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Synthesis of phosphinodepsipeptides via the pseudo-four-component condensation reaction

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ABSTRACT

Phosphinodepsipeptides are recognized as an important class of enzyme inhibitors as tetrahedrally structural transition-state analogues to natural peptides. A series of phosphinodepsipeptides was synthesized in satisfactory yields via pseudo-four-component condensation reaction of 2-(*N*-benzoxycarbonylamino)alkanamides/peptide amides, aldehydes, and aryldichlorophosphines, followed by alcoholysis with hydroxyl esters.

1. Introduction

Phosphonopeptides as important phosphorus analogs of naturally occurring peptides have received considerable attention in bioorganic, biological, and medicinal chemistry due to the fact that they can be considered as stable mimetics of tetrahedral transition states in ester and amide hydrolysis and formation.[1–4] Phosphonopeptide is a general name for peptides containing a phosphonamide linkaged bond or 1-aminoalkylphosphonic acid at their C-terminal. Phosphinopeptides are peptides involving a phosphinamide bond or 1-aminoalkylphosphinic acid at their C-terminal. Phosphonodepsipeptides are peptides involving the phosphonate junction and phosphinodepsipeptides contain the phosphinate connection in the peptides or peptides containing a 1-hydroxyalkylphosphonic acid or 1-hydroxyalkylphosphinic acid at their C-terminal, respectively.[5] All of them have been widely used as enzyme inhibitors,[1–4,6–10] haptens for production of catalytic antibodies,[11] antibacterials,[1,12] and herbicidal agents,[1] and potential antihypertensive agents.[13] Recently, it was shown that vancomycin-resistant bacteria can produce D-Ala-D-lactate didepsipeptide instead of D-Ala-D-Ala dipeptide. D-Ala-D-lactate didepsipeptide not only binds much more weakly to vancomycin but also can be incorporated into the peptidoglycan layer.[11,14] On the other hand, phosphonodepsipeptides and phosphinodepsipeptides show generally better stability than the corresponding phosphonopeptides and phosphinopeptides, respectively. Thus, the new phosphonodidepsipeptides and phosphinodidepsipeptides are interesting candidates for use as inhibitors of VanX D,D-dipeptidase.

Phosphonopeptides and phosphinopeptides have been widely prepared and applied in organic and biological chemistry fields.[1–4] Phosphonodepsipeptides have also been synthesized via the reaction of N-protected aminoalkylphosphonochloridates with hydroxy esters,[6b,7,9,10,14] via the condensation of N-protected aminoaklylphosphonic acids or their monoester with hydroxy esters using coupling reagents, such as DIAD/PPh_3,[11b,15] DPPA, BOP, PyBOP, BOP-Cl. HBTU, BroP, TPyClU, etc.[6a,11a,16] Alternatively, they were synthesized via condensation of the corresponding phosphonous acids and hydroxy esters with DCC as a coupling reagent followed by oxidation with sodium periodate[17] or via the reaction of the corresponding phosphonous chlorides and hydroxy esters and subsequent oxidation with sodium periodate.[18] They were also prepared via nucleophilic displacement of the corresponding phosphonate sodium salts and ethyl 2-trifluoromethanesulfonyloxyalkanoates[12] and our recent phosphorus-Mannich-type reactions of carbamates, aldehydes, and chlorophosphites, and subsequent alcoholysis with hydroxy esters.[19] However, the synthesis of phosphinodepsipeptides has not been reported to date. Recently, we reported a novel method for the preparation of phosphinopeptides or hybrid sulfonophosphinopeptides via the Mannich-type condensation of *N*-Cbz protected amino amides/peptide amides or *N*-Cbz protected aminoalkanesulfonamides,

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aldehydes, aryldichlorophosphines, and subsequent aminolysis with amino acid esters/peptide esters or hydrolysis in high yields.[20,21] We herein present the first and facile synthesis of phosphinodepsipeptides via the pseudo-four-component condensation reaction, which is a convergent and atom-economic synthetic strategy.

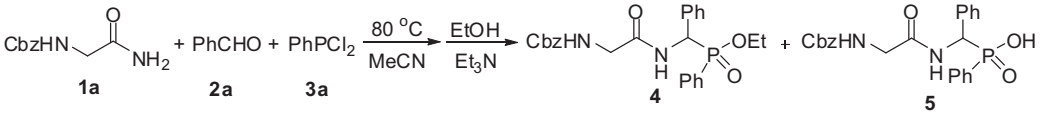
2. Results and discussion

Several *N*-benzyloxycarbonyl(Cbz)-amino amides and an *N*-Cbz protected peptide amide (*N*-Cbz-glycylglycinamide) were prepared from the corresponding acids by the mixed anhydride method via activation with ethyl chloroformate and aminolysis with ammonia. The reaction of *N*-Cbz-glycinamide (**1a**), benzaldehyde (**2a**), and phenyldichlorophosphine (**3a**) followed by alcoholysis with ethanol in the presence of triethylamine was selected to optimize the reaction conditions. It is worth mentioning that it is not easy to detect the reaction progress by TLC as the intermediate (*N*-Cbz-glycyl)-1-aminophenylmethylphosphinic chloride is sensitive to water and possesses weak UV absorbance. Thus, on the basis of our previous investigations,[20,21] we chose 1.0:1.2:1.2:2.0 as the molar ratio of *N*-Cbz-glycinamide (**1a**), benzaldehyde (**2a**), phenyldichlorophosphine (**3a**), and ethanol, and conducted the reaction in anhydrous acetonitrile, in which *N*-Cbz amino amides show good solubility. A mixture of *N*-Cbz-glycinamide (**1a**), benzaldehyde (**2a**), and phenyldichlorophosphine (**3a**) was refluxed in anhydrous acetonitrile under a nitrogen atmosphere for 12 h and alcoholyzed for another 24 h. After sequential washing with saturated sodium bicarbonate and brine to remove the corresponding phosphinic acid, the residue was separated by flash column chromatography to obtain the desire phosphinodepsipeptide **4** in a low yield of 36%. The aqueous solution was adjusted to pH 1 and extracted with ethyl acetate. After removal of the solvent, the residue was crystallized to give the corresponding phosphinic acid **5a** in 38% yield (Table 1, entry 1). Similar to the mechanism described in our and others' previously published papers,[22,23] the acid **5a** should be generated from the corresponding phosphinic anhydride via alcoholysis with ethanol. It is possible to reduce its formation to improve the yield of the desired product **4** by avoiding the formation of the phosphinic anhydride, which is formed from the corresponding phosphinic chloride and phosphinic acid **5a**. The acid **5a** should be generated via the addition of phenylphosphonous acid to the in situ generated imine in the reaction mixture or via hydrolysis of the phosphinic chloride during workup (Scheme 1). So we tried to optimize the reaction conditions. When we shortened the Mannich reaction to 6 h and the alcoholysis to 12 h, the yield of the product **4** was improved to 42%, and the yield of **5a** was reduced simultaneously (Table 1, entry 2). It is obvious that using shorter reaction time, especially the first step Mannich reaction time, is beneficial to improve the yield of the phosphinodepsipeptide **4**. Further using shorter reaction time, the yield of **4** was improved obviously to 51% and 68% (Table 1, entries 3 and 4). However, when the Mannich reaction was shortened to 0.5 h, the yield of **4** decreased to 60% (Table 1, entry 5). In each of cases, we can recover some *N*-Cbz-glycinamide (**1a**) after workup. To improve the conversion of *N*-Cbz-glycinamide (**1a**), we increased the amount of phenyldichlorophosphine (**3a**) to 1.33 and 1.67 equiv to *N*-Cbz-glycinamide (**1a**), respectively. However, the yield of the desired product **4** was improved slightly to 70% and 71% (Table 1, entries 6 and 7). Therefore, the optimized reaction conditions are that *N*-Cbz-aminoamide (**1a**), aldehyde (**2a**), and aryldichlorophosphine (**3a**) in a molar ratio of 1.0:1.2:1.3:2.0 were refluxed in anhydrous acetonitrile under a nitrogen atmosphere for 1 h and then the resulting mixture was alcoholyzed for another 6 h.

Under the optimized conditions, a series of phosphinodepsipeptides, including a phosphinotetradepsipeptide, was prepared using different aldehydes, *N*-Cbz-amino amides, aryldichlorophosphines, and hydroxyl esters. The results are summarized in Table 2. The results indicate that different aldehydes, *N*-Cbz-amino amides, aryldichlorophosphines, and hydroxyl esters do not affect the yields obviously. All reactants used work very well for the reaction (Table 2, entries 1–11). Aromatic aldehydes show slightly higher yields than aliphatic aldehyde. Both electron-rich and electron-deficient aromatic aldehydes and aryldichlorophosphines gave rise to the phosphinodepsipeptides in similar yields. The structures of all phosphinodepsipeptides **7** and the corresponding byproduct phosphinic acids **4** were characterized by ^{1}H NMR, ^{13}C NMR, ^{31}P NMR, and MS spectrometries.

