Supporting Information

A Route to *3*-Dimensional Fragments using Diversity-Oriented Synthesis

Contents:

I. *Synthetic schemes for building blocks **1**,**2** and **3***

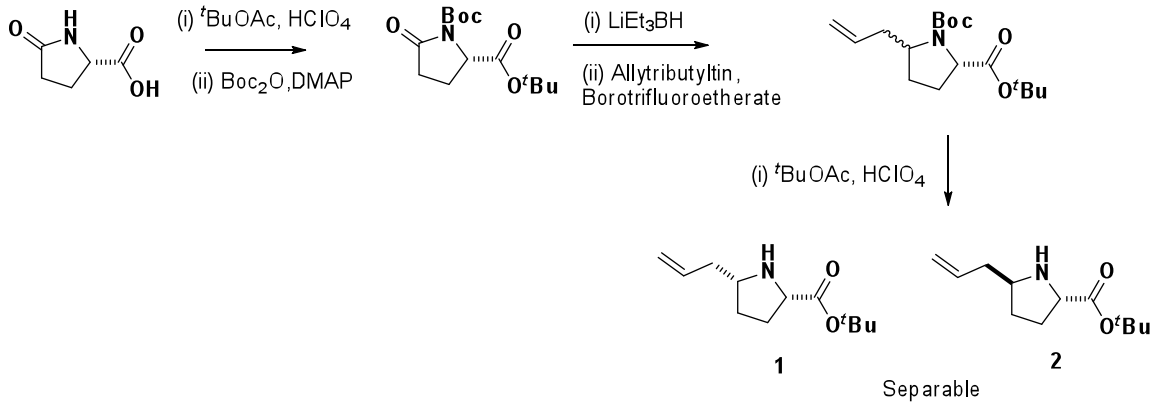
II. *3D fragment library used for computational studies*

III. *Materials and Methods – computational analysis*

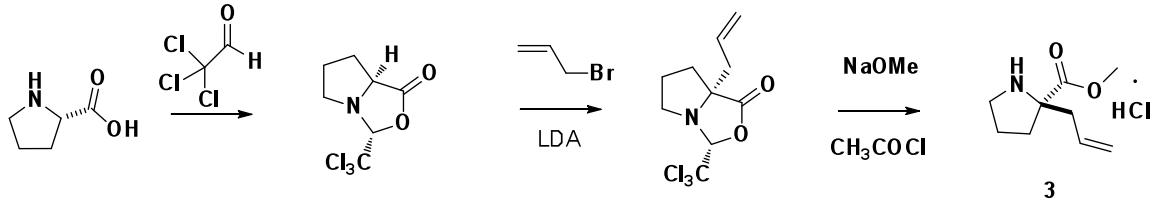
IV. *Materials and Methods – synthesis*

V. *Experimental procedures*

*(I) Synthetic schemes of building blocks **1,2** and **3**.*



Scheme 1. Synthesis of proline building blocks **1** and **2**[1-2].



Scheme 2. Synthesis of proline building block **3**[3-4].

(II) 3D fragment library used for computational studies

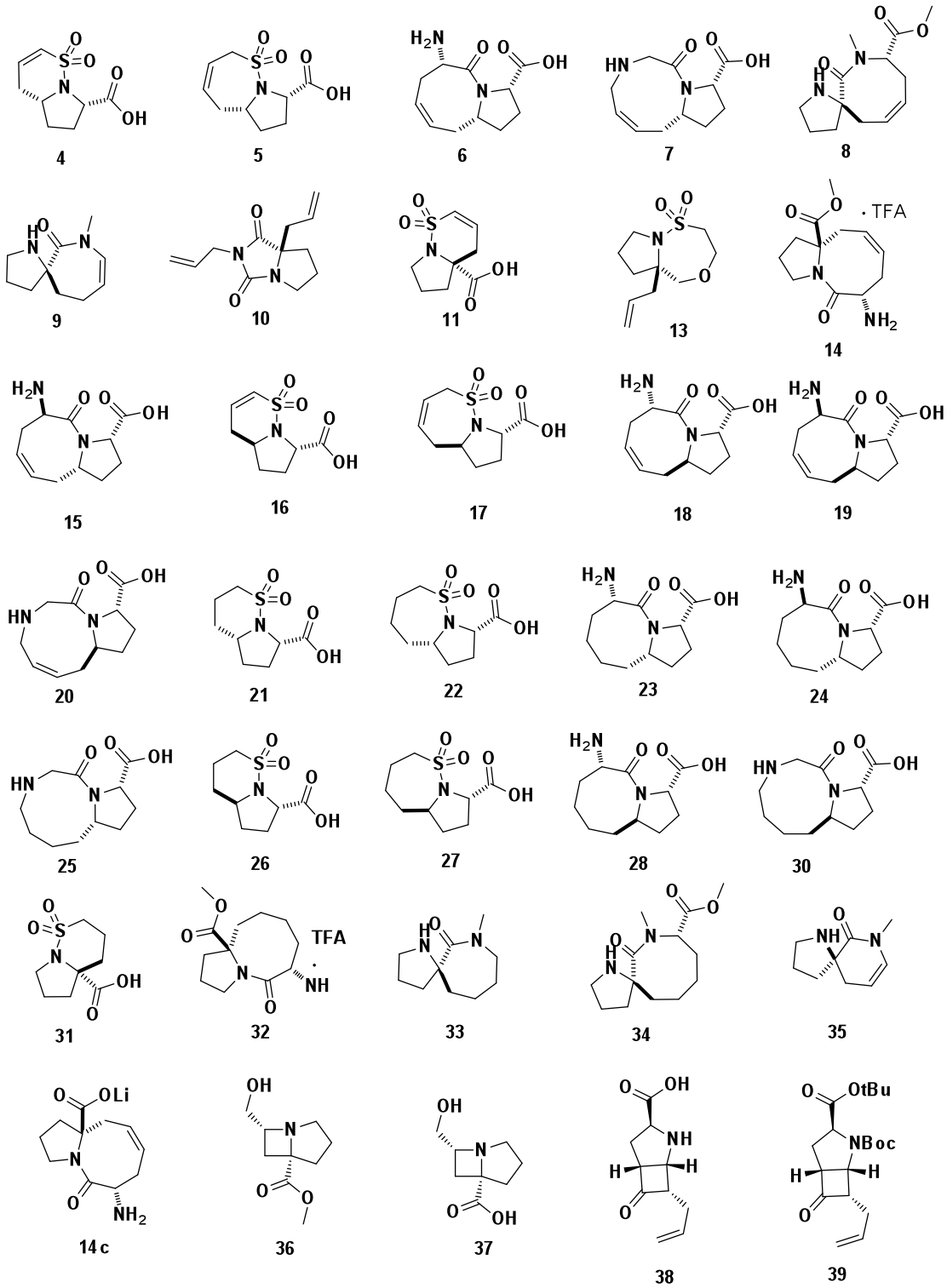


Figure 1. 35 *3D* fragments used for computational studies. Additional compounds **36** – **39** [5-6] were synthesized and added to the library for computational studies.

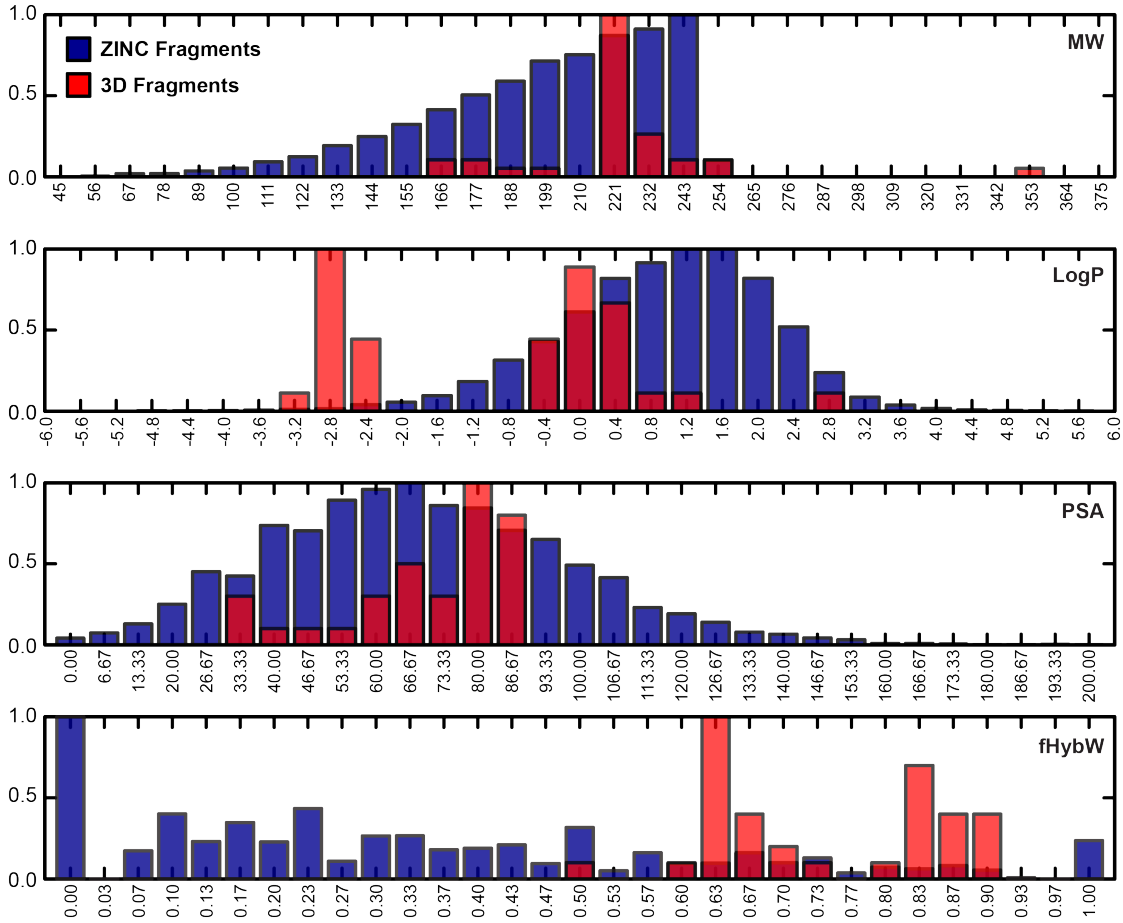


Figure 2. Histogram of properties calculated for synthesized fragments compared with 18, 534 from ZINC. (MW = molecular weight, LogP = ALogP, PSA = Polar Surface Area, fHybW = $sp^3/(sp^3 + sp^2)$).

(III) Materials and Methods – computational analysis

As a reference set, we acquired 313361 fragment compounds from the ZINC database[7-8]. We filtered this set down to a manageable subset of size 18534 with diverse molecular properties as described by Bienfait *et al*. .[9] We used Pipeline Pilot (Accelrys, Inc.; San Diego, CA, USA) to generate SMILES[10] representations for all 35 members of the fragment library studied here, and the diverse comparison set from ZINC.

3D models were built for each compound and then expanded to a set of conformers by a conformational sampling run, both performed in Pipeline Pilot with ChemAxon tools (ChemAxon Ltd., Budapest, Hungary) using default sampling and energy-minimization parameters. We filtered the resulting conformers by free energy and kept the lowest energy conformer for PMI calculations, which represented the global minimum of the search.

Heavy atom counts (C,N,O,S, etc) and Lipinski-Weber (molecular weight, AlogP, polar surface area, # of H-bond donors, # of H-bond acceptors, # of rotatable bonds, etc.) molecular descriptors for both set of compounds were computed again in Pipeline Pilot. To be able to provide a more detailed comparison, we matched library members with a representative set of compounds from the comparison set from ZINC. To accomplish this we pooled both the diverse subset (18534) and privileged *3D* library (35) and calculated normalized Z-scores for the pooled compounds. We then computed pairwise Euclidian distances between the members and used the resulting distance matrix to select top 5 ZINC compounds per library member and uniquified the lists for comparison purposes. We also used identical procedure to select a representative subset with similar Lipinski properties to compare to a subset with similar molecular properties rather than an exact molecular formula match.

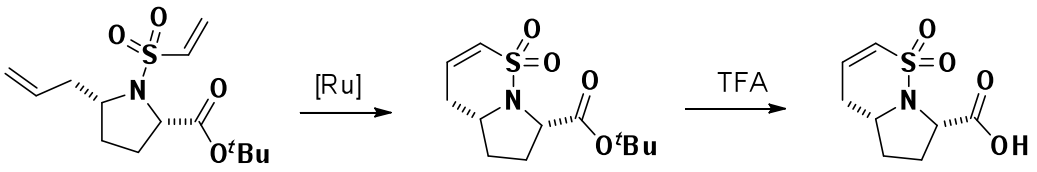
In our implementation of Sauer and Schwartz[11] PMI ratio method, we calculated ratios of the smallest and medium eigenvalues of the diagonalized mass tensor to the largest (i.e., $X = \mathbf{I}_{small}/\mathbf{I}_{large}$, $Y = \mathbf{I}_{medium}/\mathbf{I}_{large}$). The canonical coordinates are [0 1] rod, [0.5 0.134] flat, and [1 1] spherical.

