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A concise and efficient synthesis of isoindolin-1-ones. New synthetic approach to the polycyclic framework of vitedoamine A

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Abstract—A concise and efficient synthesis of 2,3-dihydro-1*H*-isoindol-1-ones based upon the Parham-type cyclization of iodinated benzyldicarbamates is reported. The synthetic potential of this approach was further emphasized by the assembly of the polycyclic framework of vitedoamine A.

1. Introduction

There is an increasing interest in the development of new synthetic methodologies for the preparation of isoindolinone derivatives of generic structure **1** (Fig. 1) because of their importance as key intermediates in organic synthesis[1] and their profound physiological and chemotherapeutic activities.[2] Many compounds containing the isoindolinone skeleton have indeed shown biological properties as exemplified by the anti-inflammatory activities of indoprofen **2**[3] and the inhibitory activities on tumor necrosis factor production and on histone deacetylase (HDAC) of deoxythalidomide[4] and hydroxamic acid derivatives,[5] **3** and **4**, respectively (Fig. 1). The isoindolinone moiety is also an integral part of a variety of naturally occurring bioactive compounds.[6]

During the past few decades a number of synthetic strategies have been developed for the elaboration of isoindolin-1-ones **1** and among the possible synthetic routes the simplest one is undoubtedly the transformation of lactones to lactams.[7] They are also accessible (i) by reduction of the corresponding phthalimides,[8] (ii) by amination and cyclization of 2-bromomethylbenzoyl esters,[9] (iii) by $Pd(OAc)_2$-catalyzed carbonylation of secondary amines,[10] (iv) by a base-induced cyclization–dephosphorylation sequence applied to 2-halogeno-*N*-(phosphorylmethyl)benzamide derivatives,[11] and (v) by a base-induced cyclization of 2-hydroxymethylbenzamide derivatives.[12]

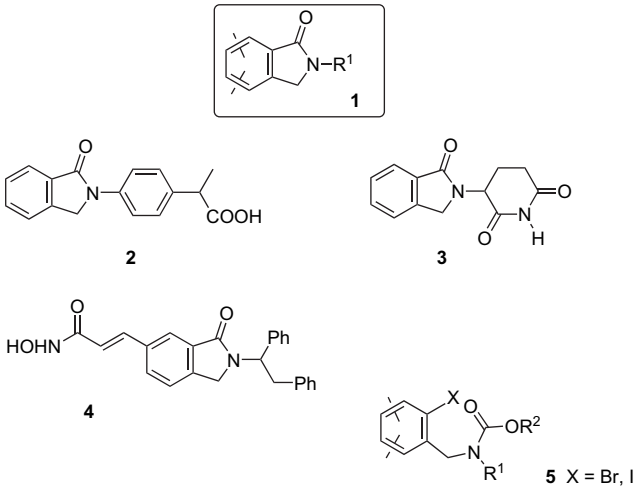

Figure 1.

Isoindolinones can also be synthesized (i) by Ph_3P and n-Bu_3N catalyzed carbonylation of *ortho*-bromoanilines,[13] (ii) by palladium nanoparticle-catalyzed carbonylation–amination reaction of 2-iodobenzylbromides,[14] (iii) by palladium catalyzed reaction of 2-iodobenzamides,[15] and (iv) by a reductive amination process applied to 2-acylbenzoic acids.[16] All these synthetic approaches are of procedural simplicity and generally proceed in good yields but they are generally fraught with difficulties associated with the elaboration of models equipped with specific substituents in particular positions on the basic benzene nucleus and particularly when the synthetic routes inevitably lead to mixture of regioisomers. Furthermore all models elaborated by these methods are invariably *N*-substituted on the lactam

