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Synthesis of the NK1 Receptor Antagonist GW597599. Part 2: Development of a Scalable Route to a Key Chirally Pure Arylpiperazine

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Abstract:

GW597599 1 is a novel NK-1 antagonist currently under investigation for the treatment of CNS disorders and emesis. The initial chemical development synthetic route, derived from the one used by medicinal chemistry, involved several hazardous reagents, gave low yields, and produced high levels of wastes. Through a targeted process of research and development, application of novel techniques, and extensive route scouting, a synthetic route for GW597599 has been developed. This paper reports the optimisation work of the second stage in the chemical synthesis of GW597599: the development of a pilot-plant-suitable process for the manufacturing of an optically pure arylpiperazine derivative. In particular, the new process eliminates the need to purchase and store dangerous and expensive borane by generating it in situ and also the need for a chlorinated solvent, thereby improving the safety of the process and substantially reducing the overall waste. The final yield and throughput will be significantly enhanced.

1. Introduction

Substance P (SP) is a member of the neurokinin family that exerts its pleiotropic role by preferentially binding to the neurokinin receptor classified as NK1. Substance P and the NK1-receptors that mediate its activity are present in the brain stem centres that elicit the emetic reflex. Nausea and vomiting have been reported as the most distressing side effects of chemotherapy, and the disruptive effects of these symptoms on patients' daily lives have been well documented. In light of the need for the continued routine use of emetogenic chemotherapy, effective prevention of chemotherapy-induced nausea and vomiting (CINV) is a central goal for physicians administering cancer chemotherapy. GW597599 **1** is a novel NK-1 antagonist currently being developed to relieve these symptoms. This and other NK-1 antagonists have also been investigated for the treatment of CNS disorders such as depression. In this paper we describe the successful efforts to define a synthetic process for large-scale manufacturing.

2. Initial Medicinal Chemistry Route

The synthetic route followed to synthesise the first few grams of GW597599 is shown in Scheme 1.

2.1. Synthetic Objective. The aim of this paper is to describe the reduction of chiral derivative **13**, identified as an isolable intermediate in a previous communication,[1] to the corresponding arylpiperazine **14**.

2.2. Evaluation of the Process. The chemistry involved the reduction of the amido group of **13** followed by the isolation of **14** as its dihydrochloride salt (Scheme 2). The first step was the free basing of the ketopiperazine mandelate salt in a mixture of dichloromethane and aqueous sodium hydroxide. The reduction step was achieved by using a borane solution in THF and heating the mixture at reflux. A treatment with hydrochloric acid in refluxing methanol decomposed the intermediate boron complex, allowing the desired product to be isolated as a salt upon cooling. On an 11 kg scale, the overall yield for the stage was 63% theoretical. However the process, even if simple for a functional group interconversion point of view, had to employ up to three different reactors, and it produced about 110 kg of waste for each kilogram of output. Even the need for a chlorinated solvent seemed to be unavoidable as the free base of **13** was difficult to recover from the aqueous layer without using dichloromethane.

3. Development of a Practical Convergent Synthesis

3.1. Synthetic Strategy: the Borane Replacement. The development of this stage focussed on the replacement of the expensive and unstable borane−THF complex alongside the maximization of the yield.

Diborane gas, which can easily be evolved from borane−THF complex, has a very low auto ignition temperature of about 38−52 °C and a wide explosive range in air (0.8−90% vol).[2] The reduction of the carbonyl moiety was performed in refluxing THF at 65−67 °C. In the case of a vessel at atmospheric pressure and open to a scrubber, the diborane gas would be able to easily escape at temperatures above 38 °C, possibly causing an explosion. In addition the borane−THF complex must be transported and stored below 8 °C due to its instability. This special handling measure increases the costs and the difficulties of using such a reagent. Finally, it is an expensive reagent considering that it is routinely sold at a concentration of 1 M solution in THF (26£/L on 5000 L scale) and produces a large amount of waste.[3]

Several alternative reduction conditions were tried, but they mostly failed or gave very little conversion. In particular, $LiAlH_4$, sodium metal, and Red-Al gave only partial reduction to the desired product and degradation, while $NaBH_4$ alone,

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† Chemical Development.

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(1) Guercio, G.; Bacchi, S.; Goodyear, M.; Carangio, A.; Tinazzi, F.; Curti, S. *Org. Process Res. Dev.* **2008**, *12*, 1188.

