Intramolecular 1,3-dipolar cycloadditions of dihydroimidazolium ylides: synthesis of pyrrolo[1,2,3-*de*]quinoxalines and imidazo[1,2-*a*]indoles

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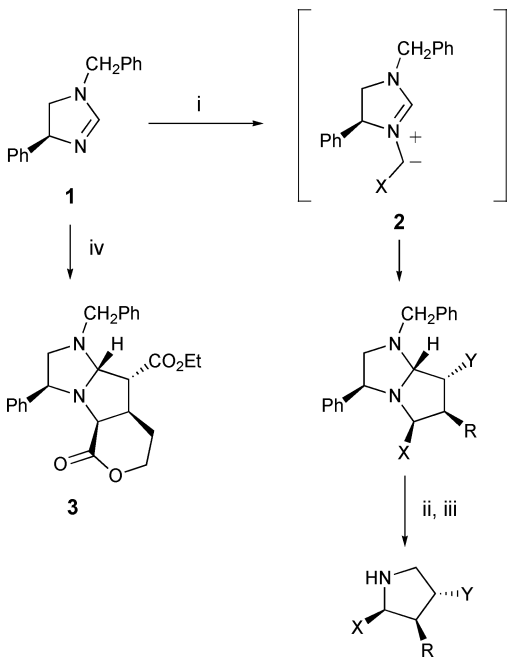
N-Alkylation of 4,5-dihydroimidazoles with alkene-containing bromomethyl ketones and treatment of the so-formed 4,5-dihydroimidazolium ions with DBU gives rise to an intramolecular 1,3-dipolar cycloaddition reaction that affords (*via* a reaction cascade involving eliminative ring-opening, recyclisation and prototropic tautomerism) unexpected hexahydropyrrolo[1,2,3-*de*]quinoxaline products. Steric bulk in both the dihydroimidazole and the dipolarophile allows isolation of an imidazo[1,2-*a*]indole, the initial product of cycloaddition. When the bromomethyl ketone contains no other functionality, or when cycloaddition is inhibited due to steric constraints, the dihydroimidazolium ion undergoes ring-opening hydrolysis followed by recyclization of the exposed amino ketone to afford either 3-alkyl-1-formylpiperazine-2-ones or 3-aryl-1-formyl-1,4,5,6-tetrahydropyrazines.

Introduction

4,5-Dihydroimidazolium ylides **2**, formed *in situ* from dihydroimidazoles **1** and an appropriate alkylating agent, undergo *inter*molecular 1,3-dipolar cycloaddition reactions,[1] and we have described the elaboration of the so-formed cycloadducts as part of the synthesis of optically active pyrrolidines (Scheme 1) and thence of pyrrolizidines and indolizidines.[2,3] As part of this on-going programme, we have additionally established an *intra*molecular cycloaddition that makes use of an α-haloester that contains a suitable dipolarophile in the ester alkyl group; this latter reaction affords the tricyclic adducts **3**.[4] In these sequences three of the bonds in the newly-formed pyrrolidine are made during the alkylation–deprotonation–cycloaddition cascade. Related studies of asymmetric induction in azomethine ylide cycloaddition by an auxiliary rotationally constrained at nitrogen have been disclosed by others.[5–8]

Aware that the octahydroindole skeleton forms an integral part of several natural products, such as the aeruginosins that have protease inhibitor activity[9] and the stenine sub-set of the *Stemona* alkaloids used in Chinese medicine for respiratory disorders,[10] we reasoned that this system ought to be accessible *via* the corresponding intramolecular cycloaddition of a dihydroimidazolium ylide derived from an α-haloketone (Scheme 2).

Herein we report our efforts to realise this cycloaddition strategy. While the primary imidazo[1,2-*a*]indole cycloadduct can be isolated through the use of bulky substituents in both the dihydroimidazole and the dipolarophile, in general the formation of hexahydropyrrolo[1,2,3-*de*]quinoxalines is favoured. This latter ring system has been reported only sporadically,[11–20] and is mentioned in the pharmaceutical patent literature,[21–25] some of its derivatives possessing affinity for the NMDA (*N*-methyl-D-aspartate) glycine binding site.[18,19] Since previous syntheses of these tricyclic ring systems have involved annulation of a preformed bicyclic aromatic system (quinoxaline or indole), the approach we describe here is new and describes the pyrrolo[1,2,3-*de*]quinoxalines in a rarely reported partial saturation pattern. We also describe the formation of tetra- and hexahydropyrazines that arise from competitive hydrolysis and rearrangement of the *N*-(2′-oxoalkyl)dihydroimidazolium ion precursors of the ylides required for cycloaddition. Some of the results have been communicated previously.[26]



Scheme 1 Dipolar cycloaddition of 4,5-dihydroimidazolium ylides derived from a chiral imidazoline ((*S*)-enantiomer illustrated). Reagents: (i) XCH_2Br, RCH=CHY, DBU; (ii) $NaBH_3CN$, H^+; (iii) $Pd(OH)_2$, H_2; (iv) *E*-$BrCH_2CO_2(CH)_2CH{=}CHCO_2Et$, DBU; X = Y = ester functionalities.

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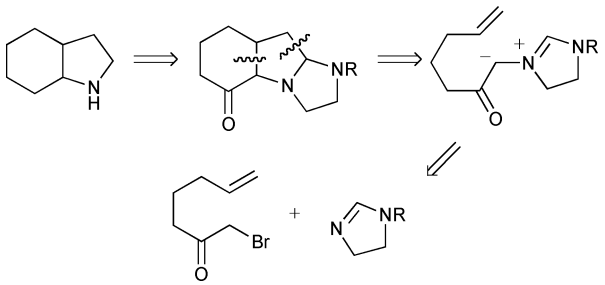
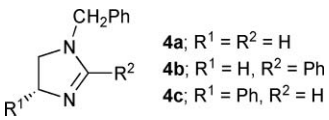


Scheme 2 A retrosynthetic analysis of the octahydroindole core.

Results and discussion

Dihydroimidazoles **4a**, **4b** and the enantiopure (*R*)-4-phenyl compound **4c** were available from our previous work[1,27,28] while **4b** is commercially available. Thus, our attention focused on the synthesis of the suitably functionalized bromomethyl ketones **8** (Scheme 3). Synthesis of the ketone precursors **7a**–**e** was achieved, as outlined in Scheme 3, *via* 5-oxohexanal **6a**, itself obtained in 32 per cent yield in three steps from commercial 2-(2-bromoethyl)-1,3-dioxolane **5**.[29] Chain extension of **6a** using standard Wittig olefination methodology afforded the methyl ketones **7a**–**e** in 32–90% yield. In the case of **7a**–**b**, the alkenes were produced as a separable mixture (8 : 1) of the *E*- and *Z*-isomers. Subsequent regiospecific bromination of the methyl ketones was achieved *via* reaction of their silyl enol ethers with *N*-bromosuccinimide, affording the dipolarophiles **8a**–**e** in 40–45% yield.

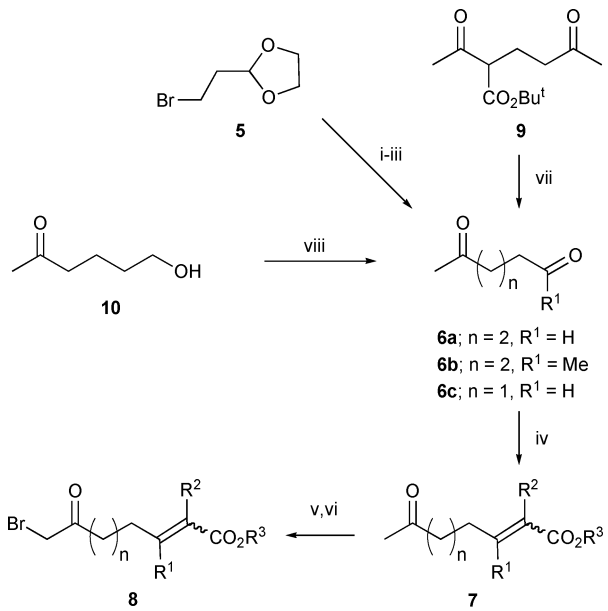


4a; $R^1 = R^2 = H$
4b; $R^1 = H$, $R^2 = Ph$
4c; $R^1 = Ph$, $R^2 = H$

In the case of **8f**, an approach involving compound **9**, itself readily available from *tert*-butyl acetoacetate and but-1-en-3-one,[30] was adopted; acid catalysed ester cleavage and decarboxylation of **9** using excess trifluoroacetic acid at room temperature for 30 min led to 2,6-heptanedione **6b** in 98% yield. Wadsworth–Emmons mono-olefination of diketone **6b** with trimethyl phosphonoacetate afforded an inseparable 1 : 1 mixture (by ^{1}H NMR analysis) of methyl *E*- and *Z*-3-methyl-7-oxooct-2-enoate **7f** in 40% yield. Subsequent bromination of this isomeric mixture proceeded normally to afford, in 30% yield, methyl *E*-8-bromo-3-methyl-7-oxooct-2-enoate (**8f**) as the only isolable stereoisomer.

Synthesis of the shorter chain bromoketone **8g** started with commercial 5-hydroxypentan-2-one (**10**). Oxidation of **10** with PCC afforded 4-oxopentanal (**6c**). Subsequent conversion of **6c** into **7g** was accomplished through standard Wittig olefination methodology. In the case of the longer chain bromoketone **8h**, we were fortunate to have access to the ethyl ester, **7h**, of the honeybee pheromone *E*-9-oxodec-2-enoic acid.[31] Regioselective bromination of **7g** and **7h** proceeded uneventfully to give the corresponding bromoketones **8g** and **8h** in yields of 36 and 34%, respectively.

With the desired bromoketones in hand, we examined the proposed alkylation–cycloaddition strategy. Thus, compound **8a** was heated with the dihydroimidazole **4a** in THF at reflux, with dropwise addition of DBU over 4 h. We found that, in contrast to our previous studies,[1,32] it was essential to heat the solution containing the dihydroimidazole and bromoketone at reflux for at

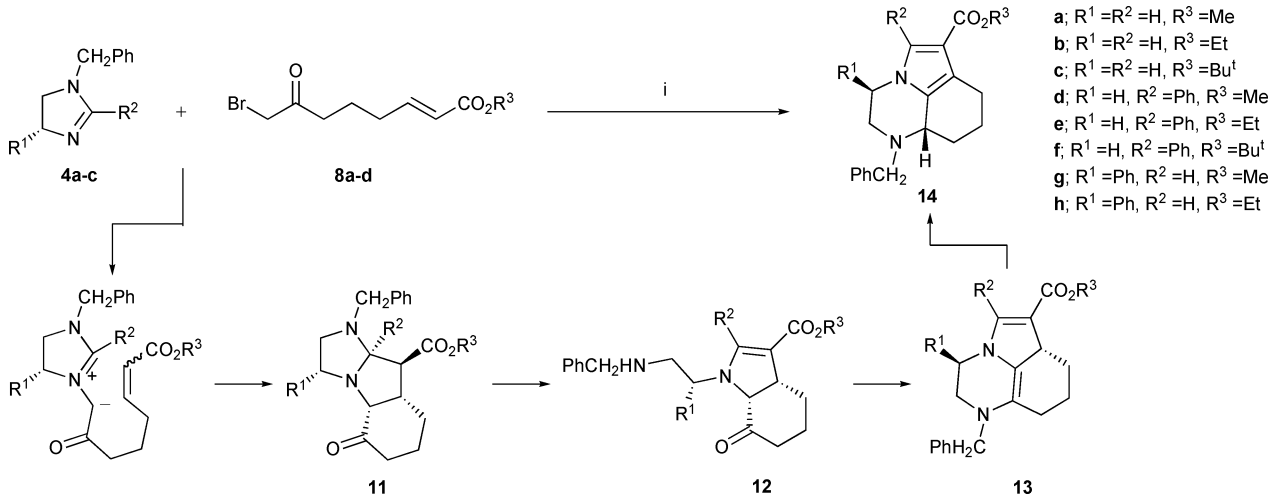


	n	R^1	R^2	R^3	*E*/*Z*
a	2	H	H	Me	*E*
b	2	H	H	Me	*Z*
c	2	H	H	Et	*E*
d	2	H	H	Bu^t	*E*
e	2	H	Me	Et	*E*
f	2	Me	H	Me	*E*/*Z* (**7**); *E* (**8**)
g	1	H	H	Me	*E*
h	4	H	H	Et	*E*

Scheme 3 Synthesis of the α-keto dienophiles **8a**–**g**. Reagents: (i) CH_3COCH_2COOEt–NaH, THF, reflux; (ii) 5% aq. NaOH, reflux; (iii) 1M aq.HCl, 50 °C; (iv) $Ph_3PCR^2COOR^3$ or $(EtO)_2POCH_2COOEt$–NaH; (v) LDA, THF, −78 °C, TMSCl; (vi) NBS, $NaHCO_3$, THF −78 °C → 80 °C; (vii) TFA; (viii) PCC.

least 2 h prior to the addition of DBU, presumably to enable the intermediate *N*-alkyldihydroimidazolium bromide to form; addition of DBU before 2 h invariably led to the recovery of both starting materials. However, the product of this reaction was not the expected cycloadduct **11**, but the hexahydro-1*H*-pyrrolo[1,2,3-*de*]quinoxaline **14a**, which was isolated in 31% yield (Scheme 4). Evidence for the structure **14a** comes from the following: (i) the mass spectrum contains a protonated molecular ion at *m*/*z* 311 rather than the expected *m*/*z* 329, indicating the loss of H_2O; (ii) the ^{1}H NMR spectrum exhibits a one proton singlet at δ 7.12, consistent with the presence of an isolated aromatic hydrogen atom; (iii) the ^{13}C NMR spectrum did not display the ketone signal expected for **11** but did contain four signals at δ 113.8, 117.0, 124.3, and 130.2 that are consistent with the presence of a pyrrole aromatic ring (that at δ 124.3 bears the hydrogen atom that gives rise to the δ 7.12 signal in the ^{1}H NMR spectrum); and (iv) the DEPT ^{13}C NMR spectra revealed only two CH carbon atoms at δ 59.7 and δ 124.3.

