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A Versatile Annulation Protocol toward Novel Constrained Phosphinic Peptidomimetics

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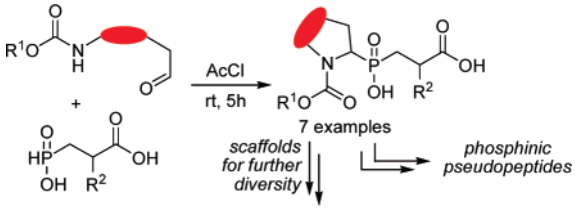


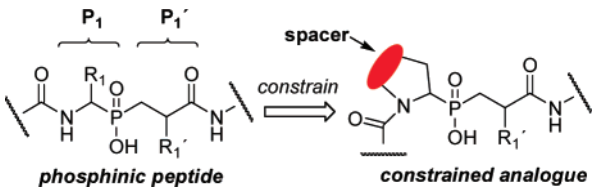
The development of a novel 3-center 2-component annulation reaction between α,ω-carbamoylaldehydes and suitably monoalkylated phosphinic acids is reported. Depending on the starting α,ω-carbamoylaldehyde, diverse phosphinic scaffolds varying in the size of their rigidity element, the nature and stereochemistry of substituents, and the participation of heteroatoms in the azacyclic ring system can be obtained in one synthetic step and in high yield. In addition, this methodology allows the synthesis of Fmoc-protected constrained aminophosphinic acids that can be easily converted to suitable pseudodipeptide building blocks compatible with the requirements of peptide synthesis on the solid phase. Finally, the careful choice of both substituents and protecting groups can provide functionally diverse, orthogonally protected constrained scaffolds for extended derivatization of the target phosphinic peptidomimetic structrures.

Introduction

Introduction of structural elements conferring rigidity in bioactive peptides or peptidomimetics can stabilize certain conformations of the molecule which in turn induce favorable fit to the complementary active site of an enzyme. This drug optimization technique can result in conformationally constrained derivatives with enhanced activity since entropy penalties upon binding can be minimized.[1] The success of the above concept is reflected by a huge number of publications where various types of constrained peptidomimetic inhibitors are synthesized and evaluated.[2] Interestingly, due to the lack of any reliable synthetic technology, no such study has ever been conducted in the field of phosphinic peptides.[3]

Phosphinic peptides (Scheme 1) are able to potently inhibit the proteolytic activity of Zn-metalloproteases and aspartyl proteases acting as transition state analogues (TSA).[4] Moreover, it has been demonstrated that the structural features of phosphinic peptides can allow selective inhibition of structurally and

SCHEME 1. Rigidification of Phosphinic Scaffolds



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(1) Velazquez-Campoy, A.; Luque, I.; Freire, E. *Thermochim. Acta* **2001**, *380*, 217.

(2) For reviews, see: (a) Olson, G. L.; Bolin, D. R.; Bonner, M. P.; Bos, M.; Cook, C. M.; Fry, D. C.; Graves, B. J.; Hatada, M.; Hill, D. E.; Kahn, M.; Madison, V. S.; Rusiecki, V. K.; Sarabu, R.; Sepinwall, J.; Vincent, G. P.; Voss, M. E. *J. Med. Chem.* **1993**, *36*, 3039. (b) Gante, J. *Angew. Chem., Int. Ed.* **1994**, *33*, 1699. (c) Hanessian, S.; McNaughton-Smith, G.; Lombart, H.-G.; Lubell, W. D. *Tetrahedron* **1997**, *53*, 12789.

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functionally related proteases.[4d] In recent years, we have exploited this property in targeting specific Zn-proteases and overcoming the disadvantages of known broad-spectrum inhibitors.[5]

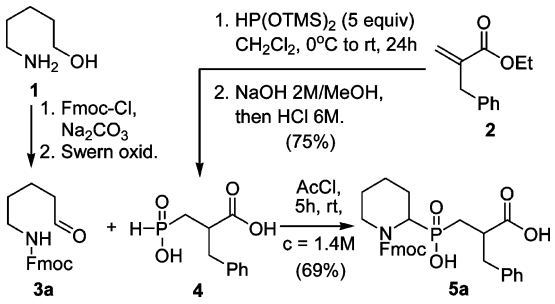
As part of our ongoing research on selective matrix metalloproteinases (MMP) inhibitors, we turned our attention in setting conformational constraints within phosphinic backbones (Scheme 1). Hanessian et al. utilized constrained hydroxamates to demonstrate that tight binding of the P_1 position enhances activity toward MMPs.[6] Given the few crystallographic data concerning P_1-S_1 interactions we decided to probe the topography of MMPs S_1 subsite by restricting the mobility of P_1 entities of phosphinic inhibitors. We anticipated that optimal unprimed interactions would favor cooperative effects in the binding pattern of phosphinic ligands.[7] In the case of phosphinic inhibitors which bear a weak zinc binding group, these effects are crucial in bringing out subtle differences between MMPs and increasing selectivity factors[7] as we recently pointed out with the development of a highly selective MMP-12 inhibitor.[8]

In this article, we report on the development of a novel ring formation reaction that gives access to the first series of constrained phosphinic peptidomimetics that vary in the size of their rigidity element, the nature and stereochemistry of substituents, and the participation of heteroatoms in the ring. The products can be directly transformed to Fmoc-protected building blocks compatible with the requirements of solid-phase peptide synthesis.[9] Moreover, aiming at maximum molecular diversity in the subsequent construction of phosphinic combinatorial libraries from a single precursor, a functionally diverse and orthogonally protected proline-type scaffold was designed and synthesized.

Results and Discussion

A convergent retrosynthetic plan that could afford a large number of diverse rings requires the annulation to be performed at a late stage of the synthesis. From the different disconnections considered, ring closing metathesis (RCM) seemed adequately general since it has been previously applied to the synthesis of different types of constrained peptidomimetics.[10] Nevertheless, in our case, the desired molecular diversity would necessitate the parallel synthesis of numerous RCM precursors which would render the method inexpedient. Another attractive solution would be the intramolecular amidoalkylation of monoalkylated phosphinic acids by α,ω-carbamoylaldehydes, a reaction which, quite interestingly, is completely unexplored.[11]

SCHEME 2. Synthesis of Pipecolic Acid Phosphinic Analogue 5a



To this respect, 5-aminopentanol (**1**) was converted to aldehyde **3a**, which was slowly added to a solution of phosphinic acid **4**[11b] in AcCl. After stirring for 5 h at room temperature, evaporation of the volatiles, and aqueous workup, a major product was isolated in 69% yield, which was found to be the Fmoc-protected aminophosphinic analogue of pipecolic acid **5a** (Scheme 2).

