A Straightforward Approach towards Functionalized γ-Hydroxy and Heterocyclic Amino Acids

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Abstract: Regioselective ring opening of epoxides by chelated enolates in combination with Dess–Martin oxidation provides a straightforward approach towards γ-oxo amino acids, which are ideal substrates for carbonyl additions and the synthesis of heterocycles.

Key words: amino acids, chelated enolates, epoxides, epoxide openings, γ-hydroxy amino acids, γ-oxo amino acids

Hydroxylated amino acids are important building blocks found also in proteins, resulting from post-translational modification. γ-Hydroxyproline (Hyp) is widespread in collagen and is involved in the stabilization of the collagen triple helix.[1] γ-Hydroxyarginine occurs in proteins forming adhesive plaques of marine mussels,[2] and γ-hydroxyvaline is incorporated in several conopeptides from the venoms of *Conus gladiator* and *Conus mus*.[3] Other γ-hydroxylated amino acids are found in natural products such as biphenomycin[4] und glidobactine.[5] The occurrence of these γ-hydroxy acids in nature is not obvious, since the γ-hydroxy group can easily undergo lactonization, resulting in a cleavage of the peptide bond. For example, the lactone of *N*-acetyl-γ-hydroxyvaline was found in *streptomycetes* in marine sediments.[6] Not surprisingly, such γ-lactones form the C-terminus of natural products.[7] The γ-hydroxy group can also be incorporated in heterocyclic structures such as in dysiherbaine[8] or lycoperdic acid,[9] (Figure 1) glutamate-derived natural products with strong agonist activity at the ionotropic glutamate receptors (iGluRs) of the central nervous system.[10] In these cases, the γ-hydroxy group is located at a quaternary center. Therefore, straightforward synthetic protocols towards these types of interesting γ-hydroxy amino acids are highly desirable.

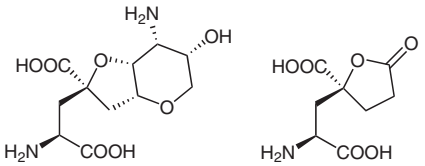

Figure 1 Heterocyclic natural products derived from γ-hydroxy amino acids

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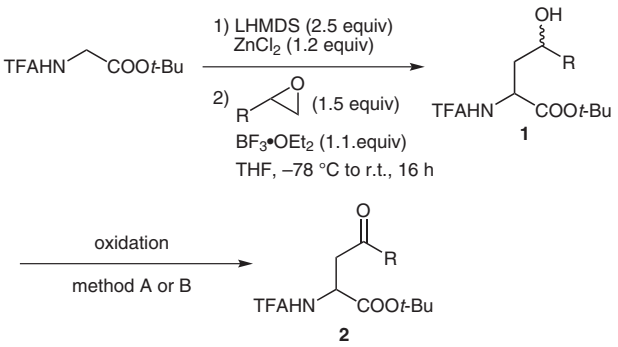
Our group is involved in amino acid synthesis since almost two decades, investigating reactions of chelated amino acid ester enolates.[11] These enolates are excellent nucleophiles for a wide range of reactions such as Claisen rearrangements,[12] transition-metal-catalyzed allylic alkylations[13] or epoxide openings.[14] The last approach is especially suitable for the synthesis of γ-hydroxy amino acids, and the substitution pattern depends on the structure of the epoxide used. While aryl-substituted epoxides react preferentially at the benzylic position giving rise to the terminal primary alcohols,[14b] the corresponding alkyl-substituted epoxides provide secondary alcohols **1** via nucleophilic attack of the enolate at the sterically least hindered position.[14a]

These alcohols can easily be oxidized by Swern oxidation[15] or using the Dess–Martin periodinane (DMP)[16] to γ-oxo amino acids (Table 1). In principle both protocols are suitable for oxidation, but in general the yields obtained were better with the Dess–Martin period-

Table 1 Synthesis of γ-Keto Amino Acids **2**



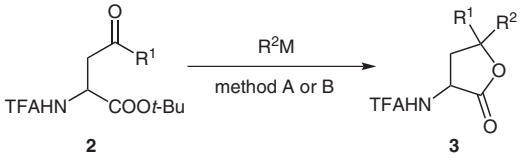
1	R	Yield (%) of 1	2	Yield (%) of 2 A[a]	Yield (%) of 2 B[b]
1a	Me	92[14a]	**2a**	78	91
1b	Bu	86[14a]	**2b**	81	89
1c	CH_2Cl	82[14a]	**2c**	75	90
1d	CH_2OPh	86[14a]	**2d**	76	93
1e	$CH_2O(C_6H_4Cl\text{-}4)$	88	**2e**	72	82
1f	$CH_2O(C_6H_4CN\text{-}2)$	85	**2f**	76	84
1g	$CH_2O(C_6H_4NO_2\text{-}2)$	84	**2g**	75	87

[a] Method A: Swern oxidation.
[b] Method B: DMP oxidation.

inane (82–93%), while under Swern conditions the yields were in the range of 75 ± 3%.

These γ-oxo amino acids can be easily converted into a wide range of highly functionalized quarternary γ-hydroxy amino acids by simple carbonyl addition (Table 2). In our first instance, we investigated Barbier reactions using allyl bromide as a nucleophile precursor (method A). Interestingly, not the expected γ-hydroxy amino acid ester was formed, but directly the lactone, although the relatively stable *tert*-butyl ester was used. Probably, the zinc(II) bromide formed in situ acts as a strong Lewis acid, catalyzing the lactonization process. Even with the chloromethyl-substituted ketone **2c** (Table 2, entry 3) only the lactone was formed and no epoxide, which was actually expected. The yields were acceptable and reproducible in the range of 60–70%, but unfortunately no significant diastereoselectivity was observed. Similar results were obtained in methylation reactions (method B) using trimethylaluminum. In the presence of zinc(II) chloride, the lactone was formed here also exclusively.

Table 2 Synthesis of α-Amino-γ-Butyrolactones **3**

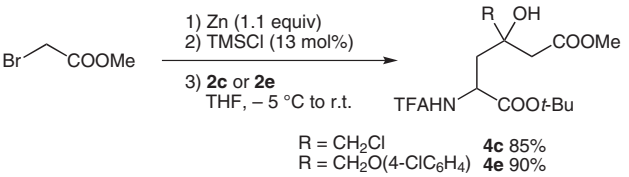


Entry	2	R^1	R^2	Method	3	Yield (%)
1	**2a**	Me	allyl	A[a]	**3a**	70
2	**2b**	Bu	allyl	A[a]	**3b**	65
3	**2c**	CH_2Cl	allyl	A[a]	**3c**	64
4	**2d**	CH_2OPh	allyl	A[a]	**3d**	60
5	**2e**	$CH_2O(C_6H_4Cl\text{-}4)$	allyl	A[a]	**3e**	66
6	**2a**	Me	Me	B[b]	**3f**	60
7	**2c**	CH_2Cl	Me	B[b]	**3g**	66
8	**2d**	CH_2OPh	Me	B[b]	**3h**	60
9	**2e**	$CH_2O(C_6H_4Cl\text{-}4)$	Me	B[b]	**3i**	58
10	**2f**	$CH_2O(C_6H_4CN\text{-}2)$	Me	B[b]	**3k**	66

[a] Method A: allyl bromide (1.0 equiv), Zn (2.0 equiv), THF, r.t., 1 h.
[b] Method B: Me_3Al (2.0 equiv), $ZnCl_2$ (1.3 equiv), THF, 0 °C to r.t., 3 h.

