# A convenient synthesis and cytotoxic evaluation of β-aryl-α-methylidene-γ-lactones and β-aryl-α-methylidene-γ-lactams

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3-Aryl-2-diethoxyphosphoryl-4-nitrohexanoates **8**, obtained by Michael addition of ethyl diethoxyphosphorylacetate **6** to 1-aryl-2-nitro-1-butenes **7**, were utilized as convenient common intermediates in the synthesis of β-aryl-γ-ethyl-α-methylidene-γ-lactones **17** and β-aryl-γ-ethyl-α-methylidene-γ-lactams **21**. Transformation of the nitro functionality in **8** into a hydroxyl or amino group and cyclization yielded lactones **16** or lactams **19**, which were used in Horner–Wadsworth–Emmons olefination of formaldehyde to give target compounds in good yields. Cytotoxicity of these compounds was evaluated *in vitro* against mouse leukemia cell line L-1210 and two human leukemia cell lines, HL-60 and NALM-6. Two of the obtained compounds **17b,c** with 4-bromophenyl and 4-methylphenyl substituents in the β position proved to be very potent against all three cell lines with $IC_{50}$ values lower than 6 μM.

## Introduction

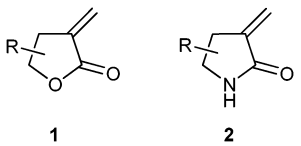
Sesquiterpene lactones are a large and diverse group of natural products which are the active components of many medicinal plants mainly from the Asteraceae family.[1,2] Their phytotoxic, antimicrobial, antifungal, cardiovascular, anti-inflammatory and in particular anticancer activity make them an extremely interesting group of potentially useful drugs with many possible applications, *e.g.* in both cancer chemotherapy and chemoprevention.[3] Bioactivity, molecular mechanism of action as well as structure–activity relationship (SAR) of these compounds have been intensively studied.[3–6] Numerous investigations confirmed that the presence of α-methylidene-γ-lactone moiety **1** (Fig. 1) in the sesquiterpene lactone structure is the most important parameter for their activity. It is now generally accepted that the covalent binding of this moiety, *via* Michael-type addition, to free mercapto groups in proteins or free intracellular glutathione leads to reduction of enzyme activity or causes the disruption of glutathione metabolism and the vitally important intracellular cell redox balance.[3] α-Methylidene-γ-lactams **2** (Fig. 1) are less prevalent in nature and their activity is much less recognized. However, moderate cytotoxic activity of these compounds was reported.[7–9]

Not surprisingly, many strategies for the synthesis of α-methylidene-γ-lactones and lactams with diverse substitution patterns have been developed.[1,10–12] One of them uses 2-diethoxyphosphoryl-4-nitroalkanoates **5** as convenient common intermediates.[9,13,14] Transformation of the nitro functionality into a hydroxyl or amino group, cyclization and Horner–Wadsworth–Emmons olefination of formaldehyde using thus formed lactones or lactams give access to the target compounds **1** or **2**. Phosphorylnitroalkanoates **5** have so far been synthesized by Michael addition of nitroalkanes **4** to 2-diethoxyphosphorylacrylates **3** in the presence of base (Scheme 1). However, the scope of these reactions is limited to diethoxyphosphorylacrylate **3** ($R^2$ = H) as Michael acceptor[13] or to nitromethane ($R^3$ = H) or nitroethane ($R^3$ = Me) as Michael donors.[15]

In this paper we report that the Michael addition of ethyl diethoxyphosphorylacetate **6** to 1-aryl-2-nitro-1-butenes **7** gives access to, so far unknown, 3-aryl-2-diethoxyphosphoryl-4-nitrohexanoates **8**. These compounds were next transformed into β-aryl-γ-ethyl-α-methylidene-γ-lactones **17** and β-aryl-γ-ethyl-α-methylidene-γ-lactams **21**, employing a Horner–Wadsworth–Emmons olefination pathway. Target compounds were next tested for their cytotoxic activity against mouse leukemia cell line L-1210 and two human leukemia cell lines, HL-60 and NALM-6.

## Results and discussion

Starting (*E*)-1-aryl-2-nitro-1-butenes **7a–d** were prepared by nitroaldol condensation of nitropropane with selected aromatic aldehydes applying a modified literature procedure.[16] Additions of diethoxyphosphorylacetate **6** to nitrobutenes **7a–d** were performed in THF using sodium hydride as a base and were completed after 24 h. Crude products were purified by column




1 2

**Fig. 1** General structures of α-methylidene-γ-lactones and -γ-lactams.

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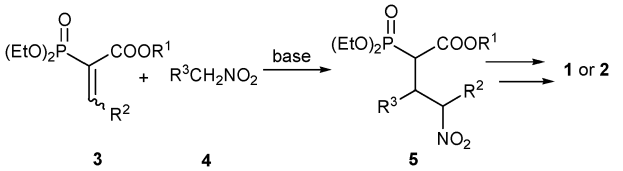



**Scheme 1** Methods for the synthesis of 2-diethoxyphosphoryl-4-nitroalkanoates **5**.

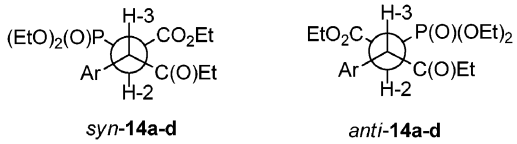


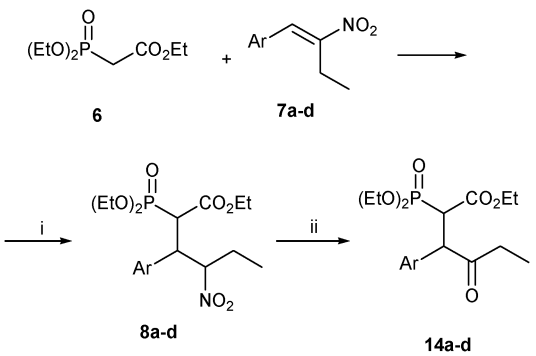

**Fig. 2** Newman projections for *syn*- and *anti*-**14a–d**.

chromatography. Pure ethyl 3-aryl-2-diethoxyphosphoryl-4-nitrohexanoates **8a–d** were obtained in good yields as mixtures of four diastereomers (Scheme 2, Table 1). Their ratios were determined from the signals integration in $^{31}$P NMR spectra. For **8c** only three signals were visible in $^{31}$P NMR spectra, probably because of the overlap of the signals of two diastereomers. Due to the complex diastereomeric mixtures of the adducts **8** their full characterization by $^{13}$C NMR was not possible.

Obtained nitrohexanoates **8a–d** were next tested in the Nef reaction. In this regard, our initial reactions were performed in classic conditions (MeONa/MeOH, r.t. then $H_2SO_4$/MeOH, −60 °C), which worked well in our laboratory for 3-unsubstituted analogues.[13] However, in these conditions rather complex mixtures of products were formed. $^1$H and $^{31}$P NMR analysis of the reaction mixtures revealed that ethyl diethoxyphosphoryl-acetate **6** and nitropropane **11**, along with the starting material, were among the products. Formation of these compounds can be rationalized assuming that in strongly basic conditions retro-Michael reaction takes place instead of the Nef reaction (Scheme 3). Evidently, the presence of an aromatic substituent in position 3 facilitates the retro-Michael reaction due to the conjugation of the newly formed double bond with this substituent.

In view of the above, we decided to perform the Nef reaction under much milder, ozonolytic conditions.[17] Passing ozone through the solution of nitroalkanoates **8a–d** in the presence of Triton B at −78 °C and standard work up of the reaction mixture gave crude ethyl 3-aryl-2-diethoxyphosphoryl-4-oxohexanoates **14a–d** which were purified by column chromatography. Pure hexanoates **14** were obtained in good yields as mixtures of two diastereomers (Scheme 2, Table 1). Efforts undertaken to separate these diastereomers by column chromatography were unsuccessful.

Careful analysis of $^1$H, $^{13}$C and $^{31}$P NMR spectra confirmed the structure of all obtained products **14a–d** and allowed us to




**Scheme 2** *Reagents and conditions*: (i) NaH/THF; (ii) Triton B®/$O_3$, EtOH/$Me_2S$, −78 °C to r.t.

assign the relative stereochemistry at the C-2 and C-3 stereogenic centers. Diagnostic were large coupling constants $^3J_{H2H3}$ in $^1$H NMR spectra of both diastereomers (7.9–8.4 Hz for major and 9.9–10.4 Hz for minor diastereomer) which clearly proves an antiperiplanar arrangement of H-2 and H-3.[18] Furthermore, in $^{13}$C NMR spectra of major diastereomers signals of the carbonyl carbon atoms appeared as doublets with large phosphorus–carbon coupling constants ($^3J_{PC=O}$ = 16.1–16.4 Hz) and signals of the aromatic carbon atoms in the *ipso* position were singlets ($^3J_{PCipso}$ = 0 Hz). These values clearly indicate an antiperiplanar arrangement of the carbonyl and phosphoryl groups as well as a *gauche* arrangement of the aromatic substituent and phosphoryl group (Fig. 2).[19] Therefore the *syn* configuration was assigned to major diastereomers of **14a–d**. Corresponding coupling constants for minor diastereomers were $^3J_{PC=O}$ = 0 Hz and $^3J_{PCipso}$ = 16.4–16.7 Hz which proves an antiperiplanar relationship of phosphoryl and aryl groups and a *gauche* relationship of carbonyl and phosphoryl groups. Consequently, the *anti* configuration was assigned to minor diastereomers of **14a–d**.

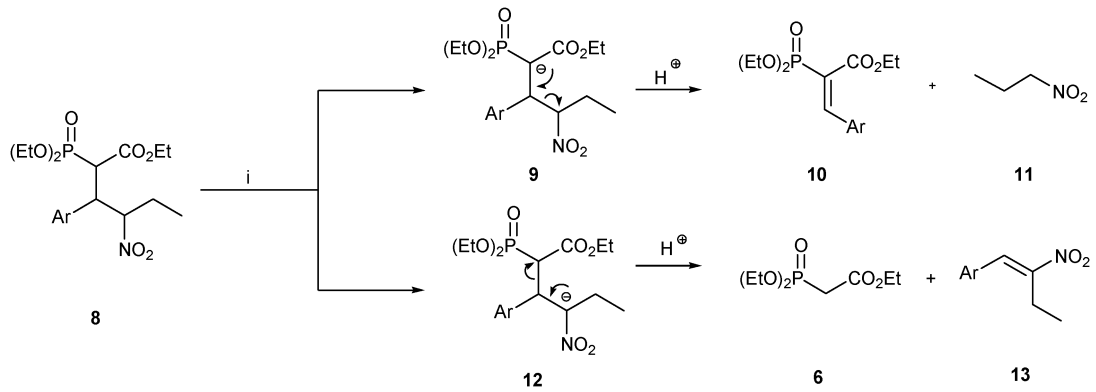
Oxohexanoates **14a–d** were next subjected to chemoselective reduction of the carbonyl group using potassium borohydride in methanol. Short reaction time (~50 min) appeared to be crucial for the efficiency of the reductions. Initially formed 4-hydroxyalkanoates **15** lactonized spontaneously providing α-diethoxyphosphoryl-γ-lactones **16a–c** in good yields (Scheme 4). Only reduction of **14d** was not chemoselective and gave a complex mixture of compounds which were difficult to identify. Interestingly, lactones **16a–c** were formed as a mixtures of only two, out of four possible diastereomers in the ratio given in Table 2. Attempts to separate these mixtures failed.

Pleasingly, careful analysis of $^1$H, $^{13}$C and $^{31}$P NMR spectra of lactones **16a–c** allowed us to assign the (*r*-3, *t*-4, *c*-5) configuration for all major diastereomers and the (*r*-3, *t*-4, *t*-5) configuration for all minor diastereomers. The observed values of coupling constant $^3J_{PCipso}$ = 0 Hz (Table 3) clearly proved the *trans* arrangement of the phosphoryl and aryl groups in both major and minor diastereomers. On the other hand, lower values of the chemical shifts observed for H-5 protons in major diastereomers in comparison with the same protons in minor diastereomers (*e.g.* for **16a** corresponding values were 4.35 ppm and 4.88 ppm, respectively) indicated a *trans* relationship of ethyl and aryl groups in the former due to the shielding effect exerted by the benzene ring on the *cis*-oriented proton H-5. Also, coupling constants $^3J_{PC5}$ and $J_{H3H4}$ were in agreement with this assignment. Dihedral angles estimated from these coupling constants, using the Karplus equation,[18,19] had values given in parentheses in Table 3 and were in good agreement with the dihedral angles taken from the corresponding Cochranes orbit size molecular models of (*r*-3,*t*-4,*c*-5)-**16a–c**

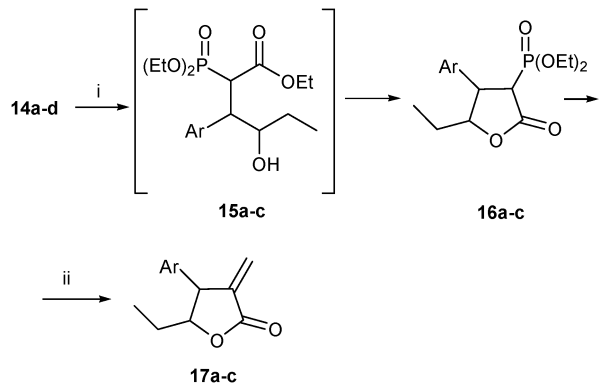
**Table 1** Synthesis of ethyl 3-aryl-2-diethoxyphosphoryl-4-nitrohexanoates **8a–d** and ethyl 3-aryl-2-diethoxyphosphoryl-4-oxohexanoates **14a–d**

| | | **8** | | **14** | |
|---|---|---|---|---|---|
| Ar | | Yield [%][a] | Diastereomeric ratio[b] | Yield [%][a] | Diastereomeric ratio[b] |
| **a** | $C_6H_5$- | 89 | 3 : 33 : 21 : 43 | 66 | 65 : 35 |
| **b** | 4-Br-$C_6H_4$- | 80 | 45 : 21 : 34 | 65 | 65 : 35 |
| **c** | 4-$CH_3$-$C_6H_4$- | 70 | 8 : 35 : 22 : 35 | 53 | 60 : 40 |
| **d** | 4-$NO_2$-$C_6H_4$- | 75 | 6 : 19 : 26 : 39 | 53 | 60 : 40 |

[a] Yield of isolated, pure product based on **6** or **8** respectively. [b] Taken from $^{31}$P NMR spectra of the crude products.




