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Synthesis of Bicyclic Guanidines from Pyrrolidin-2-one

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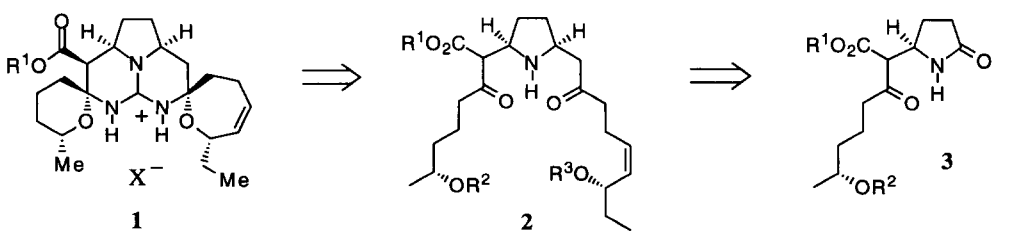
Abstract: The syntheses of three bicyclic guanidines as model compounds for the guanidine alkaloid ptilomycalin A are described. The guanidines are prepared from pyrrolidin-2-one via an *N*-acyliminium ion coupling reaction with silyl enol ethers and a direct guanylation with bis-Boc-thiourea and $HgCl_2$ as the key steps.

INTRODUCTION

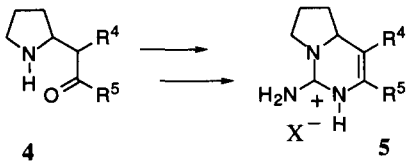
The recent upsurge of interest in guanidine alkaloids[1] renders molecules containing a guanidine moiety important targets for the organic synthetic chemist. The guanidine functional group is a key feature in many biologically active compounds[2], due to hydrogen bond mediated interaction with phosphate- and carboxylate-containing molecules[3]. Several of the guanidine alkaloids recently isolated have been shown to possess interesting biological activities[1]. The most remarkable alkaloid ptilomycalin A[4] was first reported in 1989 after its isolation from the Caribbean sponge *Ptilocaulus spiculifer* and from a Red Sea sponge of *Hemimycale* sp, and was shown to exhibit cytotoxic, antiviral and antifungal activities[4,5]. A number of different approaches have been reported for the synthesis of the pentacyclic guanidine moiety of ptilomycalin A[6]. Recently, the first total synthesis of this natural product was achieved by Overman et al[6a].

In connection with our research towards the total synthesis of ptilomycalin A the synthesis of bicyclic guanidines was investigated. Our retrosynthetic analysis of the pentacyclic core of ptilomycalin A (**1**) is outlined in Scheme 1. The 2,5-disubstituted pyrrolidine **2** was deemed a plausible precursor of the pentacyclic guanidine **1**, and was envisaged to arise from the monosubstituted lactam **3**. Studies on the synthesis of enantiopure **3** are described in a separate paper[7]. This article presents model studies for the guanylation of **2**. More specifically, the synthesis of a number of 2-substituted pyrrolidines of type **4** are described as well as their *N*-functionalization and cyclization to bicyclic guanidines of type **5** (Scheme 2).



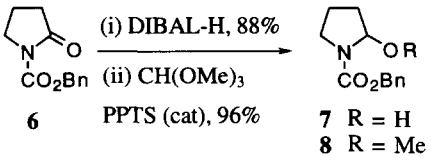
1 **2** **3**

Scheme 1. Retrosynthetic analysis.



4 5

Scheme 2. Synthetic strategy



6 7 R = H 8 R = Me

Scheme 3. Synthesis of the precursor

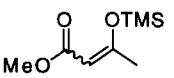
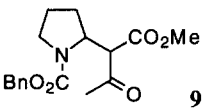
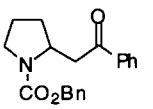
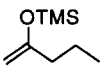
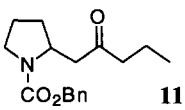
RESULTS AND DISCUSSION

Synthesis of C-2 substituted pyrrolidines

Three different 2-substituted pyrrolidines **9-11** (Scheme 3) were prepared in racemic form from benzyl carbamate **6**. Chemoselective reduction of the ring carbonyl of **6** was performed with 2 equiv of DIBAL-H in dichloromethane[8] at low temperature to give the alcohol **7** as a sensitive oil. Treatment of **7** with trimethyl orthoformate in methanol in the presence of a catalytic amount of PPTS gave the *N*-acyliminium ion precursor **8** in good yield.

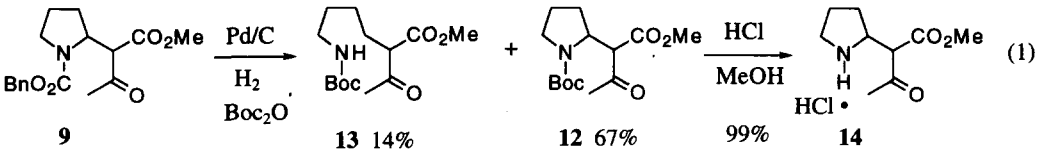
Table 1 shows the results of the Lewis acid-induced coupling reactions of **8** with three different silyl enol ethers, producing 2-substituted pyrrolidines in high yield. The results of entries 2 and 3 compare well with the work of Shono and co-workers[9,10], who reported the coupling of the corresponding methyl carbamate of **8** with these silyl enol ethers.

Table 1 Coupling Reactions of **8** with Silyl Enol Ethers.

entry	silyl enol ether	product	yield
1		 **9**	100%
2		 **10**	90%
3		 **11**	100%

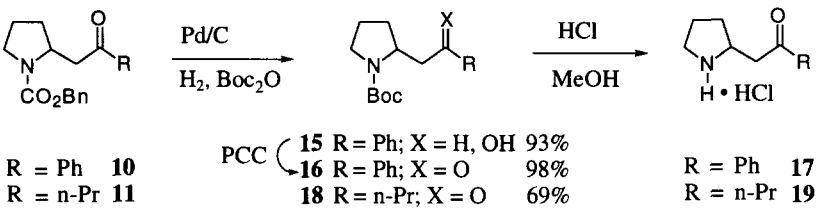
Reagents and conditions: silyl enol ether (1.1 equiv), TMSOTf (1.1 equiv), CH_2Cl_2, -78 °C 1 h, room temperature 45 min.

Transprotection of the benzyl carbamates **9-11** in a one pot reaction[11] gave the corresponding Boc-protected amines which could be easily purified, stored and deprotected with acid. Thus, hydrogenation of **9** in the presence of Boc_2O (eq 1) gave the transprotected carbamate **12** in 67% yield. The acyclic amine **13** was obtained as a side product. The formation of **13** may be explained by ring opening in a retro-Michael reaction followed by hydrogenation of the resulting enone to the saturated compound. The Boc-protected amine **12** was deprotected to the HCl salt of the amine **14** with hydrogen chloride in methanol in high yield.



(1)

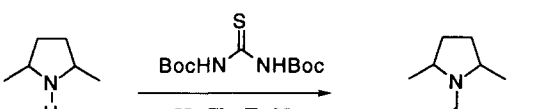
In the transprotection of the phenyl-substituted carbamate **10**, alcohol **15** was obtained in high yield as a 39:61 mixture of diastereomers (eq 2). Apparently, the ketone is reduced under these conditions. Oxidation with PCC in the presence of 4 Å mol sieves afforded the desired ketone **16** in high yield. Deprotection of the carbamate with HCl in methanol gave the HCl salt of the amine **17** quantitatively. The transprotection of the alkyl-substituted lactam **11** proceeded in a moderate yield. No side product was isolated after the reaction. Deprotection gave the amine **19** in a similar way.



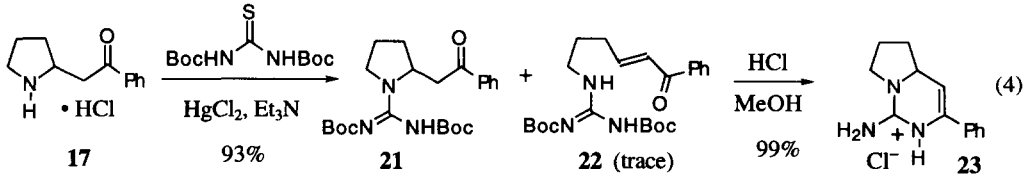
(2)

Synthesis of bicyclic guanidines

Recently, a number of novel methods to convert an amine directly into a (protected) guanidine have been reported[12]. Preliminary studies on 2,5-dimethylpyrrolidine as a model compound for secondary amines revealed that in our hands the procedure of Kim and Qian[12h] using *N,N'*-bis-(*tert*-butoxycarbonyl)-thiourea in the presence of $HgCl_2$ gave the best results. Treatment of a technical ca. 10:1 mixture of *cis*- and *trans*-2,5-dimethylpyrrolidine with *N,N'*-bis-(*tert*-butoxycarbonyl)-thiourea and $HgCl_2$ afforded protected guanidine **20** in 82% yield (eq 3). This method was therefore selected for the synthesis of bicyclic guanidines from the pyrrolidines **14**, **17** and **19**. Reaction of **17** with bis-Boc-thiourea in the presence of $HgCl_2$ (eq 4) afforded the desired coupled product **21** in 93% yield containing a trace of the acyclic product **22**. Treatment of the mixture of **21** and **22** with methanolic HCl gave the guanidine salt **23** in high yield as a single product. Thus, deprotection of **21** is directly followed by cyclisation of the free guanidine and dehydration to the conjugated product **23**. Apparently, deprotection of **22** leads to regeneration of the pyrrolidine via Michael addition[13].

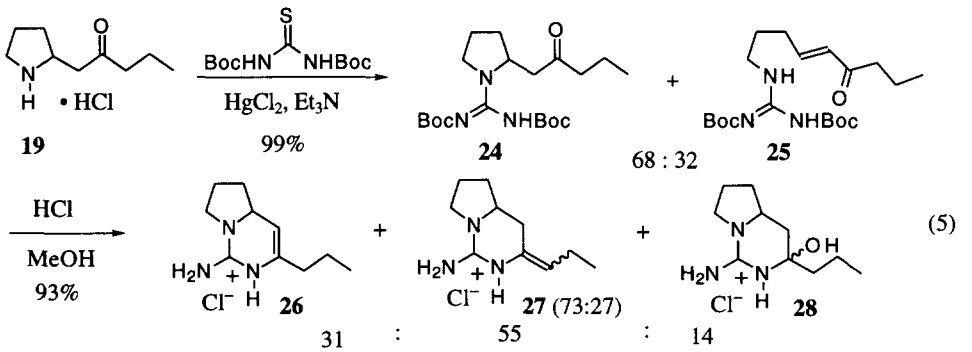


(3)

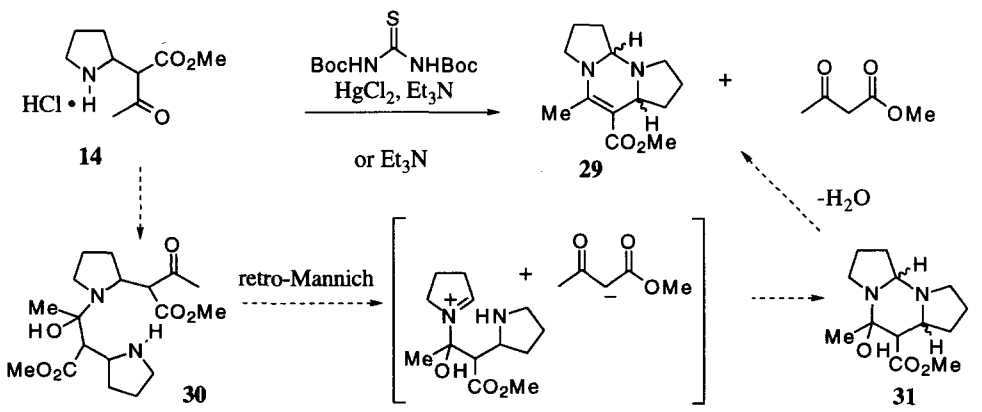


(4)

The direct guanylation of the amine HCl salt **19** is presented in equation 5. Reaction of **19** with bis-Boc-thiourea in the presence of $HgCl_2$ and Et_3N afforded in 99% yield a 73:27 mixture of the desired coupled product **24** and the acyclic product **25**. In this case a relatively large amount of acyclic product was obtained as compared to the guanylation of **17**. Both **22** and **25** are products of a formal retro-Michael reaction[14,15]. Upon deprotection of the mixture of **24** and **25** with HCl in methanol, a mixture of five different guanidines (**26-28**) was obtained in 93% yield. The ratio of these guanidines was inferred from the guanidinium protons and the double bond protons in the ^1H NMR spectrum. Along with the dehydration products **26** and **27**, a substantial amount of hemiaminals **28** was formed in this reaction. Attempts to favour dehydration by prolonged heating of this mixture did not lead to different product ratios.

