Amide-Assisted Hydrolysis of β-Carboxamido-Substituted Phosphinic Acid Esters

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Amide-Assisted Hydrolysis of β-Carboxamido-Substituted Phosphinic Acid Esters

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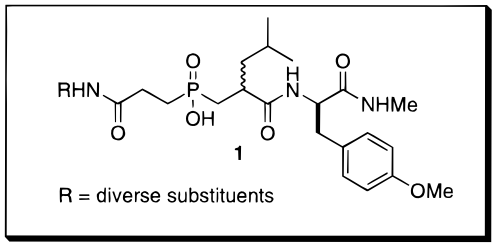
Phosphinic acids are of interest due to their ability to inhibit metalloproteases. The hydrolysis of a phosphinic acid ester is typically one of the final steps in the synthesis of such inhibitors. We have found that the acid-catalyzed hydrolysis of a phosphinic acid ester containing a β-carboxamido group is facilitated by the presence of the amide. The promotion of the hydrolysis is dependent on the electron density of the amide suggesting the intermediacy of a cyclic imidate structure (**C**). The hydrolysis of phosphinic acid esters containing a β-carboxamido group is conveniently and quantitatively effected by treating the ester with 10:90 H_2O:TFA.

Phosphinic acids are chelating agents for inorganic metal ions, and appropriately substituted phosphinic acids have proven to be effective inhibitors of metalloproteases such as stromelysin (MMP-3),[1] angiotensin converting enzyme,[2] endothelin converting enzyme,[2a,3] neutral endopeptidase 24.11,[2a] endopeptidases 3.4.24.15 and 3.4.24.16,[4] NAALADase,[5] bacterial collagenase,[6] and thermolysin.[7] The phosphinic acid moiety in an inhibitor of this class ligates the metal ion at the enzyme's active site and mimics the tetrahedral geometry attained by the scissile amide bond of the enzyme's substrate during cleavage. We have been studying the potential of phosphinic acids as inhibitors of human fibroblast collagenase (MMP-1) and sought to prepare a library of compounds with general structure **1**. To this end we prepared the



1

phosphinic acid ester **2** and treated it with neat trifluoroacetic acid in order to release the carboxylic acid which we intended to broadly derivatize (Scheme 1). Under these conditions, however, the phosphinic acid ester was also cleaved.[8] Our initial assumption that the released carboxylic acid was assisting in the hydrolysis of the phosphinic acid ester via **A** was, however, at variance with the observation that the phosphinic acid ester of **3** remained intact upon treatment with neat TFA, yielding the monoacid **4**.[8] This suggested that rather than the carboxylic acid, the carboxamide of **2** was responsible for promoting the cleavage of the phosphinic acid ester via intermediate **B**.

Interactions between β-carbonyl groups and phosphorus acid derivatives have been observed with β-carboxamido-substituted phosphonamidates,[9] α-acylaminophosphinates,[9,10] and α-acylaminophosphonates,[11] and the acid-catalyzed hydrolysis of phosphonate esters containing a 2-carboxamidophenyl group has been reported.[12] Thus, assisted hydrolysis of a phosphinic acid ester by a β-substituted carboxamide did not seem unlikely. Since the hydrolysis of phosphinic acid esters with this particular motif has not been studied nor has such an acid-catalyzed process been promoted as a method for phosphinic acid ester cleavage, we chose to study this reaction in more detail with the aim of delineating an alternate procedure for the cleavage of phosphinic acid esters of this type. An alternate method for the cleavage of phosphinic acid esters would be useful because the hydrolysis of a phosphinic acid ester is typically one of the final steps in the synthesis of phosphinic acid-based inhibitors and current methods have limitations. For example, hydrolyses with base (e.g. LiOH) at room temperature are often slow and higher temperatures may be too harsh for sensitive substrates. Likewise, hydroly-

