A New Synthesis of Optically Active 3-Substituted (3*S*)-3,4-Dihydro-5-(perfluoroalkyl)-2*H*-[1,4]oxazepin-7-ones

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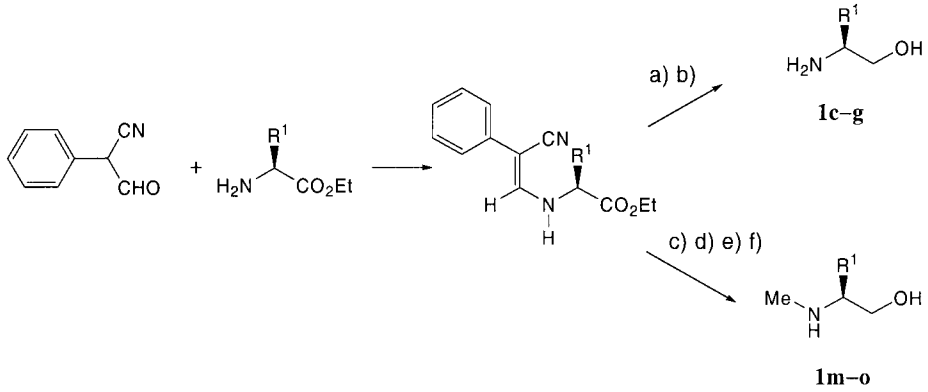
Optically active (perfluoroalkyl)-oxazepin-7-ones were synthesized in two steps starting from ethyl perfluorobut-2-ynoate by direct addition of optically active amino alcohols *via* intermolecular *Michael* addition and lactone formation.

Introduction. – Much attention has been paid to the development of new methodologies for the synthesis of (perfluoroalkyl)-substituted heterocycles [1], which are an important class of biologically active compounds [2]. Several interesting reports have been published on the construction of six-membered heterocyclic compounds [3]. Recent reports have described the synthesis of F-containing heterocyclic compounds through, for example, *Michael* addition reactions with bifunctional heteronucleophiles, such as ethane-1,2-dithiol, 2-sulfanyl ethanol and ethylene glycol [4][5]. *Marchesini* and co-workers synthesized 2-acyl-2,3-dihydro-1,3-oxazin-6-ones from the Na salts of isoxazolin-5-ones [6]. *Hamper* reported that the reaction of perfluoro-2-alkynoates with methylhydrazine yields 5-(perfluoroalkyl)pyrazoles [7]. However, only a few syntheses of seven-membered heterocyclic compounds containing a perfluoroalkyl group have been reported so far [4][5][8]. We developed an effective synthesis of optically pure, substituted 5-(perfluoroalkyl)-3,4-dihydro-2*H*-[1,4]oxazepin-7-ones starting from ethyl perfluorobut-2-ynoate [9]. The synthesis of this type of compound has not been reported previously.

Results and Discussion. – The first aim was the synthesis of chiral, enantiomerically pure, substituted amino(perfluoroalkyl)alkenoates. We decided to examine the reactivity of ethyl perfluorobut-2-ynoate with bifunctional heteronucleophiles such as enantiomerically pure β-amino alcohols of type **1**. These amino alcohols were prepared from commercially available natural amino acids as described in [10] (*Scheme 1*).

The reactions of ethyl 3-perfluoroalk-2-ynoates with **1a**–**1i** and with **1m**–**1o** occurred in the absence of a base and without a catalyst, and yielded the corresponding *Michael* adducts, the 3-amino-3-(perfluoralkyl)alkenoates **2a**–**2o** (*Scheme 2*). The results are summarized in *Table 1*.

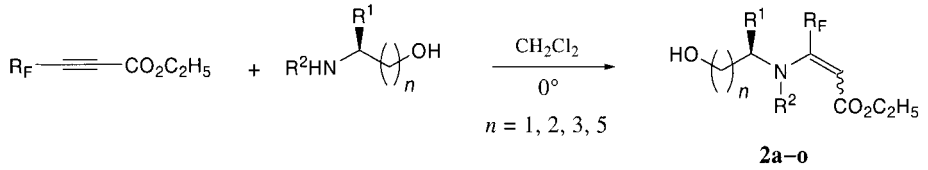
Scheme 1[a])



a) $LiBH_4$. b) H_3O^+, OH^-. c) NaH, DMF. d) Me_2SO_4. e) $LiBH_4$. f) H_3O^+, OH^-.

[a]) For R^1, see *Table 1.*

Scheme 2[a])



