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Crystal Structure and Spectroscopic Properties of Cyclic Dipeptide: A Racemic Mixture of *cyclo*(D-Prolyl-L-Tyrosyl) and *cyclo*(L-Prolyl-D-Tyrosyl)

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Two diastereoisomers of *cyclo*(Pro-Tyr) have been synthesized simultaneously. The crystal structures and conformations of both *cyclo*(L-Pro-L-Tyr) and a racemic mixture of *cyclo*(D-Pro-L-Tyr) and *cyclo*(L-Pro-D-Tyr), abbreviated as *rac-cyclo*(D-Pro-L-Tyr/L-Pro-D-Tyr), have been determined by a single-crystal X-ray diffraction study at low temperature. The crystals of *rac-cyclo*(D-Pro-L-Tyr/L-Pro-D-Tyr) belong to orthorhombic space group $Pna2_1$ with a = 10.755 (1), b = 12.699 (1), c = 9.600 (1) Å and Z = 4. The tyrosine side chain is folded towards the diketopiperazine (DKP) ring. The DKP ring adopts a twist boat conformation with pseudo symmetry C_{2v}. The pyrrolidine ring has an envelope conformation with the N5, C4, C7 and C8 atoms in a plane. The crystal of *rac-cyclo*(D-Pro-L-Tyr/L-Pro-D-Tyr) is stabilized by hydrogen bonds between amide N2-H2 and carbonyl oxygen O2 in the neighbor. The hydroxyl group of tyrosine residue is also hydrogen bonded to the oxygen of the carbonyl group of the DKP ring in the next molecule. The spectroscopic properties of both isomers are also described.

Key Words : Crystal structure, Conformation, *rac-cyclo*(D-Pro-L-Tyr/L-Pro-D-Tyr), Cyclic dipeptide, Spectral data

Introduction

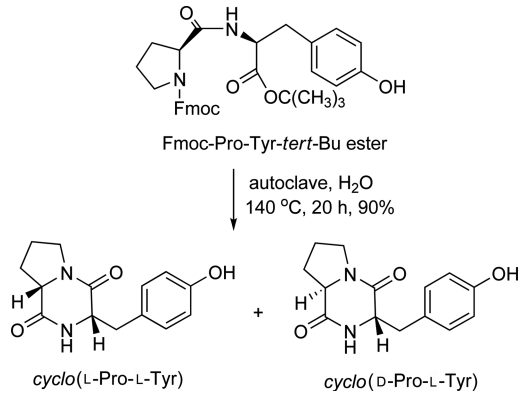
Cyclic peptides are relatively simple molecules that occur both naturally and synthetically. Some cyclic dipeptides have shown potentially beneficial biological activities such as antiviral, anti-tumor, antibiotics, toxins, ion-transport regulators, protein binding inhibitors and enzyme inhibitors.[1-4] Because cyclic dipeptides have many potential biological functions, investigating the preferred conformations of cyclic dipeptides is very important thing to exploring their functionary mechanism and their further undiscovered biological characteristics. In addition, the cyclic dipeptides are very useful for studying the influence that intramolecular forces impose on conformation and structure. To understand the specific function of each peptide, it is necessary to determine their detailed structure and conformation.[5] Recently, results have been presented of an NMR study supported by *ab initio* calculations and X-ray diffraction of four zwitterionic dipeptides.[6]

The *cyclo*(L-Pro-L-Tyr), commonly known as maculosin, is a hostspecific phytotoxin produced by the *Alternaria alternate* fungus, a pathogen for spotted knapweed. The *cyclo*(Pro-Tyr) was isolated from *Photorhabdus temperata subsp. temperata* (PTT) fermentation and structurally identified using spectroscopic methods. The preparation, spectral data, crystal structure and chitinase inhibitor of *cyclo*(L-Pro-L-Tyr) have been reported.[7-9] The *cyclo*(L-Pro-L-Tyr) was formed *via* the cyclization of L-Tyr-L-Pro derivatives. Interestingly, the unknown dipeptide a racemic mixture of *cyclo*(D-Pro-L-Tyr) and *cyclo*(L-Pro-D-Tyr) isomers could be prepared from a L-Pro-L-Tyr derivative, Fmoc-Pro-Tyr-^{t}Bu ester coupled from Fmoc-L-proline and L-tyrosine *tert*-butyl ester.

