# Synthesis of 3-Substituted Dihydro-1-phenylamino-1*H*-pyrrolo[1,2-*a*]imidazole-2,5(3*H*,6*H*)-diones from α-Amino Acid Phenylhydrazides and Levulinic Acid

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*Dedicated to the memory of Professor Angelo G. Giumanini, University of Udine[‡]*

**Keywords:** Amino acids / Cyclization / Heterocycles / Hydrazides / Levulinic acid

α-Amino acid phenylhydrazides **1** readily react with levulinic acid to produce the imidazolidin-4-one intermediates **4**, which undergo a second ring closure to afford the dihydro-1*H*-pyrrolo[1,2-*a*]imidazole-2,5-dione derivatives **5**. It has been established that the solvent polarity has a great influence on the rate of the second condensation reaction, but not on the first. A mechanism, supported by experimental evidence, has been proposed to explain how the imidazolidin-4-one intermediates **4**, obtained as expected as a mixture of two diastereoisomers, give a single isomer for the bicyclic derivatives **5**; the absolute stereochemistry of these compounds has been determined by X-ray crystallographic analysis.



## Introduction

We have recently described the synthesis of 3-phenylamino-substituted imidazolidin-4-ones[1] from the reaction of some phenylhydrazides of natural α-amino acids (**1**) with several carbonyl compounds. We now wish to report an extension of this reaction employing levulinic acid (**2a**), which bears two reactive sites. The use of this γ-keto acid allowed us to obtain a series of 1-phenylamino-substituted dihydro-1*H*-pyrrolo[1,2-*a*]imidazole-2,5-diones containing both the 2-pyrrolidinone and 4-imidazolidinone moieties, which are recognized as important frameworks for cognition-enhancing activity.[2] We are aware of only two reports of this ring system[3] but none of the compounds described in these papers have the phenylamino group at the 1-position because the authors used α-amino amides as starting materials. Thus, considering the potential interest of our compounds, we have optimised the experimental conditions and investigated the reaction mechanism.

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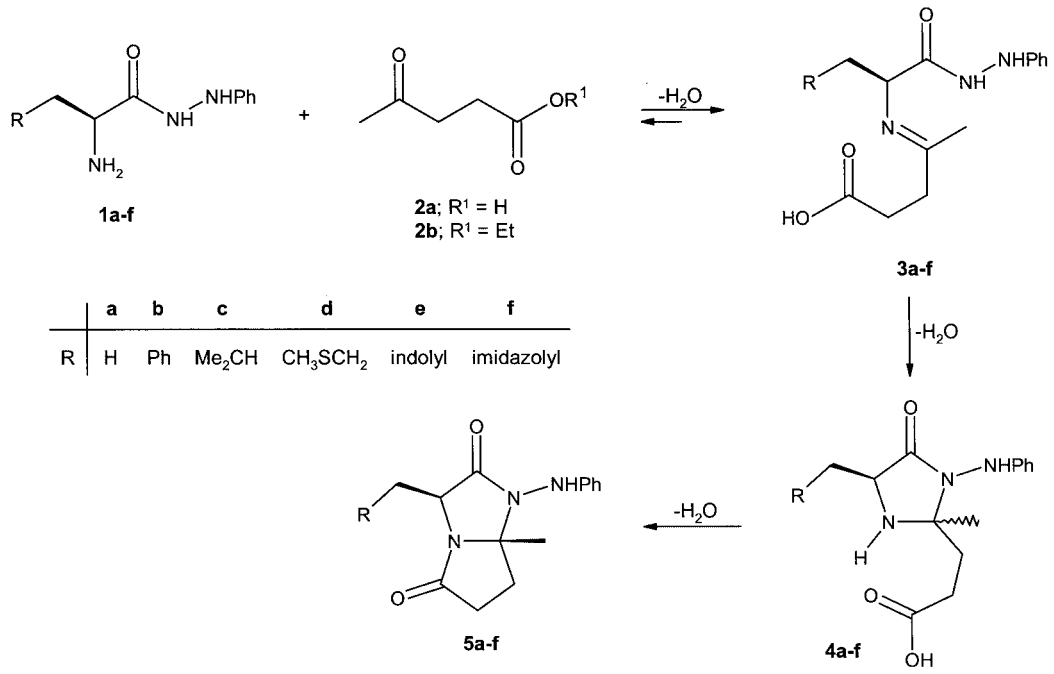
## Results and Discussion

When an α-amino acid phenylhydrazide of type **1** and levulinic acid (**2a**) were mixed under appropriate experimental conditions, a cyclocondensation reaction took place yielding the imidazolidin-4-one intermediate **4**, which rapidly underwent a second ring closure affording the bicyclic compound **5** (Scheme 1).

We initially examined the behaviour of **2a** with the phenylhydrazides of alanine (**1a**), phenylalanine (**1b**), leucine (**1c**) and methionine (**1d**) whose side chains do not induce further reactions other than the double ring closure to **5**.[1] On the basis of previous results[1] obtained from **1** and ketones, we decided to carry out the reaction in refluxing toluene but, in this case, the addition of an acidic catalyst (*p*-toluenesulfonic acid, PTSA) to improve the reactivity of both **2a** and the imine **3** was not necessary due to the presence of the carboxylic function in **2a**. We did not observe any significant difference in reactivity among these phenylhydrazides, and all afforded the bicyclic derivatives **5** in high yield within five hours using a slight excess of **2a**.

