

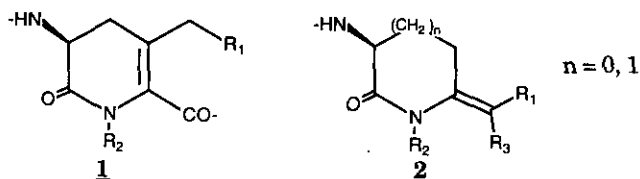
**SYNTHESIS OF CHIRAL LACTAMS AS TEMPLATES FOR  
ENZYME INHIBITORS: AN UNUSUAL ANNULATION IN THE  
INTRAMOLECULAR WADSWORTH-HORNER-EMMONS  
REACTION†**

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**Abstract** - Intramolecular carbonylolefination of a dipeptide keto phosphonate furnished unexpected lactams through rearrangement of the phosphonate carbanion

Effective inhibition of the target enzyme is an important goal in chemotherapeutics. Although the discovery of lead compounds provides the critical template for recognition and primary interaction with the target enzyme, the desired potency in biological activity is only achieved through structural fine tuning of the lead compound. A detailed analysis of various enzyme-substrate and enzyme-inhibitor systems revealed that precise control of the spatial disposition of functional groups and not their reactivity *per se* is necessary to realize the desired biological interactions. We reasoned that for any given class of enzymes, a template structure can be designed and synthesized to contain structural sites to control the reactivity and geometry. Choosing proteases as our target class, we identified chiral lactams (**1** and **2**) to possess the minimum necessary structural elements for further elaboration. Herein we report a simple and convenient synthesis of the derivatives of **1** and **2** through a normal and an abnormal intramolecular Wadsworth-Horner-Emmons (WHE) reaction.

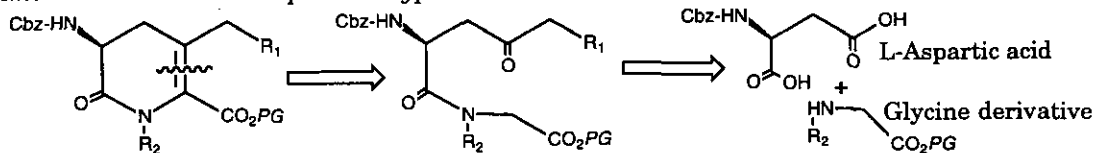


Our initial strategy for the synthesis of **1** (Scheme 1;  $R_1 = \text{OAc}$ ,  $R_2 = \text{CH}_3$ ) involved selective reaction of the  $\beta$ -carboxyl in L-aspartic acid to the desired keto derivative followed by condensation of the  $\alpha$ -carboxyl with sarcosine ester to arrive at the critical cyclo-olefination through an intramolecular Claisen reaction. Thus, L-aspartic acid was selectively protected<sup>1</sup> (as **3**, Scheme 2) and the  $\beta$ -carboxyl was homologated to the  $\alpha$ -keto alcohol (**4**) through hydrolysis of the diazoketone followed by hydrolysis of the oxazolidine. Selective protection of the alcohol followed by coupling of the  $\alpha$ -carboxyl with *t*-butyl sarcosine gave the ketodipeptide (**5**) which failed to cyclize to the desired pyrrolidinone derivatives under conditions

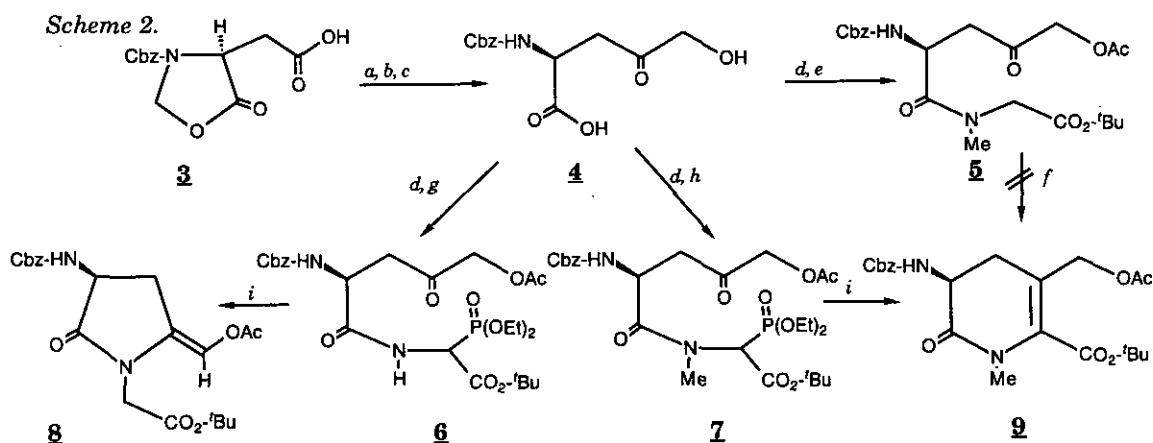
† Dedicated to Prof. A. R. Katritzky on the occasion of his 65th birthday.

