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A stereoselective synthesis of 3-substituted (*S*)-pyroglutamic and glutamic acids via OBO ester derivatives

Claus Herdeis* and Bernd Kelm

Institut für Pharmazie und Lebensmittelchemie der Universität Würzburg, Am Hubland, 97074 Würzburg, Germany

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Abstract—(*S*)-Pyroglutamic acid is transformed to the Cbz-protected 4-methyl-2,6,7-trioxabicyclo[2.2.2] octane (OBO) ester. This *ortho* ester functionality is employed as a bulky steering group for stereoselective introduction of alkyl and aryl groups via 1,4-cuprate addition to 3,4-unsaturated pyroglutamates. After deprotection and ringopening, 3-substituted glutamic acids are obtained.

1. Introduction

Enantiopure non-proteinogenic amino acids play a major role in the synthesis of peptidomimetics like HIV protease inhibitors, thrombin inhibitors and inducers for the formation of β-turns to influence protein folding. Especially 3,(4)-substituted prolines[1] and (pyro)glutamates[2] as building blocks in bioactive peptides can give additional information about receptor recognition[1f] and affinity.

In the course of our investigations on the synthesis of non-proteinogenic amino acids, we recently synthesized the active *R*(−) form (eutomer **1**) of rac. Baclofen® an antispastic agent via pyroglutamic acid derivative **2** and **3**[3] (see Fig. 1). Unsaturated pyroglutamic ester urethanes like **4** are configurationally unstable at the C-2 centre under cuprate 1,4-addition reaction conditions. Furthermore dimerisation of compound **4** via Michael addition was observed.[4] These problems could be circumvented using pyroglutamate derivative **3**. As we and others have shown, *cis* and *trans* 3-substituted pyroglutamates and prolines are available on this route.[5]

Although the above procedure was capable of providing usable quantities of e.g. **1** and **2** the protocol was not easily amenable to large scale preparations. One serious drawback is the use of TBDPS as a protecting group while upscaling the process.

In the last years, Corey's 2,6,7-trioxabicyclo[2.2.2]octane (OBO-ester) group gained a renaissance as a protecting group for the carboxylic functionality.[6] It reduces the acidity of the α-proton allowing a variety of transformations of the side chain without racemization at the α-carbon.[7]

Compound **9** (Scheme 1) was chosen as a target for the 1,4-addition of Grignard cuprates to the Michael system for three reasons. First Cbz as a protecting group is stable under the acidic conditions necessary for the ring cleavage of the OBO-ester. Second, its acceptor properties are strong enough to pull electron density from the amide moiety

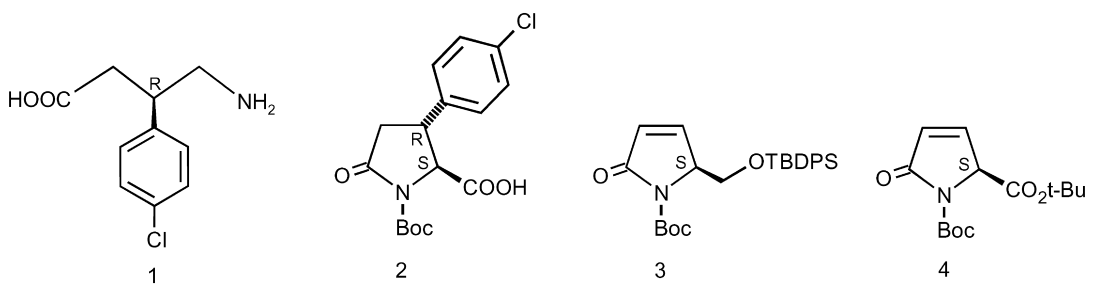

Figure 1.

Keywords: OBO ester; pyroglutamic acid; cuprate addition; glutamic acid derivatives.

* Corresponding author. Tel.: +49-931-888-5443; fax: +49-931-888-5494; e-mail: herdeis@pharmazie.uni-wuerzburg.de

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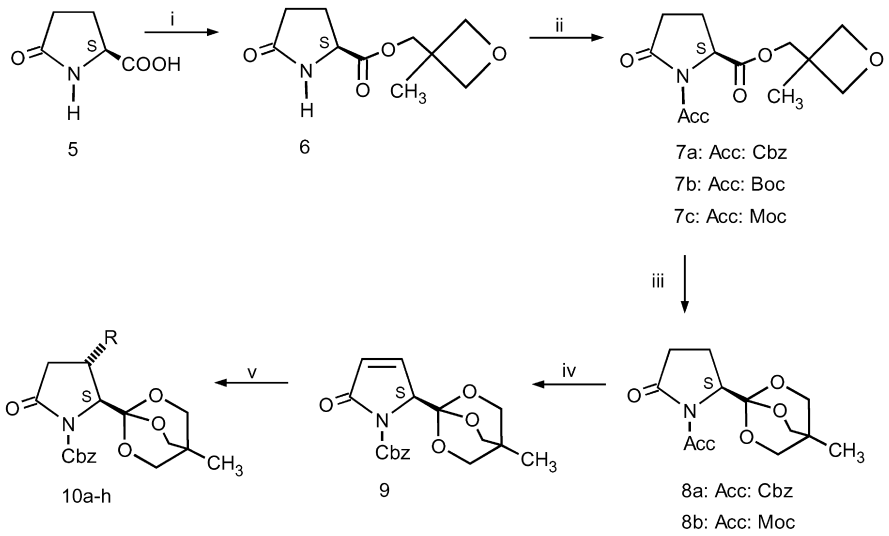


Scheme 1. (i) 3-hydroxymethyl-3-methyl-oxetane, DCC, DMAP, CH_2Cl_2, 2 h; (ii) (a) BuLi/DABCO, CbzCl, −78°C, THF, (b) BuLi/HMDS, Boc_2O, −78°C, (c) BuLi/DABCO, $CNCO_2CH_3$, −78°C, THF; (iii) $BF_3{\cdot}OEt_2$, CH_2Cl_2, Et_3N, 0°C; (iv) (a) BuLi/HMDS, PhSeCl, −78°C, THF, (b) *m*CPBA, DABCO; (v) RMgBr, $CuBr{\cdot}S(CH_3)_2$, −78→−20°C.

and therefore activate the Michael system. Third, the ring opening after 1,4-addition with dilute sodium hydroxide solution under mild conditions will be successful.[8]

2. Results and discussion

Towards this end, 3-hydroxymethyl-3-methyl-oxetane, which was prepared according to literature methods,[6a] was reacted with DCC and catalytic amounts of DMAP in methylene chloride to provide ester **6** in acceptable yields (75%). The rearrangement of the *N*-unprotected oxetane ester derivative according to Corey's procedure was unsuccessful. An insoluble precipitate was formed resulting from a Lewis acid/base reaction of the boron trifluoride with the amide moiety. Finally success was achieved by *N*-urethane protection.

The introduction of the *N*-protecting groups followed published procedures.[8,9] So compound **6** was deprotonated with butyllithium in the presence of 1,4-diazabicycloctane (DABCO) to provide the amide anion which was reacted with CbzCl, Boc_2O or methylcyanoformate, respectively, to yield *N*-protected pyroglutamate derivative **7a** (39%), **b** (66%), **c** (49%). A smooth rearrangement to the OBO-ester derivatives occurred when **7a** or **7c** was treated with boron trifluoride etherate to give compound **8a**,**c** in satisfactory yields (60 and 56%, respectively). As anticipated the Boc protecting group of compound **7b** was unstable under these conditions and we moved forward with **8a**. The introduction of the double bond into **8a** followed established procedures via phenylselenylation and oxidative elimination.[10]

For analytical purposes the phenylselenylated derivative of **8a** was isolated as a crystalline compound in a *cis*/*trans* diasteromeric ratio of 3:7. For the elimination reaction a series of standard procedures (e.g. H_2O_2, $NaIO_4$, *m*CPBA) in different solvent systems were screened with little success. It is noteworthy that *m*CPBA only in the presence of DABCO provided compound **9** in reasonable yields (48%) (Scheme 1).

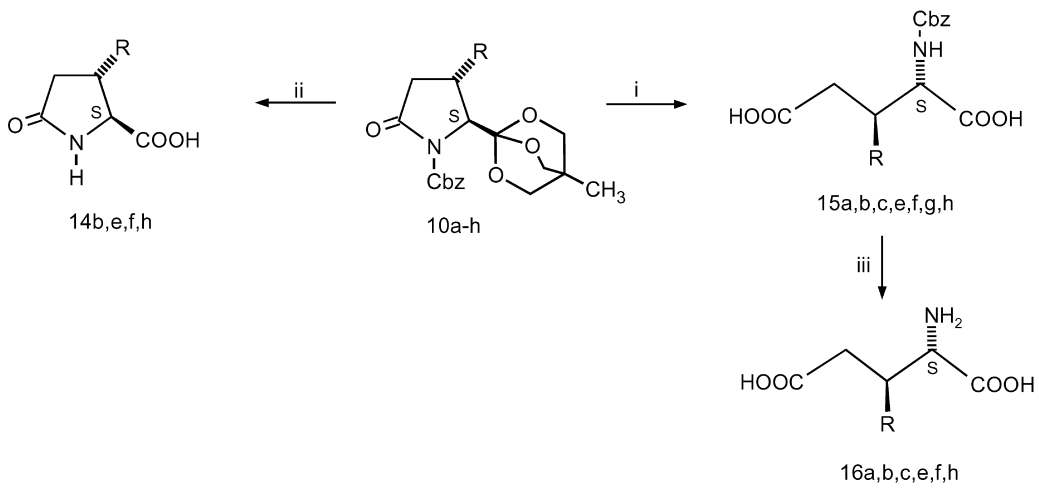
With compound **9** in hand we treated this Michael-system with Grignard-cuprates according to previously published method for **3** and analogues.[5a–d] Table 1 show the yields of 1,4 adducts **10**. As anticipated, the OBO-ester function serves as an excellent steering group for the 1,4-addition reaction. In all cases we observed only one diastereomer by NMR spectroscopy, namely the *trans* configurated products,[5a] in the crude reaction mixture. The *ortho* esters **10** are the relay compounds for the preparation of 3-substituted pyroglutamic acids and glutamic acids respectively. After catalytic hydrogenation and hydrolysis of the OBO-ester group the pyroglutamic acid derivatives **14** were obtained. Comparison of the spectral characteristics, in particular the α-H/β-H coupling constants (e.g. 5.6 Hz for **14e**), published in the literature,[2g,11a] revealed the *trans* configuration of compounds **14**.

On the other hand after cleavage of the *ortho* ester with trifluoroacetic acid a concomitant ringopening and ester hydrolysis with cesium carbonate solution occurred to furnish the Cbz-protected glutamic acid derivatives **15**, which were deprotected hydrogenolytically to the 3-substituted glutamic acid derivatives (Scheme 2).

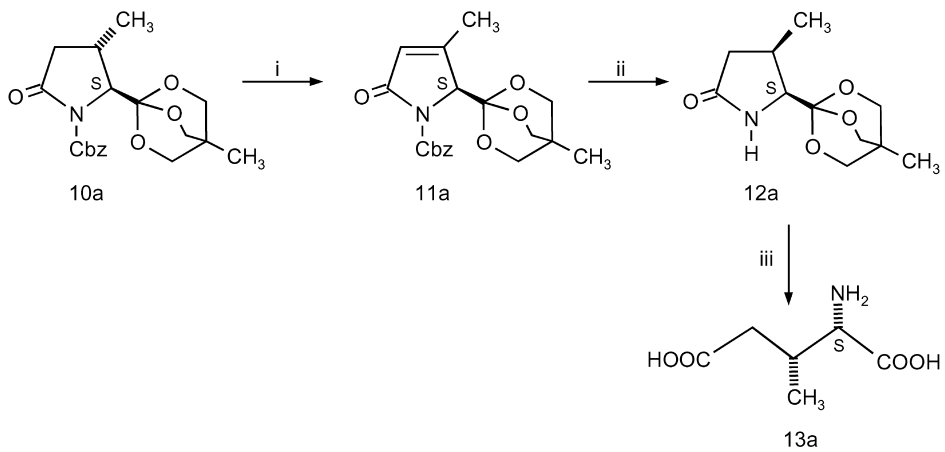
To confirm our stereochemical assignments we synthesized the *cis* configurated compound **12a** and **13a** (Scheme 3). After phenylselenation of **10a** and oxidative elimination, the double bond of compound **11a** was catalytically hydrogenated from the less hindered α-face to provide Cbz

Table 1.

10	R	Yield
a	Me	75
b	Et	62
c	*n*-Bu	70
d	Allyl	48
e	Ph	50
f	*p*-Cl-Ph	55
g	Biphenyl	30
h	Naphthyl	55



Scheme 2. (i) (a) TFA/H_2O/CH_2Cl_2, (b) 1 M NaOH; (ii) (a) H_2/Pd/C, EtOAc/MeOH, (b) TFA/H_2O/CH_2Cl_2, (c) 10% Cs_2CO_3/H_2O; (iii) H_2/Pd/C, EtOAc/MeOH.



Scheme 3. (i) (a) BuLi/HMDS, PhSeCl, −78°C, THF, (b) *m*CPBA, DABCO; (ii) (a) H_2/Pd/C, EtOAc; (iii) 6 M HCl, reflux.

deprotected compound **12a** as the only diastereomer. ^{1}H NMR of the crude reaction product showed a coupling constant $J_{4,5}$ of 7.9 Hz which is in accordance with literature data.[11b]

This work has demonstrated that the OBO-ester functionality serves as a reliable protecting group for the carboxylic function of pyroglutamic ester and derivatives. Excellent stereoselectivities were observed in the cuprate addition reactions to compounds **10**. Furthermore the change of the oxidation state of the carboxylic acid group as previously described[3,11b] could be avoided.

3. Experimental

3.1. General procedures

^{1}H-, HH COSY and ^{13}C NMR: Bruker AC 200, HMBC and HMQC: Bruker AC 600. Chemical shifts are given referring to the solvent as internal standard. IR spectra: Perkin–Elmer 681. TLC: Merck silica gel 60 F_{254} plates. Optical rotation: Perkin–Elmer 241. Melting points are uncorrected. Column chromatography: silica gel 60 (0.063–0.2 mm). Petroleum ether (PE) with a boiling range of 30–50°C was used. All reactions were carried out under nitrogen. THF and ether were distilled from potassium sodium couple, acetone from calcium chloride, DMF, dichloromethane and triethylamine from calcium hydride.