Prompted by the success of this model reaction we decided to explore the scope and limitations of the transformation. Therefore, the reactivity of a number of Fmoc-protected α,ω-carbamoylaldehydes was screened under condensation conditions.[12] The versatility of the method is evident from the numerous constrained pseudodipeptides that can be obtained in a single step, depending on the α,ω-carbamoylaldehyde (**3**) used (Table 1). In particular, unsubstituted 5-, 6-, or 7-membered azacycles (**5a**−**c**) are efficiently produced (entries a−c), while smaller rings, such as azetidines **5g**, are not favored (entry g). Moreover, introduction of more heteroatoms that results in higher heterocycles such as 1,3-oxazinane **5e** or piperazine **5f** is feasible. Finally, substituents of specific configuration can be easily linked to the ring, since the necessary chiral -substituted α,ω-carbamoylaldehydes can be derived from natural α-aminoacids (entry d). For example, the necessary aldehyde **3d** for the preparation of phosphinic block **5d** can be obtained from L-phenylalanine. In particular, phthalyl-protected alcohol **6**, derived from H-(L)Phe-OH according to the literature,[13a,b] was oxidized in Swern conditions (Scheme 3).[13c] After the Horner−Wadsworth−Emmons reaction of **7** with triethyl phosphonoacetate,[13c] nickel boride reduction,[5c] and acidic deprotection, the resulting γ-aminoacid **9** was reduced with borane/DMS complex, protected with the Fmoc group, and oxidized toward the final aldehyde by Swern oxidation.

Notably, the success of this reaction was rather unexpected since *N*-alkylated carbamates should be considerably less

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(12) See the Supporting Information for the synthesis of the precursor Fmoc-protected aminoalcohols.

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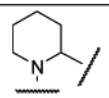
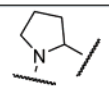
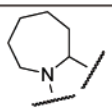
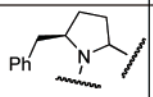
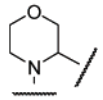
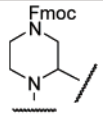
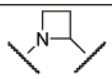
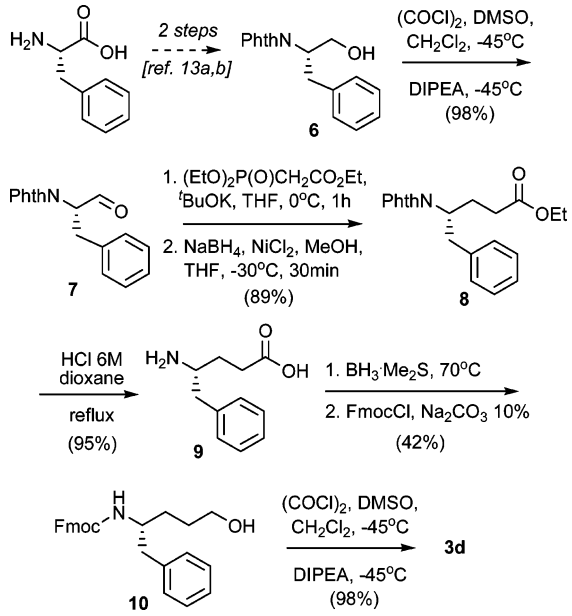
TABLE 1. Yields for the Synthesis of Compounds 5a−g

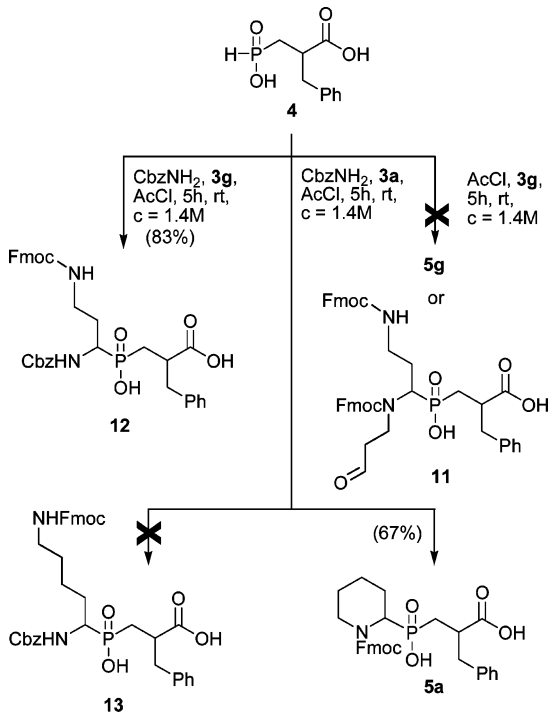
entry	Spacer (in red)	Azacycle	Yield (%)
a	-$(CH_2)_3$-		69
b	-$(CH_2)_2$-		82
c	-$(CH_2)_4$-		81
d	-$C_{(s)}$H(Bn)CH_2-		80
e	-$(CH_2)_2$O-		61
f	-$(CH_2)_2$N(Fmoc)-		52
g	-CH_2-		0

reactive than unsubstituted ones, such as $FmocNH_2$ or $CbzNH_2$. For example, aldehyde **3g** fails to form azetidine **5g** but, in addition, cross-reaction product from intermolecular condensation (i.e., **11**) does not form either (Scheme 4). This implies that an *N*-alkylated carbamate, such as **3g**, not only fails to cyclize but it is also unable to participate in a 3-component condensation, a known reaction for unsubstituted carbamates ($FmocNH_2$, $CbzNH_2$). The lack of reactivity of *N*-alkylated carbamates toward intermolecular 3-component condensation was further established by the observation that a mixture of $CbzNH_2$, aldehyde **3g**, and phosphinic acid **4** leads exclusively to **12** (Scheme 4), as was determined by MS analysis of the crude product. The above observations dictate that the driving force of the annulation reaction is the cyclization process of α,ω-carbamoylaldehydes that can only lead to 5-, 6-, and 7-membered azacycles. In another competition experiment, when a mixture of $CbzNH_2$, aldehyde **3a**, and phosphinic acid **4** was subjected to condensation conditions only the annulation product **5a** was produced with no traces of the intermolecular reaction product **13**. This means that when the size of the formed ring

