Organic Process Research & Development **1998**, *2*, 157–168

Process Development of the PDE IV Inhibitor 3-(Cyclopentyloxy)-*N*-(3,5-dichloropyrid-4-yl)-4-methoxybenzamide

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Abstract:

Development of an industrial process for 3-(cyclopentyloxy)-*N*-(3,5-dichloropyrid-4-yl)-4-methoxybenzamide, a potent PDE IV type inhibitor, is described. The rapid identification of scalable reaction conditions allowed pilot-scale synthesis of kilogramme quantities for early clinical evaluation. However, as more compound was demanded, better reaction conditions were required in the interests of safety, economics, and environmental impact. This led to the derivation of a high-yielding and very robust procedure which included various safeguards to ensure that high-quality product was obtained and that new trace impurities were effectively removed. The large-scale oxidation of a benzaldehyde derivative to the corresponding benzoic acid using hydrogen peroxide under aqueous alkaline conditions is described.

Introduction

Since the discovery[1,2] of the novel PDE IV inhibitor 3-(cyclopentyloxy)-*N*-(3,5-dichloropyrid-4-yl)-4-methoxybenzamide (**1**) (piclamilast) and its potent action as a potential novel antiasthmatic agent, multikilo quantities were required for pharmacological profiling and clinical trials. The promise shown by compound **1** was sufficient to initiate industrialisation studies and thus derive a manufacturing process which was clean, safe, high-yielding, reliable, and robust.

Discussion

The original synthesis used by discovery chemistry changed little in terms of the starting materials and intermediates, but the reagents and reaction conditions were altered considerably for all of the standard scale-up reasons. The route (Scheme 1) involves the initial alkylation of the commercially available isovanillin (**2**) followed by oxidation of the carboxaldehyde **3** to the corresponding carboxylic acid **4** and subsequent acid chloride **5** formation. This acid chloride **5** is coupled with 4-amino-3,5-dichloropyridine (**7**) (which itself is prepared by chlorination of commercially available 4-aminopyridine (**6**)) to give **1**.

The need for change to the discovery conditions is obvious. Stage 1 constituted an explosion risk and suffered from a modest yield and high effluent burden. Stage 2 was also particularly environmentally unfriendly. The use of thionyl chloride as solvent for stage 3 was both hazardous and unnecessarily costly, and the stage 4 process at first sight appeared to present a risk in terms of instability of hydrogen peroxide (potential pressure rise) and in terms of possible by-product formation (such as *N*-oxides). The stage 5 procedure gave concern for reasons of yield, effluent, practicality, and safety since the coupling was achieved by reacting the two key intermediates at the melt.

As is often the case, the first process chemistry route was a "quick fix" to give a workable process that could be used on a reasonable scale (e.g., pilot plant) with relative ease of processing and safety to give a suitable-quality product in respectable yield and in good time. The second process chemistry route was the result of a much more in-depth investigation to ensure that the most robust, economical, and environmentally acceptable procedure was obtained.

Derivation of Stage 1. The stage 1 process used in discovery was relatively straightforward, but the well-known[3] incompatibility between *N*,*N*-dimethylformamide and sodium hydride had to be immediately addressed. This was effected simply by changing the base to potassium carbonate. With subsequent slight modifications to the method of product isolation, the yield was improved dramatically and was operated with ease on a 3.5 kg scale (of isovanillin (**2**)). However, for further scale-up and industrialisation, this method had to be reexamined due to the effluent burden arising from the use of *N*,*N*-dimethylformamide, which was unlikely to be economical to recover in this case. A number of other solvents were thus examined, amongst which ethanol showed particular promise. Ethanol is available in a variety of guises from spectroscopically pure (which would be expensive) to several denatured grades, and fortuitously, no difference could be established between reactions performed in any of the grades. This allowed selection of industrial methylated spirit (95% ethanol, 5% methanol) as a convenient and cheap solvent. The work-up procedure developed was to drown with water and then distil out the ethanol as an azeotrope, leaving the stage 1 product **3** as an oil in water, which was extracted into toluene for subsequent use. The resulting ethanol azeotrope was found to be suitable as a solvent for stage 1 thus allowing the direct recycle of solvent to minimise waste (in fact, up to 20% water could be tolerated in the reaction). One effect which we did observe when changing from the dipolar aprotic solvent (*N*,*N*-

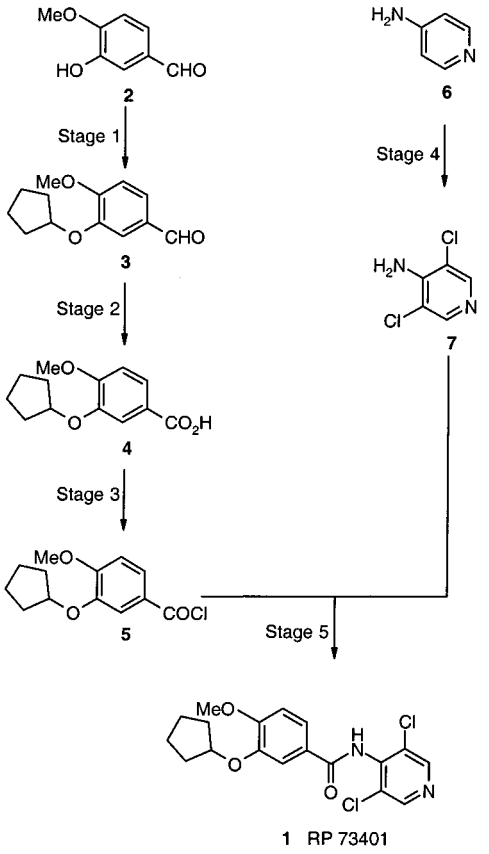
(1) Ashton, M. J.; Cook, D. C.; Fenton, G.; Hills, S. J.; McFarlane, I. M.; Palfreyman, M. N.; Ratcliffe, A. J.; Vicker, N. PCT Int. Publ. WO 92/12961.

(2) Ashton, M. J.; Cook, D. C.; Fenton, G.; Karlsson, J.-A.; Palfreyman, M. N.; Raeburn, D.; Ratcliffe, A. J.; Souness, J. E.; Thurairatnam, S.; Vicker, N. *J. Med. Chem.* **1994**, *37*, 1696.

(3) Buckley, J.; Webb, R. L.; Laird, T.; Ward, R. J. *Chem. Eng. News* **1982**, *60* (28), 5. De Wall, G. *Chem. Eng. News* **1982**, *60* (37), 5, 43.

S1083-6160(97)00038-8 CCC: $15.00
Published on Web 04/11/1998

Scheme 1



Reagents and conditions :
Discovery method :
Stage 1; DMF, NaH, C_5H_9Br, 50°C, 22h; Yield 57%:
Stage 2; i) aq. $KMnO_4$, Na_2CO_3, 50°C, 1h; ii) HCl, $NaHSO_3$; Yield 60%:
Stage 3; $SOCl_2$, reflux, 3h; Yield 76%:
Stage 4; i) c HCl, 15% w/w H_2O_2, 80°C, 3h; ii) aq. NaOH; Yield 88%:
Stage 5; Heated at the melt, 10 mins; Yield 20%.

Scale 0.1g-10g Overall yield from isovanillin = 5.2%

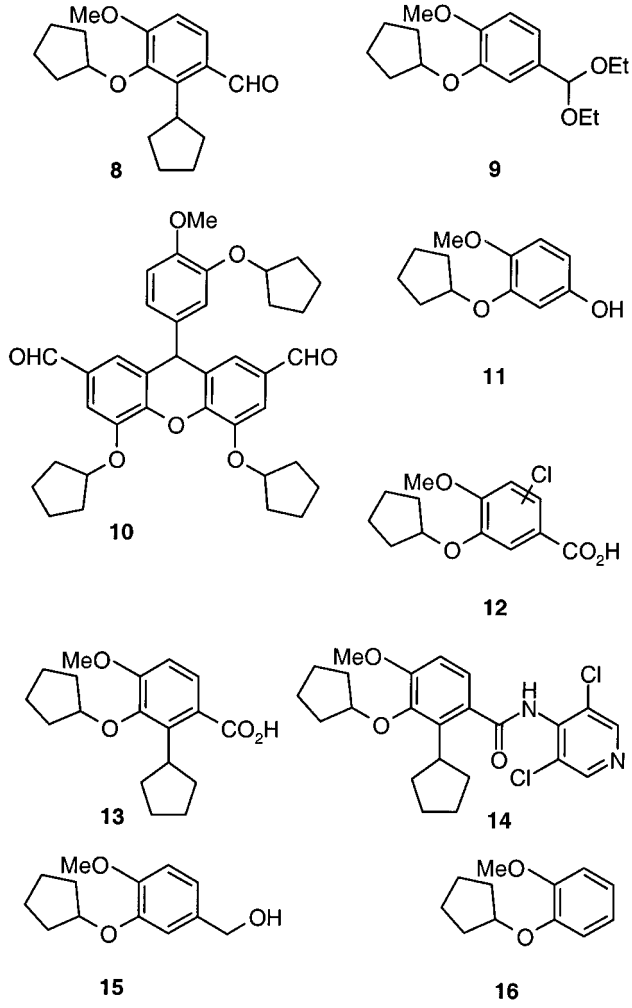
1st Process Chemistry method :
Stage 1; DMF, K_2CO_3, C_5H_9Br, 65°C, 8h; Yield 84%:
Stage 2; AcOH, H_2NSO_3H, $NaClO_2$, 20°C, 2h; Yield 92%:
Stage 3; $SOCl_2$, DMF (cat), toluene, reflux, 5h; Yield 98%:
Stage 4; i) c HCl, NaOCl, 80°C, 3h; ii) aq. NaOH; Yield 81%:
Stage 5; i) THF, NaH, 10°C, 1.5h; ii) aq. HCl; Yield 69%.

