Organic Process Research & Development **2003**, *7*, 115–120

Development of a Scaleable Route for the Production of *cis*-*N*-Benzyl-3-methylamino-4-methylpiperidine

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Abstract:

The synthesis of *cis*-*N*-benzyl-3-methylamino-4-methylpiperidine (5) via hydroboration of tetrahydropyridine 3 followed by oxidation and reductive amination was optimized and scaled up to produce 10-kg quantities of product. Three routes to 3 were identified, and the reduction of pyridinium salt 7 was selected as the most preferable to run on-scale. The hydroboration and oxidative workup were carefully studied to optimize throughput on that transformation, as was the reductive amination.

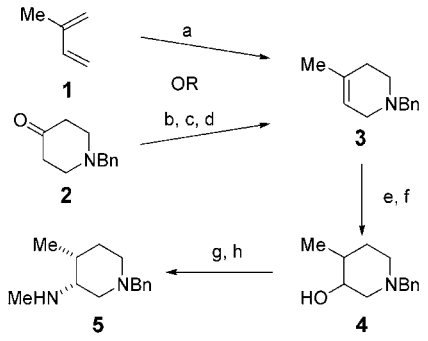
Initial Synthesis

cis-*N*-Benzyl-3-methylamino-4-methylpiperidine (**5**) was identified as a useful intermediate in the synthesis of a clinical drug candidate, necessitating its production on kilogram scale. The original route used to produce this compound relied on a hydroboration−oxidation sequence starting from tetrahydropyridine **3**[1] followed by oxidation and reductive amination to install the methylamino functionality.

Two routes to the tetrahydropyridine were used to make initial lots of material (Scheme 1). Addition of methyllithium to piperidone **2** followed by tertiary chloride formation and elimination provided olefin **3** in 45% yield.[1] Direct elimination of the tertiary alcohol was not successful under a variety of conditions and necessitated the intermediacy of the chloride. Alternatively, an aqueous Diels−Alder reaction produced the material directly from isoprene (**1**) and was the favored route to intermediate **3**;[2] however, the reaction required 7−10 days to run to completion, and the product (an oil) was difficult to separate from the excess benzylamine in the reaction.[3] Lewis acid catalysts such as $Nb(OTf)_3$ failed to improve the speed or efficiency of this reaction.[4]

From a scalability perspective, the Diels−Alder reaction was sluggish and difficult to work up, the oxidation step of the hydroboration was messy and sluggish, the Jones oxidation[5] needed replacing with a chromium-free oxidation, and the diastereoselectivity of the reductive amination was not reproducible. Nonchromatographic purifications were needed for some of the intermediates as well as a way to upgrade the diastereomeric excess (de) of the final product.

Scheme 1[a]



[a] Reaction conditions: a) $BnNH_2$, HCHO, H_2O, 60%; b) MeLi; c) $SOCl_2$; d) KOH, 45%, three steps; e) BH_3·THF; f) H_2O_2, 45%, two steps; g) Jones Oxidation; h) $MeNH_2$, $NaHB(OAc)_3$, 70%, two steps.

As an alternative, an asymmetric synthesis was explored. A route was investigated using α-methylbenzylamine in place of benzylamine in the Diels−Alder reaction. The hydroboration of the corresponding olefin did not proceed in high diastereoselectivity, but the diastereomers could be separated and one was crystalline. Unfortunately, the C-4 methyl-bearing stereocenter was easily racemized during the oxidation and reductive amination, thus obviating any advantage of this route over the achiral variant. Attempts at doing a Mitsunobu displacement on the alcohol led to ring-contracted product.[6]

Route Modification To Develop a Scaleable Process

As an alternative to the methods described above for making tetrahydropyridine **3**, pipecoline (**6**) was benzylated

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(1) Iorio, M. A.; Ciuffa, P.; Damia, G. *Tetrahedron* **1970**, *26*, 5519-5527.

(2) Larsen, S. D.; Grieco, P. A. *J. Am. Chem. Soc.* **1985**, *107*, 1768−1769.

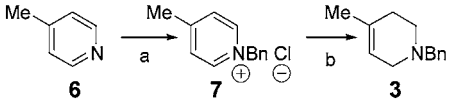
(3) The unreacted benzylamine could be removed by treatment of the worked-up reaction mixture with acetic anhydride, extraction of the desired product into acidic water, and then neutralization of the aqueous phase to recover the product.

