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Process Research and Scale-up of a Commercialisable Route to Maraviroc (UK-427,857), a CCR-5 Receptor Antagonist

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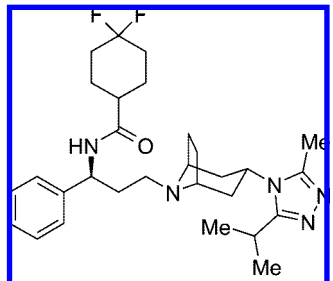
Abstract:

A six-step synthetic route to the CCR-5 receptor antagonist, Maraviroc (UK-427,857) (1) has been developed and demonstrated at scale in a pilot plant. The route has supported four Pilot-Plant campaigns and has produced multikilogram quantities of 1. Continued development of the synthetic route has resulted in a robust process with improved throughput compared to that of the original synthesis (Haycock-Lewandowski, S. J.; Mawby, N. J.; Wilder, A.; Ahman, J. *Org. Process Res. Dev.* 2008, *12*, 1094−1103).

1. Introduction

Maraviroc (**1**) is a potent CCR-5 receptor antagonist for the treatment of HIV.[1] Due to high medical need and the exciting prospect of a new class of drugs for HIV, development of **1** has been rapid.



Maraviroc (UK-427,857)

1

An initial bulk enabling route (route 1) to **1** (Scheme 1) was developed to support toxicology and early clinical trials.[1] This route was demonstrated in the laboratory and Kilo Laboratory facility to provide rapid access to **1**, but the following challenges were identified with route 1: (1) 20-step synthesis with a longest linear sequence of 10 steps; (2) lack of solid intermediates with four steps performed without purification; (3) Cbz protection of **2** and deprotection of **9** adds two synthetic steps; the deprotection via hydrogenolysis is nonrobust and required several recharges of catalyst on scale to reach completion; (4) a cyclic carbamate byproduct, formed during the reduction of **3** to **4**, represented a potential scale-up issue. This step also utilised 2 M BH_3·tetrahydrofuran (THF), which has safety/stability issues upon storage.[2,3] (5) Parikh−Doering oxidation of **4** generates dimethyl sulfide (DMS) as a byproduct, which is smelly and difficult to contain. Approximately 20% of the Pummerer rearrangement product was also formed in this reaction, although its level could be reduced to less than 5% by careful base selection.[4] (6) The yields obtained in the reductive amination step were low and variable. (7) Lastly, the final step acylation yield was considerably lower on scale than in laboratory runs (54% vs 75%) due to the lower chemical purity of **10** produced on scale.

Consequently, a robust, plant-suitable synthesis of **1** was urgently required to manufacture larger quantities to support development activities. The process research and development of a commercialisable route to **1** is described herein.

2. Results and Discussion

2.1. Commercialisable Route Identification. Process research was focused on the development of a route that allowed early introduction of the 4,4-difluorocyclohexanecarboxylic acid **11**, avoiding the use of protecting groups and potentially generating solid intermediates (Scheme 2). More significantly, the triazole tropane fragment was the most expensive starting material; forming the central carbon−nitrogen bond last would reduce cost and provide a highly convergent synthesis. External suppliers were secured for the acid **11**[1,5] and synthesis of the β-amino ester **13** (Scheme 2) via an enzymatic resolution route.[6] The triazole tropane fragment **7** was prepared via the synthesis developed as part of route 1.[1]

The second-generation synthesis of **1** utilised transformations similar to those developed for route 1, including the coupling strategy (Scheme 3). Coupling of acid chloride **12** with the hydrochloride salt of β-amino ester **13** under modified Schotten−Baumann conditions (DCM, $Na_2CO_{3\ aq}$) gave amide

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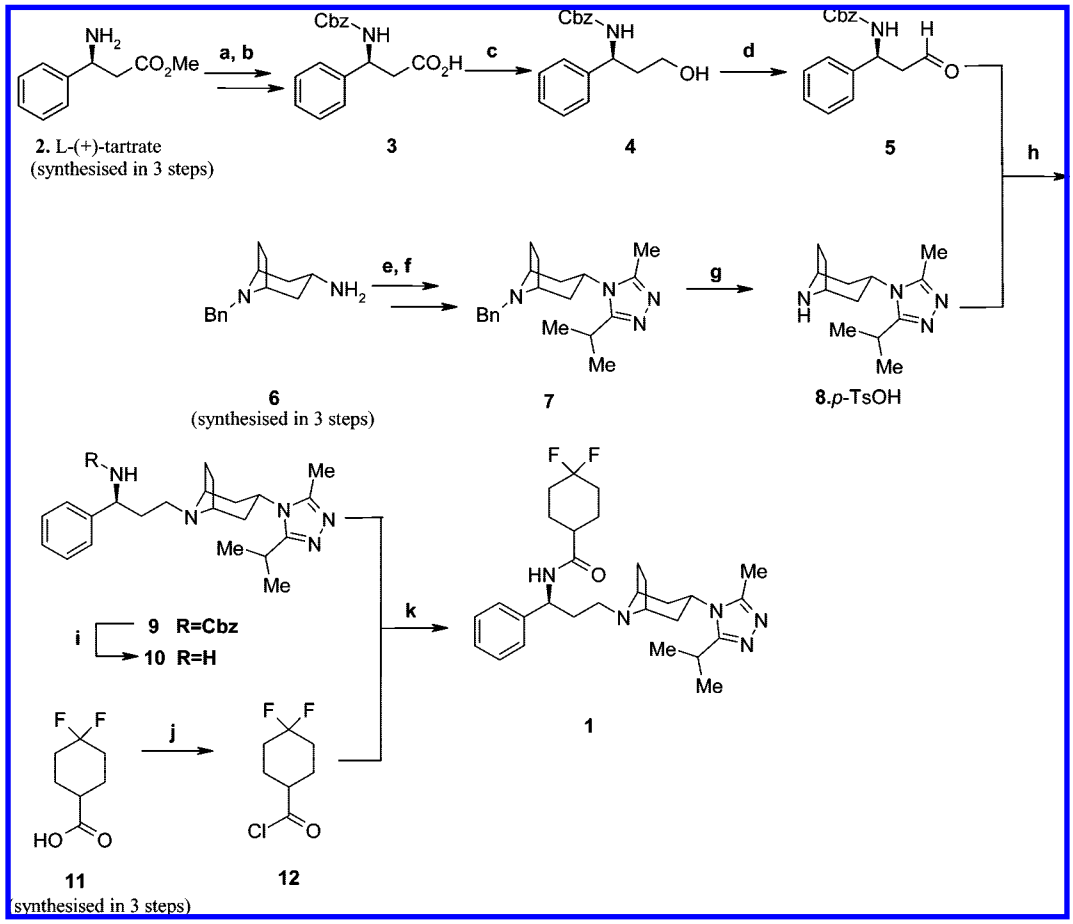
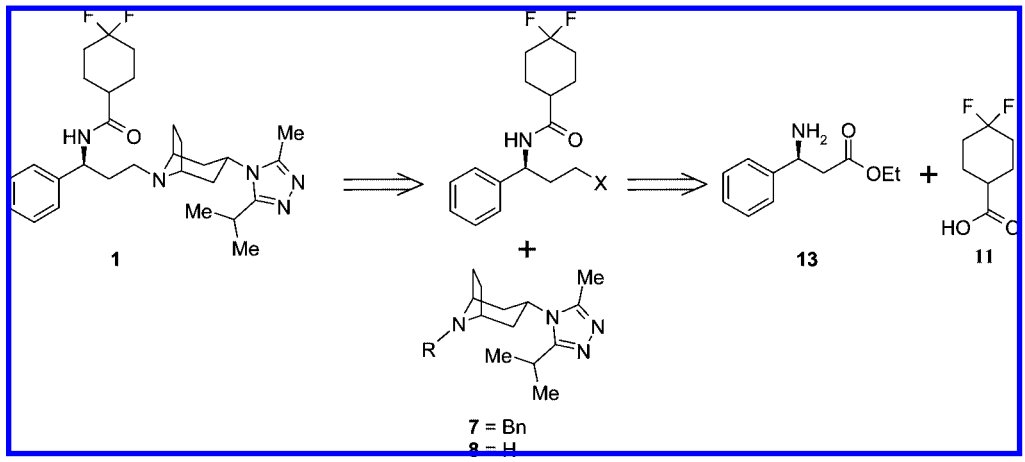
Scheme 1. **Route 1: chemical research and development (CRD) bulk enabling route**[a]