R^1 = H, alkyl, aryl,...; R^2 = H, CH_3; R_F = CF_3, CF_3–CF_2

[a]) For R^1, R^2, R^F, see *Table 1.*

Table 1. *Synthesis of 3-Amino-3-(perfluoroalkyl)alkenoates* **2**

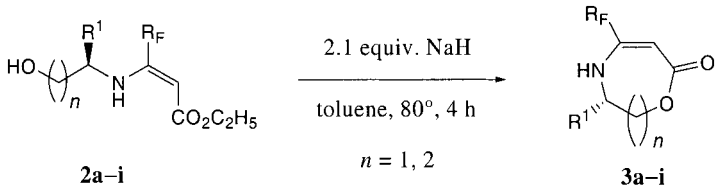
Entry	R_F	Amino alcohols	R^1	R^2	*n*	No.	(*Z*)/(*E*)	$[\alpha]_D^{20}$[a])	Yield [%]
1	CF_3	**1a**	H	H	1	**2a**	100 : 0	–	95
2	CF_3	**1b**	H	H	2	**2b**	100 : 0	–	96
3	CF_3	**1c**	$CH_3S(CH_2)_2$	H	1	**2c**	100 : 0	– 52	83
4	CF_3	**1d**	Bn	H	1	**2d**	100 : 0	– 133	96
5	CF_3	**1e**	i-Bu	H	1	**2e**	100 : 0	– 64	91
6	CF_3	**1f**	CH_3SCH_2	H	1	**2f**	100 : 0	– 106	87
7	C_2F_5	**1e**	i-Bu	H	1	**2g**	100 : 0	– 102	85
8	C_2F_5	**1f**	CH_3SCH_2	H	1	**2h**	100 : 0	– 129	82
9	C_2F_5	**1c**	$CH_3S(CH_2)_2$	H	1	**2i**	100 : 0	– 38	78
10	CF_3	**1g**	$C_2H_5CH(CH_3)CH_2$	H	1	**2j**	100 : 0	– 58	86
11	CF_3	**1h**	H	H	5	**2k**	100 : 0	–	93
12	CF_3	**1i**	H	H	3	**2l**	100 : 0	–	94
13	CF_3	**1m**	Bn	CH_3	1	**2m**	3 : 97	–	90
14	CF_3	**1n**	i-Bu	CH_3	1	**2n**	4 : 96	–	89
15	CF_3	**1o**	i-Pr	CH_3	1	**2o**	4 : 96	–	89

[a]) *c* = 1% in MeOH.

From the available optically active amino alcohols **1c**–**1g**, we obtained optically pure β-amino-β-(perfluoroalkyl)alkenoates **2c**–**2j**. No products from the addition of the O-atom were detected; only the N-atom added to the alkyne C-atom bearing the perfluoroalkyl group, and no aminolysis of the ester function was observed [11]. Only the (*Z*)-isomers **2a**–**2l** were obtained when primary amino alcohols **1a**–**1i** were used. This can be explained by chelation between the H-atom of the amine and the O-atom of the ester function. On the other hand, (*E*)/(*Z*)-mixtures **2m**–**2o** were obtained in the case of *N*-methylated amino alcohols **1m**–**1o**, the (*E*)-isomer being favored. The inversion of the selectivity was confirmed by NOESY experiments. It is also known that, in the ^{1}H-NMR spectrum, the vinylic H-atom (H–C(2)) further absorbs downfield in the (*E*)-isomer than in the (*Z*)-isomer. Similar results were previously obtained when primary or secondary amines were added to ethyl 3-(perfluoroalk)alk-2-ynoates [12].

The next step involved the formation of the optically active, perfluorinated heterocyclic compounds *via* cyclization. The treatment of (*Z*)-β-amino-β-(perfluoroalkyl)alkenoates **2a**–**2i** with NaH (2.1 equiv.) in toluene at 80° provided good yields of the desired substituted 5-(perfluoroalkyl)-3,4-dihydro-2*H*-[1,4]oxazepin-7-ones **3a**–**3i** (*Scheme 3*). The results are summarized in *Table 2*.

Scheme 3[a])



2a–i **3a–i**

[a]) For R^1, R^F, see *Table 2*.

Table 2. *Synthesis of 3-Substituted 5-(Perfluoroalkyl)-3,4-dihydro-2*H*-[1,4]oxazepin-7-ones* **3**

Entry	R_F	R^1	*n*	No.	$[\alpha]_D^{20}$[a])	Yield [%]
1	CF_3	H	1	**3a**	–	87
2	CF_3	H	2	**3b**	–	74
3	CF_3	$CH_3S(CH_2)_2$	1	**3c**	–105	80
4	CF_3	Bn	1	**3d**	–60	82
5	CF_3	i-Bu	1	**3e**	–59	79
6	CF_3	CH_3SCH_2	1	**3f**	–102	85
7	C_2F_5	i-Bu	1	**3g**	–79	83
8	C_2F_5	CH_3SCH_2	1	**3h**	–26	82
9	C_2F_5	$CH_3S(CH_2)_2$	1	**3i**	–23	78

[a]) $c = 1\%$ in MeOH.

Only the (*Z*)-isomers of β-amino-β-perfluoroalkylalkenoates gave the corresponding cyclization products, whereas the (*E*)-isomers remained unchanged. As previously reported, no products resulting from the bis-nucleophilic intermolecular–intramolec-

ular *Michael* addition were detected [4][5]. It should be noted that no cyclization product was observed under the same experimental conditions when $n > 2$ (**2k** and **2l**). This is probably a consequence of the distance between the OH group and the carbonyl C-atom of the ester function. In addition, no racemization took place during our cyclization process.

Conclusions. – In conclusion, we have developed a convenient two-step method for the preparation of optically active 3-substituted 5-(perfluoroalkyl)-3,4-dihydro-2*H*-[1,4]oxazepin-7-ones from ethyl 3-perfluoroalk-2-ynoate. The first step involves a *Michael*-type addition of the optically active amino alcohol to give stereoselective access to the corresponding enamino ester in high yield. The second step is a cyclization of the (*Z*)-ester under basic conditions. The reactions presented here show a general and convenient method for the synthesis of various optically active azaheterocycles carrying a perfluoroalkyl group.

