Synthetic strategies of phosphonodepsipeptides

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Abstract
Phosphonodepsipeptides are phosphorus analogues of depsipeptides and phosphonate-linked analogues of naturally occurring peptides. They are more stable than phosphonopeptides and have been widely applied as enzyme inhibitors, haptens for the production of antibodies, biological agents, and prodrugs. The synthetic strategies towards phosphonodepsipeptides are reviewed, including the phosphorylation of hydroxy esters with phosphonochloridates, the condensation of phosphonic monoesters and hydroxy esters, the alkylation of phosphonic monoesters with 1-(alkoxycarbonyl)alkyl halides or sulfonates, multicomponent condensation of amides, aldehydes, and dichlorophosphites followed by alcoholysis with hydroxy esters, the phosphorylation of hydroxy esters with phosphonochloridites followed by oxidation, and the carbene insertion of \( N \)-protected amino acids with 1-diazoalkylphosphonates. This review includes the synthesis of \( \alpha \)-, \( \beta \)-, and \( \gamma \)-phosphonodepsipeptides and phosphonodepsipeptides with C-1-hydroxyalkylphosphonic acids.

Introduction
Both, phosphonopeptides and phosphonodepsipeptides are phosphorus analogues of peptides [1-5]. The phosphonopeptides are peptides with a phosphonamidate bond instead of an amide bond whereas the phosphonodepsipeptides are peptides with a phosphonate linkage instead of an amide. Phosphonodepsipeptides are structurally close analogues of depsipeptides (Figure 1). In general, phosphonodepsipeptides are more stable than the corresponding phosphonopeptides because the phosphonate bond is more inert than a phosphonamidate bond. Phosphonodepsipeptides are widely used as enzyme inhibitors [6-10], haptens for inducing catalytic antibodies [11,12], and produgs [8,9,13]. They have potential applications as antibiotics [14], antimicrobials [15], antimalarials [16], antitumor agents [17], and medicinal agents [18]. Thus, much attention has been paid to the synthesis of phosphonodepsipeptides.

To date, diverse synthetic strategies of phosphonodepsipeptides have been developed. The strategies comprise the phosphorylation of hydroxy esters with \( N \)-protected aminooalkylphosphonochloridates (method I), reactions of \( N \)-protected aminooalkylphosphonic monoesters with hydroxy esters (method II) or with 1-(alkoxycarbonyl)alkyl halides or...
Review

Synthesis of phosphonodepsipeptides via the phosphonylation of hydroxy esters with phosphonochloridates

The phosphonylation of hydroxy esters 2 with alkyl N-protected aminoalkylphosphonochloridates 3 is a general and widely applied method for the synthesis of α-, β-, and γ-phosphonodepsipeptides 1. The N-protected aminoalkylphosphonic monomethyl/ethyl esters are very useful materials for the preparation of N-protected aminoalkylphosphonochloridates 3. N-Protected aminoalkylphosphonic diaryl esters should be converted into the corresponding monomethyl/ethyl esters via transesterification and selective hydrolysis.

Synthesis of α-phosphonodepsipeptides

In 1987, a series of phosphonodepsipeptides 10 was synthesized as phosphorus analogues of peptides and evaluated as inhibitors of leucine aminopeptidase from porcine kidney and two compounds, i.e., 10e and 10h (R = isobutyl, benzyl) were modest inhibitors. The synthesis started from diphenyl N-Cbz-1-aminoalkylphosphonates 11 (Scheme 1). They were transformed to dimethyl esters via transesterification and further to monomethyl esters 12 via basic hydrolysis. After chlorination...
with thionyl chloride, the monomethyl esters 12 were converted into N-Cbz-1-aminoalkylphosphonochloridates 13, which were further coupled with methyl (S)-2-hydroxy-4-methylpentanoate (14), affording the protected phosphonodepsidipeptides 15. Finally, after deprotection the free phosphonodepsidipeptides 10 were obtained [19].

The disodium salts of the trans and cis isomers of 2-hydroxy-2-oxo-3-[(phenoxyacetyl)amino]-1,2-oxaphosphorinane-6-carboxylic acid (16, Figure 3) were prepared and evaluated as inhibitors of the zinc-containing β-lactamase II from B. cereus. However, neither stereoisomer had any significant activity [6].

