Synthesis of highly substituted pyroglutamates *via* a domino Michael addition–Claisen rearrangement–lactamisation approach

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Received 4th July 2008, Accepted 20th August 2008
First published as an Advance Article on the web 28th October 2008
DOI: 10.1039/b811382c

Chelated enolates are versatile nucleophiles for Michael additions to α,β-unsaturated allylic esters. By quenching the reaction with TMSCl and heating a subsequent Ireland–Claisen rearrangement can occur. Direct cyclisation of the rearrangement product gives rise to highly substituted pyroglutamic acid derivatives.

Introduction

Pyroglutamic acid can be looked upon as an internally protected glutamic acid. It can be found as the *N*-terminal end group in many natural products such as gonadotropin-[1] and thyrotropin-releasing[2] hormones, depsipeptides like the didemnines[3] as well as many others.[4] Pyroglutamic acid is also a valuable chiral building block for natural product synthesis,[5] such as for domoic[6] and kainic acid.[7] In addition it serves as a starting material for the synthesis of chiral auxiliaries, such as RAMP.[8]

Substituted pyroglutamates can easily be obtained by lactamisation of the corresponding glutamates, which themselves are accessible *via* Michael addition of suitably protected glycine enolates. Very popular in this respect are the enolates of O'Donnell's phenylimino glycine esters,[9] which also allow the preparation of an asymmetric version using chiral alcohols in the ester moieties[10] or chiral phase transfer catalysts.[11] Also frequently used are the "chiral glycine enolates" described by Schöllkopf *et al.*[12] and Seebach and Suzuki.[13] These enolates can also be applied in Michael-induced ring closures (MIRC),[14] if Michael acceptors bearing a leaving group are used.[15]

Our group is also involved in amino acid synthesis, investigating reactions of chelated ester enolates.[16] These enolates were found to be excellent nucleophiles in a wide range of reactions, including Michael additions to nitroalkenes[17] and α,β-unsaturated esters.[18] In reactions of unsaturated esters containing a leaving group in a suitable position, cyclic products could be obtained *via* a subsequent ring closure (MIRC).[19] Interestingly, the selectivities in the Michael addition step are significantly better with the (*Z*)-α,β-unsaturated esters, compared with the (*E*)-isomers.

Based on our long term research on Claisen rearrangements,[20] especially for the synthesis of unsaturated amino acids and peptides,[21] we were interested to see if it was also possible to combine the Michael addition with a subsequent Claisen rearrangement, preferentially under Ireland conditions.[22] A first example of such a domino process was described by Kuwajima and Aoki.[23] They reported on Cu-catalysed additions of Grignard reagents to α,β-unsaturated allylic esters in the presence of TMSCl. Subsequent heating initiated a Claisen rearrangement of the *in situ* formed silylketenacetal. The carboxylic acid obtained was formed as a 2 : 1 (*syn* : *anti*) diastereoisomeric mixture, indicating a moderate *E*/*Z*-selectivity in the enolate formation step. Yamazaki and Kitazume investigated the addition of lithium enolates to fluorinated allylic acrylates.[24] They obtained good selectivities but moderate yields. Unfortunately, this reaction was limited to unsubstituted allyl esters.

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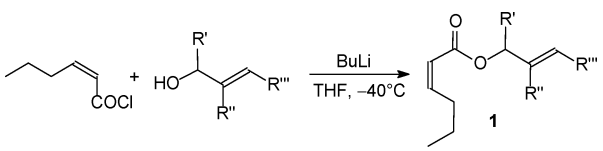
Results and discussion

To investigate such a domino sequence with chelated enolates, we synthesised several (2*Z*)-configured unsaturated allylic esters **1**, because of their better selectivities in the Michael addition step.[18] Surprisingly, this was not as easy as expected. Attempts to introduce the *cis* double bond *via* Lindlar hydrogenation were unsuccessful, because especially with terminal allylic esters the double bond was also hydrogenated, and we were not able to separate the allylic esters from the saturated ones. Coupling of (2*Z*)-hexenoic acid with several allylic alcohols under Steglich conditions[25] resulted in the formation of an *E*/*Z*-mixture. Probably, the DMAP used as a catalyst undergoes 1,4-addition–elimination on the α,β-unsaturated ester, resulting in an isomerisation. Therefore, we decided to deprotonate the alcohol with BuLi, and add the lithium alcoholate obtained to the acyl halide at −40 °C (Scheme 1). Under these mild conditions, the allylic esters **1** could be obtained in good yield and without isomerisation (Table 1).



Scheme 1 Preparation of *α*,*β*-unsaturated allylic esters **1**

To get an impression of the selectivity in the Michael addition step we first investigated this part of our planned domino process

Table 1 Preparation of *α*,*β*-unsaturated allylic esters **1**

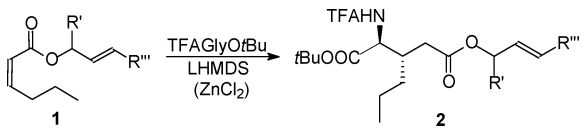
Entry	R′	R″	R‴	Yield (%)	Ester
1	H	H	H	73	**1a**
2	H	Me	H	82	**1b**
3	Ph	H	H	89	**1c**
4	H	H	Ph	78	**1d**
5	*i*Pr	H	H	88	**1e**

Table 2 Michael additions to α,β-unsaturated allylic esters **1**

Entry	Ester	R′	R‴	Product	Yield (%)	*anti* : *syn*
1[a]	**1a**	H	H	**2a**	86	>99 : 1
2	**1a**	H	H	**2a**	91	98 : 2
3	**1c**	Ph	H	**2c**	90	98 : 2
4	**1d**	H	Ph	**2d**	73	97 : 3

[a] Reaction in the presence of $ZnCl_2$.

