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Bisphosphine-Functionalized Cyclic Decapeptides Based on the Natural Product Gramicidin S: A Potential Scaffold for Transition-Metal Coordination

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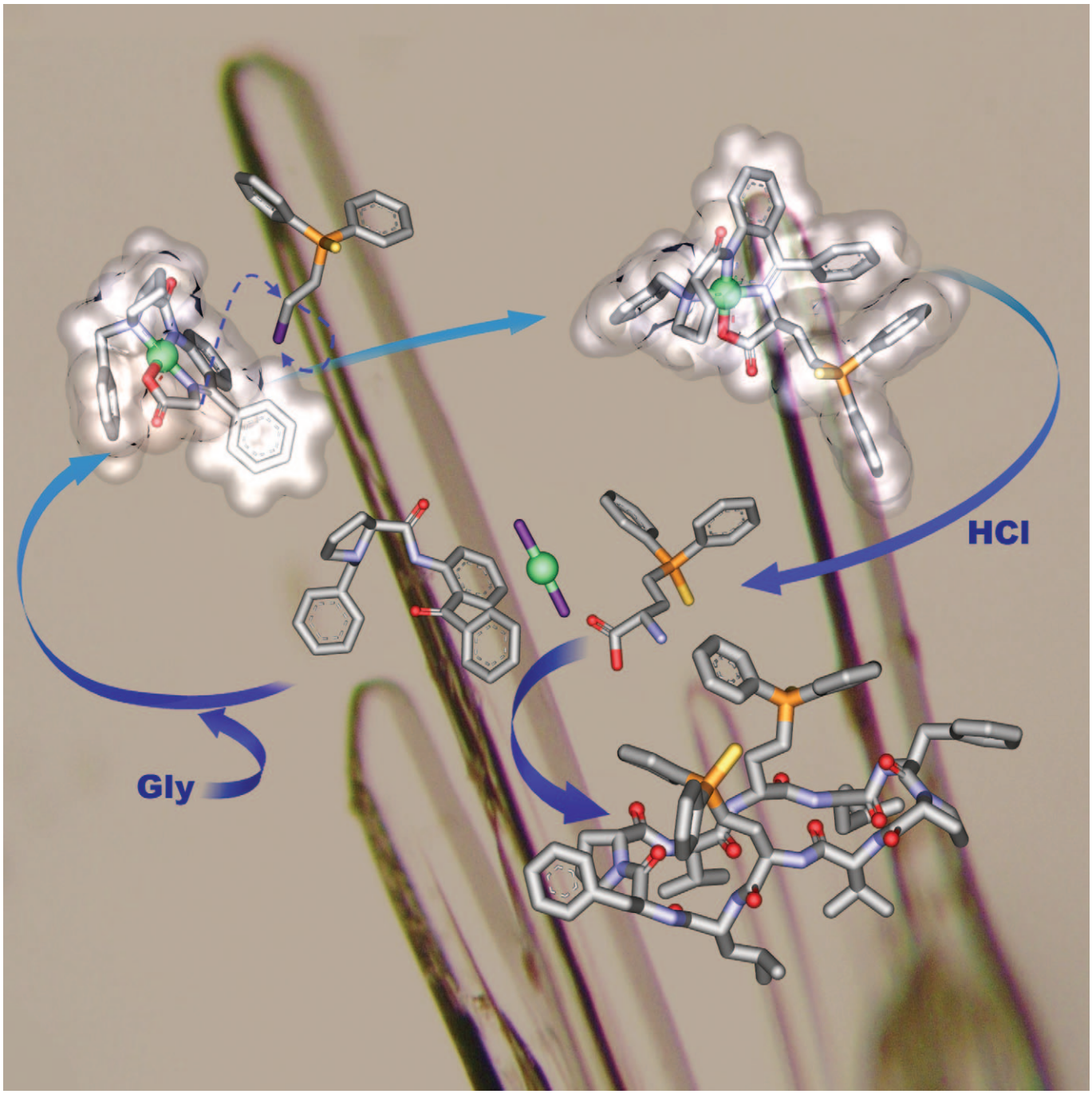

Abstract: The natural product Gramicidin S is a promising scaffold for novel oligopeptide-based bisphosphine ligands, combining the advantageous rigid chiral backbone with the close proximity of phosphine substituents. The required unnatural, phosphine-containing, amino acid building blocks were synthesized by means of a novel protocol that involves the enantioselective alkylation of a chiral nickel Schiff base template. Three Ni complexes were prepared with different alkyl chains between the phosphine group and the α-carbon atom of the incorporated glycine; the absolute stereochemistry of two of them was determined by single-crystal X-ray structure analysis. By detaching the template, enantiopure L-phosphine amino acids resulted enabling the solid-phase, stepwise construction of a linear sequence of the phosphine-modified oligopeptides. On cyclization three bisphosphine-substituted Gramicidin S analogues resulted, differing only in the size and shape of the linkage between the phosphine groups and the oligopeptides backbone. Their crystal structures suggest these species to have potential as chelating ligands.

Keywords: amino acids · peptides · phosphanes · solid-phase synthesis · X-ray diffraction

Introduction

Designer-modified oligopeptides (peptide engineering) provide access to new molecules with unique functional properties, while retaining the structural characteristics of the parent system.[1] Exemplary is their use in asymmetric catalysis both as organocatalysts[2] and as ligands for transition-metal complexes.[3,4] In their pioneering work, Gilbertson and co-workers showed phosphine-derivatized oligopeptides to function as transition-metal ligands in asymmetric catalytic reactions, such as hydrogenation and allylic substitution.[4] Crucial to the design of oligopeptide catalysts for bidentate metal chelation is the spatial orientation of the two phosphine moieties, necessitating proper placements of these functional groups in the secondary structure of the peptide backbone. Rhodium complexes of such α-helices and palladium complexes of β-turn motifs (Figure 1, left), even embedded on solid support, reportedly display varying degrees of catalytic activity for different turn motifs and sequences.[4] Intrigued by the demonstrated catalytic prospects we recognized the void in structural information of the polypeptides and the tunability of the oligopeptide ligands.

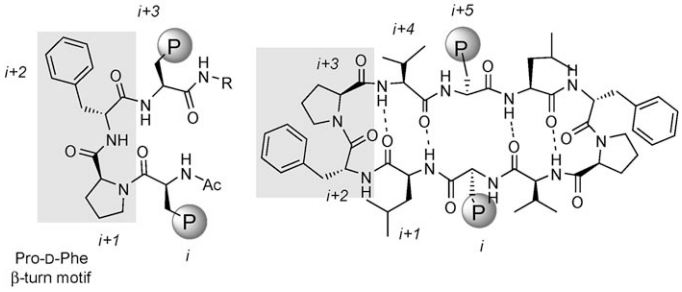

Figure 1. Gilbertson's peptide-based ligand with β-turn motif (left) and the bisphosphine-functionalized Gramicidin S analogue (right).

In search of a system that would enforce close proximity with some flexibility of the ligating phosphine groups, we decided to construct a rigid cyclic oligopeptide. As a rigid peptide scaffold, we selected the structurally well-studied antimicrobial peptide Gramicidin S (GS, cyclo(Val-Orn-Leu-D-Phe-Pro)$_2$), which is a C_2-symmetric cyclic decapeptide that adopts a rigid cyclic β-hairpin structure.[5,6] The GS structure is stabilized by four intramolecular hydrogen-bonding interactions at the opposing Val and Leu residues and the two 2-residue turns of the D-Phe-Pro sequences. The two Orn residues, as part of the short β-strand sequences (Val-Orn-Leu), have their side chains in close spatial proximity and are therefore ideally suited to be replaced by phosphine amino acids. Such a designer oligopeptide (Figure 1, right) necessitates the phosphine substituents to have minimal effect on the steric properties of the amino acids to avoid disturbing the peptide backbone through

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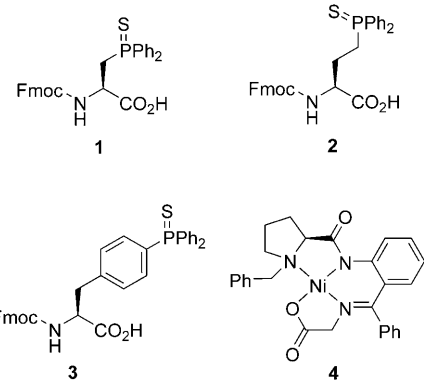
altered dihedral and torsional angles and hydrogen-bonding interactions.

The synthesis of the designer cyclic decapeptides requires the preparation of amino acid building blocks with different lengths and rigidities of the phosphine-containing side chain. Whereas there is a great variety in tailor-made amino acids with which to study and modify proteins and polypeptides, those with non-natural substituents remain rare. This is particularly true for phosphine-containing amino acids, in part due to the sensitivity of the phosphine groups toward oxidation, which would hamper its chelation to transition metals. In this paper we report on the synthesis of three phosphine amino acids with different substituents using a template approach for two of them. The appropriateness of a chiral Ni^{II} Schiff base template is examined as they are used increasingly in the synthetic design of tailor-made amino acids. We further address the incorporation of the three derivatized chiral amino acids into the backbone of the cyclic decapeptide GS and examine the geometrical features of the bisphosphine derivatives by X-ray crystal structures.

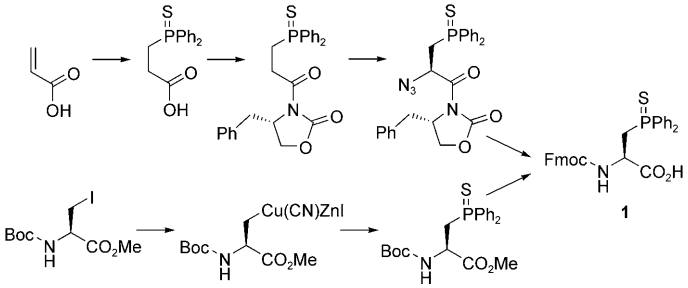
Results and Discussion

Synthesis of amino acids: To evaluate phosphine-functionalized amino acids for incorporation into Gramicidin S we considered **1**, **2**, and **3** with their respective methylene, ethylene, and benzylene linkages, and Belekon's template **4** (see below). The three derivatized amino acids must be obtained



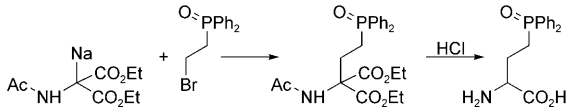
enantiomerically pure in the depicted L-configuration with an Fmoc-protected amino function (Fmoc = 9-fluorenylmethoxycarbonyl) and an unprotected carboxylic acid to enable their use in standard peptide methods to synthesize the Gramicidin S derivatives. To avoid oxidation of the amino acids during the peptide synthesis, the phosphorus atom is protected with a sulfur atom, which can be removed at a later stage to obtain the desired bisphosphine-substituted cyclic decapeptides.[4,7]

Two different syntheses of enantiomerically pure **1** have been described earlier by Gilbertson (Scheme 1).[4] The first route utilizes Evans'[8] chiral oxazolidone chemistry and involves chromatographic separation of diastereomeric azides, while the less elaborate route based on Knochel's protocol for the preparation of zinc cuprates[9] starts with a commercially available, chiral iodo amino acid. Neither route is readily extended to phosphine-derivatized amino acids with linkages different from methylene.



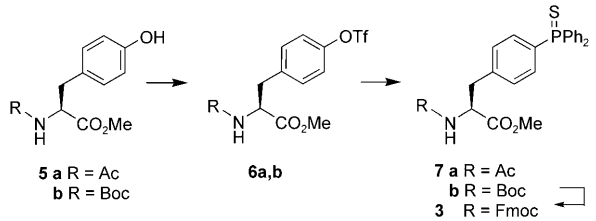
Scheme 1. Enantioselective synthesis of **1** based on the Evans' (top) and Knochel's (bottom) protocol.

