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Investigation of an Alternative Route to ZD3638 and Cost-Benefit Analysis Comparison of Raw Materials with the Previous Route

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Abstract:

A convergent synthesis to ZD3638 was proposed starting with alternative raw materials. A cost-benefit analysis for the new route was performed which demonstrated that significant savings in raw materials costs could be made over the previous linear sequence. The convergent route was then proved in principle by experimental work. LiTMP was shown to be a superior base to LDA in the modified lithiation reaction.

Introduction

ZD3638 is an atypical antipsychotic agent for the treatment of schizophrenia which was in development at Zeneca Pharmaceuticals from 1993 to 1997. It was a follow-up to AstraZeneca's recently launched antipsychotic quetiapine (AstraZeneca tradename "Seroquel") and acts by a different mechanism of action. It also had a potential further application in the treatment of migraine. The project was transferred within PR&D from Macclesfield to Avlon in January, 1997, to continue development of processes for campaign 4.

The first three campaigns (0.7, 3.7, and 25 kg, respectively) had relied on a linear sequence of 11 chemical steps and a final recrystallisation, starting from 9-anthraldehyde (**1**). For campaign 4 (170 kg demand), it was intended to out-source methanoaldehyde (**2**) as the key raw material from a commercial supplier using a six-step procedure.[1] The subsequent five steps (Scheme 1) would be essentially unchanged from the previous campaigns. The reductive alkylation of **2** with piperidone ketal **3** to give ketal **4** (now not isolated), deprotection to piperidone **5**, and the ethane thiolate displacement to give sulphide **8** were all in good shape. The two stages most in need of improvement were the coupling of 2-fluoropyridine (**6**) with piperidone **5** to give fluoropyridine **7**, and the asymmetric Kagan oxidation[2] of sulphide **8** to give crude **9** (yields as shown in Scheme 1).

During the next 3−4 months, the yield achieved in the asymmetric oxidation (with an acceptable ee) was significantly improved to 55%.[3] However, the organolithium-mediated coupling of **6** to piperidone **5** had resisted improvement over the three previous campaigns despite considerable efforts.[4] Rather than attempt further development of this process, we considered that a convergent synthesis, desirable in its own right, might also solve this issue. To further justify investigation on a potential new route at this late stage, we conducted a cost-benefit analysis of the raw materials costs. This clearly indicated that there were considerable financial and material savings to be made from any of our new route options, as discussed in detail below.

Chemistry Background. In earlier extensive work on the key coupling step of **5** and **6**, the process had lacked robustness, varying in yield from 40 to 65%, and could not be improved beyond 65% in the laboratory environment. The reaction was less reliable on the plant scale, although after much process development work, an overall yield of 63% was reliably achieved for campaign 3 (25 kg). Further problems concerned the output, operability, and a complex work-up procedure. The manifestations of this moderate yielding reaction were several; typically 10−15% unreacted piperidone **5** could be recovered at the end of the reaction (the use of higher equivalents of **6** and LDA did not help); 10−20% mass balance of the piperidone **5** input material could not be accounted for (recovered, in the product, or in the liquors); and there was some LC−MS evidence to suggest that high-molecular weight aldol products were being formed. All of this evidence strongly indicated that the highly basic lithiation conditions were abstracting the enolisable protons α to the ketone of **5**, and either protecting it against further reaction (until work-up) or promoting aldol condensations with more **5** to give high-molecular weight, lipophilic impurities. To test this hypothesis, the identical reaction conditions were performed on nonenolisable benzaldehyde. A strength-corrected overall yield of 86% of authenticated alcohol[5] **10** was obtained without optimisation, indicating that the reaction conditions were capable of delivering high yields for well-behaved substrates. Attempts to soften the

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basicity of the nucleophile, for example by trans-metalation

(1) Sunagawa, M.; Sato, H.; Katsube, J.; Yamamoto, H. *Chem. Pharm. Bull.* **1979**, *27*, 1806. Zeneca modifications to this route on scale-up to be reported in this journal in due course.

(2) For reviews see: Zhao, S. H.; Samuel, O.; Kagan, H. B. *Tetrahedron* **1987**, *43*, 5135−5144. Kagan, H. B. Asymmetric Oxidation of Sulphides. In *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; VCH: New York, 1993; pp 203−226.

(3) Moss, W. O. Zeneca internal 6-monthly report, January−July, 1997.

(4) Robinson, G. E. Zeneca internal 6-monthly reports (three), July, 1993, to December, 1994.

(5) Gungor, T.; Marsais, F.; Queguiner, G. *J. Organomet. Chem.* **1981**, *215*, 139.

