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ASYMMETRIC SYNTHESIS OF A CONFORMATIONALLY CONSTRAINED *N*-PHOSPHONOALKYL DIPEPTIDE

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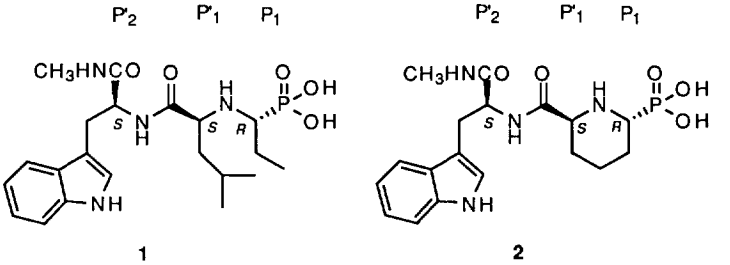
Abstract: An asymmetric synthesis has been developed to prepare a phosphono-protected (2*S*,6*R*)-6-phosphono-piperidine-2-carboxylic acid and its (2*R*, 6*S*) isomer. Coupling with tryptophan derivative afforded conformationally constrained *N*-phosphonoalkyl dipeptides (*S*,*S*,*R*)-**2** and (*S*,*R*,*S*)-**14** which have been both evaluated as human matrix metalloprotease inhibitors. © 1997 Elsevier Science Ltd.

Design and synthesis of low MW collagenase inhibitors, based on the structure of the enzyme action site, has been an active research field in recent years.[1] Among various types of compounds studied, peptides containing hydroxamic acid and β-mercaptocarbonyl ligands display interesting inhibitory activity.

Recently, a series of *N*-phosphonoalkyl dipeptides has been synthesized and tested as human collagenase inhibitors.[2] The most potent of this series was compound **1** with a tryptophan residue at the P'_2 site which exhibits an IC_{50} value of 0.05 μM on purified human lung fibroblast collagenase.

We initiated a project aimed at the preparation of some conformationally constrained molecules related to **1**. Herein we report the synthesis of compound **2** which represents a constrained analogue having the same absolute configuration as compound **1** and for which the side chains corresponding to P_1 and P'_1 are gathered to form a piperidine ring (Figure).



Figure

One retrosynthetic analysis is shown in Scheme 1. Disconnection of the amide bond gives 6-phosphono-piperidine-2-carboxylic acid (**3**) and tryptophan derivative **4**. The main task was then the synthesis of unknown (2*S*,6*R*)-6-phosphono-piperidine-2-carboxylic acid (**3**) in enantiomerically pure form. We thought that the CN(*R*,*S*) method[3] developed in our laboratory is well suited for this purpose. The nitrile function could be considered as a latent carboxyl group, while the phosphonyl group might be introduced onto the oxazolidine ring with high diastereoselectivity as recently reported.[4]

