Azadepsipeptides: Synthesis and Evaluation of a Novel Class of Peptidomimetics

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A general route to azadepsipeptides, a new class of pseudopeptides, has been established. The methodology was applied to the synthesis of a bis-aza analogue of the antiparasitic cyclooctadepsipeptide PF1022A. Comparison of the X-ray crystal structures of natural PF1022A (**8**) and the chimeric aza analogue **9** revealed that the introduction of nitrogen in the backbone of PF1022A results in almost complete conservation of the 3D structure with only minor deviations at the new nitrogen positions.

Introduction

A wealth of peptidic natural products with manifold biological activities have been published within the past decade.[1]Additionally, peptide−protein or protein−protein interactions, playing key roles in most of the signal-transduction processes, have been recognized as promising targets for novel pharmaceuticals with possible applications, for instance, in cancer, asthma, gastrointestinal, and antihypertensive therapy.[2] As a consequence, immense efforts[3] have been directed at improving the pharmacological properties of biologically active peptides by incorporating amino acid and peptide mimetics. These peptide analogues are usually characterized by improved enzymatic stability, bioavailability, and duration of action.[4] The alteration of peptides to peptidomimetics encompasses side-chain manipulation, turn-mimics,[5] amino acid extension,[6] and backbone modifications.[7] The latter approach seems to be particularly promising since the structure and conformation of the original peptide should be largely preserved in the resulting biomimetic polymer.

The most common manipulations involving the α-carbon atoms of peptides include inversion of configuration (D-amino acids),[8] substitution of the α-hydrogen (by alkyl or other groups),[1a] and replacement of the α-carbon atom isoelectronically by a trivalent nitrogen, yielding azapeptides (Figure 1). This class of pseudopeptides lacks chirality in the α-position and can be considered intermediate in configuration between D- and L-amino acids.[9] Azapeptides provide improved resistance against enzymatic cleavage, adopt conformations similar to their natural counterparts, and display increased biological activity in many cases.[10] Although the alteration of the backbone by replacement of α-carbons by nitrogen is a common manipulation in peptide chemistry, only little attention has been devoted to the synthesis of aza analogues of depsipeptides (Figure 1).[11] This is surprising since many depsipeptides, such as the enniatins and the cyclooctadepsipeptide PF1022A (**8**), have been found to

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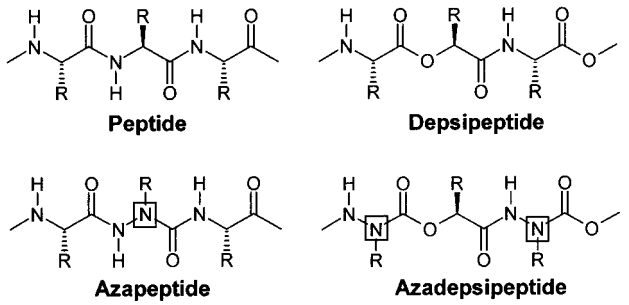

Figure 1. Comparison of peptide/azapeptide and depsipeptide/azadepsipeptide structures.

be biologically highly active and are currently subject of extensive studies in organic and medicinal chemistry.[12]

We became interested in the evaluation of azadepsipeptide structures in connection with our ongoing work on the antiparasitic cyclooctadepsipeptide PF1022A (**8**).[13] The primary goal in developing a synthesis of aza analogues was to elucidate the functional role of the depsipeptide backbone and the importance of the chiral centers. In this paper, we outline the general synthesis of azadepsipeptide building blocks as a new class of peptidomimetics and give a full account of the synthesis and conformational studies (X-ray and NMR) of the chimeric cyclic depsipeptide **9** (bis-aza-PF1022A), as the first example of an aza analogue of a natural depsipeptide.

Results and Discussion

Azadepsipeptide Building Blocks. The azadepsipeptide building blocks required for our purposes structurally represent carbazates between an N,N′-substituted hydrazine as the aza-amino acid portion and an α-hydroxycarboxylic acid (Figure 1). For the generation of a set of these building blocks a number of suitably protected *N*-alkylaza-amino acids had to be prepared. The synthesis of protected alkyl hydrazines can be achieved in general via two different routes, either by alkylation of hydrazines and subsequent introduction of the protecting group or vice versa by reductive alkylation of protected hydrazines.[14] In contrast, the synthesis of protected unsymmetrical *N*,*N*′-dialkyl hydrazines (**3**) has not been investigated systematically. To be able to introduce a broad variety of natural and unnatural amino acid side chains, we developed a three-step protection/reductive alkylation protocol for alkyl hydrazines **3** as outlined in Scheme 1.

Scheme 1. Preparation of Boc-Protected Unsymmetrical *N*,*N*′-Dialkyl Hydrazines

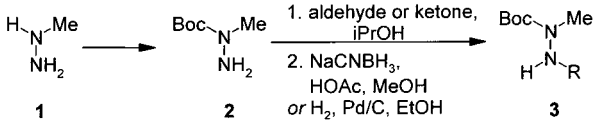

Table 1. *N*,*N*′-Dialkylhydrazines

	R	yield (%)
3a	Me	83
3b	*i*-Pr	92
3c	Pr	89
3d	*i*-Bu	78
3e	Bu	93
3f	Bn	98
3g	4-Br-Bn	75

Monoalkyl hydrazines **1** are either commercially available or may be easily prepared following standard literature procedures.[15] The more nucleophilic secondary nitrogen of the hydrazine is selectively protected with the Boc-group under carefully controlled conditions to give **2**.[15] The side chains are best introduced in a two-step sequence via hydrazone formation and reduction giving excellent yields of the unsymmetrical Boc-protected dialkyl hydrazines **3** (Table 1). Compared to the direct one-step reductive alkylation of **2**, hydrazone formation prior to reduction resulted in much cleaner reactions. In the case of hydrazines **3a**−**e**, reduction was accomplished with $NaCNBH_3$ in methanol under acidic conditions whereas for hydrazines **3f** and **3g** hydrogenation of the intermediate hydrazones proved to be the method of choice. The compounds were obtained practically pure and in excellent yields after simple hydrolytic workup and filtration through silica gel. If required, the carbazates **3** can be further purified by column chromatography or distillation under reduced pressure. However, distillation resulted in lower yields due to decomposition.

