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A new synthetic route to highly enantioenriched 3-substituted-2,3-dihydro-1*H*-isoindol-1-ones

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Abstract—A concise and efficient synthesis of highly enantioenriched 3-alkyl and 3-aryl-2,3-dihydro-1*H*-isoindolinones is reported. The key step relies on the diastereoselective reduction of the *N*-acylhydrazonium salts generated by acidic treatment of hemiaminal precursors bearing the (*S*)-2-methoxymethylpyrrolidin-1-yl (SMP) auxiliary.

1. Introduction

2,3-Dihydro-1*H*-isoindol-1-ones (isoindolinones) also called phthalimidines represent a class of bicyclic lactams which have attracted much attention from the scientific community since they represent the core unit of a wide range of naturally occurring and/or bio-active substances.[1]

In particular, enantiopure compounds substituted at C-3 (Fig. 1), such as thiazoloisoindolone **1**[2] (non-nucleosidic HIV-reverse transcriptase inhibitor), pazinaclone **2**[3] (anxiolytic), 3-piperazinylethyl isoindolinone derivative **3**[4] (dopamine D4 receptor antagonist) as well as the architecturally more sophisticated staurosporine analog **4**[5] (protein kinase C inhibitor), have been extensively studied. Surprisingly, only a few efforts have been devoted to the asymmetric synthesis of chiral 3-substituted isoindolinones even though it has been well established that the absolute configuration of the stereogenic center at C-3 plays a crucial role for the biological activity.[4,5] These bicyclic lactams are accessible by different chemical processes which includes (i) an asymmetric intramolecular Heck reaction,[6] (ii) the carbonylation of a chiral *N*-pivaloyl-α-methylbenzylamine,[7] (iii) a tandem nucleophilic 1,2-addition/ring closure via SAMP or RAMP hydrazones[8] or (iv) the Lewis acid mediated diastereoselective aminal ring-opening with carbon or hydride nucleophiles of tricyclic γ-lactams.[9] Very recently, Royer et al. developed a new conceptual approach[10] to the synthesis of chiral 3-alkyl-isoindolinones based upon a diastereoselective metallation, α-aminoalkylation sequence. However, these elegant and complementary synthetic approaches suffer from several drawbacks mainly associated with the multistep removal of the chiral inductor.[9,10] Moreover, a few methodologies allow the connection of both aliphatic and aromatic groups at the benzylic position of the lactam ring.

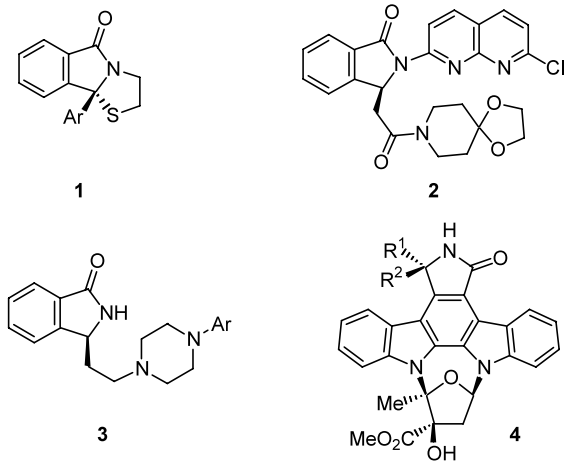

Figure 1. Examples of synthetic pharmacalogically active chiral 3-substituted isoidolinones.

