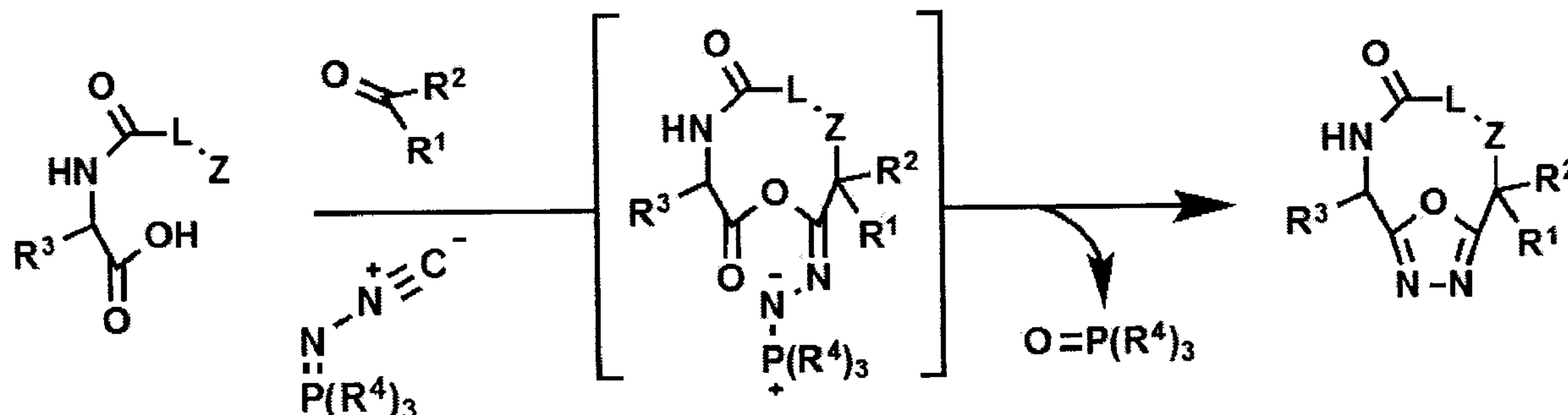




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(54) **Titre : PEPTIDES CYCLIQUES D'OXYDIAZOLE**
(54) **Title: OXADIAZOLE CYCLIC PEPTIDES**



(57) **Abrégé/Abstract:**

The present invention relates to cyclic amino acid molecules, in particular 1,3,4-oxadiazole containing macrocyclic peptides, and a process to produce the same. The process involves the macrocyclization of amino acids or linear peptides. Specifically, the process comprises reacting an amino acid molecule with an isocyano-iminophosphorane and an aldehyde or a ketone.

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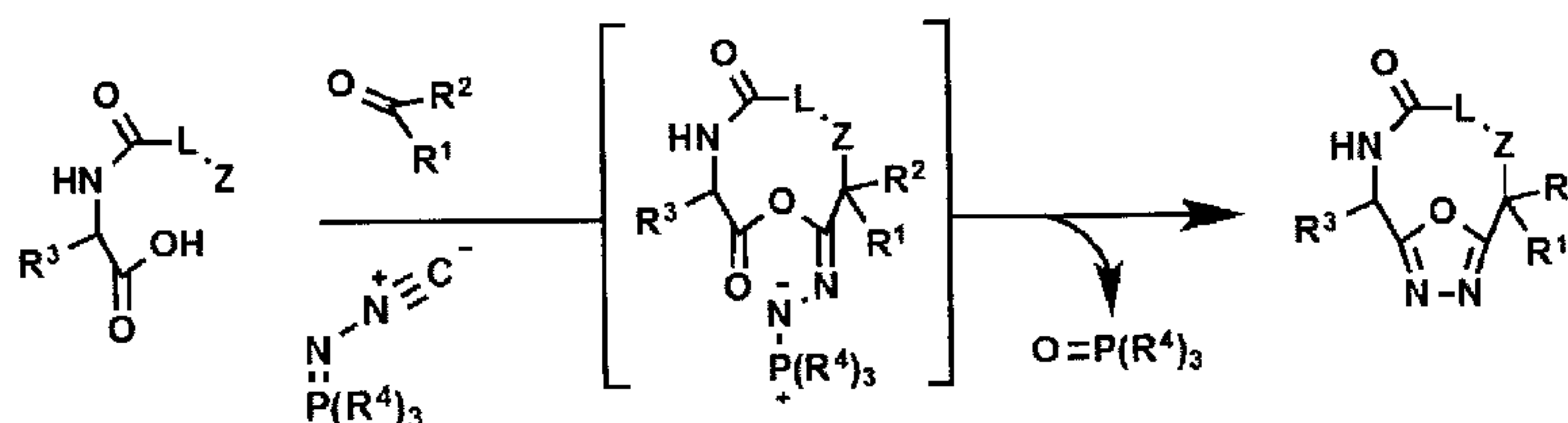


FIGURE 1

(57) Abstract: The present invention relates to cyclic amino acid molecules, in particular 1,3,4-oxadiazole containing macrocyclic peptides, and a process to produce the same. The process involves the macrocyclization of amino acids or linear peptides. Specifically, the process comprises reacting an amino acid molecule with an isocyanato-iminophosphorane and an aldehyde or a ketone.

OXADIAZOLE CYCLIC PEPTIDES

FIELD

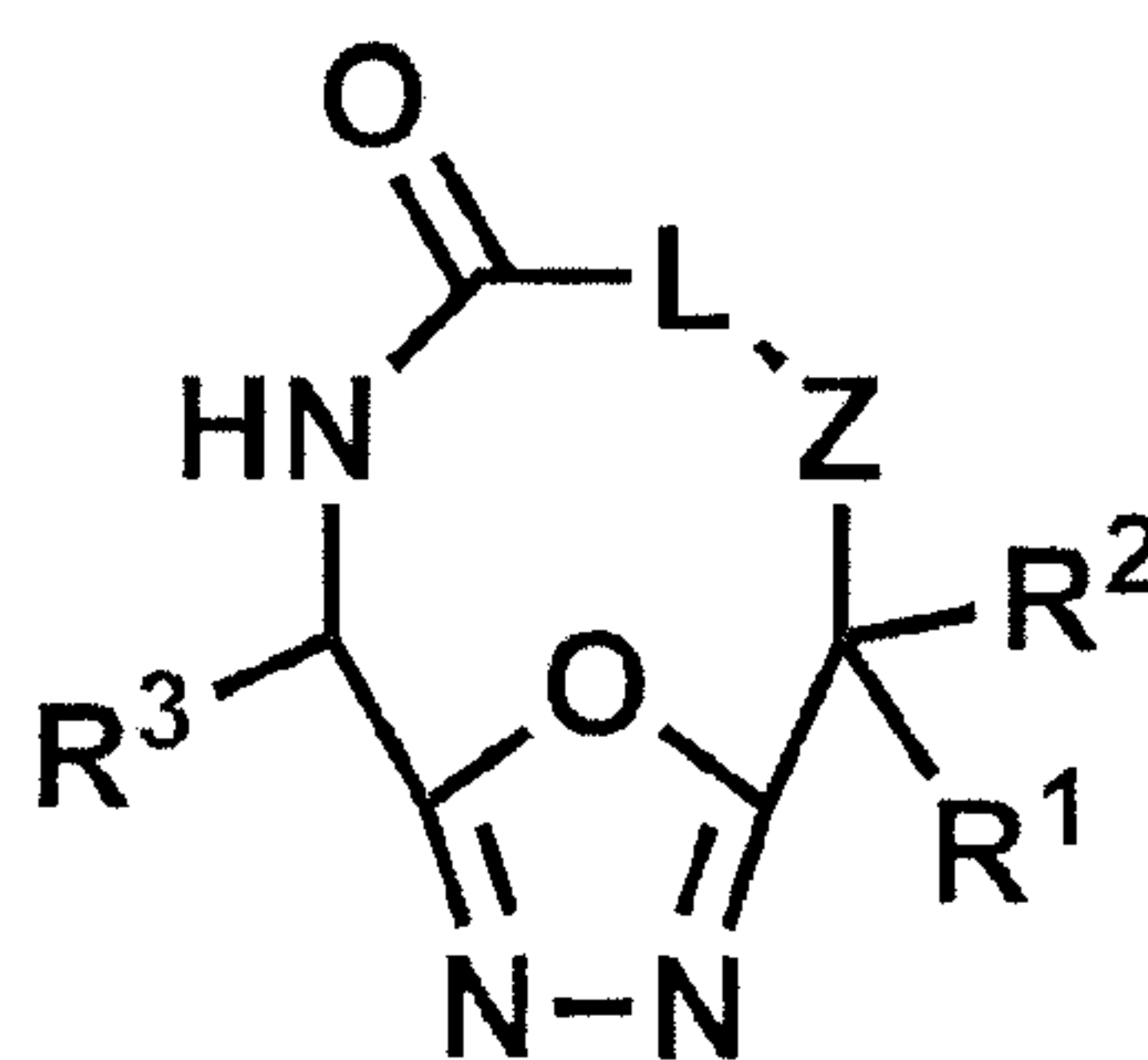
The present invention relates to cyclic amino acid molecules and methods of preparing
5 the same, and in particular the macrocyclization of amino acids or linear peptides.

BACKGROUND

Cyclic topology is a common motif in natural product structures.¹ A subset of natural
products, cyclic peptides, display a wide variety of biological activities, and unique
10 conformational properties due to their circular architecture.²⁻⁶ In 2010, a multicomponent
peptide macrocyclization reaction mediated by aziridine aldehydes was reported. These
amphoteric species incorporate a nucleophilic amino group and electrophilic aldehyde.⁷⁻
⁸ The final macrolactamization step, which involved a transannular attack by the
exocyclic NH aziridine on a mixed anhydride intermediate, furnished a N-acyl aziridine
15 containing macrocycle with an exocyclic amide bond. The non-canonical exocyclic
amide moiety was later found to modulate a well defined intramolecular hydrogen
bonding network.⁹ The success of this multicomponent macrocyclization reaction relies
upon on the reversible dimerization of the aziridine-aldehyde monomer, which allowed
both aziridine and aldehyde functional groups to maintain independent reactivity.¹⁰
20 However, improved macrocyclization processes are desirable.

SUMMARY OF THE INVENTION

In an embodiment, there is disclosed a cyclic molecule of formula [(I)]:



[(I)]

wherein,

Z is an amino terminus of an amino acid;

5 -C=O- is a carboxy terminus of an amino acid;

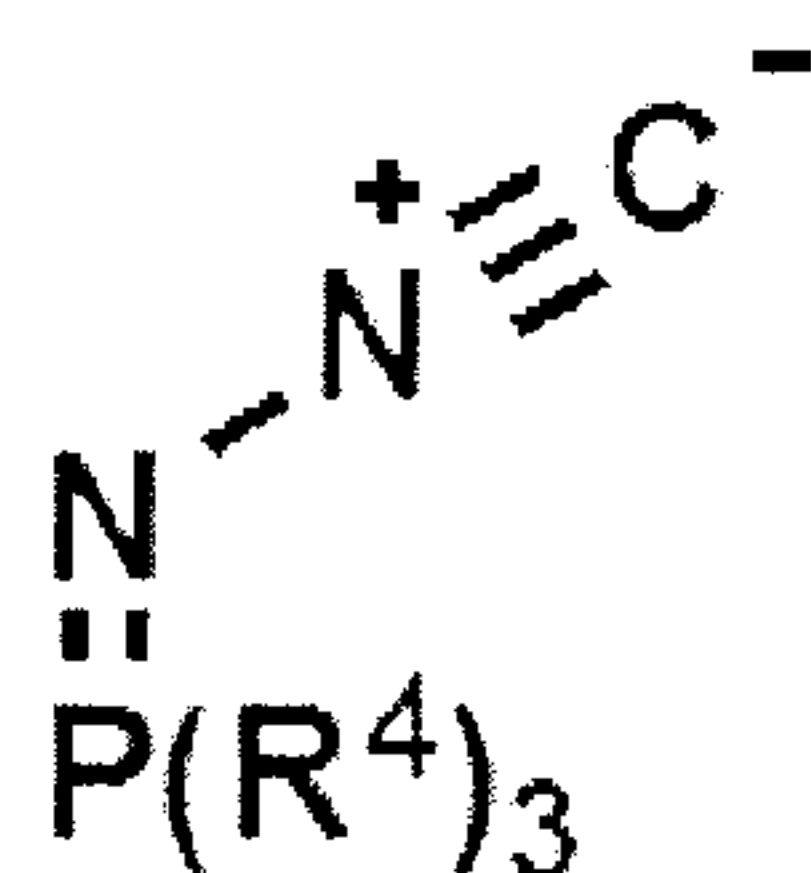
L, along with Z and -C=O- is an amino acid molecule;

R¹ and R² are each independently hydrogen or an organic group;

R³ is equivalent to an amino acid side-chain; and

the amino acid molecule is a linear peptide or a salt of the foregoing.

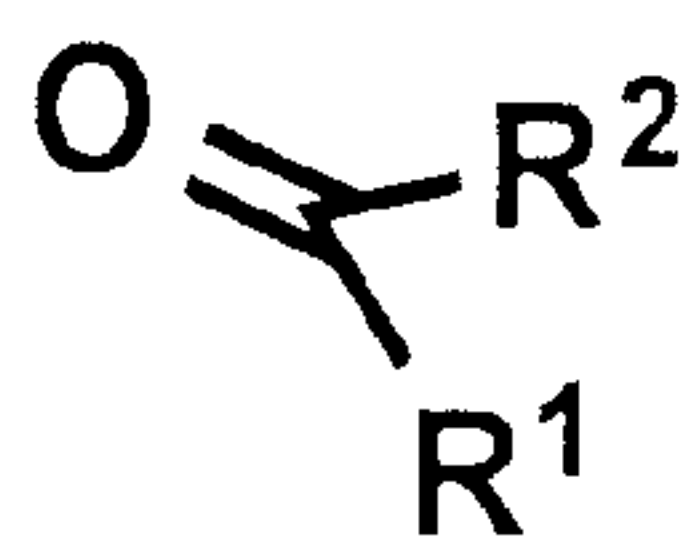
10 In another embodiment, there is disclosed a process to produce a cyclic amino acid molecule comprising reacting an amino acid molecule, having an amino terminus and a carboxyl terminus, with an isocyano-iminophosphorane having the formula [(II)]:



(II)

15

and a compound having the formula [(III)]:



(III)

wherein,

- 5 R¹ and R² are each independently hydrogen or an organic group;
- each R⁴ is independently an organic group;
- and the amino acid molecule is an amino acid, a linear peptide or a salt of the foregoing.

10 **BRIEF DESCRIPTION OF THE FIGURES**

These and other features of the preferred embodiments of the invention will become more apparent in the following detailed description in which reference is made to the appended drawings wherein:

- 15 **Figure 1** shows (A) a schematic of the synthesis of 1,3,4-oxadiazole containing cyclic peptides and (B) a schematic of an alternative depiction of the synthesis of 1,3,4-oxadiazole containing cyclic peptides. Z is an amino terminus of an amino acid molecule; HO-C=O is a carboxy terminus of an amino acid; R¹ and R² are each independently hydrogen or an organic group; R³ is equivalent to an amino acid side-chain; and each R⁴ is independently an organic group.

- 20 **Figure 2** shows NMR solution structures of compound 17 conformers (A) major conformer (B) minor conformer.

Figure 3 shows a proposed mechanism for (*N*-isocyanimino)triphenylphosphorane mediated multicomponent peptide cyclization.

Figure 4 shows hydrogen bonding within cyclo[PGLGF]odz/ethyl diastereomers (Compound 1). Hydrogen atoms that participate are highlighted in red. The diastereomeric aldehyde center is highlighted with an asterisk..

Figure 5 shows the hydrogen bonding profile and temperature shift coefficients (T. Coeff) of **a**, oxadiazole and **b**, homodetic peptide macrocycles, based on the PGLGF sequence, as measured by variable temperature ¹H NMR. Hydrogen atoms engaged in intramolecular hydrogen bonding and their corresponding NMR signals are highlighted. The oxadiazole-containing macrocycle exhibits an alternative hydrogen bonding pattern and displays increased conformational rigidity as compared to the homodetic variant..

Figure 6 shows hydrogen bonding within Compound **20** (cyclo[PSLYG]odz/benzyl) major diastereomer. Hydrogen atoms that participate are highlighted in red.

Figure 7 shows hydrogen bonding within 18-membered oxadiazole-containing macrocycles. Hydrogen atoms that participate are highlighted in red.

Figure 8 shows Crystallographic Data for cyclo[PGLGF]odz/ethyl (**1**).

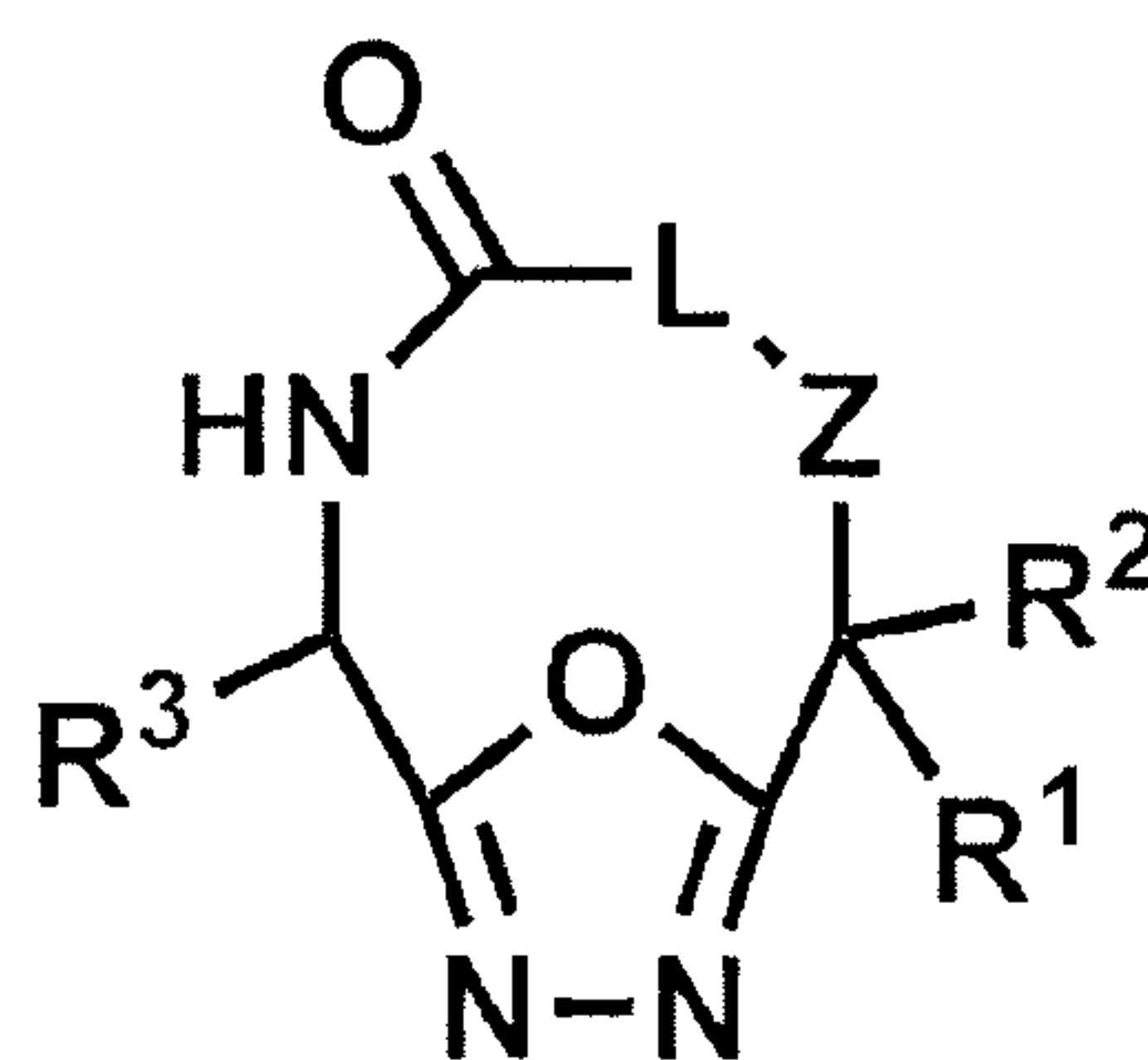
Figure 9 shows the structural analysis of Compound **1**, *cyclo*[PGLGF]odz/ethyl *S*-diastereomer (a) X-ray crystal structure and (b) overlay of NMR solution structure in D₆-DMSO (green) with crystal structure (grey).

Figure 10 shows measured PAMPA values (-logP_e) and structure comparison of oxadiazole-containing and homodetic peptide macrocycles are provided. Differing connectivities are highlighted in blue.

DETAILED DESCRIPTION

In the following description, numerous specific details are set forth to provide a thorough understanding of the invention. However, it is understood that the invention may be practiced without these specific details.

In an embodiment, there is disclosed a cyclic molecule of formula **[I]**:



[(I)]

wherein,

Z is an amino terminus of an amino acid;

5 -C=O- is a carboxy terminus of an amino acid;

L, along with Z and -C=O- is an amino acid molecule;

R¹ and R² are each independently hydrogen or an organic group;

R³ is equivalent to an amino acid side-chain; and

10 the amino acid molecule is an amino acid, a linear peptide or a salt of the foregoing.

In some embodiments, R¹ and R² are each independently selected from the group consisting of hydrogen, an alkyl group, a heteroalkyl group, a cycloalkyl group, an alkenyl group, a heteroalkenyl group, an alkynyl group, a heteroalkynyl group, an aryl group, a heteroaryl group, a heterocyclic group, an acyl group, an α-MIDA
15 borylaldehyde, CF₃, CH₂-CF₃, a macrocycle, a fluorophore, an orthogonal reactive group, an affinity tag, an isotopically labeled molecule, a nucleoside, a nucleotide, a lipid, a carbohydrate, a small molecule, a functionalized solid support and a biologic.

As used herein, the term “amino acid molecule” is meant to include single amino acids and also peptides.

20 As used herein, the term “amino acid” refers to molecules containing an amine group, a carboxylic acid group and a side chain that varies. Amino acid is meant to include not

only the twenty amino acids commonly found in proteins but also non-standard amino acids and unnatural amino acid derivatives known to those of skill in the art, and therefore includes, but is not limited to, alpha, beta, gamma and delta amino acids. Peptides are polymers of at least two amino acids and may include standard, non-
5 standard, and unnatural amino acids.

Although in certain embodiments, cyclization of peptides are described, a person skilled in the art would understand based on the present description that the described methods could also be applied to cyclize a single amino acid.

In some embodiments, the organic group is substituted with one or more halide,
10 hydroxyl, alkoxy, acyloxy or acyl groups.

The term “alkyl group” means a group formed by removing a hydrogen from a carbon of an alkane, where an alkane is an acyclic or cyclic compound consisting entirely of hydrogen atoms and saturated carbon atoms. An alkyl group may include one or more substituent groups.

15 The term “heteroalkyl group” means a group formed by removing a hydrogen from a carbon of a heteroalkane, where a heteroalkane is an acyclic or cyclic compound consisting entirely of hydrogen atoms, saturated carbon atoms, and one or more heteroatoms. A heteroalkyl group may include one or more substituent groups.

The term “alkenyl group” means a group formed by removing a hydrogen from a carbon
20 of an alkene, where an alkene is an acyclic or cyclic compound consisting entirely of hydrogen atoms and carbon atoms, and including at least one carbon-carbon double bond. An alkenyl group may include one or more substituent groups.

The term “heteroalkenyl group” means a group formed by removing a hydrogen from a carbon of a heteroalkene, where a heteroalkene is an acyclic or cyclic compound
25 consisting entirely of hydrogen atoms, carbon atoms and one or more heteroatoms, and including at least one carbon-carbon double bond. A heteroalkenyl group may include one or more substituent groups.

The term “alkynyl group” means a group formed by removing a hydrogen from a carbon of an alkyne, where an alkyne is an acyclic or cyclic compound consisting entirely of

hydrogen atoms and carbon atoms, and including at least one carbon-carbon triple bond. An alkynyl group may include one or more substituent groups.

The term “heteroalkynyl group” means a group formed by removing a hydrogen from a carbon of a heteroalkyne, where a heteroalkyne is an acyclic or cyclic compound
5 consisting entirely of hydrogen atoms, carbon atoms and one or more heteroatoms, and including at least one carbon-carbon triple bond. A heteroalkynyl group may include one or more substituent groups.

The term “aryl group” means a group formed by removing a hydrogen from a ring carbon atom of an aromatic hydrocarbon. An aryl group may be monocyclic or
10 polycyclic and may include one or more substituent groups.

The term “heteroaryl group” means a group formed by replacing one or more methine (-C=) and/or vinylenes (-CH=CH-) groups in an aryl group with a trivalent or divalent heteroatom, respectively. A heteroaryl group may be monocyclic or polycyclic and may include one or more substituent groups.

15 The term “substituent group” means a group that replaces one or more hydrogen atoms in a molecular entity.

The term “heterocyclic group” means a group formed by removing a hydrogen from a cyclic compound that has atoms of at least two different elements as members of its ring(s).

20 The term “acyl group” means a group formed by removing one or more hydroxyl groups from an oxoacid, i.e. RCO-.

The term “hydroxyl group” means the group containing an oxygen atom connected by a covalent bond to a hydrogen atom, i.e. OH-.

The term “alkoxy group” means an alkyl group singularly bonded to oxygen, i.e. R-O.

25 In yet other embodiments, R¹ and R² are each independently selected from the group consisting of ethyl, benzyl and phenyl.

In some aspects, the α -MIDA boron aldehyde is C₆H₉BNO₄.

In some embodiments, the orthogonal reactive group is selected from the group consisting of a cyclic alkyne, a linear alkyne, a cyclic azide, a linear azide, a cyclic tetrazole and a linear tetrazole.

In yet other embodiments, the affinity tag is biotin.

- 5 In other embodiments, the biologic is selected from the group consisting of a functionalized peptide, protein, or amino acid.

In further embodiments, the functionalized solid support is a solid surface or resin bead.

In yet other embodiments, the small molecule is a drug.

In some embodiments, the cyclic amino acid is a lariat type macrocycle.

- 10 In still other embodiments, R^1 and R^2 are covalently linked to each other. In an aspect, R^1 and R^2 form cyclopentanone or other cycloalkanone.

In other embodiments, the amino terminus of the amino acid molecule is a primary amino group.

- 15 In yet other embodiments, the amino terminus of the amino acid molecule is a secondary amino group.

the amino acid molecule comprises a D or L amino acid.

In some embodiments, the amino acid molecule comprises an alpha-amino acid.

In other embodiments, the amino acid molecule comprises a beta-amino acid.

In still other embodiments, the amino acid molecule comprises a gamma-amino acid.

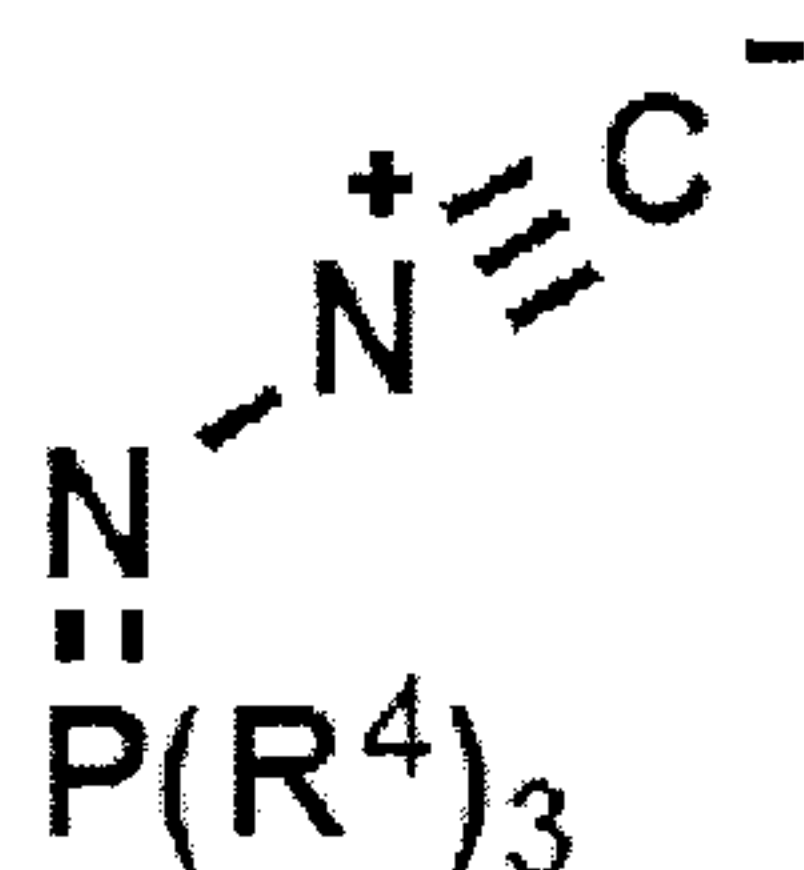
- 20 In some embodiments, the cyclic amino acid comprises a diastereomer at the carbon atom proximal to the aldehyde group.

In an aspect, the diastereomer is an (S) diastereomer.

In another aspect, the diastereomer is an (R) diastereomer

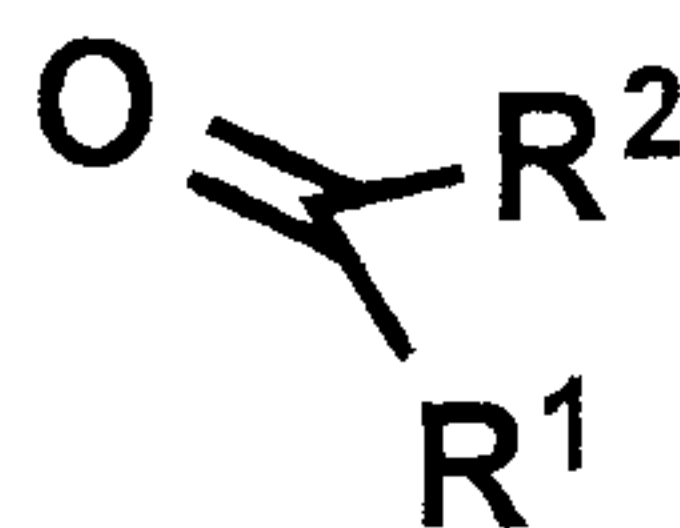
In an embodiment, the peptide comprises at least 2 amino acids.

In another embodiment, there is disclosed a process to produce a cyclic amino acid molecule comprising reacting an amino acid molecule, having an amino terminus and a carboxyl terminus, with an isocyano-iminophosphorane having the formula (II):



5 (II)

and a compound having the formula (III):



(III)

wherein,

10 R^1 and R^2 are each independently hydrogen or an organic group;

each R^4 is independently an organic group; and

and the amino acid molecule is an amino acid, a peptide or a salt of the foregoing.

In some embodiments, R^4 is Ph. In other embodiments, R^4 is selected from the group consisting of an alkyl, an aryl and an alkoxy.

15 In some embodiments, the process further comprises conjugating a fluorescent tag to the cyclic molecule.

In some embodiments, the process further comprises deprotecting one or more side chains of the cyclic amino acid molecule if one or more of said side chains are protected with protecting groups.

The advantages of the present invention are further illustrated by the following examples. The examples and their particular details set forth herein are presented for illustration only and should not be construed as a limitation on the claims of the present invention.

EXAMPLES

5 *Materials and Methods*

General Information: Dichloroethane (DCE) was of reagent grade quality and Acetonitrile (MeCN) was HPLC grade. Linear peptide precursors were synthesized by Fmoc solid-phase-based peptide synthesis using 2-chlorotrityl chloride resin and double coupling steps with HBTU. Amino acid reagents were sourced from AAPP'Tec LLC,
10 Louisville, Kentucky, USA and P3 BioSystems, LLC, Shelbyville, Kentucky, USA. Peptide grade DIPEA was sourced from Sigma Aldrich (Oakville, ON). Peptide grade NMP and DMF were sourced from Caledon Laboratories Ltd., Georgetown, Ontario, Canada. (*N*-isocyanimino)triphenylphosphorane was synthesized according to literature procedure described by Bio *et.al.* ²⁷

15 *Nuclear magnetic resonance spectra:* ¹H and ¹³C NMR spectra were recorded Agilent 500 MHz, 600 MHz, and 700 MHz spectrometers. ¹H NMR spectra were referenced to DMSO-*d*₆ (δ 2.50 ppm). ¹³C NMR spectra were referenced to DMSO-*d*₆ (δ 39.52 ppm). Peak multiplicities are designated by the following abbreviations: s, singlet; bs, broad singlet; d, doublet; t, triplet; q, quartet; m, multiplet; ds, doublet of singlets; dd, doublet
20 of doublets; dt, doublet of triplets; ddd, doublet of doublet of doublets; bt, broad triplet; td, triplet of doublets; tdd, triplet of doublets of doublets.

Mass Spectrometry: High-resolution mass spectra were obtained on a VG 70-250S (double focusing) mass spectrometer at 70 eV on a QStar XL (AB Sciex, Concord, ON, Canada) mass spectrometer with electrospray ionization (ESI) source, MS/MS and
25 accurate mass capabilities. Alternatively, a JEOL AccuTOF model JMS-T1000LC mass spectrometer equipped with a Direct Analysis in Real Time (DART) ion source was used to acquire high-resolution mass spectra.

LC/MS: Low-resolution mass spectra (ESI) were collected on an HPLC paired to a single-quad mass spectrometer. Compounds were resolved on an Agilent Poroshell 120
30 EC-C₁₈, 2.7 μm, 4.6 x 50 mm² column at room temperature with a flow of 1 mL/min.

The gradient consisted of elutents A (0.1% formic acid in double distilled water) and B (0.1% formic acid in HPLC-grade acetonitrile). Absorbance was monitored at $\lambda=214$ nm.

LC/MS Method A: The gradient method started at 5% of B for the first 1.0 minutes, followed by a linear gradient from 5% to 95% B in 15 minutes. The column was then
5 washed with 95% B for 1.0 minutes and re-equilibrated at 5% B for 2 minutes.

LC/MS Method B: The gradient method started at 5% of B and increased from 5% to 95% B in 4.0 minutes. The column was then washed with 95% B for 1.0 minutes and re-equilibrated at 5% B for 1.5 minutes.

General cyclization and deprotection procedure:

10 In a oven dried 1 dram vial equipped with a magnetic stir bar, the linear peptide (0.05 mmol, 1 eq) was suspended in a 1:1 mixture of Dichloroethane and Acetonitrile (DCE:MeCN, 2.0 mL). Due to limited the solubility of the linear peptide the heterogeneous solution was sonicated to form a viscous homogeneous suspension. Aldehyde (0.075 mmol, 1.5 eq) was added to the suspension followed by (*N*-
15 isocyanimino)triphenylphosphorane (0.05 mmol, 1 eq). The solution was stirred for 12 h at 50°C. Following completion of the reaction as monitored by LCMS the reaction mixture was dried under reduced pressure via rotary evaporation. The protected peptides were resuspended in 2.0 mL of deprotection solution (95% Trifluoroacetic Acid + 2.5% H₂O + 2.5% Triethylsilane) and stirred gently for 1 hour then the solvent was removed
20 using a stream of N₂ then under reduced pressure.

RP-HPLC Separation: The crude mixture from the side chain deprotection was resuspended in 3.0 mL of 1:1 H₂O:MeCN then resolved on a Biotage SNAP® cartridge (KP-C18-HS) 30 g column on a Teledyne ISCO Combiflash® Rf 200 at room temperature with a flow of 30 mL/min. The gradient consisted of eluents A (0.1% formic
25 acid in double distilled water) and B (0.1% formic acid in HPLC-grade acetonitrile). The gradient method started at 10% of B for the first 3.0 minutes, followed by a linear gradient from 10% to 65% B in 22 minutes, then a linear gradient from 65% to 100%B in 3 minutes. The column was then washed with 100% B for 5.0 minutes and equilibrated at 10% B for 2 minutes. Fractions containing the target macrocycle were
30 combined and lyophilized to afford the pure peptides as white powders.

Results and Discussion

Over the years, we have sought alternative multicomponent macrocyclization strategies that would place an intercepting nucleophile in the vicinity of a mixed anhydride. However, it was difficult to think of an amine other than aziridine that would be stable in the presence of the other macrocyclization components, in particular the aldehyde functionality. As part of a search for nucleophilic “interceptors”, we recently came across isocyano-iminophosphoranes (ICIPs) as bench-stable reagents that incorporate both a nucleophilic amino group and an isocyanide into a single species.¹¹⁻¹² These reagents have previously been applied for the synthesis of substituted 1,3,4-oxadiazoles via a one-pot multicomponent reaction.¹³ Oxadiazoles have been a point of interest in medicinal chemistry as less polar proteolytically resistant isosteres of amide linkages.¹⁴ We envisioned that ICIPs could also be applied in reactions with linear peptides to generate 1,3,4-oxadiazole containing peptide macrocycles, which we expected to exhibit unique conformational properties based on the rigid, planar, and de-peptidized nature of the oxadiazole linkage imbedded within the peptide backbone. Herein we report a broadly applicable multicomponent peptide macrocyclization reaction, mediated by isocyano-iminophosphoranes (ICIPs), to rapidly assemble structurally and functionally diverse 1,3,4-oxadiazole containing macrocyclic peptides of varying ring size and amino acid composition. (**Figure 1**)

Preliminary Experiments

To investigate the feasibility of using ICIPs to generate oxadiazole containing macrocyclic peptides, we subjected the N-nucleophilic isocyanide, (*N*-isocyanimino)triphenylphosphorane, to a reaction with a model pentapeptide Pro-Gly-Leu-Gly-Phe (PGLGF), (**1**, **Table 1**) which has been well studied in the context of aziridine aldehyde mediated peptide cyclization. Propionaldehyde was chosen as the aldehyde component as it remains in solution at room temperature. After 3 h, at room temperature, a complete conversion of the linear precursor was observed and two isobaric species, in a 3:1 mixture, with masses corresponding to the target macrocycle were identified by LCMS analysis.

Following completion of the macrocyclization reaction the two species were separated and isolated then subjected to a detailed NMR investigation, which confirmed the oxadiazole linkage in each case, and revealed that the species were diastereomers with alternative stereocenters at the position corresponding to the aldehyde carbonyl carbon.

- 5 The major *S*- product and was isolated in 50% yield. The minor *R*- product was isolated in 18% yield for a combined isolated yield of 68%. Both species exhibited conformational homogeneity by NMR, implying that the products are well ordered and conformationally rigid.

Variable Amino Acid Sequences and Ring Sizes

- 10 To investigate the applicability of this method across a broad range of sequences we next turned our attention to collection of 10 pentapeptides with varying residues in the peptide backbone. (2-11, **Table 1**) This collection was projected to generate a series of 18 membered rings, which has been show to be the most prevalent ring size in macrocyclic natural products.¹⁵ As the hydrophobicity of the linear precursors increased, due to the
15 protecting groups, their solubility in the reaction solvent became very low. To remedy this issue the reactions were heated to 50°C, which provided sufficient solubility to conduct the reactions. In each case, cyclization of the linear polypeptide precursor in the presence of (*N*-isocyanimino)triphenylphosphorane and propionaldehyde afforded the desired macrocyclic product in protected form, as a single product, with high (>95%)
20 conversion, as determined by LCMS analysis. The resulting macrocycles were deprotected without isolation and then subjected to reverse phase purification. As outlined in **Table 1**, isolated yields ranged between 4-70%, with an average isolated yield of 38%, which is acceptable range for this type of purification.

