Synthesis and Comparative Study on the Reactivity of Peptidyl-Type Phosphinic Esters: Intramolecular Effects in the Alkaline and Acidic Cleavage of Methyl β-Carboxyphosphinates

Dimitris Georgiadis,[†] Vincent Dive,[‡] and Athanasios Yiotakis*,[†]

Department of Chemistry, Laboratory of Organic Chemistry, University of Athens, Panepistimiopolis Zografou, 15771, Athens, Greece, and CEA, Département d'Ingénerie et d'Etudes des Protéines, 91191 Gif/Yvette Cedex, France

agiotak@cc.uoa.gr

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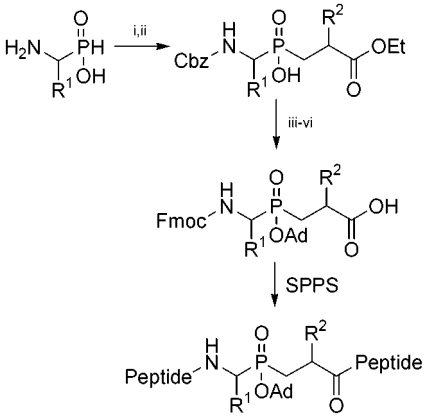
Using the phosphinic analogue of Cbz-Phe-Gly-OEt **1a** as a template for this study, several phosphinic esters (**2a**−**g**) were prepared, employing an efficient method for each case. The reactivity of these derivatives under conventional deprotection conditions was studied, and the results are listed comparatively. The effect of steric hindrance as well as the contribution of neighboring groups in the rate of hydrolysis of suitably selected β-carboxyphosphinates under acidic and alkaline deprotection conditions was examined. The results clearly demonstrate that a significant acceleration of phosphinate cleavage occurs due to the intermediacy of a five-membered, mixed anhydride-type species. This was supported by the observation that similar interactions were not observed in the case of hindered α-carboxyphosphinate homologous derivatives.

Introduction

Phosphinic peptides, an important class of protease inhibitors, are peptidic isosters containing the chemically stable phosphinic moiety −PO(OH)CH$_2$− which mimics the transition state tetrahedral geometry of a scissile peptide bond during enzymatic hydrolysis.[1] In the past decade, several studies have demonstrated that the synthesis of phosphinic peptides is a very effective approach for the development of highly potent inhibitors of zinc metalloproteases.[2] In addition, the development of solid-phase synthesis of phosphinic peptides, making possible the use of either parallel or combinatorial chemistry strategies, has been proven to be a fruitful approach to the development of both potent and selective inhibitors of zinc metalloproteases.[3−5] Toward this end, we have reported a strategy for the synthesis of phosphinic peptides by classical Fmoc solid-phase methodology, where it was envisaged that proper protection of the hydroxyphosphinyl group is essential for the efficient preparation of phosphinic peptides (Scheme 1).[6]

Scheme 1. General Procedure for the Synthesis of Phosphinic Peptides on a Solid Phase[a]



[a] Reagents and conditions: (i) CbzCl, NaOH; (ii) HMDS, $H_2C{=}C(R^2)COOEt$ and then EtOH; (iii) 1-AdBr, Ag_2O; (iv) 0.4 M NaOH/MeOH and then aq HCl; (v) $HCOO^-NH_4^+$, 10% Pd/C; (vi) FmocCl, Na_2CO_3.

The protocol for the synthesis of phosphinic peptides consists of two main parts: (i) preparation of the pseudodipeptidic synthon; (ii) peptide elongation, using either solid phase or solution methodologies. After a thorough overview of the literature, numerous contradictory reports concerning the protection of the hydroxyphosphinyl function in both parts of the synthetic protocol mentioned above were found. Some researchers claim that protection of the hydroxyphosphinyl function is not necessary during peptide coupling reactions, either on the solid phase or

* Corresponding author. Fax: 0030-1-7274498. Tel: 0030-1-7274498.
[†] University of Athens.
[‡] CEA, Gif/Yvette.

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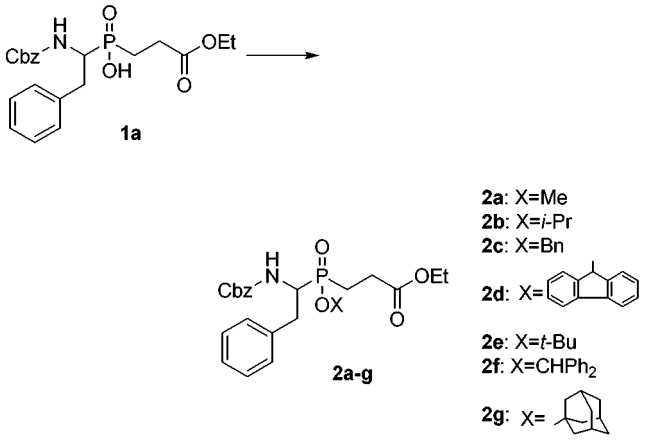
in solution,[1,7] while others strongly emphasize the serious limitations of coupling methods when phosphinopeptidic units are not protected at the phosphorus center.[8,9] It has been previously reported that the 1-adamantyl (1-Ad) group is a suitable protecting group for the hydroxyphosphinyl group during both the synthesis of phosphinic building blocks and the development of the pseudopeptides on the solid phase.[6,10] Nevertheless, 1-adamantyl phosphinates exhibit increased sensitivity during hydrogenation (Scheme 1), thus complicating the preparation of the target compounds.[6] Furthermore, as described in the literature, the most commonly used methyl phosphinates exhibit a structure-dependent behavior during deprotection while, in many cases, the harsh conditions needed for demethylation (e.g. TMSBr,[8] I^-/reflux[11]) limit the flexibility of the synthetic plan.

The confusion caused by the lack of a reliable guide to the behavior of phosphinic esters prompted us to investigate the protection and deprotection conditions of the hydroxyphosphinyl moiety in a more systematic manner. In this paper, the synthesis of a series of phosphinic esters are described and their behavior under basic, acidic and hydrogenation conditions is studied. Accordingly, the effect of neighboring functional groups and steric hindrance in the deprotection rate is investigated. Finally, the involvement of intramolecular carboxyl assistance in the cleavage of methyl β-carboxyphosphinates is described.