The second constitutive structural element of azadepsipeptides, α-hydroxycarboxylic esters, were obtained in high optical purity and good to excellent yields from the corresponding (*R*)- or (*S*)-amino acids following a desamination/hydroxylation protocol.[16] The cesium salts of the resulting hydroxy acids were subsequently benzylated with benzyl bromide in ethanol.

The formation of carbazates from dialkylhydrazines and α-hydroxy carboxylic esters can in principle be achieved either by converting the dialkylhydrazines into an acylating agent or vice versa by activating the hydroxycarboxylic acids (Scheme 2). The first route turned out to be difficult since the alkyl hydrazines are poorer nucleophiles than simple amines or amino acids and thus require a highly activated carbonyl synthon. Our initial attempts to couple the two building blocks using bis-pentafluorophenyl carbonate,[17] triphosgene, or *p*-nitrophenyl chloroformate suffered from unsatisfying yields and side reactions, mainly caused by the formation of carbonates and azatides.

To overcome these problems, we decided to use phosgene as carbonyl reagent to activate the α-hydroxycar-

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Scheme 2. Synthesis of Azadepsipeptide Building Blocks

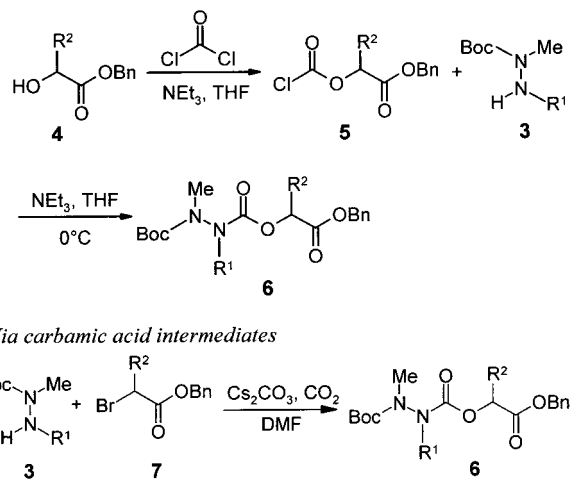

Table 2. Azadidepsipeptides

	R^1	R^2	yield (%)	method
6a	Me	H	96	2
6b	*i*-Pr	H	87	2
6c	Pr	H	67	2
6d	*i*-Bu	H	84	2
6e	Bu	H	76	2
6f	Bn	H	97	2
6g	4-Br-Bn	H	85	2
6h	*i*-Bu	Bn	76	1
6i	*i*-Bu	Me	59	1

boxylic ester. In a stepwise procedure, depicted in Scheme 2, the hydroxycarboxylic esters were first converted to the corresponding chloroformates using an excess of phosgene. The intermediate chloroformates were isolated and immediately reacted with the hydrazines **3** in the presence of NEt_3. Using this coupling method, **6h** and **6i** were obtained in good yields of 76% and 59%. The results are summarized in Table 2.

During the course of our work, we also attempted to find an alternative for the use of toxic phosgene. The use of carbon dioxide as a phosgene equivalent seemed to be promising, since the formation of carbamate esters has been reported in the literature.[18] As shown in Scheme 2, the reaction of hydrazines **3** with carbon dioxide and α-bromo acetate in the presence of cesium carbonate afforded the expected azadidepsipeptides **6** in excellent yields. This alternative procedure for the synthesis of **6** is based on alkylation of carbamic acid intermediates, formed through the reaction of hydrazines **3** with carbon dioxide. The reaction, however, turned out to be limited to primary alkyl halides as alkylating agents. When α-chloropropionate esters were subjected to these reaction conditions, only small amounts of the desired products **6h** and **6i** were obtained. Instead α,*β*-unsaturated esters were formed through the elimination of HCl under basic conditions. In summary, phosgene remains the most general applicable reagent for the synthesis of azadidepsipeptides **6**. For the synthesis of building blocks unsubstituted in the α-hydroxy ester moiety, carbon dioxide/cesium carbonate is an excellent and simple to use alternative. The techniques outlined above allow azadepsipeptide chain building either by fragment condensation of didepsipeptide units or by iterative coupling of hydrazines and chloroformates.

Chimeric Bis-aza-PF1022A. To evaluate the properties of azadepsipeptides as peptidomimetics, we devised the synthesis of an aza analogue of PF1022A (**9**, Figure 2). Although the structural change compared to the original peptide is minimal, the conformation of the aza analogue—due to the loss of chiral centers—may be quite different from the original structure. Since the binding affinity and selectivity of a peptidic ligand to its receptor is largely determined by the overall conformation and certain key structural features of the sequence, we decided to replace only one-half of the C_2-symmetric PF1022A structure by an azatetradepsipeptide in order to largely preserve the native conformation (Figure 2).

