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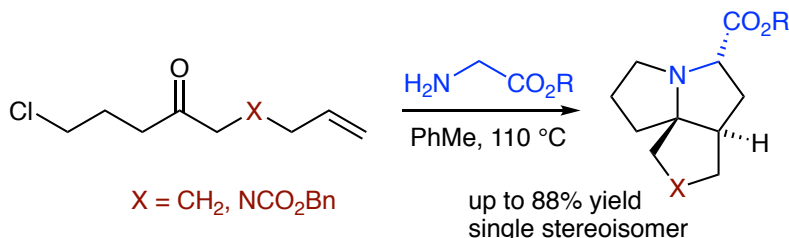
# Synthesis of spirocyclic amines by 1,3-dipolar cycloaddition of azomethine ylides and azomethine imines

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**Abstract** Simple ketone starting materials with a halide leaving group and an alkene were prepared in one step and heated with glycine or glycine esters to promote a tandem imine formation, cyclization, and dipolar cycloaddition cascade. The chemistry was also feasible with acetylhydrazide. In each case a single stereoisomer of the tricyclic amine or pyrazolidine product was formed and the stereochemistry was verified by single crystal X-ray diffraction. When the reaction with glycine, which occurs with loss of  $\text{CO}_2$ , was unsuccessful, the cascade process could be promoted by cross metathesis to give the vinylsulfone starting material that provides a more reactive dipolarophile. Reductive cleavage of the pyrazolidine gave a spirocyclic diamine product.

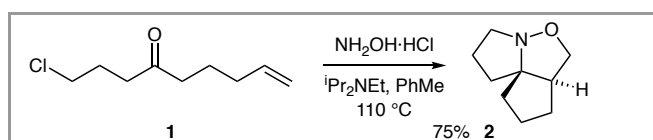
**Key words** Amines; Cyclization; Cycloaddition; Diastereoselectivity; Spiro compounds

Intramolecular dipolar cycloaddition reactions of azomethine ylides are a popular method for the preparation of bicyclic amines.<sup>1–4</sup> A common approach is to heat an aldehyde with a secondary amine to give the intermediate iminium ion that either loses a proton adjacent to an electron-withdrawing group (such as an ester), or loses carbon dioxide, to give the azomethine ylide.<sup>5–10</sup> Intramolecular cycloaddition with a pendant alkene then gives the bicyclic pyrrolidine product.

Building on early work by Pearson and co-workers,<sup>11</sup> our research group has developed a simple approach to tricyclic amines that involves dipolar cycloaddition chemistry as part of a cascade process.<sup>12</sup> Typically an aldehyde with a leaving group such as a chloride or bromide in the 4- or 5-position is heated with a primary amine. This promotes cyclization of the intermediate imine to give an iminium ion and hence an azomethine ylide that undergoes a dipolar cycloaddition reaction. This cascade process can occur in a single pot to give tricyclic products from acyclic starting materials.<sup>12–17</sup> We have applied the chemistry to the synthesis of several alkaloids including aspidospermidine and quebrachamine.<sup>12</sup> Other researchers have studied similar chemistry, in which cyclization of the imine occurs by reactions such as conjugate addition to give the 1,3-dipole that undergoes intramolecular cycloaddition.<sup>18–23</sup>

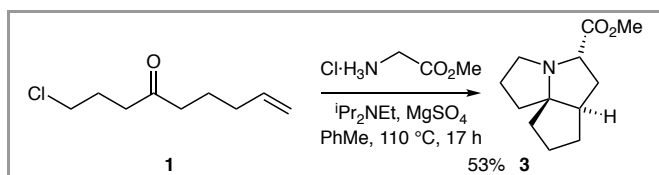
Recently, we have achieved such a successful cascade process, involving cyclization and dipolar cycloaddition, with ketone starting materials instead of aldehydes on heating with hydroxylamine (Scheme 1).<sup>24</sup> The chemistry proceeds by formation of an intermediate oxime from the ketone **1**, that cyclizes with displacement of chloride to give a nitron that then undergoes dipolar cycloaddition to give the product **2**. This has allowed access to spirocyclic amine products.

With the current medicinal chemistry interest in three dimensionally rigid structures, particularly nitrogen-containing heterocycles such as spirocyclic amines,<sup>25</sup> we were interested to obtain further examples of this cascade methodology. This paper describes the extension of the nitron cycloaddition chemistry to the preparation of tricyclic amines and pyrazolidines by cycloaddition of azomethine ylides and azomethine imines.