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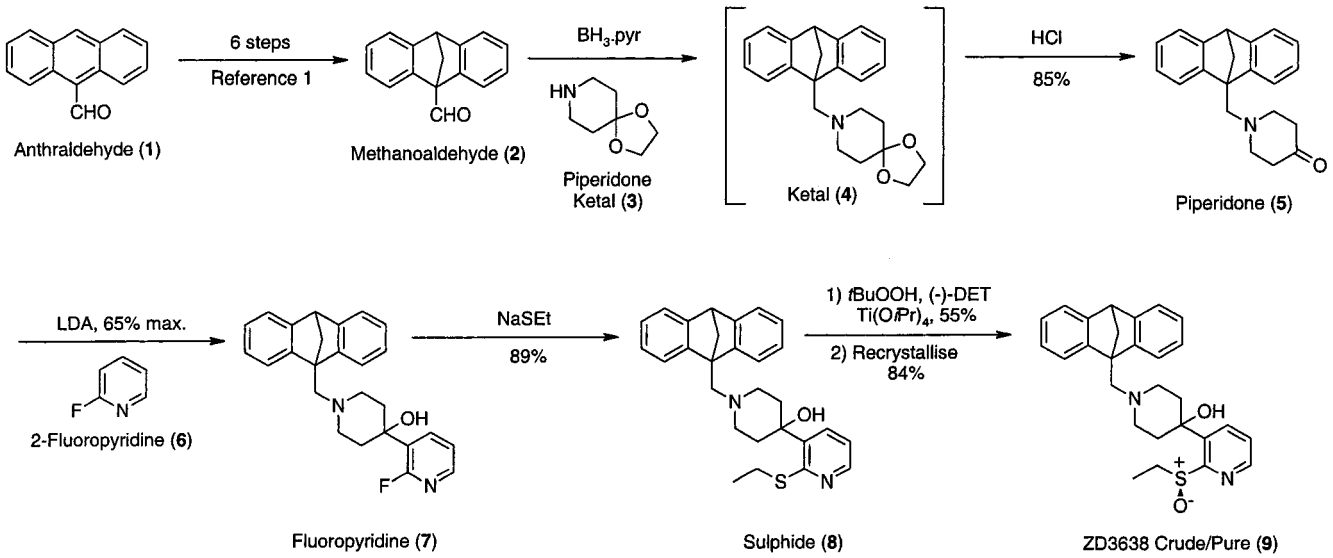
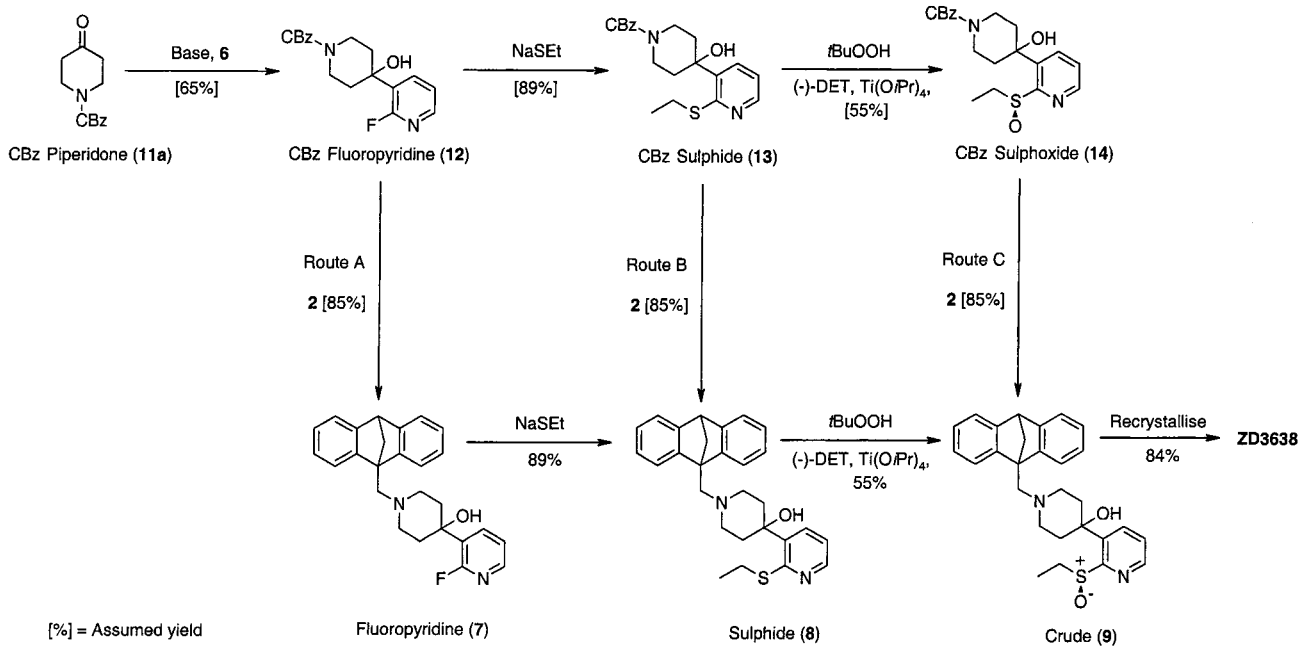
Scheme 1

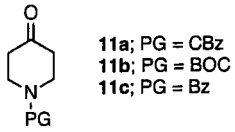


Scheme 2



with $ClTi(OiPr)_3$,[6] use of Lewis acids ($ZnBr_2$, $MgBr_2$), or activation of the carbonyl oxygen with dried $CeCl_3$,[7] were all unsuccessful, giving only trace amounts (<10%) of product **7** in each case. Since much other work[4] had been carried out previously and had failed to improve the process further, we decided a more radical strategy was now justified.