The phosphonodepsidipeptide 17 was synthesized via the coupling of methyl N-Cbz-1-aminoethylphosphonochloridate (13b) generated from phosphonic monomethyl ester 12b and methyl (S)-2-hydroxy-4-methylpentanoate (14) followed by hydrogenolysis. It was further coupled to cyclen to afford various cyclen-containing phosphonodepsipeptides as inhibitors of carboxypeptidase A (Scheme 2) [20].

VanX is a Zn(II)-dependent d-Ala-d-Ala dipeptidase. To prepare novel inhibitors of VanX, N-[[(1-aminoethyl)hydroxyphosphinyl]-d-lactate (20a), and S-[aminoethyl)hydroxyphosphinyl][thio]acetic acid (20b) were synthesized via coupling of the methyl N-Cbz-protected 1-aminoethylphosphono-

Scheme 1: Synthesis of α-phosphonodepsidipeptides as inhibitors of leucine aminopeptidase.

Scheme 2: Synthesis of α-phosphonodepsidipeptide 17 as coupling partner for cyclen-containing phosphonodepsipeptides as inhibitors of carboxypeptidase A.

Scheme 3: Structure of 2-hydroxy-2-oxo-3-[(phenoxyacetyl)amino]-1,2-oxaphosphorinane-6-carboxylic acid (16).

Scheme 4: Synthesis of phosphonodepsidipeptide 2-[(1-aminoethyl)(hydroxy)phosphoryl]oxy]propanoic acid (25b).

It was discovered that the enzymatic activity of VanX was inhibited competitively by phosphonodepsidipeptide 2-[[[(1-aminoethyl)hydroxy]phosphoryl]oxy]propanoic acid (25b). Seven phosphonodepsidipeptides 25 as analogues of d-Ala-d-Ala with various substituents were prepared through the reaction of methyl N-Cbz 1-aminoethylphosphonochloridate (13b) with different benzyl 1-hydroxyalkanoates 26 followed by hydrogenolysis and hydrolysis. The bioassay results indicated that six out of the seven synthetic phosphonodepsidipeptides 25 inhibited VanX with IC₅₀ values ranging from 0.48 to 8.21 mM (Scheme 4) [7].
Two optically active phosphonodepsidipeptides 28 were prepared and investigated as VanX inhibitors. The racemic N-Cbz 1-aminoethylphosphonic acid (29) was separated by chemical resolution with quinine, affording the (S)-N-Cbz-1-aminoethylphosphonic acid ((S)-29), which was transformed to the corresponding phosphonochloridate and further reacted with benzyl (R)-lactate ((R)-26b) or benzyl (R)-2-phenyllactate ((R)-26f). The optically active phosphonodepsidipeptides 28 were obtained after hydrogenolysis and tested for their biological activity (Scheme 5) [22].

The phosphonodepsidipeptides 31 were synthesized by the esterification of N-Cbz-aminoalkylphosphonic acids 32 and 4-nitrobenyl 2-hydroxyalkanoates 33 in the presence of SOCl$_2$.
in DMF. This was an efficient coupling reaction for the synthesis of phosphonodepsipeptides from \( N \)-protected phosphonic acids and hydroxy esters. The phosphonodepsipeptide 31 (\( R^1 = R^2 = H \), Scheme 6) was converted to the free phosphonodepsipeptide 34 in 80\% yield and the \( N \)-Cbz-phosphonodepsipeptide 35 in 85\% yield, respectively, via hydrogenolysis and basic hydrolysis, respectively (Scheme 6) [23]. The method actually is a convenient and direct method to synthesize phosphonodepsipeptides from \( N \)-protected phosphonic acids and hydroxy esters through phosphonochloridates as in situ-generated intermediates.

To prepare an antigen to induce monoclonal catalytic antibodies capable of catalyzing peptide-bond formation reactions, the phosphonodepsipeptide 39 was synthesized via the coupling of the hydroxy analog of tryptophan amide with 4-nitrobenzyl (\( R \))-\( N \)-Fmoc 1-amino(cyclohexyl)methylphosphonochloridate (38), which was prepared from diethyl (\( R \))-\( N \)-Fmoc 1-amino(cyclohexyl)methylphosphonate (36) via a selective basic hydrolysis, chlorination, esterification with 4-nitrobenzyl alcohol, selective basic hydrolysis, and chlorination. After the treatment of compound 39 with piperidine, the \( N \)-terminal free dipeptide was obtained and acylated with hexanedioic anhydride to afford the designed hapten 40 (Scheme 7) [11].