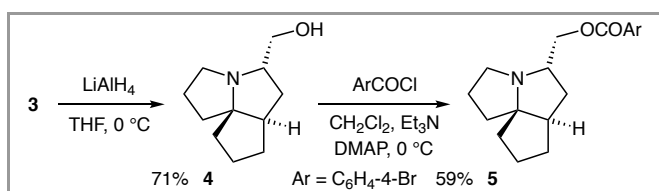
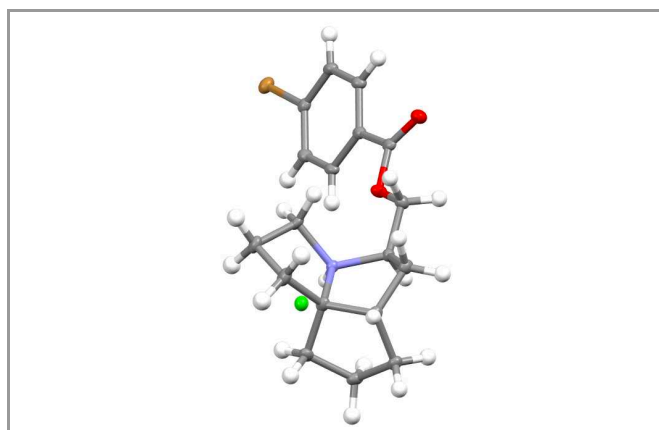


Scheme 1 Cascade condensation, cyclization, cycloaddition of ketone **1** to give tricyclic product **2**.<sup>24</sup>

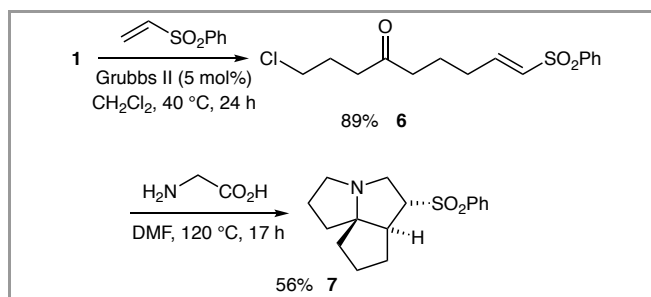
The ketone **1** was prepared in a single step by addition of 4-pentenyl magnesium bromide to 4-chlorobutanoyl chloride according to the literature.<sup>24</sup> Heating this ketone with glycine methyl ester gave the desired tricyclic product **3** as a single stereoisomer (Scheme 2). We found that the yield was improved from 33% to 53% by addition of excess magnesium sulfate drying agent. This presumably helps to form a higher concentration of the imine that undergoes the cyclization then dipolar cycloaddition cascade process.

Scheme 2 Synthesis of the tricyclic amine **3**.

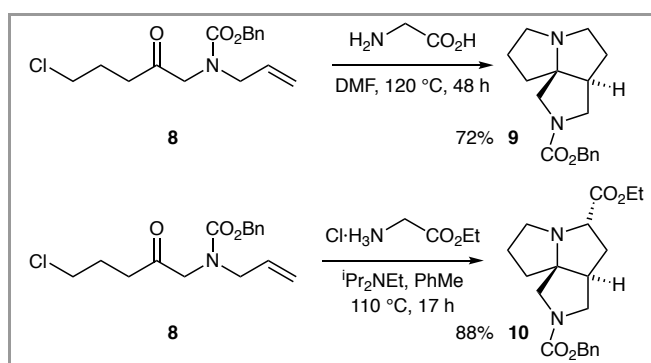
The stereochemistry of the product **3** was determined by reduction of the ester to give the alcohol **4**, followed by acylation to give the ester **5** (Scheme 3). Single crystal X-ray analysis of the hydrochloride salt of the ester **5** revealed that the ester group was *cis* to the ring junction proton, hence the stereochemistry as drawn (Figure 1). This implies that the dipolar cycloaddition reaction occurs through a geometry in which the azomethine ylide has an S shape (rather than W or U shape) and this is consistent with related cycloadditions.<sup>4</sup>

Scheme 3 Synthesis of the alcohol **4** and ester **5**.Figure 1 X-ray crystal structure of ester **5**·HCl.

Unfortunately, the chemistry was not amenable to the use of alanine methyl ester under the same conditions. In this case the ketone **1** was consumed but no desired product could be isolated. Additionally, no product was isolated on heating the ketone **1** with glycine. To help promote the chemistry, we converted the ketone **1** to the ketone **6** by cross metathesis with phenyl vinyl sulfone (Scheme 4). We were pleased to find that heating the ketone **6** with glycine did give the desired product **7**. As expected, we isolated only one stereoisomer and the stereochemistry is believed to be as shown, with concerted cycloaddition leading to the phenyl sulfone group *cis* to the ring junction proton.