Convergent Route Strategy. A convergent route (Scheme 2) would make more efficient use of the expensive methanoaldehyde **2** by introducing it later in the synthesis compared to the linear sequence (Scheme 1). However, for this strategy to succeed, a readily available and cheap alternative to piperidone ketal **3** would be required. As replacements, we considered the CBz-, BOC-, and benzyl-protected piperidones **11a**−**c**. The urethanes were preferred



over the benzyl-protected compound **11c** because the lower basicity of the urethane nitrogen should reduce the potential for enolisation. In addition, the benzyl piperidone **11c** was not favoured (although it was cheap) because of expected problems with the removal of the benzyl group.[8] The BOC piperidone **11b** was not readily available at the time on the scale required, but fortunately the CBz piperidone **11a** was

(6) Weidmann, B.; Widler, L.; Olivero, A. G.; Maycock, C. D.; Seebach, D. *Helv. Chim. Acta* **1981**, *64*, 357.

(7) Dimitrov, V.; Kostova, K.; Genov, M. *Tetrahedron Lett.* **1996**, *37*, 6787 and references therein.

(8) The Research Department had investigated the use of this intermediate and had indeed encountered problems with removal of the benzyl group later in the synthesis.

Table 1. **Projected raw material costs for old and new routes**

				old route		route A		route B		route C	
raw material	MW	mol ratio	cost/kg[a]	cost/kg pure	% cost of route	cost/kg pure	% cost of route	cost/kg pure	% cost of route	cost/kg pure	% cost of route
methanoaldehyde (**2**)	220	1.00	430	910	61.7	592	55.6	531	52.5	294	37.3
piperidone ketal (**3**)	143	1.50	127	267	18.1	n/a[b]	n/a	n/a	n/a	n/a	n/a
2-fluoropyridine (**6**)	97	1.25	64	65	4.4	61	5.7	63	6.3	61	7.7
(−)-diethyl tartrate	206	2.08	114	233	15.8	233	21.9	230	22.8	254	32.2
CBz piperidone (**11a**)	233	1.00	80	n/a	n/a	179	16.8	186	18.4	180	22.8
ZD3638 pure (**9**)	459	n/a	n/a	1475	100	1064	100	1011	100	789	100

[a] Cost/kg in £'s. [b] n/a: not applicable.

both cheap and available on the desired scale.[9]

For a convergent synthesis to be viable, we decided that further criteria to be met were the following: yields comparable to those previously achieved for equivalent chemical transformations, no hazard or environmental issues, and a seamless interface with the existing route. This would make best use of the known late-stage chemistry so as not to delay delivery of campaign 4 bulk drug and to minimise the impact on quality and changes to the impurity profile. However, the potential benefits were significant. There was the strong possibility of making more efficient use of the expensive raw materials, there was the potential for yield and process improvements, and there was the possibility that performing the asymmetric oxidation on an alternative intermediate might give an improved resolution, either directly or on crystallisation.

Raw Materials Costs Analysis. Methanoaldehyde **2** was the most expensive of several raw materials at £430/kg, but the contribution from the others was also significant (Table 1). In particular, piperidone ketal **3** and 2-fluoropyridine (**6**) were also relatively expensive, as were some of the reagents for the asymmetric oxidation (e.g., (−)-DET), since they were required at stoichiometric levels. The high cost of the raw materials was therefore an additional factor in searching for a different route.

The predicted demand of ZD3638 was between 5 and 10 tonnes per annum at mature peak sales for the antipsychotic indication. We calculated the raw materials costs alone, based on the current campaign 4 processes and yields (Scheme 1). The costs and equivalents of reagents are shown in Table 1, the cost figures being correct at the time (early 1997). For convenience, the costs of solvents and commodity chemicals were assumed to be negligible.[10] The three convergent routes shown in Scheme 2 were also costed under the same criteria, changing the raw materials and reagents where appropriate. For comparative purposes, some assumptions had to be made. The major assumption was that identical yields could be achieved for the equivalent chemical transformations in the proposed new routes. This seemed reasonable to us, given the similarity of most of the intermediates. Furthermore, with the chemical experience that had already been generated, we were confident that given time to develop the processes, we could at least achieve comparable yields.

Table 2. **Costs of proposed new routes relative to old route**

route	cost/kg pure (£)	cost of old route (%)	saving (%)
old route	1475	100.0	0.0
route A	1064	72.1	27.9
route B	1011	68.5	31.5
route C	789	53.5	46.5

