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Asymmetric Synthesis of 4,4-Disubstituted-2-Imidazoli-dinones: Potent NK_1 Antagonists

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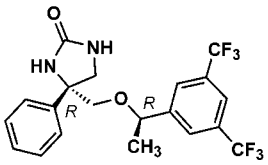
ABSTRACT



Sch 425078
$K_i(NK_1)$ = 0.6 nM

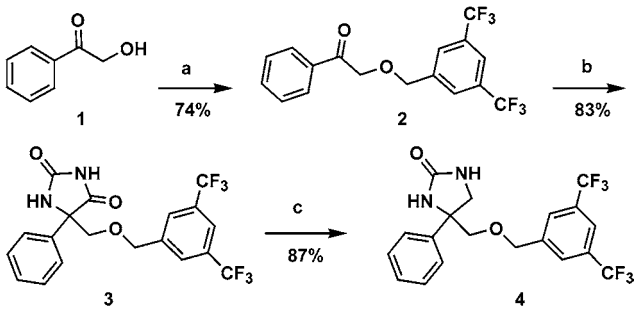
A highly efficient and practical synthesis of 4,4-Disubstituted-2-Imidazolidinones utilizing a "self-reproduction of the center of chirality" strategy is described.

We have recently disclosed a series of 4,4-disubstituted-2-imidazolidinones as potent NK_1 antagonists.[1] To perform a comparative analysis of our most promising compounds in this class, multigram quantities of several analogues were needed in optically pure form. To meet these material requirements, a thorough investigation of various synthetic methods toward an optically pure imidazolidinone core was undertaken.

Initially, a practical racemic synthesis of the imidazolidinone ring was developed (Scheme 1). Alkylation of α-hydroxy acetophenone by treatment of the triflate of 3,5-bis(trifluoromethyl)benzyl alcohol in the presence of 2,6-di-*tert*-butyl-4-methyl pyridine was followed by subsequent hydantoin formation under standard conditions. Reduction with lithium aluminum hydride/aluminum trichloride provided the desired imidazolidinone.

Numerous methods to resolve the hydantoin intermediate or imidazolidinone product were surveyed, and a practical chiral chromatographic method was discovered allowing

Scheme 1. Racemic Synthesis of 4,4-Disubstituted 2-Imidazolidinones[a]



[a] Reagents and conditions: (a) 3,5-bis(trifluoromethyl)benzyl alcohol, 2,6-di-*tert*-butyl-4-methyl-pyridine, trifluoromethane sulfonic anhydride, CH_2Cl_2; (b) potassium cyanide, ammonium carbonate, 50% aqueous ethanol; (c) lithium aluminum hydride, aluminum trichloride, THF.

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(1) Shih, N.-Y.; Shue, H.-J.; Reichard, G. A.; Paliwal, S.; Blythin, D. J.; Piwinski, J. J.; Xiao, D.; Chen, X. PCT Int. Appl. WO 0144200, 2001.

