Regioselective ring opening of epoxides by chelated amino acid esters enolates

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Dedicated to Professor Siegfried Blechert on the occasion of his 65th birthday

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Abstract
Chelated enolates of α-amino acids and peptides are suitable nucleophiles for the regioselective ring opening of epoxides. Depending on the substitution pattern, the reaction proceeds either in a S_N1-type (arylepoxides) or a S_N2-type (alkylepoxides) fashion, giving rise to γ-hydroxy α-amino acids.

Keywords: Amino acids, chelates, epoxides, epoxide opening, peptide modifications

Introduction

Epoxides are very versatile building blocks in organic synthesis, which can be opened up with a wide range of nucleophiles.[1] Elegant ring opening cascades found interesting applications in natural product synthesis, e.g. for macrocyclic polyethers.[2] To apply this protocol also to peptidic natural products, suitable amino acid and / or peptide nucleophiles are required. The epoxide opening with glycine enolates should give rise to γ-hydroxy α-amino acids, a structural motif widespread found in nature, e.g. in the glidobactins,[3] arborcandins[4] or the biphenomycins.[5] Suitable C-nucleophiles are either isocyanoacetates,[6] aminomalonates[7] or imino esters.[8] With chiral modified nucleophiles the stereochemical outcome of the reaction can be controlled.[9] Berkowitz *et al.* reported the ring opening of ethylene oxide with various α-amino acid ester enolates.[10] Very recently, Crousse *et al.* reported the aminolysis of epoxides using α-amino acid and peptide esters.[11]

Results and Discussion

Our group is also involved in amino acid and peptide synthesis, investigating reactions of chelated α-amino acid ester enolates.[12] These enolates not only show a higher stability compared

to non-chelated enolates, but also a higher selectivity in a wide range of reactions such as aldol[13] and Michael additions,[14] as well as transition metal catalyzed allylic alkylations.[15] These reactions are not limited to amino acid enolates but can also be carried out with peptides,[16] while in several cases the stereochemical outcome of the reaction can be controlled by the stereogenic centers of the peptide chain.[17] To enlarge the synthetic potential of these chelated enolates we were interested to see if these enolates can also be used for regioselective epoxide openings. In general, a S_N2-type mechanism is discussed[1] resulting in an attack at the sterically least hindered position. This is reasonable for alkyl-substituted epoxides. Li[18] and Ramachandran[19] *et al.* investigated the opening of arylepoxides with allenoates and observed also a selective S_N2-attack at the terminal epoxide position, even in the presence of Lewis acids. This is also true for α-metalated carboxylic acids,[20] while with malonates either S_N1-type products are obtained or mixtures of both isomers.[21]

Therefore, we investigated the reaction of both, alkyl- and aryl-substituted epoxides **1** (Table 1). As nucleophile we used the enolate of TFA-protected *t*-butyl glycinate, which gave excellent results e.g. in Michael additions or allylic alkylations. $ZnCl_2$ was used for chelation of the enolate and $BF_3 \cdot OEt_2$ for the activation of the epoxide. The epoxide was used in slight excess (1.5 equiv.) to allow a complete conversion. In principle, two different products (**2** and **3**) can be formed. **2** is the preferred product of a S_N2-type ring opening, while **3** should be found under S_N1-conditions.

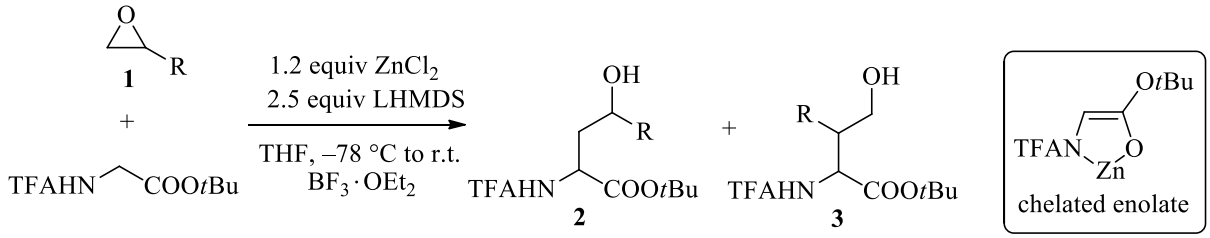

Table 1. Regioselective epoxide opening with chelated amino acid ester enolates

Entry	Epoxide	R	Product	Yield (%)	Diast.-ratio
1	**1a**	CH_3	**2a**	92	68:32
2	**1b**	C_2H_5	**2b**	88	68:32
3	**1c**	C_4H_9	**2c**	86	66:34
4	**1d**	$ClCH_2$	**2d**	74	56:44
5	**1e**	$CH_2{=}CH(CH_2)_3$	**2e**	87	65:35
6	**1f**	$C_6H_5OCH_2$	**2f**	86	56:44
7	**1g**	*p*-$CH_3C_6H_4OCH_2$	**2g**	81	55:45
8	**1h**	*p*-$CH_3OC_6H_4OCH_2$	**2h**	85	60:40

9	**1i**	C_6H_5	**3i**	67	75:25

Table 1. Continued

Entry	Epoxide	R	Product	Yield (%)	Diast.-ratio
10	**1k**	*p*-$CH_3OC_6H_4$	**3k**	71	67:33
11	**1l**	*o*-ClC_6H_4	**3l**	72	75:25

With aliphatic epoxides the S_N2-product **2** was formed exclusively in high yield as a diastereomeric mixture (entries 1-5). The same is true for glycidyl ethers (entries 6-8). In contrast, with aryl-substituted epoxides only the formation of the S_N1-product **3** was observed, giving rise to β-substituted phenylalanines (entries 9-11). Obviously, under the mild reaction conditions the nucleophilic attack on the *in situ* formed benzylic carbenium ion is significantly faster than the S_N2-attack.

