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A conceptually new approach to the asymmetric synthesis of 3-aryl and alkyl poly-substituted isoindolinones

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ABSTRACT

A conceptually new and efficient asymmetric synthesis of C-3 arylated or alkylated poly-substituted isoindolinones is reported. The key step is the diastereoselective reduction of an *N*-acylhydrazonium species derived from the previously assembled corresponding hydroxyl derivative bearing the (*S*)-2-methoxymethylpyrrolidine (SMP) auxiliary.

1. Introduction

Chiral non-racemic three-substituted isoindolinones have recently attracted much attention from the scientific community since they constitute the main core of an increasing number of biologically active substances. Typical examples are the synthetic products thiazoloisoindolone **1**[1] (non-nucleosidic HIV-reverse transcriptase inhibitor), pazinaclone **2**[2] (anxiolytic drug candidate), PD 172938 **3**[3] (dopamine D_4 receptor antagonist) as well as pyrroloisoindolinone **4**[4] (Cyclin Dependent Kinase 1,2,4,6 inhibitor) (Fig. 1).

Paradoxically, despite the great progress made in the area of asymmetric synthesis over the last decade, only a few flexible and general methods are available for the synthesis of highly enantioenriched chiral poly-substituted isoindolinones alkylated or arylated at C-3 even though it has been well established that the absolute configuration of this stereogenic center plays a crucial role for the biological activity.[3] Among these methods, the most straightforward ones are those where the alkyl or aryl groups at the C-3 position are introduced directly onto a pre-constructed model equipped with a chiral auxiliary (Scheme 1). This has been achieved via a diastereoselective nucleophilic addition[5] (path a) or hydride reduction[6] (path b) of an *N*-acyliminium species. These chiral bicyclic lactams can also be accessed via an α-amino alkylation reaction involving a three-metallated isoindolinone and various electrophiles[7] (path c). An alternative synthetic approach depicted on Scheme 1 is based upon the lactam ring construction with concomitant creation of the stereogenic center at the C-3 position. This has been achieved by a two component reaction involving an *ortho*-lithiated dialkylbenzamide with chiral hydrazones[8] (path d) or by a diastereoselective imine addition–cyclization sequence[9,10] (path e, f). Enantioenriched isoindolinones have also been assembled by Heck[11] or radical induced cyclization[12] and an elegant method based upon an anionic cyclization and re-aromatization of α-aminocarbanionic species derived from *N*-benzylbenzamide derivatives and a chiral base has been also described.[13]

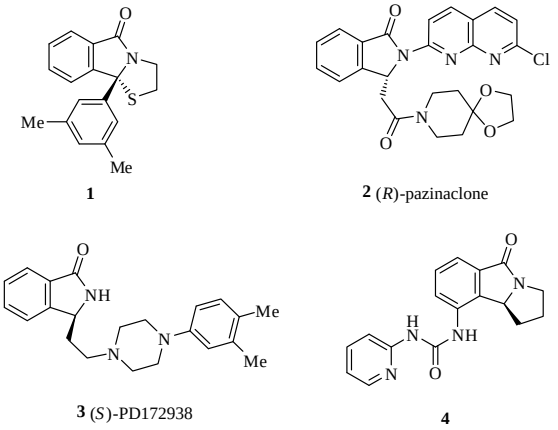

Figure 1.

However, these elegant and complementary synthetic approaches suffer from several drawbacks, mainly from the restriction in the choice of substituents at some specific sites on the basic benzene nucleus and from difficulties associated with the connection of aromatic and aliphatic groups, as well at the benzylic position of the lactam ring, in a stereospecific manner. Accordingly, the development of new efficient methods for the asymmetric synthesis of these as diversely substituted isoindolinones still constitutes an area of interest and alternative methods are currently the object of synthetic endeavor.

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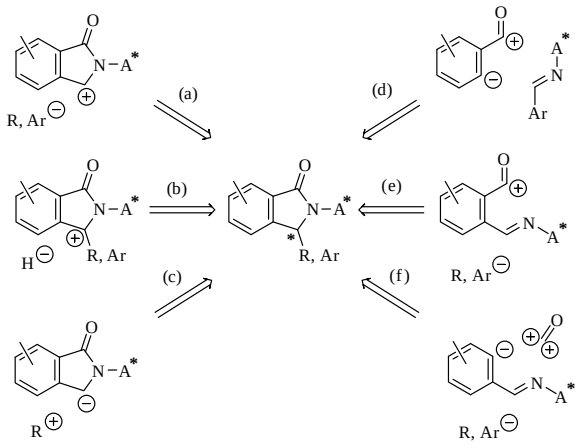
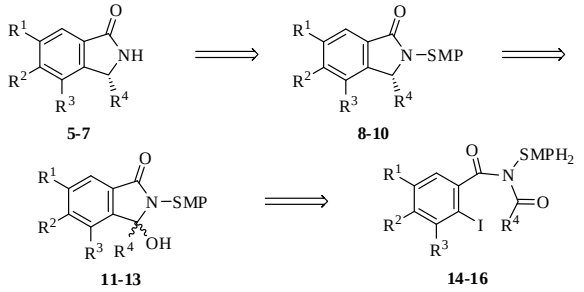


Scheme 1.