Scale 100g-5kg Overall yield from isovanillin = 52.3%

2nd Process Chemistry method :
Stage 1; EtOH, K_2CO_3, C_5H_9Br, reflux, 8h; Yield 95%:
Stage 2; i) H_2O_2, NaOH, 45°C, 9h; ii) HCl; Yield 89%:
Stage 3; $SOCl_2$, DMF (cat), toluene, reflux, 3h; Yield 99%:
Stage 4; i) c HCl, 35% w/w H_2O_2, 70°C, 3h; ii) aq. NaOH; Yield 93%:
Stage 5; Toluene, KOtBu, 6h; aq. HCl; Yield 84%.

Scale 5kg-25kg Overall yield from isovanillin = 70.3%

dimethylformamide) to the protic solvent (ethanol) was two new impurities at about 1% level each. These were identified (following isolation by preparative HPLC) as the C-cyclopentylated derivative **8** and the diethyl acetal **9**, both of which could be expected and explained on the basis of the change of solvent.[4] Following high-vacuum distillation of a sample of the stage 1 product (to obtain a pure sample of the aldehyde **3** as an analytical reference standard), the still residue became greatly enriched in less volatile impurities, which



allowed their simple isolation by flash chromatography (to provide reasonable quantities for analytical tools). The impurities from the still residue were identified as the C-cyclopentylated derivative **8** and the unlikely xanthene derivative **10**, which was possibly formed during the long exposure to the high-temperature distillation. The acetal **9** was not isolated from the distillation (possibly as a consequence of instability during the high-temperature distillation) and was thus made unambiguously to obtain an authentic reference standard. Since there had been a change in the impurity profile of the stage 1 product, it was important to ensure that consequent impurities did not translate to the final product; this will be discussed under the subsequent stage headings.

With the procedure fully optimised, this was operated routinely and reliably at a 10 kg scale, giving a 95% yield of the stage 1 product **3**.

Derivation of Stage 2. The stage 2 process used in discovery was not suitable (on the basis of the effluent load and yield) and had to be immediately modified. The use of sodium perborate (a useful, cheap, relatively clean reagent

(4) For C-cyclopentylation of phenols, ample precedent is available; for example, see: Kornblum, N.; Berrigan, P. J.; Le Noble, W. J. *J. Am. Chem. Soc.* **1963**, *85*, 1141. For an explanation of solvent effects on the reactivity of ambident anions, see: *Solvents and Solvent Effects in Organic Chemistry*, 2nd ed.; Reichardt, C., Ed.; VCH: Cambridge, 1990; p 239.

Table 1. **Key parameters for the stage 2 oxidation**

parameter	optimum	boundary conditns and effect of further deviation
reaction temp	45 °C	±5 °C above 50 °C: an increase in rate of reaction (which is very exothermic); need to ensure plant cooling capacity; risk of corrosion of glass pH probe below 40 °C: a decrease in rate of reaction, which risks the accumulation of peroxide and the potential for sudden reaction with not only the liberation of heat but also sudden evolution of oxygen
peroxide rate of addn	9 h	±2 h above 11 h: not detrimental to the yield but impacts cycle time less than 7 h: a correspondingly shorter time for the rate of oxygen evolution (obviously compromising safe venting); the rate of cooling needs to be increased (plant capacity issues)
reaction pH	11.5	±0.5 above pH 12: an increase in the rate of peroxide decomposition with respect to the desired reaction, thus leading to incomplete reaction and, hence, lower yields (unless an increase in the charge of peroxide can be accommodated in the reaction vessel) below pH 11: a significant decrease in the rate of reaction and in the rate of peroxide decomposition, which leads to dangerous accumulation of peroxide in the batch

which has been used[5] successfully for many benzaldehyde derivatives) only gave the phenol **11**, but the use of sodium chlorite in the presence of sulfamic acid (as chlorine scavenger)[6] gave a good yield of required product **4**. This procedure was quick and efficient and was operated safely on a 4.7 kg scale (of stage 1 product **3**) but still suffered from a relatively high effluent burden. When interrogated for robustness, a lower charge of sulfamic acid gave major problems. The product **4** became contaminated with ring-chlorinated derivatives **12**. Also, of even greater significance, chlorine dioxide (an unstable and violently explosive gas) was found to be present in the gas phase. The proof that chlorine dioxide could be liberated led to investigation of safer and more environmentally acceptable methods. We were aware that alkaline hydrogen peroxide was suitable for the oxidation of piperonal,[7] and since hydrogen peroxide is one of the cleanest oxidants in common use, we studied its suitability for our substrate. The hazards of hydrogen peroxide are well-known,[8] and thus the concentration was limited to the commercially available 35% w/w solution. Since the stage 1 product **3** was generated in toluene solution, the toluene had to be removed prior to charging the hydrogen peroxide to remove the flammability risk. Thus, the toluene was removed by azeotropic distillation, leaving the stage 1 product **3** as an oil in water. The stage 1 product **3** was virtually insoluble in water and required efficient agitation to ensure a well-dispersed emulsion to effect reaction. The temperature, pH, and rate of peroxide addition proved to be key parameters and were optimised by application of simple fractional factorial experimental design,[9] and a subsequent deviation study derived the boundary conditions for each parameter (Table 1).[10]

The process safety of this stage was examined critically. Providing efficient agitation was maintained (to prevent separation of the stage 1 product **3** as an upper oil), the flammability concerns were minimised due to the low organic inventory. The high exothermicity of the reaction together with the oxygen evolution[11] profile dictated the safe maximum rate for the addition of hydrogen peroxide. The maintenance of the pH at 11.5 ± 0.5 was essential, requiring the continual addition of sodium hydroxide solution to replenish that consumed by the acid **4** as it formed. Hydrogen peroxide addition was immediately terminated if the pH fell below 11.

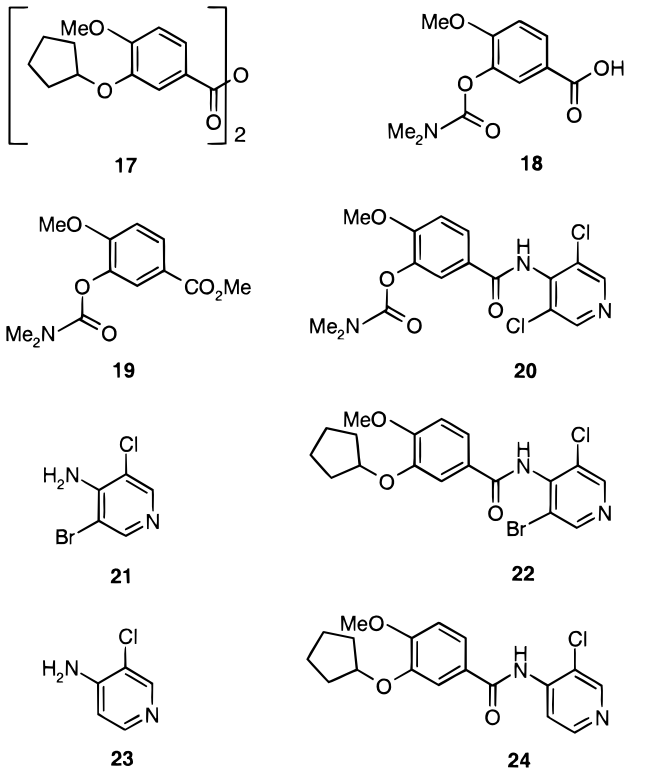
The development of this procedure was coincidental with the change in solvent at stage 1 from DMF to ethanol. This meant that the C-cyclopentylated aldehyde **8** and the acetal **9** were present as impurities in the stage 1 product **3**. It was proven that the acetal **9** was converted to the required acid **4** under the reaction conditions, but the other impurity **8** was more problematic. The higher lipophilicity of this compound **8** greatly influenced the kinetics for its oxidation: indeed about half of the aldehyde **8** was recovered unchanged and was removed in the toluene wash at the end of the reaction. However, the small amount which had been oxidised (to compound **13**) was isolated in the stage 2 product **4** following simple precipitation of the batch and subsequent filtration (which had been the standard practice). Use tests of this "contaminated" material led to a corresponding impurity **14** in the final product **1**, and unfortunately, no simple method was found to reduce the levels of this impurity (typically 0.3% w/w in the final drug substance; such impurity levels had never been observed in the previous pilot-

(5) McKillop, A.; Kemp, D. *Tetrahedron* **1989**, *45*, 3299. Muzart, J. *Synthesis* **1995**, 1325−1346. McKillop, A.; Sanderson, W. R. *Tetrahedron* **1995**, *51*, 6145.
(6) Lindgren, B. O.; Nilsson, T. *Acta Chem. Scand.* **1973**, *27*, 888.
(7) Dobrowsky, A. *Monatsh. Chem.* **1955**, *86*, 325.
(8) See various literature available from Interox, especially "Hydrogen Peroxide," ref P. 1.1.1, and "Hydrogen Peroxide; Manual for Handling and Storage," ref P 1.3.1.
(9) Plackett, R. L.; Burman, J. P. *Biometrika* **1946**, *33*, 305. Stowe, R. A.; Mayer, R. P. *Ind. Eng. Chem.* **1966**, *58*, 36.
(10) Although the statistically designed experiments were simple, the use of an automated laboratory reactor proved invaluable to eliminate operator error, achieve precise pH control, and control long linear additions.
(11) An important side reaction is the decomposition of hydrogen peroxide to liberate oxygen: under these totally aqueous conditions, the decomposition was significant, requiring a 10−12 mol excess of hydrogen peroxide for complete reaction.

scale batches). It was obvious that control of the contaminant **13** in the stage 2 product **4** was critical, and fortuitously, this was achieved simply by extraction of the batch into hot toluene (following acidification at the end of the reaction) and subsequent crystallisation, which left the impurity **13** dissolved in the toluene mother liquor. Anticipated by-products such as the alcohol **15** (in case of a Cannizzaro reaction) or the phenol **11** (following a Dakin reaction) proved not to be formed (by reference with authentic samples of compounds **15** and **11)**. One unexpected degradant was identified, however, as the neutral species **16**, presumably formed by some minor decarboxylation mechanism.

