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Phthalimide as a chromophoric tag in the circular dichroism determination of absolute configuration of α-aminoacid amides and dipeptides. A case of a dipeptide isostructurality

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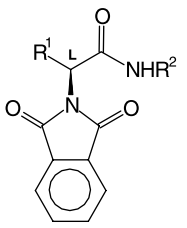
Abstract—Both *N*-phthaloyl aminoacid amides and methyl amides as well as *N*-phthaloyl dipeptide methyl esters give Cotton effects of opposite signs at around 220 and 240 nm. The signs of these Cotton effects are directly correlated with the absolute configuration of the *N*-phthaloyl substituted stereogenic center: for L-configuration the Cotton effect at 240 nm is positive and the Cotton effect at 220 is negative. The X-ray analysis shows that the diastereomeric L,D and L,L *N*-phthaloyl alanylvaline methyl esters form isostructural orthorombic crystals due to the conformational flexibility of the molecules and a similar space requirements of the methoxycarbonyl and isopropyl groups.

1. Introduction

The amino group, often present in chiral compounds, is a non-Cottonogenic group. This limits its use as a chromophore in chiroptical (i.e. electronic circular dichroism, CD) studies. Some time ago we introduced the *N*-phthaloyl group as a chromophoric derivative of the amino group for CD studies.[1] This group offers the advantage of having a strong charge-transfer $\pi-\pi^*$ transition at 220 nm, suitable for exciton coupling with other transitions. In addition, this transition is polarized along the C_2 axis of the phthalimide chromophore, i.e. it is collinear with the amine C–N bond[2]—a feature of essential significance in the analysis of the exciton-split Cotton effects. Apart from absolute configuration determination, the above method has been used in conformational analysis[3] and it has been extended to some other phthalimide analogues.[4]

Prompted by continuing applications of the phthaloyl group in peptide chemistry[5] in this paper we wish to present the application of the CD method to the determination of absolute configuration of *N*-phthaloyl aminoacid amides (**1**) and dipeptides (**2**).



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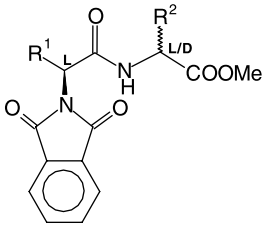

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2. Results and discussion

Table 1 presents the CD data for *N*-phthaloyl derivatives of L-aminoacid amides. In all cases studied the observed Cotton effect at 219–226 nm is negative and it originates from exciton coupling of the phthalimide long axis polarized electric dipole transition moment with the $\pi-\pi^*$ electric dipole transition moment of the amide group.[6] These results can be readily correlated with the low-energy

Table 1. CD data for acetonitrile solutions of L-*N*-phthaloyl aminoacid amides **1**

R^1	R^2	$\Delta\varepsilon$ (nm)	
Me	H	+1.7 (242)	−4.3 (223)
Me	Me	+2.1 (243)	−5.3 (226)
*i*Pr	H	+1.8 (242)	−4.3 (223)
*i*Pr	Me	+2.3 (239)	−7.9 (219)
*i*Bu	H	+2.6 (239)	−7.8 (220)
*i*Bu	Me	+1.8 (244)	−6.8 (226)

Keywords: amino acids and derivatives; circular dichroism; configuration.
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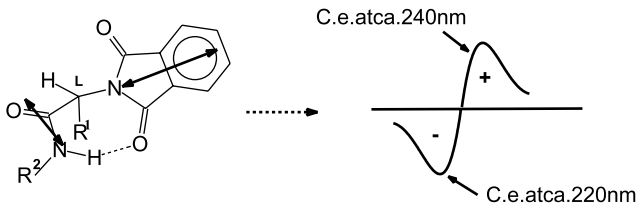

Figure 1. Negative helicity of the $\pi-\pi^*$ transition dipole system of the amide and phthalimide bichromophoric system in the hydrogen bonded conformation and the resulting Cotton effects for L aminoacid.

methanol solution do not show the Cotton effect at ca. 240 nm, while the UV spectra obtained in this solvent do not show any changes in the λ_{max} and absorbance of the phthalimide chromophore, compared to acetonitrile solution. This is a result of free rotation of the phthalimide chromophore around the C–N axis caused by replacing the intramolecular N–H···O=C (phthalimide) hydrogen bond by intermolecular ones with the solvent molecules.