2. Results and discussion

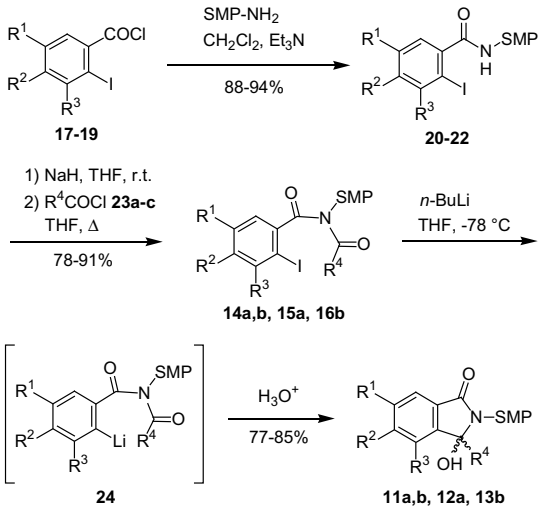
Herein, we report on an alternative and conceptually new synthetic route that offers easy access to an array of optically active three-substituted isoindolinones **5–7** of high enantiopurity. This new procedure, which is depicted in the retrosynthetic Scheme 2, relies upon the construction of the isoindolinone ring system via a Parham type anionic cyclization[14] reaction involving imides **14–16**. The diastereoselective reduction of hemiaminals **11–13** equipped with a (*S*)-2-methoxymethylpyrrolidine (SMP)[15] chiral auxiliary would give access to the adducts **8–10**. Finally, removal of the SMP group from these adducts would deliver the targeted enantioenriched poly-substituted isoindolinones **5–7**.



Scheme 2.

The first facet of the synthesis was preliminary elaboration of the chiral hydrazides **14–16**, which were easily prepared by coupling the *ortho*-halogenobenzoyl chlorides **17–19** with (*S*)-1-amino-2-methoxymethylpyrrolidine (SAMP)[16] (Scheme 3). Hydrazides **20–22** were then smoothly deprotonated and allowed to react with an array of acyl chlorides **23a–c** (Table 1) to give the imides **14–16** candidates for the planned anionic cyclization process. Exposure of imides **14–16** to *n*-BuLi at −78 °C ensured the mandatory halogen/lithium interconversion giving rise to the aryllithiated species **24**, led to complete consumption of the starting material, and to the isolation of the targeted hemiaminals **11–13** in fairly good yields as a mixture of diastereomers.

It is worth noting that this approach was confined to the assembly of hemiaminals equipped with pendant aromatic units at the benzylic position of the lactam nucleus (R^4 = Ar). This could be secured owing to the absence of deprotonation sites, for example, R^4 = alkyl that can compete unfavorably with the required halogen–metal interconversion process. To alleviate this problem, an alternative and complementary synthetic route to hemiaminals



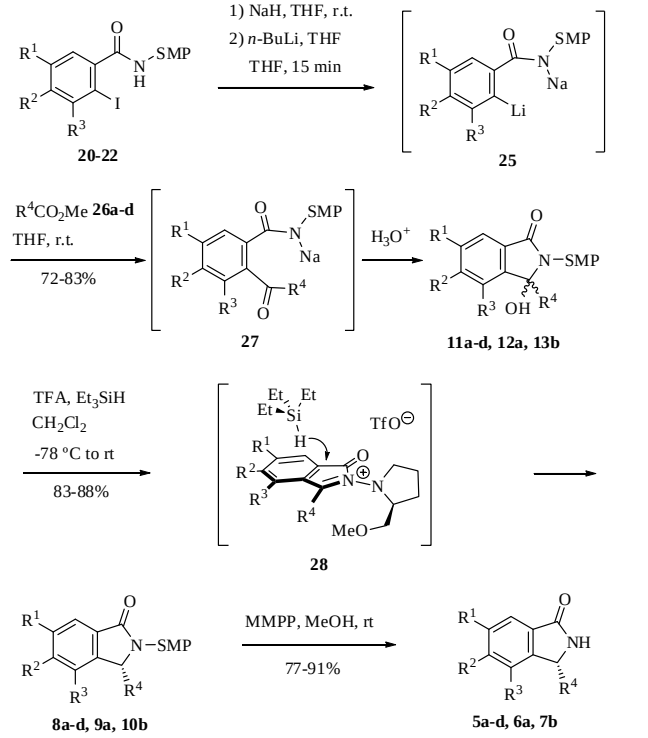
Scheme 3.

11–13 was investigated and is shown in Scheme 4. This alternative pathway is based upon the capture of a bis-metallated species **25**, easily obtained from the chiral hydrazides **20–22**, with an array of aliphatic or aromatic carboxylic acid esters **26a–d** (Table 2). Inter-

Table 1
Compounds **11–16** prepared

R^1	R^2	R^3	R^4	**14–16**	Yield[a] (%)	**11–13**	Yield[a] (%)
H	H	H	Ph	**14a**	85	**11a**	77
H	H	H	4-MeOC$_6$H$_4$	**14b**	91	**11b**	85
OMe	OMe	OMe	Ph	**15a**	78	**12a**	79
OCH$_2$O		H	4-MeOC$_6$H$_4$	**16b**	87	**13b**	84

[a] After purification.



Scheme 4.

Table 2
Compounds **11**–**13** prepared

R^1	R^2	R^3	R^4	**11**–**13**	Yield[a] (%)
H	H	H	Ph	**11a**	81
H	H	H	4-$MeOC_6H_4$	**11b**	78
H	H	H	3,4,5-$MeOC_6H_2$	**11c**	76
H	H	H	Me	**11d**	80
OMe	OMe	OMe	Ph	**12a**	83
OCH_2O		H	4-$MeOC_6H_4$	**13b**	72

[a] After purification.

estingly, these techniques give rise to poly and unsymmetrically substituted models and offered, at least, complementary and at best, significant advantages over classical methodology.[6c]

With the alkylated and arylated hemiaminals in hand, the formation of the targeted virtually enantiopure C-3-substituted isoindolinones was investigated. For this purpose, the resulting 3-hydroxy isoindolinone derivatives **11**–**13** were subsequently treated with trifluoroacetic acid and triethylsilane[17] in sequence; this operation triggered the formation of the 3-alkyl and 3-aryl isoindolinones **8**–**10** released from the hydroxy appendage (Scheme 4) with a high level of diastereoselection.[6c,18] Removal of the chiral auxiliary without racemization was readily achieved by oxidative cleavage of the nitrogen–nitrogen bond promoted by magnesium mono-peroxyphthalate hexahydrate (MMPP).[19] This deamination method afforded the targeted enantioenriched poly-substituted 3-alkyl and 3-aryl isoindolinones **5**–**7** released from the stereocontrolling agent with satisfactory yields (Table 3).