Experimental Part

General. All reactions were carried out under an inert atmosphere (Ar or N_2). The amino alcohols **1a**, **1b**, **1k**, and **1l** are commercially available. THF and Et_2O were dried and freshly distilled from Na/benzophenone. Toluene was dried by distillation over Na. Flash chromatography (FC): silica gel (*Merck*, 230–400 Mesh). M.p.: uncorrected. Optical rotations: *Polarimeter ADP 220*, *Bellingham + Stanley Ltd.* IR Spectra: *Perkin-Elmer 781* IR spectrophotometer or *Perkin-Elmer 1600 series FTIR* spectrophotometer. ^{1}H-NMR Spectra: *Bruker AC-200* (200 MHz) or *Bruker ARX-400* (400 MHz) spectrometer, with $CDCl_3$ as solvent; findings, reported with the residual solvent proton resonance of $CDCl_3$ (δ(H) 7.25 ppm) as internal reference; chemical shifts (δ) in ppm with respect to Me_4Si; coupling constants (J) in Hz). ^{13}C-NMR Spectra: at 50.3 MHz on the same instruments, the $CDCl_3$ solvent peak at δ(C) = 77.0 ppm as reference. ^{19}F-NMR Spectra: in $CDCl_3$ with C_6F_6 as external reference (^{19}F, –164.9 ppm). MS: *Hewlett-Packard* (*5989A*) in the GC/MS (70 eV) mode.

Typical Procedure: Preparation of Ethyl (Z)-3-{[(S)-1-Benzyl-2-hydroxyethyl]amino}-4,4,4-trifluorobut-2-enoate (**2d**). A soln. of 4,4,4-trifluorobut-2-ynoate (1 g, 6 mmol) in Et_2O (10 ml) was added dropwise to 876 mg (5.8 mmol) of the amino alcohol **1d** in Et_2O (5 ml) at –20° under Ar. The mixture was allowed to warm to r.t. Then, it was diluted with Et_2O, dried ($MgSO_4$), and concentrated under vacuum. The residue was chromatographed (SiO_2; petroleum ether/Et_2O 70:30) to yield **2d** (1.76 g, 96%; for yields see *Table 1*).

Ethyl (Z)-4,4,4-Trifluoro-3-[(2-hydroxyethyl)amino]but-2-enoate (**2a**). IR (neat): 3401, 3302, 2984, 1729, 1632, 1208. ^{1}H-NMR (200 MHz): 1.23 (*t*, *J* = 7.1, 3 H); 3.40 (*dt*, *J* = 5.3, 5.4, 2 H); 3.73 (*t*, *J* = 5.3, 2 H); 3.84 (br. *s*, 1 H); 4.10 (*q*, *J* = 7.1, 2 H); 5.07 (br. *s*, 1 H); 8.38 (br. *s*, 1 H). ^{13}C-NMR: 13.8; 45.8; 59.5; 61.1; 84.4 (*q*, *J*(C,F) = 5.8); 120 (*q*, *J*(C,F) = 277); 148.2 (*q*, *J*(C,F) = 31); 170. ^{19}F-NMR (188 MHz): –70.4. EI-MS: 227 (11, $M^{+\cdot}$), 209 (14), 196 (26), 168 (18), 150 (100), 138 (17), 45 (16). Anal. calc. for $C_8H_{12}F_3NO_3$: C 42.29, H 5.32; found: C 42.20, H 5.36.

Ethyl (Z)-4,4,4-Trifluoro-3-[(3-hydroxypropyl)amino]but-2-enoate (**2b**). IR (neat): 3400–3100, 2950, 1720, 1640. ^{1}H-NMR (200 MHz): 1.21 (*t*, *J* = 7.1, 3 H); 1.78 (*qt*, *J* = 6.3, 2 H); 3.38 (br., *dt*, *J* = 6.3, 7.6, 2 H); 3.56 (br. *s*, 1 H); 3.7 (*t*, *J* = 6.3, 2 H); 4.09 (*q*, *J* = 7.1, 2 H); 5.02 (*s*, 1 H); 8.1 (br. *s*, 1 H). ^{13}C-NMR: 14.2; 32.7; 41; 59.3; 59.5; 84 (*q*, *J*(C,F) = 5.8); 120 (*q*, *J*(C,F) = 277); 148.5 (*q*, *J*(C,F) = 31); 170.6. ^{19}F-NMR (188 MHz): –70.1. Anal. calc. for $C_9H_{14}F_3NO_3$: C 44.81, H 5.85; found: C 44.75, H 5.87.

Ethyl (Z)-4,4,4-Trifluoro-3-{[(S)-1-(hydroxymethyl)-3-(methylsulfanyl)propyl]amino}but-2-enoate (**2c**). IR (neat): 3430, 2980, 2880, 1750, 1630, 1220. ^{1}H-NMR (200 MHz): 1.26 (*t*, *J* = 7, 3 H); 1.75–1.9 (*m*, 2 H); 2.08 (*s*, 3 H); 2.48–2.58 (*m*, 3 H); 3.60–3.75 (*m*, 3 H); 4.13 (*q*, *J* = 7.1, 2 H); 5.11 (*s*, 1 H); 8.21 (*d*, *J* = 9, 1 H). ^{13}C-NMR: 14.6; 15.6; 30.7; 31.2; 55.7; 60.2; 65.2; 86; 120 (*q*, *J*(C,F) = 276); 148 (*q*, *J*(C,F) = 31); 170. ^{19}F-NMR (188 MHz): –69.2. Anal. calc. for $C_{11}H_{18}F_3NO_3S$: C 43.85, H 6.02; found: C 43.86, H 6.10.

