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REARRANGEMENT OF *N*-ALLYL-α,α-DICHLOROAMIDES, β- OR γ-FUNCTIONALIZED, TO SUBSTITUTED ANALOGUES OF THE γ-AMINOBUTYRIC ACID (GABA)

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Abstract: The rearrangement of γ-chloro, β-hydroxy or β-vinyl N-allyl-N-benzyl-α,α-dichlorocarboxyamides to γ-aminobutyric acid analogues is efficiently promoted by CuCl\N,N,N',N'-tetramethylethylendiamine. With the β-vinyl functionalization a tandem radical-radical reaction, yielding 3-aza-2-oxo-bicyclo[3,3,0]octane adducts, is also observed.

γ-Aminobutyric acid (GABA) has been implicated in several neurologic and psychiatric disorders such as epilepsy, Huntigton's disease and parkinsonism.[1] To increase the brain uptake of GABA the prodrug approach using γ-lactam derivatives appears one of the most promising.[2]

Among the different strategies devised for the synthesis of the γ-lactam skeleton, particularly efficient is the radical cyclization of *N*-allyl-α,α-halocarboxyamides, which entails the closure between the C(3) and C(4) ring sites.[3] The most attractive way to perform this cyclization is the use of redox-catalysts, since a profitable C-Cl function is preserved in the product (Scheme 1).[3]

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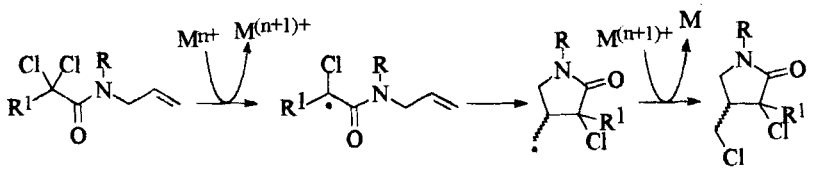
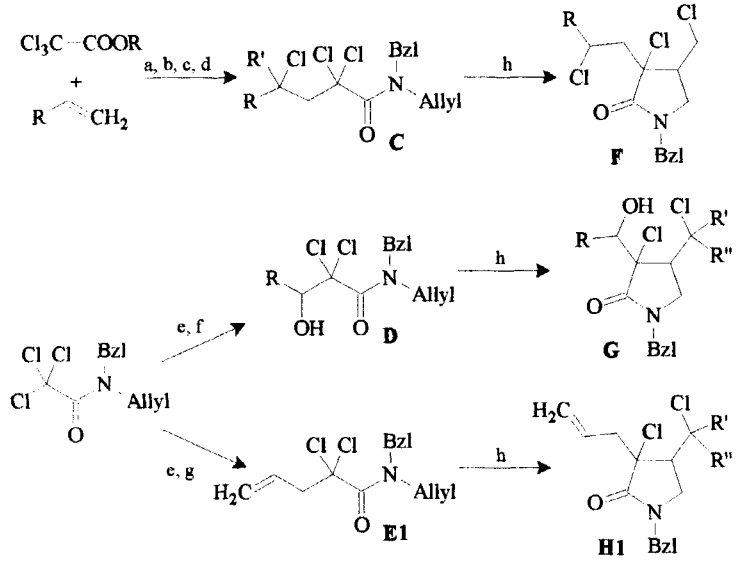


Scheme 1

We recently showed that CuCl\N,N,N'N'-tetramethylethyldiammina (TMEDA) is an excellent catalyst for the rearrangement of scheme 1.[4,5]

The recent report of GABA analogues with a C-3 functionalized substituent[6] spurred us to try the rearrangement of γ-chloro (**C**), β-hydroxy (**D**) or β-vinyl (**E**) N-allyl-N-benzyl-α,α-dichlorocarboxyamides. The γ-lactams thus obtainable, besides being interesting GABA analogues,[6] are also synthetically appealing adducts that could be used for the preparation of bioactive molecules, such as potential non peptide substance P (SP) antagonists.[7]



a) $Fe^0/FeCl_3$, DMF, 100°C; b) LiOH, i-C_3H_7OH/OH, -7°C; c) $(COCl)_2$/DMF, CH_2Cl_2, 20-40°C; d) Triethylamine, room temperature; e) n-Butyllitium, THF, -78°C; f) RCHO, THF, -78°C; g) Allylbromide, THF, -78°C; h) CuCl/TMEDA, CH_3CN, 60°C.

