Abstract
The first synthesis of α-(trifluoromethyl)-β-lactam (1) is reported. The route starts from α-(trifluoromethyl)acrylic acid (2). Conjugate addition of α-(p-methoxyphenyl)ethylamine ((S)-3b), generated an addition adduct 4b which was cyclised to β-lactam 5b. Separation of the diastereoisomers by chromatography gave ((αS,3S)-5b). N-Debenzylation afforded the desired α-(trifluoromethyl)-β-lactam ((S)-1). The absolute stereochemistry of diastereoisomers 5 was determined by X-ray crystallographic determination of a close structural analogue, ((αS,3S)-5c, and then 1H and 19F NMR correlation to the individual diastereoisomers of 5a and 5b.

Introduction
β-Lactams (azetidin-2-ones) have played a prominent role in medicinal chemistry and many structural variants have been prepared and elaborated [1]. Similarly, the CF₃ group is an ubiquitous substituent in pharmaceutical research, where it is used to modify the activity of a drug candidate or to block adventitious metabolism and improve the pharmacokinetic profiles [2,3]. Likewise, the substituent is found widely distributed in agrochemical products [4]. The majority of CF₃ containing compounds reported in the literature are CF₃-aryl, CF₃-ether [5,6] or CF₃-heteroaromatic in nature, and these substituents have contributed significantly to the fine chemicals and related industries. However, there is an increasing awareness and demand for molecular building blocks which carry the CF₃ group at a stereogenic centre [7,8] and some such motifs are emerging in new chemical entities licenced for the pharmaceuticals market, but also in organic materials area, e.g., liquid crystals [9]. Methodologies continue to emerge for the asymmetric introduction of the CF₃ group [10-13]. In this contribution, we report a synthesis of α-(trifluoromethyl)-β-lactam (1) which allows access to its enantiomerically pure forms, (R)-1 and (S)-1 as illustrated in Figure 1.
commercially available source of the CF₃ group. It was envisaged that conjugate addition of an enantiomerically pure amide such as (R)- or (S)-3 would generate the addition adducts, carboxylate salts 4, as a mixture of diastereoisomers. Cyclisation to the N-substituted β-lactams 5 would give a mixture of two stereoisomers which might be separated into their individual diastereoisomers 5 by chromatography. N-Benzyl deprotection of the individual diastereoisomers would then provide β-lactam 1 as a single enantiomer. At the outset, (S)-(α-phenyl)ethylamine (3a) was explored as the enantiomerically pure amine. In the event 4a was generated after aza-Michael addition as a mixture of two stereoisomers, without any obvious diastereoisomeric bias (1:1, 0% de) as judged by both ¹H and ¹⁹F NMR. β-Lactam ring closure, using thionyl chloride and triethylamine gave the N-methylbenzyl-β-lactam 5a with a modest diastereoisomeric bias (~50% de) indicating some epimerisation of the α-trifluoromethyl stereogenic centre, to a thermodynamic product ratio. This was supported in an analytical reaction by the observation of deuterium exchange at this stereogenic centre after the addition of D₂O to the reaction on work up. The major and minor diastereoisomers of 5a were separated by careful chromatography on silica gel into single stereoisomers. Completion of the syntheses required hydrogenolysis of the (S)-N-methylbenzyl moiety of 5a. A range of conditions and catalysts were explored for the hydrogenolysis of 5a, however cleavage of the C–N bond proved very difficult and a satisfactory method could not be found. Therefore, (S)-α-(p-methoxyphenyl)ethylamine (3b) was explored as an alternative amine for the aza-Michael reaction, as removal of this amine using ceric ammonium nitrate (CAN) oxidation offered a milder deprotection method [15]. The aza-Michael reaction proved straightforward to generate 4b and then cyclisation again using thionyl chloride and triethylamine gave β-lactams 5b in a 40% de, presumably again a thermodynamically biased isomer ratio. The diastereoisomers of 5b could be separated by careful chromatography over silica gel and this led to the recovery of each isomer as a major and a minor product. Finally, oxidative scission of the major β-lactam stereoisomer (αS,3S)-5b, using CAN was relatively straightforward generating β-lactam (S)-1 in 67% yield. This novel β-lactam is a crystalline solid, and a suitable crystal was subjected to X-ray structure analysis. The structure of 1 is shown in Figure 2a.

