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Methyl 1-alkyl-4-(diethoxyphosphoryl)-5-oxopyrrolidines-3-carboxylate – versatile intermediates in the synthesis of α-methylene-γ-lactams and α,β-difunctionalized pyrrol-2(*3H*)-ones

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ABSTRACT

A general and efficient one-pot synthesis of a novel class of methyl 1-alkyl-4(diethoxyphosphoryl)-5-oxopyrrolidine-3-carboxylate 2 is presentedfor the first time. This approach is based on the Michael addition of dimethyl 2-(diethoxyphosphoryl)-3methylenesuccinate 1 toprimary amines. Application of the $_{\alpha}$-phosphono-γ-lactams obtained forthe preparation of $_{\alpha}$-methylene-γ-lactams is also reported.

KEYWORDS

Dimethyl 2-(diethoxyphosphoryl)-3-methylenesuccinate;
Primary amines;
Methyl 1-alkyl-4-(diethoxyphosphoryl)-5-oxopyrrolidine-3-carboxylate;
α-methylene-γ-lactams.

INTRODUCTION

Biologically active substances possessing lactam units are found common in natural sources[1,2]. According to some recent researches, the γ-lactam skeleton shows cytotoxicity, antitumor, and anti-inflammatory activities and are less toxic compared to the corresponding lactones[3]. Especially highly substituted lactams possess different biological activities[4]. In addition, the γ lactam functionality is a prevalent theme in various natural product synthesis and serves as a crucial intermediate for numerous natural products[5]. Although different methods have been developed to construct this kind of structures[6], much more attention can never be enough. As a potential precursor for synthesis of natural products, α-alkylidene-γ-lactams attracted our interest. A large number of α-alkylidene-γ-lactams have been shown to exhibit significant pharmacological activities such as cytotoxicity[7], antitumor[8], and anti-inflammatory[9]. Although, a route involving the synthesis of α-diethoxyphosphoryl-γ-lactams followed by their HornerWadsworth-Emmons (HWE) reaction with formaldehyde has emerged as a very attractive method for the preparation of disubstituted-α-methylene-γ-lactams. All the previous successful syntheses of *N*-unsubstituted-α-phosphono-γ-lactams involved chemoselective reduction of 2diethoxyphosphoryl-4-nitroalkanoates followed by lactamization of the resulting 2diethoxyphosphoryl-4-aminoalkanoates[7e,10]. In these contexts, Krawczyk, H. and co-workers[7d] showed that the conjugate ad-

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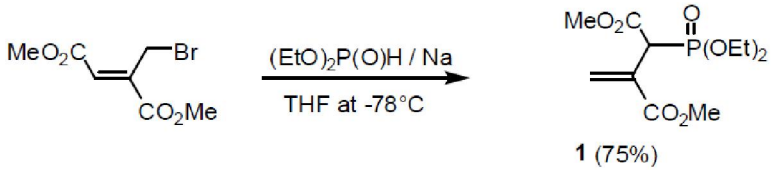
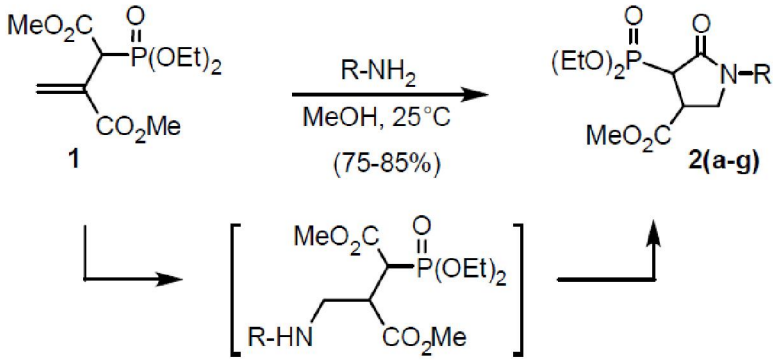


Scheme 1



Scheme 2

dition of primary nitroalkanes to *t*-butyl (*E*)-3-aryl-2(diethoxyphosphoryl)-acrylates constituted a key step in the synthesis of a wide range of αphosphono-γ-lactams[7d].

The aim of the present paper is to present and discuss a simple and new strategy for the first application of methyl 1-alkyl-4-(diethoxyphosphoryl)-5-oxopyrrolidine-3-carboxylate 2 for the synthesis of a mixture of two stereoisomers *Z* and *E* of α-alkylidene-γ-lactams 5a,b based on the utilization of dimethyl 2-(diethoxyphosphoryl)-3-methylenesuccinate 1 as an excellent Michael acceptor (Scheme 1).

RESULTS AND DISCUSSION

We have previously described a simple and stereoselective synthesis of dimethyl 2-(diethoxyphosphoryl)-3-methylenesuccinate 1[11],an activated alkene bearing three functional groups, and we have demonstrated that the latter can be used as an efficient electrophilic synthon for the synthesis of a new family of (*E*,*Z*)-1-alkyl-2,3-dimethoxycarbonylbuta-1,3-dienes[11] and a total stereospecific route to α-alkylidene-γ-lactames[12]. Prompted by the versatility of the allyl phosphonate 1, we conceived that it's coupling reaction with a variety of primary amines would provide a convenient pathway for the formation of new family of methyl 1-alkyl-4(diethoxyphosphoryl)-5-oxopyrrolidine-3-carboxylate 2.