Data of **2d**. IR (neat): 3430, 3040, 2960, 2870, 1740, 1630, 1590, 1210. ^{1}H-NMR (200 MHz): 1.27 (*t*, *J* = 7.1, 3 H); 2.89–2.98 (*m*, 2 H); 3.49–3.59 (*m*, 3 H); 3.74–3.76 (*m*, 1 H); 4.15 (*q*, *J* = 7.1, 2 H); 5.11 (*s*, 1 H); 7.12–7.32 (*m*, 5 H); 8.46 (*d*, *J* = 10.7, 1 H). ^{13}C-NMR: 14.7; 39.5; 58.1; 60.3; 63.8; 85.7 (*q*, *J*(C,F) = 5.8); 120.7 (*q*, *J*(C,F) = 277); 127.1; 128.9; 129.8; 138; 148.5 (*q*, *J*(C,F) = 30.8); 170.4. ^{19}F-NMR (188 MHz): –69.3. EI-MS:

317 (1, $M^{+\cdot}$), 226 (49), 180 (89), 138 (27), 91 (100), 77 (15), 65 (30). Anal. calc. for $C_{15}H_{18}F_3NO_3$: C 56.78, H 5.72; found: C 56.79, H 5.73.

*Ethyl (*Z*)-4,4,4-Trifluoro-3-{[(*S*)-1-(hydroxymethyl)-3-methylbutyl]amino}but-2-enoate* (**2e**). IR (neat): 3400, 2960, 2880, 1730, 1630, 1220. ^{1}H-NMR (200 MHz): 0.9 (*d*, *J* = 6.4, 2 H); 0.92 (*d*, *J* = 6.4, 3 H); 1.28 (*t*, *J* = 7, 3 H); 1.42–1.48 (*m*, 2 H); 1.52–1.63 (*m*, 1 H); 1.90 (br. *s*, 1 H); 3.61–3.67 (*m*, 3 H); 4.16 (*q*, *J* = 7, 2 H); 5.12 (*s*, 1 H); 8.12 (*d*, *J* = 11, 1 H). ^{13}C-NMR: 14.7; 22.7; 23.2; 25; 42; 55; 60; 66; 85.7; 120 (*q*, *J*(C,F) = 276); 149 (*q*, *J*(C,F) = 31); 170.4. ^{19}F-NMR (188 MHz): −69.3. Anal. calc. for $C_{12}H_{20}F_3NO_3$: C 50.88, H 7.12; found: C 50.90, H 7.13.

*Ethyl (*Z*)-4,4,4-Trifluoro-3-{[(*S*)-2-hydroxy-1-(methylsulfanyl)methyl]amino}but-2-enoate* (**2f**). IR (neat): 3370, 1740, 1630, 1212. ^{1}H-NMR (200 MHz): 1.22 (*t*, *J* = 7, 3 H); 2.08 (*s*, 3 H); 2.67–2.73 (*m*, 2 H); 3.10 (br. *s*, 1 H); 3.62–3.90 (*m*, 3 H); 4.1 (*q*, *J* = 7, 2 H); 5.08 (*s*, 1 H); 8.42 (*d*, *J* = 10, 1 H). ^{13}C-NMR: 14.5; 16.5; 36.7; 55.5; 60.2; 63.2; 86 (*q*, *J*(C,F) = 5.5), 120 (*q*, *J*(C,F) = 277); 147 (*q*, *J*(C,F) = 31). ^{19}F-NMR (188 MHz): −67.2. EI-MS: 301 (1, $M^{+\cdot}$), 222 (24), 176 (13), 85 (16), 61 (100), 45 (14), 43 (14), 41 (17). Anal. calc. for $C_{10}H_{16}F_3NO_3S$: C 41.81, H 5.61; found: C 41.79, H 5.62.

*Ethyl (*Z*)-4,4,5,5,5-Pentafluoro-3-{[(*S*)-1-(hydroxymethyl)-3-methylbutyl]amino}pent-2-enoate* (**2g**). IR (neat): 3410, 1733, 1632, 1205. ^{1}H-NMR (200 MHz): 0.92 (*d*, *J* = 6.3, 6 H); 1.3 (*t*, *J* = 6.8, 3 H); 1.40–1.55 (*m*, 3 H); 2.0 (br. *s*, 1 H); 3.58–3.71 (*m*, 3 H); 4.19 (*q*, *J* = 6.8, 2 H); 5.13 (*s*, 1 H); 8.24 (*d*, *J* = 12, 1 H). ^{13}C-NMR: 14.4; 22.8; 23.2; 25.2; 42.5; 55.5; 60.3; 65.5; 89.6 (*t*, *J*(C,F) = 8); 111.5 (*tq*, *J*(C,F) = 257, 39); 118.6 (*qt*, *J*(C,F) = 285, 39), 148.7 (*t*, *J*(C,F) = 22); 170. ^{19}F-NMR (188 MHz): −144, −83.6. EI-MS: 333 (6, $M^{+\cdot}$), 246 (21), 214 (92), 188 (18), 84 (20), 83 (100), 55 (57), 43 (47), 41 (38). Anal. calc. for $C_{13}H_{20}F_5NO_3$: C 46.85, H 6.05; found: C 46.86, H 6.03.

