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Version: Published

http://eprints.gla.ac.uk/102997/

Deposited on: 02 April 2015
Short and efficient synthesis of fluorinated δ-lactams†

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The diastereoselective synthesis of fluorinated δ-lactams has been achieved through an efficient five step process. The route can tolerate a range of functionalities, and provides a quick route for the generation of new fluorinated medicinal building blocks.

Introduction

Fluorination has been used to increase the potency and ‘drug-like’ nature of active compounds for many years, making organo-fluorine compounds a cornerstone in medicinal chemistry.1 Fluorination has also been extensively used to alter the basicity of N-heterocycles, and as a tool through which hydrogen bonding can be probed and assessed.2 As such, new ways to selectively incorporate fluorine atoms into different substructures is an ever expanding area of research.1,2

δ-Lactams on the other hand are also present widely in medicinal chemistry and natural systems. For instance, aripiprazole 1 is used currently for the treatment of schizophrenia and bipolar disorders (Fig. 1).3

Thus, it is not surprising that considerable time and efforts have been directed towards the synthesis of fluorinated δ-lactams.4–6 However to date, there are a relatively small number of examples and few general routes available to enable synthesis of compound libraries to drive structure–activity relationship understanding in medicinal chemistry programmes. Herein, we would like to report a short and efficient route to the synthesis of fluorinated δ-lactams starting from commercial aldehydes. The methodology is amenable for the generation of a wide range of δ-lactams, and has the potential to allow entry into several different classes of N-heterocyclic compounds.

Results and discussion

Our initial studies towards the synthesis of fluorinated δ-lactams began with benzaldehyde, which upon amino allylation under Kobayashi conditions afforded amine 3.7 Amide coupling of amine 3 with 2-fluoroacrylic acid 4 then afforded the desired diene 5 in 85% yield over the 2 steps (Scheme 1).

Amide 5 was then treated with a range of metathesis catalysts in an attempt to induce ring closure (Scheme 2), however only a complex mixture of cross metathesis products resulted, with no desired cyclised product 6 being detected.

The lack of cyclisation could be attributed to the interaction of the ruthenium catalyst with the amide group which prevents

Note:

† Electronic supplementary information (ESI) available: Full refinement details and crystallographic data (excluding structural factors). CCDC 1006297. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c4ob01547a
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the ring closing metathesis from taking place, in a situation similar to that reported by Vilar and co-workers.8

To test this hypothesis, the route was altered to incorporate a protecting group on the amide to prevent the amide from interacting with the Ru catalyst. The protecting group of choice was the p-methoxybenzyl group due to its electron donating properties, and the ease of removal via oxidative cleavage.9

Thus, reaction of p-methoxybenzylamine with benzaldehyde yielded the corresponding imine which upon allyl Grignard addition produced the secondary amine 7a in near quantitative yield. HBTU promoted coupling between the amine 7a and 2-fluorocrylic acid 4 and then proceeded to generate the desired amide 8a in good yield.

Gratifyingly, PMB protection of the amide unit allowed the ring closing metathesis reaction to proceed smoothly to yield the unsaturated lactam 9a in quantitative yield (Table 1).

With the benzaldehyde example working efficiently, the scope of the methodology was explored (Table 1). Electron donating and electron withdrawing substituents on the aromatic ring were both tested with good results in all cases through the four step sequence. The electron withdrawing analogue being slightly less efficient in the first three steps, however, the RCM reaction produced the desired unsaturated lactam 9e in quantitative yield.

Aliphatic substrates are also well tolerated, and afforded the corresponding fluorinated lactams 9f, 9g cleanly and in good yield over the 4 step sequence.

Finally, furan, pyrrole and pyridine frameworks were also explored due to their widespread use in medicinal and biological chemistry. Furfural and N-tosylpyrrole carboxaldehyde proceeded to generate the structurally interesting fluorinated δ-lactams 9h, 9i in good yield. In the case of the pyridine unit, the amino allylation and amide coupling proceeded in reasonable yields, affording intermediates 7j and 8j respectively. Unfortunately, the ring closing metathesis failed to generate the desired fluorinated δ-lactam 9j under any of the conditions attempted. This was rationalised in the same manner as the previous example (Scheme 2), where an unprotected nitrogen atom was thought to bind to the Ru catalyst.

Table 1: Synthesis of α,β-unsaturated lactams 9a–j with isolated yields for the intermediates 7a–j and 8a–j

<table>
<thead>
<tr>
<th>R</th>
<th>Yield</th>
<th>Yield</th>
<th>Yield</th>
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<tbody>
<tr>
<td>Ph</td>
<td>95%</td>
<td>7a</td>
<td>63%</td>
</tr>
<tr>
<td>4-MeOPh</td>
<td>80%</td>
<td>7b</td>
<td>66%</td>
</tr>
<tr>
<td>4-ClPh</td>
<td>66%</td>
<td>7c</td>
<td>45%</td>
</tr>
<tr>
<td>1-Naphthyl</td>
<td>99%</td>
<td>7d</td>
<td>31%</td>
</tr>
<tr>
<td>4-BrPh</td>
<td>97%</td>
<td>7e</td>
<td>54%</td>
</tr>
<tr>
<td>i-Butyl</td>
<td>76%</td>
<td>7f</td>
<td>74%</td>
</tr>
<tr>
<td>Cyclohexyl</td>
<td>74%</td>
<td>7g</td>
<td>70%</td>
</tr>
<tr>
<td>2-Furyl</td>
<td>83%</td>
<td>7h</td>
<td>28%</td>
</tr>
<tr>
<td>N'-Ts 2-pyrole</td>
<td>83%</td>
<td>7i</td>
<td>50%</td>
</tr>
<tr>
<td>2-Pyridyl</td>
<td>73%</td>
<td>7j</td>
<td>68%</td>
</tr>
</tbody>
</table>

Table 2: Synthesis of δ-lactams 11a–g

<table>
<thead>
<tr>
<th>R</th>
<th>Yield</th>
<th>Yield</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ph</td>
<td>94%</td>
<td>10a</td>
<td>98%</td>
</tr>
<tr>
<td>4-MeOPh</td>
<td>40%</td>
<td>10b</td>
<td>83%</td>
</tr>
<tr>
<td>4-ClPh</td>
<td>47%</td>
<td>10c</td>
<td>Quant</td>
</tr>
<tr>
<td>Naph</td>
<td>61%</td>
<td>10d</td>
<td>Quant</td>
</tr>
<tr>
<td>4-BrPh</td>
<td>72%</td>
<td>10e</td>
<td>Quant</td>
</tr>
<tr>
<td>i-Butyl</td>
<td>97%</td>
<td>10f</td>
<td>Quant</td>
</tr>
<tr>
<td>Cyclohexyl</td>
<td>79%</td>
<td>10g</td>
<td>Quant</td>
</tr>
</tbody>
</table>

With the fluorinated ring system in place, the removal of the p-methoxybenzyl protecting group and reduction of the olefin unit were explored. Removal of the PMB group was achieved with cerium ammonium nitrate to yield the desired fluoro-pyridones 10a–g in variable yields (Table 2). Unfortunately, treatment of the furyl and pyrrole substituted pyridones 9h–i with CAN failed to yield the desired unprotected pyridones, resulting instead in substrate decomposition.

Hydrogenation of the fluoro-olefin unit, on the other hand, proceeded in near quantitative yield in most cases, and with complete diastereoselectivity to yield the desired fluorinated δ-lactams 11a–g. The only exception was the brominated analogue 10e, which unsurprisingly yielded the unbrominated lactam 11a upon hydrogenation in excellent yield.