(Scheme 2). Esters **1** were found to be much less reactive than the esters investigated before, having a leaving group at the γ-position.[19] The reactions with zinc-chelated glycine ester enolates had to be warmed to room temperature for complete conversion (Table 2, entry 1). But even under these conditions the selectivity was excellent. Interestingly, the corresponding lithium enolate reacted at −78 °C and gave comparable yield and selectivity, independent of the allylic ester used (entries 2–4).



Scheme 2 Michael additions to α,β-unsaturated allylic esters **1**.

With these results in hand we next focused on the combination of Michael addition and Ireland–Claisen rearrangement. Attempts to trap the zinc enolate with TMSCl and to initiate the rearrangement by heating were unsuccessful (Table 3, entry 1). Only the Michael adduct **2** could be obtained, albeit in high yield. Probably the zinc enolate formed *in situ* is either too stable or a Reformatsky type *C*-enolate, which can not undergo Claisen rearrangement. Therefore, we repeated the reaction with the lithium enolate. TMSCl was added at −78 °C after all the Michael acceptor was consumed, and the mixture was warmed to room temperature and refluxed for 12 h. A clean conversion was observed (only 7% Michael adduct **2**) but interestingly it was not the acyclic rearrangement product that was obtained but the pyroglutamic acid derivative **3a** (Scheme 3).

Obviously, under these reaction conditions the deprotonated amide attacks the silylester formed in the rearrangement step, and under the workup conditions (1 M $KHSO_4$) the TFA-protecting group is directly cleaved. Interestingly, **3a** was formed as a nearly 1 : 1 diastereoisomeric mixture. With respect to the highly selective

Table 3 Domino Michael addition–Claisen rearrangement–lactamisations

		Yield (%)		d.r.	d.r.
Entry	Ester	**2**	**3**	(C-3 : C-4)	(C-4 : C-6)
1[a]	**1a**	88	—	—	—
2	**1a**	7	89	43 : 57	—
3	**1b**	21	71	42 : 58	—
4	**1c**	26	52	44 : 56	—
5	**1d**	29	58	31 : 69	83 : 17
6	**1e**	10	81	48 : 52	—

[a] Reaction in the presence of $ZnCl_2$.

Scheme 3 Domino Michael addition–Claisen rearrangement–lactamisations.

Michael addition, these two stereoisomers have to be formed in the rearrangement step, probably *via* an *E*/*Z*-enolate mixture. This would be in good agreement with the results described by Kuwajima and Aoki.[23]

The determination of the relative configuration was relatively easily possible with these products by NOESY NMR experiments. The major *cis*-product showed interactions between 9-H and 2-H as well as 6-H, whereas the minor *trans*-isomer showed interactions between 9-H and the ring protons at C-2 and C-4 (Fig. 1).

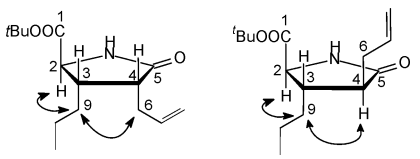


Fig. 1 Determination of configuration of **3a**.

To prove the generality of this reaction sequence we also investigated the rearrangements of the other substrates **1b–1e** (Table 3, entries 3–6). All substrates underwent Claisen rearrangement, although not always completely. This was especially the case with the phenyl-substituted derivatives **1c** and **1d**, where a significant amount of Michael product was obtained. With the cinnamyl substrate **1d** 4 stereogenic centres were formed in one step. While the configuration of C-2/C-3 is controlled by the Michael addition step (which is highly selective) the stereogenic centres at C-4 and C-6 are the result of the Claisen rearrangement. No induced diastereoselectivity (C-3/C-4) was observed, and the moderately simple diastereoselectivity (C-4/C-6), which provides information about the enolate geometry, indicates that probably a low *E*/*Z*-enolate selectivity is responsible for this observation.

Conclusion

In conclusion we can show that the combination of a Michael addition of chelated enolates with the Ireland–Claisen rearrangement is a straightforward protocol towards highly substituted pyroglutaminic acid derivatives. Up to four stereogenic centres can be generated in one step.

Further investigations, especially concerning the control of stereoselectivity and the absolute configuration are in progress.