(4) (a) Kobayashi, S.; Hachiya, I.; Araki, M.; Ishitani, H. *Tetrahedron Lett.* **1993**, *34*, 3755−3758. (b) Kobayashi, S.; Araki, M.; Ishitani, H.; Satoshi, N.; Hachiya, I. *Synlett.* **1995**, 233−234. (c) Kobayashi, S.; Hachiya, I.; Takahori, T.; Araki, M.; Ishitani, H. *Tetrahedron Lett.* **1992**, *33*, 6815−6818. (d) Yu, L.; Chen, D.; Wang, P. G. *Tetrahedron Lett.* **1996**, *37*, 2169−2172.

(5) Bowers, A.; Halsall, T. G.; Jones, E. R. H.; Lemin, A. J. *J. Chem. Soc.* **1953**, 2548−2560.

10.1021/op025599x CCC: $25.00
Published on Web 12/02/2002

Scheme 2[a]



[a] Reaction conditions: a) BnCl, acetone, 55 °C, 73%; b) $NaBH_4$, EtOH, 15 °C, 73%.

with benzyl chloride to produce the pyridinium salt, which was then reduced with sodium borohydride[7] (Scheme 2). The generation of the benzylpyridinium salt was run in acetone at 55°C with addition of benzylchoride to the heated solution of pipecoline. Benzyl chloride was used as the limiting reagent to minimize the amounts of the lachrymator present in the isolated product, which was recovered in 73% yield and >99% purity by filtration (1 crop, 87.7 kg).

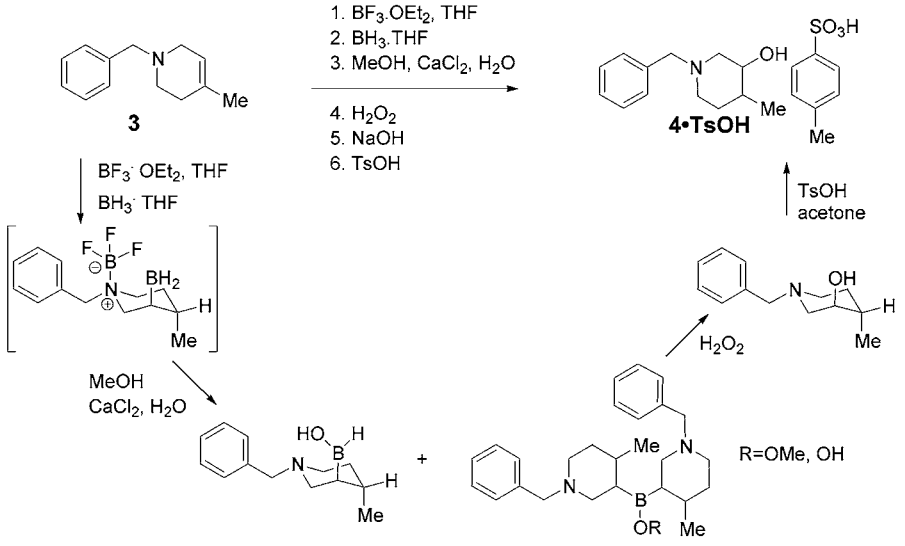
The pyridinium salt (**7**) was cleanly reduced to the 3,4-dehydropiperidine (**3**) using sodium borohydride in ethanol. Originally, the sodium borohydride was charged to the ethanol as pellets, followed by addition of the pyridinium salt. The reduction required 2.5−3.5 equiv of sodium borohydride to go to completion, but the amount of borohydride used could be reduced by more than 2-fold (to 1.25 equiv) by adding the solid to a premixed solution of the salt. The reaction was run in ethanol over 7 h (40-kg scale) while maintaining the internal reaction temperature between 10 and 15 °C. The lower amount of borohydride also reduced the amount of hydrogen generated in the workup of the reaction, which was quenched with water. After removing most of the ethanol from the solution in vacuo, the pH of the solution was adjusted to ∼pH 8 with sodium hydroxide, and the product was extracted with methyl *tert*-butyl ether (MTBE) to provide 73% yield of the desired product in 91% purity (HPLC) along with 3.6% of the $HB(OH)_2$ complex (molecular weight (MW) of **3** + 46).

