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Stereoselective syntheses of 1*H*-imidazo[2,1-*a*]isoindole-2,5(3*H*,9b*H*)-diones †

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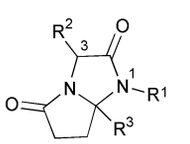
Received (in Cambridge, UK) 9th May 2001, Accepted 13th June 2001
First published as an Advance Article on the web 13th July 2001

1*H*-Imidazo[2,1-*a*]isoindole-2,5(3*H*,9b*H*)-diones **6a**–**i** are synthesized in 67–96% yields with high stereoselectivities (de 88–99%, except **6e** with a 58% de value) *via* intermolecular condensation of 2-formylbenzoic acid (**5**) and α-amino amides **4a**–**i** in the presence of a catalytic amount of toluene-*p*-sulfonic acid. Intermediates **4** are obtained in two steps from easily available chiral *N*-Boc-α-amino acids **1**.

Introduction

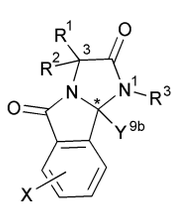
Pyrrolidinones possess varied biological activities and have been used as cognition enhancing pharmaceuticals.[1] The synthesis of substituted pyrrolidinones has been widely studied.[2] Dihydro-1*H*-pyrrolo[1,2-*a*]imidazole-2,5(3*H*,6*H*)-diones **I** have shown cognition enhancing activities.[3] Some have been used in therapy, in particular as nootropic agents.[4] Related compounds, 1*H*-imidazo[2,1-*a*]isoindole-2,5(3*H*,9b*H*)-diones **II**, are important herbicides for bud growth inhibition[5,6] and plant growth regulation.[7]

The reported syntheses of 1*H*-imidazo[2,1-*a*]isoindole-2,5(3*H*,9b*H*)-diones **II** are multiple-step, afford moderate overall yields, and the R^3 group is limited in published examples to hydrogen.[5b,8] Furthermore, no stereoselectivity was found and products with one (9b position) or two (3 and 9b positions) chiral centers were obtained as racemates[5] or diastereoisomeric mixtures.[5b,8] We now report simple and efficient syntheses of 3-substituted 1*H*-imidazo[2,1-*a*]isoindole-2,5(3*H*,9b*H*)-diones **6a**–**i** in good to excellent yields with high stereoselectivities starting from easily available *N*-Boc-α-amino acids **1**.



I

R^1 = H, Et, COMe, CH_2CO_2Et, CO_2CH_2Ph;
R^2 = H, Me, *i*-Bu, CH_2OH, CH_2Ph;
R^3 = H, Me, CO_2H, CO_2Et, $CONH_2$

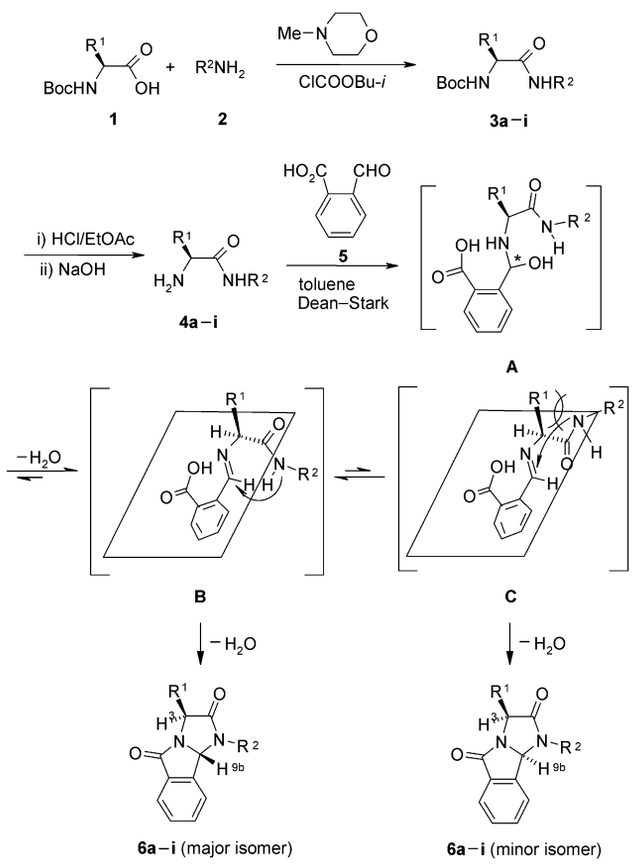


II

R^1 = alkyl; R^2 = alkyl, Ph, ClC_6H_4, $PhCH_2$; R^3 = H
X = H, Me, OMe, Cl, NO_2;
Y = H, alkoxy, alkylthio, alkylamino, OH, SH, NH_2

