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Functional rearrangement of 3-Cl or 3,3-diCl-γ-lactams bearing a secondary 1-chloroalkyl substituent at C-4

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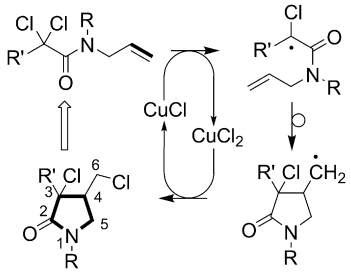
ABSTRACT

The study of the reaction with MeONa/MeOH of chlorinated γ-lactams, prepared from the atom transfer radical cyclization of *N*-allyl-α-perchloroamides, has been extended to the case of substrates carrying an *exo* halogen atom on a branched carbon. Only with secondary *exo* C–Cl groups, that are not located on a fused ring, does the functional rearrangement follow the typical transformation route, which with trichloro-lactams can proceed further to give 4-alkylidene derivatives. From a practical point of view, the outcome of the reaction with di- or trichloro *N*-cinnamylamides is synthetically valuable, affording the 5-methoxy-1H-pyrrol-2(5*H*)-one or 3-benzylidenepyrrolidine-2,5-dione, respectively, in good to excellent yield.

1. Introduction

Reducing the number of corrective oxidation or reduction steps in organic synthesis is one of the endeavours of 'redox economy'.[1] These steps often undermine the overall efficiency of a process. Additionally, many redox reactions are difficult to scale up in industrial settings and frequently are the source of noxious by-products and environmental problems. One way to reduce the number of redox steps along a synthetic path is to turn to systems that may undergo refunctionalization by isomerisation, which are equivalent to internal redox reactions.[1] Examples are the redox isomerisation of allylic systems to aldehydes developed by Trost,[2] refunctionalization involving *N*-heterocyclic carbenes,[3] and the transition metal catalysed-atom transfer radical cyclization (TMC-ATRC).

TMC-ATRC is a modern and powerful technique for the preparation of *N*- or *O*-heterocycles, generally performed with copper or ruthenium catalysts.[4] Among the various applications of this technique, the synthesis of polyhalogenated 2-pyrrolidinones from *N*-protected-*N*-allyl-α-haloamides plays a major role (Scheme 1).[5] Despite a key feature of the reaction being the preservation of all the halo functions in the final product,[4] the interest in the preparation of polychlorinated 2-pyrrolidinones using TMC-ATRC has essentially been confined to the development of new catalysts,[5] whereas the exploitation of the C-X functionality in the cyclic products has been somewhat neglected. As far as we are aware, the few previous applications have regarded: stepwise or sequential radical processes,[6] the preparation of [3,2,0]-hexan-2-ones,[7] the *endo*-dehydrochlorination of *N*-tosyl dichloropyrrolidin-2-ones,[8] aromatization of bicyclic adducts,[6b,c] the substitution of the *exo*-Cl group with oxygen nucleophiles,[9] and, above all, hydro-dechlorinations.[6c,9b,c,10]



Scheme 1. Atom transfer radical cyclization (in bold are highlighted the functional groups involved in the transformation and their new appearance and position in the product).

Some years ago, with the aim of applying the synthetic utility of the TMC-ATRC to the preparation of *N*-protected-*N*-allyl-α-perchloroamides, we serendipitously discovered that the

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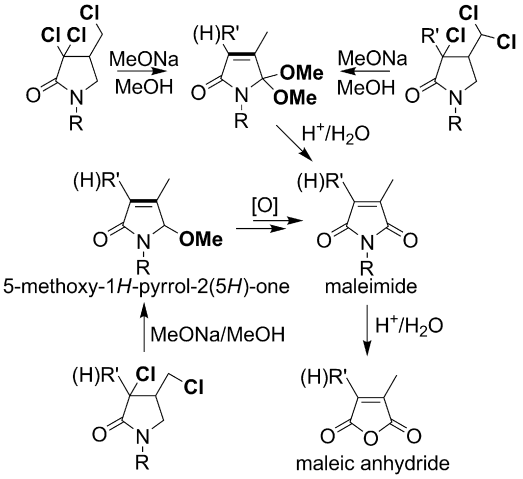
polychlorinated 2-pyrrolidinones, when treated with the methoxide ion in methanol, underwent a redox neutral refunctionalization to give 5-methoxy- or 5,5-dimethoxy-3-pyrrolin-2-ones, depending on the number of halogen atoms at the C-3 and C-6 positions (Scheme 2).[11] We named the transformation a functional rearrangement (FR). The FR is synthetically useful because the products are precursors of cyclic *N*-acyliminium ions[12] and maleic anhydrides,[13] pivotal structures in organic synthesis[14] and in the realm of natural compounds.[15] We have successfully used the sequence ATRC/FR for the synthesis of chaetomellic anhydrides A and C (FPTase inhibitors),[13a,16] roccellic acid (metabolite lichenico)[16c] and tyromicin A (APase inhibitor).[17]

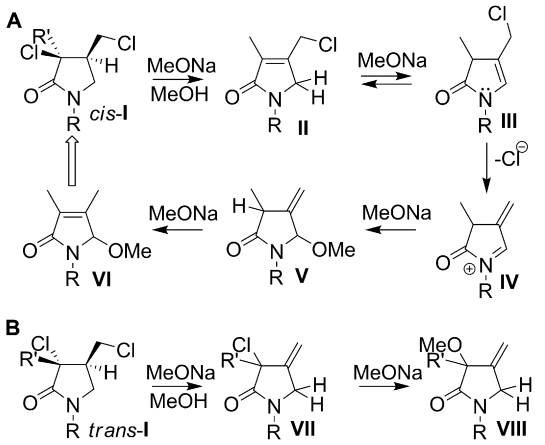


Scheme 2. FR of polychloro-γ-lactams prepared by ATRC (in bold are highlighted the functional groups involved in the transformation and their new appearance and position in the product).

The FR is stereoselective as only *cis*-3-alkyl-3-chloro-4-chloromethyl-pyrrolidin-2-ones undergo the transformation, which by chance are predominantly produced by the TMC-ATRC; the reaction proceeds under thermodynamic control to give predominantly the more stable *cis* isomer.[6b,13,16b] The mechanism of the FR starts with an *endo* bimolecular hydro-halo-elimination, which is possible only in the presence of a *trans* geometry between the C(4)-H and C(3)-Cl bonds of the starting γ-lactam.[16b] Accordingly, the representative chloro-pyrrolidin-2-one *cis*-**I** is transformed by MeONa/MeOH into the 3-pyrrolin-2-one **II** (Scheme 3, A). Owing to the acidity of the vinylogous C(5)-H hydrogen atom, the conjugated C=C bond migrates from the α,β-position to the β,γ-position (**III**). This shift triggers the subsequent stepwise substitution of the *exo* chlorine, giving, through an intermediate *N*-acyliminium **IV**, the 5-methoxy lactam **V**, which by a C=C *exo*/Δ^3 base catalyzed transposition leads to the final 5-methoxy-3-pyrrolin-2-one **VI**. If chlorine atoms are also present at the C-3 and C-6 positions of **VI**, the reaction proceeds further, following similar steps, to yield the 5,5-dimethoxy adduct.

