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Synthesis of 5-methoxylated 3-pyrrolin-2-ones via the rearrangement of chlorinated pyrrolidin-2-ones

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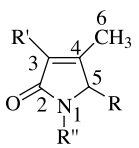
Abstract—The reaction of N-substituted 4-methyl-2-pyrrolidinones or 4-diethoxyphosphoryl analogues, carrying at least two chlorine atoms between the C(3) and C(6) carbons, with alkaline methoxide in methanol afforded the corresponding 5-methoxylated 3-pyrrolin-2-ones, useful adducts for the preparation of agrochemicals or medicinal compounds.

1. Introduction

Research and development in the field of crop protection is no longer distinguishable, in terms of scientific rigour and demand of high quality results, from the one driving the pharmaceutical industry.[1] The need to safeguard consumers' health, and to protect natural equilibria, imposes nowadays the development of more specific and environmentally friendly active compounds. This challenge has been accepted by the agrochemical industry and now stands for one of its primary objectives.[1]

Among the new chemical structures, the 3-pyrrolin-2-one (α,β-unsaturated-γ-lactam or 1,5-dihydro-2*H*-pyrrol-2-one) compounds[2–6] (Fig. 1) exhibit remarkable bio-activity, showing high herbicidal power against annual weeds at extremely low doses.[7] For example 0.25 Kg/ha of the *N*-(5-*t*-butyl-1,3,4-thiadiazol-2-yl)-3,4-dimethyl-5-oxo-3-pyrrolin-2-ones gave complete control of *Amarantus lividus* and *Chenopodium album* while leaving the preemergent corn unaffected.[4]



R = OH, O, SH, halo, amino

Figure 1.

Since α,β-unsaturated-γ-lactams are important synthetic intermediates[8–10] and their structural unit is frequently found in natural products (many of them displaying pharmacological activity),[11–15] the development of general methods for the preparation of these heterocycles is still an issue of increasing interest.[8,9,12,15–21] As far as compounds with herbicidal characteristics are concerned, a synthetic route which has the opportunity to introduce substituents on the C-5 carbon of the lactam ring is advantageous. The most convenient way at the moment (Scheme 1) starts from the reduction of maleimides (**A**).[4–6] The 5-hydroxy-3-pyrrolin-2-ones (**B**), thus obtained, being precursors of cyclic *N*-acyliminium ions,[22] afford a viable way to insert a wide range of functionalities at the C(5) position (Scheme 1).[23]

The OH function, however, is not a good nucleofuge and requires the presence of a Bronsted or Lewis acid for weakening the C–O bond.[22,23] Recently, it was demonstrated that the scope of the substitution protocol at C(5) could be improved with Cl as the leaving group. The replacement of the halo function in 5-chloro-pyrrolin-2-ones **D** can in fact be smoothly accomplished with a wide variety of C-, N- and O-nucleophiles (Scheme 2).[24,25] The preparation of **D** typically involves substitution of the 5-hydroxy group of the 1,5-dihydro-2*H*-pyrrol-2-one **B** using thionyl chloride (Scheme 2). However, the two-step procedure, first methoxylation of **B**, followed by chloro-demethoxylation with PCl_5 (Scheme 2), proved preferable

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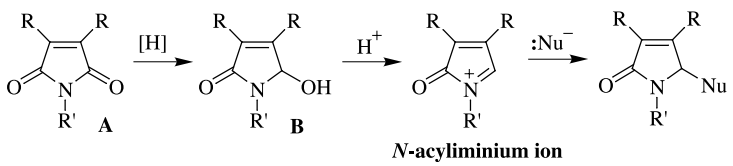
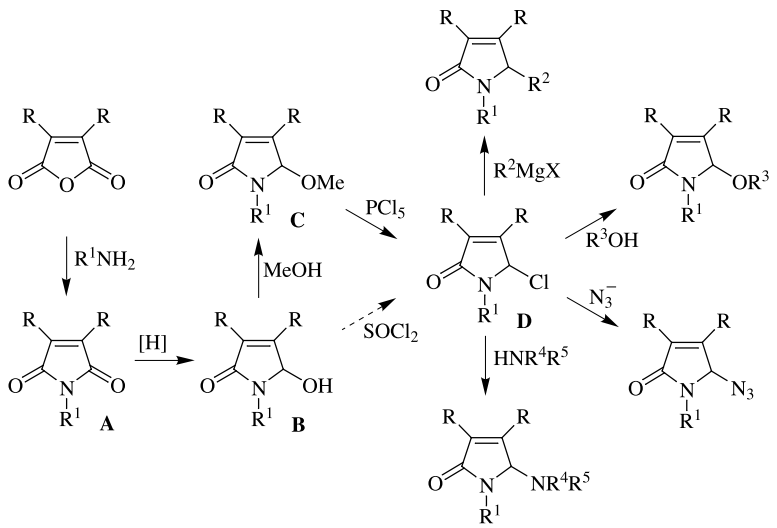


Scheme 1.



Scheme 2.

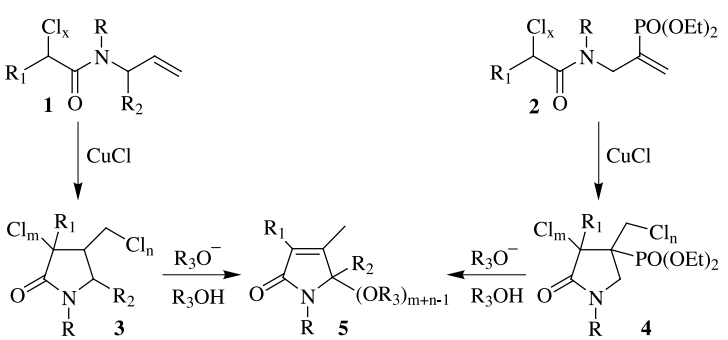
since it avoids the formation of hydrogen chloride which complicates some further transformations.[25]

An alternative route to the α,β-unsaturated-γ-lactams **C**, circumventing the need to start from substituted maleic anhydrides, has been serendipitously found experimenting with chlorinated pyrrolidin-2-ones, formed by halogen atom transfer radical cyclization (HATRC) of *N*-allyl α-perchloroamides, as substrates for the production of paraconic acids.[26] The novel approach to the 5-methoxy-3-pyrrolin-2-ones through a remarkable functional rearrangement of chlorinated lactams is described in this article (Scheme 3).[26] The reaction appears to be quite general: similar chlorinated 1-diethoxyphosphorylmethyl and even 4-diethoxyphosphoryl lactams undergo the rearrangement.[27] The phosphonated lactams were evaluated in view of the importance of many acyclic phosphonic acids as agrochemicals, e.g. glyphosate and bialaphos. Since the research on azaheterocyclic phosphonates is much more limited, the phosphonated lactams proved valuable substances to study this class of compounds in more detail.

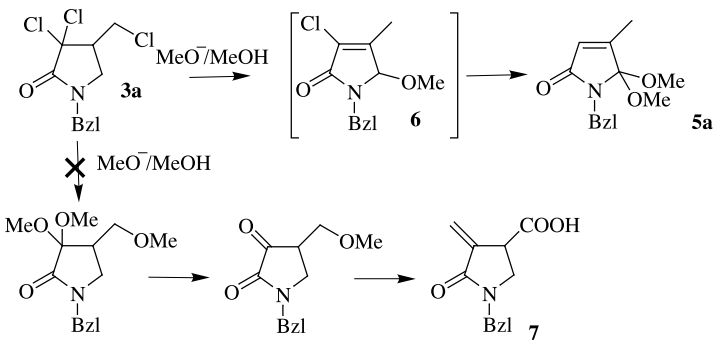
2. Results and discussion

The halogen atom transfer radical cyclization of *N*-allyl α-perchloroamides **1** (HATRC) is a valuable technique for the preparation of pyrrolidin-2-ones **3** (Scheme 3).[28–30] One of the more appealing features of this rearrangement is the preservation of all the carbon–halogen functions on the final skeleton. To date, the synthetic utility of chlorinated lactams has been largely overlooked.[31–33] Only the hydro-de-halogenation, resulting in a functionality decrease of the molecules, has been widely employed.[30,32–37]

Aiming at the chemo-enzymatic synthesis of aza-analogues[38] of α-methylene paraconic acids, we planned a synthetic strategy to the target structure **7** from *N*-benzyl-4-



Scheme 3.