Results and discussion

Following a literature method,[9] reactions of chiral *N*-Boc-α-amino acids **1** (R^1 = Me, *i*-Pr, *i*-Bu or $PhCH_2$) with aryl, alkyl or cycloalkyl primary amines **2** in the presence of isobutyl chloroformate and 4-methylmorpholine afforded *N*-Boc-α-amino amides **3a**–**i** in 86–94% yields (Scheme 1). The structures of the *N*-Boc-α-amino amides **3a**–**i** are supported by their ^1H, ^{13}C NMR spectra and microanalyses. The crude products **3** could be used directly for subsequent reactions without further purification. Acid hydrolysis of **3a**–**i** with excess HCl–EtOAc (*ca.* 1 M) at room temperature easily removed the *N*-Boc protection group to generate α-amino amide hydrochloride salts, which by subsequent treatment with aqueous NaOH gave the free base α-amino amides **4a**–**d** and **4f**–**i** in good to excellent yields (Table 1). Compound **4e** was obtained as a hydrochloride salt.

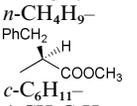


Scheme 1

† Electronic supplementary information (ESI) available: characterization data for compounds **3b**–**i** and **4b**–**i**. See http://www.rsc.org/suppdata/p1/b1/b104060j/

DOI: 10.1039/b104060j

Table 1 Isolated yields of *N*-Boc-α-amino amides **3a**–**i**, α-amino amides **4a**–**i** and **6a**–**i** with de values of **6**

	R^1	R^2	**3**[a]	**4**[b]	**6** (de,[c] %)
a	*i*-Bu	4-$CH_3C_6H_4$–	94	91	95 (>99)
b	*i*-Bu	C_6H_5–	86	80	81 (>99)
c	*i*-Bu	4-FC_6H_4–	87	83	96 (90)
d	*i*-Bu	*n*-CH_4H_9–	86	60	67 (88)
e	*i*-Bu		87	87[d]	84 (58)
f	*i*-Bu	*c*-C_6H_{11}–	88	81	86 (94)
g	Me	4-$CH_3C_6H_4$–	88	71	88 (>99)
h	*i*-Pr	4-$CH_3C_6H_4$–	94	92	89 (>99)
i	$C_6H_5CH_2$–	4-$CH_3C_6H_4$–	94	85	92 (>99)

[a] Isolated yield based on *N*-Boc-α-amino acids **1**. [b] Isolated yield based on *N*-Boc-α-amino amides **3**. [c] Determined by ^{1}H NMR spectroscopy. [d] Compound **4e** was obtained and characterized as a hydrochloride salt.

1*H*-Imidazo[2,1-*a*]isoindole-2,5(3*H*,9b*H*)-diones **6a**–**i** were prepared in 67 to 96% yields by the reactions of 2-formylbenzoic acid (**5**) with 1 equiv. of α-amino amides **4a**–**i** and catalytic toluene-*p*-sulfonic acid (0.1 equiv.) in refluxing toluene for 12 h with a Dean–Stark apparatus to separate the water formed (Scheme 1). The isolated yields and the de values (determined from ^{1}H NMR spectra) of **6a**–**i** are summarized in Table 1. The structures of **6a**–**i** were clearly supported by their ^{1}H, ^{13}C NMR spectra and microanalyses. For **6a**, the number (8) of carbon peaks in the aromatic region was two fewer than that expected (10) in $CDCl_3$, but it was correct in DMSO-d_6.

