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A convenient procedure for the synthesis of chiral 6,7-dihydroxy-1-phenylamino-dihydro-1*H*-pyrrolo[1,2-*a*] imidazole-2,5(3*H*,6*H*)-diones

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ABSTRACT

The cyclocondensation reactions between L-α-amino acid phenylhydrazides and 2,3-*O*-isopropylidene-L-erythruronolactone in the presence of a catalytic amount of *p*-toluenesulfonic acid afforded diastereomerically pure (3*S*,6*R*,7*R*,7a*S*)-3-substituted-6,7-isopropylidenedioxy-1-phenylamino-dihydro-1*H*-pyrrolo[1,2-*a*]imidazole-2,5(3*H*,6*H*)-diones, which were converted by acidic hydrolysis with MeOH–HCl into their corresponding optically active (3*S*,6*R*,7*R*,7a*S*)-3-substituted-6,7-dihydroxy-1-phenylamino-dihydro-1*H*-pyrrolo[1,2-*a*]imidazole-2,5(3*H*,6*H*)-diones in good yields.

1. Introduction

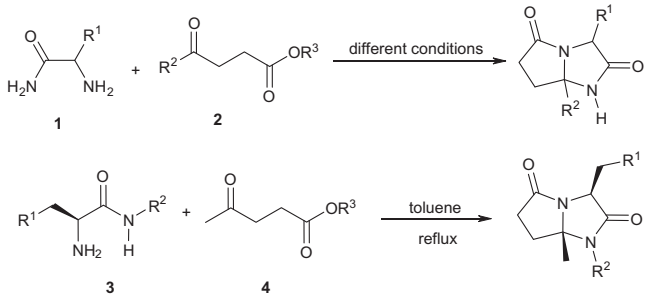
Pyrrolo[1,2-*a*]imidazolones are a common feature of many interesting biologically active compounds as central nervous system depressants, sedatives, and anticonvulsants.[1–3] In particular, pyrrolo[1,2-*a*]imidazole-2,5-diones, which contain both the pyrrolidin-2-one and imidazolidin-4-one moieties, are recognized as important frameworks for cognition-enhancing activity[4] and for the treatment of neuropathic pain.[5]

A few reports have been published concerning the synthesis of dihydro-1*H*-pyrrolo[1,2-*a*]imidazole-2,5-diones and include (Scheme 1) the following: (i) the condensation of α-amino amides **1** with γ-oxoesters **2**;[4] and (ii) the reaction between N-substituted α-amino amides **3** and levulinic acid derivatives **4**.[6,7] To the best of our knowledge, no 6,7-dihydroxy-dihydro-1*H*-pyrrolo[1,2-*a*]imidazole-2,5-diones have been reported, because the authors used γ-keto acid derivatives as starting materials. In addition, several structural analogues of these biheterocycles are found in the alkaloid family such as, ergotamine and kifunensine.[8,9]

We have been interested in the synthesis of various heterocyclic systems using α-amino acid derivatives as chiral pool substrates.[10–14] Herein we report a short method for the preparation of chiral 3-substituted-6,7-dihydroxy-1-phenylamino-dihydro-1*H*-pyrrolo[1,2-*a*]imidazole-2,5(3*H*,6*H*)-diones by a one-pot two-step cyclization from L-α-amino acid phenylhydrazides and 2,3-*O*-isopropylidene-L-erythruronolactone. These heterocycles have potentially great pharmaceutical importance and are required for the evaluation of biological activities and as starting materials to prepare new drugs.

2. Results and discussion

The starting L-α-amino acid phenylhydrazides **6** were prepared in a manner similar to well-known procedures (Scheme 1).[15–17]



Scheme 1. Known routes to dihydro-1*H*-pyrrolo[1,2-*a*]imidazole-2,5-diones.

Thus, the treatment of commercially available L-α-amino acid ester hydrochlorides **5** with phenylhydrazine under mild conditions in the presence of triethylamine afforded the corresponding phenylhydrazides **6a–f** in good yields (Table 1). In each case, only one enantiomer was detected by ^{1}H NMR spectroscopy using Eu(hfc)$_3$ as a chiral shift reagent (see Scheme 2).

The reaction of the readily available α-amino acid phenylhydrazides **6a–f** with 2,3-*O*-isopropylidene-L-erythruronolactone **7**

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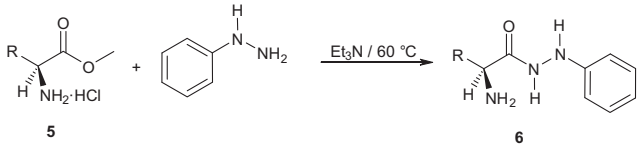
Table 1
Synthesis of α-amino acid phenylhydrazides **6a–f**

Product	R	Yield[a] (%)	Mp (°C)	$[\alpha]_D^{25}$[b]
6a	Me	80	122–124	+34.2
6b	*i*-Pr	65	152–154	+30.8
6c	*i*-Bu	72	138–140	+22.8
6d	Bn	85	142–144	+39.4
6e	CH_2–OH	68	163–165	+42.6
6f	CH_2–CH_2–SMe	78	128–130	+29.8

[a] Yield of the isolated product
[b] (*c* 0.2, MeOH).



Scheme 2. Synthesis of the starting α-amino acid phenylhydrazides **6**.