In contrast, the *trans*-**I** isomer, when treated with methoxide ion undergoes dehydrohalogenation, affording 4-alkyliden-pyrrolidin-2-one **VII** (Scheme 3, B), which can be methoxy-de-halogenated when the R′ group is small.[16b] The *exo* dehydrohalogenated adduct, however, can undergo the FR, if the *trans*-**I** intermediate carries a hydrogen atom at C(3) (such as for *N*-benzyl-4-dichloromethyl-2-pyrrolidinone). In this way the *exo* C=C bond is allowed to move into conjugation, and so the rearrangement can start. Inomata experienced a refunctionalization similar to the one we have described in the preparation of phycocyanobilin and phycochromobilin.[12b]

All the previous FR reactions have considered only halogenated γ-lactams bearing a chloromethyl substituent, or at most a dichloromethyl group, at the C(4) position. The investigated



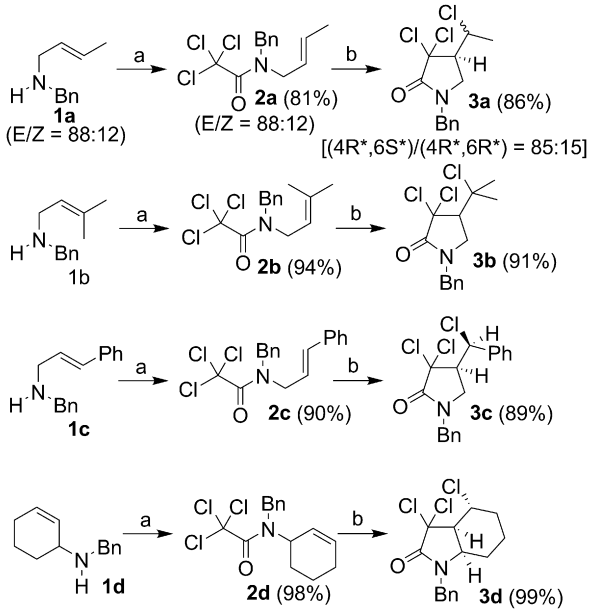
Scheme 3. Mechanism of the functional rearrangement (FR).

molecules have differed in the chain bound at position C(3), or in the group attached at the nitrogen atom.[11,13,16,17]

With this work we aim to complete an examination of the scope of the FR, by studying the reaction of a number of substrates where the C(4) position has secondary or tertiary 1-chloroalkyl substituents. From a synthetic point of view this is appealing since monosubstituted maleimides or alkylidensuccinimides could be prepared. The change, however, is not so innocent as it seems. Indeed it may have an influence on the regioselectivity of the first dehydrochlorination of the starting polychlorinated γ-lactam, because the *exo*-elimination would be favoured by the formation of a more stable C=C bond.

2. Results and discussion

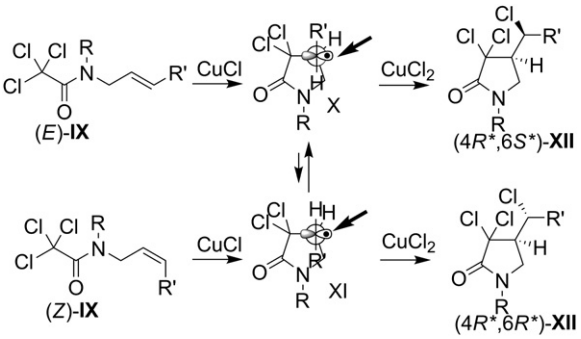
Our attention was first directed to the trichloro-γ-lactams **3a**–**c**, distinguished by the substituent bound at the C-4 position: 1-chloroethyl (**3a**), 1-chloro-1-methylethyl (**3b**) or α-chlorobenzyl (**3c**) (Scheme 4). A cyclic compound (**3d**) was also added to the series and it was of interest to explore these variations because the nature of the C-4 group was expected to influence the rate of *exo*-elimination.



Scheme 4. (a) Trichloroacetyl chloride, Py, CH_2Cl_2, 20 h, 25 °C; (b) CuCl/TMEDA CH_3CN, argon, 14–24 h, 25 °C.

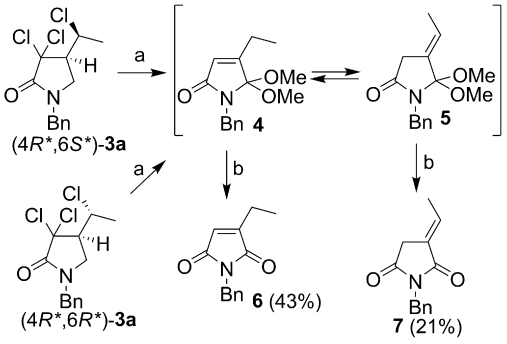
The cycloisomerization proceeded excellently and, with the substrates carrying a stereoisomeric double bond (**2a**, **2c** and **2d**), it was also highly diastereoselective, as observed by us in the past[10a] and, in similar cases, by other researchers.[18]

The configuration of the major diastereoisomer is consistent with an *anti*-addition mechanism and was originally explained by assuming free rotation around the C(4)–C(6) bond of the intermediate pyrrolidinone radical (this is obviously impossible for the radical arising from **2d**) and the preferential adoption of the conformation **X** rather than **XI** (Scheme 5). Assuming the intermediate radical has an almost planar structure,[19] this can be explained on the basis of steric interactions: for conformer **X**, the R′ side-chain takes an outward orientation with respect to the lactam ring. The facial selectivity of the ensuing attack by $CuCl_2$/TMEDA on **X** should be very high, owing to the presence of the two chloro groups at C(3).



Scheme 5. Interpretation of the stereoselective Cl atom transfer in the ATRC to form γ-lactams.

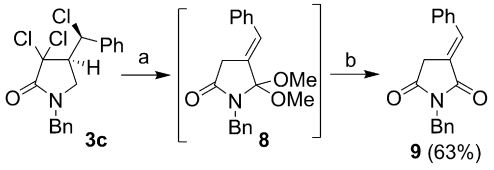
The FR of **3a** (Scheme 6) was performed on the individual isomers, (4*R**,6*S**) and (4*R**,6*R**). To prevent the isolation of the unstable acetals **4** and **5**, the reaction mixtures underwent an acid work-up. Both transformations afforded the same results, indicating that the different configuration of lactams **3** has no influence on the outcome of the FR. Not unexpectedly, from the crude reaction product, the maleimide **6** (yield 43%) and the thermodynamically more stable (*E*)-alkylidensuccinimide **7** (yield 27%) were isolated.[20] Since the **6**/**7** ratio doesn't change on doubling the hydrolysis time (from 48 h to 96 h) we believe that the prototropic migration just occurs on the acetal intermediate **4**. This hypothesis is enforced by the failed hydrogen shift on **6** or **7** under the conditions of the FR (opening of the ring was only observed), and by the observation that at 0 °C the formation of **6** precedes that of **7** (following quenching of the reaction after 3 h).



Scheme 6. (a) MeONa/MeOH/diethyl ether, 10 °C, 3 h; (b) HCl/H_2O, rt, 48 h.

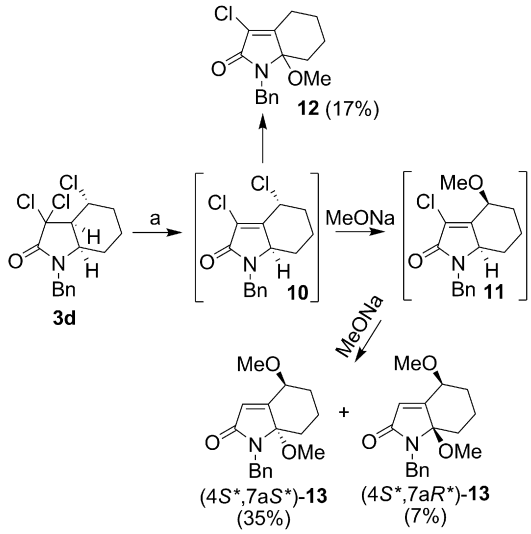
The FR of the halo-lactam **3b**, was, on the contrary, completely unselective, yielding a complex mixture of unidentified products.

We were delighted by the outcome of the FR of **3c** where the (*E*)-benzylidensuccinimide **9** was formed selectively in good yield (Scheme 7). The Δ^3/*exo* shift of the double bond is a clear consequence of the extra-stabilization energy gained by conjugation with the aromatic ring. There are some medicinally important targets with similar structures to **9**.[21]



Scheme 7. (a) MeONa/MeOH/toluene, 10 °C, 3 h; (b) HCl/H_2O, rt, 48 h.

When the bicyclic lactam **3d** was exposed to MeONa, two products were recovered: the monomethoxy **12** (17%) and the dimethoxy **13** (42%) bicyclic 3-pyrrolin-2-ones (Scheme 8). Adduct **13** was, moreover, made up of a mixture of two diastereomers, (4*S**,7a*S**)-**13** and (4*S**,7a*R**)-**13** (in a 83:17 ratio). A plausible interpretation of the reaction outcome is proposed in Scheme 8. After the initial dehydrochlorination, the intermediate **10** can proceed along the FR path to afford **12**, or sustain a preferential nucleophilic substitution of the chloro atom, bound at C(4), made easier by the axial configuration of the halo function.



Scheme 8. (a) MeONa/MeOH/diethyl ether, 25 °C, 3 h.