The absolute configurations of the new chiral center for **6a**–**i** were initially determined by NOE experiments. ^{1}H NMR spectra show that in **6** H(9b) appears in the range of 5.1–6.4 ppm as a singlet; H(3) at 4.5–4.9 ppm as a doublet-doublet (for **6a**–**c**, **e**, **f**, **i**), a multiplet (for **6d**, **g**) or a doublet (for **6h**). For each compound **6**, when H(9b) was irradiated, no distinct NOE effect was observed for H(3), and *vice versa*. This suggests that H(9b) and H(3) in **6a**–**h** are located in *trans*-orientations. For **6a**, irradiation of each hydrogen of the methylene group (2.10–1.80 ppm) in $(CH_3)_2CHCH_2$– resulted in a distinct positive NOE effect of H(9b). This fact further demonstrates the *trans*-orientation of H(9b) and H(3). Similar results were also observed in **6b**–**f**. For **6g**, irradiation of the CH_3(3) doublet at 1.64 ppm caused a strong positive NOE effect of H(9b). For **6h**, irradiation of the CH_3 doublet at 1.13 ppm gave a strong positive NOE effect of H(9b); while irradiation of the CH_3 doublet at 1.27 ppm gave a smaller, but distinct positive NOE effect of H(9b). The facts above demonstrate that H(9b) and H(3) in **6g**, **h** are located in *trans*-orientations.

The structure of **6i** was further confirmed by single crystal X-ray crystallography. Chiral **6i** crystallized as very fine needles that were unsuitable for X-ray structure determination. After repeated crystallization attempts, small plates were finally obtained and these were subjected to X-ray structure determination and found to be racemic **6i**. Fig. 1 shows a perspective view of one enantiomer of racemic **6i**, which confirms the *trans*-orientation of H(9b) and H(3). We later found that compound **6i** is indeed partially racemized slowly in refluxing DMF. The optical activity (25 °C; *c* 1.25 in DMF) decreased from −200.9 to −111.4° after refluxing in DMF for 24 h, while the NMR spectrum remained unchanged.

As regards the reaction mechanism (*cf*. Scheme 1), the α-amino group in **4a**–**i** attacks the aldehydic carbon atom (the most electrophilic center in **5**) to generate the transient intermediate α-carbinolamine **A**, which eliminates 1 equiv. of water to afford the *trans*-imine intermediate. Similar intermediate α-carbinolamines were previously believed to be formed when primary amines reacted with 2-formylbenzoic acid (**5**).[10] Conformation **B** of the *trans*-imine intermediate is much more stable than conformation **C** due to the larger repulsion between

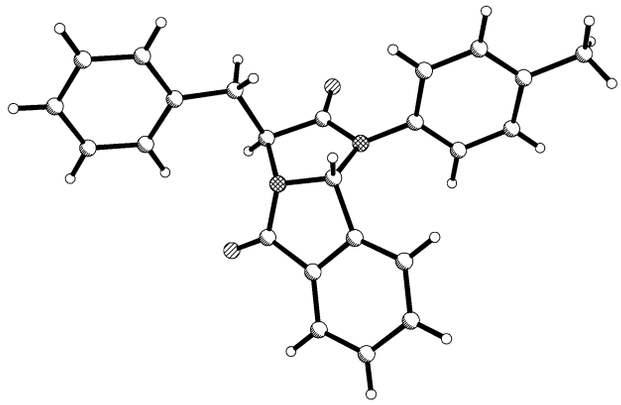


Fig. 1 Perspective view of one enantiomer of the X-ray crystal structure of racemic **6i**.

the R^1 group and –NHR^2 group in **C**. The lone electron pair of the nitrogen in the predominant conformation **B** attacks the imine below the ArC=N– coplane, followed by elimination of another equivalent of water, to form the *trans*-isomers **6** as major products.

Comparisons of data in Table 1 show that the de values depend significantly on the R^2 groups. When R^2 is *p*-methylphenyl or phenyl, only one diastereoisomer (**6a**, **b** and **6g**–**i**) was obtained, whatever the R^1 group. When R^2 is *p*-fluorophenyl, the de value of **6c** is slightly lower (90%). However, when the R^2 group changes from aryl to cyclohexyl (**6f**), *n*-butyl (**6d**) or –$CH(CH_2Ph)COOCH_3$ (**6e**), the stereoselectivities become lower. In the mechanism mentioned above, larger R^2, *e.g.* aryl groups, should have increased the repulsion with R^1, decreasing the stability of conformation **C** (leading to the minor isomers), and thus giving higher stereoselectivities.

Conclusion

In summary, we have developed an efficient and simple route to synthesize chiral 1*H*-imidazo[2,1-*a*]isoindole-2,5(3*H*,9b*H*)-diones **6a**–**i** in good to excellent yields with high stereoselectivities by intermolecular reactions of 2-formylbenzoic acid (**5**) and α-amino amides **4a**–**i**, which are readily prepared in two steps from *N*-Boc-α-amino acids **1**.