*Ethyl (*Z*)-4,4,5,5,5-Pentafluoro-3-{[(*S*)-1-(hydroxymethyl)-2-(methylsulfanyl)ethyl]amino}pent-2-enoate* (**2h**). IR (neat): 3405, 2966, 2880, 1732, 1636, 1215. ^{1}H-NMR (200 MHz): 1.29 (*t*, *J* = 7, 3 H); 2.14 (*s*, 3 H); 2.55 (br. *s*, 1 H); 2.78–2.72 (*m*, 2 H); 3.65–3.95 (*m*, 3 H); 4.18 (*q*, *J* = 7, 2 H); 5.14 (*s*, 1 H); 8.62 (*d*, *J* = 12, 1 H). ^{13}C-NMR: 14.4; 16.5; 36.7; 56; 60.4; 63; 89.7 (*t*, *J*(C,F) = 6); 112 (*tq*, *J*(C,F) = 258, 40); 119 (*qt*, *J*(C,F) = 287, 37); 147 (*t*, *J*(C,F) = 23); 170. ^{19}F-NMR (188 MHz): −114.5, −83.7. EI-MS: 337 (3, $M^{+\cdot}$), 276 (34), 230 (16), 188 (47), 89 (27), 62 (29), 61 (100), 43 (32). Anal. calc. for $C_{11}H_{16}F_5NO_3S$: C 39.17, H 4.78; found: C 39.18, H 4.80.

*Ethyl (*Z*)-4,4,5,5,5-Pentafluoro-3-{[(*S*)-1-(hydroxymethyl)-3-(methylsulfanyl)propyl]amino}pent-2-enoate* (**2i**). IR (neat): 3430, 2984, 2870, 1736, 1630, 1215. ^{1}H-NMR (200 MHz): 1.3 (*t*, *J* = 6.4, 3 H); 1.85–1.97 (*m*, 2 H); 2.12 (*s*, 3 H); 2.51–2.60 (*m*, 2 H); 4.18 (*q*, *J* = 6.4, 2 H); 5.15 (*s*, 1 H); 8.35 (*d*, *J* = 10, 1 H). ^{13}C-NMR: 14.5; 15.5; 30.7; 32.7; 56; 60.3; 65; 89.8 (*t*, *J*(C,F) = 9); 111.5 (*tq*, *J*(C,F) = 287, 39); 148 (*t*, *J*(C,F) = 19); 170. ^{19}F-NMR (188 MHz): −114.3, −83.5. EI-MS: 351 (3, $M^{+\cdot}$), 246 (19), 232 (49), 101 (61), 71 (31), 70 (95), 61 (100), 56 (18), 55 (30), 43 (57), 41 (29). Anal. calc. for $C_{12}H_{18}F_5NO_3S$: C 41.02, H 5.16; found: C 41.01, H 5.17.

*Ethyl (*Z*)-4,4,4-Trifluoro-3-{[(*S*)-1-(hydroxymethyl)-3-methylpentyl]amino}but-2-enoate* (**2j**). IR (neat): 3420, 1735, 1635, 1215. ^{1}H-NMR (200 MHz): 0.95 (*t*, *J* = 7, 3 H); 0.96 (*d*, *J* = 6.4, 3 H); 1.10–1.27 (*m*, 2 H); 1.3 (*t*, *J* = 7, 3 H); 1.53–1.65 (*m*, 3 H); 3.43–3.7 (*m*, 2 H); 3.70 (*d*, *J* = 6, 2 H); 4.19 (*q*, *J* = 7, 2 H); 5.15 (*s*, 1 H); 8.33 (*d*, *J* = 10, 1 H). ^{13}C-NMR: 12; 14.7; 15.7; 25.4; 27.6; 37.5; 60; 61.3; 63.6; 85 (*q*, *J*(C,F) = 5); 120 (*q*, *J*(C,F) = 277); 149 (*q*, *J*(C,F) = 31); 170.5. ^{19}F-NMR (188 MHz): −68.7. Anal. calc. for $C_{13}H_{22}F_3NO_3$: C 52.52, H 7.46; found: C 52.50, H 7.47.

*Ethyl (*Z*)-4,4,4-Trifluoro-3-[(6-hydroxyhexyl)amino]but-2-enoate* (**2k**). IR (neat): 3300, 2945, 1735, 1635. ^{1}H-NMR (200 MHz): 1.22 (*t*, *J* = 7.1, 3 H); 1.32–1.37 (*m*, 4 H); 1.50–1.55 (*m*, 4 H); 2.1 (br. *s*, 1 H); 3.2–3.23 (*m*, 2 H); 3.56 (*t*, *J* = 6.4, 2 H); 4.09 (*q*, *J* = 7.1, 2 H); 5.01 (*s*, 1 H); 8.13 (br. *s*, 1 H). ^{13}C-NMR: 14.7; 26; 26.8; 31; 33; 44.4; 60.1; 62.8; 84.3 (*q*, *J*(C,F) = 6); 120.7 (*q*, *J*(C,F) = 277); 149 (*q*, *J*(C,F) = 31); 170.6. ^{19}F-NMR (188 MHz): −70.4. EI-MS: 283 (9, $M^{+\cdot}$), 238 (27), 198 (16), 196 (32), 184 (19), 168 (24), 150 (100), 138 (32), 99 (43), 81 (36), 55 (53), 41 (45). Anal. calc. for $C_{12}H_{20}F_3NO_3$: C 50.88, H 7.12; found: C 50.89, H 7.10.