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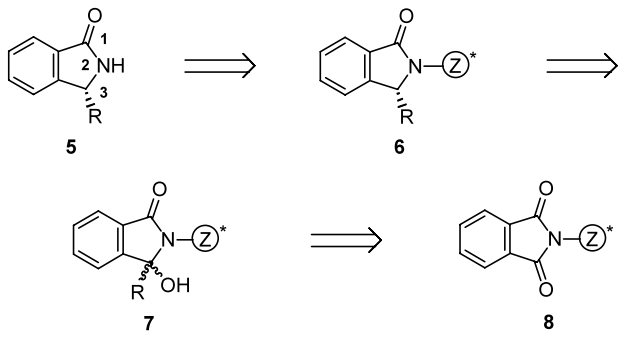
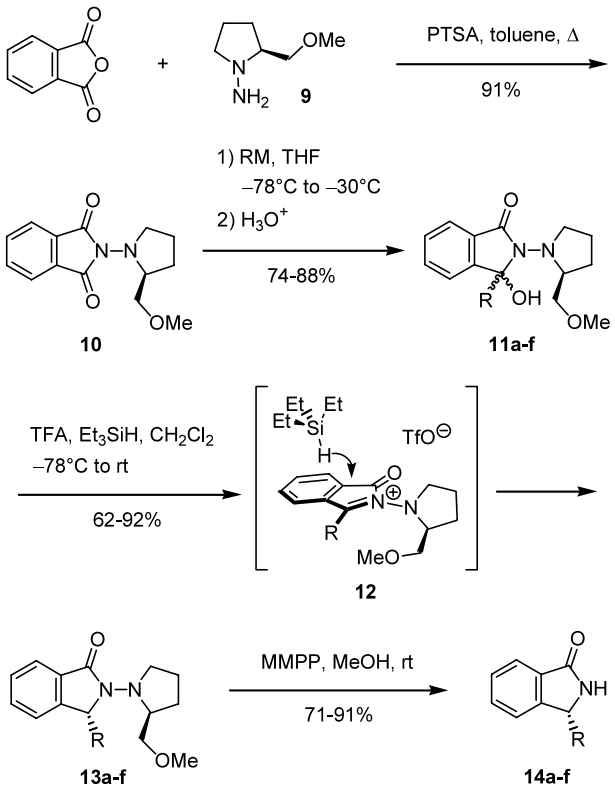


Scheme 1. Retrosynthetic analysis of chiral 3-substituted isoindolinones.

2. Results and discussion

Herein, we describe a new, concise and efficient synthetic route that offers an easy access to chiral 3-alkyl and 3-aryl-2,3-dihydro-1*H*-isoindol-1-ones **5** of high enantiomeric purity. This new procedure, which is depicted in the retrosynthetic Scheme 1, relies upon the diastereoselective reduction of alkylated or arylated hemiaminals **7**, which can be obtained by reacting imide **8** equipped with a chiral auxiliary connected to the nitogen atom with an appropriate organometallic reagent. Crucial for the success of our strategy was, therefore, to identify an easily incorporated stereocontrolling agent, which would be sufficiently robust to survive the projected addition reaction and would be also labile enough to be removed in the final step without racemization. This requirement and the recent results obtained in this area of hydrazide chemistry[8,11] prompted us to incorporate the (*S*)-2-methoxymethylpyrrolidin-1-yl (SMP)[12] group in our models (Z*).

This new synthetic route, depicted in Scheme 2, necessitated the preliminary elaboration of the chiral phthalhydrazide **10**, which was easily prepared by condensation between phthalic anhydride and (*S*)-1-amino-2-methoxymethylpyrrolidine (SAMP)[13] **9**. Imide **10** was then allowed to react with an array of organometallic reagents (Table 1) and this procedure delivered the hemiaminals **11a–f** with fairly good yields and as a mixture of diastereomers. The resulting 3-hydroxy isoindolinone derivatives **11a–f** were subsequently treated with trifluoroacetic acid and triethylsilane[14] which triggered the formation of the 3-alkyl and 3-aryl isoindolinones **13a–f** released from the hydroxy appendage. As can be seen from Table 1, the formation of compounds **13a–f** occurs with a high level of diastereoselection. Based upon a model proposed by Kibayashi et al.,[15] one can reasonably assume that high facial selectivity observed in the nucleophilic addition onto the prochiral C=N group of the *N*-acylhydrazonium ions **12** might be attributed to the pyramidal stability of the adjacent trivalent nitrogen, which thus constitutes a stereogenic center. The antiperiplanar approach of the hydride to the azomethine group therefore should occur preferentially from the sterically less hindered face of the energetically favored



Scheme 2. Asymmetric synthesis of 3-substituted isoindolinones **14a–f**.