3.1.1. (2*S*)-5-Oxo-pyrrolidine-2-carboxylic acid 3-methyl-oxetan-3-ylmethyl ester (6). To a suspension of L-pyroglutamic acid (20.00 g, 0.155 mol) and 3-hydroxymethyl-3-methyl–oxetane (15.82 g, 0.155 mol) in dichloromethane (300 ml), was added a solution of DMAP (0.950 g, 0.008 mol) and DCC (31.96 g, 0.155 mol) in CH_2Cl_2 (180 ml) over 30 min at ambient temperature. The suspension was stirred for 2 h and the colourless solid was removed by suction and rinsed with CH_2Cl_2. The organic phases were concentrated to 200 ml and extracted with water (2×250 ml). The combined water extracts were concentrated under reduced pressure to give **6** as a colourless oil, which was purified by column chromatography on silica gel using EtOAc as an eluent. Yield: 24.7 g (75%). TLC: R_f~0.2 (EtOAc). $[\alpha]_D^{20}=-6.7$ (c=6.1, EtOAc). $C_{10}H_{15}NO_4$ (213.23): calcd C 56.33, H 7.09, N 6.57; found C 56.68, H 7.08, N 6.23. IR (neat): ν (cm^{-1})=3250, 2970, 2890 (C–H), 1750, 1700 (C=O), 1470 (C–H), 1200. ^{1}H NMR ($CDCl_3$):

δ=1.31 (s, 3H, CH_3), 2.10–2.65 (m, 4H, H-3a/b and H-4a/b), 4.20 and 4.25 (d, 2H, J=12.0 Hz, $COOCH_2$), 4.20–4.35 (m, 1H, H-2), 4.38 (d, J=7.0 Hz, 2H, CH_2OCH_2), 4.47 and 4.48 (2d, 2H, J=7.0 Hz, CH_2OCH_2), 7.08 (s, 1H, NH). ^{13}C NMR ($CDCl_3$): δ=20.81 (CH_3), 24.79 (C-3), 29.12 (C-4), 39.98 ($CCH_3(CH_2O)_2$), 55.41 (C-2), 69.27 ($COOCH_2$), 79.11 (2×CH_2O), 172.1 (C=O, ester), 178.2 (C=O, lactam). MS (70 eV), m/z (%): 213 (2) [M^+], 169 (1), 84 (100) [M^+−oxetylate], 56 (11), 41 (11).

3.1.2. (2*S*)-1-Benzyloxycarbonyl-5-oxo-pyrrolidine-2-carboxylic acid 2-(3-methyl-oxetan-3-yl-methyl) ester (7a). To a solution of **6** (7.74 g, 0.036 mol) and DABCO (4.07 g, 0.036 mol) in THF (100 ml) was added butyllithium (25.0 ml, 0.040 mol, 1.6 M in hexane) at −78°C. The mixture was stirred for 30 min, then benzyloxycarbonylchloride (6.81 g, 0.040 mol) was added. After stirring for 3 h at −78°C and then room temperature, the reaction was quenched with satd. ammonium chloride solution (100 ml) and the organic layer was diluted with ethylacetate (100 ml). The organic phase was washed with satd. ammonium chloride solution, brine, dried over sodium sulfate and concentrated. The residue was column chromatographed on silica gel with EtOAc/petroleum ether (10+1) to give **7a** as a colourless oil. Yield: 4.74 g (39%). TLC: R_f~0.4, EtOAc/petroleum ether (10+1). $[\alpha]_D^{20}$=−19.9 (c=3.0, CH_2Cl_2). $C_{18}H_{21}NO_6$ (347.37): calcd C 62.24, H 6.09, N 4.03; found C 62.19, H 6.15, N 3.93. IR (neat): ν (cm^{-1})=2960, 2880, 1470 (C–H), 1800, 1750 (C=O). ^{1}H NMR ($CDCl_3$): δ=1.24 (s, 3H, CH_3), 2.05–2.75 (m, 4H, H-3a/b, H-4a/b), 4.14 and 4.20 (2d, 2H, J=11.0 Hz, $COOCH_2$), 4.31 and 4.32 (2d, 2H, J=8.0 Hz, CH_2OCH_2), 4.39 and 4.40 (2d, 2H, J=8.0 Hz, CH_2OCH_2), 4.72 (m, 1H, H-2), 5.22 (d, 1H, J=12.1 Hz, CH_2, benzyl), 5.30 (d, 1H, J=12.1 Hz, CH_2, benzyl), 7.39–7.31 (m, 5H, aryl). ^{13}C NMR ($CDCl_3$): δ=20.81 (CH_3), 21.85 (C-3), 30.91 (C-4), 39.05 ($CCH_3(CH_2O)_2$), 58.61 (C-2), 68.36 (CH_2, benzyl), 69.48 ($COOCH_2$), 79.08 (2×CH_2O), 128.1, 128.4, 128.5 (5×C, aryl), 134.9 (1×C, aryl), 150.9 (C=O, urethane), 171.0 (C=O, lactam), 172.5 (C=O, ester). MS (70 eV), m/z (%): 347 (9) [M^+], 212 (4) [M^+−Cbz], 157 (25), 91 (100) [benzyl], 84 (53), 65 (7).

3.1.3. (2*S*)-1-(*t*-Butoxycarbonyl)-5-oxo-pyrrolidine-2-carboxylic acid 2-(3-methyl-oxetan-3-yl-methyl) ester (7b). To a solution of HMDS (6.57 g, 0.032 mol) in THF (25 ml) butyllithium (11.10 ml, 0.030 mol, 2.7 M in heptane) was added with stirring at −78°C for 15 min. Then a solution of **6** (6.20 g, 0.029 mol) in THF (25 ml) was added dropwise. After 15 min $(Boc)_2O$ (9.38 g, 0.043 mol) dissolved in THF (20 ml) was added slowly to the stirred suspension. After vigorous stirring for 3 h at −78°C the reaction was quenched with satd. ammonium chloride solution (100 ml), the organic layer was diluted with ethylacetate (150 ml) and washed with satd. ammonium chloride solution, brine and water, dried over sodium sulfate and concentrated in vacuo. The oily residue was column chromatographed on silica gel with EtOAc/petroleum ether (10+1) to give **7b** as a yellow oil. Yield. 6.10 g (66%). TLC: R_f~0.45, EtOAc/petroleum ether (10+1). $[\alpha]_D^{20}$=−23.8 (c=1.40, CH_2Cl_2). $C_{15}H_{23}NO_6$ (313.35): calcd C 57.50, H 7.40, N 4.47; found C 57.41, H 7.42, N 4.44. IR (neat): ν (cm^{-1})=2960, 2880 (C–H), 1790, 1760, 1740 (C=O), 1470 (C–H). ^{1}H NMR ($CDCl_3$): δ=1.32 (s, 3H, CH_3, oxetane), 1.48 (s, 9H, CH_3, Boc), 1.79–2.21 (m, 1H, H-4a/b), 2.23–2.73 (m, 3H, H-3a/b and H-4a/b), 4.24 and 4.30 (2d, 2H, J=12.0 Hz, $COOCH_2$), 4.39 (d, 2H, J=6.1 Hz, CH_2OCH_2), 4.47 and 4.48 (2d, 2H, J=6.1 Hz, CH_2OCH_2), 4.62–4.68 (m, 1H, H-2). ^{13}C NMR ($CDCl_3$): δ=20.93 (CH_3, oxetane), 21.64 (C-3), 27.85 ($C(CH_3)_3$, Boc), 31.09 (C-4), 39.18 ($CCH_3(CH_2O)_2$), 58.76 (C-2), 69.59 ($COOCH_2$), 79.22 (2×CH_2O), 83.66 ($C(CH_3)_3$, Boc), 149.4 (C=O, urethane), 171.4 (C=O, lactam), 172.8 (C=O, ester). MS (70 eV), m/z (%): 313 (0) [M^+], 213 (2) [M^+−Boc], 130 (16), 84 (100), 57 (49).

3.1.4. (2*S*)-1-(Methoxycarbonyl)-5-oxo-pyrrolidine-2-carboxylic acid 2-(3-methyl-oxetan-3-yl-methyl) ester (7c). To a suspension of **6** (8.74 g, 0.041 mol) and DABCO (5.05 g, 0.045 mol) in THF (150 ml) was added butyllithium (16.60 ml, 0.045 mol, 2.7 M in heptane) at −78°C. After 15 min methylcyano formate (3.87 ml, 0.049 mol) was added dropwise. After vigorous stirring for 3 h at −78°C, the reaction was quenched with satd. ammonium chloride solution (100 ml). The mixture was diluted with ethylacetate (150 ml), and the organic phase was washed with satd. ammonium chloride solution, brine and water, dried over sodium sulfate and concentrated in vacuo. The oily residue was column chromatographed on silica gel with EtOAc/petroleum ether (10+1) to give **7c** as a colourless oil. Yield: 5.40 g (49%). TLC: R_f~0.4, EtOAc/petroleum ether (10+1). $[\alpha]_D^{20}$=−26.7 (c=6.75, CH_2Cl_2). $C_{12}H_{17}NO_6$ (271.26): calcd C 53.13, H 6.32, N 5.16; found C 52.90, H 6.07, N 5.09. IR (neat): ν (cm^{-1})=2960, 2875 (C–H), 1790, 1730 (C=O), 1440 (C–H), 1300. ^{1}H NMR ($CDCl_3$): δ=1.25 (s, 3H, CH_3), 1.96–2.15 (m, 1H, H-4a/b), 2.23–2.63 (m, 3H, H-3a/b, H-4a/b), 3.77 (s, 3H, OCH_3), 4.17 and 4.23 (2d, 2H, J=12.1 Hz, $COOCH_2$), 4.30 (d, 2H, J=6.0 Hz, CH_2OCH_2), 4.40 and 4.41 (2d, 2H, J=6.0 Hz, CH_2OCH_2), 4.63–4.69 (m, 1H, H-2). ^{13}C NMR ($CDCl_3$): δ=20.68 (CH_3, oxetane), 21.63 (C-3), 30.82 (C-4), 39.00 ($CCH_3(CH_2O)_2$), 53.64 (OCH_3), 58.50 (C-2), 69.26 ($COOCH_2$), 79.93 (2×CH_2O), 151.6 (C=O, urethane), 170.9 (C=O, lactam), 172.4 (C=O, ester). MS (70 eV), m/z (%): 271 (1) [M^+], 188 (27), 142 (100) [M^+−oxetylate], 98 (58), 70 (13).

3.1.5. (2*S*)-2-(4-Methyl-2,6,7-trioxa-bicyclo[2.2.2]oct-1-yl)-5-oxo-pyrrolidine-1-carboxylic acid benzyl ester (8a). To a solution of **7a** (4.52 g, 0.013 mol) in dichloromethane (50 ml) was added $BF_3{\cdot}OEt_2$ (1.85 g, 0.013 mol) at 0°C under nitrogen. The mixture was allowed to reach room temperature, and was quenched with triethylamine (3.16 g, 0.130 mol). After 1 h the end of reaction was monitored by TLC. The reaction mixture was concentrated in vacuo to give an oily residue which was purified by column chromatography on silica gel with EtOAc/petroleum ether (10+1) to give **8a** as colourless crystals. Yield: 2.71 g (60%). TLC: R_f~0.6, EtOAc/petroleum ether (10+1). Mp 165°C. $[\alpha]_D^{20}$=−77.5 (c=5.0, $CHCl_3$). $C_{18}H_{21}NO_6$ (347.37): calcd C 62.24, H 6.09, N 4.03; found C 61.87, H 5.81, N 4.07. IR (KBr): ν (cm^{-1})=2960, 2880 (C–H), 1760, 1680 (C=O), 1470 (C–H). ^{1}H NMR ($CDCl_3$): δ=0.77 (s, 3H, CH_3), 2.17 (m J_{gem}~13.2 Hz, J_{3b-4b}~11.9 Hz, J_{3b-4a}~9.7 Hz, J_{3b-2}~9.0 Hz, 1H, H-3b), 2.37 (ddd, J_{gem}=13.2 Hz, J_{3a-4a}=11.6 Hz, J_{3a-4b}=9.2 Hz 1H, H-3a),

2.41 (ddd, J_{gem}=17.4 Hz, J_{4a-3a}=11.6 Hz, J_{4a-3a}=9.7 Hz, 1H, H-4a), 2.97 (ddd, J_{gem}=17.4 Hz, J_{4b-3b}=11.9 Hz, J_{4b-3a}=9.2 Hz, 1H, H-4b), 3.84 (s, 6H, 3×OCH_2, *ortho* ester), 4.42 (d, 1H, J_{2-3b}=9.0 Hz, H-2), 5.23 (d, 1H, *J*=7 Hz, CH_2, benzyl), 5.31 (d, 1H, *J*=7 Hz, CH_2, benzyl), 7.29–7.47 (m, 5H, aryl). ^{13}C NMR ($CDCl_3$): δ=14.27 (CH_3), 20.24 (C-3), 30.62 ($CCH_3(CH_2O-)_3$), 31.85 (C-4), 59.89 (C-2), 67.90 (CH_2, benzyl), 72.63 (3×CH_2O), 118.5 ($CCH_3(OCH_2)_3$), 128.1, 128.2, 128.4, 135.1 (6×C, aryl), 150.9 (C=O, urethane), 166.0 (C=O, lactam). MS (70 eV), *m/z* (%): 347 (48) [M^+], 241 (21), 157 (78), 91 (100) [benzyl], 84 (30), 65 (7).