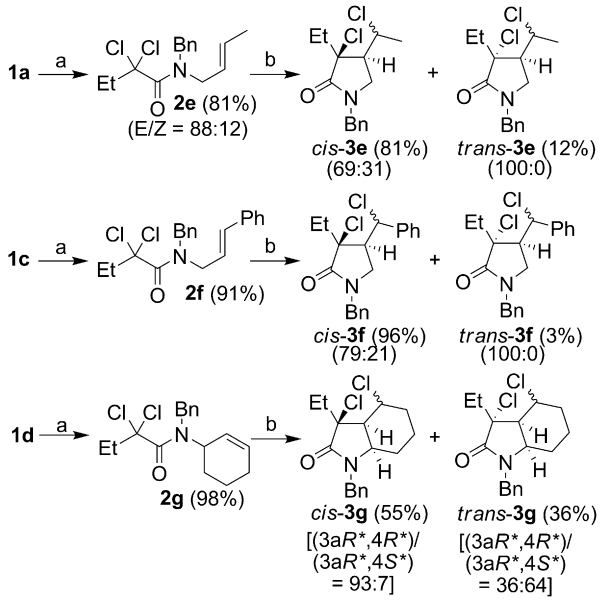
After these initial results, we explored the reactivity of C(3)-substituted dichloro γ-lactams prepared by the CuCl/TMEDA catalyzed ATRC of the 2,2-dichlorobutanamides **2e**, **2f** and **2g** (Scheme 9). Owing to the poor result of the FR of **3b**, the γ-lactam attainable from the allylamine **1b** was not investigated.

As we expected, the cycloisomerization of **2e**–**g** was effective, with product yields between 91–97%, and excluding **2g**, the prevalence of *cis* adducts was high.

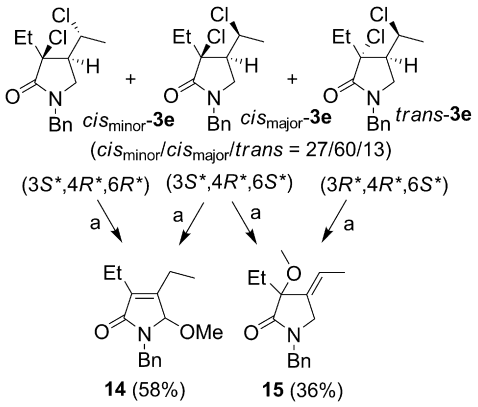
Differently from what we observed with the trichloroamides **2a**, **2c** and **2d**, the stereochemistry of the carbon carrying the Cl external to the lactam ring is not so rigidly controlled. It appears that replacing a Cl atom with a relatively small alkyl group makes the abstraction reaction of the intermediate radical less diastereoselective.[5a]

The 1-benzyl-3,4-diethyl-5-methoxy-1*H*-pyrrol-2(5*H*)-one **14** (yield 58%) and the (*E*)-1-benzyl-3-ethyl-4-ethylidene-3-methoxypyrrolidin-2-one **15** (yield 36%) were secured from the FR of **3e** (Scheme 10). This result is astonishing. Indeed, looking at the *cis*/

trans ratio (87/13) of the starting 2-pyrrolidinone, we had estimated a similar ratio in the rearrangement product **14** and in the product derived from *exo* elimination **15**. Evidently a substantial amount of **15** arises from the *exo*-elimination of *cis*-**3e** as well as, in part, from the elimination of *trans*-**3e**.



Scheme 9. (a) 2,2-Dichlorobutanoyl chloride, Py, CH_2Cl_2, 20 h, 25 °C; (b) CuCl/TMEDA, CH_3CN, argon, 24 h, 50 °C.

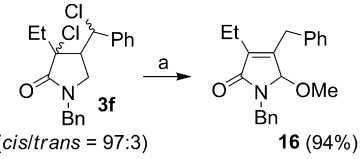


Scheme 10. (a) MeONa/MeOH/diethyl ether, 25 °C, 22 h.

This statement was unequivocally proved, by subjecting the major *cis*-isomer of **3e** to FR, which yielded both the adduct **14** (t_R=8.79 min; $GC_{area\%}$=66%) and **15** (t_R=10.17 min; $GC_{area\%}$=31%).[†] From the *E*-geometry of the C=C bond in **15**, it is possible to trace back the configuration of the C(6) site for all the diastereomers **3e**. Since the *exo*-elimination is stereoselective, it should reasonably follow an E2 mechanism. As a consequence, the *E*-geometry of the alkylidene lactam **15** requires a relative configuration of 4*R**,6*S** between the stereogenic centres at C(4) and C(6) in cis_{major}-**3e** and *trans*-**3e**, therefore the same atoms in the cis_{minor}-**3e** must have the configuration 4*R**,6*R**. Since the stereoisomer *Z*-**15** is virtually absent from the reaction mixture, it is clear that the transition state for the *endo*-elimination of cis_{minor}-**3e** is much more stable than the one for the *exo*-elimination, and thus fully followed.

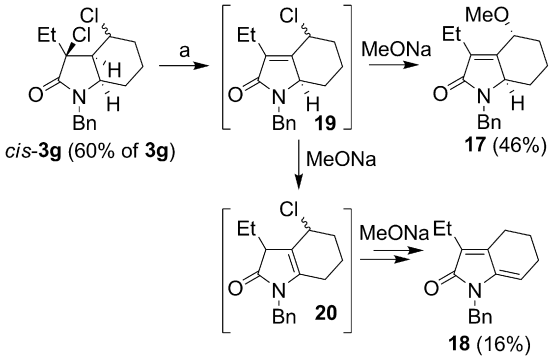
[†] Column HP-5, 30 m, i.d.=0.25 mm; GC conditions: $T_{injector}$=250 °C, $T_{detector}$=280 °C, $T_{initial}$=150 °C (5 min), rate=10 °C/min.

The FR of **3f** was completely selective giving, in excellent yield (94%), the 1,4-dibenzyl-3-ethyl-5-methoxy-1*H*-pyrrol-2(5*H*)-one (Scheme 11). Differently from **3e**, and despite the presence of an aromatic substituent at C(6), the *exo*-elimination did not enter into competition with the *endo*-process. In all likelihood the *anti*-coplanar transition state for the *exo*-dehydrochlorination, owing to the steric bulkiness of the aromatic substituent, is energetically unfavourable.



Scheme 11. (a) MeONa/MeOH/diethyl ether, 37 °C, 22 h.

Finally, the FR of **3g** was considered (Scheme 12). Unfortunately, the TMC-ATRC of **2g** was only moderately stereoselective (*cis*/*trans* ratio=60/40). The (4*R**,7a*R**)-1-benzyl-3-ethyl-4-methoxy-5,6,7,7a-tetrahydro-1*H*-indol-2(4*H*)-one **17** (46%) and the 1-benzyl-3-ethyl-5,6-dihydro-1*H*-indol-2(4*H*)-one **18** (14%) were the products recovered from the reaction mixture (Scheme 12). Both arise from *cis*-**3g**, and their formation can be rationalised by a mechanism similar to the one depicted for **3d** (Scheme 8). The intermediate adduct **19**, afforded from *cis*-**3g** by the *endo*-elimination of HCl, can undergo a premature, but favoured, methoxy-de-chlorination to give **17**. Alternatively, it can follow the FR path, which now proceeds further,[12] providing the doubly eliminated adduct **18**.



Scheme 12. (a) MeONa/MeOH/diethyl ether, 50 °C, 4 h.

As predicted, the crude reaction mixture also included the recovered diastereomer (3*R**,3a*R**,4*R**,7a*R**)-**3g**, which, due to the relative *cis* configuration of the two C–Cl functions and the proton C(3a)-H, cannot undergo elimination. However, this diastereomer was isolated in a slightly higher yield (19%) than that present in the original **3g** mixture (13%). This is a clear sign of partial epimerization of the stereogenic centre C(3)–Cl of diastereomer (3*R**,3a*R**,4*S**,7a*R**)-**3g** under the reaction conditions of the FR.[13b]

3. Conclusions

With this work we have extended the study of the reaction of chlorinated γ-lactams, derived from the TMC-ATRC of *N*-allyl-α-perchloroamides, with MeONa/MeOH to the case of substrates carrying an *exo* halogen atom on a branched carbon. Only with secondary *exo* C–Cl groups, that are not located on a fused ring, did the FR proceed via the desired transformation route. With trichloro-lactams the FR can proceed further and give 4-alkylidene derivatives. For *cis*-(4*R**,6*R**)-3-chloro-4-(1-chloroalkyl)lactam **3e**, in the initial elimination step, an unfavourable *exo*/*endo* competition was observed. From a practical point of view, the outcome of the reaction with di- or trichloro *N*-cinnamylamides, **3c** and **3f**, is

synthetically valuable, affording the 5-methoxy-1*H*-pyrrol-2(5*H*)-one or 3-benzylidenepyrrolidine-2,5-dione nuclei, **16** and **9**, respectively, in good to excellent yields.

