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Synthesis of the NK1 Receptor Antagonist GW597599. Part 1: Development of a Scalable Route to a Key Chirally Pure Arylpiperazine

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Abstract:

GW597599 1 is a novel NK-1 antagonist currently under investigation for the treatment of CNS disorders and emesis. The initial synthetic route devised from the medicinal chemistry one, used several hazardous reagents, gave low yields, and produced high levels of wastes. By targeted process of research and development, application of novel techniques, and extensive route scouting, a novel synthetic route for GW597599 has been developed.This paper reports the optimisation work of the first stage in the chemical synthesis of GW597599: the development of a pilot-plant suitable process for the synthesis of the arylpiperazine derivative 7 in an optically pure fashion. In particular, the process definition allowed eliminating the initial need for cryogenic conditions and copper catalysis in Grignard chemistry. It also allowed replacing a classical resolution step with a more efficient dynamic kinetic resolution, substantially enhancing the overall yield and throughput.

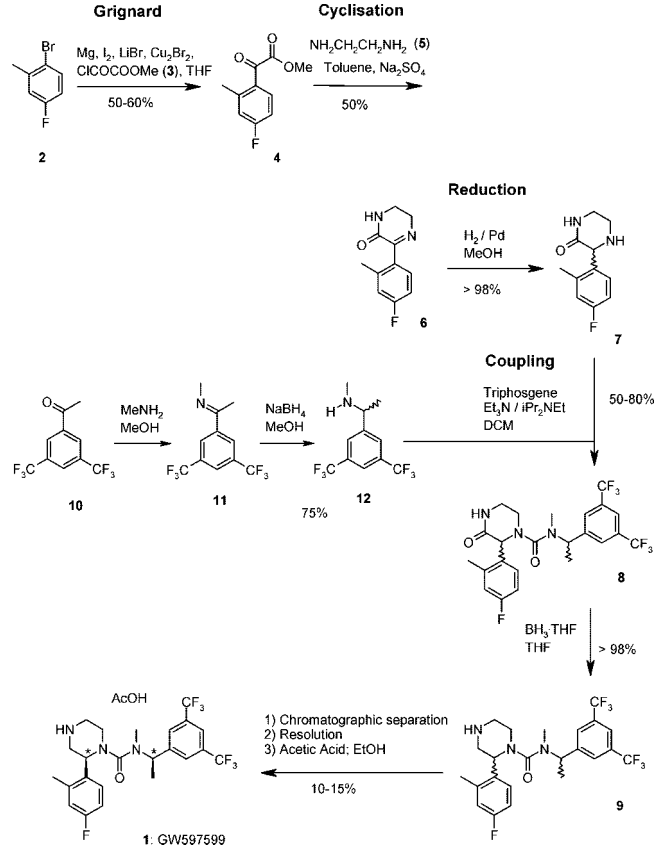
1. Introduction

Substance P (SP) is a member of the neurokinin family that exerts its pleiotropic role by preferentially binding to the neurokinin receptor classified as NK1. The role of SP in mood disorders may also partly depend on its interaction with serotonin (5-HT) receptors. Preclinical studies suggest that NK1 antagonists and selective serotonin reuptake inhibitors (SSRIs) may synergise to produce a final common effect on serotonergic neurotransmission. In fact GW597599 is under development to tackle central nervous system (CNS) diseases. Furthermore, substance P and the NK1-receptors that mediate its activity are present in the brain stem centres that elicit the emetic reflex. Nausea and vomiting have been reported as the most distressing side effects of chemotherapy, and the disruptive effects of these symptoms on patients' daily lives have been well documented. In light of the need for continued routine use of emetogenic chemotherapy, effective prevention of chemotherapy-induced nausea and vomiting (CINV) is a central goal for physicians administering cancer chemotherapy. GW597599 1 is a novel NK-1 antagonist currently being developed to relieve also those symptoms. In this paper we describe the successful efforts to define a synthetic route for large-scale manufacturing.

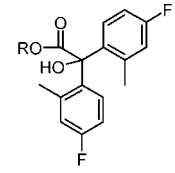
2. Initial synthetic Route

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

Scheme 1. **Initial synthetic route**



2.1. Experimental Details. The synthesis started with the *in situ* preparation of a Grignard reagent of 2-bromo-5-fluorotoluene **2** which was then added to a solution of methyl oxalyl chloride **3** in THF. The temperature was maintained between −55 to −65 °C in order to minimize the formation of the tertiary alcohol **13a**.



Tertiary alcohol **13a R=Me; 13b R=Et**

Furthermore, the heat evolution was controlled by diluting the reaction to such an extent that the conversion of even gram quantities of 2-bromo-5-fluorotoluene might have required unacceptably high volumes of solvents.[1]

The keto-ester derivative **4** was reacted with ethylenediamine **5**[2] in the presence of anhydrous sodium sulfate to give imine **6**, which was reduced *via* catalytic hydrogenation, though

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requiring long reaction time and a high hydrogen pressure, to give racemic ketopiperazine **7**.

