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β- And γ-Lactams by Nickel Powder Mediated 4-exo or 5-endo Radical Cyclisations. A Concise Construction of the Mesembrine Skeleton

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Abstract: *N*-Alkenyl trichloroacetamides, upon treatment with nickel powder and acetic acid in refluxing 2-propanol undergo reversible 4-exo radical cyclisation. The cyclised radical can be trapped in different ways leading to β-lactams. When the trap is omitted or not efficient enough, unusual irreversible 5-endo cyclisation occurs affording functionalised five-membered lactams. Synthesis of bicyclic γ-lactams has also been examined providing in few steps an access to the *Sceletium* alkaloids skeleton.

INTRODUCTION

Following the general development of free radical chemistry during the past twenty years,[1] radical cyclisation reactions have been of particular interest[2] and have found extensive use in natural product synthesis.[3] These reactions indeed possess desirable qualities for ring construction within complex molecules. Among them, the ability to form new bonds, usually carbon-carbon bonds, even at congested sites such as between quaternary centres, combined with functional group tolerance, regioselectivity and more recently stereoselectivity. This growing interest was confirmed by the recent emergence of metal-induced radical reactions[4] as an alternative to the usual tributyltin hydride method, whose synthetic scope is somewhat limited by the loss of functionality resulting from the final reduction by hydrogen atom transfer. In contrast, redox-based radical sequences can be terminated by introducing functionality into the molecule.

For reductive processes, the difficulty lies in finding a system able to transfer one electron to the radical precursor while the second one electron reduction remains sufficiently slow to allow the radical intermediate to undergo cyclisation. A few years ago, we introduced such a method based on the use of nickel powder and acetic acid.[5] We found this combination capable of cleaving an oxime ester into a carboxylate anion and a iminyl radical. We then reported that, under the same conditions, haloamides can be reduced to give carbon centred radicals which undergo 5-exo cyclisations affording γ-lactams,[6] or cyclisations onto aromatic rings leading to indolones.[7] Very recently, we described our preliminary observations concerning the ability of this system to generate sufficiently long-lived radicals from *N*-alkenyl-trichloroacetamides to undergo difficult cyclisations such as 4-exo cyclisations leading to β-lactams and even, in some cases, disfavoured 5-endo cyclisations.[8] In the present paper, we wish to give a full account of this work completed by recent results concerning the synthesis of functionalised γ-lactams by 5-endo radical cyclisations.

RESULTS AND DISCUSSION

Synthesis of β-lactams. In contrast to standard cyclisations of 5-hexenyl radicals to give five- or six-membered rings which are generally irreversible processes,[9] formation of smaller rings such as β-lactams involves a slow and reversible cyclisation step.[10] Different strategies have been used to circumvent this difficulty and allow the formation of β-lactams via 4-exo radical cyclisation.[11] The most popular approach[11a-g] consists of introducing substituents which either accelerate the rate of the cyclisation or stabilize the final radical, but its synthetic scope remains somewhat limited. We were rather interested in a second strategy involving an irreversible step following the cyclisation which would drive the equilibrium towards the formation of the cyclised product (Scheme 1).

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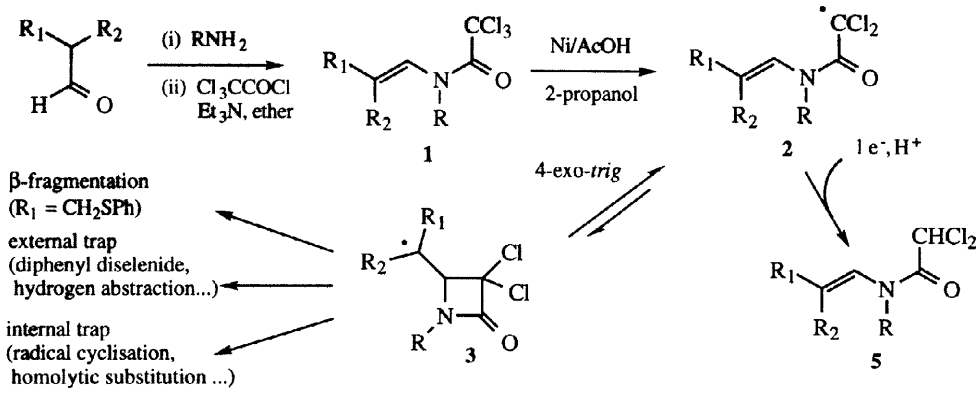
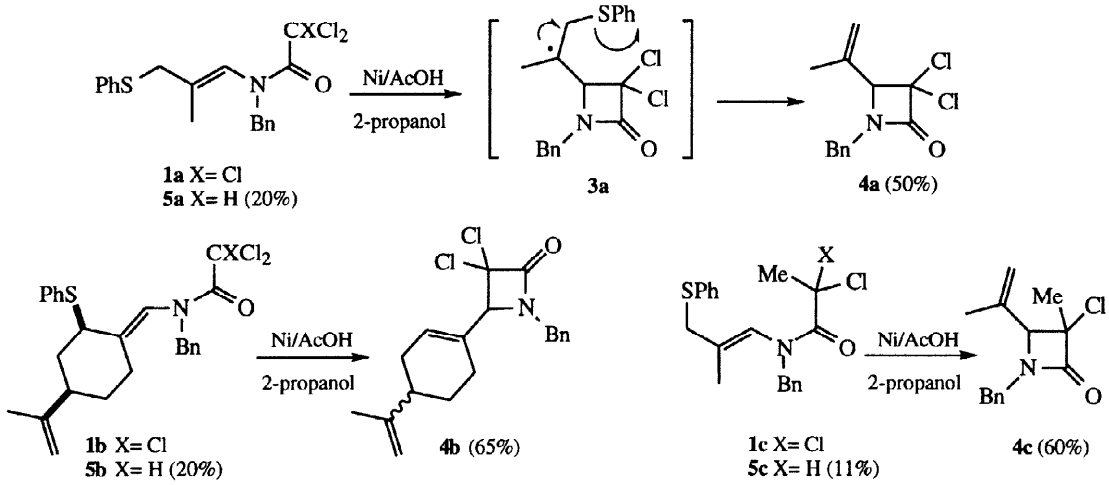


Scheme 1

Radical precursors **1** were prepared by condensation of an aldehyde or a ketone with a primary amine followed by acylation of the resulting imine with trichloroacetyl chloride. When subjected to nickel powder (30 eq.) and acetic acid (20 eq.) in refluxing 2-propanol, these compounds gave radicals **2** via an intermediate radical anion. As the second one-electron reduction leading to reduced products **5** is relatively slow, 4-exo cyclisation occurs to give radical **3** which can be trapped in various manners to afford β-lactams.

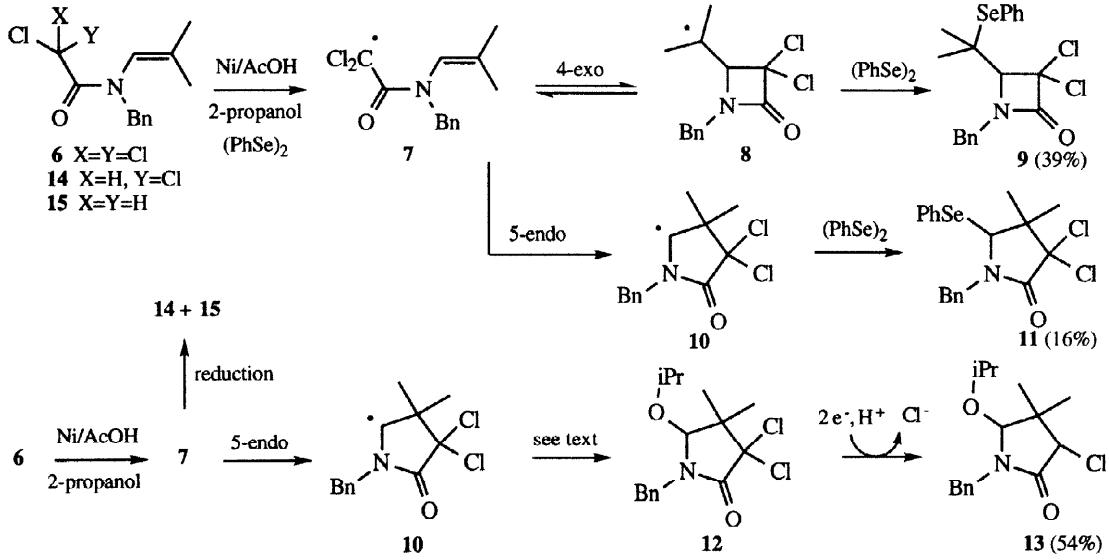


Scheme 2

As such systems do not involve radical chain processes, it is possible to introduce a fragmentation step such as β-fragmentation of a sulfide.[12] Thus, compound **1a**, prepared from 3-phenylthiyl isobutyraldehyde, led to β-lactam **4a** in 50% yield after rapid elimination of a phenylthiyl radical within **3a** (Scheme 2). Monoreduced enamide **5a** was also obtained in 20% yield. Under the same conditions, trichloroacetamide **1b** afforded β-lactam **4b** in 65% yield along with 20% of reduced product **5b**. This method therefore provides a new entry into β-lactams which can be further functionalised at the 3- and 4-positions (β-lactam numbering). The presence of the two chlorine atoms at the 3-position is especially useful. Moreover, a side chain at the 3-position can be introduced directly within the precursor as shown by the slower reaction (36 hours instead of 8 hours) of dichloropropionamide **1c** which led to β-lactam **4c** in 60% yield along with uncyclised monochloroenamide **5c** (11%).

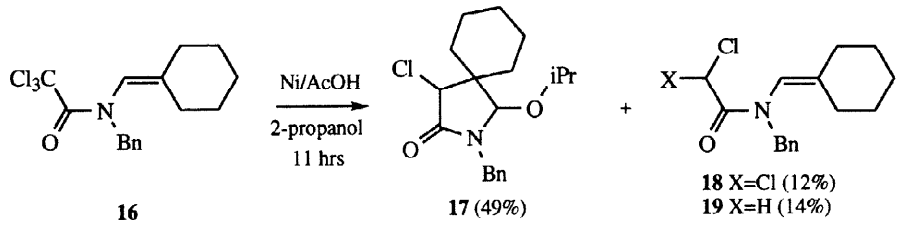
Competition between 4-exo and 5-endo cyclisation. Encouraged by these promising results, our attention was next turned to the utilisation of an external trap to capture the cyclised radical. Diphenyl diselenide is known to be a highly radicophilic reagent and the resulting selenides are useful synthetic intermediates.[13] Thus, trichloroacetamide **6** was subjected to our usual conditions in the presence of two equivalents of diphenyl diselenide to afford the expected β-lactam **9** in 39% yield along with γ-lactam **11** (16%). The latter was formed by an unexpected 5-endo-trig cyclisation to give radical **10** which was captured by diphenyl diselenide (Scheme 3). By replacing the fast intramolecular fragmentation step by a slower

intermolecular capture of the cyclised radical, we favoured the re-opening of radical **8** and therefore allowed an unusual but irreversible 5-endo cyclisation.[14] In order to confirm this observation, the trap was omitted and compound **6** subjected to our standard conditions. As expected, no β-lactam was formed but γ-lactam **13** was isolated in 54% yield along with uncyclised reduced materials **14** and **15** (28%).



