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TETRAHEDRON

The Influence of Benzylic Protection and Allylic Substituents on the CuCl-TMEDA Catalyzed Rearrangement of N-Allyl-N-Benzyl-2,2-Dihaloamides to γ-Lactams. Application to the Stereoselective Synthesis of Pilolactam.

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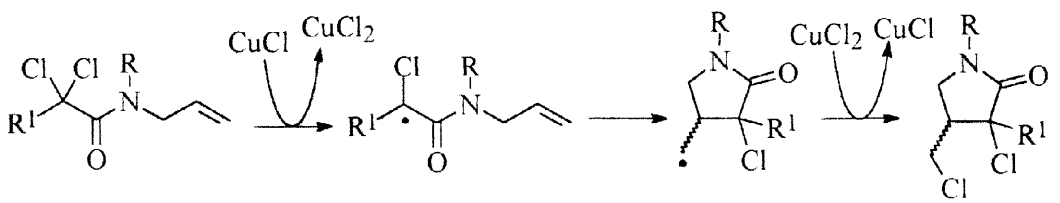
Abstract: A number of N-benzylic protecting groups and allylic substituents have been investigated for the rearrangement, promoted by CuCl-TMEDA, of N-allyl-2,2-dihaloamides to 3,4-disubstituted γ-lactams. An appreciable chiral induction was observed at the C-4 site when α-phenylethylamine was used as a chiral protecting group, while an unexpected Diels-Alder reaction occurred when using a 2-furyl-methyl protection. This rearrangement has been applied to the synthesis of pilolactam, a drug with muscarinic activity. © 1999 Elsevier Science Ltd. All rights reserved.

Keywords: Radicals and radical reactions; Cyclisation; Pyrrolidinones; Lactams.

Recently we have reported the use of CuCl-TMEDA as a promoter for halogen atom transfer *via* radical rearrangement of *N*-allyl-*N*-protected-2,2-dihaloamides to 2-pyrrolidinones (scheme 1).[1] Compared to the classic but more expensive combination of CuCl-2,2'-bypyridine,[2-4] better yields at lower catalyst concentrations were obtained under similar operating conditions. $RuCl_2(PPh_3)_3$[5,6] is the other traditional catalyst, but its use is



Scheme 1

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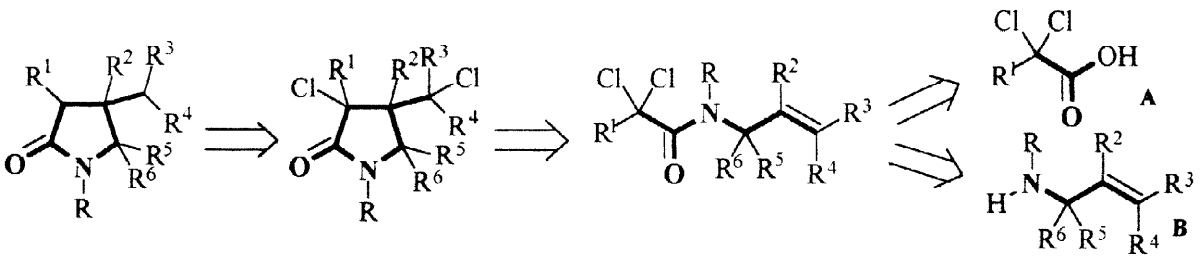
restricted because it is expensive, greater than catalytic amounts are often required for complete conversion, and harsh reaction conditions need to be used. Besides, comparing the rearrangement of the same substrates,[1,5] $RuCl_2(PPh_3)_3$ afforded worse *cis/trans* (typically 26:95) ratios than CuCl-TMEDA (typically 80:100).

From a retrosynthetic point of view the application of the "atom transfer transform" on a 2-pyrrolidinone ring leads to a rearrangement of atoms shown by the bold bonds in scheme 2. This strategy is highly convergent since the γ-lactam is resolved into two simple and easily prepared fragments: a 2,2-dichlorocarboxylic acid **A**[7,8] and an allylic amine **B**.[9] Previously we have limited our attention to the C-3 appendages (R_1) derived from the carboxylic acid **A**.[1] In an effort to increase the synthetic value of this method we have now directed our attention to the allylic unit **B**, responsible for the C-4 and C-5 appendages. In addition, a number of benzylic protecting



Scheme 2

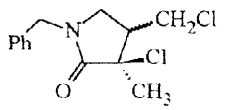
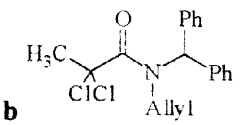
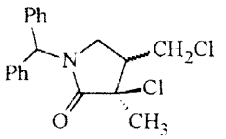
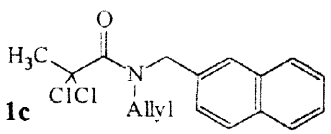
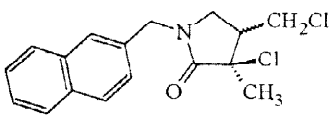
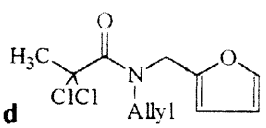
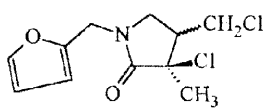
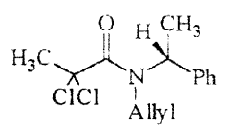
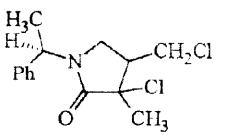
groups have been investigated to show the effect of *N*-substitution on yields and stereochemistry. This method was then applied to the synthesis of pilolactam, an isostere of isopilocarpine recently patented by Allergan®.[10] This drug has muscarinic activity, and appears to be selective for the m5 muscarinic receptor subtype.[11,12]

RESULTS AND DISCUSSION

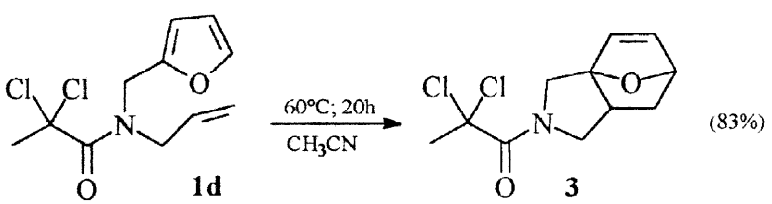
We have previously shown that for the cyclization of *N*-allyl-2,2-dichloroamides, an *N*-protecting group is necessary for excellent yields of halogen atom transfer leading to 2-pyrrolidinones. Protection forces the amides skeleton to adopt a conformation which has the alkene and haloalkyl groups on the same side.[13] Benzylic type protections are useful owing to the number of methods that are available for their removal, this includes hydrolysis, hydrogenolysis, radical halogenation and oxidative cleavages.[14,15] The use of benzyl substituents of varying sizes could effect the efficiency and stereoselectivity of radical cyclization. In addition, there are efficient procedures for the preparation of optically active benzyl amines,[16] and these could be transformed to radical precursors containing chiral *N*-protecting groups. As far as we are aware, chiral induction between the C(3) and C(4) position of 2-pyrrolidinones (on atom transfer cyclization of *N*-allyl-2-haloamides) has only been achieved to produce γ-lactams with a chiral centre at C(5).[17,18] We have investigated a number of benzyl protecting groups for the CuCl-TMEDA promoted cyclization of *N*-allyl-*N*-protected-2,2-dichloropropanamides and the results are reported in Table 1.

Compared to the reference substrate (**1a**), the introduction of bulkier benzhydril or methyl-β-naphthyl groups, in (**1b**) and (**1c**) respectively, produced no marked improvement in the *cis-/trans-* ratio[1,5] whereas the yields (at 25, 40 and 60°C) were generally worse (Table 1, n° 1-3). Of particular interest was the outcome of the reaction of the methyl-2-furyl derivative (**1d**) (n° 4). At room temperature, the main product was derived from an intramolecular Diels-Alder (IMDA) addition between the *N*-allyl and *N*-(methyl-2-furyl) appendages. At higher temperature (60°C) and in the absence of CuCl-TMEDA the IMDA reaction was found to be exclusive (scheme 3). It is interesting to note that the corresponding *N*-acetamide derivative was stable and did not undergo

Table 1. The CuCl-TMEDA promoted cyclization of N-allyl-N-protected-2,2-dichloropropanamide.[a]

n°	Substrate	product	T	conv.[b]	yield[c,d]
			°C	%	% (*cis*:*trans*)
1	 **1a**	 **2a**	25	100	99 (51:49)
			40	100	99 (58:42)
			60	100	99 (66:34)
2	 **1b**	 **2b**	25	83	74 (59:41)
			40	84	74 (58:42)
			60	94	78 (60:40)
3	 **1c**	 **2c**	25	31	27 (61:39)
			40	50	41 (67:33)
			60	68	58 (73:27)
4	 **1d**	 **2d**	25	100	34 (56:44)
5	 **1e**	 **2e**	25	24	20 (75:25)
			40	82	77 (73:27)
			60	100	96 (76:24)[e]

a) $2\cdot10^{-3}$ mol of substrate, $2\cdot10^{-4}$ mol of CuCl, $4\cdot10^{-4}$ mol of TMEDA and 4 ml of acetonitrile (AN) were used; reaction time 20 h. b) GC values. c) Yield of isolated product. d) Ratio determined by GC. e) diastereoisomer ratio (d.r.): *cis* I/II = 54:46 and *trans* I/II = 53:47 (determined by NMR).