4. Experimental part

4.1. General

Reagents and solvents were standard grade commercial products, purchased from Aldrich, Acros, Fluka or RdH, and used without further purification, except acetonitrile and CH_2Cl_2 that were dried over three batches of 3 Å sieves (5% w/v, 12 h). The silica gel used for flash-chromatography was Silica Gel 60 Merck (0.040–0.063 mm). All of the amines **1a**–**d** were obtained by N-alkylation of benzylamine with the appropriate allyl chloride, adapting the procedure of Shipman.[22] The 2,2-dichlorobutanoyl chloride was prepared from 2,2-dichlorobutanoic acid[23] by halo-de-hydroxylation with $(COCl)_2$, following a reported method.[10e] NMR spectra were recorded on a Bruker DPX 200, a Bruker Avance 400 and a Jeol GSX 400 spectrometer. NMR peaks attributions were based on gradient-enhanced $^1H,^1H$-DQF-COSY and $^1H,^{13}C$-Edited-HSQC spectroscopy, using standard pulse programs. The double bond configurations in compounds **7**, **9** and **15** and the relative configurations of **3e**–**g**, **13** and **17** were determined by NOESY experiments. IR, MS and HRMS spectra were recorded, respectively, on a Perkin Elmer 1600 Series FTIR, a HP 5890 GC-HP 5989A MS and a Bruker microTOF instrument.

4.2. 1-Benzyl-3,3-dichloro-4-(1-chloroethyl)-2-pyrrolidinone (3a)-typical procedure

CuCl (0.40 g, 4 mmol) and the 2,2-dichloroamide **2a** (12.27 g, 40 mmol) were weighed in a Schlenk tube fitted with a pierceable septum (blocked by a screw cap) and a magnetic stirring bar. Dry CH_3CN (30 mL) and TMEDA (1.2 mL, 8 mmol) were then added under argon. The mixture was stirred at 25 °C and after 24 h diluted with H_2O (30 mL), acidified with HCl 10% w/v, and extracted with CH_2Cl_2 (3×20 ml). The combined organic layers were concentrated and the crude product was purified by flash-chromatography on silica gel, eluting with a petroleum ether (bp 40–60 °C)/diethyl ether gradient (from 100/0 to 80/20). This gave the pyrrolidinones (4*R**,6*S**)-**3a** (9.00 g, 73%) [Found: C, 50.9; H, 4.6; N, 4.6. $C_{13}H_{14}Cl_3NO$ requires C, 50.92; H, 4.60; N, 4.57] and (4*R**,6*R**)-**3a** (1.58 g, 13%) [Found: C, 51.0; H, 4.6; N, 4.5. $C_{13}H_{14}Cl_3NO$ requires C, 50.92; H, 4.60; N, 4.57], both as a white crystalline solid.

4.2.1. (R)-1-Benzyl-3,3-dichloro-4-[(S*)-1-chloroethyl]-pyrrolidin-2-one [(4R*,6S*)-**3a**].* Mp 68–69 °C; ν_{max} (KBr) 1733 cm^{-1}; d_H (200 MHz, $CDCl_3$) 7.22–7.43 (m, 5H, 5 Ph), 4.65 (1H, d, *J*=16.7 Hz, CH*H*Ph), 4.44 (1H, d, *J*=16.7 Hz, C*H*HPh), 4.31 (1H, dq, *J*=9.6, 6.5 Hz, C(4)CHCl), 3.50 (1H, dd, *J*=10.2, 7.3 Hz, C(5)H*H*), 3.10 (1H, dd, *J*=10.2, 8.9 Hz, C(5)*H*H), 2.91 (1H, ddd, *J*=9.6, 8.9, 7.3 Hz, C(4)H), 1.83 (3H, d, *J*=6.5 Hz, CH_3); d_C (50 MHz, $CDCl_3$) 166.2, 134.6, 129.0, 128.3, 128.2, 83.5, 56.6, 56.2, 48.1, 47.8, 23.7; *m*/*z* (EI, 70 eV) 305 (0.5, M^+), 270 (45), 236 (7), 91 (100).

4.2.2. (R)-1-Benzyl-3,3-dichloro-4-[(S*)-1-chloroethyl]-pyrrolidin-2-one [(4R*,6R*)-**3a**].* Mp 100–101 °C; ν_{max} (KBr) 1718 cm^{-1}; d_H (200 MHz, $CDCl_3$) 7.19–7.42 (m, 5H, 5 Ph), 4.61 (d, *J*=14.7 Hz, 1H, CH*H*Ph), 4.45 (1H, d, *J*=14.7 Hz, C*H*HPh), 4.27–4.45 (1H, m, C(4)CHCl), 3.25–3.40 (m, 1H, C(5)H*H*), 2.94–3.10 (2H, m, C(4)H and C(5)*H*H), 1.43 (3H, d, *J*=6.6 Hz, CH_3); d_C (CDCl3, 50 MHz) 166.4, 134.4, 129.1, 128.4, 128.2, 84.2, 55.5, 53.9, 47.7, 45.9, 22.1; *m*/*z* (EI, 70 eV) 305 (0.5, M^+), 270 (45), 236 (7), 91 (100).

4.3. 1-Benzyl-3,3-dichloro-4-(1-chloro-1-methylethyl)-2-pyrrolidinone (3b)

Following the procedure for the preparation of **3a**, **2b** (12.83 g, 40 mmol) gave, after flash-chromatography of the crude product on silica gel, using a petroleum ether (bp 40–60 °C)/diethyl ether gradient (from 100/0 to 70/30), 11.62 g of **3b** (91%), as a white solid [Found: C, 52.2; H, 5.1; N, 4.3. $C_{14}H_{16}Cl_3NO$ requires C, 52.44; H, 5.03; N, 4.37]; mp 73–74 °C. ν_{max} (KBr) 1716 cm^{-1}; d_H (200 MHz, $CDCl_3$) 7.24–7.44 (m, 5H, 5 Ph), 4.66 (d, *J*=14.7, 1H, CH*H*Ph), 4.50 (1H, d, *J*=14.7 Hz, C*H*HPh), 3.35–5.55 (m, 2H, C(4)H and C(5)H*H*), 3.19 (1H, dd, *J*=9.4, 7.1 Hz, C(5)*H*H), 1.90 (3H, s, CH_3), 1.88 (3H, s, CH_3); d_C (50 MHz, $CDCl_3$) 166.1, 134.6, 129.0, 128.2, 128.1, 82.8, 68.7, 59.3, 47.8, 45.5, 33.4, 29.9; *m*/*z* (EI, 70 eV) 284 (25, M^+-Cl), 248 (2), 206 (3), 91 (100).

4.4. (*R**)-1-Benzyl-3,3-dichloro-4-((*R**)-chloro(phenyl)methyl)-2-pyrrolidinone (3c)

Following the procedure for the preparation of **3a**, but lowering the reaction time to 14 h, **2c** (14.75 g, 40 mmol) gave, after flash-chromatography of the crude product on silica gel, using a petroleum ether (bp 40–60 °C)/diethyl ether gradient (from 100/0 to 70/30), 13.13 g of **3b** (89%), as a white solid [Found: C, 58.6; H, 4.4; N, 3.8. $C_{18}H_{16}Cl_3NO$ requires C, 58.64; H, 4.37; N, 3.80]; mp 138–139 °C; ν_{max} (KBr) 1721 cm^{-1}; d_H (200 MHz, $CDCl_3$) 7.28–7.57 (m, 10H, 2 Ph), 5.27 (1H, d, *J*=9.9 Hz, C(4)HC*H*Ph), 4.69 (1H, d, *J*=14.7 Hz, CH*H*Ph), 4.48 (1H, d, *J*=14.7H, C*H*HPh), 3.67 (1H, dd, *J*=9.7, 6.6 Hz, C(5)H*H*), 3.45 (1H, ddd, *J*=9.9, 8.9, 6.6 Hz, C(4)HCCl), 3.29 (1H, dd, *J*=9.7, 8.9 Hz, C(5)*H*H); d_C (50 MHz, $CDCl_3$) 166.3, 137.7, 134.7, 129.5, 129.1, 128.6, 128.4, 128.3, 83.6, 61.7, 55.7, 48.1, 47.8; *m*/*z* (EI, 70 eV) 367 (1, M^+), 332 (58), 296 (2), 206 (7), 125 (21), 91 (100).

