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Metal-catalysed radical cyclisations leading to *N*-heterocycles: new approaches to gabapentin and pulchellalactam

Justin S. Bryans,[a] Nicola E. A. Chessum,[b] Nathalie Huther,[b] Andrew F. Parsons[b,*] and Franco Ghelfi[c]

[a]*Pfizer Global Research and Development, Sandwich, Kent CT13 9NJ, UK*
[b]*Department of Chemistry, University of York, Heslington, York YO10 5DD, UK*
[c]*Dipartimento di Chimica, Universitá degli Studi di Modena e Reggio Emilia, Via Campi 183, I-41100 Modena, Italy*

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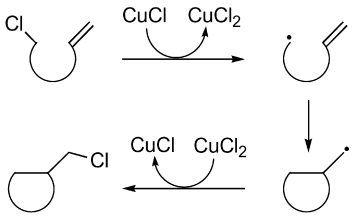
Abstract—The copper(I) or ruthenium(II)-mediated radical cyclisation of halo-amides has been utilised to afford functionalised pyrrolidinones via 5-*endo-trig* or 5-*exo-trig* radical cyclisation pathways. This methodology has been applied to novel and concise syntheses of the anti-epileptic drug gabapentin and the biologically active natural product pulchellalactam.

1. Introduction

The formation of 5-membered nitrogen heterocycles using radical cyclisation reactions has attracted the attention of synthetic chemists for many years. A wide range of *N*-heterocycles have been prepared from unsaturated organohalides using a variety of radical cyclisation methods, the most popular of which involves reductive cyclisation using tributyltin hydride.[1] The high toxicity of organotin derivatives and the difficulty of removing organotin halide derivatives from organic products has recently led to the development of alternative radical reagents to organotin derivatives.

One particularly useful alternative method involves treatment of unsaturated organohalides with copper(I) or ruthenium(II) complexes in atom transfer radical cyclisation (ATRC) reactions.[2] In these oxidative cyclisations, abstraction of a halogen atom by for example, CuCl is followed by radical cyclisation (Scheme 1). The resulting cyclic carbon-centred radical can then abstract a halogen-atom from the $CuCl_2$ to form the cyclic organohalide and CuCl, which can continue the chain reaction. There are a number of attractive features of this approach including the fact that functionalised cyclic products are formed using catalytic amounts of easily recovered and inexpensive metal complexes.

ATRC reactions have been used to prepare a variety of



Scheme 1.

nitrogen heterocycles although most studies have concentrated on the use of 4-*exo-trig* or 5-*exo-trig* radical cyclisation reactions to prepare substituted β-lactams or pyrrolidinones, respectively.[3] More recently, however, attention has turned towards the use of 'disfavoured' 5-*endo-trig* radical cyclisations.[4] Our group and others have shown that haloenamide precursors can undergo cyclisation to form functionalised pyrrolidinones in excellent yield and suitable metal catalysts include copper(I) chloride/bipyridine or dichlorotris-(triphenylphosphine)-ruthenium(II).[5] Following on from these studies we now wish to report for the first time, the application of ATRC reactions to the formal synthesis of gabapentin **1** and the total synthesis of pulchellactam **2** (Fig. 1). The key-step in these syntheses involves an ATRC of a halo-enamide precursor.

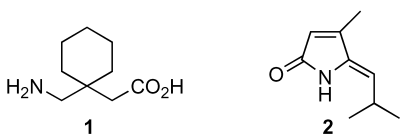


Figure 1.

Keywords: amino acids; cyclisations; nitrogen heterocycles; radical reactions.
* Corresponding author. Tel.: +44-1904-432608; fax: +44-1904-432516; e-mail: afp2@york.ac.uk

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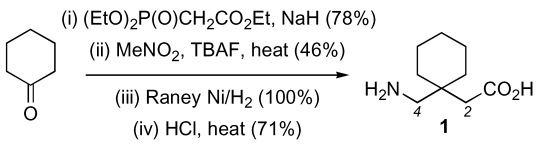
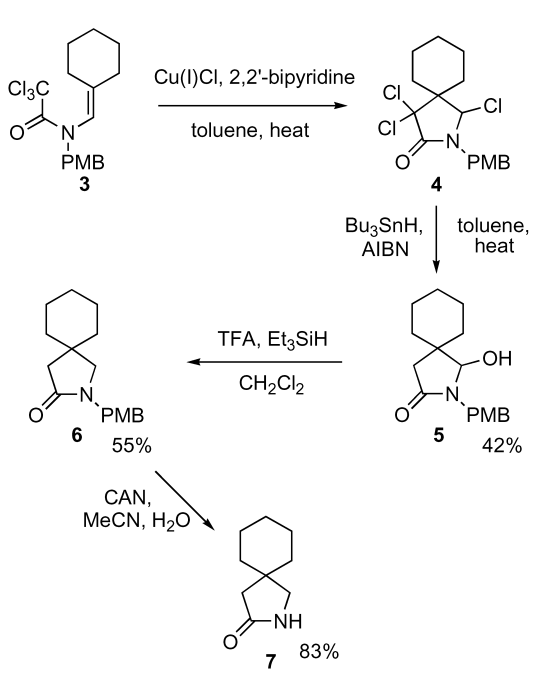
2. Results and discussion

Gabapentin **1**, sold under the name neurontin®, is an anti-epileptic drug marketed by Pfizer. Although originally designed as a lipophilic GABA analogue, it has been shown that it does not interact with any of the enzymes on the GABA metabolic pathway. It also does not directly interact with either the $GABA_A$ or $GABA_B$ receptors.[6] Instead, gabapentin **1** has been shown to bind with high affinity to a binding site of a calcium channel and it is thought that gabapentin **1** exerts its biological activity through interaction at this site.[7] Gabapentin **1** can be prepared from cyclohexanone by the short 4-step sequence shown in Scheme 2.[8] Good yields are observed for each step apart from the Michael-addition step and the overall yield of **1** is 25%. The main problem with this approach is that it cannot be used to access a wide range of analogues. Hence, although a variety of different groups have been introduced at different sites of the cyclohexane ring, it is not easy to introduce substituents at the 2 and 4 positions of **1**.[9] As a consequence, an alternative and potentially more flexible approach to **1** was designed as described below.



Scheme 2.

Initially, trichloro-enamide **3** was prepared (in 15% yield) by reaction of cyclohexane carboxaldehyde with 4-methoxybenzylamine under Dean–Stark conditions followed by immediate *N*-acylation of the crude imine using trichloroacetyl chloride at 0°C (Scheme 3). Enamide **3** was then heated with copper(I) chloride/bipyridine in order to affect the desired 5-*endo-trig* radical cyclisation.[10] This afforded the desired trichlorinated spirocycle **4**, which was



Scheme 3.

prone to hydrolysis on silica and so the crude reaction mixture was filtered through a celite plug to remove the copper complex. Spirocycle **4** was then reacted with tributyltin hydride (3.3 Equiv.) in order to remove all three chlorine atoms. Surprisingly, hydrolysis rather than reduction of the chlorine atom α- to nitrogen occurs to give the hydroxy-pyrrolidinone **5** in a reasonable yield of 42% over the two steps.[11] Hydroxy-pyrrolidinone **5** was also formed when tributyltin hydride (3.3 Equiv.) was added directly to the crude cyclisation product (containing the copper complex).[12] This may be explained by the presence of residual water in the reaction mixture. It should also be noted that hydroxy-pyrrolidinone **5** is formed in moderate yield (26%) on reaction of 3.3 Equiv. of tributyltin hydride with trichloro-enamide **3** and so even under these reducing conditions a chlorine ATRC can take place.[13] The hydroxy group in **5** was however, easily removed using trifluoroacetic acid and triethylsilane[14] to give pyrrolidinone **6** in 55% yield. Finally, oxidative deprotection of the PMB group was achieved using 10 Equiv. of cerium(IV) ammonium nitrate to provide the desired spirocycle **7** in 83% yield. When the number of equivalents of cerium(IV) ammonium nitrate was reduced to 3, some starting material was recovered (13%) and **7** was isolated in a lower yield of 53%. The approach shown in Scheme 2 involves hydrolysis of spirocycle **7** to form the hydrochloride salt of gabapentin **1** (in 71% yield) and so this completes a new formal synthesis of **1**.

The formation of the intermediate trichloride **4** offers a potentially flexible approach to a range of gabapentin **1** analogues. Substitution of the chlorine atoms could allow the selective introduction of a variety of substituents at the 2 and 4 positions of gabapentin **1** (e.g. reaction of the *N*-benzyl analogue of **4** with methanol leads to selective substitution of the chlorine adjacent to the nitrogen, the resulting methoxy derivative is presumably formed via an intermediate *N*-acyl iminium ion[5b]). The convergent nature of the 5-*endo* cyclisation approach also allows the rapid preparation of a range of substituted precursors. For example, reaction of the imine derived from cyclohexane carboxaldehyde and *p*-methoxybenzylamine with 2-bromo-isobutyryl bromide affords bromo-enamide **8** in 64% yield (Fig. 2). Reaction of **8** with tributyltin hydride (added over 5 h) affords pyrrolidinone **9** in 45% yield (together with 46% of the simple reduced product), which on *N*-deprotection gives the dimethylated compound **10** (in 88% yield). Cyclisation of **8** using copper(I) chloride/bipyridine was also successful and spirocycle **9** was isolated after reduction of the intermediate cyclic product using triethylsilane and trifluoroacetic acid (in 11% overall yield from **8**). The copper(I)-mediated cyclisation gave **11** (in 21% yield) as an inseparable mixture with the β-lactam by-product **12** (in

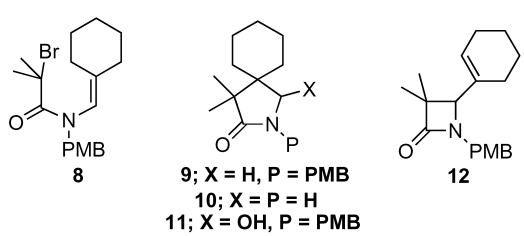
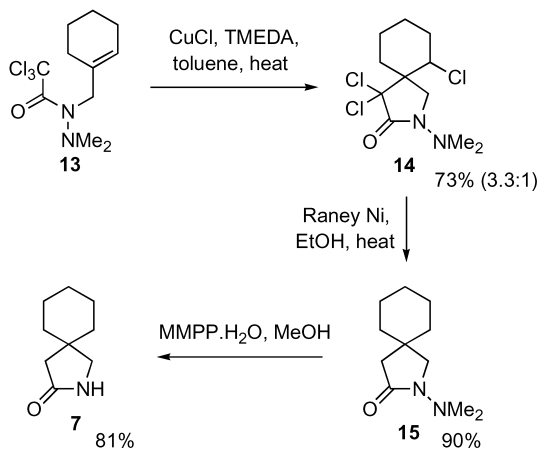


Figure 2.

36% yield), which is derived from a competitive 4-*exo* radical cyclisation[3d,15]—this is not surprising as the 5-*endo* cyclisation requires the formation of two adjacent and sterically hindered quaternary centres in **11**.

Although the 5-*endo* approach offers an alternative strategy to gabapentin **1** and related compounds the overall yield of **1** from the copper(I) catalysed approach (Scheme 3) is only 2% primarily because of the inefficient formation of trichloroenamide **4**. In order to develop a more efficient synthesis of **1**, an alternative 5-*exo* radical cyclisation approach was also investigated as shown in Scheme 4. The key step in this approach involved the radical cyclisation of the cyclohexene derivative **13**, which bears an *N*-dimethylamino protecting group.[3a]

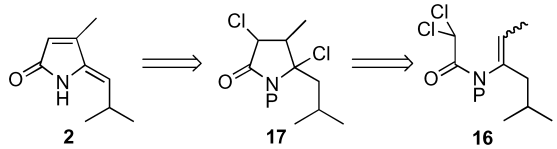


Scheme 4.