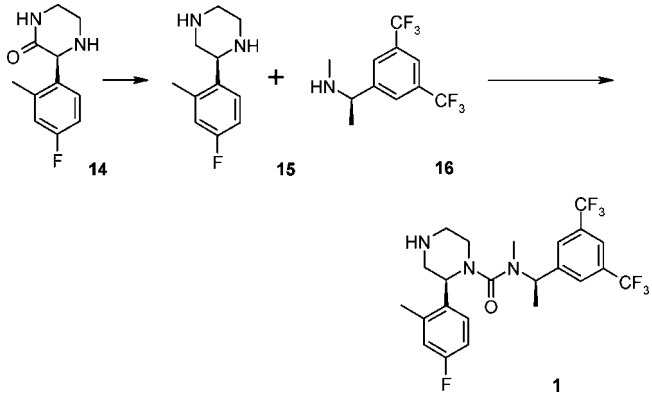
The carbamoyl chloride formed by the treatment of the racemic ketopiperazine **7** with the highly toxic triphosgene,[3] was reacted with the benzylamine **12** giving the urea **8** as a mixture of four stereoisomers. The amide group in the piperazine ring was then reduced by treatment with a solution of borane in THF at reflux. The resulting crude material was purified by chromatography to isolate a single diastereoisomer of **1** which underwent further classical resolution procedures to obtain the optically pure GW597599. The active moiety was finally crystallized as its acetate salt.

2.2. Evaluation of the Route. The overall yield obtained from the initial route was only about 2% theoretical; thus, a more efficient alternative was sought to provide larger quantities of GW597599. In addition to the low yield, when a purified single diastereoisomer isolated from mixture **8** was reduced with borane, partial epimerization was observed at the chiral centre of the piperazine ring.[4] It was therefore not possible to improve the efficiency of the process by isolating the ketopiperazine **7** in enantiomerically pure form by maintaining the borane reduction as the final step. Also, the use of BH_3 solution in THF was not recommended as pilot-plant first choice. This is because the borane exists in solution as a dimeric species with a problematically low auto-ignition temperature (38 °C). Finally, the acetate salt of **1** proved to be unstable at above 60 °C due to loss of acetic acid, which would cause difficulties both preparing and drying the final compound.[5,6]

3. Development of a Practical Convergent Synthesis

3.1. Synthetic Strategy. The disconnection of **1** into the two chiral fragments **15** and **16**, shown in Scheme 2, provided the basis of a more efficient route, avoiding the need for the last-stage resolution and the issue of the racemisation in the final chemical step caused by borane. The synthesis of the chiral ketopiperazine **14** followed by reduction and final coupling, formed the basis of our potential new route.

Scheme 2. **New potential route**



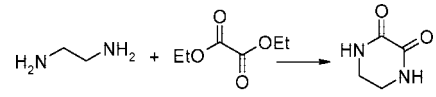
3.2. Grignard. The activation of magnesium in the synthesis of the Grignard reagent **19** was performed with the Gillman catalyst;[1] under these conditions a temperature of 50 °C was required for a successful initiation step. The use of TMSCl in the activation of magnesium for Grignard reagents has been reported to be effective for large-scale production.[7] When applying this procedure to our chemistry on the laboratory scale, we found that by addition of 5 mol % of TMSCl, the Grignard formation initiated smoothly and quickly at room temperature, and the amount of catalyst could be reduced as low as 0.5 mol % without affecting the yield and the initiation time. After initiation, the reaction was kept at room temperature reaching completion within 2 h with no need for higher temperature. During the following scale-up and optimisation it was seen that, with a temperature of 25 °C and 0.5 mol % TMSCl, the initiation time might be temperamental upon scale-up. Less borderline conditions (1 mol % TMSCl and 35 °C) were therefore tested on several grams scale and were subsequently chosen as working conditions for the 200 kg pilot-plant campaign.

A further improvement in the process was achieved by decreasing the amount of magnesium used in the synthesis (from 1.2 to 1 equiv with respect to **2**). This last change in the process, whilst having no effect on the yield and the quality of the final intermediate **14**, was of pivotal importance from an operational point of view in the pilot plant, as it significantly decreased the filtration time of the residual metal from several hours to 30 min.

A quick win was the replacement of methyl oxalyl chloride **3** with diethyl oxalate **17** that increased the yield from 50−60% to almost 80% theoretical. Additionally the less reactive diethyl oxalate did not require smoothing the hardness of the Grignard reagent *via* copper transmetalation, resulting in a simplified workup when getting rid of relatively low soluble copper salts. However, the low-temperature chemistry was still required for this reaction to minimise formation of tertiary alcohol **13b**, which despite a temperature as low as −50 °C, accounted for ∼17% of the final output weight.