Accordingly, (S)-α-(p-methoxyphenyl)ethylamine (3b) emerged as the more satisfactory amine over 3a for the preparation of 1, due to the straightforward benzylic cleavage. Enantiomeric purity analysis of the resultant β-lactam 1 was evaluated by ¹⁹F NMR using a europium chiral shift reagent [Eu(hfc)₃]. The
comparison of a racemic sample of 1 and then a sample after diastereisomer separation of 5b as described above, indicated that \( \beta \)-lactam 1 was prepared in an enantiomerically pure form. There was no evidence that benzylic cleavage of the (S)-\( \alpha \)-(p-methoxyphenyl)ethyl moiety with CAN resulted in epimerisation at the stereogenic centre of the \( \beta \)-lactam.

Finally, it was necessary to determine the absolute configuration of the resultant \( \beta \)-lactam. To this end, X-ray crystallography of the major diastereoisomers of 5a and 5b was attempted after chromatographic separation. Despite considerable effort however we could not obtain crystals of single isomers of 5a or 5b suitable for X-ray structure analysis. Thus, a preparation of 5c was carried out as illustrated in Scheme 2. The presence of the naphthyl ring in amine (R)-3c rendered the resultant \( \beta \)-lactam diastereoisomers 5c more crystalline, and a single crystal X-ray structure was solved for the major-diastereomer revealing the (aR,3R)-5c configuration. The structure is shown in Figure 2b.

With this structural information in hand it was necessary to correlate to the stereoisomers of 5b. The \(^1\)H and \(^19\)F NMR spectra of the major and minor diastereoisomers of 5a-c were now compared. Clear chemical shift trends are observed as illustrated and tabulated in Table 1 and Table 2. For example, in all cases, the \(^1\)H NMR chemical shifts of the C-3 hydrogens (H\(_3\)) of the \( \beta \)-lactam are shifted downfield in the major relative to the minor diastereoisomers. The non-equivalent faces of the planar \( \beta \)-lactam ring differentiates the two diastereotopic hydrogens at C-4 (H\(_4\) and H\(_{4}'\)).

It is clear that for all three major isomers the \(^1\)H NMR signals for H\(_4\) and H\(_{4}'\) have a larger chemical shift difference than that between the H\(_5\) and H\(_{5}'\) signals of the minor isomers. Also the chemical shifts for H\(_5\) and H\(_{5}'\) of the minor isomers lie within those of the major isomers. For the \(^19\)F NMR spectra shown in Table 2 the major isomers all have their trifluoromethyl signals downfield of the minor diastereoisomers.

On this basis, the NMR spectra of (aR,3R)-5c, where the absolute stereochemistry was determined by X-ray crystallography, allows the absolute stereochemistry of diastereoisomers 5a and 5b to be deduced by correlation, and it follows that benzylic cleavage of (S)-\( \alpha \)-(p-methoxyphenyl)ethylamine (3b) gave rise to \( \beta \)-lactam (S)-1. Ready access to the (R)-1 enantiomer would require starting the synthetic route from (S)-\( \alpha \)-(p-methoxyphenyl)ethylamine (3b).
Table 1: Comparison of the $^1$H NMR data of Hb and Hc of the diastereoisomers of 5a–c.