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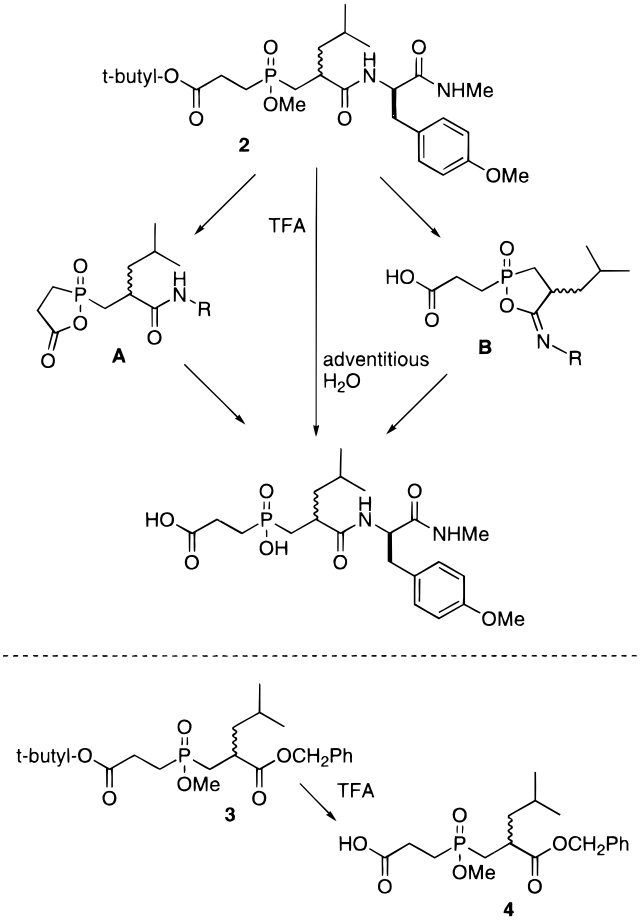
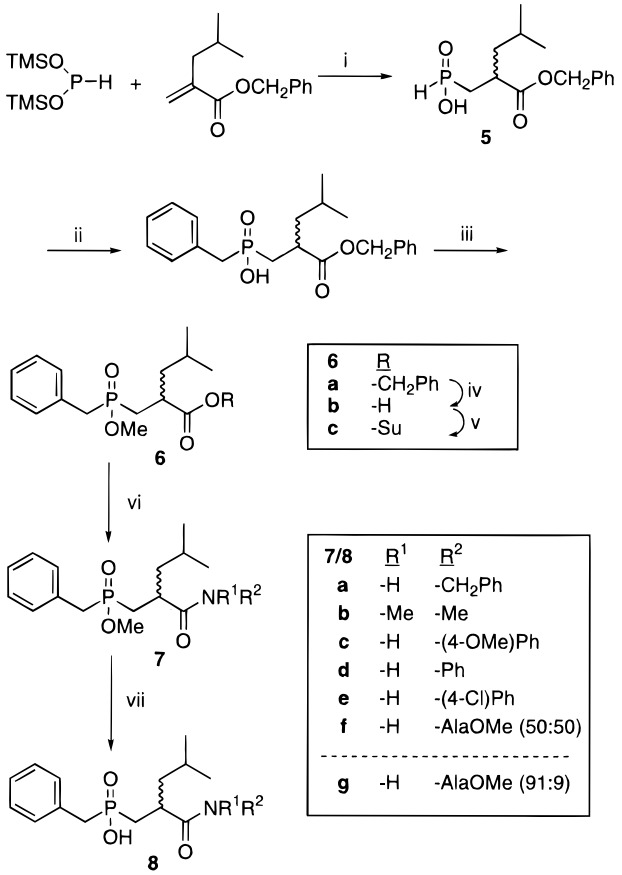
Scheme 1. Phosphinate Ester Hydrolysis—Initial Observations



Scheme 2. Synthesis of Phosphinate Esters 7a—7f; Hydrolysis of Phosphinate Esters 7a—7g[a]



[a] Reagents, reaction conditions, and yields: (i) 5 equiv of BTSP, CH_2Cl_2, rt, 16 h (~100%); (ii) 1.1 equiv of BnBr, 3 equiv of BSA, CH_2Cl_2, reaction purged with N_2, rt/reflux, 40 h (~100%); (iii) excess $TMSCHN_2$, 4:1 toluene:MeOH, rt, 15 min (70% for 3 steps); (iv) H_2/5% Pd—$BaSO_4$, 45 psi, MeOH, rt, 1 h (100%); (v) 1.5 equiv of EDC•HCl, 1.5 equiv of HOSu, DMF, rt, 18 h (96%); (vi) 1.2 equiv of HNR^1R^2, CH_2Cl_2, rt to reflux until conversion complete by TLC or HPLC (29—88%); (vii) aqueous TFA, 0 °C to rt (100%); (viii) 1.1 equiv of EtI or BnBr, 2 equiv of Cs_2CO_3, DMF, rt, 2—3 d (28—66%).

ses with trimethylsilyl bromide may be incompatible with other functionalities. Herein we demonstrate that the acid-catalyzed hydrolysis of β-carboxamido-substituted phosphinic acid esters is an effective, rapid, and mild method for the preparation of β-carboxamido-substituted phosphinic acids.

Results and Discussion

A key intermediate in our study, phosphinate **6a**, was prepared through a Michael addition[13] of bis(trimethylsilyl)phosphonite[14] with benzyl α-isobutylacrylate[15] followed by an Arbuzov reaction[16] with benzyl bromide mediated by *N*,*O*-bis(trimethylsilyl)acetamide and subsequent methylation with (trimethylsilyl)diazomethane[17] (Scheme 2). Conversion of the benzyl ester into the desired amides **7** was effected by hydrogenation and coupling with *N*-hydroxysuccinimide followed by reaction of the resulting active ester **6c** with various amines. Preparation of the enantiomerically enriched compound **7g** began with the crystallization of the (*S*)-α-methylbenzylamine salt of **5** (Scheme 3).[1a] After two recrystallizations, the salt was substantially enriched in one of the diastereomers.[18] Reconversion of the salt into the corresponding free acid **5*S*** and repeating the steps outlined in Scheme 2 for the preparation of **7f** from **5** led to **7g**. HPLC analysis of the diastereomeric mixture **7g** revealed a 91:9 mixture of diastereomers. The ethyl and benzyl phosphinates, **7h** and **7i**, respectively, were prepared by O-alkylation of the corresponding phosphinic acid **8**, which was prepared as described below.

