of **9** with NaH in anhydrous DMF initiated the desired 6-*exo* cyclization; however, the desired ketopiperazine product **15** was isolated in only a disappointing 26% yield. The remaining mass balance consisted of 4-benzyloxyaniline and numerous other unidentified polar byproducts. The hydrolytic mechanism responsible for formation of the 4-benzyloxyaniline byproduct under the anhydrous conditions remains unclear. Further, the low yield of **15** proved to be highly variable under these conditions and was successful only in DMF. Other solvents (THF, THF/DMF mixtures, and toluene) led exclusively to the formation of polar byproducts.

However, we were greatly pleased to discover that prolonged exposure of chlorohydrin **14** to aqueous 5% NaOH at room temperature led to cyclization and the formation of ketopiperazine **15** in a greatly improved 77% yield. TLC monitoring of the reaction indicated that the addition of NaOH to chlorohydrin **15** led to the rapid formation of epoxide **9**, followed by a slow cyclization and formation of **15**. Hydrogenation of **15** in the presence of Boc_2O led to facile formation of the desired product **1** in an excellent yield.

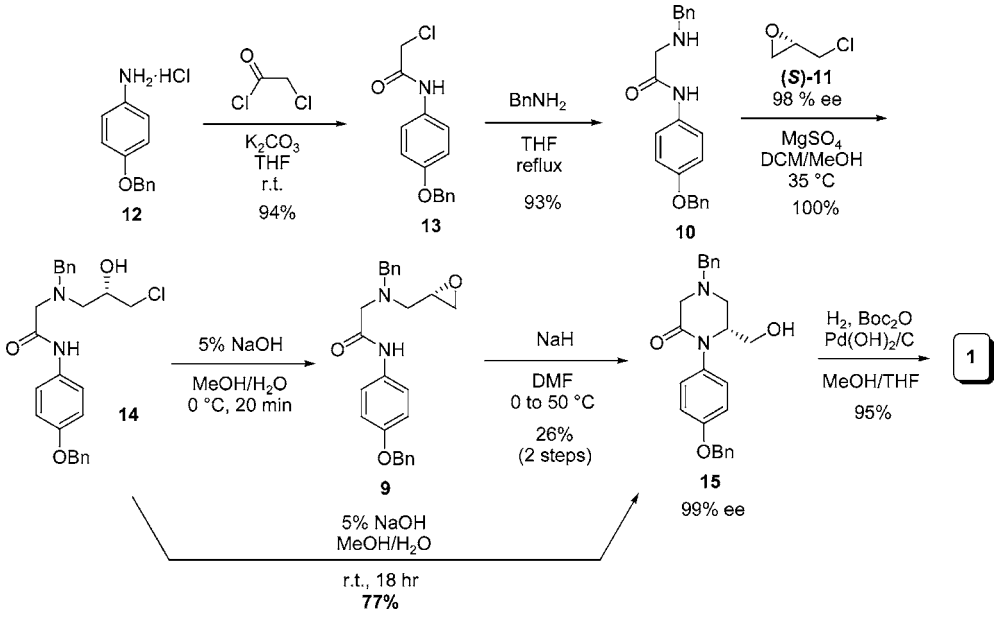
This synthetic route to ketopiperazine **1** satisfied our requirements for a concise and robust synthesis that was amenable to the preparation of >200 g quantities of **1**. No chromatography was required, as all intermediates could be isolated by precipitation or used without purification. To determine the enantiomeric purity of this route, the enantiomeric ketopiperazine **16** was prepared in an analogous fashion, using (*R*)-epichlorohydrin. Chiral HPLC analysis of the enantiomers **1** and **16** indicated that the epichlorohydrin

(4) Schultz, R. J.; Staas, W. H.; Spurlock, L. A. *J. Org. Chem.* **1973**, *38*, 3091−3093.

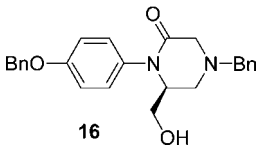
(5) Abe, H.; Aoyagi, S.; Kibayashi, C. *J. Am. Chem. Soc.* **2000**, *122*, 4583−4592.

(6) (a) Bergeron, R. J.; Yao, G. W.; Yao, H.; Weimar, W. R.; Sninsky, C. A.; Raisler, B.; Feng, Y.; Wu, Q.; Gao, F. *J. Med. Chem.* **1996**, *39*, 2461−2471. (b) Bergeron, R. J.; Ludin, C.; Müller, R.; Smith, R. E.; Phanstiel, O. *J. Org. Chem.* **1997**, *62*, 3285−3290.

