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Synthetic strategies of phosphonodepsipeptides

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Review

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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 phosphonylation 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 phosphinylation 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 α-, β-, and γ-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 phopshonamidate 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 **1** have been developed. The strategies comprise the phosphonylation of hydroxy esters **2** with *N*-protected aminoalkylphosphonochloridates **3** (method I), reactions of *N*-protected aminoalkylphosphonic monoesters **4** with hydroxy esters **2** (method II) or with 1-(alkoxycarbonyl)alkyl halides or

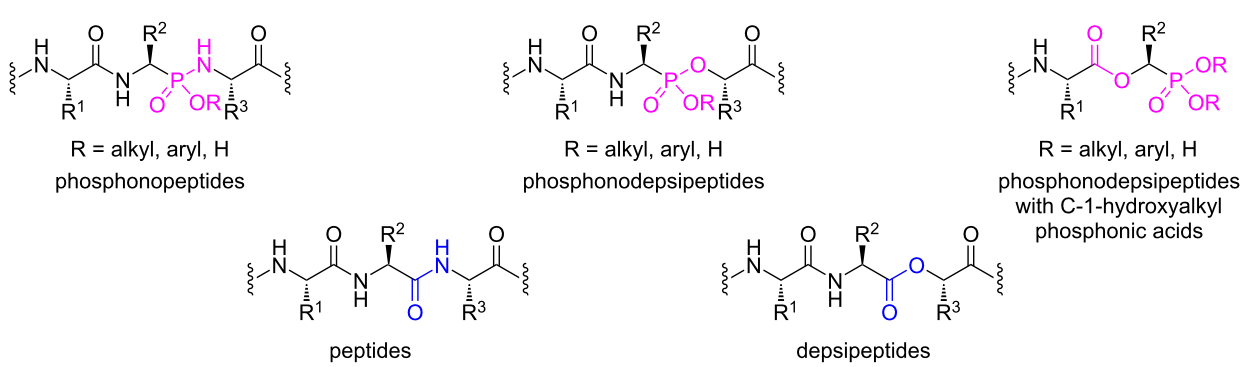


Figure 1: Phosphonopeptides, phosphonodepsipeptides, peptides, and depsipeptides.

sulfonates **5** (method III), pseudo-four-component condensations (method IV), and the phosphinylation of hydroxy esters **2** with *N*-protected aminoalkylphosphonochloridites **9** followed by oxidation (method V) (Figure 2). This review focuses on the synthetic methods of phosphonodepsipeptides and phosphonodepsipeptides with C-1-hydroxyalkylphosphonic acids, excluding peptides with side-chain phosphonic acids.

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 phosphonodepsidipeptides **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

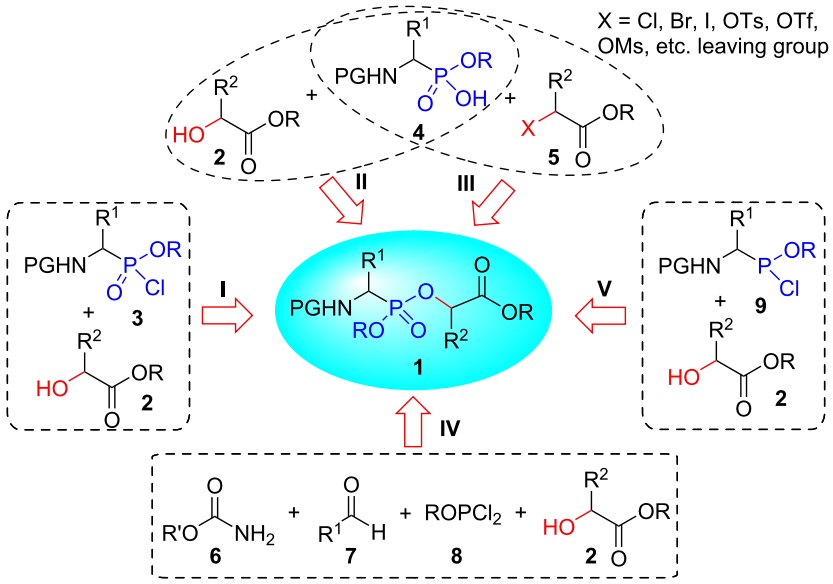
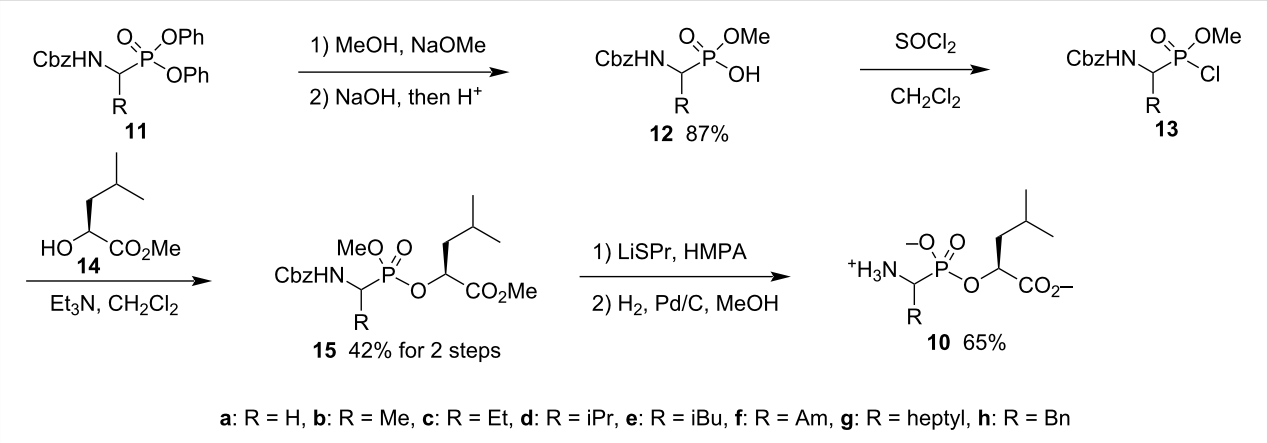


Figure 2: The diverse strategies for phosphonodepsipeptide synthesis.



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

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].

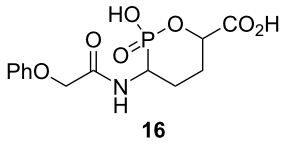
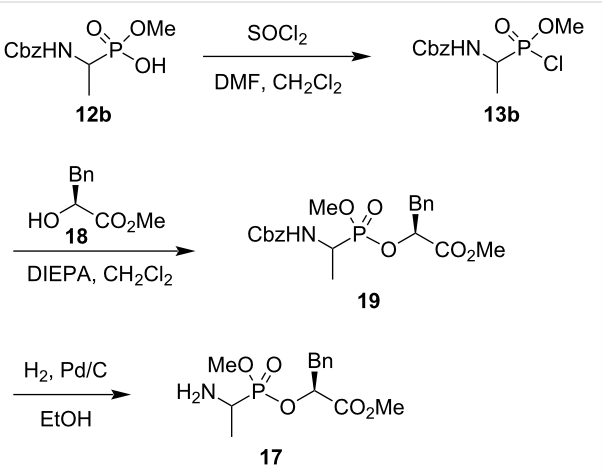


Figure 3: Structure of 2-hydroxy-2-oxo-3-[(phenoxyacetyl)amino]-1,2-oxaphosphorinane-6-carboxylic acid (**16**).

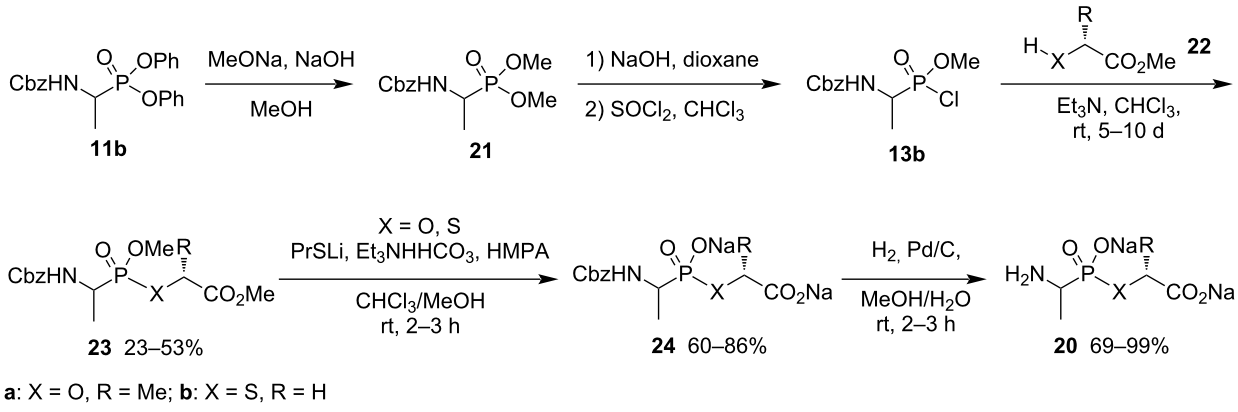
The phosphonodepsidipeptide **17** was synthesized via the coupling of methyl *N*-Cbz-1-aminoethylphosphonochloridate (**13b**) generated from phosphonic monomethyl ester **12b** and methyl (*S*)-2-hydroxy-3-phenylpropanoate (**18**) followed by hydrogenolysis. It was further coupled to cyclen to afford 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-aminoethylphosphonochloridate **13b** with methyl D-lactate (**22a**) and methyl mercaptoacetate (**22b**), respectively, followed by a basic hydrolysis and hydrogenolysis. The bioassay results indicated that the phosphonothiodepsidipeptide **20b** did not inhibit VanX (Scheme 3) [21].

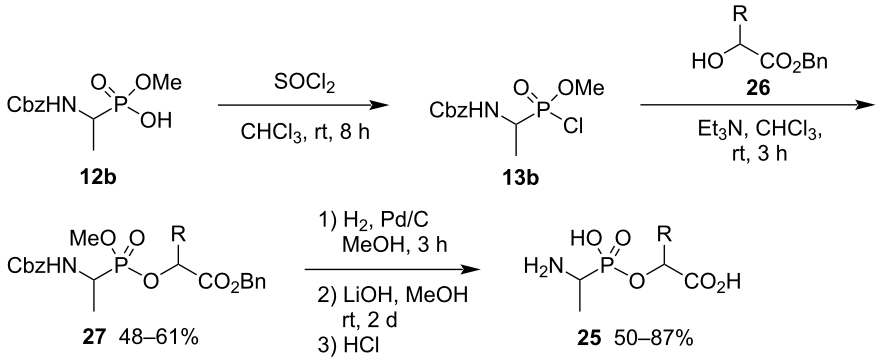


Scheme 2: Synthesis of α-phosphonodepsidipeptide **17** as coupling partner for cyclen-containing phosphonodepsipeptides as inhibitors of carboxypeptidase A.

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 phosphonodepsipeptides **25** inhibited VanX with IC_{50} values ranging from 0.48 to 8.21 mM (Scheme 4) [7].