SCHEME 3. Synthesis of α,ω-Carbamoylaldehyde 3d



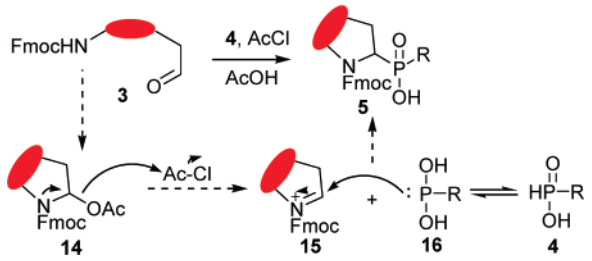
SCHEME 4. Competition Experiments of 4 with Aldehydes 3a and 3g and $CbzNH_2$



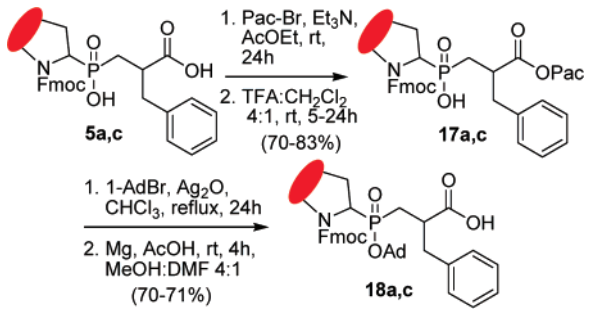
allows stabilization of the intermediate species the reactivity of *N*-alkylated carbamates can exceed that of unsubstituted ones. This cyclization-induced reactivity enhancement of *N*-alkylated carbamates also explains why there are no detectable traces of 3-component intermolecular condensation byproducts in all the examples of Table 1, even under high concentration conditions (>1.4 M).

From a mechanistic point of view, Soroka has shown that mixtures of amides, acyl chlorides, and aldehydes form mixed acylated *O*,*N*-hemiaminals which degrade to ylidene carboxamides and react with tervalent phosphorus species.[14] In addition, it is well-known that *N*-carbamoyl-protected 1,4-aminoaldehydes tend to cyclize in slightly acidic conditions to *N*-carbamoyl-

SCHEME 5. Putative Reaction Mechanism



SCHEME 6. Synthesis of Fmoc-Protected Building Blocks 18a,c



protected 1-hydroxy pyrrolidines.[15] A combination of the above observations leads to the hypothesis that the reactive partners in the reported intramolecular amidoalkylation are heterocycles of type **15** and tervalent phosphonites **16**, as illustrated in Scheme 5.

For the condensation products **5** to be incorporated into peptide backbones by means of Fmoc-synthetic solid-phase protocol, they should be suitably protected on the hydroxyphosphinyl moiety. According to previous reports of our laboratory, 1-adamantyl (Ad) protection is an excellent choice for this case.[9,16] The conversion of products **5** to the final phosphinic building blocks **18** can be performed in 4 steps, according to our previously described protocol.[17] This includes protection of the acidic units by the phenacyl (Pac) group, chemoselective cleavage of the phosphinic Pac-ester, reprotection of the hydroxyphosphinyl group with the 1-Ad group, and reductive cleavage of the carboxylic Pac-ester. These transformations proceeded smoothly, as is shown in Scheme 6 for the cases of **5a** and **5c**.

The versatility of the reported methodology allows the introduction of additional functional groups on the phosphinic scaffold as well as the orthogonal protection of the resulting blocks, thus expanding diversification possibilities and widening the scope of our strategy. Such an approach can serve as a valuable tool for medicinally oriented chemistry where the generation of as many compounds as possible from a single precursor is an issue of primary importance. For example, a multifunctional building block that could potentially serve as a "molecular generator" for our MMPs project is shown in Figure 1. In particular, the presence of a dipolarophilic terminal alkyne in the P_1' position of **19** can offer an effective entry to isoxazole

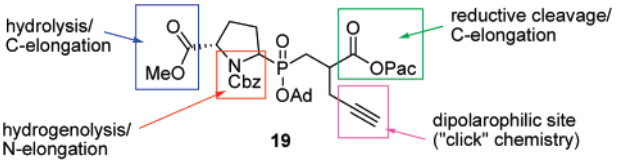
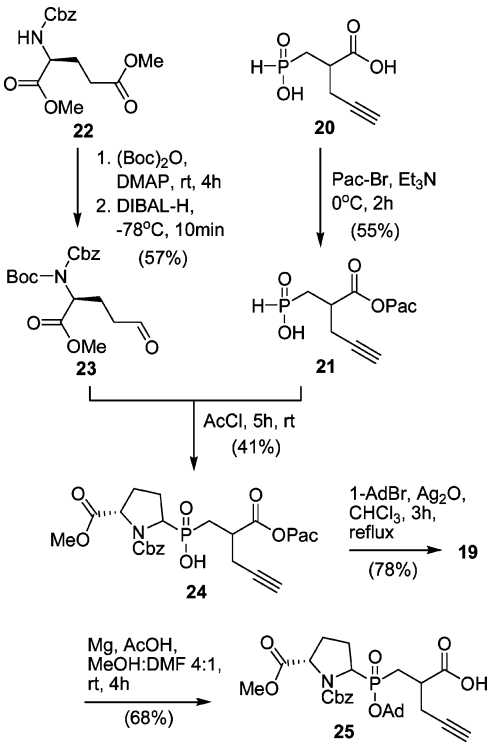


FIGURE 1. Proline-type scaffold **19** suitable for diversification.

SCHEME 7. Synthesis of Multifunctional Blocks 19 and 25



side chains, as we have described before,[18] or lead to triazole analogues by means of "click" chemistry.[19] Furthermore, the azacycle of **19** (Figure 1) bears an additional carboxyl group that can facilitate the reliable probing of the S_1 subsite of MMPs, unaffected by any side chain flexibility. Elongation of N and C peptide extremities is also possible in solution and on the solid phase.[9] Finally, the synthetic requirements of molecule **19**, and peptide derivatives thereof, tolerate the presence of the convenient adamantyl protecting group, which can be easily removed with TFA at the end of the synthesis.[16]

The synthesis of target molecule **19** is outlined in Scheme 7. The right-hand side (**21**) of compound **19** is directly obtained by chemoselective Pac protecion of carboxylate **20**[11b] in the presence of unprotected phosphinic acid, in 63% yield (Scheme 7). For the construction of the left-hand side, the L-glutamic acid derivative **22** is protected with a Boc group[20] and the lateral carboxylate is selectively reduced by DIBAL-H.[21] The removal of the Boc group and the condensation was performed in a one-pot procedure by slowly adding a solution of **23** in TFA/AcOH/AcCl 1/1/5 into a solution of **21** in AcCl (Scheme 7). Mild

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(19) For a review, see: Kolb, H. C.; Sharpless, K. B. *Drug Discovery Today* **2003**, *8*, 1128.
(20) Xiong, H.; Huang, J.; Ghosh, S. K.; Hsung, R. P. *J. Am. Chem. Soc.* **2003**, *125*, 12694.
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adamantylation of the resulting pseudodipeptide **24** toward target **19** proceeded in 44% yield (78% based on the recovered material) with 1-AdBr/Ag_2O. Finally, the Pac group can be successfully removed by reductive cleavage, without affecting the remaining structural entities. The utilization of multifunctional compounds such as **19** in diversity oriented synthesis (DOS) toward the development of potent and selective MMP inhibitors is currently under way and will be reported in due course.

