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A convenient synthesis and cytotoxic evaluation of *N*-unsubstituted α-methylene-γ-lactams

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ABSTRACT

Chemoselective reduction of 3-aryl-2-diethoxyphosphoryl-4-nitroalkanoates provided the corresponding α-diethoxyphosphoryl-γ-lactams in completely diastereoselective manner. The products were shown to be useful substrates for the synthesis of mono-β-substituted and β,γ-disubstituted α-methylene-γ-lactams. Cytotoxicity of these compounds was evaluated.

1. Introduction

α-Methylene-γ-lactams serve as isosteric analogs of the naturally occurring α-methylene-γ-lactones. In the recent years, the synthesis of α-methylene-γ-lactams has received a considerable attention as a consequence of the proven biological properties of this structural motif.[1–3] The *N*-substituted α-methylene-γ-lactams are readily available by addition of various organometallic reagents derived from 2-(bromomethyl)acrylates to aldimines.[4–9] Other alternative approaches involve alkylation of dianions derived from secondary methacrylamides with aldehydes and subsequent cyclization of the resulting α-methylene-γ-hydroxyamides,[10] regioselective addition of primary amines to (*E*)-1-alkyl-2,3-dimethoxycarbonyl butadienes[11] as well as regioselective ring-opening reactions of *N*-tosylaziridines with aniline.[12] To the best of our knowledge, the Michael addition of nitroalkanes to acetates of Baylis–Hillman adducts followed by chemoselective reduction and lactamization of the resulting 2-alkylidene-4-nitroalkanoates is the only method for the synthesis of *N*-unsubstituted α-alkylidene-γ-lactams.[13] The *N*-unsubstituted α-methylene-γ-lactams are also of particular interest for the systematic study of their biological activity[14] and from a synthetic point of view.[14–16] However, no general syntheses were disclosed in the literature and therefore the development of new efficient routes to these derivatives is of great importance.

Our preliminary studies revealed that the method consisting of chemoselective reduction of 2-diethoxyphosphoryl-4-nitroalkanoates followed by lactamization and Horner–Wadsworth–Emmons reaction of the resulting α-diethoxyphosphoryl-γ-lactams with formaldehyde provides a useful tool for the synthesis of γ-substituted α-methylene-γ-lactams.[17] The method would significantly benefit from the availability of substituted 2-diethoxyphosphoryl-4-nitroalkanoates. Recently, we have developed a new, general route for diastereoselective synthesis of 3-aryl-2-diethoxyphosphoryl-4-nitroalkanoates **1** and **2**.[18] It becomes evident that alkanoates of this type are suitable intermediates to access various *N*-unsubstituted α-methylene-γ-lactams. In this paper, we report that a variety of β-monosubstituted and β,γ-disubstituted α-diethoxyphosphoryl-γ-lactams **5** and **6** can be prepared in a completely diastereoselective manner from the corresponding nitroalkanoates **1** and **2**, respectively. We also demonstrate that the resulting α-diethoxyphosphoryl-γ-lactams **5** and **6** can be converted to α-methylene-γ-lactams **11** and **12**, respectively, thus providing a new approach to this class of compounds. Moreover, we tested selected lactams **11** and **12** for their cytotoxic activity against human leukemia cell lines.

2. Results and discussion

Nitroalkanoates **1** and **2** were obtained according to the previously reported procedure.[18] The chemoselective reduction of the

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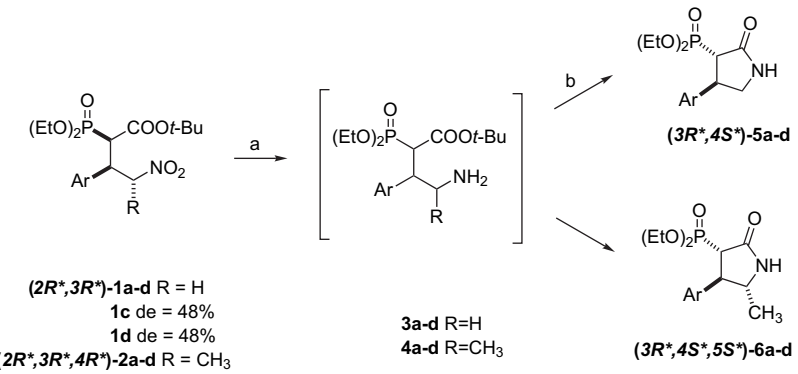


Scheme 1. Reagents and conditions: (a) $NiCl_2 \cdot 6H_2O$ (2 equiv), $NaBH_4$ (10 equiv), CH_3OH, rt, 1 h; (b) Na_2CO_3 (3 equiv), CH_3OH, Δ, 4 h.

nitro group of 4-nitrobutanoates **1** by sodium borohydride in the presence of $NiCl_2 \cdot 6H_2O$[19–23] afforded the expected 4-aminobutanoates **3** accompanied by the corresponding α-diethoxyphosphoryl-γ-lactams **5**. The aminobutanoates **3** were completely converted into the α-diethoxyphosphoryl-γ-lactams **5** by simple heating in methanol in the presence of Na_2CO_3. Reduction of 4-nitropentanoates **2** under the same conditions provided directly α-diethoxyphosphoryl-γ-lactams **6** as the only products. In all the cases, reactions proceeded in a completely diastereoselective manner leading to the formation of lactams **5** and **6** as single diastereoisomers (Scheme 1, Table 1).

The trans relative stereochemistry at the stereogenic centers C-3 and C-4 of lactams **6** was assigned on the basis of ^1H and ^{13}C NMR data.[24–26] The observed values of the coupling constants $^3J_{PH4}$= 18.0–18.4 Hz, $^3J_{H3H4}$=9.3–9.5 Hz, and $^3J_{PC5}$=10.7–11.1 Hz clearly proved the trans arrangement of the phosphoryl and aryl groups. However, spectroscopic studies did not allow us to assign unambiguously the relative stereochemistry at C-4 and C-5 stereogenic centers ($^3J_{H3H4}$=6.9–7.1 Hz). This was established by single crystal X-ray analysis of the *N*-Boc lactam **8c**, which unequivocally confirmed the trans relationship between the phosphoryl and aryl groups, as well as aryl and methyl groups (Fig. 1) and allowed us to assign the relative configuration 3*R**,4*S**,5*S** to the obtained products **6a–d**. In the structure **8c**, the pyrrolidinone five membered ring adopts an envelope conformation with N, C1, C2, and C3 atoms almost coplanar and C4 situated at the flap. The three lowest ring asymmetry parameters[27] are C_2(C1)=0.49(4), C_s(N–C1)=5.70(4), and C_s(C4)=6.10(4)°. The 4-methoxyphenyl group is placed in a sterically favored perpendicular position in respect to the pyrrolidinone fragment. In the crystal, symmetrically equivalent phenyl rings are located too far from one another for the stacking interactions.

These findings provided clear evidence that the reduction of 4-nitropentanoates **2** proceeded with complete diastereocontrol and the formation of the 4-aminopentanoates **4** followed by their ring closure occurred with epimerization giving the lactams **6** as thermodynamically more stable trans diastereoisomers, exclusively. Unfortunately, the spectra of the lactams **5a–d** could not be interpreted so unequivocally. Therefore, taking into account the method

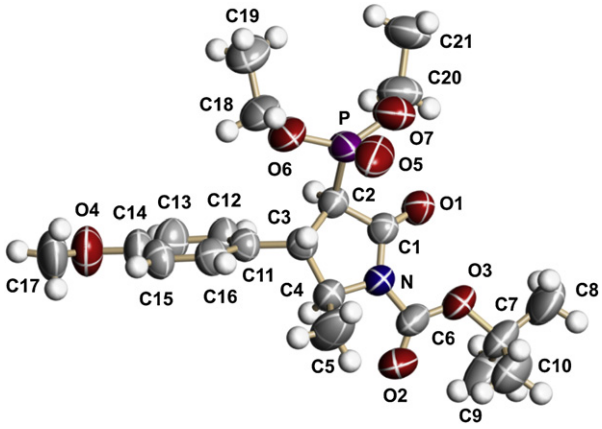


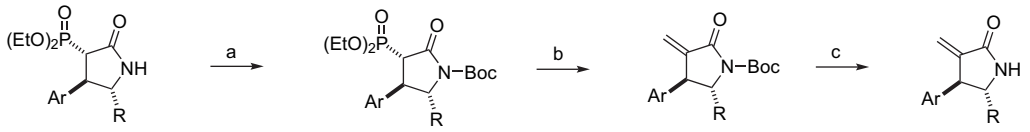
Figure 1. The crystal structure of *N*-Boc lactam **8c**. Both ethoxy groups at phosphorus exhibit orientational disorder. Each of the respective atoms was refined in two partially occupied positions. The picture shows sites for which the occupation factors were 0.64(2) as for O6, C18, C19, and 0.69(1) for O7, C20, and C21. For clarity, the less occupied positions are not shown. Displacement ellipsoids are drawn at the 50% probability level.

of preparation and the structural similarity, we by analogy also assigned trans stereochemistry between the phosphoryl and aryl groups in the lactams **5a–d**.

With the desired α-diethoxyphosphoryl-γ-lactams **5** and **6** in hand, we turned our attention to their effective transformation into the corresponding α-methylene-γ-lactams **11** and **12**, respectively (Scheme 2, Table 1). Our initial attempts to obtain the lactams **11** and **12** by Horner–Wadsworth–Emmons reaction with formaldehyde under previously reported conditions[17,28] indicated that the products are accompanied by their *N*-hydroxymethyl derivatives. The problem was eventually solved by protection of the amide nitrogen by Boc group. *N*-Boc α-diethoxyphosphoryl-γ-lactams **7** and **8** were generated by treatment of the respective lactams **5** and **6** with Boc_2O in the presence of catalytic DMAP. Notably, all the *N*-Boc lactams **7** and **8** were obtained as single diastereoisomers. The *N*-Boc lactams **7** and **8** displayed similar values of the coupling constants to those observed for *N*-unprotected lactams **5** and **6**.