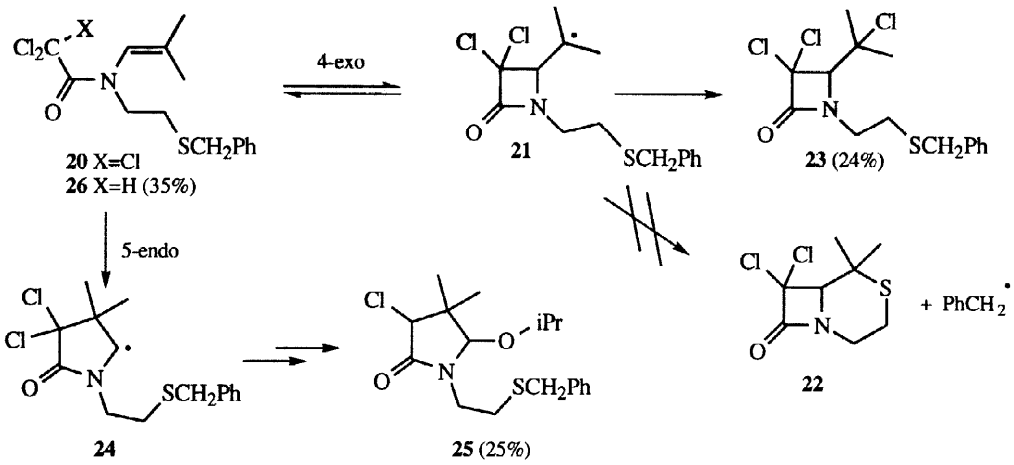
Scheme 3

Clearly, when no irreversible step follows the 4-exo cyclisation, 5-endo cyclisation occurs predominantly leading to radical **10** which is surprisingly formally oxidised to **12** and then, finally, further reduced to **13**. The oxidation step occurs either by a direct chlorine atom exchange or, more likely, by an electron transfer from starting material to **10** affording a trichlorinated compound which reacts with 2-propanol to give **12**. Even if an oxidation step is not expected in such a mildly reducing medium, the second pathway operates because radicals such as **10**, adjacent to a heteroatom, are readily oxidised. In a similar manner, trichloroacetamide **16**, upon treatment with nickel and acetic acid led to γ-lactam **17** in 49% yield along with uncyclised dichloroacetamide **18** (12%) and monochloroacetamide **19** (14%; Scheme 4). We have noticed that further reduction to the monochloro derivative occurs invariably when aminals (such as **13** or **17**) or enamides (see below) are produced. This is probably due to the slight modification of the reduction potential in the intermediate dichloroamide (e. g. **12**) by the mildly electron-withdrawing nature of the substituent on nitrogen.



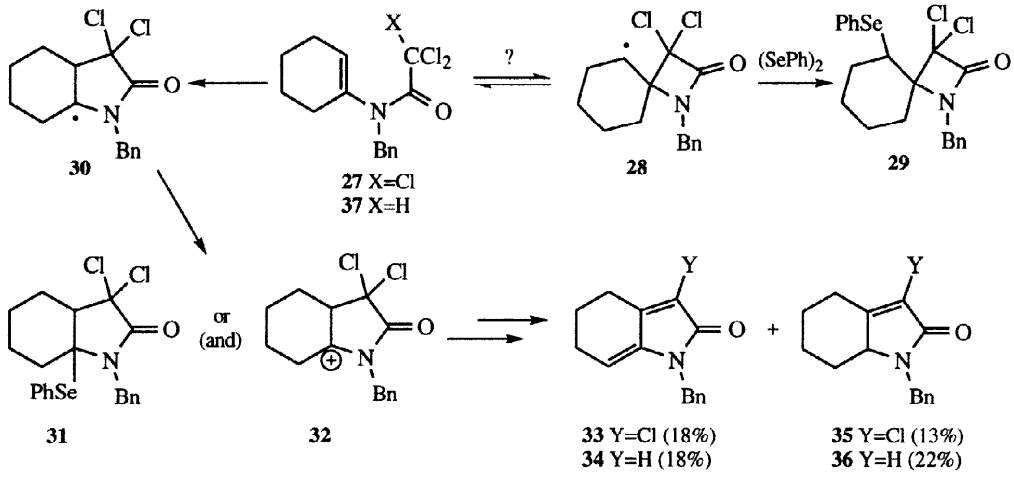
Scheme 4

In order to favour β-lactam formation, we next investigated the third pathway described in Scheme 1, involving an internal trap which would capture the cyclised radical. Thus, we examined the cyclisation of compound **20** which bears a side chain on nitrogen including a sulfide group known to undergo homolytic substitution (Scheme 5). However, exposure of **20** to our standard conditions did not afford any expected derivative **22** but gave instead β-lactam **23** (24%) and γ-lactam **25** (25%) along with uncyclised enamide **26** (35%). The substitution on sulfur seems too sluggish to compete with the alternative routes open to the radical: irreversible 5-endo cyclisation led to **25** whereas formal oxidation of **21** gave **23**. Compared to cyclisation of **16** where only γ-lactam was isolated, the cyclisation of **20** provided γ-lactam **25** and also β-lactam **23**, due probably to less steric congestion within radical **21**.



Scheme 5

The nickel powder/acetic acid combination thus allows disfavoured 5-endo-trig radical cyclisations of *N*-alkenyl-trichloroacetamides, a process analogous to that observed by Ikeda and co-workers using stannane chemistry.[15] But what is remarkable in our case is the fact that this unusual cyclisation occurs not only when the 5-endo approach is favoured by substitutions at the 3-position but even when disfavoured by the presence of substituents on the terminus of the double bond as for **6, 16** and **20**. Consequently, in addition to being a new route to γ-lactams, the present method is noteworthy because of the highly functionalised products obtained. These preliminary results were next applied to the synthesis of bicyclic fused γ-lactams, with the purpose of finding a short pathway to a few classes of alkaloids.

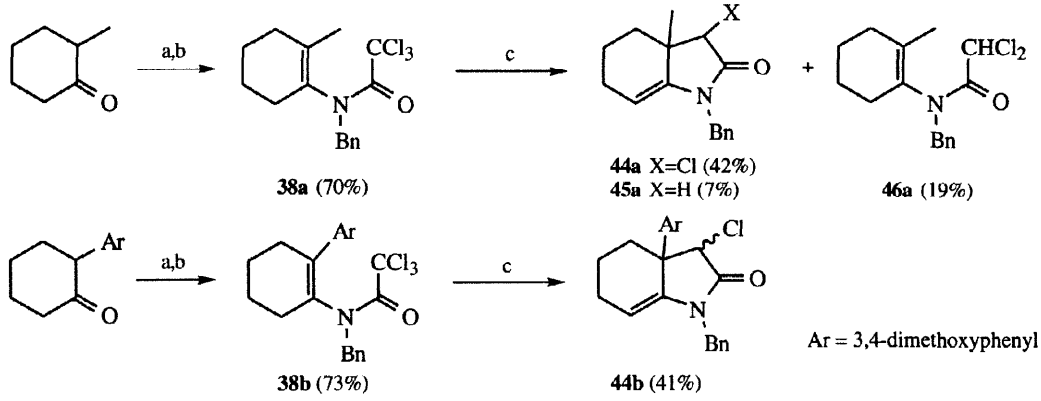


Scheme 6

Synthesis of bicyclic γ-lactams using 5-endo cyclisation. Compound **27** was prepared by condensation of cyclohexanone with benzylamine followed by *N*-acylation of the imine intermediate with trichloroacetyl chloride. By comparison with the preceding examples, the 4-exo approach should be even more disfavoured by the additional substituent on the 3-position (β-lactam numbering) and the 5-endo attack undoubtedly accelerated by the less steric congestion at the other carbon. Thus, when **27** was subjected to our usual conditions, no β-lactam was formed, even in the presence of diphenyl diselenide which could have trapped radical **28** into β-lactam **29**, but four five-membered lactams **33-36** were isolated in 71% combined yield along with monoreduced lactam **37** in 9% yield (Scheme 6).

The 4-exo cyclisation step is far too slow in this case to compete with the formation of the 5-endo products. In addition, no selenide was detected which means that either the cyclised radical **30** is particulary quickly oxidised to give cation **32** which led to the four observed products **33-36** via reduction, elimination of hydrochloric acid or isomerisation, or the selenide **31** if formed can in turn be converted to **33-36**. The γ-

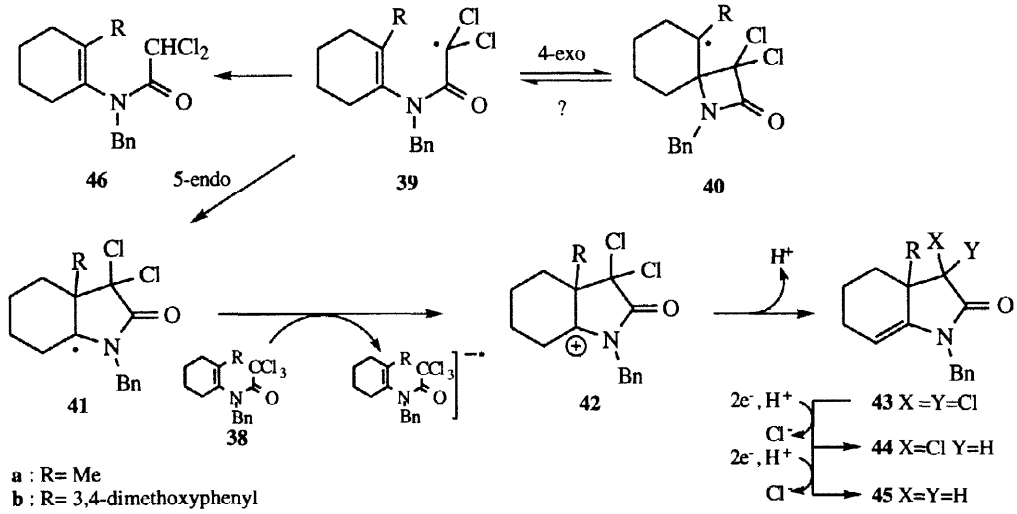
lactams thus obtained are highly functionalised but the number of products of the reaction limits so far its synthetic utility.



a) $PhCH_2NH_2$, PhMe, Dean-Stark; b) Cl_3CCOCl, Et_3N, ether 0°C;
c) Ni/AcOH, 2-propanol, reflux.