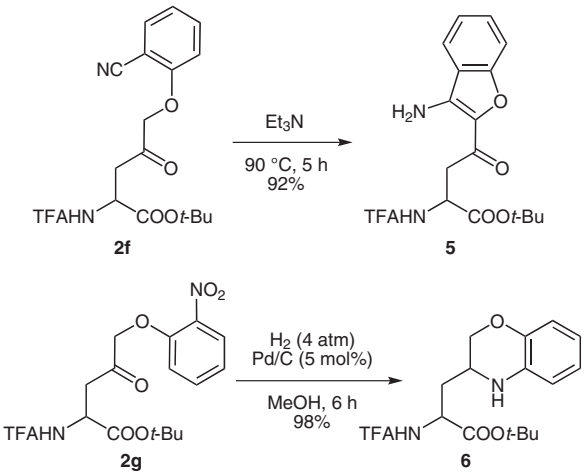
Interestingly, no cyclization was observed in the corresponding Reformatsky reactions. The reaction mixtures were allowed to warm up to room temperature (from –5 °C) overnight, and the required γ-hydroxy homoglutamates **4** were obtained in high yields as 1:1 diastereomeric mixtures (Scheme 1).

Finally, the use of γ-keto amino acid derivatives **2** for the synthesis of heterocyclic amino acids was investigated. The cyano- and nitro-substituted derivatives **2f** and **2g** are



Scheme 1 Synthesis of γ-hydroxy homoglutamates **4**

especially good candidates for this purpose. The benzofuran derivative **5** was obtained from **2f** by simple heating in the presence of triethylamine.[17] The nitro group in **2g** could be reduced by catalytic hydrogenation, which directly results in a reductive amination and the formation of dihydrobenzoxazine amino acid **6** in almost quantitative yield[18] (Scheme 2).



Scheme 2 Synthesis of heterocyclic amino acids

In conclusion we could show that γ-oxo amino acids, resulting from an epoxide opening/oxidation sequence, are excellent starting materials for subsequent modifications. Addition of organometallics allows the introduction of a range of other functionalities, and intramolecular cyclizations of functionalized aryl ethers are suitable for the synthesis of heterocyclic amino acids. Further investigations on the scope and limitations of this protocol and synthetic applications are on the way.

All reactions were carried out in oven-dried glassware (100 °C) under N_2. All solvents were dried before use. THF was distilled from $LiAlH_4$. The products were purified by flash chromatography on silica gel (0.063–0.2 mm). Mixtures of EtOAc and hexanes were generally used as eluents. Analysis by TLC was carried out on commercially precoated Polygram SIL-G/UV 254 plates (Macherey-Nagel, Düren). Visualization was accomplished with UV light, $KMnO_4$ solution, or I_2. ^1H and ^{13}C NMR spectroscopic analyses were performed on a Bruker Avance II 400 MHz spectrometer. Chemical shifts are reported on the δ (ppm) scale and the coupling constants are given in Hz. The epoxide openings and carbonyl additions proceed without significant diastereoselectivity and therefore the relative configuration was not determined. Selected signals for the minor isomers are extracted from the spectra of the isomeric mixture and are those signals, which could be clearly assigned. HRMS were measured with Finnigan MAT 95S mass spectrometer.

Elemental analyses were carried out at the Department of Chemistry, Saarland University, Saarbrücken, Germany.

Epoxide Opening with Amino Acid Enolates; General Procedure

In a Schlenk tube hexamethyldisilazane (497 mg, 3.08 mmol, 2.8 equiv) was dissolved in anhyd THF (5.0 mL). After cooling the solution to –78 °C, a 1.6 M solution of *n*-BuLi (1.72 mL, 2.75 mmol, 2.5 equiv) was added slowly. The solution was stirred for 10 min before the cooling bath was removed and the solution was stirred for a further 10 min. In a second Schlenk flask, $ZnCl_2$ (180 mg, 1.32 mmol, 1.2 equiv) was dried with a heat gun under vacuum and dissolved in THF (5.0 mL). After cooling the solution to r.t., TFA-Gly-O*t*-Bu (250 mg, 1.1 mmol, 1 equiv) was added and cooled to –78 °C before the LHMDS solution was added slowly. The resulting solution was stirred for 30 min at –78 °C. Then the epoxide (2.0 equiv) was added followed by $BF_3{\cdot}OEt_2$ (78.1 mg, 0.55 mmol, 0.5 equiv) directly to the enolate at –78 °C. The reaction mixture was allowed to warm to r.t. overnight before it was hydrolyzed with aq 1 M HCl (15 mL) and extracted with EtOAc (3 × 20 mL). The combined organic layers were dried (Na_2SO_4), the solvent was evaporated in vacuo, and the crude product was purified by flash chromatography (silica gel, hexanes–EtOAc) (Table 1).

tert-Butyl 5-(4-Chlorophenoxy)-4-hydroxy-2-(2,2,2-trifluoroacetamido)pentanoate (1e)

Colorless oil; yield: 399 mg (0.97 mmol, 88%); R_f = 0.32 (CH_2Cl_2–hexanes, 95:5).

^{1}H NMR (400 MHz, $CDCl_3$): δ [major diastereomer (55%)] = 7.77 (d, *J* = 7.0 Hz, 1 H), 6.83–6.85 (m, 4 H), 4.73 (dt, *J* = 7.4, 4.5 Hz, 1 H), 4.10 (m, 1 H), 3.79–3.93 (m, 2 H), 3.11 (d, *J* = 3.3 Hz, 1 H), 2.03–2.13 (m, 2 H), 1.49 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ [major diastereomer (55%)] = 171.5, 157.4 (q, *J* = 37.4 Hz), 152.2, 130.0, 129.0, 115.7 (q, *J* = 285.6 Hz), 115.4, 114.9, 83.4, 72.6, 65.5, 55.8, 51.2, 27.9.

^{1}H NMR (400 MHz, $CDCl_3$): δ [minor diastereomer (45%), selected signals] = 7.44 (s, 1 H), 4.53 (q, *J* = 5.9 Hz, 1 H), 4.10 (m, 1 H), 2.22 (m, 1 H), 1.49 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ [minor diastereomer (45%), selected signals] = 171.3, 152.1, 129.9, 129.0, 115.5, 114.7, 83.4, 72.6, 65.5, 55.6, 51.2, 27.8.