The low yield was made even worse by the cyclisation of the residual diethyl oxalate **17** with the ethylenediamine **5** employed in the subsequent step (Scheme 3).

Scheme 3. **Side-product identified during cyclisation step 2**



The resulting cyclic amide **18** was able to undermine the resolution of racemic ketopiperazine to optically pure **14**, in a

(1) Gilman, H.; Heck, L. L. *Bull. Soc. Chim. Fr.* **1929**, *45*, 250.
(2) (a) Fokin, A. S.; Burgart Ya, V.; Saloutin, V. I. *Russ. J. Org. Chem.* **2006**, *42* (6), 887–896. (b) Ogawa and Co, Jpn. Kokai Tokkyo Koho, 57062269, 1982.
(3) (a) Rosiak, A.; Hoenke, C.; Christoffers, J. *Eur. J. Org. Chem.* **2007**, *26*, 4376–4382. (b) Jacobsen, E. J.; Stelzer, L. S.; Belonga, K. L.; Carter, D. B.; Im, W. B.; Sethy, V. H.; Tang, A. H.; VonVoigtlander, P. F.; Petke, J. D. *J. Med. Chem.* **1996**, *39* (19), 3820–3836.
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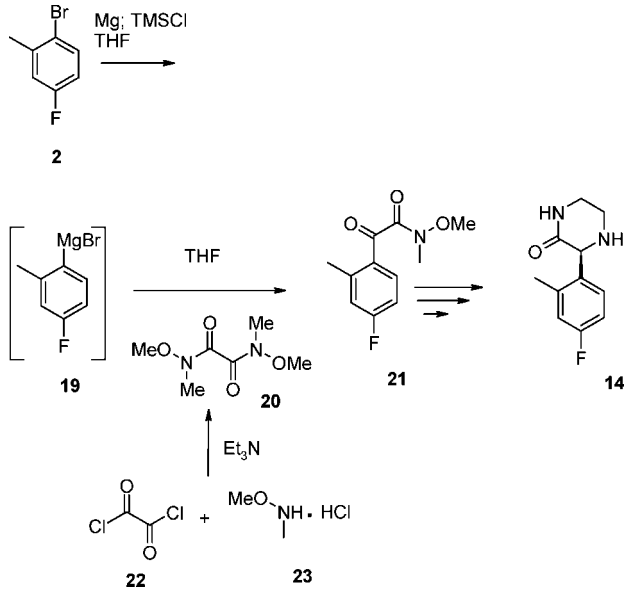
(7) (a) Bellingham, R.; Ace, K.; Armitage, M.; Blackler, P.; Ennis, D.; Hussain, N.; Lathbury, D.; Morgan, D.; O'Connor, N.; Oakes, G.; Passey, S.; Powling, L. *Org. Process Res. Dev.* **2001**, *5*, 479. (b) See Supporting Information for the Process Safety Evaluation of **19**.

way that a silica pad or a multiple crops precipitation, time and yield demanding, was necessary to achieve the target 96% ee.

A plethora of possible route modifications was tested, but the real breakthrough was found when substituting the ketoester **4** with the Weinreb amide derivative **21** (Scheme 4).[8]

Scheme 4. **Weinreb amide approach**



The α-keto amide derivative **21** was easily prepared from the same Grignard **19** by reaction with *N,N′*-dimethoxy-*N,N′*-dimethylethanediamide **20**, in a quantitative yield at 0 °C, avoiding the tertiary alcohol contamination.[9] Moreover, **21** underwent the transformations showed in the Scheme 4 achieving the targeted 96% ee for **14** in a single crop and with a considerably higher yield.

3.3. Cyclisation. A solvent screening (Table 1) identified methanol as the best solvent to use to perform the cyclisation step. The use of molar quantities of additives (Table 2) allowed gaining some additional yield. In particular acetic acid aided the minimisation of the level of the impurity **24** formed by the ethylendiamine nucleophilic substitution of the aromatic fluorine atom (Scheme 5).

Table 1. **Solvent screening for cyclisation (24 h up to 90−95°C)**

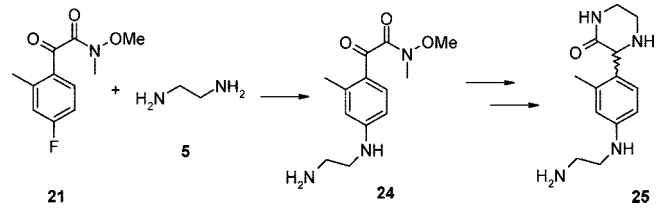
solvent	yield (%)	**24** (%)
toluene	19	<3
2-propanol	50	<3
ethanol	63	<3
IMS	68	<3
MeOH	**78**	**<3**
1,4-dioxane	28	<3
MTBE	24	<3
ethylene glycol dimethyl ether	25	<3
N,N-dimethyl-acetamide	63	19
1-methyl-2-pyrrolidinone	45	41
acetonitrile	39	<3
ethyl acetate	24	<3

A further step of fine optimisation was performed to minimise volumes of methanol and amounts of both ethylenediamine **5** and acetic acid. The result was a simplified workup procedure and a consistent lower level of the impurity **24** and consequently of **25**.