Scheme 7

On the basis of these results, we examined the behaviour of substrates substituted on the double bond in the absence of diphenyl diselenide. Thus, cyclisation of compound **38a**, prepared from 2-methylcyclohexanone following the general procedure, afforded γ-lactams **44a** and **45a** in 42% and 7% yield respectively along with uncyclised dichloroacetamide **46a** in 19% yield (Scheme 7).

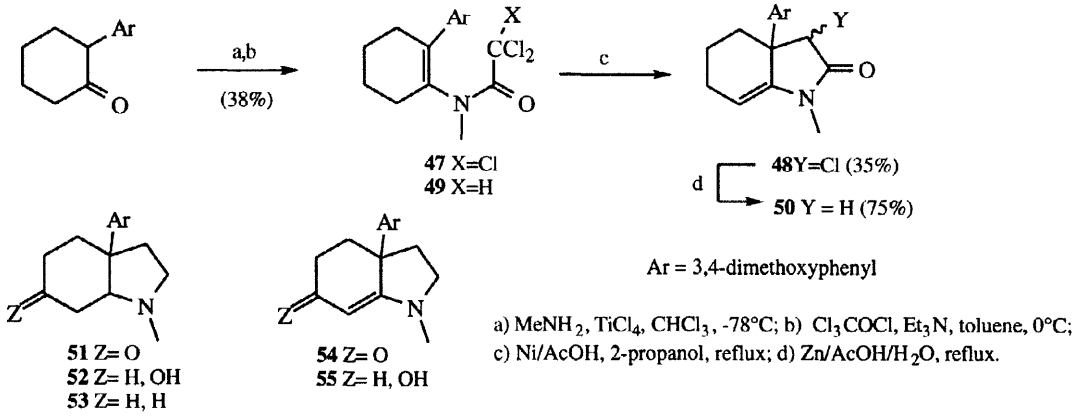


Scheme 8

Introducing a methyl group at the 4-position should have reduced the rate of 5-endo cyclisation of radical **39**, but previous results (e.g. **6** or **16**) have shown that even in such cases 5-endo attack is preferred to 4-exo cyclisation and the true competing reaction is the reduction of the starting material leading to uncyclised product **46**. Moreover, even if 4-exo cyclisation occurs, the produced radical **40** would not be trapped easily and its re-opening is the most probable outcome (Scheme 8). By contrast, cyclised radical **41** is readily oxidised, as previously mentioned, giving cation **42**, which subsequently affords γ-lactam **43**. The latter may undergo further reduction to afford **44** and **45**. The most probable agent responsible for the oxidation of **41** is the starting tricloroacetamide **38**. Therefore, the reaction would consist of a radical chain reaction initiated by a redox process. However, this hypothesis has not thus far been confirmed.

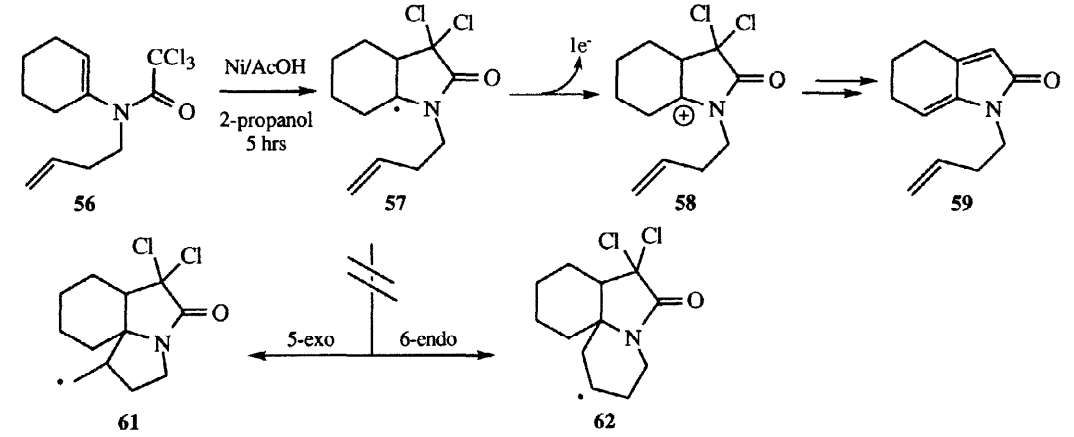
We next examined the reaction of compound **38b**, obtained from 2-(3,4-dimethoxyphenyl) cyclohexanone in 73% yield, in order to observe the influence of an aromatic substituent at the centre where cyclisation occurs. Thus, treatment of **38b** under the usual conditions afforded cyclised γ-lactam **44b** in 41% yield, the main side product being the reduced but uncyclised material (Scheme 7). Clearly, the aromatic

substitution does not affect to a great extent the cyclisation step, except that the reaction is slower. In particular, no β-lactam is formed, even though the ensuing radical **40b** would be stabilised by the presence of the aromatic ring (Scheme 8, R = 3,4-dimethoxyphenyl).



Scheme 9

Clearly we have in hand a short route to skeletons of *Sceletium* alkaloids[16] such as mesembrine **51**,[17,18] mesembranol **52**, mesembrane **53** and the related mesembrenone **54** or mesembrenol **55**. Our efforts were therefore turned to the cyclisation of trichloroacetamide **47**, obtained from 2-(3,4-dimethoxyphenyl)-cyclohexanone after formation of the *N*-methylated imine. Upon treatment with nickel and acetic acid in refluxing 2-propanol for 12 hrs, **47** afforded γ-lactam **48** in 35% yield along with uncyclised material **49** in 25% yield. Further dechlorination of **48** using zinc and acetic acid gave the known compound **50** in 75% yield (Scheme 9). It is perhaps worth pointing out that the presence of the chlorine atom next to the carbonyl group and the olefin within the ring in **48** opens access to the more complex *Amaryllidaceae*[19] and *Erythrina*[20] alkaloids.



Scheme 10

The oxidation of cyclised radicals such as **41** is a key but still obscure step, and we wondered if this oxidation step would compete with a fast intramolecular capture of this radical, such as in a tandem 5-exo cyclisation. Thus, we prepared trichloroacetamide **56** from 1-amino-3-butene and cyclohexanone. Ikeda and co-workers have indeed shown[15d] that the monochlorinated analogue of **56** undergoes tandem radical cyclisation upon treatment with Bu_3SnH and AIBN to afford the 5-endo/5-exo and 5-endo/6-endo products along with minor products. We found that treatment of **56** under our usual conditions did not afford any of the tricyclic compound resulting from 5-exo (**61**) or 6-endo (**62**) cyclisation of radical **57** but led to the bicyclic compound **59** in 51% yield along with uncyclised dichloroacetamide **60** in 11% yield (Scheme 10). Clearly, oxidation of radical **57** is faster than cyclisation to either **61** or **62**. This observation seems to be more compatible with oxidation by electron transfer than by a transfer of a chlorine atom from the starting trichloroacetamide **56**. It must be recalled that when cyclisation leads to a simple primary or secondary

radical, no oxidation or chlorine transfer are observed.[6] Stabilised radical **57**, in contrast, is particulary sensitive to oxidation, as previously observed for tertiary or allylic radicals as well as radicals adjacent to a heteroatom.[6,7]

In summary, the present study, expanding on our previous results, extends the scope of our nickel/acetic acid combination and demonstrates its ability for producing in few steps highly functionalised β-lactams and γ-lactams according to a mild and selective procedure and avoids the use of tributyltin hydride which necessitates high dilution and the removal of tin residues. This provides the basis for short synthetic approaches to a number of alkaloids which are now under investigation.

EXPERIMENTAL SECTION

Melting points were determined with a Reichert hot stage apparatus and are uncorrected. IR spectra are for neat films and were recorded with a Nicolet 205 FT-IR spectrometer. ^1H and ^{13}C NMR spectra were obtained on Brucker AC 200, AC 250 or AM 300 spectrometers for solutions in $CDCl_3$ (δ ppm). Mass spectra were recorded on MS 80 (high resolution) spectrometer. Matrex 60 (35-70 μm) silica gel was used for column chromatography. Solvents and reagents were purified according to standard laboratory techniques.

General Procedure for the Preparation of N-Alkenyl-Trichloro-Acetamides. Imines were obtained by condensation of an aldehyde or a ketone with a primary amine The formation of the imines was confirmed by IR absorption, the C=O band (1710-1735 cm^{-1}) being replaced by the C=N band (1650-1675 cm^{-1}). In all cases imines were used directly for the next step.

Method A: The aldehyde (x mmol) was added slowly to a solution of the primary amine (x mmol) in dichloromethane (x ml) at 0 °C. The mixture was stirred for 3 hours at 20 °C, then dried over sodium sulfate and concentrated in vacuo.

Method B: A solution of the ketone (x mmol) and the primary amine (x mmol) in toluene (0.5x ml) was stirred under reflux in a Dean-Stark apparatus. After 5 hrs, the solvent was removed in vacuo.

The imine (x mmol) was then dissolved in dry toluene (0.5 ml) and added dropwise to a stirred and ice-cooled solution of trichloroacetyl chloride or dichloropropionyl chloride (1.1x mmol) in dry toluene (3x ml) under argon. After stirring for 1 hr at 20 °C, the mixture was cooled to 0 °C and triethylamine (3x mmol) in toluene (0.5x ml) was added slowly. The stirring was continued for 2 hrs at ambient temperature and the resulting mixture was then added to a solution of saturated aqueous Na_2CO_3. After stirring for 3 hrs at 20 °C, the mixture was extracted with ether, dried over sodium sulfate and concentrated in vacuo to give a residue which was purified by silica gel column chromatography.