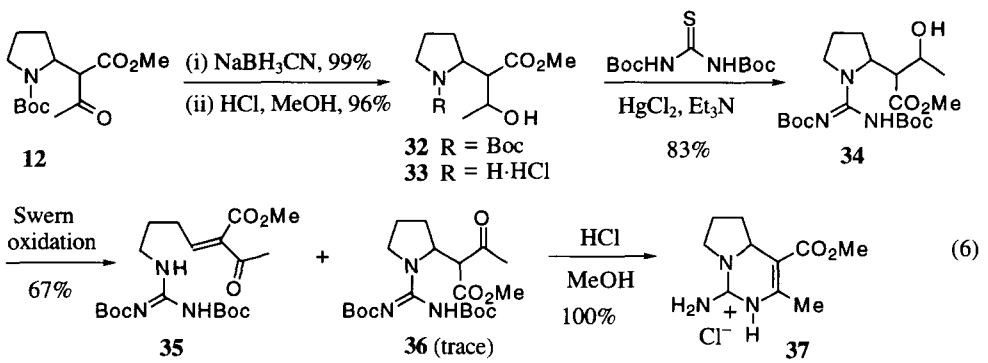


The reaction of the β-ketoester substituted pyrrolidine **14** with bis-Boc-thiourea in the presence of $HgCl_2$ and Et_3N did not produce the expected guanidine (Scheme 4). Instead, the tricyclic compound **29** was isolated as a 1:1 mixture of diastereomers in 37% yield. In order to investigate the formation of this compound, **14** was treated with Et_3N in THF in a separate experiment. After work-up, a mixture of **29** (96% yield) and methyl acetoacetate (49% yield) was obtained. The presence of methyl acetoacetate was proven by TLC and NMR analysis. After prolonged evaporation the methyl acetoacetate was removed and **29** was obtained pure. A possible mechanism for the formation of **29** is presented in Scheme 4. Deprotonation of the amine HCl salt leads to the free amine which dimerizes by addition of the amine to the ketone to give **30**. In a retro-Mannich reaction[16,17] methyl acetoacetate is liberated and subsequent cyclization produces **31**. Elimination of water then leads to the tricyclic compound **29**.



Scheme 4. Proposed Mechanism for the Formation of **29**.

It is evident from the reactions presented above, that the ketone function in **14** interferes with the guanylation of the amine. Apparently, the intermolecular reaction to the tricyclic compound **29** competes favourably with the coupling to bis-Boc-thiourea. To prevent this side reaction the ketone in **12** was reduced prior to the coupling reaction with *N,N'*-bis-Boc-thiourea (eq 6). Reduction of the Boc-protected amine with $NaBH_3CN$ in acetic acid selectively produced the β-hydroxyester **32** in good yield. This reaction probably proceeds by reduction of the enol tautomer of **12**[18]. Deprotection of the amine with HCl in methanol afforded the aminoalcohol **33** as the HCl salt. Now, reaction with bis-Boc-thiourea in the presence of $HgCl_2$ and Et_3N indeed produced the desired guanidine **34** in good yield.



(6)

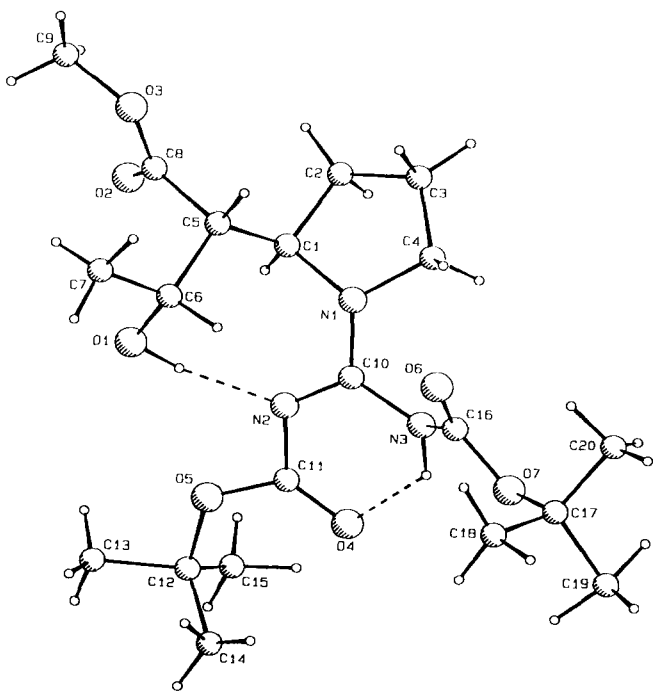


Figure 1. ORTEP-diagram of **34a**.

One of the diastereomers of **34** was a obtained as a solid. One single recrystallisation of this diastereomer led to beautiful crystals (mp 122-123 °C), which appeared suitable for X-ray analysis (Figure 1)[19]. The X-ray analysis nicely proved the structure of the protected guanidine **34**. Figure 1 also reveals two intramolecular hydrogen bonds in the crystal. For the synthesis of the desired bicyclic guanidine, the β-hydroxyester **34** should be oxidized to the β-ketoester. Swern oxidation[19] of **33** led to the unexpected formation of the linear product **35** as a mixture of *E*-and *Z*-isomers in 67% yield, containing only a trace of the desired pyrrolidine **36**. The formation of the retro-Michael product **35** as the main product is not readily explained. Application of other oxidation methods (e.g. PDC, PCC, TPAP[20], Dess-Martin[21], IBX[22]) did not lead to the formation of the desired pyrrolidine **36** either. Removal of the Boc protecting groups from **35** by treatment with HCl in methanol resulted in the formation of the desired bicyclic guanidine **37**. Apparently, deprotection of the guanidine leads to regeneration of the pyrrolidine via Michael addition, followed by a second ring closure and dehydration to the guanidine **37**.

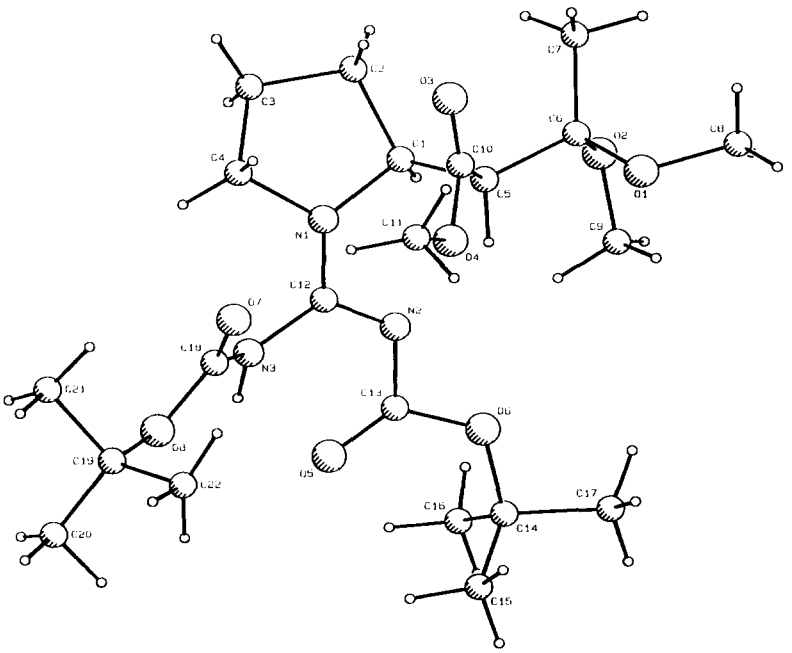
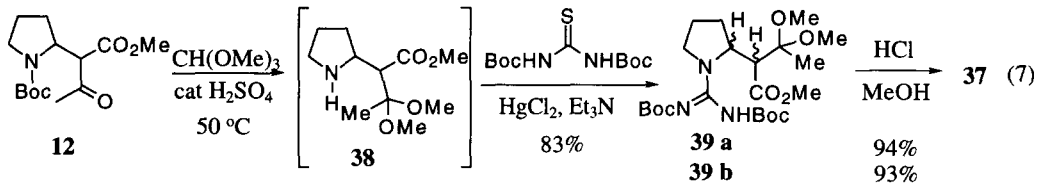


Figure 2. ORTEP-diagram of **39a**.

In the projected enantioselective synthesis of ptilomycalin A (Scheme 1), the valuable stereocentres α to the nitrogen atom in the pyrrolidine **2** should be retained throughout the synthesis. Therefore, introduction of the guanidine moiety via the route described in eq 6 will not be useful for our synthesis of ptilomycalin A, as this will lead to loss of this stereocentre. In order to avoid this racemization, the dimethoxyacetal was selected as a protecting group for the β-ketoester. After much experimentation we found that reaction of the Boc-protected amine **12** with trimethyl orthoformate in methanol in the presence of a catalytic amount of H_2SO_4 gave, the desired dimethoxyacetal **38** with concomitant deprotection of the pyrrolidine (eq 7). Attempts to purify the free amine (with basic aluminia) resulted in partial decomposition. Therefore, crude **38** was used immediately in the coupling with *N,N'*-bis(*tert*-butoxycarbonyl)thiourea, $HgCl_2$ and Et_3N to give the desired guanidine **39** in 83%

overall yield from the protected amine **12**. Satisfactorily, the guanylation of **38** did not produce any of the retro-Michael product. Guanidine **39** was obtained as a 66:34 mixture of diastereomers, which were separated by chromatography. The major diastereomer (**39a**) was obtained as a solid, and recrystallisation led to crystals suitable for X-ray analysis (Figure 2). The X-ray analysis nicely proved the structure of the protected guanidine. Treatment of both diastereomers (**39a** and **b**) with HCl in methanol in separate experiments selectively afforded the desired bicyclic guanidine **37** in high yield in both cases. Presumably, one of the Boc groups of the guanidine moiety is deprotected first. The resulting nitrogen atom then effects acid-mediated substitution of a methoxy group to form the six-membered ring. Further elimination of methanol and removal of the second Boc group produces product **37**. In this sequence, ring opening of the pyrrolidine seems highly improbable, although repetition of the experiment with enantiopure **12** will provide definitive proof.



In conclusion, successful syntheses of three different bicyclic guanidines have been achieved starting from pyrrolidin-2-one. The C-2 substituted pyrrolidines were prepared via an *N*-acyliminium ion coupling reaction with silyl enol ethers. An efficient direct guanylation of the 2-monosubstituted pyrrolidines was carried out with *N,N'*-bis-(*tert*-butoxycarbonyl)thiourea in the presence of $HgCl_2$ and Et_3N. In the case of the β-ketoester **12** it was shown that the β-ketoester should be properly protected in this process to avoid dimerization. The guanidine **37** is closely related to structural features of crambescin A[1f] and the batzelladines A and B[1i]. Furthermore, this approach to the synthesis of polycyclic guanidines will be applied in the total synthesis of ptilomycalin A.