(LHMDS or LDA in THF at  $-78^{\circ}\text{C}$ ) successfully employed to cyclize similar peptide derivatives in the synthesis of carbapenem antibiotics.<sup>2</sup>

**Scheme 1. Route to template 1 type**



To overcome this problem, we decided to utilize the intramolecular WHE reaction employing a phosphono-glycine peptide.<sup>3</sup> Thus, the  $\alpha$ -ketoacetate prepared from **4** was separately coupled with *t*-butyl  $\alpha$ -(diethoxy)-phosphonoglycinate and *t*-butyl- $\alpha$ -(diethoxy)phosphonosarcosinate<sup>4</sup> to furnish **6** and **7** respectively.

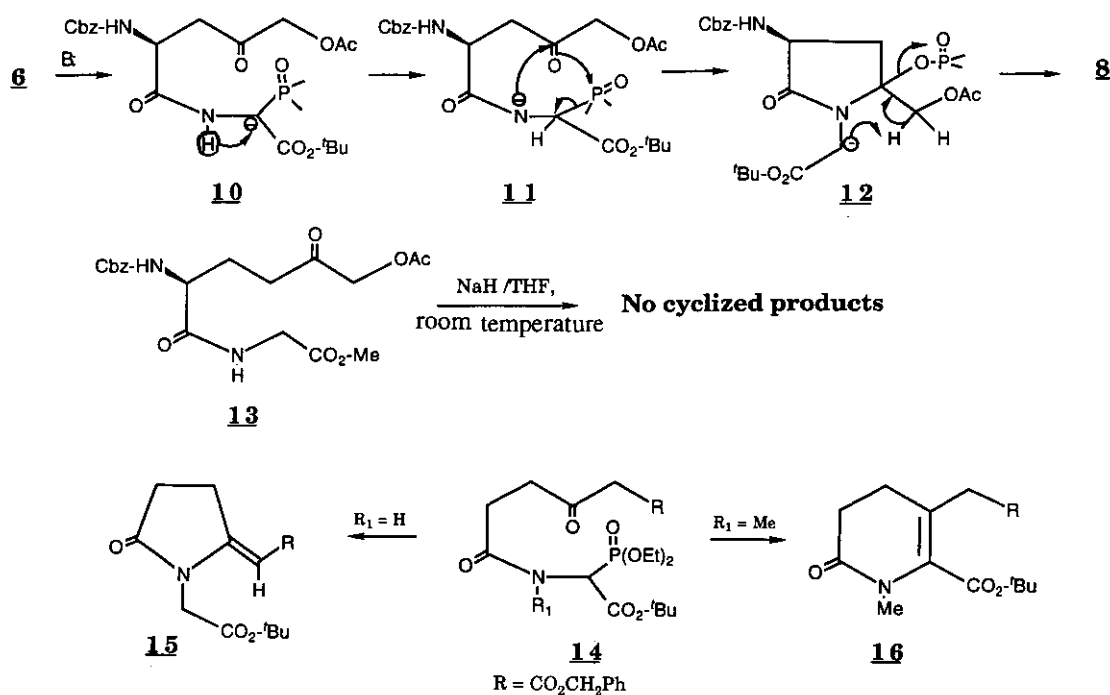


**Reagents:** (Cbz =  $\text{PhCH}_2\text{OCO}$ ): a,  $\text{SOCl}_2/\text{CH}_2\text{Cl}_2/\Delta/16\text{ h}$  (85%); b,  $\text{CH}_2\text{N}_2/0^{\circ}\text{C}/3\text{ h}$  (95%); c,  $\text{H}_2\text{SO}_4/\text{Dioxan}; 1\text{N NaOH, MeOH}$  (60%); d,  $\text{Ac}_2\text{O/py}$  (90%); e,  $\text{CH}_3\text{NHCH}_2\text{CO}_2^t\text{Bu}/2\text{-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline/PhH}/16\text{ h}$  (80%); f,  $\text{LiN}(\text{SiMe}_3)_2/\text{THF}/-78^{\circ}\text{C}$  or  $\text{LDA}/\text{THF}/-78^{\circ}\text{C}$ ; g,  $\text{H}_2\text{NCH}(\text{PO}_3\text{Et}_2)\text{CO}_2^t\text{Bu}/2\text{-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline/PhH}/16\text{ h}$  (85%); h,  $\text{MeNHCH}(\text{PO}_3\text{Et}_2)\text{CO}_2^t\text{Bu}/2\text{-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline/PhH}/16\text{ h}$  (70%); i,  $\text{NaH/DME}/\text{rt}$  (85%)