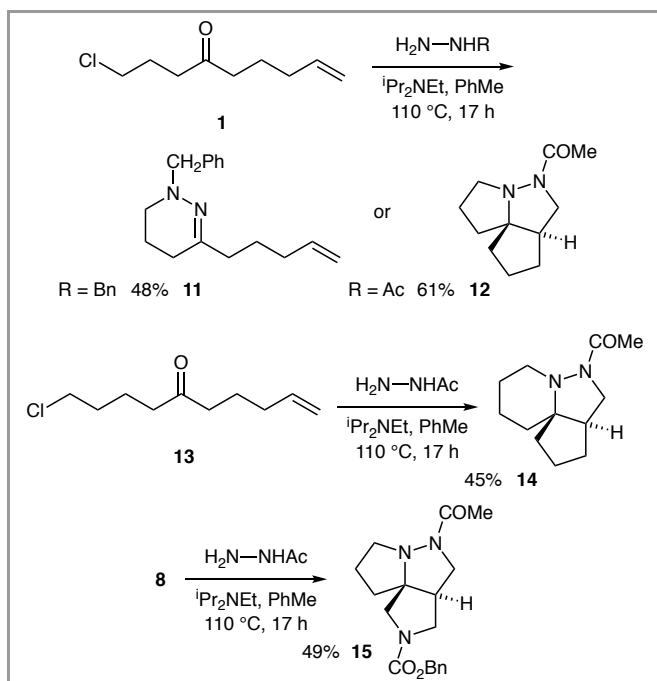
Scheme 4 Synthesis of the ketone **6** and cycloadduct **7**.

In contrast to the ketone **1**, the ketone **8** (prepared as reported in the literature)<sup>24</sup> allowed successful condensation, cyclization, cycloaddition with glycine to give the product **9** (Scheme 5). This reaction required switching to the solvent DMF, as the use of toluene gave only recovered ketone **8**. The more polar solvent is thought to aid solubility of the glycine. Additionally, the presence of the N-CO<sub>2</sub>Bn group presumably affects the cascade process favourably either electronically by increasing reactivity or through an altered conformation with slightly different bond angles due to the sp<sup>2</sup> nitrogen atom in the chain. The cascade chemistry was also successful with glycine ethyl ester to give the cycloadduct **10**. The stereochemistry of **10** was verified by <sup>1</sup>H NOESY and matches that of the related cycloadduct **3**.

Scheme 5 Cycloadditions with the ketone **8**.

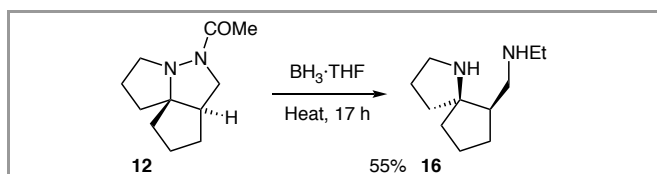
We also investigated the cascade chemistry with hydrazines.<sup>26</sup> Heating ketone **1** with TsNHNH<sub>2</sub>, BocNHNH<sub>2</sub> or PhNHNH<sub>2</sub> gave decomposition and heating with benzylhydrazine gave the hydrazone **11** (Scheme 6). However, we were pleased to find that AcNHNH<sub>2</sub> was successful and led to the tricyclic product **12**. In a similar way, the homologous ketone **13** (prepared in the same way as the ketone **1**)<sup>24</sup> and the ketone **8** were heated with AcNHNH<sub>2</sub> to give the pyrazolidine products **14** and **15**.

Unfortunately, attempts to carry out the cascade chemistry using glycine or glycine methyl ester failed with the ketone **13**. In all attempts, only recovered ketone **13** was isolated. This is surprising given that the related cascade process with ketone **13** and hydroxylamine was successful.<sup>24</sup> A possible reason for this is the low concentration of the imine in solution that is required for cyclization to displace the chloride. The addition of MgSO<sub>4</sub> or *n*-Bu<sub>4</sub>NI did not alter this outcome.



Scheme 6 Cycloadditions with hydrazines.

Finally, we carried out a reductive cleavage of the acylhydrazine **12**, which was successful using borane as the reducing agent.<sup>27</sup> This gave the product **16**, in which the acetamide had also been reduced to the secondary amine (Scheme 7).

Scheme 7 Ring-opening to give the spirocyclic amine **16**.

In conclusion, we have demonstrated that simple ketones can undergo a cascade of reactions involving condensation with glycine, a glycine ester, or  $\text{AcNHNH}_2$  followed by cyclization with displacement of a chloride, followed by *in situ* intramolecular dipolar cycloaddition. A selection of tricyclic products was obtained with complete regio- and stereoselectivity. Ring-opening of the pyrazolidine product could be achieved with borane to give a spirocyclic amine with defined stereochemistry. These results could find use for the formation of rigid, low molecular weight scaffolds in drug discovery.