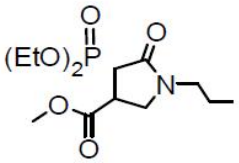
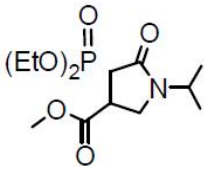
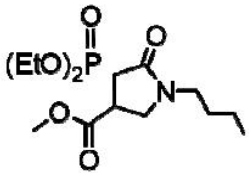
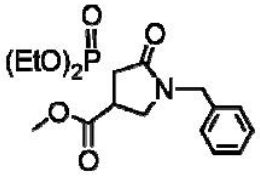
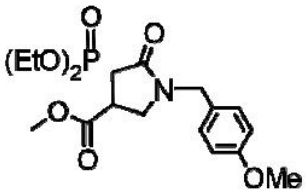
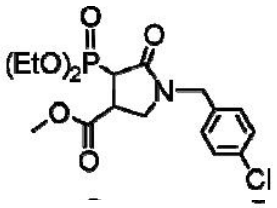
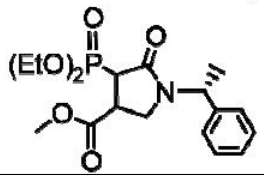
Assessing the functional properties of high-density phosphonate 1, we found it useful to examine its reactivity in a heterocyclization process to obtain a series of 2 whose representative has been recently reported[7d,13]. In our approach, the construction of the nitrogen heterocycle[14-17] is based on an efficient coupling of the primary amines and allyl phosphonate 1. The latter Michael acceptor 1 offers the possibility to react with one equivalent of primary amine in methanol as polar protic solvent, involving as expected two-step sequence: conjugate addition of the amine on the terminal ethylenic carbon leading the γ-amino-ester intermediate, which spontaneously undergoes an intramolecular cyclization *via5-exo-trig* process[18], to provide the corresponding 3,4-difunctionalized γ-lactam 2 in good yields (Scheme 2, TABLE 1).

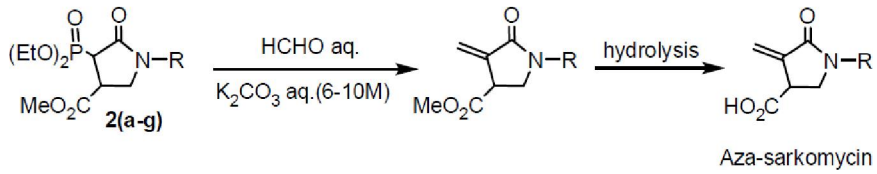
The different cyclic phosphonates prepared is gathered in the TABLE 1.

Obtaining these α-phosphono-γ-lactams 2 led us to consider an easy access to aza-sarkomycin methyl ester, analogue of the sarkomycin[19-22], by direct application of Wittig-Horner reaction in a slightly basic solid-liquid heterogeneous medium, followed by hydrolysis (Scheme 3).

In fact, the coupling reaction between aqueous formaldehyde (30%) and the exocyclic phosphonate

TABLE 1 : Methyl 1-alkyl-4-(diethoxyphosphoryl)-5-oxopyrrolidine-3-carboxylates 2a-g

Entry	R	Time (h)	Pyrrolidine 2	Yield(*) (%)
2a	*n*Pr	12		78
2b	*i*Pr	12		79
2c	^{n}Bu	8		77
2d	$C_6H_5CH_2$	16		85
2e	$PMeOC_6H_4CH_2$	20		75
2f	$PClC_6H_4CH_2$	16		77
2g	$Ph(CH_3)CH$	24		85



Scheme 3

2, in the presence of aqueous potassium carbonate (6-10M) in THF, gives the azasarkomycin methyl ester which we did not isolate. Indeed, the deprotonation in α function of ester in a basic medium led to a carbanion whose hydroxymethylation provides mainly $_{\alpha}$methylene-γ-lactams 3a-g type A. Alternatively, the aza-sarkomycin