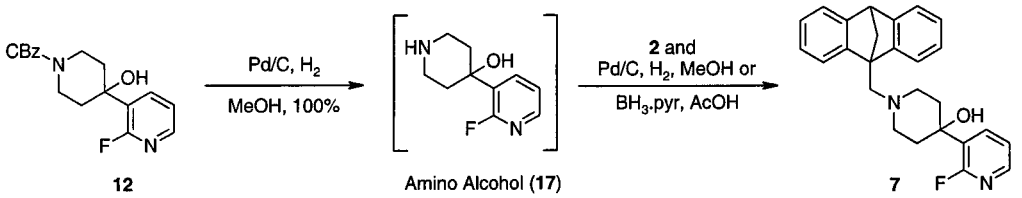
The figures in Table 1 also show the actual cost and the percent contribution that each kilogram of raw material makes per kilogram of pure **9** for each of the four routes. From these figures, the total relative cost for each route was derived, and the results proved to be significant, as shown in Table 2. Any of the three proposed convergent routes indicated that major financial savings could be made, with savings of 28, 32 and 47% for Routes A, B, and C, respectively (always assuming the linear route yields could be reproduced). Any improvement in yield would gain yet further savings. This did not take account of possible plant efficiencies due to using a convergent synthesis, which might also be substantial. Route C also involved the asymmetric oxidation of the alternative CBz sulphide **13**. This might result in both an improved ee during the oxidation, and more efficient improvement by crystallisation to enantiomerically pure material, leading to a higher overall conversion for this key step.

Unfortunately we had only a few months and limited resources before we had to decide on the route if we were to avoid a delay in the manufacture, and hence in the clinical programme. This was largely due to the long lead time on our key raw materials, **2** and **3** (or its substitute, **11a**). We dismissed Route B because although the displacement on **12** with ethane thiolate was expected to be facile, the assumed high yield (89%) of this additional step over Route A meant that the financial saving was marginal (only a further 4%). In addition, we had in mind to investigate hydrogenation methods on the resulting CBz sulphide **13** in the presence of methanoaldehyde **2** to achieve an efficient reductive alkylation, which we anticipated might prove troublesome in the presence of the thioether functionality. We postponed work on the most advantageous Route C, because our experiences of the asymmetric oxidation on this and other projects led us to believe that the optimal conditions for high yield and ee in the conversion of **13** to **14** might not be

(9) CBz piperidone had been required for a previous compound (ZD7944) and was potentially available from Ubichem on the scale required.

(10) The figures were put through Zeneca's in-house "Procost" system, an Excel-based software package, to generate the predicted raw material production costs.

Scheme 3



12 Amino Alcohol (**17**) **7**

quickly discovered. Therefore, we concentrated on Route A. If we could prove the principle of the convergent synthesis by Route A, this would buy extra time and resources which could then be used to investigate Route C.

Results and Discussion

Ortho lithiation of 2-fluoropyridine (**6**) was achieved under literature conditions[5,11] by adding 1.30 equiv of 2.0 M LDA in THF/heptane/ethyl benzene to 1.25 equiv of **6** at −78 °C for 1 h. CBz piperidone **11a** was added dropwise to the 2-fluoro-3-lithiopyridine anion, followed by quenching at −20 °C with a simplified work-up which led to 32−40% yields of CBz fluoropyridine **12** after chromatography. Some CBz piperidone was recovered in up to 15%, giving a corrected yield of 47% with recycled starting material. This compared favourably with the original route under identical conditions (i.e., **5** and **6** gave **7** in 65% without chromatography) and became the baseline experiment against which other preparations were then compared.

Alternative Bases. LDA.mono-THF (1.5 M in cyclohexane) gave a yield similar to that of the baseline experiment (36% after chromatography), indicating that the solvent mixture was not critical. An experiment with LDA in hexane was not attempted due to the known low solubility of the lithiopyridine anion at −78 °C even in THF.[11] Attempts to use bases weaker than LDA (pK_a 36)[12] to reduce unwanted enolisation were unsuccessful. For example, NaHMDS (pK_a 30) gave no reaction even on warming to room temperature (the Li and K salts were not investigated due to their similar basicity). The less basic magnesium diisopropylamide[13] also failed to react at room temperature. Stronger bases such as *n*-BuLi and *s*-BuLi (pK_a ∼40) both gave only trace quantities of the desired CBz fluoropyridine **12** as determined by HPLC (<10%). It is well reported that these strong alkyllithiums readily add to the pyridine ring even at low temperatures,[14] and although such products were not identified here, they had been seen in previous work.[4] Addition of stoichiometric TMEDA to an *n*-BuLi preparation to modify its reactivity also gave no improvement.

It was reasoned that a more hindered base might result in greater nucleophilic addition by the anion on the carbonyl rather than directly abstract the enolisable α protons itself. Addition of *n*-BuLi to 2,2,6,6-tetramethylpiperidine (TMP, **15**) generated the lithium tetramethylpiperidide (LiTMP) anion, slightly more basic than LDA (pK_a 37)[12] but considerably more hindered. When the standard reaction conditions were employed, a reproducible yield of 65% of CBz fluoropyridine **12** was readily achieved after chromatography. Some modest process development work was then conducted on these conditions to improve the yield and work-up, particularly to remove the chromatographic purification and also to recycle the TMP, but the project was canceled before much progress had been made in this area.