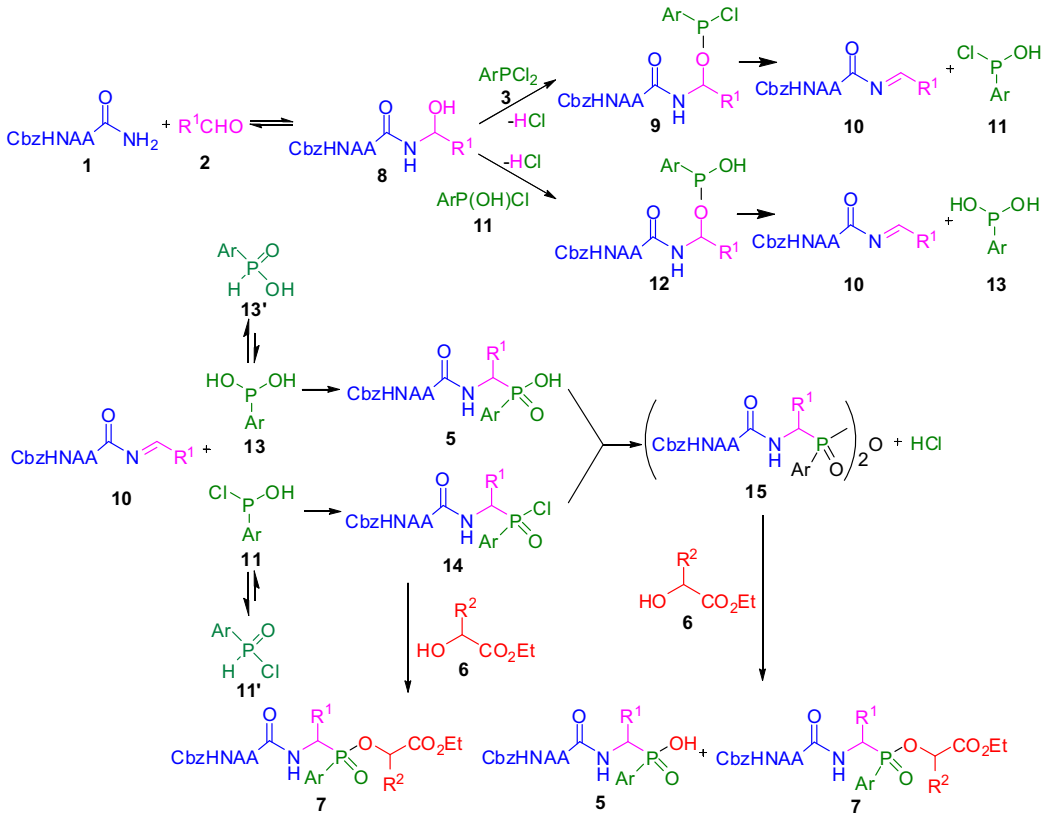
As for the reaction mechanism, in a manner similar to previous one in the synthesis of *N*-Cbz-1-amino-1-arylalkylphosphonate mixed diesters,[22] it is assumed that an aminoamide **1** first attacks an aldehyde **2** to form an *N*-acylaminohydrin adduct **8**, which further reacts with an aryldichlorophosphine **3** to produce an arylchlorophosphinate **9**. The phosphinate **9** undergoes an elimination to give rise to an imine **10** and an arylchlorophosphonous acid **11**, which can tautomerize into a relatively stable arylphosphinic chloride **11′** and exists in an equilibrium between the arylchlorophosphonous acid **11** and the arylphosphinic chloride **11′**. Alternatively, the reaction of the *N*-acylaminohydrin **9** and the arylchlorophosphonous acid **11** yields arylphosphinic monoester **12**, which undergoes an elimination to form the imine **10** and an arylphosphonous acid **13**. Similarly, the arylphosphonous acid **13** exists in an equilibrium between the arylphosphonous acid **13** and an arylphosphinic acid **13′**. Both the arylchlorophosphonous acid **11** and arylphosphonous acid **13** undergo an addition to the imine **10** to produce an aminoalkylphosphinic chloride **14** and the phosphinic acid **5**, respectively. The aminoalkylphosphinic chloride **14**

Table 1
Optimizing reaction conditions for the synthesis of phosphinodepsipeptide from *N*-Cbz-glycinamide, benzaldehyde, phenyldichlorophosphine, and ethanol.



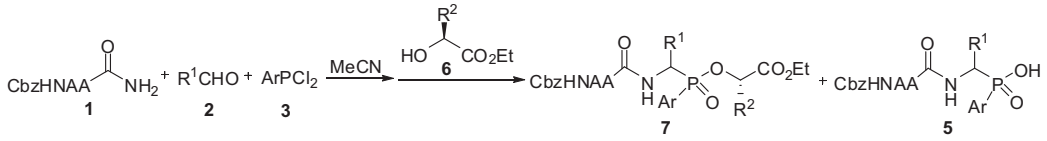
Entry	**1**:**2**:**3**:EtOH (mmol)	Reaction time (h)		Yield of **4** (%)[a]	Yield of **5** (%)[a]
		Mannich reaction	Alcoholysis		
1	3.0:3.5:3.5:6.0	12	24	36	38
2	3.0:3.5:3.5:6.0	6	12	42 (56)	23 (30)
3	3.0:3.5:3.5:6.0	4	12	51 (56)	21 (24)
4	3.0:3.5:3.5:6.0	1	6	68 (74)	18 (20)
5	3.0:3.5:3.5:6.0	0.5	6	60 (63)	22 (24)
6	3.0:3.5:4.0:6.0	1	6	70 (72)	19 (20)
7	3.0:3.5:5.0:6.0	1	6	71 (75)	19 (21)

[a] Isolated yield, the yield in parentheses based on the consumed starting *N*-Cbz-glycinamide.



Scheme 1. Proposed mechanism in the synthesis of phosphinodepsipeptides **7**.

Table 2
Synthesis of phosphinodepsipeptides **7**.



Entry	Peptide	AA	R^1	Ar	R^2	Yield of **7** (%)	Dr (*syn*:*anti*)[a]	Yield of **5** (%)
1	**7a**	Gly	Ph	Ph	H	64	60:40	18
2	**7b**	Gly	Ph	*p*-MePh	H	60	69:31	23
3	**7c**	Gly	Ph	*p*-ClPh	H	65	66:34	18
4	**7d**	Gly	*p*-MePh	Ph	H	66	66:34	26
5	**7e**	Gly	*p*-ClPh	Ph	H	61	62:38	21
6	**7f**	Gly	^{i}Pr	Ph	H	59	69:31[b]	25
7	**7g**	Gly	*p*-MePh	Ph	(*S*)-CH_3	62	50:26:12:12[b,c]	24
8	**7h**	Gly	*p*-MePh	Ph	(*S*)-Ph	66	NA[d]	25
9	**7i**	β-Ala	Ph	Ph	H	60	76:24	22
10	**7j**	(*S*)-Val	*p*-MePh	Ph	H	50	NA	18
11	**7k**	Gly-Gly	*p*-MePh	Ph	H	56	77:23	20

[a] Diastereomeric ratio *syn*:*anti* on the basis of isolated yield.
[b] Diastereomeric ratio on the basis of integration in ^{31}P NMR analysis.
[c] (*R*,R_P,*S*):(*S*,S_P,*S*):(*R*,S_P,*S*):(*S*,R_P,*S*)=50:26:12:12.
[d] Not available.

undergoes an alcoholysis with a hydroxyl ester **6** to afford the desired product phosphinodepsipeptide **7**, or it reacts with the phosphinic acid **5** to generate the phosphinic anhydride **15**, which is followed by alcoholysis with the hydroxyl ester **6** to generate the phosphinodepsipeptide **7** and the byproduct phosphinic acid **5** (Scheme 1). The intermediates were observed previously in ^{31}P NMR tracing experiments.[22,23]

