Pyrrolidine-5,5-*trans*-lactams 3. Alternative Regiochemical Outcome of the Acyl-Iminium Coupling Reaction.

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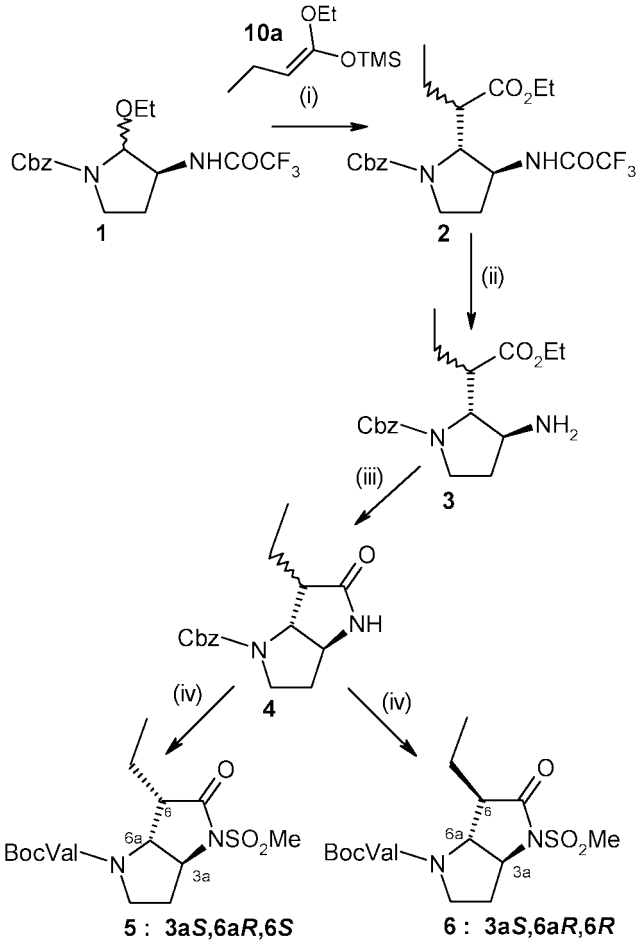
This paper is dedicated to the memory of Helene Chaignot, who died on the 13th May 2003.

Abstract: Enantio- and regioselective syntheses of the pyrrolidine 5,5-*trans*-lactams benzyl (3a*S*,6a*R*)-6,6-dimethyl-5-oxohexahydropyrrolo[3,2-*b*]pyrrole-1(2*H*)-carboxylate and benzyl (3a*S*,6a*R*)-6*S*-ethyl-5-oxohexahydropyrrolo[3,2-*b*]pyrrole-1(2*H*)-carboxylate from a common intermediate 2-ethoxy-3*S*-(2,2,2-trifluoro-acetylamino)-pyrrolidine-1-carboxylic acid benzyl ester are reported. The key step in both syntheses is the acyl iminium ion mediated condensation of the pyrrolidine with a ketene acetal.

Key words: antiviral agents, lactams, neighboring-group effects, regioselectivity, steric hindrance

The synthesis of the ethyl-substituted pyrrolidine-5,5-*trans*-lactams **5** and **6** and their activity as inhibitors of hepatitis C virus (HCV) NS3/4A protease has been recently reported (see Scheme 1).[1]