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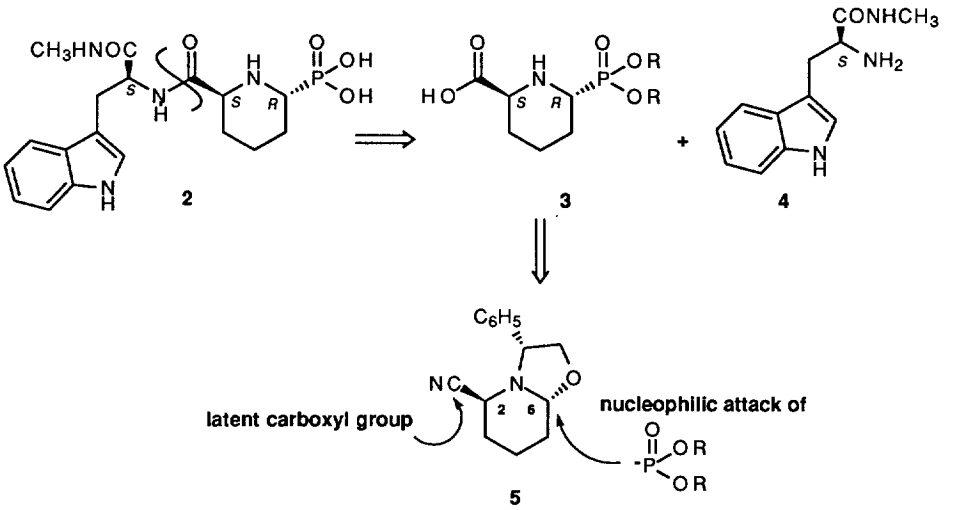
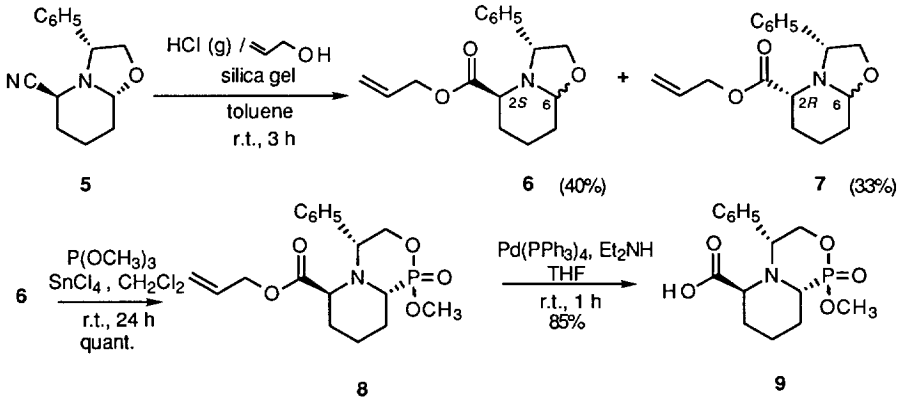


Scheme 1. Retrosynthetic analysis of compound **2**

Synthesis of 6-phosphonylpipecolic acid derivative **9** is shown in Scheme 2. Solvolysis of the nitrile group was accomplished using the methodology we already published.[5] Treatment of compound **5** with gaseous HCl in allylic alcohol afforded the ester derivative[6] in good yield but as a mixture of two pairs of isomers: **6** (with the same 2*S* configuration) and **7** (2*R*). The major pair **6** was readily separated by flash chromatography and obtained in 40% yield (while isomers **7** were isolated in 33% yield). The configuration at C-2 of **6** was determined as *S* by converting **6** into (*S*)-pipecolic acid.[5] As the configuration at C-6 was of no consequence in the subsequent C-P bond forming process (iminium intermediate), **6** (pair of epimers at C-6) was used without further separation.

