Synthesis of Phosphonic Acid Derivatives by Oxidative Activation of Phosphinate Esters

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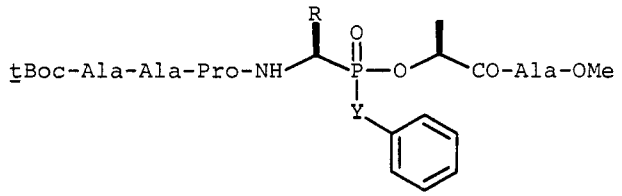
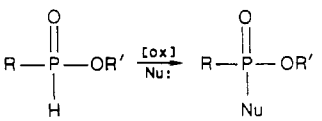
A convenient method for the synthesis of amide esters and mixed esters of phosphonic acids is described. A phosphorus monoester at the phosphinate oxidation level (4) is converted to the trimethylsilyl phosphonite tautomer, 5, and oxidized with CCl_4 to generate the phosphonochloridate 6. This oxidative activation is carried out in the presence of the amine or alcohol nucleophile so that stoichiometric formation of the chloridate is avoided and side reactions are minimized.

Electrophilic phosphonate peptide analogues, exemplified by structure 1, are of interest as covalent inactivators of serine peptidases.[1] The phenylthio and phenyl esters achieve the necessary balance of reactivity such that they are effective inhibitors of the target enzymes without being so sensitive as to react with normal peptide linkages or to present stability problems during synthesis or purification. Nevertheless, the synthesis of such compounds



1a: R = iPr; Y = S
b: R = $PhCH_2$; Y = O

posed a challenge because conventional methods for derivatization of phosphonic acids cannot be carried out in the presence of peptide bonds. The strategy that we developed involves the construction of a precursor in which the phosphorus moiety is present at the phosphinic acid oxidation level; this group is then activated by an oxidative process as the last step (eq 1). Hydrogen is thus used both as a protecting group as well as the key to activation of the phosphonate. In this paper we describe the optimization of this synthetic method and its application to the construction of a variety of phosphonate peptide derivatives, including amides and mixed esters.



(1)

The most commonly used method for the synthesis of phosphonate peptide analogues[2] begins with an N-protected monomethyl ester **2**, which is readily obtained from the diphenyl ester in either racemic[3] or optically active form.[4] This material is activated by formation of the phosphonochloridate and then coupled to the appropriate carboxyl terminal peptide fragment (Scheme I). Deprotection of the nitrogen atom followed by attachment of the amino terminal peptide using standard amino acid coupling techniques provides the phosphonate **3**. A variety of reagents are available for cleavage of the phosphonate methyl ester under nucleophilic conditions.[5] However, at this stage, activation of the phosphonate is not possible since stoichiometric formation of the normal intermediate in this process, the phosphonochloridate, is precluded by the reactivity of amides toward thionyl chloride or other comparable chlorinating agents. Even the milder reagent, diphenyl phosphorazidate, leads to side products resulting from intramolecular reaction when applied to phosphonate peptides.[6]

An alternative strategy, namely introduction of the phosphonate active ester prior to construction of the peptide backbone, is in turn prevented by the incompatibility of this electrophile with the chemistry required for formation of peptide linkages. All peptide coupling protocols proceed through reaction of a nucleophilic amine with a carboxyl active ester, and sufficient selectivity between the two active esters would appear to be unlikely.

Karanewsky and his colleagues have reported a route to phosphonate monoesters which involves a DCC-mediated coupling to generate the corresponding phosphinates followed by oxidation with aqueous sodium periodate (Scheme II).[7] We envisaged that a modification of this sequence could offer a solution to the synthetic difficulties outlined above, if the oxidative step could be utilized for simultaneous activation and coupling of the phosphorus moiety. If a general, activating oxidant could be found, an attractive element in this approach would be the ease with which the active ester could be varied, allowing leaving groups of differing size and reactivity to be explored readily. Initial experiments were carried out with phenylsulfenyl chloride and with iodine and phenol and were directed specifically toward the synthesis of the phenylthio and phenyl esters **1a** and **1b**, respectively. These experiments demonstrated the viability of the approach, and also revealed some limitations. For example, iodination of phenol, and subsequent generation of iodinated products, was observed in competition with formation of the phenyl ester **1b**.

