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Stereoselective synthesis of β-carboethoxy-γ-lactams via imino Mukaiyama aldol-type reaction of 1,4-bis(trimethylsilyloxy)-1,4-diethoxy-1,3-butadiene

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Abstract—The reaction of the (bis)trimethylsilyloxy derivative of diethyl succinate with imines in the presence of $ZnCl_2$ provides a general stereoselective entry to β-carboethoxy-γ-lactams.

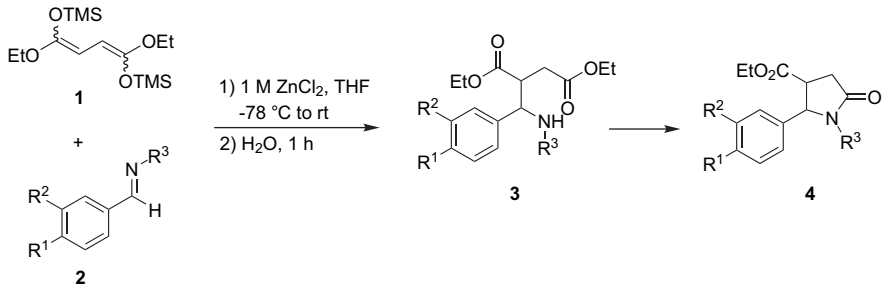
1. Introduction

The γ-lactam structure is an important subunit widely found in many classes of nitrogen heterocycles.[1] Moreover, this class of compound can be utilised as a versatile starting material for many synthetic manipulations.[2] Numerous synthetic methods for the construction of γ-lactams have been, therefore, extensively investigated. The general methods are based on Rh-catalysed intramolecular C–H insertion of diazo derivatives,[3] Pd-catalysed cyclisation,[4] *N*-heterocyclic carbene-catalysed addition of enals to imines,[5] addition of homoenolates to imines,[6] ring-expansion of β-lactams[7] and cycloaddition strategies.[8]

In continuation of our work in developing new synthetic methods using succinic ester derivatives as four-carbon building blocks,[9] it was anticipated that the reaction of (bis)trimethylsilyloxy derivative **1** derived from diethyl succinate[10] with imine **2** in the presence of a Lewis acid[11] would lead to adduct **3**, which should undergo subsequent cyclisation to afford β-carboethoxy-γ-lactam **4** (Scheme 1).

2. Results and discussion

1,4-Bis(trimethylsilyloxy)-1,4-diethoxy-1,3-butadiene **1** was readily prepared according to Rathke's procedure.[10] The ^1H and ^{13}C NMR spectra of **1** revealed that it was a mixture of at least two geometrical isomers in the ratio of 2:3. In the preliminary study, a search for a Lewis acid suitable for promoting the reaction was carried out. A collection of Lewis acids ($BF_3{\cdot}OEt_2$, $SnCl_4$, $Yb(OTf)_3$, $ZnBr_2$ and $ZnCl_2$) was employed to mediate the reaction of (bis)trimethylsilyloxy derivative **1** derived from diethyl succinate[10] with imine **2g** (Table 1). The best yield of lactam **4g** (48%) was obtained when the reaction was carried out in



Scheme 1.

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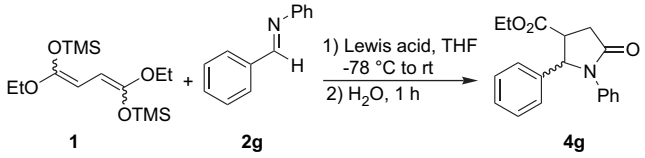
Table 1. Lewis acid optimization



1 2g 4g

Entry	Lewis acid	% Lactam **4a**[a] (cis/trans)[b]
1	$BF_3 \cdot OEt_2$	36 (30:70)
2	$SnCl_4$	27 (27:73)
3	$Yb(OTf)_3$	36 (24:76)
4	$ZnBr_2$	41 (30:70)
5	$ZnCl_2$	48 (20:80)

[a] Isolated yields.
[b] Determined by integration of the ^{1}H NMR (300 MHz) spectra of the crude product.

the presence of $ZnCl_2$ (Table 1, entry 5). Therefore, $ZnCl_2$ was chosen for further study in order to test the generality of the reaction.

The scope of the Mukaiyama aldol-type reaction of 1,4-bis-(trimethylsilyloxy)-1,4-diethoxy-1,3-butadiene **1** with a range of imine derivatives was examined under the optimised conditions using $ZnCl_2$ as a Lewis acid (Table 2). Treatment of **1** (1 equiv), as a 2:3 mixture of stereoisomers, with imine **2a** (R^3=benzyl) (1 equiv) in THF in the presence of $ZnCl_2$ (1 equiv, 1 M solution in THF) at –78 °C to room temperature overnight provided γ-lactam **4a** in 70% yield, as a 90:10 mixture of cis- and trans-isomer (J_{cis}=9.2 Hz and J_{trans}=5.4 Hz) (Table 2, entry 1).[12] No trace of the corresponding β-lactam was observed. Similar results were obtained when **1** was reacted with imines **2b–e** to afford good yields of the expected *cis*- and *trans*-γ-lactam **4b–e** (Table 2, entries 2–5).

However, the reaction of **1** with imine **2f** under the same conditions gave a mixture of γ-lactam **4f** (57% yield, cis/trans=75:25) and an uncyclised adduct **3f** (33% yield, *diastereomeric ratio*=42:58). Fortunately, treatment of the crude mixture of **3f** (*diastereomeric ratio*=42:58) and **4f** (cis/trans=75:25) with 1 equiv of K_2CO_3 under refluxing ethanol (4 h) led to complete cyclisation of the initial adduct **3f** to the desired γ-lactam **4f** (90% yield, cis/trans=20:80) (J_{cis}=9.3 Hz and J_{trans}=5.8 Hz). The equivalent of base (K_2CO_3) employed is critical to the stereochemistry of the γ-lactam. When an excess of K_2CO_3 (3 equiv) was employed, a 10:90 ratio of cis- and trans-isomer **4f** resulted. This observation indicated that the *cis*-**4f** having a larger coupling constant (J_{cis}=9.3 Hz) was isomerised to a thermodynamically more stable *trans*-**4f** whose coupling constant was smaller (J_{trans}=5.8 Hz). This experiment confirmed the assigned stereochemistry of both *cis*- and *trans*-γ-lactam **4**.

Table 2. Reaction of compound **1** with imines **2** catalysed by $ZnCl_2$

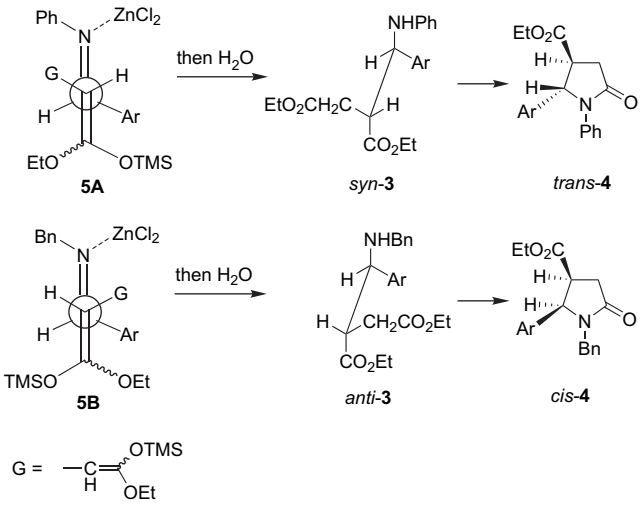
Entry	Imine **2**				% Lactam **4**[a] (cis/trans)[b]	% Adduct **3**[a] (*diastereomeric ratio*)[b]
	2	R^1	R^2	R^3		
1	**2a**	H	H	Bn	**4a**, 70 (90:10)	**3a** (—)
2	**2b**	OMe	H	Bn	**4b**, 72 (90:10)	**3b** (—)
3	**2c**	Cl	H	Bn	**4c**, 76 (92:8)	**3c** (—)
4	**2d**	NO_2	H	Bn	**4d**, 70 (92:8)	**3d** (—)
5	**2e**	H	OMe	Bn	**4e**, 75 (85:15)	**3e** (—)
6	**2f**	OMe	OMe	Bn	**4f**, 57 (75:25)	**3f**, 33 (42:58)
7	**2g**	H	H	Ph	**4g**, 48 (20:80)	**3g**, 32 (83:17)
8	**2h**	Cl	H	Ph	**4h**, 48 (9:91)	**3h**, 36 (60:40)
9	**2i**	NO_2	H	Ph	**4i**, 16 (0:100)	**3i**, 62 (50:50)
10	**2j**	H	OMe	Ph	**4j**, 81 (25:75)	**3j**, 13 (42:58)
11	**2k**	OMe	OMe	Ph	**4k**, 33 (16:84)	**3k**, 53 (60:40)
12	**2l**	OMe	H	Ph	**4l**, 83 (20:80)	**3l** (—)

[a] Isolated yields.
[b] Determined by integration of the ^{1}H NMR (300 MHz) spectra of the crude products.

With the optimum conditions established, we sought to examine the reaction with other *N*-phenylimines. Therefore, **1** and **2g** were subjected to the standard conditions, resulting in a mixture of γ-lactam **4g** (48% yield, cis/trans=20:80) and uncyclised adduct **3g** (32% yield, *diastereomeric ratio*=83:17) (Table 2, entry 7). To our surprise, the reaction of **1** with *N*-phenylimine **2g** gave the *trans*-γ-lactam **4g** as the major isomer. It should be noted that, the stereochemical outcomes are in sharp contrast to those observed when *N*-benzyl imines were employed as imine partners. Treatment of the crude mixture of **3g** and **4g** with anhydrous K_2CO_3 (1 equiv) in refluxing ethanol furnished γ-lactam **4g** in 82% yield as a 10:90 mixture of cis- and trans-isomer. As summarised in Table 2 (entries 8–12), the mixtures of adducts **3h–k** and γ-lactams **4h–k** were afforded from the condensation of **1** with imines **2h–k**, except for the reaction with **2l**, where only γ-lactam **4l** was obtained as the sole product (Table 2, entry 12). The reactions of the mixtures of **3g/4g**, **3j/4j** and **3k/4k** (Table 2, entries 7, 10 and 11) with anhydrous K_2CO_3 in absolute ethanol under reflux for 4 h led to complete cyclisation and furnished the corresponding γ-lactams **4g** (82% yield, cis/trans=10:90), **4j** (90% yield, cis/trans=0:100) and **4k** (75% yield, cis/trans=5:95), respectively.

