Synthesis of New 3-(1-Ethylsulfanyl-2-perfluoroalkyl)-5-hydroxy-5-methyl (or 5-phenyl)-1,5-dihydro-pyrrol-2-ones Starting from γ-Keto Thioesters and Amines

Jean-Philippe Bouillon,*[a] Bernard Tinant,[b] Jean-Marc Nuzillard,[c] Charles Portella[a]

[a] Laboratoire 'Réactions Sélectives et Applications', UMR CNRS 6519, Université de Reims, Faculté des Sciences B.P. 1039, 51687 Reims Cedex 2, France
Fax +33(3)26913166; E-mail: jp.bouillon@univ-reims.fr

[b] Université Catholique de Louvain, Laboratoire de Chimie Physique et de Cristallographie, 1 Place Louis Pasteur, 1348 Louvain-la-Neuve, Belgium

[c] Laboratoire de Pharmacognoise, UMR CNRS 6013, Université de Reims, Faculté des Sciences, Batiment 18, Moulin de las Housse B. P. 1039, 51687 Reims Cedex 2, France

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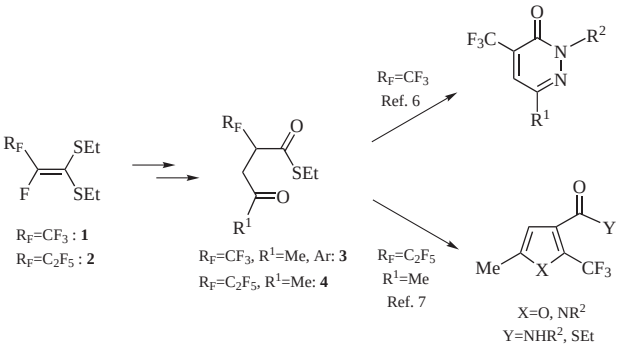
Abstract: γ-Keto thioesters were easily transformed into α,β-unsaturated lactams using a two-step process (via furans) or by a one-pot reaction. This methodology is general and efficient leading to a varied substitution pattern. The structures of all new heterocycles were assigned using 2D NMR experiments, computer-assisted elucidation, and X-ray diffraction analyses.

Key words: fluorine, nitrogen heterocycles, lactam, pyrrol-3-one

Perfluoroketene dithioacetals **1** and **2** are versatile building blocks owing to the ease at which vinylic fluoride undergoes nucleophilic substitution and to the presence of a masked carboxylic function.[1–3] We have recently reported the convenient conversion of perfluoroketene dithioacetals into their corresponding γ-keto thioesters **3** and **4** (Scheme 1).[2,3] The increasing interest in trifluoromethylated heterocycles[4,5] and the need for new fluorinated building blocks for parallel synthesis prompted us to investigate the applications of the bifunctionalized intermediates **3**, **4** towards the synthesis of a large variety of heterocycles. The γ-keto thioester **3** ($R_F = CF_3$, R^1 = Me, Ar) was shown to be an excellent precursor for the preparation of trifluoromethyl γ-lactones,[2] γ-lactams,[3] pyridazin-3-ones,[6] and pyridazines[6] (Scheme 1). The higher homolog **4** ($R_F = C_2F_5$, R^1 = Me) offered further opportunities, since an additional HF elimination easily occurred under basic conditions. Indeed, when **4** was treated with primary amines (which are basic as well as nucleophilic reagents), trifluoromethylated furans and pyrroles were obtained in good yields (Scheme 1).[7]

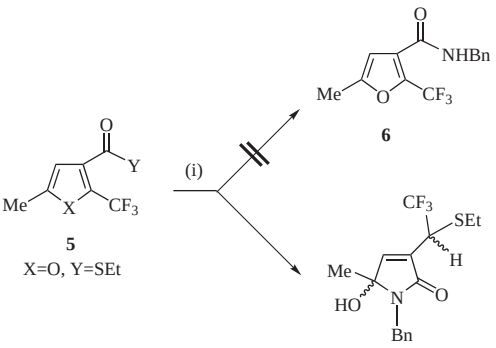


Scheme 1

As previously reported,[7] the reaction of γ-keto thioester **4** with non-nucleophilic diisopropylamine led exclusively to the furan thioester **5**. Surprisingly, when pure furan **5** was treated with benzylamine, the new heterocyclic compound **7** was isolated as a mixture (47:53) of diastereomers, instead of the expected furan **6** (Scheme 2). The present paper reports on the full investigation of this new reaction in order to lead to a preparative one-pot methodology for α,β-unsaturated lactams.

Besides some specialized methodologies,[8] the majority of 5-hydroxy-1,5-dihydro-pyrrol-2-ones syntheses (which we simply call α,β-unsaturated lactams) are based on cyclization reactions of α,β-unsaturated keto-amides[9] or on amination reactions of the corresponding γ-lactones.[10] No example of a 1,5-dihydro-pyrrol-2-one bearing a fluorinated substituent has been reported so far.

The γ-keto thioesters **4**, **12**, **13** were prepared according to our reported procedure:[2,3] nucleophilic substitution of the vinylic fluoride of the starting perfluoroketene dithioace-



Scheme 2 *Reagents and conditions*: (i) $BnNH_2$, Et_2O, r.t., 16 h

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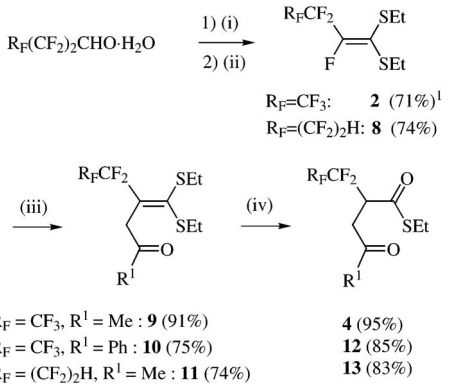
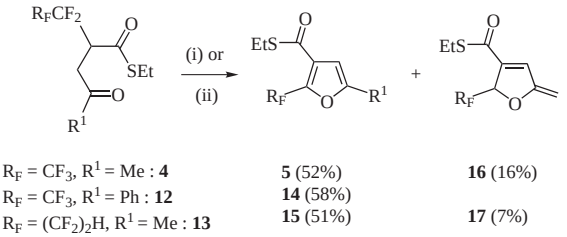
tals **2** or **8** by potassium enolates of ketones, followed by acid hydrolysis of intermediates **9**–**11** (Scheme 3). This methodology allowed us to introduce structural diversity at the initial step (using various perfluoroalkyl-substituted aldehydes) as well as at the vinylic substitution step (both aliphatic and aromatic enolates worked well).



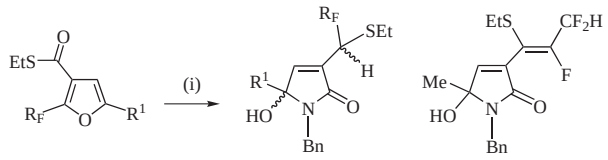
Scheme 3 *Reagents and conditions*: (i) EtSH, $TiCl_4$, CH_2Cl_2, –20 to 25 °C, 16 h; (ii) KOHaq, Bu_4NBr, CH_2Cl_2, 25 °C, 12h; (iii) R^1COMe, KH, THF, 0–25 °C, 10 h; (iv) TFA, H_2O, reflux, 10 h

We then prepared the 2-perfluoroalkyl furans **5**, **14**, and **15** by treatment of γ-keto thioesters **4**, **12**, **13** with diisopropylamine in diethyl ether. We used our reported procedure[7] (Scheme 4, Method 1) for compounds **4** and **13**, while the phenyl-substituted derivative **12** required stronger conditions – 3 equivalents of diisopropylamine in boiling diethyl ether for 22 hours (Scheme 4, Method 2). Except for **14**, the reactions led to mixtures of furan and its tautomer, in moderate to good yields. Although we have not studied this issue further, we assume that the reaction occurs under thermodynamic control owing to the acidic-basic medium (i-$Pr_2NH_2^+$/i-Pr_2NH). The conjugated methylene derivatives **16** and **17** would have a resonance energy only slightly lower than that of the corresponding furans **5** and **15**, respectively.[7]



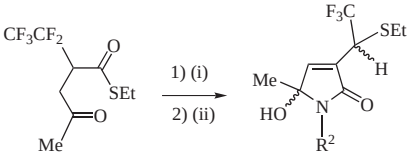
Scheme 4 *Reagents and conditions*: Method 1: **5**[7] and **15**: i-Pr_2NH (2 equiv.), Et_2O, r.t., 24 h; Method 2: **14**: i-Pr_2NH (3 equiv), Et_2O, reflux, 22 h.

In the first experiment, furan **5** was treated with a slight excess of benzylamine (1.2 equiv) under mild conditions (Et_2O, r.t., 16 h) to give the new α,β-unsaturated lactam **7** (yield: 84%) as a mixture of diastereomers (Scheme 5, de ^{19}F NMR). The structure 1,5-dihydro-pyrrol-2-one was assigned using 2D NMR experiments such as ^1H-^1H (COSY) and ^1H-^{13}C (HMQC, HMBC) correlations and X-ray diffraction analysis (vide infra). Then the reaction was successfully extended to the γ-keto thioesters bearing various R_F and R^1 substituents. The yield of lactam **18** was good but compound **19** (yield: 49%) was accompanied by the unsaturated derivative **20** as a single stereoisomer (Scheme 5). The full determination of the structure of **20** will be discussed later.



