Cyclodepsitripeptides. Synthesis, Crystal Structures† and Molecular Conformations of *cyclo*(-L-2-Hydroxyisovaleryl-L-prolyl-L-prolyl-) and *cyclo*(-D-2-Hydroxyisovaleryl-L-prolyl-L-prolyl-)‡

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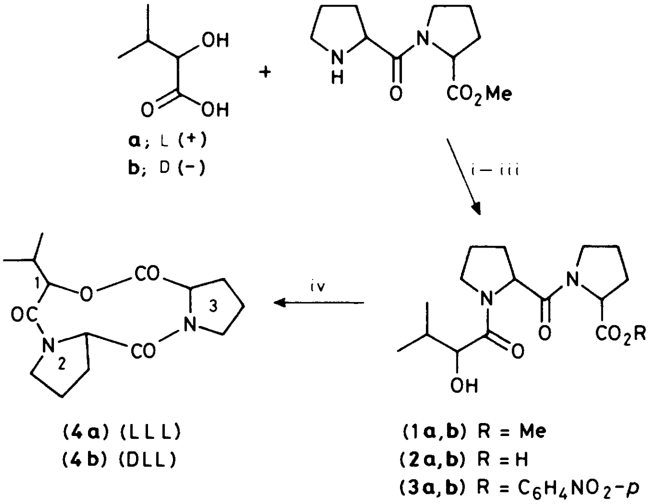
The molecular and crystal structures of two diastereoisomeric nine-membered-ring heterodetic cyclotripeptides have been studied by *X*-ray analysis and compared with those of homodetic ring systems. *cyclo*(-Hylv-Pro-Pro-) (LLL) and *cyclo*(-D-Hylv-Pro-Pro-) (DLL) have been synthesized, through lactone-bond formation, starting from the corresponding linear precursors. The prolyl residues possess approximate C_2 symmetry in LLL and C_S symmetry in DLL. All peptide bonds adopt the *cis*-conformation and the two lactone bonds the *trans*-conformation. The most pronounced deviation from planarity is shown by the Pro-Pro bond in LLL ($\omega_2 = +22.6°$) and by the lactone bond in DLL ($\omega_3 = -153.6°$). An unusual value of the ($\theta - \varphi$) parameter (36.8°) was found for Pro_3 in LLL; this has been related to the pyramidality of N_3. The C_2 pseudosymmetry assigned to the backbone conformations of LLL and DLL is discussed and compared with that of *cyclo*(-Pro_2-D-Pro-).

Their relative structural simplicity and reduced molecular flexibility make nine-membered-ring cyclotripeptides of special interest as model compounds for conformational investigations.[1] Studies on the chemistry and backbone conformation of homodetic cyclotripeptides have provided interesting insights into unusual peptide properties. It is now well established that in the sterically constrained nine-membered ring, the *trans*-conformation of the amide bonds is energetically disfavoured. All three peptide groups thus adopt *cis*-arrangements and impose crown or boat conformation on the backbone.[1c]

Although several models of homodetic cyclotripeptides have been investigated, the corresponding class of heterodetic nine-membered rings (cyclodepsitripeptides), containing a lactone bond in place of a peptide bond, has received comparatively little attention.[2,3] This is despite the biological relevance of cyclodepsipeptides[4] and the structural differences between ester and amide bonds, which are expected to introduce significant conformational changes in the ring system.

As a part of a program aimed at defining the structural and conformational properties of cyclodepsitripeptides as well as the relation between the chirality of the residues and the backbone conformation, we report here the synthesis, characterization, and *X*-ray crystallographic analysis of two nine-membered-ring cyclodepsitripeptides. As suitable models for initial studies, systems containing two proline residues and a chiral 2-hydroxy acid were chosen. The presence of the proline residues was expected to favour ring-closure reactions and provide useful information concerning the conformations adopted by the pyrrolidine ring in constrained heterodetic systems.



Scheme. Absolute configuration of all prolyl residues is L. Compounds (**a**) contain the L(+)-2-hydroxyisovaleric acid residue (Hylv) and compounds (**b**) the D(−)-2-hydroxyisovaleric acid residue (D-Hylv). *Reagents*: i, hydroxybenzotriazole, dicyclohexylcarbodi-imide; ii, 2M-NaOH, methanol; iii, dicyclohexylcarbodi-imide, *p*-nitrophenol; iv, diazabicycloundecene, dry benzene

Results and Discussion

Synthesis.—Since the initial objective was the comparative study of two diastereoisomeric cyclodepsitripeptides possessing the same configuration at the proline chiral centres and opposite chirality at the hydroxy acid residue, the two hydroxy peptides (**1a** and **b**) were synthesized (see Scheme), by coupling L-prolyl-L-proline methyl ester with L(+)- and D(−)-2-hydroxyisovaleric acid, respectively. Ring closure, through formation of the lactone bond, was attempted with unsatisfactory results directly from the hydroxy acids (**2a** and **b**) by using dicyclohexylcarbodi-imide–4-dimethylaminopy-

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† *Supplementary data available* (No. SUP 56343, 7pp.): thermal parameters. For details of Supplementary Publications see Instructions for Authors, *J. Chem. Soc., Perkin Trans. 2*, 1985, Issue 1. Structure factor tables are available from the editorial office on request.

‡ Preliminary reports on this subject were presented at the 7th European Crystallographic Meeting, Jerusalem (Israel), August 1982 and at the 13th International Congress of I.U.Cr., Hamburg (Federal Rep. of Germany), August 1984.

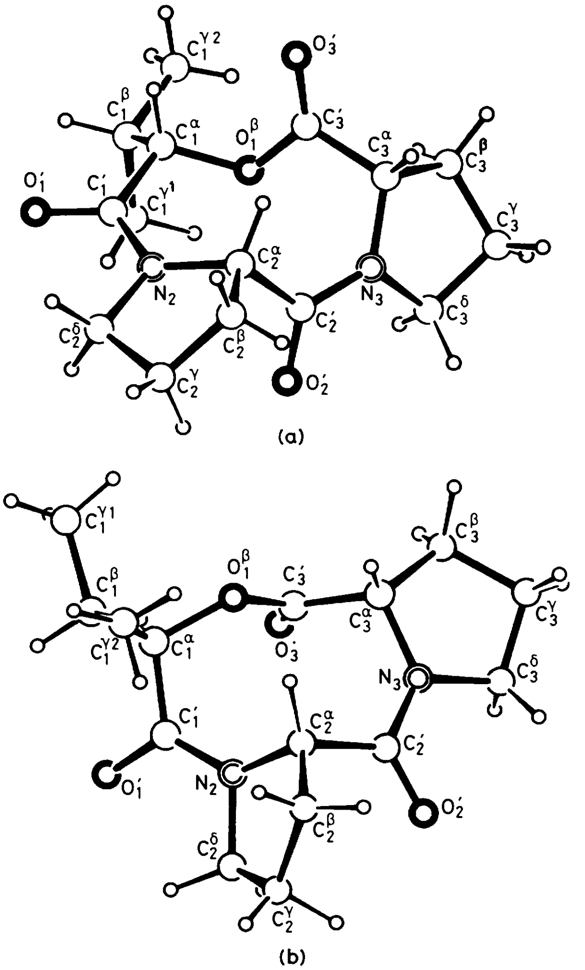

Figure 1. (a) Perspective view of *cyclo*(-Hylv-Pro-Pro-) (LLL), projected onto the plane containing C_1', N_3, and C_3^{α}; (b) perspective view of *cyclo*(-D-Hylv-Pro-Pro-) (DLL), projected onto the plane containing C_1', C_1^{α}, and N_3