This stage was the one we expected to produce difficulties during scale-up, but in the event, the simultaneous addition of both hydrogen peroxide and sodium hydroxide whilst the temperature was maintained within the boundary conditions was a relatively simple task in a very simple plant and was operated on a 15 kg scale,[12] giving an 89% yield of the stage 2 product **4**.

Derivation of Stage 3. The discovery method was changed little except to use thionyl chloride as a reagent in almost stoichiometric ratios rather than as an unnecessary and expensive solvent. Toluene was selected as a cheap, inert, recoverable solvent since a high concentration of the acid **4** in hot toluene could be achieved. The addition of DMF was required as a catalyst to achieve an efficient rate of reaction at reflux and to avoid formation of the anhydride **17**. Discolouration of the batch could be avoided by



performing reactions at 80 °C instead of reflux. The decrease in reaction rate was of no concern, but gas evolution profiles revealed that only sulfur dioxide was liberated, with the hydrogen chloride remaining dissolved in the batch until subsequent concentration. This lack of controlled gas release led to return to reactions at reflux, where the gases were disengaged readily.

As analytical methods improved during the development, a new impurity was detected in the final product at levels of about 0.05% w/w. This impurity was subsequently isolated and proven to be carbamate **20**. This product could only arise as a consequence of the catalytic DMF being oxidised (presumably to dimethylcarbamoyl chloride), and we also assumed that the cyclopentyl ether was cleaved to give the phenol. Certainly it is established that thionyl chloride can function as an oxidant, and therefore the stage 3 reaction mixture was examined for the precursors to the resulting impurity **20**. The acid **18** was made unambiguously (via the ester **19**), and isovanillic acid and dimethylcarbamoyl chloride were purchased as analytical tools, but none of these species were detected. It is now presumed that the analytical methods used were not sufficiently sensitive following recent publication[13] confirming that dimethylcarbamoyl chloride is formed from DMF during such reaction conditions. Although the author[13] was highlighting the toxicity issue of the resulting dimethylcarbamoyl chloride, our concern was a new impurity in the drug substance which could not be removed by standard methods, and therefore minimisation at stage 3 would have to be assured (fortuitously, no batch of final product ever contained more than 0.05% w/w).

Derivation of Stage 4. When the discovery route was examined, the known hazards of hydrogen peroxide were sufficient to warrant changing the method to a safer procedure which would be capable of more rapid scale-up. Elemental chlorine gave low yields, but sodium hypochlorite solution under acid conditions (as a convenient source of chlorine) afforded isolated yields in excess of 80% in a very simple reaction and was operated without problem on 2 kg scale (of 4-aminopyridine (**6**)). However, with improving analytical methods, an impurity was noted in the final product **1** by HPLC which was previously obscured by the main peak using former elution conditions. This impurity was identified as the bromo chloro compound **22**, which had obviously arisen from the bromochloropyridine derivative **21** present in the isolated stage 4 product **7**. The cause of **21** was subsequently proven to be due to bromide in the sodium hypochlorite, which raised immediate concerns regarding the availability of suitable-quality sodium hypochlorite. Although the isolated yield was respectable, a further concern was highlighted by failure to achieve a mass balance. During the course of development of this whole synthesis, hydrogen peroxide became the oxidant of choice for stage 2, and it thus made good sense to reinvestigate the discovery route since there would be a plentiful supply of 35% w/w hydrogen peroxide solution on site. It was consequently established that a high yield could be obtained provided that the concentration of chloride was not allowed to fall below about

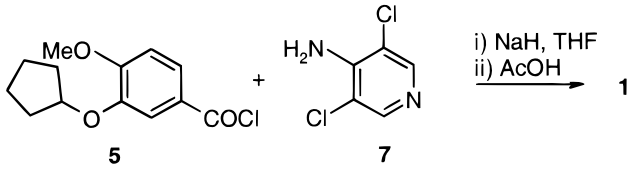
(12) The additions were performed with the aid of metered dosing pumps, and the pH and temperature were monitored by using a pump loop system to ensure good mixing at the early stages of the reaction when the vessel contents were approaching the minimum stirred volume.

(13) Levin, D. *Chem. Ind. (London)* **1997**, 2; *Chem. Br.* **1997**, *33*, 20; *Org. Process Res. Dev.* **1997**, *1*, 182.

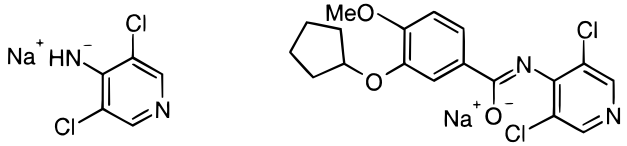
20%[14] and a good throughput could be maintained if 9 mol of 37% w/w hydrochloric acid and 3 mol of 35% w/w hydrogen peroxide were used per mole of 4-aminopyridine (**6**) (when the mixture approached 20% chloride concentration only towards the end of the reaction). The quality of hydrochloric acid was much higher than the quality of the hypochlorite used in the previous method, and so quantities of bromide (which led to the brominated derivative **21**) were not an issue and the only impurity of any significance was the monochloro compound **23**. However, this impurity **23** was less problematic since it was more soluble in the mother liquors than the product **7**, and some drastic deviations were necessary to produce contaminations in excess of 1% w/w. Although levels of the monochloro impurity **23** were typically less than 0.1% w/w in the isolated stage 4 product **7**, we demonstrated that the stage 5 process was suitably robust to be able to tolerate at least 1% w/w of the impurity **23**, giving less than 0.1% w/w of the corresponding impurity **24** in the final isolated product at stage 5. This stage 4 procedure was found to be suitably robust with reproducible yields obtained at a range of reaction temperatures although 70 °C was selected as optimal. Despite the high yield (93%), the remainder of the 4-aminopyridine (**6**) could not immediately be accounted for. Sublimation had been observed (during drying at oven temperatures >60 °C), but subsequent sublimation studies did not support this mechanism for losses of this magnitude.[15] The first insight into the mass balance issue was established during deviation studies when a reaction and subsequent precipitation were performed at 80 °C. The laboratory study indicated that filtrations were more rapid when precipitation was performed at 80 °C, and this was evaluated in the pilot plant. However, when this was performed, a white solid formed in the condenser and was found to be ammonium carbonate. After an intensive effort, in addition to ammonia and carbon dioxide, hexachloroacetone was isolated and traces of chloroform, carbon tetrachloride, and carbon monoxide were also found,[16] suggesting fragmentation of the ring; but despite many deliberate attempts, a greater degree of fragmentation could not be produced in laboratory-scale trials and, significantly, nitrogen trichloride was not detected. In terms of a mass balance, with the finding that ammonium carbonate is formed during some degradative pathway, the scrubber liquors were examined in the pilot plant and found to contain the outstanding nitrogen as ammonia. This reaction was performed on a 6.3 kg scale, giving a 93% yield of the stage 4 product **7**.

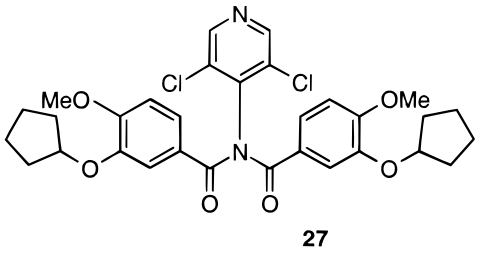
Derivation of Stage 5. The final stage in the synthesis of any new pharmaceutical agent is the most important since it is this stage which largely controls the quality of the resulting product. When clinical studies become advanced, the impurity profile should not change, and for this reason, it is beneficial to identify the best reaction conditions and subsequent purification procedure as early as possible. The discovery method of intimate fusion was instantly dismissed, but it was quickly appreciated why such conditions had been employed. When obvious amidification conditions were tried, no reaction occurred when the acid chloride **5** was added to a solution of the amine **7**. This was probably a consequence of the steric congestion around the amino functionality. In an attempt to make the amine more nucleophilic, deprotonation of the amine with a strong base seemed appropriate. Of the bases examined, only sodium hydride showed immediate promise, and with 1 molar equiv of sodium hydride, yields were modest. When pK_a's of the amine **7** and resulting amide **1** were calculated,[17] it became obvious that 2 mol of sodium hydride was required (Scheme 2).

Scheme 2



If only 1 equiv of sodium hydride was used, the greater acidity of the amide proton in **1** compared to the starting amine **7** led to a subsequent reaction with acid chloride **5**, giving the imide **27**, with a product ratio of 1:1:1 for **1**, **7**, and **27**.





Hence, to achieve high yields of product, it was necessary to use 2 equiv of sodium hydride. Thus, the amine **7** (1 equiv) was added to a suspension of the sodium hydride (2 equiv), giving the anion **25** (1 equiv) and unreacted sodium hydride (1 equiv). Upon addition of the acid chloride **5**, the anion **25** reacted to give the product **1**, which was spontaneously deprotonated by unreacted anion **25**,[18] giving the amide anion **26** with regeneration of amine **7**. Since excess sodium hydride was present, this regenerated amine **7** was immediately deprotonated, giving further anion **25**, which was more reactive than the anion **26**, resulting in a kinetically favoured reaction to give the desired product **1**.[19,20]

(14) If the concentration is allowed to fall significantly below 20% w/w, the reaction is incomplete and the 4-amino-3,5-dichloropyridine becomes contaminated with the monochlorinated derivative.

