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Asymmetric Synthesis of a Potent CXCR7 Modulator Featuring a Hindered Tertiary β-Amino Amide Stereocenter

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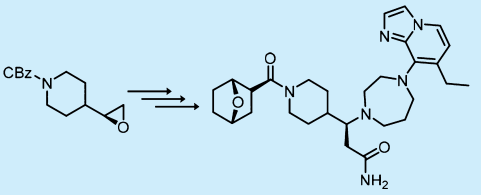
Supporting Information

ABSTRACT: A practical and asymmetric synthesis of a small-molecule CXCR7 modulator featuring a highly functionalized and hindered tertiary β-amino amide framework is reported. The cornerstone of this strategy relied on the intermediacy of a reactive aziridinium species, which, following regioselective ring opening with cyanide, furnished the desired chiral β-tertiary amino nitrile for further elaboration. As a means of further highlighting this synthetic strategy, an expanded scope of hindered β-amino amide synthesis is also presented.



Stromal-cell-derived factor 1α (SDF-1α) is the natural ligand of the G-protein-coupled receptor CXCR7, which, in conjunction with CXCR4, has been reported to play a protective role following a cardiac event to improve both function and cardiac injury repair processes.[1] We postulated that a potent small-molecule CXCR7 modulator could interact with the target receptor to prevent binding, internalization, and degradation of SDF-1α.[2] By increasing the bioavailability SDF-1α, we sought its prolonged interaction with CXCR4 and thus enhanced cardioprotection in the event of heart failure. As a result of a rigorous medicinal chemistry campaign targeting upregulation of the systemic circulation of SDF-1α,[3] the sterically hindered tertiary β-amino amide **1** was identified as a promising candidate for further in vivo efficacy evaluations on the basis of its potent and selective binding of CXCR7 as well as its desirable physicochemical properties (Figure 1).

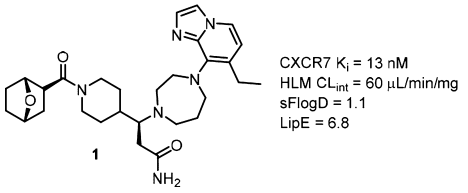
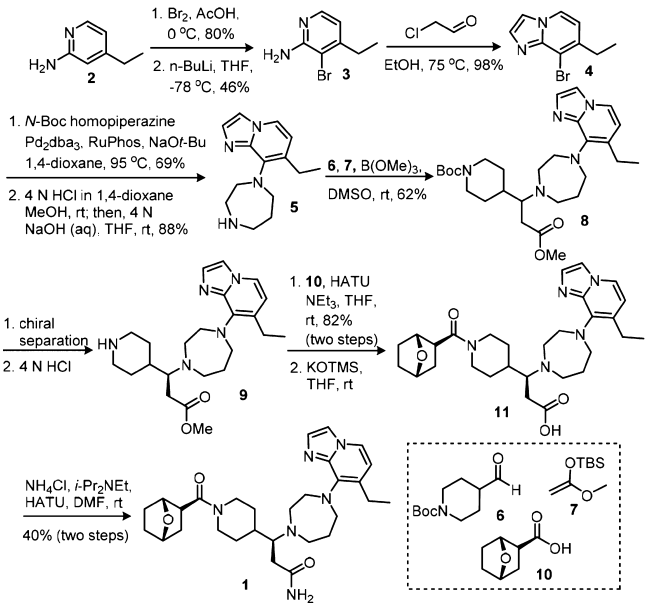


Figure 1. Potent CXCR7 inhibitor **1** and its physicochemical properties.

The medicinal chemistry strategy employed en route to the identification of **1** relied heavily on the use of advanced versatile synthetic intermediates to rapidly drive our understanding of the structure−activity relationships for this program via highly enabled parallel chemical synthesis. After optimizing this series for potency against CXCR7 as well as desirable physicochemical properties,[3] we required more significant quantities of **1** for compound-demanding efficacy studies, which necessitated investigation to find a more refined asymmetric synthesis.