Experimental Section

Allyl (2*Z*)-hexenoate (1a)

(2*Z*)-Hexenoic acid (2.79 g, 24.47 mmol) was dissolved in acetonitrile (20 mL) before ethyldiisopropylamine (4.70 mL, 27.45 mmol) was added at 0 °C. Allyl bromide (3.46 mL, 40 mmol) was added and the mixture was allowed to warm to room temperature overnight. The solvent was removed *in vacuo* and the residue was

dissolved in ether. The solution was washed with 1 N $KHSO_4$ and the aqueous layer was extracted twice with CH_2Cl_2. The combined organic layers were dried (Na_2SO_4) and after evaporation of the solvent the crude product was purified by flash chromatography (hexanes : EtOAc 95 : 5) giving rise to **1a** (2.77 g, 18.00 mmol, 73%) as a colourless oil. ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 0.93$ (t, $J =$ 7.4 Hz, 3H), 1.46 (tq, $J = 7.4$, 7.4 Hz, 2H), 2.62 (ddt, $J = 7.5$, 7.4, 1.7 Hz, 2H), 4.60 (ddd, $J = 5.7$, 1.4, 1.4 Hz, 2H), 5.22 (ddt, $J =$ 10.4, 1.4, 1.4 Hz, 1H), 5.31 (ddt, $J = 17.2$, 1.4, 1.4 Hz, 1H), 5.79 (dt, $J = 11.5$, 1.7 Hz, 1H), 5.93 (ddt, $J = 17.2$, 10.4, 5.7 Hz, 1H), 6.23 (td, $J = 11.5$, 7.5 Hz, 1H). ^{13}C NMR (125 MHz): $\delta = 13.7$ (q), 22.3 (t), 31.0 (t), 64.5 (t), 118.0 (d), 119.4 (d), 132.4 (t), 151.9 (d), 166.0 (s). HRMS (CI) calcd for $C_9H_{15}O_2$ $[M + H]^+$: 155.1072. Found: 155.1080.

Preparation of the unsaturated allylic esters 1

(2*Z*)-Hexenoic acid chloride was freshly prepared by the addition of oxalyl chloride (4 mmol) to hexenoic acid[26] (2 mmol) at room temperature. After stirring for 20 min, the excess of oxalyl chloride was removed *in vacuo* (40 °C, 200 mbar). The crude acyl chloride was used without further purification.

The corresponding allylic alcohol (1 mmol) was dissolved in THF (5 mL) and cooled to –40 °C before *n*-BuLi (1.1 mmol) was added. After stirring for 10 min the crude acyl halide (2 mmol) was added and the mixture was allowed to warm to room temperature. After 2 h 1 N $KHSO_4$ was added and after the usual workup the esters **5** were purified by flash chromatography (hexanes : EtOAc ~ 95 : 5).

2-Methylallyl (2*Z*)-hexenoate (1b)

According to the general procedure for the preparation of the unsaturated allyl esters, **1b** was obtained from (2*Z*)-hexenoic acid (804 mg, 7.05 mmol) and methylallylalcohol (240 mg, 3.33 mmol) in 82% yield (426 mg, 2.73 mmol) as a colourless oil. ^{1}H NMR (500 MHz): $\delta = 0.93$ (t, $J = 7.4$ Hz, 3H), 1.46 (tq, $J = 7.4$, 7.4 Hz, 2H), 1.75 (s, 3H), 2.62 (ddt, $J = 7.5$, 7.5, 1.7 Hz, 2H), 4.52 (s, 2H), 4.91 (s, 1H), 4.97 (s, 1H), 5.80 (dt, $J = 11.5$, 1.6 Hz, 1H), 6.22 (td, $J = 11.5$, 7.5 Hz, 1H). ^{13}C NMR (125 MHz): $\delta = 13.7$ (q), 19.5 (q), 22.3 (t), 31.0 (t), 67.2 (t), 112,8 (t), 119.5 (d), 140,2 (t), 150.9 (d), 166.0 (s). HRMS (CI) calcd for $C_{10}H_{17}O_2$ $[M + H]^+$: 169.1229. Found: 169.1227.

1-Phenylallyl (2*Z*)-hexenoate (1c)

According to the general procedure for the preparation of the unsaturated allyl esters, **1c** was obtained from (2*Z*)-hexenoic acid (854 mg, 7.49 mmol) and 1-phenylallylalcohol (502 mg, 3.75 mmol) in 89% yield (767 mg, 3.34 mmol) as a colourless oil. ^{1}H NMR (500 MHz): $\delta = 0.91$ (t, $J = 7.4$ Hz, 3H), 1.45 (m, 2H), 2.62 (ddt, $J = 7.4$, 3.2, 1.7 Hz, 2H), 5.23 (dt, $J = 10.4$, 1.3, 1.3 Hz, 1H), 5.29 (dt, $J = 17.1$, 1.3, 1.3 Hz, 1H), 5.84 (dt, $J =$ 11.5, 1.7 Hz, 1H), 6.02 (ddt, $J = 17.1$, 10.4, 5.9 Hz, 1H), 6.24 (dt, $J = 11.5$, 7.5 Hz, 1H), 6.29 (d, $J = 5.9$ Hz, 1H), 7.28 (m, 1H), 7.32–7.37 (m, 4H). ^{13}C NMR (125 MHz): $\delta = 13.7$ (q), 22.3 (t), 31.0 (t), 75.7 (t), 116.8 (d), 119.6 (d), 127.1 (d), 128.5 (d), 128.0 (d), 136.5 (d), 139.1 (s), 151.2 (d), 165.3 (s). HRMS (CI) calcd for $C_{15}H_{18}O_2$ $[M]^+$: 230.1307. Found: 230.1318.