Conclusions

In conclusion, we have presented a versatile approach for the preparation of conformationally constrained phosphinic peptidomimetics that can be suitably functionalized to meet the requirements of combinatorial chemistry protocols. The proposed strategy is based on a novel annulating condensation reaction between α,ω-carbamoylaldehydes and suitably monoalkylated phosphinic acids. In addition, from a number of competition experiments we concluded that *N*-alkylated carbamates are completely unreactive under amidoalkylation conditions but, interestingly, this behavior is reversed when stabilization by cyclization is feasible. Furthermore, the versatility of the procedure was illustrated by the synthesis of a suitably functionalized phosphinic scaffold for extended derivatization. Given the well-studied application of lead optimization via constrained analogues in drug discovery, we believe that the described methodology will offer new perspectives to the development of potent and selective protease inhibitors of phosphinic type.

Experimental Section

General Method for the Synthesis of Compounds of Type 5. In a solution of DMSO (2.20 mmol) in anhydrous CH_2Cl_2 (1.0 mL), oxalyl chloride (2 M in CH_2Cl_2, 0.61 mL) is slowly added at −45 °C. The reaction is stirred for 5 min at −45 °C and then a solution of the appropriate Fmoc-protected amino alcohol (1.00 mmol) in anhydrous CH_2Cl_2 (6.0 mL) is added dropwise. After stirring for an additional 15 min at −45 °C, DIPEA (3.00 mmol, 0.5 mL) is introduced to the reaction mixture. At this time, the reaction mixture is allowed to warm to −30 °C and stirring is continued for 30 min. Then, the solvent is removed, and the residue is taken up in AcOEt (30 mL), washed with H_2O (10 mL), 5% $NaHCO_3$ (2 × 10 mL), H_2O (3 × 10 mL), and brine, and dried over Na_2SO_4. Evaporation of the solvent affords the crude aldehydes of type **3** in high yield (90−100% by NMR). These products are unstable to silica gel column purification, so further purification is not attempted. The crude aldehyde of type **3** is dissolved in AcCl (0.4 mL) and added to a solution of phosphinic acid **4** (1.00 mmol) in AcCl (0.3 mL) at 0 °C. The reaction mixture is allowed to stir at rt for 5 h, the volatiles are removed by evaporation, and the crude product is purified by column chromatography.

2-Benzyl-3-[{1-[(9*H*-fluoren-9-ylmethoxy)carbonyl]-2-piperidinyl}(hydroxy)phosphoryl]propanoic Acid (5a). Following the general procedure from **4** (320 mg, 1.40 mmol), after column purification with chloroform/methanol/acetic acid (70:4:4) and trituration with petroleum ether 40−60 °C compound **5a** (516 mg, 69%) was obtained as a white foam. TLC R_f 0.38 (chloroform/methanol/acetic acid = 70:5:5); HPLC t_R(1) 41.11, 41.42;[22] ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.44−2.19 (m, 8H), 2.42−3.85 (m, 4H), 3.99−4.67 (m, 5H), 7.10−7.82 (m, 13H); ^{31}P NMR (81 MHz, $CDCl_3$) δ 55.98, 56.63, 57.23; ESMS *m*/*z* calcd for $C_{30}H_{33}NO_6PNa$ $(M + Na)^+$ 556.2, found 556.4.

2-Benzyl-3-[{1-[(9*H*-fluoren-9-ylmethoxy)carbonyl]-2-pyrrolidinyl}(hydroxy)phosphoryl]propanoic Acid (5b). Following the general procedure from **4** (410 mg, 1.80 mmol), after column purification with chloroform/methanol/acetic acid (70:3.5:3.5) and trituration with petroleum ether 40−60 °C compound **5b** (765 mg, 82%) was obtained as a white foam. TLC R_f 0.39 (chloroform/methanol/acetic acid = 70:5:5); HPLC t_R(1) 39.28, 39.94; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.53−2.52 (m, 6H), 2.54−3.30 (m, 3H), 3.32−3.85 (m, 2H), 4.09−4.42 (m, 4H), 7.14−7.81 (m, 13H); ^{31}P NMR (81 MHz, $CDCl_3$) δ 54.32, 54.53, 54.93; ESMS *m*/*z* calcd for $C_{29}H_{31}NO_6P$ $(M + H)^+$ 520.2, found 520.4.

2-Benzyl-3-[{1-[(9*H*-fluoren-9-ylmethoxy)carbonyl]-2-azepanyl}(hydroxy)phosphoryl]propanoic Acid (5c). Following the general procedure from **4** (230 mg, 1.01 mmol), after column purification with chloroform/methanol/acetic acid (70:4:4) and trituration with petroleum ether 40−60 °C compound **5c** (447 mg, 81%) was obtained as a white foam. TLC R_f 0.40 (chloroform/methanol/acetic acid = 70:5:5); HPLC t_R(1) 42.70, 43.18; ^{1}H NMR (200 MHz, d_6-DMSO) δ 0.61−2.18 (m, 11H), 2.33−3.08 (m, 4H), 3.23−3.80 (m, 1H), 3.83−4.72 (m, 3H), 7.03−7.95 (m, 13H); ^{31}P NMR (81 MHz, d_6-DMSO) δ 44.87, 45.05, 45.67, 45.82; ESMS *m*/*z* calcd for $C_{31}H_{33}NO_6P$ $(M - H)^-$ 546.2, found 546.5.