To prove if this concept is also suitable for the modification of peptides, we subjected a phenylalanine dipeptide to analogous reaction conditions. Only the amount of base had to be increased to 3.5 equiv. LHMDS (lithium hexamethyldisilazide). To make the NMR spectra more clear by reducing the number of stereoisomers, the ring opening products were directly oxidized to the corresponding ketones **4** (Table 2). The yields obtained were slightly lower compared to the amino ester enolates but with 64-72% (over both steps) still in a preparative useful range.

Table 2. Regioselective epoxide opening with chelated peptide enolates

Entry	Epoxide	R	Product	Yield (%)	Diast.-ratio
1	**1a**	CH_3	**4a**	64	68:32
2	**1b**	C_2H_5	**4b**	68	67:33
3	**1d**	$ClCH_2$	**4d**	66	68:32
4	**1f**	$C_6H_5OCH_2$	**4f**	66	70:30
5	**1h**	*p*-$CH_3OC_6H_4OCH_2$	**4h**	65	69:31
6	**1m**	*p*-$ClC_6H_4OCH_2$	**4m**	68	64:36

7	**1n**	*p*-$NO_2C_6H_4OCH_2$	**4n**	72	68:32

Conclusions

In conclusion we could show that chelated enolates of α-amino acids and peptides are suitable nucleophiles for the regioselective ring opening of epoxides. Depending on the substitution pattern, the reaction proceeds either in a S_N1-type (arylepoxides) or a S_N2-type (alkylepoxides) fashion. Attempts to increase the stereoselectivity of these processes as well as synthetic applications are currently under investigation.

Experimental Section

General. All reactions were carried out in oven-dried glassware (100°C) under nitrogen. 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 ethyl acetate and hexanes were generally used as eluents. Analysis by TLC was carried out on commercially precoated Polygram SIL-G/UV 254 plates (Macherey-Nagel, Dueren). Visualization was accomplished with UV light, $KMnO_4$ solution or iodine. ^{1}H- and ^{13}C-NMR spectroscopic analysis was performed on a Bruker Avance II 400 MHz spectrometer. Chemical shifts are reported on the δ (ppm) scale and the coupling constant are given in Hz. HRMS were measured with Finnigan MAT 95S mass spectrometer. Elemental analyses were carried out at the Department of Chemistry at Saarland University.

General procedure for epoxide opening with amino acid enolates

In a Schlenk tube hexamethyldisilazane (497 mg, 3.08 mmol) was dissolved in dry THF (5 mL) under Ar. After the solution was cooled to –78 °C, a 1.6 M solution of *n*-BuLi (1.72 mL, 2.75 mmol) 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) was dried with a heat gun under vacuum and dissolved in THF (5 mL) under Ar. Tfa-Gly-O*t*Bu (250 mg, 1.1 mmol) was added and the solution was cooled to –78 °C before the LHMDS solution was added slowly via syringe. The resulting solution was stirred for 30 min at –78 °C. Then the corresponding epoxide (1.65 mmol) was added followed by $BF_3.OEt_2$ (78.1 mg, 0.55 mmol) directly to the enolate at –78 °C. The reaction mixture was allowed to warm to r.t. over night before it was hydrolyzed with 1M HCl and extracted thrice with ethyl acetate. 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).

***tert*-Butyl 4-hydroxy-2-(2,2,2-trifluoroacetamido)pentanoate (2a).** Major diastereomer (68%): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.66 (d, *J* = 5.5 Hz, 1 H), 4.63 (td, *J* = 8.2, 3.6 Hz, 1 H), 3.85 (m, 1 H), 2.74 (d, *J* = 3.2 Hz, 1 H), 1.91 (ddd, *J* = 14.2, 10.4, 3.7 Hz, 1 H), 1.83 (ddd, *J* = 11.1,

8.5, 2.6 Hz, 1 H), 1.48 (s, 9 H), 1.24 (d, *J* = 6.2 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.7, 157.4 (*J* = 37.2 Hz), 115.7 (*J* = 285.6 Hz), 83.2, 64.8, 51.5, 39.9, 27.8, 23.5. Minor diastereomer (32%): ^{1}H NMR (400 MHz, $CDCl_3$): *δ* = 7.53 (d, *J* = 4.0 Hz, 1 H), 4.43 (q, *J* = 6.2 Hz, 1 H), 3.97 (m, 1 H), 2.04 (ddd, *J* = 14.5, 5.7, 3.2 Hz, 1 H), 1.98 (bs, 1 H), 1.90 (ddd, *J* = 14.5, 9.4, 6.5 Hz, 1 H), 1.47 (s, 9 H), 1.24 (d, *J* = 6.0 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.8, 156.8 (*J* = 37.3 Hz), 115.6 (*J* = 285.8 Hz), 83.1, 65.5, 52.1, 39.4, 27.8, 24.1. HRMS (CI) calcd. for $C_{11}H_{18}F_3NO_4$ $[M+H]^+$: 286.1221. Found: 286.1273. Anal. Calcd for $C_{11}H_{18}F_3NO_4$ (285.11): C 46.31; H 6.36; N 4.91. Found: C 46.46; H 6.21; N 5.18.