The synthetic strategy is a convergent one in which both parts of the molecule, the tetradepsipeptide fragment **15**[19] bearing the natural part of the molecule and fragment **16** which contains the bis-aza portion, are preassembled separately and then connected to give the linear precursor which was finally cyclized. On the basis of our experience with the synthesis of PF1022A and several derivatives, BOP-Cl was employed as simple and efficient coupling reagent to form all *N*-methylamide linkages including the final cyclization.[19] Other coupling reagents such as HATU, TBTU, or PyBroP did not give better yields.[20]

The preparation of fragment **15** was started by first constructing its two didepsipeptide subunits **9** and **10** through coupling of *N*-methyl-(*S*)-leucine with 3-phenyl-(*R*)-lactate and (*R*)-lactate, following established procedures (Scheme 3).[13] After deprotection of **9** by catalytic hydrogenolysis and **10** by acidic cleavage with TFA, the resulting didepsipeptide units MeLeu-PheLac (**11**) and MeLeu-Lac (**12**) were coupled with BOP-Cl to give **15** in 80% yield. In a similar way, the appropriately protected azatetradepsipeptide fragment **16** was formed by coupling the azadidepsipeptide building blocks **6h** and **6i.** These were synthesized as described above by first reacting benzyl 3-phenyl-(*R*)-lactate or benzyl (*R*)-lactate with phosgene as carbonyl equivalent and subsequent coupling with Boc-protected *N*-methyl-*N*′-isobutylhydrazine (**3d**). After standard protecting group manipulation, the condensation of the resulting two crude products **13** and **14** with BOP-Cl as coupling reagent furnished **16** in a reasonable yield of 45%. With the two fragments in hand, the final steps of the synthesis proved to be straightforward. Deprotection of **15** and **16** and coupling of the resulting products **17**[19] and **18** furnished **19**, the fully protected chimeric azadepsipeptide, as the linear precursor of **9**. Acidic hydrolysis of the N-terminal Boc group and hydrogenolytic cleavage of the C-terminal benzyl ester followed by subsequent macrocyclization under high dilution conditions afforded the bis-aza PF1022A analogue **9** as a stable pale yellow solid after flash chromatography and additional HPLC purification.

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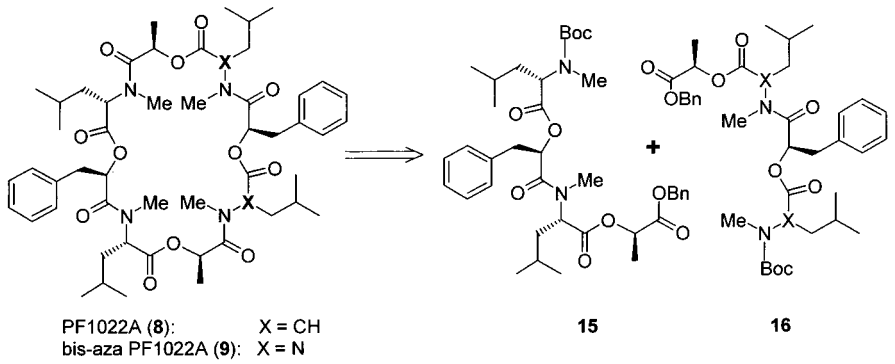
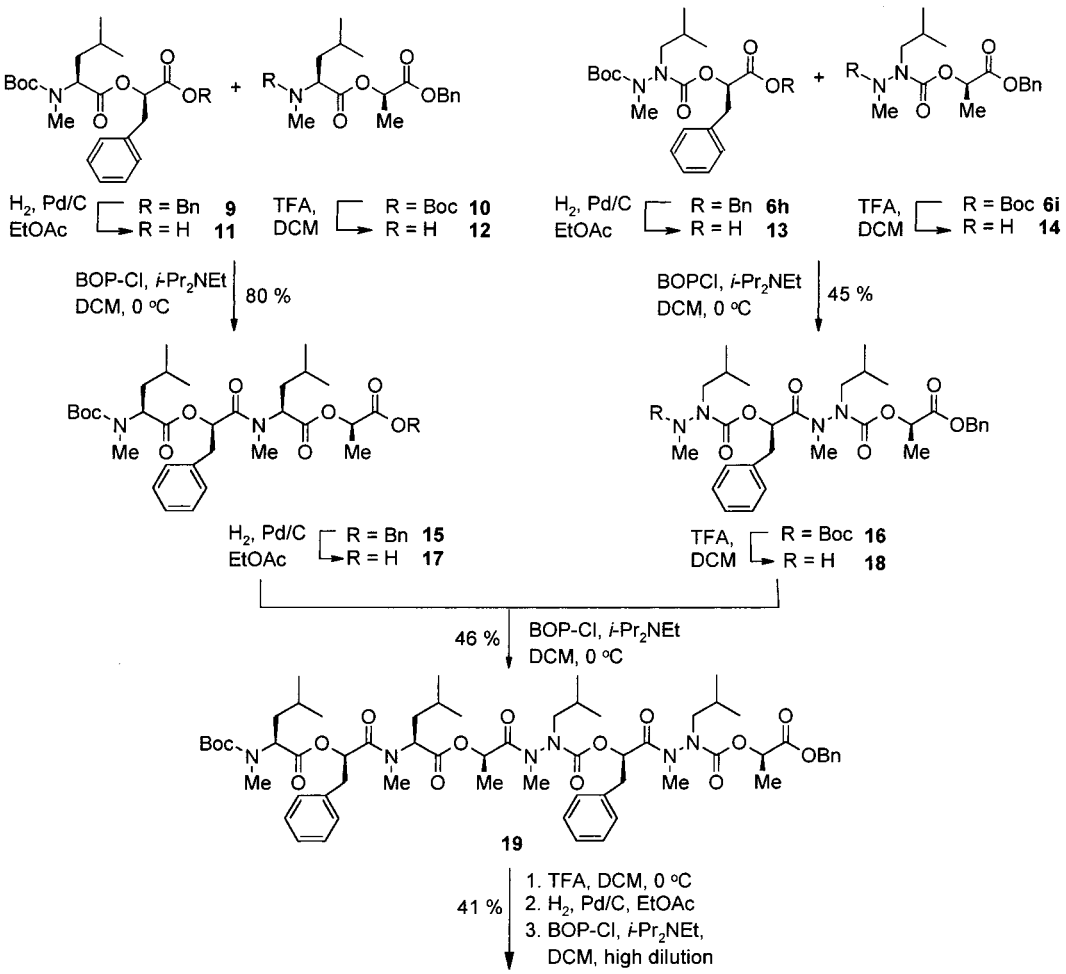


Figure 2. PF1022A and bis-aza PF1022A.