2-Benzyl-3-[(5*S*)-5-benzyl-1-[(9*H*-fluoren-9-ylmethoxy)carbonyl]tetrahydro-1*H*-pyrrol-3-yl(hydroxy)phosphoryl]propanoic Acid (5d). Following the general procedure from **4** (57 mg, 0.25 mmol), after column purification with chloroform/methanol/acetic acid (70:4:4) and trituration with petroleum ether 40−60 °C compound **5d** (122 mg, 80%) was obtained as a white foam. TLC R_f 0.38 (chloroform/methanol/acetic acid = 70:5:5); HPLC t_R(1) 49.18, 49.75; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.35−2.38 (m, 7H), 2.40−3.21 (m, 5H), 3.61−4.23 (m, 3H), 4.43−4.85 (m, 2H), 6.57−7.74 (m, 18H); ^{31}P NMR (81 MHz, $CDCl_3$) δ 54.31, 54.55; ESMS *m*/*z* calcd for $C_{36}H_{37}NO_6P$ $(M + H)^+$ 610.2, found 610.2.

2-Benzyl-3-[{4-[(9*H*-fluoren-9-ylmethoxy)carbonyl]-1,4-oxazinan-3-yl}(hydroxy)phosphoryl]propanoic Acid (5e). Following the general procedure from **4** (180 mg, 0.79 mmol), after column purification with chloroform/methanol/acetic acid (70:6:6) and trituration with petroleum ether 40−60 °C compound **5e** (258 mg, 61%) was obtained as a white foam. TLC R_f 0.49 (chloroform/methanol/acetic acid = 70:20:10); HPLC t_R(1) 36.34, 36.89; ^{1}H NMR (200 MHz, d_6-DMSO) δ 1.38−1.75 (m, 1H), 1.78−2.12 (m, 1H), 2.63−3.08 (m, 3H), 3.10−3.85 (m, 6H), 3.90−4.57 (m, 4H), 7.12−7.91 (m, 13H); ^{31}P NMR (81 MHz, d_6-DMSO) δ 43.13, 43.75; ESMS *m*/*z* calcd for $C_{29}H_{31}NO_7P$ $(M + H)^+$ 536.2, found 536.2.

2-Benzyl-3-[{1,4-bis[(9*H*-fluoren-9-ylmethoxy)carbonyl]-2-piperazinyl}(hydroxy)phosphoryl]propanoic Acid (5f). Following the general procedure from **4** (165 mg, 0.72 mmol), after column purification with chloroform/methanol/acetic acid (70:6:6) and trituration with petroleum ether 40−60 °C compound **5f** (285 mg, 52%) was obtained as a white foam. TLC R_f 0.52 (chloroform/methanol/acetic acid = 70:5:5); HPLC t_R(3) 39.21; ^{1}H NMR (200 MHz, d_6-DMSO) δ 1.21−1.79 (m, 1H), 1.81−2.16 (m, 1H), 2.57−3.08 (m, 5H), 3.22−4.11 (m, 4H), 4.12−4.55 (m, 7H), 7.12−7.89 (m, 21H); ^{31}P NMR (81 MHz, d_6-DMSO) δ 43.62, 44.32, 44.40; ESMS *m*/*z* calcd for $C_{44}H_{42}N_2O_8P$ $(M + H)^+$ 757.3, found 757.1.

(2*S*)-2-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-3-phenylpropanal (7). To a solution of DMSO (855 mg, 10.9 mmol) in anhydrous CH_2Cl_2 (7 mL) is slowly added oxalyl chloride (2 M in CH_2Cl_2, 1.02 mL) at −45 °C. The reaction is stirred for 5 min at −45 °C and then a solution of the phthalyl-protected amino alcohol **6** (1.4 g, 4.97 mmol) in anhydrous CH_2Cl_2 (5.6 mL) is added dropwise. After stirring for an additional 15 min, DIPEA (1.93 g, 14.9 mmol) is introduced to the reaction mixture. At this point, the reaction mixture is allowed to warm to −30 °C and stirred for an additional 30 min. Then, the solvent is removed, and the residue is taken up in AcOEt (100 mL), washed with H_2O (40 mL), 10% Na_2CO_3 (2 × 40 mL), H_2O (3 × 40 mL), and brine, and dried over Na_2SO_4. Evaporation of the solvent affords the pure aldehyde

(22) See the Supporting Information for HPLC experimental conditions.

7 (1.36 g, 98%) as a white solid; TLC R_f 0.55 (chloroform/methanol = 95:5); ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.31 (dd, J = 10.4, 14.3 Hz, 1H), 3.55 (dd, J = 5.4, 14.3 Hz, 1H), 4.96 (dd, J = 5.4, 10.4 Hz, 1H), 7.06−7.17 (m, 5H), 7.65−7.79 (m, 4H), 9.72 (s, 1H); ESMS *m*/*z* calcd for $C_{17}H_{14}NO_3$ $(M + H)^+$ 280.1, found 280.1.

Ethyl (4*R*)-4-(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-5-phenylpentanoate (8). To a solution of triethyl phosphonoacetate (835 mg, 3.72 mmol) in anhydrous THF (3 mL) is added a solution of ^{t}BuOK (418 mg, 3.72 mmol) in anhydrous THF (20 mL) at 0 °C in one portion. The mixture is stirred at room temperature for 1 h. Then, a solution of the phthalyl-protected amino aldehyde **7** (1.30 g, 4.65 mmol) in anhydrous THF (7 mL) is introduced slowly to the reaction mixture at 0 °C. The mixture is stirred at room temperature for an additional 2 h. The reaction is quenched by the addition of 5% Na_2CO_3 (30 mL). The mixture is extracted with Et_2O (3 × 40 mL) and the combined organic phase is dried over Na_2SO_4 and concentrated in vacuo. The crude product is purified by column chromatography (eluent: petroleum ether 40−60 °C: Et_2O = 2:1) to afford 1.40 g of a mixture of E and Z isomers. The product is dissolved in THF (16 mL) and MeOH (10 mL) and $NiCl_2 \cdot 6H_2O$ (2.85 g, 12 mmol) is added. The resulting mixture is cooled at −30 °C and $NaBH_4$ (757 mg, 20.00 mmol) is added portionwise for 30 min. Then, the mixture is stirred at −30 °C for 10 min. After the end of the reaction, the mixture is evaporated and the residue is partitioned with AcOEt (30 mL) and 1 M HCl (20 mL). The organic phase is separated, washed with H_2O (10 mL), and dried over Na_2SO_4. The crude product is purified by column chromatography (eluent: petroleum ether 40−60 °C/Et_2O = 4:1) to afford compound **8** (1.25 g, 89%) as a colorless oil. TLC R_f 0.33 (petroleum ether 40−60°/Et_2O = 2:1); $[\alpha]^{20}_D$ −117.7 (*c* 1.0, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.17 (t, J = 7.3 Hz, 3H), 2.06−2.21 (m, 1H), 2.28 (t, J = 7.2 Hz, 2H), 2.42−2.60 (m, 1H), 3.12 (dd, J = 6.6, 13.9 Hz, 1H), 3.34 (dd, J = 10.3, 13.9 Hz, 1H), 4.02 (q, J = 7.3 Hz, 2H), 4.45−4.60 (m, 1H), 7.06−7.27 (m, 5H), 7.60−7.74 (m, 4H); ESMS *m*/*z* calcd for $C_{21}H_{22}NO_4$ $(M + H)^+$ 352.2, found 352.3; HRMS (ES) *m*/*z* calcd for $C_{21}H_{22}NO_4$ $(M + H)^+$ 352.1549, found 352.1528.