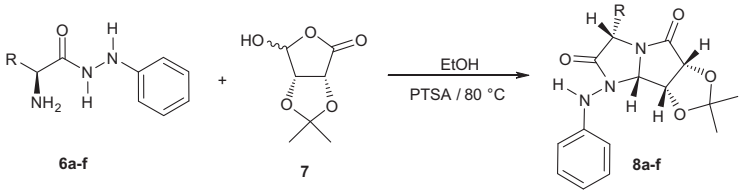
(obtained from D-ribose based on a reported protocol[18–21] with good overall yield) and PTSA in EtOH at 80 °C for 12 h afforded the 3-substituted-6,7-isopropylidenedioxy-1-phenylamino-dihydro-1*H*-pyrrolo[1,2-*a*]imidazole-2,5(3*H*,6*H*)-diones **8a–f** (Scheme 3).

as ethanol (entry 3, 72% yield) and acetonitrile (entry 4). In less polar solvents, the reaction proceeded more slowly and with moderate yields (entries 5 and 6). No significant improvement in the yield was observed when acetic acid was used (entry 7).

The results shown in Table 3 indicate that the reaction can be carried out effectively with a variety of α-amino acid phenylhydrazides using the optimal conditions described in entry 3 (Table 2). Moderate to good yields were obtained in most cases, with the formation of single diastereoisomers as determined by ^{1}H and ^{13}C NMR analysis of the crude product.

The stereochemistry of **8a–f** was determined by NOE NMR experiments. Using **8a** as an example (Fig. 1), the ^{1}H NMR spectrum showed that H(3), H(6), H(7), and H(7a) appeared at 4.10 ppm (q), 4.80 ppm (d), 4.70 ppm (dd), and 5.24 ppm (d), respectively. A significant positive NOE effect was observed between H(7a) and H(7); a positive NOE effect was also observed between H(7a) and either H(3) or H(6). Furthermore, no NOE effect was observed between H(6), H(7), H(7a), and the annular methyl group (1.76 ppm, d) in **8a**. Thus, NOE analysis demonstrated that in **8a** H(7a) is in a *cis*-orientation with H(3), H(6), and H(7). Very similar NOE results were observed for **8b–f** indicating the same configuration as that of **8a**.

Cleavage of the acetonide protecting group of **8a–f** afforded the corresponding dihydro-1*H*-6,7-dihydroxypyrrolo[1,2-*a*]imidazole-2,5-diones **9a–f** (Scheme 4) in good yields (Table 4) and with the same stereochemistry at the asymmetric carbons as established



Scheme 3. Synthesis of 6,7-isopropylidenedioxy-dihydro-1*H*-pyrrolo[1,2-*a*]imidazole-2,5(3*H*,6*H*)-diones **8**.

First, the reaction of L-alanine phenylhydrazide **6a** and 2,3-*O*-isopropylidene-L-erythruronolactone **7** was used as the model reaction, by mixing reagents **6a** and **7** in CH_2Cl_2, without adding any catalyst, at room temperature for 24 h. However these conditions failed to provide any products and only the unreacted starting materials were recovered (Table 2, entry 1). When the reaction was carried out in the presence of a catalytic amount of PTSA in dry toluene at reflux, the yield of **8a** was only 25% (entry 2). The low yield of the product prompted us to investigate the effect of either the solvent or acid catalyst on the reaction yields. For this purpose the reactions were run at 80 °C in the presence of 10 mol % of PTSA; the yields were determined after 12 h for the sake of comparison. The best results were obtained in polar solvents such

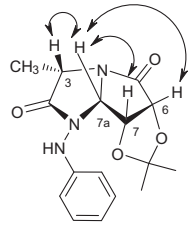


Figure 1. NOEs showing the stereochemistry of compound **8a**.

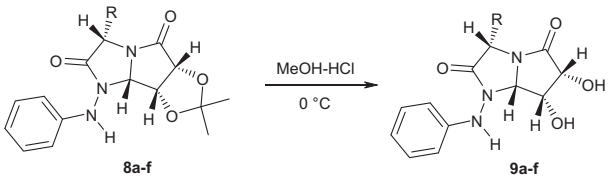
Table 2
Optimization of the reaction conditions for the preparation of **8a**

Entry	Solvent	Catalyst	Temperature (°C)	Yield (%)
1	CH_2Cl_2	none	25	—
2	toluene	PTSA	110	25
3	EtOH	PTSA	80	72
4	MeCN	PTSA	80	58
5	benzene	PTSA	80	33
6	xylene	PTSA	80	20
7	EtOH	AcOH	80	69

Table 3
Synthesis of products **8a–f**

Product	R	Yield[a] (%)	Mp (°C)	$[\alpha]_D^{25}$ in $CHCl_3$
8a	Me	72	236–238	−22.1 (*c* 1.06)
8b	*i*-Pr	53	208–210	+18.6 (*c* 0.45)
8c	*i*-Bu	58	199–201	+12.9 (*c* 0.83)
8d	Bn	68	241–243	−31.4 (*c* 1.25)
8e	CH_2–OH	66	238–240	−16.2 (*c* 0.79)
8f	CH_2–CH_2–SMe	81	183–185	+26.5 (*c* 0.58)

[a] Yield of the pure product after flash chromatography.



Scheme 4. Synthesis of dihydro-1*H*-6,7-dihydroxypyrrolo[1,2-*a*]imidazole-2,5(3*H*,6*H*)-ones **9**.

