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Brönsted Acid Catalyzed Multicomponent Synthesis of Phosphorus and Fluorine-Derived γ-Lactam Derivatives.

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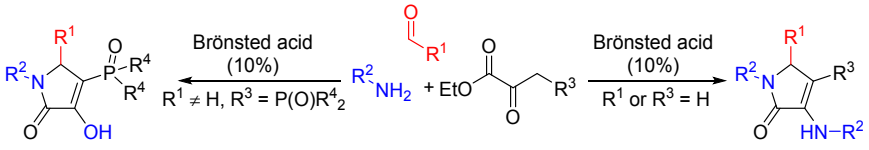


Abstract

A Brönsted acid multicomponent reaction between pyruvate derivatives, amines and aldehydes for the preparation of phosphorus and fluorine substituted γ-lactam derivatives is presented. Depending on the substitution in the resulting 1,5-dihydro-2*H*-pyrrol-2-one substrates, the reaction provides enol or enamine derived γ-lactams. Some enantioselective examples of this reaction are also reported, using chiral phosphoric acids as organocatalyst. Moreover, several synthetic applications of γ-lactam derivatives are presented, including some examples of highly diastereoselective transformations.

Introduction

Multicomponent reactions (MCRs) are (strictly) defined as synthetic processes where multiple substrates are mixed together and react, concomitantly, to yield a new molecule that contains substantial portions of all the starting materials.[1] The drug development demands the intensification of our efforts in the production of potentially active compounds and, taking into consideration the importance of the γ-lactam ring **I** (Figure 1) in medicinal sciences,[2] during the last decades MCR protocols have demonstrated to be an excellent tool for the synthesis of a wide number of densely functionalized γ-lactam substrates.[3] In particular, 1,5-dihydro-2*H*-pyrrol-2-ones[4] **II** (Figure 1) are the unsaturated conjugated derivatives of γ-lactams that are the main part of the structure in numerous bioactive natural products[5] and, there are a number of synthetic 1,5-dihydro-2*H*-pyrrol-2-one derivatives that show assorted pharmacological activities such as FPR1 antagonists,[6a] antivirals HIV-1,[6b] antitumorals[6c] or anticancer VEGF-R enzyme inhibitors.[6d]

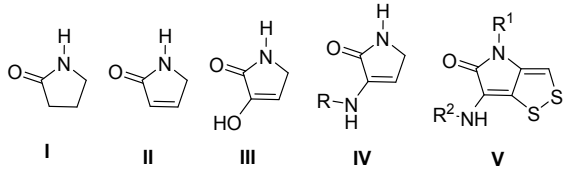


Figure 1. General structure of γ-lactam structures **I-IV**, and 1,2-dithiole annulated antibiotics **V**.

A simple multicomponent protocol for the construction of the skeleton of 1,5-dihydro-2*H*-pyrrol-2-ones consists in the three-component reaction of pyruvate or acetylene carboxylate derivatives, aldehydes, and amines in the presence of an acid catalyst that leads to the formation of cyclic enol derivatives **III**[7] or their enamine substrates, 3-amino 1,5-dihydro-2*H*-pyrrol-2-ones **IV**.[8,9] Natural products containing enol derived 1,5-dihydro-2*H*-pyrrol-2-ones have been isolated from marine mollusks, sponges and cyanobacteria, terrestrial and marine

microorganisms and display a broad range of biological properties, showing very often antimicrobial, antitumor and antiviral activities.[10] Besides, 3-amino 1,5-dihydro-2*H*-pyrrol-2-ones **IV** contain the enamine moiety in their structure and, therefore, they are excellent synthetic tools in organic synthesis[11] and have been successfully used as key intermediates for the synthesis of *Amaryllidaceae* and *Sceletium* alkaloids.[12] Moreover, γ-lactam derivatives **IV** can be seen as cyclic α-dehydro α-amino acids and such skeleton is known to be present in many bioactive compounds as antimicrobials with anti-biofilm activity, caspase-3 inhibitors, analgesics or antipyretics[13] and it is also the basic structure of 1,2-dithiole annulated antibiotics **V**.[14]

Several multicomponent procedures for the preparation of 3-amino 1,5-dihydro-2*H*-pyrrol-2-ones were reported to date.[8,15] In particular, some years ago, we reported a three-component reaction of pyruvate derivatives, aldehydes, and amines mediated by sulfuric acid that yields very efficiently highly functionalized γ-lactam derivatives.[8a] It has been also established that such reaction can be performed under organocatalysis[8b] and, very recently, we reported a highly enantioselective MCR for the synthesis of γ-lactam derivatives, using BINOL derived chiral phosphoric acids as catalysts.[16]

In the past we have been involved in the development of synthetic procedures for the preparation of fluorine[17] and phosphorus[18] containing compounds and their biological evaluation.[19] It is well known that the introduction of fluorine or phosphorus substituents in bioactive substrates very often leads to increased or new activities. Due to their chemical similitude to natural phosphate metabolites, phosphonate derivatives show multiple biological activities and, for this reason, they have found numerous applications in medicine and agrochemistry.[20] In addition, the introduction of fluorine groups into a bioactive structure is

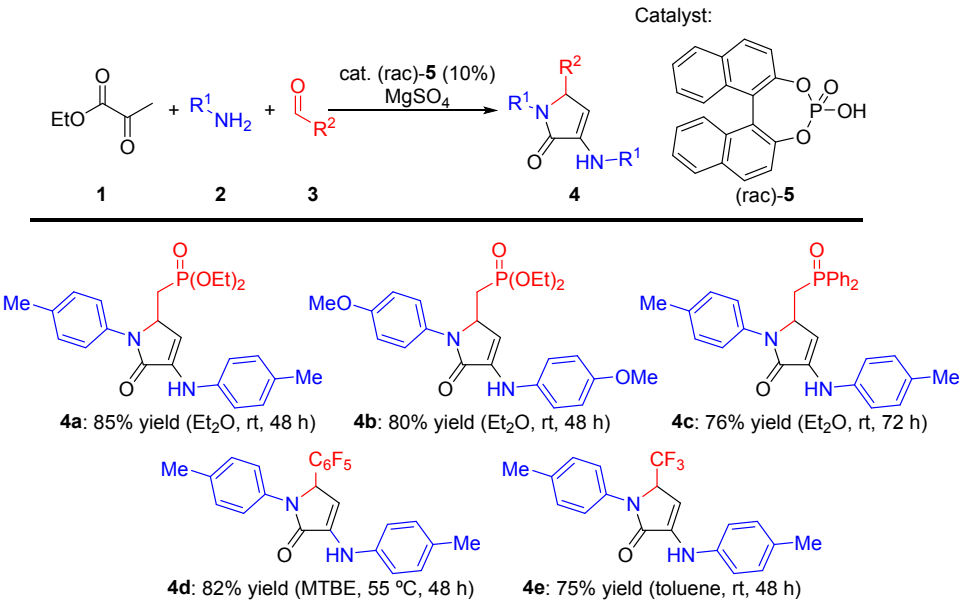
known to result in an increase of its lipophilic character, often improving its capability to cross cell membranes, converting them into more potent and effective drugs.[21]

Taking into account the relevance of γ-lactam core and the advantages of incorporating fluorine and phosphorus moieties into potentially active substrates, we thought that an extension of our organocatalyzed MCR for the synthesis of 3-amino 1,5-dihydro-2*H*-pyrrol-2-ones[16] to the synthesis of the fluorine and phosphorus containing γ-lactam derivatives would be of great interest in the field.

Results and Discussion

First we tested our model MCR, using ethyl pyruvate (**1**), aromatic amines **2** and aldehydes **3** holding fluorinated or phosphorylated substituents in the presence of a catalytic amount of racemic phosphoric acid catalyst **5**. Several γ-lactam derivatives **4** bearing fluorinated and phosphorylated substituents in the position 5 of the ring were obtained in good yields. The results are summarized in chart 1.

Chart 1. MCR for the synthesis of phosphorus and fluorine containing γ-lactams **4**.

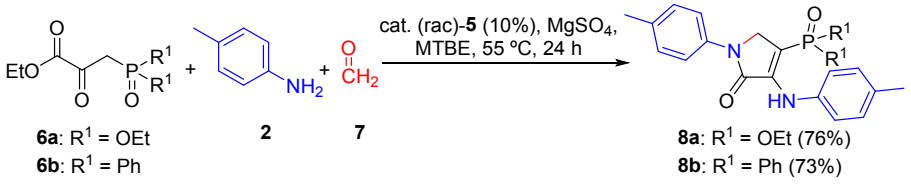


The starting β-phosphorylated aldehydes **3a-b** derived from phosphonate (R^2 = $CH_2P(O)(OEt)_2$) or phosphine oxide (R^2 = $CH_2P(O)Ph_2$) are typically synthesized from methylphosphonates or methylphosphine oxides and *N*,*N*-dimethylformamide (DMF) or ethyl formate, using Savignac's method.[22] The reaction of aldehyde **3a** derived from phosphonate with ethyl pyruvate (**1**) and *p*-toluidine (**2a**, R^1 = *p*-$CH_3C_6H_4$) or *p*-anisidine (**2b**, R^1 = *p*-$CH_3OC_6H_4$) at room temperature in the presence of racemic phosphoric acid catalyst **5**, using Et_2O as solvent, smoothly yields the corresponding phosphorylated 3-amino γ-lactams **4a-b**. The MCR using aldehyde **3b** derived from phosphine oxide requires however longer reaction times to achieve the reaction in good yields. This different reactivity may be attributed to a higher steric hindrance present in the diphenylphosphoryl moiety with respect to the diethylphosphonate functionality. On the other hand, under the same conditions, commercially available perfluorobenzaldehyde (**3c**, R^2 = C_6F_5), pyruvate **1** and *p*-toluidine (**2a**, R^1 = *p*-$CH_3C_6H_4$) did not show any reactivity. In this case, the use of less volatile methyl *tert*-butylether (MTBE) as solvent allows to perform the reaction at higher temperature, under reflux, to afford perfluorophenyl-substituted γ-lactam **4d** in very good yield. Moreover, trifluoroacetaldehyde

(**3d**, $R^2 = CF_3$) can be generated *in situ* from its commercially available hydrate, using refluxing toluene and a Dean-Stark, and its reaction with ethyl pyruvate (**1**) and *p*-toluidine (**2a**, R^1 = *p*-$CH_3C_6H_4$) affords trifluoromethyl substituted lactam **4e** in good yield (Chart 1).

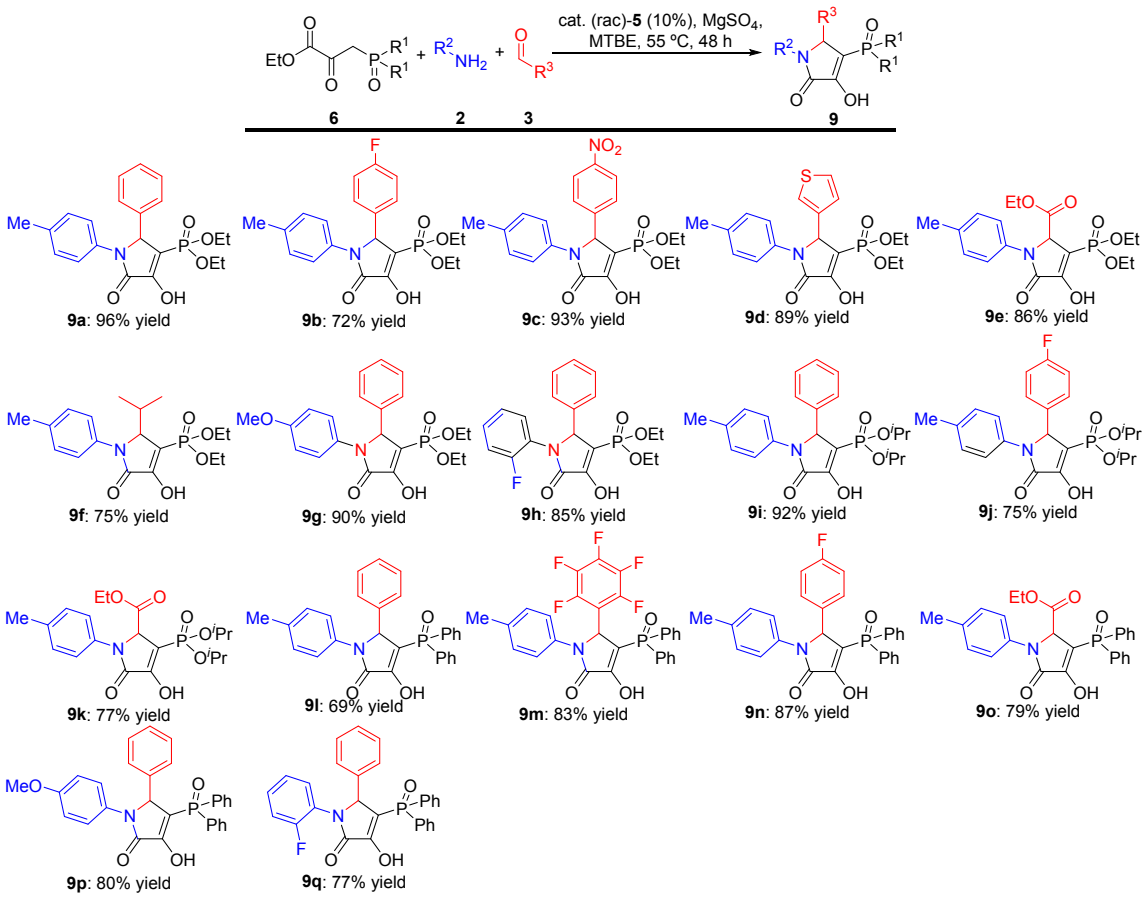
Next, in order to further expand the scope of the MCR, the utilization of phosphorylated pyruvate derivatives was then explored. Analogously to β-phosphorylated aldehydes, pyruvates containing phosphonate **6a** (R^1 = OR) or phosphine oxide **6b** (R^1 = Ph) moieties are obtained by metalation of methylphosphonate esters or methyldiphenylphosphine oxide, followed by the addition of diethyl oxalate or ethyl oxalyl chloride.[23] The MCR of such phosphorylated pyruvates **6** with *p*-toluidine **2a** and formaldehyde (**7**) in the presence of phosphoric acid catalyst **5**, using refluxing MTBE as the reaction media and magnesium sulfate in order to capture the water released, affords 3-amino γ-lactams **8a-b** derived from phosphonate and phosphine oxide (Scheme 1).

Scheme 1. Three-component reaction for the synthesis of phosphorylated γ-lactams **8a-b**.



Remarkably, when other aldehydes different from formaldehyde are used in the MCR using phosphorus substituted pyruvates **6**, phosphorylated 3-hydroxy γ-lactams **9** are obtained (Chart 2).

Chart 2. Scope of the MCR for the synthesis of phosphorus-containing 3-hydroxy γ-lactams **9**.



The scope of this reaction concerning the substituents of the three substrates of the multicomponent reaction was proved to be very wide. Regarding the phosphorus substituent, γ-lactams **9** derived from different phosphonate or phosphine oxide groups can be obtained in very good yields (Chart 2). Moreover, aromatic amines holding weakly or strong electron donating groups can be used in the MCR such as *p*-toluidine (Chart 2, **9a-f,i-o**), *p*-anisidine (Chart 2, **9g,p**) and even *o*-fluoroaniline (Chart 2, **9h,q**). Unfortunately, the use of aliphatic amines or electron poor anilines proved to be non-effective in this MCR and no formation of γ-lactam substrates was observed in that case.

