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Strategy for the Enantioselective Synthesis of *trans*-2,4-Disubstituted Piperidines: Application to the CCR3 Antagonist IS811

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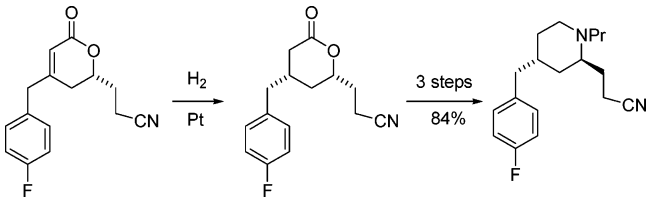
Received August 15, 2006



A strategy for the enantioselective synthesis of *trans*-2,4-disubstituted piperidines is proposed and applied to the preparation of IS811, a potent CCR3 antagonist. The C2 stereocenter is derived from commercial (*R*)-epichlorohydrin, while the C4 stereocenter is installed via diastereoselective hydrogenation of an α,β-unsaturated lactone intermediate. Inversion of the original stereocenter via an efficient intramolecular S_N2 amination affords the piperidine core of IS811. An improved protocol for the lithiation of ethyl propiolate is reported.

Interest in 2,4-disubstituted piperidines as pharmacophores has grown rapidly in recent years. It has been known for decades that 4-substituted pipecolic acid[1] derivatives can exhibit high levels of biological activity; commercial examples include the anticoagulant argatroban[2] and the veterinary antibiotic pirlimycin.[3] However, the current flurry of activity utilizes a greatly expanded palette of 2,4-disubsituted piperidine building blocks and has provided promising results in therapeutic areas as diverse as depression,[4] asthma,[5] Alzheimer's disease,[6] schizophrenia,[7] and antihistaminics.[8]

Despite this increasing interest, options for the synthesis of enantiomerically pure 2,4-disubstituted piperidines remain limited. In contrast, there is substantial literature concerning the enantioselective synthesis of 2,6-disubstituted piperidines, which include such alkaloids as (−)-solenepsin and (−)-dihydropinidine.[9]

The literature does provide a number of protocols for preparing *trans*-2,4-disubstituted piperidines in racemic form. In certain cases, cyanation of the 2-position of 4-alkylpiperidines under oxidative conditions,[10] addition of Grignard reagents to a 2-methoxy-4-alkylpiperidine formamidine,[11] nucleophilic additions to acyliminium ions,[12] and even radical cyclizations[13] have all been demonstrated to provide high levels of *trans*-diastereoselectivity. The combination of any of these protocols with a suitable nonracemic substrate could in principle provide an enantioselective synthesis. Moreover, Hanessian and coworkers prepared an entire library of enantiopure 2,4-disubstituted piperidines by conjugate addition of organocuprates to an optically enriched 4,5-unsaturated 2-substituted 6-oxopiperidine nucleus and diastereomer separation.[14]

Several of these protocols rely on the A(1,3) strain[15] which arises between an *N*-acyl or *N*-alkoxycarbonyl group and a substituent on a carbon atom adjacent to the nitrogen of a piperidine ring. This effect forces the substituent at C2 into the axial position. One consequence is that, with a sufficiently electron-withdrawing substituent at either the 2-position[16] or the 4-position,[17] a *cis*-2,4-disubstituted piperidine can be epimerized to its thermodynamically favored *trans*-diastereomer. We previously reported an approach to *trans*-2,4-disubstituted piperidines based on A(1,3) strain, namely, the dissolving metal reduction of 2-substituted *N*-acylpiperidines bearing an exocyclic alkylidene group at the 4-position.[18] The 2,3-dihydro-4-pyridone starting materials used in that approach are readily available using the efficient chemistry developed by Comins and co-

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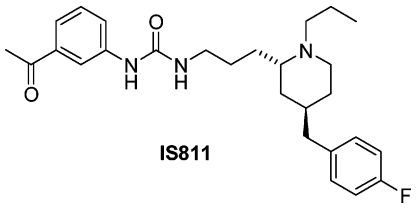
10.1021/jo0616963 CCC: $33.50
Published on Web 10/14/2006

workers.[19] However, a limitation of the approach is that the dissolving metal conditions are incompatible with many functional groups including the fluorophenyl group required in the current study.

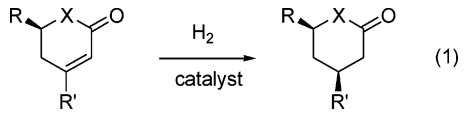
Our interest in this area resulted from the need for an efficient synthesis of an asthma drug candidate. IS811 was discovered as part of a major effort to identify potent, selective CCR3



antagonists to explore the therapeutic value of preventing eosinophil recruitment into pulmonary airways.[20] Establishing both the relative (*trans*) and absolute (2*S*,4*R*) stereochemistry of the piperidine ring presented a significant challenge to the discovery analogue effort.