3. Conclusion

In conclusion, we have completed a conceptually new approach to the asymmetric synthesis of poly-substituted isoindolinones that are both alkylated and arylated. This new route hinges upon the initial construction of the isoindolinone ring system equipped with an hemiaminal moiety and subsequent diastereoselective reduction of chiral iminium salts bearing the (*S*)-2-methoxymethylpyrrolidine (SMP) auxiliary. We also believe that this work demonstrates a general methodology widely adaptable for the preparation of natural and/or biologically active compounds.

4. Experimental

4.1. General

Melting points were determined on a Reichert-Thermopan apparatus and are uncorrected. ^1H (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 Hertz and rounded to the nearest 0.1 Hz. Elemental analyses were determined by the CNRS microanalysis center. TLC was performed with plates coated with Kieselgel 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 argon. Argon 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. 2-Iodobenzoyl chlorides **17**, **18**, **19** were prepared following a literature method.[20]

4.2. Typical procedure for the preparation of the hydrazides 20–22

A solution of 2-iodoaroyl chloride **17**–**19** (20 mmol) in dry CH_2Cl_2 (10 mL) was added dropwise under argon to a cooled (0 °C) solution of (*S*)-aminomethylprolinol (SAMP) (2.9 g, 22 mmol) and Et_3N (4.0 g, 40 mmol) in CH_2Cl_2 (100 ml). Stirring was maintained for 3 h at room temperature. The reaction mixture was then washed with water (20 mL) and dried over $MgSO_4$. The solvent was removed under vacuum and the residue was purified by recrystallization from hexane–toluene to afford the hydrazides **20**–**22**.

4.2.1. 2-Iodo-*N*-((*S*)-2-(2-methoxymethylpyrrolidin-1-yl)benzamide 20

Yield: 79%; mp 124–125 °C; $[\alpha]_D^{21} = -39.1$ (*c* 0.79, $CHCl_3$); ^1H NMR ($CDCl_3$): 1.56–1.72 (m, 1H), 1.76–1.91 (m, 2H), 1.93–2.08 (m, 1H), 2.95 (q, *J* = 8.5, 1H), 3.12–3.24 (m, 1H), 3.32 (s, 3H, OMe), 3.34–3.48 (m, 2H), 3.58 (dd, *J* = 5.1, 9.5, 1H), 7.00 (br s, 1H, NH), 7.02–7.09 (m, 1H, H_{arom}), 7.29–7.34 (m, 2H, H_{arom}), 7.80 (d, *J* = 7.9, 1H, H_{arom}); ^{13}C NMR ($CDCl_3$): *C* 168.0 (CO), 141.1, 92.8, *CH* 139.6, 131.1, 128.3, 128.0, 64.1, CH_2 75.1, 55.0, 26.5, 21.3, CH_3 59.2. Anal. Calcd for $C_{13}H_{17}IN_2O_2$: C, 43.35; H, 4.76; N, 7.78. Found: C, 43.52; H, 4.49; N, 7.61.

4.2.2. 2-Iodo-3,4,5-trimethoxy-*N*-((*S*)-2-(2-methoxymethylpyrrolidin-1-yl)benzamide 21

Yield: 82%; mp 145–146 °C; $[\alpha]_D^{21} = -44.3$ (*c* 0.95, $CHCl_3$); ^1H NMR ($CDCl_3$): 1.61–1.77 (m, 1H), 1.82–1.96 (m, 2H), 1.97–2.06 (m, 1H), 2.98 (q, *J* = 8.5, 1H), 3.14–3.26 (m, 1H), 3.36 (s, 3H, OMe), 3.39–3.52 (m, 2H), 3.64 (dd, *J* = 5.1, 9.5, 1H), 3.86 (s, 9H, 3 × OMe), 6.80 (br s, 2H, NH+H_{arom}); ^{13}C NMR ($CDCl_3$): *C* 167.7 (CO), 154.0, 153.4, 143.3, 136.7, 81.4, *CH* 108.4, 64.3, CH_2 75.3, 55.2, 26.6, 21.4, CH_3 61.1, 60.9, 59.3, 56.3. Anal. Calcd for $C_{16}H_{23}IN_2O_5$: C, 42.68; H, 5.15; N, 6.22. Found: C, 42.53; H, 5.12; N, 6.11.

Table 3
Isoindolinones **5**–**13** prepared

R^1	R^2	R^3	R^4	**8**–**10**	Yield[a] (%)	de[b] (%)	**5**–**7**	Yield[a] (%)	ee[d] (%)
H	H	H	Ph	**8a**	91	>96	**5a**	85	>96
H	H	H	4-$MeOC_6H_4$	**8b**	88	>96	**5b**	91	>96
H	H	H	3,4,5-$MeOC_6H_2$	**8c**	83	>96	**5c**	88	>96
H	H	H	Me	**8d**	85	84 (>96)[c]	**5d**	77	>96
OMe	OMe	OMe	Ph	**9a**	86	>96	**6a**	86	>96
OCH_2O		H	4-$MeOC_6H_4$	**10b**	81	>96	**7b**	84	>96

[a] After purification.
[b] Determined by ^1H NMR spectroscopy.
[c] After recrystallization from pentane.
[d] In correlation to the value of the corresponding hydrazide **8**–**10** assuming that the deprotection step takes place without detectable racemization.[6c,8]

4.2.3. 6-Iodo-1,3-benzodioxole-5-carboxylic acid ((*S*)-2-methoxymethylpyrrolidin-1-yl)amide 22

Yield: 78%; mp 176–177 °C; $[\alpha]_D^{21} = -35.8$ (*c* 1.47, $CHCl_3$); ^1H NMR ($CDCl_3$): 1.41–1.62 (m, 1H), 1.72–2.33 (m, 3H), 2.97 (q, *J* = 8.7, 1H), 3.10–3.22 (m, 1H), 3.36 (s, 3H, OMe), 3.32–3.48 (m, 2H), 3.61 (dd, *J* = 5.3, 9.5, 1H), 6.00 (s, 2H), 6.87 (s, 2H, NH+H_{arom}), 7.20 (s, 1H, H_{arom}); ^{13}C NMR ($CDCl_3$): *C* 167.6 (CO), 149.5, 148.2, 134.5, 81.7, *CH* 119.1, 108.9, 64.2, CH_2 102.1, 75.2, 55.1, 26.5, 21.4, CH_3 59.3. Anal. Calcd for $C_{14}H_{17}IN_2O_4$: C, 41.60; H, 4.24; N, 6.93. Found: C, 41.43; H, 4.31; N, 6.98.