The hydroboration of **3** was achieved using borane−THF, either as a commercially available solution in THF, or generated in situ from BF_3•etherate and sodium borohydride.[8] When the amount of borane used in the hydroboration was reduced to 1.2 equiv, the yield of the hydroboration began to vary from lot-to-lot. It was observed that the first equivalent of BH_3 cleanly complexes the amine and does not react any further[9] as evidenced by the vinylic hydrogen in the NMR of the complex. In lots of starting olefin that contained higher amounts of the $HB(OH)_2$ complex from the previous reaction, higher conversion was observed, presumably due to the availability of more borane after the initial complexation of the amine. The yield could be improved either by using 2.2 equiv of BH_3, or by first forming a complex with 1.2 equiv of BF_3 etherate followed by hydroboration with 1.4 equiv of BH_3 (Scheme 3). Both procedures gave >85% yield, with the procedure utilizing BF_3 generating less hydrogen gas during the work-up as compared to the reaction with excess borane. As some diorganoborane intermediates were observed (vide infra), it seems likely that the amount of borane used could be further reduced.

To minimize the amounts of hydrogen liberated in a quench in the presence of an oxidizing agent, an initial nonoxidative quench of any B−H bonds remaining prior to oxidation of the B−C bonds was investigated. This procedure also effected decomplexation of the amine−borane complex. A methanol/1 N HCl quench with calcium chloride added (pH = 2) was utilized. The calcium chloride was added to trap any fluoride liberated from the quench of BF_3 in the case where BF_3 was used to form the amine−borane complex. It is interesting to note that this quench does not destroy all of the B−H bonds in the mixture as evidenced by hydrogen evolution during the final salt formation of the product (vide infra). This was further supported by the MS data of one of the intermediates observed after the hydrolysis which appears to be of structure RB(H)OH (MW = 217). Heating the mixture did not push the B−H quench any further, although it did convert the initially formed ester of the boronic acid (R_2BOMe) to the corresponding acid R_2-BOH (which had no apparent effect on the oxidation).

We have previously reported that oxidation of the resulting alkylboranes under basic conditions led to sluggish and messy reactions.[10] This could be avoided by using an Oxone oxidation of the alkylborane intermediate. As previ-

Scheme 3

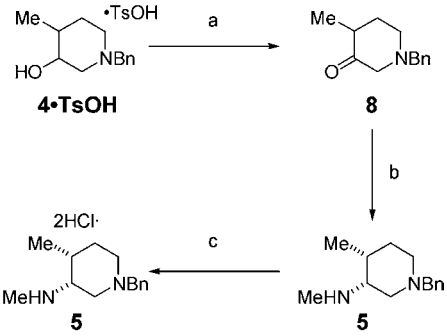


ously noted, this procedure has the liability that large volumes are required to dissolve all of the Oxone required for the oxidation. A catalytic (10%) amount of Oxone along with hydrogen peroxide resulted in only 60% conversion of the alkylborane to the corresponding alcohol. This could have been a result of the pH of the resulting solution, as the Oxone mixture contains a stoichiometric amount of an acidic salt ($KHSO_4$), and a substoichiometric quantity of the reagent was used. Using hydrogen peroxide under acidic conditions (pH 2) did provide rapid oxidation of the alkylborane intermediate without requiring the extended reaction times at elevated temperature. This protocol required significantly lower volumes of solvent to execute than did the Oxone procedure. Other protocols for the oxidation of the B−C bond led to lower yields and numerous byproducts.[11]

A tosylate salt (**4·TsOH**) was identified that allowed isolation of the alcohol in high purity. Interestingly, formation of the salt from product derived from the acidic hydrogen peroxide oxidation generated a significant amount of hydrogen (∼1 mol equiv), while the material from the Oxone oxidation evolved only small amounts of hydrogen in the same salt-forming procedure. The salt is made by addition of 1.1 equiv of *p*-toluenesulfonic acid monohydrate to the product in acetone with seed crystal added to the acid solution. Product thus obtained reproducibly had purity higher than 99% in a yield of 80−90% for the transformation of the olefin to the alcohol (four runs). The material isolated from the hydroboration sequence was between 3.5:1 to 4.7:1 *trans*:*cis*.[12]

The Jones oxidation[5] originally reported[1] could be replaced with a Swern[13] oxidation using either oxalyl chloride or SO_3·pyridine[14] as the activating agent (Scheme 4). On scale, the SO_3·pyridine oxidation was selected due to the noncryogenic reaction temperature, easier to handle reagents,

Scheme 4[a]

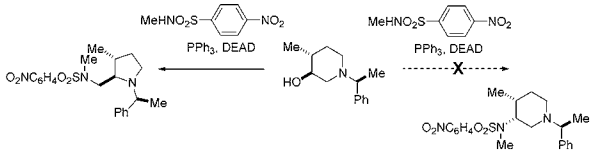


[a] Reaction conditions: a) SO_3·pyridine, DMSO, Et_3N; b) $MeNH_2$, $NaHB(OAc)_3$, toluene, EtOH, THF, HOAc; c) HCl, EtOH, EtOAc.