Table 1. Isoindolinones **11a–f**, **13a–f**, **14a–f** prepared

Entry	RM	Compound	Yield (%)	Compound	Yield (%)[a]	De (%)[b]	Compound	Yield (%)[a]	Ee (%)[c]
1	MeMgCl	**11a**	88	**13a**	85	85 (>96)[d]	**14a**	77	>96
2	*tert*-BuMgCl	**11b**	85	**13b**	62	85 (>96)[d]	**14b**	71	>96
3	PhMgCl	**11c**	84	**13c**	91	>96	**14c**	85	>96
4	2-NaphtylLi	**11d**	78	**13d**	92	>96	**14d**	91	>96
5	2-MeOC$_6$H$_4$Li	**11e**	74	**13e**	88	>96	**14e**	87	>96
6	3-MeOC$_6$H$_4$Li	**11f**	77	**13f**	91	>96	**14f**	83	>96

[a] After purification.
[b] Determined by ^{1}H NMR spectroscopy.
[c] In correlation to the de value of the corresponding hydrazides **13a–f** assuming that the deprotecting step takes place without detectable racemization.[8]
[d] After recrystallisation from pentane.

conformers **12**, providing the isoindolinones **13a–f**. This hypothesis was corroborated by comparing ^{1}H and ^{13}C NMR spectra of 3-phenyl isoindolinone **13c** with its previously described epimer.[8] Finally, removal of the chiral auxiliary was readily achieved by oxidative cleavage of the hydrazide N–N bond. Treatment of the preliminarily obtained 3-alkyl and aryl isoindolinones **13a–f** with magnesium mono-peroxyphthalate (MMPP)[11a,b] afforded the targeted enantioenriched 3-substituted isoindolinones **14a–f**. At this stage we were intrigued by the specific rotation value of the (*R*)-3-methyl isoindolinone **14a** ($[\alpha]_D = +44.0$ in MeOH instead of the reported value[9c] $[\alpha]_D = -89.7$ in the same solvent). To clear up this point, we decided to synthesize the (*R*)-configured compound by the alternative synthesis developed by Stevenson.[7b] Once again the specific rotation value ($[\alpha]_D = +40.4$ in EtOH) matched those of our synthetic compound and of the (*S*)-configured epimer[7b] ($[\alpha]_D = -38.8$ in EtOH).

3. Conclusion

By means of a new synthetic approach involving the diastereoselective reduction of iminium salts bearing the (*S*)-2-methoxymethylpyrrolidin-1-yl (SMP) type auxiliary, we have disclosed a concise and efficient asymmetric synthesis of virtually enantiopure 3-alkyl and 3-aryl isoindolinones. Owing to the efficiency and simplicity of this new methodology, this protocol shows potential for further development and should undoubtedly be broadened to the synthesis of natural and biologically active compounds.

4. Experimental

4.1. General

Melting points were determined on a Reichert–Thermopan apparatus and are uncorrected. ^{1}H (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded on a Bruker AM 300 spectrometer and were referenced against internal tetramethylsilane; Coupling constants (*J*) are given in Hz and rounded to the nearest 0.1 Hz. IR absorption spectra were run on a Perkin–Elmer 881. Mass spectral analyses were performed on a Thermo–Finnigan mass spectrometer. Optical rotations were measured on a Perkin Elmer P 241 polarimeter. Elemental analyses were determined by the CNRS microanalysis center. TLC was performed with plates coated with Kiesselgel G (Merck). The silica gel used for flash column chromatography was Merck Kieselgel of 0.040–0.063 mm particle size. Dry glassware was obtained by oven-drying and assembly under Ar. Ar was used as the inert atmosphere and was passed through a drying tube to remove moisture. The glassware was equipped with rubber septa and reagent transfer was performed by syringe techniques. Tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl immediately before use. Methanol was distilled from magnesium turning. Methyl magnesium chloride (3.0 M in THF), *tert*-butyl magnesium chloride (1.0 M in THF) and phenyl magnesium chloride (2.0 M in THF) were purchased from Aldrich. Aryllithiums were freshly prepared by halogen–metal exchange reaction from the corresponding bromides.