*Ethyl (*Z*)-4,4,4-Trifluoro-3-[(4-hydroxybutyl)amino]but-2-enoate* (**2l**). IR (neat): 3300, 2950, 1710, 1635. ^{1}H-NMR (200 MHz): 1.17 (*t*, *J* = 7.1, 3 H); 1.56 (*m*, 4 H); 3.03 (br. *s*, 1 H); 3.23 (br. *t*, *J* = 6, 2 H); 3.55 (*t*, *J* = 6, 2 H); 4.04 (*q*, *J* = 7.1, 2 H); 4.97 (*s*, 1 H); 8.08 (br. *s*, 1 H). ^{13}C-NMR: 14; 26.7; 29.3; 43.6; 59.7; 61.6; 83.8 (*q*, *J*(C,F) = 5.8); 120 (*q*, *J*(C,F) = 277); 148.4 (*q*, *J*(C,F) = 31), 170. ^{19}F-NMR (188 MHz): −70.3. EI-MS: 255 (21, $M^{+\cdot}$), 210 (12), 196 (28), 168 (23), 164 (29), 150 (100), 138 (36), 71 (55). Anal. calc. for $C_{10}H_{16}F_3NO_3$: C 47.06, H 6.32; found: C 47.04, H 6.34.

*Ethyl (*E*)-3-{[(*S*)-1-Benzyl-2-hydroxyethyl](methyl)amino}but-2-enoate* (**2m**). IR (neat): 3450, 3050, 2980, 2870, 1750, 1630, 1580, 1215. ^{1}H-NMR (200 MHz): 1.30 (*t*, *J* = 7.2, 3 H); 2.79 (*s*, 3 H); 2.90 (*s*, 1 H); 2.87–2.97 (*m*, 2 H); 3.31–3.46 (*m*, 2 H); 3.73–3.85 (*m*, 1 H); 4.16 (*q*, *J* = 7.2, 2 H); 5 (*s*, 1 H); 7.19–7.33 (*m*, 5 H). ^{13}C-NMR: 14.5; 34.2; 35.8; 59; 60.8; 61.5; 86.3; 120 (*q*, *J*(C,F) = 277); 127; 129 (2 C); 129.5 (2 C); 138.3; 147

(q, J(C,F) = 32); 166. ^{19}F-NMR (188 MHz): – 62. EI-MS: 300 (30, [M – 31]$^{+\cdot}$), 254 (61), 180 (15), 150 (72), 149 (28), 121 (29), 91 (100), 45 (78). Anal. calc. for $C_{16}H_{20}F_3NO_3$: C 58.00, H 6.08; found: C 58.08, H 6.1.

*Ethyl (*E*)-4,4,4-Trifluoro-3-[[(*S*)-1-(hydroxymethyl)-3-methylbutyl](methyl)amino]but-2-enoate* (**2n**). IR (neat): 3440, 2970, 2890, 1760, 1620, 1210. ^{1}H-NMR (200 MHz): 0.90 (d, J = 6.3, 3 H); 0.93 (d, J = 6.3, 3 H); 1.27 (t, J = 7.2, 3 H); 1.29 – 1.34 (m, 3 H); 2.72 (s, 3 H); 3.53 – 3.57 (m, 4 H); 4.15 (q, J = 7.2, 2 H); 5.46 (s, 1 H). ^{13}C-NMR: 14.7; 22.5; 23.3; 25.3; 34.1; 55.2; 60.1; 66.4; 86; 120 (q, J(C,F) = 277); 148.8 (q, J(C,F) = 30), 170. ^{19}F-NMR (188 MHz): – 66.7. EI-MS: 297 (1, $M^{+\cdot}$), 240 (11), 228 (100), 211 (23), 152 (73), 55 (31), 43 (47), 41 (70). Anal. calc. for $C_{13}H_{22}F_3NO_3$: C 52.52, H 7.46; found: C 52.50, H 7.45.

*Ethyl (*E*)-4,4,4-Trifluoro-3-[[(*S*)-1-(hydroxymethyl)-2-methylpropyl](methyl)amino]but-2-enoate* (**2o**). IR (neat): 3440, 2980, 2890, 1740, 1620, 1220. ^{1}H-NMR (200 MHz): 0.90 (d, J = 6.6, 3 H); 0.94 (d, J = 6.6, 3 H); 1.26 (t, J = 7, 3 H); 1.70 – 2.0 (m, 2 H); 2.72 (s, 3 H); 3.21 – 3.37 (m, 1 H); 3.50 – 3.70 (m, 2 H); 4.15 (q, J = 7, 2 H); 5.41 (s, 1 H). ^{13}C-NMR: 14.4; 19.6; 27; 37.4; 61; 61.7; 67; 89; 125 (q, J(C,F) = 280); 149 (t, J(C,F) = 30); 168. ^{19}F-NMR (188 MHz): – 76.2. EI-MS: 282 (18, [M – 1]$^{+\cdot}$), 264 (41), 240 (29), 196 (100), 43 (37), 42 (69), 41 (49). Anal. calc. for $C_{12}H_{20}F_3NO_3$: C 50.88, H 7.12; found: C 50.87, H 7.13.