and the flexibility to charge more reagent if the reaction does not proceed to completion. Oxidation of alcohol **4** to ketone **8** was accomplished without first breaking the tosylate salt.[15] After oxidation, the pH of the workup had to be carefully controlled to maximize product recovery. When the aqueous layer pH was kept around 10 with 25% ammonium hydroxide, a 93% yield of product was extracted into toluene (HPLC purity of 87%, with 6% of the methylthiomethyl ether as the major contaminant[16]). Interestingly, the sulfate ester of the *cis*-alcohol (*cis*-**4**) was identified in the aqueous phase after workup, indicating a divergent reactivity pattern for this diastereomer.[17] The product from this step was carried into the reductive amination crude as a toluene solution. Unreacted alcohol was always observed as a major impurity (1−5%) from the oxidation, but this material readily purged in the downstream chemistry (vide infra). After workup, nitrogen was sparged through the organic phase containing the ketone via an immersed tube at 50 °C for 1 h, and the dimethyl sulfide was trapped in a bleach scrubber.[18]

Several parameters were evaluated in an effort to optimize the selectivity and reproducibility of the reductive amination. In general, $NaB(OAc)_3H$ was found to be a more selective reagent than $NaBH_4$. On a laboratory scale, a *cis*:*trans* ratio of 97:03 was obtained when 1.3 equiv of $NaB(OAc)_3H$ was added to the imine, formed by treating the ketone with methylamine (2 equiv, 2 M solution in THF) and acetic acid

(6) 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 **3** unattractive synthetically.



(7) (a) Oediger, H.; Joop, N. *Justus Liebigs Ann. Chem.* **1972**, *764*, 21−27. (b) Oediger, H.; Moeller, F. German Patent DE 2101997, 1971. (c) Massiot, G. *Bull. Soc. Chim. Belg.* **1990**, *99*, 717−728. (d) Keay, J. G. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon: New York, 1991; Vol. 8, Chapter 3.6.

(8) (a) Brown, H. C. *Tetrahedron* **1961**, *12*, 117−138. (b) Brown, H. C.; Rao, B. C. S. *J. Org. Chem.* **1957**, *22*, 1135−1136.

(9) Hutchins, R. O.; Learn, K.; Nazer, B.; Pytlewski, D.; Pelter, A. *Org. Prep. Proced. Int.* **1984**, *16*, 337−372.

(10) Ripin, D. H. B.; Cai, W.; Brenek, S. J. *Tetrahedron Lett.* **2000**, *41*, 5817−5819.

(11) The workup with alkaline hydrogen peroxide required refluxing for several hours to consume the alkylborane. Also tried were trimethylamine *N*-oxide, MCPBA, and sodium perborate.

(12) Based on ^{1}H NMR analysis.

(13) Mancuso, A. J.; Swern, D. *Synthesis* **1981**, 165−185.

(14) Parikh, J. R.; Doering, W. von E. *J. Am. Chem. Soc.* **1967**, *89*, 5505−5507.

(15) Water in the starting alcohol was found to have a large effect on the yield of the oxidation. For example, while material with 0.1% water content provided a 99% conversion in the oxidation, material with 2% water only went to 42% conversion under the same conditions. The free base could be azeotropically dried more reproducibly than the salt. The salt could be free-based in toluene with aqueous sodium hydroxide followed by distillation of toluene and additional drying by stripping with two more additions of toluene. This procedure gave 0.1−0.2% water levels in the bulk reproducibly. For tosylate salt lots with sufficiently low water levels, no free-basing was performed.

(16) This structural assignment is based on ^{1}HNMR and GC/MS (M = 265).

(17) Structure assigned by ^{1}HNMR coupling constants. This difference in reactivity pathway might be attributed to intramolecular conjugate base assistance of the piperidine nitrogen on the axially disposed alcohol in the *cis*-alcohol. The possibility that this sulfate ester is produced by inversion of an activated intermediate from the *trans*-alcohol is discounted on the basis of the results discussed in ref 6. This finding seems to be distinct from the faster oxidation of axial alcohols (of cyclohexanols) as compared to equatorial alcohols observed in the literature in that it is a difference in reaction mechanism as opposed to rate. (a) Eliel, E. L.; Schroeter, S. H.; Brett, T. J.; Biros, F. J. Richter, J.-C. *J. Am. Chem. Soc.* **1967**, *89*, S **1966**, *88*, 3327−3334. (b) Mueller, P.; Perlberger, J.-C. *J. Am. Chem. Soc.* **1976**, *98*, 8407−8413.