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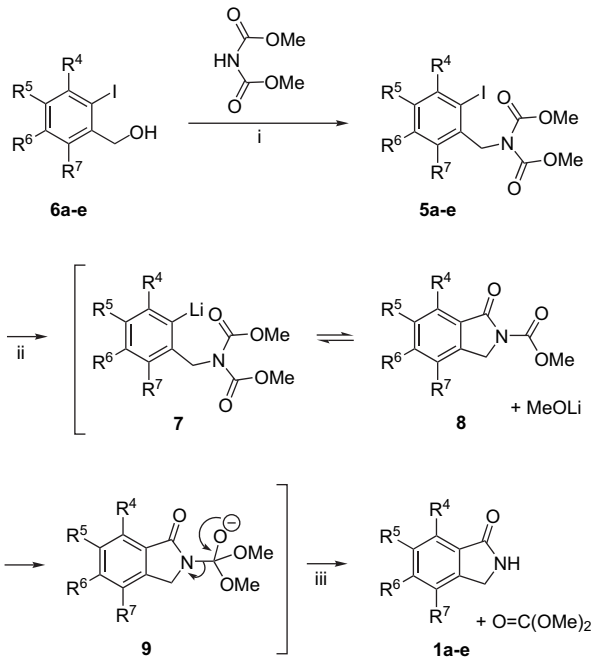
unit and consequently the construction of unsubstituted models **1** (R^1=H), which may serve as a handle for further synthetic planning, e.g., *N*- and *C*-benzyl functionalizations[17] require a supplementary deprotection step. In this respect structural modification of the most commonly used benzyl *N*-lactam protecting group was necessary to address the problem associated with the selective removal of the benzylic side chain.[18]

2. Results and discussion

We therefore considered that for the convenient synthesis of a variety of differentially substituted 2,3-dihydroisoindol-1-ones **1** (R^1=H) a more versatile procedure would be necessary and we wish to delineate in this paper a concise and efficient synthesis of the title compounds that relies upon our long standing experience in the field of the Parham cyclization reactions.[19] This annulation technique, which hinges upon aromatic lithiation and subsequent trapping with an internal electrophile has been used for the assembling of a wide array of carbo- and heterocyclic systems[20] but applications of this concept for the elaboration of five-membered lactams are scarce.[21] In recent years our group has developed a new synthetic approach to 2-alkylisoindol-1-ones **1** based on the Parham-type cyclization of the suitably substituted 2-bromo- or iodobenzylcarbamates **5** (Fig. 1). This operation released an alkoxide species as the internal nucleofuge and we then reasoned that incorporation in the annulated compounds **1** of a temporary protecting group R^1 that is highly sensitive to nucleophilic attacks would conceivably deliver the NH free models **1** (R^1=H) in a straightforward manner. The choice of the alkoxycarbonyl group (R^1=COOR^3) originated from the following premises: (i) the carbamate group is endowed with a remarkable propensity to react with basic and nucleophilic reagents, particularly with alkoxy moieties, inter- and intramolecularly[22] and (ii) the presence of a symmetrical *N*-diacyl functionality in the parent model **5** should not alter the annulation process leading to the fused benzolactams **1**.

The first facet of the synthesis was the elaboration of a range of iodinated benzyldicarbamates **5a–e**, which are liable to favor halogen–metal interconversion[20b,e] upon treatment with organolithiated reagents while sparing the diacylamine functionality. We envisaged building up these parent compounds on reliance with the Mitsunobu coupling reaction and for this purpose the appropriate 2-iodobenzyl alcohols **6a–e** were allowed to react with dimethyl iminodicarboxylate (Scheme 1). The bulkiness of the reagents had no steric impact on the coupling reaction since compounds **5a–e**, candidates for the planned Parham cyclization reaction were obtained with very satisfactory yields (Table 1).

To ensure the formation of the mandatory lithiated intermediate **7**, a THF solution of dicarbamates **5a–e** was subsequently exposed to *n*-butyllithium at −90 °C for few minutes. The intramolecular ring closure was instantaneous as demonstrated by the essentially complete consumption of the parent compounds **5a–e** and we were pleased to observe that subsequent warming to rt followed by refluxing the reaction mixture for a short period delivered the desired NH annulated products **1a–e** upon acidic work up (Scheme 1).



Scheme 1. *Reagents and conditions*: (i) PPh_3, DEAD, THF, 0 °C then rt overnight; (ii) *n*-BuLi, THF, −90 °C then rt, then reflux for 30 min; and (iii) H_3O^+.