4.5. (3a*R**,4*R**,7a*R**)-1-Benzyl-3,3,4-trichlorohexahydro-1*H*-indol-2(3*H*)-one (3d)

Following the procedure for the preparation of **3a**, **2d** (6.65 g, 20 mmol) gave, after flash-chromatography of the crude product on silica gel, using a petroleum ether (bp 40–60 °C)/diethyl ether (from 100/0 to 70/30) gradient, 5.51 g of **3d** (83%), as a white solid; mp 84–86 °C.[10f]

4.6. 1-Benzyl-3-chloro-4-(1-chloroethyl)-3-ethyl-2-pyrrolidinone (3e)

Following the procedure for the preparation of **3a**, but increasing the reaction temperature to 50 °C, **2e** (7.21 g, 24 mmol) gave, after flash-chromatography of the crude product on silica gel, using a petroleum ether (bp 40–60 °C)/diethyl ether (from 100/0 to 70/30) gradient, 6.71 g of **3e** (93%), as a pale yellow oil [Found: C, 60.2; H, 6.3; N, 4.7. $C_{15}H_{19}Cl_2NO$ requires C, 60.01; H, 6.38; N, 4.67]; $cis_{major}/cis_{minor}/trans$=60:27:13 ($^1H$ NMR); ν_{max} (liquid film) 1711 cm^{-1}; d_H (400 MHz, $CDCl_3$) (cis_{major}) 7.15–7.45 (m, 5H, Ph), 4.60 (1H, d, *J*=14.8, CH*H*Ph), 4.45 (1H, d, *J*=14.8 Hz, C*H*HPh), 4.28 (1H, dq, *J*=10.1, 6.5 Hz, C(4)CHCl), 3.44 (1H, dd, *J*=10.3, 7.4 Hz, C(5)H*H*), 3.12 (1H, dd, *J*=10.3, 10.1 Hz, C(5)*H*H), 2.62 (1H, td, *J*=10.1, 7.4 Hz, C(4)H), 2.54 (1H, dq, *J*=14.5, 7.3 Hz, C(3)CH*H*), 2.06 (1H, dq, *J*=14.5, 7.3 Hz, C(3)C*H*H), 1.69 (3H, d, *J*=6.5 Hz, C(4)CHClCH_3), 0.99 (3H, t, *J*=7.3 Hz, CH_2CH_3); d_H (cis_{minor}) 7.15–7.45 (m, 5H, Ph), 4.59 (1H, d, *J*=14.8 Hz, CH*H*Ph), 4.44 (1H, d, *J*=14.8 Hz, C*H*HPh), 4.37 (1H, dq, *J*=9.3, 6.6 Hz, C(4)CHCl), 3.16 (1H, dd, *J*=9.3, 7.4 Hz, C(5)H*H*), 2.95 (1H, t, *J*=9.3 Hz, C(5)*H*H), 2.69 (1H, td, *J*=9.3, 7.4 Hz, C(4)H), 2.48 (1H, q, *J*=7.5 Hz, C(3)CH*H*), 1.47 (3H, d, *J*=6.6 Hz, C(4)CHClCH_3), 0.99 (3H, t, *J*=7.5 Hz, CH_2CH_3); d_H (*trans*) 7.15–7.45 (5H, m, Ph), 4.60 (1H, d, *J*=14.6 Hz, CH*H*Ph), 4.44 (1H, d, *J*=14.6 Hz, C*H*HPh), 4.23 (1H, qn, *J*=7.0 Hz, C(4)CHCl), 3.49 (1H, dd, *J*=10.4, 7.0 Hz, 3.08 (1H, dd, *J*=10.4, 7.0 Hz, C(5)*H*H), 2.81 (1H, q, *J*=7.1 Hz, C(4)H), C(5)H*H*), 2.06

(1H, dq, *J*=14.7, 7.3 Hz, C(3)CH*H*), 1.97 (1H, dq, *J*=14.7, 7.3 Hz, C(3)C*H*H), 1.66 (3H, d, *J*=7.0 Hz, C(4)CHClCH_3), 1.16 (3H, t, *J*=7.3 Hz, CH_2CH_3); d_C (100 MHz, $CDCl_3$) (*cis*$_{major}$) 170.3, 135.4, 128.8, 128.2, 127.9, 127.8, 72.5, 58.2, 48.5, 47.0, 46.4, 31.02, 23.7, 10.1; d_C (*cis*$_{minor}$) 170.7, 135.4, 128.8, 128.2, 127.9, 127.8, 74.0, 55.1, 46.9, 46.6, 46.3, 30.5, 23.0, 10.0; d_C (*trans*) 170.6, 135.4, 128.8, 128.2, 127.9, 127.8, 72.8, 55.7, 53.0, 47.1, 46.9, 26.9, 24.4, 9.0; *m*/*z* (EI, 70 eV) 299 (3, M^+), 264 (63), 208 (13), 200 (35), 91 (100).

4.7. 1-Benzyl-3-chloro-4-[chloro(phenyl)methyl]-3-ethyl-2-pyrrolidinone (3f)

Following the procedure for the preparation of **3a**, but increasing the reaction temperature to 50 °C, **2f** (8.69 g, 24 mmol) gave, after flash-chromatography of the crude product on silica gel, using a petroleum ether (bp 40–60 °C)/diethyl ether (from 100/0 to 70/30) gradient, 8.58 g of **3f** (99%), as a white solid [Found: C, 66.4; H, 5.9; N, 3.9. $C_{20}H_{21}Cl_2NO$ requires C, C, 66.30; H, 5.84; N, 3.87]; *cis*$_{major}$/*cis*$_{minor}$/*trans*=77:20:3 (^{1}H NMR); ν_{max} (KBr) 1699 cm^{-1}; d_H (400 MHz, $CDCl_3$) (*cis*$_{major}$) 0.66 (3H, t, *J*=6.6 Hz, CH_3), 7.45–7.55 (2H, m, CH_{Ar}), 7.20–7.45 (8H, m, CH_{Ar}), 5.22 (1H, d, *J*=9.8 Hz, C(4)CHCl), 4.68 (1H, d, *J*=14.8 Hz, CH*H*Ph), 4.47 (1H, d, *J*=14.8 Hz, C*H*HPh), 3.59 (dd, *J*=9.8, 7.1 Hz, 1H, C(5)H*H*), 3.30 (1H, t, *J*=9.8 Hz, C(5)*H*H), 3.12 (1H, td, *J*=9.8, 7.1 Hz, C(4)H), 1.99 (1H, dq, *J*=13.2, 6.6 Hz, C(3)CH*H*), 0.66–0.80 (1H, m, C(3)C*H*H); d_H (*cis*$_{minor}$) 7.20–7.45 (8H, m, CH_{Ar}), 7.15–7.20 (2H, m, CH_{Ar}), 5.20 (1H, d, *J*=9.8 Hz, C(4)CHCl), 4.63 (1H, d, *J*=14.8 Hz, CH*H*Ph), 4.23 (1H, d, *J*=14.8 Hz, C*H*HPh), 3.19 (1H, td, *J*=9.8, 7.4 Hz, C(4)H), 2.75 (1H, t, *J*=9.8H, C(5)H*H*), 2.65 (2H, q, *J*=7.4 Hz, C(3)CH_2), 2.56 (1H, dd, *J*=9.8, 7.4 Hz, C(5)*H*H), 1.12 (3H, t, *J*=7.4 Hz, CH_3); d_H (*trans*) 7.00–7.70 (10H, m, 2 Ph), 5.14 (1H, d, *J*=7.2 Hz, C(4)CHCl), CH_2Ph not detectable, 3.50–3.60 (1H, m, C(5)H*H*), 3.30–3.40 (1H, m, C(5)*H*H), 3.13–3.25 (1H, m, C(4)H), 2.15 (1H, dq, *J*=7.4 Hz, C(3)CH*H*), 2.00–2.10 (1H, m, C(3)C*H*H), 1.18 (3H, t, *J*=7.4 Hz, CH_3); d_C (100 MHz, $CDCl_3$) (*cis*$_{major}$) 170.3, 138.8, 135.5, 129.3, 128.8, 128.6, 128.0, 127.8, 73.4, 62.8, 48.3, 46.9, 46.2, 28.9, 9.7; d_C (*cis*$_{minor}$)=170.6, 138.7, 135.4, 129.1, 129.0, 128.7, 127.7, 127.6, 127.3, 74.0, 61.0, 47.0, 46.8, 45.9, 30.5, 10.2; d_C (*trans*)=unobservable due to the too low intensity; *m*/*z* (EI, 70 eV) 361 (3, M^+), 326 (53), 290 (3), 208 (37), 200 (68), 125 (30), 91 (100).