Table 2. **Additives screening for cyclisation in refluxing methanol**

additive	yield (%)	**24** (%)
none	78	2.8
$MgSO_4$	77	2.7
KF	79	2.6
CH_3COOH	**84**	**1.2**
$BF_3 \cdot Et_2O$	83	2.1
$HCl \cdot Et_2O$	79	2.7
$CeCl_3$	78	2.7
$AlCl_3$	81	2.4
$ZnCl_2$	78	2.5
CSA	79	2.7
CF_3COOH	82	2.3
citric acid	81	2.8

Scheme 5. **New side products identified during cyclisation step 2**



3.4. Reduction. The reduction step was somehow problematic to be performed at plant scale due to very long reaction time, high hydrogen pressure, and high catalyst loading.

The optimisation of the reduction of the imine **6** implied a screening of catalysts which allowed the identification of wet platinum on charcoal as a faster and safer hydrogenation catalyst rather than the dry palladium on charcoal (Figure 1) initially employed in the synthesis. A further refinement of the reaction conditions via a half-factorial statistical design of experiment (DoE), four

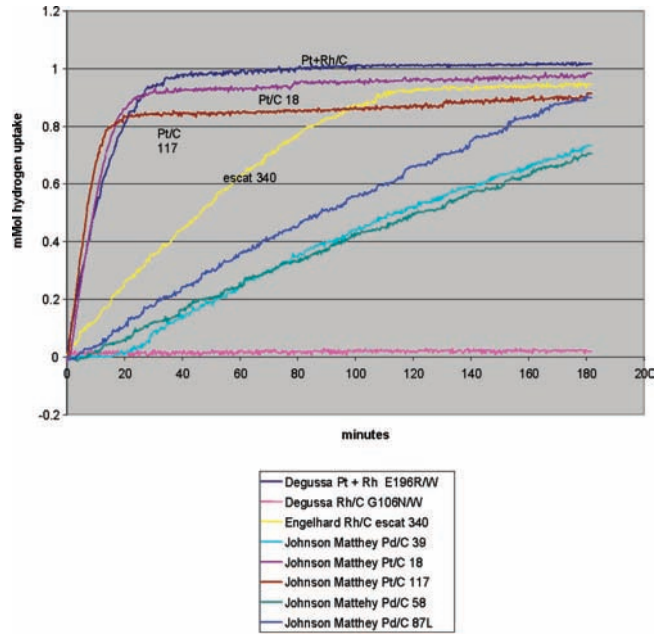


Figure 1. **Screen of hydrogenation catalysts.**

reactions only, permitted identifying the optimal process operating region to maximise the throughput (Table 3).

Table 3. **Hydrogenation DoE ranges and best conditions**

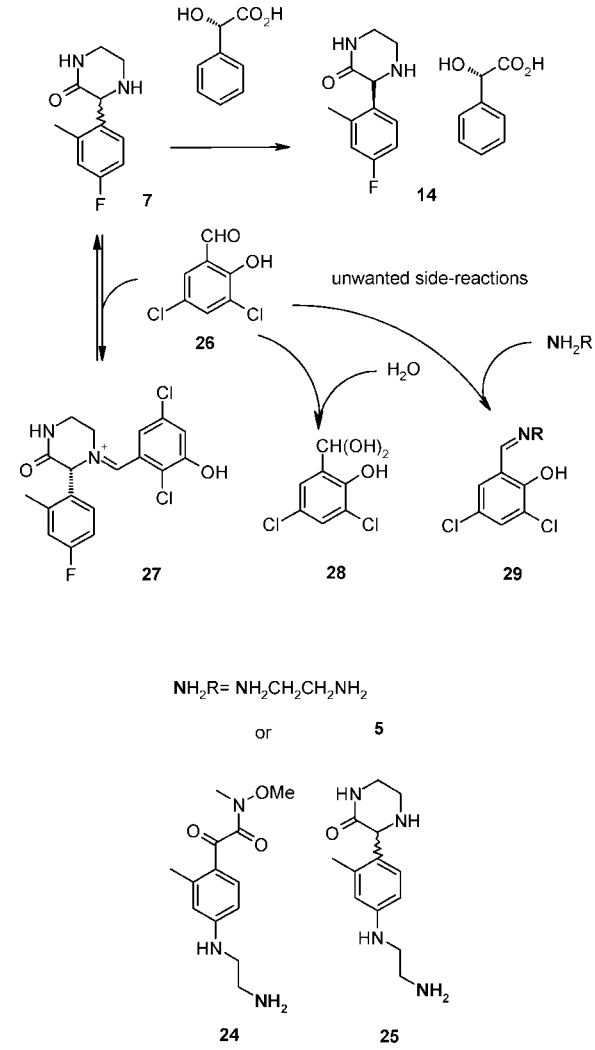
	low	high	best conditions
hydrogen pressure (bar)	0.3	4.3	1.5
temperature (°C)	20	40	40
catalyst charge (% wt/wt)	2	10	4