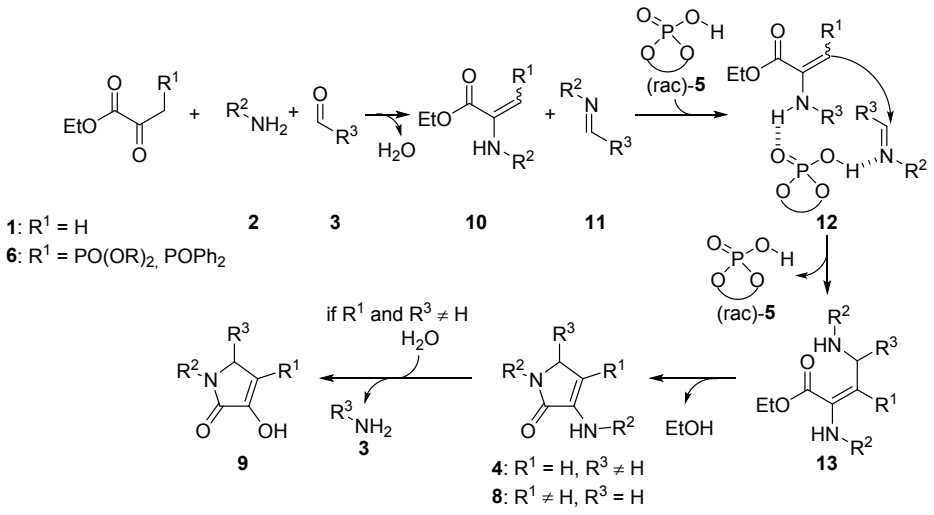
In relation to the carbonyl compound **3** used in the multicomponent process, besides the model reaction using benzaldehyde as imine prescursor, the scope can be also extended to the use of other aromatic aldehydes such as *p*-fluorobenzaldehyde, for the synthesis of fluorine

containing γ-lactams **9b,j,n**, or *p*-nitrobenzaldehyde, for the synthesis of γ-lactam **9c**, that bears an electron poor aromatic ring as substituent at the position 5 (Chart 2). The reaction is equally effective for the synthesis of substrates derived from heteroaromatic aldehydes (Chart 2, **9d**). Moreover, ethyl glyoxalate is also a good substrate for this MCR, leading to the formation of α-aminoacid derived γ-lactams (Chart 2, **9e,k,o**). Finally, *iso*-propyl substituted substrate **9f** derived from an aliphatic aldehyde is also obtained in good yield (Chart 2).

3-Hydroxy γ-lactams **9** show a very characteristic pattern in ^{1}H NMR with a signal in the interval 4.5-6.5 ppm, that couples with the phosphorus atom of ($^{3}J_{PH}$ = 12-15 Hz) and, especially, the broad signal in the interval 9.5-11.0 ppm, that corresponds to the enol hydroxyl group which presents a very low nuclear shielding. Anyway, due to the structural resemblance between all the γ-lactam derivatives, and in view that 3-hydroxy 1,5-dihydro-2*H*-pyrrol-2-one and 3-aminofuran-2(5*H*)-one derivatives have identical molecular formula, in order to unambiguously confirm the identity of the substrates of the reaction, a single crystal of enol **9j** was prepared, and its X-ray diffraction structure was obtained (See ESI).

Intrigued by the fact that enols **9** or their enamine derivatives **4** and **8** could be obtained depending on the substrates used in the reaction, we proposed a mechanism for the process where the selectivity is related to the steric hindrance present in the 5-membered ring heterocycle (Scheme 2).

Scheme 2. Proposed mechanism for the MCR for the synthesis of enol or enamine derived γ-lactam derivatives.

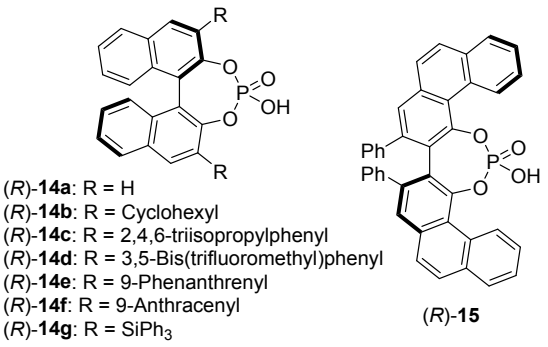


According to this mechanism, the reaction starts with a concomitant formation of enamine and imine substrates **10** and **11** through a double condensation of pyruvate derivatives **1** or **6** and aldehyde **3** with amine **2**. The presence of enamine **10** and imine **11** in the reaction media is evident by the presence of the ^{1}H NMR signals corresponding to the olefinic enamine protons of *E* and *Z* enamine species and the singlet about $\delta = 8.5$ ppm, that is typical for iminic protons. Then a double activation of nucleophile and electrophile by the phosphoric acid catalyst would promote the Mannich reaction between **10** and **11**. According to this mode of activation, we propose a tentative transition state **12** where the phosphoryl oxygen and the acidic proton of the Brönsted acid catalyst establish each hydrogen bonds with the enamine proton and the iminic nitrogen, respectively. The electronic character of the amine substrate is crucial at this point since, while the reactivity of enamine nucleophile **6** may benefit from the use of nucleophilic amines, this may result in a deactivation of imine electrophile **11**. On the contrary very reactive imine species **11** but unreactive enamine nucleophile **10** are expected if arylamines bearing electron withdrawing groups are used as substrates. The Mannich reaction would lead to the formation of intermediate **13** and the phosphoric acid catalyst (rac)-**5** is then released, in order to return to the catalytic cycle. A subsequent intramolecular cyclization driven by the formation of an internal amide bond would yield 3-amino γ-lactam substrates **4** and **8**

with the loss of ethanol. If simple ethyl pyruvate (**1**) is used, the resulting γ-lactam **4** (R^1 = H) holds no substituent at the position 4 while, if formaldehyde is used as starting material, γ-lactams **8** (R^3 = H) are obtained which are not substituted at the position 5. On the contrary if a substituted pyruvate derivative **6** and other aldehyde different than formaldehyde are used as starting materials, the resulting γ-lactam derivative presents an extreme steric crowding in the 5-membered ring and, in this case, a spontaneous hydrolysis of enamine moiety occurs to afford the enol moiety in γ-lactams **9** (Scheme 2). In view that 4,5-disubstituted 3-amino γ-lactams could not be detected as precursors of enols **9**, even under anhydrous conditions, we tried the aqueous hydrolysis of a stable enamine substrate **4** in order to support the last step of our tentative mechanism. However only decomposition of enamine substrates was observed under aqueous either acidic or basic conditions. Nevertheless 4-ethoxycarbonyl substituted 3-amino 1,5-dihydro-2*H*-pyrrol-2-ones have been reported to give the corresponding enols under aqueous acidic conditions.[9d] In addition, similar enamine derived 4-substituted γ-lactam derivatives have been isolated from a similar multicomponent reaction using pyruvates bearing small substituents such as methyl or benzyl groups.[16] This fact may support the theory that bulky substitution in the lactam ring may favor the formation of endocyclic enol moiety in such substrates. Likewise, x-ray structure of enol derived γ-lactam **9j** illustrates the potential steric crowding expected in a potential enamine substrate with a vicinal phosphorylated substituent if compared with the presence of an enol moiety (See ESI).

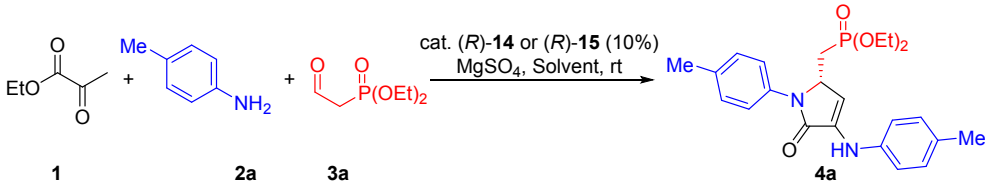
Considering the transition state proposed for the above transformation, it is reasonable to think that the use of chiral Brönsted acid catalysts in this MCR reaction may afford enantioenriched γ-lactam derivatives. For this reason, BINOL and VAPOL derived phosphoric acids (*R*)-**14** and (*R*)-**15** were tested as organocatalysts (Figure 2).

Figure 2. Phosphoric acids (*R*)-**14** and (*R*)-**15** used as catalyst in the MCR.



The enantioselectivity of the multicomponent process was explored using as model the reaction between ethyl pyruvate (**1**), *p*-toluidine (**2a**) and phosphorylated aldehyde **3a** in dichloromethane at room temperature and in the presence of magnesium sulfate to trap the water generated during the amine carbonyl condensation. Disappointingly, switching from racemic to optically pure BINOL phosphoric acid (*R*)-**14a** did not result in any enantioselectivity (Table 1, Entry 1). However, when substituted BINOL phosphoric acid derivatives (*R*)-**14b-g** were used as catalyst in the model MCR reaction, moderate to good enantioselectivities were obtained (Table 1, Entries 2-7). In those cases, lower reactivity of the substrates was observed and the reaction times had to be duplicated in order to observe good conversions. Surprisingly, the use of VAPOL derived phosphoric acid (*R*)-**15** resulted in a very poor enantiomeric excess (Table 1, Entry 8). The best enantioselection was observed for triphenylsilyl substituted BINOL derivative (*R*)-**14g** with an enantiomeric excess of 84% (Table 1, Entry 7).

Table 1. Optimization of the catalyst and solvent in the MCR.



entry	cat.	solv.	time (h)	conv. (%)	ee (%)[a]
1	(*R*)-**14a**	CH_2Cl_2	24	100	0

2	(*R*)-**14b**	CH_2Cl_2	48	100	66 (*S*)
3	(*R*)-**14c**	CH_2Cl_2	48	100	68 (*S*)
4	(*R*)-**14d**	CH_2Cl_2	48	85	38 (*S*)
5	(*R*)-**14e**	CH_2Cl_2	48	85	4 (*S*)
6	(*R*)-**14f**	CH_2Cl_2	48	85	32 (*S*)
7	(*R*)-**14g**	CH_2Cl_2	48	100	84 (*S*)
8	(*R*)-**15**	CH_2Cl_2	48	85	6 (*S*)
9	(*R*)-**14g**	$CHCl_3$	48	100	88 (*S*)
10	(*R*)-**14g**	toluene	48	100	87 (*S*)
11	(*R*)-**14g**	CH_3CN	48	55	87 (*S*)
12	(*R*)-**14g**	Et_2O	48	100	90 (*S*)
13	(*R*)-**14g**	$^{i}Pr_2O$	48	60	88 (*S*)
14	(*R*)-**14g**	MTBE	48	90	88 (*S*)
15	(*R*)-**14g**	DME	48	60	86 (*S*)
16	(*R*)-**14g**	THF	48	40	92 (*S*)

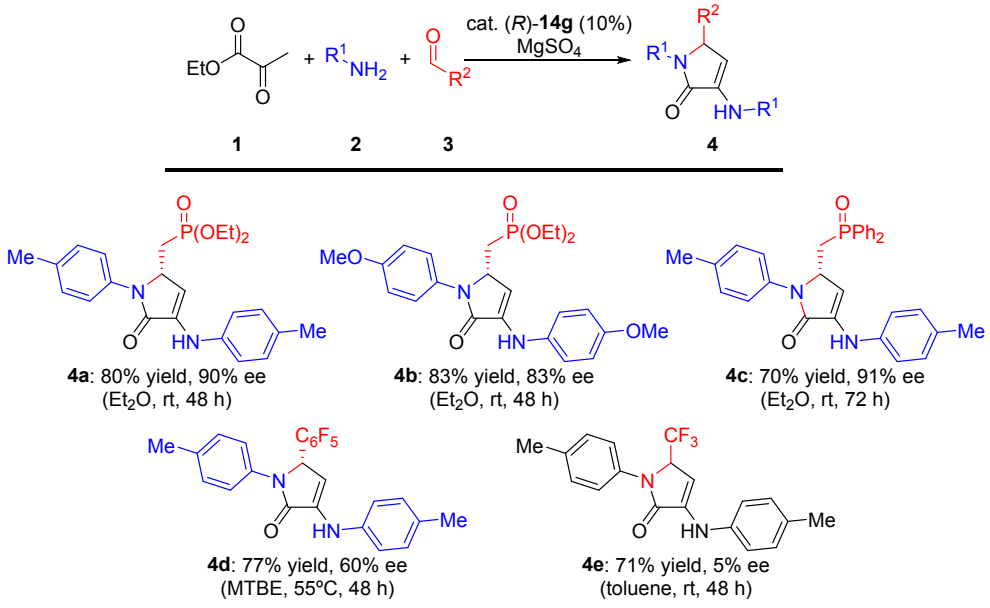
(a) Determined by chiral HPLC.

Next, in order to further improve the ee values, a study of the solvent effect was performed using Brönsted acid catalyst (*R*)-**14g**. Switching from dichloromethane to less polar chloroform resulted in a slight improvement in the enantioselectivity (Table 1, Entry 9). However, nearly the same improvement was observed when dichloromethane was exchanged by a very low polar solvent such as toluene (Table 1, Entry 10) or by a strong polar solvent such as acetonitrile (Table 1, Entry 11). To our delight, an excellent ee value was observed when diethyl ether was used as the reaction media (Table 1, Entry 12). This fact prompted us to test other ethers a solvents and, although similar results were observed for di-*iso*-propyl ether, MTBE, dimethoxyethane or THF, the conversion rates were found to be lower in those cases (Table 1, Entries 13-16).

With an optimal catalytic system in hands, next we tried to expand the scope of the enantioselective MCR to diverse 3-amino γ-lactam derivatives **4** (Chart 3). In Et_2O, under the optimal conditions, the utilization of an aromatic amine with a strong electron donating group such as *p*-anisidine instead of *p*-toluidine, resulted in a drop of the ee from 90% to 83% (Chart 3, **4a-b**). It should be noted that, although the use of an electron rich amine in our MCR would

result in a more reactive enamine nucleophile **10**, the effect of the use of such amine on the imine intermediate **11** would be the opposite, decreasing its electrophilic character (see Scheme 6). Disparate effects into the reactivity of the intermediate species have been already observed when differently substituted amines where used in this multicomponent process.[8a,16]

Chart 3. Generalization of enantioselective MCR for the synthesis of phosphorus containing γ-lactams **4**.



Although diphenylphosphine oxides show normally very limited solubility in organic solvents, and particularly in ethers, in our case, the MCR using aldehyde **3b** ($R^2 = CH_2POPh_2$) derived from phosphine oxide in Et_2O proceeded in suspension, to afford phosphorylated γ-lactam **4c**, with an optimal ee of 91% (Chart 3). On the contrary, when perfluorobenzaldehyde (**3c**, $R^2 = C_6F_5$) was used instead of phosphorylated aldehydes **3a-b** the reaction did not proceed at all at room temperature. However, in this case, the reaction in refluxing MTBE proceeded relatively fast to afford enantioenriched perfluorophenyl substituted lactam **4d** in moderate ee (Chart 3). Remarkably, the use of trifluoroacetaldehyde (**3d**, $R^2 = CF_3$) using toluene as solvent

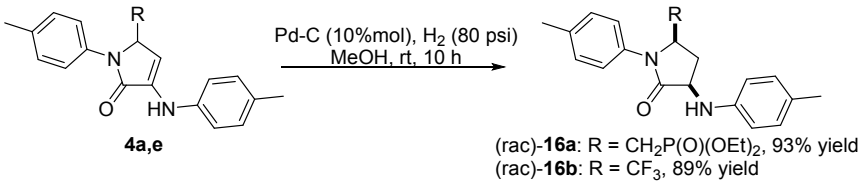
provided the racemic mixture of lactam **4e**. The lack of enantioselectivity in this case could be attributed to the small size of trifluoromethyl substituent and/or a possible racemization through an aromatic pyrrole intermediate that may be originated as a consequence of the strong acidity of the proton at the stereogenic carbon, due to the presence of the strong electron withdrawing trifluoromethyl group. In order to determine the absolute configuration of the major enantiomer obtained in the MCR, monocrystals of the major enantiomer of γ-lactam **4a** were obtained from diethyl ether and an *S* absolute configuration was determined from its x-ray diffraction spectrum (See ESI).