The strategy which we describe below does not appear to have been utilized previously, perhaps because the notion of building a *trans*-disubstituted heterocycle from a *cis*-disubstituted heterocycle is mildly counterintuitive. Nevertheless, the individual steps used in our approach are amply precedented and have considerable scope. Consequently, we believe that this approach may have general utility beyond the current example of IS811.

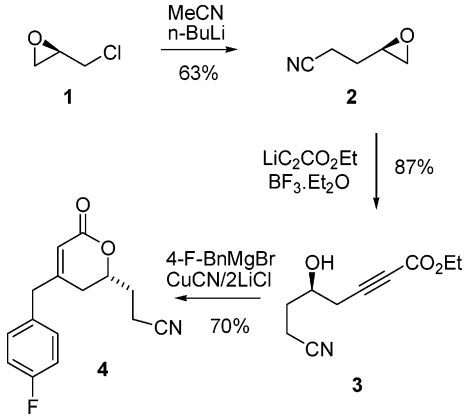
For reasons of synthetic efficiency, we wished to establish the chirality at one of the two asymmetric carbons and then use it to induce the stereochemistry of the other. A particularly clean and efficient method for inducing the C4 stereocenter in C2-substituted heterocycles is heterogeneous hydrogenation of a suitable unsaturated derivative. However, if the substrate is an α,*β*-unsaturated lactam (eq 1, X = NR″), anti delivery of hydrogen is known[21] to result in the undesired *cis*-2,4 relationship.



This problem might be circumvented by using an α,*β*-unsaturated lactone as substrate (eq 1, X = O). Hydrogenation would still give a *cis*-disubstituted product,[22] but in this case inversion of the C2 stereocenter during introduction of nitrogen (via an S_N2 process) would afford the requisite *trans*-2,4 relationship required for IS811.

To test this notion, we developed a three-step synthesis of lactone **4** as shown in Scheme 1. Although not fully optimized,

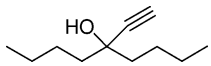
SCHEME 1. Preparation of Unsaturated Lactone 4



this procedure allows the ready preparation of 25 g quantities of **4** as an enantiopure crystalline solid.

(*R*)-1,2-Epoxy-4-cyanobutane (**2**) was prepared by the addition of acetonitrile anion to (*R*)-epichlorohydrin. Somewhat surprisingly, *n*-butyllithium was found to be the most effective base. (LDA is usually employed for addition of acetonitrile to epoxides.[23]) Extractive workup of the reaction mixture provides substantially pure **2** in 91% yield. We observed that decomposition occurs during distillation of this material, so that the yield of distilled **2** falls to 63%. Apparently this degradation is caused by impurities present in the crude product since purified **2** can be redistilled without decomposition.

Ring opening of epoxide **2** with ethyl propiolate was carried out in the presence of equimolar boron trifluoride etherate following the Yamaguchi protocol.[24] In our initial studies, the deprotonation of ethyl propiolate was accomplished using *n*-butyllithium following the standard protocol first reported by Midland.[25] We noted that the crude product obtained from addition of this material to epoxynitrile **2** even at −78 °C contained ca. 25% of a side product, which was isolated and identified as the tertiary alcohol from double addition of *n*-butyllithium to the carbonyl group of ethyl propiolate:



This is a relatively innocuous side reaction, and the literature contains many applications of the Midland protocol that proceed in 95−100% yield[26] (typically using a 1.5−3-fold excess of BuLi and ethyl propiolate). However, to avoid the need for excess reagents and chromatographic purification, we examined other lithium bases. Suzuki suggested[27] the use of LDA to circumvent this problem, but the use of lithium amides is precluded in our case because the resulting amines would

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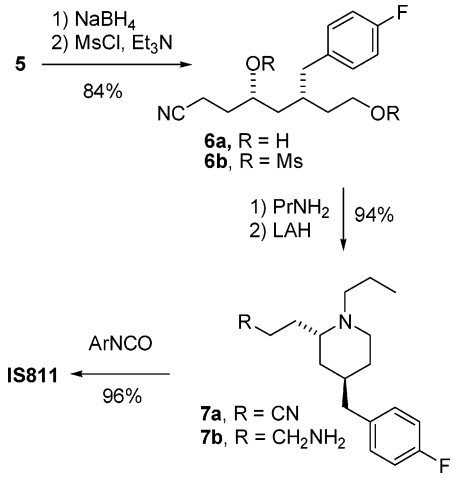
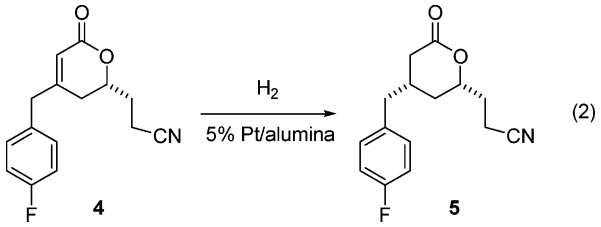
SCHEME 2. Completion of Synthesis



deactivate the boron trifluoride etherate required for epoxide ring opening. Use of more sterically encumbered *sec*-butyllithium still resulted in competing 1,2-addition. Treatment of ethyl propiolate with mesityllithium at −78 °C instantly resulted in a dark brown solution which was not further investigated. However, treatment of ethyl propiolate with 1 equiv of hexynyllithium generated in situ gave a clean reaction without requiring excess organolithium.