Table 1
α-Diethoxyphosphoryl-γ-lactams **5**, **6**, *N*-Boc α-diethoxyphosphoryl-γ-lactams **7**, **8**, *N*-Boc α-methylene-γ-lactams **9**, **10**, and α-methylene-γ-lactams **11**, **12** prepared

	Ar	Yield (%)							
		5 (R=H)	**6** (R=CH_3)	**7** (R=H)	**8** (R=CH_3)	**9** (R=H)	**10** (R=CH_3)	**11** (R=H)	**12** (R=CH_3)
a	4-Br–C_6H_4–	70	88	98	94	51	67	73	79
b	4-CH_3–C_6H_4–	84	69	91	87	74	68	82	62
c	4-CH_3O–C_6H_4–	67	82	92	94	87	80	51	81
d	3,4-(OCH_2O)–C_6H_3–	73	72	91	95	89	80	82	81



(3*R,4*S**)-5a-d** R=H
(3*R,4*S**,5*S**)-6a-d** R=CH_3

(3*R,4*S**)-7a-d** R=H
(3*R,4*S**,5*S**)-8a-d** R=CH_3

9a-d R=H
(2*R,3*S**)-10a-d** R=CH_3

11a-d R=H
(4*R,5*S**)-12a-d** R=CH_3

Scheme 2. Reagents and conditions: (a) Boc_2O (1.2 equiv), DMAP (0.25 equiv), CH_2Cl_2, rt, 3 h; (b) *t*-BuOK (1.2 equiv), THF, rt, 0.5 h; then HCHO (5 equiv), THF, rt, 1 h; (c) CF_3COOH/CH_2Cl_2 (1:2), rt, 1 h.

Table 2
Cytotoxic activity of compounds **11a**,**d** and **12a**,**b**

Compound	Cytotoxicity IC_{50}[a] (μM)	
	HL-60	NALM-6
11a	548.9±29.6	433.6±39.2
11d	524.1±47.4	515.2±19.4
12a	515.7±47.6	439.2±40.8
12b	537.8±39.3	445.8±33.9
Carboplatin	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.

The Horner–Wadsworth–Emmons reaction of the *N*-Boc-α-diethoxyphosphoryl-γ-lactams **7** and **8** with excess paraformaldehyde in the presence of *t*-BuOK afforded the corresponding α-methylene-γ-lactams **9** and **10**, respectively. Free α-methylene-γ-lactams were regenerated from the *N*-Boc derivatives **9** and **10** by treatment with CF_3COOH. All the obtained lactams **11** and **12** were isolated as crystalline solids in high yield.

Because of their potential biological activity as isosteric analogs of α-methylene-γ-lactones, selected lactams **11** and **12** were evaluated for their cytotoxic activity against HL-60 and NALM-6 human leukemia cell lines.[29] Obtained results (Table 2) are expressed as IC_{50} values, which are the concentrations (μM) required to inhibit tumor cell proliferation by 50% after 48 h of exposure of the cells to a tested compound. Carboplatin was used as a reference compound. As can be seen from Table 2, cytotoxicities of the tested lactams **11a**,**d** and **12a**,**b** are higher against NALM-6 cell line than against HL-60 cell line. Disappointingly, all IC_{50} values are greater than 400 and are well over the range of compounds, which can be considered highly potent according to Kupchan's classification (IC_{50}<15 μM).[30]

3. Conclusions

In summary, motivated by the lack of an efficient method for the preparation of *N*-unsubstituted α-methylene-γ-lactams and their potential cytotoxic activity, we have developed a simple and highly diastereoselective method for the synthesis of α-diethoxyphosphoryl-γ-lactams from the corresponding 3-aryl-2-diethoxyphosphoryl-4-nitroalkanoates. As demonstrated, the former can be conveniently transformed into α-methylene-γ-lactams. Target compounds displayed very weak cytotoxic activity.

4. Experimental

4.1. General

NMR spectra were recorded on a Bruker DPX 250 instrument at 250.13 MHz for ^1H, 62.9 MHz for ^{13}C, and 101.3 MHz for ^{31}P NMR using tetramethylsilane as internal standard and 85% H_3PO_4 as external standard. The multiplicity of carbons was determined by DEPT experiments. IR spectra were measured on a Specord M80 (Zeiss) instrument. Elemental analyses were performed on a Perkin–Elmer PE 2400 analyzer. Melting points were determined in open capillaries and are uncorrected. *tert*-Butyl 3-aryl-2-(diethoxyphosphoryl)-4-nitrobutanoates **1a–d** and *tert*-butyl 3-aryl-2-(diethoxyphosphoryl)-4-nitropentanoates **2a–d** were prepared according to the literature procedure.[18]

4.2. General procedure for the preparation of 4-aryl-3-(diethoxyphosphoryl)pyrrolidin-2-ones 5a–d

To a stirred solution of *tert*-butyl 3-aryl-2-(diethoxyphosphoryl)-4-nitrobutanoate **1** (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, the residue was dissolved in $CHCl_3$ (30 mL), and washed with $NaHCO_3$ (15 mL). The water layer was extracted with $CHCl_3$ (15 mL), combined organic layers were dried over $MgSO_4$, and the solvent was evaporated under reduced pressure. The oily residue was dissolved in MeOH (20 mL) and Na_2CO_3 (1.27 g, 12 mmol) was added. The resulting mixture was heated at reflux for 4 h. After that time, methanol was removed under reduced pressure, the residue was dissolved in $CHCl_3$ (30 mL), washed with water (2×15 mL), dried over $MgSO_4$, and evaporated. Evaporation of the solvent under reduced pressure afforded a crude product, which was purified by column chromatography (eluent: $CHCl_3$/MeOH 97:3).

4.2.1. (3R,4S*)-4-(4-Bromophenyl)-3-(diethoxyphosphoryl)-pyrrolidin-2-one (**5a**)*

Yield 1.05 g, 70%, white solid, mp 113–115 °C; IR (CCl_4): 1704, 1480, 1368, 1312, 1264, 1180, 1096, 1056, 1024; ^{31}P NMR ($CDCl_3$): δ=22.8; ^1H NMR ($CDCl_3$): δ=1.25 (dt, 3H, $^3J_{HH}$=7.1 Hz, $^4J_{HP}$=0.5 Hz, CH_3CH_2OP), 1.30 (dt, $^3J_{HH}$=7.1 Hz, $^4J_{HP}$=0.5 Hz, CH_3CH_2OP), 2.99 (dd, 1H, $^3J_{HH}$=5.5 Hz, $^3J_{HP}$=22.9 Hz, PC*H*), 3.37–3.41 (m, 1H, C*H*Ar), 3.87–4.04 (m, 2H, CH_2N), 4.05–4.26 (m, 4H, 2×CH_3CH_2OP), 7.26 (s, 1H, N*H*), 7.29–7.37 (m, 4H, 4×CH_{Ar}); ^{13}C NMR ($CDCl_3$): δ=172.2 (d, $^2J_{CP}$=1.6 Hz), 142.3 (d, $^3J_{CP}$=7.4 Hz), 128.6 (2×), 127.0, 126.5 (2×), 62.7 (d, $^2J_{CP}$=6.3 Hz), 62.0 (d, $^2J_{CP}$=6.7 Hz), 48.9 (d, $^3J_{CP}$=6.9 Hz), 48.5 (d, $^1J_{CP}$=147.1 Hz), 41.7 (d, $^2J_{CP}$=1.5 Hz), 16.0 (d, $^3J_{CP}$=3.2 Hz), 15.9 (d, $^3J_{CP}$=3.2 Hz). Anal. Calcd for $C_{14}H_{19}BrNO_4P$: C, 44.70; H, 5.09; N, 3.72. Found: C, 44.58; H, 5.00; N, 3.61.

4.2.2. (3R,4S*)-3-(Diethoxyphosphoryl)-4-(4-methylphenyl)-pyrrolidin-2-one (**5b**)*

Yield 1.05 g, 84%, white solid, mp 122–124 °C; IR (CCl_4): 1701, 1455, 1372, 1315, 1291, 1163, 1122, 1016; ^{31}P NMR ($CDCl_3$): δ=22.9; ^1H NMR ($CDCl_3$): δ=1.25 (t, 3H, $^3J_{HH}$=7.1 Hz, CH_3CH_2OP), 1.32 (t, 3H, $^3J_{HH}$=7.1 Hz, CH_3CH_2OP), 2.33 (s, 3H, CH_3Ar), 2.96 (dd, 1H, $^3J_{HH}$=4.7 Hz, $^3J_{HP}$=22.7 Hz, PC*H*), 3.34–3.40 (m, 1H, C*H*Ar), 3.86–4.01 (m, 2H, CH_2N), 4.02–4.26 (m, 4H, 2×CH_3CH_2OP), 5.74 (s, 1H, N*H*), 7.15 (s, 4H, 4×CH_{Ar}); ^{13}C NMR ($CDCl_3$): δ=172.3, 139.4 (d, $^3J_{CP}$=7.4 Hz), 136.6, 129.2 (2×), 126.4 (2×), 62.7 (d, $^2J_{CP}$=6.2 Hz), 62.1 (d, $^2J_{CP}$=6.6 Hz), 49.0 (d, $^3J_{CP}$=6.3 Hz), 48.6 (d, $^1J_{CP}$=141.6 Hz), 41.4, 20.7, 16.0 (d, $^3J_{CP}$=2.2 Hz), 16.0 (d, $^3J_{CP}$=3.0 Hz). Anal. Calcd for $C_{15}H_{22}NO_4P$: C, 57.87; H, 7.12; N, 4.50. Found: C, 57.68; H, 7.00; N, 4.61.