*Typical Procedure: Preparation of (*S*)-3-Benzyl-3,4-dihydro-5-(trifluoromethyl)-2*H*-[1,4]oxazepin-7-one* (**3d**). NaH (100.8 mg, 4.2 mmol) under N_2 was added to a soln. of **2d** (650 mg, 2 mmol) in toluene (10 ml) at 0°. The mixture was heated to 80° for 4 h. After cooling, the mixture was hydrolyzed with 0.1M HCl and extracted with CH_2Cl_2. The org. layer was washed with H_2O, dried ($MgSO_4$), and concentrated under vacuum. The residue was chromatographed (SiO_2; petroleum ether/Et_2O 50 : 50) to yield **3d** (444 mg, 82%).

*3,4-Dihydro-5-(trifluoromethyl)-2*H*-[1,4]oxazepin-7-one* (**3a**). IR (neat): 3304, 2962, 1664, 1635, 1200. ^{1}H-NMR (200 MHz, (D_6)acetone): 3.72 (t, J = 3.7, 1 H); 3.74 (t, J = 3.7, 1 H); 4.41 (br. t, J = 3.7, 1 H); 4.90 (d, J = 1.9, 1 H); 7.41 (br. s, 1 H). ^{13}C-NMR ((D_6)acetone): 47; 65.8; 86.3 (q, J(C,F) = 4); 121.8 (q, J(C,F) = 276); 142.3 (q, J(C,F) = 31); 168.4. ^{19}F-NMR ((D_6)acetone, 188 MHz): – 72.6. EI-MS: 181 (9, $M^{+\cdot}$), 151 (36), 124 (52), 123 (64), 54 (100), 69 (21). Anal. calc. for $C_6H_6F_3NO_2$: C 39.79, H 3.34; found: C 39.80, H 3.35.

*5,6,7,8-Tetrahydro-4-(trifluoromethyl)-2*H*-[1,5]oxazocin-2-one* (**3b**). IR (neat): 3275, 2979, 1737, 1636, 1202. ^{1}H-NMR (200 MHz): 1.73 – 1.93 (m, 2 H); 3.40 (dt, J = 11, 6, 2 H); 4.41 (t, J = 6, 2 H); 4.88 (d, J = 1.3, 1 H); 5.39 (br. s, 1 H). ^{13}C-NMR: 29.6; 39.4; 65.4; 84.4; 120.6 (q, J(C,F) = 277); 143 (q, J(C,F) = 31), 169. ^{19}F-NMR (188 MHz): – 73. EI-MS: 195 (26, $M^{+\cdot}$), 139 (19), 137 (21), 126 (30), 124 (19), 111 (15), 69 (16), 68 (100), 43 (15), 42 (24), 39 (16). Anal. calc. for $C_7H_8F_3NO_2$: C 43.08, H 4.13; found: C 43.10, H 4.14.

*(*S*)-3,4-Dihydro-3-[2-(methylsulfanyl)ethyl]-5-(trifluoromethyl)-2*H*-[1,4]oxazepin-7-one* (**3c**). IR (neat): 3375, 2982, 1692, 1632, 1207. ^{1}H-NMR (200 MHz): 2.0 (q, J = 6.5, 2 H); 2.17 (s, 3 H); 2.70 (t, J = 6.5, 2 H); 3.98 – 4.10 (m, 1 H); 4.40 (d, J = 4, 2 H); 5.23 (d, J = 2.2, 1 H); 5.90 (br. s, 1 H). ^{13}C-NMR: 16; 28.8; 30.8; 56; 68; 88 (q, J(C,F) = 3); 120.4 (q, J(C,F) = 277); 141 (q, J(C,F) = 32); 169. ^{19}F-NMR (188 MHz): – 70. Anal. calc. for $C_9H_{12}F_3NO_2S$: C 42.35, H 4.74; found: C 42.34, H 4.75.

*(*S*)-3-Benzyl-3,4-dihydro-5-(trifluoromethyl)-2*H*-[1,4]oxazepin-7-one* (**3d**). IR (neat): 3280, 1670, 1630. ^{1}H-NMR (200 MHz): 2.85 – 3.07 (m, 2 H); 3.98 (tt, J = 7, 4, 1 H); 4.26 – 4.43 (m, 2 H); 5.16 (d, J = 2.1, 1 H); 5.94 (br. s, 1 H); 7.22 – 7.42 (m, 5 H). ^{13}C-NMR: 36.3; 57.4; 77; 86.3 (q, J(C,F) = 3); 120.7 (q, J(C,F) = 278); 127.3; 128.9 (2 C); 129.1 (2 C); 135.6; 141.4 (q, J(C,F) = 32); 169.1. ^{19}F-NMR (188 MHz): – 72.6. EI-MS: 271 (24, $M^{+\cdot}$), 180 (41), 152 (15), 138 (19), 92 (26), 91 (100). Anal. calc. for $C_{13}H_{12}F_3NO_2$: C 57.57, H 4.46; found: C 57.56, H 4.47.

*(*S*)-3,4-Dihydro-3-(2-methylpropyl)-5-(trifluoromethyl)-2*H*-[1,4]oxazepin-7-one* (**3e**). IR (neat): 3372, 2979, 2869, 1688, 1630, 1203. ^{1}H-NMR (200 MHz): 1.01 (d, J = 6.5, 3 H); 1.03 (d, J = 6.5, 3 H); 1.55 (dd, J = 7.3, 7, 2 H); 1.64 – 1.77 (m, 1 H); 3.73 – 3.79 (m, 1 H); 4.35 (d, J = 4.4, 2 H); 5.19 (br. s, 1 H); 5.24 (br. s, NH). ^{13}C-NMR: 22.8; 23.1; 25; 55.1; 69; 83.3; 121.5 (q, J(C,F) = 277); 142 (q, J(C,F) = 32); 170. ^{19}F-NMR (188 MHz): – 70. MS: 237 (8, $M^{+\cdot}$), 181 (14), 151 (61), 69 (15), 57 (16), 43 (87), 41 (100), 39 (55). Anal. calc. for $C_{10}H_{14}F_3NO_2$: C 50.63, H 5.95; found: C 50.64, H 5.97.