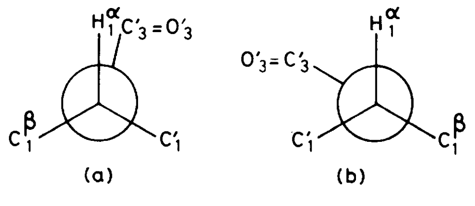

Figure 2. Newman projection along the C_1^{α}–O_1^{β} bond; (a) for LLL and (b) for DLL

ridine,[5] or by treating the active esters (**3a** and **b**) with di-isopropylethylamine in pyridine. When the active ester (**3a**) was left at room temperature in benzene solution (10^{-2}M) with diazabicycloundecene (DBU) (1.2 equiv.), the cyclodepsipeptide (**4a**) (LLL) was obtained in high yield. An analogous result was obtained when the active ester (**3b**) was heated in benzene with DBU: the corresponding cyclodepsipeptide (**4b**) (DLL) was formed in 40% yield. Although DBU was previously used by us for cyclization reactions leading to peptidic *N*-acyl-lactams,[6] its use for the synthesis of lactones has not been reported before. The potential of this procedure, which is regarded at present as DBU-mediated internal alcoholysis, favoured by the conformational properties of the acyclic precursors, is now under investigation in our laboratories.

Conformation in the Crystals.—Figures 1(a) and 1(b) show the conformation in the crystals of the diastereoisomeric cyclodepsitripeptides LLL and DLL. Table 1 reports the fractional atomic co-ordinates and Table 2 the bond lengths and valence angles for the non-hydrogen atoms. The mean values of bond distances and angles involving hydrogen atoms are 0.99(4) Å and 100(3)° for LLL, and 1.03(6) Å and 110(6)° for DLL. The bond lengths and valence angles found for proline and the 2-hydroxy acid residue in the two molecules (Table 2) compare well with the corresponding values observed in proline-containing homodetic cyclotripeptides[7–10] and in cyclodepsipeptides containing 2-hydroxy acids.[11–13] Mention should be made, however, of the ring angle at N_2 in DLL (C_1'–N_2–C_2^{α} = 131.5°); such a high value finds correspondence only in *cyclo*(-Pro_2-D-Pro-).[9]

Table 3 reports the conformational parameters of LLL and DLL. The pyrrolidine rings in LLL are to some extent twisted and possess approximate C_2 symmetry (half-chair) whereas in DLL they show C_s symmetry (envelope). According to the classification proposed by Ashida and Kakudo,[14] such conformations can be described as C_2-C^{β}-*exo* for Pro_2 and C_2-C^{γ}-*exo* for Pro_3 in LLL, the asymmetry parameters[15] ΔC_2 being 3.5 and 7.9°, respectively. In the case of DLL a C_s-C^{α}-*endo*-conformation (ΔC_s = 2.0°) can be assigned to Pro_2, and a C_s-C^{γ}-*exo* conformation (ΔC_s = 3.5°) to Pro_3. The phase angle of pseudorotation *P* and the puckering amplitude χ_m, which describe the envelope (*E*) and twist (*T*) conformations of pyrrolidine rings in terms of *N*/*S* notation,[1d,16] are reported in Table 4.

A significant pyramidality of the nitrogen atoms is observed in both the prolyl residues of LLL, but only in Pro_2 of DLL. A quantitative evaluation of this feature can be obtained from the data reported in Table 4. Here the displacement *d*(*N*) of each N atom from the plane of its substituents is reported together with the value assumed by the ($\theta'' - \varphi$) parameter ($\theta'' - \varphi$ = 180° for a planar environment).

The endocyclic torsion angles φ_2, θ_2 and φ_3, θ_3 around the proline N–C^{α} bonds are of particular interest (see Table 3). In the proline-containing homodetic cyclotropeptides studied to date, φ_i(i = 1, 2, or 3) values range from −46 to −110°, and the difference $\theta - \varphi$ invariably occurs in the range 60—80°;[17] both these values have been usefully related to proline and backbone conformations.[1d,16] In the two cyclodepsipeptides studied in the present work, the φ angles of Pro_3 in LLL (−29.5°) and of Pro_2 in DLL (−114.2°) are outside limits reported for homodetic systems. Moreover, a very unusual value for the difference $\theta - \varphi$ (Table 4) is found in Pro_3 of LLL ($\theta_3 - \varphi_3$ = 36.8°). We correlate this anomalous value with the pyramidality of N_3, which, as reported in Table 4, is displaced by 0.164 Å from the plane of its substituents, on the opposite side of C_3'.

The backbone conformation of the two nine-membered rings is characterized by the presence of a *trans*-lactone bond, in addition to the expected two *cis*-amide bonds. The deviations from planarity of the lactone and amide bonds in LLL are large and similar in magnitude (see angles ω in Table 3), the highest value being shown by the Pro-Pro amide bond (torsion angle ω_2 = −22.6°). These deviations appear to be related to the endoannular short-contact interactions between O_1^{β} and C_2^{α}, C_2', and N_3, located on the opposite sides of the ring. The corresponding distances (2.68, 2.66, and 2.64 Å) are in fact shorter than the sums of the van der Waals radii.

In DLL the torsion angles of peptide and lactone bonds show a pattern of discrepancy from the ideal values, different from that found in LLL. The bond joining the two proline residues is nearly planar (ω_2 = −4.8°), and relevant deviations are shown by the D-Hylv-Pro amide bond (ω_1 = 11.9°) and by the lactone