**Scheme 3** *Reagents and conditions*: (i) MeONa/MeOH.




**Scheme 4** *Reagents and conditions*: (i) $KBH_4$/MeOH then HCl/$H_2O$; (ii) *t*-BuOK/$Et_2O$ then $(CH_2O)_n$/$Et_2O$.

and (*r*-3,*t*-4,*t*-5)-**16a–c**, in which the diethoxyphosphoryl and aryl groups were assumed to occupy *pseudo*-equatorial positions. Based on these results it can be assumed that reduction followed by lactonization proceeds with epimerization at the C-3 carbon atom giving lactones **16** with a more stable *trans* arrangement of the phosphoryl and aryl groups.

Finally, olefination of the formaldehyde using phosphorylated lactones **16a–c** as the Horner–Wadsworth–Emmons reagents in the presence of potassium *tert*-butoxide gave, after standard work-up and purification by column chromatography, pure α-methylidene-γ-lactones **17a–c** in good yields. These compounds were formed as mixtures of two diastereoisomers in the same ratio as starting lactones **16a–c** (Scheme 4, Table 2). Their structure was confirmed by the analysis of $^1$H and $^{13}$C NMR spectra. For example, values of the chemical shifts of H-4 and H-5 protons were always smaller for the protons of the major diastereomers ($\delta_{H\text{-}4}$ = 3.74–3.79 ppm, $\delta_{H\text{-}5}$ = 4.30–4.35 ppm) in comparison with the corresponding protons of the minor diastereomers ($\delta_{H\text{-}4}$ = 4.10–4.32 ppm, $\delta_{H\text{-}5}$ = 4.60–4.63 ppm). This observation can be rationalized by the shielding effect of the phenyl ring or ethyl group exerted on the protons which are *cis*-orientated to one of these groups and proves that major diastereomers have the *trans* configuration. Furthermore it confirms the correctness of the configurational assignments made for lactones **16**.

Next we turned our attention to the application of nitrohexanoates **8a–d** in the synthesis of β-aryl-γ-ethyl-α-methylidene-γ-lactams **21**. Chemoselective reduction of the nitro

**Table 2** Synthesis of α-diethoxyphosphoryl-γ-lactones **16a–c** and α-methylidene-γ-lactones **17a–c**

| | | **16** | | **17** | |
|---|---|---|---|---|---|
| Ar | | Yield [%][a] | Diastereomeric ratio[b] | Yield [%][a] | *trans* : *cis*[c] |
| **a** | $C_6H_5$- | 60 | 70 : 30 | 68 | 70 : 30 |
| **b** | 4-Br-$C_6H_4$- | 59 | 70 : 30 | 69 | 70 : 30 |
| **c** | 4-$CH_3$-$C_6H_4$- | 80 | 60 : 40 | 71 | 60 : 40 |

[a] Yield of isolated, pure product based on **14** or **16** respectively. [b] Taken from $^{31}$P NMR spectra of the crude products. [c] Taken from $^1$H NMR spectra of the crude products.

**Table 3** Selected chemical shifts and coupling constants for (*r*-3,*t*-4,*c*-5)-**16a–c** and (*r*-3,*t*-4,*t*-5)-**16a–c**[a]

| | $\delta$ ($^1$H) H-5 [ppm] | $^3J_{PCipso}$/Hz | $^3J_{PC5}$/Hz | $^3J_{H3H4}$/Hz |
|---|---|---|---|---|
| (*r*-3,*t*-4,*c*-5)-**16a** | 4.35 | 0 (110–120°) | 13.3 (150–160°) | 10.4 (150–160°) |
| (*r*-3,*t*-4,*t*-5)-**16a** | 4.88 | 0 | 3.2 (130–40°) | 2.6 (120–130°) |
| (*r*-3,*t*-4,*c*-5)-**16b** | 4.20 | 0 | 12.9 | 10.5 |
| (*r*-3,*t*-4,*t*-5)-**16b** | 4.83 | 0 | 3.5 | 2.7 |
| (*r*-3,*t*-4,*c*-5)-**16c** | 4.51 | 0 | 13.1 | 10.4 |
| (*r*-3,*t*-4,*t*-5)-**16c** | 4.85 | 0 | 3.3 | 2.6 |

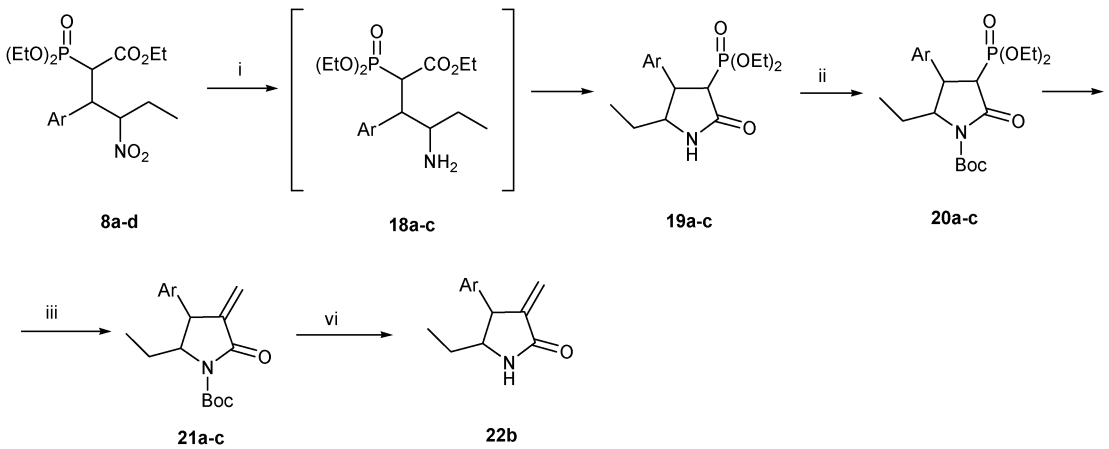
[a] Taken from the $^1$H and $^{13}$C NMR spectra of the mixtures of diastereomers.

group by sodium borohydride in the presence of $NiCl_2{\cdot}6H_2O$[20–22] yielded 4-aminohexanoates **18a–c** which lactamized spontaneously to α-diethoxyphosphoryl-γ-lactams **19a–c** (Scheme 5, Table 4). Disappointingly the reduction of **8d** was not chemoselective and proceeded with partial reduction of the aromatic nitro group. Our efforts to improve chemoselectivity of this reaction or separate the desired product were unsuccessful. Lactams **19a–c** were formed as mixtures of two, out of four possible stereoisomers. Spectroscopic studies confirmed their structure, but did not allow us to assign unequivocally the relative configuration at C-2, C-3 and C-4 stereogenic centers. However, keeping in mind the facile epimerization of lactones **16** and taking into account the strongly basic conditions of the reduction, it can be assumed that similar epimerization of lactams **19** at the C-3 carbon atom gives rise to two thermodynamically more stable diastereomers with *trans* configuration at C-3 and C-4 carbon atoms but opposite configuration at C-4 and C-5 carbon atoms.

When lactams **19a–c** were used in the Horner–Wadsworth–Emmons olefination of formaldehyde applying conditions tested for lactones **16**, along with the desired α-methylidene-γ-lactams **22**, their *N*-hydroxymethyl derivatives were also formed in substantial amounts. To overcome this problem the Boc protecting group was introduced onto the amide nitrogen atom by treatment of lactams **19a–c** with $Boc_2O$ in the presence of a catalytic amount of DMAP. Obtained *N*-Boc lactams **20a–c** were purified by column chromatography and used in the olefination of formaldehyde. We were pleased to observe that the reactions proceeded effectively yielding, after purification by column chromatography, *N*-Boc-α-methylidene-γ-lactams **21a–c** in good yields (Scheme 5, Table 4). Furthermore, analysis of the $^1$H and $^{13}$C NMR spectra revealed that chemical shifts of H-4 and H-5 carbon atoms in major diastereomers have smaller values than chemical shifts of the same protons in minor diastereomers. On this basis, using the same rationale as for lactones **17a–c**, we assigned the *trans* configuration to all major diastereomers and the *cis* configuration to all minor diastereomers of lactams **21**. Deprotection of α-methylidene-γ-lactams **21** can be easily achieved using a standard procedure. This was demonstrated by treatment of lactam **21b** with 33% TFA in $CH_2Cl_2$ at room temperature. Standard work-up and purification by column chromatography provided pure α-methylidene-γ-lactam **22b** in 68% yield.

Due to the anticipated biological activity, lactones **17a–c** as well as lactam **22b** were tested *in vitro* against mouse leukemia cell line L-1210 and two human leukemia cell lines, HL-60 and NALM-6. Cytotoxic activity of these compounds is expressed as the concentration (μM) required to inhibit tumor cells proliferation by 50% after 48 h exposure of the cells to a tested compound ($IC_{50}$ values). Carboplatin was used as a reference compound.[23] Obtained results are shown in Table 5.

All tested compounds exhibited a consistent cytotoxic activity with $IC_{50}$ values ranging from 0.60 to 81.2 μM. Furthermore, we were pleased to observe that the $IC_{50}$ values of 4-bromophenyl and 4-methylphenyl substituted lactones **17b,c** were in all tests smaller than 5.6 μM and therefore these compounds can be considered as highly potent according to Kupchan's classification ($IC_{50} \leq 15$ μM).[24] It is also noteworthy that introduction of the unsubstituted phenyl group in the β-position (lactone **17a**) diminishes the activity significantly against all three cell lines. Lactam **22b** displayed




**Scheme 5** *Reagents and conditions*: (i) $NiCl_2{\cdot}6H_2O$/MeOH then $NaBH_4$/MeOH; (ii) $Boc_2O$, DMAP/$CH_2Cl_2$; (iii) *t*-BuOK/THF then $(CH_2O)_n$/THF; (iv) $CF_3CO_2H/CH_2Cl_2$.

**Table 4** Synthesis of α-diethoxyphosphoryl-γ-lactams **19a–c**, *N*-Boc-α-diethoxyphosphoryl-γ-lactams **20a–c** and *N*-Boc-α-methylidene-γ-lactams **21a–c**

| | | **19** | | **20** | | **21** | |
|---|---|---|---|---|---|---|---|
| Ar | | Yield [%][a] | Diastereomeric ratio[b] | Yield [%][a] | Diastereomeric ratio[b] | Yield [%][a] | *trans* : *cis*[c] |
| **a** | $C_6H_5$- | 92 | 55 : 45 | 69 | 55 : 45 | 59 | 55 : 45 |
| **b** | 4-Br-$C_6H_4$- | 79 | 60 : 40 | 72 | 60 : 40 | 52 | 60 : 40 |
| **c** | 4-$CH_3$-$C_6H_4$- | 85 | 60 : 40 | 82 | 60 : 40 | 80 | 60 : 40 |

[a] Yield of isolated, pure product based on **8**, **19** or **20** respectively. [b] Taken from $^{31}$P NMR spectra of the crude products. [c] Taken from $^{1}$H NMR spectra of the crude products.

**Table 5** Cytotoxic activity of compounds **17a–c**, **22b** and **23**

| | Cytotoxicity $IC_{50}/\mu M$[a] | | |
|---|---|---|---|
| Compound | L-1210 | HL-60 | NALM-6 |
| **17a** | 35.0 ± 2.8 | 56.05 ± 3.53 | 59.99 ± 4.05 |
| **17b** | 1.60 ± 0.21 | 1.16 ± 0.02 | 0.60 ± 0.03 |
| **17c** | 0.85 ± 0.06 | 5.5 ± 0.5 | 5.6 ± 0.3 |
| **22b** | 43.0 ± 1.9 | 65.8 ± 2.2 | 81.2 ± 2.5 |
| **23**[b] | | 515.7 ± 47.6 | 439.2 ± 40.8 |
| Carboplatin | 9.7 ± 1.2 | 2.9 ± 0.1 | 0.7 ± 0.3 |

[a] $IC_{50}$, 50% inhibitory concentration represents the mean from dose response curves of at least three experiments. [b] Data taken from ref. 9.

moderate cytotoxicity, confirming previous reports that the cytotoxicities of α-methylidene-γ-lactones are generally much higher than the cytotoxicities of α-methylidene-γ-lactams.[8] However, the cytotoxicity of lactam **22b** was significantly higher than the reported cytotoxicity[9] of its γ-methyl analogue β-(4-bromophenyl)-γ-methyl-α-methylidene-γ-lactone **23** (Table 5). Evidently, a very small structural change such as the presence of an ethyl instead of a methyl substituent in the γ position increases the cytotoxicity several times.