(IV) Materials and Methods – synthesis

Except as otherwise noted, reactions were carried out under nitrogen. Reaction solvents were dispensed from a solvent purification system (Innovative Technology Solvent Purification Systems) wherein solvents were passed through a packed activated alumina column. All reagents were obtained from commercial sources and used without further purification. NMR spectra were recorded at 500 MHz using a Varian I-500 instrument. Chemical shifts for proton NMR spectra are reported in parts per million (ppm). Data are represented as follows: chemical shift [s = singlet, d = doublet, m = multiplet], integration and coupling constants in Hertz (Hz). High-resolution mass spectra were obtained through the Harvard University mass spectrometry facility. Flash chromatography was performed either with the indicated solvent on E. Merck silica gel 60 (230-400 mesh) or using a CombiFlash companion system (Teledyne ISCO, Inc.) with pre-packed FLASH silica gel columns.

(V) Experimental Procedures

(4a*R*,7*S*)-4a,5,6,7-tetrahydro-4*H*-pyrrolo[1,2-b][1,2]thiazine-7-carboxylic acid 1,1-dioxide (4)

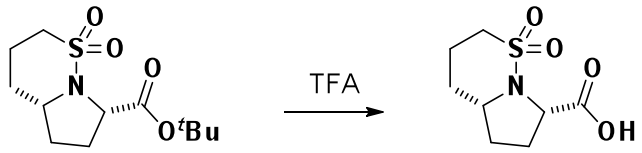


To a stirred solution of (2*S*, 5*R*)-*tert*-butyl-5-allylpyrrolidine-2-carboxylate **1** (0.100 g, 0.47 mmol) and triethylamine (0.198 ml, 1.42 mmol) in dichloromethane (5 mL) at 0 ^{o}C was added dropwise 2-chloroethanesulfonyl chloride (0.049 mL, 0.47 mmol). The reaction was stirred for a further 2 h at 0 ^{o}C. Water (5 mL) was added to the reaction mixture and the aqueous phase was extracted with dichloromethane (3 x 5 mL). The combined extracts were dried over sodium sulfate and concentrated *in vacuo*. Purification by column chromatography (gradient 0 – 20% ethyl acetate/hexane) gave coupled product **4a** as a white solid (0.066 g, 46%).

To a stirred solution of the sulfonamide **4a** (0.066 g, 0.22 mmol) was added benzylidene[1,3- bis(2,4,6-trimethylphenyl)-2-imidazolidinylidene]dichloro (tricyclohexylphosphine)ruthenium (Grubbs 2nd generation catalyst) (0.019 g, 0.02 mmol) in dichloromethane (15 mL). The reaction mixture was heated at reflux for 0.5 h. The reaction mixture was then left to cool to 25 ^{o}C and concentrated *in vacuo*. Purification by column chromatography (gradient 20 – 50% ethyl acetate/hexane) gave cyclized sultam **4b** as a white solid (0.050 g, 80%). Deprotection of the *tert*-butyl group with 2 ml neat trifluoroacetic acid (15 mins) followed by concentration *in vacuo*, gave the product **4** as a white solid (0.037 g, 93%).

^{1}H (500 MHz, d-chloroform): δ 6.46-6.54 (m, 2H), 4.64 (dd, 1H, *J* = 1.1 Hz, *J* = 9.7 Hz), 3.88-4.00 (m, 1H), 2.52-2.60 (m, 1H), 2.15-2.46 (m, 4H), 1.76-1.89 (m, 1H) ppm.
^{13}C (125 MHz, d-methanol): δ 174.5, 138.0, 127.5, 60.0, 56.5, 31.5, 31.4, 29.1.
HRMS (ESI-TOF) calcd. for $C_8H_{11}NO_4S$ $[M+H]^+$ 218.04815, found 218.04893.

(4a*R*,7*S*)-hexahydro-2*H*-pyrrolo[1,2-b][1,2]thiazine-7-carboxylic acid 1,1-dioxide (21)

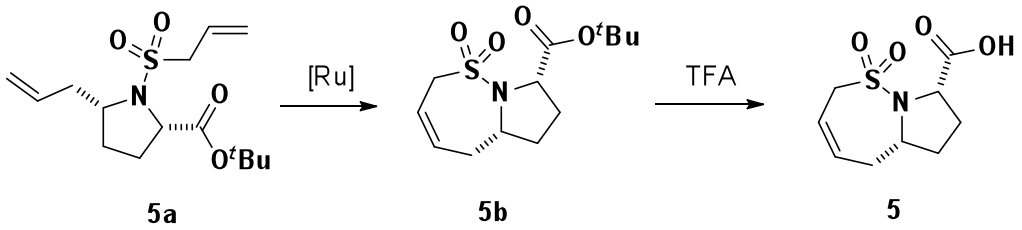


21b **21**

A solution of (4a*R*,7*S*)-*tert*-butyl 4a,5,6,7-tetrahydro-4*H*-pyrrolo[1,2-b][1,2]thiazine-7-carboxylate 1,1-dioxide **4b** (0.022 g, 0.08 mmol) and palladium hydroxide (20 wt.% on carbon, 0.007 g) in methanol (7 mL) was stirred at 25 ^{o}C under an atmosphere of hydrogen gas for 16 h. The suspension was then filtered through a Celite pad and the filtrate evaporated to give the saturated sultam product **21b**. Deprotection of the *tert*-butyl group with 2 ml neat trifluoroacetic acid (15 mins) followed by concentration *in vacuo*, gave the product **21** as a white solid (70% after 2 steps).

^{1}H (500 MHz, d-chloroform): δ 4.53-4.60 (m, 1H), 3.64-3.74 (m, 1H), 3.05-3.19 (m, 2H), 2.10-2.30 (m, 5H), 1.98-2.04 (m, 1H), 1.68-1.79 (m, 1H), 1.48-1.59 (m, 1H) ppm.
^{13}C (125 MHz, d-chloroform): δ 62.1, 58.4, 49.4, 31.9, 30.0, 28.3, 24.0.
HRMS (ESI-TOF) calcd. for $C_8H_{13}NO_4S$ $[M+H]^+$ 220.06381, found 220.06416.

(5a*R*,8*S*)-2,5,5a,6,7,8-hexahydropyrrolo[1,2-b][1,2]thiazepine-8-carboxylic acid 1,1-dioxide (5)



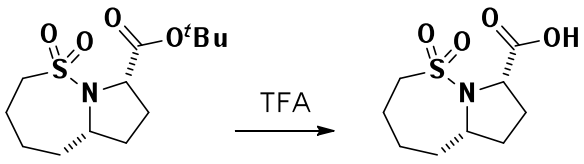
5a **5b** **5**

To a stirred solution of (2*S*, 5*R*)-*tert*-butyl-5-allylpyrrolidine-2-carboxylate **1** (0.140 g, 0.66 mmol) and triethylamine (0.138 ml, 0.99 mmol) in dichloromethane (10 mL) at 0 ^{o}C was added dropwise prop-2-ene-1-sulfonyl chloride (0.093 g, 0.66 mmol). The reaction was stirred for a further 1 h at 0 ^{o}C. Saturated aqueous sodium bicarbonate (15 mL) was added to the reaction mixture and the aqueous phase was extracted with dichloromethane (3 x 8 mL). The combined extracts were dried over sodium sulfate and concentrated *in vacuo*. Purification by column chromatography (20% ethyl acetate/hexane) gave sulfonamide coupled product **5a** as colorless oil (0.100 g, 48%).

To a stirred solution of the sulfonamide **5a** (0.085 g, 0.27 mmol) was added benzylidene[1,3- bis(2,4,6-trimethylphenyl)-2-imidazolidinylidene]dichloro (tricyclohexylphosphine)ruthenium (Grubbs 2nd generation catalyst) (0.023 g, 0.03 mmol) in dichloromethane (15 mL). The reaction mixture was heated at reflux for 1 h. The reaction mixture was then left to cool to 25 ^{o}C and concentrated *in vacuo*. Purification by column chromatography (gradient 20 – 50% ethyl acetate/hexane) gave cyclized sultam **5b** as a white solid (0.070 g, 90%). Deprotection of the *tert*-butyl group with 2 ml neat trifluoroacetic acid (15 mins) followed by concentration *in vacuo*, gave the product **5** as a white solid (quantitative).

^{1}H (500 MHz, d-chloroform): δ 6.14-6.24 (m, 1H), 5.80-5.88 (m, 1H), 4.79 (dd, 1H, *J* = 3.2 Hz, *J* = 8.2 Hz), 4.36-4.44 (m, 1H), 3.98-4.07 (m, 1H), 3.77 (dd, 1H, *J* = 8.9 Hz, *J* = 14.9 Hz), 2.66-2.76 (m, 1H), 2.35-2.42 (m, 1H), 2.12-2.31 (m, 3H), 1.78-1.86 (m, 1H) ppm.
^{13}C (125 MHz, d-chloroform): δ 178.6, 134.6, 121.1, 61.6, 60.9, 54.4, 35.6, 33.3, 29.1.
HRMS (ESI-TOF) calcd. for $C_9H_{13}NO_4S$ $[M+H]^+$ 232.06381, found 232.06450.

(5a*S*,8*S*)-octahydropyrrolo[1,2-b][1,2]thiazepine-8-carboxylic acid 1,1-dioxide (22)

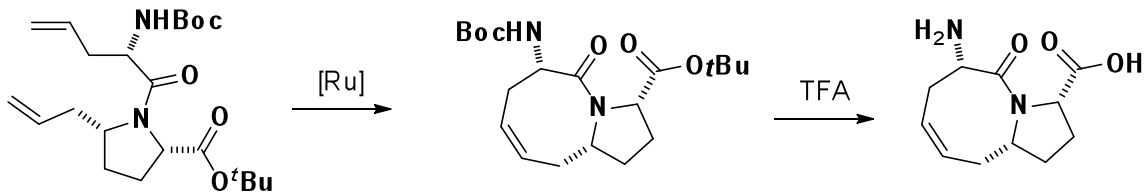


22b **22**

To a solution of **5b** (0.029 g, 1.38 mmol) in methanol was added palladium hydroxide (20 wt.% on carbon, 0.008 g) in methanol (8 mL). The reaction was stirred at 25 ^{o}C under an atmosphere of hydrogen gas for 2 h. The suspension was then filtered through a Celite pad and the filtrate evaporated to give compound **22b** as a white solid. Deprotection of the *tert*-butyl group with 2 ml neat trifluoroacetic acid (15 mins) followed by concentration *in vacuo*, gave the product **22** as a white solid (0.018 g, 76% over two steps).

^{1}H (500 MHz, d-chloroform): δ 4.65-4.70 (m, 1H), 3.82-3.90 (m, 1H), 3.38-3.46 (m, 1H), 3.20-3.26 (m, 1H), 2.25-2.35 (m, 1H), 1.70-2.20 (m, 9H) ppm.
^{13}C (125 MHz, d-chloroform): δ 178.3, 60.8, 58.4, 54.9, 33.1, 32.3, 29.5, 24.7, 21.8.
HRMS (ESI-TOF) calcd. for $C_9H_{15}NO_4S$ $[M+H]^+$ 234.07946, found 234.08056.

(3*S*,6*R*,10a*R*,*Z*)-6-amino-5-oxo-1,2,3,5,6,7,10,10a-octahydropyrrolo[1,2-a]azocine-3-carboxylic acid (6)



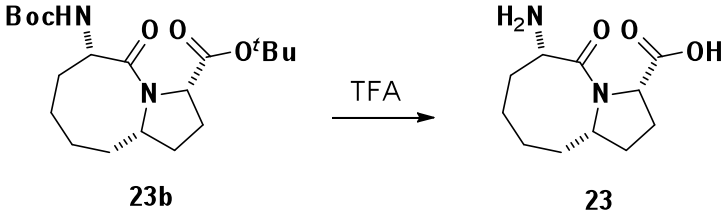
6a **6b** **6**

To a stirred solution of (2*S*, 5*R*)-*tert*-butyl-5-allylpyrrolidine-2-carboxylate **1** (0.319 g, 1.509 mmol), (*S*)-2-(Boc-amino)-4-pentenoic acid dicyclohexylamine salt (0.718 g, 1.811 mmol) and ethyl(hydroxyimino)cyanoacetate (0.322 g, 2.264 mmol) in dichloromethane (38 mL) was added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.351 g, 2.264 mmol). The reaction was stirred for 4 h at 25 ^{o}C. Saturated aqueous sodium bicarbonate (5 mL) was added to the reaction mixture and the aqueous phase was extracted with dichloromethane (3 x 8 mL). The combined extracts were dried over sodium sulfate and concentrated *in vacuo*. Purification by column chromatography (gradient 20 – 50% ethyl acetate/hexane) gave coupled product **6a** as a yellow oil (0.614 g, 98%).

To a degassed and stirred solution of diene **6a** (0.113 g, 0.278 mmol) was added bis(tricyclohexylphosphine)benzylidineruthenium dichloride (Grubbs 1st generation catalyst) (0.069 g, 0.083 mmol) in dry dichloromethane (62 mL) under an atmosphere of argon. The reaction mixture was heated at reflux for 5.5 h. The reaction mixture was then left to cool to 25 ^{o}C and concentrated *in vacuo*. Purification by column chromatography (gradient 20 – 50% ethyl acetate/hexane) gave cyclized alkene **6b** as a yellow solid (0.092 g, 87%). Deprotection of the *tert*-butyl groups with 2 ml neat trifluoroacetic acid (15 mins) followed by concentration *in vacuo*, gave the product **6** as a white solid (quantitative).