Scheme 4.

chloromethyl-3,3-dichloropyrrolidin-2-one **3a**, relying on the introduction of the methylidene group at the C(3)Cl_2 carbon after its conversion in a 3-oxo group via the intermediate 3,3-dimethoxy function (Scheme 4).

The alkoxy-de-halogenation of **3a**, using an excess of lithium methoxide in methanol at room temperature, was evaluated at first. To our satisfaction the reaction gave a single, easy recoverable, product. However the isolated material emerged not to be the expected acetal but *N*-benzyl-5,5-dimethoxy-4-methyl-3-pyrrolin-2-one **5a** (Scheme 4). The compound **5a** clearly originates from a functional rearrangement of the polyhalogenated pyrrolidin-2-one **3a**, which relocates the C(3) acetal function at the C(5) carbon. A similar dehydrochlorination of 3,3-dichloro-4-chloromethyl-γ-lactones by a non-nucleophilic base (DBU) has been reported.[39] The potential usefulness of this rearrangement became apparent considering the difficulties for the direct functionalization of the lactam C(5)H_2, for which only relatively inefficient oxidations are mentioned in the literature.[40]

The reaction variables for the model compound **3a** were at first carefully adjusted in order to get the optimal conditions (Table 1). Reagent concentration, temperature and amount of the base appeared to strongly affect the performance of the rearrangement. The highest efficiency was observed at 0°C, when 4 mmole of alkaline methanolate (excess) and 4 mL of MeOH, for each mmole of substrate, were used (Table 1, entry 3). The yields never exceeded 62% due to polymerization.[41] A test on the stability of **5a** at 25°C (4 mmol, LiH 12 mmole, MeOH 16 mL) in fact resulted, after 4 h, in a 3-pyrrolin-2-one degradation of about 20% (25% after 24 h). The polymerization reaction was observed either by working below 0°C (Table 1, entries 4–6), or by using a stoichiometric amount of base (Table 1, entry 7). Even changing to less basic systems, such as LiOH or Li_2CO_3/MeOH (Table 1, entries 8, 9) the undesiderable pathway could not be prevented. On the contrary, the conversions were drastically reduced or no advantages were found, e.g. the reaction with LiOH. Dilution of methanol with ethyl ether, modifications of the reaction protocol (LiOMe or **3a** slowly added (2 h) to the reaction mixture with a syringe pump) provided no better results (Table 1, entries 10–12). The yields of **5a**, in any case, can be considered satisfactory in view of the functionalisation of the lactam ring. Interestingly, under the mildest conditions tested, small amounts of *N*-benzyl-3-chloro-4-methyl-5-methoxy-3-pyrrolin-2-one **6** (Scheme 4) were observed. Since **6** was smoothly converted into **5a**, it should be considered as an intermediate on the route to *N*-benzyl-5,5-dimethoxy-4-methyl-3-pyrrolin-2-one.

Table 1. Reaction of **3a** with LiOMe

No.	LiH/MeOH (mmol)/(mL)	*T* (°C)	*t* (h)	Conv.[a] (%)	Yield[b,c] **5a** (%)
1	16/8	0	1.33	100	55
2	16/16	0	2.5	97	62
3	16/32	0	2	94	38 (11)
4	16/8	−8	2	40	20 (8)
5	16/8	−23	1	29	3 (14)
6	16/8	−45	2	0	0
7	12/8	0	1.5	92	43 (16)
8	16[d]/8	0	2	96	54 (4)
9	12[e]/8	0	1	0	0
10	16/16[f]	25	2.5	100	56
11[g]	16/16[f]	25	2	97	56 (11)
12[h]	16/16[f]	25	2	100	62

4 mmole of **3a** were used.
[a] GC value.
[b] Determined on isolated material.
[c] In parentheses the *N*-benzyl-3-Cl-4-methyl-5-methoxy-3-pyrrolin-2-one **6**.
[d] LiH was replaced by LiOH.
[e] LiH was replaced by Li_2CO_3.
[f] Reaction performed in 16 mL of MeOH/ether (1/1).
[g] LiOMe added to the reaction mixture with a syringe pump (2 h).
[h] Addition of **3a** to the reaction mixture with a syringe pump (2 h).

Secondly the scope and generality of the rearrangement was examined. The educts **3b**–**n**, were prepared and then treated with alkaline methanolate/methanol under the best conditions (Table 2). To our satisfaction all the compounds tested displayed the same behaviour as **3a**, i.e. a dehydrohalogenation associated with the introduction in position C(5) of as many methoxy groups as the remaining halogens, consistently with the number of the C(5) hydrogens. Moreover for a given carbon skeleton, the final product relates to the total number of halide atoms carried on the C(3) and C(6) carbons and not to their distribution between the same positions (Table 2, entries 1, 8, 9, and 11–15). Remarkably, substrate **3e** gave the highest yields; the methyl substituent at C(3) prevents in fact, likely for steric reasons, the degradation of the lactam ring (polymerization) otherwise observable in all the other cases.

Replacing the lithium ion with the sodium ion (a less acidic counterion) a more active system was obtained and therefore, reaction times and temperatures could be shortened or lowered (Table 2, entries 2, 11, 14 and 3, 12,

Table 2. Reaction of the polychloro 2-pyrrolidinones **3** with R^3OM/R^3OH (see Scheme 3)

No.		*m*	*n*	Educts	R^1	R^2	Products			R^3OM	*t* (h)	*T* (°C)	Conv.[a] (%)	Yield[b] (%)
				R				R^1	R^2					
1	**3a**	2	1	Bzl	–	H	**5a**	H	–	MeOLi	2.5	0	97	62
2[c]	**3a**	2	1	Bzl	–	H	**5a′**	H	–	EtOLi	1.5	0	95	56
3	**3a**	2	1	Bzl	–	H	**5a′**	H	–	EtONa	2	0	100	58
4	**3b**	2	1	$N(CH_3)_2$	–	H	**5b**	H	–	MeOLi	3	25	100	45
5	**3c**	2	1	$CH_2PO(OEt)_2$	–	H	**5c**	H	–	MeONa	15	25	100	66
6	**3c**	2	1	$CH_2PO(OEt)_2$	–	H	**5c′**	H	–	*i*-PrONa	15	25	100	40
7	**3d**	2	1	$CH(Ph)PO(OEt)_2$	–	H	**5d**	H	–	MeONa	15	25	100	10
8	**3e**	1	1	Bzl	H	H	**5e**	H	H	MeOLi	16	25	93	61
9	**3e**	1	1	Bzl	H	H	**5e**	H	H	MeONa	2.33	25	100	60
10	**3f**	1	1	Bzl	Me	H	**5f**	Me	H	MeOLi	24	25	91	78
11	**3g**	1	2	Bzl	H	H	**5a**	H	–	MeOLi	1.5	80	100	47
12	**3g**	1	2	Bzl	H	H	**5a**	H	–	MeONa	2	25	100	64
13	**3h**	2	0	Bzl	–	H	**5e**	H	H	MeOLi	6	25	100	6
14	**3i**	0	2	Bzl	H	H	**5e**	H	H	MeOLi	24	80	100	56
15	**3i**	0	2	Bzl	H	H	**5e**	H	H	MeONa	6	80	100	60
16[d]	**3l**	1	2	Bzl	Cl	H	**5g**	Cl	H	MeONa	2	25	100	66
17	**3m**	1	1	Bzl	Cl	Me	**5h**	Cl	Me	MeONa	3	0	100	60
18	**3n**	1	1	Bzl	H	Me	**5i**	H	Me	MeONa	24	25	100	54 (4)[e]
19	**4a**	2	1	*t*-but	–	H	**5l**	H	–	MeONa	6	65	100	65
20	**4b**	2	1	Bzl	–	H	**5a**	H	–	MeONa	1	65	100	18[f]
21	**4c**	2	1	*i*-Pr	–	H	**5m**	H	–	MeONa	3.5	65	100	20[f]
22	**4d**	2	1	*c*-Hex	–	H	**5n**	H	–	MeONa	1	65	90	16[f]

4 mmol of substrate, 16 mmole of R^3OM and 16 mL of R^3OH were used.
[a] GC value.
[b] Determined on isolated material.
[c] Reaction performed in 8 mL of ethanol.
[d] 20 mmole of NaOMe were used.
[e] In parentheses the *N*-benzyl-4-methyl-5-methylene-3-pyrrolin-2-one **13**.
[f] The yield drops considerably during purification.