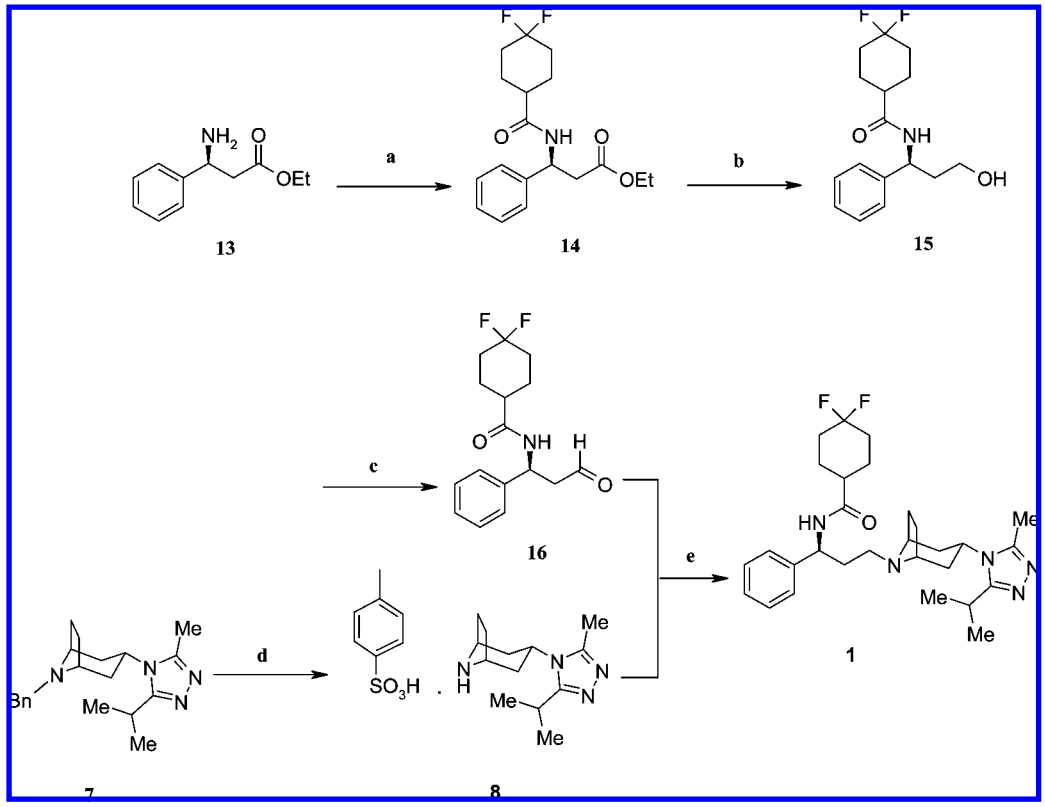
[a] (a) BnOC(O)Cl, Na_2CO_{3aq}, DCM, 0 °C−rt, isolated as an *i*-propanol/methanol solution. (b) 1 M NaOH, rt, 90%. (c) BH_3·THF, THF, 0 °C−rt, 70%. (d) SO_3·py, Et_3N, DMSO, DCM, 0 °C−rt, isolated as a toluene solution. (e) Isobutyryl chloride, Na_2CO_{3aq}, DCM, 0 °C−rt, 76%. (f) PCl_5, DCM, $AcNHNH_2$, AcOH, 0 °C−80 °C, 73%. (g) *p*-TsOH, H_2 (50 psi), Pd/C, MeOH, rt, 83%. (h) $NaBH(OAc)_3$, DCM, AcOH, rt−30 °C, isolated as a toluene concn. (i) $Pd(OH)_2$, H_2, 50 psi, MeOH, 78%. (j) $SOCl_2$, toluene, quantitative. (k) DCM, Na_2CO_{3aq}, 15 °C−rt, 54−75%.

Scheme 2. **Disconnection strategy for the synthesis of 1**



ester **14** which was isolated as a solid following crystallisation from toluene/heptane. Ester **14** was directly reduced to alcohol **15** with sodium bis(2-methoxyethoxy)aluminum hydride (Red-Al) in toluene in 78% yield following workup. Oxidation of alcohol **15** to the aldehyde **16** was achieved using modified Parikh−Doering conditions (SO_3·py, diisopropylethylamine, DMSO, DCM) in a crude yield of approximately 95% and with <5% of the methylthiomethyl ether byproduct. The byproduct has been isolated and characterized from earlier process research[1] Finally, coupling of aldehyde **16** and amine tosylate salt **8** (prepared by hydrogenolysis of **7** as in route 1)[1] via reductive amination in dichloromethane furnished the target compound **1** in moderate yield (45−55%), following crystallisation from ethyl acetate. This sequence was successfully demonstrated in the laboratory, and all intermediates were solids. Although this route addresses the majority of the issues

Scheme 3. **Chemical research and development**[a]



[a] Route 2 original conditions: (a) (i) 1.1 equiv of **12**, DCM, Na_2CO_{3aq}, 20 °C; (ii) toluene, heptane, 93%. (b) 1.6 equiv of Red-Al (65 wt % in toluene), 0−10 °C; (ii) EtOAc, 2 M NaOH, $NaCl_{aq}$; (iii) toluene, heptane, 96%. (c) (i) 3 equiv of SO_3·py, 3 equiv of $(^iPr)_2NEt$, DMSO, DCM, 0−10 °C; (ii) H_2O, 0.5 M HCl, $NaCl_{aq}$, 95%. (d) (i) MeOH, 1 equiv of *p*-TsOH, 10 wt % of 10% Pd/C, H_2 (50 psi), rt; (ii) *i*-PrOH, rt−0 °C, 83%. (e) (i) 1.1 equiv **16**, DCM, 1.2 equiv of $NaBH(OAc)_3$, 0.2 mL/g of AcOH, 0 °C−rt; (ii) 2 M NaOH, 10 M NaOH; (iii) EtOAc, 45−55%. Developed conditions: (a) (i) **12**, EtOAc, Na_2CO_{3aq}, 10 °C−rt; (ii) toluene, heptane, 93%. (b) $NaBH_4$, MeOH, THF, reflux; (ii) acetone, 2 NaOH, (iii) THF, cyclohexane, 90%. (c) (i) TEMPO, NaOCl, NaBr, $NaHCO_3$, DCM, 5 °C; (ii) $Na_2S_2O_3$·$5H_2O_{aq}$, (iii) toluene, heptane, 88%. (d) (i) MeOH, *p*-TsOH, 10% Pd/C; (ii) *i*-PrOH, 92%. (e) (i) EtOAc, THF, $NaBH(OAc)_3$, 0 °C−rt; (ii) 2 M NaOH; (iii) EtOAc; (iv) H_2O, 91%.

identified with route 1, critical review identified three factors that would impede scale-up: (1) safety issues associated with the handling of Red-Al on scale (2-methoxyethanol is a teratogen) and complex workup to remove aluminium salts; (2) oxidation of alcohol **15** generates a methylthiomethyl ether impurity, which requires additional processing to purge, and generates DMS as a byproduct; (3) final step reductive amination utilises dichloromethane as a solvent and is low yielding. Portionwise addition of $NaBH(OAc)_3$ was not possible in our plant on scale due to the potential for hydrogen evolution.