The original synthesis of **1** suffered from several low-yielding and poorly scalable synthetic steps as well as a requisite chiral separation of an advanced racemic intermediate midway through the synthetic sequence (Scheme 1).[3] Indeed, the key step featured a Lewis acid-mediated three-component Mannich reaction using amine **5**, aldehyde **6**, and silyl ketene

Scheme 1. Original Synthesis of 1[3]



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acetal **7** that furnished the racemic ester **8**,[4] which necessitated a laborious chiral separation to achieve the requisite enantiomeric excess. Following deprotection of the piperidine, a HATU-mediated amide bond formation with the known chiral bicyclic carboxylic acid **10**[5] was executed in good yield. The resulting pendent ester was hydrolyzed to the corresponding carboxylic acid with KOTMS, followed by a low-yielding HATU-mediated amidation with NH_4Cl to generate the target tertiary β-amino amide **1** after arduous chromatography. Notably, the yields of this ester-to-amide sequence were highly variable during larger-scale campaigns.

Taking into account the observed limitations of the current synthesis, several alternative disconnections were considered when approaching an improved and scalable asymmetric synthesis of **1** (Figure 2). Whereas strategies centered on

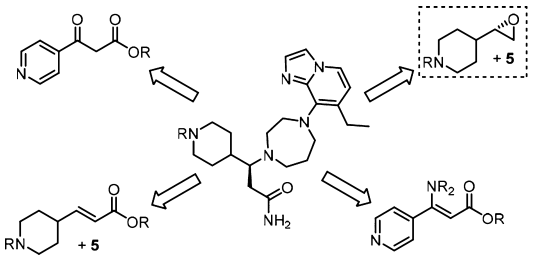
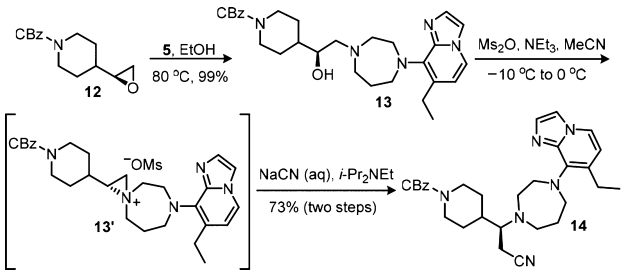


Figure 2. Retrosynthetic options for the asymmetric synthesis of **1**.

asymmetric reductions of suitably substituted β-keto esters[6] or dehydro amino acid derivatives[7] were considered heavily, the risks associated with enone formation or the uncertainty of de novo homopiperazine synthesis prevented further investigation. Additionally, the scant precedent for enantioselective aza-Michael additions[8] with hindered secondary amines, such as homopiperazine, or enantioselective Mannich reactions of enolate equivalents with imines[9] presented significant pause for investing into reaction identification and optimization. A consistent theme identified while assessing the synthesis of chiral β-amino acids was that the current state of the literature significantly catered to amines that lacked the requisite steric profile of the tertiary β-amino amide in **1**.[10] With the objective of preparing **1** with exquisite enantiomeric excess and being able to translate the asymmetric route to bulk synthesis, we elected to focus our efforts on maximizing the route efficiency while minimizing low-risk procedures. As such, we prioritized our efforts around robust and scalable chiral epoxide ring-opening strategies for accessing the requisite enantiomeric excess of **1**.

