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Investigation of Practical Routes for the Kilogram-Scale Production of *cis*-3-Methylamino-4-methylpiperidines

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Abstract:

Two routes for the synthesis of *cis*-*N*-protected-3-methylamino-4-methylpiperidine (3) were examined: a route hinging on the electrochemical oxidation of carbamate 1 to install a ketone at the 3 position of the piperidine followed by reductive amination (disconnection A), and a route involving the hydrogenation of an appropriately functionalized pyridine (disconnection B). While both routes to the desired compound were ultimately successful, the pyridine hydrogenation approach proved to be more amenable to kilogram-scale preparations due to the crystallinity and purity of intermediates in that route.

Introduction

cis-*N*-Protected-3-methylamino-4-methylpiperidine **3** was identified as a useful intermediate in the synthesis of a clinical drug candidate, necessitating its production on kilogram scale. The route originally used to produce this compound relied on a hydroboration−oxidation sequence starting from tetrahydropyridine **6** followed by oxidation and reductive amination to install the methylamino functionality[1] (Scheme 1).

Although the route depicted above was able to provide 10 kg quantities of the desired piperidine, identifying an alternate route was desirable[1a] for the following reasons. The sulfur-based oxidations, although far preferable to the chromium oxidations they replaced, leave the product contaminated with dimethyl sulfide leading to handling problems. The hydroboration reaction requires the use of large volumes of solvent during the workup and isolation. The overall route required five steps to complete.

From a retrosynthetic perspective, the methylamino functionality could either originate from the ketone via reductive amination or could be installed by hydrogenation of an aminopyridine (Scheme 2). Strategies where the methylamine is installed via addition of a nitrogen nucleophile to an activated C3 do not appear to be viable due to a facile ring contraction[2] when the ring nitrogen is nucleophilic in nature. A Dieckmann condensation approach to 3-ketopiperidines has been reported,[3] but more intriguing to us was a strategy to install the ketone oxidatively at the unactivated 3 position.

Electrochemical Approach to 3

Shono has reported the electrochemical oxidation of carbamate-protected piperidines directly to 2,3-diacetate[4] **10**, which can be converted to ketone[5] **12** (Scheme 3). The oxidation of piperidines can be achieved without the use of electrochemistry as well,[6] but systems relevant to the target at hand did not perform well under the reported conditions.

The electrochemical oxidation of carbamate-protected piperidines reported by Shono is a close model for the production of the desired ketone.[4] The oxidation is run in acetic acid with potassium acetate as the electrolyte, and a close analogue to the desired system reported by Shono was high yielding.

The oxidation of the methyl and *tert*-butyl carbamates of 4-methylpiperidine proceeded to provide the desired prod-

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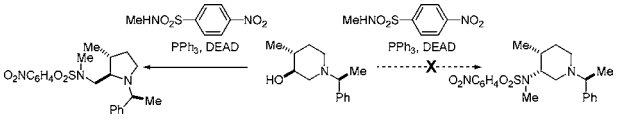
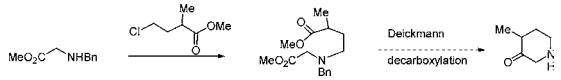
(1) (a) Ripin, D. H. B.; Abele, S.; Cai, W.; Blumenkopf, T.; Casavant, J. M.; Doty, J. L.; Flanagan, M.; Koecher, C.; Laue, K. W.; McCarthy, K.; Meltz, C.; Munchhoff, M.; Pouwer, K.; Shah, B.; Sun, J.; Teixeira, J.; Vries, T.; Whipple, D. A.; Wilcox, G. *Org. Process Res. Dev.* **2003**, *7*, 873−878. (b) Iorio, M. A.; Ciuffa, P.; Damia, G. *Tetrahedron* **1970**, *26*, 5519−5527.

(2) Fukuyama, T.; Jow, C.-K.; Cheung, M. *Tetrahedron Lett.* **1995**, *36*, 6373−6374. On attempting to invert the alcohol stereocenter using *N*-methyl-*p*-nitrobenzenesulfonamide under Mitsunobu conditions, the five-membered ring product was isolated. This was presumably formed via displacement of the activated alcohol by the piperidine nitrogen followed by opening of the aziridine at the less hindered position. This instability also made the epoxide intermediate that would be derived from compound **6** unattractive synthetically.



(3) Use of an intramolecular Dieckmann reaction: Knight, D. W.; Lewis, N.; Share, A. C.; Haigh, D. *J. Chem. Soc., Perkin Trans. 1* **1998**, *22*, 3673−3684. Alkylation of methyl *N*-benzylglycine with methyl 4-chloropentanoate provided the Dieckmann precursor. Clean cyclization was not achieved, and the prohibitive cost of the alkylating agent led to the discontinuation of this route.