The stereochemistry of the product phosphinodepsipeptides is discussed below. Most phosphinodepsipeptides **7a**–**e**,**i**,**k** were separated into their diastereomers by silica gel column and the diastereomeric ratio values were determined on the basis of the isolated yields. Although phosphinodepsipeptides **7f** and **7g**, and **7h** and **7j** possess two and three chiral carbon atoms, respectively, they are inseparable. For **7h** and **7j**, they even show single peaks in ^{31}P NMR analysis possibly due to the close similarity of their diastereomers. The diastereomeric ratios of the phosphinodepsipeptides **7f**,**g** were measured as 50:26:12:12 and 69:31, respectively, on the basis of their integrations in ^{31}P NMR analyses (Table 2, entry 7). Low diastereoselectivities were observed in the addition step of arylchlorophosphonous acid **11** to the *N*-acyl imine **10** in the reaction because the chiral center in optically active amino amides is too far away from the reactive center. The *syn*-products were assumed as

major diastereomers in the products on the basis of the reaction mechanism (Scheme 1). The reaction of *N*-Cbz-glycinamide (**1a**), *p*-methylbenzaldehyde (**2b**), phenyldichlorophosphine (**3a**), and ethyl (*S*)-(−)-lactate (**6b**) was selected as an example to illustrate the reaction diastereoselectivity. As mentioned above, the reaction produces an *N*-acyl imine **10b** and phenylchlorophosphonous acid (**11a**) firstly. Phenylchlorophosphonous acid (**11a**) is a chiral compound. The (*R*)- and (*S*)-isomers of phenylchlorophosphonous acid (**11a**) predominately attack the imine **10b** from its *Si* and *Re* sides, respectively, producing (S,S_P)- and (R,R_P)-*N*-(*N*-Cbz-glycinyl)-1-amino-(4-methylphenyl)methylphosphinic chlorides (S,S_P)-**14b** and (R,R_P)-**14b**, which undergo alcoholysis with ethyl (*S*)-lactate (**6b**) to generate the products phosphinodepsipeptides (S,S_P,S)-**7g** and (R,R_P,S)-**7g** through the backside attack via a pentacoordinate phosphorus transition state on the basis of the reported stereochemical investigation on the alcoholysis.[24] Although the configuration of the phosphorus atom undergoes an inversion during the alcoholysis, its configuration still keeps original assignment according to the IUPAC nomenclature rule. The (R,R_P,S)-**7g** should be the major product as its all substituents are in *anti*-position and the yield of (S,S_P,S)-**7g** should be ranked in the second one because phenyl and methyl locate in more steric hindrance *syn*-position. Similarly, the (*R*)- and (*S*)-isomers of phenylchlorophosphonous acid (**11a**) can also attack the imine **10b** from its *Re* and *Si* sides, respectively, to produce (R,S_P)- and (S,R_P)-*N*-(*N*-Cbz-glycinyl)-1-amino-(4-methylphenyl)methylphosphinic chlorides (R,S_P)-**14b** and (S,R_P)-**14b** followed by alcoholysis with ethyl (*S*)-lactate (**6b**) to afford (R,S_P,S)-**7g** and (S,R_P,S)-**7g**, respectively, in lower yields (Scheme 2). Because the addition step is the stereoselective step, generating *anti*-phosphinic chlorides as major intermediates on the basis of the conformational analysis (Scheme 2), and the phosphorus center undergoes an inversion during alcoholysis, the *syn*-products are major diastereomers in the products.

3. Conclusion

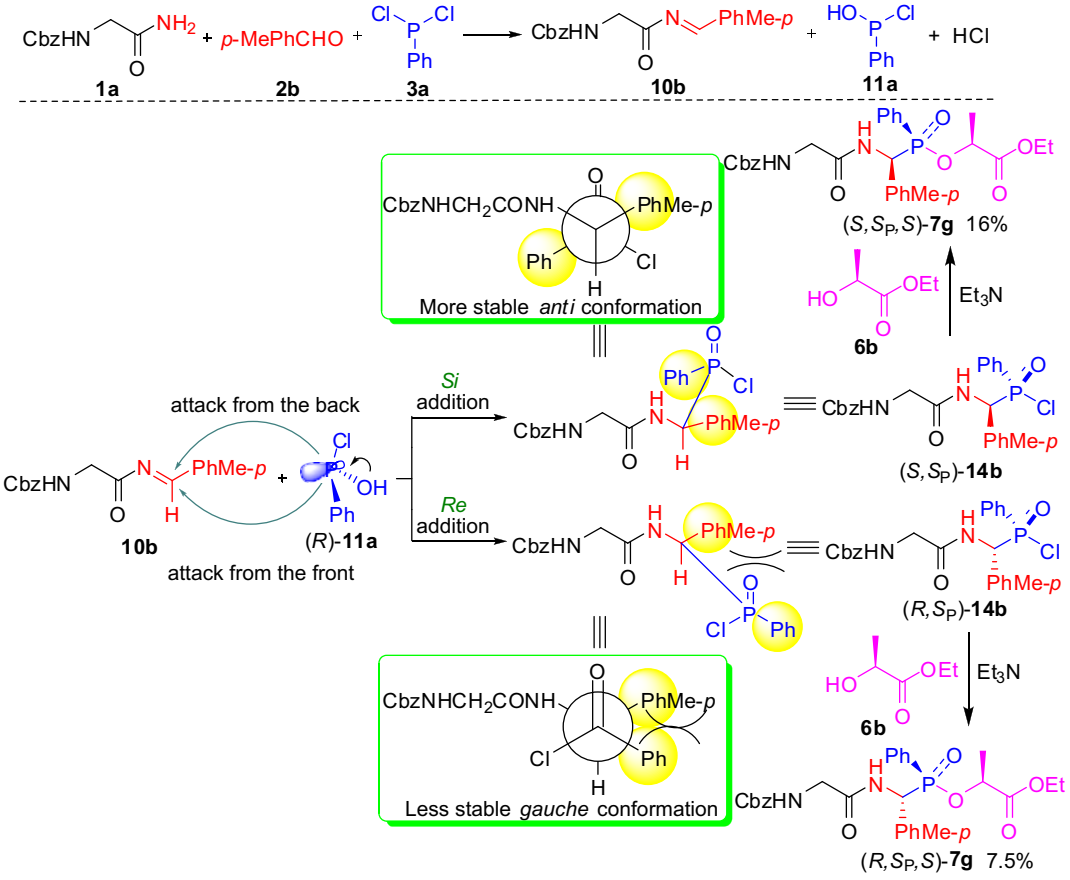
In conclusion, a series of phosphinodepsipeptides was synthesized in satisfactory yields via a facile pseudo-four-component condensation reaction of 2-(*N*-benzoxycarbonylamino)alkanamides/peptide amides, aldehydes, and aryldichlorophosphines, and subsequent alcoholysis with hydroxy esters. The current synthetic route is convergent and atom-economic method. It is an efficient pathway to prepare phosphonodepsipeptides from simple starting materials.

4. Experimental section

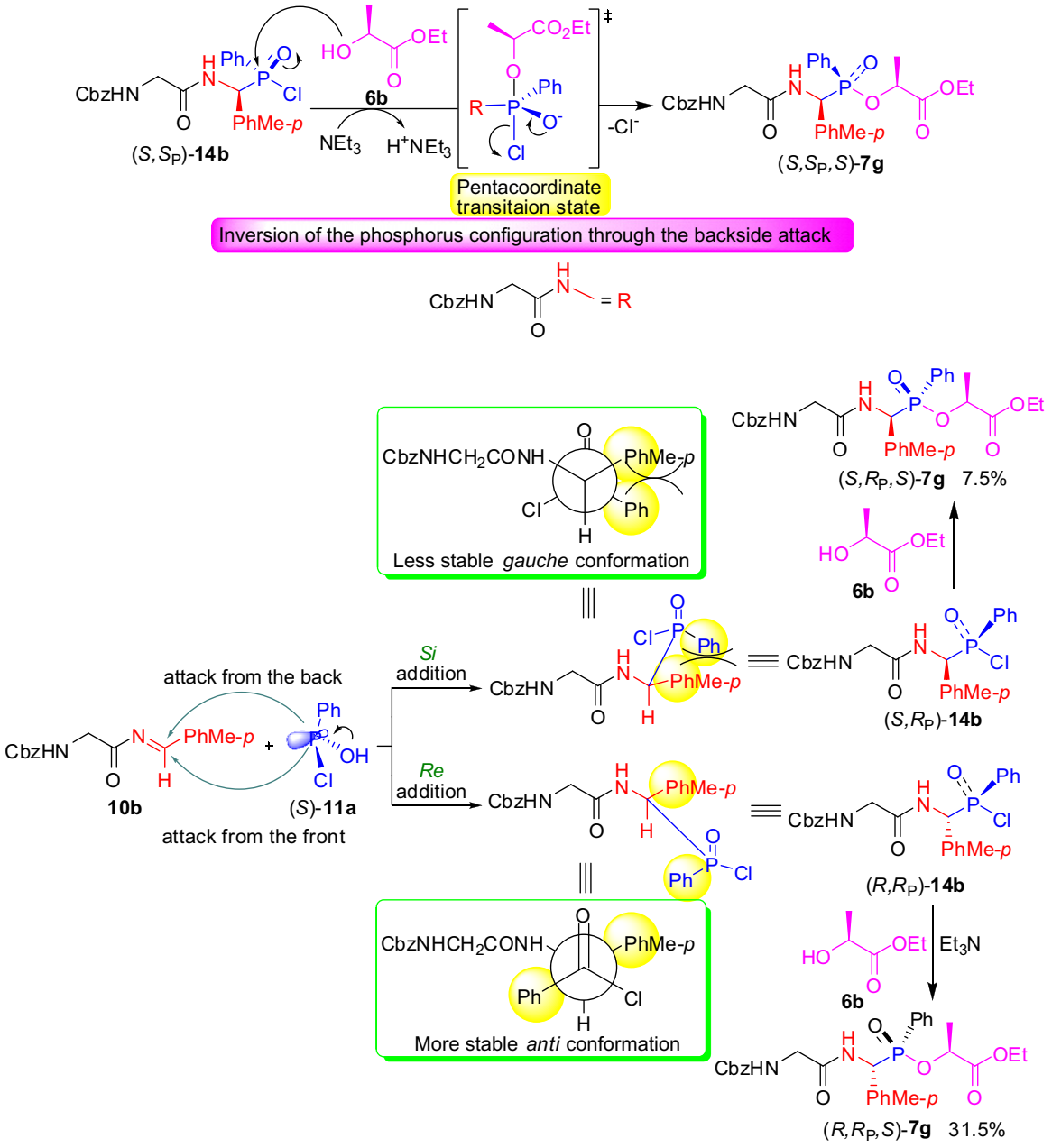
4.1. General

Melting points were measured on a Yanaco MP-500 melting point apparatus and are uncorrected. ^{1}H, ^{13}C and ^{31}P NMR spectra were recorded on a Brucker 400 NMR spectrometer at 400 MHz, 100 MHz, and 162 MHz, or a Varian 300 NMR spectrometer at 300 MHz, 75 MHz, 121 MHz, respectively, in $CDCl_3$ or DMSO-d_6 with TMS as an internal standard and 85% H_3PO_4 as an external standard for ^{31}P NMR. HRMS data was carried out on an Agilent LC/MSD TOF mass spectrometer. IR spectra were determined on a Nicolet AVATAR 330 FTIR spectrometer.

