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Hydro-de-halogenation and consecutive deprotection of chlorinated *N*-amido-pyrrolidin-2-ones with Raney-Ni: an effective approach to gabapentin

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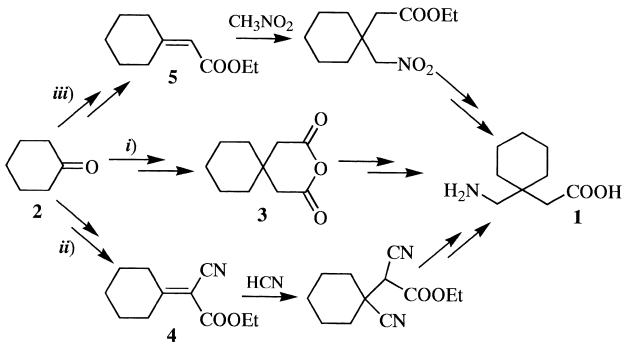
Abstract—The benzoylamino group was identified as a useful radical cyclization auxiliary that can be smoothly removed on hydro-de-halogenation of chlorinated *N*-substituted-pyrrolidin-2-ones with Raney-Ni. This methodology was successfully implemented in a new and appealing route to the anti-epileptic drug gabapentin.

1. Introduction

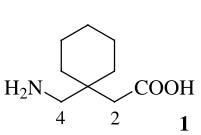
Gabapentin (**1**), which is sold under the name neurontin®, is an anti-epileptic drug marketed by Pfizer that displays an extremely low toxicity (Fig. 1). Although originally designed as a lipophilic GABA analogue, it is now known that gabapentin **1** does not interact with any of the enzymes on the GABA metabolic pathway. It also does not directly interact with either the $GABA_A$ or $GABA_B$ receptors.[1] Instead, gabapentin **1** has been shown to bind with high affinity to a binding site of a calcium channel and it is thought that it exerts the biological activity through interaction at this site.[2]

Until relatively recently, all the reported syntheses of **1**[3] followed the route outlined by Sircar in 1928,[4] which involved formation of the intermediate glutaric-anhydride derivative **3** (in several steps) from cyclohexanone (**2**) (Scheme 1, path *i*). Unfortunately, this route, which entails a Hofmann, Curtius or Lossen rearrangement to form **1**, requires expensive safety precautions for the handling of thermally unstable azides and isocyanates. In 1990, Mettler devised a more economical and technically more attractive pathway to gabapentin **1**, which exploited the addition of hydrocyanic acid to cyano(cyclohexylidene)acetate (**4**) (Scheme 1, path *ii*).[5] However, the problem of using toxic HCN[6] spurred the development of a safer procedure by Geibel.[7] In this approach, nitromethane was reacted with cyclohexylideneacetate (**5**) in order to introduce the aminomethyl moiety in **1** (Scheme 1, path *iii*).[8] Although all of these approaches utilise cyclohexanone as a starting material, more recently, alternative routes to **1** have appeared that start from benzonitrile[9a] or cyclohexane carboxaldehyde.[9b]



Scheme 1.

The main problem with these approaches is the difficulty in preparing a wide range of analogues. Hence, although a variety of different groups have been placed at different sites within the cyclohexane ring, it is not easy to locate substituents at the C-2 and C-4 positions of 1.[10]



gabapentin

Figure 1.

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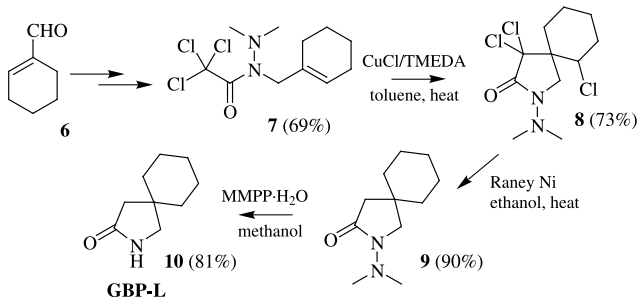
A short time ago we were involved in a project to develop potentially more flexible routes to gabapentin **1**.[11] Among the pathways we proposed, the 5-*exo* halogen atom transfer radical cyclisation of the cyclohexene derivative **7** to form **8**, using copper(I) chloride and TMEDA, emerged as the most efficient and promising approach (Scheme 2). The cyclohexyl precursor **7** was prepared by condensation of 1,1-dimethylhydrazine with cyclohex-1-ene carboxaldehyde **6**, followed by reduction of the hydrazone and *N*-acylation of the resulting hydrazine.[12] Heating trichloride **8** with Raney nickel resulted in the formation of spirocycle **9** in high yield, thereafter the nitrogen protecting group was efficiently removed on treatment of **9** with magnesium monoperoxyphthalate in methanol. This afforded the 2-azaspiro[4.5]decan-3-one (GBP-L) **10** and since the spirocycle **10** can be easily hydrolyzed to **1**, this completed our formal synthesis of gabapentin **1**.[6a–c,7,8a,13]



Scheme 2.

Importantly, this new approach to **1** involves the formation of trichloride **8**, which has chlorine atoms adjacent to the lactam carbonyl and within the cyclohexane ring. These chlorine atoms can potentially be used to further functionalise the cyclohexane ring and the C-2 position of **1**. Another useful feature of our route to gabapentin **1** is the preparation of GBP-L **10**, which also exhibits significant pharmacological activity.[14]

The choice of the dimethylamino group as a 'cyclization auxiliary'[15] offers the opportunity to combine *N*-deprotection with C–Cl bond reduction by for example, hydrogenation using Raney-Ni, as has been observed for more simple 2-pyrrolidinones.[15] Unfortunately, this expectation was not realized and the synthesis of GBP-L **10** needed to be lengthened so as to include a final *N*-deprotection step (under oxidizing conditions).

This approach would certainly gain in appeal if a quicker route to GBP-L **10** from chlorinated pyrrolidin-2-one **8** could be realized. Hence we have been prompted to look for a more easily removable cyclization auxiliary such as the benzoylamino group, which we now report to be smoothly removed by Raney-Ni during the hydro-de-chlorination step.

2. Results and discussion

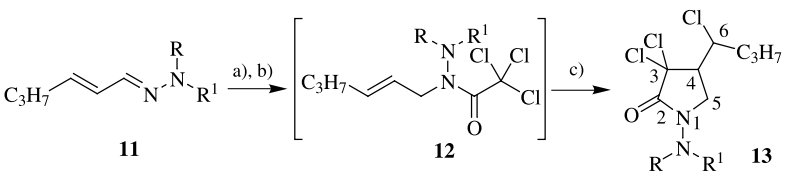
While Raney-Ni[16] has regularly been employed in the reductive cleavage of the N–N bond of hydrazines, the situation is much more different for hydrazides, which are preferably cleaved with alkali metals in liquid ammonia.[17,18] In fact, the few reported cases for preparing *N*-unsubstituted γ-lactams from *N*-(*N*RR′)-pyrrolidin-2-ones generally use Li^0/NH_3.[19] Although this method is efficient it is short of practicality. In contrast the use of Raney-Ni, which is inexpensive, easily prepared in the laboratory and commercially available in a number of different forms with varying activities, offers an attractive alternative approach to reductive deprotection under non-anhydrous conditions.[20]

The first studies on the cleavage of hydrazides with Raney-Ni were conducted in the late 1950's by Ainsworth[21] and Hinmam.[22] It was observed that monoalkyl substituted monoacylhydrazines and unsubstituted 1,2-diacylhydrazines could be cleaved readily, but when one of the hydrogen atoms on nitrogen was replaced by another substituent, the reaction proceeded with difficulty or not at all.[22] Since then, only limited and marginal applications have been reported.[19c,23]

