Organic & Biomolecular Chemistry

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Cite this: *Org. Biomol. Chem.*, 2011, **9**, 7921

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**PAPER**

# Cascade cyclization, dipolar cycloaddition of azomethine imines for the synthesis of pyrazolidines†

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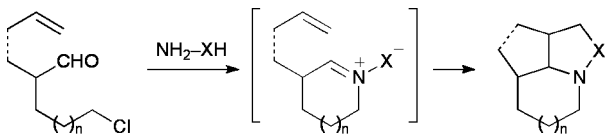
***Received 8th July 2011, Accepted 17th August 2011***
**DOI: 10.1039/c1ob06122d**



A tandem multi-step, one-pot reaction of aldehydes with hydrazines has been used for the preparation of tetrahydropyrazoles and dihydropyrazoles. The chemistry involves condensation then cyclization, followed by inter- or intramolecular dipolar cycloaddition of the resulting azomethine imine intermediates. The intramolecular cycloaddition gives fused tricyclic compounds as single diastereoisomers. The intermolecular cycloaddition was successful with a variety of activated alkene and alkyne dipolarophiles.

## Introduction

The formation of more than two chemical bonds or ring systems in a one-pot reaction provides a rapid and efficient synthesis of complex molecules from simple substrates. Such sequential, multi-step processes are called cascade, domino, or tandem reactions and can lead to the construction of polycyclic compounds with high levels of regio- and stereochemical control.[1] In addition, this chemistry is atom-economic, efficient on time and reduces waste that would be associated with separate steps. With this in mind, we have reported the synthesis of fused and bridged tricyclic compounds by a cascade of condensation, cyclization, then dipolar cycloaddition.[2] The chemistry uses the condensation of an aldehyde and a primary amine (an amino-acid, amino-ester, or hydroxylamine), cyclization onto a tethered alkyl halide, then *in situ* deprotonation or decarboxylation to give an azomethine ylide or nitrone, followed by intramolecular or intermolecular dipolar cycloaddition (Scheme 1).

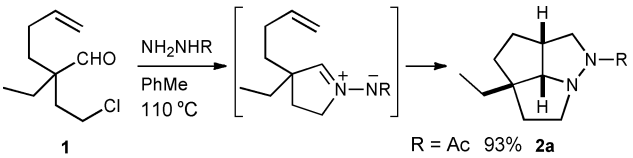



**Scheme 1** Cascade strategy.

One type of dipole that we have not previously explored is an azomethine imine (Scheme 1, X = NR). Azomethine imines are less common than other 1,3-dipoles but are known to react with alkenes or alkynes in inter-[3] or intramolecular[4] cycloadditions to construct a variety of substituted pyrazolidines.[5] Recently, asymmetric 1,3-dipolar cycloadditions of azomethine imines have been reported to give enantiomerically enriched pyrazolidines,[6] and azomethine imines have been used in alkaloid synthesis.[7] We were therefore keen to test the use of hydrazines $H_2N$–NHR as the primary amine starting material. This should give rise to intermediate hydrazones then, after cyclization onto the tethered alkyl halide and deprotonation, to intermediate azomethine imine dipoles. *In situ* cycloaddition would provide an efficient synthesis of ring-fused pyrazolidines.[8] In this paper we report the results of our efforts using this strategy, describing the successful reaction of hydrazines with a variety of different aldehyde substrates for the condensation, cyclization, dipolar cycloaddition cascade.

## Results and discussion

We have reported an efficient synthesis of aldehyde **1** using alkylations of a nitrile anion followed by DIBAL-H reduction.[2a] Heating the aldehyde **1** in toluene or in xylene with hydrazine monohydrate gave predominantly the hydrazone intermediate rather than the desired cycloadduct. However, we were pleased to find that heating the aldehyde **1** with acetylhydrazine or benzyl hydrazine·2HCl (with $^{i}Pr_2NEt$) in toluene for 2–3 h gave the cycloadducts **2a** and **2b** in excellent yield each as a single diastereoisomer (Scheme 2). The all *cis* configuration was confirmed by single-crystal X-ray




**Scheme 2** Treatment of aldehyde **1** with hydrazines.

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† Electronic supplementary information (ESI) available: Computational data; crystallographic information and ORTEP diagrams for **2a**, **8**, **10a**, **10b′**, **11a**, **11b**, **12**, **16** (CCDC reference numbers 822805, 822806, 822811, 822807, 822809, 822812, 822810 and 822808 respectively); copies of NMR spectra. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c1ob06122d

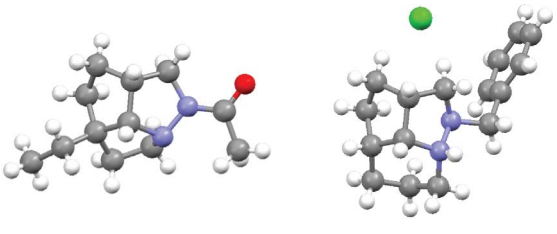
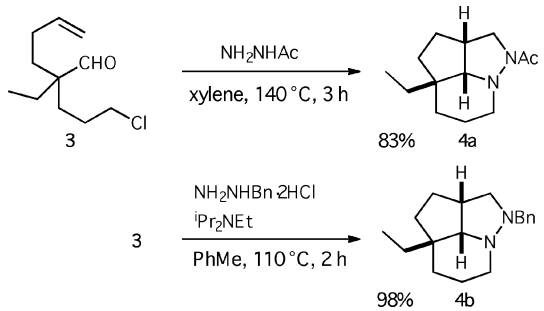


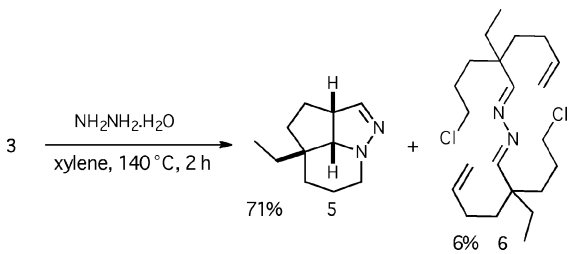

**Fig. 1** X-ray structures of the products **2a** and **8**·HCl.

analysis of the product **2a** (Fig. 1). To obtain the cycloadduct **2c**, aldehyde **1** was heated with phenylhydrazine in toluene for 14 h. The all-*cis* stereochemistry of the products **2** is expected from related chemistry using azomethine ylides or nitrones.[2c]

In a similar way, the aldehyde **3** was prepared,[2c] and was heated with acetylhydrazine or benzylhydrazine to give the tricyclic products **4a** and **4b** (Scheme 3). High yields of a single diastereoisomer (assumed all-*cis* configuration) were obtained. Heating the aldehyde **3** with phenylhydrazine did not give the desired cycloadduct and only the hydrazone intermediate was isolated. However, in contrast with aldehyde **1**, heating the aldehyde **3** with hydrazine (in xylene) gave the cycloadduct **5** in good yield together with a small amount of the dimer **6** (Scheme 4). To form the product **5**, an *in situ* oxidation of the first-formed cycloadduct must have taken place.