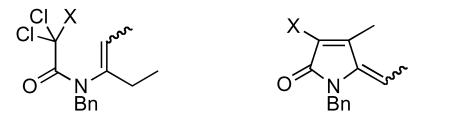
The cyclohexyl precursor **13** was prepared (in 69% yield) from condensation of dimethylhydrazine with cyclohex-1-ene carbaldehyde, followed by reduction of the imine and *N*-acylation of the resulting hydrazine.[16] On treatment of trichloride **13** with copper(I) chloride and TMEDA[3a] the desired spirocycle **14** was formed in 73% yield as a 3.3:1 mixture of separable diastereoisomers.[17] Using bipyridine as the ligand in place of TMEDA resulted in a lower yield of **14** (around 41%) and the formation of reduced by-products. Heating trichloride **14** with Raney nickel at 110°C resulted in the formation of spirocycle **15** in a crude yield of around 90% - there was no evidence for cleavage of the N–N hydrazide bond.[3a] However, the nitrogen protecting group could be efficiently removed on treatment of **15** with magnesium monoperoxyphthalate in methanol.[18] This afforded spirocycle **7** in 81% yield and this completes a second formal synthesis of gabapentin **1**. The overall yield of gabapentin **1** prepared via this 7-step approach is 26%, which is the same yield as that reported for the synthesis shown in Scheme 2. Importantly, this new approach involves the formation of **14**, which has chlorine atoms adjacent to the lactam carbonyl and within the cyclohexane ring. These chlorine atoms could be used to further functionalise the cyclohexane ring and the C-2 position of gabapentin **1**.[19]

Following the successful formation of spirocyclic compounds using copper(I)-mediated ATRC reactions, our attention turned to the use of a similar 5-*endo* cyclisation in the formation of the unsaturated pyrrolidinone pulchellalactam **2**. Pulchellalactam **2** has recently been isolated from the marine fungus *Corallospora pulchella* and is a potent inhibitor of a protein tyrosine phosphatase, CD45, which has an important role in the activation of B and T cells.[20] This makes it a therapeutic target for autoimmune and chronic anti-inflammatory diseases.

Previous work within our group[21] and elsewhere[5] has shown that unsaturated pyrrolidinones can be isolated from some copper(I)- or ruthenium(II)-mediated 5-*endo* ATRC reactions if the intermediate cyclic halides can undergo elimination of HX. As a consequence, it was proposed that on heating the N-protected enamide **16** with a copper(I) or ruthenium(II) complex the intermediate cyclic dichloride **17** would undergo elimination to form the core ring system of pulchellalactam **2** (Scheme 5). Model studies supported this hypothesis as reaction of dichloride **18** (formed in 75% yield as a single unassigned enamide isomer from reaction of 3-pentanone, benzylamine and dichloroacetyl chloride) with copper(I) chloride/bipyridine (1 Equiv.) afforded conjugated dienone **20** in 34% yield as a 1:1 mixture of double bond isomers (Fig. 3). Interestingly, when the same reaction was carried out in the presence of $RuCl_2(PPh_3)_3$ (0.5 Equiv.) dienone **20** was isolated in an excellent 94% yield (as a 1:1 mixture of isomers). Cyclisation of the corresponding trichloroenamide **19** also showed that the use of $RuCl_2(PPh_3)_3$ was more effective than copper(I) chloride/bipyridine, the corresponding chloro-dienone **21** was isolated in 67 and 34% yields, respectively.



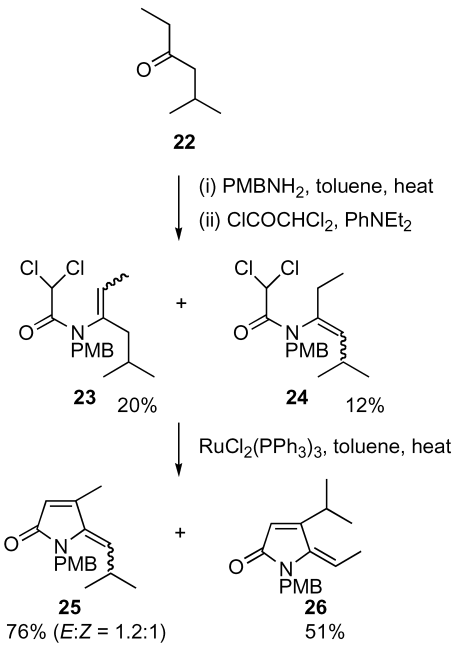
Scheme 5.



18; X = H (*E* or *Z*)
19; X = Cl (*E* or *Z*)
20; X = H (*E*:*Z* = 1:1)
21; X = Cl (*E*:*Z* = 1.2-1:1)

Figure 3.

Our studies towards the synthesis of **2** started with the formation of the precursor dichloro-enamide **23** (Scheme 6). On reaction of ketone **22** with *p*-methoxybenzylamine followed by dichloroacetyl chloride, enamide **23** was formed together with regioisomer **24** as an inseparable mixture (after column chromatography) in a combined yield of 32%. The ^1H NMR spectrum indicated a 1.7:1 ratio of enamides **23**:**24**, respectively and this mixture was then heated with $RuCl_2(PPh_3)_2$ in toluene (under the same conditions as for the model system). Reaction with the Ru(II) catalyst afforded the desired pyrrolidinone **25** as a 1:1.2 mixture of *cis*-:*trans*-isomers in a combined yield of 76% from enamide **23**. The *trans*-pyrrolidinone isomer **26** was also formed from cyclisation of enamide **24** in 51% yield. *N*-Deprotection of the double bond isomers of **25** was



Scheme 6.

then attempted using CAN (under a variety of conditions) but this resulted in the formation of a complicated mixture of products presumably derived from oxidation of the protecting group and the diene. Heating **25** with TFA[22] in chloroform was also unsuccessful and so the synthesis was restarted using an alternative nitrogen protecting group.

The 2,4-dimethoxybenzyl group was chosen as the *N*-protecting group because this particularly electron-rich benzyl group has been shown to be especially susceptible to oxidative deprotection.[23] Hence, reaction of 2,4-dimethoxybenzylamine with ketone **22** followed by dichloroacetyl chloride produced an inseparable 1.5:1 mixture of the enamide regioisomers **27** and **28** respectively, in 32% yield (Fig. 4). On heating this mixture with $RuCl_2(PPh_3)_3$ (0.5 Equiv.) in toluene, enamide **27** gave the desired dienones **29** and **30** in 32 and 41% yield while the alternative enamide **28** gave the cyclic products **31** and **32** (tentatively assigned) in much lower yields of 17 and 14%,

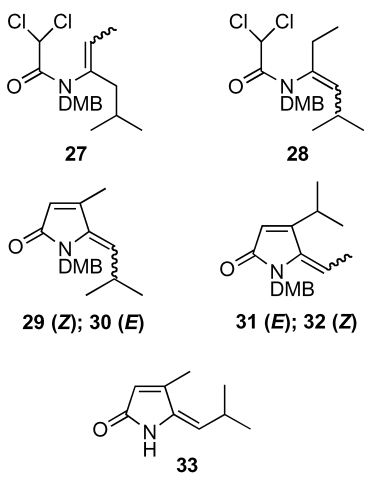


Figure 4.

respectively. Dienones **29** and **30** could be isolated separately on column chromatography and these were subjected to a variety of deprotection conditions. Surprisingly, oxidative deprotection using cerium(IV) ammonium nitrate or alternatively dipotassium hydrogen phosphate and potassium persulfate[23] was unsuccessful and both gave rise to complex reaction mixtures. However, stirring **29** in neat TFA at rt resulted in clean *N*-deprotection and the formation of pulchellalactam **2** in 66% yield. A similar reaction of the *trans*-double bond isomer **30** gave the *trans*-isomer of pulchellalactam, namely compound **33**, in 83% yield. A trace amount (<5%) of pulchellalactam **2** was also observed in the ^{1}H NMR spectrum and this was presumably derived from isomerisation of the double bond in **33**. The spectroscopic data for both **2** and **33** was consistent with that recently reported by Li and co-workers.[24]

Although the overall yield of (*Z*)- and (*E*)-pulchellalactam **2** and **33** is modest (10% from ketone **22**) this represents a very quick and convergent route to **2** and structurally related compounds, which could possess a variety of interesting biological properties. Variation of the ketone precursor followed by enamide formation and then radical cyclisation, under the mild reaction conditions, could therefore be used to rapidly access a range of analogues.

3. Experimental

3.1. General

IR spectra were recorded on an ATI Mattson Genesis FT IR spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on a Jeol EX 270 spectrometer. The carbon spectra were assigned using DEPT experiments. Coupling constants (*J*) were recorded in Hertz to the nearest 0.5 Hz. Mass spectra were recorded on a Fisons Instruments VG Analytical Autospec Mass Spectrometer. Thin layer chromatography (tlc) was performed on Merck aluminium-backed silica gel plates. Compounds were visualised under a UV lamp, using alkaline potassium permanganate solution and/or iodine. Column chromatography was performed using silica gel (Matrix Silica 60, 70–200 μm Fisons or ICN flash silica 60, 32–63 μm).

3.1.1. Representative formation of an enamide precursor: formation of 2,2,2-trichloro-*N*-(cyclohexylidenemethyl)-*N*-(4-methoxybenzyl)acetamide (3). Cyclohexane carboxaldehyde (1.56 g, 1.68 mL, 13.9 mmol) and *p*-methoxybenzylamine (1.97 g, 1.88 mL, 14.4 mmol) were combined in toluene (50 mL) and heated to reflux under nitrogen in a Dean–Stark apparatus overnight. The solvent was then removed in vacuo. The imine residue was re-dissolved in dry toluene (5 mL) and slowly added to a stirring solution of trichloroacetyl chloride (2.88 g, 1.77 mL, 15.84 mmol) in dry toluene (50 mL) at 0°C under nitrogen. The reaction was allowed to stir for 1 h with warming to rt, after which time the reaction was cooled back to 0°C and Et_3N (4.37 g, 6.02 mL, 43.2 mmol) was added. The reaction was allowed to stir for a further 2 h with warming to rt before saturated aqueous Na_2CO_3 (50 mL) was added and the reaction left to stir for 48 h, after which time the aqueous and organic layers were separated and the

aqueous layer extracted with ether (3×50 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo. Column chromatography (silica; 9:1, petroleum ether–EtOAc) gave enamide **3** as a white solid (798 mg, 15%); mp 53–54°C; R_f 0.2 (9:1, petroleum ether–EtOAc); (Found: C, 54.2; N, 3.7; H, 5.4. $C_{17}H_{20}Cl_3NO_2$ requires C, 54.2; N, 3.7; H, 5.4%); ν_{max}/cm^{-1} ($CHCl_3$) 3010 (m), 2937 (s), 2856 (m), 1679 (s, C=O), 1612 (m), 1511 (s), 1252 (s); δ_H (270 MHz, $CDCl_3$) 7.20 (2H, d, J=9.0 Hz, 2×C*H*=COMe, aromatics), 6.85 (2H, d, J=9.0 Hz, 2×C*H*=CCH_2N, aromatics), 6.01 (1H, s, C*H*=C), 4.64 (2H, s, CH_2Ar), 3.78 (3H, s, OCH_3), 2.15–2.00 (4H, m, 2×CH_2-cyclohexane ring), 1.60 (6H, m, 3×CH_2-cyclohexane ring); δ_C (67.5 MHz, $CDCl_3$) 160.6, 159.1 (*C*=O and *C*OMe), 143.5 (*C*=CH), 129.9 (2×*C*H=COMe, aromatics), 128.0 (*C*=CH), 120.1 (N*C*H), 113.8 (2×*C*H=CCH_2N, aromatics), 93.4 (*C*Cl_3), 56.0 (*C*H_2Ar), 55.1 (O*C*H_3), 32.8, 28.7, 27.3 (3×*C*H_2-cyclohexane ring), 26.0 (2×*C*H_2-cyclohexane ring); *m*/*z* (CI, NH_3) 376 ($^{35}M+H^+$, 100%), 342 (10), 306 (60), 272 (10), 215 (7), 121 (100), 35 (7); HRMS found 376.0637. $C_{17}H_{20}Cl_3NO_2$ requires for ^{35}MH, 376.0638.