Scheme 5 Reagents and conditions: (i) $BnNH_2$, Et_2O, r.t., 16h.

In order to increase the overall yield of our procedure, we tried to perform a one-pot reaction starting from γ-keto thioesters. Compound **4** was first treated with 2 equivalents of diisopropylamine in diethyl ether at room temperature for 24 hours then benzylamine (1.2 equiv) was added to the resulting mixture. After stirring for 16 hours at the same temperature and usual work-up (see experimental section), the corresponding lactam **7** was isolated, after flash chromatography on silica gel, in 68% yield (Scheme 6, Table 1), a higher yield compared to the two-step procedure (Schemes 4 and 5; **5**, **7**). The reaction was general and worked well (yields: 55–80%) with a wide variety of primary amines: linear and branched aliphatic amines (entries 1–3), aromatic and heteroaromatic derivatives (entries 4,5), and functionalized amines bearing one hydroxyl or one ester group (entries 6,7, and 9). It is worth noting that the reactions with 2-aminoethanol and phenylglycinol were chemoselective. Interestingly, the resulting compounds **25** and **26** bear an additional hydroxyl group, which could be used for further cyclisations. Unfortunately, these reactions were not selective: we obtained an almost equal mixture of both diastereomers. The diastereoselectivity was assigned using ^{19}F chemical shifts. It was generally impossible to separate the diastereomers except for lactam **26** which could be separated by preparative HPLC. All pure diastereomers of **26** are oils.



Scheme 6 Reagents and conditions: (i) Method 1: i-Pr_2NH (2 equiv), Et_2O, r.t., 24 h; (ii) R^2NH_2, r.t., 16 h.

Table 1 One-pot Synthesis of α,β-Unsaturated Lactams **7, 21–28**

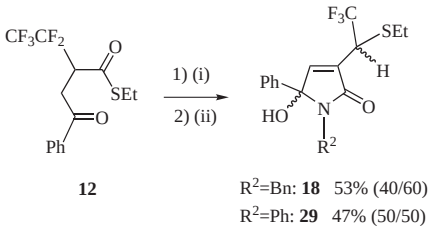
Entry	R^2	Lactam (%)	Diastereoselectivity[b]
1	Bn	**7** (68)	(47:53)
2	nC_5H_{11}	**21** (68)	(47:53)
3	*i*Pr	**22** (80)	(55:45)
4	Ph	**23** (76)	(50:50)
5	C_5H_4N	**24** (31)[a]	(48:52)
6	$(CH_2)_2OH$	**25** (60)	(50:50)
7	$CHPhCH_2OH$	**26** (56)	(50:28:20:traces)
8	$(CH_2)_3NMe_2$	**27** (55)	(55:45)
9	CH_2CO_2Me	**28** (67)	(44:56)

[a] Lactam **24** was accompanied with the furan **5** (yield: 10%).
[b] The diastereoselectivity was assigned using ^{19}F chemical shifts.

Compound **22** was unambiguously given a planar formula using the available knowledge about its synthetic origin and information collected from 1D and 2D NMR spectra. The 55:45 mixture of diastereomers was submitted to analysis, but the signals were easily paired by chemical shift value and/or coupling pattern similarity. The identification of S-Et, C-CF_3, and N-*i*Pr groups, the presence of 12 carbon atoms in the ^{13}C NMR spectrum, the observation of a carbonyl group (δ = 166 ppm) and a molecular mass of 297 led to the formula $C_{12}H_{18}F_3NO_2S$, which is in good agreement with combustion data. The construction of the planar formula was achieved using the LSD program[11] (www.univ-reims.fr/LSD). All the hydrogen atoms except one are attached to carbon atoms, and the exchangeable one is bound either to an oxygen or to a nitrogen atom. This results in two LSD data sets. The processing of the identified molecular fragments, and of HMQC and HMBC data provided a single solution, the one proposed for **22**, when the presence of an OH group was assumed. No structure was produced in the hypothesis of an NH group, thus eliminating other alternative structures. The presence of the 1,5-dihydro-pyrrol-2-one nucleus in α,β-unsaturated lactams is fully supported by the X-ray diffraction analysis of **18a**, and by the solution NMR study of **22**.

Then, to assess the scope and limitations of our methodology, the one-pot reaction was extended to phenyl-substituted γ-keto thioester. Compound **12** was first reacted with diisopropylamine using Method 2 then benzylamine or aniline was added to the resulting mixture to afford the new α,β-unsaturated lactam **18** or **29** in moderate yield as a mixture of diastereomers (Scheme 7). Both diastereomers of **18**, obtained as white solids, were completely separated by preparative TLC using hexane–EtOAc (85:15) as eluent.

After slow evaporation of hexane–$CHCl_3$ crystals of the major diastereomer **18a** were obtained for X-ray diffraction analysis, the X-ray structure obtained is shown in Figure 1 and shows a relative of 5*R**,14*S**.



12

R^2=Bn: **18** 53% (40/60)
R^2=Ph: **29** 47% (50/50)

Scheme 7 Reagents and conditions: (i) Method 2: *i*-Pr_2NH (3 equiv), Et_2O, reflux, 22 h; (ii) R^2NH_2, r.t., 16 h.

Then, in order to optimise the yield of lactam **19** (Scheme 5), γ-keto thioester **13** was submitted to the one-pot procedure. Surprisingly we did not obtain the expected lactam **19** but the unsaturated derivative **20**, which was isolated in an overall yield of 48%. This compound was previously obtained in low yield (21%) as a by-product (Scheme 5). Compound **20** which was isolated as one stereoisomer, exhibited a characteristic ^{19}F NMR spectra: a vinylic fluorine at –113.3 ppm as a triplet of doublets ($^3J_{F,F}$ = 22.0, $^3J_{F,H}$ = 16.3 Hz) and a difluoromethylene group at –123.3 ppm as a doublet of doublets ($^2J_{F,H}$ = 52.5, $^3J_{F,F}$ = 22.0 Hz). Similarly the phenyl-substituted derivative **30** was obtained in 40% yield, after silica gel chromatography (Scheme 8). Again, only one stereoisomer was characterised even in the crude mixture (^{19}F and ^1H NMR spectra). Such unsaturated derivatives have not been reported in the literature even in a non-fluorinated series.

An important problem was to determine the stereochemistry of the newly created double bond as ^{19}F, ^1H or ^{13}C NMR spectra were devoid of any useful information. Fortunately, compound **30** slowly crystallised in hexane–EtOAc allowing X-ray diffraction analysis. The X-ray clearly showed a *cis*-relationship between the ethylsulfanyl and difluoromethylene groups (Figure 2). This was

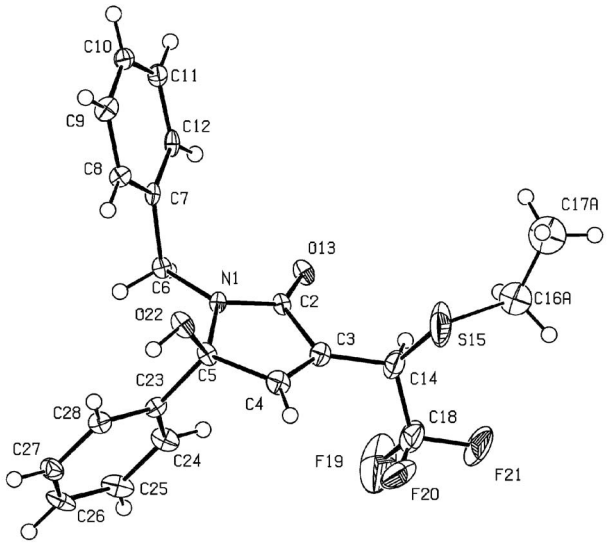
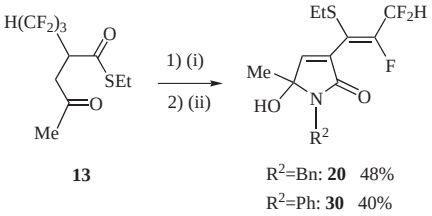


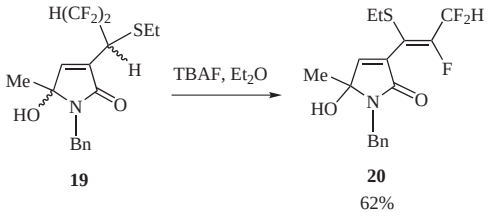
Figure 1 View and atom labelling of **18a**.[12]



Scheme 8 Reagents and conditions: (i) Method 1: *i*-Pr_2NH, Et_2O, r.t., 24 h; (ii) R^2NH_2, r.t., 16 h.

probably the result of steric interaction between the carbonyl oxygen (O6) and the fluorine atom (F12). The dihydropyrrole and the vinylic substituents are not co-planar and the observed torsion angle C2-C3-C7-C11 is 43°. The poor conjugation in the solid state is confirmed by the endocyclic bond length values, which are very similar to those observed for **18a**.