Scheme 3. Synthesis of Bis-aza PF1022A (8)



Bis-aza PF1022A **(9)**

Both X-ray crystal structure analysis[21] and NMR studies (COSY, TOCSY, ROESY) of **9** revealed that the introduction of nitrogen in the backbone of PF1022A (**8**) results in almost complete conservation of the 3D structure of the natural product with only minor changes at the new nitrogen positions. Like the native PF1022A (**8**), the chimeric aza analogue (**9**) also consists of two conformers in solution, a symmetrical one with all amide bonds in the trans configuration and an asymmetrical conformation with one *trans*-amide bond. The *trans*-amide bond in **9** is found between azaleucine and the lactic acid moiety, stabilizing the asymmetrical conformer significantly (100:7 in **9** compared to 3:1 in **8**). However, when tested in vivo in sheep infected with the two nematodes *Haemonchus contortus* and *Trichostrongylus colubriformis* a decrease in biological activity by a factor of 5−10 was observed compared with the natural product.[13b] It seems to be most reasonable that the reduced anthelmintic activity can be attributed either to the loss of chirality and an increased flexibility at the α-carbons or to a reduced metabolic stability.

(21) X-ray structure of **8**: Kodama, Y.; Takeuchi, Y.; Suzuki, A. *Sci Rep. of Meji Seika Kaisha* **1992**, *31*, 1.

In summary, we have established a general synthesis for azadepsipeptides of variable length and applied this methodology to the synthesis of a bis-aza analogue of the antiparasitic cyclooctadepsipeptide PF1022A (**8**). Although the substitution of two α-carbons by nitrogens caused only minor alterations in the 3D structure, the anthelmintic activity of **9** was significantly reduced. By subtly changing the synthetic route and by choosing differently substituted hydrazines the substitution pattern can be modified in a flexible manner and novel heterocyclic ring systems of different size are accessible. The strategy described above should be generally applicable to the construction of azadepsipeptide libraries either by solution or by solid-phase chemistry.

Experimental Section

All reactions were performed in oven-dried glassware under a positive pressure of argon. Solvents were dried by filtration through basic alumina (ICN alimina, act. I). Solvent evaporation was performed under reduced pressure at 40 °C using a rotary evaporator. The instrumentation used was as follows: ^{1}H NMR AMX 500 (Bruker); FT-IR FTS-60 (BIORAD); MS (Finnigan); CI-MS MAT 8340; FAB-MS MAT 900; EI-MS MAT 212. LC: preparative low-pressure chromatography was performed using silica gel 60 μm (230−400 mesh, E. Merck), Ismatec pump, UV detector Uvicord SII (Pharmacia LKB). HPLC analyses were performed on analytical columns (25 cm, RP 18) using an acetonitrile−water gradient and flow-rates of 1.0−1.5 mL/min. UV absorption was measured at 214 nm. Abbreviations: Bop-Cl, *N*,*N*′-bis(2-oxo-3-oxazolidinyl)phosphinic chloride; HATU, 2-(1*H*-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate; TBTU, 2-(1*H*-Benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate; PyBroP, bromotripyrrolidinophosphonium hexafluorophosphate.

General Procedure for the Synthesis of 1-Boc-1-methyl-2-alkylhydrazines (3). (a) Preparation of the hydrazones. Boc-methylhydrazine was reacted for 1−2 h with the aldehyde or ketone as a 1:1 mixture in *i*-PrOH under reflux. The solvent was removed under vacuo, and the crude products were filtered over a pad of silica gel to give the hydrazones virtually pure in quantitative yield. **(b) Reduction of the Hydrazones.** To a solution of the above-prepared crude hydrazones (68.4 mmol) in MeOH (150 mL), $NaCNBH_3$ (88 mmol), and acetic acid (pH 3−4) were added at 0 °C. The reaction mixture was stirred for 3−5 h at 0 °C. During this time, the pH of the reaction mixture was kept at pH 3−4 by addition of acetic acid. The reaction mixture was evaporated, the residue dissolved in ethyl acetate (350 mL), and the solution washed with water (20 mL). After drying with $MgSO_4$, the solvent was evaporated and the crude products **3a**−**e** were purified by filtration over silica gel (ethyl acetate/hexane). The hydrazines **3** were obtained in 78−93% yield and were used as crude products. They can be further purified either by distillation or column chromatography. **(b) Hydrogenation of the Hydrazones.** A solution of the hydrazone (90 mmol) in 300 mL of ethanol was hydrogenated at atmospheric hydrogen pressure in the presence of 260 mg of Pd/C (10%) until the reaction was complete. The catalyst was removed by filtration through Celite, and the solvent was evaporated to give the crude hydrazines **3f** and **3g** in 75−98% yield. The hydrazines **3** were used as crude products.