- In addition, shorter and longer sequences of 4, 6, and 7 amino acid residues were tested
25 and were found to also undergo efficient macrocyclization to generate 15-, 21-, and 24-membered rings, respectively. (12-16, **Table 2**) It is important to note that over the course of these reactions no oligomerization products were observed. All together these experiments demonstrate that this method is tolerant to a wide range of peptide lengths and amino acid substitutions.

30 *N-methylated Residues*

N-methylated amino acids are present in a number of biologically relevant cyclic-peptide natural products, perhaps most notably, in Cyclosporine A, a broad spectrum immunosuppressant. The vast extent of N-methylation in cyclosporine A allows the macrocycle to undergo a conformational switching between inactive solution and active binding conformations via *cis/trans* isomerization of the amide bonds. In addition the conformational influences of N-methylation within synthetic peptides has been linked to increased membrane permeability,¹⁶⁻¹⁷ enhanced metabolic stability,¹⁸⁻²⁰ heightened bioavailability,²¹⁻²² and receptor selectivity.²³⁻²⁴ Over methylation has, however, been shown to have deleterious effects.²⁵ To investigate the influence of N-methylation in the context of ICIP mediated cyclization, we referred back to the PGLGF model peptide and introduced a sarcosine residue in place of Glycine2 (sequence NH-Pro-Sar-Leu-Gly-Phe-CO₂H) (**17**, **Table 3**). Interestingly, when we isolated the major product of the macrocyclization reaction with propionaldehyde, we discovered that a 3:1 mixture of two species was present by ¹H NMR. EXSY experiments revealed that the two species were inter-converting conformers through selective irradiation and exchanged between the Phenylalanine α- protons of the major and minor species. The ROESY data, specifically the coupling between the Proline α-proton to Sarcosine α-protons for the two conformers, revealed that the major conformer had a *cis*- amide bond at the proline/sarcosine junction whereas the minor conformer exhibited all *trans*- amide bond geometry throughout the molecule. The NMR solution structure was solved for the major *cis*- and minor *trans*- conformers. As shown in **Figure 2**, the major conformer (**A**) displays an unique boat-like geometry, while the minor conformer (**B**) displays a more conventional turn geometry. The 6-mer linear peptide NH-Pro-Sar-Leu-Gly-Phe-Ala-CO₂H also cyclized readily via this approach (**18**, **Table 3**).

25 *Variable Aldehydes and Ketones*

During the method development and investigation of the preliminary macrocyclization scope, the aldehyde component, propionaldehyde, served only as a linker between the N-terminus and the oxadiazole. We envisioned that this aldehyde component could be leveraged to introduce important functionalities into the peptide backbone. First, we envisioned varying the aldehyde to mimic the side chain of an amino acid, which could be used to actively engage a target or influence the conformational properties of the

resulting macrocycles. To this end, we employed phenylacetaldehyde, which would correspond to a phenylalanine side chain and isovaleraldehyde, which would correspond to a leucine side chain. Reaction of the peptides Pro-Ser(OtBu)-Trp(Boc)-Ala-Gly, Pro-Ser(OtBu)-Leu-Tyr(OtBu)-Gly, and Pro-Gly-Leu-Gly-Phe with phenylacetaldehyde
5 afforded the target macrocycles in yields comparable to the macrocycles formed with propionaldehyde. (19-21, Table 4). The peptide, Pro-Gly-Leu-Gly-Phe was also reacted in the presence of isovaleraldehyde to demonstrate that a single sequence can be successfully cyclized in the presence of multiple aldehydes (22, Table 4).

In order to facilitate rapid post cyclization derivatization, we also utilized an α -MIDA
10 borylaldehyde in the cyclization reaction with PSarLFG.²⁶ (23, Table 2) The protected boronic acid could serve as a chemical handle for rapid combinatorial post cyclization derivatization via transition metal mediated cross coupling. In addition, boronic acids have recently become of interest as modulators of cellular permeability. This methodology therefore affords us the opportunity to rapidly modulate the composition
15 and functionality of the macrocyclic products by varying the nature of the aldehyde prior to cyclization, or the coupling partner, post cyclization. It is attractive to envision also introducing alternative biologically relevant functional groups such as fluorophores or affinity tags to aid in screening peptide ligands.

Ketones could also be utilized in the cyclization reaction. As shown in Table 5, both
20 acetone and cyclohexanone could be employed in the (N-isocyanimino)triphenylphosphorane mediated cyclization of 5-mer peptides based on the Pro-Phe-Leu-Asp-Ala sequence, affording oxadiazole-containing macrocycles that are not formed as a mixture of diastereomers (24-25, Table 5).

Primary N-terminal Residues

25 In addition to proline terminated peptides we were also interested in applying the present method for the cyclization of peptides with a primary N-terminus and for peptides containing no proline residues, substrate classes that remained unreactive in aziridine aldehyde mediated cyclization. We investigated the reactivity of several varied 4-mer and 5-mer sequences with different aldehyde components, namely propionaldehyde,
30 phenylacetaldehyde, and benzaldehyde. (26-34, Table 6). Each substrate and aldehyde

reacted successfully in the presence of (*N*-isocyanimino)triphenylphosphorane to generate the desired macrocyclic products with isolated yields ranging from 15-70%. These reactions demonstrate the opportunity to rapidly modulate the product composition by varying the nature of the peptidic and aldehyde component and reveal
5 that proline or other turn inducing residues are not required to achieve macrocyclization.

Mechanistic Discussion

The macrocyclization reaction is proposed to go through a stepwise process starting with condensation of the aldehyde with the peptide N-terminus to form an iminium intermediate, which is then intercepted via addition of the isocyanide, setting a
10 stereocenter in the final products. Macrolactonization of the isonitrilium intermediate by the peptide C-terminus results in the formation of an imino-anhydride intermediate. Finally, the exocyclic imino phosphorane, which is only 3 atoms away from iminoanhydride, coordinates an aza-Wittig type reaction, via a favorable 5 membered transition state, to generate the 1,3,4-oxadiazole linkage. (**Figure 3**) The success of this
15 reaction, and the lack of detectable oligomerization products at relatively high concentrations (25-100 mM depending on peptide solubility), is likely a manifestation of zwitterionic control over cyclization efficiency, which was also operative in the aziridine aldehyde-based process. Our proposal is that within the isonitrillium intermediate the positively charged triphenylphosphonium ion of the iminophosphorane accounts for the
20 attractive electrostatic interaction with the negatively charged carboxylate ion, ultimately leading to the efficient formation of the iminoanhydride intermediate, and finally the macrocyclic product.

Hydrogen Bonding in 1,3,4-oxadiazole containing macrocycles

Variable temperature NMR was used to probe the hydrogen bonding patterns exhibited
25 by 1,3,4-oxadiazole containing peptides synthesized via this approach. First, the hydrogen bonding within both diastereomers of **Compound 1** (*cyclo*[PGLF]/propionaldehyde) in D₆-DMSO was investigated using variable temperature ¹H NMR (25-55°C). As shown in **Figure 4**, both diastereomers exhibited identical hydrogen patterns (H-bonds are defined by a ppb K⁻¹ below 4) suggesting that
30 the aldehyde derived stereo-center does not significantly influence the overall

conformational geometry of the macrocyclic products. Based on these experiments it was concluded that the Gly2 and Phe5 NHs participate in hydrogen bonding, while the Leu3 and Gly4 NHs do not. The hydrogen bonding pattern of the **Compound 1** major diastereomer was also compared to an analogous 18 membered homodetic macrocycle based on the PGLGF sequence (**Figure 5**). The variable temperature ¹H-NMR spectra and temperature shift coefficients show two major differences. First, the oxadiazole-containing macrocycle displays an alternative hydrogen bonding pattern as compared to its homodetic counterpart. Second, the oxadiazole-containing macrocycle (**Compound 1**) exists as a single conformer in solution while the homodetic macrocycle exists as a mixture of conformers at all temperatures.

In addition to **Compound 1** we also investigated the H-bonding pattern exhibited by several other macrocycles. Compound **20**, (*cyclo*[PSLYG]/phenylacetaldehyde) an 18 membered oxadiazole containing macrocycle comprised of different amino acid residues and a different aldehyde component than **Compound 1**. Importantly, as shown in **Figure 6**, **Compound 20** displays the same hydrogen bonding pattern, more specifically at the residues in positions 2 and 5. This result suggested that the proline-aldehyde-oxadiazole linkage can serve as a robust turn stabilizing motif regardless of the aldehyde component or peptide sequence composition. To further investigate the generality of this hydrogen bonding pattern we also defined the intramolecular hydrogen bonding patterns of several other macrocycles using the same variable temperature NMR experiments (**Figure 7**). Importantly, all oxadiazole-containing 18 membered rings showed the same 2,5-hydrogen bonding pattern. In some cases additional hydrogen bonds were also observed.

Structural characteristics and turn inducing elements

The X-ray crystal structure was solved for the major (*S*-) diastereomer of **Compound 1** (**Figure 8**). The crystal structure supports the outlined H-bonding pattern described above (**Figure 9A**). Both the tertiary proline derived amino group and the oxadiazole oxygen are with appropriate distance (< 3Å) from the Gly2 NH to serve as H-bonding acceptors. Also, the Gly2 Carbonyl is appropriately positioned to engage the Phe5 NH. By overlaying the modeled NMR solution structure of **Compound 1** with the obtained crystal structure reveals a remarkable similarity between the two, thereby highlighting the conformational homogeneity and structural rigidity exhibited by oxadiazole

containing macrocycles in solution. (**Figure 9B**) Most importantly, the Leu3 and Gly4 ψ / ϕ angles ($= \psi_1 -64^\circ$, $\psi_2 86^\circ$, $\phi_1 113^\circ$, $\phi_2 8^\circ$) obtained from the X-ray crystal structure match very closely with the theoretical angles for a Type II β -turn ($= \psi_1 -60^\circ$, $\psi_2 80^\circ$, $\phi_1 120^\circ$, $\phi_2 0^\circ$), the most prevalent turn structure in biologically active peptides. This observation suggests that the outlined methodology can be utilized to stabilize biologically relevant secondary structures in macrocyclic peptides.

Passive membrane permeability of oxadiazole-containing peptide macrocycles

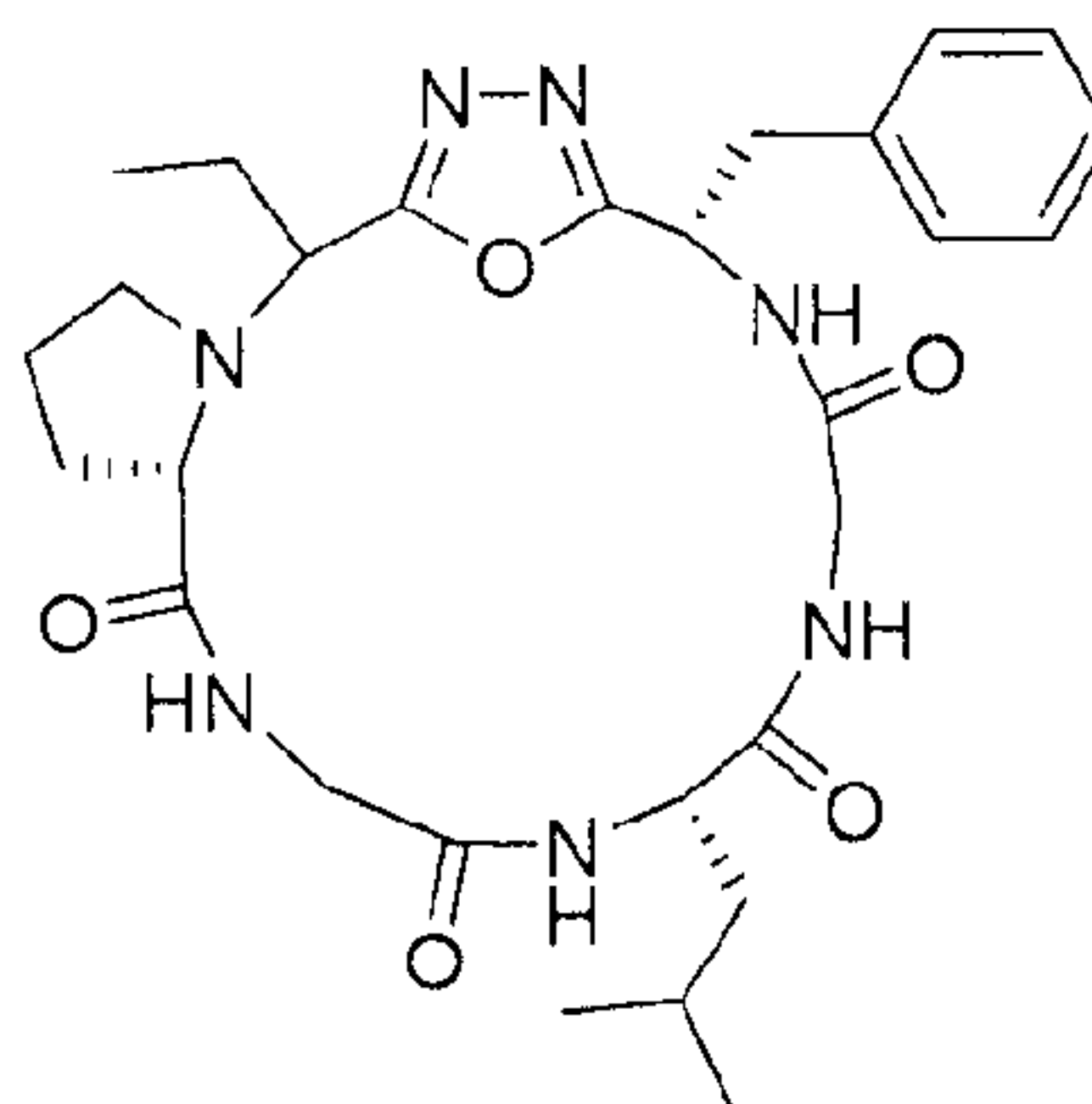
Passive membrane permeability is an important property for the development of new therapeutics. A passive artificial membrane permeability (PAMPA) assay was utilized to measure the extent of passive membrane permeability displayed by oxadiazole-containing peptide macrocycles. Using this analysis method a $-\log P_e$ value <6.0 is indicative of a passively membrane permeable compound, while a $-\log P_e >6.0$ is indicative of a poorly permeable or non-permeable compound. As shown in **Figure 10**, a collection of oxadiazole-containing peptide macrocycles (entries 1-7) and their analogous homodetic counterparts (entries 8-12) were subjected to PAMPA analysis. Importantly, in all cases, the oxadiazole containing peptide macrocycles (entries 1-7, **Figure 10**) were passively membrane permeable (evidenced by $-\log P_e$ values <6.0) and displayed higher passive membrane permeability than their homodetic counterparts. In 4 out of 5 cases the homodetic macrocycles were not passively membrane permeable with the single exception being the highly hydrophobic cyclo[PFLFLFA] (entry 12).

Conclusions

We have developed a robust approach to rapidly access structurally diverse macrocycle peptides via a multicomponent reaction. This method relies on the application of (*N*-isocyanimino)triphenylphosphorane, which places a pendant exocyclic amine in position to intercept an iminoanhydride intermediate. The resulting product is cyclic molecule with a 1,3,4-oxadiazole imbedded within the peptide backbone. By varying the length and composition of the peptidic component we were able to generate 15, 18, 21, and 24 membered rings using this approach. By varying the nature of the aldehyde component alternative functional groups were introduced into the macrocyclic products. *N*-methylation studies revealed an opportunity to generate macrocycles that undergo

conformational exchange, via *cis/ trans* amide isomerization, and exhibit unique structural properties. Variable temperature NMR investigations revealed a conserved H-bonding pattern than persists in 18 membered macrocyclic products independent of the peptide or aldehyde compositions. Overlay of the crystal structure and NMR solution structure revealed a highly conserved conformational geometry wherein the oxadiazole oxygen and tertiary N-terminal amino group may both contribute to the conformational stabilization by accepting hydrogen bonds, as observed in the X-ray crystal structure. A unique enabling feature of this approach involves the formation of a unprecedented motif in the form of a contiguous non-amidated N-terminal amino group, variable aldehyde, and 1,3,4-oxadiazole triad, which accommodates the formation of a stable Type I and Type II β -turns. β -turns are present in a number of biologically active peptides, supporting the application of this methodology for the development of new therapeutics and biological probes. Oxadiazole-containing macrocycles can display passive membrane permeability and therefore represent attractive candidates for the development of new probes and therapeutics.

Compound characterization



cyclo[PGLGF]odz/ethyl (**1**)

The peptide NH-Pro-Gly-Leu-Gly-Phe-CO₂H (24.5 mg, 0.05 mmol, 1 eq) was dissolved in a mixture of 1:1 Dichloroethane:Acetonitrile (1 mL). Propionaldehyde (5.4 μ L, 0.075 mmol, 1.5 eq) and (*N*-isocyanimino)triphenylphosphorane (15.1 mg, 0.05 mmol, 1 eq) were added to the reaction mixture. After cyclization and reverse phase purification the pure fractions were pooled and lyophilized to afford 14 mg of the title compound major diastereomer **1a** (50% yield) and 5 mg of the minor diastereomer **1b** (18 % yield) for a total 68% overall yield.

Major (*S,S*)- **1a**: HR-MS (ESI) calculated for C₂₈H₄₀N₇O₅ [M+H]⁺ : 554.3085 found: 554.3086

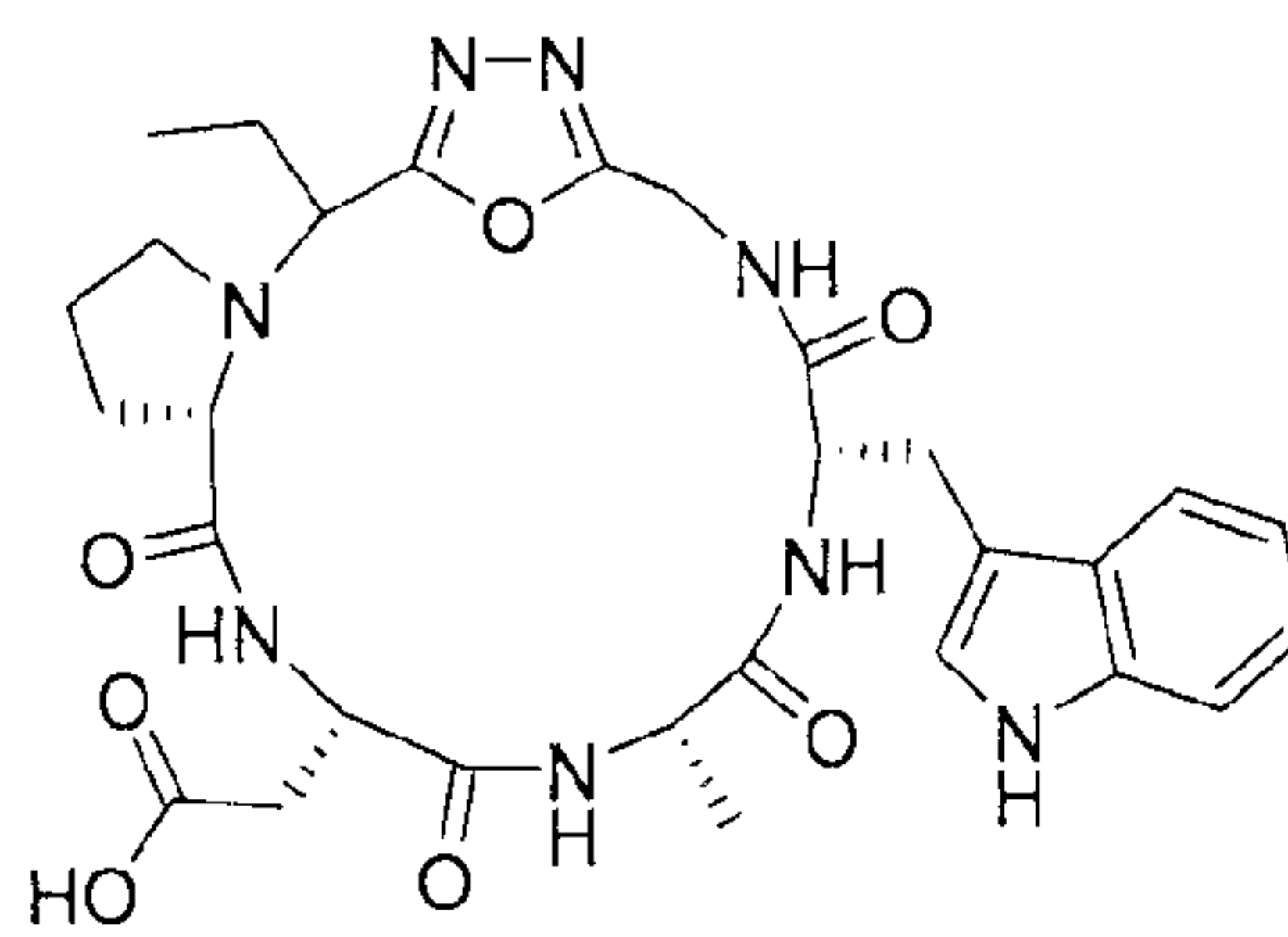
HPLC Method A: Retention Time 7.85 min.

The HPLC and spectra data has been redacted for all of the the compounds for brevity.

- 5 Minor (*R,S*)- **1b**: HR-MS (ESI) calculated for C₂₈H₄₀N₇O₅ [M+H]⁺ : 554.3085 found: 554.3083

HPLC Method A: Retention Time 8.15 min

10



cyclo[PDAWG]odz/ethyl (**2**)

- 15 The peptide NH-Pro-Asp(O^tBu)-Ala-Trp(Boc)-Gly-CO₂H (35 mg, 0.05 mmol, 1 eq) was dissolved in a mixture of 1:1 Dichloroethane:Acetonitrile (2 mL). Propionaldehyde (5.4 μL, 0.075 mmol, 1.5 eq) and (*N*-isocyanimino)triphenylphosphorane (15.1 mg, 0.05 mmol, 1 eq) were added to the reaction mixture. After cyclization, deprotection, and reverse phase purification the pure fractions were pooled and lyophilized to afford 6.7 mg of the title compound in 22% overall yield as a 3.5:1 mixture of diastereomers.

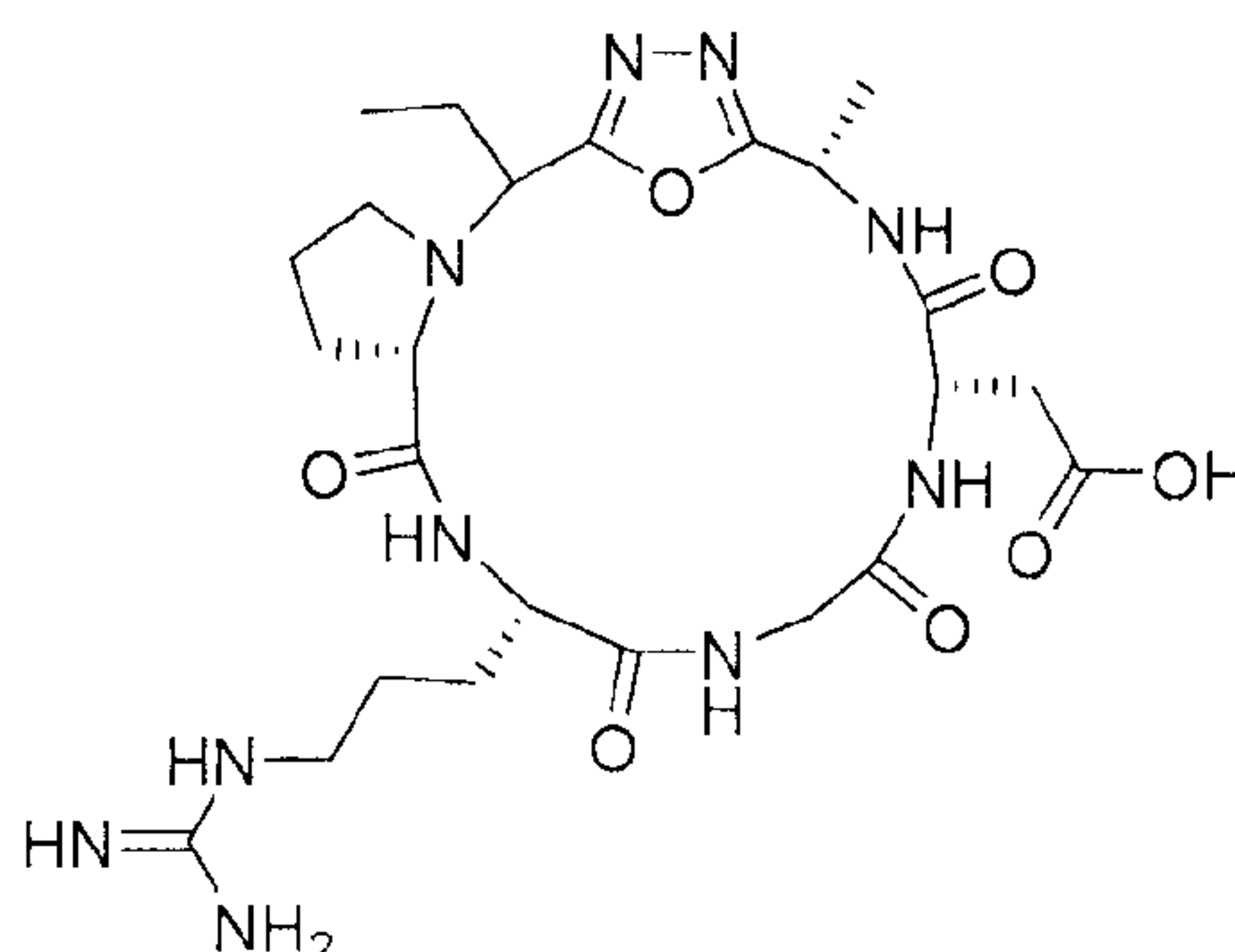
20

HR-MS (ESI) calculated for C₂₉H₃₇N₈O₇ [M+H]⁺ : 609.278 found: 609.2791

HPLC Method A:

Retention time (major diastereomer) 6.28 min

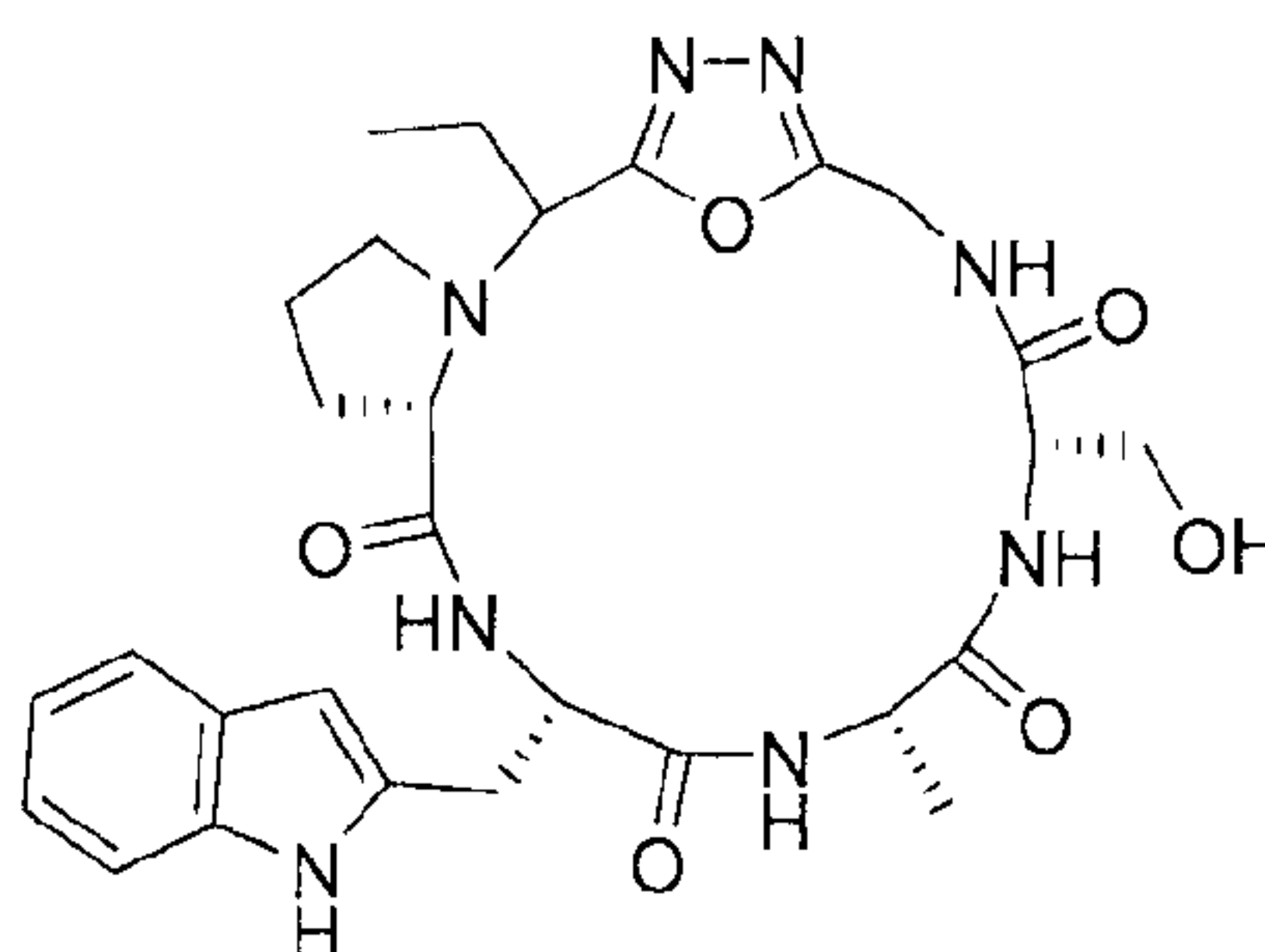
Retention time (minor diastereomer) 6.39 min



5 *cyclo*[PRGDA]odz/ethyl (**3**)

The peptide NH-Pro-Arg(Pbf)-Gly-Asp(OtBu)-Ala-CO₂H was cyclized at 0.05 mmol scale with propionaldehyde (1.5 eq) and (*N*-isocyanimino)triphenylphosphorane (1 eq). After cyclization, deprotection, and reverse phase purification the pure fractions were pooled and lyophilized to afford 20.2 mg of the title compound in 70% overall yield.

HR-MS (ESI) calculated for C₂₄H₃₉N₁₀O₇ [M+H]⁺ : 579.2998 found: 579.3006



15

cyclo[PWASG]odz/ethyl (**4**)

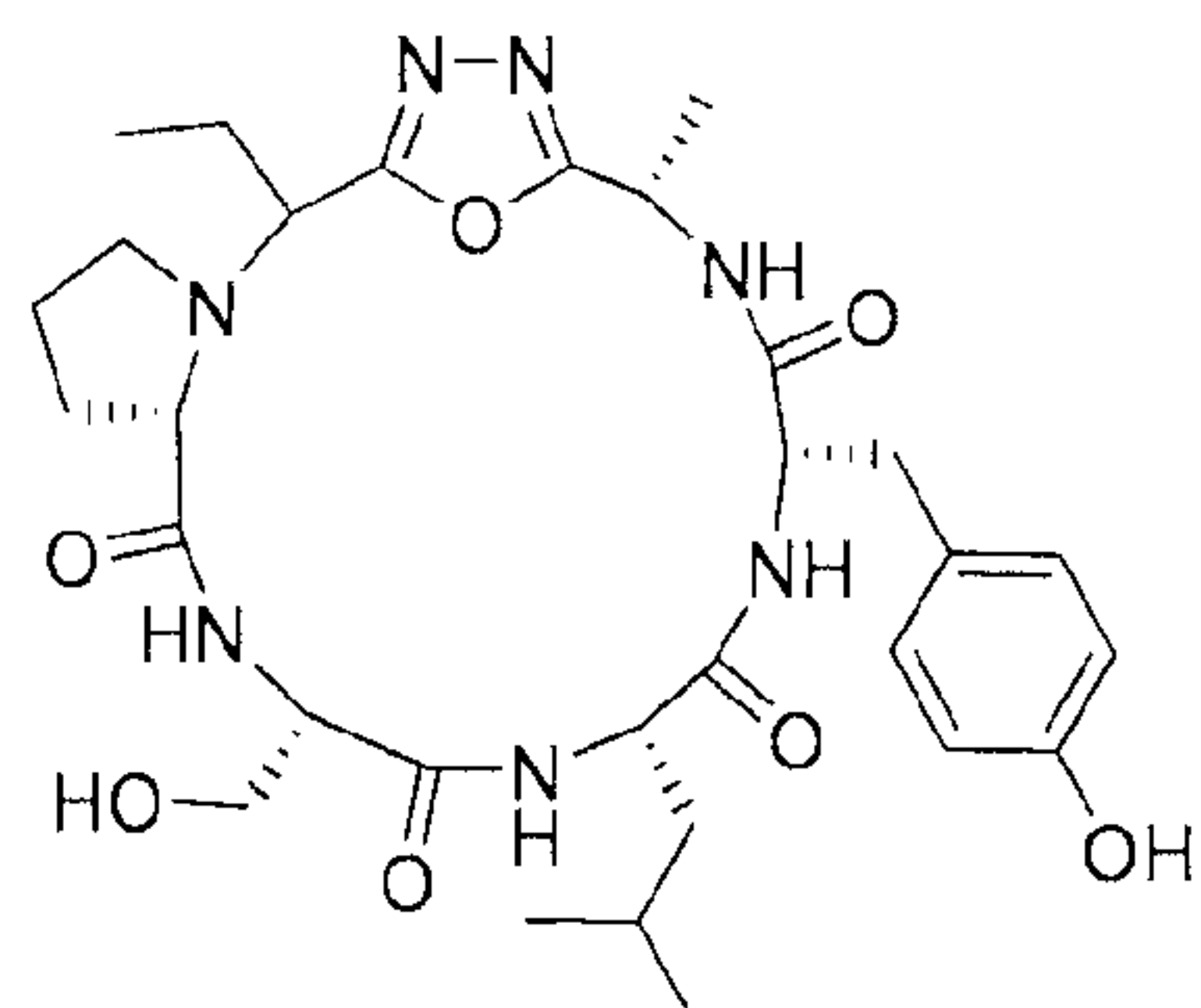
The peptide NH-Pro-Trp(Boc)-Ala-Ser(O^tBu)-Gly-CO₂H (33.6 mg, 0.05 mmol, 1 eq) was dissolved in a mixture of 1:1 Dichloroethane:Acetonitrile (2 mL). Propionaldehyde (5.4 μL, 0.075 mmol, 1.5 eq) and (*N*-isocyanimino)triphenylphosphorane (15.1 mg, 0.05 mmol, 1 eq) were added to the reaction mixture. After cyclization, deprotection, and
5 reverse phase purification the pure fractions were pooled and lyophilized to afford 8.2 mg of the title compound in 28% overall yield as a 2.9:1 mixture of diastereomers.

HR-MS (ESI) calculated for C₂₈H₃₇N₈O₆ [M+H]⁺ : 581.2831 found: 581.2826

HPLC Method A:

Retention time (major diastereomer) 6.80 min

10 Retention time (minor diastereomer) 6.91 min



cyclo[PSLYA]odz/ethyl (**5**)

15

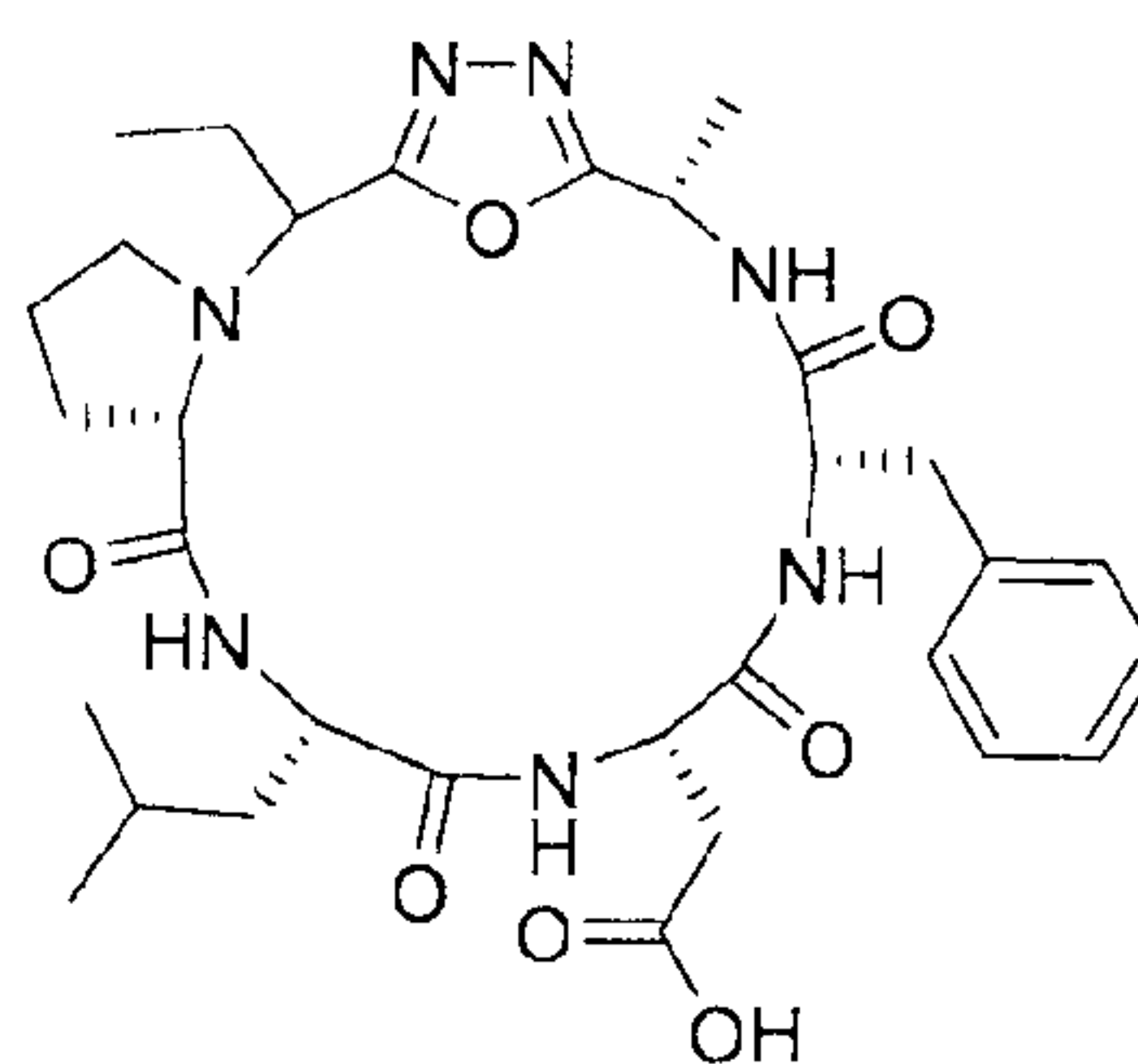
The peptide NH-Pro-Ser(O^tBu)-Leu-Tyr(O^tBu)-Ala-CO₂H (33.1 mg, 0.05 mmol, 1 eq) was dissolved in a mixture of 1:1 Dichloroethane:Acetonitrile (2 mL). Propionaldehyde (5.4 μL, 0.075 mmol, 1.5 eq) and (*N*-isocyanimino)triphenylphosphorane (15.1 mg, 0.05 mmol, 1 eq) were added to the reaction mixture. After cyclization, deprotection, and
20 reverse phase purification the pure fractions were pooled and lyophilized to afford 7.4 mg of the title compound in 24 % overall yield as a 3:1 mixture of diastereomers.