The susceptibility of trivalent phosphorus derivatives toward polychlorinated alkanes[8] suggested that carbon

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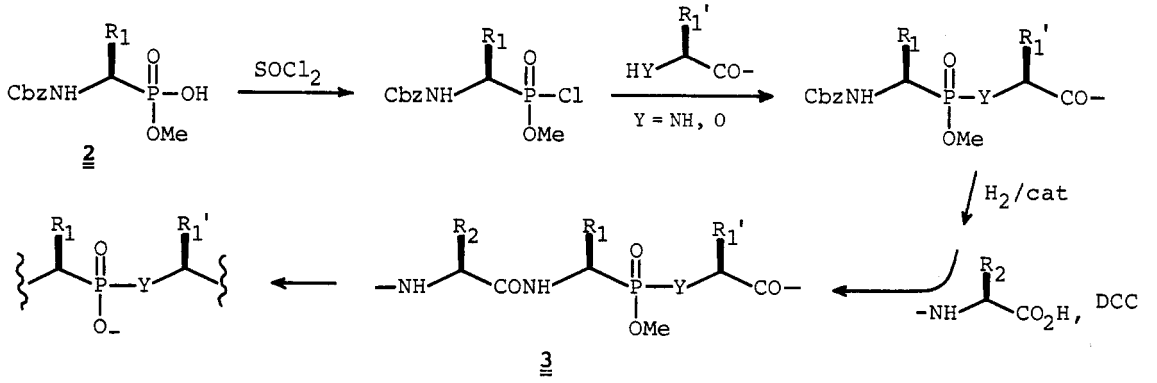
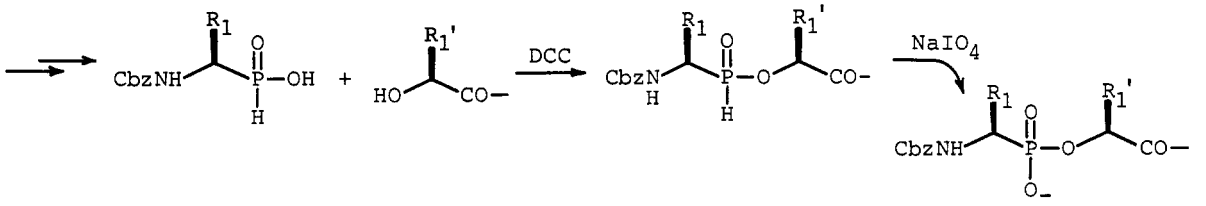
Scheme I