Likewise, the CD data of *N*-phthaloyl dipeptide methyl

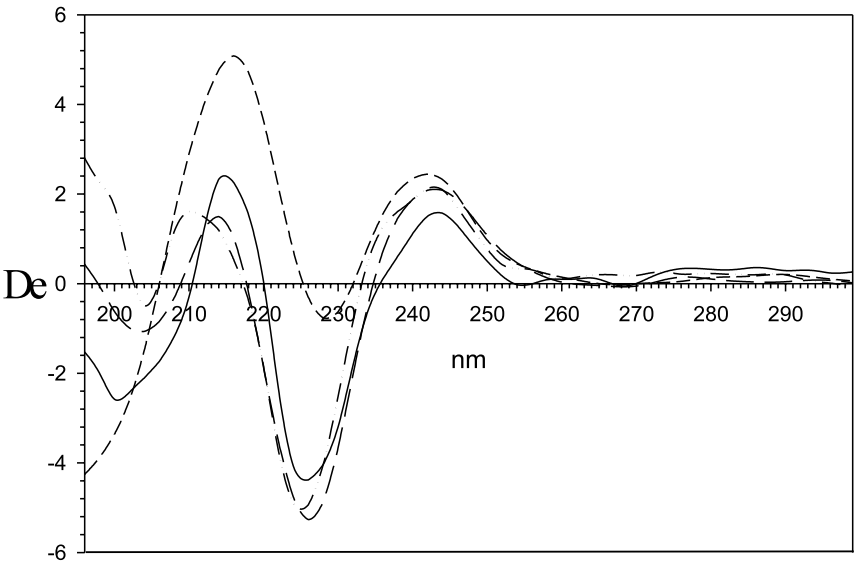

Figure 2. CD spectra of *N*-phthaloyl-L-alanine amide (**1**, R^1=Me, R^2=H, solid line), methylamide (**1**, R^1=R^2=Me, long dashed line), and dipeptides (**2**, R^1=R^2=Me) of L,L (short dashed line) and L,D (dash-dot line) configuration.

conformer of **1** (R^1=Me, R^2=H or Me) calculated by the semiempirical method (AM1), as shown in Fig. 1.

Fig. 2 shows the typical CD spectra for derivatives of *N*-phthaloyl-L-alanyl amides and dipeptides. The lower energy CD band at 239–244 nm results from the weak phthalimide transition (present in the UV spectra as a shoulder of the strong 220 nm band) which is polarized orthogonally to the 220 nm transition[2] and hence its sign is positive in all cases. This coupling was not seen for *N*-phthaloyl aminoacids or their esters[7] as $\pi-\pi^*$ transition in carboxyl and ester chromophores is blue shifted compared to $\pi-\pi^*$ transition in amides. The CD spectra of amides and methylamides **1** are a superposition of exciton Cotton effects arising from coupling the $\pi-\pi^*$ transitions in the amide chromophore with both $\pi-\pi^*$ transitions in the phthalimide

The low-energy conformer shown in Fig. 1 is evidently stabilized by a hydrogen bond between the N–H donor and the phthalimide C=O acceptor. The presence of such a hydrogen bond in acetonitrile solution of the amide and *N*-methylamide of *N*-phthaloyl-L-alanine is suggested by the presence of the IR bands at 3360 and 3397 cm^{-1}, respectively. A similar conformation was suggested for *N*-acetyl aminoacid methylamides from analysis of the CD and NMR spectra.[8] Furthermore, the CD spectra recorded in esters **2** are collected in Table 2 (see also Fig. 2). As in the case of amides **1**, the dipeptides **2** show a first (230–240 nm) positive Cotton effect, followed by a negative one at 216–228 nm. The signs of the Cotton effects are insensitive to the configuration of the second, *N*-acylated aminoacid, and they faithfully reflect the absolute configuration of the *N*-phthaloyl aminoacid according to the general scheme shown in Fig. 1. The conformation shown in Fig. 1 (R^2=aminoacid residue) is supported by the presence of the IR band at ca. 3370 cm^{-1} in acetonitrile solution due to the intramolecular hydrogen bond, as well as by semiempirical calculation (AM1) of the minimum energy conformation.