## Conclusions

We have developed an efficient and straightforward route to β-aryl-γ-ethyl-α-methylidene-γ-lactones **17** and β-aryl-γ-ethyl-α-methylidene-γ-lactams **21** *via* 3-aryl-2-diethoxyphosphoryl-4-nitrohexanoates **8** as the key intermediates. Relative configurations of the intermediates and all target compounds were unequivocally assigned using spectroscopic techniques. Furthermore, all target compounds were evaluated for their cytotoxic activity towards mouse leukemia cell line L-1210 and two human leukemia cell lines, HL-60 and NALM-6, and two of the prepared lactones **17b,c** exhibited remarkable cytotoxicity against all three cell lines.

## Experimental results

### General information

Organic solvents and reagents were purified by the appropriate standard procedures. Column chromatography was performed on Fluka® silica gel 60 (230–400 mesh). IR spectra were recorded on a Specord M 80 spectrometer. $^{1}$H NMR (250 MHz), $^{13}$C NMR (62.9 MHz) and $^{31}$P NMR (101 MHz) spectra were recorded on a Bruker DPX-250 spectrometer with TMS as an internal standard for $^{1}$H NMR and $^{13}$C NMR, and 85% $H_3PO_4$ as an external standard for $^{31}$P NMR. $^{31}$P NMR spectra were recorded using broad-band proton decoupling. *J* values are given in Hz. 1-aryl-2-nitro-1-butenes **7a–d** were prepared according to a modified literature procedure.[16]

### General procedure for the preparation of ethyl 3-aryl-2-diethoxyphosphoryl-4-nitrohexanoates 8a–d

To a slurry of sodium hydride (0.45 g, 18.7 mmol) in THF (40 mL) at room temperature a solution of ethyl diethoxyphosphorylacetate (**6**) (4.0 g, 17.8 mmol) in THF (5 mL) was added dropwise. The resulting solution was stirred for 30 min at room temperature and then cooled to −5 °C. A solution of the corresponding 1-aryl-2-nitro-1-butene **7** (35.6 mmol) in THF (15 mL) was next added dropwise. The reaction mixture was allowed to warm to room temperature, stirred for an additional 24 h at that temperature and quenched with saturated ammonium chloride solution (50 mL). THF was removed under reduced pressure and the residue extracted with $CH_2Cl_2$ (3 × 30 mL). Combined organic layers were dried over $MgSO_4$, filtered and the solvents were removed *in vacuo*. Crude product was purified by column chromatography (eluent: chloroform–acetone 95 : 5).

**Ethyl 2-(diethoxyphosphoryl)-4-nitro-3-phenylhexanoate (8a).** (89%) yellow oil (Found: C, 53.6; H, 6.8. $C_{18}H_{28}NO_7P$ requires C, 53.9; H, 7.0%); $\nu_{max}$(film)/cm$^{-1}$ 1724, 1552, 1386, 1368, 1256, 1164 and 1020; $\delta_H$(250 MHz; $CDCl_3$; $Me_4Si$) 0.84–1.14 (6 H, m, C*H*$_3$CH$_2$, CH$_3$C*H*$_2$O), 1.26–1.40 (8 H, m, (C*H*$_3$CH$_2$O)$_2$P(O), C*H*$_2$), 1.60–1.99 (2 H, m, C*H*$_2$), 3.43–3.56 (1 H, m, C*H*P), 3.71–3.90 (4 H, m, CH$_3$C*H*$_2$O, C*H*, C*H*P), 3.96–4.38 (4 H, m, (CH$_3$C*H*$_2$O)$_2$P(O)), 4.69–4.77 (1 H, m, C*H*N), 5.11–5.28 (1 H, m, C*H*N), 7.07–7.17 (2 H, m, Ph) and 7.24–7.31 (3 H, m, Ph); $\delta_P$(101 MHz; $CDCl_3$; $H_3PO_4$) 19.7 (3%), 19.9 (33%), 20.3 (21%) and 20.93 (43%).

**Ethyl 3-(4-bromophenyl)-2-(diethoxyphosphoryl)-4-nitrohexanoate (8b).** (80%) yellow oil (Found: C, 45.3; H, 6.0. $C_{18}H_{27}BrNO_7P$ requires C, 45.0; H, 5.6%); $\nu_{max}$(film)/cm$^{-1}$ 1724, 1548, 1392, 1288, 1248, 1156 and 1024; $\delta_H$(250 MHz; $CDCl_3$; $Me_4Si$) 0.83–1.11 (6 H, m, C*H*$_3$CH$_2$, CH$_3$C*H*$_2$O), 1.29–1.44 (8 H, m, (C*H*$_3$CH$_2$O)$_2$P(O), C*H*$_2$), 1.58–1.97 (2 H, m, C*H*$_2$), 3.36–3.49 (1 H, m, C*H*P), 3.58–4.37 (8 H, m, (CH$_3$C*H*$_2$O)$_2$P(O), CH$_3$C*H*$_2$O, C*H*, C*H*P), 4.68–4.87 (1 H, m, C*H*N), 5.10–5.28 (1 H, m, C*H*N), 7.00–7.20 (2 H, m, 2 × C*H*-Ar) and 7.37–7.47 (2 H, m, 2 × C*H*-Ar); $\delta_P$(101 MHz; $CDCl_3$; $H_3PO_4$) 19.3 (45%), 19.9 (21%) and 20.4 (34%).

**Ethyl 2-(diethoxyphosphoryl)-4-nitro-3-*p*-tolylhexanoate (8c).** (70%) yellow oil (Found: C, 54.9; H, 7.0. $C_{19}H_{30}NO_7P$ requires C, 54.9; H, 7.3%); $\nu_{max}$(film)/cm$^{-1}$ 1732, 1552, 1392, 1368, 1252,

1160 and 1028; $\delta_H$(250 MHz; $CDCl_3$; $Me_4Si$) 0.84–1.16 (6 H, m, $CH_3CH_2$, $CH_3CH_2O$), 1.26–1.41 (8 H, m, $(CH_3CH_2O)_2P(O)$, $CH_2$), 1.60–1.83 (2 H, m, $CH_2$), 2.28 (3 H, s, $CH_3$), 2.29 (3 H, s, $CH_3$), 2.32 (3 H, s, $CH_3$), 2.34 (3 H, s, $CH_3$), 3.41–3.54 (1 H, m, CHP), 3.75–4.07 (3 H, m, $CH_3CH_2O$, CH), 4.15–4.30 (4 H, m, $(CH_3CH_2O)_2P(O)$), 4.67–4.77 (1 H, m, CHN), 5.09–5.27 (1 H, m, CHN) and 6.95–7.21 (4 H, m, 4 × CH-Ar); $\delta_P$(101 MHz; $CDCl_3$; $H_3PO_4$) 20.1 (8%), 20.3 (35%), 20.7 (22%) and 21.4 (35%).

**Ethyl 2-(diethoxyphosphoryl)-4-nitro-3-(4-nitrophenyl)hexanoate (8d).** (75%) yellow oil (Found: C, 48.2; H, 6.4. $C_{18}H_{27}N_2O_9P$ requires C, 48.4; H, 6.1%); $\nu_{max}$(film)/$cm^{-1}$ 1720, 1548, 1368, 1252, 1172 and 1024; $\delta_H$(250 MHz; $CDCl_3$; $Me_4Si$) 0.88–1.42 (12 H, m, $CH_3CH_2$, $CH_3CH_2O$, $(CH_3CH_2O)_2P(O)$, $CH_2$), 1.54–1.84 (2 H, m, $CH_2$), 3.36–4.38 (8 H, m, $(CH_3CH_2O)_2P(O)$, $CH_3CH_2O$, CH, CHP), 4.77–5.01 (1 H, m, CHN), 7.31–7.55 (2 H, m, 2 × CH-Ar) and 8.12–8.20 (2 H, m, 2 × CH-Ar); $\delta_P$(101 MHz; $CDCl_3$; $H_3PO_4$) 19.0 (39%), 19.1 (6%), 19.6 (19%) and 20.0 (26%).

### General procedure for the preparation of ethyl 3-aryl-2-diethoxyphosphoryl-4-oxohexanoates 14a–d

A solution of the corresponding ethyl 3-aryl-2-diethoxyphosphoryl-4-nitrohexanoate **8** (2.15 mmol) and Triton B (40% solution in methanol, 1.02 mL, 2.24 mmol) in anhydrous ethanol (10 mL) was cooled to −78 °C and treated with a stream of ozone until the reaction mixture turned light blue (about 30 min). Dimethyl sulfide (0.58 mL, 7.90 mmol) was then added and the mixture was allowed to warm to room temperature. The reaction mixture was stirred for an additional 20 h at that temperature and then evaporated to dryness under reduced pressure. The residue was acidified with 3 M HCl and extracted with chloroform (3 × 15 mL). Combined organic layers were dried over $MgSO_4$, filtered and the solvents were removed *in vacuo*. Crude product was purified by column chromatography (eluent: ethyl acetate–hexane 6 : 4).

**Ethyl 2-(diethoxyphosphoryl)-4-oxo-3-phenylhexanoate (14a).** (66%) yellow oil (Found: C, 58.7; H, 7.4. $C_{18}H_{27}O_6P$ requires C, 58.4; H, 7.35%); $\nu_{max}$(film)/$cm^{-1}$ 1717, 1640, 1551, 1392, 1368, 1248, 1154 and 1016; $\delta_H$(250 MHz; $CDCl_3$; $Me_4Si$) 0.88–1.41 (12 H, m, $(CH_3CH_2O)_2P(O)$, $CH_3$, $OCH_2CH_3$, 65% + 35%), 2.34–2.61 (2 H, m, $CH_2$, 65% + 35%), 3.55–4.22 (9 H, m, H-2, $(CH_3CH_2O)_2P(O)$ $CH_2$, $OCH_2CH_3$, 65% + 35%), 4.45 (1 H, dd, *J* 10.4 and 11.8, H-3, 35%), 4.56 (1 H, dd, *J* 8.4 and 11.7, H-3, 65%) and 7.23–7.34 (5 H, m, 5 × CH-Ar, 65% + 35%); $\delta_C$(62.9 MHz; $CDCl_3$; $Me_4Si$) 7.5 ($CH_2CH_3$, 35%), 7.8 ($CH_2CH_3$, 65%), 13.6 ($C(O)OCH_2CH_3$, 35%), 14.0 ($C(O)OCH_2CH_3$, 65%), 15.9 (d, *J* 6.1, $CH_3CH_2O$-P(O), 65%), 16.0 (d, *J* 6.2, $CH_3CH_2OP(O)$, 65%), 16.2 (d, *J* 5.8, $CH_3CH_2OP(O)$, 35%), 16.3 (d, *J* 5.6, $CH_3CH_2OP(O)$, 35%), 34.3 ($CH_2CH_3$, 65%), 35.3 ($CH_2CH_3$, 35%), 48.2 (d, *J* 126.8, C-2, 35%), 48.6 (d, *J* 131.6, C-2, 65%), 55.8 (d, *J* 1.9, C-3, 35%), 56.7 (C-3, 65%), 61.1 ($C(O)OCH_2CH_3$, 35%), 61.6 ($C(O)OCH_2CH_3$, 65%), 62.2 (d, *J* 6.7, $CH_3CH_2OP(O)$, 65%), 62.4 (d, *J* 7.0, $CH_3CH_2OP(O)$, 65%), 62.8 (d, *J* 6.5, $CH_3CH_2OP(O)$, 35%), 63.0 (d, *J* 6.3, $CH_3CH_2OP(O)$, 35%), 127.8 (CH-Ar, 35%), 127.9 (CH-Ar, 65%), 128.7 (2 × C-Ar, 35%), 128.7 (2 × C-Ar, 65%), 128.8 (2 × C-Ar, 35%), 129.4 (2 × C-Ar, 65%), 134.9 (C-Ar, 65%), 135.5 (d, *J* 16.2, C-Ar, 35%), 167.2 (d, *J* 5.0, C-1, 35%), 168.8 (d, *J* 4.7, C-1, 65%), 207.5 (C-4, 35%) and 208.7 (d, *J* 16.4, C-4, 65%); $\delta_P$(101 MHz; $CDCl_3$; $H_3PO_4$) 21.3 (65%) and 21.5 (35%).

**Ethyl 3-(4-bromophenyl)-2-(diethoxyphosphoryl)-4-oxohexanoate (14b).** (65%) yellow oil (Found: C, 48.3; H, 6.0. $C_{18}H_{26}BrO_6P$ requires C, 48.1; H, 5.8%); $\nu_{max}$(film)/$cm^{-1}$ 1714, 1589, 1392, 1368, 1245, 1155 and 1009; $\delta_H$(250 MHz; $CDCl_3$; $Me_4Si$) 0.90–1.41 (12 H, m, $P(O)(OCH_2CH_3)_2$, $CH_3$, $OCH_2CH_3$, 65% + 35%), 2.33–2.39 (2 H, m, $CH_2$, 65% + 35%), 3.64–4.26 (9 H, m, H-2, $(CH_3CH_2O)_2P(O)$, $CH_2$, $OCH_2CH_3$, 65% + 35%), 4.41 (1 H, dd, *J* 10.2 and 11.9, H-3, 35%), 4.51 (1 H, dd, *J* 8.2 and 11.8, H-3, 65%), 7.14–7.20 (2 H, m, 2 × CH-Ar, 65% + 35%) and 7.40–7.48 (2 H, m, 2 × CH-Ar, 65% + 35%); $\delta_C$(62.9 MHz; $CDCl_3$; $Me_4Si$) 7.3 ($CH_2CH_3$, 35%), 7.6 ($CH_2CH_3$, 65%), 13.6 ($C(O)OCH_2CH_3$, 35%), 13.8 ($C(O)OCH_2CH_3$, 65%), 15.8 (d, *J* 5.9, $CH_3CH_2OP(O)$, 65%), 15.9 (d, *J* 5.9, $CH_3CH_2OP(O)$, 65%), 16.0 (d, *J* 5.7, $CH_3CH_2OP(O)$, 35%), 16.1 (d, *J* 5.3, $CH_3CH_2OP(O)$, 35%), 34.3 ($CH_2CH_3$, 65%), 35.3 ($CH_2CH_3$, 35%), 48.1 (d, *J* 126.8, C-2, 35%), 48.3 (d, *J* 131.7, C-2, 65%), 55.0 (d, *J* 2.3, C-3, 35%), 55.8 (d, *J* 2.2, C-3, 65%), 61.1 ($C(O)OCH_2CH_3$, 35%), 61.5 ($C(O)OCH_2CH_3$, 65%), 62.2 (d, *J* 6.7, $CH_3CH_2OP(O)$, 65%), 62.4 (d, *J* 6.8, $CH_3CH_2OP(O)$, 65%), 62.7 (d, *J* 6.6, $CH_3CH_2OP(O)$, 35%), 62.9 (d, *J* 6.6, $CH_3CH_2OP(O)$, 35%), 121.9 (C-Ar, 35%), 122.0 (C-Ar, 65%), 130.2 (2 × C-Ar, 35%), 130.9 (2 × C-Ar, 65%), 131.7 (2 × C-Ar, 35%), 131.8 (2 × C-Ar, 65%), 133.8 (C-Ar, 35%), 134.5 (d, *J* 16.3, C-Ar, 65%), 166.8 (d, *J* 5.2, C-1, 35%), 168.3 (d, *J* 4.8, C-1, 65%), 207.9 (C-4, 35%) and 208.0 (d, *J* 16.1, C-4, 65%); $\delta_P$(101 MHz; $CDCl_3$; $H_3PO_4$) 21.2 (65%), 21.4 (35%).