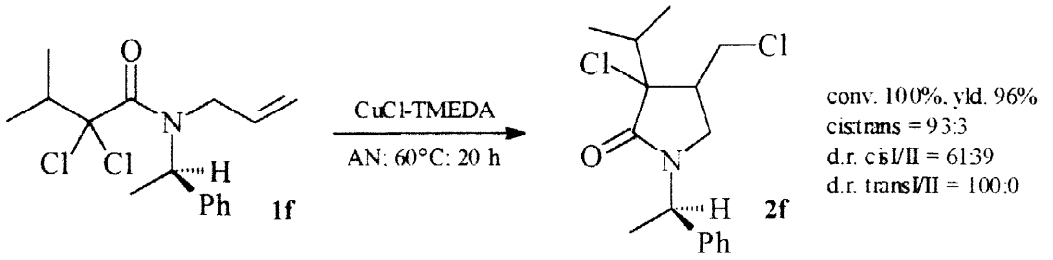


Scheme 3

cycloaddition on heating at 60°C. *N*-allyl-*N*-(2-furyl-methyl)-2,2-dichloro-propionamide (**1d**) is indeed unstable and even at room temperature the IMDA proceeds slowly.

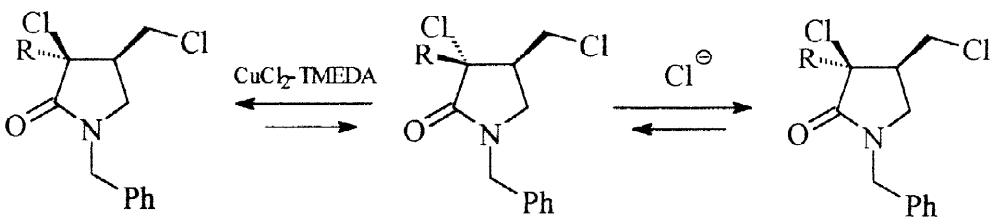
A modest but significant chiral induction was observed for both the *cis* and *trans* diastereomers on introduction of the (*R*)-1-phenyl-1-ethyl group (**1e**) (n°5). The insertion of a methyl at the α-position of the benzyl group was shown to slow down the reaction and the complete conversion of (**1e**) was only observed at 60°C. A related cyclization of *N*-allyl-*N*-(1-phenyl-1-ethyl)-2-iodoacetamide has been reported but this gave rise to a racemic mixture of γ-lactams.[19] The selectivity we detected was promising, so we tested the rearrangement of *N*-allyl-*N*-(1-phenyl-1-ethyl)-2,2-dichloro-3-methyl-propanamide (**1f**), which contained a larger alkyl substituent at the site of radical generation (scheme 4). This produced a satisfactory chiral induction and represents the first example of diastereoselective 5-*exo* radical cyclization of amides to 2-pyrrolidinones, without a chiral C(5) centre. The chiral auxiliary can therefore influence the radical leading to a selective addition to the

alkene double bond. This can be compared with the racemic cyclization of *N*-allyl-*N*-(1-phenyl-1-ethyl)-2,2-dichloro-3-methyl-propanamide by Orena,[19,20] which lacked the bulky isopropyl substituent.



Scheme 4

We then explored some alternative allylic appendages and the results are collected in Table 2. As reported previously,[1,5] the C-3 chiral centre is configurationally unstable under the reaction conditions. This may result from nucleophilic substitution by chloride or alternatively radical generation at C-3 followed by chlorine atom transfer (scheme 5). The lack of Karasch adducts, when (**2a**) is treated with CuCl-TMEDA and 1-octene (under the usual reaction conditions), and the epimerization observed on replacement of CuCl with $CuCl_2$ support strongly the first alternative.[21] As the result, the thermodynamically more stable isomer, *i. e.* that which has the bulkier C-3 and C-4 appendages *trans*-, is formed. However increasing the substitution of the allylic double bond,

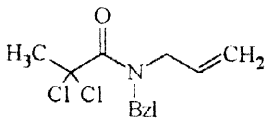
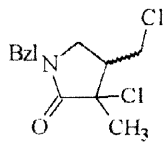
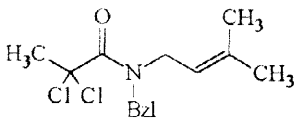
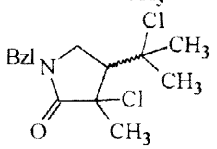
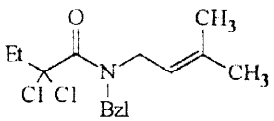
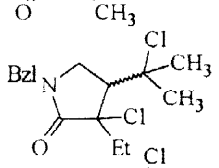
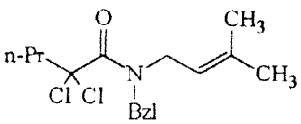
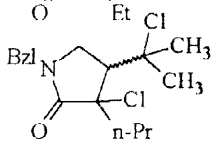
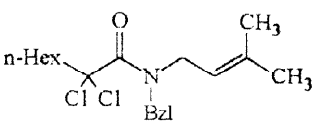
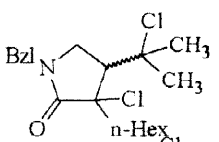
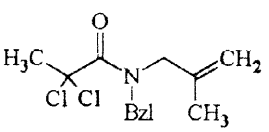
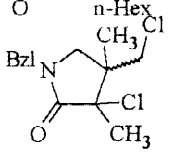
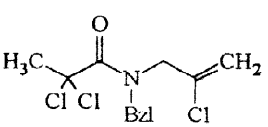
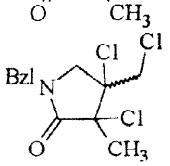
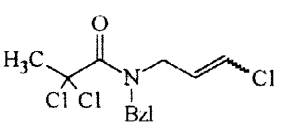
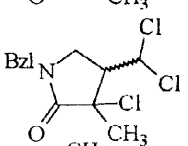
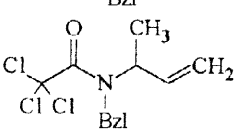
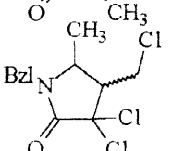
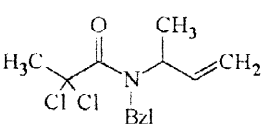
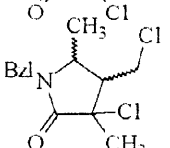
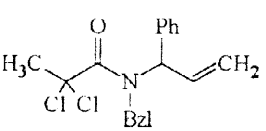
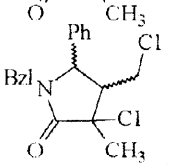


Scheme 5

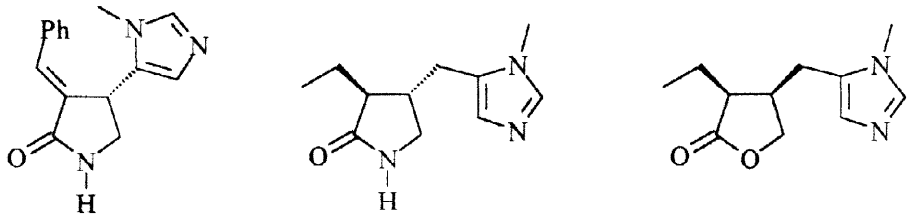
as for (**1g**), was found to lead to a 1:1 mixture of isomers (Table 2, n° 2). It is clear that the C-4 substituent experiences similar steric interactions with the Cl and CH_3 at C-3. A preference for the *cis*- diastereomer was recovered on replacing the C-3 methyl substituent with larger groups such as ethyl (**1h**), n-propyl (**1i**) or n-hexyl radicals (**1l**) (n° 3-5). We observed no competitive 6-*endo* cyclization even after the introduction of an internal alkene substituent as in (**1m**) and (**1n**) (n° 6-7).[17] It is interesting that while (**1o**) efficiently rearranged to the 2-pyrrolidinone (**2o**), which has a potentially useful latent formyl group, the corresponding alkene isomer (**1n**) gave a poor conversion (n° 7-8). The poor yield was attributed to the instability of (**2n**) under the reaction conditions; it was thought to react with the TMEDA, and when (**2n**) was added to other halide precursors (0.3/2 mmoles/mmoles), such as (**1a**) and (**1m**), no cyclization was observed. We also found, in agreement with observations of other authors [6,23] that a substituent at the C-5 position forces the C-4 substituent on to the opposite face of the ring (n° 9), and this preference is in no way influenced by the incorporation of other side chains bonded to C-3 (n° 10-11).