In this paper, we report a new synthetic method, and describe the crystal structural and spectroscopic properties of *cyclo*(L-Pro-L-Tyr) and *rac-cyclo*(D-Pro-L-Tyr/L-Pro-D-Tyr) in order to elucidate the conformation of the different isomer and understand the intermolecular forces that lead to a preference for specific conformation.

Experimental

Materials and Physical Measurements. All reagents were of commercial quality, were purchased from commercial sources (Aldrich, Fluka) and were used without further purification. The solvents were of reagent grade, and were



Scheme 1. Syntheses of *cyclo*(L-Pro-L-Tyr), **1** and *cyclo*(D-Pro-L-Tyr), **2**.

purified by the usual methods. The NMR spectra were obtained on a Bruker AVANCE digital 400 MHz nuclear magnetic resonance spectrometer. The mid-infrared spectrum was obtained from a KBr pellet with a JASCO 460 plus series FT-IR spectrophotometer. Analyses for C, H, N and O were performed on a Carlo Erba 1108 Elemental Vario EL analyzer.

Synthesis. Fmoc-L-Pro-L-Tyr-^{t}Bu ester (4.59 g, 8.24 mmol) in a teflon flask was dissolved in water (165 mL). The reaction vessel was fixed inside a stainless autoclave with a pressure regulating system. The autoclave was sealed and the mixture was heated to 140 °C for 20 h (Scheme 1).

The reaction mixture was then stopped by cooling and depressurizing the autoclave. After water was evaporated *in vacuo*, the remaining residue was purified by column chromatography using silica gel (MeOH/MC, 1:20) to obtain the desired *rac-cyclo*(D-Pro-L-Tyr/L-Pro-D-Tyr) 0.96 g (45%) and its diastereoisomer *cyclo*(L-Pro-L-Tyr) 0.95 g (45%).

Spectral Data for *cyclo*(L-Pro-L-Tyr), 1: ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.19 (s, 1H), 7.87 (s, 1H), 7.06 (d, J = 8.4 Hz, 2H), 6.65 (d, J = 8.4 Hz, 2H), 4.26-4.24 (m, 1H), 4.05 (t, J = 6.8 Hz, 1H), 3.44-3.36 (m, 2H), 3.29-3.23 (m, 1H), 2.98-2.89 (m, 1H), 2.05-1.98 (m, 1H), 1.80-1.71 (m, 2H), 1.46-1.35 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 168.89, 165.09, 155.88, 130.80, 127.05, 114.76, 58.38, 56.00, 44.54, 34.69, 27.83, 21.85. IR (KBr, cm^{-1}): 3453 vs and 3400 vs (ν OH), 3260 vs, 3216 s and 3172 m (ν NH), 3046 m and 3015 m (aromatic ν CH), 2954 m, 2900 s and 2873 w (ν CH), 1680 vs and 1651 s (ν C=O), 1594 m (ν C=C), 1515 m, 1479 s and 1446 m (δ NH), 1359 w (ν CN), 1332 s, 1306 s, 1272 s (δ NH), 1252 s, 1233 m, 1207 w, 1115 s, 1062 m, 1008 w, 962 m and 949 m, 875 m, 844 m, 823 m, 808 s, 722 s, 582 s, 507 s, 454 s, 426 m. *Anal.* calcd. C 64.60, H 6.20, N 10.76, O 18.44%; found C 64.30, H 6.04, N 10.74, O 18.65%.