This prompted further development of the route to deliver a robust, scaleable synthesis.

2.2. Route Development. The handling and workup issues associated with Red-Al could be avoided by reducing ester **14** to alcohol **15** with sodium borohydride and methanol in THF at reflux.[7−11] The transformation could also be effected with lithium borohydride·THF solution; however, concerns with the safety and stability on storage of the reagent meant that sodium borohydride was preferred for scale-up. Despite the levels of hydrogen generated in this process, these conditions were preferred for scale-up. The process safety evaluation of this chemistry determined the maximum rate of hydrogen evolution was 2.6 L/min per g-mol of **14**, following methanol addition and subsequent heating to reflux and did not pose any safety concerns, providing the reactor pressure is monitored to ensure adequate venting of the gas.

As the sodium borohydride and methanol charges were found to be critical to the success of the reduction, a series of experiments was performed varying the sodium borohydride and methanol charges and monitoring reaction conversion by HPLC (Table 1). HPLC analysis showed that the reaction proceeds via a less polar intermediate, which was isolated and characterized as the methyl ester analogue of **14** formed via trans-esterification. Levels of the methyl ester are not quoted but quantified as **14**. No other byproduct or impurities are observed by HPLC.

Despite the presence of at least three active hydrides (reducing the equivalents of both reagents relative to each other significantly decreased the reaction rate) all experiments failed to reach completion even on prolonged reflux. The optimum charge of the reagents was therefore set at sodium borohydride (2 equiv) to methanol (5 equiv) from these investigations.

In preparation for scale-up the reduction protocol was developed to control the rate of hydrogen evolution. Conse-

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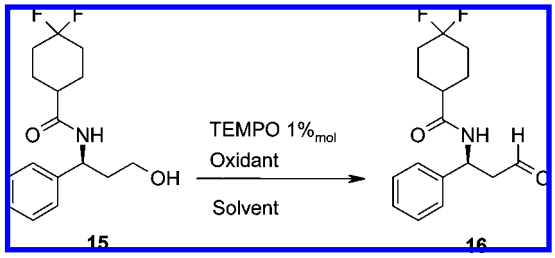
Table 1. **Effect of hydride equivalents and sodium borohydride:methanol ratio on the reduction of ester 14 to alcohol 15**

				HPLC results (% **14**)[a]				
				time (h)				
entry	$NaBH_4$ (equiv)	MeOH (equiv)	effective hydrides	**2**	**4**	**5.2**	**7.5**	**22**
1	2	5	3	1.43	0.4	0.4	0.3	0.1
2	2	5.5	2.5	10.2	10.0	9.8	9.7	9.1
3	2	6	2	15.7	15.4	15.0	14.8	14.4
4	1.2	1.5	3.3	64.0	30.8	22.9	17.5	6.5
5	1.2	1.2	3.6	73.6	42.2	31.3	20.7	5.7
6	1.2	0.9	3.9	76.6	44.5	32.1	21.1	6.4
7	1.3	1.6	3.6	77.5	50.6	39.2	26.2	17.7
8	1.3	1.0	4.2	81.6	56.0	44.7	32.1	8.4

[a] Conditions: MeOH was added at 50 °C, and then the reaction was heated at reflux for the indicated time.

Scheme 4



quently, methanol was added to a slurry of ester **14** and sodium borohydride in THF at 50 °C. Slow heating to reflux then controls the rate of hydrogen evolution, and promotes reduction. The mixture was quenched by the addition of aqueous sodium hydroxide (2 M), and alcohol **15** was isolated as a white solid from toluene/heptane in 92% yield.

All activated DMSO oxidation procedures produce as a byproduct, DMS, which has an unpleasant odour and can be difficult to contain on scale even with scrubbing. A screen was therefore undertaken to identify a process-friendly alternative, with nitroxyl radical (TEMPO)-based oxidations emerging as showing most potential. Accordingly a range of stoichiometric oxidants was evaluated for the oxidation following literature procedures (Scheme 4, Table 2).

TEMPO with 1.05 equiv of bleach/NaBr gave the cleanest conversion of **15** to **16**, with 7−10% unreacted **15** and the over-oxidized corresponding acid, as the only byproduct (Table 2, entry 1). Fortunately the acid was removed in the aqueous liquors during workup. In an attempt to improve conversion and suppress acid formation we screened some non-aqueous terminal oxidants, but they were inferior to NaOCl (Table 2, entries 2−4).

An initial limited solvent screen identified ethyl acetate as the solvent of choice, and the reaction was optimised under these conditions (Table 3). Although dichloromethane gave comparable results, ethyl acetate was preferred for scale-up. Addition of excess bleach failed to promote reaction completion but gave diminished yields due to over-oxidation of the desired **16** to the corresponding acid. The isolated aldehyde typically contained 7−10% unreacted alcohol, irrespective of bleach charge. It was evident from these early investigations that the acid is formed at a slow rate during the reaction and the optimum yield could only be achieved as a compromise between acid formation and unreacted alcohol. Fortunately relatively high levels of alcohol **15** in aldehyde **16** had no detrimental effect on the downstream chemistry and can be purged down to acceptable levels by incorporating an acid/base cycle in the workup of the following step.

The use of DCM in the reductive amination step was a concern due to current regulatory guidelines on solvent selection in a final active pharmaceutical ingredient (API) covalent bond-forming step. Although DCM could be substituted with ethyl acetate without impact on yield or quality of isolated **1**, the laboratory process was not suitable for transfer to scale-up facilities due to the portionwise addition of sodium triacetoxyborohydride[12] (STAB) to a slurry of aldehyde **16** and amine salt **8** in ethyl acetate, potentially generating hydrogen. The low isolated yield was also a concern due to competing reduction of the aldehyde by STAB. The limited solubility of both the amine salt **8** and STAB in any compatible, process-friendly solvent determined the order of addition for this process. Aldehyde **16** was found to be soluble in THF and was therefore added to the reaction mixture of **8** and STAB in ethyl acetate. As the reduction of aldehyde **16** to alcohol **15** was found to be fast under the reaction conditions, competing reduction of the aldehyde was minimised by controlling the rate of addition (1.5 h) and reducing the reaction temperature to 10 °C. Following workup and crystallisation from ethyl acetate, **1** was isolated as a white solid in 80% yield with excellent purity (99%), determined by HPLC.

2.3. Route Scale-up. This modified synthesis was demonstrated in the laboratory in a 20 L fixed rig (Table 4) and provided a 1.5 kg batch of **1**, 53% overall yield compared to 25% for route 1.

Subsequent transfer first to the Kilo Laboratory, and then without modification to the Pilot Plant gave final product **1** in 54% and 50%, overall yields respectively, from amine **13** (Table 4). The transfer went without any serious issues but some areas of improvement were identified:

1. The aqueous liquors from the reduction of ester **14** to alcohol **15** were giving off hydrogen at a slow rate so an acetone quench was added prior to addition of caustic.

2. Isolation of alcohol **15** was nonrobust, crystallisation temperature was variable, precipitation was rapid and resulted in a slurry that was difficult to agitate and transfer.

3. Yield in the oxidation of alcohol **15** to aldehyde **16** was on the low side (∼70% corrected for **15**). The high level (7−10%) of alcohol **15** in isolated aldehyde **16** required extra processing (acid/base cycle) in the following step.