A representative series of compounds, which have been prepared by this method are presented in Table 1 where it may be seen that this simple procedure affords satisfactory yields of the targeted 2,3-dihydro-1*H*-isoindol-1-ones. From a mechanistic point of view one can reasonably assume that as anticipated, the methoxylate released upon the annulation step giving rise to **8** can attack the latent methoxycarbonyl group of the *N*-acylated carbamate moiety to afford the highly reactive alkoxyketal-type intermediate **9**. Ultimate rearrangement according to the mechanistic pathway portrayed in Scheme 1 triggered off the formation of the NH free annulated models **1a–e**, with the release of dimethylcarbonate upon aqueous work up under acidic conditions.

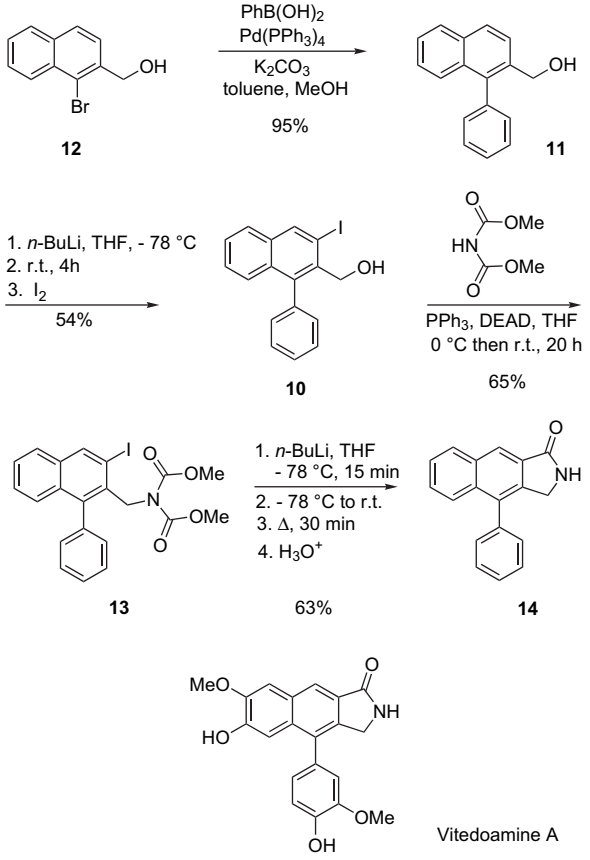
To evaluate the synthetic potential of this new conceptual approach we then set out to prepare the 4-phenylbenzoisoindolinone framework of alkaloid vitedoamine A. Vitedoamine A is a new phenylnaphthalene-type lignan alkaloid recently isolated from the seeds of *Vitex negundo* that are used as a folk medicine for analgesia and sedation, and is endowed with strong anti-oxidative activity.[23]

The synthesis started with the elaboration of the requisite iodinated benzyl alcohol **10**. This compound was readily assembled from the easily accessible 1-bromo-2-naphthalenemethanol **12** by the two step sequence depicted in Scheme 2.

Table 1. Dicarbamates **5a–e** and isoindolin-1-ones **1a–e** produced via Scheme 1

Compd	Yield (%)	Compd	Yield (%)	R^4	R^5	R^6	R^7
5a	71	**1a**	55	OMe	H	H	H
5b	69	**1b**	51	H	H	OMe	H
5c	81	**1c**	52	OCH_2O		H	H
5d	79	**1d**	64	OBn	OMe	H	H
5e	76	**1e**	65	H	H	C_4H_4	

Initially Suzuki cross-coupling reaction between **12** and phenylboronic acid afforded 1-phenyl-2-naphthalenemethanol **11**. Even though the hydroxymethyl group ranks modestly in the hierarchy of *ortho*-directing metalation groups,[24] aromatic lithiation and then electrophilic iodination of **11** occurred regioselectively at the *ortho*-site to deliver the required 3-iodo-1-phenyl-2-naphthalenemethanol **10** albeit in modest yield. The subsequent installation of the *N*-diacyl functionality was ensured by Mitsunobu reaction with dimethyl imidodicarboxylate to afford the rather congested compound **13** possessing the appropriate functionalities liable to secure the creation of the lactam unit. Gratifyingly the cyclization reaction following the previously described annulation protocol proceeded uneventfully to afford the benzoindolinone derivative **14**; the arylated tricyclic nucleus of alkaloid vitedoamine A with a fairly good yield (Scheme 2).



