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Synthesis of medium-sized rings via Conjugate Addition/Ring Expansion (CARE) cascade reactions of diketopiperazines and related bislactams

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Dedicated to Professor Teresa Pinho e Melo, to celebrate her outstanding scientific achievements and remarkable contributions to the field of heterocyclic and organic chemistry

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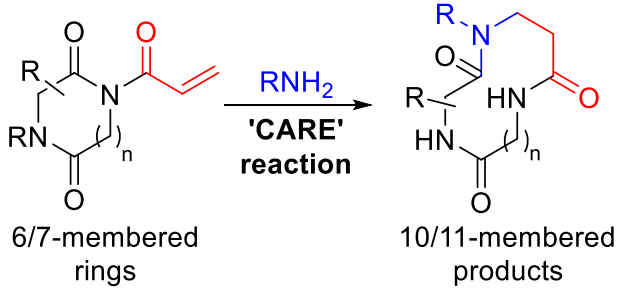
Abstract

A Conjugate Addition/Ring Expansion (CARE) cascade approach has been used for the ring expansion of acryloyl imides derived from 6-membered ring diketopiperazines and 7-membered ring bislactams. Using this approach, a library of 10- and 11-membered ring cyclic triamides (small cyclic peptides) was prepared directly from the acryloyl imide starting materials, via reaction with primary amines at room temperature.



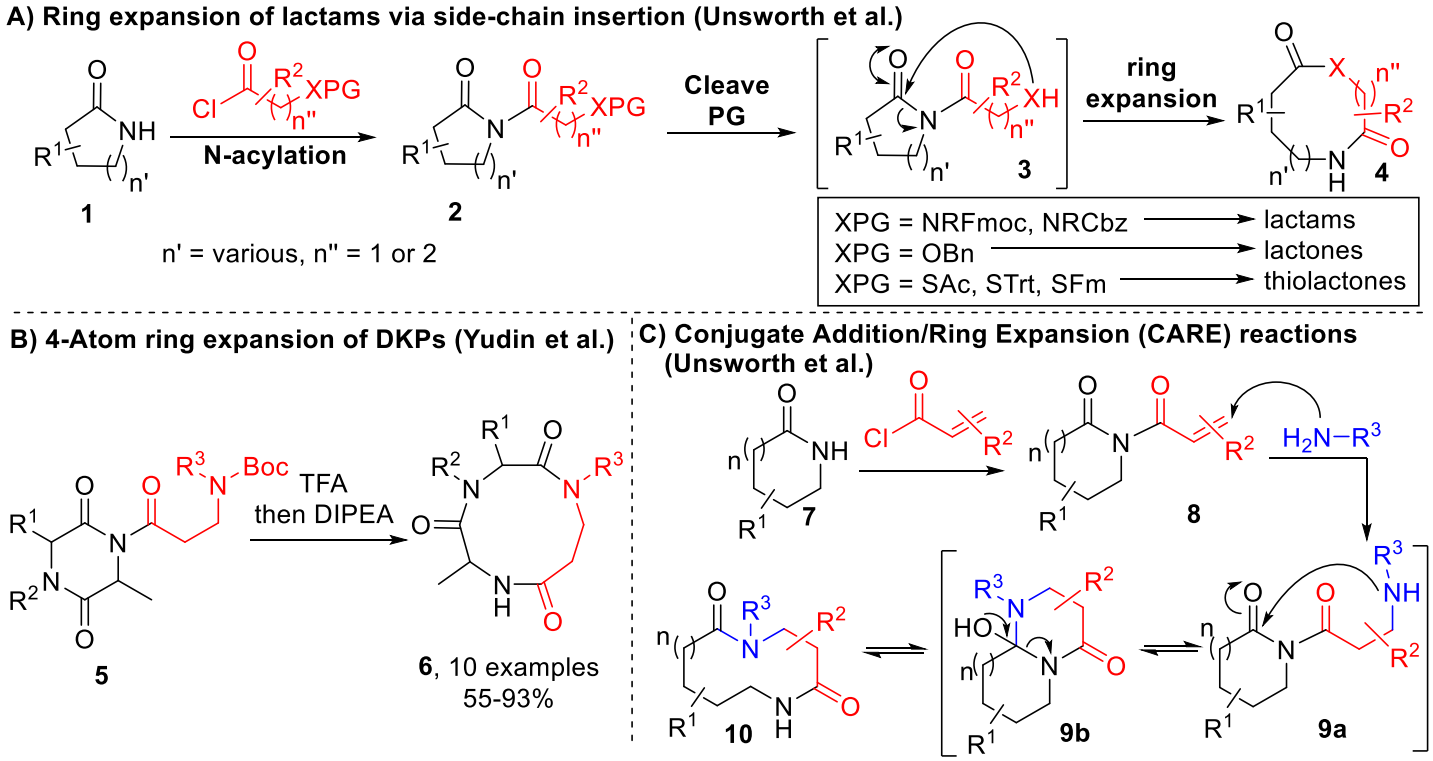
Keywords: Medium-sized rings, ring expansion, diketopiperazine, rearrangement, amide

Introduction

Functionalised medium-sized rings (8–11-membered rings) are important scaffolds in medicinal chemistry.[1-3] Compared to normal-sized (5–7-membered) rings systems, medium-sized rings have been far less well explored in medicinal chemistry research and development. This relates to both their inclusion in small molecule compound screening collections and their subsequent development into drugs, with the challenge of synthesising medium-sized rings being a significant contributing factor. Medium-sized rings are most commonly made via the end-to-end cyclisation of a linear starting material. However, due to a combination of loss of entropy upon cyclisation and the relatively high strain typically observed in medium-sized rings, cyclisation is often inefficent.[2,4,5] In particular, competing intermolecular side reactions means that medium-sized ring cyclisation reactions are often low yielding, and to mitigate against this, impractical high-dilution reaction conditions are routinely needed. If the challenges associated with their synthesis can be overcome, medium-sized rings represent a powerful vehicle to enable the biological examination of small molecule scaffolds in relatively under-explored regions of chemical space.

Ring expansion reactions are of much current interest in this context, as they allow medium-sized rings to be synthesised without needing high-dilution reaction conditions.[6-15] Ring expansion methods that proceed via rearrangement reactions that operate exclusively via normal-sized ring (5–7-membered) cyclisation steps are especially effective; for example, a series of lactam ring expansion reactions (**1** → **4**, Scheme 1A) have been reported by our laboratory in recent years,[16-24] and have been shown to work well at standard reaction concentrations (0.1 M typically). In this study, we sought to explore related ring expansion reactions of diketopiperazine (DKP) derivatives.[25] The earliest example of a ring expansion of a DKP ring expansion was reported in 1963 by Antonov and coworkers, and used to prepare cyclotetradepsipeptides.[26] DKP ring expansion reactions have received relatively little attention since, with a few notable exceptions.[27-30] The previous diketopiperazine ring expansion most closely related to methods developed in this study was reported in 2017 by Yudin and coworkers.[30] In this work, diketopiperazine derivatives **5** were shown to undergo ring expansion to form 10-membered ring products **6** following cleavage of a Boc protecting group with TFA, followed by reaction under basic conditions at 50 °C to promote ring expansion.

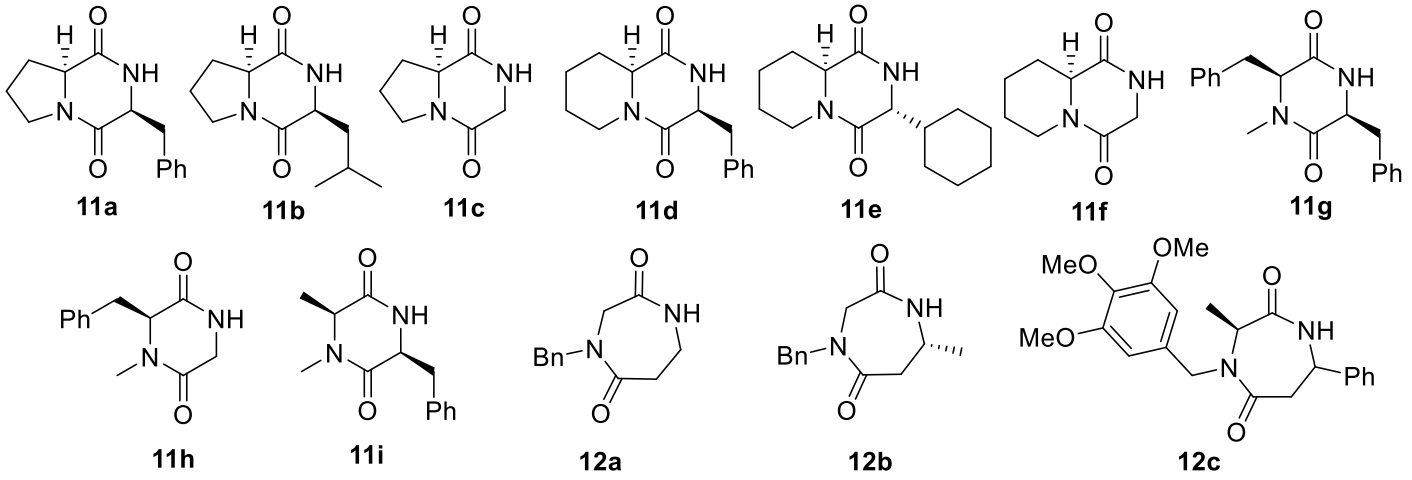
More recently, our laboratory introduced a method for the ring expansion of *N*-acryloyl imides **8**, via Conjugate Addition/Ring Expansion (CARE) cascade reactions (**8** → **9a** → **9b** → **10**, Scheme 1C).[31-36] Compared with the ring expansion methods summarised in Scheme 1A, the CARE approach benefits from being protecting-group free, thus making it more atom- and step-economical. The CARE approach also enables much faster generation of diverse product libraries, via simple variation of the primary amine reagent (depicted in blue). In this study, we describe work to expand the CARE approach for use on DKPs and related 7-membered ring bislactams for the first time, culminating in the synthesis of a library of 19 medium-sized ring (10- and 11-membered ring) cyclic triamides. The products – which can be considered to be small cyclic peptides – are formed in yields of 20–86%, using mild and simple reaction conditions at RT.



Scheme 1. A) Ring expansion of lactams via side chain insertion ; B) Yudin and coworkers' DKP ring expansion ; C) Conjugate Addition/Ring Expansion (CARE) cascade reactions.

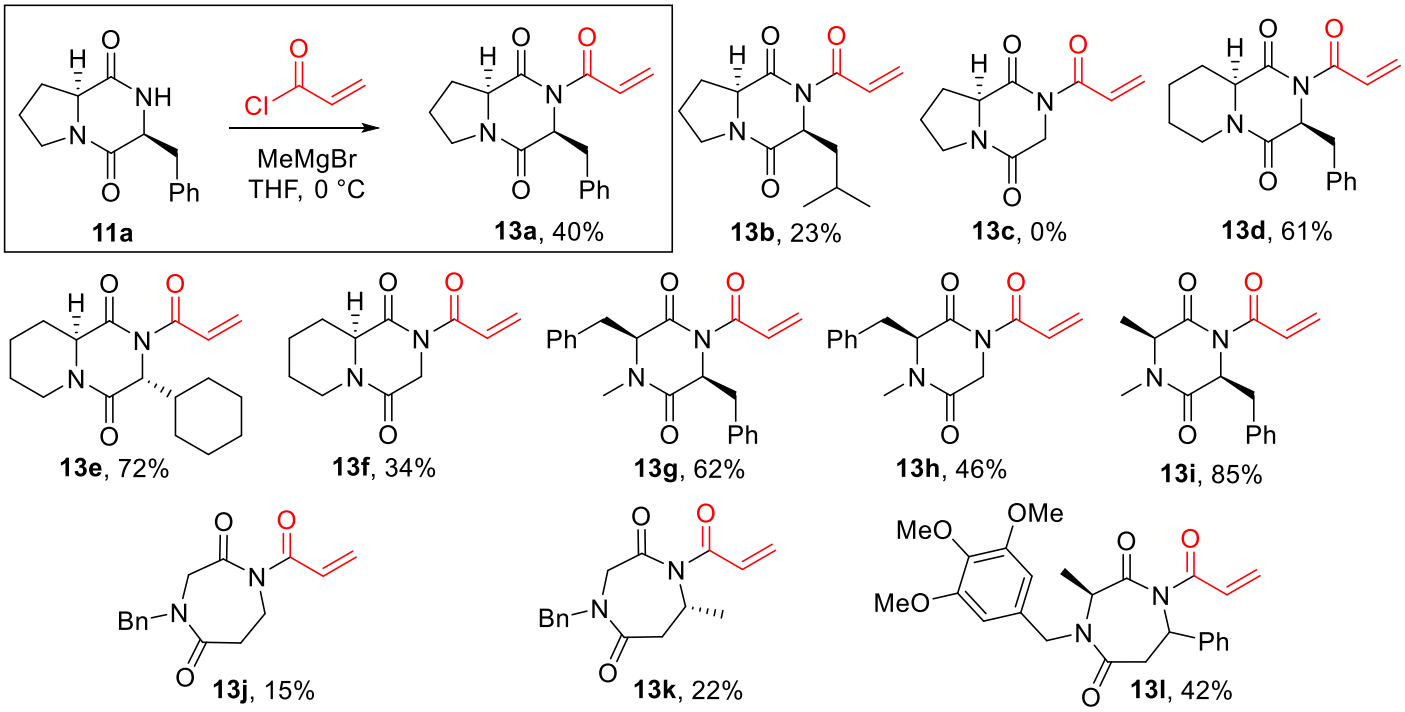
Results and Discussion

Several DKP starting materials **11a–i** were synthesized for use in this study, using literature methods or minor variations (Scheme 2, see experimental section for preparative details).[37-43] In addition, 7-membered bislactams **12a–c** (akin to DKPs but derived from one α- and one β-amino acid) were also prepared, using procedures adapted from the work of Van der Eycken and coworkers.[44]



Scheme 2. DKPs and bislactams prepared and used in this study.

With DKPs **11a–i** and 7-membered bislactams **12a–c** in hand, attention turned to their conversion into *N*-acryloyl imides (Scheme 3). Starting with DKP **11a**, *N*-acylation was done using conditions adapted from previous work;[31] thus, DKP **11a** was reacted with methyl magnesium bromide, followed by acryloyl chloride, to afford acryloyl imide **13a** in 40% yield. The *N*-acylation of DKPs **11b–11i** and bislactams **12a–c** was then performed in the same way, and in most cases the expected acryloyl imide product was obtained (**13b**, **13d–13i**, **13j–l**, 15–85% yield). An exception was DKP **11c** which we were unable to convert into **13c**, likely due to its very low solubility in THF.



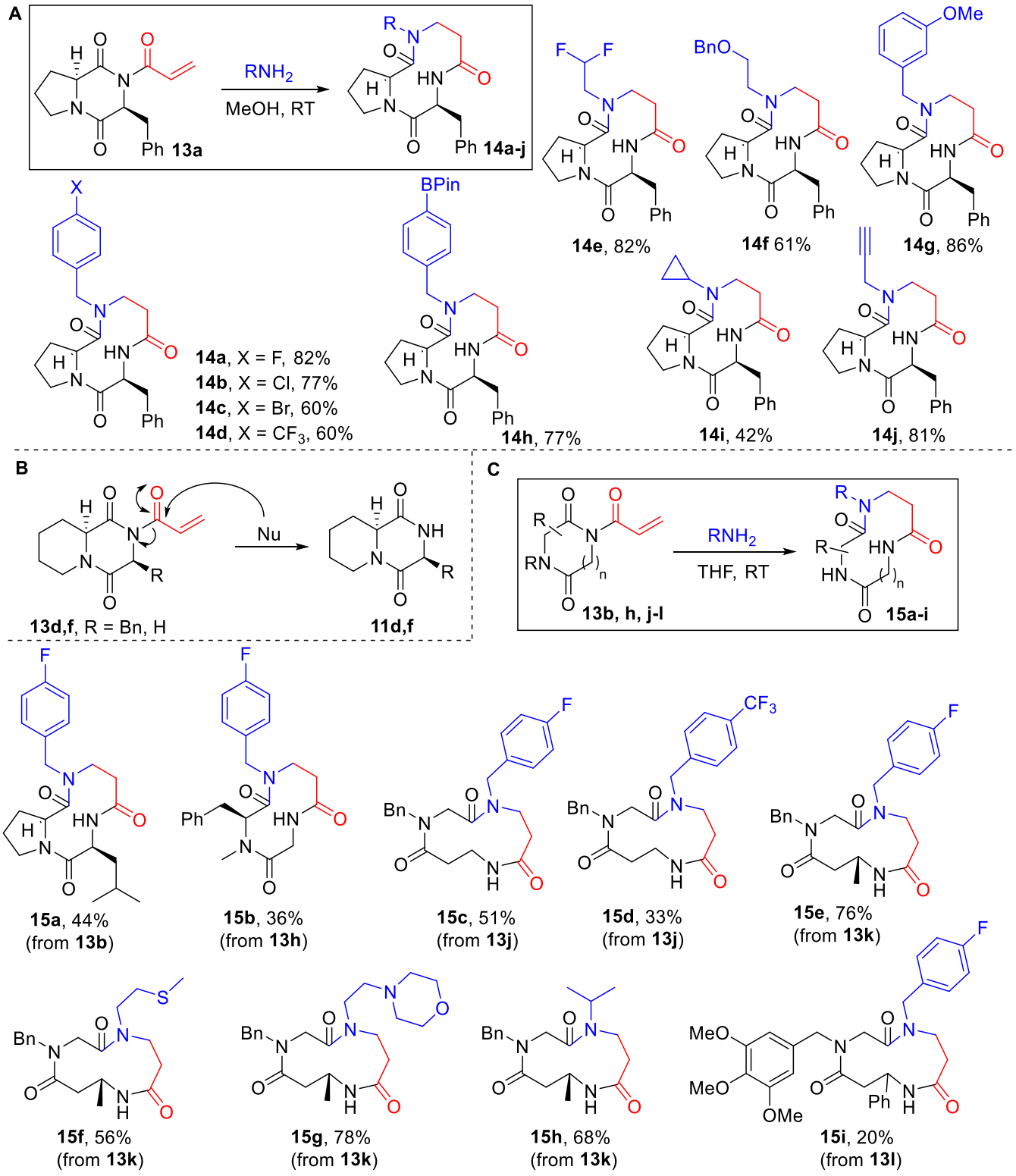
Scheme 3. Synthesis of *N*-acryoyl imides.

Acryloyl imides **13a–l** were then tested in CARE reactions. Imide **13a** was found to participate well in CARE reactions; **13a** was reacted with 10 different primary amines using the conditions summarised in Scheme 4A, and all resulted in good conversion into the expected ring expanded products **14a–j** (42–85% yield).

The CARE reactions of some other DKP-derived acryloyl imides did not proceed so smoothly. For example, when pipecolic acid derived imides **13d** and **13f** were reacted with 4-fluorobenzylamine in methanol, the only isolable products were DKPs **11d** and **11f** respectively. This presumably is a result of competing nucleophilic attack (from the amine and/or methanol) at the exocyclic carbonyl group out-competing the desired conjugate addition (Scheme 4B).[31-36] The same unwanted side reaction was also observed when imide **13g** was reacted in the same way. Cyclohexyl derivative **13e** did not react, most likely due to increased steric hindrance arising from the two cyclohexane rings. Similar low reactivity was also seen for acryloyl imide **13i**, likely due to a combination of low solubility of the imide and steric hindrance.

Successful cases using other DKPs and 7-membered bislactam starting materials are summarised in Scheme 4C. A notable change in the reaction conditions in this series was to change the reaction solvent from methanol to THF; this was done in an attempt to avoid methanol promoting the unwanted side depicted in Scheme 4B. Pleasingly, relatively bulky DKPs **13b** and **13h** reacted with 4-fluorobenzylamine in THF at RT to afford 10-membered ring products **15a** and **15b** in 44% and 36% yield respectively. To the best of our knowledge,

7-membered bislactam derivatives of the form **13j–l** have not been used in ring expansion reactions of this type previously. We were therefore pleased to find that all three acryloyl imides **13j–l** participated well in CARE reactions with different functionalised primary amines, enabling the synthesis of 11-membered ring triamides **15c–i**.



Scheme 4. Conjugate Addition/Ring Expansion (CARE) cascade reactions.

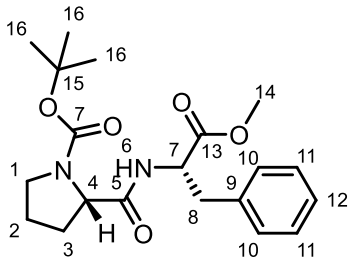
Conclusions

In summary, the Conjugate Addition/Ring Expansion (CARE) cascade approach has been successfully adapted for used in for the ring expansion of acryloyl imides derived from 6-membered ring diketopiperazines and 7-membered ring bislactams. This work expands the scope of an important cascade ring expansion reaction method and has enabled a library of diversely functionalised 10- and 11-membered ring cyclic triamides to be prepared, with the ring expansion products all containing three α- or β-amino acids in their cyclic scaffold. The formation of cyclic tripeptides via direct end-to-end cyclisation is notoriously challenging – the CARE approach represents versatile and practical way to synthesize these useful small cyclic peptide frameworks.[45-47]

Experimental Section

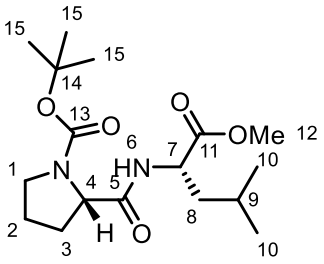
General. Anhydrous THF and CH_2Cl_2 was obtained from a PureSolv MD 5 solvent purification system/anhydrous solvent dispenser & pump. All other reagents and solvents were purchased from commercial sources and used directly without further purification. All experiments were carried out in oven-dried glassware under inert atmosphere (Argon) unless otherwise stated. Thin layer chromatography was carried out using Merck silica gel 60F254 pre-coated aluminium foil sheets and were visualised using UV light (254 nm) and stained with basic aqueous potassium permanganate. Flash column chromatography was carried out using Sigma-Aldrich high-purity grade silica gel (SiO_2) 35–70 µm, 60 Å, under a light positive pressure, eluting with the specified solvent system. Solvent systems used are written as a ratio of volumes. ^{1}H, ^{13}C and ^{19}F NMR experiments were recorded on a JEOL ECS400 spectrometer operating at 400 MHz, 100 and 376 MHz respectively. All spectroscopic data was acquired at 298 K unless stated otherwise. Chemical shifts (δ) are quoted in parts per million (ppm). The residual solvent peaks δ_H 7.26 and δ_C 77.16 for $CDCl_3$ were used as a reference. Coupling constants (J) are reported in Hertz (Hz) to the nearest 0.5 Hz. The multiplicity abbreviations used are: s singlet, d doublet, t triplet, q quartet, m multiplet, dd doublet of doublets, td triplet of doublets, tt triplet of triplets, ddd doublet of doublets of doublets, dddd doublet of doublet of doublet of doublets; where br indicates a broad signal. Signal assignment was achieved by analysis of COSY, HSQC and HMBC experiments where required. For ^{1}H NMR assignments of compound containing mixtures of rotamers, 1H represents 1 proton, 2H represents 2 protons etc, regardless of the ratio of rotamers present. Infrared (IR) spectra were recorded on a PerkinElmer IR UATR 2 spectrometer as a thin film dispersed from either CH_2Cl_2 or $CDCl_3$. High resolution mass spectra (HRMS) were obtained by the University of York Mass Spectrometry Service, using Electrospray Ionisation (ESI) on a Bruker Daltonics, Micro-tof spectrometer.