Scheme 2



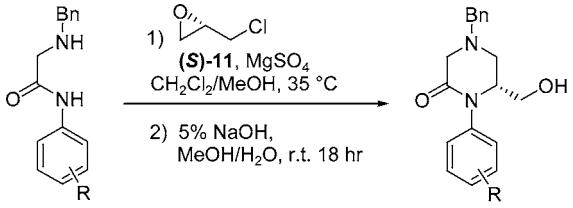
condensation and cyclization steps occurred without any racemization of the enantiomeric center.[7]

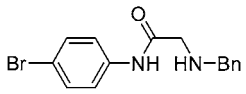
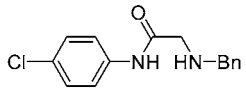
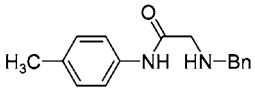
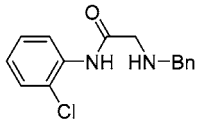
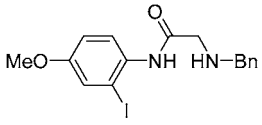
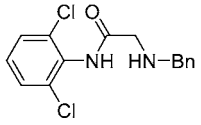


Having developed a novel intramolecular 6-*exo* amide−epoxide cyclization route to 1-aryl-6-(hydroxymethyl)-2-ketopiperazine **1**, we were interested in exploring the scope and limitations of this methodology. We prepared a number of 2-benzylamino-*N*-aryl-acetamides **17a**−**f** and subjected them to the standard epichlorohydrin condensation/cyclization conditions (Table 1). *N*-Aryl acetamides **17a**−**c**, containing halides and alkyl groups, underwent smooth cyclization under the standard reaction conditions to afford the desired ketopiperazines **18a**−**c** in excellent yields. We were particularly pleased to find that the sterically hindered ortho-substituted substrates **17d**−**f** underwent smooth cyclization to yield the corresponding ketopiperazines **18d**−**f** in good yield.

A significant limitation of this methodology was discovered when chlorohydrin **19**, containing an electron-withdrawing 4-diethylsulfonamide substituent, was subjected to the standard NaOH cyclization conditions (Scheme 3). In this case, diol **20** was the major product formed, with only trace amounts of the desired ketopiperazine **21** observed. Other substrates containing para electron-withdrawing groups (4-

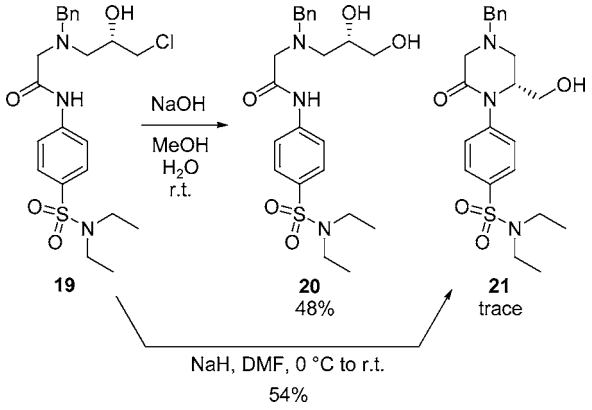
Table 1. Scope of the Cyclization of *N*-Aryl Acetamides **17**



entry	substrate **17**	2-step yield of **18**
a		83%
b		83%
c		69%
d		72%
e		85%
f		62%

(7) Absolute configurations of **1** and **16** were determined unambiguously following conversion into the corresponding final analogues and X-ray crystallography of the enzyme-analogue complexes. See: Powell N. A.; Clay, E. H.; Holsworth, D. H.; Edmunds, J. J.; Jalaie, M.; Bryant, J. W.; Zhang, E., *Bioorg. Med. Chem. Lett.* **2004**, submitted.

Scheme 3



CN and 4-NO_2) behaved similarly (data not shown). The competitive formation of the corresponding diols was not observed in the previous relatively electron-rich substrates **17a**−**f**. It was expected that the cyclization of *N*-aryl acetamides with aryl electron-withdrawing substituents would be more facile, due to the inductive decrease of the acetamide NH pK_a by the para electron-withdrawing aryl substituents. The preferential formation of diol **20** indicates that nucleophilicity of the amide anion is reduced by the inductive stabilization by the electron-withdrawing aryl substituent, resulting in a slower rate of cyclization and competitive epoxide ring opening by hydroxide anion.

We theorized that the use of a nonnucleophilic base in an aprotic solvent would circumvent the competitive epoxide ring-opening side reaction. Accordingly, treatment of chlorohydrin **19** with NaH in DMF led to smooth cyclization and formation of the desired ketopiperazine **21** in 54% yield. Formation of diol **20** was not observed under these conditions. This result contrasts with the poor yields encountered in the attempted deprotonation and cyclization of epoxide **9** with NaH (Scheme 2). While NaH is compatible with electron-poor aryl acetamides, we hypothesize that the presence of electron-donating aryl substituents inductively destabilizes the amide anion and promotes undesirable side reactions. The equilibrium conditions established with the weaker NaOH base in a protic medium circumvent these side reactions by avoiding the formation of acetamide anion.

In conclusion, we have developed a concise and practical synthesis of chiral 1-aryl-6-(hydroxymethyl)-2-ketopiperazines via an intramolecular *6-exo* amide−epoxide cyclization that is amenable to large-scale synthesis. This methodology is applicable to a variety of electron-rich *N*-aryl acetamides. Conditions have also been developed to allow for the successful cyclization of substrates with electron-withdrawing substituents. Further elaboration of the 1-aryl-6-(hydroxymethyl)-2-ketopiperazines in the context of our medicinal chemistry program will be reported in due course.

Acknowledgment. We thank Mark Lovdahl and Norm Colbry for technical assistance in the high-pressure reactions, Partha Mukherjee and Frank Riley for chiral HPLC analysis, and Dana DeJohn for obtaining the mass spectral data.

Supporting Information Available: Experimental procedures and characterization information for compounds **1**, **8**, **15**, **16**, **18a**−**f**, and **21**. This material is available free of charge via the Internet at http://pubs.acs.org.

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