4.2.3. (3R,4S*)-3-(Diethoxyphosphoryl)-4-(4-methoxyphenyl)-pyrrolidin-2-one (**5c**)*

Yield 877 mg, 67%, white solid, mp 97–99 °C; IR (CCl_4): 1704, 1516, 1480, 1368, 1312, 1296, 1248, 1180, 1048, 1032; ^{31}P NMR ($CDCl_3$): δ=23.0; ^1H NMR ($CDCl_3$): δ=1.25 (t, 3H, $^3J_{HH}$=7.1 Hz, CH_3CH$_2$OP), 1.31 (t, 3H, $^3J_{HH}$=7.5 Hz, CH_3CH$_2$OP), 2.94 (dd, 1H, $^3J_{HH}$=4.9 Hz, $^3J_{HP}$=22.9 Hz, PC*H*), 3.31–3.35 (m, 1H, C*H*Ar), 3.80 (s, 3H, CH_3OAr), 3.84–4.03 (m, 2H, CH_2N), 4.06–4.25 (m, 4H, 2×CH$_3$CH_2OP), 6.36 (s, 1H, N*H*), 6.87 (d, 2H, $^3J_{HH}$=8.8 Hz, 2×CH_{Ar}), 7.20 (d, 2H, $^3J_{HH}$=8.8 Hz, 2×CH_{Ar}); ^{13}C NMR ($CDCl_3$): δ=172.2 (d, $^2J_{CP}$=2.3 Hz), 158.4, 134.4 (d, $^3J_{CP}$=7.6 Hz), 127.6 (2×), 113.9 (2×), 62.7 (d, $^2J_{CP}$=6.3 Hz), 62.0 (d, $^2J_{CP}$=6.3 Hz), 54.9, 48.6 (d, $^1J_{CP}$=141.8 Hz), 49.0 (d, $^3J_{CP}$=7.0 Hz), 41.0 (d, $^2J_{CP}$=1.3 Hz), 16.0 (d, $^3J_{CP}$=5.9 Hz), 15.9 (d, $^3J_{CP}$=5.9 Hz). Anal. Calcd for $C_{15}H_{22}NO_5P$: C, 55.04; H, 6.77; N, 4.28. Found: C, 55.23; H, 6.63; N, 4.18.

4.2.4. (3R,4S*)-3-(Diethoxyphosphoryl)-4-(3,4-methylenedioxyphenyl)pyrrolidin-2-one (**5d**)*

Yield 996 mg, 73%, white solid, mp 95–97 °C; IR (CCl_4): 1697, 1441, 1245, 1036, 1015; ^{31}P NMR ($CDCl_3$): δ=22.9; ^1H NMR ($CDCl_3$): δ=1.29 (t, 3H, $^3J_{HH}$=7.0 Hz, CH_3CH$_2$OP), 1.31 (t, 3H, $^3J_{HH}$=7.0 Hz, CH_3CH$_2$OP), 2.92 (dd, 1H, $^3J_{HH}$=5.6 Hz, $^3J_{HP}$=22.9 Hz, PC*H*), 3.32–3.38 (m, 1H, C*H*Ar), 3.83–3.93 (m, 2H, CH_2N), 4.04–4.26 (m, 4H, 2×CH$_3$CH_2OP), 5.95 (s, 2H, CH_2O_2), 6.21 (s, 1H, N*H*), 6.74–6.77 (m, 3H, 3×CH_{Ar}); ^{13}C NMR ($CDCl_3$): δ=172.2 (d, $^2J_{CP}$=2.6 Hz), 148.0, 146.7, 136.4 (d, $^3J_{CP}$=8.0 Hz), 120.0, 108.3, 106.9, 101.0, 63.1 (d, $^2J_{CP}$=6.4 Hz), 62.3 (d, $^2J_{CP}$=6.8 Hz), 49.0 (d, $^3J_{CP}$=6.7 Hz), 48.8 (d, $^1J_{CP}$=141.2 Hz), 41.7 (d, $^2J_{CP}$=1.6 Hz), 16.2 (d, $^3J_{CP}$=3.5 Hz), 16.1 (d, $^3J_{CP}$=3.4 Hz). Anal. Calcd for $C_{15}H_{20}NO_6P$: C, 52.79; H, 5.91; N, 4.10. Found: C, 52.91; H, 6.03; N, 4.18.

4.3. General procedure for the preparation of 4-aryl-3-(diethoxyphosphoryl)-5-methylpyrrolidin-2-ones 6a–d

To a stirred solution of *tert*-butyl 3-aryl-2-(diethoxyphosphoryl)-4-nitropentanoate **2** (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, the residue was dissolved in $CHCl_3$ (30 mL), and washed with $NaHCO_3$ (15 mL). The water layer was extracted with $CHCl_3$ (2×15 mL) and combined organic layers were 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).

4.3.1. (3R,4S*,5S*)-4-(Bromophenyl)-3-(diethoxyphosphoryl)-5-methylpyrrolidin-2-one (**6a**)*

Yield 1.37 g, 88%, white solid, mp 108–110 °C; IR (CCl_4): 1708, 1548, 1496, 1440, 1372, 1312, 1248, 1164, 1028; ^{31}P NMR ($CDCl_3$): δ=23.1; ^1H NMR ($CDCl_3$): δ=1.14 (t, 3H, $^3J_{HH}$=7.1 Hz, CH_3CH$_2$OP), 1.21 (t, 3H, $^3J_{HH}$=7.1 Hz, CH_3CH$_2$OP), 1.29 (d, 3H, $^3J_{HH}$=6.2 Hz, CH_3CH), 3.17 (dd, 1H, $^3J_{HH}$=9.4 Hz, $^2J_{HP}$=22.5 Hz, PC*H*), 3.36 (ddd, 1H, $^3J_{HH}$=9.4, 7.0 Hz, $^3J_{HP}$=18.0 Hz, C*H*Ar), 3.72 (dq, 1H, $^3J_{HH}$=6.2 Hz, 7.0 Hz, C*H*N), 3.91–4.04 (m, 2H, CH$_3$CH_2OP), 4.05–4.24 (m, 2H, CH$_3$CH_2OP), 7.04 (s, 1H, N*H*), 7.24–7.31 (m, 4H, 4×CH_{Ar}); ^{13}C NMR ($CDCl_3$): δ=171.2, 140.6 (d, $^3J_{CP}$=3.0 Hz), 128.5 (2×), 127.4 (2×), 127.1, 62.7 (d, $^2J_{CP}$=6.2 Hz), 61.9 (d, $^2J_{CP}$=6.7 Hz), 57.2 (d, $^3J_{CP}$=10.9 Hz), 50.9 (d, $^2J_{CP}$=2.4 Hz), 49.2 (d, $^1J_{CP}$=147.4 Hz), 20.2, 16.0 (d, $^3J_{CP}$=6.9 Hz), 15.8 (d, $^3J_{CP}$=6.3 Hz). Anal. Calcd for $C_{15}H_{21}BrNO_4P$: C, 46.17; H, 5.42; N, 3.59. Found: C, 46.31; H, 5.57; N, 3.69.

4.3.2. (3R,4S*,5S*)-3-(Diethoxyphosphoryl)-5-methyl-4-(methylphenyl)pyrrolidin-2-one (**6b**)*

Yield 898 mg, 69%, white solid, mp 137–138 °C; IR (CCl_4): 1704, 1520, 1440, 1372, 1336, 1312, 1256, 1184, 1160, 1052, 1016; ^{31}P NMR ($CDCl_3$): δ=23.1; ^1H NMR ($CDCl_3$): δ=1.15 (t, 3H, $^3J_{HH}$=7.1 Hz, CH_3CH$_2$OP), 1.23 (t, 3H, $^3J_{HH}$=7.1 Hz, CH_3CH$_2$OP), 1.28 (d, 3H, $^3J_{HH}$=6.2 Hz, CH_3CH), 2.34 (s, 3H, CH_3Ar), 3.12 (dd, 1H, $^3J_{HH}$=9.3 Hz, $^2J_{HP}$=22.7 Hz, PC*H*), 3.34 (ddd, 1H, $^3J_{HH}$=9.3, 6.9 Hz, $^3J_{HP}$=18.4 Hz, C*H*Ar), 3.69 (dq, 1H, $^3J_{HH}$=6.2, 6.9 Hz, C*H*N), 3.92–4.04 (m, 2H, CH$_3$CH_2OP), 4.05–4.22 (m, 2H, CH$_3$CH_2OP), 6.34 (s, 1H, N*H*), 7.15 (s, 4H, 4×CH_{Ar}); ^{13}C NMR ($CDCl_3$): δ=171.2, 137.6 (d, $^3J_{CP}$=3.1 Hz), 136.6, 127.2 (2×), 129.1 (2×), 62.5 (d, $^2J_{CP}$=6.2 Hz), 61.8 (d, $^2J_{CP}$=6.7 Hz), 57.3 (d, $^3J_{CP}$=10.7 Hz), 50.4 (d, $^2J_{CP}$=2.5 Hz), 49.2 (d, $^1J_{CP}$=147.2 Hz), 20.7, 20.2, 15.9 (d, $^3J_{CP}$=6.3 Hz), 15.81 (d, $^3J_{CP}$=6.3 Hz). Anal. Calcd for $C_{16}H_{24}NO_4P$: C, 59.07; H, 7.44; N, 4.31. Found: C, 59.25; H, 7.59; N, 4.42.

4.3.3. (3R,4S*,5S*)-3-(Diethoxyphosphoryl)-4-(methoxyphenyl)-5-methylpyrrolidin-2-one (**6c**)*

Yield 1.12 g, 82%, white solid, mp 118–120 °C; IR (CCl_4): 1704, 1612, 1516, 1440, 1376, 1336, 1304, 1256, 1180, 1120, 1016; ^{31}P NMR ($CDCl_3$): δ=23.4; ^1H NMR ($CDCl_3$): δ=1.15 (dt, 3H, $^3J_{HH}$=7.1 Hz, $^4J_{HP}$=0.5 Hz, CH_3CH$_2$OP), 1.24 (dt, 3H, $^3J_{HH}$=7.1 Hz, $^4J_{HP}$=0.5 Hz, CH_3CH$_2$OP), 1.28 (d, 3H, $^3J_{HH}$=6.1 Hz, CH_3CH), 3.09 (dd, 1H, $^3J_{HH}$=9.5 Hz, $^2J_{HP}$=22.7 Hz, PC*H*), 3.33 (ddd, 1H, $^3J_{HH}$=9.5, 7.0 Hz, $^3J_{HP}$=18.3 Hz, C*H*Ar), 3.67 (dq, 1H, $^3J_{HH}$=6.1, 7.0 Hz, C*H*N), 3.80 (s, 3H, CH_3OAr), 3.91–4.07 (m, 2H, CH$_3$CH_2OP), 4.08–4.23 (m, 2H, CH$_3$CH_2OP), 6.10 (s, 1H, N*H*), 6.87 (d, 2H, $^3J_{HH}$=8.7 Hz, 2×CH_{Ar}), 7.18 (d, 2H, $^3J_{HH}$=8.7 Hz, 2×CH_{Ar}); ^{13}C NMR ($CDCl_3$): δ=171.2, 158.6, 132.6 (d, $^3J_{CP}$=2.6 Hz), 128.4 (2×), 113.8 (2×), 62.6 (d, $^2J_{CP}$=6.1 Hz), 61.8 (d, $^2J_{CP}$=6.6 Hz), 57.3 (d, $^3J_{CP}$=11.1 Hz), 55.0, 50.1 (d, $^2J_{CP}$=1.9 Hz), 49.2 (d, $^1J_{CP}$=147.1 Hz), 20.1, 16.0 (d, $^3J_{CP}$=6.4 Hz), 15.9 (d, $^3J_{CP}$=6.4 Hz). Anal. Calcd for $C_{16}H_{24}NO_5P$: C, 56.30; H, 7.09; N, 4.10. Found: C, 56.17; H, 6.97; N, 4.01.