15). Other alcoholate/alcohol combinations were also evaluated and compared to the alkaline methanolate/methanol couple. While the EtONa/EtOH produced a result indistinguishable from that with MeONa/MeOH (Table 2, entries 1, 2), it was clear that on increasing further the size of the alcoholate, the yields decreased to some extent (Table 2, entries 5, 6).

In contrast to the 1-diethylphosphorylmethyl-2-pyrrolidinones **3c**,**d**, where the phosphonate moiety can be seen as an inert group behaving like a standard alkyl appendage, in the lactams **4a**–**d** the phosphonate function appeared labile and, under the appropriate reaction conditions, the same functional rearrangement was observed as with **3** (Table 2, entries 19–22). The synthesis of **4** proved not to be straightforward. The starting diethyl 1-bromomethylvinylphosphonate was synthesised from tetraethyl methylenebisphosphonate after reaction with formaldehyde and phosphorus tribromide;[42] this appears the method of choice to get multigram quantities, other reported procedures are less convenient.[43,44]

Ensuing acylation of the diethyl 1-aminomethylvinylphosphonates (prepared by reaction of diethyl 1-bromomethylvinylphosphonate and the proper amine; slow addition of the phosphonate) with trichloroacetyl chloride (TCAC)/triethylamine (TEA) ought to lead smoothly to the precursors **2**. However, because of the low nucleophilicity of the amino group, long reaction times were needed and this resulted in variable amounts of 4-diethylaminobut-3-ene-2-one. This side product is formed through an ionic pathway from trichloroacetyl chloride and triethylamine, an old and unexpected reaction, seldom taken into account, but perceptible during trichloroacetylation of low reactive amines with TCAC/TEA.[45] Finally, the HATRC of **2** proved as satisfactory (yields 44–71%) as with the analogous precursors **1** (yields 40–66%), which does not bear the phosphono group on the vinyl moiety.

2.1. Reaction mechanism

All the transformations from **3** to **5** start with a hydro-halo-elimination, since, otherwise, the alkoxy group could not be located at the C(5) position. The lack of reactivity under the optimum conditions of *N*-benzyl-4-chloromethyl-3,3-dichloro-4-methyl-pyrrolidin-2-one **8** (Fig. 2), apart from some polymerization, strongly supports this hypothesis. The starting elimination can split into two paths: an *endo*-dehydrochlorination at the C(3) and C(4) positions or, alternatively, an *exo*-dehydrochlorination at the C(4) and C(6) carbons. Since the rearrangement is related to the base strength, infact **3a** with Li_2CO_3/CH_3OH showed quite unreactive (Table 1, entry 9), a bimolecular process is clearly involved.[46] The easier the required *periplanar* conformation is achieved the more favored the corresponding elimination should be. Molecular mechanics calculations are able to provide some insights for the alternative

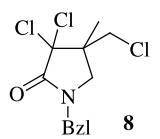


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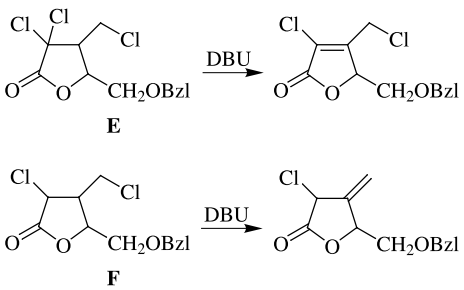
Figure 2.

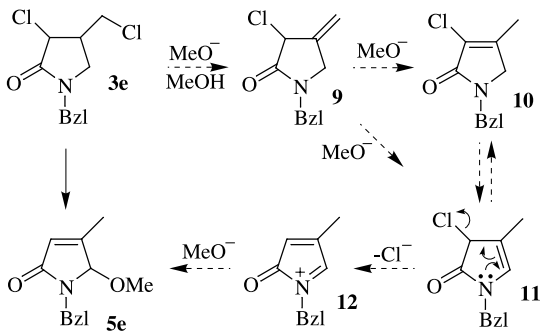
Table 3. ΔE (kcal/mole) of the *periplanar* conformations required for the elimination of **3a** and **3e** (Calculations were performed using MM2.)

Conformations	**3a**	**3e**[a]	
		cis	*trans*
endo[b] *syn*	4.42	–	2.60
endo[b] *anti*	1.13	1.89	–
exo[c] *syn*	4.57	4.66	4.69
exo[c] *anti*	3.48	3.57	0.43

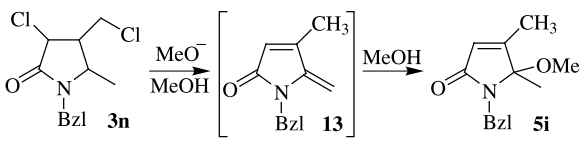
[a] The *cis* and *trans* stereoisomers under basic conditions easily interconvert.
[b] C(4)HC(3)Cl.
[c] C(4)HC(6)Cl.



Scheme 5.



Scheme 6.



Scheme 7.

paths. The computed potential energies of the *anti-periplanar* and *syn-periplanar* conformations relative to the dihedral arrangements C(4)HC(3)Cl and C(4)HC(6)Cl of **3a** and **3e** have been collected in Table 3. These data show that the course of the dehydrochlorination is governed by the number of chloro atoms bound at the C(3): two Cl's (**3a**) should drive towards an *endo* elimination, whereas one (**3e**) should lead to an *endo* or *exo* process depending on the relative substitution geometry between the C(3) and C(4) positions. For **3e**, in particular, owing to the configurational instability of the carbon C(3) under basic conditions, the *exo* path should be favoured. The result of the hydro-dehalogenation of chlorinated lactones **E** and **F** (Scheme 5) with DBU, investigated by Takano,[39] strengthens this arguments.

The formation of the intermediate **6** and the products **5g** and **5h**, being all 3-Cl-3-pyrrolin-2-ones, implies that once the first chloro atom is removed, the remaining Cl atoms at C(6) are much more mobile than any Cl bound at the C(3). Likely, this behaviour could have a connection with the different performances observed from **3e** and **3i**, on one hand, and **3h** on the other hand (Table 2, entries 8, 13, 14), which in any case reveal that for a satisfactory functional rearrangement, at least one *exo* chlorine atom has to be carried by the C(6) carbon.

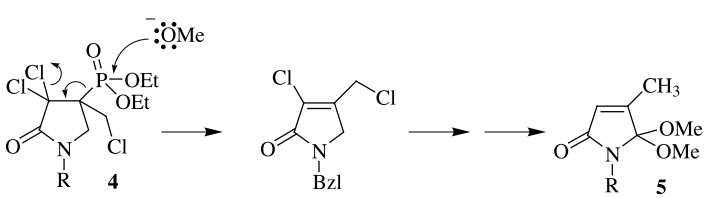
A tentative mechanism for **3e** is outlined in Scheme 6. After the initial formation of the *exo*-methylene intermediate **9**, the double bond shifts inside the ring affording the Δ^3 (**10**) or the Δ^4 (**11**) pyrrolin-2-ones. The two species are in equilibrium,[47] but **11** can react further and through an easy solvolysis delivers the stable cation **12**, which, collapsing with a methoxide anion, affords the ending product **5e**. Analogous steps are reasonably involved in the rearrangement of all the other chlorinated pyrrolidin-2-ones.

Interestingly on monitoring the rearrangement of **3n**, we observed that at low conversions **13** was the main product, this then smoothly added a molecule of MeOH (Scheme 7) behaving as an enamine reagent (*endo* attack) and not as a Michael acceptor (*exo* attack).

For the lactams bearing a 4-diethylphosphonate group (**4a–d**), the rearrangement should start instead with a Grob-type elimination:[48] i.e. attack of the alkoxide on the phosphonate group (Scheme 8), followed by an *anti* elimination of the chloride on the C(3) carbon. The diethyl methyl phosphate observed among the reaction products strongly stresses this rationale. From that point on, the reaction mechanism is identical to the one of the alkyl pyrrolidin-2-ones including the switch of the functionality from the C(3) to the C(5) position.

2.2. Structural characterizations of 5

The correct regiochemistry of *N*-benzylpyrrolidin-2-ones **5a** and **5e–i** was derived from H,C inverse-detection NMR



Scheme 8.