4. Finally lengthy processing in the reductive amination was of concern.

Prior to the start of the second Pilot Plant campaign, the process to synthesise **1** was revisited, addressing the issues and observations made during the first Kilo Laboratory and Pilot Plant campaigns. The chemistry to prepare **15** was identical to that demonstrated in the previous campaigns, with the exception of the acetone quench included in the workup. Isolation issues initiated an investigation into the crystallisation of **15** from toluene/heptane. Interestingly the meta-stable zone width for

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Table 2. **Evaluation of oxidants for the TEMPO-catalysed conversion of 15 to 16**

entry	oxidant	solvent	results/comments	yield **16** %[a]
1	NaOCl/NaBr[b]	EtOAc/toluene/H_2O	isolated **16** contains ~10% **15** by ^{1}H NMR	83 (10)
2	BAIB[c,d]	DCM	reaction failed to reach completion	57 (10)
3	NCS[e]	DCM/$NaHCO_{3aq}$	complex mixture of impurities formed	0
4	*m*-CPBA[f]	DCM	**16** not formed	0

[a] Figure in brackets is the amount of residual **15** in isolated **16**. [b] 0.01 equiv TEMPO, 1.1equiv NaOCl, 1.03 equiv NaBr, 2.93 equiv $NaHCO_3$, EtOAc/toluene (1:1), water, ambient, 1 h. [c] BAIB = bisacetoxyiodobenzene. [d] 0.1 equiv TEMPO, 1.1 equiv BAIB, DCM, ambient, 3 h. [e] 0.1 equiv TEMPO, 1.1 equiv TBACl, 1.3 equiv NCS, aq $NaHCO_3$, aq K_2CO_3, ambient, 3 h. [f] 1.5 equiv *m*-CPBA, DCM, ambient, 2 h.

Table 3. **Evaluation of solvents for the TEMPO-catalysed conversion of 15 to 16**

entry	solvent	isolated yield **16** %[a]
1	EtOAc	84.6 (7.4)
2	*t*-BME	14 (0)
3	DCM	84.5 (6.4)
4	toluene	0 (48)[b]

[a] Figure in brackets is the amount of residual **15** in isolated **16**. [b] Limited solubility of **15** in toluene.

Table 4. **Comparison of the scale-up campaigns for route 2**

	% yield				
campaign	**14**	**15**	**16**[a]	**1**[b]	overall yield (from **13**)
20 L fixed rig	93	93	84 (7.0)	80	53
Kilo Laboratory	93	92	84 (6.3)	79	54
Pilot Plant	94	94	80 (10)	80	50

[a] Figure in brackets is the amount of residual **15** in isolated **16**. [b] Amine **8** was manufactured by contract synthesis for Kilo Laboratory and Pilot Plant campaigns.

Table 5. **Evaluation of solvents for the TEMPO-catalysed conversion of 15 to 16**

entry	solvent[a]	HPLC[b] % **16**	HPLC[b] % **15**	yield[c] **16** %
1	EtOAc	74.6	2.4	74
2	EtOAc/toluene	73.1	2.4	not isolated
3	*i*-PrOAc	58.0	17.0	58
4	BuAc	30.0	14.0	30
5	MeCN	73.9	7.5	not isolated
6	*tert*-amyl alcohol	50.6	27.9	not isolated
7	DCM	84.5	0.5	85

[a] NaOCl 1.1 equiv was added over 90 min to a biphasic mixture of **15**, NaBr, and $NaHCO_3$ in water and indicated solvent at 5 °C. [b] HPLC analysis 20 min after addition NaOCl. [c] Yield corrected for alcohol in isolated product.

Table 6. **Organic waste/kg API produced**

	waste water (kg/kg)	inorganic waste (kg/kg)	organic waste (kg/kg)	solvent (kg/kg)
route 2	55	5.5	1.4	95
route 2 DCM[a]	29	3.46	0.91	53

[a] Figures include waste reduction from optimization of the synthesis of **8**.

this crystallisation is very narrow. It was therefore concluded that development of a controlled crystallisation protocol of **15** from toluene/heptane would be difficult. THF/cyclohexane (1:3 by volume) appeared to give a more controlled precipitation of **15** and broader meta-stable zone width. The physical form did not differ significantly from the toluene/heptane process; however, holding at the crystallisation temperature for a short period followed by a slow cool-down rate gave a more mobile slurry of **15**. This protocol was included in the second Pilot Plant campaign, and although the crystallisation temperature did vary between batches, the isolation problems observed previously were mainly avoided by the switch in isolation solvents. Efficient agitation was key during the crystallisation; initially, rapid crystallisation is observed to yield a thick but mobile slurry. Continued agitation sees significant thinning of the slurry as the product ages. Poor agitation of the first batch during the initial precipitation of **15** led to setting of the solid, except areas directly around the impeller. It was possible to salvage this batch by reheating the mixture into solution, followed by a second crystallisation, with increased agitation. For the proceeding batches the impeller was changed from a single curved blade turbine impeller (4 blades, diameter 735 mm) to a pitched bladed turbine (3 blades with fin, diameter 400 mm) with a secondary pitch turbine (3 blades, diameter 500 mm), and no problems were met with the crystallisation. The yields using this process were comparable to the previous toluene/heptane crystallisation (90%), and purity was not compromised.

Although the crude yield for the oxidation of alcohol **15** to aldehyde **16** from the first Pilot Plant campaign was reasonable (79%), the isolated product contained up to 10% of the unreacted alcohol. Therefore a second solvent screen for the oxidation was initiated, supported by a quantitative HPLC method, developed to monitor the reaction. Increased accuracy in the oxidant titration and minimisation of variation of the reaction parameters such as mass transfer, temperature, and dosing rates was achieved by conducting the screen in a parallel reactor system. Results are summarised in Table 5.

Interestingly DCM emerged as a solvent superior to ethyl acetate, giving the highest conversion (84.5%) with only 0.5% of unreacted **15** and excellent reproducibility. Isolation of the product gave confirmation of this result by ^{1}H NMR. Although DCM is a class II solvent (according to ICH guidelines for residual solvents) and special precautions have to be taken to minimise release to the environment during handling, the increased yield and quality of isolated **16** were considered to outweigh these issues. The workup could also be simplified to an aqueous sodium thiosulfate quench, followed by phase separation. The additional potassium hydrogen sulfate and brine washes in the original process were not necessary, and as a result the cycle time for the oxidation was reduced significantly. On scale-up to multikilogram batches, yields for this stage were increased to 89%, with high chemical purity. DCM is not considered to be a green solvent; however, a review of the waste data revealed that the switch to DCM reduces the solvent and organic waste produced over the last five steps by approximately

Table 7. **Comparison of cycle times for the hydrogenolysis of 7**

reactor	stirred tank	stirred tank	Buss loop	Buss loop	Buss loop	Buss loop	Buss loop
reaction solvent	*i*-PrOH/H_2O	*i*-PrOH/H_2O	MeOH	MeOH	MeOH	MeOH	MeOH
input **7** (kg)	35.0	40	25.0	25.0	30.0	40.0	40.0
reaction time (h)	4	4	2	2	2	2	2
distillation time (h)	9.5	9.5	4	3	4	5	4
total cycle time (h)	13.5	13.5	6	5	6	7	6
yield (%)	80.0	96.5	94.7	90.9	96.0	90.0	96.0

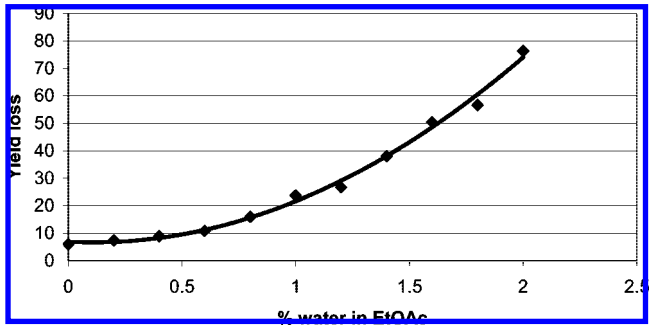

Figure 1. **Solubility curve for 1 (concentration = 0.65 M) in ethyl acetate (containing 1% THF, typical level at distillation end point) (3 mL/g)/water.**

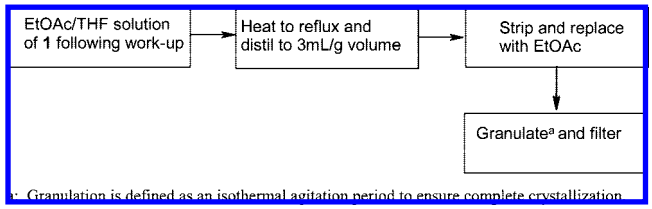

Figure 2. **Flow diagram for the crystallisation of 1.**

21.5 kg/kg isolated API due to the increased yield and quality in this step (Table 6).