Recently, we considered the formation of 5-membered nitrogen heterocycles by 5-*exo*-trig atom transfer radical cyclisation (ATRC) of hydrazide precursors. The ATRC has captured the attention of synthetic chemists owing to its attractive features, including the fact that functionalized cyclic products are formed using catalytic amounts of inexpensive metal complexes.[11,15,24] For ring closure of the intermediate α-*N*-allyl-carbamoyl radical, a substituent bound to the nitrogen atom is critical. Usually, this cyclization auxiliary is the benzyl group, but its efficient removal from the cyclic amides has proved problematic.[25] Instead, the dimethylamino group proved to be a promising alternative, since it could be easily and efficiently cleaved with Raney-Ni in ethanol/water at 100–110°C.[15]

When the same hydro-de-chlorination/deprotection protocol was explored in the final stage of our new approach to the gabapentin **1** (Scheme 2) we were, however, disappointed to observe only reduction of the three C–Cl bonds. This may be attributed to the steric bulk of the spiro substituent at the C(4) position of the γ-lactam **8**, which shields the (CO)N–$N(CH_3)_2$ segment from the metal surface.[21b,26] This failure encouraged us to engineer an alternative nitrogen protecting group that could be more easily reduced using Raney-Ni. So we aimed to prepare, and then subject to hydrogenolysis, a number of *N*-amino or *N*-amido 2-pyrrolidinones **13** using reliable preparative routes that we have recently devised (Scheme 3).[12,24b]

The starting α,β-unsaturated hydrazones **11a–g** of *trans*-2-hexenal were thus easily converted into the corresponding *N*-allyl hydrazines by reaction with dimethylamine-borane/methanesulfonic acid, which were subsequently acylated by trichloroacetyl chloride/pyridine and, without isolation, rearranged to the desired polychlorinated pyrrolidin-2-ones **13** in satisfactory yields (Table 1). The use of methanesulfonic acid in the reduction step, as a substitute for *p*-toluenesulfonic acid (PTS), simplified the procedure because commercial PTS had to be dried (by azeotropic distillation) prior to use.[12] It should also be noted that in order to prevent the formation of 4-diethylaminobut-3-en-2-one, from the parasitic reaction between trichloroacetyl



Scheme 3. (a) DMAB/methanesufonic acid, ether, 0°C, 3 h, argon. (b) Trichloroacetyl chloride, pyridine, CH_2Cl_2, 0°C, overnight, argon. (c) CuCl/TMEDA, acetonitrile, 60°C, 20 h, argon.

Table 1. Preparation of the polychlorinated γ-lactams **13a–g**[a]

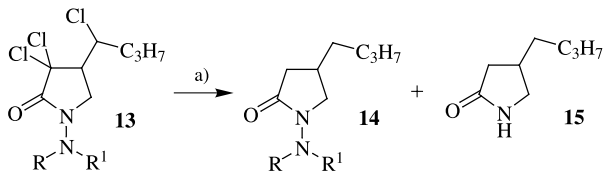
Entry	Precursor		Product		Yield (%)[b]	d.r.[b]
	R	R^1				
1	CH_3	CH_3	**11a**	**13a**	43	92:8
2	$(CH_2)_5$		**11b**	**13b**	44	94:6
3	$(CH_2)_2O(CH_2)_2$		**11c**	**13c**	40	96:4
4	H	PhCO	**11d**	**13d**	46	100:0
5	H	CH_3CO	**11e**	**13e**	48	96:4
6	COArCO		**11f**	**13f**	37	92:8
7	CH_3	PhCO	**11g**	**13g**	35	100:0

[a] See Scheme 3, reactions performed using 10 mmol of **11**.
[b] Determined on isolated material.

chloride and triethylamine (observed during the acylation step),[27] pyridine was preferred as the base.

The ATRC of trichloride **12** proceeds with excellent diastereoselectivity. The higher yield of the (4*R**,6*S**)-diastereoisomer of **13** (*anti*-addition) is consistent with the intermediate pyrrolidinone radical preferentially adopting conformation **A** rather than **B** (Scheme 4). Assuming the intermediate radical has an almost planar structure, like that of a carbocation centre,[28a] this can be explained on the basis of steric interactions: for conformer **A**, the bulky propyl side-chain is pointing in the opposite direction to the large hydrazone group. The facial selectivity of the ensuing attack by $CuCl_2$/TMEDA on **A** should be very high owing to the steric hindrance of the chloro groups. An example of a similar ATRC exhibiting a highly stereoselective *anti*-addition has been described by Ikeda.[28b] The Mn(III)-based oxidative free-radical cyclization of substituted allyl α-methyl-β-ketoesters proceeded analogously.[28c]

The chlorinated and *N*-substituted pyrrolidin-2-ones **13** were then heated at 110°C with wet Raney-Ni in ethanol for 21 h (Scheme 5). The quantity of the metal (~2 g/0.5 mmol of substrate) was halved compared with the amount suggested in our previous work (~4 g/0.5 mmol of substrate).[15] This change in the original experimental procedure was designed to make the effects of the N(1) substituents on the effectiveness of the N–N cleavage more evident.



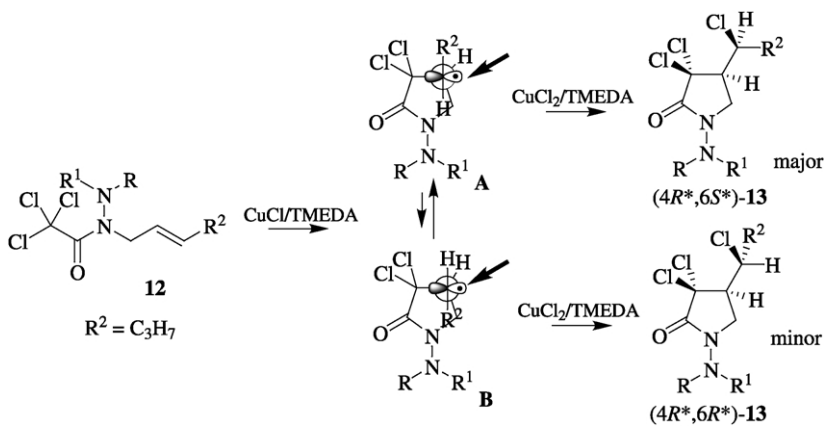
Scheme 5. (a) Wet Raney-Ni, ethanol, 110°C, 21 h.

It is clear from the results obtained (Table 2), that the benzoylamino group is by far the most easily removable substituent among those investigated (Table 2, entry 4). To explain this behaviour the ipotetic mechanism, described by Horner and Jordan for the electoreductive cleavage of

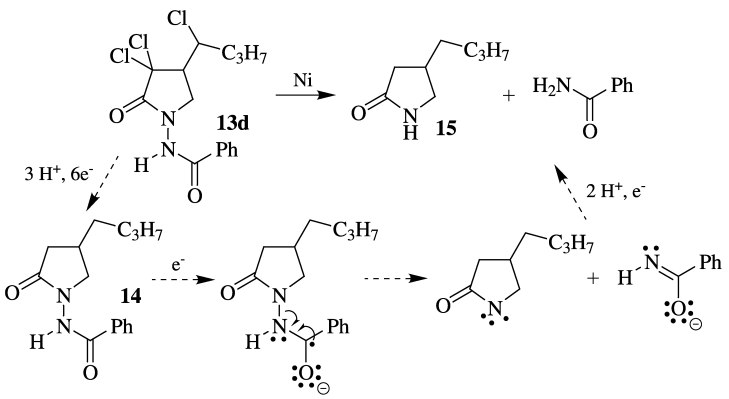
Table 2. Reaction of the γ-lactams **13** with Raney-Ni[a]

Entry	Precursor	Conv. (%)[b]	Products	
			(%)[c]	
1	**13a**	100	**14a** (99)	**15** (0)[b]
2	**13b**	100	**14b** (78)	**15** (8)
3	**13c**	100	**14c** (97)	**15** (1)[b]
4	**13d**	100	**14d** (0)[b]	**15** (90)
5	**13e**	100	**14e** (74)	**15** (10)
6	**13f**	100	–[d]	**15** (0)[b]
7	**13g**	100	**14g** (94)	**15** (0)[b]

[a] Substrate 0.5 mmol, Raney-Ni ~2 g, ethanol 2 mL, *T*=110°C.
[b] GC values.
[c] Determined on isolated material.
[d] A complex mixture of products was isolated but there was no trace of N–N bond cleavage.