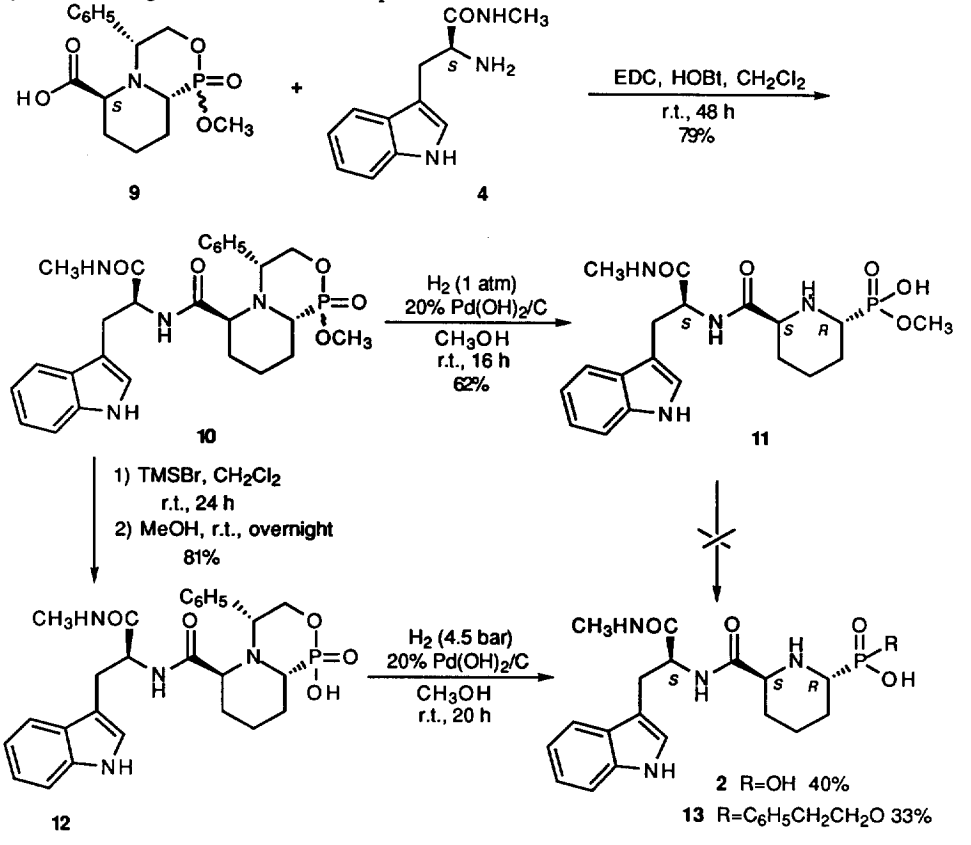


Scheme 2. Synthesis of the piperidine moiety

Formation of the P-C bond at C-6 was realized by employing our recently developed conditions.[4] Thus, treatment of **6** with trimethylphosphite in the presence of tin tetrachloride at room temperature gave the desired compound **8** in quantitative yield as an unseparable mixture of two diastereomers. Formation of the C-P bond proved highly diastereoselective; the two isomers originated from the P chiral centre. The relative configuration of

8 was assigned by comparison of its NMR spectra with the corresponding cyano derivative whose configuration had been secured *via* X-ray analysis.[4a] Treatment of **8** in THF with a catalytic amount of $Pd(PPh_3)_4$ and diethylamine[7] afforded the desired α-amino acid **9** in 85% yield. By-products (PPh_3 and $Ph_3P{=}O$) were easily removed by extraction with organic solvent, evaporation of the aqueous solution then gave the pure amino acid **9**.

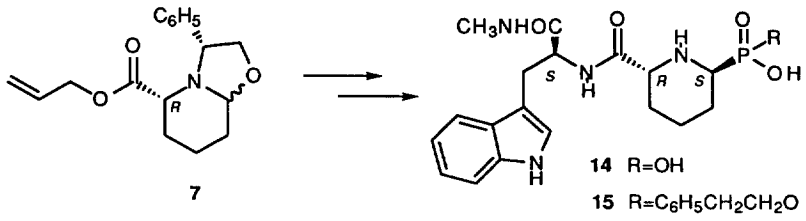
The synthesis of target molecule was accomplished as shown in Scheme 3.



Scheme 3. Peptide bond formation: 2*S* series

Coupling of acid **9** with tryptophan derivative **4** using 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (EDC) as the coupling agent in the presence of 1-hydroxybenzotriazole (HOBt) furnished dipeptide **10** in 79% yield. Reductive removal of the chiral auxiliary by hydrogenolysis (H_2, 20% $Pd(OH)_2/C$, MeOH, atmospheric pressure) afforded **11** in 62% yield. Hydrolysis of methyl monoester **11** proved to be extremely difficult. So the reaction sequence was reversed: the methyl ester group of **10** was first removed by treatment with TMSBr at room temperature to give monoester **12** in 81% yield, subsequent hydrogenolysis at 4.5 bar using 20% $Pd(OH)_2/C$ as catalyst in methanol then afforded the final compound **2**[8] in 40% yield. Phenylethyl monoester **13** was also isolated under these conditions (33%).