Results and Discussion

The phosphinic pseudodipeptidic analogue of Cbz-Phe-Gly-OEt **1a**[6] was used as a template in this study. Seven phosphinic esters of **1a** with diverse protecting groups covering a wide range of reactivity were prepared in high yields (Scheme 2). Methyl (**2a**), 9-fluorenyl (**2d**), and diphenylmethyl (**2f**) phosphinates were efficiently obtained by the action of diazomethane, diazodiphenylmethane,[12] and 9-diazofluorene, respectively, on **1a**. Introduction of isopropyl and benzyl groups was successfully achieved by reacting the cesium phosphinate of **1a** with isopropyl and benzyl bromide, respectively. Attempts to prepare adamantyl phosphinate **2g** using the cesium phosphinate of **1a** and 1-bromoadamantane failed, mainly due to the low rate of bromide ion displacement caused by the angle strain of adamantane in the nonplanar transition state of this proccess.[13] Thus, **2g** was prepared by conversion of **1a** to silver phosphinate and reaction of the latter with 1-bromoadamantane, as previously described.[6] Finally, *tert*-butyl ester **2e** was prepared by refluxing **1a** with an excess of *N*,*N*-dimethylformamide di-*tert* butyl acetal in benzene under neutral conditions.[14] Attempts to protect the hydroxyphosphinyl moiety by prior activation with coupling reagents (DCC/DMAP, BOP/Et_3N, pyBOP) gave only poor results while Mitsunobu esterification, as modified by Campbell et al.[15] for analogous phosphonic derivatives, proceeded satisfactorily for **2a,c** but sluggishly for the rest of the cases (<20%).[16] This low reactivity of phosphinic acids could be attributed to the reduced basicity and presumably nucleophilicity of phosphinate anions, as compared to carboxylates,[17] which would prevent the formation of the phosphinyloxy-activated species.

Scheme 2. Preparation of Phosphinates 2a−g[a]



[a] Reagents and conditions: **2a**, CH_2N_2, Et_2O, 10 min, 0 °C, 85% or MeOH, $(4\text{-ClPh})_3P$, DIAD, Et_3N, 2 h, rt, 72%; **2b**, Cs_2CO_3, *i*-PrBr, DMF, 48 h, 50 °C, 86%; **2c**, Cs_2CO_3, BnBr, DMF, 4 h, rt, 87% or BnOH, $(4\text{-ClPh})_3P$, DIAD, Et_3N, 2 h, rt, 67%; **2d**, 9-diazofluorene, CH_2Cl_2, reflux, 24 h, 80%; **2e**, $HC(Ot\text{-Bu})_2N(Me)_2$, benzene, reflux, 4 h, 76%; **2f**, $Ph_2C{=}NNH_2$, $PhI(OAc)_2$, $CHCl_3$, 25 °C, 15 min, 90%; Ag_2O, 1-AdBr, $CHCl_3$, reflux, 3.5 h, 81%.

With these esters in hand, their reactivity was examined using common deprotection conditions. Therefore, phosphinates **2a−g** were subjected to (i) saponification conditions using 0.35 N NaOH/MeOH, (ii) acidolysis conditions using TFA/CH_2Cl_2/H_2O in various concentrations, and (iii) hydrogenation conditions using 10% Pd/C as a catalyst and either H_2 or $HCOONH_4$ as a hydrogen donor. The progress of the reactions was being monitored by TLC, and the conversion percentages were determined after workup of the reaction mixtures and isolation of the products. The results are summarized in Tables 1−3.

Cleavage of the phosphinic ester follows the saponification of the ethyl carboxylate in all cases except from the case of **2g** (Table 1). Phosphinates **2a,b** were cleaved simultaneously with the carboxylic ester while the benzyl and fluorenyl groups were partially removed from the corresponding phosphinates (**2c,d**) under saponification conditions, but complete cleavage took place during the acidification step. **2e,f** appeared to be stable to saponification conditions; however, rapid cleavage took place during the acidification step (diphenylmethyl phosphinate is cleaved even in pH ~ 5). Upon treatment with

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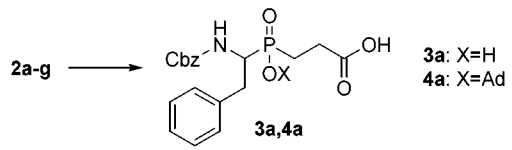
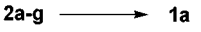
Table 1. Reactivity of 2a−g under Base-Catalyzed Hydrolysis Conditions[a]



ester	product	time	conversion (%)
2a	**3a**	40 min	98
2b	**3a**	60 min	100
2c	**3a**	45 min	91
2d	**3a**	60 min	95
2e	**3a**	60 min	100
2f	**3a**	45 min	100
2h	**4a**	24 h	89

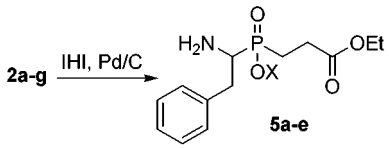
[a] Conditions used: 0.35 N NaOH/MeOH.

Table 2. Reactivity of 2a−g under Acid-Catalyzed Hydrolysis Conditions



ester	TFA/CH_2Cl_2/H_2O	time	conversion (%)
2a	99.5/0/0.5	24 h	<5
2b	10/89.5/0.5	24 h	4
2b	50/49.5/0.5	24 h	35
2b	99.5/0/0.5	24 h	81
2c	10/89.5/0.5	24 h	66
2c	50/49.5/0.5	4 h	100
2c	99.5/0/0.5	1 h	100
2d	5/94.5/0.5	5 min	100
2e	5/94.5/0.5	5 min	100
2f	5/94.5/0.5	5 min	100
2g	10/89.5/0.5	3 h	95
2g	50/49.5/0.5	30 min	100

Table 3. Reactivity of 2a−g under Catalytic Hydrogenation Conditions



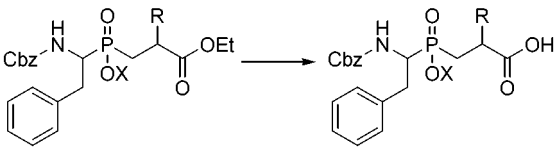
ester	product	X	conversion (%)[a]
2a	**5a**	Me	91 (89)
2b	**5b**	*i*-Pr	84 (87)
2c	**5c**	H	96 (100)
2d	**5c**	H	90 (100)
2e	**5d**	*t*-Bu	93 (82)
2f	**5c**	H	91 (100)
2g	**5e**	1-Ad	95 (90)

[a] Conversion yields given outside and within parentheses correspond to H_2 and $HCOONH_4$ hydrogen donors, respectively.

TFA, **2a** is the only compound that remained unaffected (Table 2). Phosphinates **2d**−**f** were immediately cleaved using 5% TFA/CH_2Cl_2/H_2O, whereas **2c,g** were sufficiently cleaved only in more concentrated TFA solutions. Isopropyl phosphinate (**2b**) was less resistant than **2a** since it was significantly cleaved using concentrated TFA solutions. Finally, under catalytic hydrogenation, benzyl, diphenylmethyl, and fluorenyl groups were removed simultaneously with the Cbz group while methyl, isopropyl, *tert*-butyl, and adamantyl groups were stable under these conditions (Table 3).