Cinnamyl (2*Z*)-hexenoate (1d)

According to the general procedure for the preparation of the unsaturated allyl esters, **1d** was obtained from (2*Z*)-hexenoic acid (811 mg, 7.11 mmol) and cinnamylalcohol (451 mg, 3.37 mmol) in 78% yield (573 mg, 2.63 mmol) as a colourless oil. ^{1}H NMR (500 MHz): $\delta = 0.93$ (t, $J = 7.4$ Hz, 3H), 1.46 (tq, $J = 7.4$, 7.4 Hz, 2H), 2.63 (ddt, $J = 7.5$, 7.5, 1.7 Hz, 2H), 4.75 (dd, $J = 6.4$, 1.3 Hz, 2H), 5.80 (dt, $J = 11.5$, 1.5 Hz, 1H), 6.21–6.32 (m, 2H), 6.64 (d, $J = 15.9$ Hz, 1H), 7.23 (m, 1H), 7.29, 7.37 (2 m, 4H). ^{13}C NMR (125 MHz): $\delta = 13.7$ (q), 22.3 (t), 31.0 (t), 64.4 (t), 119.5 (d), 123.5 (d), 126.6 (d), 128.6 (d), 128.0 (d), 133.9 (d), 136.3 (s), 151.0 (d), 166.1 (s). HRMS (CI) calcd for $C_{15}H_{18}O_2$ $[M]^+$: 230.1307. Found: 230.1301.

1-Isopropylallyl (2*Z*)-hexenoate (1e)

According to the general procedure for the preparation of the unsaturated allyl esters, **1e** was obtained from (2*Z*)-hexenoic acid (798 mg, 7.00 mmol) and 1-isopropylallylalcohol (338 mg, 3.38 mmol) in 88% yield (547 mg, 2.97 mmol) as a colourless oil. ^{1}H NMR (500 MHz): $\delta = 0.90$–0.94 (m, 9H), 1.45 (m, 2H), 1.88 (m, 1H), 2.61 (ddt, $J = 7.5$, 7.5, 1.7 Hz, 2H), 5.08 (m, 1H), 5.17–5.23 (m, 2H), 5.73– 5.80 (m, 2H), 6.20 (dt, $J = 11.5$, 7.5 Hz, 1H). ^{13}C NMR (125 MHz): $\delta = 13.7$ (q), 17.9 (q), 18.0 (q), 22.3 (t), 31.0 (t), 31.9 (d), 78.8 (d), 117.3 (t), 120.0 (d), 134.9 (d), 150.3 (d), 165.8 (s). HRMS (CI) calcd for $C_{12}H_{20}O_2$ $[M]^+$: 196.1463. Found: 196.1457.

Michael addition of chelated enolates to allylic esters 1

In a Schlenk flask hexamethyldisilazane (0.3 mL, 1.42 mmol) was dissolved in THF (2 mL). The solution was cooled to –78 °C before *n*-BuLi (1.6 M, 0.78 mL, 1.25 mmol) was added. The cooling bath was removed and the solution was allowed to warm up for 15 min, before it was cooled again to –78 °C. In a second Schlenk flask $ZnCl_2$ (80 mg, 0.57 mmol) was dried with a heat gun under high vacuum, before it was dissolved in THF (3 mL). After addition of TFA-Gly-O*t*Bu (115 mg, 0.5 mmol) the solution was cooled to –78 °C, before the freshly prepared LHMDS solution was added. 15 Min later the Michael acceptor (0.5 mmol) was added in THF (2 mL). After complete consumption of the starting materials (TLC control) the solution was diluted with ether before 1 N $KHSO_4$ was added. The layers were separated, the aqueous phase was washed twice with CH_2Cl_2 and the combined organic layers were dried (Na_2SO_4). After evaporation of the solvent *in vacuo* the crude product was purified by flash chromatography.

5-Allyl 1-*tert*-butyl 3-propyl-2-(trifluoroacetylamino)-pentanedioate (2a)

According to the general procedure for the Michael additions, **2a** was obtained from TFA-Gly-O*t*Bu (475 mg, 2.09 mmol) and allyl ester **1a** (293 mg, 1.90 mmol) in 91% yield (660 mg, 1.73 mmol) as a colourless oil. ^{1}H NMR (500 MHz): $\delta = 0.87$ (t, $J = 6.9$ Hz, 3H), 1.27–1.40 (m, 4H), 1.44 (s, 9H), 2.33–2.48 (m, 3H), 4.51–4.60 (m, 3H), 5.28 (ddt, $J = 10.4$, 2.4, 1.2 Hz, 1H), 5.28 (ddt, $J = 17.2$, 1.5, 1.2 Hz, 1H), 5.86 (ddt, $J = 17.2$, 10.4, 5.9 Hz, 1H), 7.85 (d, $J = 8.0$ Hz, 1H). ^{13}C NMR (100 MHz): $\delta = 13.8$ (q), 19.9 (t), 27.8 (q), 32.8 (t), 35.0 (t), 36.6 (d), 55.3 (d), 65.7 (t), 83.2 (s), 115.8 (q,

J = 287 Hz), 118.8 (t), 131.6 (d), 157.1 (q, J = 37 Hz), 169.2 (s), 172.8 (s). Anal. calcd for $C_{17}H_{26}F_3NO_5$ (381.39): C 53.54; H 6.87; N 3.67. Found: C 53.65; H 6.62; N 3.88.