*(*S*)-3,4-Dihydro-3-[(methylsulfanyl)methyl]-5-(trifluoromethyl)-2*H*-[1,4]oxazepin-7-one* (**3f**). IR (neat): 3388, 2979, 1690, 1630, 1207. ^{1}H-NMR (200 MHz): 2.18 (s, 3 H); 2.65 (dd, J = 14, 9, 1 H); 2.88 (dd, J = 14, 5.4, 1 H); 3.83 – 3.87 (m, 1 H); 4.30 – 4.45 (m, 2 H); 5.20 (d, J = 2, 1 H); 6.0 (br. s, 1 H). ^{13}C-NMR: 15.7; 35; 54.6; 68; 87.3; 121.2 (q, J(C,F) = 278); 142 (q, J(C,F) = 32), 169. ^{19}F-NMR (188 MHz): – 70.3. Anal. calc. for $C_8H_{10}F_3NO_2S$: C 39.83, H 4.18; found: C 39.84, H 4.20.

*(*S*)-3,4-Dihydro-3-(2-methylpropyl)-5-(1,1,2,2,2-pentafluoroethyl)-2*H*-[1,4]oxazepin-7-one* (**3g**). M.p. 77°. IR (KBr): 3370, 2980, 2870, 1690, 1629, 1206. ^{1}H-NMR (200 MHz): 0.95 (d, J = 6.4, 6 H); 1.44 – 1.77 (m, 3 H); 3.80 – 3.84 (m, 1 H); 4.30 (d, J = 4.5, 2 H); 5.02 (br. s, 1 H); 6.14 (br. s, 1 H). ^{13}C-NMR: 22.5; 23; 25; 39; 55; 69; 88; 112 (tq, J(C,F) = 260, 38); 118.7 (qt, J(C,F) = 286, 38); 141 (t, J(C,F) = 22); 169. ^{19}F-NMR (188 MHz): – 121,

– 84.4. MS: 287 (13, $M^{+\cdot}$), 231 (42), 214 (37), 201 (100), 132 (25), 57 (19), 43 (78). Anal. calc. for $C_{11}H_{14}F_5NO_2$: C 46.00, H 4.91; found: C 46.08, H 4.96.

(S)-3,4-Dihydro-3-[(methylsulfanyl)methyl]-5-(1,1,2,2,2-pentafluoroethyl)-2H-[1,4]oxazepin-7-one (**3h**). IR (neat): 3341, 2977, 2874, 1686, 1628, 1204. ^{1}H-NMR (200 MHz): 2.14 (*s*, 3 H); 2.58 (*dd*, *J* = 13.8, 9.3, 1 H); 2.85 (*dd*, *J* = 13.8, 5, 1 H); 3.82 – 3.88 (*m*, 1 H); 4.31 – 4.48 (*m*, 2 H); 5.05 (*s*, 1 H); 6.31 (br. *s*, 1 H). ^{13}C-NMR: 15.5; 34.7; 54.7; 68; 89; 111 (*tq*, *J*(C,F) = 260, 39); 119 (*qt*, *J*(C,F) = 287, 39); 140.6 (*t*, *J*(C,F) = 23); 168.5. ^{19}F-NMR (188 MHz): – 120.8, – 84.4. EI-MS: 291 (7, $M^{+\cdot}$), 244 (9), 103 (6), 62 (21), 61 (100). Anal. calc. for $C_9H_{10}F_5NO_2S$: C 37.12, H 3.46; found: C 37.10, H 3.47.

(S)-3,4-Dihydro-3-[2-(methylsulfanyl)ethyl]-5-(1,1,2,2,2-pentafluoroethyl)-2H-[1,4]oxazepin-7-one (**3i**). M.p. 74°. IR (KBr): 3432, 3054, 2986, 1689, 1629, 1542, 1265, 1203. ^{1}H-NMR (200 MHz): 1.95 (*dt*, *J* = 8, 7, 2 H); 2.13 (*s*, 3 H); 2.64 (*t*, *J* = 7, 2 H); 3.97 – 4.03 (*m*, 1 H); 4.38 (*d*, *J* = 4, 2 H); 5.09 (br. *s*, 1 H); 6.34 (br. *s*, 1 H). ^{13}C-NMR: 15.6; 28.5; 30.5; 55.8; 68; 88.7 (*t*, *J*(C,F) = 9), 111 (*tq*, *J*(C,F) = 259, 39); 118.6 (*qt*, *J*(C,F) = 287, 39); 140.7 (*t*, *J*(C,F) = 23); 169. ^{19}F-NMR (188 MHz): – 120.7; – 84.3. EI-MS: 305 (1, $M^{+\cdot}$), 231 (16), 212 (23), 188 (16), 132 (18), 100 (45), 75 (47), 61 (100), 41 (47). Anal. calc. for $C_{10}H_{12}F_5NO_2S$: C 39.35, H 3.96; found: C 39.36, H 3.97.

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