ACKNOWLEDGEMENT

We thank J. Fraanje and K. Goubitz of the AIMS' Laboratory of Crystallography for the X-ray crystal structure determinations. We wish to thank Professor W. N. Speckamp for stimulating discussions.

EXPERIMENTAL

General information. Experimental techniques and analytical measurements were applied as previously described.[7] IR spectral data are reported in cm $^{-1}$ and NMR chemical shifts in ppm with $CDCl_3$ as a solvent (unless stated otherwise). 2-(Trimethylsiloxy)-1-pentene[10] and *N, N'*-bis-(*tert*-butoxycarbonyl)thiourea[23] were prepared according to literature procedures. Pyrrolidin-2-one, methyl-3-trimethylsiloxy-2-butenoate, 1-phenyl-1-trimethylsiloxyethylene, and mercury(II)chloride ($HgCl_2$) were commercially available. 2,5-Dimethylpyrrolidine was commercially available as a technical (ca. 90:10) *cis/trans* mixture, and was used as such.

2-Oxo-pyrrolidine-1-carboxylic Acid Benzyl Ester (6). To a solution of pyrrolidin-2-one (4.7 mL, 62 mmol) in 250 mL of THF was added at -78 °C 69 mL of a 1.0 M solution of LiHMDS in hexane (69 mmol). After stirring at -78 °C for 30 min, benzylcyanoformate was added (7.5 mL, 62.4 mmol), and the mixture was stirred at -78 °C for 30 min. After warming to room temperature, the mixture was stirred for an additional 1.5 h, poured out into a saturated aqueous solution of NH_4Cl (250 mL) and extracted with EtOAc (3 times 250 mL). The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo. Flash chromatography (EtOAc/hexanes 1:2) afforded **6** (12.0 g, 54.6 mmol, 87%) as a light yellow oil. R_f 0.3 (EtOAc/hexanes 1:2). IR

3020, 2980, 2950, 2880, 1780, 1740, 1715. ^{1}H NMR (400 MHz) 1.94-2.02 (m, 2H, H-4), 2.49 (t, J = 8.1 Hz, 2H, H-3), 3.77 (t, J = 7.2 Hz, 2H, H-5), 5.24 (s, 2H, CH_2O), 7.26-7.41 (m, 5H, Ar-H). ^{13}C NMR (100 MHz) 17.45 (C-4), 32.69 (C-3), 46.40 (C-5), 67.91 (CH_2O), 128.16, 128.37 and 128.55 (Ar-CH), 135.29 (Ar-C), 151.42 (C=O), 174.27 (C=O amide). HRMS calculated for $C_{12}H_{13}NO_3$ 219.0895, found 219.0879.

2-Hydroxy-pyrrolidine-1-carboxylic Acid Benzyl Ester (7). To a solution of **6** (11.0 g, 50.2 mmol) in 200 mL of CH_2Cl_2 was added at -78 °C 100 mL of a 1.0 M solution of DIBAL-H in toluene (100 mmol) over a periode of 40 min. After stirring for 1.5 h at -78 °C, MeOH (14 mL) and a saturated aqueous solution of potassium sodium tartrate (200 mL) were added in succession. After warming to room temperature, the mixture was stirred for an additional 3 h. Water (50 mL) was added and the mixture was extracted with CH_2Cl_2 (4 times 200 mL). The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. Flash chromatography (EtOAc/hexanes 1:1) afforded **7** (9.72 g, 43.9 mmol, 88%) as a colourless oil. R_f 0.25 (EtOAc/hexanes 1:1). IR 3580, 3420, 3020, 2990, 2960, 2870, 1680. ^{1}H NMR (400 MHz, mixture of rotamers) 1.79-2.14 (m, 4H, H-3 and H-4), 3.05 (br s, 0.35H, OH), 3.31-3.40 (m, 1H, H-5), 3.56-3.64 (m, 1H, H'-5), 3.86 (br s, 0.65H, OH), 5.15 (s) and 5.18 (s, 2H, CH_2O), 5.49-5.54 (m, 1H, H-2), 7.26-7.37 (m, 5H, Ar-H). ^{13}C NMR (100 MHz, mixture of rotamers) 21.86 and 22.71 (C-4), 32.98 and 33.95 (C-3), 45.69 and 46.08 (C-5), 64.72 and 66.83 (CH_2O), 81.08 and 81.75 (C-2), 126.86, 127.23, 127.82, 128.00, 128.32 and 128.46 (Ar-CH), 136.54 and 141.31 (Ar-C), 154.34 and 155.38 (C=O). HRMS calculated for $C_{12}H_{15}NO_3$ 221.1052, found 221.1036.

2-Methoxy-pyrolidine-1-carboxylic Acid Benzyl Ester (8). To a solution of **7** (3.42 g, 15.5 mmol) in 20 mL of MeOH were added trimethyl orthoformate (8.5 mL, 77.7 mmol) and PPTS (602 mg, 2.4 mmol). After stirring at room temperature for 2 h, Na_2CO_3 was added and the mixture was concentrated in vacuo. Water (20 mL) and a saturated aqueous solution of Na_2CO_3 (20 mL) were added and the mixture was extracted with Et_2O (4 times 50 mL). The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. Flash chromatography (EtOAc/hexanes 1:2) afforded **8** (3.48 g, 14.8 mmol, 96%) as a colourless oil. R_f 0.3 (EtOAc/hexanes 1:2). IR 3020, 2990, 2940, 2890, 2830, 1700. ^{1}H NMR (400 MHz, mixture of rotamers) 1.72-2.08 (m, 4H, H-3 and H-4), 3.25-3.54 (m, 5H, H-5 and CH_3O), 5.15-5.23 (m, 2H, CH_2O), 7.26-7.38 (M, 5H, Ar-H). ^{13}C NMR (100 MHz, mixture of rotamers) 21.67 and 22.62 (C-4), 31.93 and 32.52 (C-3), 45.72 and 45.89 (C-5), 55.33 and 55.90 (CH_3O), 66.85 and 67.10 (CH_2O), 88.52 and 89.13 (C-2), 126.83, 127.26, 127.65, 127.72, 127.70, 127.98, 128.35 and 128.45 (Ar-CH), 136.66, 141.40 (Ar-C), 154.89 and 155.77 (C=O). HRMS calculated for $C_{13}H_{17}NO_3$ 235.1208, found 235.1214.

2-(1-Methoxycarbonyl-2-oxo-propyl)-pyrrolidine-1-carboxylic Acid Benzyl Ester (9). To a solution of **8** (49.0 mg, 0.208 mmol) in 1.0 mL of CH_2Cl_2 were added at -78 °C methyl-3-trimethylsiloxy-2-butenoate (50 µL, 0.26 mmol) and TMSOTf (42 µL, 0.23 mmol), and the mixture was stirred at -78 °C for 1 h. After warming to room temperature, the mixture was stirred for an additional 45 min, poured out into a saturated aqueous solution of $NaHCO_3$ (4 mL) and extracted with CH_2Cl_2 (4 times 5 mL). The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. Flash chromatography (EtOAc/hexanes 1:1) afforded **9** (66.6 mg, 0.208 mmol, 100%) as a colourless oil. R_f 0.35 (EtOAc/hexanes 1:1). IR 3020, 3000, 2950, 2880, 1735, 1710, 1690. ^{1}H NMR (400 MHz, mixture of diastereomers and rotamers) 1.76-2.25 (m, 7H, CH_3CO, H-3 and H-4), 3.30-4.68 (m, 7H, H-5, CH_3O, H-2 and $CH(CO)_2$), 5.07-5.16 (m, 2H, CH_2O), 7.16-7.39 (m, 5H, Ar-H). ^{1}H NMR (400 MHz, toluene-d_8, 378K, mixture of 2 diastereomers) 1.29-1.40 (m, 1H), 1.47-1.58 (m, 1H), 1.77-1.99 (m, 5H, including characteristic signals for CH_3CO: 1.89 (s) and 1.91 (s)), 3.14-3.20 (m, 1H, H-5), 3.28-3.42 (m, 4H, H'-5 and CH_3O, including characteristic signals for CH_3O: 3.31 (s) and 3.33 (s)), 4.16 (d, J = 5.4 Hz) and 4.25 (d, J = 5.0 Hz, 1H, $CH(CO)_2$), 4.33-4.42 (m, 1H, H-2), 5.03 (s, 2H, CH_2O), 7.01-7.22 (m, 5H, Ar-H). ^{13}C NMR (100 MHz, D_1 = 10s, mixture of diastereomers and rotamers) 22.69 and 23.40 (C-4), 28.15 and 28.30 (C-3), 28.98, 29.84 and 31.14 (CH_3), 46.34, 46.61 and 49.49 (C-5), 52.01 and 52.04 (CH_3O), 56.07, 56.55, 57.13, 59.04, 60.64 and 60.80 (C-2 and *C*H(CO)$_2$), 64.66, 66.48 and 66.82 (CH_2O), 126.59, 127.02, 127.44, 127.53, 127.70, 128.12, 128.22, 128.34 and 128.48 (Ar-CH), 136.58 and 141.21

(Ar-C), 154.63 (C=O), 167.30, 168.55 and 169.01 (C=O ester), 200.23 and 201.41 (C=O ketone). HRMS calculated for $C_{17}H_{21}NO_5$ 319.1419, found 319.1408.

2-(2-Oxo-2-phenyl-ethyl)-pyrrolidine-1-carboxylic Acid Benzyl Ester (10). To a solution of **8** (894 mg, 3.80 mmol) in 4.0 mL of CH_2Cl_2 were added at -78 °C 1-phenyl-1-trimethylsiloxyethylene (860 µL, 4.2 mmol) and TMSOTf (760 µL, 4.2 mmol), and the mixture was stirred at -78 °C for 1 h. After warming to room temperature, the mixture was stirred for an additional 45 min, poured out into a saturated aqueous solution of $NaHCO_3$ (25 mL) and extracted with CH_2Cl_2 (4 times 30 mL). The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. Flash chromatography (EtOAc/hexanes 1:3, then 1:2) afforded **10** (1.06 g, 3.41 mmol, 90%) as a colourless oil. R_f 0.3 (EtOAc/hexanes 1:3). IR 3050, 3020, 2990, 2960, 2870, 1680, 1590, 1490, 685. ^{1}H NMR (400 MHz, mixture of rotamers) 1.75-2.15 (m, 4H, H-3 and H-4), 2.80 (dd, J = 15.5, 10.3 Hz, 1H, CH_2CO), 3.41-3.54 (m, 2.4H, CH_2CO and H-5), 3.84 (dd, J = 2.3, 15.3 Hz, 0.6H, H-5), 4.35-4.40 (m, 1H, H-2), 5.11-5.15 (m, 2H, CH_2O), 7.26-8.05 (m, 10H, Ar-H). ^{1}H NMR (400 MHz, toluene-d_8, 378K) 1.31-1.40 (m, 1H), 1.44-1.62 (m, 2H), 1.70-1.80 (m, 1H), 2.57 (dd, J = 9.6, 15.1 Hz, 1H, CH_2C=O), 3.17-3.29 (m, 2H, CH_2C=O and H-5), 3.59 (d, J = 14.5 Hz, 1H, H'-5), 4.26-4.32 (m, 1H, H-2), 5.03 (d, J = 12.5 Hz, 1H, CH_2O), 5.08 (d, J = 12.5 Hz, 1H, CH_2O), 7.01-7.87 (m, 10H, Ar-H). ^{13}C NMR (100 MHz, mixture of rotamers) 22.77 and 23.59 (C-4), 30.36 and 31.20 (C-3), 42.84 and 43.73 (CH_2C=O), 46.45 and 46.79 (C-5), 54.20 and 54.98 (C-2), 66.60 and 66.97 (CH_2O), 126.85, 127.78, 127.93, 128.25, 128.33, 128.48, 128.60 and 133.15 (Ar-CH), 136.73 and 136 89 (Ar-C), 154.59 and 154.74 (C=O), 198.43 and 198.78 (C=O ketone). HRMS-FAB $[M+H]^+$ calculated for $C_{20}H_{22}NO_3$ 324.1600, found 324.1588.