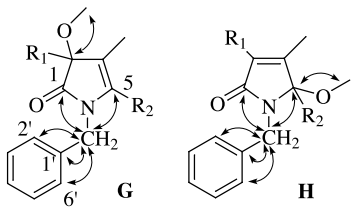


Figure 3.

techniques. Both heteronuclear multiple-quantum (HMQC)[49] and multiple-bond (HMBC)[50] experiments were employed to find the H,C pairs directly bonded, and the ones separated by two or three bonds, respectively. In both cases experimental conditions were optimized on the basis of the expected coupling constant values. For all derivatives the long-range H,C correlations involving benzylic protons play a crucial role in the reconstruction of the molecular structure. In fact, benzylic protons show four correlations (Fig. 3) in HMBC spectra, three with carbons at chemical shift values typical of Csp^2 signals (C=O, C-1′ and C-2′,6′), and one with a carbon (C-5) which correlates also with the methoxy protons. This picture enable the originally expected structure, **G** in Fig. 3, to be ruled out in favour of structure **H**. The correlations involving the remaining protons agree with **H** type regiochemistry and permit to unambiguously locate all the ring substituents. For instance, the methyl on C-3 is readily distinguished from the methyl on C-4 in derivative **5f**, (once their casual chemical shift equivalence has been removed adding C_6D_6 to the $CDCl_3$ solution) because the former correlates with the carbonyl carbon at 171.0 ppm, whereas the latter correlates with the carbon at 87.7 ppm, which in turn correlates also with the methoxy and the benzylic protons. Finally, it is worth noting that, in derivatives **5a** and **5e–i**, the *N*-benzylic group shifts for −0.2 to −0.5 ppm the methoxy proton signals (with respect to the typical spectral position of methyl ether or acetal at 3.2–3.3 ppm) as a consequence of the magnetic anisotropy effect exerted by the phenyl ring. This shielding effect is absent in derivative **5b**, where methoxy signal is found in its usual position.

As an additional proof for the identification of the rearranged products, **5l**, the adduct from the functional rearrangement of **4a**, was hydrolized using hydrochloric acid, and the maleimide, thus generated, was fully identified by comparison with original material.

3. Conclusion

In summary, a satisfactory and unusual preparation of *N*-substituted 5-methoxy or 5,5-dimethoxy-4-methyl-3-pyrrolin-2-ones has been described by reaction of the corresponding 4-methyl-pyrrolidin-2-ones, polychlorinated at C(3) and C(6), with alkaline methoxide in methanol under mild conditions. The functional rearrangement is fairly appealing since the 3-pyrrolin-2-ones obtained can be envisaged as precursors for cyclic *N*-acyliminium ions, which are in turn very useful intermediates in organic synthesis[22,23] and in the preparation of agrochemicals.[24,25] The availability of polychloro 2-pyrrolidinones makes this route to cyclic *N*-acyliminium ions alternative or competitive in comparison with the usual approach, which starts from succinimide derivatives.[51] Although the yields still need to be improved in the series of the phosphonate analogues, the reaction mechanism proves to be quite general, and is even accompanied by a Grob elimination if the lactam ring is carrying a phosphonate moiety on C(4). Further studies directed towards the application of the methodology in biologically active compound synthesis are currently under investigation.

4. Experimental

4.1. General

^1H NMR spectra were recorded in $CDCl_3$ solutions with a Bruker 400AMX WB and a Jeol EX 270 spectrometer, and the chemical shifts reported are in ppm relative to tetramethylsilane as external standard. Conditions for HMQC[49] spectra were: evolution delay=3.57 ms, spectral width=7 ppm with 2048 complex points in f_2; 256 t_1 values and 32 scans for t_1 value. A squared sine function (SSB=2) in f_2 and f_1 was applied before Fourier transformation. Similar conditions were used for HMBC[50] experiments except: delay for low-pass filter=3.57 ms, evolution delay=50 ms (optimization of ^nJ(H,C)=10 Hz responses) and 64 scans for t_1 value. IR spectra were obtained with Perkin–Elmer 1600 Series FTIR. Mass spectra were acquired with a combined HP 5890 GC/HP 5989A MS Engine. Reagents and solvents were standard grade commercial products, purchased from Aldrich or Fluka, and used without further purification. All the chlorinated pyrrolidin-2-ones **3** were prepared through HATRC, promoted by CuCl-TMEDA, of *N*-allyl-α-perchloroamides **1**,[30,52] except **3h**, which was assembled by cyclization of the *N*-allyl-*N*-benzyl-trichloroacetamide with Bu^t_3SnH/AIBN,[53] and **3i**, which was instead obtained from **3g** through selective hydro-de-chlorination of the most labile 3-chloro function with Zn/HOAc.[30] The diethyl *N*-allyl-aminomethylphosphonate[54] and the diethyl 1-bromo-methylvinylphosphonate[42] were secured according to literature.

4.1.1. Preparation of *N*-diethoxyphosphorylmethyl-3,3-dichloro-4-chloromethyl-pyrrolidin-2-one (3c). CuCl (0.8 g, 8 mmol) and *N*-allyl-*N*-diethoxyphosphorylmethyl trichloroacetamide (4.23 g, 12.0 mmol) were weighted in a 50 mL flask; then deoxygenated acetonitrile (25 mL) was added, under argon. The mixture was refluxed for 2 h, diluted with water (20 mL) and extracted with CH_2Cl_2 (2×25 mL). The combined organic layers were dried over $MgSO_4$, concentrated and chromatographed, eluting with chloroform/acetonitrile gradient, to give **3c** (3.45 g, 82%), as a yellowish oil; [Found: C, 34.2; H, 4.8; N, 3.8. $C_{10}H_{17}Cl_3NO_4$ requires C, 34.07; H, 4.86; N, 3.97]; ν_{max} (NaCl) 1730, 1240 cm^{-1}; δ_H (270 MHz $CDCl_3$) 4.20–4.13 (4H, m, $P(OCH_2Me)_2$), 4.02–3.60 (5H, m, NCH_2, CH_2Cl, NCH_aH_bP), 3.49 (1H, dd, J_{AB}=8.1 Hz, J_{HP}=10.1 Hz, NCH_aH_bP), 3.17–3.11 (1H, m, $CHCH_2Cl$), 1.41–1.31 (6H, m, $P(OCH_2CH_3)_2$); δ_C (270 MHz $CDCl_3$) 165.89, 82.89, 63.02 (J_{PC}=6.4 Hz), 62.92 (J_{PC}=6.1 Hz), 51.88, 48.97, 40.88, 39.62 (J_{PC}=156.3 Hz), 16.46 (J_{PC}=2.5 Hz), 16.37 (J_{PC}=2.5 Hz); *m/z* (EI): 351 (2 M^+), 317 (17), 315

(25), 279 (41), 251 (36), 223 (32), 216 (15), 214 (19), 178 (14), 130 (20), 125 (14), 42 (100).

4.1.2. *N*-(Phenyl-diethoxylphosphorylmethyl)-3,3-dichloro-4-chloromethyl-pyrrolidin-2-one (3d). According to the previous procedure, but using xylene and 15 h of reflux, the *N*-allyl-*N*-diethoxyphosphorylmethyl trichloroacetamide (1.00 g, 2.3 mmol) gave **3d** (0.37 g, 37%) as a brownish oil (two isomers A and B, not separable); [Found: C, 44.8; H, 4.9; N, 3.2. $C_{16}H_{21}Cl_3NO_4P$ requires C, 44.83; H, 4.94; N, 3.27]; ν_{max} (liquid film) 1732, 1260 cm^{-1}; δ_H (270 MHz $CDCl_3$) 7.64–7.38 (5H, m, Ph), 5.67 (1H, d, J_{HP}=21.1 Hz, C*H*P, B), 5.65 (1H, d, J_{HP}=20.8 Hz, C*H*P, A), 4.26–3.89 and 3.77–3.52 (8H, m, $P(OCH_2Me)_2$, CH_2Cl, CH_2N), 2.98–2.85 (1H, m, C*H*CH_2Cl), 1.36 (3H, t, *J*=7.1 Hz, OCH_2*Me*, B), 1.35 (3H, t, *J*=7.1 Hz, OCH_2*Me*, A), 1.15 (3H, t, *J*=7.1 Hz, OCH_2*Me*, B), 1.14 (3H, t, *J*=7.1 Hz, OCH_2*Me*, A); δ_P (270 MHz $CDCl_3$) 18.53, 18.19; *m*/*z* (ES): 427 (100 MH^+).