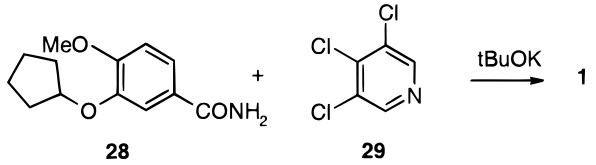
(15) Interestingly, this product sublimes even at ambient temperature and, if stored in a polythene bag, will penetrate the bag to leave the exterior coated with fine needles after a few months.

(16) This study was performed in part by Rhône-Poulenc Industrialisation at Décines in France.

(17) Using the CAMEO package, the pK_a of the amine **7** is 22 and the pK_a of the amide **1** is 11.

(18) Whether this deprotonation actually occurs by excess sodium hydride directly or by the anion was not established.

Scheme 3

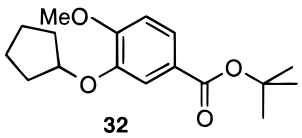


This reaction was simple, was conducted at ambient temperature, gave high yields, and was operated without problem on a 5.5 kg scale (of stage 4 product **7**). However, for industrialisation purposes, the lack of simple recyclability of wet tetrahydrofuran, the flammability of sodium hydride,[21] and the liberation of hydrogen gas gave cause for concern.

Respectable yields were obtained when the benzamide **28** was reacted with 3,4,5-trichloropyridine (**29**) in the presence of a strong base (Scheme 3), but this was a complete departure from the former reaction and was thus abandoned in favour of better reaction conditions for the established reaction.

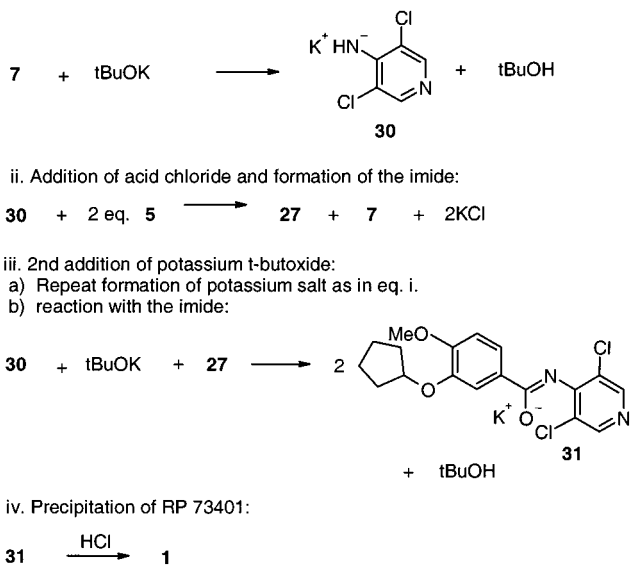
A wide variety of bases (to replace sodium hydride, and hence avoid the issues with liberation of hydrogen) were screened for the stage 5 reaction, but most (e.g., LDA, ^{n}BuLi, LHMDS, NaOMe) gave multicomponent mixtures. Only potassium *tert*-butoxide gave reasonable results, and optimisation of reaction conditions using this base quickly followed. The key to this reaction was the realisation that the reaction proceeded via the intermediate imide **27** (in contrast to the reaction with sodium hydride) (Scheme 4).

After the initial formation of the potassium salt **30**, the acid chloride **5** was added, giving the imide **27** and the amine **7** in equal amounts. A second charge of potassium *tert*-butoxide was then added to re-create the potassium salt **30**, which reacted with the imide to give the required product **1**. This entire reaction was best carried out in toluene at reflux; toluene was an ideal solvent for recoverability purposes. Two new impurities were created, the imide **27** and the *tert*-butyl ester **32** derived from the acid chloride **5** with butoxide, and



even though these were minor, levels of less than 0.1% w/w were ensured by including an additional crystallisation. Thus, at the end of the reaction when all salts had been removed during washes, the product was crystallised from the toluene before being recrystallised from the standard solvent used throughout for production of the drug substance

Scheme 4



(2-propanol). This procedure avoided all the issues raised with the sodium hydride method (especially explosion risk of hydrogen liberation and recoverability of the solvent). Despite the extra toluene crystallisation, the yield from the potassium *tert*-butoxide method was at least as good as the sodium hydride method, and this was operated on a 6.1 kg scale, giving an 84% yield of **1**.

Fortuitously, polymorphism was not a problem with this molecule **1**, and thus changes to the final stage were not an issue in this regard. Although the product **1** was being micronised for use in an inhaled formulation, the flow properties of the material were appalling. This physical property led to long feed times during micronisation and required several passes to achieve full micronisation. A typical batch of drug substance consisted of needles with a wide spread (typically 50−2000 μm). Better feed rates might be obtained if the drug substance could be produced possessing a much narrower range of particle size.

Careful examination of the crystallisation profile and seeding regime would be important to achieve the desired narrow range of particle size. Examination of the solubility curve allowed the metastable zone to be determined and thence the selection of an optimal temperature for seeding and a good cooling profile to be established. By using a simple equation,[22] the necessary quantity and particle size of the seed could be calculated. The acquisition of seed of uniform particle size was simple: a batch of micronised product had a narrow range of about 3 μm. Assuming a 100% yield from the recrystallisation, use of the simplistic equation suggests that 3 wt % of the micronised seed would give needles of about 100 μm. This was investigated in the laboratory and indeed produced material of precisely the desired result; small-scale micronisation trials subsequently confirmed good characteristics. Examination in different

(19) Despite the finding that the reaction proceeds via the imide **27** in some cases for other bases, we have no evidence that this is the case when sodium hydride is used. In fact, this is highly unlikely since none was ever detected as an intermediate (by TLC) during this method, and if the imide **27** was formed, it is likely that this would require more forcing conditions to convert it to the product **1** (by analogy with the potassium salt, discussed later).

(20) The acidity of the amide proton in the final product **1** is of interest and had a measured pK_a value of 9.3. This enabled us to isolate the sodium salt (and the potassium salt) as well-defined crystalline solids.

(21) Although sodium hydride can be supplied in solvent-soluble bags, which avoids handling issues, use in the final stage of the process was perceived to be a problem due to the uncertain fate of the soluble bags.

(22) The simplified equation is $m_s = m_c(d_s/d_c)^i$, where m_s and d_s are the mass and size of seed; m_c and d_c are the mass and size of the crystals obtained; and i is equal to 1 for needles (growth in one dimension), 2 for plates (growth in two dimensions), and 3 for cubes/spheres (growth in 3 dimensions).

vessel geometries in the laboratory demonstrated good reproducibility, and this was confirmed on a 25 kg scale in the pilot plant.

Conclusion

The synthesis of the PDE IV inhibitor **1** has been scaled up in the pilot plant using a safe, cheap, high-yielding, environmentally friendly procedure to generate multikilo quantities of material for extensive clinical trials.

Experimental Section

^{1}H NMR spectra were recorded at 200 or 400 MHz on Varian XL-200 or VXR 400 instruments and are reported in parts per million downfield from tetramethylsilane as the internal reference. Unless otherwise stated, NMR spectra were measured in deuteriochloroform. Melting points were recorded on a Gallenkamp 595 apparatus and are uncorrected. Elemental analyses were determined using a Carlo-Erba elemental analyser model 1106. Where products were purified by flash chromatography, the separations were performed using Merck Kieselgel 60 (230−400 mesh). Concentration and evaporation refers to the removal of volatile materials under reduced pressure (10−15 mmHg at 25−70 °C) on a Heidolph or Buchi rotary evaporator.

Experimental details for the discovery methods used for stages 1−5 are described elsewhere.[1]

Stage 1: 3-(Cyclopentyloxy)-4-methoxybenzaldehyde (3). *First Process Chemistry Method.* 3-Hydroxy-4-methoxybenzadehyde **2** (20.0 g, 0.131 mol) was added to a stirred suspension of potassium carbonate (27.2 g, 0.197 mol) in dry *N*,*N*-dimethylformamide (100 mL) under an inert atmosphere. The suspension was warmed to 65 °C, and cyclopentyl bromide (25.5 g, 0.171 mol) was added over a period of 0.25 h. The resulting mixture was stirred at 65 °C (8 h) and then diluted with toluene (250 mL). The mixture was extracted with aqueous sodium hydroxide solution (2 × 100 mL of a 1 M solution), and the combined extracts were then back-extracted with toluene (100 mL). The combined toluene solutions were washed with water (3 × 100 mL), and the solution was then evaporated under reduced pressure (rotary evaporator) to give 3-(cyclopentyloxy)-4-methoxybenzaldehyde (**3**) (25.5 g, 84%) as a light brown oil. A sample was purified by high-vacuum distillation to give 3-(cyclopentyloxy)-4-methoxybenzaldehyde (**3**) as a colourless liquid, bp 140 °C at 0.6 mmHg. ^{1}H NMR: δ 1.6−2.1 (m, 8H), 3.93 (s, 3H), 4.87 (m, 1H), 6.95 (d, 1H, J = 9 Hz), 7.42 (m, 2H), 9.84 (s, 1H). Anal. Calcd for $C_{13}H_{16}O_3$: C, 70.89; H, 7.32. Found: C, 71.0; H, 7.4.