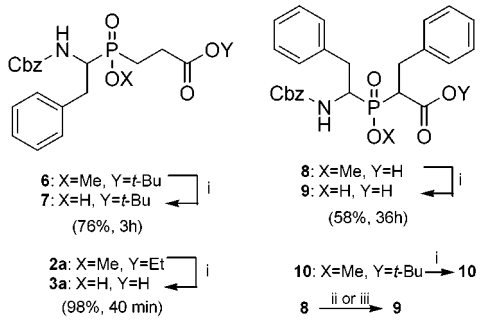
Our next objective was to investigate the contribution of steric and neighboring effects to the base-catalyzed hydrolysis of *β*-carboxyphosphinates. At the outset, we examined the rate of carboxylate saponification in adamantyl phosphinates **2g**−**I,** where the bulkiness of the side chain in the α-position of the carboxylate function was increased. Comparison of the half-life values in these processes indicates that the reaction is significantly slower with bulkier side chains, since nucleophilic attack of OH^- is prevented by steric encumbrance (Table 4). Interestingly, when phosphinates **1a**−**c** were subjected to the same conditions, a considerable acceleration of the ethyl carboxylate hydrolysis was observed (Table 4). We assumed that the free hydroxyphosphinyl group of **1a**−**c** is participating to the ethyl carboxylate cleavage while in the case of **2g**−**i** any hydroxyphosphinyl contribution to the saponification rate is suppressed. This effect is dependent on the size of the side chain R, reaching a maximum in the case of R = H (∼3-fold acceleration based on the half-lives). This acceleration was attributed to an intramolecular effect of the phosphinic anion assisting in the hydrolysis of the ethyl carboxylate, probably via a five-membered intermediate.

Table 4. Base-Catalyzed Hydrolysis of 2g−i and 1a−c (0.35 N NaOH/MeOH)



reactant	product	R	X	$T_{1/2}$ (min)
2g	**4a**	H	Ad	12
2h	**4b**	Me	Ad	72
2i	**4c**	*i*-Bu	Ad	450
1a	**3a**	H	H	4.1
1b	**3b**	Me	H	27
1c	**3c**	*i*-Bu	H	220

Scheme 3. Demethylation Conditions of 6, 8, and 10[a]

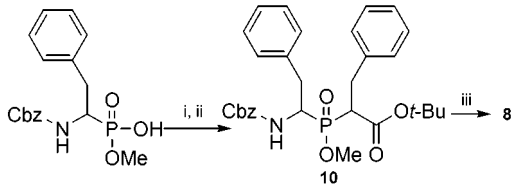


[a] Reagents and conditions: (i) 0.35 N NaOH/MeOH and then aq HCl; (ii) TMSBr, CH_2Cl_2, 2 h, rt, 93%; (iii) PhSH/Et_3N/dioxane (2/2/1), 5 h, rt, 89%

To explore further this observation we initially examined whether the aforementioned intermediate can be formed by the attack of a carboxylic anion to the vicinal phosphorus center. When the alkaline hydrolysis rates of **2a** (Table 1) and **6** were compared, it was observed that conversion of **6** to **7** is 78% after 3 h while **2a** is converted quantitatively to **3a** within 40 min (Scheme 3). In the case of **6**, where the carboxylic moiety remains protected throughout the reaction, assisting effects are not operable and hydrolysis occurs only due to the direct action of OH^-. On the contrary, in the case of **2a** the initially liberated carboxylate anion significantly accelerates methyl phosphinate cleavage.

The assumption of the cyclic intermediate was confirmed by the following experiment: methyl phosphinates

Scheme 4. Synthesis of 8 and 10[a]



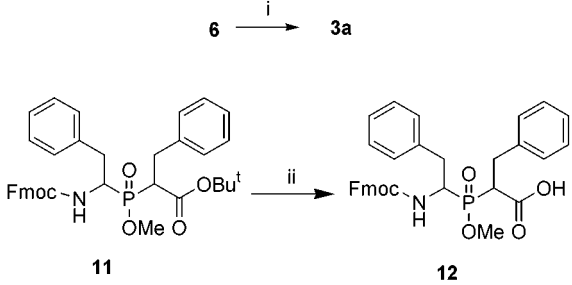
[a] Reagents and conditions: (i) $SOCl_2$, CH_2Cl_2, rt, 2 h; (ii) $BnCH_2COOEt$, LDA, THF, −78 to −10 °C, 45 min; (iii) TFA, rt, 3 h.

8 and **10**, bearing free carboxylic acid and *tert*-butyl carboxylate functions in their α-position respectively, were synthesized (Scheme 4) and subjected to saponification conditions. We observed that cleavage of methyl phosphinate **8** proceeded extremely slowly (58%, 36 h) while phosphinate **10** was completely stable even after several days (Scheme 3). This observation is in perfect accordance with our previous remarks since an analogous four-membered cyclic intermediate of an α-carboxyl-substituted phosphinate would not be thermodynamically favorable. In the case of such hindered structures as methyl α-carboxyphosphinate **8**, cleavage by nucleophilic displacement using Me_3SiBr[18] or $PhS^-Et_3NH^+$[19] proved to be more efficient for demethylation.

Similar intramolecular solvolysis effects have been previously reported for the cases of *β*-carboxyphosphonic and *β*-carboxyphosphonamidic acids[20] as well as for various structurally diverse phosphates and phosphonates.[21] However, in the case of phosphinates the effect is weaker probably due to reduced electrophilicity of the phosphorus atom. Attempts to differentiate between the significantly more stable methyl phosphinate and the ethyl carboxylate moieties of **2a** using 1 equiv of base afforded only poor results.[22] It has been previously described that differentiation can be achieved by enzymatic cleavage of the carboxylic ester but, even in these cases, cleavage of methyl phosphinate due to intramolecular catalysis cannot be completely suppressed.[1,22a]

As we wished to examine whether a similar assisting effect to the one mentioned above could participate in the acid-catalyzed cleavage of phosphinates, we compared the stability of methyl phosphinates **2a** and **6** upon treatment with dilute TFA (50/49.5/0.5 TFA/CH_2Cl_2/H_2O). **2a** was stable even when 99.5/0.5 TFA/H_2O is used for prolonged periods (Table 2). Surprisingly, in the case of **6**, the methyl group was removed quantitatively within 14 h (Scheme 5). This unexpected observation implies that the released carboxylic acid can promote methyl phosphinate hydrolysis via a five-membered intermediate even under mild acidic conditions. Furthermore, in the case of the α-carboxy-substituted methyl phosphinate **11**, unmasking of the hydroxyphosphinyl group did not occur even after treatment with 99.5/0.5 TFA/H_2O for 15 days. In fact, this methyl phosphinate is resistant even on treatment with 33% HBr/AcOH for a long period of time. Obviously, as noted above for **8**, in the case of **11** the formation of a four-membered intermediate that would promote phosphinate cleavage is unfavorable due to steric hindrance as well as thermodynamic constraint.