***N*-Benzyl-2,2,2-trichloro-*N*-(2-methyl-3-phenylsulfanyl-propenyl)-acetamide 1a.** 3-Phenylsulfanyl isobutyraldehyde was prepared by Michael addition of thiophenol on methacrolein with triethylamine as a catalyst. The imine was obtained directly by condensation with benzylamine according to method A and the enamide isolated as a colourless oil (eluent: heptane/ethyl acetate-95/5 to 9/1) in 35% overall yield; ^1H NMR: δ 1.72 (d, J = 1.1 Hz, 3H, CH_3); 3.51 (s, 2H, NCH_2); 4.59 (s, 2H, SCH_2); 6.27 (br s, 1H, HC=C); 7.01-7.36 (m, 10H, C_6H_5); ^{13}C NMR: δ 16.1; 40.1; 56.2; 92.6; 126.1; 126.8; 127.8; 128.3; 128.6; 129.0; 130.4; 135.2; 135.7; 137.0; 160.4; IR (cm^{-1}): 3061; 1685 (C=O); 1663; 1246; 821; h.r.m.s.: Calc. for $C_{19}H_{18}Cl_3NOS$: 413.0175. Found: 413.0127.

***N*-Benzyl-2,2,2-trichloro-*N*-(4-isopropenyl-2-phenylsulfanyl-cyclohexylidene-methyl)-acetamide 1b.** The aldehyde was prepared by Michael addition of thiophenol to perillaldehyde with triethylamine as a catalyst. The imine was then obtained directly by condensation with benzylamine according to method A and the enamide isolated as colourless crystals (eluent: heptane/ethyl acetate-95/5 to 9/1) in 23% overall yield; m.p. 89 °C (from pentane/ether); ^1H NMR: δ 1.03-1.24 (m, 1H, CH_2CHHCH); 1.69 (s, 3H, CH_3); 1.71 (m, 1H, CHCHHCH); 1.80-1.93 (m, 1H, CH_2CHHCH); 2.16 (m, 1H, CHCHHCH); 2.32-2.43 (m, 2H, $HC{=}CCH_2$); 2.55 (tt, J = 12.0 Hz, 3.0 Hz, 1H, $CH_2{=}CCH$); 4.03 (t, J = 2.6 Hz, 1H, SCH); 4.40 (d, $J_{A'B'}$ = 14.2 Hz, 1H, NCHH); 4.67 (s, 1H, C=CHH); 4.73 (s, 1H, C=CHH); 4.76 (d, $J_{A'B'}$ = 14.2 Hz, 1H, NCHH); 6.16 (br s, 1H, HC=C); 7.06-7.51 (m, 10H, C_6H_5); ^{13}C NMR: δ 21.1; 24.4; 30.5; 37.4; 39.2; 51.8; 57.2; 109.5; 122.9; 127.8; 128.2; 128.6; 129.1; 133.0; 134.5; 135.8; 141.5; 148.5; 160.5; IR (cm^{-1}): 1685 (C=O); 1648; 1265; 815; Anal. Calcd for $C_{25}H_{26}Cl_3NOS$: C: 60.67; H: 5.30; N: 2.83. Found: C: 60.81; H: 5.17; N: 2.72.

***N*-Benzyl-2,2-dichloro-*N*-(2-methyl-3-phenylsulfanyl-propenyl)-propionamide 1c.** Using 3-phenylsulfanyl isobutyraldehyde prepared as above, the imine was obtained according to method A and the enamide (using 2,2-dichloropropionyl chloride) isolated as a colourless oil (eluent: heptane/ethyl acetate-95/5) in 21% overall yield; ^1H NMR: δ 1.74 (s, 3H, $HC{=}CCH_3$); 2.27 (s, 3H, CCl_2CH_3); 3.53 (s, 2H, NCH_2); 4.55 (s, 2H, SCH_2); 6.46 (br s, 1H, HC=C); 7.02-7.43 (m, 10H, C_6H_5); ^{13}C NMR: δ 16.2; 36.3; 40.5; 54.9; 92.6; 126.7; 127.5; 128.0; 128.4; 128.5; 129.0; 130.5; 135.3; 135.4; 136.4; 165.0.

***N*-Benzyl-2,2,2-trichloro-*N*-(2-methyl-propenyl)-acetamide 6.** The imine was prepared from isobutyraldehyde and benzylamine according to method A and the enamide obtained as colourless crystals (eluent: heptane/ethyl acetate-9/1) in 45% overall yield; m.p. 36 °C (from pentane); ^1H NMR: δ 1.58 (d, J = 1.3 Hz, 3H, CH_3); 1.71 (d, J = 1.4 Hz, 3H, CH_3); 4.72 (s, 2H, NCH_2); 6.10 (m, 1H, HC=C), 7.18-7.40 (m, 5H, C_6H_5); ^{13}C NMR: δ 18.5; 21.8; 56.1; 93.2; 123.3; 127.8; 128.4; 128.6; 136.0; 137.6; 160.6; IR (cm^{-1}): 3356; 2952; 1692 (C=O); 1689; 1667; 1247; 822; h.r.m.s.: Calc. for $C_{13}H_{14}Cl_3NO$: 305.0141. Found: 305.0140; Anal. Calcd for $C_{13}H_{14}Cl_3NO$: C: 50.92; H: 4.60; N: 4.57. Found: C: 50.66; H: 4.88; N: 4.45.

***N*-Benzyl-2,2,2-trichloro-*N*-cyclohexylidenemethyl-acetamide 16.** The imine was prepared from cyclohexane carboxaldehyde and benzylamine according to method A and the enamide obtained as a colourless oil (eluent: heptane/ethyl acetate-9/1) in 60% overall yield; ^1H NMR: δ 0.80-2.30 (m, 10H, CH_2); 4.73 (m, 2H, NCH_2); 6.06 (br s, 1H, HC=C); 7.19-7.51 (m,

5H, C_6H_5); ^{13}C NMR: δ 26.0; 26.1; 27.4; 28.8; 32.9; 56.7; 93.4; 120.3; 127.8; 128.4; 128.6; 136.1; 143.6; 160.8; IR (cm^{-1}): 2933; 1688 (C=O); 1665; 1449; 1388; 815; Anal. Calcd for $C_{16}H_{18}Cl_3NO$: C: 55.43; H: 5.23; N: 4.04. Found: C: 55.44; H: 5.32; N: 3.76.

***N*-(2-Benzylsulfanyl-ethyl)-2,2,2-trichloro-*N*-(2-methyl-propenyl)-acetamide 20.** The imine was prepared from isobutyraldehyde and S-benzyl 2-aminoethanethiol[21] according to method A and the enamide obtained as colourless crystals (eluent heptane/ethyl acetate-9/1) in 35% overall yield; m.p. 56 °C (from pentane); ^1H NMR: δ 1.60 (d, J = 1.0 Hz, 3H, CH_3); 1.73 (d, J = 1.5 Hz, 3H, CH_3); 2.64 (t, J = 7.2 Hz, 2H, SCH_2CH_2); 3.65 (t, J = 7.2 Hz, 2H, NCH_2); 4.72 (s, 2H, CH_2Ph); 6.20 (m, 1H, *H*C=C), 7.18-7.45 (m, 5H, C_6H_5); ^{13}C NMR: δ 18.5; 21.8; 28.1; 36.2; 52.4; 93.1; 123.5; 127.1; 128.6; 129.0; 137.2; 138.1; 160.4; IR (cm^{-1}): 2911; 1664 (C=O); 1383; 1241; 811; Anal. Calcd for $C_{15}H_{18}Cl_3NOS$: C: 49.13; H: 4.95; N: 3.82. Found: C: 49.01; H: 4.91; N: 3.64.

***N*-Benzyl-2,2,2-trichloro-*N*-cyclohex-1-enyl-acetamide 27.** The imine was prepared from cyclohexanone and benzylamine according to method B and the enamide obtained as a colourless oil (eluent heptane/ethyl acetate-95/5) in 57% overall yield; ^1H NMR: δ 1.30-2.40 (m, 8H, CH_2); 4.12-4.40 (m, 1H, NCH*H*); 4.92-5.18 (m, 1H, NCH*H*); 5.47-5.63 (m, 1H, *H*C=C); 7.10-7.39 (m, 5H, C_6H_5); ^{13}C NMR: δ 20.9; 22.2; 24.5; 27.4; 53.1; 93.2; 127.5; 128.2; 128.6; 131.1; 136.1; 160.7; IR (cm^{-1}): 2935; 2861; 1680 (C=O); 1391; 1247; 813; Anal. Calcd for $C_{15}H_{16}Cl_3NO$: C: 54.16; H: 4.85; N: 4.21. Found: C: 54.21; H: 5.14; N: 3.97.

***N*-Benzyl-2,2,2-trichloro-*N*-(2-methyl-cyclohex-1-enyl)-acetamide 38a.** The imine was prepared from 2-methylcyclohexanone and benzylamine according to method B and the enamide obtained as a colourless oily mixture of two isomers (ratio 4:1), 2- and 6-methylcyclohexenyl (eluent heptane/ethyl acetate-95/5) in 70% overall yield; ^1H NMR: major isomer: δ 1.28 (br s, 3H, CH_3); 1.2-2.4 (m, 8H, CH_2,); 4.57-4.80 (m, 2H, NCH_2); 7.28-7.41 (m, 5H, C_6H_5); minor isomer: δ 1.28 (m, 3H, CH_3); 1.20-2.40 (m, 1H, C*H*); 4.57-4.80 (m, 2H, NCH_2); 5.20-5.36 (m, 1H, C=C*H*); 7.28-7.41 (m, 5H, C_6H_5); ^{13}C NMR: major isomer: δ 20.3; 22.1; 22.9; 29.7; 30.9; 55.1; 127.8; 128.2; 129.4; 131.3; 135.0; 136.2; 161.0; IR (cm^{-1}): 2934; 1675 (C=O); 1456; 1384; 808; Anal. Calcd for $C_{16}H_{18}Cl_3NO$: C: 54.43; H: 5.23; N: 4.04. Found: C: 54.21; H: 5.26; N: 4.03.