3.1.2. Representative copper(I)-mediated cyclisation of an enamide: formation of 1,4,4-trichloro-2-(4-methoxybenzyl)-2-azaspiro[4.5]decan-3-one (4). Copper(I) chloride (28 mg, 0.28 mmol) and 2,2′-bipyridine (44 mg, 0.28 mmol) were added to a stirred solution of enamide **3** (211 mg, 0.56 mmol) in dry, degassed toluene (6 mL) under nitrogen. The mixture was heated to reflux for 11 h, after which time the solvent was removed in vacuo. The sample was then dissolved in toluene and filtered through celite to remove the catalyst complex, which afforded crude **4** (0.21 g) as a brown semi-solid and this was used directly in the subsequent reaction. R_f 0.1 (dichloromethane); ν_{max}/cm^{-1} (CH_3Cl) 3019 (m), 2935 (s), 2859 (m), 1787 (w), 1727 (s, C=O), 1612 (m), 1513 (m), 1247 (s), 1084 (m), 1033 (m); δ_H (270 MHz, $CDCl_3$) 7.28–7.14 (2H, m, 2×C*H*=COMe, aromatics), 6.92–6.80 (2×C*H*=CCH_2N, aromatics), 4.92 (1H, d, J=14.5 Hz, CH_AH_BAr), 4.77 (1H, s, C*H*Cl), 4.14 (1H, d, J=14.5 Hz, CH_AH_BAr), 3.78 (3H, s, OCH_3), 2.58–2.22 (1H, m, cyclohexane ring), 2.10–0.90 (9H, m, cyclohexane ring); δ_C (67.5 MHz, $CDCl_3$) 166.2 (*C*=O), 159.3 (*C*OMe), 130.0 (2×*C*H=COMe, aromatics), 128.1 (*C*=CH, aromatic), 114.1 (2×*C*H=CH_2N, aromatics), 91.2 (*C*Cl_2), 83.0 (*C*HCl), 55.2 (O*C*H_3), 50.0 (*C*CCl_2), 44.6 (*C*H_2Ar), 32.6, 26.1, 25.1, 22.1, 21.5 (5×*C*H_2-cyclohexane ring); *m*/*z* (CI, NH_3) 393 ($^{35}M+NH_4^+$, 15%), 375 (15), 358 (30), 324 (65), 306 (100), 272 (95), 121 (90); HRMS found 393.0903. $C_{17}H_{20}Cl_3NO_2$ requires for $^{35}M+NH_4$, 393.0899.

3.1.3. Representative tributyltin hydride-mediated reduction: formation of 1-hydroxy-2-(4-methoxybenzyl)-2-azaspiro[4.5]decan-3-one (5). Bu_3SnH (0.54 g, 0.50 mL, 1.85 mmol) and AIBN (28 mg, 0.17 mmol) were added to a stirred solution of γ-lactam **4** (0.21 g, 0.56 mmol) in dry, degassed toluene (20 mL) under nitrogen. The reaction was heated to reflux for 0.75 h, after which time the solvent was removed in vacuo. The resultant residue was re-dissolved in diethyl ether (20 mL) and stirred vigorously with an aqueous potassium fluoride solution (10% by weight, 20 mL) overnight. The organic and aqueous layers were then separated and the organic layer washed with water (20 mL), brine (20 mL), dried ($MgSO_4$) and concentrated in vacuo. Column chromatography (silica; 3:1, petroleum ether–EtOAc) gave the product **5** (68 mg, 42%) as a yellow oil. R_f 0.2 (2:1 petroleum ether–EtOAc); ν_{max}/cm^{-1} (CH_3Cl) 3588 (w, OH), 3027 (m), 2933 (m), 2856 (m), 1686 (s, C=O), 1612 (w), 1513 (s), 1451 (m), 1246 (s), 1033 (m); δ_H (270 MHz, $CDCl_3$) 7.25–7.10 (2H, m, 2×C*H*=COMe, aromatics), 6.90–6.85 (2H, m, 2×C*H*=CCH_2N, aromatics), 4.81 (1H, d, J=15.0 Hz, CH_AH_BAr), 4.51 (1H, s, C*H*OH), 4.01 (1H, d, J=15.0 Hz, CH_AH_BAr), 3.75 (3H, s, OCH_3), 2.35 (1H, d, J=17.0 Hz, CH_AH_BCO), 2.22 (1H, d, J=17.0 Hz, CH_AH_BCO), 1.90–1.10 (10H, m, 5×CH_2-cyclohexane ring); δ_C (67.5 MHz, $CDCl_3$) 174.5 (*C*=O), 158.8 (*C*OMe), 129.4 (2×*C*HCOMe, aromatics), 128.6 (*C*=CH, aromatic), 113.9 (2×*C*H=CCH_2N, aromatics), 88.6 (*C*HOH), 55.2 (O*C*H_3), 42.9 (*C*H_2Ar), 40.9 (*C*H_2CO), 40.4 (*C*CHOH), 35.1, 31.5, 25.6, 22.8, 22.1 (5×*C*H_2-cyclohexane ring); *m*/*z* (CI, NH_3) 290 (M+H^+, 100%), 272 (100), 152 (17), 136 (7), 121 (20); HRMS found 290.1748. $C_{17}H_{23}NO_3$ requires for MH, 290.1756.

3.1.4. 2-(4-Methoxybenzyl)-2-azaspiro[4.5]decan-3-one (6). Triethylsilane (1 mL) and trifluoroacetic acid (1 mL) were added to a stirred solution of alcohol **5** (68 mg, 0.23 mmol) in anhydrous dichloromethane (1 mL) at rt under nitrogen. The reaction was allowed to stir for 0.5 h, after which time the reaction was diluted with dichloromethane (15 mL) and washed with water (15 mL). The organic layer was dried ($MgSO_4$) and concentrated in vacuo. Column chromatography (silica; 1:1 petroleum ether–EtOAc) afforded the required product **6** (34 mg, 55%) as a colourless oil. R_f 0.2 (1:1 petroleum ether–EtOAc); ν_{max}/cm^{-1} (thin film) 2925 (s), 2850 (m), 1685 (s, C=O), 1511 (m), 1245 (s), 1033 (m); δ_H (270 MHz, $CDCl_3$) 7.16 (2H, d, J=9.0 Hz, 2×C*H*=COMe, aromatics), 6.84 (2H, d, J=9.0 Hz, 2×C*H*=CH_2N, aromatics), 4.36 (2H, s, CH_2Ar), 3.79 (3H, s, OCH_3), 2.69 (2H, s, CH_2N), 2.28 (2H, s, CH_2CO), 1.60–1.40 (10H, m, 5×CH_2-cyclohexane ring); δ_C (67.5 MHz, $CDCl_3$) 173.9 (*C*=O), 158.9 (*C*OMe), 129.4 (2×*C*H=COMe, aromatics), 128.6 (*C*=CH, aromatic), 113.9 (2×*C*H=CH_2N, aromatics), 57.9 (*C*H_2Ar), 55.2 (O*C*H_3), 45.8 (*C*H_2N), 44.1 (*C*H_2CO), 36.8 (2×*C*H_2-cyclohexane ring), 36.0 (*C*$(CH_2)_4$), 25.5 (1×*C*H_2-cyclohexane ring), 22.7 (2×*C*H_2-cyclohexane ring); *m*/*z* (CI, NH_3) 274 (M+H^+, 100%), 166 (5), 121 (25), 49 (7); HRMS found 274.1808. $C_{17}H_{23}NO_2$ requires for MH, 274.1807.

3.1.5. 2-Azaspiro[4.5]decan-3-one (7). Cerium(IV) ammonium nitrate (0.60 g, 1.1 mmol) was added to a solution of lactam **6** (30 mg, 0.11 mmol) in acetonitrile (5 mL) and water (1 mL). The reaction was left to stir at rt overnight and the aqueous layer was diluted with brine (15 mL) and the aqueous and organic layers separated. The aqueous layer was then extracted with EtOAc (3×30 mL), the combined organic layer was dried ($MgSO_4$) and concentrated in vacuo. Column chromatography (silica; diethyl ether) afforded product **7**[8] (14 mg, 83%) as an oil. R_f 0.1 (diethyl ether); ν_{max}/cm^{-1} (CH_3Cl) 3228 (w, NH), 2925 (m), 2854 (w), 1697 (s, C=O), 1450 (w), 1313 (w), 1251 (w), 1068 (w); δ_H (270 MHz, $CDCl_3$) 5.80 (1H, br s, N*H*), 3.16 (2H, s, CH_2N), 2.19 (2H, s, CH_2CO), 1.62–1.37 (10H,

m, 5×CH_2-cyclohexane ring); *m*/*z* (CI, NH_3) 154 ($M+H^+$, 100%); HRMS found 154.1232. $C_9H_{15}NO$ requires for MH, 154.1231.

3.1.6. *N*-Benzyl-2-bromo-*N*-(cyclohexylidenemethyl)-2-methylpropanamide (8). Following the same procedure as for the preparation of **3**, cyclohexane carboxaldehyde (1.56 g, 1.68 mL, 13.9 mmol), *p*-methoxybenzylamine (1.97 g, 1.88 mL, 14.4 mmol) and 2-bromoisobutyryl bromide (2.88 g, 1.96 mL, 15.8 mmol) were reacted to give enamide **8** as a yellow oil (3.52 g, 64%). R_f 0.2 (9:1 petroleum ether–EtOAc); ν_{max}/cm^{-1} (thin film) 2929 (s), 2854 (m), 1637 (s, C=O), 1511 (m), 1245 (m), 1174 (m), 1108 (m), 1035 (m); δ_H (270 MHz, $CDCl_3$) 7.18 (2H, d, *J*=9.0 Hz, 2×C*H*=COMe, aromatics), 6.84 (2H, d, *J*=9.0 Hz, 2×C*H*=CCH_2N, aromatics), 6.25 (1H, s, C=C*H*), 4.61 (2H, s, CH_2Ar), 3.79 (3H, s, OCH_3), 2.15–2.00 (4H, m, 2×CH_2-cyclohexane ring), 1.97 (6H, s, 2×CH_3), 1.65–1.40 (6H, m, 3×CH_2-cyclohexane ring); δ_C (67.5 MHz, $CDCl_3$) 170.4 (*C*=O), 158.7 (*C*OMe), 141.0 (*C*=CH), 129.4, 129.3 (*C*=CH and 2×*C*H=COMe, aromatics), 122.6 (C=*C*H), 113.7 (2×*C*H=CCH_2N, aromatics), 58.5 (*C*BrMe_2), 55.1 (OCH_3), 54.3 (*C*H_2N), 32.8 (*C*H_2-cyclohexane ring), 32.3 (2×*C*H_3), 28.5, 27.4, 26.2, 26.0 (4×*C*H_2-cyclohexane ring); *m*/*z* (CI, NH_3) 382 ($^{81}M+H^+$, 50%), 380 ($^{79}M+H^+$, 50), 300 (33), 121 (100); HRMS found 380.1225. $C_{19}H_{26}BrNO_2$ requires for ^{79}MH, 380.1231.