4.3.4. (3R,4S*,5S*)-3-(Diethoxyphosphoryl)-5-methyl-4-(3,4-methylenedioxyphenyl)pyrrolidin-2-one (**6d**)*

Yield 1.02 g, 72%, white solid, mp 155–157 °C; IR (CCl_4): 1704, 1488, 1440, 1372, 1312, 1252, 1184, 1040, 1016; ^{31}P NMR ($CDCl_3$): δ=22.9; ^1H NMR ($CDCl_3$): δ=1.19 (t, 3H, $^3J_{HH}$=7.1 Hz, CH_3CH$_2$OP), 1.25 (t, 3H, $^3J_{HH}$=7.1 Hz, CH_3CH$_2$OP), 1.28 (d, 3H, $^3J_{HH}$=6.1 Hz, CH_3CH), 3.10 (dd, 1H, $^3J_{HH}$=9.3 Hz, $^2J_{HP}$=22.9 Hz, PC*H*), 3.30 (ddd, 1H, $^3J_{HH}$=9.3, 7.1 Hz, $^3J_{HP}$=18.4 Hz, C*H*Ar), 3.66 (dq, 1H, $^3J_{HH}$=6.1, 7.1 Hz, C*H*N), 3.94–4.10 (m, 2H, CH$_3$CH_2OP), 4.11–4.23 (m, 2H, CH$_3$CH_2OP), 5.96 (s, 2H, CH_2O_2), 6.74–6.79 (m, 3H, 3×CH_{Ar}); ^{13}C NMR ($CDCl_3$): δ=170.9 (d, $^2J_{CP}$=1.7 Hz), 147.6, 146.4, 134.3 (d, $^3J_{CP}$=3.2 Hz), 120.8, 107.9, 107.3, 100.8, 62.5 (d, $^2J_{CP}$=6.2 Hz), 61.7 (d, $^2J_{CP}$=6.7 Hz), 57.1 (d, $^3J_{CP}$=10.8 Hz), 50.5 (d, $^2J_{CP}$=2.3 Hz), 49.1 (d, $^1J_{CP}$=147.1 Hz), 20.1, 15.9 (d, $^3J_{CP}$=6.0 Hz), 15.8 (d, $^3J_{CP}$=6.0 Hz). Anal. Calcd for $C_{16}H_{22}NO_6P$: C, 54.08; H, 6.24; N, 3.94. Found: C, 53.93; H, 6.10; N, 3.81.

4.4. General procedure for the preparation of *tert*-butyl 4-aryl-3-(diethoxyphosphoryl)-2-oxo pyrrolidine-1-carboxylates 7a–d or *tert*-butyl 4-(aryl)-3-(diethoxyphosphoryl)-5-methyl-2-oxopyrrolidine-1-carboxylates 8a–d

To a solution of the corresponding lactam **5** or **6** (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) and 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).

4.4.1. (3R,4S*)-tert-Butyl 4-(4-bromophenyl)-3-(diethoxyphosphoryl)-2-oxopyrrolidine-1-carboxylate (**7a**)*

Yield 1.40 g, 98%, white solid, mp 87–89 °C; IR (CCl_4): 1788, 1748, 1456, 1368, 1308, 1160, 1056; ^{31}P NMR ($CDCl_3$): δ=20.9; ^{1}H NMR ($CDCl_3$): δ=1.21 (dt, 3H, $^3J_{HH}$=7.1 Hz, $^4J_{HP}$=0.6 Hz, CH_3CH$_2$OP), 1.31 (dt, 3H, $^3J_{HH}$=7.1 Hz, $^4J_{HP}$=0.5 Hz, CH_3CH$_2$OP), 1.53 (s, 9H, C(CH_3)), 3.18 (dd, 1H, $^3J_{HH}$=6.1 Hz, $^2J_{HP}$=23.7 Hz, PC*H*), 3.71–3.89 (m, 2H, CH_AH$_B$N, C*H*Ar), 4.05–4.11 (m, 2H, CH$_3$CH_2OP), 4.17–4.27 (m, 3H, CH$_3$CH_2OP, CH$_A$$H_B$N), 7.21–7.39 (m, 4H, 4×CH_{Ar}); ^{13}C NMR ($CDCl_3$): δ=166.2 (d, $^2J_{CP}$=2.8 Hz), 149.4, 141.5 (d, $^3J_{CP}$=8.0 Hz), 129.0 (2×), 127.6, 126.6 (2×), 83.3, 63.6 (d, $^2J_{CP}$=6.5 Hz), 62.4 (d, $^2J_{CP}$=6.9 Hz), 52.6 (d, $^3J_{CP}$=6.2 Hz), 50.8 (d, $^1J_{CP}$=139.8 Hz), 37.8 (d, $^2J_{CP}$=2.2 Hz), 27.9, 16.2 (d, $^3J_{CP}$=6.2 Hz), 16.0 (d, $^3J_{CP}$=6.2 Hz). Anal. Calcd for $C_{19}H_{27}BrNO_6P$: C, 47.91; H, 5.71; N, 2.94. Found: C, 47.77; H, 5.55; N, 2.80.

4.4.2. (3R,4S*)-tert-Butyl 3-(diethoxyphosphoryl)-4-(4-methylphenyl)-2-oxopyrrolidine-1-carboxylate (**7b**)*

Yield 1.12 g, 91%, yellow oil; IR (CCl_4): 1780, 1724, 1512, 1360, 1308, 1252, 1032; ^{31}P NMR ($CDCl_3$): δ=21.4; ^{1}H NMR ($CDCl_3$): δ=1.22 (dt, 3H, $^3J_{HH}$=7.1 Hz, $^4J_{HP}$=0.4 Hz, CH_3CH$_2$OP), 1.31 (dt, 3H, $^3J_{HH}$=7.1 Hz, $^4J_{HP}$=0.4 Hz, CH_3CH$_2$OP), 1.52 (s, 9H, C(CH_3)$_3$), 2.33 (s, 3H, CH_3Ar), 3.16 (dd, 1H, $^3J_{HH}$=5.8 Hz, $^2J_{HP}$=23.7 Hz, PC*H*), 3.68–3.86 (m, 2H, CH_AH$_B$N, C*H*Ar), 4.02–4.14 (m, 2H, CH$_3$CH_2OP), 4.18–4.30 (m, 3H, CH$_3$CH_2OP, CH$_A$$H_B$N), 7.10–7.17 (m, 4H, 4×CH_{Ar}); ^{13}C NMR ($CDCl_3$): δ=167.7 (d, $^2J_{CP}$=1.7 Hz), 149.1, 138.2 (d, $^3J_{CP}$=8.1 Hz), 136.8, 129.2 (2×), 126.2 (2×), 82.8, 63.2 (d, $^2J_{CP}$=6.5 Hz), 62.0 (d, $^2J_{CP}$=6.8 Hz), 52.5 (d, $^3J_{CP}$=6.1 Hz), 50.5 (d, $^1J_{CP}$=139.7 Hz), 37.2, 27.5, 20.6, 15.9 (d, $^3J_{CP}$=6.1 Hz), 15.7 (d, $^3J_{CP}$=6.3 Hz). Anal. Calcd for $C_{20}H_{30}NO_6P$: C, 58.39; H, 7.35; N, 3.40. Found: C, 58.52; H, 7.47; N, 3.49.

4.4.3. (3R,4S*)-tert-Butyl 3-(diethoxyphosphoryl)-4-(4-methoxyphenyl)-2-oxopyrrolidine-1-carboxylate (**7c**)*

Yield 1.18 g, 92%, white solid, mp 72–75 °C; IR (CCl_4): 1788, 1720, 1512, 1368, 1312, 1252, 1156, 1032; ^{31}P NMR ($CDCl_3$): δ=21.0; ^{1}H NMR ($CDCl_3$): δ=1.23 (dt, 3H, $^3J_{HH}$=7.0 Hz, $^4J_{HP}$=0.5 Hz, CH_3CH$_2$OP), 1.32 (dt, 3H, $^3J_{HH}$=7.0 Hz, $^4J_{HP}$=0.5 Hz, CH_3CH$_2$OP), 1.52 (s, 9H, C(CH_3)$_3$), 3.14 (dd, 1H, $^3J_{HH}$=6.1 Hz, $^2J_{HP}$=23.7 Hz, PC*H*), 3.47–3.50 (m, 2H, CH_2N), 3.66–3.72 (m, 1H, C*H*Ar), 3.80 (s, 3H, CH_3OAr), 4.01–4.12 (m, 2H, CH$_3$CH_2OP), 4.15–4.29 (m, 2H, CH$_3$CH_2OP), 6.87 (d, 2H, $^3J_{HH}$=8.8 Hz, 2×CH_{Ar}), 7.16 (d, 2H, $^3J_{HH}$=8.8 Hz, 2×CH_{Ar}); ^{13}C NMR ($CDCl_3$): δ=167.8 (d, $^2J_{CP}$=2.3 Hz), 158.7, 149.2, 133.3 (d, $^3J_{CP}$=8.0 Hz), 127.5 (2×), 114.1 (2×), 83.1, 63.4 (d, $^2J_{CP}$=6.5 Hz), 62.2 (d, $^2J_{CP}$=6.5 Hz), 55.0, 52.7 (d, $^3J_{CP}$=6.4 Hz), 50.8 (d, $^1J_{CP}$=139.6 Hz), 37.0 (d, $^2J_{CP}$=1.7 Hz), 27.7, 16.1 (d, $^3J_{CP}$=6.2 Hz), 15.9 (d, $^3J_{CP}$=6.2 Hz). Anal. Calcd for $C_{20}H_{30}NO_7P$: C, 56.20; H, 7.07; N, 3.28. Found: C, 56.42; H, 7.19; N, 3.39.