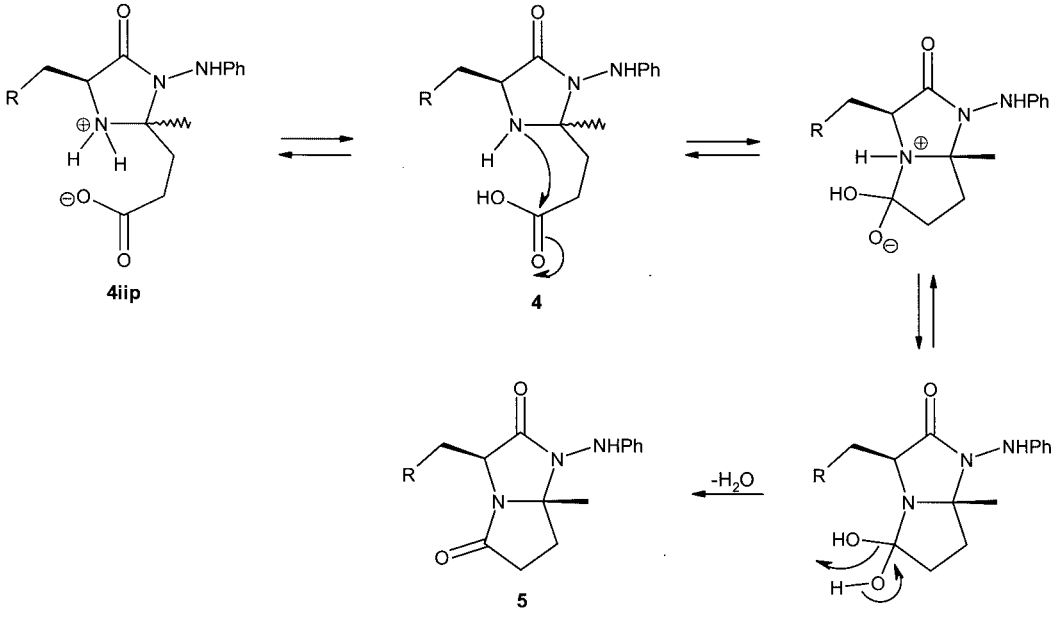
The phenylhydrazide of tryptophan (**1e**) is slightly soluble in refluxing toluene giving, after the addition of **2a**, an unmanageable brown gum. To avoid this problem, toluene was substituted by *i*PrOH and the reaction was carried out at 80 °C; however, even after long reaction times (30 h), although the DI-MS and NMR analyses of the reaction mixture showed the presence of the desired bicyclic compound **5e**, a large amount (40%, HPLC yield) of the 4-imidazolidinone intermediate **4e** was still present. Thus, to improve the conversion of **4e** into **5e**, when the HPLC analysis of the reaction mixture in *i*PrOH showed the complete disappear-




Scheme 1

ance of the starting phenylhydrazide **1e** (2 h), the temperature was raised to 110−120 °C (oil bath) and toluene was added in small portions in order to remove *i*PrOH by azeotropic distillation. The resulting mixture was refluxed for an additional six hours affording, after workup, the desired bicyclic compound **5e** in 87% yield. The phenylhydrazide of histidine (**1f**) exhibited a similar behaviour, therefore the same reaction conditions as used for **1e** were employed.

The low rate of conversion of **4e**,**f** into the bicyclic compounds **5e**,**f** in *i*PrOH, prompted us to investigate how the solvent influenced the reaction. For this purpose we monitored the reaction between the phenylhydrazide of phenylalanine (**1b**) and levulinic acid (**2a**) by HPLC both in EtOH and *i*PrOH at 80 °C: after 90 min the analysis of both the reaction mixtures showed the complete conversion of **1b** into **4b** and only traces (2%, HPLC yield) of the bicyclic compound **5b**. The imidazolidin-4-one **4b** was by far the main product (90%, HPLC yield) after five hours. Since this behaviour might be due to the lower reaction temperature (80 °C instead of 110−120 °C with toluene), the same reaction was carried out both in *n*BuOH and DMF at 110−120 °C (oil bath). As previously observed, the conversion into




Scheme 2

**4b** occurred rapidly (1 h, as in toluene at 110−120 °C) but it was still the major product (75%, HPLC yield), even after prolonged reaction times (24 h). These findings allow us to infer that the rate of the first condensation reaction leading to **4** does not depend on the nature of the solvent used, while the second ring closure affording **5**, even though it is an intramolecular reaction, is slower and is strongly solvent dependent. A plausible explanation of such behaviour could be the different ability of the solvent system to solvate the zwitterionic intermediate **4**. In a non-polar solvent such as toluene, **4** is an intimate ion pair (**4iip**), thus the proton transfer between nitrogen at the 1-position of the imidazolidinone ring and the carboxylate, fundamental to obtain the second condensation reaction to **5**, is extremely easy and fast (Scheme 2). Otherwise, in polar solvents such as alcohols and DMF, the solvent-separated ion pair is more stable and the proton transfer is slower.

When **2a** was substituted by the corresponding ethyl ester **2b** the reaction rate drastically decreased without acid catalysis both in *i*PrOH and toluene, as observed previously with several ketones.[1] In fact, the HPLC analysis of the reaction between **1b** and **2b** in *i*PrOH at 80 °C showed the complete conversion of **1b** into the 5-benzyl-2-[2-(ethoxycarbonyl)ethyl]-3-(phenylamino)imidazolidin-4-one (**6**) and only traces (1%, HPLC yield) of the bicyclic adduct **5b** after 25 h. In toluene, working at 110 °C, the reaction leading to **6** was faster (8 h) but the intermediate **6** was still present (20%, HPLC yield) after 100 h. The addition of an acidic catalyst (PTSA) to the reaction carried out in toluene increased the rate of both the ring closures, giving the complete conversion into **5b** after 30 h.