4.3. Typical procedure for the preparation of hydrazimides 14–16

A suspension of hydrazide **20**–**22** (10 mmol) and NaH 60% (460 mg, 12 mmol) in THF (25 mL) was stirred at room temperature for 3 h and then allowed to react with a solution of acyl chloride **23a**–**d** (12 mmol) in THF (5 mL). The mixture was refluxed for 6 h and then warmed to room temperature. Water (10 mL) was added and the organic layer was separated. The aqueous solution was extracted with CH_2Cl_2 (2 × 50 mL) and the combined organic layers dried over $MgSO_4$. Evaporation of the solvent furnished the crude imides **14**–**16**, which were purified by flash column chromatography using CH_2Cl_2–Et_2O–hexane (2:1:1) as an eluent.

4.3.1. *N*-(2-Iodobenzoyl)-*N*-((*S*)-2-methoxymethyl-pyrrolidin-1-yl)benzamide 14a

Oil; $[\alpha]_D^{21} = -88.2$ (*c* 0.74, $CHCl_3$); ^1H NMR ($CDCl_3$): 1.28–1.49 (m, 1H), 1.60–1.78 (m, 1H), 1.90–2.22 (m, 2H), 2.80–3.00 (m, 1H), 3.09 (s, 3H, OMe), 3.15–3.48 (m, 2H), 3.51–3.72 (m, 1H), 3.80–4.08 (m, 1H), 6.97–7.12 (m, 1H, H_{arom}), 7.25–7.47 (m, 5H, H_{arom}), 7.61–7.83 (m, 3H, H_{arom}); ^{13}C NMR ($CDCl_3$): *C* 173.7 (CO), 171.2 (CO), 142.6, 134.9, 91.5, *CH* 139.3, 131.5, 130.6, 129.0 (2 × CH), 127.9, 128.7, 127.6 (2 × CH), 61.7, CH_2 76.3, 51.8, 27.8, 23.6, CH_3 58.5. Anal. Calcd for $C_{20}H_{21}IN_2O_3$: C, 51.74; H, 4.56; N, 6.03. Found: C, 51.80; H, 4.44; N, 6.21.

4.3.2. *N*-(2-Iodobenzoyl)-4-methoxy-*N*-((*S*)-2-methoxymethyl-pyrrolidin-1-yl)benzamide 14b

Oil; $[\alpha]_D^{21} = -72.3$ (*c* 1.77, $CHCl_3$); ^1H NMR ($CDCl_3$): 1.35–1.48 (m, 1H), 1.64–1.85 (m, 1H), 1.96–2.26 (m, 2H), 2.89–3.10 (m, 2H), 3.12 (s, 3H, OMe), 3.33–3.48 (m, 1H), 3.52–3.72 (m, 1H), 3.80 (s, 3H, OMe), 3.89–4.04 (m, 1H), 6.87 (d, *J* = 11.0, 1H, H_{arom}), 6.96–7.04 (m, 1H, H_{arom}), 7.23–7.38 (m, 2H, H_{arom}), 7.68–7.83 (m, 3H, H_{arom}); ^{13}C NMR ($CDCl_3$): *C* 172.9 (CO), 171.4 (CO), 162.5, 142.6, 126.5, 91.4, *CH* 139.4, 131.7 (2 × CH), 130.6, 128.0, 113.0 (2 × CH), 61.9, CH_2 76.1, 51.7, 27.8, 23.5, CH_3 58.6, 55.4. Anal. Calcd for $C_{21}H_{23}IN_2O_4$: C, 51.02; H, 4.69; N, 5.67. Found: C, 51.23; H, 4.72; N, 5.60.

4.3.3. *N*-(2-Iodo-3,4,5-trimethoxybenzoyl)-*N*-((*S*)-2-methoxymethylpyrrolidin-1-yl)benzamide 15a

Oil; $[\alpha]_D^{21} = -81.1$ (*c* 1.58, $CHCl_3$); ^1H NMR ($CDCl_3$): 1.31–1.52 (m, 1H), 1.63–1.76 (m, 1H), 1.97–2.15 (m, 2H), 2.81–3.28 (m, 2H), 3.13 (s, 3H, OMe), 3.32–3.51 (m, 1H), 3.56–4.12 (m, 2H), 3.79 (s, 3H, OMe), 3.83 (s, 6H, 2 × OMe), 6.77 (s, 1H, H_{arom}), 7.22–7.43 (m, 5H, H_{arom}); ^{13}C NMR ($CDCl_3$): *C* 173.7 (CO), 171.0 (CO), 153.9, 153.0, 142.9, 132.2, 130.1, 81.5, *CH* 131.4, 130.1 (2 × CH), 128.5 (2 × CH), 108.2, 61.8, CH_2 76.5, 51.8, 27.7, 23.5, CH_3 61.0, 60.8, 58.6, 56.2. Anal. Calcd for $C_{23}H_{27}IN_2O_6$: C, 49.83; H, 4.91; N, 5.05. Found: C, 50.03; H, 5.12; N, 4.88.