Table 1. Fractional atomic co-ordinates

(a) LLL

	x	*y*	*z*		*x*	*y*	*z*
O_1^{β}	0.171 4(2)	0.107 6(2)	0.720 3(1)	$H–C_1^{\alpha}$	0.182	−0.027	0.622
C_1^{α}	0.208 7(3)	0.067 1(2)	0.635 2(1)	$H–C_1^{\beta}$	0.160	0.128	0.512
C_1^{β}	0.130 4(3)	0.154 5(3)	0.571 9(1)	$H_a–C_1^{\gamma 1}$	0.125	0.348	0.541
$C_1^{\gamma 1}$	0.167 4(3)	0.298 6(3)	0.583 6(2)	$H_b–C_1^{\gamma 1}$	0.128	0.339	0.638
$C_1^{\gamma 2}$	0.025 7(3)	0.134 2(4)	0.581 5(2)	$H_c–C_1^{\gamma 1}$	0.262	0.313	0.580
C_1'	0.365 7(3)	0.078 5(2)	0.624 3(1)	$H_a–C_1^{\gamma 2}$	−0.055	0.050	0.566
O_1'	0.410 8(2)	0.081 7(2)	0.551 3(1)	$H_b–C_1^{\gamma 2}$	−0.075	0.180	0.540
N_2	0.450 9(2)	0.086 0(2)	0.692 3(1)	$H_c–C_1^{\gamma 2}$	−0.053	0.150	0.636
C_2^{α}	0.423 1(3)	0.052 5(3)	0.782 7(2)	$H–C_2^{\alpha}$	0.350	−0.021	0.791
C_2^{β}	0.566 8(4)	0.014 2(4)	0.815 8(2)	$H_a–C_2^{\beta}$	0.586	−0.084	0.809
C_2^{γ}	0.668 3(4)	0.093 7(5)	0.762 2(2)	$H_b–C_2^{\beta}$	0.578	0.035	0.878
C_2^{δ}	0.600 9(3)	0.099 7(4)	0.674 7(2)	$H_a–C_2^{\gamma}$	0.680	0.181	0.788
C_2'	0.369 2(3)	0.173 1(3)	0.831 3(1)	$H_b–C_2^{\gamma}$	0.760	0.046	0.760
O_2'	0.435 9(2)	0.274 6(2)	0.830 9(1)	$H_a–C_2^{\delta}$	0.637	0.028	0.635
N_3	0.251 6(3)	0.161 7(2)	0.877 9(1)	$H_b–C_2^{\delta}$	0.623	0.187	0.646
C_3^{α}	0.139 9(3)	0.063 2(3)	0.866 4(2)	$H–C_3^{\alpha}$	0.159	−0.018	0.903
C_3^{β}	0.009 8(4)	0.137 6(4)	0.896 4(2)	$H_a–C_3^{\beta}$	−0.036	0.184	0.846
C_3^{γ}	0.063 7(4)	0.234 6(3)	0.961 7(2)	$H_b–C_3^{\beta}$	−0.062	0.076	0.922
C_3^{δ}	0.199 1(4)	0.279 6(3)	0.921 8(2)	$H_a–C_3^{\gamma}$	0.081	0.192	1.019
C_3'	0.124 7(3)	0.016 7(3)	0.775 5(2)	$H_b–C_3^{\gamma}$	−0.002	0.311	0.972
O_3'	0.079 2(3)	−0.087 2(3)	0.755 3(1)	$H_a–C_3^{\delta}$	0.179	0.354	0.881
				$H_b–C_3^{\delta}$	0.264	0.313	0.967

(b) DLL

	x	*y*	*z*		*x*	*y*	*z*
O_1^{β}	0.607 3(4)	−0.154 7(1)	0.762 4(1)	$H–C_1^{\alpha}$	0.907	−0.192	0.786
C_1^{α}	0.812 5(5)	−0.142 7(2)	0.806 7(2)	$H–C_1^{\beta}$	0.915	−0.137	0.930
C_1^{β}	0.764 6(6)	−0.148 0(2)	0.902 7(2)	$H_a–C_1^{\gamma 1}$	0.735	−0.258	0.983
$C_1^{\gamma 1}$	0.702 9(9)	−0.239 6(3)	0.927 6(2)	$H_b–C_1^{\gamma 1}$	0.565	−0.260	0.902
$C_2^{\gamma 2}$	0.589 3(7)	−0.086 7(3)	0.931 0(2)	$H_c–C_1^{\gamma 1}$	0.792	−0.250	0.902
C_1'	0.922 8(5)	−0.059 4(2)	0.783 1(2)	$H_a–C_1^{\gamma 2}$	0.587	−0.087	0.944
O_1'	1.117 0(4)	−0.055 0(2)	0.802 1(2)	$H_b–C_1^{\gamma 2}$	0.620	−0.044	0.917
N_2	0.818 9(4)	0.005 4(2)	0.745 2(2)	$H_c–C_1^{\gamma 2}$	0.453	−0.094	0.903
C_2^{α}	0.584 9(5)	0.021 6(2)	0.730 5(2)	$H–C_2^{\alpha}$	0.485	−0.022	0.764
C_2^{β}	0.555 7(7)	0.114 0(2)	0.763 6(2)	$H_a–C_2^{\beta}$	0.415	0.141	0.736
C_2^{γ}	0.774 5(7)	0.156 8(3)	0.745 2(3)	$H_b–C_2^{\beta}$	0.542	0.110	0.824
C_2^{δ}	0.942 4(7)	0.086 5(3)	0.733 2(3)	$H_a–C_2^{\gamma}$	0.743	0.190	0.684
C_2'	0.536 6(6)	0.019 4(2)	0.634 5(2)	$H_b–C_2^{\gamma}$	0.815	0.197	0.776
O_2'	0.576 6(6)	0.082 2(2)	0.592 0(2)	$H_a–C_2^{\delta}$	1.016	0.082	0.667
N_3	0.451 6(5)	−0.051 1(2)	0.599 0(2)	$H_b–C_2^{\delta}$	1.100	0.083	0.765
C_3^{α}	0.406 6(5)	−0.135 2(2)	0.638 4(2)	$H–C_3^{\alpha}$	0.493	−0.127	0.686
C_3^{β}	0.334 6(8)	−0.190 0(2)	0.563 0(2)	$H_a–C_3^{\beta}$	0.440	−0.233	0.547
C_3^{γ}	0.251 0(8)	−0.127 3(3)	0.497 3(2)	$H_b–C_3^{\beta}$	0.200	−0.226	0.578
C_3^{δ}	0.401 3(7)	−0.052 3(2)	0.507 2(2)	$H_a–C_3^{\gamma}$	0.270	−0.153	0.439
C_3'	0.620 1(5)	−0.164 8(2)	0.678 1(2)	$H_b–C_3^{\gamma}$	0.072	−0.103	0.523
O_3'	0.777 7(4)	−0.188 7(2)	0.641 4(2)	$H_a–C_3^{\delta}$	0.567	−0.061	0.468
				$H_b–C_3^{\delta}$	0.330	0.005	0.495

bond ($\omega_3 = -153.6°$). In this case the shortest contacts from O_1^{β} are to C_2^{α} (2.82 Å) and N_2 (2.84 Å). Analogous values of intramolecular distances between the ring oxygen and C^{α} of the subsequent residue have been found by Konnert and Karle,[11] in the twelve-membered ring of *cyclo*(-D-Hylv-Melleu-D-Hylv-Leu-).

The O–CO group assumes the *trans*-conformation in both LLL and DLL. Furthermore, of the two possible *trans*-arrangements obtainable through mutual rotation around the C_1^{α}–O_1^{β} and C_3^{α}–C_3' bonds, only that with the carbonyl oxygen O_3' on the same side of the Hylv α-hydrogen atom is adopted. Owing to the opposite chirality of the Hylv residue in the two molecules, such conformational preference results in a very different spatial relation between the proline α-hydrogen atoms and the lactone oxygen atoms in LLL and DLL. As shown by the Newman projections along the C_1^{α}–O_1^{β} bond in Figure 2, the arrangement adopted by the lactone bond avoids short-contact interactions between C_1^{β} and the carbonyl oxygen O_3' in the two molecules.