3.1.7. Tributyltin hydride-mediated cyclisation of enamide (8): preparation of 2-(4-methoxybenzyl)-4,4-dimethyl-2-azaspiro[4.5]decan-3-one (9). A solution (0.014 M) of tributyltin hydride (215 mg, 0.20 mL, 0.74 mmol) and AIBN (11 mg, 0.07 mmol) in dry, degassed toluene (53 mL) was slowly added (over 5 h) to a stirred, refluxing solution (0.024 M) of enamide **8** (253 mg, 0.67 mmol) in dry degassed toluene (28 mL) under nitrogen. Following the same workup procedure as for the preparation of **5** afforded *N*-benzyl-*N*-(cyclohexylidenemethyl)-2-methylpropanamide (92 mg, 46%) as a colourless oil and γ-lactam **9** (90 mg, 45%) as a colourless oil after column chromatography. γ-Lactam **9**: R_f 0.2 (1:1 petroleum ether–EtOAc); ν_{max}/cm^{-1} (CH_3Cl) 2932 (s), 2852 (s), 1681 (s, C=O), 1512 (s), 1445 (m), 1247 (s); δ_H (270 MHz, $CDCl_3$) 7.13 (2H, d, *J*=7.0 Hz, 2×C*H*=COMe, aromatics), 6.85 (2H, d, *J*=7.0 Hz, 2×C*H*=CCH_2N, aromatics), 4.37 (2H, s, CH_2Ar), 3.79 (3H, s, OCH_3), 2.97 (2H, s, CH_2N), 1.70–0.90 (10H, m, 5×CH_2-cyclohexane ring), 0.98 (6H, s, 2×CH_3); δ_C (67.5 MHz, $CDCl_3$) 180.0 (*C*=O), 159.0 (*C*OMe), 129.5 (2×*C*H=COMe, aromatics), 129.0 (*C*=CH, aromatic), 114.0 (2×*C*H=CCH_2N, aromatics), 55.2 (O*C*H_3), 51.3 (*C*H_2Ar), 47.5 (*C*Me_2), 46.2 (*C*H_2N), 42.1 (*C*CMe_2), 33.6 (2×*C*H_2-cyclohexane ring), 26.0 (*C*H_2-cyclohexane ring), 23.0 (2×*C*H_2-cyclohexane ring), 19.6 (2×*C*H_3); *m*/*z* (CI, NH_3) 302 ($M+H^+$, 100%); HRMS found 302.2114. $C_{19}H_{28}NO_2$ requires for MH, 302.2115.

3.1.8. 4,4-Dimethyl-2-azaspiro[4.5]decan-3-one (10). According to the procedure described for the deprotection of **6**, the reaction of cerium(IV) ammonium nitrate (1.59 g, 2.9 mmol) with γ-lactam **9** (87 mg, 0.29 mmol) in MeCN/H_2O (5:1, 18 mL) gave **10** (46 mg, 88%) as a white solid; mp 102–103°C; R_f 0.2 (EtOAc); ν_{max}/cm^{-1} ($CHCl_3$) 3441 (m, NH), 3013 (m), 2938 (m), 2857 (m), 1694 (s, C=O), 1490 (m), 1448 (m), 1313 (w), 970 (m), 674 (m); δ_H (270 MHz, $CDCl_3$) 6.67 (1H, br s, N*H*), 3.19 (2H, s, CH_2N), 1.71–1.50 (5H, m, CH_2-cyclohexane ring), 1.30–1.10 (5H, m, CH_2-cyclohexane ring), 0.98 (6H, s, 2×CH_3); δ_C (67.5 MHz, $CDCl_3$) 183.5 (*C*=O), 46.8 (*C*H_2N), 46.1 (*C*Me_2), 44.3 (*C*CMe_2), 30.3 (2×*C*H_2-cyclohexane ring), 26.3 (*C*H_2-cyclohexane ring), 23.1 (2×*C*H_2-cyclohexane ring), 19.5 (2×*C*H_3); *m*/*z* (CI, NH_3) 182 ($M+H^+$, 100%); HRMS found 182.1540. $C_{11}H_{19}NO$ requires for MH, 182.1544.

3.1.9. Copper(I)-mediated cyclisation of enamide (8). Following the procedure used for the formation of **4**, copper(I) chloride (37 mg, 0.37 mmol) and 2,2′-bipyridine (58 mg, 0.37 mmol) were heated with enamide **8** (280 mg, 0.74 mmol) in toluene (7 mL) for 27 h. Column chromatography (silica; 2:1 petroleum ether–EtOAc) afforded an inseparable mixture of **11** (50 mg, 21%) and **12** (43 mg, 36%) as an oil. 1-Hydroxy-2-(4-methoxybenzyl)-4,4-dimethyl-2-azaspiro[4.5]decan-3-one **11**. The presence of this compound was indicated by ^{1}H NMR spectroscopy and mass spectrometry; R_f 0.3 (2:1 petroleum ether–EtOAc); δ_H (270 MHz, $CDCl_3$) 7.20 (2H, d, *J*=8.5 Hz, 2×C*H*=COMe, aromatics), 6.83 (2H, d, *J*=8.5 Hz, 2×C*H*=CCH_2N, aromatics), 4.83 (1H, s, C*H*OH), 4.77 (1H, d, *J*=14.5 Hz, CH_AH_BN), 4.18 (1H, d, *J*=14.5 Hz, CH_AH_BN), 3.78 (3H, s, OCH_3), 2.02–1.88 (2H, m, CH_2-cyclohexane ring), 1.20 (3H, s, CH_3), 0.98 (3H, s, CH_3), 1.80–1.05 (8H, m, 4×CH_2-cyclohexane ring); *m*/*z* (CI, NH_3) 318 ($M+H^+$, 33%). 4-Cyclohexyl-1-(4-methoxybenzyl)-3,3-dimethylazetidin-2-one **12**. The presence of this compound was indicated by ^{1}H NMR spectroscopy and mass spectrometry; R_f 0.3 (2:1 petroleum ether–EtOAc); δ_H (270 MHz, $CDCl_3$) 7.15 (2H, d, *J*=9.0 Hz, 2×C*H*=COMe, aromatics), 6.85 (2H, d, *J*=9.0 Hz, 2×C*H*=CCH_2N, aromatics), 5.56 (1H, br s, C=C*H*), 4.76 (1H, d, *J*=15.0 Hz, CH_AH_BN), 3.79 (1H, d, *J*=15.0 Hz, CH_AH_BN), 3.79 (3H, s, OCH_3), 3.32 (1H, s, C*H*N), 2.14–2.03 (2H, m, CH_2-cyclohexane ring), 1.86–1.49 (6H, m, 3×CH_2-cyclohexane ring), 1.23 (3H, s, CH_3), 1.04 (3H, s, CH_3); *m*/*z* (CI, NH_3) 300 ($M+H^+$, 100%), 136 (46), 121 (63).

3.1.10. Copper(I)-mediated cyclisation of enamide (8) followed by reduction using triethylsilane. Following the procedure used for the formation of **4**, copper(I) chloride (59 mg, 0.60 mmol) and 2,2′-bipyridine (94 mg, 0.60 mmol) were heated with enamide **8** (398 mg, 1.05 mmol) in toluene for 6 days. The crude product was filtered through celite, the solvent evaporated and dichloromethane (4 mL) followed by triethylsilane (4 mL) and trifluoroacetic acid (4 mL) added. After stirring at rt for 2.5 h, further dichloromethane (20 mL) was added and the mixture was washed with water (20 mL) and then brine (20 mL). The organic phase was dried ($MgSO_4$), evaporated and column chromatography (silica; 19:1, petroleum ether–EtOAc) gave **11** (37 mg, 11%) as a colourless oil.

3.1.11. *N*-Cyclohex-1-enylmethyl-*N*′,*N*′-dimethylhydrazine, trichloroacetylated (13). Dimethylamino-borane (0.094 g, 1.6 mmol) and 1-cyclohexen-1-carboxaldehyde *N*,*N*-dimethylhydrazone (0.152 g, 1 mmol), obtained quantitatively by condensation of dimethylhydrazine with

cyclohex-1-ene carbaldehyde,[16] were weighed in a screw capped Schlenk tube equipped with a septum. Then, under argon and at 0°C, diethyl ether (2 mL) and a solution of anhydrous *p*-toluenesulfonic acid (1.033 g, 6 mmol) in diethyl ether (2 mL), both cooled to 0°C, were added. After 3 h, the reaction mixture was quenched with Na_2CO_3 (10% w/v, 6 mL), under an inert atmosphere. The organic phase (ether) was cannulated into another Schlenk tube, evaporated and dichloromethane (2 mL) added. After cooling to 0°C, triethylamine (0.12 g, 0.17 mL, 1.2 mmol) and trichloroacetyl chloride (0.20 g, 0.12 mL, 1.1 mmol) were introduced. After overnight stirring, the mixture was diluted with NaOH (5% w/v, 6 mL), and extracted with dichloromethane. The combined organic layers were dried over $MgSO_4$ and concentrated. Column chromatography of the crude product on silica gel, using a petroleum ether/diethyl ether gradient, gave 0.23 g of a yellow semi-solid. This product was an 89/11 mixture of **13** (69%) and trichloroacetylated *N*-[(cyclohexyl)-methyl]-*N*′,*N*′-dimethyl-hydrazine (8%) as indicated by the ^{1}H NMR spectrum. R_f 0.4 (5:1 petroleum ether–EtOAc); ν_{max}/cm^{-1} (thin film) 2927 (s), 2859 (m), 2834 (m), 1690 (s, C=O), 1457 (m), 1400 (m), 1269 (m), 1152 (m), 1111 (m); δ_H (270 MHz, $CDCl_3$) 5.57 (1H, app. quin., *J*=2.0 Hz, C*H*=C), 3.97 (2H, s, CH_2N), 2.64 (6H, s, 2×CH_3), 1.60–1.40 (4H, m, 2×CH_2-cyclohexane ring), 1.75–1.45 (4H, m, 2×CH_2-cyclohexane ring); δ_C (67.5 MHz, $CDCl_3$) 187.1 (*C*=O), 162.4 (*C*=CH), 133.7 (*C*Cl_3), 123.8 (C=*C*H), 47.0 (*C*H_2N), 44.6 (2×*C*H_3), 26.5, 25.6, 23.1, 22.8 (4×*C*H_2-cyclohexane ring); *m*/*z* (CI, NH_3) 299 (^{35}M+H$^+$, 98%), 265 (20), 95 (30); HRMS found 299.0485. $C_{11}H_{17}Cl_3N_2O$ requires for ^{35}MH, 299.0485.

3.1.12. 4,4,6-Trichloro-2-(dimethylamino)-2-azaspiro-[4.5]decan-3-one (14). Copper(I) chloride (7 mg, 0.07 mmol) and TMEDA (0.02 mL, 0.14 mmol) were added to a solution of enamide **13** (204 mg, 0.68 mmol) in dry, degassed toluene (7 mL) under nitrogen. The reaction was heated to 60°C for 24 h, after which time the solvent was removed in vacuo. Column chromatography (silica; 1:1 pentane–EtOAc) gave product **14** (150 mg, 73%) as a 3.3:1 mixture of diastereomers. Major diastereoisomer; white solid; mp 76–77°C; R_f 0.6 (1:1 pentane–EtOAc); ν_{max}/cm^{-1} (thin film) 2943 (m), 2863 (m), 2785 (w), 1732 (s, C=O), 1447 (m), 1402 (m), 1282 (m), 921 (m), 851 (m); δ_H (270 MHz, $CDCl_3$) 4.28 (1H, dd, *J*=11.5, 4.0 Hz, C*H*Cl), 3.60 (1H, d, *J*=10.0 Hz, CH_AH_BN), 3.26 (1H, d, *J*=10.0 Hz, CH$_A$*H*$_B$N), 2.74 (6H, s, 2×CH_3), 2.39 (1H, br dq, *J*=14.0, 3.5 Hz, C*H*-cyclohexyl-ring), 2.32–2.20 (1H, m, C*H*-cyclohexyl ring), 1.97–1.75 (3H, m, C*H*-cyclohexyl ring), 1.59 (1H, td, *J*=13.5, 3.5 Hz, C*H*-cyclohexyl ring), 1.49–1.09 (2H, m, C*H*-cyclohexyl-ring); δ_C (67.5 MHz, $CDCl_3$) 164.2 (*C*=O), 91.4 (*C*Cl_2), 63.6 (*C*HCl), 50.3 (*C*CCl_2), 46.9 (*C*H_2N), 42.7 (2×*C*H_3), 34.6, 32.9, 25.6, 22.0 (4×*C*H_2-cyclohexyl ring); *m*/*z* (CI, NH_3) 317 (^{35}M+NH_4^+, 40%), 299 (^{35}M+H$^+$, 100); HRMS found 299.0479. $C_{11}H_{17}Cl_3N_2O$ requires for ^{35}MH, 299.0479. Minor diastereoisomer; semi-solid; R_f 0.1 (1:1 pentane–EtOAc); ν_{max}/cm^{-1} (thin film) 2923 (s), 2853 (m), 1720 (s, C=O), 1650 (w), 1449 (m), 1320 (m), 963 (m), 816 (w); δ_H (270 MHz, $CDCl_3$) 4.19 (1H, dd, *J*=12.0, 4.0 Hz, C*H*Cl), 3.91 (1H, d, *J*=11.0 Hz, CH_AH_BN), 3.46 (1H, d, *J*=11.0 Hz, CH$_A$*H*$_B$N), 2.85 (6H, s, 2×CH_3), 2.25–2.15 (1H, m, C*H*-cyclohexane ring), 1.89–1.16 (5H, m, CH_2-cyclohexane ring), 0.94–0.77 (2H, m, CH_2-cyclohexane ring); δ_C (67.5 MHz, $CDCl_3$) 157.6 (*C*=O), 77.8 (*C*Cl_2), 62.0 (*C*HCl), 50.6 (*C*CCl_2), 46.5 (*C*H_2N), 43.7 (2×*C*H_3), 34.2, 33.8, 30.3, 25.6 (4×*C*H_2-cyclohexane ring); *m*/*z* (CI, NH_3) 299 (^{35}M+H$^+$, 5%), 277 (30), 262 (80), 245 (100).

