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Active Methylene Phosphinic Peptides: A New Diversification Approach

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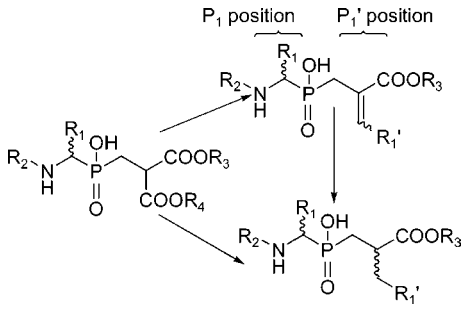
ABSTRACT



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 residue[1] at the P_1' position[2] 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)CH_2]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 synthesized[9] and evaluated,[10] exhibiting inhibitory potencies in the low nanomolar range.

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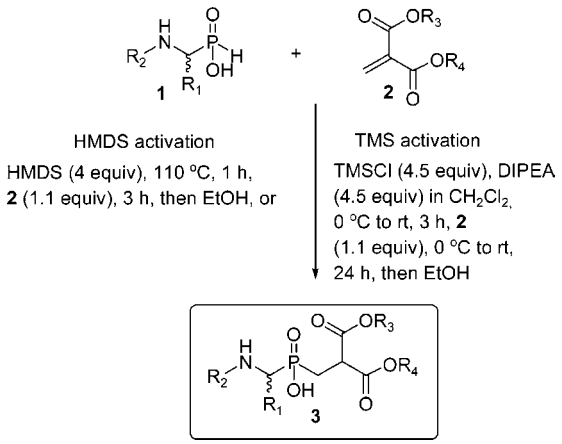
Scheme 1. Synthesis of Active Methylene Phosphinic Peptide Scaffolds **3**



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.

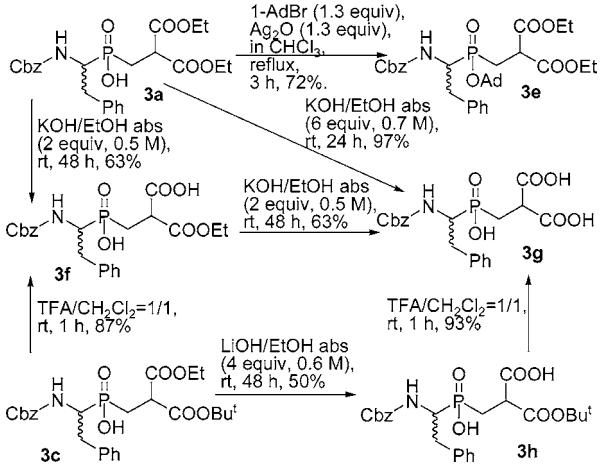
Table 1. Yields, Protecting Groups, and Side Chains of Blocks **3**

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	$(CH_3)_2CH$	Cbz	Et	Et	51[a]

[a] HMDS activation. [b] TMS activation. [c] *S* stereochemistry at the P_1 position.

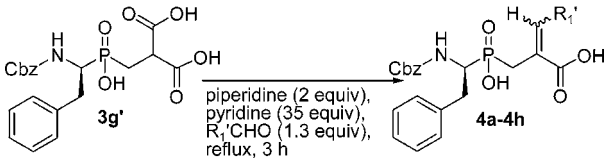
Selective protection and deprotection conditions of phosphinoyl malonates **3a** and **3c** (Scheme 2) lead to various useful intermediates. Diethyl ester **3a** can be converted to diacid **3g** by saponification or to ethyl ester **3f** under milder conditions. **3c** provides **3f** and **3h** under 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.

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



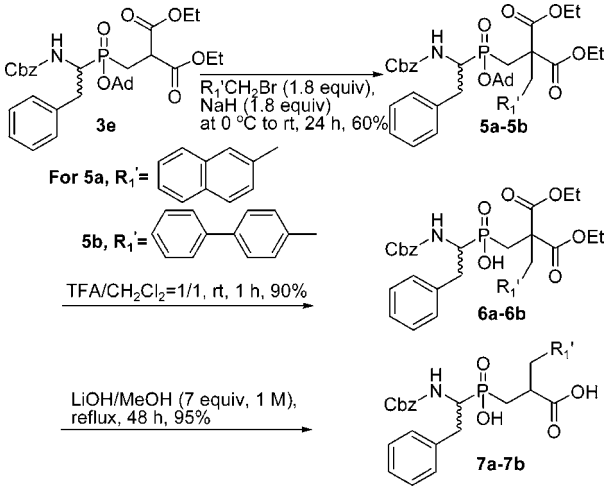
Phosphinic pseudodipeptide **3g′**, namely the *S* isomer at the P_1 position, was subjected to Knoevenagel-type condensations with aldehydes (Scheme 3), leading to variously P_1'

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



diversified dehydrophosphinic 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



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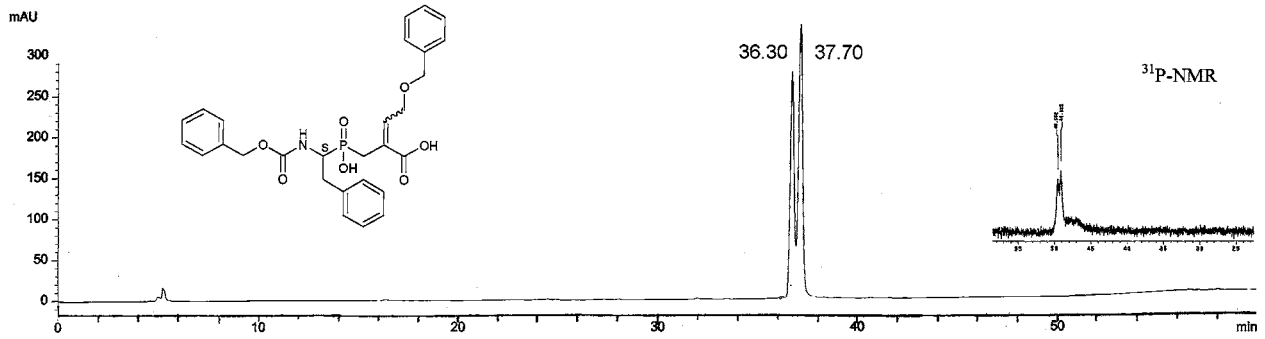

Figure 1. HPLC chromatogram and ^{31}P NMR of compound **4d**.

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 (%)	*E*/*Z* ratio[13]
4a	H	55	
4b	Ph	66	100:0
4c	$Ph(CH_2)_2$	57	67:33
4d	$PhCH_2OCH_2$	55	56:44
4e	$(CH_3)_2CHCH_2$	62	54:46
4f	4-imidazole	75	77:23
4g	*p*-chlorophenyl	53	100:0
4h	*p*-benzoic(OBu^t)	56	100:0
4i	*p*-benzoic	71	100:0

Asymmetric reduction of **4a** was attempted with rhodium catalysts.[14] In the best case $Rh(COD)_2OTf$ 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 strategies[16] 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.

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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.

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