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Highly Efficient Synthesis of Covalently Cross-Linked Peptide Helices by Ring-Closing Metathesis**

Helen E. Blackwell and Robert H. Grubbs*

Due to the frequency of helical secondary structures in peptides and proteins,[1] considerable effort has been directed toward the design of small-molecule helix mimetics and stabilized helix structures. Designed organic template molecules that initiate α-helix formation in peptide sequences have been reported.[2] Short α-helical peptides have also been stabilized by incorporation of naturally occurring capping motifs[3] and by stabilization of the intrinsic helix dipole.[4] Notably, significant progress has been made toward stabilizing synthetic α-helical peptides through the incorporation of covalent or noncovalent linkages between constituent amino acid side chains. Examples include salt bridges,[5] lactams,[6] disulfide bridges,[7] hydrophobic interactions,[8] and metal ligation between natural[9] and unnatural amino acids.[10] In several of these cases, it was found that substantial helix stabilization was achieved when the linkage was placed between the i and $i+4$ residues in the peptide backbone. Such a linkage encompasses approximately one turn of the helical peptide backbone and places the tethered side chains on the same side of the helix. Recently, the extraordinary functional group tolerance of olefin metathesis catalyst $[(PCy_3)_2Cl_2Ru{=}CHPh]$ (**1**)[11] has enabled the synthesis of cyclic amino acids[12] and peptides exhibiting β-turn[13] and β-sheet[14] secondary structure by ring-closing olefin metathesis (RCM).[15] This transformation effectively introduces nonnative carbon – carbon bond constraints which may afford enhanced biostability. Here we present a concise synthesis and structural analysis of a series of cyclic helical peptides wherein RCM is used to incorporate a carbon – carbon tether between amino acid side chains.

We chose to study hydrophobic peptide model systems from the outset, because the use of apolar sequences permits characterization of conformation in poorly solvating organic solvents where folding is mainly controlled by intramolecular hydrogen bonding, nonbonding interactions, and electrostatic effects.[16] We became interested in a hydrophobic peptide (**2**) studied by Karle and Balaram et al.,[17] whose solubility in organic solvents would be compatible with alkylidene **1**.[18] Heptapeptide **2** contains two repeat units of valine – alanine – leucine (Val-Ala-Leu) separated by one α-aminoisobutyric acid residue (Aib), as shown schematically in Figure 1. The Aib residue is known to stabilize 3_{10}- and/or α-helical

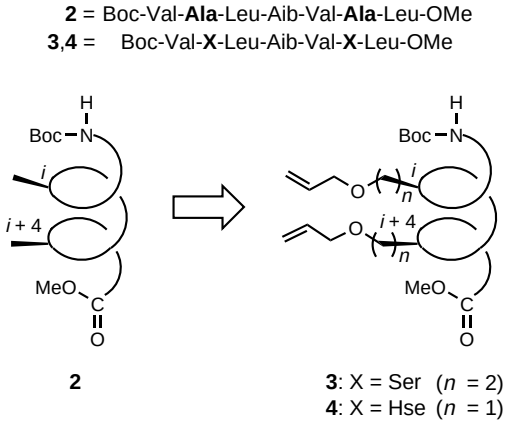

Figure 1. Karle and Balaram's heptapeptide **2**, and two dienic analogues **3** and **4**. Boc = *tert*-butoxycarbonyl.

conformations in apolar oligopeptides and is frequently found in peptides produced by microbial sources.[19] Examples of such Aib-rich peptides include the antibiotics alamethicin, zervamicin, and trichogin A IV, which are purported to adopt helical conformations within lipid bilayer membranes and aggregate therein to form ion channels. Heptapeptide **2** was shown to adopt an α-helical conformation in the solid state by X-ray crystallography and was found to adopt a similar helical conformation in $CDCl_3$ by solution-phase 2D NMR analyses.

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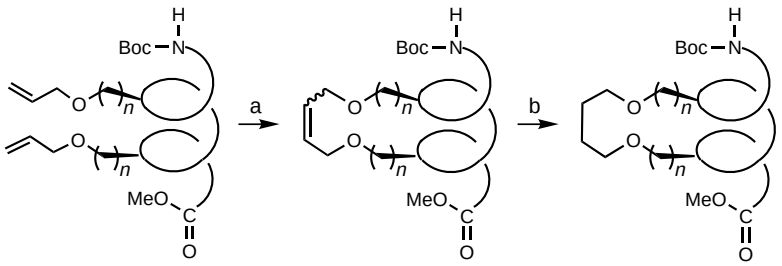
Encouraged by these structural results, we endeavored to use heptapeptide **2** as a scaffold upon which to build acyclic peptide dienes. Furthermore, we were excited about the prospect of eventually applying RCM to the synthesis of constrained analogues of the previously mentioned peptide antibiotics in order to probe the requirements of a helical conformation on their ion channel forming activity.