***tert*-Butyl 4-hydroxy-2-(2,2,2-trifluoroacetamido)hexanoate (2b).** Major diastereomer (68%): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.75 (d, *J* = 6.3 Hz, 1 H), 4.66 (m, 1 H), 3.58 (m, 1 H), 2.68 (bs, 1 H), 1.87–1.93 (m, 2 H), 1.51–1.54 (m, 2 H), 1.49 (s, 9 H), 0.95 (t, *J* = 7.5 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.7, 157.4 (*J* = 37.2 Hz), 115.7 (*J* = 285.6 Hz), 83.2, 70.1, 52.4, 38.2, 30.4, 27.9, 9.8. Minor diastereomer (32%, selected signals): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.46 (bs, 1 H), 4.42 (m, 1 H), 3.70 (m, 1 H), 2.11 (ddd, *J* = 14.5, 5.8, 2.7 Hz, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.9, 156.8, (*J* = 37.3 Hz), 115.6 (*J* = 285.8 Hz), 83.1, 70.6, 52.1, 37.1, 30.7, 27.8, 9.5. HRMS (CI) calcd. for $C_{12}H_{20}F_3NO_4$ $[M]^+$: 299.1344. Found: 299.1329. Anal. Calcd for $C_{12}H_{20}F_3NO_4$ (299.13): C 48.16; H 6.74; N 4.68. Found: C 48.08; H 6.47; N 4.64.

***tert*-Butyl 4-hydroxy-2-(2,2,2-trifluoroacetamido)octanoate (2c).** Major diastereomer (66%): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.85 (d, *J* = 6.3 Hz, 1 H), 4.63 (m, 1 H), 3.64 (m, 1 H), 2.83 (bs, 1 H), 1.85–1.88 (m, 2 H), 1.47 (s, 9 H), 1.23–1.37 (m, 6 H), 0.88 (t, *J* = 6.9 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.7, 157.4 (*J* = 37.2 Hz), 115.7 (*J* = 285.6 Hz), 83.1, 68.8, 51.5, 37.7, 37.2, 27.8, 27.6, 22.4, 13.9. Minor diastereomer (34%, selected signals): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.56 (bs, 1 H), 4.43 (m, 1 H), 3.70 (m, 1 H), 2.07 (ddd, *J* = 14.5, 5.8 Hz, 2.6 Hz, 1 H), 1.48 (s, 9 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.9, 156.8, (*J* = 37.3 Hz), 115.6 (*J* = 285.8 Hz), 83.0, 69.3, 52.2, 38.4, 37.7, 27.8, 27.4. HRMS (CI) calcd. for $C_{14}H_{24}F_3NO_4$ $[M-C_4H_9]^+$: 270.0953. Found: 270.0942. Anal. Calcd for $C_{14}H_{24}F_3NO_4$ (327.33): C 51.37; H 7.39; N 4.28. Found: C 51.41; H 7.38; N 3.80.

***tert*-Butyl 5-chloro-4-hydroxy-2-(2,2,2-trifluoroacetamido)pentanoate (2d).** Major diastereo mer (56%): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.70 (d, *J* = 7.3 Hz, 1 H), 4.68 (dt, *J* = 7.7, 3.8 Hz, 1 H), 3.87 (m, 1 H), 3.53 (dd, *J* = 10.0, 4.0 Hz, 1 H), 3.49 (dd, *J* = 10.0, 5.2 Hz, 1 H), 3.35 (d, *J* = 3.9 Hz, 1 H), 1.94–2.08 (m, 2 H), 1.47 (s, 9 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.2, 157.4 (*J* = 37.2 Hz), 115.7 (*J* = 285.6 Hz), 83.7, 66.7, 51.1, 48.7, 35.5, 27.8. Minor diastereomer (44%, selected signals): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.46 (d, *J* = 6.0 Hz, 1 H), 4.50 (q, *J* = 5.9 Hz, 1 H), 3.95 (m, 1 H), 3.57 (dd, *J* = 11.2, 4.1 Hz, 1 H), 3.49 (dd, *J* = 11.2, 6.6 Hz, 1 H), 2.72 (d, *J* = 5.1 Hz, 1 H), 2.20 (ddd, *J* = 14.5, 5.9, 2.9 Hz, 1 H), 2.02 (m, 1 H), 1.47 (s, 9 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.4, 157.4 (*J* = 37.2 Hz), 115.7 (*J* = 285.6 Hz), 83.6, 68.4, 51.3, 49.3, 35.0, 27.7. HRMS (CI) calcd. for $C_{11}H_{17}ClF_3NO_4$ $[M+H]^+$: 321.0769. Found: 321.0795. Anal. Calcd for $C_{11}H_{17}ClF_3NO_4$ (319.07): C 41.32; H 5.36; N 4.38. Found: C 41.43; H 5.08; N 4.54.