HRMS (CI): *m*/*z* $[M]^+$ calcd for $C_{17}H_{21}ClF_3NO_5$: 411.1060; found: 411.1075.

tert-Butyl 5-(2-Cyanophenoxy)-4-hydroxy-2-(2,2,2-trifluoroacetamido)pentanoate (1f)

Colorless oil; yield: 376 mg (0.94 mmol, 85%); R_f = 0.31 (CH_2Cl_2–hexanes, 95:5).

^{1}H NMR (400 MHz, $CDCl_3$): δ [major diastereomer (57%)] = 7.68 (d, *J* = 7.5 Hz, 1 H), 7.52–7.58 (m, 2 H), 7.05 (t, *J* = 7.5 Hz, 1 H), 6.97 (m, 1 H), 4.74 (m, 1 H), 4.18–4.24 (m, 2 H), 3.99 (m, 1 H), 3.34 (d, *J* = 4.0 Hz, 1 H), 2.08–2.13 (m, 2 H), 1.50 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ [major diastereomer (57%)] = 168.0, 157.2 (q, *J* = 37.4 Hz), 134.4, 134.1, 122.2, 115.5 (q, *J* = 285.8 Hz), 114.8, 112.1, 102.6, 83.9, 72.7, 48.8, 40.3, 27.7.

^{1}H NMR (400 MHz, $CDCl_3$): δ [minor diastereomer (43%), selected signals] = 7.42 (d, *J* = 5.8 Hz, 1 H), 4.55 (dt, *J* = 5.7, 5.7 Hz, 1 H), 4.21–4.18 (m, 2 H), 2.66 (d, *J* = 4.5 Hz, 1 H), 2.32 (ddd, *J* = 14.5, 5.7, 3.2 Hz, 1 H), 2.18 (m, 1 H), 1.50 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ [minor diastereomer (43%), selected signals] = 168.5, 122.2, 114.8, 112.1, 102.6, 83.6, 72.7, 48.8, 40.4, 27.8.

HRMS (CI): *m*/*z* $[M + 1]^+$ calcd for $C_{18}H_{21}F_3N_2O_5$: 403.1436; found: 403.1482.

tert-Butyl 4-Hydroxy-5-(2-nitrophenoxy)-2-(2,2,2-trifluoroacetamido)pentanoate (1g)

Colorless oil; yield: 390 mg (0.92 mmol, 84%); R_f = 0.31 (CH_2Cl_2–hexanes, 95:5).

^{1}H NMR (400 MHz, $CDCl_3$): δ [major diastereomer (66%)] = 7.87 (dd, *J* = 8.5, 1.7 Hz, 1 H), 7.81 (d, *J* = 7.5 Hz, 1 H), 7.54 (m, 1 H), 7.01–7.06 (m, 2 H), 4.53 (q, *J* = 5.7 Hz, 1 H), 4.13–4.18 (m, 2 H), 4.03 (m, 1 H), 2.91 (d, *J* = 4.9 Hz, 1 H), 2.04–2.16 (m, 2 H), 1.49 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ [major diastereomer (66%)] = 169.1, 157.4 (q, *J* = 37.4 Hz), 151.8, 139.8, 134.4, 125.9, 121.3, 115.7 (q, *J* = 285.6 Hz), 115.1, 83.5, 73.2, 67.1, 51.1, 34.2, 27.8.

^{1}H NMR (400 MHz, $CDCl_3$): δ [minor diastereomer (34%), selected signals] = 7.87 (dd, *J* = 8.1, 1.7 Hz, 1 H), 7.55 (m, 1 H), 7.81 (d, *J* = 7.3 Hz, 1 H), 7.05–7.11 (m, 2 H), 4.72 (dt, *J* = 7.4, 4.2 Hz, 1 H), 4.11–4.18 (m, 2 H), 4.03 (m, 1 H), 3.52 (d, *J* = 2.5 Hz, 1 H), 2.30 (ddd, *J* = 14.5, 5.6, 2.9 Hz, 1 H), 2.10 (ddd, *J* = 14.6, 9.6, 5.4 Hz, 1 H), 1.51 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ [minor diastereomer (34%), selected signals] = 169.3, 151.9, 134.5, 126.0, 121.3, 115.0, 83.6, 73.2, 66.7, 51.4, 33.6, 27.8.

HRMS (CI): *m*/*z* $[M]^+$ calcd for $C_{17}H_{21}F_3N_2O_7$: 423.1334; found: 423.1413.

Dess–Martin Oxidation; General Procedure

To a solution of the corresponding γ-hydroxy amino acid ester **1** (1.32 mmol) in anhyd CH_2Cl_2 (5 mL) was added Dess–Martin periodinane (721 mg, 1.7 mmol) at 0 °C under N_2 and the mixture was allowed to stir at r.t. for 3 h. After quenching the reaction with sat. aq $NaHCO_3$ containing $Na_2S_2O_3$ (10 mL), the mixture was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were washed with brine (10 mL), dried (Na_2SO_4), and the solvent removed in vacuo. The corresponding γ-keto amino acid ester **2** was obtained after column chromatography (silica gel, EtOAc–hexanes) (Table 1).

tert-Butyl 4-Oxo-2-(2,2,2-trifluoroacetamido)pentanoate (2a)

Colorless oil; yield: 340 mg (1.20 mmol, 89%); R_f = 0.53 (hexanes–EtOAc, 75:25).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.37 (br s, 1 H), 4.59 (dt, *J* = 7.8, 3.8 Hz, 1 H), 3.22 (dd, *J* = 18.6, 4.0 Hz, 1 H), 3.97 (dd, *J* = 18.6, 4.0 Hz, 1 H), 2.10 (s, 3 H), 1.43 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 206.1, 168.0, 156.8 (q, *J* = 37.4 Hz), 115.5 (q, *J* = 285.6 Hz), 83.4, 49.0, 43.5, 29.7, 27.6.

HRMS (CI): *m*/*z* $[M + 1]^+$ calcd for $C_{11}H_{16}F_3NO_4$: 284.1065; found: 284.1080.

tert-Butyl 4-Oxo-2-(2,2,2-trifluoroacetamido)octanoate (2b)

Colorless oil; yield: 382 mg (1.17 mmol, 89%); R_f = 0.53 (hexanes–EtOAc, 75:25)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.38 (br s, 1 H), 4.61 (dt, *J* = 7.9, 3.9 Hz, 1 H), 3.22 (dd, *J* = 18.4, 3.9 Hz, 1 H), 2.94 (dd, *J* = 18.4, 3.9 Hz, 1 H), 2.41 (dt, *J* = 7.4, 2.6 Hz, 2 H), 1.50–1.58 (m, 2 H), 1.43 (s, 9 H), 1.29 (sext, *J* = 7.3 Hz, 2 H), 0.89 (t, *J* = 7.3 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 208.9, 168.1, 156.8 (q, *J* = 37.4 Hz), 115.6 (q, *J* = 285.6 Hz), 83.3, 49.1, 42.9, 42.3, 27.7, 25.6, 22.1, 13.8.