For **2** only the synthesis of a racemic mixture of the phosphine oxide functionalized free amino acid has been reported.[10] This route involves the reaction of bromoethylphosphine oxide with diethylacetamidomalonate and subsequent acid hydrolysis of the resulting alkylation product (Scheme 2).



Scheme 2. Synthesis of racemic phosphine oxide analogue of **2**.

The synthesis of a tyrosine derivative related to **3**, containing Ac and CO_2Me instead of Fmoc and CO_2H groups, respectively, and its implementation into a linear pentapeptide has been reported earlier, but no structural details were provided other than spectroscopic data (Scheme 3).[4] We



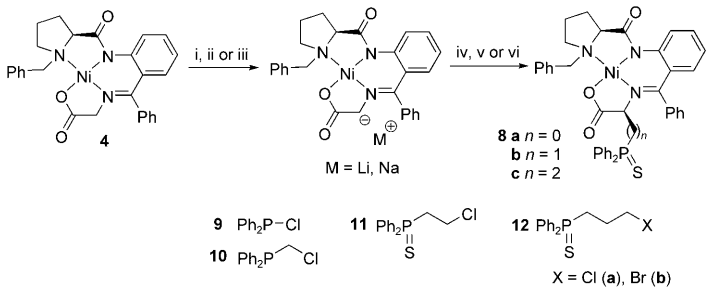
Scheme 3. Synthesis of tyrosine derivative **3**.

adapted this procedure and provide full details in the Experimental Section to render the Fmoc-protected **3** from compounds **5**–**7**, for use in the standard peptide synthetic protocol.

We wondered whether a general protocol can be developed that allows for varying the length of the $-(CH_2)_n-$ link-

age between the α-carbon atom of a chiral amino acid and its phosphine moiety. Belekon's template, the Ni^{II} Schiff base of (*S*)-2-[*N*-(benzylpropyl)-amino]benzophenone (**4**), is an ideal candidate for enantioselective alkylation to render enantiomerically pure phosphine-derivatized amino acids. It has been demonstrated already that glycine incorporated in **4** can be functionalized[11] and that the resulting unnatural amino acid can be removed readily from the template in high yields and large quantities.[12] However, we are aware of only one example introducing a phosphorus-containing substituent, namely the synthesis of phosphinato- and phosphonato-substituted amino acids.[13] Here, we describe our efforts to use template **4** for introducing phosphine substituents with carbon linkages ranging from $n=0$–2 (compounds **8a–c**).

Deprotonation of **4** with *n*BuLi, NaH or NaOH rendered the corresponding anion. In situ phosphanation with **9** and alkylation with the phosphine-containing reagents **10** and **11**, followed by sulfurization in the case of **9** and **10**, afforded after column chromatography the functionalized templates **8a–c** as red powders in yields of about 90% (Scheme 4). The need for using slightly different reaction



Scheme 4. Enantioselective alkylation of template **4**. i) *n*BuLi, THF, −78°C. ii) NaH, acetonitrile. iii) NaOH, acetonitrile. iv) addition of **9**, −78°C; addition of S_8 at RT, 16 h. v) addition of **10**, after 8 h addition of S_8, 16 h. vi) addition of **11**, 16 h.

conditions (see Experimental Section) is ascribed to the difference in reactivity of **9**, **10**, and **11**. Whereas chlorophosphine **9** reacts readily with $Li^{+}4^{-}$, the more reactive $Na^{+}4^{-}$ ion pair is needed for chloromethylphosphine **10**. Interestingly, the corresponding phosphine sulfide (**10**·S) displayed no reactivity, which we attribute to deactivation of the leaving group by the electron-withdrawing nature of the phosphine sulfide. Attempts to extend the alkylation with the next higher homologue ($n=3$), the propyl-containing **12a** or its bromo derivative **12b**, was unsuccessful, probably due to self alkylation of the substrate under the reaction conditions.[14]

Stereochemistry of amino acids: Products **8a–c** were each obtained as single diastereomers, whereas the phosphanation and alkylation of the anion of chiral **4** might have given two. The high selectivity is evident from the single, sharp ^{31}P NMR resonance (**8a** 49.3; **8b** 36.7; **8c** 42.3 ppm) observed in the crude reaction mixtures. Single-crystal X-ray structure determinations established the stereochemistry of two of the products. Suitable red needles of solvate **8b** were obtained from a solution of the compound in acetonitrile at 4°C. Compound **8c** crystallized as orange needles with two independent molecules per unit cell on vapor diffusion of *n*-hexane into a solution of **8c** in ethyl acetate. Their molecular structures (Figure 2, Table 1) show pseudo square-planar coordination of nickel by three nitrogen atoms and one oxygen atom, like that for the non-functionalized template **4**.[14] The bond lengths and angles around nickel are very similar for **8b** and the two independent molecules for **8c**. A notable difference is the manner in which the *N*-benzyl and alkylphosphinyl groups are rotated, which may be due to packing effects in the solid state. Importantly, the desired and expected *S* configuration at the α-carbon atom of the embedded glycine fragment is confirmed for both **8b** and **8c**.

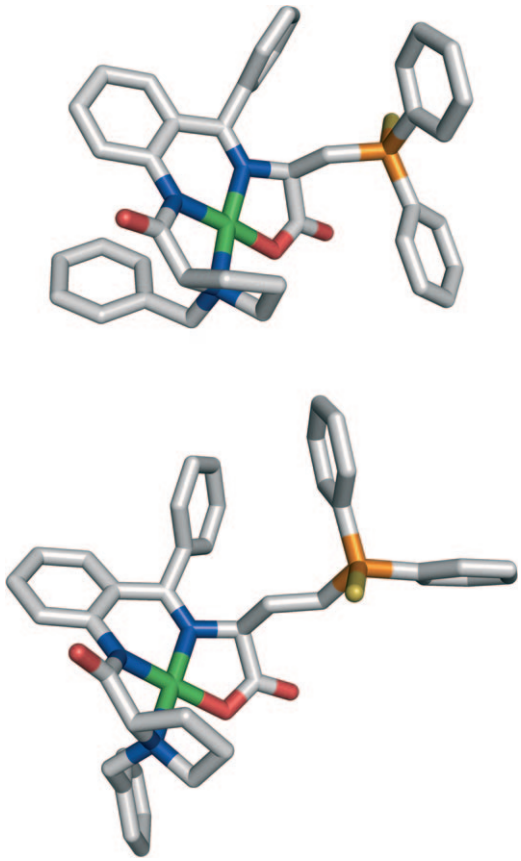


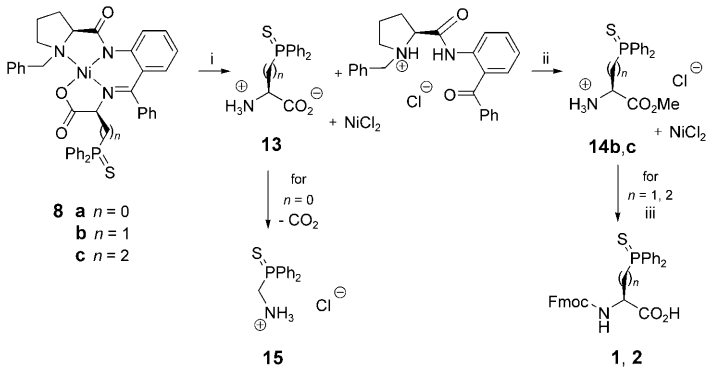
Figure 2. Molecular structure of **8b** (top) and **8c** (bottom). H atoms have been omitted for clarity. Selected bond lengths (Å) and angles (°), **8b**: Ni(1)–N(1) 1.946(7), Ni(1)–N(8) 1.847(7), Ni(1)–N(22) 1.859(7), Ni(1)–O(26) 1.865(6); N(8)-Ni(1)-N(22) 94.5(3), N(8)-Ni(1)-O(26) 175.0(3), N(22)-Ni(1)-O(26) 87.1(3), N(8)-Ni(1)-N(1) 88.4(3), N(22)-Ni(1)-N(1) 173.4(3), O(26)-Ni(1)-N(1) 90.5(3). **8c**: Ni(1)-N(5) 1.845(7), Ni(1)-N(9) 1.822(7), Ni(1)-N(12) 1.940(7), Ni(1)-O(1) 1.848(6), N(9)-Ni(1)-N(5) 93.7(3), N(9)-Ni(1)-O(1) 176.2(3), N(5)-Ni(1)-O(1) 87.0(3), N(9)-Ni(1)-N(12) 84.1(3), N(5)-Ni(1)-N(12) 174.4(3), O(1)-Ni(1)-N(12) 94.9(3).

Table 1. Selected crystallographic data for compounds **8b**, **8c**, **19b** and **19c**.

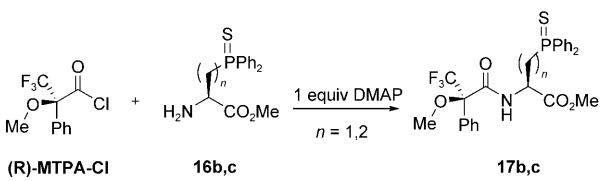
	8b	**8c**	**19b**	**19c**
formula	$C_{40}H_{36}N_3NiO_3PS$ $4(C_2H_3N)$ H_2O	$2(C_{41}H_{38}N_3NiO_3PS)$	$2(C_{82}H_{104}N_{10}O_{10}P_2S_2)$ $7(H_2O)$	$C_{92}H_{108}N_{10}O_{10}P_2S_2$ H_2O
M_r [g mol^{-1}]	910.69	742.47	3157.78	1657.99
λ [Å]	0.71073	1.5418	1.5418	1.5418
crystal system	orthorhombic	triclinic	monoclinic	monoclinic
space group	$P2_12_12_1$	$P1$	$P2_1$	$P2_1$
a [Å]	11.8645(7)	9.2751(5)	19.936(4)	9.3998(6)
b [Å]	18.2225(8)	13.7542(6)	19.008(4)	27.6013(19)
c [Å]	21.1364(13)	14.2109(6)	23.812(5)	17.1335(12)
α [°]	90	79.029(2)	90	90
β [°]	90	88.427(3)	100.03(3)	95.552(4)
γ [°]	90	87.292(5)	90	90
V [Å^3]	4569.7(4)	1777.5(1)	8886(3)	4424.4(5)
ρ_{calcd} [g cm^{-3}]	1.324	1.387	1.175	1.245
Z	4	1	2	2
μ [mm^{-1}]	0.557	2.110	1.39	1.407
$F(000)$	1912	776	3344	1764
crystal size [mm]	0.08×0.10×0.70	0.03×0.08×0.18	0.01×0.02×0.09	0.02×0.02×0.11
T [K]	100.0(1)	110.0(1)	100.0(1)	100.0(1)
θ range [°]	1.48–20.81	3.17–54.24	1.90–50.40	2.59–47.48
reflns collected	32704	71873	64214	24272
reflns unique	4801	8607	17558	7899
$R_{(int)}$	0.0892	0.1214	0.0620	0.0777
data	4775	8607	17558	7899
restraints	4	32	1012	1407
parameters	318	902	1006	1069
GOF on F^2	1.341	1.124	2.43	1.327
$R1$ indices [$I>2\sigma(I)$]	0.0671	0.0805	0.1753	0.1098
$wR2$ indices [$I>2\sigma(I)$]	0.1491	0.1839	0.4868	0.2904
$R1$ indices (all data)	0.0912	0.0956	0.1792	0.1279
$wR2$ indices (all data)	0.1599	0.2033	0.4990	0.3123
absolute structure	0.01(3)	0.00(3)	0.30(5)	0.08(5)
largest difference peak/hole [e Å^{-3}]	0.59/−0.44	1.46/−0.56	1.77/−0.72	0.53/−0.50