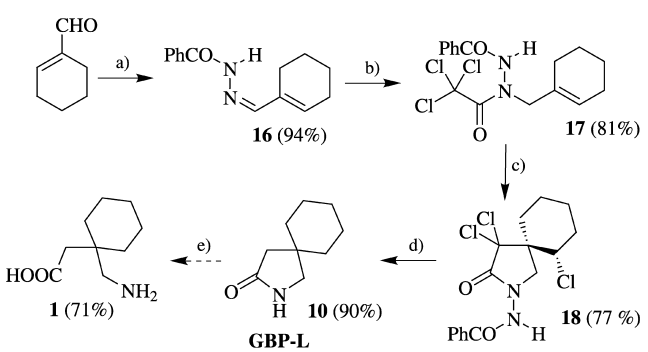
Scheme 4.



Scheme 6.

hydrazides,[29] could be helpful. These authors suggested that the N–N bond cleavage is facilitated by electron-transfer to the carbonyl group (Scheme 6). The highest reactivity observed with **13d** can thus be related to the low energy of its LUMO as a consequence of the extensive conjugation between the electron-withdrawing carbonyl group and the aromatic ring. When the hydrogen atom of the hydrazide group of **13d** is replaced by a methyl substituent, the extent of conjugation is reduced due to steric effects and the N–N bond of pyrrolidin-2-one **13g** stood up to the reaction conditions (Table 2, entry 7).

Encouraged by these promising results, our attention turned to the use of this method to prepare GBP-L **10** from halogenated pyrrolidin-2-one **8** (Scheme 2). The hydrazone precursor **16** was prepared, in 94% yield, from condensation of benzoylhydrazine with cyclohex-1-ene carboxaldehyde **6** (Scheme 7). The ensuing reduction of the C=N bond with dimethylamine-borane/methanesulfonic acid and *N*-acylation of the resulting hydrazine gave the amide **17** with high efficiency (81%). On treatment of **17** with CuCl/TMEDA[3a] the desired spirocycle **18** was formed in 77% yield, as a single diastereoisomer, which was tentatively assigned as having (5*R* *,6*S* *) stereochemistry in accord with a selective anti-addition of the chlorine atom (see earlier). Finally, we were pleased to see that heating the intermediate trichloride γ-lactam **18** with Raney-Ni at 110°C smoothly resulted in the formation of GBP-L **10** (90%), and this step completed our formal synthesis of gabapentin **1**. The overall yield of **1** prepared via this 5-step approach is 37%, which is higher



Scheme 7. (a) Benzoylhydrazine, CH_2Cl_2, rt, overnight. (b): i) DMAB/-methanesulfonic acid, ether, 0°C, 3 h, argon; ii) trichloroacetyl chloride, pyridine, CH_2Cl_2, 0°C, overnight, argon. (c) CuCl/TMEDA, acetonitrile, 60°C, 20 h, argon. (d) Wet Raney-Ni, ethanol, 110°C, 21 h. (e) HCl, heat.[8a]

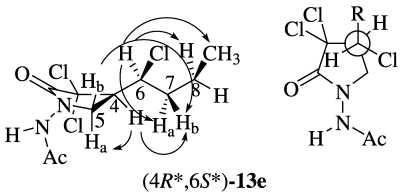
than that reported for the conventional 4-step nitromethane route (26%) (Scheme 1, step *iii*).[8a]

2.1. Structural characterization of substituted pyrrolidinones 13

The regiochemistry of the two diastereoisomers of *N*-(acetylamino)-3,3-dichloro-4-(1-chlorobutyl)-2-pyrrolidinone **13e** was derived through heteronuclear multiple-quantum (HMQC)[30a] and multiple-bond (HMBC)[30b] experiments and through ^{1}H Nuclear Overhauser Exchange Spectroscopy (NOESY).[30c] The first two experiments allow us to find the directly bonded H,C pairs and those separated by two or three bonds. These experiments are very useful for the determination and assignment of the methylene protons: the protons at 2.25 and 1.85 ppm correlate with a carbon at 37.4 ppm, are attributed to CH_2(7), whereas those at 1.72 and 1.54 ppm which correlate with a carbon at 18.9 ppm, are assigned to CH_2(8) of the butyl chain. The protons at 3.90 and 3.56 ppm correlate with a carbon at 50.6 ppm and are assigned to the CH_2(5) of the pyrrolidinone ring. The assignment of the methylene groups is necessary in order to find the relative configuration of the two chiral centers C(4) and C(6) in **13e**. This goal was obtained through a NOESY experiment performed with a mixing time of 600 ms. The NOESY spectrum displays a strong cross peak between H(4) (at 3.19 ppm) and H(5a) (at 3.90 ppm) and a cross peak of lower intensity with H(5b) (at 3.56 ppm), suggesting a *cis*-relationship between H(4) and H(5a). Furthermore, H(4) displays a NOE of medium intensity with only one proton (at 1.85 ppm) belonging to the CH_2(7) group. A *trans*-relationship between H(4) and H(6) (at 4.30 ppm) was suggested by the lack of a NOE and this allows us to define the relative configuration of C(4) and C(6) (4*R* * and 6*S* *) of the major diastereoisomer (**A**). Cross-peaks between H(5b) (3.56 ppm) and H(7b) (at 1.85 ppm), and cross peaks of H(6) with H(7a) (2.25 ppm), H(8) (1.54 ppm) and the methyl protons hint that the butyl chain adopts the conformation depicted in Figure 2.

The proton spectrum of the second diastereoisomer (**B**) shows similar peaks for the pyrrolidinone ring protons, whereas marked differences are found for the butyl chain protons, that are clearly diastereotopic in **A** but not in **B**.

Applying the same experiments, we were able to obtain the complete characterisation of diastereoisomer **B** and to



(4*R**,6*S**)-**13e**

Figure 2.

establish, through a NOESY experiment, the relative configuration of the two chiral centers: a high intensity cross-peak between H(4) (at 3.19 ppm) and H(6) (at 4.29 ppm), besides the expected NOEs allows us to attribute a (4*R* *-6*R* *) relative configuration to **B**.

On the same basis, a confident attribution of the configuration can be made for lactams **13a**–**d**,**f**,**g**.

3. Conclusion

Our endeavour to increase the appeal of a new route to gabapentin **1** from cyclohexane carboxaldehyde **6** was fulfilled by the discovery that the benzoylamino group is an effective radical cyclization auxiliary, which can be smoothly removed during the hydro-de-halogenation of the chlorinated spirocycle intermediate **18** with Raney-Ni. Importantly, the formation of the polychlorinated adduct **18**, which has chlorine atoms adjacent to the lactam carbonyl and within the cyclohexane ring, has the potential to be used to further functionalise the cyclohexane ring and the C-2 position of **1**. Moreover with the replacement of trichloroacetyl chloride with other α-perchloroacyl chlorides the procedure is also potentially adaptable to the preparation of a vast array of modified gabapentins. Another useful feature of our route to **1** is the intermediate formation of GBP-L **10**, a substance with an interesting pharmacological activity.

Studies on the application of this approach to the synthesis of the GABA analogue pregabalin[31] will be reported in due course.