Aryldichlorophosphines were prepared according to literature procedure[25] and their analytical data are identical to those reported previously.[25,26] The analytical data of known phosphinopeptides **5** are identical to those reported previously.[20b] Acetonitrile was



Scheme 2. Diastereoselectivity in the synthesis of phosphinodepsipeptide **7g**.



Scheme 2. (*Continued*)

refluxed with calcium hydride and freshly distilled prior to use. All reactions were performed under a nitrogen atmosphere.

4.2. General procedure for synthesis of phosphinodepsipeptides 7

To a solution of an *N*-Cbz-2-aminoalkanamide **1** (3.0 mmol) and aldehyde **2** (3.5 mmol) in dried acetonitrile (15 mL) was added aryldichlorophosphine **3** (4.0 mmol) under stirring and a nitrogen atmosphere. After the *N*-Cbz-2-aminoalkanamide **2** was dissolved completely, the resulting solution was stirred in refluxing acetonitrile at 80 °C for 1 h. The reaction mixture was allowed to cool to room temperature under stirring. Hydroxyl ester **6** or ethanol (6.0 mmol) was added dropwise. After stirring for 15 min, triethylamine (1.67 mL, 1.22 g, 12 mmol) was added dropwise and the resulting reaction mixture was stirred for another 6 h. After removal of the solvent, the residue was dissolved in ethyl acetate. The solution was washed with saturated aqueous sodium bicarbonate (50 mL×3), saturated brine (50 mL×2), and dried over anhydrous sodium sulfate. After concentration at reduced pressure, the residue was separated on a silica gel column with a mixture of petroleum ether (30–60 °C) and ethyl acetate as an eluent with gradient elution to give the desired product phosphinodepsipeptide **7**. (Caution: The silica gel column was buffered by 0.5% triethylamine before the sample was loaded. The desired peptide **7** shows very weak fluorescent intensity under UV light. It is better to monitor collective fractions in the column separation after concentration). The aqueous solution was adjusted to pH 1 with 6 mol/L HCl and extracted with ethyl acetate (50 mL×3), the organic phase was dried over anhydrous sodium sulfate. After concentration at reduced pressure, the residue was crystallized from a mixture of ethyl acetate

and hexanes or methanol (ethanol) and diethyl ether to afford the corresponding phosphinic acid **5**.

*4.2.1. Ethyl anti-/syn-phenyl[N-[N-benzyloxycarbonylglycinyl]-1-aminophenylmethyl]phosphinate (**4**).* White solid, mp 155–157 °C; R_f=0.67 (Silica gel plate, ethyl acetate), mixture of diastereomers (*anti*:*syn* 15:1). IR (KBr) ν (cm^{-1}): 1713 (C=O), 1675 (C=O), 1202 (P=O); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.04 (t, J=7.2 Hz, 3H, CH_3, *anti*), 1.30 (t, J=7.2 Hz, 3H, CH_3, *syn*), 3.60–4.00 (m, 4H, NCH_2 & $POCH_2$), 4.98 (s, 2H, OCH_2, *anti*), 5.05 (s, 2H, OCH_2, *syn*), 5.62–5.80 (m, 2H, POCH & CO_2NH), 7.25–7.91 (m, 15H, ArH), 9.07 (d, J=9.6 Hz, 1H, CONH); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 16.2 (d, J_{P-C}=5.9 Hz), 44.1, 52.2 (d, J_{P-C}=109.3 Hz), 62.2 (d, J_{P-C}=7.3 Hz), 66.7, 127.61, 127.63, 127.9, 128.0, 128.01, 128.07, 128.4, 128.5, 128.57, 128.7, 128.76, 131.7, 131.9, 132.8, 132.88, 134.49, 134.5, 136.3, 156.1, 168.7; ^{31}P NMR (121.5 MHz, $CDCl_3$) δ: 37.4, 39.5 (85% H_3PO_4 as an external standard); HRMS (ESI) calcd for $C_{25}H_{28}N_2O_5P$ $[M+H]^+$ m/z 467.1730; found 467.1719.

*4.2.2. Ethyl syn-[[phenyl[N-[N-benzyloxycarbonylglycinyl]-1-aminophenylmethyl]phosphinyl]oxy] acetate (major) (syn-**7a**).* White solid, mp 126–128 °C; R_f=0.51 (Silica gel plate, ethyl acetate:hexanes 2:1, v/v). IR (KBr) ν (cm^{-1}): 1734 (C=O), 1718 (C=O), 1684 (C=O), 1216 (P=O); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.18 (t, J=7.1 Hz, 3H, CH_3), 3.78–3.89 (m, 2H, NCH_2), 4.13 (q, J=7.1 Hz, 2H, CO_2CH_2), 4.26 (dd, J=10.3, 16.1 Hz, 1H in $POCH_2$), 4.34 (dd, J=10.1, 16.1 Hz, 1H in $POCH_2$), 5.04 (s, 2H, OCH_2), 5.65 (s, br, 1H, CO_2NH), 5.77 (dd, J=9.9, 13.0 Hz, 1H, POCH), 7.20–7.77 (m, 15H, ArH), 8.69 (dd, J=3.7, 9.7 Hz, 1H, CONH); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 13.7, 43.8, 52.4 (d, J_{P-C}=107.7 Hz), 61.0 (d, J_{P-C}=6.2 Hz), 61.3, 66.4, 126.7, 127.6, 127.6, 127.9, 128.1, 128.2, 128.3, 131.4, 131.5, 131.7, 132.9, 133.8, 136.2, 155.9, 167.8 (d, J_{P-C}=4.3 Hz), 168.7 (d, J_{P-C}=5.3 Hz); ^{31}P NMR (121.5 MHz, $CDCl_3$) δ: 40.3 (85% H_3PO_4 as an external standard); HRMS (ESI) calcd for $C_{27}H_{30}N_2O_7P$ $[M+H]^+$ m/z 525.1785; found 525.1784.

*4.2.3. Ethyl anti-[[phenyl[N-[N-benzyloxycarbonylglycinyl]-1-aminophenylmethyl]phosphinyl]oxy] acetate (minor) (anti-**7a**).* White solid, mp 139–140 °C; R_f=0.64 (Silica gel plate, ethyl acetate:hexanes 2:1, v/v). IR (KBr) ν (cm^{-1}): 1734 (C=O), 1725 (C=O), 1675 (C=O), 1215 (P=O); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.21 (t, J=7.1 Hz, 3H, CH_3), 3.94–4.05 (m, 2H, NCH_2), 4.17 (q, J=7.1 Hz, 2H, CO_2CH_2), 4.44 (dd, J=10.7, 16.1 Hz, 1H in $POCH_2$), 4.59 (dd, J=9.8, 16.1 Hz, 1H in $POCH_2$), 5.12 (s, 2H, OCH_2), 5.68 (dd, J=9.4, 13.4 Hz, 1H, POCH), 5.78 (dd, J=4.6, 4.7 Hz, 1H, CO_2NH), 7.16–7.69 (m, 15H, ArH), 8.23 (dd, J=4.2, 9.2 Hz, 1H, CONH); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 13.7, 43.8, 52.4 (d, J_{P-C}=107.2 Hz), 61.0 (d, J_{P-C}=6.5 Hz), 61.3, 66.3, 126.7, 127.6, 127.9, 128.1, 128.2, 128.3, 128.4, 131.5, 131.7, 132.9, 133.8, 136.2, 155.9, 167.8 (d, J_{P-C}=5.0 Hz), 168.8 (d, J_{P-C}=6.2 Hz); ^{31}P NMR (121.5 MHz, $CDCl_3$) δ: 41.1 (85% H_3PO_4 as an external standard); HRMS (ESI) calcd for $C_{27}H_{30}N_2O_7P$ $[M+H]^+$ m/z 525.1785; found 525.1780.