|                  | $\delta \ ^1$H [ppm] | $\delta \ ^1$H [ppm] | $J_1$ [Hz] | $J_2$ [Hz] | $\delta \ ^1$H [ppm] | $J_1$ [Hz] | $J_2$ [Hz] |
|------------------|------------------------|------------------------|------------|------------|------------------------|------------|------------|
| (αS,3S)-5a major | 3.78                   | 3.39                   | 8.38       | 5.40       | 3.13                   | 4.20       |            |
| (αS,3R)-5a minor | 3.64                   | 3.20                   | 6.24       | 2.60       | 3.21                   | 6.76       | 6.06       |
| (αS,3S)-5b major | 3.78                   | 3.36                   | 6.43       | 6.18       | 3.11                   | 6.18       | 2.83       |
| (αS,3R)-5b minor | 3.73                   | 3.27                   | 6.47       | 2.45       | 3.18                   | 6.55       | 5.27       |
| (αS,3S)-5c major | 3.79                   | 3.31                   | 7.49       | 6.61       | 2.77                   | 6.40       | 2.48       |
| (αS,3R)-5c minor | 3.76                   | 3.25                   | 6.66       | 2.12       | 2.85                   | 6.85       | 6.00       |

Table 2: Comparison of the $^{19}$F NMR chemical shifts of the diastereoisomers of 5a–c.

|                  | $\delta \ ^{19}$F major [ppm] | $J$ [Hz] | $\delta \ ^{19}$F minor [ppm] | $J$ [Hz] |
|------------------|-------------------------------|----------|--------------------------------|----------|
| 5a               | -68.72                        | 8.73     | -68.85                        | 8.94     |
| 5b               | -69.21                        | 8.36     | -69.35                        | 8.36     |
| 5c               | -68.62                        | 9.14     | -69.62                        | 8.94     |
Conclusion
In a short single enantiomer synthesis of β-lactam (S)-I is reported which took advantage of an aza-Michael addition between (S)-α-(p-methoxyphenyl)ethylamine (3b) and α-(trifluoromethyl)acrylic acid (2). Cyclisation and then chromatographic resolution of the β-lactam diastereoisomers 5b, followed by deprotection with ceric ammonium nitrate generated the β-lactam (S)-I. This contributes diversity to the known β-lactam motifs and incorporates the CF₃ group.

Experimental
General
All reagents were obtained from commercial sources and were used without further purification unless otherwise stated. Air- and moisture-sensitive reactions were carried out under a positive pressure of argon in flame-dried glassware using standard Schlenk-line techniques. Dry CH₂Cl₂ was obtained from the Solvent Purification System MB SPS-800. Room temperature (RT) refers to 20–25 °C. Reaction temperatures of 0 °C were obtained in an ice/water bath. Reaction reflux conditions were obtained using an oil bath equipped with a contact thermometer. Solvent evaporations were carried out under reduced pressure on a Büchi rotary evaporator. Thin layer chromatography (TLC) was performed using Macherey-Nagel Polygram Sil G/UV254 plastic plates. Visualisation was achieved by inspection under UV light (255 nm). Column chromatography was performed using silica gel 60 (40–63 micron). NMR spectra were recorded on Bruker AVANCE 300, 400 or 500 MHz instruments. ¹H and ¹³C NMR spectra were recorded in CDCl₃ as solvent. ¹⁹F NMR spectra were referenced to CFCl₃ as the external standard. Chemical shifts are reported in parts per million (ppm) and coupling constants (J) are given in Hertz (Hz). IR spectra were recorded on a Nicolet Avatar 360 FT-IR from a thin film (either neat or combined with nujol) supported between NaCl plates. Optical rotations [α]D are given in 10⁻¹° deg cm² g⁻¹ and were measured using a Perkin Elmer Model 341 polarimeter. Mass spectrometric (m/z) data was acquired by electrospray ionisation (ESI). High resolution mass analyses were recorded on a Micromass LCT TOF mass spectrometer using ES ionisation in positive ion mode.