Enantiomerically pure amino acids are generally obtained from Schiff base Ni^{II} complexes by simple hydrolysis, requiring little purification, but there is diversity in reaction conditions, yield, and stereoselectivity.[12] We wondered how the phosphine-containing compounds **8a–c** would sustain the hydrolysis. Liberation of the derivatized amino acids required prolonged heating in a mixture of MeOH and 2 M HCl for the red color of the solutions to fade to pale green or yellow (Scheme 5). After simple work-up, including the recovery of the free ligand of the template for reuse towards **4**, formation of the phosphine substituted amino acid intermediate **13**, and removal of the nickel salts, methyl esters **14b** and **14c** were isolated in respectively 93 and 82% yield, respectively, and were fully characterized by NMR spectroscopy. However, in case of **8a** the desired product **14a** was not obtained. The ^{1}H NMR spectrum did not show the presence of an ester or carboxylic acid group and the ^{13}C-DEPT NMR spectrum revealed a methylene group. We identify the product as amino-phosphine **15**, formed by decarboxylation of the intermediate phosphine-substituted amino acid **13a**. Decarboxylation was reported earlier in attempts to synthesize a phosphinyl glycine[16] and represents a common degradation of phosphine acetic acids.[17]

Base-catalyzed ester cleavage of **14b** and **c**, followed by the standard protocol for introducing the Fmoc group in protected amino acids,[4] gave after purification by column chromatography analytically pure **1** and **2** in 72 and 62% yield, respectively (Scheme 5, step iii). Their enantiomeric purity was established by the Mosher's ester procedure for the methyl esters of the amine-deprotected **16b** and **c** (Scheme 6). Based on the integration of the ^{19}F NMR resonances of the two possible diastereomeric products **17b** and **c** resulting from the reaction of the free amines with (*R*)-α-methoxy-α-(trifluoromethyl)phenylacetic acid chloride (MTPACl) and one equivalent of 4-dimethylaminopyridine (DMAP) in chloroform (Scheme 6), verified by the reaction with racemic MTPACl, the enantiomeric ratios of **1** and **2** were determined to be 94:6 and >200:1, respectively.



Scheme 5. Liberation of PAA's **1** and **2**. i) MeOH, HCl (2N), 2 h. ii) MeOH, Et_2O/HCl, 16 h. iii) $LiOH_{aq}$, THF, 2 h; FmocOSu, $NaHCO_3$, dioxane, H_2O, 0 °C, 4 h.



Scheme 6. Determination of the enantiomeric purity of the PAAs by derivatization with Mosher's acid chloride.

Synthesis of cyclic decapeptides: The phosphine-functionalized amino acids (PAAs) **1**–**3** are now available for the construction of the desired bisphosphine-substituted oligopeptides. Previous studies have shown that cyclic decapeptides such as Gramicidin S and derivatives can be readily synthesized by cyclization of their corresponding linear precursors. The efficiency of the cyclization reaction of an activated linear decameric precursor depends strongly on the ability to preorganize into a β-hairpin conformation.[19] These previously cyclized peptide precursors generally have two bulky protected ornithine side chains presumable comparable in size with bulky phosphine-modified side chains and an otherwise identical sequence as our target peptide derivatives. Thus, a standard solid-phase peptide synthesis protocol,[19] starting with leucine as the first immobilized amino acid and the tailor-made Fmoc- and sulfur-protected PAAs **1**–**3** was followed toward the synthesis of the immobilized dimeric sequence **18a**–**c** (Scheme 7). The phosphorus-containing amino acids could be readily incorporated and are stable under Fmoc deprotection conditions, as anticipated. After acid treatment, cyclization, and purification the cyclic decamers **19a**–**c** were obtained in yields ranging from 45–65%.

The three cyclic decamers **19a**–**c** were fully characterized and their structures analyzed with high-field 1D and 2D NMR spectroscopy. Of the three cyclic peptides, **19a** proved to be less soluble, requiring more methanol and an elevated temperature to effectively record the NMR spectrum. Because of this, possibly in combination with the close proximity of the bulky $CH_2P(S)Ph_2$ groups, the NH signals of the amides appear broader and shifted as relative to those of peptides **19b** and **c**. The overall NMR data of compounds **19a**–**c**, however, are in full accord with the anticipated cyclic β-hairpin secondary structure,[20] which was established unequivocally for compounds **19b** and **19c** by single-crystal X-ray analysis. The structures (Figure 3) show that the molecules maintain the general β-strand arrangement of the parent GS molecule with twist angles of 15° and 37° for **19b** (both independent molecules) and **19c**, respectively (Figure 4). The twist angle is defined as the angle between straight lines drawn through opposing C-α atoms of the valine and leucine residues of the GS backbone. For native GS these angles are 18 and 47° for the structures determined by Llamas-Saiz et al. and Tishchenko et al., respectively,[5,6] suggesting that compound **19b** has a conformation less twisted than any of the native GS structures. The more twisted backbone conformation of **19c** is possibly induced by the more bulky phenyl group in the spacer. The side chains of the modified amino acids are more flexible in compound **19b** with respect to compound **19c**, as evidenced by disordered multiple conformations observed in the crystal structure. The distance between the phosphine atoms in **19b** is 6.2–6.5 Å, depending on the conformation, while for compound **19c** the distance is about 6.1 Å. Upon deprotection, the flexible phosphine-containing side chains should be able to act as chelating ligands. Preliminary modeling studies show indeed that

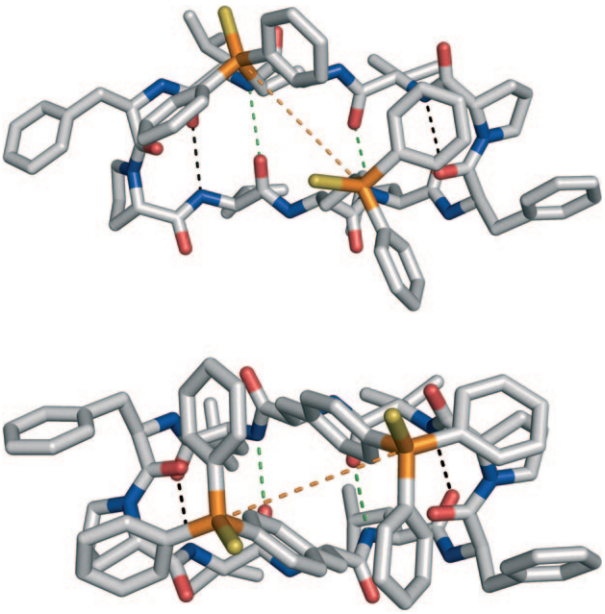
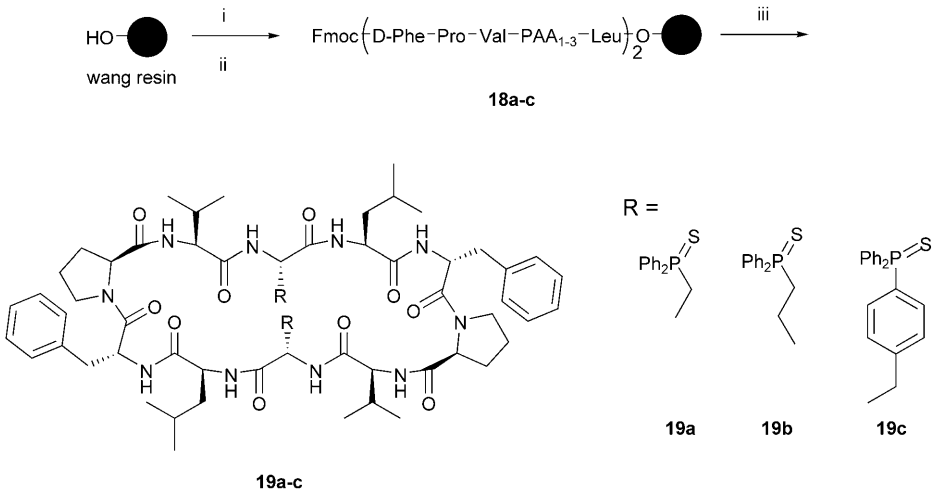


Figure 3. Molecular structure of functionalized GS compounds **19b** (top) and **19c** (bottom). Hydrogen atoms were omitted for clarity. Dashed lines display the "inner" (green) and "outer" (black) hydrogen bonds. The distance between phosphorus atoms is indicated by orange dashed lines.



Scheme 7. Synthesis of bisphosphine-functionalized Gramicidin S analogues **19a**–**c**. i) Fmoc-Leu-OH, DIC, DMAP. ii) Repetitive deprotection: 20% piperidine in NMP, peptide bond formation with **1**–**3** (denoted as PAA_{1-3}), HATU or the corresponding Fmoc-AA-OH, HCTU, DiPEA. iii) a) 20% piperidine in NMP, b) TFA/TIS/H_2O (95:2.5:2.5, v/v/v). iv) PyBOP, HOBt, DiPEA.

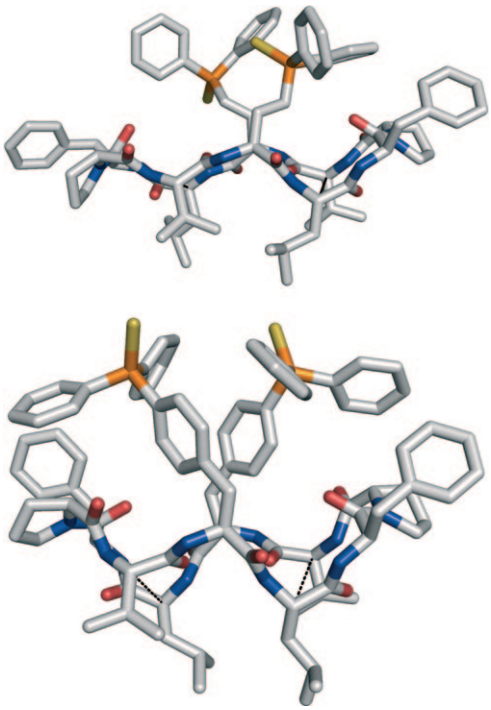


Figure 4. Side view of the molecular structure of functionalized GS compounds **19b** (top) and **19c** (bottom) indicating the twist angles.

these bisphosphine-functionalized Gramicidin S analogues are ideally suited for transition-metal complexation favoring the elusive *trans*-bisphosphine coordination over the typical *cis* configuration.[21] The synthesis of these metal complexes and their application in transition-metal catalysis is under active investigation.

Conclusions

The synthesis and structural characterization of three novel bisphosphine-substituted oligopeptides based on the natural product Gramicidin S were achieved by cyclization of their linear precursors obtained by a solid-phase peptide-coupling protocol. The notable difference between the GS analogues is found in the size and shape of the linkage between the phosphine group and the oligopeptide backbone. As a starting point, two of the three synthesized phosphine-containing amino acid building blocks were obtained by the enantioselective alkylation of a chiral nickel Schiff base complex with phosphine-containing reagents, which allows the introduction of varying alkyl chains between the phosphine group and the amino acid part. The selective formation of one diastereomer was observed by ^{31}P NMR spectroscopy and the absolute stereochemistry of the α-carbon atom of the generated phosphine amino acid was established by X-ray structure analysis. Acid-catalyzed liberation gave access to enantiopure free phosphine amino acids, which were purified and properly protected to enable their use in standard peptide-coupling protocols. The cyclic β-hairpin structure of GS analogues was proven by NMR spectroscopic studies and in two cases X-ray structures provided unique insight in the structural conformations of the phosphine-modified oligopeptides. The rigid peptide backbone enforces a close proximity of the two phosphorus atoms, which are available for transition-metal coordination after removal of the protecting sulfur atoms. The synthesis of the free ligands and their metal complexes as well as their potential in enantioselective catalysis is currently under active investigation.