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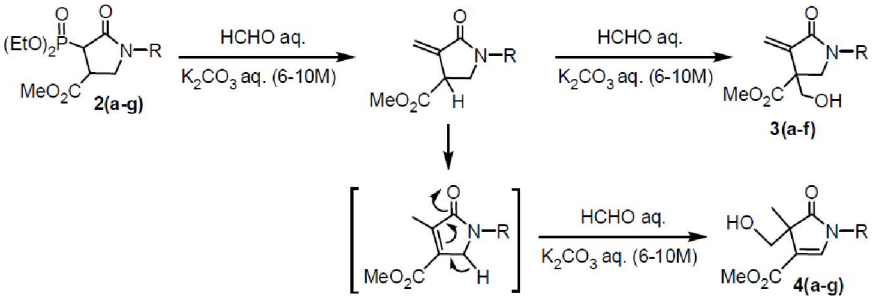
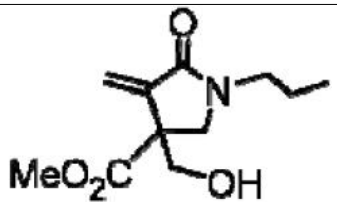
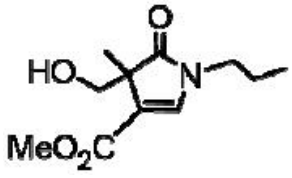
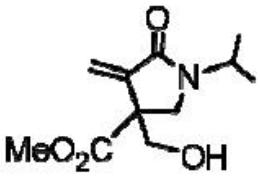
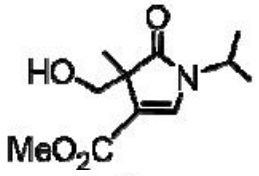
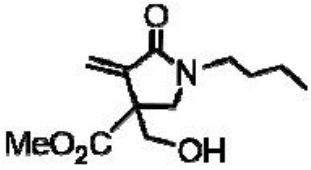
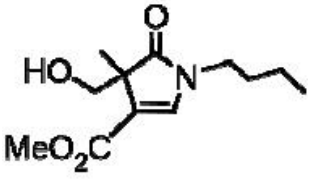
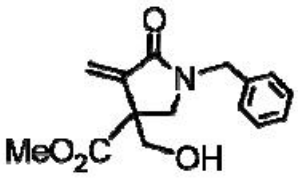
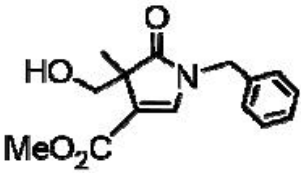
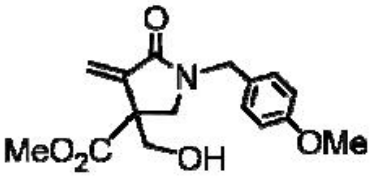
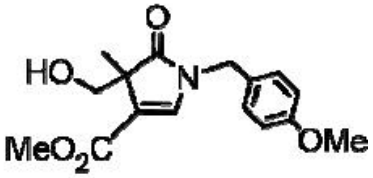
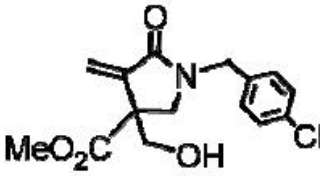
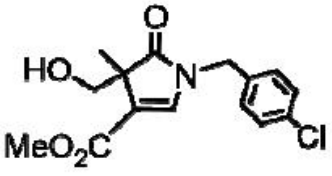
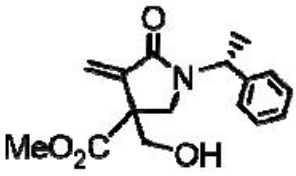
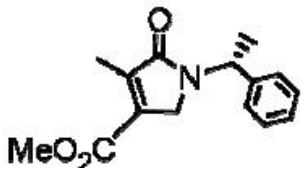
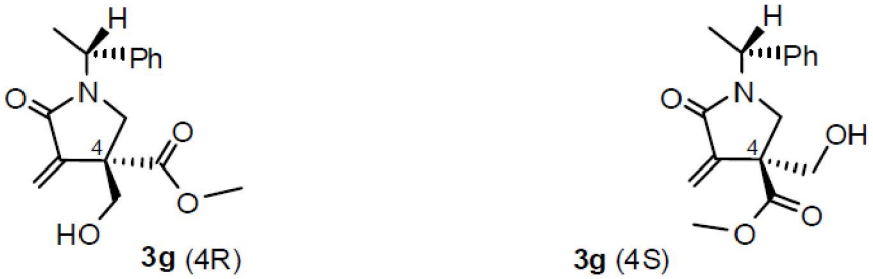


Scheme 4

TABLE 2 : Functionalized γ-lactams 3a-g and 4a-f

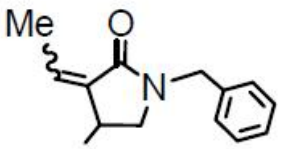
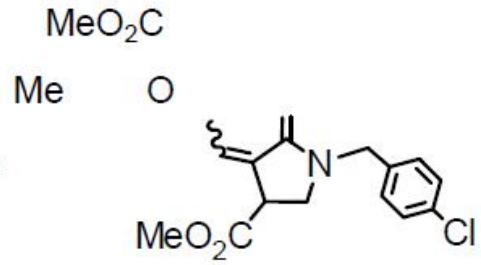
Entry	R	3a-g(A)	Yield(*) (%)	4a-f(B)	Yield(*) (%)
a	nPr		51		21
b	iPr		44		20
c	^{n}Bu		47		18
d	$C_6H_5CH_2$		49		19
e	$PMeOC_6H_4CH_2$		54		20
f	$PClC_6H_4CH_2$		49		18
g	$Ph(CH_3)CH$		57		15

(*)Yields refer to the pure isolated products after chromatography.

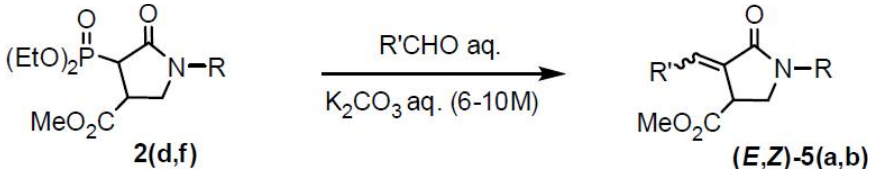


Scheme 6

TABLE 3 : 1-Alkyl-4-ethylidene-5-oxopyrrolidine-3-carboxylic acid 5a,b

Entry	R'	R	Pyrrolidine 5	*Z/E* (%)	Yield(*) (%)
5a	Me	$C_6H_5CH_2$		60/40	65
5b	Me	$PClC_6H_4CH_2$		68/32	49

(*)**Yields refer to the pure isolated products after chromatography.**



Scheme 5

methyl ester can be isomerized in C who, in basic medium and in the presence of an excess of formaldehyde, gave Δ^4-pyrrolinones 4a-f of type B with poor yield (18-21%) Scheme 4.

The analysis of results presented in TABLE 2, shows that for the various compounds a-f, a mixture of two γ-lactams is obtained with a prevalence of $_{\alpha}$-methylene-γ-lactams 3a-g of type A compared to Δ^4-pyrrolinones 4a-f of type B. On the other hand for the compound g where R = $C_6H_5CH(CH_3)$, we have isolated 57% from the compound 3g soiled product of isomerization (15%).