2-(2-Oxo-pentyl)-pyrrolidine-1-carboxylic Acid Benzyl Ester (11). To a solution of **8** (315 mg, 1.34 mmol) in 2.0 mL of CH_2Cl_2 were added at -78 °C 2-(trimethylsiloxy)-1-pentene (300 mg, 1.89 mmol) and TMSOTf (290 µL, 1.60 mmol), and the mixture was stirred at -78 °C for 1 h. After warming to room temperature, the mixture was stirred for an additional 45 min, poured out into a saturated aqueous solution of $NaHCO_3$ (10 mL) and was extracted with CH_2Cl_2 (4 times 15 mL). The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. Flash chromatography (EtOAc/hexanes 1:3) afforded **11** (386.3 mg, 1.33 mmol, 100%) as a light yellow oil. R_f 0.3 (EtOAc/hexanes 1:3). IR 3020, 3000, 2960, 2870, 1680, 695. ^{1}H NMR (400 MHz, mixture of rotamers) 0.82-4.65 (m, 16H), 5.05-5.24 (m, 2H, CH_2O), 7.21-7.33 (m, 5H, Ar-H). ^{13}C NMR (100 MHz, mixture of rotamers) 12.58 and 13.66 (CH_3), 17.13 and 18.47 (CH_2), 22.80 and 23.58 (($CH_3)_3C$), 30.85 and 31.62 (CH_2), 45.07, 46.33, 46.49 and 46.62 (2× CH_2), 53.29 and 54.04 (C-2), 65.01 (CH_2), 66.53 and 66.79 (CH_2), 126.84, 127.32, 127.75, 127.88, 128.37 and 128.43 (Ar-CH), 136.68, 136.88 and 141.27 (Ar-C), 154.59 (C=O), 209.34 and 209.53 (C=O ketone). HRMS calculated for $C_{17}H_{23}NO_3$ 289.1678, found 289.1693.

2-(1-Methoxycarbonyl-2-oxo-propyl)-pyrrolidine-1-carboxylic Acid tert-Butyl Ester (12). To a solution of **9** (1.05 g, 3.29 mmol) in 6 mL of MeOH were added Boc_2O (3.6 g, 16.5 mmol) and 10% Pd on coal (100 mg). The mixture was stirred under a hydrogen atmosphere (3 atm) at room temperature for 18 h. After filtration through a path of celite, the mixture was concentrated in vacuo. Flash chromatography (EtOAc/hexanes 1:5, then 1:2) afforded two fractions. The first fraction consisted of **12** (631 mg, 2.21 mmol, 67%) as a colourless oil. R_f 0.35 (EtOAc/hexanes 1:2). IR 2990, 2970, 2920, 2870, 1735, 1705, 1675, 1390, 1160. ^{1}H NMR (400 MHz, mixture of diastereomers and rotamers) 1.31-1.48 (m, 9H, $(CH_3)_3C$), 1.70-2.12 (m, 4H, H-3 and H-4), 2.18 (s) and 2.19 (s, 3H, CH_3CO), 3.17-4.34 (m, 7H, H-5, CH_3O, H-2 and $CH(CO)_2$, including characteristic signals for CH_3O: 3.65(s) and 3.68 (s)). ^{1}H NMR (400 MHz, toluene-d_8, 378K, mixture of 2 diastereomers) 1.25-1.58 (m, 11H, including characteristic signals for $(CH_3)_3C$: 1.40 (s) and 1.41 (s)), 1.76-2.00 (m, 5H, including characteristic signals for CH_3CO: 1.96 (s) and 1.97 (s)), 3.08-3.15 (m, 1H, H-5), 3.27-3.43 (m, 4H, H'-5 and CH_3O, including characteristic signals for CH_3O: 3.33 (s) and 3.37 (s)), 4.13 (d, J = 6.0 Hz, 0.5H, $CH(CO)_2$), 4.28-4.41 (m, 1.5H, H-2 and $CH(CO)_2$). ^{13}C NMR (63 MHz, mixture of diastereomers and rotamers) 23.44 (C-4), 28.05 and 28.63 (C-3), 28.34 (($CH_3)_3C$), 31.47 (CH_3CO), 46.50 and

46.77 (C-5), 52.16 (CH_3O), 56.35, 56.90, 59.50 and 61.34 (C-2 and $CH(CO)_2$), 79.65 ($(CH_3)_3C$), 154.39 (C=O), 168.79 and 169.28 (C=O ester), 201.58 (C=O ketone). FAB-HRMS $[M+H]^+$ calculated for $C_{14}H_{24}NO_5$ 286.1654, found 286.1636. The second fraction consisted of ***N*-Boc-2-Acetyl-6-amino-hexanoic Acid Methyl Ester (13)** (129 mg, 0.476 mmol, 14%) as a colourless oil. R_f 0.2 (EtOAc/hexanes 1:2). IR 3450, 2970, 2930, 2850, 1735, 1705, 1500. ^1H NMR (400 MHz) 1.22-1.88 (m, 15H, including characteristic signal for $(CH_3)_3C$: 1.43 (s)), 2.22 (s, 3H, CH_3CO), 3.08-3.15 (m, 2H, CH_2N), 3.41 (t, J = 7.3 Hz, 1H, $CH(CO)_2$), 3.73 (s, 3H, CH_3O), 4.52 (br s, 1H, NH). ^{13}C NMR (50 MHz) 24.36 (CH_2), 27.52 (CH_2), 28.16 ($(CH_3)_3C$), 28.62 (CH_3CO), 29.59 (CH_2), 39.95 (CH_2N), 52.15 (CH_3O), 59.28 ($CH(CO)_2$), 78.93 ($(CH_3)_3C$), 155.70 (C=O), 169.96 (C=O ester), 202.69 (C=O ketone). FAB-HRMS $[M+H]^+$ calculated for $C_{14}H_{26}NO_5$ 288.1811 found 288.1754.

3-Oxo-2-pyrrolidin-2-yl-butyric Acid Methyl Ester Hydrochloride (14). To a solution of **12** (121.9 mg, 0.427 mmol) in 0.5 mL of MeOH was added 1.0 mL of a 4.7 M solution of HCl in MeOH (4.7 mmol). After stirring at room temperature for 3 h, evaporation of the volatiles gave **14** (93.5 mg, 0.422 mmol, 99%) as a colourless oil. IR ($CHCl_3$) 3400, 2950, 2700, 1740, 1715. ^1H NMR (400 MHz, D_2O, mixture of 2 diastereomers) 1.67-1.81 (m, 1H), 1.92-2.31 (m, 3H), 2.40 (s) and 2.43 (s, 3H, CH_3), 3.30-3.42 (m, 2H, H-5), 3.85 (s, 3H, CH_3O), 4.04-4.11 (m, 1H, H-2), 4.32-4.39 (m, 0.2H, $CH(CO)_2$, partially exchanged with D_2O). ^{13}C NMR (63 MHz, D_2O, mixture of 2 diastereomers) 25.89 and 25.91 (C-4), 30.76 and 30.92 (C-3), 32.13 and 32.60 (CH_3), 48.66 (C-5), 56.39 and 56.50 (CH_2O), 59.80 and 59.90 (C-2), 61.33, 61.66, 61.99 and 62.11 (2× t, J_{CD} circa 20 Hz, $CD(CO)_2$), 170.85 and 171.27 (C=O ester), 206.89 and 207.58 (C=O ketone). HRMS-FAB $[M-Cl]^+$ calculated for $C_9H_{16}NO_3$ 186.1130, found 186.1126.

2-(2-Oxo-2-phenyl-ethyl)-pyrrolidine-1-carboxylic Acid tert-Butyl Ester (15). To a solution of **10** (123 mg, 0.40 mmol) in 0.8 mL of MeOH were added Boc_2O (260 mg, 1.2 mmol) and 10% Pd on coal (12 mg). The mixture was stirred under a hydrogen atmosphere (3 atm) at room temperature for 18 h. After filtration through a path of celite, the mixture was concentrated in vacuo. Flash chromatography (EtOAc/hexanes 1:5, then 1:3) afforded two fractions. The first fraction consisted of **15a** (41.4 mg, 0.14 mmol, 36%) as a colourless oil. R_f 0.2 (EtOAc/hexanes 1:5). IR 3590, 3390, 3000, 2970, 2920, 2860, 1660, 1400, 695. ^1H NMR (400 MHz, mixture of rotamers) 1.41-2.04 (m, 16H, including characteristic signal for $(CH_3)_3C$): 1.49 (s)), 3.37-3.40 (m, 2H, H-5), 4.28 (br s, 1H), 4.63-4.66 (m, 1H), 7.19-7.39 (m, 5H, Ar-H). ^1H NMR (400 MHz, toluene-d_8, 378K) 1.24-1.63 (m, 14H, including characteristic signal for $(CH_3)_3C$: 1.40 (s)), 1.73-1.79 (M, 1H), 3.09-3.14 (m, 1H, H-5), 3.20-3.26 (m, 1H, H'-5), 4.12-4.14 (m, 1H), 4.70-4.74 (m, 1H), 7.05-7.37 (m, 5H, Ar-H). ^{13}C NMR (50 MHz, mixture of rotamers) 23.37 (C-4), 28.22 ($(CH_3)_3C$), 30.99 (C-3), 46.11 and 46.1 (C-5 and CH_2CHOH), 53.74 (C-2), 69.75 (CHOH), 79.87 ($(CH_3)_3C$), 125.43, 126.58 and 127.98 (Ar-CH), 144.19 (Ar-C), 156.80 (C=O). HRMS calculated for $C_{17}H_{25}NO_3$ 291.1834, found 291.1842. The second fraction consisted of **15b** (65.9 mg, 0.23 mmol, 57%) as a colourless oil. R_f 0.1 (EtOAc/hexanes 1:5). IR 3590, 3360, 3000, 2970, 2870, 1665, 1400, 695. ^1H NMR (400 MHz, mixture of rotamers) 1.44 (s, 9H, $(CH_3)_3C$), 1.68-2.12 (m, 6H, H-3, H-4 and CH_2CHOH), 2.47-4.73 (m, 5H, H-5, H-2 and *CHOH*), 7.22-7.36 (m, 5H, Ar-H). ^1H NMR (400 MHz, toluene-d_8, 378K) 1.34-1.68 (m, 15H, including characteristic signal for $(CH_3)_3C$: 1.41 (s)), 2.75 (br s, 1H, OH), 3.08-3.13 (m, 1H, H-5), 3.21-3.27 (m, 1H, H'-5), 3.97-4.02 (m, 1H, H-2), 4.62 (d, J = 8.4 Hz, 1H, *CHOH*), 7.01-7.28 (m, 5H, Ar-H). ^{13}C NMR (100 MHz, mixture of rotamers) 23.13 and 23.74 (C-4), 28.50 ($(CH_3)_3C$), 32.14 (C-3), 45.91 and 46.38 (C-5 and CH_2CHOH), 55.53 (C-2), 72.54 (CHOH), 79.69 ($(CH_3)_3C$), 125.61, 126.93 and 128.22 (Ar-CH), 145.21 (Ar-C), 155.41 (C=O). HRMS calculated for $C_{17}H_{25}NO_3$ 291.1834, found 291.1833.