The initial synthesis was based upon the application of the flexible acyliminium ion methodology developed by Macdonald et al.[2,3] When tested in a biochemical assay measuring inhibition of the HCV NS3/4A protease, the (3a*S*,6a*R*,6*S*) compound **5** was found to be two- to four-fold more potent than the alternate diastereomer **6**. Diastereomer **5** and analogues thereof thus became the focus of our synthetic efforts. Under the initial reaction conditions explored in the production of **2**, no stereoinduction was seen for the introduction of the ethyl group at position 6, and so the route was a very inefficient means of producing the desired single isomer **5**. In particular, the two diastereomers produced in the condensation step could only be efficiently separated by first derivatising the lactam **4** with the *tert*-butyldimethylsilyl group. The silyl lactams so produced were completely separated by Biotage chromatography (cyclohexane–EtOAc, 6:1). Fluoride deprotection using tetrabutyl ammonium fluoride buffered with acetic acid, yielded the separated isomers of **4** in less than 10% overall yield from the precursor **1**. This was in marked contrast to the synthesis of the elastase inhibitor intermediate **7** (Figure 1), which was produced by analogous methodology from the enantiomer of **1** in 44% overall yield.[2] The difference in yield was attributable to three main factors: no stereoinduction for the introduction of the ethyl side chain in **2**; the poor isolated yield of **3**; and the cumbersome silylation/desilylation step to separate the isomers of **4**.



Scheme 1 (i) $BF_3{\cdot}OEt_2$, CH_2Cl_2; (ii) K_2CO_3, EtOH, 37% from **1**; (iii) *t*-BuMgCl, THF; (iv) Multiple steps as described in ref.[1]

Closer inspection revealed that the most inefficient step in the reaction sequence was the coupling of the acyliminium precursor **1** with the ketene acetal reagent **10a** ([1-ethoxy-but-1-enyloxy]-trimethylsilane). Work-up and analysis of the potassium carbonate hydrolysis step indicated that in addition to the desired product **3** (formed in 50% theoretical yield and as a 1:1 mixture of diastereomers), an isomeric oxazolidine **8a** (Figure 2) was formed in 40% yield – also as a potential mixture of diastereomers.

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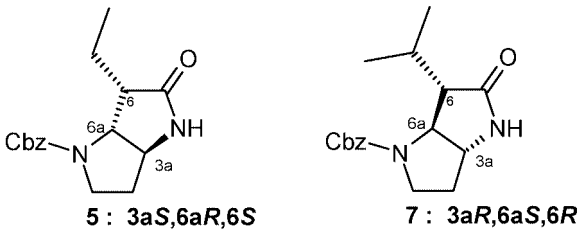


Figure 1

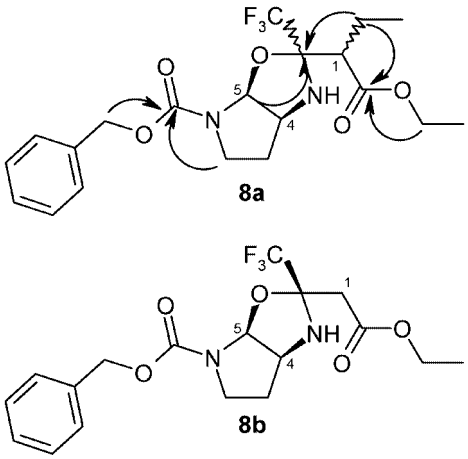
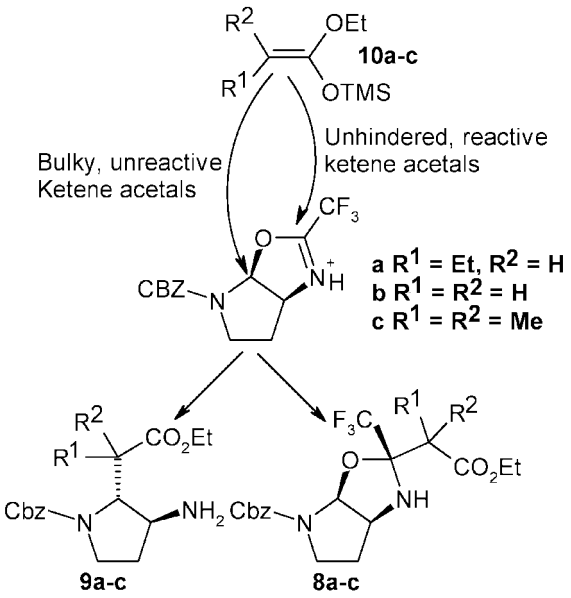