HR-MS (ESI) calculated for C₃₀H₄₄N₇O₇ [M+H]⁺ : 614.3297 found: 614.3312

HPLC Method A:

Retention time (major diastereomer) 6.64 min

25 Retention time (minor diastereomer) 6.82 min



cyclo[PLDFA]odz/ethyl (6)

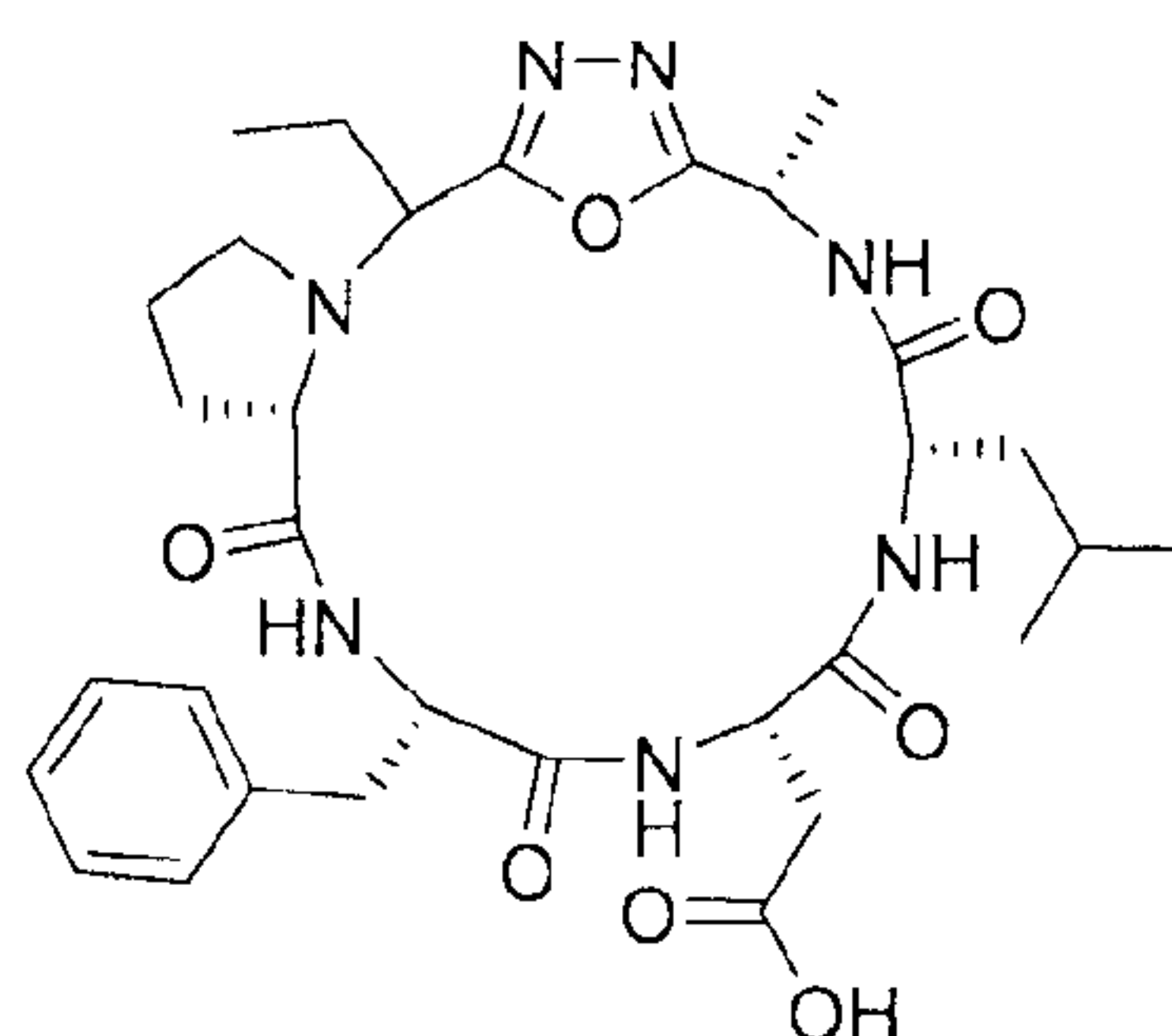
- 5 The peptide NH-Pro-Leu-Asp(O^tBu)-Phc-Ala-CO₂H (30.9 mg, 0.05 mmol, 1 eq) was dissolved in a mixture of 1:1 Dichloroethane:Acetonitrile (2 mL). Propionaldehyde (5.4 μL, 0.075 mmol, 1.5 eq) and (*N*-isocyanimino)triphenylphosphorane (15.1 mg, 0.05 mmol, 1 eq) were added to the reaction mixture. After cyclization, deprotection, and reverse phase purification the pure fractions were pooled and lyophilized to afford 16.2
- 10 mg of the title compound in 52 % overall yield as a single diastereomer.

HR-MS (ESI) calculated for C₃₁H₄₄N₇O₇ [M+H]⁺ : 626.3297 found: 626.3307

HPLC Method A:

Retention time (major diastereomer) 8.32 min

15



cyclo[PFDLA]odz/ethyl (7)

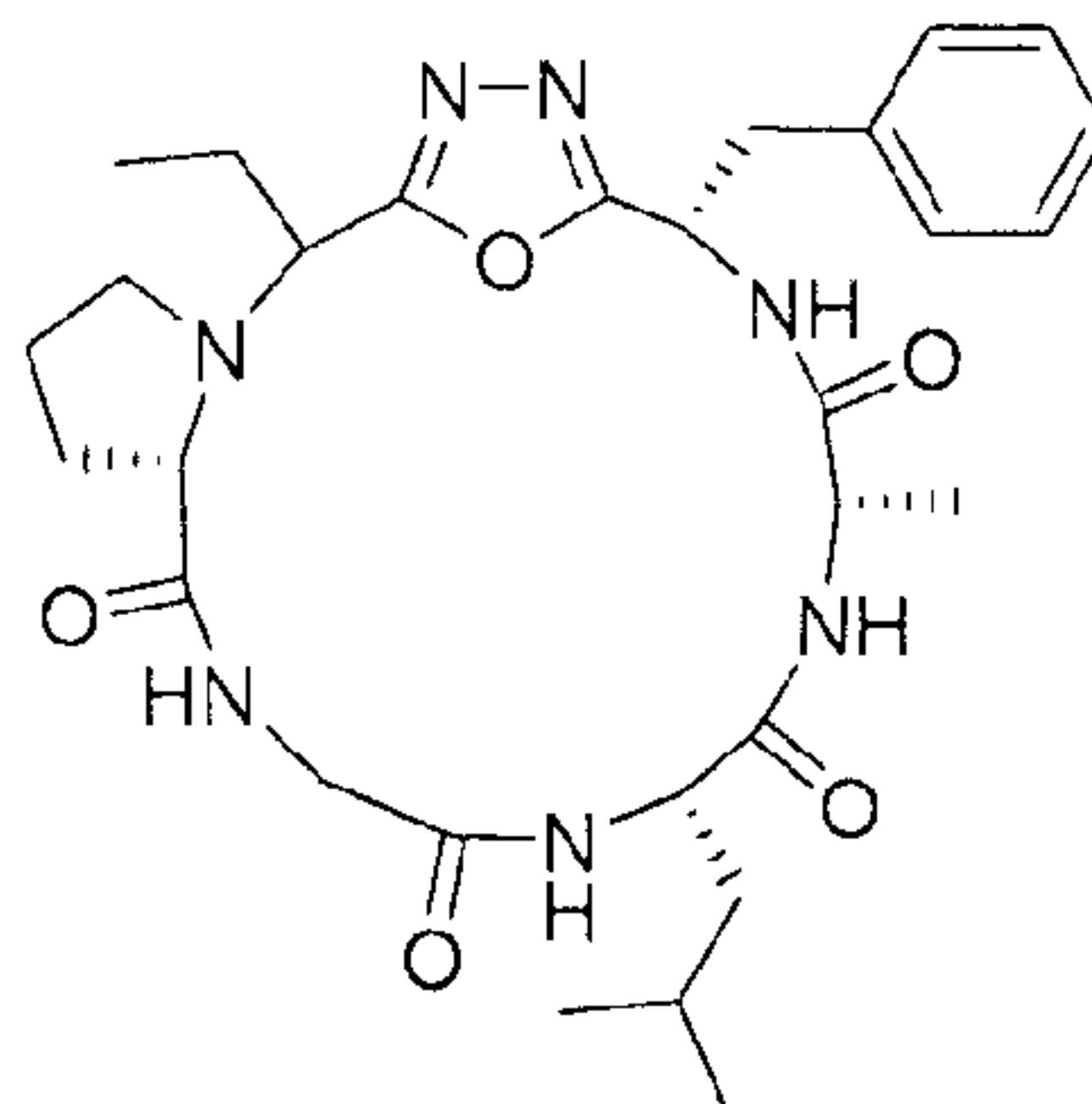
The peptide NH-Pro-Phe-Asp(O^tBu)-Leu-Ala-CO₂H (30.9 mg, 0.05 mmol, 1 eq) was dissolved in a mixture of 1:1 Dichloroethane:Acetonitrile (2 mL). Propionaldehyde (5.4 μL, 0.075 mmol, 1.5 eq) and (*N*-isocyanimino)triphenylphosphorane (15.1 mg, 0.05 mmol, 1 eq) were added to the reaction mixture. After cyclization, deprotection, and reverse phase purification the pure fractions were pooled and lyophilized to afford 14 mg of the title compound in 45 % overall yield as a 5.9:1 mixture of diastereomers.

HR-MS (ESI) calculated for C₃₁H₄₄N₇O₇ [M+H]⁺ : 626.3297 found: 626.3301

HPLC Method A:

Retention time (major diastereomer) 8.21 min

10 Retention time (minor diastereomer) 8.29 min



cyclo[PGLAF]odz/ethyl (**8**)

The peptide NH-Pro-Gly-Leu-Ala-Phe-CO₂H (25.2 mg, 0.05 mmol, 1 eq) was dissolved in a mixture of 1:1 Dichloroethane:Acetonitrile (2.5 mL). Propionaldehyde (5.4 μL, 0.075 mmol, 1.5 eq) and (*N*-isocyanimino)triphenylphosphorane (15.1 mg, 0.05 mmol, 1 eq) were added to the reaction mixture. After cyclization, deprotection, and reverse phase purification the pure fractions were pooled and lyophilized to afford 6.5 mg of the title compound in 23% overall yield as a 4.9:1 mixture of diastereomers.

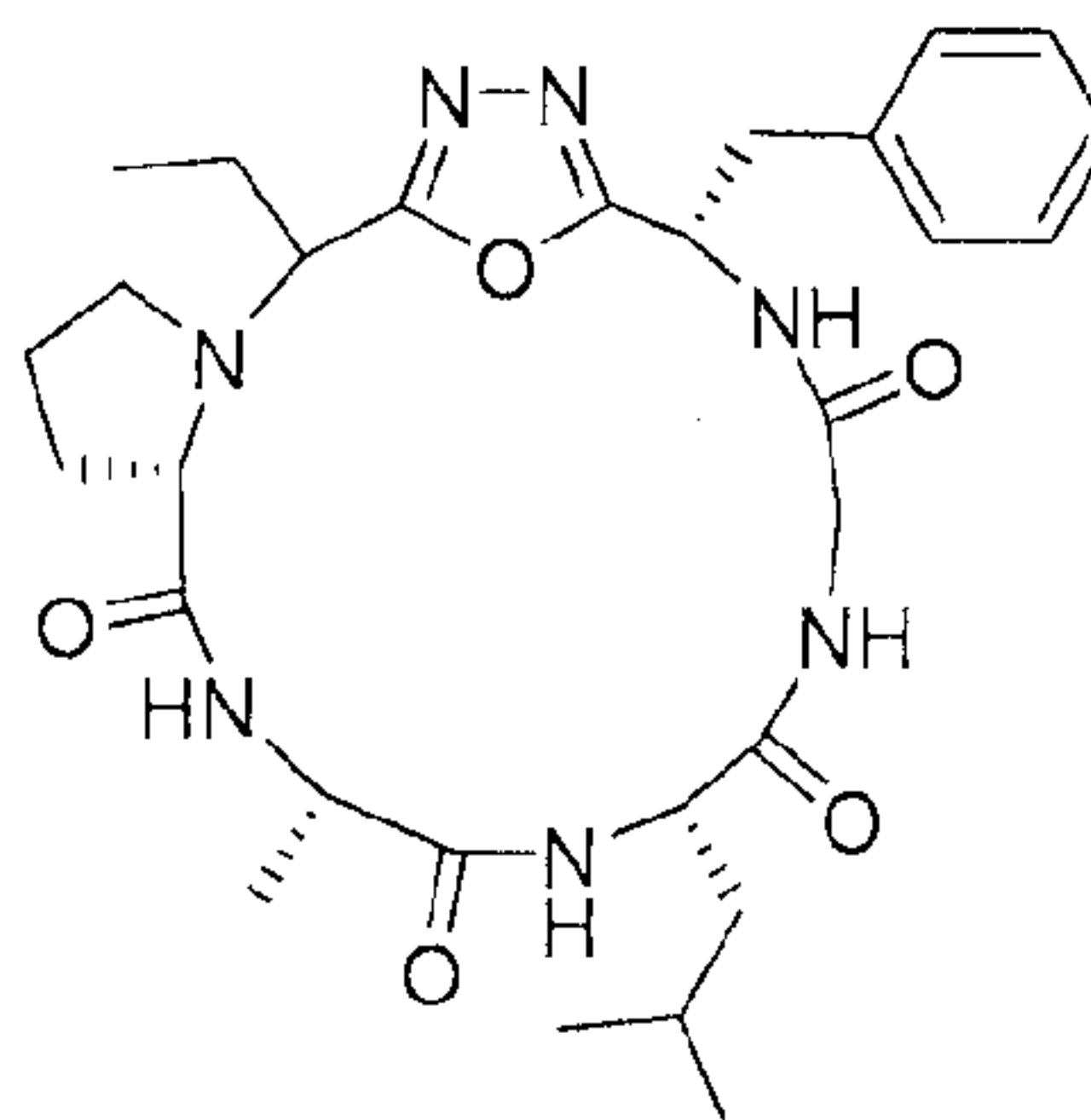
20 HR-MS (ESI) calculated for C₂₉H₄₁N₇O₅ [M+H]⁺ : 568.3169 found: 568.3250

HPLC Method A:

Retention time (major diastereomer) 8.05 min

Retention time (minor diastereomer) 8.21 min

25



cyclo[PALGF]odz/ethyl (**9**)

The peptide NH-Pro-Ala-Leu-Gly-Phe-CO₂H (25.2 mg, 0.05 mmol, 1 eq) was dissolved
 5 in a mixture of 1:1 Dichloroethane:Acetonitrile (2.5 mL). Propionaldehyde (5.4 μ L, 0.075 mmol, 1.5 eq) and (*N*-isocyanimino)triphenylphosphorane (15.1 mg, 0.05 mmol, 1 eq) were added to the reaction mixture. After cyclization, deprotection, and reverse phase purification the pure fractions were pooled and lyophilized to afford 7 mg of the title compound in 25% overall yield as a 1.8:1 mixture of diastereomers.

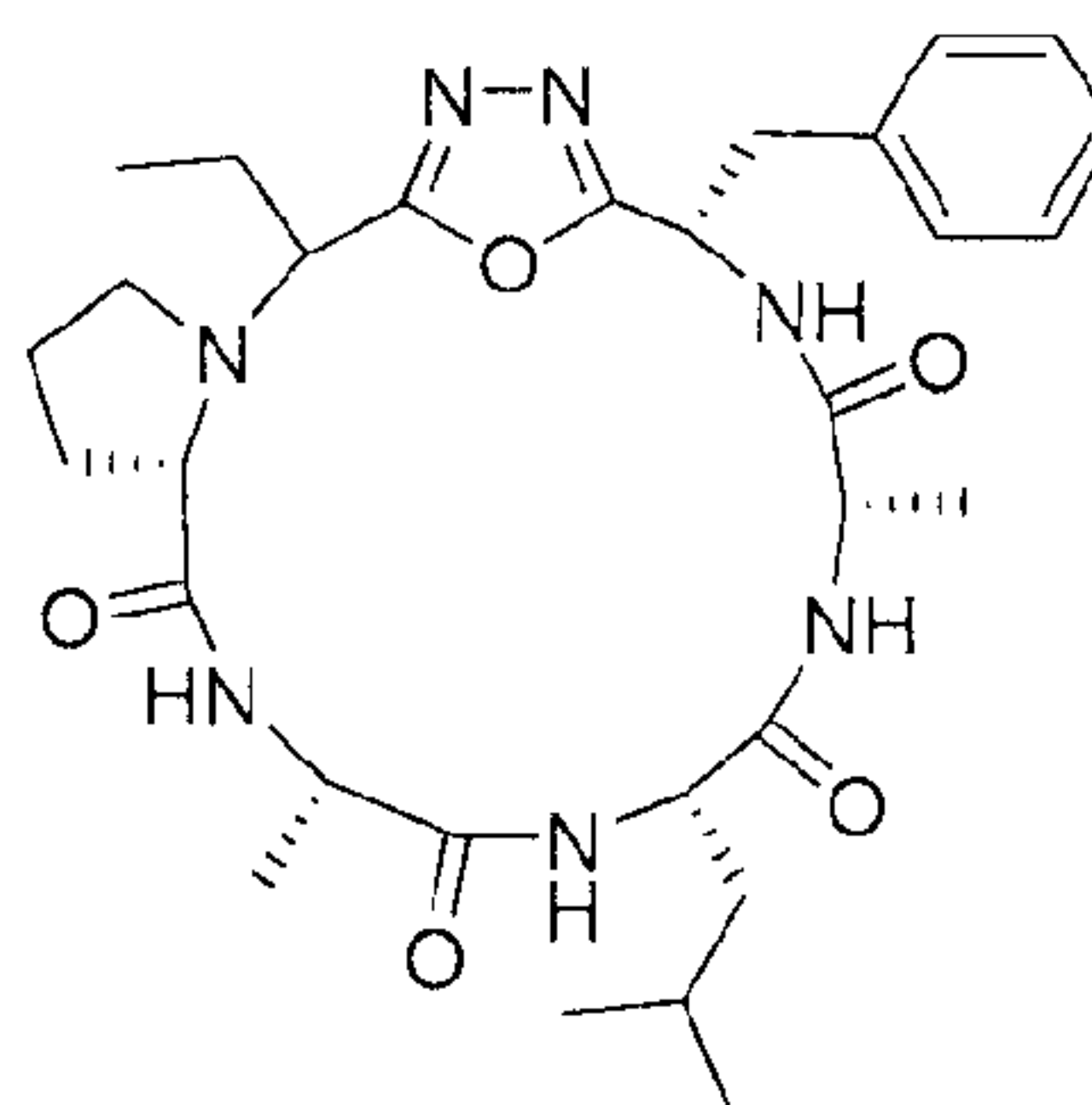
10 HR-MS (ESI) calculated for C₂₉H₄₁N₇O₅ [M+H]⁺ : 568.3169 found: 568.3242

HPLC Method A:

Retention time (major diastereomer) 8.87 min

Retention time (minor diastereomer) 9.18 min

15



cyclo[PALAF]odz/ethyl (**10**)

The peptide NH-Pro-Ala-Leu-Ala-Phe-CO₂H (25.9 mg, 0.05 mmol, 1 eq) was dissolved
 20 in a mixture of 1:1 Dichloroethane:Acetonitrile (2.5 mL). Propionaldehyde (5.4 μ L, 0.075 mmol, 1.5 eq) and (*N*-isocyanimino)triphenylphosphorane (15.1 mg, 0.05 mmol, 1

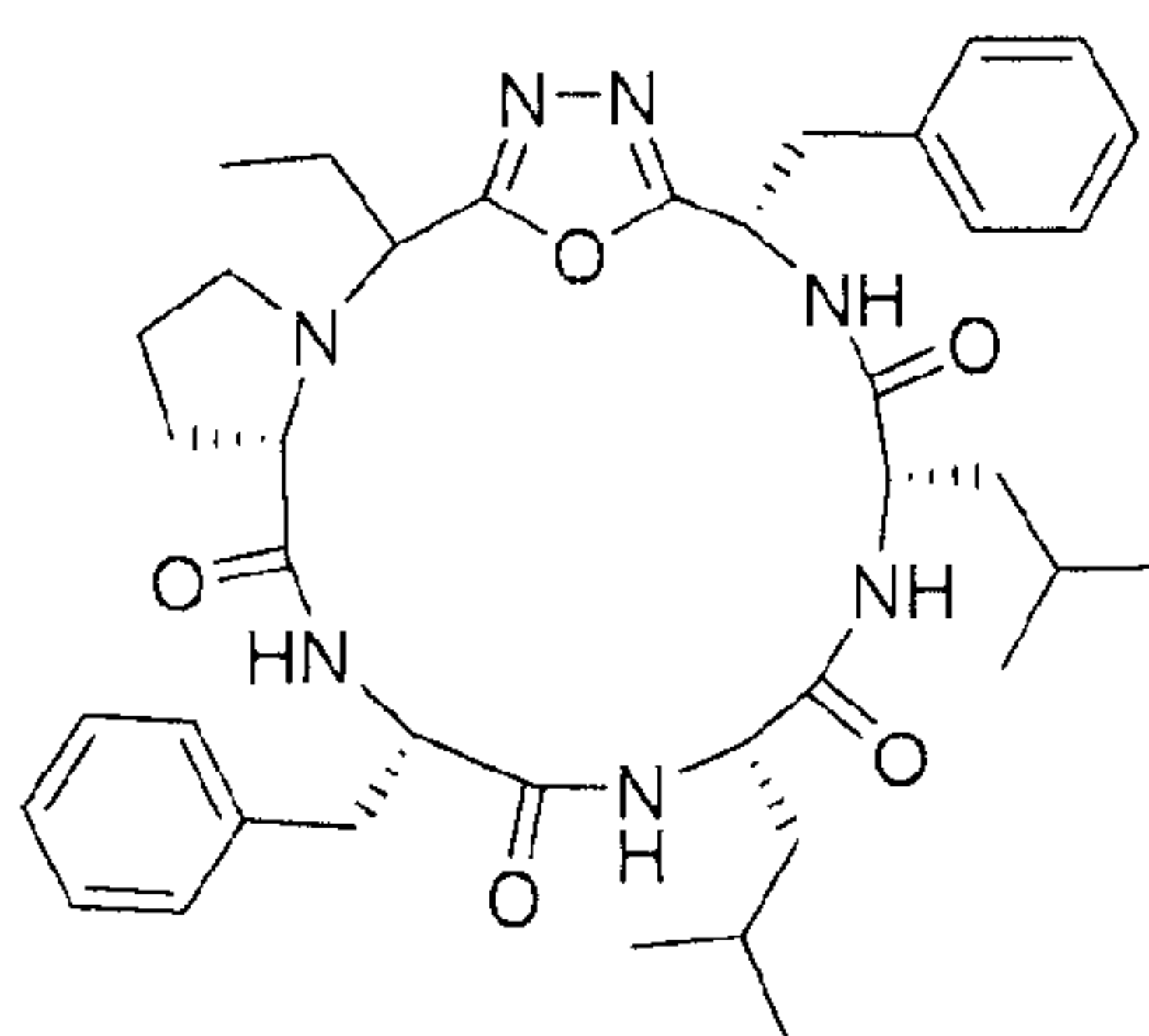
eq) were added to the reaction mixture. After cyclization, deprotection, and reverse phase purification the pure fractions were pooled and lyophilized to afford 5.9 mg of the title compound in 20% overall yield as a 3.4:1 mixture of diastereomers.

HR-MS (ESI) calculated for $C_{30}H_{43}N_7O_5$ $[M+H]^+$: 582.3326 found: 582.3381

5 HPLC Method A:

Retention time (major diastereomer) 9.05 min

Retention time (minor diastereomer) 9.24 min



10 *cyclo*[PFLLF]odz/ethyl (11)

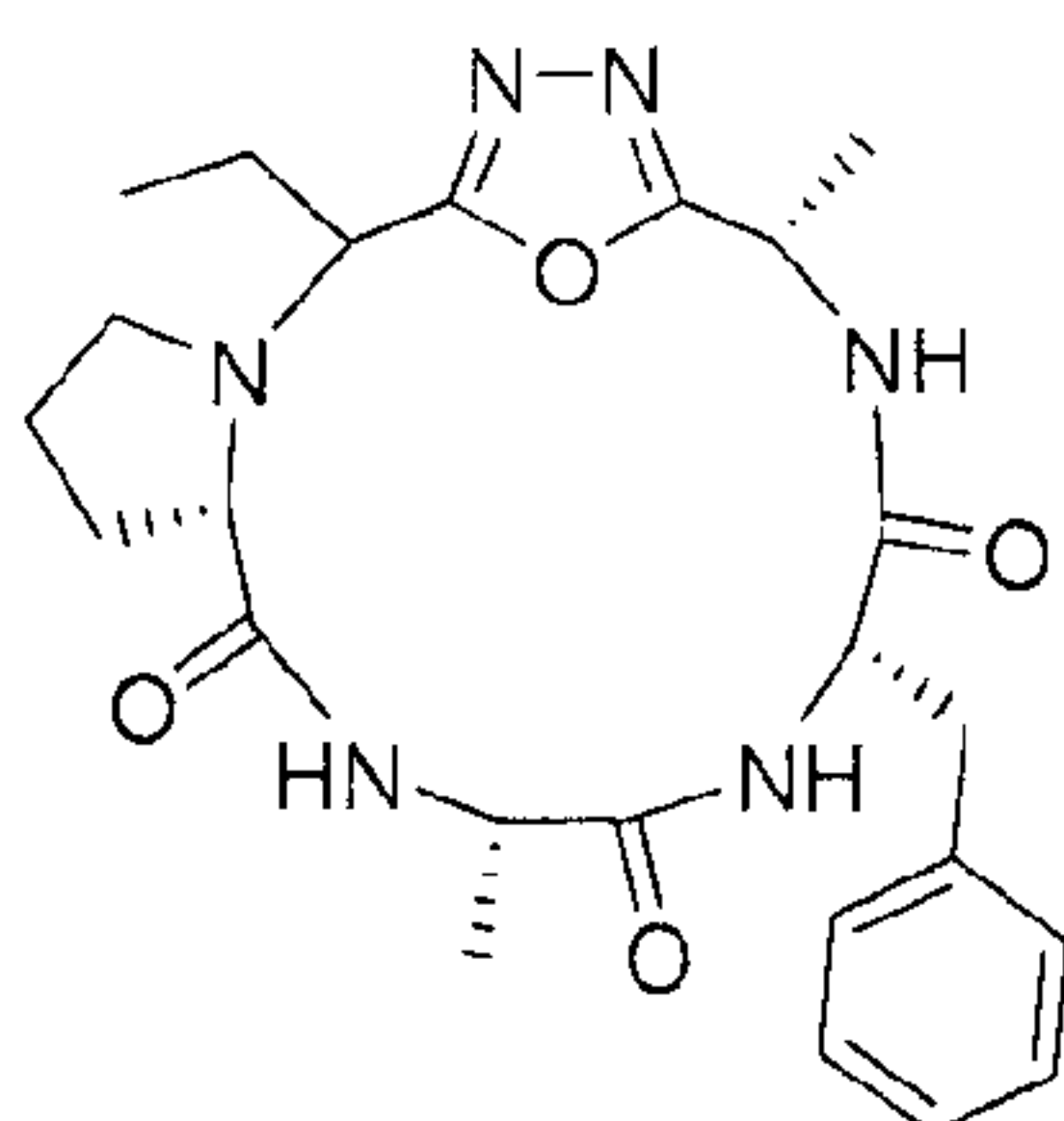
The peptide NH-Pro-Phe-Leu-Leu-Phe-CO₂H (31.8 mg, 0.05 mmol, 1 eq) was dissolved in a mixture of 1:1 Dichloroethane:Acetonitrile (3 mL). Propionaldehyde (5.4 μ L, 0.075 mmol, 1.5 eq) and (*N*-isocyanimino)triphenylphosphorane (15.1 mg, 0.05 mmol, 1 eq) were added to the reaction mixture. After cyclization, deprotection, and reverse phase purification the pure fractions were pooled and lyophilized to afford 8.8 mg of the title compound in 25% overall yield as a 2.7:1 mixture of diastereomers.

HR-MS (ESI) calculated for $C_{39}H_{53}N_7O_5$ $[M+H]^+$: 700.4108 found: 700.4182

HPLC Method A:

Retention time (major diastereomer) 11.71 min

20 Retention time (minor diastereomer) 11.90 min



cyclo[PAFA]odz/ethyl (12)

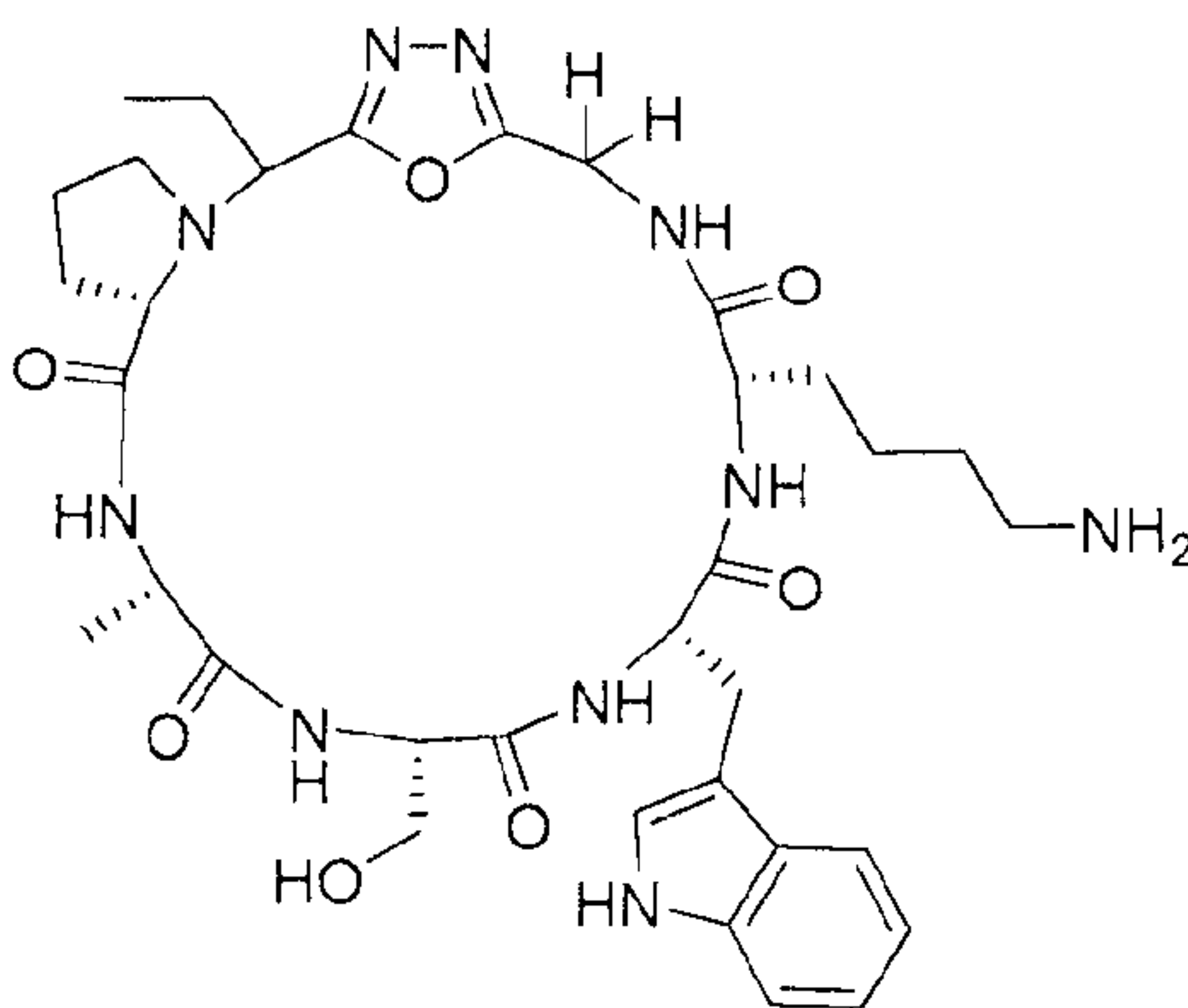
The peptide NH-Pro-Ala-Phe-Ala-CO₂H (20.2 mg, 0.05 mmol, 1 eq) was dissolved in a mixture of 1:1 Dichloroethane:Acetonitrile (2 mL). Propionaldehyde (5.4 μL, 0.075 mmol, 1.5 eq) and (*N*-isocyanimino)triphenylphosphorane (15.1 mg, 0.05 mmol, 1 eq) were added to the reaction mixture. After cyclization, deprotection, and reverse phase purification the pure fractions were pooled and lyophilized to afford 5.4 mg of the title compound in 23% overall yield as a 5.2:1 mixture of diastereomers.

HR-MS (ESI) calculated for C₂₄H₃₂N₆O₄ [M+H]⁺ : 469.2485 found: 469.2544

10 HPLC Method A:

Retention time (major diastereomer) 7.00 min

Retention time (minor diastereomer) 7.18 min



15

cyclo[PASWKG]odz/ethyl (13)

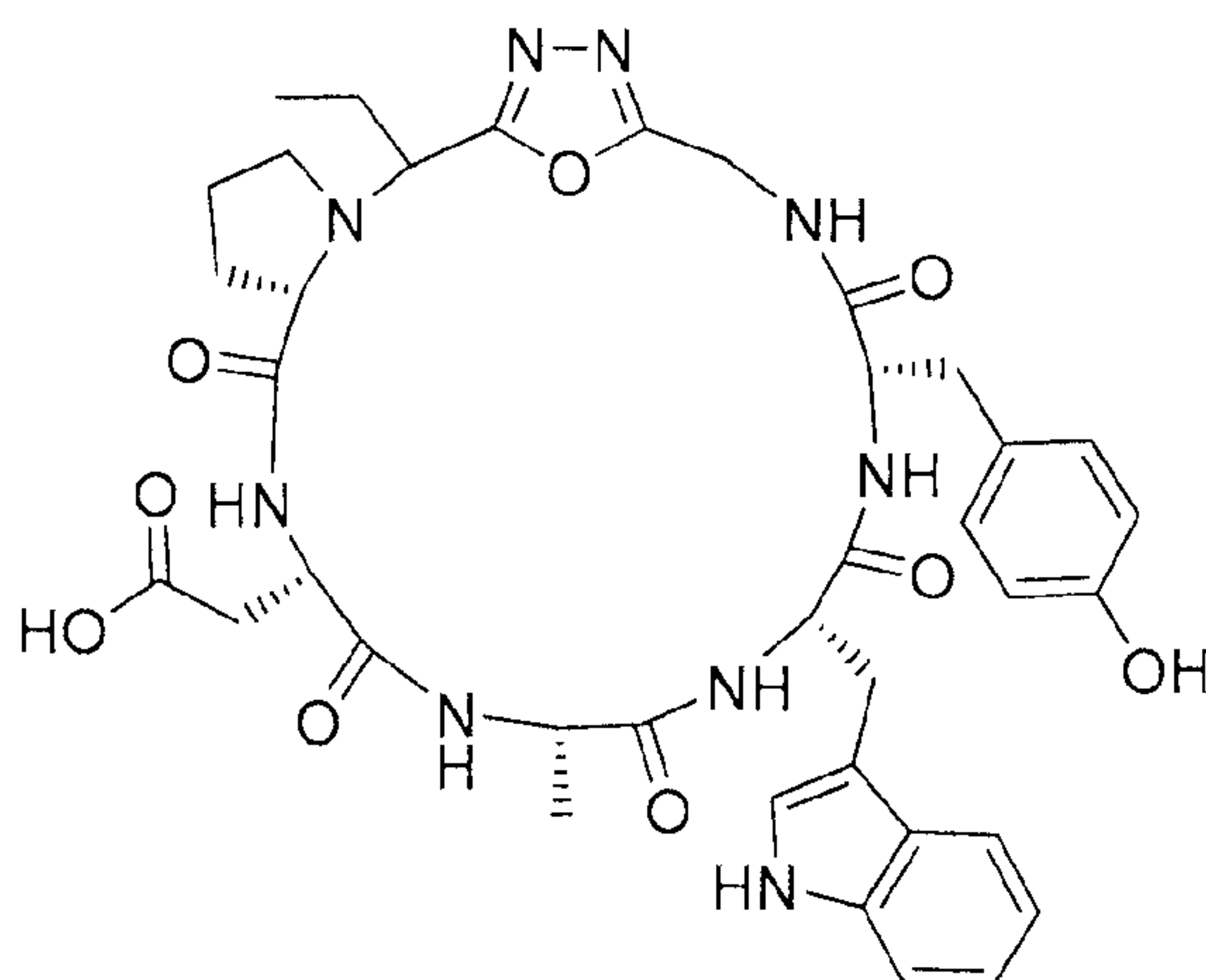
The peptide NH-Pro-Asp(OtBu)-Ser(OtBu)-Trp(Boc)-Lys(Boc)-Gly-CO₂H was cyclized at 0.05 mmol scale with propionaldehyde (1.5 eq) and (*N*-

5

The peptide NH-Pro-Gly-Leu-Gly-Phe-Ala-CO₂H (28 mg, 0.05 mmol, 1 eq) was dissolved in a mixture of 1:1 Dichloroethane:Acetonitrile (2 mL). Propionaldehyde (5.4 μL, 0.075 mmol, 1.5 eq) and (*N*-isocyanimino)triphenylphosphorane (15.1 mg, 0.05 mmol, 1 eq) were added to the reaction mixture. After cyclization, deprotection, and reverse phase purification the pure fractions were pooled and lyophilized to afford 12.8 mg of the title compound in 41 % overall yield as a single diastereomer.

HPLC Method A:

28



cyclo[PDAWYG]odz/ethyl (**15**)

The peptide NH-Pro-Asp(O^tBu)-Ala-Trp(Boc)-Tyr(O^tBu)-Gly-CO₂H (46 mg, 0.05 mmol, 1 eq) was dissolved in a mixture of 1:1 Dichloroethane:Acetonitrile (2 mL).