The HPLC profile of all the reactions between **1b** and **2b** shows two peaks with similar intensity for the 4-imidazolidinone intermediate **6**. As previously observed with carbonyl groups bearing different substituents,[1] this could be an indication that **6** is present as two diastereoisomers in a 1:1 ratio. In fact, the DI-MS analysis of the residue obtained from the reaction carried out in *i*PrOH (80 °C, 25 h) showed the presence of a single compound with a fragmentation pattern consistent with **6**, while the $^{13}C$ NMR spectrum exhibits two close signals for each different carbon atom according to the existence of two very similar molecules.

Otherwise, when **1a**−**f** were used in conjunction with **2a**, the HPLC monitoring invariably showed a single peak for **4a**−**f**, but the $^{13}C$ NMR spectrum of the residue obtained from the reaction of **1b** with **2a** in *i*PrOH (80 °C, 1.5 h) shows, as in the case of **6**, two close signals of similar intensity for each different carbon atom of **4b**. These results confirmed that, as expected, the imidazolidinones **4** are also present as two diastereoisomers; the HPLC conditions employed did not allow their separation.

At this point, since the reaction between **1** and **2** afforded **4** as a diastereoisomeric mixture, it was obvious to suppose that the second ring closure also led to a mixture of two diastereoisomers. Surprisingly, the $^{1}H$ and $^{13}C$ NMR spectra of the bicyclic compounds **5** reveal a single set of peaks consistent with the presence of a single isomer.

X-ray diffraction analysis of 3-(1*H*-indol-3-ylmethyl)-7a-methyldihydro-1-phenylamino-1*H*-pyrrolo[1,2-*a*]imidazole-2,5(3*H*,6*H*)-dione (**5e**) confirmed the presence of a single diastereoisomer and allowed us to determine its absolute

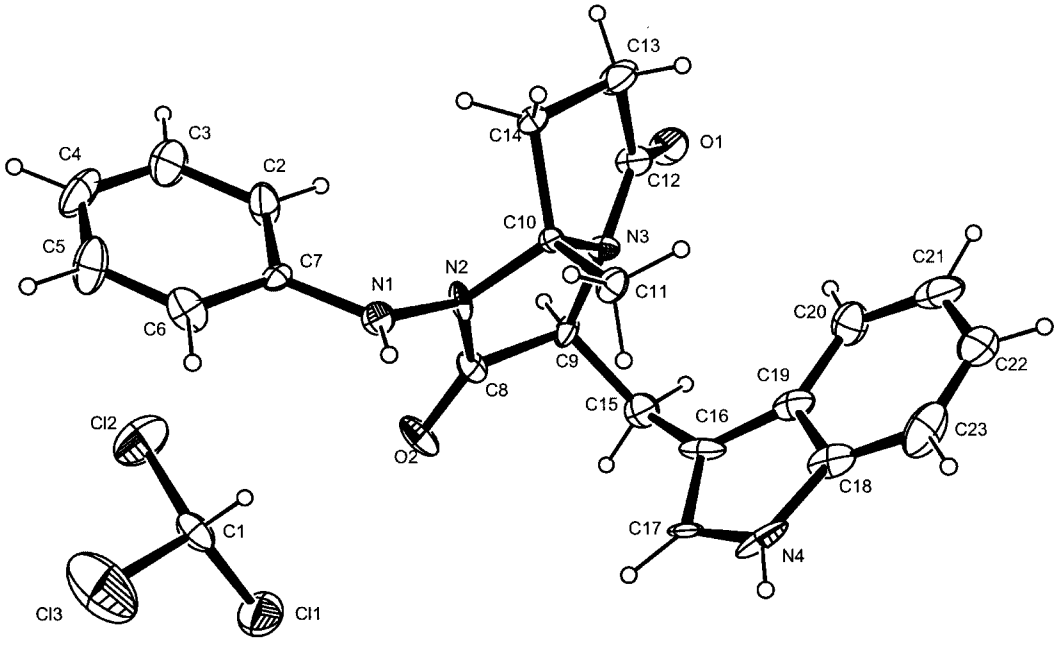



Figure 1. ORTEP drawing of **5e**

configuration. The ORTEP drawing of **5e**, crystallized from $CHCl_3$ with a molecule of solvent, is shown in Figure 1.

The following features should be noted (see Figure 1 for atom numbering):

the bicyclic skeleton is distorted, with the N2−C8−C9 and N3−C12−C13 bond angles particularly small (105.6° and 104.8°, respectively) for an $sp^2$-hybridized carbon atom;

the imidazolidinone moiety, which is almost planar with small distortions due to the steric requirements of the substituents, has an N2−C10−N3 bond angle of 98.1°, which is much smaller than that expected for an $sp^3$-hybridized carbon atom;

the phenylamino group is oriented *anti* to both the amino acid side chain and the methyl group and is almost perpendicular to the imidazolidinone ring (the C7−N1−N2−C8 torsion angle is −84.8°);

the two nitrogen atoms of the phenylhydrazide moiety and the phenyl ring are approximately coplanar (the C2−C7−N1−N2 torsion angle is −14.3°);

the methyl group deriving from levulinic acid is oriented *syn* to the amino acid side chain and eclipsed to the indole ring.

