Pergamon

Tetrahedron Letters 40 (1999) 1027–1030

TETRAHEDRON LETTERS

Synthesis and Chemical Resolution of Unique α,β-Didehydroamino Acids with a Chiral Axis

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Received 5 October 1998; accepted 23 November 1998

Abstract

The synthesis, resolution and characterisation of dipeptides containing axially chiral R_a and S_a N^2-[N^1-benzoyl-(4-methylcyclohexylidene)glycyl]-(*S*)-phenylalanine cyclohexylamide is described. These compounds are the first examples of disymmetric α,β-didehydroamino acids. © 1999 Elsevier Science Ltd. All rights reserved.

Keywords: Amino acids and derivatives, asymmetry, resolution, peptides.

The design and synthesis of new structures capable of controlling steric and electronic relationships of portions of peptide chains is a challenge of continuing interest [1-4]. Bioactive peptides have enormous applications in biological, chemical and pharmaceutical areas and rationally designed peptidomimetics usually increase the desired properties of bioactive peptides, such as chemical and metabolic stability, bioavailability and receptor selectivity and affinity.

In addition to the significant limitation of side chain orientations possible in didehydro residues, α,β-didehydroamino acids have proven to be strong inducers of folded conformations and, in this context, have been used as structural modifications in the design of model peptides with well-defined structures [5-10].

Figure 1

As far as we know, there have been no examples of chiral α,β-didehydroamino acids reported to date. The structural features of these compounds remove the asymmetric centre on the amino acid moiety, so we have therefore designed, synthesised, resolved and

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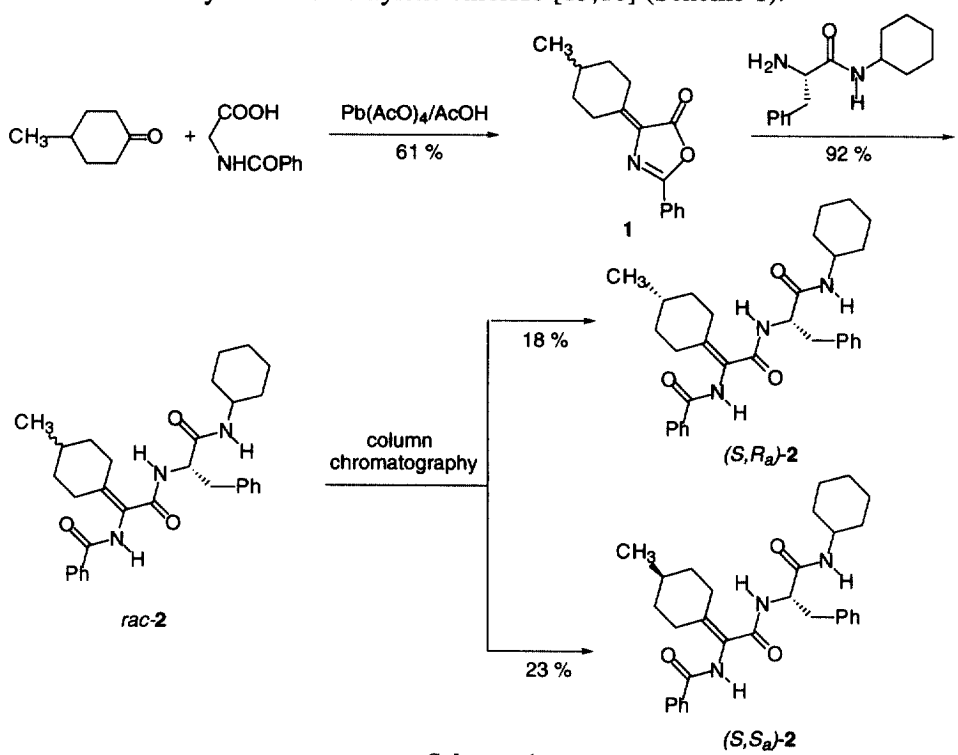
0040-4039/99/$ - see front matter
PII: S0040-4039(98)02517-9

stereochemically characterised an α,β-didehydroamino acid derivative possessing an axis as the element of chirality. Both enantiomers of this kind of compound are represented in Figure 1. These compounds were synthesised in order to study the conformational preferences induced by such systems when incorporated into a model peptide, especially for the study of the relationship between absolute configuration of axially chiral residues and the helix handedness of the peptide.