***tert*-Butyl 4-hydroxy-2-(2,2,2-trifluoroacetamido)non-8-enoate (2e).** Major diastereomer (65%): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.70 (d, *J* = 7.3 Hz, 1 H), 5.78 (m, 1 H), 4.93–5.02 (m,

2 H), 4.65 (dt, *J* = 7.7, 4.3 Hz, 1 H), 3.62 (m, 1 H), 2.72 (bs, 1 H), 2.03–2.08 (m, 2 H), 1.81–1.92 (m, 4 H), 1.48 (s, 9 H), 1.25–1.42 (m, 4 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.8, 136.6, 114.5, 157.4 (*J* = 37.2 Hz), 115.7 (*J* = 285.6 Hz), 83.3, 68.6, 51.4, 38.8, 37.3, 33.5, 28.6, 27.9, 24.9. Minor diastereomer (35%, selected signals)^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.51 (bs, 1 H), 5.77 (m, 1 H), 4.93–5.01 (m, 2 H), 4.64 (q, *J* = 6.0 Hz, 1 H), 3.75 (bs, 1 H), 2.02–2.10 (m, 3 H), 1.85–1.92 (m, 2 H), 1.47 (s, 9 H), 1.28–1.41 (m, 4 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.9, 157.6 (*J* = 37.2 Hz), 138.5, 115.7 (*J* = 285.6 Hz), 114.5, 83.1, 69.2, 52.1, 37.8, 37.7, 33.5, 28.6, 27.8, 24.7. HRMS (CI) calcd. for $C_{16}H_{26}F_3NO_4$ $[M+1]^+$: 354.1847. Found: 357.1879. Anal. Calcd for $C_{16}H_{26}F_3NO_4$ (353.37): C 54.38; H 7.42; N 3.96. Found: C 54.40; H 7.10; N 4.42.

***tert*-Butyl 5-phenoxy-4-hydroxy-2-(2,2,2-trifluoroacetamido)pentanoate (2f).** Major diastereomer (56%): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.77 (d, *J* = 7.8 Hz, 1 H), 7.23–7.29 (m, 2 H), 6.95 (dd, *J* = 7.4 Hz, 1 H), 6.85–6.87 (m, 2 H), 4.71 (dt, *J* = 7.5, 4.4 Hz, 1 H), 4.06 (m, 1 H), 3.91 (dd, *J* = 7.9, 3.1 Hz, 1 H), 3.88 (dd, *J* = 7.8, 5.2 Hz, 1 H), 3.83 (d, *J* = 3.3 Hz, 1 H), 1.98–2.09 (m, 2 H), 1.47 (s, 9 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.2, 158.1, 157.4 (*J* = 37.4 Hz), 129.5, 121.4, 115.7 (*J* = 285.6 Hz), 114.4, 83.4, 71.3, 67.4, 51.2, 34.5, 27.9. Minor diastereomer (44%, selected signals): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.43 (bs, 1 H), 7.23–7.28 (m, 2 H), 6.96 (dd, *J* = 7.4 Hz, 1 H), 6.85–6.87 (m, 2 H), 4.51 (q, *J* = 5.9 Hz, 1 H), 4.12 (m, 1 H), 3.94 (dd, *J* = 9.4, 3.5 Hz, 1 H), 3.88 (dd, *J* = 9.3, 7.1 Hz, 1 H), 2.52 (d, *J* = 4.3 Hz, 1 H), 2.15 (m, 1 H), 1.47 (s, 9 H).^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.4, 158.1, 157.4 (*J* = 37.4 Hz), 129.6, 121.4, 115.7 (*J* = 285.6 Hz), 114.5, 83.4, 71.4, 67.4, 51.7, 33.8, 27.8. HRMS (CI) calcd. for $C_{17}H_{22}F_3NO_5$ $[M]^+$: 377.1450. Found: 377.1447. Anal. Calcd for $C_{17}H_{22}F_3NO_5$ (377.35): C 54.11; H 5.88; N 3.71. Found: C 54.64; H 5.62; N 3.95.

***tert*-Butyl 4-hydroxy-5-(4-tolyloxy)-2-(2,2,2-trifluoroacetamido)pentanoate (2g).** Major diastereomer (55%): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.81 (d, *J* = 7.5 Hz, 1 H), 7.08 (d, *J* = 8.3 Hz, 2 H), 6.77–6.80 (m, 2 H), 4.73 (dt, *J* = 7.4, 4.2 Hz, 1 H), 4.11 (m, 1 H), 3.81–3.97 (m, 2 H), 2.29 (s, 3 H), 2.03–2.13 (m, 2 H), 1.49 (s, 9 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.2, 157.4 (*J* = 37.4 Hz), 156.0, 130.0, 129.0, 115.7 (q, $J_{8,F}$ = 285.6 Hz), 114.3, 83.4, 71.6, 67.5, 51.2, 34.5, 27.9, 20.4. Minor diastereomer (45%, selected signals): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.47 (d, *J* = 5.5 Hz, 1 H), 4.53 (q, *J* = 5.9 Hz, 1 H), 2.28 (s, 3 H), 2.03–2.13 (m, 2 H), 1.49 (s, 9 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.2, 155.8, 130.7, 83.3, 71.6, 67.4, 51.6, 33.8, 27.8. HRMS (CI) calcd. for $C_{18}H_{24}F_3NO_5$ $[M]^+$: 391.1607. Found: 391.1616.