Scheme 5. Chemical Behavior of 6 and 11 upon Treatment with TFA[a]



[a] Reagents and conditions: (i) TFA/CH_2Cl_2/H_2O (50/49.5/0.5), 14 h, quant; (ii) TFA/H_2O (99.5/0.5), 15 d.

Some authors claim that the methyl group of methyl carboxyphosphinates can be removed in acidic conditions (TFA,[23] HCl/dioxane[24]) while others report that it is completely stable upon treatment with TFA[25,26] or even refluxing HBr/H_2O for 6 h.[8] Furthermore, Reiter and Jones mention that cleavage of a phosphinic acid methyl ester with TFA can be promoted by a *β*-situated carboxamide due to the formation of a five-membered reactive intermediate that involves the carboxamidic function.[27] In the structural motifs described herein, a five-membered intermediate involving the vicinal carbamate can be safely ruled out, since if the carbamate were involved in the cleavage, no differentiation between the α and *β*-carboxyphosphinates examined would be observed. All these observations perfectly supplement the study of Reiter and Jones and reveal the strong dependence of methyl phosphinates' behavior on the type and positioning of carbonyl-containing functional groups within the molecule at hand.

In Scheme 6, a general pathway for the mechanism of the alkaline and acidic cleavage of methyl *β*-carboxyphosphinates is proposed. In the case of basic hydrolysis, an intramolecular nucleophilic attack can lead to a phosphorane-type anionic TS intermediate (**Ia**) which is readily cleaved to give the deprotected derivative via the five-membered cyclic mixed-anhydride **II**.[28] In the case of acidic cleavage, the mechanism involves protonation of the phosphinate which could lead to two open protonated TS intermediates being in equilibrium with two cyclic phosphorane-type cationic TS intermediates.[28] When protonation of the methanolic oxygen occurs (**Ib**), equilibrium is rapidly displaced to the five-membered intermediate **II**, via its protonated form in equilibrium in the acidic medium, affording the fully deprotected compound after hydrolysis. The breakdown of the TS

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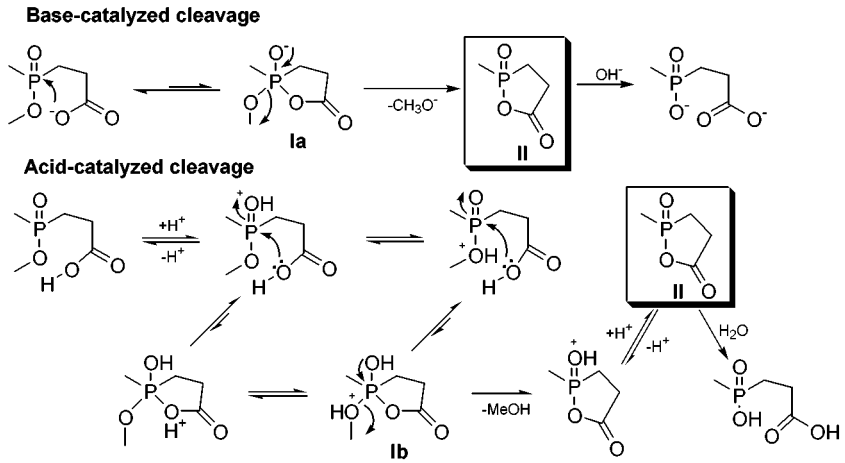
Scheme 6. Putative Mechanistic Pathways for the Base- and Acid-Catalyzed Cleavage of Methyl *β*-Carboxyphosphinates



intermediates (**Ia,b**) to the intermediate cyclic phosphinate (**II**) is irreversible in both pathways. In addition, two main structural features limit the rate enhancement effect, as compared to electron-richer phosphates, phosphonates, and phosphonamidates: first, the reduced electrophilicity of the phosphorus atom, which favors the acyclic charged intermediates (Scheme 6), and, second, the presence of an endocyclic P−C bond, in lieu of a P−O or a P−N bond, in the intermediate (**II**) which could relieve the ring from the large strain described in the case of the more reactive phosphonate and phosphate (and less in phosphonamidate) intermediates.[17,29]

Conclusion

Several diverse phosphinates have been synthesized, and results concerning the behavior of these compounds under typical deprotection conditions have been obtained. Upon examination of the dependency of steric factors and intramolecular interactions on acid- and base-catalyzed hydrolysis, using methyl *β*-carboxyphosphinates as templates, we concluded that a five-membered cyclic intermediate (**II**) is responsible for promoting cleavage in both processes. Absence of this assisting effect in methyl α-carboxyphosphinate hydrolysis strongly supports this proposal. The results of this study aim to improve the understanding of the reactivity of phosphinates, thus offering a consistent guide to the protection/deprotection conditions during the synthesis of this important class of bioactive molecules.

Experimental Section

All of the compounds, for which analytical and spectroscopic data are quoted, were homogeneous by TLC (silica gel 60 F-254). In most solvent systems close, but different, R_f values have been observed for the various stereoisomers of these compounds. Column chromatography was carried out on silica gel (70−230 mesh). Melting points are uncorrected. Assignment of the ^{1}H NMR signals was achieved using COSY and, in some cases only, HOM2DJ experiments. ^{13}C partial assignment is based on DEPT experiments. ^{1}H, ^{13}C, and ^{31}P NMR spectra were recorded on a 200 MHz Mercury Varian spectrometer. The presence of asymmetric centers in the described compounds complicates the interpretation of the spectra, especially when the hydroxyphosphinyl function is protected by the adamantyl group. Numbers I and II are used for the assignment of NMR signals that correspond to resonances of different diastereoisomers. ^{13}C and ^{31}P NMR spectra are fully proton decoupled. ^{31}P chemical shifts are reported on the δ scale (in ppm) downfield from 85% H_3PO_4 (external standard). Before microanalyses, samples were dried under high vacuum at 40 °C for 24 h in a dry pistol. Electron impact mass spectra (EIMS) were obtained on a mass spectrometer with positive ionization mode.