The syn selectivity of hydrogenation, and hence the stereochemistry of the newly formed C3 stereocentre, is dictated by the C6 substituent. The relative stereochemistry was corroborated by X-ray crystallography (Fig. 2).10

The bromo-lactam intermediate 10e, on the other hand, presented us with an opportunity to further explore the scope of the fluoro-lactam intermediates as medicinal chemistry building blocks. Thus treatment of fluoro-lactam 10e under Suzuki-Miyaura conditions with phenylboronic acid generated the tricyclic unit 12 in near quantitative yield.11

Alkene reduction under standard conditions then generated the desired fluoro-lactam unit 13 in excellent yield and with complete diastereocntrol (Scheme 3).
Conclusions

In conclusion, we have developed a fast and reliable approach to the synthesis of a number of fluorinated δ-lactams in an efficient 5 step process. Work is now underway to expand the methodology to allow access to other fluorinated ring systems including pyridines and pyrroles as well as developing an enantioselective variant of this methodology.

Experimental

All reactions were performed in oven-dried glassware under an inert argon atmosphere unless otherwise stated. Tetrahydrofuran (THF), diethyl ether, toluene and dichloromethane were purified through a solvent purification system. Petroleum ether refers to the fraction boiling between 40 and 60 °C. All reagents were used as received, unless otherwise stated. Solvents were evaporated under reduced pressure at 40 °C unless otherwise stated. IR spectra were recorded as thin films on NaCl plates using a Fourier Transform spectrometer. Only significant absorptions \( (v_{\text{max}}) \) are reported in wavenumbers \( (\text{cm}^{-1}) \). Proton magnetic resonance spectra (\(^1\)H NMR), fluorine magnetic resonance spectra (\(^19\)F NMR) and carbon magnetic resonance spectra (\(^13\)C NMR) were recorded at 400 MHz, 377 MHz and 100 MHz or at 500 MHz, 470 MHz and 125 MHz respectively. \(^13\)C NMR spectra were recorded with 1H noise decoupling. Chemical shifts \( (\delta) \) are reported in parts per million (ppm) and are referenced to the residual solvent peak. The order of citation in parentheses is (1) the number of equivalent nuclei (by integration), (2) multiplicity \((s = \text{singlet}, d = \text{doublet}, t = \text{triplet}, q = \text{quartet}, quint = \text{quintet}, sext = \text{sextet}, \text{m} = \text{multiplet}, b = \text{broad})\), (3) and the coupling constant \( (J) \) quoted in hertz to the nearest 0.1 Hz. High resolution mass spectra were obtained by electrospray (ESI) chemical ionisation (CI) mass spectrometry operating at a resolution of 15,000 full widths at half height. Flash chromatography was performed using silica gel (40–63 micron) as the stationary phase. TLC was performed on aluminium sheets pre-coated with silica (Silica Gel 60 F254) unless otherwise stated. The plates were visualised by the quenching of UV fluorescence \( (\lambda_{\text{max}} 254 \text{ nm}) \) and/or by staining with either anisaldehyde, potassium permanganate, iodine or cerium ammonium molybdate followed by heating.

1-Phenylbut-3-en-1-ylamine, 3

Benzaldehyde (0.21 g, 2.0 mmol) was dissolved in methanol (4 mL) and the resulting solution was cooled to −78 °C. NH\(_3\) \((\text{ca. } 4 \text{ mL})\) was condensed into the solution, and the resulting reaction mixture was warmed to −10 °C and stirred until the excess ammonia had evaporated (3 h). Allylboronic pinacol ester (0.76 mL, 4.0 mmol) was added and the reaction was stirred for 2 h. The reaction vessel was then allowed to warm up to room temperature and stirred for a further 1 h. Aq. HCl (6 M) was added slowly to the solution until pH 1 and the mixture was extracted with diethyl ether \((3 \times 20 \text{ mL})\). The aqueous phase was collected, and aq. NaOH (2 M) was added slowly until pH 14. The aqueous solution was extracted with CH\(_2\)Cl\(_2\) \((3 \times 20 \text{ mL})\). The combined CH\(_2\)Cl\(_2\) phases were then dried \((\text{Na}_2\text{SO}_4)\) filtered and evaporated in vacuo to yield amine 3 as a colourless oil \((0.28 \text{ g, } 1.9 \text{ mmol, } 95\%)\) which was of sufficient purity to enable the substance to be used without further purification.

\( ^1\text{H} \) (CDCl\(_3\), 400 MHz) \( \delta \): 7.27–7.15 (5H, m), 5.68–5.63 (1H, m), 5.06–5.00 (2H, m), 3.91 (1H, dd, \( J_{\text{HH}} = 8.0, 5.2 \text{ Hz} \)), 2.40–2.27 (2H, m), 1.60 (2H, br s). \(^{13}\text{C} \) (CDCl\(_3\), 125 MHz) \( \delta \): 145.8, 135.4, 128.4, 127.9, 126.4, 117.7, 55.4, 44.2.

2-Fluoroacrylic acid, 4\(^{13}\)

Commercially available 2-fluoroacrylic acid methyl ester \((0.87 \text{ mL, } 9.6 \text{ mmol})\) was dissolved in EtOH–H\(_2\)O \((8.7 : 1.3, 10 \text{ mL})\). Aq. NaOH (2 M) was then added dropwise until pH 11 was reached, and the resulting mixture was stirred for 30 min. After which, the solution was evaporated to dryness under vacuum to yield the sodium salt as a white solid. Diethyl ether \((20 \text{ mL})\) was added to the salt, followed by aq. HCl (6 M) dropwise until the solid dissolved. The layers were then separated, and the aqueous layer was extracted with diethyl ether \((10 \text{ mL})\). The organics were combined, dried over sodium sulfate and evaporated in vacuo to yield the desired acid 4 as a white solid \((0.74 \text{ g, } 8.0 \text{ mmol, } 87\%)\) with no need for further purification.

\( ^1\text{H} \) (CDCl\(_3\), 400 MHz) \( \delta \): 11.51 (1H, br s), 5.92 (1H, dd, \( J_{\text{HH}} = 42.8, J_{\text{HF}} = 3.6 \text{ Hz} \)), 5.52 (1H, dd, \( J_{\text{HH}} = 12.4, J_{\text{HF}} = 3.2 \text{ Hz} \)).

\(^{19}\text{F} \) (CDCl\(_3\), 470 MHz) \( \delta \): −118.3. \(^{13}\text{C} \) (CDCl\(_3\), 125 MHz) \( \delta \): 165.4 (d, \( J_{\text{CF}} = 46.3 \text{ Hz} \)), 151.3 (d, \( J_{\text{CF}} = 323.8 \text{ Hz} \)), 105.2 (d, \( J_{\text{CF}} = 18.8 \text{ Hz} \)).
(3.0 g, 15.0 mmol) was added, and the reaction mixture was stirred for a further 15 min at 0 °C before being allowed to warm up to room temperature and stirred overnight. The reaction mixture was quenched with H2O (20 mL), and extracted with CH2Cl2 (2 × 25 mL). The combined organics were then dried (Na2SO4) and the solvent was removed in vacuo. The resulting crude residue was purified by flash column chromatography (0–10% EtOAc in petroleum ether) to yield the tosylated pyrrole as a white solid (2.47 g, 9.9 mmol, 94%).