Although the N-debenzylation of **7** to the corresponding amine tosylate salt **8** progressed smoothly in the previous campaigns, safety concerns were raised with the removal of 10% Pd/C in MeOH in further scale-up, due to its pyrophoric nature, on filtration as water is removed from the catalyst. Further investigations revealed that this reaction is primarily driven by temperature, and by increasing the reaction temperature from ambient to 50−80 °C, a catalyst with a lower palladium loading (5% Pd/C) could be utilised. To simplify the workup the solvent was switched to *i*-propanol/water (10:1). Removal of the catalyst by filtration following reaction completion and azeotropic removal of the water with *i*-propanol led to the crystallisation of amine **8** as the monohydrate tosylate salt in high yield (90%). The process scaled well in a stirred tank reactor; however, transfer of the process to the Buss-loop hydrogenator was problematic, since the reaction mixture had to be transferred as a solution at ambient external temperature due to location of the reactor. The first experiment was to run in January; ambient external temperatures were therefore anticipated to be less than 5 °C. A solution of the *N*-benzylamine **7** and *p*-TsOH in *i*-propanol/H_2O (10:1) was prepared in a stirred tank for transfer to the Buss-loop. However after stirring at ambient temperature overnight, **7** had precipitated out of solution as the tosylate salt. Fortunately, an additional charge of water solubilised the amine salt to re-form a solution, which was subsequently transferred to the Buss-loop reactor. Circulation of the solution saw severe foaming issues preventing use of the loop reactor. Switching the solvent to methanol reduced the foaming to operable levels. A total of five multikilogram batches were run using methanol as the solvent, in the loop reactor, which significantly reduced the reaction time, decreasing the overall cycle time, and providing the amine **8** as its tosylate salt in 93% average yield following workup (Table 7).

Conducting the reductive alkylation with minimal workup gave almost quantitative yield of **1**, suggesting significant product losses could be attributed to the workup procedure. A screen of the current reductive alkylation workup using an automated liquid−liquid extraction instrument was performed to quantify and determine where product losses occur in the workup. The results from this screen clearly indicated that

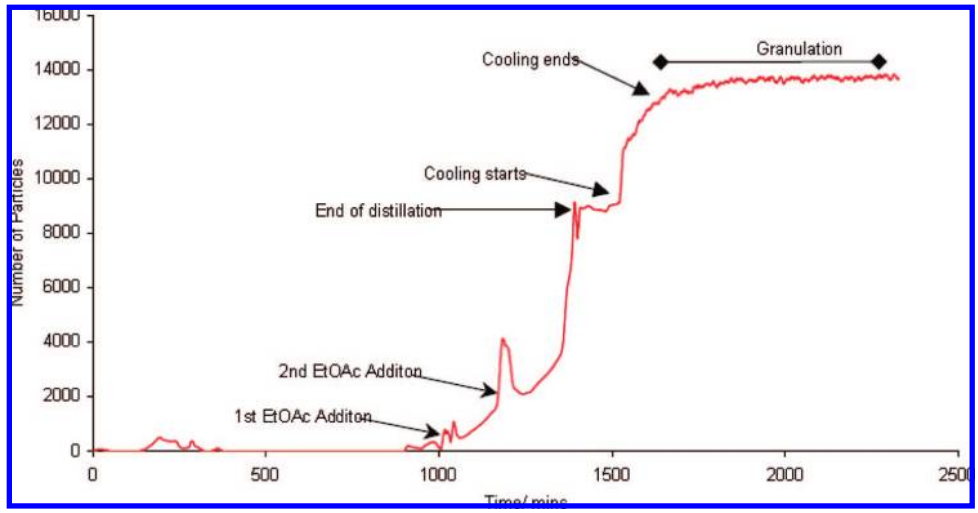

Figure 3. **FBRM data for the crystallisation of 1.**

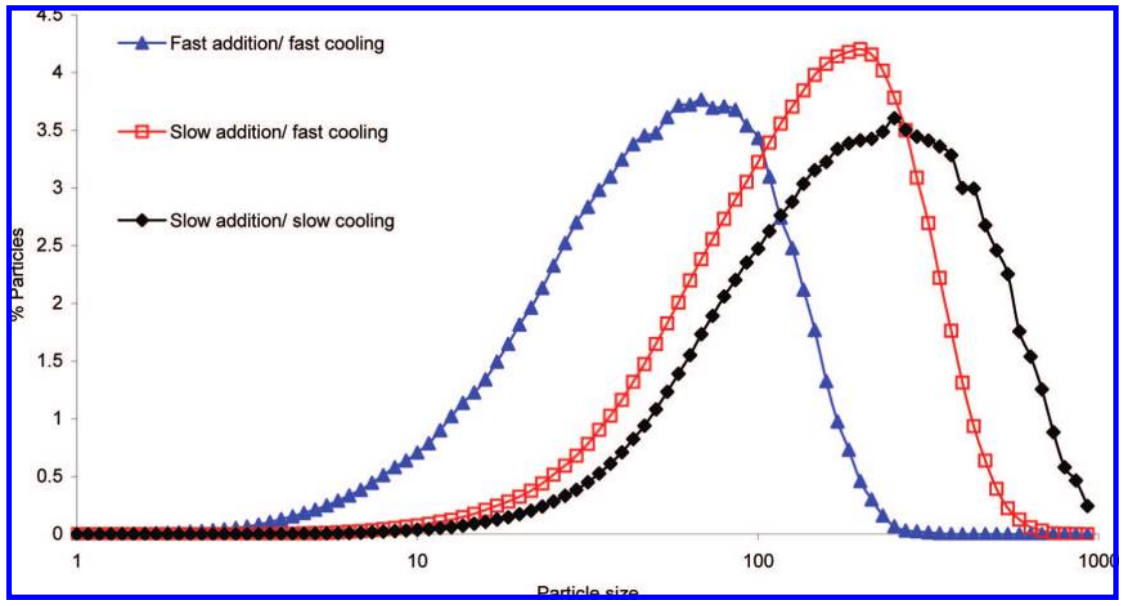

Figure 4. **FBRM data demonstrating the effect of ethyl acetate addition/cooling rate on particle size of 1.**

significant product losses were occurring in the aqueous acidic extraction (part of the acid/base cycle) and final water wash of the workup.

The acid/base cycle was incorporated into the workup of **1**, as it was originally required to purge alcohol **15**, carried over from the oxidation step, and other process-related impurities associated with the synthesis. As the quality of the input intermediates in the final step had been improved, it was envisaged that a simplified workup would be feasible, and subsequently the workup was simplified to an aqueous sodium hydroxide quench and pH adjustment, followed by a second aqueous sodium hydroxide wash.

Removal of the final water wash, which gave a poor and slow separation accompanied by product losses, led to increased levels of sodium tosylate in the final isolated product. Other aqueous washes (brine, sodium hydroxide) failed to efficiently remove the residual *p*-TsOH, even with repeated washing. Fortuitously, a water reslurry of isolated dried **1** with entrained sodium tosylate effectively removed all inorganic salts, with almost quantitative recovery of **1** (99%).