The formation of **14a** is rationalised by the pathway shown in Scheme 4. We anticipate the initial cycloadduct **11** to have the relative stereochemistries shown, based on the transition state model we have previously proposed for such reactions.[1,2] Such a model (Fig. 1) predicts addition involving an *anti* dipole to a dipolarophile that approaches in an *endo* orientation. The cycloadduct **11** can undergo eliminative ring-opening to **12**,



Scheme 4 Formation of cycloadducts **11** and pyrroloquinazolines **14** from dihydroimidazoles **4**. Reagents: (i) DBU, THF, reflux.

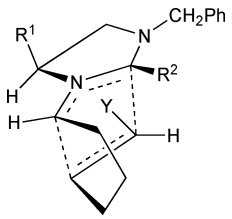


Fig. 1 Transition state proposed for the intramolecular cycloaddition of a dihydroimidazolium ylide with a dipolarophile (*S*-series illustrated for convenience; $Y = CO_2R^3$).

followed by ring closure of the secondary amino group onto the ketone giving the enamine **13** (or its regioisomer), and finally a prototropic shift to form **14a**.

As expected, since the stereochemistry of the ester substituent in **11** is lost upon eliminative ring-opening, use of the diastereomeric *Z*-dipolarophile **8b** also afforded the pyrroloquinoxaline **14a** (albeit in a somewhat lower yield of 20%). The eliminative ring opening shown in Scheme 4 is potentially a base-catalysed process; we therefore performed the alkylation/dipole formation/cycloaddition sequence using 0.7 equiv. of DBU but nonetheless **14a** was still isolated. Presumably the basic nature of the intermediates is sufficient to promote elimination.

In an exploration of its scope, seven further examples of this dipolar cycloaddition–ring-opening–recyclisation cascade were observed by employing alternative dihydroimidazoles and alternative ester dipolarophiles. Use of **4a** and the ethyl ester **8c** led to the corresponding hexahydropyrroloquinoxaline **14b** in 30% yield, while **4a** and *tert*-butyl ester **8d** afforded **14c** in 33% yield. When reacted separately with the three α-bromoketone variants (**8a**, **8c** and **8d**) 1-benzyl-2-phenyl-4,5-dihydroimidazole **4b** similarly gave the corresponding 5-phenyl substituted heterocycles **14d**–**f** in 33, 31 and 34% yields, respectively. Reaction of the chiral (*R*)-1-benzyl-4-phenyl-4,5-dihydroimidazole **4c** with bromoketones **8a** and **8c** led to the isolation of the optically active tricyclic adducts **14g** and **14h** in 30% yield in both cases.

Given the unexpected nature of the products **14**, we obtained X-ray crystal structure determinations for **14b**, **14d** and **14g**. Those for **14d** and **14g** are shown in Fig. 2 (a similar structure was obtained for **14b**; it differs from **14d** only in the ester moiety), and these confirm the presence of the pyrroloquinoxaline ring system and the relative stereochemistry illustrated.

A noteworthy feature of the structure of **14g** is the relative stereochemical relationship between the 3-phenyl group and the 9a-H atom, which have a *cis* disposition. This can be understood in terms of the transition state model illustrated by Fig. 1. The dipolarophile would be expected to approach the dipole from the face *anti* to the 4-phenyl group in the dihydroimidazole moiety. This initially places the phenyl group and the alkene β-H atom, which becomes the 8a-H atom in the cycloadduct **11**, on opposite faces of the ring system (as shown in Scheme 4). However, ring opening followed by rotation and recyclisation results in the same two groups having a *cis* relationship in **13**. A suprafacial [1,3]-hydrogen shift would transform **13** into **14**, although we cannot exclude a protonation–deprotonation sequence under thermodynamic control.

The sequence leading to compounds **14** (Scheme 4) involves at least three hydrogen atom migrations. We reasoned, therefore, that the incorporation of non-migrating methyl groups at strategic sites in the bromoketone precursors ought to prevent rearrangement of the desired adduct **11**. In the first instance, the presence of a methyl group α- to the methoxycarbonyl functionality, as in **8e**, should block the eliminative ring-opening of the primary cycloadduct, *i.e.* the step **11** to **12**. Alternatively, incorporation of a β-methyl group, as in **8f**, should block the aromatisation step that converts **13** into **14**.

Thus, we investigated the respective reactions of bromoketones **8e** and **8f** with dihydroimidazole **4a**. In the case of **8e**, we isolated a compound that was neither the imidazoindole **11** nor the pyrroloquinoxaline **14**. This new compound was characterised by the following: two carbonyl stretching frequencies at 1693 and 1715 cm^{-1}, respectively, in the IR spectrum; an M^+-28 peak (loss of CO) in the EIMS; and in the ^1H NMR spectrum, separate resonances for two diastereotopic protons of the *N*-benzyl group (implying that there is a chiral centre present in the molecule), an alkene resonance at δ 6.73 (implying the alkene group originating from **8e** remains intact), and a one-proton resonance at δ 9.47

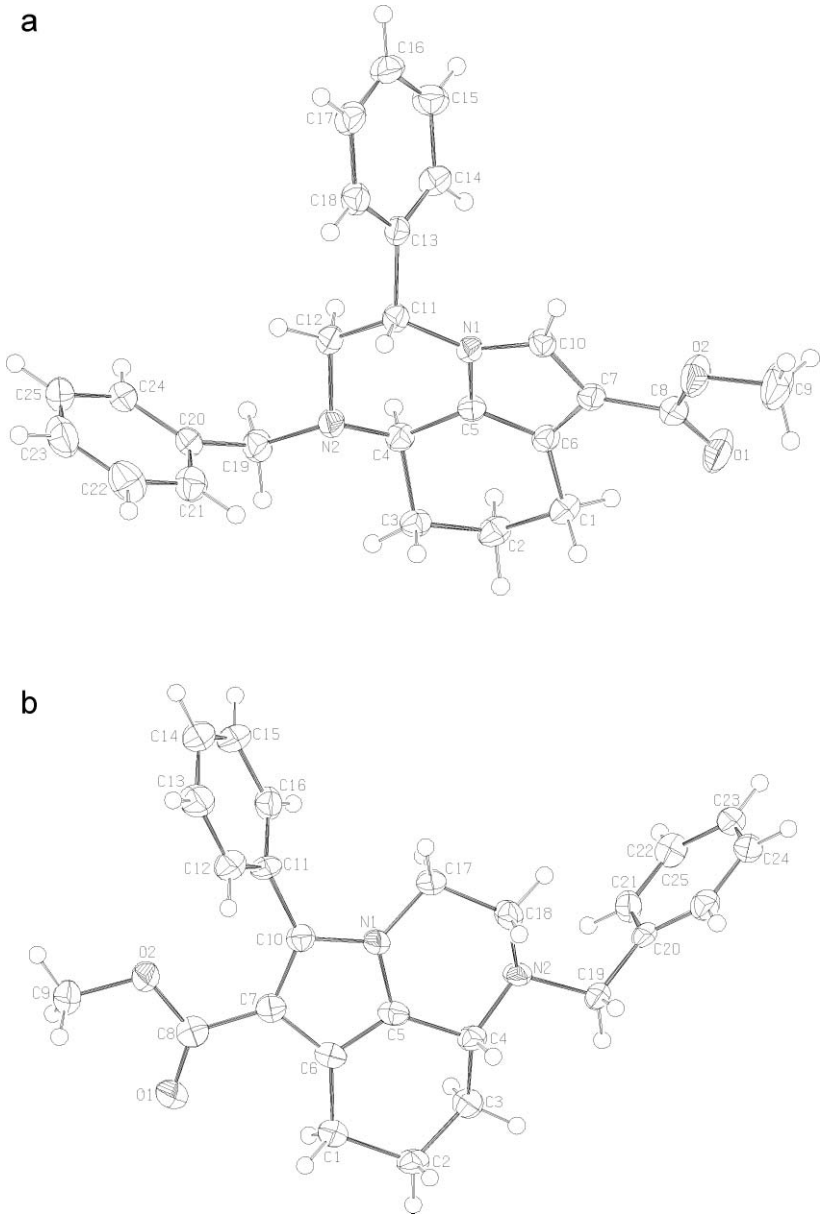
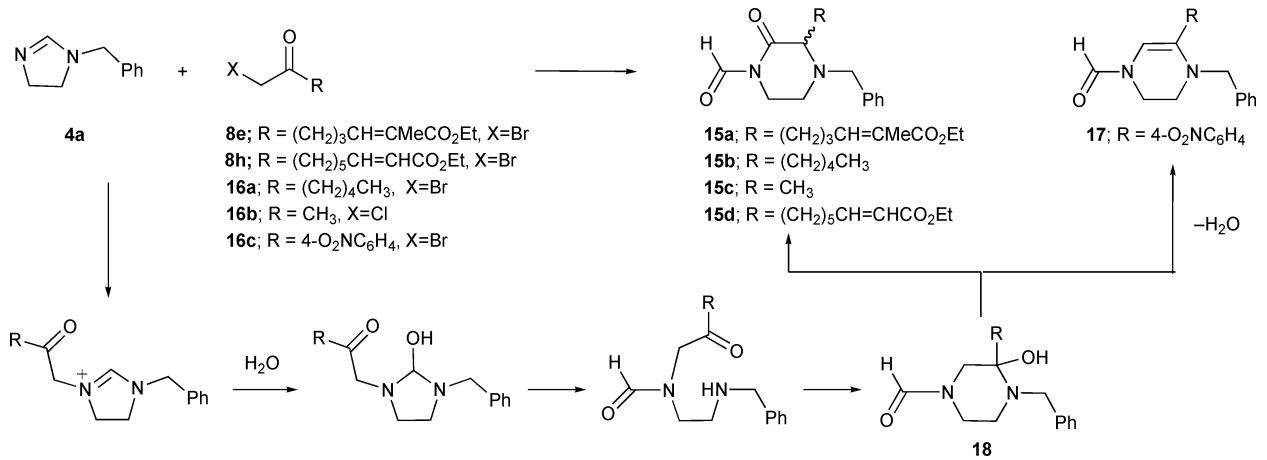


Fig. 2 X-Ray crystal structures of (a) **14d** and (b) **14g**: ORTEP plots, thermal ellipsoids at 50% probability level.