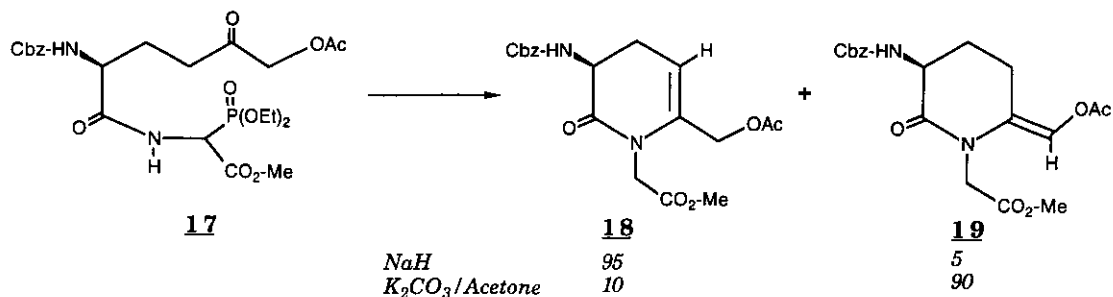
On treatment with NaH in THF ( $\text{K}_2\text{CO}_3$  in acetone for 6h was equally effective), **6** furnished exclusively a single product identified by spectroscopic and analytical methods as a 3-amino-5-methylene-2-pyrrolidinone derivative (**8**) belonging to the template class **2**. The formation of **11** by rapid rearrangement of the initially generated phosphonate carbanion, **10** through a 1,2  $\text{H}^+$  shift of the amide proton is followed by a Mannich annulation (Scheme 3). In the absence of the  $\alpha$ -phosphono group as **13**, no cyclization is observed (NaH in THF, rt) indicating that amide ion by itself is incapable of leading to Mannich annulation. Elimination of the phosphonate from **12** is stereospecific to obtain only the *E*-isomer. When rearrangement of the

phosphonate carbanion is prevented due to substitution on the amide nitrogen as in **7**, the desired piperidone derivative (**9**) was obtained in high yields. Essentially similar results were obtained with the 3-deamino derivatives(**14**)(prepared from succinic anhydride).

Scheme 3



Although the glycine phosphonates have been extensively employed in the synthesis of  $\beta$ -lactam derivatives, dehydroamino acids and dehydropeptides,<sup>5</sup> to our knowledge this is the first instance of an abnormal condensation involving the participation of the amide nitrogen in phosphonoglycine peptides.



Similar abnormal reaction was also observed when ketophosphono peptide (**17**) prepared from L-glutamic acid was employed. In this case, a mixture of olefins (**18** and **19**) from the two possible elimination modes was obtained, the ratio (**18/19**) being dependent on the base employed, although the *N*-methyl analog of **17** failed

to cyclize for reasons still unclear. A number of peptide derivatives incorporating these template structures have been prepared and evaluated for their biological properties which will be described elsewhere.