Thus, while in homodetic cyclotripeptides the endoannular interactions and the ring-closure conditions require three *cis*-peptide bonds, the molecular structures found for LLL and DLL show that nine-membered rings containing two homochiral prolyl residues can accommodate *trans*-lactone bonds the deviations from planarity of which do not exceed those found in some peptide bonds of cyclic systems. As a consequence of the presence of the *trans*-lactone bond, the crown and boat conformations which describe the symmetries of homodetic cyclotripeptides do not correspond with the heterodetic systems under study.

Backbone Conformations of LLL and DLL and Correlation with cyclo(-Pro$_2$-D-Pro-).—An examination of the signs and magnitudes of the ring torsion angles of LLL and DLL (Table

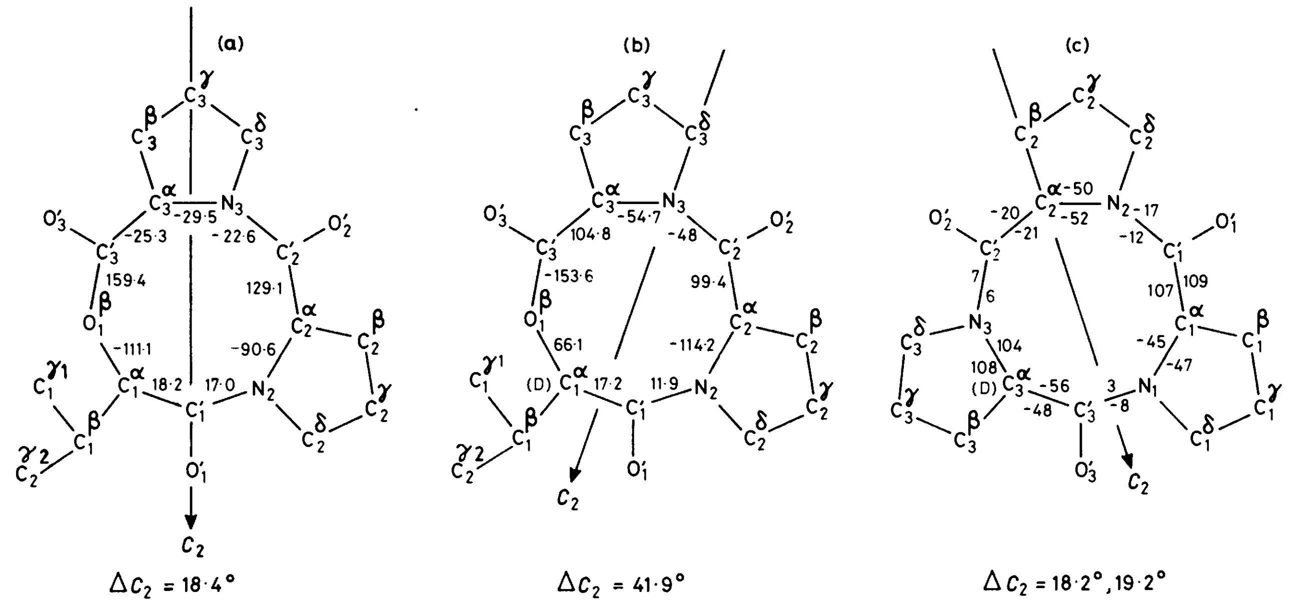

Figure 3. Backbone torsion angles, pseudosymmetry binary axes (C_2), and asymmetry parameters (ΔC_2): (a) for LLL, (b) for DLL, and (c) for the two molecules found in the asymmetric unit of the crystal of *cyclo*(-Pro$_2$-D-Pro-)

3) reveals that a pseudosymmetry binary axis (C_2) can be recognized in both the nine-membered heterodetic rings. Since this is the only symmetry element present in each of the two structures, these can be described in terms of twist conformation.[18,19] As shown in Figure 3(a), the pseudobinary axis of LLL passes through C_1' and the midpoint of the N_3–C_3^α bond and implies the following relationships amongst the torsion angles: $\omega_1 \sim \psi_1$, $\varphi_1 \sim \varphi_2$, $\psi_2 \sim \omega_3$, $\omega_2 \sim \psi_3$, φ_3 unmatched. In DLL the pseudobinary axis passes through N_3 and the midpoint of the C_1^α–C_1' bond and requires the following relationships: $\varphi_1 \sim \omega_1$, $\varphi_2 \sim \omega_3$, $\psi_2 \sim \psi_3$, $\omega_2 \sim \varphi_3$, ψ_1 unmatched [Figure 3(b)].

In order to correlate the backbone symmetry found in the two heterodetic rings with that of analogous homodetic systems, *cyclo*(-Pro$_2$-D-Pro-)[9] was chosen as a suitable model [Figure 3(c)]. This compound has been described in terms of a boat conformation, characterized by a pseudosymmetry mirror plane (C_S) passing through C_3^α and the midpoint of the C_1'–N_2 bond. The relationships imposed by the mirror symmetry to the backbone torsion angles are: $\omega_1 \sim 0$; $\varphi_2 \sim -\psi_1$; $\psi_2 \sim -\varphi_1$; $\omega_2 \sim -\omega_3$; $\varphi_3 \sim -\psi_3$.

The root-mean-square deviations from the ideal C_2 *symmetry* (ΔC_2) which can be calculated for LLL and DLL are 18.4 and 41.9°, respectively. If the analogous parameters, indicating the deviation from mirror symmetry, are calculated in the case of the boat conformations assigned to *cyclo*(-Pro$_2$-D-Pro-), high values of ΔC_S (49.4 and 53.8°) are obtained for both the molecules found in the asymmetric unit of the crystal.[9] By contrast, lower values of the asymmetry parameters (ΔC_2 = 18.2 and 19.2°) are found if, as in the case of LLL and DLL, a C_2 pseudosymmetry is assumed for *cyclo*(-Pro$_2$-D-Pro-). As shown in Figure 3(c), the binary axis passes through C_2^α and the midpoint of the opposite peptide bond and imposes the following relationships on the backbone torsion angles: $\varphi_2 \sim \psi_2$, $\omega_1 \sim \omega_2$, $\psi_1 \sim \varphi_3$, $\varphi_1 \sim \psi_3$, ω_3 unmatched. Thus, as indicated in Figure 3, all three backbone conformations found in the crystalline state of LLL, DLL, and *cyclo*(-Pro$_2$-D-Pro-) can be described in terms of C_2 pseudosymmetry (twist conformation).