4. Experimental

4.1. General

^{1}H NMR spectra were recorded in $CDCl_3$ solutions with a Bruker 400AMX WB and a Jeol EX 270 spectrometer, and the chemical shifts are reported in ppm relative to tetramethylsilane as external standard. Conditions for HMQC[30a] spectra were: evolution delay=3.57 ms, spectral width=10 ppm with 2048 complex points in *f*2; 256 *t*1 values and 32 scans for *t*1 value. A squared sine function (SSB=2) in *f*2 and *f*1 was applied before Fourier transformation. Similar conditions were used for HMBC[30b] experiments except: delay for low-pass filter=3.57 ms, evolution delay=50 ms (optimization of ^nJ(H,C)=10 Hz responses) and 64 scans for *t*1 value. Conditions for NOESY[30c] phase-sensitive spectra by time-proportional phase incrementation (TPPI) were: mixing time of 600 ms, spectral width 8.16 ppm with 2048 complex points in *f*2; 128 *t*1 values and 64 scans for *t*1 value. A squared sine function (SSB=2) in *f*2 and Gaussian multiplication (LB=−1, GB=0.01) in *f*1 were applied before Fourier transformation. IR spectra were obtained with a Perkin–Elmer 1600 Series FTIR. Mass spectra were acquired with a combined HP 5890 GC/HP 5989A MS Engine. Reagents and solvents were standard grade commercial products, purchased from Aldrich or Fluka, and used without further purification. The acyl hydrazones **11e** and **11g** were secured following the protocol of Feid–Allah.[32]

4.1.1. Typical procedure for the preparation of hydrazones: *trans*-2-hexenal *N*,*N*-dimethylhydrazone (11a). In a single-necked round-bottom flask (100 mL) *trans*-2-hexenal (5.8 mL, 50.0 mmol) and *N*,*N*-dimethylhydrazine (4.1 mL, 52.5 mmol) were successively dissolved, at room temperature, in CH_2Cl_2 (50 mL), and the solution was stirred until complete conversion (16–24 h). Afterward the reaction mixture was diluted with water (50 mL) and extracted. The organic phases were collected and dried by azeotropic distillation with toluene, and concentrated. The crude product **11a**, was recovered (6.59 g, 94%) as a reddish oil, which did not require further purification. [Found: C, 68.4; H, 11.4; N, 20.2. $C_8H_{16}N_2$ requires C, 68.52; H, 11.50; N, 19.98]; δ_H (200 MHz, $CDCl_3$) 7.05 (1H, d, *J*=8.8 Hz, C*H*=N), 6.22 (1H, ddt, *J*=15.5, 8.8, 1.3 Hz, CH=C*H*CH=N), 5.83 (1H, dt, *J*=15.5, 7.5 Hz, C*H*=CHCH=N), 2.84 (6H, s, N*Me*$_2$), 2.14 (2H, dq, *J*=7.5, 1.3 Hz, CH_2-allylic), 1.47 (2H, sex, *J*=7.5 Hz, CH_2Me), 0.94 (3H, t, *J*=7.5 Hz, CH$_2$*Me*); *m*/*z* (EI): 140 (100, M$^+$), 125 (16), 111 (77), 96 (51), 82 (38), 68 (36).

4.1.2. 1-(1-Aza-1,3-eptadienyl)-piperidine (11b). According to the general procedure *trans*-2-hexenal (5.8 mL, 50.0 mmol) gave **11b** (8.38 g, 93%) as a dark orange oil; [Found: C, 73.4; H, 11.3; N, 15.6. $C_{11}H_{20}N_2$ requires C, 73.28; H, 11.18; N, 15.54]; δ_H (200 MHz, $CDCl_3$) 7.30 (1H, d, *J*=8.7 Hz, C*H*=N), 6.23 (1H, ddt, *J*=15.6, 8.7, 1.3 Hz, CH=C*H*CH=N), 5.86 (1H, dt, *J*=15.6, 6.8 Hz, C*H*=CHCH=N), 3.02 (4H, m, 2×CH_2(α)-pip), 2.14 (2H, dq, *J*=7.5, 1.3 Hz, CH_2-allylic), 1.70 (4H, m, 2×CH_2(β) -pip) 1.52 (2H, m, CH_2(γ) -pip), 1.47 (2H, sex, *J*=7.50 Hz, CH_2Me), 0.93 (3H, t, *J*=7.5 Hz, CH$_2$*Me*); *m*/*z* (EI): 180 (95 M$^+$), 164 (8), 151 (100), 137 (18), 122 (18), 96 (27), 84 (72).

4.1.3. 4-(1-Aza-1,3-eptadienyl)-morpholine (11c). According to the general procedure *trans*-2-hexenal (5.8 mL, 50.0 mmol) gave **11c** (8.57 g, 94%) as an orange oil; [Found: C, 66.1; H, 9.9; N, 15.6. $C_{10}H_{18}N_2O$ requires C, 65.90; H, 9.95; N, 15.37]; δ_H (200 MHz, $CDCl_3$) 7.31 (1H, d, *J*=8.7 Hz, C*H*=N), 6.20 (1H, ddt, *J*=15.5, 8.7, 1.3 Hz, CH=C*H*CH=N), 5.90 (1H, dt, *J*=15.5, 7.5 Hz, C*H*=CHCH=N), 3.82 (4H, m, CH_2OCH_2), 3.02 (4H, m, CH_2NCH_2), 2.13 (2H, dq, *J*=7.5, 1.3 Hz, CH_2-allylic), 1.45 (2H, sex, *J*=7.5 Hz, CH_2Me), 0.91 (3H, t, *J*=7.5 Hz, CH$_2$*Me*); *m*/*z* (EI): 182 (100 M$^+$), 153 (58), 125 (12), 110 (13), 96 (62), 86 (32), 82 (30), 56 (47).

4.1.4. *N*-(1-Aza-1,3-eptadienyl)-phthalimide (11f). According to the general procedure *trans*-2-hexenal (1,2 mL, 10.0 mmol) gave **11f** (2.23 g, 92%) as a slightly orange solid, mp 73–75°C; [Found: C, 69.6; H, 5.9; N, 11.5.

$C_{14}H_{14}N_2O_2$ requires C, 69.41; H, 5.82; N, 11.56]; δ_H (200 MHz, $CDCl_3$) 8.98 (1H, m, C*H*═N), 7.92–7.73 (4H, m, Ph), 6.58–6.28 (2H, m, C*H*═C*H*CH═N), 2.27 (2H, m, CH_2-allylic), 1.52 (2H, sex, *J*=7.5 Hz, CH_2Me), 0.97 (3H, t, *J*=7.5, CH_2*Me*); *m*/*z* (EI): 242 (67 M^+), 199 (88), 148 (52), 130 (55), 105 (100), 104 (82), 96 (55), 80 (50), 76 (65).

4.1.5. *trans*-2-Hexenal benzoylhydrazone (11d). According to the procedure of Feid–Allah,[32] *trans*-2-hexenal (5.8 mL, 50.0 mmol) gave **11d** (10.27 g, 95%) as a white powder mp 105–107°C; [Found: C, 72.1; H, 7.3; N, 12.8. $C_{13}H_{16}N_2O$ requires C, 72.19; H, 7.46; N, 12.95]; δ_H (200 MHz, $CDCl_3$) 9.08 (1H, bs, N*H*), 7.87–7.43 (6H, m, *Ph*–C*H*═N), 6.42–6.11 (2H, m, C*H*═C*H*CH═N), 2.24 (2H, q, *J*=7.5 Hz, CH_2-allylic), 1.47 (2H, sex, *J*=7.5 Hz, CH_2Me), 0.97 (3H, t, *J*=7.5 Hz, CH_2*Me*); *m*/*z* (EI): 216 (7 M^+), 173 (4), 147 (7), 105 (100), 77 (63), 51 (27).

4.1.6. *trans*-2-Hexenal acetylhydrazone (11e). According to the procedure of Feid–Allah,[32] *trans*-2-hexenal (5.8 mL, 50.0 mmol) gave **11e** (7.02, 91%) as a reddish oil; [Found: C, 62.2; H, 9.3; N, 18.3. $C_8H_{14}N_2O$ requires C, 62.31; H, 9.15; N, 18.17]; δ_H (200 MHz, $CDCl_3$) 10.5 (1H, s, N*H*), 7.53 (1H, m, C*H*═N), 6.24–6.10 (2H, m, C*H*═C*H*CH═N), 2.27 (3H, s, CO*Me*), 2.17 (2H, m, CH_2-allylic), 1.50 (2H, sex, *J*=7.5 Hz, CH_2Me), 0.95 (3H, t, *J*=7.4, CH_2*Me*); *m*/*z* (EI): 154 (96 M^+), 111 (15), 96 (84), 83 (77), 69 (99), 60 (65), 43 (100).