In this particular case and since we used a pure enantiomeric amine of configuration *R*, the application of Wittig-Horner reaction to cyclic phosphonate 2g led us to a mixture of two diastereoisomers 3g (1'R, 4S) and 3g (1'R, 4R) of type A, separable by column chromatography using a mixture of dichloromethane / ethyl acetate (6: 4).

In the case of aldehydes RCHO, the application of Wittig-Horner reaction to αdiethoxyphosphinyl-γ-lactams 2d,f, gives in a stereoselective way, a mixture of two stereoisomers (*Z,E*) of α-alkylidene-γ-lactams 5a,b with preponderance of the form (*E*) Scheme 5. The synthesized products are presented in TABLE 3.

Both stereoisomers are separated by column chromatography. The form (*E*) is a liquid whereas the form (*Z*) is a solid.

CONCLUSION

In summary, we successfully developed through

a valuation of a difunctionalized phosphonate 1, a convenient and efficient route of a single-step synthetic way to prepare methyl 1-alkyl-4(diethoxyphosphoryl)-5-oxopyrrolidine-3-carboxylate 2 using commercially available reagents. The notable advantages of this method are operational simplicity, mild reaction conditions and ease of isolation of racemic *cis* and *trans* products. This simple protocol developed in this study paves the way for further biological studies and we believe that this work provides a strong incentive for the elaboration of structurally modified models.

Experimental section general

Tetrahydrofuran (THF) was distilled prior to use from a deep-blue solution of sodiumbenzophenone ketyl. All other reagents and solvents were obtained from commercial sources and used without further purification. Reactions were routinely carried out under an atmosphere of dry nitrogen with magnetic stirring. Organic layers were dried with anhydrous magnesium sulfate before concentration in vacuo. All reactions were monitored by TLC on silica gel plates (Fluka Kieselgel 60 F254, Merck) and visualized by a 254 nm UV lamp, aqueous potassium permanganate solution and iodine. Crude products were purified using column chromatography on silica gel, Fluka Kieselgel 70-230 mesh was used. ^{1}H-NMR and ^{13}C-NMR spectra were recorded on Bruker AMX 300 spectrometer working at 300 MHz, 282 MHz and 75 MHz respectively for ^{1}H, and ^{13}C with $CDCl_3$ as the solvent and TMS as the internal standard. The chemical shifts (δ) and coupling constants *(J)* are, respectively, expressed in parts per million (ppm) and Hertz (Hz). All NMR spectra were acquired at room temperature. Multiplicity of peaks is indicated by the following: s: singlet; d: doublet; t: triplet; q: quartet; qt: quintuplet; sept: septuplet; m: multiplet. Mass spectra were accomplished with an HP 5889A quadripolar spectrometer by electronic impact EI (70 eV) or chemical ionization CI (500 eV) with NH_3 gas. High-Resolution Mass Spectrometry (HRMS) analyses were performed at the "Centre Commun de Spectrométrie de Masse" in Lyon (France), on a Micro-TOFOII Thermofischer Scientific for electro-spray ionization (ESI) measurements.

Preparation of dimethyl 2-diethoxyphosphinyl-3-methylene succinate 1

A 15 moles of freshly distilled diethylphosphite and 15 moles of sodium in 20 mL of dry THF were placed in a round flask attached to a water cooling condenser and under nitrogen atmosphere. Solution was left under stirring at ambient temperature until disappearance of sodium. The containing soda diethylphosphite thus prepared is added, drop by drop and at low temperature (-78°C) to 10 moles of allyl bromide, in 15 mL of anhydrous THF and under atmosphere of nitrogen. Once addition of the anion finished, the reaction was monitored by CCM until a total disappearance of the starting material and the formation of allyl phosphonate **1**. After hydrolysis, extraction with ether, drying on $MgSO_4$ and evaporation of solvent, the obtained oily residue is distilled under reduced pressure. Dimethyl 2-Diethoxyphosphoryl-3- methylene succinate **1** is thus obtained with a yield of 75%.

Dimethyl 2-diethoxyphosphoryl-3-methylene succinate 1

Yield: (0.36g, 75%) as a yellow oil; IR (cm^{-1}): νC=O = 1731, νC=C = 1628 ; ^{1}H NMR ($CDCl_3$, δ ppm, *J* Hz): 1.32 (m, 6H), 3.76 ; 3.79 (2s, 6H), 4.18 (m, 4H), 4.55 (d, 1H, *J* = 25.1), 6.42 ; 6.61 (2d, 2H, *J* = 4.3 ; 4.8) ; ^{13}C NMR ($CDCl_3$, δ ppm): 16.0, 43.7, 45.5, 52.2, 52.6, 63.0, 130.2, 165.0, 165.7, 167.2 ; Mass (m/z) : 39 (19) ; 59 (16) ; 81 (23) ; 98 (25) ; 109 (23) ; 125 (27) ; 157 (100) ; 179 (47) ; 207 (28) ; 235 (84) ; 294 ($M^{+\cdot}$, 1).

Preparation of methyl 1-alkyl-4-(diethoxyphosphoryl)-5-oxopyrrolidine-3-carboxylate2a-g

Typical procedure

To a solution of dimethyl 2-diethoxyphosphoryl-3-methylene succinate 1 (10 mmol) in 15 mL of methanol, was added 21 moles of primary amine in 5 ml of methanol. The reaction mixture is maintained under agitation at the ambient temperature for one length of time which varies between 12 and 24 hours. The advance of the reaction is controlled by TLC. Methanol is evaporated under reduced pressure and the liquid obtained is purified by column chromatography using a mixture of ethyl acetate /dichloromethane (6 : 4).