Spectral Data for *rac-cyclo*(D-Pro-L-Tyr/L-Pro-D-Tyr), 2: ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.32 (s, 1H), 8.12 (s, 1H), 6.91 (d, J = 8.4 Hz, 2H), 6.68 (d, J = 8.4 Hz, 2H), 3.94-3.91 (m, 1H), 3.45-3.39 (m, 1H), 3.23-3.17 (m, 1H), 2.95-2.85 (m, 2H), 2.77 (d, J = 13.6, 4.8 Hz, 1H), 2.00-1.91 (m, 1H), 1.81-1.76 (m, 1H), 1.62-1.50 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 168.32, 164.86, 156.34, 130.77, 125.88, 115.07, 58.14, 57.17, 44.55, 38.61, 28.55, 21.30. IR (KBr, cm^{-1}): 3404 vs (ν OH), 3191 vs (ν NH), 3054 m (aromatic ν CH), 2955 s, 2930 s and 2870 m (ν CH), 1660 vs (ν C=O), 1590 w (ν C=C), 1453 s (δ NH), 1356 m (ν CN), 1337 s, 1305 s, 1277 s, 1249 m, 1231 m, 1207 m, 1115 s, 1069 w, 1002 w, 957 m, 873 m, 844 s, 821 m, 729 s, 586 s, 497 w, 456 s, 431 m. *Anal.* calcd. C 64.60, H 6.20, N 10.76, O 18.44%; found C 64.33, H 6.04, N 10.74, O 18.87%.

Crystal Structure Analysis. The colorless block crystal of isomer **1** (0.30 × 0.20 × 0.10 mm^3) and prismatic crystal of isomer **2** (0.40 × 0.30 × 0.20 mm^3) were mounted with a cryoloop and flash-cooled with cold nitrogen stream. All measurements were conducted on a Rigaku RAXIS RAPID imaging plate area detector with graphite monochromated Mo-Kα radiation at low temperature. The structures were solved by direct methods[10] and expanded using SHELXL-97.[11] The non-hydrogen atoms were refined anisotropically, while the hydrogen atoms were refined isotropically. All calculations were performed using the Crystal Structure[12] crystallographic software package. A summary of crystallographic data, the experimental details and the refinement results are listed in Table 1. Molecular graphics were produced using DIAMOND-3.[13]

Table 1. Crystallographic data and structure refinement for *cyclo*(L-Pro-L-Tyr), **1** and *rac-cyclo*(D-Pro-L-Tyr/L-Pro-D- Tyr), **2**

	1	**2**
Chemical formula	$C_{14}H_{16}N_2O_3$	$C_{14}H_{16}N_2O_3$
M_r	260.29	260.29
Crystal system	Orthorhombic	Orthorhombic
Space group	$P2_12_12$	$Pna2_1$
Temperature (K)	191 (2)	185 (2)
a (Å)	11.873 (2)	10.755 (1)
b (Å)	12.031 (2)	12.699 (1)
c (Å)	18.388 (2)	9.600 (1)
V (Å^3)	2626.5 (4)	1311.2 (2)
Z	8	4
Radiation type	Mo $K\alpha$	Mo $K\alpha$
μ (mm^{-1})	0.09	0.09
Crystal size (mm^3)	0.30 × 0.20 × 0.10	0.40 × 0.30 × 0.20
T_{min}, T_{max}	0.972, 0.991	0.963, 0.982
No. of measured, independent and observed [$I > 2\sigma(I)$] reflections	23443, 5968, 4603	12245, 2967, 2747
R_{int}	0.044	0.025
$R[F^2 > 2\sigma(F^2)]$, $wR(F^2)$, S	0.037, 0.072, 1.011	0.032, 0.087, 1.10
No. of reflections	5968	2967
No. of parameters	472	237
$\Delta\rho_{max}$, $\Delta\rho_{min}$ (e Å^{-3})	0.16−0.15	0.26−0.13

Results and Discussion

Crystallography. The structures of both *cyclo*(L-Pro-L-Tyr), **1** and *rac-cyclo*(D-Pro-L-Tyr/L-Pro-D-Tyr), **2** have been determined using single crystal X-ray analysis at low temperature. The crystals of the LL isomer **1** are orthorhombic, space group $P2_12_12$, a = 11.873 (2), b = 12.031 (2), c = 18.388 (2) Å and Z = 8 which are consistent with the previously reported X-ray structural results.[7] We can confirm that two conformers of the LL isomer differ with respect to their tyrosyl side chains, the diketopiperazine (DKP) and pyrrolidine rings. However, the structure analysis of the DL/LD isomer **2** shows the space group of orthorhombic, space group $Pna2_1$, a = 10.746 (1), b = 12.699 (1), c = 9.600 (8) Å and Z = 4. The intramolecular bond lengths and angles not involving hydrogen atoms for *cyclo*(L-Pro-L-Tyr), **1** and *rac-cyclo*(D-Pro-L-Tyr/L-Pro-D-Tyr), **2** are listed in Tables 2 and 3, respectively.

