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# Sustainable synthesis of enantiopure fluorolactam derivatives by a selective direct fluorination – amidase strategy†

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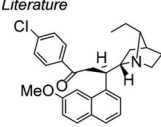
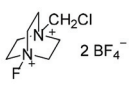
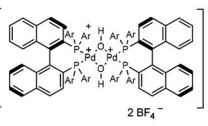
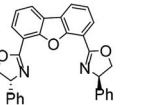
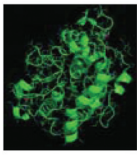
Pharmaceutically important chiral fluorolactam derivatives bearing a fluorine atom at a stereogenic centre were synthesized by a route involving copper catalyzed selective direct fluorination using fluorine gas for the construction of the key C–F bond and a biochemical amidase process for the crucial asymmetric cyclisation stage. A comparison of process green metrics with reported palladium catalyzed enantioselective fluorination methodology shows the fluorination-amidase route to be very efficient and more suitable for scale-up.

## Introduction

Enzyme catalysed reaction of functional fluoromalonate building blocks, prepared using fluorine gas, has been used for the first time for the enantioselective synthesis of a pharmaceutically important chiral fluorolactam derivative. An inexpensive, highly economically competitive, lower waste stream process that does not rely on precious metal catalysis and has been quantified by green metric analysis is described.

The synthesis of chemical intermediates bearing a fluorine atom at a stereogenic centre is becoming increasingly important for applications across the materials and life-science sectors.<sup>1</sup> While fluoroaromatic derivatives appear as sub-units in many commercially valuable pharmaceutical products,<sup>2</sup> there are far fewer fluorinated drugs on the market where a single fluorine atom is attached to an sp<sup>3</sup> carbon, apart from several anti-inflammatory fluorosteroid derivatives.<sup>3</sup> One reason for the relative lack of commercial products that bear fluorine at a stereogenic centre is the often very difficult synthesis, but much progress in the field of enantioselective chemical fluorination has been made in recent years.<sup>4</sup> Fluorination of positions  $\alpha$  to a carbonyl group by an electrophilic fluorination process is a common approach to the synthesis of enantiopure fluorinated systems and various Selectfluor<sup>TM</sup>-

cinchona alkaloid combinations,<sup>5</sup> palladium or zinc catalysed processes using *N*-fluorobenzenesulfonamide (NFSI),<sup>6</sup> organo-catalyst-fluorinating agent combinations<sup>7</sup> and chiral fluorinating agents based upon Selectfluor<sup>TM</sup>-type derivatives<sup>8</sup> have been devised and successfully implemented to give a range of enantiopure fluorinated building blocks (Scheme 1). Whilst these chemical approaches can be very valuable at the discov-

Catalyst	Fluorinating agent	Advantage/disadvantages
Literature 	 2 BF <sub>4</sub> <sup>–</sup> Selectfluor <sup>TM</sup> [Reference 5]	One-step enantioselective fluorination  Small scale discovery chemistry  Multi-step syntheses of catalysts
	(PhSO <sub>2</sub> ) <sub>2</sub> N-F NFSI [Reference 15]	Low atom economy, low PMI  Selectfluor <sup>TM</sup> and NFSI are synthesised from F <sub>2</sub>
	(PhSO <sub>2</sub> ) <sub>2</sub> N-F NFSI [Reference 6c]	Expensive fluorinating reagents
This work 	F <sub>2</sub>	Low-cost lipase catalyst and fluorinating reagent  Higher atom economy and appropriate for scale-up  Catalyst recycling readily achieved  Multi-step fluorination/resolution strategy
CAL-B 10,000		

**Scheme 1** Examples of reagent combinations used for the synthesis of enantiopure systems with fluorine located at a stereogenic centre.

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†Electronic supplementary information (ESI) available: For experimental details (SI-1), metrics calculations (SI-2), HPLC analysis (SI-3), X-ray crystallography (SI-4) and NMR spectra (SI-5). CCDC 1401917–1401922. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c5gc02209f

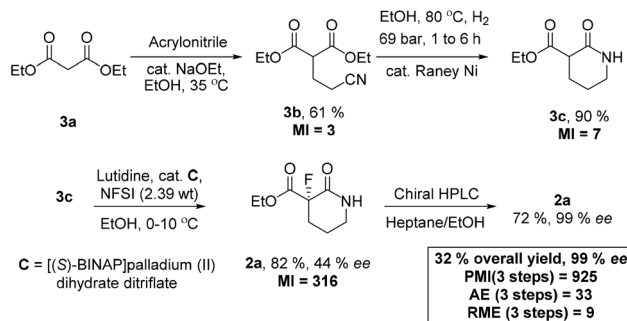


ery stage of a medicinal chemistry process, the application of chemical enantioselective fluorination strategies at larger scale is severely hampered by the usually prohibitive expense of the reagent-ligand combinations and the large waste streams generated.