Scheme 2.

3. Conclusion

In conclusion we have developed a new, general concise and efficient approach for the synthesis of poly and diversely substituted isoindol-1-ones based on readily available precursors. The synthetic potential of this method has been further demonstrated by the synthesis of the vitedoamine A framework. Our synthetic approach involving an *N*-diacyl moiety enriches the repertoire of the annulation reactions relying on the Parham cyclization process then emphasizing the prominent place of this technique in the arsenal of the synthetic tactics for the assembling of heterocyclic systems, namely alkaloids.

4. Experimental

4.1. General

Tetrahydrofuran (THF) was pre-dried with anhydrous Na_2SO_4 and distilled over sodium benzophenone ketyl under Ar before use. DMF, CH_2Cl_2, NEt_3, and toluene were distilled from CaH_2. Dry glassware was obtained by oven-drying and assembly under dry Ar. The glassware was equipped with rubber septa and reagent transfer was performed by syringe techniques. For flash chromatography, Merck silica gel 60 (40–63 μm; 230–400 mesh ASTM) was used. The melting points were obtained on a Reichert–Thermopan apparatus and are not corrected. NMR spectra: Bruker AM 300 (300 MHz and 75 MHz, for ^1H and ^{13}C), $CDCl_3$ or DMSO-d_6 (for **1a**–**e**) as solvent, TMS as an internal standard. Microanalyses were performed by the CNRS microanalysis center.

4.1.1. Syntheses of the 2-iodobenzyl alcohol derivatives 6a–e and 10. The 2-iodobenzyl alcohol derivatives **6a**,[25] **6b**,[26] and **6e**,[25] were synthesized according to literature methods.

4.1.1.1. 2-Iodo-3,4-methylenedioxybenzyl alcohol (6c). From piperonol (3,4-methylenedioxybenzyl alcohol), following the procedure described for **6a**.[25] Yield 53%; white solid; mp 106–107 °C (from hexane–toluene); ^1H NMR (δ_H): 2.13 (br s, 1H, OH), 4.62 (s, 2H, CH_2O), 6.05 (s, 2H, OCH_2O), 6.75 (d, J=7.8 Hz, 1H, aromatic H), 6.92 (d, J=7.8 Hz, 1H, aromatic H) ppm; ^{13}C NMR (δ_C): 68.2 (CH_2O), 76.6 (C–I), 100.7 (OCH_2O), 108.0 (CH), 122.2 (CH), 135.6 (C), 145.7 (C), 149.7 (C) ppm. Anal. calcd for $C_8H_7IO_3$ (277.9): C, 34.56; H, 2.54%. Found: C, 34.42; H, 2.81%.

4.1.1.2. 3-Benzyloxy-2-iodo-4-methoxybenzyl alcohol (6d). By reduction of 3-benzyloxy-2-iodo-4-methoxybenzaldehyde[27] with $NaBH_4$ in MeOH. Yield 92%; white solid; mp 78–79 °C (from hexane–toluene); ^1H NMR (δ_H): 2.15 (br s, 1H, OH), 3.90 (s, 3H, OCH_3), 4.67 (s, 2H, CH_2O), 5.03 (s, 2H, CH_2O), 6.94 (d, J=8.3 Hz, 1H, aromatic H), 7.20 (d, J=8.3 Hz, 1H, aromatic H) ppm; ^{13}C NMR (δ_C): 56.1 (CH_3), 69.2 (CH_2), 74.3 (CH_2), 97.2 (C–I), 112.3 (CH), 122.6 (C), 124.5 (CH), 128.1 (CH), 128.4 (2×CH), 128.6 (2×CH), 135.8 (C), 137.1 (C), 152.2 (C) ppm. Anal. calcd for $C_{15}H_{15}IO_3$ (370.0): C, 48.67; H, 4.08%. Found: C, 48.51; H, 4.05%.