As it was previously assumed (Scheme 5), the derivative **20** could result from HF elimination from lactam **19** owing to the basic medium. This hypothesis was confirmed by treating pure **19** with a slight excess of TBAF (2 equiv) in THF solution (Scheme 9). The same stereoisomer of **20** was isolated in 62% yield after flash chromatography.



Scheme 9

The formation of α,β-unsaturated lactams **7**, **19**, **20**, **22**–**30** may be explained by the mechanism depicted in Scheme 10. Owing to the enhanced nucleophilicity of the primary amine, the first step could be a substitution reaction of ethylsulfanyl group leading to the corresponding furan **31**. This compound exhibits an interesting conjugated system, which is activated by both the trifluoromethyl

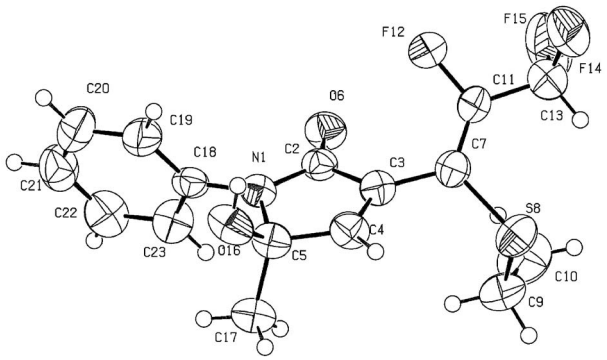
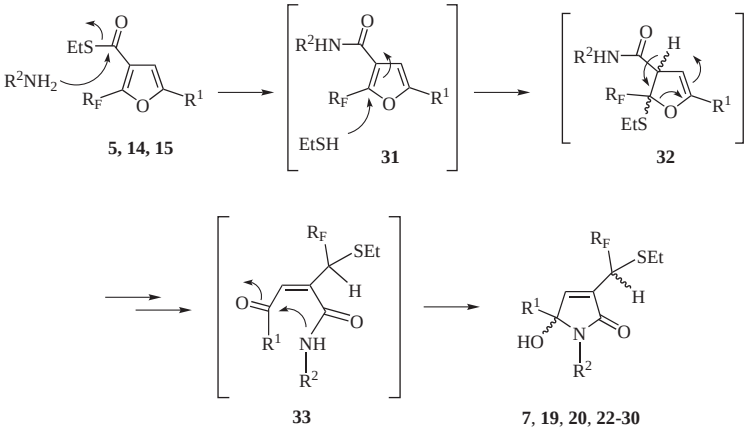


Figure 2 View and atom labelling of **30**.[12]

substituent and the amide function. Furan **31** could react as a Michael acceptor with thiol released in the medium, to give the dihydro derivative **32**. Such an intermediate might undergo ring opening followed by a 1,3-proton migration to afford the γ-keto amide **33**. Finally **33** could cyclise into the desired α,β-unsaturated lactam **7**, **19**, **20**, **22**–**30** (Scheme 10). This hypothesis is supported by the following feature: non-fluorinated analogues of **33** were already used as key intermediates in 1,5-dihydro-pyrrol-2-one syntheses.[9] Nevertheless we cannot exclude the alternative sequence *ring opening of **32** – cyclisation of the amide on the ketone function – 1,3-proton migration* to give the final lactam.

In conclusion, this study extends the field of synthetic applications of perfluoroketene dithioacetals. The synthons **2** and **8** are easily converted into the corresponding furans **5**, **14**, and **15**, which behave as key intermediates for the preparation of 5-hydroxy-1,5-dihydro-pyrrol-2-ones. The α,β-unsaturated lactams **7** and **18**–**30** were prepared in moderate to good yields from γ-keto thioesters using a two-step sequence (via isolated furans) or using a one-pot reaction. The scope of our methodology was exemplified by the syntheses of new lactams bearing a large variety of substituents [$R_F = CF_3$, $(CF_2)_2H$; R^1 = Me, Ph; R^2 = Alkyl, Ar, Hetar]. An efficient synthesis of unsaturated lactams **20** and **30** was also performed starting from the tetrafluoroethyl-substituted γ-keto thioester **13**. The



Scheme 10

structure of lactams **7** and **18**–**30** were confirmed by 2-D NMR experiments, X-ray diffraction analyses (for **18a** and **30**) and computer-assisted structural elucidation (for **22**). The α,β-unsaturated lactams exibit interesting features: a conjugated amide system and a hemiaminal function which could be a precursor of an iminium salt. These new aspects of synthetic applications are under investigation.

For information on instruments used see ref.[13] Compounds **2**,**8**[1], **9**–**11**[2] and **4**, **12**, **13**[3,7] were prepared according to reported procedures.

1,1-Bis(ethylthio)-2,3,3,4,4,5,5-heptafluoropentene (8)
Yield: 74% (23.4 g); oil; bp 105–107 °C/6 mbar.

IR (film): 2977, 1604, 1452, 1264, 1162 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 1.24 (t, $^3J_{H,H}$ = 7.3 Hz, 3 H), 1.26 (t, $^3J_{H,H}$ = 7.3 Hz, 3 H), 2.81 (q, $^3J_{H,H}$ = 7.3 Hz, 2 H), 2.89 (qd, $^3J_{H,H}$ = 7.3, $^5J_{H,F}$ = 1.0 Hz, 2 H), 6.04 (tt, $^2J_{H,F}$ = 52.2, $^3J_{H,F}$ = 5.5 Hz, 1 H).

^{13}C NMR (Selected signals, $CDCl_3$): δ = 14.2 (s, CH_3), 14.6 (s, CH_3), 27.2 (d, $^4J_{C,F}$ = 4.3 Hz, CH_2), 28.0 (s, CH_2), 107.8 (tt, $^1J_{C,F}$ = 253.1, $^2J_{C,F}$ = 31.2 Hz, CF_2 H), 126.4 (d, $^2J_{C,F}$ = 19.9 Hz, C_4), 145.4 (dt, $^1J_{C,F}$ = 263.8, $^2J_{C,F}$ = 26.3 Hz, CF).

^{19}F NMR ($CDCl_3$): δ = –100.3 (m, 1 F), –111.3 (m, 2 F), –131.0 (m, 2 F), –137.5 (d, $^2J_{F,H}$ = 52.2 Hz, 2 F, CF_2H).

GC-MS: *m*/*z* (%) = 316 [M^+], 287, 215, 125 (100).

Furans 5, 15 and Tautomers 16, 17; General Procedure (Scheme 4, Method 1)
i-Pr_2NH (15.0 mmol, 2.0 equiv) was added to a solution of γ-keto thioester **4** or **13** (7.5 mmol, 1.0 equiv) in Et_2O (100 mL). A white solid precipitated immediately. The mixture was stirred for 24 h at r.t., then diluted with Et_2O (50 mL) and washed with brine (50 mL). The aq phase was extracted with Et_2O (4 × 50 mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was chromatographed on silica gel (hexane–EtOAc) to give the furan **5**[7] or **15** and the corresponding tautomer **16**[7] or **17** (Table 2).

Reaction of γ-Keto Thioester 12 with Diisopropylamine (Scheme 4, Method 2)
i-Pr_2NH (3 equiv, 1.35 mL, 9.63 mmol) was added to a solution of γ-ketothioester **12** (1.09 g, 3.21 mmol) in Et_2O (30 mL), and the mixture refluxed for 22 h. The same work-up was applied as for method 1, the residue was chromatographed on silica gel (*n*-hexane–EtOAc, 97:3) to give the furan **14** (0.56 g, yield: 58%). The spectroscopic data of **14** are collected in Table 3.

Reactions of Furans 5, 14, 15 with Benzylamine; General Procedure (Scheme 5)
A mixture of furan **5**, **14** or **15** (5.0 mmol, 1 equiv) and benzylamine (6.0 mmol, 1.2 equiv) in Et_2O (10 mL) was stirred for 16 h at r.t. The crude was then diluted with Et_2O (30 mL) and washed with brine (30 mL). The aq phase was extracted with Et_2O (4 × 30 mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was chromatographed on silica gel (PE–EtOAc or hexane–EtOAc) to give the corresponding lactam **7**, **18** or **19** and the compound **20**.

1-Benzyl-3-(1-ethylthio-2,3,3-trifluoroprop-1-en-1-yl)-5-hydroxy-5-methyl-1,5-dihydro-2*H*-pyrrol-2-one (20)
Yield: 48% (1.72 g); oil.

IR (film): 3346, 2929, 1689, 1621, 1363 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 1.24 (t, $^3J_{H,H}$ = 7.3 Hz, 3 H), 1.44 (s, 3 H), 2.5 (br s, 1 H, OH), 2.62 (q, $^3J_{H,H}$ = 7.3 Hz, 2 H), 4.54 (d, $^2J_{H,H}$ = 15.4 Hz, 1 H), 4.66 (d, $^2J_{H,H}$ = 15.4 Hz, 1 H), 7.00 (s, 1 H), 7.01 (td, $^2J_{H,F}$ = 52.5, $^3J_{H,F}$ = 16.3 Hz, 1 H), 7.3–7.4 (m, 5 H).