Pharmaceutical companies are increasingly concerned about the environmental impact of their commercial products and, for example, GSK recently announced an environmental strategy with the objective that the company's operations become carbon neutral by 2050.<sup>9a</sup> Additionally, the European Federation of Pharmaceutical Industries and Associations (EFPIA) continues to develop the Eco-Pharmaco-Stewardship (EPS) proposal to develop methods to minimise the effect of pharmaceuticals within the environment including in the development and manufacturing stages.<sup>9b</sup>

Consequently, highly efficient low-waste synthetic processes for pharmaceutical manufacture are required to meet the industry's ambitious environmental goals. Therefore, methods for assessing the efficiency and amount of waste generated by a synthetic strategy are used, in part, to identify a suitable final process for pharmaceutical manufacture. Green metrics packages allow a holistic comparison between potential synthetic reaction pathways using a mixture of quantitative and qualitative assessment criteria.<sup>10</sup> Calculations of total process mass intensity (PMI) enables the synthetic chemist to simply compare the environmental effect of competing synthetic strategies from common starting materials, thus aiding the selection of the final preparative route.<sup>11</sup>

A series of pre-clinical candidate spleen tyrosine kinase (Syk) inhibitors<sup>12</sup> **1** have been synthesised from chiral fluorolactam building blocks **2** (Scheme 2). General synthetic procedures for the preparation of enantiopure 2-fluoro-1,3-amidoesters are relatively rare<sup>13</sup> and are limited to enantio-



**Scheme 3** Process mass intensity (PMI), mass intensity (MI), atom economy (AE) and reaction mass efficiency (RME) calculations for the literature synthesis of **2a**.

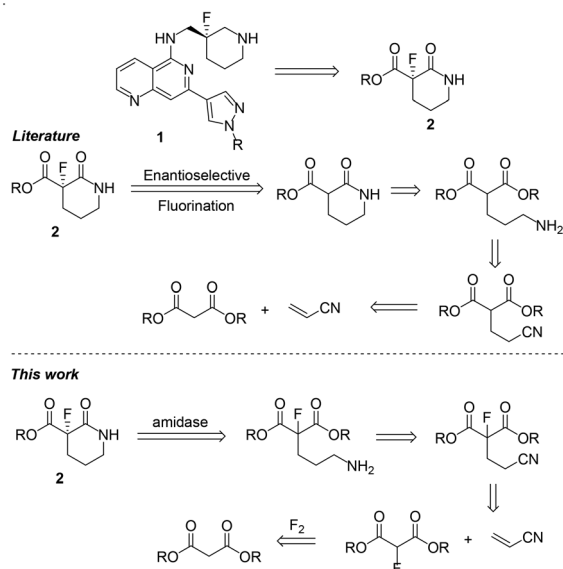
selective fluorination of malonate esters using NFSI with  $\text{Zn}(\text{OAc})_2/\text{DBFOX-Ph}$  catalyst followed by amide formation,<sup>6c</sup> ligand catalysed chiral alkylation of fluoromalonate derivatives followed by amide formation<sup>14</sup> or fluorination using NFSI with chiral palladium catalysis.<sup>12,15</sup>

The NFSI-palladium catalysis protocol reported by Sodeoka<sup>15</sup> was adopted for scale up and **2a** was synthesised on 100 g scale<sup>12</sup> (Scheme 3). However, the route<sup>12a,15</sup> requires a structurally complex palladium catalyst prepared by multi-step procedures and purification of the desired enantiomer by time-consuming chiral HPLC due to the relatively low 44% ee obtained for the fluorination stage when performed on the large scale.