(2) Urben, P. G., Ed. *Bretherick's Handbook of Reactive Chemical Hazards*, 6th ed.; Butterworth-Heinemann: Boston, 1999; p 1937.

(3) Burkhardt, E. R.; Corella, J. A., II. U.S. Patent 6,048,985, 2000.

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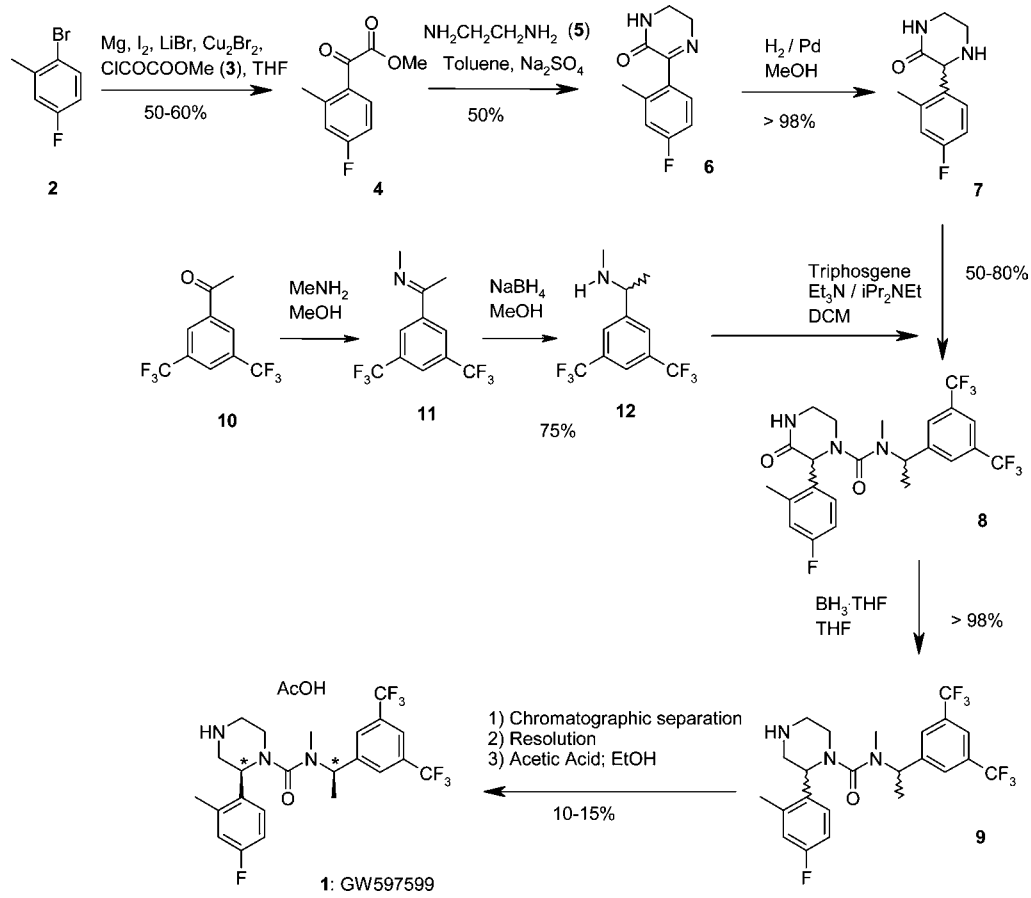
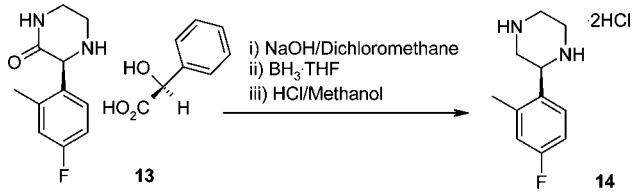
Scheme 1. **Synthetic route used by the medicinal chemistry department**



$NaBH_4$ in diglyme, $NaBH_4$/methanol, $LiBH_4$, amine−borane complexes, borane dimethyl sulfide, and sodium acyloxyborohydride[4] gave almost no reaction. The literature covers the possibility of generating diborane in situ using $NaBH_4$ in combination with several Lewis acids. A plethora of possibilities were tried, obtaining variable amounts of the desired product: I_2, H_2SO_4, TFA, $TiCl_4$, $SnCl_4$, $FeCl_3$, $AlCl_3$, $ZnCl_2$, $BF_3 \cdot Et_2O$, TMSCl.[5] The one that gave the highest conversion was the couple $NaBH_4$ plus $BF_3 \cdot Et_2O$ complex. Thus, the work was focused in optimising the relative ratio of the two reagents, the temperature, and the reaction concentration.