(which we assign to a formyl proton). The overall spectroscopic data are consistent with the 1-formylpiperazin-2-one structure **15a** (Scheme 5). The isolated yield of this compound was 34%. Compounds of this general structure are known, and are reported to have characteristic infrared absorptions in the region of 1695 and 1725 cm^{-1}.[33–35]

The formylpiperazine skeleton of **15a** implies that, for **8e**, cycloaddition did not occur, and is such that similar structures should be formed from any α-haloketone. Two further reactions confirmed this: compound **4a** was reacted separately with 1-bromoheptan-2-one **16a** and chloroacetone **16b** under the standard conditions for the 1,3-dipolar cycloaddition reactions; the piperazin-2-one products **15b** and **15c** were afforded in 56 and 47%, respectively (Scheme 5). In contrast, reaction of **4a** with commercial 2-bromo-4′-nitroacetophenone **16c** gave the related tetrahydropyrazine **17** in 87% yield. The presence of more than two signals for several of the resonances in the ^{1}H and ^{13}C NMR spectra of **17** clearly reveal this compound to be a mixture of *syn* and *anti* rotamers of the formamide functionality.

We presume compounds **15a**–**c** and **17** arise through hydrolysis, due to the presence of adventitious moisture, of the initially formed *N*-alkyldihydroimidazolium ion (or the corresponding ylide) that results from alkylation of **4a** by the α-haloketones (Scheme 5). We do not observe either type of piperazine product in those reactions where cycloaddition takes place, so conclude that hydrolysis must be slow compared to intramolecular cycloaddition and therefore that the presence of the α-methyl group in **8e** inhibits the cycloaddition reaction. Hydrolytic ring opening will lead to the formation of an aminoketone in which the secondary amino group can attack the ketone carbonyl to afford the intermediate piperazine **18**. Loss of water then leads to the 3-aryltetrahydropyrazine **17**. If compounds **15** are formed by a similar pathway, then



Scheme 5 Formation of 1,4-piperazin-2-ones **15** and **17** from dihydroimidazoles **4** and α-haloketones **8** or **16**.

the corresponding 3-alkyltetrahydropyrazine would require either addition of water (in the opposite sense to its elimination from **18**) followed by oxidation of the so-formed carbinolamine (or possibly disproportionation, though we did not observe any saturated piperazine co-product), or an enamine-type oxidation of the core tetrahydropyrazine ring system present in **17**. Indeed, the oxidation of enamine systems by means of molecular oxygen has been reported in the literature.[36–38] Presumably, the presence of adventitious molecular oxygen, perhaps originating from undegassed solvents, is the cause of this oxidation process. The reason for different outcomes for the alkyl and aryl bromoketones is unclear but may be due to stabilisation of **17** through conjugation of the double bond with the 3-aryl system.

When reaction of **4a** was attempted with **8f**, as predicted no product of cycloaddition or subsequent transformation was observed. The only isolated species was **7f**, presumably *via* hydrodehalogenation of the substrate.

We next attempted to block decomposition of the primary cycloadduct **11** by incorporating steric bulk into both the dihydroimidazole and the dipolarophile group of the bromoketone. When the dihydroimidazole **4c** and the *tert*-butyl ester **8d** were subjected to the usual cycloaddition conditions, the primary cycloadduct **11** (R^1 = Ph, R^2 = H, R^3 = Bu^t) was isolated in 31% yield as a single enantiomer. The isolation of **11** in this reaction supports the suggested sequence outlined in Scheme 4. It would appear that the combination of the (4*R*)-phenyl group in the dipole and the *tert*-butyl ester in the dipolarophile inhibits the eliminative ring-opening process. The relative stereochemistry of cycloadduct **11**, as determined by X-ray crystallography, is illustrated in Fig. 3. Again, this relative stereochemistry is that predicted from the transition state shown in Fig. 1 if the dipolarophile approaches the dipole from the face *anti* to the phenyl group at C-4 of the dihydroimidazole ring.

Having achieved the synthesis of the imidazoindole skeleton, we explored the reactions of systems that involved shorter, as well as longer, chains linking the ketone and alkene functionalities, *i.e.* **8g** and **8h**. In principle, this would allow access to smaller and larger carbocyclic analogues, respectively, either of the pyrroloquinoxalines **14a**–**h** or of the adduct **11**. Upon attempted reaction of **4a** with **8g**, however, the major isolated materials were the starting compounds. In contrast, reaction of

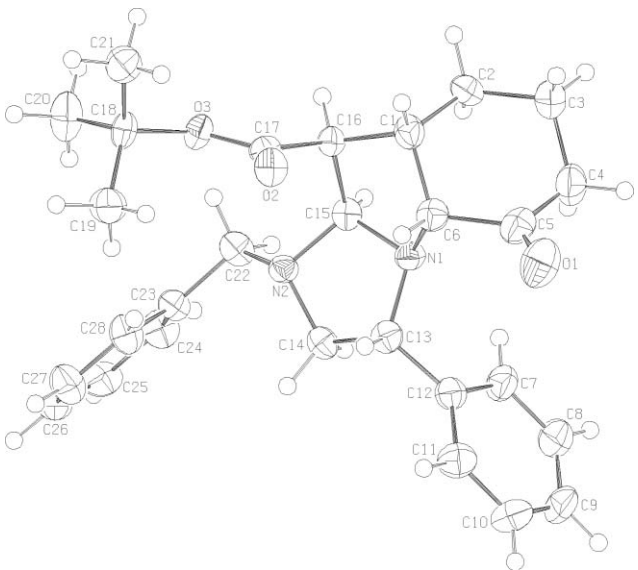


Fig. 3 X-Ray crystal structure of **11** (R^1 = Ph, R^2 = H, R^3 = Bu^t): ORTEP plot, thermal ellipsoids at 50% probability level.

8h with **4a** afforded the formylpiperazin-2-one **15d** rather than the anticipated cycloadducts or transformation products. Presumably, unfavourable interactions in the transition state that would lead to the larger ring preclude formation of the tricyclic adduct **11**; the reaction then follows the pathway described in Scheme 5.

In conclusion, we have demonstrated that intramolecular 1,3-dipolar cycloaddition reactions of ylides derived from 4,5-dihydroimidazoles and appropriately substituted α-haloketones can afford the decahydroimidazo[1,2-*a*]indole or hexahydropyrrolo[1,2,3-*de*]quinoxaline ring systems. The reaction appears to be limited to those dipolarophiles that are able to form a six-membered carbocyclic ring system.

Experimental

General methods

NMR spectra were recorded in $CDCl_3$ using either JEOL EX400 (400 MHz for ^{1}H and 100 MHz for ^{13}C, respectively) or JEOL

LA300 spectrometers (300 MHz ^{1}H and 75 MHz ^{13}C, respectively). Chemical shifts are reported in parts per million (ppm) from tetramethylsilane (TMS) as the internal standard and coupling constants (J) are expressed in Hz. Multiplicities are: s-singlet, d-doublet, t-triplet, q-quartet, quin-quintet, sex-sextet, m-multiplet, br-broad signal. IR spectra were recorded using a Perkin-Elmer 1710 Fourier transform infrared spectrophotometer. Low resolution mass spectra were recorded using a VG Micromass VG-20–250 mass spectrometer by electron impact (EI), chemical ionisation (CI) or fast atom bombardment (FAB) methods, the latter employing a thioglycerol matrix in both positive and negative ion modes. Accurate mass measurements were performed by the EPSRC National Mass Spectrometry Service (University of Wales, Swansea). Elemental analyses were performed by MEDAC Ltd, Brunel Science Centre, Surrey, TW20 0JZ, UK. X-Ray crystallography was performed by the EPSRC X-Ray Crystallographic Service (University of Southampton). Optical rotations were measured on a JASCO DIP-1000 digital polarimeter. Melting points were measured on a Kofler hot-stage apparatus and are uncorrected. Column chromatography was carried out using Fluka Silica Gel 60 (220–440 mesh) (Brockmann 2–3). TLC analysis was carried out using Machery-Nagel Polygram SIL G/UV$_{254}$ plates on a plastic backing and visualised by ultraviolet light or aqueous potassium permanganate spray ($KMnO_4$–K_2CO_3–water, 6 : 1 : 100, *w*/*w*/*v*).

All chemicals were purified by distillation or recrystallisation where appropriate. THF, THP, diethyl ether, toluene, ethanol and glyme were dried over sodium or potassium and distilled. DCM and DMSO were dried over sodium or calcium hydride and distilled. Anhydrous reactions were carried out using flamed dried glassware with all transfers performed using oven-dried syringes and needles.

The following were purchased from commercial sources: 2-(2-bromoethyl)dioxolane (**5**), chloroacetone (**8j**), 2-bromo-4′-nitroacetophenone (**8k**), 5-hydroxypentan-2-one (**10**).

Wittig salts and phosphoranes were synthesised from the appropriate alkyl bromoacetate by a literature method.[39] Other compounds that were prepared by known literature methods, and that had spectral characteristics identical to those already published, are as follows: 1-benzyl-4,5-dihydroimidazole (**4a**),[1] 2-phenyl-1-benzylimidazole (**4b**),[27] (*R*)-1-benzyl-4-phenyl-4,5-dihydroimidazole (**4c**),[28] 5-oxohexanal (**6a**),[29] 4-oxopentanal (**6c**),[40] methyl *E*-7-oxooct-2-enoate and methyl *Z*-7-oxooct-2-enoate (**7a** and **7b**),[29] 1-bromoheptan-2-one (**8i**),[41] *tert*-butyl 2-acetyl-5-oxohexanoate (**9**).[30]

2,6-Heptanedione (6b). *tert*-Butyl 2-acetyl-5-oxohexanoate (**9**, 0.66 g; 2.89 mmol) was treated with trifluoroacetic acid (30 ml) and the resulting red solution was stirred for 30 min at room temperature. The excess acid was removed under reduced pressure and the residue distilled to afford the title compound as a colourless oil (0.35 g; 98%): b.p. 92 °C/10 mmHg (lit.,[42] 94 °C/12 mmHg); ν_{max} (film)/cm^{-1} 2942, 1714, 1428, 1360, 1171; δ_H 1.86 (quin, 2H, $J = 7.1$, $CH_2CH_2CH_2$), 2.14 (s, 6H, 2 × CH_3CO), 2.46 (t, 4H, $J = 7.1$, 2 × $COCH_2$); δ_C 17.6 ($CH_2CH_2CH_2$), 29.9 (CH_3CO), 42.4 ($COCH_2$), 209.1 (CO).

Ethyl *E*-7-oxooct-2-enoate (7c). Prepared by the method used for **7a**,[29] using 5-oxohexanal (**6a**, 6.65 g; 58.3 mmol) and ethyl (triphenylphosphoranylidene)acetate (22.31 g; 64.1 mmol). The crude product was purified by silica gel column chromatography using ethyl acetate–hexane (8 : 92 *v*/*v*) as eluant to afford the title compound as a colourless oil (6.40 g; 59%): ν_{max} (film)/cm^{-1} 2982, 1718, 1655, 1447, 1368, 1270, 1191, 1045, 985; δ_H 1.28 (t, 3H, $J = 7.1$, OCH_2CH_3), 1.75 (quin, 2H, $J = 7.3$, $CH_2CH_2CH{=}CH$), 2.14 (s, 3H, CH_3CO), 2.20 (m, 2H, $CH_2CH{=}CHCO_2Et$), 2.46 (t, 2H, $J = 7.3$, CH_3COCH_2), 4.19 (q, 2H, $J = 7.1$, OCH_2CH_3), 5.82 (dt, 1H, $J = 1.6$, 15.5, $CH{=}CHCO_2Et$), 6.92 (dt, 1H, $J = 6.9$, 15.5, $CH{=}CHCO_2Et$); δ_C 14.2 ($CO_2CH_2CH_3$), 21.8 ($CH_2CH_2CH{=}CH$), 29.9 (CH_3CO), 31.2 ($CH_2CH{=}CH$), 42.5 ($COCH_2$), 60.2 (OCH_2CH_3), 122.0 ($CHCO_2Et$), 147.9 ($CH{=}CHCO_2Et$), 166.4 (CO_2), 208.1 (CH_3CO); *m*/*z* (CI) 202 (MNH_4^+, 100%), 185 (10%), 158 (12%); (EI) 185 (MH^+, 10%), 139 (44%), 138 (70%), 127 (23%), 114 (42%), 110 (28%), 99 (93%), 95 (71%), 86 (38%), 81 (75%), 68 (53%), 58 (49%), 43 (100%). HRMS: (CI) MNH_4^+ 202.1443, $C_{10}H_{16}O_3$ requires MNH_4^+ 202.1443.