4.1.3. Preparation of *N*-benzyl-3,3-dichloro-4-dichloromethyl-pyrrolidin-2-one (3l). CuCl (0.04 g, 0.4 mmol) and *N*-benzyl-*N*-(3-chloro-2-propenyl) trichloroacetamide (1.31 g, 4.0 mmol) were weighted in a Schlenk tube; then acetonitrile (8 mL) and TMEDA (0.092 g, 0.8 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 (2×10 mL). The combined organic layers were dried over $MgSO_4$, concentrated and chromatographed, eluting with a petroleum ether (bp 40–60°C)/diethyl ether/methanol gradient, to give **3l** (1.15 g, 88%), as pale brown solid, mp 93–94°C; [Found: C, 44.0; H, 3.5; N, 4.4. $C_{12}H_{11}Cl_4NO$ requires C, 44.07; H, 3.39; N, 4.28]; ν_{max} (KBr) 1710 cm^{-1}; δ_H (400 MHz $CDCl_3$) δ 7.46–7.25 (5H, m, Ph), 6.05 (1H, d, *J*=8.2 Hz, C*H*Cl_2), 4.64 (1H, d, *J*=14.6 Hz, CH_aH_bPh), 4.52 (1H, d, *J*=14.6 Hz, CH_aH_bPh), 3.58–3.40 (2H, m, NCH_aH_bC*H*), 3.18 (1H, dd, *J*=9.3, 6.6 Hz, NCH_aH_b); *m*/*z* (EI): 325 (1 M^+), 290 (58), 254 (2), 206 (6), 91 (100).

4.1.4. *N*-Benzyl-3-chloro-4-chloromethyl-5-methyl-pyrrolidin-2-one (3m). According to the previous procedure the *N*-benzyl-*N*-(2-methyl-prop-2-enyl) dichloroacetamide (1.09 g, 4.0 mmol) gave **3m** (0.92 g, 84%) as pale yellow powder, mixture of four diastereomers (1/1/0.5/0.2); [Found: C, 57.4; H, 5.4; N, 5.0. $C_{13}H_{15}Cl_2NO$ requires C, 57.37; H, 5.55; N, 5.15]; ν_{max} (KBr) 1715 cm^{-1}; δ_H first main isomer (400 MHz $CDCl_3$) 7.41–7.25 (5H, m, Ph), 5.08 (1H, d, *J*=14.9 Hz, CH_aH_bPh), 4.32 (1H, d, *J*=9.7 Hz, C*H*Cl), 4.04 (1H, d, *J*=14.9 Hz, CH_aH_bPh), 3.88–3.70 (2H, m, CH_aH_bCl and C*H*Me), 3.60 (1H, dd, *J*=11.0, 10.0 Hz, CH_aH_bCl), 2.85–2.69 (1H, m, C*H*), 1.19 (3H, d, *J*=6.7 Hz, *Me*); δ_H second main isomer (400 MHz $CDCl_3$): ^1H NMR ($CDCl_3$): δ 7.41–7.22 (5H, m, Ph), 5.01 (1H, d, *J*=15.1 Hz, CH_aH_bPh), 4.51 (1H, d, *J*=7.8 Hz, C*H*Cl), 4.15 (1H, d, *J*=15.1 Hz, CH_aH_bPh), 3.89–3.63 (2H, m, CH_aH_bCl), 360–3.43 (1H, m, C*H*Me), 2.50–2.39 (1H, m, C*H*), 1.32 (3H, d, *J*=6.3 Hz, *Me*); *m*/*z* (EI): 271 (11 M^+), 236 (100), 186 (17), 106 (12), 91 (61).

4.1.5. Preparation of *N*-benzyl-3,3-dichloro-4-methyl-pyrrolidin-2-one (3h). According to the literature procedure[53] *N*-allyl-*N*-benzyl-trichloroacetamide (1.17 g, 4.0 mmol) was cycled with But_3SnH/AIBN and gave **3h** (0.62 g, 60%) as a white powder, mp 68–72°C; [Found: C, 56.0; H, 5.3; N, 5.6. $C_{12}H_{13}Cl_2NO$ requires C, 55.83; H, 5.08; N, 5.43]; ν_{max} (Nujol) 1713 cm^{-1}; δ_H (400 MHz $CDCl_3$) 7.44–7.24 (5H, m, Ph), 4.61 (1H, d, *J*=14.7 Hz, CH_aH_bPh), 4.49 (1H, d, *J*=14.7 Hz, CH_aH_bPh), 3.25 (1H, dd, *J*=9.5, 6.8 Hz, NCH_aH_b), 2.94 (1H, dd, *J*=9.5, 8.4 Hz, NCH_aH_b), 2.69–2.86 (1H, m, C*H*), 1.15 (3H, d, *J*=6.5 Hz, *Me*); *m*/*z* (EI): 222 (67), 91 (100).

4.1.6. Preparation of *N*-benzyl-4-dichloromethyl-pyrrolidin-2-one (3i). According to the literature procedure[29] **3g** (1.17 g, 4.0 mmol) with Zn (2.34 g) in HOAc (16 mL) gave **3i** (0.61 g, 59%) as colourless oil; [Found: C, 55.9; H, 4.9; N, 5.2. $C_{12}H_{13}Cl_2NO$ requires C, 55.83; H, 5.08; N, 5.43]; ν_{max} (film) 1688 cm^{-1}; δ_H (400 MHz $CDCl_3$) 7.42–7.24 (5H, m, Ph), 5.76 (1H, d, *J*=5.5 Hz, C*H*Cl_2), 4.53 (1H, d, *J*=14.7 Hz, CH_aH_bPh), 4.39 (1H, d, *J*=14.7 Hz, CH_aH_bPh), 3.47 (1H, dd, *J*=10.3, 8.6 Hz, COCH_aH_b), 3.30 (1H, dd, *J*=10.3, 6.0 Hz, COCH_aH_b), 3.20–3.02 (1H, m, C*H*), 2.74 (1H, dd, *J*=17.3, 9.1 Hz, NCH_aH_b), 2.62 (1H, dd, *J*=17.3, 7.4 Hz, NCH_aH_b); *m*/*z* (EI): 257 (77 M^+), 256 (16), 222 (14), 91 (100).

4.2. Preparation of 4-phosphonated lactams

In a 25 mL flask, nitrogen gas was passed (20 min) through xylene (15 mL), followed by the addition of *N*-*t*-butyl-*N*-2-diethoxyphosphoryl-allyl trichloroacetamide (0.43 g, 1.1 mmol) and CuCl (1.5 equiv.). After refluxing the reaction mixture for 3–15 h (^{31}P NMR monitoring), it was cooled to room temperature, poured into an aqueous solution and extracted with toluene (2×15 mL). The combined organic layers were dried over $MgSO_4$, filtered and evaporated under reduced pressure. The crude product **4a** was purified by flash chromatography (50% petroleum ether/ethyl acetate) (0.29 g, 67%).

4.2.1. *N*-*t*-Butyl-3,3-dichloro-4-chloromethyl-4-diethoxyphosphorylpyrrolidin-2-one (4a). Yellowish solid, mp 59–63°C; [Found: C, 39.8; H, 5.8; N, 3.7. $C_{13}H_{23}Cl_3NO_4P$ requires C, 39.56; H, 5.87; N, 3.55]; ν_{max} (KBr) 1735, 1249 cm^{-1}; δ_H (270 MHz $CDCl_3$) 4.24–4.19 (6H, m, $P(OCH_2Me)_2$, NCH_2), 4.10 (1H, dd, J_{HP}=16.8 Hz, J_{AB}=10.8 Hz, CH_aH_bCl), 3.50 (1H, dd, J_{HP}=16.8 Hz, J_{AB}=10.8 Hz, CH_aH_bCl), 1.43 (9H, s, CMe_3), 1.44–1.34 (6H, m, $P(OCH_2Me)_2$); δ_P (270 MHz $CDCl_3$) 20.69; *m*/*z* (EI): 393 (1 M^+), 206 (10), 164 (13), 138 (78), 111 (23), 108 (10), 86 (35), 84 (56), 82 (10), 81 (15), 57 (55), 51 (32), 49 (100), 47 (18), 41 (26).