^{1}H (500 MHz, d-methanol): δ 5.76-5.82 (m, 1H), 5.71-5.76 (m, 1H), 4.50 (dd, 1H, J = 5.9 Hz, J = 7.6 Hz), 4.40 (dd, 1H, J = 6.0 Hz, J = 8.8 Hz), 2.82-2.89 (m, 1H), 2.56-2.62 (m, 1H), 2.37-2.48 (m, 2H), 2.22-2.29 (m, 1H), 2.07-2.13 (m, 1H),1.96-2.03 (m, 1H),1.85-1.91 (m, 1H) ppm.
^{13}C (125 MHz, d-methanol): δ 173.9, 167.9, 129.3, 125.5, 60.8, 58.7, 52.34, 32.9, 32.6, 30.5, 27.0.
HRMS (ESI-TOF) calcd. for $C_{11}H_{16}N_2O_3$ $[M+H]^+$ 247.10531, found 247.10582.

(3*S*,6*S*,10a*S*)-6-amino-5-oxodecahydropyrrolo[1,2-*a*]azocine-3-carboxylic acid (23)

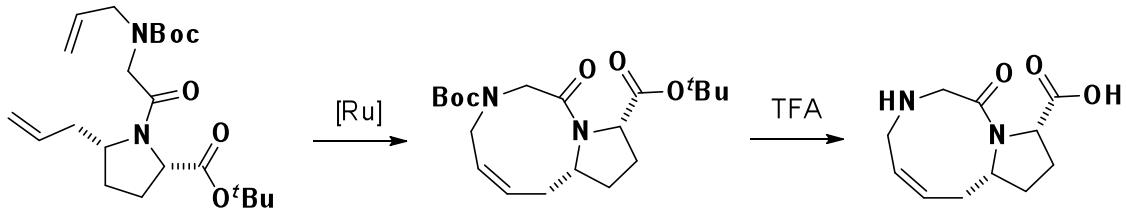


23b **23**

A solution of (3*S*,6*S*,10a*R*,*Z*)-*tert*-butyl 6-((*tert*-butoxycarbonyl)amino)-5-oxo-1,2,3,5,6,7,10,10a-octahydropyrrolo[1,2-*a*]azocine-3-carboxylate **6b** (0.045 g, 0.201 mmol) and palladium hydroxide (20 wt.% on carbon, 0.014 g, 0.020 mmol) in methanol (30 mL) was stirred at 25 ^{o}C under an atmosphere of hydrogen gas for 2 h. The suspension was then filtered through a Celite pad and the filtrate evaporated to give the saturated product **23b**. Deprotection of the Boc and *tert*-butyl group with 2 ml neat trifluoroacetic acid (15 mins) followed by concentration *in vacuo*, gave the product **23** as a white solid (quantitative).

^{1}H (500 MHz, d-methanol): δ 4.40 (d, 1H, *J* = 8.4 Hz, *J* = 8.4 Hz), 4.32-4.37 (m, 1H), 4.16-4.22 (m, 1H), 2.30-2.38 (m, 1H), 1.95-2.16 (m, 4H), 1.86-1.95 (m, 1H), 1.65-1.84 (m, 4H), 1.48-1.64 (m, 2H)ppm.
^{13}C (125 MHz, d-methanol): δ 174.9, 168.3, 60.8, 52.3, 36.9, 34.5, 33.2, 28.5, 26.0, 23.2.
HRMS (ESI-TOF) calcd. for $C_{11}H_{18}N_2O_3$ $[M+Na]^+$ 249.12096, found 249.12117.

(7a*R*,10*S*,*Z*)-1-oxo-2,3,4,7,7a,8,9,10-octahydro-1*H*-pyrrolo[1,2-d][1,4]diazonine-10-carboxylic acid (7)



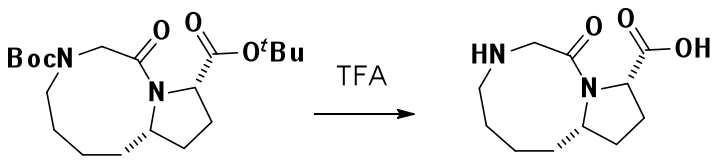
7a **7b** **7**

To a stirred solution of (2*S*, 5*R*)-*tert*-butyl-5-allylpyrrolidine-2-carboxylate **1** (0.205 g, 0.970 mmol), 2-(allyl(*tert*-butoxycarbonyl)amino)acetic acid (0.230 g, 1.067 mmol) and ethyl(hydroxyimino)cyanoacetate (0.207 g, 1.455 mmol) in dichloromethane (36 mL) was added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.226 g, 1.455 mmol). The reaction was stirred for 12 h at 25 ^{o}C. Saturated aqueous sodium bicarbonate (5 mL) was added to the reaction mixture and the aqueous phase was extracted with dichloromethane (3 x 10 mL). The combined extracts were dried over sodium sulfate and concentrated *in vacuo*. Purification by column chromatography (gradient 20 – 50% ethyl acetate/hexane) gave coupled product **7a** as a yellow oil (0.305 g, 97%).

To a degassed and stirred solution of diene **7a** (0.052 g, 0.127 mmol) was added bis(tricyclohexylphosphine)benzylidineruthenium dichloride (Grubbs 1st generation catalyst) (0.031 g, 0.038 mmol) in dry dichloromethane (40 mL) under an atmosphere of argon. The reaction mixture was heated at reflux for 12 h. The reaction mixture was then left to cool to 25 ^{o}C and concentrated *in vacuo*. Purification by column chromatography (gradient 20 – 50% ethyl acetate/hexane) gave cyclized alkene **7b** as a brownish solid (0.029 g, 60%). Deprotection of the Boc and *tert*-butyl groups with 2 ml neat trifluoroacetic acid (15 mins) followed by concentration *in vacuo*, gave the product **7** as a white solid (quantitative).

^{1}H (500 MHz, d-methanol): δ 6.46 (dd, 1H, *J* = 8.9 Hz, *J* = 19.2 Hz), 5.66-5.73 (m, 1H), 4.50 (dd, 1H, *J* = 8.8 Hz *J* = 8.8 Hz), 4.21 (dd, 1H, *J* = 7.6 Hz, *J* = 7.6 Hz) 4.00 (d, 1H, *J* = 12.8 Hz), 3.98 (dd, 1H, *J* = 12.3 Hz, *J* = 12.3 Hz), 3.69-3.74 (m, 1H), 3.59 (d, 1H, *J* = 12.8 Hz), 2.98-3.06 (m, 1H), 2.42-2.50 (m, 1H), 2.16-2.29 (m, 2H), 1.96-2.07 (m, 2H) ppm.
^{13}C (125 MHz, d-methanol): δ 175.2, 165.2, 140.8, 122.1, 61.7, 61.0, 45.2, 43.1, 35.9, 34.5, 28.5.
HRMS (ESI-TOF) calcd. for $C_{11}H_{16}N_2O_3$ $[M+H]^+$ 225.12337, found 225.12405.

(7a*S*,10*S*)-di-*tert*-butyl 1-oxooctahydro-1*H*-pyrrolo[1,2-*d*][1,4]diazonine-3,10(2*H*)-dicarboxylate (25)

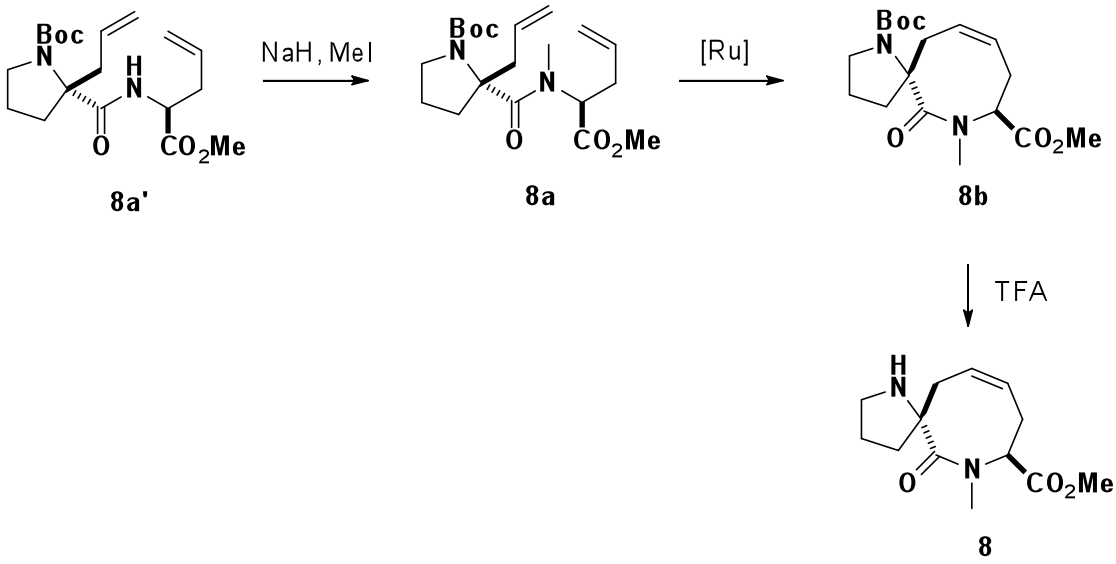


25b **25**

A solution of (7a*R*,10*S*,*Z*)-di-*tert*-butyl 1-oxo-4,7,7a,8,9,10-hexahydro-1*H*-pyrrolo[1,2-*d*][1,4]diazonine-3,10(2*H*)-dicarboxylate **7b** (0.0683 g, 0.180 mmol) and palladium hydroxide (20 wt.% on carbon, 0.013 g, 0.018 mmol) in methanol (25 mL) was stirred at 25 ^{o}C under an atmosphere of hydrogen gas for 2 h. The suspension was then filtered through a Celite pad and the filtrate evaporated to give the saturated product **25b**. Deprotection of the Boc and *tert*-butyl groups with 2 ml neat trifluoroacetic acid (15 mins) followed by concentration *in vacuo*, gave the product **25** as a white solid (quantitative).

^{1}H (500 MHz, d-methanol): δ 4.49-4.55 (m, 1H), 4.26 (d, 1H, *J* = 13.3 Hz), 4.24-4.30 (m, 1H), 3.68 (d, 1H, *J* = 13.4 Hz), 3.50-3.57 (m, 1H), 3.21-3.21 (m, 1H), 2.33-2.40 (m, 1H), 2.14-2.27 (m, 2H), 2.01-2.10 (m, 2H), 1.75-2.01 (m, 5H) ppm.
^{13}C (125 MHz, d-methanol): δ 175.1, 165.4, 63.7, 62.0, 48.15, 44.4, 35.0, 34.5, 28.8, 26.0, 25.9.
HRMS (ESI-TOF) calcd. for $C_{11}H_{18}N_2O_3$ $[M+Na]^+$ 249.12096, found 247.12139.

(5*R*,8*S*,*Z*)-methyl 7-methyl-6-oxo-1,7-diazaspiro[4.7]dodec-10-ene-8-carboxylate (8)



To a stirred solution of proline derivative **3'** (0.110 g, 0.43 mmol), (*S*)-methyl 2-aminopent-4-enoate trifluoroacetic acid (0.125 g, 0.52 mmol), ethyl(hydroxyimino)cyanoacetate (0.092 g, 0.65 mmol) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.124 g, 0.65 mmol) in dichloromethane (16 mL) was added triethylamine (0.240 mL, 1.72 mmol). The reaction was stirred for 4 h at 25 ^{o}C. Saturated aqueous sodium bicarbonate (15 mL) was added to the reaction mixture and the aqueous phase was extracted with dichloromethane (3 x 15 mL). The combined extracts were dried over sodium sulfate and concentrated *in vacuo*. Purification by column chromatography (gradient 20 – 30% ethyl acetate/hexane) gave the ally amide **8a'** as colourless oil (0.140 g, 89%).

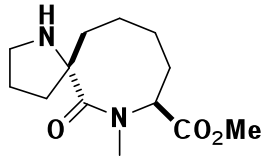
To a stirred solution of the secondary amide **8a'** (0.140 g, 0.38 mmol) in anhydrous dimethylformamide (7.6 mL), methyl iodide (2.17 g, 15.3 mmol) was added. The resulting solution was cooled to 0 ^{o}C and sodium hydride (60% in mineral oil, 45.8 mg, 1.15 mmol) was added. The reaction was stirred for 4 h at 0 ^{o}C. Saturated aqueous ammonium chloride (20 mL) was added to the reaction mixture and the aqueous phase was extracted with dichloromethane (3 x 15 mL). The combined extracts were dried over sodium sulfate and concentrated *in vacuo*. Purification by column chromatography

(gradient 20 – 30% ethyl acetate/hexane) gave the ally methyl amide **8a** as colourless oil (0.129 g, 89%).

To a stirred mixture of **8a** (0.129 g, 0.34 mmol) in anhydrous dichloromethane (16 mL) was added 1,3-Bis-(2,4,6-trimethylphenyl)-2-(imidazolidinylidene) (dichlorophenylmethylene)(tricyclohexylphosphine)ruthenium Grubb's 2nd generation catalyst (0.058 g, 0.07 mmol). The reaction mixture was heated to reflux for 16 h. The solvent was removed *in vacuo*. Purification by column chromatography (gradient 25 – 45% ethyl acetate/hexane) gave product **8b** as a white solid (0.012 g, 34%). Deprotection of the Boc group on either product with 2 ml neat trifluoroacetic acid followed by concentration *in vacuo* gave the product **8** as yellow oil (quantitative).

^{1}H (500 MHz, d-chloroform): δ 5.75-5.68 (m, 2 H), 5.20 (dd, *J* = 10.2, 6.2 Hz, 1 H), 3.78 (s, 3 H), 3.49 (bs, 2 H), 3.17-3.13 (m, 1 H), 2.87-2.83 (m, 5 H), 2.78-2.71 (m, 1 H), 2.51-2.47 (m, 1 H), 2.17-2.08 (m, 2 H), 2.03-1.98 (m, 1 H) ppm.
^{13}C (125 MHz, d-chloroform): δ 169.7, 168.9, 129.8, 125.1, 73.0, 59.6, 52.9, 45.8, 36.9, 35.0, 33.9, 28.0, 22.4.
HRMS (ESI-TOF) calcd. for $C_{13}H_{20}N_2O_3$ $[M+H]^+$ 253.15467, found 253.15519.