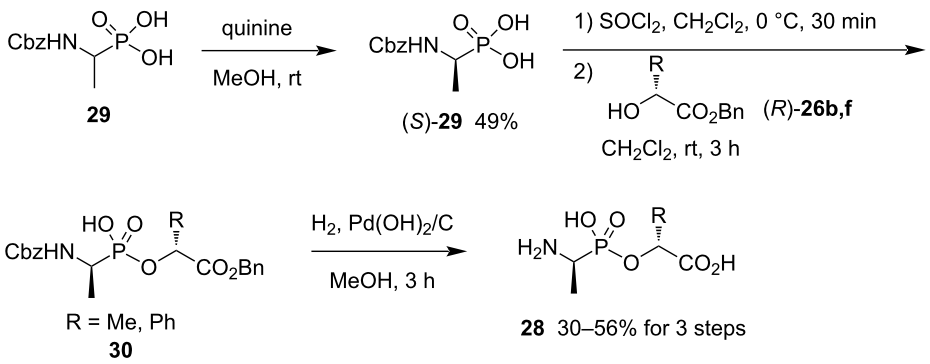
Scheme 3: Synthesis of α-phosphonodepsidipeptides containing enantiopure hydroxy ester as VanX inhibitors.



Scheme 4: Synthesis of α-phosphonodepsidipeptides as VanX inhibitors.

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 $SOCl_2$

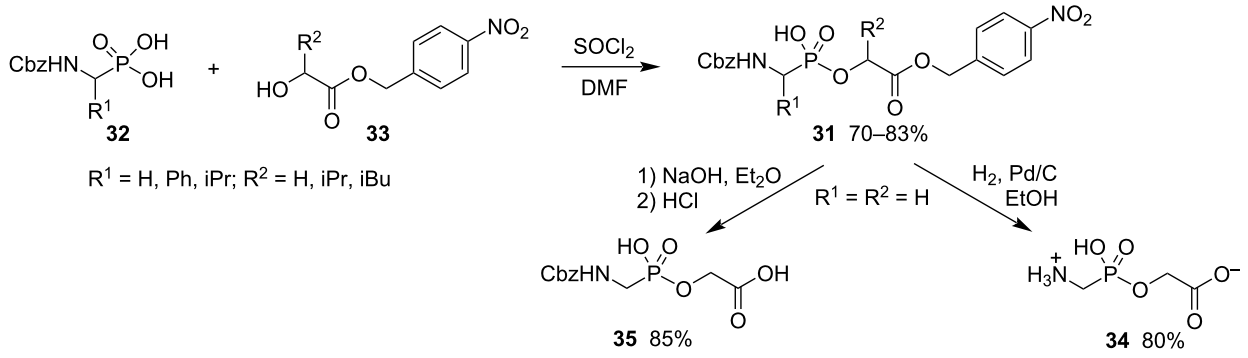


Scheme 5: Synthesis of optically active α-phosphonodepsidipeptides as VanX inhibitors.

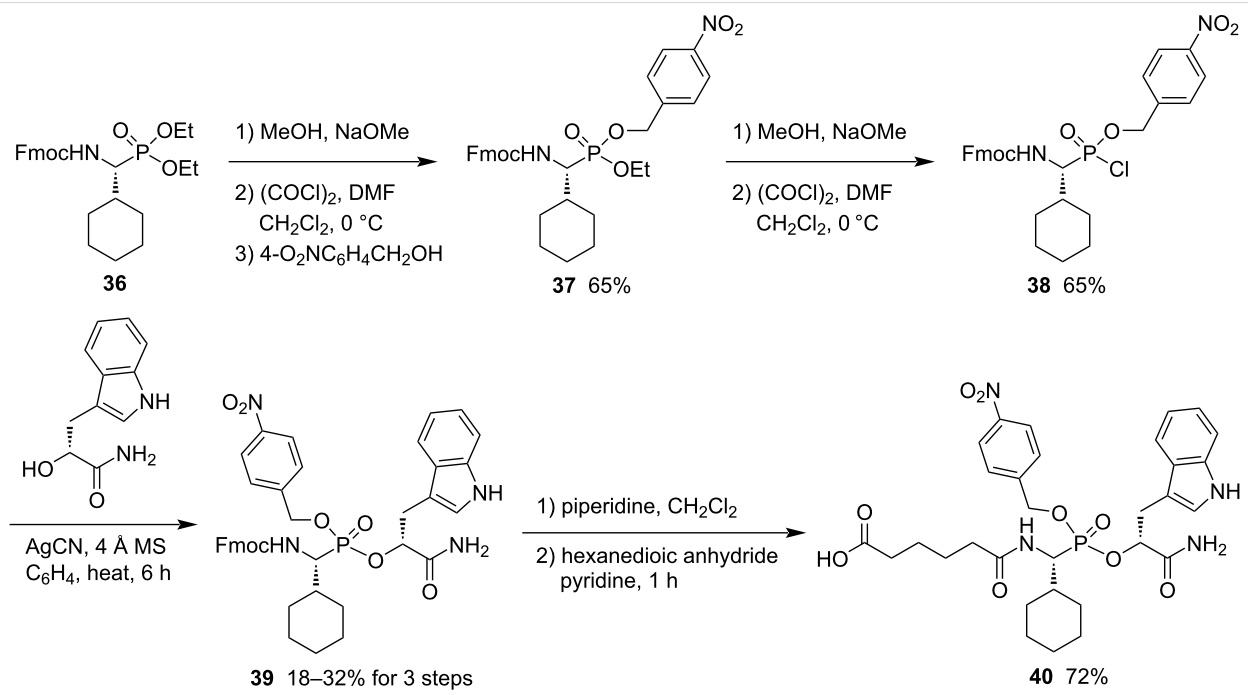
in DMF. This was an efficient coupling reaction for the synthesis of phosphonodepsipeptides from *N*-protected phosphonic acids and hydroxy esters. The phosphonodepsidipeptide **31** (R^1 = R^2 = H, Scheme 6) was converted to the free phosphonodepsidipeptide **34** in 80% yield and the *N*-Cbz-phosphonodepsidipeptide **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 phosphonodepsidipeptide **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 6: The synthesis of phosphonodepsipeptides through a thionyl chloride-catalyzed esterification of *N*-Cbz aminoalkylphosphonic acids **32** and 4-nitrobenyl 2-hydroxyalkanoates **33**.

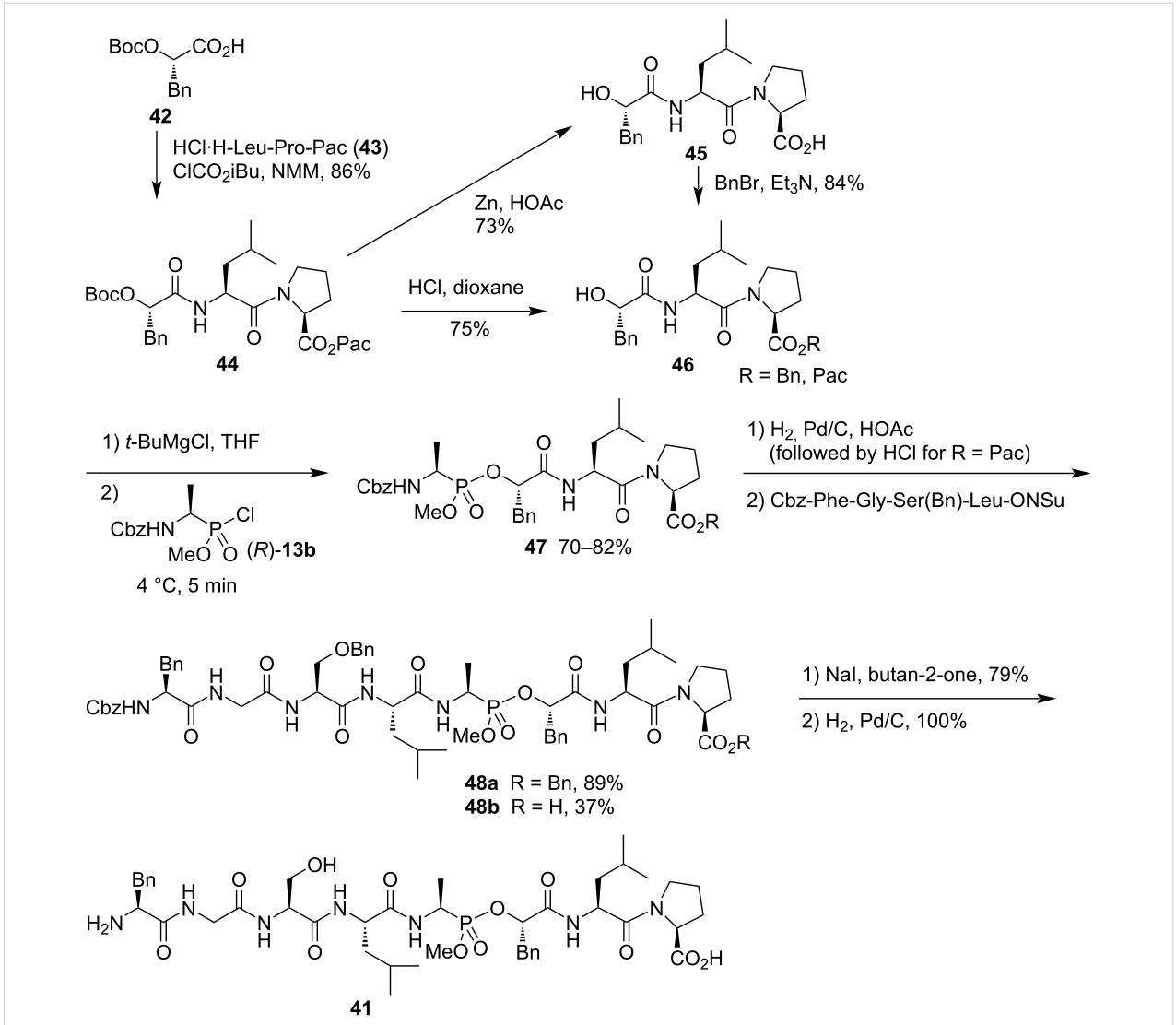


Scheme 7: Synthesis of α-phosphinodipeptidamide as a hapten.

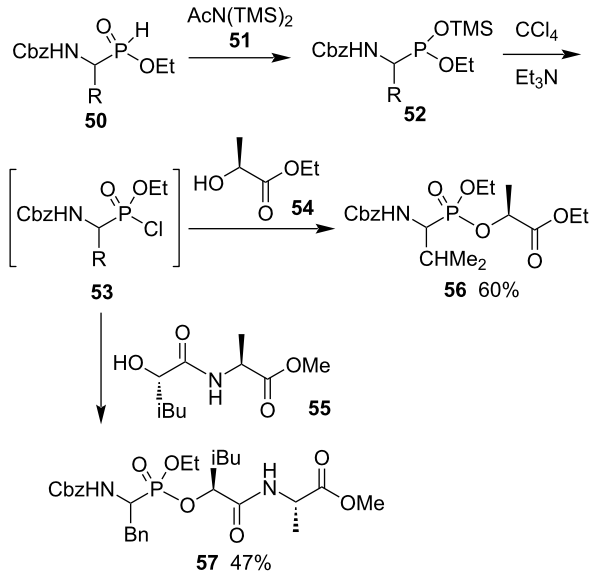
ly coupled with methyl *N*-Cbz-1-aminoethylphosphonochloridate ((*R*)-**13b**) by use of their magnesium salts because the direct coupling of the hydroxypeptide esters **46** with the phosphonochloridate (*R*)-**13b** failed. The magnesium salts were in situ generated from the hydroxypeptide esters **46** with a Grignard reagent (Scheme 8) [24].