4.1.7. Preparation of *N*-methyl-benzoylhydrazone (11g). In a double-necked round-bottom flask (100 mL) fitted with a Liebig condenser and a rubber septum adapter, *N*-methylhydrazine (2.7 mL, 50 mmol) was dissolved, at 0°C, in CH_2Cl_2 (50 mL), then a solution of *trans*-2-hexenal (5.8 mL, 50.0 mmol) solubilized in CH_2Cl_2 (20 mL) was added. After 1 h, under vigorous stirring, pyridine (6.1 mL 75, mmol) and, slowly, benzoyl chloride (8.7 mL, 75 mmol) were added by syringe. The reaction mixture was left at room temperature for 2 h, then diluted with water (50 mL) and extracted. The aqueous phase was further washed with CH_2Cl_2 (2×10 mL). The organic phases were then collected, dried by azeotropic distillation with toluene, and concentrated. Flash chromatography of the crude product on silica gel, using a petroleum ether (bp 40–60°C)/diethyl ether gradient, gave **11g** (9.67 g, 84%) as an orange solid; mp 63–64°C; [Found: C, 72.8; H, 7.8; N, 12.2. $C_{14}H_{18}N_2O$ requires C, 73.01; H, 7.88; N, 12.16]; δ_H (200 MHz, $CDCl_3$) 7.71–7.37 (6H, m, Ph+C*H*═N), 6.25–6.11 (2H, m, C*H*═C*H*CH═N), 3.48 (3H, s, N*Me*), 2.19 (2H, dq, *J*=1.3, 7.5 Hz, CH_2-allylic), 1.48 (2H, sex, *J*=7.5 Hz CH_2Me), 0.95 (3H, t, *J*=7.5, CH_2*Me*); *m*/*z* (EI): 230 (5 M^+), 134 (15), 105 (77), 77 (42), 51 (13).

4.1.8. Typical procedure for the preparation of chlorinated lactams 13: *N*-(dimethylamino)-3,3-dichloro-4-(1-chlorobutyl)-2-pyrrolidinone (13a). DMAB (0.94 g, 16 mmol) and *trans* 2-hexenal *N*,*N*-dimethylhydrazone **11a** (1.40 g, 10 mmol) were weighted in a screw capped Schlenk tube equipped with a perforable septum; then, under argon and at 0°C, diethyl ether (20 mL) and a solution of methanesulfonic acid (3.89 mL, 60 mmol) in diethyl ether (20 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) and left under stirring for a further 0.5 h to cleave any residual boron-nitrogen bond, always keeping an inert atmosphere. The organic phase (ether) was cannulated into another Schlenk tube, evaporated and CH_2Cl_2 (20 mL) added. After cooling at 0°C, pyridine (0.97 mL, 12 mmol) and trichloroacetyl chloride (1.23 mL, 11 mmol) were introduced. After overnight stirring, the mixture was diluted with NaOH (5% w/v, 60 mL), and extracted with CH_2Cl_2 (2×10 mL). The combined organic layers were dried over $MgSO_4$ and concentrated into a Schlenk tube. Then CuCl (0.1 g, 1 mmol) was introduced, followed by dry acetonitrile (20 mL) and TMEDA (0.30 mL, 2 mmol) under argon. The mixture was stirred at 60°C for 20 h, then diluted with H_2O (10 mL) and extracted with CH_2Cl_2 (2×10 mL). The organic phases were collected, dried by azeotropic distillation with toluene, and concentrated. Flash chromatography of the crude product on silica gel, using a petroleum ether (bp 40–60°C)/diethyl ether gradient, gave the major diastereoisomer (4*R* *,6*S* *)-**13a** (1.14 g, 40%) as an orange solid; mp 73–75°C; [Found: C, 41.8; H, 5.8; N, 9.8. $C_{10}H_{17}Cl_3N_2O$ requires C, 41.76; H, 5.96; N, 9.74]; ν_{max} (KBr) 1734 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 4.29 (1H, dt, *J*=2.7, 9.5, 9.5 Hz, H6), 3.70 (1H, dd, *J*=7.2, 10.0 Hz, H5b), 3.25 (1H, dd, *J*=8.7, 10.0 Hz, H5a), 2.97 (1H, m, H4), 2.72 (6H, s, NMe_2), 2.40–1.39 (4H, m, CH_2CH_2Me), 0.99 (3H, t, *J*=7.3 Hz, CH_2CH_2*Me*); *m*/*z* (EI): 286 (15 M^+), 244 (100), 118 (38), 93 (8), 72 (55), 43 (48). From flash chromatography, the minor diastereoisomer (4*R* *,6*S* *)-**13a** (98 mg, 3%) was also recovered as a dark red oil; [Found: C, 41.8; H, 5.8; N, 9.8. $C_{10}H_{17}Cl_3N_2O$ requires C, 41.76; H, 5.96; N, 9.74]; ν_{max} (liquid film) 1734 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 4.31 (1H, m, H6), 3.52 (1H, dd, *J*=7.2, 9.6 Hz, H5b), 3.24 (1H, dd, *J*=7.4, 9.6 Hz, H5a), 3.07 (1H, m, H4), 2.75 (6H, s, N(CH_3)$_2$), 1.84–1.39 (4H, m, CH_2C$H_2$$CH_3$), 0.97 (3H, t, *J*=7.3 Hz, $CH_2CH_2CH_3$); *m*/*z* (EI): 286 (15 M^+), 244 (100), 118 (38), 93 (8), 72 (54), 43 (48).

4.1.9. *N*-(1-Piperazinyl)-3,3-dichloro-4-(1-chlorobutyl)-2-pyrrolidinone (13b). According to the general procedure, the hydrazone **11b** (10.0 mmol, 1.80 g) gave the major diastereoisomer (4*R* *,6*S* *)-**13b** (1.36 g, 41%) as an orange oil; [Found: C, 47.8; H, 6.5; N, 8.7. $C_{13}H_{21}Cl_3N_2O$ requires C, 47.65; H, 6.46; N, 8.55]; ν_{max} (liquid film) 1732 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 4.29 (1H, dt, *J*=2.8, 9.6, Hz, H6), 3.72 (1H, dd, *J*=7.3, 10.1 Hz, H5b), 3.28 (1H, dd, *J*=8.7, 10.1 Hz, H5a), 3.16–2.89 (5H, m, H4+CH_2(α)-pip), 2.50–1.10 (10H, m, 2×CH_2(β)+2×CH_2(γ)-pip+CH_2CH_2Me), 0.99 (3H, t, *J*=7.3 Hz, CH_2CH_2*Me*); *m*/*z* (EI): 326 (2 M^+), 244 (8), 199 (12), 139 (5), 111 (8), 83 (100), 55 (23). From flash chromatography, the minor diastereoisomer (4*R* *,6*R* *)-**13b** (85 mg, 3%) was also recovered as a pallid orange oil; [Found: C, 47.8; H, 6.5; N, 8.7. $C_{13}H_{21}Cl_3N_2O$ requires C, 47.65; H, 6.46; N, 8.55]; ν_{max} (liquid film) 1732 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 4.30 (1H, m, H6), 3.52 (1H, dd, *J*=7.3, 9.8 Hz, H5b), 3.24 (1H, dd, *J*=7.3, 9.8 Hz, H5a), 3.16–2.89 (5H, m, H4+2×CH_2(α)-pip), 2.50–1.10 (10H, m, 2×CH_2(β)+2×CH_2(γ)-pip+CH_2CH_2Me), 0.96 (3H, t, *J*=7.3 Hz, CH_2CH_2*Me*); *m*/*z* (EI): 326 (2 M^+), 244 (8), 199 (12), 139 (5), 111 (8), 83 (100), 55 (23).