Experimental Section

General: ^{1}H, ^{13}C, ^{19}F and ^{31}P NMR spectra were recorded on Bruker Avance 250, Bruker AV 400, and MSL 400 spectrometers at 298 K, unless stated otherwise. NMR chemical shifts are internally referenced to tetramethylsilane (^{1}H and ^{13}C NMR) and externally for ^{19}F to $CFCl_3$ and for ^{31}P to 85% H_3PO_4. Coupling constants (J) are given in Hz. Where indicated, NMR peak assignments were made using COSY and TOCSY experiments. Infrared spectra were recorded on a Paragon-PE 1000 and Shimadzu FTIR-84005 spectrophotometer and data are reported in cm^{-1}. High-resolution mass spectra were recorded on a Finnigan LTQ Orbitrap system, a JEOL JMS SX/SX 102A four-sector mass spectrometer, coupled to a JEOL MS-MP9021D/UPD system program and electrospray ionization (ESI) mass spectrometry was carried out with a micrOTOF-Q instrument in positive ion mode. Melting points were measured on samples in sealed capillaries and are uncorrected. Analytical LC-MS analysis was conducted on a Jasco system (detection simultaneously at 214 nm and 254 nm) equipped with an Alltima C-18 analytical column (Alltech, 4.6×150 mm, 5 μm particle size). Solvent system: A: 100% water, B: 100% acetonitrile, C: 1% aq. trifluoroacetic acid (TFA). Purification of the cyclic decapeptides was conducted on a BioCAD "Vision" automated HPLC system (PerSeptive Biosystems, Inc.), supplied with a semipreparative Alltima CN column (Alltech, 10.0×250 mm, 5 μm particle size). Solvent system: A: 100% water, B: 100% acetonitrile, C: 1% aq. TFA (linear gradient of 50%→80% B). Compounds **4**,[22,11] and **12b**[14] were synthesized according to literature procedures.

Synthesis of chloromethyldiphenylphosphine (10):[23a] *n*BuLi (0.63 mL of a 1.6 M solution in *n*-hexane; 1.0 mmol) was added slowly to a solution of Ph_2PH (0.19 g, 1.0 mmol) in dry THF (15 mL) at −78 °C, after which the solution turned orange. Subsequently, the mixture was allowed to warm up to room temperature and the in situ generated Ph_2PLi was added slowly to CH_2Cl_2 (50 mL) at −78 °C and stirred until the orange color disappeared. The resulting colorless solution was allowed to warm up to room temperature and evaporated to dryness. The product was extracted into toluene (25 mL) and filtered. Evaporation of all volatiles in vacuo yielded **10** as a colorless oil (1.83 g, 78%), which was used without further purification. ^{31}P{^{1}H} NMR ($CDCl_3$): $\delta = -8.9$ ppm (s); ^{1}H NMR ($CDCl_3$): $\delta = 7.57$–7.30 (m, 10H; Ph*H*), 4.10 ppm (d, $^{2}J_{PH} = 5.0$ Hz, 2H; CH_2).

Synthesis of (2-chloroethyl)diphenylphosphine sulfide (11): *n*BuLi (3.38 mL of a 1.6 M solution in *n*-hexane; 5.4 mmol) was added slowly to a solution of Ph_2PH (1.00 g, 5.4 mmol) in dry THF (10 mL) at −78 °C, after which the solution turned orange. Subsequently, the mixture was allowed to warm up to room temperature, diluted with more THF (50 mL), and the in situ generated Ph_2PLi was added slowly to 1,2-dichloroethane (50 mL) at −20 °C. After complete addition, the orange color disappeared and the reaction mixture was allowed to warm up to room temperature. Elemental sulfur (0.43 g, 13.5 mmol) was added and the resulting mixture was stirred for 16 h. Evaporation to dryness and chromatography of the remaining white solid over silica gel eluting with *n*-hexane/dichloromethane (2:1) and subsequent recrystallization from diethyl ether/*n*-hexane gave **11** as colorless needles (0.94 g, 62%). M.p. 77 °C; ^{31}P{^{1}H} NMR ($CDCl_3$): $\delta = 37.8$ ppm (s); ^{13}C{^{1}H} NMR ($CDCl_3$): $\delta = 132.1$ (d, $^{1}J_{CP} = 81.3$ Hz; *ipso*-Ph), 132.1 (d, $^{4}J_{CP} = 3.0$ Hz; *p*-Ph), 131.1 (d, $^{2}J_{CP} = 10.4$ Hz; *o*-Ph), 129.0 (d, $^{3}J_{CP} = 12.6$ Hz; *m*-Ph), 38.4 (d, $^{2}J_{CP} =$

4.0 Hz; CH_2Cl), 36.5 ppm (d, $^1J_{CP}=52.1$ Hz; PCH_2); ^1H NMR ($CDCl_3$) $\delta=7.88$–7.82 (m, 4H; *o*-Ph*H*), 7.51–7.47 (m, 6H; *m*/*p*-Ph*H*), 3.83–3.74 (m, 2H; CH_2Cl), 3.02–2.91 ppm (m, 2H; PCH_2); HR FAB-MS: *m*/*z* calcd for $C_{14}H_{15}PSCl$: 281.0321; found: 281.0320; MS: *m*/*z* (%): 281.0 (100) $[M]^+$, 218.0 (39) $[M-C_2H_3Cl]^+$; IR: $\tilde{\nu}=3051$ (w), 1677 (w), 1557 (w), 1477 (m), 1437 (s), 1404 (w), 1313 (m), 1296 (m), 1199 (w), 1116 (m), 1099 (s), 1068 (m), 1026 (s), 997 (m), 923 (m), 833 cm^{-1} (m).

Synthesis of (3-chloropropyl)diphenylphosphine sulfide (12a): *n*BuLi (15.6 mL of a 1.6 M solution in *n*-hexane; 1.0 mmol) was added slowly to a solution of Ph_2PH (4.65 g, 25.0 mmol) in dry THF (50 mL) at −78 °C, after which the solution turned orange. Subsequently, the mixture was allowed to warm up to room temperature and the in situ generated Ph_2PLi was slowly added over a period of 2 h to a solution of 1,3-dichloropropane (4.00 g, 20.0 mmol) in toluene (10 mL) at 0 °C. Elemental sulfur (1.12 g, 35.0 mmol) was added and the resulting mixture was evaporated to dryness. Chromatography of the remaining white solid over silica gel eluting with *n*-hexane/dichloromethane (2:1) and subsequent recrystallization from ethanol/*n*-hexane gave **12a** as colorless needles (1.87 g, 32%). M.p. 81–82 °C; $^{31}P\{^1H\}$ NMR ($CDCl_3$): $\delta=42.1$ ppm (s); $^{13}C\{^1H\}$ NMR ($CDCl_3$): $\delta=132.4$ (d, $^1J_{CP}=80.5$ Hz; *ipso*-Ph), 131.5 (d, $^4J_{CP}=3.1$ Hz; *p*-Ph), 130.9 (d, $^2J_{CP}=10.7$ Hz; *o*-Ph), 128.5 (d, $^3J_{CP}=12.6$ Hz; *m*-Ph), 45.2 (d, $^2J_{CP}=5.3$ Hz; CH_2), 30.0 (d, $^1J_{CP}=58.5$ Hz; PCH_2), 25.6 ppm (s; CH_2Cl); ^1H NMR ($CDCl_3$): $\delta=7.89$–7.83 (m, 4H; *o*-Ph*H*), 7.49–7.43 (m, 6H; *m*/*p*-Ph*H*), 3.60 (t, $^3J_{HH}=6.0$ Hz, 2H; CH_2Cl), 2.67–2.56 (m, 2H; PCH_2), 2.17–2.07 ppm (m, 2H; CH_2); HR ESI-MS: *m*/*z* calcd for $C_{15}H_{17}PSCl$ $[M+H]^+$: 295.0472; found: 295.0460; IR: $\tilde{\nu}=1703$ (m), 1653 (m), 1437 (m), 1105 (m), 740 (m), 666 (m), 513 (m), 477 cm^{-1} (m).

Synthesis of 8a: *n*BuLi (0.55 mL of a 1.6 M solution in *n*-hexane) was added slowly to a solution of **4** (0.40 g, 0.8 mmol) in dry THF (40 mL) at −78 °C, after which the deep red solution turned green. Subsequently, the reaction mixture was stirred for 1 h at the same temperature followed by the slow addition of Ph_2PCl (0.20 g, 0.88 mmol) that resulted in a color change to red. After complete addition, the reaction mixture was allowed to warm up to room temperature. Elemental sulfur (0.06 g, 2.0 mmol) was added and the resulting mixture was stirred for 16 h. The reaction mixture was added to H_2O (200 mL) and the product was extracted into CH_2Cl_2 (3×75 mL). The combined organic layers were dried over $MgSO_4$ and all volatiles were removed in vacuo. Chromatography of the remaining red solid over silica gel eluting with $CHCl_3$/acetone (5:1) and subsequent recrystallization by layering a saturated ethyl acetate solution with *n*-hexane gave **8a** as red crystals (0.43 g, 77%). M.p. 198 °C (decomp.); $^{31}P\{^1H\}$ NMR ($CDCl_3$): $\delta=49.3$ ppm (s); $^{13}C\{^1H\}$ NMR ($CDCl_3$): $\delta=180.9$ (s; *C*O), 173.3 (d, $J_{CP}=1.7$ Hz; *C*=N), 172.5 (d, $J_{CP}=6.3$ Hz; CO_2), 143.6 (s; C), 134.2 (s; CH), 133.7 (d, $J_{CP}=1.1$ Hz; C), 133.3 (s; CH), 133.2 (s; CH), 132.7 (s; CH), 132.6 (s; C), 132.2 (d, $J_{CP}=3.1$ Hz; CH), 131.8 (s; CH), 131.7 (s; CH), 131.5 (s; CH), 131.3 (s; C), 130.1 (s; CH), 129.9 (s; C), 129.6 (s; CH), 128.9 (s; CH), 126.7 (s; CH), 128.5 (s; CH), 128.5 (s; CH), 128.3 (s; CH), 128.2 (s; CH), 128.0 (s; CH), 126.7 (s; CH), 126.0 (d, $J_{CP}=2.4$ Hz; C), 123.5 (s; CH), 120.6 (s; CH), 75.3 (d, $^1J_{CP}=35.7$ Hz; C_{Gly}), 71.3 (s; αC_{Pro}), 63.7 (s; CH_2Ph), 57.8 (s; δC_{Pro}), 31.5 (s; βC_{Pro}), 24.0 ppm (s; γC_{Pro}); ^1H NMR ($CDCl_3$): $\delta=8.41$ (d, $^3J_{HH}=8.6$ Hz, 1H; C*H*), 8.11–7.96 (m, 4H; C*H*), 7.70–7.58 (m, 2H; C*H*), 7.54–7.04 (m, 13H; C*H*), 6.74 (t, $^3J_{HH}=7.4$ Hz, 1H; C*H*), 6.66–6.48 (m, 3H; C*H*), 5.08 (d, $^3J_{PH}=7.1$ Hz, 1H; H_{Gly}), 4.35 (d, $^2J_{HH}=12.6$ Hz, 1H; CH_2Ph), 3.58–3.34 (m, 3H; αH_{Pro}, δH_{Pro}, γH_{Pro}), 3.51 (d, $^2J_{HH}=12.6$ Hz, 1H; CH_2Ph), 3.15–3.09 (m, 1H; βH_{Pro}), 2.55–2.46 (m, 1H; βH_{Pro}), 2.12–1.99 ppm (m, 2H; δH_{Pro}, γH_{Pro}); HR FAB-MS: *m*/*z* calcd for $C_{39}H_{35}N_3O_3PSNi$ $[M+H]^+$: 714.1490; found: 714.1500; MS: *m*/*z* (%): 736 (2) $[M+Na]^+$, 714 (15) $[M+H]^+$, 670 (75) $[M-CO_2]^+$, 497 (14) $[M-C_{12}H_{10}PS]^+$, 482 (10) $[M-C_{26}H_{21}N_2NiPS]^+$, 217.0 (13) $[M-C_{27}H_{25}N_3O_3Ni]^+$, 160 (100) $[M-C_{28}H_{21}N_2O_3PSNi]^+$, 91 (62) $[M-C_{32}H_{28}N_3O_3PSNi]^+$, 77 (12) $[M-C_{33}H_{29}N_3O_3PSNi]^+$; IR: $\tilde{\nu}=1668$ (m, br), 1645 (s, br), 1585 (m, br), 1541 (m), 1437 (m), 1332 (m, br), 1255 (s), 1163 (m), 1130 (w), 1103 (m), 1062 (w, br), 1014 (w), 997 (w), 923 (w, br), 841 cm^{-1} (w).