Scheme 2

Table. Rearrangement of the N-allyl-N-benzyl-2,2-dichloroamides.[a]

item	Substrate	R; R'	Product	conv. %[c]	yield %[b] (*cis*:*trans*)	*Cis* ratio %
1	**C1**	-CH_2Cl; H	**F1**	100	96(89:11)[d]	52:48[e]
2[f]	**C1**	-CH_2Cl; H	**F1**	93	86(52:48)[d]	
3[g]	**C1**	-CH_2Cl; H	**F1**	100	98(67:33)[d]	
4[h]	**C1**	-CH_2Cl; H	**F1**	100	98(44:56)[d]	
5	**C2**	-$CH_2OC_2H_5$; H	**F2**	100	95(93:7)[d]	53:47[e]
6[f]	**C2**	-$CH_2OC_2H_5$; H	**F2**	41	37(81:19)[d]	
7	**C3**	-CH_2Cl; -CH_3	**F3**	100	98(98:2)[d]	53:47[e]
8	**C4**	-$(CH_2)_9OBzl$; H	**F4**	100	98(100:0)[d]	55:45[e]
9	**D1**	-CH_3	**G1**	100	76	
10[i]	**D2**	-CH_3	**G2**	100	97(95:5)[c]	62:38[c]
11[l]	**D3**	-CH_3	**G3**	100	98(91:9)[c]	65:35[c]
12[m]	**D4**	-CH_3	**G4**	100	97(84:16)[c]	51:49[c]
13[i]	**D5**	-2-furyl	**G5**	90	78(90:10)[c]	53:47[e]
14	**E1**		**H1**	100	43[n]	

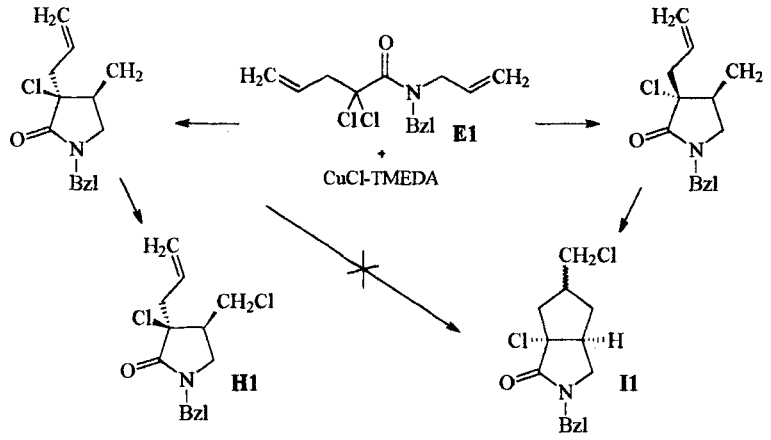
a) $2 \cdot 10^{-3}$ mol of substrate, $2 \cdot 10^{-4}$ mol of CuCl, $4 \cdot 10^{-4}$ mol of TMEDA and 4 ml of acetonitrile (AN) were used; reaction time 20 h, T=60°C. b) yield of isolated material. c) GC value. d) determined by HPLC. e) determined by H-NMR. f) bipyridine replaces TMEDA. g) T=20°C. h) T=-10°C. i) OH protected as acetate. l) OH protected as isobutanoate. m) OH protected as benzoate. n) 56% of 3-aza-3-benzyl-7-chloromethyl-1-methyl-2-oxo-[3,3,0]-bicyclooctane **I1** was observed, as mixture of two diastereoisomers (3:1).

By using methodologies developed in our laboratory, we performed the synthesis of the β- or γ-functionalized N-allyl-N-benzyl-α,α-dichlorocarboxyamides with yields ranging from good to excellent (Scheme 2).[4,8] The rearrangement of **C**, **D** and **E** to the respective 2-pyrrolidinones **F**, **G** and **H** (Scheme 2) was then carried out in acetonitrile (AN) with CuCl\TMEDA at 60 °C, and Table reports the results obtained. Good yields were afforded with all substrates **C**. The cyclization is *cis*-stereoselective,[5] and the *cis*:*trans* ratio is strongly affected by the reaction temperature (Table: items 1, 3 and 4). This result can be understood by considering that the C(3) stereogenic centre is configurationally unstable.[5] As a result, the isomer thermodynamically more stable, *i.e.* the one with the C(3) and C(4) bulkier appendages *trans*, is formed, and the higher is the temperature the faster is the equilibrium reached.