***tert*-Butyl (*S*)-2-(((*S*)-1-methoxy-1-oxo-3-phenylpropan-2-yl)carbamoyl)pyrrolidine-1-carboxylate**



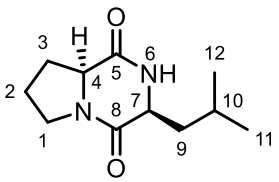
Boc-*L*-Proline-OH (1.00 g, 4.65 mmol, 1 equiv.), DCC (1.15 g, 5.58 mmol, 1.2 equiv.), NEt_3 (1.62 mL, 11.6 mmol, 2.5 equiv.) were dissolved in anhydrous CH_2Cl_2 (13 mL) at 0 °C, followed by the addition of HOBt (0.75 g, 5.58 mmol, 1.2 equiv.) and *L*-phenylalanine methyl ester hydrochloride (1.10 g, 5.11 mmol, 1.1 equiv.). The reaction was allowed to warm to room temperature and stirred for 18 h. The reaction mixture was filtered, and the filtrate was collected, then washed with sat. $NaHCO_{3(aq)}$ (20 mL × 3), 1 M aq. HCl (20 mL × 3) and brine (20 mL × 2). The collected organic extracts were dried over $MgSO_4$, filtered and concentrated in vacuo. Purification by flash column chromatography (9:1 hexane:ethyl acetate) yielded the title compound as a waxy white solid (1.58 g, 90%). R_f 0.25 (1:1 hexane:ethyl acetate); δ_H (400 MHz, $CDCl_3$) 7.18–7.07 (3H, m, C(12)H and C(10/12) 2 × H, 6.98 (2H, d, *J* = 7.0 Hz, C(10/12) 2 × H), 6.50 (1H, br s, N(6)H), 4.75 (1H, br s, C(7)H), 4.22–4.02 (1H, m, C(4)H), 3.59 (3H, s, C(14)H_3), 3.32–3.13 (2H, m, C(1)H_2), 3.07 (1H, dd, *J* = 14.0, 5.5 Hz, C(8)**H**H'), 2.89 (1H, dd, J = 14.0, 7.0 Hz, C(8)H**H'**), 2.19–1.57 (4H, m, C(2)H_2 and C(3)H_2), 1.30 (9H, s, C(16) 3 × H_3); HRMS (ESI) calcd. for $C_{20}H_{28}N_2NaO_5$ 399.1890 Found: $[MNa]^+$, 399.1890 (−0.2 ppm error). The spectroscopic data are in agreement with those reported in the literature.[37]

***tert*-Butyl (*S*)-2-(((*S*)-1-methoxy-4-methyl-1-oxopentan-2-yl)carbamoyl)pyrrolidine-1-carboxylate**



Boc-*L*-Proline-OH (2.00 g, 9.30 mmol, 1 equiv.), DCC (2.30 g, 11.16 mmol, 1.2 equiv.), NEt_3 (3.24 mL, 23.25 mmol, 2.5 equiv.) were dissolved in anhydrous CH_2Cl_2 26 mL) at 0 °C, followed by the addition of HOBt (1.50 g, 11.16 mmol, 1.2 equiv.) and *L*-Leucine methyl ester hydrochloride (1.86 g, 10.20 mmol, 1.1 equiv.). The reaction was allowed to warm to room temperature and stirred for 18 h. The reaction mixture was filtered, and the filtrate was collected, then washed with sat. $NaHCO_{3(aq)}$ (40 mL × 2), 1 M aq. HCl (40 mL × 2) and brine (40 mL × 2). The collected organic extracts were dried over $MgSO_4$, filtered and concentrated in vacuo. Purification by flash column chromatography (4:1 hexane:ethyl acetate) yielded the title compound as a waxy white solid (3.17 g, 9.25 mmol, 99%). R_f 0.06 (4:1 hexane:ethyl acetate); δ_H (400 MHz, $CDCl_3$) 4.66–4.46 (1H, m, C(7)H), 4.35–4.18 (1H, m, C(4)H), 3.70 (3H, s, C(12)H_3), 3.51–3.25 (2H, m, C(1)H_2), 1.96–1.77 (3H, m, C(8)H_2 and C(9)H), 1.73–1.50 (4H, m, C(2)H_2 and C(3)H_2), 1.45 (9H, s, C(15) 3H_3), 0.90 (6H, s, C(10) 2H_3); HRMS (ESI) calcd. for $C_{17}H_{30}N_2NaO_5$ 365.2047 Found: $[MNa]^+$, 365.2037 (3.4 ppm error). The spectroscopic data are in agreement with those reported in the literature.[38]

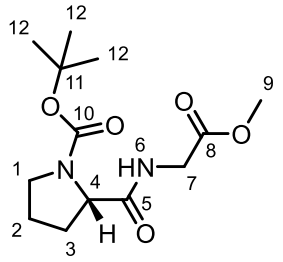
(3*S*,8a*S*)-3-Isobutylhexahydropyrrolo[1,2-a]pyrazine-1,4-dione (11b)



tert-Butyl (*S*)-2-(((*S*)-1-methoxy-4-methyl-1-oxopentan-2-yl)carbamoyl)pyrrolidine-1-carboxylate (1.47 g, 4.29 mmol, 1 equiv.) was dissolved in formic acid (44 mL) and stirred for 2 hours at room temperature. The solution was concentrated in vacuo, and the resulting oil was redissolved in a mixture of *s*-butanol (105 mL) and toluene

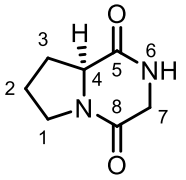
(37 mL). The reaction mixture was heated under reflux for 16 hours, allowed to cool to room temperature and concentrated in vacuo. Purification by flash column chromatography (hexane 1:4 ethyl acetate) afforded the title compound as a white solid (444 mg, 2.11 mmol, 49%). R_f 0.19 (1:4 hexane:ethyl acetate); m.p. 131 – 133 °C; $[\alpha]_D^{20}$ +128.5 (*c* 0.25, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 6.86 (1H, s, N(6)H), 4.07 (1H, app t, *J* = 8.5 Hz, C(7)H), 3.96 (1H, dd, *J* = 9.0, 3.5 Hz, C(4)H), 3.59–3.45 (2H, m, C(1)H_2), 2.33–2.25 (1H, m, C(9)**H**H'), 2.12–1.90 (3H, m, C(9)H**H'** , C(3)**H**H' and C(2)**H**H'), 1.90–1.73 (2H, m, C(10)H and C(2)H**H'**), 1.49 (1H, ddd, *J* = 14.5, 9.5, 4.5 Hz, C(3)H**H'**), 0.94 (3H, d, *J* = 6.5 Hz, C(11)H_3), 0.90 (3H, d, *J* = 6.5 Hz, C(12)H_3); δ_C (100 MHz, $CDCl_3$) 170.7 (C5/C8), 166.4 (C5/C8), 59.0 (C7), 53.5 (C4), 45.5 (C1), 38.5 (C3), 28.1 (C9), 24.6 (C10), 23.3 (C11/C12), 22.8 (C2), 21.4 (C11/C12); HRMS (ESI) calcd. for $C_{11}H_{19}N_2O_2$ 211.1441 Found: $[MH]^+$, 211.1444 (−1.2 ppm error). The spectroscopic data in are in agreement with those reported in the literature.[39]

***tert*-Butyl (*S*)-2-((2-methoxy-2-oxoethyl)carbamoyl)pyrrolidine-1-carboxylate**



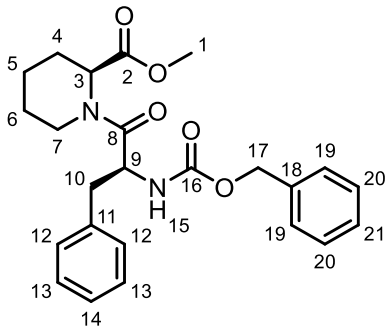
Boc-*L*-Proline-OH (1.00 g, 4.65 mmol, 1 equiv.), DCC (1.15 g, 5.58 mmol, 1.2 equiv.), NEt_3 (1.62 mL, 11.63 mmol, 2.5 equiv.) were dissolved in anhydrous CH_2Cl_2 (13 mL) at 0 °C, followed by the addition of HOBt (0.75 g, 5.58 mmol, 1.2 equiv.) and glycine methyl ester hydrochloride (642 mg, 5.11 mmol, 1.1 equiv.). The reaction was allowed to warm to room temperature and stirred for 18 h. The reaction mixture was filtered, and the filtrate was collected, then washed with sat. $NaHCO_{3(aq)}$ (20 mL × 3), 1 M aq. HCl (20 mL × 3) and brine (20 mL × 2). The collected organic extracts were dried over $MgSO_4$, filtered and concentrated in vacuo. Purification by flash column chromatography (1:1 hexane:ethyl acetate) yielded the title compound as a white solid as a 2:1 mixture of rotamers (1.10 g, 3.86 mmol, 83%). R_f 0.04 (7:3 hexane:ethyl acetate); ν_{max}/cm^{-1} (thin film) 3317, 2980, 1753, 1669, 1534, 1392, 1367, 1205, 1162, 1126, 733, 701; δ_H (400 MHz, DMSO-d_6) 8.27 (1H, t, *J* = 5.5 Hz, N(6)H, major rotamer), 8.22 (1H, t, *J* = 5.5 Hz, N(6)H, minor rotamer), 4.13 (1H, d, *J* = 8.5 Hz, C(4)H, minor rotamer), 4.09 (1H, d, *J* = 8.5 Hz, C(4)H, major rotamer), 3.90–3.76 (4H, m, C(7)H_2, both rotamers), 3.62 (6H, s, C(9)H_3, both rotamers), 3.42–3.34 (2H, m, C(1)**H**H', both rotamers), 3.31–3.23 (2H, m, C(1)H**H'**, both rotamers), 2.17–1.99 (2H, m, C(3)**H**H', both rotamers), 1.87–1.68 (6H, m, C(2)H_2, both rotamers and C(3)H**H'**, both rotamers), 1.39 (9H, s, C(12)C(CH_3)$_3$, minor rotamer), 1.33 (9H, s, C(12)C(CH_3)$_3$, major rotamer); δ_C (100 MHz, DMSO-d_6) 173.1 (C5/C8, major rotamer), 172.8 (C5/C8, minor rotamer), 170.3 (C5/C8, minor rotamer), 170.2 (C5/C8, major rotamer), 153.7 (C10, minor rotamer), 153.4 (C10, major rotamer), 78.6 (C11, minor rotamer), 78.6 (C11, major rotamer), 59.7 (C4, major rotamer), 59.4 (C4, minor rotamer), 51.6 (C9, both rotamers), 46.7 (C1, minor rotamer), 46.4 (C1, major rotamer), 40.5 (C7, both rotamers), 31.0 (C3, major rotamer), 29.9 (C3, minor rotamer), 28.1 (3 × C12, minor rotamer), 27.9 (3 × C12, major rotamer), 23.8 (C2, minor rotamer), 23.1 (C2, major rotamer); HRMS (ESI) calcd. for $C_{13}H_{22}N_2NaO_5$ 309.1421 Found: $[MNa]^+$, 309.1415 (1.3 ppm error).

(*S*)-Hexahydropyrrolo[1,2-a]pyrazine-1,4-dione (11c)



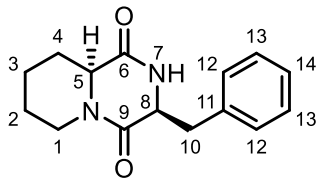
tert-Butyl (*S*)-2-((2-methoxy-2-oxoethyl)carbamoyl)pyrrolidine-1-carboxylate (190 mg, 0.66 mmol, 1 equiv.) was heated at 230 °C for 1 hour. Purification by column chromatography (ethyl acetate:hexane:methanol 5:4:1) afforded the title compound as an off white solid (64 mg, 0.41 mmol, 62%). R_f 0.09 (ethyl acetate); m.p. 135–138 °C; ν_{max}/cm^{-1} (thin film) 3204, 3114, 2888, 1678, 1648, 1458, 1297, 1005, 779, 499; δ_H (400 MHz, DMSO-d_6) 8.08 (1H, d, *J* = 4.5 Hz, N(6)H), 4.15–4.08 (1H, m, C(4)H), 3.99 (1H, dd, *J* = 16.5, 1.0 Hz, C(7)**H**H'), 3.50 (1H, dd, *J* = 16.5, 4.5 Hz, C(7)H**H'**), 3.45–3.30 (2H, m, C(1)H_2), 2.17–2.07 (1H, m, C(3)**H**H'), 1.90 (3H, m, C(2)H_2 and C(3)H**H'**); δ_C (100 MHz, DMSO-d_6) 169.3 (C8), 163.9 (C5), 58.0 (C4), 45.9 (C7), 44.7 (C1), 27.9 (C3), 22.1 (C2); HRMS (ESI) calcd. for $C_7H_{10}N_2NaO_2$ 177.0634 Found: [MNa]$^+$, 177.0642 (−1.3 ppm error). The spectroscopic data are in agreement with those reported in the literature.[40]

Methyl (*S*)-1-(((benzyloxy)carbonyl)-*L*-phenylalanyl)piperidine-2-carboxylate



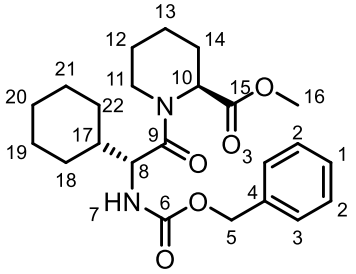
Methyl (*S*)-piperidine-2-carboxylate hydrochloride (1.00 g, 5.57 mmol, 1 equiv.), *N*-Cbz-*L*-phenylalanine (2.60 g, 6.12 mmol, 1.1 equiv.), HATU (2.33 g, 6.12 mmol, 1.1 equiv.) and DIPEA (3.88 mL, 22.3 mmol, 4 equiv.) in anhydrous DMF (20 mL) were stirred at room temperature for 18 hours. The reaction mixture was diluted with ethyl acetate (50 mL), then washed with sat. aq. NH_4Cl (50 mL × 2) and brine (50 mL × 3). The organic layer was collected, dried over $MgSO_4$, filtered and concentrated in vacuo. Purification by flash column chromatography (9:1 CH_2Cl_2:ethyl acetate) yielded the product as a clear oil (2.28 g, 5.36 mmol, 96%). In solution in $CDCl_3$, the product exists as a 4:1 mixture of rotamers. R_f 0.48 (9:1 CH_2Cl_2:ethyl acetate); $[\alpha]_D^{20}$ −21.3 (*c* 0.50, $CHCl_3$); ν_{max}/cm^{-1} (thin film); 3301, 3063, 2948, 2861, 1715, 1637, 1527, 1497, 1445, 1434, 1338, 1211, 1161, 911, 734, 698; δ_H (400 MHz, $CDCl_3$) NMR data for the major rotamer only 7.38–7.17 (10H, m, ArH), 5.66 (1H, d, *J* = 8.0 Hz, N(15)H), 5.40 (1H, d, *J* = 5.0 Hz, C(3)H), 5.12–4.95 (3H, m, C(9)H and C(17)H_2), 3.85–3.77 (1H, m, C(7)**H**H'), 3.75 (3H, s, C(1)H_3), 3.18–3.04 (2H, m, C(7)H**H'** and C(10)**H**H'), 2.87 (1H, dd, *J* = 13.5, 6.5 Hz, C(10)H**H'**), 2.31–2.22 (1H, m, C(5)**H**H'), 1.80–1.04 (5H, m, C(4)H_2, C(5)H**H'** and C(6)H_2); δ_C (100 MHz, $CDCl_3$) NMR data for the major rotamer only 171.5 (C2), 170.9 (C8), 155.7 (C16), 136.5 (ArC), 136.0 (ArC), 129.8 (ArC), 128.5 (ArC), 128.4 (ArC), 128.1 (ArC), 128.0 (ArC), 126.9 (ArC), 66.8 (C17), 52.4 (C1), 52.3 (C3), 51.8 (C9), 43.6 (C7), 38.6 (C10), 26.7 (C5), 25.4 (C4), 21.0 (C6); HRMS (ESI) calcd. for $C_{24}H_{28}N_2NaO_5$ 447.1890 Found: [MNa]$^+$, 447.1883 (1.3 ppm error). Diagnostic NMR resonances for the minor rotamer can be found at: δ_H (400 MHz, $CDCl_3$) 5.76 (1H, d, *J* = 8.0 Hz, N(15)H), 3.63 (3H, s, C(1)H_3); δ_C (100 MHz, $CDCl_3$) 171.6 (C2), 170.8 (C8), 155.5 (C18).

(3*S*,9a*S*)-3-Benzylhexahydro-4H-pyrido[1,2-a]pyrazine-1,4(6H)-dione (11d)



Methyl (*S*)-1-(((benzyloxy)carbonyl)-L-phenylalanyl)piperidine-2-carboxylate (2.13 g, 5.02 mmol, 1 equiv.) was added to an argon-purged round bottom flask, and dissolved in anhydrous methanol (100 mL). 10wt.% Pd/C (100 mg, 0.15 mmol, 0.03 equiv.) was added to the round bottom flask. The reaction mixture was purged with hydrogen and stirred under a hydrogen atmosphere for 24 hours. The reaction was filtered through Celite, and the filtrate was concentrated in vacuum. Purification by flash column chromatography (1:9 ethyl acetate:methanol) yielded the product as a waxy white solid (939 mg, 3.64 mmol, 72%). R_f 0.06 (ethyl acetate); $[\alpha]_D^{20}$ −30.0 (*c* 0.50, $CHCl_3$); ν_{max}/cm^{-1} (thin film) 3327, 2946, 2859, 1675, 1635, 1465, 1444, 1340, 1322, 911, 747, 727, 701, 591, 493; δ_H (400 MHz, $CDCl_3$) 7.91 (1H, br s, N(7)H), 7.33–7.27 (2H, m, C(12/13)2H), 7.27–7.19 (2H, m, C(12/13)2H and C(14)H), 4.62 (1H, ddt, *J* = 13.0, 4.0, 2.0 Hz, C(1)**H**H'), 4.35 (1H, q, *J* = 4.5 Hz, C(8)H), 3.55 (1H, dd, *J* = 12.5, 2.0 Hz, C(5)H), 3.34 (1H, dd, *J* = 13.5, 4.5 Hz, C(10)**H**H'), 2.97 (1H, dd, *J* = 13.5, 4.5 Hz, C(10)H**H'**), 2.31 (1H, td, *J* = 13.0, 2.5 Hz, C(1)H**H'**), 1.80 (1H, dd, *J* = 13.0, 2.5 Hz, C(4)**H**H'), 1.59 (1H, d, *J* = 13.0 Hz, C(3)**H**H'), 1.52 (1H, d, *J* = 13.0 Hz, C(2)**H**H'), 1.29 (1H, qt, *J* = 13.0, 4.0 Hz, C(3)H**H'**), 1.09 (1H, qt, *J* = 13.0, 4.0 Hz, C(2)H**H'**), −0.19 (1H, qd, *J* = 13.0, 4.0 Hz, C(4)H**H'**); δ_C (100 MHz, $CDCl_3$) 168.1 (C6), 162.9 (C9), 135.2 (C11), 130.9 (2 × C12/C13), 128.6 (2 × C12/C13), 127.4 (C14), 58.9 (C5), 55.9 (C8), 42.6 (C1), 40.6 (C10), 30.0 (C4), 24.3 (C3), 24.1 (C2); HRMS (ESI) calcd. for $C_{15}H_{19}N_2O_2$ 259.1441 Found: $[MH]^+$, 259.1453 (−0.6 ppm error).

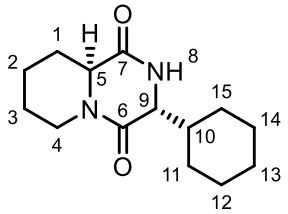
Methyl (2*S*)-1-[(2*R*)-2-(benzyloxycarbonylamino)-2-cyclohexyl-acetyl]piperidine-2-carboxylate



Methyl (2*S*)-piperidine-2-carboxylate hydrochloride (1.00 g, 5.56 mmol, 1 equiv.), *N*-Cbz-*D*-cyclohexylglycine (1.76 g, 6.06 mmol, 1.1 equiv.), HATU (2.30 g, 6.06 mmol, 1.1 equiv.) and DIPEA (3.90 mL, 22.26 mmol, 4 equiv.) in anhydrous DMF (20 mL) were stirred at room temperature for 18 hours. The reaction mixture was diluted with ethyl acetate (50 mL), then washed with sat. aq. NH_4Cl (50 mL × 2) and brine (50 mL × 3). The organic layer was collected, dried over $MgSO_4$, filtered and concentrated in vacuo. Purification by flash column chromatography (1:50 MeOH:CH_2Cl_2) yielded the product as a clear oil (2.28 g, 5.36 mmol, 96%). R_f 0.80 (1:50 MeOH:CH_2Cl_2); $[\alpha]_D^{20}$ +2.5 (*c* 1.00, $CHCl_3$); ν_{max}/cm^{-1} (thin film) 3289, 3032, 2928, 2853, 1736, 1715, 1636, 1527, 1499, 1446, 1338, 1324, 1300, 1282, 1231, 1215, 1163, 1142, 1108, 1080, 1057, 1019, 911, 857, 821, 797, 775, 697, 654, 604; δ_H (400 MHz, $CDCl_3$) 7.34–7.25 (5 H, m, C(1)H, C(2)2H and C(3)2H), 5.65 (1 H, d, *J* = 9.0 Hz, N(7)H), 5.33–5.29 (1 H, m, C(10)H), 5.08–5.06 (2 H, m, C(5)H_2), 4.62 (1 H, dd, *J* = 9.0, 5.5 Hz, C(8)H), 3.87–3.80 (1 H, m, C(11)**H**H'), 3.69 (3 H, s, C(16)H_3), 3.30–3.22 (1 H, m, C(11)H**H'**), 2.33–2.24 (1 H, m, C(17)H), 1.74–0.96 (16 H, m, C(12)H_2, C(13)H_2, C(14)H_2, C(18)H_2, C(19)H_2, C(20)H_2, C(21)H_2 and C(22)H_2); δ_C (100 MHz, $CDCl_3$) 171.6 (C15),

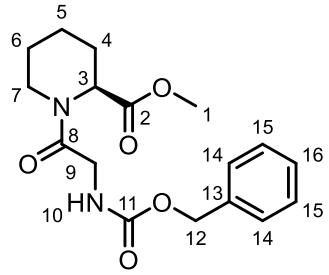
171.3 (C9), 156.4 (C6), 136.5 (C4), 128.6 (2 × C2/C3), 128.1 (C1), 128.0 (2 × C2/C3), 66.9 (C5), 55.2 (C8), 52.5 (C10), 52.4 (C16), 43.9 (C11), 41.9 (C17), 30.1 (C12), 27.5 (C18/C22), 26.9 (C18/C22), 26.3 (C19/C21), 26.2 (C19/C21), 26.1 (C14), 25.5 (C20), 21.0 (C13); HRMS (ESI) calcd. for $C_{23}H_{32}N_2NaO_5$ 439.2203 Found: $[MNa]^+$, 439.2206 (−0.5 ppm error).

(3*R*,9*aS*)-3-cyclohexyl-3,6,7,8,9,9*a*-hexahydro-2*H*-pyrido[1,2-a]pyrazine-1,4-dione (11e)



Methyl (2*S*)-1-[(2*R*)-2-(benzyloxycarbonylamino)-2-cyclohexyl-acetyl]piperidine-2-carboxylate (2.08 g, 5.01 mmol) was added to an argon-purged round bottom flask, and dissolved in anhydrous methanol (100 mL). 10wt.% Pd/C (100 mg, 0.15 mmol, 0.03 equiv.) was added to the round bottom flask. The reaction mixture was purged with hydrogen, and stirred under a hydrogen atmosphere for 24 hours. The reaction was filtered through celite, and the filtrate was concentrated in vacuum. Purification by flash column chromatography (1:50 methanol:CH_2Cl_2) yielded the product as a waxy white solid (875 mg, 3.49 mmol, 70%). R_f 0.75 (1:50 methanol:CH_2Cl_2); $[\alpha]_D^{20}$ +2.8 (*c* 1.00, $CHCl_3$); ν_{max}/cm^{-1} (thin film) 3229, 2924, 2853, 1676, 1654, 1648, 1444, 1370, 1330, 1313, 1272, 1258, 1233, 1149, 1122, 1081, 1036, 973, 897, 851, 793, 697, 578, 480; δ_H (400 MHz, $CDCl_3$) 6.25 (1 H, br s, N(8)H), 4.67–4.73 (1 H, m, C(4)**H**H'), 3.85 (1 H, s, C(5)H), 3.79 (1 H, dd, *J* = 11.5, 2.5 Hz, C(9)H), 2.49 (1 H, td, *J* = 13.0, 2.5 Hz, C(4)H**H'**), 2.39–2.34 (1 H, m, C(10)H), 2.10 (1 H, tq, *J* = 12.5, 3.0 Hz, C(1)**H**H'), 1.99–1.94 (1 H, m, C(1)H**H'**), 1.82–1.17 (14H, m, C(2)H_2, C(3)H_2, C(11)H_2, C(12)H_2, C(13)H_2, C(14)H_2 and C(15)H_2; δ_C (100 MHz, $CDCl_3$) 168.1 (C7), 164.5 (C6), 60.0 (C5), 58.2 (C9), 43.0 (C4), 42.6 (C10), 31.2 (C1), 29.3 (C11/C15), 26.3 (C11/C15), 26.2 (C13), 25.9 (C12/C14), 25.7 (C12/C14), 24.6 (C3), 24.3 (C2); HRMS (ESI) calcd. for $C_{14}H_{22}N_2NaO_2$ 273.1573 Found: $[MNa]^+$, 273.1581 (−2.7 ppm error).

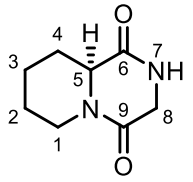
Methyl (*S*)-1-(((benzyloxy)carbonyl)glycyl)piperidine-2-carboxylate



Methyl (*S*)-piperidine-2-carboxylate hydrochloride (1.00 g, 5.57 mmol, 1 equiv.), *N*-Cbz-glycine (1.28 g, 6.12 mmol, 1.1 equiv.), HATU (2.33 g, 6.12 mmol, 1.1 equiv.) and DIPEA (3.88 mL, 22.3 mmol, 4 equiv.) in anhydrous DMF (20 mL) were stirred at room temperature for 18 hours. The reaction mixture was diluted with ethyl acetate (50 mL), then washed with sat. aq. NH_4Cl (50 mL × 2) and brine (50 mL × 3). The organic layer was collected, dried over $MgSO_4$, filtered and concentrated in vacuo. Purification by flash column chromatography (9:1 CH_2Cl_2:ethyl acetate) yielded the product as a clear oil (1.77 g, 5.30 mmol, 95%). In solution in $CDCl_3$, the product exists as a 4:1 mixture of rotamers. R_f 0.76 (9:1 CH_2Cl_2:ethyl acetate); $[\alpha]_D^{20}$ −45.9 (*c* 0.50, $CHCl_3$); ν_{max}/cm^{-1} (thin film); 3322, 2948, 2862, 1722, 1651, 1499, 1435, 1350, 1212, 1166, 1053, 1019, 740, 699; δ_H (400 MHz, $CDCl_3$)

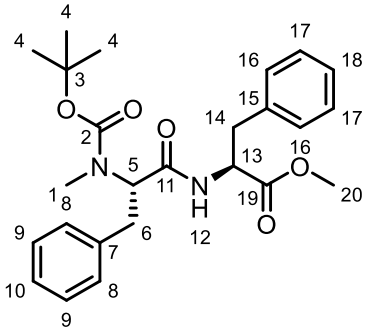
NMR data for the major rotamer only 7.39–7.28 (5H, m, 2 × C(14)H, 2 × C(15)H and C(16)H), 5.88–5.76 (1H, m, N(10)H), 5.31 (1H, d, *J* = 5.5 Hz, C(3)H), 5.12 (2H, s, C(12)H_2), 4.15 (1H, dd, *J* = 17.0, 4.0 Hz, C(9)**H**H'), 4.02 (1H, dd, *J* = 17.0 Hz, 4.0 Hz, C(9)H**H'**), 3.77 (3H, s, C(1)H_3), 3.63–3.55 (1H, m, C(7)**H**H'), 3.23 (1H, td, *J* = 13.5, 3.0 Hz, C(7)H**H'**), 2.27 (1H, d, *J* = 13.5 Hz, C(4)**H**H'), 1.78–1.59 (3H, m, C(4)H**H'**, C(5)**H**H' and C(6)**H**H'), 1.52–1.29 (2H, m, C(5)H**H'** and C(6)H**H'**); δ_C (100 MHz, $CDCl_3$) NMR data for the major rotamer only 171.5 (C2), 168.2 (C8), 156.3 (C11), 136.6 (C13), 128.6 (2 × C14/15), 128.2 (C16), 128.1 (2 × C14/15), 67.0 (C12), 52.5 (C1), 52.5 (C3), 43.0 (C9), 42.4 (C7), 26.6 (C4), 25.0 (C6), 20.9 (C5); HRMS (ESI) calcd. for $C_{17}H_{22}KN_2O_5$ 373.1160 Found: $[MK]^+$, 373.1159 (0.2 ppm error). Diagnostic NMR resonances for the minor rotamer can be found at: δ_H (400 MHz, $CDCl_3$) 3.76 (3H, s, C(1)H_3); δ_C (100 MHz, $CDCl_3$) 170.7 (C2), 167.8 (C8), 42.7 (C9), 40.1 (C7). HRMS (ESI) calcd. for $C_{17}H_{22}KN_2O_5$ 373.1160 Found: $[MK]^+$, 373.1159 (0.2 ppm error).