1-Boc-1-methyl-2-methylhydrazine 3a: yield 83% (HPLC purity 100%); colorless liquid; $R_f = 0.36$ (cyclohexanes−ethyl acetate 2:1); IR 1672 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.49 (s, 9H), 2.55 (s, 3H), 3.0 (s, 3H); MS (CI) *m*/*e* 161 ([M + H]$^+$, 3), 105 (100). HRMS (ESI) *m*/*e* 183.1104 (calcd for $C_7H_{16}N_2O_2Na$ 183.1104).

1-Boc-1-methyl-2-isopropylhydrazine 3b: yield 92% (HPLC purity 100%); colorless liquid; $R_f = 0.57$ (cyclohexane−ethyl acetate 2:1); IR 1694 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.02 (d, 6H, $J = 8$ Hz), 1.48 (s, 9H), 3.03 (s, 3H); MS (CI) *m*/*e* 133 (8), 89 (100).

1-Boc-1-methyl-2-propylhydrazine 3c: yield 89% (HPLC purity 100%); colorless liquid; $R_f = 0.46$ (cyclohexanes−ethyl acetate 3:1); IR 1694 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.94 (t, 3H, $J = 8$ Hz), 1.48 (s, 9H + m, 2H), 2.77 (t, 2H, $J = 8$ Hz), 3.0 (s, 3H); MS (CI) *m*/*e* 132 (38), 103 (25), 87 (30); HRMS (ESI) *m*/*e* 211.1415 (calcd for $C_9H_{20}N_2O_2Na$ 211.1417).

1-Boc-1-methyl-2-isobutylhydrazine 3d: yield 78% (HPLC purity 100%); colorless liquid; $R_f = 0.86$ (cyclohexanes−ethyl acetate 1:1); IR 1700 cm^{-1} (CO); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.12 (d, 6H, $J = 8$ Hz), 1.54 (s, 9H), 2.63 (m, 1H), 3.17 (s, 3H), 6.88 (d, 1H, $J = 8$ Hz); MS (CI) *m*/*e* 202 (M$^+$, 4), 146 (43), 103 (77); HRMS (ESI) *m*/*e* 225.1572 (calcd for $C_{10}H_{22}N_2O_2Na$ 225.1573).

1-Boc-1-methyl-2-butylhydrazine 3e: yield 93% (HPLC purity 97%); colorless liquid; IR 1694 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.91 (t, 3H, $J = 8$ Hz), 1.48 (s, 9H), 1.3−1.6 (m, 4H), 2.80 (t, 2H, $J = 8$ Hz), 3.01 (s, 3H); MS (ESI) *m*/*e* 203 ([M + H]$^+$, 100); HRMS (ESI) *m*/*e* 203.1752 (calcd for $C_{10}H_{22}N_2O_2Na$ 203.1754).

1-Boc-1-methyl-2-benzylhydrazine 3f: yield 98% (HPLC purity 97%); pale yellow liquid; $R_f = 0.62$ (cyclohexanes−ethyl acetate 2:1); IR 1702 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.48 (s, 9H), 2.93 (s, 3H), 3.91 (s, 2H), 7.3 (m, 5H); MS (CI) *m*/*e* 181 (8), 137 (100); HRMS (ESI) *m*/*e* 259.1417 (calcd for $C_{13}H_{20}N_2O_2Na$ 259.1417).

1-Boc-1-methyl-2-(4-bromobenzyl)hydrazine 3g: yield 75% (HPLC purity 97%); pale yellow liquid; $R_f = 0.66$ (cyclohexanes−ethyl acetate 2:1); 1680 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.47 (s, 9H), 2.91 (s, 3H), 3.90 (s, 2H), 7.35 (m, 4H); MS (CI) *m*/*e* 259 (10), 214 (10), 171 (38), 169 (40); HRMS (ESI) *m*/*e* 337.0520 (calcd for $C_{13}H_{19}BrN_2O_2Na$ 337.0522).

General Procedure for the Synthesis of Boc-Protected Azadidepsipeptides A (6). 1. Phosgene Procedure (Procedure 1). A solution of the α-hydroxycarboxylic ester (15.0 mmol) and triethylamine (16 mmol) in THF (10 mL) was added slowly (1 h) to a 1.93 M solution of phosgene (18.0 mmol) in toluene at 0 °C. The reaction mixture was stirred for 30 min at 0 °C, warmed to room temperature, stirred for another 1 h, filtered, and concentrated in vacuo. The residue was dissolved in THF (8 mL) and cooled to 0 °C. Within 1 h, a solution of the hydrazine **3** (16.0 mmol) and triethylamine (16.0 mmol) in THF (10 mL) was added dropwise. After the solution was stirred for 12 h at room temperature, the solvent was evaporated. The residue was dissolved in ethyl acetate, and the solution was washed three times with brine, dried over Na_2SO_4, and evaporated. Chromatographic purification afforded the didepsipeptides **6** in yields ranging from 59 to 76%.

2. Carbon Dioxide Procedure (Procedure 2). Carbon dioxide was passed through a suspension of cesium carbonate (70.0 mmol) and hydrazine **3** (35.0 mmol) in DMF (140 mL) for 30−60 min. *tert*-Butyl bromoacetate (35.0 mmol) was added slowly, and carbon dioxide was bubbled through the mixture for another 45 min. After being stirred for 12 h at room temperature, the mixture was poured into water and extracted with ethyl acetate (three times). The organic layers were combined, dried over Na_2SO_4, filtered, and concentrated. Chromatographic purification afforded the didepsipeptides **6** in yields ranging from 67 to 97%.

Benzyl N-Boc-*N*-methylazaalanylhydroxyaectate 6a: procedure 2; yield 96% (HPLC purity 96%); yellow viscous oil; IR 1712, 1758 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.45 (s, 9H), 3.1 (s, 6H), 4.40−5.30 (m, 4H), 7.35 (5H); MS (FAB) *m*/*e* 353 ([M + H]$^+$, 100), 295 ([M − *t*-Bu]$^+$, 5), 253 ([M + H − Boc]$^+$, 40), 91 (100); HRMS (ESI) *m*/*e* 375.1523 (calcd for $C_{17}H_{24}N_2O_6Na$ 375.1526).