Obrecht *et al.* succeeded in the resolution of a wide variety of unusual amino acids *via* diastereomeric dipeptide derivatives obtained by treatment of saturated 2-phenyloxazol-5(4*H*)-ones with L-phenylalanine cyclohexylamide, used as chiral resolving agent [11-14].

Taking into account these precedents, we chose a direct route involving condensation of 4-methylcyclohexanone with hippuric acid for the synthesis of the required 2-phenyloxazol-5(4*H*)-one. Under typical Erlenmeyer conditions the reaction afforded 4-(4-methylcyclohexylidene)-2-phenyloxazol-5(4*H*)-one (**1**) as a racemic mixture in 61% yield. Coupling of this compound with L-phenylalanine cyclohexylamide cleanly afforded the desired peptide **2** as an equimolar mixture of diastereoisomers in 92% yield. Analytically pure samples of both diastereoisomers could be obtained after careful flash chromatography on silica gel, using methylene chloride/ethyl acetate (3:1) as the eluent, followed by crystallisation from ethyl acetate/methylene chloride [15,16] (Scheme 1).



Scheme 1

The absolute configuration of the less polar peptide was unambiguously assigned by single crystal X-ray analysis based on the known *(S)*-configuration of L-phenylalanine. This analysis

established the absolute configuration of the chiral α,β-didehydroamino acid residue as R_a for this compound. Clearly the more strongly retained peptide has the S_a configuration.

In addition to stereochemical information, X-ray analysis revealed interesting information about the conformational preferences of peptide *(S,R_a)*-**2**, indicating that this compound adopts a β-turn of type II' with the two amino acids in the β-turn positions and a transannular H-bond between the benzoyl C=O and the cyclohexylamide NH groups. (Figure 2).

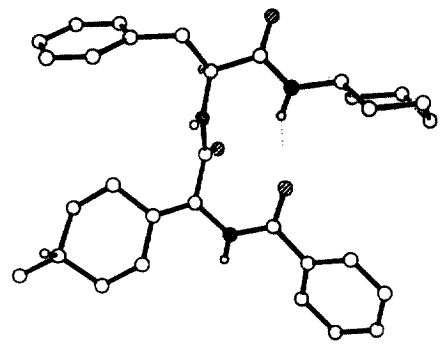


Figure 2.

Initial ^{1}H-NMR analysis of peptide *(S,R_a)*-**2** carried out in $CDCl_3$ solution suggested that the β-turn found in the solid state is maintained in $CDCl_3$ solutions, as chemical shift solvent dependence in $CDCl_3$/DMSO-d_6 mixtures clearly shows the involvement of the NH group of cyclohexylamide in an intramolecular hydrogen bond [17]. The cyclohexylamide NH group is practically unaffected by changes in the solvent composition (Figure 3a). Investigation of the chemical shift solvent dependence in $CDCl_3$/DMSO-d_6 mixtures carried out for peptide *(S,S_a)*-**2** also indicated the involvement of the NH group of cyclohexylamide in an intramolecular hydrogen bond (Figure 3b).