General aza-Michael procedure
NaHCO₃ (840 mg, 10.0 mmol) was added to a solution of α-(trifluoromethyl)acrylic acid (2, 1.41 g, 10.0 mmol) in methanol (10 mL), and then after 30 min stirring, a single enantiomer amine 3 (10.0 mmol) was added. The reaction was stirred at RT for 24 h. The solvent was evaporated under reduced pressure to afford the aza-Michael product as a colourless oil (quart) which solidified upon standing. Optionally, the sodium salt was converted to the amino acid HCl salt by treatment with aq HCl, followed by evaporation of the water and redissolving in DCM.

Synthesis of aza-Michael adduct diastereoisomers
4a
General procedure with α-(trifluoromethyl)acrylic acid 2 (431 mg, 3.08 mmol), NaHCO₃ (258 mg, 3.02 mmol) and (S)-phenylethylamine (318 µL, 3.02 mmol) in methanol (20 mL), gave after 96 h 830 mg (95%) of the title compound as a mixture of diastereoisomers (93% purity). Product 4a was used without further purification. ¹H NMR (400 MHz, CD₃OD) 7.42–7.25 (m, 5H, Ar), 4.02–3.90 (m, 1H, PhCH₂CH₃), 3.30–3.13 (m, 1H, CH₂CHF₂), 3.10–2.91 (m, 1H, NCH₂CH₂), 2.90–2.76 (m, 1H, NCH₂CH₂), 1.44 (d, J = 6.7 Hz, 3H, CH₃CH₂); ¹³C NMR (100 MHz, CD₃OD) 172.3 (q, J = 2.0 Hz, COONa), 172.2 (q, J = 2.0 Hz, COONa), 143.9 (C-Ar), 143.5 (C-Ar), 129.9 (C-Ar), 129.8 (C-Ar), 128.9 (C-Ar), 128.8 (C-Ar), 128.1 (C-Ar), 128.0 (C-Ar), 126.8 (q, J = 278 Hz, CCF₂), 126.9 (q, J = 278 Hz, CCF₂), 59.6 (PhCH₂CH₂), 59.0 (PhCH₂CH₂), 52.6 (q, J = 25.0 Hz, CHF₂), 52.6 (q, J = 25.0 Hz, CHF₂), 52.1 (q, J = 25.0 Hz, CHF₂), 45.12 (q, J = 3.5 Hz, NCH₂CH₂), 44.7 (q, J = 3.5 Hz, NCH₂CH₂), 23.1 (CH₂CH₂), 22.9 (CH₂CH₂); ¹⁹F NMR (376 MHz, CD₃OD) −69.0 (d, J = 9.3 Hz), −69.1 (d, J = 9.3 Hz); HRMS–ESI (m/z): Calcd for C₁₂H₁₄NO₂F₃Na, 284.0874; found, 284.0869.

Synthesis of aza-Michael adduct diastereoisomers
4b
General procedure with α-(trifluoromethyl)acrylic acid 2 (1.52 g, 10.8 mmol), NaHCO₃ (912 mg, 10.8 mmol) and (S)-p-methoxyphenylethylamine (1.595 mL, 10.08 mmol) in methanol (20 mL), gave after 2 h 3.06 g (98%) of the title compound as a mixture of diastereoisomers (93% purity). The material was used without further purification. ¹H NMR (400 MHz, CD₃OD) 7.17–7.12 (m, 2H, Ar), 6.85–6.80 (m, 2H, Ar), 4.86 (q, J = 6.5 Hz, 1H, PhCH₂CH₂), 3.74 (s, 3H, PhOCH₃), 3.73–3.65 (m, 1H, CH₂CHF₂), 3.27 (dd, J = 6.3 Hz, J = 6.3 Hz, 1H, NCH₂CH₂), 3.01 (dd, J = 6.4 Hz, J = 2.7 Hz, 1H, NCH₂CH₂), 1.52 (d, J = 6.7 Hz, 3H, CH₃CH₂); ¹³C NMR (100 MHz, MeOD) 167.4 (NOCH), 167.3 (NOCH), 162.2 (C-Ar), 131.6 (C-Ar), 130.4 (C-Ar), 128.5 (C-Ar), 128.4 (C-Ar), 128.1 (q, J = 275 Hz, CF₃), 125.5 and 125.1 (q, J = 275 Hz, CF₃), 115.83 (C-Ar), 115.51 (C-Ar), 60.61 (PhCH₂CH₂), 55.9 (PhOCH₃), 48.2 (q, J = 30.2 Hz, CHF₂), 48.1 (q, J = 30.2 Hz, CHF₂), 42.6 (NCH₂CH₂), 19.9 (CH₂CH₂), 19.5 (CH₂CH₂); ¹⁹F NMR (376 MHz, MeOD) −68.8 (d, J = 8.7 Hz, CHF₂), −68.9 (d, J = 8.1 Hz, CHF₂); HRMS–ESI (m/z): Calcd for C₁₃H₁₄NO₂F₃Na, 314.0980; found, 314.0975.
Synthesis of aza-Michael adduct diastereoisomers 4c