4.2.2. *N*-Benzyl-3,3-dichloro-4-chloromethyl-4-diethoxyphosphorylpyrrolidin-2-one (4b). According to the general procedure the *N*-alkyl-*N*-(2-diethoxyphosphoryl)-allyl trichloroacetamide (1.28 g, 3 mmol) gave **4b** (0.86 g, 73%, purity 70%) as brown oil; ν_{max} (KBr) 1736, 1244 cm^{-1}; δ_H (270 MHz $CDCl_3$) 7.35–7.28 (5H, m, Ph), 4.53 (2H, s, NCH_2Ph), 4.21–4.12 (6H, m, $P(OCH_2Me)_2$, NCH_2), 3.86 (1H, dd, J_{HP}=12.5 Hz, J_{AB}=10.8 Hz, CH_aH_b-Cl), 3.31 (1H, dd, J_{HP}=17.0 Hz, J_{AB}=10.8 Hz, CH_aH_bCl), 1.32 (3H, t, *J*=7.6 Hz, OCH_2*Me*), 1.29 (3H, t, *J*=7.3 Hz, OCH_2*Me*); δ_P (270 MHz $CDCl_3$) 20.24; *m*/*z* (EI): 391 (55

M^+-HCl), 390 (52), 389 (77), 356 (23), 355 (71), 256 (100), 255 (26), 254 (100), 220 (20), 91 (55).

4.2.3. *N*-*i*-Propyl-3,3-dichloro-4-chloromethyl-4-diethoxyphosphorylpyrrolidin-2-one (4c). According to the general procedure, but heating during 6 h, the *N*-alkyl-*N*-(2-diethoxyphosphoryl)-allyl trichloroacetamide (0.5 g, 1.3 mmol) gave **4c** (0.22 g, 44%) as yellowish solid, mp 56–60°C; [Found: C, 38.0; H, 5.6; N, 3.7. $C_{12}H_{21}Cl_3NO_4P$ requires C, 37.87; H, 5.56; N, 3.68]; ν_{max} (KBr) 1679, 1258 cm^{-1}; δ_H (270 MHz $CDCl_3$) 4.35 (1H, sept, J=6.8 Hz, NC*H*Me_2), 4.26–4.20 (6H, m, P(OCH_2Me)$_2$, NCH_2), 3.99 (1H, dd, J_{HP}=23.4 Hz, J_{AB}=10.7 Hz, CH_aH_bCl), 3.34 (1H, dd, J_{HP}=17.2 Hz, J_{AB}=10.7 Hz, CH_aH_bCl), 1.43–1.33 (6H, m, P(OCH$_2$*Me*)$_2$), 1.16 (3H, d, J=6.8 Hz, CH*Me*), 1.13 (3H, d, J=6.8 Hz, CHMe); δ_P (270 MHz $CDCl_3$) 20.52; *m*/*z* (EI): 380 (1 MH^+), 235 (36), 193 (42), 173 (35), 168 (43), 150 (44), 139 (43), 138 (46), 122 (51), 109 (93), 91 (100), 82 (59), 81 (58), 72 (40), 65 (45), 55 (71), 43 (80).

4.2.4. *N*-*c*-Hexyl-3,3-dichloro-4-chloromethyl-4-diethoxyphosphorylpyrrolidin-2-one (4d). According to the general procedure the *N*-alkyl-*N*-(2-diethoxyphosphoryl)-allyl trichloroacetamide (1.51 g, 3.6 mmol) gave **4d** (1.01 g, 67%) as brown solid, mp 91–93.5°C; [Found: C, 43.1; H, 6.1; N, 3.2. $C_{15}H_{25}Cl_3NO_4P$ requires C, 42.83; H, 5.99; N, 3.33]; ν_{max} (KBr) 1737, 1260 cm^{-1}; δ_H (270 MHz $CDCl_3$) 4.27–4.18 (5H, m, P(OCH_2Me)$_2$, NCH_a-H_b), 4.11 (1H, d, J=11.9 Hz, NCH_aH_b), 4.00 (1H, dd, J_{HP}=12.0 Hz, J_{AB}=11.0 Hz, CH_aH_bCl), 3.92–3.94 (1H, m, NC*H*), 3.42 (1H, dd, J_{HP}=16.8 Hz, J_{AB}=11.0 Hz, CH_aH_b-Cl), 2.00–1.70 (5H, m, C–Hex), 1.37 (3H, t, J=7.0 Hz, OCH$_2$*Me*), 1.36 (3H, t, J=7.0 Hz, OCH$_2$*Me*), 1.44–1.13 (5H, m, C–Hex); δ_P (270 MHz $CDCl_3$) 20.46; *m*/*z* (EI): 383 (12 M^+-HCl), 349 (31), 348 (83), 284 (36), 282 (36), 249 (70), 247 (44), 246 (100), 212 (31), 166 (52), 138 (78), 111 (39).

4.3. Typical procedure: functional rearrangement of 3a to 5a

In a Schlenk, fitted with a perforable septum blocked by a screw cap, CH_3OH (14 mL) and LiH (0.128 g, 16 mmol) were added.[†] When the effervescence ceased, the alkaline solution was thermostated at 0°C and a solution of 3,3-dichloro-4-chloromethyl-pyrrolidin-2-one **3a** (1.170 g, 4 mmol) in CH_3OH (14 mL) was syringed. The reaction was stirred for 2.5 h (complete conversion monitored by GC analysis), afterwards was diluted with water (20 mL) and extracted with CH_2Cl_2 (2×15 mL). The combined organic layers were dried over $MgSO_4$ and concentrated. Column chromatography of the crude product on silica gel, using a petroleum ether (bp 40–60°C)/diethyl ether gradient, gave 0.578 g of the 3-pyrrolin-2-one **5a** (62%) as colourless oil. On using the solution CH_3OH/diethyl ether (1/1), as reaction solvent, the reaction mixture was as an alternative diluted with brine (10 mL) and extracted with ether (2×15 mL).

4.3.1. *N*-Benzyl-4-methyl-5,5-dimethoxy-3-pyrrolin-2-one (5a). Colourless oil; [Found: C, 78.1; H, 7.8; N, 6.5. $C_{14}H_{17}NO_3$ requires C, 78.10; H, 7.96; N, 6.51]; ν_{max} (liquid film) 1710 cm^{-1}; δ_H (400 MHz $CDCl_3$) 7.50–7.21 (5H, m, Ph), 6.02 (1H, q, J=1.7 Hz, COC*H*), 4.35 (2H, s, CH_2Ph), 2.81 (6H, s, C(OMe)$_2$), 1.86 (3H, d, J=1.7 Hz, *Me*); δ_C (400 MHz $CDCl_3$) 168.84, 153.32, 137.45, 129.49, 128.26, 127.37, 125.54, 113.49, 50.78, 41.43, 11.47; *m*/*z* (EI): 248 (11 MH^+), 247 (64), 232 (29), 216 (23), 142 (20), 127 (76), 106 (32), 91 (100).

4.3.2. *N*-Benzyl-3-chloro-4-methyl-5-methoxy-3-pyrrolin-2-one (6). According to the general procedure (entry 2 of Table 1 for the reaction conditions) **3a** (1.170 g, 4 mmol) gave a separable mixture of **5a** (0.401 g, 43%) and **6** (0.141 g, 14%). Pale brown oil; [Found: C, 61.9; H, 5.7; N, 5.5. $C_{13}H_{14}ClNO_2$ requires C, 62.03; H, 5.61; N, 5.56]; ν_{max} (liquid film) 1718 cm^{-1}; δ_H (400 MHz $CDCl_3$) 7.43–7.24 (5H, m, Ph), 5.08 (1H, s, NC*H*), 5.01 (1H, d, J=14.7 Hz, NCH_aH_b), 4.12 (1H, d, J=14.7 Hz, NCH_aH_b), 3.01 (3H, s, –OMe), 1.99 (3H, s, *Me*); δ_C (400 MHz $CDCl_3$) 164.70, 146.40, 136.46, 128.28, 128.18, 127.78, 127.02, 86.76, 49.56, 43.89, 11.45; *m*/*z* (EI): 251 (42 M^+), 236 (5), 220 (18), 158 (5), 146 (28), 131 (11), 118 (8), 91 (100).

4.3.3. *N*-Benzyl-4-methyl-5,5-diethoxy-3-pyrrolin-2-one (5a′). According to the general procedure **3a** (1.170 g, 4 mmol) gave **5a′** (0.618 g, 56%) as colourless oil; [Found: C, 71.0; H, 6.5; N, 5.1. $C_{16}H_{21}NO_3$ requires C, 70.83; H, 6.32; N, 5.16]; ν_{max} (liquid film) 1709 cm^{-1}; δ_H (400 MHz $CDCl_3$) 7.28–7.18 (5H, m, Ph), 5.9 (1H, q, J=1.6 Hz, COC*H*), 4.88 (1H, d, J=14.8 Hz, NCH_aH_b), 4.09 (1H, d, J=14.8 Hz, NCH_aH_b), 3.04–3.29 (4H, m, C(OCH_2Me)$_2$), 1.92 (3H, d, J=1.6 Hz, *Me*), 1.10 (6H, t, J=7.0 Hz, C(OCH$_2$*Me*)$_2$); *m*/*z* (EI): 276 (5 MH^+), 275 (28), 246 (38), 230 (15), 141 (68), 124 (100), 91 (67).