An ellipsoid plot of both the LL and DL isomers together with the atomic labeling are also illustrated in Figures 1 and 2, respectively. Hydrogen atoms are shown as arbitrary

Table 2. Selected bond distances (Å) and angles (°) for *cyclo*(L-Pro-L-Tyr), **1**

O1—C3	1.2438 (17)	C11—C12	1.394 (2)
O2—C6	1.2406 (18)	C11—C16	1.395 (2)
O3—C14	1.369 (2)	C12—C13	1.387 (2)
O31—C36	1.239 (2)	C13—C14	1.384 (2)
O32—C33	1.2403 (19)	C14—C15	1.394 (2)
O33—C44	1.3731 (19)	C15—C16	1.384 (2)
N2—C3	1.323 (2)	C31—C36	1.514 (2)
N2—C1	1.460 (2)	C31—C40	1.541 (2)
N5—C6	1.323 (2)	C33—C34	1.497 (2)
N5—C4	1.460 (2)	C37—C38	1.518 (3)
N5—C7	1.473 (2)	N35—C34	1.457 (2)
N32—C33	1.323 (2)	N35—C37	1.479 (2)
N32—C31	1.465 (2)	C38—C39	1.533 (3)
N35—C36	1.323 (2)	C39—C34	1.528 (3)
C1—C6	1.515 (2)	C40—C41	1.503 (2)
C1—C10	1.549 (2)	C41—C46	1.392 (2)
C3—C4	1.501 (2)	C41—C42	1.394 (2)
C4—C9	1.516 (2)	C46—C45	1.388 (2)
C9—C8	1.531 (3)	C45—C44	1.386 (2)
C8—C7	1.519 (3)	C44—C43	1.384 (2)
C10—C11	1.508 (2)	C43—C42	1.388 (2)

Table 3. Selected bond distances (Å) and angles (°) for *rac-cyclo*(D-Pro-L-Tyr/L-Pro-D-Tyr), **2**

O1—C3	1.2382 (18)	O2—C6	1.2351 (19)
O3—C14	1.3687 (19)	N2—C1	1.4606 (19)
N2—C3	1.3326 (18)	N5—C4	1.4692 (19)
N5—C6	1.3277 (18)	N5—C7	1.471 (2)
C1—C6	1.522 (2)	C8—C9	1.532 (3)
C1—C10	1.547 (2)	C11—C16	1.391 (2)
C3—C4	1.514 (2)	C11—C12	1.401 (2)
C4—C9	1.519 (2)	C12—C13	1.395 (2)
C7—C8	1.527 (3)	C14—C15	1.393 (2)
O1—C3—N2	122.71 (13)	C15—C16	1.393 (2)
O2—C6—C1	120.94 (12)	O1—C3—C4	120.76 (12)
O3—C14—C13	122.76 (14)	O2—C6—N5	122.65 (13)
C3—N2—C1	125.01 (12)	O3—C14—C15	117.38 (14)
C6—N5—C4	125.30 (12)	C6—N5—C7	123.10 (14)
N2—C1—C6	112.07 (12)	C4—N5—C7	111.59 (13)
N2—C3—C4	116.53 (13)	N2—C1—C10	112.16 (12)
N5—C4—C9	101.84 (12)	N5—C4—C3	112.88 (11)
N5—C6—C1	116.39 (12)	C3—C4—C9	114.82 (13)
C6—C1—C10	109.91 (12)	N5—C7—C8	103.30 (14)
C4—C9—C8	102.05 (15)	C12—C11—C10	121.14 (14)
C7—C8—C9	105.41 (15)	C13—C12—C11	120.78 (14)
C11—C16—C15	121.38 (14)	C15—C14—C13	119.86 (14)
C16—C11—C10	120.34 (13)	C16—C11—C12	118.45 (14)

circles.