## Results and discussion

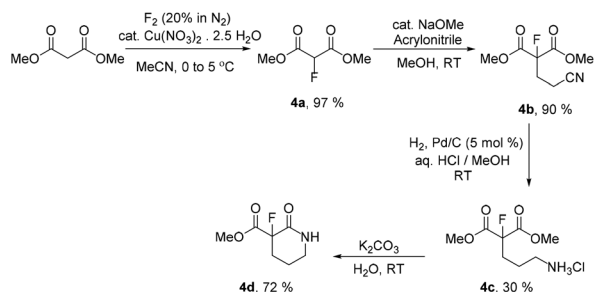
Our assessment of the reported synthesis of **2** (Scheme 3) using green metric analysis (SI-2<sup>†</sup>), shows that the single-step enantioselective fluorination reaction has an estimated calculated process mass intensity (PMI) value of 925 (SI-2<sup>†</sup>). Inspection of each stage of the synthetic route shows that most waste is generated in the key enantioselective fluorination stage because, of course, NFSI is synthesised by reaction of the corresponding sulfonamide with fluorine gas,<sup>16</sup> which must be taken into account when calculating PMI measurements, and loss of material due to the low ee and subsequent resolution. We assumed that all solvent used in the HPLC resolution was recycled and the waste generated in the multi-step synthesis of the palladium catalyst was not included in the PMI calculation. Consequently, the PMI 925 is a low estimate and offers a reasonable benchmark for process development.

As an alternative synthetic strategy, initially we investigated the synthesis of related fluorolactam derivative **2b** ( $\text{R} = \text{Me}$ ) using a combined chemical and biochemical synthetic approach from fluoromalonate ester starting materials (Scheme 2). While enzyme catalysed asymmetric hydrolysis of various fluoromalonate derivatives have been developed,<sup>17</sup> no asymmetric amidase reactions of fluoromalonate derivatives have been reported.



**Scheme 2** Retrosynthetic approach to Syk inhibitors **1**.<sup>12</sup>





**Scheme 4** Initial unoptimised synthesis of racemic **4a–d**.

Fluoromalonate ester **4a** is synthesised in the high yield direct fluorination reaction of dimethyl malonate ester using fluorine gas catalysed by copper nitrate in acetonitrile solution.<sup>18a</sup> Recently, we described the optimisation of this process which is routinely carried out on the 50 g scale and assessed to have a mass intensity MI = 9 (Scheme 4).<sup>18b</sup>

Initial unoptimised synthesis of a range of racemic mono-fluorinated functional precursors **4** for subsequent enzymatic transformation reactions were carried out. Michael addition of acrylonitrile<sup>19</sup> to fluoromalonate **4a** gave the desired nitrile **4b** in 90% yield and subsequent reduction of the nitrile group of **4b** by hydrogen over palladium enabled the isolation of salt **4c**. Base catalysed ring closure gave racemic fluorolactam **4d** (Scheme 4, SI-1.2†). With products **4b–d** in hand we began attempts to resolve each fluorinated intermediate by appropriate enzymatic methods to identify the most effective synthetic sequence for the large scale synthesis of the desired enantiopure chiral fluorolactam **2b**.

Initially, hydrolase catalysed resolution of **4b** was attempted adapting literature protocols.<sup>20</sup> However, nitrile **4b** was unstable in mildly basic aqueous media (pH 7.0–7.1) and so this approach was discounted as a viable starting material for desymmetrisation (SI-1.3†).

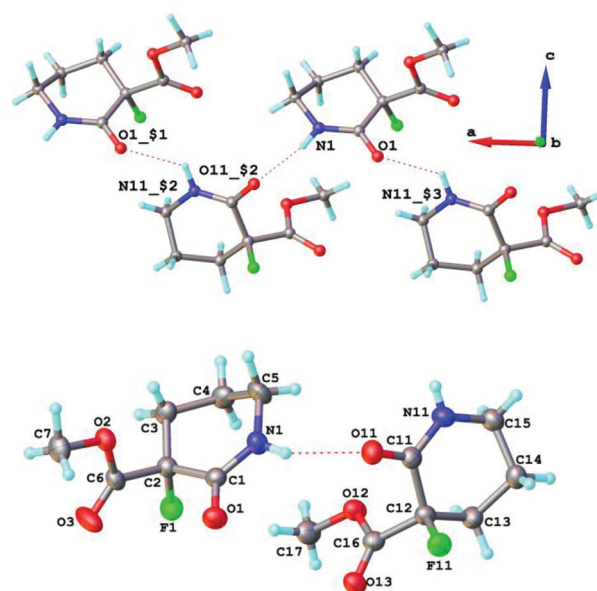
Attempted hydrolase promoted amidation in anhydrous tertiary amyl alcohol as the solvent<sup>21</sup> gave only racemic product **4d** from salt **4c** using various enzyme catalysts (SI-1.4†). After determining that **4d** does not hydrolyse in aqueous phosphate buffer (pH 7.3) to the corresponding acid at 20–25 °C over 16 hours (SI-1.4†), enzymatic transformations of **4c** were explored in this aqueous buffered medium and, indeed, **4d** could be resolved by a variety of hydrolases. Following an initial screening process of 56 enzymes (SI-1.5†), 25 promising hydrolases that afforded 10–60% hydrolysis of **4d** in 8 hours were analysed further (SI-1.5†). A number of highly enantioselective processes were observed (Table 1) giving both acids **5a,b** by hydrolysis (SI-1.6†) and the corresponding esters **2b,c** as reaction products. Both **2b** and **2c** were isolated by preparative scale HPLC (SI-3†) and their structures and absolute stereochemistries confirmed by X-ray crystallography (Fig. 1, SI-4†).