Scheme 2. **Initial synthetic approach**



3.2. Initial Optimisation. From the very beginning of the work it appeared clear that excesses of both $NaBH_4$ and $BF_3 \cdot Et_2O$[6] in refluxing THF were required to ensure the reduction in acceptable yield.

Table 1. **DoE performed at 55−57 °C**

$BF_3 \cdot Et_2O$ (equiv)	$NaBH_4$ (equiv)	conv. (%) at 5 h
3.00	1.00	10.5
1.75	4.00	74.9
0.50	4.00	27.9
1.75	2.50	61.2
1.75	2.50	57.4
3.00	4.00	96.4
3.00	2.50	66.5
0.50	2.50	16.0
1.75	1.00	8.2
0.50	1.00	0.0

A first set of trials performed by using an Endeavor[7] system allowed us to find out that both the amount of solvent (THF) and the temperature played a key role; low dilution and high temperature being required to get a good conversion. Then a design of experiment (DoE, central composite design with two central points, Table 1, Figure 1) was planned in order to optimise the equivalents of $NaBH_4$ and $BF_3 \cdot Et_2O$ in combination with the temperature. The data indicates the importance of the Lewis acid amount to drive the conversion close to completion.

(4) Thomas, J. B.; Atkinson, R. N.; Vinson, N. A.; Catanzaro, J. L.; Perretta, C. L.; Fix, S. E.; Mascarella, S. W.; Rothman, R. B.; Xu, H.; Dersch, C. M.; Cantrell, B. E.; Zimmerman, D. M.; Carroll, F. I. *J. Med. Chem.* **2003**, *46* (14), 3127.

(5) For a general review about methods of generating diborane in situ from sodium borohydride see: Souza, M. V. N.; Vasconcelos, T. R. A. *Appl. Organomet. Chem.* **2006**, *20*, 798.

(6) Sengupta, S.; Sahu, D. P.; Chatterjee, S. K. *Indian J. Chem.* **1994**, *33B*, 285.

(7) Endeavor, Argonaut, is a system made of eight reactor vessels with independent temperature and pressure controls. It works on a maximum scale of ~5 mL, and it permits feeding a reactant in the closed vials, monitoring the pressure trend versus time.

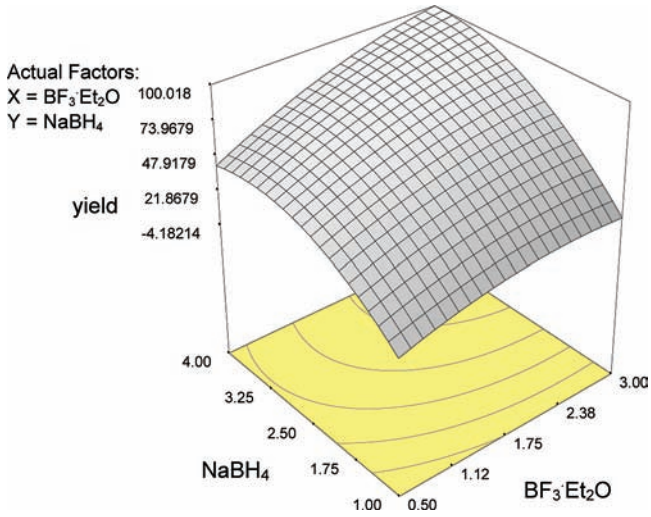


Figure 1. **Effect of $NaBH_4$ and BF_3 equivalents on conversion.**

The best conditions were found to be ~3.5 equiv of $NaBH_4$ and ~3 equiv of $BF_3 \cdot Et_2O$ in 5 volumes of THF. However some potentially explosive diborane gas might be generated at 55−57 °C. Thus, we started to investigate the possibility of performing the step in a closed system. Another set of experiments was designed with the aim of confirming those data. The output of this second DoE study (central composite design with two central points) showed that conversion above 90% could in fact be achieved in a closed vessel with 3 equiv of $NaBH_4$ and 2.7−3 equiv of $BF_3 \cdot Et_2O$ at 55 °C only. After the reaction completion and nitrogen venting, the unreacted diborane should be decomposed to boric acid and hydrogen by adding water.