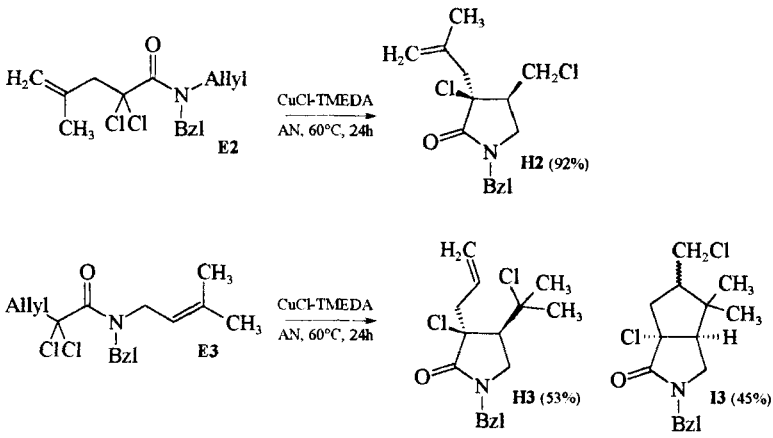
Besides the marked stereoselectivity, a little but significative diastereoselectivity between the two *cis*-adduct **F**, induced by the γ-stereocenter, was also observed. Only few other examples of stereoselective radical cyclizations which use extra-annular stereocenters are known, given that the use of stereogenic centres inside the cyclizing unit is generally preferred.[9] The β-OH in **D1**, shifting the asymmetric carbon to a position next to the radical centre, should give a higher diastereoselectivity.[10] The rearrangement (Table: item 9), however, was unclean and by-products from the nucleophilic attack of the hydroxyl on the near C-Cl groups were also afforded. We then resorted to protect the OH as acetate (**D2**), and excellent yields of the rearranged adduct (**G2**) were thus obtained (Table: item 10). The *cis* diastereoisomer was selectively afforded, as expected, but the *cis* ratio, even if higher than the one with γ-stereocenters (**C**), was still unsatisfactory. The selectivity was disappointing notwithstanding the increase of protective group size for the OH function (Table: items 11 and 12), and even after the replacement of the end methyl with 2-furyl (Table: item 13).

The rearrangement of **E1** gave **H1** with unsatisfactory yields because of a competitive tandem radical-radical reaction, which includes the 3-aza-3-benzyl-1-chloro-7-chloromethyl-2-oxo-bicyclo-[3,3,0]-octane **I1** as a by-product.[11] **I1** appears rather interesting as prodrug, owing to the conformational constriction produced by the bridge between the C(3) and C(4) carbon of the 2-pyrrolidinone ring.[12] Its formation is outlined in scheme 3, where it is clear that a basic requirement for the double cyclization is the *cis* setting between C(3) allyl and C(4) radical appendage.[13]

When we increased the crowding on the carbon which carries out the second cyclization (Scheme 4: **E3**), cascade appeared unaffected; on the contrary the build up of the steric bulk on the *endo* carbon of the C=C final acceptor (Scheme 4: **E2**) virtually stopped the sequence at the first stage, whereas the alternative *endo*-closure showed to be not competitive. Finally the N-



Scheme 3



Scheme 4

allyl-N-benzyl-2,2-dichloro-4-pentinamide rearrangement was attempted, however with very poor result. The reaction showed a not complete conversion (90%), and was unselective, being observed numerous products.

EXPERIMENTAL PART

^{1}H NMR spectra were recorded on a Bruker DPX200 spectrometer. Mass spectra were obtained on a combined HP 5890 GC - HP 5989A MS Engine. Reagents and solvents were

standard grade commercial products and used without further purification. The 2-pyrrolidinones stereochemistry was assigned on rationale reported..[6]

Procedure for synthesis of D1 or E. To a stirred solution of N-allyl-N-benzyl-trichloroamide (100 mmol) in 300 ml of anhydrous THF at –78°C under argon, a 1.6 M solution of butyl-litium in hexane (62.5 ml) was dripped, and after 10 min a solution of acetaldehyde or allylbromide (106 mmol) in 25 ml of anhydrous THF was added. The mixture was stirred at –78°C for another hour before to be quenched with saturated aq. NH_4Cl. The solution was partitioned between CH_2Cl_2 (3 x 100 ml) and brine; the organic phases were collected, dried over $MgSO_4$, filtered and then evaporated. Silica-gel chromatography, using petroleum ether (b.p. 40-60°C)/diethyl ether (3:1), gave **D1** (99%) or **E** (88-98%).

Procedure for esterification of D1: *i)* Acetylation. N-allyl-N-benzyl-2,2-dichloro-3-hydroxy-butanamide **D1** (40 mmol), acetic anhydride (80 mmol) and pyridine (84 mmol) were stirred at room temperature. When conversion was completed, the mixture was acidified with 2.5% HCl and extracted with ethyl ether (3 x 50 ml). The organic layer was dried over $MgSO_4$ and evaporated. Silica gel chromatography, using a petroleum ether (b.p. 40-60°C)/diethyl ether gradient, gave **G2** (99%). ***ii)* Isobutanoylation and benzoylation**. N-allyl-N-benzyl-2,2-dichloro-3-hydroxy-butanamide **D1** (40 mmol), isobutanoic or benzoic anhydride (60 mmol) and pyridine (64 mmol) were stirred at 120°C till complete conversion. Work-up and purification were performed as described above. **G3** and **G4** were afforded in 98% yield.