***tert*-Butyl *E*-7-oxooct-2-enoate (7d).** Prepared as for **7c** using 5-oxohexanal (**6a**, 4.83 g; 42.0 mmol) and *tert*-butyl (triphenylphosphoranylidene)acetate (17.54 g; 46.6 mmol). The crude product was purified by silica gel column chromatography using ethyl acetate–hexane (8 : 92 *v*/*v*) as eluant to afford the title compound as a colourless oil (5.2 g; 58%): ν_{max} (film)/cm^{-1} 2979, 1713, 1654, 1478, 1393, 1368, 1317, 1293, 1257, 1223, 1162, 984; δ_H 1.48 (s, 9H, $(CH_3)_3$), 1.73 (quin, 2H, $J = 7.3$, $CH_2CH_2CH_2$), 2.14 (s, 3H, CH_3CO), 2.20 (m, 2H, $CH_2CH{=}CH$), 2.45 (t, 2H, $J = 7.3$, $COCH_2$), 5.74 (dt, 1H, $J = 1.5$, 15.5, $CHCO_2{}^tBu$), 6.80 (dt, 1H, $J = 7.0$, 15.5, $CH{=}CHCO_2{}^tBu$); δ_C 21.9 ($CH_2CH_2CH_2$), 28.1 ($(CH_3)_3$), 29.9 ($CH_2CH{=}CH$), 31.1 (CH_3CO), 42.6 ($COCH_2$), 80.2 ($OC(CH_3)_3$), 123.7 ($CHCO_2{}^tBu$), 146.7 ($CH{=}CHCO_2{}^tBu$), 167.1 (CO_2), 206.4 (CH_3CO); *m*/*z* (CI) 230 (MNH_4^+, 68%), 174 (100%); (EI) 156 (8%), 139 (8%), 138 (22%), 120 (3%), 111 (11%), 95 (16%), 84 (7%), 81 (18%), 68 (18%), 57 (80%), 43 (100%). HRMS: (CI) MNH_4^+ 230.1752; $C_{12}H_{20}O_3$ requires MNH_4^+ 230.1756.

Ethyl *E*-2-methyl-7-oxooct-2-enoate (7e). Prepared as for **7a** using 5-oxohexanal (**6a**, 5.07 g; 43.8 mmol) and ethyl 2-(triphenylphosphoranylidene)propionate. The crude product was purified by silica gel column chromatography using ethyl acetate–hexane (1 : 9 *v*/*v*) as eluant to afford the title compound as a colourless oil (2.8 g; 32%): ν_{max} (film)/cm^{-1} 2983, 1713, 1650, 1446, 1389, 1261, 1163, 1123, 1088; δ_H (300 MHz) 1.29 (t, 3H, $J = 7.1$, OCH_2CH_3), 1.73 (quin, 2H, $J = 7.3$, $CH_2CH_2CH_2$), 1.82 (br s, 3H, $C(CH_3)CO_2CH_3$), 2.14 (s, 3H, CH_3CO), 2.20 (q, 2H, $J = 7.3$, $CH_2CH{=}C$), 2.45 (t, 2H, $J = 7.3$, $COCH_2$), 4.18 (q, 2H, $J = 7.1$, OCH_2CH_3), 6.71 (t, 1H, $J = 7.5$, $CH{=}C(CH_3)CO_2CH_3$); δ_C 12.4 (OCH_2CH_3), 14.3 ($C(CH_3)CO_2CH_3$), 22.5 ($CH_2CH_2CH_2$), 27.8 (CH_3CO), 29.9 ($CH_2CH{=}C$), 42.8 ($COCH_2$), 60.5 (OCH_2CH_3), 129.2 ($C(CH_3)CO_2CH_3$), 140.9 ($CH{=}C$), 167.1 (CO_2CH_3), 206.2 (CH_3CO); *m*/*z* (EI) 199 (MH^+, 13%), 172 (16%), 152 (51%), 125(15%), 109 (42%), 95 (41%), 84 (71%), 67 (25%), 51 (38%). HRMS: (EI) MH^+ 199.1330; $C_{11}H_{18}O_3$ requires MH^+ 199.1334.

Methyl *E*- and *Z*-3-methyl-7-oxooct-2-enoate (7f). A solution of commercial trimethyl phosphonoacetate (3.70 ml; 23 mmol) in dry THF (10 ml) was added dropwise with cooling (ice–water bath) to a suspension of NaH (0.60 g; 25 mmol) in dry THF (30 ml) under nitrogen. The water bath was removed and the mixture stirred at room temperature for a further 30 min. A solution of 2,6-heptanedione (**6b**) (2.6 g; 20.9 mmol) in dry THF (10 ml) was

then added dropwise, and the reaction stirred at room temperature for a further 10 h. The solvent was removed under reduced pressure and the residue purified by silica gel column chromatography using ethyl acetate–hexane (7.5 : 92.5 *v*/*v*) as eluant to afford the title compound as a yellow oil (1.55 g; 40%), that was an inseparable mixture (50 : 50, by ^{1}H NMR) of *E*- and *Z*-isomers: ν_{max} (film)/cm^{-1} 2951, 1718, 1651, 1436, 1363, 1227, 1151, 1085, 1028, 921, 866; δ_H 1.77 (m, 2H, $CH_2CH_2CH_2CH$), 1.89 (d, 1.5H, $J = 1.3$, $C(CH_3)$=C for *Z*-isomer), 2.14 (s, 3H, CH_3CO for both *Z*- and *E*-isomers), 2.16 (d, 1.5H, $J = 1.3$, $C(CH_3)$=CH for *E*-isomer), 2.20 (t, 1H, $J = 7.5$, $CH_2C(CH_3)$=C for *E*-isomer), 2.44 (t, 1H, $J = 7.1$, CH_3COCH_2 for *E*- or *Z*-isomer), 2.49 (t, 1H, $J = 7.1$, CH_3COCH_2 for *E*- or *Z*-isomer), 2.62 (t, 1H, $J = 7.5$, $CH_2C(CH_3)$=C for *Z*-isomer), 3.67 (s, 1.5H, OCH_3 for *Z*-isomer), 3.69 (s, 1.5H, OCH_3 for *E*-isomer), 5.66 (sext, 0.5H, $J = 1.3$, C=$CHCO_2CH_3$ for *Z*-isomer), 5.68 (br m, 0.5H, C=$CHCO_2CH_3$ for *E*-isomer); δ_C 21.1, 21.9 ($CH_2CH_2CH_2$ for *E*- and *Z*-isomers), 24.9, 27.9 ($C(CH_3)$=CH for *E*- and *Z*-isomers), 29.9, 30.0 (CH_3CO for *E*- and *Z*-isomers), 32.4 (CH_3COCH_2 for *E*- and *Z*-isomers), 42.5, 43.1 ($CH_2C(CH_3)$=C for *E*- and *Z*-isomers), 50.8, 50.9 (OCH_3 for *E*- and *Z*-isomers), 115.7, 116.2 (C=$CHCO_2CH_3$ for *E*- and *Z*-isomers), 159.2, 160.0 ($C(CH_3)$=C for *E*- and *Z*-isomers), 166.7, 167.1 (CO_2CH_3 for *E*- and *Z*-isomers), 208.2, 208.7 (CH_3COCH_2 for *E*- and *Z*-isomers); *m*/*z* (CI) 202 (MNH_4^+, 100%), 185 (11%), 172 (13%), 152 (18%), 127 (14%), 109 (38%), 95 (53%), 82 (24%), 79 (7%), 67 (32%), 59 (8%), 55 (20%), 49 (39%), 43 (100%). HRMS: (CI) MNH_4^+ 202.1489; $C_{10}H_{16}O_3$ requires MNH_4^+ 202.1443.

Methyl *E*-6-oxohept-2-enoate (7g). Prepared as for **7a** using 4-oxopentanal (**6c**, 0.36 g; 3.56 mmol) and methyl (triphenylphosphoranylidene)acetate (1.31 g; 3.90 mmol).

Colourless oil (0.40 g; 72%): ν_{max} (film)/cm^{-1} 2847, 1723, 1713, 1659, 1462, 1368, 1318, 1276, 1203, 1161, 1097, 1041, 924, 849, 719; δ_H 2.14 (s, 3H, CH_3CO), 2.45 (m, 2H, CH_2CH=CH), 2.58 (t, 2H, $J = 6.8$, $COCH_2$), 3.69 (s, 3H, OCH_3), 5.80 (dt, 1H, $J = 1.6$, 15.6, C=$CHCO_2Me$), 6.90 (dt, 1H, $J = 6.8$, 15.6, CH=$CHCO_2Me$); δ_C 25.9 (CH_2CH=C), 29.9 (CH_3CO), 41.4 ($COCH_2$), 51.4 (OCH_3), 121.6 (C=$CHCO_2Me$), 147.4 (CH=$CHCO_2Me$), 166.8 (CO_2CH_3), 206.6 (CH_3CO); *m*/*z* (EI) 156 (M^+, 98%), 149 (78%), 141 (79%), 135 (34%), 133 (49%), 113 (21%), 81 (39%), 43 (100%). HRMS: (EI) MH^+ 157.0863; $C_8H_{12}O_3$ requires MH^+ 157.0864.

General method for the synthesis of α-bromoketones 8a–h

All glassware was flame dried and all reagents freshly distilled. A solution of the ketoester **7** (9.58 mmol) in dry THF (10 ml) at −78 °C was added dropwise to a freshly prepared solution of LDA (1.2 eq; 11.5 mmol), prepared from *n*-BuLi (2.5M solution in hexanes; 4.60 ml; 11.5 mmol) and diisopropylamine (1.74 ml; 12.4 mmol), in dry THF (10 ml) at −78 °C. The resulting mixture was allowed to stir at −78 °C for 20 min before a solution of chlorotrimethylsilane (6.07 ml; 47.9 mmol) in dry THF (5 ml), also at −78 °C, was added. After stirring for 5 min, triethylamine (6.67 ml; 4.84 g) was added and the mixture allowed to warm to room temperature. Saturated sodium hydrogen carbonate (3 ml) was added and the mixture extracted with diethyl ether (3 × 30 ml). The organic phase was dried ($MgSO_4$) and the solvent removed under reduced pressure to afford the crude silyl enol ether, which was used directly without further purification.

A solution of the silyl enol ether (7.60 mmol) in dry THF (10 ml) at −78 °C was treated with solid $NaHCO_3$ (1.12 g; 13.41 mmol), and the mixture allowed to stir at that temperature for 10 min. *N*-Bromosuccinimide (2.21 g; 12.45 mmol) was then added portionwise and the resulting mixture stirred for 4 h at −78 °C. The mixture was warmed to room temperature and subsequently heated at 80 °C for 2 h. Upon cooling, the solvent was evaporated under reduced pressure and the residue purified by column chromatography using ethyl acetate–hexane (15 : 85 *v*/*v*) as eluant to afford the desired compound as a dark liquid. Synthesised in this way were:

Methyl *E*-8-bromo-7-oxooct-2-enoate (8a). (0.85 g; 45%): ν_{max} (film)/cm^{-1} 2951, 1719, 1646, 1439, 1408, 1369, 1174, 1092, 1039; δ_H 1.80 (quin, 2H, $J = 7.1$, $CH_2CH_2CH_2$), 2.23 (m, 2H, CH_2CH=CH), 2.67 (t, 2H, $J = 7.1$, $COCH_2$), 3.79 (s, 3H, OCH_3), 3.91 (s, 2H, $BrCH_2$), 5.82 (dt, 1H, $J = 1.6$, 15.6, $CHCO_2$), 6.87 (dt, 1H, $J = 6.9$, 15.6, CH=$CHCO_2Me$); δ_C 21.9 ($CH_2CH_2CH_2$), 31.1 (CH_2CH=CH), 34.1 ($BrCH_2$), 38.7 ($COCH_2$), 51.5 (OCH_3), 121.8 ($CHCO_2Me$), 147.9 (CH=$CHCO_2Me$), 166.8 (CO_2CH_3), 201.4 ($BrCH_2CO$); *m*/*z* (CI) 266 (MNH_4^+), 100%), 258 (14%), 244 (23%), 214 (8%), 202 (9%), 188 (93%), 171 (5%). HRMS: (CI^+) MNH_4^+ 266.0392; $C_9H_{13}BrO_3$ requires MNH_4^+ 266.0392.