2-(2-Oxo-2-phenyl-ethyl)-pyrrolidine-1-carboxylic Acid *tert*-Butyl Ester (16). To a solution of **15** (356.2 mg, 1.22 mmol, 39:61 mixture of diastereomers) in 10 mL of CH_2Cl_2 were added molecular sieves (4Å, powder, 1.05 g) and PCC (532 mg, 2.47 mmol). After stirring at room temperature for 3.5 h, the reaction mixture was directly subjected to flash chromatography (EtOAc/hexanes 1:3) to afford **16** (345.9 mg, 1.20

mmol, 98%) as a colourless oil. R_f 0.3 (EtOAc/hexanes 1:3). IR 3020, 3000, 2970, 2930, 2880, 1675, 1400, 690. ^{1}H NMR (400 MHz, mixture of rotamers) 1.42 (s, 9H, $(CH_3)_3C$), 1.68-2.09 (m, 4H, H-3 and H-4), 2.75-2.86 (m, 1H), 3.30-3.75 (m, 3H), 4.26-4.32 (m, 1H, H-2), 7.35-7.55 (m, 3H, Ar-H), 7.95-8.00 (m, 2H, Ar-H). ^{1}H NMR (400 MHz, toluene-d_8, 378K) 1.32-1.63 (m, 12H, including characteristic signal for $(CH_3)_3C$: 1.42 (s)), 1.71-1.80 (m, 1H), 2.62 (dd, J = 9.5, 14.9 Hz, 1H, CH_2C=O), 3.14-3.27 (m, 2H), 3.58 (d, J = 14.0 Hz, 1H), 4.25-4.31 (m, 1H, H-2), 7.08-7.17 (m, 3H, Ar-H), 7.91-7.93 (m, 2H, Ar-H). ^{13}C NMR (50 MHz, mixture of rotamers) 17.84 and 18.23 (C-4), 23.38 ($(CH_3)_3C$), 25.24 and 26.18 (C-3), 38.07 and 41.27 (C-5 and CH_2C=O), 49.12 (C-2), 74.41 ($(CH_3)_3C$), 123.11, 123.45 and 127.97 (Ar-CH), 131.70 (Ar-C), 149.20 (C=O), 193.62 (C=O ketone). HRMS calculated for $C_{17}H_{23}NO_3$ 289.1678, found 289.1685.

1-Phenyl-2-pyrrolidin-2-yl-ethanone Hydrochloride (17). To a solution of **16** (65.3 mg, 0.226 mmol) in 0.25 mL of MeOH was added 0.25 mL of a 7.3 M solution of HCl in MeOH (1.8 mmol). After stirring at room temperature for 3.5 h, evaporation of the volatiles gave **17** (50.9 mg, 0.226 mmol, 100%) as a colourless oil. IR ($CHCl_3$) 3400, 2990, 2920, 2880, 2650, 1695, 1600, 685. ^{1}H NMR (200 MHz, D_2O) 1.72-1.94 (m, 1H), 1.94-2.21 (m, 2H), 2.24-2.43 (m, 1H), 3.24-3.39 (m, 2H, H-5), 3.53 (dd, J = 9.5, 19.0 Hz, 1H, CH_2C=O), 3.79 (dd, J = 3.8, 19.0 Hz, 1H, CH_2C=O), 4.00-4.09 (m, 1H, H-2), 7.56 (t, J = 7.7 Hz, 2H, Ar-H), 7.68-7.75 (m, 1H, Ar-H), 7.99 (d, J = 7.9 Hz, 2H, Ar-H). ^{13}C NMR (50 MHz, D_2O) 24.85 (C-4), 31.43 (C-3), 42.27 and 47.17 (C-5 and CH_2O), 57.60 (C-2), 129.91, 130.69, 136.24 (Ar-CH), 137.12 (Ar-C), 202.41 (C=O ketone). HRMS-FAB $[M-Cl]^+$ calculated for $C_{12}H_{15}NO$ 212.1051, found 212.1080.

2-(2-Oxo-pentyl)-pyrrolidine-1-carboxylic Acid *tert*-Butyl Ester (18). To a solution of **17** (182.5 mg, 0.631 mmol) in 1.5 mL of MeOH were added Boc_2O (692 mg, 3.17 mmol) and 10% Pd on coal (20 mg). The mixture was stirred under a hydrogen atmosphere (3 atm) at room temperature for 18 h. After filtration through a path of celite, the mixture was concentrated in vacuo. Flash chromatography (EtOAc/hexanes 1:5) afforded **18** (111.4 mg, 0.436 mmol, 69%) as a colourless oil. R_f 0.2 (EtOAc/hexanes 1:5). IR 2990, 2960, 2930, 2870, 1700, 1670, 1400. ^{1}H NMR (400 MHz, mixture of rotamers) 0.77 (t, J = 7.3 Hz) and 0.84 (t, J = 7.4 Hz, 3H, CH_3), 1.35-2.39 (m, 19H, including characteristic signal for $(CH_3)_3C$: 1.39 (s)), 2.92 (br s, 1H), 3.25-3.31 (m, 2H, H-5), 4.05-4.10 (m, 1H, H-4). ^{1}H NMR (400 MHz, toluene-d_8, 378K) 0.79 (t, J = 7.4 Hz, 3H, CH_3), 1.26-1.53 (m, 17H, including characteristic signal for $(CH_3)_3C$: 1.42 (s)), 1.74-1.79 (m, 1H), 2.11-2.18 (m, 1H), 2.87 (dd, J = 3.2, 15.6 Hz, 1H), 3.12-3.24 (m, 2H, H-5), 4.06-4.10 (m, 1H, H-2). ^{13}C NMR (100 MHz, mixture of rotamers) 13.62 (CH_3), 17.11 (CH_2), 20.61 and 23.14 (CH_2), 27.32 and 28.44 ($(CH_3)_3C$), 31.08 (CH_2), 45.11 and 46.25 (CH_2), 52.24, 52.56, 52.88 and 54.74 (2× CH_2), 53.40, 57.74 (C-2), 79.21 ($(CH_3)_3C$), 154.20 (C=O), 209.55 (C=O ketone). HRMS-FAB $[M+H]^+$ calculated for $C_{14}H_{26}NO_3$ 256.1912, found 256.1912.

1-Pyrrolidin-2-yl-pentan-2-one Hydrochloride (19). To a solution of **18** (84.5 mg, 0.331 mmol) in 0.5 mL of MeOH was added 0.5 mL of a 7.3 M solution of HCl in MeOH (3.7 mmol). After stirring at room temperature for 4 h, evaporation of the volatiles gave **19** (62.2mg, 0.324 mmol, 98%) as a colourless oil. IR ($CHCl_3$) 3400, 2960, 2870, 2700, 1710. ^{1}H NMR (400 MHz, D_2O), 0.89 (t, J = 7.4 Hz, 3H, CH_3), 1.57 (sextet, J = 7.4 Hz, 2H, CH_2CH_3), 1.63-1.73 (m, 1H), 1.94-2.09 (m, 2H), 2.20-2.31 (m, 1H), 2.54 (t, J = 7.4 Hz, 2H, CH_2CH_2C=O), 2.99 (dd, J = 9.3, 19.0 Hz, 1H, CH_2C=O), 3.19 (dd, J = 4.2, 19.0 Hz, 1H, CH_2C=O), 3.21-3.37 (m, 2H, H-5), 3.83-3.91 (m, 1H, H-2). ^{13}C NMR (100 MHz, D_2O) 15.57 (CH_3), 19.50 (CH_2), 25.72 (CH_2), 32.23 (CH_2), 46.46 (CH_2), 46.94 (CH_2), 48.15 (CH_2), 58.26 (C-2), 216.33 (C=O). HRMS-FAB $[M-HCl+H]^+$ calculated for $C_9H_{18}NO$ 156.1388, found 156.1370.

***N*, *N'*-Bis-Boc[(2,5-dimethyl-pyrrolidin-1-yl)-imino-methyl]-amine (20).** To a solution of 2,5-dimethyl-pyrrolidine (92.4 mg, 0.932 mmol) in 0.45 mL of DMF were added at 0 °C *N*, *N'*-bis-(*tert*-butoxycarbonyl)thiourea (258 mg, 0.934 mmol), mercury(II)chloride (253 mg, 0.932 mmol) and Et_3N (300 µL, 2.15 mmol). The mixture was stirred at 0 °C for 30 min, allowed to warm to room temperature and stirred for an

additional 18 h. The mixture was diluted with EtOAc (5 mL) and filtered through a pad of celite. The filtrate was washed with brine (5 mL), and the water layer was extracted with EtOAc (3 times 5 mL). The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo. The residue was dissolved in Et_2O/hexanes 1:1 (5 mL) and washed with saturated aqueous $NaHCO_3$ (5 mL). The water layer was extracted with Et_2O/hexanes 1:1 (3 times 5 mL). The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo. Recrystallisation from Et_2O/hexanes afforded *cis*-**20** (207.5 mg, 0.608 mmol, 65%) as white crystals, mp. 116-117 °C. ^1H NMR (400 MHz) 1.24 (d, J = 6.4 Hz, 6H, 2× CH_3), 1.43 (s, 18H, 2× $C(CH_3)_3$), 1.59-1.67 (m, 2H, H-3 and H-4), 1.97-2.04 (m, 2H, H-3 and H-4), 4.24-4.25 (m, 2H, H-2 and H-5), 9.10 (br s, 1H, NH). ^{13}C NMR (62.5 MHz) 20.92 (2× CH_3), 28.12 ($C(CH_3)_3$), 31.37 (C-3 and C-4), 55.81 (C-2 and C-5), 87.05 ($C(CH_3)_3$), 151.50 (C=N), 162.11 (2× C=O). HRMS calculated for $C_{17}H_{31}O_4N_3$ 341.2315, found 341.2323. Anal. Found C, 59.81; H, 9.15; N, 12.24. Calculated for $C_{17}H_{31}O_4N_3$ C, 59.80; H, 9.15; N, 12.31. Flash chromatography of the residue (EtOAc/hexanes 1:6) yielded a 60:40 *cis/trans* mixture of **20** (54.2 mg, 0.159 mmol, 17%). R_f 0.50 (EtOAc/hexane 1:20) IR 3400, 2960, 2930, 2860, 1730, 1590. Characteristic signals for *trans*-**20:** ^1H NMR (400 MHz, 60:40 mixture of *cis*- and *trans*-isomers) 1.17 (d, J = 6.1 Hz, 6H, 2× CH_3), 1.45 (s, 18H, 2× $C(CH_3)_3$), 1.49-1.53 (m, 2H, H-3 and H-4), 2.1-2.15 (m, 2H, H-3 and H-4), 4.3-4.35 (m, 2H, H-2 and H-5), 9.10 (br s, 1H, NH).