Through analysis of the structure of **2** and molecular modeling, we predicted that replacement of the i and $i+4$ Ala residues of **2** with residues containing unbranched terminal olefin groups in the side chains would place the two olefins in proximity to one another, provided our dienic analogues also adopted a helical conformation and the derivatized side chains were of appropriate length. L-Serine (Ser) and L-homoserine (Hse) *O*-allyl ethers were selected as olefin-containing residues due to their ready availability and trivial derivatization as allyl ethers.[20] Acyclic peptide dienes **3** and **4**, shown schematically in Figure 1, were then prepared by standard solution-phase peptide chemistry.[21]

Dienes **3** and **4** were each treated with alkylidene **1** (20 mol% **1**, 5 mM in **3** or **4**, $CHCl_3$, 25 °C, 3–4 h) to yield 21- and 23-membered macrocyclic alkenes **5** and **6** in 85 and 90% yields, respectively (Scheme 1).[22] Each macrocycle was



Scheme 1. Synthesis of peptide macrocycles. a) 20 mol% of **1**, $CHCl_3$, 25 °C; b) cat. 10% Pd/C, 1 atm H_2, EtOH, 25 °C.

isolated as a mixture of olefin isomers (ca. 5:1 *E*/*Z*).[23] Catalytic hydrogenation (10% Pd/C, 1 atm H_2, EtOH, 25 °C, 2 h) then afforded the saturated species **7** and **8** in excellent yields.[24] The high yield and relatively fast rate of the RCM transformation suggested that the acyclic dienes were preorganized for ring closure in organic solvents. This prompted closer examination of the structures of acyclic peptides **3** and **4**, along with cyclic products **7** and **8**.

Far-UV circular dichroism (CD) spectra of solutions of peptides **3**, **4**, **7**, and **8** in trifluoroethanol (TFE) at 25 °C are shown in Figure 2. For peptides and proteins, TFE has been shown to be a strongly helix-promoting solvent comparable to $CHCl_3$,[25] and thus CD measurements in TFE can be correlated to the conformations accessed by the peptides during the RCM reaction. Two negative bands at approximately 203–205 (π-π*) and 218–222 nm (n-π*) are observed for all four compounds, transitions characteristic of largely helical conformations in short peptides. The n-π* absorptions are considerably weaker than those for π-π*, a trend that has been observed experimentally for numerous short 3_{10}-helical

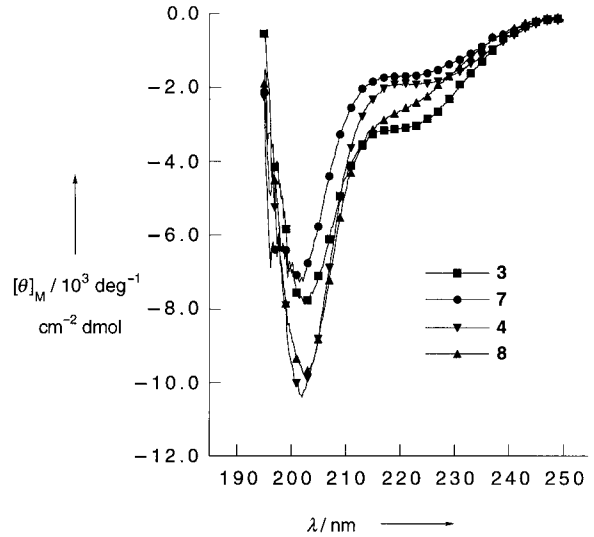


Figure 2. CD spectra (250–195 nm) of peptides **3**, **4**, **7**, and **8** (1 mM) in TFE at 25 °C. Total molar ellipticity values are given.

peptides[26] and reported recently to be the standard CD pattern for right-handed 3_{10}-helical peptides by Tonolio and co-workers.[27] Importantly, these data suggest that the peptide backbones of dienes **3** and **4** are *preorganized* in a helical conformation for RCM in organic solvents. Furthermore, the ellipticities for macrocycles **7** and **8** do not appear to differ noticeably from their acyclic precursors **3** and **4**, indicating that significant conformational change did not take place upon cyclization.[28]