## ACKNOWLEDGEMENT

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6. Spectral data for selected compounds:  
**15**:  $^1\text{H-Nmr}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  1.40 (s, 9H,  $\text{C}(\text{CH}_3)_3$ ), 2.52 (m, 2H,  $\text{CH}_2\text{-CH}_2\text{-C}=\text{C}$ ), 3.23 (m, 2H,  $\text{CH}_2\text{-C}=\text{C}$ ), 4.12 (s, 2H,  $-\text{N-CH}_2\text{-CO}_2$ ), 5.08 (s, 1H,  $-\text{C}=\text{CH}-$ ), 5.1 (s, 2H,  $\text{Ph-CH}_2$ ), 7.22 - 7.38 (m, 5H, ar-H).  $^{13}\text{C-Nmr}$  (125 MHz,  $\text{CDCl}_3$ )  $\delta$  24.6 ( $\text{CH}_2\text{-C}=\text{C}$ ), 27.4 ( $\text{CH}_2\text{-CH}_2\text{-C}=\text{C}$ ), 27.6 ( $\text{C}(\text{CH}_3)_3$ ), 42.1 ( $\text{N-CH}_2\text{-CO}_2$ ), 65.2 ( $\text{Ph-CH}_2$ ), 83.7 ( $\text{C}(\text{CH}_3)_3$ ), 91.1 ( $\text{C}=\text{CH-CO}_2$ ), 127.6-128.3, 136.1 (ar-C), 159.6 ( $\text{C}=\text{CH}$ ), 165.2, 166.4 and 176.2 ( $>\text{CO}$ ). **16**:  $^1\text{H-Nmr}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  1.45 (s, 9H,  $\text{CO}_2\text{-C}(\text{CH}_3)_3$ ), 2.32 and 2.40 (each m, 2H,  $\text{CH}_2\text{-CH}_2\text{-C}=\text{C}$ ), 3.00 (s, 3H,  $\text{N-CH}_3$ ), 3.40 (s, 2H,  $=\text{C-CH}_2\text{-CO}$ ), 5.10 (s, 2H,  $\text{Ph-CH}_2$ ), 7.23 - 7.35 (ar-H).  $^{13}\text{C-Nmr}$  (125 MHz,  $\text{CDCl}_3$ )  $\delta$  25.9 ( $\text{CH}_2\text{-CH}_2\text{-CO}$ ), 27.8 ( $\text{C}(\text{CH}_3)_3$ ), 30.3 ( $=\text{C-CH}_2\text{-CO}_2$ ), 31.7 ( $\text{N-CH}_3$ ), 37.7 ( $\text{CH}_2\text{-CH}_2\text{-C}=\text{C}$ ), 66.6 ( $\text{Ph-CH}_2$ ), 83.2 ( $\text{C}(\text{CH}_3)_3$ ), 119.0 ( $\text{N-C}=\text{C}$ ), 128.1 - 128.4, 135.4 (ar-C), 133.9 ( $\text{N-C}=\text{C}$ ), 161.9, 169.9 and 170.2 ( $>\text{CO}$ ). **18**:  $^1\text{H-Nmr}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  2.05 (s, 3H,  $\text{COCH}_3$ ), 2.25 (bt, 1H) and 2.81 (m, 1H,  $\text{CH}_2\text{-C}=\text{C}$ ), 3.7 (s, 3H,  $\text{CO}_2\text{CH}_3$ ), 4.36 (ABq, 2H,  $\text{J} = 30$  Hz,  $=\text{C-CH}_2\text{-CO}_2$ ), 4.35 (m, 1H,  $\text{HN-CH-CH}_2$ ), 4.56 (ABq, 2H,  $\text{J} = 25$  Hz,  $-\text{N-CH}_2\text{-CO}_2$ ), 5.09 (s, 2H,  $\text{Ph-CH}_2$ ), 5.49 (dd, 1H,  $\text{J} = 10, 4$  Hz,  $\text{C}=\text{CH}$ ), 5.80 (d, 1H,  $\text{J} = 10$  Hz,  $\text{NH}$ ), 7.2 - 7.32 (5H, ar-H).  $^{13}\text{C-Nmr}$  (125 MHz,  $\text{CDCl}_3$ )  $\delta$  20.6 ( $\text{COCH}_3$ ), 26.1 ( $\text{C-CH}_2\text{-C}=\text{C}$ ), 43.7 ( $=\text{C-CH}_2\text{-O}$ ), 50.1 ( $\text{HN-CH}$ ), 66.8 ( $\text{Ph-CH}_2$ ), 111.2 ( $-\text{CH}=\text{C}$ ), 127.9-128.4, 136.2 (ar-C), 155.9 ( $\text{NH-C}=\text{O}$ ), 168.8, 169.2 and 169.9 ( $>\text{C}=\text{O}$ ). **19**:  $^1\text{H-Nmr}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  1.59 and 2.53 (each m, 1H,  $\text{HN-CH-CH}_2$ ), 2.37 and 2.89 (each m, 1H,  $\text{CH}_2\text{-C}=\text{C}$ ), 2.06 ( $\text{COCH}_3$ ), 3.62 (s, 3H,  $\text{CO}_2\text{CH}_3$ ), 4.15 (m, 1H,  $\text{HN-CH}$ ), 4.31 (ABq, 2H,  $\text{J} = 24$  Hz,  $-\text{N-CH}_2\text{-CO}_2\text{CH}_3$ ), 4.97 (s, 2H,  $\text{Ph-CH}_2$ ), 5.90 (bd, 1H,  $\text{J} = 10$  Hz,  $\text{NH}$ ), 6.84 (s, 1H,  $-\text{CH}=\text{C}$ ), 7.20 - 7.32 (m, 5H, ar-H).  $^{13}\text{C-Nmr}$  (125 MHz,  $\text{CDCl}_3$ )  $\delta$  20.4 ( $\text{COCH}_3$ ), 21.2 ( $\text{CH}_2\text{-C}=\text{C}$ ), 24.9 ( $-\text{NH-CH-CH}_2$ ), 45.2 ( $\text{N-CH}_2\text{-CO}_2\text{CH}_3$ ), 52.1 ( $\text{CO}_2\text{CH}_3$ ), 52.2 ( $\text{HN-CH}$ ), 62.5 ( $\text{Ph-CH}_2$ ), 120.9 ( $-\text{CH}=\text{C}$ ), 127.4 ( $\text{CH}=\text{C}$ ), 127.7 - 128.2, 136.6 (ar-C), 155.9 ( $\text{HN-CO}$ ), 167.3, 168.0 and 168.7 ( $>\text{CO}$ ).

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