4.1.1.3. 1-Phenyl-2-naphthalenemethanol (11). A solution of 1-bromo-2-naphthalenemethanol[28] (1 g, 4.22 mmol) and $Pd(PPh_3)_4$ (46 mg, 0.04 mmol) in toluene (14 mL) was added to a solution of phenylboronic acid (616 mg, 5.06 mmol) in EtOH (12 mL), followed by addition of K_2CO_3 (1.11 g, 9.3 mmol). The mixture was refluxed for 20 h under N_2 and allowed to cool to rt. To the reaction mixture was added 0.5 M NaOH solution (30 mL) and the mixture was extracted with CH_2Cl_2 (2×50 mL). The organic layers were combined, dried ($MgSO_4$), and filtered. The solvent was removed under reduced pressure and the yellow oily residue was purified by column chromatography using AcOEt–hexane (30:70) as an eluent to give a colorless oil. Yield 95% (938 mg); ^1H NMR (δ_H): 2.18 (br s, 1H, OH), 4.56 (s, 2H, CH_2O), 7.27–7.33 (m, 2H, aromatic H), 7.38–7.43 (m, 6H, aromatic H), 7.71 (d, J=8.5 Hz, 1H,

aromatic H), 7.88–7.73 (m, 2H, aromatic H) ppm; ^{13}C NMR (δ_C): 63.3 (CH_2), 125.7 (CH), 125.8 (CH), 126.1 (CH), 126.7 (CH), 127.5 (CH), 127.9 (CH), 128.0 (CH), 128.5 (2×CH), 130.2 (2×CH), 132.7 (C), 132.9 (C), 135.7 (C), 137.9 (C), 138.2 (C) ppm. Anal. calcd for $C_{17}H_{14}O$ (349.1): C, 87.15; H, 6.02%. Found: C, 87.05; H, 6.07%.

4.1.1.4. 2-Iodo-1-phenyl-2-naphthalenemethanol (10). From **11** following the procedure described for **6e**.[25] The crude oily reaction product was purified by column chromatography using AcOEt–hexane (30:70) as an eluent to afford a pale yellow oil. Yield 54%; ^{1}H NMR (δ_H): 2.13 (br s, 1H, OH), 4.65 (s, 2H, CH_2O), 7.28–7.42 (m, 4H, aromatic H), 7.46–7.56 (m, 4H, aromatic H), 7.76 (d, J=8.1 Hz, 1H, aromatic H), 8.49 (s, 1H, aromatic H) ppm; ^{13}C NMR (δ_C): 66.8 (CH_2), 98.1 (C–I), 126.7 (CH), 126.8 (CH), 126.9 (CH), 127.4 (CH), 127.8 (CH), 128.4 (2×CH), 130.1 (2×CH), 132.6 (C), 134.4 (C), 136.2 (C), 138.3 (C), 139.0 (CH), 141.1 (C) ppm. Anal. calcd for $C_{17}H_{13}IO_3$ (360.0): C, 56.69; H, 3.64%. Found: C, 56.75; H, 3.61%.

4.1.2. Syntheses of the dicarbamates 5a–e and 11. General procedure. A solution of DEAD (2.5 mL, 40% in toluene, 5.5 mmol) was added dropwise at 0 °C under N_2 to a stirred solution of the appropriate 2-iodobenzyl alcohol derivative (5 mmol), triphenylphosphine (1.44 g, 5.5 mmol), and dimethyl iminodicarboxylate (1.33 g, 10 mmol) in dry THF (50 mL). The mixture was then stirred at rt for an additional 24 h, quenched with water (2 mL), and concentrated under vacuum. The oily residue was purified by column chromatography (CH_2Cl_2–Et_2O–hexane, 50:30:20). The solid iminodicarboxylates were recrystallized from hexane–toluene.

4.1.2.1. 2-Iodo-3-methoxy-*N*,*N*-di(methoxycarbonyl)-benzylamine (5a). Yield 71%; yellow solid; mp 96–98 °C; ^{1}H NMR (δ_H): 3.81 (s, 6H, 2×OCH_3), 3.89 (s, 3H, OCH_3), 4.92 (s, 2H, CH_2), 6.67 (d, J=7.5 Hz, 1H, aromatic H), 6.74 (d, J=7.9 Hz, 1H, aromatic H), 7.24–7.29 (m, 1H, aromatic H) ppm; ^{13}C NMR (δ_C): 54.2 (2×CH_3), 55.5 (CH_2), 56.6 (CH_3), 89.2 (C–I), 109.5 (CH), 117.9 (CH), 129.3 (CH), 141.0 (C), 153.9 (C), 158.0 (2×CO) ppm. Anal. calcd for $C_{12}H_{14}INO_5$ (379.0): C, 38.01; H, 3.72; N, 3.69%. Found: C, 37.85; H, 3.89; N, 3.71%.