Methyl N-propyl-4-(diethoxyphosphoryl)-5-

oxopyrrolidine-3-carboxylate2a

Yield: (0.36g, 75%) as a yellow oil; IR (cm^{-1}): νC(O)O = 1738, νC(O)N = 1693; ^1H NMR ($CDCl_3$, δ ppm, *J* Hz): 0.93 (t, 3H, *J* = 7.4), 1.32 (t, 6H, *J* = 7.2), 1.57 (m, 2H), 3.25-3.56 (m, 6H), 3.76 (s, 3H), 4.18 (m, 4H); ^{13}C NMR ($CDCl_3$, δ ppm): 10.8; 13.9; 20.1; 38.2; 43.1; 45.0; 48.1; 52.5; 62.4; 167.3; 172.3; Mass (m/z): 41 (15); 96 (22); 124 (38); 234 (51); 262 (100); 321 ($M^{+\cdot}$, 5).

Methyl N-isopropyl-4-(diethoxyphosphoryl)-5-oxopyrrolidine-3-carboxylate2b

Yield: (0.36g, 75%) as a yellow oil; IR (cm-1) : νC(O)O = 1738, νC(O)N = 1682; 1H NMR (CDCl3, δ ppm, *J* Hz): 1.13-1.37 (m, 12H), 3.35-3.77 (m, 5H), 3.79 (s, 3H), 4.21 (m, 4H); ^{13}C NMR ($CDCl_3$, δ ppm): 15.9, 19.2, 38.2, 43.0, 43.5, 45.4, 52.5, 62.3, 166.5, 172.2; Mass (m/z): 29 (13); 82 (27); 110 (27); 170 (26); 234 (45); 262 (100); 321 ($M^{+\cdot}$, 8).

Methyl N-butyl-4-(diethoxyphosphoryl)-5-oxopyrrolidine-3-carboxylate2c

Yield: (0.36g, 75%) as a yellow oil; IR (cm-1): νC(O)O = 1738, νC(O)N = 1693; 1H NMR (CDCl3, δ ppm, *J* Hz): 0.92 (t, 3H, *J* = 7.2), 1.35 (m, 8H), 1.49 (m, 2H), 3.29-3.75 (m, 6H), 3.76 (s, 3H), 4.19 (m, 4H); ^{13}C NMR ($CDCl_3$, δ ppm): 13.1; 15.8; 28.4; 30.8; 37.8; 42.8; 44.7; 47.7; 52.2; 61.9; 166.9; 171.9; Mass (m/z): 41 (39); 96 (59); 138 (44); 220 (55); 276 (76); 293 (100); 335 ($M^{+\cdot}$, 5).

Methyl N-benzyl-4-(diethoxyphosphoryl)-5-oxopyrrolidine-3-carboxylate2d

Yield: (0.36g, 75%) as a yellow oil; IR (cm-1): νC(O)O = 1739, νC(O)N = 1695; 1H NMR (CDCl3, δ ppm, *J* Hz): 1.34 (m, 6H), 3.51 (m, 4H), 3.71 (s, 3H), 4.17 (m, 4H), 4.36; 4.54 (AB, 2H, *J* = 14.8), 7.26 (m, 5H); ^{13}C NMR ($CDCl_3$, δ ppm): 13.9; 38.0; 47.7; 52.5; 62.4; 42.9; 44.8; 127.5; 127.7; 128.3; 128.4; 135.2; 167.4; 172.1; Mass (m/z): 65 (11); 91 (100); 119 (23); 172 (19); 309 (21); 368 (17); 369 ($M^{+\cdot}$, 4).

Methyl N-(4-methoxybenzyl)-4-(diethoxyphosphoryl)-5-oxopyrrolidine-3-carboxylate2e

Yield: (0.36g, 75%) as a yellow oil; IR (cm-1): νC(O)O = 1730, νC(O)N = 1693; 1H NMR (CDCl3, δ ppm, *J* Hz): 1.32 (m, 6H), 3.50 (m, 4H), 3.71 (s, 3H), 3.78 (s, 3H), 4.12 (m, 4H), 4.27; 4.36 (AB, 2H, *J*= 14.1), 6.83; 7.14 (A_2B_2, 4H, *J* = 8.7); ^{13}C NMR ($CDCl_3$, δ ppm): 14.0; 38.1; 43.0; 44.9; 47.6; 52.6; 55.1; 63.2; 113.9; 127.3; 129.2; 159.0; 167.4; 172.2; Mass (m/z): 29 (6); 77 (9); 121 (100); 149 (75); 202 (55); 233 (28); 262 (26); 398 (31); 399 ($M^{+\cdot}$, 7).

Methyl N-(4-chlorobenzyl)-4-(diethoxyphosphoryl)-5-oxopyrrolidine-3-carboxylate2f

Yield: (0.36g, 75%) as a yellow oil; IR (cm^{-1}): νC(O)O = 1738, νC(O)N = 1697; ^1H NMR ($CDCl_3$, δ ppm, *J* Hz): 1.33 (m, 6H), 3.59 (m, 4H), 3.74 (s, 3H), 4.16 (m, 4H), 4.33; 4.52 (AB, 2H, *J* = 14.7), 7.17; 7.28 (A_2B_2, 4H, *J* = 8.1); ^{13}C NMR ($CDCl_3$, δ ppm): 13.9; 38.0; 42.8; 44.7; 47.6; 47.6; 52.5; 62.3; 128.6; 129.0; 133.3; 133.8; 167.4; 172.2; Mass (m/z): 29 (9); 89 (15); 125 (100); 153 (18); 206 (15); 223 (38); 402 (23); 403 ($M^{+\cdot}$, 5).