HRMS (CI): *m*/*z* $[M + 1]^+$ calcd for $C_{14}H_{22}F_3NO_4$: 325.1501; found: 325.1512.

***tert*-Butyl 5-Chloro-4-oxo-2-(2,2,2-trifluoroacetamido)pentanoate (2c)**

White solid; yield: 377 mg (1.18 mmol, 90%); mp 51–52 °C; R_f = 0.50 (hexanes–EtOAc, 75:25).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.29 (br s, 1 H), 4.69 (dt, *J* = 8.0, 4.2 Hz, 1 H), 3.24 (dd, *J* = 18.6, 4.2 Hz, 1 H), 3.19 (dd, *J* = 18.8, 4.4 Hz, 1 H), 2.17 (d, *J* = 2.8 Hz, 2 H), 1.45 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 200.7, 167.7, 157.1 (q, *J* = 37.7 Hz), 118.3 (q, *J* = 285.8 Hz), 84.0, 49.0, 47.4, 40.5, 27.7.

HRMS (CI): *m*/*z* [M]$^+$calcd for $C_{11}H_{15}ClF_3NO_4$: 317.0642; found: 317.0764.

***tert*-Butyl 4-Oxo-5-phenoxy-2-(2,2,2-trifluoroacetamido)pentanoate (2d)**

White solid; yield: 461 mg (1.23 mmol, 93%); mp 57–58 °C; R_f = 0.55 (hexanes–EtOAc, 7:3).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.29–7.33 (m, 2 H), 7.02 (t, *J* = 7.6 Hz, 1 H), 6.86–6.88 (m, 2 H), 4.73 (dt, *J* = 7.6, 4.3 Hz, 1 H), 4.57 (d, *J* = 1.2 Hz, 2 H), 3.21 (dd, *J* = 18.8, 4.4 Hz, 1 H), 3.42 (dd, *J* = 18.8, 4.4 Hz, 1 H), 1.45 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 205.9, 168.0, 157.3 157.2 (q, *J* = 37.4 Hz), 129.7, 122.1, 115.5 (q, *J* = 289.0 Hz), 114.4, 83.7, 72.5, 48.7, 40.4, 27.7.

HRMS (CI): *m*/*z* [M]$^+$ calcd for $C_{17}H_{20}F_3NO_5$: 375.1294; found: 375.1289.

***tert*-Butyl 5-(4-Chlorophenoxy)-4-oxo-2-(2,2,2-trifluoroacetamido)pentanoate (2e)**

Colorless oil; yield: 444 mg (1.08 mmol, 85%); R_f = 0.51 (hexanes–EtOAc, 7:3).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.32 (d, *J* = 7.3 Hz, 1 H), 7.22–7.25 (m, 2 H), 6.77–6.81 (m, 2 H), 4.71 (dt, *J* = 8.0, 4.2 Hz, 1 H), 4.53 (d, *J* = 1.3 Hz, 2 H), 3.36 (dd, *J* = 18.8, 4.2 Hz, 1 H), 3.19 (dd, *J* = 18.8, 4.2 Hz, 1 H), 1.43 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 205.1, 167.9, 157.2 (q, *J* = 37.4 Hz), 155.9, 129.6, 127.0, 115.7, 115.5 (q, *J* = 285.8 Hz), 114.0, 83.8, 72.6, 48.7, 40.3, 27.7.

HRMS (CI): *m*/*z* [M]$^+$ calcd for $C_{17}H_{19}ClF_3NO_5$: 409.0904; found: 409.0883.

***tert*-Butyl 5-(2-Cyanophenoxy)-4-oxo-2-(2,2,2-trifluoroacetamido)pentanoate (2f)**

White solid; yield: 444 mg (1.11 mmol, 84%); mp 71–72 °C; R_f = 0.49 (hexanes–EtOAc, 7:3).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.51–7.64 (m, 2 H), 7.28 (d, *J* = 6.8 Hz, 1 H), 7.10 (t, *J* = 7.2 Hz, 1 H), 6.82 (d, *J* = 8.4 Hz, 1 H), 4.78 (dt, *J* = 7.6, 4.4 Hz, 1 H), 4.69 (d, *J* = 3.7 Hz, 2 H), 3.48 (dd, *J* = 18.8, 4.4 Hz, 1 H), 3.28 (dd, *J* = 18.8, 4.3 Hz, 1 H), 1.43 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 204.1, 168.0, 157.2 (q, *J* = 37.4 Hz), 134.4, 134.1, 122.2, 115.5 (q, *J* = 285.8 Hz), 112.1, 102.6, 83.9, 72.7, 48.8, 40.3, 27.7.

HRMS (CI): *m*/*z* [M + 1]$^+$ calcd for $C_{18}H_{19}F_3N_2O_5$: 401.1280; found: 401.1334.

***tert*-Butyl 5-(2-Nitrophenoxy)-4-oxo-2-(2,2,2-trifluoroacetamido)pentanoate (2g)**

White solid; yield: 483 mg (1.15 mmol, 87%); mp 90–91 °C; R_f = 0.49 (hexanes–EtOAc, 7:3).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.93 (dd, *J* = 8.1, 1.7 Hz, 1 H), 7.55 (m, 1 H), 7.28 (br s, 1 H), 7.14 (m, 1 H), 6.96 (dd, *J* = 8.5, 1.0 Hz, 1 H), 4.79 (dt, *J* = 7.8, 4.3 Hz, 1 H), 4.72 (d, *J* = 5.0 Hz, 2 H), 3.50 (dd, *J* = 18.8, 4.5 Hz, 1 H), 3.32 (dd, *J* = 18.8, 4.2 Hz, 1 H), 1.46 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 204.2, 168.0, 157.2 (q, *J* = 37.4 Hz), 150.7, 134.4, 126.2, 122.0, 115.5 (q, *J* = 285.8 Hz), 114.6, 83.9, 73.3, 48.8, 40.6, 27.7.

HRMS (CI): *m*/*z* [M]$^+$ calcd for $C_{17}H_{19}F_3N_2O_7$: 420.1144; found: 420.1156.

Allylation of 2; General Procedure

To a suspension of Zn dust (19.1 mg, 0.29 mmol) in anhyd THF (0.5 mL) at r.t. was added allyl bromide (18 mg, 0.15 mmol). After stirring for 30 min, a solution of the corresponding γ-keto amino acid ester **2** (0.15 mmol) in THF (0.15 mL) was added dropwise and the stirring was continued for 1 h. The reaction was quenched with aq NH_4Cl (1 mL), extracted with CH_2Cl_2 (2 × 5 mL), the combined organic extracts were dried (Na_2SO_4), and the solvent was removed under vacuo. The crude product was purified by column chromatography (silica gel, EtOAc–hexanes) (Table 2).