The synthetic utility of the CuCl-TMEDA promoted rearrangement was finally explored by application to the formal synthesis of pilolactam. Pilolactam has a similar structure and biological activities to the anatine alkaloids and pilocarpine (scheme 6).[24] The target compound was (**4a**) which had previously been prepared and converted to pilocarpine by Allergan®.[10] For the preparation of (**4a**) we devised a retrosynthetic analysis, shown in Scheme 7, which leads back to the cheap and readily available starting materials (**10**) and (**12**). These could be converted to (**7**) in an unoptimized 52% yield (from **10**) as a 85:15 *trans*:*cis* mixture of diastereomers. Hydro-de-

Table 2. The CuCl-TMEDA promoted cyclization of N-allyl-N-benzyl-2,2-dichloroamide.[a]

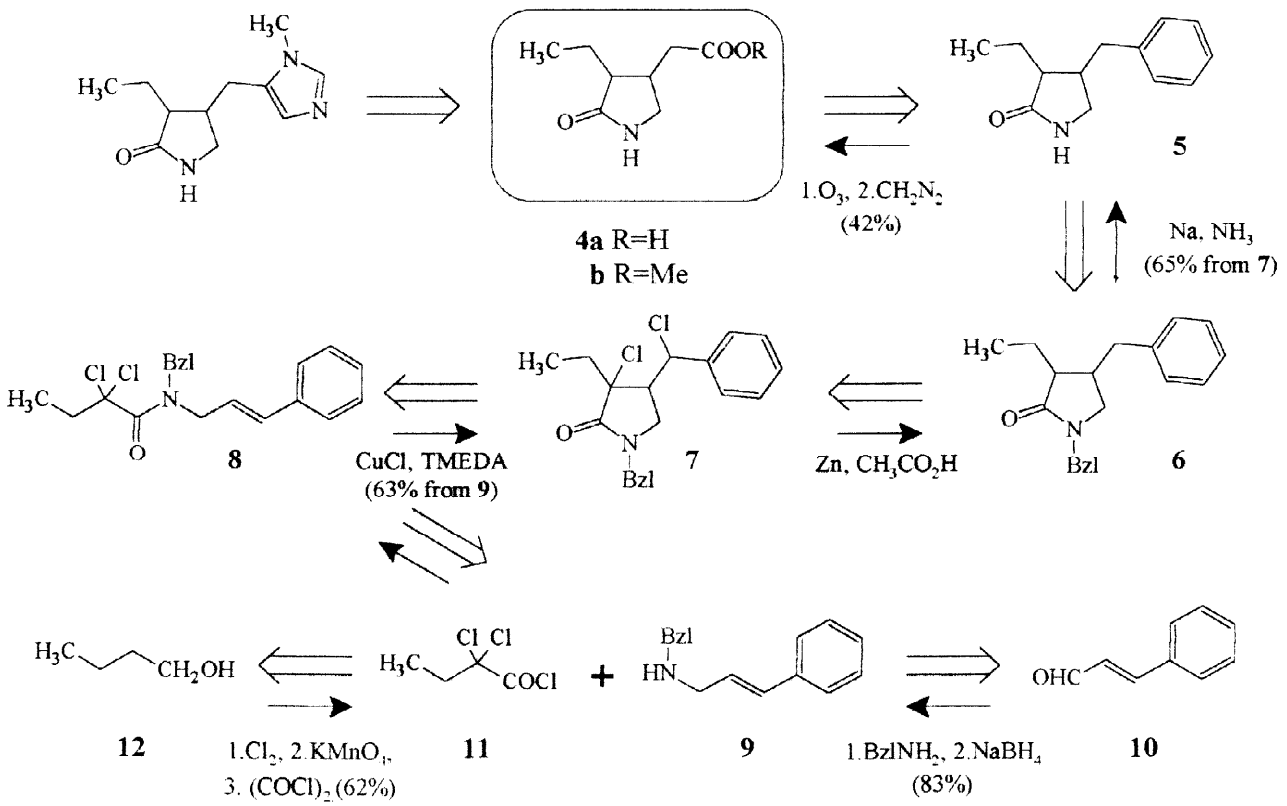
n°	Substrate	product	T °C	conv.[b] %	yield[c,d] % (*cis*:*trans*)
1	 **1a**	 **2a**	25 60	100 100	99 (51:49) 99 (66:34)
2	 **1g**	 **2g**	25 60	91 100	90 (50:50) 99 (50:50)
3	 **1h**	 **2h**	25 60	/ 100	/ 97 (71:29)[e]
4	 **1i**	 **2i**	25 60	/ 100	/ 98 (79:21)[e]
5	 **1l**	 **2l**	25 60	/ 100	/ 98 (76:21)[e]
6	 **1m**	 **2m**	25 60	92 100	91 (53:47) 99 (31:69)
7	 **1n**	 **2n**	25 60	20 22	9 (0:100) 0
8	 **1°**	 **2o**	25 60	100 100	99 (67:33) 100 (80:20)
9	 **1p**	 **2p**	25 60	100 100	94 (3:97) 92 (7:92)
10	 **1q**	 **2q**	25 60	96 100	94 (1:6:30:63)[f] 98 (1:7:22:70)[f]
11	 **1r**	 **2r**	25 60	56 100	54 (2:2:43:53)[f] 98 (2:5:26:67)[f]

a) $2\cdot10^{-3}$ mol of substrate. $2\cdot10^{-4}$ mol of CuCl, $4\cdot10^{-4}$ mol of TMEDA and 4 ml of AN were used; reaction time 20 h. b) GC values. c) Yield of isolated product. d) Ratio determined by GC. e) Ratio determined by ^{1}H NMR. f) Ratio % t-4,t-5:c-4,c-5:t-4,c-5:c-4,t-5 taking r-3-Cl.[22]



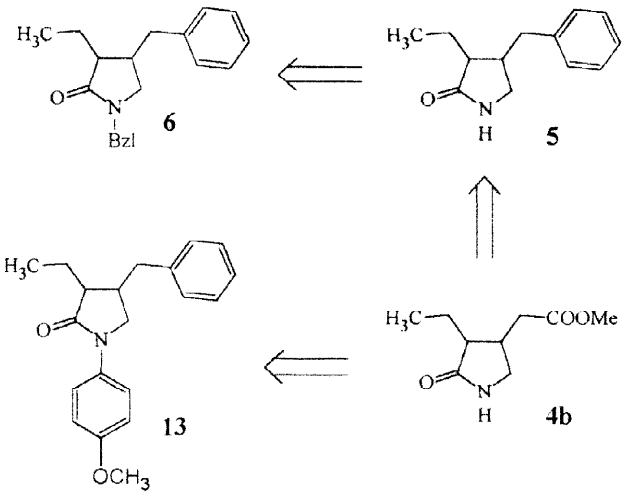
Scheme 6

halogenation of (**7**) with Zn in acetic acid[25] followed by de-benzylation using Na/NH_3[23] provided (**5**) in 65% yield (unoptimized) as a 81:19 *trans:cis* mixture of diastereomers. Finally, oxidation of the aromatic side chain of (**5**) could be achieved using ozone[26] and this gave (**4a**) which was methylated with diazomethane (to make the isolation and purification easier) to give (**4b**) in 42% yield as a 82:18 mixture of *trans*-:*cis*- isomers. The mixtures of diastereoisomers **7**, **6**, **5** and **4a** cannot be separated.



Scheme 7

A more straightforward route to (**4b**), which by-passes the *N*-benzyl deprotection of (**6**), is outlined in scheme 8. The replacement of *N*-benzyl protection with the readily oxidizable *N*-*p*-methoxy-phenyl group makes possible, on ozonization of (**13**), both *N*-deprotection and generation of the carboxylic acid function. Following this alternative route (**4b**) was indeed afforded in slightly better yield (45%), but with a somewhat worse stereochemistry (*cis:trans*, 66:34), this being due to the poor stereoselectivity observed in the preparation of (**13**), which was obtained, following the same procedure used for (**6**), in 72% yield starting from 2,2-dichloro-propanoylchloride and *N*-(4-methoxyphenyl)-cinnamylamine.