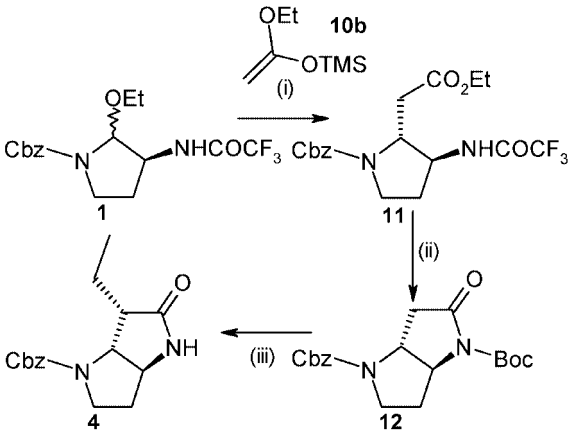
Figure 2 Oxazolidine **8a**. Key HMBC's connectivities are marked with arrows. In addition, strong NOE's are observed between the protons at C4 and C5; a coupling constant of 5.5 Hz is also observed for these protons, providing additional confirmatory evidence. Oxazolidine **8b**. NOE's were observed between the bridgehead carbons (positions C4 and C5) and the methylene of the sidechain (marked position 1), confirming the configuration of the CF_3 substituent.

We postulated that the oxazolidine **8a** arises as a consequence of the ketene acetal reacting between the nitrogen and oxygen atoms of the oxazoline ring, as shown in Scheme 2. Condensation of a trifluoromethyl ketone β ester with aminoethanol yields the corresponding monocyclic oxazolidine system,[4] but this is the first report of the synthesis of the bicyclic system as a consequence of iminium ion-mediated condensation. The ^{1}H NMR spectrum of **8a** was complex due to the presence of rotamers at room temperature, but these coalesced at 100 °C into a single, major set of peaks. It appeared that the major product was a single diastereoisomer, but the configuration of the CF_3 group could not be directly established due to the absence of diagnostic NOE's. A related minor diastereomeric component (ca. 10%) was also present, most likely the opposite stereoisomer at the ethyl sidechain. The configuration of the CF_3 group in this diastereoisomer could also not be established due to the absence of diagnostic NOE's. We postulated, therefore, that the ketene acetal would most likely approach the oxazoline from the least hindered alpha face, with the result that in both the major and minor isomers, the CF_3 substituent adopts a β configuration (c.f. **8b**, vide infra). The potential 10:1 diastereomeric NMR ratio for **8a** implies further diastereoselectivity in this reaction at the position of the ethyl substituent.



Scheme 2 Regiochemical outcome observed with hindered and unhindered silyl ketene acetals.

The alkylation of the unsubstituted *trans*-lactam template **12** has been previously described,[5] and we postulated that by accessing **12** via the unsubstituted *tert*-butyldimethylsilyl protected ketene acetal **10b** and the acyl iminium methodology described herein, we would be able to synthesize the desired '*SRS*' alkylated product in good yield (Scheme 3). An important advantage is that this route utilizes stereoselective alkylation for the introduction of the ethyl side-chain and avoids the complication of the formation of a mixture of diastereomers in the iminium ion condensation.



Scheme 3 (i) $BF_3{\cdot}OEt_2$, CH_2Cl_2; (ii) Multiple steps as described; (iii) LHMDS (1.1 equiv)/THF –78 °C, then EtI (2 equiv).

Disappointingly, the isolated product of initial experiments was shown to be exclusively the oxazolidine **8b** (Scheme 2). Spectrum doubling at room temperature

again hampered characterization of **8b** by NMR, but at 100 °C in DMSO-d_6, spectra coalesced into a single set of sharp peaks. On this occasion, HMBC and NOE studies provided complete confirmation of relative stereochemistry, confirming that the ketene acetal did indeed approach the oxazoline from the least-hindered face, giving rise to the single diastereoisomer **8b** (Figure 2).