*4.2.4. Ethyl syn-[[4-methylphenyl[N-[N-benzyloxycarbonylglycinyl]-1-aminophenylmethyl]phosphinyl]oxy]acetate (major) (syn-**7b**).* White solid, mp 143–144 °C; R_f=0.21 (Silica gel plate, ethyl acetate:hexanes 1:1, v/v). IR (KBr) ν (cm^{-1}): 1761 (C=O), 1733 (C=O), 1674 (C=O), 1217 (P=O); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.21 (t, J=7.1 Hz, 3H, CH_3), 2.29 (s, 3H, CH_3, minor rotamer), 2.34 (s, 3H, CH_3, major rotamer), 3.96–4.02 (m, 2H, NCH_2), 4.151 (q, J=7.1 Hz, 2H, CO_2CH_2, major rotamer), 4.155 (q, J=7.1 Hz, 2H, CO_2CH_2, minor rotamer), 4.37 (dd, J=10.6, 16.0 Hz, 1H in $POCH_2$, major rotamer), 4.38 (dd, J=10.5, 16.2 Hz, 1H in $POCH_2$, minor rotamer), 4.49 (dd, J=9.8, 15.5 Hz, 1H in $POCH_2$, major rotamer), 4.50 (dd, J=9.9, 16.2 Hz, 1H in $POCH_2$, minor rotamer), 5.11 (s, 2H, OCH_2), 5.63 (dd, J=9.5, 13.3 Hz, 1H, POCH), 5.78, 5.98, & 6.07 (br, 1H, CO_2NH), 7.17–7.71 (m, 14H, ArH), 8.25 (m, 1H, CONH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ: 14.0, 21.7, 44.5, 53.3 (d, J_{P-C}=102.2 Hz), 61.0 (d, J_{P-C}=6.4 Hz), 61.7, 67.0, 126.6, 128.0, 128.1, 128.13, 128.4, 128.5, 128.8, 129.2, 129.3, 132.0 (d, J_{P-C}=10.3 Hz), 132.5 (d, J_{P-C}=10.0 Hz), 133.47, 133.5, 136.3, 143.9, 156.5, 168.7 (d, J_{P-C}=5.2 Hz), 169.0 (d, J_{P-C}=6.2 Hz); ^{31}P NMR (121.5 MHz, $CDCl_3$) δ: 41.5 (85% H_3PO_4 as an external standard); HRMS (ESI) calcd for $C_{28}H_{32}N_2O_7P$ $[M+H]^+$ m/z 539.1942; found 539.1949.

*4.2.5. Ethyl anti-[[4-methylphenyl[N-[N-benzyloxycarbonylglycinyl]-1-aminophenylmethyl]phosphinyl]oxy]acetate (minor) (anti-**7b**).* White solid, mp 96–98 °C; R_f=0.29 (Silica gel plate, ethyl acetate:hexanes 1:1, v/v). IR (KBr) ν (cm^{-1}): 1761 (C=O), 1734 (C=O), 1676 (C=O), 1218 (P=O); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.17 (t, J=7.1 Hz, 3H, CH_3, major rotamer), 1.18 (t, J=7.1 Hz, 3H, CH_3, minor rotamer), 2.32 (s, 3H, CH_3, minor rotamer), 2.38 (s, 3H, CH_3, major rotamer), 3.80–4.0 (m, 2H, NCH_2), 4.13 (q, J=7.1 Hz, 2H, CO_2CH_2, major rotamer), 4.14 (q, J=7.1 Hz, 2H, CO_2CH_2, minor rotamer), 4.25–4.40 (m, 2H, $POCH_2$), 5.04 (s, 2H, OCH_2, major rotamer), 5.10 (s, 2H, OCH_2, minor rotamer), 5.71–5.80 (m, 2H, POCH & CO_2NH), 7.18–7.65 (m, 14H, ArH), 8.70 (s, br, 1H, CONH); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 13.9, 21.2 (minor rotamer), 21.7 (major rotamer), 44.04 (minor rotamer), 44.08 (major rotamer), 53.0 (d, J_{P-C}=95.7 Hz), 61.0 (d, J_{P-C}=6.5 Hz), 61.6 (major rotamer), 61.63 (minor rotamer), 67.7, 125.2, 127.9, 127.93, 128.0, 128.3, 128.4, 128.5, 128.9, 129.0, 129.2, 129.4, 131.9 (d, J_{P-C}=10.5 Hz), 132.3 (d, J_{P-C}=9.7 Hz), 134.2, 136.3, 143.8, 156.1, 168.5 (d, J_{P-C}=5.5 Hz), 168.7 (d, J_{P-C}=7.1 Hz); ^{31}P NMR (112.0 MHz, $CDCl_3$) δ: 40.5, 40.6 (85% H_3PO_4 as an external standard); HRMS (ESI) calcd for $C_{28}H_{32}N_2O_7P$ $[M+H]^+$ m/z 539.1942; found 539.1935.

*4.2.6. Ethyl syn-[[4-chlorophenyl[N-[N-benzyloxycarbonylglycinyl]-1-aminophenylmethyl]phosphinyl]oxy]acetate (major) (syn-**7c**).* White solid, mp 140–141 °C; R_f=0.37 (Silica gel plate, ethyl acetate:hexanes 1:1, v/v). IR (KBr) ν (cm^{-1}): 1761 (C=O), 1727 (C=O), 1686 (C=O), 1215 (P=O); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.19 (t, J=7.1 Hz, 3H, CH_3), 3.82–3.88 (m, 2H, NCH_2), 4.15 (q, J=7.0 Hz, 2H, CO_2CH_2), 4.24–4.36 (m, 2H, $POCH_2$), 5.06 (s, 2H, OCH_2), 5.60 (s, br, 1H, CONH), 5.72 (dd, J=9.7, 13.0 Hz, 1H, POCH), 7.23–7.65 (m, 14H, ArH), 8.50 (br, 1H, CONH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ: 13.9, 44.2, 53.0 (d, J_{P-C}=106.8 Hz), 61.1 (d, J_{P-C}=5.9 Hz), 61.8, 66.9, 125.7, 127.0, 127.9, 128.1, 128.3, 128.4, 128.5, 128.8, 128.9, 133.3, 133.4, 133.8, 136.3, 139.8, 139.9, 156.2, 168.6, 168.7 (d, J_{P-C}=6.7 Hz); ^{31}P NMR (162.0 MHz, $CDCl_3$) δ: 39.0 (85% H_3PO_4 as an external standard); HRMS (ESI) calcd for $C_{27}H_{28}ClN_2O_7P$ $[M+Na]^+$ m/z 581.1215; found 581.1210.

*4.2.7. Ethyl anti-[[4-chlorophenyl[N-[N-benzyloxycarbonylglycinyl]-1-aminophenylmethyl]phosphinyl]oxy]acetate (minor) (anti-**7c**).* White solid, mp 135–136 °C; R_f=0.42 (Silica gel plate, ethyl acetate:hexanes 1:1, v/v). IR (KBr) ν (cm^{-1}): 1760 (C=O), 1724 (C=O), 1686 (C=O), 1216 (P=O); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.23 (t, J=7.1 Hz, 3H, CH_3), 3.95 (dd, J=5.3, 16.9 Hz, 1H in NCH_2), 4.03 (dd, J=5.9, 16.9 Hz, 1H in NCH_2), 4.18 (q, J=7.1 Hz, 2H, CO_2CH_2), 4.43 (dd, J=11.2, 16.2 Hz, 1H in $POCH_2$), 4.57 (dd, J=10.1, 16.2 Hz, 1H in $POCH_2$), 5.13 (d, J=12.3 Hz, 1H in OCH_2), 5.16 (d, J=12.3 Hz, 1H in OCH_2), 5.61 (d, J=5.4 Hz, 1H, CONH), 5.63 (dd, J=9.4, 13.4 Hz, 1H, POCH), 7.22–7.61 (m, 14H, ArH), 7.90 (s, br, 1H, CONH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ: 14.0, 44.4, 53.2 (d, J_{P-C}=103.8 Hz), 61.3 (d, J_{P-C}=6.6 Hz), 61.7, 66.9, 125.4, 126.7, 127.9, 128.0, 128.1, 128.14, 128.4, 128.5, 128.7, 128.9, 133.3, 133.4, 133.5, 136.2, 139.7, 139.77, 156.5, 168.2 (d, J_{P-C}=4.7 Hz), 168.9 (d, J_{P-C}=6.0 Hz); ^{31}P NMR (162.0 MHz, $CDCl_3$) δ: 39.4 (85% H_3PO_4 as an external standard); HRMS (ESI) calcd for $C_{27}H_{28}ClN_2O_7P$ $[M+Na]^+$ m/z 581.1215; found 581.1210.