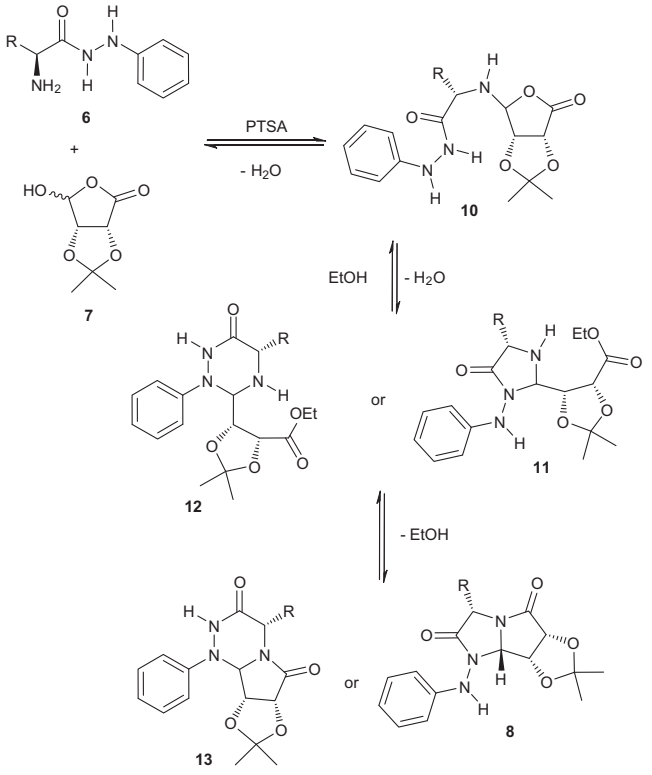
Table 4
Synthesis of products **9a**–**f**

Product	R	Yield (%)[a]	Mp (°C)	$[\alpha]_D^{25}$ in MeOH
9a	Me	87	197–199	+14.7 (*c* 1.12)
9b	*i*-Pr	75	200–202	−20.5 (*c* 0.61)
9c	*i*-Bu	83	211–213	+32.0 (*c* 0.46)
9d	Bn	85	232–234	+19.2 (*c* 1.15)
9e	CH_2–OH	70	242–244	−33.8 (*c* 0.94)
9f	CH_2–CH_2–SMe	79	187–189	+24.4 (*c* 0.96)

[a] Yield of the pure product after flash chromatography.

by NOE NMR experiments with those of **8a**–**f**. In addition, no epimerization was observed by ^{1}H NMR and HPLC analysis.

Analyzing the mechanism of the reaction between 2,3-*O*-isopropylidene-L-erythruronolactone **7** and α-amino acid phenylhydrazides **6**, we assumed that in the first step, the amino group attacks the electrophilic carbon atom of the hemiacetal, which leads to intermediate **10** (Scheme 5). In the second step, two



Scheme 5. Proposed mechanism for the cyclocondensation reaction.

nucleophilic attacks are possible, resulting in either a five-membered imidazolidin-4-one **11** or a six-membered 1,2,4-triazin-6-one **12**. Finally, a second cyclization step could afford either products **8** or **13**. The products were characterized by HRMS, as well as ^{1}H and ^{13}C spectra. Structure **13** was excluded considering the ^{1}H NMR features of the NHNHPh skeleton: these two protons usually resonate for α-amino acid phenylhydrazides at ≈6 ppm as a singlet for the NH attached to the phenyl group and at ≈9 ppm as a broad singlet for the NH attached to the carbonyl group.[22] In products **8** only the chemical shifts assigned to NH attached to the phenyl group were present. Furthermore, this last signal showed an HMBC correlation with the quaternary carbon signal of the phenyl group at ≈147 ppm. Both of these facts give good evidence for the cyclic structure **8** and not **13**.

3. Conclusion

In conclusion, we have developed a short and efficient procedure for the diastereoselective synthesis of novel (3*S*,6*R*,7*R*,7a*S*)-3-substituted-6,7-isopropylidenedioxy-1-phenylamino-dihydro-1*H*-pyrrolo[1,2-*a*]imidazole-2,5(3*H*,6*H*)-diones starting from commercially available and inexpensive materials. The cleavage of the acetonide protecting group under mild conditions has enabled us to obtain (3*S*,6*R*,7*R*,7a*S*)-3-substituted-6,7-dihydroxy-1-phenylamino-dihydro-1*H*-pyrrolo[1,2-*a*]imidazole-2,5(3*H*,6*H*)-diones in good yields for further pharmacological studies.

4. Experimental

4.1. General

All reactions are carried under an argon atmosphere in oven dried glassware equipped with a magnetic stirrer and a rubber septum unless otherwise indicated. All solvents were freshly distilled before use. All other commercial reagents were used without further purification. Reactions were monitored by thin layer chromatography (TLC) of aliquots using Merck 60F-254 silica gel plates (0.25 mm layered thickness). Column chromatography was carried out with silica gel 60–120 mesh (Merck). ^{1}H, ^{13}C, HMBC, and NOESY NMR spectra were recorded in deuterated solvents, on a Bruker AC-300 spectrometer. IR spectra were recorded with Biorad FTS-6000 spectrometer. HRMS were obtained on a Waters Micromass Q-Tof analytical instrument. Optical rotations were measured with Atago Polax-2L digital polarimeter. Melting points were recorded on a Fisher Johns melting point apparatus. The shift reagent was Eu(hfc)$_3$ (Aldrich Chem. Co.).

4.2. HRMS analysis

The samples were weighed, 0.5 mg of each compound, dissolved and diluted to 1 mL with methanol. From each solution an aliquot of 5 μL was injected on an analytical column, Ace C18 3 μm, 150 × 3.0 mm. Separated through a gradient (5–95% acetonitrile in 0.2% formic acid, flow rate 0.5 mL/min, column oven temperature 50 °C) and detected by a diode-array detector (190–350 nm) and quadrupole time-of-flight mass spectrometer (Q-Tof micro, Micromass Amiens, France) operated in electrospray ionization positive ion mode (capillary voltage 3.0 KV, cone voltage 40 V, ion energy 10 eV, mass range 80–1000 *m*/*z*, scan rate 1 s and inter scan delay 0.1 s).