We began our study by confirming that a β-situated carboxamide would facilitate the acid-catalyzed hydrolysis of a phosphinic acid ester and indeed, treatment of **7a** with 10% aqueous TFA at room temperature led to the rapid hydrolysis (<15 min) of the phosphinic acid ester, quantitatively yielding **8a**,[19] presumably via **C**. The corresponding benzyl ester **6a** was not affected by treatment with 10% aqueous TFA at 0 °C; however, the

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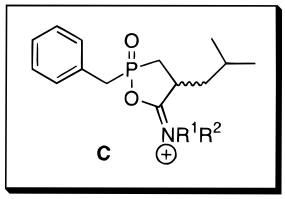
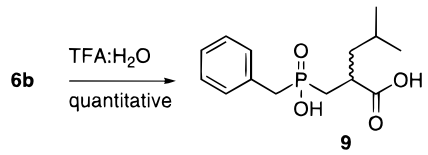
(18) ^{1}H-NMR of the initially formed diastereomeric salt showed a "shoulder" on the P—*H* resonance which diminished upon two recrystallizations. Direct quantitative assessment of the diastereomeric purity of the salt by ^{1}H-NMR or ^{31}P-NMR was not successful and attempts to determine the e.e. of **5*S*** by chiral HPLC, ^{1}H-NMR, and ^{31}P-NMR were likewise unsuccessful. On the basis of the literature precedent (ref 1a), we assume the isolated salt is enriched in the *S*-isomer of the phosphinic acid.
(19) We did not observe any of the alternate cleavage which would yield **6b** or **9**. This is consistent with the observations of Kluger and Chan (ref 12).



carboxylic acid **6b** was, like the amide **7a**, rapidly converted to the respective phosphinic acid (i.e. **9**) under



these conditions. Although both a β-carboxamido or β-carboxy group promote the hydrolysis of a phosphinic acid ester, under more dilute conditions (1:9:90 H_2O:TFA:CH_2Cl_2 at 0 °C) the carboxamide-induced hydrolysis proved to be more rapid with the hydrolysis being complete in about 3 h and the hydrolysis of the acid being only about 25% complete after 4 h (Figure 1).[20] With the effectiveness of the β-carboxamido-induced hydrolysis confirmed, we next investigated the effect of altering the amide substituents. Under the dilute conditions used above, the dimethylamide **7b** hydrolyzed even more rapidly than **7a**, demonstrating that increased electron density of the amide promoted the hydrolysis and that the presence of a proton on the amide nitrogen was unnecessary.[21] Hydrolysis of the anilide **7d** was slower than the benzyl amide and, as anticipated, the 4-methoxyanilide **7c** hydrolyzed more rapidly than **7d** while the 4-chloroanilide **7e** hydrolyzed more slowly (Figure 2). The overall dependency of the hydrolysis on the electron density of the carboxamide supports the intermediacy of **C** in the hydrolysis process.

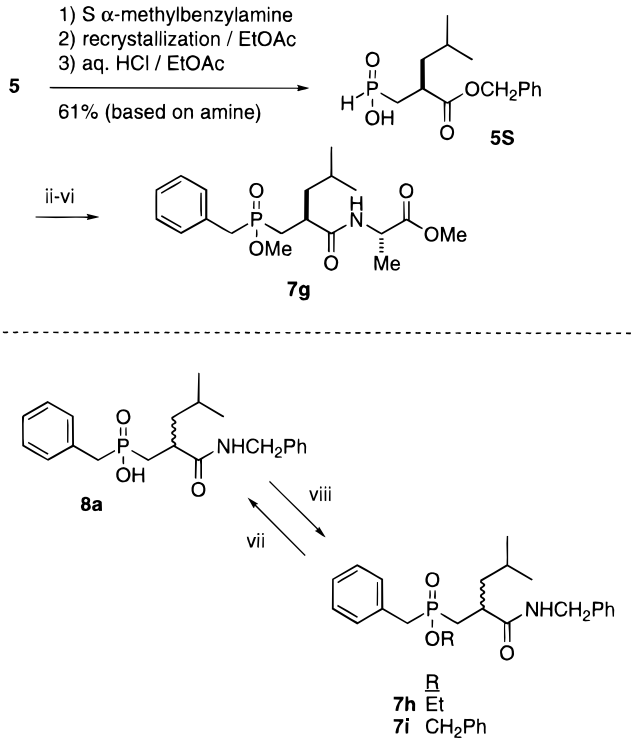
Altering the phosphinate ester functionality from methyl to ethyl (**7h**) or benzyl (**7i**) diminished the reaction rate, presumably due to steric inhibition in forming intermediate **C** (Figure 3). However, since the reaction rate diminution was only slight, we expect that the method will be effective in general, that is, not limited to methyl phosphinates.

Since many of the phosphinic acids of interest as protease inhibitors have chiral centers adjacent to the participating carboxamido group or a chiral amino acid as the carboxamido moiety, we examined whether the integrity of these chiral centers was affected by the hydrolysis procedure. To determine whether epimerization at either center of concern occurred, we compared the hydrolysis of **7f** with that of **7g**. Compound **7f** is a mixture of four diastereomers that upon hydrolysis yields equal amounts of the two diastereomeric phosphinic acids. Hydrolysis of compound **7g**, which is also a mixture of four diastereomers but which is enriched in two diastereomers to the extent of 91:9, led to the same two diastereomeric phosphinic acids as above and in the same ratio as the initial mixture (i.e. 91:9). Had either chiral center epimerized this ratio would have been diminished. Thus, epimerization of either center adjacent to the carboxamide does not appear to occur to an appreciable extent under the hydrolysis conditions.