To minimize the side reactions of 1-aminoalkylphosphonochloridates, a convenient method for the synthesis of phosphonodepsipeptides was described. The *N*-Cbz-protected 2-aminoalkylphosphinates **50** were converted to their trimethylsilyl phosphonites **52** through the treatment with bis(trimethylsilyl)acetamide (**51**). The phosphonites **52** were then oxidized with CCl_4 to generate the corresponding phosphonochloridates **53** as intermediates, which reacted with hydroxy esters **54** and **55** to give rise to the desired phosphonodepsipeptides **56** and **57**, respectively. The oxidative activation was carried out in the presence of alcohols as nucleophiles so that stoichiometric formation of the phosphonochloridate was avoided and side reactions were minimized (Scheme 9) [25]. The current chlorination is a mild and neutral method for the preparation of phosphonochloridates.

Eleven phosphonodepsitetrapeptides **58** were synthesized and evaluated as inhibitors of the aspartic peptidase pepsin. The synthesis started from methyl (*R*)-*N*-Cbz-1-amino-2-phenylethylphosphinate (**59**). In wet acetonitrile compound **59** was oxidized into the corresponding phosphonic monomethyl ester (*R*)-**12h** with carbon tetrachloride due to hydrolysis of the phophonochloridate intermediate. The phosphonic monomethyl ester (*R*)-**12h** was further chlorinated to the phosphonochloridate (*R*)-**13h**, which was coupled with 3-(pyridin-4-yl)propyl



Scheme 8: Synthesis of α-phosphonodepsioctapeptide **41**.



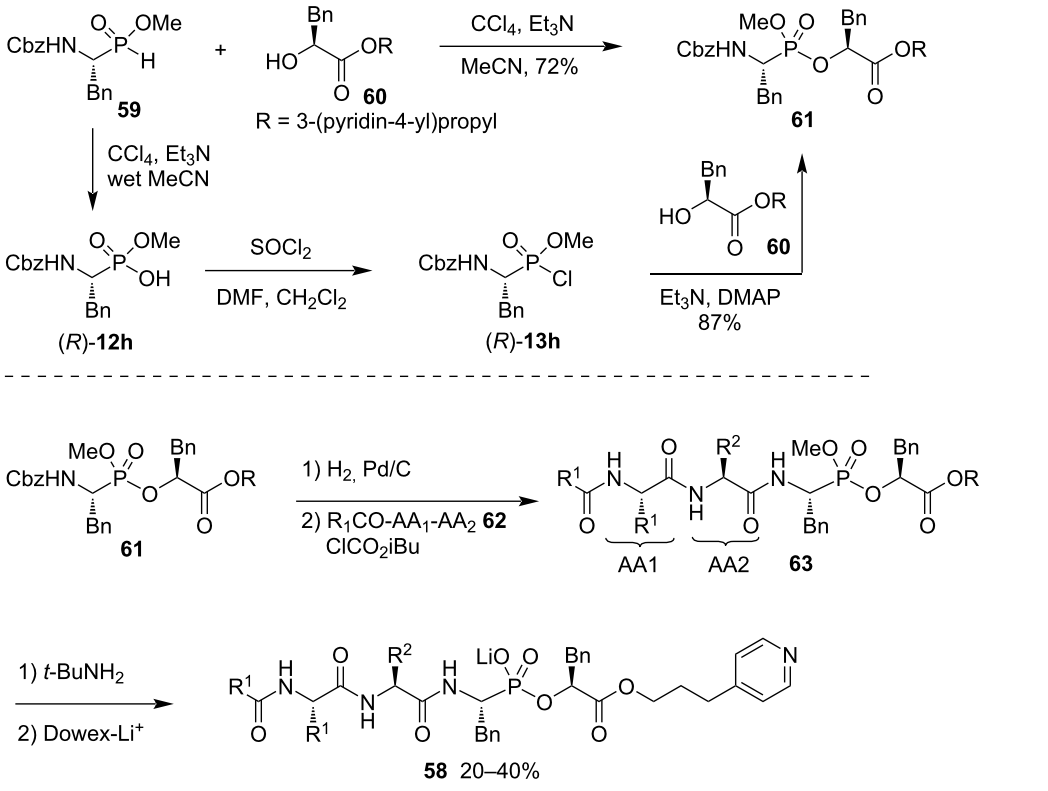
Scheme 9: Synthesis of phosphonodepsipeptides via an in situ-generated phosphonochloridate.

(*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 phosphonodepsitetrapeptides **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].

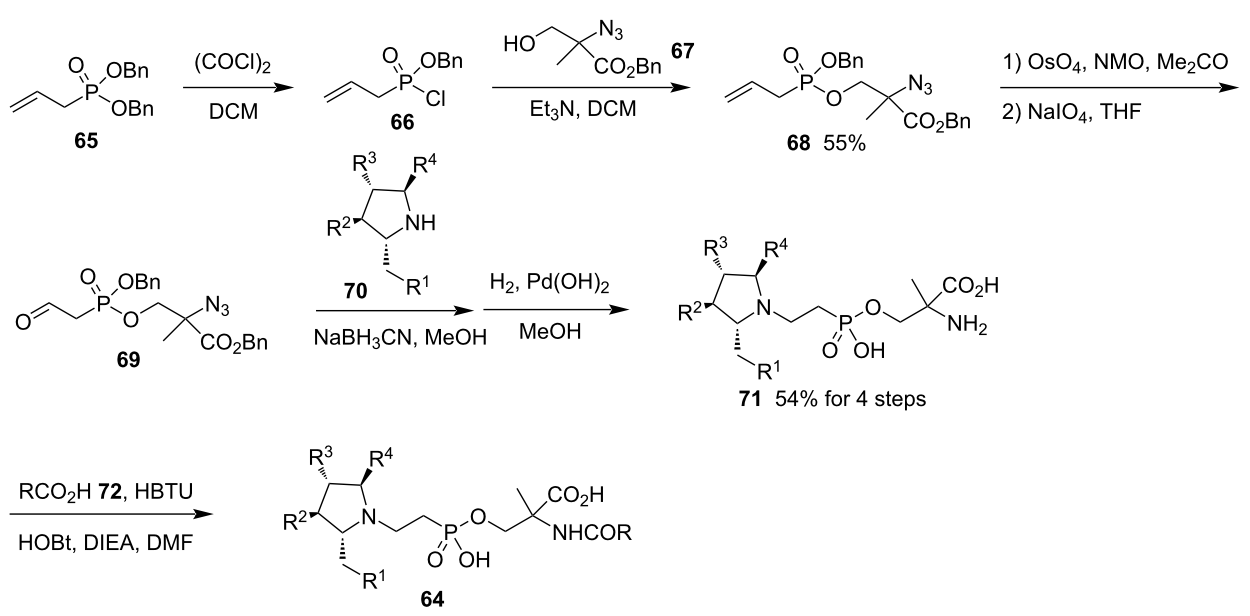
Synthesis of β-phosphonodepsipeptides

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



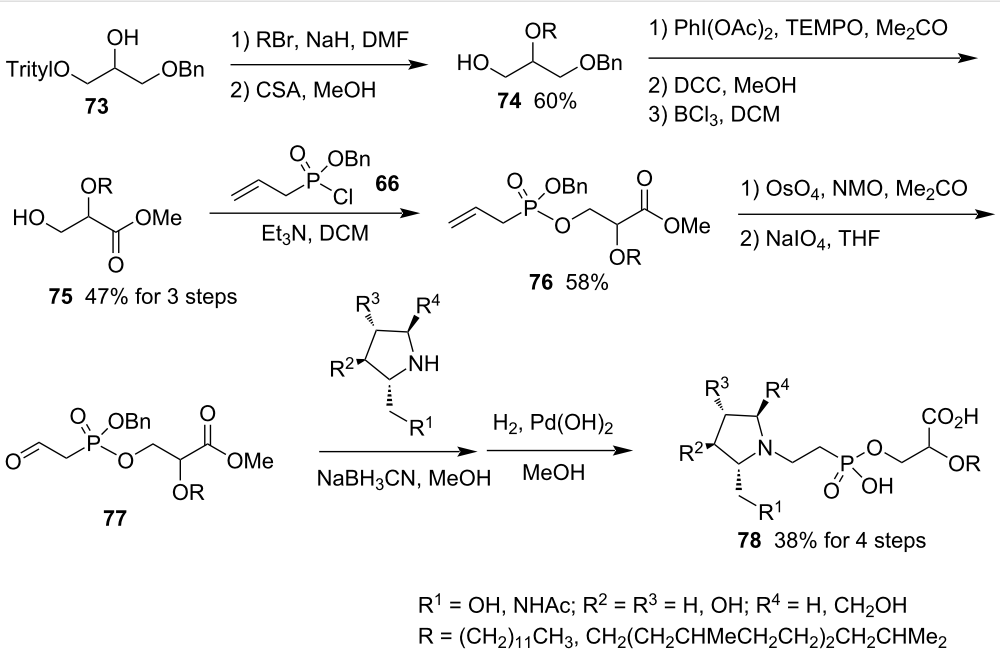
Scheme 10: Synthesis of α-phosphonodepsitetrapeptides **58** as inhibitors of the aspartic peptidase pepsin.



Scheme 11: Synthesis of a β-phosphonodepsidipeptide 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].



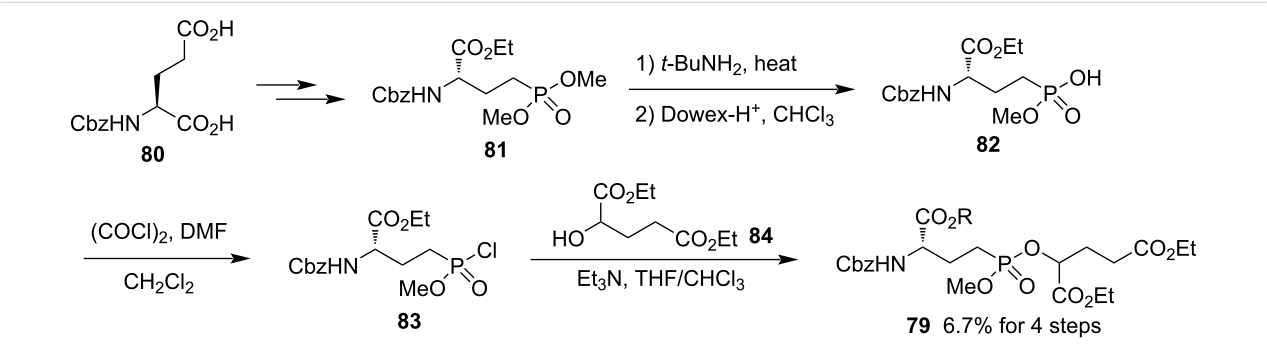
Scheme 12: Synthesis of another β-phosphonodepsidipeptide library.