4.3. HPLC analysis

HPLC analyses were performed on a JASCO (UV-2075 plus, PU-2080 plus, Japan) apparatus, using Alltech Adsorbosphere C18 column (4.6 mm × 25.0 cm) with a flow of 0.9 mL/min, UV detection at λ = 254 nm and different mobile phase as follows: mixture of acetonitrile/water in ratio 6:4 with 1% NEt_3 (v/v) adjusted to pH 7.3 with H_3PO_4 for **9a** (t_r = 11.8 min), **9b** (t_r = 15.1 min), **9c**

(t_r = 18.5 min), **9d** (t_r = 10.4 min), **9f** (t_r = 25.3 min) and mixture of acetonitrile/water in ratio 5:5 with 1.3% NEt_3 (v/v) adjusted to pH 7.3 with H_3PO_4 for **9e** (t_r = 19.6 min).

4.4. General procedure for the synthesis of L-α-amino acid phenylhydrazides 6a–f

Freshly distilled phenylhydrazine (12 mmol), triethylamine (10 mmol), and L-α-amino acid methyl ester hydrochloride (10 mmol) were mixed in a flask fitted with a condenser and a magnetic stirring bar. The mixture was stirred at 60 °C for 4 h under an inert atmosphere. Next, it was allowed to cool down to room temperature and stirred overnight. Then, 100 mL of $CHCl_3$, 6 g of Na_2CO_3, and 5 mL of H_2O were added. The mixture was stirred vigorously for 3 h. After filtration of the salts, the solvent was concentrated in vacuo and the unreacted phenylhydrazine was removed under reduced pressure. After the addition of 50 mL of Et_2O and 5 mL of hexane, the mixture was stirred for 1 h and the solid product was filtered and washed with Et_2O. All products were obtained in a spectroscopically pure form.

4.4.1. L-Alanine phenylhydrazide 6a

Yield (80%), mp = 122–124 °C (lit.[16] 116 °C), $[\alpha]_D^{25} = +34.2$ (*c* 0.2, MeOH) [lit.[16] +30.8 (*c* 0.17, MeOH)], IR (cm^{-1}): 3275, 3215 (NH), 1665 (C=O). ^1H NMR (300 MHz, $CDCl_3$): δ 1.42 (d, 3H, *J* = 8.1 Hz, CH_3), 1.55 (sbr, 2H, NH_2), 3.63 (q, 1H, *J* = 8.1 Hz, CH–CH_3), 6.15 (s, 1H, NH–Ph), 6.84–7.24 (m, 5H, ArH), 8.20 (sbr, 1H, NH–CO). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.51, 13.67, 62.10, 127.30, 128.31, 132.53, 151.40, 167.37.

4.4.2. L-Valine phenylhydrazide 6b

Yield (65%), mp = 152–154 °C, $[\alpha]_D^{25} = +30.8$ (*c* 0.2, MeOH), IR (cm^{-1}): 3266, 3110 (NH), 1655 (C=O). ^1H NMR (300 MHz, $CDCl_3$): δ 0.90 (d, 3H, *J* = 6.9 Hz, CH_3) 1.02 (d, 3H, *J* = 6.9 Hz, CH_3), 1.70 (sbr, 2H, NH_2), 2.36 (m, 1H, CH–$(CH_3)_2$), 3.42 (d, 1H, *J* = 6.9 Hz, CH–NH_2), 6.20 (s, 1H, NH–Ph), 6.84–7.25 (m, 5H, ArH), 8.95 (sbr, 1H, NH–CO). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 16.19, 19.50, 30.86, 59.61, 113.71, 121.20, 129.17, 148.12, 174.05.

4.4.3. L-Leucine phenylhydrazide 6c

Yield (72%), mp = 138–140 °C (lit.[16] 148 °C), $[\alpha]_D^{25} = +22.8$ (*c* 0.2, MeOH) [lit.[16] +20.7 (*c* 0.2, MeOH)], IR (cm^{-1}): 3271, 3152 (NH), 1661 (C=O). ^1H NMR (300 MHz, $CDCl_3$): δ 0.91 (d, 3H, *J* = 6.9 Hz, CH_3) d, 3H, *J* = 6.9 Hz, CH_3), 1.43 (m, 1H, CH–$(CH_3)_2$), 1.74 (m, 2H, CH_2), 3.51 (dd, 1H, *J* = 9.9 and3.9 Hz, CH–NH_2), 6.10 (s, 1H, NH–Ph), 6.79–7.26 (m, 5H, ArH), 9.12 (sbr, 1H, NH–CO). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.43, 23.28, 24.74, 44.00, 52.93, 113.62, 121.08, 129.13, 148.07, 175.01.