3.1.6. (2*S*)-2-(4-Methyl-2,6,7-trioxa-bicyclo[2.2.2]oct-1-yl)-5-oxo-pyrrolidine-1-carboxylic acid methyl ester (8c). To a solution of **7c** (4.52 g, 0.013 mol) in dichloromethane (50 ml) $BF_3{\cdot}OEt_2$ (1.85 g, 0.013 mol) was added dropwise under nitrogen at 0°C. The mixture was allowed to reach room temperature. The end of the reaction was monitored by TLC (1 h). To the mixture was added triethylamine (13.16 g, 0.130 mol) and the solution was concentrated in vacuo to give an oily residue which was diluted with EtOAc. The organic phase was washed with satd. ammoniumchloride solution, brine and water, then concentrated and purified by column chromatography on silica gel with EtOAc/petroleum ether (10+1) to give **8c** as colourless crystals. Yield: 2.03 g (56%). TLC: R_f~0.5, EtOAc/petroleum ether (10+1). Mp 184°C. $[\alpha]_D^{20}$=−79.1 (*c*=2.5, CH_2Cl_2). $C_{12}H_{17}NO_6$ (271.27): calcd C 53.13, H 6.32, N 5.16; found C 52.30, H 5.89, N 4.90. IR (KBr): ν (cm^{-1})=2950, 2885 (C–H), 1750, 1730 (C=O), 1440 (C–H). ^{1}H NMR ($CDCl_3$): δ=0.77 (s, 3H, CH_3, *ortho* ester), 1.90–2.34 (m, 3H, H-3a/b and H-4a/b), 2.67–2.86 (m, 1H, H-4a/b), 3.81 (s, 3H, $COOCH_3$), 3.86 (s, 6H, 3×OCH_2, *ortho* ester), 4.83 (d, 1H, J_{2-3}=8 Hz, H-2). ^{13}C NMR ($CDCl_3$): δ=14.20 (CH_3, *ortho* ester), 20.24 (C-3), 30.54 ($CCH_3(CH_2O-)_3$), 31.84 (C-4), 53.33 ($COOCH_3$), 59.81 (C-2), 72.63 (3×CH_2O, *ortho* ester), 109.1 ($CCH_3(OCH_2)_3$), 152.2 (C=O, urethane), 174.9 (C=O, lactam). MS (70 eV), *m/z* (%): 272 (2) [M+1$^+$], 241 (66), 142 (100), 98 (38), 85 (9), 70 (7).

3.1.7. (2*S*)-2-(4-Methyl-2,6,7-trioxa-bicyclo[2.2.2]oct-1-yl)-5-oxo-2,5-dihydro-pyrrole-1-carboxylic acid benzyl ester (9). To a solution of HMDS (2.18 g, 0.013 mol) and butyllithium (4.92 ml, 0.013 mol, 2.7 M in heptane) in THF (40 ml) at −78°C was added a solution of **8a** (2.00 g, 0.006 mol) in THF (15 ml) under nitrogen over a period of 30 min. The reaction was allowed to warm to 0°C then it was cooled to −78°C. and a solution of phenylselenenyl chloride (1.21 g, 0.006 mol) in THF (40 ml) was added and the reaction mixture was stirred for 2 h, then allowed to warm to room temperature. The reaction was quenched by adding satd. ammonium chloride solution (60 ml), and EtOAc (120 ml) and the organic phase was washed with satd. ammonium chloride sol. (2×). The organic layer was concentrated in vacuo to give a yellow oily residue. The residue was dissolved in THF (40 ml) and DABCO (2.92 g, 0.026 mol) was added under vigorous stirring at −20°C. After 10 min a solution of *m*-chloroperbenzoic acid (6.73 g, 0.039 mol) in dichloromethane (150 ml) was added slowly to the reaction mixture over a period of 30 min. The reaction mixture was allowed to reach room temp., was diluted with EtOAc (600 ml) and the organic phase was washed with satd. sodium bisulfite, satd. sodium bicarbonate and satd. brine. The concentrated and dried organic phase gave an oily residue which was purified by column chromatography on silica gel with EtOAc/petroleum ether (2+1) to give **9** as colourless crystals. Yield 2.15 g (48%). TLC: R_f~0.4, EtOAc/petroleum ether (2+1)]. Mp 125°C. $[\alpha]_D^{20}$=−190.5 (*c*=0.4, CH_2Cl_2). $C_{18}H_{19}NO_6$ (345.35): calcd C 62.60, H 5.55, N 4.06; found C 62.51, H 5.52, N 4.06. IR (KBr): ν (cm^{-1})=3060, 2950, 2860 (C–H), 1760, 1680 (C=O), 1600, 1470 (C–H). ^{1}H NMR ($CDCl_3$): δ=0.76 (s, 3H, CH_3), 3.81 (s, 6H, 3×OCH_2, *ortho* ester), 4.94 (t, 1H, J_{2-3}~J_{2-4}= 2.0 Hz, H-2), 5.23 (d, 1H, *J*=12.0 Hz, CH_2, benzyl), 5.33 (d, 1H, *J*=12.0 Hz, CH_2, benzyl), 6.08 (dd, 1H, J_{4-3}=6.0 Hz, J_{4-2}=1.5 Hz, H-4), 7.12 (dd, 1H, J_{3-4}=6.0 Hz, J_{3-2}= 2.5 Hz, H-3), 7.26–7.47 (m, 5H, aryl). ^{13}C NMR ($CDCl_3$): δ=14.07 (CH_3), 30.55 ($CCH_3(CH_2O-)_3$), 64.48 (C-2), 67.99 (CH_2, benzyl), 72.72 (3×CH_2O), 107.3 (CCH_3-$(OCH_2)_3$), 126.7 (C-4), 128.0, 128.1, 128.3, 128.5, 135.5 (6×C, aryl), 146.8 (C-3), 151.0 (C=O, urethane), 169.2 (C=O, lactam). MS (70 eV), *m/z* (%): 345 (6) [M^+], 301 (17), 239 (57), 109 (25), 91 (100) [benzyl], 85 (19), 65 (17).

3.1.8. (2*S*,3*S*)-2-(4-Methyl-2,6,7-trioxa-bicyclo[2.2.2]oct-1-yl)-5-oxo-3-methyl-pyrrolidine-1-carboxylic acid benzyl ester (10a). To a suspension of $CuBr{\cdot}S(CH_3)_2$ (4.12 g, 20.00 mmol) in diethyl ether (30 ml) was added methyllithium (25.00 ml, 40.00 mmol, 1.6 M in diethyl ether) at −20°C under nitrogen. After 10 min the reaction was cooled to −78°C. Then a solution of trimethylsilyl chloride (1.02 ml, 8.00 mmol) and **9** (1.38 g, 4.00 mmol) in THF (20 ml) was added under vigorous stirring. After keeping the reaction temperature at −78°C for 1 h the reaction mixture was allowed to reach −20°C. The reaction was stopped by adding satd. ammonium chloride solution. The organic layer was diluted with diethyl ether, washed with satd. ammonium chloride (3×) and brine, then concentrated in vacuo to give an solid residue which was purified by column chromatography on silica gel using EtOAc/petroleum ether (1+1) to give **10a** as colourless crystals. Recrystallization from dichloromethane/ethanol yielded 1.09 g (75%). TLC: R_f~0.50, EtOAc/petroleum ether (2+1). Mp 192°C. $[\alpha]_D^{20}$=−63.6 (*c*=0.50, CH_2Cl_2). $C_{19}H_{23}NO_6$ (361.39): calcd C 63.15, H 6.41, N 3.88; found C 62.93, H 6.15, N 4.16. IR (KBr): ν (cm^{-1})=2960, 2940 (C–H), 2870, 1770 (C=O), 1490 (C–H). ^{1}H NMR ($CDCl_3$): δ=0.74 (s, 3H, CH_3, *ortho* ester), 1.05 (d, 3H, J_{CH3-3}=7.3 Hz, CH_3), 1.89 (d, 1H, J_{gem}=17.4 Hz, H-4b), 2.53 (dt, 1H, J_{3-4a}=8.2 Hz, $J_{3\text{-}CH3}$=7.3 Hz, H-3), 2.96 (dd, 1H, J_{gem}=17.4 Hz, J_{4a-3}=8.2 Hz, H-4a), 3.80 (s, 6H, 3×OCH_2, *ortho* ester), 4.00 (s, 1H, H-2), 5.19 (d, 1H, *J*=12.5 Hz, CH_2, benzyl), 5.29 (d, 1H, *J*=12.2 Hz, CH_2, benzyl), 7.23–7.44 (m, 5H, aryl). ^{13}C NMR ($CDCl_3$): δ=14.72 (CH_3), *ortho* ester), 21.61 (CH_3, methyl), 27.66 (C-3), 31.04 ($CCH_3(CH_2O-)_3$), 40.51 (C-4), 67.22 (C-2), 68.36 (CH_2, benzyl), 73.04 (3×CH_2O), 109.2 (CCH_3-$(OCH_2)_3$), 128.5, 128.6, 128.8, 129.0, 129.1, 136.0 (6×C, aryl), 152.3 (C=O, urethane), 175.1 (C=O, lactam). MS (70 eV), *m/z* (%): 361 (21) [M^+], 317 (3) [M^+− carboxylate], 255 (11), 226 (7), 172 (9), 171 (82) [M^+− benzyl], 144 (5), 98 (18), 91 (100) [benzyl], 85 (7), 69 (20), 65 (11).

3.1.9. (2*S*,3*S*)-2-(4-Methyl-2,6,7-trioxa-bicyclo[2.2.2]oct-1-yl)-5-oxo-3-ethyl-pyrrolidine-1-carboxylic acid benzyl ester (10b). To a suspension of CuBr·S(CH_3)$_2$ (8.94 g, 43.43 mmol) in diethyl ether (90 ml) was added freshly prepared Grignard solution of ethylmagnesium bromide (11.57 g, 86.84 mmol) in diethyl ether (120 ml) at −40°C under nitrogen in one portion. After 30 min reaction was cooled −78°C. Then a solution of trimethylsilyl chloride (3.53 ml, 27.79 mmol) and **9** (3.00 g, 8.68 mmol) in THF (30 ml) was added under vigorous stirring. After keeping the reaction temperature at −78°C for 1 h the reaction mixture was allowed to reach −20°C. The reaction was stopped by adding satd. ammonium chloride solution. The organic layer was diluted with diethyl ether, washed with satd. ammonium chloride solution (3×) and brine, then concentrated in vacuo to give an solid residue which was purified by column chromatography on silica gel using EtOAc/petroleum ether (2+1) to give **10b** as colourless crystals. Recrystallization from dichloromethane/ethanol yielded 2.02 g (62%). TLC: R_f~0.55, EtOAc/petroleum ether (2+1). Mp 183°C. $[\alpha]_D^{20}$=−60.7 (c=0.29, CH_2Cl_2). $C_{20}H_{25}NO_6$ (375.42): calcd C 63.99, H 6.71, N 3.73; found C 63.45, H 6.36, N 3.93. IR (KBr): ν (cm^{-1})=2960, 2940 (C−H), 2880, 1770 (C═O), 1460 (C−H). ^{1}H NMR ($CDCl_3$): δ=0.74 (s, 3H, CH_3, *ortho* ester), 0.87 (t, 3H, J=7.3 Hz, CH_3, ethyl), 1.27–1.48 (m, 2H, CH_2, ethyl), 2.01 (d, 1H, J_{gem}=17.7 Hz, H-4b), 2.30 (2d, 1H, J_{3-4a}~8.5 Hz, $J_{3\text{-}CH2,ethyl}$=7.6 Hz, H-3), 2.91 (dd, 1H, J_{gem}=17.7 Hz, J_{4a-3}=8.5 Hz, H-4a), 3.79 (s, 6H, 3×OCH_2, *ortho* ester), 4.09 (s, 1H, H-2), 5.19 (d, 1H, J=12.5 Hz, CH_2, benzyl), 5.28 (d, 1H, J=12.5 Hz, CH_2, benzyl), 7.27–7.38 (m, 5H, aryl). ^{13}C NMR ($CDCl_3$): δ=11.42 (CH_3, ethyl), 14.74 (CH_3, *ortho* ester), 28.16 (CH_2, ethyl), 31.04 ($C$$CH_3$($CH_2$-O−)$_3$), 34.34 (C-3), 38.42 (C-4), 65.34 (C-2), 68.34 (CH_2, benzyl), 73.06 (3×CH_2O), 109.3 ($C$$CH_3$($OCH_2$)$_3$), 128.4, 128.5, 128.6, 129.0, 136.1 (6×C, aryl), 152.2 (C═O, urethane), 175.2 (C═O, lactam). MS (70 eV), *m*/*z* (%): 375 (18) [M^+], 269 (15), 240 (14), 185 (53) [M^+−benzyl], 144 (4), 112 (15), 107 (6), 91 (100) [benzyl], 85 (8), 65 (11).

3.1.10. (2*S*,3*S*)-2-(4-Methyl-2,6,7-trioxa-bicyclo[2.2.2]-oct-1-yl)-5-oxo-3-butyl-pyrrolidine-1-carboxylic acid benzyl ester (10c). To a suspension of CuBr·S(CH_3)$_2$ (7.43 g, 36.19 mmol) in diethyl ether (70 ml) was added butyllithium (26.00 ml, 72.38 mmol, 2.7 M in heptane) at −40°C under nitrogen. After 30 min the reaction was cooled to −78°C. Then a solution of trimethylsilyl chloride (2.94 ml, 23.16 mmol) and **9** (2.50 g, 7.24 mmol) in THF (30 ml) was added under vigorous stirring. After keeping the reaction temperature at −78°C for 1 h the reaction mixture was allowed to warm to −20°C. The reaction was stopped by adding satd. ammonium chloride solution and the organic layer was diluted with diethyl ether, washed with satd. ammonium chloride sol. (3×) and brine, then concentrated in vacuo to give an oily yellow residue which was purified by column chromatography on silica gel using EtOAc/petroleum ether (1+1) as eluent to give **10c** as colourless crystals. Yield 2.04 g (70%). TLC: R_f~0.50, EtOAc/petroleum ether (2+1). Mp 126°C. $[\alpha]_D^{20}$=−61.0 (c=0.39, CH_2Cl_2). $C_{22}H_{29}NO_6$ (403.47): calcd C 65.49, H 7.24, N 3.47; found C 64.62, H 7.39, N 3.38. IR (KBr): ν (cm^{-1})=2930 (C−H), 1790 (C═O), 1490 (C−H). ^{1}H NMR ($CDCl_3$): δ=0.74 (s, 3H, CH_3, *ortho* ester), 0.84 (t, 3H, J=6.7 Hz, CH_3, butyl), 0.89–1.03 (m, 6H, 3×CH_2, butyl), 2.01 (d, 1H, J_{gem}=17.7 Hz, H-4b), 2.36 (m, 1H, H-3), 2.91 (dd, 1H, J_{gem}=17.7 Hz, J_{4a-3}=8.5 Hz, H-4a), 3.80 (s, 6H, 3×OCH_2, *ortho* ester), 4.09 (s, 1H, H-2), 5.20 (d, 1H, J=12.5 Hz, CH_2, benzyl), 5.29 (d, 1H, J=12.5 Hz, CH_2, benzyl), 7.23–7.36 (m, 5H, aryl). ^{13}C NMR ($CDCl_3$): δ=14.36 (CH_3, *ortho* ester), 14.72 (CH_3, butyl), 22.87 (CH_2, butyl), 29.05 (CH_2, butyl), 31.02 ($C$$CH_3$($CH_2O$−)$_3$), 32.76 (C-3), 35.00 ($CH_2$, butyl), 38.75 (C-4), 65.57 (C-2), 68.31 (CH_2, benzyl), 73.04 (3×CH_2O), 109.0 ($C$$CH_3$($OCH_2$)$_3$), 128.5, 128.6, 128.8, 129.0, 136.1 (6×C, aryl), 152.2 (C═O, urethane), 175.3 (C═O, lactam). MS (70 eV), *m*/*z* (%): 403 (19) [M^+], 269 (15), 240 (11), 213 (34) [M^+−benzyl], 144 (35), 140 (39), 111 (10), 91 (100) [benzyl], 85 (10), 65 (9).