**Ethyl 2-(diethoxyphosphoryl)-4-oxo-3-(*p*-tolyl)hexanoate (14c).** (53%) yellow oil (Found: C, 59.0; H, 7.3. $C_{19}H_{29}O_6P$ requires C, 59.4; H, 7.6%); $\nu_{max}$(film)/$cm^{-1}$ 1733, 1548, 1391, 1368, 1250, 1154 and 1016; $\delta_H$(250 MHz; $CDCl_3$; $Me_4Si$) 0.88–1.40 (12 H, m, $(CH_3CH_2O)_2P(O)$, $CH_3$, $OCH_2CH_3$, 60% + 40%), 2.28 (3 H, s, $CH_3$, 40%, 2.32 (3 H, s, $CH_3$, 60%), 2.37 (2 H, q, $CH_2$, *J* 7.3, 60% + 40%), 3.59–4.26 (9 H, m, H-2, $(CH_3CH_2O)_2P(O)$, $CH_2$, $OCH_2CH_3$, 60% + 40%), 4.40 (1 H, dd, *J* 10.3 and 11.8, H-3, 40%), 4.51 (1 H, dd, *J* 8.4 and 11.8, H-3, 60%) and 7.06–7.20 (4 H, m, 4 × CH-Ar, 60% + 40%); $\delta_C$(62.9 MHz; $CDCl_3$; $Me_4Si$) 7.6 ($CH_2CH_3$, 40%), 7.8 ($CH_2CH_3$, 60%), 13.7 ($C(O)OCH_2CH_3$, 40%), 14.0 ($C(O)OCH_2CH_3$, 60%), 15.9 (d, *J* 6.0, $CH_3CH_2OP(O)$, 60%), 16.0 (d, *J* 6.1, $CH_3CH_2OP(O)$, 60%), 16.2 (d, *J* 5.9, $(CH_3CH_2O)_2P(O)$, 40%), 16.3 (d, *J* 5.8, $CH_3CH_2OP(O)$, 40%), 21.0 ($CH_3$, 60% + 40%), 34.2 ($CH_2CH_3$, 60%), 35.2 ($CH_2CH_3$, 40%), 48.3 (d, *J* 126.5, C-2, 40%), 48.6 (d, *J* 131.5, C-2, 60%), 55.5 (d, *J* 2.8, C-3, 40%), 56.3 (C-3, 60%), 61.1 ($C(O)OCH_2CH_3$, 40%), 61.6 ($C(O)OCH_2CH_3$, 60%), 62.2 (d, *J* 7.5, $CH_3CH_2OP(O)$, 60%), 62.3 (d, *J* 7.4, $CH_3CH_2OP(O)$, 60%), 62.7 (d, *J* 6.5, $CH_3CH_2OP(O)$, 40%), 63.0 (d, *J* 6.4, $CH_3CH_2OP(O)$, 40%), 128.6 (2 × C-Ar, 40%), 129.2 (2 × C-Ar, 60%), 129.4 (2 × C-Ar, 40%), 129.5 (2 × C-Ar, 60%), 131.8 (C-Ar, 40%), 132.5 (d, *J* 16.3,C-Ar, 60%), 137.6 (C-Ar, 40%), 137.7 (C-Ar, 60%), 167.3 (d, *J* 5.1, C-1, 40%), 168.9 (d, *J* 5.0,

*C*-1, 60%), 207.6 (*C*-4, 40%) and 208.8 (d, *J* 16.2, *C*-4, 60%); $\delta_P$(101 MHz; $CDCl_3$; $H_3PO_4$) 21.4 (60%) and 21.7 (40%).

**Ethyl 2-(diethoxyphosphoryl)-3-(4-nitrophenyl)-4-oxohexanoate (14d).** (53%) colourless oil (Found: C, 52.4; H, 6.2. $C_{18}H_{26}NO_8P$ requires C, 52.1; H, 6.3%); $\nu_{max}$(film)/$cm^{-1}$ 1712, 1636, 1551, 1392, 1364, 1248, 1154 and 1024; $\delta_H$(250 MHz; $CDCl_3$; $Me_4Si$) 0.91–1.42 (12 H, m, $(CH_3CH_2O)_2P(O)$, C$H_3$, OC$H_2$C$H_3$, 60% + 40%), 2.32–2.53 (2 H, m, C$H_2$, 60% + 40%), 3.73–4.28 (9 H, m, *H*-2, $(CH_3CH_2O)_2P(O)$, C$H_2$, OC$H_2$CH$_3$, 60% + 40%), 4.58 (1 H, dd, *J* 9.9 and 11.7, *H*-3, 40%), 4.67 (1 H, dd, *J* 7.9 and 11.8, *H*-3, 60%), 7.47–7.52 (2 H, m, 2 × C*H*-Ar, 60% + 40%) and 8.14–8.22 (2 H, m, 2 × C*H*-Ar, 60% + 40%); $\delta_C$(62.9 MHz; $CDCl_3$; $Me_4Si$) 7.7 ($CH_2CH_3$, 40%), 7.9 ($CH_2CH_3$, 60%), 14.1 (C(O)OC$H_2$C$H_3$, 40%), 14.3 (C(O)OC$H_2$C$H_3$, 60%), 16.3 (d, *J* 7.7, C$H_3$CH$_2$OP(O), 60%), 16.3 (d, *J* 5.1, C$H_3$CH$_2$OP(O), 60%), 16.5 (d, *J* 6.0, C$H_3$CH$_2$OP(O), 40%), 16.5 (d, *J* 5.6, C$H_3$CH$_2$OP(O), 40%), 35.3 ($CH_2CH_3$, 60%), 36.3 ($CH_2CH_3$, 40%), 48.6 (d, *J* 127.0, *C*-2, 40%), 48.8 (d, *J* 127.6, *C*-2, 60%), 55.7 (d, *J* 2.4, *C*-3, 40%), 56.6 (*C*-3, 60%), 61.8 (C(O)O*C*H$_2$CH$_3$, 40%), 62.2 (C(O)O*C*H$_2$CH$_3$, 60%), 62.8 (d, *J* 6.7, CH$_3$*C*H$_2$OP(O), 60%), 63.1 (d, *J* 7.1, CH$_3$*C*H$_2$OP(O), 60%), 63.4 (d, *J* 6.5, CH$_3$*C*H$_2$OP(O), 40%), 63.5 (d, *J* 6.8, CH$_3$*C*H$_2$OP(O), 40%), 123.6 (2 × *C*H-Ar, 40%), 124.1 (2 × *C*H-Ar, 60%), 129.9 (2 × *C*-Ar, 40%), 130.6 (2 × *C*-Ar, 60%), 142.7 (*C*-Ar, 60 + 40%), 146.8 (*C*-Ar, 40%), 147.9 (d, *J* 5.4, *C*-Ar, 60%), 167.1 (d, *J* 5.5, *C*-1, 40%), 168.6 (d, *J* 3.9, *C*-1, 60%), 207.7 (*C*-4, 40%), and 207.9 (d, *J* 7.1, *C*-4, 60%); $\delta_P$(101 MHz; $CDCl_3$; $H_3PO_4$) 20.3 (60%) and 20.5 (40%).

### General procedure for the preparation of 4-aryl-3-diethoxyphosphoryl-5-ethyldihydrofuran-2(3*H*)-ones 16a–c

To a stirred solution of the corresponding ethyl 3-aryl-2-diethoxyphosphoryl-4-oxohexanoate **14** (5 mmol) in methanol (20 mL) potassium borohydride (405 mg, 7.5 mmol) was added in portions at 0 °C. Stirring was continued for 45 min (for compounds **14c,d**) or 55 min (for compound **14a**) and the reaction mixture was acidified to pH 1.5 with concentrated HCl. Next water (15 mL) was added and methanol was evaporated under reduced pressure. The residue was extracted with chloroform (4 × 20 mL). The combined organic layers were dried over $MgSO_4$ and the solvent was evaporated under reduced pressure to afford a crude product which was purified by column chromatography (eluent: $CHCl_3$).

**3-Diethoxyphosphoryl-5-ethyl-4-phenyldihydrofuran-2(3*H*)-one (16a).** (60%) colourless oil (Found: C, 58.7; H, 7.5. $C_{16}H_{23}O_5P$ requires C, 58.9; H, 7.1%); $\nu_{max}$(film)/$cm^{-1}$ 1772, 1508, 1164 and 1028; $\delta_H$(250 MHz; $CDCl_3$; $Me_4Si$) 0.85–1.11 (3 H, m, C$H_3$CH$_2$, 70% + 30%), 1.23–1.44 (6 H, m, $(CH_3CH_2O)_2P(O)$, 70% + 30%), 1.65–1.80 (2 H, m, CH$_3$C$H_2$, 70% + 30%), 3.27 (1 H, dd, *J* 2.6 and 24.6, C*H*P, 30%), 3.32 (1 H, dd, *J* 10.4 and 23.6, C*H*P, 70%), 3.53–3.69 (1 H, m, C*H*Ar, 70% + 30%), 3.92–4.24 (4 H, m, $(CH_3CH_2O)_2P(O)$, 70% + 30%), 4.35 (1 H, ddd, *J* 6.1, 8.5 and 12.3, OC*H*, 70%), 4.88 (1 H, ddd, *J* 5.3, 9.4 and 11.7, OC*H*, 30%) and 7.01–7.34 (5 H, m, 5 × C*H*-Ar, 70% + 30%); $\delta_C$(62.9 MHz; $CDCl_3$; $Me_4Si$) 9.7 ($CH_3CH_2$, 70% + 30%), 16.0 (d, *J* 5.9, $(CH_3CH_2O)_2P(O)$, 30% + 70%), 16.1 (d, *J* 6.5, $(CH_3CH_2O)_2P(O)$, 70% + 30%), 27.1 ($CH_3CH_2$, 70% + 30%), 47.3 (*C*-4, 70%), 50.1 (d, *J* 130.8, *C*-3, 70%), 51.4 (d, *J* 143.9, *C*-3, 30%), 53.3 (*C*-4, 30%), 63.8 (d, *J* 6.4, $(CH_3CH_2O)_2P(O)$, 70% + 30%), 64.9 (d, *J* 6.5, $(CH_3CH_2O)_2P(O)$, 70% + 30%), 83.7 (d, *J* 3.2, *C*-5, 30%), 87.7 (d, *J* 13.3, *C*-5, 70%), 125.3 (*C*-Ar, 70%), 125.7 (*C*-Ar, 30%), 128.7 (2 × *C*-Ar, 70% + 30%), 130.1 (2 × *C*-Ar, 70%), 131.3 (2 × *C*-Ar, 30%), 141.9 (*C*-Ar, 30%), 142.6 (*C*-Ar, 70%), 170.4 (d, *J* 6.5, *C*-2, 70%) and 172.9 (d, *J* 4.4, *C*-2, 30%); $\delta_P$(101 MHz; $CDCl_3$; $H_3PO_4$) 19.8 (30%) and 20.2 (70%).