(4) (a) Shono, T.; Matsumura, Y.; Onomura, O.; Kanazawa, T.; Habuka, M. *Chem. Lett.* **1984**, 1101−1104. (b) Shono, T.; Matsumura, Y.; Onomura, O.; Ogaki, M.; Kanazawa, T. *J. Org. Chem.* **1987**, *52*, 536−541. (c) Shono, T.; Matsumura, Y.; Tsubata, K.; Sugihara, Y.; Yamane, S.; Kanazawa, T. *J. Am. Chem. Soc.* **1982**, *104*, 6697−6703. (d) Shono, T.; Matsumura, Y.; Tsubata, K. *Org. Synth.* **1985**, *63*, 206−213.

(5) Matsumura, Y.; Takeshima, Y.; Okita, H. *Bull. Chem. Soc. Jpn.* **1994**, *67*, 304−306.

(6) (a) Scully, F. E., Jr. *J. Org. Chem. Soc.* **1980**, *45*, 1515−1517. (b) Scully, F. E., Jr.; Davis, R. C. *J. Org. Chem. Soc.* **1978**, *43*, 1467−1468. (c) Quick, J.; Oterson, R. *Synthesis* **1976**, 745−746.

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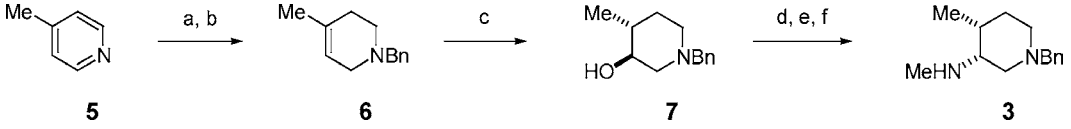
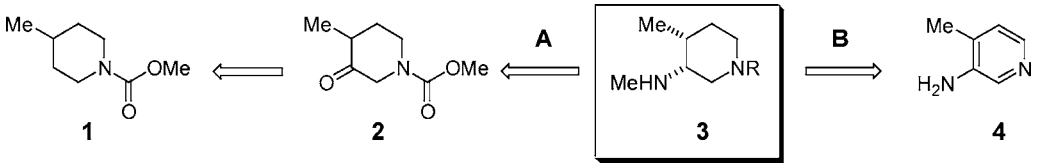
Scheme 1. **Hydroboration approach to 3**[a]



5 **6** **7** **3**

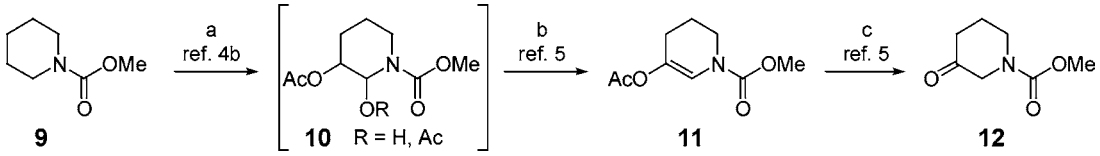
[a] Reaction conditions: a) BnCl, acetone, 55 °C, 73%; b) $NaBH_4$, EtOH, 15 °C, 73%; c) i) $BF_3{\cdot}OEt_2$, BH_3**.**THF, THF; ii) HCl, H_2O_2; iii) TsOH, 88%; d) $SO_3{\cdot}$pyridine, DMSO, Et_3N; e) $MeNH_2$, $NaHB(OAc)_3$, toluene, EtOH, THF, HOAc; f) HCl, EtOH, EtOAc, 53%, 3 steps.

Scheme 2. **Retrosynthesis of N-protected 3**



1 **2** **3** **4**

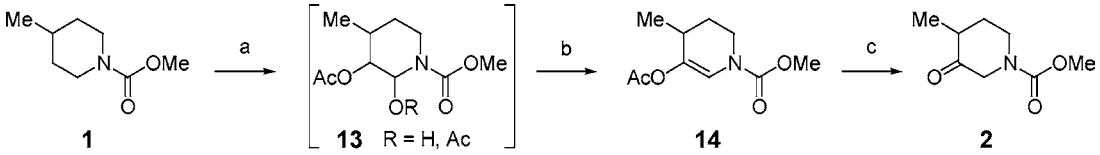
Scheme 3. **Reported electrochemical route to analogue of 3**[a]



9 **10** R = H, Ac **11** **12**

[a] Reaction conditions: a) [O], HOAc, KOAc, 87%; b) AcOH, Δ, 75%; c) MeOH, $NaHCO_3$, 95%.