(18) Liu, C.; Ng, J. S.; Behling, J. R.; Yen, C. H.; Campbell, A. L.; Fuzail, K. S.; Yonan, E. E.; Mehrotra, D. V. *Org. Process Res. Dev.* **1997**, *1*, 45−54.

(1 equiv, T < 30 °C, 30 min). Under the same reaction conditions, a *cis*:*trans* ratio of 93:07 could be obtained using a EtOH/THF solvent mixture. The order of addition did not have a significant effect on the diastereoslectivity; addition of a solution of the imine to a suspension of the reducing reagent or adding a solution of methylamine and acetic acid to the ketone and $NaB(OAc)_3H$, at 0−5 °C did not influence the selectivity.

On-scale, sourcing issues prompted us to use an 8 M solution of methylamine in EtOH and dilute it with 3 vols of THF. While 2 equiv of methylamine was found to be sufficient for complete conversion on lab scale, 4 equiv of methylamine with 1 equiv of HOAc was used on-scale to ensure a rapid and clean conversion to the imine. The obtained solution of the imine was added to a suspension of $NaB(OAc)_3H$ in THF (2.3 vols) at 10 °C internal temperature. Online IR data indicated that the imine is quite stable in solution at 20 °C for several hours, but when vacuum was applied, a significant amount of ketone was regenerated. Partial vacuum had been used for transfer of the imine solution to a feed tank for the reduction, and this feed tank had been put under vacuum prior to transfer. To solve the problems on-scale, extra methylamine was used to generate the imine (4.1 equiv vs 4.0 equiv), and all transfers and inerting were performed under nitrogen pressure as opposed to partial vacuum. These changes resulted in a clean product solution (86% purity, 86:14 *cis*:*trans*) in toluene, with <4% of alcohol 4 and 5−8% of the methylthiomethyl ether as the major contaminants. This material was purified via formation of the HCl salt.

The bis-HCl salt (**5**·2HCl**)** was identified as an efficient purge of the undesired trans isomer of the product, as well as being a nicely stable form of the material. The salt is formed by adding HCl in ethanol to the crude toluene solution from the reductive amination. The initially formed salt precipitates with a diastereomeric ratio of 91:9. The diastereomeric purity of this salt can be upgraded by slurry in ethanol, recrystallization from methanol, or recrystallization from methanol/ethyl acetate. All three methods gave comparable *cis*:*trans* ratios (98.6:1.4 to 98.9:1.1), with the ethanol repulp yielding much more (91% recovery) than either of the recrystallizations (79−83% for two crops). The isolated yield over the last three steps (oxidation, reductive amination, and salt formation) was 47−63%. A total of 34.2 kg of material was made via this process.

Two salts have been identified that cleanly resolve the racemic amine, the (*S*)-(+)-Andeno acid[19] (phencyphos, (*S*)-(+)-2-hydroxy-5,5-dimethyl-4-phenyl-1,3,2-dioxyphosphorinane-2-oxide) salt and the di-*p*-toluoyl-L-tartaric acid salt. The Andeno acid is not commercially available for a reasonable cost; consequently, the tartaric acid salt was utilized on-scale. The salt that resolves nicely is a 2:1 amine:acid salt, meaning that in theory, 0.25 equiv of the acid are needed for complete resolution. An unusual aspect of this resolution is the fact that the free-basing step to neutralize the bis-HCl salt can be combined with the resolution, without isolation of the free base. The resolution has to be seeded with salt of high ee. If seeding is not done, a low ee salt is initially recovered (∼60% ee), and the ee has to be upgraded with successive reworks. The procedure is to free-base using 2.04 equiv of 2 N NaOH in *i*-PrOH/MeOH(3:2), add the tartaric acid (0.5 equiv), reflux, cool with seeding at 72 °C, and slurry prior to isolation. The pH of the solution after addition of the NaOH was 10; a previous run where 2.11 equiv of NaOH was used went to pH 13 and resulted in a lower isolated yield (37% vs 44%). Using this resolution, material of 99.2% ee was obtained. This procedure resolves, but does not effectively purge, the trans isomer from the reductive amination, and it is therefore important to upgrade the de at the bis-HCl salt stage. Reworks of the tartrate salt do not significantly improve the de or ee of the material beyond what is initially isolated after seeding.

Conclusions

In conclusion, a synthesis of **9** has been developed and scaled to produce 19.4 kg (10.3 kgA) of resolved material in 7.2−11.4% overall yield (two batches), 97.8% purity (1.9% trans diastereomer), and 99.4% ee.