General procedure with α-(trifluoromethyl)acrylic acid 2 (236 mg, 1.69 mmol), NaHCO₃ (142 mg, 1.685 mmol) and (R)-1-naphthylethylamine (295.4 mg, 1.685 mmol) in methanol (10 mL), gave after 96 h 550 mg (98%) of the title compound as a mixture of diastereoisomers (89% purity). The material was used without further purification.

H NMR (400 MHz, CDCl₃): 8.20 (t, J = 8.2 Hz, 1H, H-Ar), 7.91–7.86 (m, 1H, Ar), 7.83–7.79 (m, 1H, Ar), 7.72–7.68 (m, 1H, Ar), 7.59–7.46 (m, 3H, Ar), 4.99–4.88 (m, 1H, PhCH₂CH₃), 3.35–3.22 (m, 1H, CH₂CH₂F), 3.21–3.09 (m, 1H, NCH₂CH₂), 3.03–2.94 (m, 1H, NCH₂CH₂), 1.57 and 1.56 (d, J = 6.7 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) 172.2 (COONa), 172.0 (COONa), 139.5 (C-Ar), 138.9 (C-Ar), 135.5 (C-Ar), 132.48 (C-Ar), 132.45 (C-Ar), 130.08 (C-Ar), 130.05 (C-Ar), 129.2 (C-Ar), 129.15 (C-Ar), 127.5 (C-Ar), 127.4 (C-Ar), 126.8 (C-Ar), 126.75 (C-Ar), 126.7 (C-Ar), 126.6 (C-Ar), 124.2 (C-Ar), 123.7 (C-Ar), 123.5 (C-Ar), 54.5 (PhCH₂), 54.1 (PhCH₂), 52.5 (q, J = 25.0 Hz, CHF₂), 52.2 (q, J = 25.0 Hz, CHF₂), 45.2 (q, J = 3.0 Hz, NCH₂CH₂), 44.9 (q, J = 3.0 Hz, NCH₂CH₂), 22.51 (CH₂CH₃), 22.46 (CH₂CH₃); ¹⁹F NMR (375 MHz, CDCl₃): 69.0 (d, J = 9.7 Hz, CHF₂), 69.1 (d, J = 9.7 Hz, CHF₂); HRMS–ESI (m/z): Calcd for C₁₆H₁₆NO₃F₃Na, 334.1031; found, 334.1031.