General procedure for cyclization. CuCl (0.2 mmol) and N-allyl-N-benzyl-2,2-dichloroamide (**C, D** or **E**) (2 mmol) were weighted in a Schlenk tube; then AN (4 ml) and TMEDA (0.4 mmol) were added, under argon. The mixture was stirred at 60°C, and after 20 h diluted with 2.5% HCl (20 ml) and extracted with CH_2Cl_2 (2 x 6 ml). The organic layer was dried over Na_2CO_3 and evaporated.Silica gel chromatography, using a petroleum ether (b.p. 40-60°C)/diethyl ether gradient, gave the γ-lactam (**F, G** or **H**), generally as a mixture of inseparable diastereomers.

***cis*-N-bzl-3-chloro-4-chloromethyl-3-(2,3-dichloro-propyl)-pyrrolidin-2-one (F1)**
IR (film): ν = 1705 (C=O). Oil mix of diastereoisomers. ^{1}H NMR ($CDCl_3$): *cis I*, δ = 2.56 [1H, dd, J = 8.6, 15.4 Hz, CHClC$\underline{H}_2$C(3)], 3.02 [1H, dd, J = 2.5, 15.4 Hz, CHClC$\underline{H}_2$C(3)], 3.11 [1H, dd, J = 8.6, 9.7 Hz, C(5)H], 3.19 [1H, m, C(4)H], 3.46 [1H, dd, J = 7.4, 9.7 Hz, C(5)H], 3.60-3.90 [3H, m, C(4)CH_2Cl and CHCl$\underline{CH}_2$Cl], 4.02 [1H, dd, J = 5.5, 11.0 Hz, C(4)CH_2Cl], 4.16 [1H, m, C$\underline{H}$ClCH_2C(3)], 4.36 (1H, d, J = 14.7 Hz, benzyl H), 4.72 (1H, d, J = 14.7 Hz, benzyl H), 7.20-7.40 (5H, m, H Ph). ^{1}H NMR ($CDCl_3$): *cis II*, δ = 2.58 [1H, dd, J = 9.2, 16.0 Hz, CHClC$\underline{H}_2$C(3)], 2.92 [1H, m, C(4)H], 2.99 [1H, dd, J = 2.5, 16.0 Hz, CHClC$\underline{H}_2$C(3)], 3.08 [1H, dd, J = 8.6, 9.7 Hz, C(5)H], 3.46 [1H, dd, J = 7.4, 9.7 Hz, C(5)H], 3.60-3.90 [4H, m, C(4)CH_2Cl e CHCl$\underline{CH}_2$Cl], 4.46 [1H, m, C$\underline{H}$ClCH_2C(3)], 4.48 (1H, d, J = 14.7 Hz, benzyl H), 4.58 (1H, d, J = 14.7 Hz, benzyl H), 7.20-7.40 (5H, m, H Ph). MS (EI, 70 eV) *m/z*: 332 (7%); 298 (2%); 208 (6%); 91 (100%). Found: C, 49.0; H, 4.7; N, 3.7. $C_{15}H_{17}Cl_4NO$ required C, 48.81; H, 4.64; N 3.79.

***cis*-N-bzl-3-chloro-4-chloromethyl-3-(2-chloro-3-ethoxy-propyl)-pyrrolidin-2-one (F2)**
IR (film): ν = 1705 (C=O). ^{1}H NMR ($CDCl_3$): *cis I* (oil), δ = 1.23 [3H, t, C$\underline{H}_3$CH_2O], 2.52 [1H, dd, J = 9.4, 15.6 Hz, CHClC$\underline{H}_2$C(3)], 2.87 [1H, dd, J = 2.2, 15.6 Hz, CHClC$\underline{H}_2$C(3)], 2.98 [1H, m, C(4)H], 3.08 [1H, dd, J = 8.3, 10.0 Hz, C(5)H], 3.46 [1H, dd, J = 7.4, 10.0 Hz, C(5)H], 3.54-3.71 [5H, m, C(4)CH_2Cl e CH$_3$C$\underline{H}_2$O$\underline{CH}_2$], 4.05 [1H, dd, J = 4.4, 11.4 Hz, C(4)CH_2Cl], 4.31 [1H, m, C$\underline{H}$ClCH_2C(3)], 4.47 (1H, d, J = 14.7 Hz, benzyl H), 4.58 [1H, d, J = 14.7 Hz, benzyl H), 7.20-7.40 (5H, m, H Ph). ^{1}H NMR ($CDCl_3$): *cis II* (oil), δ = 1.24 [3H, t, C$\underline{H}_3$CH_2O], 2.49 [1H, dd, J = 8.8, 15.6 Hz, CHClC$\underline{H}_2$C(3)], 2.96 [1H, dd, J = 2.4, 15.6 Hz, CHClC$\underline{H}_2$C(3)], 3.10 [1H, dd, J = 9.0, 9.8 Hz, C(5)H], 3.26 [1H, m, C(4)H], 3.44 [1H, dd, J = 6.8, 9.8 Hz, C(5)H], 3.51-3.70 [5H, m, C(4)CH_2Cl e CH$_3$C$\underline{H}_2$O$\underline{CH}_2$], 3.87 [1H, dd, J = 4.5, 11.0 Hz, C(4)CH_2Cl], 3.98 [1H, m, C$\underline{H}$ClCH_2C(3)], 4.34 (1H, d, J = 14.7 Hz, benzyl H), 4.73 [1H, d, J = 14.7 Hz, benzyl H), 7.20-7.40 (5H, m, H Ph). MS (EI, 70 eV) *m/z*: 342 (3%); 306 (2%); 221 (5%); 146 (22%); 91 (100%). Found: C, 54.1; H, 5.9; N, 3.6. $C_{17}H_{22}Cl_3NO_2$ required C, 53.91; H, 5.85; N 3.70.