4.1.10. *N*-(4-Morpholinyl)-3,3-dichloro-4-(1-chlorobutyl)-2-pyrrolidinone (13c). According to the general procedure, the hydrazone **11c** (10.0 mmol, 1.82 g) gave

the major diastereoisomer (4*R* *,6*S* *)-**13c** (1.27 g, 38%) as a pale orange solid; mp 121–124°C; [Found: C, 43.8; H, 5.9; N, 8.3. $C_{12}H_{19}Cl_3N_2O_2$ requires C, 43.72; H, 5.81; N, 8.50]; ν_{max} (KBr) 1736 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 4.29 (1H, dt, *J*=2.7, 9.5 Hz, H6), 3.78 (4H, t, *J*=5.4 Hz, 2×C*H*$_2$(O)-mor), 3.73 (1H, dd, *J*=7.3, 10.0 Hz, H5b), 3.30 (1H, dd, *J*=8.7, 10.0 Hz, H5a), 3.21–2.92 (5H, m, H4+2×C*H*$_2$(N)-mor), 2.32–1.41 (4H, m, C*H*$_2$C*H*$_2$Me), 0.99 (3H, t, *J*=7.3 Hz, CH_2CH_2*Me*); *m/z* (EI): 328 (3 M^+), 244 (15), 201 (3), 118 (5), 85 (100), 55 (73). From flash chromatography, the minor diastereoisomer (4*R* *,6*R* *)-**13c** (53 mg, 2%) was also recovered as an orange solid; mp 110–112°C; [Found: C, 43.8; H, 5.9; N, 8.3. $C_{12}H_{19}Cl_3N_2O_2$ requires C, 43.72; H, 5.81; N, 8.50]; ν_{max} (KBr) 1736 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 4.31 (1H, m, H6), 3.78 (4H, t, *J*=5.4 Hz, 2×C*H*$_2$(O)-mor), 3.57 (1H, dd, *J*=7.3, 9.7 Hz, H5b), 3.29 (1H, dd, *J*=7.4, 9.7 Hz, H5a), 3.21–3.04 (5H, m, H4+2×C*H*$_2$(N)-mor), 1.78–1.41 (4H, m, C*H*$_2$C*H*$_2$Me), 0.99 (3H, t, *J*=7.3 Hz, CH_2CH_2*Me*); *m/z* (EI): 328 (3 M^+), 244 (15), 201 (3), 118 (5), 85 (100), 55 (73).

4.1.11. *N*-(Benzoylamino)-3,3-dichloro-4-(1-chlorobutyl)-2-pyrrolidinone (13d). According to the general procedure, the hydrazone **11d** (10.0 mmol, 2.16 g) gave the single diastereoisomer (4*R* *,6*S* *)-**13d** (1.67 g, 46%) as a white solid; mp 171–172°C; [Found: C, 49.5; H, 4.8; N, 7.8. $C_{15}H_{17}Cl_3N_2O_2$ requires C, 49.54; H, 4.71; N, 7.70]; ν_{max} (KBr) 1757, 1656 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 8.59 (1H, s, N*H*), 7.85–7.22 (5H, m, Ph), 4.35 (1H, dt, *J*=2.8, 9.6 Hz, H6), 4.02 (1H, dd, *J*=7.4, 9.6 Hz, H5a), 3.68 (1H, t, *J*=9.6 Hz, H5b), 3.30 (1H, m, H4), 2.41–1.50 (4H, m, C*H*$_2$C*H*$_2$Me), 1.03 (3H, t, *J*=7.4 Hz, CH_2CH_2*Me*); *m/z* (EI): 362 (4 M^+), 135 (13), 105 (100), 77 (35), 51 (5).

4.1.12. *N*-(Acetylamino)-3,3-dichloro-4-(1-chlorobutyl)-2-pyrrolidinone (13e). According to the general procedure, the hydrazone **11e** (10.0 mmol, 1.54 g) gave the major diastereoisomer (4*R* *,6*S* *)-**13e** (1.39 g, 46%) as a pale yellow solid; mp 115–118°C; [Found: C, 39.8; H, 5.2; N, 9.4. $C_{10}H_{15}Cl_3N_2O_2$ requires C, 39.82; H, 5.01; N, 9.29]; ν_{max} (KBr) 1748, 1681 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 8.53 (1H, s, N*H*), 4.30 (1H, dt, *J*=2.7, 9.8 Hz, H6), 3.90 (1H, dd, *J*=7.5, 9.8 Hz, H5a), 3.56 (1H, t, *J*=9.8 Hz, H5b), 3.19 (1H, dt, *J*=9.8, 7.6 Hz, H4), 2.25 (1H, m, H7a), 2.07 (3H, s, CO*Me*), 1.85 (1H, m, H7b), 1.72 (1H, m, H8a), 1.54 (1H, m, H8b), 0.99 (3H, t, *J*=7.4 Hz, $CH_2CH_2CH_2$*Me*); δ_c (100.6 MHz, $CDCl_3$) 168.8 (*C*OMe), 165.6 (C2), 81.7 (C3), 61.1 (C6), 53.6 (C4), 50.6 (C5), 37.4 (C7), 20.8 (C11), 18.9 (C8), 13.2 (C9); *m/z* (EI): 300 (1 M^+), 258 (100), 223 (85), 187 (8), 133 (17), 43 (73). From flash chromatography, the minor diastereoisomer (4*R* *,6*R* *)-**13e** (57 mg, 2%) was also recovered as a white solid; mp 168–172°C; [Found: C, 39.8; H, 5.2; N, 9.4. $C_{10}H_{15}Cl_3N_2O_2$ requires C, 39.82; H, 5.01; N, 9.29]; ν_{max} (KBr) 1748, 1681 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 8.75 (1H, s, N*H*), 4.29 (1H, dt, *J*=2.7, 9.4 Hz, H6), 3.73 (1H, dd, *J*=7.8, 9.4 Hz, H5a), 3.49 (1H, t, *J*=9.4 Hz, H5b), 3.19 (1H, dt, *J*=9.4, 7.8 Hz, H4), 2.07 (3H, s, CO*Me*), 1.72–1.68 (2H, m, H7), 1.52–1.48 (2H, m, H8), 0.95 (3H, t, *J*=7.0 Hz, $CH_2CH_2CH_2$*Me*); δ_c (100.6 MHz, $CDCl_3$) 169.0 (*C*OMe), 165.8 (C2), 82.4 (C3), 58.5 (C6), 53.8 (C4), 48.8 (C5), 36.6 (C7), 20.8 (C11), 18.8 (C8), 13.3 (C9); *m/z* (EI): 300 (1 M^+), 258 (100), 223 (85), 187 (8), 133 (17), 43 (73).