Synthesis of γ-phosphonodepsipeptides

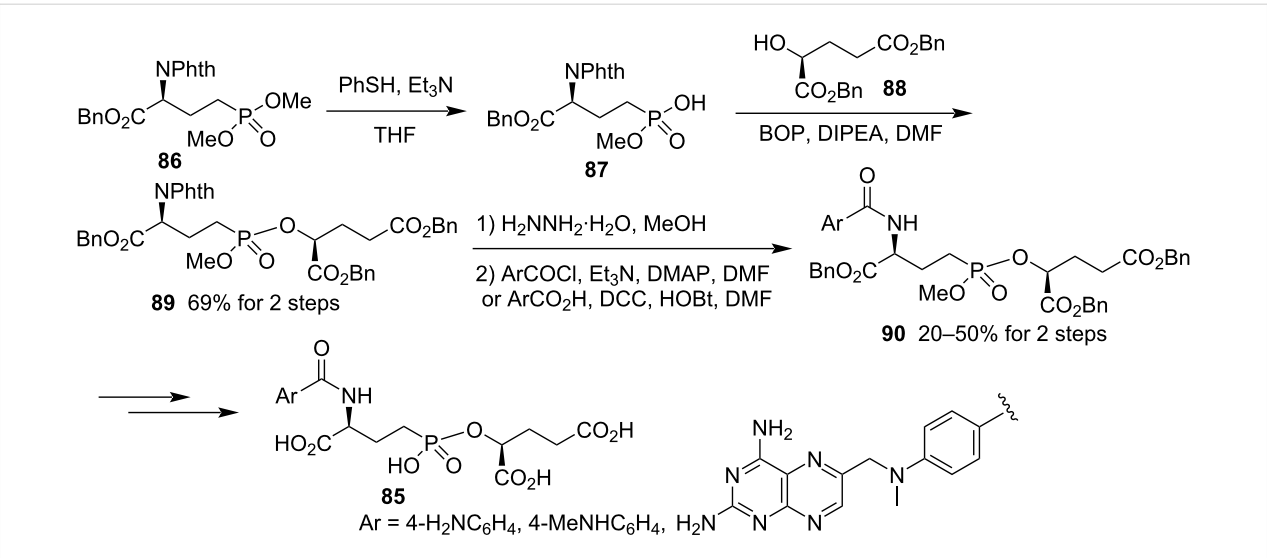
γ-Phosphonodepsipeptides **79** have been prepared from *N*-Cbz-L-glutamic acid (**80**) and diethyl 2-hydroxyglutarate (**84**). To prepare phosphorus analogues of γ-glutamyl peptide, the starting *N*-Cbz-L-glutamic acid (**80**) was first transformed to the corresponding dimethyl phosphonate **81**. After aminolysis and chlorination the corresponding phosphonochloridate **83** was obtained. The latter was further reacted with diethyl 2-hydroxyglutarate (**84**), affording γ-phosphonodepsidipeptide **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-phosphonodepsidipeptide 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-phosphonodepsidipeptide **89**. After hydrazinolysis, acylation with arenecarbonyl chlorides or arenecarboxylic acids, and further modification, the γ-phosphonodepsidipeptide 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-



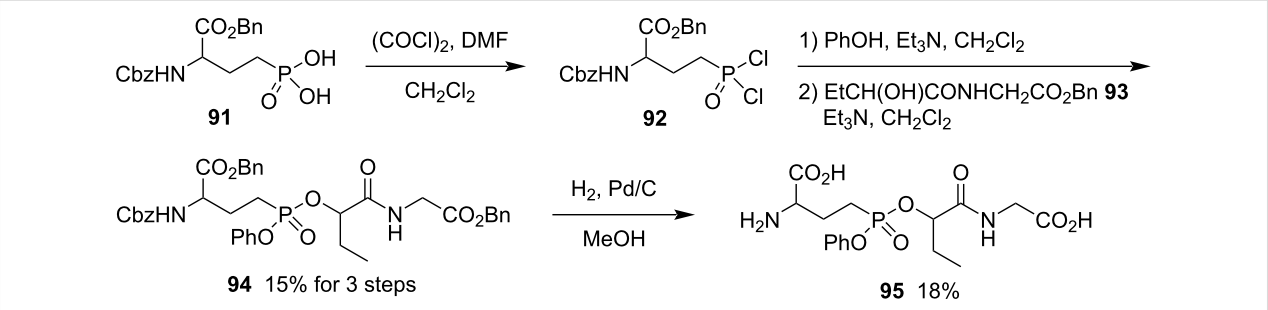
Scheme 13: Synthesis of γ-phosphonodepsidipeptides.



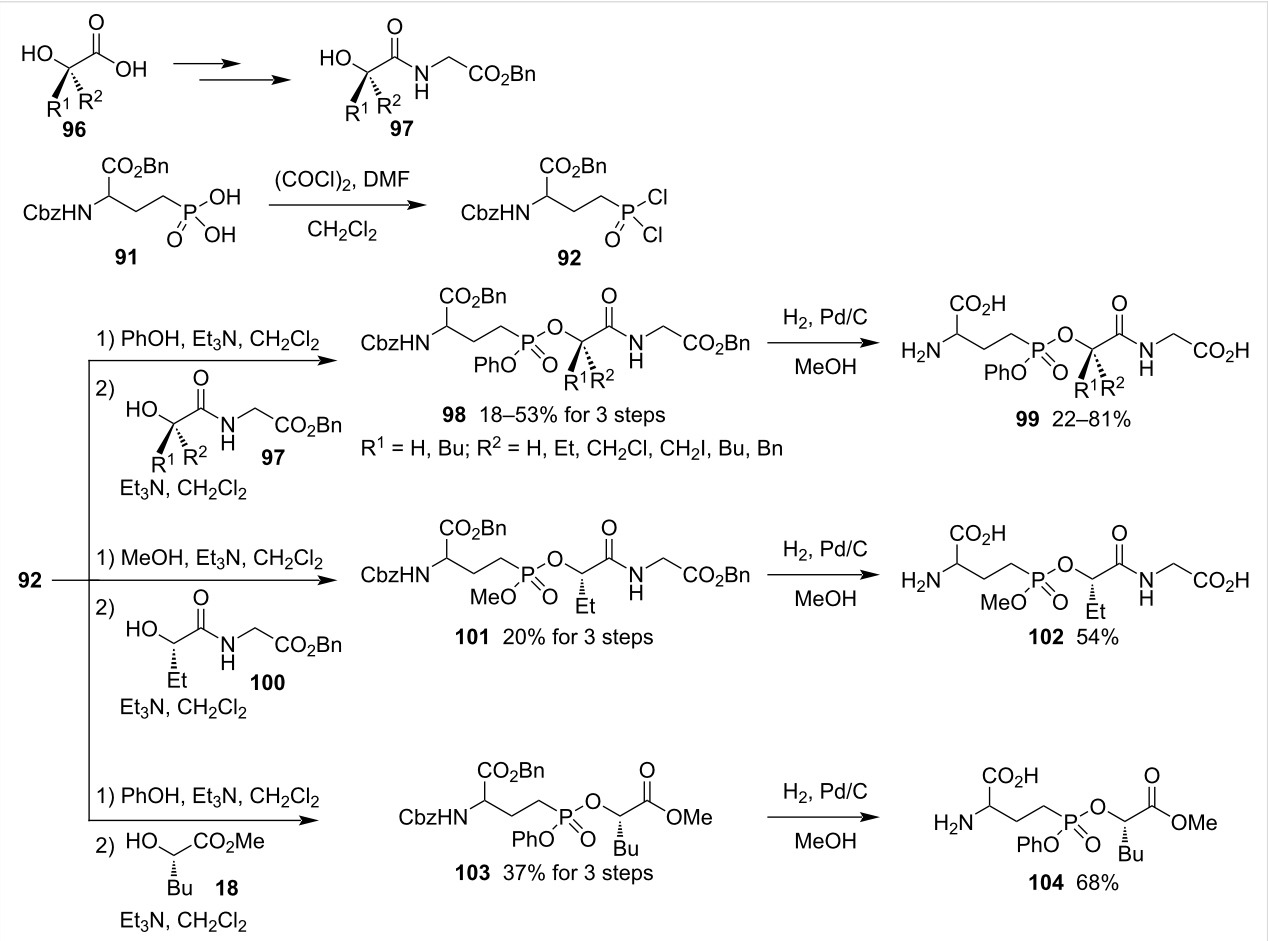
Scheme 14: Synthesis of phosphonodepsipeptides **85** as folylpolyglutamate synthetase inhibitors.

went a sequential alcoholysis 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].



Scheme 15: Synthesis of the γ-phosphonodepsitripeptide **95** as an inhibitor of γ-gutamyl transpeptidase.



Scheme 16: Synthesis of phosphonodepsipeptides as inhibitors and probes of γ-glutamyl transpeptidase.

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

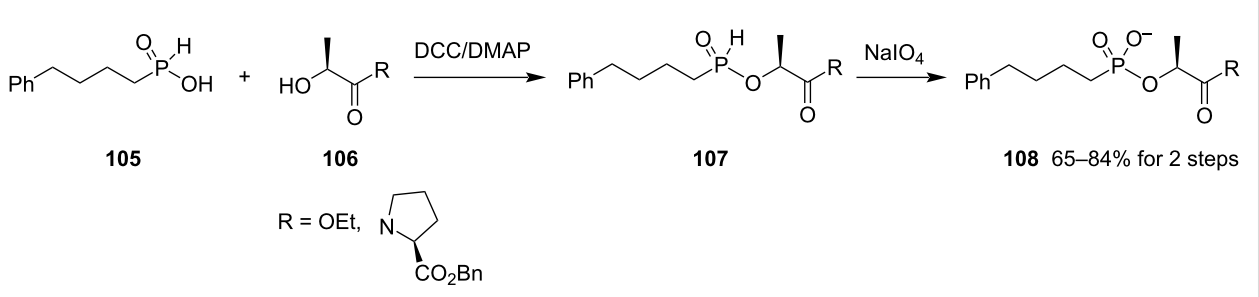
N,N'-Dicyclohexylcarbodiimide (DCC) was the first attempted coupling reagent in the synthesis of phosphonyl depsipeptides **108** from hydrogen 4-phenylbutylphosphinic acid (**105**) and 2-hydroxypropanoic acid derivatives **106** followed by oxidation. The corresponding phosphinyl depsipeptides **107**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

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

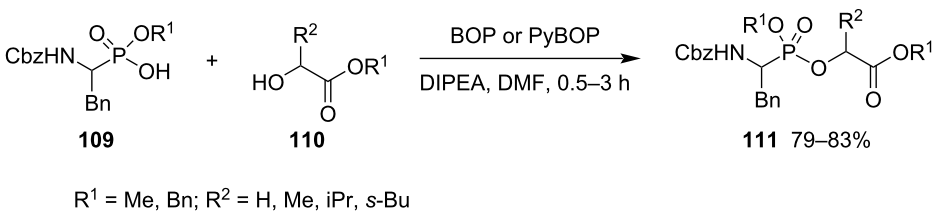
The synthetic method was further investigated and compared with alternative coupling reagents. Various optically active phosphonodepsidipeptides **113**–**118** were synthesized. The reaction mechanism was further studied, revealing that the reaction proceeds through benzotriazolyl esters as was shown by the comparison with other coupling reagents, including DCC, DCC/DMAP, DCC/1-hydroxybenzotriazole (HOBt), bromotris(dimethylamino)phosphonium hexafluorophosphate (BroP), or *O*-(1*H*-benzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (HBTU) and by ^{31}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].