Scheme 8

Three main results have been achieved from this work: *i*) CuCl-TMEDA has been shown to be a good promoter for the radical rearrangement of various *N*-allyl-*N*-protected-2,2-dihaloamides to γ-lactams and the best yields were obtained with *N*-benzyl protected precursors, *ii*) the C-4 asymmetric induction, caused by an *N*-*exo*-chiral centre, is more pronounced with a precursor bearing a large C-3 substituent and *iii*) the intramolecular Diels-Alder reaction, between allylic and furyl groups tethered to the nitrogen of a 2,2-dichloroamide, can be realized under unusually mild reaction conditions. These promising achievements will be the subject of further investigations.

EXPERIMENTAL PART

^{1}H NMR and IR spectra were recorded on a Bruker DPX200 and a Philips PU 9716 spectrometers, respectively. Mass spectra were acquired on a combined HP 5890 GC - HP 5989A MS Engine. Reagents and solvents were standard grade commercial products and used without further purification, except AN that was dried over three batches of 3Å sieves (5% w/v, 12 h). CuCl was purchased from Fluka. The following amines were prepared by *N*-alkylation with organic halides, adapting the procedure of Shipman[27]: *N*-benzyl-allylamine, *N*-(R-1-phenylethyl)-allylamine, *N*-benzyl-prenylamine, *N*-benzyl-3-Cl-allylamine, *N*-benzyl-2-Cl-allylamine, *N*-benzyl-2-Cl-allylamine, *N*-benzyl-methallylamine and *N*-(diphenylmethyl)-allylamine. The Guy's reductive amination[28] and the Overman approach[29] were used for the synthesis of *N*-(β-napthyl-methyl)-allylamine, *N*-(2-furyl-methyl)-allylamine, *N*-benzyl-cinnamylamine (**9**), *N*-(4-methoxyphenyl)-cinnamylamine, *N*-benzyl-1-phenyl-2-propenylamine and *N*-benzyl-1-methyl-2-propenylamine. Methyl 2,2-dichloro-3-methyl-butanoate was prepared by oxidation-chlorination of 2-(2-methyl-propyl)-4,5-dimethyl-1,3-dioxolane with trichloroisocyanuric acid,[7] whereas 2,2-dichlorobutanoic, 2,2-dichlorohexanoic and 2,2-dichlorooctanoic acids were obtained by chlorination (Cl_2) of parent alcohols in the system DMF-$CHCl_3$-$MgCl_2$ following the De Buyck's method.[8]

The **(2m)** and **(2o)** stereochemistry was assigned by NOE between the metyl or hydrogen on C(4) and the C(3)CH_3 respectively. For the other compounds the bulkier substituent at C(3) preferentially occurs *trans* to the C(4)-(2-chloroalkyl) group.[1,30]

2,2-Dichloro-propanoylchloride.[31] In a three-necked round bottom flask (500 ml) fitted with a $CaCl_2$ tube, a dropping funnel and a thermometer, sodium 2,2-dichloropropanoate (660 mmol) was suspended in a solution of

pyridine (1 ml) in CH_2Cl_2 (200 ml). The stirred solution was thermostated at 25 °C and the oxalyl chloride (770 mmol) added dropwise (bubbles, due to the formation of CO, CO_2 and HCl). Addition completed, the mixture was stirred for an additional 2 hours, and then the by-product NaCl filtered off. The 2,2-dichloro-propanoylchloride was isolated by distillation at 260 mmHg, collecting the fraction between 70-80°C; yield ~70%.

2,2-Dichloro-3-methyl-butanoic acid. In a round bottom flask (100 ml) methyl 2,2-dihalocarboxylate (20 mmol), isopropyl alcohol (20 ml) and 1.5 M aq. LiOH (20 ml) were added. The stirred mixture was thermostated at -7°C, acidified with 1.0 M aq. HCl (80 ml), after 30 minutes, and then extracted with CH_2Cl_2 (2 x 20 ml). The organic phases were collected and dried over $MgSO_4$. The 2,2-dichloro-3-methyl-butanoic acid, recovered after solvent removal, required no further purification.

General procedure for the preparation of *N*-allyl-*N*-benzyl-2,2-dihaloamides from 2,2-dihalocarboxylic acids.[1] The 2,2-dihalo-carboxylic acid (20 mmol) was weighed in a round bottom Schlenk tube fitted with a rubber seal, then dry CH_2Cl_2 (10 ml) and 5 drops of DMF were added under argon. The stirred mixture was thermostated at 20-40°C, and oxalyl chloride (40 mmol) injected with a syringe. The side arm was then fitted with a $CaCl_2$ tube, and the stopcock opened to vent out the gases (CO, CO_2 and HCl) produced during the reaction. After 1-3 h, solvent and excess oxalyl chloride were removed under reduced pressure. The crude acyl chloride was then diluted with CH_2Cl_2 (40 ml), thermostated at 20-30°C and quenched with *N*-allyl-*N*-benzylamine (60 mmol). The reaction mixture was stirred for 1-5 h and then washed with 2.5% aq. HCl (2 x 25 ml). The organic phase was dried over $MgSO_4$, and evaporated. The crude *N*-allyl-*N*-benzyl-2,2-dihaloamides were purified by silica gel chromatography, using a petroleum ether (b.p. 40-60°C)/diethyl ether gradient; yields 85-98%. All products gave consistent MS spectra.

General procedure for the cyclizations. CuCl ($0.2 \cdot 10^{-3}$ mol) and N-allyl-2,2-dichloroamide (**1a-r**) and (**8**) ($2 \cdot 10^{-3}$ mol) were weighted in a Schlenk tube; then AN (4 ml) and TMEDA ($0.4 \cdot 10^{-3}$ mol) were added, under argon. The mixture was stirred at the temperature reported in table 1-3, 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. Chromatographic separation by silica gel chromatography, using a petroleum ether (b.p. 40-60°C)/diethyl ether gradient, gave the γ-lactam (**2a-r**) and (**7**), generally as a mixture of inseparable diastereomers.

Hydro-de-chlorination of (7). To a stirred solution of (**7**) (10 mmol) in glacial acetic acid (40 ml) was added Zn dust (110 mmol) . The mixture was thermostated to 80°C, monitored by TLC (1-2 h) and filtered to remove the metal. The acetic solution was diluted with water (200 ml) and extracted with diethyl ether (2 x 20 ml). The organic phase was washed with 5% Na_2CO_3 to remove residual acetic acid, dried over $MgSO_4$ and evaporated. The crude product (**6**) was purified by silica gel chromatography, using petroleum ether (b.p. 40-60°C)/diethyl ether gradient. *N*-debenzylation with Na/NH_3 to (**5**) according to literature;[11] overall yield 65%; *trans*:*cis* ratio, 81:19.

Ozonization of (5) . Ozone/O_2 (7.5 %) was bubbled (10 l/h) into a solution of (**5**) (1.42 mmol) in formic acid/H_2O (12 ml; 5:1) for 20 h. H_2O_2 (15%, 8 ml) was then added and the mixture stirred for further 48 h. The solvent was removed under vacuum and the crude pyrrolidinone (**4a**) dissolved in diethyl ether/CH_3OH (3 ml; 5:1). Finally, reaction with diazomethane gave methyl ester (**4b**), which, after concentration, was purified by silica gel chromatography (diethyl ether/CH_3OH gradient; yield 42%, *trans*:*cis* ratio, 82:18).

N-(β-Napthyl-methyl)-3-chloro-4-chloromethyl-3-methyl-pyrrolidin-2-one (2c)

IR (film): ν = 1700 (C=O). ^{1}H NMR ($CDCl_3$): δ = 1.66 [0.41·3H, s, $CH_3C(3)$, *trans*], 1.86 [0.59·3H, s, $CH_3C(3)$, *cis*], 2.51 [0.59·1H, m, C(4)H, *cis*], 2.88 [0.41·1H, m, C(4)H, *trans*], 2.8-3.0 [1H, m, C(5)H], 3.2-3.85 [3H, m, C(5)H and $C(4)CH_2Cl$], 4.85-5.15 (2H, m, CH_2-β-naphtyl), 7.4-8.1 (7H, m, aromatic H). MS (EI, 70 eV) *m/z*: 287 [(M^++1)-Cl, 5%]; 252 (58); 141 (100). Found: C, 63.3; H, 5.2; N, 4.2. $C_{17}H_{17}Cl_2NO$ requires C, 63.37; H, 5.32; N 4.35. Oil.