(*S*)-Hexahydro-4H-pyrido[1,2-a]pyrazine-1,4(6H)-dione (11f)



Methyl (*S*)-1-(((benzyloxy)carbonyl)glycyl)piperidine-2-carboxylate (1.65 g, 4.93 mmol, 1 equiv.) was added to an argon-purged round bottom flask and dissolved in anhydrous methanol (93 mL). Pd/C (98 mg, 0.15 mmol, 0.03 equiv.) was added to the round bottom flask in anhydrous methanol (5 mL). The reaction mixture was purged with hydrogen and stirred under a hydrogen atmosphere for 24 hours. The reaction was filtered through Celite, and the filtrate was concentrated in vacuum. Purification by flash column chromatography (5:4:1 hexane:ethyl acetate:methanol) yielded the product as a white solid (514 mg, 3.06 mmol, 62%). R_f 0.18 (5:4:1 hexane:ethyl acetate:methanol); m.p. 134–136°C; $[\alpha]_D^{20}$ −22.9 (*c* 0.13, $CHCl_3$); ν_{max}/cm^{-1} (thin film) 3254, 2942, 2860, 1679, 1645, 1470, 1446, 1329, 1122; δ_H (400 MHz, DMSO-d_6) 8.03 (1H, br s, N(7)H), 4.37 (1H, dd, *J* = 13.0, 2.0 Hz, C(1)**H**H'), 3.87–3.71 (3H, m, C(5)H and C(8)H_2), 2.53–2.44 (1H, m, C(1)H**H'**), 2.09–2.01 (1H, m, C(4)**H**H'), 1.85–1.77 (1H, m, C(3)**H**H'), 1.64–1.56 (1H, m, C(2)**H**H'), 1.50 (1H, qt, *J* = 13.0, 3.5 Hz, C(3)H**H'**), 1.37 (1H, qd, *J* = 13.0, 3.5 Hz, C(4)H**H'**), 1.24 (1H, qt, *J* = 13.0, 3.5 Hz, C(2)H**H'**); δ_C (100 MHz, DMSO-d_6) 166.5 (C6), 162.2 (C9), 57.9 (C5), 43.9 (C8), 41.5 (C1), 30.1 (C4), 24.3 (C2), 23.7 (C3); HRMS (ESI) calcd. for $C_8H_{12}N_2NaO_2$ 191.0791 Found: $[MNa]^+$, 191.0802 (−3.7 ppm error).

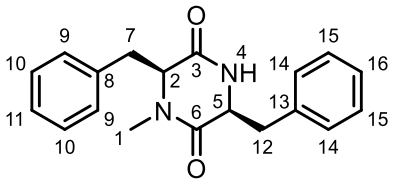
Methyl *N*-(*tert*-butoxycarbonyl)-*N*-methyl-*L*-phenylalanyl-*L*-phenylalaninate



N-Me-*L*-Phenylalanine-OH (1.00 g, 3.58 mmol, 1 equiv.), DCC (0.890 g, 4.30 mmol, 1.2 equiv.), NEt_3 (1.25 mL, 8.95 mmol, 2.5 equiv.) were dissolved in anhydrous CH_2Cl_2 (10 mL) at 0 °C, followed by the addition of HOBt

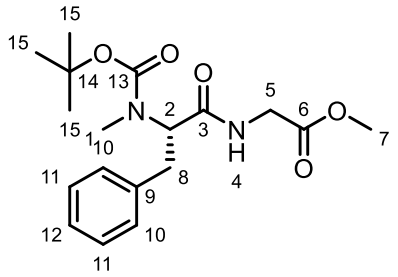
(0.580 g, 4.30 mmol, 1.2 equiv.) and *L*-phenylalanine methyl ester hydrochloride (1.24 g, 5.75 mmol, 1.6 equiv.). The reaction was allowed to warm to room temperature and stirred for 18 h. The reaction mixture was filtered, and the filtrate was collected, then washed with sat. $NaHCO_{3(aq)}$ (20 mL × 3), 1 M aq. HCl (20 mL × 3) and brine (20 mL × 2). The collected organic extracts were dried over $MgSO_4$, filtered and concentrated in vacuo. Purification by flash column chromatography (4:1 hexane:ethyl acetate) yielded the title compound as a clear oil as a 1:1 mixture of rotamers (1.50 g, 3.40 mmol, 95%). R_f 0.19 (4:1 hexane:ethyl acetate); ν_{max}/cm^{-1} (thin film) 3343, 2976, 1743, 1682, 1498, 1455, 1391, 1367, 1322, 1215, 1167, 746, 700; δ_H (400 MHz, $CDCl_3$) 7.31–7.03 (20H, m, C(8)2H, C(9)2H, C(10)H, C(16)2H, C(17)2H and C(18)H, both rotamers) 6.53 (1H, d, *J* = 7.0 Hz, N(12)H, single rotamer), 6.28 (1H, d, *J* = 7.0 Hz, N(12)H, single rotamer), 4.95 – 4.73 (4H, m, C(5)H and C(13)H, both rotamers), 3.73 (3H, s, C(20)H_3, single rotamer), 3.69 (3H, s, C(20)H_3, single rotamer) 3.34–3.21 (2H, m, C(6)**H**H', both rotamers), 3.18 (2H, dd, *J* = 14.0, 5.5 Hz, C(14)**H**H', both rotamers), 3.08–2.95 (2H, m, C(14)H**H'**, both rotamers), 2.93–2.75 (2H, m, C(6)H**H'**, both rotamers), 2.56 (3H, s, C(1)H_3, single rotamer), 2.48 (3H, s, C(1)H_3, single rotamer), 1.34 (9H, s, C(4)3CH_3, single rotamer), 1.22 (9H, s, C(4)3CH_3, single rotamer); δ_C (100 MHz, $CDCl_3$) 171.8 (C19, single rotamer), 171.8 (C19, single rotamer), 170.5 (C11, single rotamer), 170.2 (single rotamer), 156.4 (C2, single rotamer), 155.0 (C2, single rotamer), 137.9 (C7/C15, single rotamer), 137.5 (C7/C15, single rotamer), 136.1 (C7/C15, single rotamer), 135.7 (C7/C15, single rotamer), 129.3–128.4 (16C, 2 × C8, 2 × C9, 2 × C16 and 2 × C17, both rotamers), 127.4 (C10/C18, single rotamer), 127.1 (C10/C18, single rotamer), 126.7 (C10/C18, single rotamer), 126.5 (C10/C18, single rotamer), 80.9 (C3, single rotamer), 80.5 (C3, single rotamer), 61.1 (C5, single rotamer), 59.4 (C5, single rotamer), 53.2 (C13, both rotamers), 52.5 (C20, both rotamers), 38.1 (C14, both rotamers), 33.9 (C6, both rotamers), 30.7 (C1, single rotamer), 30.1 (C1, single rotamer), 28.3 (3 × C4, single rotamer), 28.1 (3 × C4, single rotamer); HRMS (ESI) calcd. for $C_{25}H_{32}N_2NaO_5$ 463.2203 Found: $[MNa]^+$, 463.2213 (−2.0 ppm error).

(3*S*,6*S*)-3,6-Dibenzyl-1-methylpiperazine-2,5-dione (11g)



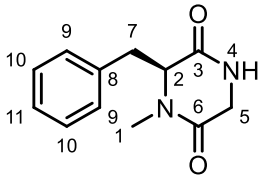
Methyl *N*-(*tert*-butoxycarbonyl)-*N*-methyl-*L*-phenylalanyl-*L*-phenylalaninate (100 mg, 0.23 mmol, 1 equiv.) was heated at 230°C for 1 hour. Purification by column chromatography (ethyl acetate 4:1 CH_2Cl_2) afforded the title compound as a white solid (49 mg, 5.36 mmol, 70%). R_f 0.26 (1:4 hexane:ethyl acetate); ν_{max}/cm^{-1} (thin film) 3223, 3029, 2930, 1678, 1646, 1497, 1455, 1405, 1048, 1031, 747, 701; δ_H (400 MHz, $CDCl_3$) 7.39 (2H, t, *J* = 7.5 Hz, ArH), 7.32–7.23 (3H, m, ArH), 7.21–7.14 (3H, m, ArH), 6.93–6.89 (2H, m, ArH), 5.93 (1H, s, N(4)H), 4.17 (1H, t, *J* = 4.0 Hz, C(2)H), 3.87 (1H, dt, *J* = 11.5, 3.0 Hz, C(5)H), 3.14 (2H, dq, *J* = 12.0, 4.0 Hz, C(7)H_2), 3.08 (3H, s, C(1)H_3), 2.87 (1H, dd, *J* = 13.5, 3.0 Hz, C(12)**H**H'), 0.85 (1H, dd, *J* = 13.5, 11.5 Hz, C(12)H**H'**); δ_C (100 MHz, $CDCl_3$) 165.8 (C3), 165.5 (C6), 136.2 (C8/C13), 135.0 (C8/C13), 130.5 (2×C9/C10/C14/C15), 129.3 (2×C9/C10/C14/C15), 129.2 (2×C9/C10/C14/C15), 129.0 (2×C9/C10/C14/C15), 127.9 (C11/C16), 127.3 (C11/C16), 63.2 (C2), 56.9 (C5), 40.7 (C12), 36.7 (C7), 33.3 (C1); HRMS (ESI) calcd. for $C_{19}H_{20}N_2NaO_2$ 331.1417 Found: $[MNa]^+$, 331.1426 (−2.6 ppm error). The spectroscopic data are in agreement with those reported in the literature.[41]

Methyl *N*-(*tert*-butoxycarbonyl)-*N*-methyl-*L*-phenylalanylglycinate



Boc-*N*-Me-*L*-Phenylalanine-OH (1 g, 3.58 mmol, 1 equiv.), DCC (0.89 g, 4.30 mmol, 1.2 equiv.), NEt_3 (1.25 mL, 8.95 mmol, 2.5 equiv.) were dissolved in anhydrous CH_2Cl_2 (13 mL) at 0 °C, followed by the addition of HOBt (0.58 g, 4.30 mmol, 1.2 equiv.) and glycine methyl ester hydrochloride (495 mg, 3.94 mmol, 1.1 equiv.). The reaction was allowed to warm to room temperature and stirred for 18 h. The reaction mixture was filtered, and the filtrate was collected, then washed with sat. $NaHCO_{3(aq)}$ (20 mL × 3), 1 M aq. HCl (20 mL × 3) and brine (20 mL × 2). The collected organic extracts were dried over $MgSO_4$, filtered and concentrated in vacuo. Purification by flash column chromatography (19:1 CH_2Cl_2:ethyl acetate) yielded the title compound as a white solid as a 2:1 mixture of rotamers (813 mg, 2.32 mmol, 65%). R_f 0.17 (9:1 hexane:ethyl acetate); ν_{max}/cm^{-1} (thin film); 3333, 2976, 1755, 1668, 1519, 1453, 1439, 1390, 1367, 1322, 1206, 1165, 1140, 752, 700, 483; δ_H (400 MHz, DMSO-d_6) 8.41–8.31 (2H, m, N(4)H, both rotamers), 7.33–7.12 (10H, m, C(10)2H, C(11)2H and C(12)H, both rotamers), 4.95 (1H, dd, *J* = 7.0, 4.0 Hz, C(2)H, minor rotamer), 4.73 (1H, dd, *J* = 11.0, 4.0 Hz, C(2)H, major rotamer), 3.95–3.75 (4H, m, C(5)H_2, both rotamers), 3.64 (6H, s, C(7)H_3, both rotamers), 3.21–3.13 (2H, m, C(8)**H**H', both rotamers), 2.88–2.78 (2H, m, C(8)H**H'**, both rotamers), 2.69 (6H, s, C(1)H_3, both rotamers), 1.25 (9H, s, C(15)3CH_3, minor rotamer), 1.16 (9H, s, C(15)3CH_3, major rotamer); δ_C (100 MHz, DMSO-d_6) 170.9 (C3/C6, minor rotamer), 170.6 (C3/C6, major rotamer), 170.3 (C3/C6, both rotamers), 155.3 (C13, minor rotamer), 154.5 (C13, major rotamer), 138.4 (C9, major rotamer), 137.9 (C9, minor rotamer), 129.1 (2 × C10/C11, major rotamer), 128.9 (2 × C10/C11, minor rotamer), 128.3 (2 × C10/C11, major rotamer), 128.1 (2 × C10/C11, minor rotamer), 126.2 (C12, both rotamers), 78.9 (C14, both rotamers), 60.4 (C2, major rotamer), 58.4 (C2, minor rotamer), 51.8 (C7, both rotamers), 40.9 (C5, major rotamer), 40.8 (C5, minor rotamer), 34.2 (C8, both rotamers), 30.5 (C1, both rotamers), 28.0 (3 × C15, minor rotamer), 27.7 (3 × C15, major rotamer); HRMS (ESI) calcd. for $C_{18}H_{26}KN_2O_5$ 389.1473 Found: $[MK]^+$, 389.1469 (−0.2 ppm error).

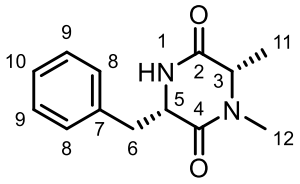
(*S*)-6-Benzyl-1-methylpiperazine-2,5-dione (11h)



Methyl *N*-(*tert*-butoxycarbonyl)-*N*-methyl-*L*-phenylalanylglycinate, (813 mg, 2.32 mmol, 1 equiv.) was heated at 230 °C for 1 hour. Purification by column chromatography (ethyl acetate) afforded the title compound as an off white solid (486.4 mg, 2.32 mmol, 96%). R_f 0.11 (ethyl acetate); m.p. 82–85°C; ν_{max}/cm^{-1} (thin film); 3240, 2935, 1652, 1455, 1406, 1328, 1125, 1079, 1034, 736, 703; δ_H (400 MHz, DMSO-d_6) 7.98 (1H, d, *J* = 2.5 Hz, N(4)H), 7.30–7.25 (3H, m, C(11)H and C(9/10)2H), 7.12–7.07 (2H, m, C(9/10)2H), 4.17 (1H, br t, *J* = 4.5 Hz, C(2)H), 3.24 (1H, dd, *J* = 17.0, 3.5 Hz, C(5)**H**H'), 3.13 (1H, dd, *J* = 14.0, 5.0 Hz, C(7)**H**H'), 3.05 (1H, dd, *J* = 14.0, 4.0 Hz, C(7)H**H'**), 2.88 (3H, s, C(1)H), 2.33 (1H, d, *J* = 17.0 Hz, C(5)H**H'**); δ_C (100 MHz, DMSO-d_6) 167.1 (C6), 164.2 (C3), 135.5 (C8),

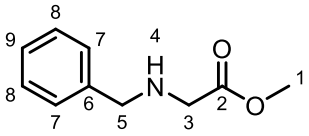
129.8 (2 × C9/C10), 128.3 (2 × C9/C10), 127.2 (C11), 62.6 (C2), 43.3 (C5), 36.0 (C7), 31.8 (C1); HRMS (ESI) calcd. for $C_{12}H_{14}KN_2O_2$ 257.0687 Found: $[MK]^+$, 257.0691 (0.2 ppm error).

(3S,6S)-3-Benzyl-1,6-dimethylpiperazine-2,5-dione (11i)



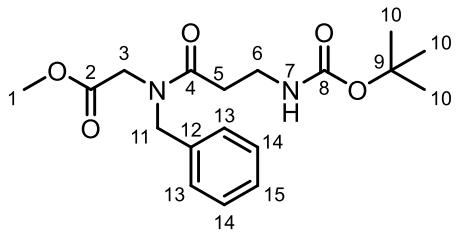
A solution of Boc-*N*-Me-Ala-OH (0.95 g, 4.65 mmol, 1 equiv.) in anhydrous CH_2Cl_2 (12 mL) was cooled to 0°C before the addition of *N*,*N*'-dicyclohexylcarbodiimide (DCC, 1.15 g, 5.58 mmol, 1.2 equiv.) and triethylamine (1.62 mL, 11.63 mmol, 2.5 equiv.). To the cooled solution was then added hydroxybenzotriazole (HOBt, 0.75 g, 5.58 mmol, 1.2 equiv.) and L-phenylalanine methyl ester hydrochloride (1.10 g, 5.11 mmol, 1.1 equiv.) after which the solution was warmed to room temperature and stirred overnight. Cyclohexylurea-derived byproducts were removed from the reaction mixture *via* gravity filtration before the filtrate was washed with sat. $NaHCO_3$ (20 mL), 1% HCl (20 mL), and brine (20 mL). The organic extracts were then dried over $MgSO_4$ and concentrated *in vacuo* to give the crude material as a pale-yellow oil. The crude dipeptide *N*-Me-Boc-Ala-Phe-OMe (1.05 g, 2.88 mmol, 1 equiv.) was heated in a sealed tube without solvent at 230 °C for 2 h. After this time, the reaction mixture was purified by FCC (SiO_2, 19:1; ethyl acetate: methanol) to afford the title compound as a waxy white solid (568 mg, 2.44 mmol, 53%). R_f = 0.10 (19:1; ethyl acetate: methanol); ν_{max}/cm^{-1} (thin film) 3235, 2933, 1682, 1654, 1456, 1340, 749, 702; δ_H (400 MHz, $CDCl_3$) 7.37–7.16 (5H, m, C(8)2H, C(9)2H and C(10)H), 6.43 (1H, br s, N(1)H), 4.32–4.24 (1H, m, C(5)H), 3.77 (1H, q, *J* = 7.0 Hz, C(3)H), 3.20–3.06 (2H, m, C(6)H_2), 2.91 (3H, s, C(12)H_3), 0.96 (3H, d, *J* = 7.0 Hz, C(11)H_3); δ_C (100 MHz, $CDCl_3$) 168.9 (C2), 164.9 (C4), 135.5 (C7), 130.3 (2 x C8/9), 128.7 (2 x C8/9), 127.4 (C10), 57.4 (C3), 56.7 (C5), 40.9 (C6), 32.3 (C12), 17.9 (C11); HRMS (ESI^+): calc. for $C_{13}H_{16}N_2NaO_2$, 255.1104. Found $[MNa]^+$ 255.1101. The data obtained match those previously reported.[42]

Methyl benzylglycinate



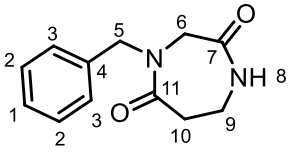
Benzyl glycine (1.00 g, 6.05 mmol, 1 equiv.) was dissolved in anhydrous methanol (40 mL), followed by the addition of thionyl chloride (1.7 mL, 23.3 mmol, 3.85 equiv.), and the reaction mixture was stirred for 18 hours at room temperature. The reaction mixture was quenched with sat. $NaHCO_{3(aq)}$ (50 mL), extracted with ethyl acetate (3 × 50 mL) and washed with brine (50 mL). The collected organic extracts were dried over $MgSO_4$, filtered and concentrated in vacuo to leave the title compound as a yellow oil (965 mg, 5.39 mmol, 89%). R_f 0.64 (1:1 methanol:ethyl acetate); δ_H (400 MHz, $CDCl_3$) 7.31 (4H, d, *J* = 4.5 Hz, C(7/8)4H), 7.27–7.21 (1H, m, C(9)H), 3.79 (2H, s, C(5)H_2), 3.70 (3H, s, C(1)H_3), 3.40 (2H, s, C(3)H_2), 1.99 (1H, s, N(4)H); HRMS (ESI) calcd. for $C_{10}H_{14}N_2O$ 180.1019 Found: $[MH]^+$, 180.1022 (0.7 ppm error). The spectroscopic data are in agreement with those reported in the literature.[28]

Methyl *N*-benzyl-*N*-(3-((*tert*-butoxycarbonyl)amino)propanoyl)glycinate



Methyl benzylglycinate (965 mg, 5.39 mmol, 1 equiv.), Boc-β-alanine-OH (1.12 g, 5.93 mmol, 1.1 equiv.), HATU (2.25 g, 5.93 mmol, 1.1 equiv.) and DIPEA (3.75 mL, 22.56 mmol, 4 equiv.) in anhydrous DMF (21 mL) were stirred at room temperature for 40 hours. The reaction mixture was diluted with ethyl acetate (50 mL), then washed with sat. aq. NH_4Cl (50 mL × 2) and brine (50 mL × 3). The organic layer was collected, dried over $MgSO_4$, filtered and concentrated in vacuo. Purification by flash column chromatography (7:3 hexane:ethyl acetate) yielded the product as a clear oil (1.88 g, 5.36 mmol, 99%). In solution in $CDCl_3$, the product exists as a 5:2 mixture of rotamers. R_f 0.39 (1:1 hexane:ethyl acetate); ν_{max}/cm^{-1} (thin film) 3355, 2977, 1748, 1704, 1645, 1497, 1437, 1366, 1249, 1199, 1167, 730, 698; δ_H (400 MHz, $CDCl_3$) 7.36–7.24 (6H, m, 2 × C(13/14)2H and C(15)H, both rotamers), 7.21–7.17 (2H, m, 2 × C(13/14)2H, minor rotamer), 7.16–7.12 (2H, m, 2 × C(13/14)2H, major rotamer), 5.39–5.25 (2H, m, N(7)H, both rotamers), 4.62 (2H, s, C(11)H_2, minor rotamer), 4.58 (2H, s, C(11)H_2, major rotamer), 4.03 (2H, s, C(3)H_2, major rotamer), 3.90 (2H, s, C(3)H_2, minor rotamer), 3.69 (3H, s, C(1)H_3, major rotamer), 3.67 (3H, s, C(1)H_3, minor rotamer), 3.47–3.39 (4H, m, C(6)H_2, both rotamers), 2.64 (2H, t, *J* = 5.5 Hz, C(5)H_2, major rotamer), 2.48 (2H, t, *J* = 5.5 Hz, C(5)H_2, minor rotamer), 1.41 (9H, s, 3 × C(10)CH_3, minor rotamer), 1.40 (9H, s, 3 × C(10)CH_3, major rotamer); δ_C (100 MHz, $CDCl_3$) 172.8 (C4, major rotamer), 172.4 (C4, minor rotamer), 169.8 (C2, major rotamer), 169.4 (C2, minor rotamer), 156.1 (C8, minor rotamer), 156,1 (C8, major rotamer), 136.5 (C12, minor rotamer), 135.7 (C12, major rotamer), 129.1 (2 × C13/14, major rotamer), 128.7 (2 × C13/14, minor rotamer), 128.4 (2 × C13/14, minor rotamer), 128.0 (C15, major rotamer), 127.8 (C15, minor rotamer), 126.8 (2 × C13/14, major rotamer), 79.1 (C9, both rotamers), 52.5 (C1, minor rotamer), 52.2 (C1, major rotamer), 52.0 (C11, major rotamer), 49.7 (C11, minor rotamer), 48.2 (C3, minor rotamer), 47.0 (C3, major rotamer), 36.4 (C6, both rotamers), 33.3 (C5, minor rotamer), 33.2 (C5, major rotamer), 28.5 (3 × C10, both rotamers); HRMS (ESI) calcd. for $C_{18}H_{26}N_2NaO_5$ 373.1734 Found: $[MNa]^+$, 373.1730 (1.0 ppm error).

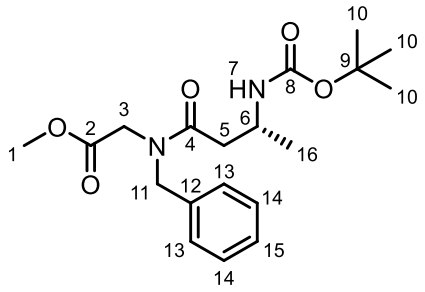
4-Benzyl-1,4-diazepane-2,5-dione (12a)



Methyl *N*-benzyl-*N*-(3-((*tert*-butoxycarbonyl)amino)propanoyl)glycinate (127 mg, 0.36 mmol, 1 equiv.) was dissolved in ethyl acetate (1.2 mL) and methanol (0.15 mL), and 12M hydrochloric acid (0.30 mL, 3.62 mmol, 10 equiv.) was added dropwise, and the reaction mixture was stirred at room temperature for 16 hours. The reaction mixture was concentrated under vacuum, and the resulting residue was redissolved in methanol (2 mL) and concentrated to dryness a further 3 times, to leave impure methyl *N*-(3-aminopropanoyl)-*N*-benzylglycinate as a yellow oil [HRMS (ESI) calcd. for $C_{13}H_{19}N_2O_3$ 251.1390 Found: $[MH]^+$, 251.1389 (3.6 ppm error)]. The impure product was dissolved in methanol (0.5 mL), and freshly prepared 3.34M sodium methoxide (made by adding 54 mg of sodium into 0.7 mL methanol) was added. The reaction mixture was stirred for 30 minutes, then

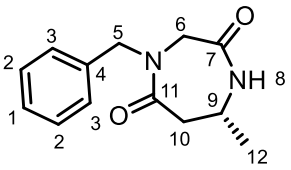
quenched with water (2 mL). The reaction mixture was extracted with CH_2Cl_2 (2 mL × 3), then washed with water (2 mL) and brine (2 mL). The combined organic layers were collected, dried over $MgSO_4$, filtered and concentrated in vacuo to yield the title compound as a white solid (26 mg, 0.12 mmol, 33%). R_f 0.06 (ethyl acetate); δ_H (400 MHz, $CDCl_3$) 7.36–7.22 (5H, m, C(1)H, C(2)2H and C(3)2H), 6.60 (1H, br s, N(7)H), 4.64 (2H, s, C(5)H_2), 4.00 (2H, s, C(6)H_2), 3.55–3.50 (2H, m, C(9)H_2), 2.95–2.91 (2H, m, C(10)H_2); HRMS (ESI) calcd. for $C_{12}H_{14}KN_2O_2$ 257.0687 Found: $[MK]^+$,257.0687 (2.3 ppm error). The spectroscopic data are in agreement with those reported in the literature.