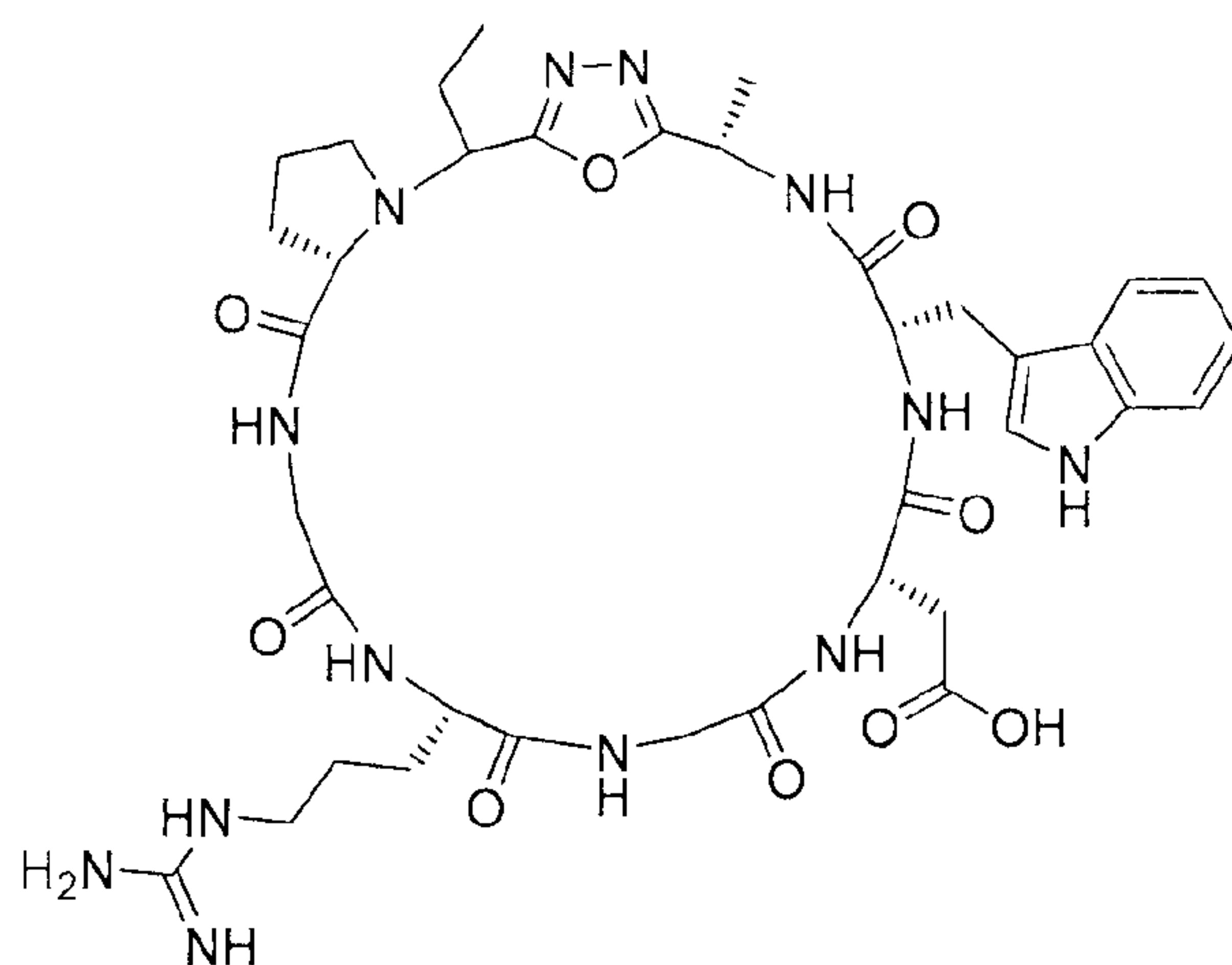
- 5 Propionaldehyde (5.4 μ L, 0.075 mmol, 1.5 eq) and (*N*-isocyanimino)triphenylphosphorane (15.1 mg, 0.05 mmol, 1 eq) were added to the reaction mixture. After cyclization, deprotection, and reverse phase purification the pure fractions were pooled and lyophilized to afford 10 mg of the title compound in 28 % overall yield as a 6.4:1 mixture of diastereomers.

- 10 HR-MS (ESI) calculated for C₃₈H₄₆N₉O₉ [M+H]⁺ : 772.3413 found: 772.3411

HPLC Method B:

Retention time (major diastereomer) 3.05 min

Retention time (minor diastereomer) 3.10 min



15

cyclo[PGRGDWA]odz/ethyl (16)

The peptide NH-Pro-Gly-Arg(Pbf)-Gly-Asp(O^tBu)-Trp(Boc)-Ala-CO₂H (58.3 mg, 0.05 mmol, 1 eq) was dissolved in a mixture of 1:1 Dichloroethane:Acetonitrile (2 mL).
5 Propionaldehyde (5.4 μL, 0.075 mmol, 1.5 eq) and (*N*-isocyanimino)triphenylphosphorane (15.1 mg, 0.05 mmol, 1 eq) were added to the reaction mixture. After cyclization, deprotection, and reverse phase purification the pure fractions were pooled and lyophilized to afford 9 mg of the title compound in 22 % overall yield (95% purity) as a 1:7.4 mixture of diastereomers.

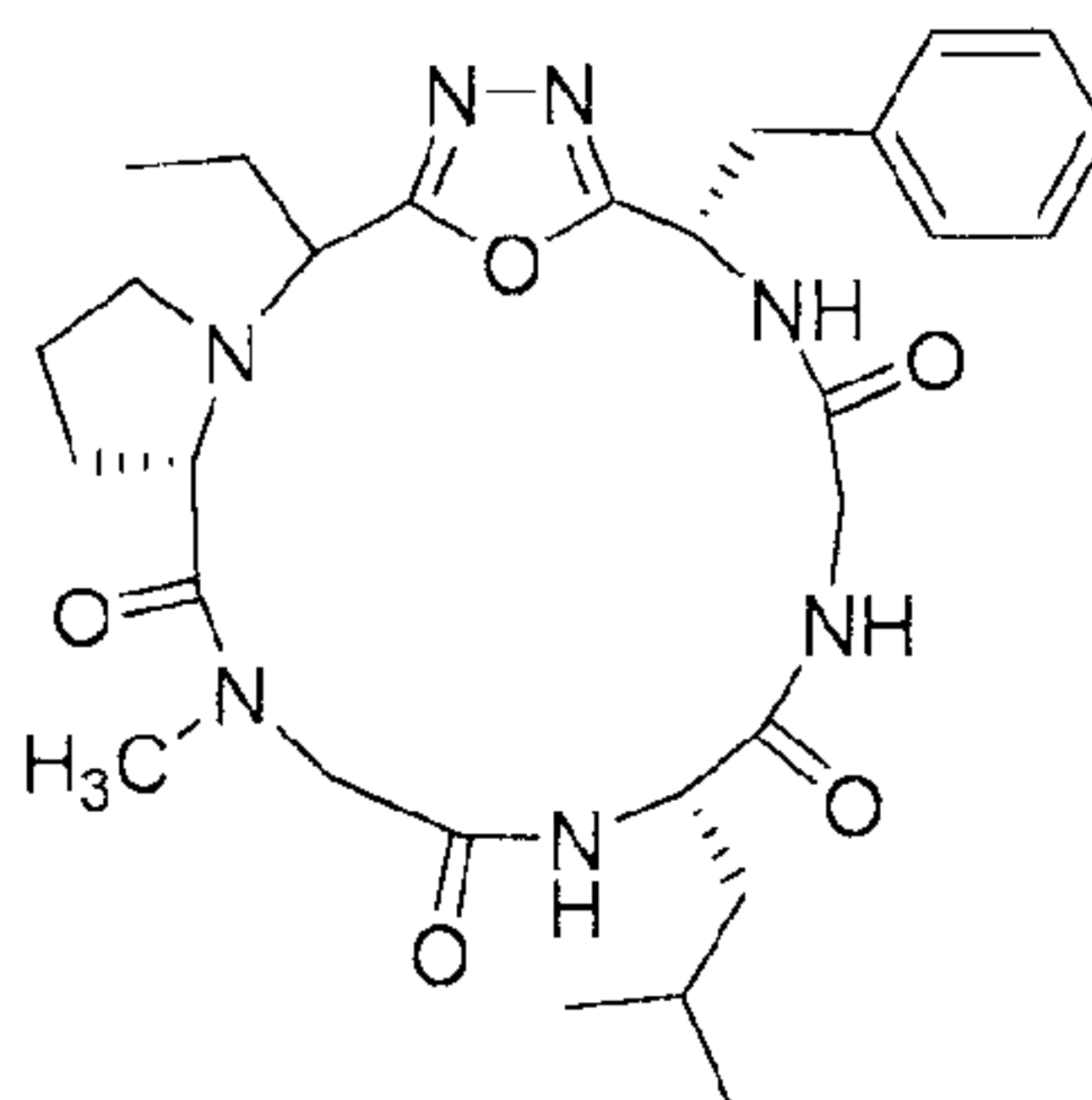
10 HR-MS (ESI) calculated for C₃₇H₅₂N₁₃O₉ [M+H]⁺ : 822.4005 found: 822.4006

HPLC Method A:

Retention time (major diastereomer) 6.39 min

Retention time (minor diastereomer) 5.11 min

15



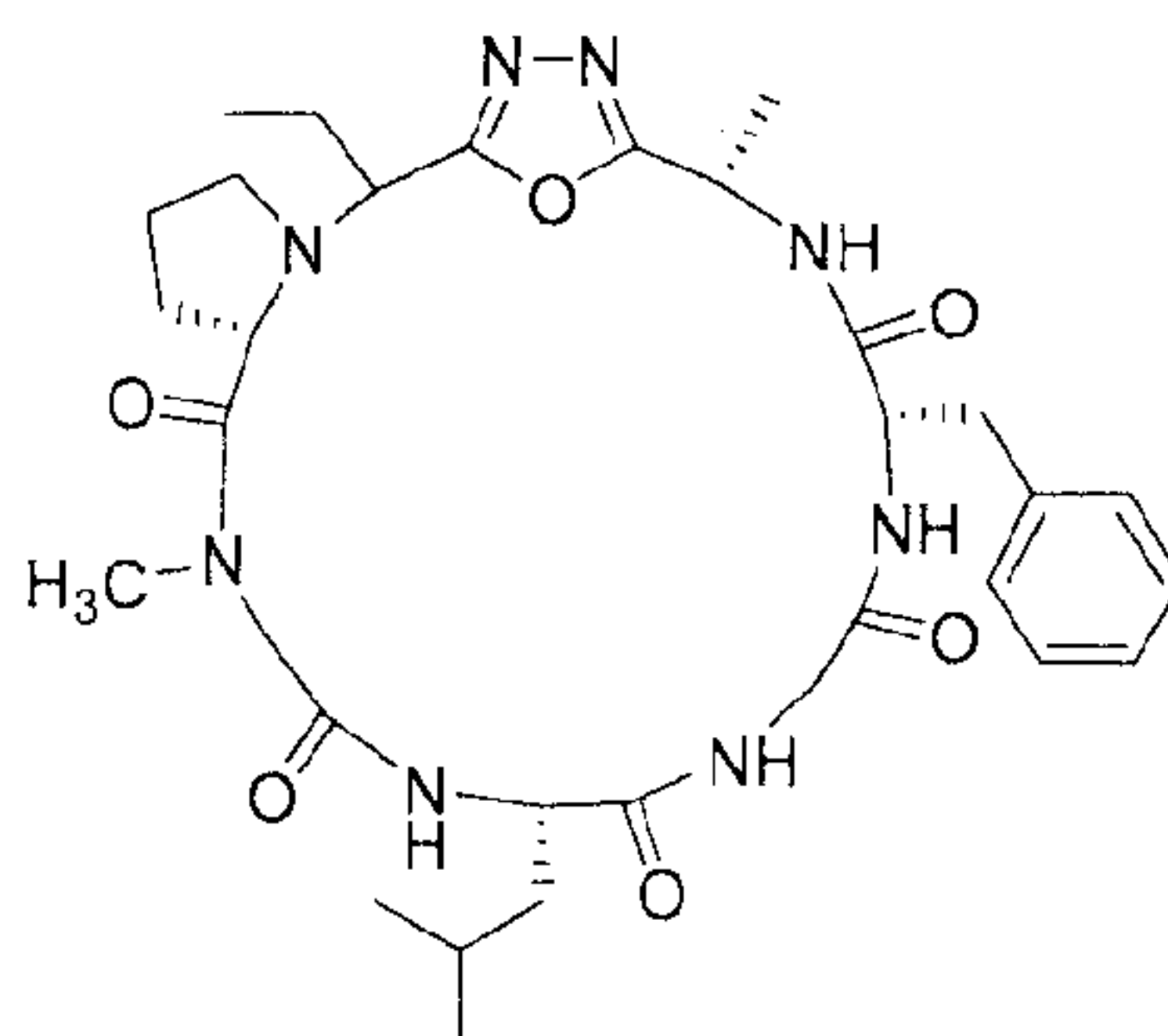
cyclo[PSarLGF]odz/ethyl (17)

The peptide NH-Pro-Sar-Leu-Gly-Phe-CO₂H (25.2 mg, 0.05 mmol, 1 eq) was dissolved in a mixture of 1:1 Dichloroethane:Acetonitrile (2 mL). Propionaldehyde (5.4 μL, 0.075
20 mmol, 1.5 eq) and (*N*-isocyanimino)triphenylphosphorane (15.1 mg, 0.05 mmol, 1 eq) were added to the reaction mixture. After cyclization, deprotection, and reverse phase purification the pure fractions were pooled and lyophilized to afford 8 mg of the title compound in 28 % overall yield as a single diastereomer.

HR-MS (ESI) calculated for C₂₉H₄₂N₇O₅ [M+H]⁺ : 568.3242 found: 568.3252

25 HPLC Method A:

Retention time 6.14 min



cyclo[PSarL.GFA]odz/ethyl (**18**)

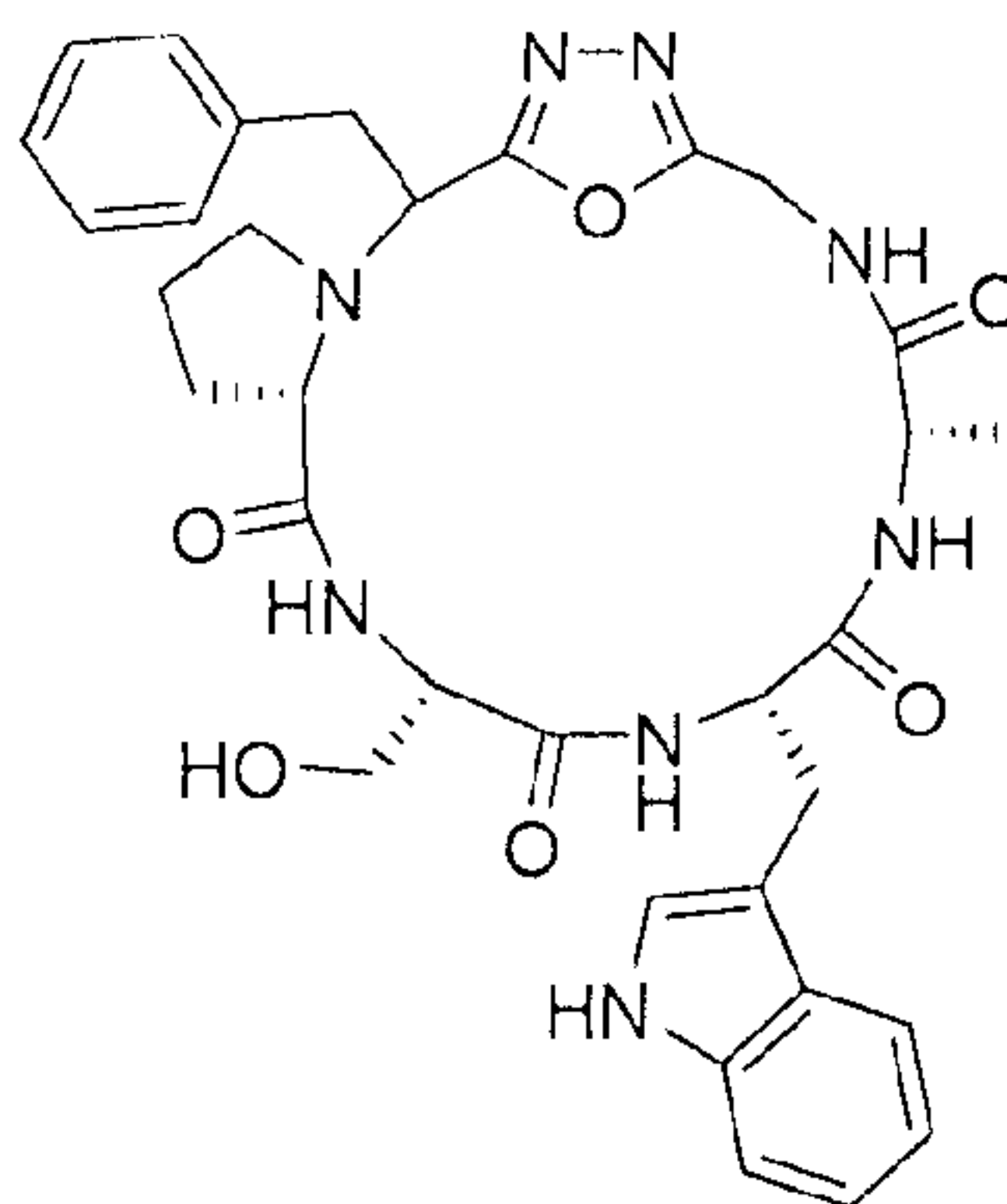
- 5 The peptide NH-Pro-Sar-Leu-Gly-Phe-Ala-CO₂H (28.7 mg, 0.05 mmol, 1 eq) was dissolved in a mixture of 1:1 Dichloroethane:Acetonitrile (2 mL). Propionaldehyde (5.4 μ L, 0.075 mmol, 1.5 eq) and (*N*-isocyanimino)triphenylphosphorane (15.1 mg, 0.05 mmol, 1 eq) were added to the reaction mixture. After cyclization, deprotection, and reverse phase purification the pure fractions were pooled and lyophilized to afford 13.4 mg of the title compound in 42 % overall yield as a single diastereomer.

HR-MS (ESI) calculated for C₃₂H₄₇N₈O₆ [M+H]⁺ : 639.3613 found: 639.3617

HPLC Method A:

Retention time 6.13 min

15



cyclo[PSWAG]odz/benzyl (**19**)

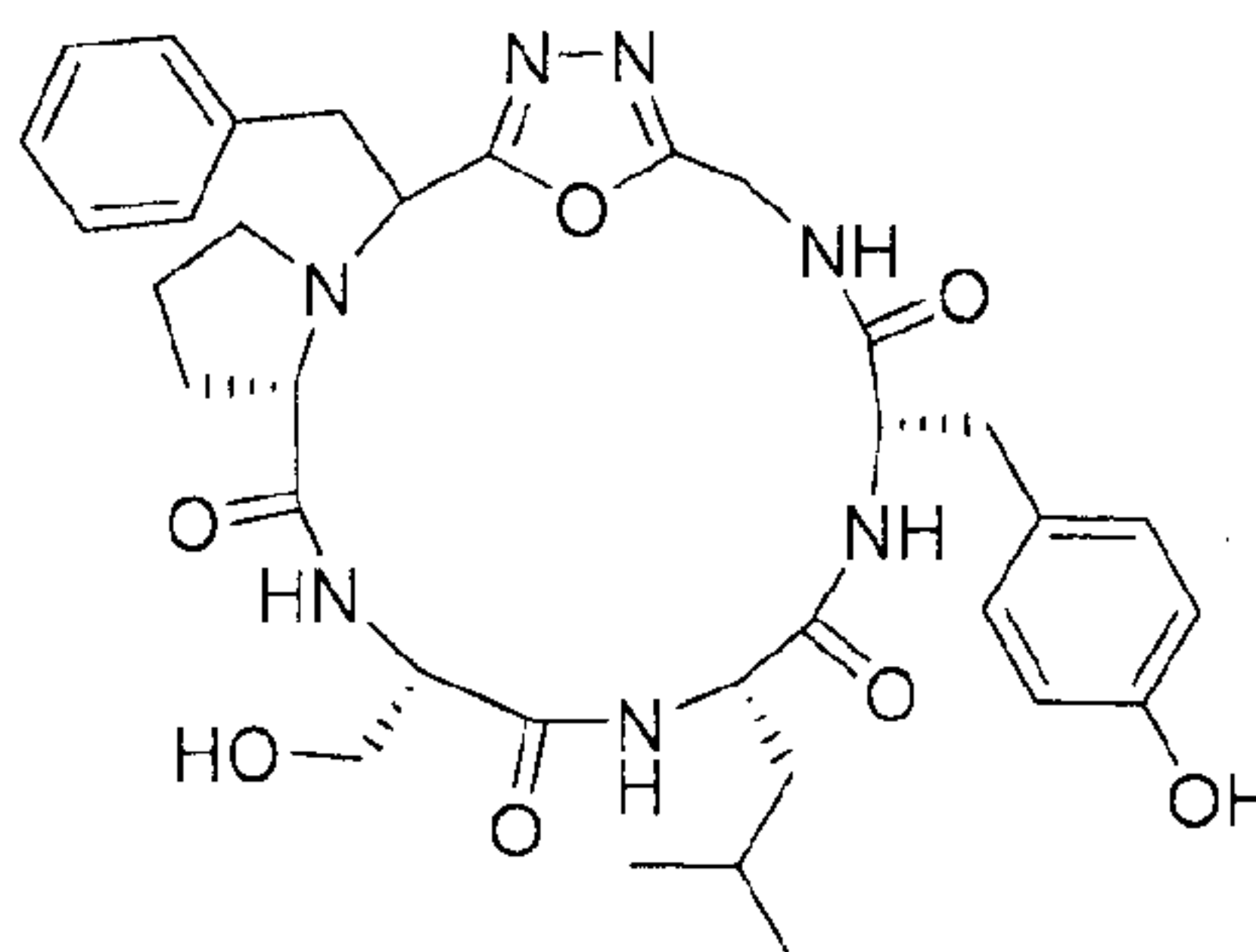
The peptide NH-Pro-Ser(O^tBu)-Trp(Boc)-Ala-Gly-CO₂H (33.6 mg, 0.05 mmol, 1 eq) was dissolved in a mixture of 1:1 Dichloroethane:Acetonitrile (2 mL). Phenylacetaldehyde (8.35 μL, 0.075 mmol, 1.5 eq) and (*N*-isocyanimino)triphenylphosphorane (15.1 mg, 0.05 mmol, 1 eq) were added to the reaction mixture. After cyclization, deprotection, and reverse phase purification the pure fractions were pooled and lyophilized to afford 8.3 mg of the title compound in 26 % overall yield as a 2.1:1 mixture of diastereomers.

HR-MS (ESI) calculated for C₃₃H₃₉N₈O₆ [M+H]⁺ : 643.2987 found: 643.298

HPLC Method A:

Retention time (major diastereomer) 7.46 min

Retention time (minor diastereomer) 7.65 min



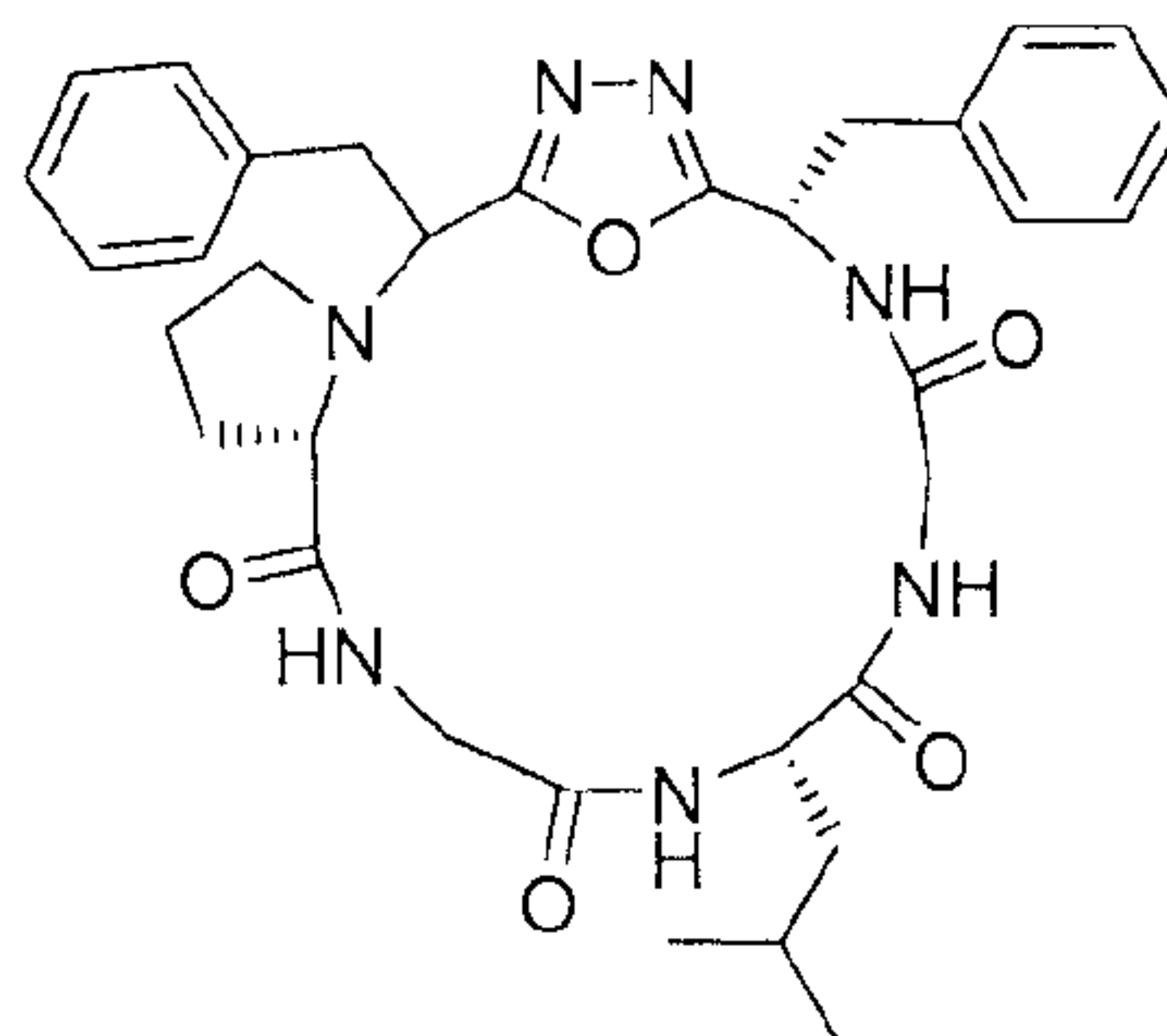
cyclo[PSLYG]odz/benzyl (**20**)

The peptide NH-Pro-Ser(O^tBu)-Leu-Tyr(O^tBu)-Gly-CO₂H (32.4 mg, 0.05 mmol, 1 eq) was dissolved in a mixture of 1:1 Dichloroethane:Acetonitrile (2 mL). Phenylacetaldehyde (8.35 μL, 0.075 mmol, 1.5 eq) and (*N*-isocyanimino)triphenylphosphorane (15.1 mg, 0.05 mmol, 1 eq) were added to the reaction mixture. After cyclization, deprotection, and reverse phase purification the pure fractions were pooled and lyophilized to afford 7 mg of the title compound in 22 % overall yield as a single diastereomer.

HR-MS (ESI) calculated for C₃₄H₄₄N₇O₇ [M+H]⁺ : 662.3297 found: 662.3294

HPLC Method A:

Retention time 7.38 min



cyclo[PGLGF]odz/benzyl (**21**)

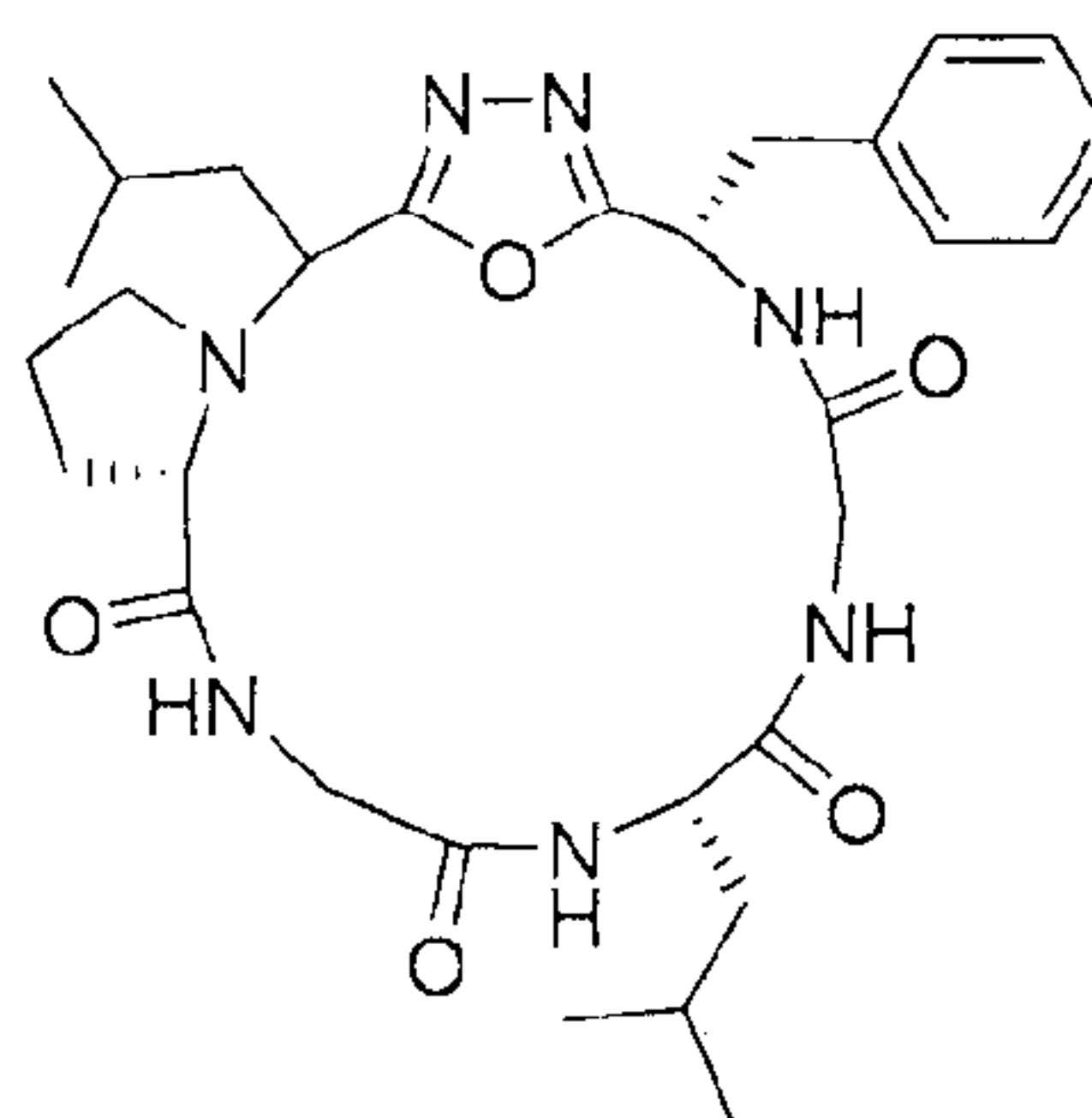
- 5 The peptide NH-Pro-Gly-Leu-Gly-Phe-CO₂H (24.5 mg, 0.05 mmol, 1 eq) was dissolved in a mixture of 1:1 Dichloroethane:Acetonitrile (2 mL). Phenylacetaldehyde (8.35 μ L, 0.075 mmol, 1.5 eq) and (*N*-isocyanimino)triphenylphosphorane (15.1 mg, 0.05 mmol, 1 eq) were added to the reaction mixture. After cyclization, deprotection, and reverse phase purification the pure fractions were pooled and lyophilized to afford 9 mg of the title compound in 29 % overall yield as a single diastereomer. The diastereoselectivity of the
- 10 crude reaction was 2.7:1.

HR-MS (ESI) calculated for C₃₃H₄₂N₇O₅ [M+H]⁺ : 616.3242 found: 616.3244

HPLC Method B:

Retention time (major diastereomer) 3.81 min

15



cyclo[PGLGF]odz/iBu (**22**)

- The peptide NH-Pro-Gly-Leu-Gly-Phe-CO₂H (24.5 mg, 0.05 mmol, 1 eq) was dissolved in a mixture of 1:1 Dichloroethane:Acetonitrile (2.5 mL). Isovaleraldehyde (8.8 μ L, 0.075 mmol, 1.5 eq) and (*N*-isocyanimino)triphenylphosphorane (15.1 mg, 0.05 mmol, 1 eq) were added to the reaction mixture. After cyclization, deprotection, and reverse phase
- 20

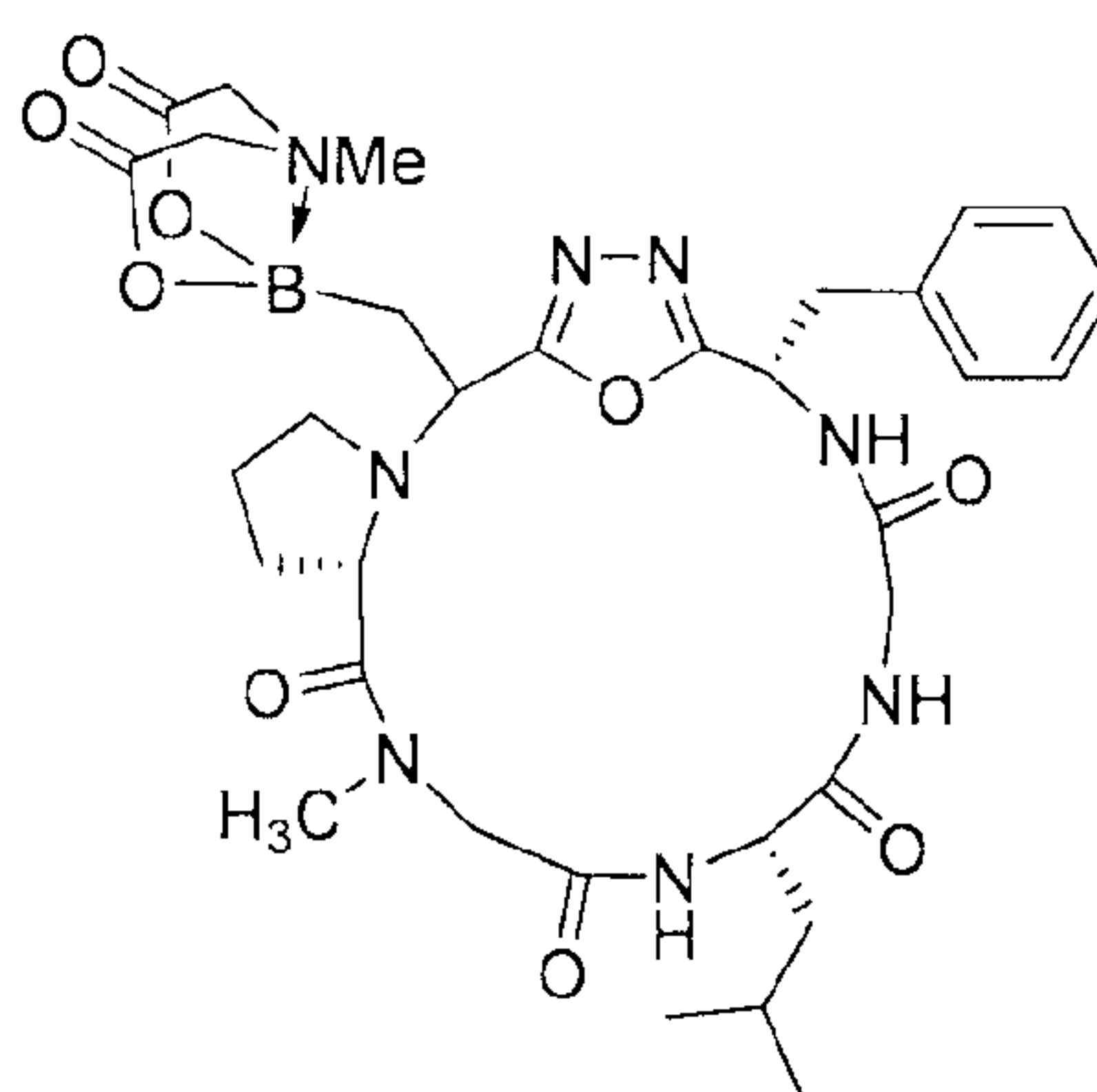
purification the pure fractions were pooled and lyophilized to afford 8.9 mg of the title compound in 32% overall yield as a 6.3:1 mixture of diastereomers.

HR-MS (ESI) calculated for $C_{30}H_{43}N_7O_5$ $[M+H]^+$: 582.3326 found: 582.3399

HPLC Method A:

5 Retention time (major diastereomer) 9.0 min

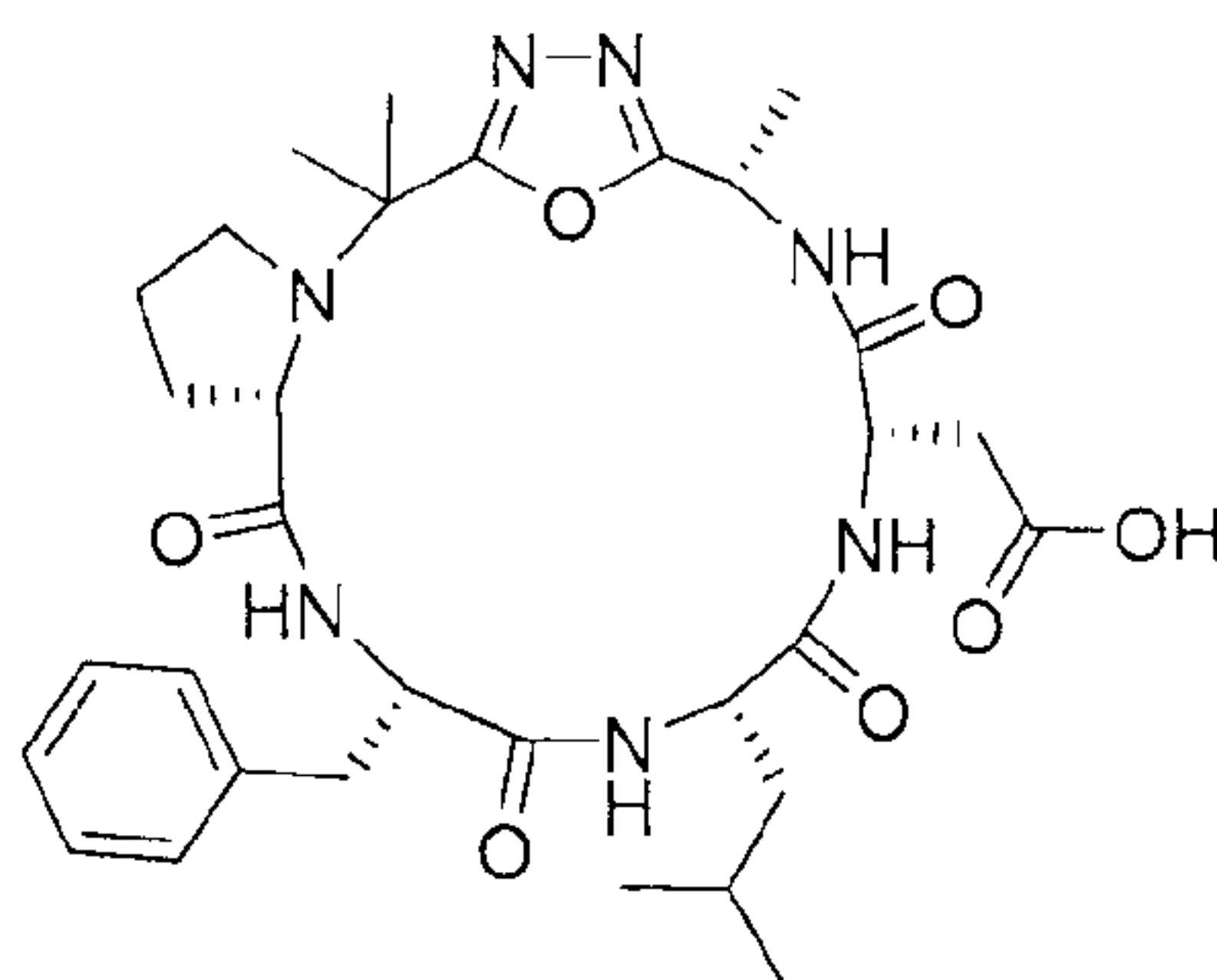
Retention time (minor diastereomer) 9.35 min



10 *cyclo*[PSarLGF]odz/ α -borylaldehyde (**23**)

The peptide NH-Pro-Sar-Leu-Gly-Phe-CO₂H was cyclized at 0.05 mmol scale with α -MIDA-borylaldehyde(1.5 eq) and (*N*-isocyanimino)triphenylphosphorane (1 eq). After cyclization, deprotection, and reverse phase purification the pure fractions were pooled and lyophilized to afford 10 mg of the title compound in 28 % overall yield.