Phosphonodepsioctapeptide 41 was prepared as a variation of the partial sequence of a gene product of erb B-2. Two different hydroxypeptide esters 46 were first prepared and successful-
Scheme 8: Synthesis of $\alpha$-phosphonodepsioctapeptide 41.
Scheme 9: Synthesis of phosphonodepsipeptides via an in situ-generated phosphonochloridate.

(S)-2-hydroxy-3-phenylpropanoate (60) to give rise to the phosphonodepsidipeptide 61. The phosphonodepsidipeptide 61 was also obtained directly by the oxidation of the phosphinate 59 with carbon tetrachloride in the presence of the hydroxy ester 60. After hydrogenolysis of 61 and coupling with various N-protected dipeptides 62, the N-protected phosphonodeptides 63 were obtained and further transformed to the N-protected phosphonodepsipeptide ester lithium salts 58 after aminolysis with tertiary butylamine and treatment with Dowex-Li⁺ (Scheme 10) [26].

Synthesis of α-phosphonodepsipeptides

To develop iminocyclitol-based small molecule libraries against a bacterial TGase, an iminocyclitol was conjugated with a pyrophosphate mimic. After in situ screening, the first potent iminocyclitol-based inhibitor against bacterial TGases was efficiently developed [27].

The synthesis of N-pyrrolidine-derived β-phosphonodepsipeptides 64 is shown in Scheme 11. First, dibenzyl allylphosphonate (65) was converted to benzyl allylphosphonochloridate

Scheme 10: Synthesis of α-phosphonodepsitrapeptides 58 as inhibitors of the aspartic peptidase pepsin.
Scheme 11: Synthesis of a β-phosphonodepsipeptide library 64.

(66), which was then coupled with benzyl 2-azido-3-hydroxy-2-methylpropanoate (67) producing benzyl [allyl(benzyloxy)phosphoryl]oxy]propanoate (68). After the dihydroxylation with osmium tetroxide and oxidation with sodium periodate, benzyl 2-azido-3-((benzyloxy)(2-oxoethyl)phosphoryl]oxy)-2-methylpropanoate (69) was obtained. The latter was further transformed to the final phosphonodepsipeptide library 64 after the reductive amination with pyrrolidine derivatives 70 and acylation with a library of carboxylic acids 72 in the presence of coupling reagents (Scheme 11) [27].

Alternatively, the 1,3-protected glycerol 73 was first converted into various 2,3-protected glycerols 74, which were further transformed to methyl 2-alkoxy-3-hydroxypropanoates 75. Following a similar strategy as above, another library of phosphonodepsipeptides 78 was prepared (Scheme 12) [27].

Scheme 12: Synthesis of another β-phosphonodepsipeptide library.
Synthesis of γ-phosphonodepsipeptides

γ-Phosphonodepsipeptides 79 have been prepared from N-Cbz-L-glutamic acid (80) and diethyl 2-hydroxyglutarate (84). To prepare phosphorus analogues of γ-glutamyl peptide, the starting N-Cbz-L-glutamic acid (80) was first transformed to the corresponding dimethyl phosphonate 81. After aminolysis and chlorination the corresponding phosphonochloridate 83 was obtained. The latter was further reacted with diethyl 2-hydroxyglutarate (84), affording γ-phosphonodepsipeptide 79 in only 6.7% yield, indicating that this strategy was not suitable for the synthesis of γ-phosphonodepsipeptides (Scheme 13) [28].

Folylpolyglutamate synthetase catalyzes an ATP-dependent ligation reaction. The reaction results in the synthesis of poly(γ-glutamate) metabolites of folates and some antifolates. Three γ-phosphonodepsipeptide derivatives 85 were designed as prototypes and mechanism-based folylpolyglutamate synthetase inhibitors. The synthesis started with dimethyl N-phthaloyl-protected γ-aminophosphonate 86 that was selectively hydrolyzed with thiophenol, affording the corresponding phosphonic monomethyl ester 87. The ester 87 was then coupled with dibenzyl (S)-2-hydroxypentanedioate (88) using BOP as the activating agent to generate the γ-phosphonodepsipeptide 89. After hydrazinolysis, acylation with arenecarbonyl chlorides or arenecarboxylic acids, and further modification, the γ-phosphonodepsipeptide derivatives 85 were obtained. The phosphonate moiety in these analogues represented an important new lead in the development of folylpolyglutamate synthetase inhibitors (Scheme 14) [29].