1-*tert*-Butyl 5-(2-methylallyl) 3-propyl-2-(trifluoroacetylamino)-pentanedioate (2b)

According to the general procedure for the Michael additions, **2b** was obtained from TFA-Gly-O*t*Bu (110 mg, 0.48 mmol) and allyl ester **1b** (73 mg, 0.43 mmol) as the minor product (besides pyroglutamate **3b**) in 21% yield (36 mg, 0.09 mmol) as a colourles oil. ^{1}H MR (500 MHz): δ = 0.89 (t, J = 7.0 Hz, 3H), 1.29–1.41 (m, 4H), 1.46 (s, 9H), 1.73 (s, 3H), 2.38–2.48 (m, 3H), 4.48 (d, J = 13.0 Hz, 1H), 4.52 (d, J = 13.0 Hz, 1H), 4.58 (dd, J = 8.3, 4.0 Hz, 1H), 4.93 (s, 1H), 4.96 (s, 1H), 7.86 (d, J = 8.3 Hz, 1H). ^{13}C NMR (125 MHz): δ = 13.8 (q), 19.4 (q), 20.0 (t), 27.9 (q), 32.9 (t), 35.1 (t), 36.7 (d), 55.4 (d), 68.4 (t), 83.3 (s), 113.5 (t), 115.8 (q, J = 288 Hz), 139.4 (s), 157.1 (q, J = 37 Hz), 169.2 (s), 172.7 (s). HRMS calcd for $C_{18}H_{29}F_3NO_5$ [M + H]$^+$: 396.1999. Found: 396.2005.

5-(1-Phenylallyl) 1-*tert*-butyl 3-propyl-2-(trifluoroacetylamino)-pentanedioate (2c)

According to the general procedure for the Michael additions, **2c** was obtained from TFA-Gly-O*t*Bu (120 mg, 0.53 mmol) and allyl ester **1c** (107 mg, 0.46 mmol) in 90% yield (192 mg, 0.42 mmol) as a 1 : 1 diastereoisomeric mixture. ^{1}H NMR (500 MHz): δ = 0.81, 0.86 (2t, J = 7.1, 7.0 Hz, 3H), 1.19–1.38 (m, 4H), 1.42, 1.44 (2s, 9H), 2.24–2.51 (m, 3H), 4.54–4.59 (m, 1H), 5.24–5.30 (m, 2H), 5.95–6.03 (m, 1H), 6.25–6.27 (m, 1H), 7.27–7.36 (m, 5H), 7.74–7.78 (m, 1H). ^{13}C NMR (125 MHz): δ = 13.78, 13.83 (2q), 19.95, 19.99 (2t), 27.89, 27.90 (2q), 32.73, 32.87, 35.25, 35.35 (4t), 36.79, 36.80 (2d), 55.37, 55.43 (2d), 77.07 (d), 83.29 (s), 117.46, 117.53 (2t), 127.20 (d), 127.22 (d), 128.57 (d), 128.60 (d), 128.4 (d), 135.68, 135.73 (2d), 138.31, 138.35 (2 s), 169.23, 171.99 (2 s), signals for TFA-group not observed. HRMS calcd for $C_{23}H_{30}F_3NO_5$ [M + H]$^+$: 457.2076. Found: 457.2066.

5-Cinnamyl 1-*tert*-butyl 3-propyl-2-(trifluoroacetylamino)-pentanedioate (2d)

According to the general procedure for the Michael additions (without $ZnCl_2$), **2d** was obtained from TFA-Gly-O*t*Bu (111 mg, 0.49 mmol) and allyl ester **1d** (105 mg, 0.46 mmol) in 73% yield (153 mg, 0.36 mmol) as a colourless oil. ^{1}H NMR (500 MHz): δ = 0.90 (t, J = 6.9 Hz, 3H), 1.31–1.42 (m, 4H), 1.46 (s, 9H), 2.37–2.51 (m, 3H), 4.35 (dd, J = 8.4, 4.0 Hz, 1H), 4.74 (d, J = 6.6 Hz, 2H), 6.25 (dt, J = 15.9, 6.6 Hz, 1H), 6.65 (d, J = 15.9 Hz, 1H), 7.26 (m, 1H), 7.29–7.37 (m, 4H), 7.87 (d, J = 8.4 Hz, 1H). ^{13}C NMR (125 MHz): δ = 13.9 (q), 20.0 (t), 27.9 (q), 32.9 (t), 35.2 (t), 36.7 (d), 55.4 (d), 65.8 (t), 83.3 (s), 115.6 (q, J = 288 Hz), 122.4 (d), 126.6 (d), 128.6 (d), 128.2 (d), 134.9 (d), 136.0 (s), 157.1 (q, J = 37 Hz), 169.2 (s), 172.8 (s). HRMS calcd for $C_{23}H_{30}F_3NO_5$ [M + H]$^+$: 457.2076. Found: 457.2089.