Benzyl *N*-Boc-*N*-methylazavalylhydroxyacetate 6b: procedure 2; yield 87% (HPLC purity 97%); yellow viscous oil; IR 1715, 1764 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.20 (d, 6H, $J = 8$ Hz), 1.45 (s, 9H), 3.08 (m, 3H), 4.3−5.25 (m, 5H), 7.35 (m, 5H); MS (FAB) *m*/*e* 325 (5), 281 ([M + H − Boc]$^+$); HRMS (ESI) *m*/*e* 403.1836 (calcd for $C_{19}H_{28}N_2O_6Na$ 403.1839).

Benzyl *N*-Boc-*N*-methylazanorvalylhydroxyacetate 6c: procedure 2; yield 67% (HPLC purity 95%); yellow viscous

oil; IR 1715, 1729, 1762 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.93 (t, 3H, J = 9 Hz); 1.47 (s, 9H), 1.63 (m, 2H), 2.90−3.55 (m, 5H), 4.4−5.25 (m, 4H), 7.36 (m, 5H); MS (FAB) *m/e* 381 ($[M + H]^+$, 5), 281 ($[M + H - Boc]^+$, 50), 280 ($[M - Boc]^+$, 53); HRMS (ESI) *m/e* 403.1834 (calcd for $C_{19}H_{28}N_2O_6Na$ 403.1839).

Benzyl *N*-Boc-*N*-methylazaleucylhydroxyacetate 6d: procedure 2; yield 84% (HPLC purity 92%); yellow viscous oil; IR 1716, 1731 cm^{-1};^1H NMR (500 MHz, $CDCl_3$) δ 0.95 (d, 6H, J = 8 Hz), 1.45 (s, 9H), 1.95 (m, 1H), 3.0−3.4 (m, 5H), 4.4−5.25 (m, 4H), 7.35 (m, 5H); MS (FAB) *m/e* 395 ($[M + H]^+$, 20), 340 (25), 339 (100), 295 ($[M + H - Boc]^+$, 18); HRMS (ESI) *m/e* 417.1992 (calcd for $C_{20}H_{30}N_2O_6Na$ 417.1996).

Benzyl *N*-Boc-*N*-methylazanorleucylhydroxyacetate 6e: procedure 2; yield 76% (HPLC purity 100%); yellow viscous oil; IR 1714, 1731, 1764 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.95 (m, 3H), 1.30−1.60 (m, 13H), 3.05−3.65 (m, 5H), 4.4−5.3 (m, 4H), 7.35 (m, 5H); MS (FAB) *m/e* 395 ($[M + H]^+$, 5), 339 ($[M + H - t\text{-}Bu]^+$, 80), 295 ($[M + 1 - Boc]^+$, 100); HRMS (ESI) *m/e* 417.1999 (calcd for $C_{20}H_{30}N_2O_6Na$ 417.1996).

Benzyl *N*-Boc-*N*-methylazaphenylalanylhydroxyacetate 6f: procedure 2; yield 97% (HPLC purity 97%); yellow viscous oil; IR 1714 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.45 (s, 9H), 2.80 (s, 3H), 4.3−5.3 (m, 6H), 7.35 (m, 10H); MS (FAB) *m/e* 429 ($[M + H]^+$, 5), 371 (75), 329 ($[M + H - Boc]^+$, 100), 328 (80); HRMS (ESI) *m/e* 451.1832 (calcd for $C_{23}H_{28}N_2O_6Na$ 451.1839).

Benzyl *N*-Boc-*N*-methylaza-4-bromophenylalanylhydroxyacetate 6g: procedure 2; yield 85% (HPLC purity 95%); yellow viscous oil; IR 1720 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.45 (ms, 9H), 2.85 (ms, 3H), 4.25−5.35 (m, 6H), 7.45 (m, 9H); MS (FAB) *m/e* 507 (M^+, 10), 453 (70), 451 (80), 409 (85), 407 (100); HRMS (ESI) *m/e* 529.0950 (calcd for $C_{23}H_{27}BrN_2O_6$-Na 529.0945).

Benzyl *N*-Boc-*N*-methylazaleucyl-(*R*)-3-phenyllactate 6h: procedure 1; yield 76% (HPLC purity 100%); yellow viscous oil; R_f = 0.82 (cyclohexanes−ethyl acetate 2:1); $[\alpha]^{20}_D$ = +4.676 (c = 0.38, $CHCl_3$); IR 1744 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.94 (d, 6H, J = 8 Hz), 1,47 (s, 9H), 1.85 (m, 1H), 2,62 (d, 2H, J = 8 Hz), 3.0 (s, 3h), 3,15 (m, 2H), 5.1 (m, 3H), 7.2 (m, 10H); MS (FAB) *m/e* 484 (M^+, 1), 428 (10), 385 (40), 91(100); HRMS (ESI) *m/e* 507.2467 (calcd for $C_{27}H_{36}N_2O_6Na$ 507.2466).