3.5. Preparation of the Optically Pure Ketopiperazine via Dynamic Kinetic Resolution (DKR). The resolution of the racemic ketopiperazine into the pure enantiomer **14** was initially achieved by classical fractional crystallization using the *S*-(+)-mandelic acid in ethyl acetate in a 38% theoretical yield.

To avoid wasting the unwanted enantiomer we considered implementing a DKR (Scheme 6).[10] The piperazine secondary amine could form an iminium derivative with an appropriate aldehyde increasing the acidity of the benzylic proton. The resulting derivative could easily racemise, allowing the wanted enantiomer to precipitate out as its mandelate salt leaving the unwanted enantiomer in solution ready to be further racemised. After a short screen, the dichlorosalicylaldehyde **26** was selected, leading in the end to ~90% yield of a pure enantiomer of the ketopiperazine. Unfortunately, this process required purification on silica gel because it was easily undermined by the amine impurities such as **5**, **24**, and **25**.

While, as mentioned before, optimisation of the cyclisation step greatly decreased the amount of **24** and **25**, impurity **5** can only by removed by introducing an aqueous workup before the DKR step. This meant that the water contamination of the organic layer containing the raceme ketopiperazine had to be eliminated before the aldehyde addition. On a larger scale, it was very difficult to azeotropically remove the water to the target level, thus minimizing the formation of nonreactive hydrate of the aldehyde. In fact while the yield achieved on a 5 L scale was about 70%, the overall yield in plant was only about 50%. In addition, the slurry was difficult to stir, leaving a considerable amount of product adhering to the reactor walls. Hence, it was evident that the DKR needed further optimization. This was accomplished by means of full factorial DoE study, implying 12 reactions and two center points to evaluate the curvature, which looked into reaction

Scheme 6. **DKR**



conditions and stirring rates (Figure 2). As a result of the DoE study, stirring rate was the most significant factor influencing the primary yield of the reaction. Moreover, a larger amount of water was buffered by a larger amount of aldehyde. Finally, computer modeling enabled us to design an appropriate reactor configuration to ensure efficient mixing. The initially employed round bottomed vessel with baffles led to the tendency to form dead mixing zones (see Figure 3, yellow/green/blue areas) which subsequently turned into encrustation. The computer modelling suggested using a conical vessel without baffles, as this would be ideal for thick suspensions and would avoid the dead mixing zones issue. When the process was repeated on pilot-plant scale with the new conditions (more aldehyde and the suggested vessel configuration) it was possible to reproduce the yield and purity achieved on 5 L scale.

4. Conclusions

In summary, we have developed a safe, robust and scalable process for the first stage of the synthesis of GW597599 **1**. When the sequence of Grignard addition, cyclisation, reduction, and DKR (Scheme 7) was progressed into the rest of the GW597599 possible manu-

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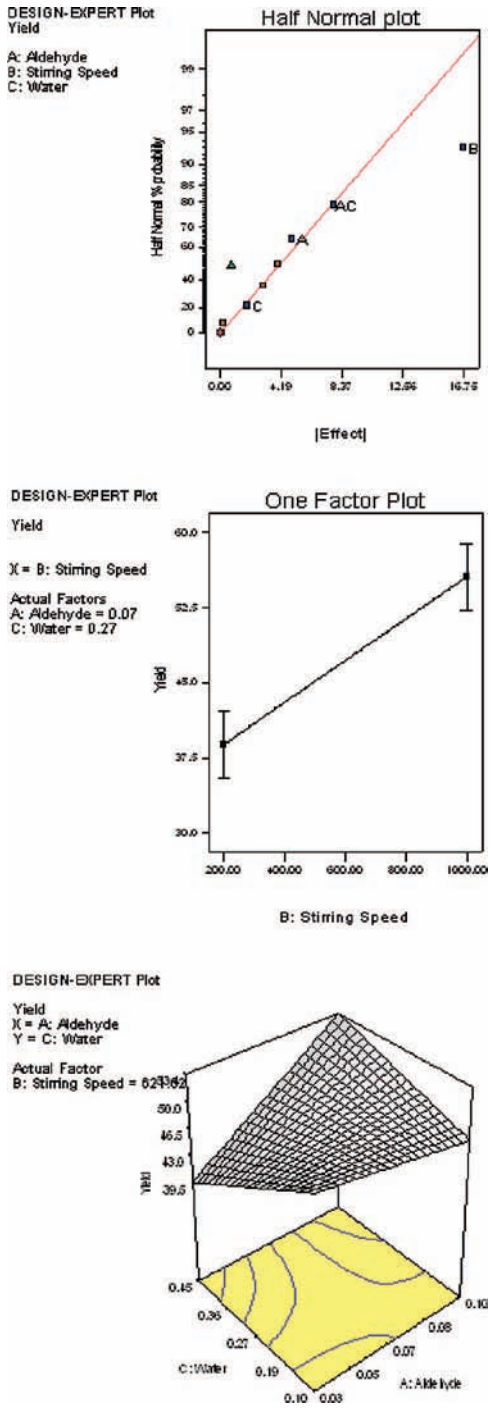