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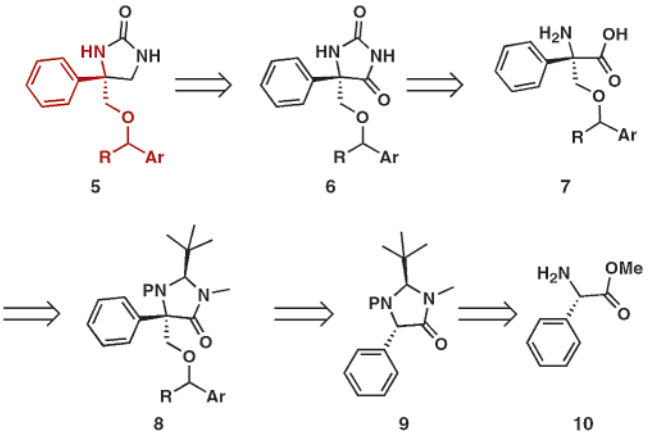
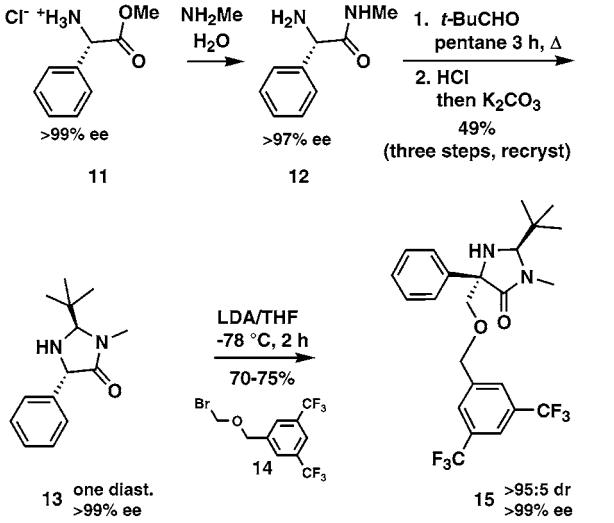
Scheme 2. Retrosynthetic Analysis: Asymmetric Route



Scheme 3. Alkylation of Imidazolidinone **13**



access to multigram quantities of optically pure imidazolidinone **4**. Further structural changes around this lead compound resulted in targets that could be separated via chiral chromatography with varying degrees of success. To circumvent chromatographic resolution procedures, a general and practical asymmetric synthesis of 4,4-disubstituted 2-imidazolidinones was sought.

Our approach (Scheme 2) is based on the "self reproduction of the center of chirality" method developed by D. Seebach.[2] The cyclic urea, **5**, would be made from hydantoin intermediate **6**, which can readily be prepared from the α,α-disubstituted phenylglycine amino acid **7**. This amino acid would result from hydrolytic opening of the imidazolidinone **8**. Diastereoselective alkylation of the imidazolidinone **9** should occur with bottom face approach of the incoming aryl bromomethyl ether. This bond disconnection represents an efficient way of preparing the minimal pharmacophoric elements (highlighted below) of phenylglycinol-based NK_1 antagonists[3] on fully substituted systems with the overall absolute stereochemistry originating from phenylglycine.

The initial synthetic implementation of our strategy utilized the *N*-benzoyl-protected imidazolidinone;[4] however, we encountered problems with the extreme conditions needed to hydrolyze the benzoyl group of the dialkylated *N*-benzoyl-imidazolidinones.[5,6] To circumvent this problematic cleavage, we sought to explore the *"unprotected"* imidazolidinone **13** (Scheme 3).[7,8]

Thus, treatment of phenylglycine methyl ester **11** with an *aqueous* solution of methylamine provided the amide **12** with minimal epimerization.[9] Treatment of the amino amide **12** with pivalaldehyde in pentane with azeotropic removal of water followed by treatment with hydrochloric acid installs the temporary *tert*-butyl stereocenter (trans/cis ratio of 6:1). Neutralization of the amine hydrochloride salt with potassium carbonate and isolation via aqueous workup provided the *crystalline* free base imidazolidinone **13**. Recrystallization from MTBE removed the minor cis isomer to provide pure **13** in >99% ee as one diastereomer by ^{1}HNMR with excellent recovery.

Imidazolidinone **13** was alkylated with **14**[10] using LDA /THF[11] to provide the α,α-disubstituted phenylglycine derivative **15** in >95:5 diastereomeric ratio with excellent isolated yields in the range of 70−75%.[12]

Various bromomethyl ethers containing substitution at the benzylic center were also employed for structure−activity relationship investigation purposes (data not shown). The most biologically interesting of these targets contained a chiral benzylic methyl group.[13] Preparation of the required bromomethyl ether in quantity (Scheme 4) required a large supply of (*R*)-α-methyl 3,5-bis(trifluoromethyl)benzyl alco-

(2) Seebach, D.; Imwinkelried, R.; Weber, T. *Mod. Synth. Methods* **1986**, 129.