4-Allyl-4-methyl-2-(2,2,2-trifluoroacetamido)butyrolactone (3a)

White solid; yield: 26 mg (0.11 mmol, 70%); mp 81–82 °C; R_f = 0.44 (hexanes–EtOAc, 7:3).

^{1}H NMR (400 MHz, $CDCl_3$): δ [major diastereomer (55%)] = 6.80 (br s, 1 H), 5.75 (m, 1 H), 5.17–5.27 (m, 2 H), 4.81 (ddd, *J* = 11.6, 8.7, 5.7 Hz, 1 H), 2.69 (dd, *J* = 12.7, 8.8 Hz, 1 H), 2.43–2.57 (m, 2 H), 2.06 (t, *J* = 12.7 Hz, 1 H), 1.46 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ [major diastereomer (55%)] = 172.5, 157.6 (q, *J* = 37.4 Hz), 130.8, 120.7, 115.6 (q, *J* = 285.7 Hz), 84.8, 50.1, 45.6, 39.1, 23.6.

^{1}H NMR (400 MHz, $CDCl_3$): δ [minor diastereomer (45%)] = 6.97 (br s, 1 H), 5.78 (m, 1 H), 5.22–5.27 (m, 2 H), 4.71 (ddd, *J* = 11.1, 9.4, 6.1 Hz, 1 H), 2.86 (dd, *J* = 13.0, 9.3 Hz, 1 H), 2.43–2.44 (m, 2 H), 2.06 (dd, *J* = 13.0, 11.3 Hz, 1 H), 1.51 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ [minor diastereomer (45%), selected signals] = 173.0, 131.0, 121.0, 85.2, 50.5, 44.4, 39.0, 23.5.

HRMS (CI): *m*/*z* [M]$^+$ calcd for $C_{10}H_{12}F_3NO_3$: 251.0769; found: 251.0789.

4-Allyl-4-butyl-2-(2,2,2-trifluoroacetamido)butyrolactone (3b)

White solid; yield: 29 mg (0.09 mmol, 65%); mp 79–81 °C; R_f = 0.45 (hexanes–EtOAc, 8:2).

^{1}H NMR (400 MHz, $CDCl_3$): δ [major diastereomer (58%)] = 6.90 (br s, 1 H), 5.77 (m, 1 H), 5.19–5.30 (m, 2 H), 4.65–4.72 (m, 1 H), 2.76–2.82 (m, 1 H), 2.44 (d, *J* = 7.0 Hz, 2 H), 1.99 (dd, *J* = 12.9, 11.3 Hz, 1 H), 1.69–1.78 (m, 2 H), 1.30–1.38 (m, 4 H), 0.89–0.94 (m, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ [major diastereomer (58%)] = 172.8, 157.6 (q, *J* = 37.4 Hz), 130.8, 121.0, 115.6 (q, *J* = 285.7 Hz), 87.5, 50.5, 42.3, 39.6, 37.5, 25.1, 22.7, 13.8.

^{1}H NMR (400 MHz, $CDCl_3$): δ [minor diastereomer (42%), selected signals] = 6.95 (br s, 1 H), 5.72 (m, 1 H), 5.16–5.29 (m, 2 H), 4.72 (dt, *J* = 10.0, 6.0 Hz, 1 H), 2.70 (dd, *J* = 12.8, 9.5 Hz, 1 H), 2.03 (dd, *J* = 13.0, 11.3 Hz, 1 H), 1.66–1.73 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ [minor diastereomer (42%), selected signals] = 172.9, 130.8, 120.6, 87.3, 50.1, 43.2, 38.0, 37.3, 25.6, 22.7, 13.8.

HRMS (CI): *m*/*z* [M]$^+$ calcd for $C_{13}H_{18}F_3NO_3$: 294.1272; found: 294.1292.

4-Allyl-4-chloromethyl-2-(2,2,2-trifluoroacetamido)butyrolactone (3c)

White solid; yield: 27 mg (0.09 mmol, 64%); mp 81–82 °C; R_f = 0.52 (hexanes–EtOAc, 7:3).

^{1}H NMR (400 MHz, $CDCl_3$): δ [major diastereomer (55%)] = 7.33 (br s, 1 H), 5.76 (m, 1 H), 5.21–5.33 (m, 2 H), 4.81 (dt, *J* = 10.2, 6.6 Hz, 1 H), 3.61–3.74 (m, 2 H), 2.88 (t, *J* = 11.8 Hz, 1 H), 2.63 (d, *J* = 7.3 Hz, 2 H), 2.29 (dd, *J* = 13.5, 10.5 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ [major diastereomer (55%)] = 172.5, 157.6 (q, *J* = 37.4 Hz), 129.7, 122.3, 115.6 (q, *J* = 285.7 Hz), 85.0, 50.4, 49.4, 42.9, 35.4.

^{1}H NMR (400 MHz, $CDCl_3$): δ [minor diastereomer (45%), selected signals] = 7.34 (br s, 1 H), 5.78 (m, 1 H), 5.22–5.27 (m, 2 H), 4.71 (dt, *J* = 10.2, 6.8 Hz, 1 H), 2.74 (dd, *J* = 13.2, 10.2 Hz, 1 H), 2.58 (d, *J* = 7.3 Hz, 2 H), 2.21 (dd, *J* = 14.5, 4.2 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ [minor diastereomer (45%), selected signals] = 172.1, 157.6 (q, *J* = 37.4 Hz), 129.5, 121.6, 84.7, 49.8, 49.2, 40.9, 34.9.

HRMS (CI): *m*/*z* [M + 1]$^+$ calcd for $C_{10}H_{11}ClF_3NO_3$: 285.0380; found: 285.0395.

4-Allyl-4-phenoxymethyl-2-(2,2,2-trifluoroacetamido)butyrolactone (3d)

White solid; yield: 31 mg (0.09 mmol, 60%); mp 85–87 °C; R_f = 0.54 (hexanes–EtOAc, 7:3).

^{1}H NMR (400 MHz, $CDCl_3$): δ [major diastereomer (53%)] = 7.26–7.32 (m, 3 H), 7.04 (m, 1H), 6.86–6.90 (m, 2 H), 5.81 (m, 1 H), 5.21–5.31 (m, 2 H), 4.81 (dt, *J* = 10.0, 6.5 Hz, 1 H), 4.09 (d, *J* = 10.0 Hz, 1 H), 4.00 (d, *J* = 10.1 Hz, 1 H), 2.95 (dd, *J* = 12.9, 9.6 Hz, 1 H), 2.56–2.65 (m, 2 H), 2.32 (dd, *J* = 13.7, 8.1 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ [major diastereomer (53%)] = 173.1, 157.6 (q, *J* = 37.4Hz), 157.5, 129.9, 129.7, 122.0, 121.1, 115.6 (q, *J* = 285.7 Hz), 114.6, 84.8, 72.5, 50.8, 41.5, 36.0.