Synthesis of 8b: NaH (0.18 g, 7.5 mmol) was added to a solution of **4** (2.48 g, 5.0 mmol) in dry acetonitrile (100 mL) at room temperature and the resulting mixture was stirred for 1 h, during which the red solution turned deep red. Subsequently, a solution of **10** (1.76 g, 7.5 mmol) in acetonitrile (10 mL) was added and the reaction mixture was stirred for 8 h. Elemental sulfur (0.32 g, 10.0 mmol) was added and the resulting mixture was stirred for an additional 16 h. The reaction mixture was added to H_2O (100 mL) and the product was extracted into CH_2Cl_2 (3×100 mL). The combined organic layers were dried over $MgSO_4$ and all volatiles were removed in vacuo. Chromatography of the residue over silica gel eluting with $CHCl_3$/acetone (4:1) yielded **8a** as a red solid (3.23 g, 89%). M.p. 155–156 °C; $^{31}P\{^1H\}$ NMR (C_6D_6): $\delta=36.7$ ppm (s); $^{13}C\{^1H\}$ NMR (C_6D_6): $\delta=180.5$ (s; *C*O), 176.1 (d, $J_{CP}=1.8$ Hz; CO_2), 171.2 (s; *C*=N), 144.6 (s; C), 135.2 (s; C), 134.6 (s; C), 134.1 (s; C), 133.6 (d, $^1J_{CP}=80.9$ Hz; *ipso*-C), 133.5 (s; CH), 133.1 (d, $^1J_{CP}=88.0$ Hz; *ipso*-C), 132.0 (d, $^2J_{CP}=10.6$ Hz; *C*H), 131.9 (s; *C*H), 131.5 (d, $^2J_{CP}=10.6$ Hz; *C*H), 131.2 (d, $^3J_{CP}=3.1$ Hz; *C*H), 131.0 (d, $^3J_{CP}=3.0$ Hz; *C*H), 129.5 (s; *C*H), 129.3 (s; *C*H), 129.1 (s; *C*H), 128.9 (s; *C*H), 128.8 (s; *C*H), 128.7 (s; *C*H), 128.6 (s; *C*H), 127.2 (s; *C*H), 126.4 (s; *C*H), 125.6 (s; *C*), 124.3 (s; *C*H), 120.1 (s; *C*H), 70.6 (s; αC_{Pro}) 66.9 (d, $^2J_{CP}=1.7$ Hz; *C*H), 63.1 (s; CH_2Ph), 57.4 (s; δC_{Pro}), 38.0 (d, $^1J_{CP}=50.6$ Hz;;PCH_2), 31.1 (s; βC_{Pro}), 24.1 ppm (s; γC_{Pro}); ^1H NMR (C_6D_6): $\delta=9.03$ (d, $^3J_{HH}=8.7$ Hz, 1H; C*H*), 8.04–7.90 (m, 4H; C*H*), 7.80 (d, $^3J_{HH}=7.2$ Hz, 2H; C*H*), 7.19–6.78 (m, 13H; C*H*), 6.53 (dd, $^3J_{HH}=8.2$ Hz, $^4J_{HH}=1.5$ Hz, 1H; C*H*), 6.46 (dd, $^3J_{HH}=4.6$ Hz, $^4J_{HH}=1.5$ Hz, 2H; C*H*), 6.29 (t, $^3J_{HH}=8.0$ Hz, 1H; C*H*), 4.64–4.48 (m, 1H; C*H*), 4.14 (d, $^2J_{HH}=12.5$ Hz, 1H; CH_2Ph), 3.58–3.25 (m, 4H; PCH_2, αH_{Pro}, δH_{Pro}, γH_{Pro}), 3.23–3.05 (m, 1H; βH_{Pro}), 3.14 (d, $^2J_{HH}=12.5$ Hz, 1H; CH_2Ph), 3.03–2.87 (m, 1H; PCH_2), 2.22–2.06 (m, 1H; βH_{Pro}), 1.63–1.43 ppm (m, 2H; δH_{Pro}, γH_{Pro}); HR FAB-MS: *m*/*z* calcd for $C_{40}H_{37}N_3O_3PSNi$ $[M+H]^+$: 728.1647; found: 728.1639; *m*/*z* (%): 750 (11) $[M+Na]^+$, 728 (63) $[M+H]^+$, 510 (21) $[M-C_{12}H_{10}PS]^+$, 466 (13) $[M-C_{13}H_{10}O_2PS]^+$, 91 (28) $[M-C_{33}H_{29}N_3O_3PSNi]^+$, 77.0 (15) $[M-C_{34}H_{31}N_3O_3PSNi]^+$; IR: $\tilde{\nu}=1686$ (w, br), 1633 (s, br), 1585 (m), 1541 (m), 1467 (w), 1435 (s), 1357 (m), 1332 (m, br), 1253 (s), 1163 (m), 1128 (w), 1099 (m), 1060 (w), 1028 (w), 1016 (w), 999 (w), 962 (w), 842 (m), 748 (m), 734 (m), 692 cm^{-1} (s, br).

Synthesis of 8c: Carefully ground NaOH (0.33 g, 8.3 mmol) was added to a solution of **4** (1.65 g, 3.3 mmol) in dry acetonitrile (50 mL) at room temperature and the resulting mixture was stirred for 1 h, during which the red solution turned deep red. Subsequently, **11** (1.39 g, 5.0 mmol) was added and the reaction mixture was stirred for 16 h. The reaction mixture was quenched with 0.1 M HCl (50 mL) and the product was extracted into CH_2Cl_2 (4×40 mL). The combined organic layers were dried over $MgSO_4$ and all volatiles were removed in vacuo. Chromatography of the residue over silica gel eluting with $CHCl_3$/acetone (5:1) yielded **8a** as a red solid (2.20 g, 90%). M.p. 230–231 °C; $^{31}P\{^1H\}$ NMR ($CDCl_3$): $\delta=42.3$ ppm (s); $^{13}C\{^1H\}$ NMR ($CDCl_3$): $\delta=180.5$ (s; *C*O), 178.7 (s; CO_2), 171.2 (s; *C*=N), 142.5 (s; *C*), 133.5 (s; *C*H), 133.4 (s; *C*), 133.3 (s; *C*), 133.1 (s; *C*), 133.0 (s; *C*), 132.5 (s; *C*H), 131.7 (s; *C*H), 131.4 (d, $^2J_{CP}=10.2$ Hz; *C*H), 131.2 (d, $^2J_{CP}=10.2$ Hz; *C*H), 129.8 (s; *C*H), 129.5 (s; *C*H), 129.1 (s; *C*H), 129.1 (s; *C*H), 129.0 (s; *C*H), 128.9 (s; *C*H), 128.8 (s; *C*H), 127.7 (s; *C*H), 126.9 (s; *C*H), 126.3 (s; *C*), 124.0 (s; *C*H), 120.9 (s; *C*H), 70.4 (s; αC_{Pro}), 70.3 (d, $^3J_{CP}=17.4$ Hz; CH_{Gly}), 63.2 (s; CH_2Ph), 57.2 (s; δC_{Pro}), 30.8 (s; βC_{Pro}), 29.3 (s; CH_2), 29.0 (d, $^1J_{CP}=57.2$ Hz; PCH_2), 23.8 ppm (s; γC_{Pro}); ^1H NMR ($CDCl_3$): $\delta=8.15$ (d, $^3J_{HH}=8.6$ Hz, 1H; C*H*), 8.03 (d, $^3J_{HH}=7.2$ Hz, 2H; C*H*), 7.92–7.81 (m, 2H; C*H*), 7.79–7.68 (m, 2H; C*H*), 7.53–7.29 (m, 11H; C*H*), 7.23–7.08 (m, 3H; C*H*), 6.78 (d, $^3J_{HH}=7.5$ Hz, 1H; C*H*), 6.69–6.56 (m, 2H; C*H*), 4.37 (d, $^2J_{HH}=12.6$ Hz, 1H; CH_2Ph), 3.80 (dd, $^3J_{HH}=9.2$ Hz, $^3J_{HH}=3.9$ Hz, 1H; H_{Gly}), 3.40–3.36 (m, 2H; δH_{Pro}, αH_{Pro}), 3.52 (d, $^2J_{HH}=12.6$ Hz, 1H; CH_2Ph), 3.26–3.18 (m, 2H; γH_{Pro}, CH_2), 2.60–2.45 (m, 2H; δH_{Pro}, βH_{Pro}), 2.43–2.30 (m, 2H; βH_{Pro}, PCH_2), 2.05–1.92 ppm (m, 3H; δH_{Pro}, γH_{Pro}, CH_2); HR FAB-MS: *m*/*z* calcd for $C_{41}H_{39}N_3O_3PSNi$ $[M+H]^+$: 742.1803; found: 742.1805; MS: *m*/*z* (%): 764 (11) $[M+Na]^+$, 742 (100) $[M+H]^+$, 511 (5) $[M-C_{13}H_{12}PS]^+$, 160 (92) $[M-C_{30}H_{25}N_2O_3PSNi]^+$, 91.0 (62) $[M-C_{34}H_{32}N_3O_3PSNi]^+$, 77.0 (16) $[M-C_{35}H_{33}N_3O_3PSNi]^+$; IR: $\tilde{\nu}=1670$ (s), 1637 (s), 1589 (m), 1548 (w), 1441 (m), 1473 (m), 1363 (m), 1350 (m), 1334 (m), 1319 (w), 1292 (m), 1259 (s), 1209 (m), 1161 (m), 1130 (w), 1099 (m), 1070 (w), 1031 (w), 989 (w), 929 (w), 883 (w), 812 cm^{-1} (w).

General procedure for the liberation of 14a–c: Compound **8a–c** (2 mmol) was dissolved in a mixture of MeOH (30 mL) and 2 M HCl (20 mL) and heated at 65 °C for 3 h, which resulted in a color change of the reaction mixture to pale green or yellow. All volatiles were removed

in vacuo to give a pale yellow residue that was redissolved in H_2O (40 mL) to remove the insoluble, white (S)-2-[N-(benzylpropyl)-amino]-benzophenone·HCl salt (BPB·HCl) by filtratation; residual BPB·HCl can be removed by extraction with Et_2O. After removal of all volatiles in vacuo, the residue was dissolved in a mixture of MeOH (30 mL) and with HCl(g) saturated Et_2O (15 mL) and the reaction mixture was stirred for 16 h at room temperature. Again, all volatiles were removed in vacuo and the residue was extracted into CH_2Cl_2 (20 mL) to separate it from the yellow, insoluble $NiCl_2$, which was filtered off. Evaporation to dryness yielded the methyl esters **14b** and **c** as a pale yellow solid. Compound **15** was isolated instead of **14a**.