All experiments were carried out under an atmosphere of nitrogen or argon with dry glassware and stirring. Solvents were obtained from a Grubbs dry solvent system (model: SPS-200-6 or SPS-400-6). Reactions were monitored by using TLC plates that were obtained from Merck (silica gel 60 F<sub>254</sub>). Melting points were recorded on a Gallenkamp hot stage. IR spectra were measured on a Perkin Elmer Spectrum RX Fourier Transform – IR System and only selected peaks are reported. A Bruker AC400 spectrometer was used for  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra. Peak multiplicity is indicated as follows: s (singlet), d (doublet), t (triplet), q (quartet), quin (quintet), m (multiplet), and  $J$  values are given in Hertz. The X-ray crystal structure was obtained using a Bruker D8 Venture CMOS Photon 100. Low and high resolution (accurate mass) mass spectra were recorded on a Walter LCT instrument for electrospray (ES).

## Procedures

### Methyl Octahydro-1H-cyclopenta[h]pyrrolizine-5-carboxylate **3**

Ketone **1**<sup>24</sup> (200 mg, 1.15 mmol), glycine methyl ester hydrochloride (216 mg, 1.72 mmol), *N,N*-diisopropylethylamine (0.6 mL, 3.44 mmol) and  $\text{MgSO}_4$  (1 g) were heated in toluene (14 mL) at  $110^\circ\text{C}$  for 17 h. The mixture was allowed to cool to room temperature and the solvent was evaporated. Purification by column chromatography, eluting with  $\text{CH}_2\text{Cl}_2\text{-MeOH-NH}_3$  (98:2:1), gave the amine **3** (127 mg, 53%) as an oil:

$R_f$  0.17 [ $\text{CH}_2\text{Cl}_2\text{-MeOH-NH}_3$  (98:2:0.6)].

IR ( $\text{cm}^{-1}$ ) 2949, 2864, 1738, 1449, 1434, 1196, 1155, 1104, 917, 733.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  = 3.90–3.84 (1H, m), 3.74 (3H, s), 3.01–2.93 (1H, m), 2.61–2.52 (1H, m), 2.30–2.19 (2H, m), 1.93–1.63 (9H, m), 1.52–1.40 (1H, m), 1.35–1.23 (1H, m).

$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  = 172.9, 82.3, 64.6, 51.6, 49.6, 48.7, 41.7, 39.7, 34.7, 33.2, 26.3, 26.0.

HRMS (ESI) calculated for  $\text{C}_{12}\text{H}_{20}\text{NO}_2$ : 210.1489 (M+H); found: 210.1495.

LRMS (ESI) 210 (100%,  $\text{MH}^+$ ).

### {Octahydro-1H-cyclopenta[h]pyrrolizin-5-yl}methanol **4**

Lithium aluminium hydride (108 mg, 2.84 mmol) was added to the ester **3** (258 mg, 1.23 mmol) in THF (21 mL) at  $0^\circ\text{C}$ . After 1 h, aqueous saturated  $\text{NaHCO}_3$  (3 mL) and water (3 mL) were added and the mixture was allowed to warm to room temperature. The mixture was filtered through celite, washing with  $\text{Et}_2\text{O}$  ( $3 \times 30$  mL). The organic layer was separated, washed with brine (30 mL), dried ( $\text{MgSO}_4$ ), and evaporated to give the alcohol **4** (159 mg, 71%) as an oil:

$R_f$  0.01 [ $\text{CH}_2\text{Cl}_2\text{-MeOH-NH}_3$  (98:2:0.6)].

IR ( $\text{cm}^{-1}$ ) 3225, 2943, 2862, 1449, 1045, 909, 728.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  = 3.92 (1H, br s), 3.81 (1H, dd,  $J$  = 11, 8 Hz), 3.68 (1H, dd,  $J$  = 11, 5.5 Hz), 3.41–3.27 (1H, m), 2.93–2.83 (1H, m), 2.63–2.47 (1H, m), 2.09 (1H, q,  $J$  = 8 Hz), 1.97–1.56 (9H, m), 1.46–1.34 (2H, m), 1.33–1.19 (1H, m).

$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  = 81.7, 62.9, 62.8, 50.3, 47.0, 41.7, 40.8, 33.8, 33.3, 26.5, 25.9.

HRMS (ESI) calculated for  $\text{C}_{11}\text{H}_{20}\text{NO}$ : 182.1539 (M+H); found: 182.1542.

LRMS (ESI) 182 (100%,  $\text{MH}^+$ ).