**4-(4-Bromophenyl)-3-diethoxyphosphoryl-5-ethyldihydrofuran-2(3*H*)-one (16b).** (59%) colourless oil (Found: C, 47.1; H, 5.2. $C_{16}H_{22}BrO_5P$ requires C, 47.4; H, 5.5%); $\nu_{max}$(film)/$cm^{-1}$ 1770, 1508, 1168 and 1024; $\delta_H$(250 MHz; $CDCl_3$; $Me_4Si$) 0.97 (3 H, t, *J* 7.1, C$H_3$CH$_2$, 30%), 0.98 (3 H, t, *J* 7.4, C$H_3$CH$_2$, 70%), 1.15 (3 H, t, *J* 7.1, C$H_3$CH$_2$OP(O), 70%), 1.26 (3 H, t, *J* 7.1, C$H_3$CH$_2$OP(O), 70%), 1.36 (3 H, t, *J* 6.5, C$H_3$CH$_2$OP, 30%), 1.41 (3 H, t, *J* 7.1, C$H_3$CH$_2$OP, 30%), 1.75 (2 H, q, *J* 7.4, CH$_3$C$H_2$, 70%), 1.76 (2 H, q, *J* 7.1, CH$_3$C$H_2$, 30%), 3.20 (1 H, dd, *J* 2.7 and 24.7, C*H*P, 30%), 3.25 (1 H, dd, *J* 10.5 and 23.7, C*H*P, 70%), 3.43–3.70 (1 H, m, C*H*Ar, 70% + 30%), 3.94–4.09 (4 H, m, $(CH_3CH_2O)_2P(O)$, 70% + 30%), 4.20 (1 H, dt, *J* 7.1 and 9.1, OC*H*, 70%), 4.83 (1 H, ddd, *J* 5.3, 6.1 and 11.6, OC*H*, 30%), 7.13–7.17 (2 H, m, 2 × C*H*-Ar, 70% + 30%) and 7.47–7.52 (2 H, m, 2 × C*H*-Ar, 70% + 30%); $\delta_C$(62.9 MHz; $CDCl_3$; $Me_4Si$) 9.8 ($CH_3CH_2$, 70% + 30%), 16.1 (d, *J* 5.8, $(CH_3CH_2O)_2P(O)$, 30% + 70%), 16.3 (d, *J* 6.4, C$H_3$CH$_2$OP, 70% + 30%), 25.0 ($CH_3CH_2$, 70% + 30%), 41.0 (*C*-4, 70%), 49.9 (d, *J* 98.4, *C*-3, 70%), 50.4 (d, *J* 144.8, *C*-3, 30%), 56.6 (*C*-4, 30%), 62.6 (d, *J* 6.3, $(CH_3CH_2O)_2P(O)$, 70% + 30%), 63.8 (d, *J* 6.5, $(CH_3CH_2O)_2P(O)$, 70% + 30%), 83.6 (d, *J* 3.5, *C*-5, 30%), 87.5 (d, *J* 12.9, *C*-5, 70%), 129.3 (2 × *C*-Ar, 30%), 129.7 (2 × *C*-Ar, 70%), 131.1 (*C*-Ar, 70% + 30%), 132.2 (2 × *C*-Ar, 30%), 134.7 (2 x *C*-Ar, 70%), 140.8 (*C*-Ar, 70%), 141.4 (*C*-Ar, 30%), 172.3 (d, *J* 6.5, *C*-2, 70%) and 173.0 (d, *J* 4.4, *C*-2, 30%); $\delta_P$(101 MHz; $CDCl_3$; $H_3PO_4$) 19.1 (30%) and 19.6 (70%).

**3-Diethoxyphosphoryl-5-ethyl-4-(4-methylphenyl)dihydrofuran-2(3*H*)-one (16c).** (80%) colourless oil (Found: C, 59.8; H, 7.0. $C_{17}H_{25}O_5P$ requires C, 60.0; H, 7.4%); $\nu_{max}$(film)/$cm^{-1}$ 1772, 1388, 1256 and 1028; $\delta_H$(250 MHz; $CDCl_3$; $Me_4Si$) 0.86–1.20 (3 H, m, C$H_3$CH$_2$, 60% + 40%), 1.25–1.46 (6 H, m, $(CH_3CH_2O)_2$-P(O), 60% + 40%), 1.70–1.81 (2 H, m, CH$_3$C$H_2$, 60% + 40%), 2.32 (3 H, s, C$H_3$, 40%), 2.33 (3 H, s, C$H_3$, 60%), 3.23 (1 H, dd, *J* 2.6 and 24.7, C*H*P, 40%), 3.29 (1 H, dd, *J* 10.4 and 23.6, C*H*P, 60%), 3.39–3.62 (1 H, m, C*H*Ar, 60% + 40%), 3.94–4.09 (4 H, m, $(CH_3CH_2O)_2P(O)$, 60% + 40%), 4.51 (ddd, 1 H, *J* 8.5, 8.5 and 11.8, OC*H*, 40%), 4.85 (1 H, ddd, *J* 5.3, 6.2 and 11.4, OC*H*, 60%), 6.98–7.02 (2 H, m, 2 x C*H*-Ar, 60% + 40%) and 7.12–7.15 (2 H, m, 2 × C*H*-Ar, 60% + 40%); $\delta_C$(62.9 MHz; $CDCl_3$; $Me_4Si$) 9.9 ($CH_3CH_2$, 60%), 10.6 ($CH_3CH_2$, 40%), 16.0 (d, *J* 6.1, C$H_3$CH$_2$OP(O), 60% + 40%), 16.2 (d, *J* 6.2, C$H_3$CH$_2$OP(O), 60% + 40%), 21.0 ($CH_3$, 60% + 40%), 26.9 ($CH_3CH_2$, 60% + 40%), 34.1 (*C*-4, 60%), 48.0 (d, *J* 137.2, *C*-3, 40%), 48.2 (d, *J* 147.8, *C*-3, 60%), 56.3

(*C*-4, 40%), 62.2 (d, *J* 7.1, $CH_3CH_2OP(O)$, 40%), 62.5 (d, *J* 6.7, $CH_3CH_2OP(O)$, 60%), 63.0 (d, *J* 7.3, $CH_3CH_2OP(O)$, 40%), 63.5 (d, *J* 6.2, $CH_3CH_2OP(O)$, 60%), 83.7 (d, *J* 3.3, *C*-5, 40%), 87.8 (d, *J* 13.1, *C*-5, 60%), 126.2 (2 × *C*H-Ar, 60%), 127.4 (2 × *C*H-Ar, 40%), 128.6 (*C*H-Ar, 60%), 128.9 (*C*H-Ar, 40%), 129.2 (2 × *C*H-Ar, 40%), 129.6 (2 × *C*H-Ar, 60%), 135.6 (*C*-Ar, 40%), 137.6 (*C*-Ar, 60%), 168.8 (d, *J* 4.5, *C*-2, 40%) and 170.7 (d, *J* 6.4, *C*-2, 60%); $\delta_P$(101 MHz; $CDCl_3$; $H_3PO_4$) 19.6 (40%) and 20.0 (60%).

### General procedure for the preparation of 4-aryl-5-ethyl-3-methylidenedihydrofuran-2(3*H*)-ones 17a–c

To a stirred solution of a corresponding 4-aryl-3-diethoxyphosphoryl-5-ethyldihydrofuran-2(3*H*)-one **16** (1 mmol) in diethyl ether (5 mL) potassium *tert*-butoxide (134 mg, 1.2 mmol) was added and the resulting mixture was stirred at room temperature for 30 min. Then paraformaldehyde (150 mg, 5 mmol) was added in one portion. After 1 h the reaction mixture was quenched with brine (5 mL) and the water layer was extracted with diethyl ether (4 × 10 mL). The combined organic layers were dried over $MgSO_4$ and evaporated. The crude product was purified by column chromatography (eluent: $CHCl_3$).

**5-Ethyl-3-methylidene-4-phenyldihydrofuran-2(3*H*)-one (17a).** (68%) colourless oil (Found: C, 77.5; H, 6.9. $C_{13}H_{14}O_2$ requires C, 77.2; H, 7.0%); $\nu_{max}$(film)/$cm^{-1}$ 1768, 1276 and 1128; $\delta_H$(250 MHz; $CDCl_3$; $Me_4Si$) 0.89 (3 H, t, *J* 7.3, $CH_3CH_2$, 30%), 1.02 (3 H, t, *J* 7.4, $CH_3CH_2$, 70%), 1.13–1.30 (2 H, m, $CH_3CH_2$, 30%), 1.69–1.86 (2 H, m, $CH_3CH_2$, 70%), 3.79 (1 H, ddd, *J* 7.4, 3.0 and 3.0, *H*-4, 70%), 4.10 (ddd, 1 H, *J* 7.2, 2.5, and 2.5, *H*-4, 30%), 4.35 (1 H, ddd, *J* 4.9, 7.4 and 12.2, *H*-5, 70%), 4.63 (1 H, ddd, *J* 4.2, 7.2 and 9.6, *H*-5, 30%), 5.39 (1 H, d, *J* 3.0, $H_2CC$, 70%), 5.61 (1 H, d, *J* 2.5, $H_2CC$, 30%), 6.35 (1 H, d, *J* 3.0, $H_2CC$, 70%), 6.45 (1 H, d, *J* 2.5, $H_2CC$, 30%) and 7.13–7.41 (5 H, m, 5 × C*H* Ar, 70% + 30%); $\delta_C$(62.9 MHz; $CDCl_3$; $Me_4Si$) 9.6 ($CH_3CH_2$, 70%), 10.3 ($CH_3CH_2$, 30%), 25.8 ($CH_3CH_2$, 30%), 27.6 ($CH_3CH_2$, 70%), 49.2 (*C*-4, 30%), 51.6 (*C*-4, 70%), 83.0 (*C*-5, 30%), 86.8 (*C*-5, 70%), 123.9 ($CH_2C$, 30%), 124.0 ($CH_2C$, 70%), 128.2 (2 × *C*H-Ar, 70%), 129.0 (2 × *C*H-Ar, 30%), 129.2 (2 × *C*H-Ar, 70%), 129.8 (2 × *C*H-Ar, 30%), 135.4 (*C*H-Ar, 30%), 136.7 (*C*H-Ar, 70%), 137.9 (*C*-Ar, 30%), 138.2 (*C*-Ar, 70%), 139.0 ($CH_2C$, 30%), 140.6 ($CH_2C$, 70%) and 170.0 (*C*-2, 70% + 30%).

**4-(4-Bromophenyl)-5-ethyl-3-methylidenedihydrofuran-2(3*H*)-one (17b).** (69%) colourless oil (Found: C, 56.0; H, 5.0. $C_{13}H_{13}BrO_2$ requires C, 55.5; H, 4.7%); $\nu_{max}$(film)/$cm^{-1}$ 1768, 1276 and 1128; *trans*-**17b**: $\delta_H$(250 MHz; $CDCl_3$; $Me_4Si$) 1.03 (3 H, t, *J* 7.4, $CH_3CH_2$), 1.73–1.84 (2 H, m, $CH_3CH_2$), 3.77 (1 H, ddd, *J* 6.3, 3.0 and 3.0, *H*-4), 4.30 (1 H, ddd, *J* 5.2, 6.3 and 12.2, *H*-5), 5.39 (1 H, d, *J* 3.0, $H_2CC$), 6.37 (1 H, d, *J* 3.0, $H_2CC$), 7.10 (2 H, d, *J* 8.4, 2 × C*H*-Ar) and 7.52 (2 H, d, *J* 8.5, 2 × C*H*-Ar); $\delta_C$(62.9 MHz; $CDCl_3$; $Me_4Si$) 9.5 ($CH_3CH_2$), 27.7 ($CH_3CH_2$), 51.5 (*C*-4), 86.3 (*C*-5), 121.8 (*C*-Ar), 123.8 ($CH_2C$), 130.0 (2 × *C*H-Ar), 132.3 (2 × *C*H-Ar), 138.3 (*C*-Ar), 140.1 ($CH_2C$) and 169.3 (*C*-2). *cis*-**17b**: $\delta_H$(250 MHz; $CDCl_3$; $Me_4Si$) 0.91 (3 H, t, *J* 7.3, $CH_3CH_2$), 1.07–1.29 (2 H, m, $CH_3CH_2$), 4.32 (1 H, ddd, *J* 7.8, 2.5 and 2.5, *H*-4), 4.61 (1 H, ddd, *J* 4.2, 7.8, and 9.7, *H*-5), 5.59 (1 H, d, *J* 2.5, $H_2CC$), 6.45 (1 H, d, *J* 2.5, $H_2CC$), 7.03 (2 H, d, *J* 8.3, 2 × C*H*-Ar) and 7.16 (2 H, d, *J* 8.5, 2 × C*H*-Ar); $\delta_C$(62.9 MHz; $CDCl_3$; $Me_4Si$) 10.3 ($CH_3CH_2$), 25.8 ($CH_3CH_2$), 48.8 (*C*-4), 82.8 (*C*-5), 121.7 (*C*-Ar), 124.5 ($CH_2C$), 130.7 (2 × *C*H-Ar), 131.9 (2 x *C*H-Ar), 136.7 (*C*-Ar), 138.8 ($CH_2C$) and 170.0 (*C*-2).

**5-Ethyl-3-methylidene-4-*p*-tolyldihydrofuran-2(3*H*)-one (17c).** (71%) yellow oil (Found: C, 77.5; H, 7.9. $C_{14}H_{16}O_2$ requires C, 77.7; H, 7.5%); $\nu_{max}$(film)/$cm^{-1}$ 1772, 1256 and 1132; $\delta_H$(250 MHz; $CDCl_3$; $Me_4Si$) 0.89 (3 H, t, *J* 7.2, $CH_3CH_2$, 40%), 1.01 (3 H, t, *J* 7.3, $CH_3CH_2$, 60%), 1.07–1.43 (2 H, m, $CH_3CH_2$, 40%), 1.69–1.86 (2 H, m, $CH_3CH_2$, 60%), 2.34 (3 H, s, $CH_3$, 40%), 2.35 (3 H, s, $CH_3$, 60%), 3.74 (1 H, ddd, *J* 7.6, 3.0 and 3.0, *H*-4, 60%), 4.21 (1 H, ddd, *J* 7.5, 2.5 and 2.5, *H*-4, 40%), 4.31 (ddd, 1 H, *J* 4.7 and 7.6, *J* 12.2, *H*-5, 60%), 4.60 (ddd, 1 H, *J* 4.2, 7.5 and 9.3, *H*-5, 40%), 5.37 (1 H, d, *J* 3.0, $H_2CC$, 60%), 5.59 (1 H, d, *J* 2.5, $H_2CC$, 40%), 6.33 (1 H, d, *J* 3.0, $H_2CC$, 60%), 6.42 (1 H, d, *J* 2.5, $H_2CC$, 40%) and 7.01–7.19 (4 H, m, 2 × C*H*-Ar, 60% + 40%); $\delta_C$(62.9 MHz; $CDCl_3$; $Me_4Si$) 9.6 ($CH_3CH_2$, 60%), 10.2 ($CH_3CH_2$, 40%), 21.0 ($CH_3$, 60% i 40%), 25.7 ($CH_3CH_2$, 40%), 27.6 ($CH_3CH_2$, 60%), 49.0 (*C*-4, 40%), 51.7 (*C*-4, 60%), 83.3 (*C*-5, 40%), 86.7 (*C*-5, 60%), 123.9 ($CH_2C$, 40%), 123.3 ($CH_2C$, 60%), 128.1 (2 × *C*H-Ar, 60%), 128.9 (2 × *C*H-Ar, 40%), 129.3 (2 × *C*H-Ar, 60%), 129.7 (2 × *C*H-Ar, 40%), 134.5 (*C*-Ar, 40%), 136.1 (*C*-Ar, 60%), 137.3 (*C*-Ar, 40%), 137.5 (*C*-Ar, 60%), 139.2 ($CH_2C$, 40%), 140.6 ($CH_2C$, 60%) and 169.8 (*C*-2, 60% + 40%).