(5*S*,8*S*)-methyl 7-methyl-6-oxo-1,7-diazaspiro[4.7]dodecane-8-carboxylate (34)

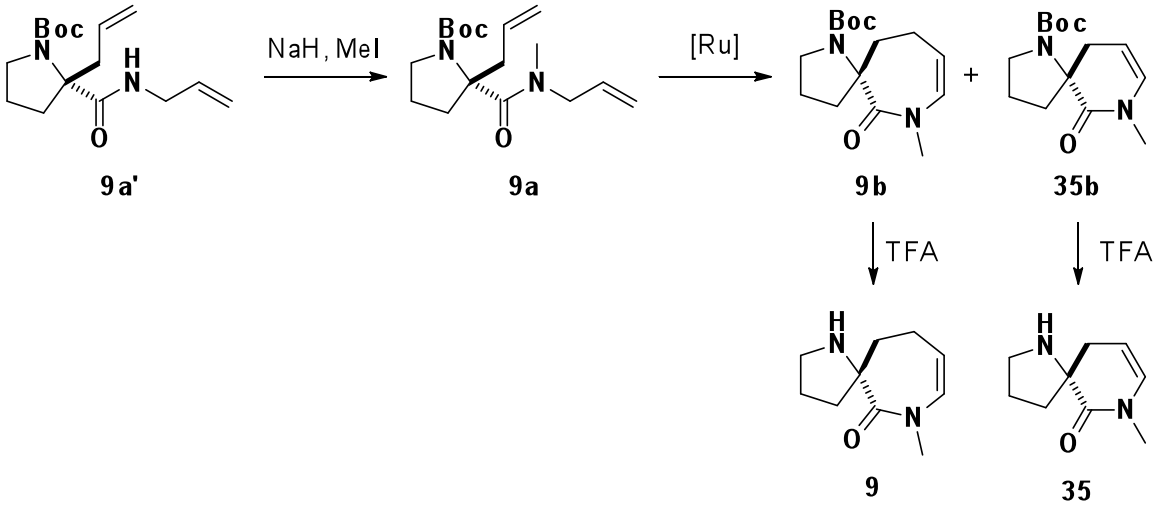


A solution of **8** (0.019 g, 0.075 mmol) and palladium hydroxide (20 wt.% Pd on carbon, wet, 0.011 g) in methanol (8 mL) was stirred at 25 °C under an atmosphere of hydrogen gas for 2 h. The suspension was then filtered through a Celite pad and the filtrate was concentrated *in vacuo* to give compound **34** as yellow oil (0.016 g, 84%).

^{1}H (500 MHz, d4-methanol): δ 4.80 (dd, *J* = 7.5, 7.5 Hz, 1 H), 3.80 (s, 3 H), 3.50-3.43 (m, 2 H), 2.95 (s, 3 H), 2.63-2.60 (m, 1 H), 2.26-2.16 (m, 2 H), 2.11-2.01 (m, 4 H), 1.98-1.92 (m, 1 H), 1.83-1.79 (m, 1 H), 1.70-1.61 (m, 2 H), 1.36-1.28 (m, 1H) ppm.

^{13}C (125 MHz, d4-methanol): δ 172.7, 171.8, 74.7, 61.6, 53.3, 47.8, 39.5, 36.8, 28.6, 23.5, 23.4, 22.5.
HRMS (ESI-TOF) calcd. for $C_{13}H_{22}N_2O_3$ $[M+H]^+$ 255.17032, found 255.17059.

(*S*)-7-methyl-1,7-diazaspiro[4.6]undec-8-en-6-one (9) and **(*R*)-7-methyl-1,7-diazaspiro[4.5]dec-8-en-6-one (35)**



To a stirred solution of proline derivative **3'** (0.200 g, 0.78 mmol), allyamine (0.067 g, 1.18 mmol), ethyl(hydroxyimino)cyanoacetate (0.167 g, 1.18 mmol) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.225 g, 1.18 mmol) in dichloromethane (16 mL) was added triethylamine (0.328 mL, 2.35 mmol). The reaction was stirred for 4 h at 23 ^{o}C. Saturated aqueous sodium bicarbonate (15 mL) was added to the reaction mixture and the aqueous phase was extracted with dichloromethane (3 x 15 mL). The combined extracts were dried over sodium sulfate and concentrated *in vacuo*. Purification by column chromatography (gradient 20 – 30% ethyl acetate/hexane) gave the ally amide **9a'** as colourless oil (0.210 g, 91%).

To a stirred solution of ally amide **9a'** (0.066 g, 0.22 mmol) in anhydrous dimethylformamide (4.5 mL), methyl iodide (0.64 g, 4.5 mmol) was added. The

resulting solution was cooled to 0 ^{o}C and sodium hydride (60% in mineral oil, 26.9 mg, 0.67 mmol) was added. The reaction was stirred for 4 h at 0 ^{o}C. Saturated aqueous ammonium chloride (20 mL) was added to the reaction mixture and the aqueous phase was extracted with dichloromethane (3 x 15 mL). The combined extracts were dried over sodium sulfate and concentrated *in vacuo*. Purification by column chromatography (gradient 20 – 30% ethyl acetate/hexane) gave the ally methyl amide **9a** as colourless oil (0.050 g, 72%).

To a stirred mixture of **9a** (0.070 g, 0.23 mmol) in anhydrous toluene (23 mL) was added 1,3-Bis-(2,4,6-trimethylphenyl)-2-(imidazolidinylidene) (dichlorophenylmethylene)(tricyclohexylphosphine)ruthenium Grubb's 2nd generation catalyst (0.019 g, 0.02 mmol). The reaction mixture was heated to 50 ^{o}C for 4 h followed by the addition of another portion of Grubbs 2nd generation catalyst (0.019 g, 0.02 mmol). After another 12 hours at 50 ^{o}C, ethylvinylether (0.327 g, 4.5 mmol) was added to the reaction and then the solvent was removed *in vacuo*. Purification by column chromatography (gradient 25 – 60% ethyl acetate/hexane) gave product **9b** as yellow oil (0.038 g, 60%) and product **35b** (0.005 g, 8%) as yellow oil. Deprotection of the Boc group on either product was performed in 2 ml neat trifluoroacetic acid for 5 minutes. The reaction was then concentrated *in vacuo*. The remaining TFA was quenched with anhydrous Na_2CO_3. The extracts were extracted with DCM and concentrated *in vacuo* respectively to gave product **9** and **35** (quantitative).

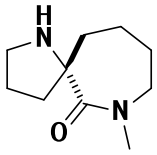
(*S*)-7-methyl-1,7-diazaspiro[4.6]undec-8-en-6-one (9)

^{1}H (500 MHz, d-chloroform): δ 5.86 (d, *J* = 9.5 Hz, 1 H), 5.36 (ddd, *J* = 9.5, 4.5, 4.5 Hz, 1 H), 3.65-3.60 (m, 1 H), 3.42-3.37 (m, 1 H), 3.17 (s, 3 H), 2.65-2.61 (m, 1 H), 2.51-2.46 (m, 1 H), 2.40-2.22 (m, 4H), 2.19-2.14 (m, 1 H), 1.87-1.79 (m, 1 H) ppm.
^{13}C (125 MHz, d-chloroform): δ 170.8, 128.4, 117.1, 73.0, 45.5, 37.9, 31.9, 31.9, 23.8, 23.6.
HRMS (ESI-TOF) calcd. for $C_{10}H_{16}N_2O$ $[M+H]^+$ 181.13354, found 181.13419.

(*R*)-7-methyl-1,7-diazaspiro[4.5]dec-8-en-6-one (35)

^{1}H (500 MHz, d-chloroform): δ 6.00-5.98 (m, 1 H), 5.16-5.12 (m, 1 H), 3.25-3.21 (m, 1 H), 3.09 (s, 3 H), 3.08-3.04 (m, 1 H), 2.53-2.49 (m, 1 H), 2.33 (dd, *J* = 17.0, 6.0 Hz, 1 H), 1.93-1.80 (m, 4 H) ppm.
^{13}C (125 MHz, d-chloroform): δ 167.6, 130.5, 104.7, 66.9, 46.8, 35.0, 34.5, 29.7, 23.3.
HRMS (ESI-TOF) calcd. for $C_9H_{14}N_2O$ $[M+Na]^+$ 189.09983, found 189.09997.

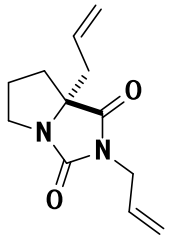
(*S*)-7-methyl-1,7-diazaspiro[4.6]undecan-6-one (33)



A solution of **9** (0.007 g, 0.039 mmol) and palladium hydroxide (20 wt.% Pd on carbon, wet, 0.011 g) in methanol (8 mL) was stirred at 25 ^{o}C under an atmosphere of hydrogen gas for 16 h. The suspension was then filtered through a Celite pad and the filtrate was concentrated *in vacuo* to give compound **33** as a yellow solid (0.006 g, 90%).

^{1}H (500 MHz, d-chloroform): δ 9.46 (bs, 1H), 3.60-3.54 (m, 2H), 3.36-3.31 (m, 1H), 3.29-3.25 (m, 1H), 3.08 (s, 3H), 2.35-2.30 (m, 2H), 2.25-2.15 (m, 2H), 2.03-1.85 (m, 4H), 1.72-1.63 (m, 1H), 1.53-1.45 (m, 1H) ppm.
^{13}C (125 MHz, d-chloroform): δ 171.7, 73.4, 51.1, 45.1, 39.0, 32.0, 31.8, 26.9, 25.0, 24.6.
HRMS (ESI-TOF) calcd. for $C_{10}H_{18}N_2O$ $[M+H]^+$ 183.14919, found 183.14985.

(*R*)-2,7a-diallyltetrahydro-1*H*-pyrrolo[1,2-c]imidazole-1,3(2*H*)-dione (10)



10

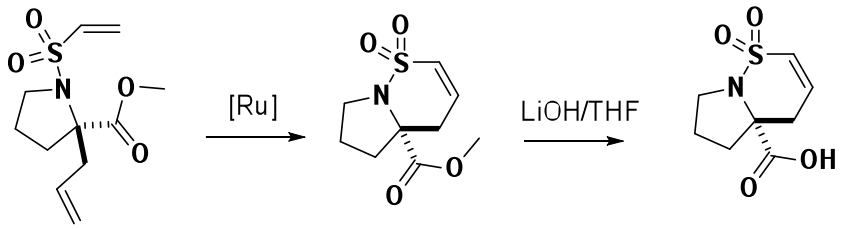
To a stirred solution of (*R*)-methyl 2-allylpyrrolidine-2-carboxylate **3** (0.093 g, 0.45 mmol) and triethylamine (0.063 ml, 0.45 mmol) in dichloromethane (10 mL) was added dropwise allyl isocyanate (0.044 mL, 0.50 mmol). The reaction was stirred for a further 0.5 h at 25 ^{o}C. Saturated aqueous sodium bicarbonate (15 mL) was added to the reaction

mixture and the aqueous phase was extracted with dichloromethane (3 x 8 mL). The combined extracts were dried over sodium sulfate and concentrated *in vacuo* to give crude **10a** as a yellow gum (0.080 g, 70%).

To a stirred solution of a crude mixture of **10a** (0.080 g, 0.32 mmol) in DMF (6 mL) was added NaH 60% in mineral oil (0.038 g, 0.95 mmol) at 0°C. The solution was stirred for a further 2 h and concentrated in *in vacuo*. Saturated ammonium chloride was added to the concentrated solution and the aqueous phase was extracted with dichloromethane (3 x 8 mL). The combined extracts were dried over sodium sulfate and concentrated *in vacuo*. Purification by column chromatography (20% ethyl acetate/hexane) gave cyclized product **10** as colorless oil (0.065 g, 93%).

^{1}H (500 MHz, d-chloroform): δ 5.66-5.86 (m, 2H), 5.12-5.23 (m, 4H), 3.99-4.11 (m, 2H), 3.80 (ddd, 1H, *J* = 6.2 Hz, *J* = 8.4 Hz, *J* = 11.7 Hz), 3.22 (ddd, 1H, *J* = 6.1 Hz, *J* = 8.3 Hz, *J* = 11.7 Hz), 2.60 (dd, 1H, *J* = 7.8 Hz, *J* = 13.9 Hz), 2.41 (dd, 1H, *J* = 6.7 Hz, *J* = 13.9 Hz), 2.00-2.14 (m, 2H), 1.86-1.97 (m, 2H) ppm.
^{13}C (125 MHz, d-chloroform): δ 175.7, 160.2, 131.3, 131.3, 120.5, 117.9, 72.5, 45.3, 41.1, 39.7, 32.4, 26.3.
HRMS (ESI-TOF) calcd. for $C_{12}H_{16}N_2O_2$ $[M+H]^+$ 221.12845, found 221.12953.