4.1.13. *N*-(Phthalimido)-3,3-dichloro-4-(1-chlorobutyl)-2-pyrrolidinone (13f). According to the general procedure, the hydrazone **11f** (10.0 mmol, 2.42 g) gave the major diastereoisomer (4*R* *,6*S* *)-**13f** (1.32 g, 34%) as a white solid; mp 110–114°C; [Found: C, 49.4; H, 4.1; N, 7.4. $C_{16}H_{15}Cl_3N_2O_3$ requires C, 49.32; H, 3.88; N, 7.19]; ν_{max} (KBr) 1766, 1739 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 7.98–7.81 (4H, m, Ph), 4.40 (1H, dt, *J*=2.8, 9.7 Hz, H6), 3.96 (1H, dd, *J*=7.4, 9.7 Hz, H5a), 3.74 (1H, t, *J*=9.7 Hz, H5b), 3.49 (1H, m, H4), 2.50–1.50 (4H, m, C*H*$_2$C*H*$_2$Me), 1.04 (3H, t, *J*=7.4 Hz, CH_2CH_2*Me*); *m/z* (EI): 388 (2 M^+), 353 (41), 317 (9), 254 (13), 206 (16), 150 (59), 148 (41), 130 (32), 105 (49), 104 (100), 99 (50), 76 (73). From flash chromatography, the minor diastereoisomer (4*R* *,6*R* *)-**13f** (0.12 g, 3%) was also recovered as a white solid; mp 181–185°C; [Found: C, 49.4; H, 4.1; N, 7.4. $C_{16}H_{15}Cl_3N_2O_3$ requires C, 49.32; H, 3.88; N, 7.19]; ν_{max} (KBr) 1766, 1739 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 7.97–7.82 (4H, m, Ph), 4.42 (1H, m, H6), 3.85 (1H, dd, *J*=7.4, 8.7 Hz, H5a), 3.68 (1H, dd, *J*=7.5, 8.7 Hz, H5b), 3.46 (1H, m, H4), 1.78–1.50 (4H, m, C*H*$_2$C*H*$_2$Me), 0.98 (3H, t, *J*=7.4 Hz, CH_2CH_2*Me*); *m/z* (EI): 388 (2 M^+), 353 (41), 317 (9), 254 (13), 206 (16), 150 (59), 148 (41), 130 (32), 105 (49), 104 (100), 99 (50), 76 (73).

4.1.14. *N*-(Benzoylmethylamino)-3,3-dichloro-4-(1-chlorobutyl)-2-pyrrolidinone (13g). According to the general procedure, the hydrazone **11g** (10.0 mmol, 2.30 g) gave the single diastereoisomer (4*R* *,6*S* *)-**13g** (1.32 g, 35%) as a brownish solid; mp 75–77°C; [Found: C, 50.9; H, 5.2; N, 7.5. $C_{16}H_{19}Cl_3N_2O_2$ requires C, 50.88; H, 5.07; N, 7.42]; ν_{max} (KBr) 1752, 1676 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 7.47–7.43 (5H, m, Ph), 4.20 (1H, m, H6), 3.70 (1H, m, H5a), 3.45 (1H, m, H5b), 3.30 (3H, s, *Me*N), 3.10 (1H, m, H4), 2.40–1.40 (4H, m, C*H*$_2$C*H*$_2$Me), 0.97 (3H, t, *J*=7.2 Hz, CH_2CH_2*Me*); *m/z* (EI): 376 (5 M^+), 135 (14), 105 (100), 77 (35), 51 (5).

4.1.15. Typical procedure for the reaction of 12 with Raney-Ni: *N*-(dimethylamino)-4-butyl-2-pyrrolidinone (14a). In a Schlenk tube fitted with a stirring bar was added 20 mL of a Fluka suspension of Raney-Ni in H_2O. After sedimentation of the nickel, supernatant water was carefully removed. To the wet Raney-Ni (~2 g), the lactam **13a** (144 mg, 0.5 mmol) and ethanol (2 mL) were added in succession. The mixture was stirred at 110°C, and after 21 h it was filtered and concentrated. Chromatography of the crude product on silica gel, eluting with a diethyl ether/methanol gradient, gave **14a** (91 mg, 99%), as a colourless oil; [Found: C, 65.3; H, 10.8; N, 15.1. $C_{10}H_{20}N_2O$ requires C, 65.18; H, 10.90; N, 15.20]; ν_{max} (liquid film) 1699 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 3.50 (1H, t, *J*=9.4 Hz, H5a), 2.98 (1H, dd, *J*=7.5, 9.4 Hz, H5b), 2.62 (6H, s, N*Me*$_2$), 2.56–188 (3H, m, H3a,b+H4), 1.52–1.20 (6H, m, C*H*$_2$C*H*$_2$C*H*$_2$Me), 0.90 (3H, t, *J*=6.1 Hz, $CH_2CH_2CH_2$*Me*); *m/z* (EI): 184 (17 M^+), 169 (5), 155 (5), 142 (100), 84 (8), 72 (20), 55 (15), 44 (48).

4.1.16. *N*-(1-Piperazinyl)-4-butyl-2-pyrrolidinone (14b). According to the general procedure lactam **13b** (164 mg, 0.5 mmol) gave **14b** (87 mg, 78%) as a colourless oil; [Found: C, 69.5; H, 10.9; N, 12.5. $C_{13}H_{24}N_2O$ requires C, 69.60; H, 10.78; N, 12.49]; ν_{max} (liquid film) 1698 cm^{-1}; δ_H

(200 MHz, $CDCl_3$) 3.53 (1H, dd, *J*=8.4, 9.1 Hz, H5a), 3.02 (1H, dd, *J*=7.3, 9.1 Hz, H5b), 2.86 (4H, m, 2×*CH*$_2$N-pip), 2.44 (1H, dd, *J*=4.0, 8.7 Hz, H3a), 2.20 (1H, m, H4), 1.96 (1H, dd, *J*=4.0, 8.7 Hz, H3b), 1.78–1.15 (12H, m, C*H*$_2$C*H*$_2$C*H*$_2$Me+C*H*$_2$C*H*$_2$C*H*$_2$-pip), 0.87 (3H, t, *J*=6.4 Hz, $CH_2CH_2CH_2$*Me*); *m/z* (EI): 224 (10 M^+), 142 (100), 84 (100), 83 (77), 68 (7), 55 (35). The hydro-dehalogenated and deprotected lactam **15** (6 mg, 8%) was also recovered on column chromatography.

4.1.17. *N*-(4-Morpholinyl)-4-butyl-2-pyrrolidinone (14c). According to the general procedure, lactam **13c** (165 mg, 0.5 mmol) gave **14c** (110 mg, 97%) as a colourless oil; [Found: C, 63.7; H, 9.8; N, 12.3. $C_{12}H_{22}N_2O_2$ requires C, 63.69; H, 9.80; N, 12.38]; ν_{max} (liquid film) 1697 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 3.78 (4H, m, 2×C*H*$_2$(O)-mor), 3.54 (1H, t, *J*=8.4 Hz, H5a), 3.04 (1H, t, *J*=8.4 Hz, H5b), 2.95 (4H, m, 2×*CH*$_2$(N)-mor), 2.52–1.80 (3H, m H3a,b+H4), 1.50–1.18 (6H, m, C*H*$_2$C*H*$_2$C*H*$_2$Me), 0.88 (3H, t, *J*=6.7 Hz, $CH_2CH_2CH_2$*Me*); *m/z* (EI): 226 (8 M^+), 169 (2), 142 (100), 86 (67), 85 (45), 55 (45).

4.1.18. *N*-(Acetylamino)-4-butyl-2-pyrrolidinone (14e). According to the general procedure, lactam **13e** (151 mg, 0.5 mmol) gave **14e** (73 mg, 74%) as a colourless oil; [Found: C, 60.6; H, 9.3; N, 14.3. $C_{10}H_{18}N_2O_2$ requires C, 60.58; H, 9.15; N, 14.13]; ν_{max} (liquid film) 1717, 1679 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 9.18 (1H, s, NH), 3.69 (1H, t, *J*=8.3 Hz, H5a), 3.31 (1H, t, *J*=8.3 Hz, H5b), 2.70–2.16 (3H, m H3a,b + H4), 1.99 (3H, s, CO*Me*), 1.55–1.17 (6H, m, C*H*$_2$C*H*$_2$C*H*$_2$Me), 0.88 (3H, t, *J*=6.7 Hz, $CH_2CH_2CH_2$*Me*); *m/z* (EI): 198 (2 M^+), 156 (67), 140 (63), 99 (18), 55 (23), 45 (100), 43 (25). The hydro-dehalogenated and deprotected lactam **15** (7 mg, 10%) was also recovered on column chromatography.