Methyl *Z*-8-bromo-7-oxooct-2-enoate (8b). (0.60 g; 45%): ν_{max} (film)/cm^{-1} 2954, 1717, 1643, 1434, 1410, 1370, 1171, 1092, 1039; δ_H 1.76 (quin, 2H, $J = 7.3$, $CH_2CH_2CH_2$), 2.23 (s, 3H, CH_3CO), 2.66 (dq, 2H, $J = 1.6$, 7.5, CH_2CH=CH), 2.72 (t, 2H, $J = 7.3$, $COCH_2$), 3.70 (s, 3H, OCH_3), 3.75 (s, 2H, $BrCH_2$), 5.84 (dt, 1H, $J = 1.6$, 11.5, $CHCO_2Me$), 6.23 (dt, 1H, $J = 7.7$, 11.5, CH=$CHCO_2Me$); δ_C 22.8 ($CH_2CH_2CH_2$), 27.9 (CH_2CH=CH), 34.3 ($BrCH_2COCH_2$), 38.9 (CH_3COCH_2), 51.1 (CO_2CH_3), 120.4 (CH=$CHCO_2Me$), 148.9 (CH=$CHCO_2Me$), 167.2 (CO_2CH_3), 202.3 (CH_3COCH_2). HRMS: (CI^+) MNH_4^+ 266.0392; $C_9H_{13}BrO_3$ requires MNH_4^+ 266.0392.

Ethyl *E*-8-bromo-7-oxooct-2-enoate (8c). (2.30 g; 41%): ν_{max} (film)/cm^{-1} 2980, 1714, 1655, 1394, 1271, 1186, 1096, 1042, 981, 843; δ_H 1.19 (t, 3H, $J = 7.1$, CH_2CH_3), 1.70 (quin, 2H, $J = 7.2$, CH_2CH_2CH=CH), 2.23 (m, 2H, CH_2CH=CH), 2.54 (t, 2H, $J = 7.3$, $COCH_2$), 3.76 (s, 2H, $BrCH_2$), 4.08 (q, 2H, $J = 7.1$, CO_2CH_2), 5.73 (dt, 1H, $J = 1.6$, 15.6, $CHCO_2Et$), 6.80 (dt, 1H, $J = 6.9$, 15.6,CH=$CHCO_2Et$); δ_C 14.5 ($CO_2CH_2CH_3$), 22.1 ($CH_2CH_2CH_2$), 31.5 (CH_2CH_2CH=CH), 34.2 ($BrCH_2CO$); 38.9 ($COCH_2CH_2$), 60.5 ($CO_2CH_2CH_3$), 122.5 (CH=$CHCO_2Et$), 148.2 (CH=$CHCO_2Et$), 166.6 ($CO_2CH_2CH_3$), 201.6 ($BrCH_2CO$); *m*/*z* (CI) 280 (MNH_4^+, 100%), 266 (23%), 254 (31%), 242 (18%), 240 (32%), 237 (26%), 204 (19%), 202 (100%), 158 (28%); (EI) 263 (MH^+, 12%), 191 (7%), 169 (5%), 137 (38%), 123 (24%), 109 (18%), 99 (31%), 95 (55%), 85 (46%), 68 (33%), 55 (61%), 43 (100%). HRMS: (CI) MNH_4^+ 280.0550; $C_{10}H_{15}BrO_3$ requires MNH_4^+ 280.0548.

***tert*-Butyl *E*-8-bromo-7-oxooct-2-enoate (8d).** (2.20 g; 40%): ν_{max} (film)/cm^{-1} 2978, 1713, 1654, 1477, 1393, 1368, 1318, 1295, 1155, 982, 890; δ_H 1.48 (s, 9H, $(CH_3)_3$), 1.79 (quin, 2H, $J = 7.3$, $CH_2CH_2CH_2$), 2.21 (m, 2H, CH_2CH=CH), 2.68 (t, 2H, $J = 7.3$, $COCH_2$), 3.71 ($BrCH_2$), 5.76 (dt, 1H, $J = 1.6$, 15.5, $CHCO_2{}^tBu$), 6.80 (dt, 1H, $J = 6.7$, 15.5, CH=$CHCO_2{}^tBu$); δ_C 22.0 ($CH_2CH_2CH_2$), 28.1 (($CH_3)_3$), 30.9 (CH_2CH=CH), 34.1 ($BrCH_2$), 38.7 ($COCH_2$), 80.3 ($C(CH_3)_3$), 123.9 ($CHCO_2{}^tBu$),

146.2 (*C*H=CHCO$_2$^{t}Bu), 165.8 (*C*O$_2$^{t}Bu), 201.4 (CH$_2$*C*OCH$_2$); *m/z* (CI) 308 (MNH_4^+, 7%), 230 (49%), 175 (10%), 174 (100%), 158 (13%), 52 (21%); (EI) 137 (6%), 95 (7%), 81 (8%), 68 (19%), 57 (100%), 41 (67%). HRMS: (CI) MNH_4^+ 308.0856; $C_{12}H_{19}BrO_3$ requires MNH_4^+ 308.0861.

Ethyl *E*-8-bromo-2-methyl-7-oxooct-2-enoate (8e). (1.16 g; 44%): ν_{max} (film)/cm^{-1} 2982, 1713, 1650, 1446, 1393, 1368, 1262, 1184, 1124, 1088; δ_H 1.29 (t, 3H, J = 7.1, OCH$_2$C*H*$_3$), 1.78 (quin, 2H, J = 7.2, CH$_2$C*H*$_2$CH$_2$); 1.83 (d, 3H, J = 1.3, C(C*H*$_3$)CO$_2$Et), 2.21 (q, 2H, J = 7.5, C*H*$_2$CH=C), 2.60 (t, 2H, J = 7.1, COC*H*$_2$), 3.87 (s, 2H, BrC*H*$_2$), 4.19 (q, 2H, J = 7.1, OC*H*$_2$CH$_3$), 6.70 (tq, 1H, J = 1.3, 6.1, C*H*=C); δ_C 12.4 (CO$_2$CH$_2$*C*H$_3$), 14.3 (C(*C*H$_3$)CO$_2$Et), 22.6 (CH$_2$*C*H$_2$CH$_2$), 27.6 (*C*H$_2$CH=C); 34.1 (Br*C*H$_2$), 38.9 (CO*C*H$_2$), 60.5 (O*C*H$_2$CH$_3$), 128.9 (*C*(CH$_3$)CO$_2$Et), 140.4 (*C*H=C), 160.3 (*C*O$_2$CH$_2$CH$_3$), 201.6 (CH$_2$*C*OCH$_2$); *m/z* (CI) 294 (MNH_4^+, 100%), 277 (5%), 254 (12%), 216 (98%); (EI) 203 (28%), 197 (22%), 169 (62%), 151 (27%), 123 (31%), 112 (30%), 95 (62%), 83 (4%), 82 (27%), 81 (39%), 79 (24%), 67 (33%), 43 (100%). HRMS: (CI) MNH_4^+ 294.0705; $C_{11}H_{17}BrO_3$ requires MNH_4^+ 294.0705.

Methyl *E*-8-bromo-3-methyl-7-oxooct-2-enoate (8f). (0.30 g; 30%): ν_{max} (film)/cm^{-1} 2950, 1713, 1651, 1436, 1379, 1228, 1155, 1087, 921, 857; δ_H 1.70 (quin, 2H, J = 7.6, CH$_2$C*H*$_2$CH$_2$), 1.78 (d, 3H, J = 1.4, C(C*H*$_3$)=CH), 2.49 (br t, 2H, J = 6.6, C*H*$_2$C(CH$_3$)=C), 2.59 (t, 2H, J = 7.3, COC*H*$_2$), 3.56 (s, 3H, OC*H*$_3$), 3.79 (s, 2H, BrC*H*$_2$), 5.59 (br s, 1H, C=C*H*CO$_2$Me); δ_C 22.1 (CH$_2$*C*H$_2$CH$_2$), 25.1 (C(*C*H$_3$)=CH), 32.3 (*C*H$_2$CH=C), 34.4 (Br*C*H$_2$), 39.3 (CO*C*H$_2$), 51.1 (O*C*H$_3$), 116.7 (C=*C*HCO$_2$Me), 159.7 (*C*=CHCO$_2$Me), 166.9 (*C*O$_2$CH$_3$), 202.0 (CH$_2$*C*OCH$_2$); *m/z* (CI) 280 (MNH_4^+, 100%), 263 (11%), 258 (13%), 232 (14%), 216 (11%), 203 (12%), 202 (100%), 200 (5%), 185 (16%), 172 (11%); (EI) 151 (42%), 109 (57%), 95 (100%), 82 (44%), 81 (63%), 79 (40%), 67 (68%), 43 (100%). HRMS: (CI) MNH_4^+ 280.0551; $C_{10}H_{15}BrO_3$ requires MNH_4^+ 280.0548.

Methyl *E*-7-bromo-6-oxohept-2-enoate (8g). (0.18 g; 34%): ν_{max} (film)/cm^{-1} 2840, 1721, 1716, 1665, 1457, 1369, 1312, 1276, 1164, 1091, 1040, 923, 844, 716; δ_H 2.38 (m, 2H, C*H*$_2$CH=C), 2.70 (t, 2H, J = 7.3, COC*H*$_2$), 3.56 (s, 3H, OC*H*$_3$), 3.74 (s, 2H, BrC*H*$_2$), 5.71 (dt, 1H, J = 1.5, 15.6, C=C*H*CO$_2$Me), 6.77 (dt, 1H, J = 6.8, 15.6, C*H*=CHCO$_2$Me); δ_C 25.6 (*C*H$_2$CH=CH), 32.9 (Br*C*H$_2$), 37.6 (CO*C*H$_2$), 51.4 (O*C*H$_3$), 121.9 (C=*C*HCO$_2$Me), 146.5 (*C*H=CHCO$_2$Me), 166.6 (*C*O$_2$CH$_3$), 200.3 (BrCH$_2$*C*O); *m/z* (CI) 174 (MH^+–Br, 100%), (EI) 156 (100%), 149 (75%), 141 (75%), 133 (48%), 81 (34%), 43 (100%). HRMS: (CI) MNH_4^+ 252.0232; $C_8H_{11}BrO_3$ requires MNH_4^+ 252.0235).

Ethyl *E*-10-bromo-9-oxodec-2-enoate (8h). (2.0 g; 36%): ν_{max} (film)/cm^{-1} 2981, 2937, 1713, 1655, 1463, 1393, 1368, 1310, 1269, 1184, 1044, 983; δ_H 1.28 (t, 3H, J = 7.1, OCH$_2$C*H*$_3$), 1.34 (quin, 2H, J = 7.2, C*H*$_2$CH$_2$CH$_2$CH=C), 1.48 (quin, 2H, J = 7.2, C*H*$_2$CH$_2$CH=C), 1.62 (quin, 2H, J = 7.4, COCH$_2$C*H*$_2$), 2.20 (m, 2H, C*H*$_2$CH=CH), 2.66 (t, 2H, J = 7.3, COC*H*$_2$), 3.87 (s, 2H, BrC*H*$_2$), 4.18 (q, 2H, J = 7.1, OC*H*$_2$CH$_3$), 5.81 (dt, 1H, J = 1.6, 15.5, C=C*H*CO$_2$Et), 6.94 (dt, 1H, J = 6.9, 15.5, C*H*=CHCO$_2$Et); δ_C 14.3 (OCH$_2$*C*H$_3$), 23.5 (*C*H$_2$CH$_2$CH$_2$CH=C), 27.7 (*C*H$_2$CH$_2$CH=CH), 28.4 (COCH$_2$*C*H$_2$), 31.9 (*C*H$_2$CH=C), 34.2 (Br*C*H$_2$), 39.6 (CO*C*H$_2$), 60.2 (O*C*H$_2$CH$_3$), 121.5 (C=*C*HCO$_2$Et), 148.8 (*C*H=CHCO$_2$Et), 166.7 (OCH$_2$*C*H$_3$), 202.0 (CH$_2$*C*OCH$_2$); *m/z* (CI) 308 (MNH_4^+, 100%), 213 (10%), 202 (8%); (EI) 244 (100%), 217 (21%), 197 (43%), 165 (10%), 137 (17%), 123 (23%), 95 (50%), 81 (54%), 67 (23%), 55 (61%), 43 (100%). HRMS: (CI) MNH_4^+ 308.0858; $C_{12}H_{19}BrO_3$ requires MNH_4^+ 308.0861.