***cis*-N-bzl-3-chloro-4-chloromethyl-3-(2,3-dichloro-2-methyl-propyl)-pyrrolidin-2-one (F3)**
IR (film): ν = 1695 (C=O). Oil mix of diastereoisomers. ^{1}H NMR δ ($CDCl_3$): 1.63 [0.47·3H, s, (CH$_3$)CClC(4), *cis II*], 1.80 [0.53·3H, s, (CH$_3$)CClC(4), *cis I*], 2.60 [0.47·1H, d, J = 15.6 Hz, C(CH$_3$)ClC$\underline{H}_2$C(3), *cis II*], 2.78 [0.53·1H, d, J = 15.6 Hz, C(CH$_3$)ClC$\underline{H}_2$C(3), *cis I*], 296 [0.47·1H, d, J = 15.6 Hz, C(CH$_3$)ClC$\underline{H}_2$C(3), *cis II*], 3.09-3.18 [1H, m, C(5)H], 3.18 [0.53·1H, d, J = 15.6 Hz, C(CH$_3$)ClC$\underline{H}_2$C(3), *cis I*], 3.33 [0.47·1H, m, C(4)H, *cis II*], 3.41 [0.53·1H, m, C(4)H, *cis I*], 3.47-3.57 [1H, m, C(5)H], 3.62-3.84 [4H, m, ClC$\underline{H}_2$C(CH$_3$)Cl e C(4)CH_2Cl], 4.46 (0.47·1H, d, J = 14.6 Hz, benzyl H, *cis II*), 4.51 (0.53·1H, d, J = 14.6 Hz, benzyl H, *cis I*), 4.56 (0.53·1H, d, J = 14.6 Hz, benzyl H, *cis I*), 4.60 (0.47·1H, d, J = 14.6 Hz, benzyl H, *cis II*), 7.20-7.40 (5H, m, H Ph). MS (EI, 70 eV) *m/z*: 310 (9%); 274 (3%); 131 (13%); 91 (100%). Found: C, 50.2; H, 5.0; N, 3.8. $C_{16}H_{19}Cl_4NO$ required C, 50.16; H, 5.00; N 3.66.

***cis*-N-bzl-3-chloro-3-(2-chloro-11-benzyloxy-undecyl)-4-chloromethyl-pyrrolidin-2-one (F4)**
IR (film): ν = 1700 (C=O). ^{1}H NMR ($CDCl_3$): *cis I* (oil), δ = 1.35-1.95 [16H, m, CHCl(C$\underline{H}_2$)$_8$CH_2O], 2.50 [1H, dd, J = 9.1, 15.4 Hz, CHClC$\underline{H}_2$C(3)], 2.88 [1H, dd, J = 1.8, 15.4 Hz, CHClC$\underline{H}_2$C(3)], 3.13 [1H, dd, J = 8.5, 9.0 Hz, C(5)H], 3.33 [1H, m, C(4)H], 3.42-3.55 [3H, m, CHCl(CH$_2$)$_8$C$\underline{H}_2$O e C(5)H], 3.70 [1H, dd, J = 9.6, 11.0 Hz, C(4)CH_2Cl], 3.82 [1H, m, C$\underline{H}$ClCH_2C(3)], 3.91 [1H, dd, J = 4.3, 11.0 Hz, C(4)CH_2Cl], 4.39 (1H, d, J = 14.7 Hz, PhCH_2N), 4.54 (2H, s, PhCH_2O), 4.74 (1H, d, J = 14.7 Hz, PhCH_2N), 7.20-7.45 (10H, m, H Ph). ^{1}H NMR ($CDCl_3$): *cis II* (oil), δ = 1.35-1.95 [16H, m, CHCl(C$\underline{H}_2$)$_8$CH_2O], 2.61 [1H, dd, J = 9.2, 15.7 Hz, CHClC$\underline{H}_2$C(3)], 2.79 [1H, dd, J = 2.7, 15.7 Hz, CHClC$\underline{H}_2$C(3)], 3.06 [1H, m, C(4)H], 3.10 [1H, dd, J = 8.0, 8.5 Hz, C(5)H], 3.40-3.57 [3H, m, CHCl(CH$_2$)$_8$C$\underline{H}_2$O e C(5)H], 3.65 [1H, dd, J = 8.7, 11.0 Hz, C(4)CH_2Cl], 4.11 [1H, dd, J = 5.1, 11.0 Hz, C(4)CH_2Cl], 4.22 [1H, m, C$\underline{H}$ClCH_2C(3)], 4.54 (2H, s, benzyl H), 4.55 (2H, m, benzyl H), 7.20-7.45