Figure 2. **DoE on parameters affecting DKR.**

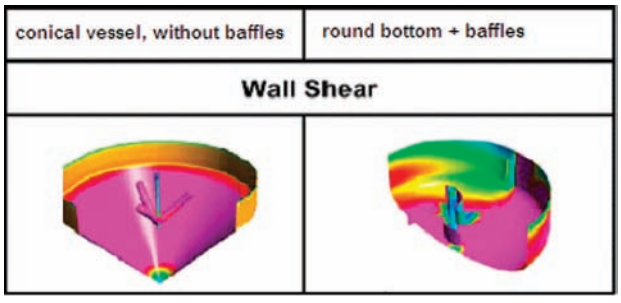
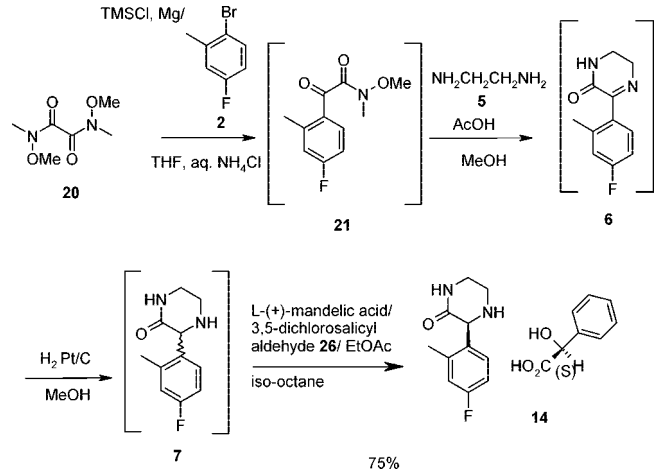


Figure 3. **computer modelling.**

facturing route, it contributed considerably to the overall scoring of the new process in terms of safer and more environmentally friendly conditions such as lower amounts of solvents and reagents, better reproducibility and plant operability compared to those of the original route.

The new process was successfully scaled up in pilot plant and delivered almost 400 kg of intermediate **14** in high yield (average 75% over four steps) and excellent purity.

Scheme 7. **Final manufacturing route**



Experimental Section

***N-N′*-Dimethoxy-*N-N′*-dimethyl oxaldiamide 20.** To *N,O*-Dimethylhydroxylamine hydrochloride **23** (231 g, 2.37 mol) in dichloromethane (2300 mL) was added oxalyl chloride **22** (100 mL, 1.18 mol) all at once. The resulting mixture was cooled down to 0 °C. A solution of triethylamine (666 mL, 4.78 mol) in dichloromethane (1800 mL) was added dropwise over 30 min. The suspension was stirred at 0 °C and then washed twice with water (2 × 1500 mL).

The aqueous layer was extracted two additional times with dichloromethane (2 × 1300 mL). The combined organic phases were concentrated to ~380 mL, and cyclohexane (3100 mL) was added dropwise. Crystallisation occurred almost immediately. The resulting white solid was stirred for 30 min at room temperature and for 1.5 h at 0 °C, filtered, washed with cyclohexane (1000 mL), and finally dried under high vacuum to obtain 188 g of **20** as a white solid (yield = 90%).

^{1}H NMR (400 MHz, DMSO-d_6): δ 3.13−3.18 (bs, 6H); 3.65−3.70 (bs, 6H); MS (ES$^+$) *m/z* 176.17 (MH$^+$); IR (nujol): 1679−1655 (str. C═O) (cm^{-1}); mp 89−90 °C.

HPLC Zorbax Eclipse XDB C8; Mobile phase A: water and B: acetonitrile; Gradient: 0 min 55% A to 18 min 20% A. Flow 1 mL/min; Detector UV DAD @215 nm. Retention time **20**: 2.00 min. Purity >99.8% a/a.