4.1.2.2. 2-Iodo-5-methoxy-*N*,*N*-di(methoxycarbonyl)-benzylamine (5b). Yield 69%; yellow solid; mp 77–79 °C; ^{1}H NMR (δ_H): 3.74 (s, 3H, OCH_3), 3.81 (s, 6H, 2×OCH_3), 4.83 (s, 2H, CH_2), 6.54 (d, J=8.6 Hz, 1H, aromatic H), 6.23 (s, 1H, aromatic H), 6.68 (d, J=8.6 Hz, 1H, aromatic H) ppm; ^{13}C NMR (δ_C): 54.2 (2×CH_3), 54.8 (CH_2), 55.4 (CH_3), 85.4 (C–I), 112.8 (C), 114.0 (C), 139.9 (C), 140.1 (C), 153.9 (C), 160.3 (2×CO) ppm. Anal. calcd for $C_{12}H_{14}INO_5$ (379.0): C, 38.01; H, 3.72; N, 3.69%. Found: C, 37.77; H, 3.62; N, 3.78%.

4.1.2.3. 2-Iodo-3,4-methylenedioxy-*N*,*N*-di(methoxycarbonyl)benzylamine (5c). Yield 81%; yellow solid; mp 141–142 °C; ^{1}H NMR (δ_H): 3.82 (s, 6H, 2×OCH_3), 4.83 (s, 2H, CH_2), 6.03 (s, 2H, OCH_2O), 6.58 (d, J=8.0 Hz, 1H, aromatic H), 6.71 (d, J=8.0 Hz, 1H, aromatic H) ppm; ^{13}C NMR (δ_C): 53.4 (CH_2), 54.2 (2×CH_3), 74.3 (C–I), 100.7 (OCH_2O), 108.2 (CH), 119.1 (CH), 131.9 (C), 145.2 (C), 149.6 (C), 154.0 (2×CO) ppm. Anal. calcd for $C_{12}H_{12}INO_6$ (393.0): C, 36.66; H, 3.08; N, 3.56%. Found: C, 36.55; H, 3.03; N, 3.25%.

4.1.2.4. 3-Benzyloxy-2-iodo-4-methoxy-*N*,*N*-di(methoxycarbonyl)benzylamine (5d). Yield 79%; yellow solid; mp 105–107 °C; ^{1}H NMR (δ_H): 3.84 (s, 6H, 2×OCH_3), 3.87 (s, 3H, OCH_3), 4.89 (s, 2H, CH_2), 5.03 (s, 2H, CH_2), 6.82 (d, J=8.5 Hz, 1H, aromatic H), 6.90 (d, J=8.5 Hz, 1H, aromatic H), 7.33–7.44 (m, 3H, aromatic H), 7.62 (d, J=7.2 Hz, 2H, aromatic H) ppm; ^{13}C NMR (δ_C): 54.2 (2×CH_3), 54.7 (CH_2), 56.1 (CH_3), 74.3 (CH_2), 96.6 (C–I), 112.5 (CH), 121.3 (CH), 128.1 (CH), 128.4 (2×CH), 128.5 (2×CH), 132.0 (C), 137.1 (C), 147.6 (C), 151.7 (C), 154.1 (2×CO) ppm. Anal. calcd for $C_{19}H_{20}INO_6$ (485.0): C, 47.03; H, 4.15; N, 2.89%. Found: C, 46.79; H, 4.37; N, 3.05%.