1H (CDCl3, 400 MHz) δ: 10.01 (1H, s), 7.83 (2H, d, JHH = 8.3 Hz), 7.65 (1H, dd, JHH = 3.0, 1.8 Hz), 7.35 (2H, d, JHH = 8.3 Hz), 7.12 (1H, dd, JHH = 3.7, 1.8 Hz), 6.43 (1H, br appt, JHH = 3.4 Hz), 2.45 (3H, s). 13C (CDCl3, 125 MHz) δ: 178.9, 145.9, 135.3, 133.6, 130.1, 129.5, 127.6, 124.4, 112.4, 112.4, 21.7.

**General procedure A: synthesis of PMB protected allylic amines from aldehydes**

Na2SO4 (2 g) was dried under vacuum in a round bottom flask and treated under vacuum and the residue was removed in vacuo. The resulting crude residue was purified by flash column chromatography (0–10% EtOAc in petroleum ether) to yield the tosylated pyrrole as a white solid (2.47 g, 9.9 mmol, 94%).

1H (CDCl3, 400 MHz) δ: 7.30 (2H, d, JHH = 8.8 Hz), 7.19 (2H, d, JHH = 8.6 Hz), 6.92 (2H, d, JHH = 8.8 Hz), 6.87 (2H, d, JHH = 8.6 Hz), 5.75–5.68 (1H, m), 5.12–5.04 (2H, m), 3.85 (3H, s) 3.82 (3H, s), 3.68–3.60 (2H, m), 3.47 (1H, d, JHH = 12.9 Hz), 2.43–2.39 (2H, m). 13C (CDCl3, 125 MHz) δ: 158.6, 158.5, 133.9, 135.6 (2C), 132.8, 129.3 (2C), 128.3 (2C), 117.4, 113.7 (2C), 60.81, 55.3, 55.2, 50.7, 43.2.

**4’-Methoxy-N-[1-(4′-trifluoromethanephényl)-3-butenyl]benzylamine, 7c**

Following general procedure A, 4-(trifluoromethyl)benzaldehyde (0.78 mL, 5.7 mmol) was reacted with 4-methoxybenzylamine (0.83 mL, 6.3 mmol) and allylmagnesium bromide (8.6 mL 1.0 M in THF, 8.6 mmol). The crude product was purified by flash column chromatography (0–5% diethyl ether in petroleum ether) to yield the expected amine 7c (1.27 g, 3.8 mmol, 66% yield) as a pale yellow oil.

1H (CDCl3, 400 MHz) δ: 7.62 (2H, d, JHH = 8.2 Hz), 7.51 (2H, d, JHH = 8.2 Hz), 7.18 (2H, d, JHH = 8.8 Hz), 6.88 (2H, d, JHH = 8.8 Hz), 5.75–5.65 (1H, m), 5.12–5.08 (2H, m), 3.83 (3H, s), 3.77 (1H, dd, JHH = 7.6, 5.6 Hz), 3.64 (1H, d, JHH = 13.2 Hz), 3.45 (1H, d, JHH = 13.2 Hz), 2.45–2.34 (2H, m). 19F (CDCl3, 377 MHz) δ: −62.3, 13C (CDCl3, 125 MHz) δ: 158.7, 148.2, 134.8, 132.4, 129.8 (2C), 127.7 (2C), 125.7, 125.4 (2C), 125.3, 118.2, 113.8 (2C), 61.2, 55.3, 44.2, 33.6. m/z [CI (+ve)] 336.1 [M + H]+. HRMS found [M + H]+ 336.1572. C19H21F3NO requires 336.1575. IR (thin film) νmax = 2935, 1612, 1511, 1246, 1120, 1066 cm−1.

**4’-Methoxy-N-[1-(naphthalen-1″-yl)-3-butenyl]benzylamine, 7d**

Following general procedure A, 1-naphthaldehyde (0.86 mL, 6.40 mmol) was reacted with 4-methoxybenzylamine (0.84 mL, 7.0 mmol) and allylmagnesium bromide (9.6 mL 1.0 M in THF, 9.6 mmol). The crude product was purified by flash column chromatography (0–10% diethyl ether in petroleum ether) to yield the expected amine 7d (2.03 g, 6.3 mmol, 99% yield) as a pale yellow oil.

1H (CDCl3, 400 MHz) δ: 8.10 (1H, appd, JHH = 7.4 Hz), 7.81–7.79 (1H, m), 7.72–7.67 (2H, m), 7.44–7.38 (3H, m), 7.09 (2H, d, JHH = 8.6 Hz), 6.76 (2H, d, JHH = 8.6 Hz), 5.75–5.67 (1H, m), 5.05–4.97 (2H, m), 3.71 (3H, s), 3.60 (1H, d, JHH = 13.0 Hz), 3.44 (1H, d, JHH = 13.0 Hz), 2.59–2.54 (1H, m), 2.41–2.35 (1H, m). 13C (CDCl3, 125 MHz) δ: 158.7, 139.7, 138.9, 135.8, 134.1, 132.9, 131.7, 129.4 (2C), 129.0, 127.4, 125.7, 125.3, 123.9, 123.1, 117.7, 113.8 (2C), 56.9, 55.4, 51.1. m/z [CI (+ve)] 318.2 [M + H]+. HRMS found [M + H]+ 318.1862. C19H18F2NO requires 318.1858. IR (thin film) νmax = 2960, 1512, 1426, 1355, 1035 cm−1.
4′-Methoxy-N-(1-isobutyl-3-butenyl)benzylamine, 7f

Following general procedure A, isovaleraldehyde (1.25 mL, 11.6 mmol) was reacted with 4-methoxybenzylamine (1.7 mL, 12.7 mmol) and allylmagnesium bromide (17.4 mL 1.0 M in THF, 17.4 mmol). The crude product was purified by flash column chromatography (0–5% diethyl ether in petroleum ether) to yield 7f (2.06 g, 8.44 mmol, 76% yield) as a pale yellow oil.

1H (CDCl3, 400 MHz) δ: 7.26 (2H, d, JHH = 8.8 Hz), 8.68 (2H, d, JHH = 8.8 Hz), 5.82–5.70 (1H, m), 5.14–5.00 (2H, m), 3.81 (3H, s), 3.73 (1H, quint, JHH = 6.4 Hz), 2.70–2.65 (1H, m), 2.25–2.03 (2H, m), 1.62 (1H, appteq, JHH = 6.8 Hz), 1.46–1.23 (2H, m), 0.90 (3H, d, JHH = 6.6 Hz), 0.87 (3H, d, JHH = 6.6 Hz).

13C (CDCl3, 100 MHz) δ: 135.8, 135.8, 133.0, 129.3 (2C), 118.7, 113.7 (2C), 53.5, 54.0, 50.5, 41.2, 38.6, 24.7, 22.5, m/z [Cl (+ve)] 248.2 [M + H]+, HRMS found [M + H]+ 248.2018, C16H18NO requires 248.2014.

IR (thin film) νmax = 2953, 2906, 1612, 1512, 1465, 1246 cm⁻¹.

4′-Methoxy-N-(1-cyclohexyl-3-butenyl)benzylamine, 7g

Following general procedure A, cyclohexanecarboxaldehyde (1.08 mL, 8.87 mmol) was reacted with 4-methoxybenzylamine (1.2 mL, 9.8 mmol) and allylmagnesium bromide (13.3 mL 1.0 M in THF, 13.3 mmol). The crude product was purified by flash column chromatography (0–25% diethyl ether in petroleum ether) to yield the desired amine 7g (1.81 g, 6.66 mmol, 74% yield) as a pale yellow oil.