Bromo-(4-fluoro-2-methylphenyl)magnesium 19. To a suspension of magnesium turnings (16.5 g, 0.68 mol) in anhydrous THF (450 mL), TMSCl (0.75 mL, 5.91 mmol) was added at 25 °C under nitrogen. A portion (~5 mL) of 2-bromo-5-fluorotoluene **2** (134 g, 0.71 mol) was added to the magnesium in THF. The suspension was stirred at 35 °C (jacket temperature) until initiation of reaction was seen (heat evolution, ~10 °C internal temperature increase and mixture discoloration). The remaining 2-bromo-5-fluorotoluene **2** was added, keeping the internal temperature in the range of 35−45 °C. The progress

of the reaction was followed by continuously monitoring the heat released during addition of **2**. The reaction mixture was stirred for 3 h and then cooled to 25 °C and used as such in the synthesis of **21**.

2-(4-Fluoro-2-methylphenyl)-*N*-methyl-*N*-(methoxy)-2-oxoacetamide 21. 20 (100 g, 0.56 mol) was suspended in anhydrous THF (450 mL) and cooled to 0 °C. The previously prepared solution of Grignard reagent **19** (0.71 mol) was added through an online filter to the suspension of **20** over at least 40 min, maintaining a temperature of 0 °C. The resulting pale-green solution was stirred at 0−5 °C for 2−2.5 h. An aqueous solution of NH_4Cl 13% w/w (550 mL) was added, keeping the temperature below 10 °C. After heat ceased to evolve, the temperature was increased to 25 °C, and the mixture was stirred for 15−30 min at 25 °C, dissolving any solid present. The two phases were allowed to separate, and the aqueous phase was discarded. Methanol (1200 mL) was added and the mixture concentrated under reduced pressure to 600 mL, cooled to 25 °C, and used as such in the subsequent step.

^{1}H NMR (400 MHz, DMSO-d_6): δ 2.57 (s, 3H); 3.28 (s, 3H); 3.58 (s, 3H); 7.25 (dt, J = 8.38, 2.73 Hz, 1H); 7.31 (dd, J = 9.94, 2.53 Hz, 1H); 7.76 (dd, J = 8.58, 5.85 Hz, 1H); MS (ES$^+$) m/z 226.1 (MH$^+$).

HPLC Phenomenex LUNA C18; Mobile phase A: 0.05% TFA/water and B: 0.05% TFA/acetonitrile; Gradient: 0 min 0% B to 8 min 95% B. Flow 1 mL/min; Detector UV DAD @210 nm. Retention time **21**: 2.47 min. Purity >75% a/a.

3-(4-Fluoro-2-methylphenyl)-5,6-dihydro-2(1*H*)-pyrazinone 6. Methanol (900 mL) was added to the previous solution of **21** (∼0.69 mol), followed by ethylenediamine **5** (113 mL, 1.69 mol) and glacial acetic acid (119 mL, 2.08 mol), keeping the temperature at 25 °C. The resulting pale-yellow solution was heated to reflux for 16−20 h. The solution was concentrated under reduced pressure to 800 mL and used as such in the subsequent step.

^{1}H NMR (400 MHz, DMSO-d_6): δ 2.21 (s, 3H); 3.38 (t, J = 5.9 Hz, 2H), 3.79 (t, J = 6.2 Hz, 2H), 6.99−7.09 (m, 2H), 7.26−7.29 (m, 1H), 8.49 (s, 1H), MS (ES$^+$) m/z 207.1 (MH$^+$).

HPLC Phenomenex LUNA C18; Mobile phase A: 0.05% TFA/water and B: 0.05% TFA/acetonitrile; Gradient: 0 min 0% B to 8 min 95% B. Flow 1 mL/min; Detector UV DAD @210 nm. Retention time **6**: 2.64 min. Purity >75% a/a.

3-(4-Fluoro-2-methylphenyl)-2-piperazinone 7. Platinum on charcoal (5% loading, 50% water wet, 4 g, 0.5 mmol) was added to the previously prepared solution of **6** (∼0.65 mol), and the resulting suspension was stirred at 40 °C under 2.5 bar hydrogen pressure for ∼1 h. The mixture was filtered and the solution concentrated under reduced pressure to 400 mL. Ethyl acetate (1200 mL) was added and the solution concentrated under reduced pressure to 400 mL and used as such in the subsequent step.

^{1}H NMR (400 MHz, DMSO-d_6): δ 2.36 (s, 3H); 2.82−2.89 (m, 1H); 2.94−2.99 (m, 1H); 3.15−3.19 (m, 1H); 3.31−3.37 (m, 1H); 4.46 (s, 1H); 6.94 (dt, J = 8.56, 2.85 Hz, 1H); 7.00 (dd, J = 10.10, 2.64 Hz, 1H); 7.26 (dd, J = 8.34, 2.20 Hz, 1H); 7.77−7.84 (bm, 1H); MS (ES$^+$) m/z 209.1 (MH$^+$).