*4.2.8. Ethyl syn-[[phenyl[N-[N-benzyloxycarbonylglycinyl]-1-amino(4-methylphenyl)methyl]phosphinyl]oxy]acetate (major) (syn-**7d**).* White solid, mp 149–150 °C; R_f=0.56 (Silica gel plate, ethyl acetate:hexanes 2:1, v/v). IR (KBr) ν (cm^{-1}): 1761 (C=O), 1725 (C=O), 1678 (C=O), 1214 (P=O); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.18 (t, J=7.1 Hz, 3H, CH_3), 2.31 (s, 3H, CH_3), 3.82 (dd, J=3.8, 17.0 Hz, 1H in NCH_2), 3.85 (dd, J=3.8,

17.0 Hz, 1H in NCH_2), 4.13 (q, J=7.1 Hz, 2H, CO_2CH_2), 4.29 (d, J=9.9, 16.0 Hz, 1H in $POCH_2$), 4.30 (d, J=10.1, 16.0 Hz, 1H in $POCH_2$), 5.0 (s, 2H, OCH_2), 5.63 (s, br, 1H, CO_2NH), 5.72 (dd, J=10.1, 12.6 Hz, 1H, POCH), 7.03–7.77 (m, 14H, ArH), 8.57 (dd, J=3.5, 9.6 Hz, 1H, CONH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ: 13.9, 21.1, 44.1, 52.7 (d, J_{P-C}=106.5 Hz), 61.1 (d, J_{P-C}=6.4 Hz), 61.6, 66.7, 127.3, 127.9, 127.94, 128.36, 128.4, 128.5, 129.1, 131.0, 131.8, 131.9, 133.0, 136.3, 137.9, 156.1, 168.5 (d, J_{P-C}=5.0 Hz), 168.6 (d, J_{P-C}=6.9 Hz); ^{31}P NMR (162.0 MHz, $CDCl_3$) δ: 39.7 (85% H_3PO_4 as an external standard); HRMS (ESI) calcd for $C_{28}H_{31}N_2NaO_7P$ $[M+Na]^+$ m/z 561.1761; found 561.1757.

*4.2.9. Ethyl anti-[[phenyl[N-[N-benzyloxycarbonylglycinyl]-1-amino(4-methylphenyl)methyl]phosphinyl]oxy]acetate (minor) (anti-**7d**).* White solid, mp 111–112 °C; R_f=0.67 (Silica gel plate, ethyl acetate:hexanes 2:1, v/v). IR (KBr) ν (cm^{-1}): 1761 (C=O), 1724 (C=O), 1685 (C=O), 1214 (P=O); ^1H NMR (400 MHz, $CDCl_3$) δ: 1.21 (t, J=7.1 Hz, 3H, CH_3), 2.25 (s, 3H, CH_3), 3.96 (dd, J=5.6, 16.9 Hz, 1H in NCH_2), 4.03 (dd, J=5.3, 16.9 Hz, 1H in NCH_2), 4.17 (q, J=7.1 Hz, 2H, CO_2CH_2), 4.43 (dd, J=10.6, 16.1 Hz, 1H in $POCH_2$), 4.59 (dd, J=9.8, 16.1 Hz, 1H in $POCH_2$), 5.12 (s, 2H, OCH_2), 5.65 (dd, J=9.2, 13.1 Hz, 1H, POCH), 5.77 (s, br, 1H, CO_2NH), 6.96–7.69 (m, 14H, ArH), 8.15 (dd, J=3.2, 8.8 Hz, 1H, CONH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ: 14.0, 21.0, 44.4, 52.9 (d, J_{P-C}=103.0 Hz), 61.1 (d, J_{P-C}=6.6 Hz), 61.6, 66.9, 126.9, 127.97, 128.0, 128.3, 128.4, 128.41, 128.49, 130.4, 132.0, 132.1, 133.0, 136.3, 137.1, 156.4, 168.5 (d, J_{P-C}=4.7 Hz), 168.8 (d, J_{P-C}=6.0 Hz); ^{31}P NMR (162.0 MHz, $CDCl_3$) δ: 40.6 (85% H_3PO_4 as an external standard); HRMS (ESI) calcd for $C_{28}H_{31}N_2NaO_7P$ $[M+Na]^+$ m/z 561.1761; found 561.1762.

*4.2.10. Ethyl syn-[[phenyl[N-[N-benzyloxycarbonylglycinyl]-1-amino(4-chlorophenyl)methyl]phosphinyl]oxy]acetate (major) (syn-**7e**).* White solid, mp 145–147 °C; R_f=0.34 (Silica gel plate, ethyl acetate:hexanes 1:1, v/v). IR (KBr) ν (cm^{-1}): 1761 (C=O), 1727 (C=O), 1687 (C=O), 1215 (P=O); ^1H NMR (400 MHz, $CDCl_3$) δ: 1.19 (t, J=7.0 Hz, 3H, CH_3), 3.70–3.92 (m, 2H, NCH_2), 4.13–4.17 (m, 2H, CO_2CH_2), 4.30 (dd, J=10.6, 15.9 Hz, 1H in $POCH_2$), 4.43 (dd, J=10.0, 15.9 Hz, 1H in $POCH_2$), 5.05 (s, 2H, OCH_2), 5.62 (s, br, 1H, CO_2NH), 5.71 (dd, J=9.8, 13.1 Hz, 1H, POCH), 7.18–7.71 (m, 14H, ArH), 8.61 (s, br, 1H, CONH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ: 13.9, 44.1, 52.5 (d, J_{P-C}=106.4 Hz), 61.1 (d, J_{P-C}=5.8 Hz), 61.8, 66.9, 126.8, 127.9, 128.0, 128.4, 128.6, 128.7, 129.8, 131.8, 131.9, 132.7, 133.3, 134.08, 134.1, 136.3, 156.2, 168.5 (d, J_{P-C}=3.8 Hz), 168.8 (d, J_{P-C}=6.8 Hz); ^{31}P NMR (162.0 MHz, $CDCl_3$) δ: 39.5 (85% H_3PO_4 as an external standard); HRMS (ESI) calcd for $C_{27}H_{28}ClN_2NaO_7P$ $[M+Na]^+$ m/z 581.1220; found 581.1225.

*4.2.11. Ethyl anti-[[phenyl[N-[N-benzyloxycarbonylglycinyl]-1-amino(4-chlorophenyl)methyl]phosphinyl] oxy]acetate (minor) (anti-**7e**).* White solid, mp 214–215 °C; R_f=0.40 (Silica gel plate, ethyl acetate:hexanes 1:1, v/v). IR (KBr) ν (cm^{-1}): 1725 (C=O), 1693 (C=O), 1581 (C=O), 1128 (P=O); ^1H NMR (400 MHz, $CDCl_3$) δ: 1.20 (t, J=7.1 Hz, 3H, CH_3), 3.91–4.03 (m, 2H, NCH_2), 4.14 (q, J=7.1 Hz, 2H, CO_2CH_2), 4.38 (dd, J=11.0, 16.0 Hz, 1H in $POCH_2$), 4.51 (dd, J=10.1, 16.0 Hz, 1H in $POCH_2$), 5.11 (s, 2H, OCH_2), 5.58 (dd, J=9.2, 13.5 Hz, 1H, POCH), 5.79 (s, br, 1H, CO_2NH), 6.99–7.92 (m, 14H, ArH), 8.31 (s, br, 1H, CONH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ: 14.0, 44.4, 52.8 (d, J_{P-C}=102.4 Hz), 61.2 (d, J_{P-C}=6.6 Hz), 61.8, 67.0, 126.4, 127.7, 128.0, 128.3, 128.4, 128.5, 128.6, 128.9, 129.4, 129.45, 131.9, 132.0, 132.1, 133.3, 133.98, 134.0, 135.1, 136.3, 156.5, 168.3 (d, J_{P-C}=4.3 Hz), 169.1 (d, J_{P-C}=6.3 Hz); ^{31}P NMR (162.0 MHz, $CDCl_3$) δ: 40.3 (85% H_3PO_4 as an external standard); HRMS (ESI) calcd for $C_{27}H_{28}ClN_2NaO_7P$ $[M+Na]^+$ m/z 581.1220; found 581.1225.