4.2. Typical procedure for the preparation of the imide 10

To a suspension of phthalic anhydride (20 g, 0.135 mol) and hydrazine **9** (19.5 g, 0.15 mol) in toluene (300 ml) was added *p*-toluenesulfonic acid (200 mg) and the mixture was refluxed for 3 hours while removing the reaction water via a Dean–Stark apparatus. After warming to room temperature, the toluene was removed under reduced pressure and the crude product dissolved in CH_2Cl_2 (200 ml). The solution was then washed sequentially with a saturated aqueous solution of $NaHCO_3$ (25 ml), with water (50 ml) and brine (50 ml). After drying over Na_2SO_4 and removal of the solvent, the crude phthalimide was chromatographed on SiO_2 column using Et_2O/hexanes as eluent (60/40) and recrystallized from hexane to afford **10** as a pale yellow solid.

4.2.1. (2*S*)-2-(2-Methoxymethylpyrrolidin-1-yl)-phthalimide 10. Mp 61–62°C; $[\alpha]_D^{28} = +14.0$ (*c* 1.00, $CHCl_3$); ^{1}H NMR ($CDCl_3$): 1.55–1.66 (m, 1H), 1.82–2.10 (m, 3H), 3.11 (s, 3H, OMe), 3.24–3.30 (m, 1H), 3.32 (d, $J = 6.0$, OCH_2), 3.41 (q, $J = 8.1$, 1H), 3.74–3.82 (m, 1H), 7.62–7.68 (m, 2H, H_{arom}), 7.72–7.78 (m, 2H, H_{arom}); ^{13}C NMR ($CDCl_3$): C 167.3 (2CO), 130.2 (2C), CH 133.9 (2CH), 123.0 (2CH), 61.0, CH_2 75.9, 52.3, 26.8, 22.2, CH_3 58.9. MS (EI) *m*/*z* (%): 260 (M^+, 4), 215 (100), 130 (18). IR (KBr) *v* 1719, 1380, 1208, 1112, 884, 715. Anal. calcd for $C_{14}H_{16}N_2O_3$: C, 64.60; H, 6.20; N, 10.76. Found: C, 64.82; H, 6.36; N, 10.59.

4.3. Typical procedure for the preparation of hemiaminals 11a–f

A solution of organometallic reagent (8.5 mmol) was slowly added to a solution of phthalimide **10** (2.0 g, 7.7 mmol) in THF at −78°C and stirred under argon for 15 min. The mixture was then progressively warmed to −30°C, quenched with a saturated aqueous solution of NH_4Cl (10 ml) and the aqueous layer extracted with Et_2O (3×50 ml). The combined organic layers were washed with brine (20 ml), dried over Na_2SO_4 and concentrated under vacuum to furnish the crude hemiaminals **11a–f** which were used for the next step without further purification.

4.4. Typical procedure for the preparation of 3-substituted isoindolinones 13a–f

A solution of hemiaminal **11a–f** (5.9 mmol) in a mixture of trifluoroacetic acid (20 ml) and CH_2Cl_2 (10 ml) was cooled to −78°C and stirred under argon. The solution was then treated with triethylsilane (1.9 ml, 11.8 mmol), progressively warmed to room temperature and stirred until no starting material could be detected (TLC control). The mixture was then poured into ice–water, made alkaline by the addition of solid K_2CO_3

and extracted with Et_2O (3×50 ml). The extracts were combined, dried over $MgSO_4$, concentrated under vacuum and the residue purified by flash chromatography on silica gel using diethyl ether/hexane as eluent (60/40). Finally compounds **13a**,**b** were recrystallised from pentane.

4.4.1. (2*S*,3*R*)-2-(2-Methoxymethylpyrrolidin-1-yl)-3-methyl-2,3-dihydro-1*H*-isoindol-1-one 13a. Mp 96–97°C; $[\alpha]_D^{28} = -16.4$ (*c* 1.30, $CHCl_3$); ^1H NMR ($CDCl_3$): 1.50 (d, $J = 6.6$, 3H, CH_3), 1.70–2.05 (m, 3H), 2.07–2.22 (m, 1H), 3.13–3.24 (m, 1H), 3.29 (s, 3H, OMe), 3.31–3.37 (m, 2H), 3.48 (q, $J = 8.0$, 1H), 4.10–4.20 (m, 1H), 4.48 (q, $J = 6.6$, 1H, $CHCH_3$), 7.30–7.45 (m, 2H, H_{arom}), 7.46 (dt, $J = 1.4$, 7.4, 1H, H_{arom}), 7.70 (d, $J = 7.7$, 1H, H_{arom}); ^{13}C NMR ($CDCl_3$): C 167.0 (CO), 145.6, 131.7, CH 131.6, 127.9, 123.1, 122.0, 60.1, 57.3, CH_2 74.2, 51.6, 26.8, 22.5, CH_3 58.9. MS (EI) *m*/*z* (%): 260 (M^+, 4), 215 (100), 148 (60), 114 (46). IR (KBr) *v* 2905, 1692, 1370, 1106, 771, 706. Anal. calcd for $C_{15}H_{20}N_2O_2$: C, 69.20; H, 7.74; N, 10.76. Found: C, 69.35; H, 7.82; N, 10.59.