3.1.11. (2*S*,3*S*)-2-(4-Methyl-2,6,7-trioxa-bicyclo[2.2.2]-oct-1-yl)-5-oxo-3-allyl-pyrrolidine-1-carboxylic acid benzyl ester (10d). To a suspension of CuBr·S(CH_3)$_2$ (5.96 g, 28.95 mmol) in diethyl ether (60 ml) was added a freshly prepared Grignard solution of allylmagnesium bromide (8.41 g, 57.89 mmol) in diethyl ether (80 ml) at −40°C under nitrogen in one portion. After 30 min the reaction was cooled to −78°C. Then a solution of trimethylsilyl chloride (2.35 ml, 18.53 mmol) and **9** (2.00 g, 5.79 mmol) in THF (20 ml) was added under vigorous stirring. After keeping the reaction temperature at −78°C for 1 h, the reaction mixture was allowed to warm to −20°C. The reaction was stopped by adding satd. ammonium chloride sol. The organic layer was diluted with diethyl ether, washed with satd. ammonium chloride (3×) and brine, then concentrated in vacuo to give an oily residue which was purified by column chromatography on silica gel using EtOAc/petroleum ether (2+1) to give **10d** as colourless crystals. Recrystallization from dichloromethane/ethanol yielded 1.33 g (48%). TLC: R_f~0.55, EtOAc/petroleum ether (1+1). Mp 93°C. $[\alpha]_D^{20}$=−49.1 (c=0.21, CH_2Cl_2). $C_{21}H_{25}NO_6$ (387.43): calcd C 65.10, H 6.50, N 3.62; found C 64.61, H 6.58, N 3.62. IR (KBr): ν (cm^{-1})=3060, 2960, 2940 (C−H), 2880, 1770 (C═O), 1690, 1460 (C−H). ^{1}H NMR ($CDCl_3$): δ=0.74 (s, 3H, CH_3, *ortho* ester), 1.98–2.20 (m, 2H, H-1′), 2.05 (d, 1H, J_{gem}=17.1 Hz, H-4b), 2.49 (2d, 1H, J_{3-4a}~8.5 Hz, J_{3-1}= 7.3 Hz, H-3), 2.90 (dd, 1H, J_{gem}=17.7 Hz, J_{4a-3}=8.5 Hz, H-4a), 3.80 (s, 6H, 3×OCH_2, *ortho* ester), 4.14 (s, 1H, H-2), 5.01 (d, 1H, J_{gem}=1 Hz, H-3′), 5.06 (d, 1H, J_{gem}=1 Hz, H-3′), 5.20 (d, 1H, J=12.5 Hz, CH_2, benzyl), 5.28 (d, 1H, J=12.5 Hz, CH_2, benzyl), 5.57–5.74 (m, 1H, H-2′), 7.25–7.40 (m, 5H, aryl). ^{13}C NMR ($CDCl_3$): δ=14.73 (CH_3, *ortho* ester), 31.04 ($C$$CH_3$($CH_2O$−)$_3$), 32.15 (C-3), 38.12 (C-4), 39.38 (C-1′, allyl), 64.91 (C-2), 68.33 (CH_2, benzyl), 73.07 (3×CH_2O), 109.3 ($C$$CH_3$($OCH_2$)$_3$), 118.6 (C-3′, allyl), 128.5, 128.6, 128.8, 129.1 (6×C, aryl), 134.8 (C-2′, allyl), 152.0 (C═O, urethane), 175.0 (C═O, lactam). MS (70 eV), *m*/*z* (%): 387 (21) [M^+], 281 (8), 280 (5), 240 (57), 197 (3) [M^+−benzyl], 138 (7), 107 (6), 91 (100) [benzyl], 85 (11), 65 (10).

3.1.12. (2*S*,3*R*)-2-(4-Methyl-2,6,7-trioxa-bicyclo[2.2.2]-oct-1-yl)-5-oxo-3-phenyl-pyrrolidine-1-carboxylic acid benzyl ester (10e). To a suspension of CuBr·S(CH_3)$_2$ (5.96 g, 27.95 mmol) in diethyl ether (50 ml) was added a freshly prepared Grignard solution of phenylmagnesium bromide (10.50 g, 57.89 mmol) in diethyl ether (50 ml) at

−40°C under nitrogen in one portion. After 30 min the mixture was cooled to −78°C. Then a solution of trimethylsilyl chloride (2.35 ml, 18.53 mmol) and **9** (2.00 g, 5.79 mmol) in THF (25 ml) was added under vigorous stirring. After keeping the reaction temperature at −78°C for 1 h, the reaction mixture was allowed to warm to −20°C. The reaction was quenched by adding satd. ammonium chloride solution and the organic layer was diluted with diethyl ether, washed with satd. ammonium chloride (3×) and brine, then concentrated in vacuo, to give an oily yellow residue which was purified by column chromatography on silica gel using EtOAc/petroleum ether (1+1) to give **10e** as colourless crystals. Yield 1.00 g (50%). TLC: R_f~0.45 EtOAc/petroleum ether (1+1). Mp 181°C. $[\alpha]_D^{20}$=−23.4 (c=0.41, CH_2Cl_2). $C_{24}H_{25}NO_6$ (423.46): calcd C 68.07, H 5.95, N 3.31; found C 67.72, H 6.00, N 3.35. IR (KBr): ν (cm^{-1})=2920, 2880 (C−H), 1770 (C=O), 1690 (urethane), 1450 (C−H). ^1H NMR ($CDCl_3$): δ=0.80 (s, 3H, CH_3), 2.46 (d, 1H, J_{gem}=18.0 Hz, H-4b), 3.29 (dd, 1H, J_{gem}=17.7 Hz, J_{4a-3}=9.2 Hz, H-4a), 3.68 (d, 1H, J_{3-4a}=9.2 Hz, H-3), 3.80 (s, 6H, 3×OCH_2, *ortho* ester), 4.42 (s, 1H, H-2), 5.22 (d, 1H, J=12.5 Hz, CH_2, benzyl), 5.32 (d, 1H, J=12.5 Hz, CH_2, benzyl), 7.14−7.33 (m, 9H, aryl). ^{13}C NMR ($CDCl_3$): δ=14.74 (CH_3), 31.14 (CCH_3-($CH_2O-)_3$), 37.85 (C-3), 39.84 (C-4), 67.30 (C-2), 68.42 (CH_2, benzyl), 73.17 (3×CH_2O), 109.2 ($CCH_3(OCH_2)_3$), 126.7, 127.5, 128.5, 128.8, 129.4, 136.0, 144.1, (12×C, aryl), 151.9 (C=O, urethane), 174.9 (C=O, lactam). MS (70 eV), m/z (%): 423 (19) [M^+], 288 (7), 233 (51) [M^+−benzyl], 185 (8), 131 (25), 104 (11), 91 (100) [benzyl], 85 (8), 77 (5), 65 (9).

3.1.13. (2*S*,3*R*)-2-(4-Methyl-2,6,7-trioxa-bicyclo[2.2.2]-oct-1-yl)-5-oxo-3-(4-chlorophenyl)-pyrrolidine-1-carboxylic acid benzyl ester (10f). To a suspension of CuBr·$S(CH_3)_2$ (1.49 g, 7.24 mmol) in diethyl ether (15 ml) was added a freshly prepared Grignard solution of *para*-chlorophenylmagnesium bromide (2.77 g, 14.48 mmol) in diethyl ether (10 ml) at −40°C under nitrogen in one portion. After 30 min the mixture was cooled to −78°C. Then a solution of trimethylsilyl chloride (0.59 ml, 4.63 mmol) and **9** (0.50 g, 1.45 mmol) in THF (15 ml) was added under vigorous stirring. After keeping the reaction temperature at −78°C for 1 h, the reaction mixture was allowed to reach −20°C. The reaction was quenched by adding satd. ammonium chloride solution. The organic layer was diluted with diethyl ether, washed with satd. ammonium chloride (3×) and brine, then concentrated in vacuo to give an oily yellow residue which was purified by column chromatography on silica gel using EtOAc/petroleum ether (1+1) give **10f** as colourless crystals. Yield 0.37 g (55%). TLC: R_f~0.45, EtOAc/petroleum ether (1+1). Mp 166°C. $[\alpha]_D^{20}$=−20.4 (c=0.5, CH_2Cl_2). $C_{24}H_{24}ClNO_6$ (457.91): calcd C 62.95, H 5.28, N 3.06; found C 62.88, H 5.42, N 3.08. IR (KBr): ν (cm^{-1})=2950, 2870 (C−H), 1780, 1690 (C=O) 1490 (C−H). ^1H NMR ($CDCl_3$): δ=0.80 (s, 3H, CH_3), 2.39 (d, 1H, J_{gem}=18.3 Hz, H-4b), 3.28 (dd, 1H, J_{gem}=17.7 Hz, J_{4a-3}=9.2 Hz, H-4a), 3.66 (d, 1H, J_{3-4a}=9.3 Hz, H-3), 3.87 (s, 6H, 3×OCH_2, *ortho* ester), 4.35 (s, 1H, H-2), 5.21 (d, 1H, J=12.5 Hz, CH_2, benzyl), 5.32 (d, 1H, J=12.5 Hz, CH_2, benzyl), 7.06−7.41 (m, 9H, aryl). ^{13}C NMR ($CDCl_3$): δ=14.25 (CH_3), 30.70 ($CCH_3(CH_2O-)_3$), 36.89 (C-3), 39.16 (C-4), 66.80 (C-2), 68.08 (CH_2, benzyl), 72.73 (3×CH_2O), 108.7 ($CCH_3(OCH_2)_3$), 127.6, 128.1, 128.3, 128.4, 129.1, 132.9, 135.4, 142.0, (12×C, aryl), 151.3 (C=O, urethane), 174.0 (C=O, lactam). MS (70 eV), m/z (%): 457 (17) [M^+], 267 (45) [M^+−benzyl], 165 (18), 138 (13), 91 (100) [benzyl], 85 (11), 65 (10).

3.1.14. (2*S*,3*R*)-2-(4-Methyl-2,6,7-trioxa-bicyclo[2.2.2]-oct-1-yl)-5-oxo-3-biphenyl-pyrrolidine-1-carboxylic acid benzyl ester (10g). To a suspension of CuBr·$S(CH_3)_2$ (2.98 g, 14.47 mmol) in abs. diethyl ether (30 ml) was added a freshly prepared Grignard solution of 4-biphenylmagnesium bromide (6.75 g, 28.95 mmol) in abs. diethyl ether (60 ml) at −40°C under nitrogen in one portion. After 30 min the mixture was cooled to −78°C. Then, a solution of trimethylsilyl chloride (1.18 ml, 9.23 mmol) and **9** (1.00 g, 2.90 mmol) in abs. THF (10 ml) was added under vigorous stirring. After keeping the reaction temperature at −78°C for 1 h the mixture was allowed to warm to 0°C. The reaction was quenched by adding satd. ammonium chloride solution. The organic layer was diluted with diethyl ether, washed with satd. ammonium chloride sol. (3×) and brine, then concentrated in vacuo to give an oily yellow residue which was purified by column chromatography on silica gel using EtOAc/petroleum ether (1+1) as an eluent to give **10g** as colourless crystals. Yield 0.43 g (30%). TLC: R_f~0.50 (EtOAc/petroleum ether (1+1). Mp 219°C. $[\alpha]_D^{20}$=+18.2 (c=0.32, CH_2Cl_2). $C_{30}H_{29}NO_6$ (499.56): calcd C 72.13, H 5.85, N 2.80; found C 71.20, H 5.61, N 2.78. IR (KBr): ν (cm^{-1})=3047 (aryl), 2938, 2880 (C−H), 1785 (C=O), 1705 (urethane). ^1H NMR ($CDCl_3$): δ=0.80 (s, 3H, CH_3), 2.48 (d, 1H, J_{gem}=18.0 Hz, H-4b), 3.31 (dd, 1H, J_{gem}=17.7 Hz, J_{4a-3}=9.2 Hz, H-4a), 3.71 (d, 1H, J_{3-4a}=8.9 Hz, H-3), 3.88 (s, 6H, 3×OCH_2, *ortho* ester), 4.45 (s, 1H, H-2), 5.22 (d, 1H, J=12.5 Hz, CH_2, benzyl), 5.33 (d, 1H, J=12.5 Hz, CH_2, benzyl), 7.18−7.62 (m, 14H, aryl). ^{13}C NMR ($CDCl_3$): δ=17.09 (CH_3), 39.28 ($CCH_3(CH_2O-)_3$), 40.35 (C-4), 41.02 (C-3), 66.56 (C-2), 67.77 (CH_2, benzyl), 73.20 (3×CH_2O), 108.0 ($CCH_3(OCH_2)_3$), 127.3, 127.4, 128.0, 128.4, 128.5, 128.7, 128.8, 129.0, 129.1, 129.2, 129.3, 135.1, 139.9, 140.6, 141.5 (18×C, aryl), 151.5 (C=O, urethane), 172.3 (C=O, lactam). MS (70 eV), m/z (%): 499 (18) [M^+], 364 (46), 309 (20) [M^+−benzyl], 262 (11), 207 (12), 180 (28), 147 (12), 91 (100) [benzyl], 85 (13), 65 (6).

3.1.15. (2*S*,3*R*)-2-(4-Methyl-2,6,7-trioxa-bicyclo[2.2.2]-oct-1-yl)-5-oxo-3-naphthyl-pyrrolidine-1-carboxylic acid benzyl ester (10h). To a suspension of CuBr·$S(CH_3)_2$ (5.96 g, 28.95 mmol) in diethyl ether (20 ml) was added a freshly prepared Grignard solution of 1-naphthylmagnesium bromide (13.34 g, 57.91 mmol) in diethyl ether (80 ml) at −40°C under nitrogen. After 30 min the mixture was cooled down to −78°C and a solution of trimethylsilyl chloride (2.35 ml, 18.53 mmol) and **9** (2.00 g, 5.79 mmol) in THF (25 ml) was added under vigorous stirring. After keeping the reaction temperature at −78°C for 1 h the mixture was allowed to warm to −20°C. The reaction was quenched by adding satd. ammonium chloride solution and the organic layer was diluted with diethylether, washed with satd. ammonium chloride (3×) and brine, then concentrated in vacuo to give an oily yellow residue which was purified by column chromatography on silica gel using EtOAc/petroleum ether (1+1) to give **10h** as colourless crystals.