Scheme 4. **Electrochemical route to 3**[a]



1 **13** R = H, Ac **14** **2**

[a] Reaction conditions: a) [O], HOAc, KOAc, 45%; b) Ac_2O, Δ, 90%; c) MeOH, $NaHCO_3$, Na_2CO_3 85%.

ucts, although in lower yield than the example reported by Shono (Scheme 4). The methyl carbamate **1** provided a higher yield with fewer byproducts. At best, approximately 45% of **13** could be obtained from the reaction as a mixture of diastereomers and with partial cleavage of the anomeric acetate. The effects of varying current density, rigorously drying the reaction mixture, and adding water scavengers such as acetic anhydride were examined but did not improve the yield of the reaction or the complexity of the product mixture.[7]

The electrochemical oxidation reaction mixture could be carried directly into a thermal elimination of the anomeric acetate run in acetic anhydride.[5,8] This provided vinyl acetate **14** in good in situ yield, and cleavage of the acetate in a sodium carbonate/sodium bicarbonate buffer solution and methanol finally provided the desired ketone.[5] None of these intermediates were solids, nor do they contain a basic nitrogen functionality from which a salt could be formed. As a consequence, the material had to be carried through the sequence without purification and provided material of low purity. Distillation failed to provide material of acceptable purity (50%), and the compound had to be purified by chromatography. Although the overall yield for the three-step process was about 35%, the lack of scaleable cleanups led us to examine alternate routes. Additionally, the conformational change in the six-membered ring imparted by the sp^2-hybridized nitrogen (a change from the benzyl-protected system depicted in Scheme 1) resulted in low selectivity in attempted reductive aminations to install the methylamino group.

Pyridine Reduction Approach to 3

An alternative to the reductive amination to install the methylamino functionality would be the reduction of the appropriately functionalized pyridine[9] such as **15** (Scheme 5).[10] Hydrogenation should provide the desired product **16** with the required stereochemistry.[11] The commercially available 4-methyl-3-aminopyridine **4** is a fully functionalized precursor to the desired piperidine and requires only reduction, protection of the piperidine nitrogen, and installation of the methyl group to provide the desired product.

The methyl carbamate **15** of amine **4** was prepared as a hydrogenation substrate (KO*t*Bu, $MeOCO_2Me$, THF, 61%). The methyl carbamate was selected over the formamide, as the formamide was hydrolysis-prone under some of the

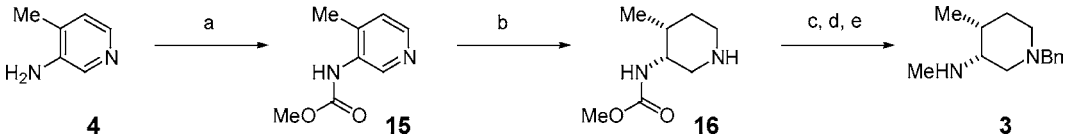
(7) Current densities of 50−100 mA/cm^2, starting material concentrations around 0.5 M, and 20 faradays/mol of starting material were investigated. Smaller-scale reactions (5−7 g) were run in a 100 mL undivided glass cell with a 20 cm^2 Pt mesh anode; larger reaction in the range of 30−40 g were run in a 500 mL undivided glass cell with a 60 cm^2 Pt mesh anode.

(8) Use of acetic anhydride as solvent in place of acetic acid led to clean conversion to vinyl acetate **14** as opposed to a mixture of vinyl acetate **14** and anomeric alcohols **13**, **R=H** in acetic acid.

(9) Keay, J. G. in *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon: New York, 1991; Vol. 8, Chapter 3.6.

(10) Other protecting groups were investigated such as a formamide in the hope of obtaining the methylaminopiperidine directly from the hydrogenation. These protecting groups did not provide as clean a reaction profile as the methyl carbamate, with solvolysis of the protecting group in the solvents necessary to hydrogenate the pyridine ring as the main side reaction.

Scheme 5. **Pyridine hydrogenation route to 3**[a]



[a] Reaction conditions: a) KOtBu, $(MeO_2C)_2O$, THF, 61%; b) 5% Rh/C (type 23), AcOH, H_2, 75%; c) PhCHO, $NaHB(OAc)_3$, CH_2Cl_2, HOAc, 68%; d) $LiAlH_4$, THF; e) HCl, EtOH, 47%, 2 steps.

hydrogenation conditions in nucleophilic solvents. The carbamate also provides the carbon of the methylamine functionality in the final product.

The hydrogenation was initially investigated using Rh/alumina and PtO_2. The cis:trans selectivity of the reduction was measured by ^{1}HNMR of the isolated product of the hydrogenation. Under the conditions originally investigated, a disappointing 3:1 ratio of cis:trans isomers was obtained from the process (Rh/Al_2O_3, ethanol, 100 psi, 80 °C; or PtO_2, acetic acid, 100 psi, 60 °C). Although not optimal, the purity and de of the desired isomer could be upgraded downstream as the HCl salt of the final product.[1a] The high levels of trans isomer observed are indicative of a stepwise reduction with the C-4 methyl bearing stereocenter scrambling via an imine intermediate or of a decomplexation−recomplexation of the metal catalyst prior to complete reduction of the ring.

A number of catalysts (PtO_2, Rh/C (several types), RuO_2, Rh/Al_2O_3, Ru/C (several types), Lindlar's catalyst, and Wilkinson's catalyst) and solvents (AcOH, *i*PrOH, EtOH, MeOH/NH_4OH, MeCN, THF, cyclohexane, heptanes, PhMe, DMF, water) were screened for the hydrogenation. Ultimately, hydrogenation with 5%Rh/C in acetic acid was most effective for the transformation, providing the product in 11:1 selectivity. The product could be isolated as a solid by precipitating the hydrochloride salt, but on larger scale it was more practical to carry the material forward in solution or as an oil since the free base is required for the next step. Several of the other conditions screened did provide complete hydrogenation of the pyridine, but with lower diastereoselectivity.