(*R,R,S,S*)-3-((1′-(*N*-Benzyloxycarbonylamino)-2′-phenylethyl)methyloxyphosphinyl)propanoic Acid, Ethyl Ester (2a). To an ice-cooled mixture of 40% KOH (3 mL) and Et_2O (20 mL) was added *N*-nitrosomethylurea (1.03 g, 10.0 mmol) under vigorous stirring. After the mixture was stirring for 15 min, the organic layer was added to a suspension of compound **1a** (0.84 g, 2.0 mmol) in Et_2O (20 mL). In the resulting yellow solution, some drops of AcOH were added. The colorless solution obtained was washed with 5% $NaHCO_3$ (2 × 10 mL) and H_2O (10 mL). The organic layer was dried with Na_2SO_4 and concentrated to dryness. The crude product was purified by column chromatography using $CHCl_3$/*i*-PrOH (9.7/0.3) as eluent: yield 0.74 g (85%); ^{1}H NMR ($CDCl_3$) δ 1.25 (t, $^3J_{HH}$ = 7.2 Hz, 3H, CH_2CH_3), 2.01−2.29 (m, 2H, PCH_2), 2.50−2.74 (m, 2H, CH_2CO), 2.80−3.06 (m, 1H, PhC*H*H), 3.14−3.37 (m, 1H, PhCH*H*), 3.66 (s, 3H/2, $POCH_3$, I), 3.70 (s, 3H/2, $POCH_3$, II), 4.14 (q, $^3J_{HH}$ = 7.2 Hz, 2H, CH_2CH_3), 4.28−4.50 (m, 1H, PC*H*), 5.00 (s, 2H, OCH_2Ph), 6.47 (d, $^3J_{HH}$ = 9.7 Hz, 1H, N*H*), 7.11−7.35 (m, 10H, aryl); ^{31}P NMR ($CDCl_3$) δ 53.54, 54.24; ESMS (*m*/*z*) calcd for $C_{22}H_{29}NO_6P$ $(M + H)^+$ 434.2, found 434.1. Anal. Calcd for $C_{22}H_{28}NO_6P$: C, 60.96; H, 6.51; N, 3.23. Found: C, 61.03; H, 6.78; N, 3.21.

(*R,R,S,S*)-3-((1′-(*N*-Benzyloxycarbonylamino)-2′-phenylethyl)isopropyloxy phosphinyl)propanoic Acid, Ethyl Ester (2b). Compound **1a** (0.84 g, 2.0 mmol) and Cs_2CO_3 (0.33 g, 1.0 mmol) were dissolved in 50% EtOH−H_2O (20 mL). The resulting solution was concentrated to dryness, and the residue was well dried over P_2O_5. To a solution of the resulting cesium salt in dry DMF (10 mL) was added *i*-PrBr (9.1 mL, 96.0 mmol). The mixture was stirred for 24 h at 50 °C, and then the solvents were evaporated. The residue was dissolved in H_2O (10 mL) and Et_2O (25 mL). The organic phase was washed with 5% $NaHCO_3$ (2 × 10 mL) and H_2O (10 mL), dried

(28) It is emphasized that the structures in Scheme 6 are only indicative and nothing is implied for the geometry and the stereochemistry of the TS phosphorane-type intermediates. According to the rules established by Westheimer (Westheimer, F. H. *Acc. Chem. Res.* **1968**, *1*, 70), (i) attack of a nucleophile in tetrahedral P leads to trigonal bipyramidal (TBP) intermediates which are rather transitional state forms and (ii) nucleophile enters and leaving group leaves from apical positions. We should also note that these forms are presumably in constant polytopic isomerisation. All the above have been demonstrated for a large number of phosphorous analogues of tetrahedral ground-state geometry (Thatcher, G. R. J.; Kluger, R. *Adv. Phys. Org. Chem.* **1989**, *25*, 99). Nevertheless, the case of such phosphinates has never been studied.

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with Na_2SO_4, and concentrated to dryness. The residue was treated with Et_2O/hexane (1/1). After cooling of the mixture at 0 °C for 24 h, the white crystalline precipitate was filtered out and dried: yield 0.79 g (86%); mp 107−109 °C; ^{1}H NMR ($CDCl_3$) δ 1.25 (t, $^3J_{HH}$ = 7.1 Hz, 3H, CH_2CH_3), 1.23 (d, $^3J_{HH}$ = 6.4 Hz, 3H, $CH(CH_3)_2$, I), 1.29 (d, $^3J_{HH}$ = 6.4 Hz, 3H, $CH(CH_3)_2$, II), 1.98−2.20 (m, 2H, PCH_2), 2.49−2.73 (m, 2H, CH_2CO), 2.75−2.93 (m, 1H, PhC*H*H), 3.20−3.40 (m, 1H, PhCH*H*), 4.16 (q, $^3J_{HH}$ = 7.1 Hz, 2H, CH_2CH_3), 4.23−4.42 (m, 1H, PC*H*), 4.71 (q, $^3J_{HH}$ = 6.4 Hz, 1H/2, C*H*$(CH_3)_2$, I), 4.75 (q, $^3J_{HH}$ = 6.4 Hz, 1H/2, C*H*$(CH_3)_2$, II), 4.99 (s, 2H, OCH_2Ph), 5.41 (d, $^3J_{HH}$ = 10.3 Hz, 1H, N*H*), 7.01−7.39 (m, 10H, aryl); ^{31}P NMR ($CDCl_3$) δ 51.37, 52.43; ESMS (*m*/*z*) calcd for $C_{24}H_{33}NO_6P$ $(M + H)^+$ 462.2, found 462.1. Anal. Calcd for $C_{24}H_{32}NO_6P$: C, 62.46; H, 6.99; N, 3.04. Found: C, 62.18; H, 6.99; N, 3.27.

(*R*,*R*,*S*,*S*)-3-((1′-(*N*-Benzyloxycarbonylamino)-2′-phenylethyl)benzyloxyphosphinyl)propanoic Acid, Ethyl Ester (2c). Compound **1a** (0.84 g, 2.0 mmol) was converted to its cesium salt as described above. To a solution of this salt in dry DMF (10 mL) was added BnBr (0.24 mL, 2.3 mmol). The reaction mixture was stirred for 4 h at room temperature, and then the solvents were evaporated. The residue was treated with H_2O (10 mL) and Et_2O (30 mL). The organic phase was washed with 5% $NaHCO_3$ (2 × 10 mL) and H_2O (10 mL), dried with Na_2SO_4, and concentrated to dryness. The oily residue was treated with Et_2O/hexane (1/4). After cooling of the mixture at 0 °C for 48 h, the white crystalline precipitate was filtered out and dried: yield 0.89 g (87%); mp 111−112 °C;^{1}H NMR ($CDCl_3$) δ 1.22 (t, $^3J_{HH}$ = 7.1 Hz, 3H, CH_2CH_3), 2.04−2.31 (m, 2H, PCH_2), 2.48−2.69 (m, 2H, CH_2CO), 2.83−3.08 (m, 1H, PhC*H*H), 3.12−3.38 (m, 1H, PhCH*H*), 4.09 (q, $^3J_{HH}$ = 7.1 Hz, 2H, CH_2CH_3), 4.33−4.55 (m, 1H, PC*H*), 4.90−5.20 (m, 4H, $POCH_2$Ph, $OCOCH_2$Ph), 6.80 (d, $^3J_{HH}$ = 10.1 Hz, 1H, N*H*), 7.15−7.45 (m, 15H, aryl); ^{31}P NMR ($CDCl_3$) δ 53.47, 53.95; ESMS (*m*/*z*) calcd for $C_{28}H_{33}NO_6P$ $(M + H)^+$ 510.2, found 510.1. Anal. Calcd for $C_{28}H_{32}NO_6P$: C, 66.00; H, 6.33; N, 2.75. Found: C, 65.65; H, 6.67; N, 2.60.