(10H, m, H Ph). MS (EI, 70 eV) *m/z*: 515 (1%); 460 (1%); 409 (4%); 360 (16%); 236 (22%); 91 (100%). Found: C, 65.3; H, 7.3; N, 2.6. $C_{30}H_{40}Cl_3NO_2$ required C, 65.16; H, 7.29; N 2.53.

cis-N-bzl-3-(1-acetoxy-ethyl)-3-chloro-4-chloromethyl-pyrrolidin-2-one (G2)
IR (film): ν = 1695 (C=O,lactam) 1750 (C=O, ester). Oil mix of diastereoisomers. ^{1}H NMR ($CDCl_3$): *cis I*, δ = 1.43 (3H, d, J = 6.5, $C\underline{H}_3CH$), 2.13 [3H, s, $CH_3(CO)$], 2.96 [1H, m, 1H, m, C(4)H], 3.14 [1H, dd, J = 8.5, 10.0 Hz, C(5)H], 3.51 [1H, dd, J = 7.2, 10.0 Hz, C(5)H], 3.67 [1H, dd, J = 10.5, 11.2 Hz, $C(4)C\underline{H}_2Cl$], 3.98 [1H, dd, J = 4.2, 11.1 Hz, $C(4)C\underline{H}_2Cl$], 4.46 (1H, d, J = 14.7 Hz, benzyl H), 4.61 (1H, d, J = 14.7 Hz, benzyl H), 5.57 (1H, q, J = 6.5 Hz, $CH_3C\underline{H}$), 7.20-7.45 (5H, m, H Ph). ^{1}H NMR ($CDCl_3$): *cis II*, δ = 1.54 (3H, d, J = 6.4, $C\underline{H}_3CH$), 2.05 [3H, s, $CH_3(CO)$], 3.00 [1H, m, 1H, m, C(4)H], 3.14 [1H, dd, J = 8.2, 10.0 Hz, C(5)H], 3.57 [1H, dd, J = 7.4, 10.0 Hz, C(5)H], 3.67 [1H, dd, J = 10.5, 11.2 Hz, $C(4)C\underline{H}_2Cl$], 3.90 [1H, dd, J = 3.9, 11.2 Hz, $C(4)C\underline{H}_2Cl$], 4.46 (1H, d, J = 14.7 Hz, benzyl H), 4.61 (1H, d, J = 14.7 Hz, benzyl H), 5.42 (1H, q, J = 6.4 Hz, $CH_3C\underline{H}$), 7.20-7.45 (5H, m, H Ph). MS (EI, 70 eV) *m/z*: 307 (3%); 248 (62%); 208 (7%); 200 (9%); 91 (100%). Found: C, 56.0; H, 5.7; N, 4.0. $C_{16}H_{19}Cl_2NO_3$ required C, 55.83; H, 5.56; N 4.07.

cis-N-bzl-3-[acetoxy-(2-furyl)-methyl]-3-chloro-4-chloromethyl-pyrrolidin-2-one (G5)
^{1}H NMR ($CDCl_3$) *cis I* (oil), δ = 2.2 (3H, s, $-C\underline{H}_3$); 3.13 (1H, dd, J = 6.21, 8.82 Hz, $-NC\underline{H}_2CH$-); 3.16 (1H, m, $-NCH_2C\underline{H}$-); 3.39 (1H, dd, J= 6.43, 8.82 Hz, $-NC\underline{H}_2CH$-); 3.71 (1H, dd, J = 10.6, 10.8 Hz, $-C\underline{H}_2Cl$); 4.06 (1H, dd, J = 3.9, 10.8 Hz, $-C\underline{H}_2Cl$); 4.38 [(1H, d, J = 14 Hz, (2-furyl)$C\underline{H}_2$]; 4.53 [(1H, d, J = 14 Hz, (2-furyl)$C\underline{H}_2$]; 6.42 (1H, dd, J = 1.82, 3.3 Hz, 2-Furyl H); 6.55 (1H, d, J = 4.1 Hz, 2-furyl H); 6.56 (1H, s, $C\underline{H}OCOCH_3$); 7.09-7.32 (5H, m, H Ph); 7.43 (1H, dd , J = 0.7, 1.8 Hz, 2-furyl H): *cis II* (oil), δ = 2.07 (3H, s, $-C\underline{H}_3$), 3.12-3.67 (5H, m, $-NC\underline{H}_2C\underline{H}C\underline{H}_2Cl$); 4.44 (1H, d, J = 14.7 Hz, benzyl H); 4.71 (1H, d, J = 14.7 Hz, benzyl H); 6.30 (1H, s, $C\underline{H}OCOCH_3$); 6.44 (1H, dd, J = 1.8, 3.3 Hz, 2-Furyl H); 6.58 (1H, m, 2-Furyl H); 7.25-7.44 (5H, m, H Ph); 7.48 (1H, dd, J=1.8, J=0.6, 2-Furyl H). MS (EI, 70 eV) *m/z*: 360 (5%); 301 (11%); 208 (31%); 91 (100%). Found: C, 57.8; H, 4.4; N, 3.7. $C_{19}H_{17}Cl_2NO_4$ required C, 57.88; H, 4.35; N 3.55.