4.3.4. *N*-Dimethylamino-4-methyl-5,5-dimethoxy-3-pyrrolin-2-one (5b). According to the general procedure **3b** (0.982 g, 4 mmol) gave **5b** (0.360 g, 45%) as colourless oil; [Found: C, 57.9; H, 8.6; N, 7.4. $C_9H_{16}N_2O_3$ requires C, 58.05; H, 8.66; N, 7.52]; ν_{max} (liquid film) 1724 cm^{-1}; δ_H (400 MHz $CDCl_3$) 5.86 (1H, q, J=1.72 Hz, COC*H*), 3.35 (6H, s, C(OMe)$_2$), 2.96 (6H, s, NMe_2), 1.86 (3H, d, J=1.72 Hz, *Me*); *m*/*z* (EI): 200 (68 M^+), 185 (23), 169 (22), 158 (33), 127 (100), 94 (22), 59 (30), 44 (30).

4.3.5. *N*-Diethylphosphorylmethyl-4-methyl-5,5-dimethoxy-3-pyrrolin-2-one (5c). According to the general procedure **3c** (0.398 g, 1.13 mmol) gave **5c** (0.229 g, 66%) as brownish oil; [Found: C, 46.9; H, 7.4; N, 4.7. $C_{12}H_{22}NO_6P$ requires C, 46.91; H, 7.22; N, 4.56]; ν_{max} (NaCl) 1720 cm^{-1}; δ_H (270 MHz $CDCl_3$) 6.06 (1H, q, J=1.6 Hz, COC*H*), 4.25–4.14 (4H, m, P(OCH_2Me)$_2$), 3.59 (2H, d, J_{HP}=11.6 Hz, NCH_2P), 3.14 (6H, s, C(OMe)$_2$), 1.94 (3H, d, J=1.6 Hz, *Me*), 1.35 (6H, t, J=6.9 Hz, P(OCH$_2$*Me*)$_2$); δ_C (270 MHz $CDCl_3$) 168.66, 154.25, 125.56, 112.92, 62.42 (J_{CP}=6.1 Hz), 51.28, 33.49 (J_{CP}=163.6 Hz), 16.38 (J_{CP}=6.1 Hz), 11.87; *m*/*z* (EI): 307 (2 M^+), 277 (21), 276 (25), 262 (28), 188 (9), 171 (10), 170 (100), 140 (46), 127 (11), 124 (30), 110 (15), 95 (11), 86 (25), 84 (40), 59 (18), 56 (14).

4.3.6. *N*-Diethylphosphorylmethyl-4-methyl-5,5-diisopropoxy-3-pyrrolin-2-one (5c′). According to the general

[†] When the base was NaOMe, the same equivalents of Na replaced LiH.

procedure **3c** (0.201 g, 0.57 mmol) gave **5c′** (0.083 g, 40%) as pale yellow oil; [Found: C, 52.8; H, 8.4; N, 4.0. $C_{16}H_{30}NO_6P$ requires C, 52.88; H, 8.32; N, 3.85]; ν_{max} (NaCl) 1720 cm^{-1}; δ_H (270 MHz $CDCl_3$) 5.87 (1H, q, J=1.6 Hz, COC*H*), 4.22–4.14 (4H, m, $P(OCH_2Me)_2$), 3.95–3.91 (2H, m, $C(OCHMe_2)_2$), 3.56 (2H, d, J_{HP}=12.2 Hz, NCH_2P), 2.03 (3H, d, J=1.3 Hz, *Me*), 1.33 (6H, t, J=7.1 $P(OCH_2Me)_2$ Hz,), 1.19 (3H, d, J=5.9 Hz, $OCHMe_aMe_b$), 1.17 (3H, d, J=6.3 Hz, $OCHMe_aMe_b$); δ_C (270 MHz $CDCl_3$) 168.75, 157.48, 123.14, 111.28, 67.37, 62.35 (J_{CP}=7.3 Hz), 35.78 (J_{CP}=163.6 Hz), 23.90, 16.43 (J_{CP}=6.1 Hz), 13.33; *m/z* (EI): 363 (1 M^+), 262 (12), 155 (18), 126 (10), 124 (18), 113 (22), 98 (100), 82 (17), 56 (21), 45 (17), 43 (20), 42 (16), 41 (36).

4.3.7. *N*-(1-Phenyl-diethylphosphorylmethyl)-4-methyl-5,5-dimethoxy-3-pyrrolin-2-one (5d). According to the general procedure **3d** (0.214 g, 0.5 mmol) gave **5d** (0.019 g, 10%) as brown oil; [Found: C, 56.3; H, 6.9; N, 3.7. $C_{18}H_{26}NO_6P$ requires C, 56.39; H, 6.84; N, 3.65]; ν_{max} (NaCl) 1721, 1254 cm^{-1}; δ_H (270 MHz $CDCl_3$) 7.79–7.27 (5H, m, Ph), 6.05 (1H, q, J=1.3 Hz, COC*H*), 4.66 (1H, d, J_{HP}=26.1 Hz, C*H*P), 4.40–4.27 (2H, m, OCH_2Me), 4.17–3.89 (2H, m, OCH_2Me), 3.38 (3H, s, OMe), 2.44 (3H, s, OMe), 1.88 (3H, d, J=1.7 Hz, *Me*), 1.29 (3H, t, J=7.0 Hz, OCH_2Me), 1.23 (3H, t, J=7.0 Hz, OCH_2Me); δ_C (270 MHz $CDCl_3$) 168.21, 153.38, 136.40, 129.94, 129.85, 128.17, 127.88, 125.86, 113.86 (J_{CP}=6.1 Hz), 64.00 (J_{CP}=6.1 Hz), 61.83 (J_{CP}=7.3 Hz), 52.23 (J_{CP}=155.0 Hz), 51.70, 51.01, 16.36 (J_{CP}=6.1 Hz), 16.22 (J_{CP}=6.1 Hz), 11.86; *m/z* (EI): 352 (100), 227 (57).

4.3.8. *N*-Benzyl-4-methyl-5-methoxy-3-pyrrolin-2-one (5e). According to the general procedure **3e** (1.032 g, 4 mmol) gave **5e** (0.529 g, 61%) as colourless oil; [Found: C, 71.8; H, 6.8; N, 6.7. $C_{13}H_{15}NO_2$ requires C, 71.87; H, 6.96; N, 6.45]; ν_{max} (liquid film) 1707 cm^{-1}; δ_H (400 MHz $CDCl_3$) 7.37–7.23 (5H, m, Ph), 5.96 (1H, dq, J=1.7, 0.7 Hz, COC*H*), 5.02 (1H, br s, NC*H*), 4.95 (1H, d, J=14.8 Hz, NCH_aH_b), 4.04 (d, J=14.8 Hz, 1H, NCH_aH_b), 2.98 (3H, s, OMe), 1.95 (3H, dd, J=1.7, 0.6 Hz, *Me*); δ_C (400 MHz $CDCl_3$) 169.97, 155.02 137.19, 128.64, 128.42, 127.49, 124.91, 88.62, 49.24, 43.03, 13.60; *m/z* (EI): 217 (66 M^+), 202 (4), 186 (18), 156 (26), 112 (100), 106 (21), 91 (92).

4.3.9. *N*-Benzyl-3,4-dimethyl-5-methoxy-3-pyrrolin-2-one (5f). According to the general procedure **3f** (1.088 g, 4 mmol) gave **5f** (0.721 g, 78%) as colourless oil; [Found: C, 72.8; H, 7.6; N, 6.0. $C_{14}H_{17}NO_2$ requires C, 72.70; H, 7.41; N, 6.06]; ν_{max} (liquid film) 1701 cm^{-1}; δ_H (400 MHz 50% $CDCl_3/C_6D_6$) 7.20–7.00 (5H, m, Ph), 4.82 (1H, d, J=14.7 Hz, $PhCH_aH_b$), 4.68 (1H, br s, NC*H*), 3.88 (1H, d, J=14.7 Hz, $PhCH_aH_b$), 2.63 (3H, s, OMe), 1.65 (3H, dq, J=1.2, 1.2 Hz, *Me*), 1.45 (3H, dq, J=1.2, 0.7 Hz, *Me*); δ_C (400 MHz $CDCl_3$) 171.00, 145.72, 137.38, 131.63, 128.58, 128.47, 127.40, 87.68, 49.01, 43.23, 11.25, 8.49; *m/z* (EI): 231 (34 M^+), 216 (8), 200 (26), 91 (100).