TMP (**15**) **6**; X = F
16; X = Cl

Alternative Raw Materials. The standard reaction conditions were also applied to the considerably cheaper 2-chloropyridine (**16**), although the literature indicated that the deprotonation with LDA is less efficient than for 2-fluoropyridine (**6**) which might necessitate the use of higher equivalents of LDA/**16**.[15] Furthermore the intermediate anion is not as stable and is more prone to pyridyne formation.[11,16] There was also concern over the ease of displacement of the chloride group by sodium ethane thiolate in the subsequent stage, and whether the chloride would survive the proposed hydrogenation conditions, for which there is good precedent.[17] The coupling reaction[15,17] was not a success, and no further work was attempted, although other substituted pyridine substrates were briefly considered.[18]

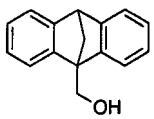
Deprotection and Reductive Alkylation Stages. Removal of the CBz group by hydrogenolysis was facile at room temperature and occurred in under 3 h in near quantitative yield to give the crude amino alcohol **17** (Scheme 3). The HPLC purity of the product was 95%, but this could not be improved by normal phase chromatography due to the amino alcohol's high polarity. The structure was confirmed by NMR and MS and by subsequent synthesis to authentic fluoropyridine **7** by two methods. The crude amino alcohol **17** was subjected to the reductive alkylation conditions of the existing ketal **4** process using BH_3·pyridine in methanol with methanoaldehyde **2** and acetic acid, to give the product **7** after chromotography in 73% overall yield from CBz fluoropyridine **12**. The structure of the product was confirmed by comparison with authentic material generated from the original route by HPLC t_R's and by NMR and MS data. Since both the hydrogenation and the borane reduction

(11) Gribble, G. W.; Saulnier, M. G. *Tetrahedron Lett.* **1980**, *21*, 4137.
(12) *Encyclopaedia of Reagents for Organic Synthesis*; Paquette, L. A., Ed.; John Wiley and Sons: Chichester, 1995.
(13) Bradlee, M. J.; Helquist, P. *Org. Synth.* **1997**, *74*, 137.
(14) Marsais, F.; Granger, P.; Queguiner, G. *J. Org. Chem.* **1981**, *46*, 4494.
(15) Trecourt, F.; Marsais, F.; Gungor, T.; Queguiner, G. *J. Chem. Soc., Perkin Trans. 1* **1990**, 2409.
(16) Gribble, G. W.; Saulnier, M. G. *Heterocycles* **1993**, *35*, 151.
(17) Comins, D. L.; Myoung, Y. C. *J. Org. Chem.* **1990**, *55*, 292.
(18) For example, 3-alkoxypyridines have been successfully ortho-lithiated, but the results were poor for a limited study on the comparable 2-substituted series: Marsais. F.; Queguiner, G. *Tetrahedron* **1983**, *39*, 2009.

were conducted in methanol, it should have been possible to telescope this sequence into one operation. The yield of 73% was very encouraging for a first small-scale reaction and was not far from the 85% yield for the equivalent transformation in the original route. Furthermore, the highly crystalline nature of **7** should have obviated the need for chromatography after only moderate process development effort.

Effecting the deprotection, iminium ion formation, and subsequent reduction all under reductive alkylation conditions in a hydrogenation vessel was an obvious alternative approach for a telescoped reaction sequence. Two reactions were tried under slightly differing conditions. CBz fluoropyridine **12**, methanoaldehyde **2**, catalyst, and a few drops of HCl were dissolved in methanol and hydrogenated under 3 bar hydrogen at room temperature for 22 h. After filtration and flash chromatography authentic fluoropyridine **7** was again produced, albeit in modest 43% yield.[19]

In the second case, the methanoaldehyde **2** was not added until the CBz group had been quantitatively cleaved from the precursor, as monitored by HPLC after 3 h. Methanoaldehyde **2** and acetic acid were then added to the crude amino alcohol **17** and stirred under nitrogen for 2 h to allow formation of the iminium ion, before the hydrogenation was restarted for a further 22 h. This had the advantage of not consuming any valuable methanoaldehyde before it could react with **17** (by reduction to the unreactive methanoalcohol **18**). The yield of fluoropyridine **7** after an identical work-



Methanoalcohol (**18**)

up and chromatography was again 43%, but with 36% recovered methanoaldehyde **2**, giving an overall yield of 67% allowing for unreacted starting material. Indeed, the recovered methanoaldehyde indicated that more forcing conditions could be used in the hydrogenation, and there is clearly scope for process optimisation on this stage. The quality of the product **7** generated by either of these new routes was very good, even more so if the borane reduction was used instead of the hydrogenation method. Once again, chromatography should easily have been avoided with process improvements and the new route was expected to be advantageous in the quality aspect also.

Hazard and Environment. A DSC on a sample of CBz fluoropyridine **12** showed it to have a melting point from about 122 °C and to be free from self-heating to 286 °C.[20] Although further tests would be needed for greater scale-up, this indicated that the sample could be safely manipulated up to 60 °C, the temperature of the hot extractions in the original process and a reasonable temperature for drying. None of the proposed new reaction stages had a high environmental impact factor or low output, and hazard issues were unlikely to be a major concern, largely because much of the chemistry was conserved and judged to be already acceptable (e.g., the BH_3·pyridine complex had already been used on the pilot plant at Macclesfield for campaign 3 delivery).

(19) There was some evidence that ZD3638 fluoropyridine sublimed under reduced pressure (e.g., on concentration), and this may have led to mechanical losses that would have been exaggerated on the small scale.