Examination of the three structures shown in Figure 3 reveals that each of the C_2 pseudosymmetry axes bisects a different type of bond: C^α–N in LLL, C^α–C′ in DLL, and C′–N in *cyclo*(-Pro$_2$-D-Pro-). The twist conformations of Figure 3 thus represent examples of the three possible cyclic permutations of the angles φ, ψ, and ω in a nine-membered ring with C_2 symmetry. The three sets of relationships imposed on the backbone torsion angles by the C_2 pseudosymmetry are reported in Table 5.

In order to clarify the correlation between the cited boat and twist conformations, reference can be made to a simple molecular model such as *cyclo*(-Gly$_3$-) and to the three indistinguishable boat (C_S) conformations which the nine-membered ring can assume. It is easy to see that the three twist conformations of Table 5 are precisely the midway forms, between two consecutive boat conformations, encountered during the pseudorotation cycle of the nine-membered ring.

It is worth mentioning that in nine-membered rings twist conformations, as compared with boats, release the short-contact interactions between the two inwardly oriented C^α-hydrogen atoms and between the third C^α-hydrogen atom and the opposite peptide bond.[1c]

Crystal Packing.—The molecules of both LLL and DLL interact in the crystals only through van der Waals forces. The shortest intermolecular contacts, which occur between sp^3 carbon atoms and carbonyl oxygens O_1' and O_2', are reported in Table 6.

Experimental

I.r. spectra were recorded with a Perkin-Elmer 521 spectrophotometer. ^{1}H N.m.r. spectra were recorded with a Varian EM 390 spectrometer. ^{13}C N.m.r. spectra were recorded with a Varian CFT 20 instrument for LLL and with a Brüker WP 200 (50.28 MHz) instrument for DLL. Mass spectra were determined with a Hewlett-Packard 5980 A spectrometer operating at 70 eV. Optical rotations were taken at 20 °C with a Schmidt-Haensch 16065 polarimeter.

N-(L-2-*Hydroxyisovaleryl*)-L-*prolyl*-L-*proline Methyl Ester* (**1a**).—To a stirred ice-cold solution of L-prolyl-L-proline methyl ester hydrochloride (7.8 g, 29.7 mmol) in dichloro-

Table 2.

(a) Bond distances (Å) with e.s.d.s (in parentheses)

	LLL	DLL		LLL	DLL
$O_1^{\beta}-C_1^{\alpha}$	1.438(3)	1.453(4)	$C_2^{\beta}-C_2^{\gamma}$	1.524(5)	1.530(4)
$O_1^{\beta}-C_3'$	1.342(3)	1.344(3)	$C_2^{\gamma}-C_2^{\delta}$	1.516(5)	1.522(6)
$C_1^{\alpha}-C_1^{\beta}$	1.530(4)	1.546(4)	$C_2'-O_2'$	1.217(4)	1.218(4)
$C_1^{\alpha}-C_1'$	1.527(4)	1.518(5)	$C_2'-N_3$	1.353(4)	1.346(4)
$C_1^{\beta}-C_1^{\gamma 1}$	1.520(4)	1.538(5)	$N_3-C_3^{\alpha}$	1.482(4)	1.485(4)
$C_1^{\beta}-C_1^{\gamma 2}$	1.525(4)	1.511(5)	$N_3-C_3^{\delta}$	1.471(4)	1.482(4)
$C_1'-O_1'$	1.222(3)	1.231(4)	$C_3^{\alpha}-C_3^{\beta}$	1.538(5)	1.535(4)
$C_1'-N_2$	1.346(3)	1.342(4)	$C_3^{\alpha}-C_3'$	1.506(4)	1.525(4)
$N_2-C_2^{\alpha}$	1.477(3)	1.477(4)	$C_3^{\beta}-C_3^{\gamma}$	1.512(5)	1.519(5)
$N_2-C_2^{\delta}$	1.479(4)	1.493(5)	$C_3^{\gamma}-C_3^{\delta}$	1.518(5)	1.504(6)
$C_2^{\alpha}-C_2^{\beta}$	1.529(5)	1.553(4)	$C_3'-O_3'$	1.188(4)	1.188(4)
$C_2^{\alpha}-C_2'$	1.534(4)	1.545(4)			

(b) Valence angles (°) with e.s.d.s (in parentheses)

	LLL	DLL
$C_3'-O_1^{\beta}-C_1^{\alpha}$	118.7(2)	116.2(2)
$O_1^{\beta}-C_1^{\alpha}-C_1^{\beta}$	108.0(2)	107.4(2)
$O_1^{\beta}-C_1^{\alpha}-C_1'$	109.2(2)	112.3(3)
$C_1'-C_1^{\alpha}-C_1^{\beta}$	111.9(2)	111.8(3)
$C_1^{\alpha}-C_1^{\beta}-C_1^{\gamma 1}$	111.5(2)	110.3(3)
$C_1^{\alpha}-C_1^{\beta}-C_1^{\gamma 2}$	110.4(2)	113.0(3)
$C_1^{\gamma 1}-C_1^{\beta}-C_1^{\gamma 2}$	110.1(3)	110.2(3)
$O_1'-C_1'-C_1^{\alpha}$	117.3(2)	114.9(3)
$O_1'-C_1'-N_2$	121.3(3)	121.7(3)
$C_1^{\alpha}-C_1'-N_2$	121.4(2)	123.4(3)
$C_1'-N_2-C_2^{\alpha}$	129.2(2)	131.5(3)
$C_1'-N_2-C_2^{\delta}$	117.1(2)	117.5(3)
$C_2^{\alpha}-N_2-C_2^{\delta}$	112.2(2)	109.1(3)
$N_2-C_2^{\alpha}-C_2^{\beta}$	102.6(2)	102.7(3)
$N_2-C_2^{\alpha}-C_2'$	110.5(2)	109.7(2)
$C_2'-C_2^{\alpha}-C_2^{\beta}$	110.1(2)	109.2(2)
$C_2^{\alpha}-C_2^{\beta}-C_2^{\gamma}$	105.1(3)	104.2(3)
$C_2^{\beta}-C_2^{\gamma}-C_2^{\delta}$	103.9(3)	107.4(3)
$C_2^{\gamma}-C_2^{\delta}-N_2$	104.3(3)	105.0(3)
$O_2'-C_2'-C_2^{\alpha}$	119.8(3)	119.0(3)
$O_2'-C_2'-N_3$	121.2(3)	120.9(3)
$C_2^{\alpha}-C_2'-N_3$	118.8(2)	120.1(3)
$C_2'-N_3-C_3^{\alpha}$	127.0(2)	128.8(3)
$C_2'-N_3-C_3^{\delta}$	118.0(3)	119.9(3)
$C_3^{\alpha}-N_3-C_3^{\delta}$	111.0(2)	111.2(2)
$N_3-C_3^{\alpha}-C_3^{\beta}$	102.9(2)	103.0(2)
$N_3-C_3^{\alpha}-C_3'$	113.4(2)	106.5(2)
$C_3^{\beta}-C_3^{\alpha}-C_3'$	111.3(3)	113.3(3)
$C_3^{\alpha}-C_3^{\beta}-C_3^{\gamma}$	104.2(3)	105.3(3)
$C_3^{\beta}-C_3^{\gamma}-C_3^{\delta}$	102.4(3)	103.3(3)
$C_3^{\gamma}-C_3^{\delta}-N_3$	104.0(3)	103.8(3)
$O_3'-C_3'-C_3^{\alpha}$	124.5(3)	126.6(3)
$O_3'-C_3'-O_1^{\beta}$	124.6(3)	124.6(3)
$O_1^{\beta}-C_3'-C_3^{\alpha}$	110.9(2)	108.7(2)