With the hydrogenation of the pyridine complete, the benzylamine was installed by reductive amination with benzaldehyde and sodium triacetoxyborohydride to provide the benzylamine in 68% yield. This material could then be carried crude into the methyl carbamate reduction using lithium aluminum hydride. After workup, the free base diamine could be isolated as the HCl salt in 47% yield for the reduction and salt formation. The HCl salt is an effective purification point and allows the de of the material to be upgraded to >97:3.[1a] For the five-step process, a 15% overall yield of desired piperidine was achieved on 50 g scale. This route was selected for further optimization for large-scale manufacture.

Optimization of the Pyridine Approach

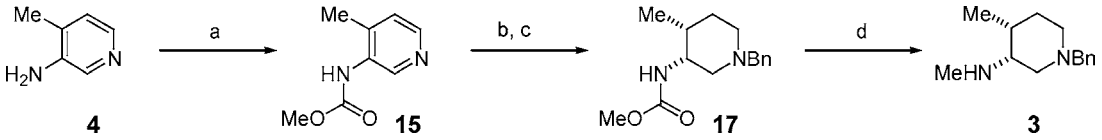
Optimization of the route began with the carbamate formation. In the laboratory, the aminopyridine and 3.0 equiv of base were slurried in THF, cooled, then reacted by portionwise addition of 1.5 equiv of dimethyl carbonate. This order of addition generated intense colors that sometimes carried through to the isolated product and left a sticky residue in the reaction vessel. After a water quench, four ethyl acetate washes were required to extract the product out of the aqueous layer. The organics were concentrated, and the product was crystallized from an ethyl acetate/diisopropyl ether (IPE) mixture. The reaction appeared to proceed very smoothly, but significant yield losses were encountered during the isolation and purification, giving the carbamate in a modest 61% yield. One surprising finding was the high aqueous solubility of this and all the other intermediates in the route. Care had to be taken to minimize the volume of any necessary aqueous wash, or the recovery of product was highly diminished. To address this issue, a solvent screen was carried out. The ethers were superior solvents for the reaction,[12] and 2-methyltetrahydrofuran (2-MeTHF) was selected because of its low miscibility with water. After the reaction was complete, minimal water was added to remove the residual salts, and no back-extractions were required. The color generated in the reaction could be avoided by changing the order of addition and adding a solution of **4** last to the reaction mixture. Displacement of the 2-MeTHF with toluene gave the desired product in 87% yield. During the displacement it was important to azeotropically remove any residual water to very low levels since it has a negative impact on recovery. Additionally, the presence of water during the crystallization results in formation of material with very poor filtration properties (Scheme 6).

The original goal during optimization of this route was to combine the pyridine reduction and reductive amination into one step. Several catalysts were examined for their ability to effect both transformations. The only catalyst that gave promising results was $Rh_2(COD)_2Cl_2$. However, during the reactions, the catalyst plated out on the reaction vessel

(11) (a) Moon, M. W.; Morris, J. K.; Heier, R. F.; Childester, C. G.; Hoffmann, W. E.; Piercey, M. F.; Althaus, J. S.; VonVoigtlander, P. F.; Evans, D. L.; Figur, L. M.; Lahti, R. A. *J. Med. Chem.* **1992**, *35*, 1076−1092. (b) Reitsema, R. H.; Hunter, J. H. *J. Am. Chem. Soc.* **1949**, *71*, 1680−1682. (c) Ebnoether, A.; Jucker, E.; Rissi, E.; Rutschmann, J.; Shreier, E.; Steiner, R.; Suess, R.; Vogel, A. *Helv. Chim. Acta* **1959**, *42*, 918−955. (d) Biel, J. H.; Hoya, W. K.; Leiser, H. A. *J. Am. Chem. Soc.* **1959**, *81*, 2527−2532. (e) Cooper, G. H.; Rickard, R. L. *J. Chem. Soc. C* **1971**, 772−776. (f) Crider, A. M.; Lamey, R.; Floss, H. G.; Cassady, J. M.; Bradner, W. J. *J. Med. Chem.* **1980**, *23*, 848−851. (g) Armour, D. R.; Chung, K. M. L.; Congreve, M.; Evans, B.; Guntrip, S.; Hubbard, T.; Kay, C.; Middlemiss, D.; Mordaunt, J. E.; Pegg, N. A.; Vinader, M. V.; Ward, P.; Watson, S. P. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 1015−1020. (h) Nienburg, H. *Chem. Ber.* **1937**, *70*, 635−638. (i) Glennon, R. A.; Jacyno, J. M.; Salley, J. J.; *J. Med. Chem.* **1982**, *25*, 68−70. (j) Ledoussal, B.; Almstead, J.-I. K.; Gray, J. L.; Hu, X. E. World Patent WO99/14214, 1999.