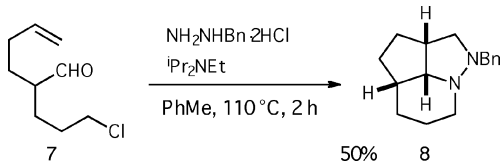



**Scheme 3** Treatment of aldehyde **3** with hydrazines.




**Scheme 4** Treatment of aldehyde **3** with hydrazine.

We reported previously that enolizable aldehydes are more problematic substrates for this type of chemistry, particularly using azomethine ylide intermediates.[2d] Therefore we were interested to test whether the cascade chemistry with azomethine imines was possible starting with an enolizable aldehyde. The aldehyde **7** was prepared in three steps (nitrile alkylation, chlorination and DIBAL-H reduction)[2d] and was heated with benzylhydrazine in toluene (Scheme 5). We were pleased that the tricyclic compound **8** was obtained in reasonable yield. The all-*cis* configuration of

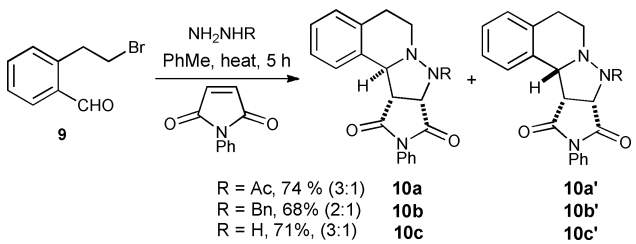



**Scheme 5** Treatment of aldehyde **7** with benzylhydrazine.

the compound **8** was confirmed by single-crystal X-ray analysis (Fig. 1). Unfortunately, the aldehyde **7** gave the hydrazone intermediates rather than the cycloadducts on heating with acetylhydrazine or hydrazine.

The preparation of tricyclic products **2a–c**, **4a**, **4b**, **5**, and **8** demonstrate some of the scope of this chemistry using intramolecular cycloadditions. We then studied the aldehyde **9**, as a substrate for cascade condensation, cyclization, then intermolecular cycloaddition.

The aldehyde **9** was prepared from isochroman in one pot.[9] Heating the aldehyde **9** with acetylhydrazine or benzylhydrazine and *N*-phenylmaleimide as the dipolarophile at 60 °C gave the cycloadducts as a mixture of two diastereoisomers, **10a/a′** and **10b/b′** (Scheme 6). The stereochemistry of the compounds **10a** and **10b′** were confirmed by single-crystal X-ray analysis (Fig. 2). Heating the aldehyde **9** with hydrazine and *N*-phenylmaleimide at 110 °C gave the cycloadducts **10c/c′** (major diastereoisomer assumed to be **10c**).




**Scheme 6** Treatment of aldehyde **9** with hydrazines and *N*-phenylmaleimide.

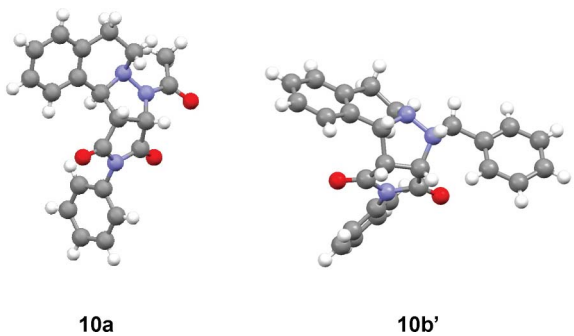
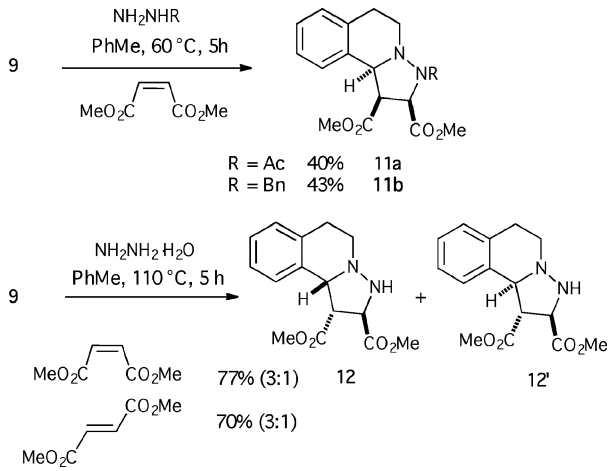



**Fig. 2** X-ray structures of the products **10a** and **10b′**.

We next attempted cycloadditions with dimethyl maleate as the dipolarophile. Cycloadducts **11a** and **11b** were formed as single diastereoisomers (Scheme 7). The cycloaddition reactions were carried out at 60 °C as the compound **13** (Fig. 3) was obtained by heating the aldehyde **9** with benzylhydrazine at 110 °C, and decomposition occurred on heating the aldehyde **9** with acetylhydrazine at 110 °C. Single-crystal X-ray analysis of




**Scheme 7** Treatment of aldehyde **9** with hydrazines and dimethyl maleate or dimethyl fumarate.

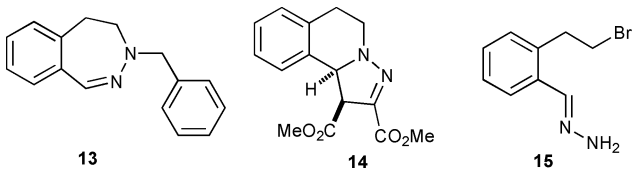



**Fig. 3** Structures derived from aldehyde **9**.

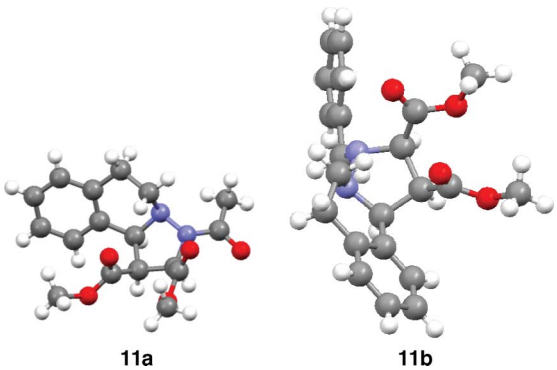



**Fig. 4** X-ray structures of the products **11a** and **11b**.

compound **11b** confirmed the *cis* relationship of the esters (Fig. 4). The product **11b** was unstable and slow oxidation took place to give the dihydropyrazole **14** (Fig. 3). Heating the aldehyde **9** with hydrazine and dimethyl maleate gave the cycloadducts **12/12′**, in which the ester groups were *trans* to one another, as confirmed by single crystal X-ray analysis of the isomer **12** (Fig. 5). The same products were formed by using dimethyl fumarate as the dipolarophile. Heating dimethyl maleate with hydrazine was found to promote isomerization to dimethyl fumarate.[10]

Finally, we examined the cascade condensation, cyclization, intermolecular cycloadditions with alkyne dipolarophiles. The aldehyde **9**, on heating with hydrazine and methyl phenylpropiolate in toluene at 110 °C for 14 h gave a mixture of the hydrazone **15** (Fig. 3, 22%) and the products **16** and **17** (63%, ratio 3 : 1). The stereochemistry of the isomer **16** was confirmed by single crystal X-ray analysis (Fig. 5). Further heating of the reaction caused decomposition. However, at 60 °C the hydrazone **15** could be isolated (46% yield), and on heating the hydrazone **15** with methyl

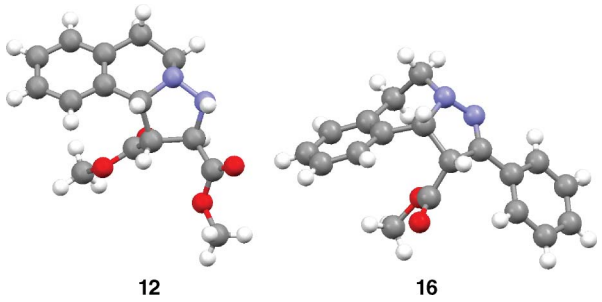
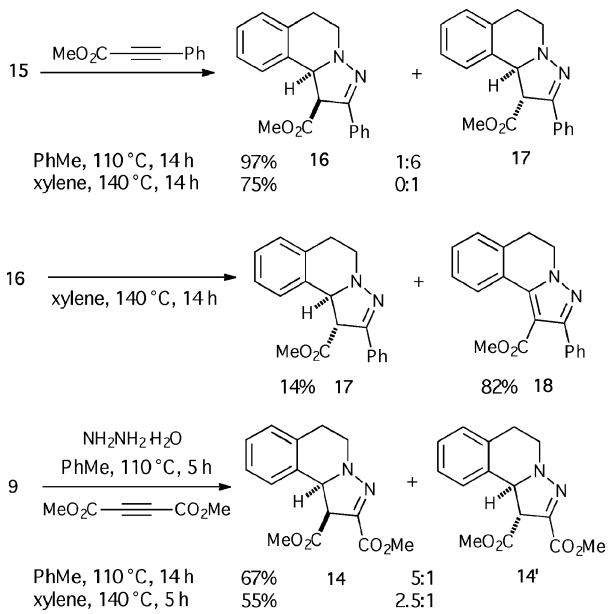