We attempted to draw upon analogous experience with the substituted *trans*-lactams, which indicated that it might be possible to influence the regiochemical outcome of the reaction by replacing dichloromethane with acetonitrile as solvent. Some improvement was noted by HPLC reaction monitoring (in that the reaction proceeded to a 1:1 mixture of **11** and **8b**), but as this tactic did not greatly influence reaction outcome in the case of the ethyl-substituted compound, this was not pursued further (see Table 1).

Table 1 Influence of Solvent and Substituents on the Yield and Regiochemistry

R^1	R^2	Solvent	Aminoester Isolated Yield (%)	Oxazoline Isolated Yield (%)
Et	H	CH_2Cl_2	51	39
Et	H	MeCN	51	21
H	H	CH_2Cl_2	0	43
H	H	MeCN	1:1[a]	
Me	Me	CH_2Cl_2	90	0

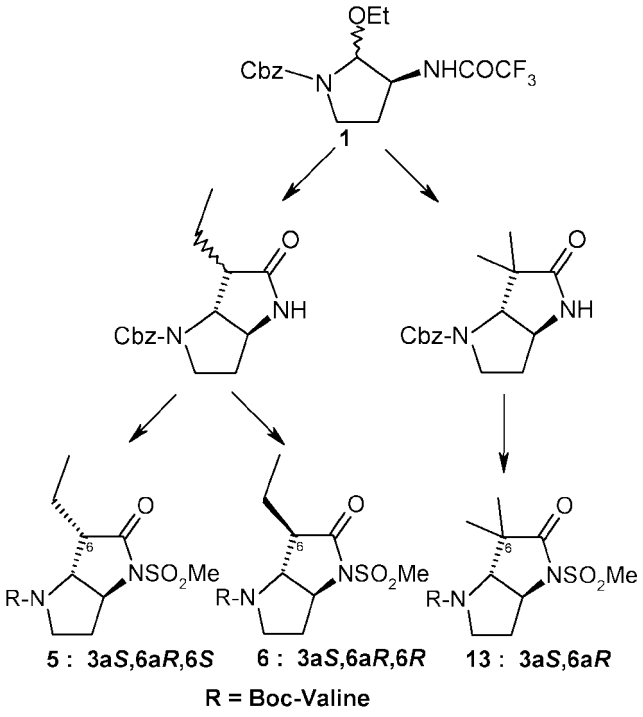
[a] HPLC ratio of products – products not isolated.

Observing that the hindered isobutyryl-derived silyl ketene acetal gave rise to excellent yields en route to the isopropyl *trans*-lactam **7**, we postulated that reaction outcome was determined by steric bulk, as indicated in Scheme 2. The poor results demonstrated with the unsubstituted ketene acetal are entirely consistent with this hypothesis. It thus became apparent that the medicinal chemical search for an optimal P1 substituent either needed to be refocused away from the problematic ethyl substituent, or that the acyl iminium methodology needed to be dramatically modified, or abandoned.

Modeling studies (based upon crystal structures of ethyl *trans*-lactams soaked into NS3 protease) and our knowledge of the relative potency of diastereomers **5** and **6** suggested that a very attractive target for synthesis was the α,α-dimethyl *trans*-lactam.[6] From a synthetic perspective, the advantages of working with the corresponding dimethyl silyl ketene acetal **10c** were two-fold: firstly, we postulated that since **10c** was the most sterically-hindered ketene acetal examined to date, it would give rise to the most favorable regiochemical outcome; secondly, since the newly introduced acetic acid ethyl ester side-chain is α,α-dimethyl substituted, no diastereomer problem exists. Gratifyingly, **10c** did indeed perform well in the condensation step, and **9c** was produced in 90% isolated yield over two steps from **1** (Scheme 2 and Table 1). Compound **9c** was converted by standard methodology to the α,α-dimethyl *trans*-lactam **13**. The comparison of overall yield dramatically illustrates the gain in synthetic efficiency derived by working in the disubstituted series; the α-ethyl diastereomer **5** was produced in less than 9% overall yield from **1** c.f. the dimethyl analogue **13**, furnished in 74% overall yield (Table 2)

Compounds were tested in a biochemical hepatitis C NS3/4A protease assay.[7] Further to the greatly enhanced synthetic accessibility, the initial hypothesis that disubstitution would be tolerated biologically was amply confirmed when the potency of **5**, **6**, and **13** were compared (Scheme 4 and Table 2).