(12) A number of precautions are used when selecting ether solvents: distillations and solvent displacements are never run to near dryness, inhibitors are added immediately to the distillates, and oxidation reactions are avoided in these solvents. Laird, T. *Org. Process Res. Dev.* **2004**, *8*, 815.

Scheme 6. **Optimized conditions of the pyridine reduction route to 3**[a]



[a] Reaction conditions: KOtBu, $(MeO_2C)_2O$, 2-MeTHF; toluene, 87%; b) 5% Rh/C (JM type C101023-5), AcOH, H_2; c) PhCHO, $NaHB(OAc)_3$, toluene, 73%, 2 steps; d) $LiAlH_4$, THF; HCl, IPO, 87%.

surfaces, which would not be acceptable for scale-up. Several additives (phosphine ligands, Celite) were tried to avoid the deposition or adsorb the catalyst as it precipitated, but all of them retarded the pyridine reduction significantly and caused erosion of the diastereoselectivity. Therefore, it was decided to optimize the two-step sequence.

The laboratory procedure for the pyridine reduction required the use of 5% Rh/C (Johnson-Matthey type C101023-5) in acetic acid. The reduction proceeded with reasonable diastereoselectivity, giving an 11:1 ratio of cis:trans isomers. After reaction completion, the catalyst was removed by filtration, and the majority of the acetic acid was removed under reduced pressure. Residual acid was quenched with saturated $NaHCO_3$, and the product was extracted into EtOAc. A large portion of the product still remained in the aqueous layer after three extractions; thus, the aqueous layer was stripped to dryness and re-extracted. The combined lots could either be carried into the next step, or the intermediate could be isolated as its HCl salt (all the intermediates after the carbamate are oils, but all form solid salts readily). During the optimization, which made use of different sized and configured reactors, it was noted that the ratio of diastereomers sometimes improved to approximately 20:1. It is believed that the final intermediate prior to the stereochemically defining step may be the tetra-substituted olefin. In setups in which the hydrogen available for reaction was plentiful (low fill volumes, good mixing), the reduction proceeded with little stereochemical leakage. In those situations in which the reaction may have been hydrogen-starved (high fill volumes, poor mixing), there was some analytical evidence[13] to suggest that olefin migration prior to reduction was a competing event, which led to eroded diastereomeric ratios.

In the optimized conditions, the reduction was run in 10 volumes of acetic acid. The catalyst loading could be lowered from the initial 30 wt % to as little as 10 wt %, but was kept at 20 wt % on large scale to ensure complete reduction. After the reaction was complete, the catalyst was removed by filtration, and the majority of the acetic acid was removed under vacuum prior to proceeding to the reductive amination. Since the procedure for the next step uses acetic acid, it was decided that the quench and extractions were unnecessary and the acid solution could be carried forward directly into the reductive amination. Lab pilots confirmed that there was no negative impact on the purity profile of the reaction by omitting the aqueous washes.

The reductive amination was originally carried out by mixing the amine and benzaldehyde in methylene chloride followed by portionwise addition of sodium triacetoxyborohydride (STAB). After reaction completion, the mixture was quenched with saturated $NaHCO_3$ and extracted three times with EtOAc. The solvent was replaced with IPE, and the HCl salt was precipitated by bubbling gaseous HCl into the solution. The salt was then recrystallized from EtOH to obtain the product in 68% over the two steps. For environmental reasons and ease of handling, one of the first objectives was to replace the methylene chloride with a more benign solvent. Toluene was found to be a convenient replacement and had the added benefit of facilitating the displacement of the acetic acid from the previous step. Extensive displacement of the acetic acid led to the precipitation of the acetate salt of the product. However, the salt was thixotropic and the yield was low, so the displacement was stopped once there were fewer than four equiv of acetic acid remaining. This gave a convenient solution for the reductive amination and minimized the amount of acid to quench at the end of the reaction. A solution of the piperidine and benzaldehyde was added to a slurry of STAB in toluene, which avoided the need to add solids portionwise to a reactor. The excess STAB and acetic acid were quenched with aqueous sodium hydroxide. It was necessary to control the pH of the quench to avoid the formation of thick emulsion layers, and a range of 6−7 was found to be optimal. Addition of concentrated HCl to the toluene solution precipitated the desired product as its salt. The salt formation was best performed at elevated temperatures to purge the trans diastereomer and to grow larger crystals for faster filtrations. After cooling and filtration, the *N*-benzylamine was isolated in 73% yield.