3.1.13. 2-(Dimethylamino)-2-azaspiro[4.5]decan-3-one (15). Wet Raney nickel (2.3 g) was added to a solution of lactam **14** (88 mg, 0.3 mmol) in ethanol (10 mL) and the mixture was heated to reflux overnight. The reaction was filtered through celite to remove the nickel catalyst and concentrated in vacuo. A ^{1}H NMR spectrum of the crude product suggested **15** was formed in around 90% yield and this was immediately reacted with MMPP·H_2O. A pure sample of **15** could be obtained by filtration of the crude product through a silica plug (19:1 diethyl ether–methanol); oil; R_f 0.2 (19:1 diethyl ether–methanol); ν_{max}/cm^{-1} (CH_3Cl) 2981 (m), 2928 (m), 2857 (m), 1691 (s, C=O), 1452 (m) 1248 (m); δ_H (270 MHz, $CDCl_3$) 3.13 (2H, s, CH_2N), 2.60 (6H, s, 2×CH_3), 2.15 (2H, s, CH_2CO), 1.44 (10H, app br s, 5×CH_2-cyclohexyl ring); δ_C (67.5 MHz, $CDCl_3$) 172.5 (*C*=O), 51.2 (*C*H_2N), 43.9 (2×*C*H_3), 37.4 (*C*H_2CO), 35.5 (*C*CH_2), 26.1 (2×*C*H_2-cyclohexyl ring), 23.2 (3×*C*H_2-cyclohexyl ring); *m*/*z* (CI, NH_3) 197 (M+H$^+$, 100%); HRMS found 197.1654. $C_{11}H_{20}N_2O$ requires for MH, 197.1654.

3.1.14. Deprotection of hydrazide (15) using MMPP. Magnesium monoperoxyphthalate hexahydrate (0.46 g, 0.93 mmol) was added to a solution of hydrazide **15** (62 mg, 0.31 mmol) in methanol (0.8 mL) and the reaction was allowed to stir at rt for 3 h. The solvent was removed in vacuo and the resulting residue re-dissolved in ethyl acetate (20 mL). The organic layer was washed with water (15 mL), brine (15 mL) and dried ($MgSO_4$). Column chromatography (silica; diethyl ether) gave **7** as an oil (39 mg, 81%).

3.1.15. (*E* or *Z*)-3-(*N*-Benzyl-2,2-dichloroethanamido)-pent-2-ene (18). The same procedure as for the synthesis of **19** was used, but at 0°C dichloroacetyl chloride (0.98 mL, 10.23 mmol) then *N*,*N*-diethylaniline (1.63 mL, 10.23 mmol) were added. After 3 h, the mixture was worked-up and purified by column chromatography (silica, petroleum ether–ethyl acetate, 20:1) to afford **18** (2.00 g, 75%) as a yellow gum; R_f 0.3 (petroleum ether–ethyl acetate, 20:1); ν_{max} (thin film) 2973 (m), 1679 (s, C=O), 1455 (w), 1401 (m), 1204 (w), 806 (m), 757 (m), 699 (m), 469 (vs) cm^{-1}; δ_H (270 MHz, $CDCl_3$) 7.39–7.23 (5H, m, aromatics), 6.39 (1H, s, C*H*Cl_2), 5.23 (1H, q, *J*=7 Hz, C*H*CH_3), 4.61 (2H, s, CH_2Ph), 2.31 (2H, q, *J*=7.5 Hz, CH_2CH$_3$), 1.59 (3H, d, *J*=7 Hz, CHCH_3), 1.01 (3H, t, *J*=7.5, CH$_2$CH_3); δ_C (67.5 MHz, $CDCl_3$) 164.2 (N*C*O), 138.8 (*C*=CHCH$_3$), 135.8 (C=*C*HCH$_3$), 127.8 (*C*=CH), 127.9, 127.4, 126.8 (5×*C*H=C), 63.9 (*C*HCl_2), 49.4 (*C*H_2Ph), 21.2 (*C*H_2CH$_3$), 12.5 (*C*H$_3$CH), 11.2 (*C*H$_3$CH$_2$); *m*/*z* (CI, NH_3) 303 (^{35}M+NH_4^+, 47%), 286 (^{35}M+H$^+$, 100), 250 (93), 216 (46), 200 (6), 174 (8), 108 (7), 91 (15); HRMS found 286.0763. $C_{14}H_{17}Cl_2NO$ requires for ^{35}MH, 286.0765.

3.1.16. (*E* or *Z*)-3-(*N*-Benzyl-2,2,2-trichloroethanamido)-pent-2-ene (19). A solution of benzylamine (1.00 g,

9.3 mmol) and pentan-3-one (0.8 g, 9.3 mmol) in toluene (45 mL) with a catalytic amount of *p*-toluenesulfonic acid (10 mg) was refluxed in a Dean–Stark apparatus for 15 h. The reaction was cooled to 0°C and trichloroacetyl chloride (1.14 mL, 10.23 mmol) followed by triethylamine (1.68 mL, 10.23 mmol) was added dropwise. After 2 h, the solvent was removed in vacuo and the residue was worked-up as described in the representative procedure for **3**. The crude product was purified by column chromatography (silica, petroleum ether–ethyl acetate, 20:1) to afford **19** (3.67 g, 62%) as a yellow oil; R_f 0.3 (petroleum ether–ethyl acetate, 20:1); ν_{max} ($CHCl_3$) 2975 (m), 1665 (s, C=O), 1495 (w), 1454 (m), 1433 (w), 1393 (s), 1355 (w), 1275 (w), 1243 (m), 824 (s), 739 (w), 700 (m) cm^{-1}; δ_H (270 MHz, toluene-d_8, 80°C) 7.34–7.12 (5H, m, aromatics), 5.42 (1H, q, J=7 Hz, C*H*CH_3), 4.83 (2H, s, CH_2Ph), 2.31 (2H, q, J=7.5 Hz, CH_2CH_3), 1.52 (3H, d, J=7 Hz, CHCH_3), 1.12 (3H, t, J=7.5 Hz, CH_2CH_3); δ_C (67.5 MHz, $CDCl_3$) 160.2 (N*C*O), 138.2 (*C*=CHCH$_3$), 135.3 (C=*C*HCH$_3$), 128.7 (*C*=CH), 127.8, 127.3, 126.9 (5×*C*H=C), 92.9 (*C*Cl$_3$), 53.4 (*C*H$_2$Ph), 24.2 (*C*H$_2$CH$_3$), 12.4 (*C*H$_3$CH), 11.2 (*C*H$_3$CH$_2$); *m/z* (CI, NH_3) 320 (^{35}M+H$^+$, 100%), 286 (34), 250 (30), 214 (36), 202 (14), 174 (14), 105 (50), 91 (93); HRMS found 320.0379. $C_{14}H_{16}Cl_3NO$ requires for ^{35}MH, 320.0376.

3.1.17. (*E*/*Z*)-*N*-Benzyl-4-methyl-5-ethylidene-3-pyrrolin-2-one (20). A solution of enamide **18** (100 mg, 0.35 mmol) and $RuCl_2(PPh_3)_3$ (167 mg, 0.17 mmol) was heated in dry degassed toluene (2.8 mL) until complete consumption of starting material. Evaporation of the solvent in vacuo followed by column chromatography (dichloromethane–diethyl ether, 30:1) afforded **20** (70 mg, 94%) as a 1:1 mixture of alkene isomers. *Z*-isomer: 47%; R_f 0.21 (dichloromethane–diethyl ether, 30:1); ν_{max} (thin film) 3088 (w), 2926 (w), 1682 (s, C=O), 1438 (s), 757 (m) cm^{-1}; δ_H (270 MHz, $CDCl_3$) 7.30–7.08 (5H, m, aromatics), 5.96 (1H, s, C*H*CO), 5.31 (1H, q, J=8 Hz, C*H*CH_3), 5.05 (2H, s, CH_2Ph), 2.11 (3H, s, CCH_3), 1.77 (3H, d, J=8 Hz, CHCH_3); δ_C (67.5 MHz, $CDCl_3$) 171.3 (N*C*O), 148.8 (C*C*CH$_3$), 140.5 (*C*=CH), 138.3 (N*C*CH), 128.6, 126.9, 125.6 (5×*C*H=C), 118.4 (CO*C*H), 108.4 (C*C*HCH$_3$), 44.1 (*C*H$_2$Ph), 12.5 (*C*H$_3$C), 10.9 (*C*H$_3$CH); *m/z* (CI, NH_3) 214 (M+H$^+$, 100%), 91 (6); HRMS found 214.1224. $C_{14}H_{15}NO$ requires for MH, 214.1231. *E*-isomer: 47%; R_f 0.19 (dichloromethane–diethyl ether, 30:1); ν_{max} (thin film) 3011 (m), 2926 (w), 1679 (s, C=O), 1216 (m), 758 (s) cm^{-1}; δ_H (270 MHz, $CDCl_3$) 7.31–7.11 (5H, m, aromatics), 6.01 (1H, s, C*H*CO), 5.36 (1H, q, J=8 Hz, C*H*CH_3), 4.80 (2H, s, CH_2Ph), 2.39 (3H, s, CCH_3), 1.95 (3H, d, J=8 Hz, CHCH_3); δ_C (67.5 MHz, $CDCl_3$) 169.0 (N*C*O), 146.7 (C*C*CH$_3$), 139.7 (*C*=CH), 137.6 (N*C*CH), 128.5, 127.0, 126.6 (5×*C*H=C), 122.8 (CO*C*H), 110.8 (C*C*HCH$_3$), 42.3 (*C*H$_2$Ph), 17.1 (*C*H$_3$C), 12.9 (*C*H$_3$CH); *m/z* (CI, NH_3) 214 (M+H$^+$, 100%).