***tert*-Butyl (3*R*,4a*R*,8a*S*,9*S*,9a*R*)-1-benzyl-5-oxo-3-phenyldecahydro-1*H*-imidazo[1,2-*a*]indole-9-carboxylate (11, R^1 = Ph, R^2 = H, R^3 = Bu^t).** To a solution of (*R*)-1-benzyl-4-phenyl-4,5-dihydroimidazole (**4c**, 0.26 g; 1.12 mmol) in dry THF (15 ml) under an atmosphere of nitrogen was added a solution of *tert*-butyl *E*-8-bromo-7-oxooct-2-enoate (**8d**, 0.36 g; 1.23 mmol) in dry THF (5 ml). The resulting solution was refluxed for 2 h. DBU (0.20 ml; 1.35 mmol) was added dropwise over 4 h and the reaction kept at reflux for a further 4 h. The reaction was cooled, the solvent was removed under reduced pressure and the residue purified by silica gel column chromatography using ethyl acetate–hexane (1 : 9 *v*/*v*) as eluant to afford the title compound as a white solid (0.15 g; 31%). Recrystallisation from methanol–hexane gave white needles for X-ray crystallographic analysis: m.p. 169–171 °C; $[\alpha]_D^{20}$ +14.25; (*c* 2; DCM); ν_{max} (nujol)/cm^{-1} 2926, 2855, 1715, 1490, 1379, 1219, 1147; δ_H 1.45 (s, 9H, (C*H*$_3$)$_3$), 1.80–1.82 (m, 2H, 8-C*H*H and 7-C*H*H), 1.90–1.92 (m, 2H, 8-CH*H* and 7-CH*H*), 2.14 (m, 1H, 6-C*H*H), 2.32 (dd, 1H, J = 9.2, 10.0, 2-C*H*H), 2.50 (m, 1H, 6-CH*H*), 2.83 (t, 1H, J = 6.9, 9-C*H*), 3.17 (m, 1H, 8a-C*H*), 3.22 (d, 1H, J = 12.9, CH*H*Ph), 3.25 (dd, 1H, J = 5.5, 9.2, 2-CH*H*), 3.62 (d, 1H, J = 6.6, 4a-C*H*), 4.09 (dd, 1H, J = 5.5, 10.0, 3-C*H*), 4.11 (d, 1H, J = 12.9, CH*H*Ph), 4.58 (d, 1H, J = 6.9, 9a-C*H*), 7.28–7.32 (m, 10H, Ar–*H*); δ_C 24.2 (*C*-8), 26.2 (*C*-7),. 28.3 (*C*H$_3$)$_3$), 39.3 (*C*-6), 45.5 (*C*-8a), 53.5 (*C*-9), 58.6 (*C*H$_2$Ph), 63.0 (*C*-2), 68.1 (*C*-3), 73.0 (*C*-4a), 81.2 (*C*(CH$_3$)$_3$), 86.7 (*C*-9a), 126.6, 126.9, 127.2, 128.1, 128.2, 128.9 (6 × Ar–*C*H), 138.1 and 141.2 (2 × Ar–*C*), 170.3 (*C*O$_2$), 210.3 (*C*-5); *m/z* (EI) 447 (MH^+, 28%), 389 (90%), 373 (63%), 369 (22%), 345 (38%), 299 (61%), 291 (100%), 250 (46%), 249 (52%), 91 (100%), 57 (70%), 43 (16%), 41 (33%). HRMS: (EI) MH^+ 447.2646; $C_{28}H_{34}N_2O_3$ requires MH^+ 447.2647).

General method for the synthesis of compounds 14

To a solution of the dihydroimidazole **4a**–**c** (1 mmol) in dry THF (15 ml) under an atmosphere of nitrogen was added a solution of the bromoketone **8a**–**d** (1.08 mmol) in dry THF (5 ml). The resulting solution was refluxed for 2 h following which DBU (1.1 mmol) was added dropwise over 4 h. The reaction was kept at reflux for a further 4 h, cooled and the solvent evaporated under reduced pressure. The residue was purified by silica gel column chromatography using ethyl acetate–hexane (3 : 7 *v*/*v*) as eluant to afford the pyrrolo[1,2,3-*de*]quinoxalines **16**. Synthesised in this way were the following compounds.

Methyl 1-benzyl-2,3,7,8,9,9a-hexahydro-1*H*-pyrrolo[1,2,3-*de*]-quinoxaline-6-carboxylate (14a). White solid (0.095 g; 31%); m.p. 120–123 °C; ν_{max} (nujol)/cm^{-1} 2881, 2944, 1735, 1697, 1524, 1463, 1390, 1248, 1172, 1098, 1051, 916, 732; δ_H 1.45 (dtd, 1H, J = 2.5, 11.6, 13.5, 9-C*H*H), 1.76 (dddt, 1H, J = 2.1, 6.0, 11.6, 13.7, 8-CH*H*), 2.12 (m, 1H, 8-C*H*H), 2.29 (m, 1H, 9-CH*H*), 2.49 (ddd, 1H, J = 7.5, 10.0, 12.5, 2-CH*H*), 2.66 (dddd, 1H, J = 2.1, 5.8, 11.2, 16.8, 7-CH*H*), 2.85 (dd, 1H, J = 6.4, 16.8, 7-C*H*H), 3.02 (ddd, 1H, J = 2.3, 3.9, 12.5, 2-C*H*H), 3.13 (d, 1H, J = 13.2,

PhCH_2), 3.28 (br d, 1H, J = 10.6, 9a-CH), 3.76 (s, 3H, OCH_3), 3.85 (m, 2H, 3-CH_2), 4.25 (d, 1H, J = 13.2, PhCH_2), 7.12 (s, 1H, 5-CH), 7.23–7.37 (m, 5H, Ar–H); δ_C 22.4, 22.5 (*C*-8 and *C*-7), 27.9 (*C*-9), 44.9 (*C*-2), 49.7 (*C*-3), 50.6 (O*C*H$_3$), 57.3 (Ph*C*H$_2$), 59.7 (*C*-9a), 113.8 (*C*-6a), 117.0 (*C*-6), 124.3 (*C*-5), 127.2, 128.4, 129.0 (3 × Ar–*C*H), 130.2 (*C*-9b), 138.4 (Ar–*C*), 165.9 (*C*O$_2$CH$_3$); *m*/*z* (EI) 311 (MH$^+$, 10%), 283 (10%), 282 (41%), 191 (39%), 161 (6%), 91 (100%), 49 (21%), 43 (17%). HRMS: (EI) MH$^+$ 311.1763; $C_{19}H_{22}N_2O_2$ requires MH$^+$ 311.1759.

Ethyl 1-benzyl-2,3,7,8,9,9a-hexahydro-1*H*-pyrrolo[1,2,3-*de*]-quinoxaline-6-carboxylate (14b). White solid (0.10 g; 30%). Recrystallisation from methanol–hexane gave white needles for X-ray crystallographic analysis: m.p. 122–123 °C; ν_{max} (nujol)/cm^{-1} 2942, 2880, 1730, 1698, 1530, 1662, 1175, 1098, 1054, 918, 730; δ_H 1.19 (t, 3H, J = 7.1, OCH$_2$CH_3), 1.35 (dtd, 1H, J = 2.5, 11.6, 13.5, 9-CHH), 1.65 (dddt, 1H, J = 2.1, 6.0, 11.6, 13.7, 8-CHH), 2.02 (m, 1H, 8-CHH), 2.17 (m, 1H, 9-CHH), 2.36 (ddd, 1H, J = 7.5, 10.0, 12.5, 2-CHH), 2.54 (dddd, 1H, J = 2.1, 5.8, 11.2, 16.8, 7-CHH), 2.75 (dd, 1H, J = 6.4, 16.8, 7-CHH), 2.90 (ddd, 1H, J = 2.3, 3.9, 12.5, 2-CHH), 3.01 (d, 1H, J = 13.2, PhCHH), 3.16 (br d, 1H, J = 10.6, 9a-CH), 3.72 (m, 2H, 3-CH_2), 4.12 (m, 3H, OCH_2CH$_3$ and PhCHH), 7.02 (s, 1H, 5-CH), 7.18–7.25 (m, 5H, Ar–H); δ_C 14.6 (OCH$_2$*C*H$_3$), 22.5, 22.6 (*C*-8 and *C*-7), 27.9 (*C*-9), 45.0 (*C*-2), 49.8 (*C*-3), 57.3 (Ph*C*H$_2$), 59.2 (O*C*H$_2$CH$_3$), 59.7 (*C*-9a), 114.2 (*C*-6a), 117.0 (*C*-6), 124.3 (*C*-5), 127.3, 128.4, 129.0 (3 × Ar–*C*H), 129.3 (*C*-9b), 138.5 (Ar–*C*), 165.6 (*C*O$_2$CH$_2$CH$_3$); *m*/*z* (EI) 325 (MH$^+$, 100%), 235 (15%), 233 (12%), 106 (7%), 91 (100%), 65 (18%), 52 (38%). HRMS: (EI) MH$^+$ 325.1921; $C_{20}H_{24}N_2O_2$ requires MH$^+$ 325.1916. Found: C, 73.18; H, 7.35; N, 8.18%; $C_{20}H_{24}N_2O_2$·0.25 MeOH requires C, 73.16; H, 7.58; N, 8.43%;

***tert*-Butyl 1-benzyl-2,3,7,8,9,9a-hexahydro-1*H*-pyrrolo[1,2,3-*de*]-quinoxaline-6-carboxylate (14c).** Yellow oil (0.14 g; 33%): ν_{max} (film)/cm^{-1} 2983, 1736, 1698, 1524, 1466, 1374, 1246, 1174, 1096, 1048, 914, 735; δ_H 1.47 (dtd, 1H, J = 2.5, 11.6, 13.5, 9-CHH), 1.52 (s, 9H, (CH_3)$_3$), 1.74 (dddt, 1H, J = 2.1, 6.0, 11.6, 13.7, 8-CHH), 2.08 (m, 1H, 8-CHH), 2.27 (m, 1H, 9-CHH), 2.47 (ddd, 1H, J = 7.5, 10.0, 12.5, 2-CHH), 2.63 (dddd, 1H, J = 2.1, 5.8, 11.2, 16.8, 7-CHH), 2.85 (dd, 1H, J = 6.4, 16.8, 7-CHH), 3.00 (ddd, 1H, J = 2.3, 3.9, 12.5, 2-CHH), 3.12 (d, 1H, J = 13.2, PhCH_2), 3.27 (br d, 1H, J = 10.6, 9a-CH), 3.82 (m, 2H, 3-CH_2), 4.22 (d, 1H, J = 13.2, PhCH_2), 7.07 (s, 1H, 5-CH), 7.28–7.32 (m, 5H, Ar-H); δ_C 22.0, 22.6 (*C*-8 and *C*-7), 27.8 (*C*-9), 28.3 ((*C*H$_3$)$_3$), 44.9 (*C*-2), 49.7 (*C*-3), 57.1 (Ph*C*H$_2$), 59.6 (*C*-9a), 79.1 (O*C*(CH$_3$)$_3$), 115.7 (*C*-6a), 116.6 (*C*-6), 124.1 (*C*-5), 128.1, 128.3, 128.9 (3 × Ar–CH), 130.5 (*C*-9b), 138.5 (Ar–*C*), 165.0 (*C*O$_2$C(CH$_3$)$_3$); *m*/*z* (EI) 353 (MH$^+$, 28%), 324 (21%), 268 (38%), 177 (32%), 91 (100%), 65 (15%), 57 (50%), 41 (33%). HRMS: (EI) MH$^+$ 353.2228; $C_{22}H_{28}N_2O_2$ requires MH$^+$ 353.2229.