^{1}H NMR (400 MHz, $CDCl_3$): δ [minor diastereomer (47%), selected signals] = 6.97–7.04 (m, 2 H), 5.81 (m, 1 H), 5.22–5.28 (m, 2 H), 4.88 (m, 1 H), 4.09 (d, *J* = 10.7 Hz, 1 H), 3.98 (d, *J* = 10.3 Hz, 1 H), 2.77 (dd, *J* = 13.0, 10.3 Hz, 1 H), 2.55–2.66 (m, 2 H), 2.22 (dd, *J* = 12.9, 10.8 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ [minor diastereomer (47%), selected signals] = 172.5, 156.8, 130.0, 129.8, 129.6, 122.2, 121.1, 114.8, 85.0, 72.2, 49.4, 40.6, 34.4.

HRMS (CI): *m*/*z* [M]$^+$ calcd for $C_{16}H_{16}F_3NO_4$: 343.1031; found: 343.1068.

4-Allyl-4-(4-chlorophenoxy)methyl-2-(2,2,2-trifluoroacetamido)butyrolactone (3e)

White solid; yield: 37 mg (0.10 mmol, 66%); mp 89– 90 °C; R_f = 0.53 (hexanes–EtOAc, 8:2).

^{1}H NMR (400 MHz, $CDCl_3$): δ [major diastereomer (58%)] = 7.23–7.27 (m, 2 H), 6.96 (d, *J* = 5.0 Hz, 1 H), 6.80–6.84 (m, 2 H), 5.80 (m, 1 H), 5.27–5.32 (m, 2 H), 4.81 (q, *J* = 8.8 Hz, 1 H), 4.06 (d, *J* = 10.1 Hz, 1 H), 3.96 (d, *J* = 10.1 Hz, 1 H), 2.79 (dd, *J* = 13.6, 10.2 Hz, 1 H), 2.53–2.63 (m, 2 H), 2.79 (dd, *J* = 13.6, 8.6 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ [major diastereomer (58%)] = 172.2, 156.8 (q, *J* = 37.4 Hz), 156.3, 129.7, 127.2, 122.0, 116.8, 116.2, 115.6 (q, *J* = 285.7 Hz), 84.9, 72.5, 49.6, 40.6, 34.3.

^{1}H NMR (400 MHz, $CDCl_3$): δ [minor diastereomer (42%)] = 7.23–7.27 (m, 2 H), 6.79–6.85 (m, 3 H), 5.81 (m, 1 H), 5.23–5.33 (m, 2 H), 5.02 (dt, *J* = 10.2, 5.8 Hz, 1 H), 4.08 (d, *J* = 10.0 Hz, 1 H), 3.98 (d, *J* = 10.0 Hz, 1 H), 2.99 (dd, *J* = 13.0, 9.5 Hz, 1 H), 2.55–2.66 (m, 2 H), 2.21 (dd, *J* = 13.0, 10.7 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ [minor diastereomer (42%), selected signals] = 172.7, 156.2, 129.6, 121.4, 116.0, 84.7, 72.9, 50.8, 41.6, 36.1.

HRMS (CI): *m*/*z* [M]$^+$ calcd for $C_{16}H_{15}ClF_3NO_4$: 377.0642; found: 377.0635.

Methylation of 2; General Procedure

To a solution of $ZnCl_2$ (34 mg, 0.25 mmol) in anhyd THF (3.0 mL) was added a solution of the corresponding γ-keto amino acid ester **2** (0.19 mmol) in THF (2 mL) at r.t. and the mixture was allowed to stir for 30 min. The resulting solution was transferred into a 2 M solution of $AlMe_3$ in toluene (0.19 mL, 27.8 mg, 0.38 mmol) at 0 °C and warmed up to r.t. The reaction mixture was decomposed with MeOH (5 mL) at 0 °C. The solvent was removed and diluted with 5% aq H_2SO_4. The aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL), the combined organic layers were dried (Na_2SO_4), and the crude product was purified by column chromatography (silica gel, EtOAc–hexanes) (Table 2).

4,4-Dimethyl-2-(2,2,2-trifluoroacetamido)butyrolactone (3f)

White solid; yield: 26 mg (0.11 mmol, 60%); mp 88–90 °C; R_f = 0.26 (hexanes–EtOAc, 8:2).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.00 (br s, 1 H), 4.78 (ddd, *J* = 11.8, 8.7, 6.1 Hz, 1 H), 2.79 (dd, *J* = 12.6, 8.7 Hz, 1 H), 2.79 (t, *J* = 12.2 Hz, 1 H), 1.54 (s, 3 H), 1.48 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.2, 157.2 (q, *J* = 38.8 Hz), 115.5 (q, *J* = 285.8 Hz), 83.6, 50.5, 41.5, 28.8, 26.8.

HRMS (CI): *m*/*z* [M + 1]$^+$ calcd for $C_8H_{10}F_3NO_3$: 226.0646; found: 226.0673.

4-Chloromethyl-4-methyl-2-(2,2,2-trifluoroacetamido)butyrolactone (3g)

White solid; yield: 33 mg (0.13 mmol, 66%); mp 94–95 °C; R_f = 0.28 (hexanes–EtOAc, 75:25).

^{1}H NMR (400 MHz, $CDCl_3$): δ [major diastereomer (59%)] = 6.87 (br s, 1 H), 4.80 (m, 1 H), 3.73 (d, *J* = 11.8 Hz, 1 H), 3.62 (d, *J* = 11.8 Hz, 1 H), 2.75 (dd, *J* = 13.0, 9.0 Hz, 1 H), 2.31 (dd, *J* = 13.0, 11.1 Hz, 1 H), 1.59 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ [major diastereomer (59%)] = 172.2, 157.2 (q, *J* = 38.8 Hz), 115.5 (q, *J* = 285.8 Hz), 83.6, 50.5, 50.3, 37.7, 24.1.

^{1}H NMR (400 MHz, $CDCl_3$): δ [minor diastereomer (41%), selected signals] = 6.86 (br s, 1 H), 4.80 (m, 1 H), 3.00 (dd, *J* = 13.5, 10.0 Hz, 1 H), 2.31 (dd, *J* = 13.5, 10.3 Hz, 1 H), 1.59 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ [minor diastereomer (41%), selected signals] = 172.2, 83.6, 50.5, 50.3, 37.7, 24.1.

HRMS (CI): *m*/*z* [M]$^+$ calcd for $C_8H_9ClF_3NO_3$: 259.0223; found: 259.0182.

4-Methyl-4-phenoxymethyl-2-(2,2,2-trifluoroacetamido)butyrolactone (3h)

White solid; yield: 36 mg (0.11 mmol, 60%); mp 107–108 °C; R_f = 0.28 (hexanes–EtOAc, 75:25).