Minor isomer (aS,3R)-5a (29 mg, 14%): [α]D²⁰ = −36.7 (c 0.09, CH₂Cl₂); IR (neat): 2976 (s), 1756 (vs), 1184 (s), 1191 (s), 700 (s) cm⁻¹; ¹H NMR (500 MHz, CDCl₃): 7.42–7.27 (m, 5H, Ar), 4.94 (q, J = 7.0 Hz, 1H, ArCH₂), 3.80–3.71 (m, 1H, CHF₂CH₃), 3.30 (dd, J = 6.5 Hz, J = 2.2 Hz, 1H, NCH₂CH₂), 3.22 (dd, J = 7.2 Hz, J = 6.0 Hz, 1H, NCH₂CH₂), 1.67 (d, J = 7.1 Hz, 3H, CH₃CH₂), ¹³C NMR (125 MHz, CDCl₃): 159.3 (q, J = 4.2 Hz), 139.3 (C-Ar), 129.0 (C-Ar), 128.1 (C-Ar), 126.7 (C-Ar), 123.8 (q, J = 275 Hz, CF₃), 52.5 (PhCH₂), 51.3 (q, J = 30.8 Hz, CHF₂), 37.7 (q, J = 3.1 Hz, NCH₂CH₂), 18.4 (CH₂CH₃); ¹⁹F NMR (470 MHz, CDCl₃): −68.85 (d, J = 9.1 Hz, CHF₂); HRMS–ESI (m/z): Calcd for C₁₂H₁₂NOF₃Na, 266.0769; found, 266.0766.

Preparation of diastereoisomers 5b

Sodium salt of 4b (1.18 g, 3.77 mmol) and SOCl₂ (1.36 mL, 18.8 mmol) in DCM (100 mL) and DMF (5 drops), followed by Et₃N (2.6 mL, 39.8 mmol), gave 5b as a colourless oil.

Major isomer (aS,3S)-5b (447 mg, 43%): [α]D²⁰ +96.5 (c 0.31, CH₂Cl₂); IR (neat): 2980 (s), 1756 (vs), 1612 (s), 1515 (s), 1372 (s), 1180 (s), 1120 (s), 1010 (s), 835 (s) cm⁻¹; ¹H NMR (400 MHz, CDCl₃): 7.30–7.25 (m, 2H, Ar), 6.95–6.90 (m, 2H, Ar), 4.94 (q, J = 6.5 Hz, 1H, PhCH₂), 3.85 (s, 3H, PhOCH₂), 3.84–3.73 (m, 1H, CH₂CH₂F), 3.36 (dd, J = 6.0 Hz, J = 6.0 Hz, 1H, NCH₂CH₂), 3.11 (dd, J = 6.3 Hz, J = 2.6 Hz, 1H, NCH₂CH₂), 1.61 (d, J = 7.1 Hz, 3H, CH₃CH₂); ¹³C NMR (100 MHz, CDCl₃): 159.7 (NOCOH), 131.6 (C-Ar), 128.3 (C-Ar), 124.4 (q, J = 275 Hz, CF₃), 114.6 (C-Ar), 55.8 (PhCH₂), 51.7 (PhCH₂), 51.4 (q, J = 30.2 Hz, CHF₂), 37.9 (q, J = 3.3 Hz, NCH₂CH₂), 18.6 (CH₂CH₃); ¹⁹F NMR (376 MHz, CDCl₃): −69.2 (d, J = 8.1 Hz, CHF₂); HRMS–ESI (m/z): Calcd for C₁₂H₁₂NOF₃Na, 296.0874; found, 296.0868.

Minor isomer (aS,3R)-5b (140 mg, 14%): [α]D²⁰ −42.1 (c 0.18, CH₂Cl₂); IR (neat): 2975 (s), 1760 (vs), 1611 (s), 1515 (s), 1370 (s), 1244 (vs), 1121 (s), 1031 (s), 1010 (s), 833 (s) cm⁻¹; ¹H NMR (400 MHz, CDCl₃): 7.25–7.22 (m, 2H, Ar), 6.94–6.90 (m, 2H, Ar), 4.91 (q, J = 7.0 Hz, 1H, PhCH₂), 3.83 (s, 3H, PhOCH₂), 3.78–3.68 (m, 1H, CH₂CH₂F); 3.27 (dd, J = 6.4 Hz, J = 3.1 Hz, NCH₂CH₂).
Preparation of diastereoisomers 5c
From sodium salt 4c (500 mg, 1.50 mmol), SOCl₂ (544 μL, 7.5 mmol) in DCM (20 mL), followed by Et₃N (1.05 mL, 7.5 mmol) gave 5c as a yellow solid.