N-(Diphenylmethyl)-3-chloro-4-chloromethyl-3-methyl-pyrrolidin-2-one (2b)

IR (film): ν = 1700 (C=O). ^{1}H NMR ($CDCl_3$): δ = 1.68 [0.40·3 H, s, $CH_3C(3)$, *trans*], 1.89 [0.60·3 H, s, $CH_3C(3)$, *cis*], 2.60 [0.60·1H, m, C(4)H, *cis*], 2.99 [0.40·1H, m, C(4)H, *trans*], 2.9-3.15 [1H, m, C(5)H], 3.3-3.95 [3H, m, C(5)H and $C(4)CH_2Cl$], 6.62 (1H, s, CH-benzhydryl), 7.15-7.5 (10H, m, aromatic H). MS (EI, 70 eV) *m/z*: 347 (1%); 312 (60); 252 (58); 262 (30); 167 (100); 165 (60). Found: C, 65.3; H, 5.5; N, 3.9. $C_{19}H_{19}Cl_2NO$ requires C, 65.53; H, 5.50; N 4.02. Oil.

N-(*R*-1-Phenyl-ethyl)-3-chloro-4-chloromethyl-3-methyl-pyrrolidin-2-one (2e)

IR (film): ν = 1700 (C=O). ^{1}H NMR ($CDCl_3$): diastereoisomer *trans* I (oil), δ = 1.59 (3H, d, J = 7.1 Hz, $C\underline{H}_3CHN$), 1.71 [3H, s, $CH_3C(3)$], 2.85 [1H, m, C(4)H], 3.16 [1H, dd, J = 4.5, 10.4 Hz, C(5)H], 3.28 [1H, dd, J = 6.8, 10.4 Hz, C(5)H], 3.45 [1H, dd, J = 9.9, 11.2 Hz, $C(4)CH_2Cl$], 3.76 [1H, dd, J = 4.5, 11.2 Hz, $C(4)CH_2Cl$], 5.51 (1H, q, J = 7.1 Hz, $CH_3C\underline{H}N$), 7.25-7.50 (5 H, m, aromatic H); diastereoisomer *trans* II (oil), δ = 1.61 (3H, d, J = 7.1 Hz, $C\underline{H}_3CHN$), 1.61 [3H, s, $CH_3C(3)$], 2.75-3.0 [2H, m, C(4)H and C(5)H], 3.22 [1H, dd, C(5)H], 3.55-3.75 [2H, m, $C(4)CH_2Cl$], 5.51 (1H, q, J = 7.1 Hz, $CH_3C\underline{H}N$), 7.25-7.50 (5 H, m, aromatic H); diastereoisomer *cis* I (oil), δ = 1.59 (3H, d, J = 7.1 Hz, $C\underline{H}_3CHN$), 1.83 [3H, s, $CH_3C(3)$], 2.43 [1H, m, C(4)H], 3.05-3.30 [2H, m, C(5)H], 3.69 [1H, dd, J = 8.9, 11.2 Hz, $C(4)CH_2Cl$], 3.85 [1H, dd, J = 5.6, 11.2 Hz, $C(4)CH_2Cl$], 5.49 (1H, q, J = 7.1 Hz, $CH_3C\underline{H}N$), 7.25-7.50 (5 H, m, aromatic H); diastereoisomer *cis* II (oil), δ = 1.61 (3H, d, J = 7.1 Hz, $C\underline{H}_3CHN$), 1.84 [3H, s, $CH_3C(3)$], 2.55 [1H, m, C(4)H], 2.71 [1H, dd, J = 9.2, 9.9 Hz, C(5)H], 3.43 [1H, dd, J = 6.7, 9.9 Hz, C(5)H], 3.62 [1H, dd, J = 9.9, 11.2 Hz, $C(4)CH_2Cl$], 3.82 [1H, dd, J = 5.2, 11.2 Hz, $C(4)CH_2Cl$], 5.54 (1H, q, J = 7.1 Hz, $CH_3C\underline{H}N$), 7.25-7.50 (5 H, m, aromatic H). MS (EI, 70 eV) *m/z*: 285 (2%); 270 (6); 250 (42); 105 (100). Found: C, 58.5; H, 6.1; N, 5.0. $C_{14}H_{17}Cl_2NO$ requires C, 58.75; H, 5.99; N 4.89.

***cis* N-(*R*-1-Phenyl-ethyl)-3-chloro-4-chloromethyl-3-(1-methyl-ethyl)-pyrrolidin-2-one (2f)**

IR (film): ν = 1695 (C=O). ^{1}H NMR ($CDCl_3$): δ = 1.06 (0.61·3H, d, J = 7.0 Hz, $(C\underline{H}_3)_2CH$, diastereoisomer I), 1.09 [0.39·3H, d, J = 7.2 Hz, $(C\underline{H}_3)_2CH$, diastereoisomer II], 1.19 [0.61·3H, d, J=2.8 Hz, $(C\underline{H}_3)_2CH$, diastereoisomer I], 1.22 [0.39·3H, d, J = 2.8 Hz, $(C\underline{H}_3)_2CH$, diastereoisomer II], 1.61 (3H, d, J = 7.1 Hz, $C\underline{H}_3CHN$), 2.5-2.9 [2H, m, $(CH_3)_2C\underline{H}$ and C(4)H], 3.05-3.35 [1H, m, C(5)H], 3.5-3.95 [3H, m, $C(4)CH_2Cl$ and C(5)H], 5.53 (0.61·1H, q, J = 7.1 Hz, $CH_3C\underline{H}N$, diastereoisomer I), 5.57 (0.39·1H, q, J = 7.1 Hz, $CH_3C\underline{H}N$, diastereoisomer I), 7.25-7.50 (5 H, m, aromatic H). MS (EI, 70 eV) *m/z*: 313 (2%); 298 (3); 278 (26); 228 (13); 105 (100). Found: C, 61.2; H, 6.6; N, 4.3. $C_{16}H_{21}Cl_2NO$ requires C, 61.15; H, 6.74; N 4.46. Oil.

***trans* N-(*R*-1-Phenyl-ethyl)-3-chloro-4-chloromethyl-3-(1-methyl-ethyl)-pyrrolidin-2-one (2f)**

IR (film): ν = 1695 (C=O). ^{1}H NMR ($CDCl_3$): δ = 1.09 [3H, d, J = 6.8 Hz, $(C\underline{H}_3)_2CH$], 1.21 [3H, d, J = 7.0 Hz, $(C\underline{H}_3)_2CH$], 1.60 [3H, d, J = 7.1 Hz, $C\underline{H}_3CHN$], 2.58 [1H, m, $(CH_3)_2C\underline{H}$], 2.7-2.9 [2H, m, C(4)H and C(5)H], 3.40-3.65 [2H, m, C(5)H and $C(4)CH_2Cl$], 3.82 [1H, dd, J = 3.6, 11.1 Hz, $C(4)CH_2Cl$], 5.57 (1H, q, J = 7.1 Hz, $CH_3C\underline{H}N$), 7.25-7.50 (5H, m, aromatic H). MS (EI, 70 eV) *m/z*: 313 (2%); 298 (3); 278 (26); 228 (13); 105 (100). Found: C, 61.3; H, 6.7; N, 4.6. $C_{16}H_{21}Cl_2NO$ requires C, 61.15; H, 6.74; N 4.46. Oil.

N-(2-Furyl-methyl)-3-chloro-4-chloromethyl-3-methyl-pyrrolidin-2-one (2d)

IR (film): ν = 1695 (C=O). ^{1}H NMR ($CDCl_3$): diastereoisomer *trans*, δ = 1.67 [3H, s, $CH_3C(3)$], 2.97 [1H, m, C(4)H], 3.22 [1H, dd, J = 4.8, 10.3 Hz, C(5)H], 3.42 [1H, dd, J = 9.7, 11.1 Hz, $C(4)CH_2Cl$], 3.68 [1H, dd, J = 3.5,

10.3 Hz, C(5)H], 3.76 [1H, dd, J = 4.5, 11.1 Hz, C(4)CH_2Cl], 4.47 (1H, d, J = 15.4 Hz, furyl-CH_2N), 4.62 (1H, d, J = 15.4 Hz, furyl-CH_2N), 6.25-6.40 and 7.41 (3H, m, aromatic H); diastereoisomer *cis*, δ = 1.83 [3H, s, $CH_3C(3)$], 2.58 [1H, m, C(4)H], 3.17 [1H, dd, J = 9.0, 10.0 Hz, C(5)H], 3.53 [1H, dd, J = 3.0, 10.1 Hz, C(5)H], 3.71 [1H, dd, J = 9.0, 11.3 Hz, C(4)CH_2Cl], 3.86 [1H, dd, J = 5.5, 11.4 Hz, C(4)CH_2Cl], 4.54 (2H, s, furyl-CH_2N), 6.25-6.40 and 7.41 (3H, m, aromatic H). MS (EI, 70 eV) *m/z*: 261 (2%); 226 (85); 176 (30); 81 (100). Found: C, 50.2; H, 5.1; N, 5.5. $C_{11}H_{13}Cl_2NO_2$ requires C, 50.40; H, 5.00; N 5.34. Oil.