Yield 1.34 g (55%). TLC: R_f~0.50, EtOAc/petroleum ether (1+1). Mp 190°C. $[\alpha]_D^{20}=-61.8$ (c=0.44, CH_2Cl_2). $C_{28}H_{27}NO_6$ (473.52): calcd C 71.02, H 5.75, N 2.96; found C 67.64, H 5.62, N 2.87. IR (KBr): ν (cm^{-1})=3040 (aryl), 2930, 2870 (C–H), 1780 (C=O), 1690 (urethane). ^1H NMR ($CDCl_3$): δ=0.77 (s, 3H, CH_3), 2.48 (d, 1H, J_{gem}=17.7 Hz, H-4b), 3.45 (dd, 1H, J_{gem}=17.7 Hz, J_{4a-3}= 8.9 Hz, H-4a), 3.87 (s, 6H, 3×OCH_2, *ortho* ester), 4.37 (d, 1H, J_{3-4a}=8.9 Hz, H-3), 4.52 (s, 1H, H-2), 5.12 (d, 1H, J=12.5 Hz, CH_2, benzyl), 5.25 (d, 1H, J=12.5 Hz, CH_2, benzyl), 7.14–7.34 (m, 2H, naphthyl, 5H, benzyl), 7.40–7.52 (m, 2H, naphthyl), 7.68 (d, 1H, J=8.5 Hz, naphthyl), 7.78 (m, 1H, J=8.5 Hz, naphthyl), 8.15 (d, 1H, J=8.5 Hz, naphthyl). ^{13}C NMR ($CDCl_3$): δ=14.75 (CH_3), 31.12 ($CCH_3(CH_2O-)_3$), 35.98 (C-3), 38.12 (C-4), 65.80 (C-2), 68.70 (CH_2, benzyl), 73.24 (3×CH_2O), 108.0 (CCH_3-$(OCH_2)_3$), 122.8, 123.2, 125.8, 126.7, 127.5, 128.6, 129.0, 129.2, 129.8, 131.1, 134.5, 135.1, 136.1 (16×C, aryl), 151.6 (C=O, urethane), 171.5 (C=O, lactam). MS (70 eV), *m/z* (%): 473 (32) [M^+], 338 (30), 283 (29) [M^+−benzyl], 236 (12), 181 (19), 165 (9), 154 (37), 153 (25), 152 (13), 91 (100) [benzyl], 85 (11), 65 (7).

3.1.16. (2*S*,3*S*)-1-(Benzyloxycarbonyl)-3-methyl-glutamic acid (15a). To a solution of **10a** (1.00 g, 2.77 mmol) in dichloromethane (10 ml) was added a 10% aqueous solution of trifluoro acetic acid (10 ml). After stirring for 1 h the solvent was removed in vacuo to give a colourless oily residue which was dissolved in a mixture of THF (5 ml) and 1 M aqueous sodium hydroxide (15 ml). This solution was stirred for 12 h, then THF was removed in vacuo and the reaction mixture was adjusted with hydrochloric acid (6N) to pH 1. The aqueous phase was extracted with diethyl ether (3×20 ml) and the combined and dried organic phases were concentrated in vacuo to give **15a** as colourless crystals after recrystallization from chloroform/diethyl ether. Yield 0.61 g (75%). TLC: R_f~0.7, EtOAc/acetic acid (10+1). Mp 133°C. $[\alpha]_D^{20}=+7.4$ (c=0.34, EtOAc). $C_{14}H_{27}NO_6$ (295.29): calcd C 56.95, H 5.80, N 4.74; found C 56.95, H 5.48, N 4.69. IR (KBr): ν (cm^{-1})=3330 (NH), 3100 (COOH), 2960 (C–H), 1700 (C=O), 1530 (C–H). ^1H NMR (DMSO-d_6): δ=0.99 (d, 3H, J_{CH3-3}=6.1 Hz, CH_3, methyl), 2.19–2.41 (m, 3H, H-3 and H-4a/b), 4.08 (2d, 1H, J_{2-NH}=8.2 Hz, J_{2-3}=4.9 Hz, H-2), 5.12 (s, 2H, CH_2, benzyl), 7.30–7.44 (m, 5H, aryl), 7.65 (d, 1H, J_{NH-2}= 8.2 Hz, N–H), 12.6 (s, 2H, carboxylate). ^{13}C NMR (DMSO-d_6): δ=17.18 (CH_3, methyl), 32.42 (C-3), 37.84 (C-4), 58.96 (C-2), 66.36 (benzyl), 128.6, 128.7, 129.2, 137.8 (6×C, aryl), 157.2 (urethane), 173.7, 174.3 (2×COOH, carboxylate). MS (70 eV), *m/z* (%): 295 (2) [M^+], 277 (3), 160 (5), 144 (17), 109 (3), 108 (44), 107 (29), 98 (21), 91 (100), 79 (19), 77 (10).

3.1.17. (2*S*,3*S*)-1-(Benzyloxycarbonyl)-3-ethyl-glutamic acid (15b). To a solution of **10b** (1.00 g, 2.66 mmol) in dichloromethane (10 ml) was added a 10% aqueous solution of trifluoroacetic acid (10 ml). After stirring for 1 h the solvent was removed in vacuo to give a colourless oily residue which was dissolved in a mixture of THF (5 ml) and 1 M aqueous sodium hydroxide (15 ml). This solution was stirred for 12 h, then THF was removed in vacuo and the reaction mixture was adjusted with hydrochloric acid (6N) to pH 1. The water phase was extracted with diethyl ether (3×20 ml) and the combined and dried organic phases were concentrated in vacuo to give **15b** as colourless crystals after recrystallization from chloroform/diethyl ether. Yield 0.68 g (82%). TLC: R_f~0.7, EtOAc/acetic acid (10+1). Mp 156°C.-$[\alpha]_D^{20}=+12.6$ (c=0.39, EtOAc). $C_{15}H_{19}NO_6$ (309.32): calcd C 58.25, H 6.19, N 4.53; found C 57.68, H 6.04, N 4.43. IR (KBr): ν (cm^{-1})=3340 (NH), 3150 (COOH), 2960 (C–H), 1720, 1650 (C=O), 1540 (C–H). ^1H NMR (DMSO-d_6): δ=0.88 (t, 3H, J=7.0 Hz, CH_3, ethyl), 1.33 (dt, 2H, J_{CH2-3}=6.7 Hz, J~7.0 Hz, CH_2, ethyl), 2.17–2.33 (m, 3H, H-3, H-4a/b), 4.14 (2d, 1H, J_{2-NH}= 8.2 Hz, J_{2-3}=3.0 Hz, H-2), 5.04 (d, 1H, J_{gem}~15.0 Hz, CH_2, benzyl), 5.10 (d, 1H, J_{gem}~15.0 Hz, CH_2, benzyl), 7.27–7.32 (m, 5H, aryl), 7.57 (d, 1H, J_{NH-2}=8.5 Hz, N–H), 12.5 (s, 2H, carboxylate). ^{13}C NMR (DMSO-d_6): δ=12.17 (CH_3, ethyl), 24.11 (CH_2, ethyl), 35.58 (C-4), 38.78 (C-3), 56.09 (C-2), 66.39 (benzyl), 108.6, 128.6, 128.7, 129.2, 137.8 (6×C, aryl), 157.4 (urethane), 174.2, 174.6 (2×COOH, carboxylate). MS (70 eV), *m/z* (%): 309 (1) [M^+], 291 (4), 158 (20), 112 (35), 109 (3), 108 (35), 107 (28), 91 (100), 79 (17), 77 (9).

3.1.18. (2*S*,3*S*)-1-(Benzyloxycarbonyl)-3-butyl-glutamic acid (15c). To a solution of **10c** (1.00 g, 2.49 mmol) in dichloromethane (10 ml) was added trifluoro acetic acid (10% in water) (10 ml). After stirring for 1 h the solvent was removed under vacuo to give a colourless oily residue which was dissolved in a mixture of THF (5 ml) and 1 M sodium hydroxide sol. (15 ml). This solution was stirred for 12 h, then THF was removed under vacuo and the mixture was treated with 6 M hydrochloric acid to reach pH 1. The water phase was extracted with diethyl ether (3×20 ml) and the combined and dried organic phases were concentrated under vacuo to give **15c** as colourless crystals after recrystallization from chloroform/diethyl ether. Yield 0.57 g (68%). TLC: R_f~0.7, EtOAc/acetic acid (10+1). Mp 131°C. $[\alpha]_D^{20}=+10.3$ (c=0.58, EtOAc). $C_{17}H_{23}NO_6$ (337.37): calcd C 60.52, H 6.87, N 4.15; found C 60.30, H 6.74, N 4.20. IR (KBr): ν (cm^{-1})=3300 (NH), 2980 (COOH), 2900 (C–H), 1700 (C=O), 1560 (C–H). ^1H NMR (DMSO-d_6): δ=0.79 (s, 3H, CH_3, butyl), 1.20–1.25 (m, 6H, 3×CH_2, butyl), 2.04–2.23 (m, 3H, H-3, H-4a/b), 4.14 (dd, 1H, J_{2-NH}~8.6 Hz, H-2), 4.98 (d, 1H, J_{gem}~15.0 Hz, CH_2, benzyl), 5.04 (d, 1H, J_{gem}~15.0 Hz, CH_2, benzyl), 7.27–7.32 (m, 5H, aryl), 7.42 (d, 1H, J_{NH-2}=8.6 Hz, N–H), 12.4 (s, 2H, carboxylate). ^{13}C NMR (DMSO-d_6): δ=14.67 (CH_3, butyl), 22.95 (CH_2, butyl), 29.30 (CH_2, butyl), 31.00 (CH_2, butyl), 36.00 (C-4), 37.50 (C-3), 56.30 (C-2), 66.32 (benzyl), 128.5, 129.2, 137.9 (6×C, aryl), 157.0 (urethane), 173.0, 174.6 (2×COOH, carboxylate). MS (70 eV), *m/z* (%): 337 (1) [M^+], 319 (5), 186 (23), 140 (45), 109 (2), 108 (24), 107 (23), 91 (100), 79 (12), 77 (12).

3.1.19. (2*S*,3*R*)-1-(Benzyloxycarbonyl)-3-phenyl-glutamic acid (15e). To a solution of **10e** (1.00 g, 2.36 mmol) in dichloromethane (10 ml) was added a 10% aqueous solution of trifluoroacetic acid (10 ml). After stirring for 1 h the solvent was removed under vacuo to give a colourless oily residue which was dissolved in a mixture of THF (5 ml) and 1 M sodium hydroxide sol. (15 ml). This solution was stirred for 12 h, then THF was removed under vacuo and the mixture was treated with 6 M hydrochloric acid to reach pH 1. The water phase was extracted with diethyl ether

(3×20 ml) and the combined and dried organic phases were concentrated under vacuo to give **15e** as colourless crystals after recrystallization from chloroform/diethyl ether. Yield 0.68 g (80%). TLC: R_f~0.75, EtOAc/acetic acid (10+1). Mp 171°C. $[\alpha]_D^{20}$=+4.6 (c=0.24, EtOAc). $C_{19}H_{18}ClNO_6$ (357.36): calcd C 63.86, H 6.36, N 3.92; found C 62.33, H 5.21, N 3.90. IR (KBr): ν (cm^{-1})=3310 (NH), 3010 (COOH), 1700 (C=O), 1550 (C–H). ^{1}H NMR (DMSO-d_6): δ=2.55 (dd, 1H, J_{gem}~16.5 Hz, J_{4a-3}=4.0 Hz, H-4a), 2.80 (dd, 1H, J_{gem}=16.3 Hz, J_{4b-3}=11.3 Hz, H-4b), 3.54 (dt, 1H, J_{3-4a}~4.0 Hz, J_{3-4b}~11.3 Hz, J_{3-2}~7.3 Hz, H-3), 4.24 (dd, 1H, J_{2-3}=7.3 Hz, $J_{2\text{-NH}}$=8.5 Hz, H-2), 4.92 (d, 1H, J=12.8 Hz, CH_2, benzyl), 5.02 (d, 1H, J=12.8 Hz, CH_2, benzyl), 7.25–7.36 (m, 10H, aryl), 7.69 (d, 1H, J_{NH-2}= 8.5 Hz, N–H), 12.5 (s, 2H, carboxylate). ^{13}C NMR (DMSO-d_6): δ=38.10 (C-4), 45.42 (C-3), 61.41 (C-2), 68.04 (benzyl), 129.4, 130.2, 130.4, 130.7, 130.9, 131.0, 139.6, 142.8 (12×C, aryl), 158.7 (urethane), 174.9, 175.3 (2×COOH, carboxylate). MS (70 eV), m/z (%): 357 (1) [M^+], 339 (7), 206 (18), 160 (34), 149 (8), 117 (14), 108 (14), 107 (40), 104 (17), 92 (10), 91 (100), 79 (17), 78 (6), 77 (15).