^{13}C NMR ($CDCl_3$): δ = 14.6 (s, CH_3), 23.5 (s, CH_3), 27.4 (s, CH_2), 42.1 (s, CH_2), 88.2 (s, C_4), 107.0 (td, $^1J_{C,F}$ = 238.0, $^2J_{C,F}$ = 25.8 Hz, CF_2H), 112.8 (m, C_4), 127.4 (s, CH), 128.0 (s, 2 × CH), 128.6 (s, 2 × CH), 131.0 (s, C_4), 138.1 (s, C_4), 149.3 (s, CH), 152.4 (dt, $^1J_{C,F}$ = 283.2, $^2J_{C,F}$ = 23.4 Hz, CF), 165.7 (s, CO).

^{19}F NMR ($CDCl_3$): δ = –113.3 (td, $^3J_{F,F}$ = 22.0, $^3J_{F,H}$ = 16.3 Hz, 1 F), –123.3 (dd, $^2J_{F,H}$ = 52.5, $^3J_{F,F}$ = 22.0 Hz, 2 F).

MS: *m*/*z* (%) = 358 [M^+ + 1], 357 [M^+], 340, 328, 324 (100), 106.

Preparation of α,β-Unsaturated Lactams 7, 20–28, 30; General One-Pot Procedure (Schemes 6, 8)
i-Pr_2NH (10.0 mmol, 2 equiv) was added to a solution of γ-keto thioester **4** or **13** (5.0 mmol, 1 equiv) in Et_2O (30 mL). The mixture was stirred for 24 h at r.t. Primary amine (6.0 mmol, 1.2 equiv) was added to the resulting solution, and the stirring continued for a further 16 h at r.t. After the usual work-up, the residue was chromatographed on silica gel (PE–EtOAc or hexane–EtOAc) to give the corresponding lactam **7**, **20**–**28** or **30** (Table 4).

3-(1-Ethylthio-2,3,3-trifluoroprop-1-en-1-yl)-5-hydroxy-5-methyl-1-phenyl-1,5-dihydro-2*H*-pyrrol-2-one (30)
Yield: 40% (0.69 g); yellow solid; mp 101–103 °C.

IR (KBr): 3346, 2976, 1686, 1663, 1601, 1504 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 1.28 (t, $^3J_{H,H}$ = 7.4 Hz, 3 H), 1.58 (s, 3 H), 2.70 (q, $^3J_{H,H}$ = 7.4 Hz, 2 H), 2.8 (br s, 1 H, OH), 7.05 (td, $^2J_{H,F}$ = 53.0, $^3J_{H,F}$ = 16.2 Hz, 1 H), 7.12 (s, 1 H), 7.3–7.4 (m, 1 H), 7.45 (dd, $^3J_{H,H}$ = 8.2, $^3J_{H,H}$ = 7.4 Hz, 2 H), 7.55 (d, $^3J_{H,H}$ = 8.2 Hz, 2 H).

^{13}C NMR ($CDCl_3$): δ = 14.5 (s, CH_3), 23.2 (s, CH_3), 27.3 (s, CH_2), 89.4 (s, CH_2), 107.0 (td, $^1J_{C,F}$ = 238.0, $^2J_{C,F}$ = 25.8 Hz, CF_2H), 112.7 (dt, $^2J_{C,F}$ = 14.5, $^3J_{C,F}$ = 7.5 Hz, C_4), 126.5 (s, 2 × CH), 127.1 (s, CH), 128.9 (s, 2 × CH), 130.8 (s, C_4), 135.0 (s, C_4), 149.4 (s, CH), 152.3 (dt, $^1J_{C,F}$ = 283.2, $^2J_{C,F}$ = 23.4 Hz, CF), 165.0 (s, CO).

^{19}F NMR ($CDCl_3$): δ = –112.5 (td, $^3J_{F,F}$ = 22.4, $^3J_{F,H}$ = 16.2 Hz, 1 F), –123.4 (dd, $^2J_{F,H}$ = 53.0, $^3J_{F,F}$ = 22.4 Hz, 2 F).

GC-MS: *m*/*z* (%) = 344 [M^+ + 1], 343 [M^+], 314, 310 (100), 106.

Preparation of α,β-Unsaturated Lactams 18, 29; General One-Pot Procedure (Scheme 7)
i-Pr_2NH (9.0 mmol, 3 equiv) was added to a solution of γ-keto thioester **12** (3.0 mmol, 1 equiv) in Et_2O (20 mL) and refluxed for 22 h. The crude mixture was chromatographed on silica gel (*n*-hexane–EtOAc) to give the lactam **18** or **29** as mixture of diastereomers (Table 4).

Reaction of Lactam 19 with TBAF (Scheme 9)

A solution of TBAF in THF (0.56 mL, 0.56 mmol, 2 equiv) was added to a solution of lactam **19** (0.11 g, 0.28 mmol) in Et_2O (2 mL). The mixture was stirred for 5 h at r.t., then diluted with Et_2O (5 mL) and washed with H_2O (7 mL). The aq phase was extracted with Et_2O (2 × 5 mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was chromatographed on silica gel (PE–EtOAc, 70:30) to give compound **20** as a single stereoisomer (62 mg, yield: 62%).

X-Ray Crystal Structure Determination of Compounds 18a, 30 (Figures 1 and 2)
Compound 18a
$C_{21}H_{20}F_3NO_2S$, Mr = 407.44, monoclinic, C2/c (Nr 15) *a* = 41.117(2), *b* = 5.873(1), *c* = 17.242(2) Å, β = 109.93(1)°,

Table 2 Spectroscopic Data of Ketene Dithioacetals **10** and **11** and γ-Keto Thioesters **12** and **13**

Compd[a]	Solvents[b]	IR (cm^{-1})	GC-MS *m/z*	^{19}F NMR[c] δ, *J* (Hz)	^{1}H NMR[c] δ, *J* (Hz)	^{13}C NMR[c] δ, *J* (Hz)
10	PE–EtOAc (96:4)	2926, 1695, 1449, 1213	384 [M^+], 326, 279, 105	–83.2 (m, 3 F), –107.4 (m, 2 F)	1.20 (t, $^3J_{H,H}$ = 7.3, 3 H), 1.36 (t, $^3J_{H,H}$ = 7.3, 3 H), 2.84 (q, $^3J_{H,H}$ = 7.3, 2 H), 2.89 (q, $^3J_{H,H}$ = 7.3, 2 H), 4.35 (t, $^3J_{H,F}$ = 1.6, 2 H), 7.50 (m, 2 H), 7.6-7.7 (m, 1 H), 8.00 (m, 2 H)	14.5 (s, CH_3), 14.7 (s, CH_3), 28.1 (s, CH_2), 29.3 (s, CH_2), 42.5 (t, $^3J_{C,F}$ = 3.8, CH_2), 113.2 (tq, $^1J_{C,F}$ = 256.8, $^2J_{C,F}$ = 38.7, CF_2), 119.2 (qt, $^1J_{C,F}$ = 288.0, $^2J_{C,F}$ = 39.5, CF_3), 127.7 (t, $^2J_{C,F}$ = 20.4, C_4), 128.0 (s, CH), 128.6 (s, CH), 133.2 (s, CH), 136.0 (s, C_4), 148.3 (t, $^3J_{C,F}$ = 3.2, C_4), 193.8 (s, CO)
11	hexane–EtOAc (92:8)	2930, 1726, 1261, 1136	354 [M^+], 311, 221, 75	–104.8 (m, 2 F), –129.4 (m, 2 F), –137.4 (d, $^2J_{F,H}$ = 52.2, 2 F)	1.22 (t, $^3J_{H,H}$ = 7.3, 3 H), 1.30 (t, $^3J_{H,H}$ = 7.3, 3 H), 2.21 (s, 3 H), 2.84 (q, $^3J_{H,H}$ = 7.3, 4 H), 3.76 (m, 2 H), 6.11 (tt, $^2J_{H,F}$ = 52.2, $^3J_{H,F}$ = 5.8, 1 H)	14.5 (s, CH_3), 14.7 (s, CH_3), 28.2 (s, CH_2), 29.2 (s, CH_3), 29.3 (s, CH_2), 47.3 (t, $^3J_{C,F}$ = 4.4, CH_2), 107.8 (tt, $^1J_{C,F}$ = 252.8, $^2J_{C,F}$ = 30.8, CF_2 H), 110.9 (t, $^1J_{C,F}$ = 261.0, CF_2), 115.7 (tt, $^1J_{C,F}$ = 256.0, $^2J_{C,F}$ = 32.2, CF_2), 128.3 (t, $^2J_{C,F}$ = 20.9, C_4), 147.8 (t, $^3J_{C,F}$ = 3.7, C_4), 202.7 (s, CO)
12[d]	PE	2928, 1687, 1594, 1449	341 [M^+], 327, 279, 259	–82.4 (m, 3 F), –114.8 (dd, $^2J_{F,F}$ = 273.3, $^3J_{F,H}$ = 14.7, 1 F), –116.8 (dd, $^2J_{F,F}$ = 273.3, $^3J_{F,H}$ = 14.7, 1 F)	1.27 (t, $^3J_{H,H}$ = 7.4, 3 H), 2.96 (m, 2 H), 3.40 (dd, $^2J_{H,H}$ = 18.1, $^3J_{H,H}$ = 2.9, 1 H), 3.91 (dd, $^2J_{H,H}$ = 18.1, $^3J_{H,H}$ = 10.1, 1 H), 4.16 (m, 1 H), 7.48 (m, 2 H), 7.63 (m, 1 H), 7.98 (m, 2 H)	14.0 (s, CH_3), 24.3 (s, CH_2), 35.2 (s, CH_2), 49.7 (t, $^2J_{C,F}$ = 20.7, CH), 113.6 (tq, $^1J_{C,F}$ = 259.5, $^2J_{C,F}$ = 37.9, CF_2), 118.7 (qt, $^1J_{C,F}$ = 287.1, $^2J_{C,F}$ = 36.2, CF_3), 128.1 (s, CH), 128.7 (s, CH), 133.9 (s, CH), 135.5 (s, C_4), 193.1 (t, $^3J_{C,F}$ = 2.6, COS), 194.7 (s, CO)
13	PE–EtOAc (88:12)	2937, 1725, 1683, 1154	328 [M + 18], 311 [M + 1], 268, 248[e]	–113.2 (m, 2 F), –128.8 (m, 2 F), –137.7 (d, $^2J_{F,H}$ = 52.2, 2 F)	1.27 (t, $^3J_{H,H}$ = 7.4, 3 H), 2.21 (s, 3 H), 2.8–3.1 (m, 3 H), 3.28 (dd, $^2J_{H,H}$ = 18.4, $^3J_{H,H}$ = 9.9, 1 H) 3.9–4.1 (m, 1 H), 6.03 (tt, $^2J_{H,F}$ = 52.2, $^3J_{H,F}$ = 5.7, 1 H)	13.9 (s, CH_3), 24.1 (s, CH_2), 29.5 (s, CH_3), 39.4 (m, CH_2), 49.2 (t, $^2J_{C,F}$ = 20.9, CH), 107.6 (tt, $^1J_{C,F}$ = 253.7, $^2J_{C,F}$ = 31.0, CF_2 H), 105-115 (m, CF_2), 115.8 (tt, $^1J_{C,F}$ = 257.8, $^2J_{C,F}$ = 32.4, CF_2), 193.2 (t, $^3J_{C,F}$ = 3.2, COS), 203.1 (s, CO)