At this point, on the basis of the stereochemistry seen in the reactions summarised in Table 2, we shall advance a model for the mechanism of Lewis acid mediated reactions of (bis)-trimethylsilyloxy derivative **1** with *N*-phenyl imines and *N*-benzyl imines. The transition state model employed to explain the stereochemical outcomes observed in our study has been proposed based on previous report by Mukaiyama.[13] The work described Lewis base catalysed Mannich-type reactions between trimethylsilyl enol ethers and *N*-tosyl imines, irrespective of geometries of the silyl enol ethers, to give the corresponding adducts with stereoconvergent (*anti*) selectivity.

The reaction was assumed to undergo via the staggered acyclic transition states. Selectivity was achieved by the steric effect in the way that repulsion of the group attached to nitrogen atom and substituent of the enol ether being greater than that of an aryl group of imine and the group on nitrogen atom. In our current study, we employed Lewis acid ($ZnCl_2$) to catalyse the reaction. It is assumed that $ZnCl_2$ occupies a coordination site on the nitrogen atom such that it is cis to the substituent at the imine carbon (Scheme 2). In the case of *N*-benzyl imines, the selectivity was achieved by the steric effect caused by the repulsive interaction of the benzyl group and the substituent G of **1**, leading preferably to *anti*-adduct **3** via transition state **5B** (Scheme 2). This observation is analogous to the results previously reported by Mukaiyama.[13] Except for **3f**, most often, the firstly formed *anti*-adduct **3**



Scheme 2.

was not isolated but underwent cyclisation under the reaction conditions to yield *cis*-γ-lactam **4**. Opposite stereoselectivity was observed when *N*-phenyl imines were employed as the reaction partners. This could be attributed to a greater steric demanding of $ZnCl_2$ causing 1,4-bis(trimethylsilyloxy)-1,4-diethoxy-1,3-butadiene **1** to approach the *N*-phenyl imines such that the substituent G being *anti* to the $ZnCl_2$ (transition state **5A**, Scheme 2), leading to *syn*-adduct **3**. However, due to a poor nucleophilicity of the nitrogen atom of the *N*-phenyl amine, cyclisation did not readily occur and a mixture of adduct **3** as a mixture of two diastereoisomers in varying ratio[14] and γ-lactam **4** (favouring trans-isomer) was obtained. We believed that cyclisation of the *syn*-adduct **3** to *trans*-γ-lactam **4** proceeded more rapidly than that of the *anti*-adduct **3** to *cis*-γ-lactam **4**. Therefore, the observed diastereoselectivity of adducts **3g–k** in the *N*-phenyl series does not reflect the cis/trans ratios of the γ-lactams **4g–k**. Attempted separation of both isomers of **4a–f** by preparative thin-layer chromatography (silica gel) was unsuccessful, except for *cis*-**4a** wherein a white solid was obtained upon standing at room temperature.

Ultimately, the isomerisation of *cis*-γ-lactam to the thermodynamically more stable *trans*-γ-lactam was investigated. Thus, treatment of a mixture of *cis*- and *trans*-γ-lactam **4a–d** and **4f** with catalytic DBU in THF at room temperature overnight furnished the *trans*-γ-lactams **4a–d** and **4f** as the major isomer. The results are listed in Table 3.

Table 3. Equilibration of cis/trans mixture of γ-lactam **4** employing DBU (0.25 equiv) in THF at rt

γ-Lactam **4** (cis/trans)[a]	% Yield[b] of γ-lactam **4** (trans/cis)[c]
4a (90:10)	80 (80:20)
4b (90:10)	85 (85:15)
4c (92:8)	80 (90:10)
4d (92:8)	60 (80:20)
4f (80:20)	70 (90:10)

[a] Isolated products were used.
[b] Isolated yields.
[c] Determined by integration of the ^{1}H NMR (300 MHz) spectra of the isolated products.

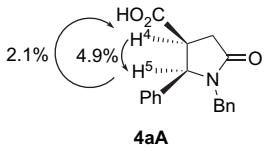


Figure 1.

The cis or trans stereochemistry of γ-lactam **4a** was conclusively established by the NOE experiment of the corresponding carboxylic acid derivative **4aA** of *cis*-γ-lactam **4a**, which was obtained by hydrolysis of the 90:10 mixture of **4a** employing 6 M HCl in dioxane under reflux for 1 h (Fig. 1).

3. Conclusion

In conclusion, we have established an efficient stereoselective synthesis of γ-lactams possessing β-carboethoxy group by treatment of bis(trimethylsilyloxy) derivative of diethyl succinate with imines catalysed by $ZnCl_2$. This type of compound might be useful as starting materials in organic synthesis. Simplicity of the procedure, readily available starting materials and a possible stereocontrol of the reaction are noteworthy. Work aimed at enantioselective synthesis of this type of γ-lactam is currently underway.

4. Experimental

4.1. General

The ^{1}H and ^{13}C NMR spectra were recorded on Bruker DPX-300 (300 MHz), Bruker DPX-400 (400 MHz) and Bruker DPX-500 (500 MHz) spectrometers in $CDCl_3$ using tetramethylsilane as an internal standard. The chemical shifts (δ) reported are given in parts per million (ppm) and the coupling constants (J) are in hertz (Hz). Melting points were recorded on a Buchi 501 Melting Point Apparatus and were uncorrected. The IR spectra were recorded on a GX FTIR system Perkin–Elmer infrared spectrometer. The EI mass spectra were recorded by using a Thermo Finnigan Polaris Q mass spectrometer. The high-resolution mass spectra were recorded on HR-TOF-MS Micromass model at Chiangmai University. The elemental analyses were performed by a Perkin–Elmer Elemental Analyzer 2400 CHN. Merck silica gel 60 PF_{254} was used for preparative thin-layer chromatography.

4.2. Reaction of the 1,4-bis(trimethylsilyloxy)-1,4-diethoxy-1,3-butadiene (1) with imines using $ZnCl_2$ as a catalyst

4.2.1. Ethyl 1-benzyl-5-oxo-2-phenylpyrrolidine-3-carboxylate (4a).

4.2.1.1. General procedure. A mixture of imine **2a** (0.195 g, 1 mmol) and zinc chloride solution (1 M in THF, 1 mL) was added dropwise at –78 °C to a solution of 1,4-bis(trimethylsilyloxy)-1,4-diethoxy-1,3-butadiene (**1**) (0.318 g, 1 mmol) in THF (2 mL) under an argon atmosphere. The resulting mixture was slowly warmed up to room temperature overnight (16 h). The resulting mixture was quenched with H_2O, stirred to reach room temperature

for 1 h, and then extracted with EtOAc (3×30 mL). The combined organic layers were washed with water, brine and dried over anhydrous Na_2SO_4. After removal of solvent under reduced pressure, a crude product **4a**, which consisted of a 90:10 mixture of cis/trans isomer, was purified by preparative thin-layer chromatography (SiO_2, 20% EtOAc in hexanes, triple runs) to give a 90:10 mixture of cis/trans isomer of **4a** (0.226 g, 70% yield). The pale yellow solid obtained from PLC was recrystallised from *i*-PrOH–/hexanes to give a white solid of a pure *cis*-**4a** isomer (0.203 g, 62%, mp 80–81 °C) and a pale yellow oil of *trans*-**4a** (0.023 g, 8% yield) contaminated with a small amount of *cis*-**4a**.

4.2.1.2. *cis*-4a. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.40–7.20 (m, 6H), 7.18–7.01 (m, 4H), 5.15 (d, J=14.7 Hz, 1H), 4.63 (d, J_{cis}=9.2 Hz, 1H), 3.80–3.48 (m, 3H), 3.43 (d, J=14.7 Hz, 1H), 3.21 (dd, J=17.3, 10.2 Hz, 1H), 2.62 (dd, J=17.3, 9.2 Hz, 1H), 0.87 (t, J=7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.1, 169.9, 135.9, 135.7, 128.8, 128.7, 128.6, 128.4, 127.7, 127.6, 62.2, 60.9, 44.5, 43.0, 31.9, 13.9. IR ($CHCl_3$): ν_{max} 1734 (C=O of ester), 1683 (C=O of amide) cm^{-1}. MS: *m*/*z* (%) relative intensity 324 ([M+1]$^+$, 23), 323 ([M]$^+$, 6), 232 (100), 119 (18), 118 (32), 117 (13), 105 (6), 91 (27), 77 (4), 65 (6). Anal. Calcd for $C_{20}H_{21}NO_3$: C, 74.28; H, 6.55; N, 4.33. Found: C, 74.57; H, 6.80; N, 4.44.

4.2.1.3. *trans*-4a. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.35–7.25 (m, 3H), 7.25–7.15 (m, 3H), 7.15–7.01 (m, 2H), 7.01–6.91 (m, 2H), 5.03 (d, J=14.7 Hz, 1H), 4.53 (d, J_{trans}=5.4 Hz, 1H), 4.04 (q, J=7.1 Hz, 2H), 3.41 (d, J=14.7 Hz, 1H), 3.20–2.60 (m, 3H), 1.09 (t, J=7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.9, 172.1, 138.9, 135.5, 129.1, 128.6, 128.4, 127.6, 126.9, 63.6, 61.3, 46.0, 44.4, 33.5, 14.0. IR (neat): ν_{max} 1732 (C=O of ester), 1695 (C=O of amide) cm^{-1}. MS: *m*/*z* (%) relative intensity 324 ([M+1]$^+$, 23), 323 ([M]$^+$, 6), 232 (100), 119 (18), 118 (32), 117 (13), 105 (6), 91 (27), 77 (4), 65 (6). HRMS (ESI-TOF) calcd for $C_{20}H_{22}NO_3$ [M+Na]$^+$: 346.1419; found: 346.1415.