The cornerstone of our strategy relied on the intermediacy of a reactive aziridinium species,[11] which, following ring opening with cyanide, would furnish the desired chiral tertiary β-amino nitrile for further elaboration (Scheme 2). As a starting point for asymmetric route development, the known epoxide **12** was prepared using a two-step epoxidation/Co-catalyzed kinetic resolution sequence initiated from benzyl 4-formylpiperidine-1-carboxylate.[12] Aminolysis of chiral epoxide **12** with advanced homopiperazine intermediate **5** was readily achieved in refluxing EtOH solvent to access chiral β-amino alcohol **13** in excellent yield with complete regioselectivity.[12] Subsequent treatment of **13** with methanesulfonic anhydride and triethylamine in acetonitrile generated aziridinium intermediate **13′**,[11] which was then subjected to an aqueous solution of sodium cyanide in one pot to selectively open the

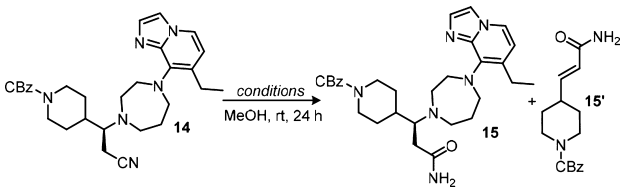
Scheme 2. Asymmetric Synthesis of Nitrile 14



aziridinium ring to prepare hindered tertiary β-amino nitrile **14** with excellent enantiomeric excess.[11a] Although this approach has been employed to access less-hindered systems, we believe that this tactic represents a general and powerful way to access systems featuring strongly sterically encumbered substituents, as represented by the synthesis of **14** (Scheme 2).

Having established a robust and scalable synthesis of chiral nitrile **14**, we next focused our efforts on the nitrile hydrolysis to access the requisite carboxamide **15**. At the outset of this effort, we surmised that the hindered nature of the nitrile, coupled with the potential for unproductive β-amino elimination of the nitrile (or amide), could present challenges for efficiently achieving this hydrolysis. Initially, our attempts to hydrolyze **14** under acidic or metal-mediated conditions led to either no reaction or decomposition of the starting material,[13] which prompted us to explore alternative basic conditions (Table 1). Whereas the use of aqueous NaOH or

Table 1. Optimization of the Hydrolysis of Nitrile 14 to Amide 15



entry	conditions	**15** (%)[a]	**15′** (%)[a]
1	LiOH (1 equiv), H_2O_2 (1 equiv)	35	5
2	LiOH (2 equiv), H_2O_2 (2 equiv)	45	10
3	LiOH (5 equiv), H_2O_2 (5 equiv)	45	45
4	LiOH (1 equiv), H_2O_2 (10 equiv)	40	60
5	NaOH (2 equiv), H_2O_2 (2 equiv)	50	25
6	NaOH (1 equiv), H_2O_2 (1.5 equiv), DMSO (1.2 equiv)	65 (63[b])	<1

[a]Yields determined by LC−MS analysis. [b]Isolated yield.

LiOH solutions in methanol proved to be unreactive toward **14**, employing basic hydrogen peroxide reaction conditions began to provide partial conversion to the desired amide **15**, albeit with concomitant formation of the α,β-unsaturated side product **15′** (Table 1, entry 1). Attempts to favor nitrile hydrolysis relative to the unproductive oxidative β-amino elimination pathway by increasing the amounts of base and oxidant resulted in modest yield gains but were accompanied by increased side-product formation (Table 1, entries 2−4). Using previously documented conditions for the hydrolysis of challenging nitrile substrates,[14] we successfully executed the hydrolysis of **14** using a mixture of NaOH and H_2O_2 in conjunction with DMSO as an additive to prepare **15** in 63% isolated yield with only trace amounts of **15′** (Table 1, entry

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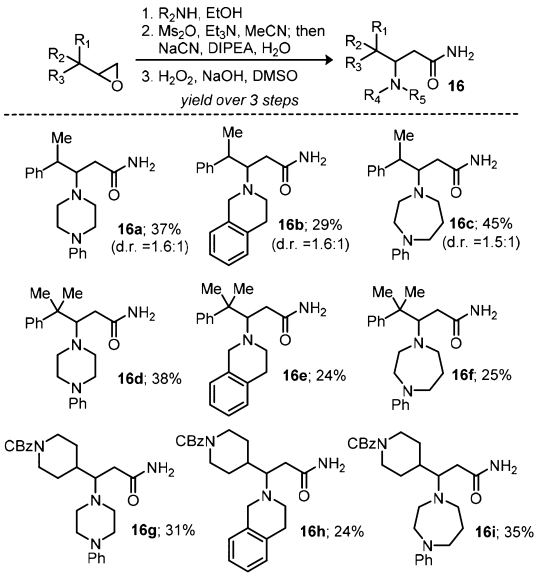
6). Of importance, these conditions were seamlessly translated to the decagram synthesis of advanced intermediate **15** without any loss in yield or purity profile.