15 HR-MS (ESI) calculated for $C_{33}H_{46}BN_8O_9$ $[M+H]^+$: 708.348 found: 708.3484

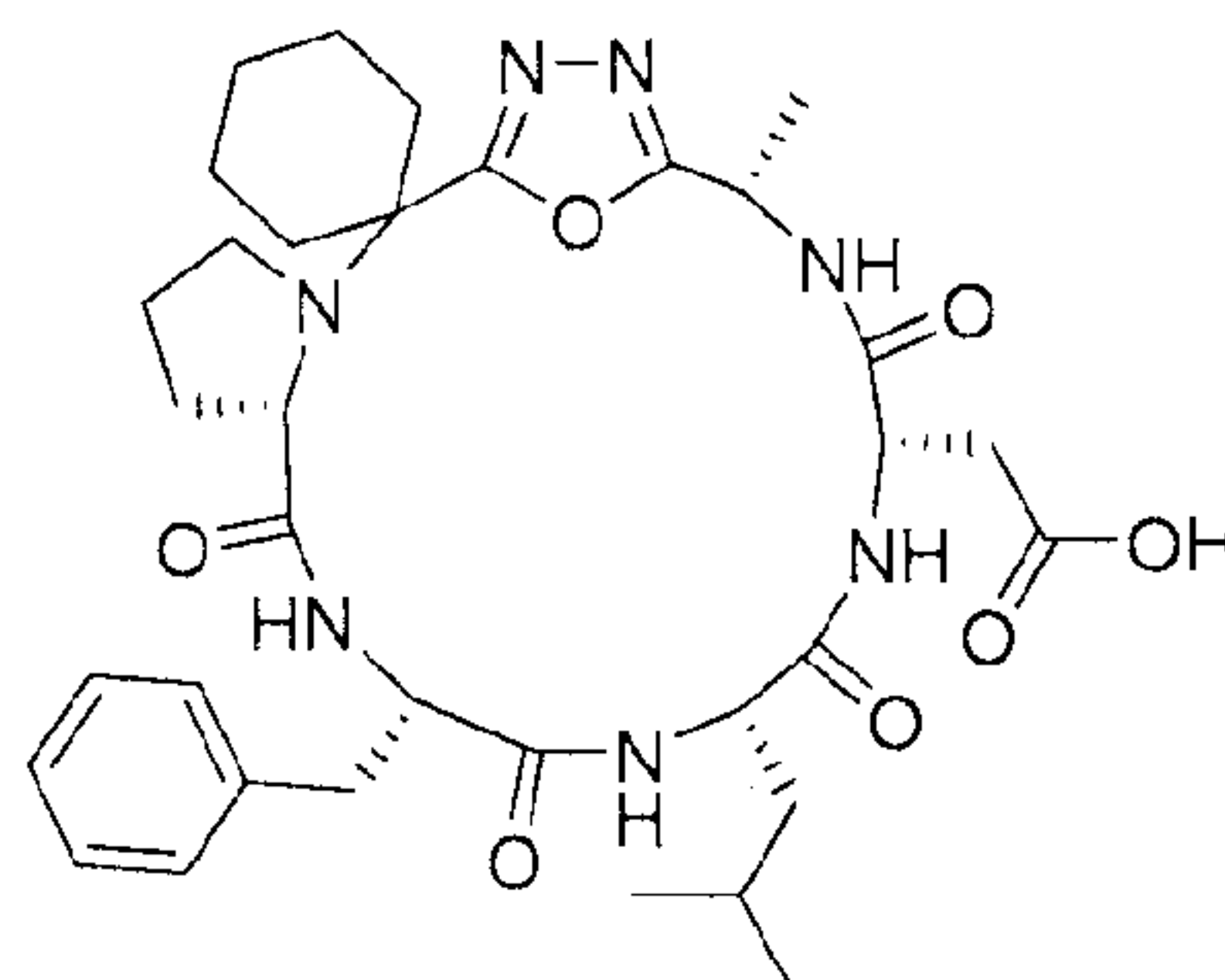


cyclo[PFDLA]odz/dimethyl (**24**)

The peptide NH-Pro-Phe-Leu-Asp(O^tBu)-Ala-CO₂H (30.9 mg, 0.05 mmol, 1 eq) was dissolved in a mixture of 1:1 Dichloroethane:Acetonitrile (2 mL). Acetone (30% by volume) and (*N*-isocyanimino)triphenylphosphorane (15.1 mg, 0.05 mmol, 1 eq) were added to the reaction mixture. After cyclization, deprotection, and reverse phase purification the pure fractions were pooled and lyophilized to afford 3 mg of the title compound in 10 % overall yield.

HR-MS (ESI) calculated for C₃₁H₄₃N₇O₇ [M+H]⁺ : 626.3224 found: 626.3230

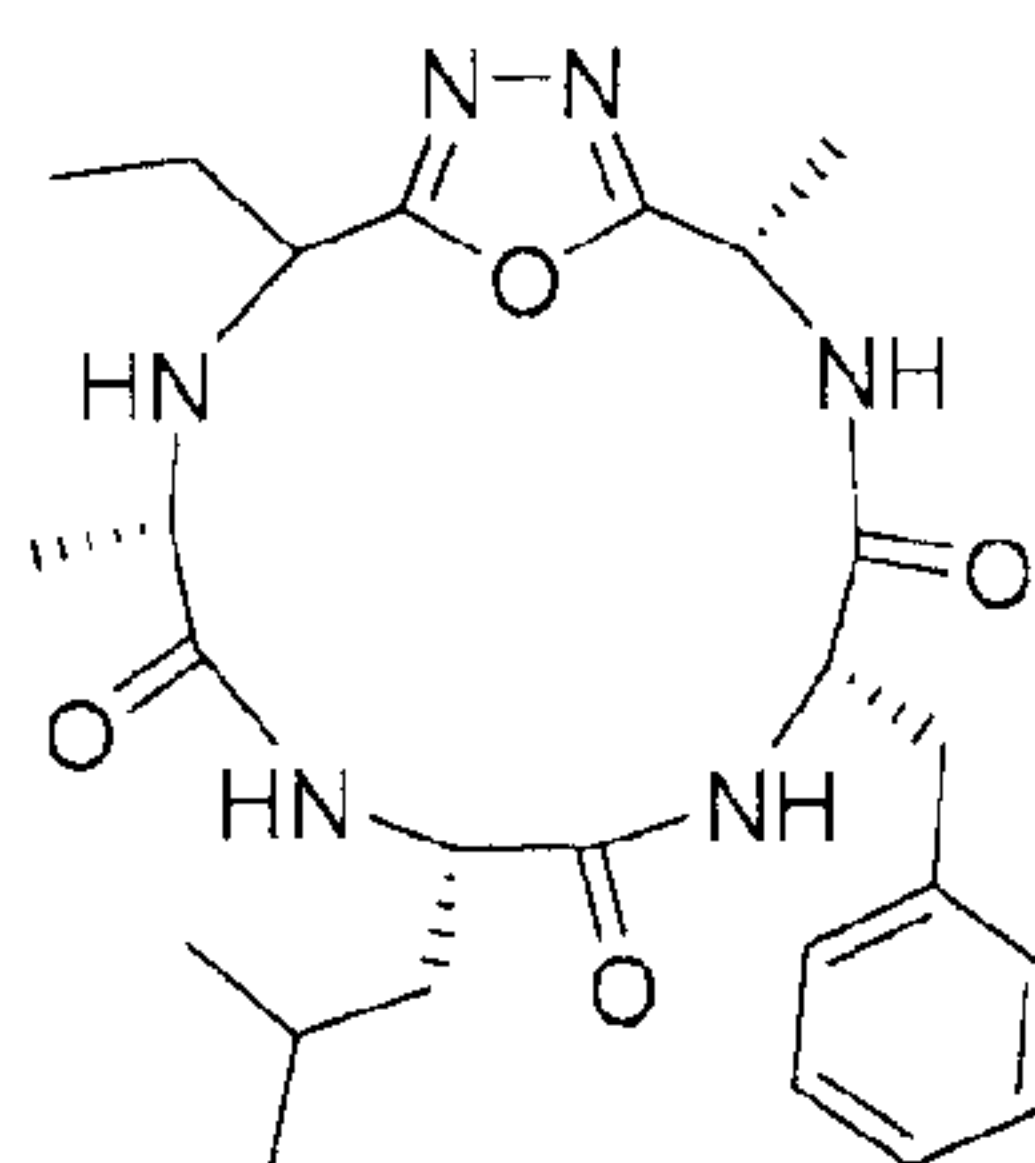
10



cyclo[PFLDA]odz/cyclohexyl (**25**)

The peptide NH-Pro-Phe-Leu-Asp(O^tBu)-Ala-CO₂H (30.9 mg, 0.05 mmol, 1 eq) was dissolved in a mixture of 1:1 Dichloroethane:Acetonitrile (2 mL). Cyclohexanone (0.1 mmol, 2 eq) and (*N*-isocyanimino)triphenylphosphorane (15.1 mg, 0.05 mmol, 1 eq) were added to the reaction mixture. After cyclization, deprotection, and reverse phase purification the pure fractions were pooled and lyophilized to afford 3.3 mg of the title compound in 10 % overall yield.

HR-MS (ESI) calculated for C₃₄H₃₇N₇O₇ [M+H]⁺ : 666.3537 found: 666.3539



cyclo[ALFA]odz/ethyl (**26**)

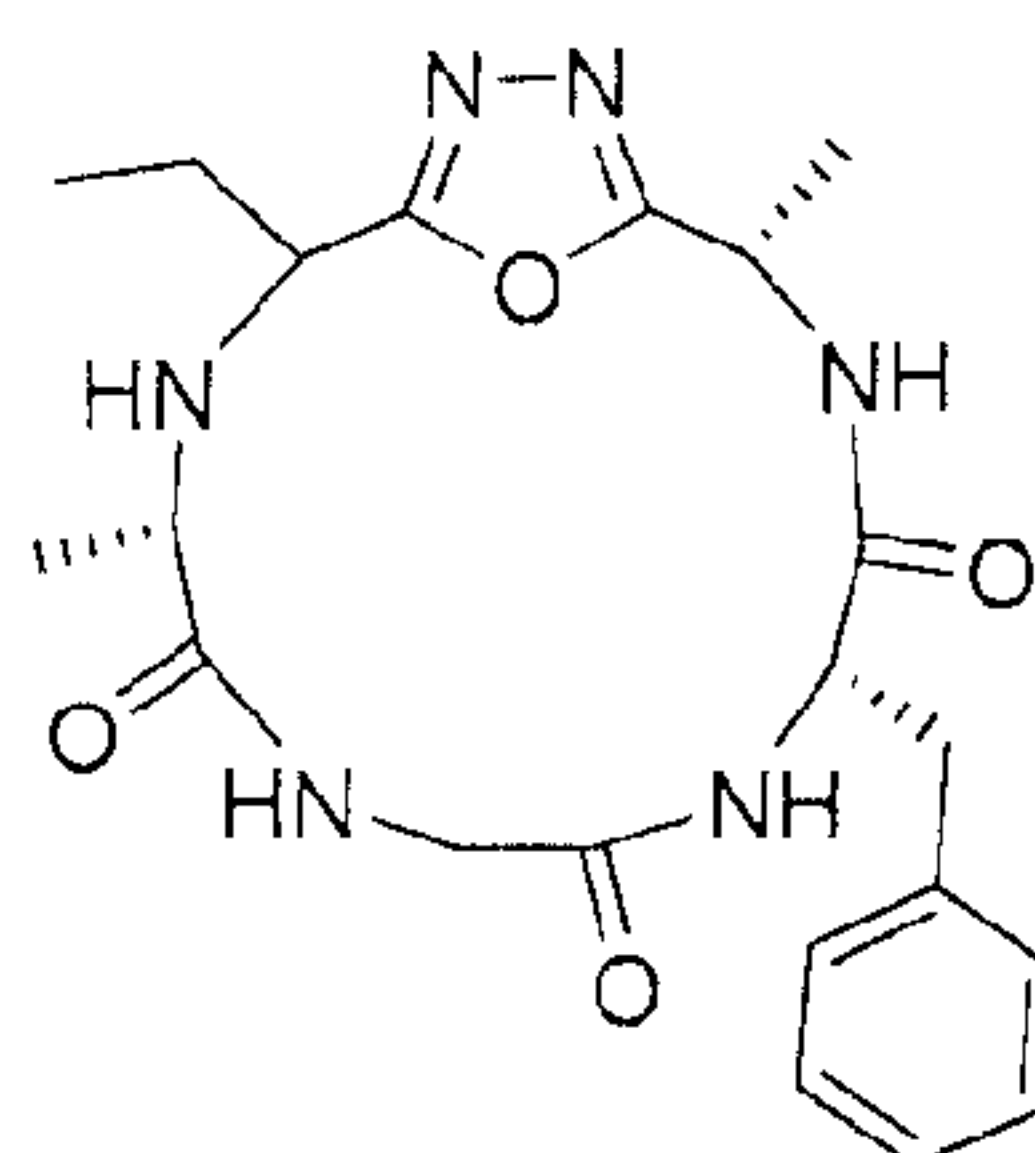
5 The peptide NH₂-Ala-Leu-Phe-Ala-CO₂H (21.0 mg, 0.05 mmol, 1 eq) was dissolved in a mixture of 1:1 Dichloroethane:Acetonitrile (2 mL). Propionaldehyde (5.4 μL, 0.075 mmol, 1.5 eq) and (*N*-isocyanimino)triphenylphosphorane (15.1 mg, 0.05 mmol, 1 eq) were added to the reaction mixture. After cyclization, deprotection, and reverse phase purification the pure fractions were pooled and lyophilized to afford 4.9 mg of the title compound in 20% overall yield as a 8.3:1 mixture of diastereomers.

10 HR-MS (ESI) calculated for C₂₅H₃₆N₆O₄ [M+H]⁺ : 485.2798 found: 485.2866

HPLC Method A:

Retention time (major diastereomer) 8.61 min

Retention time (minor diastereomer) 9.05 min



15

cyclo[AGFA]odz/ethyl (**27**)

20 The peptide NH₂-Ala-Gly-Phe-Ala-CO₂H (18.2 mg, 0.05 mmol, 1 eq) was dissolved in a mixture of 1:1 Dichloroethane:Acetonitrile (2 mL). Propionaldehyde (5.4 μL, 0.075 mmol, 1.5 eq) and (*N*-isocyanimino)triphenylphosphorane (15.1 mg, 0.05 mmol, 1 eq) were added to the reaction mixture. After cyclization, deprotection, and reverse phase purification the pure fractions were pooled and lyophilized to afford 5.2 mg of the title compound in 24% overall yield as a 2.8:1 mixture of diastereomers.

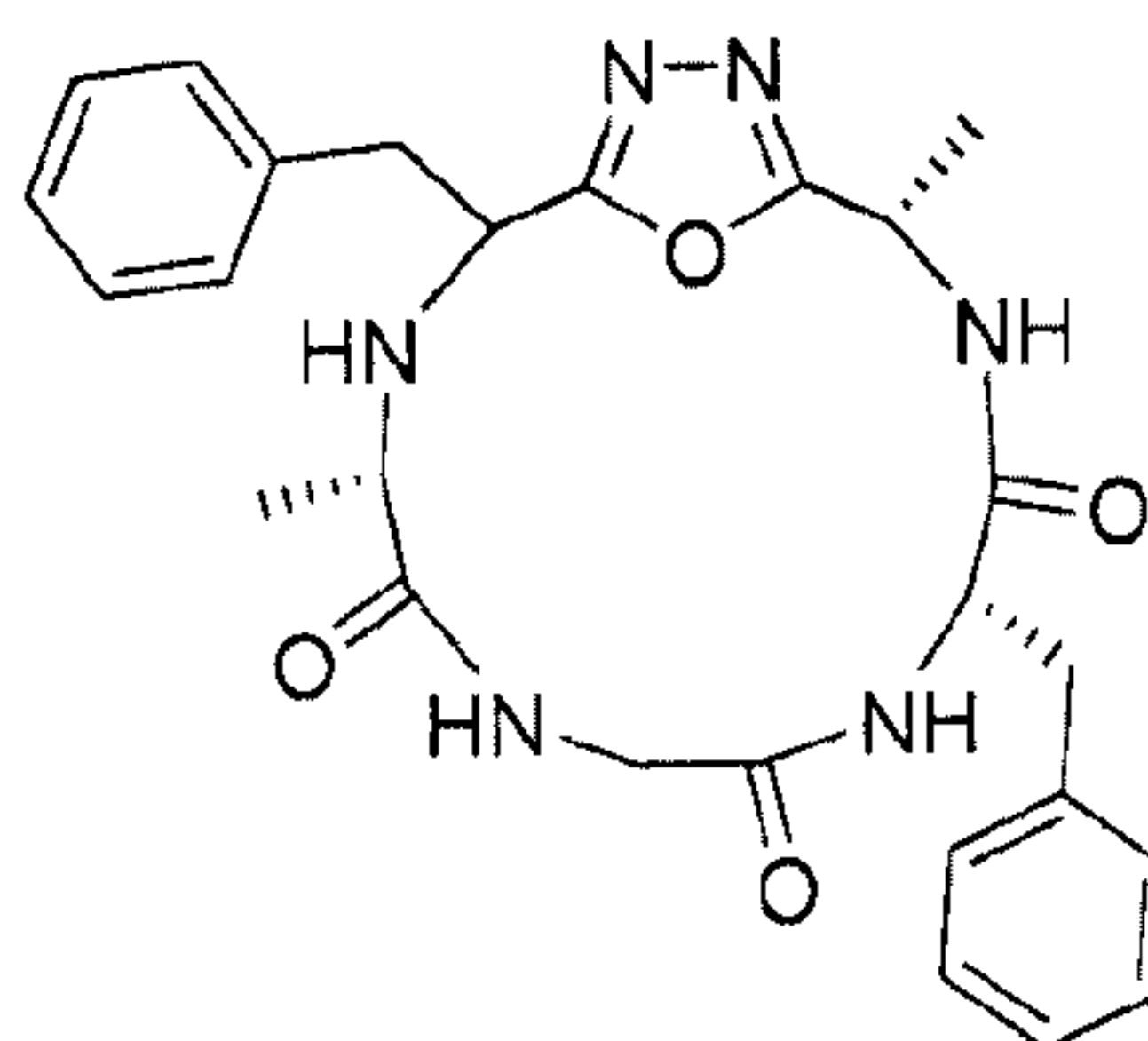
HR-MS (ESI) calculated for $C_{21}H_{28}N_6O_4$ $[M+H]^+$: 429.2172 found: 429.2238

HPLC Method A:

Retention time (major diastereomer) 4.83 min

Retention time (minor diastereomer) 5.01 min

5



cyclo[AGFA]odz/benzyl (**28**)

- 10 The peptide NH_2 -Ala-Gly-Phe-Ala- CO_2H (18.2 mg, 0.05 mmol, 1 eq) was dissolved in a mixture of 1:1 Dichloroethane:Acetonitrile (2 mL). Phenylacetaldehyde (8.35 μ L, 0.075 mmol, 1.5 eq) and (*N*-isocyanimino)triphenylphosphorane (15.1 mg, 0.05 mmol, 1 eq) were added to the reaction mixture. After cyclization, deprotection, and reverse phase

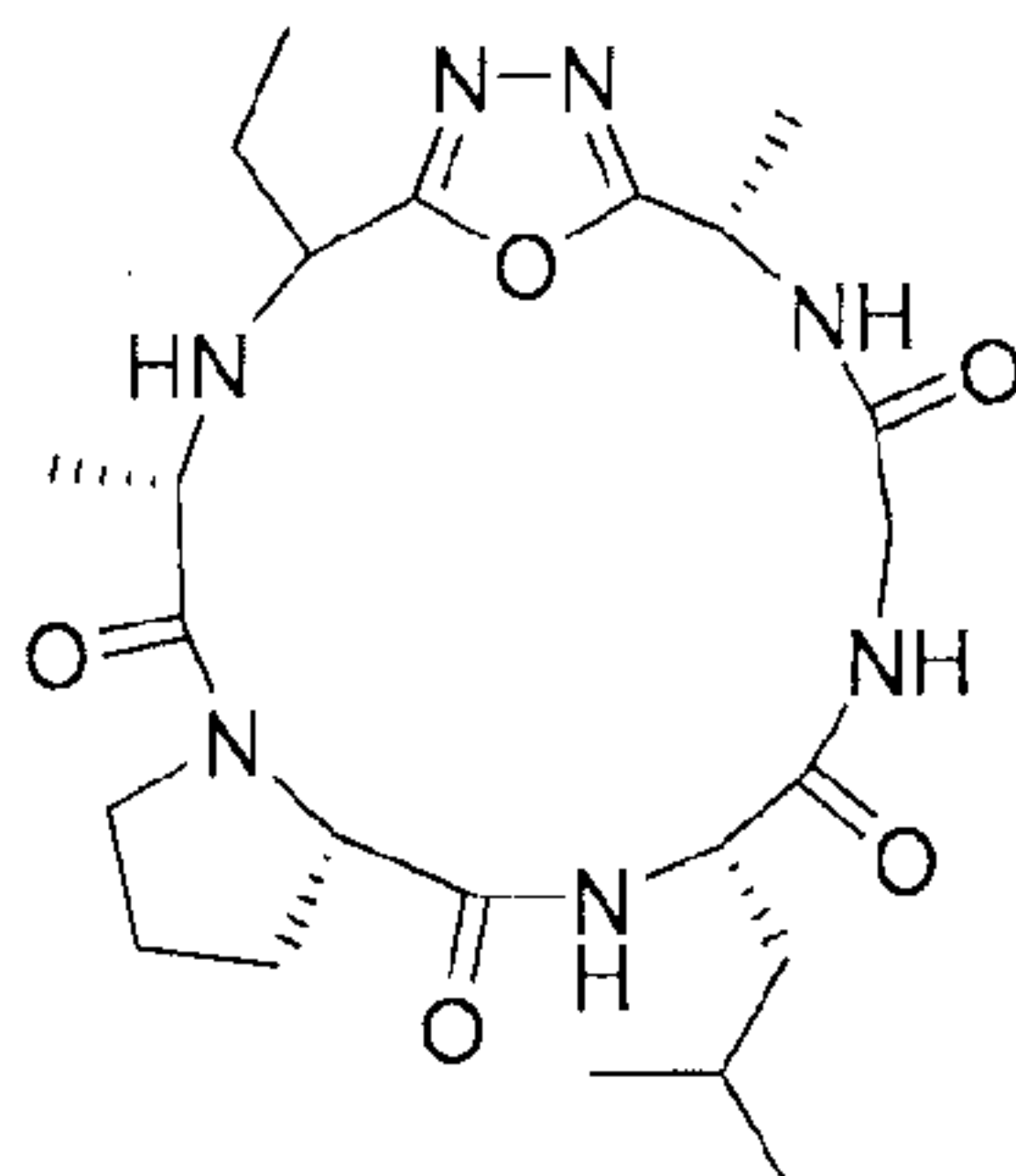
purification the pure fractions were pooled and lyophilized to afford 8.0 mg of the title compound in 32% overall yield as a 1.3:1 mixture of diastereomers.

HR-MS (ESI) calculated for $C_{26}H_{30}N_6O_4$ $[M+H]^+$: 491.2329 found: 491.2397

HPLC Method A:

5 Retention time (major diastereomer) 6.85 min

Retention time (minor diastereomer) 6.73 min



cyclo[APLGA]odz/ethyl (**29**)

- 10 The peptide NH_2 -Ala-Pro- Leu-Gly-Ala- CO_2H (21.4 mg, 0.05 mmol, 1 eq) was dissolved in a mixture of 1:1 Dichloroethane:Acetonitrile (2 mL). Propionaldehyde (5.4 μ L, 0.075 mmol, 1.5 eq) and (*N*-isocyanimino)triphenylphosphorane (15.1 mg, 0.05 mmol, 1 eq) were added to the reaction mixture. After cyclization, deprotection, and reverse phase purification the pure fractions were pooled and lyophilized to afford 3.7
- 15 mg of the title compound in 15 % overall yield as a 1:2.6 mixture of diastereomers.

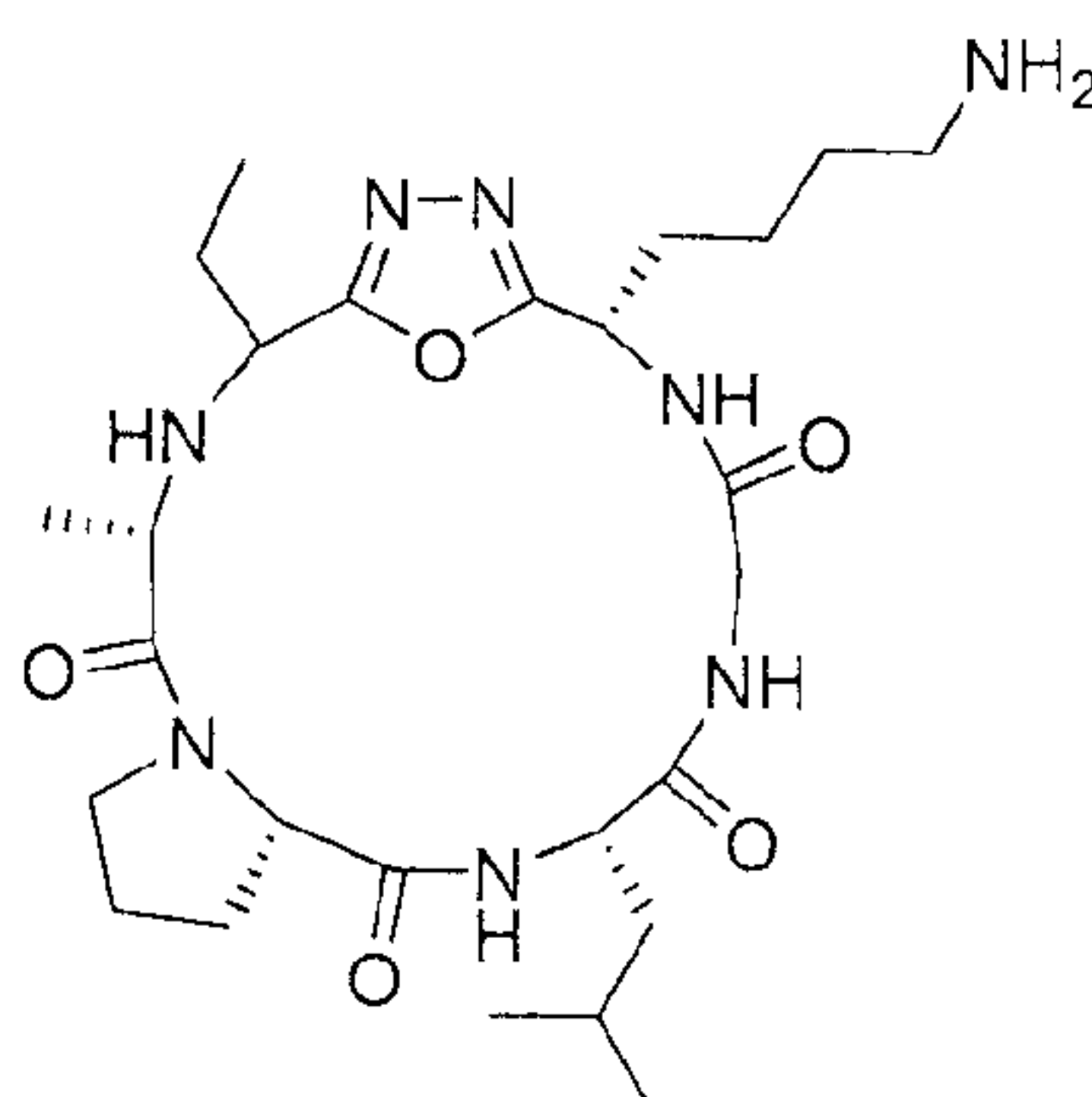
HR-MS (ESI) calculated for $C_{23}H_{38}N_7O_5$ $[M+H]^+$: 492.2916 found: 492.2918

HPLC Method A:

Retention time (major diastereomer) 4.98 min

Retention time (minor diastereomer) 4.76 min

20

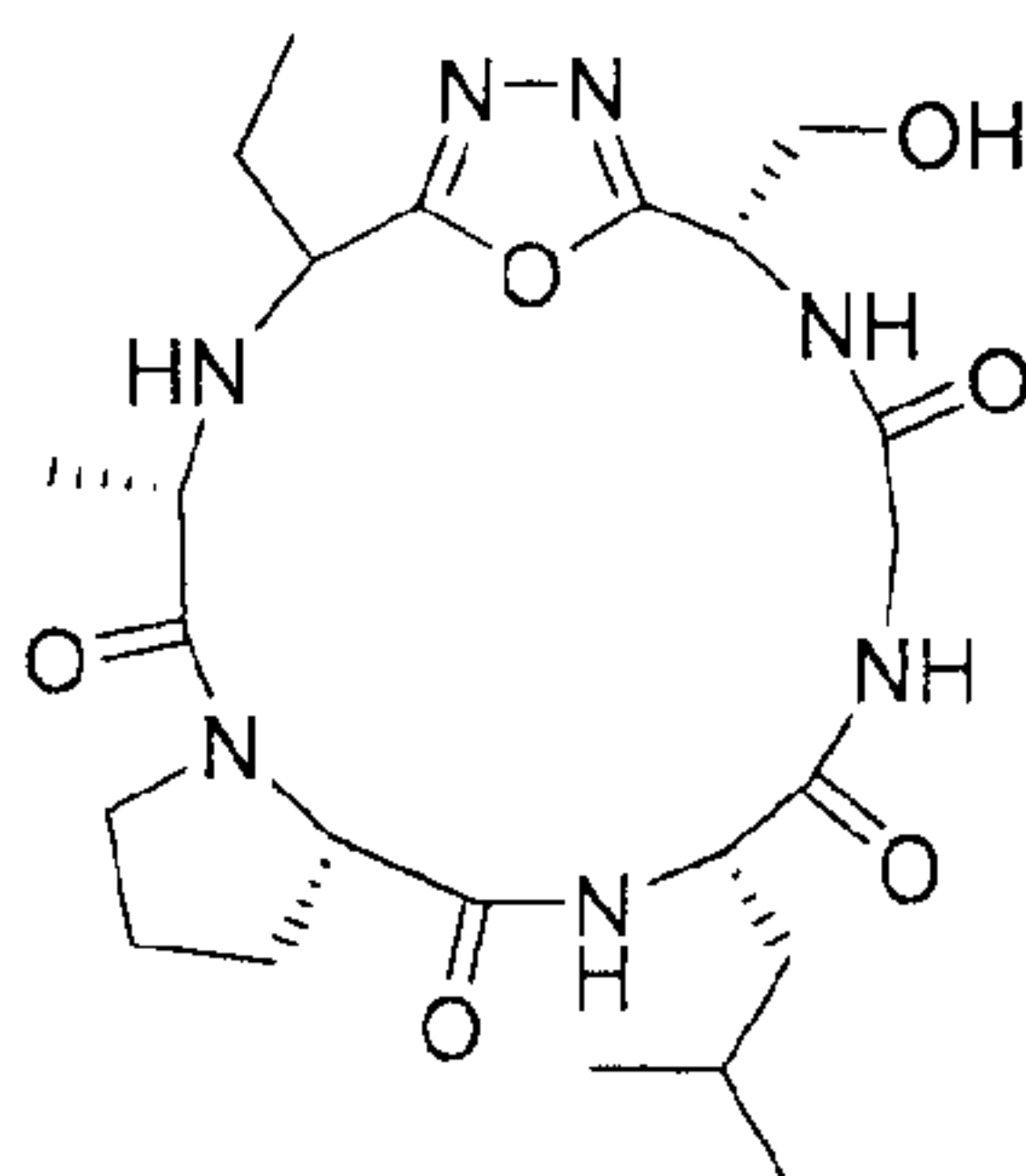


cyclo[APLGK]odz/ethyl (**30**)

5 The peptide NH₂-Ala-Pro- Leu-Gly-Lys(Boc)-CO₂H was cyclized at 0.05 mmol scale with propionaldehyde (1.5 eq) and (*N*-isocyanimino)triphenylphosphorane (1 eq). After cyclization, deprotection, and reverse phase purification the pure fractions were pooled and lyophilized to afford 16.3 mg of the title compound in 60 % overall yield.

HR-MS (ESI) calculated for C₂₆H₄₅N₈O₅ [M+H]⁺ : 549.3507 found: 549.3507

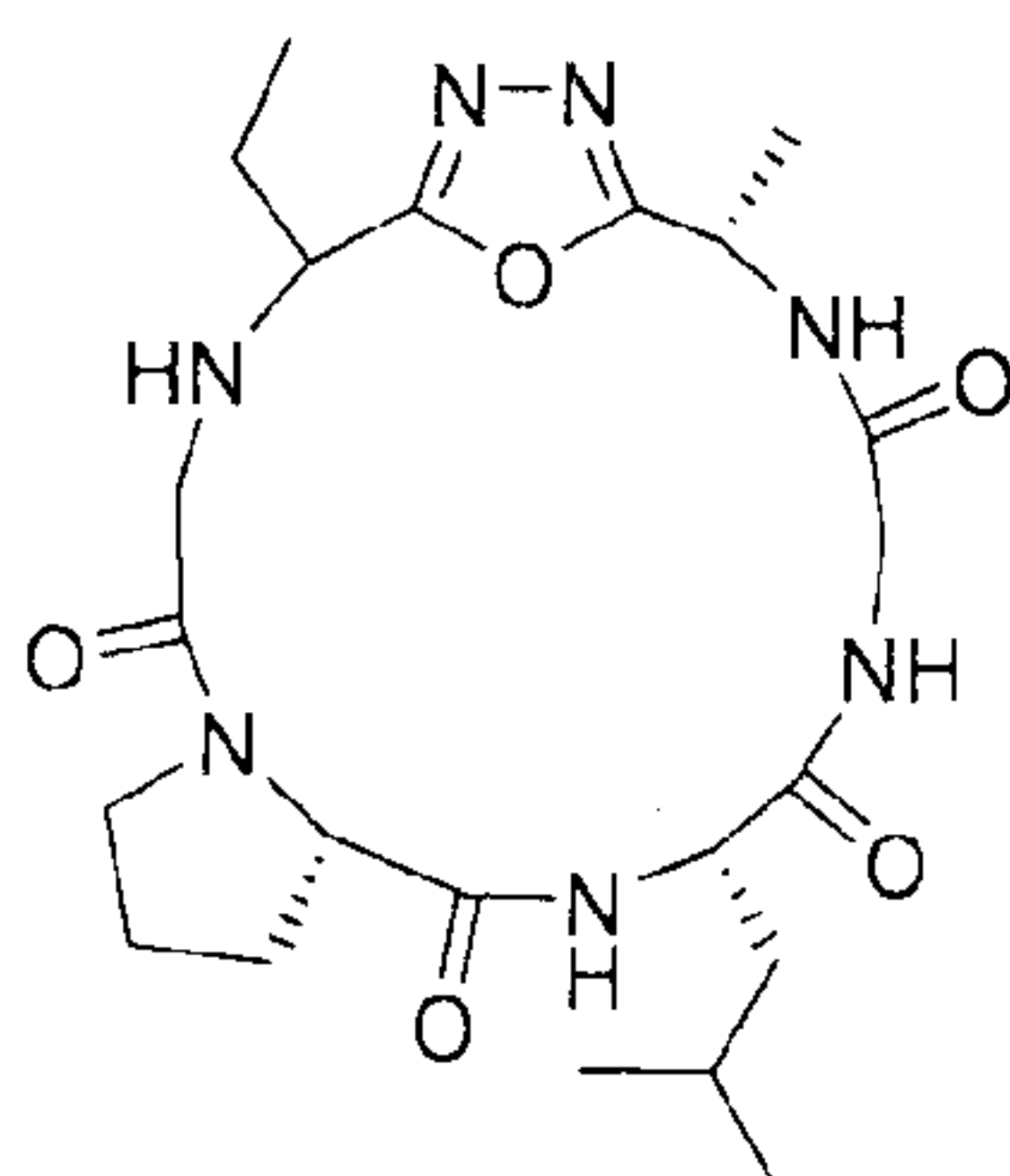
10



cyclo[APLGS]odz/ethyl (**31**)

15 The peptide NH₂-Ala-Pro- Leu-Gly-Ser(OtBu)-CO₂H was cyclized at 0.05 mmol scale with propionaldehyde (1.5 eq) and (*N*-isocyanimino)triphenylphosphorane (1 eq). After cyclization, deprotection, and reverse phase purification the pure fractions were pooled and lyophilized to afford 24 mg of the title compound in 70 % overall yield.