4.2.2. Ethyl 1-benzyl-2-(4-methoxyphenyl)-5-oxopyrrolidine-3-carboxylate (4b). According to the general procedure as described for compound **4a**, a solution of **1** (0.318 g, 1 mmol) in THF (2 mL) was treated with imine **2b** (0.225 g, 1 mmol) under an argon atmosphere. A crude product **4b**, which consisted of a 90:10 mixture of cis/trans isomer, was purified by preparative thin-layer chromatography (SiO_2, 20% EtOAc in hexanes, triple runs) to give a pale yellow solid of product **4b** (0.254 g, 72% yield, cis/trans=90:10, mp=55–56 °C). ^{1}H NMR (300 MHz, $CDCl_3$, cis-isomer marked as *): δ 7.29–7.10 (m, 4H, Ar*H* of cis- and trans-isomer), 7.10–6.89 (m, 10H, Ar*H* of cis- and trans-isomer), 6.89–6.71 (m, 4H Ar*H* of cis- and trans-isomer), 5.07* (d, J=14.7 Hz, 1H), 5.00 (d, J=14.7 Hz, 1H), 4.57* (d, J_{cis}=9.3 Hz, 1H), 4.49 (d, J_{trans}=5.8 Hz, 1H), 4.05 (q, J=7.1 Hz, 2H), 3.48–3.80* (m, 3H), 3.76 (s, 3H), 3.73* (s, 3H), 3.35 (d, J=14.7 Hz, 2H, NCH*H*Ar of cis- and trans-isomer), 3.00–2.90 (m, 1H), 2.85–2.65 (m, 2H), 3.18* (dd, J=17.3, 10.3 Hz, 1H), 2.53* (dd, J=17.3, 9.3 Hz, 1H), 1.09 (t, J=7.1 Hz, 3H), 0.85* (t, J=7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, cis-isomer marked as *): δ 172.9*, 172.6, 172.1, 169.9*, 159.8*, 159.6, 135.9*, 135.6, 128.7 (cis- and trans-isomer), 128.6*, 128.4, 128.35*, 128.3, 128.1, 127.6*, 127.5, 127.4*, 114.3, 113.9*, 63.1, 61.7*, 61.2, 60.9*, 55.2, 55.16*, 46.1, 44.3*, 44.2, 42,9*, 33.6, 31.9*, 13.9, 13.6*. IR (KBr): ν_{max} 1726 (C=O of ester), 1675 (C=O of amide) cm^{-1}. MS: *m*/*z* (%) relative intensity 354 ([M+1]$^+$, 9), 353 ([M]$^+$, 18), 262 (100), 119 (23), 118 (25), 91 (84), 77 (10), 65 (13). HRMS (ESI-TOF) calcd for $C_{21}H_{23}NO_4Na$ [M+Na]$^+$: 376.1525; found: 376.1525.

4.2.3. Ethyl 1-benzyl-2-(4-chlorophenyl)-5-oxopyrrolidine-3-carboxylate (4c). According to the general procedure as described for compound **4a**, a solution of **1** (0.318 g, 1 mmol) in THF (2 mL) was treated with imine **2c** (0.229 g, 1 mmol) under an argon atmosphere. A crude product **4c**, which consisted of a 92:8 mixture of cis/trans isomer, was purified by preparative thin-layer chromatography (SiO_2, 20% EtOAc in hexanes, triple runs) to give a pale yellow oil of product **4c** (0.271 g, 76% yield, cis/trans=92:8). ^{1}H NMR (300 MHz, $CDCl_3$, cis-isomer marked as *): δ 7.30–6.80 (m, 18H, Ar*H* of cis- and trans-isomer), 5.08* (d, J=14.7 Hz, 1H), 5.03 (d, J=14.7 Hz, 1H), 4.58* (d, J_{cis}=9.3 Hz, 1H), 4.49 (d, J_{trans}=5.4 Hz, 1H), 4.05 (q, J=7.1 Hz, 2H), 3.90–3.30* (m, 3H), 3.33 (d, J=14.7 Hz, 2H, NCH*H*Ar of cis- and trans-isomer), 2.55* (dd, J=17.3, 9.4 Hz, 1H), 3.09* (dd, J=17.3, 10.2 Hz, 1H), 3.10–2.85 (m, 1H), 2.85–2.60 (m, 2H), 1.09 (t, J=7.1 Hz, 3H), 0.85* (t, J=7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, cis-isomer marked as *): δ 172.9*, 172.6, 172.8, 169.7*, 137.5, 135.6*, 135.3, 134.6*, 134.3 (cis- and trans-isomer), 129.3, 128.9, 128.8*, 128.7 (cis- and trans-isomer), 128.3*, 127.8*, 127.6, 62.9, 61.5*, 61.4, 60.9*, 46.0, 44.5*, 44.4, 42.8*, 33.4, 31.7*, 13.9, 13.6*. IR (neat): ν_{max} 1724 (C=O of ester), 1678 (C=O of amide) cm^{-1}. MS: *m*/*z* (%) relative intensity 358 ([M+1]$^+$, 15), 357([M]$^+$, 7), 266 (100), 119 (28), 118 (33), 91 (50), 77 (4), 65 (14). HRMS (ESI-TOF) calcd for $C_{20}H_{20}NO_3ClNa$ [M+Na]$^+$: 380.1029; found: 380.1028.

4.2.4. Ethyl 1-benzyl-2-(4-nitrophenyl)-5-oxopyrrolidine-3-carboxylate (4d). According to the general procedure as described for compound **4a**, a solution of **1** (0.318 g, 1 mmol) in THF (2 mL) was treated with imine **2d** (0.241 g, 1 mmol) under an argon atmosphere. A crude product **4d**, which consisted of a 92:8 mixture of cis/trans isomer, was purified by preparative thin-layer chromatography (SiO_2, 20% EtOAc in hexanes, triple runs) to give a brown oil of product **4d** (0.257 g, 70% yield, cis/trans=92:8). ^{1}H NMR (300 MHz, $CDCl_3$, cis-isomer marked as *): δ 8.20 (d, J=8.5 Hz, 4H, Ar*H* of cis- and trans-isomer), 7.40–7.20 (m, 10H, Ar*H* of cis- and trans-isomer), 7.15–7.00 (m, 4H Ar*H* of cis- and trans-isomer), 5.16* (d, J=14.7 Hz, 1H), 5.00 (d, J=14.7 Hz, 1H), 4.69* (d, J_{cis}=9.4 Hz, 1H), 4.62 (d, J_{trans}=6.0 Hz, 1H), 4.05 (q, J=7.1 Hz, 2H), 3.85–3.40* (m, 3H), 3.37 (d, J=14.7 Hz, 2H, NCH*H*Ar of cis- and trans-isomer), 3.08* (dd, J=17.4, 10.2 Hz, 1H), 2.57* (dd, J=17.4, 9.4 Hz, 1H), 3.10–2.85 (m, 1H), 2.85–2.65 (m, 2H), 1.10 (t, J=7.1 Hz, 3H), 0.93* (t, J=7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, cis-isomer marked as *): δ 172.9*, 172.7, 171.4, 169.4*, 148.1*, 146.4, 143.4 (cis- and trans-isomer), 135.2*, 134.9, 128.9*, 128.7, 128.6 (cis- and trans-isomer), 128.4*, 128.3, 128.0*, 127.9, 124.3, 123.8*, 62.8, 61.7, 61.5*, 61.2*, 45.8, 44.9*, 44.8, 42.8*, 33.3, 31.7*, 14.0, 13.7*. IR (neat): ν_{max} 1732 (C=O of ester),

1695 (C═O of amide) cm^{-1}. MS: *m/z* (%) relative intensity 369 ($[M+1]^+$, 9), 368 ($[M]^+$, 13), 274 (100), 147 (30), 146 (56), 119 (27), 118 (47), 116 (20), 115 (13), 106 (23), 104 (52), 91 (80), 77 (8), 65 (20). Anal. Calcd for $C_{20}H_{20}N_2O_5$: C, 64.21; H, 5.47; N, 7.60. Found: C, 64.24; H, 5.13; N, 7.75.

4.2.5. Ethyl 1-benzyl-2-(3-methoxyphenyl)-5-oxopyrrolidine-3-carboxylate (4e). According to the general procedure as described for compound **4a**, a solution of **1** (0.318 g, 1 mmol) in THF (2 mL) was treated with imine **2e** (0.225 g, 1 mmol) under an argon atmosphere. A crude product **4e**, which consisted of an 85:15 mixture of cis/trans isomer, was purified by preparative thin-layer chromatography (SiO_2, 20% EtOAc in hexanes, triple runs) to give a pale yellow solid of product **4e** (0.264 g, 75% yield, cis/trans=85:15, mp=160–164 °C). ^1H NMR (300 MHz, $CDCl_3$, cis-isomer marked as *): δ 7.30–6.53 (m, 18H, Ar*H* of cis- and trans-isomer), 5.10* (d, *J*=14.7 Hz, 1H), 5.02 (d, *J*=14.7 Hz, 1H), 4.58 (d, *J*=9.2 Hz, 1H), 4.51* (d, *J*=5.5 Hz, 1H), 4.05 (q, *J*=7.1 Hz, 2H), 3.80–3.25* (m, 3H), 3.81* (s, 3H), 3.83 (s, 3H), 3.37 (d, *J*=14.7 Hz, 2H, NCH*H*Ar of cis- and trans-isomer), 3.21* (dd, *J*=17.3, 10.2 Hz, 1H), 2.55* (dd, *J*=17.3, 9.3 Hz, 1H), 3.10–2.85 (m, 1H), 2.85–2.65 (m, 2H), 1.16 (t, *J*=7.1 Hz, 3H), 0.87* (t, *J*=7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, cis-isomer marked as *): δ 173.1*, 172.8, 172.1, 169.9*, 160.2, 159.7*, 140.6, 137.3*, 135.9*, 135.6, 130.2*, 129.7, 128.6*, 128.5, 128.43*, 128.40, 127.7*, 127.6, 119.8*, 119.0, 113.9*, 113.86, 113.3*, 112.3, 63.5, 62.1*, 61.3, 60.8*, 55.24, 55.2*, 45.8, 44.5*, 44.4, 42.9*, 33.5, 31.9*, 14.0, 13.6. IR (neat): ν_{max} 1732 (C═O of ester), 1695 (C═O of amide) cm^{-1}. MS: *m/z* (%) relative intensity 354 ($[M+1]^+$, 23), 353 ($[M]^+$, 6), 225 (50), 147 (39), 146 (28), 119 (28), 118 (51), 104 (34), 91 (100), 77 (18), 65 (25). HRMS (ESI-TOF) calcd for $C_{21}H_{24}NO_4$ $[M+1]^+$: 354.1705; found: 354.1705.