(*R*,*R*,*S*,*S*)-3-((1′-(*N*-Benzyloxycarbonylamino)-2′-phenylethyl)-9-fluorenyloxyphosphinyl)propanoic Acid, Ethyl Ester (2d). A solution of compound **1a** (0.84 g, 2.0 mmol) and 9-diazofluorene (0.38 g, 2.0 mmol) in CH_2Cl_2 (15 mL) was refluxed for 4 h. Then the reaction mixture was stirred for 24 h in room temperature. The mixture was concentrated, and the residue was taken up to Et_2O (20 mL). The organic phase was washed with 5% $NaHCO_3$ (10 mL) and H_2O (10 mL), dried with Na_2SO_4, and concentrated to dryness. The residue was treated with Et_2O/hexane (1/1) After cooling of the mixture at 0 °C for 24 h, the white crystalline precipitate was filtered out and dried: yield 0.93 g (80%); mp 117−119 °C; ^{1}H NMR ($CDCl_3$) δ 1.29 (t, $^3J_{HH}$ = 7.1 Hz, 3H, CH_2CH_3), 2.20−2.42 (m, 2H, PCH_2), 2.59−2.92 (m, 3H, CH_2CO, PhC*H*H), 3.38−3.55 (m, 1H, PhCH*H*), 4.18 (q, $^3J_{HH}$ = 7.1 Hz, 2H, CH_2CH_3), 4.43−4.63 (m, 1H, PC*H*), 4.98 (s, 2H, OCH_2Ph), 5.20 (d, $^3J_{HH}$ = 10.3 Hz, 1H, N*H*), 6.31 (s, 1H/2, $POCHC_{12}H_8$, I), 6.34 (s, 1H/2, $POCHC_{12}H_8$, II), 7.07−7.89 (m, 18H, aryl); ^{31}P NMR ($CDCl_3$) δ 54.58, 54.79; ESMS (*m*/*z*) calcd for $C_{34}H_{35}NO_6P$ $(M + H)^+$ 584.2, found 584.1. Anal. Calcd for $C_{34}H_{34}NO_6P$: C, 69.97; H, 5.87; N, 2.40. Found: C, 69.65; H, 6.01; N, 2.25.

(*R*,*R*,*S*,*S*)-3-((1′-(*N*-Benzyloxycarbonylamino)-2′-phenylethyl)-tert-butyloxy phosphinyl)propanoic Acid, Ethyl Ester (2e). A suspension of compound **1a** (0.83 g, 2.0 mmol) in dry benzene (4 mL) was heated to reflux. *N*,*N*-Dimethylformamide di-*tert*-butyl acetal (1.92 mL, 8.0 mmol) was added dropwise to the refluxing mixture over a period of 15 min. The mixture was refluxed for an additional 2 h and then was concentrated in vacuo. The oily residue was treated with Et_2O (10 mL) and 5% $NaHCO_3$ (10 mL). The organic layer was separated, and two more extractions with Et_2O (2 × 10 mL) were performed. The combined organic layers were dried with Na_2SO_4 and concentrated in vacuo. The residue was purified by column chromatography using $CHCl_3$/*i*-PrOH (9.7/0.3): yield 0.72 g (76%); ^{1}H NMR ($CDCl_3$) δ 1.21 (t, $^3J_{HH}$ = 7.1 Hz, 3H, CH_2CH_3), 1.51 (bs, 9H, $C(CH_3)_3$), 1.64−1.93 (m, 2H, CH_2CO), 2.22−2.55 (m, 2H, PCH_2), 2.70−2.98 (m, 1H, PhC*H*H), 3.12−3.35 (m, 1H, PhCH*H*), 4.13 (q, $^3J_{HH}$ = 7.1 Hz, 2H, CH_2CH_3), 4.10−4.39 (m, 1H, PC*H*), 4.95 (s, 2H, OCH_2Ph), 6.44 (d, $^3J_{HH}$ = 10.3 Hz, 1H, N*H*), 6.99−7.37 (m, 10H, aryl); ^{31}P NMR ($CDCl_3$) δ 52.32, 52.66; ESMS (*m*/*z*) calcd for $C_{25}H_{35}NO_6P$ $(M + H)^+$ 476.2, found 476.1. Anal. Calcd for $C_{25}H_{34}NO_6P$: C, 63.15; H, 7.21; N, 2.95. Found: C, 63.42; H, 6.93; N, 2.86.

(*R*,*R*,*S*,*S*)-3-((1′-(*N*-Benzyloxycarbonylamino)-2′-phenylethyl)diphenylmethyloxyphosphinyl)propanoic Acid, Ethyl Ester (2f). To a solution of compound **1a** (0.63 g, 1.5 mmol) in $CHCl_3$ (8 mL) were added benzophenone hydrazone (0.35 g, 1.8 mmol) and diacetoxy(phenyl)iodine (0.58 g, 1.8 mmol) portionwise and alternately. After 30 min the solvent was evaporated and the residue was dissolved in AcOEt (40 mL). The solution was rinsed with 0.1 N HCl (2 × 15 mL), 5% $NaHCO_3$ (2 × 15 mL), and H_2O (15 mL) and then dried with Na_2SO_4. The solvent was removed in vacuo, and the residue was treated with Et_2O/hexane (3/7). The white crystalline precipitate was filtered out and dried: yield 0.78 g (89%); mp 115−117 °C; ^{1}H NMR ($CDCl_3$) δ 1.20 (t, $^3J_{HH}$ = 7.1 Hz, 3H, CH_2CH_3), 1.97−2.18 (m, 2H, PCH_2), 2.29−2.63 (m, 2H, CH_2CO), 2.74−3.04 (m, 1H, PhC*H*H), 3.15−3.33 (m, 1H, PhCH*H*), 4.05 (q, $^3J_{HH}$ = 7.1 Hz, 2H, CH_2CH_3), 4.23−4.47 (m, 1H, PC*H*), 4.97 (s, 2H, OCH_2Ph), 6.40 (d, $^3J_{HH}$ = 6.7 Hz, 1H, N*H*), 6.63 (s, 1H/2, $POCHPh_2$, I), 6.67 (s, 1H/2, $POCHPh_2$, II), 7.00−7.48 (m, 20H, aryl); ^{31}P NMR ($CDCl_3$) δ 54.23, 54.32; ESMS (*m*/*z*) calcd for $C_{34}H_{37}NO_6P$ $(M + H)^+$ 586.2, found 586.1. Anal. Calcd for $C_{34}H_{36}NO_6P$: C, 69.73; H, 6.20; N, 2.39. Found: C, 69.64; H, 6.55; N, 2.25.

