

Active Methylene Phosphinic Peptides: A New Diversification Approach

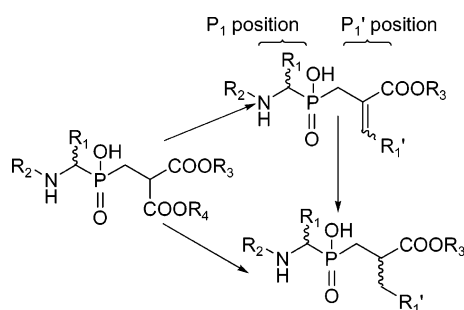
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Received March 8, 2006

ABSTRACT



Simple, rapid, and efficient methods for P_1' diversification of phosphinic peptides have been developed, employing alkylation and Knoevenagel-type condensation reactions with active methylene phosphinic scaffolds, thus leading to a wide variety of diversified phosphinic and dehydrophosphinic peptides.

We have recently reported synthetic strategies focused on the post-modification of phosphinopeptidic precursors, which can give access to a wide variety of diversified structures. Thus, diversification of phosphinic di- or tripeptides that bear a dehydrolanine residue¹ at the P_1' position² provided potent and selective cysteine-analogue inhibitors of MMP-11,³ and a propargyl glycine analogue at the same position allowed the identification of potent isoxazole-containing phosphinopeptidic inhibitors of MMP-13 and -14.⁴ Most recently, selective isoxazole phosphinic inhibitors of MMP-12 were identified, using combinatorial chemistry.⁵

Active methylene compounds have been widely used in organic synthesis as highly versatile reagents for carbon–carbon bond formation.⁶ A useful example of their use in

phosphinic peptide chemistry is the synthesis of the Pheψ-[P(O)(OH)CH₂]Arg dipeptide isostere.⁷

In this Letter we report a new and efficient strategy for diversification of phosphinic peptides, using β -phosphinoyl malonates of type **3** (Scheme 1), namely active methylene phosphinic scaffolds, which give access to a wide variety of P_1' -substituted phosphinic peptides, through alkylation and subsequent decarboxylation (compounds of type **7**, Scheme 4). Alternatively, building blocks **3** can be submitted to Knoevenagel-type condensation reactions, providing dehydrophosphinic peptides of type **4** (Scheme 3). Such compounds are of great interest, as useful intermediates for enantioselective hydrogenation. Most importantly compounds **4** are useful in their own right, as metalloprotease inhibitors that exhibit a preference for dehydro substrates at the P_1' position, such as renal dipeptidase.⁸ Actually, P_1' dehydrophosphinic inhibitors have been synthesized⁹ and evaluated,¹⁰ exhibiting inhibitory potencies in the low nanomolar range.

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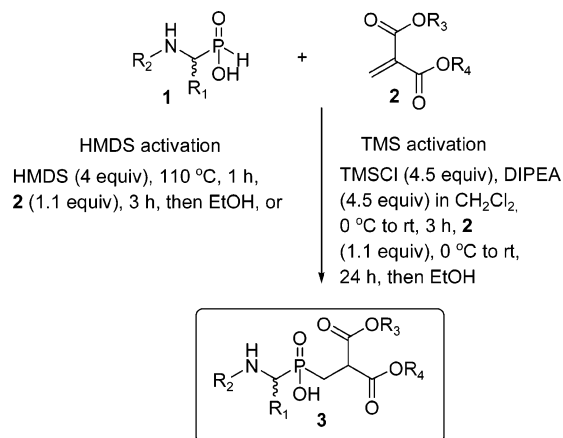
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Scheme 1. Synthesis of Active Methylene Phosphinic Peptide Scaffolds **3**



Methylenemalonates **2** (Scheme 1), serving as the Michael acceptors, were synthesized by a Knoevenagel-type condensation of HCHO with malonate esters, using Cu(OAc)₂ as catalyst (reactions not shown).¹¹ Both HMDS (using 1,1,1,3,3,3-hexamethyldisilazane) and TMS (chlorotrimethylsilane) activation of **1**¹² were applied, providing the active methylene phosphinic scaffolds of type **3**. Yields, protecting groups, and side chains are shown in Table 1.