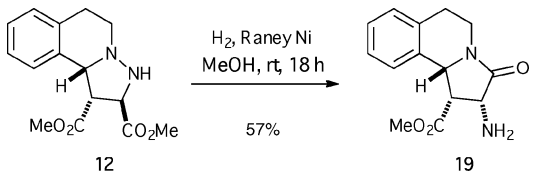

**Fig. 5** X-ray structures of the products **12** and **16**.

phenylpropiolate in toluene, the cycloadducts **16** and **17** (ratio 1 : 6) were obtained in excellent yield (Scheme 8). Heating the hydrazone **15** with methyl phenylpropiolate in xylene gave the cycloadduct **17** exclusively (single regio- and stereoisomer). This suggests that the isomer **17** is the thermodynamic product and this was supported by DFT calculations using the SMP version of the Gaussian 09 program package with the B3LYP functional method (6-311G** basis set, see ESI†). This predicted that isomer **17** was lower in energy than **16** by 10.9 kJ mol$^{-1}$. Further support was obtained by heating the isomer **16** in xylene, which led to the isomer **17**, together with, predominantly, the pyrazole **18**. Another example, starting with the aldehyde **9** and using dimethyl acetylenedicarboxylate as the alkyne in toluene or in xylene, gave the compounds **14** and **14′**.




**Scheme 8** Treatment of aldehyde **9** with hydrazine and alkynes.

Finally, we investigated the potential of this chemistry for the formation of α-amino carbonyl compounds (ester/amide) by breaking the N–N bond in the product. Treating the cycloadduct **12** with RANEY® nickel over hydrogen promoted the desired N–N bond cleavage and concomitant lactam formation to give the product **19** (Scheme 9). The lactam **19** was a single stereoisomer, assumed to have the relative configuration as shown. This was supported by $^1$H NOESY studies. This chemistry therefore provides a method to access novel 5-membered lactams with a 2-amino group.




**Scheme 9** Treatment of cycloadduct **12** with RANEY® nickel.

## Conclusions

In summary, cascade chemistry involving condensation, cyclization, and then intra- or intermolecular dipolar cycloaddition has been extended successfully using hydrazines. The chemistry involves intermediate hydrazones and azomethine imines and leads to pyrazolidines, dihydropyrazoles or pyrazoles with high levels of regio- and stereocontrol. In addition, one of the products has been shown to be amenable to breaking the N–N bond to prepare a 2-aminopyrrolidinone.

## Experimental

### General methods

For general experimental details, including information on solvent purifications and the spectrometers used in this research, see previous descriptions.[11] For further data, see ESI.†

**1-((2a*R**,4a*S**,6b*S**)-4a-Ethyl-octahydro-1,6a-diaza-cyclopenta[*cd*]pentalen-1-yl)-ethanone 2a.** The aldehyde **1**[1] (181 mg, 0.96 mmol), acetylhydrazine (142 mg, 1.92 mmol) in PhMe (14 mL) were heated under reflux for 3 h. After cooling to room temperature, the solvent was evaporated. Purification by column chromatography, eluting with $CH_2Cl_2$–MeOH (9 : 1), gave the cycloadduct **2a** (185 mg, 93%) as an amorphous solid: m.p. 53–55 °C; $R_f$ 0.65 [$CH_2Cl_2$–MeOH (9 : 1)]; $\nu_{max}$/cm$^{-1}$ 2930, 1665, 1460; $^1$H NMR (500 MHz, $CDCl_3$) $\delta$= 4.30 (1H, t, *J* 13.5 Hz), 3.50 (1H, d, *J* 7 Hz), 3.29–3.23 (1H, m), 2.91–2.79 (2H, m), 2.73–2.69 (1H, m), 2.13 (3H, s), 1.83–1.78 (1H, m), 1.74–1.68 (3H, m), 1.63–1.60 (1H, m), 1.54–1.47 (2H, m), 1.45–1.38 (1H, m), 0.90 (3H, t, *J* 7.5 Hz); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ = 170.3, 80.6, 54.5, 53.4, 46.6, 45.4, 35.1, 34.9, 31.1, 30.5, 20.8, 9.7; HRMS (ES) Found: MH$^+$, 209.1652 $C_{12}H_{21}N_2O$ requires MH$^+$, 209.1654; LRMS *m*/*z* (ES) 210 (20%), 209 (100, MH$^+$).

**(2a*R**,4a*S**,6b*S**)-1-Benzyl-4a-ethyl-octahydro-1,6a-diaza-cyclopenta[*cd*]pentalene 2b.** The aldehyde **1**[2a] (179 mg, 0.95 mmol), benzylhydrazine dihydrochloride (222 mg, 1.14 mmol) and *N*,*N*-diisopropylethylamine (0.75 mL, 4.3 mmol) in PhMe (14 mL) were heated under reflux for 2 h. After cooling to room temperature, the solvent was evaporated. Purification by column chromatography, eluting with $CH_2Cl_2$–MeOH (99.5 : 0.5), gave the cycloadduct **2b** (222 mg, 91%) as an oil; $R_f$ 0.5 [$CH_2Cl_2$–MeOH (99.5 : 0.5)]; $\nu_{max}$/cm$^{-1}$ 2940, 2865, 1460; $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ = 7.34–7.22 (5H, m), 4.12 (1H, d, *J* 13 Hz), 3.80 (1H, d, *J* 6.5 Hz), 3.71 (1H, d, *J* 13 Hz), 3.21 (1H, dt, *J* 11, 6.5 Hz), 2.95 (1H, dt, *J* 11, 6.5 Hz), 2.89–2.82 (2H, m), 2.79–2.75 (1H, m), 1.86–1.80 (1H, m), 1.79–1.73 (1H, m), 1.70–1.65 (1H, m), 1.63–1.53 (3H, m), 1.48–145 (2H, m), 0.90 (3H, t, *J* 7.5 Hz); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ = 138.2, 128.7, 128.4, 127.2, 80.1, 60.5, 57.1, 54.7, 53.4, 44.3, 36.9, 34.9, 30.8, 29.9, 9.9; HRMS (ES) Found: MH$^+$, 257.2006 $C_{17}H_{25}N_2$ requires MH$^+$, 257.2018; LRMS *m*/*z* (ES) 258 (30%), 257 (100, MH$^+$).