Experimental

All mps were determined using a Bristoline hot-stage microscope and are uncorrected. ^{1}H (300 MHz) and ^{13}C (75 MHz) NMR spectra were recorded on a 300 NMR spectrometer in $CDCl_3$ (with TMS for ^{1}H and $CDCl_3$ for ^{13}C as the internal reference), unless otherwise stated. Optical rotation values were measured with a Perkin-Elmer 341 polarimeter with the use of the sodium D line and are reported in units of 10^{-1} deg cm^2 g^{-1}. All of the reactions were carried out under N_2. Column chromatography was performed on silica gel (230–400 mesh).

General procedure for the preparation of *N*-Boc-α-amino amides 3a–i from *N*-Boc-α-amino acids 1

To a cold solution (−15 °C) of chiral *N*-Boc-α-amino acid **1** (10 mmol) and 4-methylmorpholine (1.01 g, 10 mmol) in dry THF (30 mL), isobutyl chloroformate (1.36 g, 10 mmol) in THF (5 mL) was added dropwise in 15 min. After stirring for another 15 min, an appropriate primary amine **2** (10 mmol) was added in one portion. Then the reaction mixture was allowed to warm to room temperature and stirred overnight. After evaporation of the solvent *in vacuo*, the residue was diluted with EtOAc and the organic phase was washed with 10% Na_2CO_3, 0.1 M HCl, brine and dried over anhydrous Na_2SO_4. Removal of the solvent *in vacuo* gave crude *N*-Boc-α-amino amides **3a**–**i**, which can

be used for the subsequent step without further purification. For microanalysis purposes, the crude solid was recrystallized from $CHCl_3$–hexanes.

For **3e**, 2 equiv. of 4-methylmorpholine (2.02 g, 20 mmol) were used, because we used L-phenylalanine methyl ester hydrochloride as the starting material.

***tert*-Butyl *N*-[(1*S*)-1-(4-toluidinocarbonyl)-3-methylbutyl]-carbamate (3a).** Recrystallized from $CHCl_3$–hexanes to give colorless needles; mp 142–143 °C; $[\alpha]_D^{25} = -35.4$ (*c* 1.11 in EtOH) (Found: C, 67.67; H, 9.18; N, 8.77. Calc. for $C_{18}H_{28}N_2O_3$: C, 67.47; H, 8.81; N, 8.74%); δ_H (300 MHz, $CDCl_3$, Me_4Si) 8.67 (1H, br s, ArN*H*CO), 7.36 (2H, d, *J* 8.1), 7.03 (2H, d, *J* 7.4), 5.28 (1H, br s), 4.34 (1H, br s, NHC*H*CO), 2.27 (3H, s), 1.86–1.65 (2H, m), 1.65–1.56 (1H, m), 1.42 (9H, s), 0.96 (3H, d, *J* 5.9), 0.94 (3H, d, *J* 5.6); δ_C (75 MHz, $CDCl_3$, Me_4Si) 171.4, 156.3, 135.4, 133.3, 129.1, 119.8, 80.0, 53.8, 41.2, 28.3, 24.7, 23.0, 21.8, 20.8.

General procedure for the preparation of α-amino amides 4a–i from *N*-Boc-α-amino amides 3a–i

To a stirred solution of *N*-Boc-α-amino amides **3a**–**i** (2.2 mmol) in EtOAc (10 mL), HCl in EtOAc (*ca.* 1 M, 10 mL) was added. The mixture was stirred at room temperature until TLC showed the disappearance of the starting material **3** (10–20 h). Then the mixture was treated with 1 M NaOH and extracted with EtOAc. The organic phase was washed with brine and dried over anhydrous Na_2SO_4. Evaporation of solvent *in vacuo* gave the α-amino amides **4a**–**i**, which were recrystallized from appropriate solvents (if solid) or purified by column chromatography with hexanes–EtOAc as eluent (if oil).

For **4e**, after acid hydrolysis of **3e** for 6 h, the precipitate formed was filtered and washed with diethyl ether. Recrystallization of the solid from EtOH afforded methyl (2*S*)-2-{[(2*S*)-2-amino-4-methylpentanoyl]amino}-3-phenylpropanoate hydrochloride (**4e**) as a hydrochloride salt.