1H (CDCl3, 400 MHz) δ: 7.26 (2H, d, JHH = 8.6 Hz), 6.87 (2H, d, JHH = 8.6 Hz), 5.85–5.75 (1H, m), 5.11–5.06 (2H, m), 3.82 (3H, s), 3.71 (2H, s), 2.42–2.38 (1H, m), 2.32–2.26 (1H, m), 2.16–2.09 (1H, m), 1.81–1.70 (4H, m), 1.47–1.43 (1H, m), 1.31–1.18 (4H, m), 1.10–1.00 (2H, m).

13C (CDCl3, 125 MHz) δ: 158.5, 136.8, 133.3, 129.3 (2C), 116.8, 113.7 (2C), 61.1, 55.3, 51.3, 40.6, 35.3, 29.4, 28.9, 26.8, 26.7, 26.7, m/z [Cl (+ve)] 274.2 [M + H]+, HRMS found [M + H]+ 274.2171, C18H18NO requires 274.2168.

IR (thin film) νmax = 2924, 1511, 1246, 1037 cm⁻¹.

4′-Methoxy-N-(1-furan-2-yl)-3-butenylbenzylamine, 7h

Following general procedure A, 2-furaldehyde (0.86 mL, 10.4 mmol) was reacted with 4-methoxybenzylamine (1.3 mL, 11.4 mmol) and allylmagnesium bromide (15.6 mL 1.0 M in THF, 15.6 mmol). The crude product was purified by flash column chromatography (0–5% diethyl ether in petroleum ether) to yield the desired amine 7h (2.21 g, 8.59 mmol, 83% yield) as a pale yellow oil.

1H (CDCl3, 400 MHz) δ: 7.42 (2H, d, JHH = 1.8, 0.8 Hz), 7.23 (2H, d, JHH = 8.7 Hz), 6.88 (2H, d, JHH = 8.7 Hz), 6.36 (1H, dd, JHH = 3.7, 1.8 Hz), 6.21 (1H, d, JHH = 3.7 Hz), 5.79–5.62 (1H, m), 5.14–5.06 (2H, m), 3.83 (3H, s), 3.79 (1H, t, JHH = 6.8 Hz), 3.72 (1H, d, JHH = 13.0 Hz), 3.56 (1H, d, JHH = 13.0 Hz), 2.58–2.53 (2H, m).

13C (CDCl3, 125 MHz) δ: 158.6, 156.3, 141.5, 134.9, 132.4, 129.4 (2C), 117.5, 113.8 (2C), 109.9, 106.6, 55.3, 54.7, 50.5, 39.3, m/z [Cl (+ve)] 258.2 [M + H]+, HRMS found [M + H]+ 258.1492, C16H17BrNO requires 258.1494.

IR (thin film) νmax = 2930, 2850, 1511, 1441, 1246, 1035 cm⁻¹.
2-Fluoroacrylic acid (1.5 eq.) and HBTU (1.5 eq.) were dry mixed and then dissolved in CH₂Cl₂ (20 mL). DIPEA (1.5 eq.) was added followed by the corresponding amine (1 eq.). The resulting solution was stirred and refluxed for 17 h. The reaction was cooled down to room temperature and the solvent was then evaporated under reduced pressure. The crude material was purified by flash column chromatography.

2'-Fluoro-N-(4''-methoxybenzyl)-N-[1-(4''''-butenyl)-acrylamide, 8a

Amine 7a (0.5 g, 1.8 mmol) was coupled with 2-fluoroacrylic acid (0.25 g, 2.8 mmol) using HBTU (1.1 g, 2.8 mmol) following general procedure B. The crude product was purified by flash column chromatography (0-5% diethyl ether in petroleum ether) to yield the desired diakene 8a (0.38 g, 1.10 mmol, 63% yield) as a pale yellow oil.

1H (CDCl₃, 400 MHz) δ: 7.36–7.32 (5H, m), 6.97 (2H, d, JHH = 8.6 Hz), 6.76 (2H, d, JHH = 8.3 Hz), 5.75–5.66 (1H, m), 5.35 (1H, br s), 5.26 (1H, br s), 5.08–4.99 (3H, m), 4.47 (1H, d, JHH = 15.7 Hz), 4.16 (1H, br s), 3.78 (3H, s), 2.74 (2H, br s). 13F (CDCl₃, 470 MHz) δ: –102.4, –114.2. 13C (CDCl₃, 125 MHz) δ: 163.3 (d, JCF = 30.0 Hz), 158.7, 158.2 (d, JCF = 271.3), 138.1, 134.2, 134.1 (2C), 129.2 (2C), 128.6 (2C) 128.1 (2C), 118.4, 113.6 (2C), 99.4 (d, JCF = 16.3 Hz), 55.2 (2C), 35.7, 33.5. m/z [EI (+ve)] 339.2 [M]+, HRMS found [M]+ 339.1639, C21H22FNO2 = 15.7 Hz), 4.16 (1H, br s), 3.78 (3H, s), 2.74 (2H, br s). 19F (CDCl₃, 470 MHz) δ: –102.4, –114.2. 13C (CDCl₃, 125 MHz) δ: 163.4 (d, JCF = 29.8 Hz), 159.0, 158.0 (d, JCF = 273.0 Hz), 142.5, 139.0, 137.8, 133.9, 129.9, 129.2 (2C), 128.8 (2C), 125.3 (2C), 125.0, 122.9, 118.5, 113.7 (2C), 99.8 (d, JCF = 12.5 Hz), 59.8, 55.2, 35.4. m/z [EI (+ve)] 407.1 [M]+, HRMS found [M]+ 407.1504, C₂₂H₂₁F₃NO₂ requires 407.1508. IR (thin film) νmax = 2939, 1639, 1514, 1415, 1325, 1246, 1120, 1068 cm⁻¹.

2'-Fluoro-N-(4''-methoxybenzyl)-N-[1-(naphthalen-1''''-yl)-3-butenyl]acrylamide, 8d

Amine 7d (0.5 g, 1.5 mmol) was coupled with 2-fluoroacrylic acid (0.21 g, 2.3 mmol) using HBTU (0.89 g, 2.3 mmol) following general procedure B. The crude product was purified by flash column chromatography (0-9% diethyl ether in petroleum ether) to yield the desired diakene 8d (0.21 g, 0.53 mmol, 36%) as a pale yellow oil.

1H (CDCl₃, 400 MHz) δ: 8.07 (1H, d, JHH = 8.4 Hz), 7.87 (1H, br d, JHH = 8.4 Hz), 7.82 (1H, t, JHH = 4.6 Hz), 7.59–7.51 (2H, m), 7.44 (2H, d, JHH = 5.0 Hz), 6.76 (2H, d, JHH = 8.3 Hz), 6.63 (2H, d, JHH = 8.3 Hz), 6.57 (1H, br s), 5.87–5.76 (1H, m), 5.32 (1H, br d, JHH = 47.8 Hz), 5.14–5.05 (3H, m), 4.40 (1H, br d, JHH = 16.2 Hz), 3.91 (1H, dd, JHH = 16.2, 1.7 Hz), 3.75 (3H, s), 2.77 (2H, appt, JHH = 6.7 Hz). 19F (CDCl₃, 377 MHz) δ: –103.7, –103.8. 13C (CDCl₃, 100 MHz) δ: 162.9 (d, JCF = 30.4 Hz), 158.7, 158.2 (d, JCF = 263.3 Hz), 134.7, 133.9, 132.6, 132.5, 129.2, 128.8, 128.6 (2C), 126.9, 126.5, 124.7, 124.6, 117.7, 114.4, 113.4 (2C), 99.9 (d, JCF = 15.8 Hz), 55.2 (2C), 54.1, 36.0. m/z [EI (+ve)] 389.2 [M]+, HRMS found [M]+ 389.1794, C₂₅H₂₁F₃NO₂ requires 389.1791. IR (thin film) νmax = 2970, 1632, 1513, 1416, 1176 cm⁻¹.