*4.2.12. Ethyl syn-[[phenyl[N-[N-benzyloxycarbonylglycinyl]-1-amino-2-methylpropyl]phosphinyl]oxy]acetate (syn-**7f**).* White solid, mp 123–125 °C; R_f=0.18 (Silica gel plate, ethyl acetate:hexanes 1:1, v/v). IR (KBr) ν (cm^{-1}): 1762 (C=O), 1727 (C=O), 1681 (C=O), 1213 (P=O); ^1H NMR (400 MHz, $CDCl_3$) δ: 1.05 (d, J=6.6 Hz, 6H, $2CH_3$), 1.22 (t, J=7.1 Hz, 3H, CH_3), 2.40 (dheptet, J=5.1, 6.6 Hz, 1H, CH), 3.69 (dd, J=5.2, 16.5 Hz 1H in NCH_2), 3.78 (dd, J=4.7, 16.7 Hz, 1H in NCH_2), 4.17 (q, J=7.1 Hz, 2H, CO_2CH_2), 4.31 (dd, J=9.0, 15.8 Hz, 1H in $POCH_2$), 4.59 (dd, J=10.5, 15.8 Hz, 1H in $POCH_2$), 4.61 (ddd, J=5.1, 11.1, 16.0 Hz, 1H, POCH), 5.03 (d, J=12.4 Hz, 1H in OCH_2), 5.06 (d, J=12.4 Hz, 1H in OCH_2), 5.75 (s, br, 1H, CO_2NH), 7.30–7.80 (m, 11H, ArH & CONH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ: 13.9, 18.4 (d, J_{P-C}=4.8 Hz), 20.7 (d, J_{P-C}=9.7 Hz), 28.5, 44.0, 52.4 (d, J_{P-C}=112.2 Hz), 60.8 (d, J_{P-C}=6.5 Hz), 61.5, 66.8, 127.6, 127.9, 128.0, 128.4, 128.5, 128.8, 131.8, 131.9, 132.9, 136.3, 156.2, 167.8 (d, J_{P-C}=6.5 Hz), 169.2; ^{31}P NMR (162.0 MHz, $CDCl_3$) δ: 42.9 (85% H_3PO_4 as an external standard); HRMS (ESI) calcd for $C_{24}H_{31}N_2NaO_7P$ $[M+Na]^+$ m/z 513.1761; found 513.1758.

*4.2.13. Ethyl (S)-2-[[phenyl[N-[N-benzyloxycarbonylglycinyl]-1-amino(4-methylphenyl)methyl]phosphinyl]oxy]propionate (mixture of (R,S$_P$S):(S,S$_P$S):(S,R$_P$S):(R,R$_P$S)=50:26:12:12) (**7g**).* Pale yellow oil; R_f=0.35 (Silica gel plate, ethyl acetate:hexanes 1:1, v/v). IR (KBr) ν (cm^{-1}): 1728 (C=O), 1676 (C=O), 1513 (C=O), 1211 (P=O); ^1H NMR (400 MHz, $CDCl_3$) δ: 1.04, 1.09, & 1.24 (t, J=7.1 Hz, 3H, CH_3), 1.16, 1.45, & 1.53 (d, J=6.9 Hz, 3H, CH_3), 2.23, 2.25, & 2.36 (s, 3H, CH_3), 3.71, 3.94, & 3.96 (dd, J=5.2, 16.5 Hz, 1H in NCH_2), 3.79, 3.94, & 3.96 (dd, J=4.7, 16.7 Hz, 1H in NCH_2), 4.00, 4.05, & 4.18 (dq, J=10.8, 7.1 Hz, 1H in $POCH_2$), 4.01, 4.08, & 4.20 (dq, J=10.9, 7.1 Hz, 1H in $POCH_2$), 4.60 & 4.86 (dq, J=15.6, 7.2 Hz, 1H, CH), 5.04 (s, 2H, OCH_2), 5.10 (d, J=12.4 Hz, 1H in OCH_2), 5.14 (d, J=12.4 Hz, 1H in OCH_2), & 5.13 (d, J=12.3 Hz, 1H in OCH_2), 5.16 (d, J=12.3 Hz, 1H in OCH_2), 5.04, 5.54–5.72 (s, br, & m, 1H, CO_2NH), 5.61–5.75 (m, 1H, POCH), 6.90–7.90 (m, 14H, ArH), 8.10 (s, br, 1H, CONH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ: 13.8, 13.84, 14.0; 18.86, 18.9, 19.6; 21.1, 21.2; 44.2, 44.5, 44.6; 52.4 (d, J_{P-C}=109.2 Hz), 53.0 (d, J_{P-C}=101.0 Hz), 53.2 (d, J_{P-C}=105.0 Hz); 61.4, 61.5, 61.9; 66.9, 69.5, 70.35; 67.0, 69.54, 70.4; 127.8, 127.9, 128.05, 128.1, 128.2, 128.3, 128.4, 128.45, 128.5, 128.6, 129.0, 129.2, 129.3, 129.4, 130.4, 130.8, 131.07, 131.1, 131.8, 131.9, 132.2, 132.3, 132.8, 132.9, 138.3, 137.59, 137.6, 137.7, 137.8, 137.97, 137.99, 156.2, 156.4, 168.4 (d, J_{P-C}=6.9 Hz), 168.5, 168.8 (d, J_{P-C}=6.8 Hz), 170.4 (d, J_{P-C}=3.5 Hz), 170.5 (d, J_{P-C}=4.4 Hz), 171.1 (d, J_{P-C}=3.1 Hz); ^{31}P NMR (162.0 MHz, $CDCl_3$) δ: 39.0, 39.4, 40.2 (85% H_3PO_4 as an internal standard); HRMS (ESI) calcd for $C_{29}H_{34}N_2O_7P$ $[M+H]^+$ m/z 553.2098; found 553.2092.

*4.2.14. Ethyl anti/syn-[[phenyl[N-[N-benzyloxycarbonylglycinyl]-1-amino(4-methylphenyl)methyl]-phosphinyl]oxy]-(S)-2-phenylacetate (**7h**).* White solid, mp 149–150 °C; R_f=0.37 (Silica gel plate, ethyl acetate:hexanes 1:1, v/v). IR (KBr) ν (cm^{-1}): 1754 (C=O), 1728 (C=O), 1681 (C=O), 1212 (P=O); ^1H NMR (400 MHz, $CDCl_3$) δ: 1.00 (t, J=7.1 Hz, 3H, CH_3), 2.30 (s, 3H, CH_3), 3.61 (dd, J=5.0, 16.7 Hz, 1H in NCH_2), 3.68 (dd, J=4.9, 17.3 Hz, 1H in NCH_2), 3.97 (q, J=7.1 Hz, 2H, CO_2CH_2), 5.05 (s, 2H, OCH_2), 5.29 (dd, J=4.7, 4.7 Hz, 1H, CO_2NH), 5.36 (d, J=8.7 Hz, 1H, OCH), 5.70 (dd, J=10.6, 12.1 Hz, 1H, POCH), 6.90–7.97 (m, 19H, ArH), 8.06 (s, br, 1H, CONH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ: 13.7, 21.1, 43.9, 52.2 (d, J_{P-C}=109.6 Hz), 61.6, 66.7, 75.1 (d, J_{P-C}=6.5 Hz), 127.0, 127.9, 128.2, 128.4, 128.5, 128.55, 128.6, 128.62, 128.7, 129.1, 129.2, 130.66, 130.68, 131.8, 131.9, 133.0, 134.8, 134.9, 136.4, 137.7, 156.0, 168.7; ^{31}P NMR (162.0 MHz, $CDCl_3$) δ: 36.8 (85% H_3PO_4 as an external standard); HRMS (ESI) calcd for $C_{34}H_{35}N_2NaO_7P$ $[M+Na]^+$ m/z 637.2074; found 637.2069.

*4.2.15. Ethyl syn-[[phenyl[N-[N-benzyloxycarbonyl-β-alaninyl]-1-aminophenylmethyl]phosphinyl]oxy]acetate (**7i**).* White solid, mp 156–158 °C; R_f=0.51 (Silica gel plate, ethyl acetate:hexanes 2:1, v/v). IR (KBr) ν (cm^{-1}): 1760 (C=O), 1720 (C=O), 1673 (C=O), 1230 (P=O); ^1H NMR (400 MHz, $CDCl_3$) δ: 1.21 (t, J=7.1 Hz, 3H, CH_3), 2.52–2.55 (m, 2H, CH_2CO), 3.46 (dt, J=5.8, 5.8 Hz, 2H, NCH_2), 4.17 (q,

J=7.1 Hz, 2H, CO_2CH_2), 4.48 (dd, J=10.1, 16.1 Hz, 1H in $POCH_2$), 4.58 (dd, J=9.6, 16.1 Hz, 1H in $POCH_2$), 5.06 (s, 2H, OCH_2), 5.63 (s, br, 1H, CO_2NH), 5.70 (dd, J=9.3, 13.6 Hz, 1H, POCH), 7.16–7.65 (m, 15H, ArH), 7.87 (s, br, 1H, CONH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ: 13.9, 35.7, 37.1, 53.2 (d, J_{P-C}=102.8 Hz), 61.1 (d, J_{P-C}=6.5 Hz), 61.7, 66.4, 126.9, 127.9, 128.07, 128.1, 128.3, 128.5, 131.9 (J_{P-C}=9.8 Hz), 133.0, 133.8, 136.6, 156.4, 168.5 (d, J_{P-C}=5.2 Hz), 171.3 (d, J_{P-C}=5.7 Hz); ^{31}P NMR (162.0 MHz, $CDCl_3$) δ: 40.6 (85% H_3PO_4 as an external standard); HRMS (ESI) calcd for $C_{28}H_{31}N_2NaO_7P$ $[M+Na]^+$ m/z 561.1761; found 561.1765.