(3) Swain, C. J.; Cascieri, M. A.; Owens, A.; Saari, W.; Sadowski, S.; Strader, C.; Teall, M.; Van Neal, M. B.; Williams, B. J. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 2161.

(4) Typically, the nitrogen of the imidazolidinone employed for Seebach's approach is functionalized as a carbamate or acyl derivative in order to control the cis/trans ratio of the temporary stereocenter or confer crystallinity for purification purposes.

(5) Hydrolytic cleavage of bulky disubstituted imidazolidinones can be quite problematic, particularly for substituents larger than methyl on the phenylglycine system (ref 6a,b). The structural requirements for our compounds were not tolerant of these conditions.

(6) (a) Studer, A.; Seebach, D. *Liebigs Ann.* **1995**, 217. (b) Obrecht, D.; Heimgartner, H. *Helv. Chim. Acta* **1981**, *64*, 482.

(7) Although the diastereoselective ethylation of imidazolidinone **13** has been reported (see ref 8), we could find no characterization of imidazolidinone **13** or any further reference of its use.

(8) See: Seebach, D.; Aebi, J. D.; Naef, R.; Weber, T. *Helv. Chim. Acta* **1985**, *68*, 144.

(9) Standard amidation conditions utilizing a *methanolic* solution of methylamine require long reaction times (>14 h) and epimerize the α-proton resulting in the isolation of **12** in 70% ee. An alternative solution to this racemization problem employs the coupling of *N*-Boc phenylglycine with methylamine using HOOBT to provide *N*-Boc amino amide in >98% ee. Standard deprotection conditions provide **12** in excellent yield.

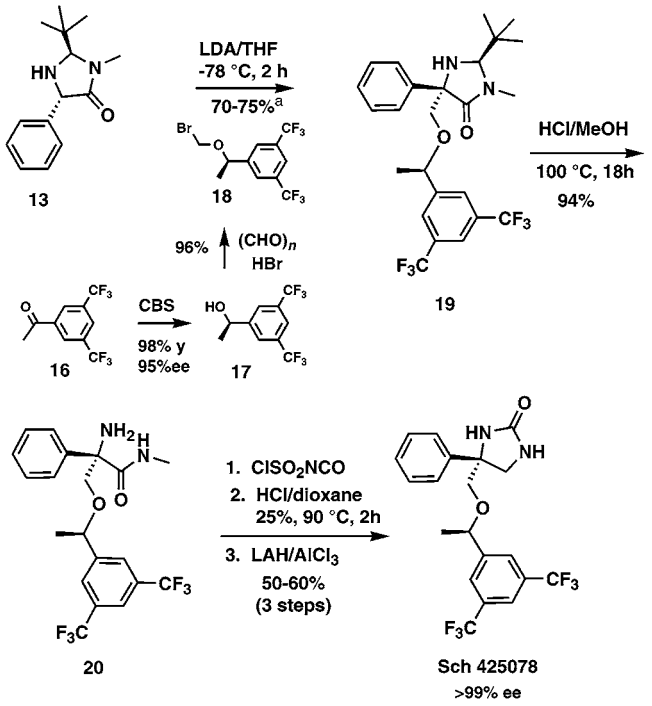
(10) Prepared from treatment of a melt of paraformaldehyde and 3,5-bis(trifluoromethyl)benzyl alcohol with gaseous hydrobromic acid.

(11) Deoxygenation of the solvent and reagents is critical for clean and reproducible runs of the alkylation.

(12) Isolated yields after column chromatography. Generally, for large-scale reactions, the product was purified by crystallization, which provided **15** in 50% isolated yield (see Experimental Section).