4.4.4. L-Phenylalanine phenylhydrazide 6d

Yield (85%), mp = 142–144 °C (lit.[16] 147 °C), $[\alpha]_D^{25} = +39.4$ (*c* 0.2, MeOH) [lit.[16] +37.1 (*c* 0.27, MeOH)], IR (cm^{-1}): 3285, 3219 (NH), 1648 (C=O). ^1H NMR (300 MHz, $CDCl_3$): δ 1.50 (sbr, 2H, NH_2), 3.22 (dd, 1H, *J* = 9.6 and 12 Hz, CH_2–Ph), 3.28 (dd, 1H, *J* = 4.8 and 12 Hz, CH_2–Ph), 3.76 (dd, 1H, *J* = 9.6 and 4.8 Hz, CH–CH_2), 6.15 (s, 1H, NH–Ph), 6.76–7.40 (m, 10H, ArH), 8.86 (sbr, 1H, NH–CO). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 40.94, 55.89, 113.70, 121.21, 127.00, 129.00, 129.12, 129.42, 137.24, 147.87, 173.71.

4.4.5. L-Serine phenylhydrazide 6e

Yield (68%), mp = 163–165 °C, $[\alpha]_D^{25} = +42.6$ (*c* 0.2, MeOH), IR (cm^{-1}): 3248 (NH), 3000 (OH), 2905 (NH), 1680 (C=O). ^1H NMR (300 MHz, CD_3OD): δ 3.49 (t, 1H, *J* = 5.7 Hz, CH–NH_2), 3.74 (d, 2H, *J* = 5.4 Hz, CH_2–OH), 6.79–7.21 (m, 5H, ArH), 8.86 (sbr, 1H, NH–CO). ^{13}C NMR (75 MHz, CD_3OD): δ = 56.78, 65.61, 114.22, 121.09, 129.94, 149.76, 175.60. HRMS (ES) found MH^+ *m*/*z* = 196.0512, $C_9H_{14}N_3O_2$ requires 196.0503.

4.4.6. L-Methionine phenylhydrazide 6f

Yield (78%), mp = 128–130 °C, $[\alpha]_D^{25} = +29.8$ (*c* 0.2, MeOH), IR (cm^{-1}): 3230, 2918 (NH), 1647 (C=O). ^1H NMR (300 MHz, $CDCl_3$): δ 1.86 (dt, 1H, *J* = 6.9 and 13.8 Hz, CH_2–CH), 2.10 (s, 3H, –S–CH_3), 2.16 (dt, 1H, *J* = 6.9 and 13.8 Hz, CH_2–CH), 2.62 (t, 2H, *J* = 6.9 Hz S-CH_2), 3.65 (t, 1H, *J* = 13.8 Hz, CH–NH_2), 6.27 (s, 1H, NH–Ph), 6.81–7.28 (m, 5H, ArH), 8.97 (sbr, 1H, NH–CO). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.84, 29.99, 33.43, 52.98, 113.11, 120.66, 128.68, 147.47, 173.70.

4.5. General procedure for the synthesis of 6,7-isopropylidenedioxy-1-phenylamino-dihydro-1*H*-pyrrolo[1,2-*a*]imidazole-2,5(3*H*,6*H*)-diones 8a–f

To a stirred solution of the appropriate L-α-amino acid phenylhydrazide (2.8 mmol) in anhydrous ethanol (25 mL) were added 2,3-*O*-isopropylidene-L-erythruronolactone (0.6 g, 3.4 mmol) and PTSA (0.05 g, 0.28 mmol). The reaction mixture was then heated under argon at 80 °C for 12 h. After evaporation of the solvent under reduced pressure, the residue was dissolved in $CHCl_3$ (25 mL) and then stirred vigorously with Na_2CO_3 (0.2 g) and H_2O (1 mL) for 15 min. The mixture was then dried over anhydrous $MgSO_4$ and filtered after which $CHCl_3$ was evaporated. Purification of the residue by column chromatography on silica gel (30% AcOEt–70% hexane) afforded diastereopure 6,7-isopropylidenedioxy-1-phenylamino-dihydro-1*H*-pyrrolo[1,2-*a*]imidazole-2,5(3*H*,6*H*)-diones.

4.5.1. (3*S*,6*R*,7*R*,7a*S*)-6,7-Isopropylidenedioxy-3-methyl-1-phen ylamino-dihydro-1*H*-pyrrolo[1,2-*a*]imidazole-2,5(3*H*,6*H*)-dione 8a

Yield (78%), mp = 128–130 °C, $[\alpha]_D^{25} = -22.1$ (*c* 1.06, MeOH), IR (cm^{-1}): 3280 (NH), 2910 (CH), 1730, 1745 (C=O), 1610 (C=C). ^1H NMR (300 MHz, $CDCl_3$): δ 1.40 (s, 3H, CH_3), 1.50 (s, 3H, CH_3), 1.76 (d, 3H, *J* = 6.9 Hz, CH_3), 4.10 (q, 1H, *J* = 7.2 Hz, CH), 4.70 (dd, 1H, *J* = 3.5 and 4.2 Hz, CH); 4.80 (d, H, *J* = 4.2 Hz, CH), 5.24 (d, H, *J* = 3.5 Hz, CH), 6.07 (s, 1H, NH), 6,84–7,28 (m, 5H, ArH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.19, 26.45, 27.54, 54.23, 72.39, 74,04, 79.71, 113.79, 114.19, 121.94, 129.37, 144.90, 171.06, 172,13. HRMS (ES) found MH^+ *m*/*z* = 318.1458, $C_{16}H_{20}N_3O_4$ requires 318.1454.