The orientation of the aromatic ring in the tyrosyl residue is folded towards the DKP ring. These side chain conformations are very similar to the folded arrangement of LL isomer **1**. A point of interest is the conformation of the DKP ring which involves two cis peptide bonds. The DKP ring is nearly planar and adopts a twist boat conformation with pseudo symmetry C_{2v}. The six-membered DKP ring exists as either a flat chair or slightly puckered twist boat forms.[14]

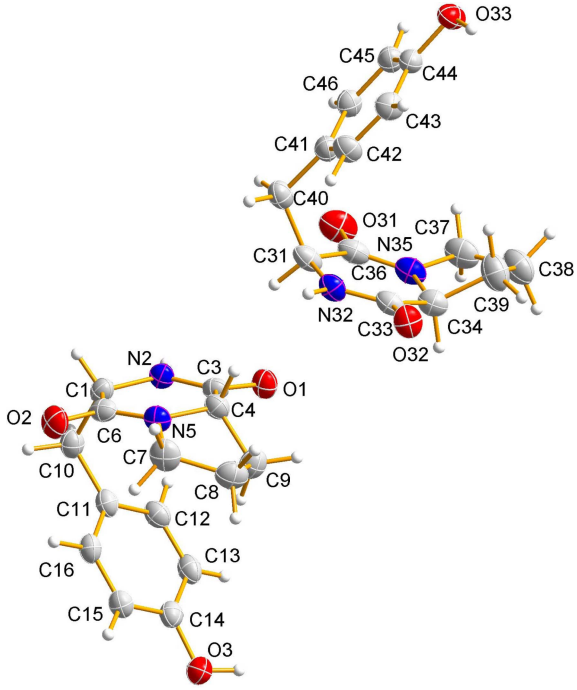


Figure 1. Perspective view of the *cyclo*(L-Pro-L-Tyr) showing the atom-labeling scheme. Displacement ellipsoids are drawn at the 50% probability level.

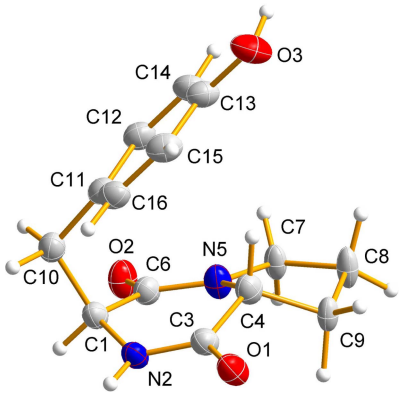


Figure 2. Perspective view of the *cyclo*(D-Pro-L-Tyr) showing the atom-labeling scheme. Displacement ellipsoids are drawn at the 50% probability level.

The conformation of the DKP ring in DL/LD isomer **2** is significantly different from the observed flattened chair conformations in the two conformers of LL isomer **1**.[7] The H atoms on C1 and C4 are in the axial positions and are oriented towards the opposite side of the DKP ring. The C1-C10 bond of 1.547 (2) Å has a normal value, but is slightly longer than the C4-C9 bond of 1.519 (2) Å. It appears that the longer distance can be attributed to the steric hindrance of the phenol group connected to C10. As expected, the O1-C3 and O2-C6 bond lengths of the DKP ring are shorter than

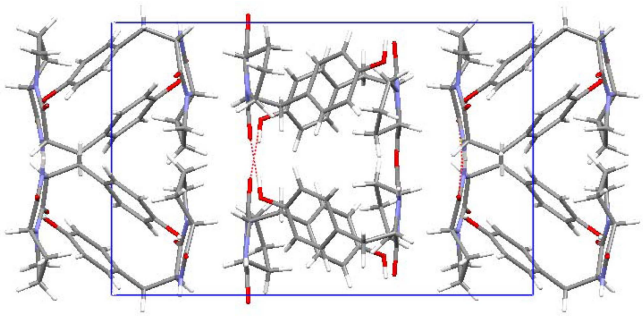


Figure 3. Hydrogen-bonded structure of *cyclo*(L-Pro-L-Tyr), viewed along the *b* axis.