The workup procedure for the isolation of **1** was consequently simplified from a sodium hydroxide quench, separation, acid/base cycle, water wash, and solvent replacement to an aqueous sodium hydroxide quench and pH adjustment, followed by a second aqueous sodium hydroxide wash and removal of THF/water by solvent replacement with ethyl acetate. Although there were concerns sodium hydroxide entrained in the ethyl acetate may cause hydrolysis in the distillation generating ethanol, with the potential to affect the crystallization of **1**, no issues were encountered on prolonged distillation. A solubility curve was generated for **1** in ethyl acetate containing 1% THF/water. The tetrahydrofuan level was not varied as scale-up data had demonstrated that at distillation end THF levels were typically 1% and did not vary significantly. Solubility data showed that only 4 equiv of water are required to form a complete solution and that the water level at the end of distillation had to be carefully controlled (Figure 1).

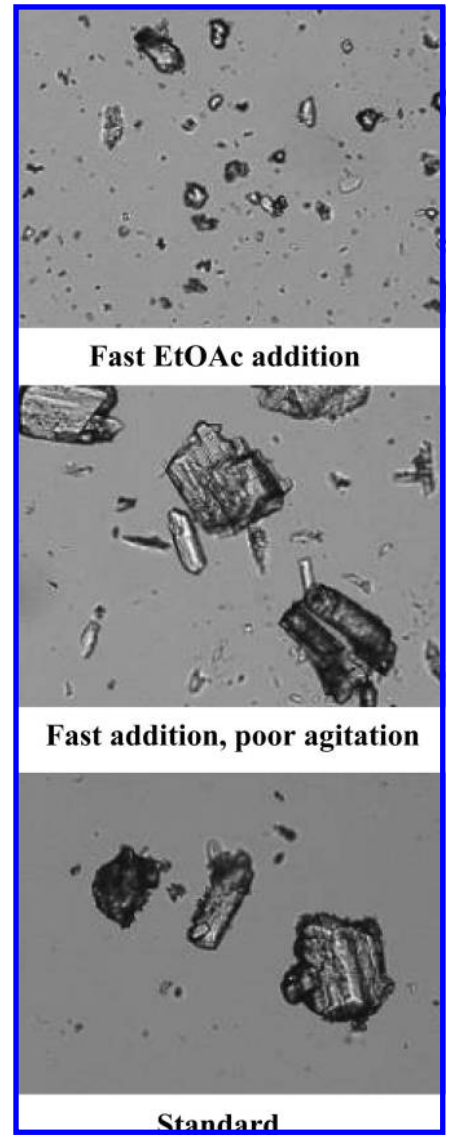

Figure 5. **Photomicrographs demonstrating the effect of ethyl acetate addition on particle size of 1.**

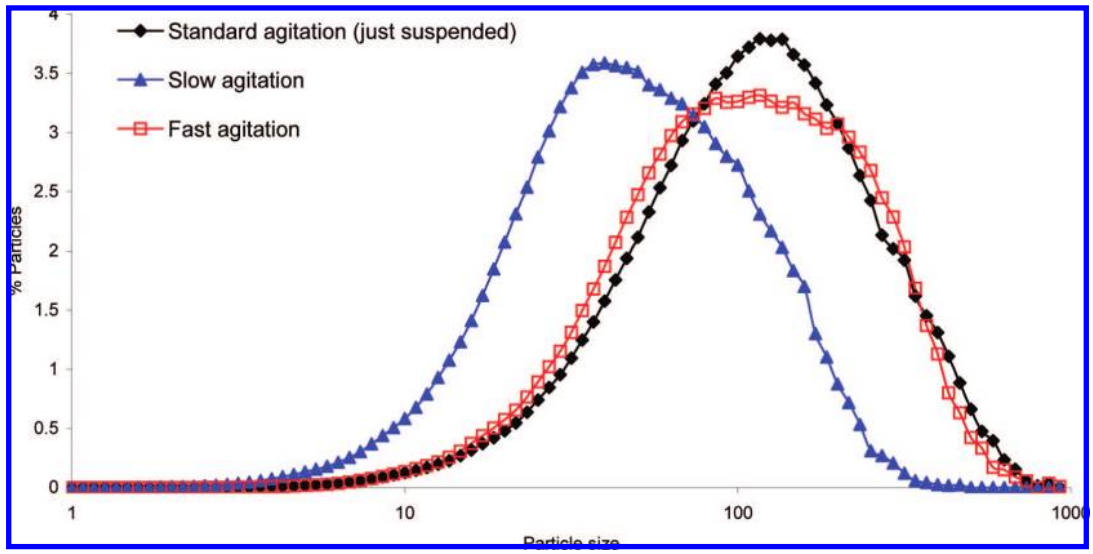

Figure 6. **FBRM data demonstrating the effect of agitation on particle size of 1.**

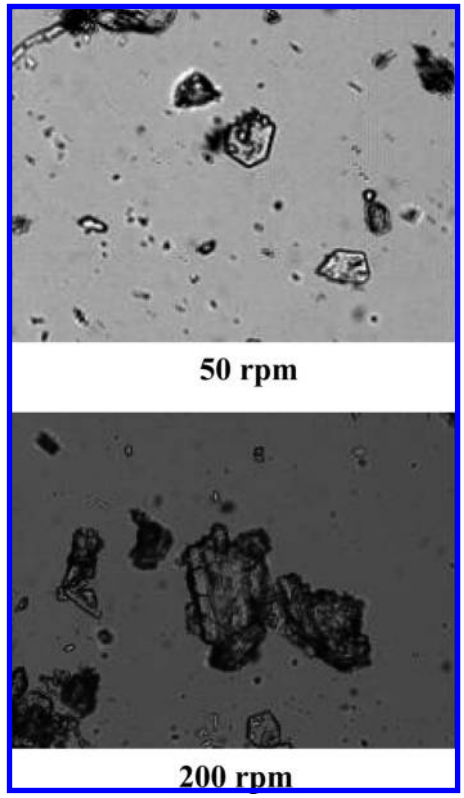

Figure 7. **Photomicrographs demonstrating the effect of agitation on particle size of 1.**

The free base of **1** was crystallised, either at reflux or on cooling, isolated by filtration, and dried, prior to a water reslurry to remove entrained inorganics. The complete isolation including the water reslurry could be performed in a filter dryer. This process was demonstrated in the Pilot Plant on multikilogram scale affording **1** in high yield (90%) and excellent purity.

2.4. Particle Size Investigation. To obtain a better understanding of the factors determining the particle size and distribution of isolated **1** the crystallisation process (Figure 2) was investigated using a focused beam reflectance measurement (FBRM) probe, an online particle measurement tool, on Pilot Plant scale (Figure 3).

The following key events were identified in the crystallisation of **1**:

(1) During solvent replacement in the distillation, ethyl acetate is added in portions, precipitation is always observed after addition of a portion of ethyl acetate.

(2) Nucleation occurs during cooling with substantial formation of fines.

(3) Little change of particle size occurs on granulation.

This prompted us to investigate the effects of the rate of ethyl acetate addition, the rate of cooling during nucleation (Figures 4, 5), and agitation (Figures 6, 7) on particle size. Interestingly, the addition rate of ethyl acetate had the most pronounced effect on particle size; slow addition gave a smaller bulk temperature decrease during the addition, which resulted in larger particles. The cooling rate during nucleation had a less significant effect, although slower cooling rates also generated larger particles. Agitation also had some influence, faster agitation giving larger particles, presumably because localised, high super-saturation hotspots were not generated. Although the agitation experiments were carried out at 50 and 200 rpm, the agitation was increased/decreased to 100 rpm during FBRM data acquisition, as FBRM data has a dependence on agitation. These experiments coupled with the Pilot Plant FBRM probe helped us design a robust large-scale crystallisation process.