[a] Oils. Satisfactory microanalyses obtained.
[b] Solvent used for chromatographic separation.
[c] NMR solvent: $CDCl_3$.
[d] Compound **12** was distilled under reduced pressure (102–106°C/0.05 mbar) then was recrystallised from petroleum ether; mp 35–36 °C
[e] CI (NH_3).

V = 3914.1(3) Å^3, Z = 8, Dx = 1.38 gcm^{-3}. A total of 13856 reflections were collected using a Brucker CCD detector and Cu Kα radiation (λ = 1.54178 Å), 2822 independent reflections (Rint = 0.17). The structure was solved by direct methods with SHELXS-97[14] and refined by least square using F^2 values and anisotropic thermal parameters for non-hydrogen atoms with SHELXL-97.[14] The H atoms were calculated and included in the refinement with a common isotropic temperature factor. The ethyl group is disordered: two positions were refined with site occupation factors of 0.5. The data have been deposit with the Cambridge Crystallographic Data Centre (Nr CCDC219335). Selected bond lengths (Å): N(1)-C(2) = 1.351(5), C(2)-C(3) = 1.500(6), C(3)-C(4) = 1.323(6), C(4)-C(5) = 1.516(6), N(1)-C(5) = 1.474(5).

Compound 30

$C_{16}H_{16}F_3NO_2S$, Mr = 343.36, orthorhombic, Pbca (Nr 61) *a* = 10.421(4), *b* = 24.666(8), *c* = 12.687(4) Å, V = 3261(2) Å^3, Z = 8, Dx = 1.40 gcm^{-3}. A total of 8746 reflections were collected using a MAR345 image plate detector and Mo Kα radiation (λ = 0.71069 Å), 1696 independent reflections (Rint = 0.077). The structure was solved by direct methods with SHELXS-97[14] and refined by least square using F^2 values and anisotropic thermal parameters for non-hydrogen atoms with SHELXL-97.[14] The H atoms were calculated and included in the refinement with a common isotropic temperature factor. The data have been deposit with the Cambridge Crystallographic Data Centre (Nr CCDC 219336). Selected bond lengths (Å): N(1)-C(2) = 1.362(4), C(2)-C(3) = 1.498(5), C(3)-C(4) = 1.322(5), C(4)-C(5) = 1.496(5), N(1)-C(5) = 1.477(5), C(3)-C(7) = 1.473(5), C(7)-C(11) = 1.319(5).

Table 3 Spectroscopic Data of Furans **14**, **15** and Compound **17**

Compd[a]	Solvents[b]	IR (cm^{-1})	GC-MS *m/z*	^{19}F NMR[c] δ, *J* (Hz)	^{1}H NMR[c] δ, *J* (Hz)	^{13}C NMR[c] δ, *J* (Hz)
14[d]	hexane–EtOAc (97:3)	2928, 1767, 1450, 1148	300 [M^+], 267, 239, 105	–58.8 (d, $^5J_{F,H}$ = 2.6)	1.25 (t, $^3J_{H,H}$ = 7.4, 3 H), 3.04 (q, $^3J_{H,H}$ = 7.4, 2 H), 6.63 (m, 1 H), 7.35 (m, 3 H), 7.62 (m, 2 H)	14.1 (s, CH_3), 28.8 (q, $^6J_{C,F}$ = 2.8, CH_2), 101.0 (q, $^4J_{C,F}$ = 4.1, CH), 122.6 (q, $^1J_{C,F}$ = 276.7, CF_3), 125.5 (s, 2 × CH), 127.2 (s, C_4), 127.8 (q, $^3J_{C,F}$ = 2.8, C_4), 128.9 (s, 2 × CH), 131.0 (s, CH), 135.1 (q, $^2J_{C,F}$ = 33.1, C_4), 155.5 (q, $^4J_{C,F}$ = 2.3, C_4), 164.9 (s, COS)
15	hexane–EtOAc (94:6)	2933, 1769, 1638, 1114	270 [M^+], 237, 209, 69	–112.9 (m, 2 F), –136.2 (dt, $^2J_{F,H}$ = 53.4, $^3J_{F,F}$ = 8.1, 2 F)	1.26 (t, $^3J_{H,H}$ = 7.4, 3 H), 2.18 (s, 3 H), 3.05 (q, $^3J_{H,H}$ = 7.4, 2 H), 6.13 (m, 1 H), 6.14 (tt, $^2J_{H,F}$ = 53.4, $^3J_{H,F}$ = 4.5, 1 H)	14.0 (s, CH_3), 14.5 (s, CH_3), 30.6 (s, CH_2), 104.3 (t, $^4J_{C,F}$ = 6.7, CH), 109.6 (tt, $^1J_{C,F}$ = 253.0, $^2J_{C,F}$ = 36.6, CF_2H), 115.3 (tt, $^1J_{C,F}$ = 253.5, $^2J_{C,F}$ = 28.5, CF_2), 132.0 (m, C_4), 133.6 (t, $^2J_{C,F}$ = 23.5, C_4), 157.8 (t, $^4J_{C,F}$ = 3.2, C_4), 164.4 (s, COS)
17	hexane–EtOAc (92:8)	2933, 1775, 1654, 1112	270 [M^+], 210, 190, 120	–118.7 (m, 2 F), –135.3 (dd, $^2J_{F,F}$ = 300.7, $^2J_{F,H}$ = 53.9, 1 F), –140.5 (ddt, $^2J_{F,F}$ = 300.7, $^2J_{F,H}$ = 53.9, $^3J_{F,F}$ = 8.1, 1 F)	1.29 (t, $^3J_{H,H}$ = 7.4, 3 H), 2.6–2.8 (m, 2 H), 4.18 (m, 1 H), 5.02 (d, $^2J_{H,H}$ = 2.6, 1 H), 5.34 (d, $^2J_{H,H}$ = 2.6, 1 H) 6.24 (t, $^2J_{H,F}$ = 53.9, 1 H), 7.39 (s, 1 H)	14.0 (s, CH_3), 27.1 (s, CH_2), 39.6 (t, $^2J_{C,F}$ = 23.6, CH), 99.5 (s, CH_2), 109.1 (t, $^1J_{C,F}$ = 253.6, CF_2H), 116.4 (t, $^1J_{C,F}$ = 253.6, CF_2), 128.7 (s, C_4), 138.8 (s, CH), 153.3 (s, C_4), 168.5 (s, COS)

[a] Satisfactory microanalyses obtained.
[b] Solvent used for chromatographic separation.
[c] NMR solvent: $CDCl_3$.
[d] Recrystallisation in PE–EtOAc; mp 92–93 °C