2'-Fluoro-N-(4''-methoxybenzyl)-N-[1-(4''''-bromophenyl)-3-butenyl]acrylamide, 8e

Amine 7e (0.50 g, 1.4 mmol) was coupled with 2-fluoroacrylic acid (0.19 g, 2.2 mmol) using HBTU (0.82 g, 2.2 mmol) following general procedure B. The crude product was purified by flash column chromatography (0-5% diethyl ether in petroleum ether) to yield the desired diakene 8e (0.24 g, 0.57 mmol, 41%) as a colourless oil.

1H (CDCl₃, 400 MHz) δ: 7.47 (2H, d, JHH = 8.1 Hz), 7.21 (2H, d, JHH = 8.1 Hz), 6.99 (2H, d, JHH = 8.6 Hz), 6.79 (2H, d, JHH = 8.6 Hz), 5.74–5.63 (1H, m), 5.40–5.25 (2H, m), 5.19–5.05 (3H, m), 4.44 (1H, d, JHH = 16.0 Hz), 4.25 (1H, m), 3.81 (3H, s), 2.74–2.69 (2H, m). 19F (CDCl₃, 470 MHz) δ: –102.3, –104.2. 13C (CDCl₃, 125 MHz) δ: 163.3 (d, JCF = 29.4 Hz), 158.9, 157.9 (d, JCF = 273.3 Hz), 137.3, 133.9, 131.6 (2C), 130.3 (2C), 129.1 (2C), 129.0, 122.0, 118.3, 113. 7 (2C), 99.6 (d, JCF = 15.6 Hz), 55.3 (2C), 35.6, 23.9. m/z [EI (+ve)] 417.0 [M]+, HRMS found
[M]+ 417.0739. C22H3179BrFNO2 requires 417.0740. IR (thin film) νmax = 2940, 1639, 1513, 1247, 1176 cm⁻¹.

2'-Fluoro-N-(4'-methoxybenzyl)-N-(1-isobutyl-3-butenyl)-acrylamide, 8f

Amine 7f (0.27 g, 1.1 mmol) was coupled with 2-fluorooacrylic acid (0.25 g, 2.8 mmol) using HBTU (1.1 g, 2.8 mmol) following general procedure B. The crude product was purified by flash column chromatography (0-25% diethyl ether in petroleum ether) to yield the desired dialkene 8f (0.26 g, 0.81 mmol, 74%) as a colourless oil.

1H (CDCl3, 400 MHz) δ: 7.27 (2H, d, JHH = 8.0 Hz), 6.85 (2H, d, JHH = 7.2 Hz), 5.73-5.62 (1H, m), 5.26 (1H, br s), 5.15 (1H, br s), 5.13-5.02 (2H, m), 4.54-4.39 (2H, m), 4.19-4.01 (1H, m), 3.81 (3H, s), 2.33-2.19 (2H, m), 1.52-1.16 (3H, m), 0.85 (3H, d, JHH = 6.4 Hz), 0.74 (3H, d, JHH = 6.0 Hz). 19F (CDCl3, 470 MHz) δ: -4.43 (2H, s), 3.81 (3H, s), 3.69 (1H, br s), 2.49 (1H, br t, JHH = 8.6 Hz), 2.33-2.25 (1H, m), 1.85-1.51 (5H, m), 1.20-1.05 (2H, m), 0.97-0.81 (4H, m). IR (thin film) νmax = 2940, 2852, 1635, 1513, 1442, 1246 cm⁻¹.

HRMS found [M+H]+ 346.2176, C21H29FNO2 requires 346.2182. IR (thin film) νmax = 2958, 1637, 1514, 1246 cm⁻¹.

2'-Fluoro-N-(4'-methoxybenzyl)-N-(1-cyclohexyl-3-butenyl)-acrylamide, 8g

Amine 7g (0.48 g, 1.8 mmol) was coupled with 2-fluorooacrylic acid (0.24 g, 2.6 mmol) using HBTU (1.0 g, 2.6 mmol) following general procedure B. The crude product was purified by flash column chromatography (0-25% diethyl ether in petroleum ether) to yield the desired dialkene 8g (0.44 g, 1.3 mmol, 70%) as a colourless oil.

1H (CDCl3, 400 MHz) δ: 7.32 (2H, d, JHH = 8.6 Hz), 6.84 (2H, d, JHH = 8.6 Hz), 5.63-5.56 (1H, m), 5.27-4.91 (4H, m), 4.43 (2H, s), 3.81 (3H, s), 3.69 (1H, br t, JHH = 9.3 Hz), 2.51-2.44 (1H, m), 2.33-2.25 (1H, m), 1.85-1.51 (5H, m), 1.20-1.05 (2H, m), 0.97-0.81 (4H, m). 19F (CDCl3, 470 MHz) δ: -102.7. 13C (CDCl3, 125 MHz) δ: 164.6 (d, JCF = 30.0 Hz), 158.7, 158.2 (d, JCF = 270.0 Hz), 134.6, 131.0, 129.8 (2C), 117.7, 113.7 (2C), 98.5 (d, JCF = 15.0 Hz), 64.7, 55.3, 44.8, 40.9, 35.1, 30.5, 30.4, 26.3, 26.1, 26.0. m/z [Cl (+ve)] 346.3 [M + H]+, HRMS found [M + H]+ 346.2176, C21H27FNO2 requires 346.2182.

IR (thin film) νmax = 2924, 2852, 1635, 1513, 1442, 1246 cm⁻¹.

2'-Fluoro-N-(4'-methoxybenzyl)-N-(1-furan-2'-yl)-3-butenyl-acrylamide, 8h

Amine 7h (0.5 g, 1.9 mmol) was coupled with 2-fluorooacrylic acid (0.26 g, 2.9 mmol) using HBTU (1.1 g, 2.9 mmol) following general procedure B. The crude product was purified by flash column chromatography (0-10% diethyl ether in petroleum ether) to yield the desired dialkene 8h (0.18 g, 0.54 mmol, 28%) as a yellow oil.

1H (CDCl3, 400 MHz) δ: 7.36 (1H, br s), 7.00 (2H, d, JHH = 8.6 Hz), 6.77 (2H, d, JHH = 8.6 Hz), 6.35-6.25 (2H, m), 5.72-5.64 (1H, m), 5.38-5.24 (2H, m), 5.10-5.05 (3H, m), 4.55 (1H, d, JHH = 15.7 Hz), 4.27 (1H, m), 3.80 (3H, s), 2.65-2.59 (2H, m).

IR (thin film) νmax = 2958, 1637, 1514, 1246, 1176 cm⁻¹.
3-Fluoro-1-(4′-methoxybenzyl)-6-phenyl-5, 6-dihydro-1H-pyridin-2-one, 9a

Dialkene 8a [0.11 g, 0.32 mmol] was subjected to general procedure C. The crude product was purified by flash column chromatography (0-10% EtOAc in petroleum ether) to yield the desired α,β-unsaturated lactam 9a [0.10 g, 0.32 mmol, quantitative yield] as a colourless oil.