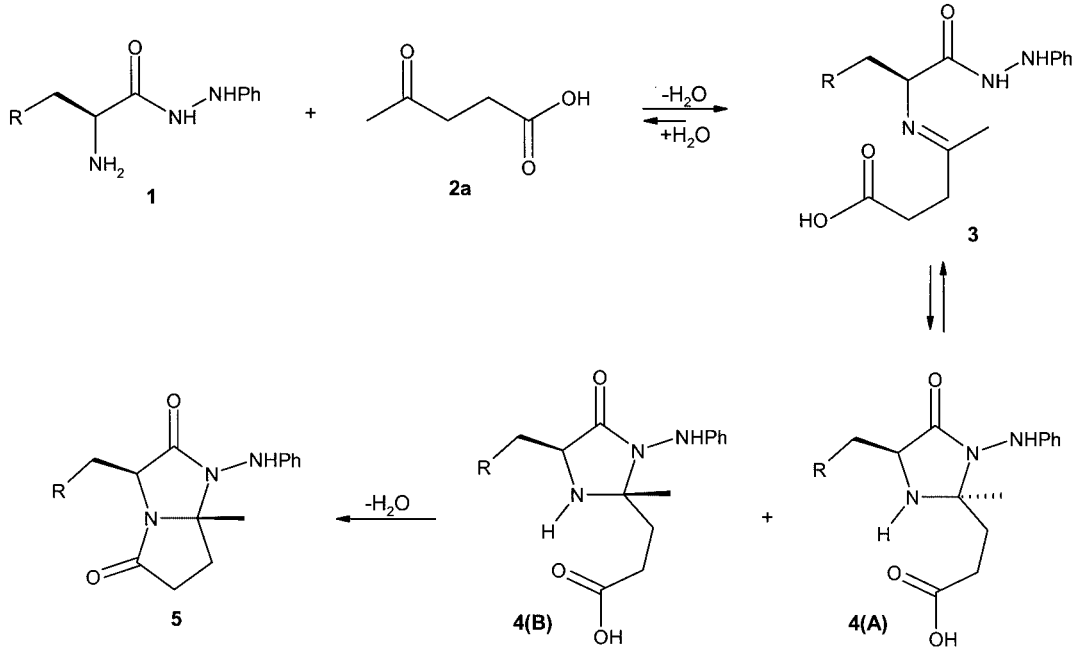
The configuration at C9 (C3 following the IUPAC convention) is *S* since it derives from the α-chiral centre of the starting phenylhydrazide **1e** and it does not undergo any modification during the condensation reactions leading to **5e**. Therefore, the absolute configuration at C10 (C7a following the IUPAC convention) determined by X-ray diffraction analysis is *R*; presumably the C7a and, even more so, the C3 stereochemistry of all the other bicyclic derivatives **5** is the same.

The $^1H$ NMR spectra of the bicyclic compounds bearing non-aromatic side chains at the 3-position, such as **5a,c,d**, exhibit a singlet for the $CH_3$ protons at $\delta = 1.6$ ppm. This signal, as further evidence of the *syn* stereochemistry of the $CH_3$ group, is shifted upfield by 0.5−0.7 ppm for **5b,d,e** due to the shielding effect of the aromatic side chains (phenyl, indolyl and imidazolyl, respectively) present in these compounds. The $^{13}C$ NMR spectra of all the compounds **5** display the $CH_3$ signal at ca. $\delta = 25.0$ ppm.

To explain the unexpected stereochemical course of this reaction, we suggest the following mechanism (Scheme 3): compound **1** reacts with **2a** to form the imine **3**, which promptly cyclizes to give a mixture of the two diastereoisomes **4(A)** and **4(B)**. At this point, only **4(B)** has the correct geometry to allow the second ring closure leading to **5**, while **4(A)**, which has a disfavoured structure probably due to steric hindrance, isomerises to **4(B)** via the imine **3**.

To test the proposed mechanism the two diastereoisomers **6A** and **6B**, obtained from the reaction of **1b** with **2b** in *i*PrOH (80 °C, 20 h), were isolated by preparative TLC ($Et_2O$ on basic alumina). The two compounds (**6A** and **6B**) were separately dissolved in toluene and the solutions were heated to reflux in order to obtain **5b**. The HPLC monitoring confirmed the epimerisation of the starting isomer to the other in both the reaction mixtures and showed that while this process was faster with **6A** than with **6B**, the rate of formation of **5b** was much slower but quite similar in both cases (Table 1).

In conclusion, we have easily synthesised a series of bicyclic compounds, namely dihydro-1*H*-pyrrolo[1,2-*a*]imidazole-2,5-diones, with a rigid framework containing natural amino acid moieties. Contrary to what we expected, NMR spectroscopy and X-ray diffraction analysis showed that only one of the two possible diastereoisomers was formed. In addition to the 2-pyrrolidinone and 4-imidazolidinone frameworks, which are recognized as important for cognition-enhancing activity, these bicyclic derivatives present




Scheme 3

Table 1. Results of the epimerization of **6A** and **6B**[a]

| Time | Relative percentages[b] starting from **6A** | | | Relative percentages[b] starting from **6B** | | |
|---|---|---|---|---|---|---|
| [h] | **6A** | **6B** | **5b** | **6B** | **6A** | **5b** |
| 3 | 49 | 51 | 0 | 81 | 17 | 2 |
| 8 | 39 | 57 | 4 | 68 | 28 | 4 |
| 11 | 34 | 59 | 7 | 65 | 27 | 8 |
| 15 | 33 | 57 | 10 | 64 | 26 | 10 |
| 30 | 27 | 40 | 31 | 49 | 19 | 32 |
| 60 | 10 | 19 | 71 | 21 | 9 | 71 |

[a] Reactions were carried out in toluene at reflux temperature (110−120 °C, oil bath) under Ar. [b] The relative percentages were determined by HPLC.

an amino nitrogen atom that could affect the pharmacological properties and could be attractive for the design of new structures having biological activity.