Table 2. CD data for acetonitrile solutions of *N*-phthaloyl dipeptide methyl esters **2**

R^1	R^2	Configuration	$\Delta\varepsilon$ (nm)	
Me	Me	L,L	+2.2 (240)	−0.8 (228)
Me	Me	L,D	+2.1 (240)	−5.0 (225)
Me	*i*Pr	L,L	+1.8 (240)	[a]
Me	*i*Pr	L,D	+2.4 (240)	−2.0 (225)
*i*Pr	Me	L,L	+6.0 (238)	−-5.1 (218)
*i*Pr	Me	L,D	+4.7 (238)	−-8.2 (218)
*i*Pr	*i*Pr	L,L	+9.7 (230)	−-8.6 (216)
*i*Pr	*i*Pr	L,D	+7.5 (233)	−12.8 (219)

[a] Minimum not reached due to additional positive Cotton effect at a shorter wavelength.

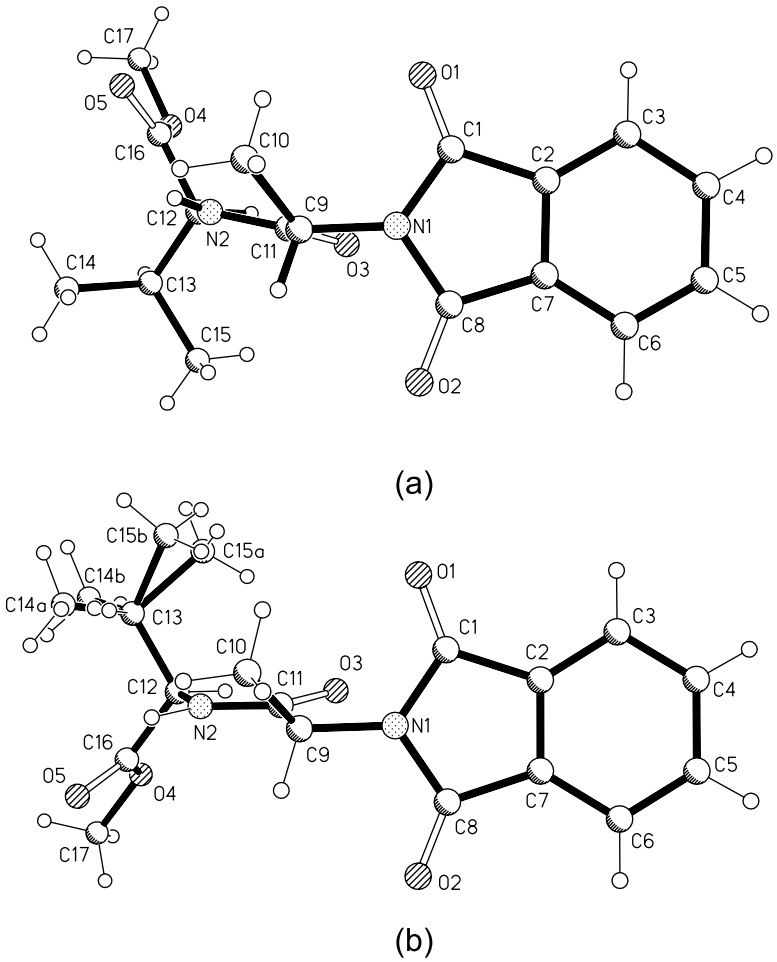

Figure 3. Molecules of diastereomers L,L (a), and L,D (b), viewed perpendicular to the phtalimide moieties. Both sites of the disordered isopropyl substituent are shown for the L,D molecule.

The positive CD band of **2** at above 240 nm vanishes in polar solvents like methanol, as was seen and explained in the case of *N*-phthaloyl aminoacid amides **1**.

Incidentally, similarity of the Cotton effects pattern of the L,L and L,D dipeptide pairs is corroborated by the results of structure determination in the crystal. X-Ray structure determination of *N*-phthaloyl alanylvaline methyl esters revealed that the crystals of L,L and L,D isomers are clearly isostructural, as can be seen from the same space group and similar unit cell dimensions, listed in Table 4 (Section 4). The L,L and L,D molecules are shown in Fig. 3. It is apparent that the overall shape of the molecules, as present in the crystal structure, is similar despite the different chirality of the valine residues. This is due to the opposite conformation about the valine C–N bond. Consequently, as seen clearly from Fig. 3, the ester and the isopropyl groups interchange their positions in these compounds, and the molecules assume similar shapes and similar packing in the crystal lattice. It thus appears that it is the crystal environment that enforces the conformations of the terminal moieties in L,L and L,D isomers. Interestingly, the isopropyl group in L,D isomer is disordered. It is plausible that this is due to the fact that it is located in the volume similar to that occupied by the larger ester group in isomer L,L. Thus the smaller isopropyl group experiences weaker intermolecular interactions and is either statically or dynamically disordered.