### {Octahydro-1H-cyclopenta[h]pyrrolizin-5-yl}methyl 4-bromobenzoate **5**

Alcohol **4** (205 mg, 1.13 mmol) and 4-(dimethylamino)pyridine (276 mg, 2.26 mmol) in  $\text{CH}_2\text{Cl}_2$  (13 mL) were added to 4-bromobenzoyl chloride [prepared from 4-bromobenzoic acid (455 mg, 2.26 mmol), oxalyl chloride (0.21 mL, 2.49 mmol) and DMF (10 drops) in  $\text{CH}_2\text{Cl}_2$  (4 mL)] at  $0^\circ\text{C}$ , followed by  $\text{Et}_3\text{N}$  (0.47 mL, 3.39 mmol). The mixture was stirred for 1 h at  $0^\circ\text{C}$  and then saturated aqueous  $\text{NaHCO}_3$  (20 mL) and  $\text{CH}_2\text{Cl}_2$  (100 mL) were added. The organic layer was separated, dried ( $\text{MgSO}_4$ ) and evaporated. Purification by column chromatography on silica gel, eluting with  $\text{CH}_2\text{Cl}_2\text{-MeOH-NH}_3$  (97:3:1), gave the ester **5** (243 mg, 59%) as an oil:

$R_f$  0.23 [ $\text{CH}_2\text{Cl}_2\text{-MeOH-NH}_3$  (98:2:0.6)].

IR ( $\text{cm}^{-1}$ ) 2948, 2858, 1718, 1589, 1396, 1265, 1104, 1070, 1012, 846, 753.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  = 7.94 (2H, d,  $J$  = 8.5 Hz), 7.60 (2H, d,  $J$  = 8.5 Hz), 4.66–4.42 (2H, m), 3.59 (1H, td,  $J$  = 12, 6 Hz), 2.99–2.85 (1H, m), 2.74–2.61 (1H, m), 2.17 (1H, q,  $J$  = 7.5 Hz), 2.03–1.60 (9H, m), 1.58–1.23 (3H, m).

$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  = 166.0, 131.7, 131.3, 129.0, 128.1, 82.0, 65.3, 59.3, 50.1, 47.9, 42.0, 40.8, 33.9, 33.7, 26.4, 26.3.

HRMS (ESI) calculated for  $C_{18}H_{22}^{79}BrNO_2$ : 364.0907 (M+H); found: 364.0908. Calculated for  $C_{18}H_{22}^{81}BrNO_2$ : 366.0886 (M+H); found: 366.0893.

LRMS (ESI) 366 (100%, MH<sup>+</sup>), 364 (100%, MH<sup>+</sup>).

CCDC 1969988.

*(8E)-9-(Benzenesulfonyl)-1-chloronon-8-en-4-one 6*

The ketone **1**<sup>24</sup> (666 mg, 3.81 mmol) and phenyl vinyl sulfone (1.25 g, 7.43 mmol) in  $CH_2Cl_2$  (185 mL) were heated at 50 °C under argon. Once at reflux, Grubbs catalyst 2<sup>nd</sup> generation<sup>28</sup> (161 mg, 0.19 mmol) in  $CH_2Cl_2$  (9.5 mL) was added. After 24 h, the mixture was allowed to cool to room temperature and the solvent was evaporated. Purification by column chromatography, eluting with petrol–EtOAc (9:1), gave the ketone **6** as a dark oil. This was purified further by addition of DMSO (0.68 mL) to the product in  $CH_2Cl_2$  (192 mL) at room temperature. After 16 h the solvent was evaporated and the product was purified by column chromatography, eluting with petrol–EtOAc (9:1), to give the ketone **6** (1.06 g, 89%) as an oil:

$R_f$  0.4 [EtOAc–petrol (50:50)].

IR (cm<sup>-1</sup>) 3057, 2961, 1711, 1626, 1447, 1307, 1145, 736.

<sup>1</sup>H NMR (400 MHz,  $CDCl_3$ )  $\delta$  = 7.93–7.87 (2H, m), 7.67–7.61 (1H, m), 7.60–7.53 (2H, m), 6.97 (1H, dt,  $J$  = 15.0 Hz, 7.0 Hz), 6.36 (1H, dt,  $J$  = 15.0 Hz, 1.5 Hz), 3.58 (2H, t,  $J$  = 7.0 Hz), 2.59 (2H, t,  $J$  = 7.0 Hz), 2.47 (2H, t,  $J$  = 7.0 Hz), 2.32–2.24 (2H, m), 2.04 (2H, quin,  $J$  = 7.0 Hz) 1.78 (2H, quin,  $J$  = 7.0 Hz).

<sup>13</sup>C NMR (100 MHz,  $CDCl_3$ )  $\delta$  = 208.6, 145.8, 140.5, 133.4, 131.2, 129.3, 127.6, 44.4, 41.6, 39.4, 30.6, 26.2, 21.4.

HRMS (ESI) calculated for  $C_{18}H_{23}NO_4S$ : 315.0816 (M+H); found: 315.0821.

LRMS (ESI) 315 (100%, MH<sup>+</sup>).

*6-(Benzenesulfonyl)-octahydro-1H-cyclopenta[h]pyrrolizine 7*

Glycine (43 mg, 0.57 mmol) was added to the ketone **6** (154 mg, 0.29 mmol) in DMF (4 mL) and the mixture was heated at 120 °C. After 17 h the mixture was cooled to room temperature and the solvent was evaporated. Purification by column chromatography, eluting with  $CH_2Cl_2$ –MeOH–NH<sub>3</sub> (99:1:0.1), gave the amine **7** (47 mg, 56%) as an amorphous solid:

m.p. 72–75 °C.