(2*S*)-2-Amino-4-methyl-*N*-(4-methylphenyl)pentanamide (4a). Recrystallized from $CHCl_3$–hexanes to give colorless flakes; mp 99–100 °C; $[\alpha]_D^{25} = +10.1$ (*c* 1.45 in EtOH) (Found: C, 71.10; H, 9.51; N, 12.70. Calc. for $C_{13}H_{20}N_2O$: C, 70.87; H, 9.15; N, 12.72%); δ_H (300 MHz, $CDCl_3$, Me_4Si) 9.41 (1H, br s), 7.48 (2H, d, *J* 8.2), 7.11 (2H, d, *J* 8.2), 3.49 (1H, dd, *J* 10.2 and 2.7), 2.31 (3H, s), 1.83–1.75 (2H, m), 1.53 (2H, s, N*H*$_2$), 1.45–1.38 (1H, m), 0.99 (3H, d, *J* 6.7), 0.96 (3H, d, *J* 6.4); δ_C (75 MHz, $CDCl_3$, Me_4Si) 173.5, 135.2, 133.2, 129.2, 119.2, 53.7, 43.7, 24.8, 23.3, 21.2, 20.7.

General procedure for the preparation of 1*H*-imidazo[2,1-*a*]-isoindole-2,5(3*H*,9b*H*)-diones 6a–i

α-Amino amide **4a**–**i** (2 mmol), 2-formylbenzoic acid (**5**, 0.30 g, 2 mmol) and toluene-*p*-sulfonic acid monohydrate (0.038 g, 0.2 mmol) were dissolved in toluene (20 mL) and refluxed for 12 h with Dean–Stark apparatus. The reaction mixture was cooled to room temperature. After removal of the solvent *in vacuo*, the residue was purified by column chromatography (silica gel) with hexanes–EtOAc (8 : 1 to 4 : 1) as eluent to give 1*H*-imidazo-[2,1-*a*]isoindole-2,5(3*H*,9b*H*)-diones **6a**–**i**, which are readily recrystallized from hexanes–EtOAc.

For **6e**, 1 equiv. of triethylamine (0.20 g, 2 mmol) was added to the reaction mixture because **4e** was used as a hydrochloride salt.

(3*S*,9b*R*)-1-(4-Methylphenyl)-3-isobutyl-1*H*-imidazo[2,1-*a*]-isoindole-2,5(3*H*,9b*H*)-dione (6a). Recrystallized from EtOAc–hexanes to give colorless needles; mp 124–125 °C; $[\alpha]_D^{25} = -192.9$ (*c* 1.45 in $CHCl_3$) (Found: C, 75.19; H, 6.90; N, 8.33. Calc. for $C_{21}H_{22}N_2O_2$: C, 75.42; H, 6.63; N, 8.38%); δ_H (300 MHz, $CDCl_3$, Me_4Si) 7.91 (1H, d, *J* 7.4), 7.56 (1H, dd, *J* 7.5 and 7.5), 7.46 (1H, dd, *J* 6.5 and 6.5), 7.28–7.15 (5H, m), 6.34 [1H, s, *H*(*9b*)], 4.68 [1H, dd, *J* 11.1 and 3.6, *H*(*3*)], 2.40 (3H, s), 2.09–1.93 (1H, m), 1.88–1.80 (1H, m), 1.76–1.64 (1H, m), 1.17 (3H, d, *J* 6.4), 1.06 (3H, d, *J* 6.5); δ_C (75 MHz, DMSO-d_6, Me_4Si) 172.8, 171.6, 142.9, 136.3, 133.0, 132.9, 131.9, 130.7, 129.6, 124.8, 124.6, 124.2, 73.6, 57.5, 39.2, 25.0, 23.0, 21.3, 20.7; δ_C (75 MHz, $CDCl_3$, Me_4Si) 173.3, 172.8, 142.6, 137.6, 132.6(2), 130.6(2), 130.0, 125.2, 124.8, 124.5, 74.6, 58.2, 39.9, 25.5, 23.2, 21.4, 21.1.