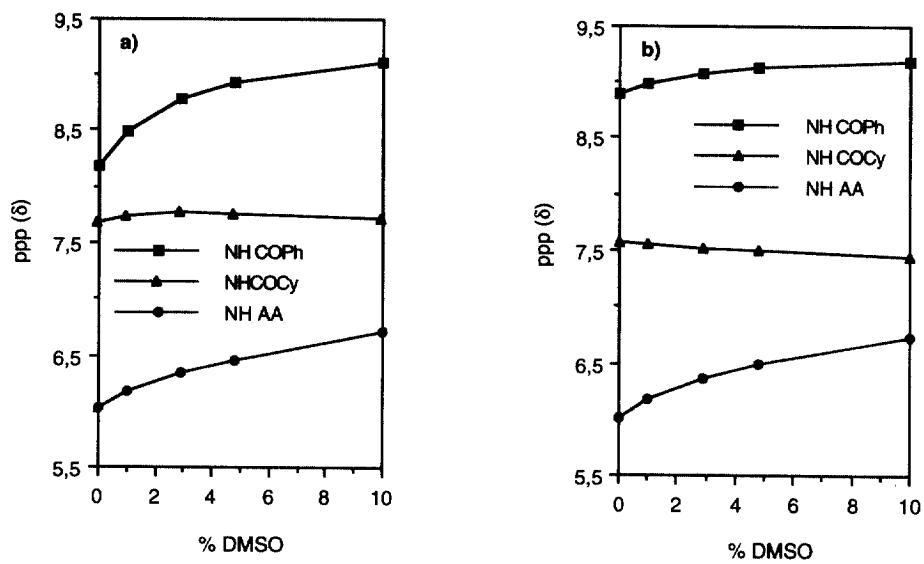


Figure 3. Chemical shift dependence of the NH resonances as a function of the DMSO concentration (% v/v) in $CDCl_3$ solution **a**: for dipeptide *(S,R_a)*-**2**; **b**: for dipeptide *(S,S_a)*-**2**

In summary, the first model peptides incorporating chiral α,β-didehydroamino acid residues have been prepared and characterised. Initial structural studies have shown the potential of this system in the stabilisation of β-turn conformations. A detailed study of the influence of the absolute configuration of the residue on the conformational behaviour of peptides, synthesis of chiral α,β-didehydroamino acid residues with different side chains and asymmetric synthesis of these compounds is currently under investigation and will be published in due course.

Acknowledgement: This work was made possible by the generous financial support of the *Dirección General de Investigación Científica y Técnica*, project number PB97-0998.

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[15] R_a-**2**: M.p. = 195 °C (dec). $[\alpha]_D$ = –74.4 (*c* = 0.5, methanol). ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 0.84 (d, 3H, *J* = 6.3 Hz); 1.00–1.94 (m, 17H); 1.95–2.02 (m, 1H); 2.50–2.56 (m, 1H); 3.05 (dd, 1H, *J* = 14.5 Hz, *J* = 9.3 Hz); 3.43 (dd, 1H, *J* = 14.5 Hz, *J* = 4.8 Hz); 3.68–3.80 (m, 1H); 4.80–4.93 (m, 1H); 6.02 (bd, 1H, *J* = 8.7 Hz); 7.15–7.40 (m, 8H); 7.48 (bd, 1H, *J* = 8.0 Hz); 7.60–7.65 (m, 2H); 9.01 (bs, 1H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 21.4; 25.2; 25.3; 25.7; 28.8; 29.1; 31.7; 32.6; 32.8; 34.5; 35.6; 37.5; 48.7; 54.6; 123.0; 126.9; 127.3; 128.3; 128.7; 129.1; 131.7; 132.3; 137.1; 139.7; 166.8; 167.2; 169.5.

[16] S_a-**2**: M p. = 245 °C (dec). $[\alpha]_D$ = –84.2 (*c* = 0.5, methanol). ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 0.88 (d, 3H, *J* = 6.3 Hz); 1.00–1.90 (m, 17H); 1.98–2.02 (m, 1H); 2.47–2.60 (m, 1H); 3.09 (dd, 1H, *J* = 14.5 Hz, *J* = 9.3 Hz); 3.46 (dd, 1H, *J* = 14.5 Hz, *J* = 4.5 Hz); 3.74–3.90 (m, 1H); 4.85–5.02 (m, 1H); 6.03 (bd, 1H, *J* = 9.0 Hz); 7.12–7.85 (m, 8H); 7.62–7.68 (m, 2H); 7.71 (bd, 1H, *J* = 8.4 Hz); 9.54 (bs, 1H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ = 21.8; 25.3; 25.4; 25.7; 29.1; 29.3; 32.4; 32.6; 32.9; 35.0; 36.1; 37.3; 48.7; 54.6; 123.1; 127.0; 127.4; 128.1; 128.7; 129.0; 131.6; 132.1; 137.2; 138.3; 166.7; 167.8; 169.3.

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