Naturally, one could argue that the reciprocal reasoning could be applied to the isopropyl group of the L,L isomer, while the isopropyl is perfectly ordered in L,L. However, the environments of the ester group in L,D and the isopropyl group in L,L isomer are different from the environments of the ester group in L,L and the isopropyl group in L,D, and consequently their properties are also different. It appears that the former of the sites is smaller than the second one, and the stronger intermolecular interactions do not leave space for disorder. This would be supported by a smaller crystal unit cell volume of L,D than L,L (Table 2), despite of the fact that this is the L,D molecule which is disordered and one would expect it to occupy larger molecular volume than the ordered L,L.

The crystal packing in L,L and L,D isomers is shown in Fig. 4.

The torsion angles in the molecules are compared in Table 3. Very weak intermolecular hydrogen bonds, 3.265(6) and 3.191(5) Å in L,L and L,D isomers, respectively, between the N–H and the imide C=O groups can be considered as contributing to the similarity of crystal

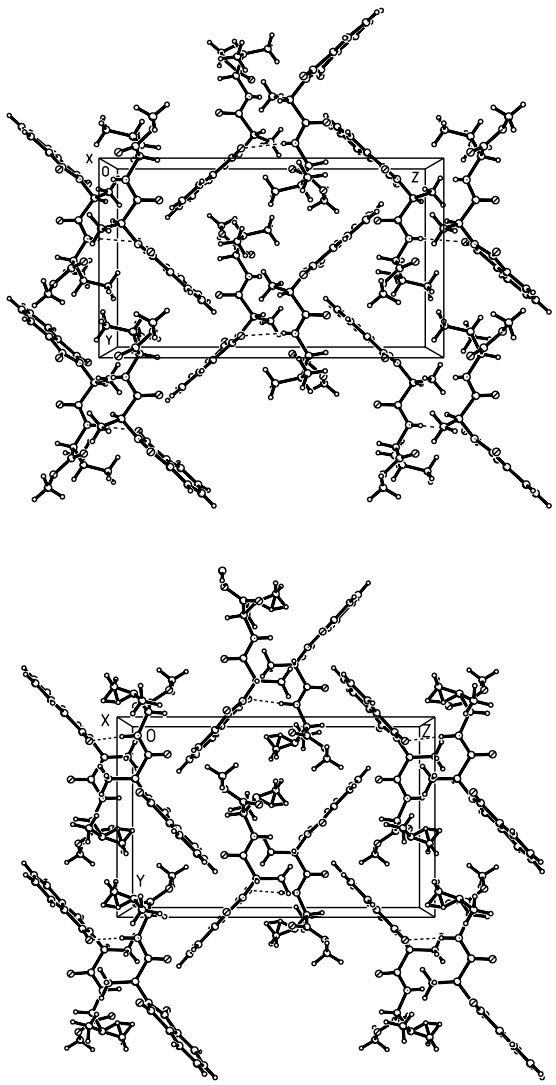

Figure 4. Arrangements of diastereomers L,L (top), and L,D (bottom), in their crystal structures viewed down [100]. In the disordered diastereomer L,D only atoms C(14a) and C(15a) have been shown for clarity. The weak hydrogen bonds have been indicated with the dashed lines.

Table 3. Selected torsion angles for diastereomers L,L and L,D. The first of the values given for L,D describe the torsions involving sites C(14a) or C(15b), and the second torsion involves C(14b) or C(15b)

	Diastereomer	
	L,L	L,D
C8–N1–C9–C10	140.7 (4)	134.0(4)
C1–N1–C9–C10	−56.9 (5)	−59.0(5)
C8–N1–C9–C11	−89.2 (4)	−98.1(4)
C1–N1–C9–C11	73.2 (4)	68.8(4)
C12–N2–C11–O3	−1.5 (6)	1.2(6)
C12–N2–C11–C9	−178.8 (3)	−176.4(4)
N1–C9–C11–O3	17.1 (5)	1.9(5)
N1–C9–C11–N2	−165.5 (3)	179.6(3)
C11–N2–C12–C16	−126.9 (4)	126.3(4)
C11–N2–C12–C13	108.4 (4)	−111.4(6)
N2–C12–C13–C14	58.6 (6)	−69.1(12)/−160.6(14)
N2–C12–C13–C15	−66.4 (6)	79.0(15)/43.0(17)
C13–C12–C16–O5	108.1 (5)	−88.4(7)
N2–C12–C16–O4	162.2 (3)	−144.5(4)

packing. H-bonded molecules form helices along crystal direction [100].