(3*S*,9b*R*)-1-Phenyl-3-isobutyl-1*H*-imidazo[2,1-*a*]isoindole-2,5(3*H*,9b*H*)-dione (6b). Recrystallized from EtOAc–hexanes to give colorless needles; mp 127–128 °C; $[\alpha]_D^{25} = -197.2$ (*c* 1.37 in $CHCl_3$) (Found: C, 75.33; H, 6.68; N, 8.75. Calc. for $C_{20}H_{20}N_2O_2$: C, 74.98; H, 6.29; N, 8.74%); δ_H (300 MHz, $CDCl_3$, Me_4Si) 7.91 (1H, d, *J* 7.5), 7.59–7.32 (7H, m), 7.18 (1H, d, *J* 7.6), 6.42 [1H, s, *H*(*9b*)], 4.71 [1H, dd, *J* 11.1 and 3.9, *H*(*3*)], 2.04–1.91 (1H, m), 1.90–1.83 (1H, m), 1.78–1.73 (1H, m), 1.18 (3H, d, *J* 6.5), 1.07 (3H, d, *J* 6.7); δ_C (75 MHz, $CDCl_3$, Me_4Si) 173.2, 172.6, 142.4, 135.2, 132.6, 132.5, 130.6, 129.4, 127.5, 125.0, 124.7, 124.4, 74.4, 58.2, 39.8, 25.4, 23.2, 21.4.

(3*S*,9b*R*)-1-(4-Fluorophenyl)-3-isobutyl-1*H*-imidazo[2,1-*a*]-isoindole-2,5(3*H*,9b*H*)-dione (6c). Recrystallized from EtOAc–hexanes to give colorless needles; mp 140–141 °C; $[\alpha]_D^{25} = -136.7$ (*c* 1.39 in $CHCl_3$) (Found: C, 70.62; H, 5.67; N, 8.31. Calc. for $C_{20}H_{19}FN_2O_2$: C, 70.99; H, 5.66; N, 8.28%); δ_H (300 MHz, $CDCl_3$, Me_4Si) 7.92 (1H, d, *J* 7.5), 7.58 (1H, dd, *J* 7.3 and 7.3), 7.48 (1H, dd, *J* 6.5 and 6.5 Hz), 7.30–7.26 (2H, m), 7.20–7.12 (3H, m), 6.32 [1H, s, *H*(*9b*)], 4.70 [1H, dd, *J* 11.2 and 3.7, *H*(*3*)], 2.05–1.88 (1H, m), 1.86–1.82 (1H, m), 1.78–1.67 (1H, m), 1.18 (3H, d, *J* 6.5), 1.07 (3H, d, *J* 6.7); δ_C (75 MHz, $CDCl_3$, Me_4Si) 173.2, 173.0, 161.6 (d, *J* 247.1), 142.3, 132.7, 132.6, 131.1 (d, *J* 3.0), 130.8, 127.4 (d, *J* 8.6), 125.0, 124.3, 116.5 (d, *J* 22.7), 74.7, 58.2, 39.9, 25.5, 23.2, 21.4.

(3*S*,9b*R*)-1-Butyl-3-isobutyl-1*H*-imidazo[2,1-*a*]isoindole-2,5(3*H*,9b*H*)-dione (6d). Recrystallized from EtOAc–hexanes to give colorless needles; mp 74–75 °C; $[\alpha]_D^{25} = -35.0$ (*c* 1.73 in $CHCl_3$) (Found: C, 71.70; H, 8.36; N, 9.34. Calc. for $C_{18}H_{24}N_2O_2$: C, 71.97; H, 8.05; N, 9.33%); δ_H (300 MHz, $CDCl_3$, Me_4Si) 7.91 (1H, d, *J* 6.8), 7.71–7.59 (3H, m), 5.88 [1H, s, *H*(*9b*)], 4.51 [1H, dd, *J* 11.3 and 3.7, *H*(*3*)], 3.74–3.66 (1H, m), 3.33–3.24 (1H, m), 1.96–1.90 (1H, m), 1.82–1.52 (4H, m), 1.43–1.38 (2H, m), 1.14 (3H, d, *J* 6.5), 1.08–0.95 (6H, m); δ_C (75 MHz, $CDCl_3$, Me_4Si) 173.2, 173.2, 142.2, 132.7, 130.5, 125.0, 123.7, 72.1, 57.9, 40.1, 39.8, 29.5, 25.4, 23.1, 21.3, 19.9, 13.6.