(13) Swain, C. J.; Williams, B. J.; Baker, R.; Cascieri, M. A.; Chicchi, G.; Forrest, M.; Herbert, R.; Keown, L.; Ladduwahetty, T.; Luell, S.; Macintyre, D. E.; Metzger, J.; Morton, S.; Owens, A. P.; Sadowski, S.; Watt, A. P. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 2959.

Scheme 4. Asymmetric Synthesis of 4,4-Disubstituted 2-Imidazolidinones



[a] Isolated yields of **19** in >95:5 diastereomeric ratio after column chromatography.

hol (**17**). CBS reduction[14] of 3,5-bis(trifluoromethyl)-acetophenone (**16**) was optimized to provide over 300 g of **17**. Treatment of a melt of paraformaldehyde and chiral alcohol **17** with gaseous hydrobromic acid for 2 h followed by anhydrous extractive workup with hexane and distillation gave the bromomethyl ether **18** in >90% yield on scales of >100 g.[15]

Imidazolidinone **13** was alkylated with **18** using LDA/THF to afford the α,α-disubstituted phenylglycine derivative **19** in >95:5 diastereomeric ratio with isolated yields in the range of 70−75%. Recrystallization of **19** from pentane provided material that is diastereomerically and enantiomerically pure in 55% isolated yield. The absolute configuration of **19** was confirmed by X-ray crystallographic analysis (Figure 1).

Subsequent treatment of **19** with methanolic/aqueous HCl gave the desired amino amide **20** in >95% yield with no need for chromatographic purification. The resulting amino amide was then treated with chlorosulfonylisocyanate followed by 25% aqueous HCl/dioxane to afford the desired crystalline hydantoin. The hydantoin was reduced to the

(14) For an excellent review, see: Corey, E. J.; Helal, C. J. *Angew. Chem., Int. Ed.* **1998**, *37*, 1986.

(15) The % ee of **18**, checked by hydrolysis back to the chiral alcohol **17** by treatment on silica gel, was found to be unchanged (95% ee) as a result of the conditions required for bromomethyl ether formation.

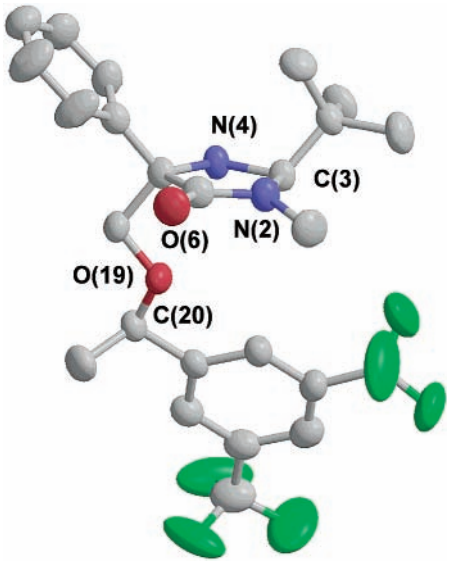


Figure 1. ORTEP representation of the crystal structure of **19**.

required cyclic urea as before using LAH/$AlCl_3$. Recrystallization from hot MTBE provided the final product in >99% ee as a single diastereomer.

Thus, the employment of crystalline imidazolidinone **13** resulted in the discovery of a highly efficient route to optically pure 4,4-disubstituted 2-imidazolidinones. The yields for the seven-step synthesis are generally very good; the transformations can be carried out on very large scale, and little chromatography is needed to provide 4,4-disubstituted 2-imidazolidinone NK_1 antagonists in optically pure form. A procedure for the amidation of stereochemically labile phenylglycine esters with minimal racemization has been established. Furthermore, the utility of employing substituted benzylbromomethyl ether electrophiles to stereoselectively install the NK_1 pharmacophore in hindered disubstituted systems has been discovered. The generality of this key step with other core systems to give rise to novel NK_1 antagonists is the focus of current work and will be the subject of future publications.

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Supporting Information Available: Experimental procedures and spectral data for compounds **12**−**20** and **Sch 425078** and crystallographic details for compound **19** in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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