3.1.18. (*E*/*Z*)-*N*-Benzyl-3-chloro-4-methyl-5-ethylidene-3-pyrrolin-2-one (21). A solution of enamide **19** (200 mg, 0.62 mmol) and $RuCl_2(PPh_3)_3$ (296 mg, 0.31 mmol) was heated in dry degassed toluene (5.6 mL) until complete consumption of starting material. Evaporation of the solvent in vacuo followed by column chromatography (dichloromethane–diethyl ether, 30:1) afforded **21** (103 mg, 67%) as a 1.2:1 mixture of alkene isomers. *Z*-isomer: 30%; R_f 0.33 (dichloromethane–diethyl ether, 30:1); ν_{max} (thin film) 3019 (s), 2382 (w), 1698 (m, C=O), 1215 (vs) cm^{-1}; δ_H (270 MHz, $CDCl_3$) 7.34–7.24 (5H, m, aromatics), 5.40 (1H, q, J=8 Hz, C*H*CH_3), 5.11 (2H, s, CH_2Ph), 2.14 (3H, s, CCH_3), 1.82 (3H, d, J=8 Hz, CHCH_3); δ_C (67.5 MHz, $CDCl_3$) 165.9 (N*C*O), 141.3 (*C*Cl), 138.0 (N*C*CH), 137.7 (C*C*CH$_3$), 128.7 (*C*=CH), 127.1, 125.7, 122.6 (5×*C*H=C), 109.5 (C*C*HCH$_3$), 45.1 (*C*H$_2$Ph), 12.7 (*C*H$_3$C), 10.3 (*C*H$_3$CH); *m/z* (CI, NH_3) 248 (^{35}M+H$^+$, 100%), 91 (31); HRMS found 248.0838. $C_{14}H_{14}ClNO$ requires for ^{35}MH, 248.0842. *E*-isomer: 37%; R_f 0.27 (dichloromethane–diethyl ether, 30:1); ν_{max} (thin film) 3015 (s), 2371 (w), 1691 (m, C=O), 1220 (s) cm^{-1}; δ_H (270 MHz, $CDCl_3$) 7.31–7.15 (5H, m, aromatics), 5.44 (1H, q, J=8 Hz, C*H*CH_3), 4.85 (2H, s, CH_2Ph), 2.31 (3H, s, CCH_3), 1.96 (3H, d, J=8 Hz, CHCH_3); δ_C (67.5 MHz, $CDCl_3$) 164.7 (N*C*O), 139.2 (*C*Cl), 137.5 (N*C*CH), 137.0 (C*C*CH$_3$), 128.6 (*C*=CH), 127.2, 126.9, 123.1 (5×*C*H=C), 112.0 (C*C*HCH$_3$), 41.6 (*C*H$_2$Ph), 12.0 (*C*H$_3$C), 11.5 (*C*H$_3$CH); *m/z* (CI, NH_3) 248 (^{35}M+H$^+$, 100%), 214 (6), 91 (22); HRMS found 248.0836. $C_{14}H_{14}ClNO$ requires for ^{35}MH, 248.0842.

3.1.19. (*E* or *Z*)-3-(*N*-4-Methoxybenzyl-2,2-dichloroethanamido)-5-methyl-hex-2-ene (23). Following the same procedure as for the preparation of **3**, a solution of 2-methyl-hexan-3-one **22**[25] (1.00 g, 8.76 mmol) and 4-methoxybenzylamine (1.14 mL, 8.76 mmol) was refluxed in toluene (45 mL) for 15 h and then, at 0°C, dichloroacetyl chloride (0.93 mL, 9.64 mmol) was added dropwise followed by the addition of *N*,*N*-diethylaniline (1.53 mL, 9.64 mmol). After 4 h, the mixture was worked-up and purified by column chromatography (silica, petroleum ether–ethyl acetate, 11:2) to afford **23** (0.61 g, 20%) as an inseparable mixture with **24** (0.36 g, 12%) as an oil. Enamide **23**: R_f 0.3 (petroleum ether–ethyl acetate, 11:2); ν_{max} (thin film) (as a mixture with **24**; **23**:**24**=63:37) 3040 (br, w), 2958 (br, m), 1680 (m, C=O), 1613 (w), 1526 (m), 1249 (m), 1177 (m), 698 (br, m), 469 (s) cm^{-1}; δ_H (270 MHz, $CDCl_3$) 7.19 (2H, d, J=9 Hz, aromatics), 6.81 (2H, d, J=9 Hz, aromatics), 6.40 (1H, s, C*H*Cl$_2$), 5.29 (1H, q, J=7 Hz, C*H*CH_3), 5.10 (1H, d, J=14 Hz, C*H*Ar), 4.10 (1H, d, J=14 Hz, C*H*Ar), 3.77 (3H, s, OCH_3), 2.10 (1H, d, J=7 Hz, CH_2CH), 1.64 (3H, d, J=7 Hz, CHCH_3), 1.21 (1H, m, CH_2C*H*), 0.94 (6H, br m, (CH_3)$_2$CH); δ_C (67.5 MHz, $CDCl_3$) 165.2 (N*C*O), 160.6 (*C*OCH$_3$), 139.2 (*C*=CHCH$_3$), 137.4 (*C*=CH), 131.7, 131.2 (*C*H=C), 114.9 (C=*C*HCH$_3$), 65.7 (*C*HCl$_2$), 55.6 (O*C*H$_3$), 50.4 (N*C*H$_2$C), 39.0 (*C*H$_2$CH), 27.5 (CH$_2$*C*H), 23.0, 14.0 (C=CH*C*H$_3$ and CH(*C*H$_3$)$_2$); *m/z* (CI, NH_3) 361 (^{35}M+NH$_4^+$, 4%), 344 (^{35}M+H$^+$, 33), 274 (27), 230 (4), 150 (11), 121 (100); HRMS found 344.2795. $C_{17}H_{23}Cl_2NO_2$ requires for ^{35}MH, 344.2797. The presence of **24** was indicated by ^{1}H and ^{13}C NMR spectroscopy: δ_H (270 MHz, $CDCl_3$) 6.31 (1H, s, C*H*Cl$_2$), 5.20 (1H, br d, J=14.5 Hz, C*H*Ar), 4.85 (1H, d, J=10.2 Hz, C*H*CH(CH$_3$)$_2$), 3.95 (1H, br d, J=14.5 Hz, C*H*Ar), 1.05 (3H, t, J=8 Hz, CH_2CH_3); δ_C (67.5 MHz, $CDCl_3$) 164.3 (N*C*O), 159.0 (*C*OCH$_3$), 140.4 (*C*=CHCH), 137.7 (*C*=CH), 135.7, 129.9 (*C*H=C), 113.7 (C=*C*HCH), 63.9 (*C*HCl$_2$), 55.1 (O*C*H$_3$), 48.8 (N*C*H$_2$C), 27.0 (*C*H(CH$_3$)$_2$), 22.1 (*C*H$_2$CH$_3$), 14.1 (CH(*C*H$_3$)$_2$), 7.8 (CH$_2$*C*H$_3$).

3.1.20. (*E*/*Z*)-*N*-(4-Methoxy-benzyl)-4-methyl-5-isobutylidene-3-pyrrolin-2-one (25). A solution of enamides **23** and **24** (1.7:1, 189 mg, 0.55 mmol) and $RuCl_2(PPh_3)_3$ (268 mg, 0.28 mmol) was heated in dry degassed toluene (8 mL) until complete consumption of starting material. Evaporation of the solvent in vacuo followed by column chromatography (dichloromethane–diethyl ether, 30:1) afforded *E*-**25** (39 mg, 41% from **23**) and an inseparable mixture of *Z*-**25** and **26** (33 mg, 35% from **23**; 28 mg, 51% from **24**) in a 1:1.2 ratio from the ^{1}H NMR spectrum. *Z*-**25**: 35%; R_f 0.15 (dichloromethane–diethyl ether, 30:1); ν_{max} (thin film) 2963 (m), 2927 (m), 1687 (s, C=O), 1530 (s), 1266 (s), 758 (s) cm^{-1}; δ_H (270 MHz, $CDCl_3$) 7.00 (2H, d, *J*=9 Hz, aromatics), 6.84 (2H, d, *J*=9 Hz, aromatics), 5.95 (1H, s, C*H*CO), 4.96 (1H, d, *J*=11 Hz, C*H*–CH(CH$_3$)$_2$), 4.94 (2H, s, C*H*$_2$Ph), 3.78 (3H, s, OC*H*$_3$), 2.79 (1H, m, C*H*(CH$_3$)$_2$), 2.11 (3H, s, CC*H*$_3$), 0.82 (6H, d, *J*=6 Hz, CH(C*H*$_3$)$_2$); δ_C (67.5 MHz, $CDCl_3$) 170.9 (N*C*O), 158.5 (*C*OCH$_3$), 149.3 (*C*CH$_3$), 137.0 (NCH$_2$*C*), 130.1 (N–*C*=C), 126.8 (2×*C*H=C), 121.2 (CO*C*H), 119.0 (*C*HCH(CH$_3$)$_2$), 113.9 (2×*C*HCOCH$_3$), 55.2 (OCH$_3$), 43.6 (*C*H$_2$Ar), 26.1 (*C*H(CH$_3$)$_2$), 23.3, 12.6 (CH(*C*H$_3$)$_2$ and C*C*H$_3$); *m*/*z* (CI, NH_3) 272 (M+H$^+$, 100%), 152 (7), 121 (25); HRMS found 272.1646. $C_{17}H_{21}NO_2$ requires for MH, 272.1650. *E*-**25**: 41%; R_f 0.1 (dichloromethane–diethyl ether, 30:1); ν_{max} (thin film) 3012 (m), 2928 (m), 1680 (s, C=O), 1513 (m), 1215 (m), 758 (s) cm^{-1}; δ_H (270 MHz, $CDCl_3$) 7.11 (2H, d, *J*=9 Hz, aromatics), 6.83 (2H, d, *J*=9 Hz, aromatics), 5.98 (1H, s, C*H*CO), 5.14 (1H, d, *J*=11 Hz, C*H*(CH$_3$)$_2$), 4.73 (2H, s, C*H*$_2$Ph), 3.77 (3H, s, OC*H*$_3$), 2.99 (1H, m, C*H*(CH$_3$)$_2$), 2.29 (3H, s, CC*H*$_3$), 0.99 (6H, d, *J*=6 Hz, CH(C*H*$_3$)$_2$); δ_C (67.5 MHz, $CDCl_3$) 168.9 (N*C*O), 158.0 (*C*OCH$_3$), 146.0 (*C*CH$_3$), 136.9 (NCH$_2$*C*), 129.7 (N–*C*=C), 128.0 (2×*C*H=C), 124.4 (CO*C*H), 123.3 (*C*HCH(CH$_3$)$_2$), 113.7 (2×*C*HCOCH$_3$), 55.2 (OCH$_3$), 41.6 (*C*H$_2$Ar), 26.3 (*C*H(CH$_3$)$_2$), 23.6, 16.6 (CH(*C*H$_3$)$_2$ and C*C*H$_3$); *m*/*z* (CI, NH_3) 272 (M+H$^+$, 100%), 152 (6), 121 (27). The presence of (5*E*)-5-ethylidene-4-isopropyl-*N*-(4-methoxy-benzyl)-3-pyrrolin-2-one **26** was indicated by NMR spectroscopy. δ_H (270 MHz, $CDCl_3$) 6.92 (2H, d, *J*=7 Hz, aromatics), 6.75 (2H, d, *J*=7 Hz, aromatics), 5.80 (1H, s, CO*CH*), 5.29 (1H, q, *J*=7.8 Hz, C=C*H*CH$_3$), 4.80 (2H, s, C*H*$_2$Ar), 3.70 (3H, s, C*H*$_3$O), 2.71 (1H, m, C*H*Me$_2$), 1.75 (3H, d, *J*=8 Hz, C=CHC*H*$_3$), 1.14 (6H, d, *J*=6.8 Hz, CH(C*H*$_3$)$_2$); δ_C (67.5 MHz, $CDCl_3$) 170.9 (N*C*O), 158.4 (*C*OCH$_3$), 149.3 (*C*=CHCO), 137.0, 130.1 (N*C*=CH and NCH$_2$*C*=C), 126.8 (2×*C*H=C), 115.4 (CO*C*H), 113.8 (2×*C*H=C), 107.5 (*C*HCH$_3$), 55.1 (*C*H$_3$O), 43.6 (Ar*C*H$_2$), 30.8 (*C*H(CH$_3$)$_2$), 22.9, 12.5 (CH(*C*H$_3$)$_2$ and CH*C*H$_3$).