The coupling reagents BroP and *N,N,N',N'*-bis(tetramethylene)chlorouronium tetrafluoroborate (TPyCIU) were applied as activating agents in the synthesis of phosphonodepsidipeptides **121** from *N*-Cbz-1-amino-2-phenylethylphosphonic acid (**119**) and hydroxy esters **120** in the presence of diisopropylethylamine (DIPEA) in CH_2Cl_2 (Scheme 20) [35].

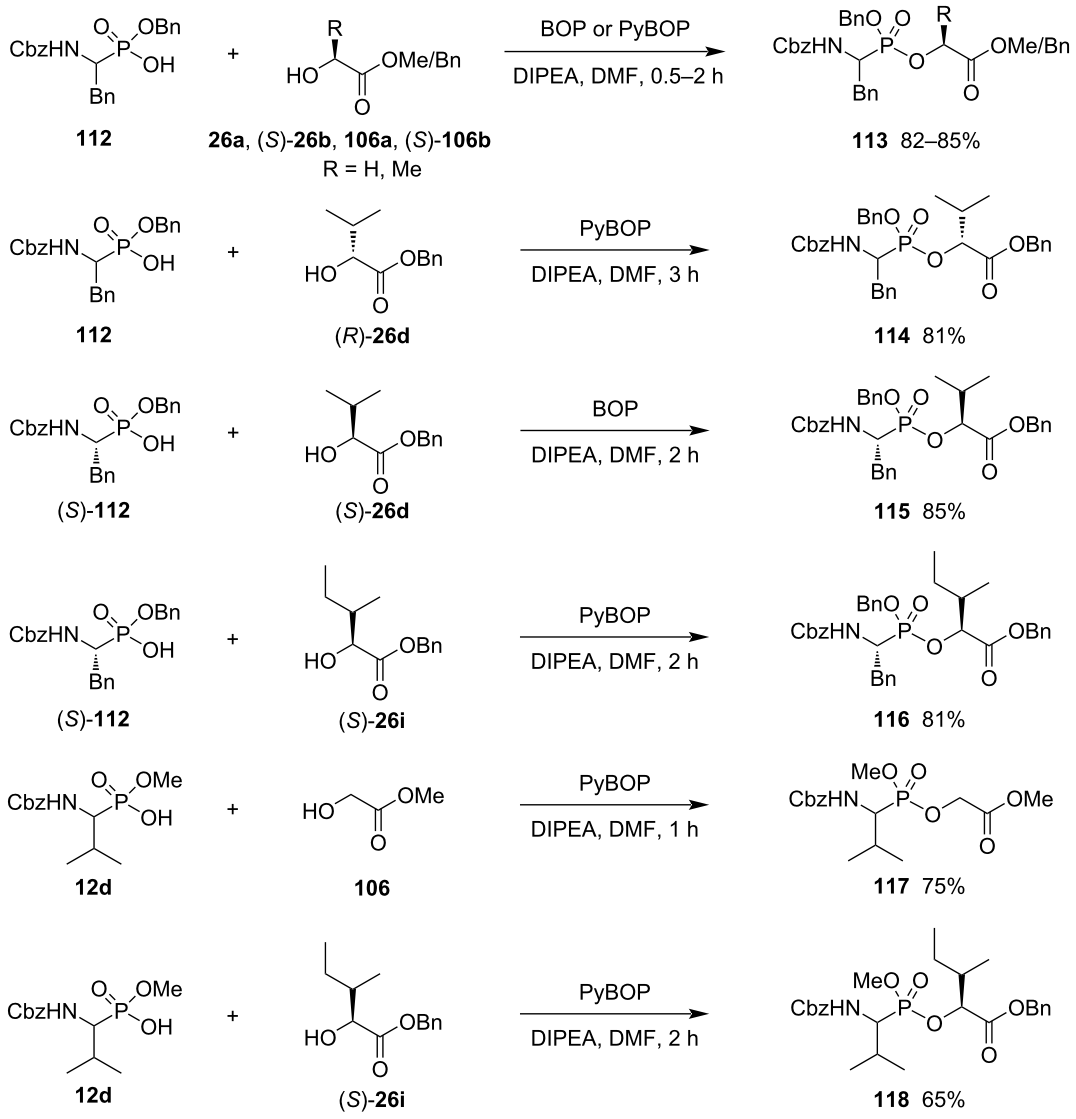
Vancomycin resistance became a serious health care problem currently. The development of a catalytic monoclonal antibody to hydrolyze the depsidipeptide D-Ala-D-Lac was a new antibiotic strategy. In this regard, the phosphonodepsipeptide hapten **127** was designed to induce the antibody. First, *N*-Boc-(*S*)-1-aminoethylphosphinic acid (**122**) was coupled with benzyl alcohol in the presence of DCC as the coupling reagent, affording the benzyl *N*-Boc-1-aminoethylphosphinate **123**. Oxidation with sodium periodate and neutralization with adamantan-1-amine (**124**), afforded the adamantan-1-ammoni-



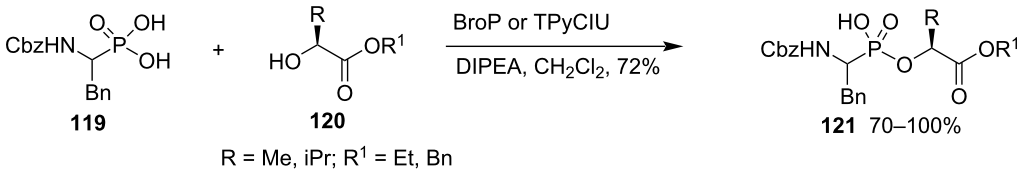
Scheme 17: Synthesis of phosphonyl depsipeptides **108** via DCC-mediated condensation and oxidation.



Scheme 18: Synthesis of phosphonodepsipeptides **111** with BOP and PyBOP as coupling reagents.



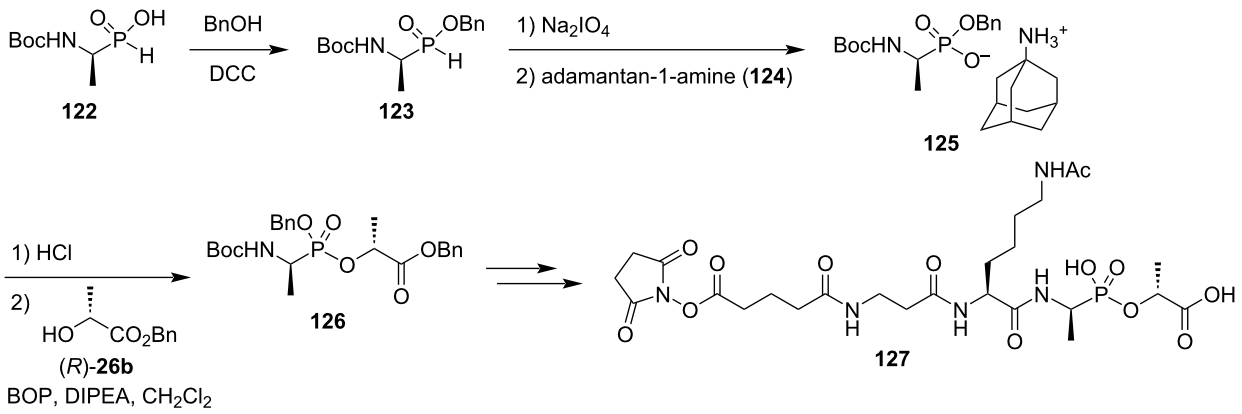
Scheme 19: Synthesis of optically active phosphonodepsipeptides with BOP and PyBOP as coupling reagents.



Scheme 20: Synthesis of phosphonodepsipeptides with BroP and TPyCIU as coupling reagents.

um benzyl phosphonate **125**. After treated with hydrochloride and coupled with benzyl D-lactate ((*R*)-**26b**) 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)aminoethylphosphonate (**12b**) and (*R*)-2-hydroxyglutaric acid dimethyl ester (**128**) with BOP as coupling reagent, followed by



Scheme 21: Synthesis of a phosphonodepsipeptide hapten with BOP as coupling reagent.

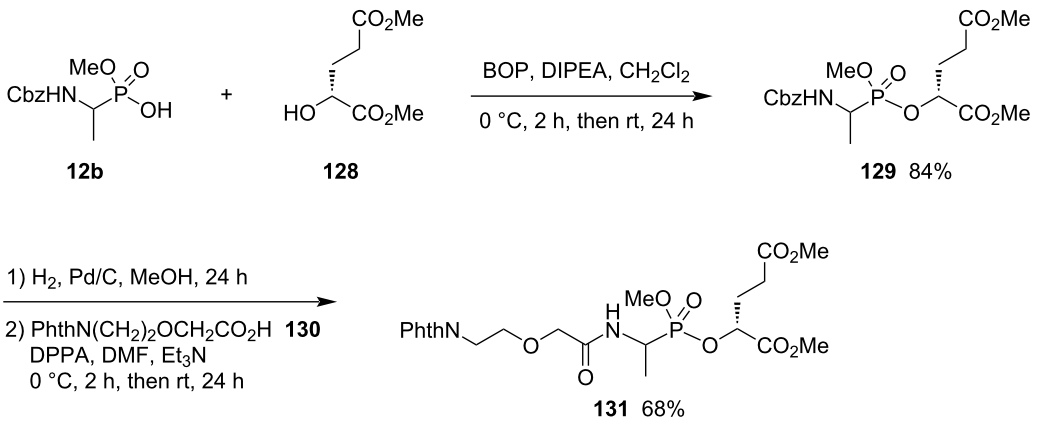
hydrogenolysis and coupling with 2-(2-phthalimidoethoxy)acetic acid (**130**). The amide bond between L-Ala and D-Glu was replaced by a phosphonate isostere, giving the phosphonodepsipeptide **131** (Scheme 22) [36].

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].