Methyl 1-benzyl-5-phenyl-2,3,7,8,9,9a-hexahydro-1*H*-pyrrolo-[1,2,3-*de*]quinoxaline-6-carboxylate (14d). White solid (0.13 g; 33%). Recrystallisation from methanol–hexane gave white needles for X-ray crystallographic analysis: m.p. 148–150 °C; ν_{max} (nujol)/cm^{-1} 2932, 2857, 1694, 1489, 1466, 1382, 1348, 1264, 1193, 1170, 1086, 911, 736, 701; δ_H 1.55 (dtd, 1H, J = 2.5, 11.6, 13.5, 9-CHH), 1.80 (dddt, 1H, J = 2.1, 6.0, 11.6, 13.7, 8-CHH), 2.14 (m, 1H, 8-CHH), 2.33 (m, 1H, 9-CHH), 2.45 (ddd, 1H, J = 7.5, 10.0, 12.5, 2-CHH), 2.72 (dddd, 1H, J = 2.1, 5.8, 11.2, 16.8, 7-CHH), 2.94 (m, 2H, 7-CHH and 2-CHH), 3.12 (d, 1H, J = 13.3, PhCH_2), 3.34 (br d, 1H, J = 10.6, 9a-CH), 3.52 (m, 2H, 3-CH_2), 3.60 (s, 3H, OCH_3), 4.26 (d, 1H, J = 13.3, PhCH_2), 7.26–7.32 (m, 10H, Ar–H); δ_C 22.5, 23.0 (*C*-8 and *C*-7), 28.0 (*C*-9), 44.2 (*C*-2), 49.9 (*C*-3), 50.4 (O*C*H$_3$), 57.3 (Ph*C*H$_2$), 59.7 (*C*-9a), 111.2 (*C*-6a), 117.5 (*C*-6), 127.1, 127.8, 127.9, 128.3, 128.5, 128.9 (6 × Ar–*C*H), 130.4 (*C*-9b), 132.0 (*C*-5), 136.7, 138.3 (2 × Ar–*C*), 165.9 (*C*O$_2$CH$_3$); *m*/*z* (EI) 387 (MH$^+$, 21%), 359 (26%), 358 (98%), 267 (54%), 237 (22%), 207 (11%), 180 (12%), 167 (8%), 91 (100%), 65 (8%), 49 (4%). HRMS: (EI): MH$^+$ 387.2077; $C_{25}H_{26}N_2O_2$ requires MH$^+$ 387.2072.

Ethyl 1-benzyl-5-phenyl-2,3,7,8,9,9a-hexahydro-1*H*-pyrrolo-[1,2,3-*de*]quinoxaline-6-carboxylate (14e). White solid (0.11 g; 31%): m.p. 124–125 °C; ν_{max} (nujol)/cm^{-1} 2932, 2857, 1694, 1489, 1414, 1382, 1348, 1264, 1170, 1148, 1067, 773, 736; δ_H 1.08 (t, 3H, J = 7.1, OCH$_2$CH_3), 1.50 (dtd, 1H, J = 2.5, 11.6, 13.5, 9-CHH), 1.78 (dddt, 1H, J = 2.1, 6.0, 11.6, 13.7, 8-CHH), 2.17 (m, 1H, 8-CHH), 2.32 (m, 1H, 9-CHH), 2.45 (ddd, 1H, J = 7.5, 10.0, 12.5, 2-CHH), 2.73 (dddd, 1H, J = 2.1, 5.8, 11.2, 16.8, 7-CHH), 2.94 (m, 2H, 7-CHH and 2-CHH), 3.12 (d, 1H, J = 13.3, PhCH_2), 3.34 (br d, 1H, J = 10.6, 9a-CH), 3.53 (ddd, 1H, J = 7.5, 10.0, 12.5, 3-CHH), 3.63 (ddd, 1H, J = 2.3, 3.9, 12.5, 3-CHH), 4.07 (q, 2H, J = 1.29, 7.1, CO$_2$CH_2CH$_3$), 4.26 (d, 1H, J = 13.3, PhCH_2), 7.28–7.31 (m, 10H, Ar–H); δ_C 14.1 (OCH$_2$*C*H$_3$), 22.5, 22.9 (*C*-8 and *C*-7), 28.0 (*C*-9), 44.2 (*C*-2), 49.9 (*C*-3), 57.3 (Ph*C*H$_2$), 58.9 (O*C*H$_2$CH$_3$), 59.7 (*C*-9a), 112.8 (*C*-6a), 117.5 (*C*-6), 127.1, 127.7, 17.8, 128.3, 128.5, 128.9 (6 × Ar–*C*H), 130.5 (*C*-9b), 132.1 (*C*-5), 138.4 (2 × Ar–*C*), 165.4 (*C*O$_2$CH$_2$CH$_3$); *m*/*z* (EI) 401 (MH$^+$, 25%), 373 (22%), 372 (100%), 299 (23%), 281 (23%), 253 (34%), 237 (31%), 207 (31%), 178 (28%), 91 (100%), 55 (35%), 43 (68%). HRMS: (EI) MH$^+$ 401.2234; $C_{26}H_{28}N_2O_2$ requires MH$^+$ 401.2229.

***tert*-Butyl 1-benzyl-5-phenyl-2,3,7,8,9,9a-hexahydro-1*H*-pyrrolo[1,2,3-*de*]quinoxaline-6-carboxylate (14f).** White solid (0.14 g; 34%): m.p. 52–54 °C; ν_{max} (nujol)/cm^{-1} 2927, 2855, 1687, 1460, 1377, 1164, 1148; δ_H 1.27 (s, 9H, (CH_3)$_3$), 1.51 (dtd, 1H, J = 2.5, 11.6, 13.5, 9-CHH), 1.81 (dddt, 1H, J = 2.1, 6.0, 11.6, 13.7, 8-CHH), 2.15 (m, 1H, 8-CHH), 2.30 (m, 1H, 9-CHH), 2.42 (ddd, 1H, J = 7.5, 10.0, 12.5, 2-CHH), 2.74 (dddd, 1H, J = 2.1, 5.8, 11.2, 16.8, 7-CHH), 2.93 (m, 2H, 7-CHH and 2-CHH), 3.09 (d, 1H, J = 13.4, PhCH_2), 3.32 (br d, 1H, J = 10.6, 9a-CH), 3.46 (ddd, 1H, J = 7.5, 10.0, 12.5, 3-CHH), 3.57 (ddd, 1H, J = 2.3, 3.9, 12.5, 3-CHH), 4.23 (d, 1H, J = 13.4, PhCH_2), 7.26–7.30 (m, 10H, Ar–H); δ_C 22.5, 22.8 (*C*-8 and *C*-7), 27.9 (*C*-9), 28.1 ((*C*H$_3$)$_3$), 44.0 (*C*-2), 49.9 (*C*-3), 57.1 (Ph*C*H$_2$), 59.6 (*C*-9a), 78.7 (O*C*(CH$_3$)$_3$), 112.9 (*C*-6a), 117.3 (*C*-6), 126.9, 127.6, 127.7, 128.2, 128.3, 128.8 (6 × Ar–*C*H), 130.4 (*C*-9b), 132.4 (*C*-5), 136.8, 138.4 (2 × Ar–*C*), 164.5 (*C*O$_2$C(CH$_3$)$_3$); *m*/*z* (EI) 429 (MH$^+$, 12%), 401 (21%), 400 (77%), 371 (9%), 355 (7%), 345 (13%), 344 (100%), 253 (8%), 91 (100%), 65 (8%), 57 (43%). HRMS: (EI) MH$^+$ 429.2546; $C_{28}H_{32}N_2O_2$ requires MH$^+$ 429.2542. Found: C, 77.70; H, 7.48; N, 6.32%; $C_{28}H_{32}N_2O_2$·0.25 MeOH requires C, 77.72; H, 7.62; N, 6.42%.

Methyl (3*R*,9*S*)-1-benzyl-3-phenyl-2,3,7,8,9,9a-hexahydro-1*H*-pyrrolo[1,2,3-*de*]quinoxaline-6-carboxylate (14g). White solid (0.10 g; 30%). Recrystallisation from methanol–hexane gave white needles for X-ray crystallographic analysis: m.p. 176–176 °C; $[\alpha]_D^{20}$

+32.01 (*c* 0.345; DCM); ν_{max} (nujol)/cm^{-1} 2945, 1704, 1631, 1518, 1495, 1454, 1358, 1334, 1243, 1208, 1092, 892, 737, 701; δ_H 1.53 (dtd, 1H, $J = 2.5, 11.6, 13.5$, 9-C*H*H), 1.82 (dddt, 1H, $J = 2.1, 6.0, 11.6, 13.7$, 8-C*H*H), 2.15 (m, 1H, 8-CH*H*), 2.35 (m, 1H, 9-CH*H*), 2.40 (dd, 1H, $J = 4.9, 12.4$, 2-C*H*H), 2.71 (dddd, 1H, $J = 2.1, 5.8, 11.2, 16.8$, 7-C*H*H), 2.92 (dd, 1H, $J = 6.4, 16.8$, 7-CH*H*), 3.08 (dd, 1H, $J = 4.9, 12.4$, 2-CH*H*), 3.12 (d, 1H, $J = 13.3$, PhCH_2), 3.45 (br d, 1H, $J = 10.6$, 9a-C*H*), 3.72 (s, 3H, OCH_3), 4.24 (d, 1H, $J =$ 13.3, PhCH_2), 4.90 (dd, 1H, $J = 4.9, 12.4$, 3-C*H*), 6.86 (s, 1H, 5-C*H*), 7.28–7.31 (m, 10H, Ar–*H*); δ_C 22.3, 22.6 (*C*-8 and *C*-7), 28.1 (*C*-9), 50.6 (O*C*H$_3$), 57.1 (Ph*C*H$_2$), 59.1 (*C*-2), 59.5 (*C*-9a), 60.3 (*C*-3), 114.1 (*C*-6a), 117.1 (*C*-6), 124.3 (*C*-5), 127.2, 127.7, 128.4, 128.5, 128.7, 128.9 (6 × Ar–*C*H), 130.2 (*C*-9b), 138.2, 138.6 (2 × Ar–*C*), 165.8 (*C*O$_2$CH$_3$); *m*/*z* (EI) 387 (MH$^+$, 20%), 359 (27%), 358 (92%), 268 (20%), 267 (100%), 238 (7%), 206 (8%), 91 (100%), 65 (6%). HRMS: (EI) MH$^+$ 387.2069; $C_{25}H_{26}N_2O_2$ requires MH$^+$ 387.2072. Found: C, 76.87; H, 6.66; N, 7.00%; $C_{25}H_{26}N_2O_2 \cdot 0.25$ MeOH requires C, 76.88; H, 6.90; N, 7.10%.

Ethyl (3*R*,9*S*)-1-benzyl-3-phenyl-2,3,7,8,9,9a-hexahydro-1*H*-pyrrolo[1,2,3-*de*]quinoxaline-6-carboxylate (14h). Yellow oil (0.10 g; 30%): $[\alpha]_D^{20}$ +47.12 (*c* 2; DCM); ν_{max} (film)/cm^{-1} 2858, 2362, 2341, 1716, 1699, 1577, 1419, 1359, 1334, 1244, 1197, 1186, 1094, 1064, 853, 701; δ_H1.26 (t, 3H, $J = 7.0$, OCH$_2$CH_3), 1.49 (dtd, 1H, $J = 2.5, 11.6, 13.5$, 9-C*H*H), 1.82 (dddt, 1H, $J = 2.1, 6.0, 11.6, 13.7$, 8-C*H*H), 2.13 (m, 1H, 8-CH*H*), 2.37 (m, 1H, 9-CH*H*), 2.42 (dd, 1H, $J = 4.9, 12.4$, 2-C*H*H), 2.72 (dddd, 1H, $J = 2.1, 5.8, 11.2, 16.8$, 7-C*H*H), 2.94 (dd, 1H, $J = 6.4, 16.8$, 7-CH*H*), 3.09 (dd, 1H, $J = 4.9, 12.4$, 2-CH*H*), 3.16 (d, 1H, $J =$ 13.2, PhC*H*H), 3.45 (br d, 1H, *J* 10.6, 9a-C*H*), 4.21 (q, 2H, $J =$ 7.0, OCH_2CH$_3$ and d, 1H, $J = 13.2$, PhCH*H*), 4.88 (dd, 1H, $J = 4.9, 12.4$, 3-C*H*), 6.87 (s, 1H, 5-C*H*), 7.31–7.35 (m, 10H, Ar–*H*); δ_C 14.5 (OCH$_2$*C*H$_3$), 22.3, 22.5 (*C*-8 and *C*-7), 29.5 (*C*-9), 52.7 (*C*-2), 57.0 (Ph*C*H$_2$), 59.2 (O*C*H$_2$CH$_3$), 59.5 (*C*-9a), 60.3 (*C*-3), 114.7 (*C*-6a), 117.2 (*C*-6), 124.2 (*C*-5), 127.1, 127.6, 128.3, 128.4, 128.7, 128.9 (6 × Ar–*C*H), 130.6 (*C*-9b), 138.2, 128.62 (2 × Ar–*C*), 168.5 (*C*O$_2$CH$_2$CH$_3$); *m*/*z* (EI) 401 (MH$^+$, 23%), 372 (88%), 300 (41%), 281 (100%), 252 (60%), 208 (36%), 206 (44%), 180 (34%), 149 (53%), 91 (100%), 55 (30%), 43 (59%). HRMS: (EI) MH$^+$ 401.2229; $C_{26}H_{28}N_2O_2$ requires MH$^+$ 401.2229.