γ-Phosphonodepsipeptides were also designed and synthesized as potent inhibitors and active site probes of γ-glutamyl transpeptidase, which catalyzes the transfer of the γ-glutamyl group of glutathione and related γ-glutamyl amides to amino acids and peptides (transpeptidation) or to water (hydrolysis). For this purpose, N-Cbz-aminophosphonic acid 91 was first transformed to the corresponding dichloride 92, which under-
went a sequential alcoholyysis with phenol and benzyl (4-hydroxybutanoyl)glycinate (93), respectively, to give the protected phosphonodepsitripeptide 94. After hydrogenolysis, the free γ-phosphonodepsitripeptide 95 was obtained (Scheme 15) [30].

Seven years later, various enantiopure 2-hydroxyalkanoic acids 96 were prepared from optically pure amino acids and converted to the benzyl or methyl [2-hydroxyalkanoyl]glycinates 97. Following the similar strategy, phosphonodepsitripeptides 99 and 102 were synthesized. The phosphonodepsidipeptide 104 was prepared through the sequential coupling of N-Cbz-γ-aminophosphonodichloride 92 with phenol and methyl (S)-2-hydroxypentanoate (18). All synthetic phosphonodepsipeptides 99, 102, and 104 were considered as glutathione-analogue phosphonopeptides as mechanism-based inhibitors of γ-glutamyl transpeptidase for probing the cysteinyl-glycine binding site (Scheme 16) [31].
Synthesis of phosphonodepsipeptides via the condensation of phosphonic monoesters and hydroxy esters

The condensation of N-protected aminoalkylphosphonic monoesters and hydroxy esters is an alternative general strategy that has been widely used for the synthesis of phosphonodepsipeptides with various coupling reagents including the Mitsunobu reagent.

**Synthesis of α-phosphonodepsipeptides**

\( \text{N,N'-Dicyclohexylcarbodiimide (DCC)} \) was the first attempted coupling reagent in the synthesis of phosphonyl depsipeptides \( 108 \) from hydrogen 4-phenylbutylphosphinic acid \( 105 \) and 2-hydroxypropanoic acid derivatives \( 106 \) followed by oxidation. The corresponding phosphinyl depsipeptides \( 107 \) were generated and further oxidized into phosphonyl depsipeptides \( 108 \) (Scheme 17) [32].

The protected phosphonodepsidipeptides \( 111 \) were prepared without racemization from \( \text{N-Cbz-protected α-aminoalkylphosphonic monomethyl (12h)} \) or benzyl esters \( 109 \) and hydroxy esters \( 110 \) by using \( (1H\text{-benzotriazol-1-yloxy})\text{trimethylamino} \)phosphonium hexafluorophosphate \( (\text{BOP}) \) or \( (1H\text{-benzotriazol-1-yloxy})\text{tripyrrolidinophosphonium hexafluorophosphate} \) \( (\text{PyBOP}) \) as activating agents as well (Scheme 18) [33].

The synthetic method was further investigated and compared with alternative coupling reagents. Various optically active phosphonodepsipeptides \( 113–118 \) were synthesized. The reaction mechanism was further studied, revealing that the reaction proceeds through benzotriazolyl esters as was shown by the comparison with other coupling reagents, including DCC, DCC/DMAP, DCC/1-hydroxybenzotriazole (HOBt), bromotris(dimethylamino)phosphonium hexafluorophosphate \( (\text{BroP}) \), or \( O-(1H\text{-benzotriazol-1-yl})\text{-N,N',N'-tetramethyluronium hexafluorophosphate} \) \( (\text{HBTU}) \) and by \( ^{31}\text{P} \) NMR analysis. The results indicated that the intermediates, benzotriazolyl phosphonates, were more reactive toward alcohols (hydroxy esters) than toward amines (amino esters), contrary to their carboxylic partners (Scheme 19) [34].