3. Conclusion

We demonstrated that simple measurement of Cotton effects of *N*-phthaloyl aminoacid amide derivatives at ca. 220 nm (the position of the phthalimide $\pi-\pi^*$ absorption maximum) and at ca. 240 nm can be successfully used for determining the aminoacid absolute configuration. From a practical point of view, the correlation with the sign of the 240 nm Cotton effect could be safely extended to other *N*-phthaloyl oligopeptides since any additional contribution coming from the peptide chain Cotton effect is not expected in this spectral region. The L,L and L,D isomers of *N*-phthaloyl alanylvaline methyl esters show remarkable isostructuralism in the crystalline state, as determined by the analysis of X-ray diffraction data.

4. Experimental

4.1. X-Ray structure determination

The crystal data for *N*-phthaloyl L-alanyl-L (or D)-valine methyl esters have been measured using a KUMA KM-4 diffractometer (Table 3). The structures have been solved straightforwardly by direct methods and refined by full-matrix least squares.[9] The difference Fourier maps for the L,D isomer showed two strong electron-density peaks approximately 1.5 Å from C(13)—they indicated that the isopropyl group is disordered in two positions. The model assuming this disorder considerably reduced the reliability factors, and the occupation of the isopropyl group in two sites refined to 0.5. In both L,L and L,D isomers all the hydrogen atoms, except those at N(2), were assumed from molecular geometry and their isotropic thermal parameters were calculated as 1.5 times the equivalent thermal parameters of their carriers; the H(2) atoms were located from difference Fourier maps and refined with isotropic

Table 4. Crystal data and structure refinement for diastereomeric L,L and L,D *N*-phthaloyl alanylvaline methyl esters

	Diastereomer	
	L,L	L,D
Empirical formula	$C_{17}H_{20}N_2O_5$	$C_{17}H_{20}N_2O_5$
Formula weight	332.35	332.35
Temperature (K)	293(2)	293(2)
Wavelength (Å)	0.71073	0.71073
Crystal system	Orthorhombic	Orthorhombic
Space group	$P2_12_12_1$	$P2_12_12_1$
Unit cell dimensions (Å)		
a	9.109 (2)	8.662 (2)
b	10.553 (2)	11.277 (2)
c	18.244 (4)	17.901 (2)
Volume (Å^3)	1753.7 (6)	1748.6 (3)
Z	4	4
Density (calculated) (g/cm^3)	1.259	1.262
Goodness-of-fit on F^2	1.053	1.118
Final R_1/wR_2 indices $I>2\sigma(I)$	0.0568/0.1499	0.0471/0.1259

thermal parameters. The crystal data for L,L and L,D isomers have been deposited in The Cambridge Crystallographic Data Centre as supplementary publications with reference codes CCDC 185535 and CCDC 185536, respectively (Table 4).

4.2. General

IR spectra were recorded with a FT IR Bruker IFS 113v spectrophotometer. ^{1}H NMR were recorded on a Varian EM-360 spectrometer in $CDCl_3$ solutions unless noted otherwise. CD spectra were taken with a Jobin-Yvon III dichrograph in acetonitrile solutions. Optical rotations were measured with a Perkin–Elmer 243B polarimeter. Melting points are uncorrected. High-resolution mass spectra were measured on AMD 402.

Amides of N-phthaloyl-α-aminoacids—general procedure. A solution of *N*-phthaloyl-α-aminoacid chloride (1 mmol) in CH_2Cl_2 (5 ml) was saturated with excess gaseous NH_3 for 30 min. After evaporation, products were purified by column chromatography on silica gel (CH_2Cl_2 as eluent) and crystallized from chloroform–hexane.

N-Methylamides of N-phthaloyl-α-aminoacids—general procedure. To a stirred solution of *N*-phthaloyl-α-amino-acid chloride (1 mmol) in CH_2Cl_2 (5 ml) was added at −10°C a 5.5 M solution of $MeNH_2$ in THF (2 equiv.). Products were purified as above.