Polymorphism of **1** has been extensively evaluated. A comprehensive polymorph screen has generated two anhydrous forms, one amorphous (Form A) and one crystalline (Form B). Form B has been consistently and exclusively produced by the bulk enabling (route 1) and commercial routes (route 2), and repeated attempts to generate Form A for further studies have failed.

3. Conclusion

A process to generate Maraviroc (**1**) was developed and demonstrated in 20 L laboratory glassware to deliver 1.5 kg of API in 53% overall yield. The laboratory sequence was transferred to both the Kilo Laboratory and Pilot Plant to deliver further multikilogram quantities of API from two campaigns in 54% and 50% overall yields, respectively. Observations made

from the scale-up campaigns prompted further development of the route to address key issues. These improvements were incorporated in the second Pilot Plant campaign to deliver multikilogram quantities of API **1** in an overall yield of 72%, from ester **13**, triazole substituted tropane **7**, and acid **11**, an increase of ~20% over the previous two campaigns. We have also developed an understanding of the crystallisation so that we can control the particle size and hence avoid having to mill the product.

4. Experimental Section

4.1. General. All raw materials, reagents, and solvents were purchased from commercial suppliers and used without further purification. All reactions were conducted under an atmosphere of nitrogen unless noted otherwise. Reactions were monitored for completion by removing a small sample from the reaction mixture and analysing by HPLC. HPLC analysis was performed using one of the following systems: C18 or C8 reverse phase column 15 cm × 0.46 cm, 5 μ; mobile phase consisting of solvent A, 20 mM dipotassium hydrogen orthophosphate; solvent B acetonitrile; eluent gradients ranging from 2−55%, 20−60%, or 30−70% mobile phase B over 45, 55, or 25 min; λ 210 nm. C18 normal phase column 250 mm × 4.6 mm eluting with THF/heptane, 16:24 v/v, saturated with water over 15 min.

4.2. 4,4-Difluoro-*N*-{(1*S*)-3-[exo-3-(3-isopropyl-5-methyl-4H-1,2,4-triazol-4-yl)-8-azabicyclo[3.2.1]oct-8-yl]-1-phenylpropyl}cyclohexanecarboxamide (1). Amine tosylate salt **8** (70.0 kg, 172.2 mol) and sodium triacetoxyborohydride (54.7 kg, 258.3 mol) were slurried in ethyl acetate (505.1 L) and cooled to 0 °C under a nitrogen atmosphere. A solution of **16** (55.9 kg, 189.4 mol) in THF (280 L) was added to the reaction mixture maintaining the temperature below 10 °C. The resultant slurry was warmed to 15 °C over 30 min, stirred for 1.5 h, and treated with 2 M sodium hydroxide solution (280 L). The aqueous layer was adjusted to pH 11−12 by addition of 10 M sodium hydroxide solution, and the layers were separated. The organic phase was washed with 2 M sodium hydroxide solution (210 L). The organic phase was distilled and replaced at atmospheric pressure with ethyl acetate and reduced to a total volume of 210 L. The mixture was cooled to 0 °C and granulated. The product was collected by filtration, washed with ethyl acetate (70 L), and dried at 50 °C under vacuum. The solid was then slurried in water (210 L) at ambient temperature, collected by filtration, washed with water (70 L), and dried at 50 °C under vacuum to give **1** as a white crystalline solid (80.55 kg, 91%). Mp 193.5 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ [ppm] 7.36 (m, 2), 7.23 (m, 3), 6.61−6.48 (m, br, 1), 5.15 (m, 1), 4.28 (m, 1), 3.36 (d, br, 2), 2.85 (m, 1), 2.48 (s, 3), 2.28 (m, 2), 2.18−1.61 (m, 19), 1.39 (d, 6). ^{1}H NMR (500 MHz, DMSO) δ [ppm] 8.22 (d, 1), 7.30 (m, 4), 7.20 (m, 1), 4.96 (dt, 1), 4.21 (tt, 1), 3.28 (m, 1), 3.27 (m, 1), 3.13 (septet, 1), 2.38 (s, 3), 2.33 (t, 2), 2.32 (m, 1), 2.06−1.63 (m, 4), 2.03−1.82 (m, 2), 2.03−1.76 (m, 2),1.91−1.65 (m, 4), 1.82−1.6 (m, 2), 1.81 (m, 2), 1.74−1.56 (m, 2), 1.24 (d, 6). ^{13}C NMR (125 MHz, DMSO) δ [ppm] 12.2, 21.7, 24.7, 25.4 (J ^{13}C−^{19}F 9 Hz), 25.6 (J ^{13}C−^{19}F 9 Hz), 25.8, 25.9, 32.1 (J ^{13}C−^{19}F 24, 7 Hz), 32.3 (J ^{13}C−^{19}F 24, 7 Hz), 35.5, 35.8, 40.9, 46.7, 48.0, 50.3, 58.2, 58.4, 123.6, 126.2, 126.4, 128.1, 144.1, 149.6, 158.4, 172.9. FT-IR (cm^{-1}): 3264 (NH, 2° amide); 3062, 3022 (CH, aryl); 2955−2825 (CH, alkyl); 1662 (C═O, amide); 1531 (NH, amide); 1513, 1494 (C═C, aryl, *C*═N); 1453 (C−CH_3 asymmetric); 1432 (C−CH_2, scissor vibration); 1370 (C−CH_3, symmetric); 1290−1195 (CH in plane deformations, aryl); 1103 (CF); 962 (C−CH_3 rock), 754, 702 (CH out of plane deformations, monosubstituted aromatic). MS *m*/*z* 514.4 $[M + H]^+$. Anal. Calcd for $C_{29}H_{41}F_2N_5O$: C, 67.75; H, 8.06; N, 13.54. Found: C, 67.81; H, 8.04; N, 13.63. HPLC purity: 97.5%. *p*-TsOH: 0.11%. Water: 0.14%. Palladium: <10 ppm. Residue on ignition [Sulphated Ash]: <0.2%.

4.3. *exo*-3-(3-Isopropyl-5-methyl-4H-1,2,4-triazol-4-yl)-8-azabicyclo[3.2.1]octane *p*-Toluenesulfonate (8). *N*-Benzyl tropane **7** (40.0 kg, 123.3 mol) and *p*-TsOH·H_2O (23.45 kg, 123.3 mol) were dissolved in methanol (132 L) at ambient temperature, under a nitrogen atmosphere. To the reaction solution were added 5%Pd/C (ESCAT 147, 1.0 kg, 2.5 wt %) and activated carbon (NORIT SX3, 0.80 kg, 2 wt %). Hydrogen (3 bar) was applied to the mixture, which was then heated to 50 °C. Hydrogen was applied until the uptake had ceased. The reaction was cooled to 22 °C, filtered to remove catalyst, and washed with methanol (60.0 L). The methanol solution was distilled at atmospheric pressure and replaced with *i*-propanol (240 L) to a final volume of 120 L. The mixture was cooled to 0 °C over 4 h and granulated. The product was collected by filtration, washed with *i*-propanol (40.0 L), and dried at 55 °C under vacuum, to yield amine tosylate salt **8** as a crystalline white solid (46.25 kg, 92% yield). Mp 213.1 °C. ^{1}H NMR (300 MHz, CD_3OD) δ [ppm] 7.71 (d, 2), 7.23 (d, 2), 4.54 (m, 1), 4.23 (s, br, 2), 3.30−3.25 (m, 1), 2.52 (s, 3), 2.47−2.43 (m, 2), 2.36 (s, 3), 2.22−2.10 (m, 6), 1.34 (d, 6). ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 1.23 (d, J = 6.84 Hz, 18 H), 2.01 (s, 18 H), 2.28 (s, 15 H), 3.15−3.38 (m, 13 H), 4.23−4.38 (m, 3 H), 7.12 (d, J = 7.82 Hz, 6 H), 7.50 (d, J = 8.06 Hz, 5 H). ^{13}C NMR (75 MHz, CD_3OD) δ [ppm] 11.30, 20.20, 21.07, 25.38, 25.46, 33.25, 46.25, 55.34, 125.74, 128.79, 140.74, 142.33, 151.43, 160.36. HPLC purity: 95.3%.