(20) Continued reaction at room temperature for 20 h led to complete conversion.

(21) The hydrolysis of the dimethyl amide **7b** was complete within 10 min vs 180 min for **7a**.

Scheme 3. Synthesis of Phosphinate Esters 7g−7i; Hydrolysis of 7h−i[a]



[a] See footnote to Scheme 2 for reagents, reaction conditions, and yields.

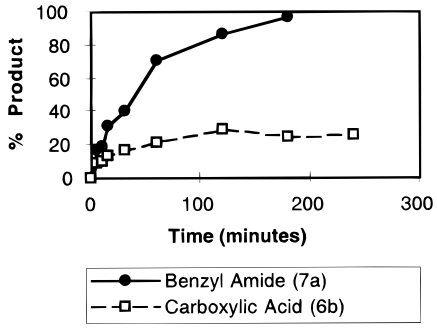


Figure 1. Phosphinate ester hydrolysis promoted by a carboxamide vs a carboxylic acid.

These results demonstrate that the acid-catalyzed hydrolysis of phosphinic acid esters containing a β-carboxamido group is an effective method for converting such esters into the corresponding acids. The carboxamido group may be secondary or tertiary and chiral centers adjacent to the carboxamido group are unaffected. The ready hydrolysis of methyl, ethyl, and benzyl phosphinic acid esters suggests that phosphinic acid esters of this general motif should all be readily cleaved, and thus, esters especially sensitive to acid hydrolysis such as diphenylmethyl[3a] or adamantyl[22] need not be utilized for this purpose. This method compliments existing methods for phosphinic acid ester hydrolysis and should prove useful in the preparation of phosphinic acid-containing inhibitors of metalloproteases; we have successfully applied the method, using the "standard" conditions, to the preparation of a wide variety of phosphinic acid-based inhibitors of MMP-1.

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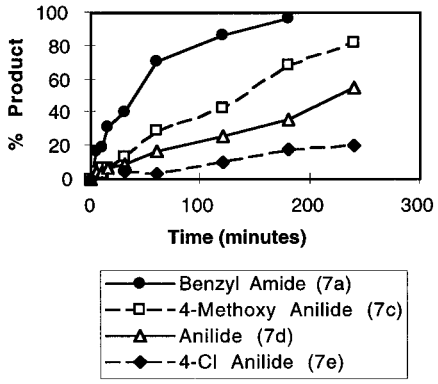

Figure 2. Phosphinate ester hydrolysis promoted by carboxamides of differing electron density.

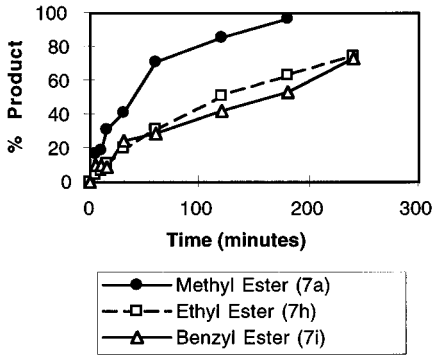

Figure 3. Carboxamide-promoted hydrolysis of differing phosphinate esters.

Experimental Section

Caution: bis(trimethylsilyl)phosphonite (BTSP), used in the preparation of **5**, is highly pyrophoric; appropriate precaution should be taken to avoid contacting this reagent with air.

Solvents and reagents were used as obtained from commercial sources. Sure/Seal® quality solvents were purchased from Aldrich Chemical Co., Inc., and used when dry solvents were required. HPLC was performed using a Waters NovaPak C_{18} column (3.9 mm × 15 cm) with a CH_3CN (0.1% TFA):H_2O (0.1% TFA) gradient (CH_3CN concentrations in the gradient are listed for each compound) and a flow rate of 1.0 mL/min. All preparative chromatography was performed on 40 μM silica gel.

Methyl Benzyl[(2-(benzyloxycarbonyl)-4-methylpentyl]phosphinate (6a). In a flame-dried flask under N_2, hexamethyldisilazane (24.6 mL, 116.8 mmol) was added to $NH_4H_2PO_2$ (9.7 g, 117 mmol) and the mixture heated at 105 °C with stirring for 2 h. The mixture was cooled to 0 °C in an ice bath and benzyl α-isobutylacrylate (5.1 g, 23.4 mmol) in dry CH_2Cl_2 (60 mL) was added by syringe. The reaction mixture was stirred at room temperature for 16 h and then carefully quenched (still under N_2) with 1 N HCl (40 mL). After 30 min, the organic layer was separated and washed with 1 N HCl (2 × 50 mL) and brine and dried over $MgSO_4$. Filtration and concentration *in vacuo* gave **5** (quantitative yield) as an oil: ^{1}H-NMR ($CDCl_3$) δ 0.90/0.92 (6H, 2d), 1.41 (1H, m), 1.5−1.75 (2H, m), 1.86 (1H, m), 2.15 (1H, m), 2.92 (1H, m), 5.13 (2H, dd), 7.12 (1H, d, J = 559 Hz), 7.37 (5H, m), 10.76 (1H, s); ^{31}P-NMR ($CDCl_3$) δ 35.05 (dm, J = 559 Hz).