Domino Michael addition–Ireland–Claisen rearrangement–lactamisation

According to the general procedure for the Michael additions, TFA-Gly-O*t*Bu (1 mmol) was reacted with allylic ester **1** (0.8 mmol). After complete consumption of **1** (~ 30 min) freshly dist. TMSCl (4 mmol) was added at −78 °C. The cooling bath was removed and the reaction mixture was allowed to warm to rt. After refluxing for 12–14 h the reaction mixture was cooled to rt before ether and 1 N $KHSO_4$ were added. The aqueous layer was washed twice with CH_2Cl_2, the combined organic layers were dried (Na_2SO_4) and the solvent was evaporated *in vacuo.* The crude product was purified by flash chromatography.

tert-Butyl 4-allyl-3-propyl-pyroglutamate (3a)

According to the general procedure for the domino reactions, **3a** was obtained from TFA-Gly-O*t*Bu (128 mg, 0.50 mmol) and allyl ester **1a** (79 mg, 0.51 mmol) in 89% yield (122 mg, 0.46 mmol) as a diastereoisomeric mixture. Ratio of **(3,4-*cis*)-3a** : **(3,4-*trans*)-3a** = 57 : 43. **(3,4-*cis*)-3a**: R_f: 0.27 (hexanes : EtOAc 9 : 1). ^{1}H NMR (500 MHz): δ = 0.90 (t, J = 7.0 Hz, 3H), 1.3–1.22 (m, 4H), 1.43 (s, 9H), 2.16 (m, 1H), 2.44–2.49 (m, 2H), 2.59 (m, 1H), 3.74 (d, J = 3.4 Hz, 1H), 5.02 (dd, J = 10.2, 1.0 Hz, 1H), 5.07 (dd, J = 17.1, 1.0 Hz, 1H), 5.81 (m, 1H), 6.65 (bs, 1H). ^{13}C NMR (125 MHz): δ = 13.7 (q), 20.3 (t), 27.9 (q), 29.5 (t), 29.8 (t), 41.9 (d), 42.9 (d), 59.1 (d), 82.2 (s), 116.3 (t), 135.8 (d), 171.1 (s), 179.1 (s). **(3,4-*trans*)-3a**: R_f: 0.17 (hexanes : EtOAc 9 : 1). ^{1}H NMR (500 MHz): δ = 0.90 (t, J = 7.3 Hz, 3H), 1.36 (dqd, J = 7.5, 7.5, 7.3 Hz, 2H), 1.43 (s, 9H), 1.52 (m, 2H), 2.15 (m, 1H), 2.21 (m, 1H), 2.29 (m, 1H), 2.41 (m, 1H), 3.67 (d, J = 4.7 Hz, 1H), 5.03 (m, 2H), 5.70 (m, 1H), 6.58 (bs, 1H). ^{13}C NMR (125 MHz): δ = 13.9 (q), 19.8 (t), 27.9 (q), 35.2 (t), 37.5 (t), 42.2 (d), 46.9 (d), 60.1 (d), 82.1 (s), 117.5 (t), 135.0 (d), 171.3 (s), 178.8 (s). Anal. calcd for $C_{15}H_{25}NO_3$ (267.36): C 67.38; H 9.42; N 5.24. Found: C 67.20; H 8.99; N 5.01. HRMS calcd for $C_{15}H_{26}NO_3$ [M + H]$^+$: 268.1913. Found: 268.1895.

tert-Butyl 4-(2-methylallyl)-3-propyl-pyroglutamate (3b)

According to the general procedure for the domino reactions, **3b** was obtained from TFA-Gly-O*t*Bu (110 mg, 0.48 mmol) and allyl ester **1b** (73 mg, 0.43 mmol) as the major product (besides Michael adduct **2b**) in 71% yield (82 mg, 0.31 mmol) as a colourless oil. Ratio **(3,4-*cis*)-3b** : **(3,4-*trans*)-3b** = 58 : 42. **(3,4-*cis*)-3b**: R_f: 0.26 (hexanes : EtOAc 9 : 1). ^{1}H NMR (500 MHz): δ = 0.90 (t, J = 6.9 Hz, 3H), 1.18–1.31 (m, 3H), 1.42 (m, 1H), 1.44 (s, 9H), 1.73 (s, 3H), 2.05 (d, J = 16.4, 11.4 Hz, 1H), 2.46–2.53 (m, 2H), 2.75 (m, 1H), 3.74 (s, 1H), 4.68 (s, 1H), 4.78 (s, 1H), 6.31 (bs, 1H). ^{13}C NMR (125 MHz): δ = 13.6 (q), 20.2 (t), 22.7 (q), 29.7 (d), 32.6 (d), 40.9 (d), 41.8 (d), 58.6 (d), 82.1 (s), 110.6 (t), 143.3 (d), 171.4 (s), 179.0 (s). **(3,4-*trans*)-3b**: R_f: 0.16 (hexanes : EtOAc 9 : 1). ^{1}H NMR (500 MHz): δ = 0.90 (t, J = 6.9 Hz, 3H), 1.36 (m, 2H), 1.45 (s, 9H), 1.52 (m, 2H), 1.69 (s, 3H), 2.10–2.25 (m, 3H), 2.48 (dd, J = 13.5, 3.3 Hz, 1H), 3.69 (d, J = 3.4 Hz, 1H), 4.68 (s, 1H), 4.78 (s, 1H), 6.25 (bs, 1H). ^{13}C NMR (125 MHz): δ = 13.9 (q), 29.7 (t), 21.8 (q), 37.8 (d), 39.8 (d), 42.4 (d), 45.4 (d), 60.0 (d), 82.1 (s), 113.2 (t), 142.8 (d), 171.7 (s), 179.3 (s). Anal. calcd for $C_{16}H_{27}NO_3$ (281.40): C 68.29; H 9.67; N 4.98. Found: C 68.12; H 9.45; N 5.10.

tert-Butyl 4-(3-phenylallyl)-3-propyl-pyroglutamate (3c)

According to the general procedure for the domino reactions, **3c** was obtained from TFA-Gly-O*t*Bu (126 mg, 0.55 mmol) and allyl ester **1c** (112 mg, 0.49 mmol) as the major product (besides Michael adduct **2c**) in 52% yield (88 mg, 0.26 mmol) as a colourless oil.