Methyl N-(1-phenylethyl)-4-(diethoxyphosphoryl)-5-oxopyrrolidine-3-carboxylate2g

Yield: (0.36g, 75%) as a yellow oil; IR (cm-1) : νC(O)O = 1738, νC(O)N = 1688; 1H NMR (CDCl3, δ ppm, *J* Hz): 1.34 (m, 6H), 1.54 (dd, 3H, J = 2.5 ; 7.0), 3.28-3.62 (m, 4H), 3.71 (s, 3H), 4.22 (m, 4H), 5.47 (m, 1H), 7.32 (m, 5H); ^{13}C NMR ($CDCl_3$, δ ppm): 15.7; 16.1; 38.2; 43.2; 45.2; 49.3; 52.5; 62.9; 126.6; 127.4; 128.3; 138.8; 167.1; 172.0; Mass (m/z): 79 (25); 105 (100); 133 (97); 190 (35); 218 (52); 246 (54); 278 (38); 382 (47); 383 ($M^{+\cdot}$, 11).

Preparation of methyl 3-(hydroxymethyl)-4-methylene-5-oxo-1-alkylpyrrolidine-3carboxylate 3a-g and methyl 4-(hydroxymethyl)-4-methyl-5-oxo-1-alkyl-4,5-dihydro-*1H*pyrrole-3-carboxylate 4a-f

General procedure

To a solution ofmethyl 1-alkyl-4-(diethoxyphosphoryl)-5-oxopyrrolidine-3-carboxylate 2 (5 mmol) and THF (5 mL), was added 25 moles of aqueous formaldehyde (30%) and 10 moles of potassium carbonate (6-10M). The mixture was stirred at the ambient temperature until complete dis-

appearance of cyclic phosphonate (CCM).

After hydrolysis, the solution is extracted with the ether (3x30 mL) and is dried on $MgSO_4$. After evaporation of solvent, the residue obtained is purified by column chromatography on silica gel (CH_2Cl_2:AcOEt/6:4).

Methyl 3-(hydroxymethyl)-4-methylene-5-oxo-1-propylpyrrolidine-3-carboxylate 3a

Yield: (0.36g, 75%) as a yellow oil; IR (cm^{-1}): $\nu_{C(O)O}$ = 1735, $\nu_{C(O)N}$ = 1681, $\nu_{C=C}$ = 1655; ^{1}H NMR ($CDCl_3$, δ ppm, *J* Hz): 0.93 (t, 3H, *J* = 7.4), 1.64 (m, 2H), 2.80 (br s, 1H), 3.35 (m, 2H), 3.52 ; 3.87 (AA', 2H, *J* = 10.7), 3.62 (2dl, 2H, *J* = 11.2), 3.76 (s, 3H), 5.53 ; 6.13 (2s, 2H); ^{13}C NMR ($CDCl_3$, δ ppm): 11.1; 20.3; 44.5; 50.1; 52.0; 52.9; 67.2; 118.3; 140.2; 165.5; 172.4; Mass (m/z): 42(44); 137(66); 169(100); 198(99); 227($M^{+\cdot}$, 23).

Methyl 3-(hydroxymethyl)-4-methylene-5-oxo-1-isopropylpyrrolidine-3-carboxylate 3b

Yield: (0.36g, 75%) as a yellow oil; IR (cm^{-1}): $\nu_{C(O)O}$ = 1733, $\nu_{C(O)N}$ = 1679, $\nu_{C=C}$ = 1653; ^{1}H NMR ($CDCl_3$, δ ppm, *J* Hz): 1.23 (2d, 6H, *J* = 7.4), 3.45 (m, 3H), 3.60; 3.83 (2dl, 2H, *J* = 11.2), 3.76 (s, 3H), 5.52; 6.12 (2s, 2H), 8.45 (m, 1H); ^{13}C NMR ($CDCl_3$, δ ppm): 19.5; 45.2; 50.1; 52.0; 52.9; 67.9; 118.1; 140.6; 164.8; 172.4; Mass (m/z): 56 (44); 151 (67); 183 (50); 212 (100); 227 ($M^{+\cdot}$, 23).

Methyl 3-(hydroxymethyl)-4-methylene-5-oxo-1-butylpyrrolidine-3-carboxylate 3c

Yield: (0.36g, 75%) as a yellow oil; IR (cm^{-1}): $\nu_{C(O)O}$ = 1731, $\nu_{C(O)N}$ = 1685, $\nu_{C=C}$ = 1655; ^{1}H NMR ($CDCl_3$, δ ppm, *J* Hz): 0.96 (t, 3H, *J* = 7.4), 1.43 (m, 2H), 1.60 (m, 2H), 3.37 (m, 3H), 3.55; 3.92 (AA', 2H, *J* = 10.7), 3.61; 3.99 (2dl, 2H, *J* = 11), 3.76 (s, 3H), 5.55; 6.11 (2s, 2H); ^{13}C NMR ($CDCl_3$, δ ppm): 13.6; 19.8; 28.9; 42.6; 49.9; 50.1; 52.8; 67.1; 118.3; 140.1; 165.5; 172.1; Mass (m/z): 29 (25); 108 (35); 150 (100); 166 (47); 178 (16); 209 (35); 241 ($M^{+\cdot}$, 1)