4.5.2. (3*S*,6*R*,7*R*,7a*S*)-3-Isopropyl-6,7-isopropylidenedioxy-1-phenylamino-dihydro-1*H*-pyrrolo[1,2-*a*]imidazole-2,5(3*H*,6*H*)-dione 8b

Yield (78%), mp = 128–130 °C, $[\alpha]_D^{25} = +18.6$ (*c* 0.45, MeOH), IR (cm^{-1}): 3228 (NH), 2960 (CH), 1729, 1738 (C=O), 1612 (C=C). ^1H NMR (300 MHz, $CDCl_3$): δ 0.98 (d, 3H, *J* = 6.6 Hz, CH_3), 1,14 (d, 3H, *J* = 7.2 Hz, CH_3), 1.30 (s, 3H, CH_3), 1.39 (s, 3H, CH_3), 3.25 (qd, 1H, *J* = 7.2 and 2.7 Hz, CH), 3.93 (d, 1H, *J* = 2.4 Hz, CH), 4.71 (m, 2H, 2 CH), 5.03 (d, 1H, *J* = 4.1 Hz, CH), 5.99 (s, 1H, NH), 6.85–7.19 (m, 5H, ArH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 16.44, 16.68, 25.28, 26.87, 29.68, 63.00, 72.66, 73.38, 79.77, 114.21, 114.29, 121.98, 129.17, 145.58, 169.27, 172.47. HRMS (ES) found MH^+ *m*/*z* = 346.2350, $C_{18}H_{24}N_3O_4$ requires 346.2348.

4.5.3. (3*S*,6*R*,7*R*,7a*S*)-3-Isobutyl-6,7-isopropylidenedioxy-1-phenylamino-dihydro-1*H*-pyrrolo[1,2-*a*]imidazole-2,5(3*H*,6*H*)-dione 8c

Yield (78%), mp = 128–130 °C, $[\alpha]_D^{25} = +12.9$ (*c* 0.83, MeOH), IR (cm^{-1}): 3220 (NH), 2966 (CH), 1723, 1751 (C=O), 1606 (C=C). ^1H NMR (300 MHz, $CDCl_3$): δ 0.98 (d, 6H, *J* = 6 Hz, $(CH_3)_2$–CH), 1.40 (s, 3H, CH_3), 1.50 (s, 3H, CH_3), 1.81 (m, 1H, CH), 2.29 (m, 2H, CH_2), 4.05 (t, 1H, *J* = 6.0 Hz, CH), 4.71 (t, 1H, *J* = 4.2 Hz, CH), 4.76

(d, 1H, J = 4.2 Hz, CH), 5.18 (d, 1H, CH, J = 4.3 Hz), 6.04 (s, 1H, NH), 6.87–7.27 (m, 5H, ArH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 22.15, 22.91, 24.87, 26.28, 27.29, 36.16, 56.93, 72.49, 73.68, 79.72, 114.05, 114.18, 121.96, 129.30, 145.17, 170.07, 172.42. HRMS (ES) found MH^+ m/z = 360.2984, $C_{19}H_{26}N_3O_4$ requires 360.2978.

4.5.4. (3*S*,6*R*,7*R*,7a*S*)-3-Benzyl-6,7-isopropylidenedioxy-1-phenylamino-dihydro-1*H*-pyrrolo[1,2-*a*]imidazole-2,5(3*H*,6*H*)-dione 8d

Yield (78%), mp = 128–130 °C, $[\alpha]_D^{25} = -31.4$ (c 1.25, MeOH), IR (cm^{-1}): 3275 (NH), 3019 (CH), 1721, 1742 (C=O), 1609 (C=C). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.31 (s, 3H, CH_3), 1.45 (s, 3H, CH_3), 3.15 (dd, 1H, J = 13,8 Hz and 5,1 Hz, CH_2), 3.31 (dd, 1H, J = 13,8 Hz and 5,1 Hz, CH_2), 3.98 (t, 1H, J = 5.1 Hz, CH), 4.63–4.72 (m, 3H, CH), 5.79 (s, 1H, NH), 6.54–7.21 (m, 5H, ArH), 7.25–7.35 (m, 5H, ArH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 25.58, 26.66, 36.31, 59.08, 77.47, 78.21, 81.54, 113.73, 115.04, 122.29, 127.84, 128.85, 129.45, 129.45, 135.20, 145.54, 172.96, 174.11. HRMS (ES) found MH^+ m/z = 394.3024, $C_{22}H_{24}N_3O_4$ requires 394.3021.

4.5.5. (3*S*,6*R*,7*R*,7a*S*)-3-Hydroxymethyl-6,7-isopropylidenedioxy-1-phenylamino-dihydro-1*H*-pyrrolo[1,2-*a*]imidazole-2,5(3*H*,6*H*)-dione 8e

Yield (78%), mp = 128–130 °C, $[\alpha]_D^{25} = -16.2$ (c 0.79, MeOH), IR (cm^{-1}): 3354 (OH), 3195 (NH), 2918 (CH), 1711, 1743 (C=O), 1647 (C=C). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.27 (s, 3H, CH_3), 1.43 (s, 3H, CH_3), 3.87–3.92 (dd, 1H, J = 12.0 Hz and 4.2 Hz, CH_2), 4.09–4.12 (sbr, 1H, OH), 4.39–4.46 (dd, 1H, J = 12.0 Hz and 4.2 Hz, CH_2), 4.70–4.75 (t, 1H, J = 3.6 Hz), 4.79–4.84 (m, 2H, CH), 5.27–5.28 (d, 1H, J = 4.7 Hz, CH), 6.73–7.14 (m, 5H, ArH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 26.59, 27.47, 58.76, 62.49, 74.00, 75.80, 81.42, 114.90, 115.46, 121.81, 113.02, 147.35, 171.85, 174.14. HRMS (ES) found MH^+ m/z = 334.1566, $C_{16}H_{20}N_3O_5$ requires 334.1562.