(4*R*)-4-Amino-5-phenylpentanoic acid (9). A solution of compound **8** (400 mg, 1.14 mmol) in dioxane (2 mL) and 6 M HCl (15 mL) is refluxed for 15 h. After cooling to room temperature, the mixture is washed with AcOEt (3 × 30 mL). The aqueous phase is concentrated in vacuo to afford the product **9** (210 mg, 95%) as a white solid. TLC R_f 0.26 (chloroform/methanol/acetic acid = 70:20:10); $[\alpha]^{20}_D$ −29.1 (*c* 1.0, 3 M HCl) {lit.[23] $[\alpha]^{20}_D$ −28.2 (*c* 1.0, 3.4 M HCl)}; ^{1}H NMR (200 MHz, CD_3OD) δ 1.75−1.90 (m, 2H), 2.39 (br t, J = 7.3 Hz, 2H), 2.86 (br d, J = 6.6 Hz, 2H), 3.42−3.63 (m, 1H), 7.18−7.34 (m, 5H); ESMS *m*/*z* calcd for $C_{11}H_{16}NO_2$ $(M + H)^+$ 194.2, found 194.2.

9*H*-Fluoren-9-ylmethyl *N*-[(1*R*)-1-benzyl-4-hydroxybutyl]carbamate (10). To a mixture of compound **9** (170 mg, 0.8 mmol) in anhydrous THF (8 mL) is added borane dimethyl sulfide complex (2 M in THF, 2.20 mL) at 70 °C. The mixture is refluxed for 12 h. At this point, an additional quantity of borane dimethyl sulfide complex (2 M in THF, 2.20 mL) is added and the reaction is continued for 3 h. After cooling to room temperature the excess of borane is quenched by the slow addition of 2.8 mL of a 1:1 THF:H_2O solution followed by 4 M NaOH (9.8 mL). The resulting two-phase mixture is heated at reflux for 1 h, cooled at room temperature, and filtered through a coarse fritted funnel. The filtrate is extracted with CH_2Cl_2 (3 × 20 mL), dried over Na_2SO_4, and concentrated in vacuo to afford the crude aminoalcohol, which was diluted in dioxane (0.5 mL) and 10% Na_2CO_3 (3 mL). The mixture is cooled to 0 °C and a solution of Fmoc-Cl (1.32 mmol, 341 mg) in dioxane (1.5 mL) is slowly added. The mixture is stirred vigorously at room temperature overnight. Then, AcOEt (30 mL) and 1 M HCl (15 mL) are added, and the organic layer is separated, washed with brine, and dried over Na_2SO_4. Evaporation of the solvent and purification by column chromatography with chloroform/methanol = 98:2 afforded pure Fmoc-protected amino alcohol **10** (150 mg, 42%) as a white solid; TLC R_f 0.25 (chloroform/methanol = 95:5); HPLC t_R(3) 25.13; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.24−1.74 (m, 4H), 2.77 (br d, J = 6.4 Hz, 2H), 3.41−3.72 (m, 2H), 3.76−4.09 (m, 1H), 4.16−4.73 (m, 3H), 4.81−4.96 (m, 1H), 7.12−7.82 (m, 13H); ESMS *m*/*z* calcd for $C_{26}H_{27}NO_3Na$ $(M + Na)^+$ 424.2, found 424.2.

General Method for the Synthesis of Compounds of Type 17. Phosphinic acid of type **5** (1.00 mmol) is dissolved in AcOEt (1 mL), then cooled at 0 °C, and PacBr (4.00 mmol) is added, followed by Et_3N (4.00 mmol). After being stirred at room temperature for 24 h the reaction mixture is diluted with AcOEt (30 mL), washed with 1 M HCl (10 mL) and brine, and dried over Na_2SO_4. Evaporation of the solvent and purification by column chromatography, using chloroform/methanol = 98:2 as eluent, affords the pure Pac-diester as white foams, after trituration with petroleum ether 40−60 °C. The above diester (1.00 mmol) is dissolved in CH_2Cl_2 (1.6 mL), and TFA (6.4 mL) is added. The reaction mixture is allowed to stir at room temperature and the progress of the reaction is followed by TLC (reaction time: 5−24 h). Compounds of type **17** were obtained after evaporation of the solvent and purification of the residue by column.

2-Benzyl-3-oxo-3-(2-oxo-2-phenylethoxy)propyl{1-[(9*H*-fluoren-9-ylmethoxy)carbonyl]-2-piperidinyl}phosphinic Acid (17a). Following the general procedure from **5a** (300 mg, 0.56 mmol), after column purification with chloroform/methanol/acetic acid (70:2:2) and trituration with petroleum ether 40−60 °C compound **17a** (256 mg, 70%) was obtained as a white foam. TLC R_f 0.53 (chloroform/methanol/acetic acid = 70:5:5); HPLC t_R(2) 43.21; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.43−2.52 (m, 8H), 2.89−3.06 (m, 1H), 3.07−3.35 (m, 3H), 3.98−4.79 (m, 5H), 5.04−5.44 (m, 2H), 7.09−7.81 (m, 18H); ^{31}P NMR (81 MHz, $CDCl_3$) δ 56.85, 57.53, 58.11; ESMS *m*/*z* calcd for $C_{38}H_{38}NO_7PNa$ $(M + Na)^+$ 674.2, found 674.3.