***tert*-Butyl 4-hydroxy-5-(4-methoxyphenoxy)-2-(2,2,2-trifluoroacetamido)pentanoate (2h).** Major diastereomer (60%): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.78 (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), 3.77 (s, 3 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 = 171.5, 157.4 (*J* = 37.4 Hz), 152.2, 130.0, 129.0, 115.7 (*J* = 285.6 Hz), 115.4, 83.4, 72.6, 65.5, 55.8, 51.2, 36.5, 27.9. Minor diastereomer (40%, selected signals): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.44 (s, 1 H), 4.53 (q, *J* = 5.9 Hz, 1 H), 4.10 (m, 1 H), 3.77 (s, 3 H), 2.19–2.25 (m, 2 H), 1.49 (s, 9 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.3, 152.1, 129.9, 129.0, 115.5, 83.4, 72.6, 65.5, 55.6, 51.2, 36.9, 27.8. HRMS (CI) calcd. for $C_{18}H_{24}F_3NO_6$ $[M]^+$: 407.1556. Found: 407.1550.

***tert*-Butyl 4-hydroxy-3-phenyl-2-(2,2,2-trifluoroacetamido)butanoate (3i).** Major diastereomer (75%): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.66 (d, *J* = 7.5 Hz, 1 H), 7.22–7.31 (m, 5 H), 4.79 (dd, *J* = 7.7 Hz, 1 H), 3.91–3.99 (m, 2 H), 3.19 (dt, *J* = 7.6, 5.3 Hz, 1 H), 2.66 (s, 1 H), 1.24 (s, 9 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.9, 157.1 (q, *J* = 37.4 Hz), 137.1, 128.6, 128.5, 127.8, 115.6 (q, *J* = 285.8 Hz), 83.3, 63.7, 55.8, 49.3, 27.5. Minor diastereomer (25%, selected signals)**:** ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.29–7.33 (m, 3 H), 7.07–7.06 (m, 2 H), 7.03 (d, *J* = 7.2 Hz, 1 H), 5.03 (dd, *J* = 7.9, 3.4 Hz, 1 H), 3.73–3.83 (m, 2 H), 3.56 (ddd, 9.6, 5.6, 3.4 Hz, 1 H), 3.39 (dd, *J* = 8.1, 6.2 Hz, 1 H), 1.41 (s, 9 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.5, 135.3, 128.8, 128.4, 128.3, 115.6 (*J* = 285.5 Hz), 84.1, 62.1, 53.5, 50.3, 27.9 HRMS (CI) calcd. for $C_{12}H_{11}F_3NO_4$ $[M\text{-}C_4H_9]^+$: 290.0646. Found: 290.0612. Anal. Calcd for for $C_{16}H_{20}F_3NO_4$ (347.13): C 55.33; H 5.80; N 4.03. Found: C 54.99; H 5.81; N 4.29.

***tert*-Butyl 4-hydroxy-3-(4-methoxyphenyl)-2-(2,2,2-trifluoroacetamido)butanoate (3k).** Major diastereomer (67%): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.48 (d, *J* = 8.1 Hz, 1 H), 6.85–6.95 (m, 4 H), 4.90 (t, *J* = 6.8 Hz, 1 H), 4.10 (dd, *J* = 11.2, 6.4 Hz, 1 H), 4.00 (dd, *J* = 11.1, 5.4 Hz, 1 H), 3.83 (s, 3 H), 3.19 (dt, *J* = 7.6, 5.3 Hz, 1 H), 1.32 (s, 9 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.7, 157.2 (*J* = 37.4 Hz), 156.9, 135.6, 121.1, 115.6 (*J* = 285.8 Hz), 114.6, 82.8, 63.2, 55.3, 55.2, 43.0, 27.7. Minor diastereomer (33%, selected signals): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.74 (d, *J* = 5.9 Hz, 1 H), 7.23–7.29 (m, 4 H), 4.95 (dd, *J* = 8.2, 5.0 Hz, 1 H), 4.00 (dd, *J* = 11.1, 5.4 Hz, 1 H), 3.84 (s, 3 H), 1.28 (s, 9 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.7, 156.5, 136.1, 114.9, 83.2, 63.2, 55.2, 45.5, 27.7. HRMS (CI) calcd. for $C_{17}H_{22}F_3NO_5$ $[M+1]^+$: 378.1484. Found: 378.1499.

***tert*-Butyl 4-hydroxy-3-(2-chlorophenyl)-2-(2,2,2-trifluoroacetamido)butanoate (3l).** Major diastereomer (75%): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.46 (d, *J* = 7.5 Hz, 1 H), 7.30–7.32 (m, 2 H), 7.23–7.26 (m, 2 H), 4.83 (t, *J* = 7.8 Hz, 1 H), 3.98 (dd, *J* = 4.8, 1.9 Hz, 1 H), 3.94 (dd, *J* = 4.8, 1.9 Hz), 3.19 (dt, *J* = 7.6, 4.8 Hz, 1 H), 1.30 (s, 9 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.7, 157.4 (*J* = 37.4 Hz), 135.9, 133.8, 129.9, 129.7, 127.5, 126.2, 115.6 (*J* = 285.8 Hz), 83.7, 63.4, 55.5, 48.9, 27.6. Minor diastereomer (25%, selected signals): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.78 (d, *J* = 7.8 Hz, 1 H), 5.02 (dd, *J* = 7.8, 3.4 Hz, 1 H), 3.71–3.76 (m, 2 H), 3.55 (ddd, *J* = 9.6, 5.6, 3.4 Hz, 1 H), 3.45 (bs, 1 H), 1.45 (s, 9 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.4, 129.6, 129.0, 84.4, 62.0, 53.4, 49.7, 28.0. HRMS (CI) calcd. for $C_{16}H_{19}ClF_3NO_4$ $[M+1]^+$: 383.0925. Found: 383.0943.