The next stage in the development of our enantioselective multicomponent methodology was obviously its extension to the use of phosphorus substituted pyruvate derivatives **9** (R = $P(O)R_2$). However, the presence of the enol moiety resulted in a strong polar character in γ-lactams **9** and the separation of both enantiomers using chiral HPLC resulted a very difficult task. Attempts to resolve the enantiomers using chiral shift reagents were also unsuccessful. Acceptable separation conditions were finally found using chiral HPLC but only for di-*iso*-propylphosphonate substituted γ-lactam **9k**. However, our MCR using substituted pyruvate derivatives as substrates is known to proceed only at high temperatures and, unfortunately, only the almost racemic mixture of phosphonate substituted lactam **9k** was obtained using the optimal catalytic system in refluxing MTBE. Besides, a clear separation of enantiomers was obtained when γ-lactam **9a** was treated with TMS-CHN_2 in order to generate the less polar enolether but, unfortunately very poor enantiomeric excess were observed for this substrate when phosphoric acid (*R*)-**14g** was used as catalyst.

In order to underscore the synthetic potential of enamine derived γ-lactams **4** some diastereoselective transformations were next explored. Starting from racemic mixtures of γ-

lactam derivatives **4a-e**, the hydrogenation of dihydropyrrolone skeleton was performed under hydrogen pressure and the presence of a palladium catalyst. Under these conditions, phosphorylated and fluorinated γ-lactams (rac)-**16a-b** are obtained in excellent yield as a single *cis* diastereoisomer (Scheme 3).

Scheme 3. Diastereoselective hydrogenation of γ-lactams **4a,e**.

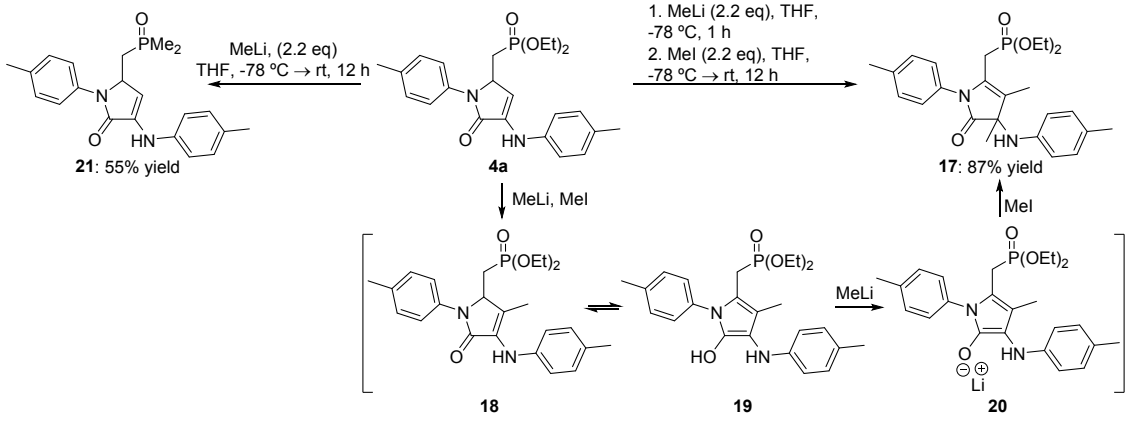


The relative configuration of the stereocenters in saturated γ-lactams (rac)-**16** was determined by NOESY (see ESI). NMR experiments with compound (rac)-**16b** showed NOE of both protons at the two stereogenic centers, at δ = 4.16 and 4.63 ppm, respectively, with the same NMR signal corresponding to one of the protons of the diastereotopic CH_2 group at δ = 3.04 ppm, indicating that these three atoms are oriented in the same direction. As expected, a strong NOE is observed between both diastereotopic protons. The fact that no NOE is observed between the signal corresponding to the second of the diastereotopic protons, at δ = 2.13 ppm, and the two protons at both stereogenic centers confirms a relative *cis* configuration between the trifluoromethyl and the amino groups. This relative configuration is in agreement with the accepted mechanism for a catalytic hydrogenation of a carbon-carbon double bond, consisting in a *syn* addition of hydrogen that, in our case, approaches to the double bond from the less hindered face, that is, the opposite to the substituent in the stereogenic carbon.

As it has been addressed above, 3-amino 1,5-dihydro-2*H*-pyrrol-2-one derivatives **4** contain the enamine moiety in their structure. Then, in view of the potential nucleophilic character of γ-lactams **4**, a simple alkylation reaction was performed in order to demonstrate

that the enamine moiety can be functionalized. Our attempts using bases such as tertiary amines, hydrides or alkoxides afforded complex mixtures. The use of a strong base such as lithium di-*iso*-propylamide provided the unaltered starting materials but, using small methyllithium as a base and methyl iodide as electrophile, dialkylated γ-lactam **17** was obtained. Due to the several positions available for the second functionalization step, the structure of **17** was unambiguously determined by x-ray diffraction (see ESI). The double functionalization may be explained by a first alkylation of enamine moiety to afford mono-methylated γ-lactam **18**, which *via* tautomerization would be in equilibrium with hydroxypyrrole **19**. Species **19** contains an enol moiety that would be deprotonated to enolate **20** and then undergo a second alkylation process (Scheme 4).

Scheme 4. Alkylation of γ-lactam **4a**.

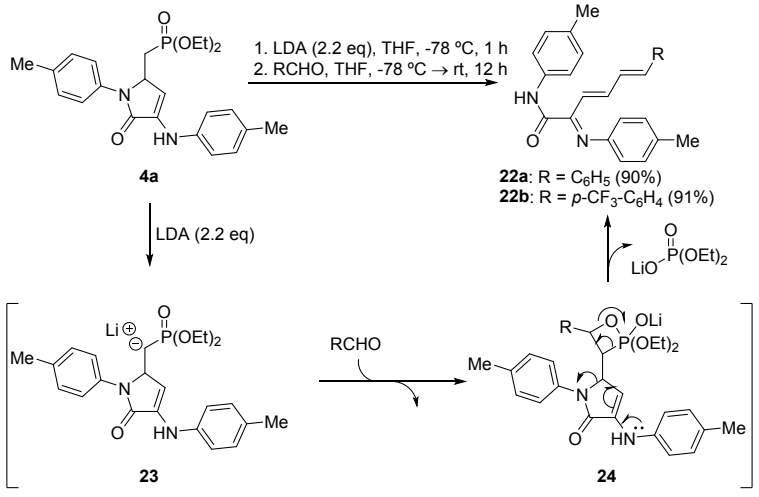


Although we tried to balance the ratios of methyllithium and methyl iodide in order to obtain selectively the mono-alkylated compound, in all our attempts dimethylated lactam **17** was obtained. It is clear that dihydropyrrolone skeleton in **4a** could also behave as a Michael acceptor due to the presence of a α,β-unsaturated carbonyl moiety. Then, another key question to be addressed is, if both methyl groups are originated from methyl iodide or if any of them arises from a conjugate addition of organometallic reagent. For this reason we treated

phosphorylated γ-lactam **4a** with an excess of methyllithium without the presence of any electrophile and, to our surprise, we observed as the main reaction, the transformation of the phosphonate into a phosphine oxide group through the displacement of ethoxy groups by the strong nucleophile methyllithium to afford phosphorated lactam **21** (Scheme 2).

Stabilized phosphonate carbanions were long time ago described as efficient precursors of *E*-olefins by their reaction with aldehydes in what today is known as Horner-Wadsworth-Emmons reaction.[24] In our case, the treatment of phosphonate derived lactam **4a** with LDA at low temperature followed by the addition of benzaldehyde or *p*-trifluoromethylbenzaldehyde surprisingly led to the formation of conjugated aza-trienes **22**, where a ring opening of the γ-lactam core occurred.

Scheme 5. Horner-Wadsworth-Emmons reaction of γ-lactam **4a**.



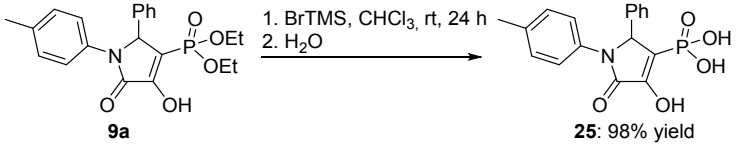
Although other explanations can be accepted, we may justify the formation of compounds **22** by an initial formation of anionic species **23** by the presence of a strong base followed by the expected nucleophilic attack reaction with the aldehyde to afford intermediate 4-membered oxaphosphetane **24**. Then, an internal elimination of the nitrogen of amide moiety

with the concomitant elimination of the phosphorus species would lead to the formation of aza-trienes **22**, which are obtained in excellent yields (Scheme 5). We were aware, however, that the mechanism of the reaction could imply a simple olefination reaction followed by a ring opening and, for this reason, we prepared the known γ-lactam substrate expected as the product of the olefination reaction of **4a** with benzaldehyde, using ethyl pyruvate *p*-toluidine and cinnamaldehyde as substrates in the multicomponent reaction[16]. Then we submitted the resulting unsaturated γ-lactam to strong basic conditions and/or strong heating and the starting material was recovered unaltered. This fact may suggest that the ring opening step occurs from the oxaphosphentane intermediate **24** as proposed in our tentative mechanism

Due to the complex pattern observed in NMR and considering that the exact mass of the open azatrienes **22** and their γ-lactam precursors **4** is coincident, next we isolated a monocrystal of lactam **22a** and its structure was unambiguously established by x-ray diffraction (See ESI).

Additionally, the transformation of phosphonate substituted γ-lactam **9a** into its phosphonic acid derivative can be performed under mild conditions in the presence of trimethylsilyl bromide at room temperature. A subsequent aqueous workup yields phosphonic acid substituted γ-lactam **25** in almost quantitative yield (Scheme 6).

Scheme 6. Hydrolysis of phosphonate **9a**.



9a **25**: 98% yield

Conclusion

We report a Brönsted acid catalyzed multicomponent methodology for the synthesis of fluorine and/or phosphorus containing γ-lactam derivatives which bear a chiral carbon. The products are obtained in the form of 3-hydroxy 1,5-dihydro-2*H*-pyrrol-2-one or their enamine derivatives depending on the substitution at the 5-membered ring heterocycle. Some examples of the enantioselective version of the reaction are also reported using substituted BINOL derived phosphoric acids as catalysts. Moreover, 3-amino 1,5-dihydro-2*H*-pyrrol-2-one derivatives have proved to be excellent synthetic intermediates in some diastereoselective transformations, making use of the stereogenic carbon present in the γ-lactam skeleton as chiral inductor. An extensive characterization of the different isomers obtained is also provided.

Experimental section.

General. Solvents for extraction and chromatography were technical grade. All solvents used in reactions were freshly distilled from appropriate drying agents before use. All other reagents were recrystallized or distilled as necessary. All reactions were performed under an atmosphere of dry nitrogen. Analytical TLC was performed with silica gel 60 F_{254} plates. Visualization was accomplished by UV light. ^{1}H, ^{13}C, ^{31}P and ^{19}F NMR spectra were recorded on a Varian Unity Plus (at 300 MHz, 75 MHz, 120 MHz and 282 MHz respectively) and on a Bruker Avance 400 (at 400 MHz for ^{1}H, 100 MHz for ^{13}C and 162 MHz for ^{31}P). Chemical shifts (δ) are reported in ppm relative to residual $CHCl_3$ (δ = 7.26 ppm for ^{1}H and δ = 77.2 ppm for ^{13}C NMR) rounded to the nearest 0.01 for ^{1}H NMR and 0.1 for ^{13}C NMR, ^{31}P NMR and ^{19}F NMR and using phosphoric acid (50 %) as an external reference (δ = 0.0 ppm) for ^{31}P NMR spectra. Coupling constants *(J)* are reported in Hertz to the nearest 0.1 Hz. Data for ^{1}H NMR spectra are reported as follows: chemical shift, multiplicity, coupling constant, integration). Multiplicity abbreviations are as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet) and br (broad). ^{13}C NMR were recorded with complete proton decoupling. Carbon types, structure assignments and attribution of peaks were determined from Distortionless Enhanced Polarization Transfer (DEPT-NMR). Relative stereochemistry was assigned based on the 1D-NOE experiments. High-resolution mass spectra (HRMS) were obtained by positive-ion electrospray ionization (ESI). Data are reported in the form *m/z* (intensity relative to base =

100). Infrared spectra (IR) were taken in a Nicolet iS10 Termo Scientific spectrometer as neat solids. Peaks are reported in cm^{-1}. Phosporylated aldehydes **3** were prepared using Savignac's method.[22] Phosphorylated pyruvates **6** were obtained according to methods described in the literature.[23]

General procedure for the racemic synthesis of γ-lactams 4. Method A. A solution of aldehyde **3** (5 mmol), ethyl pyruvate **1** (1.74 g, 15 mmol), amine **2** (10 mmol), phosphoric acid catalyst (rac)-**5** (174 mg, 0.5 mmol) and anhydrous $MgSO_4$ (2.5 g) was stirred in Et_2O (25 mL) at room temperature or in MTBE (25 mL) at 55 °C (heating plate with Heat-On) for 48 h. The volatiles were distilled off at reduced pressure and the crude residue was purified by column chromatography (AcOEt/hexanes 9:1).

General procedure for the stereoselective synthesis of γ-lactams 4. Method B. A solution of aldehyde **3** (0.1 mmol), ethyl pyruvate **1** (0.3 mmol), amine **2** (0.2 mmol), phosphoric acid catalyst (*R*)-**14g** (8.6 mg, 0.01 mmol) and anhydrous $MgSO_4$ (100 mg) was stirred in Et_2O or MTBE (1 mL) at room temperature or 55 ºC (heating plate with Heat-On) for 48 h. The volatiles were distilled off at reduced pressure and the crude residue was purified by column chromatography (AcOEt/hexanes 9/1) to afford pure lactams **4**.

Diethyl ((5-oxo-1-(4-methylphenyl)-4-(4-methylphenylamino)-2,5-dihydro-1*H*-pyrrol-2-yl)methyl)phosphonate (4a). The general procedure A was followed in Et_2O at room temperature affording 1.84 g (4.3 mmol, 85%) of pure lactam **4a** as a yellow solid. M.p. (Et_2O) 119-121 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37 (d, $^3J_{HH}$ = 8.4 Hz, 2H), 7.24 (d, $^3J_{HH}$ = 8.4 Hz, 2H,), 7.12 (d, $^3J_{HH}$ = 8.4 Hz, 2H), 7.02 (d, $^3J_{HH}$ = 8.4 Hz, 2H), 6.49 (bs, 1H, NH), 6.34 (d, $^3J_{HH}$ = 2.5 Hz, 1H), 4.93 (m, 1H), 4.20 – 4.05 (m, 4H), 2.37 (s, 3H), 2.31 (s, 3H), 1.74 – 1.56 (m, 2H), 1.35 (t, $^3J_{HH}$ = 7.1 Hz, 6H). ^{13}C NMR {^{1}H} (75 MHz, $CDCl_3$) δ 165.9 (C=O), 138.9 (C_{quat}), 135.7 (C_{quat}), 133.4 (C_{quat}), 130.9 (C_{quat}), 130.1 (CH), 130.0 (CH), 122.7 (CH), 120.5 (C_{quat}), 116.9 (CH), 105.3 (CH), 62.2 (d, $^2J_{PC}$ = 4.0 Hz, CH_2), 62.1 (d, $^2J_{PC}$ = 3.9 Hz, CH_2), 55.3 (CH), 29.9 (d, $^1J_{PC}$ = 140.3 Hz, CH_2), 21.1 (CH_3), 20.8 (CH_3), 16.7 (CH_3), 16.6 (CH_3). ^{31}P NMR (121 MHz, $CDCl_3$) δ 27.6. FTIR (neat) ν_{max}: 3411 (NH), 1682 (C=O), 1650 (C=CH), 1292 (P=O), 1118 (P-O-C). HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{23}H_{30}N_2O_4P$ 429.1943; Found 429.1936.

The general procedure B was followed in Et_2O at room temperature affording 36.1 mg (0.08 mmol, 80%) of (*S*)-**4a**. ee (90 %) was determined by HPLC analysis (Chiracel-IC, heptane/CH_2Cl_2/ethanol 50:47:3, 1 mL/min). Retention time (min): 13.6 (minor) and 14.7 (major).