Table 3. Selected torsion angles (°) with e.s.d.s (in parentheses)

Backbone		LLL	DLL
$C_3'-O_1^{\beta}-C_1^{\alpha}-C_1'$	φ_1	−111.1(2)	66.1(3)
$O_1^{\beta}-C_1^{\alpha}-C_1'-N_2$	ψ_1	18.2(3)	17.2(4)
$C_1^{\alpha}-C_1'-N_2-C_2^{\alpha}$	ω_1	17.0(3)	11.9(5)
$C_1'-N_2-C_2^{\alpha}-C_2'$	φ_2	−90.6(3)	−114.2(4)
$N_2-C_2^{\alpha}-C_2'-N_3$	ψ_2	129.1(2)	99.4(3)
$C_2^{\alpha}-C_2'-N_3-C_3^{\alpha}$	ω_2	−22.6(3)	−4.8(5)
$C_2'-N_3-C_3^{\alpha}-C_3'$	φ_3	−29.5(4)	−54.7(4)
$N_3-C_3^{\alpha}-C_3'-O_1'$	ψ_3	−25.3(3)	104.8(3)
$C_3^{\alpha}-C_3'-O_1^{\beta}-C_1^{\alpha}$	ω_3	159.4(2)	−153.6(2)
Proline rings			
$N_2-C_2^{\alpha}-C_2^{\beta}-C_2^{\gamma}$	χ_2^1	29.3(3)	31.9(3)
$C_2^{\alpha}-C_2^{\beta}-C_2^{\gamma}-C_2^{\delta}$	χ_2^2	−35.2(4)	−19.6(4)
$C_2^{\beta}-C_2^{\gamma}-C_2^{\delta}-N_2$	χ_2^3	26.8(4)	−0.3(5)
$C_2^{\gamma}-C_2^{\delta}-N_2-C_2^{\alpha}$	χ_2^4	−8.7(3)	21.7(4)
$C_2^{\delta}-N_2-C_2^{\alpha}-C_2^{\beta}$	θ_2	−12.9(3)	−33.7(3)
$C_2'-C_2^{\alpha}-N_2-C_2^{\delta}$	θ_2''	104.7(3)	82.4(3)
$N_3-C_3^{\alpha}-C_3^{\beta}-C_3^{\gamma}$	χ_3^1	−29.0(3)	−23.9(4)
$C_3^{\alpha}-C_3^{\beta}-C_3^{\gamma}-C_3^{\delta}$	χ_3^2	39.5(3)	36.3(4)
$C_3^{\beta}-C_3^{\gamma}-C_3^{\delta}-N_3$	χ_3^3	−34.6(3)	−33.9(4)
$C_3^{\gamma}-C_3^{\delta}-N_3-C_3^{\alpha}$	χ_3^4	17.0(3)	19.8(4)
$C_3^{\delta}-N_3-C_3^{\alpha}-C_3^{\beta}$	θ_3	7.3(3)	2.6(4)
$C_3'-C_3^{\alpha}-N_3-C_3^{\delta}$	θ_3''	127.4(3)	122.1(3)
Side chain			
$O_1^{\beta}-C_1^{\alpha}-C_1^{\beta}-C_1^{\gamma 1}$	$\chi_1^{1,1}$	60.1(3)	69.3(4)
$C_1'-C_1^{\alpha}-C_1^{\beta}-C_1^{\gamma 1}$	$\theta_1^{,1}$	—60.2(3)	−167.0(3)
$O_1^{\beta}-C_1^{\alpha}-C_1^{\beta}-C_1^{\gamma 2}$	$\chi_1^{1,2}$	−63.2(3)	−54.5(4)
$C_1'-C_1^{\alpha}-C_1^{\beta}-C_1^{\gamma 2}$	$\theta_1^{,2}$	176.5(2)	69.2(4)
$C_3'-O_1^{\beta}-C_1^{\alpha}-C_1^{\beta}$		127.0(2)	−170.5(3)
$C_1^{\beta}-C_1^{\alpha}-C_1'-N_2$		137.7(2)	−103.7(4)

methane (60 ml), *N*-methylmorpholine (3.0 g, 29.7 mmol) in dichloromethane (50 ml) was added. After 20 min stirring, an ice-cold solution of L-2-hydroxyisovaleric acid (3.5 g, 29.7 mmol) in dichloromethane (150 ml) and 1-hydroxybenzotriazole (8.0 g, 59.3 mmol) were added, followed dropwise by an ice-cold solution of dicyclohexylcarbodi-imide (6.1 g, 29.7 mmol) in dichloromethane (50 ml). After an additional 2 h at 0 °C and 12 h at 5 °C, the mixture was filtered and the resulting solution was washed with M-hydrochloric acid, saturated aqueous sodium hydrogen carbonate, and water; drying and evaporation followed by column chromatography (silica gel; ethyl acetate–methanol 98:2 as eluant) of the residue afforded the *methyl ester* (**1a**) (6.9 g, 71%); m.p. 124—125 °C (from diethyl ether); $[\alpha]_D$ −122° (*c* 1.00 in $CHCl_3$); $\nu_{max.}(CHCl_3)$ 3 465, 1 740, 1 660, and 1 640 cm^{-1}; $\delta_H(CDCl_3)$ 0.82 (3 H, d, *J* 6.5 Hz, C–CH_3), 1.05 (3 H, d, *J* 6.5 Hz, C–CH_3), 3.35 (1 H, d, *J* 7.5 Hz, OH), 3.70 (3 H, s, OCH_3), 4.15 (1 H, dd, *J* 3.5 and 7.5 Hz, α-H of Hylv), 4.6 (1 H, m, α-H of Pro), and 4.8 (1 H, m, α-H of Pro) (Found: C, 58.75; H, 8.0; N, 8.5. $C_{16}H_{26}N_2O_5$ requires C, 58.9; H, 8.0; N, 8.6%).

N-(D-2-*Hydroxyisovaleryl*)-L-*prolyl*-L-*proline Methyl Ester* (**1b**).—By following the procedure for the synthesis of (**1a**), the *methyl ester* (**1b**) was obtained as an oil in 60% yield; $[\alpha]_D$ −104° (*c* 1.00 in $CHCl_3$); $\nu_{max.}(CHCl_3)$ 3 440, 1 740, 1 660, and 1 635 cm^{-1}; $\delta_H(CDCl_3)$ 0.80 (3 H, d, *J* 6.5 Hz, C–CH_3), 1.05 (3 H, d, *J* 6.5 Hz, C–CH_3), 3.70 (3 H, s, OCH_3), 4.15 (1 H, m, α-H of Hylv), and 4.45—4.70 (2 H, complex, two α-H of Pro) (Found: C, 58.7; H, 7.9; N, 8.5. $C_{16}H_{26}N_2O_5$ requires C, 58.9; H, 8.0; N, 8.6%).