4.4.4. (3R,4S*)-tert-Butyl 3-(diethoxyphosphoryl)-4-(3,4-methylenedioxyphenyl)-2-oxopyrrolidine-1-carboxylate (**7d**)*

Yield 1.21 g, 91%, white solid, mp 70–72 °C; IR (CCl_4): 1788, 1720, 1368, 1304, 1248, 1164, 1041; ^{31}P NMR ($CDCl_3$): δ=21.2; ^{1}H NMR ($CDCl_3$): δ=1.25 (dt, 3H, $^3J_{HH}$=7.0 Hz, $^4J_{HP}$=0.2 Hz, CH_3CH$_2$OP), 1.33 (dt, 3H, $^3J_{HH}$=7.1 Hz, $^4J_{HP}$=0.5 Hz, CH_3CH$_2$OP), 1.53 (s, 9H, C(CH_3)), 3.11 (dd, 1H, $^3J_{HH}$=5.6 Hz, $^2J_{HP}$=23.6 Hz, PC*H*), 3.66–3.81 (m, 2H, CH_2N), 4.04–4.30 (m, 5H, C*H*Ar, 2×CH$_3$CH_2OP), 5.96 (s, 2H, CH_2O$_2$), 6.67–6.78 (m, 3H, 3×CH_{Ar}); ^{13}C NMR ($CDCl_3$): δ=167.3 (d, $^2J_{CP}$=1.7 Hz), 149.0, 147.7, 146.5, 134.7 (d, $^3J_{CP}$=7.9 Hz), 119.5, 108.0, 106.4, 100.7, 82.7, 63.1 (d, $^2J_{CP}$=6.5 Hz), 61.9 (d, $^2J_{CP}$=6.7 Hz), 52.3 (d, $^3J_{CP}$=6.4 Hz), 50.4 (d, $^1J_{CP}$=139.9 Hz), 37.2 (d, $^2J_{CP}$=1.4 Hz), 27.4, 15.8 (d, $^3J_{CP}$=6.2 Hz), 15.6 (d, $^3J_{CP}$=6.2 Hz). Anal. Calcd for $C_{20}H_{28}NO_8P$: C, 54.42; H, 6.39; N, 3.17. Found: C, 54.27; H, 6.25; N, 3.09.

4.4.5. (3R,4S*,5S*)-tert-Butyl 4-(4-bromophenyl)-3-(diethoxyphosphoryl)-5-methyl-2-oxopyrrolidine-1-carboxylate (**8a**)*

Yield 1.38 g, 94%, white solid, mp 83–85 °C; IR (CCl_4): 1784, 1724, 1368, 1300, 1256, 1156, 1028; ^{31}P NMR ($CDCl_3$): δ=21.5; ^{1}H NMR ($CDCl_3$): δ=1.25 (t, 3H, $^3J_{HH}$=7.1 Hz, CH_3CH$_2$OP), 1.32 (t, 3H, $^3J_{HH}$=7.1 Hz, CH_3CH$_2$OP), 1.52 (d, 3H, $^3J_{HH}$=6.1 Hz, CH_3CH), 1.54 (s, 9H, C(CH_3)$_3$), 3.17 (dd, 1H, $^3J_{HH}$=7.0 Hz, $^2J_{HP}$=24.8 Hz, PC*H*), 3.34 (ddd, 1H, $^3J_{HH}$=7.0, 4.9 Hz, $^3J_{HP}$=19.0 Hz, C*H*Ar), 3.95–4.11 (m, 3H, CH$_3$CH_2OP, C*H*N), 4.12–4.29 (m, 2H, CH$_3$CH_2OP), 7.21–7.30 (m, 4H, 4×CH_{Ar}); ^{13}C NMR ($CDCl_3$): δ=167.8, 149.3, 141.8 (d, $^3J_{CP}$=7.6 Hz), 128.8 (2×), 127.3 (2×), 126.7, 83.1, 63.4 (d, $^2J_{CP}$=6.5 Hz), 62.0 (d, $^2J_{CP}$=6.9 Hz), 60.8 (d, $^3J_{CP}$=7.0 Hz), 50.4 (d, $^1J_{CP}$=141.8 Hz), 45.8, 27.7, 20.3, 16.0 (d, $^3J_{CP}$=6.2 Hz), 15.8 (d, $^3J_{CP}$=6.2 Hz). Anal. Calcd for $C_{20}H_{29}BrNO_6P$: C, 48.99; H, 5.96; N, 2.86. Found: C, 49.13; H, 6.08; N, 3.02.

4.4.6. (3R,4S*,5S*)-tert-Butyl 3-(diethoxyphosphoryl)-5-methyl-4-(4-methylphenyl)-2-oxopyrrolidine-1-carboxylate (**8b**)*

Yield 1.11 g, 87%, white solid, mp 93–95 °C; IR (CCl_4): 1784, 1724, 1368, 1300, 1256, 1160, 1024; ^{31}P NMR ($CDCl_3$): δ=21.3; ^{1}H NMR ($CDCl_3$): δ=1.21 (t, 3H, $^3J_{HH}$=7.1 Hz, CH_3CH$_2$OP), 1.31 (t, 3H, $^3J_{HH}$=7.1 Hz, CH_3CH$_2$OP), 1.52 (d, 3H, $^3J_{HH}$=6.2 Hz, CH_3CH), 1.54 (s, 1H, C(CH_3)$_3$), 2.34 (s, 3H, CH_3Ar), 3.16 (dd, 1H, $^3J_{HH}$=6.8 Hz, $^2J_{HP}$=24.7 Hz, PC*H*), 3.30 (ddd, 1H, $^3J_{HH}$=6.8, 4.8 Hz, $^3J_{HP}$=18.7 Hz, C*H*Ar), 3.95–4.16 (m, 3H, CH$_3$CH_2OP, C*H*N), 4.17–4.23 (m, 2H, CH$_3$CH_2OP), 7.09–7.18 (m, 4H, 4×CH_{Ar}); ^{13}C NMR ($CDCl_3$): δ=167.9 (d, $^2J_{CP}$=1.1 Hz), 149.3, 138.9 (d, $^3J_{CP}$=6.4 Hz), 137.0 (2×), 129.4 (2×), 126.5, 83.0, 63.3 (d, $^2J_{CP}$=6.4 Hz), 62.0 (d, $^2J_{CP}$=6.8 Hz), 61.0 (d, $^3J_{CP}$=7.0 Hz), 50.4 (d, $^1J_{CP}$=142.1 Hz), 45.3 (d, $^2J_{CP}$=1.1 Hz), 27.7, 20.7, 20.3, 16.0 (d, $^3J_{CP}$=6.2 Hz), 15.8 (d, $^3J_{CP}$=6.2 Hz). Anal. Calcd for $C_{21}H_{32}NO_6P$: C, 59.28; H, 7.58; N, 3.29. Found: C, 59.42; H, 7.70; N, 3.41.

4.4.7. (3R,4S*,5S*)-tert-Butyl 3-(diethoxyphosphoryl)-4-(4-methoxyphenyl)-5-methyl-2-oxopyrrolidine-1-carboxylate (**8c**)*

Yield 1.24 g, 94%, white solid, mp 88–90 °C; IR (CCl_4): 1784, 1724, 1512, 1368, 1300, 1252, 1156, 1032; ^{31}P NMR ($CDCl_3$): δ=21.6; ^{1}H NMR ($CDCl_3$): δ=1.28 (t, 3H, $^3J_{HH}$=7.1 Hz, CH_3CH$_2$OP), 1.33 (t, 3H, $^3J_{HH}$=7.1 Hz, CH_3CH$_2$OP), 1.52 (d, 3H, $^3J_{HH}$=6.2 Hz, CH_3CH), 1.56 (s, 9H, C(CH_3)$_3$), 3.15 (dd, 1H, $^3J_{HH}$=7.1 Hz, $^2J_{HP}$=24.7 Hz, PC*H*), 3.31 (ddd, 1H, $^3J_{HH}$=7.1, 5.2 Hz, $^3J_{HP}$=18.9 Hz, C*H*Ar), 3.82 (s, 3H, CH_3OAr), 4.13–4.31 (m, 3H, CH$_3$CH_2OP, C*H*N), 4.11–3.97 (m, 2H, CH$_3$CH_2OP), 6.87 (d, 2H, $^3J_{HH}$=8.7 Hz, 2×CH_{Ar}), 7.17 (d, 2H, $^3J_{HH}$=8.7 Hz, 2×CH_{Ar}); ^{13}C NMR ($CDCl_3$): δ=167.9, 158.7, 149.3, 133.7 (d, $^3J_{CP}$=6.2 Hz), 127.8 (2×), 114.1 (2×), 83.1, 63.4 (d, $^2J_{CP}$=6.5 Hz), 62.0 (d, $^2J_{CP}$=6.9 Hz), 61.0 (d, $^3J_{CP}$=7.3 Hz), 55.0, 50.5 (d, $^1J_{CP}$=142.3 Hz), 45.1, 27.7, 20.2, 16.0 (d, $^3J_{CP}$=6.2 Hz), 15.9 (d, $^3J_{CP}$=6.2 Hz). Anal. Calcd for $C_{21}H_{32}NO_7P$: C, 57.13; H, 7.31; N, 3.17. Found: C, 57.00; H, 7.16; N, 3.04.