3.1.20. (2*S*,3*R*)-1-(Benzyloxycarbonyl)-3-(4-chlorophenyl)-glutamic acid (15f). To a solution of **10f** (0.80 g, 1.75 mmol) in dichloromethane (10 ml) was added a 10% aqueous solution of trifluoroacetic acid (10 ml). After stirring for 1 h the solvent was removed in vacuo to give a colourless oily residue which was dissolved in a mixture of THF (5 ml) and 1 M aqueous sodium hydroxide (15 ml). This solution was stirred for 12 h, then THF was removed in vacuo and the reaction mixture was adjusted with hydrochloric acid (6N) to pH 1. The water phase was extracted with diethylether (3×20 ml) and the combined and dried organic phases were concentrated in vacuo to give **15f** as colourless crystals after recrystallization from chloroform/diethylether. Yield 0.59 g (70%). TLC: R_f~0.7, EtOAc/acetic acid (10+1). Mp 176°C. $[\alpha]_D^{20}$=+1.2 (c=0.44, EtOAc). $C_{19}H_{18}ClNO_6$ (391.81): calcd C 58.24, H 4.63, N 3.57; found C 58.24, H 4.74, N 3.57. IR (KBr): ν (cm^{-1})=3310 (NH), 2950 (COOH), 1720 (C=O), 1560, 1520 (C–H). ^{1}H NMR (DMSO-d_6): δ=2.59 (dd, 1H, J_{gem}=16.5 Hz, J_{4a-3}=3.7 Hz, H-4a), 2.81 (dd, 1H, J_{gem}=16.3 Hz, J_{4b-3}=11.6 Hz, H-4b), 3.51 (dt, 1H, J_{3-4a}~3.7 Hz, J_{3-4b}~11.6 Hz, J_{3-2}~7.3 Hz, H-3), 4.24 (dd, 1H, J_{2-3}=7.3 Hz, $J_{2\text{-NH}}$=8.6 Hz, H-2), 4.96 (d, 1H, J=15.0 Hz, CH_2, benzyl), 5.02 (d, 1H, J=15.0 Hz, CH_2, benzyl), 7.25–7.33 (m, 9H, aryl), 7.79 (d, 1H, J_{NH-2}= 8.6 Hz, N–H), 12.4 (s, 2H, carboxylate). ^{13}C NMR (DMSO-d_6): δ=36.06 (C-4), 43.17 (C-3), 59.46 (C-2), 66.33 (benzyl), 128.4, 128.6, 128.9, 129.2, 131.0, 132.3, 137.8 140.1, (12×C, aryl), 157.0 (urethane), 173.0, 173.4 (2×COOH, carboxylate). MS (70 eV), m/z (%): 391 (0) [M^+], 374 (10), 342 (21), 341 (16), 340 (65), 239 (12), 194 (27), 170 (12), 151 (21), 141 (10), 109 (6), 108 (75), 107 (55), 91 (39), 89 (10), 79 (100), 78 (12), 77 (57).

3.1.21. (2*S*,3*R*)-1-(Benzyloxycarbonyl)-3-naphthyl-glutamic acid (15h): mixture with (16h) [appr. relation: 15h/16h=10:1]. To a solution of (0.50 g, 1.06 mmol) **10h** in 10 ml dichloromethane was added a 10% aqueous solution of trifluoroacetic acid (10 ml). After stirring for 1 h the solvent was removed under vacuo to give a colourless oily residue which was dissolved in a mixture of 5 ml THF and 15 ml sodium hydroxide (1 M in water). This solution was stirred for 12 h, then THF was removed carefully under vacuo and the reaction mixture was adjusted with hydrochloric acid (6N) to pH 1. The water phase was extracted with diethyl ether (3×30 ml) and the combined and dried organic phases were concentrated under vacuo to give a colourless solid mixture of **15h**+**16h** (appr. relation: **15h/16h**=10:1). Yield (75%). ^{1}H NMR (DMSO-d_6): δ=2.56 (dd, 1H, J_{gem}=17.1 Hz, J_{4a-3}=3.6 Hz, H-4a, **16h**), 2.89 (dd, 1H, J_{gem}=15.9 Hz, J_{4a-3}=4.3 Hz, H-4a, **15h**), 3.05–3.18 (m, 1H, H-4b, **15h**; 1H, H-4b, **16h**), 4.63 (m, 1H, H-2, **16h**), 4.78–4.84 (m, 2H, H-2 and H-3, **15h**; 1H, H-3, **16h**), 4.93 (d, 1H, J=12.9 Hz, CH_2, benzyl, **15h**), 5.03 (d, 1H, J=12.9 Hz, CH_2, benzyl, **15h**), 7.30–7.95 (m, 12H, aryl, **15h**; 7H, aryl, **16h**), 8.24 (m, 2H, N–H, **16h**), 8.35 (d, 1H, J=6.8 Hz, N–H, **15h**), 12.3 (s,~2H, carboxylate, **15h**; ~2H, carboxylate, **16h**). ^{13}C NMR (DMSO-d_6): δ=36.10 (C-4, **15h**), 37.24 (C-4, **16h**), 39.83 (C-3, **16h**), 42.02 (C-3, **15h**), 59.40 (C-2, **15h**), 66.30 (C-2, **16h**), 66.75 (benzyl, **15h**), 122.9, 123.1, 125.5, 126.0, 126.6, 126.9, 127.0, 127.3, 127.8, 128.0, 128.5, 128.8, 128.9, 129.1, 131.9, 134.7, 138.5, 139.1, 140.4, 141.1, 141.8 (26×C, aryl, **15h**+**16h**), 158.2 (urethane, **15h**), 173.3 (COOH, **15h**), 174.8 (COOH, **15h**), 177.0 (COOH, **16h**), 178.0 (COOH, **16h**).

3.1.22. (2*S*,3*S*)-3-Ethyl-5-oxo-pyrrolidine-2-carboxylic acid (14b). To a solution of **10b** (0.50 g, 1.47 mmol) in EtOAc/methanol (2+1) (70 ml) was added palladium on charcoal. This suspension was stirred for 2 h under hydrogen (4 bar). The catalyst was filtered off and the organic phase was concentrated in vacuo to give an oily colourless residue. The residue was treated with a mixture of trifluoroacetic acid (1 ml), water (20 ml) and dichloromethane (5 ml) for 1 h. The organic layer was diluted with dichloromethane, and the aqueous layer was extracted with dichloromethane (2×). The combined organic layers were concentrated in vacuo and the oily residue was treated with a 10% cesium carbonate solution (10 ml) for 3 h. The reaction mixture was acidified with hydrochloric acid (pH <2) and extracted with EtOAc (3×25 ml). The organic layers were dried and concentrated in vacuo to give **14b** as colourless crystals. Recrystallization from chloroform/petroleum ether. Yield 0.15 g (65%). TLC: R_f~0.40, EtOAc/acetic acid (10+1). Mp 115°C. $[\alpha]_D^{20}$=+50.5 (c=0.44, acetone). $C_7H_{11}NO_3$ (157.17): calcd C 53.49, H 7.05, N 8.91; found C 53.06, H 7.26, N 8.97. IR (KBr): ν (cm^{-1})=3380 (NH), 3010, 2940 (C–H), 1930, 1720 (C=O), 1650 (C=O, lactam), 1420 (C–H). ^{1}H NMR (DMSO-d_6): δ=0.87 (t, 3H, J=7.3 Hz, CH_3), 1.39 (dq, 1H, J=7.3, 6.1 Hz, Ha-ethyl), 1.59 (dq, 1H, J=7.3, 6.1 Hz, Hb-ethyl), 1.82 (dd, 1H, J_{gem}=16.2 Hz, J_{4b-3}=4.7 Hz, H-4b), 2.21 (m, 1H, J_{3-4a}~8.5 Hz, $J_{3\text{-}CH2}$~6.1 Hz, J_{3-4b}~4.7 Hz, J_{3-2}~4.0 Hz, H-3), 2.32 (dd, 1H, J_{gem}=16.2 Hz, J_{4a-3}= 8.5 Hz, H-4a), 3.64 (d, 1H, J_{2-3}=4.0 Hz, H-2), 7.80 (s, 1H, N–H). ^{13}C NMR (DMSO-d_6): δ=12.30 (CH_3), 28.24 (CH_2), 36.28 (C-3), 40.96 (C-4), 61.17 (C-2), 176.8 (C=O, lactam), 176.9 (COOH, carboxylate). MS (70 eV), m/z (%): 157 (3) [M^+], 113 (6) [M^+−carboxylate], 112 (100), 98 (7), 84 (2), 83 (3), 70 (5), 69 (51).

3.1.23. (2*S*,3*R*)-3-Phenyl-5-oxo-pyrrolidine-2-carboxylic acid (14e). To a solution of **10e** (1.00 g, 2.36 mmol) in

EtOAc/methanol (2+1) (100 ml) was added 10% palladium on charcoal. After the suspension was stirred for 2 h under hydrogen (4 bar), the catalyst was filtered off and the organic phase was concentrated in vacuo to give an oily colourless residue. The residue was treated with a mixture of trifluoroacetic acid (1 ml), water (20 ml) and dichloromethane (5 ml) for 1 h. The organic layer was diluted with CH_2Cl_2 and the aqueous phase was extracted with CH_2Cl_2 (2×). The combined organic layers were concentrated in vacuo and the oily residue was treated with of a 10% cesium carbonate solution (10 ml) for 3 h. The reaction mixture was acidified with hydrochloric acid (pH <2) and extracted with EtOAc (3×25 ml). The organic layers were dried and concentrated in vacuo to give **14e**. Recrystallization from chloroform/petroleum ether gave colourless crystals. Yield 0.34 g (70%). TLC: R_f~0.4, EtOAc/acetic acid (10+1). Mp 162°C. $[\alpha]_D^{20}$=+86.7 (c=0.27, acetone), $[\alpha]_D^{20}$=+84.3 (c=0.70, methanol); (lit:[2c] mp 139.0–140.0°C. $[\alpha]_D^{20}$=+82.5 (c=1.11, methanol)). $C_{11}H_{11}NO_3$ (205.21): calcd C 64.38, H 5.40, N 6.83; found C 63.23, H 5.62, N 6.44. IR (KBr): ν (cm^{-1})=3280 (NH), 2960 (C–H), 1750 (C=O), 1650 (C=O, lactam). ^{1}H NMR (DMSO-d_6): δ=2.05 (dd, 1H, J_{gem}=16.8 Hz, J_{4b-3}=6.7 Hz, H-4b), 2.43 (dd, 1H, J_{gem}=16.8 Hz, J_{4a-3}=9.2 Hz, H-4a), 3.34 (dt, 1H, J_{3-4b}~6.7 Hz, J_{3-4a}~9.2 Hz, J_{3-2}~5.5 Hz, H-3), 3.82 (d, 1H, J_{2-3}=5.6 Hz, H-2), 7.03–7.10 (m, 5H, aryl), 7.92 (s, 1H, N–H), 12.7 (s, 1H, carboxylate). ^{13}C NMR (DMSO-d_6): δ=38.95 (C-3), 44.59 (C-4), 63.16 (C-2), 127.8, 129.5, 143.5, (6×C, aryl), 174.3 (COOH, carboxylate), 176.3 (C=O, lactam). MS (70 eV), m/z (%): 205 (26) [M^+], 162 (17), 161 (13) [M^+−carboxylate], 160 (100), 118 (11), 117 (75), 116 (6), 115 (26), 104 (74), 103 (16), 91 (14), 77 (18).

3.1.24. (2*S*,3*R*)-3-(4-Chlorophenyl)-5-oxo-pyrrolidine-2-carboxylic acid (14f). To a solution of **10f** (1.04 g, 2.27 mmol) in EtOAc/MeOH (2+1) (125 ml) was added palladium (10%) on charcoal. The suspension was stirred for 3 h under hydrogen (4 bar), the catalyst was filtered off and the solvent was evaporated to give an oily colourless residue. The residue was treated with a mixture of trifluoro acetic acid (1 ml), water (20 ml) and dichloromethane (5 ml) for 2 h. The organic layer was diluted with CH_2Cl_2 and the aqueous phase was extracted with CH_2Cl_2. The combined organic layers were concentrated in vacuo and the oily residue was stirred with a 10% cesium carbonate solution (10 ml) for 3 h. The reaction mixture was acidified with hydrochloric acid (pH <2) and extracted with EtOAc (3×25 ml). The organic layers were dried and concentrated in vacuo to give **14f** as colourless crystals. Yield 0.35 g (65%). TLC: R_f~0.4, isopropanol/CH_2Cl_2/acetic acid (5+1+1). Mp 191°C. $[\alpha]_D^{20}$=+85.8 (c=0.60, acetone). $C_{11}H_{10}ClNO_3$ (239.66): calcd C 55.13, H 4.21, N 5.84; found C 55.44, H 4.32, N 6.00. IR (KBr): ν (cm^{-1})=3220 (NH), 2950, 2870 (C–H), 1730 (C=O), 1640, 1490 (C–H). ^{1}H NMR (DMSO-d_6): δ=2.07 (dd, 1H, J_{gem}=16.8 Hz, J_{4b-3}=7.1 Hz, H-4b), 2.45 (dd, 1H, J_{gem}=16.8 Hz, J_{4a-3}=9.2 Hz, H-4a), 3.40 (dt, 1H, J_{3-4b}~7.1 Hz, J_{3-4a}~9.3 Hz, J_{3-2}~6.1 Hz, H-3), 3.86 (d, 1H, J_{2-3}=6.1 Hz, H-2), 7.13–7.24 (m, 4H, aryl), 7.97 (s, 1H, N–H), 12.7 (s, 1H, carboxylate). ^{13}C NMR (DMSO-d_6): δ=38.91 (C-3), 44.00 (C-4), 62.92 (C-2), 129.4, 129.9, 132.4, 142.3, (6×C, aryl), 174.0 (COOH, carboxylate), 176.1 (C=O, lactam). MS (70 eV), m/z (%): 241 (13) [M+1$^+$], 240 (6) [M^+], 239 (40) [M-1$^+$], 196 (54) [M^+−carboxylate], 195 (13), 194 (92), 153 (15), 152 (6), 151 (47), 140 (32), 139 (10), 138 (100), 117 (19), 116 (26), 115 (23), 103 (33).