However, the technical constraint of the designated pilot-plant facilities dictated that we use the atmospheric pressure procedure. In order to ensure that the atmospheric pressure procedure could be safely carried out on pilot-plant scale, a dedicated reaction calorimetric experiment was carried out by passing the effluent gas through a scrubber containing an aqueous sodium hydroxide solution. The scrubber liquors were analysed for boron, and this suggested that a maximum level of 2% v/v diborane should have been expected in the effluent gas. To ensure safety of operation a nitrogen flow was applied to the pilot-plant equipment in order to dilute diborane to below its lower explosive limit of 0.8% v/v.

The following procedure was applied on scale: the mandelate salt **13** was suspended in dichloromethane and washed with aqueous sodium hydroxide to obtain the free base. After a swap from dichloromethane to THF, the organic solution was treated with $NaBH_4$ and BF_3 etherate, to reduce the amide moiety. Overall this process still presented a couple of obstacles. The first one was the partial racemisation of ketopiperazine derivative **13** due to the presence of residual sodium hydroxide in the organic phase. The second was the reaction temperature, high enough to both further increase the racemisation and to increase the hazards associated with the production of diborane.

The process was scaled up twice on 80 kg scale with variable results in respect to theoretical yields, 61.9% and 66.7%, and chiral purity, 99.1% ee and 95.7% ee. The preliminary work on 1 kg scale had set our expectations at a yield of 75% theoretical and chiral purity of above 99% ee. Further process development of this step was therefore needed.

3.3. Process Improvements. The residual presence of base and the high temperature were confirmed as the causes of both low yield and racemisation.

A promising idea seemed to be the direct reduction of **13** combined with the possibility of performing the chemistry at the lowest possible temperature. However, the poor solubility of **13** in THF led us to investigate alternative solvents that dissolved the organic salt **13** followed by addition of the solution of this salt to a suspension of $NaBH_4$ in THF at 0 °C. Although 1,3-dioxolane appeared suitable, it was difficult to replace it with methanol in the next step, since 34 volumes were necessary to remove it completely due to the poor azeotrope composition. This problem was solved by adding a substoichiometric amount of tetrabutylammonium bromide[8] to help the dissolution of the mandelate salt in THF at room temperature by increasing the ionic character of the solvent. This solution was then added dropwise to a suspension of $NaBH_4$ in THF at 0 °C, followed by slow addition of an excess of $BF_3 \cdot Et_2O$ at 15 °C.

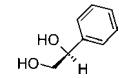
After 18−20 h at room temperature a 90% HPLC conversion was observed. Then methanol was added at 0 °C to quench the borane complexes and the small amount of unreacted $NaBH_4$ and BH_3.THF complex possibly present. The mixture was then distilled down to 6 residual volumes at atmospheric pressure. We postulate that the acidity of methanol during the lengthy distillation allowed quenching the amine borane complexes without the need to add acid to the mixture. The resulting suspension was cooled to 0 °C for 2 h to precipitate all the insoluble $NaBF_4$ which was then filtered off.

The clear organic solution was finally treated with HCl 5−6 N in IPA dropwise at 0 °C to crystallise **14**,[9] and the mixture was left at 0 °C for 4 h. The yield of this process was 75−80% theoretical, and the observed ee was 99.8−100%.

3.4. Process Understanding via ^{19}F NMR. The possibility of having a residue of fluorinated species in the mother liquors, and particularly fluorides, was considered prior to scaling up the synthesis of this intermediate. The absence of fluorides was fundamental in order to avoid possible damage to plant reactors. Confirmation of this absence was found experimentally by using ^{19}F NMR. All the ^{19}F NMR experiments described in this work were performed using a Varian INOVA 400 MHz spectrometer (^{19}F NMR operating frequency 376 MHz) equipped with an ATB probe simultaneously tuned to both ^{1}H and ^{19}F nuclei. ^{1}H NMR experiments were recorded using a Varian INOVA 600 MHz.

A sample of **14** was analyzed by means of ^{1}H NMR: only traces of impurities and about 1% M of 2-propanol were found in the spectrum recorded in DMSO-d_6.