***N*-Benzyl-2,2,2-trichloro-*N*-(2-(3,4-dimethoxyphenyl)-cyclohex-1-enyl)-acetamide 38b.** 2-(3,4-Dimethoxyphenyl) cyclohexanone was prepared in two steps from bromoveratrole[22] according to the procedure described by Lotspeich and Karickhoff.[23] The imine was then obtained by condensation with benzylamine according to method B and the enamide isolated as colourless crystals (eluent heptane/ethyl acetate-95/5) in 73% overall yield; m.p. 106 °C (from diisopropyl ether); ^1H NMR: δ 1.02-1.79 (m, 6H, CH_2); 2.15-2.51 (m, 2H, CH_2); 3.66 (d, J_{AB} = 14.1 Hz, 1H, NC*H*H); 3.77 (s, 3H, OCH_3); 3.88 (s, 3H, OCH_3); 5.17 (d, J_{AB} = 14.1 Hz, 1H, NC*H*H); 6.77-6.95 (m, 3H, C_6H_3); 7.27-7.41 (m, 5H, C_6H_5); ^{13}C NMR: δ 22.4; 22.6; 28.9; 31.5; 53.4; 55.7; 55.9; 110.6; 111.2; 119.2; 127.8; 128.2; 129.0; 129.5; 133.0; 134.8; 135.3; 148.4; 148.9; 159.2; IR (cm^{-1}): 2935; 1671 (C=O); 1512; 1390; 1263; 1243; Anal. Calcd for $C_{23}H_{24}NO_3Cl_3$: C: 59.09; H: 5.18; N: 3.00. Found: C: 58.53; H: 5.31; N: 2.98.

***N*-Methyl-2,2,2-trichloro-*N*-(2-(3,4-dimethoxyphenyl)-cyclohex-1-enyl)-acetamide 47.** To a solution of methylamine (5x mmol) and 2-(3,4-dimethoxyphenyl)cyclohexanone in chloroform (3x ml) at -78°C was added titanium tetrachloride (0.5 xmmol) and the mixture was stirred 4 days under an inert atmosphere.[24] The mixture was then diluted with ether, filtered through Celite and concentrated in vacuo to afford the imine which was directly acylated to give the enamide as colourless crystals (eluent: heptane/ethyl acetate-8/2) in 38% yield; m.p. 101 °C (from ether/pentane); ^1H NMR: δ 1.57-2.57 (m, 8H, CH_2); 3.01 (s, 3H, NCH_3); 3.84 (s, 3H, OCH_3); 3.87 (s, 3H, OCH_3); 6.71-6.84 (m, 3H, C_6H_3); ^{13}C NMR: δ 22.6; 22.8; 25.5; 31.2; 38.7; 55.7; 55.9; 110.4; 110.9; 119.0; 132.7; 134.8; 137.2; 148.2; 148.7; 159.6; IR (cm^{-1}): 2934; 1679 (C=O); 1515; 1263; 1244; 835; 810; Anal. Calcd for $C_{17}H_{20}NO_3Cl_3$: C: 52.17; H: 5.15; N: 3.58. Found: C: 52.25; H: 5.11; N: 3.52.

***N*-But-3-enyl-2,2,2-trichloro-*N*-cyclohex-1-enyl-acetamide 56.** The imine was obtained from cyclohexanone and but-3-enylamine[15d] following method B with pentane as solvent and the enamide isolated as a yellow oil (eluent: heptane/ethyl acetate-8/2) in 38% yield; ^1H NMR: (two rotamers): δ 1.63-2.20 (m, 8H, CH_2); 2.38 (q, J = 6.6Hz, 2H,$CH_2CH=CH_2$); 3.18 (m, 2/3H, NCH*H*); 3.79 (m, 4/3H, NC*H*H); 5.04-5.14 (m, 2H, CH=CH_2); 5.70-5.82 (m, 1H, C*H*=CH_2); 5.90 (m, 1H, C*H*=C); ^{13}C NMR: δ 21.2; 22.4; 24.7; 27.5; 31.4; 49.2; 117.1; 130.5; 134.6; 136.7; 160.6; IR (cm^{-1}): 2937; 1678 (C=O); 1448; 1439; 1241; 920; 812; Anal. Calcd for $C_{12}H_{16}NOCl_3$: C: 48.81; H: 5.47; N: 4.75. Found: C: 48.57; H: 5.39; N: 4.65.

General Procedure for the Radical Cyclisations of N-Alkenyl-Trichloroacetamides. To a solution of *N*-alkenyl trichloroacetamide (1 mmol) in dry 2-propanol (12 ml) were added acetic acid (20 mmol, 1.14 ml), nickel powder (30 mmol, 1.76 g, from Janssen now Acros Chemicals) and the mixture was stirred under reflux in an inert atmosphere. The reaction, monitored by T.L.C. was usually complete in a few hours. The mixture was then cooled to room temperature, diluted with ether and filtered through Celite. Water was then added to the filtrate which was subsequently neutralised with saturated aqueous sodium bicarbonate, washed with water, brine, dried over sodium sulfate and concentrated in vacuo. The residue was purified by silica gel column chromatography to give cyclised compounds, β-lactams or γ-lactams and usually a small amount of uncyclised reduced products.

Cyclisation of 1a. Following the general procedure, compounds **4a** and **5a** were separated by column chromatography (eluent: heptane/ethyl acetate-9/1 to 1/1).

1-Benzyl-3,3-dichloro-4-isopropenyl-azetidin-2-one 4a obtained as a colourless oil in 50% yield; ^1H NMR: δ 1.77 (s, 3H, CH_3); 3.98 (d, J_{AB} = 14.9 Hz, 1H, NCH*H*); 4.13 (s, 1H, NC*H*); 4.93 (d, J_{AB} = 14.9 Hz, 1H, NCH*H*); 5.05 (s, 1H, C=CH*H*); 5.27 (s, 1H, C=CH*H*); 7.20-7.46 (m, 5H, C_6H_5); ^{13}C NMR: δ 20.0; 45.7; 73.6; 116.6; 128.5; 129.2; 133.6; 137.4; 161.6; IR (cm^{-1}): 2819; 1791 (C=O); 1389; 914; h.r.m.s.: Calc. for $C_{13}H_{13}Cl_2NO$: 270.0452. Found: 270.0469.

***N*-Benzyl-2,2-dichloro-*N*-(2-methyl-3-phenylsulfanyl-propenyl)-acetamide 5a** obtained as a colourless solid in 20% yield; ^{1}H NMR: δ 1.61 (d, J = 1.4 Hz, 3H, CH_3); 3.48 (s, 2H, NCH_2); 4.53 (s, 2H, SCH_2); 5.51 (s, 1H, $CHCl_2$); 5.78 (m, 1H, HC=C); 7.10-7.49 (m, 10H, C_6H_5).

Cyclisation of 1b. Following the general procedure, compounds **4b** and **5b** were separated by column chromatography (eluent heptane/ethyl acetate-95/5 to 7/3).

1-Benzyl-3,3-dichloro-4-(4-isopropenyl-cyclohex-1-enyl)-azetidin-2-one 4b obtained as a yellow oily mixture of two isomers (ratio 5:2) in 65% yield; ^{1}H NMR: δ 1.75 (s, 3H, CH_3); 1.41-2.44 (m, 7H, $3CH_2$, CH); 3.97 (d, J_{AB} = 14.9 Hz, 5/7H, NCHH); 3.98 (d, J_{AB} = 14.9 Hz, 2/7H, NCHH); 4.12 (s, 1H, NCH); 4.73 (s, 1H, C=CHH); 4.76 (s, 1H, C=CHH); 4.87 (d, J_{AB} = 14.9 Hz, 2/7H, NCHH); 4.90 (d, J_{AB} = 14.9 Hz, 5/7H, NCHH); 5.79 (m, 1H, HC=C); 7.17-7.45 (m, 5H, C_6H_5); ^{13}C NMR: δ 20.9; 26.5; 26.6; 27.0; 30.5; 30.6; 40.7; 45.6; 45.8; 73.5; 73.9; 109.3; 128.4; 128.8; 129.1; 130.2; 133.8; 149.0; 161.6; IR (cm^{-1}): 2921; 1789 (C=O); 1399; 889; Anal. Calcd for $C_{19}H_{21}Cl_2NO$: C: 65.15; H: 6.04; N: 4.00. Found: C: 65.03; H: 6.28; N: 3.90.

***N*-Benzyl-2,2-dichloro-*N*-(4-isopropenyl-2-phenylsulfanyl-cyclohexylidenemethyl)-acetamide 5b** obtained as colourless crystals in 20% yield; m. p. 109 °C (from pentane/ether); ^{1}H NMR: δ 0.51 (m, 1H, CH); 1.54-1.75 (m, 2H, CH_2); 1.64 (s, 3H, CH_3); 1.96-2.58 (m, 4H, CH_2); 4.02-4.11 (m, 1H, SCH); 4.28 (d, J_{AB} = 13.9 Hz, 1H, NCHH); 4.61 (m, 1H, C=CHH); 4.70 (m, 1H, C=CHH); 4.75 (d, J_{AB} = 13.9 Hz, 1H, NCHH); 5.43 (s, 1H, $CHCl_2$); 5.60 (br s, 1H, HC=C); 7.12-7.55 (m, 10H, C_6H_5); IR (cm^{-1}): 1680 (C=O); 1653; 1189; Anal. Calcd for $C_{25}H_{27}Cl_2NOS$: C: 65.21; H: 5.91; N: 3.04. Found: C: 65.21; H: 5.82; N: 2.98.

Cyclisation of 1c. Following the general procedure, compounds **4c** and **5c** were separated by column chromatography (eluent: heptane/ethyl acetate-9/1 to 1/1).

1-Benzyl-3-chloro-4-isopropenyl-3-methyl-azetidin-2-one 4c obtained as a colourless oily mixture of two isomers (ratio 5:4) in 61% yield; ^{1}H NMR: δ 1.60 (s, 5/3H, CH_3CCl); 1.70-1.72 (m, 3H, CH_3C=CH_2); 1.74 (s, 4/3H, CH_3CCl); 3.69 (s, 4/9H, NCH); 3.92 (d, J_{AB} = 14.8 Hz, 4/9H, NCHH); 3.93 (s, 5/9H, NCH); 3.95 (d, J_{AB} = 14.8 Hz, 5/9H, NCHH); 4.89 (d, J_{AB} = 14.8 Hz, 1H, NCHH); 4.93-4.96 (m, 5/9H, C=CHH); 4.96-4.99 (m, 4/9H, C=CHH); 5.15-5.19 (m, 1H, C=CHH); 7.19-7.43 (m, 5H, C_6H_5); ^{13}C NMR for the major isomer: δ 19.2; 20.5; 44.7; 69.8; 72.1; 113.8; 128.0; 128.1; 128.8; 134.4; 138.2; 166.8. For the minor isomer: δ 19.9; 24.3; 45.1; 68.1; 72.2; 114.3; 127.9; 128.3; 128.8; 134.7; 138.2; 166.8; IR (cm^{-1}): 2939; 1775 (C=O); 1396; 1077; Anal. Calcd for $C_{14}H_{16}ClNO$: C: 67.33; H: 6.46; N: 5.61. Found: C: 67.18; H: 6.41; N: 5.74.