4.2.6. Ethyl 1-benzyl-2-(3,4-dimethoxyphenyl)-5-oxopyrrolidine-3-carboxylate (4f) and diethyl 2-[(benzylamino)-(3,4-dimethoxyphenyl)methyl]succinate (3f). According to the general procedure as described for compound **4a**, a solution of **1** (0.318 g, 1 mmol) in THF (2 mL) was treated with imine **2f** (0.255 g, 1 mmol) under an argon atmosphere. A crude product **4f** was purified by preparative thin-layer chromatography (SiO_2, 20% EtOAc in hexanes, triple runs) to give a pale yellow oil of a 75:25 mixture of cis/trans isomer of product **4f** (0.218 g, 57% yield cis/trans=75:25) and an adduct **3f** (0.141 g, 33% yield) as a 42:58 mixture of isomers.

4.2.6.1. Carboxylate 4f. ^1H NMR (300 MHz, $CDCl_3$, cis-isomer marked as *): δ 7.30–6.53 (m, 16H, ArH of cis- and trans-isomer), 5.05* (d, *J*=14.6 Hz, 1H), 4.96 (d, *J*=14.6 Hz, 1H), 4.56* (d, *J*=9.3 Hz, 1H), 4.47 (d, *J*=6.0 Hz, 1H), 4.02 (q, *J*=7.1 Hz, 2H), 3.30–3.90* (m, 3H), 3.82 (s, 3H), 3.80* (s, 3H), 3.74 (s, 6H, OC*H*$_3$ of cis- and trans-isomer), 3.37 (d, *J*=14.6 Hz, 2H, NC*H*HAr of cis- and trans-isomer), 3.21* (dd, *J*=17.3, 10.1 Hz, 1H), 2.55* (dd, *J*=17.3, 9.4 Hz, 1H), 3.05–2.85 (m, 1H), 2.85–2.65 (m, 2H), 1.10 (t, *J*=7.1 Hz, 3H), 0.84* (t, *J*=7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, cis-isomer marked as *): δ 172.9*, 172.6, 172.1, 170.0*, 149.4, 149.2*, 149.1, 149.0*, 135.9*, 135.7, 131.0, 128.6*, 128.4, 128.37 (cis- and trans-isomer), 127.9*, 127.6*, 127.5, 120.1*, 119.5, 111.2, 110.9*, 110.4*, 109.4, 63.6, 62.1*, 61.2, 60.8*, 55.84*, 55.8, 46.1, 44.45, 44.4*, 42.9*, 33.7, 31.9*, 14.0, 13.7*. IR ($CHCl_3$): ν_{max} 1720 (C═O of ester), 1673 (C═O of amide) cm^{-1}. MS: *m/z* (%) relative intensity 384 ($[M+1]^+$, 23), 383 ($[M]^+$, 6), 292 (58), 149 (66), 146 (28), 119 (22), 118 (23), 104 (12), 91 (100), 77 (32), 65 (26), 55 (44). HRMS (ESI-TOF) calcd for $C_{22}H_{25}NO_5Na$ $[M+Na]^+$: 408.1630; found: 408.1630.

4.2.6.2. Succinate 3f. ^1H NMR (300 MHz, $CDCl_3$, minor-isomer marked as *): δ 7.00 (t, *J*=8.1 Hz, 4H, Ar*H* of major- and minor-isomer), 6.80–6.68 (m, 6H, Ar*H* of major- and minor-isomer), 6.60–6.50 (m, 2H, Ar*H* of major- and minor-isomer), 6.50–6.39 (m, 4H Ar*H* of major- and minor-isomer), 4.63* (d, J_{minor}=5.4 Hz, 1H), 4.45 (d, J_{major}=6.8 Hz, 1H), 4.09–3.95 (m, 8H, OCH_2CH$_3$ of major- and minor-isomer), 3.77 (s, 16H, OCH_3 and NCH_2Ar of major- and minor-isomer), 3.26–3.20 (m, 1H), 3.20–3.10* (m, 1H), 2.74 (dd, *J*=17.1, 10.1 Hz, 2H, CHCH*H*CO of major- and minor-isomer), 2.45–2.32 (m, 2H, CHC*H*HCO of major- and minor-isomer), 1.22–1.02 (m, 12H, OCH$_2$CH_3 of major- and minor-isomer). ^{13}C NMR (75 MHz, $CDCl_3$, minor-isomer marked as *): δ 173.3, 172.7*, 172.0*, 171.6, 149.2, 149.1*, 148.4, 146.8*, 146.7 (major- and minor-isomer), 133.0, 132.3*, 129.04, 129.0*, 119.1, 119.0*, 117.8*, 117.6, 113.7*, 113.4, 111.14*, 111.1, 109.7*, 109.5, 61.1*, 61.0, 60.8, 60.3*, 58.7, 58.6*, 55.85, 55.8*, 48.1, 48.0*, 44.45, 44.4*, 34.8, 32.1*, 14.03, 14.0*. IR (neat): ν_{max} 3395 (N–H), 1732 (C═O of ester) cm^{-1}. MS: *m/z* (%) relative intensity 429 ($[M]^+$, 0.05), 242 (100), 104 (32), 91 (1), 77 (10). HRMS (ESI-TOF) calcd for $C_{24}H_{31}NO_6$ $[M]^+$: 429.2151; found: 429.2150.

4.2.7. Ethyl 5-oxo-1,2-diphenylpyrrolidine-3-carboxylate (4g) and diethyl 2-(phenyl(phenylamino)methyl)succinate (3g). According to the general procedure as described for compound **4a**, a solution of **1** (0.318 g, 1 mmol) in THF (2 mL) was treated with imine **2g** (0.181 g, 1 mmol) under an argon atmosphere. A crude product **4g** was purified by preparative thin-layer chromatography (SiO_2, 20% EtOAc in hexanes, triple runs) to give a pure trans-isomer (0.110 g, 36% yield as a pale yellow solid, mp=115–116 °C) and cis-isomer (38 mg, 12% yield as a yellow oil) of **4g**, and an adduct **3g** (0.113 g, 32% yield) as an 83:17 mixture of isomers.

4.2.7.1. *trans*-4g. ^1H NMR (300 MHz, $CDCl_3$): δ 7.39 (d, *J*=7.6 Hz, 2H), 7.35–7.19 (m, 7H), 7.06 (t, *J*=7.5 Hz, 1H), 5.53 (d, J_{trans}=4.6 Hz, 1H), 4.22 (q, *J*=7.1 Hz, 2H), 3.20–2.80 (m, 3H), 1.27 (t, *J*=7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.15, 172.1, 139.7, 137.5, 129.0, 128.7, 128.2, 126.1, 125.3, 122.7, 65.8, 61.6, 46.4, 34.3, 14.1. IR ($CHCl_3$): ν_{max} 1731 (C═O of ester), 1698 (C═O of amide) cm^{-1}. MS: *m/z* (%) relative intensity 310 ($[M+1]^+$, 24), 309 ($[M]^+$, 97), 236 (100), 208 (99), 180 (71), 91 (24), 77 (38), 50 (11). Anal. Calcd for $C_{19}H_{19}NO_3$: C, 73.77; H, 6.19; N, 4.53. Found: C, 73.79; H, 6.25; N, 4.41.

4.2.7.2. *cis*-4g. ^1H NMR (300 MHz, $CDCl_3$): δ 7.42 (d, *J*=7.9 Hz, 2H) 7.35–7.10 (m, 7H), 7.06 (t, *J*=7.3 Hz, 1H), 5.48 (d, J_{cis}=8.8 Hz, 1H), 3.88–3.65 (m, 3H), 3.32 (dd, *J*=17.3, 10.2 Hz, 1H), 2.72 (dd, *J*=17.3, 8.8 Hz, 1H), 0.99

(t, J=7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.7, 169.5, 137.8, 136.2, 128.7, 128.62, 128.6, 127.0, 125.3, 122.1, 65.1, 61.0, 43.7, 32.9, 13.7. IR (neat): ν_{max} 1732 (C=O of ester), 1707 (C=O of amide) cm^{-1}. MS: *m/z* (%) relative intensity 310 ([M+1]$^+$, 29), 309 ([M]$^+$, 75), 281 (51), 236 (100), 208 (78), 91 (21), 77 (33), 65 (3). HRMS (ESI-TOF) calcd for $C_{19}H_{19}NO_3Na$ [M+Na]$^+$: 332.1263; found: 332.1263.