4.4.8. (3R,4S*,5S*)-tert-Butyl 3-(diethoxyphosphoryl)-5-methyl-4-(3,4-methylenedioxyphenyl)-2-oxopyrrolidine-1-carboxylate (**8d**)*

Yield 1.29 g, 95%, white solid, mp 99–101 °C; IR (CCl_4): 1784, 1724, 1368, 1304, 1252, 1160, 1040; ^{31}P NMR ($CDCl_3$): δ=21.2; ^{1}H NMR ($CDCl_3$): δ=1.28 (t, 3H, $^3J_{HH}$=7.1 Hz, CH_3CH$_2$OP), 1.32 (t, 3H, $^3J_{HH}$=7.1 Hz, CH_3CH$_2$OP), 1.50 (d, 3H, $^3J_{HH}$=6.2 Hz, CH_3CH), 1.54 (s, 9H, C(CH_3)$_3$), 3.10 (dd, 1H, $^3J_{HH}$=6.9 Hz, $^2J_{HP}$=24.8 Hz, PC*H*), 3.25 (ddd, 1H, $^3J_{HH}$=6.9, 4.9 Hz, $^3J_{HP}$=19.1 Hz, C*H*Ar), 3.98–4.15 (m, 3H, CH$_3$CH_2OP, C*H*N), 4.16–4.27 (m, 2H, CH$_3$CH_2OP), 5.96 (s, 2H, CH_2O$_2$), 6.68 (dd, 1H, $^3J_{HH}$=8.6 Hz, $^4J_{HH}$=1.8 Hz, C*H*Ar), 6.70 (d, 1H, $^4J_{HH}$=1.8 Hz, C*H*Ar), 6,76 (d, 1H, $^3J_{HH}$=8.6 Hz, C*H*Ar); ^{13}C NMR ($CDCl_3$): δ=167.7 (d, $^2J_{CP}$=1.8 Hz), 149.2, 147.9, 146.7, 135.5 (d, $^3J_{CP}$=6.4 Hz), 120.0, 108.2, 106.7, 100.9, 83.0, 63.3 (d, $^2J_{CP}$=6.5 Hz), 62.0 (d, $^2J_{CP}$=6.9 Hz), 60.8 (d, $^3J_{CP}$=7.1 Hz), 50.4 (d, $^1J_{CP}$=142.1 Hz), 45.5, 20.2, 16.0 (d, $^3J_{CP}$=6.2 Hz), 15.8 (d, $^3J_{CP}$=6.2 Hz). Anal. Calcd for $C_{21}H_{30}NO_8P$: C, 55.38; H, 6.64; N, 3.08. Found: C, 55.24; H, 6.41; N, 3.00.

4.5. General procedure for the preparation of *tert*-butyl 4-aryl-3-methylene-2-oxopyrrolidine-1-carboxylates 9a–d and *tert*-butyl 3-aryl-2-methyl-4-methylene-5-oxopyrrolidine-1-carboxylates 10a–d

To a stirred solution of the corresponding lactam **7** or **8** (2 mmol) in THF (15 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 (300 mg, 10 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 concentrated in vacuo. The crude product was purified by column chromatography (eluent: $CHCl_3$/acetone 98:2).

4.5.1. *tert*-Butyl 4-(4-bromophenyl)-3-methylene-2-oxopyrrolidine-1-carboxylate (**9a**)

Yield 359 mg, 51%, pale-yellow oil; IR (CCl_4): 1780, 1716, 1480, 1392, 1368, 1320, 1148; ^{1}H NMR ($CDCl_3$): δ=1.56 (s, 9H, C(CH_3)$_3$), 3.66 (dd, $^3J_{HH}$=6.5 Hz, $^2J_{HH}$=10.4 Hz, CH_AH$_B$N), 4.04 (dddd, 1H, $^3J_{HH}$=6.5, 9.3 Hz, $^4J_{HH}$=2.7 Hz, 3.1 Hz, C*H*Ar), 4.17 (dd, 1H, $^3J_{HH}$=9.3 Hz, $^2J_{HH}$=10.4 Hz, CH$_A$*H*$_B$N), 5.28 (d, 1H, $^4J_{HH}$=2.7 Hz, CH_AH$_B$=C), 6.32 (d, 1H, $^4J_{HH}$=3.1 Hz, CH$_A$*H*$_B$=C), 7.21–7.41 (m, 4H, 4×C*H*$_{Ar}$); ^{13}C NMR ($CDCl_3$): δ=165.2, 149.8, 143.7, 140.5, 128.5 (2×), 127.5 (2×), 127.0, 120.9, 82.5, 51.2, 41.1, 27.6. Anal. Calcd for $C_{16}H_{18}BrNO_3$: C, 54.56; H, 5.15; N, 3.98. Found: C, 54.72; H, 5.28; N, 4.08.

4.5.2. *tert*-Butyl 3-methylene-4-(4-methylphenyl)-2-oxopyrrolidine-1-carboxylate (**9b**)

Yield 425 mg, 74%, pale-yellow oil; IR (CCl_4): 1780, 1716, 1508, 1248, 1148; ^{1}H NMR ($CDCl_3$): δ=1.55 (s, 9H, C(CH_3)$_3$), 2.34 (s, 3H, CH_3Ar), 3.62 (dd, $^3J_{HH}$=6.6 Hz, $^2J_{HH}$=10.5 Hz, CH_AH$_B$N), 4.00 (dddd, 1H, $^3J_{HH}$=6.6 Hz, 9.4 Hz, $^4J_{HH}$=2.7 Hz, 3.1 Hz, C*H*Ar), 4.14 (dd, 1H, $^3J_{HH}$=9.4 Hz, $^2J_{HH}$=10.5 Hz, CH$_A$*H*$_B$N), 5.27 (d, 1H, $^4J_{HH}$=2.7 Hz, CH_AH$_B$=C), 6.30 (d, 1H, $^4J_{HH}$=3.1 Hz, CH$_A$*H*$_B$=C), 7.11 (d, 2H, $^3J_{HH}$=8.1 Hz, 2×C*H*$_{Ar}$), 7.17 (d, 2H, $^3J_{HH}$=8.1 Hz, 2×C*H*$_{Ar}$); ^{13}C NMR ($CDCl_3$): δ=165.4, 149.9, 143.9, 137.5, 136.7, 129.2 (2×), 127.4 (2×), 120.8, 82.6, 51.4, 40.9, 27.6, 20.6. Anal. Calcd for $C_{17}H_{21}NO_3$: C, 71.06; H, 7.37; N 4.87. Found: C, 71.22; H, 7.51; N, 4.99.

4.5.3. *tert*-Butyl 4-(4-methoxyphenyl)-3-methylene-2-oxopyrrolidine-1-carboxylate (**9c**)

Yield 528 mg, 87%, pale-yellow oil; IR (CCl_4): 1780, 1716, 1512, 1252, 1148; ^{1}H NMR ($CDCl_3$): δ=1.61 (s, 9H, C(CH_3)$_3$), 3.65 (dd, $^3J_{HH}$=6.8 Hz, $^2J_{HH}$=10.5 Hz, CH_AH$_B$N), 3.86 (s, 3H, CH_3OAr), 4.04 (dddd, 1H, $^3J_{HH}$=6.8, 9.3 Hz, $^4J_{HH}$=2.8, 3.1 Hz, C*H*Ar), 4.19 (dd, 1H, $^3J_{HH}$=9.3 Hz, $^2J_{HH}$=10.5 Hz, CH$_A$*H*$_B$N), 5.32 (d, 1H, $^4J_{HH}$=2.8 Hz, CH_AH$_B$=C), 6.35 (d, 1H, $^4J_{HH}$=3.1 Hz, CH$_A$*H*$_B$=C), 6.95 (d, 2H, $^3J_{HH}$=8.7 Hz, 2×C*H*$_{Ar}$), 7.20 (d, 2H, $^3J_{HH}$=8.7 Hz, 2×C*H*$_{Ar}$); ^{13}C NMR ($CDCl_3$): δ=165.5, 158.7, 150.0, 144.1, 132.3, 128.7 (2×), 120.9, 114.0 (2×), 82.7, 54.9, 51.6, 40.6, 27.7. Anal. Calcd for $C_{17}H_{21}NO_4$: C, 67.31; H, 6.98; N, 4.62. Found: C, 67.48; H, 7.11; N, 4.77.

4.5.4. *tert*-Butyl 3-methylene-4-(3,4-methylenedioxyphenyl)-2-oxopyrrolidine-1-carboxylate (**9d**)

Yield 565 mg, 89%, white solid, mp 97–99 °C; IR (CCl_4): 1768, 1688, 1504, 1440, 1364, 1312, 1164, 1036; ^{1}H NMR ($CDCl_3$): δ=1.55 (s, 9H, C(CH_3)$_3$), 3.58 (dd, $^3J_{HH}$=6.8 Hz, $^2J_{HH}$=10.6 Hz, CH_AH$_B$N), 3.96 (dddd, 1H, $^3J_{HH}$=6.8, 9.3 Hz, $^4J_{HH}$=3.1, 2.8 Hz, C*H*Ar), 4.13 (dd, 1H, $^3J_{HH}$=9.3 Hz, $^2J_{HH}$=10.6 Hz, CH$_A$*H*$_B$N), 5.31 (d, 1H, $^4J_{HH}$=2.8 Hz, CH_AH$_B$=C), 5.97 (s, 2H, CH_2O_2), 6.32 (d, 1H, $^4J_{HH}$=3.1 Hz, CH$_A$*H*$_B$=C), 6.67–6.71 (m, 2H, 2×C*H*$_{Ar}$), 6.77–6.80 (m, 1H, C*H*Ar); ^{13}C NMR ($CDCl_3$): δ=165.4, 150.1, 147.9, 146.7, 143.8, 134.2, 121.2, 121.2, 108.2, 107.6, 101.0, 82.8, 51.5, 41.1, 27.8. Anal. Calcd for $C_{17}H_{19}NO_5$: C, 64.34; H, 6.03; N, 4.41. Found: C, 64.51; H, 6.13; N, 4.55.

4.5.5. (2R*,3S*)-*tert*-Butyl 3-(4-bromophenyl)-2-methyl-4-methylene-5-oxopyrrolidine-1-carboxylate (**10a**)

Yield 491 mg, 67%, white solid, mp 86–88 °C; IR (CCl_4): 1780, 1736, 1296, 1152; ^{1}H NMR ($CDCl_3$): δ=1.38 (d, 3H, $^3J_{HH}$=6.2 Hz, CH_3CH), 1.49 (s, 9H, C(CH_3)$_3$), 3.51 (ddd, 1H, $^3J_{HH}$=4.0 Hz, $^4J_{HH}$=2.5 Hz, 2.3 Hz, C*H*Ar), 4.04 (dq, 1H, $^3J_{HH}$=4.0, 6.2 Hz, C*H*N), 5.32 (dd, 1H, $^4J_{HH}$=2.3 Hz, $^2J_{HH}$=0.3 Hz, CH_AH$_B$=C), 6.30 (dd, 1H, $^4J_{HH}$=2.5 Hz, $^2J_{HH}$=0.3 Hz, CH$_A$*H*$_B$=C), 7.10–7.32 (m, 4H, 4×C*H*$_{Ar}$); ^{13}C NMR ($CDCl_3$): δ=165.6, 150.0, 142.8, 141.4, 128.7 (2×), 127.2 (2×), 127.1, 122.0, 82.8, 59.5, 49.8, 27.8, 20.9. Anal. Calcd for $C_{17}H_{20}BrNO_3$: C, 55.75; H, 5.50; N, 3.82. Found: C, 55.54; H, 5.36; N, 3.71.