Scheme II



Scheme III

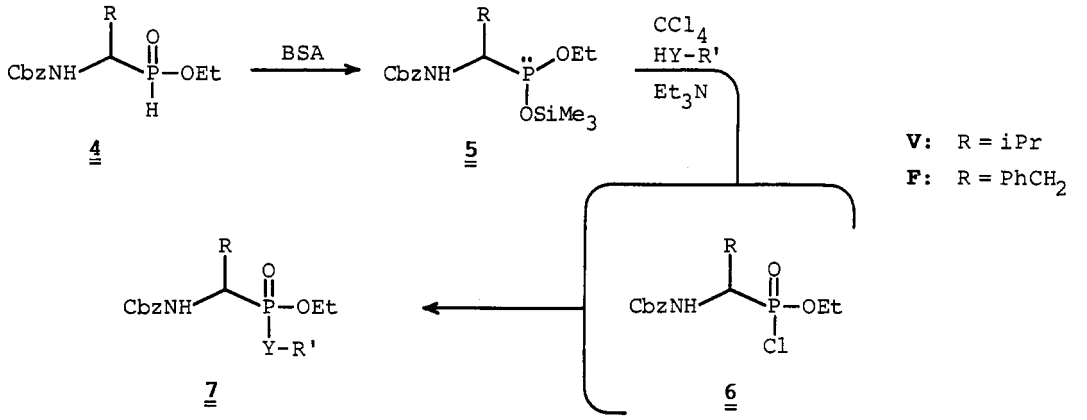


Table I. Oxidative Coupling Reactions of Phosphinate Esters

entry	substrate	nucleophile	product	equiv of Nu	equiv of Et_3N	procedure[a]	% yield[b]
1	**4V**	PhOH	**7Va**	2.0	3.0	A	99
2	**4V**	PhSH	**7Vb**	1.5	2.5	A	77
3	**4V**	L-Ala-OMe	**7Vc**	1.5	2.5	B	75
4	**4V**	L-Phe-OMe	**7Vd**	1.5	2.5	B	74
5	**4F**	L-Val-OMe	**7Fe**	1.5	2.5	B	67
6	**4V**	BnOH	**7Vf**	1.5	1.5	B	52
7	**4V**	BnOH	**7Vf**	10.0	1.2	B	68
8	**4V**	*i*-PrOH	**7Vg**	2.0	1.5	B	33
9	**4V**	*t*-BuOH	**7Vh**	1.5	1.5	B	0
10	**4V**	ethyl L-lactate	**7Vi**	1.5	1.5	B	60
11	**4F**	L-HO-Leu-L-Ala-OMe[c]	**7Fj**	1.5	1.5	B	47

[a] Procedure B: reaction carried out after silylation of phosphinate ester with 1.2 equiv (0.6 mol equiv) of bis(trimethylsilyl)acetamide (BSA); the BSA is omitted in procedure A. [b] Yield of isolated material after chromatographic purification. [c] L-HO-Leu represents the alcohol analogue of L-leucine, i.e., (*S*)-2-hydroxy-4-methylpentanoic acid.

tetrachloride could serve as a selective oxidant. Indeed, the direct conversion of hydrogen phosphonates to phosphoramidates with ammonia and CCl_4 is already known.[9] The inertness of most substances toward CCl_4 is also an advantage; for example, substitution of CCl_4 for iodine in the synthesis of **1b** provided material free from halogenated byproducts. The generality of this oxidative coupling method was explored with a variety of nucleophiles, with esters of two phosphinate substrates, **4V** and **4F** (Table I). In its present form, the oxidative coupling procedure follows the sequence outlined in Scheme III.

Following the progress of the reaction by ^{31}P NMR spectroscopy revealed several aspects of the mechanism. On combination of phosphinate **4V** with phenol and CCl_4, no reaction was observed until the addition of triethylamine; after addition of the base, the coupling reaction

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proceeded rapidly and was complete within the period of time it took to obtain the NMR spectrum (ca. 5 min). Activation of the phosphinate by CCl_4 involves deprotonation by the tertiary amine, or, possibly, establishment of an equilibrium between the tetravalent phosphinate and the trivalent phosphonite, followed by chlorination of the trivalent species to produce the phosphonyl chloride and $CHCl_3$. Since the phosphonyl chloride is generated in the presence of the nucleophile, the subsequent coupling is rapid and side reactions are minimized. If phenol or any other nucleophile is omitted from the reaction mixture, an intermediate is formed, which is presumed to be the phosphonochloridate (δ 46). However, generation of this intermediate is accompanied by the production of a variety of byproducts due to intermolecular reactions of the phosphorus derivative.[10]