HPLC Phenomenex LUNA C18; Mobile phase A: 0.05% TFA/water and B: 0.05% TFA/acetonitrile; Gradient: 0 min 0% B to 8 min 95% B. Flow 1 mL/min; Detector UV DAD @210 nm. Retention time **7**: 2.47 min. Purity >80% a/a.

2-{4-[(2-Aminoethyl)amino]-2-methylphenyl}-*N*-methyl-*N*-(methyloxy)-2-oxoacetamide 24: isolated by chromatographic column (EtOAc/MeOH 9/1) from the reaction mixture containing **7** as yellowish oil.

^{1}H NMR (600 MHz, DMSO-d_6): δ 7.30 (d, 1H), 6.84 (t, 1H), 6.47 (d, 1H), 6.45 (s, 1H), 3.55 (s, 3H), 3.21 (s, 3H), 3.09 (m, 2H), 2.69 (t, 2H), 2.45 (s, 3H), 1.85 (d, 2H).

^{13}C NMR (150 MHz, DMSO-d_6 derived from the 2D experiments): δ 170.1, 154.3, 144.2, 137.1, 120.5, 116.3, 110.2, 47.1, 42.4, 32.2, 23.4.

(3*S*)-3-(4-Fluoro-2-methylphenyl)-2-piperazinone (*S*)-mandelate Salt (1:1) 14. The above solution of **7** (∼0.65 mol) was diluted with ethyl acetate (1400 mL), treated with 60 mL of a 15% w/w Na_2CO_3 solution, and stirred at 35 °C for 30 min. The phases were allowed to separate at this temperature. A further wash with water (40 mL) was performed at 25 °C. The organic phase was concentrated under vacuum to 400 mL. Ethyl acetate (1000 mL) was added, and the mixture was concentrated again to 400 mL to azeotropically remove water.

The resulting suspension was cooled to 25 °C, (*L*)-mandelic acid (86 g, 0.56 mol) and 3,5-dichlorosalicylaldehyde **26** (11 g, 0.058 mol) were added, and the mixture was heated to 43 °C. Initial, almost complete, dissolution was observed, and crystallisation occurred within 10−30 min. The suspension was aged at 43 °C for 16 h, cooled to 20 °C, and stirred for a further 2 h.

The mixture was filtered, washed first with ethyl acetate (100 mL) and then with a mixture ethyl acetate/isooctane, 2:1 (2 × 250 mL), and dried under vacuum at not above 45 °C to obtain an overall yield of 185.4 g of **14** as ethyl acetate solvate (80.4% w/w purity, theoretical yield = 73% from **20**).

^{1}H NMR (400 MHz, DMSO-d_6): δ 1.18 (t, J = 7.10 Hz, 3H); 1.99 (s, 3H); 2.35 (s, 3H); 2.85−2.91 (m, 2H); 2.95−3.00 (m, 1H); 3.14−3.20 (m, 1H); 3.31−3.38 (m, 1H); 4.03 (q, J = 7.10 Hz, 2H); 4.49 (s, 1H); 5.00 (s, 1H); 6.94 (td, J = 8.56, 2.85 Hz, 1H); 6.98 (dd, J = 10.10, 2.64 Hz, 1H); 7.24−7.28 (m, 1H); 7.28−7.30 (m, 1H); 7.31−7.36 (m, 2H), 7.40−7.43 (m, 2H), 7.82−7.84 (bm, 1H).

^{13}C NMR (100 MHz, DMSO-d_6): δ 174.18, 169.24, 161.09 (d), 140.44, 139.95 (d), 135.26, 130.90 (d), 128.06, 127.54, 126.61, 116.52 (d), 111.68 (d), 72.46, 60.75, 41.97, 41.38, 19.14, 14.40.

IR (nujol): 3604 (OH), 3472, 3182−2000 (NH), 1724 (*O*═C−NH), 1680 (acid C═O) (cm^{-1}).

HPLC Phenomenex LUNA C18; Mobile phase A: 0.05% TFA/water and B: 0.05% TFA/acetonitrile; Gradient: 0 min 0% B to 30 min 95% B. Flow 1 mL/min; Detector UV DAD @210 nm. Retention time **14**: 5.78 min. Purity >99% a/a.

HPLC Chiralcel OJ (4.6 mm × 250 mm) from Daicel; Mobile phase *n*-hexane/ethanol 80/20 v/v; Flow 1 mL/min; Detector UV @265nm. Retention times **14**: 7.84 min and opposite enantiomer 7.07 min, ee 99%.

$[\alpha]_D^{20}$ = +17.9 (1.17, $CHCl_3$).

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Supporting Information Available

Process safety evaluation of bromo(4-fluoro-2-methylphenyl)magnesium, **19**, and chiral HPLC of (3*S*)-3-(4-fluoro-2-methylphenyl)-2-piperazinone, **14**. This material is available free of charge via the Internet at http://pubs.acs.org.

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