Diethyl ((1-(4-methoxyphenyl)-4-((4-methoxyphenyl)amino)-5-oxo-2,5-dihydro-1*H*-pyrrol-2-yl)methyl)phosphonate (4b). The general procedure A was followed in Et_2O at room temperature affording 1.84 g (4.0 mmol, 80%) of **4b** as a colorless solid. M.p. (Et_2O) 136-137°C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37 (d, $^3J_{HH}$ = 8.8 Hz, 2H), 7.07 (d, $^3J_{HH}$ = 8.9 Hz, 2H), 6.97 (d, $^3J_{HH}$ = 8.9 Hz, 2H), 6.88 (d, $^3J_{HH}$ = 8.8 Hz, 2H), 6.37 (bs, 1H), 6.26 (d, $^3J_{HH}$ = 2.2 Hz, 1H), 4.86 (m, 1H), 4.19 – 4.05 (m, 4H), 3.83 (s, 3H), 3.80 (s, 3H), 2.35 (m, 1H), 1.63 (m, 1H), 1.34 (t, $^3J_{HH}$ = 6.7 Hz, 6H). ^{13}C NMR {^{1}H} (75 MHz, $CDCl_3$) δ 166.0 (C=O), 157.7 (C_{quat}), 154.6 (C_{quat}), 134.9 (C_{quat}), 134.0 (C_{quat}), 128.9 (C_{quat}), 124.7 (CH), 118.6 (CH), 114.9 (CH), 114.8 (CH), 104.3 (CH), 62.1 (d, $^2J_{PC}$ = 6.5 Hz, CH_2), 62.1 (d, $^2J_{PC}$ = 6.5 Hz, CH_2), 55.8 (CH_3), 55.7 (CH_3), 55.6 (CH), 30.0 (d, $^1J_{PC}$ = 140.5 Hz, CH_2), 16.7 (CH_3), 16.6 (CH_3). ^{31}P NMR (121 MHz, $CDCl_3$) δ 26.9. FTIR (neat) ν_{max} 3309 (NH), 1685 (C=O), 1650 (C=CH), 1251 (P=O), 1030 (P-O-C). HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{23}H_{30}N_2O_6P$ 461.1841; Found 461.1834.

The general procedure B was followed in Et_2O at room temperature affording, 36.8 mg (0.08 mmol, 76%) of (*S*)-**4b**. ee (83 %) was determined by HPLC analysis (Chiracel-IC, heptane/CH_2Cl_2/ethanol 50:40:10, 1 mL/min). Retention time (min): 8.3 (minor) and 9.2 (major).

5-((Diphenylphosphoryl)methyl)-1-(4-methylphenyl)-3-(4-methylphenylamino)-1*H*-pyrrol-2(5*H*)-one (4c). The general procedure A was followed in Et_2O for 72 h at room temperature affording 1.87 g (3.80 mmol, 76%) of **4c** as a colorless solid. M.p. (Et_2O) 215-216 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, $^3J_{HH}$ = 8.5 Hz, 2H), 7.73 (d, $^3J_{HH}$ = 10.1 Hz, 2H), 7.62 – 7.46 (m, 6H), 7.25 (m, 2H), 7.19 (d, $^3J_{HH}$ = 7.9 Hz, 2H), 7.03 (d, $^3J_{HH}$ = 8.0 Hz, 2H), 6.74 (d, $^3J_{HH}$ = 8.0 Hz, 2H), 6.41 (s, 1H), 6.05 (s, 1H), 5.01 (m, 1H), 2.95 – 2.83 (m, 1H), 2.35 (s, 3H), 2.29 (s, 3H), 2.22 (m, 1H). ^{13}C NMR {^{1}H} (101 MHz, $CDCl_3$) δ 165.9 (C=O), 138.7 (C_{quat}), 135.5 (C_{quat}), 133.3 (C_{quat}), 132.96 (d, $^1J_{PC}$ = 102.3 Hz, C_{quat}), 132.8 (C_{quat}), 132.5 (d, $^1J_{PC}$ = 101.2 Hz, C_{quat}), 132.4 (d, $^4J_{PC}$ = 2.6 Hz, CH), 132.3 (d, $^4J_{PC}$ = 2.6 Hz, CH), 131.0 (d, $^2J_{PC}$ = 9.4 Hz, 2x CH), 130.9 (d, $^2J_{PC}$ = 9.3 Hz, CH), 130.6 (C_{quat}), 130.0 (CH), 129.9 (CH), 129.1 (d, $^3J_{PC}$ = 11.9 Hz, CH), 129.0 (d, $^3J_{PC}$ = 11.8 Hz, CH), 122.6 (CH), 116.7 (CH), 105.8 (CH), 55.0 (CH), 33.93 (d, $^1J_{PC}$ = 69.8 Hz, CH_2), 21.1 (CH_3), 20.8 (CH_3). ^{31}P NMR (121 MHz, $CDCl_3$) δ 28.3 ppm. FTIR (neat) ν_{max} 3297 (NH), 1682 (C=O), 1646 (C=CH), 1191 (P=O) cm^{-1}. HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{31}H_{30}N_2O_2P$ 493.2045; Found 493.2042.

The general procedure B was followed in Et_2O at room temperature for 72 h affording, 34.5 mg (0.07 mmol, 70%) of (*S*)-**4c**. ee (91 %) was determined by HPLC analysis (Chiracel-IB, heptane/ethanol 95/5, 1 mL/min). Retention time (min): 26.2 (major) and 40.8 (minor).

5-(Perfluorophenyl)-1-(4-methylphenyl)-3-(4-methylphenylamino)-1*H*-pyrrol-2(5*H*)-one (4d). The general procedure A was followed using MTBE at 55 °C (heating plate, Heat-On) to afford, after column chromatography (AcOEt/hexanes 9/1), 1.82 g (4.10 mmol, 82%) of **4d** as a colorless solid. M.p. (Et_2O) 224 °C (dec.). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (d, $^3J_{HH}$ = 8.4 Hz, 2H), 7.16 (d, $^3J_{HH}$ = 8.4 Hz, 2H), 7.13 (d, $^3J_{HH}$ = 8.4 Hz, 2H), 7.00 (d, $^3J_{HH}$ = 8.4 Hz, 2H), 6.66 (bs, 1H), 6.13 (d, $^3J_{HH}$ = 2.5 Hz, 1H), 5.92 (d, $^3J_{HH}$ = 2.5 Hz, 1H), 2.31 (CH_3), 2.30 (CH_3). ^{13}C NMR {^{1}H} (75 MHz, $CDCl_3$) δ 166.4 (C=O), 147.1 (m, C_{quat}), 143.8 (m, C_{quat}), 139.4 (m, C_{quat}), 138.5 (C_{quat}), 135.8 (C_{quat}), 134.7 (C_{quat}), 133.8 (C_{quat}), 131.5 (C_{quat}), 130.1 (CH), 121.6 (CH), 117.3 (CH), 111.3 (m, C_{quat}) 100.8 (CH), 54.4 (CH), 21.1 (CH_3), 20.8 (CH_3). ^{19}F NMR (282 MHz, $CDCl_3$) δ -145.3, -153.8, -161.4. FTIR (neat) ν_{max} 3322 (NH), 1693 (C=O), 1649 (C=CH) cm^{-1}. HRMS (ESI-TOF) m/z calcd for $C_{24}H_{18}F_5N_2O$ $[M+H]^+$ 445.1339, found 445.1339.

The general procedure B was followed using MTBE at 55 °C (heating plate, Heat-On) to afford 35.6 mg (0.08 mmol, 77%) of (*S*)-**4d**. ee (60 %) was determined by HPLC analysis (Chiracel-IB, heptane/ethanol 98:2, 1 mL/min). Retention time (min): 9.5 (minor) and 11.1 (major).

1-(4-methylphenyl)-3-(4-methylphenylamino)-5-(trifluoromethyl)-1,5-dihydro-2*H*-pyrrol-2-one (4e). A solution of toluidine (**2a**, 214 mg, 2 mmol), and 2,2,2-trifluoroethane-1,1-diol (122 µL, 1.5 mmol) in toluene (10 mL) was heated at 110 °C using a Dean-Stark on a heating plate (Heat-On) until the water was fully removed. When the imine was completely formed (monitored by ^{19}F NMR: 2,2,2-trifluoroethane-1,1-diol: -85,5 ppm; imine: -79 ppm), ethyl pyruvate (333 µL, 3 mmol) and phosphoric acid catalyst (rac)-**5** (34.8 mg, 0.1 mmol) were added, and the reaction was stirred for 48 h at room temperature. The volatiles were distilled off at reduced pressure and the crude residue was purified by column chromatography (AcOEt/hexanes 9/1) to afford 0.259 g (0.075 mmol, 75%) of **4e** as a colorless solid. M.p. (Et_2O) 205-206 °C. ^{1}H NMR (400 MHz, $CDCl_3$) 7.2-7.25 (m, 4H), 7.16 (d, $^3J_{HH}$ = 8.5 Hz, 2H), 7.02 (d, $^3J_{HH}$ = 8.4 Hz, 2H), 6.62 (s, 1H), 5.86 (d, $^3J_{HH}$ = 2.7 Hz, 1H), 5.12 (dq, $^3J_{HF}$= 5.3, $^3J_{HH}$ = 2.7 Hz, 1H), 2.39 (s, 3H), 2.33 (s, 3H). ^{13}C NMR {1H} (101 MHz, $CDCl_3$) δ 167.3 (C=O), 138.1 (C_{quat}), 137.3 (C_{quat}), 136.3 (C_{quat}), 133.6 (C_{quat}), 131.9 (C_{quat}), 130.1 (CH), 130.0 (CH), 125.0 (CH), 124.0 (q, $^1J_{FC}$ = 282.6 Hz, CF_3), 117.6 (CH), 94.7 (d, $^3J_{FC}$ = 2.3 Hz, CH), 61.7 (q, $^2J_{FC}$ = 32.3 Hz, CH), 21.2 (CH_3), 20.9 (CH_3). ^{19}F NMR (282 MHz, $CDCl_3$) δ -73.2 (d, $^3J_{FH}$ =

5.3 Hz, CF_3). FTIR (neat) ν_{max} 3314 (NH), 1693 (C=O), 1657 (C=CH), 1382 (CF_3). HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{19}H_{18}F_3N_2O$ 347.1371; Found 347.1370.

The same procedure was performed using 0.2 mmol of toluidine (**2a**, 21.4 mg), 0.15 mmol (12.2 μL) of 2,2,2-trifluoroethane-1,1-diol phosphoric, ethyl pyruvate (**1**, 33.3μL, 0.3 mmol) and phosphoric acid catalyst (*R*)-**14g** (8.6 mg, 0.01 mmol) to afford 24.6 mg (0.07 mmol, 71%) of **4e** as an almost racemic mixture. ee (4.9 %) was determined by HPLC analysis (Chiracel-IB, heptane/ethanol 98:2, 1 mL/min). Retention time (min): 12.1 (major) and 16.2 (minor).

Diethyl (5-oxo-1-(p-tolyl)-4-(p-tolylamino)-2,5-dihydro-1*H*-pyrrol-3-yl)phosphonate (8a). The general procedure (method A) described for the synthesis of γ-lactams **4** was followed starting from phosphorylated pyruvate **6a** (0.756 g, 3 mmol) and formaldehyde **7** (0.81 mL of 37 wt % in H_2O solution, 1 mmol), using catalyst (rac)-**5** (34.83 mg, 0.1 mmol) and refluxing in MTBE for 24 h to afford, after column chromatography (AcOEt/hexanes 9/1), 0.315 g (0.076 mmol, 76%) of **8a** as an orange solid. M.p. (Et_2O) 120-121 °C (dec.). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.79 (d, $^3J_{HH}$ = 8.5 Hz, 2H, 2xCH_{Ar}), 7.56 (bs, 1H, NH), 7.34 (d, $^3J_{HH}$ = 8.5 Hz, 2H, 2xCH_{Ar}), 7.29 – 7.21 (m, 4H, 4xCH_{Ar}), 4.61 (d, $^3J_{PH}$ = 3.2 Hz, 2H, CH_2N), 4.28 – 4.06 (m, 4H, 2x$\underline{H}_2CH_3$), 2.49 (s, 3H, CH_3 Tol), 2.48 (s, 3H, CH_3 Tol), 1.42 (t, $^3J_{HH}$ = 7.0 Hz, 6H, 2x$CH_2C\underline{H}_3$). ^{13}C NMR {^{1}H} (75 MHz, $CDCl_3$) δ 164.1 (d, $^2J_{PC}$ = 20.5 Hz, C_{quat}), 145.2 (d, $^3J_{PC}$ = 7.4 Hz, C=O), 137.0 (C_{quat}), 136.2 (C_{quat}), 135.0 (C_{quat}), 134.3 (C_{quat}), 129.8 (CH), 129.2 (CH), 123.1 (CH), 119.2 (CH), 96.2 (d, $^1J_{PC}$ = 212.8 Hz, CP), 62.1 (CH_2), 62.0 (CH_2), 50.4 (d, $^2J_{PC}$ = 16.0 Hz, CH_2), 21.1 (CH_3), 21.0 (CH_3), 16.4 (CH_3), 16.3 (CH_3). ^{31}P NMR (121 MHz, $CDCl_3$) δ 14.7. FTIR (neat) ν_{max} 3281 (NH), 1693 (C=O), 1632 (C=C), 1227 (P=O), 1018 (P-O-C). HRMS (Q-TOF) m/z: $[M+H]^+$ calcd for $C_{22}H_{28}N_2O_4P$ 415.1787; Found 415.1789.

4-(Diphenylphosphoryl)-1-(p-tolyl)-3-(p-tolylamino)-1,5-dihydro-2*H*-pyrrol-2-one (8b). The general procedure (method A) described for the synthesis of γ-lactams **4** was followed starting from phosphorylated pyruvate **6b** (0.948g, 3 mmol) and formaldehyde **7** (0.81 mL of 37 wt % in H_2O solution, 1 mmol), using catalyst (rac)-**5** (34.83 mg, 0.1 mmol) and refluxing in MTBE for 24 h to afford, after column chromatography (AcOEt/hexanes 9/1), 0.349 g (0.073 mmol, 73%) of **8b** as an orange solid. M.p. (Et_2O) 188 °C (dec.). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70 – 7.62 (m, 5H), 7.53 – 7.40 (m, 9H), 7.13 (d, $^3J_{HH}$ = 8.2 Hz, 2H, 2xCH_{Ar}), 6.92 (bs, 3H), 4.15 (d, $^3J_{PH}$ = 2.6 Hz, 2H), 2.31 (s, 3H), 2.25 (s, 3H). ^{13}C NMR {^{1}H} (75 MHz, $CDCl_3$) δ 164.2 (d, $^3J_{PC}$ = 14.0 Hz, C=O), 146.9 (d, $^2J_{PC}$ = 2.8 Hz, C_{quat}), 136.8 (C_{quat}), 136.1 (C_{quat}), 135.0 (C_{quat}), 134.1 (C_{quat}), 132.3 (d, $^1J_{PC}$ = 108.3 Hz, C_{quat}), 132.1 (d, $^4J_{PC}$ = 2.8 Hz, CH), 131.3 (d,

$^{2}J_{PC}$ = 10.1 Hz, CH), 129.7 (CH), 129.3 (CH), 128.8 (d, $^{3}J_{PC}$ = 12.3 Hz, CH), 123.5 (CH), 119.4 (CH), 99.2 (d, $^{1}J_{PC}$ = 115.1 Hz, $C_{quat}P$), 51.0 (d, $^{2}J_{PC}$ = 15.5 Hz, CH_2), 21.0 (CH_3). ^{31}P NMR (121 MHz, $CDCl_3$) δ 21.8. FTIR (neat) ν_{max} 3245 (NH), 1693 (C=O), 1601 (C=C), 1185 (P=O). HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{30}H_{28}N_2O_2P$ 479.1888; Found 479.1888.