4.4.2. (2*S*,3*R*)-3-*tert*-Butyl-2-(2-methoxymethylpyrrolidin-1-yl)-2,3-dihydro-1*H*-isoindol-1-one 13b. Mp 88–89°C; $[\alpha]_D^{26} = +40.0$ (*c* 0.93, $CHCl_3$); ^1H NMR ($CDCl_3$): 1.07 (s, 9H), 1.58–1.92 (m, 3H), 2.05–2.40 (m, 1H), 2.81–3.43 (m, 7H), 3.68–3.92 (m, 1H), 4.25 (s, 1H), 7.35–7.45 (m, 3H, H_{arom}), 7.72–7.76 (m, 1H, H_{arom}); ^{13}C NMR ($CDCl_3$): C 169.7 (CO), 143.1, 132.8, 31.0, CH 130.5, 127.6, 124.6, 122.8, 69.6, 61.2, CH_2 74.0, 52.6, 27.9, 23.1, CH_3 58.5, 27.2. MS (EI) *m*/*z* (%): 302 (M^+, 6), 257 (100), 190 (55), 188 (45), 149 (57), 134 (40), 114 (31), 83 (32). IR (KBr) *v* 2918, 1683, 1470, 1386, 1107. Anal. calcd for $C_{18}H_{26}N_2O_2$: C, 71.49; H, 8.67; N, 9.26. Found: C, 71.28; H, 8.83; N, 8.97.

4.4.3. (2*S*,3*R*)-2-(2-Methoxymethylpyrrolidin-1-yl)-(3-phenyl-2,3-dihydro-1*H*-isoindol-1-one 13c. Mp 170–171°C; $[\alpha]_D^{28} = -49.5$ (*c* 1.05, $CHCl_3$); ^1H NMR ($CDCl_3$): 1.54–1.92 (m, 3H), 2.04–2.18 (m, 1H), 2.40 (dd, $J = 4.0$, 9.3, 1H), 2.54 (dd, $J = 7.4$, 9.3, 1H), 3.10 (s, 3H, OMe), 3.16 (dt, $J = 2.7$, 7.4, 1H), 3.27 (q, $J = 8.0$, 1H), 3.68–3.80 (m, 1H), 5.43 (s, 1H), 7.05–7.18 (m, 3H, H_{arom}), 7.27–7.34 (m, 3H, H_{arom}), 7.39–7.49 (m, 2H, H_{arom}), 7.83 (dd, $J = 1.9$, 7.6, 1H, H_{arom}); ^{13}C NMR ($CDCl_3$): C 167.3 (CO), 144.7, 138.2, 131.5, CH 132.0, 128.8, 128.5 (2CH), 128.4 (2CH), 128.2, 123.3, 123.1, 65.3, 61.3, CH_2 74.7, 52.2, 27.4, 23.0, CH_3 58.5. MS (EI) *m*/*z* (%): 322 (M^+, 4), 277 (100), 210 (36), 165 (22), 114 (31). IR (KBr) *v* 2873, 1686, 1368, 1208, 1115. Anal. calcd for $C_{20}H_{22}N_2O_2$: C, 74.51; H, 6.88; N, 8.69. Found: C, 74.35; H, 6.86; N, 8.71.