4.3.4. *N*-(6-Iodo-1,3-benzodioxole-5-carbonyl)-4-methoxy-*N*-((*S*)-2-methoxymethylpyrrolidin-1-yl)benzamide 16b

Oil; $[\alpha]_D^{21} = -64.7$ (*c* 1.98, $CHCl_3$); ^1H NMR ($CDCl_3$): 1.33–1.52 (m, 1H), 1.63–1.84 (m, 1H), 1.92–2.17 (m, 2H), 2.91–3.11 (m, 2H), 3.09 (s, 3H, OMe), 3.31–3.48 (m, 1H), 3.50–3.71 (m, 1H), 3.81 (s, 3H, OMe), 3.86–4.01 (m, 1H), 5.92 (s, 2H, OCH_2O), 6.83–6.94 (m, 3H, H_{arom}), 7.02–7.21 (m, 1H, H_{arom}), 7.76 (d, *J* = 8.6, 1H, H_{arom}); ^{13}C NMR ($CDCl_3$): *C* 172.9 (CO), 171.0 (CO), 162.5, 149.2, 148.0, 135.9, 126.5, 80.8, *CH* 131.7 (2 × CH), 118.8, 113.0 (2 × CH), 108.7, 61.9, CH_2 102.1, 76.2, 51.6, 27.7, 23.4, CH_3 58.5, 55.4. Anal. Calcd for $C_{22}H_{23}IN_2O_6$: C, 49.08; H, 4.31; N, 5.20. Found: C, 49.12; H, 4.28; N, 5.17.

4.4. Typical procedure for the preparation of the hemiaminals 11, 12, 13

Method A: A solution of imide **14**–**16** (5 mmol) in dry THF (100 mL) was cooled to −78 °C under Ar, and *n*-BuLi (3.5 mL, 1.6 M in hexanes, 5.6 mmol) was added by syringe. The mixture was then progressively warmed to −30 °C, quenched with a saturated aqueous solution of NH_4Cl (10 mL), and the aqueous layer was 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 **11**–**13** which were purified by flash chromatography using CH_2Cl_2–Et_2O–hexane (5:3:2) as eluent.

Method B: A suspension of hydrazide **20**–**22** (10 mmol) and NaH 60% (460 mg, 12 mmol) in THF (25 mL) was stirred at room temperature for 3 h and then cooled to −78 °C. Next, *n*-BuLi (7.5 mL, 1.6 M in hexanes, 12 mmol) was added by syringe and the mixture was then progressively warmed to −30 °C and allowed to react with a solution of carboxylic acid esters **26a**–**d** (12 mmol) in THF (5 mL). A saturated aqueous solution of NH_4Cl (10 mL) was added and the aqueous layer was 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 **11**–**13**, which were purified by flash chromatography using CH_2Cl_2–Et_2O–hexane (5:3:2) as eluent.

4.4.1. 3-Hydroxy-2-((*S*)-2-methoxymethylpyrrolidin-1-yl)-3-phenyl-2,3-dihydro-1*H*-isoindol-1-one 11a

Oil; ^1H NMR ($CDCl_3$): 1.25–1.39 (m, 1H), 1.40–1.53 (m, 1H), 1.71–1.88 (m, 1H), 2.05–2.19 (m, 1H), 2.48 (dt, *J* = 3.1, 7.9, 1H), 3.26–3.37 (m, 3H), 3.30 (s, 3H, OMe), 3.93–4.16 (m, 1H), 6.59 (s, 1H, OH), 7.16 (dd, *J* = 1.0, 6.6, 1H, H_{arom}), 7.18–7.27 (m, 3H, H_{arom}), 7.32–7.44 (m, 4H, H_{arom}), 7.72 (dd, *J* = 1.3, 6.6, 1H, H_{arom}); ^{13}C NMR ($CDCl_3$): *C* 165.8 (CO), 147.9, 140.4, 129.9, 90.1, *CH* 132.8, 128.1 (2 × CH), 128.0, 126.7 (2 × CH), 122.9, 122.8, 61.3, CH_2 76.8, 53.5, 27.0, 23.6, CH_3 58.6. Anal. Calcd for $C_{20}H_{22}N_2O_3$: C, 70.99; H, 6.55; N, 8.28. Found: C, 71.12; H, 6.41; N, 8.12.

4.4.2. 3-Hydroxy-2-((*S*)-2-methoxymethylpyrrolidin-1-yl)-3-(4-methoxyphenyl)-2,3-dihydro-1*H*-isoindol-1-one 11b

Oil; ^1H NMR ($CDCl_3$): 1.29–1.42 (m, 1H), 1.44–1.63 (m, 1H), 1.77–1.91 (m, 1H), 2.06–2.22 (m, 1H), 2.54 (dt, *J* = 3.1, 7.9, 1H), 3.27–3.40 (m, 3H), 3.31 (s, 3H, OMe), 3.73 (s, 3H, OMe), 3.97–4.10 (m, 1H), 6.55 (s, 1H, OH), 6.80 (d, *J* = 8.8, 1H, H_{arom}), 7.20 (d, *J* = 7.2, 1H, H_{arom}), 7.30 (d, *J* = 8.8, 1H, H_{arom}), 7.33–7.50 (m, 2H, H_{arom}), 7.73 (d, *J* = 7.2, 2H, H_{arom}); ^{13}C NMR ($CDCl_3$): *C* 165.6 (CO), 159.3, 147.9, 132.3, 129.9, 90.0, *CH* 132.8, 128.9, 127.9 (2 × CH), 122.8, 122.7, 113.3 (2 × CH), 61.0, CH_2 76.8, 53.4, 26.9, 23.5, CH_3 58.5, 55.1.