Data for ***14b***: Yield: 0.66 (93%); m.p. 75°C; $^{31}P\{^1H\}$ NMR ($CDCl_3$): $\delta=$ 38.4 ppm; $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ =170.3 (s; *C*O_2), 132.5 (d, $^1J_{CP}=$ 81.5 Hz; *ipso*-Ph), 131.9 (d, $^1J_{CP}=$81.2 Hz; *ipso*-Ph), 131.6 (s; *p*-Ph), 131.6 (s; *p*-Ph), 131.3 (d, $^2J_{CP}=$10.6 Hz; *o*-Ph), 131.1 (d, $^2J_{CP}=$10.6 Hz; *o*-Ph), 128.8 (s; *m*-Ph), 128.7 (s; *m*-Ph), 53.7 (d, $^2J_{CP}=$16.1 Hz; *C*H), 53.2 (s; O*C*H_3), 28.1 ppm (d, $^1J_{CP}=$57.2 Hz; *C*H_2); ^1H NMR ($CDCl_3$): $\delta=$8.03–7.68 (m, 4H; *o*-Ph*H*), 7.65–7.35 (m, 6H; *m*/*p*-Ph*H*), 4.55–4.32 (m, 1H; C*H*), 3.61–3.28 ppm (m, 5H; CH_2, CH_3); HR FAB-MS: *m*/*z* calcd for $C_{16}H_{19}NO_2PS$ $[M+H]^+$: 320.0874; found: 320.0871; MS: *m*/*z* (%): 320 (100) $[M+H]^+$, 217 (52) $[M-C_4H_8NO_2]^+$, 77 (7) $[M-C_{10}H_{13}NO_2PS]^+$; IR: $\tilde{\nu}=$2891 (br), 1747 (s), 1481 9M0, 1437 (s), 1400 (w), 1315 (w), 1236 (m), 1187 (w), 1144 (w), 1101 (s), 1043 (m), 997 (m), 930 (w), 879 (m), 827 (s), 741 (s), 700 cm^{-1} (s).

Data for ***14c***: Yield: 0.61 (82%); m.p. 87°C; $^{31}P\{^1H\}$ NMR ($CDCl_3$): $\delta=$ 42.6 ppm; $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ =170.3 (s; *C*O_2), 132.9 (s; *ipso*-Ph), 132.2 (d, $^1J_{CP}=$24.3 Hz; *ipso*-Ph), 131.6 (s; *p*-Ph), 131.6 (s; *p*-Ph), 131.3 (d, $^2J_{CP}=$10.6 Hz; *o*-Ph), 131.1 (d, $^2J_{CP}=$10.6 Hz; *o*-Ph), 128.8 (s; *m*-Ph), 128.7 (s; *m*-Ph), 53.7 (d, $^3J_{CP}=$16.1 Hz; *C*H), 53.2 (s; *C*H_3), 28.1 (d, $^1J_{CP}=$ 57.0 Hz; *C*H_2), 24.3 ppm (s; *C*H_2); ^1H NMR ($CDCl_3$): $\delta=$8.02–7.86 (m, 4H; *o*-Ph*H*), 7.47–7.34 (m, 6H; *m*/*p*-Ph*H*), 4.22 (m, 1H; C*H*), 3.58 (s, 3H; CH_3), 2.91 (m, 2H; CH_2), 2.48–2.33 (m, 1H; CH_2), 2.32–2.14 ppm (m, 1H; CH_2); HR FAB-MS: *m*/*z* calcd for $C_{17}H_{21}NO_2PS$ $[M+H]^+$: 334.1037; found: 334.1031; MS: *m*/*z* (%): 334 (100) $[M+H]^+$, 217 (17) $[M-C_5H_{10}NO_2]^+$, 77.0 (18) $[M-C_{11}H_{15}NO_2PS]^+$; IR: $\tilde{\nu}=$2901 (br), 1740 (m), 13736 (m), 1437 (m), 1307 (w), 1229 (s), 1180 (w), 1103 (s), 1028 (w), 977 (w), 982 (m), 734 (s), 709 cm^{-1} (s).

Data for ***15***: $^{31}P\{^1H\}$ NMR ($CDCl_3$): $\delta=$42.1 ppm; ^{13}C-DEPT(135) NMR ($CDCl_3$): δ =132.2 (d, $^4J_{CP}=$2.9 Hz; *p*-Ph), 131.7 (d, $^3J_{CP}=$9.6 Hz; *m*-Ph), 129.2 (d, $^2J_{CP}=$11.7 Hz; *o*-Ph), 46.6 ppm (d, $^1J_{CP}=$51.6 Hz; *C*H_2). ^1H NMR ($CDCl_3$): $\delta=$7.93–7.75 (m, 4H; *o*-Ph*H*), 7.58–7.43 (m, 6H; *m*/*p*-Ph*H*), 3.61 (s, 2H; NH_2), 1.46 ppm (s, 2H; CH_2).

General procedure for the synthesis of 1 and 2: LiOH (10 mL of a 0.2M solution in H_2O) was added dropwise to a solution of methyl ester **14b**,**c** (1 mmol) in THF (5 mL) at 0°C and the resulting mixture was stirred for 2 h. Neutralization with conc. HCl and evaporation to dryness gave a pale yellow residue that was dissolved in a mixture of H_2O (7 mL) and dioxane (15 mL) and cooled to 0°C. After addition of $NaHCO_3$ (0.17 g, 2.0 mmol) and Fmoc-OSu (0.34 g, 1.0 mmol), the resulting mixture was stirred for 4 h. Subsequently, the reaction mixture was neutralized with conc. HCl, after which H_2O (10 mL) was added and the product was extracted into CH_2Cl_2 (2× 20 mL). The combined organic layers were dried over $MgSO_4$ and all volatiles were removed in vacuo. Chromatography of the remaining pale yellow foam over silica gel eluting with CH_2Cl_2/MeOH/TFA (20:5:1) gave **1**,**2** as a white solid.

Data for ***1***:[4] Yield: 0.38 g (72%); $^{31}P\{^1H\}$ NMR ($CDCl_3$): $\delta=$38.3 ppm; ^1H NMR ($CDCl_3$): $\delta=$7.97–7.84 (m, 4H; C*H*), 7.84–7.75 (m, 3H; C*H*), 7.69–7.64 (m, 1H; C*H*), 7.55–7.31 (m, 10H; C*H*), 5.94 (d, $^3J_{HH}=$5.9 Hz, 1H; N*H*), 4.77 (m, 1H; C*H*), 4.61 (d, $^3J_{HH}=$7.6 Hz, 1H; CH_2), 4.39 (pseudo-t, $^3J_{HH}=$7.1 Hz, 1H; CH_2), 4.22–4.12 (m, 1H; C*H*), 3.47–3.35 (m, 1H; PCH_2), 3.30–3.13 ppm (m, 1H; PCH_2).

Data for ***2***: Yield: 0.30 g (67%); m.p. 95°C; $^{31}P\{^1H\}$ NMR ($CDCl_3$): $\delta=$ 42.6 ppm (s); $^{13}C\{^1H\}$ NMR ($CDCl_3$): $\delta=$175.9 (s; *C*O_2H), 156.7 (s; *C*O), 144.2 (s; *C*), 143.9 (s; *C*), 141.7 (s; *C*), 141.7 (s; *C*), 132.5 (d, $^1J_{CP}=$ 81.2 Hz; *C*), 132.1 (d, $J_{CP}=$2.9 Hz; *C*H), 131.5 (d, $J_{CP}=$10.1 Hz; *C*H), 131.5 (d, $J_{CP}=$10.3 Hz; *C*H), 129.3 (s; *C*H), 129.0 (s; *C*H), 128.2 (s; *C*H), 127.6 (s; *C*H), 125.5 (d, $J_{CP}=$6.5; *C*H), 120.4 (s; *C*H), 67.7 (s; *C*H_2), 54.2 (d, $^3J_{CP}=$14.8 Hz; *C*H), 47.4 (s; *C*H), 29.1 (d, $^1J_{CP}=$57.2 Hz; *C*H_2), 25.9 ppm (s; *C*H_2); ^1H NMR ($CDCl_3$): $\delta=$8.60 (brs, 1H; CO_2H), 7.86–7.70 (m, 8H; C*H*), 7.65–7.46 (m, 2H; C*H*), 7.53–7.33 (m, 8H; C*H*), 7.32–7.23 (m, 2H; C*H*), 5.60 (d, $^3J_{HH}=$7.6 Hz, 1H; N*H*), 4.40 (brs, 3H; C*H*/CH_2), 4.46–4.33 (m, 3H; C*H*/CH_2), 4.24–4.13 (m, 1H; C*H*), 2.71–2.45 (m, 2H; CH_2), 2.29–1.95 ppm (m, 2H; CH_2); HR FAB-MS: *m*/*z* calcd for $C_{31}H_{29}NO_4PS$ $[M+H]^+$: 542.1555; found: 542.1548; MS: *m*/*z* (%): 564 (39) $[M+Na]^+$, 542 (62) $[M+H]^+$, 496 (9) $[M-CO_2]^+$, 363 (14) $[M-C_{14}H_{11}]^+$, 77.0 (18) $[M-C_{25}H_{23}NO_4PS]^+$; IR: $\tilde{\nu}=$1714.8 (s, br) 1647.3 (s), 1510.3 (s, br), 1437.0 (s), 1340.6 (w), 1209.4 (m, br), 1140.0 (w), 1103.2 (m), 1047.4 (m, br), 999.2 (w), 935.5 cm^{-1} (w).

Synthesis of 5b: Compound **5b** was synthesized according to literature procedures[4d] in 94% yield. ^1H NMR ($CDCl_3$): $\delta=$7.36–7.17 (m, 4H; C*H*), 5.00 (brm, 1H; N*H*), 4.59 (brm, 1H; C*H*), 3.71 (s, 3H; OCH_3), 3.21–2.99 (m, 2H; CH_2), 1.46 (s, 9H; C(CH_3)$_3$); $^{13}C\{^1H\}$ NMR ($CDCl_3$): $\delta=$171.7 (s; *C*O_2), 154.8 (s; *C*O), 148.4 (s; Ph), 136.8 (s; Ph), 130.9 (s; Ph), 121.7 (s; *C*F_3), 121.1 (s; Ph), 80.0 (s; *C*(CH$_3$)$_3$), 54.0 (s; *C*H), 52.1 (s; O*C*H_3), 37.7 (s; *C*H_2), 28.0 ppm (s; *C*H_3); $^{19}F\{^1H\}$ NMR ($CDCl_3$): $\delta=$ −73.3 ppm (s); HR FAB-MS: *m*/*z* calcd for $C_{16}H_{21}F_3NO_7$ $[M+H]^+$ 428.0991; found: 428.0995; MS: *m*/*z* (%): 428 (4) $[M+H]^+$, 372 (80) $[M-C_4H_8]^+$, 328 (100) $[M-C_5H_8O_2]^+$, 268 (55) $[M-C_7H_{12}O_4]^+$, 239 (4) $[M-C_9H_{16}NO_2]^+$, 57 (45) $[M-C_{12}H_{11}NO_7F_3S]^+$.

Synthesis of 7b: Compound **7b** was synthesized according to literature procedures[4d] in 61% yield. $^{31}P\{^1H\}$ NMR ($CDCl_3$): $\delta=$43.6 ppm (s); $^{13}C\{^1H\}$ NMR ($CDCl_3$): $\delta=$171.8 (s; *C*O_2), 154.9 (s; *C*O), 140.1 (d, $^1J_{CP}=$ 3.0 Hz; *ipso*-Ph), 133.5 (d, $^1J_{CP}=$3.0 Hz; *ipso*-Ph), 132.3 (d, $^2J_{CP}=$11.1 Hz; *o*-Ph), 132.1 (d, $^2J_{CP}=$10.7 Hz; *o*-Ph), 131.4 (d, $^3J_{CP}=$12.6 Hz; *m*-Ph), 130.7 (s; *p*-Ph), 129.4 (d, $^4J_{CP}=$12.8 Hz; *p*-Ph), 128.4 (d, $^3J_{CP}=$12.6 Hz; *m*-Ph), 80.0 (s; *C*), 54.1 (s; *C*H), 52.2 (s; OCH_3), 38.2 (s; *C*H_2), 28.1 ppm (s; *C*H_3); ^1H NMR (250.1 MHz, $CDCl_3$): $\delta=$7.72–7.64 (m, 6H; C*H*), 7.46–7.40 (m, 6H; C*H*), 7.24–7.20 (m, 2H; C*H*), 5.05 (brd, $^3J_{HH}=$7.6 Hz, 1H; N*H*), 4.55 (brm, 1H; C*H*), 3.67 (s, 3H; OCH_3), 3.15–3.07 (m, 1H; CH_2), 3.04–2.90 (m, 1H; CH_2), 1.37 ppm (s, 9H; CH_3); HR FAB-MS: *m*/*z* calcd for $C_{27}H_{31}NO_4PS$ $[M+H]^+$: 496.1711; found: 496.1712; MS: *m*/*z* (%): 496 (15) $[M+H]^+$, 440 (100) $[M-C_4H_8]^+$, 336 (6) $[M-C_7H_{10}O_4]^+$, 308.1 (11) $[M-C_8H_{14}NO_4]^+$, 217 (7) $[M-C_{15}H_{20}NO_4]^+$, 57.0 (9) $[M-C_{23}H_{21}NO_4]^+$.