*4.2.16. Ethyl syn-[[phenyl[N-[(S)-N-benzyloxycarbonylvalinyl]-1-amino(4-methylphenyl)methyl]-phosphinyl]oxy]acetate (**7j**).* White solid, mp 164–166 °C; R_f=0.47 (Silica gel plate, ethyl acetate:hexanes 1:1, v/v). IR (KBr) ν (cm^{-1}): 1764 (C=O), 1722 (C=O), 1661 (C=O), 1217 (P=O); ^1H NMR (400 MHz, $CDCl_3$) δ: 0.62 (d, J=6.7 Hz, 3H, CH_3), 0.72 (d, J=6.7 Hz, 3H, CH_3), 1.21 (t, J=7.1 Hz, 3H, CH_3), 1.83–1.91 (m, 1H, CH), 2.32 (s, 3H, CH_3), 3.09 (dd, J=5.0, 7.1 Hz, 1H, NCH), 4.16 (q, J=7.1 Hz, 2H, CO_2CH_2), 4.29 (dd, J=10.2, 16.2 Hz, 1H in $POCH_2$), 4.34 (dd, J=9.9, 19.6 Hz, 1H in $POCH_2$), 5.02 (d, J=12.2 Hz, 1H in OCH_2), 5.05 (d, J=12.2 Hz, 1H in OCH_2), 5.42 (d, J=8.9 Hz, 1H, CONH), 5.67 (dd, J=9.7, 13.1 Hz, 1H, POCH), 7.04–7.89 (m, 11H, ArH & CONH), 8.00 (s, br, CONH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ: 14.0, 17.0, 19.1, 21.1, 31.7, 45.8, 52.7 (d, J_{P-C}=106.9 Hz), 61.0 (d, J_{P-C}=6.4 Hz), 61.6, 66.8, 127.5, 127.68, 127.7, 127.9, 128.4, 128.5, 128.7, 128.76, 128.8, 129.2, 129.25, 131.1, 132.0, 132.1, 132.3, 132.4, 133.0, 133.8, 136.3, 137.8, 156.2, 168.6 (d, J_{P-C}=5.4 Hz), 171.7 (d, J_{P-C}=7.4 Hz); ^{31}P NMR (162.0 MHz, $CDCl_3$) δ: 30.6, 40.0 (85% H_3PO_4 as an internal standard); HRMS (ESI) calcd for $C_{31}H_{37}N_2NaO_7P$ $[M+Na]^+$ m/z 603.2231; found 603.2234.

*4.2.17. Ethyl syn-[[phenyl[N-[N-[N-benzyloxycarbonylglycinyl]glycinyl]-1-amino(4-methylphenyl)methyl]phosphinyl]-oxy]acetate (major) (syn-**7k**).* White solid, mp 152–154 °C; R_f=0.21 (Silica gel plate, ethyl acetate). Pure *syn*-**7k** cannot be obtained. The analytic data shown here from a mixture of *syn*-**7k** and *anti*-**7k** in a ratio of *anti*:*syn*=6.81:1. IR (KBr) ν (cm^{-1}): 1727 (C=O), 1725 (C=O), 1658 (C=O), 1578 (C=O), 1088 (P=O); ^1H NMR (400 MHz, $CDCl_3$) δ: 1.21 & 1.24 (t, J=7.1 Hz, 3H, CH_3), 2.25 & 2.29 (s, 3H, CH_3), 3.82–3.95 (m 2H, NCH_2), 3.95–4.06 (m, 2H, NCH_2), 4.18 & 4.22 (q, J=7.1 Hz, 2H, CO_2CH_2), 4.33 & 4.37 (dd, J=11.2, 17.3 Hz, 1H in $POCH_2$), 4.46–4.58 (m, 1H in $POCH_2$), 5.11 & 5.14 (s, 2H, OCH_2), 5.57 (dd, J=9.4, 13.3 Hz, 1H, POCH), 5.75 & 5.83 (s, br, 1H, CONH), 6.98–7.60 (m, 14H, ArH), 8.20 (s, br, 1H, CONH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ: 13.9, 21.1, 42.8, 44.2, 53.1 (d, J_{P-C}=105.4 Hz), 61.0 (d, J_{P-C}=6.3 Hz), 61.7, 67.0, 127.2, 127.9, 128.0, 128.3, 128.32, 128.4, 128.44, 128.5, 129.2, 130.3, 130.9, 131.9, 132.0, 133.1, 136.3, 137.9, 156.6, 168.3 (d, J_{P-C}=7.1 Hz), 168.8 (d, J_{P-C}=4.6 Hz), 169.4; ^{31}P NMR (162.0 MHz, $CDCl_3$) δ: 40.3, 40.9 (85% H_3PO_4 as an internal standard); HRMS (ESI) calcd for $C_{30}H_{35}N_3O_8P$ $[M+H]^+$ m/z 596.2156; found 596.2153; calcd for $C_{30}H_{34}N_3NaO_8P$ $[M+Na]^+$ m/z 618.1981; found 618.1971.

*4.2.18. Ethyl anti-[[phenyl[N-[N-[N-benzyloxycarbonyl-glycinyl]glycinyl]-1-amino(4-methylphenyl) methyl]phosphinyl]-oxy]acetate (minor) (anti-**7k**).* White solid, mp 66–67 °C; R_f=0.26 (Silica gel plate, ethyl acetate). IR (KBr) ν (cm^{-1}): 1735 (C=O), 1719 (C=O), 1707 (C=O), 1685 (C=O), 1220 (P=O); ^1H NMR (400 MHz, $CDCl_3$) δ: 1.21 (t, J=7.1 Hz, 3H, CH_3), 2.24 (s, 3H, CH_3), 3.97 (d, J=5.6 Hz, 2H, NCH_2), 3.97–4.10 (m, 2H, NCH_2), 4.17 (q, J=7.1 Hz, 2H, CO_2CH_2), 4.38 (dd, J=10.8, 16.2 Hz, 1H in $POCH_2$), 4.55 (dd, J=9.7, 16.2 Hz, 1H in $POCH_2$), 5.13 (s, 2H, OCH_2), 5.59 (dd, J=9.4, 12.8 Hz, 1H, POCH), 5.91 (s, br, 1H, CO_2NH), 6.93 (s, br, 1H, CONH), 6.98–7.68 (m, 14H, ArH), 7.98 (s, br, 1H, CONH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ: 14.0, 21.1, 43.1, 44.5, 53.1 (d, J_{P-C}=102.8 Hz), 61.1 (d, J_{P-C}=6.3 Hz), 61.9, 67.2, 127.0, 127.9, 128.0, 128.1, 128.2, 128.3, 128.5, 128.54, 128.6, 129.2, 130.2, 132.1, 132.2, 133.1, 136.2, 137.9, 137.94, 156.6, 168.3 (d, J_{P-C}=2.4 Hz), 169.1 (d, J_{P-C}=4.9 Hz), 169.6; ^{31}P NMR (162.0 MHz, $CDCl_3$) δ: 40.7 (85% H_3PO_4 as an internal standard); HRMS (ESI) calcd for $C_{30}H_{35}N_3O_8P$ $[M+H]^+$ m/z 596.2156; found 596.2153; calcd for $C_{30}H_{34}N_3NaO_8P$ $[M+Na]^+$ m/z 618.1981; found 618.1971.

*4.2.19. Phenyl[N-[N-benzyloxycarbonylglycinyl]-1-amino-2-methylpropyl]phosphinic acid (**5f**).* White solid, mp 274 °C (dec); IR (KBr) ν (cm^{-1}): 1728.5 (C=O), 1660.1 (C=O), 1236.3 (P=O); ^1H NMR (400 MHz, DMSO-d_6) δ: 0.87 (d, J=5.2 Hz, 3H, CH_3), 0.95 (d, J=5.2 Hz, 3H, CH_3), 2.15 (m, 1H, CH), 3.46 (d, J=12 Hz, 1H in $COCH_2$), 3.65 (d, J=12 Hz, 1H in $COCH_2$) 4.08 (m, 1H, CHPO), 5.02 (s, 2H, OCH_2), 6.26 (s, br, 1H, NH), 7.34–7.70 (m, 12H, ArH, POH & NH); ^{13}C NMR (100.6 MHz, DMSO-d_6) δ: 18.2 (d, J_{P-C}=4.0 Hz), 20.9 (d, J_{P-C}=15 Hz), 27.9, 43.3, 52.8 (d, J_{P-C}=108 Hz), 65.4, 127.6, 127.7, 128.0 (d, J_{P-C}=12 Hz), 128.3, 131.3 (d, J_{P-C}=10 Hz), 131.5, 132.6 (d, J_{P-C}=7 Hz), 133.8 (d, J_{P-C}=5 Hz), 137.1, 156.3, 169.1; ^{31}P NMR (162.0 MHz, DMSO-d_6) δ: 23.5, 26.4 (85% H_3PO_4 as an internal standard); HRMS (ESI) calcd for $C_{20}H_{26}N_2O_5P$ $[M+H]^+$ 405.1573; found 405.1577.

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Supplementary data

Analytical data of representative phosphinopeptides **5**, copies of the ^1H NMR and ^{13}C NMR spectra of phosphinopeptide **4**, phosphinodepsipeptides **7**, and phosphinopeptides **5**. Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2013.04.032. These data include MOL files and InChiKeys of the most important compounds described in this article.

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