HR-MS (ESI) calculated for C₂₃H₃₈N₇O₆ [M+H]⁺ : 508.2878 found: 508.2871



cyclo[GPLGA]odz/ethyl (**32**)

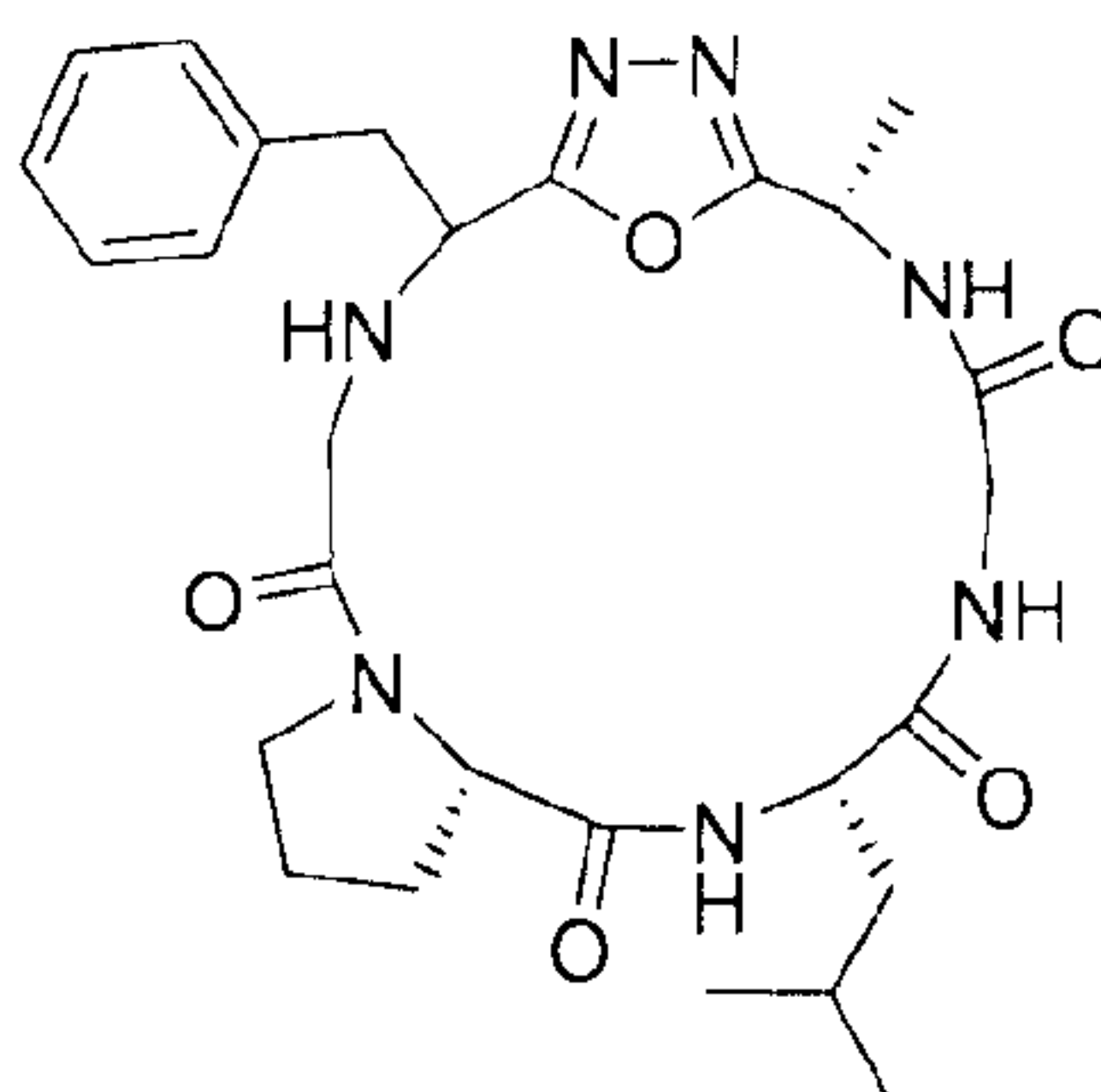
The peptide NH-Gly-Pro-Leu-Gly-Phe-CO₂H (20.7 mg, 0.05 mmol, 1 eq) was dissolved
 5 in a mixture of 1:1 Dichloroethane:Acetonitrile (2 mL). Propionaldehyde (5.4 μL, 0.075 mmol, 1.5 eq) and (*N*-isocyanimino)triphenylphosphorane (15.1 mg, 0.05 mmol, 1 eq) were added to the reaction mixture. After cyclization, deprotection, and reverse phase purification the pure fractions were pooled and lyophilized to afford 4.8 mg of the title compound in 20 % overall yield as a 1:1 mixture of diastereomers.

10 HR-MS (ESI) calculated for C₂₂H₃₆N₇O₅ [M+H]⁺ : 478.2772 found: 478.2774

HPLC Method A:

Retention time (major diastereomer) 4.73 min

Retention time (minor diastereomer) 4.90 min



15

cyclo[GPLGA]odz/benzyl (**33**)

The peptide NH₂-Gly-Pro-Leu-Gly-Ala-CO₂H (20.7 mg, 0.05 mmol, 1 eq) was dissolved
 in a mixture of 1:1 Dichloroethane:Acetonitrile (2 mL). Phenylacetaldehyde (8.35 μL,
 0.075 mmol, 1.5 eq) and (*N*-isocyanimino)triphenylphosphorane (15.1 mg, 0.05 mmol, 1
 20 eq) were added to the reaction mixture. After cyclization, deprotection, and reverse phase

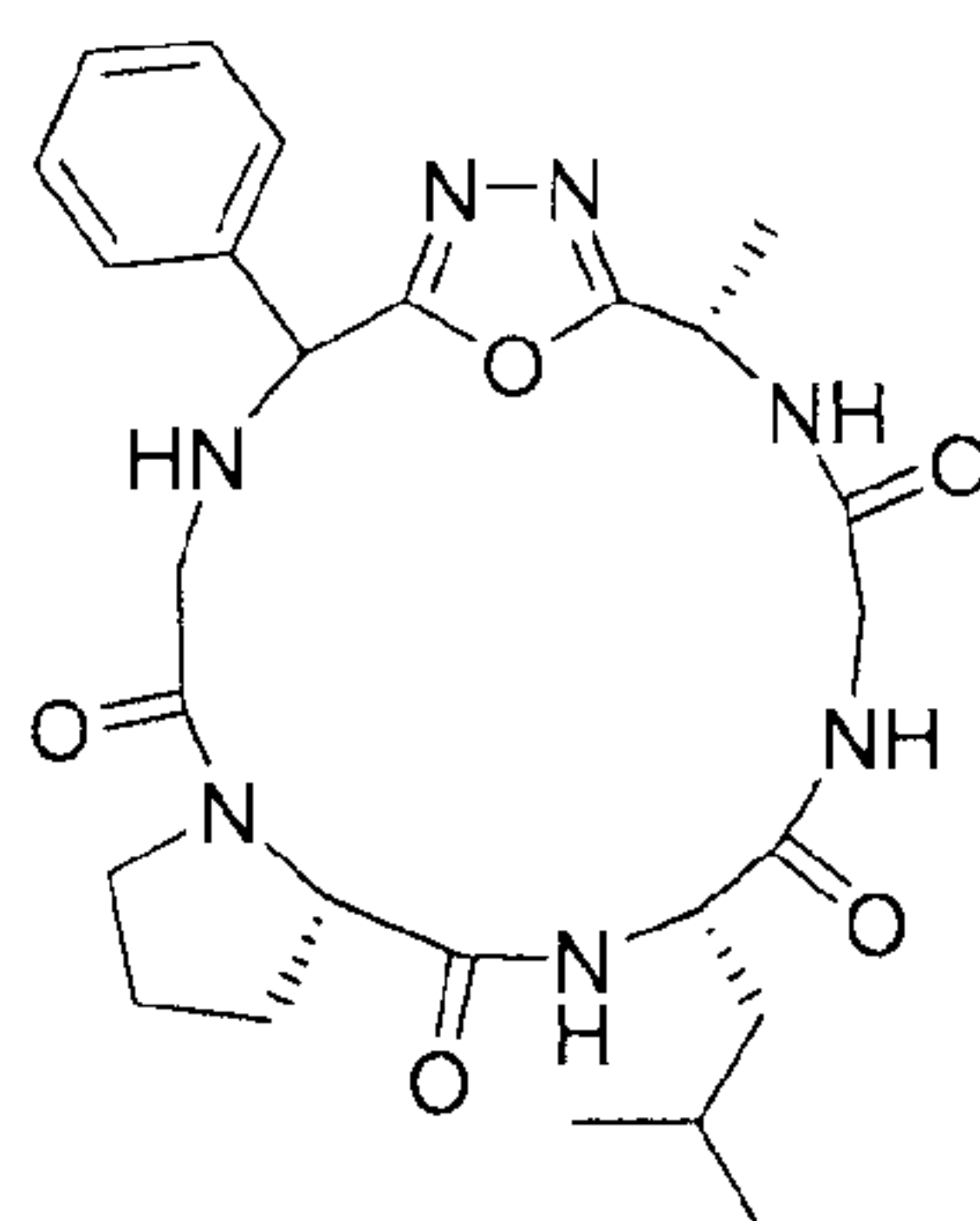
purification the pure fractions were pooled and lyophilized to afford 3.5 mg of the title compound in 13 % overall yield as a 1.1:1 mixture of diastereomers.

HR-MS (ESI) calculated for $C_{27}H_{38}N_7O_5$ $[M+H]^+$: 540.2929 found: 540.2923

HPLC Method A:

5 Retention time (major diastereomer) 6.58 min

Retention time (minor diastereomer) 6.45 min



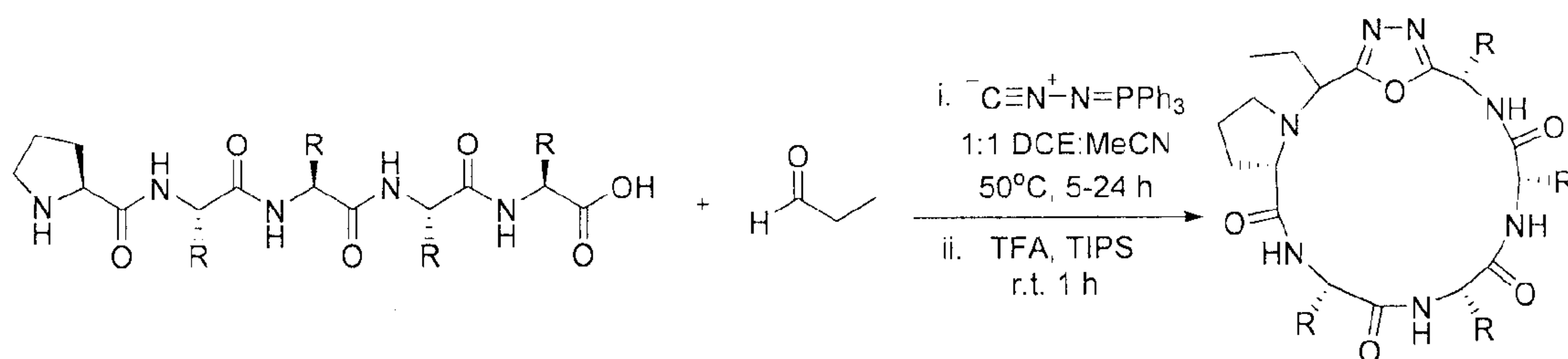
cyclo[GPLGA]odz/phenyl (**34**)

- 10 The peptide NH_2 -Gly-Pro- Leu-Gly-Ala- CO_2H was cyclized at 0.05 mmol scale with benzaldehyde (1.5 eq) and (*N*-isocyanimino)triphenylphosphorane (1 eq). After cyclization, deprotection, and reverse phase purification the pure fractions were pooled and lyophilized to afford 6.7 mg of the title compound in 25 % overall yield.

HR-MS (ESI) calculated for $C_{26}H_{36}N_7O_5$ $[M+H]^+$: 526.2772 found: 526.278

15

Table 1

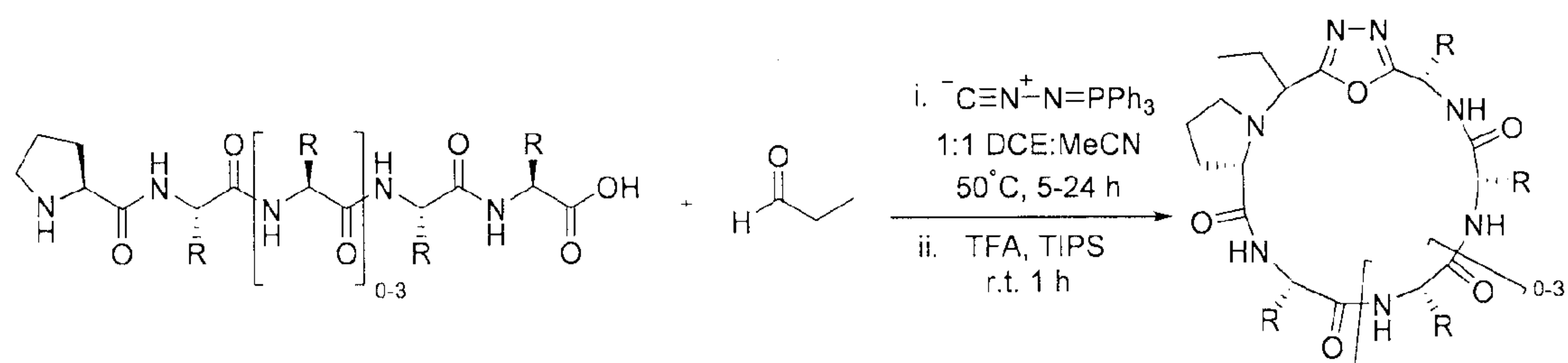


20

Compound	Length	Sequence	Aldehyde	Isolated Yield
1	5 mer	PGLGF	propionaldehyde	68 %
2	5 mer	PDAWG	propionaldehyde	22 %
3	5 mer	PRGDA	propionaldehyde	70 %
4	5 mer	PWASG	propionaldehyde	28 %
5	5 mer	PSLYA	propionaldehyde	24 %
6	5 mer	PLDFA	propionaldehyde	52 %
7	5 mer	PFDLA	propionaldehyde	45 %
8	5 mer	PGLAF	propionaldehyde	23 %
9	5 mer	PALGF	propionaldehyde	25 %
10	5 mer	PALAF	propionaldehyde	20 %
11	5 mer	PFLLF	propionaldehyde	25 %
Average				38 %

Oxadiazole containing cyclic peptides of varying sequence composition.

Table 2



5

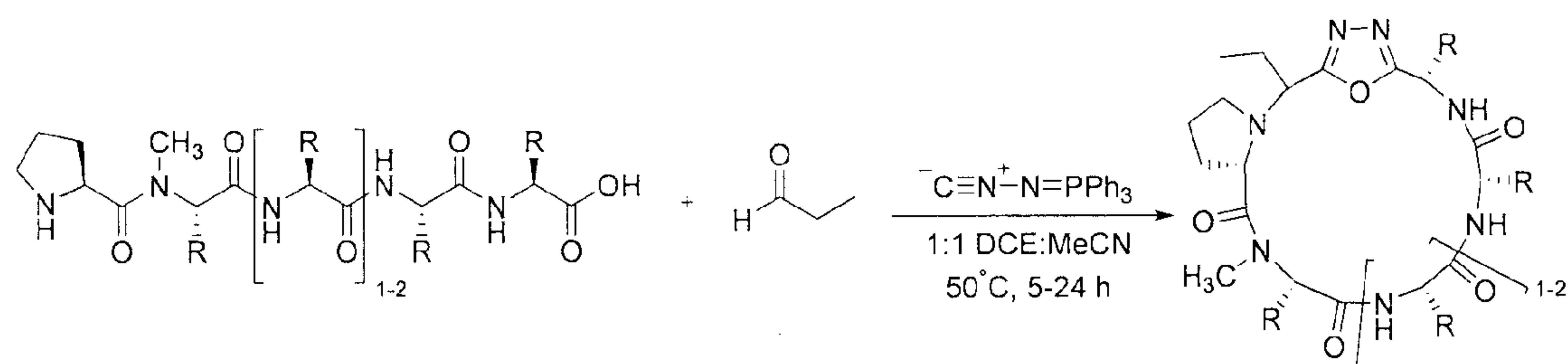
Compound	Length	Sequence	Aldehyde	Isolated Yield
12	4 mer	PAFA	propionaldehyde	23 %
13	6 mer	PASWKG	propionaldehyde	7 %
14	6 mer	PGLGFA	propionaldehyde	41 %
15	6 mer	PDAWYG	propionaldehyde	28 %
16	7 mer	PGRGDWA	propionaldehyde	22 %

Oxadiazole containing cyclic peptides of varying sequence length and composition.

10

15

Table 3



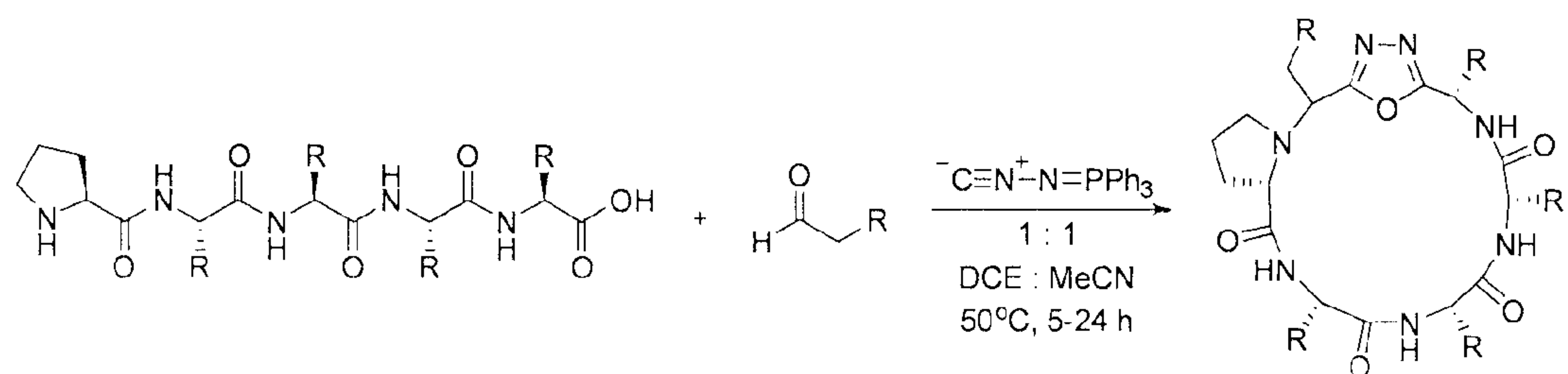
5

Compound	Length	Sequence	Aldehyde	Isolated Yield
17	5 mer	PSarLGF	propionaldehyde	28 %
18	6 mer	PSarLGFA	propionaldehyde	42 %

N-methylated oxadiazole containing cyclic peptides of varying sequence length and composition.

10

Table 4



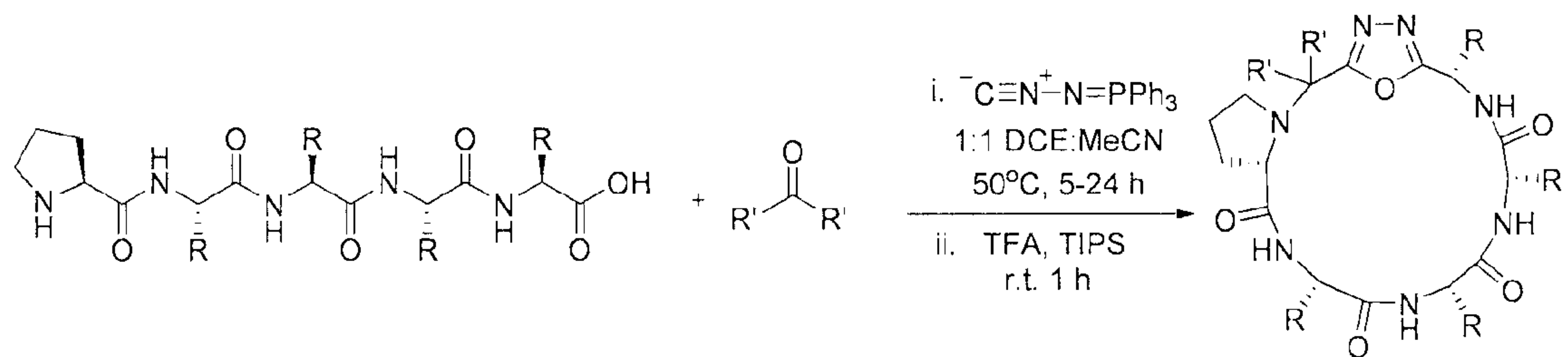
5

Compound	Length	Sequence	Aldehyde	Isolated Yield
19	5 mer	PSWAG	phenylacetaldehyde	26 %
20	5 mer	PSLYG	phenylacetaldehyde	22 %
21	5 mer	PGLGF	phenylacetaldehyde	29 %
22	5 mer	PGLGF	isovaleraldehyde	32 %
23	5 mer	PSarLGF	α -borylaldehyde	28 %

Oxadiazole containing cyclic peptides with varying aldehyde components

Table 5

5



10

Compound	Length	Sequence	Ketone	Isolated Yield
24	5 mer	PFLDA	Acetone	10 %
25	5 mer	PFLDA	Cyclohexanone	10 %

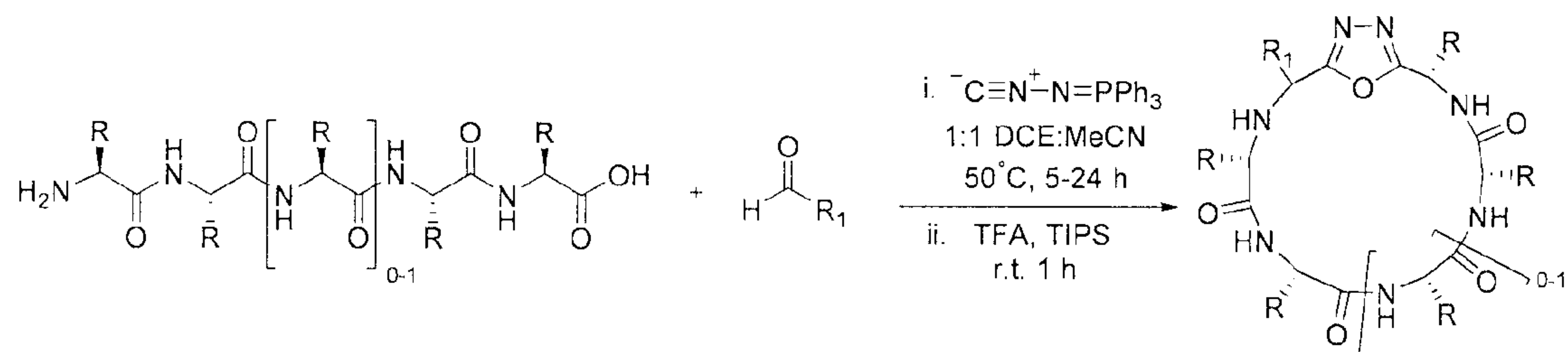
15

Oxadiazole containing cyclic peptides with varying ketone components

20

Table 6

5



Compound	Length	Sequence	R1=	Isolated Yield
26	4 mer	ALFA	Ethyl	20 %
27	4 mer	AGFA	Ethyl	24 %
28	4 mer	AGFA	Benzyl	32 %
29	5 mer	APLGA	Ethyl	15 %
30	5 mer	APLGK	Ethyl	60 %
31	5 mer	APLGS	Ethyl	70 %
32	5 mer	GPLGA	Ethyl	20 %
33	5 mer	GPLGA	Benzyl	13 %
34	5 mer	GPLGA	Phenyl	25 %

10

Oxadiazole containing cyclic peptides with varying aldehyde components

Table 7

Identification code	d15126
Empirical formula	C ₂₈ H ₄₂ N ₇ O _{6.50}
Formula weight	580.68
Temperature	147(2) K
Wavelength	1.54178 Å
Crystal system	Tetragonal
Space group	P4 ₁ 2 ₁ 2
Unit cell dimensions	a = 10.4819(3) Å b = 10.4819(3) Å c = 57.620(2) Å
Volume	6330.7(4) Å ³
Z	8
Density (calculated)	1.219 Mg/m ³
Absorption coefficient	0.724 mm ⁻¹
F(000)	2488
Crystal size	0.350 x 0.200 x 0.010 mm ³
Theta range for data collection	3.068 to 67.215°
Index ranges	-7 ≤ h ≤ 12, -12 ≤ k ≤ 11, -68 ≤ l ≤ 68
Reflections collected	36843
Independent reflections	5613 [R(int) = 0.0399]
Completeness to theta = 67.215°	99.3 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.7529 and 0.6702
Refinement method	Full-matrix least-squares on F ²
Data / restraints / parameters	5613 / 23 / 438
Goodness-of-fit on F ²	1.082
Final R indices [I > 2sigma(I)]	R1 = 0.0386, wR2 = 0.0992
R indices (all data)	R1 = 0.0399, wR2 = 0.1000
Absolute structure parameter	0.12(6)
Extinction coefficient	n/a
Largest diff. peak and hole	0.352 and -0.198 e.Å ⁻³

5

Crystal data and structure refinement for d15126

Table 8

		x	y	z	U(eq)
5	O(1)	5419(1)	5844(2)	4496(1)	30(1)
	O(2)	9428(2)	6898(2)	4926(1)	36(1)
	O(3)	10383(2)	4176(2)	4420(1)	53(1)
	O(4)	7119(2)	3813(2)	4372(1)	35(1)
	O(5)	4620(2)	2869(2)	3754(1)	60(1)
10	N(1)	3855(2)	6504(2)	4717(1)	41(1)
	N(2)	5005(2)	7072(2)	4796(1)	36(1)
	N(3)	8029(2)	5831(2)	4699(1)	27(1)
	N(4)	9382(2)	3565(2)	4748(1)	31(1)
	N(5)	8544(2)	2531(2)	4195(1)	37(1)
15	N(6)	5732(2)	4199(2)	3987(1)	47(1)
	C(2)	4150(2)	5804(2)	4544(1)	35(1)
	C(3)	5881(2)	6649(2)	4661(1)	25(1)
	C(4)	7265(2)	6957(2)	4649(1)	26(1)
	C(5)	9066(2)	5899(2)	4833(1)	28(1)
20	C(6)	9795(2)	4670(2)	4878(1)	33(1)
	C(7)	9706(2)	3414(3)	4525(1)	35(1)
	C(9)	7543(2)	3312(2)	4195(1)	34(1)
	C(10)	6946(3)	3570(3)	3960(1)	52(1)
	C(11)	4655(3)	3768(3)	3894(1)	49(1)
25	C(13)	3703(3)	3561(3)	4440(1)	53(1)
	C(14)	3589(4)	3212(3)	4692(1)	69(1)
	C(15)	7601(2)	7505(2)	4410(1)	34(1)
	C(16)	6736(2)	8586(2)	4342(1)	35(1)
	C(17)	5902(3)	8472(3)	4156(1)	41(1)
30	C(18)	5106(3)	9468(3)	4095(1)	50(1)
	C(19)	5132(3)	10587(3)	4219(1)	54(1)
	C(20)	5931(3)	10709(3)	4408(1)	51(1)
	C(21)	6731(3)	9715(3)	4469(1)	43(1)
	C(8)	9204(3)	2211(3)	4410(1)	39(1)
35	C(22)	10203(5)	1167(5)	4354(1)	49(1)
	C(23)	10969(4)	687(5)	4562(1)	60(2)

	C(24)	10172(5)	41(6)	4740(1)	77(2)
	C(25)	12024(6)	-177(7)	4477(1)	95(2)
	C(8A)	9204(3)	2211(3)	4410(1)	39(1)
	C(22A)	10510(7)	1589(7)	4351(2)	44(3)
5	C(23A)	10358(8)	137(7)	4336(1)	50(2)
	C(24A)	11288(12)	-470(11)	4175(2)	87(4)
	C(25A)	10406(12)	-432(11)	4574(2)	77(3)
	C(1)	3360(2)	4956(3)	4391(1)	49(1)
	N(7)	3604(3)	5363(3)	4151(1)	51(1)
10	C(12)	3444(4)	4460(5)	3956(1)	68(2)
	C(26)	3022(6)	5301(4)	3746(1)	78(2)
	C(27)	3250(5)	6663(4)	3828(1)	73(2)
	C(28)	2960(5)	6560(4)	4089(1)	66(2)
	C(1A)	3360(2)	4956(3)	4391(1)	49(1)
15	N(7A)	3757(16)	5357(18)	4157(1)	44(5)
	C(12A)	3518(17)	4458(19)	3964(2)	44(5)
	C(26A)	2310(18)	5009(16)	3844(4)	44(5)
	C(27A)	2480(20)	6436(15)	3875(3)	44(5)
	C(28A)	3250(30)	6615(13)	4096(3)	44(5)
20	O(1W)	11990(2)	7442(2)	5050(1)	46(1)
	O(2W)	10154(5)	4741(4)	3946(1)	62(1)

Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for d15126. $U(\text{eq})$ is defined as one third of the trace of the orthogonalized U_{ij} tensor.

Table 9

	O(1)-C(2)	1.359(3)
	O(1)-C(3)	1.364(3)
5	O(2)-C(5)	1.233(3)
	O(3)-C(7)	1.227(3)
	O(4)-C(9)	1.231(3)
	O(5)-C(11)	1.238(3)
	N(1)-C(2)	1.280(3)
10	N(1)-N(2)	1.418(3)
	N(2)-C(3)	1.279(3)
	N(3)-C(5)	1.337(3)
	N(3)-C(4)	1.455(3)
	N(3)-H(3N)	0.89(3)
15	N(4)-C(7)	1.335(3)
	N(4)-C(6)	1.449(3)
	N(4)-H(4N)	0.87(3)
	N(5)-C(9)	1.331(3)
	N(5)-C(8A)	1.456(3)
20	N(5)-C(8)	1.456(3)
	N(5)-H(5N)	0.88(3)
	N(6)-C(11)	1.330(4)
	N(6)-C(10)	1.442(4)
	N(6)-H(6N)	0.88(4)
25	C(2)-C(1A)	1.499(4)
	C(2)-C(1)	1.499(4)
	C(3)-C(4)	1.487(3)
	C(4)-C(15)	1.537(3)
	C(4)-H(4A)	1.0000
30	C(5)-C(6)	1.520(3)
	C(6)-H(6A)	0.9900
	C(6)-H(6B)	0.9900
	C(7)-C(8A)	1.519(4)
	C(7)-C(8)	1.519(4)
35	C(9)-C(10)	1.516(4)
	C(10)-H(10A)	0.9900

	C(10)-H(10B)	0.9900
	C(11)-C(12A)	1.452(11)
	C(11)-C(12)	1.507(5)
	C(13)-C(14)	1.504(5)
5	C(13)-C(1A)	1.531(4)
	C(13)-C(1)	1.531(4)
	C(13)-H(13A)	0.9900
	C(13)-H(13B)	0.9900
	C(14)-H(14A)	0.9800
10	C(14)-H(14B)	0.9800
	C(14)-H(14C)	0.9800
	C(15)-C(16)	1.503(4)
	C(15)-H(15A)	0.9900
	C(15)-H(15B)	0.9900
15	C(16)-C(17)	1.385(4)
	C(16)-C(21)	1.391(4)
	C(17)-C(18)	1.382(4)
	C(17)-H(17A)	0.9500
	C(18)-C(19)	1.374(4)
20	C(18)-H(18A)	0.9500
	C(19)-C(20)	1.380(5)
	C(19)-H(19A)	0.9500
	C(20)-C(21)	1.383(4)
	C(20)-H(20A)	0.9500
25	C(21)-H(21A)	0.9500
	C(8)-C(22)	1.548(4)
	C(8)-H(8)	1.0000
	C(22)-C(23)	1.531(7)
	C(22)-H(22A)	0.9900
30	C(22)-H(22B)	0.9900
	C(23)-C(24)	1.487(7)
	C(23)-C(25)	1.512(6)
	C(23)-H(23)	1.0000
	C(24)-H(24A)	0.9800
35	C(24)-H(24B)	0.9800
	C(24)-H(24C)	0.9800
	C(25)-H(25A)	0.9800
	C(25)-H(25B)	0.9800

	C(25)-H(25C)	0.9800
	C(8A)-C(22A)	1.552(6)
	C(8A)-H(8A)	1.0000
	C(22A)-C(23A)	1.534(8)
5	C(22A)-H(22C)	0.9900
	C(22A)-H(22D)	0.9900
	C(23A)-C(24A)	1.488(9)
	C(23A)-C(25A)	1.500(8)
	C(23A)-H(23A)	1.0000
10	C(24A)-H(24D)	0.9800
	C(24A)-H(24E)	0.9800
	C(24A)-H(24F)	0.9800
	C(25A)-H(25D)	0.9800
	C(25A)-H(25E)	0.9800
15	C(25A)-H(25F)	0.9800
	C(1)-N(7)	1.470(4)
	C(1)-H(1A)	1.0000
	N(7)-C(28)	1.469(4)
	N(7)-C(12)	1.478(4)
20	C(12)-C(26)	1.563(6)
	C(12)-H(12A)	1.0000
	C(26)-C(27)	1.523(6)
	C(26)-H(26A)	0.9900
	C(26)-H(26B)	0.9900
25	C(27)-C(28)	1.540(7)
	C(27)-H(27A)	0.9900
	C(27)-H(27B)	0.9900
	C(28)-H(28A)	0.9900
	C(28)-H(28B)	0.9900
30	C(1A)-N(7A)	1.474(7)
	C(1A)-H(1AA)	1.0000
	N(7A)-C(28A)	1.462(7)
	N(7A)-C(12A)	1.480(7)
	C(12A)-C(26A)	1.555(8)
35	C(12A)-H(12B)	1.0000
	C(26A)-C(27A)	1.517(8)
	C(26A)-H(26C)	0.9900
	C(26A)-H(26D)	0.9900

	C(27A)-C(28A)	1.521(9)
	C(27A)-H(27C)	0.9900
	C(27A)-H(27D)	0.9900
	C(28A)-H(28C)	0.9900
5	C(28A)-H(28D)	0.9900
	O(1W)-H(1WA)	0.85(4)
	O(1W)-H(1WB)	0.85(4)
	O(2W)-H(2WA)	0.8401
	O(2W)-H(2WB)	0.8400
10		
	C(2)-O(1)-C(3)	102.95(17)
	C(2)-N(1)-N(2)	106.44(19)
	C(3)-N(2)-N(1)	105.86(18)
	C(5)-N(3)-C(4)	121.2(2)
15	C(5)-N(3)-H(3N)	122.2(17)
	C(4)-N(3)-H(3N)	116.4(18)
	C(7)-N(4)-C(6)	121.3(2)
	C(7)-N(4)-H(4N)	120(2)
	C(6)-N(4)-H(4N)	118(2)
20	C(9)-N(5)-C(8A)	121.0(2)
	C(9)-N(5)-C(8)	121.0(2)
	C(9)-N(5)-H(5N)	121(2)
	C(8A)-N(5)-H(5N)	118(2)
	C(8)-N(5)-H(5N)	118(2)
25	C(11)-N(6)-C(10)	123.4(2)
	C(11)-N(6)-H(6N)	110(2)
	C(10)-N(6)-H(6N)	125(2)
	N(1)-C(2)-O(1)	112.2(2)
	N(1)-C(2)-C(1A)	131.7(2)
30	O(1)-C(2)-C(1A)	116.1(2)
	N(1)-C(2)-C(1)	131.7(2)
	O(1)-C(2)-C(1)	116.1(2)
	N(2)-C(3)-O(1)	112.5(2)
	N(2)-C(3)-C(4)	130.8(2)
35	O(1)-C(3)-C(4)	116.59(18)
	N(3)-C(4)-C(3)	110.61(19)
	N(3)-C(4)-C(15)	110.68(18)
	C(3)-C(4)-C(15)	110.29(19)

	N(3)-C(4)-H(4A)	108.4
	C(3)-C(4)-H(4A)	108.4
	C(15)-C(4)-H(4A)	108.4
	O(2)-C(5)-N(3)	123.0(2)
5	O(2)-C(5)-C(6)	119.4(2)
	N(3)-C(5)-C(6)	117.5(2)
	N(4)-C(6)-C(5)	116.01(19)
	N(4)-C(6)-H(6A)	108.3
	C(5)-C(6)-H(6A)	108.3
10	N(4)-C(6)-H(6B)	108.3
	C(5)-C(6)-H(6B)	108.3
	H(6A)-C(6)-H(6B)	107.4
	O(3)-C(7)-N(4)	122.8(2)
	O(3)-C(7)-C(8A)	121.6(2)
15	N(4)-C(7)-C(8A)	115.5(2)
	O(3)-C(7)-C(8)	121.6(2)
	N(4)-C(7)-C(8)	115.5(2)
	O(4)-C(9)-N(5)	123.2(2)
	O(4)-C(9)-C(10)	121.0(2)
20	N(5)-C(9)-C(10)	115.7(2)
	N(6)-C(10)-C(9)	110.5(2)
	N(6)-C(10)-H(10A)	109.6
	C(9)-C(10)-H(10A)	109.6
	N(6)-C(10)-H(10B)	109.6
25	C(9)-C(10)-H(10B)	109.6
	H(10A)-C(10)-H(10B)	108.1
	O(5)-C(11)-N(6)	123.1(3)
	O(5)-C(11)-C(12A)	122.4(9)
	N(6)-C(11)-C(12A)	114.5(9)
30	O(5)-C(11)-C(12)	119.8(3)
	N(6)-C(11)-C(12)	117.0(3)
	C(14)-C(13)-C(1A)	113.0(3)
	C(14)-C(13)-C(1)	113.0(3)
	C(14)-C(13)-H(13A)	109.0
35	C(1)-C(13)-H(13A)	109.0
	C(14)-C(13)-H(13B)	109.0
	C(1)-C(13)-H(13B)	109.0
	H(13A)-C(13)-H(13B)	107.8

	C(13)-C(14)-H(14A)	109.5
	C(13)-C(14)-H(14B)	109.5
	H(14A)-C(14)-H(14B)	109.5
	C(13)-C(14)-H(14C)	109.5
5	H(14A)-C(14)-H(14C)	109.5
	H(14B)-C(14)-H(14C)	109.5
	C(16)-C(15)-C(4)	112.22(19)
	C(16)-C(15)-H(15A)	109.2
	C(4)-C(15)-H(15A)	109.2
10	C(16)-C(15)-H(15B)	109.2
	C(4)-C(15)-H(15B)	109.2
	H(15A)-C(15)-H(15B)	107.9
	C(17)-C(16)-C(21)	118.4(3)
	C(17)-C(16)-C(15)	121.1(2)
15	C(21)-C(16)-C(15)	120.4(2)
	C(18)-C(17)-C(16)	120.9(3)
	C(18)-C(17)-H(17A)	119.6
	C(16)-C(17)-H(17A)	119.6
	C(19)-C(18)-C(17)	119.9(3)
20	C(19)-C(18)-H(18A)	120.0
	C(17)-C(18)-H(18A)	120.0
	C(18)-C(19)-C(20)	120.1(3)
	C(18)-C(19)-H(19A)	119.9
	C(20)-C(19)-H(19A)	119.9
25	C(19)-C(20)-C(21)	119.9(3)
	C(19)-C(20)-H(20A)	120.1
	C(21)-C(20)-H(20A)	120.1
	C(20)-C(21)-C(16)	120.7(3)
	C(20)-C(21)-H(21A)	119.7
30	C(16)-C(21)-H(21A)	119.7
	N(5)-C(8)-C(7)	110.2(2)
	N(5)-C(8)-C(22)	107.9(3)
	C(7)-C(8)-C(22)	116.3(3)
	N(5)-C(8)-H(8)	107.3
35	C(7)-C(8)-H(8)	107.3
	C(22)-C(8)-H(8)	107.3
	C(23)-C(22)-C(8)	115.0(4)
	C(23)-C(22)-H(22A)	108.5

	C(8)-C(22)-H(22A)	108.5
	C(23)-C(22)-H(22B)	108.5
	C(8)-C(22)-H(22B)	108.5
	H(22A)-C(22)-H(22B)	107.5
5	C(24)-C(23)-C(25)	111.3(5)
	C(24)-C(23)-C(22)	113.4(4)
	C(25)-C(23)-C(22)	108.9(5)
	C(24)-C(23)-H(23)	107.7
	C(25)-C(23)-H(23)	107.7
10	C(22)-C(23)-H(23)	107.7
	C(23)-C(24)-H(24A)	109.5
	C(23)-C(24)-H(24B)	109.5
	H(24A)-C(24)-H(24B)	109.5
	C(23)-C(24)-H(24C)	109.5
15	H(24A)-C(24)-H(24C)	109.5
	H(24B)-C(24)-H(24C)	109.5
	C(23)-C(25)-H(25A)	109.5
	C(23)-C(25)-H(25B)	109.5
	H(25A)-C(25)-H(25B)	109.5
20	C(23)-C(25)-H(25C)	109.5
	H(25A)-C(25)-H(25C)	109.5
	H(25B)-C(25)-H(25C)	109.5
	N(5)-C(8A)-C(7)	110.2(2)
	N(5)-C(8A)-C(22A)	109.4(4)
25	C(7)-C(8A)-C(22A)	98.0(4)
	N(5)-C(8A)-H(8A)	112.8
	C(7)-C(8A)-H(8A)	112.8
	C(22A)-C(8A)-H(8A)	112.8
	C(23A)-C(22A)-C(8A)	109.7(6)
30	C(23A)-C(22A)-H(22C)	109.7
	C(8A)-C(22A)-H(22C)	109.7
	C(23A)-C(22A)-H(22D)	109.7
	C(8A)-C(22A)-H(22D)	109.7
	H(22C)-C(22A)-H(22D)	108.2
35	C(24A)-C(23A)-C(25A)	112.3(7)
	C(24A)-C(23A)-C(22A)	113.1(7)
	C(25A)-C(23A)-C(22A)	109.7(7)
	C(24A)-C(23A)-H(23A)	107.1

	C(25A)-C(23A)-H(23A)	107.1
	C(22A)-C(23A)-H(23A)	107.1
	C(23A)-C(24A)-H(24D)	109.5
	C(23A)-C(24A)-H(24E)	109.5
5	H(24D)-C(24A)-H(24E)	109.5
	C(23A)-C(24A)-H(24F)	109.5
	H(24D)-C(24A)-H(24F)	109.5
	H(24E)-C(24A)-H(24F)	109.5
	C(23A)-C(25A)-H(25D)	109.5
10	C(23A)-C(25A)-H(25E)	109.5
	H(25D)-C(25A)-H(25E)	109.5
	C(23A)-C(25A)-H(25F)	109.5
	H(25D)-C(25A)-H(25F)	109.5
	H(25E)-C(25A)-H(25F)	109.5
15	N(7)-C(1)-C(2)	106.4(2)
	N(7)-C(1)-C(13)	114.1(3)
	C(2)-C(1)-C(13)	109.2(2)
	N(7)-C(1)-H(1A)	109.0
	C(2)-C(1)-H(1A)	109.0
20	C(13)-C(1)-H(1A)	109.0
	C(28)-N(7)-C(1)	113.5(3)
	C(28)-N(7)-C(12)	108.0(2)
	C(1)-N(7)-C(12)	120.6(3)
	N(7)-C(12)-C(11)	113.3(3)
25	N(7)-C(12)-C(26)	105.1(3)
	C(11)-C(12)-C(26)	108.9(4)
	N(7)-C(12)-H(12A)	109.8
	C(11)-C(12)-H(12A)	109.8
	C(26)-C(12)-H(12A)	109.8
30	C(27)-C(26)-C(12)	104.1(3)
	C(27)-C(26)-H(26A)	110.9
	C(12)-C(26)-H(26A)	110.9
	C(27)-C(26)-H(26B)	110.9
	C(12)-C(26)-H(26B)	110.9
35	H(26A)-C(26)-H(26B)	108.9
	C(26)-C(27)-C(28)	101.8(4)
	C(26)-C(27)-H(27A)	111.4
	C(28)-C(27)-H(27A)	111.4

	C(26)-C(27)-H(27B)	111.4
	C(28)-C(27)-H(27B)	111.4
	H(27A)-C(27)-H(27B)	109.3
	N(7)-C(28)-C(27)	102.0(3)
5	N(7)-C(28)-H(28A)	111.4
	C(27)-C(28)-H(28A)	111.4
	N(7)-C(28)-H(28B)	111.4
	C(27)-C(28)-H(28B)	111.4
	H(28A)-C(28)-H(28B)	109.2
10	N(7A)-C(1A)-C(2)	102.2(7)
	N(7A)-C(1A)-C(13)	111.9(8)
	C(2)-C(1A)-C(13)	109.2(2)
	N(7A)-C(1A)-H(1AA)	111.1
	C(2)-C(1A)-H(1AA)	111.1
15	C(13)-C(1A)-H(1AA)	111.1
	C(28A)-N(7A)-C(1A)	112.1(9)
	C(28A)-N(7A)-C(12A)	109.4(6)
	C(1A)-N(7A)-C(12A)	117.3(9)
	C(11)-C(12A)-N(7A)	112.8(14)
20	C(11)-C(12A)-C(26A)	136.9(12)
	N(7A)-C(12A)-C(26A)	103.6(7)
	C(11)-C(12A)-H(12B)	98.3
	N(7A)-C(12A)-H(12B)	98.3
	C(26A)-C(12A)-H(12B)	98.3
25	C(27A)-C(26A)-C(12A)	102.5(7)
	C(27A)-C(26A)-H(26C)	111.3
	C(12A)-C(26A)-H(26C)	111.3
	C(27A)-C(26A)-H(26D)	111.3
	C(12A)-C(26A)-H(26D)	111.3
30	H(26C)-C(26A)-H(26D)	109.2
	C(26A)-C(27A)-C(28A)	106.5(7)
	C(26A)-C(27A)-H(27C)	110.4
	C(28A)-C(27A)-H(27C)	110.4
	C(26A)-C(27A)-H(27D)	110.4
35	C(28A)-C(27A)-H(27D)	110.4
	H(27C)-C(27A)-H(27D)	108.6
	N(7A)-C(28A)-C(27A)	106.3(6)
	N(7A)-C(28A)-H(28C)	110.5

	C(27A)-C(28A)-H(28C)	110.5
	N(7A)-C(28A)-H(28D)	110.5
	C(27A)-C(28A)-H(28D)	110.5
	H(28C)-C(28A)-H(28D)	108.7
5	H(1WA)-O(1W)-H(1WB)	106(4)
	H(2WA)-O(2W)-H(2WB)	101.8

Symmetry transformations used to generate equivalent atoms:

Bond lengths [Å] and angles [°] for d15126.