4.4.4. (2*S*,3*R*)-2-(2-Methoxymethylpyrrolidin-1-yl)-3-(naphthalen-2-yl)-2,3-dihydro-1*H*-isoindol-1-one 13d. Mp 108–109°C; $[\alpha]_D^{26} = -126.0$ (*c* 1.23, $CHCl_3$); ^1H NMR ($CDCl_3$): 1.58–1.88 (m, 3H), 2.05–2.18 (m, 1H), 2.43–2.56 (m, 2H), 2.70 (s, 3H, OMe), 3.19–3.31 (m, 2H), 3.75–3.83 (m, 1H), 5.65 (s, 1H), 7.02 (dd, $J = 1.7$, 8.5, 1H, H_{arom}), 7.09–7.12 (m, 1H, H_{arom}), 7.46–7.52 (m, 4H, H_{arom}), 7.74–7.91 (m, 5H, H_{arom}); ^{13}C NMR ($CDCl_3$): C 167.2 (CO), 144.4, 135.2, 133.0, 132.1, 131.2, CH 131.7, 128.5, 128.2, 128.0, 127.5, 127.3, 126.1 (2CH), 124.9, 123.1, 122.9, 65.2, 58.0, CH_2 74.4, 51.6, 27.1, 22.6, CH_3 61.2. MS (EI) *m*/*z* (%): 372 (M^+, 4), 327 (100), 260 (54), 259 (41), 132 (56). IR (KBr) *v* 2861, 1688, 1462, 1358, 1113. Anal. calcd for $C_{24}H_{24}N_2O_2$: C, 77.39; H, 6.49; N, 7.52. Found: C, 77.52; H, 6.34; N, 7.71.

4.4.5. (2*S*,3*S*)-2-(2-Methoxymethylpyrrolidin-1-yl)-3-(2-methoxyphenyl)-2,3-dihydro-1*H*-isoindol-1-one 13e. Oil; $[\alpha]_D^{25} = -93.9$ (*c* 1.14, $CHCl_3$); ^1H NMR ($CDCl_3$): 1.50–1.85 (m, 3H), 1.95–2.20 (m, 1H), 2.36–2.81 (m, 2H), 2.95 (s, 3H, OMe), 3.00–3.40 (m, 2H), 3.60–3.80 (m, 1H), 3.88 (s, 3H, OMe), 6.21 (s, 1H), 6.60–7.10 (m, 3H, H_{arom}), 7.15–7.45 (m, 4H, H_{arom}), 7.77 (dd, $J = 2.0$, 7.6, 1H, H_{arom}); ^{13}C NMR ($CDCl_3$): C 167.0 (CO), 157.6, 144.7, 130.9, 125.9, CH 131.1, 128.6, 127.1, 122.4, 122.2, 120.1, 110.8, 60.3, 57.7, CH_2 74.4, 51.1, 26.8, 22.1, CH_3 56.1, 55.3. MS (EI) *m*/*z* (%): 352 (M^+, 6), 307 (100), 240 (58), 239 (31), 132 (28). IR ($CHCl_3$) *v* 2865, 1684, 1490, 1465, 1106. Anal. calcd for $C_{21}H_{24}N_2O_3$: C, 71.57; H, 6.86; N, 7.95. Found: C, 71.73; H, 6.51; N, 7.70.

4.4.6. (2*S*,3*R*)-2-(2-Methoxymethylpyrrolidin-1-yl)-3-(3-methoxyphenyl)-2,3-dihydro-1*H*-isoindol-1-one 13f. Mp 82–83°C; $[\alpha]_D^{26} = -75.2$ (*c* 1.05, $CHCl_3$); ^1H NMR ($CDCl_3$): 1.52–1.90 (m, 3H), 2.00–2.18 (m, 1H), 2.41–2.55 (m, 1H), 2.57–2.70 (m, 1H), 2.92 (s, 3H, OMe), 3.07–3.32 (m, 2H), 3.62–3.78 (m, 4H), 5.40 (s, 1H), 6.64 (s, 1H, H_{arom}), 6.74 (d, $J = 7.6$, 1H, H_{arom}), 6.82 (dd, $J = 2.4$, 8.3, 1H, H_{arom}), 7.02–7.10 (m, 1H, H_{arom}), 7.20 (t, $J = 7.9$, 1H, H_{arom}), 7.32–7.47 (m, 2H, H_{arom}), 7.79 (dd, $J = 1.7$, 7.6, 1H, H_{arom}); ^{13}C NMR ($CDCl_3$): C 167.3 (CO), 159.6, 144.5, 139.6, 131.2, CH 131.9, 129.4, 128.1, 123.2, 122.9, 120.9, 114.1, 113.6, 65.0, 61.3, CH_2 74.8, 51.7, 27.4, 22.8, CH_3 58.4, 55.0. MS (EI) *m*/*z* (%): 352 (M^+, 4), 307 (100), 240 (62), 239 (34), 132 (25). IR (KBr) *v* 2923, 1682, 1462, 1370, 1274, 1109, 1034. Anal. calcd for $C_{21}H_{24}N_2O_3$: C, 71.57; H, 6.86; N, 7.95. Found: C, 71.80; H, 7.02; N, 7.72.