^{1}H NMR (400 MHz, $CDCl_3$): δ [major diastereomer (54%)] = 7.28–7.33 (m, 4 H), 7.08 (d, *J* = 5.0 Hz, 1 H), 7.03 (m, 1 H), 4.78 (td, *J* = 9.6, 7.0 Hz, 1 H), 4.10 (d, *J* = 10.1 Hz, 1 H), 3.98 (d, *J* = 10.1 Hz, 1 H), 2.71 (dd, *J* = 13.5, 9.9 Hz, 1 H), 2.40 (dd, *J* = 13.5, 8.2 Hz, 1 H), 1.58 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ [major diastereomer (54%)] = 172.3, 157.6, 157.2 (q, *J* = 38.8 Hz), 129.8, 122.3, 115.5 (q, *J* = 285.8 Hz), 114.8, 83.5, 73.1, 49.5, 36.9, 23.2.

^{1}H NMR (400 MHz, $CDCl_3$): δ [minor diastereomer (46%), selected signals] = 5.07 (m, 1 H), 4.09 (d, *J* = 10.1 Hz, 1 H), 3.96 (d, *J* = 10.1

Hz, 1 H), 3.11 (dd, *J* = 13.0, 9.5 Hz, 1 H), 2.40 (dd, *J* = 13.0, 10.7 Hz, 1 H), 1.54 (s, 3 H), 1.55 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ [minor diastereomer (46%), selected signals] = 173.0, 129.7, 122.0, 114.6, 83.5, 73.1, 51.3, 38.5, 24.1.

HRMS (CI): *m*/*z* $[M]^+$ calcd for $C_{14}H_{14}F_3NO_4$: 317.0875; found: 317.0870.

4-(4-Chlorophenoxy)methyl-4-methyl-2-(2,2,2-trifluoroacetamido)butyrolactone (3i)

White solid; yield: 39 mg (0.11 mmol, 58%); mp 111–112 °C; R_f = 0.50 (hexanes–EtOAc 75:25).

^{1}H NMR (400 MHz, $CDCl_3$): δ [major diastereomer (55%)] = 7.23–7.28 (m, 2 H), 6.90 (d, *J* = 5.0 Hz, 1 H), 6.79–6.85 (m, 2 H), 5.03 (dt, *J* = 10.1, 6.0 Hz, 1 H), 4.06 (d, *J* = 10.1 Hz, 1 H), 3.94 (d, *J* = 10.1 Hz, 1 H), 3.09 (dd, *J* = 13.1, 9.5 Hz, 1 H), 2.40 (dd, *J* = 13.0, 10.8 Hz, 1 H), 1.58 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ [major diastereomer (55%)] = 172.2, 157.2 (q, *J* = 38.8 Hz), 156.3, 129.6, 127.2, 116.1, 115.5 (q, *J* = 285.8 Hz), 83.3, 73.9, 51.2, 38.4, 24.1.

^{1}H NMR (400 MHz, $CDCl_3$): δ [minor diastereomer (45%)] = 7.23–7.28 (m, 2 H), 7.01 (br s, 1 H), 6.79–6.85 (m, 2 H), 5.03 (dt, *J* = 9.4, 7.0 Hz, 1 H), 4.06 (d, *J* = 10.0 Hz, 1 H), 3.95 (d, *J* = 10.1 Hz, 1 H), 2.72 (dd, *J* = 13.3, 9.7 Hz, 1 H), 2.40 (dd, *J* = 13.0, 9.1 Hz, 1 H), 1.58 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ [minor diastereomer (45%), selected signals] = 172.1, 129.6, 127.1, 115.5, 83.4, 73.2, 49.5, 38.6, 23.1.

HRMS (CI): *m*/*z* $[M + 1]^+$ calcd for $C_{14}H_{13}ClF_3NO_4$: 353.0456; found: 353.0419.

4-(2-Cyanophenoxy)methyl-4-methyl-2-(2,2,2-trifluoroacetamido)butyrolactone (3k)

White solid; yield: 43 mg (0.13 mmol, 66%); mp 110–111 °C; R_f = 0.26 (hexanes–EtOAc, 8:2).

^{1}H NMR (400 MHz, $CDCl_3$): δ [major diastereomer (60%)] = 7.80 (d, *J* = 7.3 Hz, 1 H), 7.53–7.58 (m, 2 H), 7.08 (t, *J* = 7.6 Hz, 1 H), 6.96 (d, *J* = 8.2 Hz, 1 H), 5.09 (dt, *J* = 10.3, 7.9 Hz, 1 H), 4.27 (d, *J* = 10.3 Hz, 1 H), 4.04 (d, *J* = 10.3 Hz, 1 H), 2.67 (d, *J* = 10.5 Hz, 2 H), 1.57 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ [major diastereomer (60%)] = 171.9, 160.1, 157.2 (q, *J* = 38.8 Hz), 134.8, 133.0, 122.1, 117.0, 115.5 (q, *J* = 285.8 Hz), 113.2, 102.4, 82.6, 73.2, 51.5, 35.1, 23.2.

^{1}H NMR (400 MHz, $CDCl_3$): δ [minor diastereomer (40%), selected signals] = 7.53–7.58 (m, 2 H), 7.47 (br s, 1 H), 4.22 (d, *J* = 9.7 Hz, 1 H), 3.99 (d, *J* = 9.7 Hz, 1 H), 2.98 (dd, *J* = 12.9, 10.1 Hz, 1 H), 2.41 (dd, *J* = 13.0, 10.3 Hz, 1 H), 1.63 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ [minor diastereomer (40%), selected signals] = 171.9, 159.6, 133.6, 113.2, 112.1, 101.9, 82.2, 74.1, 36.2, 23.9.

HRMS (CI): *m*/*z* $[M]^+$ calcd for $C_{15}H_{13}F_3N_2O_4$: 342.0827; found: 342.0867.

Reformatsky Reaction; General Procedure

To a solution of the corresponding γ-keto amino acid ester **2** (0.15 mmol) in anhyd THF (0.5 mL) was added a freshly prepared 1.6 M solution of zincbromo ester in THF (0.14 mL, 0.22 mmol) at –5 °C and the mixture was allowed to warm to r.t. overnight. The reaction mixture was quenched with aq 1 M HCl (2 mL) and extracted with EtOAc (2 × 5 mL). The combined organic layers were washed with brine (5 mL), dried (Na_2SO_4), and the solvent was removed in vacuo. The product was obtained after column chromatography (silica gel, EtOAc–hexanes).