(20) Ramp rate 5 °C /min. Actual mp in the range 131−134 °C as determined by slow ramp (<1 °C /min) on hot-stage melting point apparatus; see Experimental Section.

Conclusions

The strategy adopted for rapid investigation of concerted Route A (Scheme 2) starting from the readily available CBz piperidone **11a** looked very promising. Initial studies on the coupling reaction using LiTMP as the base equalled the 65% yields obtained for the original route's coupling reaction using LDA. Subsequent transformations encompassing removal of the CBz group and some form of reductive alkylation showed that nearly comparable yields could be obtained compared to the original linear route. With more effort in this area, all of these stages should have been amenable to further process improvements and elimination of the chromatography. TMP was commercially available on a useful bulk scale, and although expensive, the cost might be expected to drop with usage. It was hoped that it might be recycled by acid−base extraction during work-up, and preliminary lab work suggested this would be possible.

In summary, the proposed new Route A has been proven to work in principle on the basis of exploratory lab work. The cost-benefit analysis demonstrated a clear financial saving in raw materials costs, and proved to be a valid exercise in itself in directing our limited resources at the time. In the longer term we would have investigated the more efficient Route C with the additional possibility of an improved asymmetric oxidation of CBz sulphide **13** to CBz sulphoxide **14** over that of **8** to **9**.

Experimental Section

General Procedures. Melting points were determined using a Griffin melting point apparatus (aluminium heating block) and are uncorrected. Elemental analysis (C, H, and N) were determined by the Research Department analytical service, Mereside. ^{1}H NMR spectra were recorded on a JEOL GX 270 MHz spectrometer with chemical shifts given in ppm relative to TMS at $\delta = 0$. Electron impact (EI) mass spectra were determined on a Micromass Autospec. The reaction mixtures and products were analysed by reverse phase HPLC on a Hewlett-Packard 1050 according to the following conditions: column, Waters Spherisorb S5ODS-1, 250 mm × 4.6 mm i.d.; eluent, 1:1 acetonitrile:water with 0.1% v/v triethylamine; flow rate 1.5 mL/min.; wavelength 228 nm; injection volume 20 μL. Typical retention times (t_R's) were: 2-fluoropyridine (**6**), 2.6 min; CBz piperidone (**11a**), 3.0 min; benzaldehyde, 3.2 min; methanoaldehyde (**2**), 5.0 min.; toluene, 5.7 min. Other retention times were as noted in the individual procedures. HPLC purities were generally % w/w against a standard of known strength as determined by ^{1}H NMR, except where noted a.n. (area % normalised). Analytical TLC was carried out on commercially prepared plates coated with 0.25 mm of self-

indicating Merck Kieselgel 60 F_{254} and visualised by UV light at 254 nm. Preparative scale silica gel flash chromatography was carried out by standard procedures using Merck Kieselgel 60 (230−400 mesh).

Preparation of Fluoropyridine (7) using Standard Conditions with LDA. 2-Fluoropyridine (**6**) (1.78 mL, 20.6 mmol) in THF (5.0 mL) was added over 10 min to a pre-cooled (−78 °C) solution of LDA (2.0 M in THF/heptane/ethyl benzene (10.7 mL, 21.5 mmol) and THF (12.5 mL) under an inert atmosphere, maintaining the temperature below −70 °C. The resulting orange solution was stirred for 1 h at below −70 °C. Piperidone (**5**) (5.0 g, 16.5 mmol) dissolved in THF (20 mL), and toluene (2 mL) was added dropwise to the solution of the 2-fluoro-3-lithio-pyridine anion over 30 min, maintaining the temperature below −70 °C. The addition funnel was rinsed with additional THF (20 mL) and added over 10 min. The resulting solution was stirred at below −70 °C for 1 h. A sample was taken after this time and analysed by HPLC (or before, as appropriate). The reaction mixture was warmed to −20 °C as evenly as possible over 1.5 h and added to a flask containing a stirred mixture of toluene (25 mL), water (17.5 mL), and glacial acetic acid (2.2 mL) over 10 min. The reaction flask was rinsed with further THF (20 mL), and this was also added. The resulting solution was heated to 55 °C for 15 min with stirring and then allowed to stand for 5 min. The lower aqueous layer was tapped off, along with some dark brown solid, and further water was added (17.5 mL). The wash and extraction procedure was repeated. The THF was removed by atmospheric distillation at 85 °C, and 64 mL of distillate was collected. Further toluene (25 mL) was added to the hot flask over 10 min, and the distillation then continued at 108 °C to remove 98 mL of toluene distillate. The resulting brown slurry was cooled evenly at 20 °C/h to 15 °C. Further toluene (4 mL) was added to mobilise the slurry, and the buff coloured solid was collected by filtration, washed twice with toluene (19 mL each), and pulled dry on the water pump for 15 min. The solid was further dried in vacuo at 70 °C over 3 days to yield the title compound **7** (4.19 g, 63% based on **5**). HPLC purity 98.3%, t_R 9.5 min; mp 210−212 °C. Other data for **7** as noted below.

