ORGANIC LETTERS

2001
Vol. 3, No. 24
3839−3842

Highly Enantioselective Enone Epoxidation Catalyzed by Short Solid Phase-Bound Peptides: Dominant Role of Peptide Helicity†

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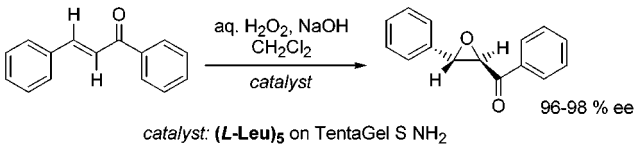
Received August 24, 2001

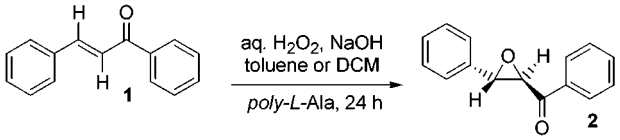
ABSTRACT



The series of L-Leu 1–20-mers, peptides carrying 1–5 N-terminal Gly residues, and oligomers of (*S*)-β^3-Leu and (1*R*,2*R*)-2-aminocyclohexanecarboxylic acid were synthesized on TentaGel S NH_2. Five L-Leu residues were found sufficient to catalyze the Juliá–Colonna epoxidation of chalcone with 96–98% ee. Experiment and molecular modeling suggest that catalysis is effected by binding of the enone to the N-terminus, and the helicity of the peptide determines the epoxide configuration through face-selective delivery of a hydroperoxide anion.

In 1980, Juliá and Colonna reported that polymeric amino acids catalyze the Weitz−Scheffer epoxidation of chalcone **1** in a highly enantioselective and intriguingly simple manner (Scheme 1): Their reaction system comprised aqueous alkaline hydrogen peroxide, the enone in a water-immiscible solvent (e.g., toluene or dichloromethane), and the polyamino acid which is insoluble both in water and the organic solvent and thus forms a third phase.[1]

Scheme 1. The Juliá−Colonna Epoxidation of Chalcone



In the subsequent years, a number of modifications and improvements have been introduced, mainly by S. Roberts et al.[2] For example, reaction rates could be increased by using a biphasic system consisting of urea−H_2O_2 and DBU in THF as solvent.[3] The potential of the Juliá−Colonna epoxidation for the enantioselective synthesis of, for example, pharmaceuticals has been demonstrated.[4]

Despite all efforts, the substrate spectrum of this peptide-catalyzed epoxidation of enones is still fairly narrow. For example, the synthetically most important endocyclic enones (such as cyclohexenones or quinones) or *Z*-enones in general are not suitable substrates. Clearly, the rational development of catalysts for these substrate classes requires mechanistic knowledge.

† Dedicated to Prof. Dr. Dr. h.c. Lutz F. Tietze on the occasion of his 60th birthday.

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10.1021/ol0166451 CCC: $20.00
Published on Web 11/09/2001

A number of studies on the effect of sequence on the catalytic efficiency can be found in the literature,[5,6] both on "free" peptides and on those bound to either soluble PEG polymers or to polystyrene supports by means of ester linkers. In summary, all these studies showed that (i) modifications at the N-terminal region of the peptide had the most pronounced effect on catalyst performance and that (ii) there is a correlation between the degree of helicity (as assessed by IR spectroscopy) and the catalytic activity of the oligo-peptides.[6]

We reasoned that the most fundamental question to be addressed is the minimum chain length of a catalytically competent peptide. To eliminate complications by aggregation of free hydrophobic peptides in solution, we decided to synthesize L-Leu oligomers of varying chain lengths (1−20) directly on TentaGel S NH_2.[7] Thus, the peptides are linked to the solid support by a chemically robust amide group and the relatively low loading of the support favors the monomeric state of the peptide(s). These materials were employed in the triphasic epoxidation of chalcone **1** with alkaline hydrogen peroxide, using methylene chloride as organic solvent.[7] The results are summarized in Figure 1.