4.4.3. 3-Hydroxy-2-((*S*)-2-methoxymethylpyrrolidin-1-yl)-3-(3,4,5-trimethoxyphenyl)-2,3-dihydro-1*H*-isoindol-1-one 11c

Oil; ^1H NMR ($CDCl_3$): 1.38–1.51 (m, 1H), 1.54–1.72 (m, 1H), 1.92–2.07 (m, 1H), 2.16–2.33 (m, 1H), 2.88 (dt, *J* = 3.1, 7.9, 1H), 3.38 (s, 3H, OMe), 3.36–3.43 (m, 2H), 3.51 (q, *J* = 8.5, 1H), 3.80 (s, 6H, 2 × OMe), 3.83 (s, 3H, OMe), 4.01–4.14 (m, 1H), 6.69 (s, 1H, OH), 6.71 (s, 2H, H_{arom}), 7.27 (d, *J* = 7.3, 1H, H_{arom}), 7.41–7.55 (m,

2H, H_{arom}), 7.78 (d, J = 7.3, 1H, H_{arom}); ^{13}C NMR ($CDCl_3$): *C* 166.0 (CO), 152.9, 147.7, 136.0, 129.4, 90.2, *CH* 132.8, 129.0, 123.0, 122.6, 103.8, 61.6, CH_2 76.6, 53.8, 27.0, 23.7, CH_3 60.7, 58.6, 56.0 (2 × CH_3).

4.4.4. 3-Hydroxy-2-((*S*)-2-methoxymethylpyrrolidin-1-yl)-3-methyl-2,3-dihydro-1*H*-isoindol-1-one 11d

Oil; ^1H NMR ($CDCl_3$): 1.41–1.58 (m, 1H), 1.70 (s, 3H, Me), 1.62–1.84 (m, 1H), 2.00–2.24 (m, 2H), 3.25 (s, 3H, OMe), 3.20–3.29 (m, 1H), 3.37 (dd, J = 3.6, 9.9, 1H), 3.46 (dd, J = 8.5, 9.9, 1H), 3.59 (q, J = 8.2, 1H), 3.98–4.11 (m, 1H), 5.81 (br s, 1H, OH), 7.37–7.45 (m, 1H, H_{arom}), 7.46–7.58 (m, 2H, H_{arom}), 7.69 (d, J = 7.4, 1H, H_{arom}); ^{13}C NMR ($CDCl_3$): *C* 164.5 (CO), 147.1, 129.2, 87.7, *CH* 132.4, 128.9, 122.9, 121.6, 60.6, CH_2 76.6, 54.0, 27.0, 23.4, CH_3 58.5, 24.2.

4.4.5. 3-Hydroxy-4,5,6-trimethoxy-2-((*S*)-2-methoxy-methylpyrrolidin-1-yl)-3-phenyl-2,3-dihydro-1*H*-isoindol-1-one 12a

Mp 177–178 °C; $[\alpha]_D^{21}$ = +66.5 (*c* 1.39, $CHCl_3$); ^1H NMR ($CDCl_3$): 1.33–1.47 (m, 1H), 1.50–1.59 (m, 1H), 1.80–1.97 (m, 1H), 2.13–2.26 (m, 1H), 2.50 (dt, J = 2.8, 8.0, 1H), 3.25–3.48 (m, 3H), 3.33 (s, 3H, OMe), 3.41 (s, 3H, OMe), 3.86 (s, 3H, OMe), 3.93 (s, 3H, OMe), 6.66 (s, 1H, H_{arom}), 7.14 (s, 1H, H_{arom}), 7.23–7.38 (m, 3H, H_{arom}), 7.47 (d, J = 6.6, 1H, H_{arom}); ^{13}C NMR ($CDCl_3$): *C* 165.3 (CO), 155.4, 148.5, 146.4, 140.7, 133.1, 125.5, 89.2, *CH* 127.8, 127.7 (2 × CH), 126.7 (2 × CH), 101.4, 61.4, CH_2 76.6, 53.5, 26.9, 23.6, CH_3 60.9, 60.2, 58.8, 56.4.

4.4.6. 7-Hydroxy-6-((*S*)-2-methoxymethylpyrrolidin-1-yl)-7-(4-methoxyphenyl)-6,7-dihydro-1,3-dioxolo-[4,5-*f*]-5*H*-isoindol-5-one 13b

Oil; ^1H NMR ($CDCl_3$): 1.32–1.43 (m, 1H), 1.47–1.62 (m, 1H), 1.82–1.95 (m, 1H), 2.10–2.24 (m, 1H), 2.57 (dt, J = 3.2, 7.9, 1H), 3.28–3.42 (m, 3H), 3.38 (s, 3H, OMe), 3.80 (s, 3H, OMe), 4.00–4.11 (m, 1H), 6.00 (s, 2H), 6.52 (s, 1H, H_{arom}), 6.65 (s, 1H, OH), 6.84 (d, J = 8.9, 2H, H_{arom}), 7.16 (s, 1H, H_{arom}), 7.34 (d, J = 8.9, 2H, H_{arom}); ^{13}C NMR ($CDCl_3$): *C* 165.4 (CO), 159.3, 151.9, 148.6, 143.8, 132.4, 123.7, 89.5,61.0, *CH* 127.9 (2 × CH), 113.3 (2 × CH), 103.5, 102.8, 61.0, CH_2 76.8, 53.5, 26.9, 23.5, CH_3 58.6, 55.2.

4.5. Typical procedure for the preparation of three-substituted isoindolinones 8–10

A solution of hemiaminals **11**–**13** (5.9 mmol) in a mixture of trifluoroacetic acid (5 mL) and CH_2Cl_2 (25 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 (60:40) as eluent to afford isoindolinones **8a**,**d**,[6c] **8b**,**c**, **9a**, **10b**.