4.2.7.3. Succinate 3g. ^{1}H NMR (300 MHz, $CDCl_3$, minor-isomer marked as *): δ 7.40–6.40 (m, 20H, Ar*H* of major- and minor-isomer), 4.67* (d, J_{minor}=5.5 Hz, 1H), 4.52 (d, J_{major}=6.5 Hz, 1H), 4.10–3.90 (m, 8H, OC*H*$_2$CH$_3$ of major- and minor-isomer), 3.35–3.20* (m, 1H), 3.20–3.10 (m, 1H), 2.85–2.70 (m, 2H, CHCH*H*CO of major- and minor-isomer), 2.45–2.30 (m, 2H, CHC*H*HCO of major- and minor-isomer), 1.12 (t, J=7.1 Hz, 6H, OCH$_2$C*H*$_3$ of major- and minor-isomer), 1.03 (t, J=7.1 Hz, 6H, OCH$_2$C*H*$_3$ of major- and minor-isomer). ^{13}C NMR (75 MHz, $CDCl_3$, minor-isomer marked as *): δ 173.2, 172.6*, 172.0*, 171.5, 146.6*, 146.5, 140.4, 139.8*, 129.1, 129.0*, 128.6 (major- and minor-isomer), 127.5 (major- and minor-isomer), 126.8*, 126.7, 117.8, 117.5*, 113.6*, 113.3, 61.1*, 61.0, 60.8 (major- and minor-isomer), 58.7 (major- and minor-isomer), 48.0, 47.9*, 34.5, 32.0*, 14.04 (major- and minor-isomer), 13.96 (major- and minor-isomer). IR (neat): ν_{max} 3386 (N–H), 1734 (C=O of ester) cm^{-1}. MS: *m/z* (%) relative intensity 356 ([M+1]$^+$, 8), 355 ([M]$^+$, 1), 182 (100), 180 (4), 104 (16), 91 (1), 77 (12). HRMS (ESI-TOF) calcd for $C_{22}H_{25}O_5Na$ [M+Na]$^+$: 356.1862; found: 356.1862.

4.2.8. Ethyl 2-(4-chlorophenyl)-5-oxo-1-phenylpyrrolidine-3-carboxylate (4h) and diethyl 2-[(4-chlorophenyl)-(phenylamino)methyl]succinate (3h). According to the general procedure as described for compound **4a**, a solution of **1** (0.318 g, 1 mmol) in THF (2 mL) was treated with imine **2h** (0215 g, 1 mmol) under an argon atmosphere. A crude product **4h** was purified by preparative thin-layer chromatography (SiO_2, 20% EtOAc in hexanes, triple runs) to give a pure trans-isomer (0.141 g, 41% yield, as a pale yellow solid, mp=117–119 °C) and cis-isomer (27 mg, 7% yield, as a yellow oil) product of **4h**, and an adduct **3h** (0.140 g, 36% yield as a 60:40 mixture of isomers).

4.2.8.1. *trans*-4h. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.27 (m, 2H), 7.20–7.05 (m, 6H), 7.01 (m, 1H), 5.44 (d, J_{trans}=4.8 Hz, 1H), 4.15 (q, J=7.1 Hz, 2H), 3.00–2.70 (m, 3H), 1.20 (t, J=7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.8, 138.2, 137.1, 134.0, 129.2, 128.8, 127.7, 125.6, 122.7, 65.0, 61.7, 46.4, 34.3, 14.1. IR (neat): ν_{max} 1731 (C=O of ester), 1714 (C=O of amide) cm^{-1}. MS: *m/z* (%) relative intensity 344 ([M+1]$^+$, 16), 343 ([M]$^+$, 68), 270 (83), 242 (100), 240 (23), 216 (59), 91 (9), 77 (81), 55 (12). Anal. Calcd for $C_{19}H_{18}NO_3Cl$: C, 66.38; H, 5.28; N, 4.07. Found: C, 66.17; H, 4.92; N, 4.00.

4.2.8.2. *cis*-4h. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.32 (m, 2H), 7.21–7.16 (m, 4H), 7.16–6.95 (m, 3H), 5.41 (d, J_{cis}=8.8 Hz, 1H), 3.90–3.60 (m, 3H), 3.22 (dd, J=17.3, 10.5 Hz, 1H), 2.67 (dd, J=17.3, 9.3 Hz, 1H), 0.96 (t, J=7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.4, 169.4, 137.4, 134.8, 134.5, 128.6, 128.4, 125.5, 122.1, 64.4, 61.2, 43.4, 32.8, 13.7. IR ($CHCl_3$): ν_{max} 1732 (C=O of ester), 1698 (C=O of amide) cm^{-1}. MS: *m/z* (%) relative intensity 344 ([M+1]$^+$, 21), 343 ([M]$^+$, 93), 270 (90), 242 (100), 216 (71), 91 (9), 77 (53), 50 (12). HRMS (ESI-TOF) calcd for $C_{19}H_{19}NO_3Cl$ [M+1]$^+$: 344.1503; found: 344.1502.

4.2.8.3. Succinate 3h. ^{1}H NMR (400 MHz, $CDCl_3$, minor-isomer marked as *): δ 7.40–7.20 (m, 8H, Ar*H* of major- and minor-isomer), 7.09 (t, J=8.0 Hz, 4H, Ar*H* of major- and minor-isomer), 6.67 (t, J=6.8 Hz, 4H, Ar*H* of major- and minor-isomer), 6.65 (t, J=7.3 Hz, 2H, Ar*H* of major- and minor-isomer), 4.78 (d, J_{major}=5.6 Hz, 1H), 4.63* (d, J_{minor}=5.6 Hz, 1H), 4.20–4.05 (m, 8H, OC*H*$_2$CH$_3$ of major- and minor-isomer), 3.45–3.35* (m, 1H), 3.35–3.25 (m, 1H), 2.91–2.80 (m, 2H, CHCH*H*CO of major- and minor-isomer), 2.60–2.40 (m, 2H, CHC*H*HCO of major- and minor-isomer), 1.22 (t, J=7.1 Hz, 6H, OCH$_2$C*H*$_3$ of major- and minor-isomer), 1.13 (t, J=7.1 Hz, 6H, OCH$_2$C*H*$_3$ of major- and minor-isomer). ^{13}C NMR (125 MHz, $CDCl_3$, minor-isomer marked as *): δ 173.9*, 173.3, 172.7, 172.2*, 147.3*, 147.15, 141.1 (major- and minor-isomer), 140.6 (major- and minor-isomer), 129.8*, 129.7, 129.3 (major- and minor-isomer), 128.3 (major- and minor-isomer), 127.5, 127.4*, 118.5*, 118.3, 114.4, 114.1*, 61.8, 61.7*, 61.5 (major- and minor-isomer), 59.5, 59.4*, 48.6 (major- and minor-isomer) 35.2*, 32.8, 14.7 (major- and minor-isomer), 14.66 (major- and minor-isomer). IR (neat): ν_{max} 3396 (N–H), 1731(C=O of ester) cm^{-1}. MS: *m/z* (%) relative intensity 401 ([M+1]$^+$, 6), 400 ([M]$^+$, 4), 227 (100), 212 (50), 104 (15), 91 (2), 77 (11). HRMS (ESI-TOF) calcd for $C_{21}H_{25}NO_4Cl$ [M+1]$^+$: 390.1472; found: 390.1471.

4.2.9. Ethyl 2-(4-nitrophenyl)-5-oxo-1-phenylpyrrolidine-3-carboxylate (4i) and diethyl 2-((4-nitrophenyl)-(phenylamino)methyl)succinate (3i). According to the general procedure as described for compound **4a**, a solution of **1** (0.318 g, 1 mmol) in THF (2 mL) was treated with imine **2i** (0.226 g, 1 mmol) under an argon atmosphere. A crude product **4i** was purified by preparative thin-layer chromatography (SiO_2, 20% EtOAc in hexanes, triple runs) to give a pure trans-isomer **4i** (58 mg, 16% yield, as a pale yellow solid, mp=132–133 °C) and an adduct **3i** (0.248 g, 62% yield, as a 50:50 mixture of isomers).

4.2.9.1. *trans*-4i. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.08 (d, J=8.6 Hz, 2H), 7.38 (d, J=8.6 Hz, 2H), 7.35–7.10 (m, 4H), 7.02 (m, 1H), 5.60 (d, J_{trans}=5.1 Hz, 1H), 4.17 (q, J=7.1 Hz, 2H), 3.10–2.81 (m, 3H), 1.22 (t, J=7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.6, 171.4, 147.7, 147.0, 137.0, 129.0, 127.3, 125.9, 124.3, 122.6, 64.7, 62.0, 46.1, 34.3, 14.1. IR (neat): ν_{max} 1731 (C=O of ester), 1714 (C=O of amide) cm^{-1}. MS: *m/z* (%) relative intensity 354 ([M]$^+$, 1), 242 (100), 216 (59), 91 (15), 77 (92), 55 (10). Anal. Calcd for $C_{19}H_{18}N_2O_5$: C, 64.21; H, 5.47; N, 7.60. Found: C, 64.24; H, 5.13; N, 7.75.

4.2.9.2. Succinate 3i. ^{1}H NMR (400 MHz, $CDCl_3$, one isomer marked as *): δ 8.19 (d, J=8.8 Hz, 4H, Ar*H* of both isomers), 7.53 (m, 4H, Ar*H* of both isomers), 7.10 (m, 4H, Ar*H* of both isomers), 6.70 (q, J=7.2 Hz, 2H, Ar*H* of both isomers), 6.47 (m, 4H, Ar*H* of both isomers), 5.10* (br, 1H), 4.75 (br, 1H), 4.86 (d, J_{major}=5.3 Hz, 1H), 4.79* (d, J_{minor}=5.1 Hz, 1H), 4.05–4.20 (m, 8H, OC*H*$_2$CH$_3$ of both isomers), 3.30–3.43 (m, 2H, CH$_2$C*H*CO$_2$Et of both

isomers), 2.90 (dd, J=17.0, 8.2 Hz, 1H), 2.84* (dd, J=17.0, 9.5 Hz, 1H), 2.66* (dd, J=17.0, 5.6 Hz, 1H), 2.43 (dd, J=17.0, 4.8 Hz, 1H), 1.23* (t, J=7.1 Hz, 3H), 1.22 (t, J=7.1 Hz, 3H), 1.15 (t, J=7.1 Hz, 3H), 1.10* (t, J=7.1 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$, one isomer marked as *): δ 173.2*, 172.6, 172.3, 171.9*, 149.3*, 148.5, 148.2, 148.1*, 146.6*, 146.5, 130.0*, 129.9, 128.6, 128.4*, 124.6, 124.5*, 119.2, 118.9*, 114.3, 113.9*, 62.2, 62.0*, 61.7 (both isomers), 59.1, 58.5*, 48.13, 48.07*, 35.0*, 32.8, 14.7 (both isomers), 14.6 (both isomers). IR (neat): ν_{max} 3400 (N–H), 1731 (C=O of ester) cm^{-1}. MS: *m/z* (%) relative intensity 401 ([M+1]$^+$, 6), 400 ([M]$^+$, 4), 227 (100), 212 (50), 104 (15), 91 (2), 77 (11). HRMS (ESI-TOF) calcd for $C_{21}H_{24}N_2O_5ClNa$ [M+Na]$^+$: 423.1532; found: 423.1531.