Benzyl *N*-Boc-*N*-methylazaleucyl-(*R*)-lactate 6i: procedure 1; yield 59% (HPLC purity 94%); yellow viscous oil; R_f = 0.61 (cyclohexanes−ethyl acetate 3:1); $[\alpha]^{20}_D$ = +3.871 (c = 0.46, $CHCl_3$); IR 1709, 1754 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.94 (d, 6H, J = 8 Hz), 1.48 (s, 9H), 1.53 (d, 3H, J = 8.5 Hz), 1.70 (m, 1H), 2.62 (d, 2H, J = 7.5 Hz), 3.02 (s, 3H), 5.06 (m, 1H), 5.20 (AB-system, 2H), 7.34 (m, 5H); MS (FAB) *m/e* 409 ($[M + H]^+$, 2), 353 (100), 309 ($[M + H - Boc]^+$, 45); HRMS (ESI) *m/e* 431.2154 (calcd for $C_{21}H_{32}N_2O_6Na$ 431.2153).

***N*-Boc-*N*-methylazaleucyl-(*R*)-3-phenyllactic Acid 13.** Compound **6g** (15.54 g, 30.0 mmol) was dissolved in ethyl acetate (150 mL) and hydrogenated (Pd/C, 10%, 400 mg) for 4 h at room temperature. After filtration of the catalyst and evaporation of the solvent, the crude product was obtained as a yellow viscous oil in quantitative yield (11.9 g): R_f = 0.08 (cyclohexanes−ethyl acetate 2:1); IR 1750, 2900−3400 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.95 (d, 6H, J = 8 Hz), 1.35−1.55 (m, 10H), 1.85 (m, 1H), 2.75 (s, 3H), 2.95−3.30 (m, 8H); 5.1 (m, 1H), 7.30 (m, 5H); MS (FAB) *m/e* 417 ($[M + Na]^+$, 20), 395 ($[M + H]^+$, 10), 394 (M^+, 5), 339 (70), 321 (40), 295 (100).

Benzyl *N*-Methylazaleucyl-(*R*)-lactate 14. TFA (27.36 g, 240 mmol) was added dropwise at 0 °C to a solution of **6h** (12.25 g, 30.0 mmol) in CH_2Cl_2 (100 mL). The reaction mixture was stirred for 24 h at room temperature. Then the solvent was evaporated, and the residue was dissolved in ethyl acetate and washed with aqueous $NaHCO_3$ solution and brine. After the solution was washed with Na_2SO_4, the solvent was removed and the residue purified by column chromatography (cyclohexanes−ethyl acetate 7:1), furnishing **14** (7.21 g, 78%, HPLC purity 98%) as a yellow viscous oil: R_f = 0.50 (cyclohexanes−ethyl acetate 2:1); ^1H NMR (500 MHz, $CDCl_3$) δ 0.90 (d, 6H, J = 8 Hz), 1.53 (d, 3H, J = 8 Hz), 2.0 (m, 1H), 2.70 (s, 3H), 3.27 (d, 2H, J = 8 Hz), 5.18 (AB system + m, 3H), 7.35 (m, 5H); MS (FAB) *m/e* 309 ($[M + H]^+$, 100), 308 (M^+, 89).

Benzyl *N*-Boc-*N*-methylazaleucyl-(*R*)-phenyllactyl-*N*-methylazaleucyl-(*R*)-lactate 16. Ethyl diisopropylamine (9.69 g, 75.0 mmol) and BOP-Cl (9.16 g, 36 mmol) were added at 0 °C to a solution of **14** (11.9 g, 30.0 mmol) and **13** (9.22 g, 30.0 mmol) in CH_2Cl_2 (120 mL). After 2 h at 0 °C, the reaction mixture was allowed to warm to room temperature and stirred for 12 h. The solution was washed three times with water, dried over Na_2SO_4, and concentrated. Column chromatography (cyclohexanes−ethyl acetate 6:1) of the residue gave **16** (9.25 g, 45%, HPLC purity 94%) as a pale yellow foam: $[\alpha]^{20}_D$ = −24.196 (c = 0.84, $CHCl_3$); IR 1691, 1720, 1753 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, mixture of conformers) δ 0.8−1.1 (m), 1.3−1.7 (m), 2.7−3.3 (m), 5.0−5.3 (m), 7.1−7.5 (m); HRMS (FAB) *m/e* 707.3628 (calcd for $C_{36}H_{52}N_4O_9Na$ 707.3627).

Benzyl *N*-Methylazaleucyl-(*R*)-phenyllactyl-*N*-methylazaleucyl-(*R*)-lactate 18. To a solution of **16** (3.08 g, 4.5 mmol) in CH_2Cl_2 (60 mL) was added TFA (5.14 g, 45 mmol) dropwise at 0 °C. The solution was allowed to warm to room temperature and stirred for 15 h. Afterward, the solvent was evaporated. The residue was dissolved in CH_2Cl_2, washed with saturated aqueous $NaHCO_3$ solution, and dried over Na_2SO_4. Evaporation of the solvent afforded crude **18** (2.67 g, quant) as a pale yellow foam that was used for subsequent reaction without further purification: MS (FAB) *m/e* 585 ($[M + H]^+$, 35), 584 (M^+, 20).

Benzyl *N*-Boc-*N*-methyl-(*S*)-leucyl-(*R*)-phenyllactyl-*N*-methyl-(*S*)-leucyl-(*R*)-lactyl-*N*-methylazaleucyl-(*R*)-phenyllactyl-*N*-methylazaleucyl-(*R*)-lactate 19. To a solution of **17** (2.67 g, 4.5 mmol), BOP-Cl (1.40 g, 5.50 mmol), and *N*-methylmorpholine (0.59 g, 5.8 mmol) in CH_2Cl_2 (45 mL)-was added **18** (2.62 g, 4.5 mmol), dissolved in CH_2Cl_2 (10 mL), dropwise at 0 °C. Another 0.59 g of *N*-methylmorpholine was added, and the reaction was stirred for 12 h at room temperature. Subsequently, the solvent vas evaporated. The residue was dissolved in ethyl acetate, washed with brine, dried over Na_2SO_4, and concentrated. Column chromatography (cyclohexanes−ethyl acetate 3:1) furnished **19** (2.40 g, 46%, HPLC purity 96%): R_f = 0.50 (cyclohexanes−ethyl acetate 1:1); $[\alpha]^{20}_D$ −54.816 (c = 0.39, $CHCl_3$); IR 1690, 1729 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, mixture of conformers) δ 0.8−1.0 (m), 1.35−1.60 (m), 2.7−3.7 (m), 4.6−5.5 (m), 7.1−7.4 (m); MS (FAB) *m/e* 1059 ($[M + H - Boc]^+$, 100), 1181 ($[M + Na]^+$, 58); HRMS (FAB) *m/e* 1181.6362 (calcd for $C_{62}H_{90}N_6O_{15}Na$ 1181.6349).