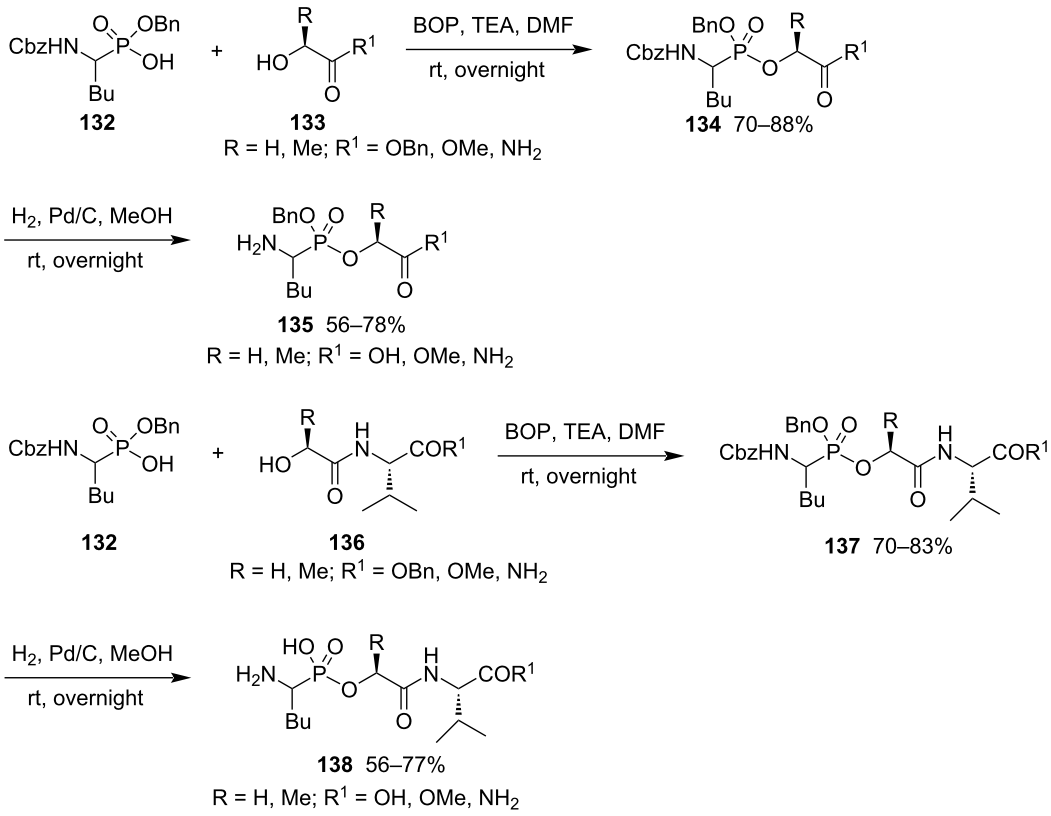
Following a similar strategy, phosphonodepsidipeptides **141** and phosphonodepsitripeptides **144** were synthesized as norleucine-derived phosphonopeptides (Scheme 24) [38].

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(O*t*-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].

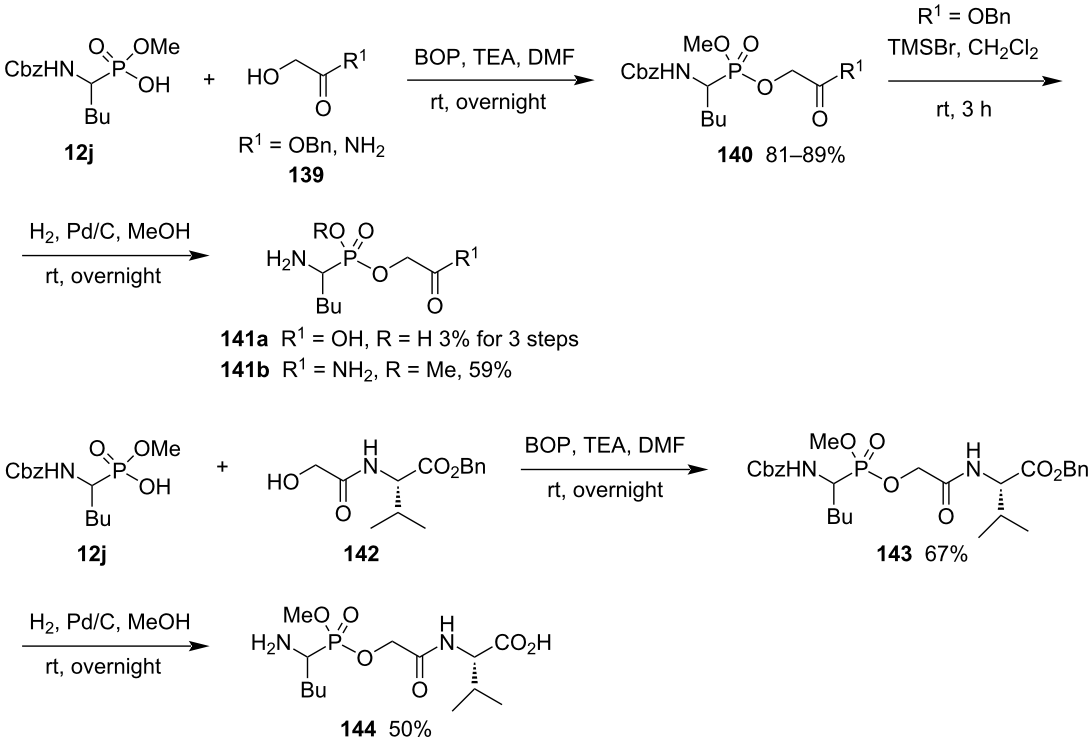
A general and high yielding synthesis of phosphonodepsidipeptides **152** was realized via a Mitsunobu reaction of the *N*-Cbz-1-aminophosphonic monomethyl esters **12b**,**d** and hydroxy esters **106** followed by the selective demethylation with TMSBr in a one-pot reaction. The method provides a mild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



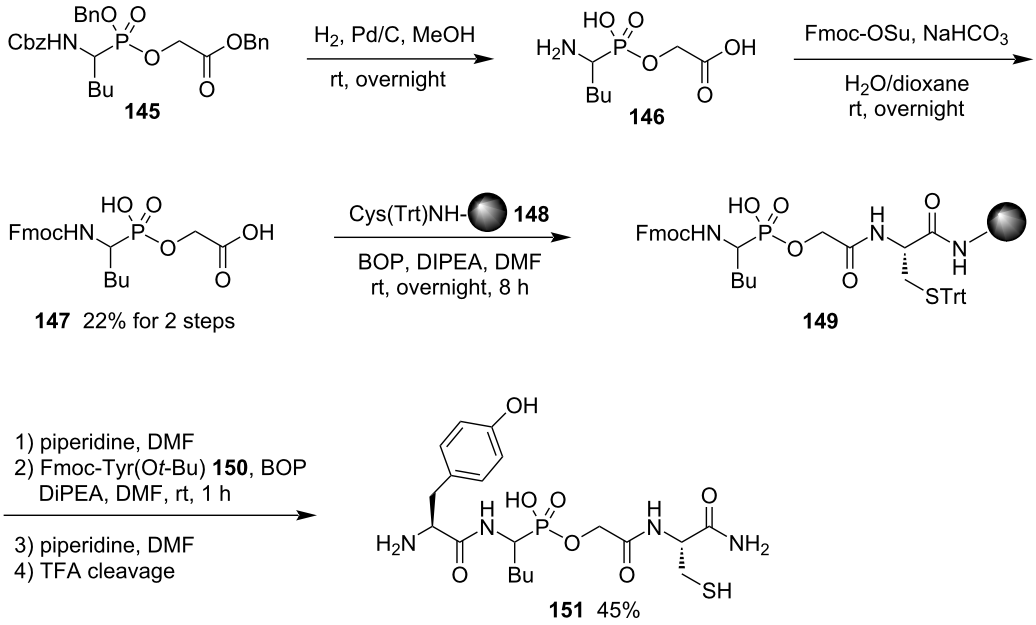
Scheme 22: Synthesis of phosphonodepsitripeptide with BOP as coupling reagent.



Scheme 23: Synthesis of norleucine-derived phosphonodepsipeptides **135** and **138**.



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

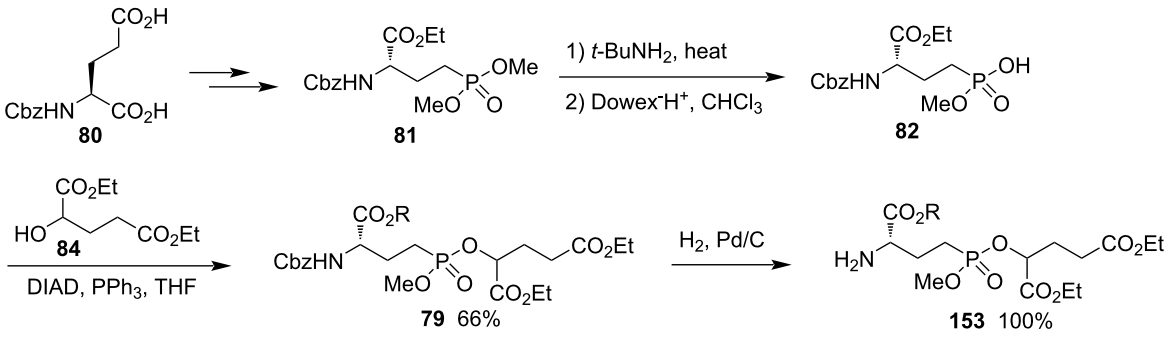


Scheme 25: Solid-phase synthesis of phosphonodepsipeptides.

Scheme 26: Synthesis of phosphonodepsidipeptides via the Mitsunobu reaction.

Synthesis of γ-phosphonodepsipeptides

To prepare phosphorus analogues of γ-glutamyl peptide, *N*-Cbz-L-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 27: Synthesis of γ-phosphonodepsipeptide via the Mitsunobu reaction.

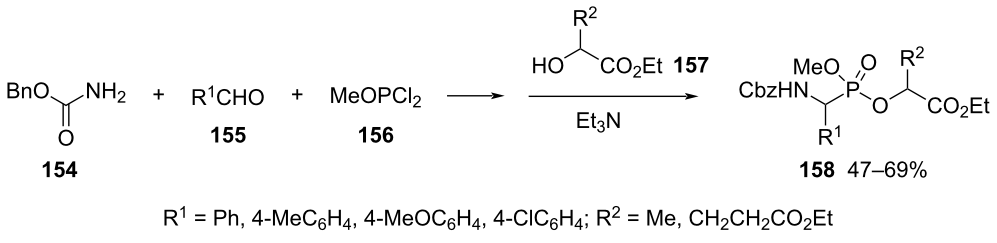
Synthesis of phosphonodepsipeptides via the multicomponent condensation of amides, aldehydes, and phosphites followed by alcoholysis with hydroxy esters

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-aminoalkylphosphonous acid derivatives first as starting materials (Scheme 28) [42].

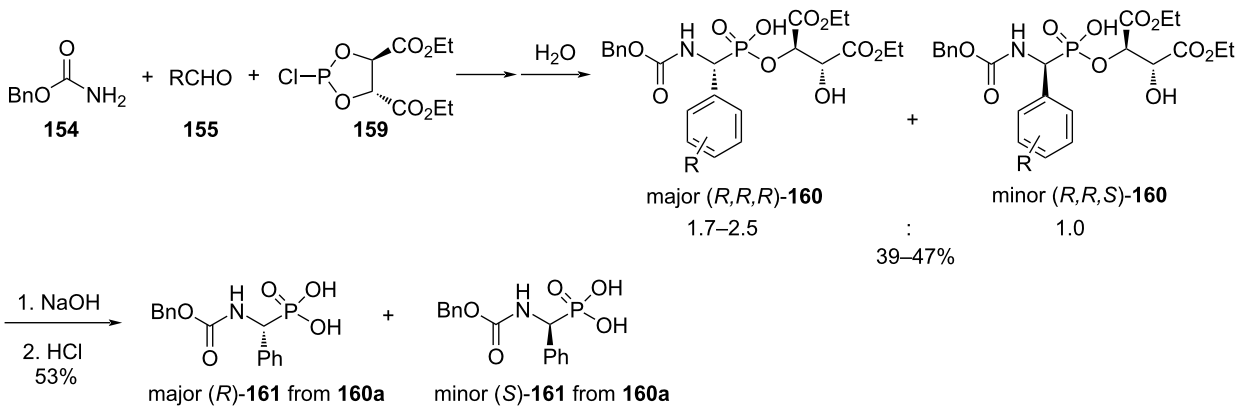
Similarly, phosphinopeptides [45,46], phosphinodepsipeptides [47], and hybrid sulfonophosphinopeptides [48,49] were prepared from amino amides and 2-aminoalkanesulfonamides by using this strategy.