4.2.10. Ethyl 2-(3-methoxyphenyl)-5-oxo-1-phenylpyrrolidine-3-carboxylate (4j) and diethyl 2-[(3-methoxyphenyl)(phenylamino)methyl]succinate (3j). According to the general procedure as described for compound **4a**, a solution of **1** (0.318 g, 1 mmol) in THF (2 mL) was treated with imine **2j** (0.211 g, 1 mmol) under an argon atmosphere. A crude product **4j** was purified by preparative thin-layer chromatography (SiO_2, 20% EtOAc in hexanes, triple runs) to give a pure trans-isomer (0.205 g, 61% yield, as a pale yellow solid, mp=117–119 °C) and cis-isomer (69 mg, 20% yield, as a yellow oil) of product **4j** (0.274 g, 81% yield), and an adduct **3j** (50 mg, 13% yield as a 42:58 mixture of isomers).

4.2.10.1. *trans*-4j. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.32 (d, J=7.7 Hz, 2H), 7.30–7.10 (m, 3H), 7.00 (t, J=7.3 Hz, 1H), 6.80–6.50 (m, 3H), 5.42 (d, J_{trans}=4.5 Hz, 1H), 4.15 (q, J=7.1 Hz, 2H), 3.66 (s, 3H), 2.80–3.10 (m, 3H), 1.21 (t, J=7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.2, 172.1, 160.0, 141.4, 137.5, 130.2, 128.8, 125.4, 122.7, 118.3, 113.4, 111.9, 65.8, 61.7, 55.2, 46.7, 34.4, 14.2. IR (neat): ν_{max} 1732 (C=O of ester), 1706 (C=O of amide) cm^{-1}. MS: *m/z* (%) relative intensity 340 ([M+1]$^+$, 7), 339 ([M]$^+$, 76), 210 (100), 91 (31), 77 (78), 55 (12). HRMS (ESI-TOF) calcd for $C_{20}H_{22}NO_4$ [M+1]$^+$: 340.1549; found: 340.1545.

4.2.10.2. *cis*-4j. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.36 (d, J=8.3 Hz, 2H), 7.25–7.05 (m, 3H), 7.01 (t, J=7.3 Hz, 1H), 6.80–6.60 (m, 3H), 5.37 (d, J_{cis}=8.8 Hz, 1H), 3.90–3.60 (m, 3H), 3.67 (s, 3H), 3.24 (dd, J=17.3, 10.8 Hz, 1H), 2.64 (dd, J=17.3, 8.8 Hz, 1H), 0.96 (t, J=7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.7, 169.5, 159.8, 137.8, 129.7, 128.8, 125.3, 122.1, 119.2, 113.6, 113.0, 65.0, 61.1, 55.2, 43.7, 33.0, 13.8. IR ($CHCl_3$): ν_{max} 1736 (C=O of ester), 1697 (C=O of amide) cm^{-1}. MS: *m/z* (%) relative intensity 340 ([M+1]$^+$, 21), 339 ([M]$^+$, 100), 266 (92), 91 (11), 77 (29), 55 (6). HRMS (ESI-TOF) calcd for $C_{20}H_{22}NO_4$ [M+1]$^+$: 340.1549; found: 340.1550.

4.2.10.3. Succinate 3j. ^{1}H NMR (300 MHz, $CDCl_3$, minor-isomer marked as *): δ 7.09 (t, J=8.3 Hz, 4H, Ar*H* of major- and minor-isomer), 6.94 (t, J=7.6 Hz, 4H, Ar*H* of major- and minor-isomer), 6.90–6.45 (m, 8H, Ar*H* of major- and minor-isomer), 6.39 (t, J=7.3 Hz, 2H, Ar*H* of major- and minor-isomer), 4.62* (d, J_{minor}=5.3 Hz, 1H), 4.44 (d, J_{major}=6.8 Hz, 1H), 4.10–3.90 (m, 8H, OC*H*$_2$CH$_3$ of major- and minor-isomer), 3.37 (s, 6H, OC*H*$_3$ of major- and minor-isomer), 3.30–3.20* (m, 1H), 3.20–3.10 (m, 1H), 2.80–2.60 (m, 2H, CHCH*H*CO of major- and minor-isomer), 2.40–2.25 (m 2H, CHC*H*HCO of major- and minor-isomer), 1.15–0.90 (m, 12H, OCH$_2$C*H*$_3$ of major- and minor-isomer). ^{13}C NMR (75 MHz, $CDCl_3$, both isomers): δ 173.9, 172.2, 160.5, 147.2, 143.0, 130.3, 129.7, 119.8, 118.2, 114.0, 113.5, 113.2, 61.7, 61.5, 59.5, 55.8, 48.6, 35.2, 14.7, 14.6. IR (neat): ν_{max} 3385 (N–H), 1721 (C=O of ester) cm^{-1}. MS: *m/z* (%) relative intensity 386 ([M+1]$^+$, 32), 385 ([M]$^+$, 4), 215 (100), 104 (26), 91 (3), 77 (16). HRMS (ESI-TOF) calcd for $C_{22}H_{28}NO_5$ [M+1]$^+$: 386.1969; found: 386.1967.

4.2.11. Preparation of ethyl 2-(3,4-dimethoxyphenyl)-5-oxo-1-phenylpyrrolidine-3-carboxylate (4k) and diethyl 2-[(3,4-dimethoxyphenyl)(phenylamino)methyl]succinate (3k). According to the general procedure as described for compound **4a**, a solution of **1** (0.318 g, 1 mmol) in THF (2 mL) was treated with imine **2k** (0.242 g, 1 mmol) under an argon atmosphere. A crude product **4k** was purified by preparative thin-layer chromatography (SiO_2, 20% EtOAc in hexanes, triple runs) to give a pure trans-isomer (0.099 g, 26% yield, as a pale yellow solid, mp=136–137 °C) and cis-isomer (28 mg, 7% yield, as a yellow oil) of product **4k**, and an adduct **3k** (0.220 g, 53% yield as a 60:40 mixture of isomers).

4.2.11.1. *trans*-4k. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.29 (d, J=8.4 Hz, 2H), 7.20–6.90 (m, 4H), 6.80–6.50 (m, 2H), 5.39 (d, J_{trans}=5.0 Hz, 1H), 4.15 (q, J=7.1 Hz, 2H), 3.75 (s, 3H), 3.72 (s, 3H), 2.78–3.08 (m, 3H), 1.21 (t, J=7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 177.3, 172.0, 149.4, 148.8, 137.5, 132.0, 128.7, 125.5, 122.9, 118.7, 111.3, 108.9, 66.0, 61.6, 55.9, 55.8, 46.7, 34.5, 14.1. IR ($CHCl_3$): ν_{max} 1731 (C=O of ester), 1695 (C=O of amide) cm^{-1}. MS: *m/z* (%) relative intensity 371 ([M+2]$^+$, 6), 370 ([M+1]$^+$, 24), 369 ([M]$^+$, 100), 240 (57), 91 (12), 77 (22). HRMS (ESI-TOF) calcd for $C_{21}H_{23}NO_5Na$ [M+Na]$^+$: 392.1474; found: 392.1477.

4.2.11.2. *cis*-4k. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.41 (d, J=8.1 Hz, 2H), 7.26 (t, J=6.7 Hz, 2H), 7.09 (t, J=7.4 Hz, 1H), 6.70 (s, 2H), 6.67 (s, 1H), 5.43 (d, J_{cis}=8.8 Hz, 1H), 3.75–3.95 (m, 3H), 3.82 (s, 3H), 3.81 (s, 3H), 3.31 (dd, J=17.3, 10.0 Hz, 1H), 2.72 (dd, J=17.3, 8.9 Hz, 1H), 1.03 (t, J=7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.7, 169.7, 149.2, 149.1, 137.9, 128.8, 128.6, 125.4, 122.3, 119.6, 111.1, 110.1, 65.0, 55.9, 55.8, 43.8, 33.1, 29.7, 13.8. IR ($CHCl_3$): ν_{max} 1731 (C=O of ester), 1696 (C=O of amide) cm^{-1}. MS: *m/z* (%) relative intensity 371 ([M+2]$^+$, 7), 370 ([M+1]$^+$, 37), 369 ([M]$^+$, 100), 91 (12), 77 (30). HRMS (ESI-TOF) calcd for $C_{21}H_{23}NO_5Na$ [M+Na]$^+$: 392.1474; found: 392.1477.