$R_f$  0.2 [ $CH_2Cl_2$ –MeOH–NH<sub>3</sub> (96:4:0.3)].

IR (cm<sup>-1</sup>) 3067, 2950, 2866, 1447, 1301, 1144, 1086.

<sup>1</sup>H NMR (400 MHz,  $CDCl_3$ )  $\delta$  = 7.94–7.86 (2H, m), 7.68 (1H, t,  $J$  = 7.5 Hz), 7.59 (2H, t,  $J$  = 7.5 Hz), 3.45–3.35 (1H, m), 3.16–3.07 (1H, m), 3.02–2.87 (2H, m), 2.85–2.72 (2H, m), 2.08–1.93 (2H, m), 1.82–1.65 (3H, m), 1.65–1.51 (3H, m), 1.38–1.21 (2H, m).

<sup>13</sup>C NMR (100 MHz,  $CDCl_3$ )  $\delta$  = 139.0, 133.8, 129.3, 128.3, 83.2, 70.8, 55.1, 52.7, 49.3, 41.0, 37.3, 32.5, 25.3, 25.0.

HRMS (ESI) calculated for  $C_{16}H_{21}NO_2S$ : 292.1366 (M+H); found: 292.1367.

LRMS (ESI) 292 (100%, MH<sup>+</sup>).

*Benzyl Octahydropyrrolo[3,4-h]pyrrolizine-2-carboxylate 9*

Glycine (108 mg, 1.44 mmol) was added to the ketone **8**<sup>24</sup> (110 mg, 0.36 mmol) in DMF (5 mL) and the mixture was heated to 120 °C. After 48 h, the mixture was cooled to room temperature and the solvent was evaporated. Purification by flash column chromatography, eluting with  $CH_2Cl_2$ –MeOH–NH<sub>3</sub> (94:5:1), gave the amine **9** (74 mg, 72%) as an oil:

$R_f$  0.28 [ $CH_2Cl_2$ –MeOH–NH<sub>3</sub> (89:10:1)].

IR (cm<sup>-1</sup>) 2950, 2865, 1695, 1445, 1415, 1360, 1220, 1095.

<sup>1</sup>H NMR (400 MHz,  $CDCl_3$ , 50 °C, rotamers)  $\delta$  = 7.43–7.25 (5H, m), 5.19–5.09 (2H, m), 3.68–3.56 (2H, m), 3.47–3.31 (2H, m), 3.22 (1H, dt,  $J$  = 11.0, 6.5 Hz), 3.14–3.05 (1H, m), 2.73–2.55 (2H, m), 2.47–2.38 (1H, m), 2.07 (1H, td,  $J$  = 13.0, 7.0 Hz), 1.93–1.77 (4H, m), 1.77–1.65 (1H, m).

<sup>13</sup>C NMR (100 MHz,  $CDCl_3$ , 50 °C, rotamers)  $\delta$  = 154.7, 137.1, 128.4, 127.8, 127.7, 80.6, 66.7, 59.1, 55.4, 55.1, 50.8, 47.9, 36.8, 31.8, 26.4.

HRMS (ESI) calculated for  $C_{17}H_{23}N_2O_2$ : 287.1754 (M+H); found: 287.1765.

LRMS (ESI) 287 (100%, MH<sup>+</sup>).

*2-Benzyl 5-Ethyl Octahydropyrrolo[3,4-h]pyrrolizine-2,5-dicarboxylate 10*

Glycine ethyl ester hydrochloride (87 mg, 0.62 mmol) was added to the ketone **8**<sup>24</sup> (128 mg, 0.41 mmol) and *N,N*-diisopropylethylamine (0.21 mL, 1.23 mmol) in toluene (5 mL) and the mixture was heated to 110 °C. After 17 h, the mixture was cooled to room temperature and the solvent was evaporated. Purification by flash column chromatography, eluting with  $CH_2Cl_2$ –MeOH (99:1), gave the amine **10** (128 mg, 88%) as an oil:

$R_f$  0.5 [ $CH_2Cl_2$ –MeOH (95:5)].

IR (cm<sup>-1</sup>) 3035, 2955, 1695.

<sup>1</sup>H NMR (400 MHz,  $CDCl_3$ , 50 °C)  $\delta$  = 7.34–7.26 (5H, m), 5.11 (2H, s), 4.18 (2H, q,  $J$  = 7.0 Hz), 3.92 (1H, t,  $J$  = 6.5 Hz), 3.61–3.54 (2H, m), 3.39–3.38 (2H, m), 3.00–2.97 (1H, m), 2.63–2.59 (2H, m), 2.34–2.27 (1H, m), 2.00–1.86 (5H, m), 1.27 (3H, t,  $J$  = 7.0 Hz).