Table 10

		U ¹¹	U ²²	U ³³	U ²³	U ¹³	U ¹²
5	O(1)	22(1)	31(1)	38(1)	-11(1)	0(1)	-1(1)
	O(2)	24(1)	41(1)	42(1)	-10(1)	-2(1)	-5(1)
	O(3)	41(1)	77(2)	41(1)	-7(1)	7(1)	-26(1)
	O(4)	34(1)	40(1)	32(1)	-12(1)	-2(1)	7(1)
	O(5)	78(2)	51(1)	50(1)	-23(1)	-32(1)	15(1)
10	N(1)	22(1)	48(1)	53(1)	-15(1)	5(1)	-4(1)
	N(2)	25(1)	47(1)	37(1)	-13(1)	4(1)	-4(1)
	N(3)	24(1)	27(1)	29(1)	-4(1)	-1(1)	-2(1)
	N(4)	28(1)	31(1)	35(1)	-1(1)	3(1)	2(1)
	N(5)	34(1)	39(1)	38(1)	-17(1)	5(1)	2(1)
15	N(6)	52(1)	51(1)	39(1)	-17(1)	-15(1)	9(1)
	C(2)	21(1)	34(1)	49(1)	-9(1)	1(1)	-2(1)
	C(3)	25(1)	26(1)	25(1)	-4(1)	0(1)	-1(1)
	C(4)	23(1)	27(1)	30(1)	-6(1)	1(1)	-2(1)
	C(5)	21(1)	36(1)	26(1)	-3(1)	4(1)	-4(1)
20	C(6)	25(1)	41(1)	33(1)	-1(1)	-3(1)	1(1)
	C(7)	22(1)	43(1)	39(1)	-2(1)	1(1)	2(1)
	C(9)	34(1)	32(1)	35(1)	-11(1)	0(1)	-2(1)
	C(10)	51(2)	70(2)	34(1)	-16(1)	-5(1)	12(2)
	C(11)	63(2)	43(2)	40(1)	-11(1)	-26(1)	12(1)
25	C(13)	34(2)	40(2)	83(2)	-19(2)	2(1)	-7(1)
	C(14)	63(2)	51(2)	92(3)	-6(2)	16(2)	-4(2)
	C(15)	31(1)	33(1)	37(1)	0(1)	9(1)	-2(1)
	C(16)	33(1)	32(1)	40(1)	7(1)	11(1)	-3(1)
	C(17)	46(2)	40(1)	35(1)	6(1)	6(1)	1(1)
30	C(18)	52(2)	51(2)	46(2)	14(1)	-1(1)	5(1)
	C(19)	49(2)	38(2)	75(2)	15(2)	2(2)	6(1)
	C(20)	46(2)	31(1)	77(2)	1(1)	4(2)	0(1)
	C(21)	38(1)	35(1)	55(2)	1(1)	4(1)	-4(1)
	C(8)	35(1)	38(1)	44(1)	-7(1)	4(1)	8(1)
35	C(22)	38(2)	31(3)	77(3)	-14(2)	11(2)	10(2)
	C(23)	40(2)	42(3)	99(4)	1(3)	4(3)	12(2)
	C(24)	52(3)	62(3)	118(5)	17(3)	-1(3)	16(3)

	C(25)	61(4)	80(4)	145(6)	2(4)	11(4)	36(3)
	C(8A)	35(1)	38(1)	44(1)	-7(1)	4(1)	8(1)
	C(1)	22(1)	42(2)	82(2)	-25(2)	-7(1)	-2(1)
	N(7)	42(2)	44(2)	66(2)	-26(1)	-28(1)	14(1)
5	C(12)	60(2)	59(2)	84(3)	-41(2)	-50(2)	19(2)
	C(26)	91(4)	74(3)	70(3)	-29(2)	-52(3)	41(3)
	C(27)	88(4)	66(3)	64(2)	-18(2)	-47(2)	29(2)
	C(28)	53(3)	48(2)	96(3)	-32(2)	-40(2)	21(2)
	C(1A)	22(1)	42(2)	82(2)	-25(2)	-7(1)	-2(1)
10	O(1W)	24(1)	62(1)	53(1)	-25(1)	1(1)	-4(1)
	O(2W)	107(4)	53(2)	26(2)	1(2)	8(2)	-38(3)

Anisotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for d15126. The anisotropic displacement factor exponent takes the form: $-2\pi^2 [h^2 a^{*2} U^{11} + \dots + 2 h k a^* b^* U^{12}]$

Table 11

		x	y	z	U(eq)
5					
	H(4A)	7458	7618	4769	32
	H(6A)	10707	4823	4844	40
	H(6B)	9728	4466	5046	40
	H(10A)	7524	4114	3867	62
10	H(10B)	6826	2754	3876	62
	H(13A)	3135	3002	4348	63
	H(13B)	4590	3403	4388	63
	H(14A)	3705	2290	4710	103
	H(14B)	2742	3454	4749	103
15	H(14C)	4244	3664	4781	103
	H(15A)	8494	7812	4412	41
	H(15B)	7537	6819	4292	41
	H(17A)	5876	7699	4070	49
	H(18A)	4542	9379	3967	60
20	H(19A)	4598	11278	4175	65
	H(20A)	5931	11474	4496	62
	H(21A)	7284	9803	4598	51
	H(8)	8562	1824	4517	47
	H(22A)	9758	432	4282	58
25	H(22B)	10807	1509	4237	58
	H(23)	11378	1444	4637	72
	H(24A)	9499	623	4793	116
	H(24B)	10707	-199	4873	116
	H(24C)	9785	-726	4673	116
30	H(25A)	12535	275	4360	143
	H(25B)	11650	-943	4407	143
	H(25C)	12569	-423	4607	143
	H(8A)	8675	1676	4516	47
	H(22C)	10829	1925	4201	53
35	H(22D)	11139	1805	4473	53
	H(23A)	9487	-35	4272	60
	H(24D)	11220	-73	4021	131

	H(24E)	11102	-1384	4162	131
	H(24F)	12154	-353	4235	131
	H(25D)	9749	-37	4672	115
	H(25E)	11248	-277	4643	115
5	H(25F)	10254	-1353	4565	115
	H(1A)	2438	5092	4428	59
	H(12A)	2759	3830	3994	81
	H(26A)	3540	5106	3607	94
	H(26B)	2110	5161	3709	94
10	H(27A)	2665	7269	3750	87
	H(27B)	4142	6932	3800	87
	H(28A)	3318	7292	4176	79
	H(28B)	2030	6508	4118	79
	H(1AA)	2429	5111	4416	59
15	H(12B)	3098	3762	4055	52
	H(26C)	2281	4774	3677	52
	H(26D)	1521	4708	3921	52
	H(27C)	1645	6864	3888	52
	H(27D)	2944	6802	3740	52
20	H(28C)	3961	7225	4070	52
	H(28D)	2705	6946	4222	52
	H(1WA)	11210(40)	7330(40)	5015(6)	66(11)
	H(1WB)	12420(40)	7070(40)	4946(7)	66(11)
	H(2WA)	10222	4575	4089	93
25	H(2WB)	10004	4017	3890	93
	H(3N)	7800(30)	5110(30)	4628(5)	31(7)
	H(4N)	8810(30)	3070(30)	4808(5)	45(8)
	H(5N)	8880(30)	2270(30)	4064(5)	47(8)
30	H(6N)	5570(30)	4790(40)	4090(6)	65(10)

Hydrogen coordinates ($\times 10^4$) and isotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for d15126.

Table 12

	C(2)-N(1)-N(2)-C(3)	-0.5(3)
	N(2)-N(1)-C(2)-O(1)	0.1(3)
5	N(2)-N(1)-C(2)-C(1A)	178.9(3)
	N(2)-N(1)-C(2)-C(1)	178.9(3)
	C(3)-O(1)-C(2)-N(1)	0.4(3)
	C(3)-O(1)-C(2)-C(1A)	-178.7(2)
	C(3)-O(1)-C(2)-C(1)	-178.7(2)
10	N(1)-N(2)-C(3)-O(1)	0.7(3)
	N(1)-N(2)-C(3)-C(4)	176.2(2)
	C(2)-O(1)-C(3)-N(2)	-0.7(3)
	C(2)-O(1)-C(3)-C(4)	-176.8(2)
	C(5)-N(3)-C(4)-C(3)	-138.0(2)
15	C(5)-N(3)-C(4)-C(15)	99.5(2)
	N(2)-C(3)-C(4)-N(3)	117.6(3)
	O(1)-C(3)-C(4)-N(3)	-67.1(2)
	N(2)-C(3)-C(4)-C(15)	-119.6(3)
	O(1)-C(3)-C(4)-C(15)	55.7(3)
20	C(4)-N(3)-C(5)-O(2)	1.0(3)
	C(4)-N(3)-C(5)-C(6)	179.11(19)
	C(7)-N(4)-C(6)-C(5)	77.7(3)
	O(2)-C(5)-C(6)-N(4)	-174.5(2)
	N(3)-C(5)-C(6)-N(4)	7.3(3)
25	C(6)-N(4)-C(7)-O(3)	1.4(4)
	C(6)-N(4)-C(7)-C(8A)	-179.9(2)
	C(6)-N(4)-C(7)-C(8)	-179.9(2)
	C(8A)-N(5)-C(9)-O(4)	0.4(4)
	C(8)-N(5)-C(9)-O(4)	0.4(4)
30	C(8A)-N(5)-C(9)-C(10)	179.8(3)
	C(8)-N(5)-C(9)-C(10)	179.8(3)
	C(11)-N(6)-C(10)-C(9)	-125.9(3)
	O(4)-C(9)-C(10)-N(6)	-12.6(4)
	N(5)-C(9)-C(10)-N(6)	168.0(2)
35	C(10)-N(6)-C(11)-O(5)	-8.2(5)
	C(10)-N(6)-C(11)-C(12A)	173.2(8)
	C(10)-N(6)-C(11)-C(12)	174.3(3)

	N(3)-C(4)-C(15)-C(16)	174.0(2)
	C(3)-C(4)-C(15)-C(16)	51.3(3)
	C(4)-C(15)-C(16)-C(17)	-113.8(3)
	C(4)-C(15)-C(16)-C(21)	64.2(3)
5	C(21)-C(16)-C(17)-C(18)	1.7(4)
	C(15)-C(16)-C(17)-C(18)	179.8(2)
	C(16)-C(17)-C(18)-C(19)	-0.4(4)
	C(17)-C(18)-C(19)-C(20)	-1.3(5)
	C(18)-C(19)-C(20)-C(21)	1.7(5)
10	C(19)-C(20)-C(21)-C(16)	-0.3(4)
	C(17)-C(16)-C(21)-C(20)	-1.3(4)
	C(15)-C(16)-C(21)-C(20)	-179.5(2)
	C(9)-N(5)-C(8)-C(7)	-58.8(3)
	C(9)-N(5)-C(8)-C(22)	173.2(3)
15	O(3)-C(7)-C(8)-N(5)	-53.6(3)
	N(4)-C(7)-C(8)-N(5)	127.7(2)
	O(3)-C(7)-C(8)-C(22)	69.6(4)
	N(4)-C(7)-C(8)-C(22)	-109.1(4)
	N(5)-C(8)-C(22)-C(23)	-178.5(4)
20	C(7)-C(8)-C(22)-C(23)	57.1(6)
	C(8)-C(22)-C(23)-C(24)	63.6(6)
	C(8)-C(22)-C(23)-C(25)	-171.9(5)
	C(9)-N(5)-C(8A)-C(7)	-58.8(3)
	C(9)-N(5)-C(8A)-C(22A)	-165.4(4)
25	O(3)-C(7)-C(8A)-N(5)	-53.6(3)
	N(4)-C(7)-C(8A)-N(5)	127.7(2)
	O(3)-C(7)-C(8A)-C(22A)	60.5(4)
	N(4)-C(7)-C(8A)-C(22A)	-118.2(4)
	N(5)-C(8A)-C(22A)-C(23A)	-91.1(6)
30	C(7)-C(8A)-C(22A)-C(23A)	154.1(6)
	C(8A)-C(22A)-C(23A)-C(24A)	151.3(8)
	C(8A)-C(22A)-C(23A)-C(25A)	-82.5(9)
	N(1)-C(2)-C(1)-N(7)	126.3(3)
	O(1)-C(2)-C(1)-N(7)	-54.9(3)
35	N(1)-C(2)-C(1)-C(13)	-110.1(3)
	O(1)-C(2)-C(1)-C(13)	68.7(3)
	C(14)-C(13)-C(1)-N(7)	173.4(3)
	C(14)-C(13)-C(1)-C(2)	54.4(3)

	C(2)-C(1)-N(7)-C(28)	-75.4(3)
	C(13)-C(1)-N(7)-C(28)	164.1(3)
	C(2)-C(1)-N(7)-C(12)	154.2(3)
	C(13)-C(1)-N(7)-C(12)	33.7(4)
5	C(28)-N(7)-C(12)-C(11)	135.0(4)
	C(1)-N(7)-C(12)-C(11)	-92.3(5)
	C(28)-N(7)-C(12)-C(26)	16.3(5)
	C(1)-N(7)-C(12)-C(26)	149.0(4)
	O(5)-C(11)-C(12)-N(7)	170.7(3)
10	N(6)-C(11)-C(12)-N(7)	-11.7(5)
	O(5)-C(11)-C(12)-C(26)	-72.8(5)
	N(6)-C(11)-C(12)-C(26)	104.8(4)
	N(7)-C(12)-C(26)-C(27)	11.6(5)
	C(11)-C(12)-C(26)-C(27)	-110.1(4)
15	C(12)-C(26)-C(27)-C(28)	-33.3(5)
	C(1)-N(7)-C(28)-C(27)	-173.7(4)
	C(12)-N(7)-C(28)-C(27)	-37.4(5)
	C(26)-C(27)-C(28)-N(7)	43.4(4)
	N(1)-C(2)-C(1A)-N(7A)	131.2(8)
20	O(1)-C(2)-C(1A)-N(7A)	-50.0(8)
	N(1)-C(2)-C(1A)-C(13)	-110.1(3)
	O(1)-C(2)-C(1A)-C(13)	68.7(3)
	C(14)-C(13)-C(1A)-N(7A)	166.8(7)
	C(14)-C(13)-C(1A)-C(2)	54.4(3)
25	C(2)-C(1A)-N(7A)-C(28A)	-72.4(12)
	C(13)-C(1A)-N(7A)-C(28A)	170.9(12)
	C(2)-C(1A)-N(7A)-C(12A)	159.8(10)
	C(13)-C(1A)-N(7A)-C(12A)	43.0(13)
	O(5)-C(11)-C(12A)-N(7A)	171.3(6)
30	N(6)-C(11)-C(12A)-N(7A)	-10.1(14)
	O(5)-C(11)-C(12A)-C(26A)	-43(3)
	N(6)-C(11)-C(12A)-C(26A)	135(2)
	C(28A)-N(7A)-C(12A)-C(11)	129.1(18)
	C(1A)-N(7A)-C(12A)-C(11)	-101.7(19)
35	C(28A)-N(7A)-C(12A)-C(26A)	-27.4(17)
	C(1A)-N(7A)-C(12A)-C(26A)	101.7(15)
	C(11)-C(12A)-C(26A)-C(27A)	-114(3)
	N(7A)-C(12A)-C(26A)-C(27A)	33.9(18)

C(12A)-C(26A)-C(27A)-C(28A)	-29(2)
C(1A)-N(7A)-C(28A)-C(27A)	-122.4(18)
C(12A)-N(7A)-C(28A)-C(27A)	10(2)
C(26A)-C(27A)-C(28A)-N(7A)	13(2)

5

Symmetry transformations used to generate equivalent atoms:

Torsion angles [°] for d15126.

Table 13

	D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
	O(1W)-H(1WA)...O(2)	0.85(4)	1.99(4)	2.837(3)	175(4)
5	O(1W)-H(1WB)...N(1)#1	0.85(4)	2.09(4)	2.909(3)	164(4)
	O(2W)-H(2WA)...O(3)	0.84	1.96	2.805(4)	179.6
	O(2W)-H(2WB)...O(5)#2	0.84	2.18	3.022(5)	179.7
	N(3)-H(3N)...O(4)	0.89(3)	2.13(3)	2.988(3)	162(2)
	N(4)-H(4N)...O(1W)#3	0.87(3)	2.00(3)	2.867(3)	178(3)
10	N(5)-H(5N)...O(5)#2	0.88(3)	1.99(3)	2.854(3)	166(3)
	N(6)-H(6N)...O(1)	0.88(4)	2.59(4)	3.416(3)	158(3)
	N(6)-H(6N)...N(7)	0.88(4)	2.17(4)	2.713(4)	119(3)
	N(6)-H(6N)...N(7A)	0.88(4)	2.03(4)	2.592(18)	121(3)
15	Symmetry transformations used to generate equivalent atoms:				
	#1 x+1,y,z #2 x+1/2,-y+1/2,-z+3/4 #3 y,x-1,-z+1				

Hydrogen bonds for d15126 [Å and °].

Although preferred embodiments of the invention have been described herein, it will be understood by those skilled in the art that variations may be made thereto without departing from the spirit of the invention or the scope of the appended claims.

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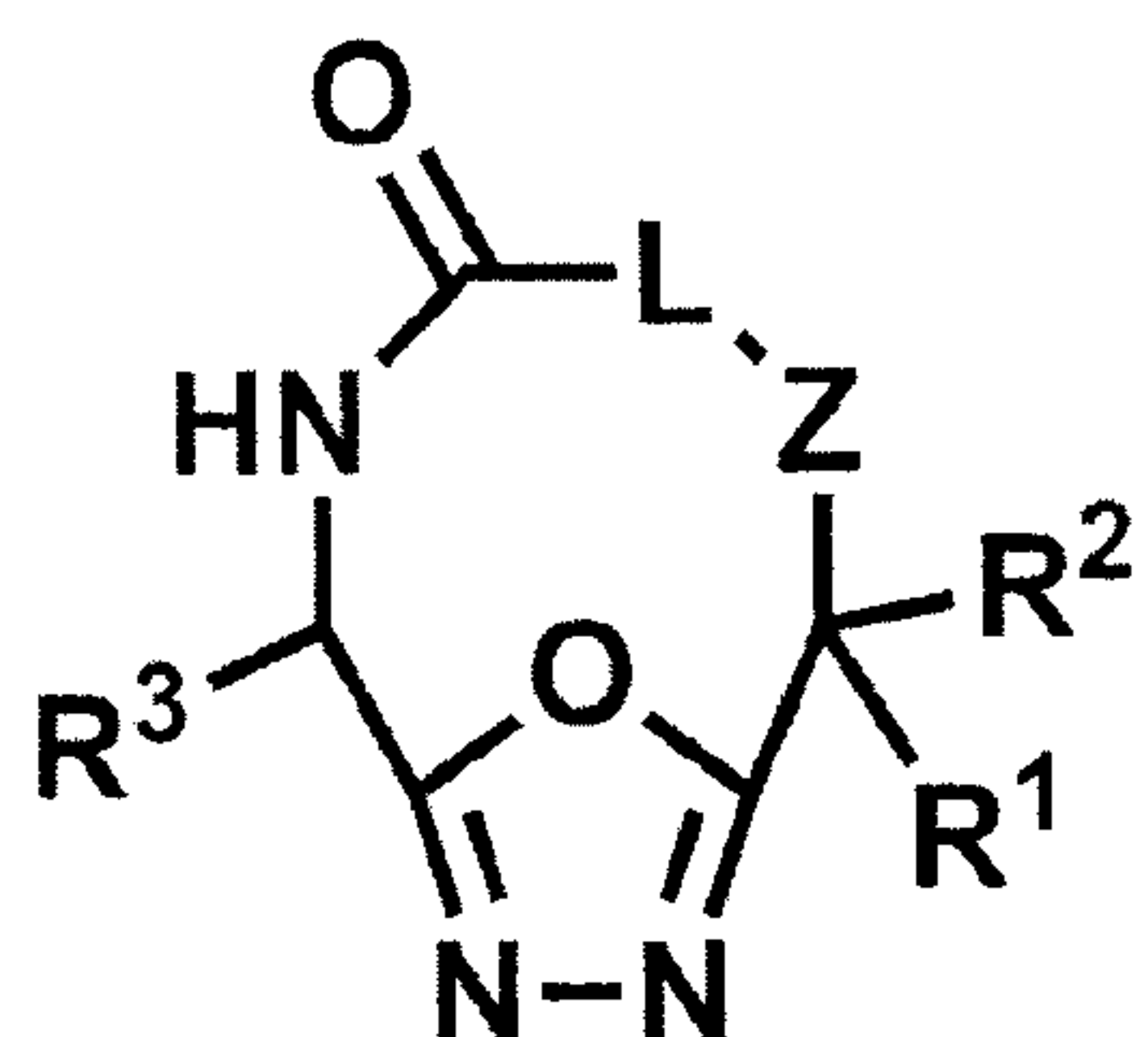
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CLAIMS:

1. A cyclic amino acid molecule of formula [(I)]:



[(I)]

5 wherein,

Z is an amino terminus of an amino acid;

-C=O- is a carboxy terminus of an amino acid;

L, along with Z and -C=O- is an amino acid molecule;

R¹ and R² are each independently hydrogen or an organic group;

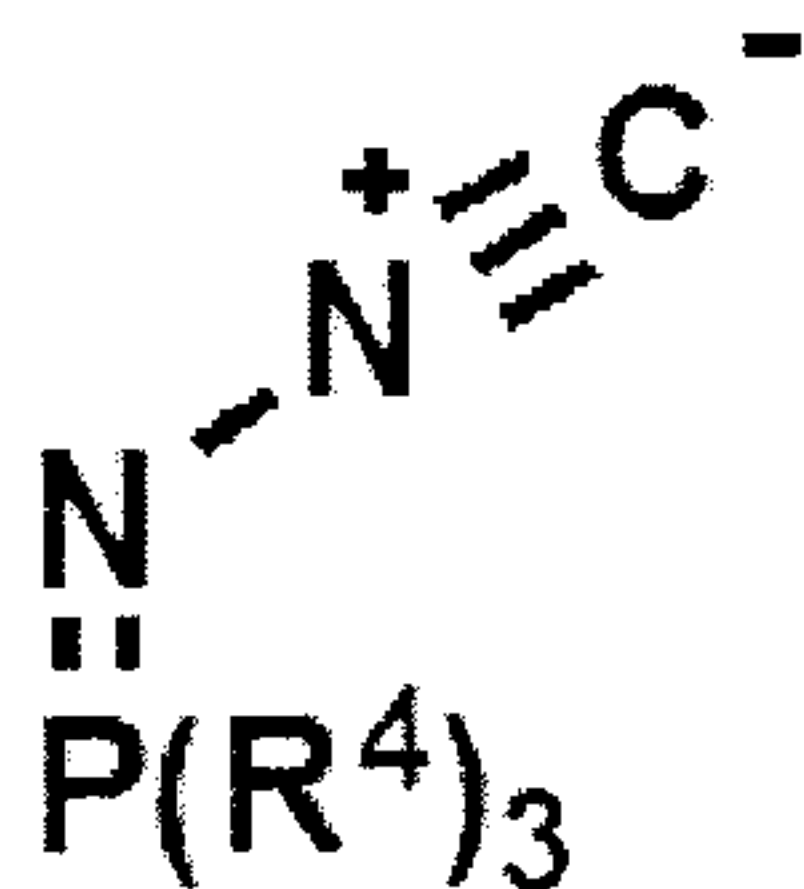
10 R³ is equivalent to an amino acid side-chain; and

the amino acid molecule is a linear peptide or a salt of the foregoing.

2. The cyclic amino acid molecule of claim 1, wherein R¹ and R² are each independently selected from the group consisting of hydrogen, an alkyl group, a heteroalkyl group, a cycloalkyl group, an alkenyl group, a heteroalkenyl group, an alkynyl group, a heteroalkynyl group, an aryl group, a heteroaryl group, a heterocyclic group, an acyl group, an α -MIDA borylaldehyde, CF₃, CH₂-CF₃, a macrocycle, a fluorophore, an orthogonal reactive group, an affinity tag, an isotopically labeled molecule, a nucleoside, a nucleotide, a lipid, a carbohydrate, a small molecule, a functionalized solid support, and a biologic.

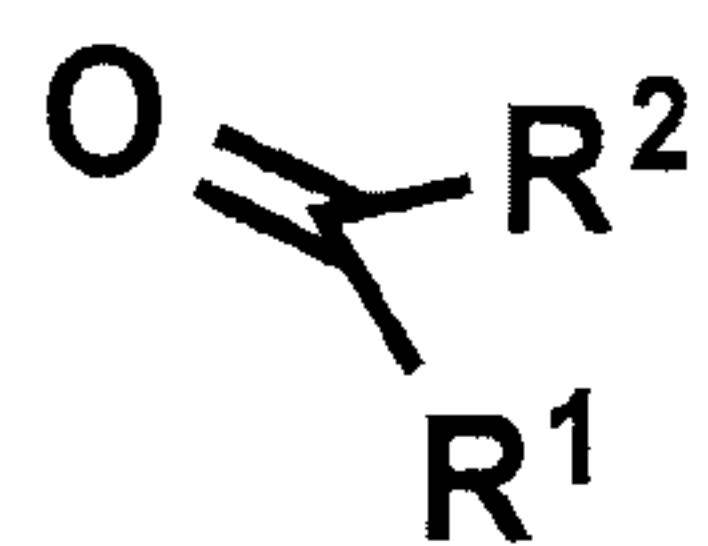
3. The cyclic amino acid molecule of claim 1, wherein R^1 and R^2 are each independently selected from the group consisting of ethyl, benzyl and phenyl.
4. The cyclic amino acid molecule of claim 2, wherein the α -MIDA borylaldehyde is $C_6H_9BNO_4$.
5. The cyclic amino acid molecule of claim 2, wherein the orthogonal reactive group is selected from the group consisting of a cyclic alkyne, a linear alkyne, a cyclic azide, a linear azide, a cyclic tetrazole and a linear tetrazole.
6. The cyclic amino acid molecule of claim 2, wherein the affinity tag is biotin.
7. The cyclic amino acid molecule of claim 2, wherein the biologic is a functionalized peptide, a functionalized protein, or a functionalized amino acid.
8. The cyclic amino acid molecule of claim 2, wherein the functionalized solid support is a solid surface or resin bead.
9. The cyclic amino acid molecule of claim 2, wherein the small molecule is a drug.
10. The cyclic amino acid molecule of claim 2, wherein the cyclic amino acid molecule is a lariat type macrocycle.
11. The cyclic amino acid molecule of claim 2, wherein R^1 and R^2 are covalently linked to each other.
12. The cyclic amino acid molecule of claim 11, wherein R^1 and R^2 form a cycloalkanone.
13. The cyclic amino acid molecule of claim 12, wherein R^1 and R^2 form cyclopentanone.
14. The cyclic amino acid molecule of any one of claims 1-13, wherein the amino terminus of the amino acid molecule is a primary amino group.
15. The cyclic amino acid molecule of any one of claims 1-13, wherein the amino terminus of the amino acid molecule is a secondary amino group.

16. The cyclic amino acid molecule of any one of claims 1- 15, wherein the amino acid molecule comprises a D or L amino acid.
17. The cyclic amino acid molecule of any one of claims 1- 16, wherein the amino acid molecule comprises an alpha-amino acid.
- 5 18. The cyclic amino acid molecule of any one of claims 1- 16, wherein the amino acid molecule comprises a beta-amino acid.
19. The cyclic amino acid molecule of any one of claims 1- 16, wherein the amino acid molecule comprises a gamma-amino acid.
20. The cyclic amino acid molecule of any one of claims 1-19, wherein the cyclic amino acid molecule comprises a diastereomer at the carbon atom proximal to the aldehyde group.
- 10 21. The cyclic amino acid molecule of claim 20, wherein the diastereomer is an (S) diastereomer.
22. The cyclic amino acid molecule of claim 20, wherein the diastereomer is an (R) diastereomer.
- 15 23. The cyclic amino acid molecule of any one of claims 1-22, wherein the linear peptide comprises at least 2 amino acids, 3 amino acids, 4 amino acids, 5 amino acids, 6 amino acids, 7 amino acids, or 8 amino acids.
24. A process to produce the cyclic amino acid molecule of claim 1 comprising reacting an amino acid molecule, having an amino terminus and a carboxyl terminus, with an isocyano-iminophosphorane having the formula (II):
- 20



(II)

and a compound having the formula (III):



(III)

wherein,

- 5 R¹ and R² are each independently hydrogen or an organic group;
- and the amino acid molecule is a linear peptide or a salt of the foregoing; and
- each R⁴ is independently an organic group.
25. The process of claim 24, wherein at least one R⁴ is Ph.
26. The process of claim 25, wherein all R⁴ are Ph.
- 10 27. The process of claim 25, wherein each R⁴ is independently selected from the
 group consisting of an alkyl, an aryl and an alkoxy.
28. The process of any one of claims 24-27 further comprising conjugating a
 fluorescent tag to the cyclic molecule.
29. The process of any one of claims 24-28, further comprising deprotecting one or
15 more side chains of the cyclic amino acid molecule if one or more of said side chains are
 protected with protecting groups.