This interesting chemical problem – and the solutions explored – illustrate a useful stratagem available to the medicinal chemist (but not often exploitable by the natural products chemist): on some occasions, difficulties in synthesis can be obviated by the removal or modification of those moieties which present current methodology with particular challenges.



Scheme 4

Table 2 Comparison of the Potency of **5**, **6**, and **13**

Compound	Yield[a]	IC_{50} (μM, 4 h preincubation) HCV protease biochemical assay
5	9%	30
6	8%	99
13	74%	34

[a] Yield over multiple steps **1** to **5**, **6**, and **13**.

NMR spectra (^{1}H 400MHz, ^{13}C 100MHz) were recorded on a Bruker DRX400, Bruker DPX400 or Varian Inova400 spectrometer. Chemical shifts (δ) are reported in ppm and coupling constants (*J*) in Hz. In $CDCl_3$ chemical shifts were referenced using TMS as an internal standard or in DMSO-d_6 using the residual solvent signal (^{1}H: δ = 2.50ppm, ^{13}C: δ = 39.5ppm). NMR Spectra were recorded at room temperature unless otherwise noted. HPLC analysis was achieved using a Hewlett Packard Series 1050 with a Phenomenex Prodigy 5 OD5-2 column (150 × 4.6mm). The mobile phase was A (H_2O + 0.1% TFA) and B (MeCN + 0.05% TFA) used as a linear gradient of 15–95% of B over 14 min with a flow rate of 1.5 mL/min; detection was at 215nm. Elution times are quoted as t_R in min. Values are ± 0.2 min. Thermospray mass spectra were recorded on an HP5989B Engine, using aqueous ammonium acetate as solvent, with the filament in positive ion mode. Accurate positive ion mass spectra were acquired as accurate mass centroided data using a Micromass Q-Tof 2 hybrid quadrupole time-of-flight mass spectrometer, equipped with a Z-spray interface, over a mass range of 80–1200 Da, with a scan time of 0.95 s and an interscan delay of 0.07 s. Reserpine was used as the external mass calibrant ([M + H]$^+$ = 609.2812 Da). The Q-Tof 2 mass spectrometer was operated in W reflectron mode to give a resolution (FWHM) of 16000-20000. Ionization was achieved with a spray voltage of 3 kV, a cone voltage of 30 V, with cone and desolvation gas flows of 5–10 and 500 L/min respectively. The source block and desolvation temperatures were maintained at 120 °C and 300 °C respectively. The elemental composition was calculated using MassLynx v3.5 for the [M + H]$^+$ and the mass error quoted as ppm. Syntheses of **1**–**6** and **13** have been previously reported.[1] Compound **10b** was prepared as previously reported.[8] Compound **10c** was purchased from Aldrich. All compounds are racemic unless otherwise indicated.

Benzyl (3a*S*,6a*S*)-2-[1-(Ethoxycarbonyl)propyl]-2-(trifluoromethyl)hexahydro-4*H*-pyrrolo[3,2-*d*][1,3]oxazole-4-carboxylate (8a)