Bis-aza PF1022A 9. TFA (1.34 g, 11.73 mmol) was added dropwise to a solution of **19** (1.36 g, 1.173 mmol) in CH_2Cl_2 (10 mL) at 0 °C. The reaction mixture was stirred for 12 h at 0 °C followed by evaporation of the solvent and dissolution of the residue in ethyl acetate. The solution was washed with saturated $NaHCO_3$ solution and brine, dried over Na_2SO_4, and concentrated. The crude material (0.95 g, 76%, MS (ESI) *m/e* 1059 (M^+, 100)) was dissolved again in ethyl acetate (30 mL) and hydrogenated (Pd/C 10%, 500 mg) at room temperature until the hydrogen consumption ceased. The catalyst was removed by filtration through Celite, followed by evaporation of the solvent. The crude product (800.6 mg, 0.825 mmol, MS (ESI) *m/e* 969 (M^+, 100)) was dissolved in CH_2Cl_2 (1000 mL), ethyl diisopropylamine (266.3 mg, 2.06 mmol) and BOP-Cl (252 mg, 0.99 mmol) were added at 0 °C, and the reaction was allowed to warm to room temperature where it was stirred for 24 h. Subsequently, the solution was washed with saturated aqueous $NaHCO_3$ solution and water. After drying over Na_2SO_4 and evaporation of the solvent, the product was purified by column chromatography (toluene−2-propanol 10:1) and preparative HPLC (CH_3CN-H_2O 75:25) to give **9** (321 mg, 41%, HPLC purity 94%) as a white solid: mp 90−91 °C; $[\alpha]^{20}_D$ = −80.613 (c = 0.34, $CHCl_3$); IR 1668, 1728 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, assignment for the asymmetrical conformer) 0.82 and 0.93 (d, 6H, H_δ-MeLeu^2, J = 8.0 Hz), 0.86 and 0.97 (d, 6H, H_δ-aza-MeLeu^4, J = 8.0 Hz), 0.88 (d, 6H, H_δ-aza-MeLeu^6, J = 8.0 Hz), 0.92 (d, 6H, H_δ-MeLeu^8, J = 8.0 Hz), 1.08 (d, 3H, H_β-Lac^3, J = 6.8 Hz), 1.32 (m, 1H, H_γ-MeLeu^8), 1.39 (d, 3H, H_β-Lac,^{7} J = 6.9 Hz), 1.53 (m, 2H, H_β-MeLeu^2), 1.54 (m, 2H, H_γ-aza-MeLeu^6 + H_γ-MeLeu^2), 1.55 (m, 1H, H_β-

MeLeu[8]), 1.65 (ddd, 2H, H_β-MeLeu[2], J = 4.2, 10.5, 14.7 Hz), 1.72 (ddd, 1H, H_β-MeLeu[8], J = 4.2, 10.8, 14.7 Hz), 2.06 (m, 1H, H_γ-aza-MeLeu[4]), 2.88 (s, 3H, NCH_3-MeLeu[8]), 2.94 (dd, 1H, H_β-aza-MeLeu[6], J = 5.1, 14.7 Hz), 2.97 (s, 3H, NCH_3-MeLeu[2]), 3.13 and 3.14 (m, 2H, H_β-PheLac[5]), 3.13 and 3.18 (m, 2H, H_β-PheLac[1]), 3.14 (s, 3H, NCH_3-aza-MeLeu[4]), 3.16, (s, 3H, NCH_3-aza-MeLeu[6]), 3.54 (dd, 1H, H_β-aza-MeLeu[4], J = 5.9, 14.4 Hz), 3.66 (dd, 1H, H_β-aza-MeLeu[4], J = 5.9, 14.4 Hz), 3.67 (dd, 1H, H_β-aza-MeLeu[6], J = 6.7, 14.7 Hz), 4.95 (q, 1H, H_α-Lac[3], J = 6.8 Hz), 5.39 (dd, 1H, H_α-MeLeu[2], J = 4.2, 11.8 Hz), 5.42 (t, 1H, H_α-PheLac,[5] 7.3 Hz), 5.55 (dd, 1H, H_α-MeLeu[8], J = 4.2, 11.9 Hz), 5.58 (t, 1H, H_α-PheLac[1], J = 7.7 Hz), 5.59 (q, 1H, H_α-Lac,[7] J = 6.9 Hz); MS (FAB) *m*/*e* 973 ($[M + Na]^+$, 100), 951 ($[M + H]^+$, 36); HR-MS (ESI) *m*/*e* 973.5264 (calcd for $C_{50}H_{74}N_6O_{12}Na$ 973.5262).

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Supporting Information Available: Copies of ^1H NMR of **3c**,**d**, **6**, **16**, **19**, and **9** and ^{13}C NMR spectra of **3**, **6**, **16**, **19**, and **9** as well as ORTEP figures for **8** and **9**. This material is available free of charge via the Internet at http://pubs.acs.org.

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