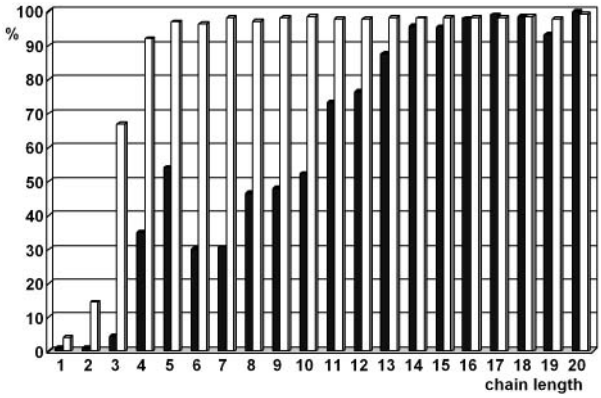

Figure 1. Effect of oligo-L-Leu chain length on catalytic performance. The light columns denote the enantiomeric excess of (2*R*,3*S*)-chalcone epoxide **2** and the black columns refer to the yield of epoxide **2** obtained after 24 h.

Maximum enantioselectivity (96−98% ee) is achieved with as little as five L-Leu residues, whereas the epoxide yields increase gradually and level off around the 14-mer. Since four amino acid residues are required to form one turn of an α-helix,[8a] we conclude that one intact helical turn is the minimum structural element necessary for efficient asymmetric induction. The increase of catalytic activity (i.e., epoxide yield, Figure 1) with chain length reflects the increasing proportion of α-helix present in the equilibrium mixture of peptide conformers.

The obvious binding site for the partially negative charged carbonyl oxygen atom of the substrate enone is the N-terminus, with its partial positive charge and three NH bonds not involved in intrahelix H-bonding. Numerous protein X-ray crystal structures demonstrate that the N-terminus of α-helices is a common motif for, for example, phosphate binding.[8] To probe the catalytic function of the N-terminus, we synthesized an "inverse" L-Leu hexamer on TentaGel S COOH.[7] This oligopeptide, which is attached to the solid phase by its N-terminus and has a free COOH group, was indeed inactive (≤1% conversion after 24 h).

β-Amino acids such as (1*R*,2*R*)-2-aminocyclohexanecarboxylic acid **3**[9] or (*S*)-*β*^{3}-leucine **4** are known to form stable helices much more readily than α-amino acids. However, the orientation of the NH bonds within the typical *β*-peptidic helices (so-called 14- or 3_1-helices) is opposite to those of α-helices (Figure 2a,b). Starting from *N*-Fmoc-**3**[10] and

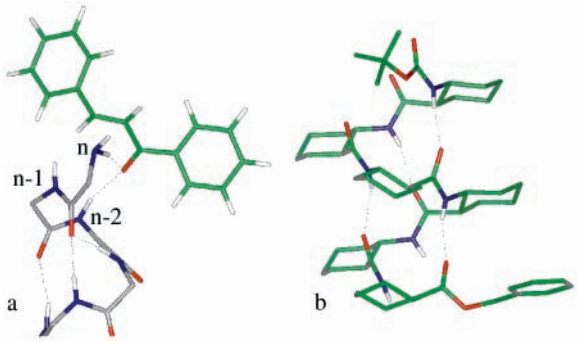

Figure 2. (a) Chalcone bound to the N-terminus of an α-helix and hydrogen bonds between the carbonyl O-atom, the N-terminus, and NH (n-2). (b) 14-Helix of the 2-aminocyclohexanecarboxylic acid hexamer (from ref 9a). Note the opposite orientation of NH bonds.

N-Fmoc-**4**,[11] we synthesized the series of the 1−5-mers of **3** and **4**, again on TentaGel S NH_2 (Scheme 2).[7] As it turned out, none of these *β*-amino acid oligomers showed catalytic activity (≤1−2% conversion after 24 h). The above results again emphasize the importance of hydrogen bonding at the N-terminus.

To shed further light on the possible binding modes of the substrate chalcone **1** to the N-terminus of a typical α-helix, we initiated a molecular modeling study [docking experiments, conformational analyses of the peptide−chal-

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(7) See Supporting Information for preparative details.

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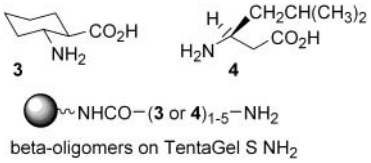
(10) Our synthesis of N-Fmoc **3** and N-Fmoc *ent*-**3** will be published elsewhere.

(11) (a) Guichard, G.; Abele, S.; Seebach, D. *Helv. Chim. Acta* **1998**, *81*, 187. (b) Müller, A.; Vogt, C.; Sewald, N. *Synthesis* **1998**, 837.