### General procedure for the preparation of 4-aryl-3-(diethoxyphosphoryl)-5-ethylpyrrolidin-2-ones 19a–c

To a stirred solution of ethyl 3-aryl-2-diethoxyphosphoryl-4-nitrohexanoate **8** (4 mmol) in MeOH (40 mL) $NiCl_2{\cdot}6H_2O$ (1.90 g, 8 mmol) was added at room temperature. After stirring for 10 min, $NaBH_4$ (1.52 g, 40 mmol) was added in small portions. The resulting mixture was stirred for 1 h at room temperature and filtered through a pad of Celite®. The solid material was thoroughly washed with MeOH. Methanol was removed under reduced pressure and the residue dissolved in $CHCl_3$ (30 mL) and washed with $NaHCO_3$ (15 mL). The aqueous layer was extracted with $CHCl_3$ (2 × 15 mL) and the combined organic layers dried over $MgSO_4$. Evaporation of the solvent under reduced pressure afforded a crude product which was purified by column chromatography (eluent: $CHCl_3$–MeOH 97 : 3).

**3-(Diethoxyphosphoryl)-5-ethyl-4-phenylpyrrolidin-2-one (19a).** (92%) yellow oil (Found: C, 59.4; H, 7.4. $C_{16}H_{24}NO_4P$ requires C, 59.1; H, 7.4%); $\nu_{max}$(film)/$cm^{-1}$ 1704, 1544, 1456, 1384, 1248, 1164 and 1032; $\delta_H$(250 MHz; $CDCl_3$; $Me_4Si$) 0.80 (3 H, t, *J* 7.5, $CH_3CH_2$, 55%), 0.91 (3 H, t, *J* 7.5, $CH_3CH_2$, 45%), 1.04–1.35 (8 H, m, $(CH_3CH_2O)_2P(O)$, 55% + 45%, $CH_3CH_2$, 45%), 1.55–1.85 (2 H, m, $CH_3CH_2$, 55%), 3.08 (1 H, dd, *J* 8.1 and 23.1, PC*H*, 45%), 3.12 (1 H, dd, *J* 1.1 and 22.2, PC*H*, 55%), 3.39–3.56 (1 H, m, C*H*Ar, 55% + 45%), 3.91–4.26 (5 H, m, $(CH_3CH_2O)_2P(O)$, 55% + 45% C*H*N, 55% + 45%), 6.20 (1 H, s, N*H*, 55%), 6.41 (1 H, s, N*H*, 45%)

and 7.18–7.34 (5 H, m, 5 × C*H*-Ar, 55% + 45%); $\delta_C$(62.9 MHz; $CDCl_3$; $Me_4Si$) 9.4 ($CH_3CH_2$, 45%), 9.9 ($CH_3CH_2$, 55%), 15.1 (d, *J* 6.9, $(CH_3CH_2O)_2P(O)$, 55%), 15.3 (d, *J* 6.3, $(CH_3CH_2O)_2P(O)$, 45%), 24.0 ($CH_3CH_2$, 55%), 27.4 ($CH_3CH_2$, 45%), 45.3 (*C*-4, 55%), 47.7 (*C*-4, 45%), 47.8 (d, *J* 137.4, *C*-3, 55%), 48.6 (d, *J* 145.9, *C*-3, 45%), 58.2 (d, *J* 3.8, *C*-5, 55%), 61.1 (d, *J* 6.9, $CH_3CH_2OP(O)$, 45%), 61.3 (d, *J* 6.9, $CH_3CH_2OP(O)$, 55%), 62.2 (d, *J* 6.3, $CH_3CH_2OP(O)$, 45%), 63.2 (d, *J* 6.3, $CH_3CH_2OP(O)$, 55%), 62.4 (d, *J* 8.8, *C*-5, 45%), 126.3 (*C*H-Ar, 45%), 126.4 (*C*H-Ar, 55%), 126.6 (2 × *C*H-Ar, 45%), 127.2 (2 × *C*H-Ar, 55%), 127.5 (2 × *C*H-Ar, 55%), 127.8 (2 × *C*H-Ar, 45%), 138.4 (d, *J* 10.7, *C*-Ar, 55%), 140.9 (*C*-Ar, 45%), 170.5 (*C*-2, 45%) and 171.5 (*C*-2, 55%); $\delta_P$(101 MHz; $CDCl_3$; $H_3PO_4$) 22.7 (55%) and 23.0 (45%).

**4-(Bromophenyl)-3-(diethoxyphosphoryl)-5-ethylpyrrolidin-2-one (19b).** (79%) yellow oil (Found: C, 47.9; H, 6.0. $C_{16}H_{23}BrNO_4P$ requires C, 47.5; H, 5.7%); $\nu_{max}$(film)/$cm^{-1}$ 1708, 1548, 1492, 1456, 1388, 1248, 1164 and 1056; $\delta_H$(250 MHz; $CDCl_3$; $Me_4Si$) 0.80 (3 H, t, *J* 7.1, C$H_3$CH$_2$, 40%), 0.92 (3 H, t, *J* 7.2, C$H_3$CH$_2$, 60%), 1.05–1.39 (8 H, m, $(CH_3CH_2O)_2P(O)$, 60% + 40%, $CH_3CH_2$, 40%), 1.61–1.72 (2 H, m, $CH_3CH_2$, 60%), 3.08 (1 H, dd, *J* 7.8 and 23.5, PC*H*, 40%), 3.12 (1 H, dd, *J* 3.2 and 22.9, PC*H*, 60%), 3.39–3.56 (1 H, m, C*H*Ar, 60% + 40%), 3.92–4.25 (5 H, m, $(CH_3CH_2O)_2P(O)$, 60% + 40% C*H*N, 60% + 40%), 6.35 (1 H, s, N*H*, 60%), 6.59 (1 H, s, N*H*, 40%) and 7.17–7.48 (4 H, m, 4 × C*H*-Ar, 60% + 40%); $\delta_C$(62.9 MHz; $CDCl_3$; $Me_4Si$) 10.3 ($CH_3CH_2$, 40%), 10.7 ($CH_3CH_2$, 60%), 15.9 (d, *J* 7.1, $CH_3CH_2OP(O)$, 40%), 16.0 (d, *J* 6.4, $CH_3CH_2OP(O)$, 60%), 16.1 (d, *J* 7.8, $CH_3CH_2OP(O)$, 60%), 16.2 (d, *J* 5.6, $CH_3CH_2OP(O)$, 40%), 24.9 ($CH_3CH_2$, 60%), 28.3 ($CH_3CH_2$, 40%), 46.1 (*C*-4, 60%), 48.1 (*C*-4, 40%), 48.7 (d, *J* 137.7, *C*-3, 60%), 49.6 (d, *J* 145.9, *C*-3, 40%), 59.3 (d, *J* 4.1, *C*-5, 60%), 61.9 (d, *J* 6.9, $CH_3CH_2OP(O)$, 40%), 62.2 (d, *J* 6.9, $CH_3CH_2OP(O)$, 60%), 62.9 (d, *J* 6.3, $CH_3CH_2OP(O)$, 40%), 63.1 (d, *J* 6.3, $CH_3CH_2OP(O)$, 60%), 63.4 (d, *J* 9.4, *C*-5, 40%), 120.9 (*C*-Ar, 40%), 127.1 (*C*-Ar, 60%), 127.2 (2 × *C*H-Ar, 40%), 127.5 (2 0× *C*H-Ar, 40%), 128.0 (2 × *C*H-Ar, 60%), 128.3 (2 × *C*H-Ar, 60%), 139.3 (*C*-Ar, 60%), 141.8 (*C*-Ar, 40%), 171.6 (*C*-2, 40%) and 172.6 (d, *J* 3.1, *C*-2, 60%); $\delta_P$(101 MHz; $CDCl_3$; $H_3PO_4$) 23.1 (60%) and 23.3 (40%).

**3-(Diethoxyphosphoryl)-5-ethyl-4-(4-methylphenyl)pyrrolidin-2-one (19c).** (85%) yellow oil (Found: C, 60.4; H, 7.5. $C_{17}H_{26}NO_4P$ requires C, 60.2; H, 7.7%); $\nu_{max}$(film)/$cm^{-1}$ 1704, 1520, 1440, 1372, 1336, 1312, 1256, 1184, 1160, 1052 and 1016; $\delta_H$(250 MHz; $CDCl_3$; $Me_4Si$) 0.79 (3 H, t, *J* 7.4, C$H_3$CH$_2$, 60%), 0.91 (3 H, t, *J* 7.4, C$H_3$CH$_2$, 40%), 1.03–1.35 (8 H, m, $(CH_3CH_2O)_2P(O)$, 60% + 40%, $CH_3CH_2$, 40%), 1.54–1.71 (2 H, m, $CH_3CH_2$, 60%), 2.33 (3 H, s, C$H_3$, 60%), 2.34 (3 H, s, C$H_3$, 40%), 3.06 (1 H, dd, *J* 5.8 and 23.3, PC*H*, 40%), 3.08 (1 H, dd, *J* 3.5 and 23.1, PC*H*, 60%), 3.71–3.91 (1 H, m, C*H*Ar, 60% + 40%), 3.96–4.25 (5 H, m, $(CH_3CH_2O)_2P(O)$, 60% + 40% C*H*N, 60% + 40%), 6.07 (1 H, s, N*H*, 60%), 6.29 (1 H, s, N*H*, 40%) and 7.08–7.15 (4 H, m, 4 × C*H*-Ar, 60% + 40%); $\delta_C$(62.9 MHz; $CDCl_3$; $Me_4Si$) 10.3 ($CH_3CH_2$, 40%), 10.8 ($CH_3CH_2$, 60%), 16.0 (d, *J* 6.4, $(CH_3CH_2O)_2P(O)$, 60%), 16.3 (d, *J* 6.1, $(CH_3CH_2O)_2P(O)$, 40%), 20.9 ($CH_3$, 60% + 40%), 24.9 ($CH_3CH_2$, 60%), 28.4 ($CH_3CH_2$, 40%), 45.8 (*C*-4, 60%), 48.2 (d, *J* 2.5, *C*-4, 40%), 49.0 (d, *J* 136.7, *C*-3, 60%), 49.6 (d, *J* 145.3, *C*-3, 40%), 59.3 (d, *J* 2.1, *C*-5, 60%), 62.0 (d, *J* 6.3, $CH_3CH_2OP(O)$, 40%), 62.2 (d, *J* 6.7, $CH_3CH_2OP(O)$, 60%), 63.0 (d, *J* 6.5, $CH_3CH_2OP(O)$, 40%), 63.2 (d, *J* 6.7, $CH_3CH_2OP(O)$, 60%), 63.4 (d, *J* 9.4, *C*-5, 40%), 127.4 (2 × *C*H-Ar, 40%), 128.0 (2 × *C*H-Ar, 60%), 129.4 (2 × *C*H-Ar, 60%), 129.4 (2 × *C*H-Ar, 40%), 136.3 (*C*-Ar, 60%), 136.4 (*C*-Ar, 40%), 136.9 (d, *J* 6.7, *C*-Ar, 60%), 138.9 (d, *J* 4.4, *C*-Ar, 40%), 171.5 (*C*-2, 40%) and 172.5 (*C*-2, 60%); $\delta_P$(101 MHz; $CDCl_3$; $H_3PO_4$) 23.1 (60%) and 23.4 (40%).

### General procedure for the preparation of *tert*-butyl 4-aryl-3-(diethoxyphosphoryl)-5-ethyl-2-oxopyrrolidine-1-carboxylates 20a–c

To a stirred solution of a corresponding 4-aryl-3-(diethoxyphosphoryl)-5-ethylpyrrolidin-2-one **19** (3 mmol) in $CH_2Cl_2$ (15 mL) $Boc_2O$ (785 mg, 3.6 mmol) and DMAP (92 mg, 0.75 mmol) were added. The resulting mixture was left at room temperature for 3 h and then washed with 3% aqueous solution of $KHSO_4$ (10 mL), water (10 mL) and dried over $MgSO_4$. Evaporation of the solvent under reduced pressure afforded a crude product which was purified by column chromatography (eluent: $CHCl_3$–acetone 95 : 5).