3.1.25. (2*S*,3*R*)-3-Naphthyl-5-oxo-pyrrolidine-2-carboxylic acid (14h). To a solution of **10h** (0.75 g, 1.59 mmol) in EtOAc/methanol (2+1) (100 ml) was added 10% palladium on charcoal. This suspension was stirred for 2 h under hydrogen (4 bar), then the catalyst was filtered off and the organic phase was concentrated in vacuo to give an oily colourless residue. The residue was treated with a mixture of trifluoro acetic acid (1 ml), water (20 ml) and dichloromethane (5 ml) for 1 h. The organic layer was diluted with CH_2Cl_2 and the aqueous phase was extracted with dichloromethane (2×). The combined organic layers were concentrated in vacuo and the oily residue was treated with a 10% caesium carbonate solution (10 ml) for 3 h. The reaction mixture was acidified with hydrochloric acid (pH <2) and extracted with EtOAc (3×25 ml). The organic layers were dried and concentrated in vacuo to give **14h** as colourless crystals. Recrystallization from chloroform/petroleum ether yielded 0.41 g (58%). TLC: R_f~0.45, EtOAc/acetic acid (10+1). Mp 210°C. $[\alpha]_D^{20}$=−20.8 (c=0.077, $CHCl_3$). $C_{15}H_{13}NO_3$ (255.27): calcd C 70.58, H 5.13, N 5.49; found C 70.27, H 5.63, N 5.37. IR (KBr): ν (cm^{-1})=3280 (NH), 3050, 2920 (C–H), 1750 (C=O), 1650 (C=O, lactam), 1440 (C–H). ^{1}H NMR (DMSO-d_6): δ=2.39 (dd, 1H, J_{gem}=16.8 Hz, J_{4b-3}=4.3 Hz, H-4b), 2.94 (dd, 1H, J_{gem}=19.7 Hz, J_{4a-3}=6.7 Hz, H-4a), 4.27 (d, 1H, J_{2-3}=3.4 Hz, H-2), 4.52 (dt, 1H, J_{3-4a}=6.7 Hz, J_{3-4b}~4.3 Hz, J_{3-2}~3.4 Hz, H-3), 7.54–7.72 (m, 4H, aryl), 7.96 (d, 1H, J=7.3 Hz, aryl), 8.07 (dd, 1H, J=7.3, 2.1 Hz, aryl), 8.29 (s, 1H, N–H), 8.31 (s, 1H, aryl), 13.2 (s, 1H, carboxylate). ^{13}C NMR (DMSO-d_6): δ=38.11 (C-3), ~40 (C-4), 62.35 (C-2), 123.9, 124.0, 126.5, 126.7, 127.4, 128.3, 129.8, 131.6, 134.5, 139.4 (10×C, aryl), 174.6 (COOH, carboxylate), 176.8 (C=O, lactam). MS (70 eV), m/z (%): 255 (40) [M^+], 211 (3) [M^+−carboxylate], 210 (16), 167 (25), 165 (20), 155 (13), 154 (94), 153 (68), 152 (34), 128 (100), 103 (16), 91 (6), 77 (5), 76 (12).

3.1.26. (2*S*,3*S*)-3-Methyl-glutamic acid (16a). To a solution of **15a** (0.74 g, 2.51 mmol) in H_2O/isopropanol (1+1) (50 ml) was added palladium on charcoal. This suspension was stirred for 3 h under hydrogen (4 bar). The catalyst was removed by filtration and the mixture was concentrated in vacuo to give a solid colourless residue. Recrystallization from H_2O/isopropanol gave **16a** as colourless crystals. Yield 0.32 g (78%). Mp 182–184°C. $[\alpha]_D^{20}$=+41.9 (c=0.82, 6 M HCl); (lit:[11b] mp 169.5–170°C. $[\alpha]_D^{20}$=+42.8 (c=0.97, 6 M HCl). Mp 169–171°C (for monoammonium salt)). $C_6H_{11}NO_4$ (161.16): calcd C 44.72, H 6.88, N 8.69; found C 43.93, H 6.77, N 8.56. IR (KBr): ν (cm^{-1})=3040 (NH), 2940, 2870 (C–H), 2620–2500 (COOH), 1690 (COO^-), 1490 (C–H), 1420 (COO^-). ^{1}H NMR (D_2O/NaOD): δ=0.85 (d, 3H, J_{CH3-3}=6.7 Hz, CH_3), 1.83 (dd, 1H, J_{gem}=12.8 Hz, J_{4b-3}=11.3 Hz, H-4b), 1.91–2.15 (m, 1H, J_{3-4a}~3.1 Hz, J_{3-4b}~11.3 Hz, J_{3-2}~5.5 Hz, $J_{3\text{-}CH3}$~6.7 Hz, H-3), 2.25 (dd, 1H, J_{gem}=13.1 Hz, J_{4a-3}=3.1 Hz, H-4a), 3.01 (d, 1H, J_{2-3}=5.5 Hz, H-2). ^{13}C NMR (D_2O/NaOD): δ=16.47 (CH_3), 35.32 (C-3), 40.96 (C-4), 61.11 (C-2), 182.4

(COO^-), 182.6 (COO^-). MS (70 eV), *m/z* (%): 161 (0) [M^+], 144 (4) [M^+-H_2O], 99 (6), 98 (100), 70 (3), 55 (69).

3.1.27. (2*S*,3*S*)-3-Ethyl-glutamic acid (16b). To a solution of **15b** (0.50 g, 1.62 mmol) in EtOAc/methanol (1+5) (100 ml) was added palladium on charcoal. This suspension was stirred for 6 h under hydrogen (4 bar). The catalyst was removed by filtration and the mixture was concentrated in vacuo to give a solid colourless residue. This residue was treated diethyl ether to give **16b** as colourless crystals. Yield 0.18 g (62%). Mp 139°C. $[\alpha]_D^{20}$=+49.3 (*c*=0.78, 6 M HCl). $C_7H_{13}NO_4$ (175.18): calcd C 47.99, H 7.48, N 8.00; found C 46.12, H 7.04, N 7.66. IR (KBr): ν (cm^{-1})=3050 (NH), 2970, 2940, 2880 (C–H), 2620–2500 (COOH), 1700 (COO^-), 1485 (C–H), 1420 (COO^-). ^{1}H NMR (D_2O): δ=0.81 (t, 3H, *J*=7.3 Hz, CH_3), 1.26 (dq, 1H, *J*=7.3 Hz, $J_{CH2\text{-}3}$=7.0 Hz, CH_2), 1.32 (dq, 1H, *J*=7.3 Hz, $J_{CH2\text{-}3}$=7.0 Hz, CH_2), 2.13–2.29 (m, 1H, H-3), 2.31 (dd, 1H, J_{gem}=16.5 Hz, J_{4b-3}=6.4 Hz, H-4b), 2.43 (dd, 1H, J_{gem}=16.5 Hz, J_{4a-3}=6.4 Hz, H-4a), 3.75 (d, 1H, J_{2-3}=3.4 Hz, H-2). ^{13}C NMR (D_2O): δ=11.19 (CH_3), 22.84 (CH_2), 35.27 (C-4), 37.86 (C-3), 56.80 (C-2), 173.6 (COOH), 177.4 (COOH). MS (70 eV), *m/z* (%): 175 (0) [M^+], 157 (3) [M^+-H_2O], 113 (7), 112 (100), 84 (2), 83 (3), 69 (50).

3.1.28. (2*S*,3*S*)-3-(1-Butyl)-glutamic acid (16c). To a solution of **15c** (1.00 g, 2.96 mmol) in EtOAc/methanol (1+5) (100 ml) was added palladium on charcoal. This suspension was stirred for 5 h under hydrogen (4 bar). The catalyst was removed by filtration. The mixture was concentrated in vacuo to give a solid colourless residue. This residue was treated diethyl ether to give **16c** as colourless crystals. Yield 0.52 g (75%). Mp 122–123°C. $[\alpha]_D^{20}$=+7.90 (*c*=0.42, methanol). $C_9H_{17}NO_4$ (203.24): calcd C 53.19, H 8.43, N 6.89; found C 52.34, H 8.03, N 6.71. IR (KBr): ν (cm^{-1})=3240 (NH), 2950, 2930, 2860 (C–H), 2620–2500 (COOH), 1710, 1680 (COO^-), 1520, 1500 (C–H), 1440 (COO^-). ^{1}H NMR (CD_3OD, 27°C): δ=0.98 (t, 3H, *J*=6.7 Hz, CH_3), 1.37–1.48 (m, 4H, 2×CH_2), 1.51–1.57 (m, 2H, 1×CH_2), 2.45–2.50 (m, 3H, H-4b and H-3), 2.70 (dd, 1H, J_{gem}=18.2 Hz, J_{4a-3}=8.0 Hz, H-4a), 3.79 (d, 1H, J_{2-3}=3.2 Hz, H-2). ^{1}H NMR (CD_3OD, 50°C): δ=0.97 (t, 3H, *J*=6.8 Hz, CH_3), 1.37–1.50 (m, 4H, 2×CH_2), 1.51–1.58 (m, 2H, 1×CH_2), 2.41–2.51 (m, 3H, H-4b and H-3), 2.71 (dd, 1H, J_{gem}=18.3 Hz, J_{4a-3}=6.9 Hz, H-4a), 3.79 (d, 1H, J_{2-3}=3.3 Hz, H-2). ^{1}H NMR (D_2O/NaOD, 27°C): δ=0.86 (t, 3H, *J*=6.7 Hz, CH_3), 1.27–1.32 (m, 6H, 3×CH_2), 1.96 (dd, 1H, J_{gem}=13.1 Hz, J_{4b-3}=10.6 Hz, H-4b), 2.05–2.13 (m, 1H, J_{3-4a}~3.5 Hz, J_{3-4b}~10.6 Hz, J_{3-2}~5.5 Hz, H-3), 2.16 (dd, 1H, J_{gem}=13.3 Hz, J_{4a-3}=3.5 Hz, H-4a), 3.29 (d, 1H, J_{2-3}=4.2 Hz, H-2). ^{1}H NMR (D_2O/NaOD, 50°C): δ=1.12 (t, 3H, *J*=6.6 Hz, CH_3), 1.50–1.60 (m, 6H, 3×CH_2), 2.23 (dd, 1H, J_{gem}=13.4 Hz, J_{4b-3}=10.3 Hz, H-4b), 2.30–2.38 (m, 1H, J_{3-4a}~3.5 Hz, J_{3-4b}~10.3 Hz, J_{3-2}~4.4 Hz, H-3), 2.43 (dd, 1H, J_{gem}=13.4 Hz, J_{4a-3}=3.5 Hz, H-4a), 3.53 (d, 1H, J_{2-3}=4.4 Hz, H-2). ^{13}C NMR (D_2O/NaOD): δ=13.75 (CH_3, butyl), 22.46 (CH_2, butyl), 28.75 (CH_2, butyl), 30.47 (CH_2, butyl), 38.94 (C-4), 39.83 (C-3), 57.93 (C-2), 182.6 (COO^-), 182.8 (COO^-). MS (70 eV), *m/z* (%): 203 (0) [M^+], 185 (2) [M^+-H_2O], 141 (9), 140 (100), 98 (3), 97 (11).

3.1.29. (2*S*,3*R*)-3-Phenyl-glutamic acid (16e). To a solution of **15e** (2.00 g, 5.60 mmol) in EtOAc/methanol (2+1) (120 ml) was added palladium on charcoal. This suspension was stirred for 4 h under hydrogen (4 bar). The catalyst was removed by filtration and the mixture was concentrated in vacuo to give an oily colourless residue. This residue was treated with diethyl ether to give **16e** as colourless crystals. Yield 0.79 g (63%). Mp 197°C. $[\alpha]_D^{20}$=+16.7 (*c*=0.60, 6 M HCl); (lit:[2c] mp 158.0–158.6°C. $[\alpha]_D^{20}$=+16.7 (*c*=1.36, 6N HCl). lit:[2k] $[\alpha]_D^{20}$=+19.1 (*c*=0.81, 6 M DCl)). $C_{11}H_{13}NO_4$ (223.23): calcd C 59.19, H 5.87, N 6.27; found C 57.91, H 6.08, N 5.77. IR (KBr): ν (cm^{-1})=3150 (NH), 2940 (C–H), 2620–2500, 1700 (COOH), 1620 (COO^-), 1500 (C–H), 1410 (COO^-). ^{1}H NMR (DMSO-d_6): δ=2.31 (dd, 1H, J_{gem}=16.8 Hz, J_{4a-3}=6.4 Hz, H-4a), 2.72 (dd, 1H, J_{gem}=16.5 Hz, J_{4b-3}=9.5 Hz, H-4b), 3.64 (dt, 1H, J_{3-4a}~6.4 Hz, J_{3-4b}~9.5 Hz, H-3), 4.08 (s, 1H, H-2), 7.21–7.45 (m, 5H, aryl), 8.15 (s,~1H, N–H), 12.5 (s,~2H, carboxylate). ^{1}H NMR (D_2O/NaOD): δ=2.53–2.69 (m, 2H, H-4), 3.21–3.56 (m, 2H, H-2 and H-3), 7.19–7.38 (m, 5H, aryl). ^{13}C NMR (D_2O/NaOD): δ=39.14 (C-4), 47.65 (C-3), 62.26 (C-2), 127.1, 128.6, 128.8, 141.6 (6×C, aryl), 181.5 (COO^-), 181.7 (COO^-). MS (70 eV), *m/z* (%): 223 (0) [M^+], 205 (25) [M^+-H_2O], 162 (16), 161 (13), 160 (100), 118 (10), 117 (73), 115 (20), 104 (63), 103 (13).

3.1.30. (2*S*,3*R*)-3-(4-Chlorophenyl)-glutamic acid (16f). To a solution of **15f** (2.00 g, 5.10 mmol) in EtOAc/methanol (2+1) (100 ml) was added palladium on charcoal. After the suspension was stirred for 3 h under hydrogen (4 bar), the catalyst was removed by filtration and the organic phase was concentrated in vacuo to give an oily colourless residue. This residue was treated with diethyl ether to give **16f** as colourless crystals. Yield 0.92 g (70%). Mp 197°C. $[\alpha]_D^{20}$=+60.9 (*c*=0.14, 1 M HCl), $[\alpha]_D^{20}$=+129 (*c*=0.07, 1 M NaOH); (lit:[2i] mp 194.7–194.9°C.[2i] $[\alpha]_D^{20}$=+21.5 (*c*=0.39, 1N NaOH)). $C_{11}H_{12}ClNO_4$ (257.67): calcd C 51.28, H 4.69, N 5.44; found C 52.69, H 4.17, N 5.36. IR (KBr): ν (cm^{-1})=3350 (NH), 2940, 2870 (C–H), 2620–2500, 1740 (COOH), 1650 (COO^-), 1490 (C–H), 1430 (COO^-). ^{1}H NMR (DMSO-d_6): δ=2.25 (dd, 1H, J_{gem}=16.7 Hz, J_{4a-3}=7.1 Hz, H-4a), 2.62 (dd, 1H, J_{gem}=16.9 Hz, J_{4b-3}=9.4 Hz, H-4b), 3.56 (dt, 1H, J_{3-4a}~7.1 Hz, J_{3-4b}~9.4 Hz, J_{3-2}~5.8 Hz, H-3), 4.03 (d, 1H, J_{2-3}=5.8 Hz, H-2), 7.31–7.40 (m, 4H, aryl), 8.11 (s, 1H, N–H), 12.7 (s,~2H, carboxylate). ^{1}H NMR (CD_3OD): δ=2.33 (dd, 1H, J_{gem}=17.1 Hz, J_{4a-3}=6.4 Hz, H-4a), 2.74 (dd, 1H, J_{gem}=17.1 Hz, J_{4b-3}=9.2 Hz, H-4b), 3.59 (dt, 1H, J_{3-4a}~6.4 Hz, J_{3-4b}~9.2 Hz, J_{3-2}~5.2 Hz, H-3), 4.11 (d, 1H, J_{2-3}=5.2 Hz, H-2), 7.20–7.28 (m, 4H, aryl). ^{13}C NMR (CD_3OD): δ=38.16 (C-4), 43.97 (C-3), 63.31 (C-2), 128.7, 129.0, 133.1, 141.5 (6×C, aryl), 173.6 (COOH), 178.3 (COOH). MS (70 eV), *m/z* (%): 257 (0) [M^+], 241 (10), 239 (36), 196 (55), 195 (14), 194 (100), 151 (51), 140 (31), 139 (9), 138 (97), 117 (19), 116 (28), 115 (21), 103 (29).