Synthesis of 3: LiOH (10 mL of a 0.2M solution in H_2O) was added dropwise to a solution of **7b** (1.0 mmol, 0.50 g) in THF (3 mL) at 0°C, and the resulting mixture was stirred for 2 h. Neutralization with conc. HCl and evaporation to dryness gave a pale yellow residue that was extracted into CH_2Cl_2 (2× 10 mL). The combined organic layers were dried over $MgSO_4$ and the solution was concentrated to approximately 5 mL and cooled to 0°C, after which TFA (1 mL) was added and the reaction mixture was stirred for 1 h. Removal of all volatiles in vacuo gave the free phosphino amino acid as a yellow solid, which was dissolved in a mixture of H_2O (7 mL) and dioxane (15 mL) and cooled to 0°C. After addition of $NaHCO_3$ (0.17 g, 2.0 mmol) and Fmoc-OSu (0.34 g, 1.0 mmol), the resulting mixture was stirred for 18 h. Subsequently, the reaction mixture was neutralized with conc. HCl and the product was extracted into ethyl acetate (2×20 mL). The combined organic layers were dried over $MgSO_4$ and all volatiles were removed in vacuo. The remaining pale yellow foam was purified by column chromatography over silica gel eluting with CH_2Cl_2/MeOH/TFA (20:5:1). The obtained salt was dissolved in ethyl acetate (25 mL) and washed with H_2O until the washing water was neutral. Evaporation of all volatiles in vacuo gave **3** as a pale yellow foam (0.50 g, 82%). M.p. 90°C; $^{31}P\{^1H\}$ NMR ($CDCl_3$): $\delta=$43.4 ppm (s); $^{13}C\{^1H\}$ NMR ($CDCl_3$): $\delta=$174.9 (s; *C*O_2), 156.1 (d, $J_{CP}=$1.4 Hz; *C*O), 144.0 (d, $J_{CP}=$6.8 Hz; *C*), 141.7 (s; *C*), 140.1 (s; *C*), 133.2 (d, $J_{CP}=$ 85.4 Hz; *C*), 133.1 (d, $J_{CP}=$85.2 Hz; *C*), 132.9 (d, $J_{CP}=$11.9 Hz; *C*H), 132.7 (d, $J_{CP}=$10.8 Hz; *C*H), 132.6 (d, $J_{CP}=$10.6 Hz; *C*H), 132.0 (d, $J_{CP}=$ 3.0 Hz; *C*H), 130.1 (s; *C*H), 129.9 (s; *C*H), 129.1 (d, $J_{CP}=$0.5 Hz; *C*H), 128.8 (d, $J_{CP}=$0.5 Hz; *C*H), 128.2 (s; *C*H), 127.5 (s; *C*H), 125.4 (s; *C*H), 125.3 (s; *C*H), 120.4 (d, $J_{CP}=$1.2 Hz; *C*H), 67.3 (s; *C*H_2), 54.7 (s; *C*H), 47.5 (s; *C*H), 37.9 ppm (s; *C*H_2); ^1H NMR ($CDCl_3$): $\delta=$9.58 (brs, 1H; CO_2H), 7.88–7.81 (d, $^3J_{HH}=$7.4 Hz, 2H; C*H*), 7.76–7.31 (m, 10H; C*H*), 7.28–7.22 (d, $^3J_{HH}=$7.4 Hz, 2H; C*H*), 5.74 (s, 1H; N*H*), 4.30–4.05 (brm, 4H; C*H*, CH_2), 3.18 (dd, $^2J_{HH}=$13.3 Hz, $^3J_{HH}=$3.2 Hz; CH_2), 2.94 ppm (dd, $^2J_{HH}=$13.3 Hz, $^3J_{HH}=$10.7 Hz; CH_2); HR FAB-MS: *m*/*z* calcd for $C_{36}H_{31}NO_4PS$ $[M+H]^+$: 604.1711; found: 604.1721; MS: *m*/*z* (%): 626

(21) $[M+Na]^+$, 604 (59) $[M+H]^+$, 425 (35) $[M-C_{14}H_{11}]^+$, 77 (18) $[M-C_{30}H_{25}NO_4PS]^+$; IR: $\tilde{\nu}=3047$ (m, br), 1716 (s, br), 1683 (s), 1652 (s), 1549 (m), 1521 (m), 1506 (s), 1448 (w), 1437 (s), 1244 (w, br), 1213 (w, br), 1180 (w, br), 1099 (s), 1045 cm^{-1} (m, br).

General procedure for the determination of the enantiomeric purity of 1–3: In an NMR tube, amino acid methyl esters **1**, **2**, or C-deprotected **7b** (0.035 mmol) and DMAP (8.5 mg, 0.070 mmol) were dissolved in $CDCl_3$ (0.5 mL) yielding the free amino acids. Subsequent cooling to 0 °C was followed by addition of Mosher's acid chloride (8.0 μL, 0.043 mmol) and the reaction mixture was allowed to warm up to room temperature and after 1 h $^{19}F\{^1H\}$-NMR spectra were recorded. This reaction scheme was carried out twice: a) with enantiomerically pure (*R*)-Mosher's acid chloride, and b) with a 1:1 mixture of (*R*)- and (*S*)-Mosher's acid. The ratio between the diastereomeric pairs was determined by integration of the ^{19}F NMR signals.

For **1**: a) $^{19}F\{^1H\}$ NMR ($CDCl_3$): $\delta=-68.8$, -69.0 ppm (ratio 94:6); b) $^{19}F\{^1H\}$ NMR ($CDCl_3$): $\delta=-68.8$, -69.0 ppm (ratio 1:1).

For **2**: a) $^{19}F\{^1H\}$ NMR ($CDCl_3$): $\delta=-69.54$, -69.86 ppm (ratio 200:1); b) $^{19}F\{^1H\}$ NMR ($CDCl_3$): $\delta=-69.54$, -69.86 ppm (ratio 1:1).

For **3** (C-deprotected **7b**): a) $^{19}F\{^1H\}$ NMR ($CDCl_3$): $\delta=-69.21$, -69.32 ppm (ratio 200:1); b) $^{19}F\{^1H\}$ NMR ($CDCl_3$): $\delta=-69.21$, -69.32 ppm (ratio: 1:1).

General procedure for the synthesis of cyclic decapeptides 19a–c

Loading of resin: Commercially available Wang (polystyrene) resin (2.00 g, 1.1 mmol g^{-1}, 2.2 mmol) was allowed to swell in CH_2Cl_2 (50 mL). A solution was prepared of *N,N'*-diisopropylcarbodiimide (DIC; 1.12 mL, 0.92 g, 7.26 mmol, 3.3 equiv), Fmoc-Leu-OH (2.33 g, 6.60 mmol, 3.0 equiv) and DMAP (cat.) in CH_2Cl_2. The mixture was left overnight with occasional shaking. The resin was filtered, washed subsequently with DMF and CH_2Cl_2 and dried (air). The loading of the resin was determined by treatment of the dried resin (2.69 mg) with a solution of piperidine in *N*-methylpyrrolidone (NMP; 1:4, v/v, 1.0 mL). After stirring for 10 min followed by dilution to 10.00 mL with EtOH, the absorption of the solution was measured at 300 nm. The loading was calculated to be 0.59 mmol g^{-1}, using the formula: Loading (mmol g^{-1}) $=[A_{300}]\times 10/[7.8\times m]$ ($m=2.69$ mg).

Stepwise elongation on a 0.2 mmol scale: 1) The Fmoc-Leu loaded resin was swollen with NMP followed by treatment with piperidine in NMP (1:4, v/v, 4 mL 2×10 min) to effect Fmoc cleavage. The resin was filtered, washed with NMP and CH_2Cl_2, filtered, and dried (air); 2a) coupling of **1–3** (1.5 equiv) in the presence of *O*-(7-azabenzotriazol-1-yl)tetramethyluronium hexafluorophosphate (HATU; 1.45 equiv) and *N,N*-diisopropylethylamine (DiPEA; 3.0 equiv) which was pre-activated for 1 min in NMP (4 mL) and subsequently shaken for 16 h; or 2b) coupling of the appropriate commercially available amino acid (Fmoc-Val-OH, Fmoc-Pro-OH, Fmoc-D-Phe-OH, Fmoc-Leu-OH) (4.0 equiv) in the presence of *O*-(6-chlorobenzotriazole-1-yl)tetramethyluronium hexafluorophosphate (HCTU; 4.0 equiv) and DiPEA (8.0 equiv), which was pre-activated for 1 min in NMP (4 mL) and subsequently shaken for 90 min; 3) washing with NMP and CH_2Cl_2. Couplings were monitored for completion by the Kaiser test[23b] or by a chloranil test after couplings with Pro-residues.[23c] By means of this procedure the immobilized linear decapeptides (**18a–c**) were obtained.

Cleavage from the resin: Resin **18a–c** was swollen with NMP followed by treatment with piperidine in NMP (1:4, v/v, 4 mL 2×10 min) to effect Fmoc cleavage. The resin was filtered, washed with NMP and CH_2Cl_2, filtered, and dried (air). The immobilized peptide was treated with mixture of TFA/TIS/H_2O (95:2.5:2.5, 8.0 mL) and shaken for 45 min and filtered. The resin was rinsed with a mixture of TFA/TIS/H_2O (95:2.5:2.5, 2.0 mL). All fractions were collected and co-evaporated with toluene.

Cyclization: The appropriate crude linear decapeptide was taken up in DMF (5.0 mL) and added dropwise over the course of 1 h to a solution of benzotriazol-1-yl-oxytripyrrolidinophosphonium hexafluorophosphate (PyBOP; 5.0 equiv), 1-hydroxybenzotriazole (HOBt; 5.0 equiv) and DiPEA (15.0 equiv) in DMF (150 mL) and allowed to stir for 16 h. The mixture was concentrated, directly applied to a LH20 Sephadex size-exclusion column eluted with MeOH and purified by RP-HPLC.