The final step to form the target amine was reduction of the methyl carbamate. Originally, the HCl salt of the starting material was broken prior to addition of the LAH solution, extracted into EtOAc, which was then displaced with THF. The reaction was quenched with sodium sulfate decahydrate at a rate that controlled the hydrogen evolution. After solvent removal, the product was dissolved in IPE and the bis(HCl) salt was formed with gaseous HCl. Recrystallization from aqueous EtOH completed the synthesis of **3** in modest yield (47%). During optimization, the salt break was found to be unnecessary since it could be effected by addition of an excess of LAH. Addition of 2.25 mol equiv of water (relative to aluminum) diluted with THF to control the exotherm during the quench successfully precipitated the aluminum salts without gumming. After filtration of the salts, the THF was displaced with 2-propanol for formation of the bis(HCl) salt with concentrated HCl. The salt formation could be carried out directly from the THF solution, but the solids formed filtered very poorly and did not purge any of the

(13) HPLC−MS indicates impurity peaks with a mass of M-2, suggesting incomplete hydrogenation.

trans diastereomer. The salt formation in 2-propanol gave larger crystals that filtered well and purged the trans diastereomer to low levels. During the salt formation, it was important to remove the water introduced with the HCl to maximize the recovery, since even small levels of residual water diminished the yield markedly. The yield for the final step was 84−87%, and the level of the trans diastereomer was <0.8%.

Conclusion

Two new routes to *cis*-*N*-protected-3-methylamino-4-methylpiperidine **3** have been identified. While the electrochemical approach to the molecule worked in reasonable yield (35%) from inexpensive starting materials, purity and isolation difficulties would make it difficult to use on large scale. The pyridine reduction route did prove to be a practical alternative to the hydroboration route previously reported and could be utilized for the preparation of multikilogram quantities of **3** in 55% overall yield.

Experimental Section

General. All materials were purchased from commercial suppliers and used without further purification. All reactions were conducted under an atmosphere of nitrogen unless noted otherwise. All reactors were glass-lined steel vessels with the exception of those used for catalytic hydrogenations, which were Hastelloy. Reactions were monitored for completion by removing a small sample from the reaction mixture and analyzing the sample by TLC, GC, or HPLC. HPLC analyses were performed using one of the following systems: Waters Symmetry Shield RP18 column (4.6 m × 75 mm, 3.5 μm) and an acetonitrile/water (0.5% trifluoroacetic acid) mobile phase, a Zorbax SB-CN 4.6 m × 150 mm column or a Symmetry C-8 3.9 m × 150 mm column, and a mobile phase consisting of acetonitrile and either 0.5% perchloric acid or 0.2% phosphoric acid. GC analyses were performed on a DBWaxEtr (15 m × 0.25 mm × 0.25 μm film). Proton and carbon NMR spectroscopies were performed on a Bruker-Spectrospin Avance 400 MHz instrument. Karl Fischer measurements were obtained on a Mettler Toledo DL38 Volumetric Karl Fischer apparatus. Melting points were determined on a Buchi B-545 melting point apparatus. Elemental analyses were performed by Quantitative Technologies Inc. of Whitehouse, NJ.

3-Methoxycarbonylamino-4-methylpyridine (15). To a clean, dry, nitrogen-purged 800 L reactor were charged 3-amino-4-methylpyridine **4** (49.9 kg, 461 mol) and 2-methyltetrahydrofuran (383 L). The reaction was heated to 32−38 °C for at least 90 min. To a clean, dry, nitrogen-purged 2000 L reactor were charged potassium *tert*-butoxide (104.0 kg, 927 mol) and 2-methyltetrahydrofuran (255 L). The reaction was stirred at 23−27 °C for at least 30 min to break up the potassium *tert*-butoxide. Dimethyl carbonate (49.9 kg, 554 mol) was added to the slurry of potassium *tert*-butoxide at a rate that maintained the temperature below 35 °C. The 3-amino-4-methylpyridine solution was added to the 2000 L reactor at a rate that maintained the temperature from 20 to 35 °C. An additional 115 L of 2-methyltetrahydrofuran was added to aid stirring. The mixture was stirred between 20 and 35 °C for at least 2 h. The reaction was sampled and checked for completion by GC, then cooled to 15−20 °C. Water (255 L) was added at a rate to maintain the temperature below 25 °C. The mixture was stirred for at least 30 min then allowed to settle for at least 60 min. The phases were separated, and 2-methyltetrahydrofuran (255 L) was added to the aqueous layer. The reaction mixture was allowed to stir for at least 60 min and then allowed to settle for at least 60 min. The phases were separated, and the 2-methyltetrahydrofuran layers were combined. Darco KBB (10.0 kg) was added to the organic layer and allowed to stir for at least 30 min. The Darco slurry was filtered through a bed of Celite, and the cake was washed with 2-methyltetrahydrofuran (51 L). The 2-methyltetrahydrofuran was displaced with toluene under vacuum to a final volume of 480−540 L, then the mixture was cooled to 23−27 °C over at least 90 min. After sampling to ensure that the water content was <1%, the slurry was stirred for at least 12 h. The resulting solids were filtered and washed with toluene (212 L). After drying under vacuum at 40−50 °C for at least 12 h with a slight nitrogen bleed, 66.5 kg (400 mol) of (4-methyl-pyridin-3-yl)carbamic acid methyl ester was isolated in 86.7% yield (99.89% purity by HPLC) mp: 115.3−116.6 °C. ^{1}H NMR (400 MHz, DMSO): δ 9.12 (bs, 1H), 8.46 (s, 1H), 8.18 (d, J = 4.9 Hz, 1H), 7.20 (d, J = 4.9 Hz, 1H), 3.64 (s, 3H), 2.19 (s, 3H). ^{13}C NMR (DMSO): 155.6, 146.5, 146.3, 141.4, 134.2, 125.9, 52.6, 17.8. Anal. Calcd for $C_8H_{10}N_2O_2$: C, 57.82; H, 6.07; N, 16.86. Found: C, 57.71; H, 5.80; N, 16.85.