***tert*-Butyl 3-(diethoxyphosphoryl)-5-ethyl-4-phenyl-2-oxopyrrolidine-1-carboxylate (20a).** (69%) yellow oil (Found: C, 59.6; H, 7.9. $C_{21}H_{32}NO_6P$ requires C, 59.3; H, 7.6%); $\nu_{max}$(film)/$cm^{-1}$ 1764, 1724, 1364, 1300, 1252, 1164 and 1012; $\delta_H$(250 MHz; $CDCl_3$; $Me_4Si$) 0.52 (3 H, t, *J* 7.5, C$H_3$CH$_2$, 45%), 0.94 (3 H, t, *J* 7.1, C$H_3$CH$_2$, 55%), 1.24–1.35 (8 H, m, $(CH_3CH_2O)_2P(O)$, 55% + 45%, $CH_3CH_2$, 45%), 1.53 (9 H, s, $(CH_3)_3C$, 45%), 1.54 (9 H, s, $(CH_3)_3C$, 55%), 1.77–2.03 (2 H, m, $CH_3CH_2$, 55%), 3.15 (1 H, dd, *J* 5.4 and 26.0, PC*H*, 45%), 3.53 (1 H, dd, *J* 11.6 and 22.3, PC*H*, 55%), 3.75–3.94 (1 H, m, C*H*Ar, 55% + 45%), 3.97–4.31 (4 H, m, $(CH_3CH_2O)_2P(O)$, 55% + 45%) and 7.21–7.38 (5 H, m, 5 × C*H*-Ar, 55% + 45%); $\delta_C$(62.9 MHz; $CDCl_3$; $Me_4Si$) 9.0 ($CH_3CH_2$, 45%), 10.2 ($CH_3CH_2$, 55%), 15.6 (d, *J* 6.5, $(CH_3CH_2O)_2P(O)$, 45%), 16.1 (d, *J* 6.5, $(CH_3CH_2O)_2P(O)$, 55%), 23.8 ($CH_3CH_2$, 55%), 26.5 ($CH_3CH_2$, 45%), 27.8 ($(CH_3)_3C$, 55% + 45%), 42.2 (*C*-4, 45%), 43.2 (d, *J* 2.2, *C*-4, 55%), 45.7 (d, *J* 149.7, *C*-3, 55%), 51.1 (d, *J* 140.1, *C*-3, 45%), 61.8 (d, *J* 11.7, *C*-5, 45%), 61.9 (d, *J* 6.9, $CH_3CH_2OP(O)$, 55%), 62.3 (d, *J* 6.7, $(CH_3CH_2O)_2P(O)$, 45%), 63.4 (d, *J* 6.2, $CH_3CH_2OP(O)$, 55%), 66.0 (d, *J* 5.2, *C*-5, 55%), 83.1 ($(CH_3)_3C$, 55%), 83.2 ($(CH_3)_3C$, 45%), 126.6 (*C*H-Ar, 45%), 127.4 (2 × *C*H-Ar, 45%), 128.2 (2 × *C*H-Ar, 55%), 128.3 (2 × *C*H-Ar, 55% + 45%), 129.0 (*C*H-Ar, 55%), 135.8 (*C*-Ar, 45%), 143.5 (d, *J* 7.7, *C*-Ar, 55%), 149.5 (N*C*(O), 45% + 55%), 168.1 (*C*-2, 55%) and 169.6 (*C*-2, 45%); $\delta_P$(101 MHz; $CDCl_3$; $H_3PO_4$) 21.2 (45%) and 21.9 (55%).

***tert*-Butyl 4-(bromophenyl)-3-(diethoxyphosphoryl)-5-ethyl-2-oxopyrrolidine-1-carboxylate (20b).** (72%) yellow oil (Found: C, 50.3; H, 5.9. $C_{21}H_{31}BrNO_6P$ requires C, 50.0; H, 6.2%); $\nu_{max}$(film)/$cm^{-1}$ 1784, 1724, 1368, 1300, 1256, 1156 and 1028;

$\delta_H$(250 MHz; $CDCl_3$; $Me_4Si$) 0.54 (3 H, t, *J* 7.6, C$H_3$CH$_2$, 40%), 0.96 (3 H, t, *J* 7.6, C$H_3$CH$_2$, 60%), 1.23–1.46 (8 H, m, (C$H_3$CH$_2$O)$_2$P(O), 60% + 40%, CH$_3$C$H_2$, 40%), 1.55 (9 H, s, (C$H_3$)$_3$C, 40%), 1.55 (9 H, s, (C$H_3$)$_3$C, 60%), 1.91–2.01 (2 H, m, CH$_3$C$H_2$, 60%), 3.18 (1 H, dd, *J* 4.9 and 26.0, PC*H*, 40%), 3.56 (1 H, dd, *J* 11.7 and 22.4, PC*H*, 60%), 3.72–3.91 (1 H, m, C*H*Ar, 60% + 40%), 4.08–4.31 (4 H, m, (CH$_3$C$H_2$O)$_2$P(O), 60% + 40%) and 7.10–7.51 (4 H, m, 4 × C*H*-Ar, 60% + 40%); $\delta_C$(62.9 MHz; $CDCl_3$; $Me_4Si$) 9.0 (*C*H$_3$CH$_2$, 40%), 10.3 (*C*H$_3$CH$_2$, 60%), 15.7 (d, *J* 6.6, *C*H$_3$CH$_2$OP(O), 40%), 16.1 (d, *J* 6.8, *C*H$_3$CH$_2$OP(O), 40%), 16.2 (d, *J* 6.4, (*C*H$_3$CH$_2$O)$_2$P(O), 60%), 23.8 (CH$_3$*C*H$_2$, 60%), 26.6 (CH$_3$*C*H$_2$, 40%), 27.9 ((*C*H$_3$)$_3$C, 60% + 40%), 42.2 (d, *J* 1.8, *C*-4, 40%), 43.3 (*J* 2.7, *C*-4, 60%), 45.8 (d, *J* 149.4, *C*-3, 60%), 51.2 (d, *J* 140.2, *C*-3, 40%), 61.8 (d, *J* 11.6, *C*-5, 40%), 62.0 (d, *J* 6.7, CH$_3$*C*H$_2$OP(O), 60%), 62.3 (d, *J* 6.9, CH$_3$*C*H$_2$OP(O), 40%), 63.5 (d, *J* 6.4, CH$_3$*C*H$_2$OP(O), 60%), 63.6 (d, *J* 6.6, CH$_3$*C*H$_2$O-P(O), 40%), 66.1 (d, *J* 5.0, *C*-5, 60%), 83.2 ((CH$_3$)$_3$*C*, 60%), 83.3 ((CH$_3$)$_3$*C*, 40%), 126.6 (2 × *C*H-Ar, 60%), 127.3 (*C*-Ar, 40%), 127.4 (*C*-Ar, 40%), 128.3 (2 × *C*H-Ar, 40%), 128.3 (2 × *C*H-Ar, 60%), 129.1 (2 × *C*H-Ar, 40%), 135.9 (d, *J* 2.0, *C*-Ar, 40%), 143.6 (d, *J* 7.5, *C*-Ar, 60%), 149.5 (N*C*(O), 60% + 40%), 168.0 (d, *J* 2.9, *C*-2, 40%) and 168.2 (d, *J* 1.2, *C*-2, 60%);. $\delta_P$(101 MHz; $CDCl_3$; $H_3PO_4$) 21.2 (60%) and 21.9 (40%).

***tert*-Butyl 3-(diethoxyphosphoryl)-5-ethyl-4-(4-methylphenyl)-2-oxopyrrolidine-1-carboxylate (20c).** (82%) yellow oil (Found: C, 59.9; H, 7.4. $C_{22}H_{34}NO_6P$ requires C, 60.1; H, 7.8%); $\nu_{max}$(film)/cm$^{-1}$ 1784, 1724, 1368, 1300, 1256, 1160 and 1024; $\delta_H$(250 MHz; $CDCl_3$; $Me_4Si$) 0.53 (3 H, t, *J* 7.6, C$H_3$CH$_2$, 30%), 0.95 (3 H, t, *J* 7.6, C$H_3$CH$_2$, 70%), 1.27 (3 H, t, *J* 7.0, C$H_3$CH$_2$OP(O), 70% + 30%), 1.31 (3 H, t, *J* 7.0, C$H_3$CH$_2$O-P(O), 70% + 30%), 1.32–1.42(2 H, m, CH$_3$C$H_2$, 30%), 1.53 (9 H, s, (C$H_3$)$_3$C, 30%), 1.53 (9 H, s, (C$H_3$)$_3$C, 70%), 1.71–1.94 (2 H, m, CH$_3$C$H_2$, 70%), 2.32 (3 H, s, C$H_3$, 30%), 2.34 (3 H, s, C$H_3$, 70%), 2.98 (1 H, dd, *J* 4.2 and 26.1, PC*H*, 30%), 3.50 (1 H, dd, *J* 5.7 and 22.4, PC*H*, 70%), 3.75–4.07 (1 H, m, C*H*Ar, 70% + 30%), 4.19–4.29 (4 H, m, (CH$_3$C$H_2$O)$_2$P(O), 70% + 30%) and 7.05–7.16 (4 H, m, 4 × C*H*-Ar, 70% + 30%); $\delta_C$(62.9 MHz; $CDCl_3$; $Me_4Si$) 8.9 (*C*H$_3$CH$_2$, 30%), 10.0 (*C*H$_3$CH$_2$, 70%), 15.5 (d, *J* 6.5, *C*H$_3$CH$_2$OP(O), 70%), 15.9 (d, *J* 6.9, *C*H$_3$CH$_2$OP(O), 30%), 16.0 (d, *J* 6.3, *C*H$_3$CH$_2$OP(O), 70%), 16.1 (d, *J* 6.6, *C*H$_3$CH$_2$OP(O), 30%), 20.7 (*C*H$_3$, 70%), 20.7 (*C*H$_3$, 30%), 23.5 (CH$_3$*C*H$_2$, 70%), 26.4 (CH$_3$*C*H$_2$, 30%), 27.6 ((*C*H$_3$)$_3$C, 70%), 27.7 ((*C*H$_3$)$_3$C, 30%), 41.7 (*C*-4, 30%), 42.7 (*C*-4, 70%), 45.7 (d, *J* 149.1, *C*-3, 70%), 51.1 (d, *J* 140.0, *C*-3, 30%), 61.6 (d, *J* 13.0, *C*-5, 30%), 61.8 (d, *J* 7.2, CH$_3$*C*H$_2$O-P(O), 70%), 62.2 (d, *J* 6.8, CH$_3$*C*H$_2$OP(O), 30%), 63.1 (d, *J* 6.4, CH$_3$*C*H$_2$OP(O), 70%), 63.4 (d, *J* 6.4, CH$_3$*C*H$_2$OP(O), 30%), 66.18 (d, *J* 4.8, *C*-5, 70%), 82.8 ((CH$_3$)$_3$*C*, 70%), 83.1 ((CH$_3$)$_3$*C*, 30%), 126.4 (2 × *C*H-Ar, 30%), 127.9 (2 × *C*H-Ar, 70%), 128.7 (2 × *C*H-Ar, 70%), 129.5 (2 × *C*H-Ar, 30%), 132.6 (*C*-Ar, 70%), 136.8 (*C*-Ar, 30%), 136.9 (*C*-Ar, 30%), 140.5 (d, *J* 7.5, *C*-Ar, 70%), 149.3 (N*C*(O), 70%), 149.4 (N*C*(O), 70%), 168.0 (*C*-2, 30%) and 168.1 (*C*-2, 70%); $\delta_P$(101 MHz; $CDCl_3$; $H_3PO_4$) 21.6 (30%) and 22.3 (70%).

**General procedure for the preparation of *tert*-butyl 3-aryl-2-ethyl-4-methylidene-5-oxopyrrolidine-1-carboxylates 21a–c**

To a stirred solution of a corresponding *tert*-butyl 4-aryl-3-(diethoxyphosphoryl)-5-ethyl-2-oxopyrrolidine-1-carboxylate **20** (1 mmol) in THF (5 mL) potassium *tert*-butoxide (269 mg, 2.4 mmol) was added and the resulting mixture was stirred at room temperature for 30 min. Then paraformaldehyde (150 mg, 5 mmol) was added in one portion. After 1 h the reaction mixture was quenched with brine (15 mL), THF was removed under reduced pressure and the water layer was extracted with $CH_2Cl_2$ (2 × 15 mL). The combined organic layers were dried over $MgSO_4$ and evaporated. The crude product was purified by column chromatography (eluent: $CHCl_3$–acetone 98 : 2).