Experimental Section

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. Reactions were monitored for completion by removing a small sample from the reaction mixture and analyzing the sample by TLC and GC or HPLC. HPLC analyses were performed using a Waters Symmetry Shield RP18 column (4.6 mm × 75 mm, 3.5 μm) and an acetonitrile/water (0.5% trifluoroacetic acid) mobile phase. GC analyses were performed on a DBWaxEtr (15 m × 0.25 mm i.d. × 0.25 μm film). ^{1}H-spectroscopy was performed at 400 MHz on a Bruker-Spectrospin Avance 400 MHz. The LOD (loss on drying) was determined by concentrating a weighed sample from the bulk material.

***N*-Benzyl-4-methyl-pyridinium Chloride (7).** A 640-L reactor was charged with 4-picoline (**6**) (54.8 kg, 586 mol), followed by acetone (150 L) at 18 °C. The solution was heated to 52 °C, and a solution of benzyl chloride (69.8 kg, 551 mol, 0.95 equiv[20]) in acetone (53 L) was added over a period of 4 h and 30 min at 50−52 °C. The suspension was aged for 16 h at 55 °C. It was then cooled to 10 °C over a period of 90 min prior to filtration over a pressure filter dryer. The filter cake was washed with acetone (2 × 54 L) and dried on the filter bed at 41 °C to give **7** (82.99 kg, 69%) as slightly pink crystalline solid. Purity: 100% a/a (HPLC); LOD = 0%.

***N*-Benzyl-4-methyl-1,2,5,6-tetrahydropyridine (3).** A 400-L reactor was charged with **7** (40.65 kg, 185 mol) and EtOH (185 L). $NaBH_4$ (8.75 kg, 231 mol, 1.25 equiv) was added to the solution via a solid dosing system over a period of 7 h and 10 min at 10−19 °C. The suspension was stirred

(19) (a) Wijnberg, H.; Ten Hoeve, W. EP180276, 1986. (b) Ten Hoeve, W.; Wijnberg, H. *J. Org. Chem.* **1985**, *50*, 4508−4514.

(20) The use of 0.95 equiv of BnCl is to minimize contamination of workers during workup. Essentially no excess is present after the reaction.

for 10 h at 15 °C. IPC (HPLC) showed >96% conversion. The quench was effected by addition of water (112 L) over a period of 3 h at 8−10 °C. Celite (8.03 kg) was charged into the reactor to achieve a more granular solid. The stirrer was turned off to allow for sedimentation overnight at 14 °C. The upper clear phase was siphoned. The lower phase (suspension) was filtered and washed with EtOH (3 × 13 L). The filtrate (288 L) was concentrated to ca. 133 L. The pH of the mixture was adjusted to 8 by addition of 1 N NaOH (2 L), the layers were separated, and the aqueous phase was extracted with TBME (2 × 50 L). The aqueous phase was mixed with 1 N NaOH (10 L) and extracted with the last organic phase. The combined organic phases were washed with water (60 L) and saturated aqueous NaCl solution (50 L) and concentrated at 35 °C to give ca. 60 L of orange oil. To remove the remaining water the oil was stripped with THF (2 × 30 L) at 39 °C to give **3** (30.35 kg, 73%) as a yellow oil. Purity: 94.8% a/a (HPLC);[21] GC headspace: 0.64% EtOH, 11.1% THF; Karl Fischer: 0.51% H_2O. Spectral data was consistent with that reported in the literature.[1]