General procedure for epoxide opening with dipeptide enolates

In a oven-dried Schlenk tube hexamethyldisilazane (411 mg, 2.54 mmol) was dissolved in dry THF (5.0 mL) under Ar. After the solution was cooled to –78 °C, a 1.6 M solution of *n*-BuLi (1.5 mL, 2.34 mmol) 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 $ZnCl_2$ (109 mg, 0.80 mmol) was dried with a heat gun under vacuum and dissolved in THF (2.0 mL) under Ar. The corresponding dipeptide (250 mg, 0.67 mmol) was added and the solution was cooled to –78 °C before the LHMDS solution was added slowly via syringe. The resulting

solution was stirred for 60 min at –78 °C. Then the corresponding epoxide (1.0 mmol) was added directly to the enolate at –78 °C, followed by $BF_3 \cdot OEt_2$ (47.4 mg, 0.34 mmol). The reaction mixture was allowed to warm to r.t. over night before it was hydrolyzed with 1M HCl and extracted three times with ethyl acetate. 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).

Oxidation of substituted peptides

The combined organic layers of the epoxide opening reaction were dried (Na_2SO_4) and the solvent was evaporated in vacuo. The crude product was re-dissolved in 10 ml dry dichloromethane and Dess-Martin periodinane (1.0 mmol) was added in one portion at 0 °C. After the oxidation was complete (tlc), the reaction was quenched by a saturated aqueous solution of $NaHCO_3$ containing $Na_2S_2O_3$ and the product was extracted three times with ethyl acetate. The combined organic layers were dried (Na_2SO_4), the solvent was removed *in vacuo*, and the crude product was purified by flash chromatography (silica gel, hexanes/EtOAc).

***tert*-Butyl 4-oxo-2-((*S*)-3-phenyl-2-(2,2,2-trifluoroacetamido)propanamido)pentanoate (4a).** Major diastereomer (68%): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.23–7.34 (m, 4 H), 7.18 (m, 1 H), 7.13 (d, *J* = 7.8 Hz, 1 H), 6.68 (d, *J* = 7.5 Hz, 1 H), 4.65 (m, 1 H), 4.60 (td, *J* = 8.2, 4.2 Hz, 1 H), 3.21 (dd, *J* = 13.9, 6.4 Hz, 1 H), 3.07–3.17 (m, 2 H), 2.90 (dd, *J* = 18.3, 9.0 Hz, 1 H), 2.14 (s, 3 H), 1.44 (s, 9 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 206.3, 168.9, 168.6, 156.9 (*J* = 37.5 Hz), 134.8, 129.3, 128.7, 127.4, 115.6 (*J* = 285.6 Hz), 82.8, 54.2, 48.9, 44.7, 38.3, 29.8, 27.8. Minor diastereomer (32%, selected signals): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.57 (bs, 1 H), 7.45 (bs, 1 H), 7.14–7.27 (m, 5 H), 4.74 (bs, 2 H), 3.20 (dd, *J* = 13.9, 6.1 Hz, 1 H), 2.91 (dd, *J* = 18.3, 4.2 Hz, 1 H), 2.12 (s, 3 H), 1.37 (s, 9 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 206.2, 168.7, 168.4, 134.8, 129.3, 128.7, 127.4, 82.8, 54.2, 48.9, 44.5, 38.3, 29.8, 27.7. HRMS (CI) calcd. for $C_{20}H_{25}F_3N_2O_5$ $[M+1]^+$: 431.1749. Found: 431.1794.

***tert*-Butyl 4-oxo-2-((*S*)-3-phenyl-2-(2,2,2-trifluoroacetamido)propanamido)hexanoate (4b).** Major diastereomer (67%): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.16–7.31 (m, 5 H), 7.14 (bs, 1 H), 6.82 (d, *J* = 7.5 Hz, 1 H), 4.69–4.74 (m, 1 H), 4.60 (td, *J* = 7.8, 4.3 Hz, 1 H), 3.06–3.29 (m, 4 H), 2.41–2.47 (m, 2 H), 1.44 (s, 9 H), 1.05 (t, *J* = 7.34 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 200.7, 169.1, 168.6, 156.9 (*J* = 37.5 Hz), 134.9, 129.2, 128.7, 127.4, 115.6 (*J* = 285.6 Hz), 83.2, 54.4, 48.9, 41.3, 35.6, 38.2, 27.6, 7.9. Minor diastereomer (33%, selected signals): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.14–7.31 (m, 6 H), 6.82 (d, *J* = 7.6 Hz, 1 H), 4.71 (m, 1 H), 4.60 (td, *J* = 7.9, 4.3 Hz, 1 H), 3.06–3.29 (m, 4 H), 2.41–2.47 (m, 2 H), 1.44 (s, 9 H), 1.06 (t, *J* = 7.3 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 200.7, 169.1, 168.6, 134.9, 129.2, 128.7, 127.4, 83.2, 54.4, 47.6, 41.3, 38.2, 27.7, 8.0. HRMS (CI) calcd. for $C_{21}H_{27}F_3N_2O_5$ $[M+1]^+$: 445.1908. Found: 445.1906.