Vancomycin resistance became a serious health care problem currently. The development of a catalytic monoclonal antibody to hydrolyze the depsidipeptide \( \text{d-Ala-d-Lac} \) was a new antibiotic strategy. In this regard, the phosphonodepsipeptide hapten \( 127 \) was designed to induce the antibody. First, \( \text{N-Boc-(S)-1-aminoethylphosphinic acid} \) \( 122 \) was coupled with benzyl alcohol in the presence of DCC as the coupling reagent, affording the benzyl \( N\text{-Boc-1-aminoethylphosphinate} \) \( 123 \). Oxidation with sodium periodate and neutralization with adamantant-1-amine \( 124 \), afforded the adamantant-1-ammoni-
um benzyl phosphonate 125. After treated with hydrochloride and coupled with benzyl d-lactate ((R26b) with BOP as activating reagent, the ammonium compound 125 was transformed to the protected phosphonodepsidipeptide 126 (Scheme 21) [12], that was further converted to the designed hapten 127. The new muramyl dipeptide (MDP) phosphorus analogue 131 related to LK 423 as potential immunomodulator was prepared by the coupling of methyl 1-(N-benzyloxycarbonyl)aminophosphonate (12b) and (R)-2-hydroxyglutaric acid dimethyl ester (128) with BOP as coupling reagent, followed by
hydrogenolysis and coupling with 2-(2-phthalimidoethoxy)acetic acid (130). The amide bond between l-Ala and d-Glu was replaced by a phosphonate isostere, giving the phosphonodepsipeptide 131 (Scheme 22) [36].

The synthesis of the norleucine-derived phosphonodepsipeptides 135 and 138 was realized by a BOP-activated coupling of N-Cbz-1-aminopentylphosphonic monobenzyl ester (132), a phosphorus analogue of norleucine, with derivatives 133 and 136 of (S)-lactic or glycolic acids followed by hydrogenolysis (Scheme 23) [37].

Following a similar strategy, phosphonodepsidipeptides 141 and phosphonodepsitripeptides 144 were synthesized as norleucine-derived phosphonopeptides (Scheme 24) [38].

The protected phosphonodepsipeptide 145 was applied in a solid-phase phosphonodepsipeptide synthesis. After hydrogenolysis and reaction with Fmoc-OSu, the N-protected phosphonodepsipeptide 145 was transformed to the N-Fmoc-protected phosphonodepsidipeptide 147, which was then coupled with the resin-loaded Cys(Trt)-NH-resin 148. The resin-loaded tripeptide 149 was deprotected with piperidine, coupled with Fmoc-Tyr(Ort-Bu) 150, deprotected again with piperidine, and cleaved with TFA and trapping agents. The free phosphonodepsipeptide 151 was obtained in 45% yield after HPLC purification (Scheme 25) [38].

A general and high yielding synthesis of phosphonodepsidipeptides 152 was realized via a Mitsunobu reaction of the N-Cbz-1-aminophosphonic monomethyl esters 12b,d and hydroxy esters 106 followed by the selective demethylation with TMSBr in a one-pot reaction. The method provides a mild route to prepare phosphonodepsipeptides. The yields were insensitive to the steric encumbrance of both reactants being coupled (Scheme 26) [39].
Scheme 23: Synthesis of norleucine-derived phosphonodepsipeptides 135 and 138.

Scheme 24: Synthesis of norleucine-derived phosphonodepsipeptides 141 and 144.
Synthesis of γ-phosphonodepsipeptides

To prepare phosphorus analogues of γ-glutamyl peptide, N-Chz-γ-glutamic acid (80) was initially converted to the corresponding dimethyl phosphonate 81 and further to the methyl phosphonic monoester 82. The ester 82 was then coupled with diethyl 2-hydroxyglutarate (84) in a Mitsunobu reaction to generate the γ-phosphonodepsipeptide 79 in a high yield of 66% (Scheme 27) [28].

Scheme 25: Solid-phase synthesis of phosphonodepsipeptides.

Scheme 26: Synthesis of phosphonodepsipeptides via the Mitsunobu reaction.