4.8. 1-Benzyl-3,4-dichloro-3-ethylhexahydro-1*H*-indol-2(3*H*)-one (3g)

Following the procedure for the preparation of **3a**, but increasing the reaction temperature to 50 °C, **2g** (6.53 g, 20 mmol) gave, after flash-chromatography of the crude product on silica gel, using a petroleum ether (bp 40–60 °C)/diethyl ether gradient (from 100/0 to 60/40), 5.94 g of **3g** (91%), as a pale yellow oil; (3*S**,3a*R**,4*R**,7a*R**)/(3*S**,3a*R**,4*S**,7a*R**)/(3*R**,3a*R**,4*S**,7a*R**)/(3*R**,3a*R**,4*R**,7a*R**)=*cis*$_{major}$/*cis*$_{minor}$/*trans*$_{major}$/*trans*$_{minor}$=56:4:26:14 (^{1}H NMR); ν_{max} (liquid film) 1705 cm^{-1}; d_H (400 MHz, $CDCl_3$) (*cis*$_{major}$) 7.20–7.38 (5H, m, Ph), 4.98, (1H, d, *J*=15.0 Hz, CH*H*Ph), 4.61 (1H, dt, *J*=3.6, 1.6 Hz, C(4)H_{eq}), 4.12 (1H, d, *J*=15.0 Hz, C*H*HPh), 3.56 (1H, ddd, *J*=11.6, 7.6, 5.6 Hz, C(7a)H_{ax}), 2.82 (1H, dd, *J*=7.6, 1.6 Hz, C(3a)H_{eq}), 2.27–2.38 (1H, m, C(5)H_{ax}), 2.20 (dq, *J*=14.8, 7.4 Hz, 1H, CH*H*CH_3), 2.16 (1H, dq, *J*=14.8, 7.4 Hz, C*H*HCH_3), 1.97–2.05 (1H, m, C(7)H_{eq}), 1.92 (1H, dq, *J*=14.7, 3.6 Hz, C(5)H_{eq}), 1.60–1.70 (2H, m, C(6)H_2), 1.43–1.56 (1H, m, C(7)H_{ax}), 1.06 (3H, t, *J*=7.4 Hz, CH_2CH_3); d_H (*cis*$_{minor}$) 7.19–7.37 (5H, m, Ph), 5.08 (1H, d, *J*=15.0 Hz, CH*H*Ph), 4.19 (1H, ddd, *J*=12.7, 7.0, 5.3 Hz, C(4)H_{ax}), 4.04 (1H, d, *J*=15.0 Hz, C*H*HPh), 3.31 (1H, ddd, *J*=11.6, 7.0, 5.7 Hz, C(7a)H_{ax}), 2.90 (1H, t, *J*=7.0 Hz, C(3a)H_{eq}), 2.42–2.63 (3H, m, C*H*$_2$CH$_3$ and C(5)H*H*), 1.85–2.02 (3H, m, C(5)*H*H, C(6)H_{eq} and C(7)H_{eq}), 1.64–1.76 (1H, m, C(7)H_{ax}), 1.20 (1H, qt, *J*=13.9, 3.5 Hz, C(6)H_{ax}), 0.94 (3H, t, *J*=7.4 Hz, CH_2CH_3); d_H (*trans*$_{maior}$) 7.10–7.30 (5H, m, Ph), 5.03 (1H, d, *J*=15.2 Hz, CH*H*Ph), 4.39 (q, *J*=3.6 Hz, C(4)H), 4.03 (1H, d, *J*=15.2 Hz, C*H*HPh), 3.89–3.97 (1H, m, C(7a)H), 2.56–2.62 (1H, m, C(3a)H), 2.53 (1H, dq, *J*=15.2, 7.3 Hz, CH*H*CH_3), 2.30–2.40 (1H, m, C*H*HCH_3), 2.00–2.12 (2H, m, C(5)H*H* and C(7)H*H*), 1.72–1.85 (2H, m, C(5)H*H* and C(6)H*H*), 1.50–1.65 (1H, m, C(7)*HH*), 1.33–1.43 (1H, m, C(6)*H*H), 1.22 (t, *J*=7.3 Hz, CH_2CH_3); d_H (*trans*$_{minor}$) 7.10–7.30 (5H, m, Ph), 5.08 (1H, d, *J*=15.2 Hz, CH*H*Ph), 3.93 (1H, q, *J*=4.7 Hz, C(7a)H_{eq}), 3.86 (1H, d, *J*=15.2 Hz, C*H*HPh), 3.73 (1H, ddd, *J*=10.9, 8.9, 4.7 Hz, C(4)H_{ax}), 2.66 (1H, dd, *J*=8.9, 4.7 Hz, C(3a)H_{ax}), 2.36 (1H, dq, *J*=14.9, 7.1 Hz, CH*H*CH_3), 2.11–2.20 (1H, m, C(5)H_{eq}), 2.07 (1H, dq, *J*=14.9, 7.1 Hz, C*H*HCH_3), 1.92–2.02 (1H, m, C(7)H_{eq}), 1.62–1.73 (1H, m, C(5)H_{ax}), 1.56–1.66 (1H, m, C(6)H_{eq}), 1.45–1.56 (1H, m, C(7)H_{ax}), 1.30 (3H, t, *J*=7.1 Hz, CH_2CH_3), 1.14–1.28 (1H, m, C(6)H_{ax}); d_C (100 MHz, $CDCl_3$) (*cis*$_{major}$) 170.0, 135.9, 128.8, 127.9, 127.8, 70.7, 57.0, 52.4, 46.9, 44.9, 32.7, 31.8, 26.7, 16.9, 9.5; δ (*cis*$_{minor}$) 170.4, 135.9, 128.8, 127.9, 127.8, 71.8, 57.8, 55.7, 45.0, 41.0, 32.7, 32.2, 26.3, 22.2, 10.6; d_C (*trans*$_{maior}$) 172.4, 135.8, 128.5, 127.8, 127.4, 75.7, 55.6, 51.6, 48.1, 43.8, 32.5, 25.7, 23.7, 15.3, 9.1; d_C (*trans*$_{minor}$) 172.3, 135.3, 128.4, 127.8, 127.7, 75.7, 56.3, 53.9, 53.7, 44.0, 35.8, 26.5, 24.8, 19.2, 10.0; HRMS-FAB (CI, NH_3): *m*/*z* MH^+, found 326.1073, $C_{17}H_{22}Cl_2NO$ requires 326.1073.

4.9. 1-Benzyl-3-ethyl-1*H*-pyrrole-2,5-dione (6)

In a Schlenk tube, fitted with a pierceable septum blocked by a screw cap, diethyl ether/CH_3OH 1/3 (4 mL) and **3a** (1.23 g, 4 mmol) were added. The solution was thermostated at 10 °C. Apart, in a second Schlenk tube, Na^0 (0.37 g, 16 mmol) was carefully dissolved in CH_3OH (8 mL) and, when the effervescence ceased, the alkaline solution was thermostated at 10 °C, after which it was poured into the first Schlenk tube. The reaction mixture was stirred for 3 h. Then it was diluted with water (15 mL), acidified with HCl 10% w/v (red litmus) and left under vigorous stirring for 48 h at room temperature. Afterwards the mixture was extracted with CH_2Cl_2 (3×10 mL). The combined organic layers were collected and concentrated. Flash-chromatography of the crude product on silica gel, using a petroleum ether (bp 40–60 °C)/diethyl ether gradient (from 100/0 to 60/40), afforded 0.37 g of **6** (43%), as a white solid [Found: C, 72.4; H, 6.1; N, 6.5. $C_{13}H_{13}NO_2$ requires C, 72.54; H, 6.09; N, 6.51]; mp 52–53 °C; ν_{max} (KBr): 1707 cm^{-1}; d_H (200 MHz, $CDCl_3$) 7.24–7.42 (5H, m, Ph), 6.30 (1H, dt, *J*=2.0, 0.5 Hz, C(3)H), 4.66 (2H, s, CH_2Ph), 2.46 (2H, dq, *J*=7.5, 2.0 Hz, C(4)HCH_2CH3), 1.21 (3H, t, *J*=7.5 Hz, CH_2CH_3); d_C (50 MHz, $CDCl_3$) 171.2, 170.6, 151.7, 136.5, 128.6, 128.4, 127.7, 125.7, 41.4, 18.9, 11.1; *m*/*z* (EI, 70 eV) 215 (100, M^+), 172 (90), 104 (28), 91 (30).