N-(L-2-*Hydroxyisovaleryl*)-L-*prolyl*-L-*proline* p-*Nitrophenyl Ester* (**3a**).—To a solution of the methyl ester (**1a**) (7.0 g, 21.5 mmol) in methanol (100 ml), 2M-sodium hydroxide (21.5 ml) was added. After 6 h at room temperature the solution was evaporated under reduced pressure and the residue taken up in water. The resulting solution was washed with ethyl acetate, acidified, and extracted with chloroform. The organic layer was washed with water, dried and evaporated to give the tripeptide acid (**2a**) as a foam, which was used without further purification.

To a solution of compound (**2a**) (2.85 g, 9.1 mmol) and *p*-nitrophenol (2.5 g, 18.2 mmol) in ethyl acetate (100 ml), dicyclohexylcarbodi-imide (1.85 g, 9.1 mmol) was added at 0 °C with stirring. After 2 h at 0 °C and 12 h at 5 °C, the mixture was filtered and the solution repeatedly washed with saturated aqueous sodium carbonate and water, dried, and evaporated. Column chromatography (silica gel; ethyl acetate–methanol 97:3 as eluant) of the residue afforded the active ester (**3a**) as an

Table 4. *N*- and *S*-Type conformations of proline rings and geometrical parameters describing the pyramidality of nitrogen atoms

	E/T[a]	N/S	$P/°$	$\chi_m/°$	d(N)/Å[b]	$(\theta'' - \varphi)/°$	$(\theta - \varphi)/°$
LLL							
Pro_2	${}_{\gamma}{}^{\beta}T$	S	176.5	35.3	0.106	195.3	77.7
Pro_3	${}_{\beta}{}^{\gamma}T$	N	7.2	39.8	−0.164	156.9	36.8
DLL							
Pro_2	${}_{\alpha}E$	S	124.6	34.9	0.113	196.6	80.6
Pro_3	${}^{\gamma}E$	N	13.7	37.4	−0.023	176.8	57.3

[a] Envelope (*E*)/Twist (*T*) conformations. [b] A negative value indicates displacement of N_i on the opposite side of C_i'.

Table 5. The three sets of relationships relating backbone torsion angles in a nine-membered-ring cyclotripeptide with C_2 pseudosymmetry

φ_i unmatched	ψ_i unmatched	ω_i unmatched
$\psi_i \sim \omega_{i-1}$	$\omega_i \sim \varphi_i$	$\varphi_{i+1} \sim \psi_i$
$\omega_i \sim \psi_{i-1}$	$\varphi_{i+1} \sim \omega_{i-1}$	$\psi_{i+1} \sim \varphi_i$
$\varphi_{i+1} \sim \varphi_{i-1}$	$\psi_{i+1} \sim \psi_{i-1}$	$\omega_{i+1} \sim \omega_{i-1}$
$\psi_{i+1} \sim \omega_{i+1}$	$\omega_{i+1} \sim \varphi_{i-1}$	$\varphi_{i-1} \sim \psi_{i-1}$

Table 6. Intermolecular contact distances (Å)

LLL			DLL		
$O_1'\ C_3^{\alpha}$	I[a]	3.28	$O_1'\ C_2^{\alpha}$	III	3.31
$O_1'\ C_3^{\beta}$	I	3.38	$O_1'\ C_3^{\alpha}$	III	3.38
$O_2'\ C_2^{\delta}$	II	3.33	$O_2'\ C_1^{\gamma 2}$	IV	3.27
$O_2'\ C_2^{\beta}$	II	3.35	$O_2'\ C_1^{\beta}$	IV	3.31
			$O_2'\ C_1^{\gamma 1}$	V	3.30

[a] Symmetry operation with respect to reference molecule: I, $(\frac{1}{2} - x, -y, -\frac{1}{2} + z)$; II, $(1 - x, \frac{1}{2} + y, \frac{3}{2} - z)$; III, $(1 + x, y, z)$; IV, $(\frac{3}{2} - x, -y, -\frac{1}{2} + z)$; V, $(1 - x, \frac{1}{2} + y, \frac{3}{2} - z)$.

oil (3.0 g, 77%); $[\alpha]_D$ −130° (*c* 1.00 in $CHCl_3$); $\nu_{max.}(CHCl_3)$ 3 470, 1 770, 1 660, and 1 630 cm^{-1}; $\delta_H(CDCl_3)$ 0.85 (3 H, d, *J* 7.0 Hz, C–CH_3), 1.1 (3 H, d, *J* 7.0 Hz, C–CH_3), 3.4 (1 H, br m, OH), 4.1 (1 H, m, α-H of Hylv), 4.75 (2 H, complex, two α-H of Pro), and 7.3 and 8.25 (4 H, m, arom.).

N-(D-2-*Hydroxyisovaleryl*)-L-*prolyl*-L-*proline* p-*Nitrophenyl Ester* (**3b**).—By the procedure adopted for the synthesis of (**3a**), the active ester (**3b**) was obtained as an oil in 75% yield; $[\alpha]_D$ −105° (*c* 1.00 in $CHCl_3$); $\nu_{max.}(CHCl_3)$ 3 430, 1 765, 1 660, and 1 630 cm^{-1}; $\delta_H(CDCl_3)$ 0.80 (3 H, d, *J* 6.5 Hz, C–CH_3), 1.10 (3 H, d, *J* 6.5 Hz, C–CH_3), 3.35 (1 H, d, *J* 7.5 Hz, OH), 4.2 (1 H, dd, *J* (3.0 and 7.5 Hz, α-H of D-Hylv), 4.6—4.9 (2 H, complex, two α-H of Pro), and 7.3 and 8.3 (4 H, m, arom.).

cyclo(-*Hylv-Pro-Pro*-) (**4a**).—To a solution of the active ester (**3a**) (1.6 g, 3.7 mmol) in dry benzene (300 ml), 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (0.67 g, 4.4 mmol) in dry benzene (70 ml) was added. After 20 h at room temperature the mixture was filtered and the resulting solution evaporated. The chloroform solution of the residue was washed with 2M-hydrochloric acid, saturated aqueous sodium carbonate, and water, dried, and evaporated to give an oily residue (1.2 g). Chromatography through silica with ethyl acetate as eluant gave the *cyclodepsitripeptide* (**4a**) (0.7 g, 65%); m.p. 124—125 °C (from diethyl ether); $[\alpha]_D$ +33° (*c* 1.00 in $CHCl_3$); $\nu_{max.}$(KBr) 1 740, 1 655, and 1 635 cm^{-1}; $\delta_H(CDCl_3)$ 0.80 (3 H, d, *J* 7.0 Hz, C–CH_3), 0.90 (3 H, d, *J* 7.0 Hz, C–CH_3), 4.15 (1 H, m, α-H of Pro), 4.5 (1 H, m, α-H of Pro), and 5.3 (1 H, d, *J* 2.5 Hz, α-H of Hylv); $\delta_C(CDCl_3)$ 16.07 and 18.99 (C^{γ} of Hylv), 22.03 and 23.78 (C^{γ} of Pro), 30.20 (C^{β} of Hylv), 31.43 and 33.12 (C^{β} of Pro), 47.45 and 49.22 (C^{δ} of Pro), 58.08 and 61.19 (C^{α} of Pro), 77.33 (C^{α} Hylv), and 167.91, 172.47, and 173.06 (–CO); *m/z* 294 (M^+, 12%), 251(2), 225(8), 197(3), 153(13), 125(67), 97(24), and 70 (pyrrolinium, 100) (Found: C, 61.15; H, 7.5; N, 9.4. $C_{15}H_{22}N_2O_4$ requires C, 61.2; H, 7.5; N, 9.5%).