***tert*-Butyl 6-Methyl 4-(chloromethyl)-4-hydroxy-2-(2,2,2-trifluoroacetamido)hexanedioate (4c)**

White solid; yield: 51 mg (0.13 mmol, 85%); mp 62–63 °C; R_f = 0.46 (CH_2Cl_2–hexanes, 95:5).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.28 (d, *J* = 6.0 Hz, 1 H), 4.69 (dt, *J* = 8.6, 4.1 Hz, 1 H), 3.92 (d, *J* = 15.3 Hz, 1 H), 3.88 (d, *J* = 15.3 Hz, 1 H), 3.70 (s, 3 H), 2.80 (d, *J* = 16.2 Hz, 1 H), 2.67 (d, *J* = 9.2 Hz, 1 H), 2.27 (m, 1 H), 2.17 (dd, *J* = 14.9, 8.6 Hz, 1 H), 1.44 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.5, 169.1, 157.2 (q, *J* = 38.8 Hz), 115.5 (q, *J* = 285.8 Hz), 83.1, 72.5, 72.4, 52.1, 50.9, 39.4, 37.2, 27.7.

HRMS (CI): *m*/*z* $[M + 1]^+$ calcd for $C_{14}H_{21}ClF_3NO_6$: 392.1088; found: 392.1071.

1-*tert*-Butyl 6-Methyl 4-[(4-chlorophenoxy)methyl]-4-hydroxy-2-(2,2,2-trifluoroacetamido)hexanedioate (4e)

White solid; yield: 65 mg (0.14 mmol, 90%); mp 69–70 °C; R_f = 0.25 (CH_2Cl_2–hexanes, 95:5).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.73 (d, *J* = 5.8 Hz, 1 H), 7.22–7.25 (m, 2 H), 6.78–6.82 (m, 2 H), 4.50 (ddd, *J* = 8.6, 6.4, 4.4 Hz, 1 H), 3.92 (d, *J* = 9.2 Hz, 1 H), 3.88 (d, *J* = 9.2 Hz, 1 H), 3.70 (s, 3 H), 2.80 (d, *J* = 16.2 Hz, 1 H), 2.67 (d, *J* = 9.2 Hz, 1 H), 2.27 (m, 1 H), 2.17 (dd, *J* = 14.9, 8.6 Hz, 1 H), 1.44 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.5, 169.1, 157.2 (q, *J* = 38.8 Hz), 156.5, 129.4, 126.6, 115.8, 115.5 (q, *J* = 285.8 Hz), 83.1, 72.5, 72.4, 52.1, 50.9, 39.4, 37.2, 27.7.

HRMS (CI): *m*/*z* $[M + 1]^+$ calcd for $C_{20}H_{25}ClF_3NO_7$: 485.1242; found: 485.1234.

***tert*-Butyl 4-(3-Aminobenzofuran-2-yl)-4-oxo-2-(2,2,2-trifluoroacetamido)butanoate (5)**

Ketone **2f** (90 mg, 0.22 mmol) was refluxed in anhyd Et_3N (2.5 mL) under N_2. After completion of the reaction, the Et_3N was removed in vacuo, and the crude product was purified by column chromatography (silica gel, hexanes–EtOAc, 8:2) to afford **5** in 92% yield (81 mg, 0.20 mmol) as a colorless oil; R_f = 0.28 (hexanes–EtOAc, 7:3).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.69 (d, *J* = 7.8 Hz, 1 H), 7.50–7.59 (m, 2 H), 7.40 (m, 1 H), 7.25 (m, 1 H), 5.69 (br s, 2 H), 4.85 (dt, *J* = 8.3, 4.2 Hz, 1 H), 3.68 (dd, *J* = 17.6, 4.3 Hz, 1 H), 3.68 (dd, *J* = 17.6, 4.3 Hz, 1 H), 1.49 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 187.4, 168.6, 157.2 (q, *J* = 38.8 Hz), 154.4, 140.0, 134.2, 130.2, 122.5, 120.7, 120.3, 115.5 (q, *J* = 285.8 Hz), 112.7, 83.0, 49.3, 38.6, 27.7.

HRMS (CI): *m*/*z* $[M]^+$ calcd for $C_{18}H_{19}F_3N_2O_5$: 400.1246; found: 400.1269.

***tert*-Butyl 3-(3,4-Dihydro-2*H*-benzo[*b*][1,4]oxazin-3-yl)-2-(2,2,2-trifluoroacetamido)propanoate (6)**

To a solution of ketone **2g** (50 mg, 0.12 mmol) in MeOH (15 mL) was added 5% Pd/C (12.5 mg) and the solution was allowed to stir under H_2 (4 bar). After stirring for 6 h, the solution was filtered over Celite, and the solvent was removed in vacuo. The crude product was purified by column chromatography (silica gel, hexanes–EtOAc, 8:2) to give **6** in ~100% yield (44 mg, 0.12 mmol) as a colorless solid; mp 63–64 °C; R_f = 0.46 (hexanes–EtOAc, 7:3).

^{1}H NMR (400 MHz, $CDCl_3$): δ [major diastereomer (56%)] = 7.28 (d, *J* = 7.3 Hz, 1 H), 6.79–6.84 (m, 2 H), 6.65–6.69 (m, 2 H), 4.69 (ddd, *J* = 10.4, 8.0, 3.5 Hz, 1 H), 4.07 (dd, *J* = 10.7, 2.8 Hz, 1 H), 3.98 (dd, *J* = 10.7, 4.1 Hz, 1 H), 3.43 (m, 1 H), 2.19 (ddd, *J* = 14.3, 10.9, 3.5 Hz, 1 H), 2.19 (ddd, *J* = 14.0, 10.3, 3.0 Hz, 1 H), 1.48 (s, 9 H), NH was missing.

^{13}C NMR (100 MHz, $CDCl_3$): δ [major diastereomer (56%)] = 170.0, 157.2 (q, *J* = 38.8 Hz), 143.5, 132.0, 122.0, 118.8, 116.7, 116.1, 115.5 (q, *J* = 285.8 Hz), 84.1, 68.2, 50.7, 46.7, 35.7, 27.9.

^{1}H NMR (400 MHz, $CDCl_3$): δ [minor diastereomer (44%)] = 7.12 (d, *J* = 6.3 Hz, 1 H), 6.76–6.82 (m, 2 H), 6.57–6.70 (m, 2 H), 4.69 (q, *J* = 6.4 Hz, 1 H), 4.09 (dd, *J* = 10.7, 2.7 Hz, 1 H), 4.00 (dd, *J* = 10.7, 4.9 Hz, 1 H), 3.57 (m, 1 H), 2.13 (ddd, *J* = 14.3, 6.1, 4.7 Hz, 1 H), 2.01 (m, 1 H), 1.45 (s, 9 H), NH was missing.

^{13}C NMR (100 MHz, $CDCl_3$): δ [minor diastereomer (44%), selected signals] = 169.7, 143.5, 131.8, 121.8, 119.1, 116.8, 116.1, 84.1, 68.0, 51.3, 47.4, 34.7, 27.8.

HRMS (CI): *m/z* $[M]^+$ calcd for $C_{17}H_{21}F_3N_2O_4$: 374.1453; found: 374.1479.

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