For more basic nucleophiles such as amines, the equivalent of HCl that is produced in the reaction interferes with the desired coupling process, even if an excess of triethylamine is employed. For example, under the conditions above (1.2 equiv of L-Ala-OMe, 3.0 equiv of Et_3N, 0.1 M CCl_4), the coupling of phosphinate **4V** with L-alanine methyl ester provides only a 30% yield (by ^{31}P NMR) of the desired phosphonamidate. In these instances, the trivalent tautomer of the substrate can be generated as the silyl ester, prior to addition of the nucleophile and CCl_4. After addition of bis(trimethylsilyl)acetamide (BSA) to a degassed acetonitrile solution of phosphinate **4V** (mixture of diastereomers with ^{31}P NMR resonances at δ 34.4 and 34.8), the trivalent species was observed at δ 161.6 and 161.9. Formation of the chloridate then occurred on addition of CCl_4, with subsequent addition of L-alanine methyl ester and base providing the desired product. In preparative reactions the carbon tetrachloride, triethylamine, and nucleophile are added simultaneously. Due to the inherently lower nucleophilicity of aliphatic alcohols, in comparison with amines and phenolate ions, their coupling reactions proceed more slowly, requiring several hours under the standard conditions. The lower yields obtained with these nucleophiles reflect side reactions of the phosphonochloridate, which begin to compete at longer reaction times. Moreover, steric bulk on the part of the nucleophile plays a more crucial role in this series, since the reaction rates are already slower. Nevertheless, the procedure offers a general and effective method for formation of mixed esters and esters with complex alcohols.

Experimental Section

General Procedures. Unless otherwise noted, materials were obtained from commercial suppliers and used without further purification. Reactions involving reagents sensitive to moisture were conducted under an atmosphere of dry argon. Dichloromethane and acetonitrile were distilled from CaH_2. Acetonitrile and carbon tetrachloride were deoxygenated by purging with argon for 5 min immediately prior to use. Dimethylformamide was dried over molecular sieves and stored over molecular sieves after distillation. Triethylamine and *N*-methylmorpholine were distilled from sodium and stored over potassium hydroxide. Preparative thin-layer chromatography (TLC) was performed with plates precoated with silica gel G.F. (Analtech, Inc., Newark, DE). Flash chromatography was performed using silica gel 60 (E. Merck, Darmstadt) with approximately 15 cm of silica regardless of column diameter. ^1H NMR data are reported in the following manner: chemical shift in ppm downfield from internal tetramethyl silane (multiplicity, integrated intensity, coupling constants in hertz). ^{31}P NMR spectra were obtained with use of broad-band ^1H decoupling; chemical shifts are reported as ppm relative to trimethyl phosphate (sealed capillary) at 3.09 ppm, downfield positive. NMR spectra were recorded in $CDCl_3$; IR spectra were recorded in $CHCl_3$.

Diastereomer ratios were determined by ^{31}P NMR analysis. "Anal." following the description of a new compound indicates that the material was characterized satisfactorily by combustion analysis (C, H, N, P, and where relevant, S were within ±0.3% of theoretical).

Ethyl [1-[[(Phenylmethoxy)carbonyl]amino]-2-methylpropyl]phosphinate (4V). To a solution of 200 mg (0.737 mmol) of [1-[[(phenylmethoxy)carbonyl]amino]-2-methylpropyl]phosphinic acid[11] in 1 mL of ethanol and 7 mL of dichloromethane was added 155 mg (0.811 mmol) of ethyl(dimethylamino)propylcarbodiimide (EDC). After 16 h the reaction mixture was diluted with EtOAc and washed with saturated KH_2PO_4, saturated $NaHCO_3$, and brine, dried (Na_2SO_4), filtered, and concentrated under reduced pressure to yield 220 mg (99% yield) of **4V** as a white solid. A small portion was recrystallized from ether for analysis: mp 89–90 °C; ^1H NMR δ 7.34 (s, 5), 7.08 (d, 0.5, J = 545.5), 6.99 (d, 0.5, J = 547.0), 5.81 (d, 0.5, J = 8.4), 5.42 (d, 0.5, J = 8.4), 4.10 (m, 2), 3.90 (m, 2), 2.24 (m, 1), 1.31 (q, 3, J = 7.0), 1.04 (m, 6); ^{31}P NMR δ 34.84; 34.39; IR 3450, 3020, 2980, 1740, 1510, 1290, 1230, 1100 cm^{-1}. Anal.