Table 1. Yields, Protecting Groups, and Side Chains of Blocks **3**

entry	R ₁	R ₂	R ₃	R ₄	yields (%)
3a	PhCH ₂	Cbz	Et	Et	77 ^a
3a	PhCH ₂	Cbz	Et	Et	69 ^b
3a'	(S) PhCH ₂	Cbz	Et	Et	74 ^{a,c}
3b	PhCH ₂	Boc	Et	Et	58 ^a
3c	PhCH ₂	Cbz	Et	Bu ^t	62 ^a
3d	(CH ₃) ₂ CH	Cbz	Et	Et	51 ^a

^a HMDS activation. ^b TMS activation. ^c S stereochemistry at the P₁ position.

Selective protection and deprotection conditions of phosphinoyl malonates **3a** and **3c** (Scheme 2) lead to various useful intermediates. Diethyl ester **3a** can be converted to diacid **3g** by saponification or to ethyl ester **3f** under milder conditions. **3c** provides **3f** and **3h** under acidic and basic treatment, respectively. Fully protected pseudodipeptidic block **3e** is afforded by **3a**, using 1-AdBr. These building blocks can be used accordingly, depending on the requirements of the particular synthetic plan.

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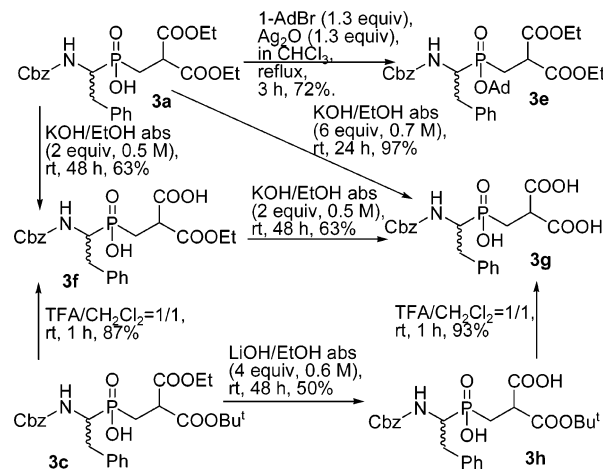
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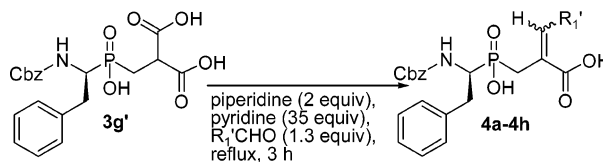
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Scheme 2. Selective Protection and Deprotection Conditions for Blocks **3e–h**



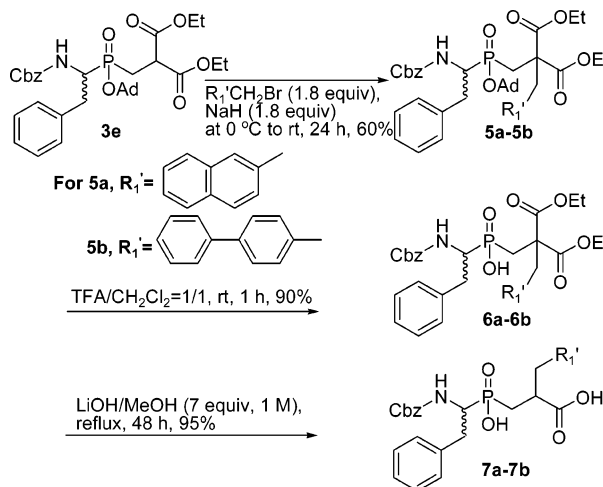
Phosphinic pseudodipeptide **3g'**, namely the S isomer at the P₁ position, was subjected to Knoevenagel-type condensations with aldehydes (Scheme 3), leading to variously P₁'

Scheme 3. Knoevenagel Type Condensation of **3g'** with Aldehydes



diversified dehydroposphinic peptides of type **4** in yields shown in Table 2. Aromatic and aliphatic aldehydes react readily with **3g'**, though ketones do not, as expected on the basis of their reduced reactivity and increased steric hindrance.