CAL-B 10 000 is a recombinant *Candida Antartica* Lipase B that is commercially available from Fermase and used to cata-

**Table 1** Initial hydrolase resolution screening of **4d**

Entry	Hydrolase	Conv. % <sup>a</sup>	Acid <b>5</b>		Ester <b>2</b>	
			ee %		ee %	
1	JM X14	30	>95	( <i>S</i> )- <b>5a</b>	62	( <i>R</i> )- <b>2c</b>
2	JM X35	19	>95	( <i>S</i> )- <b>5a</b>	19	( <i>R</i> )- <b>2c</b>
3	JM X50	28	>95	( <i>S</i> )- <b>5a</b>	37	( <i>R</i> )- <b>2c</b>
4	CAL-B 10 000	51	>95	( <i>R</i> )- <b>5b</b>	>95	( <i>S</i> )- <b>2b</b>

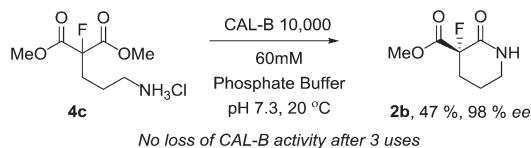
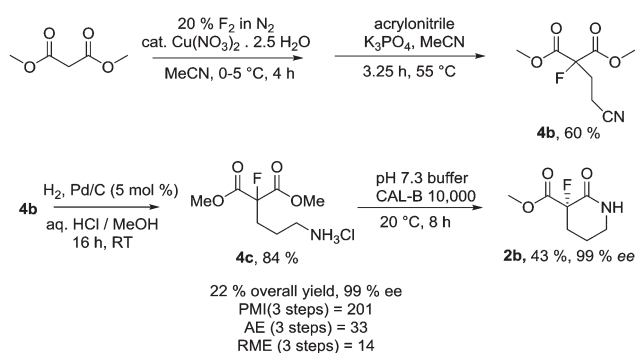
<sup>a</sup> Calibrated UPLC-MS conversion.



**Fig. 1** Molecular structures of (*S*)-**2b** (above) and (*R*)-**2c** (below).

lyse a range of biotransformations on the large scale.<sup>22</sup> Since inexpensive CAL-B 10 000 affords the desired fluorolactam (*S*)-**2b** (entry 4, Table 1), and is available for purchase on the multi-kilogram and tonne scale, this hydrolase was selected for further reaction optimisation. The possibility of telescoping the formation and resolution of **2b** from salt **4c** was explored to reduce the work-up process. Initially when **4c** was added to buffer solution at room temperature to form a 25 mM solution, we observed that the pH reduced from 7.3 to 6.7 after 15 minutes and that no side-reactions or degradation could be detected. However, when the pH of the solution was readjusted to 7.3 by addition of 2 N NaOH (0.92 equiv.), <sup>19</sup>F NMR spectroscopic and chiral HPLC (SI-3†) analysis of the crude reaction



Scheme 5 Synthesis of fluorolactam **6** from **4c**.Scheme 6 Optimised synthesis of **2b**.

mixture indicated full conversion to the desired enantiopure lactam **2b** in 47% yield and 98% ee (Scheme 5, SI-1.7†).