The fluorobenzyl fragment was then installed via conjugate addition of an organocopper reagent. As a soluble copper source, Knochel's CuCN/2LiCl reagent[28] provided superior results. Quenching the reaction mixture with anhydrous methanol allowed us to isolate the α,β-unsaturated lactone directly (99% ee by chiral HPLC).[29]

We then examined the hydrogenation of **4** over various heterogeneous catalysts (eq 2). With palladium catalysts a small amount of reduction of the arene was observed in addition to



(2)

the desired hydrogenation. This side reaction was diminished by use of a 5% Pt on carbon catalyst, and in fact no arene reduction whatsoever took place when using 5% Pt on alumina. Under the best reaction conditions (50 psi of H_2, 25 °C, 24 h), *cis*:*trans* selectivity was >95:5. A single crystallization from 2-propanol affords lactone **5** in >99% de and ee.

The functional group interconversions required to complete the synthesis of IS811 (Scheme 2) all proved straightforward and high yielding. The sequence begins with the chemoselective reduction of the lactone in the presence of a nitrile. This was accomplished by the use of sodium borohydride in *tert*-butyl alcohol in the presence of methanol.[30] The crude product **6a** was simply purified by dissolution in 1:1 ethyl acetate/diethyl ether and filtration through Celite prior to mesylation to afford **6b**. The yield for the reduction was 86%, and that for the mesylation was 98%.

Formation of the piperidine ring was achieved by treating bismesylate **6b** with solvent *n*-propylamine. This protocol is based on that used by Singaram for the synthesis of (*S*)-*N*-benzylconiine.[31] In the present case, the dialkylation afforded **7a** in essentially quantitative yield. The nitrile group was then reduced with lithium aluminum hydride to afford aminopiperidine **7b** in 94% yield.

Finally, **7b** was elaborated into IS811 by treatment with 3-isocyanatoacetophenone. Chiral HPLC and spectroscopic characterization confirmed that the crystalline product from this 9-step procedure was identical to that produced by the 14-step discovery synthesis.[20]

In the synthetic strategy outlined above, both stereogenic centers of IS811 are ultimately derived from a single molecule of (*R*)-epichlorohydrin. To date, enantiopure epichlorohydrins have been utilized for the syntheses of several dozen natural products and drug candidates, beginning with Kuehne's seminal syntheses of vincadifformine and tabersonine.[32] Recently, interest in these outstanding chiral conjunctive reagents as pharmaceutical building blocks has been bolstered as a result of new technology for their manufacture. Both enantiomers are now inexpensively available in multikilogram quantities via both the Jacobsen hydrolytic kinetic resolution[33] and microbial resolution.[34]

In addition to the readily available starting material, this approach to IS811 has other attractive features. The ability to establish the relative stereochemistry via simple hydrogenation is advantageous. Both the saturated and unsaturated lactone intermediates (compounds **4** and **5**) are crystalline solids.[35] Moreover, the functional group interconversion chemistry to transform the lactone to the piperidine (Scheme 2) is highly efficient.

Finally, we note that optically enriched epoxides are by no means restricted to those such as compound **2**, which can be prepared from epichlorohydrin. It is reasonable to believe that the chemistry outlined here could be applied to convert optically active epoxides from a variety of sources to the corresponding piperidines. Thus, it seems likely that this "buy one, get one free" approach to the two stereogenic centers of *trans*-2,4-disubstituted piperidines will find additional applications.

Acknowledgment. We thank Drs. Percy H. Carter, Carl P. Decicco, and Pat N. Confalone for their unflagging encouragement and Dr. Robert E. Waltermire for helpful technical discussions.

Supporting Information Available: General experimental procedures, structure assignment of **5** via NOE, synthetic details, and ^1H and ^{13}C NMR spectra for all compounds in Schemes 1 and 2. This material is available free of charge via the Internet at http://pubs.acs.org.

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(35) A somewhat unusual feature of the unsaturated lactone is that optically active (−)-**4** melts 10 °C higher than racemic **4**. This could facilitate shedding the undesired enantiomer via crystallization should epimerization become an issue under the less stringent conditions of scaleup.