Methyl 3-(hydroxymethyl)-4-methylene-5-oxo-1-benzylpyrrolidine-3-carboxylate 3d

Yield: (0.36g, 75%) as a yellow oil; IR (cm^{-1}): $\nu_{C(O)O}$ = 1732, $\nu_{C(O)N}$ = 1686, $\nu_{C=C}$ = 1656; ^{1}H NMR ($CDCl_3$, δ ppm, *J* Hz): 3.33 (br s, 1H), 3.45; 3.75 (AA', 2H, *J* = 10.7), 3.55; 3.93 (2dl, 2H, *J* = 12), 3.69 (s, 3H), 4.49; 4.57 (AB, 2H, *J* = 14.8), 5.58; 6.17 (2s, 2H); ^{13}C NMR ($CDCl_3$, δ ppm): 46.9; 49.6; 51.9; 52.8; 66.9; 119.1; 127.7; 127.9; 128.6; 135.3; 139.8; 165.6; 172.1; Mass (m/z): 65 (44); 91 (100); 245 ($M^{+\cdot}$, 5); 275(41).

Methyl 3-(hydroxymethyl)-4-methylene-5-oxo-1-(4-methoxybenzyl)pyrrolidine-3-carboxylate 3e

Yield: (0.36g, 75%) as a yellow oil; IR (cm^{-1}): $\nu_{C(O)O}$ = 1731, $\nu_{C(O)N}$ = 1682, $\nu_{C=C}$ = 1655; ^{1}HNMR ($CDCl_3$, δ ppm, *J* Hz): 3.01 (br s, 1H), 3.37; 3.72 (AA', 2H, *J* = 10.5), 3.57 ; 3.95 (2bl, 2H), 3.71 (s, 3H), 3.78 (s, 3H), 4.45 ; 4.51 (AB, 2H, *J* = 14.8), 5.57 ; 6.17 (2s, 2H), 6.83 ; 7.16 (A_2B_2, 4H, *J* = 8); ^{13}C NMR ($CDCl_3$, δ ppm): 46.4; 49.5; 51.8; 52.8; 55.1; 67.0; 114.0; 118; 127; 129; 140; 159.0; 165.4; 172.2; Mass (m/z): 77 (8); 91 (6); 121 (100); 275 (11); 305 ($M^{+\cdot}$, 21).

Methyl 3-(hydroxymethyl)-4-methylene-5-oxo-1-(4-chlorobenzyl)pyrrolidine-3-carboxylate 3f

Yield: (0.36g, 75%) as a yellow oil; IR (cm^{-1}) : $\nu_{C(O)O}$ = 1730, $\nu_{C(O)N}$ = 1688, $\nu_{C=C}$ = 1656; ^{1}H NMR ($CDCl_3$, δ ppm, *J* Hz): 3.22 (br s, 1H), 3.39 ; 3.75 (AA', 2H, *J* = 10.5), 3.56; 3.94 (2bl, 2H), 3.71 (s, 3H), 4.45; 4.6 (AB, 2H, *J* = 14.8), 5.6; 6.17 (2s, 2H), 7.17; 7.27 (A_2B_2, 4H, *J* = 8.1); ^{13} C NMR ($CDCl_3$, δ ppm): 46.2; 49.6; 51.9; 52.8; 66.9; 119.3; 128.8; 129.3; 133.5; 133.9; 139.6; 165.7; 171.9; Mass (m/z): 53 (17); 89 (20); 125 (100); 140 (50); 220 (32); 279 (84); 309 ($M^{+\cdot}$, 0).

Methyl 3-(hydroxymethyl)-4-methylene-5-oxo-1-(1-phenylethyl)pyrrolidine-3-carboxylate 3g

Yield: (0.36g, 75%) as a yellow oil; IR (cm^{-1}): $\nu_{C(O)O}$ = 1727, $\nu_{C(O)N}$ = 1681, $\nu_{C=C}$ = 1660; ^{1}H NMR ($CDCl_3$, δ ppm, *J* Hz): 1.58 (d, 3H, *J* = 7.17), 2.82 (br s, 1H), 3.39; 3.86 (AA', 2H, *J* =10.5), 3.42; 3.89 (2bl, 2H), 3.74 (s, 3H), 5.55 ; 6.16 (2s, 2H), 5.61 (m, 1H); ^{13}C NMR ($CDCl_3$, δ ppm): 15.9; 45.8; 49.7; 51.9; 52.9; 66.9; 118.8; 127.0; 127.7; 128.6; 139.2; 140.1; 165.1; 172.2; Mass (m/z): 104 (44); 105 (97); 185 (28); 213 (22); 245 (19); 289 ($M^{+\cdot}$, 100).

Methyl 4-(hydroxymethyl)-4-methyl-5-oxo-1-pro-

pyl-4,5-dihydro-1H-pyrrole-3-carboxylate 4a

Yield: (0.36g, 75%) as a yellow oil; IR (cm^{-1}): $\nu_{C(O)O}$ = 1721, $\nu_{C(O)N}$ = 1693, $\nu_{C=C}$ = 1615; ^1H NMR ($CDCl_3$, δ ppm, *J* Hz): 0.84 (t, 3H, J= 7.5), 1.26 (s, 3H), 1.58 (m, 2H), 2.79 (br s, 1H), 3.41 (t, 2H, *J* = 6.9), 3.73 (s, 3H), 3.78 (AA', 2H, *J* = 10.5), 7.43 (s, 1H); ^{13}C NMR ($CDCl_3$, δ ppm): 11.1; 17.5; 22.1; 43.9; 51.1; 52.6; 66.0; 115.0; 143.4; 163.7; 181.3; Mass (m/z): 41 (25); 96 (25); 138 (100); 168 (33); 197 (41); 227 ($M^{+\cdot}$, 0).