3.1.31. (2*S*,3*R*)-3-(1-Naphthyl)-glutamic acid (16h). To a solution of **15h/16h** [ratio 10:1] (0.40 g, ~0.98 mmol) in EtOAc/methanol (1+1) (50 ml) was added palladium on charcoal. This suspension was stirred for 8 h under hydrogen (4 bar). The catalyst was removed by filtration and the mixture was concentrated in vacuo to give an oily

colourless residue. This residue was treated with diethyl ether to give pure **16h** as colourless crystals. Yield 0.16 g (60%). Mp 197°C. $[\alpha]_D^{20}=-3.23$ (c=0.31, methanol). $C_{15}H_{15}NO_4$ (273.29): calcd C 65.92, H 5.53, N 5.13; found C 65.04, H 5.80, N 4.87. IR (KBr): ν (cm^{-1})=3350 (NH), 2925, 2850 (C–H), 1750 (COOH), 1650 (COO^-), 1510 (C–H), 1420, 1400 (COO^-). ^1H NMR (CD_3OD): δ=2.56 (dd, 1H, J_{gem}=17.4 Hz, J_{4a-3}=3.7 Hz, H-4a), 3.10 (dd, 1H, J_{gem}=17.1 Hz, J_{4b-3}=9.2 Hz, H-4b), 4.38 (d, 1H, J_{2-3}=3.1 Hz, H-2), 4.62 (dt, 1H, J_{3-4b}=8.9 Hz, $J_{3-4a}\sim J_{3-2}\sim$3.4 Hz, H-3), 7.48–8.28 (m, 7H, aryl). ^1H NMR (DMSO-d_6): δ=2.25 (dd, 1H, J_{gem}=17.4 Hz, J_{4a-3}= 1.5 Hz, H-4a), 2.84 (dd, 1H, J_{gem}=16.8 Hz, J_{4b-3}=9.2 Hz, H-4b), 4.08 (s, 1H, H-2), 4.40 (m, 1H, H-3), 7.47–8.05 (m, 7H, aryl), 8.24 (d, 1H, J=6.4 Hz, N–H). ^{13}C NMR (CD_3OD): δ=37.24 (C-4), 39.83 (C-3), 66.30 (C-2), 122.9, 123.1, 125.5, 126.0, 126.6, 128.0, 129.1, 131.9, 134.7, 138.5 (10×C, aryl), 177.0 (COOH), 178.0 (COOH). MS (70 eV), m/z (%): 273 (1) [M^+], 267 (16), 266 (35), 238 (10), 224 (14), 223 (15), 222 (21), 210 (36), 195 (11), 193 (16), 185 (14), 181 (24), 168 (15), 167 (59), 166 (17), 165 (35), 155 (16), 154 (100), 153 (68), 152 (42), 131 (17), 129 (17), 128 (83).

3.1.32. (2*S*,3*R*,4*S*)-3-Methyl-2-(4-methyl-2,6,7-trioxabicyclo[2.2.2]oct-1-yl)-5-oxo-4-phenylselenenyl-pyrrolidine-1-carboxylic acid benzyl ester. To a solution of HMDS (1.54 g, 9.55 mmol) and butyllithium (3.54 ml, 9.55 mmol, 2.7 M in heptane) in abs. THF (10 ml) at −78°C was added **10a** (1.50 g, 4.15 mmol) dissolved in THF (25 ml) under nitrogen over a period of 30 min. The reaction mixture was allowed to warm to 0°C, then again cooled to −78°C and phenylselenenyl chloride (0.83 g, 4.36 mmol) dissolved in abs. THF (10 ml) was added. After 2 h the mixture was allowed to warm to room temperature. The reaction was quenched by adding satd. ammonium chloride sol. (15 ml), diluted with diethyl ether (180 ml) and the organic phase was washed with satd. ammonium chloride sol. (2×). The dried organic layer was concentrated in vacuo to give an yellow oily residue, which was purified by column chromatography on silica gel using EtOAc/ petroleum ether (1+1) as an eluent to give colourless crystals. Recrystallization from dichloromethane/ethanol. Yield 1.18 g (55%). TLC: $R_f\sim$0.55, EtOAc/ petroleum ether (1+1). Mp 174°C. $[\alpha]_D^{20}=-88.6$ (c=0.50, CH_2Cl_2). $C_{25}H_{27}NO_6Se$ (516.45): calcd C 58.14, H 5.27, N 2.71; found C 58.80, H 5.50, N 2.72. IR (KBr): ν (cm^{-1})=2965, 2945 (C–H), 2882, 1720 (C=O), 1496 (C–H). ^1H NMR ($CDCl_3$): δ=0.78 (s, 3H, CH_3, *ortho* ester), 1.16 (d, 3H, J_{CH3-3}=7.3 Hz, CH_3, methyl), 2.81 (ddq, 1H, J_{3-4}=2.0 Hz, $J_{3\text{-}CH3}$=7.3 Hz, J_{3-2}=1.0 Hz, H-3), 3.23 (d, 1H, J_{4-3}= 2.0 Hz, H-4), 3.86 (s, 6H, 3×OCH_2, *ortho* ester), 4.01 (d, 1H, J_{2-3}=1.0 Hz, H-2), 5.26 (d, 1H, J=12.6 Hz, CH_2, benzyl), 5.31 (d, 1H, J=12.6 Hz, CH_2, benzyl), 7.21–7.38 (m, 6H, aryl), 7.41–7.47 (m, 2H, aryl) 7.72–7.77 (m, 2H, aryl). ^{13}C NMR ($CDCl_3$): δ=14.67 (CH_3, *ortho* ester), 22.60 (CH_3, methyl), 31.50 ($CCH_3(CH_2O-)_3$), 36.81 (C-3), 50.24 (C-4), 66.04 (C-2), 68.71 (CH_2, benzyl), 73.04 (3×CH_2O), 109.2 ($CCH_3(OCH_2)_3$), 127.9, 128.5 (2x), 128.6, 128.8, 128.9, 129.0 (2×), 129.3, 129.4, 134.2, 135.9 (18×C, aryl), 152.1 (C=O, urethane), 175.6 (C=O, lactam). MS (70 eV), m/z (%): 517 (11) [M^++1], 515 (6) [M^+−1], 382 (3), 316 (3), 254 (4), 224 (3), 186 (5), 171 (12), 144 (3), 96 (6), 91 (100) [benzyl], 85 (6), 69 (10).

3.1.33. (2*S*)-3-Methyl-2-(4-methyl-2,6,7-trioxabicyclo[2.2.2]oct-1-yl)-5-oxo-2,5-dihydro-pyrrole-1-carboxylic acid benzyl ester (11a). The crude material of the preceding compound (1.00 g, 1.94 mmol) and DABCO (0.43 g, 3.87 mmol) was dissolved in abs. THF (25 ml) at 0°C. After 10 min a solution of 3-chloroperbenzoic acid (1.00 g, 5.82 mol) in dichloromethane (50 ml) was added to the reaction mixture over a period of 30 min. Then, the reaction was allowed to reach ambient temperature with stirring for further 48 h to complete the reaction (monitored by TLC). The reaction mixture was diluted with EtOAc (125 ml) washed with satd. sodium hydrogensulfite, satd. sodium hydrogencarbonate and satd. brine. The dried and concentrated organic phase gave an oily residue which was purified by column chromatography on silica gel using EtOAc/petroleum ether (2+1) to give **11a** as colourless crystals. Yield 0.55 g (79%). TLC: $R_f\sim$0.45, EtOAc/ petroleum ether (2+1). Mp 130°C. $[\alpha]_D^{20}=-113$ (c=0.42, CH_2Cl_2). $C_{19}H_{21}NO_6$ (359.38): calcd C 63.50, H 5.89, N 3.90; found C 63.47, H 6.02, N 3.61. IR (KBr): ν (cm^{-1})=2985, 2925, 2880, 2850 (C–H), 1760, 1700 (C=O), 1640, 1470, 1450 (C–H). ^1H NMR ($CDCl_3$): δ=0.76 (s, 3H, CH_3, *ortho* ester), 2.08 (dd, 3H, $J_{CH3\text{-}4}$=1.3 Hz, $J_{CH3\text{-}2}$=0.8 Hz, CH_3), 3.82 (m, 6H, 3×OCH_2, *ortho* ester), 4.75 (t, 1H, $J_{2\text{-}CH3}\sim J_{2-4}$=1.0 Hz, H-2), 5.23 (d, 1H, J=12.4 Hz, CH_2, benzyl), 5.30 (d, 1H, J=12.4 Hz, CH_2, benzyl), 5.78 (dq, 1H, $J_{4\text{-}CH3}$=1.3 Hz, J_{4-2}=0.9 Hz, H-4), 7.26–7.45 (m, 5H, aryl). ^{13}C NMR ($CDCl_3$): δ=14.62 (CH_3, *ortho* ester), 16.92 (CH_3), 31.09 ($CCH_3(CH_2O-)_3$), 66.77 (C-2), 68.39 (CH_2, benzyl), 73.15 (3×CH_2O), 107.9 ($CCH_3(OCH_2)_3$), 123.4 (C-4), 128.5, 128.6 (2x), 128.8, 129.0, 136.1 (6×C, aryl), 151.5 (C=O, urethane), 160.2 (C-3), 169.8 (C=O, lactam). MS (70 eV), m/z (%): 359 (11) [M^+], 315 (12), 253 (31), 211 (24), 123 (18), 109 (10), 96 (17), 91 (100) [benzyl], 85 (159), 65 (14).

3.1.34. (4*R*,5*S*)-4-Methyl-5-(4-methyl-2,6,7-trioxabicyclo[2.2.2]oct-1-yl)-pyrrolidin-2-one (12a). To a solution of **11a** (0.20 g, 0.56 mmol) in EtOAc (50 ml) was added palladium on charcoal. The suspension was stirred for 2 h under hydrogen (4 bar). The catalyst was removed by filtration and the mixture was concentrated in vacuo to give an oily colourless residue. This residue was treated with diethyl ether to give **12a** as colourless crystals. Recrystallization from chloroform/petroleum ether. Yield 0.10 g (80%). TLC: $R_f\sim$0.25, EtOAc. Mp 134°C. $[\alpha]_D^{20}=+28.0$ (c=0.15, EtOAc). $C_{11}H_{17}NO_4$ (227.26): calcd C 58.14, H 7.54, N 6.16; found C 58.09, H 8.10, N 5.63. IR (KBr): ν (cm^{-1})=3390 (NH), 3220, 2930, 2880 (C–H), 1680 (C=O, lactam), 1420, 1400 (C–H). ^1H NMR ($CDCl_3$): δ=0.89 (s, 3H, CH_3, *ortho* ester), 1.11 (d, 3H, J=7.0 Hz, CH_3), 2.19 (dd, 1H, J_{gem}=16.8 Hz, J_{3a-4}=7.9 Hz, H-3a), 2.59 (dd, 1H, J_{gem}=16.8 Hz, J_{3b-4}=8.2 Hz, H-3b), 2.91 (septet, 1H, $J_{4-3a}\sim J_{4-3b}\sim J_{4\text{-}CH3}\sim J_{4-5}$=7.6 Hz, H-4), 3.82 (s, 6H, 3×OCH_2, *ortho* ester), 4.37 (d, 1H, J_{5-4}=7.9 Hz, H-5). ^{13}C NMR ($CDCl_3$): δ=14.70 (CH_3, *ortho* ester), 21.81 (CH_3, methyl), 28.20 (C-4), 31.67 ($CCH_3(CH_2O-)_3$), 40.51 (C-3), 66.22 (C-5), 72.80 (3×CH_2O), 109.1 (CCH_3-$(OCH_2)_3$), 176.1 (C=O, lactam). MS (70 eV), m/z (%): 227 (7) [M^+], 185 (4), 131 (7), 99 (6), 98 (100) [M^+−oxetylate], 97 (5), 85 (4), 83 (2), 55 (36).

3.1.35. (2*S*,3*R*)-3-Methyl-glutamic acid (13a). Compound

12a (0.09 g, 0.40 mmol) was dissolved in 6N HCl (10 ml) and this solution was allowed to reflux for 6 h. The reaction mixture was concentrated in vacuo (up to appr. 5 ml), followed by careful treatment with satd. sodium bicarbonate solution to adjust pH 2. After addition of isopropanol (5 ml), this solution was kept at 8°C to yield **13a** as colourless crystals. Yield 0.03 g (52%). Mp 170–173°C. $[\alpha]_D^{20}=+6.0$ ($c=0.25$, 1 M NaOH); (lit:[2j] $[\alpha]_D^{20}=+6.0$ (for mono-ammonium salt, $c=1.07$, H_2O)). $C_6H_{11}NO_4$ (161.16): calcd C 44.72, H 6.88, N 8.69; found C 44.05, H 6.70, N 8.52. IR (KBr): ν (cm^{-1})=3040 (NH), 2940, 2870 (C–H), 2620–2500 (COOH), 1690 (COO^-), 1490 (C–H), 1420 (COO^-). ^1H NMR (D_2O/NaOD): $\delta=0.82$ (d, 3H, $J_{CH3\text{-}3}=7.0$ Hz, CH_3), 1.81 (d, 1H, $J_{gem}=12.1$ Hz, $J_{4a-3}=5.0$ Hz, H-4a), 1.89 (d, 1H, $J_{gem}=12.1$ Hz, $J_{4b-3}=9.6$ Hz, H-4b), 2.15 (m, 1H, H-3), 2.99 (d, 1H, $J_{2-3}=3.4$ Hz, H-2). ^{13}C NMR (D_2O/NaOD): $\delta=16.40$ (CH_3), 35.85 (C-3), 40.90 (C-4), 61.10 (C-2), 182.8 (COO^-), 183.0 (COO^-). MS (70 eV), *m/z* (%): 161 (0) [M^+], 144 (5) [M^+-H_2O], 99 (7), 98 (100), 70 (3), 55 (72).

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