(*S*)-4a,5,6,7-tetrahydro-4*H*-pyrrolo[1,2-b][1,2]thiazine-4a-carboxylic acid 1,1-dioxide (11)



11a **11b** **11**

To a stirred solution of (*R*)-methyl 2-allylpyrrolidine-2-carboxylate **3** (0.140 g, 0.68 mmol) and triethylamine (0.428 ml, 3.08 mmol) in dichloromethane (5 mL) at 0 °C was

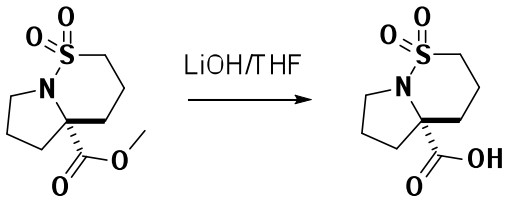
added dropwise 2-chloroethanesulfonyl chloride (0.071 mL, 0.68 mmol). The reaction was stirred for a further 2 h at 0 ^{o}C. Water (5 mL) was added to the reaction mixture and the aqueous phase was extracted with dichloromethane (3 x 5 mL). The combined extracts were dried over sodium sulfate and concentrated *in vacuo*. Purification by column chromatography (gradient 0 – 20% ethyl acetate/hexane) gave coupled product **11a** as a white solid (0.110 g, 62%).

To a stirred solution of the sulfonamide **11a** (0.110 g, 0.42 mmol) was added benzylidene[1,3- bis(2,4,6-trimethylphenyl)-2-imidazolidinylidene]dichloro (tricyclohexylphosphine)ruthenium (Grubbs 2nd generation catalyst) (0.036 g, 0.04 mmol) in dichloromethane (15 mL). The reaction mixture was heated at reflux for 0.5 h. The reaction mixture was then left to cool to 25 ^{o}C and concentrated *in vacuo*. Purification by column chromatography (gradient 20 – 50% ethyl acetate/hexane) gave cyclized methyl ester protected sultam **11b** as a white solid (0.090 g, 92%).

To a stirred solution of methyl ester protected **11b** (0.020 g, 0.09 mmol) in ethyl acetate (10 mL) was added lithium iodide (0.139 g, 1.04 mmol). The reaction mixture was protected from light and refluxed for 16 h. Saturated aqueous bicarbonate (5 mL) was added to the reaction mixture and washed with ethyl acetate (3 x 3 mL). The aqueous phase was acidified with 1M HCl until pH 1 and extract with ethyl acetate (3 x 3 mL). The combined extracts were dried over sodium sulfate and concentrated *in vacuo* giving the product **11** as a yellow solid (0.010 g, 53%).

^{1}H (500 MHz, d-chloroform): δ 6.66-6.74 (m, 1H), 6.58-6.64 (m, 1H), 3.74-3.80 (m, 1H), 3.38-3.45 (m, 1H), 2.98 (ddd, 1H, *J* = 2.7 Hz, *J* = 4.1 Hz, *J* = 17.4 Hz), 2.53-2.65 (m, 2H), 1.83-2.02 (m, 3H) ppm.
^{13}C (125 MHz, d-chloroform): δ 174.6, 137.9, 130.3, 70.8, 50.9, 39.1, 29.5, 22.6.
HRMS (ESI-TOF) calcd. for $C_8H_{11}NO_4S$ $[M+H]^+$ 218.04815, found 218.04834.

(*R*)-hexahydro-2*H*-pyrrolo[1,2-b][1,2]thiazine-4a-carboxylic acid 1,1-dioxide (31)



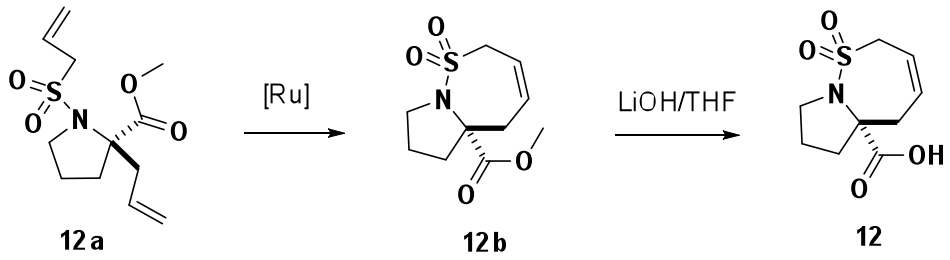
31b **31**

A solution of **11b** (0.020 g, 0.09 mmol) and palladium hydroxide (20 wt.% on carbon ,0.008 g) in methanol (8 mL) was stirred at 25 ^{o}C under an atmosphere of hydrogen gas for 2 h. The suspension was then filtered through a Celite pad and the filtrate evaporated to give compound **31b** as white solid (0.018 g, 86%)

To a stirred solution of methyl ester protected **31b** (0.018 g, 0.08 mmol) in THF (4 mL) was added 1M aqueous lithium hydroxide (0.231 mL, 0.23 mmol). The reaction mixture was stirred for 16 h at 25 ^{o}C. Water (5 mL) was added to the reaction mixture and washed with diethyl ether (3 x 3 mL). The aqueous phase was acidified with 1M HCl until pH 1 and extract with ethyl acetate (3 x 3 mL). The combined extracts were dried over sodium sulfate and concentrated *in vacuo* giving the product **31** as a white solid (0.016 g, 95%).

^{1}H (500 MHz, d-chloroform): δ 3.75-3.83 (m, 1H), 3.56-3.62 (m, 1H), 3.16 (ddd, 1H, *J* = 3.7 Hz, *J* = 3.7 Hz, *J* = 13.3 Hz), 2.88 (ddd, 1H, *J* = 4.0 Hz, *J* = 13.0 Hz, *J* = 13.0 Hz), 2.40-2.59 (m, 3H), 2.11-2.19 (m, 1H), 2.00-2.12 (m, 3H), 1.46 (ddd, 1H, *J* = 3.6 Hz, *J* = 13.5 Hz, *J* = 13.5 Hz) ppm.
^{13}C (125 MHz, d-chloroform): δ 174.7, 70.9, 49.5, 47.3, 40.8, 29.9, 22.3, 21.7.
HRMS (ESI-TOF) calcd. for $C_8H_{13}NO_4S$ $[M+H]^+$ 220.06381, found 220.06343.

(*R*)-2,5,5a,6,7,8-hexahydropyrrolo[1,2-b][1,2]thiazepine-5a-carboxylic acid 1,1-dioxide (12)



12a 12b 12

To a stirred solution of (*R*)-methyl 2-allylpyrrolidine-2-carboxylate **3** (0.120 g, 0.58 mmol) and triethylamine (0.162 ml, 1.17 mmol) in dichloromethane (15 mL) at 0 ^{o}C was added dropwise prop-2-ene-1-sulfonyl chloride (0.098 g, 0.70 mmol). The reaction was stirred for a further 0.5 h at 0 ^{o}C and left to warm to 25 ^{o}C for an additional 0.5 h. Saturated aqueous sodium bicarbonate (15 mL) was added to the reaction mixture and the aqueous phase was extracted with dichloromethane (3 x 8 mL). The combined extracts were dried over sodium sulfate and concentrated *in vacuo*. Purification by column chromatography (20% ethyl acetate/hexane) gave sulfonamide coupled product **12a** as a yellow oil (0.070 g, 44%).

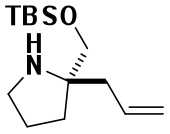
To a stirred solution of the sulfonamide **12a** (0.070 g, 0.26 mmol) was added benzylidene[1,3- bis(2,4,6-trimethylphenyl)-2-imidazolidinylidene]dichloro (tricyclohexylphosphine)ruthenium (Grubbs 2nd generation catalyst) (0.026 g, 0.03 mmol) in dichloromethane (12 mL). The reaction mixture was heated at reflux for 0.5 h. The reaction mixture was then left to cool to 25 ^{o}C and concentrated *in vacuo*. Purification by column chromatography (gradient 20 – 50% ethyl acetate/hexane) gave cyclized sultam **12b** as a white solid (0.060 g, 96%).

To a stirred solution of methyl ester protected **12b** (0.030 g, 0.12 mmol) in THF (4 mL) and water (0.8 mL) was added 1M aqueous lithium hydroxide (0.489 mL, 0.49 mmol). The reaction mixture was stirred for 6 h at 25 ^{o}C. Water (5 mL) was added to the reaction mixture and washed with diethyl ether (3 x 3 mL). The aqueous phase was acidified with 1M HCl until pH 1 and extract with ethyl acetate (3 x 3 mL). The combined extracts were

dried over sodium sulfate and concentrated *in vacuo* giving the product **12** as a white solid (0.020 g, 71%).

^{1}H (500 MHz, d-methanol): δ 5.93-6.01 (m, 1H), 5.63-5.69 (m, 1H), 4.17 (dd, 1H, *J* = 5.5 Hz, *J* = 17.5 Hz), 3.98 (dd, 1H, *J* = 3.9 Hz, *J* = 17.5 Hz), 3.66-3.72 (m, 1H), 3.46-3.53 (m, 1H), 3.26 (dd, 1H, *J* = 5.7 Hz, *J* = 15.5 Hz), 2.70 (dd, 1H, *J* = 8.1 Hz, *J* = 15.5 Hz), 2.21-2.28 (m, 1H), 2.12-2.19 (m, 1H) ppm 1.91 – 2.00 (m, 2H) ppm.
^{13}C (125 MHz, d-methanol): δ 175.7, 129.0, 121.9, 70.6, 52.7, 50.7, 37.8, 32.0, 22.5.
HRMS (ESI-TOF) calcd. for $C_9H_{13}NO_4S$ $[M+H]^+$ 232.06381, found 232.06435.

(*R*)-2-allyl-2-(((tert-butyldimethylsilyl)oxy)methyl)pyrrolidine (13b)

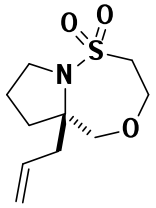


13b

To a stirred solution of (*R*)-methyl 2-allylpyrrolidine-2-carboxylate **3** (0.150 g, 0.73 mmol) in THF (15 mL) was added lithium aluminum hydride (0.055 g, 1.46 mmol). The reaction was refluxed for 2 h. Saturated aqueous sodium bicarbonate (5 mL) was added to the reaction mixture and the aqueous phase was extracted with ethyl acetate (5 x 10 mL). The combined extracts were dried over sodium sulfate and concentrated *in vacuo*. To a crude mixture of the reduced proline and triethylamine (0.152 mL, 1.09 mmol) in dichloromethane (10 mL) was added *tert*-butyldimethylsilyl chloride (0.132 g, 0.86 mmol). The reaction was stirred for 16 h at 25 ^{o}C. Saturated aqueous sodium bicarbonate (10 mL) was added to the reaction mixture and the aqueous phase was extracted with dichloromethane (3 x 12 mL). The combined extracts were dried over sodium sulfate and concentrated *in vacuo*. Purification by column chromatography (10% methanol/dichloromethane) gave **13b** as a yellow oil (0.045 g, 24% over two steps).

^{1}H (500 MHz, d-chloroform): δ 5.76-5.86 (m, 1H), 5.05-5.11 (m, 2H), 3.39 (s, 2H), 2.90-3.00 (m, 2H), 2.24-2.29 (m, 2H), 1.71-1.82 (m, 2H), 1.53-1.65 (m, 2H), 0.90 (s, 9H), 0.05 (s, 6H) ppm.

(*R*)-5a-allylhexahydro-2*H*-pyrrolo[1,2-e][1,4,5]oxathiazepine 1,1-dioxide (13)



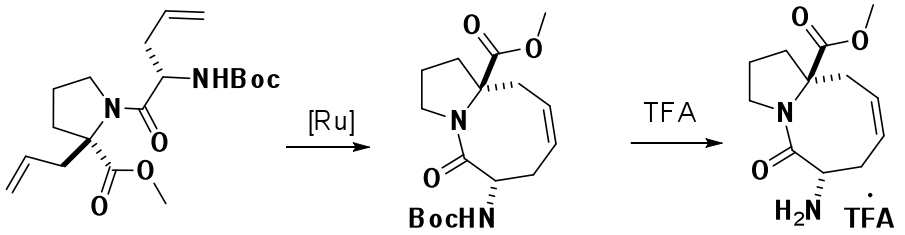
13

Following procedures described by Zhou and Hanson[12]. To a stirred solution of TBS-protected proline **13b** (0.045 g, 0.18 mmol) and triethylamine (0.074 ml, 0.53 mmol) in dichloromethane (5 mL) at 0 ^{o}C was added dropwise 2-chloroethanesulfonyl chloride (0.071 mL, 0.68 mmol). The reaction was stirred for a further 2 h at 0 ^{o}C. Water (5 mL) was added to the reaction mixture and the aqueous phase was extracted with dichloromethane (3 x 5 mL). The combined extracts were dried over sodium sulfate and concentrated *in vacuo*. Purification by column chromatography (gradient 0 – 20% ethyl acetate/hexane) gave coupled product **13a** as a colorless oil (0.020 g, 33%). To a solution of **13a** (0.020 g, 0.06 mmol) in THF (2 mL) was added tetrabutylammonium fluoride 1M in THF (0.064 mL, 0.064 mmol). The reaction was stirred for a further 1.5 h at 25 ^{o}C. Saturated aqueous ammonium chloride (2 mL) was added to the reaction mixture and the aqueous phase was extracted with ethyl acetate (3 x 5 mL). The combined extracts were dried over sodium sulfate and concentrated *in vacuo*. Purification by column chromatography (gradient 20-50% ethyl acetate/hexane) gave oxa-Michael product **13** as oil (0.006 g, 45%).