Crude **5** (23.4 mmol) from above was taken up in dry CH_2Cl_2 (120 mL), and benzyl bromide (3.06 mL, 25.7 mmol) and BSA (14.5 mL, 70.1 mmol) were added. The solution was purged for ~30 min with a slow stream of N_2. The mixture was then stirred at room temperature for 20 h, refluxed for 8 h, and stirred at room temperature for 18 h. The reaction was quenched with 1 N HCl (40 mL) and the separated organic layer washed with 1 N HCl (2 × 50 mL) and brine (50 mL) and dried over $MgSO_4$. Filtration and concentration *in vacuo* gave benzyl[2-(benzyloxycarbonyl)-4-methylpentyl]phosphinic acid (quantitative yield) as an orange oil: ^{1}H-NMR ($CDCl_3$) δ 0.82/0.87 (6H, 2d), 1.2−1.7 (4H, m), 2.04 (1H, m), 2.82 (1H, m), 2.96 (2H, d), 5.12 (2H, dd), 7.15−7.45 (10H, m), 8.34 (1H, br s).

Crude benzyl[2-(benzyloxycarbonyl)-4-methylpentyl]phosphinic acid from above (23.4 mmol) was taken up in toluene/methanol (160 mL/40 mL) and treated with excess $TMSCHN_2$ (2M solution in hexanes) for 30 min. The excess $TMSCHN_2$ was quenched with acetic acid and the reaction mixture concentrated *in vacuo* to an oil. This was chromatographed (ethyl acetate) to give 6.39 g (70.5% for three steps) of **6a** as a yellow oil: mass spectrum (CI) $M^+ + NH_4^+$ 406 (22.0), $M^+ + H^+$ 389 (100); ^{1}H-NMR ($CDCl_3$) δ 0.83/0.90 (6H, 2d), 1.29 (1H, m), 1.46 (1H, m), 1.58 (1H, m), 1.71 (1H m), 2.13 (1H, m), 2.80 (1H, m), 3.10/3.13 (2H, dd/d), 3.50/3.53 (3H, 2d), 5.12 (2H, dd), 7.2−7.3 (5H, m), 7.3−7.4 (5H, m); ^{31}P-NMR ($CDCl_3$) δ 52.09, 52.50 (2m); HPLC (30/90) 17.9 min. Anal. Calcd for $C_{22}H_{29}PO_4$ (388.45): C, 68.03; H, 7.52. Found: C, 67.63; H, 7.74.

Benzyl[2-(benzyloxycarbonyl)-4-methylpentyl]phosphinic Acid *N*-Hydroxysuccinimide Ester (6c). The benzyl ester **6a** (1.94 g, 5.0 mmol) was hydrogenated in methanol (60 mL) at 45 psi over 5% palladium on barium sulfate (1.0 g) for 1.5 h. The catalyst was filtered off and washed with methanol, and the filtrate was concentrated *in vacuo* to give **6b** (quantitative yield) as an oil: ^{1}H-NMR ($CDCl_3$) δ 0.8−0.95 (6H, m), 1.25 (1H, m), 1.55 (3H, m), 2.18 (1H, m), 2.68/2.85 (1H, 2m), 3.25/3.28 (2H, d/dd), 3.65/3.70 (3H, 2d), 7.28 (5H, m); HPLC (20/80) 13.1/13.4 min.

The crude acid **6b** (5.0 mmol) was dissolved in dry DMF (50 mL), and 1-(3-(dimethylamino)propyl)-3-ethylcarbodiimide hydrochloride (1.44 g, 7.5 mmol) and *N*-hydroxysuccinimide (863 mg, 7.5 mmol) were added. The resulting solution was stirred at room temperature for 19 h and was then diluted with ethyl acetate (100 mL) and washed with 1 N HCl (2 × 100 mL), $NaHCO_3$ (2 × 100 mL) and brine (100 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated *in vacuo* to give 1.89 g (95.5%) of **6c** as an oil: ^{1}H-NMR ($CDCl_3$) δ 0.85−1.0 (6H, m), 1.48 (1H, m), 1.75 (3H, m), 2.13 (1H, m), 2.85 (4H, s), 2.98/3.1−3.3 (3H, m), 3.62/3.68 (3H, 2d), 7.30 (5H, m).

Methyl Benzyl[2-(*N*-benzylcarbamoyl)-4-methylpentyl]phosphinate (7a). A portion of the above crude *N*-hydroxysuccinimide ester **6c** (593 mg, 1.5 mmol) in dry CH_2Cl_2 (15 mL) was treated with benzylamine (0.33 mL, 3.0 mmol). After 5 days at room temperature the reaction was diluted with additional CH_2Cl_2 (30 mL), washed with 1 N HCl (2 × 50 mL), $NaHCO_3$ (2 × 50 mL), and brine (50 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo* to an oil. This was chromatographed (ethyl acetate) to give 511 mg (87.9%) of **7a** as an oil: mass spectrum (CI) $M^+ + H^+$ 388 (100); ^{1}H-NMR ($CDCl_3$) δ 0.80−0.95 (6H, m), 1.05−1.80 (4H, m), 2.10 (1H, m), 2.57 (1H, m), 3.07 (2H, m), 3.47/3.58 (3H, 2d), 4.40 (2H, m), 6.42/6.50 (1H, 2m), 7.30 (10H, m); ^{31}P-NMR ($CDCl_3$) δ 53.23, 53.65 (2m); HPLC (30/90) 11.4/12.0 min. Exact Mass Calcd for $C_{22}H_{30}NO_3P$: 388.2042. Found: 388.2056.