Methyl (2*S*)-2-[(3*S*)-3-isobutyl-2,5-dioxo-2,3,5,9b-tetrahydro-1*H*-imidazo[2,1-*a*]isoindol-1-yl]-3-phenylpropanoate (6e). Obtained as mixtures of two diastereoisomers with *ca.* 3.8 : 1 ratio (determined from ^{1}H NMR spectra); recrystallized from EtOAc–hexanes to give colorless needles; mp 51–52 °C (Found: C, 70.90; H, 6.67; N, 6.82. Calc. for $C_{24}H_{26}N_2O_4$: C, 70.92; H, 6.45; N, 6.89%); major isomer (9b*R*): δ_H (300 MHz, $CDCl_3$, Me_4Si) 7.77 (1H, d, *J* 6.5), 7.50–7.44 (2H, m), 7.35–7.30 (1H, m), 7.05 (5H, br s), 5.78 [1H, s, *H*(*9b*)], 4.83 (1H, dd, *J* 12.7 and 4.0), 4.48 [1H, dd, *J* 11.2 and 3.0, *H*(*3*)], 3.60 (1H, dd, *J* 14.9 and 4.8), 3.50 (3H, s), 3.44–3.35 (1H, m), 1.76–1.69 (2H, m), 1.47–1.07 (1H, m), 1.04 (3H, d, *J* 6.4), 0.92 (3H, d, *J* 7.5); δ_C (75 MHz, $CDCl_3$, Me_4Si) 174.6, 170.3, 141.7, 135.8, 132.4, 132.2, 130.3, 128.8, 128.5, 127.0, 124.9, 123.5, 73.2, 57.2, 55.1, 52.4, 38.9, 25.2, 23.0, 21.2; minor isomer (9b*S*): δ_H (300 MHz, $CDCl_3$, Me_4Si) 7.90 (1H, d, *J* 6.8), 7.68–7.60 (1H, m), 7.50–7.44 (1H, m), 7.40–7.32 (1H, m), 7.22–7.18 (1H, m), 6.95–6.88 (2H, m), 6.80–6.72 (1H, m), 6.71–6.63 (1H, m), 5.58 [1H, s, *H*(*9b*)], 4.91 (1H, dd, *J* 12.1 and 4.0), 4.39 [1H, dd, *J* 11.2 and 3.0, *H*(*3*)], 3.73 (3H, s), 3.44–3.35 (1H, m), 3.18–3.04 (1H, m), 1.76–1.69 (1H, m), 1.47–1.07 (1H, m), 1.32–1.22 (1H, m), 1.08 (3H, d, *J* 6.7), 0.98 (3H, d, *J* 6.7).

(3*S*,9b*R*)-1-Cyclohexyl-3-isobutyl-1*H*-imidazo[2,1-*a*]isoindole-2,5(3*H*,9b*H*)-dione (6f). Recrystallized from EtOAc–hexanes to give colorless needles; mp 157–158 °C; $[a]_D^{25} = -24.3$ (*c* 1.41 in $CHCl_3$) (Found: C, 73.47; H, 8.31; N, 8.58. Calc. for $C_{20}H_{26}N_2O_2$: C, 73.59; H, 8.03; N, 8.58%); δ_H (300 MHz, $CDCl_3$, Me_4Si) 7.91 (1H, d, *J* 7.3), 7.79 (1H, d, *J* 7.5), 7.70–7.58 (2H, m), 5.93 [1H, s, *H*(*9b*)], 4.50 [1H, dd, *J* 11.4 and 3.4, *H*(*3*)], 3.90–3.80 (1H, m), 2.09–1.20 (13H, m), 1.13 (3H, d, *J* 6.5), 1.01 (3H, d, *J* 6.5); δ_C (75 MHz, $CDCl_3$, Me_4Si) 173.6, 173.0, 143.2, 133.1, 132.6, 130.4, 124.9, 124.7, 73.2, 57.7, 53.3, 39.8, 30.5, 30.2, 26.0, 25.7, 25.4, 25.2, 23.2, 21.4.

(3*S*,9b*R*)-1-(4-Methylphenyl)-3-methyl-1*H*-imidazo[2,1-*a*]-isoindole-2,5(3*H*,9b*H*)-dione (6g). Recrystallized from EtOAc–hexanes to give colorless needles; mp 160–161 °C; $[a]_D^{25} = -162.3$ (*c* 1.23 in $CHCl_3$) (Found: C, 74.05; H, 5.38; N, 9.46. Calc. for $C_{18}H_{16}N_2O_2$: C, 73.95; H, 5.52; N, 9.58%); δ_H (300 MHz, $CDCl_3$, Me_4Si) 7.90 (1H, d, *J* 7.5), 7.55 (1H, dd, *J* 7.4 and 7.4), 7.46 (1H, dd, *J* 7.4 and 7.4), 7.28–7.15 (5H, m), 6.38 [1H, s, *H*(*9b*)], 4.72 [1H, q, *J* 7.2, *H*(*3*)], 2.39 (3H, s), 1.64 (3H, d, *J* 7.2); δ_C (75 MHz, $CDCl_3$, Me_4Si) 173.0, 172.8, 142.4, 137.6, 132.6, 132.4, 130.5(2), 130.0, 125.1, 124.7, 124.4, 74.3, 54.7, 21.0, 17.3.