Table 4 Spectroscopic Data of Lactams **7, 18, 19** and **21**–**29**

Compd[a]	Solvents[b]	IR (cm^{-1})[c]	GC-MS[c] *m/z*	^{19}F NMR[d] δ, *J* (Hz)	^{1}H NMR[d] δ, *J* (Hz)	^{13}C NMR[d] δ, *J* (Hz)
7a	PE–EtOAc (80:20)	3347, 2932, 1686, 1648	346 [M + 1], 328, 285, 106	–69.1 (d, $^3J_{F,H}$ = 7.7)	1.35 (t, $^3J_{H,H}$ = 7.4, 3 H), 1.41 (s, 3 H), 2.22 (br s, 1 H, OH), 2.7–2.9 (m, 2 H), 4.28 (q, $^3J_{H,F}$ = 7.7, 1 H), 4.63 (m, 2 H), 6.86 (m, 1 H), 7.3–7.4 (m, 5 H)	14.1 (s, CH_3), 23.2 (s, CH_3), 27.9 (s, CH_2), 41.2 (q, $^2J_{C,F}$ = 32.5, CH), 42.1 (s, CH_2), 88.7 (s, C_4) 125.77 (q, $^1J_{C,F}$ = 278.6, CF_3), 127.3 (s, CH), 127.9 (s, 2 × CH), 128.5 (s, 2 × CH), 131.1 (s, C_4), 137.8 (s, C_4), 145.0 (s, C_4), 167.0 (s, CO)
7b[e]				–68.9 (d, $^3J_{F,H}$ = 7.7)	1.34 (t, $^3J_{H,H}$ = 7.4, 3 H), 1.44 (s, 3 H), 2.15 (br s, 1 H, OH), 4.30 (q, $^3J_{H,F}$ = 7.7, 1 H)	27.6 (s, CH_2), 88.9 (s, C_4), 125.84 (q, $^1J_{C,F}$ = 278.6, CF_3)
18a[f]	hexane–EtOAc (85:15)	3346, 2931, 1686, 1645	408 [M + 1], 347, 240, 106	–69.2 (d, $^3J_{F,H}$ = 8.6)	1.34 (t, $^3J_{H,H}$ = 7.4, 3 H), 2.72 (br s, 1 H, OH), 2.8–2.9 (m, 2 H), 3.98 (d, $^2J_{H,H}$ = 15.0, 1 H), 4.37 (q, $^3J_{H,F}$ = 8.6, 1 H), 4.68 (d, $^2J_{H,H}$ = 15.0, 1 H), 6.86 (s, 1 H), 7.21 (m, 5 H), 7.3–7.4 (m, 5 H)	14.09 (s, CH_3), 27.9 (s, CH_2), 41.2 (q, $^2J_{C,F}$ = 31.7, CH), 43.2 (s, CH_2), 91.3 (s, C_4), 122.1 (q, $^1J_{C,F}$ = 279.5, CF_3), 125.86 (s, 2 × CH), 127.18 (s, CH), 128.27 (s, 2 × CH), 128.5 (s, 2 × CH), 128.72 (s, 2 × CH), 128.78 (s, CH), 130.8 (s, C_4), 135.6 (s, C_4), 137.31 (s, C_4), 145.5 (s, CH), 167.8 (s, CO)

Table 4 Spectroscopic Data of Lactams **7, 18, 19** and **21–29** (continued)

Compd[a]	Solvents[b]	IR (cm^{-1})[c]	GC-MS[c] *m/z*	^{19}F NMR[d] δ, *J* (Hz)	^{1}H NMR[d] δ, *J* (Hz)	^{13}C NMR[d] δ, *J* (Hz)
18b[f]				–68.8 (d, $^{3}J_{F,H}$ = 8.6)	1.34 (t, $^{3}J_{H,H}$ = 7.4, 3 H), 2.57 (br s, 1 H, OH), 2.7–3.0 (m, 2 H), 3.95 (d, $^{2}J_{H,H}$ = 15.0, 1 H), 4.33 (q, $^{2}J_{H,F}$ = 8.6, 1 H), 4.73 (d, $^{2}J_{H,H}$ = 15.0, 1 H), 6.83 (s, 1 H), 7.24 (m, 5 H), 7.36 (m, 5 H)	14.05 (s, CH_3), 27.6 (s, CH_2), 41.4 (q, $^{2}J_{C,F}$ = 31.7, CH), 43.3 (s, CH_2), 91.5 (s, C_4), 122.7 (q, $^{1}J_{C,F}$ = 279.5, CF_3), 125.91 (s, 2 × CH), 127.23 (s, CH), 128.31 (s, 2 × CH), 128.6 (s, 2 × CH), 128.74 (s, 2 × CH), 128.80 (s, CH), 130.5 (s, C_4), 135.8 (s, C_4), 137.34 (s, C_4), 145.0 (s, CH), 167.9 (s, CO)
19a[f]	hexane–EtOAc (86:14)	3350, 2931, 1686, 1644	378 [M + 1], 317, 216, 106	–117.8 (ddd, $^{2}J_{F,F}$ = 266.6, $^{3}J_{F,H}$ = 18.8, $^{3}J_{F,F}$ = 8.1, 1 F), –119.9 (d, $^{2}J_{F,F}$ = 266.6, 1 F), –135.0 (ddd, $^{2}J_{F,F}$ = 300.3, $^{2}J_{F,H}$ = 53.9, $^{3}J_{F,F}$ = 8.1, 1 F), –139.7 (ddt, $^{2}J_{F,F}$ = 300.3, $^{2}J_{F,H}$ = 53.9, $^{3}J_{F,F}$ = 8.1, 1 F)	1.30 (t, $^{3}J_{H,H}$ = 7.4, 3 H), 1.40 (s, 3 H), 2.27 (br s, 1 H, OH), 2.7–2.9 (m, 2 H), 4.22 (m, 1 H) 4.54 (d, $^{2}J_{H,H}$ = 15.5, 1 H), 4.70 (d, $^{2}J_{H,H}$ = 15.5, 1 H), 6.21 (m, 1 H), 6.88 (m, 1 H), 7.2–7.4 (m, 5 H)	14.2 (s, CH_3), 23.3 (s, CH_3), 27.5 (s, CH_2), 39.2 (t, $^{3}J_{C,F}$ = 23.7, CH), 42.1 (s, CH_2), 88.8 (s, C_4), 110–120 (m, CF_2H, CF_2), 127.3 (s, CH), 127.8 (s, 2 × CH), 128.6 (s, 2 × CH), 131.7 (s, C_4), 137.9 (s, C_4), 145.5 (s, CH), 167.3 (s, CO)
19b[f]				–119.0 (m, 2 F), –135.5 (dd, $^{2}J_{F,F}$ = 298.9, $^{2}J_{F,H}$ = 53.9, 1 F), –140.3 (ddt, $^{2}J_{F,F}$ = 298.9, $^{2}J_{F,H}$ = 53.9, $^{3}J_{F,F}$ = 8.5, 1 F)	1.22 (t, $^{3}J_{H,H}$ = 7.4, 3 H), 1.35 (s, 3 H), 2.43 (br s, 1 H, OH), 2.6–2.8 (m, 2 H), 4.15 (t, $^{3}J_{H,F}$ = 16.2, 1 H), 4.47 (d, $^{2}J_{H,H}$ = 15.5, 1 H), 4.57 (d, $^{2}J_{H,H}$ = 15.5, 1 H), 6.17 (tdd, $^{2}J_{H,F}$ = 53.9, $^{3}J_{H,F}$ = 6.0, $^{3}J_{H,F}$ = 4.0, 1 H), 6.81 (m, 1 H), 7.2–7.3 (m, 5 H)	14.2 (s, CH_3), 23.2 (s, CH_3), 27.1 (s, CH_2), 39.2 (t, $^{3}J_{C,F}$ = 23.6, CH), 42.1 (s, CH_2), 88.9 (s, C_4), 109.2 (tt, $^{1}J_{C,F}$ = 250.9, $^{2}J_{C,F}$ = 32.8, CF_2H), 110–120 (m, CF_2), 127.4 (s, CH), 127.9 (s, 2 × CH), 128.6 (s, 2 × CH), 131.6 (s, C_4), 138.0 (s, C_4), 145.5 (s, CH), 167.3 (s, CO)
21a	PE–EtOAc (83:17)	3342, 2934, 1686, 1649	326 [M + 1], 325 [M], 308, 265, 196	–69.2 (d, $^{3}J_{F,H}$ = 7.6)	0.91 (t, $^{3}J_{H,H}$ = 6.7, 3 H), 1.2–1.4 (m, 7 H), 1.55 (s, 3 H), 1.6–1.8 (m, 2 H), 2.31 (br s, 1 H, OH), 2.7–2.9 (m, 2 H), 3.2–3.3 (m, 1 H), 3.4–3.5 (m, 1 H), 4.1–4.3 (m, 1 H), 6.82 (s, 1 H)	13.9 (s, CH_3), 14.0 (s, CH_3), 22.2 (s, CH_2), 22.81 (s, CH_3), 27.4 (s, CH_2), 28.6 (s, CH_2), 29.3 (s, CH_2), 38.9 (s, CH_2), 41.0 (q, $^{2}J_{C,F}$ = 31.5, CH), 88.5 (s, C_4), 125.7 (q, $^{1}J_{C,F}$ = 278.6, CF_3), 131.0 (s, C_4), 144.7 (s, CH), 166.7 (s, CO)
21b[e]				–68.9 (d, $^{3}J_{F,H}$ = 7.6)	1.54 (s, 3 H), 2.30 (br s, 1 H, OH)	22.75 (s, CH_3), 27.7 (s, CH_2), 88.6 (s, C_4), 125.8 (q, $^{1}J_{C,F}$ = 278.6, CF_3), 144.6 (s, CH), 166.6 (s, CO)
22a[g]	PE–EtOAc (82:18)	3369, 3019, 1692, 1653	298 [M + 1], 297 [M], 280, 237	–68.9 (d, $^{3}J_{F,H}$ = 11.4)	1.27 (t, $^{3}J_{H,H}$ = 7.4, 3 H), 1.39 (d, $^{3}J_{H,H}$ = 6.9, 3 H), 1.41 (d, $^{3}J_{H,H}$ = 6.9, 3 H), 1.51 (s, 3 H), 2.65–2.85 (m, 2 H), 3.25 (br s, 1 H, OH), 3.80 (sept, $^{3}J_{H,H}$ = 6.9, 1 H), 4.13 (q, $^{3}J_{H,F}$ = 11.4, 1 H), 6.72 (s, 1 H)	14.03 (s, CH_3), 20.2 (s, CH_3), 20.7 (s, CH_3), 22.8 (s, CH_3), 27.8 (s, CH_2), 40.8 (q, $^{2}J_{C,F}$ = 31.7, CH), 43.72 (s, CH), 88.89 (s, C_4), 125.8 (q, $^{1}J_{C,F}$ = 278.7, CF_3), 131.9 (s, C_4), 144.0 (s, CH), 165.87 (s, CO)
22b[e,g]				–69.2 (d, $^{3}J_{F,H}$ = 11.4)	1.26 (t, $^{3}J_{H,H}$ = 7.4, 3 H), 1.40 (d, $^{3}J_{H,H}$ = 6.9, 3 H), 1.42 (d, $^{3}J_{H,H}$ = 6.9, 3 H), 1.52 (s, 3 H), 3.29 (br s, 1 H, OH), 4.15 (q, $^{3}J_{H,F}$ = 11.4, 1 H), 6.73 (s, 1 H)	14.00 (s, CH_3), 20.3 (s, CH_3), 20.6 (s, CH_3), 22.9 (s, CH_3), 27.4 (s, CH_2), 43.74 (s, CH), 89.04 (s, C_4), 125.9 (q, $^{1}J_{C,F}$ = 278.6, CF_3), 131.8 (s, C_4), 144.2 (s, C_4), 165.89 (s, CO)
23a	PE–EtOAc (88:12)	3369, 1695, 1654, 1603, 1500	332 [M + 1], 331 [M], 314, 271, 253	–68.9 (d, $^{3}J_{F,H}$ = 7.6)	1.32 (t, $^{3}J_{H,H}$ = 7.3, 3 H), 1.50 (s, 3 H), 2.7–2.9 (m, 2 H), 4.32 (q, $^{3}J_{H,F}$ = 7.6, 1 H), 6.94 (s, 1 H), 7.31 (m, 1 H), 7.43 (dd, $^{3}J_{H,H}$ = 8.0, $^{3}J_{H,H}$ = 7.2, 2 H), 7.53 (d, $^{3}J_{H,H}$ = 7.6, 2 H)	14.1 (s, CH_3), 22.9 (s, CH_3), 28.1 (s, CH_2), 41.2 (q, $^{2}J_{C,F}$ = 31.3, CH), 90.0 (s, C_4), 115.4 (s, CH), 125.87 (q, $^{1}J_{C,F}$ = 276.8, CF_3), 126.1 (s, CH), 128.9 (s, CH), 131.1 (s, C_4), 135.0 (s, C_4), 144.4 (s, CH), 166.2 (s, CO)