N-Phthaloyl dipeptides—general procedure. To a suspension of aminoacid methyl esters hydrochloride (1 mmol) in CH_2Cl_2 (5 ml) was added at −10°C a solution of *N*-phthaloyl aminoacid (1 mmol) and DDC (1 mmol) in CH_2Cl_2 (1 ml). The solution was stirred 10 min at −10°C then 30 min at room temperature. After filtration, the clear solution was washed with 5 ml of 2 M HCl, sat. $NaHCO_3$, and water. After drying with $MgSO_4$ the solution was evaporated and the product was purified by column chromatography on silica gel (eluent 10% MeOH in CH_2Cl_2) and then crystallized from chloroform–hexane.

4.2.1. *N*-Phthaloyl-L-alanine amide. Yield 78%; white crystals; mp 201–203°C; $[\alpha]_D$=+1.3, *c*=1, MeOH; HRMS found 218.07030 $C_{11}H_{10}O_3N_2$ requires 218.06914; ^{1}H NMR (acetone-d_6) δ 1.45 (d, *J*=7.2 Hz, 3H), 4.60 (q, *J*=7.2 Hz, 1H), 6.50 (s, 1H), 7.40 (s, 1H), 7.5–7.8 (m, 4H); IR (KBr) 3437, 3305, 3180, 1775, 1720, 1682, 1610, 1467, 1397, 1345, 1080, 721 cm^{-1}.

4.2.2. *N*-Phthaloyl-L-valine amide. Yield 87%; white crystals; mp 189–191°C; $[\alpha]_D$=−10.7, *c*=1, MeOH; HRMS found 246.09854 $C_{13}H_{14}O_3N_2$ requires 246.10045; ^{1}H NMR δ 0.83 (d, *J*=6.6 Hz, 3H), 1.14 (d, *J*=6.6 Hz, 3H), 2.80 (m, 1H), 4.40 (d, *J*=11.3 Hz, 1H), 5.70 (s, 1H), 6.90 (s, 1H), 7.7–7.9 (m, 4H); IR (KBr) 3400, 3200, 2959, 1772, 1712, 1692, 1651, 1390, 1087, 902, 722, 533 cm^{-1}.

4.2.3. *N*-Phthaloyl-L-leucine amide. Yield 85%; mp 166–168°C (lit. 167°C[10]); $[\alpha]_D$=+30.8, *c*=2, $CHCl_3$ (lit. $[\alpha]_D$=+24.51, *c*=2, $CHCl_3$[10]); ^{1}H NMR (acetone-d_6) δ 0.90 (d, *J*=6.5 Hz, 3H), 0.92 (d, *J*=6.3 Hz, 3H), 1.47 (m, 1H), 1.97 (m, 1H), 2.39 (m, 1H), 4.80 (dd, *J*=4.3, 11.8 Hz, 1H), 6.56 (s, 1H), 7.17 (s,1H), 7.80 (s, 4H); IR (KBr) 3422, 3322, 3180, 1775, 1720, 1682, 1610, 1467, 1397, 1345, 1080, 721 cm^{-1}.

4.2.4. *N*-Phthaloyl-L-alanine *N'*-methylamide. Yield 80%; mp 158–160°C (lit. 160°C[11]); $[\alpha]_D$=−7.9, *c*=1, MeOH (lit. $[\alpha]_D$=−10 Hz, *c*=5.3, $CHCl_3$[11]); ^{1}H NMR δ 1.70 (d, *J*=7.4 Hz, 3H), 2.80 (d, *J*=4.7 Hz, 3H), 4.95 (d, *J*=4.4 Hz, 1H), 6.14 (s, 1H), 7.7–7.9 (m, 4H); IR (KBr) 3272, 3062, 2944, 1775, 1714, 1650, 1554, 1382, 1152, 1031, 880, 722, 529 cm^{-1}.

4.2.5. *N*-Phthaloyl-L-valine *N'*-methylamide. Yield 78%; white crystals; mp 138–141°C; $[\alpha]_D$=−25.0, *c*=1, MeOH; HRMS found 260.11574 $C_{14}H_{16}O_3N_2$ requires 260.11609; ^{1}H NMR δ 0.85 (d, *J*=6.6 Hz, 3H), 1.10 (d, *J*=6.7 Hz, 3H), 2.81 (d, *J*=4.8 Hz, 3H), 2.80 (m, 1H), 4.42 (d, *J*=11.4 Hz, 1H), 6.95 (s, 1H), 7.3–7.9 (m, 4H); IR (KBr) 3273, 2957, 1773, 1709, 1658, 1548, 1472, 1422, 1385, 1350, 1160, 1096, 904, 732, 717, 531 cm^{-1}.