***tert*-Butyl 5-chloro-4-oxo-2-((*S*)-3-phenyl-2-(2,2,2-trifluoroacetamido)propanamido) pentanoate (4d).** Major diastereomer (68%): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.16–7.31 (m, 6 H), 6.82 (d, *J* = 7.5 Hz, 1 H), 4.72 (m, 1 H), 4.60 (td, *J* = 7.8, 4.3 Hz, 1 H), 4.07 (d, *J* = 15.5 Hz,

1 H), 4.02 (d, *J* = 15.4 Hz, 1 H), 3.06–3.29 (m, 4 H), 1.44 (s, 9 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 200.7, 169.1, 168.6, 156.9 (*J* = 37.5 Hz), 134.9, 129.2, 128.7, 127.4, 115.6 (*J* = 285.6 Hz), 83.2, 54.4, 48.9, 47.6, 41.3, 38.2, 27.7. Minor diastereomer (32%, selected signals): ^{1}H NMR (400 MHz, $CDCl_3$): 6.81 (d, *J* = 7.5 Hz, 1 H), 4.69–4.74 (m, 2 H), 4.07 (d, *J* = 15.5 Hz, 1 H), 4.02 (d, *J* = 15.4 Hz, 1 H), 3.06–3.29 (m, 4 H), 1.45 (s, 9 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 200.7, 169.1, 168.6, 129.2, 128.7, 127.4, 115, 83.2, 54.4, 48.9, 47.6, 41.3, 38.2, 27.7. HRMS (CI) calcd. for $C_{20}H_{24}ClF_3N_2O_5$ $[M]^+$: 464.1326. Found: 464.1326.

***tert*-Butyl 5-phenoxy-4-oxo-2-((*S*)-3-phenyl-2-(2,2,2-trifluoroacetamido)propanamido) pentanoate (4f).** Major diastereomer (70%): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.13–7.33 (m, 9 H), 7.01 (m, 1 H), 6.85–6.88 (m, 2 H), 6.44 (d, *J* = 8.4 Hz, 1 H), 4.63–4.70 (m, 2 H), 4.41 (s, 2 H), 3.11–3.20 (m, 2 H), 2.98 (dd, *J* = 13.5, 8.8 Hz, 1 H), 2.80 (dd, *J* = 18.8, 4.3 Hz, 1 H), 1.36 (s, 9 H). ^{13}C NMR (100 MHz, $CDCl_3$) (from mixture): δ = 205.7, 168.8, 168.7, 157.4, 156.5 (*J* = 37.3 Hz), 135.3, 129.7, 129.2, 128.7, 127.2, 121.9, 114.4, 115.6 (*J* = 285.9 Hz), 82.9, 72.3, 54.6, 48.1, 41.0, 38.5, 27.7. Minor diastereomer (30%, selected signals): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.58 (d, *J* = 7.6 Hz, 1 H), 4.66–4.71 (m, 1 H), 4.62 (q, *J* = 6.7 Hz, 1 H), 4.53 (d, *J* = 6.8 Hz, 2 H), 3.28 (dd, *J* = 18.6, 4.4 Hz, 1 H), 1.44 (s, 9 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 205.9, 169.0, 168.9, 134.9, 129.6, 129.2, 128.6, 127.3, 121.8, 115.5 (*J* = 285.5 Hz), 82.9, 72.4, 54.3, 48.6, 41.0, 38.2, 27.7. HRMS (CI) calcd. for $C_{26}H_{29}F_3N_2O_6$ $[M]^+$: 522.1978. Found: 522.1953.

***tert*-Butyl 5-(4-methoxyphenoxy)-4-oxo-2-((*S*)-3-phenyl-2-(2,2,2-trifluoroacetamido) propanamido)pentanoate (4h).** Major diastereomer (69%): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.17–7.31 (m, 5 H), 7.01 (d, *J* = 7.3 Hz, 1 H), 6.79–6.84 (m, 4 H), 6.53 (d, *J* = 7.8 Hz, 1 H), 4.68 (m, 1 H), 4.61 (td, *J* = 13.4, 6.6 Hz, 1 H), 4.49 (d, *J* = 16.8 Hz, 1 H), 3.76 (s, 3 H), 3.27 (dd, *J* = 18.5, 4.3 Hz, 1 H), 3.18 (dd, *J* = 13.9, 6.7 Hz, 1 H), 3.07–3.14 (m, 2 H), 1.44 (s, 9 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 205.9, 168.8, 168.4, 156.9 (*J* = 37.5 Hz), 154.7, 151.6, 135.2, 129.2, 128.8, 127.4, 115.6 (*J* = 285.6 Hz), 115.5, 114.9, 83.0, 73.2, 55.7, 54.7, 48.2, 40.9, 38.6, 27.7. Minor diastereomer (31%, selected signals): ^{1}H NMR (400 MHz, $CDCl_3$): 7.14–7.30 (m, 6 H), 6.81–6.87 (m, 4 H), 6.31 (d, *J* = 7.8 Hz, 1 H), 4.60–4.69 (m, 2 H), 4.37 (s, 2 H), 3.77 (s, 3 H), 3.13–3.21 (m, 2 H), 2.97 (dd, *J* = 13.8, 8.8 Hz, 1 H), 2.79 (dd, *J* = 18.7, 4.3 Hz, 1 H), 1.38 (s, 9 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 206.2, 168.8, 168.6, 156.9 (*J* = 37.5 Hz), 154.6, 129.3, 128.8, 127.5, 115.6 (*J* = 285.6 Hz), 115.5, 115.0, 114.8, 83.1, 73.3, 55.6, 54.3, 48.6, 41.0, 38.2, 27.8. HRMS (CI) calcd. for $C_{27}H_{31}F_3N_2O_7$ $[M]^+$: 552.2083. Found: 552.2076.