cis-N-bzl-3-allyl-3-chloro-4-chloromethyl-pyrrolidin-2-one (H1)
IR (film): ν = 1705 (C=O,lactam) 1750 (C=O, ester). Oil. ^{1}H NMR δ ($CDCl_3$): 2.82 [1H, m, 1H, m, C(4)H], 2.95 [2H, m, CH_2=$CHC\underline{H}_2$], 3.09 [1H, dd, J = 1.1, 10.0 Hz, C(5)H], 3.41 [1H, dd, J = 2.8, 10.0 Hz, C(5)H], 3.63 [1H, dd, J = 9.3, 11.2 Hz, $C(4)C\underline{H}_2Cl$], 3.85 [1H, dd, J = 5.1, 11.2 Hz, $C(4)C\underline{H}_2Cl$], 4.44 (1H, d, J = 14.7 Hz, benzyl H), 4.65 (1H, d, J = 14.7 Hz, benzyl H), 5.2-5.4 (2H, m, $C\underline{H}_2$=CH-), 5.7-6.0 (1H, m, CH_2=$C\underline{H}$-), 7.20-7.45 (5H, m, H Ph). MS (EI, 70 eV) *m/z*: 297 (2%); 262 (48%); 212 (13%); 91 (100%). Found: C, 60.4; H, 5.8; N, 4.8. $C_{15}H_{17}Cl_2NO$ required C, 60.42; H, 5.75; N 4.70.

3-aza-3-benzyl-1-chloro-7-chloromethyl-2-oxo-bicyclo[3.3.0]octane (I1)
IR (nujol): ν = 1700 (C=O,lactam). ^{1}H NMR ($CDCl_3$): diastereoisomer I (solid, p.f. 77-79 °C), δ = 1.67 [1H, m, C(6)H], 2.03 [1H, dd, J = 10.8, 13.1 Hz, C(8)H], 2.10 [1H, m, C(6)H], 2.26 [1H, m, $C(7)\underline{H}CH_2Cl$], 2.81 [1H, dd, J = 6.1, 13.1 Hz, C(8)H], 2.88 [1H, m, C(5)H], 2.89 [1H, dd, J = 1.8, 10.5 Hz, C(4)H], 3.49 [1H, dd, J = 6.8, 11.0 Hz, $C(7)HC\underline{H}_2Cl$], 3.58 [1H, dd, J = 5.5, 11.0 Hz, $C(7)HC\underline{H}_2Cl$], 3.60 [1H, dd, J = 7.6, 10.5 Hz, C(4)H], 4.47 (1H, d, J = 14.7 Hz, benzyl H), 4.54 (1H, d, J = 14.7 Hz, benzyl H), 7.20-7.40 (5H, m, H Ph). ^{1}H NMR ($CDCl_3$): diastereoisomer II (oil), δ = 1.21 [1H, m, C(6)H], 2.25-3.00 [5H, m, C(5)H, C(6)H, C(7)H, C(8)H], 2.26 [1H, m, $C(7)\underline{H}CH_2Cl$], 2.88 [1H, m, C(4H], 2.95 [1H, dd, J = 1.7, 10.3 Hz, C(4)H], 3.46 [1H, dd, J = 6.6, 10.9 Hz, $C(7)HC\underline{H}_2Cl$], 3.56 [1H, dd, J = 7.0, 10.3 Hz, C(4)H], 3.57 [1H, dd, J = 5.5, 10.9 Hz, $C(7)HC\underline{H}_2Cl$], 4.47 (1H, d, J = 14.7 Hz, benzyl H), 4.56 (1H, d, J = 14.7 Hz, benzyl H), 7.20-7.45 (5H, m, H Ph). MS (EI, 70 eV) *m/z*: 297 (10%); 262 (42%); 226 (27%); 91 (100%). Found: C, 60.5; H, 5.7; N, 4.7. $C_{15}H_{17}Cl_2NO$ required C, 60.42; H, 5.75; N 4.70.