Scheme 27: Synthesis of γ-phosphonodepsipeptide via the Mitsunobu reaction.
Synthesis of phosphonodepsipeptides via the multicomponent condensation of amides, aldehydes, and phosphites followed by alcoholysis with hydroxy esters

Previously, the Mannich-type reaction of benzyl carbamate, aldehydes, and trialkyl phosphites in acetyl chloride gave rise to N-Cbz-1-aminoalkylphosphonates [40]. When the reactions were conducted in benzene followed by an aminolysis or alcoholysis, phosphonamidates [41], phosphonopeptide [42], and mixed esters [43,44] were obtained directly. The multicomponent condensation reaction was applied as a direct synthetic method for phosphonodepsipeptides via the formation of 1-aminoalkylphosphonic acids and simultaneous construction of the phosphonate bond. A series of phosphonodepsipeptides 158 was prepared in good yields in a one-pot reaction directly from the simple and commercially available chemicals, benzyl carbamate (154), aldehydes 155, and methyl dichlorophosphite (156), followed by the alcoholysis with the hydroxy esters 157. The current strategy is a highly efficient and convergent synthesis of phosphonodepsipeptides that does not require the preparation of 1-aminoalkylphosphonic acid or 1-aminoalkylyphosphonous acid derivatives first as starting materials (Scheme 28) [42].

Similarly, phosphinopeptides [45,46], phosphinodepsipeptides [47], and hybrid sulfonophosphinopeptides [48,49] were prepared from amino amides and 2-aminoalkanesulfonamides by using this strategy.

Also side-chain functionalized phosphonodepsipeptides 160 were prepared in satisfactory yields directly through the one-pot reactions of benzyl carbamate (154), aldehydes 155, and diethyl (R,R)-2-chloro-1,3,2-dioxaphospholane-4,5-dicarboxylate (159), which was synthesized from diethyl L-tartrate and phosphorus trichloride. A pair of diastereomeric products 160 was obtained in diasteromeric ratios of 1.7:1.0 to 2.5:1.0. The configuration of the major diastereomeric product was determined by hydrolysis of the product 160a and comparison of the obtained acid (R)-161a with the corresponding reported authentic sample (Scheme 29) [50].

A straightforward method for the synthesis of phosphonodepsi-peptides 163 was developed via the multicomponent condensation reaction of the simple starting materials, benzyl carbamate (154), aldehydes 155, and 1-ethoxycarbonylalkyl phosphorodichloridites 162, which were prepared from ethyl 2-hydroxyalkanoates 157 and phosphorus trichloride. Compared with the...
previous methods, the current strategy provides a more efficient, convenient, convergent, and practical synthetic route to phosphonodepsipeptides 163 under mild reaction conditions with good yields. Good diastereoselectivities were observed with diastereomeric ratios of 84:12 to 88:12 (Scheme 30) [51]. However, when using substrates with arylmethyl groups, the phosphorodichloridites favored an elimination reaction generating the corresponding ethyl cinnamate derivatives during their preparation.

To prepare optically active phosphonodepsipeptides, ethyl (R)-2-((dichlorophosphanyl)oxy)-2-phenylacetate ((R)-162c) was first prepared through the reaction of ethyl (R)-2-hydroxy-2-phenylacetate and phosphorus trichloride and further reacted with benzyl carbamate (154) and benzaldehyde (155a), affording a pair of optically active phosphonodepsipeptides 164 and 165 in an 86% yield and 85:15 diastereomeric ratio (Scheme 31) [51].

Following a similar strategy, the three component condensation of diethyl phosphoramidate (166), aromatic aldehydes 167, and diisopropyl (4R,5R)-2-chloro-1,3,2-dioxaphospholane-4,5-dicarboxylate (168) gave the corresponding phosphonodepsipeptides 169 in 65–86% yields under mild conditions. Although the diisopropyl ester was applied instead of diethyl t-tartrate, a low diastereoselectivity (ratios varied from 55:45 to 67:33) was observed as well. Acetophenone (170) produced the desired product 171 in 62% yield in the reaction. However, aliphatic aldehydes did not work (Scheme 32) [52].

**Synthesis of phosphonodepsipeptides via the alkylation of phosphonic monoesters with 1-(alkoxycarbonyl)alkyl halides or sulfonates**

The alkylation of N-protected 1-aminoalkylphosphonic monoesters with 1-(alkoxycarbonyl)alkyl halides or sulfonates is also a general method for the synthesis of phosphonodepsipeptides. However, the strategy has not been utilized widely.