Second Process Chemistry Method. 3-Hydroxy-4-methoxybenzadehyde (**2**) (608.0 g, 4.0 mol) was added to a stirred suspension of anhydrous potassium carbonate (938.4 g, 6.8 mol) in denatured ethanol (4000 mL) under an inert atmosphere. The suspension was heated to reflux and maintained at reflux whilst cyclopentyl bromide (894 g, 6.0 mol) was added over a period of 0.25 h. The resulting mixture was stirred at reflux (8 h) and then diluted with water (1500 mL). Distillation was then commenced (at atmospheric pressure), and the distillate (1500 mL) was collected. Further water (1500 mL) was then added, and further distillate (1500 mL) was collected. The addition/distillation regime was repeated once more, and the vapour temperature approached that of water (99 °C). The batch was cooled (70 °C) and then extracted with toluene (1320 mL). This extract was dried by azeotropic distillation to give 3-(cyclopentyloxy)-4-methoxybenzaldehyde (**3**) (1995.6 g at 42.1% w/w ≡ 840.8 g, 95.5%) as a light brown solution in toluene.

Stage 2: 3-(Cyclopentyloxy)-4-methoxybenzoic acid (4). *First Process Chemistry Method.* 3-(Cyclopentyloxy)-4-methoxybenzaldehyde (**3**) (115.0 g, 0.522 mol) was added to a stirred suspension of sulphamic acid (69.0 g, 0.711 mol) in aqueous acetic acid (900 mL of an 80% solution). A solution of 80% sodium chlorite (61.0 g, 0.54 mol) in water (250 mL) was then added over a period of 1.25 h while the temperature was maintained at about 20 °C with cooling. The mixture was then stirred (1 h) and then diluted with water (900 mL), which was added over 0.5 h. The suspension was then filtered, and the solid was washed with water (3 × 900 mL) and dried to give 3-(cyclopentyloxy)-4-methoxybenzoic acid (**4**) (113.5 g, 92%) as a white solid, mp 166−168 °C. ^{1}H NMR: δ 1.7 (s, 2H), 1.8−2.2 (m, 6H), 3.95 (s, 3H), 4.85 (m, 1H), 6.9 (br s, 1H), 7.6 (br s, 1H), 7.8 (s, 1H), 9.8 (s, 1H). Anal. Calcd for $C_{13}H_{16}O_4$: C, 66.1; H, 6.8. Found: C, 65.6; H, 6.8.

Second Process Chemistry Method. A solution of 3-(cyclopentyloxy)-4-methoxybenzaldehyde (**3**) in toluene (251.8 g of a 41.2% w/w solution ≡ 103.6 g, 0.471 mol) was added to water (250 mL), the mixture was heated at reflux, and the toluene/water azeotrope was removed whilst the lower water layer was returned to the vessel. This distillation was continued until all traces of toluene had been removed. The mixture was cooled to 45 °C and the agitation speed adjusted to give an emulsion. The pH of the mixture was adjusted to 11.5 with 35% w/v aqueous sodium hydroxide solution, and then 35% w/w hydrogen peroxide solution (735.5 g, 7.57 mol) was added (by metered addition) over 9 h whilst the pH was maintained at 11.5 ± 0.5 by constant addition of 35% w/v aqueous sodium hydroxide solution and the temperature was maintained at 45 ± 5 °C. The mixture was then stirred at 45 °C (0.5 h) and was then washed with toluene (150 mL). Additional toluene (800 mL) was then added with stirring followed by concentrated hydrochloric acid solution until the pH was 1−2. The mixture was then heated to 70 °C and stirred (0.25 h) and the lower aqueous layer then removed. The toluene phase was then washed with water (800 mL), and toluene (500 mL) was removed by distillation to concentrate and dry the batch. The batch was then cooled to 5 °C over 2.5 h with stirring, and the solid which crystallised was filtered, washed with cold toluene (50 mL), and then dried to give 3-(cyclopentyloxy)-4-methoxybenzoic acid (**4**) (98.7 g, 88.8%) as a white solid.

Stage 3: 3-(Cyclopentyloxy)-4-methoxybenzoyl Chloride (5). *First Process Chemistry Method.* 3-(Cyclopentyloxy)-4-methoxybenzoic acid (**4**) (110 g, 0.466 mol) was added to toluene (1000 mL) with stirring and the system azeodried by distillation of toluene (50 mL). The solution was then allowed to cool (90 °C), and dry *N*,*N*-dimethyl-

formamide (0.8 mL) was added, followed by thionyl chloride (45 mL, 0.62 mol), which was added over 0.25 h. The solution was then heated at reflux with stirring (5 h). The mixture was then cooled to ambient temperature and concentrated under reduced pressure to give a pale yellow oil, which slowly crystallised upon standing, giving 3-(cyclopentyloxy)-4-methoxybenzoyl chloride (**5**) (117 g, 98%) as an off-white solid, mp 44−45 °C. ^{1}H NMR: δ 1.6−1.7 (m, 2H), 1.8−1.95 (m, 4H), 1.95−2.05 (m, 2H), 3.94 (s, 3H), 4.85 (m, 1H), 6.92 (d, 1H, J = 9 Hz), 7.55 (d, 1H, J = 1 Hz), 7.82 (d,d, 1H, J = 1, 9 Hz). Anal. Calcd for $C_{13}H_{15}ClO_3$: C, 61.3; H, 5.94; Cl, 13.92. Found: C, 61.6; H, 6.07; Cl, 13.9.

Second Process Chemistry Method. 3-(Cyclopentyloxy)-4-methoxybenzoic acid (**4**) (135.5 g, 0.574 mol) was added to toluene (900 mL) with stirring under an inert atmosphere and the system dried by distillation of toluene (125 mL). Dry *N*,*N*-dimethylformamide (1 g) was then added, followed by thionyl chloride (76.53 g, 0.643 mol), which was added over 2 h whilst gentle reflux was maintained. The solution was then heated at reflux for an additional period (0.5 h) and the batch then concentrated by distillation of toluene/thionyl chloride (450 mL) at atmospheric pressure, giving 3-(cyclopentyloxy)-4-methoxybenzoyl chloride (**5**) (144.8 g at 32.8% ≡ 99%) as a light brown solution in toluene.

Stage 4: 4-Amino-3,5-dichloropyridine (7). *First Process Chemistry Method.* 4-Aminopyridine (**6**) (94 g, 1.0 mol) was dissolved in concd HCl (710 mL of a 37% w/w solution, 8.5 mol) and the mixture heated to 80 °C with stirring. Sodium hypochlorite solution (1100 mL of an aqueous solution having 14−15% available chlorine, 2.2 mol) was added slowly over 2 h whilst the temperature was maintained at about 80 °C. The solution was then cooled to about 30 °C and was basified by addition of aqueous sodium hydroxide solution (600 mL of sp gr 1.3) over 0.5 h. The slurry was then chilled (10 °C), the solid collected by filtration, washed with water (3 × 600 mL), and dried to give 4-amino-3,5-dichloropyridine (**7**) (132.1 g, 81%) as an off-white solid, mp 161.5−162.5 °C (lit.[23] mp 161 °C). ^{1}H NMR: δ 5.0 (br s, 2H), 8.2 (s, 2H). Anal. Calcd for $C_5H_4Cl_2N_2$: C, 36.84; H, 2.47; Cl, 43.50; N, 17.19. Found: C, 36.6; H, 2.4; Cl, 43.8; N, 17.2.

Second Process Chemistry Method. 4-Aminopyridine (**6**) (73.7 g, 0.784 mol) was dissolved in concd HCl (735.8 g of a 37% w/w solution, 7.06 mol) by addition over 0.25 h at 10 °C with stirring. The solution was then heated to 72 ± 3 °C, and hydrogen peroxide solution (228.5 g of a 35% w/w solution ≡ 2.35 mol) was added over 2.5 h and the mixture then stirred at 72 ± 3 °C for an additional 0.5 h. The solution was then cooled to about 45 °C, and aqueous sodium hydroxide solution (sp gr 1.3) was then added over 0.5 h until a pH of 9−10 was reached. Stirring was then continued (0.5 h), and the resulting white solid was collected by filtration. The solid product was washed (3 × 300 mL) and then dried, giving 4-amino-3,5-dichloropyridine (**7**) (118.4 g, 92.7%) as a white solid.

Stage 5: 3-(Cyclopentyloxy)-*N*-(3,5-dichloropyrid-4-yl)-4-methoxybenzamide (1). *First Process Chemistry Method*. Sodium hydride (9.6 g of a 60% dispersion in oil, 0.24 mol) was suspended in dry tetrahydrofuran (100 mL) at ambient temperature. A solution of 4-amino-3,5-dichloropyridine (**7**) (16.3 g, 0.1 mol) in dry tetrahydrofuran (160 mL) was then added slowly over 0.25 h with cooling to maintain an internal temperature of 20 ± 5 °C (**CAUTION:** hydrogen gas liberated). After stirring for an additional 0.25 h, the mixture was cooled to 7 ± 3 °C and treated with the dropwise addition of a solution of 3-(cyclopentyloxy)-4-methoxybenzoyl chloride (**5**) (26.8 g, 0.105 mol) in tetrahydrofuran (160 mL) over a period of 1 h whilst the temperature was maintained at 7 ± 3 °C (**CAUTION:** hydrogen gas liberated). The mixture was stirred for an additional 0.5 h and then was quenched by the careful slow addition of 1 M hydrochloric acid (200 mL), which was added over a period of 0.5 h, the temperature being kept below 25 °C (**CAUTION:** hydrogen gas liberated). Dichloromethane (300 mL) was added and the organic phase collected. The aqueous phase was extracted with dichloromethane (100 mL), and the organic phases were combined and washed successively with water (200 mL), 10% aqueous sodium carbonate solution (200 mL), and then water (200 mL) before being dried over magnesium sulfate. The solution was evaporated, and the solid residue was recrystallised from 2-propanol (300 mL), giving 3-(cyclopentyloxy)-*N*-(3,5-dichloropyrid-4-yl)-4-methoxybenzamide (**1**) (26.4 g, 69%) as an off-white solid, mp 155−157 °C (lit.[1] mp 155−157 °C). ^{1}H NMR: δ 1.55−2.05 (m, 8H), 3.93 (s, 3H), 4.87 (m, 1H), 6.95 (d, 1H, J = 8 Hz), 6.98−7.53 (m, 2H), 7.65 (s, 1H), 8.56 (s, 2H). Anal. Calcd for $C_{18}H_{18}Cl_2N_2O_3$: C, 56.7; H, 4.76; Cl, 18.6; N, 7.35. Found: C, 56.3; H, 4.7; Cl, 18.4; N, 7.2.