4.5.1. (*R*)-2-((*S*)-2-Methoxymethylpyrrolidin-1-yl)-(3-(4-methoxyphenyl)-2,3-dihydro-1*H*-isoindol-1-one 8b

Mp 115–116 °C; $[\alpha]_D^{21}$ = 37.1 (*c* 0.94, $CHCl_3$); ^1H NMR ($CDCl_3$): 1.57–1.70 (m, 1H), 1.71–1.96 (m, 2H), 2.07–2.22 (m, 1H), 2.46 (dd, J = 3.3, 7.8, 1H), 2.61 (t, J = 8.3, 1H), 2.97 (s, 3H, OMe), 3.19 (dt, J = 2.9, 8.0, 1H), 3.31 (q, J = 7.9, 1H), 3.72–3.83 (m, 1H), 3.81 (s, 3H, OMe), 5.43 (s, 1H), 6.87 (d, J = 8.6, 2H, H_{arom}), 7.09 (d, J = 8.6, 2H, H_{arom}), 7.13 (d, J = 7.0, 1H, H_{arom}), 7.42–7.53 (m, 2H, H_{arom}), 7.86 (dd, J = 1.5, 7.3, 1H, H_{arom}); ^{13}C NMR ($CDCl_3$): *C* 167.3 (CO), 159.9, 145.0, 131.7, 130.1, *CH* 132.0, 130.1 (2 × CH), 128.2, 123.4, 123.1, 114.0 (2 × CH), 64.8, 61.4, CH_2 75.0, 51.9, 27.6, 23.1, CH_3 58.7, 55.3. Anal. Calcd for $C_{21}H_{24}N_2O_3$: C, 71.57; H, 6.86; N, 7.95. Found: C, 71.40; H, 6.92; N, 7.74.

4.5.2. (*R*)-2-((*S*)-2-Methoxymethylpyrrolidin-1-yl)-3-(3,4,5-trimethoxyphenyl)-2,3-dihydro-1*H*-isoindol-1-one 8c

Mp 154–155 °C; $[\alpha]_D^{21}$ = −104.3 (*c* 0.83, $CHCl_3$); ^1H NMR ($CDCl_3$): 1.52–1.80 (m, 3H), 2.01–2.17 (m, 1H), 2.54 (dd, J = 3.8, 9.1, 1H), 2.66 (t, J = 8.3, 1H), 2.91 (s, 3H, OMe), 3.10 (dt, J = 2.3, 7.3, 1H), 3.22 (q, J = 8.3, 1H), 3.62–3.88 (m, 1H), 3.70 (s, 6H, 2 × OMe), 3.74 (s, 3H, OMe), 5.32 (s, 1H), 6.30 (s, 2H, H_{arom}), 7.07 (d, J = 7.0, 1H, H_{arom}), 7.31–7.48 (m, 2H, H_{arom}), 7.77 (d, J = 7.5, 1H, H_{arom}); ^{13}C NMR ($CDCl_3$): *C* 167.6 (CO), 153.4, 144.6, 138.1, 133.8, 131.2, *CH* 132.1, 128.4, 123.3, 123.2, 105.4 (2 × CH), 65.6, 61.9, CH_2 75.3, 51.9, 27.7, 23.1, CH_3 60.9, 58.8, 56.2 (2 × CH_3). Anal. Calcd for $C_{23}H_{28}N_2O_5$: C, 66.97; H, 6.84; N, 6.79. Found: C, 66.84; H, 6.93; N, 6.71.

4.5.3. (*R*)-4,5,6-Trimethoxy-2-((*S*)-2-methoxymethyl-pyrrolidin-1-yl)-3-phenyl-2,3-dihydro-1*H*-isoindol-1-one 9a

Mp 71–72 °C; $[\alpha]_D^{21}$ = −28.1 (*c* 1.21, $CHCl_3$); ^1H NMR ($CDCl_3$): 1.53–1.90 (m, 3H), 2.02–2.18 (m, 1H), 2.37–2.66 (m, 2H), 2.57 (s, 3H, OMe), 3.11–3.35 (m, 2H), 3.28 (s, 3H, OMe), 3.62–3.80 (m, 1H), 3.86 (s, 3H, OMe), 3.94 (s, 3H, OMe), 5.43 (s, 1H), 7.18 (s, 1H, H_{arom}), 7.16–7.24 (m, 2H, H_{arom}), 7.27–7.42 (m, 3H, H_{arom}); ^{13}C NMR ($CDCl_3$): *C* 167.1 (CO), 155.0, 148.3, 145.7, 138.6, 130.4, 126.9, *CH* 128.5 (2 × CH), 128.4 (2 × CH), 128.3, 101.4, 63.3, 61.5, CH_2 74.8, 52.0, 27.5, 23.1, CH_3 60.9, 59.9, 58.6, 56.4. Anal. Calcd for $C_{23}H_{28}N_2O_5$: C, 66.97; H, 6.84; N, 6.79. Found: C, 66.92; H, 7.01; N, 6.69.

4.5.4. (*R*)-6-((*S*)-2-Methoxymethylpyrrolidin-1-yl)-7-(4-methoxyphenyl)-6,7-dihydro-1,3-dioxolo[4,5-*f*]-5*H*-isoindol-5-one 10b

Mp 107–108 °C; $[\alpha]_D^{21}$ = −1.6 (*c* 1.44, $CHCl_3$); ^1H NMR ($CDCl_3$): 1.53–1.66 (m, 1H), 1.68–1.92 (m, 2H), 2.04–2.17 (m, 1H), 2.43–2.54 (m, 1H), 2.61 (t, J = 7.6, 1H), 2.97 (s, 3H, OMe), 3.15 (dt, J = 3.1, 7.5, 1H), 3.28 (q, J = 7.2, 1H), 3.68–3.81 (m, 1H), 3.80 (s, 3H, OMe), 5.30 (s, 1H), 6.01 (d, J = 1.2, 1H), 6.03 (d, J = 1.2, 1H), 6.51 (s, 1H, H_{arom}), 6.87 (d, J = 8.8, 2H, H_{arom}), 7.09 (d, J = 8.8, 2H, H_{arom}), 7.20 (s, 1H, H_{arom}); ^{13}C NMR ($CDCl_3$): *C* 167.2 (CO), 159.9, 151.6, 148.2, 140.6, 130.1, 125.4, *CH* 130.0 (2 × CH), 114.1 (2 × CH), 103.7, 102.8, 64.3, 61.4, CH_2 101.8, 74.9, 51.8, 27.5, 23.0, CH_3 58.7, 55.3. Anal. Calcd for $C_{22}H_{24}N_2O_5$: C, 66.65; H, 6.10; N, 7.07. Found: C, 66.80; H, 6.02; N, 7.22.