4.5. Typical procedure for the preparation of isoindolinones 14a–f

MMPP (1.9 g, 3.75 mmol) was added to a solution of hydrazide **13a**–**f** (1.5 mmol) in methanol (20 ml). Stirring at room temperature continued until no starting material remained (TLC monitoring). The reaction mixture was then diluted with Et_2O (100 ml) and treated with a saturated aqueous $NaHCO_3$ solution (65 ml). The aqueous layer was extracted with CH_2Cl_2 (2×50 ml) after phase separation. The combined organic extracts were dried over Na_2SO_4 and the solvents removed under vacuum to furnish the crude isoindolinones **14a**–**f** which were finally recrystallized from hexane–toluene for **14a**,**b** and from EtOH for **14c**–**f**.

4.5.1. (3*R*)-3-Methyl-2,3-dihydro-1*H*-isoindol-1-one 14a. Mp 118–119°C, lit.[9c] 129–133°C; $[\alpha]_D^{25} = +44.0$ (*c* 0.56, MeOH), lit.[9c] $[\alpha]_D^{25} = -89.7$ (*c* 1.7, MeOH); ^1H NMR ($CDCl_3$): 1.52 (d, $J = 6.8$, 3H), 4.72 (q, $J = 6.8$, 1H), 7.38–7.50 (m, 2H, H_{arom}), 7.51–7.62 (m, 1H, H_{arom}), 7.87 (d, $J = 7.3$, 1H, H_{arom}), 8.93 (brs, 1H, NH); ^{13}C

NMR ($CDCl_3$): C 171.5 (CO), 149.1, 131.8, CH 131.7, 127.9, 123.5, 122.2, 52.8, CH_3 20.2. MS (EI) m/z (%): 147 (M^+, 78), 132 (100), 104 (24), 77 (22). IR (KBr) ν 3198, 1706, 1419, 1357, 1311, 1202, 1140. Anal. calcd for C_9H_9NO: C, 73.45; H, 6.16; N, 9.52. Found: C, 73.57; H, 6.10; N, 9.45.

4.5.2. (3*R*)-3-*tert*-Butyl-2,3-dihydro-1*H*-isoindol-1-one 14b. Mp 178–179°C; $[\alpha]_D^{25}=+25.0$ (c 0.76, MeOH); ^1H NMR ($CDCl_3$): 1.04 (s, 9H), 4.35 (s, 1H), 7.45–7.54 (m, 3H, H_{arom}), 7.87 (d, $J=7.1$, 1H, H_{arom}), 8.58 (brs, 1H, NH); ^{13}C NMR ($CDCl_3$): C 171.7 (CO), 145.8, 133.1, 35.2, CH 131.1, 127.9, 124.1, 123.6, 66.5, CH_3 26.4. MS (EI) m/z (%): 189 (M^+, 2), 133 (100), 132 (24), 77 (19). IR (KBr) ν 3217, 2961, 1702, 1473, 1362, 1211, 1141. Anal. calcd for $C_{12}H_{15}NO$: C, 76.16; H, 7.99; N, 7.40. Found: C, 76.22; H, 8.12; N, 7.69.