***N*-Benzyl-2-chloro-*N*-(2-methyl-3-phenylsulfanyl-propenyl)-propionamide 5c** obtained as a colourless solid in 11% yield; ^{1}H NMR: δ 1.43 (d, J = 6.6 Hz, 3H, CH_3CH); 1.63 (s, 3H, CH_3C=CH); 3.46 (dd, J_{AB} = 14.0 Hz, J = 0.9 Hz, 1H, SCHH); 3.53 (dd, J_{AB} = 14.0 Hz, J = 0.7 Hz, 1H, SCHH); 3.97 (d, J = 6.6 Hz, 1H, $CHCH_3$); 4.35 (d, $J_{A'B'}$ = 14.2 Hz, 1H, NCHH); 4.68 (d, $J_{A'B'}$ = 14.2 Hz, 1H, NCHH); 3.13-3.18 (m, 1H, HC=C); 7.10-7.51 (m, 10H, C_6H_5).

Cyclisation of 6 in the presence of $(SePh)_2$. The reaction was carried out according to the general procedure in the presence of diphenyl diselenide (2x mmol). Compounds **9** and **11** were separated by column chromatography (eluent: heptane/ethyl acetate-1/0 to 1/1).

1-Benzyl-3,3-dichloro-4-(1-methyl-1-phenylselanyl-ethyl)-azetidin-2-one 9 obtained as colourless crystals in 39% yield; m. p. 71 °C (from pentane/ether); ^{1}H NMR: δ 1.54 (s, 3H, CH_3); 4.10 (s, 1H, NCH); 4.49 (d, J_{AB} = 15.4 Hz, 1H, NCHH); 5.12 (d, J_{AB} = 15.4 Hz, 1H, NCHH); 7.00-7.44 (m, 10H, C_6H_5); ^{13}C NMR: δ 22.9; 25.8; 44.6; 45.8; 76.7; 82.5; 126.2; 128.0; 128.2; 128.9; 129.0; 134.4; 138.2; 162.5; IR (cm^{-1}): 1786 (C=O); 1390; 1112; 909; Anal. Calcd for $C_{19}H_{19}Cl_2NOSe$: C: 53.42; H: 4.48; N: 3.28; Cl: 16.60. Found: C: 53.29; H: 4.53; N: 3.17; Cl: 16.52.

1-Benzyl-3,3-dichloro-4,4-dimethyl-5-phenylselanyl-pyrrolidin-2-one 11 obtained as a yellow oil in 16% yield; ^{1}H NMR: δ 1.17 (s, 3H, CCH_3); 1.52 (s, 3H, CCH_3); 4.20 (d, J_{AB} = 14.7 Hz, 1H, NCHH); 4.46 (s, 1H, CHSe); 5.15 (d, J_{AB} = 14.7 Hz, 1H, NCHH); 6.62-7.54 (m, 10H, C_6H_5); ^{13}C NMR: δ 22.4; 24.2; 45.9; 49.9; 72.3; 74.6; 128.0; 128.4; 128.6; 128.7; 129.7; 134.7; 137.6; 138.5; 166.1; IR (cm^{-1}): 2974; 1731 (C=O); 1420; 925; Anal. Calcd for $C_{19}H_{19}Cl_2NOSe$: C: 53.42; H: 4.48; N: 3.28. Found: C: 53.66; H: 4.57; N: 3.17.

Cyclisation of 6. Following the general procedure, compounds **13**, **14** and **15** were separated by column chromatography (eluent: heptane/ethyl acetate-9/1 to 1/1).

1-Benzyl-3-chloro-5-isopropoxy-4,4-dimethyl-pyrrolidin-2-one 13. Two isomers were separated (ratio 5:1). For the first isomer: colourless crystals (45% yield); m. p. 84 °C (from pentane/ether); ^{1}H NMR: δ 1.00 (s, 3H, CCH_3); 1.13 (s, 3H, CCH_3); 1.16 (d, J = 6.1 Hz, 6H, $CH(CH_3)_2$); 3.60 (sep., J = 6.1 Hz, 1H, $CH(CH_3)_2$); 3.95 (d, J_{AB} = 15.2 Hz, 1H, NCHH); 4.28 (s, 1H, NCH); 4.42 (s, 1H, ClCH); 5.08 (d, J_{AB} = 15.2 Hz, 1H, NCHH); 7.19-7.41 (m, 5H, C_6H_5); ^{13}C NMR: δ 20.6; 22.2; 22.4; 22.8; 43.6; 44.3; 64.8; 72.4; 92.2; 127.8; 128.1; 128.9; 136.1; 169.9; IR (cm^{-1}): 2976; 1721 (C=O); 1427; 1266; 1065; 894; 2975; Anal. Calcd for $C_{16}H_{22}ClNO_2$: C: 64.97; H: 7.50; N: 4.73. Found: C: 64.92; H: 7.45; N: 4.61. For the second isomer: colourless crystals (9% yield); m. p. 78 °C (from pentane/ether); ^{1}H NMR: δ 1.12 (s, 3H, CCH_3); 1.14 (d, J = 6.2 Hz, 3H, $CHCH_3$); 1.15 (d, J = 6.2 Hz, 3H, $CHCH_3$); 1.16 (s, 3H, CCH_3); 3.56 (sep, J = 6.2 Hz, 1H, $CH(CH_3)_2$); 4.02 (s, 1H, NCH); 4.06 (d, J_{AB} = 15.3 Hz, 1H, NCHH); 4.30 (s, 1H, ClCH); 5.03 (d, J_{AB} = 15.3 Hz, 1H, NCHH); 7.17-7.40 (m, 5H, C_6H_5); ^{13}C NMR: δ 18.8; 22.3; 22.9; 25.8; 42.7; 43.7; 63.6; 72.8; 92.9; 127.7; 127.8; 128.8; 136.3; 169.6; IR (cm^{-1}): 2975; 1711 (C=O); 1430; 1103; 1074; 911; Anal. Calcd for $C_{16}H_{22}ClNO_2$: C: 64.97; H: 7.50; N: 4.73. Found: C: 64.98; H: 7.28; N: 4.75.

***N*-Benzyl-2,2-dichloro-*N*-(2-methyl-propenyl)-acetamide 14** obtained as a colourless solid in 9% yield; ^{1}H NMR: δ 1.46 (s, 3H, CH_3); 1.74 (s, 3H, CH_3); 4.64 (s, 2H, NCH_2); 5.80 (br s, 1H, HC=C), 6.29 (s, 1H, $CHCl_2$); 7.17-7.41 (m, 5H, C_6H_5); ^{13}C NMR: 17.7; 22.0; 52.2; 64.6; 121.3; 127.9; 128.6; 128.9; 135.8; 140.4; 164.2.

***N*-Benzyl-2-chloro-*N*-(2-methyl-propenyl)-acetamide 15** obtained as a colourless oil in 19% yield; ^{1}H NMR: δ 1.43 (s, 3H, CH_3); 1.71 (s, 3H, CH_3); 4.03 (s, 2H, CH_2Cl); 4.46 (s, 2H, NCH_2); 5.80 (br s, 1H, *H*C=C), 7.18-7.41 (m, 5H, C_6H_5).

Cyclisation of 16. Following the general procedure, compounds **17**, **18** and **19** were separated by column chromatography (eluent: heptane/ethyl acetate-9/1 to 1/1).

2-Benzyl-4-chloro-1-isopropoxy-2-aza-spiro[4,5]decan-3-one 17. Two isomers were separated (ratio 4/3) in 49% yield. For the major isomer: colourless powder (28% yield); ^{1}H NMR: δ 1.12 (d, J = 6.1 Hz, 3H, $CHCH_3$); 1.15 (d, J = 6.1 Hz, 3H, $CHCH_3$); 1.1-2.2 (m, 10H, CH_2); 3.64 (sep, J = 6.1 Hz, 1H, $CH(CH_3)_2$); 4.03 (d, J_{AB} = 15.3 Hz, 1H, NCH*H*); 4.46 (s, 1H, C*H*); 4.58 (s, 1H, C*H*); 5.09 (d, J_{AB} = 15.3 Hz, 1H, NCH*H*); 7.20-7.41 (m, 5H, C_6H_5); ^{13}C NMR: δ 22.1; 22.5; 23.0; 25.3; 28.2; 28.9; 44.1; 63.7; 72.3; 89.8; 127.6; 128.7; 135.9; 169.8; IR (cm^{-1}): 2933; 1719 (C=O); 1423; 1059; Anal. Calcd for $C_{19}H_{26}ClNO_2$: C: 67.94; H: 7.80; N: 4.17. Found: C: 67.71; H: 7.59; N: 4.35. For the minor isomer: colourless crystals (21% yield); m. p. 93 °C (from pentane/ether); ^{1}H NMR: δ 1.14 (d, J = 6.1 Hz, 3H, $CHCH_3$); 1.16 (d, J = 6.1 Hz, 3H, $CHCH_3$); 1.3-2.6 (m, 10H, CH_2); 3.61 (sep., J = 6.1 Hz, 1H, $CH(CH_3)_2$); 4.02 (d, J_{AB} = 15.3 Hz, 1H, NCH*H*); 4.16 (s, 1H, C*H*); 4.17 (s, 1H, C*H*); 5.07 (d, J_{AB} = 15.3 Hz, 1H, NCH*H*); 7.19-7.42 (m, 5H, C_6H_5); ^{13}C NMR: δ 22.3; 22.5; 22.7; 25.5; 28.7; 34.8; 44.2; 59.4; 72.6; 94.3; 127.7; 127.9; 128.8; 136.2; 171.0; IR (cm^{-1}): 2930; 1716 (C=O); 1449; 1077; Anal. Calcd for $C_{19}H_{26}ClNO_2$: C: 67.94; H: 7.80; N: 4.17. Found: C: 67.51; H: 7.71; N: 4.14.

***N*-Benzyl-2,2-dichloro-*N*-cyclohexylidenemethyl-acetamide 18** obtained as a colourless oil in 12% yield; ^{1}H NMR: δ 1.10-2.20 (m, 10H, CH_2); 4.64 (s, 2H, NCH_2); 5.74 (br s, 1H, *H*C=C); 6.33 (s, 1H, $CHCl_2$); 7.20-7.52 (m, 5H, C_6H_5).