3.1.21. 2,2-Dichloro-*N*-(2,4-dimethoxybenzyl)-*N*-[(1*E* or *Z*)-1-isobutylprop-1-enyl]acetamide (27). Following the representative procedure for the preparation of **3**, ketone **22** (2.18 g, 19.1 mmol), 2,4-dimethoxybenzylamine (3.19 g, 2.87 mL, 19.1 mmol) and dichloroacetyl chloride (3.10 g, 2.02 mL, 21.0 mmol) in the presence of triethylamine (5.80 g, 7.99 mL, 57.3 mmol) were reacted to give an inseparable mixture of **27** (1.40 g, 19%) and **28** (0.92 g, 13%) as a yellow oil. R_f 0.5 (5:1 petroleum ether–EtOAc); ν_{max}/cm^{-1} ($CHCl_3$) 3008 (m), 2962 (s), 2871 (m), 1673 (s, C=O), 1613 (m), 1507 (m), 1402 (m), 1158 (m), 1038 (m). Enamide **27**: δ_H (270 MHz, $CDCl_3$) 7.21 (1H, d, *J*=8.0 Hz, C*H*=C, aromatic), 6.45–6.33 (2H, m, C*H*-aromatic), 6.41 (1H, s, C*H*Cl$_2$), 5.29 (1H, q, *J*=7.0 Hz, C*H*CH$_3$), 5.05 (1H, br d, *J*=13.5 Hz, CH$_A$H$_B$N), 4.32 (1H, br d, *J*=13.5 Hz, CH$_A$*H*$_B$N), 3.78 (3H, s, OC*H*$_3$), 3.74 (3H, s, OC*H*$_3$), 2.07 (2H, m, C*H*$_2$CH(CH$_3$)$_2$), 1.70 (1H, app. quin., *J*=7.0 Hz, C*H*(CH$_3$)$_2$), 1.59 (3H, d, *J*=7.0 Hz, CHC*H*$_3$), 0.94 (6H, d, *J*=6.5 Hz, 2×C*H*$_3$); δ_C (67.5 MHz, $CDCl_3$) 165.3, 161.2 (*C*=O and 2×*C*OMe, aromatic), 139.7 (*C*H, aromatic), 138.7 (C=*C*N), 131.5 (*C*H, aromatic), 127.2 (*C*H, aromatic or *C*HCH$_3$), 117.6 (*C*CH$_2$N), 104.8 (*C*H, aromatic or *C*HCH$_3$), 98.6 (*C*H aromatic), 65.1 (*C*HCl$_2$), 55.9 (2×OCH$_3$), 44.3 (*C*H$_2$Ar), 38.4 (*C*H$_2$CH(CH$_3$)$_2$), 27.1 (*C*H(CH$_3$)$_2$), 22.7, 12.7 (CH*C*H$_3$ and C(*C*H$_3$)$_2$); *m*/*z* (CI, NH_3) 374 (^{35}M+H$^+$, 32%), 301 (15), 151 (100); HRMS found 374.1291. $C_{18}H_{25}Cl_2NO_3$ requires for ^{35}MH, 374.1289. The presence of compound **28** was indicated by ^{1}H NMR spectroscopy; R_f 0.5 (5:1 petroleum ether–EtOAc); δ_H (270 MHz, $CDCl_3$) 4.88 (1H, d, *J*=10.0 Hz, C*H*CH(CH$_3$)$_2$), 2.48–2.31 (1H, m, C*H*(CH$_3$)$_2$), 2.13–2.03 (2H, m, C*H*$_2$CH$_3$), 1.23 (3H, t, *J*=7.0 Hz, CH$_2$C*H*$_3$).

3.1.22. Ruthenium(II)-mediated cyclisation of enamides (27) and (28). Enamides **27** and **28** (1.5:1, 457 mg, 1.22 mmol), and $RuCl_2(PPh_3)_3$ (585 mg, 0.61 mmol) were combined in dry, thoroughly degassed toluene (12 mL) and heated to reflux under nitrogen for 4 days to give **31** as a brown solid (17 mg, 12%), a mixture of **31** (9 mg, 5%) and **29** (19 mg, 10%) as a semi-solid, a mixture of **29** (42 mg, 22%) and **32** (27 mg, 14%) as an oil and **30** (90 mg, 41%) as an oil. (5*Z*)-1-(2,4-Dimethoxybenzyl)-4-methyl-5-(2-methylpropylidene)-3-pyrrolin-2-one **29**; R_f 0.3 (2:1 petroleum ether–EtOAc); ν_{max}/cm^{-1} (thin film) 2999 (w), 2959 (m), 2925 (m), 2866 (w), 1688 (s, C=O), 1615 (m), 1590 (m), 1507 (m), 1458 (m), 1260 (m), 1207 (m); δ_H (270 MHz, $CDCl_3$) 6.67 (1H, d, *J*=8.5 Hz, C*H*=C, aromatic), 6.44 (1H, d, *J*=2.5 Hz, C*H*-aromatic), 6.37 (1H, dd, *J*=8.5, 2.5 Hz, C*H*-aromatic), 5.94 (1H, s, C*H*CO), 4.96 (1H, d, *J*=11.0 Hz, C*H*CH(CH$_3$)$_2$), 4.89 (2H, s, C*H*$_2$Ar), 3.83 (3H, s, OC*H*$_3$), 3.76 (3H, s, OC*H*$_3$), 2.82–2.54 (1H, m, C*H*(CH$_3$)$_2$), 2.11 (3H, s, CHC*H*$_3$), 0.81 (6H, d, *J*=6.5 Hz, CH(C*H*$_3$)$_2$); δ_C (67.5 MHz, $CDCl_3$) 171.5 (*C*=O), 160.1, 157.4 (2×*C*OMe, aromatics), 149.4 (*C*CH$_3$), 137.6 (C*C*N), 127.0 (*C*H=C, aromatic), 121.8 (NCO*C*H), 119.6, 119.5 (NC=*C*H and NCH$_2$*C*), 104.4, 98.6 (2×*C*H=C, aromatic), 55.7 (2×OCH$_3$), 39.4 (*C*H$_2$Ar), 23.9 (2×*C*H$_3$), 26.1 (*C*H(CH$_3$)$_2$), 13.0 (*C*H$_3$); *m*/*z* (CI, NH_3) 302 (M+H$^+$, 100%), 151 (20); HRMS found 302.1759. $C_{18}H_{23}NO_3$ requires for MH, 302.1756. (5*E*)-1-(2,4-Dimethoxybenzyl)-4-methyl-5-(2-methylpropylidene)-3-pyrrolin-2-one **30**; R_f 0.3 (1:1 petroleum ether–EtOAc); ν_{max}/cm^{-1} (thin film) 2963 (m), 2926 (m), 2839 (w), 1686 (s, C=O), 1615 (m), 1590 (m), 1508 (m), 1438 (m), 1352 (m); δ_H (270 MHz, $CDCl_3$) 6.88 (1H, d, *J*=8.0 Hz, C*H*=C, aromatic), 6.42 (1H, d, *J*=2.0 Hz, C*H*-aromatic), 6.37 (1H, dd, *J*=8.0, 2.0 Hz, aromatic), 5.96 (1H, s, C*H*CO), 5.26 (1H, d, *J*=10.5 Hz, C*H*CH(CH$_3$)$_2$), 4.71 (2H, s, C*H*$_2$Ar), 3.84 (3H, s, OC*H*$_3$), 3.75 (3H, s, OC*H*$_3$), 3.09–2.91 (1H, m, C*H*(CH$_3$)$_2$), 2.27 (3H, s, C*H*$_3$), 0.98 (6H, d, *J*=6.5 Hz, 2×C*H*$_3$); δ_C (67.5 MHz, $CDCl_3$) 169.5 (*C*=O), 160.2, 157.6 (2×*C*OMe, aromatics), 146.5 (*C*CH$_3$), 137.4 (N*C*=CH), 129.1 (*C*H=C, aromatic), 124.9, 123.8 (NCO*C*H and NC=*C*H), 118.5 (NCH$_2$*C*), 104.5, 98.4 (2×*C*H=C, aromatics), 55.6 (2×OCH$_3$), 36.6 (*C*H$_2$Ar), 29.6 (*C*H(CH$_3$)$_2$),

24.1 (2×CH_3), 17.0 (CH_3); *m/z* (CI, NH_3) 302 ($M+H^+$, 100%), 167 (10), 151 (40); HRMS found 302.1754. $C_{18}H_{23}NO_3$ requires for MH, 302.1756. (5*E*)-1-(2,4-Dimethoxybenzyl)-5-ethylidene-4-isopropyl-3-pyrrolin-2-one **31**; mp 124–126°C; R_f 0.3 (2:1 petroleum ether–EtOAc); ν_{max}/cm^{-1} ($CHCl_3$) 3014 (m), 2968 (m), 1680 (s, C=O), 1655 (m), 1507 (m), 1261 (m), 1157 (m), 1038 (m), 843 (w); δ_H (270 MHz, $CDCl_3$) 6.67 (1H, d, *J*=8.0 Hz, C*H*=C aromatic), 6.44 (1H, d, *J*=2.5 Hz, C*H*-aromatic), 6.39 (1H, dd, *J*=8.0, 2.5 Hz, C*H*-aromatic), 5.92 (1H, s, C*H*CO), 5.36 (1H, q, *J*=8.0 Hz, C*H*CH_3), 4.92 (2H, s, CH_2Ar), 3.81 (3H, s, OCH_3), 3.76 (3H, s, OCH_3), 2.78 (1H, sept, *J*=7.0 Hz, C*H*$(CH_3)_2$), 1.74 (3H, d, *J*=8.0 Hz, CHCH_3), 1.21 (6H, d, *J*=7.0 Hz, CH(C$H_3)_2$); δ_C (67.5 MHz, $CDCl_3$) 172.0 (*C*=O), 160.3, 159.9, 157.6 (2×*C*OMe, aromatics and *C*CH$(CH_3)_2$), 139.8 (N*C*), 127.0 (*C*H, aromatic), 119.6 (*C*HCO), 116.2 (NCH_2C), 108.3 (*C*HCH_3), 104.6 (*C*H aromatic), 98.9 (*C*H, aromatic), 55.9 (2×*C*H_3O), 39.9 (*C*H_2Ar), 26.0 (*C*H$(CH_3)_2$), 23.6 (*C*H_3), 12.5 (2×*C*H_3); *m/z* (CI, NH_3) 302 ($M+H^+$, 100%), 151 (20); HRMS found 302.1754. $C_{18}H_{23}NO_3$ requires for MH, 302.1756. (5*Z*)-1-(2,4-Dimethoxybenzyl)-5-ethylidene-4-isopropyl-3-pyrrolin-2-one **32**; the presence of this compound was indicated by ^1H NMR spectroscopy; R_f 0.3 (2:1 petroleum ether–EtOAc); δ_H (270 MHz, $CDCl_3$) 6.81 (1H, d, *J*=8.0 Hz, C*H*=C, aromatic), 6.47–6.33 (2H, m, C*H* aromatics), 6.03 (1H, s, C*H*CO), 5.40 (1H, qd, *J*=8.0, 1.5 Hz, C*H*CH_3), 4.72 (2H, s, CH_2Ar), 3.81 (3H, s, OCH_3), 3.76 (3H, s, OCH_3), 3.09–2.96 (1H, m, C*H*$(CH_3)_2$), 1.97 (3H, d, *J*=8.0 Hz, CHCH_3), 1.23 (6H, d, *J*=7.0 Hz, CH(C$H_3)_2$).