Major isomer (αR,3R)-5c (192 mg, 41%): [α]D²⁰ = 40.9 (c 0.15, CH₂Cl₂); IR (neat): 2981 (s), 1760 (vs), 1368 (s), 1260 (s), 1158 (s), 1122 (s), 1011 (s), 780 (s) cm⁻¹. ¹H NMR (500 MHz, CDCl₃) 8.10 (d, J = 8.4 Hz, 1H, Ar), 7.92 (d, J = 7.8 Hz, 1H, Ar), 7.88 (d, J = 8.4 Hz, 1H), 7.64–7.58 (m, 1H, Ar), 7.58–7.46 (m, 3H, Ar), 5.78 (q, J = 6.7 Hz, 1H, Ar), 3.82–3.73 (m, 1H, CHFC₃), 3.31 (dd, J = 7.1 Hz, J = 6.0 Hz, 1H), 2.77 (dd, J = 6.5 Hz, J = 7.6 Hz, 1H), 1.80 (dd, J = 7.2 Hz, 3H, CH₂CH₃); ¹³C NMR (75 MHz, CDCl₃) 159.3 (q, J = 4.3 Hz, NOCOH), 133.9 (C-Ar), 133.7 (C-Ar), 130.9 (C-Ar), 129.2 (C-Ar), 128.9 (C-Ar), 127.0 (C-Ar), 126.2 (C-Ar), 123.7 (q, J = 275 Hz, CF₃), 123.7 (C-Ar), 122.7 (C-Ar), 51.0 (q, J = 31.1 Hz, CHFC₃), 47.9 (PhCH₂CH₃), 37.4 (q, J = 3.2 Hz, NCH₂CH₃), 17.8 (CH₂CH₃); ¹⁹F NMR (470 MHz, CDCl₃) –68.6 (d, J = 9.1 Hz, CHFC₃); HRMS–ESI (m/z): Calcd for C₁₄H₁₅NOF₃Na, 316.0925; found, 316.0915.

Minor isomer (αR,3S)-5c (70 mg, 15%): [α]D²⁰ = 35.7 (c 0.14, CH₂Cl₂); IR (neat): 2978 (s), 1755 (vs), 1366 (s), 1191 (s), 1120 (s), 778 (s) cm⁻¹. ¹H NMR (500 MHz, CDCl₃) 8.15 (d, J = 8.6 Hz, 1H, Ar), 7.92 (d, J = 8.6 Hz, 1H, Ar), 7.87 (dd, J = 8.5 Hz, 1H), 7.63–7.58 (m, 1H, Ar), 7.58–7.48 (m, 3H, Ar), 5.79 (q, J = 6.8 Hz, 1H, Ar), 3.69–3.60 (m, 1H, CHFC₃), 3.25 (dd, J = 6.5 Hz, J = 2.5 Hz, 1H), 2.86 (dd, J = 6.9 Hz, J = 6.2 Hz, 1H), 1.82 (d, J = 7.2 Hz, 3H, CH₂CH₃); ¹³C NMR (125 MHz, CDCl₃) 159.2 (q, J = 4.5 Hz, NOCOH), 133.9 (C-Ar), 133.8 (C-Ar), 130.9 (C-Ar), 129.2 (C-Ar), 129.0 (C-Ar), 127.1 (C-Ar), 126.2 (C-Ar), 125.1 (C-Ar), 123.9 (q, J = 275 Hz, CF₃), 123.7 (C-Ar), 122.6 (C-Ar), 47.7 (PhCH₂CH₃), 50.9 (q, J = 31.1 Hz, CHFC₃), 37.2 (q, J = 3.0 Hz, NCH₂CH₃), 17.7 (CH₂CH₃); ¹⁹F NMR (470 MHz, CDCl₃) –68.8 (d, J = 9.1 Hz, CHFC₃); HRMS–ESI (m/z): Calcd for C₁₄H₁₅NOF₃Na, 316.0925; found, 316.0919.