(*R*,*R*,*S*,*S*)-3-((1′-(*N*-Benzyloxycarbonylamino)-2′-phenylethyl)adamantyloxyphosphinyl)propanoic Acid, Ethyl Ester (2g). To a refluxing solution of compound **1a** (0.42 g, 1.0 mmol) and 1-adamantyl bromide (0.26 g, 1.2 mmol) in $CHCl_3$ (10 mL) was added silver(I) oxide (0.28 g, 1.2 mmol) portionwise over 1 h. After the solution was refluxed for 3 h, the solvent was removed in vacuo and the residue was treated with Et_2O (5 mL). The resulting mixture was filtered through Celite, and the filtrates were evaporated. The residue was purified by column chromatography, using $CHCl_3$/*i*-PrOH (9.8:0.2) as eluent. The product was treated with dry Et_2O, and the white solid, which was precipitated after cooling for 24 h, was filtered out and dried: Yield 0.45 g (81%); mp 138−140 °C; ^{1}H NMR ($CDCl_3$) δ 1.23 (t, $^3J_{HH}$ = 7.0 Hz, 3H, CH_2CH_3), 1.52−1.66 (m, 6H, $CHCH_2CH$ of Ad group), 2.00−2.19 (m, 11H, CCH_2 of Ad group, C*H* of Ad group, PCH_2), 2.20−2.42 (m, 2H, CH_2CO), 2.77−3.00 (m, 1H, PhC*H*H), 3.13−3.36 (m, 1H, PhCH*H*), 4.11 (q, $^3J_{HH}$ = 7.0 Hz, 2H, CH_2CH_3), 4.06−4.32 (m, 1H, PC*H*), 4.95 (s, 2H, OCH_2Ph), 6.41 (d, $^3J_{HH}$ = 10.3 Hz, 1H, N*H*), 7.09−7.36 (m, 10H, aryl); ^{31}P NMR ($CDCl_3$) δ 48.51, 48.76; ESMS (*m*/*z*) calcd for $C_{31}H_{41}NO_6P$ $(M + H)^+$ 554.2, found 554.2. Anal. Calcd for $C_{31}H_{40}NO_6P$: C, 67.25; H, 7.28; N, 2.53. Found: C, 67.65; H, 7.01; N, 2.25.

Procedure for the Preparation of 2a,c by Mitsunobu Esterification. In a solution of **1a** (0.2 g, 0.5 mmol) in THF (3 mL) were added tris(4-chlorophenyl)phosphine (0.13 g, 0.5 mmol), DIAD (101 mg, 0.5 mmol), and Et_3N (0.2 g, 2 mmol). Then the alcohol (0.75 mmol) was added and the reaction was stirred for 2 h in room temperature. After the end of the reaction, the solvents were evaporated and the residue was dissolved in Et_2O. The solution was washed with 0.1 N HCl (2 × 10 mL), 5% $NaHCO_3$ (2 × 10 mL), and H_2O (15 mL). After evaporation, a crude oil was obtained which was purified by column chromatography using $CHCl_3$/*i*-PrOH (9.7/0.3) as eluent. The products **2a,c** were obtained in 72 and 67% yield, respectively.

General Procedure for the Base-Catalyzed Hydrolysis Experiments. To a stirred solution of phosphinate (50 mg) in MeOH (2 mL) was added a 4 N aqueous solution of NaOH (0.2 mL) dropwise. The progress of the reaction was being monitored by TLC before and after treatment of small aliquots with dilute HCl and AcOEt.

For the determination of the data reported in Table 1, the reactions were quenched after 40−60 min (in the case of **2g**, the reaction was interrupted after 24 h) by addition of 0.3 N HCl (to pH ∼ 3) at 0 °C. The resulting suspensions were extracted with AcOEt (2 × 10 mL), and the organic layers were dried over Na_2SO_4 and concentrated to give the crude products.

The conversion ratios were determined by ^{31}P NMR. The products were purified, when necessary, by silica gel column chromatography using appropriate eluent systems and characterized.

For the determination of the data reported in Table 4, small aliquots of the reaction mixtures were collected in certain time periods (see Supporting Information) and treated with 0.3 N HCl and AcOEt at 0 °C. The organic layers were dried with Na_2SO_4 and concentrated in vacuo. The conversion percentages were determined in every case by ^{31}P NMR spectroscopy. $CDCl_3$ was used as NMR solvent, but when the samples had low solubility, D_2O/Na_2CO_3 was used. After the end of the reactions, the products were purified by silica gel column chromatography using $CHCl_3$/MeOH/AcOH (9.5/0.5/0.01) for **4a**−**c** while, in the case of **3a**−**c**, the products were obtained pure after crystallization of the crude product by AcOEt. Progress curves were generated from these data. Half-lives were calculated from the progress curves and correspond to the time required for 50% conversion.

General Procedure for the Acid-Catalyzed Hydrolysis Experiments. The phosphinate (20 mg) was dissolved in an ice-cooled solution of TFA/CH_2Cl_2 and 10 μL of H_2O (total volume: 2 mL), and the resulting mixture was stirred at room temperature. After a reaction period, judged by TLC, the mixture was concentrated to dryness. The solid residue was dissolved in Et_2O (10 mL), and the product was extracted with 5% $NaHCO_3$ (2 × 4 mL). The aqueous phase was acidified with 0.5 N HCl to pH 1, and two extractions with AcOEt (2 × 10 mL) followed. The organic phase was dried with Na_2SO_4 and concentrated in vacuo affording the crude products.

The determination of the conversion percentages reported in Table 2 was based on the mass of the isolated products, which in all cases corresponded exclusively to **1a** as determined by the ^{31}P NMR spectra of the products.