Diethyl (4-hydroxy-5-oxo-2-phenyl-1-(4-methylphenyl)-2,5-dihydro-1*H*-pyrrol-3-yl)phosphonate (9a). The general procedure described for the synthesis of γ-lactams **4** (method A, MTBE, 55 °C) was followed starting from phosphorylated pyruvate **6a** (0.756 g, 3 mmol) to afford, after column chromatography (AcOEt/hexanes 7/3), 0.385 g (0.96 mmol, 96%) of **9a** as a colorless solid. M.p. (Et_2O) 145-147 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.75 (bs, 1H), 7.36 (d, $^{3}J_{HH}$ = 8.5 Hz, 2H), 7.26 – 7.13 (m, 5H), 7.05 (d, $^{3}J_{HH}$ = 8.3 Hz, 2H), 5.58 (d, $^{3}J_{PH}$ = 2.8 Hz, 1H), 4.15 (m, 2H), 3.70 (m, 1H), 3.16 (m, 1H), 2.23 (s, 3H, CH_3), 1.39 (t, $^{3}J_{HH}$ = 7.1 Hz, 3H), 0.80 (t, $^{3}J_{HH}$ = 7.1 Hz, 3H). ^{13}C NMR $\{^{1}H\}$ (75 MHz, $CDCl_3$) δ 163.0 (d, $^{2}J_{PC}$ = 19.8 Hz), 160.0 (d, $^{3}J_{PC}$ = 6.5 Hz), 135.7 (C_{quat}), 135.5 (C_{quat}), 134.1 (C_{quat}), 129.7 (CH), 129.1 (CH), 128.7 (CH), 127.1 (CH), 121.9 (CH), 106.6 (d, $^{1}J_{PC}$ = 200.8 Hz, CP), 62.98 (d, $^{2}J_{PC}$ = 5.4 Hz, CH_2), 62.71 (CH), 62.56 (d, $^{2}J_{PC}$ = 4.5 Hz, CH_2), 21.01 (CH_3), 16.54 (d, $^{3}J_{PC}$ = 6.4 Hz, CH_3), 15.63 (d, $^{3}J_{PC}$ = 7.5 Hz, CH_3). ^{31}P NMR (121 MHz, $CDCl_3$) δ 15.4. FTIR (neat) ν_{max}: 3112 (OH), 1692 (C=O), 1663 (C=C), 1165 (P=O), 1021 (P-O-C). HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{21}H_{25}NO_5P$ 402.1470; Found 402.1468.

The general procedure B was followed using MTBE at 55 °C (heating plate, Heat-On) to afford 30.0 mg (0.08 mmol, 75%) of **9a** as an almost racemic mixture. ee (3 %) was determined by treatment with $TMSCHN_2$ followed by detection of the enolether derivative by HPLC analysis (Chiracel-IC, heptane/ethanol 90:10, 1 mL/min). Retention time (min): 11.6 (minor) and 14.0 (major).

Diethyl (2-(4-fluorophenyl)-4-hydroxy-5-oxo-1-(4-methylphenyl)-2,5-dihydro-1*H*-pyrrol-3-yl)phosphonate (9b). The general procedure described for the synthesis of γ-lactams **4** (method A, MTBE, 55 °C) was followed starting from phosphorylated pyruvate **6a** (0.756 g, 3 mmol) to afford, after column chromatography (AcOEt/hexanes 7/3), 0.302 g (0.72 mmol, 72%) of **9b** as a light yellow solid. M.p. (Et_2O) 141-142 °C. ^{1}H NMR (400 MHz, DMSO-d_6, 70°C) δ 10.99 (s, 1H), 7.39 (d, $^{3}J_{HH}$ = 8.4 Hz, 2H) 7.26 (dd, $^{4}J_{FH}$ = 5,4, $^{3}J_{HH}$= 8.8 Hz, 2H), 7.08 (d, $^{3}J_{HH}$ = 8.4 Hz, 2H), 7.03 (t, $^{3}J_{HH}$ and $^{3}J_{FH}$ = 8.9 Hz, 2H), 5.90 (d, $^{3}J_{PH}$ = 2.9 Hz, 1H), 3.97 – 3.67 (m, 4H), 2.21 (s, 3H), 1.11 (dt, $^{3}J_{HH}$ = 7.0, $^{4}J_{PH}$ = 3.2 Hz, 6H). ^{13}C NMR $\{^{1}H\}$ (101 MHz, DMSO-d_6, 70°C) δ 163.4 (d, $^{2}J_{PC}$ = 18.3 Hz, C_{quat}), 161.7 (d, $^{1}J_{FC}$ = 244.0 Hz, $C_{quat}F$), 154.9 (d,

$^{3}J_{PC}$ = 4.1 Hz, C=O), 134.7 (C_{quat}), 133.71 (C_{quat}), 132.3 (d, $^{4}J_{FC}$ = 2.8 Hz, C_{quat}), 129.9 (d, $^{3}J_{FC}$ = 21.6 Hz, CH), 129.2 (CH), 122.6 (CH), 115.1 (d, $^{2}J_{FC}$ = 21.6 Hz, CH), 108.2 (d, $^{1}J_{PC}$ = 201.6 Hz, C_{quat}P), 61.5 (s, CH), 61.3 (d, $^{2}J_{PC}$ = 5.3 Hz, CH_2), 61.2 (d, $^{2}J_{PC}$ = 5.0 Hz, CH_2), 20.4 (CH_3), 16.0 (d, $^{3}J_{PC}$ =3.4 Hz, CH_3), 15.9 (d, $^{3}J_{PC}$ =3.4 Hz, CH_3). ^{31}P NMR (162 MHz, DMSO-d_6) δ 11.4. ^{19}F NMR (282 MHz, DMSO-d_6) δ -110.0. FTIR (neat) ν_{max} 1704 (C=O), 1631 (C=C), 1226 (P=O), 1157 (C-F), 1020 (P-O-C). HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{21}H_{24}FNO_5P$ 420.1376; Found 420.1372.

Diethyl (4-hydroxy-2-(4-nitrophenyl)-5-oxo-1-(4-methylphenyl)-2,5-dihydro-1*H*-pyrrol-3-yl) phosphonate (9c). The general procedure described for the synthesis of γ-lactams **4** (method A, MTBE, 55 °C) was followed starting from phosphorylated pyruvate **6a** (0.756 g, 3 mmol) to afford, after column chromatography (AcOEt/hexanes 7/3), 0.415 g (0.93 mmol, 93%) of **9c** as a light orange solid. M.p. (Et_2O) 188 °C (dec.). ^{1}H NMR (400 MHz, DMSO-d_6, 70°C) δ 8.05 (d, $^{3}J_{HH}$ = 8.2 Hz, 2H), 7.45 (d, $^{3}J_{HH}$ = 7.6 Hz, 4H), 7.05 (d, $^{3}J_{HH}$ = 8.0 Hz, 2H), 5.84 (s, 1H), 4.06 (m, 2H), 3.73 (m, 1H), 3.27 (bs, 1H), 2.19 (s, 3H), 1.26 (t, $^{3}J_{HH}$ = 7.0 Hz, 3H), 0.74 (t, $^{3}J_{HH}$ = 7.0 Hz, 3H). ^{13}C NMR {^{1}H} (101 MHz, DMSO-d_6, 70°C) δ 169.2 (C_{quat}), 167.7 (C_{quat}), 148.3 (C_{quat}), 146.7 (C_{quat}), 134.7 (C_{quat}), 133.9 (C_{quat}), 129.1 (CH), 128.4 (CH), 123.4 (CH), 121.7 (CH), 113.7 (CP), 61.1 (CH_2), 60.3 (CH_2), 55.1 (CH), 20.4 (CH_3), 16.3 (d, $^{3}J_{PC}$ =6.5 Hz, CH_3)**,** 15.5 (d, $^{3}J_{PC}$ =6.5 Hz, CH_3). ^{31}P NMR (162 MHz, DMSO-d_6, 60°C) δ 22.3. FTIR (neat) ν_{max} 1679 (C=O), 1596 (C=C), 1511 (NO_2), 1346 (NO_2), 1294 (P=O), 1052 (P-O-C). HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{21}H_{24}N_2O_7P$ 447.1321; Found 447.1319.

Diethyl (4-hydroxy-5-oxo-2-(thiophen-2-yl)-1-(4-methylphenyl)-2,5-dihydro-1*H*-pyrrol-3-yl)phosphonate (9d). The general procedure for the synthesis of γ-lactams **4** (method A, MTBE, 55 °C) was followed starting from phosphorylated pyruvate **6a** (0.756g, 3 mmol) to afford, after column chromatography (AcOEt/hexanes 7/3), 0.362 g (0.89 mmol, 89%) of **9d** as a colorless solid. M.p. (Et_2O) 143-144 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.82 (s, 1H), 7.31 (d, $^{3}J_{HH}$ = 8.3. Hz, 2H), 7.16 (d, $^{3}J_{HH}$ = 5.0 Hz, 1H), 7.07 (d, $^{3}J_{HH}$ = 8.3. Hz, 2H), 7.02 (d, $^{3}J_{HH}$ = 3.3 Hz, 1H), 6.83 (dd, $^{3}J_{HH}$ = 5.1, $^{3}J_{HH}$ 3.5 Hz, 1H), 5.92 (d, $^{3}J_{HH}$ = 2.8 Hz, 1H), 4.12 (m, 2H), 3.88 (m, 1H), 3.49 (m, 1H), 2.24 (s, 3H), 1.35 (t, $^{3}J_{HH}$ = 7.1 Hz, 3H), 0.98 (t, $^{3}J_{HH}$ = 7.1 Hz, 3H). ^{13}C NMR {^{1}H} (101 MHz, $CDCl_3$) δ 162.4 (d, $^{2}J_{PC}$ = 19.5 Hz, C_{quat}), 159.4 (d, $^{3}J_{PC}$ = 6.3 Hz, C=O), 139.2 (d, $^{3}J_{PC}$ = 1.2 Hz, C_{quat}), 135.9 (C_{quat}), 133.4 (C_{quat}), 129.6 (CH), 127.5 (CH), 126.7 (CH), 126.1 (CH), 122.6 (CH), 106.4 (d, $^{1}J_{PC}$ = 202.6 Hz, CP), 62.9 (d, $^{2}J_{PC}$ = 5.6 Hz, CH_2)**,** 62.8 (d, $^{2}J_{PC}$ = 5.3 Hz, CH_2), 58.4 (d, $^{2}J_{PC}$ = 13.0 Hz, CH), 21.0 (CH_3), 16.4 (d, $^{3}J_{PC}$ =6.4

Hz, CH_3), 15.8 (d, $^3J_{PC}$ =7.5 Hz, CH_3). ^{31}P NMR (162 MHz, $CDCl_3$) δ 14.6. FTIR (neat) ν_{max} 1701 (C=O), 1653 (C=C), 1232 (P=O), 1017 (P-O-C). HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{19}H_{23}NO_5PS$ 408.1035; Found 408.1033.

Ethyl 3-(diethoxyphosphoryl)-4-hydroxy-5-oxo-1-(4-methylphenyl)-2,5-dihydro-1*H*-pyrrole-2-carboxylate (9e). The general procedure described for the synthesis of γ-lactams **4** (method A, MTBE, 55 °C) was followed starting from phosphorylated pyruvate **6a** (0.756g, 3 mmol) to afford, after column chromatography (AcOEt/hexanes 8/2), 0.341 g (0.86 mmol, 86%) of **9e** as a light orange solid. M.p. (Et_2O) 123-124 °C. ^{1}H NMR (400 MHz, DMSO-d_6, 60°C) δ 7.47 (d, $^3J_{HH}$ = 8.1 Hz, 2H), 7.23 (d d, $^3J_{HH}$= 8.1 Hz, 2H), 5.42 (d, $^3J_{PH}$ = 2.9 Hz, 1H), 4.13 – 3.99 (m, 6H), 2.31 (s, 3H), 1.34 – 1.23 (m, 6H), 1.07 (t, $^3J_{HH}$ = 7.0 Hz, 3H). ^{13}C NMR {^{1}H} (101 MHz, DMSO-d_6, 60°C) δ 167.8 (C=O), 163.6 (d, $^2J_{PC}$ = 18.0 Hz, C_{quat}), 156.6 (C=O), 135.4 (C_{quat}), 134.11 (C_{quat}), 129.5 (CH), 121.4 (CH), 102.5 (d, $^1J_{PC}$ = 203.6 Hz, CP), 61.8 (d, $^2J_{PC}$ = 5.3 Hz, CH_2), 61.6 (CH_2), 61.4 (d, $^2J_{PC}$ = 15.4 Hz, CH), 20.5 (CH_3), 16.1 (d, $^3J_{PC}$ = 6.4 Hz, 2x CH_3),13.7 (CH_3). ^{31}P NMR (162 MHz, DMSO-d_6) δ 10.2. FTIR (neat) ν_{max} 1748 (C=O)1710 (C=O), 1654 (C=C), 1182 (P=O), 1027 (P-O-C). HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{18}H_{25}NO_7P$ 398.1369; Found 398.1374.

Diethyl (4-hydroxy-2-isopropyl-5-oxo-1-(4-methylphenyl)-2,5-dihydro-1*H*-pyrrol-3-yl)phosphonate (9f). The general procedure described for the synthesis of γ-lactams **4** (method A, MTBE, 55 °C) was followed starting from phosphorylated pyruvate **6a** (0.756 g, 3 mmol) to afford, after column chromatography (AcOEt/hexanes 8/2), 0.275 g (0.75 mmol, 75%) of **9f** as a colorless solid. M.p. (Et_2O) 79-81 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.01 (s, 1H), 7.23 (d, $^3J_{HH}$ = 8.5 Hz, 2H), 7.18 (d, $^3J_{HH}$ = 8.5 Hz, 2H), 4.64 (t, $^3J_{HH}$ and $^3J_{PH}$ = 2.6 Hz, 1H), 4.16 (m, 4H, m, 4H), 2.32 (s, 3H), 2.10 (m, 1H), 1.40 – 1.30 (m, 6H), 0.96 (d, $^3J_{HH}$ = 7.1 Hz, 3H), 0.59 (d, $^3J_{HH}$ = 6.9 Hz, 3H). ^{13}C NMR {^{1}H} (101 MHz, $CDCl_3$) δ 162.7 (d, $^2J_{PC}$ = 19.9 Hz, C_{quat}), 161.2 (d, $^3J_{PC}$ = 5.9 Hz, C=O) 136.5 (C_{quat}), 133.94 (C_{quat}), 129.8 (CH), 124.3 (CH), 103.2 (d, $^1J_{PC}$ = 200.6 Hz, CP), 64.8 (d, $^2J_{PC}$ = 14.0 Hz, CH), 62.9 (t, $^2J_{PC}$ = 5.3 Hz, CH_2), 29.4 (CH), 21.1 (CH_3), 16.9 (CH_3), 16.3 (CH_3), 16.3 (d, $^3J_{PC}$ =6.4 Hz, CH_3), 16.2 (d, $^3J_{PC}$ =6.7 Hz, CH_3). ^{31}P NMR (162 MHz, DMSO-d_6) δ 17.1. FTIR (neat) ν_{max} 3428 (OH), 1696 (C=O), 1657 (C=C), 1242 (P=O), 1030 (P-O-C). HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{18}H_{27}NO_5P$ 368.1627; Found 368.1603.