***cyclo*-[Pro-Val-PAA$_1$-Leu-D-Phe]$_2$ (19a)**: The synthesis was performed as outlined above to obtain 350 mg (106 μmol) immobilized decapeptide **18a**. Cleavage from the resin, followed by cyclization and purification yielded compound **19a** (110 mg, 67%). ^{31}P NMR (162 MHz, MeOD/$CDCl_3$ (1:1), $T=298$ K): $\delta=38.9$ ppm (s); ^1H NMR (400 MHz, MeOD/$CDCl_3$ (1:5), $T=330$ K): $\delta=8.20$ (d, 1H; $J_{NH,H\alpha}=8.7$ Hz, NH Leu), 7.91–7.82 (m, 5H; NH D-Phe, 4×H_{ar}), 7.69, (d, 1H; $J_{NH,H\alpha}=5.8$ Hz, NH PAA), 7.47–7.37 (m, 6H; H_{ar}), 7.28 (d, 1H; 1H; $J_{NH,H\alpha}=6.9$ Hz, NH Val), 7.26–7.17 (m, 3H; H_{ar}), 7.13–7.11 (m, 2H; H_{ar}), 5.06 (m, 1H; H_α PAA), 4.61 (m, 1H; H_α D-Phe), 3.91, (m, 1H; H_α Val), 3.64 (m, 1H; H_δ Pro), 3.44 (m, 1H; H_β PAA), 3.06–2.99 (m, 2H; H_β PAA, H_β D-Phe), 2.87 (dd, 1H; $J_{H\beta,H\beta}=12.8$, $J_{H\beta,H\alpha}=5.5$ Hz, H_β D-Phe), 2.62 (m, 1H; H_δ Pro), 2.09 (m, 1H; H_β Pro), 2.00 (m, 1H; H_β Val), 1.70–1.60 (m, 3H; H_β Leu, H_β Pro, H_γ Pro), 1.56 (m, 1H; H_γ Pro), 1.49 (m, 1H; H_γ Leu), 1.32 (m, 1H; H_β Leu), 0.85–0.80 ppm (m, 12H; 6×H_δ Leu, 6×H_γ Val); ^{13}C NMR (100 MHz, MeOD/$CDCl_3$ (1:5), $T=330$ K): $\delta=173.2$, 173.2, 172.0, 171.6, 171.5 (5×C=O, Leu, PAA, D-Phe, Pro, Val), 137.0 (C_q Ar), 132.6, 132.2, 132.1, 131.8, 131.7, 130.0, 129.5, 129.4, 129.3, 129.1, 127.8 (CH_{ar}), 61.2 (C_α Pro), 54.7 (C_α D-Phe), 52.0 (C_α Leu), 50.8 (C_α PAA), 47.3 (C_δ Pro), 40.9 (C_β Leu), 38.6 (C_β D-Phe), 33.8 (C_β PAA), 32.2 (C_β Val), 29.6 (C_β Pro), 25.5 (C_γ Leu), 24.5 (C_γ Pro), 22.8, 22.6, 19.5, 18.4 ppm (2×C_δ Leu, 2×C_γ Val); HRMS (ESI): *m/z* calcd for $C_{80}H_{101}N_{10}O_{10}P_2S_2$ $[M+H]^+$: 1487.66133; found: 1487.66205; IR (thin film): $\tilde{\nu}=3290$, 2958, 1700, 1688, 1684, 1668, 1662, 1645, 1635, 1563, 1558, 1554, 1544, 1539, 1532, 1520, 1516, 1506, 1490, 1472, 1456, 1436, 1312, 1158, 1104, 799, 746, 694, 668, 6–8, 592, 506 cm^{-1}.

***cyclo*-[Pro-Val-PAA$_2$-Leu-D-Phe]$_2$ (19b)**: The synthesis was performed as outlined above to obtain 336 mg (101 μmol) immobilized decapeptide **18b**. Cleavage from the resin, followed by cyclization and purification yielded compound **19b** (86 mg, 56%). ^{31}P NMR (162 MHz, MeOD/$CDCl_3$ (1:5), $T=302$ K): $\delta=45.5$ ppm (s); ^1H NMR (400 MHz, MeOD/$CDCl_3$ (1:5), $T=302$ K): $\delta=8.73$ (d, 1H; $J_{NH,H\alpha}=9.3$ Hz, NH Leu), 8.41 (d, 1H; $J_{NH,H\alpha}=9.0$ Hz, NH PAA), 8.33 (d, 1H; $J_{NH,H\alpha}=4.3$ Hz, NH D-Phe), 8.04–7.98 (m, 2H; H_{ar}), 7.82–7.76 (m, 2H; H_{ar}), 7.47–7.43 (m, 4H; NH Val, 3×H_{ar}), 7.40–7.33 (m, 3H; H_{ar}), 7.24 (m, 3H; H_{ar}), 7.04 (m, 2H; H_{ar}), 4.88 (m, 1H; H_α PAA), 4.57 (m, 1H; H_α Leu), 4.38 (m, 1H; H_α D-Phe), 4.08 (m, 1H; H_α Pro), 4.04 (m, 1H; H_α Val), 3.62 (M, 1H; H_δ Pro), 2.96–2.86 (m, 3H; 2×H_β D-Phe, H_γ PAA), 2.65 (m, 1H; H_γ PAA), 2.37 (m, 1H; H_γ Pro), 2.23 (m, 1H; H_β Val), 2.15 (m, 1H; H_β PAA), 2.01–1.91 (m, 2H; H_β PAA, H_β Pro), 1.62 (m, 1H; H_β Leu), 1.56–1.48 (m, 4H; H_β Leu, H_β Pro, 2×H_γ Pro), 1.40 (m, 1H; H_β Leu), 0.91–0.84 ppm (m, 12H; 6×H_δ Leu, 6×H_γ Val); ^{13}C NMR (100 MHz, MeOD/$CDCl_3$ (1:5), $T=302$ K): $\delta=173.5$, 173.0, 172.5, 171.9, 171.9 (5×C=O, Leu, PAA, D-Phe, Pro, Val), 136.7, 134.7, 133.8, 133.0 (C_q Ar), 132.7, 132.6, 132.2, 132.1, 132.0, 130.2, 129.5, 129.4, 129.3, 129.2, 128.0 (CH_{ar}), 61.3 (C_α Pro), 60.1 (C_α Val), 55.4 (C_α D-Phe), 53.8 (C_α PAA), 51.1 (C_α Leu), 47.1 (C_δ Pro), 41.0 (C_β Leu), 37.3 (C_β D-Phe), 31.5 (C_β Val), 29.9 (C_β Pro), 28.2 (C_γ PAA), 26.3 (C_β PAA), 25.4 (C_γ Leu), 24.2 (C_γ Pro), 23.1, 23.0, 19.4, 18.7 ppm (2×C_δ Leu, 2×C_γ Val); HRMS (ESI): *m/z* calcd for $C_{82}H_{105}N_{10}O_{10}P_2S_2$ $[M+H]^+$: 1515.69263; found: 151.69324; IR (thin film): $\tilde{\nu}=3272$, 2958, 2364, 2338, 1657, 1652, 1532, 1506, 1436, 1105, 737, 693, 668, 610, 515 cm^{-1}.

***cyclo*-[Pro-Val-PAA$_3$-Leu-D-Phe]$_2$ (19c)**: The synthesis was performed as outlined above to obtain 384 mg (119 μmol) immobilized decapeptide **18c**. Cleavage from the resin, followed by cyclization and purification yielded compound **19c** (91 mg, 46%). ^{31}P NMR (162 MHz, MeOD/$CDCl_3$ (1:1), $T=298$ K): $\delta=44.1$ ppm (s); ^1H NMR (400 MHz, MeOD/$CDCl_3$ (1:1), $T=298$ K): $\delta=8.82$ (d, 1H; $J_{NH,H\alpha}=9.1$ Hz, NH Leu,), 8.39 (d, 1H; $J_{NH,H\alpha}=4.2$ Hz, NH D-Phe), 7.96 (d, 1H; $J_{NH,H\alpha}=9.1$ Hz, NH PAA), 7.65–7.57 (m, 7H; H_{ar}), 7.50–7.36 (m, 7H; NH Val, 6×H_{ar}), 7.29–7.19 (m, 6H; H_{ar}), 5.32 (m, 1H; H_α PAA), 4.51 (m, 1H; H_α Leu), 4.43 (m, 1H; H_α D-Phe), 4.37 (m, 1H; H_α Pro), 4.00 (dd, 1H; $J_{H\alpha,NH}=J_{H\alpha,H\beta}=9.2$ Hz, H_α Val), 3.66 (m, 1H; H_δ Pro), 3.03 (m, 3H; 2×H_β D-Phe, H_β PAA), 2.95 (m, 1H; H_β PAA), 2.33 (m, 1H; H_δ Pro), 2.25 (m, 1H; H_β Val), 1.66–1.52 (m, 6H; 2×H_β Leu, H_γ Leu, H_β Pro, 2×H_γ Pro), 0.93–0.88 ppm (m, 12H; 6×H_δ Leu, 6×H_γ Val); ^{13}C NMR (100 MHz, MeOD/$CDCl_3$ (1:1), $T=298$ K): $\delta=173.1$, 172.5, 171. 9, 171.8, 171.6 (5×C=O, Leu, PAA, D-Phe, Pro, Val), 136.2, 134.5, 133.9 (C_q Ar), 132.7, 132.6, 132.6, 132.5, 131.8, 130.1, 130.0, 129.8, 129.0, 129.0, 128.9, 128.8, 127.4

(CH_{ar}), 60.9 (C_α Pro), 59.7 (C_α Val), 55.0 (C_α D-Phe), 52.7 (C_α PAA), 51.0 (C_α Leu), 46.8 (C_δ Pro), 40.4 (C_β Leu), 37.6, 37.2 (C_β D-Phe, C_β PAA), 30.5 (C_β Val), 29.8 (C_β Pro), 25.0 (C_γ Leu), 24.0 (C_γ Pro), 22.9, 22.7, 19.2, 19.1 ppm ($2\times C_\delta$ Leu, $2\times C_\gamma$ Val); HRMS (ESI): *m/z* calcd for $C_{92}H_{109}N_{10}O_{10}P_2S_2$ $[M+H]^+$: 1639.72393; found: 1639.72534; IR (thin film): $\tilde{\nu}$ = 3272, 2958, 2363, 1718, 1700, 1684, 1657, 1652, 1563, 1558, 1540, 1520, 1506, 1472, 1436, 1190, 1101, 747, 715, 692, 668, 612, 510 cm^{-1}.

Crystallization: **8b**: Suitable red needles were obtained from a solution of **8b** in acetonitrile at 4 °C. **8c**: Orange needle-shaped crystals were obtained after vapor diffusion of the compound dissolved in ethyl acetate at 15 mg mL^{-1} against hexane. **19b**: Colorless plate-shaped crystals were obtained after slow cooling (from 65 °C to 4 °C) of a solution of **19b** in methanol at 9.7 mg mL^{-1}. **19c**: Colorless prism-shaped crystals were obtained after slow evaporation of 2 μL droplets of 29 mg mL^{-1} peptide in dimethyl formamide (DMF) plus 1 μL of *tert*-butanol under paraffin oil in Terasaki plates.

Crystal structure determination of 8b, 8c, 19b, and 19c: A crystal was mounted in air and then rapidly transferred to a low-temperature nitrogen-gas stream. Data were collected on a Bruker KappaAPEXII diffractometer with graphite monocromated $Mo_{K\alpha}$ radiation for **8b** and a Bruker Nonius FR591 Kappa CCD2000 diffractometer with confocal multilayer monochromatized $Cu_{K\alpha}$ radiation for **8c**, **19b** and **19c**. The APEX2[24] suite or COLLECT[25]/HKL2000[26] software was used for data collection and processing. Data were corrected for absorption using the multi-scan method applied either with SADABS[27] or SCALEPACK[26] programs. After treating the data of **8c** for twinning correction using UNTANGLE,[28] the structure could be solved by direct methods, like those of **8b**, **19b** and **19c**, using the SIR2004[29] program. The structures were refined by full-matrix least-squares methods on F^2 with SHELXL[30] included in the WinGX[31] package. All hydrogen positions were calculated and refined using a riding atom model except those corresponding to the water molecules in **8b** and **19c** that were located in difference-Fourier maps. There were two crystallographically independent molecules per asymmetric unit in the crystal structures of **8c** and **19b**. Selected crystallographic data are reported in Table 1. There were several disordered parts in the **19b** structure: both leucine side chains in molecule 1, one complete alkylphosphinyl group in molecule 2 and all water solvent molecules. The extensive degree of disorder together with the pseudo-translation symmetry present in the **19b** structure hinder the possibility of anisotropic refinement; therefore all atoms were refined using isotropic displacement parameters and with restraints in the geometry.

CCDC-718718 (**8b**), 718719 (**8c**), 718720 (**19b**) and 718721 (**19c**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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