To a solution of **1** (5.2 g, 14.4 mmol) in anhyd CH_2Cl_2 (160 mL) at 0 °C under nitrogen was added **10a** (5 mL, 14.4 mmol) dropwise, followed by $BF_3{\cdot}OEt_2$ (8.8 mL, 72 mmol). The mixture was stirred at 0 °C for 8 h and then at r.t. overnight. The reaction was quenched by the addition of HCl (1 M, 160 mL) and extracted with CH_2Cl_2. The organic layer was washed successively with $NaHCO_3$ solution (100 mL) and brine (100 mL), dried over $MgSO_4$ and the solvent was evaporated to afford a mixture of **2** and **8a** as a yellow oil (6.18 g). The mixture was dissolved in EtOH (56 mL), a solution of K_2CO_3 (13.54 g, 98 mmol) in H_2O (110 mL) was added and the solution heated at 60 °C for 3 h. The EtOH was removed by evaporation in vacuo, Et_2O was added to the resulting orange oil, and the ethereal layer separated. The etheral fraction was washed with HCl solution (1 M), dried, and evaporated to afford **8a** as a yellow oil (1.84g, 30%).

^{1}H NMR (DMSO-d_6,100 °C): δ = 7.28–7.40 (m, 5 H, C_6H_5), 5.81 (d, *J* = 5.5 Hz, 1 H, OCONC*H*OC), 5.16, 5.10 (2 d, *J* = 13 Hz, 2 H, $C_6H_5CH_2$), 4.23 (m, 1 H, NHC*H*CH_2), 4.08–4.16 (m, 2 H, OCH_2CH_3), 3.51 (m, 1 H, OCONC*H*HCH_2) 3.44 (m, 1 H, OCONCH*H*CH_2), 2.74 [dd, *J* = 11.5 Hz, 3.5Hz, 1 H, C*H*(C_2H_5)CO], 1.91 (m, 1 H, OCONCH$_2$C*H*H), 1.83 (m, 1 H, OCONCH$_2$CH*H*), 1.73 [m, 1 H, CH(C*H*HCH_3)], 1.67 [m, 1 H, CH(CH*H*CH_3)], 1.20 (t, *J* = 7 Hz, 3 H, OCH$_2$CH_3), 0.86 [t, *J* = 7 Hz, 3 H, CH(CH_2CH_3)].

^{13}C NMR (DMSO-d_6, 80 °C): δ = 10.5 [CH(CH_2CH_3)], 12.5 (OCH_2CH_3), 30.0 (OCONCH$_2$CH_2), 43.0 (OCONCH_2CH_2), 43.0 [CH(CH_2CH_3)], 51.0 (NH*C*HCH_2), 51.0 [*C*H(C_2H_5)CO], 59.5 (OCH_2CH_3), 65.0 ($C_6H_5CH_2$), 91.5 (OCONCHOC), 97.5 (*C*CF_3), 124.5 ($^1J_{19F\text{-}13C}$ = 287 Hz, CF_3), 125.5–127.0, 137.5 (C_6H_5), 154.0 (O*C*ON), 171.0 (*C*$O_2CH_2CH_3$).

Benzyl (3a*S*,6a*S*)-2-(2-Ethoxy-2-oxoethyl)-2-(trifluoromethyl)-hexahydro-4*H*-pyrrolo[3,2-*d*][1,3]oxazole-4-carboxylate (8b)

A mixture of 2-ethoxy-3*S*-(2,2,2-trifluoro-acetylamino)-pyrrolidine-1-carboxylic acid benzyl ester (**1**) (1.0 g, 2.89 mmol) and [(1-ethoxyvinyl)oxy](*tert*-butyldimethyl)silane (**10b**) (1.75 g, 8.65 mmol) in CH_2Cl_2 (10 mL) was cooled to 5 °C (ice bath) and treated with $BF_3{\cdot}OEt_2$ (814 mg, 5.74 mmol, 705 μL). After 1 h more [(1-ethoxyvinyl)oxy](*tert*-butyldimethyl)silane (**10b**) (583 mg, 2.89 mmol) was added and the reaction allowed to stir for a further 3 h at r.t. The mixture was quenched with sat. aq $NaHCO_3$ solution (5 mL) and the organic layer separated using a phase separation cartridge. Removal of the solvent and silica gel chromatography of the residue (eluent, CH_2Cl_2–Et_2O; 25:1) yielded **8b** as a colorless oil (501mg, 43%).