4.3.10. *N*-Benzyl-3-chloro-4-methyl-5,5-dimethoxy-3-pyrrolin-2-one (5g). According to the general procedure **3l** (1.308 g, 4 mmol) gave **5g** (0.743 g, 66%) as pale yellow oil; [Found: C, 59.7; H, 5.9; N, 4.9. $C_{14}H_{16}ClNO_3$ requires C, 59.68; H, 5.72; N, 4.97]; ν_{max} (liquid film) 1719 cm^{-1}; δ_H (400 MHz $CDCl_3$) 7.50–7.25 (5H, m, Ph), 4.40 (2H, s, NCH_2), 2.84 (6H, s, $C(OMe)_2$), 1.89 (3H, s, *Me*). δ_C (400 MHz $CDCl_3$) 163.66, 145.00, 136.62, 129.33, 128.17, 127.78, 127.44, 111.74, 50.80, 41.86, 9.41; *m/z* (EI): 265 (38 M^+), 234 (32), 160 (39), 91 (100).

4.3.11. *N*-Benzyl-3-chloro-4,5-dimethyl-5-methoxy-3-pyrrolin-2-one (5h). According to the general procedure **3m** (1.226 g, 4 mmol) gave **5h** (0.690 g, 60%) as colourless oil; [Found: C, 63.1; H, 6.2; N, 5.5. $C_{14}H_{16}ClNO_2$ requires C, 63.28; H, 6.07; N, 5.27]; ν_{max} (liquid film) 1721 cm^{-1}; δ_H (400 MHz $CDCl_3$) 7.36–7.20 (5H, m, Ph), 4.69 (1H, d, J=15.3 Hz, NCH_aH_b), 4.30 (1H, d, J=15.3 Hz, NCH_aH_b), 2.72 (3H, s, OMe), 1.91 (3H, s, *Me*), 1.30 (3H, s, NC*Me*); δ_C (400 MHz $CDCl_3$) 164.76, 149.59, 137.70, 128.44, 128.31, 127.38, 126.03, 93.17, 50.06, 42.45, 22.54, 10.12; *m/z* (EI): 281 (45 M^+), 250 (23), 234 (13), 176 (15), 161 (36), 113 (20), 91 (100).

4.3.12. *N*-Benzyl-4,5-dimethyl-5-methoxy-3-pyrrolin-2-one (5i). According to the general procedure **3n** (1.088 g, 4 mmol) gave **5i** (0.499 g, 54%) as colourless oil; [Found: C, 72.9; H, 7.3; N, 5.9. $C_{14}H_{17}NO_2$ requires C, 72.70; H, 7.41; N, 6.06]; ν_{max} (liquid film) 1711 cm^{-1}; δ_H (400 MHz $CDCl_3$) 7.35–7.16 (5H, m, Ph), 5.94 (1H, q, J=1.6 Hz, COC*H*), 4.66 (1H, d, J=15.4 Hz, NCH_aH_b), 4.21 (1H, d, J=15.4 Hz, NCH_aH_b), 2.72 (3H, s, OMe), 1.87 (3H, d, J=1.6 Hz, *Me*), 1.24 (3H, s, NC*Me*); δ_C (400 MHz $CDCl_3$) 169.91, 158.14, 138.39, 128.34, 128.07, 127.08, 123.61, 94.46, 49.80, 41.71, 12.08; *m/z* (EI): 231 (45 M^+), 200 (27), 126 (100), 111 (36), 91 (96). From the crude product, 0.114 g of *N-benzyl-4-methyl-5-methylen-3-pyrrolin-2-one* (**13**) (0.032, 4%) was also recovered as pale yellow oil; [Found: C, 73.9; H, 5.9; N, 6.4. $C_{13}H_{13}NO$ requires C, 73.99; H, 5.77; N, 6.16]; ν_{max} (liquid film) 1694 cm^{-1}; δ_H (400 MHz $CDCl_3$) 7.32–7.18 (5H, m, Ph), 6.00–5.98 (1H, m, COC*H*), 4.79 (1H, dd, J=2.2, 0.6 Hz, $=CH_aH_b$), 4.79 (2H, s, NCH_2), 4.71 (1H, dd, J=1.7, 2.2 Hz, $=CH_aH_b$), 2.11 (3H, d, J=1.5 Hz, =CMe); δ_C (400 MHz $CDCl_3$) 170.06, 147.29, 146.69, 137.24, 128.59, 127.24, 126.95, 121.28, 93.64, 42.77, 12.03; *m/z* (EI): 199 (100 M^+), 198 (51), 184 (13), 170 (26), 91 (63).

4.3.13. *N-t*-Butyl-4-methyl-5,5-dimethoxy-3-pyrrolin-2-one (5l). Following the same general procedure outlined for the substrates **3**, **4a** (1.627 g, 4.13 mmol) gave **5l** (0.572 g, 65%) as brownish oil; [Found: C, 61.8; H, 9.0; N, 6.7. $C_{11}H_{19}NO_3$ requires C, 61.95; H, 8.98; N, 6.57]; ν_{max} (KBr) 1698 cm^{-1}; δ_H (270 MHz $CDCl_3$) 5.87 (1H, q, J=2.0 Hz, COC*H*), 3.16 (6H, s, $C(OMe)_2$), 1.82 (3H, d, J=1.7 Hz, *Me*), 1.52 (9H, s, CMe_3); δ_C (270 MHz $CDCl_3$) 169.67, 152.07, 125.89, 116.06, 54.59, 50.99, 27.73, 11.07; *m/z* (EI): 213 (10 M^+), 199 (37), 198 (100), 170 (26), 168 (28), 166 (72), 126 (70), 121 (56), 119 (56), 94 (51), 88 (54), 86 (67), 84 (74), 82 (42), 73 (27), 70 (27), 51 (31), 49 (44), 47 (40).

4.3.14. *N-i*-Propyl-4-methyl-5,5-dimethoxy-3-pyrrolin-2-one (5m). Following the same general procedure outlined for the substrates **3**, **4c** (0.5 g, 1.3 mmol) gave **5m** (52 mg, 20%) as yellowish oil; [Found: C, 60.0; H, 8.7; N, 6.9. $C_{10}H_{17}NO_3$ requires C, 60.28; H, 8.60; N, 7.03.]; ν_{max} (KBr)

1707 cm^{-1}; δ_H (270 MHz $CDCl_3$) 5.92 (1H, q, J=2.0 Hz, COC*H*), 3.71 (1H, sept, J=6.9 Hz, C*H*Me_2), 3.15 (6H, s, $C(OMe)_2$), 1.88 (3H, d, J=2.0 Hz, *Me*), 1.41 (6H, d, J=6.9 Hz, CH*Me*$_2$); δ_C (270 MHz $CDCl_3$) 11.63, 20.18, 42.77, 51.34, 114.16, 126.45, 152.15, 168.71; *m/z* (EI): 200 (11, MH^+), 185 (100), 169 (37), 153 (69), 127 (62), 94 (45).

4.3.15. *N-c*-Hexyl-4-methyl-5,5-dimethoxy-3-pyrrolin-2-one (5n). Following the same general procedure outlined for the substrates **3**, **4d** (0.7 g, 1.6 mmol) gave **5m** (61 mg, 16%) as brown oil; [Found: C, 65.4; H, 8.9; N, 5.8. $C_{13}H_{21}NO_3$ requires C, 65.25; H, 8.84; N, 5.85]; ν_{max} (KBr) 1706 cm^{-1}; δ_H (270 MHz $CDCl_3$) 5.29 (1H, br s, COC*H*), 3.37–3.28 (1H, m, NC*H*), 3.14 (6H, s, $C(OMe)_2$), 2.19–1.11 (10H, m, CHex), 1.87 (3H, d, J=1.3 Hz, Me); δ_C (270 MHz $CDCl_3$) 168.66, 151.97, 126.49, 114.30, 51.43, 51.11, 29.92, 26.31, 25.32, 11.66; *m/z* (EI): 239 (45 M^+), 224 (36), 196 (35), 193 (64), 150 (43), 127 (100), 126 (93), 113 (53), 112 (57), 94 (55), 81 (30), 67 (33), 57 (80).

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