Methyl (*R*)-*N*-benzyl-*N*-(3-((*tert*-butoxycarbonyl)amino)butanoyl)glycinate



Methyl benzylglycinate (840 mg, 4.69 mmol, 1 equiv.), (*R*)-3-((*tert*-butoxycarbonyl)amino)butanoic acid (1.05 g, 5.16 mmol, 1.1 equiv.), HATU (1.96 g, 5.16 mmol, 1.1 equiv.) and DIPEA (3.26 mL, 18.75 mmol, 4 equiv.) in anhydrous DMF (19 mL) were stirred at room temperature for 24 hours. The reaction mixture was diluted with ethyl acetate (50 mL), then washed with sat. aq. NH_4Cl (50 mL × 2) and brine (50 mL × 3). The organic layer was collected, dried over $MgSO_4$, filtered and concentrated in vacuo. Purification by flash column chromatography (4:1 hexane:ethyl acetate) yielded the product as a white waxy solid (1.69 g, 4.64 mmol, 99%). In solution in $CDCl_3$, the product exists as a 2:1 mixture of rotamers. R_f 0.45 (1:1 hexane:ethyl acetate); $[\alpha]_D^{20}$ +10.3 (*c* 0.50, $CHCl_3$); ν_{max}/cm^{-1} (thin film) 3336, 2977, 1748, 1704, 1644, 1497, 1452, 1366, 1247, 1200, 1168, 1058, 701; δ_H (400 MHz, $CDCl_3$) NMR data for the major rotamer only 7.37–7.25 (3H, m, C(15)H and C(13/14)2H), 7.21–7.14 (2H, m, C(13/14)2H), 5.42 (1H, br s, N(7)H), 4.72–4.52 (2H, m, C(12)H_2), 4.12–3.88 (3H, m, C(3)H_2 and C(6)H), 3.76 (3H, s, C(1)H_3), 2.74 (1H, dd, *J* = 15.5, 4.5 Hz, C(5)**H**H'), 2.66–2.52 (1H, m, C(5)H**H'**), 1.41 (9H, s, C(10)3H_3), 1.26 (3H, d, *J* = 7.0 Hz, C(16)H_3); δ_C (100 MHz, $CDCl_3$) NMR data for major rotamer only 172.2 (C4), 169.8 (C2), 155.4 (C8), 135.9 (C12), 129.1 (2 × C13/14), 128.0 (C15), 126.8 (2 × C13/14), 79.2 (C9), 52.4 (C11), 52.2 (C1), 47.1 (C3), 44.0 (C5), 38.4 (C6), 28.5 (3 × C10), 20.3 (C16); HRMS (ESI) calcd. for $C_{19}H_{28}N_2NaO_5$ 387.1890. Found: $[MNa]^+$, 387.1897 (−1.2 ppm error); Diagnostic NMR resonances for the minor rotamer can be found at: δ_H (400 MHz, $CDCl_3$) 3.69 (3H, s, C(1)H_3), 2.46–2.37 (1H, m, C(5)H**H'**), 1.28 (3H, d, *J* = 7.0 Hz, C(16)H_3); δ_C (100 MHz, $CDCl_3$) 169.6 (C2), 155.4 (C8), 136.6 (C12), 20.4 (C16).

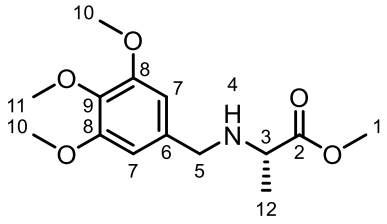
(*R*)-4-Benzyl-7-methyl-1,4-diazepane-2,5-dione (12b)



Methyl (*R*)-*N*-benzyl-*N*-(3-((*tert*-butoxycarbonyl)amino)butanoyl)glycinate (7.29 g, 20.0 mmol, 1 equiv.) was dissolved in ethyl acetate (67 mL) and methanol (9 mL), and 12M aq. hydrochloric acid (16.5 mL, 200.0 mmol, 10 equiv.) was added dropwise, and the reaction mixture was stirred at room temperature for 16 hours. The

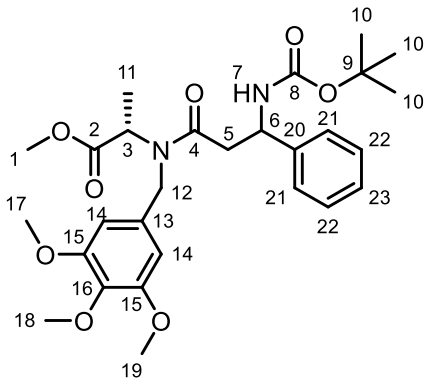
reaction mixture was concentrated under vacuum, and the resulting residue was redissolved in methanol (50 mL) and concentrated to dryness a further 3 times, to leave impure methyl *N*-(3-aminopropanoyl)-*N*-benzylglycinate as a yellow oil. HRMS (ESI) calcd. for $C_{14}H_{21}N_2O_3$ 265.1547 Found: $[MH]^+$, 265.1554 (−2.6 ppm error). The impure product was dissolved in methanol (20 mL), and freshly prepared 3.50 M sodium methoxide solution (made by adding 2.98 g sodium into 37 mL methanol) was added. The reaction mixture was stirred for 30 minutes, then quenched with water (50 mL). The reaction mixture was extracted with CH_2Cl_2 (50 mL × 3), then washed with water (50 mL) and brine (50 mL). The combined organic layers were collected, dried over $MgSO_4$, filtered and concentrated in vacuo. Purification by flash column chromatography (ethyl acetate → 9:1 ethyl acetate:methanol) yielded the title compound as a white solid (2.60 g, 11.2 mmol, 56%). R_f 0.06 (ethyl acetate); m.p. 92–94°C; $[\alpha]_D^{20}$ −6.9 (*c* 0.40, $CHCl_3$); ν_{max}/cm^{-1} (thin film) 3226, 2975, 1658, 1453. 905, 730, 701; δ_H (400 MHz, $CDCl_3$) 7.34–7.22 (5H, m, C(1)H, C(2)2H and C(3)2H), 6.55 (1H, br s, N(8)H), 4.69–4.58 (2H, m, C(5)H_2), 4.05 (1H, d, *J* = 17.5 Hz, C(6)**H**H'), 3.94 (1H, d, *J* = 17.5 Hz, C(6)H**H'**), 3.86–3.77 (1H, m, C(9)H), 2.88 (1H, dd, *J* = 14.5, 3.5 Hz, C(10)**H**H'), 2.80 (1H, dd, *J* = 14.5, 9.0 Hz, C(10)H**H'**), 1.27 (3H, d, *J* = 6.5 Hz, C(12)H_3); δ_C (100 MHz, $CDCl_3$) 170.7 (C11), 168.7 (C7), 136.5 (C4), 128.9 (2 × C2/3), 128.2 (2 × C2/3), 128.0 (C1), 52.6 (C6), 51.3 (C5), 47.3 (C9), 41.1 (C10), 23.6 (C12); HRMS (ESI) calcd. for $C_{13}H_{16}N_2NaO_2$ 255.1104 Found: $[MNa]^+$,255.1106 (0.3 ppm error).

Methyl (3,4,5-trimethoxybenzyl)-*L*-alaninate



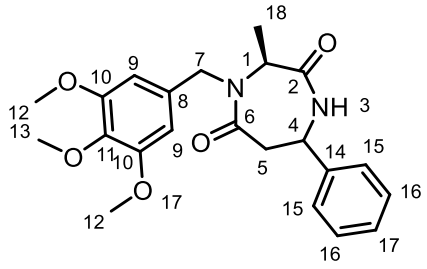
L-alanine-methyl-ester hydrochloride (200 mg, 1.43 mmol, 2 equiv.) was dissolved in anhydrous methanol (10 mL), followed by addition of acetic acid (41 µL, 0.72 mmol, 1 equiv.), 3,4,5-trimethoxybenzaldehyde (141 mg, 0.72 mmol, 1 equiv.) and sodium cyanoborohydride (54 mg, 0.86 mmol, 1.2 equiv.), and the reaction mixture was stirred at room temperature for 16 hours. The methanol was removed in vacuo, and the product was redissolved in dichloromethane (10 mL), and washed with water (10 mL) then brine (10 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated in vacuo. Purification by flash column chromatography (1:1 CH_2Cl_2:ethyl acetate) yielded the product as a clear oil (76 g, 0.27 mmol, 37%). R_f 0.22 (1:1 CH_2Cl_2:ethyl acetate); $[\alpha]_D^{20}$ –30.4 (*c* 0.50, $CHCl_3$); ν_{max}/cm^{-1} (thin film) 3329, 2940, 2839, 1733, 1590, 1506, 1455, 1420, 1327, 1233, 1154, 1121, 1007; δ_H (400 MHz, $CDCl_3$) 6.53 (2H, s, C(7)2H), 3.83 (6H, s, C(10)2H_3), 3.79 (3H, s, C(11)H_3), 3.72 (1H, d, *J* = 12.5 Hz, C(5)**H**H'), 3.71 (3H, s, C(1)H_3), 3.57 (1H, d, *J* = 12.5 Hz, C(5)H**H'**), 3.37 (1H, q, *J* = 7.0 Hz, C(3)H), 1.93 (1H, s, N(4)H), 1.30 (3H, d, *J* = 7.0 Hz, C(12)H_3); δ_C (100 MHz, $CDCl_3$) 176.2 (C2), 153.2 (2 × C8), 136.9 (C9), 135.5 (C6), 105.0 (2 × C7), 60.8 (C11), 56.1 (C10), 55.9 (C3), 52.3 (C5), 51.9 (C1), 19.2 (C12); HRMS (ESI) calcd. for $C_{14}H_{21}NNaO_5$ 306.1312. Found: $[MNa]^+$, 306.1323 (−2.4 ppm error).

Methyl *N*-(3-((*tert*-butoxycarbonyl)amino)-3-phenylpropanoyl)-*N*-(3,4,5-trimethoxybenzyl)-*L*-alaninate



Methyl (3,4,5-trimethoxybenzyl)-*L*-alaninate (582 mg, 2.05 mmol, 1 equiv.), 3-((*tert*-butoxycarbonyl)amino)-3-phenylpropanoic acid (600 mg, 2.26 mmol, 1.1 equiv.), HATU (856 mg, 2.26 mmol, 1.1 equiv.) and DIPEA (1.42 mL, 8.20 mmol, 4 equiv.) in anhydrous DMF (8.5 mL) were stirred at room temperature for 24 hours. The reaction mixture was diluted with ethyl acetate (30 mL), then washed with sat. aq. NH_4Cl (30 mL × 2) and brine (30 mL × 3). The organic layer was collected, dried over $MgSO_4$, filtered and concentrated in vacuo. Purification by flash column chromatography (4:1 hexane:ethyl acetate) yielded the product as a white solid (927 mg, 1.75 mmol, 85%). In solution in CD_3OD, the product exists as a 1:1 mixture of rotamers. m.p. 52–54°C; R_f 0.13 (9:1 CH_2Cl_2:ethyl acetate); ν_{max}/cm^{-1} (thin film) 3484, 2942, 1740, 1703, 1636, 1593, 1508, 1455, 1406, 1365, 1330, 1236, 1178, 1153, 1125, 1009, 842, 701, 558; δ_H (400 MHz, CD_3OD) 7.40–7.18 (10H, m, C(21)2H, C(22)2H and C(23)H, both rotamers), 6.62 (4H, s, C(14)2H, both rotamers), 4.72–4.47 (4H, m, N(7)H and C(12)**H**H', both rotamers), 4.39 (2H, d, *J* = 17.5 Hz, C(12)H**H'**, both rotamers), 4.13–4.03 (2H, m, C(3)H, both rotamers), 3.78 (6H, s, C(17/18/19)H_3, both rotamers), 3.76 (6H, s, C(17/18/19)H_3, both rotamers), 3.74 (6H, s, C(17/18/19)H_3, both rotamers), 3.72–3.70 (2H, m, C(6)H, both rotamers), 3.62 (3H, s, C(1)H_3, rotamer A), 3.57 (3H, s, C(1)H_3, rotamer B), 2.92–2.73 (4H, m, C(5)H_2, both rotamers), 1.40 (18H, s, C(10)3H_3, both rotamers), 1.36 (3H, d, *J* = 7.0 Hz, C(11)H_3, rotamer A), 1.31 (3H, d, *J* = 7.0 Hz, C(11)H_3, rotamer B); δ_C (100 MHz, CD_3OD) 173.2 (C2, rotamer A), 173.2 (C2, rotamer B), 172.9 (C4, rotamer A), 172.8 (C4, rotamer B), 157.3 (C8, both rotamers), 154.8 (2 × C15, both rotamers), 143.6 (C20, both rotamers), 138.2 (C13, rotamer A), 138.1 (C13, rotamer B), 134.3 (C16, rotamer A), 134.2 (C16, rotamer B), 129.4 (2 × C21/22, rotamer A), 129.4 (2 × C21/22, rotamer B), 128.3 (C23, rotamer A), 128.3 (C23, rotamer B), 127.7 (2 × C21/22, rotamer A), 127.6 (2 × C21/22, rotamer B), 104.9 (2 × C14, rotamer A), 104.8 (2 × C14, rotamer B), 82.1 (C9, both rotamers), 61.1 (C18, both rotamers), 57.4 (C3, both rotamers), 56.6 (C17/19, both rotamers), 56.6 (C17/19, both rotamers), 53.0 (C6, both rotamers), 52.7 (C1, both rotamers), 52.5 (C10, rotamer A), 52.2 (C10, rotamer B), 40.9 (C5, both rotamers), 28.7 (3 × C10, both rotamers), 14.6 (C11, rotamer A), 14.5 (C11, rotamer B); HRMS (ESI) calcd. for $C_{28}H_{38}N_2NaO_8$ 553.2520. Found: $[MNa]^+$, 553.2526 (−1.3 ppm error).

(3*S*)-3-methyl-7-phenyl-4-(3,4,5-trimethoxybenzyl)-1,4-diazepane-2,5-dione (12c)

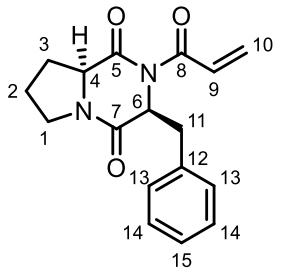


Methyl *N*-(3-((*tert*-butoxycarbonyl)amino)-3-phenylpropanoyl)-*N*-(3,4,5-trimethoxybenzyl)-*L*-alaninate (927 mg, 1.75 mmol, 1 equiv.) was dissolved in ethyl acetate (6 mL) and methanol (0.8 mL), and 12M hydrochloric acid (1.44 mL, 17.5 mmol, 10 equiv.) was added dropwise, and the reaction mixture was stirred at room temperature for 16 hours. The reaction mixture was concentrated under vacuum, and the resulting residue was redissolved in methanol (10 mL) and concentrated to dryness a further 3 times, to leave impure methyl *N*-(3-amino-3-phenylpropanoyl)-*N*-(3,4,5-trimethoxybenzyl)-*L*-alaninate as a yellow oil. HRMS (ESI) calcd. for $C_{23}H_{30}N_2NaO_6$ 453.1996 Found: $[MNa]^+$ 453.2020 (−0.8 ppm error). The impure product was dissolved in methanol (1.5 mL), and freshly prepared 3.77 M sodium methoxide (made by adding 260 mg sodium into 3 mL methanol) was added. The reaction mixture was stirred for 30 minutes, then quenched with water (5 mL). The reaction mixture was extracted with CH_2Cl_2 (15 mL × 3), then washed with water (15 mL) and brine (15 mL). The combined organic layers were collected, dried over $MgSO_4$, filtered and concentrated in vacuo. Purification by flash column chromatography (1:1 CH_2Cl_2:ethyl acetate → 9:1 ethyl acetate:methanol) yielded the title compound as a clear oil (413 mg, 1.04 mmol, 59%). The title compound exists as a 3:5 mixture of diastereomers A:B, which were partially separated and thus have been characterized separately.

Diastereomer A: R_f 0.29 (1:1 CH_2Cl_2:ethyl aceate); ν_{max}/cm^{-1} (thin film); 3242, 2941, 1651, 1592, 1507, 1455, 1421, 1348, 1327, 1236, 1124, 1005, 761, 731, 700; δ_H (400 MHz, $CDCl_3$) 7.42–7.26 (5H, m, C(15)2H, C(16)2H and C(17)H), 6.52 (2H, s, C(9)2H), 5.94 (1H, br s, N(3)H), 4.81 (1H, dd, *J* = 11.5, 2.0 Hz, C(4)H), 4.76 (1H, d, *J* = 15.0 Hz, C(7)**H**H'), 4.42 (1H, d, *J* = 15.0 Hz, C(7)H**H'**), 4.29 (1H, q, *J* = 7.5 Hz, C(1)H), 3.84 (6H, s, C(12)2H_3), 3.83 (3H, s, C(13)H_3), 3.20 (1H, dd, *J* = 14.5, 11.5 Hz, C(5)**H**H'), 2.94 (1H, dt, *J* = 14.5, 2.0 Hz, C(5)H**H'**), 1.62 (3H, d, *J* = 7.5 Hz, C(18)H_3); δ_C (100 MHz, $CDCl_3$) 171.9 (C2), 170.3 (C6), 153.6 (2×C10), 141.6 (C14), 137.7 (C11), 132.6 (C8), 129.5 (2×C16), 129.1 (C17), 125.9 (2×C15), 105.2 (2×C9), 61.0 (C13), 58.9 (C1), 56.5 (C4), 56.3 (2×C12), 51.1 (C7), 44.4 (C5), 19.7 (C18); HRMS (ESI) calcd. for $C_{22}H_{26}N_2NaO_5$ 421.1734 Found: $[MNa]^+$,421.1752 (−0.8 ppm error).

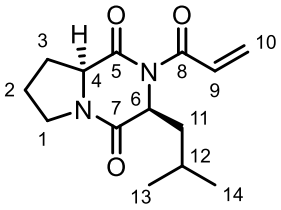
Diastereomer B: R_f 0.17 (1:1 CH_2Cl_2:ethyl aceate); ν_{max}/cm^{-1} (thin film); 3242, 2941, 1651, 1592, 1506, 1453, 1421, 1347, 1328, 1123, 1003, 911, 726, 699; δ_H (400 MHz, $CDCl_3$) 7.28–7.20 (3H, m, C(16)2H and C(17)H), 7.13–7.08 (2H, m, C(15)2H), 6.68 (1H, d, *J* = 4.0 Hz, N(3)H), 6.39 (2H, s, C(9)2H), 4.77–4.70 (1H, m, C(4)H), 4.55 (1H, d, *J* = 15.0 Hz, C(7)**H**H'), 4.49 (1H, q, *J* = 7.5 Hz, C(1)H), 4.24 (1H, d, *J* = 15.0 Hz, C(7)H**H'**), 3.78 (3H, s, C(13)H_3), 3.73 (6H, s, C(12)2H_3), 3.19–3.15 (2H, m, C(5)H_2), 1.48 (3H, d, *J* = 7.5 Hz, C(18)H_3); δ_C (100 MHz, $CDCl_3$) 172.1 (C2), 169.8 (C6), 153.3 (2×C10), 140.1 (C14), 137.4 (C11), 133.0 (C8), 128.9 (2×C16), 128.2 (C17), 125.7 (2×C15), 105.4 (2×C9), 60.9 (C13), 57.4 (C1), 56.1 (2×C12), 55.0 (C4), 49.2 (C7), 42.3 (C5), 17.3 (C18); HRMS (ESI) calcd. for $C_{22}H_{26}N_2NaO_5$ 421.1734 Found: $[MNa]^+$,421.1747 (−1.5 ppm error).

(3*S*,8a*S*)-2-acryloyl-3-benzylhexahydropyrrolo[1,2-a]pyrazine-1,4-dione (13a)



tert-Butyl (*S*)-2-(((*S*)-1-methoxy-1-oxo-3-phenylpropan-2-yl)carbamoyl)pyrrolidine-1-carboxylate (3.93 g, 9.01 mmol, 1 equiv.) was dissolved in formic acid (92 mL) and stirred for 2 hours at room temperature. The solution was concentrated in vacuo, and the resulting oil was redissolved in a mixture of *s*-butanol (220 mL) and toluene (78 mL). The reaction mixture was heated under reflux for 21 hours, allowed to cool to room temperature and concentrated in vacuo. Purification by flash column chromatography (ethyl acetate) afforded cyclo-Pro-Phe (**11a**) as an impure white solid (1.93 g). R_f 0.11 (ethyl acetate); HRMS (APCI) calcd. for $C_{14}H_{17}N_2O_2$ 245.1285 Found: $[MH]^+$, 245.1286 (−0.6 ppm error). The impure cyclo-Pro-Phe was dissolved in THF (38 mL) and cooled to 0 °C. MeMgBr (3 M solution in diethyl ether, 2.85 mL, 8.56 mmol, 1.1 equiv.) was added dropwise using a syringe pump over 30 minutes, and stirred for 15 minutes after the addition was complete. Acryloyl chloride (0.94 mL, 3.96 mmol, 1.5 equiv.) was then added as a single portion, and the reaction mixture was stirred for a further hour. The solution was quenched with sat. $NH_4Cl_{(aq)}$ (50 mL) and extracted with diethyl ether (3 × 50 mL). The combined organic layers were then washed with sat. $NaHCO_{3(aq)}$ (2 × 50 mL) and brine (2 × 50 mL), dried with $MgSO_4$, filtered, and concentrated in vacuo. Purification by flash column chromatography (7:3 hexane:ethyl acetate → 1:1 hexane:ethyl acetate) afforded the title compound as a white solid (1.07 g, 3.57 mmol, 40%). R_f 0.18 (1:1 hexane:ethyl acetate); m.p. 135–137 °C; ν_{max}/cm^{-1} (thin film) 3029, 2890, 1716, 1659, 1486, 1380, 1308, 1192, 1065, 746, 703; δ_H (400 MHz, $CDCl_3$) 7.28–7.20 (3H, m, C(13/14)2H and C(15)H), 7.04–6.99 (2H, m, C(13/14)2H), 6.90 (1H, dd, *J* = 17.0, 10.0 Hz, C(9)H), 6.54 (1H, dd, *J* = 17.0, 1.5 Hz, C(10)**H**H'), 5.85 (1H, dd, *J* = 10.5, 1.5 Hz, C(10)H**H'**), 5.18 (1H, t, *J* = 3.5 Hz, C(6)H), 3.95 (1H, dd, 11.5, 6.0 Hz, C(4)H), 3.79 (1H, dt, *J* = 12.0, 8.5 Hz, C(1)**H**H'), 3.47 (1H, dd, *J* = 14.0, 3.0 Hz, C(11)C**H**H), 3.34 (1H, dd, *J* = 14.0, 4.5 Hz, C(11)H**H'**), 3.25–3.16 (1H, m, C(1)H**H'**), 1.87–1.78 (1H, m, C(3)**H**H'), 1.71–1.56 (2H, m, $C(2)H_2$), 0.16–0.04 (1H, m, C(3)H**H'**); δ_C (100 MHz, $CDCl_3$) 168.9 (C5/7/8), 166.9 (C5/7/8), 163.8 (C5/7/8), 135.1 (C12/15), 131.1 (2 × C13/14), 130.6 (C9), 130.0 (C10), 128.7 (2 × C13/14), 127.7 (C12/15), 61.0 (C4), 59.8 (C6), 44.7 (C1), 39.0 (C11), 28.1 (C3), 21.0 (C2); HRMS (ESI) calcd. for $C_{17}H_{18}N_2NaO_3$ 321.1210 Found: $[MNa]^+$, 321.1216 (−4.1 ppm error).

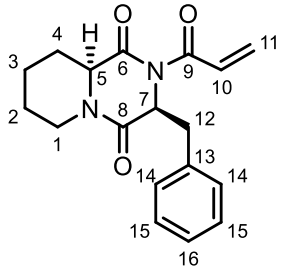
(3*S*,8a*S*)-2-Acryloyl-3-isobutylhexahydropyrrolo[1,2-a]pyrazine-1,4-dione (13b)



(3S,8aS)-3-Isobutylhexahydropyrrolo[1,2-a]pyrazine-1,4-dione **11b** was dissolved in THF (11 mL) and cooled to 0 °C. MeMgBr (3 M solution in diethyl ether, 0.75 mL, 2.32 mmol, 1.1 equiv.) was added dropwise using a syringe pump over 30 minutes, and stirred for 15 minutes after the addition was complete. Acryloyl chloride (0.27 mL,

3.17 mmol, 1.5 equiv.) was then added as a single portion, and the reaction mixture was stirred for a further hour. The solution was quenched with sat. aq. NH_4Cl (30 mL) and extracted with diethyl ether (3 × 30 mL). The combined organic layers were then washed with sat. aq. $NaHCO_3$ (2 × 30 mL) and brine (2 × 30 mL), dried with $MgSO_4$, filtered, and concentrated in vacuo. Purification by flash column chromatography (19:1 CH_2Cl_2:ethyl acetate → 9:1 CH_2Cl_2:ethyl acetate) afforded the title compound as a clear oil as a 3:1 mixture of diastereomers (126 mg, 0.48 mmol, 23%). R_f 0.39 (4:1 CH_2Cl_2:ethyl acetate); ν_{max}/cm^{-1} (thin film) 2959, 2872, 1660, 1461, 1381, 1367, 1300, 1177, 915, 728; δ_H (400 MHz, $CDCl_3$) 6.98 (1H, dd, *J* = 17.0, 10.5 Hz, C(9)H – minor diasteromer), 6.80 (1H, dd, *J* = 17.0, 10.5 Hz, C(9)H – major diastereomer), 6.37 (1H, dd, *J* = 17.0, 1.5 Hz, C(10)**H**H' – major diastereomer), 6.36 (1H, dd, *J* = 17.0, 1.5 Hz, C(10)**H**H' – minor diastereomer), 5.75 (1H, dd, *J* = 10.5, 1.5 Hz, C(10)H**H'** – minor diastereomer), 5.74 (1H, dd, *J* = 10.5, 1.5 Hz, C10(H)H**H'** – major diastereomer), 5.02 (1H, dd, *J* = 9.0, 6.5 Hz, C(6)H – minor diastereomer), 4.87 (1H, dd, *J* = 6.5, 4.5 Hz, C(6)H – major diastereomer), 4.28–4.18 (1H, m, C(4)H – both diastereomers), 3.91–3.82 (1H, m, C(1)**H**H' – major diastereomer), 3.62–3.46 (2H, m, C(1)**HH'** – minor diastereomer), 3.36–3.28 (1H, m, C(1)H**H'** – major diastereomer), 2.44–2.33 (2H, m, C(3)**H**H' – both diastereomers), 2.13–1.49 (12H, m, C(2)H_2, C(3)H**H'**, C(11)H_2 and C(12)H – both diastereomers), 0.99 (3H, d, *J* = 6.5 Hz, C(13/14)H_3 – minor diastereomer), 0.90 (3H, d, *J* = 6.5 Hz, C(13/14)H_3 – minor diastereomer), 0.84 (3H, d, *J* = 6.5 Hz, C(13/14)H_3 – major diastereomer), 0.81 (3H, d, *J* = 13/14)H_3 – major diastereomer); δ_C (100 MHz, $CDCl_3$) 170.3 (C5/C7/C8 – minor diastereomer), 169.5 (C5/C7/C8 – major diastereomer), 167.0 (C5/C7/C8 – minor diastereomer), 166.6 (C5/C7/C8 – major diastereomer), 165.8 (C5/C7/C8 – minor diastereomer), 165.1 (C5/C7/C8 – major diastereomer), 130.7 (C9 – minor diastereomer), 130.5 (C10 – minor diastereomer), 130.4 (C10 – major diastereomer), 130.0 (C9 – major diastereomer), 61.2 (C4 – major diastereomer), 59.7 (C4 – minor diastereomer), 57.7 (C6 – minor diastereomer), 57.4 (C6 – major diastereomer), 45.5 (C1 – minor diastereomer), 45.1 (C1 – major diastereomer), 43.1 (C11 – major diastereomer), 40.9 (C11 – minor diastereomer), 29.4 (C3 – minor diastereomer), 29.3 (C3 – major diastereomer), 25.1 (C12 – minor diastereomer), 24.7 (C12 – major diastereomer), 23.5 (C13/C14 – major diastereomer), 23.0 (C13/C14 – minor diastereomer), 22.8 (C13/C14 – minor diastereomer), 22.1 (C13/C14 – major diastereomer), 21.9 (C2 – minor diastereomer), 21.6 (C2 – major diastereomer); HRMS (ESI) calcd. for $C_{14}H_{20}N_2NaO_3$ 287.1366 Found: $[MNa]^+$, 287.1373 (−3.6 ppm error).