## Experimental Section

**General:** All reagents were of commercial quality (Aldrich, Fluka) and were used without further purification. The α-amino acid phenylhydrazides **1a**−**d**, [4] and **1e** and **1f**[1] were prepared as described previously. The reactions were monitored by high performance liquid chromatography (HPLC) performed with a Waters M-45 apparatus on an Alltech Adsorbosphere C18 column (250 × 4.6 mm, particle size 5 μm, flow rate 1 mL/min, detection at 254 nm) using the following mobile phase: 50:50 MeCN/$H_2O$ with 1.4% $NEt_3$ (v/v) adjusted to pH 7.3 with $H_3PO_4$. Preparative TLC was performed on basic $Al_2O_3$ 60 $F_{254}$ plates (20 × 20 cm, 1.5 mm thickness, Merck) and visualized under UV light. Direct inlet mass spectra (DI-MS) were obtained with a Fisons TRIO 2000 gas chromatograph-mass spectrometer, working in the positive ion 70 eV electron impact mode. Spectra were recorded in the range 35−450 u. Temperatures between 150 and 250 °C were found to be suitable to volatilise all the compounds into the ion source. IR spectra were obtained with a Nicolet FT-IR Magna 550 spectrophotometer using the KBr technique for solids and recorded in the range 4000−400 $cm^{-1}$. $^1H$ and $^{13}C$ NMR spectra were recorded on a Bruker AC-F 200 spectrometer at 200 and 50 MHz, respectively, using $CDCl_3$ at room temperature or [$D_6$]DMSO at 40 °C as solvents. NMR peak locations are reported as $\delta$ values from TMS. Some $^1H$ multiplets are characterized by the term app (apparent): this refers only to their appearance and may be an oversimplification. Optical rotations were determined at 20 °C (concentration in g/100 mL of solvent) using a POLAX-D polarimeter purchased from ATAGO (Japan). Elemental analyses were performed with a Carlo Erba Mod. 1106 elemental analyser. Melting points were determined with an automatic Mettler (Mod. FP61) melting point apparatus and are not corrected.

**Synthesis of 5a−d:** A stirred solution of the appropriate L-amino acid phenylhydrazide (**1a**−**d**; 1.81 mmol) in toluene (10 mL) was gently refluxed under Ar and then levulinic acid (**2a**; 0.273 g, 2.35 mmol) was added to the solution. The reaction mixture was stirred at the same temperature for 5 h (monitored by HPLC). After evaporation of the solvent under reduced pressure, the residue was dissolved in $CH_2Cl_2$ (10 mL) and vigorously stirred with $Na_2CO_3{\cdot}10H_2O$ (0.70 g, 2.35 mmol) for 1 h. The mixture was dried over anhydrous $Na_2SO_4$, filtered and then the $CH_2Cl_2$ was evaporated. The residue was triturated in hexane to give **5a**−**d** in a spectroscopically pure form.

**3,7a-Dimethyldihydro-1-phenylamino-1*H*-pyrrolo[1,2-*a*]imidazole-2,5-(3*H*,6*H*)-dione (5a):** White solid (0.441 g, 94%), m.p. 178−180 °C. $[\alpha]_D$ = +3.5 (*c* = 2.0, MeOH). IR (KBr): $\tilde{\nu}$ = 3298, 1705, 1600, 1495, 1402, 1377, 1356, 1227, 991, 754, 698 $cm^{-1}$. $^1H$ NMR ($CDCl_3$): $\delta$ = 1.47 (d, *J* = 7.3 Hz, 3 H, *CHC*H*$_3$*), 1.63 (s, 3 H, $CCH_3$), 2.00−2.56 (m, 3 H, C*H*$_2$C*H*H), 2.58−2.86 (m, 1 H, $CH_2$CH*H*), 4.47 (q, *J* = 7.3 Hz, 1 H, *CH), 6.57 (s, 1 H, NH), 6.66−6.79 (m, 2 H, Ar-*H*), 6.83−6.98 (m, 1 H, Ar-*H*), 7.09−7.25 (m, 2 H, Ar-*H*) ppm. $^{13}C$ NMR ($CDCl_3$): $\delta$ = 17.9, 26.1, 30.7, 33.7, 52.1, 82.3, 113.5, 121.5, 129.1, 146.1, 173.2, 177.5 ppm. MS (70 eV, EI): *m*/*z* (%) = 259 (36) [$M^+$], 152 (22), 134 (13), 124 (66), 108 (11), 98 (100), 92 (10), 77 (13), 65 (7), 55 (8). $C_{14}H_{17}N_3O_2$ (259.31): calcd. C 64.85, H 6.61, N 16.20; found C 64.88, H 6.58, N 16.22.

**3-Benzyl-7a-methyldihydro-1-phenylamino-1*H*-pyrrolo[1,2-*a*]-imidazole-2,5-(3*H*,6*H*)-dione (5b):** White solid (0.509 g, 84%), m.p. > 235 °C. $[\alpha]_D$ = −6.0 (*c* = 2.0, MeOH). IR (KBr): $\tilde{\nu}$ = 3273 broad, 3030, 1713, 1603, 1498, 1399, 1377, 1347, 1306, 1262, 990, 754, 697, 578 $cm^{-1}$. $^1H$ NMR ($CDCl_3$): $\delta$ = 0.94 (s, 3 H, $CH_3$), 2.00−2.48 (m, 3 H, C*H*$_2$C*H*H), 2.55−2.80 (m, 1 H, $CH_2$CH*H*), 3.08−3.30 (m, 2 H, *CHC*H*$_2$*), 4.68 (app t, *J* = 5.5 Hz, 1 H, *CH), 6.10 (s, 1 H, NH), 6.66−6.79 (m, 2 H, Ar-*H*), 6.84−6.99 (m, 1 H, Ar-*H*) 7.12−7.40 (m, 7 H, Ar-*H*) ppm. $^{13}C$ NMR ($CDCl_3$): $\delta$ = 25.0, 30.9, 35.2, 36.9, 58.4, 82.1, 113.8, 121.7, 127.1, 128.4, 129.1, 130.1, 136.2, 145.9, 171.3, 178.3 ppm. MS (70 eV, EI): *m*/*z* (%) = 335 (88) [$M^+$], 228 (13), 200 (100), 134 (26), 131 (20), 103 (10), 98 (93), 91 (28), 77 (21), 65 (18), 55 (12). $C_{20}H_{21}N_3O_2$ (335.41): calcd. C 71.61, H 6.31, N 12.53; found C 71.68, H 6.38, N 12.50.