^{1}H (500 MHz, d-chloroform): δ 5.77 (m, 1H), 5.07-5.15 (m, 2H), 4.13 (ddd, 1H, J = 1.5 Hz, J = 5.1 Hz, J = 13.1 Hz), 3.95 (s, 2H), 3.81 (ddd, 1H, J = 2.1 Hz, J = 13.0 Hz, J = 13.0 Hz), 3.61-3.65 (m, 1H), 3.47 (ddd, 1H, J = 5.1 Hz, J = 12.4 Hz, J = 14.5 Hz), 3.23-3.31 (m, 1H), 3.08 (ddd, 1H, J = 1.8 Hz, J = 1.8 Hz, J = 14.5 Hz), 2.40-2.48 (m, 1H), 2.20-2.27 (m, 1H), 2.05-2.13 (m, 1H), 1.82 – 1.98 (m, 3H) ppm.

^{13}C (125 MHz, d-chloroform): δ 133.4, 118.9, 79.9, 67.7, 66.9, 52.1, 51.3, 43.1, 35.1, 22.9.
HRMS (ESI-TOF) calcd. for $C_{10}H_{17}NO_3S$ $[M+H]^+$ 231.10019, found 232.10002.

(6*S*,10a*R*,*Z*)-methyl 6-amino-5-oxo-1,2,3,5,6,7,10,10a-octahydropyrrolo[1,2-a]azocine-10a-carboxylate .TFA (14)



14a **14b** **14**

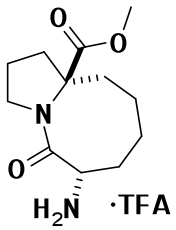
To a stirred solution of (*R*)-methyl 2-allylpyrrolidine-2-carboxylate **3** (0.283 g, 1.38 mmol), (*S*)-2-((*tert*-butoxycarbonyl)amino)pent-4-enoic acid (0.271 g, 1.26 mmol), ethyl(hydroxyimino)cyanoacetate (0.268 g, 1.89 mmol) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.361 g, 1.89 mmol) in dichloromethane (20 mL) was added triethylamine (0.263 mL, 1.89 mmol). The reaction was stirred for 16 h at 25 ^{o}C. Saturated aqueous sodium bicarbonate (5 mL) was added to the reaction mixture and the aqueous phase was extracted with dichloromethane (3 x 8 mL). The combined extracts were dried over sodium sulfate and concentrated *in vacuo*. Purification by column chromatography (gradient 20 – 50% ethyl acetate/hexane) gave coupled product **14a**[1, 13] as a yellow solid (0.220 g, 48%).

To a stirred mixture of the coupled product **14a** (0.200 g, 0.55 mmol) in dichloromethane (20 mL) was added 1,3-Bis-(2,4,6-trimethylphenyl)-2-(imidazolidinylidene) (dichlorophenylmethylene)(tricyclohexylphosphine)ruthenium Grubb's 2nd generation catalyst (0.093 g, 0.109 mmol). The reaction mixture was heated at reflux for 16 h. Dimethyl sulfoxide (0.194 mL, 2.73 mmol) was added to the cooled reaction mixture and stirred for a further 16 h. The solvent was removed *in vacuo*. Purification by column chromatography (gradient 50 – 100% ethyl acetate/hexane) gave cyclized product **14b** [1, 13-14] as a white solid (0.075 g, 41%). Deprotection of the Boc group on **14b** with 2 ml

neat trifluoroacetic acid (15 mins) followed by concentration *in vacuo* and trituration with diethyl ether gave product **14** as a white solid.

^{1}H (500 MHz, d-chloroform): δ 5.75-5.82 (m, 1H), 5.60-5.70 (m, 1H), 4.82-4.90 (m, 1H), 3.82 (s, 3H), 3.78-3.81 (m, 1H), 3.40-3.50 (m, 1H), 3.05-3.13 (m, 1H), 2.91-2.98 (m, 1H), 2.64-2.70 (m, 1H), 2.49-2.54 (m, 1H), 2.37-2.47 (m, 1H), 1.96-2.05 (m, 1H), 1.70-1.90 (m, 2H) ppm.
^{13}C (125 MHz, d-chloroform): δ 173.3, 168.6, 130.8, 123.7, 70.2, 53.8, 50.8, 49.3, 37.9, 34.6, 32.6, 20.94.
HRMS (ESI-TOF) calcd. for $C_{12}H_{18}N_2O_3$ $[M+Na]^+$ 261.12096, found 261.12162.

(6*S*,10a*S*)-methyl 6-amino-5-oxodecahydropyrrolo[1,2-a]azocine-10a-carboxylate .TFA (32)

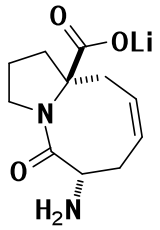


32

A solution of **14** (0.015 g, 1.38 mmol) and 20% palladium hydroxide on carbon (0.005 g) in methanol (8 mL) was stirred at 25 ^{o}C under an atmosphere of hydrogen gas for 2 h. The suspension was then filtered through a Celite pad and the filtrate evaporated to give compound **32** as a colorless oil (0.013 g, 86%)

^{1}H (500 MHz, d-chloroform): δ 4.16-4.24 (m, 1H), 3.82 (s, 3H), 3.78-3.85 (m, 1H), 3.62-3.70 (m, 1H), 2.32-2.44 (m, 2H), 2.15-2.26 (m, 1H), 2.06-2.14 (m, 1H), 1.76-1.98 (m, 6H), 1.63-1.72 (m, 1H), 1.33-1.45 (m, 1H) ppm.
^{13}C (125 MHz, d-chloroform): δ 173.7, 168.9, 69.9, 53.9, 51.4, 49.4, 40.6, 37.2, 31.9, 23.1, 22.1, 21.2.
HRMS (ESI-TOF) calcd. for $C_{12}H_{20}N_2O_3$ $[M+Na]^+$ 263.13661, found 263.13681.

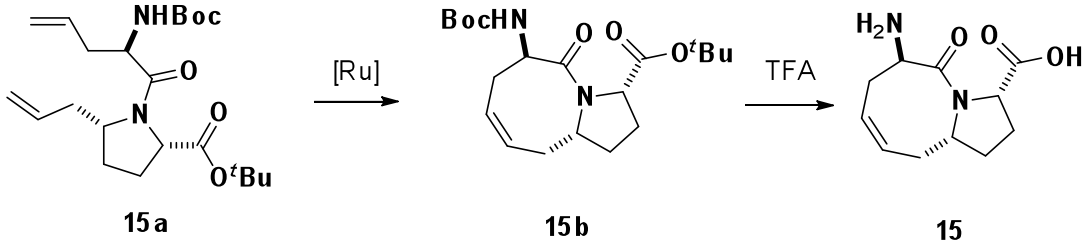
lithium (6*S*,10a*R*,*Z*)-6-amino-5-oxo-1,2,3,5,6,7,10,10a-octahydropyrrolo[1,2-a]azocine-10a-carboxylate (14c)



To a stirred solution of **14** (0.014 g, 0.04 mmol) in THF (2 mL) and Water (1.2 mL) was added 1M LiOH (0.079 mL, 0.08 mmol). The reaction mixture was stirred for 3 h at 25 ^{o}C. The solvent was removed *in vacuo* and trituration with acetone gave product as a gum (0.005 g, 55%).

^{1}H (500 MHz, d-methanol): δ 5.66–5.76 (m, 2H), 4.19 (dd, 1H, *J* = 7.0 *Hz*, *J* = 11.5 Hz), 3.72-3.79 (m, 1H), 3.27-3.35 (m, 1H), 2.84-2.91 (m, 1H), 2.64-2.74(m, 2H), 2.42-2.44 (m, 1H), 1.89-2.02 (m, 2H), 1.68-1.80 (m, 2H) ppm.
^{13}C (125 MHz, d-methanol): δ 179.3, 175.5, 130.6, 125.8, 72.0, 51.6, 48.9, 39.1, 36.3, 35.7, 20.9.
HRMS (ESI-TOF) calcd. for $C_{11}H_{15}LiN_2O_3$ $[M+H]^+$ 231.13155, found 231.13043.

(3*S*,6*R*,10a*R*,*Z*)-6-amino-5-oxo-1,2,3,5,6,7,10,10a-octahydropyrrolo[1,2-*a*]azocine-3-carboxylic acid (15)



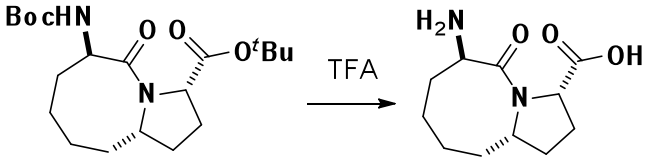
To a stirred solution of (2S, 5R)-*tert*-butyl-5-allylpyrrolidine-2-carboxylate **1** (0.297 g, 1.51 mmol), (*R*)-2-(Boc-amino)-4-pentenoic acid dicyclohexylamine salt (0.669 g, 1.687 mmol) and ethyl(hydroxyimino)cyanoacetate (0.300 g, 2.11 mmol) in dichloromethane (36 mL) was added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.327 g, 2.11 mmol). The reaction was stirred for 5 h at 25 ^{o}C. Saturated aqueous sodium bicarbonate (5 mL) was added to the reaction mixture and the aqueous phase was

extracted with dichloromethane (3 x 10 mL). The combined extracts were dried over sodium sulfate and concentrated *in vacuo*. Purification by column chromatography (gradient 20 – 50% ethyl acetate/hexane) gave coupled product **15a** as a yellow oil (0.470 g, 82%).

To a degassed and stirred solution of diene **15a** (0.158g, 0.513 mmol) was added bis(tricyclohexylphosphine)benzylidineruthenium dichloride (Grubbs 1st generation catalyst) (0.127 g, 0.154 mmol) in dry dichloromethane (105 mL) under an atmosphere of argon. The reaction mixture was heated at reflux for 24 h. The reaction mixture was then left to cool to 25 ^{o}C and concentrated *in vacuo*. Purification by column chromatography (gradient 20 – 50% ethyl acetate/hexane) gave cyclized alkene **15b** as a brownish solid (0.031g, 21%). Deprotection of the Boc and *tert*-butyl groups with 2 ml neat trifluoroacetic acid (15 mins) followed by concentration *in vacuo*, gave the product **15** as a white solid (0.025 g, 92%).

^{1}H (500 MHz, d-methanol): δ 5.79-5.86 (m, 2H), 4.68-4.70 (m, 1H), 4.54 (dd, 1H, *J* = 7.3 Hz, *J* = 14.4 Hz), 4.15-4.21 (m, 1H), 3.07-3.17 (m, 1H), 2.54-2.59 (m, 2H), 2.32-2.41 (m, 1H), 2.18-2.32 (m, 2H), 1.97-2.05 (m, 1H), 1.84-1.92 (m, 1H), 1.26-1.36 (m, 1H) ppm.
^{13}C (125 MHz, d-methanol): δ 174.0, 166.6, 131.5, 124.4, 62.3, 58.1, 54.6, 33.6, 33.5, 27.4, 26.0.
HRMS (ESI-TOF) calcd. for $C_{11}H_{16}N_2O_3$ $[M+Na]^+$ 247.10531, found 247.10545.

(3*S*,6*R*,10a*S*)-6-amino-5-oxodecahydropyrrolo[1,2-*a*]azocine-3-carboxylic acid (24)



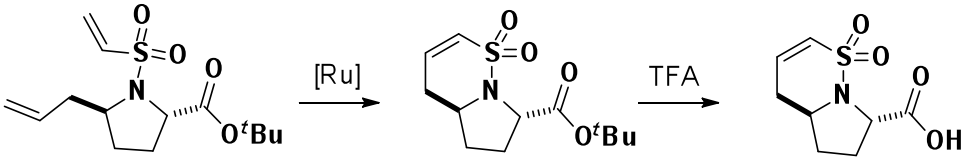
24b **24**

A solution of (3*S*,6*R*,10a*R*,*Z*)-*tert*-butyl 6-((*tert*-butoxycarbonyl)amino)-5-oxo-1,2,3,5,6,7,10,10a-octahydropyrrolo[1,2-*a*]azocine-3-carboxylate **15b** (0.015 g, 0.129 mmol) and palladium hydroxide (20% on carbon) (0.009 g, .013 mmol) in methanol (20

mL) was stirred at 25 °C under an atmosphere of hydrogen gas for 2 h. The suspension was then filtered through a Celite pad and the filtrate evaporated to give the saturated product **24b**. Deprotection of the *tert*-butyl group with 2 ml neat trifluoroacetic acid (15 mins) followed by concentration *in vacuo*, gave the product **24** as a white solid (quantitative).

^{1}H (500 MHz, d-methanol): δ 4.51-4.58 (m, 1H), 4.45 (dd, 1H, *J* = 6.0 Hz, *J* = 8.8 Hz), 4.02 (dd, 1H, *J* = 2.8 Hz, *J* = 12.4 Hz), 2.34-2.48 (m, 1H), 2.21- 2.29 (m, 1H), 2.10-2.19 (m, 1H), 1.65-2.00 (m, 9H) ppm.
^{13}C (125 MHz, d-methanol): δ 175.3, 168.5, 63.8, 59.4, 56.1, 33.9, 33.9, 29.0, 26.8, 25.5, 22.8.
HRMS (ESI-TOF) calcd. for $C_{11}H_{18}N_2O_3$ $[M+H]^+$ 227.13902, found 227.13909.