Table 4. Hydrogen-bonding geometry (Å, °) for *cyclo*(L-Pro-L-Tyr), **1** and *rac-cyclo*(D-Pro-L-Tyr/L-Pro-D-Tyr), **2**

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
Isomer **1**[a]				
O3—H3···O2[i]	0.93 (2)	1.78 (2)	2.698 (2)	166.64
O33—H33···O31[ii]	0.92 (2)	1.78 (2)	2.692 (2)	175.51
N2—H2···O1[iii]	0.91 (2)	1.99 (2)	2.899 (2)	177.46
N32—H32···O32[iv]	0.83 (2)	2.13 (2)	2.945 (2)	163.25
Isomer **2**[b]				
N2—H2···O2[i]	0.83(2)	2.02(2)	2.854(2)	175.42
O3—H3···O1[ii]	0.88(2)	1.82(2)	2.691(2)	174.17

[a]Symmetry codes: (*i*) *x*−1/2, −*y*+1/2, −*z*+1; (*ii*) −*x*+3/2, *y*−1/2, −*z*; (*iii*) −*x*+2, −*y*+1, *z*; (iv) −*x*+2, −*y*, *z*. [b]Symmetry codes: (*i*) −*x*, −*y*+1, *z*−1/2; (*ii*) −*x*+1, −*y*+1, *z*+1/2

the O3-C14 bond of the hydroxyl group. For the envelope conformation of the pyrrolidine ring, the N5, C4, C7 and C8 are almost in a plane, while C9 is out of the plane. The *cyclo*(L-Pro-L-Tyr) molecules are linked together by a network of hydrogen bonds as shown in Figure 3. The two carbonyl oxygens of the DPK ring form hydrogen bonds with the OH group of the tyrosyl residue and the NH group

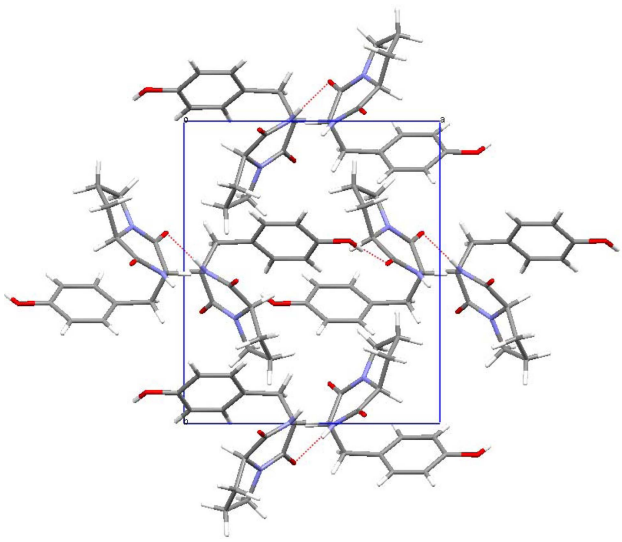


Figure 4. Hydrogen-bonded structure of *cyclo*(D-Pro-L-Tyr), viewed along the *c* axis.

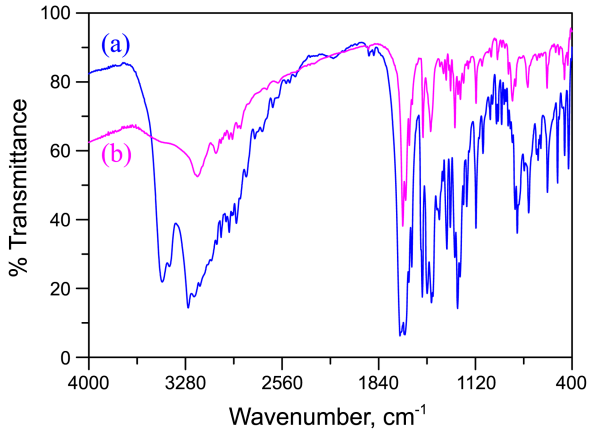


Figure 5. FT-IR spectra of (a) *cyclo*(L-Pro-L-Tyr) and (b) *rac-cyclo*(D-Pro-L-Tyr/L-Pro-D-Tyr).

of the DPK ring in the neighbor (Table 4).