***tert*-Butyl 2-ethyl-3-phenyl-4-methylidene-5-oxopyrrolidine-1-carboxylate (21a).** (59%) pale-yellow oil (Found: C, 71.3; H, 7.9. $C_{18}H_{23}NO_3$ requires C, 71.7; H, 7.7%); $\nu_{max}$(film)/cm$^{-1}$ 1782, 1736, 1296 and 1146; $\delta_H$(250 MHz; $CDCl_3$; $Me_4Si$) 0.48 (3 H, t, *J* 7.5, C$H_3$CH$_2$, 45%), 0.98 (3 H, t, *J* 7.5, C$H_3$CH$_2$, 55%), 1.36–1.43 (2 H, m, CH$_3$C$H_2$, 45%), 1.57 (9 H, s, (C$H_3$)$_3$C, 55%), 1.59 (9 H, s, (C$H_3$)$_3$C, 45%), 1.82–1.90 (2 H, m, CH$_3$C$H_2$, 55%), 3.73–3.75 (1 H, m, C*H*Ar, 55%), 4.02 (1 H, dt, *J* 2.7 and 8.2, C*H*N, 55%), 4.28–4.32 (2 H, m, C*H*N, C*H*Ar, 45%), 5.43 (1 H, d, *J* 2.2, C$H_2$C, 45%), 5.48 (1 H, d, *J* 2.6, C$H_2$C, 55%), 6.37 (1 H, d, *J* 2.2, C$H_2$C, 45%), 6.42 (1 H, d, *J* 2.6, C$H_2$C, 55%) and 7.31–7.45 (5 H, m, 5 × C*H*-Ar, 55% + 45%); $\delta_C$(62.9 MHz; $CDCl_3$; $Me_4Si$) 5.5 (*C*H$_3$CH$_2$, 55%), 9.7 (*C*H$_3$CH$_2$, 45%), 22.4 (CH$_3$*C*H$_2$, 55%), 22.6 (CH$_3$*C*H$_2$, 45%), 27.9 ((*C*H$_3$)$_3$C, 45%), 28.0 ((*C*H$_3$)$_3$C, 55%), 47.9 (*C*-3, 55%), 61.2 (*C*-4, 55%), 64.5 (*C*-3, 45%), 68.7 (*C*-4, 45%), 82.6 ((CH$_3$)$_3$*C*, 55%), 83.2 ((CH$_3$)$_3$*C*, 45%), 120.9 (*C*H$_2$C, 55%), 122.7 (*C*H$_2$C, 45%), 128.0 (2 × *C*H-Ar, 55%), 128.4 (2 × *C*H-Ar, 45%), 128.6 (2 × *C*H-Ar, 55%), 129.0 (2 × *C*H-Ar, 45%), 129.2 (*C*H-Ar, 55%), 129.9 (*C*H-Ar, 45%), 130.4 (*C*-Ar, 55%), 130.8 (*C*-Ar, 45%), 132.3 (CH$_2$*C*, 55%), 135.6 (CH$_2$*C*, 45%), 149.6 (N*C*(O), 45%), 153.5 (N*C*(O), 55%), 169.8 (*C*-5, 45%) and 170.4 (*C*-5, 55%).

***tert*-Butyl 3-(4-bromophenyl)-2-ethyl-4-methylidene-5-oxopyrrolidine-1-carboxylate (21b).** (52%) pale-yellow oil (Found: C, 57.0; H, 6.1. $C_{18}H_{22}BrNO_3$ requires C, 56.8; H, 5.8%); $\nu_{max}$(film)/cm$^{-1}$ 1780, 1736, 1296 and 1152; $\delta_H$(250 MHz; $CDCl_3$; $Me_4Si$) 0.55 (3 H, t, *J* 7.2, C$H_3$CH$_2$, 40%), 0.98 (3 H, t, *J* 7.5, C$H_3$CH$_2$, 60%), 1.18–1.28 (2 H, m, CH$_3$C$H_2$, 40%), 1.54 (9 H, s, (C$H_3$)$_3$C, 40%), 1.60 (9 H, s, (C$H_3$)$_3$C, 60%), 1.83–1.99 (2 H, m, CH$_3$C$H_2$, 60%), 3.74 (1 H, dt, *J* 2.4 and 6.7, C*H*Ar, 60%), 4.03 (1 H, dt, *J* 2.8 and 8.4, C*H*N, 60%), 4.24–4.34 (2 H, m, C*H*N, C*H*Ar, 40%), 5.44 (1 H, d, *J* 2.0, C$H_2$C, 60%), 5.48 (1 H, d, *J* 2.6, C$H_2$C, 40%), 6.37 (1 H, d, *J* 2.0, C$H_2$C, 60%), 6.42 (1 H, d, *J* 2.6, C$H_2$C, 40%) and 7.29–7.51 (4 H, m, 4 × C*H*-Ar, 60% + 40%); $\delta_C$(62.9 MHz; $CDCl_3$; $Me_4Si$) 5.3 (*C*H$_3$CH$_2$, 60%), 8.68 (*C*H$_3$CH$_2$, 40%), 22.4 (CH$_3$*C*H$_2$, 60%), 27.2 (CH$_3$*C*H$_2$, 40%), 27.7 ((*C*H$_3$)$_3$C, 60%), 27.8 ((*C*H$_3$)$_3$C, 40%), 46.3 (*C*-3, 60%), 61.6 (*C*-4, 60%), 64.4 (*C*-3, 40%), 68.2 (*C*-4, 40%), 82.9 ((CH$_3$)$_3$*C*, 40%), 83.0 ((CH$_3$)$_3$*C*, 60%), 120.7 (*C*H$_2$C, 40%), 122.5 (*C*H$_2$C, 60%), 126.8 (*C*-Ar, 60%), 126.9 (*C*-Ar, 40%), 128.3 (2 × *C*H-Ar, 60%), 128.4 (2 × *C*H-Ar, 40%), 128.7 (2 × *C*H-Ar, 40%),

128.8 (2 × *C*H-Ar, 60%), 130.2 (*C*-Ar, 60%), 130.7 (*C*-Ar, 40%), 142.7 ($CH_2C$, 60%), 142.9 ($CH_2C$, 40%), 149.2 (N*C*(O), 60%), 150.1 (N*C*(O), 40%), 160.5 (*C*-5, 40%) and 169.6 (*C*-5, 60%).

***tert*-Butyl 2-ethyl-4-methylidene-3-(4-methylphenyl)-5-oxopyrrolidine-1-carboxylate (21c).** (80%) pale-yellow oil (Found: C, 72.5; H, 8.2. $C_{19}H_{25}NO_3$ requires C, 72.4; H, 8.0%); $\nu_{max}$(film)/cm$^{-1}$ 1780, 1716, 1368, 1300 and 1156; $\delta_H$(250 MHz; $CDCl_3$; $Me_4Si$) 0.49 (3 H, t, *J* 7.4, C$H_3$CH$_2$, 30%), 0.99 (3 H, t, *J* 7.5, C$H_3$CH$_2$, 70%), 1.22–1.42 (2 H, m, CH$_3$C$H_2$, 30%), 1.56 (9 H, s, (C$H_3$)$_3$C, 70% + 30%), 1.86–1.95 (2 H, m, CH$_3$C$H_2$, 70%), 2.34 (3 H, s, C$H_3$, 70%), 2.36 (3 H, s, C$H_3$, 30%), 3.70–3.71 (1 H, m, C*H*Ar, 70%), 4.01 (1 H, dt, *J* 2.8 and 8.4, C*H*N, 70%), 4.25–4.28 (2 H, m, C*H*N, C*H*Ar, 30%), 5.43 (1 H, d, *J* 2.0, C$H_2$C, 70%), 5.46 (1 H, d, *J* 2.5, C$H_2$C, 30%), 6.38 (1 H, d, *J* 2.0, C$H_2$C, 70%), 6.40 (1 H, d, *J* 2.5, C$H_2$C, 30%) and 7.05–7.19 (4 H, m, 4 × C*H*-Ar, 70% + 30%); $\delta_C$(62.9 MHz; $CDCl_3$; $Me_4Si$) 5.3 (*C*H$_3$CH$_2$, 30%), 10.1 (*C*H$_3$CH$_2$, 70%), 20.9 (*C*H$_3$, 70%), 21.2 (*C*H$_3$, 30%), 22.6 (CH$_3$*C*H$_2$, 30%), 25.2 (CH$_3$*C*H$_2$, 70%), 27.8 ((*C*H$_3$)$_3$C, 70%), 27.9 ((*C*H$_3$)$_3$C, 30%), 47.4 (*C*-3, 70%), 60.9 (*C*-4, 70%), 61.6 (*C*-3, 30%), 68.6 (*C*-4, 30%), 82.7 ((CH$_3$)$_3$*C*, 70%), 82.9 ((CH$_3$)$_3$*C*, 30%), 120.6 (*C*H$_2$C, 70%), 126.8 (*C*-Ar, 70%), 127.0 (*C*-Ar, 30%), 127.9 (*C*H$_2$C, 30%), 128.3 (2 × *C*H-Ar, 30%), 129.2 (2 × *C*H-Ar, 70%), 129.3 (2 × *C*H-Ar, 70%), 128.6 (2 × *C*H-Ar, 30%), 132.4 (*C*-Ar, 70%), 137.2 (*C*-Ar, 30%), 140.7 (CH$_2$*C*, 30%), 142.0 (CH$_2$*C*, 70%), 149.3 (N*C*(O), 30%), 150.3 (N*C*(O), 70%), 166.3 (*C*-5, 70%) and 169.8 (*C*-5, 30%).

### Preparation of 4-(4-bromophenyl)-5-ethyl-3-methylidenepyrrolidin-2-one (22b)

To a solution of *tert*-butyl 3-(4-bromophenyl)-2-ethyl-4-methylidene-5-oxopyrrolidine-1-carboxylate (**21b**) (1 mmol) in $CH_2Cl_2$ (10 mL) trifluoroacetic acid (5 mL) was added. The reaction mixture was left at room temperature for 1 h. The solvent was evaporated and the residue was dissolved in $CH_2Cl_2$ (15 mL) and washed with $NaHCO_3$ (15 mL), water (15 mL) and dried over $MgSO_4$. Evaporation of the solvent under reduced pressure afforded a crude product which was purified by column chromatography (eluent: $CHCl_3$–acetone 95 : 5) to afford pure 4-(4-bromophenyl)-5-ethyl-3-methylidenepyrrolidin-2-one (**22b**) (68%) as a pale-yellow oil (Found: C, 55.5; H, 5.3. $C_{13}H_{14}BrNO$ requires C, 55.7; H, 5.0%); $\nu_{max}$(film)/cm$^{-1}$ 1688, 1656, 1360, 1312 and 1264; $\delta_H$(250 MHz; $CDCl_3$; $Me_4Si$) 0.80 (3 H, t, *J* 7.3, C$H_3$CH$_2$, 40%), 0.96 (3 H, t, *J* 7.4, C$H_3$CH$_2$, major), 1.17–1.34 (2 H, m, CH$_3$C$H_2$, 40%), 1.58–1.75 (2 H, m, CH$_3$C$H_2$, 60%), 3.56–3.68 (1 H, m, C*H*, 60% + 40%), 4.34 (1 H, dt, *J* 2.8 and 7.9, C*H*Ar, 60%), 4.53–4.58 (1 H, m, C*H*Ar, 40%), 5.12 (1 H, d, *J* 2.4, C$H_2$C, 60%), 5.31 (1 H, d, *J* 2.5, C$H_2$C, 40%), 6.10 (1 H, d, *J* 2.4, C$H_2$C, 60%), 6.21 (1 H, d, *J* 2.5, C$H_2$C, 40%), 7.08–7.48 (4 H, m, 4 × C*H*-Ar, 60% + 40%), 7.81 (1 H, bs, N*H*, 60%) and 7.92 (1 H, bs, N*H*, 40%); $\delta_C$(62.9 MHz; $CDCl_3$; $Me_4Si$) 7.8 (*C*H$_3$CH$_2$, 40%), 10.0 (*C*H$_3$CH$_2$, 60%), 28.7 (CH$_3$*C*H$_2$, 60%), 29.7 (CH$_3$*C*H$_2$, 40%), 51.7 (*C*-4, 60%), 53.4 (*C*-4, 40%), 62.2 (*C*-5, 60%), 62.3 (*C*-5, 40%), 117.0 (*C*H$_2$C, 40%), 118.4 (*C*H$_2$C, 60%), 127.2 (2 × *C*H-Ar, 40%), 128.2 (2 × *C*H-Ar, 60%), 128.3 (2 × *C*H-Ar, 40%), 128.6 (*C*-Ar, 60%), 128.7 (*C*-Ar, 40%), 128.9 (2 × *C*H-Ar, 60%), 132.0 (*C*-Ar, 60%), 133.1 (*C*-Ar, 40%), 141.5 ($CH_2C$, 40%), 144.7 ($CH_2C$, 60%), 169.9 (*C*-2, 40%) and 170.3 (*C*-2, 60%).

### Cells and cytotoxicity assays

Mouse leukemia L-1210 cells were cultured in RPMI 1640 medium (Sigma, St. Louis, MO) supplemented with 10% foetal calf serum (Gibco, Berlin, Germany), gentamycin (50 μg mL$^{-1}$) and 0.02 M HEPES buffer (Gibco). Cytostatic effects were assayed by measuring inhibitory effects on L-1210 cell proliferation. In this assay, cells were seeded in 2 mL aliquots onto a 24-well plate (NUNC, Denmark) at a concentration of $1.5 \times 10^3$ cells mL$^{-1}$. After 24 h drug solution was added and incubation was carried out for an additional 48 h. The cell number relative to control was determined by a tetrazolium dye method.[25]

Human leukemia promyelocytic HL-60 and lymphoblastic NALM-6 cell lines were used. Leukemia cells were cultured in RPMI 1640 medium supplemented with 10% heat-inactivated foetal bovine serum (Invitrogen, Paisley, UK) and antibiotics (100 μg mL$^{-1}$ streptomycin and 100 U/mL penicillin). Cells were grown at 37 °C in a humidified atmosphere of 5% $CO_2$ in air. Cytotoxic activity was determined by the MTT [3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide, Sigma, St. Louis, USA] assay.[26] Exponentially growing leukemia cells were seeded at $8 \times 10^3$/well on a 96-well plate (Nunc, Roskilde, Denmark). Stock solutions of the analyzed compounds were freshly prepared in DMSO and diluted with complete culture medium to obtain the concentration range from $10^{-7}$ to $10^{-3}$ M. Cells were exposed to the test compounds for 46 h, then MTT reagent was added and incubation was continued for 2 h. After incubation, MTT–formazan crystals were dissolved in 20% SDS and 50% DMF at pH 4.7 and absorbance was read at 562 and 630 nm on an ELISA-plate reader (ELX 800, Bio-Tek, USA). As a control, cultured cells were grown in the absence of drugs. The values of $IC_{50}$ (the concentration of the tested compound required to reduce the cells survival fraction to 50% of the control) were calculated from concentration-response curves and used as a measure of cellular sensitivity to a given treatment. Data points represent means of at least 6 repeats ± SD.

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