Preparation of CBz Fluoropyridine (12) using LDA. 2-Fluoropyridine (**6**) (4.7 mL, 53 mmol) in THF (5 mL) was added over 15 min to a pre-cooled (−78 °C) solution of LDA (2.0 M in THF/heptane/ethyl benzene, 27.6 mL, 55.1 mmol) and THF (50 mL) under an inert atmosphere, maintaining the temperature below −70 °C. The resulting orange solution was stirred for 1 h at below −70 °C. CBz piperidone (**11a**) (10.0 g, 42.4 mmol) dissolved in THF (50 mL) was added dropwise to the solution of the 2-fluoro-3-lithio-pyridine anion over 35 min, maintaining the temperature below −70 °C. The addition funnel was rinsed with additional THF (5 mL) and added. The resulting solution was stirred at below −70 °C for 1 h. A sample was taken after this time and analysed by HPLC (or before, as appropriate). The reaction mixture was warmed to −20 °C evenly over 1 h which formed a brown slurry and was quenched by the addition of a solution of toluene (50 mL) and acetic acid (5.6 mL) over 15 min, which produced an orange suspension. The mixture was stirred for 15 min, and then water (35 mL) was added and stirred for a further 30 min. The reaction mixture was then subjected to the hot extraction and distillation procedures described above for **7**. The residual toluene was removed under reduced pressure to yield a dark red gum (14.25 g). The crude gum was purified by silica gel flash chromatography, eluting with 1:1 hexane:ethyl acetate to yield the title compound **12** as a yellow solid (4.5 g, 32%) and recovered **11a** (1.5 g, 15%), giving an overall yield of 37% allowing for recycling of recovered **11a**. Data for **12** as noted below, except mp 133−134 °C.

Preparation of CBz Fluoropyridine (12) using LiTMP. TMP (9.4 mL, 55.2 mmol) was added to *n*BuLi (2.5 M in hexanes, 22.9 mL, 57.3 mmol) in THF (50 mL) cooled to −78 °C under an atmosphere of nitrogen, and stirred for 30 min. A solution of 2-fluoropyridine (**6**) (4.7 mL, 53.0 mmol) in THF (10 mL) was added dropwise over 10 min keeping the temperature below −70 °C, and then stirred for 1.25 h at below −70 °C. A solution of CBz piperidone **11a** (10.0 g, 42.4 mmol) dissolved in THF (50 mL) was added dropwise over 30 min, maintaining the temperature below −70 °C. The addition funnel was rinsed with THF (10 mL), and the reaction mixture was stirred for a further 1 h. The resulting orange solution was allowed to warm to −20 °C over 1.5 h before being quenched by the addition of acetic acid (5.6 mL, 97.5 mmol) in toluene (50 mL). Water (35 mL) was added dropwise over 5 min and the mixture stirred for 30 min before heating to 55 °C. The aqueous layer was separated and the organic layer given a second water wash (35 mL). The combined organic layer was concentrated under reduced pressure to a yellow gum (15.4 g) which was purified by silica gel flash chromatography, eluting with 1:1 hexane: ethyl acetate to yield the title compound **12** as a white crystalline solid (9.1 g, 65%). HPLC purity 98.0%, t_R 3.9 min.; TLC R_f 0.25 (1:1 hexane:ethyl acetate, SiO_2); mp 131−133 °C; ^{1}H NMR (270 MHz, $CDC1_3$) δ 1.78 (2H, d, J = 13.1 Hz), 2.20 (2H, bs), 2.22 (1H, d, J = 4.0 Hz), 3.31 (2H, bs), 4.13 (2H, bs), 5.16 (2H, s), 7.19−7.24 (1H, m), 7.31−7.38 (5H, m), 7.90−7.97 (1H, m), 8.12−8.15 (1H, m); MS (EI^+) 330 (M^+, 16%), 206 (M^+ − PhCHO − H_2O, 18), 91 ($PhCH_2^+$, 100). Anal. Calcd for $C_{18}H_{19}FN_2O_3$ requires C, 65.4; H, 5.8; N, 8.5. Found: C, 65.5; H, 5.8; N, 8.3%.

Preparation of Amino Alcohol (17). CBz Fluoropyridine (**12**) (9.91 g, 30.0 mmol) and the catalyst (10% Pd on C, 0.99 g, 1.0 mol %) were suspended in methanol (180 mL) and stirred for 3 h under an atmosphere of hydrogen (3 bar). The reaction mixture was filtered through a pad of Celite, washed copiously with methanol, and concentrated under reduced pressure to yield the crude title compound **17** as an off-white solid (6.07 g, ∼100%). HPLC purity 95% a.n., t_R 16.6 min.; TLC R_f < 0.05 (10% CH_3OH in CH_2Cl_2 with 1.0% NH_4OH, SiO_2); mp 188−191 °C; ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.76 (2H, dd, J = 13.9, 2.0 Hz), 2.23 (2H, dt, J = 12.9, 4.9 Hz), 2.97−3.04 (2H, m), 3.14 (2H, dt, J = 12.3, 1.5 Hz), 7.19−7.24 (1H, m), 7.94−8.01 (1H, m), 8.11−8.14 (1H, m); MS (EI^+) 196 (M^+, 35%), 178 (M − H_2O, 100), 82 (21), 57 (62), 42 (78). Anal. Calcd for $C_{10}H_{13}FN_2O$·

0.2H_2O requires C, 60.1; H, 6.7; N, 14.0. Found: C, 60.3; H, 6.8; N, 13.5%.