***cis*-3-Methoxycarbonylamino-4-methylpiperidine (16).** To a clean, nitrogen-purged 1200 L reactor were charged Darco KBB[14] (6.6 kg), (4-methyl-pyridin-3-yl)carbamic acid methyl ester (66.5 kg) and acetic acid (677 L). The mixture was stirred for at least 30 min at 20−30 °C and filtered through a bed of Celite, and the cake was washed with acetic acid (135 L). To a clean, nitrogen-purged 2000 L hydrogenation reactor were charged 5% Rh/C (Johnson-Matthey type C101023-5, 16.5 kg) and the (4-methyl-pyridin-3-yl)carbamic acid methyl ester acetic acid solution. The reaction was stirred for at least 15 min and then purged sequentially with nitrogen and hydrogen. The reaction was heated to 72−78 °C and then pressurized with hydrogen gas at 70−80 psig. The reaction was allowed to stir under these conditions until hydrogen uptake ceased. A sample was obtained for reaction completion check by GC. The reaction was purged with nitrogen, and the catalyst was filtered on a water-wet Celite-coated filter. The cake was washed with toluene (212 gal), and the filtrates were combined. The solution of (4-methyl-pipridin-3-yl)carbamic acid methyl ester (92.7% cis by GC) was used in the next step without further purification. In the lab, an aliquot (0.50 g) of the reduced product was purified via silica gel chromatography (20% EtOAc−hexanes) to yield purified product (0.38 g). The purified product was dissolved in IPE (10 mL) and treated with bubbling HCl gas. The white solid was filtered and dried under vacuum to yield a white solid (11.9 g, 75%) mp 199−200.5 °C. R_f

(14) The additional Darco treatment removes residual catalyst poison present in some lots of material.

(freebase) = 0.21 (5:1 CH_2Cl_2−CH_3OH). Anal. Calcd for $C_8H_{17}ClN_2O_2$: C,46.04; H, 8.21; N, 13.42. Found: C, 46.93; H, 8.84; N, 12.29. ^{1}H NMR (HCl salt) (400 MHz, CD_3OD): δ 6.94 (bs, 1H), 3.95 (m, 1H), 3.66 (m, 4H), 3.38 (dd, J = 13.27, 4.15, 1H), 3.28 (m, 1H), 3.14 (dd, J = 13.27, 3.11, 1H), 3.05 (ddd, J = 12.85, 9.95, 4.56 1H), 2.07 (m, 1H), 1.74 (m, 2H), 1.01 (d, J = 7.05, 3H). ^{13}C NMR (300 MHz, CD_3OD): δ 158.0, 51.6, 48.7, 46.7, 42.9, 31.1, 25.6, 15.1.