Given the lack of synthetic strategies for the robust asymmetric synthesis of hindered β-tertiary amino amides, we elected to explore this sequence on a representative set of hindered epoxide and amine reaction partners (Scheme 3). A

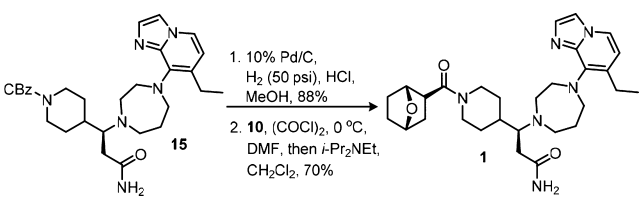
Scheme 3. Scope of the Three-Step Sequence To Generate β-Amino Amides from Epoxides[13]



series of racemic epoxides with varied steric profiles were prepared and subjected to the three-step sequence with a set of hindered cyclic amines to generate the corresponding β-amino amides. Epoxides featuring both cyclic and acyclic α-secondary as well as α-tertiary branched substitution patterns were readily accessible in comparable yields at each step of the exemplified sequence. In regard to the individual reactions of this three-step sequence, the epoxide ring opening and nitrile hydrolysis reactions proceeded in consistently good yields, whereas the aziridinium formation/cyanide addition sequence represented the more challenging reaction.[13] When combined with the minor deviations in yield observed for each representative amine tested, the reported synthetic strategy offers a robust approach for the preparation of hindered β-amino amides.

Completion of the asymmetric synthesis of CXCR7 modulator **1** required deprotection of the piperidine moiety followed by formation of the final amide bond connection to the chiral bicyclic carboxylic acid **10** (Scheme 4). Treatment of an acidic solution of **15** in methanol with palladium on carbon under a hydrogen atmosphere cleanly provided the hydrochloride salt of the unprotected piperidine. Whereas the final amide bond formation was previously established using a

Scheme 4. Completed Asymmetric Synthesis of 1



HATU coupling procedure in the original synthesis of **1** (Scheme 1),[3] the persistence of trace fluoride-containing impurities derived from the coupling reagent in the final compound led us to evaluate alternative strategies. Following a screen of conditions to identify a suitable HATU replacement, we found that reaction of the in situ-generated acyl chloride of **10** with the piperidine provided a clean and reproducible route to the target **1**. Of importance, no erosion of the enantiomeric excess of the chiral bicyclic moiety derived from **10** was observed by NMR or chiral analysis.[13]

In response to the demand for bulk quantities of the CXCR7 modulator **1** to support critical in vivo efficacy studies, we have developed a robust and scalable asymmetric synthesis that has been executed on a decagram scale. In contrast to the first-generation synthesis, the strategy reported herein capitalizes on the ready access of enantiopure starting materials via well-established chiral epoxide synthesis. Following regioselective ring opening of the epoxide with a homopiperazine derivative, the cornerstone of the synthesis features the transient preparation of a reactive aziridinium species that, when treated with cyanide, furnished the requisite tertiary β-amino nitrile. Subsequent hydrolysis of the hindered nitrile to the primary amide provided access to the sterically congested framework featured in compound **1**. Given the limited strategies available for the asymmetric preparation of hindered β-amino amides, we anticipate this tactic to be of interest to the broader synthetic community in the context of drug discovery and other complex molecule synthesis.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b02261.

Experimental procedures and characterization data of all synthesized compounds (PDF)

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Notes

The authors declare no competing financial interest.

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