**3-Isobutyl-7a-methyldihydro-1-phenylamino-1*H*-pyrrolo[1,2-*a*]-imidazole-2,5-(3*H*,6*H*)-dione (5c):** White solid (0.452 g, 83%), m.p. 148−150 °C. $[\alpha]_D$ = −22.5 (*c* = 2.0, MeOH). IR (KBr): $\tilde{\nu}$ = 3228 broad, 2961, 1721, 1605, 1496, 1396, 1374, 1348, 1241, 750 $cm^{-1}$. $^1H$ NMR ($CDCl_3$): $\delta$ = 0.99 (d, *J* = 6.3 Hz, 3 H, C*H*$_3$CHCH$_3$), 1.08 (d, *J* = 6.4 Hz, 3 H, $CH_3$CHC*H*$_3$), 1.36−1.55 [m, 1 H, C*H*(CH$_3$)$_2$], 1.62 (s, 3 H, $CCH_3$), 1.62−2.87 (m, 6 H, CC*H*$_2$C*H*$_2$ + *CHC*H*$_2$*), 4.43 (dd, $J_1$ = 11.2, $J_2$ = 3.9 Hz, 1 H, *CH), 6.60 (s, 1 H, NH), 6.63−6.79 (m, 2 H, Ar-*H*), 6.81−6.92 (m, 1 H, Ar-*H*), 7.08−7.26 (m, 2 H, Ar-*H*) ppm. $^{13}C$ NMR ($CDCl_3$): $\delta$ = 21.3, 23.2, 25.2, 26.2, 30.4, 33.4, 41.4, 55.7, 82.5, 113.4, 121.3, 129.1, 146.2, 173.0, 178.1 ppm. MS (70 eV, EI): *m*/*z* (%) = 301 (40) [$M^+$], 194 (11), 166 (45), 134 (7), 124 (14), 108 (20), 98 (100), 93 (12), 92 (13), 77 (11). $C_{17}H_{23}N_3O_2$ (301.39): calcd. C 67.73, H 7.70, N 13.95; found C 67.68, H 7.75, N 13.90.

**7a-Methyl-3-[2-(methylthio)ethyl]dihydro-1-phenylamino-1*H*-pyrrolo[1,2-*a*]imidazole-2,5-(3*H*,6*H*)-dione (5d):** White solid (0.520 g, 90%), m.p. 127−130 °C. $[\alpha]_D$ = −31.0 (*c* = 1.0, MeOH). IR (KBr): $\tilde{\nu}$ = 3241 broad, 2915, 1719, 1694, 1602, 1497, 1396, 1345, 759, 698 $cm^{-1}$. $^1H$ NMR ($CDCl_3$): $\delta$ = 1.64 (s, 3 H, $CCH_3$), 1.70−2.00 (m, 1 H, *CHC*H*H), 2.13 (s, 3 H, $SCH_3$), 2.05−2.88 (m, 7 H, *CHCH*H* + $CH_2CH_2$ + $SCH_2$), 4.47 (dd, $J_1$ = 10.5, $J_2$ = 4.4 Hz, 1 H, *CH), 6.31 (s, 1 H, NH), 6.68−6.84 (m, 2 H, Ar-*H*), 6.84−7.05 (m, 1 H, Ar-*H*), 7.10−7.35 (m, 2 H, Ar-*H*) ppm. $^{13}C$ NMR ($CDCl_3$): $\delta$ = 15.4, 26.1, 30.6, 30.8, 32.4, 33.9, 56.1, 82.4, 113.7, 121.9, 129.3, 146.0, 172.0, 178.1 ppm. MS (70 eV, EI): *m*/*z* (%) = 319 (61) [$M^+$], 184 (22), 175 (19), 164 (18), 136 (42), 124 (19), 108 (17), 98 (59), 92 (26), 91 (8), 77 (26), 65 (23), 61 (100), 55 (21). $C_{16}H_{21}N_3O_2S$ (319.42): calcd. C 60.16, H 6.63, N 13.16; found C 60.20, H 6.60, N 13.10.

**Synthesis of 5e,f:** A stirred suspension of the appropriate L-amino acid phenylhydrazide (**1e**,**f**; 1.81 mmol) in *i*PrOH (30 mL) was

heated under Ar at 80 °C (oil bath) and then levulinic acid (**2a**; 0.273 g, 2.35 mmol) was added to the suspension. The reaction mixture was stirred at the same temperature until HPLC analysis showed the complete disappearance of **1** (2 h). At this point the temperature was raised to 120 °C (oil bath) and toluene (35 mL) was added in small portions in order to remove *i*PrOH by azeotropic distillation. The resulting reaction mixture was stirred at the same temperature for an additional 6 h (monitored by HPLC). After evaporation of the solvent under reduced pressure, the residue was dissolved in $CH_2Cl_2$ (10 mL) and vigorously stirred with $Na_2CO_3{\cdot}10H_2O$ (0.70 g, 2.35 mmol) for 1 h. The mixture was dried with anhydrous $Na_2SO_4$, filtered and, after partial evaporation of the solvent under reduced pressure, the remaining solution (2 mL) was added dropwise to hexane (50 mL) whilst stirring to form a solid white precipitate which was filtered. Compounds **5e**,**f** were obtained in a spectroscopically pure form.