Scheme 4. Alkylation of **3e** with Alkylbromides



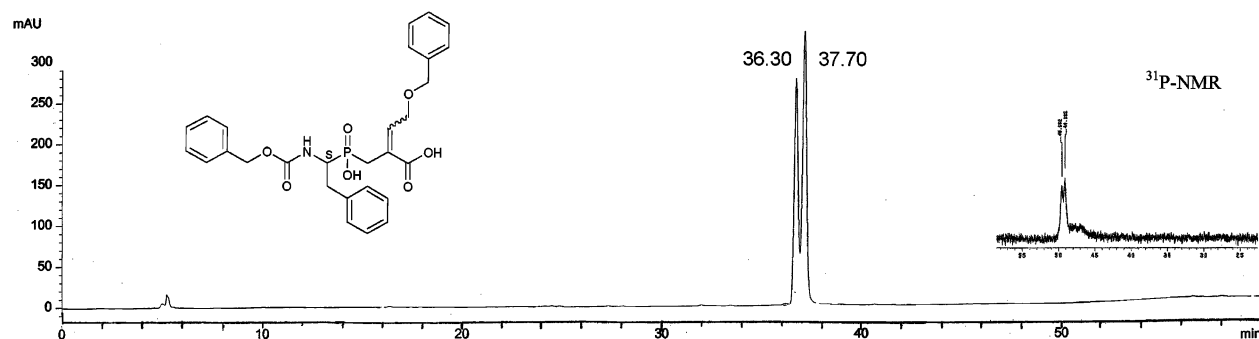


Figure 1. HPLC chromatogram and ^{31}P NMR of compound **4d**.

The *E/Z* ratio depends on the aldehyde used, varying from the exclusive formation of the one isomer (**4b**) to a nearly 1/1 ratio (**4d**), as indicated by RP-HPLC analyses and ^{31}P NMR. Separation of the two isomers of **4d** can be achieved by RP-HPLC as shown in Figure 1.

Table 2. Yields and Side Chains of Compounds **4**

entry	R_1'	yields (%)	<i>E/Z</i> ratio ¹³
4a	H	55	
4b	Ph	66	100:0
4c	$\text{Ph}(\text{CH}_2)_2$	57	67:33
4d	$\text{PhCH}_2\text{OCH}_2$	55	56:44
4e	$(\text{CH}_3)_2\text{CHCH}_2$	62	54:46
4f	4-imidazole	75	77:23
4g	<i>p</i> -chlorophenyl	53	100:0
4h	<i>p</i> -benzoic(OBu^t)	56	100:0
4i	<i>p</i> -benzoic	71	100:0

Asymmetric reduction of **4a** was attempted with rhodium catalysts.¹⁴ In the best case $\text{Rh}(\text{COD})_2\text{OTf}$ was used with the chiral ligand (*S,S*)-DuPHOS,¹⁵ at 55 psi, providing the hydrogenated product in excellent yield (91%), but in poor diastereomeric excess (22%). Further experiments are under way.

Alternatively,⁷ alkylation of **3e** with alkylbromides leads to variously diversified phosphinic blocks. It is worth

mentioning that the synthesis of **7a** with previously reported synthetic strategies¹⁶ provided an overall yield of 6.5%, whereas the method introduced herein provides the same compound in 54% overall yield.

In summary we have described here a new diversification synthetic strategy of phosphinic peptide precursors of metalloprotease inhibitors, via Knoevenagel-type condensation and alkylation of active methylene phosphinic scaffolds. Subtle modifications within the structure of phosphinic blocks can give rise to potent but mostly selective inhibitors of zinc-metalloproteases. These modifications can be conveniently and efficiently achieved by employing the strategy outlined herein.

Acknowledgment. We thank Dr. Maria Halabalaki for the 2D-NMR measurements. This work was supported in part by the European Commission (FP5RDT, QLK3-CT02-02136 and FP6RDT, LSHC-CT-2003-503297), by funds from the Laboratory of Organic Chemistry and Special Account for Research Grants of National Athens University (NKUA).

Supporting Information Available: Detailed experimental procedures, spectroscopic and analytical data for all compounds, and copies of HPLC chromatograms for compounds **4** and **7**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

OL060575M

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