Diethyl (4-hydroxy-1-(4-methoxyphenyl)-5-oxo-2-phenyl-2,5-dihydro-1*H*-pyrrol-3-yl)phosphonate (9g). The general procedure described for the synthesis of γ-lactams **4** (method

A, MTBE, 55 °C) was followed starting from phosphorylated pyruvate **6a** (0.756 g, 3 mmol) to afford, after column chromatography (AcOEt/hexanes 7/3), 0.375 g (0.9 mmol, 90%) of **9g** as a yellow solid. M.p. (Et_2O) 132-133 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.81 (s, 1H, OH), 7.34 (d, $^3J_{HH}$ = 9.0 Hz, 2H), 7.27-7.28 (m, 3H), 7.15 (d, $^3J_{HH}$ = 8.1 Hz, 2H), 6.75 (d, $^3J_{HH}$ = 9.1 Hz, 2H), 5.54 (d, $^3J_{PH}$= 2.8, 1H), 4.16-4.05 (m, 2H), 3.71 (m, 1H), 3.67 (s, 3H), 3.18 (m, 1H), 1.35 (t, $^3J_{HH}$ = 7.1 Hz, 3H), 0.79 (t, $^3J_{HH}$ = 7.1 Hz, 3H). ^{13}C NMR {^{1}H} (101 MHz, $CDCl_3$) δ162.9 (d, $^2J_{PC}$ = 20.4 Hz, C_{quat}), 159.8 (d, $^3J_{PC}$ = 6.12 Hz, C=O), 157.3 (C_{quat}), 135.48 (C_{quat}), 129.5 (C_{quat}), 128.9 (CH), 128.6 (CH), 127.1 (CH), 123.8 (CH), 114.2 (CH), 106.5 (d, $^1J_{PC}$ = 201.1 Hz, CP), 62.9 (d, $^2J_{PC}$ = 13.8 Hz, CH), 62.8 (d, $^2J_{PC}$ = 5.1 Hz, CH_2), 62.4 (d, $^2J_{PC}$ = 4.8 Hz, CH_2), 55.3 (CH_3) 16.4 (d, $^3J_{PC}$ = 6.4 Hz, CH_3), 15.5 (d, $^3J_{PC}$ = 7.5 Hz, CH_3) ppm. ^{31}P NMR (162 MHz, $CDCl_3$) δ 15.2. FTIR (neat) ν_{max} 1698 (C=O), 1628 (C=C), 1248 (P=O), 1023 (P-O-C). HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{21}H_{25}NO_6P$ 418.1419; Found 418.1424.

Diethyl (1-(2-fluorophenyl)-4-hydroxy-5-oxo-2-phenyl-2,5-dihydro-1*H*-pyrrol-3-yl) phosphonate (9h). The general procedure described for the synthesis of γ-lactams **4** (method A, MTBE, 55 °C) was followed starting from phosphorylated pyruvate **6a** (0.756 g, 3 mmol) to afford, after column chromatography (AcOEt/hexanes 7/3), 0.344 mg (0.85 mmol, 85%) of **9h** as a light orange solid. M.p. (Et_2O) 143-144 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.79 (s, 1H), 7.32 (t, $^3J_{HH}$ = 8.1 Hz, 1H), 7.25 – 7.21 (m, 3H), 7.20 – 7.12 (m, 3H), 7.09 – 6.99 (m, 2H), 5.64 (d, $^3J_{PH}$ = 2.9, 1H), 4.17 (dq, $^3J_{HH}$ = 7.1, $^3J_{PH}$ = 9.8 Hz, 2H), 3.73 (dq, $^3J_{HH}$ = 6.9, $^3J_{PH}$ =9.7 Hz, 1H), 3.28 (dq, $^3J_{HH}$ = 7.2, $^3J_{PH}$= 9.8 Hz, 1H), 1.40 (t, $^3J_{HH}$ = 7.0, 3H), 0.80 (t, $^3J_{HH}$ = 6.9, 3H). ^{13}C NMR {^{1}H} (101 MHz, $CDCl_3$) 163.1 (d, $^2J_{PC}$ = 19.7 Hz, C_{quat}), 160.0 (d, $^3J_{PC}$ = 6.7 Hz, C=O), 157.1 (d, $^1J_{FC}$ = 250.6 Hz, C_{quat}F), 134.8 (C_{quat}), 129.02 (d, $^3J_{FC}$ = 8.0 Hz, CH), 129.0 (CH), 128.9 (CH), 127.4 (d, $^4J_{FC}$ = 1.6 Hz, CH), 127.4 (CH), 124.6 (d, $^3J_{FC}$ = 3.7 Hz, CH), 123.5 (d, $^2J_{FC}$ = 11.5 Hz, C_{quat}), 116.7 (d, $^2J_{FC}$ = 20.1 Hz, CH), 107.8 (d, $^1J_{PC}$ = 200.0 Hz, CP), 63.58 (dd, $^2J_{PC}$ = 13.5, $^4J_{FC}$ = 5.1 Hz, CH), 63.1 (d, $^2J_{PC}$ = 5.4 Hz, CH_2), 62.7 (d, $^2J_{PC}$ = 4.5 Hz, CH_2), 16.5 (d, $^3J_{PC}$ = 6.3 Hz, CH_3), 15.6 (d, $^3J_{PC}$ = 7.5 Hz, CH_3). ^{31}P NMR (121 MHz, $CDCl_3$) δ 15.2. ^{19}F NMR (282 MHz, $CDCl_3$) δ -120.6. FTIR (neat) ν_{max} 1707 (C=O), 1223 (P=O), 1185 (C-F), 1045 (P-O-C). HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{20}H_{22}FNO_5P$ 406.1220; Found 406.1222.

Diisopropyl (4-hydroxy-5-oxo-2-phenyl-1-(4-methylphenyl)-2,5-dihydro-1*H*-pyrrol-3-yl)phosphonate (9i). The general procedure described for the synthesis of γ-lactams **4** (method A, MTBE, 55

°C) was followed starting from phosphorylated pyruvate **6c** (0.840 g, 3 mmol) to afford, after column chromatography (AcOEt/hexanes 7/3), 0.394 mg (0.92 mmol, 92%) of **9i** as a colorless solid. M.p. (Et_2O) 171-172 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.88 (s, 1H), 7.35 (d, $^3J_{HH}$ = 8.5 Hz, 2H), 7.28 – 7.18 (m, 3H), 7.17 – 7.11 (m, 2H), 7.03 (d, $^3J_{HH}$ = 8.5 Hz, 2H), 5.57 (d, $^3J_{PH}$ = 3.0, 1H), 4.68 (m, 1H), 4.26 (m, 1H), 2.21 (s, 3H), 1.38 (d, $^3J_{HH}$ = 6.2, 6H), 1.02 (d, $^3J_{HH}$ = 6.1, 3H), 0.63 (d, $^3J_{HH}$ = 6.1, 3H). ^{13}C NMR {^{1}H} (101 MHz, $CDCl_3$) 163.1 (d, $^2J_{PC}$ = 19.9 Hz, C_{quat}), 158.9 (d, $^3J_{PC}$ = 6.6 Hz, C=O), 135.7 (d, $^3J_{PC}$ = 1.0 Hz, C_{quat}), 135.3 (C_{quat}), 134.1 (C_{quat}), 129.5 (CH), 128.9 (CH), 128.5 (CH), 127.2 (CH), 121.8 (CH), 108.2 (d, $^1J_{PC}$ = 203.9 Hz, CP), 72.3 (d, $^2J_{PC}$ = 5.8 Hz, CH), 72.0 (d, $^2J_{PC}$ = 5.8 Hz, CH), 62.7 (d, $^2J_{PC}$ = 13.2 Hz, CH), 24.2 (d, $^3J_{PC}$ = 4.7 Hz, CH_3), 24.1 (d, $^3J_{PC}$ = 4.3 Hz, CH_3), 23.7 (d, $^3J_{PC}$ = 4.2 Hz, CH_3), 22.9 (d, $^3J_{PC}$ = 5.6 Hz, CH_3), 20.9 (CH_3). ^{31}P NMR (162 MHz, $CDCl_3$) δ 13.0. FTIR (neat) ν_{max} 1691 (C=O), 1663 (C=C), 1148 (P=O), 1102 (P-O-C). HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{23}H_{29}NO_5P$ 430.1784; Found 430.1789.

Diisopropyl (2-(4-fluorophenyl)-4-hydroxy-5-oxo-1-(4-methylphenyl)-2,5-dihydro-1*H*-pyrrol-3-yl)phosphonate (9j). The general procedure described for the synthesis of γ-lactams **4** (method A, MTBE, 55 °C) was followed starting from phosphorylated pyruvate **6c** (0.840 g, 3 mmol) to afford, after column chromatography (AcOEt/hexanes 7/3), 0.335 g (0.75 mmol, 75%) of **9j** as a colorless solid. M.p. (Et_2O) 107-108 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.34 (s, 1H), 7.44 (d, $^3J_{HH}$ = 8.5 Hz, 2H), 7.26 (dd, $^3J_{HH}$ = 8.5, $^3J_{FH}$ =5.4 Hz, 2H), 7.07 (d, $^3J_{HH}$ = 8.5 Hz, 3H), 7.03 (d, $^3J_{HH}$ = 8.5 Hz, 1H), 5.97 (d, $^3J_{HH}$ = 2.8 Hz, 1H), 4.44 (sept, $^3J_{HH}$ = 6.1 Hz, 1H), 4.27 (m, 1H), 2.18 (s, 3H), 1.16 (d, $^3J_{HH}$ = 6.1 Hz, 3H), 1.12 – 1.02 (m, 9H). ^{13}C NMR {^{1}H} (101 MHz, DMSO-d_6) δ 163.5 (d, $^2J_{PC}$ = 18.4 Hz, C_{quat}), 161.7 (d, $^1J_{FC}$ = 244.0 Hz, C_{quat}F), 154.4 (d, $^3J_{PC}$ = 4.2 Hz, C=O), 134.6 (C_{quat}), 133.77 (C_{quat}), 132.4 (d, $^4J_{FC}$ = 3.1 Hz, C_{quat}), 130.0 (d, $^3J_{FC}$ = 8.4 Hz, CH), 129.1 (CH), 122.5 (CH), 114.9 (d, $^2J_{FC}$ = 21.6 Hz, CH), 109.6 (d, $^1J_{PC}$ = 203.6 Hz, CP), 70.1 (d, $^2J_{PC}$ = 5.4 Hz, CH), 69.9 (d, $^2J_{PC}$ = 5.7 Hz, CH), 61.6 (d, $^2J_{PC}$ = 15.3 Hz, CH), 23.7 (d, $^3J_{PC}$ = 3.8 Hz, CH_3),23.6 (d, $^3J_{PC}$ = 3.9 Hz, CH_3), 23.5 (d, $^3J_{PC}$ = 5.1 Hz, CH_3), 23.3 (d, $^3J_{PC}$ = 5.4 Hz, CH_3), 20.4 (CH_3). ^{31}P NMR (162 MHz, DMSO-d_6) δ 8.9. ^{19}F NMR (282 MHz, DMSO-d_6) δ-110.1. FTIR (neat) ν_{max} 3501 (OH), 1704 (C=O), 1663 (C=C), 1226 (P=O), 1185 (C-F), 1011 (P-O-C). HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{23}H_{28}FNO_5P$ 448.1689; Found 448.1677.

Ethyl 3-(diisopropoxyphosphoryl)-4-hydroxy-5-oxo-1-(4-methylphenyl)-2,5-dihydro-1*H*-pyrrole-2-carboxylate (9k). The general procedure described for the synthesis of γ-lactams **4**

(method A, MTBE, 55 °C) was followed starting from phosphorylated pyruvate **6c** (0.840 g, 3 mmol) to afford, after column chromatography (AcOEt/hexanes 8/2), 0.327 mg (0.77 mmol, 77%) of **9k** as a colorless solid. M.p. (Et_2O) 131-132 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.00 (s, 1H), 7.43 (d, $^3J_{HH}$ = 8.4 Hz, 2H), 7.16 (d, $^3J_{HH}$ = 8.4 Hz, 2H), 5.15 (d, $^3J_{PH}$=3.0, 1H), 4.73 (m, 2H), 4.08 (m, 2H), 2.31 (s, 3H), 1.40 (d, $^3J_{HH}$ = 6.2 Hz, 3H), 1.37 (d, $^3J_{HH}$ = 6.2 Hz, 3H), 1.34 (d, $^3J_{HH}$ = 6.2 Hz, 3H), 1.24 (d, $^3J_{HH}$ = 6.2 Hz, 3H), 1.14 (t, $^3J_{HH}$ = 7.1 Hz, 3H). ^{13}C NMR {^{1}H} (101 MHz, $CDCl_3$) δ 167.3 (d, $^3J_{PC}$ = 1.1 Hz, C=O), 162.7 (d, $^2J_{PC}$ = 19.6 Hz, C_{quat}), 161.1 (d, $^3J_{PC}$ = 6.5 Hz, C=O), 136.0 (C_{quat}), 134.5 (C_{quat}), 129.9 (CH), 120.9 (CH), 101.8 (d, $^1J_{PC}$ = 206.6 Hz, CP), 73.1 (d, $^2J_{PC}$ = 5.9 Hz, CH), 72.7 (d, $^2J_{PC}$ = 6.1 Hz, CH), 62.2 (CH_2), 61.1 (d, $^2J_{PC}$ = 13.0 Hz, CH), 24.2 (d, $^3J_{PC}$ = 4.5 Hz, CH_3), 24.1 (d, $^3J_{PC}$ = 4.9 Hz, CH_3), 24.0 (d, $^3J_{PC}$ = 4.9 Hz, CH_3), 23.7 (d, $^3J_{PC}$ = 4.6 Hz, CH_3), 21.1 (CH_3), 14.0 (CH_3). ^{31}P NMR (162 MHz, $CDCl_3$) δ 11.9. FTIR (neat) ν_{max} 3425 (OH), 1742 (C=O), 1715 (C=O), 1628 (C=C), 1239 (P=O), 1106 (P-O-C). HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{20}H_{29}NO_7P$ 426.1682; Found 426.1688.

The general procedure B was followed using MTBE at 55 °C (heating plate, Heat-On) to afford 33.3 mg (0.08 mmol, 78%) of **4d** as an almost racemic mixture. Ee (4 %) was determined by HPLC analysis (Chiracel-IC, heptane/AcOEt/CH_2Cl_2/ethanol 2:3:4:1, 1 mL/min). Retention time (min): 3.4 (minor) and 5.8 (major).

4-(Diphenylphosphoryl)-3-hydroxy-5-phenyl-1-(4-methylphenyl)-1*H*-pyrrol-2(5*H*)-one (9l). The general procedure described for the synthesis of γ-lactams **4** (method A, MTBE, 55 °C) was followed starting from phosphorylated pyruvate **6b** (0.948 g, 3 mmol) to afford, after column chromatography (AcOEt/hexanes 7/3), 0.321 g (0.69 mmol, 69%) of **9l** as a light yellow solid. M.p. (Et_2O) 121-122 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.59 (bs, 1H), 7.71 (m, 2H), 7.63 (m, 1H), 7.54 (m, 2H), 7.35 (m, 1H), 7.25 – 7.12 (m, 6H), 7.03 – 6.98 (m, 3H), 6.94 (d, $^3J_{HH}$ = 6.9 Hz, 2H), 6.88 (d, $^3J_{HH}$ = 6.8 Hz, 2H), 5.58 (d, $^3J_{PH}$ = 2.1 Hz, 1H), 2.20 (s, 3H). ^{13}C NMR {^{1}H} (101 MHz, $CDCl_3$) δ 163.4 (d, $^2J_{PC}$ = 13.3 Hz, C_{quat}), 159.3 (C=O), 135.7 (C_{quat}), 134.8 (C_{quat}), 133.8 (C_{quat}), 132.9 (d, $^4J_{PC}$ = 2.8 Hz, CH), 132.2 (d, $^4J_{PC}$ = 2.8 Hz, CH), 131.5 (d, $^2J_{PC}$ = 10.8 Hz, CH), 131.4 (d, $^2J_{PC}$ = 11.2 Hz, CH), 130.4 (d, $^1J_{PC}$ = 108.3 Hz, C_{quat}), 130.1 (d, $^1J_{PC}$ = 108.4 Hz, C_{quat}), 129.6 (CH), 129.0 (d, $^3J_{PC}$ = 12.7 Hz, CH), 128.8 (CH), 128.6 (CH), 128.3 (d, $^3J_{PC}$ = 13.0 Hz, CH), 127.7 (CH), 122.6 (CH), 109.3 (d, $^1J_{PC}$ = 110.1 Hz, CP), 64.1 (d, $^2J_{PC}$ = 11.8 Hz, CH), 21.0 (CH_3). ^{31}P NMR (121 MHz, $CDCl_3$) δ 29.8. FTIR (neat) ν_{max} 3478 (OH), 1690 (C=O), 1654 (C=C), 1147 (P=O). HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{29}H_{25}NO_3P$ 466.1572; Found 466.1572.