Amides **7b**−**g** were prepared analogously.

Methyl benzyl[2-(*N*,*N*-dimethylcarbamoyl)-4-methylpentyl]phosphinate (7b): yield 76.7%; mass spectrum (CI) $M^+ + H^+$ 326 (100), $M^+ - N(Me)_2$ 281 (86); ^{1}H-NMR ($CDCl_3$) δ 0.80−0.90 (6H, m), 1.16−1.75 (4H, m), 2.27 (1H, m), 2.98/3.02 (3H, 2s), 3.05−3.2 (6H, m), 3.55/3.59 (3H, 2d), 7.30 (5H, m); HPLC (10/70) 18.6/19.4 min.

Methyl benzyl[2-(N-(4-methoxyphenyl)carbamoyl)-4-methylpentyl]phosphinate (7c): yield 66.3%; mass spectrum (CI) $M^+ + NH_4^+$ 421 (4), $M^+ + H^+$ 404 (100); ^{1}H-NMR ($CDCl_3$) δ 0.80−0.95 (6H, m), 1.00−1.90 (4H, m), 2.12 (1H, m), 2.76 (1H, m), 3.11 (2H, m), 3.50/3.65 (3H, 2d), 3.77/3.78 (3H, 2s), 6.85 (2H, m), 7.15−7.35 (5H, m), 7.48 (2H, m), 8.40/8.48 (1H, 2s); HPLC (30/90) 11.9/12.2 min.

Methyl benzyl[2-(N-phenylcarbamoyl)-4-methylpentyl]phosphinate (7d): yield 39.0%; mass spectrum (CI) $M^+ + NH_4^+$ 391 (4), $M^+ + H^+$ 374 (100); ^{1}H-NMR ($CDCl_3$) δ 0.80−0.95 (6H, m), 1.15 (1H, m), 1.5−1.9 (3H, m), 2.14 (1H, m), 2.80 (1H, m), 3.15 (2H, m), 3.48/3.65 (3H, 2d), 7.09 (1H, m), 7.15−7.35 (7H, m), 7.57 (2H, m), 8.58/8.67 (1H, 2s); HPLC (30/90) 13.7 min.

Methyl benzyl[2-(*N*-(4-chlorophenyl)carbamoyl)-4-methylpentyl]phosphinate (7e): yield 29.4%; mass spectrum (CI) $M^+ + NH_4^+$ 425 (5), $M^+ + H^+$ 408 (100); ^{1}H-NMR ($CDCl_3$) δ 0.80−1.0 (6H, m), 1.0−1.9 (4H, m), 2.20 (1H, m), 2.85−3.25 (3H, m), 3.41/3.56 (3H, 2d), 7.15−7.45 (7H, m), 7.52 (2H, m), 9.66/9.74 (1H, 2s); HPLC (30/90) 17.0 min.

Methyl benzyl[2-(*N*-((*S*)-1-(methoxycarbamoyl)-1-ethyl)carbamoyl)-4(R,S)-methylpentyl]phosphinate (7f): yield 80.9%; mass spectrum (CI) $M^+ + H^+$ 384 (100); ^{1}H-NMR ($CDCl_3$) δ 0.80−0.95 (6H, m), 1.05−1.80 (4H, m), 1.40 (3H, m), 2.12 (1H, m), 2.60 (1H, m), 3.15 (2H, m), 3.61 (3H, m), 3.74 (3H, s), 4.55 (1H, m), 6.48/6.57/6.86/6.93 (1H, 4d), 7.31 (5H, m); HPLC (10/70) 16.1/16.8 (two isomers)/17.9 min (50/50 R/S).

(S)*-α-Methylbenzylamine salt of 5*S*.** (*S*)-α-Methylbenzylamine (1.47 mL, 11.4 mmol) was added to crude **5** (6.50 g, 22.9 mmol) in dry CH_2Cl_2 (50 mL). The solvent was removed *in vacuo* and 1:1 hexane/ether (40 mL) added to the resulting oil. After standing at 0 °C, white crystals formed. These crystals were collected, washed with hexane, and recrystallized from ethyl acetate (2×) to give 2.82 g (60.9% with respect to (*S*)-α-methylbenzylamine) of the (*S*)-α-methylbenzylamine salt of **5*S as a white solid: mp 130−134 °C; ^{1}H-NMR ($CDCl_3$) δ 0.82/0.88 (6H, 2d), 1.22−2.30 (5H, m), 1.57 (3H, d), 2.72 (1H, m), 4.19 (1H, q), 5.07 (2H, dd), 6.83 (1H, d, J = 513 Hz), 7.2−7.45 (10H, m). Anal. Calcd for $C_{22}H_{32}NO_4P$ (405.48) C, 65.17; H, 7.95; N, 3.45. Found: C, 65.10; H, 8.21; N, 3.54.