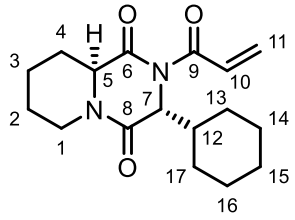
(3*S*,9a*S*)-2-Acryloyl-3-benzylhexahydro-4H-pyrido[1,2-a]pyrazine-1,4(6H)-dione (13d)



(3S,9aS)-3-Benzylhexahydro-4H-pyrido[1,2-a]pyrazine-1,4(6H)-dione **11d** (940 mg, 3.64 mmol, 1 equiv.) was dissolved in THF (18 mL) and cooled to 0 °C. MeMgBr (3 M solution in diethyl ether, 1.16 mL, 3.92 mmol, 1.1 equiv.) was added dropwise using a syringe pump over 30 minutes, and stirred for 15 minutes after the addition was complete. Acryloyl chloride (293 µL, 5.32 mmol, 1.5 equiv.) was then added as a single portion. The reaction mixture was warmed to room temperature, and stirred for 1 hour. The reaction mixture was quenched with sat. aq. NH_4Cl (40 mL) and extracted with diethyl ether (3 × 40 mL). The combined organic layers were then washed with sat. aq. $NaHCO_3$ (2 × 40 mL) and brine (2 × 40 mL), dried with $MgSO_4$, filtered, and concentrated in vacuo. Purification by flash column chromatography (9:1 CH_2Cl_2:ethyl acetate) afforded the title compound as a white

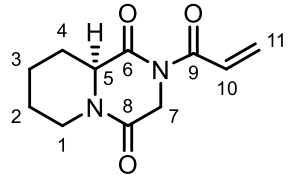
solid (693 mg, 2.22 mmol, 61%). R_f 0.34 (9:1 CH_2Cl_2:ethyl acetate); m.p. 118–121°C; ν_{max}/cm^{-1} (thin film); 3284, 2946, 2859, 1733, 1642, 1604, 1508, 1447, 1417, 1330, 1218, 824; δ_H (400 MHz, $CDCl_3$) 7.30–7.20 (3H, m, C(14/15)2H and C(16)H), 7.09–7.05 (2H, m, C(14/15)2H), 6.96 (1H, dd, *J* = 17.0, 10.5 Hz, C(10)H), 6.50 (1H, dd, *J* = 17.0, 1.5 Hz, C(11)**H**H'), 5.85 (1H, dd, *J* = 10.5, 1.5 Hz, C(11)H**H'**), 5.14 (1H, t, *J* = 4.0 Hz, C(7)H), 4.66 (1H, ddt, *J* = 13.0, 4.0, 2.0 Hz, C(1)**H**H'), 3.72 (1H, dd, *J* = 12.0, 3.0 Hz, C(5)H), 3.43 (1H, dd, *J* = 14.0, 4.0 Hz, C(12)**H**H'), 3.31 (1H, dd, *J* = 14.0, 4.0 Hz, C(12)H**H'**), 2.32 (1H, td, *J* = 13.0, 3.0 Hz, C(1)H**H'**), 1.77–1.48 (3H, m, C(2)**H**H', C(3)**H**H' and C(4)**H**H'), 1.26 (1H, qt, *J* = 13.0, 3.5 Hz, C(3)H**H'**), 1.13 (1H, qt, *J* = 13.0, 3.5 Hz, C(2)H**H'**), −0.67 (1H, qd, *J* = 13.0, 4.0 Hz, C(4)H**H'**); δ_C (100 MHz, $CDCl_3$) 169.3 (C6), 167.5 (C9), 162.9 (C8), 135.2 (C13), 131.4 (2 × C14/C15), 130.6 (C10), 130.4 (C11), 128.9 (2 × C14/C15), 127.7 (C16), 60.2 (C5), 58.1 (C7), 42.3 (C1), 38.5 (C12), 28.7 (C4), 24.1 (C3), 23.9 (C2); HRMS (ESI) calcd. for $C_{18}H_{20}N_2NaO_3$ 335.1366 Found: $[MNa]^+$, 355.1366 (−0.1 ppm error).

(3*R*,9*aS*)-3-cyclohexyl-2-prop-2-enoyl-3,6,7,8,9,9*a*-hexahydropyrido[1,2-a]pyrazine-1,4-dione (13e)



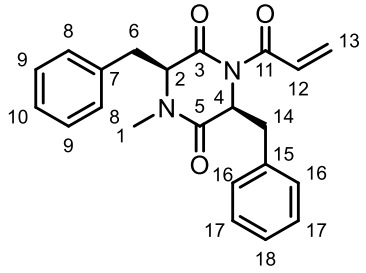
(3*R*,9*aS*)-3-cyclohexyl-3,6,7,8,9,9*a*-hexahydro-2*H*-pyrido[1,2-a]pyrazine-1,4-dione **11e** (500 mg, 2.00 mmol, 1 equiv.) was dissolved in THF (30 mL) and cooled to 0 °C. MeMgBr (3 M solution in diethyl ether, 732 µL, 2.20 mmol, 1.1 equiv.) was added dropwise using a syringe pump over 30 minutes, and stirred for 15 minutes after the addition was complete. Acryloyl chloride (240 µL, 3.00 mmol, 1.5 equiv.) was then added as a single portion. The reaction mixture was warmed to room temperature, and stirred for 1 hour. The reaction mixture was quenched with sat. aq. NH_4Cl (40 mL) and extracted with diethyl ether (3 × 40 mL). The combined organic layers were then washed with sat. aq. $NaHCO_3$ (2 × 40 mL) and brine (2 × 40 mL), dried with $MgSO_4$, filtered, and concentrated in vacuo. Purification by flash column chromatography (3:1 CH_2Cl_2:ethyl acetate) afforded the title compound as a clear oil (438 mg, 1.44 mmol, 72%). R_f 0.90 (3:1 CH_2Cl_2:ethyl acetate); $[\alpha]_D^{20}$ +2.9 (*c* 1.00, $CHCl_3$); ν_{max}/cm^{-1} (thin film) 2927, 2855, 1709, 1691, 1660, 1617, 1447, 1388, 1351, 1306, 1278, 1260, 1200, 1147, 1104, 968, 890, 859, 818, 792, 725, 573; δ_H (400 MHz, $CDCl_3$) 6.82 (1 H, dd, *J* = 16.5, 10.5 Hz, C(10)H), 6.44 (1 H, dd, *J* = 16.5, 1.5 Hz, C(11)**H**H'), 5.79 (1 H, dd, *J* = 10.5, 1.5 Hz, C(11)H**H'**), 4.82 (1 H, d, *J* = 5.0 Hz, C(7)H), 4.64 (1 H, dt, *J* = 13.5, 2.0 Hz, C(1)**H**H'), 3.91 (1 H, dd, *J* = 11.0, 3.5 Hz, C(5)H), 2.53 (1 H, td, *J* = 13.0, 3.5 Hz, C(1)H**H'**), 2.44–2.39 (1 H, m, C(2)**H**H'), 2.02–1.99 (1 H, m, C(4)**H**H'), 1.87–1.03 (15 H, m, C(2)H**H'**), $C(3)H_2$, C(4)H**H'**, C(12)H, $C(13)H_2$, $C(14)H_2$, $C(15)H_2$, $C(16)H_2$ and $C(17)H_2$); δ_C (100 MHz, $CDCl_3$) 171.8 (C6), 166.5 (C9), 165.7 (C8), 130.5 (C11), 129.7 (C10), 60.9 (C7), 59.4 (C5), 44.1 (C12), 41.8 (C1), 31.7 (C2), 29.5 (C13/C17), 28.9 (C13/C17), 26.3 (C15), 26.1 (C4), 25.8 (C14/C16), 24.1 (C14/C16), 24.0 (C3); HRMS (ESI) calcd. for $C_{17}H_{24}N_2NaO_3$ 327.1679 Found: $[MNa]^+$, 327.1687 (−2.4 ppm error).

(*S*)-2-Acryloylhexahydro-4H-pyrido[1,2-a]pyrazine-1,4(6H)-dione (13f)



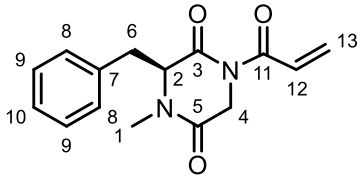
(*S*)-Hexahydro-4H-pyrido[1,2-a]pyrazine-1,4(6H)-dione **11f** (382 mg, 2.27 mmol, 1 equiv.) was dissolved in THF (10 mL) and cooled to 0 °C. MeMgBr (3 M solution in diethyl ether, 0.73 mL, 2.44 mmol, 1.1 equiv.) was added dropwise using a syringe pump over 30 minutes, and stirred for 15 minutes after the addition was complete. Acryloyl chloride (183 µL, 3.32 mmol, 1.5 equiv.) was then added as a single portion. The reaction mixture was warmed to room temperature, and stirred for 16 hours. The reaction mixture was quenched with sat. aq. NH_4Cl (30 mL) and extracted with diethyl ether (3 × 30 mL). The combined organic layers were then washed with sat. aq. $NaHCO_3$ (2 × 30 mL) and brine (2 × 30 mL), dried with $MgSO_4$, filtered, and concentrated in vacuo. Purification by flash column chromatography (7:3 CH_2Cl_2:ethyl acetate) afforded the title compound as a white solid (171 mg, 0.77 mmol, 34%). R_f 0.41 (7:3 CH_2Cl_2:ethyl acetate); m.p. 90–92°C; $[\alpha]_D^{20}$ −33.8 (*c* 0.50, $CHCl_3$); ν_{max}/cm^{-1} (thin film) 2943, 2923, 2858, 1697, 1682, 1640, 1494, 1441, 1381, 1257, 1210, 984, 961, 792, 776, 587; δ_H (400 MHz, $CDCl_3$) 7.01 (1H, dd, *J* = 17.0, 10.5 Hz, C(10)H), 6.45 (1H, dd, *J* = 17.0, 1.5 Hz, C(11)**H**H'), 5.83 (1H, dd, *J* = 10.5, 1.5 Hz, C(11)H**H'**), 4.63 (1H, ddt, *J* = 13.5, 4.0, 2.0 Hz, C(1)**H**H'), 4.42 (1H, d, *J* = 18.5 Hz, C(7)**H**H'), 4.28 (1H, d, *J* = 18.5 Hz, C(7)H**H'**), 4.00 (1H, dd, *J* = 11.5, 3.0 Hz, C(5)H), 2.56 (1H, dt, *J* = 13.5, 3.0 Hz, C(1)H**H'**), 2.37–2.30 (1H, m, C(2)**H**H'), 2.08–2.00 (1H, m, C(4)**H**H'), 1.77–1.41 (4H, m, C(2)H**H'**, C(3)H_2 and C(4)H**H'**); δ_C (100 MHz, $CDCl_3$) 168.8 (C6), 167.5 (C9), 162.4 (C8), 130.7 (C11), 130.5 (C10), 60.5 (C5), 46.1 (C7), 42.6 (C1), 31.1 (C2), 24.3 (C4), 24.2 (C2); HRMS (ESI) calcd. for $C_{11}H_{14}N_2NaO_3$ 245.0897. Found: $[MNa]^+$, 245.0899 (−1.8 ppm error).

(3*S*,6*S*)-1-Acryloyl-3,6-dibenzyl-4-methylpiperazine-2,5-dione (13g)



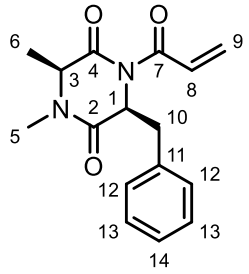
(3*S*,6*S*)-3,6-Dibenzyl-1-methylpiperazine-2,5-dione **11g** (378 mg, 1.23 mmol, 1 equiv.) was dissolved in THF (6.5 mL) and cooled to 0 °C. MeMgBr (3 M solution in diethyl ether, 439 µL, 1.85 mmol, 1.1 equiv.) was added dropwise using a syringe pump over 30 minutes, and stirred for 15 minutes after the addition was complete. Acryloyl chloride (156 µL, 1.35 mmol, 1.5 equiv.) was then added as a single portion, and the reaction mixture was stirred for a further hour. The solution was quenched with sat. aq. NH_4Cl (20 mL) and extracted with diethyl ether (3 × 20 mL). The combined organic layers were then washed with sat. aq. $NaHCO_3$ (2 × 20 mL) and brine (2 × 20 mL), dried with $MgSO_4$, filtered, and concentrated in vacuo. Purification by flash column chromatography (3:2 hexane:ethyl acetate) afforded the title compound as a clear oil (278 mg, 0.77 mmol, 62%). R_f 0.41 (1:1 hexane:ethyl acetate); ν_{max}/cm^{-1} (thin film) 3030, 2936, 1693, 1658, 1496, 1455, 1386, 1339, 1302, 1263, 1196, 1177, 910, 728, 699, 588, 491; δ_H (400 MHz, $CDCl_3$); 7.38–7.30 (4H, m, ArH), 7.30–7.23 (2H, m, ArH), 7.16–7.07 (4H, m, ArH), 6.98 (1H, dd, *J* = 17.0, 10.5 Hz, C(12)H), 6.45 (1H, dd, *J* = 17.0, 1.0 Hz, C(13)**H**H'), 5.85 (1H, dd, *J* = 10.5, 1.0 Hz, C(13)H**H'**), 5.13 (1H, dd, *J* = 6.0, 4.5 Hz, C(4)H), 4.22–4.17 (1H, m, C(2)H), 2.91 (1H, dd, *J* = 14.0, 4.5 Hz, C(6)**H**H'), 2.78 (3H, s, C(1)H_3), 2.72 (1H, dd, *J* = 14.0, 6.5 Hz, C(6)H**H'**), 2.62 (1H, dd, *J* = 14.0, 4.5 Hz, C(14)**H**H'), 2.22 (1H, dd, *J* = 14.0, 6.5 Hz, C(14)H**H'**); δ_C (100 MHz, $CDCl_3$) 168.8 (C3/C5/C11), 167.5 (C3/C5/C11), 165.2 (C3/C5/C11), 136.8 (C7/C15), 136.3 (C7/C15), 130.7 (C12), 130.5 (C13), 130.4 (2 × C8/C9/C16/C17), 129.5 (2 × C8/C9/C16/C17), 129.1 (2 × C8/C9/C16/C17), 128.9 (2 × C8/C9/C16/C17), 127.6 (C10/C18), 127.5 (C10/C18), 65.7 (C2), 58.6 (C4), 39.1 (C6/C14), 38.9 (C6/C14), 35.5 (C1); HRMS (ESI) calcd. for $C_{22}H_{23}N_2O_3$ 363.1703 Found: $[MH]^+$, 363.1708 (−1.1 ppm error).

(*S*)-1-Acryloyl-3-benzyl-4-methylpiperazine-2,5-dione (13h)



(*S*)-6-Benzyl-1-methylpiperazine-2,5-dione **11h** (460 mg, 2.10 mmol, 1 equiv.) was dissolved in THF (10 mL) and cooled to 0 °C. MeMgBr (3 M solution in diethyl ether, 0.68 mL, 2.32 mmol, 1.1 equiv.) was added dropwise using a syringe pump over 30 minutes, and stirred for 15 minutes after the addition was complete. Acryloyl chloride (0.18 mL, 3.17 mmol, 1.5 equiv.) was then added as a single portion, and the reaction mixture was stirred for a further hour. The solution was quenched with sat. aq. NH_4Cl (30 mL) and extracted with diethyl ether (3 × 30 mL). The combined organic layers were then washed with sat. aq. $NaHCO_3$ (2 × 30 mL) and brine (2 × 30 mL), dried with $MgSO_4$, filtered, and concentrated in vacuo. Purification by flash column chromatography (19:1 CH_2Cl_2:ethyl acetate → 9:1 CH_2Cl_2:ethyl acetate) afforded the title compound as a white solid (265 mg, 0.97 mmol, 46%). R_f 0.29 (9:1 CH_2Cl_2:ethyl acetate); m.p. 70–73 °C; ν_{max}/cm^{-1} (thin film) 2935, 1663, 1617, 1496, 1446, 1404, 1375, 1338, 1304, 1247, 1210, 1194, 1174, 1080, 1042, 975, 745, 703, 566; δ_H (400 MHz, $CDCl_3$) 7.34–7.26 (3H, m, C(10)H and C(8/9)2H), 7.10–7.03 (3H, m, C(12)H and C(8/9)2H), 6.42 (1H, dd, *J* = 17.0, 1.5 Hz, C(13)**H**H'), 5.84 (1H, dd, *J* = 10.5, 1.5 Hz, C(13)H**H'**), 4.33 (1H, t, *J* = 4.5 Hz, C(2)H), 4.18 (1H, d, *J* = 18.0 Hz, C(4)**H**H'), 3.29 (1H, dd, *J* = 14.0, 4.5 Hz, C(6)**H**H'), 3.19 (1H, dd, *J* = 14.0, 4.5 Hz, C(6)H**H'**), 3.04 (3H, s, C(1)H_3), 2.44 (1H, d, *J* = 18.0 Hz, C(4)H**H'**); δ_C (100 MHz, $CDCl_3$) 168.8 (C3), 166.9 (C11), 164.3 (C5), 134.1 (C10), 131.0 (C13), 130.4 (C12), 129.7 (2 × C8/C9), 129.3 (2 × C8/C9), 128.4 (C7), 65.4 (C2), 45.5 (C4), 37.7 (C6), 32.4 (C1); HRMS (ESI) calcd. for $C_{15}H_{16}KN_2O_3$ 311.0793 Found: $[MK]^+$, 311.0796 (−1.0 ppm error).

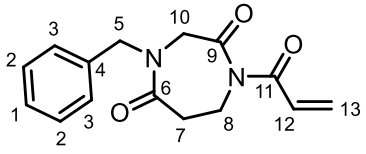
(3S,6S)-1-acryloyl-6-benzyl-3,4-dimethylpiperazine-2,5-dione (13i)



(3*S*,6*S*)-3-benzyl-1,6-dimethylpiperazine-2,5-dione **11i** (100 mg, 0.43 mmol, 1 equiv.) in dry THF (2 mL) was cooled to 0 °C before the dropwise addition of MeMgBr (3.0 M in Et_2O, 0.16 mL, 0.47 mmol, 1.1 equiv.) over 15 mins using a syringe pump. After the addition was complete, the reaction mixture was stirred at 0 °C for 15 mins. At this point, acryloyl chloride (0.05 mL, 0.65 mmol, 1.5 eqv) was added as a single portion and the reaction was stirred for 1 h at 0 °C. The reaction was then quenched with sat. aq. NH_4Cl (5 mL), the aqueous mixture extracted with Et_2O (2 x 5 mL) and the organic extracts washed with sat. $NaHCO_3$ (2 x 5 mL). The organic phase was dried over $MgSO_4$ and concentrated *in vacuo*. The crude material was purified by flash column chromatography (SiO_2, 4:1; ethyl acetate: hexane) to afford the title compound as a waxy, white solid (104 mg, 0.36 mmol, 85%); R_f = 0.28 (4:1; ethyl acetate: hexane); ν_{max}/cm^{-1} (thin film) 2943, 1690, 1654, 1452, 1385, 1243, 1196, 1101, 974, 748, 701, 599, 490; δ_H (400 MHz, $CDCl_3$) 7.29–7.14 (3H, m, C(12/13)2H and C(14)H), 7.07 – 6.99 (2H, m, C(12/13)2H), 6.93 (1H, dd, *J* = 17.0 Hz, 10.5 Hz, C(8)H), 6.44 (1H, dd, *J* = 17.0, 2.0 Hz, C(9)**H**H'), 5.80 (1H,

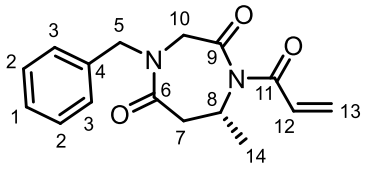
dd, *J* = 10.5, 2.0 Hz, 1H, C(9)H**H'**), 5.17 – 5.09 (1H, m, C(1)H), 3.85 (1H, q, *J* = 7.0 Hz, C(3)H), 3.34 (1H, dd, *J* = 14.0, 4.5 Hz, C(10)**H**H'), 3.24 (1H, dd, *J* = 14.0, 4.5 Hz, C(10)H**H'**), 2.81 (3H, s, C(6)H_3), 0.49 (3H, d, *J* = 7.0 Hz, C(5)H_3); δ_C (100 MHz, $CDCl_3$) 169.7 (C4), 167.4 (C7), 164.7 (C2), 135.4 (C11), 130.7 (2 × C12/13), 130.6 (C8), 130.3 (C9), 128.9 (2 × C12/13), 127.6 (C14), 58.8 (C3), 58.5 (C1), 38.5 (C10), 31.6 (C5), 16.9 (C6); HRMS (ESI$^+$): calcd. for $C_{16}H_{18}N_2NaO_3$, 309.1210. Found [MNa]$^+$, 309.1214.

1-Acryloyl-4-benzyl-1,4-diazepane-2,5-dione (13j)



4-Benzyl-1,4-diazepane-2,5-dione **12a** (374 mg, 1.72 mmol, 1 equiv.) was dissolved in THF (8.5 mL) and cooled to 0 °C. MeMgBr (3 M solution in diethyl ether, 0.56 mL, 1.89 mmol, 1.1 equiv.) was added dropwise using a syringe pump over 30 minutes, and stirred for 15 minutes after the addition was complete. Acryloyl chloride (142 µL, 2.58 mmol, 1.5 equiv.) was then added as a single portion. The reaction mixture was warmed to room temperature, and stirred for 1 hour. The reaction mixture was quenched with sat. aq. NH_4Cl (20 mL) and extracted with diethyl ether (3 × 20 mL). The combined organic layers were then washed with sat. aq. $NaHCO_3$ (2 × 20 mL) and brine (2 × 20 mL), dried with $MgSO_4$, filtered, and concentrated in vacuo. Purification by flash column chromatography (7:3 CH_2Cl_2:ethyl acetate) afforded the title compound as a clear oil (72 mg, 0.26 mmol, 15%). R_f 0.50 (1:1 CH_2Cl_2:ethyl acetate); ν_{max}/cm^{-1} (thin film) 2927, 1682, 1636, 1470, 1454, 1403, 1383, 1353, 1336, 1302, 1243, 1189, 1152, 1098, 1041, 962, 795, 731, 701, 598; δ_H (400 MHz, $CDCl_3$) 7.36–7.23 (5H, m, C(1)H, C(2)2H and C(3)2H), 6.57 (1H, dd, *J* = 17.0, 10.5 Hz, C(12)H), 6.37 (1H, dd, *J* = 17.0, 1.5 Hz, C(13)**H**H'), 5.72 (1H, dd, *J* = 10.5, 1.5 Hz, C(13)H**H'**), 4.69 (2H, s, C(5)H_2), 4.18 (2H, s, C(10)H_2), 4.06 (2H, t, *J* = 6.5 Hz, C(8)H_2), 2.95 (2H, t, *J* = 6.5 Hz, C(7)H_2); δ_C (100 MHz, $CDCl_3$) 171.0 (C9), 169.5 (C6), 168.2 (C11), 136.3 (C4), 130.3 (C12), 130.0 (C13), 129.0 (2 × C2/C3), 128.3 (2 × C2/C3), 128.2 (C1), 53.8 (C10), 52.0 (C5), 40.1 (C8), 34.7 (C7); HRMS (ESI) calcd. for $C_{15}H_{16}N_2NaO_3$ 295.1053. Found: [MNa]$^+$, 295.1045 (−2.4 ppm error).

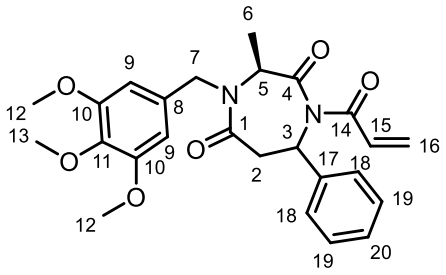
(*R*)-1-Acryloyl-4-benzyl-7-methyl-1,4-diazepane-2,5-dione (13k)



(*R*)-4-Benzyl-7-methyl-1,4-diazepane-2,5-dione **12b** (516 mg, 2.44 mmol, 1 equiv.) was dissolved in THF (11 mL) and cooled to 0 °C. MeMgBr (3 M solution in diethyl ether, 0.72 mL, 2.44 mmol, 1.1 equiv.) was added dropwise using a syringe pump over 30 minutes, and stirred for 15 minutes after the addition was complete. Acryloyl chloride (183 µL, 3.33 mmol, 1.5 equiv.) was then added as a single portion. The reaction mixture was warmed to room temperature, and stirred for 1 hour. The reaction mixture was quenched with sat. aq. NH_4Cl (30 mL) and extracted with diethyl ether (3 × 30 mL). The combined organic layers were then washed with sat. aq. $NaHCO_3$ (2 × 30 mL) and brine (2 × 30 mL), dried with $MgSO_4$, filtered, and concentrated in vacuo. Purification by flash column chromatography (7:3 CH_2Cl_2:ethyl acetate) afforded the title compound as a waxy white solid (141 mg, 0.49 mmol, 22%). R_f 0.44 (1:1 CH_2Cl_2:ethyl acetate); ν_{max}/cm^{-1} (thin film) 2984, 2932, 1662, 1465, 1454, 1395, 1311, 1243, 1188, 911, 727, 701, 617, 504; δ_H (400 MHz, $CDCl_3$) 7.29–7.21 (5H, m, C(1)H, C(2)2H and

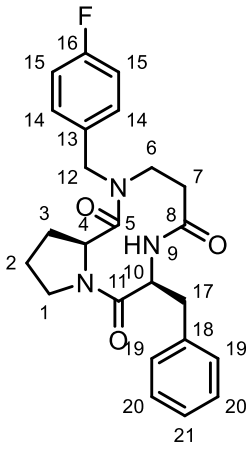
C(3)2H), 6.20 (1H, dd, *J* = 16.5, 1.5 Hz, C(13)**H**H'), 5.64 (1H, dd, *J* = 16.5, 10.5 Hz, C(12)H), 5.48 (1H, dd, *J* = 10.5, 1.5 Hz, C(13)H**H'**), 4.96 (1H, d, *J* = 14.5 Hz, C(5)**H**H'), 4.70 (1H, dp, *J* = 10.0, 6.5 Hz, C(8)H), 4.26 (1H, d, *J* = 18.5 Hz, C(7)**H**H'), 4.20 (1H, d, *J* = 14.5 Hz, C(5)H**H'**), 4.01 (1H, d, *J* = 18.5 Hz, C(7)H**H'**), 2.95 (1H, dd, *J* = 14.5, 6.5 Hz, C(10)**H**H'), 2.72 (1H, dd, *J* = 14.5, 10.0 Hz, C(10)H**H'**), 1.26 (3H, d, *J* = 6.5 Hz, C(14)H_3); δ_C (100 MHz, $CDCl_3$) 173.4 (C6), 169.6 (C9), 168.6 (C11), 136.3 (C4), 130.0 (C12), 129.1 (2 × C2/3), 128.5 (2 × C2/3), 128.3 (C13), 128.1 (C1), 54.1 (C10), 50.4 (C5), 48.1 (C8), 40.3 (C7), 21.9 (C14); HRMS (ESI) calcd. for $C_{16}H_{18}N_2NaO_3$ 309.1210. Found: $[MNa]^+$, 309.1207 (0.5 ppm error).