1H (CDCl3, 400 MHz) δ: 7.40–7.34 (3H, m), 7.19 (2H, d, JHH = 7.2 Hz), 7.15 (2H, d, JHH = 8.6 Hz), 6.86 (2H, d, JHH = 8.6 Hz), 5.77 (1H, m), 5.41 (1H, d, JHH = 14.8 Hz), 4.57 (1H, dd, JHH = 7.7, 2.6 Hz), 3.83 (3H, s), 3.51 (1H, d, JHH = 14.8 Hz), 2.99–2.93 (1H, m), 2.50–2.44 (1H, m). 13C (CDCl3, 100 MHz) δ: −126.8. 19F (CDCl3, 470 MHz) δ: −159.8 (d, JCF = 30.0 Hz), 139.2, 149.4 (d, JCF = 251.1 Hz), 131.2, 129.0, 128.9 (2C), 128.0, 126.4 (2C), 114.1 (2C), 109.5 (d, JCF = 14.6 Hz), 57.0, 55.3, 47.2, 29.4 (d, JCF = 6.0 Hz). m/z [EI (+ve)] 331.2 [M]+. HRMS found [M]+ 331.1322. (thin film) νmax = 2933, 2837, 1651, 1512, 1247, 1176, 1031 cm−1.

3-Fluoro-1-(4′-methoxybenzyl)-6-(4′-methoxyphenyl)-5,6-dihydro-1H-pyridin-2-one, 9b

Dialkene 8b [0.22 g, 0.58 mmol] was subjected to general procedure C. The crude product was purified by flash column chromatography (0-10% EtOAc in petroleum ether) to yield the desired α,β-unsaturated lactam 9b [0.19 g, 0.58 mmol, quantitative yield] as a colourless oil.

1H (CDCl3, 400 MHz) δ: 7.05 (2H, d, JHH = 8.8 Hz), 7.00 (2H, d, JHH = 8.8 Hz), 6.80 (2H, d, JHH = 8.8 Hz), 6.77 (2H, d, JHH = 8.8 Hz), 5.70–5.66 (1H, m), 5.66 (1H, d, JHH = 14.8 Hz), 4.41 (1H, dd, JHH = 7.6, 3.2 Hz), 3.74 (3H, s), 3.84 (3H, s), 3.39 (1H, d, JHH = 14.8 Hz), 2.84–2.79 (1H, m), 2.37–2.32 (1H, m). 19F (CDCl3, 470 MHz) δ: −126.7. 13C (CDCl3, 125 MHz) δ: 159.7 (d, JCF = 30.2 Hz), 159.4, 159.2, 149.4 (d, JCF = 252.5 Hz), 131.2, 129.6 (2C), 129.0, 127.6 (2C), 114.2 (2C), 114.1 (2C), 109.6 (d, JCF = 13.8 Hz), 56.6, 55.4, 55.3, 47.1, 29.6 (d, JCF = 5.0 Hz). m/z [EI (+ve)] 341.1 [M]+. HRMS found [M]+ 341.1420. C23H20FNO2 requires 361.1478. 3-Fluoro-1-(4′-methoxybenzyl)-6-(4′-bromophenyl)-5,6-dihydro-1H-pyridin-2-one, 9e

Dialkene 8e [0.17 g, 0.41 mmol] was subjected to general procedure C. The crude product was purified by flash column chromatography (0-15% EtOAc in petroleum ether) to yield the desired α,β-unsaturated lactam 9e [0.15 g, 0.39 mmol, 96%] as a colourless oil.

1H (CDCl3, 400 MHz) δ: 7.51 (2H, d, JHH = 8.5 Hz), 7.14 (2H, d, JHH = 8.6 Hz), 7.05 (2H, d, JHH = 8.5 Hz), 6.87 (2H, d, JHH = 8.6 Hz), 5.79–5.74 (1H, m), 5.50 (1H, d, JHH = 14.6 Hz), 4.52 (1H, dd, JHH = 7.6, 2.4 Hz), 3.83 (3H, s), 3.51 (1H, d, JHH = 14.6 Hz), 3.00–2.91 (1H, m), 2.46–2.38 (1H, m). 19F (CDCl3, 377 MHz) δ: −126.3. 13C (CDCl3, 100 MHz) δ: 159.6 (d, JCF = 31.0 Hz), 159.3, 149.3 (d, JCF = 253.0 Hz), 138.5, 132.1 (2C), 129.6 (2C) 128.6, 128.1 (2C), 122.0, 114.2 (2C), 109.4 (d, JCF = 15.0 Hz), 56.5, 55.3, 47.3, 29.3 (d, JCF = 6.0 Hz). m/z [CI (+ve)] 391.7 [M + H]+. HRMS found [M + H]+ 390.0489. C19H14Br2FNO2 requires 390.0505. (thin film) νmax = 2950, 1653, 1512, 1247, 1217 cm−1.
1.43–1.39 (1H, m), 1.27–1.17 (1H, m), 0.85 (3H, d, J_HH = 6.8 Hz), 0.76 (3H, d, J_HH = 6.8 Hz). 13C(CDC13, 400 MHz) δ: –127.6. 13C(CDC13, 125 MHz) δ: 159.2, 158.7 (d, J_CF = 31.3 Hz), 149.6 (d, J_CF = 252.5 Hz), 129.5, 129.4 (2C), 114.1 (2C), 109.8 (d, J_CF = 13.8 Hz), 55.3, 52.1, 46.9, 39.6, 25.1, 24.6 (d, J_CF = 5.0 Hz), 23.6, 21.5. m/z [EI (+ve)] 291.2 [M+1]. HRMS found [M+1] 291.1639. IR (thin film) ν_max = 2955, 1651, 1512, 1249, 1201 cm⁻¹.

3-Fluoro-1-(‘-methoxybenzyl)-6-cyclohexane-5, 6-dihydro-1H-pyridin-2-one, 9g

Dialkene 8g (0.35 g, 1.06 mmol) was subjected to general procedure C. The crude product was purified by flash column chromatography (0–10% EtOAc in petroleum ether) to yield the desired αβ-unsaturated lactam 9g (0.30 g, 0.94 mmol, 89%) as a colourless oil.

1H(CDC13, 400 MHz) δ: 7.23 (2H, d, J_HH = 8.8 Hz), 6.87 (2H, d, J_HH = 8.8 Hz), 5.83–5.79 (1H, m), 5.49 (1H, d, J_HH = 14.9 Hz), 3.83 (3H, s), 3.79 (1H, d, J_HH = 14.9 Hz), 1.18 (1H, br t, J_HH = 6.8 Hz), 2.64–2.54 (1H, m), 2.36–2.28 (1H, m), 1.86–1.63 (6H, m), 1.29–1.07 (4H, m), 1.00–0.94 (1H, m). 19F(CDC13, 470 MHz) δ: –128.2. 13C(CDC13, 125 MHz) δ: 159.2, 159.0 (d, J_CF = 31.1 Hz), 149.5 (d, J_CF = 253.2 Hz, CP), 129.7, 129.3 (2C), 114.1 (2C), 110.6 (d, J_CF = 14.2 Hz), 59.0, 55.3, 48.7, 40.8, 30.3, 30.2, 26.4, 26.3, 26.2, 22.8 (d, J_CF = 5.5 Hz), m/z [Cl (+ve)] 318.2 [M+1]. HRMS found [M+1] 318.1871. C17H16FNO3 requires 301.1111. IR (thin film) ν_max = 2925, 2850, 1645, 1515, 1511, 1479, 1276, 1053 cm⁻¹.

General procedure D: removal of the p-methoxybenzyl protecting group

The cyclic amide (1 eq.) was dissolved in a MeCN–H₂O (8:2, 4 mL) mixture and ceric ammonium nitrate was added portionwise. The resulting solution was stirred at room temperature until completion indicated by TLC analysis (7 h). The reaction was quenched with aq. sat. NaHCO₃ (10 mL) and extracted with diethyl ether (3 × 10 mL). The organics were combined, dried (Na₂SO₄) and evaporated in vacuo. The crude material was purified by flash column chromatography.