Preparation of Fluoropyridine (7) by Borane Reduction from 17. Crude amino alcohol (**17**) (1.64 g, 8.4 mmol) and methanoaldehyde (**2**) (1.86 g, 8.4 mmol) were suspended in methanol (25 mL) under an atmosphere of nitrogen. Acetic acid (240 μL, 4.2 mmol) was added, and the resulting orange solution was stirred at 20 °C for 1.5 h. Borane−pyridine complex (8 M, 470 μL, 3.8 mmol) was added in toluene (1.9 mL) over 4 min, with water bath cooling, and allowed to stir at 20 °C for 22 h. A precipitate formed after 10 min, and the orange colour disappeared. Aqueous HCl (2 N, 20.9 mL, 41.8 mmol) was added over 10 min after which a second solid formed and then dissipated with stirring over the next 3 h at 20 °C. Aqueous NaOH (2 N, 30 mL, 60 mmol) was added dropwise over 5 min to achieve a pH of 13−14. The combined solid and aqueous suspension were extracted with dichloromethane (4 × 50 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure to yield a crude gum (3.8 g) which was purified by silica gel flash chromatography eluting with 3:2 to 1:1 hexane:ethyl acetate to yield the title compound **7** as an off-white solid after drying in vacuo at 60 °C (2.43 g, 73%). This could be further purified by trituration in 1:1 hexane:ethyl acetate to give a white solid, mainly improved in colour rather than quality (2.08 g, 62%). HPLC t_R 9.6 min.; TLC R_f 0.21 (3:2 hexane:ethyl acetate, SiO_2); mp 209−211 °C; ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.78 (2H, dd, J = 13.7, 2.4 Hz), 2.17−2.32 (3H, m) 2.62 (2H, d, J = 1.5 Hz), 2.75 (2H, dt, J = 11.8, 1.8 Hz), 2.90−2.96 (2H, m), 3.48 (2H, s), 4.27 (1H, s), 6.89−6.99 (4H, m), 7.15−7.28 (5H, m), 7.88−7.95 (1H, m), 8.08−8.11 (1H, m); MS (EI^+) 400 (M^+, 50%), 206 (100), 195 (52). Anal. Calcd for $C_{26}H_{25}FN_2O$ requires C, 78.0; H, 6.3; N, 7.0. Found: C, 77.7; H, 6.4; N, 6.9%.

Preparation of Fluoropyridine (7) by Hydrogenation Telescope from 12. CBz Fluoropyridine (**12**) (4.31 g, 13.0 mmol) and the catalyst (10% Pd on C, 0.43 g, 1.0 mol %) were suspended in methanol (125 mL) and hydrogenated for 2 h under an atmosphere of hydrogen (3 bar). TLC (1:1 hexane:ethyl acetate) and HPLC indicated all starting material had been consumed by this time. Methanoaldehyde (**2**) (2.90 g, 13.1 mmol) and glacial acetic acid (372 μL, 6.5 mmol) suspended in methanol (40 mL) were added, and the reaction mixture was stirred for 2 h at 20 °C under nitrogen. The hydrogenation was then continued as above, for 22 h in total before the addition of a solution of sodium bicarbonate (1.09 g, 13.0 mmol) in water (20 mL). The reaction mixture was filtered through a pad of Celite, washed copiously with methanol, and concentrated under reduced pressure to a white paste (6.0 g). This was purified by silica gel flash chromatography eluting with 1:1 hexane:ethyl acetate to yield recovered **2** (1.03 g, 36%, R_f 0.86) and the title compound **7** as a white solid (2.29 g, 43%, R_f 0.25), giving an overall yield of 67% allowing for recovered **2**. Data for **7**:- HPLC purity 98.8%, t_R 10.5 min. Other data for **7** as noted above.

Preparation of Benzaldehyde Adduct 10. The method described above for the preparation of **12** using LDA was used on a 62.5 mmol scale of 2-fluoropyridine (**6**) to generate the 2-fluoro-3-lithiopyridine anion. A solution of benzaldehyde (5.1 mL, 50.0 mmol) dissolved in THF (10 mL, 1.96 volumes) was added dropwise over 15 min, maintaining the temperature below −70 °C, and stirred for a further 1.25 h. The reaction mixture was quenched as for **12**, and after a simplified aqueous extractive work-up, the organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure to yield the title compound **10** as an orange/brown oil which solidified on standing (9.8 g, 96% crude, 86% strength corrected by ^{1}H NMR). HPLC purity 89% a.n., t_R 3.1 min; mp (crude) 68−72 °C (lit.[5] 74 °C); ^{1}H NMR (270 MHz $CDC1_3$) δ 1.8−2.7 (1H, bs), 6.06 (1H, s), 7.18−7.24 (1H, m), 7.29−7.41 (5H, m, Ph), 7.97−8.04 (1H, m), 8.08−8.11 (1H, m); MS (EI^+) 203 (M^+, 100%), 185 ($M-H_2O$, 12), 124 (34), 105 ($PhCO^+$, 28), 97 (55).

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