Scheme 2. β-Amino Acids and TentaGel-Bound Oligomers



cone adducts (Monte Carlo search)].[12] Invariably, H-bonding to the enone carbonyl O-atom involved the N-terminal NH (residue n)[13] and the NH group of residue n-2 (Figure 2a). At first glance, it was tempting to assume that selective shielding of one of the enantiotopic faces of the enone by the isobutyl side chains of oligo-L-Leu may account for enantioselectivity. However, our docking experiments did not indicate any preference for chalcone binding as indicated in Figures 2a and 3a,b compared to an "180°-rotated orientation" (Figure 3c). On the other hand, inspection of the peptide−chalcone complexes strongly suggested a possible role for the NH group of the penultimate amino acid residue (n-1): upon binding of a hydroperoxide anion, the latter is ideally positioned for face-selective delivery to the enone β-carbon atom (Figure 4a,b). This peptide-steered

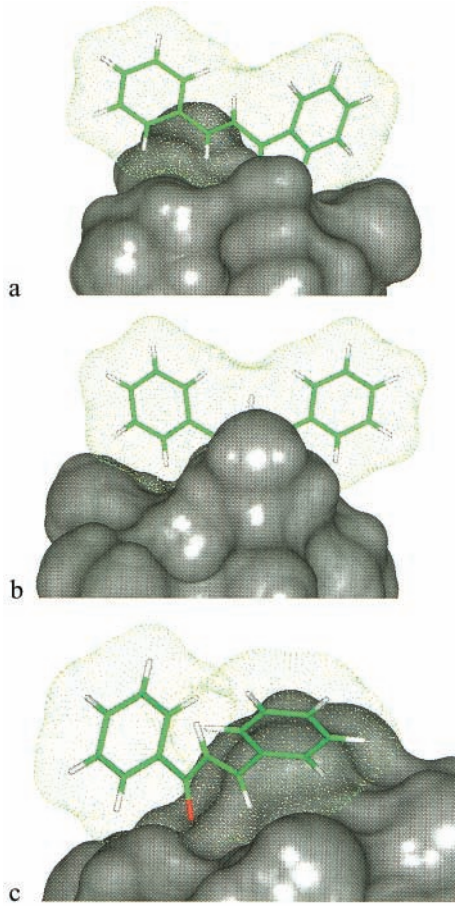


Figure 3. Binding of chalcone **1** to the N-terminus of an L-Leu-α-helix. (a) 2-*Re*-Face of the C=C-double bond accessible, 2-*Si*-face shielded, as shown in (b). (c) 2-*Si*-Face of the C=C-double bond accessible, 2-*Re*-face shielded (not shown).

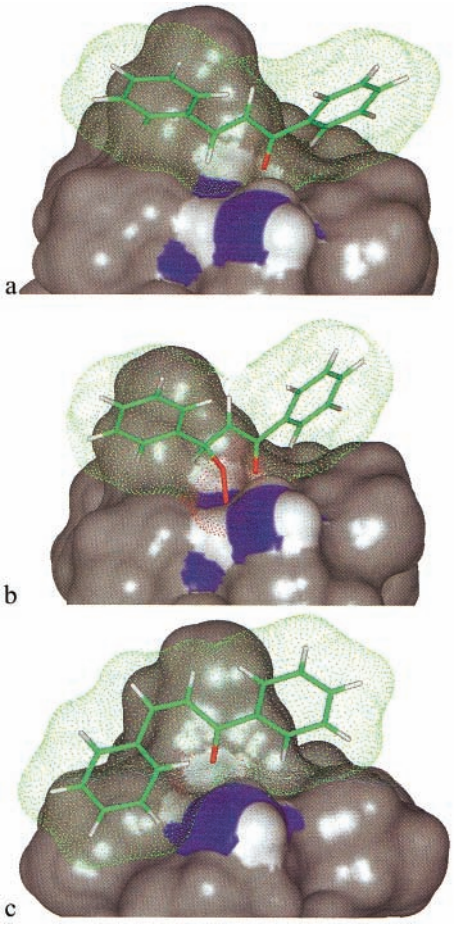


Figure 4. The N-terminus of the α-helix as the active site. (a) Bound chalcone **1**, NH of the terminal and of the preceding two amino acids are shown in blue/white. (b) Bound β-peroxyenolate resulting from the face-selective addition of a hydroperoxide anion to the enone β-C-atom. (c) Bound *Z*-chalcone.

transfer of the nucleophile can occur *only* when the substrate enone is arranged as shown in Figures 2a, 3a, and 4a, but not in the "180°-rotated orientation" (Figure 3c). Furthermore, this model explains why the *E*-configuration of the substrate enones is required. As shown in Figure 4c, docking of *Z*-chalcone prohibits peroxide binding at NH of the penultimate amino acid (n-1). Similarly, the β-C-atom of bound cyclic enones is out of reach of peroxide bound to NH [(n-1), not shown]. Our model furthermore explains why attempts to extend the range of peptide-catalyzed conjugate additions to chalcones beyond epoxidation have thus far met with little success. For example, oligo-peptides do not induce significant enantioselectivity in the related β-alkylation of chalcone by nitronate anions:[1b] whereas H-bonding of NH

(12) See Supporting Information for details of the modeling study.
(13) Analogous binding scenarios are possible when the N-terminus is acylated or alkylated (refs 5 and 6).