4.2.11.3. Succinate 3k. ^{1}H NMR (400 MHz, $CDCl_3$, minor-isomer marked as *): δ 7.00 (t, J=8.1 Hz, 4H, Ar*H* of major- and minor-isomer), 6.80–6.68 (m, 6H, Ar*H* of major- and minor-isomer), 6.60–6.50 (m, 2H, Ar*H* of major- and minor-isomer), 6.50–6.39 (m, 4H, Ar*H* of major- and minor-isomer), 4.63 (d, J=5.4 Hz, 1H), 4.45* (d, J=6.9 Hz, 1H), 4.85 (br, 1H, N*H* of major- and minor-isomer), 4.09 (q, J=7.1 Hz, 4H), 4.08* (q, J=7.1 Hz, 4H), 3.84 (s, 12H, OC*H*$_3$ of major- and minor-isomer), 3.40–3.30* (m, 1H), 3.30–3.20 (m, 1H), 2.74 (dd, J=17.1, 10.1 Hz, 1H,

CHCH*H*CO of major- and minor-isomer), 2.45–2.32 (m, CHC*H*HCO of major- and minor-isomer), 1.21* (t, J=7.1 Hz, 3H), 1.20 (t, J=7.1 Hz, 3H), 1.16 (t, J=7.1 Hz, 3H), 1.15* (t, J=7.1 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$, minor-isomer marked as *): δ 174.0*, 173.4, 172.7, 171.3*, 149.85*, 149.8, 149.05*, 149.0, 147.4, 147.3*, 133.7*, 133.0, 129.73*, 129.7, 119.8*, 119.7, 118.5, 118.3*, 114.4, 114.1*, 111.8, 111.76*, 110.4, 110.2*, 61.8, 61.7*, 61.5 (major- and minor-isomer), 59.4*, 59.2, 56.53*, 56.5, 48.8*, 48.7, 35.2*, 32.8, 14.74, 14.7*. IR (neat): ν_{max} 3395 (N–H), 1732 (C=O of ester) cm^{-1}. MS: *m/z* (%) relative intensity 416 ([M+1]$^+$, 7), 415 ([M]$^+$, 2), 242 (100), 104 (32), 91 (1), 77 (10). HRMS (ESI-TOF) calcd for $C_{25}H_{30}NO_6$ [M+1]$^+$: 416.2073; found: 416.2070.

4.2.12. Preparation of ethyl 2-(4-methoxyphenyl)-5-oxo-1-phenylpyrrolidine-3-carboxylate (4l). According to the general procedure as described for compound **4a**, a solution of **1** (0.318 g, 1 mmol) in THF (2 mL) was treated with imine **2l** (0.211 g, 1 mmol) under an argon atmosphere. A crude product **4l** was purified by preparative thin-layer chromatography (SiO_2, 20% EtOAc in hexanes, triple runs) to give a pure trans-isomer (0.210 g, 62% yield as a pale yellow oil) and cis-isomer (71 mg, 21% yield as a pale yellow oil) of product **4l**.

4.2.12.1. *trans*-4l. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.27 (d, J=7.8 Hz, 2H), 7.16 (t, J=7.3 Hz, 2H), 7.08 (d, J=8.6 Hz, 2H), 6.99 (t, J=7.3 Hz, 1H), 6.78 (d, J=8.6 Hz, 2H), 5.39 (d, J_{trans}=4.9 Hz, 1H), 4.14 (q, J=7.1 Hz, 2H), 3.66 (s, 3H), 2.75–3.10 (m, 3H), 1.19 (t, J=7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.2, 172.0, 159.3, 137.4, 131.5, 128.6, 127.4, 125.3, 122.9, 114.3, 65.4, 61.5, 55.1, 46.7, 34.4, 14.1. IR (neat): ν_{max} 1732 (C=O of ester), 1704 (C=O of amide) cm^{-1}. MS: *m/z* (%) relative intensity 340 ([M+1]$^+$, 24), 339 ([M]$^+$, 55), 210 (100), 91 (43), 77 (65). HRMS (ESI-TOF) calcd for $C_{20}H_{22}NO_4$ [M+1]$^+$: 340.1549; found: 340.1549.

4.2.12.2. *cis*-4l. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.35 (d, J=8.0 Hz, 2H), 7.15 (m, 2H), 7.05 (t, J=8.7 Hz, 3H), 6.74 (d, J=8.7 Hz, 2H), 5.38 (d, J_{cis}=8.8 Hz, 1H), 3.90–3.60 (m, 3H), 3.68 (s, 3H), 3.28 (dd, J=17.5, 10.9 Hz, 1H), 2.67 (dd, J=17.5, 8.9 Hz, 1H), 0.97 (t, J=7.1 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 172.6, 169.6, 159.6, 137.8, 128.7, 128.2, 128.0, 125.2, 122.2, 113.9, 64.7, 61.0, 55.1, 43.7, 32.9, 13.8. IR ($CHCl_3$): ν_{max} 1732 (C=O of ester), 1697 (C=O of amide) cm^{-1}. MS: *m/z* (%) relative intensity 340 ([M+1]$^+$, 20), 339 ([M]$^+$, 100), 266 (61), 210 (90), 91 (16), 77 (22). HRMS (ESI-TOF) calcd for $C_{20}H_{21}NO_4Na$ [M+Na]$^+$: 362.1368; found: 362.1368.

4.2.13. Cyclisation of a mixture of 3g and 4g to γ-lactam 4g. According to the general procedure as described for compound **4a**, a solution of **1** (0.320 g, 1 mmol) in THF (2 mL) and imine **2g** (0.181 g, 1 mmol) were employed, after aqueous work-up, to yield the crude material. Without chromatographic purification, the crude product was treated with K_2CO_3 (0.138 g, 1 mmol) in dry EtOH (20 mL) and the mixture was refluxed for 4 h under an argon atmosphere. After the mixture was cooled to room temperature, the reaction mixture was quenched with 1 M HCl, and EtOH was removed (aspirator). The residue was extracted with EtOAc (3×20 mL). The combined organic layers were washed with water and brine, and dried over anhydrous Na_2SO_4. After removal of solvent under reduced pressure, a crude product was purified by preparative thin-layer chromatography (SiO_2, 20% EtOAc in hexanes, triple runs) to give a mixture of cis/trans isomer of **4g** (82% yield, cis/trans=10:90).

4.2.14. Cyclisation of a mixture of 3j and 4j to γ-lactam 4j. According to the general procedure as described for compound **4a**, a solution of **1** (0.316 g, 1 mmol) in THF (2 mL) and imine **2j** (0.211 g, 1 mmol) were employed, after aqueous work-up, to yield the crude material. Without chromatographic purification, the crude product was treated with K_2CO_3 (0.138 g, 1 mmol) in dry EtOH (20 mL) and the mixture was refluxed for 4 h under an argon atmosphere. After the mixture was cooled to room temperature, the reaction mixture was quenched with 1 M HCl, and EtOH was removed (aspirator). The residue was extracted with EtOAc (3×20 mL). The combined organic layers were washed with water and brine, and dried over anhydrous Na_2SO_4. After removal of solvent under reduced pressure, a crude product was purified by preparative thin-layer chromatography (SiO_2, 20% EtOAc in hexanes, triple runs) to give a mixture of cis/trans isomer of **4j** (82% yield, cis/trans=0:100).

4.2.15. Cyclisation of a mixture of 3k and 4k to γ-lactam 4k. According to the general procedure as described for compound **4a**, a solution of **1** (0.318 g, 1 mmol) in THF (2 mL) and imine **2k** (0.241 g, 1 mmol) were employed, after aqueous work-up, to yield the crude material. Without chromatographic purification, the crude product was treated with K_2CO_3 (0.138 g, 1 mmol) in dry EtOH (20 mL) and the mixture was refluxed for 4 h under an argon atmosphere. After the mixture was cooled to room temperature, the reaction mixture was quenched with 1 M HCl, and EtOH was removed (aspirator). The residue was extracted with EtOAc (3×20 mL). The combined organic layers were washed with water and brine, and dried over anhydrous Na_2SO_4. After removal of solvent under reduced pressure, a crude product was purified by preparative thin-layer chromatography (SiO_2, 20% EtOAc in hexanes, triple runs) to give a mixture of cis/trans isomer of **4k** (82% yield, cis/trans=5:95).

4.3. Isomerisation of *cis*-γ-lactam 4 to *trans*-γ-lactam 4

4.3.1. General procedure. To a solution of the mixture of diastereomers of **4a** (87.5 mg, 0.25 mmol) in THF (1 mL) was added dropwise a THF solution of DBU (10 mg, 0.063 mmol) at 0 °C under an argon atmosphere. The reaction mixture was slowly warmed up to room temperature and stirred for 2 days. It was quenched with 0.5 N HCl (0.5 mL) and extracted with EtOAc (3×20 mL). The combined organic layers were washed with water and brine, and dried over anhydrous Na_2SO_4. The crude product, which consisted of an 80:20 mixture of trans/cis diastereomer was purified by preparative thin-layer chromatography SiO_2, 20% EtOAc in hexanes) to give a yellow oil (70 mg, 80% yield, trans/cis=80:20). ^{1}H NMR (300 MHz, $CDCl_3$, cis-isomer marked as *): δ 7.45–7.00 (m, 20H, Ar*H* of trans- and cis-isomer), 5.10* (d, J=14.7 Hz, 1H), 5.09 (d, J=14.7 Hz, 1H), 4.68* (d, J_{cis}=9.3 Hz, 1H), 4.60 (d, J_{trans}=5.5 Hz, 1H), 4.08 (q, J=7.1 Hz, 2H), 3.55–3.80* (m, 3H), 3.48 (d, J=14.7 Hz, 1H), 3.42* (d, J=14.7 Hz, 1H), 3.17*

(dd, J=17.3, 10.2 Hz, 1H) 2.60* (dd, J=17.3, 9.3 Hz, 1H), 3.10–2.90 (m, 1H), 2.90–2.70 (m, 2H), 1.16 (t, J=7.1 Hz, 3H), 0.87* (t, J=7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, cis-isomer marked as *): δ 173.1*, 172.7, 172.0, 169.9*, 138.8, 135.7*, 135.6*, 135.5, 129.1*, 129.0, 128.5*, 128.4, 128.3*, 128.2, 127.5*, 127.4, 126.8*, 126.7, 63.5, 62.1*, 61.2, 60.7*, 45.8, 44.4*, 44.3, 42.8*, 33.3, 31.7*, 13.9, 13.5*. IR ($CHCl_3$): ν_{max} 1731 (C=O of ester), 1682 (C=O of amide) cm^{-1}. MS: *m/z* (%) relative intensity 324 ([M+1]$^+$, 3), 323 ([M]$^+$, 9), 232 (100), 146 (10), 145 (8), 119 (9), 118 (18), 91 (31), 77 (5), 65 (7). HRMS (ESI-TOF) calcd for $C_{20}H_{21}NO_3Na$ [M+Na]$^+$: 346.1411; found: 346.1419.