<sup>13</sup>C NMR (100 MHz,  $CDCl_3$ , 50 °C)  $\delta$  = 172.5, 154.7, 137.0, 128.4, 127.8, 127.7, 81.3, 66.7, 64.9, 60.6, 59.4, 50.8, 49.1, 46.1, 37.1, 36.5, 27.2, 14.2.

1D NOESY NMR (500 MHz,  $CDCl_3$ , 50 °C) Irradiation of NCHCO ( $\delta$  = 3.92 ppm) led to enhancement of protons either side of N–CO<sub>2</sub>Bn: *i.e.*  $\delta$  = 3.61 and 3.39 (and also protons at  $\delta$  = 2.63, 2.31, and 2.00).

HRMS (ESI) calculated for  $C_{20}H_{27}N_2O_4$ : 359.1965 (M+H); found: 359.1971.

LRMS (ESI) 359 (100%, MH<sup>+</sup>).

*1-Benzyl-3-(pent-4-en-1-yl)-1,4,5,6-tetrahydropyridazine 11*

Benzylhydrazine dihydrochloride (222 mg, 1.14 mmol) and *N,N*-diisopropylethylamine (0.75 mL, 4.30 mmol) were added to the ketone **1**<sup>24</sup> (166 mg, 0.95 mmol) in PhMe (14 mL) and the mixture was heated under reflux. After 17 h the mixture was allowed to cool to room temperature and the solvent was evaporated. Purification by column chromatography on silica gel, eluting with  $CH_2Cl_2$ –MeOH (49:1), gave the hydrazone **11** (110 mg, 48%) as an oil:

$R_f$  0.56 [ $CH_2Cl_2$ –MeOH (19:1)].

IR (cm<sup>-1</sup>) 3067, 2933, 2826, 1495, 1451, 1354, 913, 736, 697.

<sup>1</sup>H NMR (400 MHz,  $CDCl_3$ )  $\delta$  = 7.42–7.22 (5H, m), 5.94–5.80 (1H, m), 5.09–4.95 (2H, m), 4.19 (2H, s), 2.60 (2H, dd,  $J$  = 7, 4 Hz), 2.22–2.01 (6H, m), 1.95–1.84 (2H, m), 1.71–1.59 (2H, m).

<sup>13</sup>C NMR (100 MHz,  $CDCl_3$ )  $\delta$  = 149.4, 138.7, 138.1, 129.2, 128.1, 127.1, 114.6, 63.2, 46.3, 37.5, 33.5, 26.2, 24.0, 20.2.

HRMS (ESI) calculated for  $C_{16}H_{23}N_2$ : 243.1856 (M+H); found: 243.1865.

LRMS (ESI) 243 (100%, MH<sup>+</sup>).

*1-[5,6-Diazatricyclo[6.3.0.0<sup>1,5</sup>]undecan-6-yl]ethan-1-one 12*

Acetylhydrazine (142 mg, 1.92 mmol) was added to the ketone **1**<sup>24</sup> (168 mg, 0.96 mmol) in PhMe (14 mL) and the mixture was heated to 110 °C. After 17 h, the mixture was cooled to room temperature and the solvent was evaporated. Purification by flash column chromatography, eluting with  $CH_2Cl_2$ –MeOH (98:2), gave the amide **12** (114 mg, 61%) as an oil:

$R_f$  0.37 [ $CH_2Cl_2$ –MeOH (9:1)].

IR (cm<sup>-1</sup>) 3479, 2949, 2866, 1651, 1409, 1218, 1127, 949, 918, 618, 591.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  = 3.97 (1H, dd,  $J$  = 12, 2 Hz), 3.39 (1H, dd,  $J$  = 12, 8 Hz), 3.28 (1H, dt,  $J$  = 10, 6 Hz), 2.65 (1H, dt,  $J$  = 10, 8 Hz), 2.41–2.30 (1H, m), 2.18 (3H, s), 2.03–1.67 (7H, m), 1.63–1.38 (3H, m).

$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  = 170.8, 82.0, 55.9, 50.8, 49.2, 40.4, 37.4, 33.3, 26.0, 24.4, 21.3.

HRMS (ESI) calculated for  $\text{C}_{11}\text{H}_{19}\text{N}_2\text{O}$ : 195.1492 (M+H); found: 195.1496.

LRMS (ESI) 195 (100%, MH<sup>+</sup>).

#### 1-{7,8-Diazatricyclo[6.4.0.0<sup>1,5</sup>]dodecan-7-yl}ethan-1-one **14**

Acetylhydrazine (142 mg, 1.92 mmol) was added to the ketone **11**<sup>24</sup> (181 mg, 0.96 mmol) in PhMe (14 mL) and the mixture was heated to 110 °C. After 17 h, the mixture was cooled to room temperature and the solvent was evaporated. Purification by flash column chromatography, eluting with  $\text{CH}_2\text{Cl}_2$ -MeOH (98:2), gave the amide **14** (90 mg, 45%) as an oil:

$R_f$  0.37 [ $\text{CH}_2\text{Cl}_2$ -MeOH (9:1)].