4-(Diphenylphosphoryl)-3-hydroxy-5-(perfluorophenyl)-1-(4-methylphenyl)-1*H*-pyrrol-2(5*H*)-one (9m). The general procedure described for the synthesis of γ-lactams (method A, MTBE, 55 °C) **4** was followed starting from phosphorylated pyruvate **6b** (0.948 g, 3 mmol) to afford, after column chromatography (AcOEt/hexanes 7/3), 0.461 g (0.83 mmol, 83%) of **9m** as a withe solid. M.p. (Et_2O) 202 °C (dec.). ^{1}H NMR (400 MHz, MeOD-d_4) δ 7.74 – 7.43 (m, 10H), 7.23 (d, $^3J_{HH}$ = 8.1 Hz, 2H), 7.03 (d, $^3J_{HH}$ = 8.1 Hz, 2H), 6.39 (bs, 1H), 2.13 (s, 3H)**.** ^{13}C NMR {^{1}H} (101 MHz, MeOD-d_4) δ 164.9 (m, C_{quat}), 157.3 (m, C=O), 146.7 (m, C_{quat}), 142.3 (m, C_{quat}), 138.4 (m, C_{quat}), 137.9 (C_{quat}), 134.4 (C_{quat} Tol), 133.70 (CH), 132.6 (d, $^2J_{PC}$ = 11.4 Hz, CH), 132.0 (d, $^2J_{PC}$ = 10.4 Hz, CH), 130.9 (d, $^1J_{PC}$ = 111.2 Hz, C_{quat}), 130.8 (CH), 130.6 (d, $^1J_{PC}$ = 124.7 Hz, C_{quat}), 129.7 (d, $^3J_{PC}$ = 4.9 Hz, CH), 129.6 (d, $^3J_{PC}$ = 4.9 Hz, CH), 123.4 (CH), 111.4 (m, C_{quat}), 55.2 (CH), 20.9 (CH_3). ^{31}P NMR (121 MHz, $CDCl_3$) δ 27.2. ^{19}F NMR (282 MHz, $CDCl_3$) δ -144.1, -152.9, -161.3. FTIR (neat) ν_{max} 3414 (OH), 1691 (C=O), 1649 (C=C), 1121 (P=O), 1088 (P-O-C). HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{29}H_{20}F_5NO_3P$ 556.1101; Found 556.1109.

4-(Diphenylphosphoryl)-5-(4-fluorophenyl)-3-hydroxy-1-(4-methylphenyl)-1,5-dihydro-2*H*-pyrrol-2-one (9n). The general procedure described for the synthesis of γ-lactams **4** (method A, MTBE, 55 °C) was followed starting from phosphorylated pyruvate **6b** (0.948 g, 3 mmol) to afford, after column chromatography (AcOEt/hexanes 7/3), 0.420 g (0.87 mmol, 87%) of **9n** as a colorless solid. M.p. (Et_2O) 208 °C (dec.). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.49, (s, 1H, OH), 7.75 – 7.55 (m, 4H), 7.53 – 7.44 (m, 2H), 7.44 – 7.38 (m, 2H), 7.32 (dd, *J* = 12.9, 7.7 Hz, 2H), 7.21 (d, $^3J_{HH}$ = 8.5 Hz, 2H), 7.03 (d, $^3J_{HH}$ = 8.0 Hz, 2H), 6.86 (dd, *J* = 8.4, 5.3 Hz, 2H), 6.60 (t, $^3J_{HH}$ = 8.6 Hz, 2H), 5.69 (bs, 1H), 2.22 (s, 3H). ^{13}C NMR {^{1}H} (101 MHz, $CDCl_3$) δ 163.7 (C=O), 163.5 (d, $^2J_{PC}$ = 13.1 Hz, C_{quat}), 159.3 (d, $^1J_{FC}$ = 258.8 Hz, CF), 135.8 (C_{quat}), 133.5 (C_{quat}), 132.6 (d, $^4J_{PC}$ = 2.9 Hz, CH), 132.2 (d, $^4J_{PC}$ = 2.5 Hz, CH), 131.6 (d, $^2J_{PC}$ = 11.1 Hz, CH), 131.4 (d, $^2J_{PC}$ = 10.1 Hz, CH), 130.6 (d, $^1J_{PC}$ = 110.1 Hz, C_{quat}), 130.5 (d, $^4J_{FC}$ = 4.0 Hz, C_{quat}), 130.4 (d, $^1J_{PC}$ = 110.1 Hz, C_{quat}),129.7 (CH), 129.5 (d, $^3J_{FC}$ = 9.1 Hz, CH), 128.8 (d, $^3J_{PC}$ = 12.1 Hz, CH), 128.3 (d, $^3J_{PC}$ = 13.1 Hz, CH), 122.5 (CH), 115.5 (d, $^2J_{FC}$ = 22.0 Hz, CH), 110.3 (d, $^1J_{PC}$ = 111.1 Hz, C_{quat}), 63.3 (d, $^2J_{PC}$ = 11.0 Hz, CH), 21.0 (CH_3).^{31}P NMR (121 MHz, $CDCl_3$) δ 29.4. ^{19}F NMR (282 MHz, $CDCl_3$) δ -113.5. FTIR (neat) ν_{max} 1696 (C=O), 1656 (C=C), 1226 (P=O), 1153 (C-F). HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{29}H_{24}FNO_3P$ 484.1478; Found 484.1473.

Ethyl 3-(diphenylphosphoryl)-4-hydroxy-5-oxo-1-(4-methylphenyl)-2,5-dihydro-1*H*-pyrrole-2-carboxylate (9o). The general procedure described for the synthesis of γ-lactams **4** (method A, MTBE, 55 °C) was followed starting from phosphorylated pyruvate **6b** (0.948 g, 3 mmol) to afford, after column chromatography (AcOEt/hexanes 8/2), 0.364 g (0.79 mmol, 79%) of **9o** as a colorless solid. M.p. (Et_2O) 107-108 °C. ^{1}H NMR (400 MHz, $CDCl_3$)δ 11.47 (s, 1H), 8.06 (dd, $^3J_{HH}$ = 7.0, $^3J_{PH}$ = 12.8 Hz, 2H), 7.75 – 7.64 (m, 3H), 7.64 – 7.55 (m, 3H), 7.51 – 7.45 (m, 2H), 7.38 (d, $^3J_{HH}$ = 8.3 Hz, 2H), 7.14 (d, $^3J_{HH}$ = 8.1 Hz, 2H), 5.08 (d, $^3J_{PH}$ = 2.2 Hz, 1H) 3.58 – 3.47 (m, 1H), 3.38 – 3.29 (m, 1H), 2.30 (s, 3H), 0.83 (t, $^3J_{HH}$ = 7.1 Hz, 3H). ^{13}C NMR {^{1}H} (101 MHz, $CDCl_3$) δ 167.3 (C=O), 163.20 (C=O), 162.8 (d, $^2J_{PC}$ = 13.0 Hz, C_{quat}), 136.0 (C_{quat}), 134.5 (C_{quat}), 133.3 – 133.2 (m, CH), 131.8 (d, $^2J_{PC}$ = 10.5 Hz, CH), 131.6 (d, $^2J_{PC}$ = 11.8 Hz, CH), 129.9 (CH_{Ar}), 129.3 (d, $^2J_{PC}$ = 13.0 Hz, CH), 128.9 (d, $^2J_{PC}$ = 12.8 Hz, CH), 128.1 (d, $^1J_{PC}$ = 110.7 Hz, C_{quat}),120.9 (CH), 101.3 (d, $^1J_{PC}$ = 110.1 Hz, C_{quat}), 62.2 (CH_2), 61.8 (d, $^2J_{PC}$ = 12.0, CH), 21.1 (CH_3), 13.6 (CH_3). ^{31}P NMR (121 MHz, $CDCl_3$) δ 32.08. FTIR (neat) ν_{max} 3467 (OH), 1737(C=O) 1697 (C=O), 1650 (C=C), 1182 (P=O). HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{26}H_{25}NO_5P$ 462.1470; Found 462.1475.

4-(Diphenylphosphoryl)-3-hydroxy-1-(4-methoxyphenyl)-5-phenyl-1,5-dihydro-2*H*-pyrrol-2-one (9p). The general procedure described for the synthesis of γ-lactams **4** (method A, MTBE, 55 °C) was followed starting from phosphorylated pyruvate **6b** (0.948 g, 3 mmol) to afford, after column chromatography (AcOEt/hexanes 7/3), 0.385 g (0.80 mmol, 80%) of **9p** as a colorless solid. M.p. (Et_2O) 175 °C (dec.). ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.74 (s, 1H), 7.87 (m, 1H), 7.74 – 7.58 (m, 3H), 7.58 – 7.48 (m, 2H), 7.42 – 7.29 (m, 2H), 7.25 – 7.11 (m, 4H), 7.02 – 6.90 (m, 2H), 6.85 (d, $^3J_{HH}$ = 7.7 Hz, 2H), 6.72 (d, $^3J_{HH}$ = 7.2 Hz, 2H), 5.52 (s, 1H), 3.68 (s, 3H). ^{13}C NMR {^{1}H} (75 MHz, $CDCl_3$) δ 163.3 (d, $^2J_{PC}$ = 12.5 Hz, C_{quat}), 159.6 (C=O), 157.5 (C_{quat}), 134.7 (C_{quat}), 132.9 (d, $^4J_{PC}$ = 2.9 Hz, CH), 132.2 (d, $^4J_{PC}$ = 3.1 Hz, CH), 131.6 (d, $^2J_{PC}$ = 10.8 Hz, CH), 131.5 (d, $^2J_{PC}$ = 11.2 Hz, CH), 130.4 (d, $^1J_{PC}$ = 108.6 Hz, C_{quat}), 130.1 (d, $^1J_{PC}$ = 110.2 Hz, C_{quat}), 129.0 (d, $^3J_{PC}$ = 12.7 Hz, CH), 128.7 (CH), 128.6 (CH), 128.3 (d, $^3J_{PC}$ = 13.0 Hz, CH), 127.8 (CH), 124.6 (CH), 120.5 (C_{quat}), 114.2 (CH), 109.0 (d, $^1J_{PC}$ = 109.9 Hz, CH), 64.6 (d, $^2J_{PC}$ = 11.7 Hz, CH), 55.4 (CH_3). ^{31}P NMR (121 MHz, $CDCl_3$) δ 30.2. FTIR (neat) ν_{max} 3490 (OH), 1690 (C=O), 1694 (C=C), 1156 (P=O). HRMS (Q-TOF) m/z: $[M+H]^+$ calcd for $C_{29}H_{25}NO_4P$ 482.1521; Found 482.1524.

4-(diphenylphosphoryl)-1-(2-fluorophenyl)-3-hydroxy-5-phenyl-1,5-dihydro-2*H*-pyrrol-2-one (9q). The general procedure described for the synthesis of γ-lactams **4** (method A, MTBE,

55 °C) was followed starting from phosphorylated pyruvate **6b** (0.948 g, 3 mmol) to afford, after column chromatography (AcOEt/hexanes 7/3), 0.361 g (0.77 mmol, 77%) of **9q** as a light yelow solid. M.p. (Et_2O) 218 °C (dec.). ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.17 (s, 1H), 7.79 – 7.70 (m, 2H), 7.69 – 7.63 (m, 1H), 7.61 – 7.54 (m, 2H), 7.36 – 7.29 (m, 1H), 7.24 – 7.17 (m, 2H), 7.17 – 7.07 (m, 4H), 7.02 – 6.94 (m, 3H), 6.93 – 6.86 (m, 2H), 6.84 – 6.77 (m, 2H), 5.63 (d, $^3J_{PH}$ = 2.0 Hz, 1H). ^{13}C NMR {^{1}H} (75 MHz, $CDCl_3$) δ 163.3 (d, $^2J_{PC}$ = 20.4 Hz, C_{quat}), 160.6 (C=O), 157.1 (d, $^1J_{FC}$ = 250.0 Hz, CF), 134.0 (C_{quat}), 133.1 (d, $^4J_{PC}$ = 2.9 Hz, CH), 132.2 (d, $^4J_{PC}$ = 3.0 Hz, CH), 131.6 (d, $^2J_{PC}$ = 10.9 Hz, CH), 131.5 (d, $^2J_{PC}$ = 11.0 Hz, CH), 130.3 (d, $^1J_{PC}$ =107,0 Hz, C_{quat}), 129.8 (d, $^1J_{PC}$ = 107.8 Hz, C_{quat}), 129.4 – 127.7 (m, CH), 124.5 (d, $^4J_{PC}$ = 3.7 Hz, CH), 123.3 (d, $^2J_{FC}$ = 11.5 Hz, C_{quat}), 116.5 (d, $^2J_{FC}$ = 20.1 Hz, CH), 109.3 (d, $^1J_{PC}$ = 110.1 Hz, C_{quat}), 64.8 (dd, $^2J_{PC}$ = 11.9, $^4J_{FC}$ = 4.9 Hz, CH). ^{31}P NMR (121 MHz, $CDCl_3$) δ 31.4. ^{19}F NMR (282 MHz, $CDCl_3$) δ -120.3. FTIR (neat) ν_{max} 3482 (OH), 1701 (C=O), 1653 (C=C), 1153 (P=O), 1118 (C-F). HRMS (Q-TOF) m/z: $[M+H]^+$ calcd for $C_{28}H_{22}FNO_3P$ 470.1321; Found 470.1302.

General procedure for the hydrogenation of γ-lactams 4. A mixture of **4** (0.5 mmol) and 52.2 mg of 10% palladium on carbon (0.05 mmol Pd) in methanol (100 mL) was stirred for 10 hours under hydrogen pressure at 80 psi. The reaction mixture was filtered through celite, and the filter washed with dichloromethane (2×50 mL). The combined organic fractions were distilled off at reduced pressure and the residue was crystallized in methanol to afford pure lactams **16**.

Diethyl ((-5-oxo-1-(4-methylphenyl)-4-(4-methylphenylamino)pyrrolidin-2-yl)methyl)phosphonate (16a). The general procedure was followed affording 0.199 g (0.46 mmol, 93%) of **16a** as a colorless solid. M.p. (Et_2O) 119-120 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 (d, $^3J_{HH}$ = 8.5 Hz, 2H), 7.19 (d, $^3J_{HH}$ = 8.5 Hz, 2H,), 7.03 (d, $^3J_{HH}$ = 8.3 Hz, 2H), 6.64 (d, $^3J_{HH}$ = 8.3 Hz, 2H), 4.50 (m, 1H), 4.17 – 4.02 (m, 5H), 3.25 (ddd, $^2J_{HH}$ = 13.6, $^3J_{HH}$ = 7.8, 6.4 Hz, 1H), 2.34 (m, 1H),2.36 (s, 3H), 2.26 (s, 3H), 1.84 (m, 1H), 1.74 – 1.59 (m, 1H),. 1.31 (t, $^4J_{PH}$ = 7.1 Hz, 3H), 1.30 (t, $^4J_{PH}$ = 7.1 Hz, 3H). ^{13}C NMR {^{1}H} (101 MHz, $CDCl_3$) δ 172.6 (d, $^4J_{PC}$ = 1.1 Hz, C=O), 145.2 (C_{quat}), 136.9 (d, $^4J_{PC}$ = 1.2 Hz, C_{quat}), 133.5 (C_{quat}), 130.1 (CH), 129.9 (CH), 127.9 (C_{quat}), 124.7 (CH), 114.0 (CH), 62.1 (d, $^2J_{PC}$ = 6.4 Hz, CH_2), 62.0 (d, $^2J_{PC}$ = 6.7 Hz, CH_2), 55.8 (CH), 52.3 (d, $^2J_{PC}$ = 2.4 Hz, CH), 37.4 (CH_2), 31.3 (d, $^1J_{PC}$ = 139.3 Hz, CH_2), 21.2 (CH_3), 20.5 (CH_3), 16.6 (CH_3), 16.5 (CH_3). ^{31}P NMR (162 MHz, $CDCl_3$) δ 26.7.