4.3.2. Isomerisation of γ-lactam 4b. According to the general procedure, a solution of **4b** (0.1765 g, 0.5 mmol) in THF (1 mL) was reacted with a THF solution of DBU (20 mg, 0.12 mmol) to give an 85:15 mixture of trans/cis isomer of **4b**. It was purified by thin-layer chromatography (SiO_2, 20% EtOAc in hexanes) to afford a pale yellow oil of **4b** (0.1498 g, 85% yield, trans/cis=85:15). ^{1}H NMR (300 MHz, $CDCl_3$, cis-isomer marked as *): δ 7.29–7.10 (m, 6H, Ar*H* of trans- and cis-isomer), 7.10–6.89 (m, 8H, Ar*H* of trans- and cis-isomer), 6.89–6.71 (m, 4H, Ar*H* of trans- and cis-isomer), 5.06* (d, J=14.7 Hz, 1H), 4.99 (d, J=14.7 Hz, 1H), 4.57* (d, J_{cis}=9.3 Hz, 1H), 4.48 (d, J_{trans}=5.8 Hz, 1H), 4.00 (q, J=7.1 Hz, 2H), 3.80–3.48* (m, 3H), 3.75 (s, 3H), 3.73* (s, 3H), 3.40 (d, J=14.7 Hz, 2H, NCH*H*Ar of trans- and cis-isomer), 3.05–2.85 (m, 1H), 2.85–2.65 (m, 2H), 3.12* (dd, J=17.3, 10.3 Hz, 1H), 2.54* (dd, J=17.3, 9.3 Hz, 1H), 1.09 (t, J=7.1 Hz, 3H), 0.85* (t, J=7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, cis-isomer marked as *): δ 174.8*, 172.9 (trans- and cis-isomer), 172.2, 159.7 (trans- and cis-isomer), 135.5 (trans- and cis-isomer), 130.6 (trans- and cis-isomer), 128.7*, 128.5, 128.44*, 128.4, 128.3*, 128.2, 127.7, 127.3*, 114.4, 114.0*, 63.3, 63.2*, 61.8*, 61.3, 55.3, 55.26*, 46.2, 45.9*, 44.4*, 44.3, 33.7, 31.9*, 14.0, 13.7*. IR ($CHCl_3$): ν_{max} 1735 (C=O of ester), 1683 (C=O of amide) cm^{-1}. MS: *m/z* (%) relative intensity 354 ([M+1]$^+$, 9), 353 ([M]$^+$, 18), 262 (100), 119 (23), 118 (25), 91 (84), 77 (10), 65 (13). HRMS (ESI-TOF) calcd for $C_{21}H_{24}NO_4Na$ [M+Na]$^+$: 376.1525; found: 376.1524.

4.3.3. Isomerisation of γ-lactam 4c. According to the general procedure, a solution of **4c** (0.168 g, 0.46 mmol) in THF (1 mL) was reacted with a THF solution of DBU (18 mg, 0.12 mmol) to give a crude product, which consisted of a 90:10 mixture of trans/cis isomer of **4c**. It was purified by preparative thin-layer chromatography SiO_2, 20% EtOAc in hexanes) to give a pale yellow oil of **4c** (0.135 g, 80% yield, trans/cis=90:10). ^{1}H NMR (300 MHz, $CDCl_3$, cis-isomer marked *): δ 7.30–6.80 (m, 18H, Ar*H* of trans- and cis-isomer), 5.08* (d, J=14.7 Hz, 1H), 5.02 (d, J=14.7 Hz, 1H), 4.58* (d, J_{cis}=9.3 Hz, 1H), 4.50 (d, J_{trans}=5.7 Hz, 1H), 4.03 (q, J=7.1 Hz, 2H), 3.90–3.40* (m, 3H), 3.45 (d, J=14.7 Hz, 2H, NCH*H*Ar of trans- and cis-isomer), 2.56* (dd, J=17.3, 9.40 Hz, 1H), 3.10* (dd, J=17.3, 10.2 Hz, 1H), 3.05–2.85 (m, 1H), 2.85–2.65 (m, 2H), 1.09 (t, J=7.1 Hz, 3H), 0.83* (t, J=7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, cis-isomer marked as *): δ 174.1*, 173.0*, 172.9, 171.8, 137.5*, 137.4, 135.2 (trans- and cis-isomer), 134.4 (trans- and cis-isomer), 129.3, 129.0*, 128.9*, 128.6, 128.44*, 128.45, 127.9*, 127.7, 63.0 (trans- and cis-isomer), 61.5, 60.4*, 46.0, 45.7*, 44.5, 42.8*, 33.5, 31.8*, 14.0, 13.7*. IR ($CHCl_3$): ν_{max} 1735 (C=O of ester), 1686 (C=O of amide) cm^{-1}. MS: *m/z* (%) relative intensity 358 ([M+1]$^+$, 15), 357([M]$^+$, 10), 266 (100), 119 (15), 118 (25), 91 (43), 77 (5), 65 (11). HRMS (ESI-TOF) calcd for $C_{20}H_{20}NO_3ClNa$ [M+Na]$^+$: 380.1022; found: 380.1029.

4.3.4. Isomerisation of γ-lactam 4d. According to the general procedure, a solution of **4d** (0.190 g, 0.5 mmol) in THF (1 mL) was reacted with a THF solution of DBU (20 mg, 0.13 mmol) to give a crude product, which consisted of an 80:20 mixture of trans/cis isomer of **4d**. Purification by preparative thin-layer chromatography (SiO_2, 20% EtOAc in hexanes) afforded a pale yellow oil of **4d** (0.114 g, 60% yield, trans/cis=80:20). γ-Lactam **4d**: ^{1}H NMR (300 MHz, $CDCl_3$, cis-isomer marked as *): δ 8.17 (d, J=8.7 Hz, 4H, Ar*H* of trans- and cis-isomer), 7.27 (d, J=8.7 Hz, 4H, Ar*H* of trans- and cis-isomer), 7.15–7.35 (m, 6H, Ar*H* of trans- and cis-isomer), 6.95–6.85 (m, 4H, Ar*H* of trans- and cis-isomer), 5.16* (d, J=14.7 Hz, 1H), 5.05 (d, J=14.7 Hz, 1H), 4.71* (d, J_{cis}=9.4 Hz, 1H), 4.64 (d, J_{trans}=5.8 Hz, 1H), 4.05 (q, J=7.1 Hz, 2H), 3.40–3.85* (m, 3H), 3.45 (d, J=14.7 Hz, 2H, NCH*H*Ar of trans- and cis-isomer), 3.10* (dd, J=17.4, 10.2 Hz, 1H), 2.61* (dd, J=17.4, 9.4 Hz, 1H), 3.00–2.85 (m, 1H), 2.85–2.60 (m, 2H), 1.11 (d, J=7.1 Hz, 3H), 0.86* (t, J=7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) of the major trans-isomer: δ 172.7, 171.3, 148.0, 146.4, 134.9, 128.7, 128.3, 127.9, 127.86, 124.3, 62.8, 61.7, 45.8, 44.8, 33.2, 14.0. IR (neat): ν_{max} 1733 (C=O of ester), 1691 (C=O of amide) cm^{-1}. MS: *m/z* (%) relative intensity 369 ([M+1]$^+$, 3), 368 ([M]$^+$, 11), 274 (100), 119 (8), 118 (19), 91 (41), 77 (5), 65 (9). HRMS (ESI-TOF) calcd for $C_{20}H_{20}N_2O_5Na$ [M+Na]$^+$: 391.1270; found: 391.1269.

4.3.5. Isomerisation of γ-lactam 4f. According to the general procedure, a solution of **4f** (0.191 g, 0.5 mmol) in THF (1 mL) was reacted with a THF solution of DBU (20 mg, 0.13 mmol) to give a crude product, which consisted of a 90:10 mixture of trans/cis isomer of **4f**. Purification by preparative thin-layer chromatography (SiO_2, 20% EtOAc in hexanes) afforded a pale yellow oil of **4f** (0.133 g, 70% yield, trans/cis=90:10). ^{1}H NMR (300 MHz, $CDCl_3$, cis-isomer marked as *): δ 7.30–6.53 (m, 16H, Ar*H* of trans- and cis-isomer), 5.13* (d, J=14.6 Hz, 1H), 5.04 (d, J=14.6 Hz, 1H), 4.64* (d, J_{cis}=9.3 Hz, 1H), 4.55 (d, J_{trans}=6.0 Hz, 1H), 4.10 (q, J=7.1 Hz, 2H), 3.90–3.30* (m, 3H), 3.90 (s, 3H), 3.88* (s, 3H), 3.82 (s, 6H, OCH_3 of trans- and cis-isomer), 3.56 (d, J=14.6 Hz, 1H), 3.48* (d, J=14.6 Hz, 1H), 3.21* (d, J=17.3, 10.1 Hz, 1H), 2.55*(dd, J=17.3, 9.4 Hz, 1H), 3.10–3.00 (m, 1H), 2.90–2.65 (m, 2H), 1.10 (d, J=7.1 Hz, 3H), 0.84* (t, J=7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, cis-isomer marked as *): δ 173.0*, 172.7, 172.2, 170.0*, 149.5, 149.2*, 149.1, 149.0*, 136.0*, 135.7, 131.1 (trans- and cis-isomer), 128.6*, 128.5, 128.4 (trans- and cis-isomer), 128.0*, 127.7*, 120.2, 119.5*, 111.2, 110.9*, 110.4*, 109.5, 63.6, 62.1*, 61.3, 60.8*, 55.9, 55.8*, 46.2, 44.5, 44.47*, 42.9*, 33.8, 32.0*, 14.0, 13.7*. IR ($CHCl_3$): ν_{max} 1730 (C=O of ester), 1682 (C=O of amide) cm^{-1}. MS: *m/z* (%) relative intensity 384 ([M+1]$^+$, 8), 383 ([M]$^+$, 34), 292 (100), 119 (11), 118 (17), 91 (56), 77 (6), 65 (12). HRMS (ESI-TOF) calcd for $C_{22}H_{25}NO_5Na$ [M+Na]$^+$: 406.1630; found: 406.1631.

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