**(2a*R**,4a*S**,6b*S**)-4a-Ethyl-1-phenyl-octahydro-1,6a-diaza-cyclopenta[*cd*]pentalene 2c.** The aldehyde **1**[2a] (223 mg, 1.18 mmol) and phenylhydrazine (0.2 mL, 2.36 mmol) in PhMe (18 mL) were heated under reflux for 14 h. After cooling to room temperature, the solvent was evaporated. Purification by column chromatography, eluting with petrol–EtOAc (95 : 5), gave the cycloadduct **2c** (212 mg, 75%) as an amorphous solid: m.p. 32–34 °C; $R_f$ 0.48 [petrol–EtOAc (95 : 5)]; $\nu_{max}$/cm$^{-1}$ 2940, 2865, 1460; $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ = 7.26–7.21 (2H, m), 7.06–7.04 (2H, m), 6.83–6.80 (1H, m), 3.65 (1H, dd, *J* 11, 8.5 Hz), 3.58 (1H, d, *J* 8 Hz), 3.37–3.33 (1H, m), 3.19 (1H, dd, *J* 11, 7.5 Hz), 2.88–2.80 (2H, m), 1.90–1.81 (1H, m), 1.79–1.64 (4H, m), 1.60–1.45 (3H, m), 0.96 (3H, t, *J* 7.5 Hz); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ = 151.2, 128.9, 118.9, 114.8, 78.9, 55.2, 53.5, 53.2, 46.3, 35.1 (two overlapping $CH_2$), 31.5, 30.0, 9.8; HRMS (ES) Found: MH$^+$, 243.1857 $C_{16}H_{23}N_2$ requires MH$^+$, 243.1861; LRMS *m*/*z* (ES) 244 (10%), 243 (100, MH$^+$); Anal. Calcd for $C_{16}H_{22}N_2$: C, 79.29; H, 9.15; N, 11.56. Found: C, 79.51; H, 9.33; N, 11.34.

**1-((2a*R**,4a*S**,7b*S**)-4a-Ethyl-octahydro-1,7a-diaza-cyclopenta[*cd*]inden-1-yl)-ethanone 4a.** The aldehyde **3**[2c] (218 mg, 1.08 mmol), acetylhydrazine (160 mg, 2.15 mmol) in xylene (15 mL) were heated under reflux for 3 h. After cooling to room temperature, the solvent was evaporated. Purification by column chromatography, eluting with $CH_2Cl_2$–MeOH (9 : 1), gave the cycloadduct **4a** (200 mg, 83%) as an oil; $R_f$ 0.78 [$CH_2Cl_2$–MeOH (9 : 1)]; $\nu_{max}$/cm$^{-1}$ 2930, 1665, 1460; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ = 4.23 (1H, dd, *J* 12, 9.5 Hz), 3.28 (1H, d, *J* 9.5 Hz), 2.97–2.94 (1H, m), 2.87 (1H, dd, *J* 12, 7 Hz), 2.82–2.71 (1H, m), 2.50–2.43 (1H, m), 2.07 (3H, s), 1.92–1.84 (1H, m), 1.67–1.57 (5H, m), 1.54–1.37 (3H, m), 1.22–1.13 (1H, m), 0.88 (3H, t, *J* 7.5 Hz); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ = 170.3, 73.7, 50.1, 47.1, 45.2, 41.6, 34.7, 30.5, 29.9 (two overlapping $CH_2$), 20.5, 20.3, 9.4; HRMS (ES) Found: MH$^+$, 223.1802 $C_{13}H_{23}N_2O$ requires MH$^+$, 223.1801; LRMS *m*/*z* (ES) 224 (10%), 223 (100, MH$^+$), 220 (20).

**(2a*R**,4a*S**,7b*S**)-1-Benzyl-4a-ethyl-decahydro-1,7a-diaza-cyclopenta[*cd*]indene 4b.** The aldehyde **3**[2c] (197 mg, 0.97 mmol), benzylhydrazine dihydrochloride (227 mg, 1.17 mmol) and *N*,*N*-diisopropylethylamine (0.76 mL, 4.37 mmol) in PhMe (14 mL) were heated under reflux for 2 h. After cooling to room temperature, the solvent was evaporated. Purification by column chromatography, eluting with $CH_2Cl_2$–MeOH (9 : 1), gave the cycloadduct **4b** (259 mg, 98%) as an oil; $R_f$ 0.52 [$CH_2Cl_2$–MeOH (9 : 1)]; $\nu_{max}$/cm$^{-1}$ 2940, 2865, 1460; $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ = 7.29–7.22 (5H, m), 4.34 (1H, d, *J* 11.5 Hz), 3.85 (1H, d, *J* 11.5 Hz), 3.69 (1H, s), 3.46 (1H, d, *J* 14 Hz), 3.25 (1H, dd, *J* 10, 7.5 Hz), 3.01 (1H, t, *J* 14 Hz), 2.93–2.86 (2H, m), 1.98–1.78 (4H, m), 1.49–1.33 (4H, m), 1.31–1.10 (2H, m), 0.76 (3H, t, *J* 7.5 Hz); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ = 145.0, 128.7, 128.5, 127.9, 71.7, 62.7, 56.8, 45.7, 44.1, 39.9, 32.5, 31.7, 31.6, 28.9, 13.8, 7.4; HRMS (ES) Found: MH$^+$, 271.2166 $C_{18}H_{27}N_2$ requires MH$^+$, 271.2174; LRMS *m*/*z* (ES) 272 (20%), 271 (100, MH$^+$).

**(2a*S**,4a*S**,7b*S**)-4a-Ethyl-2a,3,4,4a,5,6,7,7b-octahydro-1,7a-diaza-cyclopenta[*cd*]indene 5.** The aldehyde **3**[2c] (208 mg, 1.03 mmol) and hydrazine monohydrate (0.13 mL, 4.1 mmol) in xylene (15 mL) were heated under reflux for 2 h. After cooling to room



temperature, the solvent was evaporated. Purification by column chromatography, eluting with $CH_2Cl_2$–MeOH (97 : 3), gave the cycloadduct **5** (130 mg, 71%) as an oil; $R_f$ 0.5 [$CH_2Cl_2$–MeOH (95 : 5)]; $\nu_{max}$/cm$^{-1}$ 2930, 1460;$^1$H NMR (400 MHz, $C_6D_6$) $\delta$ = 6.10 (1H, s), 4.0–3.96 (1H, m), 3.35 (1H, d, *J* 9.5 Hz), 3.27–3.25 (1H, m), 2.89–2.82 (1H, m), 1.57–1.37 (3H, m), 1.32–1.22 (2H, m), 1.10–1.0 (3H, m), 0.98–0.78 (2H, m), 0.60 (3H, t, *J* 7.5 Hz); $^{13}$C NMR (100 MHz, $C_6D_6$) $\delta$ = 141.4, 68.4, 53.6, 50.0, 44.5, 33.4, 30.7, 30.5, 28.2, 19.1, 7.7; HRMS (ES) Found: MH$^+$, 179.1540. $C_{11}H_{19}N_2$ requires MH$^+$, 179.1548; LRMS *m*/*z* (ES) 180 (20%), 179 (100, MH$^+$).

In addition to cycloadduct **5**, the following compound (formed in 6% yield) was isolated as an oil and characterized: ***N*,*N*′-Bis(2-(3-chloropropyl)-2-ethylhex-5-enylidene)hydrazine 6**: $R_f$ 0.95 [$CH_2Cl_2$–MeOH (95 : 5)]; $\nu_{max}$/cm$^{-1}$ 2930, 1460;$^1$H NMR (400 MHz, $CDCl_3$) $\delta$ = 7.56 (2H, s), 5.82 (2H, ddt, *J* 17, 10, 6.5), 5.05–4.95 (4H, m), 3.55 (4H, t, *J* 6 Hz), 2.02–1.96 (4H, m), 1.75–1.54 (16H, m), 0.85 (6H, t, *J* 7.5 Hz); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ = 169.2, 139.0, 114.9, 46.0, 43.6, 34.3, 31.7, 28.3, 27.8, 27.4, 8.3; HRMS (ES) Found: MH$^+$, 401.2482. $C_{22}H_{39}Cl_2N_2$ requires MH$^+$, 401.2490; LRMS *m*/*z* (ES) 403 (60%), 401 (100, MH$^+$).