N-(2,2-Dichloro-propionyl)-8-aza-10-oxa-tricyclo[4.3.1^{1,4}.0]dec-2-ene (3)

IR (nujol): ν = 1645 (C=O). ^{1}H NMR ($CDCl_3$): diastereoisomer I, δ = 1.53 [1H, m, C(5)H], 1.84 [1H, m, C(5)H], 2.25 [1H, m, C(6)H], 2.36 [3H, s, CH_3CCl_2], 3.44 [1H, dd, J = 10.8, 11.0 Hz, C(7)H], 3.93 [1H, d, J = 14.6 Hz, C(9)H], 4.16 [1H, d, J = 14.6 Hz, C(9)H], 4.78 [1H, dd, J = 7.9, 11.0 Hz, C(7)H], 5.14 [1H, m, C(4)H], 6.45 [2H, m, C(2)H and C(3)H]; diastereoisomer II, δ = 1.54 [1H, m, C(5)H], 1.89 [1H, m, C(5)H], 2.11 [1H, m, C(6)H], 2.36 [3H, s, CH_3CCl_2], 3.27 [1H, dd, J = 9.6, 12.2 Hz, C(7)H], 4.15 [1H, m, J = 9.0, 12.2 Hz, C(7)H], 4.41 [1H, d, J = 13.1 Hz, C(9)H], 4.72 [1H, d, J = 13.1 Hz, C(9)H], 5.14 [1H, m, C(4)H], 6.45 [2H, m, C(2)H and C(3)H]. MS (EI, 70 eV) *m/z*: 261 (2%); 226 (28); 190 (27); 81 (100). Found: C, 50.3; H, 5.2; N, 5.2. $C_{11}H_{13}Cl_2NO_2$ requires C, 50.40; H, 5.00; N 5.34. Solid, mixture of *endo* and *exo* diastereoisomers.

N-Benzyl-3-chloro-4-(1-chloro-1-methyl-ethyl)-3-methyl-pyrrolidin-2-one (2g)

IR (film): ν = 1710 (C=O). ^{1}H NMR ($CDCl_3$): diastereoisomer *trans*, δ = 1.63 [3H, s, $CH_3C(3)$], 1.84 [3H, s, $(CH_3)_2CClC(4)$], 1.86 [3H, s, $(CH_3)_2CClC(4)$], 2.71 [1H, dd, J = 7.2, 9.3 Hz, C(4)H], 3.33-3.53 [2H, m, C(5)H], 4.50 (1H, d, J = 14.7 Hz, benzyl H), 4.60 (1H, d, J = 14.7 Hz, benzyl H), 7.25-7.50 (5H, m, aromatic H); diastereoisomer *cis*, δ = 1.83 [3H, s, $(CH_3)_2CClC(4)$], 1.88 [3H, s, $(CH_3)_2CClC(4)$], 1.96 [3H, s, 3H, s, $CH_3C(3)$], 2.93 [1H, dd, J = 8.0, 8.8 Hz, C(4)H], 3.33-3.53 [2H, m, C(5)H], 4.46 (1H, d, J = 14.8 Hz, benzyl H), 4.69 (1H, d, J = 14.8 Hz, benzyl H), 7.25-7.50 (5H, m, aromatic H). MS (EI, 70 eV) *m/z*: 264 (M^+-Cl, 48%); 228 (18); 186 (19); 91 (100). Found: C, 60.2; H, 6.3; N, 4.6. $C_{15}H_{19}Cl_2NO$ requires C, 60.01; H, 6.38; N 4.67. Oil.

N-Benzyl-3-chloro-4-(1-chloro-1-methyl-ethyl)-3-ethyl-pyrrolidin-2-one (2h)

IR (film): ν = 1710 (C=O). ^{1}H NMR ($CDCl_3$): diastereoisomer *trans* (solid, m.p. 65°C), δ = 1.20 (3H, t, J = 7.3 Hz, $C\underline{H}_3CH_2$), 1.66 [3H, s, $(CH_3)_2CClC(4)$], 1.86 [3H, s, $(CH_3)_2CClC(4)$], 2.21 (2H, q, J =7.3 Hz, $CH_3C\underline{H}_2$), 2.95 [1H, dd, J = 7.7, 9.8 Hz, C(4)H], 3.30-3.53 [2H, m, C(5)H], 4.50 (1H, d, J = 14.7 Hz, benzyl H), 4.61 (1H, d, J = 14.7 Hz, benzyl H), 7.25-7.50 (5H, m, aromatic H); diastereoisomer *cis* (oil), δ = 1.02 (3H, t, J = 6.4 Hz, $C\underline{H}_3CH_2$), 1.82 [3H, s, $(CH_3)_2CClC(4)$], 1.86 [3H, s, $(CH_3)_2CClC(4)$], 2.26 (1H, m, $CH_3C\underline{H}_2$), 2.55 (1H, m, $CH_3C\underline{H}_2$), 2.94 [1H, dd, J = 7.2, 9.2 Hz, C(4)H], 3.30-3.53 [2H, m, C(5)H], 4.51 (1H, d, J = 14.7 Hz, benzyl H), 4.65 (1H, d, J = 14.7 Hz, benzyl H), 7.25-7.50 (5H, m, aromatic H). MS (EI, 70 eV) *m/z*: 278 (M^+-Cl, 23%); 242 (27); 200 (30); 91 (100). Found: C, 61.3; H, 6.8; N, 4.6. $C_{16}H_{21}Cl_2NO$ requires C, 61.15; H, 6.74; N 4.46.

N-Benzyl-3-chloro-4-(1-chloro-1-methyl-ethyl)-3-propyl-pyrrolidin-2-one (2i)

IR (nujol): ν = 1710 (C=O). ^{1}H NMR ($CDCl_3$): diastereoisomer *trans* (solid, m.p. 59°C), δ = 0.96 (3H, t, J = 7.3 Hz, $C\underline{H}_3CH_2CH_2$), 1.55-1.80 (2H, m, $CH_3C\underline{H}_2CH_2$), 1.65 [3H, s, $(CH_3)CClC(4)$], 1.87 [3H, s, $(CH_3)CClC(4)$], 2.05-2.18 (2H, m, $CH_3CH_2C\underline{H}_2$), 2.92 [1H, dd, J = 7.7, 10.3 Hz, C(4)H], 3.29-3.53 [2H, m, C(5)H], 4.55 (2H, s, benzyl H), 7.25-7.50 (5H, m, aromatic H); diastereoisomer *cis* (solid, m.p. 39°C), δ = 1.03 (3H, t, J = 7.1 Hz, $C\underline{H}_3CH_2CH_2$), 1.15-1.55 (2H, m, $CH_3C\underline{H}_2CH_2$), 1.82 [3H, s, $(CH_3)_2CClC(4)$], 1.86 [3H, s, $(CH_3)_2CClC(4)$], 2.22 (1H, m, $CH_3CH_2C\underline{H}_2$), 2.46 (1H, m, $CH_3CH_2C\underline{H}_2$), 2.93 [1H, dd, J = 7.1, 9.2 Hz, C(4)H], 3.31-3.51 [2H, m, C(5)H], 4.51 (1H, d, J = 14.8 Hz, benzyl H), 4.64 (1H, d, J = 14.8 Hz, benzyl H), 7.25-7.50 (5H, m, aromatic H). MS (EI, 70 eV) *m/z*: 291 (M^+-HCl, 2%); 256 (20); 214 (53); 91 (100). Found: C, 62.2; H, 7.1; N, 4.1. $C_{17}H_{23}Cl_2NO$ requires C, 62.20;

H, 7.06; N 4.27.