Starting from the other diastereomeric mixture possessing the 2*R* configuration and applying the same reaction sequence, **7** was transformed into α-phosphonoalkyldipeptide **14**[8] with *S,R,S* stereochemistry (Scheme 4).



Scheme 4

Dipeptides (*S,S,R*)-**2** and (*S,R,S*)-**14** have been both evaluated as human matrix metalloprotease inhibitors (MMP) on human recombinant fibroplast collagenase (MMP-1) and gelatinases-A and -B (MMP-1 and 9).[9] Inhibition was quantified as described previously[10] by measuring the fluorescence emitted after the peptidomimetic substrate 2,4-dinitrophenyl-Pro-Cha-Gly-Cys(Me)-His-Ala-Lys-(*N*-methylanthranilic acid)-NH_2 (from Bachem) has been cleaved between amino acids Gly and Cys by the MMPs. In contrast to compound **1**,[1] the two dipeptides did not show any significant activity at concentations less than 10^{-4} M. These results indicate that either rotation of the side chain around the *N*-phosphonoalkyl moiety is required or that the constrained conformation in compound **2** is not suitable for the activity. These results are interesting for the design of new collagenase inhibitors.

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8. **2**: $[\alpha]_D$ -9 (*c* 0.4, MeOH); MS (FAB) *m/z* 431 ($M+Na^+$); ^1H NMR (300 MHz, D_2O) δ 7.65 (br d; 1H, *J*=7.9Hz), 7.51 (br d, 1H, *J*=8.1Hz), 7.26 (s, 1H), 7.26 (br t, 1H, *J*=7.5Hz), 7.18 (br t, 1H, *J*=7.4Hz), 4.55 (br t, 1H, *J*=7.7Hz), 4.32 (t, 1H, *J*=5.3Hz), 3.63 (ddd, 1H, *J*=13.3, 8.9, 4.4Hz), 3.29 (dd, 1H, *J*=14.4, 7.2Hz), 3.23 (dd, 1H, *J*=14.4, 8.0Hz), 2.53 (s, 3H), 2.2-1.8 (m, 5H), 1.6-1.5 (m, 1H); ^{13}C NMR (62.5 MHz, CD_3OD) δ 174.4, 170.9, 138.0, 128.6, 125.0, 122.4, 119.7, 119.4, 112.3, 110.8, 55.9, 55.8, 52.9 (d, J_{C-P}=139Hz), 29.1, 27.1, 26.4, 25.4, 20.4.

   14: $[\alpha]_D$ -20 (*c* 0.4, MeOH); MS (FAB) *m/z* 431 ($M+Na^+$); ^1H NMR (300 MHz, D_2O) δ 7.67 (br d, 1H, *J*=7.9Hz), 7.49 (br d, 1H, *J*=8.0Hz), 7.24 (s, 1H), 7.24 (br t, 1H, *J*=7.5Hz), 7.16 (br t, 1H, *J*=7.4Hz), 4.8 (m, 1H), 4.22 (t, 1H, *J*=4.9Hz), 3.41 (dd, 1H, *J*=14.7, 5.4Hz), 3.35 (ddd, 1H, *J*=14.7, 9.2, 4.5Hz), 3.15 (dd, 1H, *J*=14.7, 9.9Hz), 2.70 (s, 3H), 1.8-1.5 (m, 5H), 0.8-0.7 (m, 1H); ^{13}C NMR (75 MHz, CD_3OD) δ 174.4, 170.2, 138.1, 128.7, 124.8, 122.5, 119.9, 119.5, 112.4, 111.1, 55.6, 55.3, 52.7 (d, J_{C-P}=140Hz), 29.2, 27.2, 26.7, 24.9, 19.6 (d, *J*=7Hz).
9. from Dr. Gillian Murphy, Strangeways Laboratories, Cambridge, UK.
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