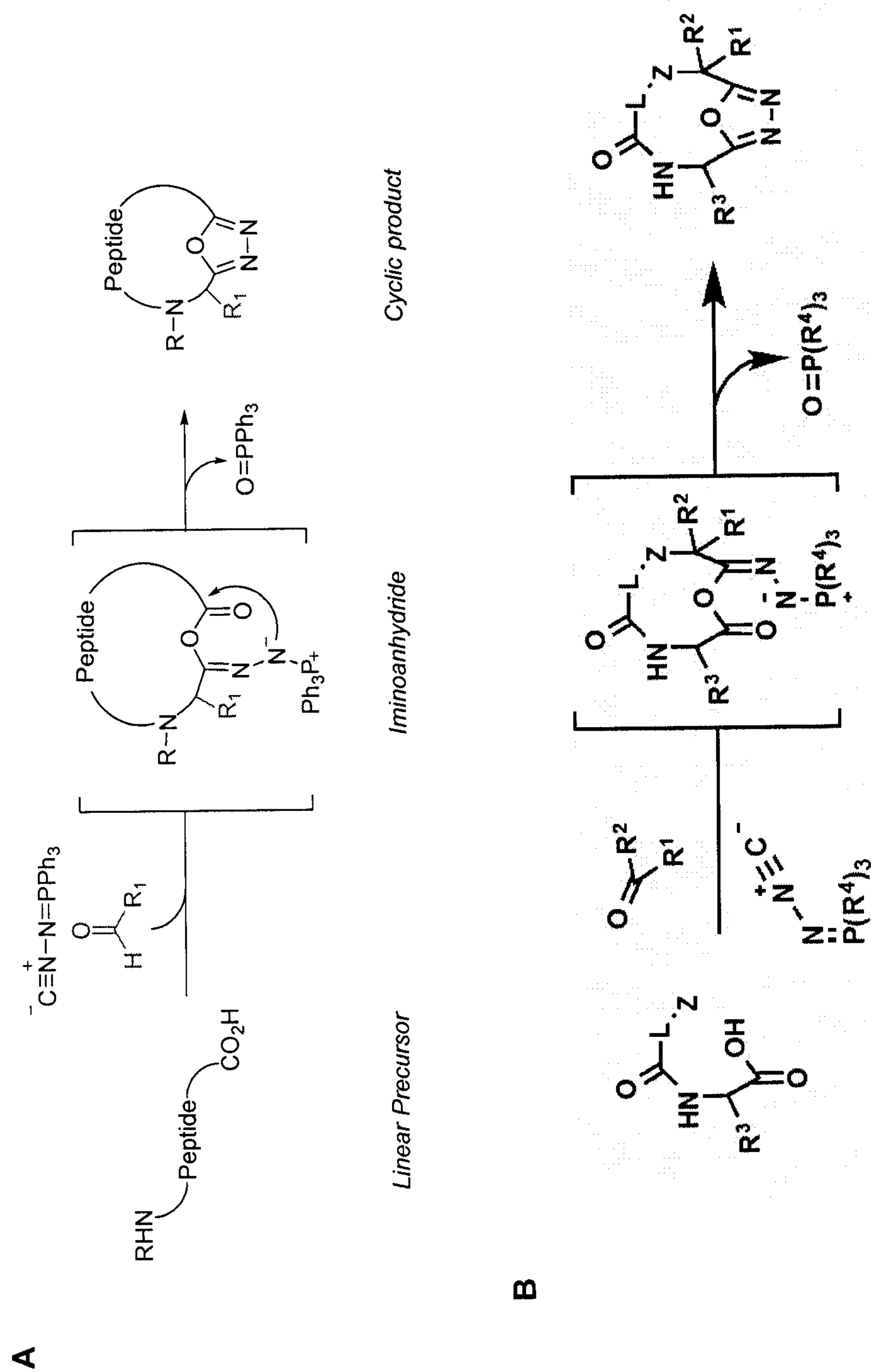


FIGURE 1

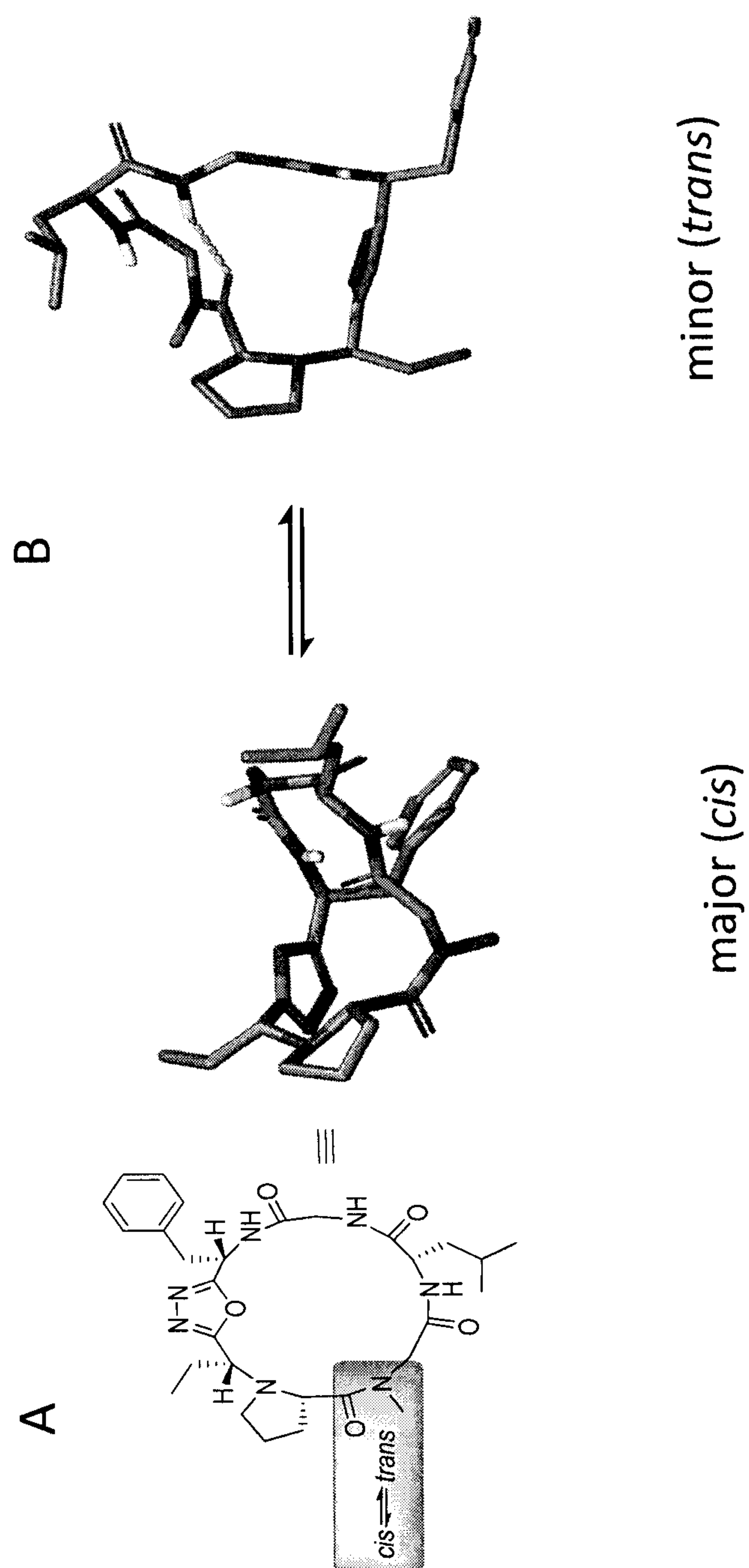


FIGURE 2

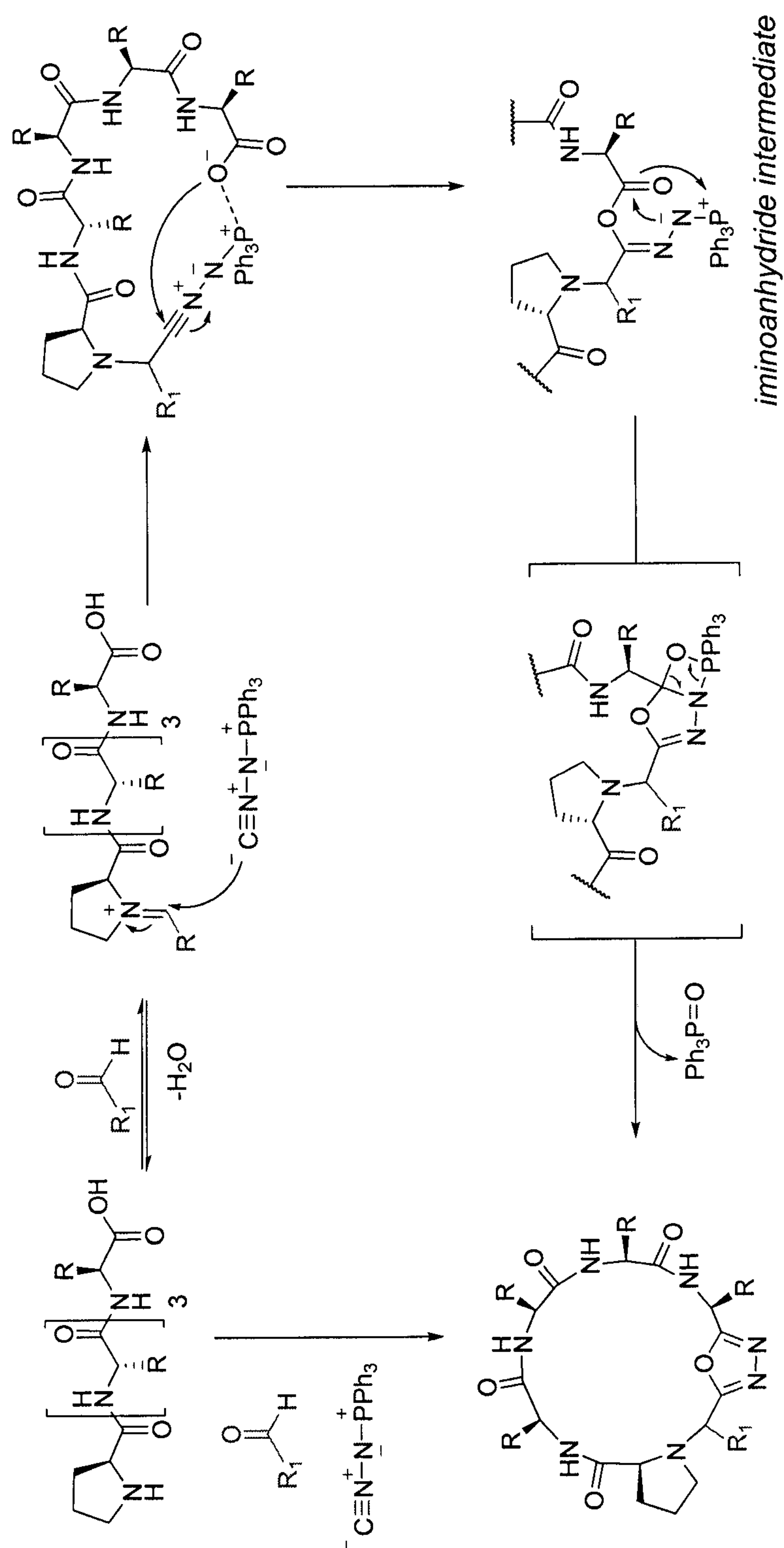


FIGURE 3

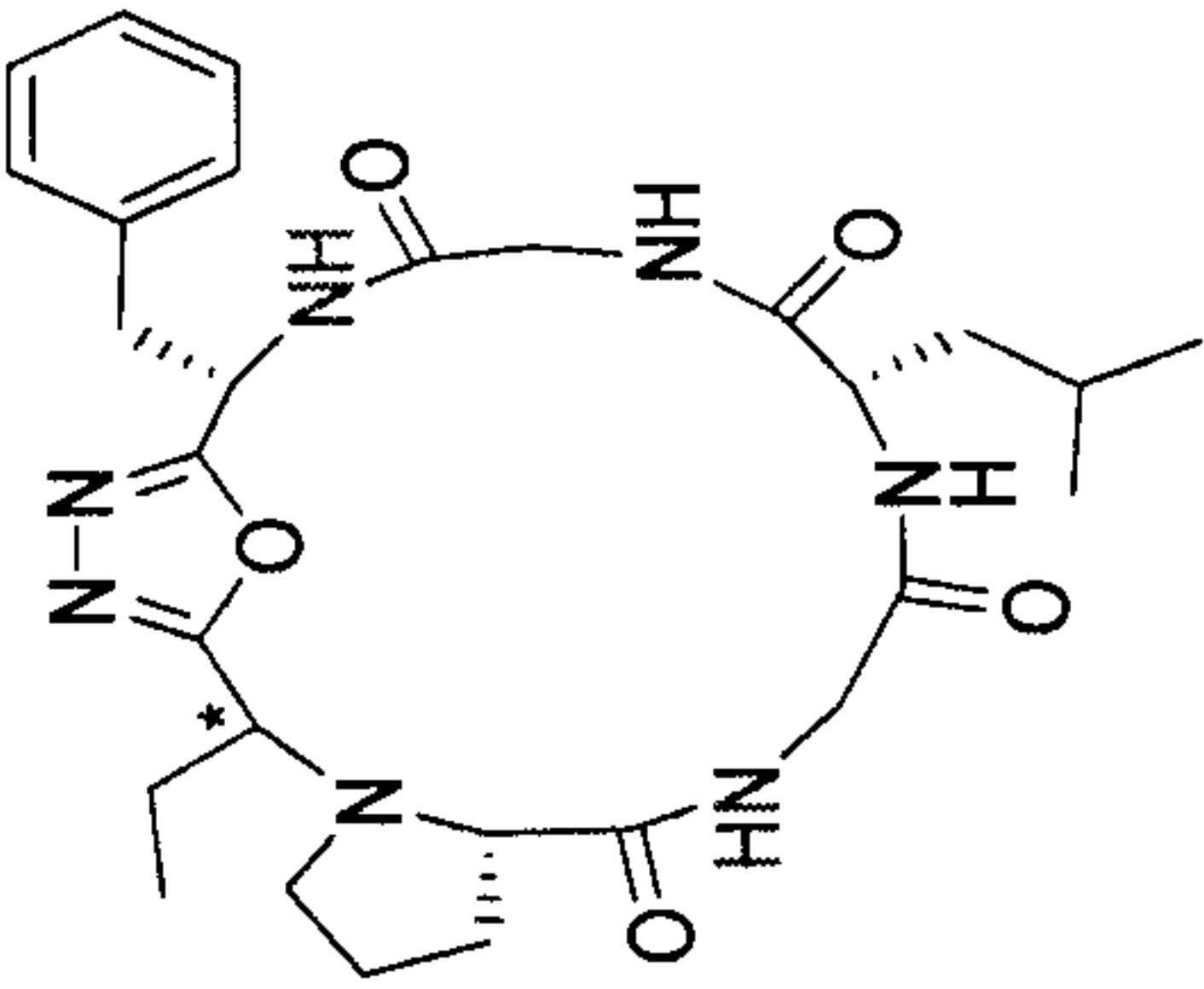
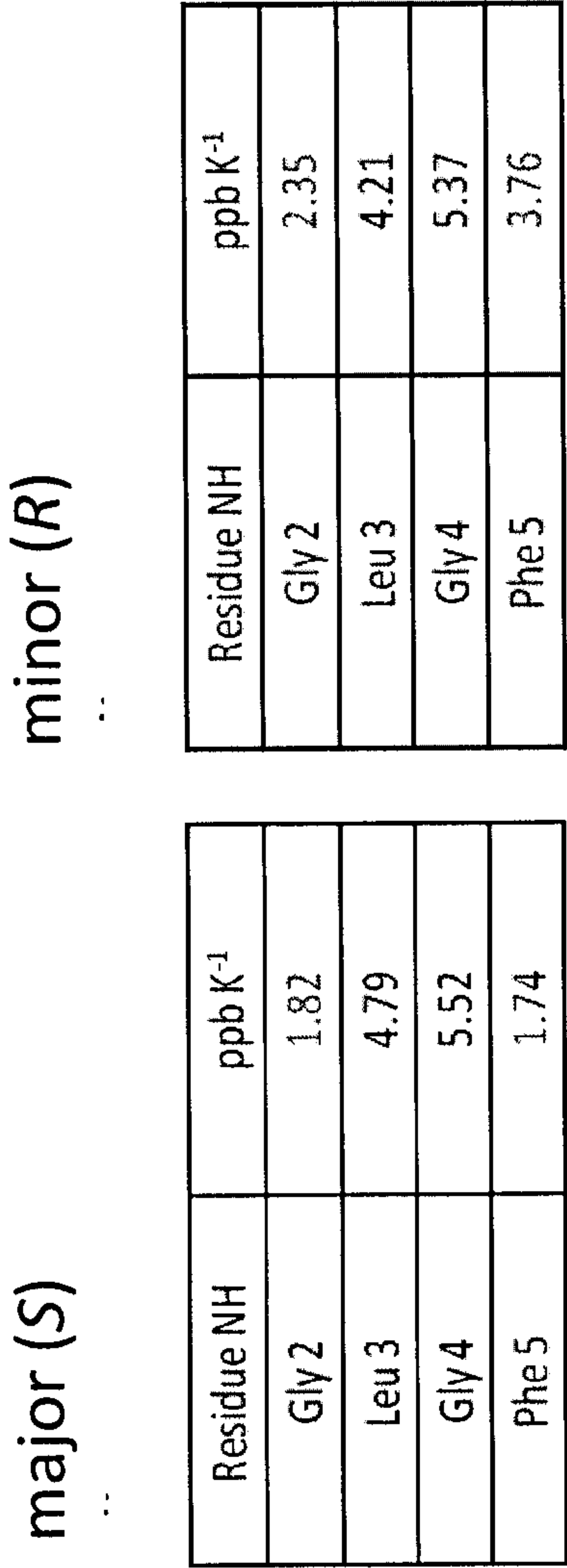


FIGURE 4

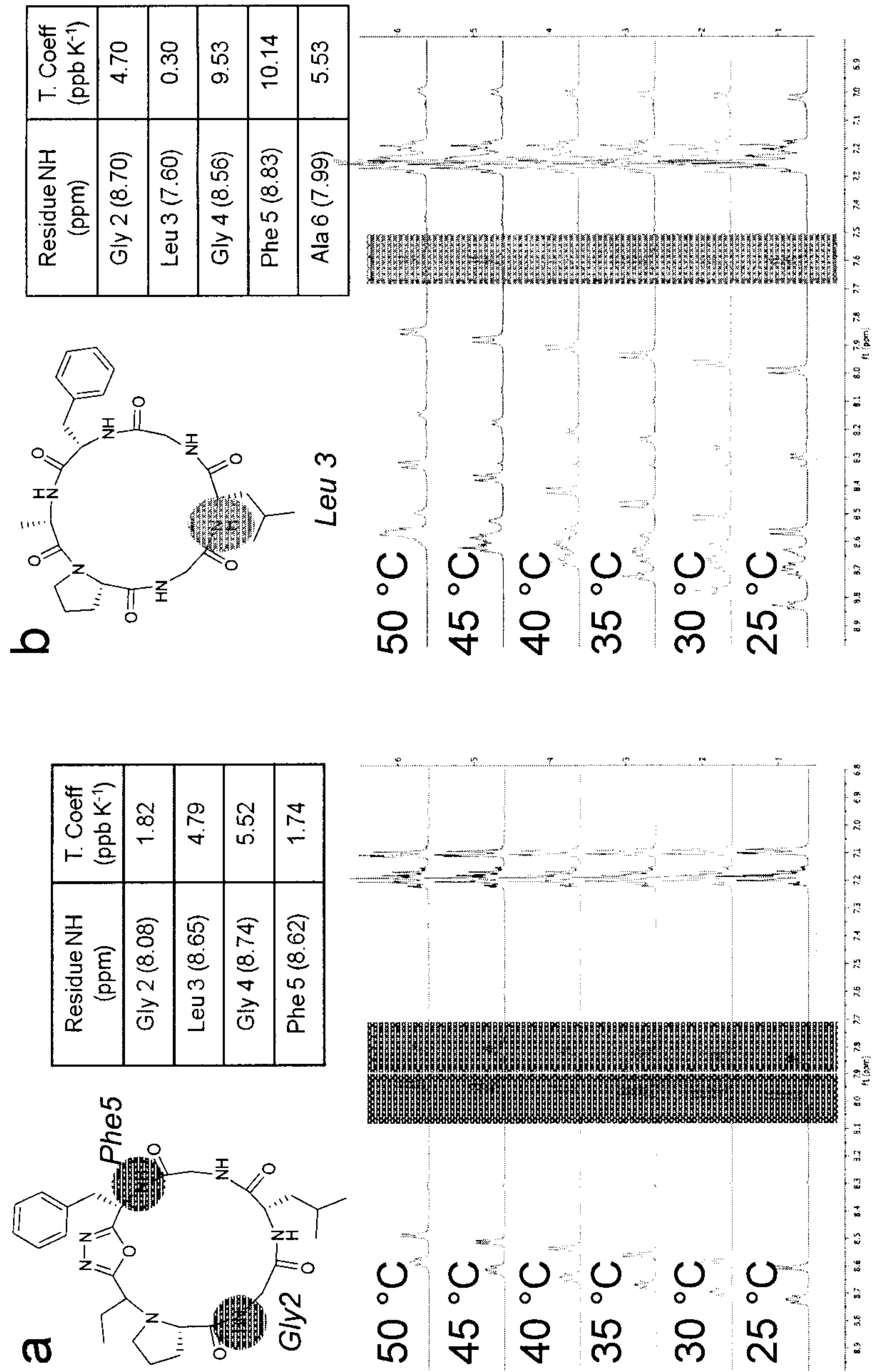
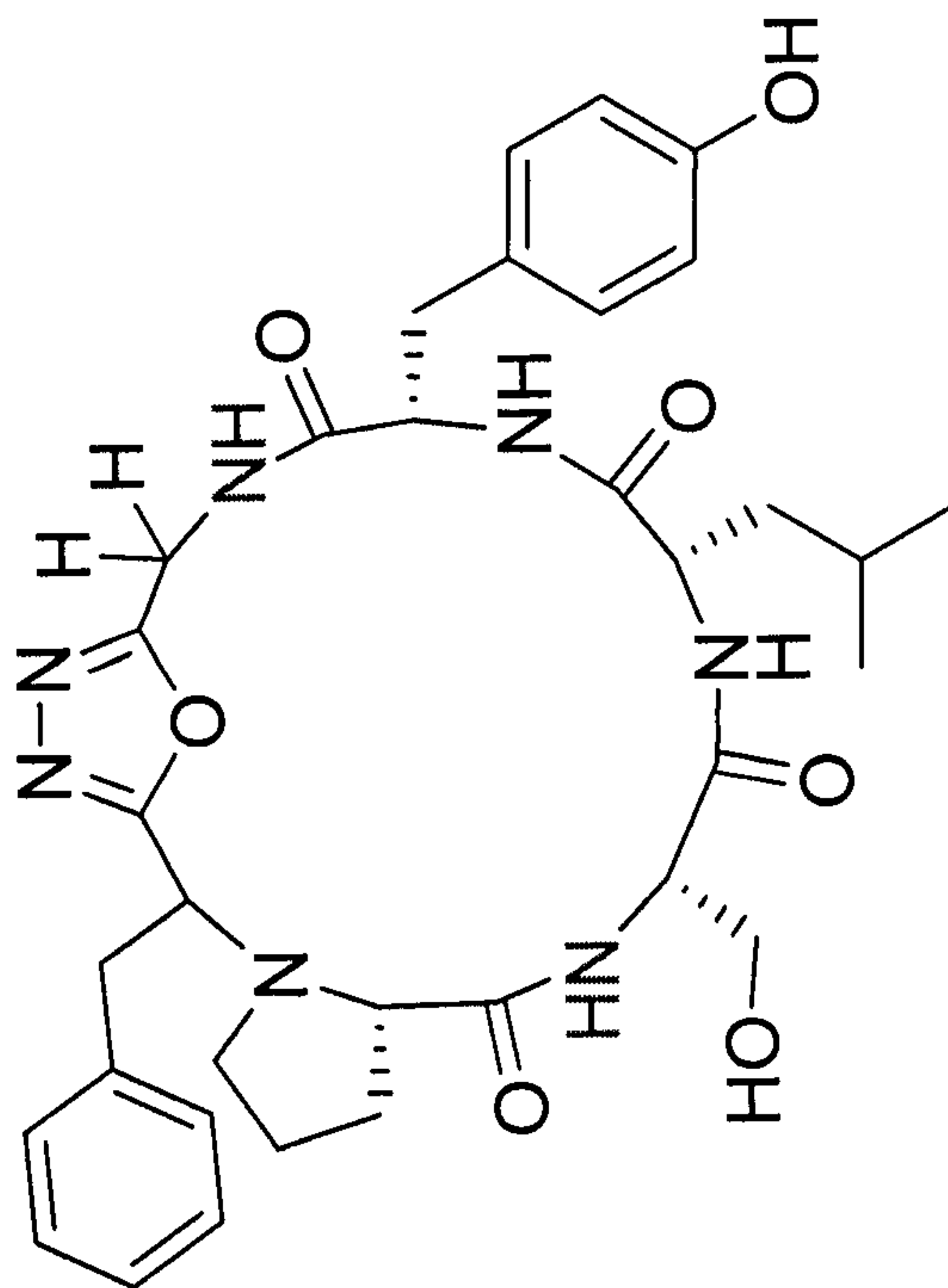


FIGURE 5



Residue NH	ppb K ⁻¹
Ser 2	1.64
Leu 3	5.25
Tyr 4	4.12
Gly 5	1.12

FIGURE 6

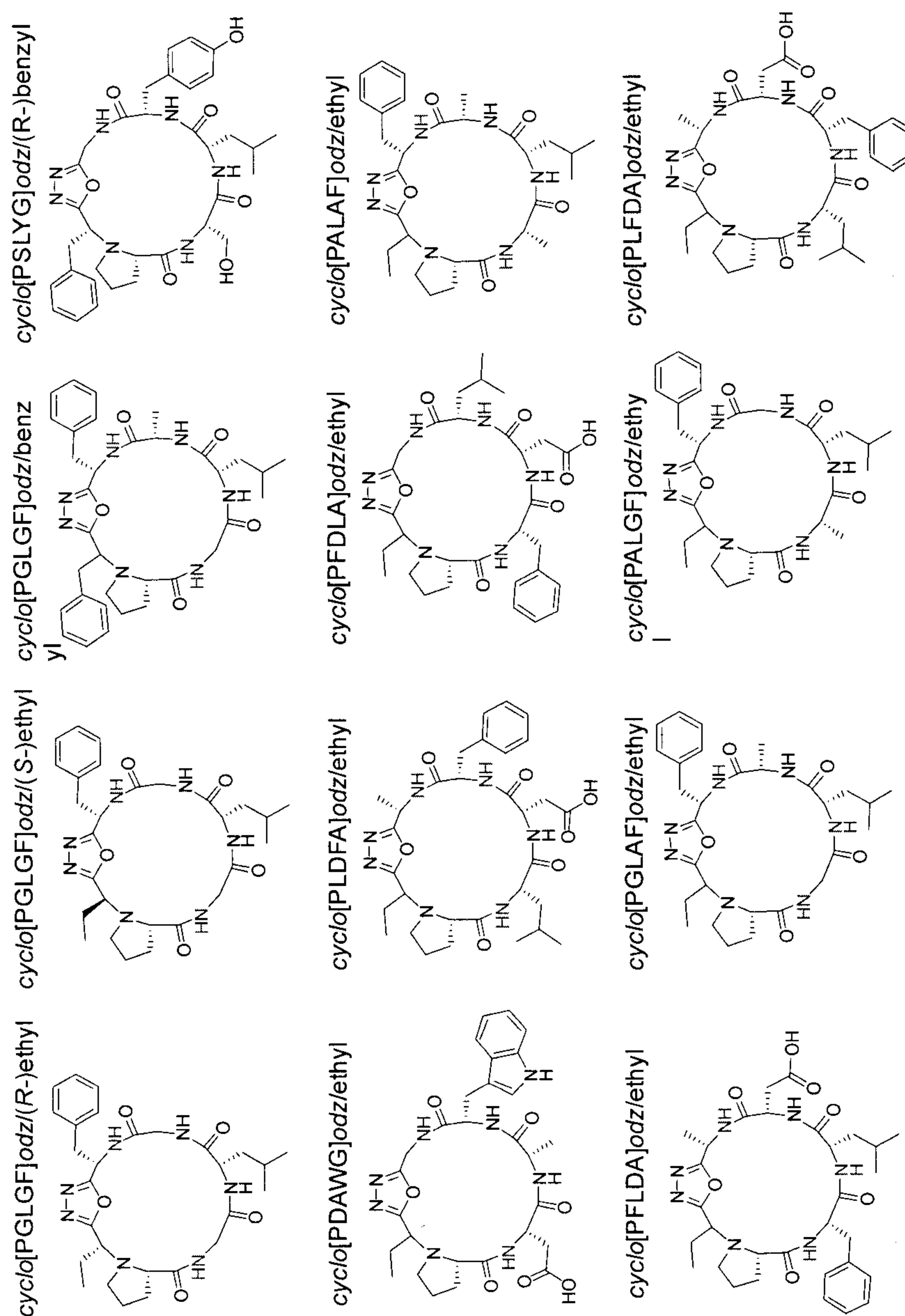


FIGURE 7

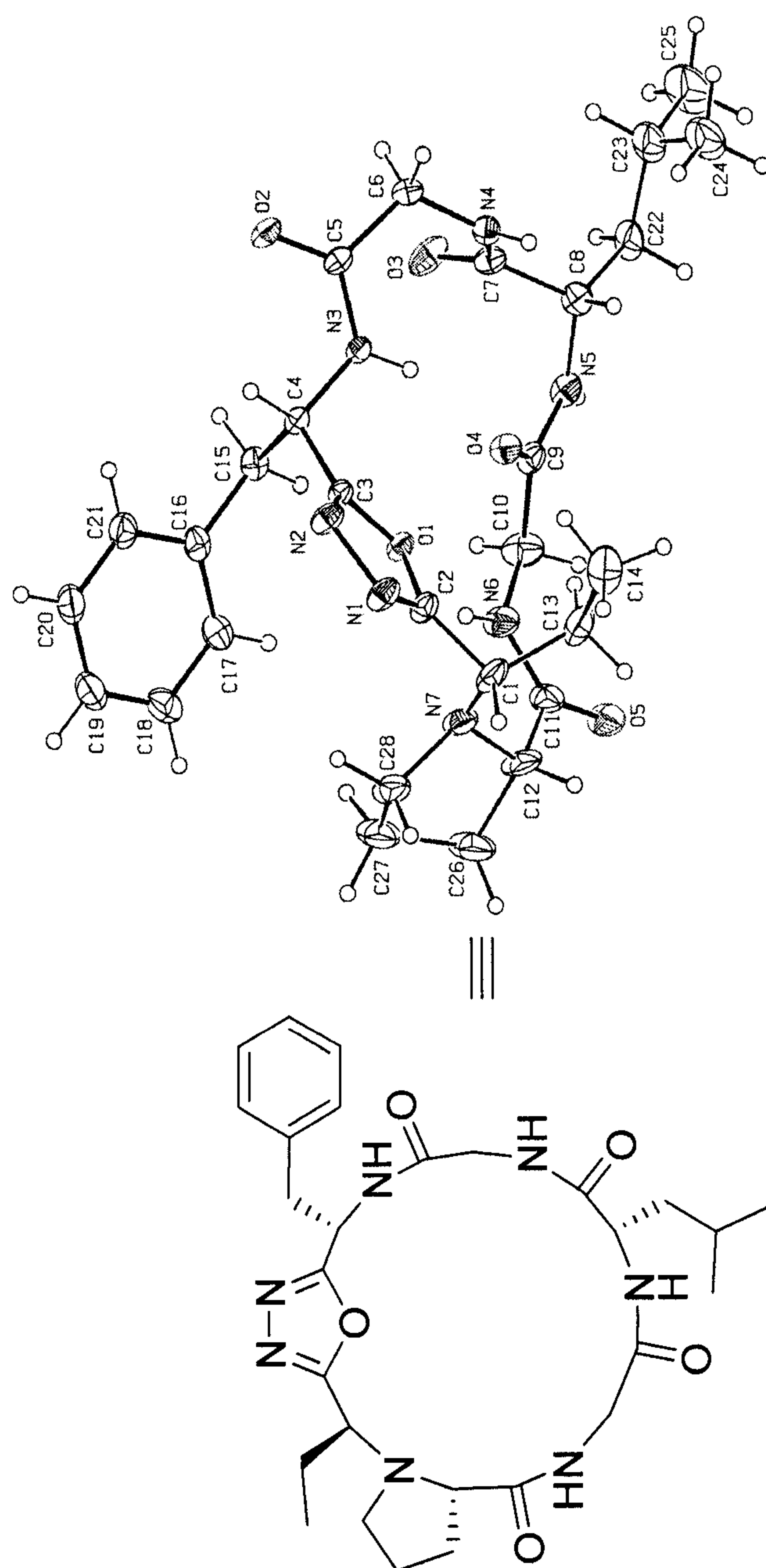
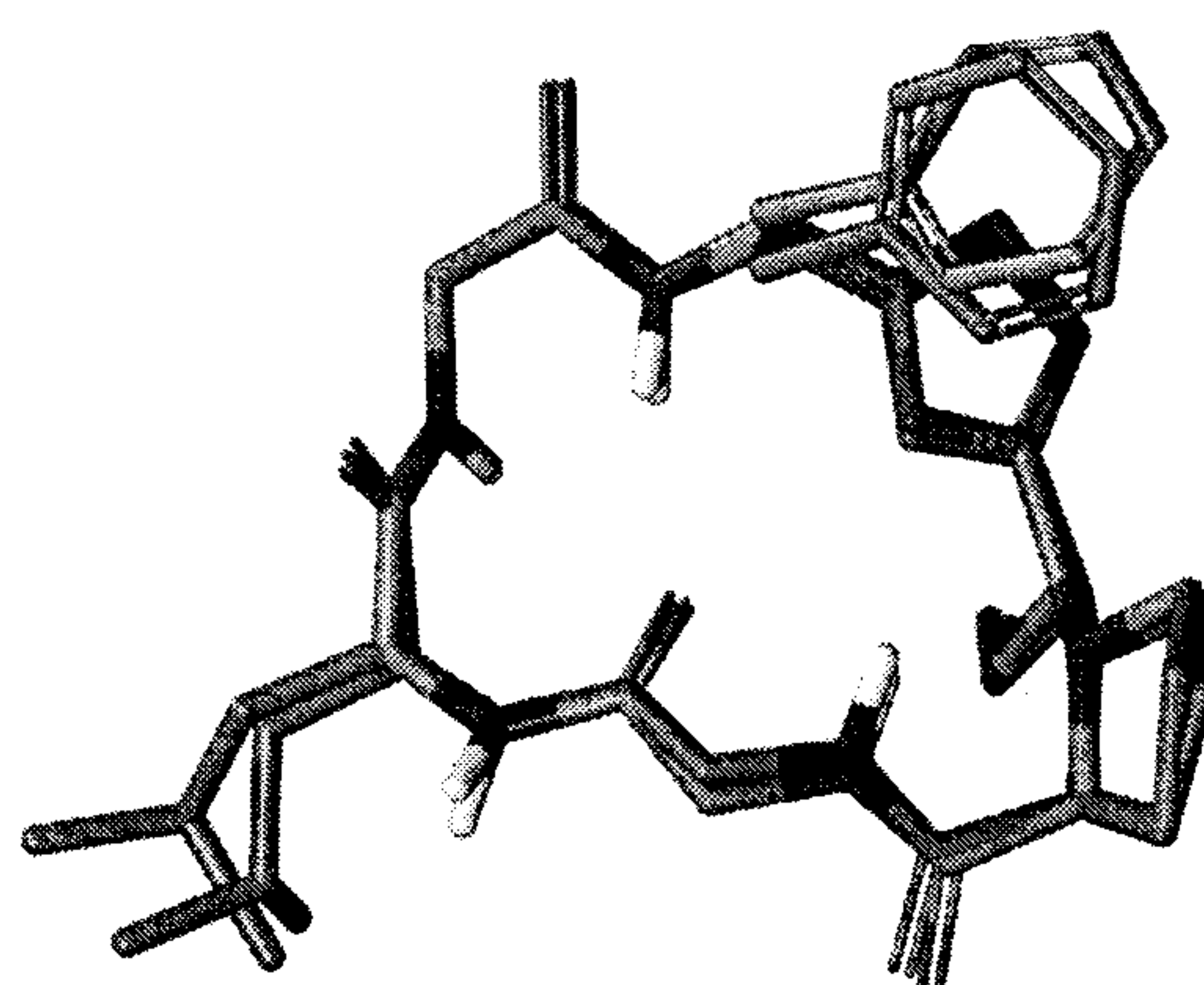
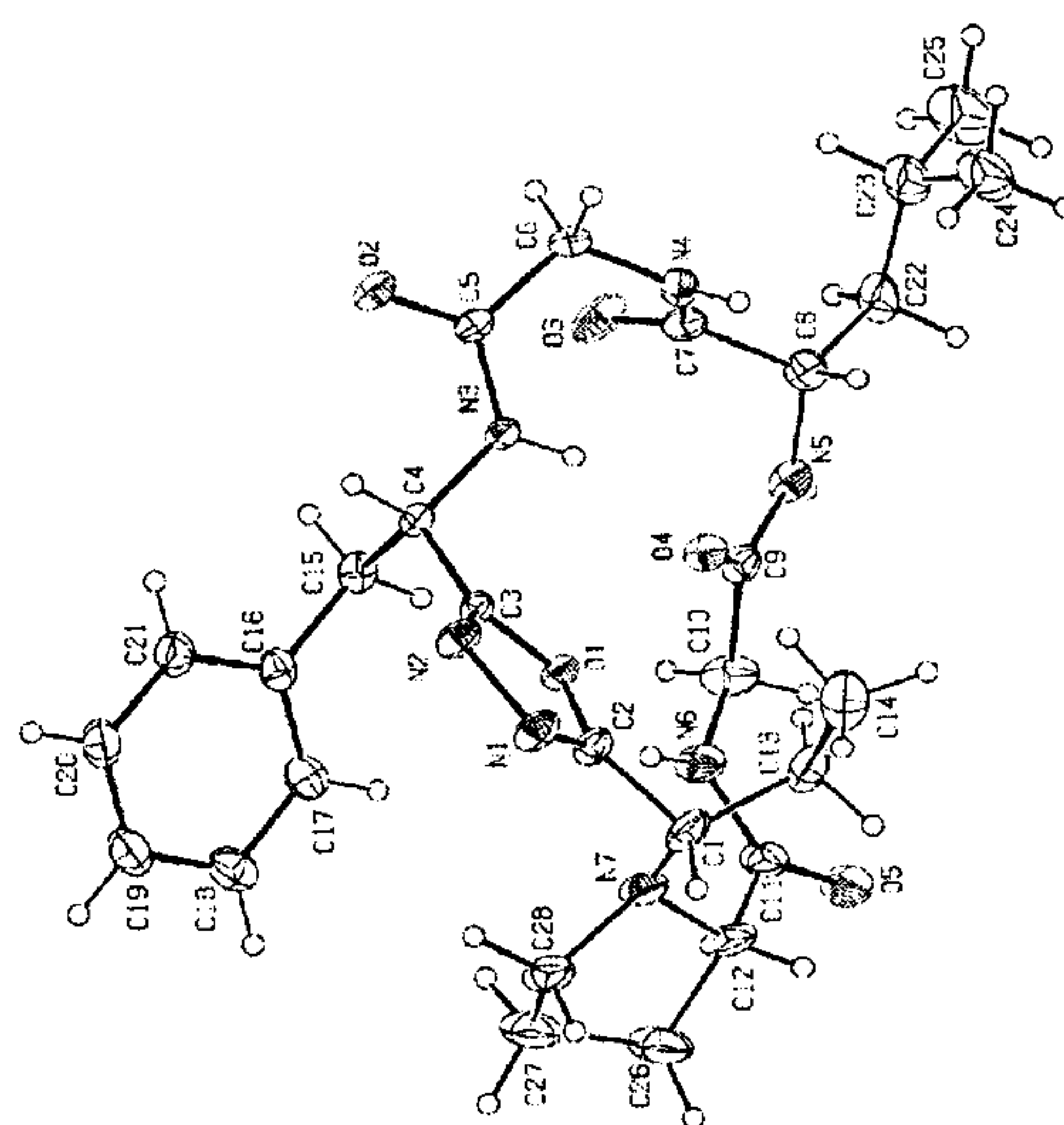
Crystallographic Data for *cyclo*[PGLGF]odz/ethyl (1)

FIGURE 8



B



A

FIGURE 9

V

Entry	R1	R2	R3	R4	R5	-logP _e
1	-CH ₂ CH ₃	-H	-H	-	-	5.81
2	-CH ₂ CH ₃	-H	-CH ₃	-	-	5.96
3	-CH ₂ CH ₃	-CH ₃	-H	-	-	5.42
4	-CH ₂ CH ₃	-CH ₃	-CH ₃	-	-	5.47
5	-CH ₂ CH ₃	-CH ₂ Ph	-CH ₂ CH(CH ₃) ₂	-	-	4.89
6	-CH ₂ Ph	-H	-H	-	-	5.27
7	-CH ₂ CH(CH ₃) ₂	-H	-H	-	-	5.27
8	-	-	-	-H	-H	6.89
9	-	-	-	-H	-CH ₃	8.06
10	-	-	-	-CH ₃	-H	7.13
11	-	-	-	-CH ₃	-CH ₃	7.33
12	-	-	-	-CH ₂ Ph	-CH ₂ CH(CH ₃) ₂	4.94

FIGURE 10

B

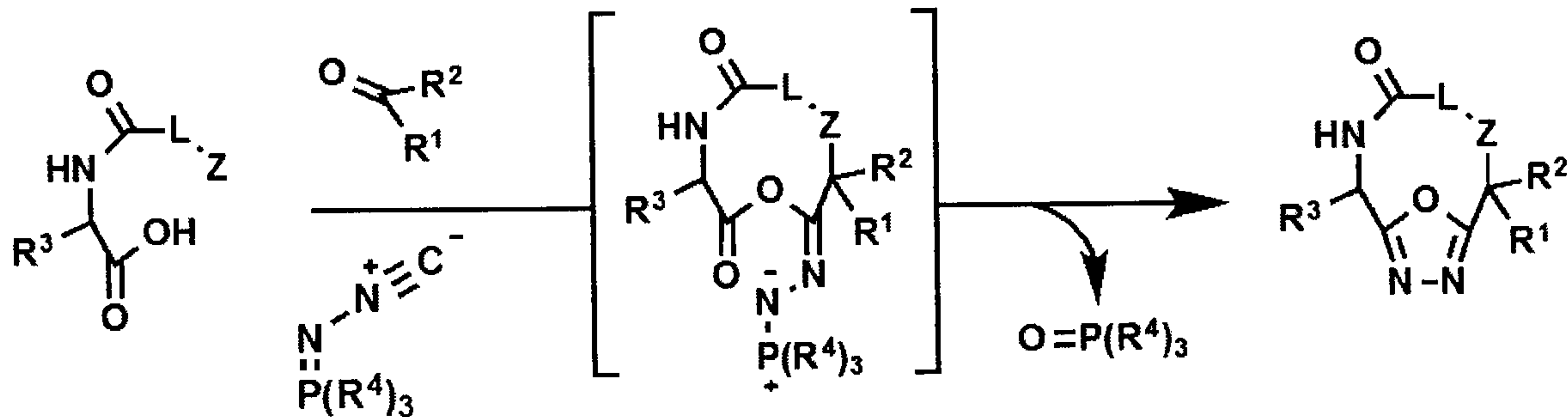


FIGURE 1