(8) Yadav, V. G.; Yadav, G. D.; Vyas, J. R. *Chim. Oggi* **2000**, *18*, 39.
(9) The collected cake was washed with methanol to eliminate the alcohol derivative (see structure below) resulting from the reduction of residual mandelic acid.



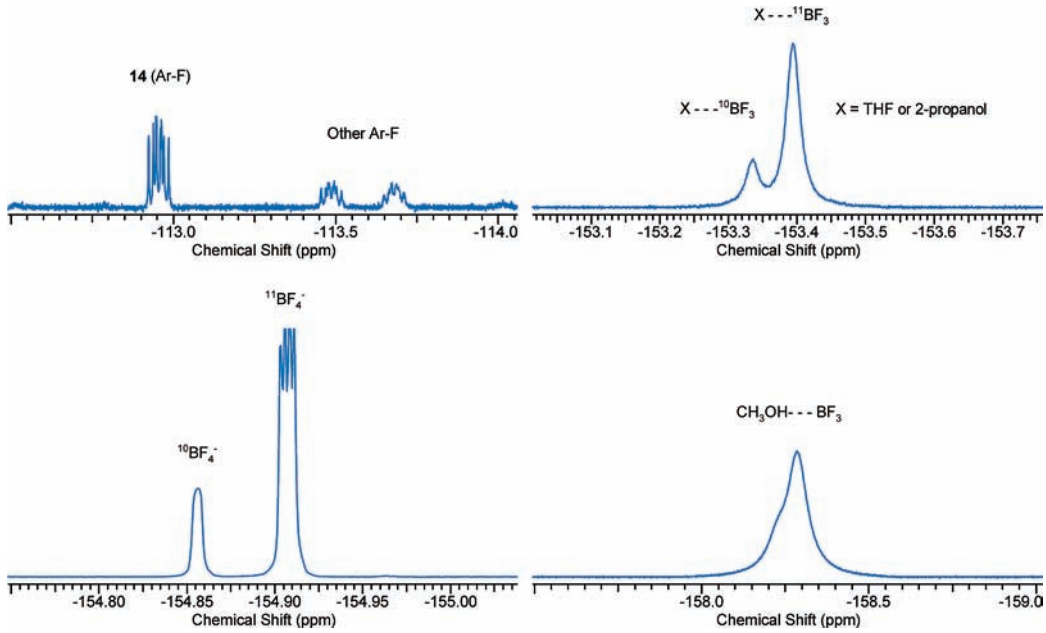


Figure 2. **^{19}F NMR spectrum of the mother liquors coming from the synthesis of 14 recorded at 376 MHz. The four expanded plots show the observed ^{19}F resonances.**

The mother liquors, after precipitation and filtration, were also analyzed by means of both ^{1}H and ^{19}F NMR to verify the possible presence of fluorinated species.

These mother liquors showed, in the ^{1}H NMR spectrum recorded with the addition of CD_3OD, the presence of methanol, 2-propanol, and THF mainly, plus some residuals of **14** and related impurities. Resonances coming from 2-propanol and THF possibly involved in complexation with BF_3 were also observed through NMR signals, very similar to those of the "parent" solvent but shifted in the spectrum.

The ^{19}F NMR spectrum showed the typical ^{19}F signals due to **14** plus two similar products in the region of aromatic fluorine signals (about −112 ppm). In addition, intense peaks were observed in the region around −150/−160 ppm. Among these, the presence of the species BF_4^- was clearly identified due to the peaks at −154.9/−154.8 ppm. Those peaks accounted for two resonances with a ratio of 80/20 due to the natural abundance of the two boron isotopes. This led to the observation of distinct ^{19}F signals for $^{11}BF_4^-/^{10}BF_4^-$. Two other species were also found at −153.3/−153.4 (20/80 ratio) and at −158.3 (single broad peak). Figure 2 shows the full ^{19}F NMR expanded plots of the regions of interest.

None of these signals can be ascribed to inorganic F^- which was expected in the region −110/−130 ppm. Had it been present, HF should be in an equilibrium with F^- and FHF^-, with chemical shift expected in a variable range (−168/−200 ppm).[10−12]

$$FHF^- \rightleftarrows HF \rightleftarrows F^- \qquad (1)$$

Further studies were carried out both to confirm the possible presence of fluorinated species in the solid **14** and to give more information on the nature of those unknown species.