**Synthesis of α-phosphonodepsipeptides**

Skwarczynski and Kafarski synthesized various alkyl 1-aminoalkylphosphonates via the nucleophilic esterification of potassium 1-(N-benzylxoycarbonylamino)alkylphosphonates 172 with alkyl halides in the presence of 18-crown-6. They also prepared a phosphonodepsidipeptide 174 with ethyl chloroacetate (173) as an electrophile (Scheme 33) [53].

The macrocyclic peptidyl phosphonodepsipeptide 180 was designed on the basis of the acyclic conformational analog bound to the aspartic protease penicillopepsin. Dimethyl N-Cbz-1-amino-2-(naphthalen-2-yl)ethylphosphonate 176 was first prepared from 7-bromo-3,4-dihyronaphthalen-1(2H)-one (175) and further transformed to the macrocyclic peptidyl phosphonic
Scheme 32: Synthesis of N-phosphoryl phosphonodepsipeptides.

Scheme 33: Synthesis of phosphonodepsipeptides via the alkylation of phosphonic monoesters.

monomethyl ester 177. The latter compound was alkylated with methyl 3-phenyl-2-trifluoromethanesulfonyloxypropanoate (178) to produce the macrocyclic peptidyl phosphonodepsipeptide 179, which was selectively hydrolyzed with TMSBr and treated with Dowex-Na⁺ to afford the macrocyclic peptidyl phosphonodepsipeptide sodium salt 180. By using a similar method, two acyclic analogues 183 and 186 were synthesized as well. The macrocyclic phosphonodepsipeptide 180 and the two acyclic analogues 183 and 186 were evaluated for their potential as inhibitors. The NMR analysis results indicated that the conformation of the macrocyclic phosphonodepsipeptide backbone closely approximated that of the lead inhibitor and showed the low-energy conformation accommodated in the active site of penicillopepsin without significant distortion (Scheme 34) [54].

Synthesis of γ-phosphonodepsipeptides

The acyloxyalkyl esters 194 are derivatives of the new antimalarial drug fosmidomycin and inhibited the 1-deoxy-ᴅ-xylosone 5-phosphate reductoisomerase. The phosphonodepsipeptides 194 were synthesized as prodrugs with an increased activity after oral administration due to a chemical modification of the phosphonate moiety. For the synthesis, diethyl 3,3-diethoxypropylphosphonate (187) was hydrolyzed to 3-oxopropylphosphonate 188, which underwent a reductive amination with benzoylxyamine to give diethyl 3-benzyl-oxyaminopropylphosphonate (189). After the sequential treatment with acetyl chloride and TMSBr, alkylation with methyl or tert-butyl chloroacetate 192, and hydrogenolysis, the target phosphonodepsipeptides 194 were obtained (Scheme 35) [8,9,13].

Synthesis of phosphonodepsipeptides via phosphinylation of hydroxy esters with phosphonochloridites followed by oxidation

Hammer’s group developed a new route to prepare phosphonodepsithiopeptides 198 via the reaction of N-protected aminospirophosphoranes 196 with the hydroxy ester (S)-106b followed by sulfur oxidation. They first transformed the N-Boc-protected 1-aminoalkylphosphinite 195 to the corresponding phosphonochloridite 196 with dichlorotriphenylphosphine. The phosphonochloridite 196 was then further reacted with methyl (S)-lactate ((S)-106b) followed by sulfurization with sulfur, affording the phosphonodepsithiopeptide 198 in a one-pot activation–coupling–oxidation procedure (Scheme 36) [55]. Although it was mentioned that the phosphonochloridites were a more active species than the corresponding phosphonochloridates in the esterification, this synthetic strategy had not been applied by others. There is only one example reported till now possibly due to the inconvenient preparation of the phosphonochloridates.

Synthesis of phosphonodepsipeptides via the addition of tetraoxyspirophosphoranes to imines

The addition reaction of the P–H bond of tetraoxyspirophosphoranes 199 to long-chain imines 200 of benzaldehyde, acetaldehyde, and dodecanal at room temperature generated the corresponding (α-aminoalkyl)spirophosphoranes 201 via the Pudovik reaction. The one-pot selective hydrolysis of the P–C bond of the spirophosphoranes 201 readily proceeded at room temperature in the presence of moist solvents to give the corresponding phosphonodepsipeptides 202 in high yields (Scheme 37) [56].
An asymmetric synthesis of this class of phosphonodepsipeptides was realized with enantiopure (S)-α-hydroxyisovaleric acid-derived spirophosphoranes as the phosphorus reagents [57]. By using a similar strategy, linker-linked bisphosphonodepsidipeptides were synthesized [10]. The current method is also an interesting synthetic strategy of phosphonodepsipep-
It can realize an asymmetric synthesis of phosphonodepsipeptides.