4.5.6. (3*S*,6*R*,7*R*,7a*S*)-6,7-Isopropylidenedioxy-3-(2-methylthioethyl)-1-phenylamino-dihydro-1*H*-pyrrolo[1,2-*a*]imidazole-2,5 (3*H*,6*H*)-dione 8f

Yield (81%), mp = 183–185 °C, $[\alpha]_D^{25} = +26.5$ (c 0.58, MeOH), IR (cm^{-1}): 3244 (NH), 2914 (CH), 1721, 1749 (C=O), 1603 (C=C). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.30 (s, 3H, CH_3), 1.46 (s, 3H, CH_3), 1.90 (m, 1H, CH_2), 2.11 (s, 3H, S-CH_3), 2.14 (m, 1H, CH_2), 2.69 (t, 2H, J = 7.2 Hz, S-CH_2), 3.69 (dd, 1H, J = 4.8 and 7.6 Hz, CH), 4.72 (t, 1H, J = 4.2 Hz, CH); 4.78 (d, 1H, J = 4.1 Hz, CH), 5.33 (d, 1H, J = 4.3 Hz, CH), 6.22 (s, 1H, NH), 6.79–7.22 (m, 5H, ArH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.86, 26.33, 27.69, 29.60, 32.63, 54.94, 72.14, 74.58, 80.25, 113.58, 113.89, 121.15, 129.37, 145.60, 171.52, 173.71. HRMS (ES) found MH^+ m/z = 378.2623, $C_{18}H_{24}N_3O_4S$ requires 378.2620.

4.6. General procedure for the synthesis of 6,7-dihydroxy-1-phenylamino-dihydro-1*H*-pyrrolo[1,2-*a*]imidazole-2,5(3*H*,6*H*)-diones 9a–f

Dihydro1-phenylamino-1*H*-6,7-isopropylidenedioxypyrrolo[1,2-*a*]imidazole-2,5(3*H*,6*H*)-dione (1 mmol) was treated with methanolic hydrochloride acid (MeOH/HCl, 15 mL) at 0 °C for 1 h. The reaction mixture was concentrated in vacuo to remove all of the solvent. The residue was quenched by adding 10% aqueous $NaHCO_3$ solution (10 mL) and stirred for 30 min. The aqueous phase was extracted with ethyl acetate (3 × 20 mL). The organic phase was washed with brine (3 × 5 mL), dried over $MgSO_4$, and concentrated in vacuo. The crude residue was purified by column chromatography on silica gel (15% MeOH–85% CH_2Cl_2) to afford a diastereopure 6,7-dihydroxy-1-phenylamino-dihydro-1*H*-pyrrolo[1,2-*a*]imidazole-2,5(3*H*,6*H*)-dione.

4.6.1. (3*S*,6*R*,7*R*,7a*S*)-6,7-Dihydroxy-3-methyl-1-phenylamino-dihydro-1*H*-pyrrolo[1,2-*a*]imidazole-2,5(3*H*,6*H*)-dione 9a

Yield (87%), mp = 197–199 °C, $[\alpha]_D^{25} = +14.7$ (c 1.12, MeOH), IR (cm^{-1}): 3321 (OH), 3267 (NH), 2916 (CH), 1726, 1705 (C=O), 1608 (C=C). ^{1}H NMR (300 MHz, CD_3OD): δ 1.68 (d, 3H, J = 7.1 Hz, CH_3), 4.45 (q, 1H, J = 7.1 Hz, CH), 4.62 (t, 1H, J = 4.4 Hz, CH); 4.69 (d, H, J = 3.5 Hz, CH), 5.54 (d, H, J = 3.4 Hz, CH), 6.90–7.35 (m, 5H, ArH). ^{13}C NMR (75 MHz, CD_3OD): δ 16.08, 60.94, 73.41, 76,13, 81.51, 113.23, 122.84, 129.25, 148.70, 172.93, 173,38. HRMS (ES) found MH^+ m/z = 266.1378, $C_{13}H_{16}N_3O_4$ requires 266.1374.

4.6.2. (3*S*,6*R*,7*R*,7a*S*)-6,7-Dihydroxy-3-isopropyl-1-phenylamino--dihydro-1*H*-pyrrolo[1,2-*a*]imidazole-2,5(3*H*,6*H*)-dione 9b

Yield (75%), mp = 200–202 °C, $[\alpha]_D^{25} = -20.5$ (c 0.61, MeOH), IR (cm^{-1}): 3309 (OH), 3231 (NH), 2957 (CH), 1721, 1740 (C=O), 1621 (C=C). ^{1}H NMR (300 MHz, CD_3OD): δ 0.95 (d, 3H, J = 6.8 Hz, CH_3), 1,11 (d, 3H, J = 7.1 Hz, CH_3), 3.09 (qd, 1H, J = 7.2 and 2.7 Hz, CH), 4.15 (d, 1H, J = 3.5 Hz, CH), 4.62 (m, 2H, 2 CH), 5.37 (d, 1H, J = 3.4 Hz, CH), 6.83–7.34 (m, 5H, ArH). ^{13}C NMR (75 MHz, CD_3OD): δ 18.32, 18.56, 28.69, 64.25, 73.60, 76.38, 82.69, 113.41, 123.78, 130.16, 146.52, 170.24, 173.49. HRMS (ES) found MH^+ m/z = 306.1510, $C_{15}H_{20}N_3O_4$ requires 306.1506.