Methyl 4-(hydroxymethyl)-4-methyl-5-oxo-1-isopropyl-4,5-dihydro-1H-pyrrole-3-carboxylate 4b

Yield: (0.36g, 75%) as a yellow oil; IR (cm^{-1}): $\nu_{C(O)O}$ = 1718, $\nu_{C(O)N}$ = 1693, $\nu_{C=C}$ = 1613; ^1H NMR ($CDCl_3$, δ ppm, *J* Hz): 1.26; 1.28 (2d, 6H), 1.31 (s, 3H), 2.98 (br s, 1H), 3.71 (s, 3H), 3.76 (AA', 2H, *J* = 10.5): 4.37 (m, 1H), 7.61 (s, 1H); ^{13}C NMR ($CDCl_3$, δ ppm): 17.3; 21.2; 43.0; 51.0; 52.9; 66.0; 115.0; 140.3; 163.7; 180.8; Mass (m/z): 27 (12); 29 (25); 41 (20); 56 (38); 151 (63); 182 (41); 183 (53); 212 (100); 227 ($M^{+\cdot}$, 10).

Methyl 4-(hydroxymethyl)-4-methyl-5-oxo-1-butyl-4,5-dihydro-1H-pyrrole-3-carboxylate 4c

Yield: (0.36g, 75%) as a yellow oil; IR (cm^{-1}): $\nu_{C(O)O}$ = 1720, $\nu_{C(O)N}$ = 1693, $\nu_{C=C}$ = 1614; ^1H NMR ($CDCl_3$, δ ppm, *J* Hz): 0.95 (t, 3H, *J* = 7.17), 1.30 (m, 2H), 1.33 (s, 3H), 1.57 (m, 2H), 3.20 (br s, 1H), 3.51 (t, 2H, *J* = 7.17), 3.74 (s, 3H), 3.85 (AA', 2H, *J* = 10.5), 7.53 (s, 1H); ^{13}C NMR ($CDCl_3$, δ ppm): 13.3; 17.3; 19.4; 20.7; 41.8; 50.9; 52.5; 65.7; 114.8; 143.4; 163.5; 181.2; Mass (m/z): 27(10); 29(24); 41(25); 96(32); 110(96); 152(100); 168(93); 211(69); 241($M^{+\cdot}$, 0).

Methyl 4-(hydroxymethyl)-4-methyl-5-oxo-1-benzyl-4,5-dihydro-1H-pyrrole-3-carboxylate 4d

Yield: (0.36g, 75%) as a yellow oil; IR (cm^{-1}): $\nu_{C(O)O}$ = 1717, $\nu_{C(O)N}$ = 1694, $\nu_{C=C}$ = 1614; ^1H NMR ($CDCl_3$, δ ppm, *J* Hz): 1.37 (s, 3H), 2.65 (br s, 1H), 3.71 (s, 3H), 3.91 (m, 2H), 4.67 (AB, 2H, *J* = 15.1), 7.22 (m, 5H), 7.35 (s, 1H); ^{13}C NMR ($CDCl_3$, δ ppm): 17.5; 45.9; 51.2; 52.7; 66.1; 115.6; 127.7; 128.1; 129; 135.6; 142.8; 163.7; 181; Mass (m/z): 77 (8); 112 (11); 121 (100); 140 (21); 275 ($M^{+\cdot}$, 7).

Methyl 4-(hydroxymethyl)-4-methyl-5-oxo-1-(4-methoxybenzyl)-4,5-dihydro-1H-pyrrole-3carboxylate 4e

Yield: (0.36g, 75%) as a yellow oil; IR (cm^{-1}): $\nu_{C(O)O}$ = 1722, $\nu_{C(O)N}$ = 1694, $\nu_{C=C}$ = 1614; ^1H NMR ($CDCl_3$, δ ppm, *J* Hz): 1.35 (s, 3H), 2.75 (br s, 1H), 3.71 (s, 3H), 3.79 (s, 3H), 3.89 (AA', 2H, *J* = 10.2), 4.62 (AB, 2H, *J* = 14.8), 6.86; 7.16 (A_2B_2, 4H, *J* = 8.7), 7.38 (s, 1H); ^{13}C NMR ($CDCl_3$, δ ppm): 17.5; 45.4; 51.0; 52.7; 55.2; 66.1; 115.4; 114.3; 127.5; 129; 159.4; 142.8; 163.6; 181.0; Mass (m/z): 121 (100); 140 (20); 275 (40).

Methyl 4-(hydroxymethyl)-4-methyl-5-oxo-1-(4-chlorobenzyl)-4,5-dihydro-1H-pyrrole-3carboxylate 4f

Yield: (0.36g, 75%) as a yellow oil; IR (cm^{-1}): $\nu_{C(O)O}$ = 1721, $\nu_{C(O)N}$ = 1695, $\nu_{C=C}$ = 1615; ^1H NMR ($CDCl_3$, δ ppm, *J* Hz): 1.33 (s, 3H), 2.88 (br s, 1H), 3.71 (s, 3H), 3.92 (AA', 2H, *J* = 10.5), 4.61 (AB, 2H, *J* = 15.1), 7.20 (A_2B_2, 4H, *J* = 8.4), 7.39 (s, 1H); ^{13}C NMR ($CDCl_3$, δ ppm): 17.4; 45.1; 51; 52.8; 65.9; 115.6; 128.9; 129; 133.9; 134.1; 142.5; 163.4; 181.0; Mass (m/z): 89(16); 125 (100); 127 (30); 140 (14); 220 (17); 278 (48); 280 (16); 308 (1); 309 ($M^{+\cdot}$, 0).

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