^{1}H NMR (DMSO-d_6, 100 °C): δ = 7.34–7.30 (m, 5 H, C_6H_5), 5.19–5.11 (m, 2 H, $C_6H_5CH_2$), 5.92 [m, 1 H, OCONC*H*(*O*)CH], 4.40 (m, 1 H, OCONC*H*CH), 4.08 [br m, 1 H, CHN*H*C(CF_3)CH_2], 4.20–4.10 (m, 2 H OCH_2CH_3), 3.52 (m, 1 H, OCONC*H*HCH_2), 3.46 [m, 1 H, OCONCH*H*CH_2], 2.80 [s, 2 H OCCH_2(CF_3)COO], 1.92 (m, 1 H, CONCH$_2$C*H*HCH), 1.83 (m, 1 H, CONCH$_2$CH*H*CH), 1.24 (t, *J* = 7 Hz, 3 H, OCH$_2$CH_3).

^{13}C NMR (DMSO-d_6, 100 °C): δ = 13.3 (OCH_2CH_3), 30.1 (ONCH*C*H$_2$CO), 30.7 (CONCH$_2$*C*H$_2$CH), 38.1 [OC*C*H$_2$(CF_3)CO], 43.6 (OCONC*H*$_2CH_2$), 59.9 (O*C*H$_2$CH$_3$), 60.8 (OCONC*H*CH), 65.6 ($C_6H_5CH_2$), 92.0 [OCONC*H*(*O*)CH], 94.7 ($^2J_{19F\text{-}13C}$ = 30.5 Hz, *C*CF_3), 123.5 ($^1J_{19F\text{-}13C}$ = 287Hz, CF_3), 126.6, 127.1, 127.7, 136.4 (C_6H_5), 153.1 (O*C*ON), 167.3 (*C*$O_2CH_2CH_2CH_3$).

MS: *m*/*z* = 420 (M + NH_4)$^+$.

MS (thermospray): *m*/*z* = 420 (M + NH_4)$^+$.

MS-ES: *m*/*z* calcd for $C_{18}H_{21}F_3N_2O_5$ (MH$^+$), 403.1463; found 403.1476.

Benzyl (2*R*,3*S*)-3-Amino-2-(2-ethoxy-1,1-dimethyl-2-oxoethyl)pyrrolidine-1-carboxylate (9c)

Prepared as reported previously[7] as a yellow oil, 8.48 g, 65%Th.

^{1}H NMR ($CDCl_3$): δ = 7.35 (m, 5 H, C_6H_5), 5.10 (s, 2 H, $C_6H_5CH_2$), 3.80–4.00 (m, 2 H, NHCHCH$_2$CH_2), 3.65 (s, 3 H, CO_2CH_3), 3.45 (m, 1 H, NH_2C*H*), 3.35 (m, 1 H, NC*H*CMe_2) 2.07 (m, 1 H, NCH$_2$CH*H*), 1.60 (m, 1 H, NCH$_2$C*H*H) 1.15–1.25 [br s, 6 H, C(CH_3)$_2$].

MS (ES, Pos.): *m*/*z* = 321 (MH$^+$).

{[(1*E*)-1-Ethoxybut-1-enyl]oxy}(trimethyl)silane (10a)

To a solution of *i*-Pr_2NH (7.7 mL, 55 mmol) in anhyd THF (50 mL) at 0 °C was added *n*-BuLi (55 mmol) and the mixture was stirred for 10 min and then cooled to –78 °C, ethyl butyrate (6.6 mL, 50 mmol) in anhyd THF (50 mL) was slowly added. The mixture was stirred at –78 °C for 30 min, chlorotrimethylsilane (6.34 mL, 55 mmol) in anhyd THF (50 mL) was added and the temperature of the mixture allowed to return to r.t. and stirred for 1 h. The mixture was quenched using sat. $NaHCO_3$ solution (50 mL) and the mixture extracted with hexanes, washed with H_2O (100 mL), brine, dried ($MgSO_4$) and concentrated, then distilled in vacuo to yield a colorless oil (6.4g, 68%) bp.98 °C at ca. 10 mm.