(3*S*)-1-Acryloyl-3-methyl-7-phenyl-4-(3,4,5-trimethoxybenzyl)-1,4-diazepane-2,5-dione (13l)



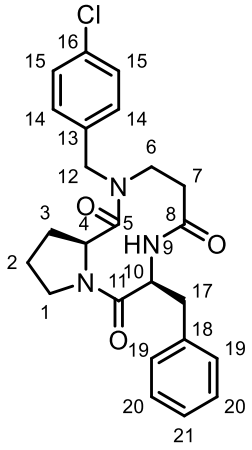
(3*S*)-3-Methyl-7-phenyl-4-(3,4,5-trimethoxybenzyl)-1,4-diazepane-2,5-dione (413 mg, 1.04 mmol, 1 equiv.) was dissolved in THF (5 mL) and cooled to 0 °C. MeMgBr (3 M solution in diethyl ether, 0.34 mL, 1.14 mmol, 1.1 equiv.) was added dropwise using a syringe pump over 30 minutes, and stirred for 15 minutes after the addition was complete. Acryloyl chloride (84 µL, 1.56 mmol, 1.5 equiv.) was then added as a single portion. The reaction mixture was warmed to room temperature, and stirred for 16 hours. The reaction mixture was quenched with sat. $NH_4Cl_{(aq)}$ (20 mL) and extracted with diethyl ether (3 × 20 mL). The combined organic layers were then washed with sat. $NaHCO_{3(aq)}$ (2 × 20 mL) and brine (2 × 20 mL), dried with $MgSO_4$, filtered, and concentrated in vacuo. Purification by flash column chromatography (1:1 hexane:ethyl acetate) afforded the title compound as a clear oil (198 mg, 0.44 mmol, 42%). The product was isolated as a 3:1 mixture of diastereomers. R_f 0.18 (1:1 hexane:ethyl acetate); ν_{max}/cm^{-1} (thin film) 2941, 2840, 1660, 1591, 1506, 1456, 1403, 1328, 1235, 1208, 1161, 1125, 910, 726, 698; δ_H (400 MHz, $CDCl_3$) Major diastereomer only 7.33–7.19 (3H, m, C(18/19)2H and C(20)H), 7.10–7.05 (2H, m, C(18/19)2H), 6.52 (2H, s, C(9)2H), 6.22 (1H, dd, *J* = 16.5, 1.5 Hz, C(16)**H**H'), 5.94 (1H, t, *J* = 8.5 Hz, C(3)H), 5.83 (1H, dd, *J* = 16.5, 10.5 Hz, C(15)H), 5.55 (1H, dd, *J* = 10.5, 1.5 Hz, C(16)H**H'**), 4.93 (1H, d, *J* = 15.0 Hz, C(7)**H**H'), 4.53 (1H, q, *J* = 7.0 Hz, C(5)H), 4.16 (1H, d, *J* = 15.0 Hz, C(7)H**H'**), 3.79 (3H, s, C(13)H_3, 3.76 (6H, s, C(12)2H_3), 3.40 (1H, dd, *J* = 14.5, 8.5 Hz, C(2)**H**H'), 3.19 (1H, dd, *J* = 14.5, 8.5 Hz, C(2)H**H'**), 1.57 (1H, d, *J* = 7.0 Hz, C(6)H_3); δ_C (100 MHz, $CDCl_3$) Major diastereomer only 176.0 (C4), 170.0 (C1), 169.0 (C14), 153.4 (2 × C10), 140.7 (C17), 137.6 (C11), 133.1 (C8), 129.7 (C15), 129.1 (2 × C19), 129.0 (C16), 127.9 (C20), 124.8 (2 × C18), 105.7 (2×C9), 60.8 (C13), 57.2 (C5), 56.1 (2 × C12), 53.5 (C3), 45.8 (C7), 42.1 (C2), 14.7 (C6); HRMS (ESI) calcd. for $C_{25}H_{29}N_2O_6$ 453.2020. Found: $[MH]^+$, 453.2016 (2.8 ppm error). Diagnostic NMR resonances for the minor diastereomer be found at δ_H (400 MHz, $CDCl_3$) 6.39 (2H, s, C(9)2H), 6.18 (1H, dd, *J* = 16.5, 1.5 Hz, C(16)**H**H'), 5.70 (1H, dd, *J* = 16.5, 10.5 Hz, C(15)H), 4.30 (1H, q, *J* = 7.0 Hz, C(5)H), 1.73 (3H, d, *J* = 7.0 Hz, C(6)H_3); δ_C (100 MHz, $CDCl_3$) 180.8 (C4), 153.7 (2×C10), 105.0 (2×C9), 17.3 (C6).

(7*S*,12a*S*)-7-Benzyl-2-(4-fluorobenzyl)octahydropyrrolo[2,1-c][1,4,7]triazecine-1,5,8(2H)-trione (14a)



(3*S*,8a*S*)-2-Acryloyl-3-benzylhexahydropyrrolo[1,2-a]pyrazine-1,4-dione **13a** (99 mg, 0.33 mmol, 1 equiv.) was dissolved in methanol (1 mL), and 4-fluoro-benzylamine (42 µL, 0.369 mmol, 1.1 equiv.) was added. The reaction was stirred for 18 h, and the solvent was removed in vacuo. Purification by flash column chromatography (7:3 ethyl acetate:hexane) yielded the product as a white solid (116 mg, 0.27 mmol, 82%). R_f 0.24 (3:7 hexane:ethyl acetate); m.p. 171–175 °C; $[\alpha]_D^{20}$ +39.2 (*c* 0.50, $CHCl_3$); ν_{max}/cm^{-1} (thin film) 3278, 3063, 3030, 2961, 2928, 2885, 1640, 1605, 1542, 1509, 1413, 1340, 1221, 1191, 1142, 910, 822, 730, 700, 587; δ_H (400 MHz, $CDCl_3$) 7.34–7.27 (2H, m, C(19/20)2H), 7.27–7.21 (1H, m, C(21)H), 7.20–7.16 (2H, m, C(19/20)H), 7.16–7.10 (2H, m, C(14/15)2H), 6.95 (2H, t, *J* = 8.5 Hz, C(14/15)H), 5.96–5.76 (1H, m, N(9)H), 5.14 (1H, dt, *J* = 8.5, 5.0 Hz, C(10)H), 4.73 (1H, d, *J* = 6,5 Hz, C(4)H), 4.63 (1H, dd, *J* = 14.5, 4.0 Hz, C(12)**H**H'), 4.33–4.22 (1H, m, C(12)H**H'**), 3.90–3.68 (3H, m, C(1)H_2 and C(6)**H**H'), 3.51–3.19 (3H, m, C(6)H**H'** and C(17)H_2), 2.23–2.02 (3H, m, C(2)**H**H' and C(7)H_2), 1.97–1.80 (3H, m, C(2)H**H'** and C(3)H_3); δ_C (100 MHz, $CDCl_3$) 175.2 (C5), 171.3 (C8), 168.4 (C11), 162.5 (d, $^1J_{CF}$ = 246.0, C16), 137.1 (C18), 133.2 (d, $^4J_{CF}$ = 3.5 Hz, C13), 129.9 (d, $^3J_{CF}$ = 8.0 Hz, 2 × C14), 129.3 (2 × C19/C20), 128.8 (2 × C19/C20), 126.9 (C21), 116.2 (d, $^2J_{CF}$ = 21.5 Hz, 2 × C15), 56.0 (C4), 52.9 (C10), 50.2 (C1), 49.7 (C12), 44.9 (C6), 37.6 (C17), 37.3 (C7), 32.7 (C3), 21.2 (C2); δ_F (376 MHz, $CDCl_3$) –113.5 (1F, s, C(16)F); HRMS (ESI) calcd. for $C_{24}H_{26}FKN_3O_3$ 462.1590 Found: $[MK]^+$, 462.1578 (−0.9 ppm error).

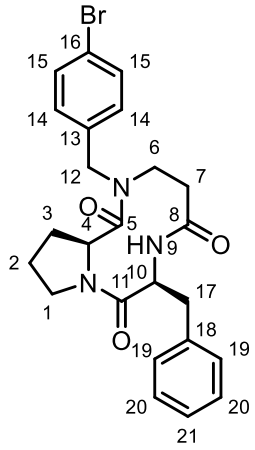
(7*S*,12a*S*)-7-Benzyl-2-(4-chlorobenzyl)octahydropyrrolo[2,1-c][1,4,7]triazecine-1,5,8(2H)-trione (14b)



(3*S*,8a*S*)-2-Acryloyl-3-benzylhexahydropyrrolo[1,2-a]pyrazine-1,4-dione **13a** (79 mg, 0.26 mmol, 1 equiv.) was dissolved in methanol (1 mL), and 4-chloro-benzylamine (34 µL, 0.277 mmol, 1.1 equiv.) was added. The reaction

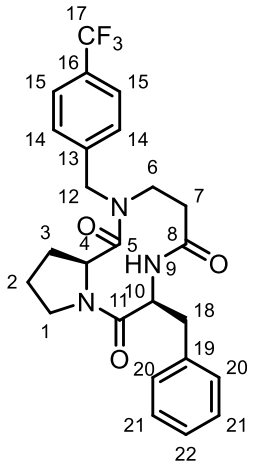
was stirred for 18 h, and the solvent was removed in vacuo. Purification by flash column chromatography (7:3 ethyl acetate:hexane) yielded the product as a white solid (89 mg, 0.20 mmol, 77%). R_f 0.09 (1:1 hexane:ethyl acetate); m.p. 206–209 °C; $[\alpha]_D^{20}$ +36.3 (*c* 0.50, $CHCl_3$); ν_{max}/cm^{-1} (thin film) 3277, 2925, 1641, 1542, 1491, 1407, 1340, 1191, 1142, 1091, 1049, 909, 801, 730, 700; δ_H (400 MHz, $CDCl_3$) 7.34–7.29 (2H, m, C(14/15/19/20)2H), 7.27–7.22 (3H, m, C(14/15/19/20)2H and C(21)H), 7.20–7.16 (2H, m, C(14/15/19/20)2H), 7.12–7.08 (2H, m, C(14/15/19/20)2H), 5.84 (1H, d, *J* = 10.0 Hz, N(9)H), 5.14 (1H, ddd, *J* = 10.0, 8.0, 5.0 Hz, C(10)H), 4.76–4.72 (1H, m, C(4)H), 4.61 (1H, d, *J* = 14.5 Hz, C(12)**H**H'), 4.27 (1H, d, *J* = 14.5 Hz, C(12)H**H'**), 3.90–3.67 (3H, m, $C(1)H_2$ and C(6)**H**H'), 3.37 (1H, dd, *J* = 14.5, 5.0 Hz, C(17)**H**H'), 3.33 – 3.25 (1H, m, C(6)H**H'**) , 3.21 (1H, dd, *J* = 14.5, 8.0 Hz, C(17)H**H'**), 2.21–2.07 (3H, m, $C(3)H_2$ and C(7)**H**H'), 1.95–1.77 (3H, m, $C(2)H_2$ and C(7)H**H'**); δ_C (100 MHz, $CDCl_3$) 175.1 (C5), 171.3 (C8), 168.5 (C11), 137.0 (C13/C16/C18), 136.0 (C13/C16/C18), 134.1 (C13/C16/C18), 129.5 (2 × C14/C15/C19/C20), 129.5 (2 × C14/C15/C19/C20), 129.3 (2 × C14/C15/C19/C20), 128.8 (2 × C14/C15/C19/C20), 127.0 (C21), 56.0 (C4), 52.9 (C10), 50.2 (C1), 49.8 (C12), 45.1 (C6), 37.6 (C17), 37.4 (C7), 32.7 (C3), 21.2 (C2); HRMS (ESI) calcd. for $C_{24}H_{26}{}^{35}ClN_3NaO_3$ 462.1555 Found: $[MNa]^+$, 462.1560 (0.2 ppm error).

(7*S*,12a*S*)-7-Benzyl-2-(4-bromobenzyl)octahydropyrrolo[2,1-c][1,4,7]triazecine-1,5,8(2H)-trione (14c)



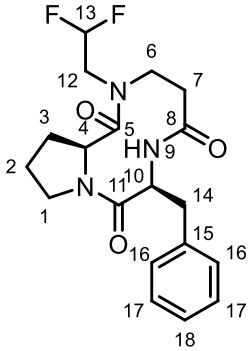
(3*S*,8a*S*)-2-Acryloyl-3-benzylhexahydropyrrolo[1,2-a]pyrazine-1,4-dione **13a** (74 mg, 0.25 mmol, 1 equiv.) was dissolved in methanol (1 mL), and 4-bromo-benzylamine (35 µL, 0.28 mmol, 1.1 equiv.) was added. The reaction was stirred for 18 h, and the solvent was removed in vacuo. Purification by flash column chromatography (4:1 CH_2Cl_2:ethyl acetate) yielded the product as a white solid (72 mg, 0.15 mmol, 60%). R_f 0.10 (4:1 CH_2Cl_2:ethyl acetate); m.p. 201–203 °C; $[\alpha]_D^{20}$ +18.7 (*c* 0.50, $CHCl_3$); ν_{max}/cm^{-1} (thin film) 3279, 2924, 2853, 1640, 1542, 1488, 1403, 1340, 1191, 1143, 1049, 908, 766, 729, 475; δ_H (400 MHz, $CDCl_3$) 7.40 (2H, d, *J* = 8.5 Hz, C(14/15)2H), 7.34–7.21 (3H, m, C(19/20)2H and C(21)H), 7.18 (2H, d, *J* = 7.0 Hz, C(19/20)2H), 7.04 (2H, d, *J* = 8.5 Hz, C(14/15)2H), 5.90 (1H, d, *J* = 10.0 Hz, N(9)H), 5.14 (1H, dt, *J* = 8.0, 5.0 Hz, C(10)H), 4.73 (1H, d, *J* = 6.5 Hz, C(4)H), 4.61 (1H, d, *J* = 14.5 Hz, C(12)**H**H'), 4.23 (1H, d, *J* = 14.5 Hz, C(12)H**H'**), 3.89 – 3.69 (3H, m, $C(1)H_2$ and C(6)**H**H'), 3.38 (1H, dd, *J* = 14.5, 5.0 Hz, C(17)**H**H'), 3.32–3.19 (2H, m, C(6)H**H'** and C(17)H**H'**), 2.22–2.08 (3H, m, C(2)**H**H', C(3)**H**H' and C(7)**H**H'), 1.95–1.78 (3H, m, C(2)H**H'**, C(3)H**H'** and C(7)H**H'**); δ_C (100 MHz, $CDCl_3$) 175.2 (C5), 171.3 (C8), 168.5 (C11), 137.1 (C18), 136.5 (C13), 132.4 (2 × C14/C15), 129.8 (2 × C14/C15), 129.4 (2 × C19/C20), 128.8 (2 × C19/C20), 126.9 (C21), 122.2 (C16), 56.0 (C4), 52.9 (C10), 50.2 (C1), 49.9 (C12), 45.1 (C6), 37.6 (C17), 37.3 (C7), 32.7 (C3), 21.2 (C2); HRMS (ESI) calcd. for $C_{24}H_{26}{}^{79}BrN_3NaO_3$ 506.1050 Found: $[MNa]^+$, 506.1083 (−2.4 ppm error).

(7*S*,12a*S*)-7-Benzyl-2-(4-(trifluoromethyl)benzyl)octahydropyrrolo[2,1-c][1,4,7]triazecine-1,5,8(2H)-trione (14d)



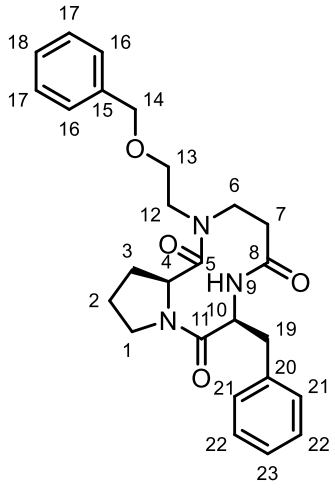
(3*S*,8a*S*)-2-Acryloyl-3-benzylhexahydropyrrolo[1,2-a]pyrazine-1,4-dione **13a** (73 mg, 0.25 mmol, 1 equiv.) was dissolved in methanol (1 mL), and 4-trifluoro-benzylamine (40 µL, 0.28 mmol, 1.1 equiv.) was added. The reaction was stirred for 18 h, and the solvent was removed in vacuo. Purification by flash column chromatography (4:1 ethyl acetate:hexane) yielded the product as a white solid (89 mg, 0.19 mmol, 77%). R_f 0.24 (1:4 hexane:ethyl acetate); m.p. 229–231 °C; $[\alpha]_D^{20}$ +19.8 (*c* 0.50, $CHCl_3$); ν_{max}/cm^{-1} (thin film) 3280, 2927, 1644, 1620, 1417, 1326, 1163, 1123, 1110, 1067, 816, 751, 700; δ_H (400 MHz, DMSO-d_6) 8.65 (1H, d, *J* = 10.5 Hz, N(9)H), 7.67 (2H, d, *J* = 8.0 Hz, C(14/15)2H), 7.39 (2H, d, *J* = 8.0 Hz, C(14/15)2H), 7.21 (4H, d, *J* = 4.0 Hz, C(20)2H and C(21)2H), 7.16–7.10 (1H, m, C(22)H), 5.32 (1H, d, *J* = 16.0 Hz, C(12)**H**H'), 4.87 (1H, td, *J* = 10.5, 3.5 Hz, C(10)H), 4.64 (1H, d, *J* = 8.0 Hz, C(4)H), 3.86 (1H, d, *J* = 16.0 Hz, C(12)H**H'**), 3.76–3.66 (1H, m, C(1)**H**H'), 3.61–3.48 (3H, m, C(6)H_2 and C(18)**H**H'), 3.26–3.18 (C(1)H**H'**), 2.65 (1H, dd, *J* = 14.0, 10.5 Hz, C(18)H**H'**), 2.35–2.25 (1H, m, C(7)**H**H'), 2.15–2.04 (1H, m, C(3)C**H**H'), 2.02–1.89 (2H, m, NC(2)**H**H' and C(7)H**H'**), 1.87–1.78 (1H, m, C(3)H**H'**), 1.78–1.68 (C(2)H**H'**); δ_C (100 MHz, $CDCl_3$) 174.2 (C5), 171.4 (C8), 168.1 (C11), 143.1 (C13/C19), 138.7 (C13/C19), 129.1 (2 × C14/C20/C21), 128.0 (2 × C14/C20/C21), 127.7 (2 × C14/C20/C21), 127.6 (q, $^2J_{CF}$ = 31.5 Hz, C16), 126.0 (C22), 125.4 (q, $^3J_{CF}$ = 3.5 Hz, 2 × C15), 124.3 (q, $^1J_{CF}$ = 270.5 Hz, C17), 55.2 (C4), 52.5 (C10), 49.3 (C6), 48.3 (C12), 44.8 (C1), 36.7 (C18), 35.9 (C7), 32.0 (C3), 20.6 (C2); δ_F (376 MHz, $CDCl_3$) –60.8 (3F, s, $ArCF_3$); HRMS (ESI) calcd. for $C_{24}H_{26}F_3N_3NaO_3$ 496.1818 Found: $[MNa]^+$, 496.1831 (−3.2 ppm error).

(7*S*,12a*S*)-7-benzyl-2-(2,2-difluoroethyl)octahydropyrrolo[2,1-c][1,4,7]triazecine-1,5,8(2H)-trione (14e)



(3*S*,8a*S*)-2-Acryloyl-3-benzylhexahydropyrrolo[1,2-a]pyrazine-1,4-dione **13a** (99 mg, 0.33 mmol, 1 equiv.) was dissolved in methanol (1 mL), and 2,2-difluoro-ethylamine was added (27 µL, 0.369 mmol, 1 equiv.) was added. The reaction was stirred for 18 h, and the solvent was removed in vacuo. Purification by flash column chromatography (1:1 ethyl acetate:CH_2Cl_2) yielded the product as an off-white solid (104 mg, 0.27 mmol, 82%). R_f 0.50 (1:9 hexane:ethyl acetate); m.p. 75–80 °C; $[\alpha]_D^{20}$ +20.5 (*c* 0.50, $CHCl_3$); ν_{max}/cm^{-1} (thin film) 3278, 2958, 1639, 1542, 1411, 1156, 1120, 1078, 1032, 753, 737, 701, 479; δ_H (400 MHz, $CDCl_3$) 7.29–7.23 (2H, m, C(16/17)2H), 7.23–7.13 (3H, m, C(16/17)2H and C(18)H), 6.36 (1H, d, *J* = 9.5 Hz, N(9)H), 5.75 (1H, tt, *J* = 56.5, 4.0 Hz, C(13)H), 5.09 (1H, ddd, *J* = 13.5, 12.0, 9.0 Hz, C(10)H), 4.70 (1H, dd, *J* = 8.0, 1.5 Hz, C(4)H), 3.92 (1H, ddd, *J* = 14.0, 11.0, 2.5 Hz, C(6)**H**H'), 3.80–3.50 (3H, m, C(1)**H**H' and C(12)H_2), 3.48–3.28 (3H, m, C(1)H**H'**, C(6)H**H'** and C(14)**H**H'), 3.20 (1H, dd, *J* = 14.5, 8.0 Hz, C(14)H**H'**), 2.35–2.23 (2H, m, C(7)H_2), 2.16–1.97 (2H, m, C(2)**H**H' and C(3)**H**H'), 1.89–1.76 (2H, m, C(2)H**H'** and C(3)H**H'**); δ_C (100 MHz, $CDCl_3$) 175.7 (C5), 171.3 (C8), 168.6 (C11), 136.9 (C15), 129.3 (2 × C16/C17), 128.7 (2 × C16/C17), 126.9 (C18), 113.3 (t, $^1J_{CF}$ 240.5 Hz, C13), 55.6 (C4), 53.0 (C10), 50.9 (t, $^2J_{CF}$ 26.5 Hz, C12), 50.1 (C1), 47.5 (C6), 37.6 (C7), 37.1 (C14), 32.4 (C3), 21.4 (C2); δ_F (376 MHz, $CDCl_3$) –119.7 (1F, dddd, *J* = 290.5, 56.5, 18.0, 12.0 Hz, CH**F**F'), –122.1 (1F, dddd, *J* = 290.5, 56.5, 16.5, 11.0 Hz, CHF**F'**); HRMS (ESI) calcd. for $C_{19}H_{23}F_2N_3NaO_3$ 420.1600 Found: $[MNa]^+$, 402.1611 (−0.5 ppm error).

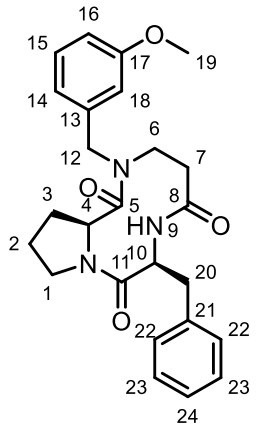
(7*S*,12a*S*)-7-Benzyl-2-(2-(benzyloxy)ethyl)octahydropyrrolo[2,1-c][1,4,7]triazecine-1,5,8(2H)-trione (14f)



(3*S*,8a*S*)-2-Acryloyl-3-benzylhexahydropyrrolo[1,2-a]pyrazine-1,4-dione **13a** (41 mg, 0.14 mmol, 1 equiv.) was dissolved in methanol (0.5 mL), and 2-benzoyloxy-1-ethanamine (21 µL, 0.15 mmol, 1.1 equiv.) was added. The reaction was stirred for 18 h, and the solvent was removed in vacuo. Purification by flash column chromatography (9:1 ethyl acetate:hexane) yielded the product as a yellow oil (38 mg, 0.08 mmol, 61%). R_f 0.15 (1:9 hexane:ethyl acetate); $[\alpha]_D^{20}$ +32.7 (*c* 0.50, $CHCl_3$); ν_{max}/cm^{-1} (thin film); 3281, 2926, 1640, 1537, 1497, 1453, 1408, 1360, 1344, 1205, 1155, 1104, 750, 699; δ_H (400 MHz, $CDCl_3$) 7.28–7.22 (2H, m , C(17/18/21/22)2H), 7.20–7.14 (3H, m, C(17/18/21/22)2H and C(18/23)H), 7.12–7.07 (3H, m, C(17/18/21/22)2H and C(18/23)H), 7.06–7.02 (2H, m, C(17/18/21/22)2H), 6.44 (1H, d, *J* = 9.5 Hz, N(9)H), 5.10 (1H, td, *J* = 9.5, 4.0 Hz, C(10)H), 4.65–4.62 (1H, m, C(4)H), 4.29 (1H, d, *J* = 12.0 Hz, C(14)**H**H'), 4.17 (1H, d, *J* = 12.0 Hz, C(14)H**H'**), 4.04–3.96 (1H, m, C(12)**H**H'), 3.90–3.75 (2H, m, C(1)**H**H' and C(6)**H**H'), 3.72–3.64 (2H, m, C(1)H**H'** and C(13)**H**H'), 3.45–3.38 (2H, m, C(13)H**H'** and C(19)**H**H'), 3.25 (1H, dt, *J* = 15.5, 4.0 Hz, C(6)**H**H'), 2.97 (1H, ddd, *J* = 14.0, 6.0, 4.0 Hz, C(19)H**H'**), 2.86 (1H, dd, *J* = 15.5 Hz, C(12)H**H'**), 2.43 (1H, td, *J* = 12.5, 3.5 Hz, C(7)**H**H'), 2.17–2.09 (1H, m, C(7)H**H'**), 2.09 – 1.98 (2H, m, C(2)**H**H' and C(3)**H**H'), 1.89–1.71 (2H, m, C(2)H**H'** and C(3)H**H'**); δ_C (100 MHz, $CDCl_3$) 175.2 (C5), 171.7 (C8), 168.7 (C11), 137.5 (C15/C20), 137.1 (C15/C20), 129.0 (2 × C16/C17/C21/C22), 128.8 (2 × C16/C17/C21/C22),

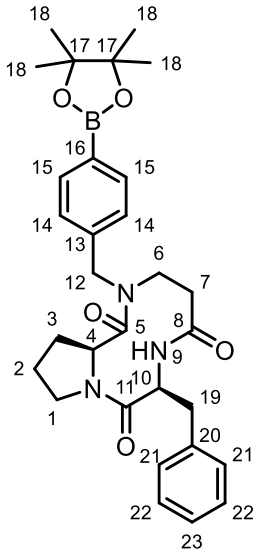
128.7 (2 × C16/C17/C21/C22), 128.3 (C18/C23), 128.1 (2 × C16/C17/C21/C22), 126.6 (C18/C23), 73.1 (C14), 66.6 (C13), 55.9 (C4), 52.8 (C10), 50.2 (C1), 48.9 (C12), 46.8 (C6), 37.8 (C19), 37.4 (C7), 32.4 (C3), 21.4 (C2); HRMS (ESI) calcd. for $C_{26}H_{32}N_3O_4$ 450.2387 Found: $[MH]^+$, 450.2402 (1.7 ppm error).