***N,N'*-Bis-Boc-2-[1-(Amino-imino-methyl)-pyrrolidin-2-yl]-1-phenyl-ethanone (21).** To a solution of **17** (48.2 mg, 0.213 mmol) in 0.4 mL of DMF were added at 0 °C *N,N'*-bis-(*tert*-butoxycarbonyl)-thiourea (59 mg, 0.213 mmol), $HgCl_2$ (58 mg, 0.214 mmol) and Et_3N (98 µL, 0.70 mmol) in succession. The mixture was stirred at 0 °C for 30 min. After warming to room temperature the reaction mixture was stirred for an additional 18 h, diluted with EtOAc (5 mL) and was filtered through a path of celite. Water (5 mL) and a saturated aqueous solution of NaCl (5 mL) were added to the filtrate and the mixture was extracted with EtOAc (4 times 15 mL). The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo. The residue was dissolved in Et_2O/hexanes 1:1 (10 mL), poured out into a saturated aqueous solution of $NaHCO_3$ (5 mL) and extracted with Et_2O/hexanes 1:1 (4 times 10 mL). The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo. Flash chromatography (EtOAc/hexanes 1:3) afforded **21** containing a trace of **22** (85.1 mg, 0.197 mmol, 93%) as a light yellow oil. R_f 0.3 (EtOAc/hexanes 1:3). IR 2975, 2930, 2870, 1730, 1670, 1600, 1140, 690. ^1H NMR (400 MHz, mixture of **21** and **22**) 1.18-4.65 (m, 26.5H, including characteristic signals for $(CH_3)_3C$: 1.46 (s), 1.47 (s), 1.48 (s) and 1.49 (s)), 6.92 (d, J = 15.43 Hz, 0.25H, CH=C*H*C=O), 6.99-7.06 (m, 0.25H, C*H*=CHC=O), 7.31-8.38 (m, 5H, Ar-H), 10.31 (br s, 0.65H) and 11.50 (br s, 0.35H, NH). ^{13}C NMR (100 MHz, mixture of **21** and **22**) Data for **21**: 27.61 (C-4), 28.03 and 28.26 (2× (CH_3)$_3$C), 30.05 (C-3), 40.17 and 43.14 (C-5 and CH_2C=O), 56.87 (C-2), 79.27 and 83.15 (2× (CH_3)$_3C$), 128.57, 132.64 and 133.18 (Ar-CH), 136.52 (Ar-C), 153.32, 156.19 and 163.58 (2× C=O and C=N), 190.53 (C=O ketone). Characteristic signals for **22**: 27.98 and 28.18 (2× (CH_3)$_3$C), 30.67 (CH_2C=C), 49.75 (CH_2N), 126.50 (C=*C*C=O), 148.00 (*C*=CC=O). HRMS calculated for $C_{23}H_{33}N_3O_5$ 431.2420, found 431.2413.

3-Phenyl-4a,5,6,7-tetrahydro-2*H*-pyrrolo[1,2-c]pyrimidin-1-ylideneamine Hydrochloride (23). To a solution of **21** with a trace of **22** (67.0 mg, 0.155 mmol) in 0.5 mL of MeOH was added 1.0 mL of a 7.3 M solution of HCl in MeOH (7.3 mmol). After stirring at room temperature for 4 h, evaporation of the volatiles gave **23** (38.3 mg, 0.153 mmol, 99%) as a light brown solid. IR (KBr) 3400, 2960, 2860, 1655, 1620, 1540, 760, 690. ^1H NMR (400 MHz, DMSO-d_6) 1.69-1.77 (m, 1H), 1.93-2.03 (m, 2H), 2.27-2.33 (m, 1H), 3.56-3.60 (m, 2H, H-7), 4.39-4.43 (m, 1H, H-4a), 5.56 (d, J = 1.7 Hz, 1H, H-4), 7.42-7.50 (m, 3H, Ar-H), 7.65-7.67 (m, 2H, Ar-H), 8.11 (br s, 2H, NH), 10.12 (br s, 1H, NH). ^{13}C NMR (50 MHz, DMSO-d_6), 27.19 (C-6), 37.15 (C-5), 51.11 (C-7), 61.74 (C-4a), 105.48 (C-4), 130.31, 133.73 and 134.30 (Ar-CH), 137.17 and 138.62 (Ar-C and C-3), 156.00 (C-1). HRMS-FAB $[M\text{-}Cl]^+$ calculated for $C_{13}H_{16}N_3$ 214.1344, found 214.1321. Anal. Found: C, 61.78; H, 6.64; N, 16.49. Calculated for $C_{13}H_{16}N_3Cl$ C, 62.52; H, 6.46; N, 16.83.

Guanylation of 19. To a solution of **19** (49.5 mg, 0.258 mmol) in 0.5 mL of DMF were added at 0 °C *N,N'*-bis-(*tert*-butoxycarbonyl)-thiourea (71.4 mg, 0.258 mmol), $HgCl_2$ (70.1 mg, 0.258 mmol) and Et_3N (120 µL, 0.86 mmol) in succession. The mixture was stirred at 0 °C for 30 min. After warming to room temperature the reaction mixture was stirred for an additional 18 h, diluted with EtOAc (5 mL) and filtered through a path of celite. Water (5 mL) and a saturated aqueous solution of NaCl (5 mL) were added to the filtrate and the mixture was extracted with EtOAc (4 times 15 mL). The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo. The residue was dissolved in Et_2O/hexanes 1:1 (10 mL), poured out into a saturated aqueous solution of $NaHCO_3$ (5 mL) and was extracted with Et_2O/hexanes 1:1 (4 times 10 mL). The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo. Flash chromatography (EtOAc/hexanes 1:3) gave two fractions. The first fraction consisted of ***E*-*N,N'*-Bis-Boc-*N''*-(6-oxo-non-4-enyl)-guanidine (25)** (17.7 mg, 0.0445 mmol, 17%) as a light yellow oil. R_f 0.35 (EtOAc/hexanes 1:3). ^1H NMR (400 MHz) 1.92 (t, *J* 7.4 Hz, 3H, CH_3), 1.48 (s) and 1.49 (s, 18H, 2× $(CH_3)_3C$), 1.55-1.67 (m, 2H), 1.72-1.79 (m, 2H), 2.25-2.30 (m, 2H), 2.50 (t, *J* = 7.4 Hz, 2H, CH_2C=O), 3.43-3.49 (m, 2H, CH_2N), 6.12 (dd, *J* = 1.4, 15.9 Hz, 1H, CH=*C*HC=O), 6.80 (dt, *J* = 6.8, 15.9 Hz, C*H*=CHC=O), 8.36 (br s, 1H, NH), 11.49 (br s, 1H, NH). ^{13}C NMR (100 MHz) 13.78 (CH_3), 17.60 (CH_2), 27.62 (CH_2), 28.03 and 28.26 (2× (CH_3)$_3$C), 29.65 (CH_2), 40.14 (CH_2), 42.09 (CH_2), 79.33 and 83.19 (2× (CH_3)$_3$*C*), 30.90 and 145.30 (*C*H=*C*H), 153.31 and 156.17 (C=O and C=N), 200.46 (C=O ketone). The second fraction consisted of ***N,N'*-diBoc-1-[1-(amino-imino-methyl)-pyrrolidin-2-yl]-pentan-2-one (24)** (83.8 mg, 0.211 mmol, 82%, 82:18 mixture of **24** and **25**) as a colourless oil. R_f 0.30 (EtOAc/hexanes 1:3). IR 2980, 2930, 2870, 1740, 1710, 1600. ^1H NMR (400 MHz, 82:18 mixture of **24** and **25**) 0.89 (t, *J* = 7.4 Hz, 3H, CH_3), 1.43-2.51 (m, 27H, including characteristic signal for $(CH_3)_3C$: 1.46 (s)), 3.28-3.61 (m, 3H), 4.45-4.55 (m, 1H, H-2), 10.2 (br s, 1H, NH). ^{13}C NMR (100 MHz, 82:18 mixture of **24** and **25**) 13.66 (CH_3), 17.59 (CH_2), 28.12 (2× (CH_3)$_3$C), 31.43 (CH_2), 40.14 (CH_2), 45.18 (CH_2), 46.38 (CH_2), 49.63 (CH_2), 55.58 (C-2), 79.29 and 83.17 (2× (CH_3)$_3$*C*), 156.17 and 163.54 (C=O and C=N), 209.49 (C=O ketone). HRMS-FAB $[M+H]^+$ calculated for $C_{20}H_{36}N_3O_5$ 398.2655 found 398.2649.

Deprotection of 24 and 25. To a solution of **24** and **25** (38.2 mg, 0.0961 mmol, 68:32 mixture) in 0.5 mL of MeOH was added 0.5 mL of a 7.3 M solution of HCl in MeOH (3.6 mmol). After stirring at room temperature for 4 h, evaporation of the volatiles gave a mixture of **3-propyl-4a,5,6,7-tetrahydro-pyrrolo[1,2-c]pyrimidin-1-ylamine (26)**, ***E*,*Z*-3-propylidene-3,4,4a,5,6,7-hexahydro-pyrrolo[1,2-c]pyrimidin-1-ylamine (27)** and **1-amino-3-propyl-3,4,4a,5,6,7-hexahydro-pyrrolo[1,2-c]pyrimidin-3-ol (28)** (19.3 mg, 0.0885 mmol, 93%) as a colourless solid. IR ($CHCl_3$) 3300, 3140, 2960, 1650. ^1H NMR (400 MHz, DMSO-d_6, complex mixture of 5 guanidines) 0.87-0.98 (m, 3H, CH_3, characteristic signals: 0.89 (t, *J* = 7.3 Hz), 0.96 (t, *J* = 7.4 Hz)), 1.46-1.67 (m), 178-2.43 (m), 2.70 (dd, *J* = 3.0, 14.0 Hz), 3.05 (dd, *J* = 3.1, 14.8 Hz), 3.38-3.58 (m), 4.18-4.21 (m), 4.58 (t, *J* = 6.9 Hz) and 4.83 (s) and 4.98 (t, *J* = 7.3 Hz, CH=C, rel. intensities 47:36:17, respectively), 7.47 (br s) and 7.60 (br s) and 7.79 (br s, 2H, NH_2), 9.61 (br s, 0.14H, NH), 9.81 (br s, 0.32H, NH), 10.02 (br s, 0.41H, NH), 10.22 (br s, 0.13H, NH). ^{13}C NMR (100 MHz, DMSO-d_6, complex mixture of 5 guanidines) 12.51, 13.15, 13.88, 14.04 and 14.64 (CH_3), 18.42, 18.80, 19.33, 20.64, 22.07, 22.19, 22.86, 22.90, 26.91, 30.75, 31.49, 31.58, 32.24, 32.40, 32.93, 45.93, 46.08 and 46.35 (CH_2), 55.07, 55.85, 56.59 and 58.73 (CH), 98.73, 109.76 and 110.53 (*C*H=C), 110.44, 124.01, 127.40, 129.02 and 134.48 (C_q), 149.54, 149.81, 150.21 and 150.61 (NCN). MS(FAB) 198 (7.4%), 180 (100%). HRMS-FAB $[M-Cl]^+$ calculated for $C_{10}H_{20}N_3O$ 198.1606 found 198.1612. HRMS-FAB $[M-Cl]^+$ calculated for $C_{10}H_{18}N_3$ 180.1501 found 180.1524.

Attempted reaction of 14 with bis-Boc-thiourea. To a solution of bis-Boc-thiourea (124 mg, 0.448 mmol), in 0.3 mL of DMF were added at 0 °C $HgCl_2$ (122 mg, 0.449 mmol) and Et_3N (125 µL, 0.88 mmol) in succession. The mixture was stirred at 0 °C for 30 min. **14** (93.5 mg, 0.422 mmol) in 0.5 mL of DMF and Et_3N (65 mL, 0.47 mmol) were added, successively, and the mixture was stirred at 0 °C for 30 min. After warming to room temperature the reaction mixture was stirred for an additional 18 h, diluted with EtOAc (5 mL) and filtered

through a path of celite. Water (5 mL) and a saturated aqueous solution of NaCl (5 mL) were added to the filtrate and the mixture was extracted with EtOAc (4 times 15 mL). The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo. The mixture was subjected to flash chromatography. Gradient elution (EtOAc/hexanes 1:5, 1:2, then EtOAc/MeOH 95:5) gave unidentified products. Elution with (EtOAc/MeOH 3:1) afforded **29** (18.7 mg, 0.079 mmol, 37%) as a light yellow oil. R_f 0.4 (EtOAc/MeOH 3:1).