**(2a*R**,4a*S**,7b*S**)-1-Benzyl-4a-ethyl-decahydro-1,7a-diaza-cyclopenta[cd]indene 8.** The aldehyde **7**[2d] (212 mg, 1.21 mmol), benzylhydrazine dihydrochloride (284 mg, 1.46 mmol) and *N*,*N*-diisopropylethylamine (0.95 mL, 5.45 mmol) in PhMe (18 mL) were heated under reflux for 2 h. After cooling to room temperature, the solvent was evaporated. Purification by column chromatography, eluting with $CH_2Cl_2$–MeOH (98 : 2), gave the cycloadduct **8** (145 mg, 50%) as an amorphous solid: m.p. 155–159 °C; $R_f$ 0.55 [$CH_2Cl_2$–MeOH (98 : 2)]; $\nu_{max}$/cm$^{-1}$ 2940, 2865, 1460;$^1$H NMR (500 MHz, $CDCl_3$) $\delta$ = 7.34–7.26 (5H, m), 4.40 (1H, d, *J* 12 Hz), 4.21 (1H, t, *J* 7.5 Hz), 3.90 (1H, d, *J* 12 Hz), 3.52 (1H, d, *J* 14.5 Hz), 3.35 (1H, t, *J* 9 Hz), 3.19–3.13 (1H, m), 3.00 (1H, q, *J* 7.5 Hz), 2.90 (1H, d, *J* 9 Hz), 2.14–2.08 (1H, m), 2.06–1.97 (1H, m), 1.91–1.70 (4H, m), 1.66–1.58 (2H, m), 1.48–1.45 (1H, m); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ = 135.6, 128.6, 128.4, 128.0, 66.2, 62.5, 56.9, 46.0, 40.4, 37.4, 33.4, 30.7, 23.5, 13.1; HRMS (ES) Found: MH$^+$, 243.1851 $C_{16}H_{23}N_2$ requires MH$^+$, 243.1861; LRMS *m*/*z* (ES) 244 (25), 243 (100%, MH$^+$).

**(7a*S**,10a*R**,10b*S**)-/(7a*S**,10a*R**,10b*R**)-7-Acetyl-9-phenyl-5,6,7,7a,10a,10b-hexahydro-6a,7,9-triaza-pentaleno[1,2-a]naphthalene-8,10-dione 10a and 10a′.** The aldehyde **9**[9] (215 mg, 1 mmol) and acetylhydrazine (148 mg, 2 mmol) in PhMe (11 mL) were heated at 60 °C for 30 min. *N*-Phenyl maleimide (381 mg, 2.2 mmol) was added and the mixture was heated at 60 °C for 5 h. After cooling to room temperature, the solvent was evaporated. Purification by column chromatography, eluting with $CH_2Cl_2$–MeOH (98 : 2), gave the cycloadduct **10a** (185 mg, 52%) as an amorphous solid and the cycloadduct **10a′** (80 mg, 22%) as an amorphous solid. Data for **10a**: m.p. 227–231 °C; $R_f$ 0.21 [$CH_2Cl_2$–MeOH (98 : 2)]; $\nu_{max}$/cm$^{-1}$ 3075, 2930, 1720, 1665, 1460; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ = 7.52–7.37 (6H, m), 7.29–7.27 (2H, m), 7.20–7.18 (1H, m), 5.34 (1H, d, *J* 8.5 Hz), 4.60 (1H, d, *J* 8.5 Hz), 3.85 (1H, t, *J* 8.5 Hz), 3.28–3.20 (2H, m), 2.92–2.84 (2H, m), 2.37 (3H, s); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ = 173.0, 172.9, 132.5, 132.0, 131.3, 129.2, 128.9, 128.3, 128.2, 128.0, 126.9, 126.3, 65.2, 59.9, 52.9, 29.0 (two overlapping $CH_2$), 22.2; HRMS (ES) Found: MH$^+$, 362.1508 $C_{21}H_{20}N_3O_3$ requires MH$^+$, 362.1505; LRMS *m*/*z* (ES) 363 (20%), 362 (100, MH$^+$). Data for **10a′**: m.p. 106–110 °C; $R_f$ 0.35 [$CH_2Cl_2$–MeOH (98 : 2)]; $\nu_{max}$/cm$^{-1}$ 3075, 2930, 1720, 1665, 1460; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ = 7.43–7.24 (6H, m), 7.18–7.12 (3H, m), 5.79 (1H, d, *J* 8.5 Hz), 4.78 (1H, d, *J* 8.5 Hz), 4.05 (1H, t, *J* 8.5 Hz), 3.40–3.36 (1H, m), 3.23–3.15 (1H, m), 2.90–2.79 (2H, m), 2.32 (3H, s); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ = 173.0, 172.9, 132.9, 131.5, 129.2, 129.1, 128.8, 128.6, 128.5, 127.9, 126.2, 125.6 (two overlapping CH), 65.3, 58.2, 50.7, 50.2, 29.6, 21.0; HRMS (ES) Found: MH$^+$, 362.1490 $C_{21}H_{20}N_3O_3$ requires MH$^+$, 362.1505; LRMS *m*/*z* (ES) 363 (15%), 362 (100, MH$^+$).

**(7a*S**,10a*R**,10b*S**)-/(7a*S**,10a*R**,10b*R**)-7-Benzyl-9-phenyl-5,6,7,7a,10a,10b-hexahydro-6a,7,9-triaza-pentaleno[1,2-a]naphthalene-8,10-dione 10b and 10b′.** The aldehyde **9**[9] (262 mg, 1.23 mmol), benzylhydrazine dihydrochloride (264 mg, 1.35 mmol) and *N*,*N*-diisopropylethylamine (0.53 mL, 3.08 mmol) in PhMe (15 mL) were heated at 60 °C for 30 min. *N*-Phenyl maleimide (319 mg, 1.85 mmol) was added and the mixture was heated at 60 °C for 6 h. After cooling to room temperature, the solvent was evaporated. Purification by column chromatography, eluting with petrol–EtOAc (8 : 2), gave the cycloadduct **10b** (237 mg, 47%) as an amorphous solid and the cycloadduct **10b′** (112 mg, 22%) as an amorphous solid. Data for **10b**: m.p. 58–62 °C; $R_f$ 0.64 [petrol–EtOAc (7 : 3)]; $\nu_{max}$/cm$^{-1}$ 3075, 2940, 2865, 1720, 1665, 1460; $^1$H NMR (500 MHz, $C_6D_6$, 60 °C) $\delta$ = 7.87–7.85 (1H, m), 7.43–7.41 (2H, m), 7.38–7.35 (2H, m), 7.20–6.98 (8H, m), 6.83–6.81 (1H, m), 4.41 (1H, bs), 4.37 (1H, d, *J* 14.5 Hz), 4.09 (1H, d, *J* 14.5 Hz), 3.65 (1H, d, *J* 8.5 Hz), 3.06 (1H, dd, *J* 8.5, 7 Hz), 2.73–2.72 (1H, m), 2.54–2.47 (3H, m); $^{13}$C NMR (125 MHz, $C_6D_6$, 60 °C) $\delta$ = 175.4, 173.4, 138.4, 135.8, 134.1, 132.9, 129.1, 128.9, 128.5, 128.3, 128.0, 127.8, 127.4, 127.3, 127.2, 126.8, 66.1, 64.2, 54.0, 28.3; HRMS (ES) Found: MH$^+$, 410.1875 $C_{26}H_{24}N_3O_2$ requires MH$^+$, 410.1869; LRMS *m*/*z* (ES) 412 (10%), 411 (30), 410 (100, MH$^+$); Data for **10b′**: m.p. 151–155 °C; $R_f$ 0.46 [petrol–EtOAc (7 : 3)]; $\nu_{max}$/cm$^{-1}$ 3075, 2940, 2865, 1720, 1665, 1460; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ = 7.56–7.10 (14H, m), 5.0 (1H, d, *J* 8.5 Hz), 4.29 (1H, d, *J* 13 Hz), 4.25 (1H, d, *J* 8.5 Hz), 4.13 (1H, d, *J* 13 Hz), 4.01 (1H, t, *J* 8.5 Hz), 3.27 (1H, ddd, *J* 10.5, 5, 2 Hz), 3.04–2.96 (1H, m), 2.80–2.74 (1H, m), 2.69–2.64 (1H, m); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ = 175.6, 173.9, 137.9, 134.2, 131.8, 130.4, 129.3 (two overlapping CH), 129.2, 129.0, 128.5, 128.4, 127.5, 127.2, 126.5, 125.8, 125.7, 67.3, 63.5, 62.6, 52.5, 50.8, 30.2; HRMS (ES) Found: MH$^+$, 410.1875 $C_{26}H_{24}N_3O_2$ requires MH$^+$, 410.1869; LRMS *m*/*z* (ES) 412 (5%), 411 (30), 410 (100, MH$^+$).