(4a*S*,7*S*)-4a,5,6,7-tetrahydro-4*H*-pyrrolo[1,2-b][1,2]thiazine-7-carboxylic acid 1,1-dioxide (16)



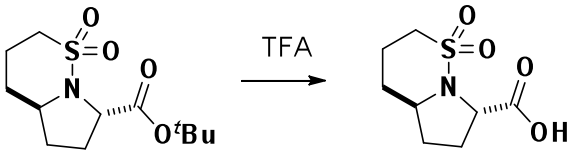
16a **16b** **16**

To a stirred solution of (2*S*, 5*S*)-*tert*-butyl-5-allylpyrrolidine-2-carboxylate **2** (0.0.83 g, 0.39 mmol) and triethylamine (0.164 ml, 1.18 mmol) in dichloromethane (5 mL) at 0 °C was added dropwise 2-chloroethanesulfonyl chloride (0.045 mL, 0.43 mmol). The reaction was stirred for a further 2 h at 0 °C. Water (5 mL) was added to the reaction mixture and the aqueous phase was extracted with dichloromethane (3 x 5 mL). The combined extracts were dried over sodium sulfate and concentrated *in vacuo*. Purification by column chromatography (gradient 0 – 20% ethyl acetate/hexane) gave coupled product **16a** as a colorless oil (0.110 g, 93%).

To a stirred solution of the sulfonamide **16a** (0.110 g, 0.37 mmol) was added benzylidene[1,3- bis(2,4,6-trimethylphenyl)-2-imidazolidinylidene]dichloro (tricyclohexylphosphine)ruthenium (Grubbs 2nd generation catalyst) (0.031 g, 0.04 mmol) in dichloromethane (15 mL). The reaction mixture was heated at reflux for 30 min. The reaction mixture was then left to cool to 25 ^{o}C and concentrated *in vacuo*. Purification by column chromatography (gradient 20 – 50% ethyl acetate/hexane) gave cyclized sultam **16b** as a white solid (0.090 g, 90%). Deprotection of the *tert*-butyl group with 2 ml neat trifluoroacetic acid (15 mins) followed by concentration *in vacuo*, gave the product **16** as a white solid (quantitative).

^{1}H (500 MHz, d-methanol): δ 6.58-6.62 (m, 1H), 6.51 (ddd, 1H, *J* = 3.0 Hz, *J* = 4.5 Hz, *J* = 8 Hz), 4.38-4.44 (m, 1H), 4.25 (dd, 1H, *J* = 3.0 Hz, *J* = 10.0 Hz), 2.44-2.56 (m, 1H), 2.14-2. 32 (m, 3H), 2.04-2.12 (m, 1H), 1.80-1.88 (m, 1H) ppm.
^{13}C (125 MHz, d-methanol): δ 174.5, 137.7, 127.3, 60.3, 58.4, 30.7, 27.9, 26.4.
HRMS (ESI-TOF) calcd. for $C_8H_{11}NO_4S$ $[M+H]^+$ 218.04815, found 218.04800.

(4a*S*,7*S*)-hexahydro-2*H*-pyrrolo[1,2-b][1,2]thiazine-7-carboxylic acid 1,1-dioxide (26)

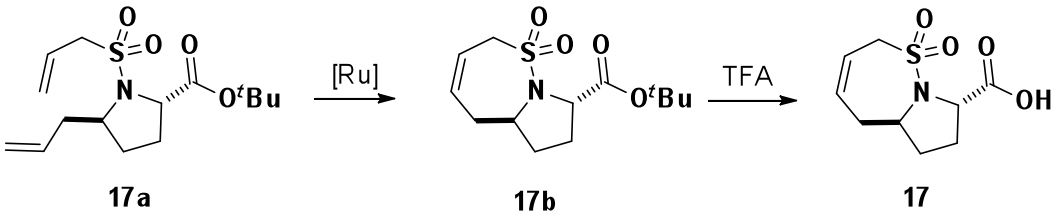


26b **26**

A solution of **16b** (0.016 g, 0.06 mmol) and palladium hydroxide (20% on carbon) (0.006 g) in methanol (5 mL) was stirred at 25 ^{o}C under an atmosphere of hydrogen gas for 2 h. The suspension was then filtered through a Celite pad and the filtrate evaporated to give the saturated sultam product **26b**. Deprotection of the *tert*-butyl group with 2 ml neat trifluoroacetic acid (15 mins) followed by concentration *in vacuo*, gave the product **26** as a white solid (quantitative).

^{1}H (500 MHz, d-methanol): δ 4.30 (dd, 1H, *J* = 2.0 Hz, *J* = 10.0 Hz), 4.02-4.10 (m, 1H), 3.02-3.10 (ddd, 1H, *J* = 3.5 Hz, *J* = 3.5 Hz, *J* = 13.5 Hz), 2.90-2.98 (m, 1H), 2.42-2.53 (m,1H), 2.14-2.24 (m, 3H), 2.00-2.06 (m, 1H), 1.73-1.80 (m, 1H), 1.56-1.64 (m, 1H), 1.36-1.48 (m, 1H) ppm.
^{13}C (125 MHz, d-methanol): δ 175.0, 61.9, 60.3, 46.7, 30.6, 28.0, 27.1, 23.2.
HRMS (ESI-TOF) calcd. for $C_8H_{13}NO_4S$ $[M+H]^+$ 220.06381, found 220.06410.

(5a*S*,8*S*)-2,5,5a,6,7,8-hexahydropyrrolo[1,2-b][1,2]thiazepine-8-carboxylic acid 1,1-dioxide (17)



17a **17b** **17**

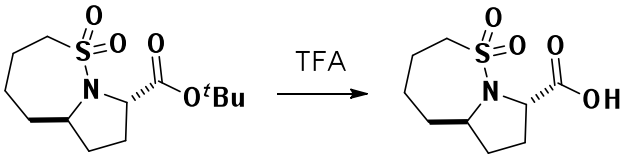
To a stirred solution of (2*S*, 5*S*)-*tert*-butyl-5-allylpyrrolidine-2-carboxylate **2** (0.180 g, 0.85 mmol) and triethylamine (0.237 ml, 1.70 mmol) in dichloromethane (10 mL) at 0 ^{o}C was added dropwise prop-2-ene-1-sulfonyl chloride (0.144 g, 1.02 mmol). The reaction was stirred for a 0.5 h at 0 ^{o}C and a further 0.5 h at 25 ^{o}C. Saturated aqueous sodium bicarbonate (15 mL) was added to the reaction mixture and the aqueous phase was extracted with dichloromethane (3 x 8 mL). The combined extracts were dried over sodium sulfate and concentrated *in vacuo*. Purification by column chromatography (20% ethyl acetate/hexane) gave sulfonamide coupled product **17a** as colorless oil (0.125 g, 47%).

To a stirred solution of the sulfonamide **17a** (0.120 g, 0.38 mmol) was added benzylidene[1,3- bis(2,4,6-trimethylphenyl)-2-imidazolidinylidene]dichloro (tricyclohexylphosphine)ruthenium (Grubbs 2nd generation catalyst) (0.032 g, 0.04 mmol) in dichloromethane (15 mL). The reaction mixture was heated at reflux for 0.5 h. The reaction mixture was then left to cool to 25 ^{o}C and concentrated *in vacuo*. Purification by column chromatography (gradient 20 – 50% ethyl acetate/hexane) gave cyclized sultam

17b as a white solid (0.089 g, 81%). Deprotection of the *tert*-butyl group with 2 ml neat trifluoroacetic acid (15 mins) followed by concentration *in vacuo*, gave the product **17** as a white solid (quantitative).

^{1}H (500 MHz, d-methanol): δ 6.08-6.14 (m, 1H), 5.69-6.16 (m, 1H), 4.45 (dd, 1H, J = 2.9 Hz, J = 9.5 Hz), 4.22-4.30 (m, 1H), 4.12-4. 18 (m, 1H), 3.76-3.84 (dd, 1H, J = 7.5 Hz, J = 16 Hz), 2.60-2.70 (m, 1H), 2.36-2.52 (m, 2H), 2.11-2.20 (m, 1H), 1.94-2.00 (m, 1H), 1.72-1.80 (m, 1H) ppm.
^{13}C (125 MHz, d-methanol): δ 175.2, 133.2, 120.9, 61.8, 60.8, 52.8, 33.0, 31.7, 28.4.
HRMS (ESI-TOF) calcd. for $C_9H_{13}NO_4S$ $[M+H]^+$ 232.06381, found 232.06400.

(5a*R*,8*S*)-octahydropyrrolo[1,2-b][1,2]thiazepine-8-carboxylic acid 1,1-dioxide (27)

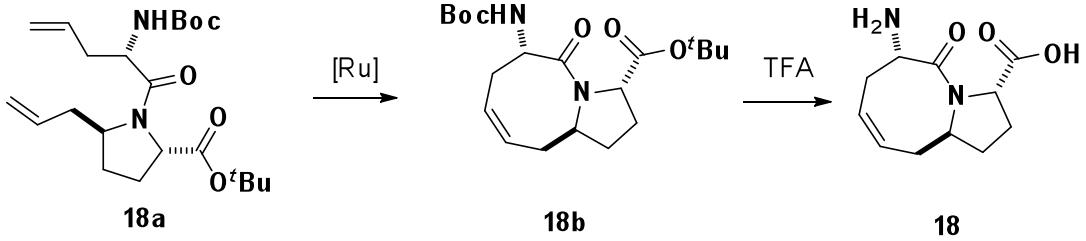


27b **27**

A solution of **17b** (0.023 g, 0.08 mmol) and palladium hydroxide (20% on carbon) (0.010 g) in methanol (5 mL) was stirred at 25 ^{o}C under an atmosphere of hydrogen gas for 2 h. The suspension was then filtered through a Celite pad and the filtrate evaporated to give the saturated sultam product **27b**. Deprotection of the *tert*-butyl group with 2 ml neat trifluoroacetic acid (15 mins) followed by concentration *in vacuo*, gave the product **27** as a white solid (quantitative).

^{1}H (500 MHz, d-methanol): δ 4.32 (dd, 1H, J = 6.5 Hz, J = 8.1 Hz), 3.86-3.95 (m, 1H), 3.16-3.22 (m, 1H), 3.07-3.15 (m, 1H), 2.33-2.40 (m, 1H), 2.12-2.20 (m, 1H), 2.00-2.07 (m, 1H), 1.70-2.00 (m, 6H), 1.53-1.64 (m, 1H) ppm.
^{13}C (125 MHz, d-methanol): δ 175.8, 62.5, 58.2, 53.2, 32.5, 31.5, 29.0, 24.1, 22.3.
HRMS (ESI-TOF) calcd. for $C_9H_{15}NO_4S$ $[M+H]^+$ 234.07946, found 234.07967.

(3*S*,6*S*,10a*S*,*Z*)-6-amino-5-oxo-1,2,3,5,6,7,10,10a-octahydropyrrolo[1,2-*a*]azocine-3-carboxylic acid (18)



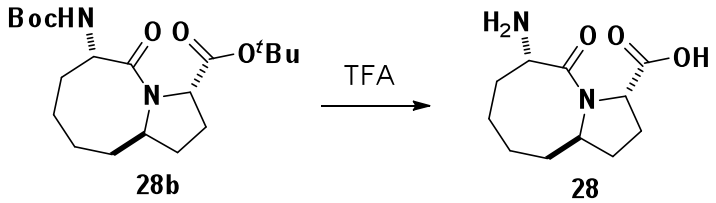
18a **18b** **18**

To a stirred solution of (2*S*, 5*S*)-*tert*-butyl-5-allylpyrrolidine-2-carboxylate **2** (0.191 g, 0.903 mmol), (*S*)-2-(Boc-amino)-4-pentenoic acid dicyclohexylamine salt (0.418 g, 1.05 mmol) and ethyl(hydroxyimino)cyanoacetate (0.189 g, 1.33 mmol) in dichloromethane (38 mL) was added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.207 g, 1.33 mmol). The reaction was stirred for 5 h at 25 ^{o}C. Saturated aqueous sodium bicarbonate (23 mL) was added to the reaction mixture and the aqueous phase was extracted with dichloromethane (3 x 8 mL). The combined extracts were dried over sodium sulfate and concentrated *in vacuo*. Purification by column chromatography (gradient 20 – 50% ethyl acetate/hexane) gave coupled product **18a**[(1)] as an orange oil (0.256 g, 69%).

To a degassed and stirred solution of diene **18a** (0.050 g, 0.122 mmol) was added bis(tricyclohexylphosphine)benzylidineruthenium dichloride (Grubbs 1st generation catalyst) (0.030 g, 0.037 mmol) in dry dichloromethane (25 mL) under an atmosphere of argon. The reaction mixture was heated at reflux for 30 h. The reaction mixture was then left to cool to 25 ^{o}C and concentrated *in vacuo*. Purification by column chromatography (gradient 20 – 50% ethyl acetate/hexane) gave cyclized alkene **18b**[(1)] as a white solid (0.022 g, 48%). Deprotection of the Boc and *tert*-butyl groups with 2 ml neat trifluoroacetic acid (15 mins) followed by concentration *in vacuo*, gave the product **18** as a white solid (0.017 g, 86%).

^{1}H (500 MHz, d-methanol): δ 5.75-5.85 (m, 2h), 4.60-4.67 (m, 1H), 4.50 (dd, 1H, *J* = 4.3 Hz, *J* = 8.9 Hz), 4.23 (dd, 1H, *J* = 3.9 Hz, *J* = 4.2 Hz), 3.04-3.13 (m, 1H), 2.42-2.51 (m, 1H), 2.22-2.42 (m, 4H), 1.86-1.94 (m, 1H), 1.75-1.84 (m, 1H) ppm.
^{13}C (125 MHz, d-methanol): δ 175.6, 168.2, 131.9, 126.3, 63.1, 59.5, 55.9, 34.6, 34.5, 29.2, 26.6.
HRMS (ESI-TOF) calcd. for $C_{11}H_{16}N_2O_3$ $[M+Na]^+$ 247.10531, found 247.10592.