***N*-Benzyl-3-chloro-4-(1-chloro-1-methyl-ethyl)-3-hexyl-pyrrolidin-2-one (2l)**

IR (film): ν = 1710 (C=O). ^{1}H NMR ($CDCl_3$): diastereoisomer *trans* (oil), δ = 0.92 [3H, t, $C\underline{H}_3(CH_2)_4CH_2$], 1.31 [8H, bs, $CH_3(C\underline{H}_2)_4CH_2$], 1.66 [3H, s, $(CH_3)CClC(4)$], 1.87 [3H, s, $(CH_3)CClC(4)$], 2.13 [2H, t, $CH_3(CH_2)_4C\underline{H}_2$], 2.93 [1H, dd, J =7.7, 9.8 Hz, C(4)H], 3.28-3.52 [2H, m, C(5)H], 4.49 (1H, d, J = 14.6 Hz, benzyl H), 4.63 (1H, d, J = 14.6 Hz, benzyl H), 7.25-7.50 (5H, m, aromatic H); diastereoisomer *cis* (oil), δ = 0.93 [3H, t, $C\underline{H}_3(CH_2)_4CH_2$], 1.20-1.55 [8H, bs, $CH_3(C\underline{H}_2)_4CH_2$], 1.82 [3H, s, $(CH_3)CClC(4)$], 1.86 [3H, s, $(CH_3)CClC(4)$], 2.22 [1H, m, $CH_3(CH_2)_4C\underline{H}_2$], 2.47 [1H, m, $CH_3(CH_2)_4C\underline{H}_2$], 2.94 [1H, dd, J = 7.2, 9.2 Hz, C(4)H], 3.30-3.53 [2H, m, C(5)H], 4.49 (1H, d, J = 14.8 Hz, benzyl H), 4.66 (1H, d, J = 14.8 Hz, benzyl H), 7.20-7.50 (5H, m, aromatic H). MS (EI, 70 eV) *m/z*: 298 (M^+-HCl-Cl, 30%); 249 (34); 214 (62); 91 (100). Found: C, 64.9; H, 8.0; N, 3.7. $C_{20}H_{29}Cl_2NO$ requires C, 64.86; H, 7.89; N 3.78.

***N*-Benzyl-3-chloro-4-chloromethyl-3,4-dimethyl-pyrrolidin-2-one (2m)**

IR (film): ν = 1695 (C=O). ^{1}H NMR ($CDCl_3$): δ = 1.20 [0.66·3 H, s, $CH_3C(4)$, *cis*], 1.34 [0.34·3 H, s, $CH_3C(4)$, *trans*], 1.65 [0.34·3 H, s, $CH_3C(3)$, *trans*], 1.73 [0.66·3 H, s, $CH_3C(3)$, *cis*], 2.86 [0.66·1H, d, J = 10.2 Hz, C(5)H, *cis*], 3.13 [0.34·1H, d, J = 10.2 Hz, C(5)H, *trans*], 3.30 [1H, d, J = 10.2 Hz, C(5)H], 3.41 [0.34·2H, m, $C(4)CH_2Cl$, *trans*], 3.73 [0.66·1H, d, J = 11.2 Hz, $C(4)CH_2Cl$, *cis*], 3.85 [0.66·1H, d, J = 11.2 Hz, $C(4)CH_2Cl$, *cis*], 4.30-4.70 (2H, m, benzyl H), 7.20-7.45 (5H, m, aromatic H). MS (EI, 70 eV) *m/z*: 285 (1%); 250 (87); 200 (23); 91 (100). Found: C, 59.0; H, 5.9; N, 4.8. $C_{14}H_{17}Cl_2NO$ requires C, 58.75; H, 5.9; N 4.89. Oil.

***trans N*-Benzyl-3,4-dichloro-4-chloromethyl-3-methyl-pyrrolidin-2-one (2n)**

IR (film): ν = 1720 (C=O). ^{1}H NMR ($CDCl_3$): δ = 1.97 [3 H, s, $CH_3C(3)$], 3.46 [1H, d, J = 11.6 Hz, C(5)H], 3.68 [1H, d, J = 11.6 Hz, C(5)H], 4.00 [1H, d, J = 12.3 Hz, $C(4)CH_2Cl$], 4.24 [1H, d, J = 12.3 Hz, $C(4)CH_2Cl$], 4.51 (1H, d, J = 14.9 Hz, benzyl H), 4.66 (1H, d, J = 14.9 Hz, benzyl H), 7.25-7.45 (5H, m, aromatic H). MS (EI, 70 eV) *m/z*: 270 (M^+-Cl, 30%); 234 (37); 200 (17); 91 (100). Found: C, 51.1; H, 4.6; N, 4.7. $C_{13}H_{14}Cl_3NO$ requires C, 50.92; H, 4.60; N 4.57. Oil.

***N*-Benzyl-3-chloro-4-dichloromethyl-3-methyl-pyrrolidin-2-one (2o)**

IR (film): ν = 1710 (C=O). ^{1}H NMR ($CDCl_3$): diastereoisomer *trans* (solid, m.p. 107°C), δ = 1.85 [3H, s, $CH_3C(3)$], 3.27-3.38 [2H, m, C(4)H and C(5)H], 3.65 [1H, dd, J = 8.4, 11.8 Hz, C(5)H], 4.41 (1H, d, J = 14.6 Hz, benzyl H), 4.72 (1H, d, J = 14.6 Hz, benzyl H), 5.91 (1H, d, J = 4.5 Hz, $CHCl_2$), 7.25-7.50 (5H, m, aromatic H); diastereoisomer *cis* (oil), δ = 2.00 [3H, s, $CH_3C(3)$], 2.85-3.00 [1H, m, C(4)H], 3.11 [1H, dd, J = 9.2, 10.2 Hz, C(5)H], 3.42 [1H, dd, J = 7.2, 10.2 Hz, C(5)H], 4.41 [1H, d, J = 14.7 Hz, benzyl H], 4.69 (1H, d, J = 14.7 Hz, benzyl H), 6.01 (1H, d, J = 9.5 Hz, $CHCl_2$), 7.25-7.50 (5H, m, aromatic H). MS (EI, 70 eV) *m/z*: 305 (1%); 270 (57); 186 (16); 91 (100). Found: C, 51.1; H, 4.7; N, 4.5. $C_{13}H_{14}Cl_3NO$ requires C, 50.92; H, 4.60; N 4.57.

***trans N*-Benzyl-3,3-dichloro-4-chloromethyl-5-methyl-pyrrolidin-2-one (2p)**

IR (film): ν = 1700 (C=O). ^{1}H NMR ($CDCl_3$): δ = 1.85 [3H, s, $CH_3C(3)$], 2.76 [1H, m, C(4)H], 3.36 [1H, m, C(5)H], 3.70 [1H, dd, J = 7.5, 11.8 Hz, $C(4)CH_2Cl$], 4.03 [1H, dd, J = 5.3, 11.8 Hz, $C(4)CH_2Cl$], 4.08 (1H, d, J = 15.1 Hz, benzyl H), 5.15 (1H, d, J = 15.1 Hz, benzyl H), 7.20-7.45 (5H, m, aromatic H). MS (EI, 70 eV) *m/z*: 305 (1%); 270 (55); 202 (3); 91 (100). Found: C, 50.8; H, 4.7; N, 4.4. $C_{13}H_{14}Cl_3NO$ requires C, 50.92; H, 4.60; N 4.57. Oil.

***N*-Benzyl-r-3-chloro-4-chloromethyl-3,5-dimethyl-pyrrolidin-2-one (2q)**

IR (film): ν = 1700 (C=O). ^{1}H NMR ($CDCl_3$): diastereoisomer c-4-t-5 (oil), δ = 1.35 [3H, d, J = 6.3 Hz, $CH_3C(5)H$], 1.93 [3H, s, $CH_3C(3)$], 2.17 [1H, m, C(4)H], 3.24 [1H, m, C(5)H], 3.66 [1H, dd, J = 5.8, 11.7 Hz, $C(4)CH_2Cl$], 3.91 [1H, dd, J = 7.3, 11.7 Hz, $C(4)CH_2Cl$], 3.99 (1H, d, J = 15.1 Hz, benzyl H), 5.17 (1H, d, J = 15.1 Hz, benzyl H),

7.20-7.45 (5H, m, aromatic H); diastereoisomer t-4-c-5 (oil), δ = 1.42 [3H, d, J = 6.4 Hz, $CH_3C(5)H$], 1.71 [3H, s, $CH_3C(3)$], 2.69 [1H, m, C(4)H], 3.36 [1H, m, C(5)H], 3.48 [1H, dd, J = 7.1, 11.6 Hz, $C(4)CH_2Cl$], 3.76 [1H, dd, J = 5.5, 11.6 Hz, $C(4)CH_2Cl$], 4.12 (1H, d, J = 14.9 Hz, benzyl H), 5.04 (1H, d, J = 14.9 Hz, benzyl H), 7.20-7.45 (5H, m, aromatic H); diastereoisomer t-4-t-5 (oil), δ = 1.27 [3H, d, J = 6.8 Hz, $CH_3C(5)H$], 1.78 [3H, s, $CH_3C(3)$], 3.01 [1H, m, C(4)H], 3.64 [1H, dd, J = 9.4, 11.5 Hz, $C(4)CH_2Cl$], 3.76-3.90 [2H, m, C(5)H and $C(4)CH_2Cl$], 4.46 (1H, d, J = 15.0 Hz, benzyl H), 5.10 (1H, d, J = 15.0 Hz, benzyl H), 7.20-7.45 (5H, m, aromatic H). MS (EI, 70 eV) *m/z*: 285 (3%); 250 (76); 200 (25); 91 (100). Found: C, 58.6; H, 6.1; N, 4.9. $C_{14}H_{17}Cl_2NO$ requires C, 58.75; H, 5.99; N 4.89.