IR ( $\text{cm}^{-1}$ ) 3454, 2935, 2864, 1645, 1443, 1416, 1276, 1200, 902, 629, 595.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  = 3.70–3.55 (2H, m), 2.99 (1H, d,  $J$  = 10.5 Hz), 2.74–2.66 (1H, m), 2.48–2.36 (1H, m), 2.16 (3H, s), 1.87–1.49 (11H, m), 1.37–1.24 (1H, m).

$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  = 169.8, 75.6, 53.0, 48.0, 43.0, 39.5, 33.8, 30.3, 24.6, 21.6, 21.3, 21.0.

HRMS (ESI) calculated for  $\text{C}_{12}\text{H}_{21}\text{N}_2\text{O}$ : 209.1648 (M+H); found: 209.1650.

LRMS (ESI) 209 (100%, MH<sup>+</sup>).

#### Benzyl 7-acetyl-3,7,8-triazatricyclo[6.3.0.0<sup>1,5</sup>]undecane-3-carboxylate **15**

Acetylhydrazine (142 mg, 1.92 mmol) was added to the ketone **8**<sup>24</sup> (297 mg, 0.96 mmol) in PhMe (14 mL) and the mixture was heated under reflux. After 17 h, the mixture was cooled to room temperature and the solvent was evaporated. Purification by flash column chromatography, eluting with  $\text{CH}_2\text{Cl}_2$ -MeOH (98:2), gave the amide **15** (155 mg, 49%) as an oil:

$R_f$  0.24 [ $\text{CH}_2\text{Cl}_2$ -MeOH (9:1)].

IR ( $\text{cm}^{-1}$ ) 2956, 2875, 1698, 1650, 1413, 1351, 1230, 1212, 1134, 1102.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ , 50 °C, rotamers)  $\delta$  = 7.42–7.25 (5H, m), 5.12 (2H, s), 4.01 (1H, dd,  $J$  = 12.0, 2.5 Hz), 3.68 (1H, dd,  $J$  = 12.0, 8.0 Hz), 3.64–3.55 (1H, m), 3.55–3.43 (2H, m), 3.43–3.28 (2H, m), 2.74–2.64 (2H, m), 2.14 (3H, s), 2.10–1.99 (2H, m), 1.99–1.83 (2H, m).

$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ , 50 °C, rotamers)  $\delta$  = 171.5, 154.4, 136.7, 128.4, 128.0, 127.9, 80.2, 67.0, 65.2, 56.5, 56.0, 50.4, 48.5, 34.8, 23.8, 20.9.

HRMS (ESI) calculated for  $\text{C}_{18}\text{H}_{24}\text{N}_3\text{O}$ : 330.1812 (M+H); found: 330.1825.

LRMS (ESI) 330 (100%, MH<sup>+</sup>).

#### {(1-Azaspiro[4.4]nonan-6-yl)methyl}(ethyl)amine **16**

$\text{BH}_3$ -THF (2.2 mL, 2.2 mmol, 1 M) was added to cycloadduct **12** (43 mg, 0.22 mmol). The mixture was heated under reflux for 17 h and was cooled to room temperature. MeOH (10 mL) was added and the solvent was evaporated. Purification by flash column chromatography, eluting with  $\text{CH}_2\text{Cl}_2$ -MeOH- $\text{NH}_3$  (9:1:0.5) to give diamine **16** (22 mg, 55%) as an oil:

$R_f$  0.11 [ $\text{CH}_2\text{Cl}_2$ -MeOH- $\text{NH}_3$  (9:1:0.5)].

IR ( $\text{cm}^{-1}$ ) 3269, 2958, 2873, 1634, 1539, 1455, 1302, 1112, 731.

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  = 5.00 (2H, br s), 3.26–3.12 (1H, m), 3.03–2.83 (2H, m), 2.83–2.69 (3H, m), 2.09–1.96 (2H, m), 1.92–1.83 (3H, m), 1.82–1.69 (4H, m), 1.64–1.53 (1H, m), 1.50–1.41 (1H, m), 1.18 (3H, t,  $J$  = 7 Hz).

$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  = 73.5, 50.6, 45.3, 43.4, 43.2, 38.4, 37.3, 28.4, 25.1, 21.6, 14.1.

HRMS (ESI) calculated for  $\text{C}_{11}\text{H}_{23}\text{N}_2$ : 183.1856 (M+H); found: 183.1860.

LRMS (ESI) 183 (100%, MH<sup>+</sup>).

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## Supporting Information

YES

## Primary Data

NO

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