Table 4 Spectroscopic Data of Lactams **7, 18, 19** and **21**–**29** (continued)

Compd[a]	Solvents[b]	IR (cm^{-1})[c]	GC-MS[c] *m/z*	^{19}F NMR[d] δ, *J* (Hz)	^{1}H NMR[d] δ, *J* (Hz)	^{13}C NMR[d] δ, *J* (Hz)
23b[e]				–69.1 (d, $^{3}J_{F,H}$ = 7.6)	1.33 (t, $^{3}J_{H,H}$ = 7.3, 3 H), 1.53 (s, 3 H), 4.29 (q, $^{3}J_{H,F}$ = 7.6, 1 H), 6.70 (d, $^{3}J_{H,H}$ = 7.6, 2 H), 6.78 (t, $^{3}J_{H,H}$ = 7.4, 1 H), 6.97 (s, 1 H), 7.17 (dd, $^{3}J_{H,H}$ = 8.0, $^{3}J_{H,H}$ = 7.2, 2 H)	27.7 (s, CH_2), 41.1 (q, $^{2}J_{C,F}$ = 31.3, CH), 90.1 (s, C_4), 119.0 (s, CH), 125.79 (q, $^{1}J_{C,F}$ = 276.8, CF_3), 127.0 (s, CH), 129.2 (s, CH), 145.0 (s, CH)
24a[g]	PE–EtOAc (93:7)	3373, 2931, 1713, 1660, 1596	333 [M + 1], 255, 95, 80[h]	–68.8 (d, $^{3}J_{F,H}$ = 8.5)	1.30 (t, $^{3}J_{H,H}$ = 7.4, 3 H), 1.826 (s, 3 H), 2.7-2.9 (m, 2 H), 4.31 (q, $^{3}J_{H,F}$ = 8.5, 1 H), 6.9 (br s, 1 H, OH), 7.08 (s, 1 H), 7.11 (m, 1 H), 7.79 (ddd, $^{3}J_{H,H}$ = 7.9, $^{3}J_{H,H}$ = 7.6, $^{4}J_{H,H}$ = 1.2, 1 H), 8.31 (d, $^{3}J_{H,H}$ = 8.5, 1 H), 8.34 (d, $^{3}J_{H,H}$ = 4.1, 1 H)	13.98 (s, CH_3), 25.3 (s, CH_3), 26.9 (s, CH_2), 41.1 (q, $^{2}J_{C,F}$ = 31.9, CH), 91.2 (s, C_4), 115.3 (s, CH), 119.7 (s, CH), 125.8 (q, $^{1}J_{C,F}$ = 278.6, CF_3), 130.9 (s, C_4), 138.84 (s, CH), 146.37 (s, CH), 146.43 (s, CH), 151.16 (s, C_4), 166.01 (s, CO)
24b[e,g]				–68.7 (d, $^{3}J_{F,H}$ = 8.5)	1.34 (t, $^{3}J_{H,H}$ = 7.4, 3 H), 1.833 (s, 3 H), 7.07 (s, 1 H)	14.11 (s, CH_3), 27.6 (s, CH_2), 41.2 (q, $^{2}J_{C,F}$ = 31.9, CH), 91.3 (s, C_4), 115.4 (s, CH), 119.6 (s, CH), 131.0 (s, C_4), 138.82 (s, CH), 145.9 (s, CH), 146.41 (s, CH), 151.23 (s, C_4), 165.98 (s, CO)
25a	PE–EtOAc (30:70)	3354, 2935, 1686, 1649	300 [M + 1], 282, 239, 221[h]	–69.1 (d, $^{3}J_{F,H}$ = 7.6)	1.30 (t, $^{3}J_{H,H}$ = 7.5, 3 H), 1.56 (s, 3 H), 1.74 (br s, 1 H, OH), 2.7–2.8 (m, 2 H), 3.3–3.4 (m, 1 H), 3.8–4.0 (m, 2 H), 4.1–4.4 (m, 2 H), 6.90 (s, 1 H)	13.9 (s, CH_3), 22.6 (s, CH_3), 27.26 (s, CH_2), 41.03 (q, $^{2}J_{C,F}$ = 31.5, CH), 41.5 (s, CH_2), 61.1 (s, CH_2), 88.1 (s, C_4), 125.69 (q, $^{1}J_{C,F}$ = 278.5, CF_3), 130.1 (s, C_4), 145.81 (s, CH), 167.69 (s, CO)
25b[e]				–68.9 (d, $^{3}J_{F,H}$ = 7.6)	1.31 (t, $^{3}J_{H,H}$ = 7.5, 3 H)	27.34 (s, CH_2), 41.09 (q, $^{2}J_{C,F}$ = 32.5, CH), 88.2 (s, C_4), 125.76 (q, $^{1}J_{C,F}$ = 278.5, CF_3), 130.2 (s, C_4), 145.85 (s, CH), 167.75 (s, CO)
26a[i]	PE–EtOAc (60:40)	3362, 2934, 1685, 1651	376 [M + 1], 375 [M], 344, 106	–68.93 (d, $^{3}J_{F,H}$ = 7.6)	1.25 (t, $^{3}J_{H,H}$ = 7.4, 3 H), 1.43 (s, 3 H), 2.59 (br s, OH, 1 H), 2.6-2.9 (m, 2 H), 3.30 (br s, OH, 1 H), 4.02 (dd, $^{2}J_{H,H}$ = 11.7, $^{3}J_{H,H}$ = 4.0, 1 H), 4.19 (q, $^{3}J_{H,F}$ = 7.6, 1 H), 4.41, (m, 1 H), 4.80 (dd, $^{3}J_{H,H}$ = 7.4, $^{3}J_{H,H}$ = 4.0, 1 H), 6.77 (s, 1 H), 7.2–7.4 (m, 5 H)	14.1 (s, CH_3), 23.4 (s, CH_3), 27.5 (s, CH_2), 41.1 (q, $^{3}J_{C,F}$ = 31.5, CH), 57.54 (s, CH), 63.0 (s, CH_2), 89.9 (s, C_4), 125.78 (q, $^{1}J_{C,F}$ = 276.8, CF_3), 127.3 (s, CH), 127.7 (s, 2 × CH), 128.5 (s, 2 × CH), 130.69 (s, C_4), 138.17 (s, C_4), 145.6 (s, CH), 167.8 (s, CO)
26b[e]				–69.10 (d, $^{3}J_{F,H}$ = 7.6)	1.31 (t, $^{3}J_{H,H}$ = 7.4, 3 H), 1.44 (s, 3 H), 2.7-2.9 (m, 2 H), 3.46 (br s, 2 H, 2 × OH), 4.07 (m, 1 H), 4.24 (m, 1 H), 4.48 (m, 1 H), 4.94 (m, 1 H), 6.81 (s, 1 H), 7.2–7.4 (m, 5 H)	27.7 (s, CH_2), 57.51 (s, CH), 62.9 (s, CH_2), 89.8 (s, C_4), 125.72 (q, $^{1}J_{C,F}$ = 276.8, CF_3), 127.6 (s, 2 × CH), 128.6 (s, 2 × CH), 130.75 (s, C_4), 138.25 (s, C_4), 145.5 (s, CH), 167.7 (s, CO)
26c[e,i]				–69.01 (d, $^{3}J_{F,H}$ = 7.6)	1.33 (s, 3 H), 1.34 (t, $^{3}J_{H,H}$ = 7.4, 3 H), 2.7–2.9 (m, 2 H), 3.93 (dd, $^{2}J_{H,H}$ = 10.7, $^{3}J_{H,H}$ = 4.1, 1 H), 4.26 (q, $^{3}J_{H,F}$ = 7.6, 1 H), 4.65 (m, 1 H), 4.79 (dd, $^{2}J_{H,H}$ = 10.7, $^{3}J_{H,H}$ = 4.1, 1 H), 6.91 (s, 1 H), 7.3–7.4 (m, 5 H)	27.4 (s, CH_2), 58.1 (s, CH), 89.0 (s, C_4), 125.83 (q, $^{1}J_{C,F}$ = 276.8, CF_3), 130.9 (s, C_4), 145.9 (s, CH), 167.6 (s, CO)
26d[e]				–68.81 (d, $^{3}J_{F,H}$ = 7.6)	3.84 (m, 1 H), 4.58 (m, 1 H), 4.73 (m, 1 H), 6.88 (s, 1 H)	29.6 (s, CH_2), 58.2 (s, CH), 88.9 (s, C_4)