4.5.6. (2R*,3S*)-*tert*-Butyl 2-methyl-4-methylene-3-(4-methylphenyl)-5-oxopyrrolidine-1-carboxylate (**10b**)

Yield 410 mg, 68%, pale-yellow oil; IR (CCl_4): 1780, 1716, 1368, 1300, 1156; ^{1}H NMR ($CDCl_3$): δ=1.43 (d, 3H, $^3J_{HH}$=6.2 Hz, CH_3CH), 1.55 (s, 9H, C(CH_3)$_3$), 2.34 (s, 3H, CH_3Ar), 3.54 (ddd, 1H, $^3J_{HH}$=4.1 Hz, $^4J_{HH}$=2.6, 2.3 Hz, C*H*Ar), 4.07 (dq, 1H, $^3J_{HH}$=4.1, 6.2 Hz, C*H*N), 5.36 (dd, 1H, $^4J_{HH}$=2.3 Hz, $^2J_{HH}$=0.4 Hz, CH_AH$_B$=C), 6.34 (dd, 1H, $^4J_{HH}$=2.6 Hz, $^2J_{HH}$=0.4 Hz, CH$_A$*H*$_B$=C), 7.05–7.26 (m, 4H, 4×C*H*$_{Ar}$); ^{13}C NMR ($CDCl_3$): δ=165.8, 150.1, 143.0, 138.4, 136.8, 129.4 (2×), 127.8 (2×), 121.9, 82.8, 59.7, 49.6, 27.8, 20.9, 20.8. Anal. Calcd for $C_{18}H_{23}NO_3$: C, 71.73; H, 7.69; N, 4.65. Found: C, 71.89; H, 7.81; N, 4.75.

4.5.7. (2R*,3S*)-*tert*-Butyl 3-(4-methoxyphenyl)-2-methyl-4-methylene-5-oxopyrrolidine-1-carboxylate (**10c**)

Yield 508 mg, 80%, pale-yellow oil; IR (CCl_4): 1776, 1736, 1512, 1300, 1252, 1156; ^{1}H NMR ($CDCl_3$): δ=1.43 (d, 3H, $^3J_{HH}$=6.2 Hz, CH_3CH), 1.55 (s, 9H, C(CH_3)$_3$), 3.52 (ddd, 1H, $^3J_{HH}$=4.4 Hz, $^4J_{HH}$=2.6, 2.3 Hz, C*H*Ar), 3.80 (s, 3H, CH_3OAr), 4.04 (dq, 1H, $^3J_{HH}$=4.4, 6.2 Hz, C*H*N), 5.36 (d, 1H, $^4J_{HH}$=2.3, $^2J_{HH}$=0.4 Hz, CH_AH$_B$=C), 6.34 (dd, 1H, $^4J_{HH}$=2.6 Hz, $^2J_{HH}$=0.4 Hz, CH$_A$*H*$_B$=C), 6.88 (d, 2H, $^3J_{HH}$=8.8 Hz, 2×C*H*$_{Ar}$), 7.10 (d, 2H, $^3J_{HH}$=8.8 Hz, 2×C*H*$_{Ar}$); ^{13}C NMR ($CDCl_3$): δ=165.8, 158.6, 150.1, 143.1, 133.3, 128.4 (2×), 121.8, 114.1 (2×), 82.9, 59.8, 55.0, 49.0, 27.8, 20.8. Anal. Calcd for $C_{18}H_{23}NO_4$: C, 68.12; H, 7.30; N, 4.41. Found: C, 68.01; H, 7.19; N, 4.30.

4.5.8. (2R*,3S*)-*tert*-Butyl 2-methyl-4-methylene-3-(3,4-methylenedioxyphenyl)-5-oxopyrrolidine-1-carboxylate (**10d**)

Yield 530 mg, 80%, white solid, mp 114–116 °C; IR (CCl_4): 1764, 1688, 1364, 1324, 1300, 1252, 1168; ^{1}H NMR ($CDCl_3$): δ=1.44 (d, 3H, $^3J_{HH}$=6.1 Hz, CH_3CH), 1.57 (s, 9H, C(CH_3)$_3$), 3.49 (ddd, 1H, $^3J_{HH}$=4.4 Hz, $^4J_{HH}$=2.6, 2.2 Hz, C*H*Ar), 4.04 (dq, 1H, $^3J_{HH}$=4.4, 6.1 Hz, C*H*N), 5.40 (dd, 1H, $^4J_{HH}$=2.2, $^2J_{HH}$=0.3 Hz, CH_AH$_B$=C), 5.98 (s, 2H, CH_2O_2), 6.36 (dd, 1H, $^4J_{HH}$=2.6 Hz, $^2J_{HH}$=0.4 Hz, CH$_A$*H*$_B$=C), 6.67 (dd, 1H, $^4J_{HH}$=1.8 Hz, $^3J_{HH}$=8.4 Hz, C*H*Ar), 6.77 (d, 1H, $^4J_{HH}$=1.8 Hz, C*H*Ar), 6.78 (d, 1H, $^3J_{HH}$=8.4 Hz, C*H*Ar); ^{13}C NMR ($CDCl_3$): δ=165.5, 150.0, 147.9, 146.6, 142.8, 135.0, 122.0, 120.6, 108.1, 107.3, 100.9, 82.9, 59.6, 49.7, 27.8, 20.8. Anal. Calcd for $C_{18}H_{21}NO_5$: C, 65.24; H, 6.39; N, 4.23. Found: C, 65.08; H, 6.25; N, 4.11.

4.6. General procedure for the preparation of 4-aryl-3-methylenepyrrolidin-2-ones 11a–d and 4-aryl-5-methyl-3-methylenepyrrolidin-2-ones 12a–d

To a solution of the corresponding lactam **9** or **10** (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, the residue was dissolved in CH_2Cl_2 (15 mL), washed with $NaHCO_3$ (15 mL) and 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).

4.6.1. 4-(4-Bromophenyl)-3-methylenepyrrolidin-2-one (**11a**)

Yield 184 mg, 73%, white solid, mp 122–124 °C; IR (CCl_4): 1688, 1656, 1360, 1312, 1264; ^{1}H NMR ($CDCl_3$): δ=3.42 (dd, 1H, $^3J_{HH}$=9.8 Hz, $^2J_{HH}$=9.5 Hz, CH_AH$_B$N), 3.86 (dd, 1H, $^3J_{HH}$=5.8 Hz, $^2J_{HH}$=9.5 Hz, CH$_A$*H*$_B$N), 4.18 (dddd, 1H, $^3J_{HH}$=9.8, 5.8 Hz, $^4J_{HH}$=3.1, 2.6 Hz, C*H*Ar), 5.19 (d, 1H, $^4J_{HH}$=2.6 Hz, CH_AH$_B$=C), 6.14 (d, 1H, $^4J_{HH}$=3.1 Hz, CH$_A$*H*$_B$=C), 6.75 (s, 1H, N*H*), 7.22–7.40 (m, 4H, 4×C*H*$_{Ar}$); ^{13}C NMR ($CDCl_3$): δ=171.0, 144.5, 141.9, 128.6 (2×), 127.6

(2×), 126.9, 117.2, 48.3, 44.5. Anal. Calcd for $C_{11}H_{10}BrNO$: C, 52.41; H, 4.00; N, 5.56. Found: C, 52.54; H, 3.84; N, 5.41.

*4.6.2. 3-Methylene-4-(4-methylphenyl)pyrrolidin-2-one (**11b**)*

Yield 154 mg, 82%, white solid, mp 146–148 °C; IR (CCl_4): 1696, 1263, 1018; ^{1}H NMR ($CDCl_3$): δ=2.35 (s, 3H, CH_3Ar), 3.39 (dd, 1H, $^3J_{HH}$=5.8 Hz, $^2J_{HH}$=9.7 Hz, CH_AH$_B$N), 3.83 (dd, 1H, $^3J_{HH}$=9.4 Hz, $^2J_{HH}$=9.7 Hz, CH$_A$$H_B$N), 4.17 (dddd, 1H, $^3J_{HH}$=9.4, 5.8 Hz, $^4J_{HH}$=3.1, 2.6 Hz, CHAr), 5.19 (d, 1H, $^4J_{HH}$=2.6 Hz, CH_AH$_B$=C), 6.13 (d, 1H, $^4J_{HH}$=3.1 Hz, CH$_A$$H_B$=C), 6.41 (s, 1H, N$H$), 7.10–7.18 (m, 4H, 4×C$H_{Ar}$); ^{13}C NMR ($CDCl_3$): δ=171.1, 144.6, 138.8, 136.6, 129.4 (2×), 127.6 (2×), 117.5, 48.5, 44.2, 20.8. Anal. Calcd for $C_{12}H_{13}NO$: C, 76.98; H, 7.00; N, 7.48. Found: C, 77.13; H, 7.12; N, 7.61.

*4.6.3. 3-Methylene-4-(4-methoxyphenyl)pyrrolidin-2-one (**11c**)*

Yield 104 mg, 51%, white solid, mp 191–193 °C; IR (CCl_4): 1697, 1510, 1296, 1244, 1175; ^{1}H NMR ($CDCl_3$): δ=3.36 (dd, 1H, $^3J_{HH}$=6.1 Hz, $^2J_{HH}$=9.7 Hz, CH_AH$_B$N), 3.81 (s, 3H, CH_3OAr), 3.81 (dd, 1H, $^3J_{HH}$=9.3 Hz, $^2J_{HH}$=9.7 Hz, CH$_A$$H_B$N), 4.14 (dddd, 1H, $^3J_{HH}$=9.3, 6.1 Hz, $^4J_{HH}$=3.1, 2.7 Hz, CHAr), 5.18 (d, 1H, $^4J_{HH}$=2.7 Hz, CH_AH$_B$=C), 6.09 (s, 1H, NH), 6.13 (d, 1H, $^4J_{HH}$=3.1 Hz, CH$_A$$H_B$=C), 6.87 (d, 2H, $^3J_{HH}$=8.8 Hz, 2×CH_{Ar}), 7.16 (d, 2H, $^3J_{HH}$=8.8 Hz, 2×CH_{Ar}); ^{13}C NMR ($CDCl_3$): δ=170.7, 158.8, 144.3, 133.8, 128.9 (2×), 117.7, 114.2 (2×), 55.2, 48.5, 44.2. Anal. Calcd for $C_{12}H_{13}NO_2$: C, 70.92; H, 6.45; N, 6.89. Found: C, 70.73; H, 6.22; N, 6.66.