Ethyl [1-[[(Phenylmethoxy)carbonyl]amino]-2-phenylethyl]phosphinate (4F). In a manner analogous to the procedure for **4V** described above, **4F** was obtained in 95% yield as a waxy white solid: ^1H NMR δ 7.22 (m, 10), 7.08 (d, 1, J = 556.8), 5.02 (m, 2), 4.25–4.06 (m, 3), 3.21 (m, 1), 2.90 (m, 1), 1.37–1.21 (m, 3); ^{31}P NMR δ 33.57, 33.27; IR 3440, 3020, 1720, 1500, 1210, 1050, 960, 700 cm^{-1}.

Coupling Reactions: General Procedures. Procedure A for Aromatic Nucleophiles (7Va,b). In a dried, argon-filled, 5-mL, round-bottomed flask fitted with a magnetic stirrer is dissolved 67 μmol of the ethyl hydrogen phosphinate (**4V** or **4F**) in 0.5 mL of CCl_4. The phenol (100 μmol) and 23 μL (167 μmol) of Et_3N are added, and the reaction mixture is stirred at room temperature for 1 h. The solvent is evaporated, and the crude product is purified by flash chromatography.[12]

Procedure B for Amino Acid Nucleophiles (7Vc–7Fe). In a dried, argon-filled, 5-mL, round-bottomed flask fitted with a magnetic stirrer is dissolved 167 μmol of the ethyl hydrogen phosphinate (**4V** or **4F**) in 0.5 mL of CH_3CN. BSA (25 μL, 100 μmol) is added, followed 1 min later by 250 μmol of the amino acid hydrochloride methyl ester, 0.5 mL of CCl_4, and 58 μL (418 μmol) of Et_3N. The solution is stirred at room temperature for 30 min, cooled to 0 °C, and quenched with 1 mL of MeOH. The solvent is evaporated, and the crude product is purified by flash chromatography.

Procedure B for Hydroxylic Nucleophiles (7Vf–7Fj). Procedure B for hydroxylic nucleophiles differs from that for the amino acids only in the use of 20 μL (250 μmol) of triethylamine and a reaction period of 12 h.

The methods of preparation, chromatographic solvent, and characterization of the phosphonates are described below.

Ethyl phenyl [1-[[(phenylmethoxy)carbonyl]amino]-2-methylpropyl]phosphonate (7Va): method A, 1:1 EtOAc–hexanes, 99% yield as a 1:1 mixture of 2 diastereomers; ^1H NMR δ 7.36–7.10 (m, 10), 5.16 (d, 0.5, J = 12.2), 5.10 (d, 0.5, J = 12.2), 5.06 (m, 2), 4.22–4.10 (m, 3), 2.28 (m, 1), 1.27 (t, 1.5, J = 7.1), 1.20 (t, 1.5, J = 7.1), 1.05 (d, 3, J = 6.5), 1.02 (d, 3, J = 6.5); ^{31}P NMR δ 21.66, 21.54; IR 3440, 3020, 2980, 1740, 1510, 1290, 1200, 1040, 930 cm^{-1}. Anal.