The most operationally simple experimental protocol for the transformation of **4c** to **2b** would be to add **4c** in one portion to the reaction mixture and then adjust the pH to 7.3. Unfortunately, at 250 mM concentrations, the solution became too acidic (pH 4.9) and hydrolysis by-products were formed. This issue was, however, resolved by slow addition of the salt and base, such that the pH was maintained between 6.8 and 7.3. Consequently, the desymmetrization reaction could be telescoped very successfully at 257 mM concentration and the desired fluorolactam **2b** was separated efficiently by solid phase extraction. CAL-B enzyme was recovered quantitatively and recycled three times without any observed loss of reactivity profile in subsequent cyclisation processes.

With basic operational parameters for the synthesis of enantiopure **2b** using inexpensive reagents and solvents in place, we carried out studies to optimise the multistep synthesis in order to assess the green metrics of the chemo-enzymatic process in comparison to the published enantioselective fluorination strategy (Scheme 6).

In order to reduce the solvent use in reaction work-up, the possibility of carrying out the subsequent Michael addition reaction of **4a** with acrylonitrile in a one-pot process without any work-up after the fluorination stage was explored. Firstly, the Michael addition reaction between the crude direct fluorination product mixture and acrylonitrile was assessed but no alkylation reaction occurred due to problems associated with the presence of copper nitrate and HF in the reaction mixture. Consequently, reactions in which a short series of environmentally benign bases including DBU, potassium phosphate and 2-methyl pyridine, were added to the crude direct fluorination

product mixture were screened. Addition of 0.5 equivalents of potassium phosphate to the reaction mixture allowed the Michael reaction to proceed to full conversion at room temperature. Scale-up of the one-pot process on 100 mmol scale, where the acrylonitrile was added to the crude direct fluorination reaction mixture *via* syringe pump over 30 minutes, gave **4b** in 60% yield after 1.5 hours.

Reduction of the nitrile group of **4b** was carried out in a Parr hydrogenator with palladium/carbon in methanol and conc. hydrochloric acid. Upon completion of the hydrogenation, a white precipitate formed upon washing the crude reaction mixture with ethanol which allowed simple filtration of the ammonium hydrochloride salt **4c**. After process optimisation, the solvent volume used for the reduction could be reduced significantly, providing **4c** in 84% yield after recrystallisation. The telescoped cyclisation and resolution process was carried out on 10 g scale to obtain realistic metrics data, generating **2b** in 43% isolated yield, 99% ee from **4c** (Scheme 6, SI-1.9–11†).

The three stage, enhanced synthesis of (*S*)-**2b** from dimethyl malonate ester gave a calculated PMI = 201, over four times lower than the corresponding enantioselective chemical synthesis strategy used previously.<sup>15</sup>

## Experimental

### Optimised synthesis of **2b** (Scheme 6)

**Telescoped fluorination-Michael addition: synthesis of dimethyl (2-cyanoethyl)-2-fluoromalonate **4b**.** Dimethyl malonate **4a** (26.40 g, 200 mmol) and copper(II) nitrate hemi(pentahydrate) (4.65 g, 20 mmol) were dissolved in acetonitrile (100 mL) and the mixture was cooled to 0–5 °C and stirred at 650 rpm using an overhead stirrer. After purging the system with N<sub>2</sub> for 5 minutes, fluorine gas (20% v/v in N<sub>2</sub>, 100 mL min<sup>−1</sup>, 220 mmol) was introduced into the reaction mixture for 4 h 25 min. After purging with nitrogen for 5 min, potassium phosphate tribasic (anhydrous) (42.45 g, 200 mmol) was added to the reaction mixture and stirred. After 1 h the potassium phosphate was removed by filtration and washed with acetonitrile (2 × 20 mL) before a further portion of potassium phosphate (42.45 g, 200 mmol) was added to the solution which was heated to 55 °C. Acrylonitrile (12.73 g, 240 mmol) in acetonitrile (10 mL) was added over 30 min and the solution stirred. After a further 3.25 h the potassium phosphate was removed by filtration and washed with acetonitrile (3 × 20 mL) and the filtrate was concentrated *in vacuo*. Vacuum distillation (140–141 °C, 6 mbar) of the crude product yielded dimethyl(2-cyanoethyl)-2-fluoromalonate **4b** (24.45 g, 60%) as a clear oil;  $[\text{M}]^{\text{D}}_{\text{D}}$ , 204.0652. C<sub>8</sub>H<sub>11</sub>FNO<sub>4</sub> requires:  $[\text{M}]^{\text{D}}_{\text{D}}$ , 204.0672; IR (neat, cm<sup>−1</sup>) 2962, 2253, 1748, 1438; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  3.85 (6H, s, OCH<sub>3</sub>), 2.60–2.49 (4H, m, CH<sub>2</sub>); <sup>19</sup>F NMR (376 MHz, CDCl<sub>3</sub>)  $\delta$  −167.85–−168.04 (m); <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$  165.42 (d, <sup>2</sup>J<sub>CF</sub> 25.3, C=O), 117.88 (s, CN), 92.73 (d, <sup>1</sup>J<sub>CF</sub> 201.0, C–F), 53.86 (s, CH<sub>3</sub>O), 30.16 (d, <sup>2</sup>J<sub>CF</sub> 21.5, CH<sub>2</sub>), 11.48 (d, <sup>3</sup>J<sub>CF</sub> 5.5, CH<sub>2</sub>); *m/z* (ASAP) 204.1 (100%,  $[\text{M}]^{\text{D}}_{\text{D}}$ ), 162.1 (25).