***N*-Benzyl-2-chloro-*N*-cyclohexylidenemethyl-acetamide 19** obtained as a colourless oil in 14% yield; ^{1}H NMR: δ 1.10-2.20 (m, 10H, CH_2); 4.07 (s, 2H, CH_2Cl); 4.60 (s, 2H, NCH_2); 5.76 (br s, 1H, *H*C=C); 7.19-7.52 (m, 5H, C_6H_5).

Cyclisation of 20. Following the general procedure, compounds **23**, **25** and **26** were separated by column chromatography (eluent heptane/ethyl acetate-95/5 to 9/1).

1-(2-Benzylsulfanyl-ethyl)-3,3-dichloro-4-(1-chloro-1-methyl-ethyl)-azetidin-2-one 23 obtained as a yellow oil in 24% yield; ^{1}H NMR: δ 1.74 (s, 3H, CH_3); 1.86 (s, 3H, CH_3); 2.75 (dd, J = 7.6 Hz, 5.9 Hz, 2H, SCH_2CH_2); 3.45 (dd, J_{AB} = 14.3 Hz, J = 5.9 Hz, 1H, NCH*H*); 3.76 (s, 2H, CH_2Ph); 3.81 (dd, J_{AB} = 14.3 Hz, J = 7.6 Hz, 1H, NCH*H*); 4.40 (s, 1H, NC*H*); 7.20-7.42 (m, 5H, C_6H_5); ^{13}C NMR: δ 26.0; 28.0; 29.0; 35.5; 41.0; 69.2; 78.7; 81.0; 127.3; 128.7; 129.1; 137.6; 161.7; IR (cm^{-1}): 2938; 1795 (C=O); 1396; 1104; Anal. Calcd for $C_{15}H_{18}Cl_3NOS$: C: 49.13; H: 4.95; N: 3.82. Found: C: 49.37; H: 5.13; N: 3.75.

1-(2-Benzylsulfanyl-ethyl)-3-chloro-5-isopropoxy-4,4-dimethyl-pyrrolidin-2-one 25 obtained as a yellow oil in 25% yield; ^{1}H NMR: δ 1.10 (s, 3H, CCH_3); 1.15 (d, J = 6.1 Hz, 3H, $CHCH_3$); 1.17 (d, J = 6.1 Hz, 3H, $CHCH_3$); 1.17 (s, 3H, CCH_3); 2.58 (ddd, J_{AB} = 13.3 Hz, J = 7.3 Hz, 6.3 Hz, 1H, $SCHHCH_2$); 2.67 (ddd, J_{AB} = 13.3 Hz, J = 7.3 Hz, 6.3 Hz, 1H, $SCHHCH_2$); 3.16 (dt, $J_{A'B'}$ = 14.1 Hz, J = 7.3 Hz, 1H, NCH*H*); 3.66 (sep, J = 6.1 Hz, 1H, $CH(CH_3)_2$); 3.75 (dt, $J_{A'B'}$ = 14.1 Hz, J = 6.3 Hz, 1H, NCH*H*); 3.76 (s, 2H, CH_2Ph); 4.33 (s, 1H, NC*H*); 4.49 (s, 1H, ClC*H*); 7.20-7.41 (m, 5H, C_6H_5); ^{13}C NMR: δ 20.6; 22.5; 22.7; 22.8; 29.2; 36.3; 40.6; 43.9; 64.6; 72.4; 93.8; 127.3; 128.7; 129.0; 162.3; IR (cm^{-1}): 3100; 1719 (C=O); 1259; 1060; Anal. Calcd for $C_{18}H_{26}ClNO_2S$: C: 64.97; H: 7.50; N: 4.73. Found: C: 64.92; H: 7.45; N: 4.61.

***N*-(2-Benzylsulfanyl-ethyl)-2,2-dichloro-*N*-(2-methyl-propenyl)-acetamide 26** obtained as a yellow oil in 35%; ^{1}H NMR: δ 1.63 (d, J = 1.5 Hz, 3H, CH_3); 1.78 (d, J = 1.5 Hz, 3H, CH_3); 2.54-2.61 (m, 2H, SCH_2CH_2); 3.57-3.63 (m, 2H, NCH_2); 4.72 (s, 2H, CH_2Ph); 5.88 (sep, J = 1.5 Hz, 1H, *H*C=C), 6.23 (s, 1H, $CHCl_2$); 7.20-7.45 (m, 5H, C_6H_5); ^{13}C NMR: δ 17.9; 22.0; 28.0; 36.0; 48.2; 64.4; 121.7; 127.2; 128.6; 129.1; 138.1; 140.0; 164.4.

Cyclisation of 27. The reaction was carried out following the general procedure using diphenyl diselenide (2x mmol) as a trap and compounds **33**, **34**, **35**, **36** and **37** were separated by column chromatography (eluent heptane/ethyl acetate-1/0 to 1/1).

1-Benzyl-3-chloro-1,4,5,6-tetrahydro-indol-2-one 33 obtained as a yellow oil in 18% yield; ^{1}H NMR: δ 1.82 (qu, J = 6.3 Hz, 2H, CH_2); 2.30 (td, J = 4.8 Hz, 6.3 Hz, 2H, CH_2); 2.62 (t, J = 6.3 Hz, 2H, CH_2); 4.80 (s, 2H, NCH_2); 5.59 (t, J = 4.8 Hz, 1H, C*H*); 7.09-7.66 (m, 5H, C_6H_5); ^{13}C NMR: δ 22.2; 22.6; 24.3; 43.4; 111.9; 119.2; 127.2; 127.4; 129.2; 132.2; 137.0; 140.0; 164.8; IR (cm^{-1}): 2947; 1705 (C=O); 1436; 1146; 952; h.m.r.s.: Calc. for $C_{15}H_{14}ClNO$: 260.0842. Found: 260.0839.

1-Benzyl-1,4,5,6-tetrahydro-indol-2-one 34 obtained as colourless crystals in 18% yield; m. p. 94 °C (from pentane/ether); ^{1}H NMR: δ 1.80 (qu, J = 6.3 Hz, 2H, CH_2); 2.26 (q, J = 6.3 Hz, 4.8 Hz, 2H, CH_2); 2.61 (t, J = 6.3 Hz, 2H, CH_2); 4.77 (s, 2H, NCH_2); 5.52 (t, J = 4.8 Hz, 1H, C*H*); 5.82 (s, 1H, C=C*H*CO); 7.11-7.48 (m, 5H, C_6H_5); IR (cm^{-1}): 3058; 1692 (C=O); 1651; 1439; 1262; Anal. Calcd for $C_{15}H_{15}NO$: C: 79.97; H: 6.71; N: 6.22. Found: C: 79.72; H: 6.92; N: 6.21.

1-Benzyl-3-chloro-1,4,5,6,7,7a-hexahydro-indol-2-one 35 obtained as colourless crystals in 13% yield; m. p. 73 °C (from pentane/ether); ^{1}H NMR: δ 0.91-1.10 (m, 1H, CH*H*); 1.16-1.43 (m, 2H, CH*H*); 1.72-2.13 (m, 3H, CH*H*); 2.24-2.39 (m, 1H, CH*H*); 2.83-2.97 (m, 1H, CH*H*); 3.59 (dd, J = 11.3 Hz, 6.1 Hz, 1H, NC*H*); 4.23 (d, J_{AB} = 15.2 Hz, 1H, NCH*H*); 5.01 (d, J_{AB} = 15.2 Hz, 1H, NCH*H*); 7.10-7.36 (m, 5H, C_6H_5); ^{13}C NMR: δ 23.2; 25.5; 25.8; 26.6; 44.6; 59.8; 127.7; 128.0; 128.8; 137.3; 140.2; 152.8; IR (cm^{-1}): 3152; 1699 (C=O); 1148; Anal. Calcd for $C_{15}H_{16}ClNO$: C: 68.83; H: 6.16; N: 5.35. Found: C: 68.54; H: 6.17; N: 5.28.

1-Benzyl-1,4,5,6,7,7a-hexahydro-indol-2-one 36 obtained as colourless crystals in 22% yield; m. p. 78 °C (from pentane/ether); ^{1}H NMR: δ 0.92-1.11 (m, 1H, CH*H*); 1.19-1.43 (m, 2H, CH*H*); 1.71-2.39 (m, 4H, CH*H*); 2.64-2.80 (m, 1H, CH*H*); 3.58 (dd, J = 11.3 Hz, 6.0 Hz, 1H, NC*H*); 4.17 (d, J_{AB} = 15.2 Hz, 1H, NCH*H*); 4.99 (d, J_{AB} = 15.2 Hz, 1H, NCH*H*); 5.80 (s, 1H, *H*C=C); 7.11-7.38 (m, 5H, C_6H_5); ^{13}C NMR: δ 23.0; 27.5; 28.4; 33.3; 44.6; 61.4; 118.0; 127.3; 127.8; 128.6;

138.0; 162.3; IR (cm^{-1}): 2947; 1685 (C=O); 1411; 1253; 849; Anal. Calcd for $C_{15}H_{17}NO$: C: 79.26; H: 7.54; N: 6.16. Found: C: 78.96; H: 7.55; N: 6.01.

***N*-Benzyl-2,2-dichloro-*N*-cyclohex-1-enyl-acetamide 37** obtained as a yellowish oil in 9% yield; ^1H NMR: δ 1.4-2.3 (m, 8H, CH_2); 4.46-4.79 (m, 2H, NCH_2); 5.51 (br s, 1H, HC=C); 6.39 (s, 1H, $CHCl_2$); 7.08-7.50 (m, 5H, C_6H_5); IR (cm^{-1}): 2948; 1683 (C=O); 1259.

Cyclisation of 38a. Following general procedure, compounds **44a**, **45a** and **46a** were separated by column chromatography (eluent heptane/ethyl acetate-9/1).