(7*S*,12a*S*)-7-Benzyl-2-(3-methoxybenzyl)octahydropyrrolo[2,1-c][1,4,7]triazecine-1,5,8(2H)-trione (14g)



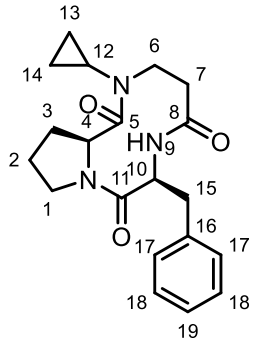
(3*S*,8a*S*)-2-Acryloyl-3-benzylhexahydropyrrolo[1,2-a]pyrazine-1,4-dione **13a** (75 mg, 0.26 mmol, 1 equiv.) was dissolved in methanol (1 mL), and 3-methoxy-benzylamine (35 µL, 0.28 mmol, 1.1 equiv.) was added. The reaction was stirred for 18 h, and the solvent was removed in vacuo. Purification by flash column chromatography (7:3 ethyl acetate:hexane) yielded the product as a white solid (94 mg, 0.22 mmol, 86%). R_f 0.24 (1:4 hexane:ethyl acetate); m.p. 178–180 °C; $[\alpha]_D^{20}$ +31.4 (*c* 0.50, $CHCl_3$); ν_{max}/cm^{-1} (thin film) 3279, 2958, 1640, 1602, 1541, 1489, 1416, 1338, 1259, 1191, 1141, 1049, 748, 698; δ_H (400 MHz, $CDCl_3$) 7.30–7.24 (2H, m, ArH), 7.23–7.14 (4H, m, ArH), 6.84–6.78 (1H, m, ArH), 6.77–6.71 (2H, m, ArH), 5.98 (1H, d, *J* = 10.0 Hz, N(9)H), 5.12 (1H, td, *J* = 10.0, 5.0 Hz, C(10)H), 4.74 (1H, dd, *J* = 7.5, 1.5 Hz, C(4)H), 4.65 (1H, d, *J* = 14.5 Hz, C(12)**H**H'), 4.25 (1H, d, *J* = 14.5 Hz, C(12)H**H'**), 3.88–3.68 (6H, m, C(6)**H**H', $C(1)H_2$ and $C(19)H_3$), 3.49 (1H, dd, *J* = 14.5, 4.5 Hz, C(20)**H**H'), 3.31 (1H, ddd, *J* = 15.5, 4.0, 3.0 Hz, C(6)H**H'**), 3.08 (1H, dd, *J* = 14.5, 9.0 Hz, C(20)H**H'**), 2.20–2.08 (3H, m, $C(3)H_2$ and C(7)**H**H'), 1.99–1.80 (3H, m, $C(2)H_2$ and C(7)H**H'**); δ_C (100 MHz, $CDCl_3$) 175.1 (C5), 171.4 (C8), 168.5 (C11), 160.2 (C17), 139.0 (C13/C21), 137.3 (C13/C21), 130.4 (C14/C15/C16/C18/C24), 129.2 (2 × C22/C23), 128.7 (2 × C22/C23), 126.8 (C14/C15/C16/C18/C24), 120.2 (C14/C15/C16/C18/C24), 114.3 (C14/C15/C16/C18/C24), 112.9 (C14/C15/C16/C18/C24), 56.0 (C4), 55.3 (C19), 53.0 (C10), 50.1 (C1), 50.1 (C12), 44.9 (C6), 37.8 (C20), 37.2 (C7), 32.7 (C3), 21.2 (C2); HRMS (ESI) calcd. for $C_{25}H_{29}N_3NaO_4$ 458.2051 Found: $[MK]^+$, 458.2051 (−1.1 ppm error).

(7*S*,12a*S*)-7-Benzyl-2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl)octahydropyrrolo[2,1-c][1,4,7]triazecine-1,5,8(2H)-trione (14h)



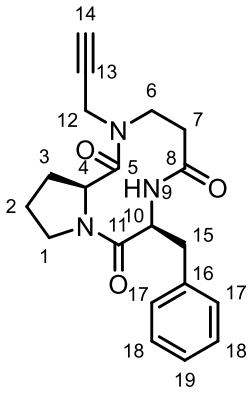
(3*S*,8a*S*)-2-Acryloyl-3-benzylhexahydropyrrolo[1,2-a]pyrazine-1,4-dione **13a** (75 mg, 0.25 mmol, 1 equiv.) was dissolved in methanol (1 mL), and (4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)methanamine (65 mg, 0.28 mmol, 1.1 equiv.) was added. The reaction was stirred for 18 h, and the solvent was removed in vacuo. Purification by flash column chromatography (1:1 hexane:ethyl acetate) yielded the product as a white solid (103 mg, 0.19 mmol, 77%). R_f 0.11 (1:1 hexane:ethyl acetate); m.p. 98–101 °C; $[\alpha]_D^{20}$ +39.5 (*c* 0.50, $CHCl_3$); ν_{max}/cm^{-1} (thin film) 3279, 2979, 2247, 1641, 1611, 1399, 1359, 1141, 1088, 908, 727, 700, 657; δ_H (400 MHz, $CDCl_3$) 7.73 (2H, d, *J* = 7.5 Hz, C(15)2H), 7.31–7.25 (2H, m, C(21/22)2H), 7.23–7.13 (5H, m, C(14)2H, C(21/22)2H and C(23)H), 6.07–5.81 (1H, m, N(9)H), 5.09 (1H, td, *J* = 9.0, 4.5 Hz, C(10)H), 4.72 (1H, d, *J* = 7.0 Hz, C(4)H), 4.61–4.51 (1H, m, C(12)**H**H'), 4.45–4.31 (1H, m, C(12)H**H'**), 3.89–3.63 (3H, m, C(1)H_2 and C(6)**H**H'), 3.55–3.41 (1H, m, C(19)**H**H'), 3.35–3.24 (1H, m, C(6)H**H'**), 3.17–3.06 (C(19)H**H'**), 2.20–2.05 (3H, m, C(3)H_2 and C(7)**H**H'), 1.96–1.72 (3H, m, C(2)H_2 and C(7)H**H'**), 1.34 (12H, s, C(18)4H_3); δ_C (100 MHz, $CDCl_3$) 175.0 (C5), 171.5 (C8), 168.5 (C11), 140.5 (C13/C16/C20), 137.2 (C13/C16/C20), 137.1 (C13/C16/C20), 135.7 (2 × C15), 129.2 (2 × C14), 128.7 (2 × C21/C22), 127.5 (2 × C21/C22), 126.8 (C23), 84.0 (2 × C17), 56.0 (C4), 53.1 (C10), 50.5 (C12), 50.1 (C1), 45.0 (C6), 37.7 (C19), 37.3 (C7), 32.6 (C3), 25.0 (4×C18), 21.2 (C2); HRMS (ESI) calcd. for $C_{30}H_{38}BKN_3O_5$ 570.2536 Found: $[MK]^+$, 570.2557 (−3.2 ppm error).

(7*S*,12a*S*)-7-Benzyl-2-cyclopropyloctahydropyrrolo[2,1-c][1,4,7]triazecine-1,5,8(2H)-trione (14i)



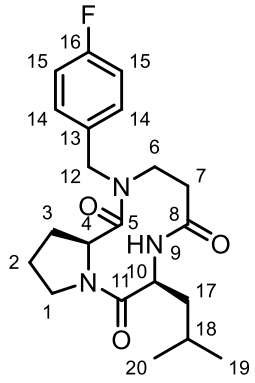
(3*S*,8a*S*)-2-Acryloyl-3-benzylhexahydropyrrolo[1,2-a]pyrazine-1,4-dione **13a** (75 mg, 0.25 mmol, 1 equiv.) was dissolved in methanol (1 mL), and cyclopropylamine (20 µL, 0.28 mmol, 1.1 equiv.) was added. The reaction was stirred for 18 h, and the solvent was removed in vacuo. Purification by flash column chromatography (4:1 ethyl acetate:CH_2Cl_2) yielded the product as a white solid as a 5:3 mixture of diastereomers (37 mg, 0.10 mmol, 42%). R_f 0.19 (9:1 ethyl acetate:CH_2Cl_2); m.p. 180–183 °C; $[\alpha]_D^{20}$ −49.4 (*c* 0.50, $CHCl_3$); ν_{max}/cm^{-1} (thin film); 3268, 2959, 1636, 1537, 1420, 1363, 1043, 913, 729, 700; δ_H (400 MHz, $CDCl_3$) 7.43–7.37 (1H, m, C(19)H – major diastereomer), 7.30–7.24 (5H, m, C(17/18)2H -both diastereomers and C(19)H – minor diastereomer), 7.23–7.16 (4H, m, C(17/18) – both diastereomers), 6.15 (1H, d, *J* = 9.5 Hz, N(9)H – major diastereomer), 5.82 (1H, d, *J* = 6.0 Hz, N(9)H – minor diastereomer), 5.18 (1H, td, *J* = 9.5, 4.5 Hz, C(10)H – major diastereomer), 4.74 (1H, d, *J* = 8.0 Hz, C(4)H – minor diastereomer) 4.68 (1H, d, *J* = 8.0 Hz, C(4)H – major diastereomer), 4.53–4.44 (1H, m, C(10)H – minor diastereomer), 4.07 (1H, dd, *J* = 13.0, 10.0 Hz, C(6)**H**H' – minor diastereomer), 3.90–3.30 (7H, m, C(1)**H** – both diastereomers, C(6)**H**H' – major diastereomer C(6)H**H'** - both diastereomers and C(15)**H**H' – both diastereomers), 3.13–2.89 (4H, m, C(1)H**H'** – both diastereomers and C(15)H**H'**Ph – both diastereomers), 2.83–2.71 (1H, m, C(12)H – minor diastereomer), 2.64–2.53 (1H, m, C(12)H – major diastereomer), 2.52–2.43 (1H, m, C(7)**H**H' – minor diastereomer), 2.34–2.20 (3H, m, C(7)**H**H' – major diastereomer, and C(7)H**H'** – both diastereomers), 2.17–1.93 (4H, m, C(2)**H**H' and C(3)H**H'** – both diastereomers), 1.91–1.71 (4H, m, C(2)H**H'** and C(3)H**H'** – both diastereomers), 1.05–0.95 (1H, m, C(13)**H**H' – major diastereomer), 0.94–0.64 (4H, m, C(13)**HH'** – minor diastereomers and C(14)**H**H' – both diastereomers), 0.61–0.52 (2H, m, C(14)H**H'** – both diastereomers), 0.47–0.38 (1H, m, C(13)H**H'** – major diastereomer); δ_C (100 MHz, $CDCl_3$) 178.4 (C5 – minor diastereomer), 177.6 (C5 – major diastereomer), 171.7 (C8 – major diastereomer), 171.5 (C8 – minor diastereomer), 168.3 (C11 – major diastereomer), 167.6 (C11 – minor diastereomer), 138.5 (C16 – minor diastereomer), 137.4 (C16 – major diastereomer), 130.4 (2 × C17/C18 – minor diastereomer), 129.3 (2 × C17/C18 – major diastereomer), 128.6 (2 × C17/C18 – major diastereomer), 128.2 (2 × C17/C18 – minor diastereomer), 126.7 (C19 – major diastereomer), 126.4 (C19 – minor diastereomer), 58.0 (C4 – minor diastereomer), 56.9 (C4 – major diastereomer), 56.1 (C10 – minor diastereomer), 53.0 (C10 – major diastereomer), 49.9 (C1 – major diastereomer), 48.7 (C1 – minor diastereomer), 46.7 (C6 – major diastereomer), 45.1 (C6 – minor diastereomer), 38.0 (C15 – minor diastereomer), 37.6 (C15 – major diastereomer), 37.4 (C7 – major diastereomer), 33.5 (C7 – minor diastereomer), 32.9 (C3 – minor diastereomer), 32.4 (C3 – major diastereomer), 30.1 (C12 – major diastereomer), 29.8 (C12 – minor diastereomer), 22.2 (C2 – minor diastereomer), 21.1 (C2 – major diastereomer), 11.5 (C13 – minor diastereomer), 9.7 (C13 – major diastereomer), 6.8 (C14 – major diastereomer), 6.6 (C14 – minor diastereomer); HRMS (ESI) calcd. for $C_{20}H_{25}N_3NaO_3$ 378.1788 Found: $[MNa]^+$, 378.1794 (−2.3 ppm error).

(7*S*,12a*S*)-7-Benzyl-2-(prop-2-yn-1-yl)octahydropyrrolo[2,1-c][1,4,7]triazecine-1,5,8(2H)-trione (14j)



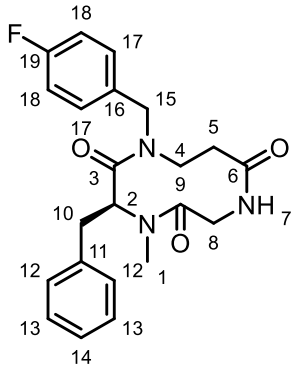
(3*S*,8a*S*)-2-Acryloyl-3-benzylhexahydropyrrolo[1,2-a]pyrazine-1,4-dione **13a** (74 mg, 0.25 mmol, 1 equiv.) was dissolved in methanol (1 mL), and propargylamine was added (18 µL, 0.28 mmol, 1.1 equiv.) was added. The reaction was stirred for 18 h, and the solvent was removed in vacuo. Purification by flash column chromatography (7:3 ethyl acetate:hexane) yielded the product as a white solid (71 mg, 0.20 mmol, 81%). R_f 0.39 (ethyl acetate); 168–171 °C; $[\alpha]_D^{20}$ +102.4 (*c* 0.50, $CHCl_3$); ν_{max}/cm^{-1} (thin film) 3280, 2967, 1640, 1538, 1410, 1278, 1193, 1143, 1056, 910, 729, 699; δ_H (400 MHz, $CDCl_3$) 7.29–7.23 (2H, m, C(17/18)2H), 7.18 (3H, t, *J* = 8.0, Hz, C17/18)2H and C(19)H), 6.27–6.10 (1H, m, N(9)H), 5.17–5.09 (1H, m, C(10)H), 4.70 (1H, d, *J* = 8.0 Hz, C(4)H), 4.47–4.34 (1H, C(6)**H**H'), 3.94 (1H, t, *J* = 14.5 Hz, C(6)H**H'**), 3.86–3.77 (1H, m, C(1)**H**H'), 3.72–3.66 (2H, m, C(12)H_2), 3.53 (1H, dt, *J* = 16.0, 3.5 Hz, C(1)H**H'**), 3.42 (1H, dd, *J* = 15.0, 5.0 Hz, C(15)**H**H'), 3.24–3.12 (1H, m, C(15)H**H'**), 2.76–2.64 (1H, m, C(7)**H**H'), 2.32–2.23 (1H, m, C(7)H**H'**), 2.19–1.75 (5H, m, C(2)H_2, C(3)H_2 and C(14)H); δ_C (100 MHz, $CDCl_3$) 174.6 (C5), 171.4 (C8), 168.5 (C11), 137.1 (C16), 129.3 (2 × C17/C18), 128.7 (2 × C17/18), 126.8 (C19), 79.7 (C13), 73.2 (C14), 55.8 (C4), 53.2 (C10), 50.1 (C12), 46.7 (C1), 37.7 (C15), 37.5 (C6), 36.8 (C7), 32.4 (C3), 21.3 (C2); HRMS (ESI) calcd. for $C_{20}H_{23}N_3NaO_3$ 376.1632 Found: $[MNa]^+$, 376.1642 (−1.9 ppm error).

(7*S*,12a*S*)-2-(4-fluorobenzyl)-7-isobutyloctahydropyrrolo[2,1-c][1,4,7]triazecine-1,5,8(2H)-trione (15a)



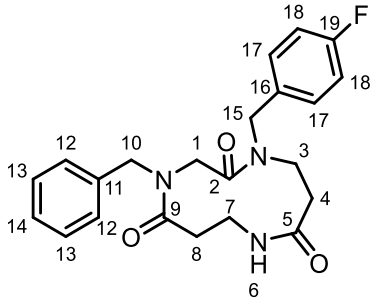
(3*S*,8a*S*)-2-Acryloyl-3-isobutylhexahydropyrrolo[1,2-a]pyrazine-1,4-dione **13b** (88 mg, 0.33 mmol, 1 equiv.) was dissolved in THF (1 mL), and 4-fluoro-benzylamine (53 µL, 0.468 mmol, 1.4 equiv.) was added. The reaction was stirred for 18 h, and the solvent was removed in vacuo. Purification by flash column chromatography (7:3 CH_2Cl_2:ethyl acetate) yielded the product as a yellow oil (57 mg, 0.15 mmol, 44%). R_f 0.27 (3:7 ethyl acetate:CH_2Cl_2); $[\alpha]_D^{20}$ +2.8 (*c* 0.50, $CHCl_3$); ν_{max}/cm^{-1} (thin film) 3264, 2959, 1639, 1606, 1509, 1414, 1222, 1047, 909, 814, 729, 584; δ_H (400 MHz, $CDCl_3$) 7.27–7.21 (2H, m, C(14)2H), 7.06–7.00 (2H, m, C(15)2H), 6.23–6.14 (1H, m, N(9)H), 4.94 (1H, d, *J* = 14.5 Hz, C(12)**H**H'), 4.81 (1H, td, *J* = 10.5, 3.5 Hz, C(10)H), 4.77–4.73 (1H, m, C(4)H), 4.13 (1H, d, *J* = 14.5 Hz, C(12)H**H'**), 3.85 (1H, dd, *J* = 15.5, 12.5 Hz, C(6)**H**H'), 3.80–3.63 (2H, m, C(1)H_2), 3.36 (1H, dt, *J* = 15.5, 3.5 Hz, C(6)H**H'**), 2.34 (1H, dd, *J* = 12.5, 3.5 Hz, C(7)**H**H'), 2.24–1.79 (6H, m, C(2)H_2, C(3)H_2, C(7)H**H'** and C(17)**H**H'), 1.57–1.42 (2H, m, C(17)H**H'** and C(18)H), 0.91 (3H, d, *J* = 6.5 Hz, C(19)H_3), 0.88 (3H, d, *J* = 6.5 Hz, C(20)H_3); δ_C (100 MHz, $CDCl_3$) 175.5 (C5), 171.6 (C8), 169.3 (C11), 126.6 (d, $^1J_{CF}$ = 246.0 Hz, C16), 162.6 (d, $^4J_{CF}$ = 3.5 Hz, C13), 133.2 (d, $^3J_{CF}$ = 8.5 Hz, 2 × C14), 116.1 (d, $^2J_{CF}$ = 21.0 Hz, 2 × C15), 56.0 (C4), 51.2 (C10), 50.3 (C1), 49.4 (C12), 44.9 (C6), 40.8 (C17), 37.3 (C7), 32.7 (C3), 24.6 (C18), 23.6 (C19/C20), 21.2 (C19/C20), 21.2 (C2); δ_F (376 MHz, $CDCl_3$) –113.5 (1F, s, C(16)F); HRMS (ESI) calcd. for $C_{21}H_{28}FN_3NaO_3$ 412.2007 Found: $[MNa]^+$, 412.2018 (−3.0 ppm error).

(*S*)-3-benzyl-1-(4-fluorobenzyl)-4-methyl-1,4,7-triazecane-2,5,8-trione (15b)



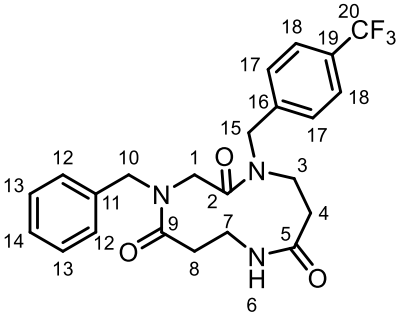
(*S*)-1-Acryloyl-3-benzyl-4-methylpiperazine-2,5-dione **13h** (164 mg, 0.601 mmol, 1 equiv.) was dissolved in anhydrous THF (1.5 mL), and 4-fluoro-benzylamine (76 µL, 0.661 mmol, 1.1 equiv.) was added. The reaction was stirred for 18 h, and the solvent was removed in vacuo. Purification by flash column chromatography (9:1 ethyl acetate:hexane) yielded the product as an off white solid (85 mg, 0.22 mmol, 36%) In $CDCl_3$, the product exists as a 4:1 mixture of rotamers. m.p. 171–172°C. R_f 0.19 (9:1 ethyl acetate:hexane); $[\alpha]_D^{20}$ +1.3 (*c* 0.50, $CHCl_3$); ν_{max}/cm^{-1} (thin film); 3268, 3065, 2926, 1634, 1548, 1509, 1453, 1434, 1392, 1221, 1097, 908, 853, 824, 730, 701; δ_H (400 MHz, $CDCl_3$); 7.97 (1H, d, *J* = 10.5 Hz, N(7)H, major rotamer), 7.66 (1H, d, *J* = 10.5 Hz, N(7)H, minor rotamer), 7.22–7.12 (14H, m, 7 × ArH, both rotamers), 7.04–6.96 (4H, m, 2×ArH, both rotamers), 5.09 (2H, d, *J* = 16.5 Hz, C(15)**H**H', both rotamers), 5.04 (2H, t, *J* = 15.0 Hz, C(8)**H**H', both rotamers), 4.61 (2H, t, *J* = 7.5 Hz, C(2)H, both rotamers), 3.68 (2H, s, *J* = 15.0 Hz, C(8)H**H'**, both rotamers), 3.47 (2H, d, *J* = 16.5 Hz, C(15)H**H'**, both rotamers), 3.20 (6H, s, $C(1)H_3$, both rotamers), 3.19–3.03 (4H, m, $C(10)H_2$, both rotamers), 2.98–2.84 (4H, m, $C(4)H_2$, both rotamers), 2.24–2.17 (4H, m, $C(5)H_2$, both rotamers); δ_C (100 MHz, $CDCl_3$); 173.8 (C9, major rotamer), 173.7 (C9, minor rotamer), 172.2 (C6, major rotamer), 172.1 (C6, minor rotamer), 170.0 (C3, major rotamer), 169.9 (C3, minor rotamer), 162.4 (d, $^1J_{CF}$ = 245.5 Hz, C19, both rotamers), 135.2 (C11, minor rotamer), 135.2 (C11, major rotamer), 132.4 (d, $^4J_{CF}$ = 3.0 Hz, C16, minor rotamer), 132.3 (d, $^4J_{CF}$ = 3.0 Hz, C16, major rotamer), 130.1 (d, $^3J_{CF}$ = 8.0 Hz, 2 × C17, minor rotamer), 130.0 (d, $^3J_{CF}$ = 8.0 Hz, 2 × C17, major rotamer), 129.1 (2 × C12/C13, both rotamers), 129.0 (2 × C12/C13, both rotamers), 127.7 (C14, both rotamers), 115.7 (d, $^2J_{CF}$ = 21.0 Hz, 2 × C18, minor rotamer), 115.7 (d, $^2J_{CF}$ = 21.0 Hz, 2 × C18, major rotamer), 57.3 (C2, both rotamers), 49.1 (C8, both rotamers), 44.5 (C15, major rotamer), 44.3 (C15, minor rotamer), 44.2 (C4, major rotamer), 44.1 (C4, minor rotamer), 38.0 (C10, both rotamers), 36.6 (C5, both rotamers), 31.7 (C1, both rotamers); δ_F (376 MHz, $CDCl_3$) −114.1 (1F, s, C(19)F); HRMS (ESI) calcd. for $C_{22}H_{24}FN_3NaO_3$ 420.1694 Found: $[MNa]^+$, 420.1700 (−2.0 ppm error).