^{1}H NMR ($CDCl_3$): δ = 3.83 (q, *J* = 7.3 Hz, 2 H, OCH_2CH_3), 3.75 (t, *J* = 7.3Hz, 1 H, CC*H*CH_2), 1.96 (dt, *J* = 7.3 Hz, 2 H, CH_2CH_3), 1.22 (t, *J* = 7.3 Hz, 3 H, OCH$_2$CH_3), 0.92 (t, *J* = 7.3 Hz, 3 H, CH$_2$CH_3), 0.22 [s, 9H, Si(CH_3)$_3$].

Benzyl (2*S*,3*R*)-2-(2-Ethoxy-2-oxoethyl)-3-[(trifluoroacetyl)-amino]pyrrolidine-1-carboxylate (11)

A reference sample of **11** (to allow the product ratio of **8b**:**11** to be quantified by HPLC) was synthesized as follows. Benzyl (2*S*,3*R*)-3-[(*tert*-butoxycarbonyl)amino]-2-(2-ethoxy-2-oxoethyl)pyrroli-

dine-1-carboxylate,[5] (500 mg, 1.23 mmol) was dissolved in CH_2Cl_2 (2 mL) and treated with trifluoroacetic acid (2 mL). The reaction mixture was left to stand at r.t. overnight. Trifluoroacetic anhydride (2 mL) was added and the reaction mixture left to stand at r.t. overnight. The volatiles were removed in vacuo and the residue dissolved in CH_2Cl_2 (10 mL). Sat. Na_2CO_3 solution (10 mL) was added and the mixture stirred for 5 min. The organic phase was separated using a phase separation cartridge and concentrated to yield **11** as a colorless oil (437 mg, 88%).

^{1}H NMR (DMSO-d_6, 100 °C): δ = 9.30 (br m, 1 H, N*H*COCF$_3$), 7.28–7.30 (m, 5 H, C_6H_5), 5.15–5.07 (m, 2 H, $C_6H_5CH_2$), 4.30 (m, 1 H, OCONCHC*H*CH$_2$), 4.11 (m, 1 H, OCONC*H*CH), 4.06 (q, *J* = 7 Hz, 2 H, OC*H*$_2$CH$_3$), 3.60 (m, 1 H, OCONC*H*HCH$_2$), 3.41 (m, 1 H, OCONCH*H*CH$_2$), 2.72 (m, 1 H, CONCHC*H*HCO), 2.57 (m, 1 H, CONCHCH*H*CO), 2.22 (m, 1 H, CONCH$_2$C*H*HCH), 1.88 (m, 1 H, CONCH$_2$CH*H*CH), 1.18 (t, *J* = 7 Hz, 3 H, OCH$_2$C*H*$_3$).

^{13}C NMR (DMSO-d_6, 100 °C): δ = 13.4 (OCH$_2$*C*H$_3$), 28.2 (CONCH$_2$*C*H$_2$CH), 37.0 (CONCH*C*H$_2$CO), 44.0 (OCONCH$_2$CH$_2$), 54.2 (OCONCHC*H*CH$_2$), 58.8 (OCONCHCH), 59.4 (OCH$_2$CH$_3$), 65.6 ($C_6H_5CH_2$), C*C*F$_3$ 115.2 ($^1J_{19F\text{-}13C}$ = 288Hz, CF$_3$), 126.7, 127.1, 127.6, 136.3 (C_6H_5), 153.1 (O*C*ON), 155.3 *C*OCF$_3$ ($^2J_{19F\text{-}13C}$ = 36Hz, CF$_3$), 169.3 (*C*O$_2$CH$_2$CH$_3$).

MS: *m*/*z* = 403 (M + H)$^+$.

MS (thermospray): *m*/*z* = 403 (M + H)$^+$.

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