Cyclic peptide **8** exhibited high crystallinity, enabling an X-ray crystal structure to be obtained (Figure 3).[29] When one views the peptide from the N to C terminus, it appears that the peptide backbone is helical for the first five residues and then the helix begins to fray for the last two (Hse 6 and Leu 7).[30] The average torsional angles ϕ (about N–C^{α}) and φ (about C^{α}–C′) for the first five residues are −57 and −34°, respectively, which approximate those for a right-handed 3_{10}-helix (−57 and −30°).[31] These torsional angles are marginally close to those for the average right-handed α-helix ($\phi = -63°$, $\varphi = -42°$), and therefore it is difficult to exclude the possibility of the peptide being α-helical or accessing a mixed $\alpha/3_{10}$-helix conformation. However, analysis of the amide N to carbonyl O distances (N···O) and respective angles (N···O=C) supports the presence of four consecutive 4→1 intramolecular hydrogen bonds (2.96–3.01 Å), involving N3–N6 and O2–O5, which are diagnostic of a 3_{10}-helix.[32] This iterative hydrogen-bonding pattern involves the carbonyl O and amide NH of amino acids that are two residues apart.[33, 34] We speculate that the Leu 3 carbonyl O5 could also be involved in a fifth extremely long 5→1 hydrogen bond with the Leu 7 amide N7 (N···O 3.50 Å), which may be lengthened due to the disorder of the helix at the C-terminus. Thereafter, the 4→1 hydrogen-bonding pattern is continued intermolecularly in a head-to-tail fashion, with the Val 5 carbonyl O7 hydrogen bonding to the Val 1 Boc amide N1 (N···O 2.91 Å) of the adjacent peptide molecule in

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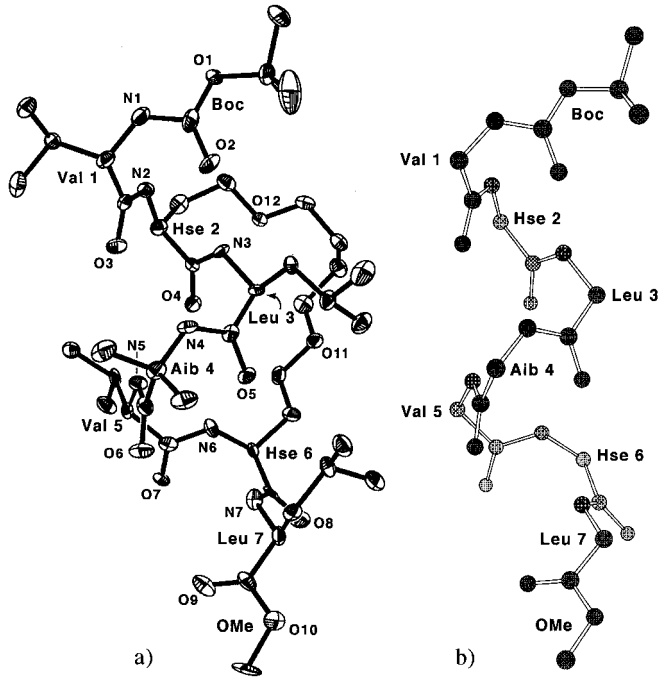

Figure 3. a) ORTEP diagram of the X-ray crystal structure of cyclic peptide **8**. Thermal ellipsoids represent 30% probability levels. Hydrogen atoms have been omitted for clarity. b) Chem 3D rendering of **8** without amino acid side chains.

the unit cell.[35] The evidence suggests that replacement of the two Ala residues in peptide **2** with tethered Hse residues in peptide **8** has induced the peptide backbone to transform from an α-helix to a predominantly 3_{10}-helix in the solid state. The constraint imposed by the side chain linkage in peptide **8** could be cause for this unique conformational shift.[36]

Acyclic dienes incorporated into a helical peptide scaffold have been treated with alkylidene **1** to afford macrocyclic peptide helices by a remarkably facile ring-closing metathesis reaction. The relative ease of introducing carbon–carbon bonds into peptide secondary structures by RCM and the predicted metabolic stability of these bonds renders olefin metathesis an exceptional methodology for the synthesis of rigidified peptide architectures. Specifically, we believe the macrocyclization of hydrophobic peptide helices is uniquely suited to RCM in organic solvents because helical conformations are frequently favored in apolar media. We are now applying RCM to the synthesis of cyclic/tethered analogues of naturally occurring helical peptide antibiotics (e.g. the trichogin family of lipopeptaibols) with the intent of exposing the requirements of a helical conformation on their activities.[37] Future work is also directed toward the syntheses of tethered peptide helix bundles and helix-turn-helix motifs by RCM, for potential use as peptide ligands for proteins and DNA. The recent advent of water-soluble olefin metathesis catalysts has accelerated our pursuit toward such complex, biologically relevant structures.[38]

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[23] Each set of olefin isomers proved inseparable on silica gel. The ratio of olefin isomers was estimated by ^1H NMR integration.
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The average R value for **3**, **4**, **7**, and **8** is 0.3. See: C. Toniolo, A. Polese, F. Formaggio, M. Crisma, J. Kamphuis, *J. Am. Chem. Soc.* **1996**, *118*, 2744 – 2745.