***O*-Ethyl *S*-phenyl [1-[[(phenylmethoxy)carbonyl]amino]-2-methylpropyl]phosphonothioate (7Vb)**: method A, 45:55 EtOAc–hexanes, 77% yield as a 1:1 mixture of 2 diastereomers: ^1H NMR δ 7.59 (d, 1, J = 7.7), 7.51 (d, 1, J = 8.1), 7.38–7.18 (m, 5), 5.14 (m, 2.5), 5.01 (d, 0.5, J = 9.3), 4.36–4.26 (m, 1), 4.21–4.06 (m, 2), 2.32 (dq, 0.5, J = 6.9, 3.5), 2.19 (dq, 0.5, J = 6.8, 3.9), 1.31 (t, 3, J = 7.1), 0.95 (d, 1.5, J = 6.9), 0.94 (d, 1.5, J = 6.9), 0.98 (d, 1.5, J = 6.9), 0.91 (d, 1.5, J = 6.9); ^{31}P NMR

(10) In addition, in the initial experiments with iodine we found that the reactions were, in general, cleaner with the phosphinate ethyl as opposed to methyl esters, presumably because the latter are more prone to nucleophilic demethylation.

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δ 51.69, 50.87; IR 3440, 3010, 2980, 1740, 1500, 1290, 1210, 1025, 720 cm^{-1}. Anal.

***N*-[Ethoxy[1-[[(phenylmethoxy)carbonyl]amino]-2-methylpropyl]phosphinyl]-L-alanine methyl ester (7Vc)**: method A, 3:1 EtOAc–hexanes, 75% yield as a mixture of 4 diastereomers in the ratio of 4:4:1:1; ^{1}H NMR δ 7.34 (m, 5), 5.10 (m, 1), 5.00 (d, 0.4, J = 10.6), 4.94 (d, 0.4, J = 10.9), 4.09–3.80 (m, 4), 3.70, 3.70, 3.67, 3.65 (4 s, 3), 3.23 (dd, 0.4, J = 9.4, 9.4), 3.10 (dd, 0.4, J = 9.7, 10.2), 2.23 (m, 1), 1.37–1.19 (m, 6), 1.00–0.93 (m, 6); ^{31}P NMR δ 28.69, 28.13, 27.99, 26.99; IR 3440, 3020, 2990, 1730 (br), 1510, 1390, 1150, 1030 cm^{-1}. Anal.

***N*-[Ethoxy[1-[[(phenylmethoxy)carbonyl]amino]-2-methylpropyl]phosphinyl]-L-phenylalanine methyl ester (7Vd)**: method A, 3:1 EtOAc–hexanes, 74% yield as a mixture of four diastereomers in the ratio of 6:17:26:1; ^{1}H NMR δ 7.36–7.06 (m, 10), 5.11 (m, 2), 5.26, 5.20, 4.96, 4.87 (4 d, 1, J = 10.6), 4.28 (m, 1), 4.03–3.53 (m, 3), 3.68, 3.63, 3.59 (3 s, 3), 3.12–2.75 (m, 3), 2.12 (m, 1), 1.21–1.10 (m, 3), 0.96–0.87 (m, 6); ^{31}P NMR δ 28.49, 28.01, 27.97, 26.85; IR 3440, 3400, 3000, 1725 (b), 1500, 1290, 1240, 1120, 1090, 1030, 700 cm^{-1}. Anal.

***N*-[Ethoxy[1-[[(phenylmethoxy)carbonyl]amino]-2-phenylethyl]phosphinyl]-L-valine methyl ester (7Fe)**: method A, 1:1 EtOAc–hexanes, 67% yield as two separate diastereomers in the ratio of 2:3. Diastereomer A: ^{1}H NMR δ 7.25 (m, 10), 5.19 (d, 1, J = 10.2), 5.01 (d, 1, J = 12.2), 4.96 (d, 1, J = 12.2), 4.28 (m, 1), 4.10–3.98 (m, 2), 3.87 (m, 1), 3.67 (s, 3), 3.21 (ddd, 1, J = 3.0, 3.0, 13.0), 2.91 (m, 1), 2.82 (m, 1), 2.07 (m, 1), 1.24 (t, 3, J = 6.8), 0.94 (d, 3, J = 6.8), 0.78 (d, 3, J = 6.9); ^{31}P NMR δ 28.28. Diastereomer B: ^{1}H NMR δ 7.25 (m, 10), 5.16 (d, 1, J = 9.5), 4.96 (m, 2), 4.27 (m, 1), 4.12–4.06 (m, 2), 3.86 (m, 1), 3.69 (s, 3), 3.23 (m, 1), 3.04 (dd, 1, J = 10.8, 10.8), 2.93 (m, 1), 2.09 (m, 1), 1.29 (m, 3), 0.89 (d, 3, J = 6.8), 0.81 (d, 3, J = 6.9); ^{31}P NMR δ 29.11; IR 3440, 3020, 1730, 1510, 1300, 1215, 1040 cm^{-1}. Anal.