4.4. Ethyl (*S*)-3-[(4,4-Difluorocyclohexyl)carboxamido]-3-phenylpropanoate (14). Sodium carbonate (8.4 kg, 79.2 mol) was dissolved in water (60 L) at ambient temperature and **13**·HCl (6.1 kg, 26.6 mol) added to the solution, followed by dichloromethane (30 L), and the mixture was cooled to 20 °C. The acid chloride **12** was added to the mixture as a toluene concentrate (30 L, 29.3 mol), maintaining the temperature below 35 °C. On completion of the addition, the reaction was cooled to 25 °C and stirred for 60 min. The aqueous phase was adjusted to pH 9−10 by the addition of 10 M sodium hydroxide. The phases were separated, and the aqueous phase was extracted further with dichloromethane (30 L). The organic extracts were combined and washed with 2 M sodium hydroxide (30 L) and water (30 L). The organics were distilled at atmospheric pressure to a total volume of ~48 L. Toluene (5 L) was added and the distillation continued to a total volume of 30 L. The mixture was cooled to 30 °C and diluted with heptane (30 L). The slurry was further cooled to 18 °C and stirred for 2 h. The solid was collected by filtration, washed with heptane (5 L), and dried at 40 °C under vacuum to yield **14** as a crystalline white solid (8.38 kg, 93%). Mp 106.2 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ [ppm] 7.30 (m, 5), 6.76 (d, br, 1), 5.40 (m, 1), 4.08 (q, 2),

2.95−2.75 (m, 2), 2.30−2.09 (m, 3), 2.04−1.62 (m, 6), 1.15 (t, 3). ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 1.11 (s, 2 H), 1.57 (s, 2 H), 1.76 (s, 4 H), 2.01 (s, 2 H), 2.28 (s, 1 H), 2.72 (s, 2 H), 4.01 (none, 2 H), 5.21 (s, 1 H), 7.22 (s, 1 H), 7.29−7.31 (m, 3 H), 8.34 (s, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$) δ [ppm] 14.25, 24.84, 33.02 (J ^{13}C−^{19}F 24, 24 Hz), 40.15, 42.89, 49.55, 61.06, 122.84 (J ^{13}C−^{19}F 242, 240 Hz), 126.34, 127.83, 128.91, 140.78, 171.63, 173.43. MS m/z 338 [M − H]$^-$. HPLC purity: 99.4%

4.5. (*S*)-4,4-Difluoro-*N*-(3-hydroxy-1-phenylpropyl)cyclohexanecarboxamide (15). Ester **14** (85.5 kg, 251.9 mol) and sodium borohydride (19.1 kg, 503.8 mol) were slurried in THF (598.5 L) at ambient temperature under a nitrogen atmosphere. The mixture was heated to 50 °C at 1 °C/min. Methanol (51.0 L) was added to the reaction over 60 min, maintaining the temperature below 55 °C. On completion of the addition, the mixture was heated to reflux and held for 90 min, then cooled to 20 °C. Acetone (92.6 L) was added over 60 min, maintaining the temperature below 25 °C. The mixture was stirred for 15 min, and then cyclohexane (299.3 L) was added. Sodium hydroxide solution (2 M, 427.5 L) was added to the reaction to give a biphasic solution, which was stirred for 15 min. The phases were separated, and the organic phase was washed with 20% brine solution (171 L). The organic solution was distilled and replaced with THF (548.6 L) at atmospheric pressure to a total volume of 270 L. Cyclohexane (769.5 L) was added to the solution over 30 min, maintaining the temperature above 55 °C. On completion of the addition, the mixture was heated to reflux, then cooled to 20 °C over 180 min, with fast agitation. The slurry formed was granulated at 20 °C, collected by filtration, washed with 3:1 cyclohexane/THF (85.5 L), and dried at 50 °C under vacuum. **15** was isolated as a crystalline white solid (74.0 kg, 99%). Mp 119.2 °C. ^{1}H NMR (75 MHz, $CDCl_3$): δ [ppm] 7.30 (5H, m), 6.23 (1H, br d), 5.20 (1H, m), 3.75−3.50 (2H, m), 3.15 (1H, br s), 2.18 (4H, m), 2.00−1.62 (7H, m). ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 1.58 (s, 9 H), 1.78 (s, 27 H), 2.02 (s, 9 H), 2.31 (s, 4 H), 3.36 (s, 9 H), 4.44 (s, 4 H), 4.89 (s, 4 H), 7.19 (s, 4 H), 7.27 (d, J = 5.37 Hz, 18 H), 8.19 (s, 4 H). ^{13}C NMR (75 MHz, $CDCl_3$) δ [ppm] 26.13 (J ^{13}C−^{19}F 10, 14, 9 Hz), 33.04 (J ^{13}C−^{19}F 25.5, 23 Hz), 38.32, 42.91, 51.10, 59.16, 122.82 (J ^{13}C−^{19}F 242, 240 Hz), 126.67, 127.76, 128.98, 141.60, 174.88. MS m/z 297.5 [M]. HPLC purity: 99.3%.

4.6. (*S*)-4,4-Difluoro-*N*-(3-oxo-1-phenylpropyl)cyclohexanecarboxamide (16). Alcohol **15** (74.0 kg, 248.9 mol), sodium bromide (26.4 kg, 256.3 mol), sodium bicarbonate (23.0 kg, 273.8 mol) and TEMPO (0.389 kg, 2.5 mol) were slurried in dichloromethane (740 L) and water (370 L) at ambient temperature, under a nitrogen atmosphere. The biphasic mixture was cooled to 10 °C. Sodium hypochlorite was added to the mixture, maintaining the temperature below 10 °C. On completion of the addition, the reaction was stirred for 20 min; 10% sodium thiosulfate (185 L) was added to the mixture, and stirring continued for 15 min to ensure all excess sodium hypochlorite has been quenched. The biphasic solution was separated. The organic phase was distilled at atmospheric pressure to a total volume of 150 L. The mixture was cooled to 40 °C and toluene (222.0 L) added before cooling further to 20 °C. On precipitation of a light slurry, heptane was added (444.0 L) over 30 min and the mixture stirred at 20 °C for 60 min. and then granulated at 10 °C. **16** was isolated by filtration, washed with heptane (148.0 L), and dried at 40 °C under vacuum to yield a crystalline white solid (64.30 kg, 88%). Mp 119.0 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ [ppm] 9.78 (1H, s) 7.30 (5H, m), 6.15 (1H, br d), 5.50 (1H, m), 3.05 (2H, m), 2.18 (3H, m), 2.00−1.55 (6H, m). ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 1.57 (s, 8 H), 1.75 (s, 17 H), 2.02 (s, 8 H), 2.29 (s, 4 H), 2.82 (s, 8 H), 5.37 (s, 4 H), 7.23 (s, 4 H), 7.30−7.32 (m, 15 H), 8.36 (d, J = 8.30 Hz, 4 H), 9.59−9.62 (m, 4 H). ^{13}C NMR (75 MHz, $CDCl_3$) δ [ppm] 26.01 (J ^{13}C−^{19}F 10.4, 10.3 Hz), 32.95 (J ^{13}C−^{19}F 23.9, 24.7 Hz), 42.77, 48.60, 49.24, 122.83 (J ^{13}C−^{19}F 242.5, 240 Hz), 126.58, 128.12, 129.14, 140.63, 173.91, 200.49. MS m/z 295 [M]. HPLC purity: 97.4%

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