(3*S*,6*S*,10a*R*)-6-amino-5-oxodecahydropyrrolo[1,2-*a*]azocine-3-carboxylic acid (28)

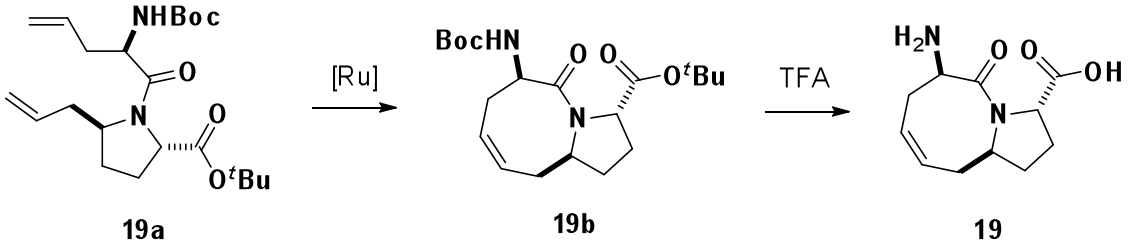


28b **28**

A solution of (3*S*,6*S*,10a*S*,*Z*)-*tert*-butyl 6-((*tert*-butoxycarbonyl)amino)-5-oxo-1,2,3,5,6,7,10,10a-octahydropyrrolo[1,2-*a*]azocine-3-carboxylate **18b** (0.026 g, 0.067 mmol) and palladium hydroxide (20% on carbon) (0.005 g, 0.007 mmol) in methanol (15 mL) was stirred at 25 ^{o}C under an atmosphere of hydrogen gas for 2 h. The suspension was then filtered through a Celite pad and the filtrate evaporated to give the saturated product **28b**. Deprotection of the *tert*-butyl group with 2 ml neat trifluoroacetic acid (15 mins) followed by concentration *in vacuo*, gave the product **28** as a white solid (0.020 g, 90%).

^{1}H (500 MHz, d-methanol): δ 4.59-4.66 (m, 1H), 4.34-4.42 (m, 1H), 4.08-4.16 (m, 1H), 2.28-2.39 (m, 1H), 2.16-2.26 (m, 1H), 2.08-2.16 (m, 1H), 1.80-2.06 (m, 7H), 1.59-1.77 (m, 2H) ppm.
^{13}C (125 MHz, d-methanol): δ 175.7, 168.5, 62.4, 54.6, 49.5, 34.3, 31.2, 31.0, 26.5, 24.9, 23.4.
HRMS (ESI-TOF) calcd. for $C_{11}H_{18}N_2O_3$ $[M+Na]^+$ 249.12096, found 247.12162.

(3*S*,6*R*,10a*S*,*Z*)-6-amino-5-oxo-1,2,3,5,6,7,10,10a-octahydropyrrolo[1,2-*a*]azocine-3-carboxylic acid (19)



19a **19b** **19**

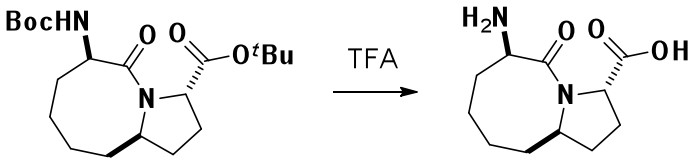
To a stirred solution of (2S, 5S)-*tert*-butyl-5-allylpyrrolidine-2-carboxylate **2** (0.213 g, 1.009 mmol), (*R*)-2-(Boc-amino)-4-pentenoic acid dicyclohexylamine salt (0.479 g, 1.210 mmol) and ethyl(hydroxyimino)cyanoacetate (0.215 g, 1.513 mmol) in dichloromethane (25 mL) was added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (0.235 g, 1.513 mmol). The reaction was stirred for 5 h at 25 ^{o}C. Saturated aqueous sodium bicarbonate (5 mL) was added to the reaction mixture and the aqueous phase was extracted with dichloromethane (3 x 10 mL). The combined extracts were dried over sodium sulfate and concentrated *in vacuo*. Purification by column chromatography (gradient 20 – 50% ethyl acetate/hexane) gave coupled product **19a** as a yellow oil (0.286 g, 69%).

To a degassed and stirred solution of diene **19a** (0.188g, 0.608 mmol) was added bis(tricyclohexylphosphine)benzylidineruthenium dichloride (Grubbs 1st generation catalyst) (0.150 g, 0.182 mmol) in dry toluene (125 mL) under an atmosphere of argon. The reaction mixture was heated at 60^{o} C for 12 h. The reaction mixture was then left to cool to 25 ^{o}C and concentrated *in vacuo*. Purification by column chromatography (gradient 20 – 50% ethyl acetate/hexane) gave cyclized alkene **19b** as a white solid (0.048 g, 29%). Deprotection of the Boc and *tert*-butyl groups with 2 ml neat trifluoroacetic acid (15 mins) followed by concentration *in vacuo*, gave the product **19** as a white solid (quantitative).

^{1}H (500 MHz, d-methanol): δ 5.69-5.78 (m 2H), 4.67 (dd, 1H, *J* = 7.3 Hz, *J* = 8.6 Hz), 4.29-4.35, (m, 2H), 2.94-2.97 (m, 1H), 2.90-2.94 (m, 1H), 2.76-2.84 (m 1H), 2.25-2.35 (m 3H), 2.14-2.20 (m, 1H), 1.77-1.90 (m, 2H) ppm.

^{13}C (125 MHz, d-methanol): δ 175.5, 169.0, 128.4, 128.3, 62.3, 59.6, 53.0, 33.5, 33.2, 31.8, 28.0.
HRMS (ESI-TOF) calcd. for $C_{11}H_{16}N_2O_3$ $[M+H]^+$ 225.12337, found 225.12419.

(3*S*,6*R*,10a*R*)-6-amino-5-oxodecahydropyrrolo[1,2-*a*]azocine-3-carboxylic acid (29)

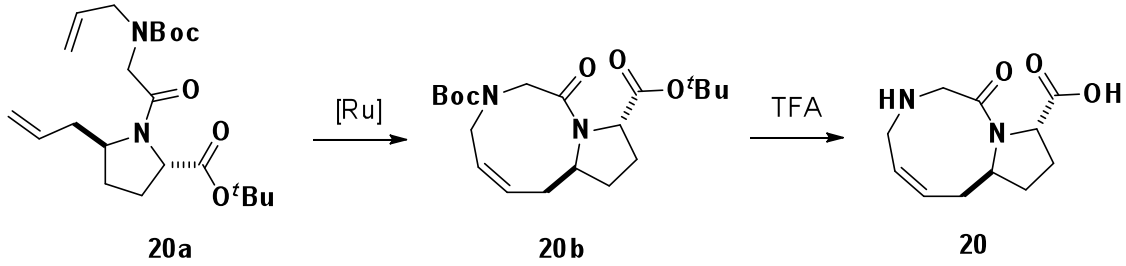


29b **29**

A solution of (3*S*,6*R*,10a*S*,*Z*)-*tert*-butyl 6-((*tert*-butoxycarbonyl)amino)-5-oxo-1,2,3,5,6,7,10,10a-octahydropyrrolo[1,2-*a*]azocine-3-carboxylate **19b** (0.119 g, 0.530 mmol) and palladium hydroxide (20% on carbon) (0.037 g, 0.053 mmol) in methanol (60 mL) was stirred at 25 ^{o}C under an atmosphere of hydrogen gas for 2 h. The suspension was then filtered through a Celite pad and the filtrate evaporated to give the saturated product **29b**. Deprotection of the Boc and *tert*-butyl groups with 2 ml neat trifluoroacetic acid (15 mins) followed by concentration *in vacuo*, gave the product **29** as a white solid (quantitative).

^{1}H (500 MHz, d-methanol): δ 4.35-4.41 (m, 2H), 4.24-4.30 (m, 1H) 2.36-2.47 (m, 1H), 2.15-2.26 (m, 1H), 1.94-2.04 (m, 2H), 1.55-1.82 (m, 7H), 1.40-1.53 (m, 1H), ppm.
^{13}C (125 MHz, d-methanol): δ 175.4, 169.5, 60.6, 60.5, 52.4, 38.0, 34.2, 32.4, 28.1, 25.7, 24.1.
HRMS (ESI-TOF) calcd. for $C_{11}H_{18}N_2O_3$ $[M+Na]^+$ 249.12096, found 249.12086.

(7a*S*,10*S*,*Z*)-di-*tert*-butyl 1-oxo-4,7,7a,8,9,10-hexahydro-1*H*-pyrrolo[1,2-*d*][1,4]diazonine-3,10(2*H*)-dicarboxylate (20)



20a **20b** **20**

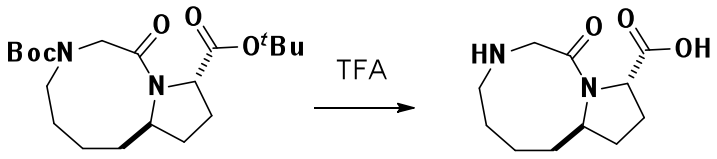
To a stirred solution of (2S, 5S)-*tert*-butyl-5-allylpyrrolidine-2-carboxylate **2** (0.451 g, 2.135 mmol), 2-(allyl(*tert*-butoxycarbonyl)amino)acetic acid (0.552 g, 2.560 mmol) and ethyl(hydroxyimino)cyanoacetate (0.455 g, 3.200 mmol) in dichloromethane (55 mL) was added 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide (0.497 g, 3.200 mmol). The reaction was stirred for 12 h at 25 ^{o}C. Saturated aqueous sodium bicarbonate (5 mL) was added to the reaction mixture and the aqueous phase was extracted with dichloromethane (3 x 10 mL). The combined extracts were dried over sodium sulfate and concentrated *in vacuo*. Purification by column chromatography (gradient 20 – 50% ethyl acetate/hexane) gave coupled product **20a** as a yellow oil (0.752 g, 86%).

To a degassed and stirred solution of diene **20a** (0.239g, 0.585 mmol) was added bis(tricyclohexylphosphine)benzylidineruthenium dichloride (Grubbs 1st generation catalyst) (0.096 g, 0.117 mmol) in dry dichloromethane (145 mL) under an atmosphere of argon. The reaction mixture was heated at reflux for 24 h. The reaction mixture was then left to cool to 25 ^{o}C and concentrated *in vacuo*. Purification by column chromatography (gradient 20 – 50% ethyl acetate/hexane) gave cyclized alkene **20b** as a white solid (0.135 g, 60%). Deprotection of the Boc and *tert*-butyl groups with 2 ml neat trifluoroacetic acid (15 mins) followed by concentration *in vacuo*, gave the product **20** as a white solid (0.106 g, 88%).

^{1}H (500 MHz, d-methanol): δ 6.30-6.41 (m, 1H), 5.70-5.79 (m, 1H), 4.51-4.60 (m, 1H), 4.29-4.37 (m, 1H), 4.01-4.07 (m, 1H), 3.46-3.55 (m, 1H), 3.26-3.32 (m, 1H), 2.54-2.66 (m, 2H), 2.23-2.40 (m, 2H), 2.00-2.08 (m, 1H), 1.92-1.99 (m, 1H) ppm.

^{13}C (125 MHz, d-methanol): δ 174.6, 174.6, 140.1, 122.5, 60.9, 59.8, 48.5, 46.0, 43.1, 35.4, 35.0, 28.3.
HRMS (ESI-TOF) calcd. for $C_{11}H_{16}N_2O_3$ $[M+H]^+$ 225.12337, found 225.12255.

(7a*R*,10*S*)-di-*tert*-butyl 1-oxooctahydro-1*H*-pyrrolo[1,2-*d*][1,4]diazonine-3,10(2*H*)-dicarboxylate (30)



30b **30**

A solution of (7a*S*,10*S*,*Z*)-di-*tert*-butyl 1-oxo-4,7,7a,8,9,10-hexahydro-1*H*-pyrrolo[1,2-*d*][1,4]diazonine-3,10(2*H*)-dicarboxylate **20b** (0.049 g, 0.30 mmol) and palladium hydroxide (20% on carbon) (0.009 g, 0.013 mmol) in methanol (32 mL) was stirred at 25 ^{o}C under an atmosphere of hydrogen gas for 2 h. The suspension was then filtered through a Celite pad and the filtrate evaporated to give the saturated product **30b**. Deprotection of the Boc and *tert*-butyl group with 2 ml neat trifluoroacetic acid (15 mins) followed by concentration *in vacuo*, gave the product **30** as a white solid (quantitative).

^{1}H (500 MHz, d-methanol): δ 4.49-4.54 (m, 1H), 4.35 (dd, 1H, *J* = 8.3 Hz, *J* = 8.3 Hz), 4.27 (d, 1H, *J* = 13.8 Hz), 3.68 (d, 1H, *J* = 13.8 Hz), 3.26-3.29 (m, 1H), 3.18-3.24 (m, 1H), 3.01 (dd, 1H, *J* =12.7 Hz, *J* = 12.7 Hz), 2.35-2.45 (m, 1H), 2.21-2.31 (m, 1H), 1.92-2.03 (m, 3H), 1.63- 1.87 (m, 5 H) ppm.
^{13}C (125 MHz, d-methanol): δ 174.6, 165.9, 62.6, 60.9, 47.5, 45.5, 34.9, 34., 28.3, 25.3, 25.0.
HRMS (ESI-TOF) calcd. for $C_{11}H_{18}N_2O_3$ $[M+Na]^+$ 249.12096, found 247.12181.

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