3.1.23. (5*Z*)-4-Methyl-5-(2-methylpropylidene)-3-pyrrolin-2-one or (*Z*)-pulchellalactam (2). Trifluoroacetic acid (4.6 mL) was added to lactam **29** (32 mg, 0.11 mmol) and the reaction left to stir at rt under nitrogen for 0.25 h. The reaction was observed to turn dark red/purple in colour almost immediately. The reaction was then diluted with $CHCl_3$ (15 mL) and the trifluoroacetic acid was co-evaporated with the $CHCl_3$ to give a purple/brown residue. Column chromatography (silica; 1:1, petroleum ether–EtOAc) gave **2**[24] as a crystalline solid (11 mg, 66%). R_f 0.2 (1:1 petroleum ether–EtOAc); ν_{max}/cm^{-1} ($CHCl_3$) 3462 (w, NH), 2965 (m), 2928 (m), 1685 (s, C=O), 1462 (m), 1347 (m), 843 (m), 672 (m); δ_H (270 MHz, $CDCl_3$) 8.71 (1H, br s, N*H*), 5.86 (1H, d, *J*=1.5 Hz, C*H*CO), 5.12 (1H, d, *J*=9.5 Hz, C*H*CH$(CH_3)_2$), 2.80–2.60 (1H, m, C*H*$(CH_3)_2$), 2.07 (3H, s, CH_3) 1.10 (6H, d, *J*=6.5 Hz, CH(C$H_3)_2$); δ_C (67.5 MHz, $CDCl_3$) 173.0 (*C*=O), 149.3 (*C*CH_3), 138.1 (C*C*N), 121.5 (*C*HCH$(CH_3)_2$), 120.7 (*C*HCO), 28.1 (*C*H$(CH_3)_2$), 23.4, 12.4 (3×*C*H_3); *m/z* (CI, NH_3) 169 ($M+NH_4^+$, 20%), 152 ($M+H^+$, 100); HRMS found 169.1338. $C_9H_{13}NO$ requires for MNH_4, 169.1340.

3.1.24. (5*E*)-4-Methyl-5-(2-methylpropylidene)-3-pyrrolin-2-one or (*E*)-pulchellalactam (33). Trifluoroacetic acid (13 mL) was added to lactam **30** (81 mg, 0.31 mmol) and the reaction left to stir at rt under nitrogen for 2 h. The reaction was observed to turn dark red/purple in colour over time. The reaction was then diluted with $CHCl_3$ (20 mL) and the trifluoroacetic acid was co-evaporated with the $CHCl_3$ to give a purple/brown residue. Column chromatography (silica; 1:1, petroleum ether–EtOAc) gave **33**[24] as a white crystalline solid (34 mg, 83%). R_f 0.2 (1:1 petroleum ether–EtOAc); ν_{max}/cm^{-1} ($CHCl_3$) 3456 (m, NH), 2967 (m), 2928 (m), 2870 (m), 1685 (s, C=O), 1464 (m), 1347 (w), 1174 (w), 976 (w), 842 (m); δ_H (270 MHz, $CDCl_3$) 9.28 (1H, br s, N*H*), 5.94 (1H, s, C*H*CO), 5.41 (1H, d, *J*=10.5 Hz, C*H*CH$(CH_3)_2$), 3.10–2.90 (1H, m, C*H*$(CH_3)_2$), 2.29 (3H, s, CH_3) 1.08 (6H, d, *J*=6.5 Hz, CH(C$H_3)_2$); δ_C (67.5 MHz, $CDCl_3$) 147.8 (*C*CH_3), 137.0 (C*C*N), 127.0 (*C*HCH$(CH_3)_2$), 121.8 (*C*HCO), 27.3 (*C*H$(CH_3)_2$), 24.0, 16.8 (3×*C*H_3); *m/z* (CI, NH_3) 152 ($M+H^+$, 100%), 136 (70); HRMS found 152.1074. $C_9H_{13}NO$ requires for MH, 152.1075.

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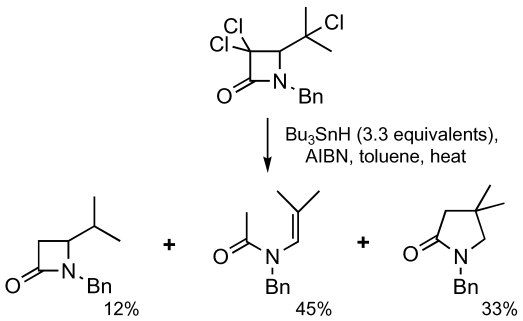
References

1. (a) Bowman, W. R.; Fletcher, A. J.; Potts, B. S. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2747. (b) Parsons, A. F. *An Introduction to Free Radical Chemistry*; Blackwell Science: Oxford, 2000. (c) Galeazzi, R.; Mobbili, G.; Orena, M.; Rossetti, M. *Targets Heterocycl. Syst.* **1997**, *1*, 355.
2. (a) Clark, A. J. *Chem. Soc. Rev.* **2002**, *31*, 1. (b) Iqbal, J.; Bhatia, B.; Nayyar, N. K. *Chem. Rev.* **1994**, *94*, 519.
3. See for example: (a) Ghelfi, F.; Parsons, A. F. *J. Org. Chem.* **2000**, *65*, 6249. (b) Ghelfi, F.; Bellesia, F.; Forti, L.; Ghirardini, G.; Grandi, R.; Libertini, E.; Montemaggi, M. C.; Pagnoni, U. M.; Pinetti, A.; De Buyck, L.; Parsons, A. F. *Tetrahedron* **1999**, *55*, 5839. (c) Ghelfi, F.; Ghirardini, G.; Libertini, E.; Forti, L.; Pagnoni, U. M. *Tetrahedron Lett.* **1999**, *40*, 8595. (d) Clark, A. J.; Battle, G. M.; Bridge, A. *Tetrahedron Lett.* **2001**, *42*, 4409.
4. For a review see: (a) Ishibashi, H.; Sato, T.; Ikeda, M. *Synthesis* **2002**, 695. (b) Chatgilialoglu, C.; Ferreri, C.; Guerra, M.; Timokhin, V.; Froudakis, G.; Gimisis, T. *J. Am. Chem. Soc.* **2002**, *124*, 10765.
5. (a) Parsons, A. F. C. R. *Acad. Sci. Sér. IIc: Chim.* **2001**, *4*, 391. (b) Bryans, J. S.; Chessum, N. E. A.; Parsons, A. F.; Ghelfi, F. *Tetrahedron Lett.* **2001**, *42*, 2901. (c) Clark, A. J.; Dell, C. P.; McDonagh, J. P. C. R. *Acad. Sci. Sér. IIc: Chim.* **2001**, *4*, 1.
6. Taylor, C. P. *Neurology* **1994**, *44*, 510.
7. Sutton, K. G.; Snutch, T. P. *Drug Dev. Res.* **2002**, *54*, 167.
8. Bryans, J. S.; Morrell, A. I. Int. Pat. Appl. WO 99/14184, 1999; *Chem. Abstr.*, 1999, *130*, 223583.
9. (a) Bryans, J. S.; Davies, N.; Gee, N. S.; Dissanayake, V. U. K.; Ratcliffe, G. S.; Horwell, D. C.; Kneen, C. O.; Morrell, A. I.; Oles, R. J.; O'Toole, J. C.; Perkins, G. M.; Singh, L.; Suman-Chauhan, N.; O'Neill, J. A. *J. Med. Chem.* **1998**, *41*, 1838. (b) Receveur, J.-M.; Bryans, J. S.; Field, M. J.; Singh, L.; Horwell, D. C. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 2329. (c) Bryans, J. S.; Horwell, D. C.; Ratcliffe, G. S.; Receveur, J.-M.; Rubin, J. R. *Bioorg. Med. Chem.* **1999**, *7*, 715. (d) Griffiths, G.; Mettler, H.; Mills, L. S.; Previdoli, F. *Helv. Chim. Acta* **1991**, *74*, 309.
10. For a similar cyclisation mediated by nickel in AcOH/^{i}PrOH see: Cassayre, J.; Quiclet-Sire, B.; Saunier, J.-B.; Zard, S. Z. *Tetrahedron* **1998**, *54*, 1029.

11. Heating the corresponding *N*-benzyl protected enamide **3** with $RuCl_2(PPh_3)_3$ in toluene gave 2-benzyl-4,4-dichloro-1-hydroxy-2-azaspiro[4.5]decan-3-one in only 20% yield (together with β-lactam products in 28% yield).
12. Copper(I) hydride can be generated from copper(I) chloride and tributyltin hydride: Tanaka, H.; Yamaguchi, Y.; Sumida, S.-I.; Kuroboshi, M.; Mochizuki, M.; Torii, S. *J. Chem. Soc., Perkin Trans. 1* **1999**, 3463.
13. For related reductive cyclisations of trichloroacetamides using $(Me_3Si)_3SiH$ see: Quirante, J.; Escolano, C.; Diaba, F.; Bonjoch, J. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1157.
14. Auerbach, J.; Zamore, M.; Weinreb, S. M. *J. Org. Chem.* **1976**, *41*, 725.
15. The 4-*exo* radical cyclisation is expected to be reversible (see Ref. 4) and this was supported by reaction of the trichloro-β-lactam shown below with Bu_3SnH (added over 5 h). In addition to the simple reduced product, this gave products derived from radical fragmentation and radical fragmentation followed by 5-*endo-trig* cyclisation.



16. Casarini, M. E.; Ghelfi, F.; Libertini, E.; Pagnoni, U. M.; Parsons, A. F. *Tetrahedron* **2002**, *58*, 7925.
17. For related cyclisations see: (a) Nagashima, H.; Ara, K.-I.; Wakamatsu, H.; Itoh, K. *J. Chem. Soc., Chem. Commun.* **1985**, 518. (b) Jolly, R. S.; Livinghouse, T. *J. Am. Chem. Soc.* **1988**, *110*, 7536. (c) Boivin, J.; Yousfi, M.; Zard, S. Z. *Tetrahedron Lett.* **1994**, *35*, 5629. (d) Ikeda, M.; Teranishi, H.; Nozaki, K.; Ishibashi, H. *J. Chem. Soc., Perkin Trans. 1* **1998**, 1691.
18. (a) Fernández, R.; Ferrete, A.; Lassaletta, J. M.; Llera, J. M.; Martin-Zamora, E. *Angew. Chem. Int. Ed.* **2002**, *41*, 831. (b) Fernández, R.; Ferrete, A.; Lassaletta, J. M.; Llera, J. M.; Monge, A. *Angew. Chem. Int. Ed.* **2000**, *39*, 2893.
19. Ghelfi, F.; Stevens, C. V.; De Buyck, L.; Laureyn, I.; Van Meenen, E.; Rogge, T. M.; Nikitin, K. V.; Grandi, R.; Libertini, E.; Pagnoni, U. M.; Schenetti, L. *Tetrahedron* **2003**, *59*, 1147.
20. Alvi, K. A.; Casey, A.; Nair, B. G. *J. Antibiot.* **1997**, *51*, 515.
21. (a) Davies, D. T.; Kapur, N.; Parsons, A. F. *Tetrahedron Lett.* **1999**, *40*, 8615. (b) Davies, D. T.; Kapur, N.; Parsons, A. F. *Tetrahedron* **2000**, *56*, 3941.
22. (a) Paquette, L. A.; Macdonald, D.; Anderson, L. G. *J. Am. Chem. Soc.* **1990**, *112*, 9292. (b) Smith, A. B.; Rano, T. A.; Chida, N.; Sulikowski, G. A.; Wood, J. L. *J. Am. Chem. Soc.* **1992**, *114*, 8008.
23. (a) Fetter, J.; Lampert, K.; Kajtár-Peredy, M.; Simig, G. *J. Chem. Soc., Perkin Trans. 1* **1988**, 1135. (b) Shiozaki, M.; Ishida, N.; Hiraoka, T.; Maruyama, H. *Tetrahedron* **1984**, *40*, 1795.
24. Li, W.-R.; Tsai Lin, S.; Hsu, N.-M.; Chern, M.-S. *J. Org. Chem.* **2002**, *67*, 4702.
25. Ali, M. H.; Wiggin, C. J. *Synth. Commun.* **2001**, *31*, 3383.