**Reduction: synthesis of dimethyl 2-(3-aminopropyl)-2-fluoromalonate, hydrochloride salt **4c**.** 10% Pd/C (2.62 g, 5 mol%) and conc. HCl (4.85 mL) were added into a Hastelloy autoclave. A solution of *dimethyl(2-cyanoethyl)-2-fluoromalonate* **4b** (10 g, 49.2 mmol) in methanol (43.3 mL) was added and the vessel sealed. The vessel was pressurized with H<sub>2</sub> (4 bar) and the contents were stirred at 600 rpm. After 16 h the solution was filtered through celite (2 g) with methanol (20 mL) and evaporated to give crude **4c**. The solid was washed with methanol (2 × 20 mL) and acetone (2 × 15 mL) to give *dimethyl 2-(3-aminopropyl)-2-fluoromalonate, hydrochloride salt* **4c** (10.43 g, 84%) as white crystals; mp 147–148 °C;  $[\text{M} - \text{Cl}]^+$ , 208.0978. C<sub>8</sub>H<sub>15</sub>FNO<sub>4</sub> requires  $[\text{M} - \text{Cl}]^+$ , 208.0985; IR (neat, cm<sup>-1</sup>) 3016, 2942, 1748, 1580, 1437, 1249, 1033; <sup>1</sup>H NMR (400 MHz, methanol-*d*<sub>4</sub>) δ 3.87 (6H, s, OCH<sub>3</sub>), 3.08–2.98 (2H, m, CH<sub>2</sub>), 2.32 (2H, ddd, <sup>3</sup>J<sub>HF</sub> 23.1, <sup>3</sup>J<sub>HH</sub> 9.2, <sup>3</sup>J<sub>HH</sub> 6.9, CH<sub>2</sub>), 1.89–1.77 (2H, m, CH<sub>2</sub>); <sup>19</sup>F NMR (376 MHz, methanol-*d*<sub>4</sub>) δ -167.20 (t, <sup>3</sup>J<sub>HF</sub> 23.1); <sup>13</sup>C NMR (101 MHz, methanol-*d*<sub>4</sub>) δ 167.60 (d, <sup>2</sup>J<sub>CF</sub> 25.8, C=O), 95.57 (d, <sup>1</sup>J<sub>CF</sub> 197.4, C-F), 54.10 (s, CH<sub>3</sub>O), 40.21 (s, CH<sub>2</sub>NH<sub>2</sub>), 32.18 (d, <sup>2</sup>J<sub>CF</sub> 21.6, CH<sub>2</sub>CF), 22.38 (d, <sup>3</sup>J<sub>CF</sub> 3.2, CH<sub>2</sub>); *m/z* (ASAP) 208.1 (100%,  $[\text{M} - \text{Cl}]^+$ ), 191 (14), 176 (8).