4-Methyl-1,2,3,5a,6,7,8,8b-octahydro-3a,8a-diaza-as-indacene-5-carboxylic Acid Methyl Ester (29). To a solution of **12** (81.2 mg, 0.285 mmol) in 0.5 mL of MeOH was added 1.5 mL of a 4.7 M solution of HCl in MeOH (4.7 mmol). After stirring at room temperature for 3.5 h, the mixture was concentrated in vacuo. The residue was dissolved in 2.0 mL of THF and Et_3N (50 µL, 0.36 mmol) was added. After stirring at room temperature for 15 min the mixture was concentrated in vacuo. Flash chromatography (EtOAc/hexanes 3:1) and short evaporation in vacuo afforded a mixture of methyl acetoacetate and **29** (40.5 mg, 1:2 mixture according to ^1H NMR). Methyl acetoacetate identified by TLC and signals in spectra: ^1H NMR (400 MHz, 2:1 mixture of **29** and MAA) 2.24 (s, 3H, CH_3), 3.43 (s, 2H, CH_2), 3.71 (s, 3H, CH_3O). ^{13}C NMR (100 MHz, mixture of **29** and MAA) 30.09 (CH_3), 49.77 (CH_2), 52.29 (CH_3O), 167.48 (C=O) (C=O ketone not observed). Prolonged evaporation in vacuo afforded **29** (32.4 mg, 0.137 mmol, 96%) as a colourless oil. R_f 0.1 (EtOAc/hexanes 3:1). IR 2940, 2870, 2800, 1700, 1550, 1430. ^1H NMR (400 MHz) 1.56-1.65 (m, 1H), 1.73-1.88 (m, 4H), 1.90-2.01 (m, 1H), 2.08-2.18 (m, 1H), 2.21-2.29 (m, 1H), 2.34 (s, 3H, CH_3), 2.61-2.67 (m, 2H), 3.34-3.54 (m, 2H), 3.61 (s, 3H, CH_3O), 3.87-3.90 (m, 1H) and 4.25-4.29 (m, 1H, H-5a and H-8b). ^{13}C NMR (100 MHz) 17.49 (CH_3), 22.54, 22.62, 29.81, 31.82, 45.05 and 47.26 (C-1, C-2, C-3, C-6, C-7 and C8), 60.95 and 74.61 (C-5a and C-8b), 96.41 and 153.90 (C-4 and C-5), 168.55 (C=O ester). HRMS calculated for $C_{13}H_{20}N_2O_2$ 236.1524, found 236.1524.

2-(2-Hydroxy-1-methoxycarbonyl-propyl)-pyrrolidine-1-carboxylic Acid *tert*-Butyl Ester (32). To a solution of **12** (91.8 mg, 0.322 mmol) in 1.0 mL of AcOH at 0 °C was added 0.4 mL of a 0.95M solution of $NaBH_3CN$ in THF (0.38 mmol). After stirring at room temperature for 30 min, the reaction mixture was poured out into a 2M aqueous solution of KOH (10 mL) and was extracted with CH_2Cl_2 (4 times 15 mL). The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo. Flash chromatography (EtOAc/hexanes 2:1) afforded **32** (91.3 mg, 0.318 mmol, 99%) as a light yellow oil. R_f 0.4 (EtOAc/hexanes 2:1). IR 3400, 2970, 2940, 2880, 1720, 1675, 1400, 1170. ^1H NMR (400 MHz, mixture of diastereomers and rotamers) 1.18-1.22 (m, 3H, CH_3), 1.27-2.00 (m, 13H, including characteristic signals for $(CH_3)_3C$: 1.40 (s), 1.41 (s) and 1.43 (s)), 2.30-4.95 (m, 9H, including characteristic signals for CH_3O: 3.64 (s), 3.67 (s) and 3.68 (s)). ^1H NMR (400 MHz, toluene-d_8, 378K, mixture of diastereomers) 1.14 (d, J = 6.3 Hz), 1.18 (d, J = 6.5 Hz) and 1.23 (d, J = 6.5 Hz, 3H, CH_3), 1.34-2.08 (m, 14H, including Characteristic signals for $(CH_3)_3C$: 1.39 (s), 1.41 (s) and 1.43 (s)), 2.58-3.58 (m, 6H, including: 2.59 (dd, J = 4.1, 8.3 Hz), 2.75 (dd, J = 3.7, 6.0 Hz), 2.88 (d, J = 9.2 Hz) and characteristic signals for CH_3O: 3.33 (s) and 3.40 (s)), 3.87-4.04 (m, 1H), 4.26-4.34 (m, 1H). ^{13}C NMR (50 MHz, mixture of diastereomers and rotamers) 20.36, 21.53 and 22.35 (CH_3), 22.99 and 23.25 (C-4), 28.12 and 28.20 ((CH_3)$_3$C), 29.66 (C-3), 46.22 and 46.44 (C-5), 51.23, 51.38, 51.58, 53.79, 55.70, 56.06, 56.32, 56.89, 64.60, 65.78 and 67.16 (CH_3O, C-2, CHOH and $CHCO_2CH_3$), 79.26, 79.65 and 80.18 ((CH_3)$_3C$), 154.19, 154.39 and 156.53 (C=O), 171.84, 173.49 and 173.96 (C=O ester). HRMS calculated for $C_{14}H_{25}NO_5$ 287.1733, found 287.1736.

3-Hydroxy-2-pyrrolidin-2-yl-butyric Acid Methyl Ester Hydrogen Chloride (33). To a solution of **32** (54.4 mg, 0.189 mmol) in 0.5 mL of MeOH was added 0.5 mL of a 7.3 M solution of HCl in MeOH (3.7 mmol). After stirring at room temperature for 2.5 h, evaporation of the volatiles gave **33** (40.5 mg, 0.181 mmol, 96%) as a colourless oil. IR ($CHCl_3$) 3650, 3340. 2970, 2870, 1730. ^1H NMR (400 MHz, D_2O, mixture of diastereomers) 1.25 (d, J = 6.2 Hz), 1.31 (d, J = 6.8 Hz) and 1.34 (d, J = 6.6 Hz, 3H, CH_3), 1.70-2.40 (m, 4H), 2.86 (t, J = 8.9 Hz, 0.33H), 2.96 (dd, J = 3.2, 8.0 Hz, 0.33H), 3.01 (dd, J = 3.4, 7.1 Hz, 0.33H), 3.28-3.41 (m, 2H), 3.74-4.03 (m, 4H, including characteristic signals for CH_3O: 3.79 (s), 3.80 (s) and 3.82 (s)),

4.14-4.21 (m, 0.66H), 4.30-4.36 (m, 0.33H). ^{13}C NMR (100 MHz, D_2O, mixture of diastereomers) 22.80, 23.44 and 23.50 (CH_3), 24.96, 25.80 and 25.94 (C-4), 30.98, 31.33 and 31.42 (C-3), 48.29, 48.56 and 48.65 (C-5), 54.72, 55.54, 55.70, 55.87 and 57.56 (CH_3O and CH), 61.11, 62.40 and 63.00 (CH), 68.51, 69.94 and 70.83 (CH), 175.35, 175.43 and 175.68 (C=O). HRMS [M-HCl] calculated for $C_9H_{17}NO_3$ 187.1208 found 187.1207.

***N,N''*-Bis-Boc-2-[1-(Amino-imino-methyl)-pyrrolidin-2-yl]-3-hydroxy-butyric Acid Methyl Ester (34).** To a solution of **33** (194.4 mg, 0.869 mmol) in 1.25 mL of DMF were added at 0 °C *N,N'*-bis-(*tert*-butoxycarbonyl)-thiourea (252 mg, 0.91 mmol), $HgCl_2$ (248 mg, 0.91 mmol) and Et_3N (400 µL, 2.87 mmol) in succession. The mixture was stirred at 0 °C for 30 min. After warming to room temperature the reaction mixture was stirred for an additional 18 h, diluted with EtOAc (10 mL) and filtered through a path of celite. Water (10 mL) and a saturated aqueous solution of NaCl (10 mL) were added to the filtrate and the mixture was extracted with EtOAc (4 times 15 mL). The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo. The residue was dissolved in Et_2O/hexanes 1:1 (10 mL), poured out into a saturated aqueous solution of $NaHCO_3$ (5 mL) and was extracted with Et_2O/hexanes 1:1 (4 times 10 mL). The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo. Flash chromatography (EtOAc/hexanes 1:5 then 1:2) gave three fractions. The first fraction consisted of **(1*R**,5*R**,6*R**)-34a** (136.4 mg, 0.318 mmol, 37%) as a white foam. R_f 0.2 (EtOAc/hexanes 1:2). Recrystallisation (EtOAc/hexanes 1:5) gave a sample of **34a** as white crystals, mp 122-123 °C. IR 3400, 2980, 2930, 1730, 1630, 1590. ^1H NMR (400 MHz, one diastereomer, rotamers) 1.22 (d, J = 6.5 Hz, 3H, CH_3), 1.44 (s), 1.45 (s) and 1.48 (s, 18H, 2× $(CH_3)_3C$), 1.88-2.15 (m, 3H), 2.42-2.44 (m, 1H), 3.40-3.43 (m, 1H), 3.53-3.67 (m, 1H), 3.72 (s, 3H, CH_3O), 3.90-3.93 (m, 1H), 4.46 (br s, 1H), 5.03 (br s, 1H), 5.40 (br s, 1H), 10.49 (br s, 1H, NH). ^{13}C NMR (50 MHz, one diastereomer) 20.22 (CH_3), 23.33 (C-4), 27.89 and 27.97 (2× $(CH_3)_3C$), 29.13 (C-3), 49.00 (C-5), 51.29, 56.77, 56.96 and 63.95 (CH_3O, C-2, CHOH and $CHCO_2Me$), 79.40 and 82.06 (2× $(CH_3)_3C$), 150.16, 156.10 and 161.59 (2× C=O and C=N), 171.27 (C=O ester). HRMS-FAB $[M+H]^+$ calculated for $C_{20}H_{36}N_3O_7$ 430.2553 found 430.2491. Anal. Found: C, 55.78; H, 8.21; N, 9.81. Calculated for $C_{20}H_{35}N_3O_7$: C, 55.93; H, 8.21; N, 9.78. **Crystallographic data for (1*R**,5*R**,6*R**)-34a.** Triclinic crystals, $P\bar{1}$, a = 9.2828 (9), b = 9.8264 (8), c = 14.783 (1) Å, α = 109.322 (8), β = 92.351 (8), γ = 109.012 (7) °, V = 1183.8 (2) $Å^3$, Z = 2, D_x = 1.21 gcm^{-3}, λ (CuKα) = 1.5418 Å, µ (Cu-Kα) = 7.19 cm^{-1}, F(000) = 464, room temperature. Final R = 0.070 for 2935 observed reflections.[24] The second fraction consisted of **34a,b,c** (59.6 mg, 0.139 mmol, 16%) mixture of 3 diastereomers as a colourless oil. The third fraction consisted of **34b,c** (113.5 mg, 0.263 mmol, 30%) mixture of 2 diastereomers as a colourless oil. R_f 0.15 (EtOAc/hexanes 1:2). IR 3410, 2980, 2930, 2880, 1740, 1715, 1620, 1590. ^1H NMR (400 MHz, mixture of two diastereomers) 1.26 (d, J = 6.5 Hz, 3H, CH_3), 1.44 (s) and 1.47 (s, 18H, 2× $(CH_3)_3C$), 1.55-2.10 (m, 4H), 2.89-2.99 (m, 1H), 3.32-4.81 (m, 8H, including characteristic signals for CH_3O: 3.71 (s) and 3.74 (s)), 10.25 (br s, 1H, NH). ^{13}C NMR (63 MHz, D_1 = 10 s, mixture of diastereomers) 18.58 and 22.55 (CH_3), 22.84 (C-4), 28.14, 28.22 and 28.26 (2× $(CH_3)_3C$), 28.72 and 29.71 (C-3), 48.04 (C-5), 45.51, 51.75, 52.04, 52.96, 57.03 58.41, 65.86 and 73.68 (CH_3O and 3× CH), 78.36 and 79.55 (2× $(CH_3)_3C$), 153.14, 156.16, 159.44, 168.62 and 173.48 (3× C=O and C=N). HRMS-FAB $[M+H]^+$ calculated for $C_{20}H_{36}N_3O_7$ 430.2553 found 430.2503.