General Procedure for Catalytic Hydrogenation Using H_2, Pd/C. The phosphinate (50 mg) was dissolved in absolute ethanol (2 mL). In this solution, 10% Pd/C (15 mg) was carefully added. Then H_2 was introduced in a pressure of 1 atm. After 3 h, the catalyst was removed by filtration through Celite and the filtrates were concentrated to dryness affording the final products. Yields are listed in Table 3. Compounds **5a,b** were isolated as hydrochloric salts after treatment with 2 N HCl/dioxane in dry THF. Compounds **5d,e** were not stable to prolonged storage because of their sensitivity to moisture and to their tendency to form of pseudodiketopiperazines.[6]

General Procedure for Catalytic Hydrogenation Using $HCOONH_4$, Pd/C. To a solution of the phosphinate (50 mg) in MeOH (0.5 mL) were added ammonium formate (20 mg, mmol) and 10% Pd/C (20 mg). After 12 min of vigorous stirring at room temperature, the catalyst was removed by filtration through Celite, and the filtrates were evaporated to dryness. CH_2Cl_2 was added to the residue, and the solution was evaporated to dryness. This procedure was repeated twice. In the cases of **5a,b**, $CHCl_3$ (5 mL) and H_2O (5 mL) were added to the mixture. The aqueous phase was separated, and the organic phase was washed with H_2O (2 × 5 mL). The organic layer was concentrated, and the residue was treated with 2 N HCl/dioxane in dry THF. The precipitate was isolated by filtration affording compounds **5a,b** as hydrochloric salts. Yields are listed in Table 3.

***(R,R,R,S,S,S)*-3-Phenyl-2-((1′-(benzyloxycarbonyl)amino-2′-phenylethyl)methyloxyphosphinyl)propanoic Acid, tert-Butyl Ester (10).** In a solution of 2-phenyl-1-(*N*-benzyloxycarbonylamino)aminophosphonic acid, monoethy lester (1.19 g, 3.4 mmol) in CH_2Cl_2 (8 mL) was added $SOCl_2$ (2.7 mL, 3.7 mmol) under an Ar atmosphere. The mixture was stirred for 2 h at room temperature and then concentrated to dryness. CH_2Cl_2 (30 mL) was added to the residue, and the solution was concentrated to dryness. This procedure was repeated twice with CH_2Cl_2 and twice with THF. A colorless thick oil was obtained. In a solution of diisopropylamine (1.43 mL, 10.2 mmol) in THF (20 mL) was added *n*-BuLi (6.75 mL of a solution 1.51 M in hexane, 10.2 mmol) under Ar at −20 °C. The resulting mixture was cooled to −78 °C, and 3-phenylpropionic acid, *tert*-butyl ester (2.1 g, 10.2 mmol), was added dropwise during 10 min. After 15 min, a solution of the phosphinochloridate in THF (13 mL) was added during 5 min. The mixture was stirred for 30 min at −10 °C, and then the reaction was quenched by the addition of 10% HCl (30 mL). Extractions with Et_2O (2 × 20 mL) followed. The organic phase was washed with 5% $NaHCO_3$ (10 mL), H_2O (10 mL), and brine (10 mL), dried with Na_2SO_4, and concentrated to dryness. The residue was purified by column chromatography using $CHCl_3$/*i*-PrOH (9.8/0.2) as eluent: yield 1.1 g (60%); ^1H NMR ($CDCl_3$) δ 1.31 (s, 9H, C(C*H*$_3$)$_3$), 2.89−3.17 (m, 2H, PhC*H*$_2$CHNH), 3.10−3.46 (m, 3H, PhCH$_2$C*H*CO, PhC*H*$_2$CHCO), 3.74 (d, 3H/2, POC*H*$_3$, I, II), 3.85 (d, 3H/2, POC*H*$_3$, III, IV), 4.51−4.75 (m, 1H, PhCH$_2$C*H*NH), 5.03 (s, 2H, OC*H*$_2$Ph), 6.64 (d, $^3J_{HH}$ = 10.0 Hz, 1H, N*H*), 7.06−7.40 (m, 15H, aryl); ^{31}P NMR ($CDCl_3$) δ 46.55, 46.64, 46.94, 48.31; ESMS (*m*/*z*) calcd for $C_{30}H_{37}NO_6P$ $(M + H)^+$ 538.2, found 538.1. Anal. Calcd for $C_{30}H_{36}NO_6P\cdot 0.5H_2O$: C, 65.92; H, 6.82; N, 2.56. Found: C, 65.99; H, 7.08; N, 2.67.

Demethylation of Phosphinate 8. Method A. A solution of **8** (50 mg, 0.10 mmol) and (TMS)Br (23 mg, 0.15 mmol) in dry CH_2Cl_2 (1 mL) was stirred for 2 h at room temperature. Then the solvent was evaporated and the residue was treated with AcOEt (2 mL) and MeOH (2 mL). The solution was stirred for 30 min at room temperature and evaporated in vacuo. The crude product was purified by column chromatography using $CHCl_3$/MeOH/AcOH (7:0/4/0.4) as eluent. Compound **9** was obtained in a yield of 45 mg (93%): mp 142−145 °C; ^1H NMR (DMSO) δ 2.69−2.97 (m, 2H, PhC*H*$_2$CHNH), 3.04−3.36 (m, 3H, PhCH$_2$C*H*CO, PhC*H*$_2$CHCO), 4.48−4.68 (m, 1H, PhCH$_2$C*H*NH), 5.01 (s, 2H, OC*H*$_2$Ph), 7.08−7.36 (m, 15H, aryl), 7.67 (d, $^3J_{HH}$ = 11.3 Hz, 1H, N*H*); ^{31}P NMR (DMSO) δ 32.79 (broad); ESMS (*m*/*z*) calcd for $C_{25}H_{27}NO_6P$ $(M + H)^+$ 468.2, found 468.1. Anal. Calcd for $C_{25}H_{26}NO_6P\cdot 0.5H_2O$: C, 63.02; H, 5.71; N, 2.94. Found: C, 62.83; H, 5.78; N, 3.18.

Method B. A solution of **8** (50 mg, 0.10 mmol) in a mixture of 2/2/1 PhSH/Et_3N/dioxane (1 mL) was stirred for 5 h at room temperature. Then the reaction was quenched by the addition of 1 N HCl (2 mL) and Et_2O (5 mL) was added. The organic phase was separated and evaporated. The residue was dissolved in a small quantity of Et_2O. A white solid was precipitated after the addition of hexane (20 mL), which was filtered out and washed with hexane to afford **9** in pure form: yield 43 mg (89%).

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Supporting Information Available: Full spectroscopic and analytical data for compounds **1a**, **3a**−**c**, **4a**−**c**, **5a**−**c**, **6**−**8**, and **12 and** ^{13}C NMR and IR data for all the compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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