***N*-Benzyl-3-hydroxy-4-methyl-piperidinium Toluene-4-sulfonate (4·TsOH).** A 640-L reactor was charged with **3** (27.78 kg, 123 mol) and THF (62 L). After cooling the solution to 5 °C, BF_3·OEt_2 (22.4 kg, 158 mol, 1.3 equiv) was added over 26 min while keeping the temperature between 5 and 10 °C. Next, BH_3·THF (1 M in THF, 171 L, 1.4 equiv) was added to the off-white suspension over a period of 3 h and 10 min, keeping the temperature between 8 and 13 °C. The solution was heated to 20 °C and stirred for 14.5 h. According to IPC (HPLC) the starting material was fully consumed. The solution was cooled to 7 °C, and MeOH (37 L) was slowly added over 2 h, keeping the temperature between 7 and 12 °C. The reaction mixture was warmed to 19 °C over 1 h and stirred at this temperature for 30 min; 10% $CaCl_2$ in 0.2 N HCl solution (40 L) was added over 17 min. The resulting solution had a pH of 2. The reaction mixture was stirred for 1 at 20 °C and then for 1 h at 41 °C. Finally, 135 L of solvent were distilled off at 40 °C. The reaction mixture was cooled to 7 °C, and H_2O_2 (17.5%, 28.4 kg, 146 mol, 1.2 equiv) was added over 2 h, keeping the temperature between 7 and 13 °C. The reaction mixture was stirred for 68 h at 19−22 °C. For workup, 10% Na_2SO_3 solution (13 L) and TBME (50 L) were added at 19 °C. The pH was adjusted to 12 by addition of 30% NaOH solution (37 L) while keeping the temperature between 9 and 18 °C. The layers were separated, and the aqueous layer was extracted twice with TBME (2 × 50 L). The combined organic layers were washed with water (25 L) and aqueous saturated NaCl solution (25 L); 155 L of solvent was distilled off at 45 °C. In a 100-L glass-lined reactor *p*-toluenesulfonic acid monohydrate (25.5 kg, 134 mol, 1.1 equiv) was dissolved in acetone (61 L). Seed crystals (0.1 g) in acetone (0.5 L) were added to this solution prior to addition to the free base. This solution was added at 44−47 °C to the solution of the free base in the 600-L vessel over 50 min (N_2 flow to dilute H_2: 8.4 m^3/h). The white suspension was stirred for 1.5 h at 5 to −2 °C before the product was filtered and washed with acetone (2 × 18 L). The solid was dried at 40 °C to afford **4** (41.37 kg, 88%) as a white, fine crystalline solid. Purity: 99.6% a/a (GC); Karl Fischer: <0.18%; TGA: <0.3% ashes. Spectral data was consistent with that reported in the literature for the free base.[1]

***N*-Benzyl-4-methyl-piperidin-3-one (8).** A 200-L scrubber was charged with 13−15% bleach (60 L) and water (60 L). A 640-L vessel was charged with SO_3·pyridine (51.47 kg, 323.1 mol, 3.0 equiv). DMSO (169 L) was added, and it was heated slowly at 33 °C IT.[22] After a solution was obtained, it was cooled to 25 °C prior to be transferred into the feed tank of the vessel. The TsOH salt **4** (40.9 kg, 107.7 mol) was added into the vessel and suspended in DMSO (50 L). After the addition of Et_3N (62 L, 43.8 mol, 4.0 equiv), the SO_3·pyridine solution in DMSO was added to the two-phase mixture in the vessel at such a rate as to keep the IT below 25 °C.[23] After 1 h stirring at 22 °C IPC showed 92% conversion. The mixture was cooled to 10 °C prior to quenching with water (182 L) over a period of 40 min at such a rate as to keep IT below 17 °C; 25% NH_3 solution (16 L) was added during 8 min. IPC showed a pH of 10. After phase separation, the aqueous phase (ca. 445 L) was extracted with three portions of toluene (3 × 60 L) while controlling the pH of the aqueous phase after each extraction: the first aqueous phase had a pH of 7, and 25% NH_3 solution (6 L) was added to reach pH 10. The second aqueous phase had a pH of 8, and 25% NH_3 solution (6 L) was added to reach pH 10. The combined organic phases (ca. 240 L) were extracted with water (61 L), and the bright-orange solution was heated at 40−50 °C jacket temperature during 1 h while blowing a nitrogen stream into the solution via an immersing tube.[24] Then, toluene (170 L) was stripped off at 50 °C to afford **8** (50.84 kg, 93%) as an orange solution in toluene. Purity: 87.4% a/a (GC); LOD = 54%; the toluene solution was processed directly in the next step. Spectral data was consistent with that reported in the literature.[1]

(*N*-Benzyl-4-methyl-piperidin-3-yl)methyl Amine (5). A 640-L reactor was charged with the toluene solution (103 kg 23%, 23.5 kg 100% **7**, 116 mol) from a second run of the previous step. A solution of methylamine in EtOH (33% in EtOH, 62 L, 496 mol, 4.3 equiv) was added over a period of 17 min at 17−18 °C, followed by the addition of HOAc (6.8 L, 116 mol) during 25 min at 18−24 °C. Online IR showed complete consumption of the ketone[7] after 54 min. This orange solution was transferred into a feed tank which had been evacuated beforehand. After the reactor was washed with THF (40 L), $NaBH_4$ (5.74 kg, 150.8 mol, 1.3 equiv) was added, followed by THF (60 L). To this suspension was added HOAc (38 L, 684 mol, 5.9 equiv) under vigorous stirring over a period of 2.5 h such as to keep the temperature

(21) Purity accounts for the sum of the two signals: product at 5.5 min (91.2% a/a) and $HB(OH)_2$ complex (3.6% a/a) at 5.1 min. This proceeding is based on the fact that the latter has been shown to be a valuable starting material.