**(7a*S**,10a*R**,10b*S**)-/(7a*S**,10a*R**,10b*R**)-9-Phenyl-5,6,7,7a,10a,10b-hexahydro-6a,7,9-triaza-pentaleno[1,2-a]naphthalene-8,10-dione 10c and 10c′.** The aldehyde **9**[9] (220 mg, 1.03 mmol) and hydrazine monohydrate (0.064 mL, 2.06 mmol) in PhMe (15 mL) were heated under reflux for 30 min. *N*-Phenyl maleimide (268 mg, 1.55 mmol) was added and the mixture was heated under reflux for 5 h. After cooling to room temperature, the solvent was evaporated. Purification by column chromatography, eluting with $CH_2Cl_2$–MeOH (98 : 2), gave the cycloadduct **10c** (177 mg, 54%) as an amorphous solid and the cycloadduct **10c′** (55 mg, 17%) as an amorphous solid. Data for **10c**: m.p. 73–75 °C; $R_f$ 0.43 [$CH_2Cl_2$–MeOH (98 : 2)]; $\nu_{max}$/cm$^{-1}$ 3075, 2930, 1720, 1665, 1460; $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ = 7.57–7.16 (9H, m), 4.66 (1H, d, *J* 5 Hz), 4.55 (1H, d, *J* 8 Hz), 3.76 (1H, dd, *J* 8, 5 Hz), 3.27 (1H, ddd, *J* 12, 7, 5.5 Hz), 3.20 (1H, ddd, *J* 12, 7, 5.5 Hz), 3.01 (1H, ddd, *J* 12, 7, 5.5 Hz),

2.90 (1H, ddd, *J* 12, 7, 5.5 Hz); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ = 175.5, 175.1, 133.5, 133.2, 131.5, 129.2, 128.8, 128.7, 128.1, 127.3, 127.0, 126.4, 67.3, 61.9, 57.7, 47.3, 25.6; HRMS (ES) Found: $MH^+$, 320.1386 $C_{19}H_{18}N_3O_2$ requires $MH^+$, 320.1399; LRMS *m*/*z* (ES) 321 (10%), 320 (100, $MH^+$). Data for **10c′**: m.p. 94–98 °C; $R_f$ 0.35 [$CH_2Cl_2$–MeOH (98 : 2)]; $\nu_{max}$/cm$^{-1}$ 3075, 2930, 1720, 1665, 1460; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ = 7.47–7.14 (9H, m), 4.60 (1H, d, *J* 8.5 Hz), 4.54 (1H, d, *J* 8.5 Hz), 3.99 (1H, t, *J* 8.5 Hz), 3.25–3.20 (1H, m), 3.11–3.03 (1H, m), 2.91–2.82 (2H, m); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ = 175.5, 175.1, 133.5, 133.2, 131.5, 129.1, 128.9, 128.5, 127.4, 125.9, 125.8, 126.4, 69.4, 62.8, 51.1, 50.4, 30.1; HRMS (ES) Found: $MH^+$, 320.1386 $C_{19}H_{18}N_3O_2$ requires $MH^+$, 3020.1399; LRMS *m*/*z* (ES) 321 (10%), 320 (100, $MH^+$).

**(1*S**,2*R**,10b*S**)-3-Acetyl-1,2,3,5,6,10b-hexahydro-pyrazolo[5,1-a]isoquinoline-1,2-dicarboxylic acid dimethyl ester 11a.** The aldehyde **9**[9] (209 mg, 0.98 mmol) and acetylhydrazine (145 mg, 1.96 mmol) in PhMe (10 mL) were heated at 60 °C for 30 min. Dimethyl maleate (0.3 mL, 2.16 mmol) was added and the mixture was heated at 60 °C for 5 h. After cooling to room temperature, the solvent was evaporated. Purification by column chromatography, eluting with $CH_2Cl_2$–MeOH (98 : 2), gave the cycloadduct **11a** (131 mg, 40%) as an amorphous solid: m.p. 158–162 °C; $R_f$ 0.33 [$CH_2Cl_2$–MeOH (98 : 2)]; $\nu_{max}$/cm$^{-1}$ 3075, 2930, 1730, 1630, 1460; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ = 7.19–7.08 (4H, m), 5.33 (1H, d, *J* 11 Hz), 4.71 (1H, d, *J* 8.5 Hz), 4.16 (1H, dd, *J* 11, 8.5 Hz), 3.82–3.75 (2H, m), 3.68 (3H, s), 3.23 (3H, s), 3.16–3.07 (1H, m), 2.83–2.78 (1H, m), 2.28 (3H, s); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ = 171.3, 171.0, 169.5, 134.1, 130.5, 128.5, 127.5 (two overlapping CH), 125.6, 64.8, 60.2, 55.0, 52.5, 51.7, 47.4, 29.2, 20.8; HRMS (ES) Found: $MH^+$, 333.1458 $C_{17}H_{21}N_2O_5$ requires $MH^+$, 333.1450; LRMS *m*/*z* (ES) 334 (20%), 333 (100, $MH^+$).

**(1*S**,2*R**,10b*S**)-1,2,3,5,6,10b-Hexahydro-pyrazolo[5,1-a]isoquinoline-1,2-dicarboxylic acid dimethyl ester 11b.** The aldehyde **9**[9] (274 mg, 1.28 mmol), benzylhydrazine dihydrochloride (326 mg, 1.67 mmol) and *N*,*N*-diisopropylethylamine (0.62 mL, 3.58 mmol) in PhMe (13 mL) were heated at 60 °C for 30 min. Dimethyl maleate (0.24 mL, 1.92 mmol) was added and the mixture was heated at 60 °C for 6 h. After cooling to room temperature, the solvent was evaporated. Purification by column chromatography, eluting with petrol–EtOAc (75 : 25), gave the cycloadduct **11b** (209 mg, 43%) as an amorphous solid: m.p. 75–79 °C; $R_f$ 0.66 [petrol–EtOAc (75 : 25)]; $\nu_{max}$/cm$^{-1}$ 3075, 2940, 1720, 1665, 1460; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ = 7.48–7.46 (2H, m), 7.32–7.23 (3H, m), 7.12–7.03 (4H, m), 4.74 (1H, d, *J* 7 Hz), 4.10 (1H, d, *J* 13 Hz), 4.05–3.97 (3H, m), 3.66 (3H, s), 3.41–3.35 (1H, m), 3.22 (3H, s), 3.0–2.95 (1H, m), 2.93–2.85 (1H, m), 2.61–2.56 (1H, m); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ = 171.5, 171.4, 138.0, 135.2, 131.9, 129.8 (two overlapping CH), 128.2 (two overlapping CH), 128.1, 128.0, 127.2, 126.8, 125.2, 68.3, 63.0, 61.9, 56.0, 52.1, 51.4, 48.5, 29.9; HRMS (ES) Found: $MH^+$, 381.1819 $C_{22}H_{25}N_2O_4$ requires $MH^+$, 381.1814; LRMS *m*/*z* (ES) 382 (30%), 381 (100, $MH^+$).