cis-N-bzl-3-allyl-3-chloro-4-(chloro-methyl-ethyl)-pyrrolidin-2-one (H3)
^{1}H NMR ($CDCl_3$) δ = 1.82 (3H, s, -C$\underline{H}_3$); 1.84 (3H, s, -C$\underline{H}_3$); 2.92 (1H, dd, J = 9.2, 14 Hz, -NC$\underline{H}_2$CH-); 2.98 (1H, dd, J = 7.25, 9.2 Hz, -NCH$_2$C$\underline{H}$-); 3.27-3.38 (2H, m, CH$_2$=CHC$\underline{H}_2$), 3.41 (1H, m, -NC$\underline{H}_2$CH-); 4.52 (1H, d, J = 14.7 Hz, benzyl H); 4.63 (1H, d, J = 14.7 Hz, benzyl H); 5.23-5.34 (2H, m, C$\underline{H}_2$=CH-); 5.58-5.5.78 (1H, m, CH$_2$=C$\underline{H}$-); 7.24-7.44 (5H, m, H Ph). MS (EI, 70 eV) *m/z*: 289 (4%); 212 (8%); 118 (11%); 91 (100%). Found: C, 62.5; H, 6.6; N, 4.4. $C_{17}H_{21}Cl_2NO$ required C, 62.58; H, 6.49; N 4.29. Oil.

3-aza-3-benzyl-1-chloro-7-chloromethyl-6,6-dimethyl-2-oxo-bicyclo[3.3.0]octane (I3)
^{1}H NMR ($CDCl_3$), main diastereoisomer (yield 31%), δ = 0.90 (3H, s, -C$\underline{H}_3$); 1.10 (3H, s, -C$\underline{H}_3$); 1.89 (1H, m, CH$_2$ClC$\underline{H}$-), 2.23 (1H, dd, J = 11.4, 13.9 Hz, CH$_2$ClCHC$\underline{H}_2$); 2.57 (1H, dd, J = 2.9, 8.3 Hz, -C$\underline{H}$CH$_2$N-); 2.98 (1H, dd, J= 6.5, 13.9 Hz, -CH$_2$ClCHC$\underline{H}_2$), 3.11 (1H, dd, J = 2.9, 10.8 Hz, -CHC$\underline{H}_2$N-); 3.41 (1H, dd, J = 8.3, 10.8 Hz, -CHC$\underline{H}_2$N-); 3.45 (1H, dd, J = 8.8, 10.9 Hz, C$\underline{H}_2$Cl-); 3.54 (1H, dd, J = 5.3, 10.9 Hz, -CH$_2$Cl); 4.51 (2H, s, benzyl H); 7.34 (5H, m, H Ph). MS (EI, 70 eV) *m/z*: 325 (5%); 290 (36%); 185 (52%); 91 (100%). Found: C, 62.5; H, 6.4; N, 4.3. $C_{17}H_{21}Cl_2NO$ required C, 62.58; H, 6.49; N 4.29. Oil.

cis-N-bzl-3-(2-methyl-prop-2-enyl)-3-chloro-4-chloromethyl-pyrrolidin-2-one (H2)
^{1}H NMR ($CDCl_3$) δ = 1.8 (3H, s, -C$\underline{H}_3$); 2.78 (1H, dd, J = 0.5, 14 Hz, -C$\underline{H}_2$CH=CH$_2$); 2.82 (1H, m, -CH$_2$C$\underline{H}$=CH$_2$Cl); 3.09 (1H, dd, J = 8.9, 9.9 Hz, -NC$\underline{H}_2$CH-); 3.15 (1H, d, J = 14 Hz, -C$\underline{H}_2$C=CH$_2$); 3.44 (1H, dd, J = 7.2, 9.9 Hz, -NC$\underline{H}_2$CH-); 3.66 (1H, dd, J = 9.2, 11.1 Hz, -C$\underline{H}_2$Cl); 3.82 (1H, dd, J = 4.8, 11.1 Hz, -C$\underline{H}_2$Cl); 4.49 (1H, d, J=14.6 Hz, benzyl H); 4.6 (1H, d, J = 14.7 Hz, benzyl H); 4.95-5.03 (2H, m, C$\underline{H}_2$=C-); 7.23-7.43 (5H, m, H Ph). MS (EI, 70 eV) *m/z*: 311 (3%); 276 (48%); 226 (13%); 91 (100%). Found: C, 61.4; H, 6.1; N, 4.6. $C_{16}H_{19}Cl_2NO$ required C, 61.55; H, 6.13; N 4.49. Oil.

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13. A number of experimental changes were tested aiming to improve the performance of the tandem reaction, but without success.

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