**3-(1*H*-Indol-3-ylmethyl)-7a-methyldihydro-1-phenylamino-1*H*-pyrrolo[1,2-*a*]imidazole-2,5-(3*H*,6*H*)-dione (5e):** White solid (0.589 g, 87%), m.p. 166−168 °C. $[\alpha]_D$ = +49.4 (*c* = 0.4, MeOH). IR (KBr): $\tilde{\nu}$ = 3302 broad, 3922, 1711, 1603, 1496, 1458, 1404, 1380, 1353, 1265, 1098, 746, 694 $cm^{-1}$. $^1H$ NMR ([D$_6$]DMSO): $\delta$ = 1.07 (s, 3 H, $CH_3$), 1.93−2.37 (m, 3 H, C$H_2$C*H*),), 2.54−2.78 (m, 1 H, $CH_2$CH*H*), 3.07−3.29 (m, 2 H, *CHC$H_2$), 4.50 (app t, *J* = 5.8 Hz, 1 H, *CH), 6.59−6.79 (m, 3 H, Ar-*H*), 6.91−7.18 (m, 4 H, Ar-*H*), 7.19−7.27 (m, 1 H, Ar-*H*), 7.31−7.41 (m, 1 H, Ar-*H*), 7.47−7.58 (m, 1 H, Ar-*H*), 8.07 (s, 1 H, PhNH), 10.86 (s, 1 H, NH) ppm. $^{13}C$ NMR ($CDCl_3$): $\delta$ = 25.2, 27.1, 30.3, 34.1, 57.6, 82.0, 109.3, 111.2, 112.3, 118.3, 119.0, 120.8, 123.9, 127.6, 128.6, 135.9, 147.0, 169.9, 177.9 ppm. MS (70 eV, EI): *m*/*z* (%) = 374 (23) [$M^+$], 267 (8), 239 (22), 171 (12), 170 (80), 143 (39), 138 (11), 130 (100), 93 (12), 77 (11). $C_{22}H_{22}N_4O_2$ (374.44): calcd. C 70.56, H 5.93, N 14.97; found C 70.60, H 5.90, N 15.01.

**3-(1*H*-Imidazol-4-ylmethyl)7a-methyldihydro-1-phenylamino-1*H*-pyrrolo[1,2-*a*]imidazole-2,5-(3*H*,6*H*)-dione (5f):** White solid (0.529 g, 90%), m.p. 139−140 °C. $[\alpha]_D$ = −8.0 (*c* = 2.0, MeOH). IR (KBr): $\tilde{\nu}$ = 3269 broad, 1712, 1603, 1499, 1404, 1348, 1264, 752, 696 $cm^{-1}$. $^1H$ NMR ($CDCl_3$): $\delta$ = 1.18 (s, 3 H, $CH_3$), 2.00−2.50 (m, 3 H, C$H_2$C*H*H), 2.54−2.84 (m, 1 H, $CH_2$CH*H*), 2.94−3.30 (m, 2 H, *CHC$H_2$), 4.62 (app t, *J* = 5.7 Hz, 1 H, *CH), 6.68−6.94 (m, 4 H, Ar-*H*), 7.10−7.29 (m, 3 H, Ar-*H* + PhNH), 7.40 (s, 1 H, Ar-*H*), 8.25 (broad s, 1 H, NH) ppm. $^{13}C$ NMR ($CDCl_3$): $\delta$ = 25.1, 29.0, 30.9, 34.8, 56.9, 82.6, 113.3, 121.2, 129.2, 134.3, 135.1, 146.2, 171.6, 178.6 ppm. MS (70 eV, EI): *m*/*z* (%) = 325 (49) [$M^+$], 218 (53), 190 (94), 172 (13), 162 (12), 138 (20), 123 (43), 121 (72), 108 (34), 98 (42), 93 (50), 92 (36), 82 (64), 81 (100), 77 (37), 65 (39). $C_{17}H_{19}N_5O_2$ (325.37): calcd. C 62.74, H 5.89, N 21.53; found C 62.69, H 5.90, N 21.48.

**Synthesis of 6:** A solution of **1b** (0.600 g, 2.35 mmol) and ethyl levulinate (**2b**; 0.44 mL, 3.06 mmol) in *i*PrOH (10 mL) was stirred under Ar at 80 °C until HPLC analysis showed the complete conversion of **1b** into the two diastereoisomers of 5-benzyl-2-[2-(ethoxycarbonyl)ethyl]-3-(phenylamino)imidazolidin-4-one (**6**) (20 h). After evaporation of *i*PrOH and excess **2b** under reduced pressure, the two epimers were separated by preparative TLC on basic $Al_2O_3$ using $Et_2O$ as eluent to afford **6A** ($R_f$ = 0.42, 0.350 g, 39%) as a yellow glass and **6B** ($R_f$ = 0.27, 0.360 g, 40%) as a white solid.

The two compounds **6A** and **6B** (0.250 g, 0.66 mmol) were separately dissolved in toluene (4 mL). The solutions were refluxed and monitored by HPLC.