Ratio **(3,4-*cis*)-3c** : **(3,4-*trans*)-3c** = 56 : 44. **(3,4-*cis*)-3c**: R_f: 0.26 (hexanes : EtOAc 9 : 1). ^{1}H NMR (500 MHz): δ = 0.93 (t, J = 7.1 Hz, 3H), 1.32–1.48 (m, 3H), 1.45 (s, 9H), 1.57 (m, 1H), 2.36 (m, 1H), 2.53 (m, 1H), 2.62–2.69 (m, 2H), 3.75 (d, J = 3.6 Hz, 1H), 6.22 (ddd, J = 15.7, 7.4, 6.1 Hz, 1H), 6.22 (bs, 1H), 6.46 (d, J = 15.7 Hz, 1H), 7.19 (m, 1H), 7.26–7.33 (m, 4H). ^{13}C NMR (125 MHz): δ = 13.8 (q), 20.4 (t), 28.0 (q), 29.5 (t), 30.0 (t), 42.0 (d), 43.4 (d), 59.1 (d), 82.3 (s), 126.1 (d), 128.5 (d), 127.2 (d), 127.5 (d), 131.8 (d), 137.3 (s), 171.1 (s), 178.6 (s), signals for TFA-group not observed. **(3,4-*trans*)-3c**: R_f: 0.17 (hexanes : EtOAc 9 : 1). ^{1}H NMR (500 MHz): δ = 0.93 (t, J = 7.3 Hz, 3H), 1.42 (s, 9H), 1.43–1.65 (m, 4H), 2.27–2.38 (m, 2H), 2.52 (m, 1H), 2.61 (m, 1H), 3.73 (d, J = 4.4 Hz, 1H), 6.14 (ddd, J = 15.7, 7.3 Hz, 7.3 Hz, 1H), 6.43 (d, J = 15.7 Hz, 1H), 6.58 (bs, 1H), 7.20 (m, 1H), 7.26–7.35 (m, 4H). ^{13}C NMR (125 MHz): δ = 13.9 (q), 19.8 (t), 27.8 (q), 34.4 (t), 37.5 (t), 42.2 (d), 47.1 (d), 60.1 (d), 82.0 (s), 126.0 (d), 128.3 (d), 126.6 (d), 127.1 (d), 132.7 (d), 137.1 (s), 171.3 (s), 178.5 (s). Anal. calcd for $C_{21}H_{29}NO_3$ (343.46): C 73.44; H 8.51; N 4.08. Found: C 72.93; H 8.63; N 4.11. HRMS calcd for $C_{21}H_{29}NO_3$ [M]$^+$: 343.2147. Found: 343.2157.

tert-Butyl 4-(1-phenylallyl)-3-propyl-pyroglutamate (3d)