3-Fluoro-6-phenyl-5,6-dihydro-1H-pyridin-2-one, 10a

αβ-Unsaturated lactam 9a (96 mg, 0.31 mmol) was subjected to general procedure D using 1.3 g of ceric ammonium nitrate (2.7 eq., 0.86 mmol). The crude product was purified by flash column chromatography (0–30% EtOAc in petroleum ether) to yield the desired dihydropropyridine 10a (60 mg, 0.29 mmol, 94%) as a white solid, m.p. 109–111 °C.

1H(CDC13, 400 MHz) δ: 7.45–7.37 (5H, m), 6.09 (1H, dd, J_HH = 11.1 Hz, J_HH = 5.9, 3.3 Hz), 5.62 (1H, br s), 4.82 (1H, dd, J_HH = 11.6, 5.8 Hz), 2.74–2.60 (2H, m). 19F(CDC13, 470 MHz) δ: –129.9. 13C(CDC13, 125 MHz) δ: 161.2 (d, J_CF = 32.8 Hz), 149.1 (d, J_CF = 253.2 Hz), 139.9, 129.2 (2C), 128.8, 126.4 (2C), 113.5 (d, J_CF = 13.8 Hz), 56.1, 31.2 (d, J_CF = 5.0 Hz). m/z [ESI (+ve)] 191.1 [M+1]. HRMS found [M+1] 191.0748. C19H15FNO requires 191.0746. IR (thin film) ν_max = 2356, 1705, 1670, 1248 cm⁻¹.

3-Fluoro-6-(‘-methoxyphenyl)-5,6-dihydro-1H-pyridin-2-one, 10b

αβ-Unsaturated lactam 9b (0.14 g, 0.42 mmol) was subjected to general procedure D using 1.3 g of ceric ammonium nitrate (5.5 eq., 2.3 mmol). The crude product was purified by flash column chromatography (0–25% EtOAc in petroleum ether) to yield the desired dihydropropyridine 10b (37 mg, 0.17 mmol, 40%) as a yellow solid. m.p. 135–137 °C.

1H(CDC13, 400 MHz) δ: 7.21 (2H, d, J_HH = 8.6 Hz), 6.84 (2H, d, J_HH = 8.6 Hz), 6.01–6.97 (1H, m), 5.57 (1H, br s), 4.67 (1H, dd, J_HH = 12.1, 5.6 Hz), 3.81 (3H, s), 2.60–2.46 (2H, m). 19F(CDC13, 470 MHz) δ: –130.6. 13C(CDC13, 125 MHz) δ: 161.1 (d, J_CF = 31.3 Hz), 159.8, 149.8 (d, J_CF = 253.8 Hz), 131.9, 127.6 (2C), 114.4 (2C), 113.6 (d, J_CF = 13.8 Hz), 55.6, 55.4, 31.2

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3-Fluoro-6-(4′-trifluoromethanepheryl)-5,6-dihydro-1H-pyridin-2-one, 10c

α,β-Unsaturated lactam 9e (0.16 g, 0.42 mmol) was subjected to general procedure D using 1.1 g of ceric ammonium nitrate (3.8 eq., 1.7 mmol). The crude product was purified by flash column chromatography (0–20% EtOAc in petroleum ether) to yield the desired dihydropyridone 10c (50 mg, 0.20 mmol, 47%) as a white solid. m.p. 104–105 °C.

3-Fluoro-6-(naphthalen-1′-yl)-5,6-dihydro-1H-pyridin-2-one, 10d

α,β-Unsaturated lactam 9d (0.11 g, 0.30 mmol) was subjected to general procedure D using 0.97 g of ceric ammonium nitrate (5.9 eq., 1.8 mmol). The crude product was purified by flash column chromatography (0–20% EtOAc in petroleum ether) to yield the desired dihydropyridone 10d (37 mg, 0.15 mmol, 51%) as a yellow solid. m.p. 135–137 °C.

3-Fluoro-6-(′bromophenyl)-5,6-dihydro-1H-pyridin-2-one, 10e

α,β-Unsaturated lactam 9e (0.19 g, 0.47 mmol) was subjected to general procedure D using 1.3 g of ceric ammonium nitrate (3.3 eq., 2.3 mmol). The crude product was purified by flash column chromatography (0–15% EtOAc in petroleum ether) to yield the desired dihydropyridone 10e (92 mg, 0.20 mmol, 92%) as a white solid. m.p. 149 °C.

3-Fluoro-6-isobutyl-5,6-dihydro-1H-pyridin-2-one, 10f

α,β-Unsaturated lactam 9f (0.13 g, 0.44 mmol) was subjected to general procedure D using 0.91 g of ceric ammonium nitrate (3.8 eq., 1.7 mmol). The crude product was purified by flash column chromatography (0–10% EtOAc in petroleum ether) to yield the desired dihydropyridone 10f (70 mg, 0.4 mmol, 92%) as a white solid. m.p. 61–63 °C.

3-Fluoro-6-cyclohexane-5,6-dihydro-1H-pyridin-2-one, 10g

α,β-Unsaturated lactam 9g (0.22 g, 0.70 mmol) was subjected to general procedure D using 1.3 g of ceric ammonium nitrate (3.3 eq., 2.3 mmol). The crude product was purified by flash column chromatography (0–10% EtOAc in petroleum ether) to yield the desired dihydropyridone 10g (0.11 g, 0.55 mmol, 79%) as a white solid. m.p. 108–110 °C.

General procedure E: hydrogenation of α,β-unsaturated lactams

A solution of dihydropyridone (1 eq.) in MeOH (2 mL) was treated with palladium activated charcoal (10% by weight) and the suspension was stirred under a H2 atmosphere until completion indicated by TLC analysis (1–4 hours). The resulting mixture was filtered through celite, dried (Na2SO4) and the solvent was removed under reduced pressure. The crude product was purified by flash column chromatography.

3-Fluoro-6-phenyl-piperidin-2-one, 11a

Dihydropyridone 10a (43 mg, 0.22 mmol) was subjected to general procedure E. The crude product was purified by flash column chromatography (0–30% EtOAc in petroleum ether) to yield the desired δ-lactam 11a (32 mg, 0.17 mmol, 75%) as a white solid. m.p. 149–151 °C.
3-Fluoro-6-(′-methoxyphenyl)-piperidin-2-one, 11b

Dihydopyridine 10b (24 mg, 0.11 mmol) was subjected to general procedure E. The crude product was purified by flash column chromatography (0–50% EtOAc in petroleum ether) to yield the desired δ-lactam 11b (14 mg, 0.06 mmol, 58%) as a white solid. m.p. 159–161 °C.

1H (CDCl3, 400 MHz) δ: 7.25 (2H, d, JHH = 8.6 Hz), 6.94 (2H, d, JHH = 8.2 Hz), 5.83 (1H, s), 4.94 (1H, dt, JHH = 71.7 Hz, JHF = 4.6 Hz), 4.56–4.51 (1H, m), 3.84 (3H, s), 2.34–2.24 (1H, m), 2.13–1.96 (3H, m). 13C (CDCl3, 125 MHz) δ: 167.2 (d, JCF = 22.1 Hz), 159.6, 133.4, 127.3 (2C), 114.4 (2C), 85.7 (d, JCF = 176.1 Hz), 57.0, 55.4, 27.4 (d, JCF = 4.6 Hz), 26.4 (d, JCF = 21.2 Hz). m/z [EI (+ve)] 223.1 [M]+. HRMS found [M]+ 223.0999, C12H14FNO requires 223.1009. IR (thin film) νmax = 2930, 1695, 1510, 1230 cm⁻¹.