**Compound 6A (2*S*,5*S* isomer):** $[\alpha]_D$ = −54.5 (*c* = 0.8, $CH_2Cl_2$). IR (KBr): $\tilde{\nu}$ = 3265, 2981, 1712, 1603, 1497, 1454, 1392, 1307, 1185, 1121, 752, 702 $cm^{-1}$. $^1H$ NMR ($CDCl_3$): $\delta$ = 1.13 (t, *J* = 7.1 Hz, 3 H, $CH_2CH_3$), 1.22 (s, 3 H, $CCH_3$), 1.75 (t, *J* = 7.1 Hz, 2 H, $CCH_2$), 1.91 (broad s, 1 H, NH), 2.07−2.22 (m, 2 H, $CH_2CO$), 2.85−3.14 (m, 2 H, $PhCH_2$), 3.81 (app t, *J* = 5.1 Hz, 1 H, *CH), 3.99 (q, *J* = 7.1 Hz, 2 H, $CH_3CH_2$), 6.14 (s, 1 H, PhNH), 6.47−6.58 (m, 2 H, Ar-*H*), 6.71−6.85 (m, 1 H, Ar-*H*), 6.99−7.13 (m, 2 H, Ar-*H*), 7.14−7.37 (m, 5 H, Ar-*H*) ppm. $^{13}C$ NMR ($CDCl_3$): $\delta$ = 14.7, 24.5, 29.1, 34.3, 37.9, 57.7, 61.2, 78.6, 114.4, 121.6, 127.5, 129.1, 129.5, 130.4, 137.5, 146.9, 173.9, 174.8 ppm. MS (70 eV, EI): *m*/*z* (%) = 381 (53) [$M^+$], 246 (28), 200 (29), 189 (13), 144 (36), 134 (17), 131 (30), 120 (20), 104 (28), 98 (53), 92 (74), 91 (100), 82 (23), 77 (51), 70 (29), 65 (58). $C_{22}H_{27}N_3O_3$ (381.47): calcd. C 69.25, H 7.14, N 11.02; found C 69.29, H 7.10, N 11.08.

**Compound 6B (2*R*,5*S* isomer):** M.p. 143−145 °C. $[\alpha]_D$ = −51.3 (*c* = 0.8, $CH_2Cl_2$) IR (KBr): $\tilde{\nu}$ = 3260, 2979, 1704, 1604, 1495, 1454, 1393, 1307, 1182, 1122, 751, 694 $cm^{-1}$. $^1H$ NMR ($CDCl_3$): $\delta$ = 1.07 (s, 3 H, $CCH_3$), 1.25 (t, *J* = 7.1 Hz, 3 H, $CH_2CH_3$), 1.67 (broad s, 1 H, NH), 1.77−2.15 (m, 2 H, $CCH_2$), 2.32−2.51 (m, 2 H, $CH_2CO$), 3.00 and 3.31 (AB of ABX, $J_{AB}$ = 14.4, $J_{AX} = J_{BX}$ = 4.9 Hz, 2 H, $PhCH_2$), 3.83 (app t, *J* = 4.9 Hz, 1 H, *CH), 4.11 (q, *J* = 7.1 Hz, 2 H, $CH_3CH_2$), 5.91 (s, 1 H, PhNH), 6.44−6.59 (m, 2 H, Ar-*H*), 6.82−6.96 (m, 1 H, Ar-*H*), 7.07−7.19 (m, 2 H, Ar-*H*), 7.20−7.53 (m, 5 H, Ar-*H*) ppm. $^{13}C$ NMR ($CDCl_3$): $\delta$ = 14.2, 25.1, 29.3, 33.3, 36.3, 57.5, 60.8, 78.1, 113.7, 121.1, 127.3, 128.8, 128.9, 130.2, 135.6, 146.6, 173.3, 174.1 ppm. MS (70 eV, EI): *m*/*z* (%) = 381 (95) [$M^+$], 335 (16), 246 (37), 200 (41), 189 (17), 160 (17), 144 (59), 134 (26), 131 (53), 120 (22), 104 (38), 98 (78), 92 (81), 91 (100), 82 (22), 77 (39), 70 (23), 65 (43). $C_{22}H_{27}N_3O_3$ (381.47): calcd. C 69.25, H 7.14, N 11.02; found C 69.20, H 7.19, N 11.08.

**X-ray Crystallographic Study:** Compound **5e** crystallized from $CHCl_3$ with a molecule of solvent. X-ray diffraction analysis of the sample was carried out with a Bruker-Axs three circle diffractometer with Smart-Apex CCD detector using graphite-monochromated Mo-$K_\alpha$ radiation ($\lambda$ = 0.7107 Å) at 298 K. 6885 Reflections were obtained (4393 unique reflection after merging) up to $\theta$ = 1.88−25.46° from a monoclinic crystal [molecular formula $C_{23}H_{23}N_4O_2Cl_3$, space group $P2_1$, *a* = 9.2329(6) Å, *b* = 12.121(1) Å, *c* = 10.987(1) Å, $\beta$ = 99.86(2)°, *V* = 1211.36(7) Å$^3$, *Z* = 2, *D* = 1.35 g/cm$^{-3}$, linear absorption coefficient $\mu$ = 0.406 $mm^{-1}$] of dimension 0.040 × 0.053 × 0.370 mm$^3$. Solution of the structure was performed with the program SHELXS-86,[5] and refined with SHELXL-97[6] using full-matrix least-squares method. Non-hydrogen atoms were refined anisotropically; H-atoms were placed in the model in calculated positions and constrained. Final *R* for the observed reflections on 289 parameters was 0.0746 and $R_w$ = 0.1433 (GOF = 0.961; $\Delta\rho_{max}$ = 0.38, $\Delta\rho_{min}$ = −0.26 e·Å$^{-3}$). Because of the low quality of the crystal, some atomic displacement parameters seem to be biased, with consequent contamination of the finer features of the crystal structure. Moreover, the data do not allow us to solve some probable effect such as disorder. Only general considerations about the overall set up of the structure are therefore reliable.

CCDC-231128 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK [Fax: + 44-1223-336033; E-mail: deposit@ccdc.cam.ac.uk].

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