4.6. Typical procedure for the preparation of isoindolinones 5–7

At first, MMPP (1.9 g, 3.75 mmol) was added to a solution of hydrazide **8**, **9**, **10** (1.5 mmol) in methanol (50 mL). Stirring at room temperature was continued until no starting material remained (TLC monitoring). The reaction mixture was then diluted with CH_2Cl_2 (100 mL) and treated with a saturated aqueous $NaHCO_3$ solution (20 mL). After phase separation, the aqueous layer was extracted with CH_2Cl_2 (2 × 50 mL). The combined organic extracts were dried over Na_2SO_4 and the solvents removed under vacuum to furnish the crude isoindolinones **5a**,**d**,[6c] **5b**,**c**, **6a**, and **7b** which were finally recrystallized from EtOH.

4.6.1. (*R*)-3-(4-Methoxyphenyl)-2,3-dihydro-1*H*-isoindol-1-one 5b

Mp 190–191 °C; $[\alpha]_D^{21}$ = −115.1 (*c* 0.95, $CHCl_3$); ^1H NMR ($CDCl_3$): 3.79 (s, 3H, OMe), 5.61 (s, 1H), 6.87 (d, J = 8.6, 2H, H_{arom}), 7.19 (d, J = 8.6, 2H, H_{arom}), 7.23 (d, J = 7.6, 1H, H_{arom}), 7.41–7.53 (m, 2H, H_{arom}), 7.77 (s, 1H, NH), 7.87 (d, J = 6.7, 1H, H_{arom}); ^{13}C NMR ($CDCl_3$): *C* 171.4 (CO), 159.6, 148.3, 131.0, 130.3, *CH* 132.2, 132.1, 128.2, 128.1, 123.6, 123.3, 114.3, 60.4, CH_3 55.3. Anal. Calcd for

$C_{15}H_{13}NO_2$: C, 75.30; H, 5.48; N, 5.85. Found: C, 75.20; H, 5.29; N, 5.62.

4.6.2. (*R*)-3-(3,4,5-Trimethoxyphenyl)-2,3-dihydro-1*H*-isoindol-1-one 5c

Mp 179–180 °C; $[\alpha]_D^{21} = -139.9$ (*c* 0.99, $CHCl_3$); ^1H NMR ($CDCl_3$): 3.81 (s, 6H, 2 × OMe), 3.82 (s, 3H, OMe), 5.58 (s, 1H), 6.49 (s, 2H, H_{arom}), 7.30 (d, *J* = 7.0, 1H, H_{arom}), 7.41–7.58 (m, 2H, H_{arom}), 7.80 (br s, 1H, NH), 7.87 (d, *J* = 7.2, 1H, H_{arom}); ^{13}C NMR ($CDCl_3$): *C* 171.5 (CO), 153.7 (2 × C), 147.8, 137.8, 133.9, 130.8, *CH* 132.3, 128.4, 123.7, 123.2, 103.5, 61.1, CH_3 60.8, 56.2 (2 × CH_3). Anal. Calcd for $C_{17}H_{17}NO_4$: C, 68.21; H, 5.72; N, 4.68. Found: C, 68.33; H, 5.54; N, 4.77.

4.6.3. (*R*)-4,5,6-Trimethoxy-3-phenyl-2,3-dihydro-1*H*-isoindol-1-one 6a

Mp 139–140 °C; $[\alpha]_D^{21} = -70.5$ (*c* 0.92, $CHCl_3$); ^1H NMR ($CHCl_3$): 3.30 (s, 3H, OMe), 3.85 (s, 3H, OMe), 3.91 (s, 3H, OMe), 5.57 (s, 1H), 7.17 (s, 1H, H_{arom}), 7.24–7.31 (m, 5H, H_{arom}), 7.74 (br s, 1H, NH); ^{13}C NMR ($CHCl_3$): *C* 171.2 (CO), 155.1, 148.5, 145.8, 138.3, 133.8, 126.5, *CH* 128.6 (2 × CH), 128.2, 127.4 (2 × CH), 101.6, 59.0, CH_3 60.9, 60.1, 56.3. Anal. Calcd for $C_{17}H_{17}NO_4$: C, 68.21; H, 5.72; N, 4.68. Found: C, 68.29; H, 5.89; N, 4.89.

4.6.4. (*R*)-7-(4-Methoxyphenyl)-6,7-dihydro-1,3-dioxolo[4,5-*f*]-5*H*-isoindol-5-one 7b

Mp 208–209 °C; $[\alpha]_D^{21} = -34.1$ (*c* 1.20, $CHCl_3$); ^1H NMR ($CDCl_3$): 3.77 (s, 3H, OMe), 5.44 (s, 1H), 5.98 (s, 1H), 6.02 (s, 1H), 6.57 (s, 1H, H_{arom}), 6.85 (d, *J* = 8.8, 2H, H_{arom}), 7.14 (d, *J* = 8.8, 2H, H_{arom}), 7.19 (s, 1H, H_{arom}), 7.34 (br s, 1H, NH); ^{13}C NMR ($CDCl_3$): *C* 171.2 (CO), 160.0, 152.1, 148.7, 144.5, 130.6, 125.1, *CH* 128.3 (2 × CH), 114.7 (2 × CH), 103.7, 103.4, 60.4, CH_2 102.3, CH_3 55.6. Anal. Calcd for $C_{16}H_{13}NO_4$: C, 67.84; H, 4.63; N, 4.94. Found: C, 67.48; H, 4.48; N, 4.89.

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