Synthesis of phosphonodepsipeptides with C-hydroxyalkylphosphonic acids

Phosphonodepsipeptides with C-1-hydroxyalkylphosphonic acids can be considered as a class of important phosphorous analogues of depsipeptides. The coupling of N-protected amino acids and 1-hydroxyalkylphosphonates is a general method to prepare these compounds [58].

(R)-1-Amino-3-methylbutylphosphonic acid (R)-204, a phosphonic t-Leu analogue, is a potent inhibitor of the metalloenzyme leucine aminopeptidase. Racemic dibenzyl 1-hydroxy-3-
methylbutylphosphonate (203), an oxyanalog of phosphonic
leucine, was partially debenzylated by the treatment with NaI to
generate the corresponding monobenzyl ester 204. The ester
204 was resolved with (−)-ephedrine and then O-benzylated
with O-benzyl-N,N′-dicyclohexylurea (205) to give the (R)-1-
hydroxy-3-methylbutylphosphonate ((R)-203). The latter was
coupled with N-Boc-protected amino acids 206 to give the cor-
responding protected phosphonopeptides 207. After deprotec-
tion by hydrogenolysis and treatment with CF₃CO₂H, the phos-
phonodepsipeptides 208 were obtained (Scheme 38) [59].

Phosphonodepsipeptides with C-1-hydroxyaliphatic phosphonic
acids are also accessible through carbene insertion reactions.
The reaction of the N-protected amino acids 209 and 210 with
diethyl 1-diazo-2,2,2-trifluoroethylphosphonate (211) gave rise
to the trifluoromethyl-containing phosphonodepsipeptides 212
and 213 with C-1-hydroxyaliphatic phosphonic acids in good yields
under the catalysis of dirhodium tetraacetate (Scheme 39)
[60,61].

To develop novel bone-targeting prodrugs, a copper-catalyzed
carbene insertion of tetraethyl diazomethylphosphonate (216)
with N-Boc-protected amino acids 214 and 215 provided a
simple method to synthesize phosphonodepsipeptides 217 and
218 containing a C-1-hydroxyalkylphosphonate motif in good
yields (Scheme 40) [62].

The transition metal-catalyzed carbene insertion of
1-diazoalkylphosphonates and N-protected amino acids is an effi-
cient and convenient method for the synthesis of phosphonodepsipeptides with C-1-hydroxyalkylphosphonic acids because
the required 1-diazoalkylphosphonates can be readily prepared
from the corresponding 1-aminoalkylphosphonates via nitroso-
tion with amyl nitrite.

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Scheme 38: Synthesis of phosphonodepsipeptides with C-1-hydroxyalkylphosphonic acid.

Scheme 39: Synthesis of phosphonodepsipeptides with C-1-hydroxyalkylphosphonate via the rhodium-catalyzed carbene insertion.
Conclusion

Phosphonodepsipeptides are phosphorus analogues of depsipeptides. They are more stable than the corresponding phosphopeptides and have been widely used as enzyme inhibitors, hapten for the production of antibodies, biological agents, and prodrugs. Various synthetic methods of phosphonodepsipeptides have been developed, including the phosphorylation of hydroxy esters with phosphonochloridates or with phosphonic monoesters in the presence of coupling reagents, the alkylation of phosphonic monoesters with 1-(alkoxycarbonyl)alkyl halides or sulfonates, the phosphinylation of hydroxy esters with phosphonochloridites and subsequent oxidation, and the Mannich-type condensation of amides, aldehydes, and dichlorophosphites followed by alcoholysis with hydroxy esters. Among the synthetic methods, the multicomponent Mannich-type condensation strategy shows a high efficiency, convergent feature, and product diversity. It can be expected that the convergent multicomponent condensation synthetic strategy will show wide applications in the preparation of biologically active phosphonodepsipeptides in the future. However, highly stereoselective asymmetric synthetic methods of phosphonodepsipeptides are of high demand and need to be developed in the near future.

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