Benzyl ethyl [1-[[(phenylmethoxy)carbonyl]amino]-2-methylpropyl]phosphonate (7Vf): method B, 1:1 EtOAc–hexanes, 52% yield as a mixture of two diastereomers: ^{1}H NMR δ 7.31 (m, 5), 5.07 (m, 5), 4.02 (m, 3), 2.19 (m, 1), 1.19 (q, 3, J = 7.1), 0.99 (d, 3, J = 6.7), 0.98 (d, 3, J = 6.7); ^{31}P NMR δ 25.31; IR 3430, 3000, 1740, 1510, 1290, 1220, 1045, 700, 670 cm^{-1}. Anal.

Ethyl isopropyl [1-[[(phenylmethoxy)carbonyl]amino]-2-methylpropyl]phosphonate (7Vg): method B, 3:2 EtOAc–hexanes, 33% yield as a mixture of two diastereomers; ^{1}H NMR δ 7.23 (m, 5), 5.13 (d, 1, J = 12.2), 5.07 (d, 1, J = 12.2), 5.00 (d, 1, J = 9.5), 4.68 (dq, 1, J = 6.3, 6.3), 4.02 (q, 2, J = 7.1), 3.95 (ddd, 1, J = 4.0, 10.8, 14.3), 2.18 (m, 1), 1.29 (d, 3, J = 6.2), 1.27 (d, 3, J = 6.2), 1.22 (t, 3, J = 7.1), 0.99 (d, 3, J = 6.8), 0.97 (d, 3, J = 6.8); ^{31}P NMR δ 23.73, 23.61; IR 3020, 2990, 1740, 1510, 1290, 1220, 1045, 1010, 725, 670 cm^{-1}. Anal.

Ethyl (2*S*)-2-[[ethoxy[1-[[(phenylmethoxy)carbonyl]amino]-2-methylpropyl]phosphinyl]oxy]propanoate (7Vi): method B, 1:1 EtOAc–hexanes, 60% yield as a mixture of two pairs of diastereomers in the ratio of 17:22:32:28. Diastereomers A and B: ^{1}H NMR δ 7.31 (m, 5), 5.43 (d, 0.5, J = 9.0), 5.11 (m, 2), 5.11–4.60 (m, 1.5), 4.21–3.98 (m, 5), 2.22 (m, 1), 1.53–1.32 (m, 3), 1.27 (t, 3, J = 7.0), 1.25 (t, 3, J = 7.2), 1.02–0.95 (m, 6); ^{31}P NMR δ 25.73, 24.72. Diastereomers C and D: ^{1}H NMR δ 7.34 (m, 5), 5.45 (d, 0.5, J = 9.0), 5.11 (m, 2.5), 5.07–4.80 (m, 1), 4.35 (q, 0.5, J = 7.1), 4.21–3.65 (m, 4.5), 2.24 (m, 1), 1.52 (d, 1.5, J = 6.9), 1.46 (d, 1.5, J = 7.0), 1.39–1.21 (m, 6), 1.01–0.95 (m, 6); ^{31}P NMR δ 26.30, 26.07. Mixture of diastereomers A–D: IR 3020, 2980, 1745, 1510, 1215, 1030, 720 cm^{-1}. Anal.