(22) The maximum jacket temperature has to be set at 40 °C due to a T_{onset} of 59 °C (687 kJ/kg) for a 22% SO_3·pyridine solution in DMSO. The obtained solution should be stirred no longer than 1−2 h at 30−35 °C.

(23) During the reaction (1 h and 45 min), a slight stream of nitrogen, via one feed tank, over the reaction mixture was maintained to chase dimethyl sulfide.

(24) This is to chase the dimethyl sulfide from the organic solution into the scrubber. For a 573 mol run of an "industrial" *Swern* oxidation see ref 18.

below 13 °C. The liberated hydrogen was diluted with a nitrogen stream after the reactor (4.9 m^3 N_2/h). This was maintained during the following reduction step. The imine solution was added from the feed tank to the suspension in the reactor over 2 h so as to keep the temperature below 16 °C and to control foaming. The mixture was stirred for 13 h at 2 °C. IPC showed complete conversion to the amine (>99%). Water (201 L) was added over 40 min keeping an IT of 5−8 °C. Subsequently, the pH of the solution was adjusted to 11 by adding 30% NaOH (35 L). The aqueous layer (ca. 310 L) was extracted with three portions of toluene (3 × 80 L).[25] All organic phases were combined (ca. 423 L) and washed with water (80 L). The organic phase was concentrated at 50 °C to yield **5** (33.93 kg, 92%) as an orange solution in toluene. Purity: 86.1% a/a sum of *cis*- and *trans*-**5** (GC); LOD = 20%; dr 86:14. R_f (freebase) = 0.24 (9:1 CH_2Cl_2−MeOH). ^{1}H NMR (freebase) (400 MHz, DMSO, 70 °C) δ 7.28 (m, 5H), 3.47 (d, J = 13.27, 1H), 3.40 (d, J = 13.27, 1H), 2.51 (m, 2H), 2.33 (m, 1H), 2.20 (s, 3H), 2.09 (m, 2H), 1.64 (m, 1H), 1.39 (m, 2H), 0.85 (d, J = 7.05, 3H). ^{13}C NMR (300 MHz, CD_3OD) δ 131.5, 130.3, 129.2, 128.7, 60.8, 55.9, 46.8, 46.4, 30.7, 27.5, 26.3, 9.5.

(*N*-Benzyl-4-methyl-piperidin-3-yl)methylamine Dihydrogenchloride (5·2 HCl). A 640-L reactor was charged with **5** (33.93 kg solution in toluene, 69%, 107 mol, dr 86:14) and EtOH (120 L). At 3 °C, 32% HCl (25 L, 249 mol) was added over 45 min keeping the IT at 3−10 °C. Then 100 L of solvent was stripped off at 55 °C. The red suspension was cooled to 30 °C, and AcOEt (215 L) was added; 210 L of solvent was stripped off at 50 °C. This was repeated with a second portion of AcOEt (215 L). Acetone (111 L) was added at 35 °C over 15 min. The suspension was cooled to −1 °C over 7 h and then filtered and washed with acetone (55 L) to give the crude product (35.77 kg, LOD 20%, dr 91:9). This crude was slurried three times with AcOEt (the crudes showed dr 95.8:4.2, 97.2:2.8) to yield **5·2 HCl** (27.38 kg, 19.44 kg corrected, 62%) as off-white powder. Purity: 99.8% a/a (GC); LOD 29%; dr 97.3:2.7; mp 260−263 °C. Anal. Calcd for $C_{14}H_{24}Cl_2N_2$: C, 57.73; H, 8.31; N, 9.62. Found: C, 57.32; H, 8.31; N, 9.48.

(25) Some solid precipitated in the interphase and was separated in the aqueous phase, as this proved not to be the product.

Acknowledgment

We acknowledge Ernie Pollard for developing and running assays for the chemistry described, (mass spec, analytical, other support) and Volker Wesseling (*CarboGen*) for developing and running the analytical methods applied in the development and in the pilot plant (IPC and assay). Technical assistance of Dario Menia and Barbara Bianchi (*CarboGen*) is gratefully acknowledged. Jim Phillips is acknowledged for collecting some analytical data.

Received for review October 11, 2002.

OP025599X