Ethyl 6-(1-benzyl-4-formyl-3-oxopiperazin-2-yl)hex-2-enoate (15a). Ethyl *E*-8-bromo-2-methyl-7-oxooct-2-enoate (**8e**, 0.78 g; 2.83 mmol) in dry THF (5 ml) was added to a solution of 1-benzyl-4,5-dihydroimidazole (**4a**, 0.38 g; 2.36 mmol) in dry THF (15 ml). The solution was refluxed for 2 h and DBU (0.42 ml; 2.83 mmol) was then added dropwise over 4 h. The mixture was refluxed for a further 4 h, the reaction flask cooled, the solvent removed under reduced pressure and the residue subjected to silica gel column chromatography using ethyl acetate–hexane (10 : 9 *v*/*v*) to yield the title compound as an oil (0.30 g; 34%): ν_{max} (film)/cm^{-1} 2979, 1715, 1693, 1455, 1365, 1335, 1262, 1218, 1161, 1116; δ_H 1.29 (t, 3H, $J = 7.3$, CO$_2$CH$_2$CH_3), 1.52 (m, 1H), 1.76 (m, 1H), 1.82 (s, 3H, CH=C(CH_3)), 1.91 (m, 1H), 2.03 (m, 1H), 2.12 (m, 2H), 2.54 (m, 1H), 3.10 (m, 1H), 3.29 (t, 1H, $J = 5.0$), 3.42 (m, 1H), 3.45 (d, 1H, $J = 13.4$, PhC*H*H), 3.76 (m, 1H), 3.96 (d, 1H, $J = 13.4$, PhCH*H*), 4.18 (q, 2H, $J = 7.3$, CO$_2$CH_2CH$_3$), 6.73 (tq, 1H, $J = 1.3, 6.1$, C*H*=C(CH$_3$)), 7.26 (m, 5H, Ar–*H*), 9.47 (s, 1H); δ_C 12.4, 14.3, 24.0, 28.4, 29.9, 39.8, 44.9, 58.1, 60.5, 65.4, (128.3, 128.6, 128.7 (3 × Ar–C*H*)), 137.2 (Ar–*C*), 141.2, 162.4, 168.1, 173.3; *m*/*z* (EI) 345 (MH$^+$–CO, 100%). HRMS: (CI) MH$^+$ 373.2127; $C_{21}H_{28}N_2O_4$ requires MH$^+$ 373.2126.

1-Benzyl-4-formyl-3-pentylpiperazine-2-one (15b). Prepared as for **15a** using **4a** (0.30 g; 1.89 mmol) and 1-bromoheptan-2-one (**16a**, 0.40 g; 2.08 mmol) and DBU (0.33 ml; 2.26 mmol).

(0.29 g; 56%): ν_{max} (film)/cm^{-1} 1725, 1695, 1228, 1174; δ_H 0.81 (t, 3H, $J = 6.8$), 1.22 (m, 6H), 1.81 (m, 1H), 1.94 (m, 1H), 2.40 (m, 1H), 2.98 (m, 1H), 3.21 (t, 1H, $J = 5.0$), 3.32 (m, 2H), 3.69 (d, 1H, $J = 13.3$, PhC*H*H), 3.88 (d, 1H, $J = 13.3$, PhC*H*H), 7.23–7.28 (m, 5H, Ar–*H*), 9.40 (s, 1H); δ_C (75 MHz) 14.0, 22.5, 24.7, 30.2, 31.7, 39.87, 44.9, 58.0, 65.6, (127.56, 128.5, 128.7 (3 × Ar–*C*H)), 137.4 (Ar–*C*), 162.5, 173.6; *m*/*z* (CI) 289 (MH$^+$, 87%), 261 (MH$^+$–CO, 96%), 106 (100%).

1-Benzyl-4-formyl-3-methylpiperazine-2-one (15c). Prepared as for **15a** using **4a** (0.66 g; 4.12 mmol) and chloroacetone **16b** (0.40 ml; 4.95 mmol).

Orange oil (0.45 g; 47%): ν_{max} (film)/cm^{-1} 1725, 1695, 1455, 1470, 1250; δ_H 1.52 (d, 3H, $J = 4.8$ Hz, NCHCH_3), 2.5 (m, 1H, 5-CH_2), 3.0 (m, 1H, 5-CH_2), 3.35 (q, 1H, $J = 4.8$ Hz, 3-C*H*), 3.38 (d, 1H, $J = 10.6$ Hz, CH_2Ph), 3.42 (m, 1H, 6-CH_2), 3.67 (m, 1H, 6-CH_2), 3.94 (d, 1H, $J = 10.6$ Hz, PhCH_2), 7.28–7.32 (m, 5H, Ar–*H*), 9.44 (s, 1H, NC*H*O); δ_C 15.3 (PhNCH*C*H$_3$), 40.7 (*C*-5), 44.9 (*C*H$_2$Ph), 57.9 (*C*-6), 61.1 (*C*-3), 127.6, 128.4, 128.7 (3 × Ar–*C*H), 137.1 (Ar–*C*), 162.6 (N*C*HO), 173.7 (N*C*OCHN); *m*/*z* (CI) 233 (MH$^+$, 100%), 205 (MH$^+$–CO, 100%). HRMS: (EI) M$^+$ 232.1212; $C_{13}H_{16}N_2O_2$ requires M$^+$ 232.1211.

Ethyl 8-(1-benzyl-4-formyl-3-oxopiperazin-2-yl)oct-2-enoate (15d). Prepared as for **15a** using **4a** (0.22 g; 1.36 mmol) and ethyl *E*-10-bromo-9-oxodec-2-enoate (**8h**, 0.43 g; 1.50 mmol).

(0.12 g; 23%): ν_{max} (film)/cm^{-1} 2935, 1720, 1689, 1266, 1217, 909, 733; δ_H 1.28 (t, 3H, $J = 7.3$, OCH$_2$CH_3), 1.46 (t, 2H, $J =$ 7.3), 1.58 (m, 2H), 1.89 (m, 1H), 2.03 (m, 1H), 2.17 (m, 2H), 2.47 (m, 1H), 3.05 (m, 1H), 3.27 (t, 1H, $J = 5.0$), 3.36 (m, 1H), 3.40 (d, 1H, $J = 13.4$, PhC*H*H), 3.76 (m, 1H), 3.94 (d, 1H, $J = 13.4$, PhCH*H*), 4.18 (q, 2H, $J = 7.3$, OCH_2CH$_3$), 5.80 (dt, 1H, $J = 1.6,$ 15.6, C*H*CO$_2$Et), 6.94 (dt, 1H, $J = 6.9, 15.6$, C*H*=C), 7.32 (m, 5H, Ar–*H*), 9.47 (s, 1H); δ_C14.3, 24.8, 27.8, 28.9, 30.0, 32.0, 39.8, 44.9, 58.1, 60.1, 65.4, 121.4, (127.6, 128.6, 128.7 (3 × Ar–*C*H)), 137.3 (Ar–*C*), 149.0, 162.4, 166.7, 173.5; *m*/*z* (CI) 387 (MH$^+$, 100%), 359 (MH$^+$–CO, 90%). HRMS: (CI) MH$^+$ 387.2287; $C_{22}H_{30}N_2O_4$ requires MH$^+$ 387.2284.

1-Benzyl-4-formyl-2-(4-nitrophenyl)-1,4,5,6-tetrahydropyrazine (17). Prepared as for **15a** using **4a** (0.40 g; 2.50 mmol) and 2-bromo-4′-nitroacetophenone (**16c**, 0.67 g; 2.75 mmol).

Orange oil (0.70 g; 87%): ν_{max} (film)/cm^{-1} 2349, 1683, 1628, 1589, 1515, 1415, 1395, 1343, 1191; δ_H (mixture of rotamers) 3.06 (m, 2H, 6-CH_2 *syn* rotamer), 3.15 (m, 2H, 6-CH_2 *anti* rotamer), 3.30 (m, 2H, 5-CH_2 *anti*), 3.42 (m, 2H, 5-CH_2 of *syn*), 3.81 (s, 2H, PhCH_2 *syn* or *anti*), 3.84 (s, 2H, PhCH_2 *anti* or *syn*), 6.48 (s, 1H, 3-C*H syn*), 6.98 (s, 1H, 3-C*H anti*), 7.21–7.32 (m, 9H, Ar–*H*), 7.66 (m, 2H, ArNO$_2$–*H syn* or *anti*), 7.90 (s, 1H, N=CO*H anti*), 8.17 (m, 2H, ArNO$_2$–*H anti* or *syn*), 8.27 (s,1H, N=CO*H syn*); δ_C 35.2 and 45.2 (*C*-5), 40.2 and 46.2 (*C*-6), 56.3 and 56.6 (Ph*C*H$_2$), 108.6 and 112.2 (*C*-3 *anti* and *syn*), 124.0 (ArNO$_2$–*C*H), 124.1 (ArNO$_2$–*C*H), 126.7 (ArNO$_2$–*C*H), 127.1 (ArNO$_2$–*C*H), 127.7, 127.9, 128.8 (3 × Ar–*C*H)), 137.1 (Ar–*C*), 142.2 (ArNO$_2$–*C*), 143.1 and 147.3 (C-2 *anti* and *syn* rotamer), 147.5 (ArNO$_2$–*C*), 159.3 and 159.9

(N=*C*HO of *anti* and *syn* rotamer); *m*/*z* (EI) 324 (MH^+, 6%), 293 (8%), 174 (8%), 118 (12%), 91 (100%), 65 (28%), 51 (9%). HRMS: (EI) M^+ 323.1268; $C_{18}H_{17}N_3O_3$ requires M^+ 323.1270.

X-Ray crystallography

Data were collected on a Nonius KappaCCD area detector situated at the window of a rotating anode [λ (Mo Kα) = 0.71073 Å].† The structure was solved by direct methods, SHELXS-97, and refined using SHELXL-97.[43] Hydrogen atoms were included in the refinement, but thermal parameters and geometry were constrained to ride on the atom to which they are bonded. The data were corrected for absorption effects using SORTAV.[44]

Crystal data for 11 (R^1 = Ph, R^2 = H, R^3 = Bu^t). $C_{28}H_{34}N_2O_3$, M = 446.57, monoclinic, a = 5.8566(4), b = 22.8548(18), c 9.1424(7) Å, 92.913(6)°, U = 1222.14(16) Å^3, T = 150(2) K, space group $P2_1$, Z = 2, μ(Mo Kα) 0.079 mm^{-1}, 6900 reflections measured, 3346 unique (R_{int} = 0.0585), R = 0.0500. The final $wR(F^2)$ was 0.0842 (all data).

Crystal data for 14b. $C_{20}H_{24}N_2O_2$, M = 324.41, triclinic, a = 5.3447(11), b = 10.854(2), c 14.722(3) Å, α = 81.91(3), 87.82(3), 88.80(3)°, U = 844.8(3) Å, T = 150(2) K, space group P-1, Z = 2, μ(Mo Kα) 0.083 mm^{-1}, 12313 reflections measured, 3729 unique (R_{int} = 0.1814), R = 0.0566. The final $wR(F^2)$ was 0.1507 (all data).

Crystal data for 14d. $C_{25}H_{26}N_2O_2$, M = 386.48, triclinic, a = 11.448(2), b = 11.905(2), c 15.067(3) Å, α = 86.50(3), 87.96(3), 77.45(3)°, U = 2000.1(7) Å^3, T = 150(2) K, space group P-1, Z = 4, μ(Mo Kα) 0.082 mm^{-1}, 17728 reflections measured, 7744 unique (R_{int} = 0.1722), R = 0.0682. The final $wR(F^2)$ was 0.2781 (all data).

Crystal data for 14g. $C_{25}H_{26}N_2O_2$, M = 386.48, monoclinic, a = 10.559(2), b = 9.6567(19), c 11.052(2) Å, β = 112.47(3)°, U = 1041.5(4) Å^3, T = 150(2) K, space group $P2_1$, Z = 2, μ(Mo Kα) 0.078 mm^{-1}, 12212 reflections measured, 4640 unique (R_{int} = 0.0362), R = 0.0373. The final $wR(F^2)$ was 0.0507 (all data).

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