***cis*-*N*-Benzyl-3-methoxycarbonylamino-4-methylpiperidine Hydrochloride (17)**. To a clean, nitrogen-purged 2000 L reactor was charged (4-methyl-pipridin-3-yl)carbamic acid methyl ester as the crude acetic acid and toluene solution from the previous step. The acetic acid was displaced with toluene under vacuum to a final volume of 500−560 L. The reaction was cooled and a sample pulled to check for an acetic acid content of <4% as determined by ^{1}H NMR. Benzaldehyde (46.4 kg, 437 mol) was added to the reaction at 20−30 °C and stirred for at least 30 min. To a clean, dry, nitrogen-purged reactor were charged sodium triacetoxyborohydride (92.6 kg, 437 mol) and toluene (472 L). The mixture was allowed to stir for at least 60 min at 20−30 °C. The benzaldehyde solution was transferred to the sodium triacetoxyborohydride reactor at a rate that maintained the temperature from 20 to 30 °C, then the reaction was stirred for at least 2 h. The reaction was sampled and checked for completion by GC. It was quenched by addition of a solution of 50% aqueous sodium hydroxide (158.9 kg diluted with 352 gal of water), maintaining the temperature at 20−30 °C, until a pH between 6 and 7 was achieved. The reaction was then stirred for at least 60 min and allowed to settle for at least 60 min, and the phases were separated. The toluene layer was heated to 70−80 °C, and concentrated HCl (47.0 kg, 477 mol) was added over at least 30 min. The reaction was held from 70 to 80 °C for at least 60 min. The reaction was cooled to 15−25 °C over at least 60 min and held for at least 2 h. The resulting solids were filtered, and the cake was washed with toluene (190 L). After drying under vacuum at 40−50 °C for at least 12 h with a slight nitrogen bleed, *cis*-*N*-benzyl-3-methoxycarbonylamino-4-methylpiperidine hydrochloride (86.8 kg, 290 mol) was isolated in 73.1% yield over two steps (96.6% cis and 2.5% trans by GC) mp: 187.3−191.4 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 12.11 (bs, 1H), 7.57−7.52 (m, 3H), 7.43−7.39 (m, 3H), 4.26 (dd, J = 13.3, 4.6 Hz, 1H), 4.16 (bd, J = 9.9 Hz, 1H), 4.07 (dd, J = 13.3, 5.8 Hz, 1H), 3.60 (s, 3H), 3.49 (bd, J = 12.0 Hz, 1H), 3.29 (dd, J = 12.9, 2.1 Hz, 1H), 2.89 (ddd, J = 12.9, 10.8, 3.3 Hz, 1H), 2.74 (dddd, J = 12.4, 12.0, 9.5, 2.9 Hz, 1H), 2.22 (dddd, J = 13.3, 13.0, 12.4, 3.9 Hz, 1H), 1.82−1.74 (m, 1H), 1.64 (bd, J = 13.0 Hz, 1H), 0.94 (d, J = 6.6 Hz, 3H). ^{13}C NMR ($CDCl_3$): 157.8, 131.8, 130.5, 129.6, 127.9, 61.3, 56.8, 53.1, 52.5, 48.6, 32.6, 26.2, 17.2. Anal. Calcd for $C_{15}H_{23}ClN_2O_2$: C, 60.29; H, 7.76; N, 9.38. Found: C, 60.21; H, 7.83; N, 9.29.

***cis*-*N*-Benzyl-3-methylamino-4-methypiperidine Bis-(hydrochloride) (3).** To a clean, dry, nitrogen-purged 2000 L reactor were charged (1-benzyl-4-methyl-piperidin-3-yl)-carbamic acid methyl ester hydrochloride (41.9 kg, 140 mol) and tetrahydrofuran (685 L). The reactor was purged three times with nitrogen and allowed to stir for at least 45 min at 20−30 °C to break up the solids. A sample was pulled to ensure that the water content was <0.2% water. The reaction was cooled to between −15 to 5 °C, and a 1.0 M solution of lithium aluminum hydride in tetrahydrofuran (181.4 kg, 200 mol) was added at a rate to maintain the temperature from −15 to 5 °C. The charge line was rinsed with tetrahydrofuran (19 gal), and the reaction was heated and held at reflux for at least 2.5 h. After cooling to 20−30 °C, the reaction was sampled and checked for completion by GC. The reaction was cooled to between −10 and 5 °C and a chilled (−10 to 5 °C) solution of tetrahydrofuran (43 L) and water (16.3 kg) was added at a rate to maintain the temperature at −10 to 5 °C with slight nitrogen bleed. The reaction was then heated to 20−25 °C over at least 60 min and purged with nitrogen to remove any traces of hydrogen. The resulting aluminum solids were filtered and washed with tetrahydrofuran (2 × 86 L). The tetrahydrofuran was displaced with 2-propanol until a temperature of at least 78 °C and a reaction volume was of 460−540 L were achieved. The reaction was cooled to 65−75 °C, and concentrated HCl (28.9 kg, 294 mol) was added over at least 60 min. The displacement was continued until additional 2-propanol (1060 L) was added and the final temp was at least 81 °C and the final volume was 390−460 L. The reaction was cooled to between 65 and 75 °C and granulated for at least 2 h. The reaction was cooled to between 15 and 25 °C, and a sample was pulled to ensure that the water content was <1%. After stirring at least 2 h at 15−25 °C, the solids were filtered and washed with 2-propanol (85 L). After drying under vacuum for at least 12 h at 40−50 °C with a slight nitrogen bleed (*cis*-*N*-benzyl-3-methylamino-4-methypiperidine bis-(hydrochloride) (35.5 kg, 122 mol) was isolated in 87.1% yield (99.3% cis and 0.70% trans by GC) mp: 261.3−267.0 °C. ^{1}H NMR (400 MHz, 1:1 CD_3CN:D_2O): δ 7.51−7.43 (m, 5H), 4.36−4.27 (m, 2H), 3.62−3.59 (m, 2H), 3.24−3.13 (m, 3H), 2.65 (s, 3H), 2. (m, 1H), 1.95−1.91 (m, 1H), 1.82−1.75 (m, 1H), 1.03 (d, J = 7.5 Hz, 3H). ^{13}C NMR (1:1 CD_3CN:D_2O): 131.8, 130.5, 129.6, 128.6, 118.7, 61.0, 55.8, 46.4, 31.3, 27.5, 26.0, 10.0. Anal. Calcd for $C_{14}H_{24}Cl_2N_2$: C, 57.73; H, 8.31; N, 9.62. Found: C, 57.77; H, 8.30; N, 9.60.

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