2-Benzyl-3-oxo-3-(2-oxo-2-phenylethoxy)propyl{1-[(9*H*-fluoren-9-ylmethoxy)carbonyl]-2-azepanyl}phosphinic Acid (17c). Following the general procedure from **5c** (260 mg, 0.47 mmol), after column purification with chloroform/methanol/acetic acid (70:2:2) and trituration with petroleum ether 40−60 °C compound **17c** (262 mg, 83%) was obtained as a white foam. TLC R_f 0.59 ($CHCl_3$:MeOH:AcOH = 70:5:5); HPLC t_R(3) 38.57, 39.23; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.15−2.37 (m, 10H), 2.92−3.36 (m, 4H), 3.53−3.82 (m, 2H), 4.05−4.66 (m, 3H), 5.13−5.32 (m, 2H), 7.03−7.95 (m, 18H); ^{31}P NMR (81 MHz, $CDCl_3$) δ 55.67, 55.89, 55.58, 56.40; ESMS *m*/*z* calcd for $C_{39}H_{41}NO_7P$ $(M + H)^+$ 666.3, found 666.2.

General Method for the Synthesis of Compounds of Type 18. To a refluxing solution of a phosphinic ester of type **17** (1.00 mmol) and 1-adamantyl bromide (1.20 mmol) in $CHCl_3$ (20 mL) is added silver(I) oxide (1.20 mmol) portionwise over 1 h. After the solution is refluxed overnight, the solvent is removed in vacuo and the residue is taken up in Et_2O (30 mL) and filtered through a pad of Celite. The filtrate is evaporated and the residue is purified by column chromatography with petroleum ether 40−60 °C:AcOEt = 1:2 to afford the protected product as white foams. To a solution of the resulting phosphinic diester (1.00 mmol) in MeOH:DMF (4:1) (17 mL) are added AcOH(35.00 mmol) and magnesium turnings (17.00 mmol). After being stirred for 4 h at room temperature the reaction mixture is filtered. The filtrate is concentrated in vacuo and the residue is diluted with CH_2Cl_2 (40 mL), washed with 1 M HCl (15 mL) and brine, and dried over Na_2SO_4. Compounds of type **18** were obtained after evaporation of the solvent and purification of the residue by column. **3-((1-Adamantyloxy){1-[(9*H*-fluoren-9-ylmethoxy)carbonyl]-2-piperidinyl}-phosphoryl)-2-benzylpropanoic acid (18a).** Following the general procedure from **17a** (180 mg, 0.28 mmol), after column purification with chloroform/methanol = 98:2 and trituration with petroleum ether 40−60 °C compound **18a** (129 mg, 70%) was obtained as a

(23) Buchschacher, P.; Cassal, J. M.; Fürst, A.; Meier, W. *Helv. Chim. Acta* **1977**, *60*, 2747.

white foam. TLC R_f = 0.24 (chloroform/methanol = 95:5); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.39−2.26 (m, 23H), 2.53−3.53 (m, 3H), 3.87−4.77 (m, 5H), 7.11−7.78 (m, 13H); ^{31}P NMR (81 MHz, $CDCl_3$) δ 49.2, 50.32, 51.5, 52.00; ESMS *m/z* calcd for $C_{40}H_{47}NO_6P$ $(M+H)^+$ 668.3, found 668.3; HRMS (ES) *m/z* calcd for $C_{40}H_{47}NO_6P$ $(M+H)^+$ 668.3141, found 668.3148.

3-((1-Adamantyloxy){1-[(9*H*-fluoren-9-ylmethoxy)carbonyl]-2-azepanyl}phosphoryl)-2-benzylpropanoic Acid (18c). Following the general procedure from **17c** (145 mg, 0.22 mmol), after column purification with chloroform/methanol = 98:2 and trituration with petroleum ether 40−60 °C compound **18c** (105 mg, 71%) was obtained as a white foam. TLC R_f 0.27 (chloroform/methanol = 95:5); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.31−2.45 (m, 25H), 2.46−3.37 (m, 5H), 3.39−3.86 (m, 1H), 4.00−4.72 (m, 3H), 7.13−8.01 (m, 13H); ^{31}P NMR (81 MHz, $CDCl_3$) δ 49.18, 49.37, 49.79, 51.11, 51.26, 51.94, 52.06, 52.41; ESMS *m/z* calcd for $C_{41}H_{49}NO_6P$ $(M + H)^+$ 682.3, found 682.4. HRMS (ES) *m/z* calcd for $C_{41}H_{49}NO_6P$ $(M + H)^+$ 682.3298, found 682.3290.

2-[(2-Oxo-2-phenylethoxy)carbonyl]-4-pentynylphosphinic Acid (21). Compound **20** (1.00 g, 5.68 mmol)[11b] is dissolved in AcOEt (60 mL), then cooled at 0 °C and Et_3N (1.15 g, 11.00 mmol) is added, followed by PacBr(1.02 g, 5.1 mmol). After the solution was stirred at room temperature for 6 h the solvent is removed in vacuo. The residue is taken up in 5% $NaHCO_3$ (60 mL) and extracted with Et_2O (2 × 20 mL). The aqueous phase is acidified with 3 M HCl to pH ∼1. This aqueous solution is extracted with AcOEt (3 × 50 mL), and the combined organic layers are dried over Na_2SO_4. Evaporation of the solvent affords compound **14** (1.05 g, 55%) as a colorless oil. TLC R_f 0.19 (chloroform/methanol/acetic acid = 70:20:10); HPLC t_R(1) 19.90; ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.11 (t, J = 1.6 Hz, 1H), 2.22−2.89 (m, 5H), 3.06−3.41 (m, 1H), 5.21−5.45 (m, 2H), 7.31 (d, J = 573.4 Hz, 1H), 7.25−7.88 (m, 5H); ^{31}P NMR (81 MHz, $CDCl_3$) δ 35.73; ESMS *m/z* calcd for $C_{14}H_{14}O_5P$ $(M - H)^-$ 293.1, found 293.3.