**Cyclization: synthesis of (S)-methyl 3-fluoro-2-oxopiperidine-3-carboxylate **2b**.** To a 500 mL round bottomed flask was added 0.06 M Na<sub>2</sub>HPO<sub>4</sub>: 0.06 M KH<sub>2</sub>PO<sub>4</sub> buffer (164 mL, 3 : 1, pH 7.3) followed by **4c** (10.00 g, 41.0 mmol) in small portions using 0.5 M NaOH to buffer the solution to pH 7.3. The solution was filled to 328 mL total volume with further 0.06 M Na<sub>2</sub>HPO<sub>4</sub>: 0.06 M KH<sub>2</sub>PO<sub>4</sub> buffer (3 : 1, pH 7.3) to give a 257 mM solution. Fermase immobilised CAL-B 10 000 (7.2 g) was added to the reaction mixture which was stirred at 100 rpm at 20 °C for 8 h. The reaction mixture was poured onto a Waters Oasis HLB 12cc 5 g LP extraction cartridge under reduced pressure and water (30 mL) was added to the cartridge such that the acid was fully eluted (*ca.* 1 mL per min). The washed enzyme was removed and the ester was eluted with 20% formic acid (30 mL). The solution was concentrated under reduced pressure at RT to give a solid, which was recrystallised from acetone (10 mL) to give (*S*)-methyl 3-fluoro-2-oxopiperidine-3-carboxylate **2b** (3.15 g, 44%, >99% ee) as white crystals; mp 115–116 °C;  $[\alpha]_{\text{D}}^{25} +14.393^\circ$  (*c* 1.00, MeCN);  $[\text{MH}]^+$ , 176.0718. C<sub>7</sub>H<sub>11</sub>FNO<sub>3</sub> requires:  $[\text{MH}]^+$ , 176.0723; IR (neat, cm<sup>-1</sup>) 3200, 3074, 2968, 2888, 1760, 1668, 1435; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.49 (1H, s, NH), 3.85 (3H, s, OCH<sub>3</sub>), 3.45–3.37 (2H, m, CH<sub>2</sub>), 2.42–2.20 (2H, m, CH<sub>2</sub>), 2.04–1.89 (2H, m, CH<sub>2</sub>); <sup>19</sup>F NMR (376 MHz, CDCl<sub>3</sub>) δ -156.07 (dd, <sup>3</sup>J<sub>HF</sub> 28.2, <sup>3</sup>J<sub>HF</sub> 20.0); <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ 168.68 (d, <sup>2</sup>J<sub>CF</sub> 26.2, NH-C=O), 165.13 (d, <sup>2</sup>J<sub>CF</sub> 22.4, CO<sub>2</sub>), 90.87 (d, <sup>1</sup>J<sub>CF</sub> 190.8, C-F), 53.29 (s, CH<sub>3</sub>O), 42.22 (s, CH<sub>2</sub>-NH), 31.25 (d, <sup>2</sup>J<sub>CF</sub> 22.4, CH<sub>2</sub>-CF), 18.26 (d, <sup>3</sup>J<sub>CF</sub> 2.6, CH<sub>2</sub>); *m/z* (ASAP) 176 (100%,  $[\text{MH}]^+$ ), 162 (9).

## Conclusions

In conclusion, the combined three stage chemo-enzymatic synthesis of enantiopure fluorolactam **2b** using fluorine gas for the construction of the C–F bond and amidase CAL-B 10 000

for the key desymmetrization step has been optimised on a reasonable scale and is suitable for scale-up. The PMI of the fluorination-amidase route is PMI = 201 compared to PMI = 925 for the enantioselective fluorination literature synthesis. Clearly, the fluorination-amidase route established here has a PMI that is highly competitive with the corresponding chemical synthesis and demonstrates the very effective use of amidase enzymes for larger scale synthesis of challenging pharmaceutically relevant enantiopure fluorinated systems. However, the still relatively high PMI for the three step synthetic process is largely due to the final resolution step which, by definition, leads to the loss of half the product material.

Perhaps of more importance for synthesis on the large scale is that the cost of the overall fluorination-amidase process is several orders of magnitude less expensive than the use of enantioselective fluorination strategies that require the utilisation of relatively expensive N–F electrophilic fluorinating agents prepared from fluorine gas and the use of structurally complex precious metal catalysts. Simple recycling of the enzyme catalyst by filtration, recycling of solvents and a high yielding inexpensive, copper catalysed fluorination step make the strategy very attractive for scale-up.

The use of the fluorine-enzyme multi-step approach complements existing chemical enantioselective fluorination procedures that are more applicable to discovery scale synthesis. Here, we have demonstrated that the development of new fluorinated sub-units within drug structures bearing fluorine at a chiral sp<sub>3</sub> centre assessed in the discovery phase by chemical enantioselective fluorination on the small scale can, when required, be scaled up by a combined inexpensive fluorination-enzyme catalysed approach thus extending the chemical space for fluorinated aliphatic units within the structures of drug candidates.

## Acknowledgements

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