(3*S*,9b*R*)-1-(4-Methylphenyl)-3-isopropyl-1*H*-imidazo[2,1-*a*]-isoindole-2,5(3*H*,9b*H*)-dione (6h). Recrystallized from EtOAc–hexanes to give colorless needles; mp 144–145 °C; $[a]_D^{25} = -181.2$ (*c* 1.43 in $CHCl_3$) (Found: C, 74.63; H, 6.29; N, 8.67. Calc. for $C_{20}H_{20}N_2O_2$: C, 74.98; H, 6.29; N, 8.74%); δ_H (300 MHz, $CDCl_3$, Me_4Si) 7.93 (1H, d, *J* 7.6), 7.56 (1H, dd, *J* 7.5 and 7.5), 7.46 (1H, dd, *J* 7.5 and 7.5), 7.29–7.11 (5H, m), 6.31 [1H, s, *H*(*9b*)], 4.49 [1H, d, *J* 3.7, *H*(*3*)], 2.49–2.46 (1H, m), 2.40 (3H, s), 1.27 (3H, d, *J* 6.8), 1.13 (3H, d, *J* 6.7); δ_C (75 MHz, $CDCl_3$, Me_4Si) 173.9, 172.1, 143.2, 137.8, 132.6, 132.6, 130.5(2), 130.2, 125.4, 124.9, 124.3, 76.3, 65.0, 31.2, 21.1, 19.7.

(3*S*,9b*R*)-1-(4-Methylphenyl)-3-benzyl-1*H*-imidazo[2,1-*a*]-isoindole-2,5(3*H*,9b*H*)-dione (6i). Recrystallized from EtOAc–hexanes to give colorless needles; mp 135–136 °C; $[a]_D^{25} = -148.2$ (*c* 1.33 in $CHCl_3$) (Found: C, 78.06; H, 5.60; N, 7.46. Calc. for $C_{24}H_{20}N_2O_2$: C, 78.24; H, 5.47; N, 7.60%); δ_H (300 MHz, $CDCl_3$, Me_4Si) 7.90 (1H, d, *J* 7.6), 7.51 (1H, dd, *J* 7.6 and 7.5), 7.40–7.34 (6H, m), 7.18 (2H, d, *J* 8.1), 6.83 (1H, d, *J* 7.5), 6.72 (2H, d, *J* 8.2), 5.12 [1H, s, *H*(*9b*)], 4.98 [1H, dd, *J* 4.8 and 3.3, *H*(*3*)], 3.49 (1H, dd, *J* 13.7 and 3.2), 3.32 (1H, dd, *J* 13.7 and 4.8), 2.36 (3H, s); δ_C (75 MHz, $CDCl_3$, Me_4Si) 173.5, 171.4, 143.0, 137.9, 135.9, 132.6, 132.3, 132.2, 130.39, 130.37, 130.0, 128.5, 127.3, 125.5, 124.8, 124.1, 75.7, 60.5, 37.6, 21.1.

Crystal data for 6i‡

$C_{24}H_{20}N_2O_2$, *M* 368.42, monoclinic, space group $P2_1/n$, $a = 12.132(4)$, $b = 8.462(3)$, $c = 18.708(6)$ Å, $\beta = 102.806(5)°$, $V = 1873(1)$ Å^3, $F(000) = 776$, $Z = 4$, $T = -105$ °C, μ (Mo-Kα) = 0.084 mm^{-1}, $D_{calcd} = 1.307$ g cm^{-3}, $2\theta_{max}$ 50° (CCD area detector, Mo-Kα radiation), GOF = 0.963, $wR(F^2) = 0.0861$ (all 3297 data), $R = 0.0345$ (2393 data with $I > 2\sigma I$).

‡ CCDC reference number 164080. See http://www.rsc.org/suppdata/p1/b1/b104060j/ for crystallographic files in .cif or other electronic format.

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