(n-1) to one of the nitronate O-atoms may well occur, the C-atom of this three-atom nucleophile is not positioned correctly for attack at C-β of the enone.

The three-point attachment of the substrates to the N-terminus of the α-helix furthermore implies that it is the helical chirality of the peptide backbone which defines the sense of asymmetric induction in the Juliá−Colonna epoxidation and not the central chirality of the α-carbon atoms.

We believe that the catalytically active zone consists of the N-terminal triad of an α-helical segment, but it does not necessarily need to involve the very first three amino acids of the peptide. As with anion binding in larger peptides,[8] the N-terminus of the α-helix may be preceded by nonhelical regions. To probe this assumption, we synthesized the 25 oligomers H_2N-$(Gly)_n$-$(L\text{-}Leu)_m$-CONH−TentaGel. Glycine as a conformationally flexible amino acid was assumed to have no propensity to continue the L-Leu α-helix.[8a] The catalytic activity of these materials is summarized in Figure 5. As expected, the number of preceding Gly residues did not affect the catalytic properties of the L-Leu stretch: again, one helical turn of L-Leu is required ($m \geq 4$) to establish full enantioselectivity, and the ee is basically unaffected by the length of the Gly stretch ($1 \leq n \leq 5$).

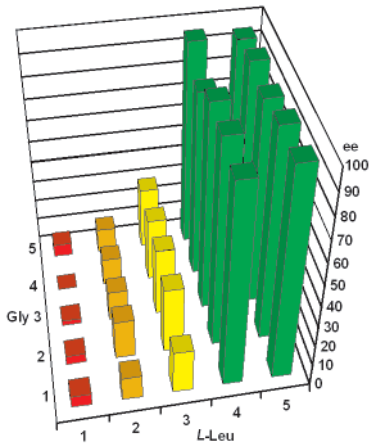


Figure 5. Asymmetric epoxidation of chalcone **1** catalyzed by H_2N-$(Gly)_n$-$(L\text{-}Leu)_m$-CONH−TentaGel.

Finally, we compared the catalytic performance of our TentaGel-bound peptides with (i) L-Leu oligomers bound to MeO-PEG-OH and (ii) free L-Leu oligomers. Interestingly, of the PEG-bound materials, the 5-mer already showed some enantioselectivity (>50% ee), whereas the onset of selectivity was found around the 10-mer in the case of the free L-Leu oligomers. This comparison of PEG-bound and TentaGel-bound peptides suggests that the attachment of the PEG peptide conjugates to a polystyrene matrix (i.e., peptide on TentaGel) further favors the helical arrangement.

Apparently, the poly(ethylene glycol) moiety can act as a "helix surrogate", i.e., peptides bound to PEG may adopt an α-helical conformation at shorter chain lengths compared to non-PEG-bound peptides. In fact, due to the gauche-effect along the C−O-bond, poly(ethylene glycol)s tend to adopt helical conformations.[14] This effect may potentially play a role whenever free and PEG-bound peptides are assumed to have comparable properties, e.g., when screening combinatorial libraries for receptor binding.

In summary, our study yielded the smallest "synzyme" reported to date: as little as five amino acids are sufficient to catalyze the epoxidation of chalcone with enzyme-like selectivity. Furthermore, our mechanistic proposal—which highlights the importance of the helical chirality of the peptide catalyst—is hoped to pave the way to peptide/peptoid catalysts of broader substrate spectrum. In this respect, tailoring of the attachment point for the substrate enone and the nucleophile appears particularly attractive.

Acknowledgment. This work was supported by the Fonds der Chemischen Industrie and by the EU, Research Training Network "Combinatorial Catalysis", Grant HPRN-CT-2000-00014.

Supporting Information Available: Experimental procedures: synthesis of the TentaGel-bound peptide oligomers, epoxidation of chalcone, analysis of the reaction mixtures; description of the molecular modeling studies. This material is available free of charge via the Internet at http://pubs.acs.org.

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