4-Benzyl-1-(4-fluorobenzyl)-1,4,8-triazacycloundecane-2,5,9-trione (15c)



1-Acryloyl-4-benzyl-1,4-diazepane-2,5-dione **13j** (83 mg, 0.30 mmol, 1 equiv.) was dissolved was dissolved in THF (0.9 mL), and 4-fluoro-benzylamine (38 µL, 0.33 mmol, 1.1 equiv.) was added. The reaction was stirred for 18 h, and the solvent was removed in vacuo. Purification by flash column chromatography (1:4 CH_2Cl_2:ethyl acetate) afforded the title compound as a clear oil (61 mg, 0.15 mmol, 51%). In $CDCl_3$, the title compound exists as a 10:5:1.5:1 (major rotamer : minor rotamer A : minor rotamer B : minor rotamer C) mixture of rotamers. R_f 0.45 (1:9 methanol:ethyl acetate); ν_{max}/cm^{-1} (thin film); 3301, 3066, 2944, 2245, 1627, 1509, 1442, 1415, 1222, 908, 726, 699, 501; δ_H (400 MHz, $CDCl_3$) NMR data for major rotamer only 7.37–7.15 (6H, m, C(12)2H, C(13)2H and C(17)2H), 7.10–7.03 (1H, m, C(14)H), 7.03–6.94 (2H, m, C(18)2H), 6.34 (1H, dd, *J* = 9.0, 3.0 Hz, N(6)H), 5.81 (1H, d, *J* = 15.0 Hz, C(10)**H**H'), 4.69 (1H, d, *J* = 16.0 Hz, C(15)**H**H'), 4.45 (1H, d, *J* = 17.0 Hz, C(1)**H**H'), 4.38 (1H, d, *J* = 16.0 Hz, C(15)H**H'**), 4.10 (1H, d, *J* = 15.0 Hz, C(10)H**H'**), 4.05 (2H, m, C(3)**H**H' and C(7)**H**H'), 3.45 (1H, d, *J* = 17.0 Hz, C(1)H**H'**), 3.30–3.20 (2H, m, C(3)H**H'** and C(7)H**H'**), 2.99–2.90 (1H, m, C(4)**H**H'), 2.78–2.67 (1H, m, C(8)**H**H'), 2.40 (1H, dd, *J* = 12.0, 8.5 Hz, C(4)H**H'**), 2.27 (1H, d, *J* = 13.5 Hz, C(8)H**H'**); δ_C (100 MHz, $CDCl_3$) NMR data for major rotamer only 173.3 (C9), 171.5 (C2), 171.1 (C6), 162.5 (d, $^1J_{CF}$ = 246.0 Hz, C19), 136.8 (C11), 131.5 (d, $^4J_{CF}$ = 2.5 Hz, C(16), 128.8 (2 × C12/13), 128.6 (d, $^3J_{CF}$ = 8.0 Hz, 2 × C17), 128.4 (2 × C12/13), 127.8 (C14), 116.2 (d, $^2J_{CF}$ = 21.5 Hz, 2 × C18), 54.2 (C15), 51.4 (C10), 46.9 (C1), 45.2 (C3), 37.6 (C7), 34.2 (C4), 33.9 (C8); δ_F (376 MHz, $CDCl_3$) NMR data for major rotamer only −113.6 (1F, s, C(19)F); HRMS (ESI) calcd. for $C_{22}H_{24}FN_3NaO_3$ 420.1469. Found: $[MNa]^+$, 420.1715 (−4.4 ppm error). Diagnostic NMR resonances for the minor rotamers can be found at: δ_H (400 MHz, $CDCl_3$) 6.45 (1H, br d, *J* = 8.5 Hz, N(6)H, minor rotamer A); δ_C (100 MHz, $CDCl_3$) 162.3 (d, $^1J_{CF}$ = 244.5 Hz, C19, minor rotamer A), 115.6 (d, $^2J_{CF}$ = 21.5 Hz, 2 × C18, minor rotamer A), 115.6 (d, $^2J_{CF}$ = 21.0 Hz, 2 × C18, minor rotamer B); δ_F (376 MHz, $CDCl_3$) −113.8 (1F, s, C(19)F, minor rotamer B) −114.7 (1F, s, C(19)F, minor rotamer A) −114.9 (1F, s, C(19)F, minor rotamer C).

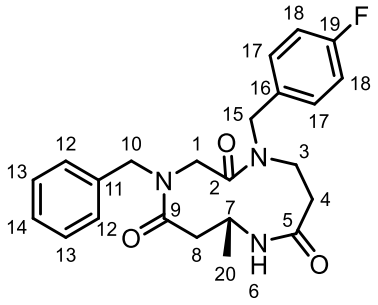
4-Benzyl-1-(4-trifluoromethylbenzyl)-1,4,8-triazacycloundecane-2,5,9-trione (15d)



1-Acryloyl-4-benzyl-1,4-diazepane-2,5-dione **13j** (74 mg, 0.27 mmol, 1 equiv.) was dissolved was dissolved in THF (0.9 mL), and 4-trifluoromethyl-benzylamine (43 µL, 0.30 mmol, 1.1 equiv.) was added. The reaction was stirred overnight, and the solvent was removed in vacuo. Purification by flash column chromatography (1:4 CH_2Cl_2:ethyl acetate) afforded the title compound as a clear oil (40 mg, 0.09 mmol, 33%). In $CDCl_3$, the title compound exists as a 4:3 mixture of rotamers. R_f 0.48 (1:9 methanol:ethyl acetate); ν_{max}/cm^{-1} (thin film) 3302, 2945, 1632, 1554, 1442, 1417, 1324, 1163, 1112, 1067, 1014, 910, 730, 699; δ_H (400 MHz, $CDCl_3$) NMR data for major rotamer only 7.61–7.55 (2H, m, C(18)2H), 7.41–7.17 (7H, m, C(12)2H, C(13)2H, C(14)H and C(17)2H), 6.30–6.12 (1H, m, N(6)H), 5.83 (1H, d, *J* = 15.0 Hz, C(10)**H**H'), 4.86–4.74 (1H, m, C(15)**H**H'), 4.51 (1H, d, *J* = 16.5 Hz, C(15)H**H'**), 4.44 (1H, d, *J* = 17.0 Hz, C(1)**H**H'), 4.17–3.96 (3H, m, C(3)**H**H', C(7)**H**H' and C(10)H**H'**), 3.45 (1H, d, *J* = 17.0 Hz, C(1)H**H'**), 3.34–3.17 (1H, m, C(7)H**H'**), 3.16–3.02 (1H, m, C(3)H**H'**), 3.02–2.91 (1H, m, C(4)**H**H'), 2.79–2.54 (1H, m, C(8)**H**H'), 2.43 (1H, dd, *J* = 12.0, 8.5 Hz, C(4)H**H'**), 2.33–2.25 (1H, m, C(8)H**H'**); δ_C (100 MHz, $CDCl_3$) NMR data for major rotamer only 173.2 (C9), 171.5 (C2/C5), 171.2 (C2/C5), 140.0 (C16), 136.7 (C11), 128.9

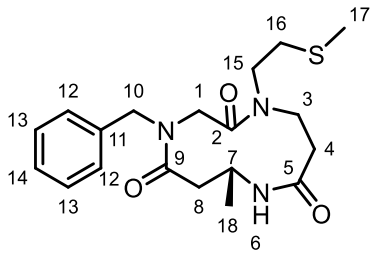
(2×C13), 128.5 (2×C12), 127.9 (q, $^{2}J_{CF}$ = 21.5 Hz, C19), 127.1 (C14), 126.6 ($^{4}J_{CF}$ = 271.5 Hz, C20), 126.2 (q, $^{4}J_{CF}$ = 3.5 Hz, 2×C17), 125.9–125.7 (m, 2×C18), 54.6 (C15), 51.5 (C10), 46.8 (C1), 45.6 (C3), 37.1 (C7), 34.3 (C4), 33.9 (C8); δ_F (376 MHz, $CDCl_3$) NMR data for major rotamer only −62.6 (3F, s, C(19)F); HRMS (ESI) calcd. for $C_{23}H_{24}F_3N_3NaO_3$ 470.1662. Found: $[MNa]^+$, 470.1667 (−2.1 ppm error). Diagnostic NMR resonances for minor rotamers be found at: δ_H (400 MHz, $CDCl_3$) 4.85–4.75 (1H, m, C(15)H, 4.36–4.26 (1H, m, C(10)H); δ_C (100 MHz, $CDCl_3$) 50.7 (C10); δ_F (376 MHz, $CDCl_3$) −62.4 (3F, s, C(19)F).

(*R*)-4-Benzyl-1-(4-fluorobenzyl)-7-methyl-1,4,8-triazacycloundecane-2,5,9-trione (15e)



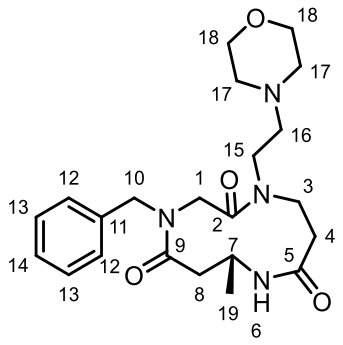
(*R*)-1-Acryloyl-4-benzyl-7-methyl-1,4-diazepane-2,5-dione **13k** (140 mg, 0.49 mmol, 1 equiv.) was dissolved was dissolved in THF (1.5 mL), and 4-fluoro-benzylamine (61 µL, 0.54 mmol, 1.1 equiv.) was added. The reaction was stirred for 18 h, and the solvent was removed in vacuo. Purification by flash column chromatography (1:1 CH_2Cl_2:ethyl acetate) afforded the title compound as a clear oil (154 mg, 0.37 mmol, 76%). In $CDCl_3$, the title compound exists as a ~13:1:1:1 mixture of rotamers. R_f 0.16 (1:1 CH_2Cl_2:ethyl acetate); $[\alpha]_D^{20}$ −114.41 (*c* 0.50, $CHCl_3$); ν_{max}/cm^{-1} (thin film) 3298, 2247, 1625, 1509, 1450, 1223, 907, 724, 646; δ_H (400 MHz, $CDCl_3$) NMR data for major rotamer only 7.38–7.15 (7H, m, C(12)2H, C(13)2H, C(14)H and C(17)2H), 7.03–6.92 (2H, m, C(18)2H), 6.50 (1H, d, *J* = 10.5 Hz, N(6)H), 5.47 (1H, d, *J* = 15.0 Hz, C(15)**H**H'), 5.34 (1H, d, *J* = 14.0 Hz, C(1)**H**H'), 4.81 (1H, d, *J* = 17.0 Hz, C(10)**H**H'), 4.75–4.62 (1H, m, C(7)H), 4.30 (1H, d, *J* = 17.0 Hz, C(10)H**H'**), 4.00–3.86 (2H, m, C(1)H**H'** and C(15)H**H'**), 3.25–3.15 (2H, m, C(3)**H**H' and C(8)**H**H'), 3.10 (1H, d, *J* = 14.5 Hz, C(3)H**H'**), 2.57 (1H, td, *J* = 13.0, 3.0 Hz, C(4)**H**H'), 2.46–2.36 (1H, m, C(8)H**H'**), 2.09 (1H, d, *J* = 13.0 Hz, C(4)H**H'**), 1.24 (3H, d, *J* = 6.5 Hz, C(20)H_3); δ_C (100 MHz, $CDCl_3$) NMR data for major rotamer only 170.1 (C5), 169.9 (C9), 168.4 (C2), 162.2 (d, $^{1}J_{CF}$ = 244.5 Hz, C19), 135.6 (C11), 132.3 (d, $^{4}J_{CF}$ = 2.0 Hz, C16), 130.0 (d, $^{3}J_{CF}$ = 8.0 Hz, 2 × C17), 128.9 (2 × C13), 127.9 (C14), 127.0 (2 × C12), 115.5 ($^{2}J_{CF}$ = 21.0 Hz, 2 × C18), 50.6 (C10), 45.8 (C1), 45.3 (C15), 44.7 (C8), 44.1 (C3), 39.7 (C7), 33.7 (C4), 22.2 (C20); δ_F (376 MHz, $CDCl_3$) NMR data for major rotamer only −114.6 (1F, s, C(19)F); HRMS (ESI) calcd. for $C_{23}H_{26}FN_3NaO_3$ 434.1850. Found: $[MNa]^+$, 434.1858 (−1.4 ppm error). Diagnostic NMR resonances for the minor rotamers can be found at: δ_H (400 MHz, $CDCl_3$) 1.38 (3H, d, *J* = 7.5 Hz, C(20)H_3, minor rotamer A), 1.35 (3H, d, *J* = 6.5 Hz, C(20)H_3, minor rotamer B), 1.22 (3H, d, *J* = 7.5 Hz, C(20)H_3, minor rotamer C); δ_C (100 MHz, $CDCl_3$) 116.1 (d, $^{2}J_{CF}$ = 21.0 Hz, 2 × C18, minor rotamer A), 115.7 (d, $^{2}J_{CF}$ = 21.0 Hz, 2 × C18, minor rotamer B); δ_F (376 MHz, $CDCl_3$) −113.3 (1F, s, C(19)F, minor rotamer A), −113.6 (1F, s, C(19)F, minor rotamer B), −114.2 (1F, s, C(19)F, minor rotamer C).

(*R*)-4-Benzyl-7-methyl-1-(2-(methylthio)ethyl)-1,4,8-triazacycloundecane-2,5,9-trione (15f)



(*R*)-1-Acryloyl-4-benzyl-7-methyl-1,4-diazepane-2,5-dione **13k** (62 mg, 0.22 mmol, 1 equiv.) was dissolved was dissolved in THF (0.65 mL), and 2-(methylthio)ethylamine (22 µL, 0.24 mmol, 1.1 equiv.) was added. The reaction was stirred overnight, and the solvent was removed in vacuo. Purification by flash column chromatography (1:1 DCM:ethyl acetate) afforded the title compound as a yellow oil (46 mg, 0.12 mmol, 56%). In $CDCl_3$, the title compound exists as a ~4:1:1:1 mixture of rotamers. R_f 0.38 (1:1 DCM:ethyl acetate); $[\alpha]_D^{20}$ −67.2 (*c* 0.50, $CHCl_3$); ν_{max}/cm^{-1} (thin film) 3289, 2975, 1633, 1540, 1496, 1449, 1343, 1286, 1243, 1203, 1156, 1078, 1030, 959, 751, 700, 587, 507; δ_H (400 MHz, $CDCl_3$) NMR data for major rotamer only 7.37–7.14 (5H, m, C(12)2H, C(13)2H and C(14)H), 6.31 (1H, d, *J* = 10.5 Hz, N(6)H), 5.33 (1H, d, *J* = 14.0 Hz, C(1)**H**H'), 4.75 (1H, d, *J* = 17.0 Hz, C(10)**H**H'), 4.72–4.61 (1H, m, C(7)H), 4.24 (1H, d, *J* = 17.0 Hz, C(10)H**H'**), 4.13–3.91 (2H, m, C(3)H_2), 3.89–3.73 (1H, m, C(15)**H**H'), 3.44–3.32 (2H, m, C(4)**H**H' and C(15)H**H'**), 3.22–3.08 (2H, m, C(1)H**H'** and C(8)H**H'**), 2.85–2.76 (2H, m, C(16)H_2), 2.53–2.33 (2H, m, C(4)H**H'** and C(8)H**H'**), 2.14 (3H, s, C(17)H_3), 1.25 (3 H, d, *J* = 7.0 Hz, C(18)H_3); δ_C (100 MHz, $CDCl_3$) NMR data for major rotamer only 170.0 (C5/9), 170.0 (C5/9), 168.2 (C2), 135.7 (C11), 129.0 (2 × C12/13), 127.9 (C4), 127.0 (2 × C12/13), 50.7 (C10), 46.9 (C1), 46.0 (C3), 44.7 (C15/18), 44.6 (C15/18), 39.7 (C7), 34.9 (C4), 30.8 (C16), 22.3 (C18), 15.6 (C17); HRMS (ESI) calcd. for $C_{19}H_{27}N_3NaO_3S$ 400.1665. Found: $[MNa]^+$, 400.1679 (−1.4 ppm error). Diagnostic NMR resonances for minor rotamers be found at: δ_H (400 MHz, $CDCl_3$) 2.17 (3H, s, C(17)H_3, minor rotamer A), 2.15 (3H, s, C(17)H_3, minor rotamer B), 2.02 (3H, s, C(17)H_3, minor rotamer C), 1.39–1.35 (3H, m, C(18)H_3, minor rotamer A), 1.31 (3H, d, *J* = 6.5 Hz, C(18)H_3, minor rotamer B), 1.23 (3H, d, *J* = 7.5 Hz, C(18)H_3, minor rotamer C); δ_C (100 MHz, $CDCl_3$) 168.6 (C2, minor rotamer A), 168.6 (C2, minor rotamer B), 168.1 (C2, minor rotamer C), 137.1 (C11, minor rotamer A), 136.5 (C11, minor rotamer B), 23.7 (C18, minor rotamer A), 23.6 (C18, minor rotamer B), 15.6 (C17, minor rotamer A).

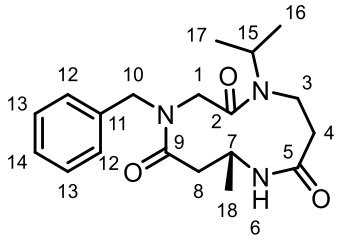
(*R*)-4-Benzyl-7-methyl-1-(2-morpholinoethyl)-1,4,8-triazacycloundecane-2,5,9-trione (15g)



(*R*)-1-Acryloyl-4-benzyl-7-methyl-1,4-diazepane-2,5-dione **13k** (57 mg, 0.20 mmol, 1 equiv.) was dissolved in THF (0.6 mL), and *N*-(2-aminoethyl)morpholine (29 µL, 0.22 mmol, 1.1 equiv.) was added. The reaction was stirred overnight, and the solvent was removed in vacuo. Purification by flash column chromatography (9:1 ethyl acetate:methanol) afforded the title compound as a clear oil (65 mg, 0.16 mmol, 78%). In solution in $CDCl_3$, the

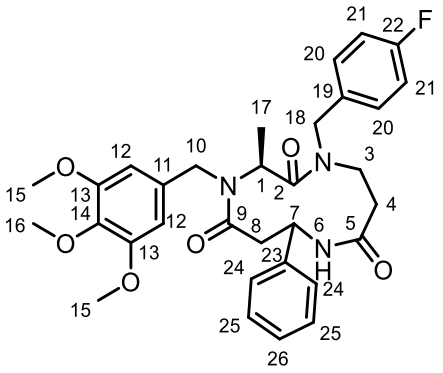
title compound exists as a ~2:3:3:6 mixture of rotamers. R_f 0.35 (1:1 methanol:ethyl acetate); $[\alpha]_D^{20}$ −48.8 (*c* 0.50, $CHCl_3$); ν_{max}/cm^{-1} (thin film) 3290, 2963, 1634, 1540, 1451, 1342, 1296, 1209, 1116, 1070, 1007, 921, 751, 700; δ_H (400 MHz, $CDCl_3$) NMR data for major rotamer only 7.36–7.06 (5H, m, C(12)2H, C(13)2H and C(14)H), 6.05 (1H, d, *J* = 10.5 Hz, N(6)H), 5.34 (1H, d, *J* = 13.5 Hz, C(1)**H**H'), 4.76 (1H, d, *J* = 17.0 Hz, C(10)**H**H'), 4.70–4.61 (1H, m, C(7)H), 4.33–4.16 (2H, m, C(3)**H**H' and C(10)H**H'**), 4.00 (1H, t, *J* = 12.5 Hz, C(15)**H**H'), 3.89–3.28 (6H, m, C(15)H**H'**, C(16)**H**H' and C(18)$2H_2$), 3.26–3.07 (2H, m, C(1)H**H'** and C(8)**H**H'), 2.99–2.90 (1H, m, C(3)H**H'**), 2.78–2.08 (8H, m, C(4)H_2, C(8)H**H'**, C(16)H**H'** and C(17)$2H_2$), 1.24 (3H, d, *J* = 7.0 Hz, C(19)H_3); δ_C (100 MHz, $CDCl_3$) NMR data for major rotamer only 170.8 (C5), 169.9 (C9), 168.2 (C2), 137.1 (C11), 129.0 (2 × C12/13), 127.0 (2 × C12/13), 126.5 (C14), 67.0 (2 × C18), 53.9 (2 × C17), 50.7 (C10), 49.8 (C3), 46.6 (C15), 46.1 (C1), 44.6 (C16), 39.8 (C7), 37.9 (C8), 34.9 (C4), 22.3 (C19); HRMS (ESI) calcd. for $C_{22}H_{32}N_4NaO_4$ 439.2316. Found: $[MNa]^+$, 439.2321 (−2.5 ppm error). Diagnostic NMR resonances for minor rotamers be found at: δ_H (400 MHz, $CDCl_3$) 1.53–1.47 (3H, m, C(19)H_3, minor rotamer A), 1.37 (3H, d, *J* = 7.0 Hz, C(19)H_3, minor rotamer B), 1.31 (3H, d, *J* = 7.0 Hz, C(19)H_3, minor rotamer C); δ_C (100 MHz, $CDCl_3$) 19.8 (C19, minor rotamer A), 19.7 (C19, minor rotamer B), 18.2 (C19, minor rotamer C).

(*R*)-4-Benzyl-1-isopropyl-7-methyl-1,4,8-triazacycloundecane-2,5,9-trione (15h)



(*R*)-1-Acryloyl-4-benzyl-7-methyl-1,4-diazepane-2,5-dione **13k** (46 mg, 0.22 mmol, 1 equiv.) was dissolved was dissolved in THF (0.5 mL) and isopropylamine (15 µL, 0.18 mmol, 1.1 equiv.) was added. The reaction was stirred overnight at RT and then the solvent was removed in vacuo. Purification by flash column chromatography (9:1 DCM:MeOH) afforded the title compound as a clear oil (37 mg, 0.11 mmol, 68%). In solution in $CDCl_3$, the title compound exists as a ~4:2:1:1 mixture of rotamers. R_f 0.55 (9:1 DCM:MeOH); $[\alpha]_D^{20}$ −4.8 (*c* 0.50, $CHCl_3$); ν_{max}/cm^{-1} (thin film) 3290, 2975, 2933, 1634, 1539, 1496, 1451, 1379, 1361, 1285, 1244, 1205, 1169, 1146, 1075, 1030, 959, 752, 702, 666; δ_H (400 MHz, $CDCl_3$) NMR data for major rotamer only 7.39–7.14 (5H, m, C(12)2H, C(13)2H, C(14)H), 6.28–6.20 (1H, m, N(6)H), 5.34–5.26 (1H, m, C(1)**H**H'), 4.79 (1H, d, *J* = 17.0 Hz, C(10)**H**H'), 4.53–4.42 (1H, m, C(7)H), 4.14–3.91 (1H, m, C(10)H**H'**), 3.90–3.44 (2H, m, C(3)**H**H' and C(15)H), 3.36–3.25 (1H, m, C(3)H**H'**), 3.13–3.03 (1H, m, C(1)H**H'**), 2.95–2.75 (2H, m, C(4)**H**H' and C(8)**H**H'), 2.33–2.23 (2H, m, C(4)H**H'** and C(8)H**H'**), 1.42–1.21 (9H, m, C(16)H_3, C(17)H_3 and C(18)H_3); δ_C (100 MHz, $CDCl_3$) NMR data for major rotamer only 170.9 (C2/C5/C9), 170.2 (C2/C5/C9), 168.6 (C2/C5/C9), 137.2 (C11), 128.6 (2 × C13), 128.2 (C14), 127.1 (2 × C12), 50.5 (C10), 48.6 (C15), 47.3 (C1), 41.9 (C7), 38.2 (C3), 38.0 (C8), 34.6 (C4), 21.5 (C16/C17/C18), 19.9 (C16/C17/C18), 19.4 (C16/C17/C18); HRMS (ESI) calcd. for $C_{19}H_{27}N_3NaO_3$ 368.1945. Found: $[MNa]^+$, 368.1952 (1.4 ppm error).

(3*S*)-1-(4-Fluorobenzyl)-3-methyl-7-phenyl-4-(3,4,5-trimethoxybenzyl)-1,4,8-triazacycloundecane-2,5,9-trione (15i)



(3*S*)-1-Acryloyl-3-methyl-7-phenyl-4-(3,4,5-trimethoxybenzyl)-1,4-diazepane-2,5-dione **13l** (198 mg, 0.44 mmol, 1 equiv.) was dissolved in THF (1.5 mL) and 4-fluorobenzylamine (55 µL, 0.48 mmol, 1.1 equiv.) was added. The reaction was stirred overnight, and the solvent was removed in vacuo. Purification by flash column chromatography (ethyl acetate:hexane 4:1) afforded the title compound as a clear oil (51 mg, 0.09 mmol, 20%). In solution in $CDCl_3$, the title compound exists as a ~3:3:5 (minor A: minor B: major) mixture of rotamers/diastereomers. R_f 0.03 (1:1 hexane:ethyl acetate); $[\alpha]_D^{20}$ −3.5 (*c* 0.50, $CHCl_3$); ν_{max}/cm^{-1} (thin film) 3312, 2939, 2839, 1634, 1593, 1509, 1455, 1417, 1330, 1236, 1181, 1157, 1127, 1072, 1046, 1005, 823, 755, 700, 666, 604, 535, 498; δ_H (400 MHz, $CDCl_3$) NMR data for major rotamer/diastereomer only 7.38–7.19 (7H, m, C(20)2H, C(24)2H, C(25)2H and C(26)H), 7.07–6.98 (2H, m, C(21)2H), 6.36 (2H, s, C(12)2H), 6.02 (1H, d, *J* = 10.5 Hz, N(6)H), 5.98–5.88 (1H, m, C(1)H), 5.86–5.76 (1H, m, C(7)H), 5.73–5.64 (1H, m, C(18)**H**H'), 4.80–4.71 (1H, m, C(10)**H**H'), 4.60–4.51 (1H, m, C(10)H**H'**), 4.40–4.30 (1H, m, C(18)H**H'**), 4.06–3.99 (1H, m, C(3)**H**H'), 3.85–3.75 (9H, m, C(15)2H_3 and C(16)H_3), 3.32–3.10 (1H, m, C(3)H**H'**), 3.01–2.89 (1H, m, C(8)**H**H'), 2.63–2.47 (1H, m, C(4)**H**H'), 2.42–2.30 (1H, m, C(8)H**H'**), 2.30–2.15 (1H, m, C(4)H**H'**), 1.20 (3H, d, *J* = 6.5 Hz, C(17)H_3); δ_C (100 MHz, $CDCl_3$) NMR data for major rotamer only 173.7 (C2/C5/C9), 173.1 (C2/C5/C9), 169.9 (C2/C5/C9), 162.3 (d, $^1J_{CF}$ = 244.5 Hz, C22), 153.9 (2 × C13), 140.7 (C19), 137.3 (C14), 134.3 (C23), 134.3 (C11), 130.1 (d, $^3J_{CF}$ = 8.0 Hz, 2 × C20), 129.0 (2 × C24/25), 126.2 (C26), 126.0 (2 × C24/25), 115.9 (d, $^2J_{CF}$ = 21.5 Hz, 2 × C21), 102.7 (2 × C12), 61.0 (C16), 56.3 (2 × C15), 55.7 (C18), 52.0 (C7), 48.1 (C10), 47.8 (C1), 45.1 (C3), 35.1 (C8), 34.5 (C4), 14.0 (C17); δ_F (376 MHz, $CDCl_3$) NMR data for major rotamer only −114.9 (1F, s, C(20)F); HRMS (ESI) calcd. for $C_{32}H_{37}FN_3O_6$ 578.2661. Found: $[MH]^+$, 578.2643 (0.7 ppm error). Diagnostic NMR resonances for minor rotamers/diastereomers be found at: δ_H (400 MHz, $CDCl_3$) 6.40 (2H, s, C(12)2H, minor A), 6.28 (2H, s, C(12)2H, minor B), 1.35 (3H, d, *J* = 6.5 Hz, C(17)H_3, minor A), 1.28 (3H ; δ_C (100 MHz, $CDCl_3$) δ_F (376 MHz, $CDCl_3$) −114.6 (1F, s, C(22)F, minor A), −114.7 (1F, s, C(22)F, minor B).

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Supplementary Material

Copies of ^{1}H and ^{13}C-NMR spectra of the synthesized compounds are given in the Supplementary Material file associated with this manuscript. Raw FID data for NMR spectra is available on request from the corresponding author.

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