cyclo(-D-*Hylv-Pro-Pro*-) (**4b**).—To a solution of DBU (0.7 g, 4.6 mmol) in dry benzene (600 ml), heated to reflux, the active ester (**3b**) (1.6 g, 3.7 mmol) in dry benzene (50 ml) was added over 1 h. The mixture was then refluxed for an additional 4 h; work-up and purification as for compound (**4a**) afforded the *cyclodepsitripeptide* (**4b**) (0.4 g, 37%); m.p. 139—140 °C (from diethyl ether); $[\alpha]_D$ +98° (*c* 1.00 in $CHCl_3$); $\nu_{max.}$(KBr) 1 740, 1 655, and 1 625 cm^{-1}; $\delta_H(CDCl_3)$ 0.90 (3 H, d, *J* 6.3 Hz, C–CH_3), 1.00 (3 H, d, *J* 6.3 Hz, C–CH_3), 4.6 (1 H, m, α-H of Pro), 5.30 (1 H, d, *J* 3.0 Hz, α-H of Hylv), and 5.65 (1 H, m, α-H of Pro); $\delta_C(CDCl_3)$ 16.20 and 18.85 (C^{γ} of D-Hylv), 21.15 and 22.95 (C^{γ} of Pro), 30.72 (C^{β} of D-Hylv), 28.60 and 31.50 (C^{β} of Pro), 47.20 and 47.38 (C^{δ} of Pro), 57.45 and 58.95 (C^{α} of Pro), 81.05 (C^{α} of D-Hylv), and 167.7, 170.3, and 170.9 (–CO); *m/z* 294 (M^+, 7%), 251(12), 225(10), 153(8), 125(60), 97(23), and 70(100) (Found: C, 61.0; H, 7.5; N, 9.5. $C_{15}H_{22}N_2O_4$ requires C, 61.2; H, 7.5; N, 9.5%).

Crystal Structure Determinations.—Suitable single crystals of *cyclo*(-Hylv-Pro-Pro-) (LLL) and of *cyclo*(-D-Hylv-Pro-Pro-) (DLL) were grown from ethyl acetate–diethyl ether. The space groups and the approximate unit-cell parameters were determined from oscillation and Weissenberg photographs. The intensity data of LLL were measured at room temperature with a Syntex $P2_1$ automatic diffractometer equipped with graphite monochromator and Mo-K_{α} radiation, in ω-scan mode. For DLL, a Nicolet P3m diffractometer, Cu-K_{α} radiation and 2θ–θ scan mode were used. The refined unit-cell parameters were determined by least-squares calculations of the angular setting (θ, φ, χ) of 15 selected reflections.

Crystal data for LLL: $C_{15}H_{22}N_2O_4$, M = 294.35, orthorhombic, a = 9.642(3), b = 10.177(2), c = 15.626(6) Å, V = 1 533 Å^3, Mo-K_{α}, λ = 0.710 69 Å, space group $P2_12_12_1$, Z = 4, D_x = 1.275 g cm^{-3}, μ(Mo-K_{α}) = 1.0 cm^{-1}, colourless crystal of dimensions 0.4 × 0.3 × 0.6 mm.

Crystal data for DLL: $C_{15}H_{22}N_2O_4$, M = 294.35, orthorhombic, a = 6.138(1), b = 15.695(3), c = 15.794(3) Å, V = 1 522 Å^3, Cu-K_{α}, λ = 1.5418 Å, space group $P2_12_12_1$, Z = 4, D_x = 1.285 g cm^{-3}, μ(Cu-K_{α}) = 7.8 cm^{-1}, colourless crystal of dimensions 0.4 × 0.4 × 0.5 mm.

Three standard reflections, measured every 50, did not reveal any *X*-ray damage of the crystals nor instability of the experimental apparatus. For LLL the data collection was carried out with the following experimental constants: $\Delta\omega$ = 0.9°, $(\sin\theta/\lambda)_{max.}$ = 0.70, scan speed 1.0—29.3° min^{-1} according to the intensity. Of the 1 988 independent reflections measured, 1 915 had $I \geqslant 2\sigma(I)$, and these were used for the structure elucidation. For the DLL the following experimental conditions were chosen: $\Delta\theta$ = 2° + 0.35 tan θ, $(\sin\theta/\lambda)_{max.}$ =

0.55, scan speed 1.5—29.3° min^{-1} depending on the intensity of the measured reflection. 1 340 independent reflections were recorded of which 1 256, having $I \geqslant 1.0\sigma(I)$, were considered observed. Lorentz and polarization corrections were applied to both data sets but intensities were not corrected for extinction or absorption effects. The data were transferred to absolute scale by Wilson statistics. The structures were solved by multisolution direct methods with MULTAN[20] using the 300 and 350 largest values for LLL and DLL, respectively.

The atomic parameters were refined by block-diagonal (9 × 9) least-squares calculations, minimizing the quantity $\Sigma w(|F_o| - |F_c|)^2$ with $w = (a + |F_o| + b|F_o|^2)^{-1}$. The parameters a and b were given values of $2F_o$(min.) and $2/F_o$(max.), respectively, in order to obtain $\langle w(|F_o| - |F_c|)^2 \rangle$ nearly constant in the ranges of F_o and sin θ/λ. Difference Fourier syntheses of electron density, computed at the end of anisotropic refinement, showed all the hydrogen atoms in stereochemically feasible positions. The co-ordinates of the hydrogen atoms, with isotropic thermal parameters equal to those of the carrier atoms, were included and kept fixed in the last few cycles of least-squares calculations. The refinement converged to $R = 0.043$ and $R_w = 0.059$ for LLL and to $R = 0.049$ and $R_w = 0.075$ for DLL. At the convergence the shift-to-error ratios were less than 0.6 for all refined parameters. The calculations for the structure solutions were carried out on the UNIVAC 1100/80 computer of the University of Rome. All the other calculations were performed on the HP 1000 minicomputer of the CNR Research Area of Rome, using the crystallographic software developed in our laboratories;[21] atomic scattering factors were taken from the literature.[22]

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