4.6.3. (3*S*,6*R*,7*R*,7a*S*)-6,7-Dihydroxy-3-isobutyl-1-phenylamino-dihydro-1*H*-pyrrolo[1,2-*a*]imidazole-2,5(3*H*,6*H*)-dione 9c

Yield (83%), mp = 211–213 °C, $[\alpha]_D^{25} = +32.0$ (c 0.46, MeOH), IR (cm^{-1}): 3310 (OH), 3228 (NH), 2959 (CH), 1726, 1736 (C=O), 1616 (C=C). ^{1}H NMR (300 MHz, CD_3OD): δ 0.95 (d, 6H, J = 6.8 Hz, $(CH_3)_2$-CH), 1.84 (m, 1H, CH), 2.23 (m, 2H, CH_2), 4.36 (t, 1H, J = 6.3 Hz, CH), 4.54 (t, 1H, J = 4,3 Hz, CH), 4.79 (d, 1H, J = 4.3 Hz, CH), 5.27 (d, 1H, CH, J = 4.2 Hz), 6.91–7.32 (m, 5H, ArH). ^{13}C NMR (75 MHz, CD_3OD): δ 22.96, 23.09, 25.61, 37.76, 64.33, 68.99, 74.68, 82.36, 114.10, 122.86, 129.90, 146.19, 171.26, 172.22. HRMS (ES) found MH^+ m/z = 320.2055, $C_{16}H_{22}N_3O_4$ requires 320.2052.

4.6.4. (3*S*,6*R*,7*R*,7a*S*)-3-Benzyl-6,7-dihydroxy-1-phenylamino-dihydro-1*H*-pyrrolo[1,2-*a*]imidazole-2,5(3*H*,6*H*)-dione 9d

Yield (85%), mp = 232–234 °C, $[\alpha]_D^{25} = +19.2$ (c 1.15, MeOH), IR (cm^{-1}): 3306 (OH), 3260 (NH), 3011 (CH), 1710, 1744 (C=O), 1618 (C=C). ^{1}H NMR (300 MHz, CD_3OD): δ 3.19 (dd, 1H, J = 13,7 Hz and J = 5,3 Hz, CH_2), 3.44 (dd, 1H, J = 13,7 Hz and J = 5,3 Hz, CH_2), 4.52 (t, 1H, J = 5.1 Hz, CH), 4.52–4.74 (m, 2H, CH), 5.31 (d, 1H, CH, J = 3.9 Hz), 6.89–7.37 (m, 10H, ArH). ^{13}C NMR (75 MHz, CD_3OD): δ 35.51, 64.00, 75.49, 77.36, 82.51, 114.03, 121.64, 126.88, 128.78, 129.39, 129.80, 136.25, 145.04, 172.36, 174.98. HRMS (ES) found MH^+ m/z = 354.2684, $C_{19}H_{20}N_3O_4$ requires 354.2679.

4.6.5. (3*S*,6*R*,7*R*,7a*S*)-6,7-Dihydroxy-3-hydroxymethyl-1-phenylamino-dihydro-1*H*-pyrrolo[1,2-*a*]imidazole-2,5(3*H*,6*H*)-dione 9e

Yield (70%), mp = 242–244 °C, $[\alpha]_D^{25} = -33.8$ (c 0.94, MeOH), IR (cm^{-1}): 3347 (OH), 3184 (NH), 2910 (CH), 1718, 1742 (C=O), 1634 (C=C). ^{1}H NMR (300 MHz, CD_3OD): δ 3.90 (dd, 1H, J = 12.6 Hz and J = 4.2 Hz, CH_2), 4.26 (dd, 1H, J = 12.6 Hz and J = 4.2 Hz, CH_2), 4.62 (t, 1H, J = 4.1 Hz), 4.34–4.56 (m, 2H, CH), 5.49 (d, 1H, J = 3.9 Hz, CH), 6.71–7.12 (m, 5H, ArH). ^{13}C NMR (75 MHz, CD_3OD): δ 59.52, 67.43, 73.09, 77.85, 82.63, 114.47, 123.66, 129.14, 150.08, 171.93, 173.74. HRMS (ES) found MH^+ m/z = 282.1513, $C_{13}H_{16}N_3O_5$ requires 282.1511.

4.6.6. (3*S*,6*R*,7*R*,7a*S*)-6,7-Dihydroxy-3-(2-methylthioethyl)-1-ph enylamino-dihydro-1*H*-pyrrolo[1,2-*a*]imidazole-2,5(3*H*,6*H*)-dio ne 9f

Yield (79%), mp = 187–189 °C, $[\alpha]_D^{25} = +24.4$ (*c* 0.96, MeOH), IR (cm^{-1}): 3313 (OH), 3232 (NH), 2918 (CH), 1715, 1730 (C=O), 1611 (C=C). ^1H NMR (300 MHz, CD_3OD): δ 2.06 (m, 1H, CH_2), 2.35 (s, 3H, S-CH_3), 2.43 (m, 1H, CH_2), 2.61 (t, 2H, J = 7.1 Hz, S-CH_2), 4.12 (dd, 1H, J = 4.6 and J = 7.3 Hz, CH), 4.60 (t, 1H, J = 4.3 Hz, CH); 4.77 (d, 1H, J = 4.3 Hz, CH), 5.41 (d, 1H, J = 4.4 Hz, CH), 6.75–7.29 (m, 5H, ArH). ^{13}C NMR (75 MHz, CD_3OD): δ 15.46, 30.50, 31.58, 53.84, 74.35, 76.78, 82.77, 114.80, 123.05, 129.33, 145.54, 171.78, 173.06. HRMS (ES) found MH^+ m/z = 338.3064, $C_{15}H_{20}N_3O_4S$ requires 338.3056.

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