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 phosphonodepsipeptides **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



Scheme 28: Synthesis of phosphonodepsipeptides via a multicomponent condensation reaction.



Scheme 29: Synthesis of phosphonodepsipeptides with a functionalized side-chain via a multicomponent condensation.

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 (4*R*,5*R*)-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 L-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].

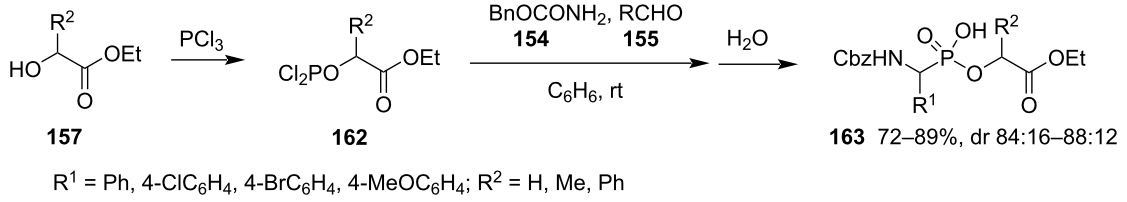
Synthesis of phosphonodepsipeptides via the alkylation of phosphonic monoesters with 1-(alkoxycarbonyl)alkyl halides or sulfonates

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.

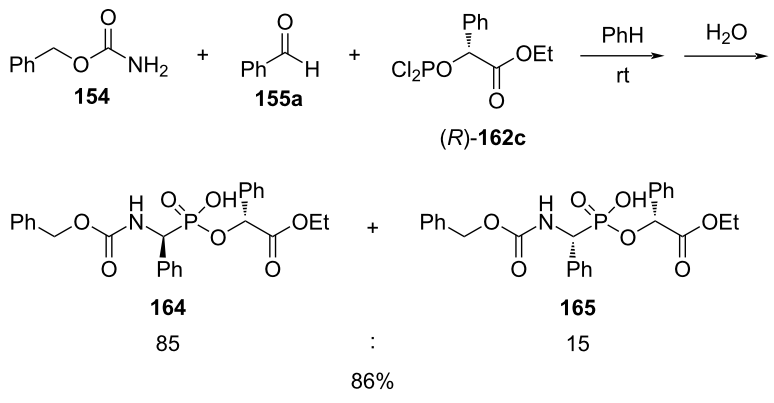
Synthesis of α-phosphonodepsipeptides

Skwarczynski and Kafarski synthesized various alkyl 1-aminoalkylphosphonates via the nucleophilic esterification of potassium 1-(*N*-benzyloxycarbonylamino)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].

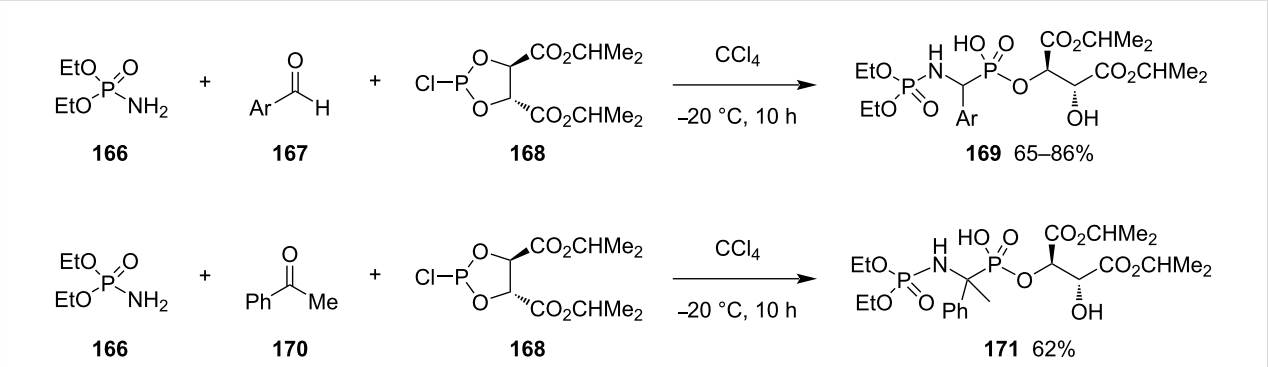
The macrocyclic peptidyl phosphonodepsipeptide **180** was designed on the basis of the acyclic conformational analog bound to the aspartic protease penicillopepsin. Dimethyl *N*-Cbz-1-amino-2-(naphthalen-2-yl)ethylphosphonate **176** was first prepared from 7-bromo-3,4-dihydronaphthalen-1(2*H*)-one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



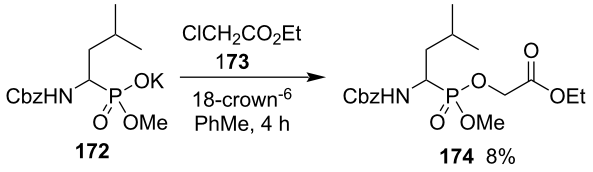
Scheme 30: High yielding synthesis of phosphonodepsipeptides via a multicomponent condensation.



Scheme 31: Synthesis of optically active phosphonodepsipeptides via a multicomponent condensation reaction.



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

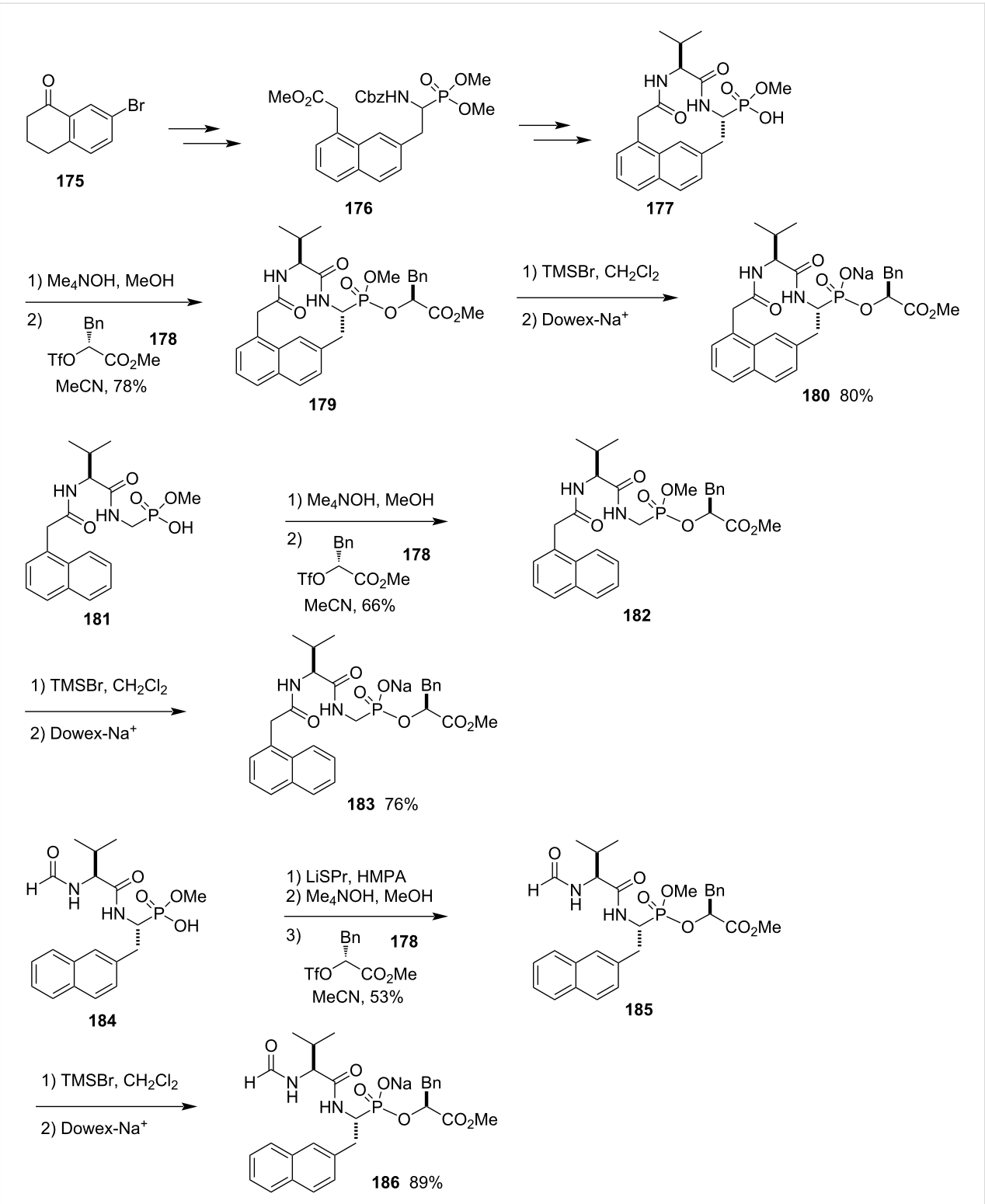
The acyloxyalkyl esters **194** are derivatives of the new antimalarial drug fosmidomycin and inhibited the 1-deoxy-D-xylulose 5-phosphate reductoisomerase. The phosphonodepsipeptides **194** were synthesized as prodrugs with an increased activity after oral administration due to a chemical modification of the phosphonate moiety. For the synthesis, diethyl 3,3-diethoxypropylphosphonate (**187**) was hydrolyzed to 3-oxopropylphosphonate **188**, which underwent a reductive amination with benzyloxyamine to give diethyl 3-benzyloxyaminopropylphosphonate (**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 phosphonodepsithioxopeptides **198** via the reaction of *N*-protected aminoalkylphosphonochloridites **196** with the hydroxy ester (*S*)-**106b** followed by sulfur oxidation. They first transformed the *N*-Boc-protected 1-aminoalkylphosphinate **195** to the corresponding phosphonochloridite **196** with dichlorotriphenylphosphorane. The phosphonochloridite **196** was then further reacted with methyl (*S*)-lactate ((*S*)-**106b**) followed by sulfurization with sulfur, affording the phosphonodepsithioxopeptide **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 phosphonochloridites.