Second Process Chemistry Method. 4-Amino-3,5-dichloropyridine (**7**) (35.86 g, 0.22 mol) was added to toluene (440 mL), and the stirred mixture was heated to reflux. Toluene (35 mL) was distilled to azeodry the system, and then the solution was cooled to 90 °C while potassium *tert*-butoxide (24.42 g, 0.218 mol) was added with stirring. The mixture was then heated at reflux (0.5 h), and then a solution of 3-(cyclopentyloxy)-4-methoxybenzoyl chloride (**5**) (50.9 g, 0.2 mol) in toluene (110 mL) was added over a period of 1 h whilst the mixture was maintained at reflux. Reflux was continued (1 h), and then the mixture was allowed to cool to 90 °C while potassium *tert*-butoxide (24.42 g, 0.218 mol) was added. The mixture was again heated at reflux (4 h) and then cooled to 70 °C. Water (100 mL) was added, followed by concentrated hydrochloric acid (25 mL). The mixture was rewarmed to 80 °C (giving two clear liquid phases) and the lower aqueous phase removed. The organic phase was washed at 80 °C with hot water (50 mL) and then washed at 80 °C with a solution of sodium hydrogen carbonate (1.5 g) in water (45 mL). The solution was then concentrated by distillation at atmospheric pressure (total distillate removed was 160 mL) and the solution allowed to cool to ambient temperature and then chilled (5 °C). The solid which had separated was collected, washed with cold

(23) Sell, W. J. *J. Chem. Soc.* **1911**, *99*, 1683.

toluene (40 mL), dried, and then recrystallised from 2-propanol (715 mL), giving 3-(cyclopentyloxy)-*N*-(3,5-dichloropyrid-4-yl)-4-methoxybenzamide (**1**) (64.0 g, 84%) as an off-white solid.

Alternative Route. Potassium *tert*-butoxide (1.4 g, 0.0125 mol) was added to a stirred suspension of 3-(cyclopentyloxy)-4-methoxybenzamide (**28**)[24] (2.58 g, 0.011 mol) in toluene (40 mL) at reflux. 3,4,5-Trichloropyridine (**29**)[25] (1.82 g, 0.01 mol) was then added and the mixture heated at reflux (4 h). More potassium *tert*-butoxide (1.4 g, 0.0125 mol) was added and reflux continued (7 h). The mixture was then allowed to cool and was filtered. The filtrate was evaporated, and the residue was extracted with aqueous sodium hydroxide solution (2 × 50 mL). The alkaline extract was then acidified (AcOH), and the solid which separated was washed with water and dried, giving 3-(cyclopentyloxy)-*N*-(3,5-dichloropyrid-4-yl)-4-methoxybenzamide (**1**) (2.09 g, 49.9%) as a buff solid.

2-Cyclopentyl-3-(cyclopentyloxy)-4-methoxybenzaldehyde (8). The still residue (40 g) from the distillation which afforded compound **2** in an analytically pure state was subjected to flash chromatography using a mixture of 6:1 cyclohexane/ethyl acetate as eluent. The relevant fractions were combined and the solvent evaporated under reduced pressure to give 2-cyclopentyl-3-(cyclopentyloxy)-4-methoxybenzaldehyde (**8**) (5.7 g) as a brown solid, mp 49−53 °C. ^{1}H NMR: δ 1.57−2.18 (m, 16H), 3.85−3.98 (m, 1H), 3.91 (s, 3H), 4.73−4.77 (m, 1H), 6.84 (d, 1H, J = 8 Hz), 7.74 (d, 1H, J = 8 Hz), 10.33 (s, 1H).

3-(Cyclopentyloxy)-4-methoxybenzaldehyde Diethyl Acetal (9). 4-Toluenesulfonic acid monohydrate (2.5 g, 0.0132 mol) was added to a solution of 3-(cyclopentyloxy)-4-methoxybenzaldehyde (**3**) (41 g, 0.186 mol) in ethanol (125 mL) containing triethyl orthoformate (125 mL). The mixture was then heated at reflux (2 h) when further triethyl orthoformate (50 mL) was added. Reflux was continued (1 h), and then the mixture was allowed to cool to ambient temperature. The mixture was diluted with dichloromethane (1 L) and was then washed with a 1:1 mixture of 5% aqueous sodium hydroxide solution and brine (2 × 100 mL) and then with brine (100 mL). The solution was dried ($MgSO_4$) and evaporated under reduced pressure. The mobile oil was then fractionally distilled under high vacuum, giving 3-(cyclopentyloxy)-4-methoxybenzaldehyde diethyl acetal (**9**) (46.1 g, 84.3%) as a pale yellow liquid, bp 136 °C at 0.4 mmHg. ^{1}H NMR: δ 1.23 (t, 6H, J = 8 Hz), 1.55−1.65 (m, 2H), 1.76−1.98 (m, 6H), 3.46−3.65 (m, 4H), 3.83 (s, 3H), 4.77−4.82 (m, 1H), 5.42 (s, 1H), 6.82 (d, 1H, J = 8 Hz), 6.98 (d,d, 1H, J = 8, 2 Hz), 7.01 (d, 1H, J = 2 Hz). Anal. Calcd for $C_{17}H_{26}O_4$: C, 69.39; H, 8.84. Found: C, 68.9; H, 8.86.

4,5-Bis(cyclopentyloxy)-9-(3-(cyclopentyloxy)-4-methoxyphenyl)-9*H*-2,7-xanthenedicarboxaldehyde (10). The still residue (40 g) from the distillation which afforded compound **2** in an analytically pure state was subjected to flash chromatography using a mixture of 6:1 cyclohexane/ethyl acetate as eluent. The relevant fractions were combined, and the solvent was evaporated under reduced pressure to give a brown solid, which was triturated with *tert*-butyl methyl ether (50 mL), then filtered off, washed with *tert*-butyl methyl ether (3 × 20 mL), and then dried, giving 4,5-bis(cyclopentyloxy)-9-(3-(cyclopentyloxy)-4-methoxyphenyl)-9*H*-2,7-xanthenedicarboxaldehyde (**10**) (2.7 g) as an off-white solid, mp 209−211 °C. ^{1}H NMR (CD_3SOCD_3): δ 1.50−1.99 (m, 24H), 3.67 (s, 3H), 4.65−4.70 (m, 1H), 5.04−5.08 (m, 2H), 5.52 (s, 1H), 6.65 (d,d, 1H, J = 8, 2 Hz), 7.83−7.86 (m, 2H), 7.34 (d, 2H, J = 2 Hz), 7.43 (d, 2H, J = 2 Hz), 9.82 (s, 2H). Anal. Calcd for $C_{37}H_{40}O_7$: C, 74.4; H, 6.76. Found: C, 74.8; H, 6.88. MS: m/z 597 ($M^{+\bullet}$).

3-(Cyclopentyloxy)-4-methoxyphenol (11). Sodium perborate tetrahydrate (3.4 g, 22 mmol) was added to a hot (75 °C) stirred solution of 3-(cyclopentyloxy)-4-methoxybenzaldehyde (**3**) (2.59 g, 11.8 mmol) in glacial acetic acid (20 mL). After stirring at 75 °C for an additional 2 h, the mixture was diluted with water (125 mL) and extracted with toluene (2 × 50 mL). The dark brown combined extract was washed with aqueous sodium bicarbonate solution (100 mL), then was dried ($MgSO_4$), and was evaporated under reduced pressure, giving a dark brown oil (2.8 g), which was purified by flash chromatography (9:1, cyclohexane/ethyl acetate). The relevant fractions were collected and combined, and the solvent was evaporated. The resulting solid residue was recrystallised (cyclohexane), giving 3-(cyclopentyloxy)-4-methoxyphenol (**11**) (0.9 g, 37%) as a buff solid, mp 110−111 °C. ^{1}H NMR: δ 1.53−1.65 (m, 2H), 1.75−1.96 (m, 6H), 3.78 (s, 3H), 4.68−4.74 (m, 1H), 6.31 (d,d, 1H, J = 8, 2 Hz), 6.46 (d, 1H, J = 2 Hz), 6.73 (d, 1H, J = 8 Hz) (O*H* not visible). Anal. Calcd for $C_{12}H_{16}O_3$: C, 69.21; H, 7.74. Found: C, 69.3; H, 7.9.