(5S)-3-(Trifluoromethyl)azetidin-2-one (S)-1
To a solution of (αS,3S)-5b (325 mg, 1.18 mmol) in a mixture of MeCN (8 mL) and water (2 mL), ceric ammonium nitrate (1.94 g, 3.54 mmol, 3 equiv) was added portionwise. The reaction mixture was stirred at RT for 16 h and then quenched with sat. sodium bicarbonate (5 mL). After 10 min of stirring (when gas evolution ceased), the mixture was extracted into Et₂O (3 × 10 mL), the combined organic phases were dried (Na₂SO₄) and the solvent was removed. Purification on silica gel (20% EtOAc in petrol) gave (S)-1 as a colourless oil which solidified upon standing (110 mg, 67%). Mp 85 °C; [α]D²⁰ = 26.9 (c 0.09, CH₂Cl₂); IR (neat): 1707 (s), 1652 (s), 1180 (s), 1120 (s) cm⁻¹; MS–ESI (m/z): 161.98 (M + Na); ¹H NMR (400 MHz, CDCl₃) 6.73 (bs, 1H, CH₂NHCO), 3.91–3.81 (m, 1H, CHF₂CH₃), 3.47 (dd, J = 6.9 Hz, J = 6.3 Hz, 1H, NCH₂CH₃), 3.37 (dd, J = 6.5 Hz, J = 3.0 Hz, 1H, NCH₂CH₃); ¹³C NMR (100 MHz, CDCl₃) 161.3 (q, J = 4.5 Hz, NOCOH), 123.7 (q, J = 275.8 Hz, CF₃), 53.7 (q, J = 31.3 Hz, CHFC₃), 36.7 (q, J = 3.5 Hz, NCH₂CH₃); ¹⁹F NMR (376 MHz, CDCl₃) –69.38 (d, J = 9.5 Hz, CHFC₃); HRMS–ESI (m/z): Calcd for C₄H₄NOF₂Na, 162.0143; found, 162.0147.

Crystallographic data
I C₄H₄F₃NO, M = 139.08, Monoclinic, space group P2₁/c, a = 9.226(11), b = 5.507(6), c = 11.229(12) Å, β = 99.401(13)°. V = 562.9(11) Å³, F(000) = 280, Z = 4, Dc = 1.641 Mg m⁻³, μ = 0.181 mm⁻¹ (Mo-Ka, λ = 0.71073 Å). The data were collected at T = 93 (2) K, 5405 reflections (2.24 to 25.39°) were measured on a Rigaku Saturn 92 detector with 007 generator yielding 2016 unique data (Rint = 0.0777). Conventional R = 0.0194 for 1860 reflections with I ≥ 2σ(I), GOF = 1.011; 171 refined parameters. The largest peak in the residual map is 0.247 eÅ⁻³. Crystallographic data has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication (CCDC 821176).

(αR,3R)-5c C₁₄H₁₄F₃NO, M = 293.28, Monoclinic, space group P2₁(1), a = 9.677(5), b = 6.094(3), c = 12.231(5) Å, β = 92.685(13)°. V = 720.5(5) Å³, F(000) = 304, Z = 2, Dc = 1.352 Mg m⁻³, μ = 0.949 mm⁻¹ (Cu-Ka, λ = 1.5418 Å). The data were collected at T = 173 (2) K, 9149 independent reflections (3.62 to 25.35°) were measured on a Rigaku Saturn 92 detector with 007 generator yielding 2504 unique data (Rint = 0.0450). Conventional R = 0.0194 for 2416 reflections with I ≥ 2σ(I), GOF = 0.973; 191 refined parameters. The largest peak in the residual map is 0.124 eÅ⁻³. Flack parameter 0.08 (13). Crystallographic data has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication (CCDC 821177).

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