4.2.6. *N*-Phthaloyl-L-leucine *N'*-methylamide. Yield 90%; mp 133–137°C (lit. 136–137°C[11]); $[\alpha]_D$=−94.0, *c*=1, MeOH (lit. $[\alpha]_D$=−31, *c*=5.16, $CHCl_3$[11]). ^{1}H NMR δ 0.95 (d, *J*=6.9 Hz, 6H), 1.45 (m, 1H), 1.84 (ddd, *J*=5.0, 9.7, 14.2 Hz, 1H), 2.37 (ddd, *J*=4.4, 11.5, 14.0 Hz, 1H), 2.80 (d, *J*=4.7 Hz, 3H), 4.91 (dd, *J*=5.0, 11.5 Hz, 1H), 6.28 (s, 1H), 7.7–7.9 (m, 4H).

4.2.7. *N*-Phthaloyl-L-alanyl-L-alanine methyl ester. White crystals; mp 160–162°C; $[\alpha]_D$=−8.6, *c*=1, MeOH; HRMS found 304.10364 $C_{15}H_{16}O_5N_2$ requires 304.10593; ^{1}H NMR δ 1.40 (d, *J*=7.1 Hz, 3H), 1.70 (d, *J*=7.3 Hz, 3H), 3.70 (s, 3H), 4.60 (q, *J*=7.1 Hz, 1H), 4.90 (q, *J*=7.3 Hz, 1H), 5.60 (d, *J*=6.6 Hz, 1H), 7.7–7.9 (m, 4H); IR (KBr) 3475, 2989, 2965, 1773, 1740, 1712, 1657, 1543, 1388, 1343, 1230, 1175, 1143, 1047, 951, 872, 730 cm^{-1}.

4.2.8. *N*-Phthaloyl-L-alanyl-D-alanine methyl ester. White crystals; mp 138–141°C; $[\alpha]_D$=+35.6, *c*=1, MeOH; HRMS found 304.10337 $C_{15}H_{16}O_5N_2$ requires 304.10593; ^{1}H NMR 1.40 (d, *J*=7.1 Hz, 3H), 1.70 (d, *J*=7.3 Hz, 3H), 3.70 (s, 3H), 4.60 (q, *J*=7.1 Hz, 1H), 4.90 (q, *J*=7.3 Hz, 1H), 5.6 (d, *J*=6.6 Hz, 1H), 7.7–7.9 (m, 4H); IR (KBr) 3472, 2991, 2962, 1775, 1739, 1725, 1654, 1544, 1383, 1347, 1228, 1173, 1145, 1054, 949, 876, 729, 713 cm^{-1}.

4.2.9. *N*-Phthaloyl-L-alanyl-L-valine methyl ester. White crystals; mp 108–111°C; $[\alpha]_D$=+6.0, *c*=1, MeOH; HRMS found 332.13971 $C_{17}H_{20}O_5N_2$ requires 332.13721; ^{1}H NMR δ 0.87 (d, *J*=6.8 Hz, 3H), 0.93 (d, *J*=6.8 Hz, 3H), 1.75 (d, *J*=7.3 Hz, 3H), 2.18 (m, 1H), 3.71 (s, 3H), 4.58 (dd, *J*=4.6, 8.5 Hz, 1H), 4.43 (q, *J*=7.3 Hz, 1H), 6.56 (d, *J*=8.3 Hz, 1H), 7.7–7.9 (m, 4H); IR (KBr) 3380, 2958, 1778, 1743, 1709, 1674, 1525, 1466, 1388, 1316, 1216, 1150, 1073, 1024, 881, 727, 531 cm^{-1}.

4.2.10. *N*-Phthaloyl-L-alanyl-D-valine methyl ester. White crystals; mp 136–138°C; $[\alpha]_D$=+43.2, *c*=1, MeOH; HRMS found 332.13617 $C_{17}H_{20}O_5N_2$ requires 332.13721; ^{1}H NMR δ 0.91 (d, *J*=7.1 Hz, 3H), 0.95 (d, *J*=6.8 Hz, 3H), 1.75 (d, *J*=7.3 Hz, 3H), 2.20 (m, 1H), 3.75

(s, 3H), 4.57 (dd, *J*=4.6, 8.5 Hz, 1H), 5.0 (q, *J*=7.3 Hz, 1H), 6.54 (d, *J*=8.3 Hz, 1H), 7.7–7.9 (m, 4H); IR (KBr) 3355, 2962, 2928, 1778, 1742, 1710, 1680, 1533, 1467, 1391, 1207, 1154, 1068, 1022, 882, 730 cm^{-1}.