4.1.19. *N*-(Benzoylmethylamino)-4-butyl-2-pyrrolidinone (14g). According to the general procedure, lactam **13g** (189 mg, 0.5 mmol) gave **14g** (129 mg, 94%) as a colourless oil; [Found: C, 70.2; H, 8.0; N, 10.1. $C_{16}H_{22}N_2O_2$ requires C, 70.04; H, 8.08; N, 10.21]; ν_{max} (liquid film) 1729, 1671 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 7.49–7.27 (5H, m, Ph), 3.64 (1H, t, *J*=9.2 Hz, H5a), 3.22 (3H, s, *Me*N), 3.18 (1H, t, *J*=9.2 Hz, H5b), 2.70–1.00 (9H, m, H3a,b+H4+C*H*$_2$C*H*$_2$C*H*$_2$Me), 0.84 (3H, t, *J*=6.2 Hz, $CH_2CH_2CH_2$*Me*); *m/z* (EI): 274 (1 M^+), 169 (7), 140 (43), 105 (100), 77 (22), 55 (12).

4.1.20. 4-Butyl-2-pyrrolidinone (15). According to the general procedure, lactam **13d** (182 mg, 0.5 mmol) gave **15** (64 mg, 90%) as a white solid; mp 70–72°C; [Found: C, 67.9; H, 10.8; N, 9.8. $C_8H_{15}NO$ requires C, 68.04; H, 10.71; N, 9.92]; ν_{max} (liquid film) 1684 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 3.45 (1H, dd, *J*=8.7, 9.4 Hz, H5a), 2.98 (1H, dd, *J*=6.2, 9.4 Hz, H5b), 2.57–1.80 (3H, m, H3a,b+H4), 1.43–1.26 (6H, m, C*H*$_2$C*H*$_2$C*H*$_2$Me), 0.87 (3H, t, *J*=6.8 Hz, $CH_2CH_2CH_2$*Me*); *m/z* (EI): 141 (18 M^+), 124 (82), 111 (33), 84 (38), 69 (32), 56 (100), 54 (97), 41 (78).

4.1.21. 1-Cyclohexen-1-carboxaldehyde benzoylhydrazone (16). In a single-necked round-bottom flask (25 mL) benzoylhydrazine (1.36 g, 10 mmol) and 1-cyclohexen-1-carboxyaldehyde (1.05 g, 9.5 mmol) were in succession dissolved, at room temperature, in CH_2Cl_2 (10 mL), and the solution was stirred until complete conversion (16–24 h). Afterward, the reaction mixture was diluted with water (10 mL) and extracted. The aqueous phase was further washed with CH_2Cl_2 (2×10 mL). The organic phases were then collected, dried by azeotropic distillation with toluene, and concentrated. The crude product **16**, which did not require additional purification, was recovered (2.04 g, 94%) as a white solid; mp 188–189°C; [Found: C, 73.5; H, 7.1; N, 12.0. $C_{14}H_{16}N_2O$ requires C, 73.66; H, 7.06; N, 12.27]; ν_{max} (KBr) 1638 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 8.9 (1H, bs, N*H*), 8.0–7.35 (6H, m, Ph+C*H*=N), 6.10 (1H, s, C*H*=CCH=N), 2.0–1.44 (8H, m, (C*H*$_2$)$_4$); *m/z* (EI): 228 (5 M^+), 122 (30), 105 (100), 77 (35), 51 (5).

4.1.22. *N′*-(1-Cyclohexenyl-methyl)-*N*-trichloroacetyl-benzohydrazide (17). DMAB (0.94 g, 16 mmol) and hydrazone **16** (2.28 g, 10 mmol) were weighted in a screw capped Schlenk tube equipped with a perforable septum; then, under argon and at 0°C, diethyl ether (20 mL) and a solution of methanesulfonic acid (3.89 mL, 60 mmol) in diethyl ether (20 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) and left to stir for a further 0.5 h to cleave any residual boron–nitrogen bond, always keeping an inert atmosphere. The organic phase (ether) was cannulated into another Schlenk tube, evaporated and CH_2Cl_2 (20 mL) added. After cooling to 0°C, pyridine (0.97 mL, 12 mmol) and trichloroacetyl chloride (1.23 mL, 11 mmol) were introduced. After stirring overnight, the mixture was diluted with NaOH (5% w/v, 60 mL) and extracted with CH_2Cl_2 (2×10 mL). The organic phases were collected, dried by azeotropic distillation with toluene, and concentrated. Flash chromatography of the crude product on silica gel, using a petroleum ether (bp 40–60°C)/diethyl ether gradient, gave **17** (3.04 g, 81%) as a yellowish solid; mp 141–144°C; [Found: C, 51.3; H, 4.3; N, 7.7. $C_{16}H_{17}Cl_3N_2O_2$ requires C, 51.15; H, 4.56; N, 7.46]; ν_{max} (KBr) 1703, 1677 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 8.8 (1H, bs, N*H*), 7.9–7.4 (5H, m, Ph), 5.65 (1H, s, C*H*=C), 4.35 (2H, bs, C*H*$_2$N), 2.1–1.5 (8H, m, (C*H*$_2$)$_4$); *m/z* (EI): 256 (27), 254 (9), 163 (25), 122 (20), 105 (100), 94 (56), 77 (57).

4.1.23. 2-(Benzoylamino)-4,4,6-trichloro-3-oxo-2-aza-spiro[4,5]decane (18). In a screw capped Schlenk tube equipped with a perforable septum were added trichloro-amide **17** (3.76 g, 10 mmol) and CuCl (0.1 g, 1 mmol), followed by acetonitrile (20 mL) and TMEDA (0.30 mL, 2 mmol) under argon. The mixture was stirred at 60°C for 20 h, then diluted with H_2O (10 mL) and extracted with CH_2Cl_2 (2×10 mL). The organic phases were collected, dried by azeotropic distillation with toluene, and concentrated. Flash chromatography of the crude product on silica gel, using a petroleum ether (bp 40–60°C)/diethyl ether gradient, gave the lactam diastereoisomer (5*R**,6*S**)-**18** (2.89 g, 77%) as a white solid; mp 120–122°C; [Found: C, 51.3; H, 4.3; N, 7.7. $C_{16}H_{17}Cl_3N_2O_2$ requires C, 51.15; H, 4.56; N, 7.46]; ν_{max} (KBr) 1755, 1663 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 9.45 (1H, bs, N*H*), 7.8–7.2 (5H, m, Ph), 4.35 (1H, dd, *J*=4.1, 10.8 Hz, C*H*Cl), 4.00 (1H, d, *J*=10.1 Hz, H5a), 3.70 (1H, d, *J*=10.1 Hz, H5b), 2.6–1.5 (8H, m, (C*H*$_2$)$_4$); *m/z* (EI): 374 (1 M^+), 339 (1), 253 (2), 218 (2), 121 (13), 105 (100), 77 (35).

4.1.24. 3-Oxo-2-aza-spiro[4,5]decane (10). In a Schlenk tube fitted with a stirring bar was added 20 mL of a Fluka suspension of Raney-Ni in H_2O. After sedimentation of the nickel, supernatant water was carefully removed. To the wet Raney-Ni (~2 g) were added lactam **18** (188 mg, 0.5 mmol) and ethanol (2 mL) in succession. The mixture was stirred at 110°C, and after 21 h it was filtered and concentrated. Chromatography of the crude product on silica gel, eluting with a diethyl ether/methanol gradient, gave **10** (69 mg, 90%), as a white solid; mp 84–89°C; [Found: C, 70.4; H, 9.7; N, 9.0. $C_9H_{15}NO$ requires C, 70.55; H, 9.87; N, 9.14]; ν_{max} (liquid film) 1679 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 6.3 (1H, bs, N*H*), 3.15 (2H, s, CH_2NH), 2.15 (2H, s, CH_2CO), 1.64–1.25 (10H, m, (CH_2)$_5$); *m/z* (EI): 153 (100 M^+), 152 (45), 110 (33), 96 (28), 81 (74), 67 (43).

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