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[29] Colorless crystals of **8** were grown from CH_2Cl_2/hexane; crystal dimensions $0.3 \times 0.5 \times 0.5$ mm, orthorhombic, space group $P2_12_12_1$, $Z = 4$, $a = 19.30(1)$, $b = 24.73(2)$, $c = 12.134(7)$ Å, $V = 5791(6)$ Å^3, $\rho_{calcd} = 1.246$ g cm^{-3}; $2\theta = 1.6 - 50.0^\circ$ ($Mo_{K\alpha}$ radiation, $\lambda = 0.7107$ Å, graphite monochromator, 2θ-θ scan, $T = 156$ K); 4698 reflections measured, 2266 unique data used [$I > 3.0\sigma(I)$]; no absorption corrections were applied; direct methods (SHELXTL 86), refinement with full-matrix least squares, hydrogen atoms refined isotropically, all other atoms refined anisotropically; $R = 0.066$, $R_W = 0.077$; maximum residual electron density 0.80 e Å^{-3}; GOF = 2.28 for 633 variables. Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Center as supplementary publication no. CCDC-101810. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

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[32] The 4 → 1 N ··· O=C angles for these four hydrogen bonds range from 118 to 131°.

[33] The analogous hydrogen-bonding pattern in α-helices is 5 → 1, spanning three residues. See reference [30].

[34] ^{1}H NMR solvent titration experiments in $CDCl_3$/$(CD_3)_2SO$ mixtures (5 mM, 25 °C) suggest that **8** may exist as a 3_{10}-helix in $CDCl_3$. Full solution-phase 1D and 2D ^{1}H NMR analyses of peptides **3**, **4**, **7**, and **8** will be reported in a separate publication.

[35] All peptide helix axes are parallel in the unit cell of **8**. Head-to-tail hydrogen bonding is commonly observed in crystalline hydrophobic peptide helices. See reference [16].

[36] The different medium from which **2** and **8** were crystallized (CH_2Cl_2/hexane for **8**; methanol/H_2O for **2**) may contribute to the disparity in their crystal structures.

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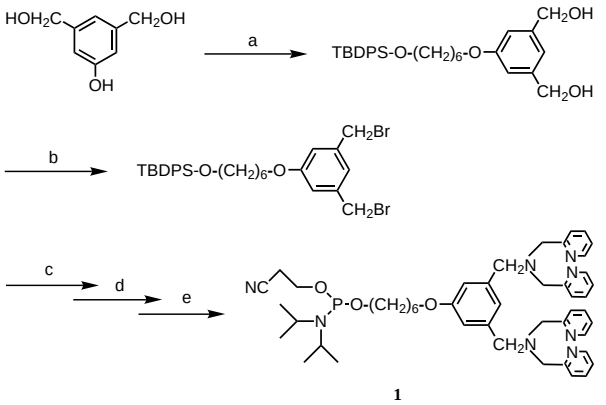
Conjugates of a Dinuclear Zinc(II) Complex and DNA Oligomers as Novel Sequence-Selective Artificial Ribonucleases**

Shigeo Matsuda, Akira Ishikubo, Akinori Kuzuya, Morio Yashiro, and Makoto Komiyama*

The sequence-selective scission of RNA has been attracting interest because of its potential applications, both in vivo and in vitro.[1] Artificial ribonucleases have been prepared by attaching catalytically active metal ions (mostly lanthanide ions) to DNA oligomers as sequence-recognizing moieties.[2–4] However, the following limitations remain: 1) divalent metal ions such as Zn^{II} and Mg^{II}, which are widely spread in vivo,[5] cannot be used, and 2) selective scission can be achieved only when free metal ions are absent in the reaction mixtures (otherwise, nonselective scission becomes dominant). Further progress is desirable.

It has previously been shown that dinuclear Zn^{II} complexes hydrolyze RNA under physiological conditions.[6, 7] Although the Zn^{II} ion itself is a rather poor candidate for RNA hydrolysis, a notable activity appears when two of them cooperate. Here we report that conjugates of a dinuclear Zn^{II} complex and DNA oligomers selectively hydrolyze RNA at the target site, even in the presence of a considerable amount of free Zn^{II} ions.

Phosphoramidite monomer **1** containing a *N*,*N*,*N*′,*N*′-tetrakis(2-pyridylmethyl)-3,5-bis(aminomethyl)benzene (TPBA) group was prepared according to Scheme 1. By use of **1** and



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Scheme 1. a) K_2CO_3, [18]crown-6, THF, reflux, 26 h; b) CBr_4, PPh_3, THF, 0 °C, 1 min; c) *N*,*N*-bis(2-pyridylmethyl)amine, *N*,*N*-diisopropylethylamine, CH_3CN, room temperature (RT), 20 h; d) tetrabutylammonium fluoride, THF, RT, 1 h; e) $(iPr_2N)_2PO(CH_2)_2CN$, 1*H*-tetrazole, CH_3CN, RT, 90 min. TBDPS = *tert*-butyldiphenylsilyl.

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