The above salt of **5*S*** (1.22 g, 3.00 mmol) was converted to **5*S*** by dissolution in EtOAc (20 mL) and washing with 1 N HCl (2 × 20 mL). The organic layer was dried with $MgSO_4$, filtered, and concentrated *in vacuo* to give **5*S*** as an oil that was used directly in the next step.

Methyl benzyl[2-(N-((*S*)-1-(methoxycarbamoyl)-1-ethyl)carbamoyl)-4(S)-methylpentyl]phosphinate (7g): yield 74.2%; mass spectrum (CI) $M^+ + H^+$ 384 (100); ^{1}H-NMR ($CDCl_3$) δ 0.80−0.95 (6H, m), 1.06−1.80 (4H, m), 1.42 (3H, d), 2.12 (1H, m), 2.58 (1H, m), 3.14 (2H, m), 3.60/3.64 (3H, 2d), 3.75 (3H, s), 4.56 (1H, m), 6.48/6.56 (1H, 2d), 7.31 (5H, m); HPLC (10/70) 17.6/18.1 (two isomers)/18.9 min (one minor isomer, 4.5% of total) (91/9 S/R).

Ethyl Benzyl[2-(*N*-benzylcarbamoyl)-4-methylpentyl]-phosphinate (7h). In a flame-dried flask under nitrogen was added **8a** (140 mg, 0.375 mmol), cesium carbonate (0.25 g, 0.75 mmol), dry DMF (4.0 mL), and ethyl iodide (0.04 mL, 0.41 mmol). After stirring at room temperature for 2 days, the reaction mixture was diluted with ethyl acetate (20 mL), washed with 1 N HCl (3 × 20 mL) and brine (20 mL), dried over $MgSO_4$, and concentrated *in vacuo* to an oil. This was chromatographed (ethyl acetate) to give 99 mg (65.6%) of **7h** as an oil: mass spectrum (CI) $M^+ + H^+$ 402 (100), $M^+ - PhCH_2NH$ 295 (23); ^{1}H-NMR ($CDCl_3$) δ 0.80−0.90 (6H, m) 1.1−1.35 (4H, m), 1.3−1.8 (3H, m), 2.10 (1H, m), 2.50/2.61 (1H, 2m), 3.09 (2H, m), 3.91 (2H, m), 4.41 (2H, m), 6.46/6.60 (1H, 2m), 7.28 (10H, m); HPLC (30/90) 13.2/13.7 min.

Benzyl Benzyl[2-(*N*-benzylcarbamoyl)-4-methylpentyl]phosphinate (7i): By the same method as above, **8a** (140 mg, 0.375 mmol), cesium carbonate (0.25 g, 0.75 mmol), dry DMF (4.0 mL), and benzyl bromide (0.050 mL, 0.41 mmol) gave after chromatography (EtOAc) 49 mg (28%) of **7i** as an oil: mass spectrum (CI) $M^+ + H^+$ 464 (100); ^{1}H-NMR ($CDCl_3$) δ 0.75−0.90 (6H, m), 1.10−1.35 (1H, m), 1.35−1.6 (1H, m), 1.70 (2H, m), 2.13 (1H, m), 2.59 (1H, m), 3.05 (2H, m), 4.40 (2H, m), 4.90 (2H, m), 6.23/6.50 (1H, 2m), 7.15/7.45 (15H, m); HPLC (30/90) 17.4/17.8 min.

Hydrolysis of Phosphinate/Amides—"Standard" Conditions: The phosphinate ester substrate, 0.1 M in 10:90 H_2O:TFA, was stirred at room temperature for 2 h. The solvent was removed *in vacuo*, CH_2Cl_2 added, the mixture re-concentrated (3×), toluene added, and the mixture re-concentrated (3×) to give a quantitative yield of the phosphinic acid.

Benzyl[2-(*N*-benzylcarbamoyl)-4-methylpentyl]phosphinic acid (8a): mass spectrum, (CI) $M^+ + H^+$ 374 (100); ^{1}H-NMR (CD_3OD) δ 0.87/0.93 (6H 2d), 1.30 (1H m), 1.4−1.75 (3H, m), 2.05 (1H, m), 2.72 (1H, m), 3.08 (2H, d), 4.37 (2H, dd), 7.26 (10H, m); ^{31}P-NMR ($CDCl_3$) δ 52.15 (m); HPLC (30/90) 9.4 min. Anal. Calcd for $C_{21}H_{28}NO_3P$ (373.43): C, 67.54; H, 7.56; N, 3.75. Found: C, 67.17; H, 7.70; N, 3.79.

Benzyl[2-(*N*-((*S*)-1-(methoxycarbamoyl)-1-ethyl)carbamoyl)-4(R,S)- methylpentyl]phosphinic acid (8f): mass spectrum (CI) $M^+ + H^+$ 370 (100), 338 (6); ^{1}H-NMR (CD_3OD) δ 0.80−1.0 (6H, m), 1.20−1.81 (4H, m), 1.39 (3H, d), 2.08 (1H, m), 2.80 (1H, m), 3.22 (2H, m) 3.68 (3H, d), 4.43 (1H, m), 7.30 (5H, m); HPLC (10/70) 17.2/17.6 min (50/50 R/S). Exact Mass Calcd for $C_{18}H_{28}NO_5P$: 370.1783. Found: 370.1811.