**(1*S**,2*R**,10b*R**)/(1*S**,2*R**,10b*S**)-1,2,3,5,6,10b-Hexahydro-pyrazolo[5,1-a]isoquinoline-1,2-dicarboxylic acid dimethyl ester 12 and 12′.** The aldehyde **9**[9] (225 mg, 1.06 mmol) and hydrazine monohydrate (0.07 mL, 2.12 mmol) in PhMe (16 mL) were heated under reflux for 30 min. Dimethyl maleate (0.2 mL, 1.58 mmol) was added and the mixture was heated under reflux for 5 h. After cooling to room temperature, the solvent was evaporated. Purification by column chromatography, eluting with $CH_2Cl_2$–MeOH (98 : 2), gave the cycloadduct **12** (177 mg, 58%) as an amorphous solid and the cycloadduct **12′** (56 mg, 19%) as an oil.

Using the same method, the aldehyde **9** (264 mg, 1.24 mmol), hydrazine monohydrate (0.12 mL, 2.48 mmol) and dimethyl fumarate (268 mg, 1.86 mmol) gave, after heating under reflux for 5 h and purification by column chromatography, the cycloadduct **12** (182 mg, 51%) and the cycloadduct **12′** (69 mg, 19%). Data for **12**: m.p. 66–70 °C; $R_f$ 0.33 [$CH_2Cl_2$–MeOH (98 : 2)]; $\nu_{max}$/cm$^{-1}$ 3075, 2930, 1720, 1665, 1460; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ = 7.33–7.09 (4H, m), 4.72 (1H, d, *J* 10 Hz), 4.63 (1H, d, *J* 7 Hz), 3.83 (3H, s), 3.64 (1H, dd, *J* 10, 7 Hz), 3.30 (3H, s), 3.29–3.25 (1H, m), 3.12–3.03 (2H, m), 2.84–2.78 (1H, m); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ = 172.6, 172.3, 134.5, 131.2, 128.3, 128.2, 127.3, 125.3, 69.0, 63.5, 57.7, 52.7, 51.8, 47.3, 29.6; HRMS (ES) Found: $MH^+$, 291.1345 $C_{15}H_{19}N_2O_4$ requires $MH^+$, 291.1345; LRMS *m*/*z* (ES) 292 (10%), 291 (100, $MH^+$). Data for **12′**: $R_f$ 0.23 [$CH_2Cl_2$–MeOH (98 : 2)]; $\nu_{max}$/cm$^{-1}$ 3075, 2930, 1720, 1665, 1460; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ = 7.23–6.97 (4H, m), 4.51 (1H, d, *J* 10 Hz), 4.33 (1H, d, *J* 7 Hz), 3.84 (3H, s), 3.76 (3H, s), 3.68 (1H, dd, *J* 10, 7 Hz), 3.14–3.03 (2H, m), 2.91–2.77 (2H, m); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ = 173.7, 173.1, 133.6, 133.5, 128.6, 127.4, 126.8, 126.0, 70.5, 66.2, 55.6, 52.7, 52.6, 49.0, 29.8; HRMS (ES) Found: $MH^+$, 291.1345 $C_{15}H_{19}N_2O_4$ requires $MH^+$, 291.1345; LRMS *m*/*z* (ES) 292 (20%), 291 (100, $MH^+$).

**3-Benzyl-4,5-dihydro-3*H*-benzo[d][1,2]diazepine 13.** The aldehyde **9**[9] (123 mg, 0.58 mmol) and benzylhydrazine dihydrochloride (135 mg, 0.7 mmol) in PhMe (7 mL) were heated under reflux for 1 h. After cooling to room temperature, the solvent was evaporated. Purification by column chromatography, eluting with petrol–EtOAc (9 : 1), gave the cyclic compound **13** (70 mg, 51%) as an amorphous solid; m.p. 53–56 °C; $R_f$ 0.72 [petrol–EtOAc (9 : 1)]; $\nu_{max}$/cm$^{-1}$ 3020, 2930, 1440; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ = 7.68–7.66 (2H, m), 7.62 (1H, s), 7.41–7.37 (2H, m), 7.31–7.22 (5H, m), 4.44 (2H, s), 3.67 (2H, t, *J* 6 Hz), 3.09 (2H, t, *J* 6 Hz); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ = 136.7, 134.7, 134.1, 132.8, 128.7, 128.6, 127.8, 126.9, 126.6, 126.2, 125.9, 51.9, 51.0, 29.4; HRMS (ES) Found: $MH^+$, 237.1387 $C_{16}H_{17}N_2$ requires $MH^+$, 237.1392; LRMS *m*/*z* (ES) 238 (20%), 237 (100, $MH^+$).

**(1*R**,10b*S**)-/(1*S**,10b*S**)-1,5,6,10b-Tetrahydro-pyrazolo[5,1-a]isoquinoline-1,2-dicarboxylic acid dimethyl ester 14 and 14′.** The aldehyde **9**[9] (251 mg, 1.18 mmol) and hydrazine monohydrate (0.12 mL, 2.36 mmol) in PhMe (12 mL) were heated under reflux for 30 min. Dimethyl acetylenedicarboxylate (0.22 mL, 1.77 mmol) was added and the mixture was heated under reflux for 12 h. After cooling to room temperature, the solvent was evaporated. Purification by column chromatography, eluting with petrol–EtOAc (7 : 3), gave the cycloadduct **14** (186 mg, 55%) as an amorphous solid and the cycloadduct **14′** (38 mg, 12%) as an amorphous solid. Data for **14**: m.p. 158–161 °C; $R_f$ 0.35 [petrol–EtOAc (7 : 3)]; $\nu_{max}$/cm$^{-1}$ 3075, 2940, 1720, 1665, 1460; $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ = 7.22–7.17 (2H, m), 7.11–7.09 (1H, m), 7.04–7.01 (1H, m), 5.60 (1H, d, *J* 13 Hz), 4.57 (1H, d, *J* 13 Hz), 4.25 (1H, ddd, *J* 13.5, 5, 1.5), 3.84 (3H, s), 3.44–3.37 (1H, m), 3.28 (3H, s), 3.09–3.01 (1H, m), 2.69–2.64 (1H, m); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ = 168.2, 162.0, 138.9, 135.8,

132.4, 129.0, 127.3, 126.9, 126.5, 65.6, 56.3, 52.2, 51.8, 48.2, 28.4; HRMS (ES) Found: $MH^+$, 289.1182 $C_{15}H_{17}N_2O_4$ requires $MH^+$, 289.1188; LRMS *m/z* (ES) 290 (10%), 289 (100, $MH^+$). Data for **14′**: m.p. 59–62 °C; $R_f$ 0.4 [petrol–EtOAc (7 : 3)]; $\nu_{max}/cm^{-1}$ 3075, 2940, 1720, 1665, 1460; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ = 7.32–7.28 (1H, m), 7.24–7.20 (2H, m), 7.08–7.06 (1H, m), 5.34 (1H, bs), 4.26–4.21 (2H, m), 3.84 (3H, s), 3.83 (3H, s), 3.55–3.48 (1H, m), 3.13–3.04 (1H, m), 2.70 (1H, dd, *J* 16, 3 Hz); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ = 170.6, 162.0, 139.4, 135.1, 134.1, 129.0, 127.6, 127.4, 126.0, 67.8, 58.1, 53.0, 52.3, 47.4, 27.3; HRMS (ES) Found: $MH^+$, 289.1182 $C_{15}H_{17}N_2O_4$ requires $MH^+$, 289.1188; LRMS *m/z* (ES) 290 (10%), 289 (100, $MH^+$).