***N*-[(2*S*)-2-[[Ethoxy[1-[[(phenylmethoxy)carbonyl]amino]-2-phenylethyl]phosphinyl]oxy]-4-methylpentanoyl]-L-alanine methyl ester (7Fj)**: method B, 3:1 EtOAc–hexanes, 47% yield as a 3:2 mixture of diastereomers; ^{1}H NMR δ 7.65 (d, 1, J = 7.4), 7.26 (m, 10), 5.34, 5.04 (br, 1), 5.00 (m, 2), 5.04–4.81 (m, 1), 4.79 (m, 2), 4.11 (m, 2), 3.70, 3.69 (s, 3), 3.26 (m, 1), 2.90 (m, 1), 1.84–1.65 (m, 3), 1.42 (d, 3, J = 7.2), 1.27, 1.25 (t, 3, J = 7.0), 0.93 (m, 6); ^{31}P NMR δ 24.62, 23.93; IR 3440, 3020, 2960, 1720 (br), 1670, 1510, 1450, 1220, 1160, 1035, 700 cm^{-1}. Anal.

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Synthesis of the Dipeptide Hyroxyethylene Isostere of Leu-Val, a Transition State Mimic for the Control of Enzyme Function

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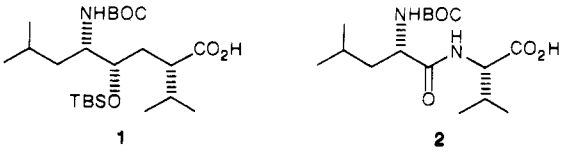
Dipeptide isosteres have recently begun to attract attention because of their ability to mimic the transition states of proteolytic enzymes or to alter or enhance the function of regulatory peptides. We have developed a general approach that may be used to prepare a diverse array of dipeptide hydroxyethylene isosteres. As an example we have prepared a mimic of Leu-Val, the cleavage site of the enzyme renin. The sequence begins with leucinal **8**, which is converted to the aldehyde **15ct** by addition of vinylmagnesium bromide to form an allylic alcohol. This is converted to the acetonide, ozonized, and equilibrated to give the trans aldehyde **15t** as the primary product. A Wadsworth–Emmons olefination followed by hydrogenation affords the ester **30** as a mixture of isomers. Hydrolysis of the acetonide and purification gives the desired lactone **26β** in 23% overall yield from BOC-leucinol.

The synthesis and biological evaluation of dipeptide isosteres for the development of novel backbone modified peptides that maintain the original side chains is an area of considerable interest.[1] In general, modifications of this type result in increased stability toward enzymatic degradation and may result in greater selectivity, prolonged activity, and improved inhibitory activity.

Scheme I



1 **2**

We now describe a stereoselective approach to the synthesis of **1**, a hydroxyethylene isostere of the dipeptide

(1) (a) Tourwe, D. *Janssen Chim. Acta* **1985**, *3*, 3. (b) Holladay, M. W.; Salituro, F. G.; Rich, D. H. *J. Med. Chem.* **1987**, *30*, 375. (c) Holladay, M. W.; Rich, D. H. *Tetrahedron Lett.* **1983**, *24*, 4401. (d) Evans, B. E.; Rittle, K. E.; Homnick, C. F.; Springer, J. P.; Hirshfield, J.; Veber, D. F. *J. Org. Chem.* **1985**, *50*, 4615. (e) Spaltenstein, A.; Carpino, P. A.; Miyake, F.; Hopkins, P. B. *Tetrahedron Lett.* **1986**, *27*, 2095. (f) Hanson, G. J.; Lindberg, T. *J. Org. Chem.* **1985**, *50*, 5399. (g) Kempf, D. J. *J. Org. Chem.* **1986**, *51*, 3921. (h) Fray, A. H.; Kaye, R. L.; Kleinman, E. F. *J. Org. Chem.* **1986**, *51*, 4828.

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