0.18 g (21%) of (*E*)-1-Benzyl-3-ethylidenepyrrolidine-2,5-dione (**7**), as a yellowish oil [Found: C, 72.5; H, 6.1; N, 6.6. $C_{13}H_{13}NO_2$ requires C, 72.54; H, 6.09; N, 6.51], was also recovered; ν_{max} (liquid film) 1709, 1679 cm^{-1}; d_H (200 MHz, $CDCl_3$) 7.20–7.43 (5H, m, Ph), 6.86 (tq, *J*=7.0, 2.4 Hz, 1H, C(4)=C*H*CH3), 4.70 (2H, s, CH_2Ph), 3.18 (2H, m, C(3)H_2), 1.83 (3H, dt, *J*=7.0, 1.5 Hz,=CHCH_3); d_C (100 MHz, $CDCl_3$) 173.4, 169.0, 135.7, 133.5, 128.4, 128.2, 127.5, 126.5, 41.8, 31.5, 15.0; *m*/*z* (EI, 70 eV) 215 (100, M^+) 186 (32), 172 (39), 104 (36), 91 (58).

4.10. (*E*)-1-Benzyl-3-benzylidenepyrrolidine-2,5-dione (9)

Following the procedure for the preparation of **6** and **7**, but replacing diethyl ether with toluene, **3c** (1.48 g, 4 mmol) gave, after crystallization of the crude product in petroleum ether/diethyl ether, 0.70 g of **9** (63%), as a white solid [Found: C, C, 77.9; H, 5.4; N, 5.1. $C_{18}H_{15}NO_2$ requires C, 77.96; H, 5.45; N, 5.05]; mp 198–199 °C; ν_{max} (KBr) 1697 cm^{-1}; d_H (400 MHz, $CDCl_3$) 7.63 (1H, m,=CHPh), 7.20–7.50 (10H, m, Ph), 4.79 (2H, s, CH_2Ph), 3.57 (2H, d, *J*=2.4 Hz, C(3)H_2); d_C (100 MHz, $CDCl_3$) 173.6, 170.6, 135.8, 134.5, 134.0, 130.13, 130.10, 129.1, 128.9, 128.6, 127.9, 123.4, 42.5, 34.1; *m*/*z* (EI, 70 eV) 277 (91, M^+), 248 (14), 144 (18), 115 (100), 91 (27).

4.11. 1-Benzyl-4,7a-dimethoxy-5,6,7,7a-tetrahydro-1*H*-indol-2(4*H*)-one (13)

Following the procedure for the preparation of **6** and **7**, but thermostating at 25 °C and increasing the reaction time to 3 h, **3d** (1.33 g, 4 mmol) gave, after flash-chromatography of the crude product on silica gel, using a petroleum ether (bp 40–60 °C)/diethyl ether (from 100/0 to 50/50) gradient, 0.41 g of (4*S**,7a*S**)-**13** (35%), as a pale brown solid [Found: C, 85.1; H, 9.2; N, 5.9. $C_{17}H_{22}NO_3$ requires C, 84.95; H, 9.22; N, 5.83], and 0.08 g of (4*R**,7a*S**)-**13** (7%), as a brownish oil.

4.11.1. (4S,7aS*)-1-Benzyl-4,7a-dimethoxy-5,6,7,7a-tetrahydro-1H-indol-2(4H)-one [(4S*,7aS*)-**13**].* Mp 78–79 °C; ν_{max} (KBr) 1693 cm^{-1}; d_H (400 MHz, $CDCl_3$) 7.10–7.29 (5H, m, Ph), 6.01 (1H, s, C(3)H), 4.63 (1H, d, *J*=15.2 Hz, CH*H*Ph), 4.09 (1H, d, *J*=15.2 Hz, C*H*HPh), 3.77 (1H, dd, *J*=11.2, 5.7 Hz, C(4)H), 3.39 (3H, s, C(4)OCH_3), 2.76 (3H, s, C(7a)OCH_3), 2.17–2.23 (1H, m, C(5)H_{eq}), 1.95–2.01 (1H, m, C(7)H_{eq}), 1.50–1.58 (2H, m, C(6)H_2), 1.11 (1H, dq, *J*=11.7, 5.4 Hz, C(5)H_{ax}), 0.96 (1H, dt, *J*=12.6, 5.4 Hz, C(7)H_{ax}); d_C (100 MHz, $CDCl_3$) 170.9, 162.0, 139.8, 129.8, 128.6, 128.5, 120.5, 95.6, 77.2, 58.7, 51.1, 43.1, 39.3, 35.2, 20.9; HRMS-FAB (CI, NH_3): *m*/*z* MH^+, found 288.1593, $C_{17}H_{22}NO_3$ requires 288.1594.

4.11.2. (4S,7aR*)-1-Benzyl-4,7a-dimethoxy-5,6,7,7a-tetrahydro-1H-indol-2(4H)-one [(4R*,7aS*)-**13**].* ν_{max} (liquid film) 1701 cm^{-1}; d_H (400 MHz, $CDCl_3$) 7.14–7.29 (5H, m, Ph), 6.10 (1H, s, C(3)H), 4.71 (d, *J*=15.2 Hz. 1H, CH*H*Ph), 4.09–4.12 (1H, m, C(4)H), 4.02 (1H, d, *J*=15.2 Hz, C*H*HPh), 3.27 (3H, s, C(4)OCH_3), 2.83 (3H, s, C(7a)OCH_3), 2.00–2.11 (2H, m, C(5)*H*H and C(7)H_{eq}), 1.79–1.90 (1H, m, C(6)*H*H), 1.24–1.35 (2H, m, C(5)H*H* and C(6)H*H*), 0.99 (1H, dt, *J*=13.4, 3.7 Hz, C(7)H_{ax}); d_C (100 MHz, $CDCl_3$) 170.3, 157.3, 139.8, 129.7, 128.6, 126.6, 94.8, 75.7, 58.7, 52.2, 42.8, 40.3, 34.0, 18.0; HRMS-FAB (CI, NH_3): *m*/*z* MH^+, found 288.1591, $C_{17}H_{22}NO_3$ requires 288.1594.

0.20 g (17%) of 1-Benzyl-3-chloro-7a-methoxy-5,6,7,7a-tetrahydro-1*H*-indol-2(4*H*)-one (**12**), as a brownish oil, was also recovered. ν_{max} (liquid film) 1702 cm^{-1}; d_H (400 MHz, $CDCl_3$) 7.13–7.30 (5H, m, Ph), 4.65 (1H, d, *J*=15.1 Hz, CH*H*Ph), 4.15 (1H, d, *J*=15.1 Hz, C*H*HPh), 2.73–2.78 (1H, m, C(4)H*H*), 2.69 (3H, s, OCH_3), 2.03–2.08 (1H, m, C(7)H*H*), 1.93 (1H, dt, *J*=13.1, 5.5 Hz, C(4)*H*H), 1.83–1.89 (1H, m, C(5)H*H*), 1.46–1.60 (2H, m, C(6)H_2), 1.14 (1H, tq, *J*=13.1, 4.4 Hz, C(5)*H*H), 0.99 (1H, dt, *J*=13.1, 5.2 Hz, C(7)*H*H); d_C (100 MHz, $CDCl_3$) 164.9, 151.3, 137.9, 128.4, 128.3, 127.3, 122.5, 91.5, 49.6, 42.2, 38.2, 26.4, 24.5, 21.3; HRMS-FAB (CI, NH_3): *m*/*z* MH^+, found 292.1096, $C_{16}H_{19}ClNO_2$ requires 292.1099.