2-Cyclopentyl-3-(cyclopentyloxy)-4-methoxybenzoic Acid (13). A solution of sodium chlorite (0.83 g, 7.3 mmol) in water (5 mL) was added slowly over 0.5 h to a stirred solution of 2-cyclopentyl-3-(cyclopentyloxy)-4-methoxybenzaldehyde (**8**) (2.0 g, 6.94 mmol) and sulfamic acid (0.92 g, 9.4 mmol) in glacial acetic acid (15 mL), the temperature being kept below 20 °C. After stirring (1 h), the mixture was diluted with water (25 mL) and a pale brown oil separated. The upper aqueous phase was decanted, and the oil was washed with water (2 × 15 mL) and was then dissolved in dichloromethane (80 mL). The organic solution was washed with water (20 mL) and was then dried ($MgSO_4$) and evaporated. The residue was subjected to flash chromatography (silica gel, 74:25:1 cyclohexane/ethyl acetate/acetic acid as eluent), and the relevant fractions were combined and evaporated, giving 2-cyclopentyl-3-(cyclopentyloxy)-4-methoxybenzoic acid (**13**) (0.8 g, 38%) as an off-white solid, mp 101−103 °C. ^{1}H NMR: δ 1.52−2.11 (m, 16H), 4.80−4.95 (m, 4H), 6.77 (d, 1H, J = 8 Hz), 7.61 (d, 1H, J = 8 Hz). Anal. Calcd for $C_{18}H_{24}O_4$: C, 71.0; H, 7.95. Found: C, 70.5; H, 8.02.

2-Cyclopentyl-3-(cyclopentyloxy)-*N*-(3,5-dichloropyrid-4-yl)-4-methoxybenzamide (14). A solution of 2-cyclo-

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pentyl-3-(cyclopentyloxy)-4-methoxybenzoic acid (**13**) (0.63 g, 2.1 mmol) in toluene (10 mL) containing thionyl chloride (3 mL) and *N*,*N*-dimethylformamide (2 drops) was heated under reflux (2 h). The mixture was then evaporated to dryness under reduced pressure to give crude 2-cyclopentyl-3-(cyclopentyloxy)-4-methoxybenzoyl chloride (assumed 100% yield).

4-Amino-3,5-dichloropyridine (**7**) (0.49 g, 3 mmol) was added to a stirred suspension of sodium hydride (0.48 g of 60% w/w in oil, 12 mmol) in dry tetrahydrofuran (8 mL) at 0−10 °C. After stirring (0.5 h), a solution of crude 2-cyclopentyl-3-(cyclopentyloxy)-4-methoxybenzoyl chloride (0.67 g, 2.1 mmol) in dry tetrahydrofuran (10 mL) was added slowly over a period of 5 min. This mixture was then stirred (1 h) before cooling to 0 °C and quenching by the cautious addition of concentrated hydrochloric acid (7 mL). Dichloromethane (50 mL) was then added, and after stirring (0.25 h), the organic phase was collected, washed with brine (20 mL), then dried ($MgSO_4$), and evaporated to a brown oil, which was subjected to flash chromatography (2:1 cyclohexane/ethyl acetate as eluent). The fractions corresponding to the major product were combined, and the solvent was evaporated. The resulting solid residue was recrystallised from 2-propanol (2 mL), giving 2-cyclopentyl-3-(cyclopentyloxy)-*N*-(3,5-dichloropyrid-4-yl)-4-methoxybenzamide (**14**) (0.23 g, 24.5%) as a white solid, mp 141−142 °C. ^{1}H NMR: δ 1.53−1.93 (m, 14H), 2.01−2.16 (m, 2H), 3.54−3.70 (m, 1H), 3.88 (s, 3H), 4.93−5.00 (m, 1H), 6.80 (d, 1H, J = 8 Hz), 7.83 (d, 1H, J = 8 Hz), 7.41 (s,br, 1H), 8.58 (s, 1H). Anal. Calcd for $C_{23}H_{26}Cl_2N_2O_3$: C, 61.47; H, 5.83; N, 6.23. Found: C, 61.44; H, 5.81; N, 6.06.

3-(Cyclopentyloxy)-4-methoxybenzyl Alcohol (15). Sodium borohydride (1.17 g, 30.9 mmol) was added to a stirred solution of 3-(cyclopentyloxy)-4-methoxybenzaldehyde (**3**) (16.85 g, 76.6 mmol) in ethanol (125 mL) at ambient temperature. The exothermic reaction raised the temperature to 40 °C, and this temperature was maintained (1 h). The mixture was then evaporated and the residue extracted with dichloromethane (150 mL). The solution was washed with brine, then dried ($MgSO_4$), and evaporated under reduced pressure and then under high vacuum to give 3-(cyclopentyloxy)-4-methoxybenzyl alcohol (**15**) (15.2 g, 89%) as a pale brown oil. ^{1}H NMR: δ 1.57−1.66 (m, 2H), 1.79−2.00 (m, 6H), 3.84 (s, 3H), 4.61 (s, 2H), 4.77−4.82 (m, 1H), 6.84 (d, 1H, J = 8 Hz), 6.88 (d,d, 1H, J = 8, 2 Hz), 6.92 (d, 1H, J = 2 Hz). Anal. Calcd for $C_{13}H_{18}O_3$: C, 70.24; H, 8.16. Found: C, 70.0; H, 7.88.

3-(Cyclopentyloxy)-4-methoxybenzoyl Anhydride (17). Triethylamine (6.0 g, 60 mmol) was added dropwise to a stirred solution of 3-(cyclopentyloxy)-4-methoxybenzoic acid (**4**) (9.5 g, 40 mmol) and 3-(cyclopentyloxy)-4-methoxybenzoyl chloride (**5**) (10.4 g, 40 mmol) in dichloromethane (100 mL) over a period of 5 min. The mixture was stirred at ambient temperature (4 h) and was then evaporated under reduced pressure. The residue was triturated with water (100 mL) and was quickly filtered off, washed with water (2 × 50 mL), and then dried under vacuum. The solid (18.2 g) was then recrystallised from toluene (80 mL) to give 3-(cyclopentyloxy)-4-methoxybenzoyl anhydride (**17**) (10.6 g, 57%) as a pale brown solid, mp 149−151 °C. ^{1}H NMR: δ 1.58−1.69 (m, 4H), 1.79−2.04 (m, 12H), 3.94 (s, 6H), 4.83−4.88 (m, 2H), 6.92 (d, 2H, J = 8 Hz), 7.62 (d, 2H, J = 2 Hz), 7.76 (d,d, 2H, J = 8, 2 Hz). Anal. Calcd for $C_{26}H_{30}O_7$: C, 68.7; H, 6.65. Found: C, 68.3; H, 6.72.

3-((Dimethylcarbamoyl)oxy)-4-methoxybenzoic Acid (18). A mixture of methyl 3-((dimethylcarbamoyl)oxy)-4-methoxybenzoate (**19**) (0.5 g, 2 mmol) and sodium hydroxide (0.08 g, 2 mmol) in methanol (10 mL) and water (2 mL) was stirred at 40 °C until solution was complete when the mixture was allowed to stand at ambient temperature(18 h). The mixture was poured into water (150 mL) and extracted with dichloromethane (2 × 50 mL). The aqueous phase was then acidified (acetic acid) and then extracted with dichloromethane (2 × 50 mL). The extract was washed with water (150 mL), then dried ($MgSO_4$), and evaporated under reduced pressure. The residue was dissolved in dichloromethane (5 mL) and diluted with *tert*-butyl methyl ether (20 mL). The solution was concentrated under reduced pressure to about one-quarter volume, and the solid which separated was collected, washed with *tert*-butyl methyl ether (2 × 1 mL), and then dried, giving 3-((dimethylcarbamoyl)oxy)-4-methoxybenzoic acid (**18**) (0.28 g, 59%) as a white solid, mp 152−154 °C. ^{1}H NMR: δ 3.02 (s, 3H), 3.13 (s, 3H), 3.90 (s, 3H), 6.99 (d, 1H, J = 8 Hz), 7.82 (d, 1H, J = 2 Hz), 7.97 (d,d, 1H, J = 8, 2 Hz). Anal. Calcd for $C_{11}H_{13}NO_5$: C, 55.23; H, 5.48; N, 5.86. Found: C, 54.81; H, 5.5; N, 6.26.

Methyl 3-((Dimethylcarbamoyl)oxy)-4-methoxybenzoate (19). Sodium hydride (1.0 g, 25 mmol of a 60% dispersion in oil) was added to a stirred solution of methyl 3-hydroxy-4-methoxybenzoate (4.55 g, 25 mmol) in dry tetrahydrofuran (70 mL) at ambient temperature (**CAUTION:** hydrogen gas liberated). After stirring (10 min), dimethylcarbamoyl chloride (4.03 g, 37.5 mmol) was added and the homogeneous solution left to stir at ambient temperature (6 h). Diisopropylethylamine (1 mL) was then added and the mixture left to stand at ambient temperature (60 h). The mixture was then poured into water (500 mL) and extracted with dichloromethane (2 × 100 mL). The organic extract was washed with saturated aqueous potassium carbonate solution (100 mL), then dried ($MgSO_4$), and evaporated under reduced pressure. The resulting oil was dissolved in dichloromethane (10 mL), and *tert*-butyl methyl ether (40 mL) was slowly added with stirring. The solid which separated was collected, washed with *tert*-butyl methyl ether (2 × 10 mL), and then dried, giving methyl 3-((dimethylcarbamoyl)oxy)-4-methoxybenzoate (**19**) (4.5 g, 71%) as a white solid, mp 124−125 °C. ^{1}H NMR: δ 3.02 (s, 3H), 3.13 (s, 3H), 3.87 (s, 3H), 3.89 (s, 3H), 6.97 (d, 1H, J = 8 Hz), 7.77 (d, 1H, J = 2 Hz), 7.91 (d,d, 1H, J = 8, 2 Hz). Anal. Calcd for $C_{12}H_{15}NO_5$: C, 56.91; H, 5.97; N, 5.53. Found: C, 57.43; H, 5.87; N, 5.95.