Solid **14** was dissolved in CD_3OD, to record the ^{19}F NMR spectrum under the same conditions applied to the mother liquors. The presence of the BF_4^- signal was surprisingly still observed but could not be quantified with respect to the aromatic ^{19}F resonance of **14**, possibly because of incomplete dissolution. A few drops of DMSO-d_6 were necessary to achieve complete dissolution of the sample. A new ^{19}F NMR spectrum was then recorded, allowing the determination of a 7.5/100 molar ratio BF_4^-/**14**.

The possible source of fluorine was identified as the $BF_3 \cdot Et_2O$ complex due to the well-known propensity of BF_3 to complex with alcohols and ethers. The ^{19}F NMR spectrum of the $BF_3 \cdot Et_2O$ was recorded in CD_3OD. This spectrum showed two ^{19}F resonances: the minor one at −155.3 (broad) due to the BF_3 complex with Et_2O and the major one at −158.5 (broad) due to the complex with CD_3OD. These data allowed us to be sufficiently confident that in the mother liquors the relevant species were in fact BF_4^- and the complex between BF_3 and methanol. The ^{19}F NMR additional couple of peaks at −153.3/−153.4 (20/80 ratio) can probably be assigned to another BF_3 complex with either THF or 2-propanol.

Having confirmed the absence of fluorides to avoid possible damage to the glass components of the pilot plant, the process was ready for the scale-up.

3.5. Final Refinements. In the final development stage three further refinements were considered necessary. First, to improve the safety of the process, the $BF_3 \cdot Et_2O$ complex was replaced with the $BF_3 \cdot$THF complex. In fact the diethyl ether could lead to peroxide formation, and its low boiling and flash points presented a problem, whereas the complex $BF_3 \cdot$THF gave comparable results upon use test, and it was commercially available in bulk.

Second, it was also clear that the reaction mixing had the potential to become another issue: different batches of $NaBH_4$ with different particle size distribution gave variable conversion. Using the granular product, the conversion was only 60% after 24 h, while the powder gave a conversion higher than 90% in a few hours, suggesting the need to examine the solubility effects. Finally, the same batch of $NaBH_4$ gave different

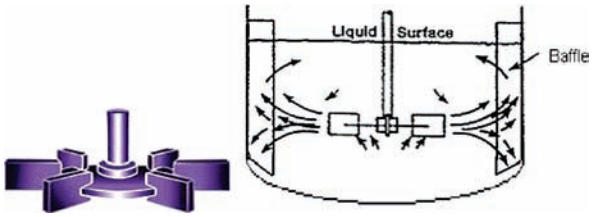
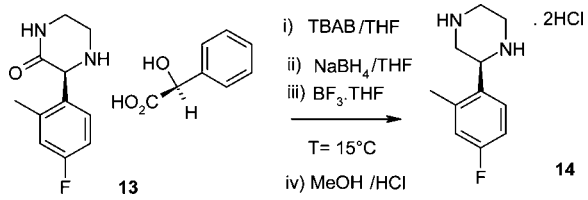


Figure 3. **Rushton turbine and mixing model.**

Scheme 3. **Final manufacturing process**



conversions, depending on the reactor configuration and the stirrer shape. An engineering assessment was carried out with the aid of computer modelling techniques, and it suggested that adopting a definite reactor configuration would ensure homogenization of $NaBH_4$ particles by mechanical shearing, resulting in a reproducible conversion. The prescribed measures were: the use of a dish base vessel; the use of a high-shear impeller like a Rushton[13] turbine; the use of four baffles (Figure 3); the need to work at relatively low vessel occupancy (liquid height at max equal to tank diameter) and to use a high stirring speed.

All the chemical (Scheme 3) and engineering suggestions were successfully applied in the final manufacturing route.

The new process produced a total of 23 kg of waste for each kilogram of output (a reduction of almost 80% of the waste relative to the original process), and delivered 46.7 kg of intermediate **14** in high yield (81.5%) and a chiral purity greater than 99% ee.

4. Conclusion

In conclusion a simple and efficient reduction process for the arylpiperazine of interest was developed and successfully scaled up in pilot plant. Key breakthroughs were the definition of a process that prevented the loss of optical purity and the development of safer conditions when handling the diborane species.