***N*-Benzyl-r-3-chloro-c-4-chloromethyl-3-methyl-t-5-phenyl-pyrrolidin-2-one (2r)**

IR (nujol): ν = 1710 (C=O). ^1H NMR ($CDCl_3$): δ = 2.06 [3H, s, $CH_3C(3)$], 2.54 [1H, m, C(4)H], 3.48 (1H, d, J = 14.5 Hz, benzyl H), 3.51 [1H, dd, J = 4.4, 11.5 Hz, $C(4)CH_2Cl$], 3.92 [1H, dd, J = 9.1, 11.5 Hz, $C(4)CH_2Cl$], 3.95 [1H, d, J = 8.7 Hz, C(5)H], 5.15 (1H, d, J = 14.5 Hz, benzyl H), 7.20-7.45 (5H, m, aromatic H). MS (EI, 70 eV) *m/z*: 347 (2%); 312 (53); 262 (33); 91 (100). Found: C, 65.7; H, 5.4; N, 4.1. $C_{19}H_{19}Cl_2NO$ requires C, 65.53; H, 5.50; N 4.02. Solid, m.p. 90°C.

***N*-Benzyl-3-chloro-3-ethyl-4-[(α-chloro)-benzyl]-pyrrolidin-2-one (7)**

IR (film): ν = 1710 (C=O). ^1H NMR ($CDCl_3$): diastereoisomer *trans*, δ = 1.18 (3H, t, $C\underline{H}_3CH_2$), 2.03 (1H, m, $CH_3C\underline{H}_2$), 2.14 (1H, m, $CH_3C\underline{H}_2$), 3.20 [1H, dd, J = 6.2, 10.4 Hz, C(5)H], 3.34 [1H, m, C(4)H], 3.54 [1H, dd, J = 7.4, 10.4 Hz, C(5)H], 4.50 (1H, d, J = 15.6 Hz, benzyl H), 4.60 (1H, d, J = 15.6 Hz, benzyl H), 5.13 [1H, d, J = 7.3 Hz, C(4)CHCl], 7.20-7.50 (10H, m, aromatic H); diastereoisomer *cis*, δ = 0.68 (3H, t, $C\underline{H}_3CH_2$), 1.97 (1H, m, $CH_3C\underline{H}_2$), 2.58 (1H, m, $CH_3C\underline{H}_2$), 3.11 [1H, m, C(4)H], 3.28 [1H, dd, J = 9.1, 10.2 Hz, C(5)H], 3.58 [1H, dd, J = 7.0, 10.2 Hz, C(5)H], 4.46 (1H, d, J = 14.7 Hz, benzyl H), 4.66 (1H, d, J = 14.7 Hz, benzyl H), 5.21 [1H, d, J = 10.5 Hz, C(4)CHCl], 7.20-7.60 (10H, m, aromatic H). MS (EI, 70 eV) *m/z*: 291 (10%); 326 (67); 208 (30); 200 (66); 91 (100). Found: C, 66.4; H, 5.9; N, 3.8. $C_{20}H_{21}Cl_2NO$ requires C, 66.30; H, 5.84; N 3.87.

***trans N*-Benzyl-3-ethyl-4-benzyl-pyrrolidin-2-one (6)**

IR (film): ν = 1665 (C=O). ^1H NMR ($CDCl_3$): δ = 0.96 (3H, t, $C\underline{H}_3CH_2$), 1.50-1.80 (2H, m, $CH_3C\underline{H}_2$), 2.22 [1H, m, C(4)H], 2.32 [1H, m, C(3)H], 2.56 [1H, dd, J = 9.3, 13.6 Hz, $C(4)CH_2(C_6H_5)$], 2.85 [1H, dd, J = 6.0, 13.6 Hz, $C(4)CH_2(C_6H_5)$], 2.88 [1H, dd, J = 6.0, 9.9 Hz, C(5)H], 3.16 [1H, dd, J = 7.8, 9.9 Hz, C(5)H], 4.39 (1H, d, J = 14.7 Hz, benzyl H), 4.45 (1H, d, J = 14.7 Hz, benzyl H), 7.00-7.40 (10H, m, aromatic H). MS (EI, 70 eV) *m/z*: 293 (47%); 264 (7); 202 (13); 174 (90); 91 (100). Found: C, 81.9; H, 7.8; N, 4.7. $C_{20}H_{23}NO$ requires C, 81.87; H, 7.90; N 4.77. Oil.

***trans* 3-Ethyl-4-benzyl-pyrrolidin-2-one (5)**

IR (film): ν = 1695 (C=O). ^1H NMR ($CDCl_3$): δ = 0.95 (3H, t, $C\underline{H}_3CH_2$), 1.55-1.75 (2H, m, $CH_3C\underline{H}_2$), 2.11 [1H, m, C(4)H], 2.48 [1H, m, C(3)H], 2.68 [1H, dd, J = 9.1, 13.6 Hz, $C(4)CH_2(C_6H_5)$], 2.91 [1H, dd, J = 6.1, 13.6 Hz, $C(4)CH_2(C_6H_5)$], 3.02 [1H, dd, J = 6.6, 9.3 Hz, C(5)H], 3.30 [1H, dd, J = 7.8, 9.8 Hz, C(5)H], 7.10-7.35 (5H, m, aromatic H). MS (EI, 70 eV) *m/z*: 203 (10%); 175 (75); 112 (15); 91 (61); 84 (100). Found: C, 76.7; H, 8.3; N, 7.0. $C_{13}H_{17}NO$ requires C, 76.81; H, 8.43; N 6.89. Solid m.p. 61-3°C (uncorrected).

3-Ethyl-4-methylcarboxymethyl-pyrrolidin-2-one (4b)

IR (film): ν = 1680 and 1720 (C=O). ^1H NMR ($CDCl_3$): δ = 0.98 [3H·0.82, t, J = 7.5 Hz, $C\underline{H}_3CH_2$, *trans*], 1.00 [3H·0.18, t, J = 7.5 Hz, $C\underline{H}_3CH_2$, *cis*], 1.39 [1H·0.18, m, C(4)H, *cis*], 1.56-1.76 [2H, m, $CH_3C\underline{H}_2$], 2.02 [1H·0.82, m, C(4)H, *trans*], 2.15-2.50 [3H·0.18, m, $C(4)CH_2CO$ and C(3)H, *cis*], 2.41 [1H·0.82, dd, J = 10.5, 17.1 Hz, $C(4)CH_2CO$, *trans*], 2.56 [1H·0.82, m, C(3)H-C(4)H, *trans*], 2.58 [1H·0.82, dd, J = 5.1, 17.1 Hz, $C(4)CH_2CO$,

trans], 2.98 [1H·0.82, dd, J = 6.2, 9.9 Hz, C(5)H, *trans*], 3.07 [1H·0.18, dd, J = 4.1, 10.0 Hz, C(5)H, *cis*], 3.46 [1H·0.18, dd, J = 7.7, 10.0 Hz, C(5)H, *cis*], 3.56 [1H·0.82, dd, J = 7.7, 9.9 Hz, C(5)H, *trans*], 3.70 (3H, s, $COOCH_3$), 6.53 (1H·0.82, bs, NH, *trans*), 6.77 (1H·0.18, bs, NH, *cis*). MS (EI, 70 eV) *m/z*: 185 (10%); 157 (47); 112 (43%); 84 (100). Found: C, 58.3; H, 8.1; N, 7.5. $C_9H_{15}NO_3$ requires C, 58.36; H, 8.16; N 7.56. Oil.

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