FTIR (neat) ν_{max} 3357 (NH), 1701 (C=O), 1239 (P=O), 1055 (P-O-C). HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{23}H_{32}N_2O_4P$ 431.2100; Found 431.2101.

(1-(4-methylphenyl)-3-(4-methylphenylamino)-5-(trifluoromethyl)pyrrolidin-2-one (16b). The general procedure was followed affording 0.154 g (0.44 mol, 89%) of **16b** as a colorless solid. M.p. (Et_2O) 183-184 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (d, $^3J_{HH}$ = 8.5 Hz, 2H), 7.19 (d, $^3J_{HH}$ = 8.5 Hz, 2H), 7.04 (d, $^3J_{HH}$ = 8.5 Hz, 2H), 6.61 (d, $^3J_{HH}$ = 8.5 Hz, 2H), 4.62 (m, 1H), 4.16 (t, $^3J_{HH}$ = 8.5 Hz, 1H), 3.05 (ddd, $^2J_{HH}$ = 13.6, $^3J_{HH}$ = 8.8, 7.9 Hz, 1H), 2.37 (s, 3H), 2.27 (s, 3H), 2.13 (ddd, $^3J_{HH}$ = 13.6, $^3J_{HH}$ = 8.3, 7.4 Hz, 1H). ^{13}C NMR {1H} (101 MHz, $CDCl_3$) δ 173.3 (C=O), 144.57 (C_{quat}), 138.2 (C_{quat}), 133.7 (C_{quat}), 130.1 (CH), 130.0 (CH), 128.4 (C_{quat}), 125.9 (CH), 124.0 (q, $^1J_{FC}$ = 197.1 Hz, CF_3), 114.0 (CH), 58.8 (q, $^2J_{FC}$ = 32.3 Hz, CH), 54.1 (CH), 29.1 (CH), 21.3 (CH_3), 20.6 (CH_3). ^{19}F NMR (282 MHz, $CDCl_3$) δ -74.3 (dd, $^3J_{HF}$ = 5.8 Hz, $^4J_{HF}$ = 2.5 Hz, CF_3). FTIR (neat) ν_{max} 3309 (NH), 1704 (C=O), 1140 (CF_3). HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{19}H_{20}F_3N_2O$ 349.1528; Found 349.1532.

Diethyl ((3,4-dimethyl-5-oxo-1-(4-methylphenyl)-4-(4-methylphenylamino)-4,5-dihydro-1*H*-pyrrol-2-yl)methyl)phosphonate (17). A solution of lactam **4a** (0.214 g, 0.5 mmol) in THF was cooled to -78 °C, a solution of methyl lithium in Et_2O (0.7 mL, 1.6M, 1.1 mmol) was dropwise added in the mixture and stirred for 1 hour. After 1 hour at -78°C a solution of methyl iodide (0.07 mL, 1.1 mmol) was slowly added and the reaction was warmed to room temperature overnight. Water (5 mL) was added and the resulting mixture was extracted with AcOEt (3x10mL). The combined organic phases were dried with anhydrous $MgSO_4$ and concentrated under reduced pressure. The crude residue was purified by column chromatography (AcOEt/hexanes 7/3) affording 0.196 g (0.43 mmol, 87%) of **17** as a yellow solid. M.p. (Et_2O) 144-145 °C . ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21 (d, $^3J_{HH}$ = 8.2 Hz, 2H), 7.09 (d, $^3J_{HH}$ = 8.2 Hz, 2H), 6.92 (d, $^3J_{HH}$ = 8.5 Hz, 2H), 6.52 (d, $^3J_{HH}$ = 8.5 Hz, 2H), 4.09 – 3.92 (m, 4H,), 3.92 – 3.81 (m, 2H), 2.36 (s, 3H), 2.20 (s, 3H), 1.80 (d, $^5J_{PH}$ = 6.1 Hz, 3H), 1.50 (s, 3H), 1.24 (t, $^3J_{HH}$ = 7.1 Hz, 2H), 1.21 (t, $^3J_{HH}$ = 7.1 Hz, 3H). ^{13}C NMR {^{1}H} (101 MHz, $CDCl_3$) δ 179.8 (C=O), 143.8 (C_{quat}), 138.0 (C_{quat}), 132.2 (C_{quat}), 129.9 (CH), 129.7 (CH), 128.3 (CH), 128.2 (C_{quat}), 127.6 (d, $^2J_{PC}$ = 13.6 Hz, C_{quat}), 120.5 (d, $^3J_{PC}$ = 12.4 Hz, C_{quat}), 115.0 (CH), 64.1 (d, $^4J_{PC}$ = 3.4 Hz, C_{quat}), 62.2 (d, $^2J_{PC}$ = 6.7 Hz, CH_2), 62.0 (d, $^2J_{PC}$ = 6.7 Hz, CH_2), 25.1 (d, $^5J_{PC}$= 5.0, CH_3), 23.6 (d, $^1J_{PC}$ = 143.1 Hz, CH_2), 21.6 (CH_3), 20.6 (CH_3), 16.6 (t, $^3J_{PC}$ = 7.4 Hz, CH_3), 16.5 (t, $^3J_{PC}$ = 7.7 Hz, CH_3), 8.9 (d, $^4J_{PC}$ = 3.6 Hz, CH_3). ^{31}P NMR (162 MHz, $CDCl_3$) δ 23.7. FTIR (neat) ν_{max} 3411 (NH), 1723 (C=O), 1672 (C=C), 1254 (P=O), 963 (P-O-C). HRMS (ESI-TOF) m/z: $[M+K]^+$ calcd for $C_{25}H_{33}KN_2O_4P$ 495.1815; Found 495.1817.

5-((Dimethylphosphoryl)methyl)-1-(4-methylphenyl)-3-(4-methylphenylamino)-1,5-dihydro-2*H*-pyrrol-2-one (21). A solution of lactam **4a** (0.214 g, 0.5 mmol) in THF was cooled to -78 °C, a solution of methyl lithium in Et_2O (0.7 mL, 1.6M, 1.1 mmol) was dropwise added in the mixture and then the reaction was warmed to room temperature overnight. Water (5 mL) was added and the resulting mixture was extracted with AcOEt (3×10 mL). The combined organic phases were dried with anhydrous $MgSO_4$ and concentrated under reduced pressure. The crude residue was purified by column chromatography (AcOEt/hexanes 9/1) affording 0.103 g (0.28 mmol, 55%) of **21** as a colorless solid. M.p. (Et_2O) 185 °C (dec.). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (d, $^3J_{HH}$ = 8.4 Hz, 2H), 7.26 (m, 2H), 7.12 (d, $^3J_{HH}$ = 8.4 Hz, 2H), 7.01 (d, $^3J_{HH}$ = 8.4 Hz, 2H), 6.52 (s, 1H), 6.40 (d, $^3J_{HH}$ = 2.6 Hz, 1H), 5.075 (m, 1H), 2.37 (s, 3H), 2.30 (s, 3H), 1.69 (m, 1H), 1.56 (d, $^2J_{PH}$ = 4.0 Hz, 3H), 1.53 (d, $^2J_{PH}$ = 4.0 Hz, 3H), 1.48 (m, 1H). ^{13}C NMR {^{1}H} (101 MHz, $CDCl_3$) δ 165.9 (C=O), 138.8 (C_{quat}), 135.9 (C_{quat}), 133.5 (C_{quat}), 133.4 (C_{quat}), 131.0 (C_{quat}), 130.2 (CH), 130.1 (CH), 122.9 (CH), 117.0 (CH), 105.5 (CH), 55.3 (CH), 35.4 (d, $^1J_{PC}$ = 67.0 Hz, CH_2), 21.1 (CH_3), 20.8 (CH_3), 18.50 (d, $^1J_{PC}$ = 69.4 Hz, CH_3), 17.6 (d, $^1J_{PC}$ = 69.2 Hz, CH_3). ^{31}P NMR (162 MHz, $CDCl_3$) δ 39.1. FTIR (neat) ν_{max} 3445 (NH), 1685 (C=O), 1656 (C=CH), 1159 (P=O), 1118. HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{21}H_{26}N_2O_2P$ 369.1732; Found 369.1728.

General procedure for the Horner-Wadsworth-Emmons reactions of γ-lactams 4. A solution of lactam **4a** (0.214 g, 0.5 mmol) in THF (2 mL) was dropwise added to a cooled solution (-78 °C) of LDA (1.1 mmol, prepared from 0.69 mL of 1.6 M *n*-butyl lithium and 0.15 mL of diisopropylamine in 5 mL of THF) and the mixture was stirred for 1 hour at -78 °C. Then, the corresponding aldehyde (0.75 mmol) was added and the reaction was warmed to room temperature overnight. The solution was quenched with 10 mL of water and extracted with dichloromethane (3×10 mL), dried with anhydrous $MgSO_4$ and concentrated at reduced pressure. The crude residue was purified by column chromatography (AcOEt/hexanes 9/1) to afford products **22**.

(2*Z*,3*E*,5*E*)-6-Phenyl-*N*-(4-methylphenyl)-2-(4-methylphenylimino)hexa-3,5-dienamide (22a). The general procedure was followed affording 0.172 g (0.045 mmol, 90%) of **22a** as a yellow solid. M.p. (Et_2O) 158-159 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.47 (s, 1H, NH), 8.02 (dd, $^3J_{HH}$ = 15.5, 10.7 Hz, 1H), 7.61 (d, $^3J_{HH}$ = 8.0 Hz, 2H), 7.42 (d, $^3J_{HH}$ = 7.4 Hz, 2H), 7.37 – 7.27 (m, 3H), 7.23 (d, $^3J_{HH}$ = 7.8 Hz, 2H), 7.19 (d, $^3J_{HH}$ = 8.0 Hz, 2H), 6.84 (d, $^3J_{HH}$ = 7.8 Hz, 2H), 6.94 – 6.69 (m, 2H), 6.29 (d, $^3J_{HH}$ = 15.5 Hz, 1H), 2.40 (s, 3H), 2.36 (s, 3H). ^{13}C NMR

{^{1}H} (101 MHz, $CDCl_3$) δ 161.8 (C=O), 157.66 (C=N), 146.0 (C_{quat}), 144.6 (CH), 139.6 (CH), 136.5 (C_{quat}), 135.1 (C_{quat}), 134.9 (C_{quat}), 134.0 (C_{quat}), 129.8 (CH), 129.6 (CH), 129.0 (CH), 128.8 (CH), 127.1 (CH), 120.7 (CH), 120.4 (CH), 119.8 (CH), 21.08 (CH_3), 21.01(CH_3). FTIR (neat) ν_{max} 3328 (NH), 1688 (C=O/C=N), 1600 (C=CH), 1590 (C=CH), 1517 (C=CH). HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{26}H_{25}N_2O$ 381.1967; Found 381.1972.

(2*Z*,3*E*,5*E*)-*N*-(4-Methylphenyl)-2-(4-methylphenylimino)-6-(4-(trifluoromethyl)phenyl)hexa-3,5-dienamide (22b). The general procedure was followed affording 0.204 g (0.455 mmol, 91%) of **22b** as an orange solid. M.p. (Et_2O) 114-115 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.48 (s, 1H), 8.02 (dd, $^3J_{HH}$ = 15.6, 10.0 Hz, 1H), 7.61 (d, $^3J_{HH}$ = 8.2 Hz, 2H), 7.57 (d, $^3J_{HH}$ = 8.4 Hz, 2H), 7.49 (d, $^3J_{HH}$ = 8.4 Hz, 2H), 7.24 (d, $^3J_{HH}$ = 8.0 Hz, 2H), 7.20 (d, $^3J_{HH}$ = 8.0 Hz, 2H), 6.85 (d, $^3J_{HH}$ = 8.2 Hz, 2H), 6.83 (m, 2H), 6.34 (d, $^3J_{HH}$ = 15.6 Hz, 1H), 2.41 (s, 3H), 2.36 (s, 3H). ^{13}C NMR {^{1}H} (101 MHz, $CDCl_3$) δ 161.7 (C=O), 157.4 (C=N), 145.9 (C_{quat}), 143.7 (CH), 139.9 (d, $^5J_{FC}$ = 1.6 Hz, C_{quat}), 137.5 (CH), 135.2 (C_{quat}), 135.1 (C_{quat}), 134.2 (C_{quat}), 131.4 (CH), 130.3 (q, $^2J_{FC}$ = 32.4 Hz, C_{quat}), 129.9 (CH), 129.7 (CH), 127.2 (CH), 125.8 (q, $^3J_{FC}$ = 3.8 Hz, CH), 124.2 (q, $^1J_{FC}$ = 271.9 Hz, CF_3), 122.2 (CH), 120.50 (CH), 119.9 (CH), 21.1 (CH_3), 21.0 (CH_3). ^{19}F NMR (282 MHz, $CDCl_3$) δ -63.1 (CF_3). FTIR (neat) ν_{max} 3335 (NH), 1732 (C=O), 1688 (C=N), 1612 (C=CH), 1587 (C=CH), 1524 (C=CH). HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{27}H_{24}F_3N_2O$ 449.1841; Found 449.1848.

Synthesis of (4-hydroxy-5-oxo-2-phenyl-1-(4-methylphenyl)-2,5-dihydro-1*H*-pyrrol-3-yl)phosphonic acid (25). A solution of lactam **9a** (0.402 g, 1 mmol) and bromotrimethylsilane (0.765 g, 5 mmol) was stirred at room temperature in dry chloroform (5 mL) for 24 hours. The reaction was monitored by ^{31}P NMR. Water was added (5 mL), the volatiles were distilled off at reduced pressure and the crude residue was crystallized in dichloromethane/methanol (95:5) affording 0.338 g (0.98 mmol, 98%) of **25** as a colorless solid. M.p. (Et_2O) 183 °C (dec.). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.81 (s, 3H), 7.39 (d, $^3J_{HH}$ = 8.3 Hz, 2H), 7.27 – 7.10 (m, 5H), 7.06 (d, $^3J_{HH}$ = 8.3 Hz, 2H), 5.86 (d, $^3J_{PH}$ = 3.0 Hz, 1H), 2.18 (s, 3H). ^{13}C NMR {^{1}H} (101 MHz, DMSO-d_6) δ 163.6 (d, $^2J_{PC}$ = 18.1 Hz, C_{quat}), 154.0 (d, $^3J_{PC}$ = 5.3 Hz, C=O), 136.4 (C_{quat}), 134.3 (C_{quat}), 134.0 (C_{quat}), 129.1 (CH), 128.2 (CH), 127.8 (CH), 127.7 (CH), 122.5 (CH), 113.6 (d, $^1J_{PC}$ = 194.0 Hz, C_{quat}), 62.1 (d, $^2J_{PC}$ = 14.2 Hz, CH), 20.5 (CH_3). ^{31}P NMR (121 MHz, DMSO-d_6) δ -1.9. FTIR (neat) ν_{max} 3464 (OH), 1688 (C=O), 1669 (C=C), 1264 (P=O), 992 (P-O-H). HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{17}H_{17}NO_5P$ 346.0844; Found 346.0848.

Supporting Information Available: Copies of ^{1}H, ^{13}C ,^{31}P and ^{19}F NMR spectra for compounds **4a-e**, **8a-b**, **9a-q**, **16a-b**, **17**, **21**, **22a-b** and **25,** cif file and thermal ellipsoid plot for **4a**, **9j**, **17**, **22a**, and chiral HPLC chromatograms for the determination of the enantiomeric excesses of compounds **4 a-e** and **9a,k**. This material is available free of charge via the Internet at http://pubs.acs.org

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