Benzyl[2-(*N*-((*S*)-1-(methoxycarbamoyl)-1-ethyl)carbamoyl)-4(S)-methylpentyl]phosphinic acid (8g): mass spectrum (CI) $M^+ + H^+$ 370 (100), 338 (6); ^{1}H-NMR (CD_3OD) δ 0.90/0.96 (6H, 2d), 1.28 (1H, m), 1.40 (3H, d), 1.60 (3H, m), 2.03 (1H, m), 2.79 (1H, m), 3.16 (2H, m), 3.69 (3H, s), 4.43 (1H, m), 7.30 (5H, m); HPLC (10/70) 17.1 min (91% *S*-isomer)/17.5 min (9% *R*-isomer). Exact Mass Calcd for $C_{18}H_{28}NO_5P$: 370.1783. Found: 370.1788.

Benzyl[2-carboxy-4-methylpentyl]phosphinic acid (9): mass spectrum, (TS) $M^+ - H^+$ 283 (100); ^{1}H-NMR ($CDCl_3$) δ 0.80/0.87 (6H 2d), 1.1−1.8 (4H, m), 2.05 (1H, m), 2.72 (1H, m), 3.12 (2H, d), 7.25 (5H, m); HPLC (20/80) 10.6 min.

Hydrolysis of Phosphinate/Amides—"Dilute" Conditions. All hydrolysis experiments plotted in Figures 1−3 were conducted at 0.10 M in 1:9:90 H_2O:TFA:CH_2Cl_2 at 0 °C. Aliquots (50 μL) were taken at 5, 10, 15, 30, 60, 120, 180, and 240 min time points and quenched in 1.0 mL of 50:50 H_2O:CH_3CN. Quenched samples were analyzed by HPLC (appropriate gradient of CH_3CN:H_2O based on HPLC retention of the starting ester and product acid). After the 240 min aliquot, the reactions were allowed to come to room temperature and stir overnight. The solvent was then removed *in vacuo*, CH_2Cl_2 added, the mixture re-concentrated (3×), and the product analyzed by HPLC and shown to be the expected phosphinic acid by ^{1}H-NMR and MS analysis.

Benzyl[2-(*N*,*N*-dimethylcarbamoyl)-4-methylpentyl]-phosphinic acid (8b): mass spectrum (CI) $M^+ + H^+$ 312 (100), $M^+ - N(Me)_2$ 267 (11); ^{1}H-NMR ($CDCl_3$) δ 0.86/0.91 (6H, 2d), 1.40 (3H, m), 1.81 (1H, m), 2.18 (1H, m), 2.97/3.05 (6H, 2s), 3.16 (3H, m/d), 7.17 (5H, m); HPLC (10/70) 17.2 min. Exact Mass Calcd for $C_{16}H_{26}NO_3P$: 312.1728. Found: 312.1714.

Benzyl[2-(*N*-(4-methoxyphenyl)carbamoyl)-4-methylpentyl]phosphinic acid (8c): mass spectrum (CI) $M^+ + H^+$ 390 (100), 267 (16); ^{1}H-NMR (CD_3OD) δ 0.85/0.88 (6H, 2d), 1.22 (1H, m), 1.4−1.8 (3H, m), 2.15 (1H, m), 2.70 (1H, m), 3.04 (2H, d), 3.74 (3H, s), 6.77 (2H, d), 7.15−7.35 (7H, m), 8.34 (1H, s); HPLC (30/90) 9.7 min. Exact Mass Calcd for $C_{21}H_{28}NO_4P$: 390.1834. Found: 390.1818.

Benzyl[2-(*N*-phenylcarbamoyl)-4-methylpentyl]phosphinic acid (8d): mass spectrum (CI) $M^+ + H^+$ 360 (100), 267 (15); ^{1}H-NMR (CD_3OD) δ 0.87/0.90 (6H, 2d), 1.22 (1H, m), 1.45−1.8 (3H, m), 2.15 (1H, m), 2.71 (1H, m), 3.02 (2H, d), 7.05−7.35 (8H, m), 7.40 (2H, d), 8.45 (1H, s); HPLC (30/90) 10.3 min. Exact Mass Calcd for $C_{20}H_{26}NO_3P$: 360.1729. Found 360.1695.

Benzyl[2-(*N*-(4-chlorophenyl)carbamoyl)-4-methylpentyl]phosphinic Acid (8e): mass spectrum (CI) $M + H^+$ 394 (100), 267 (30); ^{1}H-NMR (CD_3OD) δ 0.87/0.90 (6H, 2d), 1.23 (1H, m), 1.4−1.8 (3H, m), 2.15 (1H, m), 2.67 (1H, m), 3.05 (2H, d), 7.10−7.50 (9H, m), 8.45 (1H, s); HPLC (30/90) 13.9 min. Exact Mass Calcd for $C_{20}H_{25}ClNO_3P$: 394.1339. Found 394.1314.

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Supporting Information Available: ^{1}H-NMR spectra of **5**, **6a−c**, **7a−i**, **8a−g**, **9,** benzyl[2-(benzyloxycarbonyl)-4-methylpentyl]phosphinic acid and the (S)-α-methylbenzylamine salt of **5**, HPLC's of **6a−b**, **7a−i, 8a−g**, **9** and of a mix of **7f/7g**, and tables of the data points for Figures 1−3 (45 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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