Table 4 Spectroscopic Data of Lactams **7, 18, 19** and **21**–**29** (continued)

Compd[a]	Solvents[b]	IR (cm^{-1})[c]	GC-MS[c] *m/z*	^{19}F NMR[d] δ, *J* (Hz)	^{1}H NMR[d] δ, *J* (Hz)	^{13}C NMR[d] δ, *J* (Hz)
27a	[j]	3322, 2933, 1697, 1647	341 [M + 1], 340 [M], 325, 261	–68.5 (d, $^{3}J_{F,H}$ = 7.6)	1.29 (t, $^{3}J_{H,H}$ = 7.3, 3 H), 1.45 (s, 3 H), 2.12 (s, 6 H), 2.2–2.6 (m, 4 H), 2.7–2.9 (m, 2 H), 3.17 (m, 1 H), 3.79 (m, 1 H), 4.1–4.3 (m, 1 H), 6.87 (s, 1 H)	14.0 (s, CH_3), 23.3 (s, CH_3), 23.4 (s, CH_2), 27.0 (s, CH_2), 37.47 (s, CH_2), 40.9 (q, $^{2}J_{C,F}$ = 31.7, CH), 43.8 (s, 2 × CH_3), 57.76 (s, CH_2), 87.9 (s, C_4), 125.8 (q, $^{1}J_{C,F}$ = 278.5, CF_3), 129.0 (s, C_4), 147.2 (s, CH), 166.8 (s, CO)
27b[e]				–68.8 (d, $^{3}J_{F,H}$ = 7.6)	1.30 (t, $^{3}J_{H,H}$ = 7.3, 3 H), 1.46 (s, 3 H), 6.93 (s, 1 H)	13.9 (s, CH_3), 23.2 (s, CH_3), 27.1 (s, CH_2), 37.52 (s, CH_2), 40.6 (q, $^{2}J_{C,F}$ = 31.7, CH), 43.5 (s, 2 × CH_3), 57.70 (s, CH_2), 88.2 (s, C_4), 125.9 (q, $^{1}J_{C,F}$ = 278.5, CF_3), 129.3 (s, C_4), 148.1 (s, CH), 166.7 (s, CO)
28a[g]	PE–EtOAc (70:30)	3250, 2931, 1761, 1694, 1646	328 [M + 1], 310, 249, 189	–69.1 (d, $^{3}J_{F,H}$ = 11.4)	1.31 (t, $^{3}J_{H,H}$ = 7.3, 3 H), 1.509 (s, 3 H), 2.7–2.9 (m, 2 H), 3.18 (br s, OH), 3.78 (s, 3 H), 3.94 (d, $^{2}J_{H,H}$ = 17.9, 1 H), 4.21 (q, $^{3}J_{H,F}$ = 8.9, 1 H), 4.409 (d, $^{2}J_{H,H}$ = 17,9, 1 H), 6.96 (s, 1 H)	14.1 (s, CH_3), 22.1 (s, CH_3), 27.5 (s, CH_2), 39.7 (s, CH_2), 41.1 (q, $^{2}J_{C,F}$ = 31.9, CH), 52.7 (s, CH_3), 88.2 (s, C_4), 125.7 (q, $^{1}J_{C,F}$ = 278.5, CF_3), 130.7 (s, C_4), 146.2 (s, CH), 167.2 (s, CON), 170.7 (s, COO)
28b[e,g]				–68.9 (d, $^{3}J_{F,H}$ = 11.4)	1.30 (t, $^{3}J_{H,H}$ = 7.3, 3 H), 1.514 (s, 3 H), 3.11 (br s, 1 H, OH), 3.92 (d, $^{2}J_{H,H}$ = 17.9, 1 H), 4.22 (q, $^{3}J_{H,F}$ = 8.9, 1 H), 4.402 (d, $^{2}J_{H,H}$ = 17.9, 1 H), 6.94 (s, 1 H)	41.2 (q, $^{2}J_{C,F}$ = 31.9, CH), 88.3 (s, C_4), 125.8 (q, $^{1}J_{C,F}$ = 278.5, CF_3), 130.6 (s, C_4), 145.8 (s, CH), 167.3 (s, CON)
29a	hexane–EtOAc (85:15)[k]	3346, 2931, 1693, 1601, 1501	393 [M], 301, 241, 105	–69.1 (d, $^{3}J_{F,H}$ = 8.5)	1.27 (t, $^{3}J_{H,H}$ = 7.1, 3 H), 2.7–2.9 (m, 2 H), 3.25 (br s, 1 H, OH), 4.32 (q, $^{3}J_{H,F}$ = 8.5, 1 H), 6.85 (s, 1 H), 7.0–7.5 (m, 10H)	14.05 (s, CH_3), 27.6 (s, CH_2), 41.3 (q, $^{2}J_{C,F}$ = 32.0, CH), 92.42 (s, C_4), 124.1 (s, CH), 125.82 (s, CH), 125.86 (q, $^{1}J_{C,F}$ = 278.3, CF_3), 125.9 (s, CH), 128.6 (s, CH), 128.66 (s, CH), 128.72 (s, CH), 130.1 (s, C_4), 135.51 (s, C_4), 136.4 (s, C_4), 145.1 (s, CH), 167.35 (s, CO)
29b[e]				–68.7 (d, $^{3}J_{F,H}$ = 8.5)	1.30 (t, $^{3}J_{H,H}$ = 7.1, 3 H), 3.39 (br s, 1 H, OH), 4.34 (q, $^{3}J_{H,F}$ = 8.5, 1 H), 6.87 (s, 1 H)	14.13 (s, CH_3), 28.0 (s, CH_2), 41.2 (q, $^{2}J_{C,F}$ = 32.0, CH), 92.38 (s, C_4), 124.4 (s, CH), 125.76 (q, $^{1}J_{C,F}$ = 278.3, CF_3), 125.77 (s, CH), 126.0 (s, CH), 130.4 (s, C_4), 135.46 (s, C_4), 136.2 (s, C_4), 145.4 (s, CH), 167.26 (s, CO)

[a] Oil. Satisfactory microanalyses obtained. The compounds were obtained as a mixture of diastereomers (major diastereomers are recognised by the letter **a**).
[b] Solvent used for chromatographic separation.
[c] IR and GC-MS spectra were recorded on the mixture of diastereomers.
[d] NMR solvent: $CDCl_3$.
[e] Selected spectroscopic data of minor diastereomers.
[f] Diastereomers were separated by preparative TLC using hexane–EtOAc (85:15) as eluent.
[g] ^{1}H NMR spectra (500 MHz), ^{13}C NMR spectra (125 MHz).
[h] CI (NH_3).
[i] Pure diastereomers were obtained by preparative HPLC using hexane–EtOAc (70:30) as eluent.
[j] Crude product obtained without purification.
[k] Purification by preparative TLC.

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