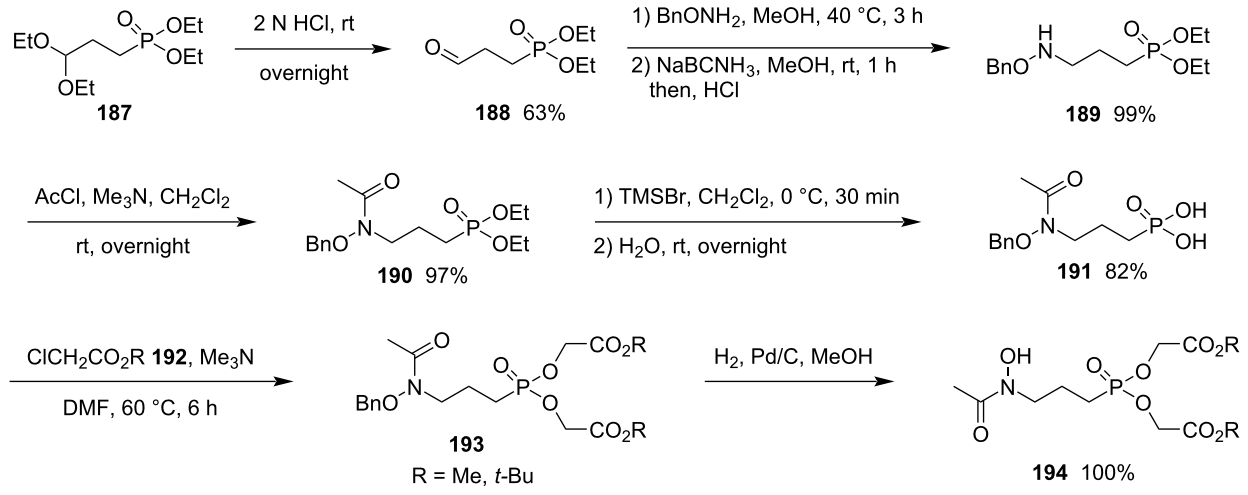
Synthesis of phosphonodepsipeptides via the addition of tetraoxyspirophosphoranes to imines

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].

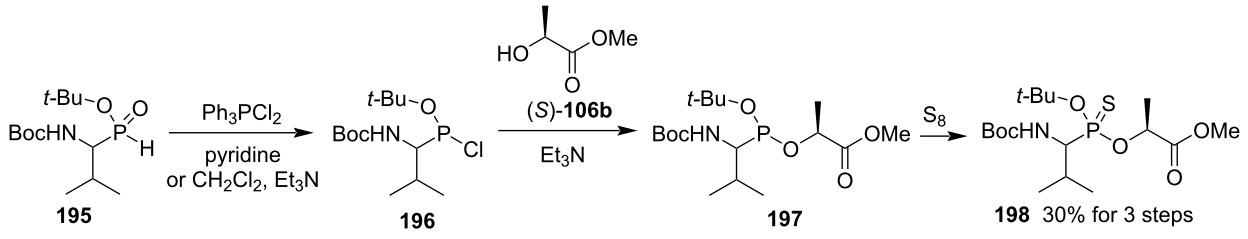


Scheme 34: Synthesis of phosphonodepsipeptides as inhibitors of aspartic protease penicillopepsin.

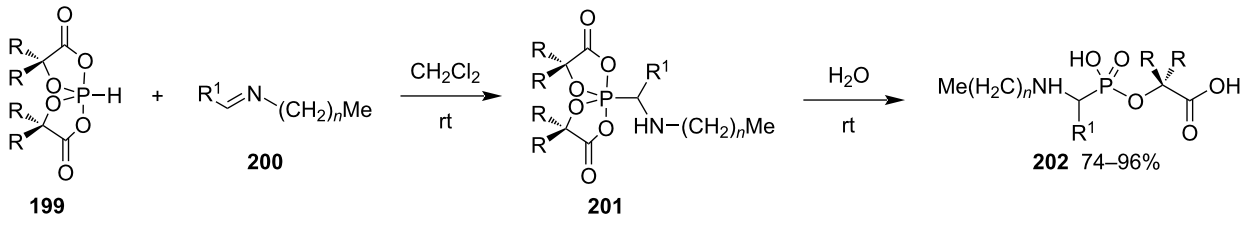
An asymmetric synthesis of this class of phosphonodepsipeptides was realized with enantiopure (*S*)-α-hydroxyisovaleric acid-derived spirophosphoranes as the phosphorus reagents [57]. By using a similar strategy, linker-linked bisphosphonodepsidipeptides were synthesized [10]. The current method is also an interesting synthetic strategy of phosphonodepsipep-



Scheme 35: Synthesis of phosphonodepsipeptides as prodrugs.



Scheme 36: Synthesis of phosphonodepsithioxopeptides **198**.



Scheme 37: Synthesis of phosphonodepsipeptides.

tides. 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].

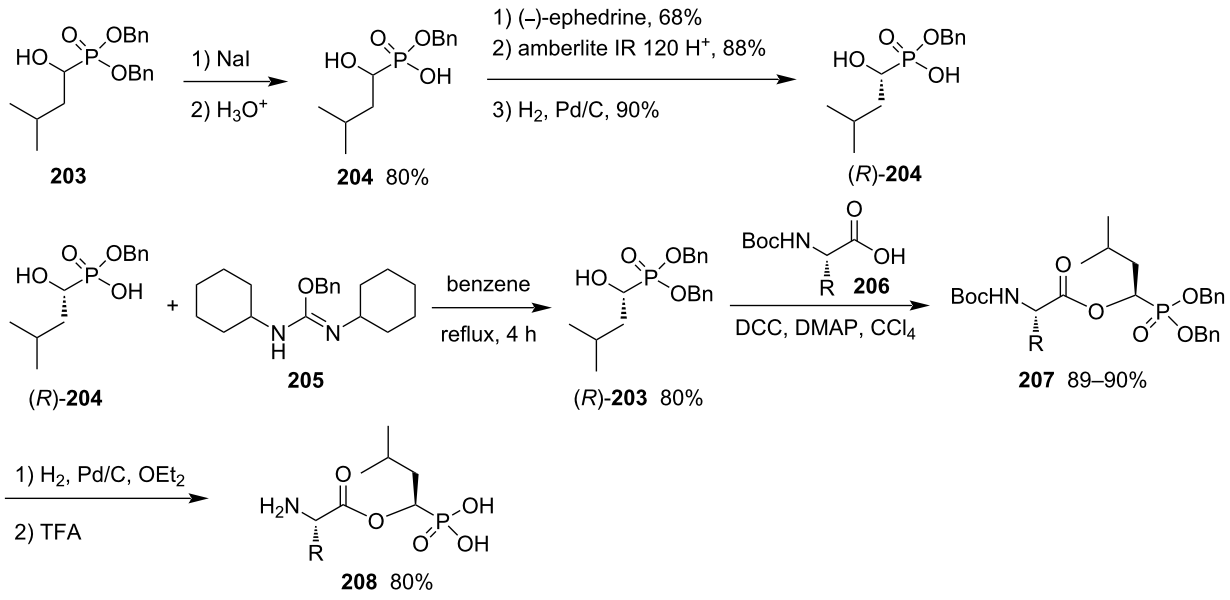
(*R*)-1-Amino-3-methylbutylphosphonic acid ((*R*)-**204**), a phosphonic L-Leu analogue, is a potent inhibitor of the metalloenzyme leucine aminopeptidase. Racemic dibenzyl 1-hydroxy-3-

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 corresponding protected phosphonopeptides **207**. After deprotection by hydrogenolysis and treatment with CF_3CO_2H, the phosphonodepsipeptides **208** were obtained (Scheme 38) [59].

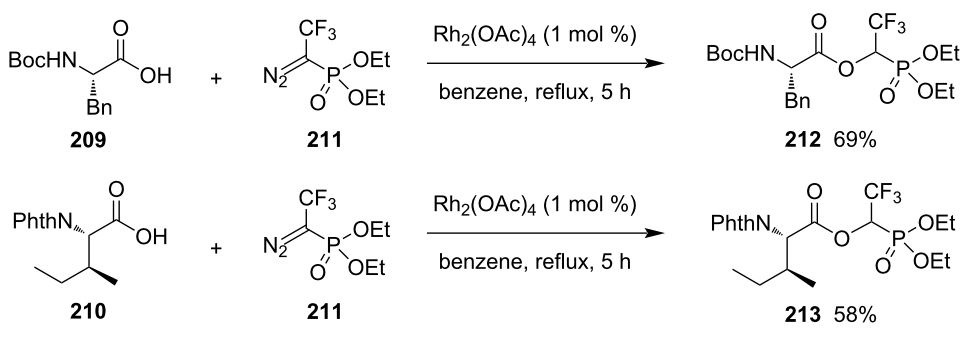
Phosphonodepsipeptides with C-1-hydroxyalkylphosphonic acids are also accessible through carbene insertion reactions. The reaction of the *N*-protected amino acids **209** and **210** with diethyl 1-diazo-2,2,2-trifluoroethylphosphonate (**211**) gave rise to the trifluoromethyl-containing phosphonodepsipeptides **212** and **213** with C-1-hydroxyalkylphosphonic 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 diazomethyldiphosphonate (**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].

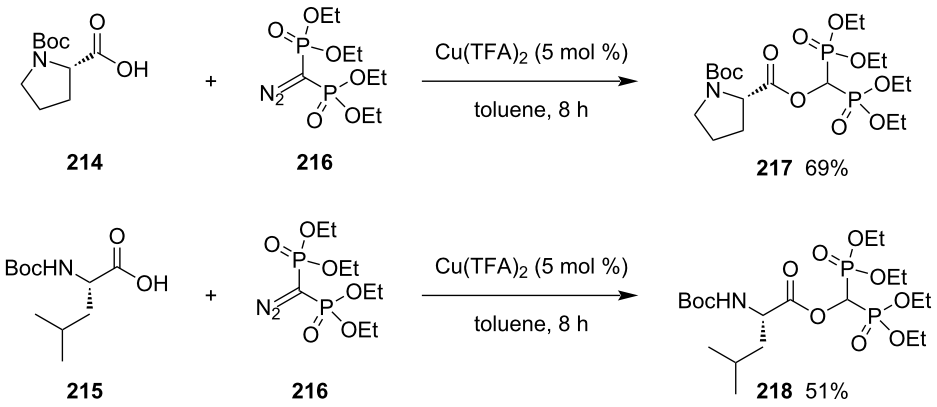
The transition metal-catalyzed carbene insertion of 1-diazoalkylphononates and *N*-protected amino acids is an efficient and convenient method for the synthesis of phosphonodepsipeptides with C-1-hydroxyalkylphosphonic acids because the required 1-diazoalkylphononates can be readily prepared from the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



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.



Scheme 40: Synthesis of phosphonodepsipeptides with a C-1-hydroxyalkylphosphonate motif via a copper-catalyzed carbene insertion reaction.

Conclusion

Phosphonodepsipeptides are phosphorus analogues of depsipeptides. They are more stable than the corresponding phosphonopeptides and have been widely used as enzyme inhibitors, haptens for the production of antibodies, biological agents, and prodrugs. Various synthetic methods of phosphonodepsipeptides have been developed, including the phosphonylation of hydroxy esters with phosphonochloridates or with phosphonic monoesters in the presence of coupling reagents, the alkylation of phosphonic monoesters with 1-(alkoxylcarbonyl)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.

Funding

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