4.5.3. (3*R*)-3-Phenyl-2,3-dihydro-1*H*-isoindol-1-one 14c. Mp 242–243°C; $[\alpha]_D^{25}=-193.3$ (c 0.73, DMSO); ^1H NMR (DMSO-d_6): 5.73 (s, 1H), 7.24–7.39 (m, 6H, H_{arom}), 7.43–7.55 (m, 2H, H_{arom}), 7.71 (d, $J=7.6$, 1H, H_{arom}), 9.08 (brs, 1H, NH); ^{13}C NMR (DMSO-d_6): C 169.9 (CO), 148.3, 139.8, 131.6, CH 132.0, 129.0 (2CH), 128.3, 128.1, 126.8 (2CH), 123.7, 123.1, 59.7. MS (EI) m/z (%): 209 (M^+, 6), 207 (100). IR (KBr) ν 3187, 1693, 1643. Anal. calcd for $C_{14}H_{11}NO$: C, 80.36; H, 5.30; N, 6.69. Found: C, 80.18; H, 5.36; N, 6.80.

4.5.4. (3*R*)-3-(Naphthalen-2-yl)-2,3-dihydro-1*H*-isoindol-1-one 14d. Mp 224–225°C; $[\alpha]_D^{25}=-201.0$ (c 0.71, DMSO); ^1H NMR (DMSO-d_6): 5.90 (s, 1H), 7.22–7.34 (m, 2H, H_{arom}), 7.42–7.54 (m, 4H, H_{arom}), 7.72–7.81 (m, 1H, H_{arom}), 7.82–7.98 (m, 4H, H_{arom}), 9.23 (s, 1H, NH); ^{13}C NMR (DMSO-d_6): C 170.0 (CO), 148.3, 137.3, 133.1, 132.9, 131.7, CH 132.1, 128.8, 128.4, 127.9, 127.8, 126.7, 126.4, 125.9, 124.5, 123.8, 123.2, 59.9. MS (EI) m/z (%): 259 (M^+, 4), 257 (100). IR (KBr) ν 3205, 1689, 1650, 1206. Anal. calcd for $C_{18}H_{13}NO$: C, 83.38; H, 5.05; N, 5.40. Found: C, 83.25; H, 5.12; N, 5.57.

4.5.5. (3*S*)-3-(2-Methoxyphenyl)-2,3-dihydro-1*H*-isoindol-1-one 14e. Mp 170–171°C; $[\alpha]_D^{25}=-294.5$ (c 0.84, DMSO); ^1H NMR (DMSO-d_6): 3.89 (s, 3H, OMe), 6.04 (s, 1H), 6.76–7.18 (m, 3H, H_{arom}), 7.21–7.60 (m, 4H, H_{arom}), 7.70 (d, $J=7.7$, 1H, H_{arom}), 8.92 (brs, 1H, NH); ^{13}C NMR (DMSO-d_6): C 170.1 (CO), 157.0, 148.4, 132.0, 127.5, CH 131.8, 129.2, 128.2, 126.1, 123.5, 123.1, 120.8, 111.6, 55.9, CH_3 54.2. MS (EI) m/z (%): 239 (M^+, 6), 237 (100). IR (KBr) ν 3174, 1692, 1659, 1249. Anal. calcd for $C_{15}H_{13}NO_2$: C, 75.30; H, 5.48; N, 5.85. Found: C, 75.45; H, 5.52; N, 5.90.

4.5.6. (3*R*)-3-(3-Methoxyphenyl)-2,3-dihydro-1*H*-isoindol-1-one 14f. Mp 183–184°C; $[\alpha]_D^{25}=-216.4$ (c 1.03, DMSO); ^1H NMR (DMSO-d_6): 3.72 (s, 3H, OMe), 5.70 (s, 1H), 6.80–6.92 (m, 3H, H_{arom}), 7.20–7.34 (m, 2H, H_{arom}), 7.41–7.56 (m, 2H, H_{arom}), 7.71 (d, $J=7.7$, 1H, H_{arom}), 9.09 (brs, 1H, NH); ^{13}C NMR (DMSO-d_6): C 169.7 (CO), 159.5, 148.0, 141.2, 131.3, CH 131.8, 129.9, 128.1, 123.5, 122.9, 118.4, 113.1, 112.3, 59.4, CH_3 55.1. MS (EI) m/z (%): 239 (M^+, 5), 237 (100). IR (KBr) ν 3215, 1697, 1658, 1285, 1048. Anal. calcd for $C_{15}H_{13}NO_2$: C, 75.30; H, 5.48; N, 5.85. Found: C, 75.21; H, 5.83; N, 5.98.

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