Experimental Section

(2*S*)-2-(4-Fluoro-2-methylphenyl)piperazine Dihydrochloride Salt 14. Tetrabutylammonium bromide (0.02 kg) and **13** (1 kg) were added to THF (6.5 L) at 25 °C and then heated at 40 °C while stirring until dissolution. This solution was added to a suspension of $NaBH_4$ (0.38 kg) in THF (1.5 L) at 25 °C. The suspension was stirred for 2 h at 25 °C, and then BF_3·THF (2.3 L) was added dropwise over about 50 min. The resulting mixture was stirred at 35 °C for at least 18 h. Methanol (3 L) was added over about 1 h, keeping conditions inert and the internal temperature at 35 °C. The mixture was refluxed for 1 h, concentrated to 4.0 L at atmospheric pressure, and diluted with 2-propanol (4 L) before being cooled to 0 °C for 3−4 h. The slurry was filtered and the cake washed with 2-propanol (2 × 1 L). The collected mother liquors were treated with methanol (3 L) first, followed by HCl 5−6 N in 2-propanol (1.4 L). The resulting suspension was kept at reflux for about 1 h, then cooled down and stirred at 0 °C for 6 h. Finally, it was filtered, and the cake was washed with methanol (4 × L). Both solids were dried under vacuum at about 50 °C to obtain an overall yield of 519 g of **14** (corrected yield of 81.5%; ratio **14**:enantiomer, 99.3:0.7).

^{1}H NMR (600 MHz, DMSO-d_6) δ 10.3 (4 H, br s), 8.03 (1 H, dd, J = 9.5, 5.7 Hz), 7.16 (2 H, m), 5.00 (1 H, dd, J = 12.0, 3.1 Hz), 3.64 (1 H, m), 3.55 (3 H, m), 3.51 (1 H, dd, J = 13.7, 3.5 Hz), 3.38 (1 H, t, J = 12.8 Hz), 2.43 (3 H, s).

^{13}C NMR (151 MHz, DMSO-d_6) δ 162.20 (1 C, d, J_{CF} = 246.6 Hz), 140.22 (1 C, d, J_{CF} = 8.5 Hz), 129.30 (1 C, d, J_{CF} = 8.5 Hz), 128.22 (1 C, d, J_{CF} = 3.1 Hz), 117.42 (1 C, d, J_{CF} = 21.4 Hz), 113.29 (1 C, d, J_{CF} = 21.4 Hz), 51.33 (1 C, s), 44.42 (1 C, s), 41.22 (1 C, s), 38.93 (1 C, s), 19.22 (1 C, d, J_{CF} = 1.2 Hz).

MS (ES+) m/z 195.1 (MH^+).

HPLC Phenomenex LUNA C18; mobile phase A: 0.05% TFA/water and B: 0.05% TFA/acetonitrile; gradient: 0 min 0% B to 30 min 95% B; flow 1 mL/min; detector UV DAD @210 nm; retention time **14** 13.2 min. Purity >95.6% a/a.

HPLC Chiralcel OD (4.6 mm × 250 mm); Mobile phase *n*-hexane/ethanol, 90:10 v/v; flow 1 mL/min; detector UV @265 nm; retention times **14** 7.8 min, opposite enantiomer 6.7 min, ratio 99.3:0.7.

Acknowledgment

We thank Giulio Camurri and Luca Martini for HPLC method development, Francesco Tinazzi for the support in the DoE setup and interpretation, and Francois Ricard and Daniela Ciccarone for the engineering suggestions.

Supporting Information Available

Process safety evaluation of **14** and chiral HPLC of (2*S*)-2-(4-fluoro-2-methylphenyl)piperazine dihydrochloride salt **14**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) Hudlicky, M. *J. Fluorine Chem.* **1985**, *28*, 461.
(12) Christe, K. O.; Wilson, W. W. *J. Fluorine Chem.* **1990**, *46*, 339.
(13) Rushton turbines are radial impellers having a higher power number (NP) than other common impellers. The power number is a dimensionless number which describes the power supplied by an impeller. An empirical correlation relates NP to the effects of fluid viscosity. Considering the same fluid physical properties, stirrer speed, and impeller size, a Rushton turbine, having a higher NP, will supply more power to the fluid and, in general, is able to supply more intense mixing which should translate to a higher particles shear. Thus, on the basis of theoretical knowledge, the use of a Rushton turbine was recommended in the present case, requiring high intense mixing, in particular strong radial flow, and high particles shear.