Both oxygens of the two carbonyl groups of the DKP ring in a racemic mixture of the DL and LD isomers, **2** are also involved in N–H···O and O–H···O type interactions with the hydrogens of the amide and hydroxyl group of tyrosine residue, respectively (Table 4 and Fig. 4). These hydrogen-bonded networks help to stabilize the crystal structure of racemic DL/LD isomer **2**. The different DKP conformations of the two LL and DL/LD isomers may be attributed to the difference in the intermolecular hydrogen pattern and crystal packing force between **1** and **2**.

Infrared Spectroscopy. The FT-infrared spectra of *cyclo*(L-Pro-L-Tyr) and *rac-cyclo*(D-Pro-L-Tyr/L-Pro-D-Tyr) recorded at room temperature are presented in Figure 5. The bands in the 3260-3000 cm^{-1} and 3000-2850 cm^{-1} region are due to the symmetric and antisymmetric N-H and C-H stretching modes, respectively.

The peaks at 3054 and 728 cm^{-1} of *rac-cyclo*(D-Pro-L-Tyr/L-Pro-D-Tyr) are assigned to the aromatic ν(C–H) and C–H out-of-plane bending modes of the tyrosine group, while a peak at 1612 cm^{-1} is assigned to the aromatic C=C stretching mode. The spectrum contains a typical ν(C=O) stretching band at 1660 cm^{-1}. Absorption bands of 1453 and 1272 cm^{-1} are assigned to δ(NH) and δ(CH) bending modes, respectively. The FT-infrared spectrum of the LL isomer **1** exhibits a more complicated splitting of the main absorptions than that of DL isomer **2**, this may be due to the crystallization of the two conformations. However, the infrared spectral properties and the spectroscopic data do not clarify whether the compound is *rac-cyclo*(D-Pro-L-Tyr/L-Pro-D-Tyr) or its diastereoisomer, *cyclo*(L-Pro-L-Tyr).

Conclusions

The pure isomers of *cyclo*(L-Pro-L-Tyr) and a racemic mixture of *cyclo*(D-Pro-L-Tyr) and *cyclo*(L-Pro-D-Tyr) were successfully synthesized. It is found that the *cyclo*(D-Pro-L-Tyr) isomer crystallizes in the space group $Pna2_1$ of the orthorhombic system with four mononuclear formula units in a cell. Thus the crystals contain both enantiomers of

cyclo(D-Pro-L-Tyr) and *cyclo*(L-Pro-D-Tyr). The orientation of the aromatic ring is folded towards the diketopiperazine (DKP) ring and the DKP ring adopts a twist boat conformation. The conformation of the DKP ring in the racemic DL/LD isomer is therefore different from the flattened chair conformation of the LL isomer. In the title compound, the crystal lattice is stabilized by the hydrogen bonding interactions between the amide NH including the hydrogen of the hydroxyl group of tyrosyl and the two oxygens of carbonyl group of the DKP ring. The spectroscopic properties are in agreement with the results from X-ray crystallography. From the biological activity tests, the compound showed high inhibiting biological activities for the phospholipase A_2 (PLA_2) enzyme, and a insecticidal property on the Diamondback moth, *Putella xylostella*.

Supplementary Material. Full crystallographic data have been deposited with the Cambridge Crystallographic Data Centre, CCDC-892344 and 892343 for structures of isomers **1** and **2**, respectively. Copies of this information may be obtained free of charge from The Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (Fax: +44-1223-336-033; E-Mail: deposit@ccdc.cam.ac.uk or www: http://www.ccdc.cam.ac.uk).

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