***E*- and *Z*-*N,N*-Bis-Boc-2-Acetyl-6-guanidino-hex-2-enoic Acid Methyl Ester (35).** To a solution of freshly distilled oxalyl chloride (9.8 µL, 0.11 mmol) in 0.25 mL of CH_2Cl_2 at -78 °C was added DMSO (16 µL, 0.23 mmol). After stirring at -78 °C for 2 min, a solution of **34** (44.3 mg, 0.103 mmol) in 125 µL of CH_2Cl_2 was added, and the mixture was stirred at -78 °C for 5 min. Et_3N (57.5 µL, 0.41 mmol) was added, the resulting mixture was stirred at -78 °C for 30 min, poured out into water (2.0 mL) and extracted with CH_2Cl_2 (4 times 5 mL). The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. Flash chromatography (EtOAc/hexanes 1:1) afforded **35** and a trace of **36** (29.4 mg, 0.069 mmol, 67%) as a colourless oil. R_f 0.3 (EtOAc/hexanes 1:2). IR 3325, 3284, 3027, 3006, 2984, 2954, 2934, 1721, 1634, 1618, 1581. ^1H NMR (400 MHz, mixture of *E* and *Z* isomers of **35** and a trace of **36**) 1.46 (s), 1.47 (s) and 1.48 (s,

18H, 2× $(CH_3)_3C$)), 1.71-1.81 (m, 2H), 2.22-2.39 (m, 5H, including characteristic signals for CH_3: 2.31 (s) and 2.35 (s)), 3.40-3.52 (m, 2H, CH_2NH), 3.76 (s) and 3.82 (s, 3H, CH_3O), 6.87 (t, J = 7.7Hz) and 6.91 (t, J = 7.8 Hz, 1H, CH=C), 8.34 (br s, 1H, NH), 11.48 (br s, 1H, NH). Characteristic signals for **36**: 1.43 $(CH_3)_3C$), 2.21 (CH_3), 3.72 (CH_3O), 4.45 (br s, CH). ^{13}C NMR (50 MHz, mixture of *E* and *Z* isomers of **35** and a trace of **36**) 26.58 (CH_2), 26.71 (CH_3), 27.21 and 27.72 (CH_2), 27.78 and 28.03 (2× $(CH_3)_3C$), 30.81 (CH_3), 39.54, 39.76 and 39.87 (CH_2), 51.92 (CH_3O), 79.03, 79.06, 82.90 and 82.94 (2× $(CH_3)_3C$), 135.60, 137.16 (C_q), 147.16 and 147.80 (*C*H=C), 153.03, 155.95, 155.99 163.31, 164.56, 166.42 (C_q), 194.77 and 200.27 (C=O ketone). Characteristic signals for **36**: 27.97 $(CH_3)_3C$), 31.89 (CH_2), 63.29 (CH), 79.35 $(CH_3)_3C$). HRMS-FAB $[M+H]^+$ calculated for $C_{20}H_{34}N_3O_7$ 428.2397 found 428.2270.

1-Amino-3-methyl-4a,5,6,7-tetrahydro-pyrrolo[1,2-c]pyrimidin-4-carboxylic Acid Methyl Ester (37). To a solution of **35** with a trace of **36** (32.2 mg, 0.0753 mmol) in 0.5 mL of MeOH was added 1.0 mL of a 4.3 M solution of HCl in MeOH (4.3 mmol). After stirring at room temperature for 3 h, evaporation of the volatiles gave **37** (18.5 mg, 0.0753 mmol, 100%) as a colourless solid. IR ($CHCl_3$) 3300, 3022, 29784, 2360, 1682, 1635, 1540. ^1H NMR (400 MHz, DMSO-d_6) 1.51-1.67 (m, 1H), 1.87-1.96 (m, 2H), 2.20 (s, 3H, CH_3), 2.47-2.50 (m, 1H), 3.48-3.64 (m, 2H, H-7), 3.68 (s, 3H, CH_3O), 4.39 (dd, J = 4.2, 10.7 Hz, 1H, H-4a), 8.07 (br s, 2H, NH_2), 10.60 (br s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6) 17.08 (CH_3), 21.49 (C-6), 32.87 (C-5), 46.47 (C-7), 51.20 (CH_3O), 56.99 (C-4a), 101.82 (C-4), 143.33 (C-3), 149.12 (C-1), 165.09 (C=O). HRMS-FAB $[M-Cl]^+$ calculated for $C_{10}H_{16}N_3O_2$ 210.1243 found 210.1125.

3,3-Dimethoxy-2-pyrrolidin-2-yl-butyric Acid Methyl Ester (38). To a solution of **12** (58.7 mg, 0.206 mmol) in 200 µL of MeOH were added trimethylorthoformate (200 µL, 1.83 mmol) and 3 drops of a 2 M solution of H_2SO_4 in MeOH. After stirring at 50 °C for 3 h, 2 drops of a 2 M solution of H_2SO_4 in MeOH were added, and the solution was stirred at 50 °C for 3 h. Evaporation of the volatiles and quick flash chromatography (EtOAc, then EtOAc/MeOH = 3:1) over a short column afforded **38** (51.0 mg) as a colourless oil. **38** was immediately used in the next reaction. IR 3460, 3028, 3008, 2952, 2838, 1735, 1231, 1010. ^1H NMR (400 MHz, $CDCl_3$, mixture of 2 diastereomers) 1.44 (s) and 1.48 (s, 3H, CH_3), 1.54-1.70 (m, 1H), 1.84-2.15 (m, 3H), 3.08-3.45 (m, 8H, 2× CH_3O and H-5; including characteristic signals for CH_3O: 3.21 (s), 3.22 (s) and 3.26 (s)), 3.62-3.77 (m, 5H, CH_3OCO, H-2 and CHC=O; including characteristic signals for CH_3OCO: 3.69 (s) and 3.70 (s)), 6.80 (br s, NH). ^{13}C NMR (100 MHz, mixture of 2 diastereomers) 18.27 and 18.65 (CH_3), 22.66 and 24.44 (C-4), 29.89 and 30.08 (C-3), 46.08 (C-5), 48.52, 48.57, 49.02 and 49.09 (2× CH_3O), 52.16, 52.27, 53.46 and 54.66 (CH_3OCO and CH), 58.22 and 58.41 (CH), 101.28 and 101.60 ($(CH_3O)_2C$), 169.88 and 171.85 (C=O). HRMS-FAB $[M+H]^+$ calculated for $C_{11}H_{22}NO_4$ 232.1549 found 232.1524.

2-[1-(Amino-imino-methyl)-pyrrolidin-2-yl]-3,3-dimethoxy-butyric Acid Methyl Ester (39). To a solution of crude **38** (51.0 mg, 0.206 mmol) in 200 µL of DMF were added at 0 °C *N,N'*-bis-(*tert*-butoxycarbonyl)-thiourea (58.7 mg, 0.216 mmol), $HgCl_2$ (59.8 mg, 0.216 mmol) and Et_3N (100 µL, 0.72 mmol) in succession. The mixture was stirred at 0 °C for 30 min. After warming to room temperature the reaction mixture was stirred for an additional 18 h, diluted with EtOAc (5 mL) and filtered through a path of celite. Water (2 mL) and a saturated aqueous solution of NaCl (3 mL) were added to the filtrate and the mixture was extracted with EtOAc (4 times 10 mL). The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo. Flash chromatography (EtOAc/hexanes 1:7 , 1:5, then 1:1) gave two fractions. The first fraction consisted of **(1*S**,5*S**)-39a** (53.3 mg, 0.113 mmol, 55%) as a white solid. R_f 0.5 (EtOAc/hexanes 1:2). Recrystallisation (EtOAc/hexanes 1:5) gave a sample of **39a** as white crystals, mp 127-128 °C. IR 3022, 2982, 1755, 1727, 1603, 1285, 1145. ^1H NMR (400 MHz) 1.10-1.55 (m, 22H, including characteristic signal for $(CH_3)_3C$): 1.36 (s) and 1.37 (s)), 1.77 (br s, 1H), 1.94-2.00 (m, 1H), 2.53 (br s, 1H), 3.09-3.33 (m, 8H, 2× CH_3O and H-2, including characteristic signal for CH_3O: 3.09 (s)), 3.55 (s, 3H, CH_3OCO), 3.97-4.01 (m, 1H, CH), 4.48 (br s, 1H, CH), 10.42 (br s, 1H, NH). ^{13}C NMR (100 MHz) 19.03 (CH_3), 25.47 and 26.50 (C-3 and C-4), 27.90 and 28.01 (2× $(CH_3)_3C$), 47.92, 48.54, 49.02, 51.53 and 57.50 (3× CH_3O and 2× CH), 50.47 (C-5), 78.23

and 81.21 (2× $(CH_3)_3C$), 101.06 ($C(OCH_3)_2$), 149.45, 153.88 and 162.43 (2× C=O and C=N), 171.73 (C=O ester). HRMS-FAB $[M+H]^+$ calculated for $C_{22}H_{40}N_3O_8$ 474.2815 found 474.2802. Anal. Found: C, 55.68; H, 8.32; N, 8.91. Calculated for $C_{22}H_{39}N_3O_8$: C, 55.80; H, 8.30; N, 8.87. **Crystallographic data for (1*S**,5*S**)-39a.** Monoclinic crystals, $P2_1/c$, a = 19.172 (1), b = 6.677 (1), c = 21.070 (2) Å, β = 97.533 (7) °, V = 2673.9 (5) $Å^3$, Z = 4, D_x = 1.18 gcm^{-3}, λ (CuKα) = 1.5418 Å, μ (Cu-Kα) = 7.06 cm^{-1}, F(000) = 1024, room temperature. Final R = 0.057 for 2820 observed reflections.[24] The second fraction consisted of **39b** (27.5 mg, 0.058 mmol, 28%) as a colourless oil. R_f 0.2 (EtOAc/hexanes 1:2). IR 3025, 2983, 1747, 1601, 1286, 1238, 1147, 1130. ^1H NMR (400 MHz) 1.40-1.61 (m, 21H, including characteristic signal for $(CH_3)_3C$): 1.4 (s)), 1.81-2.01 (m, 3H), 2.13-2.15 (m, 1H), 2.96 (d, *J* = 9.5 Hz, 1H, $CHCO_2Me$), 3.15 (s) and 3.17 (s, 6H, 2× CH_3O), 3.38-3.72 (m, 6H, including characteristic signal for CH_3OCO: 3.64 (s)), 9.2 (br s, 1H, NH). ^{13}C NMR (63 MHz, D_1 = 10 s) 18.17 (CH_3), 22.20 (C-4), 27.95 and 28.15 (2× $(CH_3)_3C$), 29.25 (C-3), 47.50 (C-5), 48.20 and 48.41 (2× CH_3O), 52.00, 54.00 and 58.34 (CH_3OCO and 2× CH), 83.28 ($(CH_3)_3C$), 101.53 ($C(OCH_3)_2$), 148.55, and 156.16 (2× C_q), 171.18 (C=O ester), (C_q not observed). HRMS calculated for $C_{22}H_{39}N_3O_8$ 473.2737 found 473.2712.

Deprotection of 39a. To a solution of **39a** (10.2 mg, 0.0215 mmol) in 0.25 mL of MeOH was added 150 μL of a 9 M solution of HCl in MeOH (1.35 mmol). After stirring at room temperature for 4 h, evaporation of the volatiles gave **37** (5.0 mg, 0.0203 mmol, 94%) as a colourless solid.

Deprotection of 39b. To a solution of **39b** (8.7 mg, 0.0184 mmol) in 0.25 mL of MeOH was added 150 μL of a 9 M solution of HCl in MeOH (1.35 mmol). After stirring at room temperature for 4 h, evaporation of the volatiles gave **37** (4.2 mg, 0.0171 mmol, 93%) as a colourless solid.

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