4.12. 1-Benzyl-3,4-diethyl-5-methoxy-1*H*-pyrrol-2(5*H*)-one (14)

Following the procedure for the preparation of **6** and **7**, but using 3 equiv of Na^0 (0.28 g, 12 mmol) and thermostating at 25 °C for 22 h, **3e** (1.20 g, 4 mmol) gave, after flash-chromatography of the crude product on silica gel, using a petroleum ether (bp 40–60 °C)/diethyl ether (from 100/0 to 60/40) gradient, 0.61 g of **14** (58%), as a pale yellow oil [Found: 74.1; H, 8.1; N, 5.4. $C_{16}H_{21}NO_2$ requires C, 74.10; H, 8.16; N, 5.40]; ν_{max} (liquid film) 1701 cm^{-1}; d_H (200 MHz, $CDCl_3$) 7.19–7.37 (5H, m, Ph), 5.09 (1H, s, C(5)H), 4.93 (1H, d, *J*=14.8 Hz, CH*H*Ph), 4.09 (1H, d, *J*=14.8 Hz, C*H*HPh), 2.92 (3H, s, OCH_3), 2.09–2.51 (4H, m, 2CH_2CH_3), 1.11 (3H, t, *J*=7.5 Hz, CH_2CH_3), 1.08 (3H, t, *J*=7.5 Hz, CH_2CH_3); d_C (50 MHz, $CDCl_3$) 170.6, 150.4, 137.5, 136.8, 128.6, 128.3, 127.4, 86.0, 49.1, 43.3, 19.1, 16.9, 13.6, 12.8; *m*/*z* (EI, 70 eV) 259 (49, M^+), 244 (7), 228 (40), 91 (100).

0.37 g (36%) of (*E*)-1-Benzyl-3-ethyl-4-ethylidene-3-methoxy-2-pyrrolidinone (**15**), as a colourless oil [Found: 74.2; H, 8.1; N, 5.3. $C_{16}H_{21}NO_2$ requires C, 74.10; H, 8.16; N, 5.40], was also recovered; ν_{max} (liquid film) 1683 cm^{-1}; d_H (400 MHz, $CDCl_3$) 7.25–7.38 (m, 5H, 5 Ph), 4.68 (d, *J*=14.9 Hz, 1H, CHPh), 4.63 (d, *J*=14.9 Hz, 1H, CHPh), 4.38 (q, *J*=6.6 Hz, 1H, H-6), 3.74 (s, 2H, 2 H-5), 3.24 (s, 3H, OCH_3), 2.34–2.46 (m, 2H, C(3)CH_2), 1.32 (3H, d, *J*=6.6 Hz,=CHCH_3), 1.16 (3H, t, *J*=7.5 Hz, CH_2CH_3); d_C (100 MHz, $CDCl_3$) 171.4, 149.7, 137.3, 135.9, 128.6, 128.0, 127.4, 72.2, 56.5, 48.3, 46.2, 20.6, 17.2, 13.5; *m*/*z* (EI, 70 eV) 259 (90, M^+), 244 (26), 228 (18), 212 (26), 200 (18), 91 (100).

4.13. 1,4-Dibenzyl-3-ethyl-5-methoxy-1*H*-pyrrol-2(5*H*)-one (16)

Following the procedure for the preparation of **14**, but thermostating at 37 °C for 22 h, **3f** (1.45 g, 4 mmol) gave, after flash-chromatography of the crude product on silica gel, using a petroleum ether (bp 40–60 °C)/diethyl ether (from 100/0 to 70/30) gradient, 1.21 g of **16** (94%), as a yellow oil [Found: 74.2; H, 8.1; N, 5.3. $C_{21}H_{23}NO_2$ requires C, 78.6; H, 7.3; N, 4.4]; ν_{max} (liquid film) 1699 cm^{-1}; d_H (200 MHz, $CDCl_3$) 7.15–7.55 (10H, m, 2 Ph); 5.01 (1H, s, C(5)H), 4.84 (1H, d, *J*=14.9 Hz, NCH*H*Ph), 4.20 (1H, d, *J*=14.9 Hz, NC*H*HPh), 3.82 (1H, d, *J*=14.8 Hz, C(4)CH*H*Ph), 3.46 (1H, d, *J*=14.8 Hz, C(4)C*H*HPh), 2.93 (3H, s, OCH_3), 2.46 (2H, q, *J*=7.5 Hz, C(3)CH_2), 1.20 (3H, t, *J*=7.5 Hz, CH_2CH_3); d_C (50 MHz, $CDCl_3$) 170.5, 147.4, 137.9, 137.4, 129.4, 128.9, 128.6, 128.0, 127.4, 126.7, 86.7, 49.4, 43.6, 32.1, 17.3, 13.5; *m*/*z* (EI, 70 eV) 321 (27, M^+), 306 (4), 290 (19), 230 (15), 91 (100).

4.14. (4*R**,7a*R**)-1-Benzyl-3-ethyl-4-methoxy-5,6,7,7a-tetrahydro-1*H*-indol-2(4*H*)-one (17)

Following the procedure for the preparation of **14**, but thermostating at 50 °C for 4 h, **3g** (1.31 g, 4 mmol) gave, after flash-chromatography of the crude product on silica gel, using a petroleum ether (bp 40–60 °C)/diethyl ether (from 90/10 to 50/50) gradient, 0.53 g of **17** (46%), as a colourless liquid; ν_{max} (liquid film) 1682 cm^{-1}; d_H (400 MHz, $CDCl_3$) 7.22–7.36 (5H, m, Ph), 4.97 (1H, d, *J*=15.2 Hz, CH*H*Ph), 4.40 (1H, t, *J*=2.6 Hz, C(4)H), 4.29 (1H, d, *J*=15.2 Hz, C*H*HPh), 3.78 (1H, dd, *J*=11.4, 5.8 Hz, C(7a)H), 3.20 (3H, s, OCH_3), 2.34–2.47 (2H, m, CH_2CH_3), 2.25–2.33 (1H, m, C(7)H_{eq}), 2.13 (1H, dqn, *J*=14.1, 2.9 Hz, C(5)H_{eq}), 1.69 (1H, tq, *J*=13.7, 3.2 Hz, C(6)H_{ax}), 1.57 (1H, dqn, *J*=13.7, 3.2 Hz, C(6)H_{eq}), 1.36 (1H, tdd, *J*=13.7, 4.3, 3.2 Hz, C(5)H_{ax}), 1.16 (3H, t, *J*=7.5 Hz, CH2CH_3), 0.90 (1H, dq, *J*=12.4, 3.8 Hz, C(7)H_{ax}); d_C (100 MHz, $CDCl_3$) 170.8, 150.3, 137.8, 134.5, 128.5, 127.8, 127.2, 72.0, 57.3, 55.9, 44.0, 33.5, 33.0, 17.7, 16.9, 13.9; HRMS-FAB (CI, NH_3): *m*/*z* MH^+, found 286.1803, $C_{18}H_{24}NO_2$ requires 286.1802.

0.16 g (16%) of 1-Benzyl-3-ethyl-5,6-dihydro-1*H*-indol-2(4*H*)-one (**18**), as a brownish oil, and 0.25 g (19%) of (3*R**,3a*R**,4*R**,7a*R**)-**3g**, as a pale yellow oil, were also recovered; ν_{max} (liquid film) 1686 cm^{-1}; d_H (400 MHz, $CDCl_3$) 7.12–7.25 (5H, m, Ph), 5.35 (1H, t, *J*=4.7 Hz, C(7)H), 4.68 (2H, s, CH_2Ph), 2.49 (2H, t, *J*=6.0 Hz, C(4)H_2), 2.30 (2H, q, *J*=7.6 Hz, CH_2CH_3), 2.16 (2H, dt, *J*=6.0, 4.7 Hz, C(6)H_2), 1.71 (2H, qn, *J*=6.0 Hz, C(5)H_2), 1.06 (3H, t, *J*=7.6 Hz, CH_2CH_3); d_C (100 MHz, $CDCl_3$) 170.6, 139.5, 138.9, 137.9, 128.9, 128.5, 127.1, 127.0, 108.5, 42.7, 24.2, 23.3, 22.4, 16.9, 13.2; HRMS-FAB (CI, NH_3): *m*/*z* MH^+, found 254.1530, $C_{17}H_{20}NO$ requires 254.1539.

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