4.2.11. *N*-Phthaloyl-L-valyl-L-alanine methyl ester. White crystals; mp 88–89°C; $[\alpha]_D=-25.0$, *c*=1, MeOH; HRMS found 332.13532 $C_{17}H_{20}O_5N_2$ requires 332.13721; ^1H NMR δ 0.87 (d, *J*=6.6 Hz, 3H), 1.11 (d, *J*=6.8 Hz, 3H), 1.43 (d, *J*=7.1 Hz, 3H), 2.87 (dq, *J*=6.6, 11.5 Hz, 1H), 3.63 (s, 3H), 4.43 (d, *J*=11.5 Hz, 1H), 4.57 (q, *J*=7.1, 7.3 Hz, 1H), 7.52 (d, *J*=7.3 Hz, 1H), 7.4–7.9 (m, 4H); IR (KBr) 3287, 3064, 3959, 1779, 1763, 1739, 1718, 1650, 1547, 1467, 1380, 1289, 1259, 1150, 1072, 884, 729, 718 cm^{-1}.

4.2.12. *N*-Phthaloyl-L-valyl-D-alanine methyl ester. White crystals; mp 108–110°C; $[\alpha]_D=+15.1$, *c*=1, MeOH; HRMS found 332.13800 $C_{17}H_{20}O_5N_2$ requires 332.13721; ^1H NMR δ 0.86 (d, *J*=6.6 Hz, 3H), 1.13 (d, *J*=6.6 Hz, 3H), 1.40 (d, *J*=7.1 Hz, 3H), 2.88 (m, 1H), 3.74 (s, 3H), 4.43 (d, *J*=11.2 Hz, 1H), 4.50 (m, 1H), 7.45 (d, *J*=6.8 Hz, 1H), 7.7–7.9 (m, 4H); IR (KBr) 3347, 2964, 2874, 1771, 1717, 1539, 1466, 1384, 1264, 1207, 1154, 1069, 1014, 765, 718, 531 cm^{-1}.

4.2.13. *N*-Phthaloyl-L-valyl-L-valine methyl ester. Colorless oil; $[\alpha]_D=-5.85$, *c*=1, MeOH; HRMS found 360.16885 $C_{19}H_{24}O_5N_2$ requires 360.16852; ^1H NMR δ 0.87 (d, *J*=6.6 Hz, 3H), 0.95 (d, *J*=7.1 Hz, 3H), 0.98 (d, *J*=6.8 Hz, 3H), 1.13 (d, *J*=6.6 Hz, 3H), 2.23 (m, 1H), 2.89 (m, 1H), 3.64 (s, 3H), 4.46 (d, *J*=11.5 Hz, 1H), 4.53 (dd, *J*=4.6, 8.8 Hz, 1H), 7.52 (d, *J*=8.5 Hz, 1H), 7.7–7.9 (m, 4H); IR (KBr) 3347, 2964, 2874, 1771, 1717, 1539, 1466, 1384, 1264, 1207, 1154, 1069, 1014, 765, 718, 531 cm^{-1}.

4.2.14. *N*-Phthaloyl-L-valyl-D-valine methyl ester. Colorless oil; $[\alpha]_D=+26.9$, *c*=1, MeOH; HRMS found 360.16805 $C_{19}H_{24}O_5N_2$ requires 360.16852; ^1H NMR δ 0.87 (d, *J*=6.6 Hz, 3H), 0.88 (d, *J*=7.1 Hz, 3H), 0.91 (d, *J*=6.8 Hz, 3H), 1.13 (d, *J*=6.6 Hz, 3H), 2.20 (m, 1H), 2.90 (m, 1H), 3.73 (s, 3H), 4.46 (d, *J*=11.2 Hz, 1H), 4.47 (dd, *J*=4.6, 8.3 Hz, 1H), 7.4 (d, *J*=8.0 Hz, 1H), 7.2–7.9 (m, 4H); IR (KBr) 3359, 2966, 2874, 1771, 1683, 1612, 1539, 1468, 1436, 1386, 1264, 1210, 1157, 1070, 1015, 994, 887, 719, 634, 531 cm^{-1}.

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