According to the general procedure for the domino reactions, **3d** was obtained from TFA-Gly-O*t*Bu (106 mg, 0.47 mmol) and allyl ester **1d** (97 mg, 0.42 mmol) as the major product (besides Michael adduct **2d**) in 58% yield (85 mg, 0.25 mmol) as a mixture of diastereomers. Ratio **(3,4-*cis*)-3d** : **(3,4-*trans*)-3d** = 69 : 31. **(3,4-*cis*)-3d** (major diastereomer): ^{1}H NMR (500 MHz): δ = 0.75 (t, J = 7.3 Hz, 3H), 1.26–1.48 (m, 4H), 1.51 (s, 9H), 2.43 (m, 1H), 3.10 (dd, J = 8.0, 8.0 Hz, 1H), 3.65 (dd, J = 8.0, 7.9 Hz, 1H), 3.77 (d, J = 3.8 Hz, 1H), 4.96 (ddd, J = 17.1, 1.3, 1.3 Hz, 1H), 5.10 (ddd, J = 10.3, 1.3, 1.3 Hz, 1H), 6.38 (bs, 1H), 6.42 (ddd, J = 17.1, 10.3, 7.9 Hz, 1H), 7.24 (m, 1H), 7.27–7.36 (m, 4H). ^{13}C NMR (125 MHz): δ = 13.7 (q), 20.2 (t), 27.9 (q), 29.2 (t), 43.0 (d), 46.2 (d), 46.9 (d), 58.5 (d), 82.1 (s), 115.7 (t), 126.5 (d), 128.0 (d), 128.5 (d), 140.4 (d), 142.2 (s), 171.0 (s), 177.7 (s), signals for TFA-group not observed. **(3,4-*cis*)-3d** (minor diastereomer, selected signals): ^{1}H NMR (500 MHz): δ = 0.93 (t, J = 7.3 Hz, 3H), 1.48 (s, 9H), 2.60 (m, 1H), 3.04 (dd, J = 8.0, 6.3 Hz, 1H), 3.34 (d, J = 6.0 Hz, 1H), 3.73 (dd, J = 6.7, 6.7 Hz, 1H), 6.19 (bs, 1H), 6.27 (ddd, J = 16.8, 10.4, 8.3 Hz, 1H). ^{13}C NMR (125 MHz): δ = 13.9 (q), 20.8 (t), 27.9 (q), 29.4 (t), 43.4 (d), 47.4 (d), 48.3 (d), 59.1 (d), 82.2 (s), 115.4 (t), 140.1 (d), 141.3 (s), 170.7 (s), 177.2 (s). **(3,4-*trans*)-3d** (major diastereomer): ^{1}H NMR (500 MHz): δ = 0.75 (t, J = 7.3 Hz, 3H), 1.16–1.18 (m, 4H), 1.42 (s, 9H), 2.17 (m, 1H), 2.46 (dd, J = 8.0, 4.1 Hz, 1H), 3.56 (dd, J = 8.2, 8.1 Hz, 1H), 3.61 (dd, J = 3.4 Hz, 1H), 5.01 (ddd, J = 17.0, 1.2, 1.2 Hz, 1H), 5.10 (ddd, J = 10.1, 0.9, 0.9 Hz, 1H), 6.25 (ddd, J = 17.0, 10.1, 8.2 Hz, 1H), 6.32 (bs, 1H), 7.17–7.28 (m, 5H). ^{13}C NMR (125 MHz): δ = 13.6 (q), 19.4 (t), 27.9 (q), 38.0 (t), 41.6 (d), 51.7 (d), 52.2 (d), 59.8 (d), 82.0 (s), 116.1 (t), 126.6 (d), 128.3 (d), 128.5 (d), 138.9 (d), 141.5 (s), 171.3 (s), 177.4 (s), signals for TFA-group not observed. **(3,4-*trans*)-3d** (minor diastereomer, selected signals): ^{1}H NMR (500 MHz): δ = 0.77 (t, J = 7.3 Hz, 3H), 1.44 (s, 9H), 3.63 (d, J = 3.4 Hz, 1H), 3.83 (dd, J = 8.6 Hz, $J_{11,3}$ = 4.4 Hz, 1H), 6.11 (ddd, J = 17.6, 9.7, 8.6 Hz, 1H). ^{13}C NMR (125 MHz): δ = 13.7 (q), 27.9 (q), 38.6 (t), 39.2 (d), 49.9 (d), 53.5 (d), 60.1 (d), 82.1 (s), 117.9 (t), 136.4 (d), 141.4 (s), 171.0 (s), 177.2 (s). HRMS calcd for $C_{21}H_{29}NO_3$ [M]$^+$: 343.2147. Found: 343.2138.

tert-Butyl 4-(4-methyl-2-pentenyl)-3-propyl-pyroglutamate (3e)

According to the general procedure for the domino reactions, **3e** was obtained from TFA-Gly-O*t*Bu (101 mg, 0.45 mmol) and allyl ester **1e** (82 mg, 0.42 mmol) as the major product (besides Michael adduct **2e**) in 81% yield (105 mg, 0.34 mmol) as a colourless oil. Ratio **(3,4-*cis*)-3e** : **(3,4-*trans*)-3e** = 52 : 48. **(3,4-*cis*)-3e**: ^{1}H NMR (500 MHz): δ = 0.90–0.95 (m, 9H), 1.29–1.43 (m, 3H), 1.45 (s, 9H), 1.54 (m, 1H), 2.11 (m, 1H), 2.23 (ddd, J = 13.2, 6.6, 6.6 Hz, 1H), 2.38–2.56 (m, 3H), 3.71 (dd, J = 3.7, 0.8 Hz, 1H), 5.34 (m, 1H), 5.45 (dd, J = 15.4, 6.6 Hz, 1H), 5.93 (bs, 1H). ^{13}C NMR (100 MHz): δ = 13.8 (q), 20.4 (t), 22.48 (q), 22.51 (q), 28.0 (q), 28.5 (t), 29.8 (t), 31.1 (d), 42.0 (d), 43.3 (d), 59.1 (d), 82.2 (s), 123.8 (d), 139.9 (d), 171.2 (s), 178.7 (s), signals for TFA-group not observed. **(3,4-*trans*)-3e**: ^{1}H NMR (500 MHz): δ = 0.89–0.95 (m, 9H), 1.36 (tdd, J = 7.5, 7.4, 7.4 Hz, 2H), 1.45 (s, 9H), 1.46–1.63 (m, 2H), 2.11 (m, 1H), 2.16–2.27 (m, 2H), 2.38 (m, 1H), 3.66 (dd, J = 5.1 Hz, 1H), 5.25 (m, 1H), 5.42 (dd, J = 15.3, 6.6 Hz, 1H), 5.99 (bs, 1H). ^{13}C NMR (100 MHz): δ = 14.0 (q), 19.9 (t), 22.5 (q), 22.6 (q), 28.0 (q), 31.0 (t), 33.9 (t), 37.5 (d), 42.0 (d), 47.2 (d), 60.0 (d), 82.1 (s), 123.2 (d), 141.1 (d), 171.4 (s), 178.5 (s), signals for TFA-group not observed. HRMS calcd for $C_{18}H_{31}O_3$ [M]$^+$: 309.2304. Found: 309.2292.

Acknowledgements

Financial support by the Deutsche Forschungsgemeinschaft as well as the Fonds der Chemischen Industrie is gratefully acknowledged.

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