Methyl (2*S*)-2-{[(Benzyloxy)carbonyl](*tert*-butoxycarbonyl)amino}-5-oxopentanoate (23). To a stirring solution of dimethyl (2*S*)-2-{[(benzyloxy)carbonyl](*tert*-butoxycarbonyl)amino}-pentanedioate (**22**)[20] (2.00 g, 4.88 mmol) in dry ether (48.8 mL) is added DIBAL-H (1 M in CH_2Cl_2, 5.37 mL) at −78 °C. The reaction is stirred for 10 min before being quenched with H_2O (0.62 mL). The mixture is stirred for an additional 30 min, dried over Na_2SO_4, and filtered through a pad of Celite. The solvent is removed and the crude residue is purified by column chromatography (eluent: petroleum ether 40−60 °C/Et_2O = 3:1) to afford compound **22** (1.22 g, 66%) as a colorless oil. TLC R_f 0.46 (petroleum ether 40−60 °C/Et_2O = 1:2); $[\alpha]^{20}_D$ −32.4 (*c* 1.0, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.40 (s, 9H), 2.04−2.25 (m, 1H), 2.40−2.64 (m, 3H), 3.59 (s, 3H), 4.95 (dd, J = 4.6, 9.2 Hz, 1H), 5.18 (s, 2H), 7.25−7.51 (m, 5H), 9.71 (s, 1H); ESMS *m/z* calcd for $C_{19}H_{26}NO_7$ $(M + H)^+$ 380.2, found 380.1; HRMS (ES) *m/z* calcd for $C_{19}H_{26}NO_7$ $(M + H)^+$ 380.1709, found 380.1690.

(5*S*)-1-[(Benzyloxy)carbonyl]-5-(methoxycarbonyl)tetrahydro-1*H*-pyrrol-2-yl{2-[(2-oxo-2-phenylethoxy)carbonyl]-4-pentynyl}-phosphinic Acid (24). To a solution of compound **23** (84 mg, 2.21 mmol) in AcOH (3.3 mL) is added TFA (3.3 mL). The mixture is stirred at room temperature for 30 min. At the end of that period, AcCl (16 mL) is added and the solution is cooled at 0 °C. Then, a solution of compound **21** (651 mg, 2.21 mmol) in AcCl (19 mL) is slowly introduced to the reaction mixture. After the solution was stirred at room temperature for 5 h, the solvents are evaporated and the residue is diluted with AcOEt (50 mL) and washed with 1 M HCl (2 × 20 mL). The organic phase is dried over Na_2SO_4 and concentrated in vacuo. The crude product is purified by column chromatography with chloroform/methanol/acetic acid = 70:4:4 to afford compound **24** (500 mg, 41%) as a colorless oil; TLC R_f 0.37 (chloroform/methanol/acetic acid = 70:5:5); HPLC t_R(1) 35.90; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.94−2.80 (m, 9H), 3.01−3.83 (m, 4H), 4.02−4.55 (m, 2H), 4.99−5.50 (m, 4H), 7.10−8.16 (m, 10H); ^{31}P NMR (81 MHz, $CDCl_3$) δ 54.16, 54.25, 54.82, 55.31; ESMS *m/z* calcd for $C_{28}H_{30}NO_9PNa$ $(M + Na)^+$ 578.2, found 578.3.

1-Benzyl 2-Methyl (2*S*)-5-((1-adamantyloxy){2-[(2-oxo-2-phenylethoxy)carbonyl]-4-pentynyl}phosphoryl)tetrahydro-1*H*-pyrrole-1,2-dicarboxylate (19). To a refluxing solution of compound **24** (230 mg, 0.41mmol) and silver(I) oxide (145 mg, 0.82 mmol) in $CHCl_3$ (8.6 mL) is added 1-adamantyl bromide(106 mg, 0.49 mmol) portionwise over 1 h. After the solution is refluxed for 3 h, an excess of 1-AdBr (106 mg, 0.49 mmol) is added and the mixture is stirred for 24 h in room temperature. Then, the solvent is removed in vacuo. AcOEt (30 mL) and 1 M HCl (30 mL) are added and the organic layer is separated and washed with 5% $NaHCO_3$ (2 × 10 mL) (102 mg of the starting material was recovered from the aqueous phase after acidification and extraction). The solvent is evaporated and the residue is purified by column chromatography, using a gradient eluent (petroleum ether 40−60 °C/AcOEt = 7:3 → AcOEt), yielding the pure product **19** (124 mg, 44%; 78% based on the recovered material) as a colorless oil. TLC R_f 0.70 ($CHCl_3$:MeOH = 95:5); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.41−1.60 (m, 6H), 1.70−2.20 (m, 15H), 2.21−2.79 (m, 5H), 3.30−3.78 (m, 3H), 4.10−4.43 (m, 2H), 4.96−5.57 (m, 4H), 7.09−7.96 (m, 10H); ^{31}P NMR (81 MHz, $CDCl_3$) δ 45.46, 45.67, 47.32, 47.67, 47.98, 48.12, 48.71; ESMS *m/z* calcd for $C_{38}H_{45}NO_9P$ $(M + H)^+$ 690.3, found 690.2; HRMS (ES) *m/z* calcd for $C_{38}H_{45}NO_9P$ $(M + H)^+$ 690.2832, found 690.2828.

2-({(1-Adamantyloxy)[(5*S*)-1-[(benzyloxy)carbonyl]-5-(methoxycarbonyl)tetrahydro-1*H*-pyrrol-2-yl]phosphoryl}methyl)-4-pentynoic Acid (25). To a solution of compound **19** (200 mg, 0.29 mmol) in MeOH:DMF (4:1) (5 mL) are added AcOH (609 mg, 10.15 mmol) and magnesium turnings (120 mg, 4.93 mmol). After the solution was stirred for 4 h at room temperature, $CHCl_3$ (20 mL) and 1 M HCl (20 mL) were added. The organic layer is separated, washed with brine, and dried over Na_2SO_4 and the solvent is removed in vacuo. The crude product is purified by column chromatography with a gradient eluent (chloroform → chloroform/methanol = 95:5), yielding the pure product **25** (113 mg, 68%) as a colorless oil; TLC R_f 0.49 ($CHCl_3$:MeOH = 95:5); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.40−3.17 (m, 25H), 3.42−3.80 (m, 3H), 4.01−4.52 (m, 2H), 4.83−5.18 (m, 2H), 7.02−7.58 (m, 5H); ^{31}P NMR (81 MHz, $CDCl_3$) δ 46.74, 47.45, 49.56, 50.06, 50.62, 50,90, 51.31, 52.63, 53.12, 53.91, 55.34; ESMS *m/z* calcd for $C_{30}H_{39}NO_8P$ $(M + H)^+$ 572.2, found 572.3; HRMS (ES) *m/z* calcd for $C_{30}H_{39}NO_8P$ $(M + H)^+$ 572.2413, found 572.2416.

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Supporting Information Available: Copies of NMR spectra and HPLC profiles, ^{13}C NMR data, and experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

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