*4.6.4. 3-Methylene-4-(3,4-methylenedioxyphenyl)pyrrolidin-2-one (**11d**)*

Yield 178 mg, 82%, white solid, mp 190–192 °C; IR (CCl_4): 1688, 1648, 1440, 1320, 1280, 1248, 1192; ^{1}H NMR ($CDCl_3$): δ=3.35 (ddd, 1H, $^3J_{HH}$=5.8, 0.7 Hz, $^2J_{HH}$=9.9 Hz, CH_AH$_B$N), 3.82 (ddd, 1H, $^3J_{HH}$=8.9, 1.0 Hz, $^2J_{HH}$=9.9 Hz, CH$_A$$H_B$N), 4.09 (dddd, 1H, $^3J_{HH}$=8.9, 5.8 Hz, $^4J_{HH}$=3.1, 2.1 Hz, CHAr), 5.20 (d, 1H, $^4J_{HH}$=2.1 Hz, CH_AH$_B$=C), 5.96 (s, 2H, CH_2O_2), 6.12 (d, 1H, $^4J_{HH}$=3.1 Hz, CH$_A$$H_B$=C), 6.69–6.79 (m, 3H, 3×CH_{Ar}), 7.37 (s, 1H, NH); ^{13}C NMR (CD_3OD): δ=172.3, 149.6, 148.3, 146.8, 137.4, 122.3, 117.8, 109.3, 108.8, 102.5, 49.5, 46.7. Anal. Calcd for $C_{12}H_{11}NO_3$: C, 66.35; H, 5.10; N, 6.45. Found: C, 66.49; H, 5.22; N, 6.62.

4.6.5. (4R,5S*)-4-(4-Bromophenyl)-5-methyl-3-methylene-pyrrolidin-2-one (**12a**)*

Yield 210 mg, 79%, white solid, mp 112–114 °C; IR (CCl_4): 1696, 1664, 1432, 1336, 1232; ^{1}H NMR ($CDCl_3$): δ=1.32 (d, 3H, $^3J_{HH}$=6.1 Hz, CH_3CH), 3.58 (ddd, 1H, $^3J_{HH}$=6.2 Hz, $^4J_{HH}$=3.2, 2.7 Hz, CHAr), 3.70 (dq, 1H, $^3J_{HH}$=6.1, 6.2 Hz, CHN), 5.12 (d, 1H, $^4J_{HH}$=2.7 Hz, CH_AH$_B$=C), 6.11 (d, 1H, $^4J_{HH}$=3.2 Hz, CH$_A$$H_B$=C), 6.64 (s, 1H, N$H$), 7.21–7.39 (m, 4H, 4×C$H_{Ar}$); ^{13}C NMR ($CDCl_3$): δ=170.0, 145.3, 140.4, 128.5 (2×), 128.1 (2×), 126.9, 116.7, 56.3, 54.0, 20.7. Anal. Calcd for $C_{12}H_{12}BrNO$: C, 54.16; H, 4.54; N, 5.26. Found: C, 54.00; H, 4.43; N, 5.13.

4.6.6. (4R,5S*)-5-Methyl-3-methylene-4-(4-methylphenyl)pyrrolidin-2-one (**12b**)*

Yield 125 mg, 62%, white solid, mp 138–140 °C; IR (CCl_4): 1698, 1514, 1438, 1391, 1333, 1261, 1231; ^{1}H NMR ($CDCl_3$): δ=1.30 (d, 3H, $^3J_{HH}$=6.1 Hz, CH_3CH), 2.35 (s, 3H, CH_3Ar), 3.55 (ddd, 1H, $^3J_{HH}$=5.9 Hz, $^4J_{HH}$=3.5, 2.8 Hz, CHAr), 3.66 (dq, 1H, $^3J_{HH}$=6.1, 5.9 Hz, CHN), 5.11 (d, 1H, $^4J_{HH}$=2.8 Hz, CH_AH$_B$=C), 5.91 (s, 1H, NH), 6.10 (d, 1H, $^4J_{HH}$=3.5 Hz, CH$_A$$H_B$=C), 7.10 (d, 2H, $^3J_{HH}$=8.4 Hz, 2×CH_{Ar}), 7.17 (d, 2H, $^3J_{HH}$=8.4 Hz, 2×CH_{Ar}); ^{13}C NMR ($CDCl_3$): δ=170.2, 145.5, 137.5, 136.7, 129.3 (2×), 128.1 (2×), 116.8, 56.5, 53.8, 20.8, 20.8. Anal. Calcd for $C_{13}H_{15}NO$: C, 77.58; H, 7.51; N, 6.96. Found: C, 77.73; H, 7.70; N, 7.11.

4.6.7. (4R,5S*)-4-(4-Methoxyphenyl)-5-methyl-3-methyl-enepyrrolidin-2-one (**12c**)*

Yield 176 mg, 81%, white solid, mp 148–150 °C; IR (CCl_4): 1656, 1512, 1424, 1380, 1328, 1300, 1256; ^{1}H NMR ($CDCl_3$): δ=1.30 (d, 3H, $^3J_{HH}$=6.1 Hz, CH_3CH), 3.52 (ddd, 1H, $^3J_{HH}$=6.2 Hz, $^4J_{HH}$=2.7, 2.1 Hz, CHAr), 3.63 (dq, 1H, $^3J_{HH}$=6.2, 6.1 Hz, CHN), 3.82 (s, 3H, CH_3OAr), 5.10 (d, 1H, $^4J_{HH}$=2.1 Hz, CH_AH$_B$=C), 5.92 (s, 1H, NH), 6.09 (d, 1H, $^4J_{HH}$=2.7 Hz, CH$_A$$H_B$=C), 6.89 (d, 2H, $^3J_{HH}$=8.8 Hz, 2×CH_{Ar}), 7.14 (d, 2H, $^3J_{HH}$=8.8 Hz, 2×CH_{Ar}); ^{13}C NMR ($CDCl_3$): δ=170.2, 158.6, 145.6, 132.4, 129.2 (2×), 116.7, 114.0 (2×), 56.5, 55.0, 53.5, 20.6. Anal. Calcd for $C_{13}H_{15}NO_2$: C, 71.87; H, 6.96; N, 6.45. Found: C, 72.02; H, 7.10; N, 6.61.

4.6.8. (4R,5S*)-5-Methyl-3-methylene-4-(3,4-methylene-dioxyphenyl)pyrrolidin-2-one (**12d**)*

Yield 187 mg, 81%, white solid, mp 149–151 °C; IR (CCl_4): 1704, 1488, 1436, 1384, 1336, 1280, 1246; ^{1}H NMR ($CDCl_3$): δ=1.30 (d, 3H, $^3J_{HH}$=6.1 Hz, CH_3CH), 3.51 (ddd, 1H, $^3J_{HH}$=5.9 Hz, $^4J_{HH}$=3.2, 2.3 Hz, CHAr), 3.62 (dq, 1H, $^3J_{HH}$=6.1, 5.9 Hz, CHN), 5.14 (d, 1H, $^4J_{HH}$=2.3 Hz, CH_AH$_B$=C), 5.97 (s, 2H, CH_2O_2), 6.11 (d, 1H, $^4J_{HH}$=3.2 Hz, CH$_A$$H_B$=C), 6.35 (s, 1H, N$H$), 6.69 (dd, 1H, $^3J_{HH}$=7.7 Hz, $^4J_{HH}$=1.8 Hz, CHAr), 6.77 (d, 1H, $^4J_{HH}$=1.8 Hz, CHAr), 6.78 (d, 1H, $^3J_{HH}$=7.7 Hz, CHAr); ^{13}C NMR ($CDCl_3$): δ=170.0, 147.8, 146.6, 145.3, 134.1, 121.6, 116.8, 108.1 (2×), 100.8, 56.4, 53.9, 20.6. Anal. Calcd for $C_{13}H_{13}NO_3$: C, 67.52; H, 5.67; N, 6.06. Found: C, 67.33; H, 5.51; N, 5.96.

4.7. X-ray single crystal analysis for 8c

Formula: $C_{21}H_{32}NO_7P$, M_w=441.45, colorless crystal 0.40×0.15×0.10 mm, a=9.867(2), b=10.363(2), c=12.865(3) Å, α=111.50(3), β=90.35(3),γ=102.00(3)°, V=1192.3(4) Å^3, Z=2, crystal system: triclinic, space group: $P\bar{1}$, ρ_{calcd}=1.23 g cm^{-3}, λ(Mo Kα)=0.71073 Å, μ=0.154 mm^{-1}, T=293 K, ω scans, 11,007 reflections collected ($\pm h$, $\pm k$, $\pm l$), $2\theta_{max}$=50.0°, semi-empirical absorption correction based on multiple scanned equivalent reflections[31] (0.906<T<0.985), 4080 unique reflections (R_{int}=0.022), 337 refined parameters, refinement on F^2 using all unique reflections, final R=0.053 for 2735 observed reflections [$I\geq 2\sigma(I)$], R_{all}=0.0773, $wR_{all}(F^2)$=0.166, max (min) residual electron density $\Delta\rho_{max}$=0.20 ($\Delta\rho_{min}$=−0.37) e Å^{-3}, all hydrogen atoms refined as riding on their parent atoms. Disordered ethoxy groups at phosphorus were satisfactory refined using a two site model with both site occupancies representing each of the disordered atoms tied to sum to unity. X-ray data were collected using the OXFORD DIFFRACTION KM4 XCALIBUR diffractometer equipped with the KM4CCD/SAPPHIRE area detector. Computer programs used: data collection, data reduction, and absorption correction CrysAlis suite of programs,[32] structure solution, refinement, and molecular graphics SHELXTL.[33]

Crystallographic data (excluding structural factors) for the structure reported, herein, have been deposited at the Cambridge Crystallographic Data Center as supplementary publication CCDC 677697. Copies of the data can be obtained free of charge on application to The Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK. Any request should be accompanied by a full literature citation.

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