***tert*-Butyl 5-(4-chlorophenoxy)-4-oxo-2-((*S*)-3-phenyl-2-(2,2,2-trifluoroacetamido)propanamido) pentanoate (4m).** Major diastereomer (64%): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.19–7.31 (m, 5 H), 7.00 (d, *J* = 7.3 Hz, 1 H), 6.76–6.83 (m, 4 H), 6.53 (d, *J* = 7.8 Hz, 1 H), 4.65–4.71 (m, 1 H), 4.61 (td, *J* = 13.4, 6.6 Hz, 1 H), 4.49 (d, *J* = 16.8 Hz, 1 H), 3.27 (dd, *J* = 18.5, 4.3 Hz, 1 H), 3.18 (dd, *J* = 13.9, 6.7 Hz, 1 H), 3.07–3.14 (m, 2 H), 1.44 (s, 9 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 205.9, 168.8, 168.4, 156.9 (*J* = 37.5 Hz), 154.7, 151.6, 135.2, 129.3, 128.8, 127.3, 115.6 (*J* = 285.6 Hz), 115.4, 83.0, 73.2, 55.6, 54.7, 48.1, 40.9, 38.6, 27.7. Minor diastereomer (36%, selected signals): ^{1}H NMR (400 MHz, $CDCl_3$): 7.16–7.31 (m, 6 H), 6.82–6.87 (m, 4 H), 6.40 (d, *J* = 8.0 Hz, 1 H), 4.63–4.71 (m, 2 H), 4.37 (s, 2 H), 3.12–3.21 (m, 2 H), 2.99 (dd, *J* = 13.9, 8.8

Hz, 1 H), 2.99 (dd, *J* = 18.7, 4.3 Hz, 1 H), 1.38 (s, 9 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 206.2, 168.8, 168.6, 154.6, 129.3, 128.8, 127.5, 115.5, 115.0, 114.8, 83.1, 73.3, 55.6, 54.3, 48.6, 41.0, 38.2, 27.8. HRMS (CI) calcd. for $C_{26}H_{28}ClF_3N_2O_6$ $[M+1]^+$: 558.1558. Found: 558.1575.

***tert*-Butyl 5-(4-nitrophenoxy)-4-oxo-2-((*S*)-3-phenyl-2-(2,2,2-trifluoroacetamido)propanamido) pentanoate (4n).** Major diastereomer (68%): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.13–7.31 (m, 6 H), 6.78–6.88 (m, 4 H), 6.31 (d, *J* = 7.3 Hz, 1 H), 4.63–4.71 (m, 2 H), 4.49 (d, *J* = 16.8 Hz, 1 H), 4.45 (d, *J* = 16.9 Hz, 1 H), 3.27 (dd, *J* = 18.5, 4.4 Hz, 1 H), 3.19 (dd, *J* = 13.9, 6.5 Hz, 1 H), 3.09 (dd, *J* = 13.8, 6.2 Hz, 1 H), 3.10–3.15 (m, 1 H), 1.43 (s, 9 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 205.9, 168.8, 168.4, 156.9 (*J* = 37.5 Hz), 154.7, 151.6, 135.2, 129.3, 128.8, 127.3, 115.6 (*J* = 285.6 Hz), 115.4, 83.0, 73.2, 55.6, 54.7, 48.1, 40.9, 38.6, 27.7. Minor diastereomer (32%, selected signals): ^{1}H NMR (400 MHz, $CDCl_3$): 7.14–7.29 (m, 6 H), 6.81–6.87 (m, 4 H), 6.40 (d, *J* = 8.0 Hz, 1 H), 4.63–4.71 (m, 2 H), 4.37 (s, 2 H), 3.12–3.21 (m, 2 H), 2.99 (dd, *J* = 13.9, 8.8 Hz, 1 H), 2.99 (dd, *J* = 18.7, 4.3 Hz, 1 H), 1.38 (s, 9 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 206.2, 168.8, 168.6, 154.6, 129.3, 128.8, 127.5, 115.5, 115.0, 114.8, 83.1, 73.3, 55.6, 54.3, 48.6, 41.0, 38.2, 27.8. HRMS (CI) calcd. for $C_{26}H_{28}F_3N_3O_8$ $[M+1]^+$: 568.1862. Found: 568.1878.

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