**2-(2-Bromoethyl)-benzaldehyde 15.** The aldehyde **9**[9] (159 mg, 0.75 mmol) and hydrazine monohydrate (0.07 mL, 1.49 mmol) in PhMe (8 mL) were heated under reflux for 1 h. After cooling to room temperature, the solvent was evaporated. Purification by column chromatography, eluting with $CH_2Cl_2$–MeOH (95 : 5), gave the hydrazone **15** (78 mg, 46%) as an amorphous solid; m.p. 50–54 °C; $R_f$ 0.5 [$CH_2Cl_2$–MeOH (95 : 5)]; $\nu_{max}/cm^{-1}$ 3320, 3050, 2930, 1440; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ = 7.34–7.21 (4H, m), 7.16 (1H, s), 6.30 (1H, bs), 3.53–3.51 (2H, m), 3.28–3.26 (2H, m); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ = 139.5, 137.5, 132.7, 132.5, 129.6, 127.8, 126.3, 47.9, 39.4; HRMS (ES) Found: $MH^+$ – HBr, 147.0916 $C_9H_{11}N_2$ requires $MH^+$, 147.0922; LRMS *m/z* (ES) 148 (10%), 147 (100, $MH^+$).

**(1*R**,10b*S**)-/(1*S**,10b*S**)-2-Phenyl-1,5,6,10b-tetrahydro-pyrazolo[5,1-a]isoquinoline-1-carboxylic acid methyl ester 16 and 17.** The hydrazone **15** (0.013 mg, 0.09 mmol) and methyl phenylpropiolate (0.02 mL, 0.11 mmol) in PhMe (1 mL) were heated under reflux for 12 h. After cooling to room temperature, the solvent was evaporated. Purification by column chromatography, eluting with petrol–EtOAc (8 : 2), gave the cycloadduct **16** (4 mg, 14%) as an amorphous solid and the cycloadduct **17** (23 mg, 83%) as an amorphous solid. **Data for 16:** m.p. 74–77 °C; $R_f$ 0.64 [petrol–EtOAc (8 : 2)]; $\nu_{max}/cm^{-1}$ 3020, 2930, 1730, 1440; $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$ = 7.58–7.57 (2H, m), 7.33–7.25 (3H, m), 7.19–7.13 (2H, m), 7.09–7.04 (2H, m), 5.45 (1H, d, *J* 12.5 Hz), 4.69 (1H, d, *J* 12.5 Hz), 4.10–4.07 (1H, m), 3.33–3.27 (1H, m), 3.13 (3H, s), 3.06–3.0 (1H, m), 2.64–2.60 (1H, m); $^{13}C$ NMR (125 MHz, $CDCl_3$) $\delta$ = 169.3, 149.1, 137.0, 133.5, 132.1, 128.7, 128.6 (two overlapping CH), 127.4, 126.2, 126.0, 125.6, 65.0, 58.4, 51.8, 48.9, 27.5; HRMS (ES) Found: $MH^+$, 307.1453 $C_{19}H_{19}N_2O_2$ requires $MH^+$, 307.1447; LRMS *m/z* (ES) 308 (20%), 307 (100, $MH^+$); **Data for 17:** m.p. 99–102 °C; $R_f$ 0.56 [petrol–EtOAc (8 : 2)]; $\nu_{max}/cm^{-1}$ 3020, 2930, 1730, 1440; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ = 7.68–7.66 (2H, m), 7.36–7.24 (5H, m), 7.20–7.16 (1H, m), 7.06–7.04 (1H, m), 5.33 (1H, d, *J* 1.5 Hz), 4.35 (1H, d, *J* 1.5 Hz), 4.22 (1H, dd, *J* 14, 5 Hz), 3.79 (3H, s), 3.48–3.40 (1H, m), 3.12–3.04 (1H, m), 2.59 (1H, dd, *J* 16, 3 Hz); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ = 170.9, 148.2, 136.0, 135.1, 131.9, 128.9, 128.7, 128.4 (two overlapping CH), 127.4, 126.9, 126.4, 126.1, 66.9, 60.3, 52.9, 47.8, 25.9; HRMS (ES) Found: $MH^+$, 307,1453 $C_{19}H_{19}N_2O_2$ requires $MH^+$, 307.1447; LRMS *m/z* (ES) 308 (10%), 307 (100, $MH^+$).

**2-Phenyl-5,6-dihydro-pyrazolo[5,1-a]isoquinoline-1-carboxylic acid methyl ester 18.** The ester **16** (107 mg, 0.35 mmol) in xylene (2 mL) was heated under reflux for 12 h. After cooling to room temperature, the solvent was evaporated. Purification by column chromatography, eluting with petrol–EtOAc (8 : 2), gave the cycloadduct **17** (15 mg, 14%) as an amorphous solid, data as above, and the cycloadduct **18** (87 mg, 82%) as an amorphous solid. Data for **18**: m.p. 82–86 °C; $R_f$ 0.41 [petrol–EtOAc (8 : 2)]; $\nu_{max}/cm^{-1}$ 3050, 2925, 1710, 1450, 1135; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ = 8.21–8.19 (1H, m), 7.64–7.62 (2H, m), 7.47–7.32 (6H, m), 4.40 (2H, t, *J* 7 Hz), 3.77 (3H, s), 3.24 (2H, t, *J* 7 Hz); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ = 165.5, 152.3, 140.2, 133.4 (two overlapping C), 133.3, 129.3, 128.7, 128.2, 128.0, 127.4, 127.0, 126.0, 51.5, 46.7, 29.5; HRMS (ES) Found: $MH^+$, 305.1282 $C_{19}H_{17}N_2O_2$ requires $MH^+$, 305.1290; LRMS *m/z* (ES) 306 (5%), 305 (100, $MH^+$). This compound is reported in the literature but only IR data were given.[12]

**(1*S**,2*R**,10b*R**)-methyl 2-amino-3-oxo-1,2,3,5,6,10b-hexahydropyrrolo[2,1-a]isoquinoline-1-carboxylate 19.** The ester **12** (0.113 g, 0.39 mmol) and a suspension of RANEY® nickel [washed with water (3 × 5 mL) and methanol (3 × 5 mL)] in methanol (6 mL) was stirred vigorously at room temperature under hydrogen (1 atm). After 12 h, triethylamine (1 mL) was added, the mixture was filtered through celite and washed with 10% solution of triethylamine in methanol (2 × 10 mL). The combined filtrates were evaporated. Purification by column chromatography, eluting with $CH_2Cl_2$–MeOH (97 : 3), gave the amine **19** (58 mg, 57%) as an oil; $R_f$ 0.25 [$CH_2Cl_2$–MeOH (97 : 3)]; $\nu_{max}/cm^{-1}$ 3430, 1680, 1435; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ = 7.24–7.10 (4H, m), 5.00 (1H, d, *J* 6 Hz), 4.43–4.39 (1H, m), 3.97 (1H, d, *J* 7.5 Hz), 3.87 (1H, dd, *J* 7.5, 6 Hz), 3.22 (3H, s), 3.02–2.88 (2H, m), 2.72–2.67 (1H, m), 1.87 (2H, bs); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ = 173.0, 169.7, 134.9, 132.1, 129.2, 127.2, 126.5, 125.8, 55.6, 55.3, 52.5, 51.1, 37.3, 28.2; HRMS (ES) Found: $MH^+$, 261.1236. $C_{14}H_{17}N_2O_3$ requires $MH^+$, 261.1239; LRMS *m/z* (ES) 262 (20%), 261 (100, $MH^+$).

## Acknowledgements

We thank the EPSRC (EP/F06313X/1) and the University of Sheffield for support of this work. We are grateful to S. Johnson and R. Hayward for help with the crystal structure analyses, and Dr Anthony J. H. M. Meijer (University of Sheffield) for the computational studies on compounds **16** and **17**.

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