***N*-(3,5-Dichloropyrid-4-yl)-3-((dimethylcarbamoyl)-oxy)-4-methoxybenzamide (20).** *N*-(3,5-Dichloropyrid-4-yl)-3-hydroxy-4-methoxybenzamide[26] (5.0 g, 0.016 mol) was added to a stirred suspension of potassium carbonate (3.31

g, 0.024 mol) in ethanol (30 mL) at ambient temperature. *N*,*N*-Dimethylcarbamoyl chloride (2.06 g, 0.019 mol) was then added and the mixture heated at reflux (4 h). Additional *N*,*N*-dimethylcarbamoyl chloride (2.06 g, 0.019 mol) was added and reflux continued (4 h). Additional ethanol (20 mL) was added, and the hot suspension was filtered. The solid was washed with hot ethanol (20 mL), and the filtrate was chilled to 0 °C. The solid which separated was collected and dried, giving *N*-(3,5-dichloropyrid-4-yl)-3-((dimethylcarbamoyl)oxy)-4-methoxybenzamide (**20**) (3.93 g, 64%) as a white solid, mp 197−198 °C. ^{1}H NMR (CD_3SOCD_3): δ 2.92 (s, 3H), 3.08 (s, 3H), 3.89 (s, 3H), 7.29 (d, 1H, J = 8 Hz), 7.78 (d, 1H, J = 2 Hz), 7.94 (d,d, 1H, J = 8, 2 Hz), 8.75 (s, 2H). Anal. Calcd for $C_{16}H_{15}Cl_2N_2O_4$: C, 50.1; H, 3.94; N, 10.94. Found: C, 49.66; H, 3.89; N, 10.89.

4-Amino-3-bromo-5-chloropyridine (21). Bromine (9.3 g, 58 mmol) was added to a stirred suspension of 4-amino-3-chloropyridine (**23**) (6.4 g, 50 mmol) in glacial acetic acid (50 mL) and the mixture stirred at ambient temperature (1.5 h). The mixture was then evaporated under reduced pressure and the residue then stirred in aqueous sodium hydroxide solution (1.5 h). The resulting solid was collected and dissolved in hot ethanol (20 mL). Hot water (20 mL) was added and the solution allowed to cool to ambient temperature. The resulting crystalline solid was collected, washed with 1:1 2-propanol/water (20 mL) and then water (2 × 20 mL), and dried under reduced pressure, giving 4-amino-3-bromo-5-chloropyridine (**21**) (5.7 g, 55%) as a pale brown solid, mp 122−124 °C. ^{1}H NMR: δ 5.04 (br,s, 2H), 8.21 (s, 1H), 8.80 (s, 1H). Anal. Calcd for $C_5H_4BrClN_2$: C, 29.0; H, 1.94; Br, 38.3; N, 13.5. Found: C, 28.8; H, 1.9; Br, 38.5; N, 13.7.

***N*-(3-Bromo-5-chloropyrid-4-yl)-3-(cyclopentyloxy)-4-methoxybenzamide (22).** A solution of 4-amino-3-bromo-5-chloropyridine (**21**) (10.0 g, 48 mmol) in tetrahydrofuran (100 mL) was added slowly to a stirred suspension of a 60% dispersion of sodium hydride in oil (5.4 g, 135 mmol) in tetrahydrofuran (30 mL) while the temperature was kept below 20 °C (**CAUTION:** hydrogen gas liberated). After additional stirrring (0.5 h), the mixture was cooled to 5 °C and was treated with a solution of 3-(cyclopentyloxy)-4-methoxybenzoyl chloride (**5**) (12.2 g, 48 mmol) in tetrahydrofuran (50 mL), the temperature being kept at 5−10 °C (**CAUTION:** hydrogen gas liberated). After additional stirring (0.5 h), the mixture was cautiously quenched by the slow addition of a solution of concentrated hydrochloric acid (20 mL) in water (40 mL) whilst the cooling was maintained (**CAUTION:** hydrogen gas liberated). The upper organic phase was collected, washed with brine, and evaporated under reduced pressure. The residue was recrystallised (2-propanol), giving *N*-(3-bromo-5-chloropyrid-4-yl)-3-(cyclopentyloxy)-4-methoxybenzamide (**22**) (10.8 g, 53%) as a pale brown solid, mp 132−134 °C. ^{1}H NMR: δ 1.58−1.68 (m, 2H), 1.78−2.04 (m, 6H), 3.93 (s, 3H), 4.85−4.90 (m, 1H), 6.93 (d, 1H, J = 8 Hz), 7.50 (d,d, 1H, J = 8, 2 Hz), 7.52 (d, 1H, J = 2 Hz), 7.76 (s br, 1H), 8.57 (s, 1H), 8.67 (s, 1H). Anal. Calcd for $C_{18}H_{18}BrClN_2O_3$: C, 50.8; H, 4.26; Br, 18.8; N, 6.58. Found: C, 50.8; H, 4.24; Br, 18.6; N, 6.53;

4-Amino-3-chloropyridine (23). Sodium hypochlorite solution (200 mL of a solution having 15% available chlorine) was added slowly to a stirred solution of 4-aminopyridine (**6**) (47 g, 0.5 mol) in concentrated hydrochloric acid (500 mL) over a period of 1 h while the temperature was maintained at 20−30 °C. After additional stirring (0.5 h), the solution was basified to pH 10 with aqueous sodium hydroxide solution and the mixture was extracted with dichloromethane (2 × 300 mL). The combined extract was washed (water), dried ($MgSO_4$), and evaporated to an oily residue, which was purified by flash chromatography (ethyl acetate as eluent). The relevant fractions were combined, and the solvent was removed by evaporation, to give 4-amino-3-chloropyridine (**23**) (23.1 g, 36%) as an off-white solid, mp 62 °C (lit.[25] mp 60.5−61.5 °C). ^{1}H NMR: δ 5.08 (bs, 2H), 6.65 (d, 1H, J = 6 Hz), 8.06 (d, 1H, J = 6 Hz), 8.25 (s, 1 Hz). Anal. Calcd for $C_5H_5ClN_2$: C, 46.71; H, 3.92; N, 21.79. Found: C, 47.23; H, 3.91; N, 21.75.

***N*-(3-Chloropyrid-4-yl)-3-(cyclopentyloxy)-4-methoxybenzamide (24).** A stirred solution of 4-amino-3-chloropyridine (**23**) (25 g, 193 mmol) and 3-(cyclopentyloxy)-4-methoxybenzoyl chloride (**5**) (51.7 g, 203 mmol) in pyridine (250 mL) was heated at 70 °C (16 h). The mixture was then evaporated under reduced pressure, giving a brown oil, which was triturated with water (300 mL). The resulting solid was collected, dried, and recrystallised (2-propanol), giving *N*-(3-chloropyrid-4-yl)-3-(cyclopentyloxy)-4-methoxybenzamide (**24**) (48.5 g, 73%) as an off-white solid, mp 124−126 °C (lit.[1] mp 124−126 °C). ^{1}H NMR: δ 1.6−2.06 (m, 8H), 3.93 (s, 3H), 4.86−4.92 (m, 1H), 6.95 (d, 1H, J = 8 Hz), 7.34 (d,d, 1H, J = 8, 2 Hz), 7.5 (d, 1H, J = 2 Hz), 8.47 (d, 1H, J = 6 Hz), 8.53 (br s, 1H), 8.54 (d, 1H, J = 6 Hz), 8.57 (s, 1H). Anal. Calcd for $C_{18}H_{19}ClN_2O_3$: C, 62.34; H, 5.52; N, 8.08. Found: C, 62.5; H, 5.55; N, 7.9.

***tert*-Butyl 3-(Cyclopentyloxy)-4-methoxybenzoate (32).** 3-(Cyclopentyloxy)-4-methoxybenzoic acid (**4**) (20.0 g, 0.085 mol) was added to toluene (114 mL), the mixture was heated at reflux, and some toluene (14 mL) was removed by distillation. The mixture was cooled to 80 °C, and *N*,*N*-dimethylformamide (0.15 mL) was added, followed by thionyl chloride (13.5 g, 0.114 mol), which was added over 0.5 h whilst the temperature of the mixture was maintained at about 80 °C. The mixture was stirred at 80 °C (1 h) and then was evaporated under reduced pressure. The residue was dissolved in dry tetrahydrofuran (20 mL) and added over 0.5 h to a stirred solution of potassium *tert*-butoxide (18.9 g, 0.17 mol) in dry tetrahydrofuran (100 mL) at ambient temperature, the temperature of the reaction mixture being maintained below 25 °C. Stirring was continued (0.5 h), and then water (100 mL) and dichloromethane (100 mL) were added. The organic phase was collected and washed with water (2 × 100 mL), then dried ($MgSO_4$), and evaporated, to give *tert*-butyl 3-(cyclopentyloxy)-4-methoxybenzoate (**32**) (15.15 g, 61%) as a yellow viscous liquid. ^{1}H NMR: δ 1.49−1.60 (m, 11H), 1.70−1.96 (m, 6H), 3.82

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(s, 3H), 4.73−4.78 (m, 1H), 6.77 (d, 1H, J = 8 Hz), 7.44 (d, 1H, J = 2 Hz), 7.51 (d,d, 1H, J = 8, 2 Hz). Anal. Calcd for $C_{17}H_{24}O_4$: C, 69.84; H, 8.27. Found: C, 69.9; H, 8.57.

Acknowledgment

This paper is based on process development contributed by many colleagues in Rhône-Poulenc Rorer; the analytical support of Steve Acott and the late David Rule and the physical chemistry support of Bryan Slater and Mike Podmore are gratefully acknowledged. We also thank Philippe Pitchen, Vic Gabriel, and Steve Timmins for valuable scientific discussions and contributions.

Received for review August 14, 1997.

OP9700385