1-Benzyl-3-chloro-3a-methyl-1,3,3a,4,5,6-hexahydro-indol-2-one 44a obtained as a colourless oily mixture of two isomers (ratio 2:1) in 42% yield; ^1H NMR: δ 1.16 (s, 2H, CH_3); 1.23 (s, 1H, CH_3); 1.46-2.23 (m, 6H, CH_2); 4.10 (s, 1/3H, CHCl); 4.34 (s, 2/3H, CHCl); 4.45 (d, J_{AB} = 15.2 Hz, 2/3H, NCHH); 4.61 (d, J_{AB} = 15.4 Hz, 1/3H, NCHH); 4.69 (d, J_{AB} = 15.4 Hz, 1/3H, NCHH); 4.83 (d, J_{AB} = 15.2 Hz, 2/3H, NCHH); 4.90 (t, J = 3.7 Hz, 2/3H, HC=C); 4.93 (t, J = 3.6 Hz, 1/3H, HC=C); 7.17-7.39 (m, 5H, C_6H_5); ^{13}C NMR: for the major isomer: δ 17.8; 20.8; 22.7; 32.6; 42.1; 43.9; 67.0; 100.1; 127.3; 127.4; 128.5; 135.7; 140.9; 168.8. For the minor isomer: δ 17.7; 22.6; 25.1; 28.6; 40.5; 43.5; 63.3; 102.0; 127.0; 127.3; 128.5; 135.8; 141.3; 170.1; IR (cm^{-1}): 2935; 1733 (C=O); 1688; 1455; 1406; 1316; Anal. Calcd for $C_{16}H_{18}ClNO$: C: 69.79; H: 6.59. Found: C: 69.27; H: 6.52.

1-Benzyl-3a-methyl-1,3,3a,4,5,6-hexahydro-indol-2-one 45a obtained as a colourless oil in 7% yield; ^1H NMR: δ 1.17 (s, 3H, CH_3); 1.49-2.20 (m, 6H, CH_2); 2.35 (s, 2H, CH_2CO); 4.40 (d, J_{AB} = 15.4 Hz, 1H, NCHH); 4.72 (t, J = 3.7 Hz, 1H, HC=C); 4.83 (d, J_{AB} = 15.4 Hz, 1H, NCHH); 7.18-7.41 (m, 5H, C_6H_5); ^{13}C NMR: δ 18.5; 22.7; 26.0; 34.0; 36.5; 43.3; 46.4; 98.3; 127.4; 128.6; 137.1; 140.9; IR (cm^{-1}): 2947; 1721 (C=O); 1681; 1400; 1312.

***N*-Benzyl-2,2-dichloro-*N*-(2-methyl-cyclohex-1-enyl)-acetamide 46a** obtained as a yellow oil in 19% yield; ^1H NMR: δ 1.27 (br s, 3H, CH_3); 1.4-2.1 (m, 8H, CH_2); 4.58 (d, J_{AB} = 13.2 Hz, 1H, NCHH); 4.70 (d, J_{AB} = 13.2 Hz, 1H, NCHH); 6.25 (s, 1H, $CHCl_2$); 7.20-7.41 (m, 5H, C_6H_5); ^{13}C NMR: 18.5; 22.2; 23.1; 29.0; 30.9; 50.5; 63.9; 127.9; 128.4; 129.5; 130.5; 135.9; 136.1; 164.0; IR (cm^{-1}): 2936; 1683 (C=O); 1399; 805; Anal. Calcd for $C_{16}H_{19}Cl_2NO$: C: 61.72; H: 6.21. Found: C: 62.16; H: 6.16.

Cyclisation of 38b. Following the general procedure, compound **44b** was obtained following silica gel column chromatography (eluent: heptane/ethyl acetate-95/5).

1-Benzyl-3-chloro-3a-(3,4-dimethoxyphenyl)-1,3,3a,4,5,6-hexahydro-indol-2-one 44b obtained as colourless crystals in 41% yield; m. p. 45 °C (from diisopropyl ether); ^1H NMR: δ 1.20 (m, 1H, CH_2CHHCH_2); 1.64 (m, 1H, CH_2CHHCH_2); 1.76 (td, J_{AB} = 12.6 Hz, J = 3.0 Hz, 1H, $CCHHCH_2$); 2.11 (m, 2H, CH_2CH=C); 2.62 (dt, J_{AB} = 12.6 Hz, J = 12.6 Hz, 3.3 Hz, 1H, $CCHHCH_2$); 3.62 (s, 3H, OCH_3); 3.82 (s, 3H, OCH_3); 4.62 (d, $J_{A'B'}$ = 14.7 Hz, 1H, NCHH); 4.65 (s, 1H, CHCl); 4.88 (d, $J_{A'B'}$ = 14.7 Hz, 1H, NCHH); 5.28 (t, J = 3.6 Hz, 1H, C=CH); 6.47 (dd, J = 8.5 Hz, 2.1 Hz, 1H, C_6H_3); 6.59 (d, J = 8.5 Hz, 1H, C_6H_3); 6.66 (d, J = 2.1 Hz, 1H, C_6H_3); 7.34-7.40 (m, 5H, C_6H_5); ^{13}C NMR: δ 18.3; 23.0; 34.3; 44.7; 50.6; 55.8; 55.9; 66.2; 102.9; 110.3; 112.7; 121.5; 128.0; 128.7; 128.8; 131.0; 135.8; 140.2; 148.2; 168.5; IR (cm^{-1}): 2935; 1735.2 (C=O); 1686; 1517; 1401; 1259. Anal. Calcd for $C_{23}H_{24}ClNO$: C: 69.43; H: 6.09. Found: C: 69.44; H: 6.01.

Cyclisation of 47. Following the general procedure, compounds **48** and **49** were separated by column chromatography (eluent: heptane/ethyl acetate-9/1 to 8/2).

1-Methyl-3-chloro-3a-(3,4-dimethoxyphenyl)-1,3,3a,4,5,6-hexahydro-indol-2-one 48 obtained as a yellowish powder in 35% yield; ^1H NMR: δ 1.23-2.69 (m, 6H, CH_2); 3.12 (s, 3H, NCH_3); 3.86 (s, 6H, OCH_3); 4.56 (s, 1H, CHCl); 5.19 (t, J = 3.6 Hz, 1H, CH=C); 6.65-6.80 (m, 3H, C_6H_3); ^{13}C NMR: δ 18.4; 22.9; 26.8; 33.6; 50.8; 55.7; 55.9; 66.1; 102.0; 110.5; 112.4; 121.2; 131.1; 141.4; 148.1; 168.1; IR (cm^{-1}): 2937; 1738 (C=O); 1688 (C=C); 1519; 1465; 1395; 1259; 1119; 1027; Anal. Calcd for $C_{17}H_{20}NO_3Cl$: C: 63.53; H: 6.28; N: 4.36. Found: C: 63.31; H: 6.43; N: 3.97.

***N*-Methyl-2,2-dichloro-*N*-(2-(3,4-dimethoxyphenyl)-cyclohex-1-enyl)-acetamide 49** obtained as a colourless oil in 25% yield; ^1H NMR: δ 1.79-2.38 (m, 8H, CH_2); 3.01 (s, 3H, NCH_3); 3.85 (s, 6H, OCH_3); 6.39 (s, 1H, $CHCl_2$); 6.61-6.83 (m, 3H, C_6H_3); ^{13}C NMR: δ 22.6; 22.8; 28.2; 31.4; 35.7; 55.8; 56.0; 63.6; 110.4; 111.3; 119.4; 131.6; 134.1; 137.6; 150.0; 150.3; 164.8; IR (cm^{-1}): 2936; 1685 (C=O); 1513; 1465; 1383; 1263; 1141; 1027; 804.

1-Methyl-3-chloro-3a-(3,4-dimethoxyphenyl)-1,3,3a,4,5,6-hexahydro-indol-2-one 50. 87 mg of compound **48** (0.27 mmol) was dissolved in 1 ml of water and 1 ml of acetic acid. 200 mg (3 mmol) of Zn powder were added and the mixture was heated under reflux in an inert atmosphere. The reaction, monitored by TLC was complete after 5 hrs. After cooling to room temperature, the mixture was diluted with ether, filtered through Celite, neutralised with saturated aqueous $NaHCO_3$, washed with water, brine, dried over magnesium sulfate and concentrated in vacuo. The residue was filtered through silice (eluent: heptane/ethyl acetate-9/1) to afford pure **50** in 75% yield;[25] ^1H NMR: δ 1.55-2.27 (m, 6H, CH_2); 2.63 (d, J_{AB} = 15.9 Hz, 1H, CHHCO); 2.77 (d, J_{AB} = 15.9 Hz, 1H, CHHCO); 2.99 (s, 3H, NCH_3); 3.85 (s, 6H, OCH_3); 5.13 (t, J = 3.5 Hz, 1H, C=CH); 6.75 (s, 3H, C_6H_3); ^{13}C NMR: δ 18.4; 22.8; 35.9; 47.1; 56.0; 100.2; 110.5; 111.0; 119.5; 138.0; 147.9.

Cyclisation of 56. Following the general procedure, compounds **59** and **60** were separated by column chromatography (eluent: heptane/ethyl acetate-9/1).

1-But-3-enyl-1,3a,4,5,6-hexahydro-indol-2-one 59 obtained as a unstable yellow oil in 51% yield; ^1H NMR: δ 1.82 (qu, J = 6.2 Hz, 2H, CH_2); 2.28-2.39 (m, 4H, CH_2); 2.62 (t, J = 6.2 Hz, 2H, CH_2); 3.60 (t, J = 7.1 Hz, 2H, NCH_2); 5.02 (d, J = 4.0 Hz, 1H, CH=CHH); 5.07 (d, J = 11.1 Hz, 1H, CH=CHH); 5.65 (t, J = 3.5 Hz, 1H, NC=CH); 5.71 (s, 1H, CHCO); 5.75 (m, 1H, $CH=CH_2$); ^{13}C NMR: δ 23.4; 24.1; 24.2; 33.1; 38.2; 109.8; 115.5; 116.6; 134.8; 139.6; 147.0; 170.0; IR (cm^{-1}): 2936, 1694 (C=O); 1440, 1413, 1358, 1346, 1331, 1322.

***N*-But-3-enyl-2,2-dichloro-*N*-cyclohex-1-enyl-acetamide 60** obtained as yellow oil in 11% yield; ^1H NMR: δ 1.59-2.17 (m, 8H, CH_2); 2.32 (q, J = 6.8 Hz, 2H, CH_2); 3.50 (m, 2H, NCH_2); 5.03 (d, J = 4.9 Hz, 1H, C=CHH)); 5.09 (d, J =

12.0 Hz, 1H, C=CH*H*); 5.75 (ddd, J = 12.0 Hz, 6.2 Hz, 4.9 Hz, 1H, C*H*=CH_2); 5.81 (m, 1H, C=C*H*); 6.36 (s, 1H, C*H*Cl_2); ^{13}C NMR: δ 21.3; 22.6; 24.8; 27.7; 31.8; 45.7; 64.1; 117.0; 129.6; 134.7; 137.3; 163.2; IR (cm^{-1}): 2937; 1683 (C=O); 1449; 1401; 1209; 805.

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