3-Fluoro-6-(′-trifluoromethylphenyl)-piperidin-2-one, 11c

Dihydopyridine 10c (29 mg, 0.11 mmol) was subjected to general procedure E. The crude product was purified by flash column chromatography (0–40% EtOAc in petroleum ether) to yield the desired δ-lactam 11c (29 mg, 0.11 mmol, quantitative yield) as a white solid. m.p. 122–124 °C.

1H (CDCl3, 400 MHz) δ: 7.60 (2H, d, JHH = 8.2 Hz), 7.38 (2H, d, JHH = 8.2 Hz), 5.93 (1H, s), 4.86 (1H, dt, JHH = 47.1 Hz, JHF = 5.0 Hz), 4.59 (1H, br t, JHH = 5.7 Hz), 2.22–2.12 (1H, m), 2.11–1.89 (3H, m). 13C (CDCl3, 125 MHz) δ: 167.4 (d, JCF = 22.3 Hz), 145.4, 130.9, 130.6, 126.6 (2C), 126.1 (2C), 85.5 (d, JCF = 176.5 Hz), 57.0, 27.2 (d, JCF = 4.2 Hz), 26.1 (d, JCF = 21.0 Hz). m/z [EI (+ve)] 261.1 [M]+. HRMS found [M]+ 261.0773, C12H11F3NO requires 261.0777. IR (thin film) νmax = 3005, 2970, 1675, 1430 cm⁻¹.

3-Fluoro-6-(naphthalen-1-yl)-piperidin-2-one, 11d

Dihydopyridine 10d (38 mg, 0.15 mmol) was subjected to general procedure E. The crude product was purified by flash column chromatography (0–40% EtOAc in petroleum ether) to yield the desired δ-lactam 11d (29 mg, 0.12 mmol, 81%) as a white solid. m.p. 144–147 °C.

1H (CDCl3, 400 MHz) δ: 7.99–7.93 (2H, m), 7.87 (1H, d, JHH = 8.0 Hz), 7.62–7.51 (4H, m), 6.02 (1H, s), 5.48–5.46 (1H, m), 5.02 (1H, dt, JHF = 46.9 Hz, JHH = 5.7 Hz), 2.43–2.33 (1H, m), 2.28–2.23 (3H, m). 19F (CDCl3, 377 MHz) δ: −186.1. 13C (CDCl3, 100 MHz) δ: 168.3 (d, JCF = 19.9 Hz), 136.6, 134.0, 129.8, 129.4, 128.9, 126.8, 126.0, 125.4, 123.7, 121.9, 85.8 (d, JCF = 177.0 Hz), 53.3, 25.9 (d, JCF = 6.0 Hz), 25.7 (d, JCF = 20.0 Hz). m/z [Cl (+ve)] 244.0 [M + H]+, HRMS found [M + H]+ 244.1137, C16H14F3NO requires 244.1138. IR (thin film) νmax = 3240, 2900, 1600, 1110 cm⁻¹.

3-Fluoro-6-isobutyl-piperidin-2-one, 11f

Dihydopyridine 10f (39 mg, 0.23 mmol) was subjected to general procedure E. The crude product was purified by flash column chromatography (0–20% EtOAc in petroleum ether) to yield the desired δ-lactam 11f (40 mg, 0.23 mmol, quantitative yield) as a white solid. m.p. 78–81 °C.

1H (CDCl3, 400 MHz) δ: 6.00 (1H, s), 4.80 (1H, dt, JHF = 48.6 Hz, JHH = 4.5 Hz), 3.40–3.37 (1H, m), 2.16–2.13 (1H, m), 1.96–1.89 (1H, m), 1.81–1.77 (1H, m), 1.64–1.58 (2H, m), 1.40–1.31 (2H, m), 0.87 (3H, d, JHH = 6.6 Hz), 0.85 (3H, d, JHH = 6.6 Hz). 13C (CDCl3, 470 MHz) δ: 167.4 (d, JCF = 20.0 Hz), 86.5 (d, JCF = 173.8 Hz), 50.8, 45.6, 26.5 (d, JCF = 21.3 Hz), 24.3, 24.0 (d, JCF = 3.7 Hz), 22.6, 22.3. m/z [Cl (+ve)] 174.1 [M + H]+, HRMS found [M + H]+ 174.1300, C12H12FNO requires 174.1294. IR (thin film) νmax = 2950, 2935, 1630 cm⁻¹.
(d, J\textsubscript{CF} = 5.7 Hz). m/z [El (+ve)] 267.1 [M\textsuperscript{+}], HRMS found [M\textsuperscript{+}] 267.1058. C\textsubscript{17}H\textsubscript{16}F\textsubscript{1}NO requires 267.1056. IR (thin film) \( \nu_{\text{max}} = 2358, 1693, 1658, 1258, 1198 \text{ cm}^{-1} \).

3-Fluoro-6-(1'-phenylphenyl)-piperidin-2-one, 13

Dihydropyridone 12 (34 mg, 0.13 mmol) was subjected to general procedure E. The crude product was purified by flash column chromatography (0–40% EtOAc in petroleum ether) to yield the desired \( \delta \)-lactam 13 (34 mg, 0.13 mmol, quantitative) as a white solid. m.p. 171–173 °C.

\( ^1\text{H} \) (CDCl\textsubscript{3}, 400 MHz) \( \delta \): 7.64 (2H, d, \( J \text{HH} = 7.5 \text{ Hz} \)), 7.61 (2H, d, \( J \text{HH} = 7.5 \text{ Hz} \)), 7.50–7.38 (5H, m), 5.91 (1H, s), 4.97 (1H, dt, \( J_{1H, 2H} = 4.37 \text{ Hz} \)), 4.67–4.63 (1H, m), 2.36–2.27 (1H, m), 2.20–2.04 (3H, m). \( ^{13}\text{C} \) (CDCl\textsubscript{3}, 100 MHz) \( \delta \): 167.5 (d, \( J_{CF} = 19.8 \text{ Hz} \)), 141.4, 140.3, 140.2, 128.9 (2C), 127.7 (2C), 127.6, 127.1 (2C), 126.6 (2C), 85.7 (d, \( J_{CF} = 176.0 \text{ Hz} \)), 57.2, 27.3 (d, \( J_{CF} = 4.0 \text{ Hz} \)), 26.3 (d, \( J_{CF} = 21.0 \text{ Hz} \)). m/z [El (+ve)] 269.0 [M\textsuperscript{+}], HRMS found [M\textsuperscript{+}] 269.1214. C\textsubscript{17}H\textsubscript{14}F\textsubscript{1}NO requires 269.1216. IR (thin film) \( \nu_{\text{max}} = 3239, 2949, 2356, 1676, 1486 \text{ cm}^{-1} \).

Crystallographic data collection and refinement details


Acknowledgements

We would like to thank the EPSRC and AstraZeneca for postgraduate support (T.C.). The authors also thank Dr Ian Sword, the EPSRC [grant EP/H005692/1] and AstraZeneca for funding.

Notes and references


10 The atomic coordinates for 11a (CCDC deposition number CCDC1006297) are available upon request from the Cambridge Crystallographic Centre, University Chemical Laboratory, Lensfield Road, Cambridge, CB2 1EW, United Kingdom. The crystallographic numbering system differs from that used in the text; therefore, any request should be accompanied by the full literature citation of this paper.