4.1.2.5. *N*,*N*-Di(methoxycarbonyl)-(2-iodonaphthalen-1-yl)methylamine (5e). Yield 76%; yellow solid; mp 84–85 °C; ^{1}H NMR (δ_H): 3.73 (s, 6H, 2×OCH_3), 5.55 (s, 2H, CH_2), 7.45 (d, J=8.7 Hz, 1H, aromatic H), 7.48–7.56 (m, 2H, aromatic H), 7.77–7.83 (m, 1H, aromatic H), 7.90 (d, J=8.7 Hz, 1H, aromatic H), 8.04–8.11 (m, 1H, aromatic H) ppm; ^{13}C NMR (δ_C): 53.3 (CH_2), 54.0 (2×CH_3), 101.7 (C–I), 123.3 (C), 123.9 (CH), 126.3 (CH), 127.3 (CH), 128.7 (CH), 129.8 (CH), 133.4 (C), 134.5 (C), 136.6 (C), 154.2 (2×CO) ppm. Anal. calcd for $C_{15}H_{14}INO_4$ (399.0): C, 45.13; H, 3.54; N, 3.51%. Found: C, 45.31; H, 3.54; N, 3.39%.

4.1.2.6. *N*,*N*-Di(methoxycarbonyl)-(3-iodo-1-phenylnaphthalen-2-yl)amine (13). Yield 65%; yellow oil; ^{1}H NMR (δ_H): 3.57 (s, 6H, 2×OCH_3), 5.16 (s, 2H, CH_2), 7.19 (d, J=8.6 Hz, 1H, aromatic H), 7.23 (d, J=7.9 Hz, 2H, aromatic H), 7.32 (t, J=8.4 Hz, 1H, aromatic H), 7.42–7.52 (m, 4H, aromatic H), 7.72 (d, J=8.2 Hz, 1H, aromatic H), 8.52 (s, 1H, aromatic H) ppm; ^{13}C NMR (δ_C): 53.4 (CH_2), 53.6 (2×CH_3), 99.1 (C–I), 126.6 (CH), 126.65 (CH), 126.7 (CH), 126.75 (CH), 127.5 (CH), 128.4 (2×CH), 130.1 (2×CH), 132.8 (C), 133.1 (C), 133.8 (C), 137.8 (C), 139.2 (CH), 140.5 (C), 153.2 (2×CO) ppm. Anal. calcd for $C_{21}H_{18}INO_4$ (475.0): C, 53.07; H, 3.82; N, 2.95%. Found: C, 52.99; H, 3.75; N, 3.10%.

4.1.3. Syntheses of the isoindolinones 1a–e and 14. General procedure. A solution of *n*-BuLi (1.4 mL, 1.6 M in hexanes, 2.2 mmol) was added dropwise at −90 °C under N_2 to a solution of the dicarbamate (2 mmol) in dry THF (30 mL). The reaction mixture was stirred at −90 °C for an additional 15 min, slowly allowed to warm to rt over 1 h and then refluxed for 30 min. The reaction mixture was cooled to rt, quenched with saturated aq NH_4Cl solution (10 mL), and extracted with Et_2O (3×10 mL). The combined organic extracts were washed with brine and dried (Na_2SO_4). After evaporation of the solvent the crude oily residue was purified by column chromatography using AcOEt as an eluent to afford the annulated compounds (recrystallization from CH_3CN–Et_2O).

4.1.3.1. 2,3-Dihydro-7-methoxy-1*H*-isoindol-1-one (1a). Yield 55%; white solid; mp 144–145 °C; ^{1}H NMR (δ_H): 3.82 (s, 3H, OCH_3), 4.27 (s, 2H, CH_2), 6.98 (d, J=7.1 Hz, 1H, aromatic H), 7.07 (d, J=7.1 Hz, 1H, aromatic

H), 7.50 (t, J=7.1 Hz, 1H, aromatic H), 8.22 (br s, 1H, NH) ppm; ^{13}C NMR (δ_C): 44.7 (CH_2), 55.8 (CH_3), 110.7 (CH), 116.0 (CH), 119.9 (C), 133.5 (CH), 147.4 (C), 157.5 (C), 169.3 (CO) ppm. Anal. calcd for $C_9H_9NO_2$ (163.0): C, 66.25; H, 5.56; N, 8.58%. Found: C, 66.38; H, 5.54; N, 8.62%.

4.1.3.2. 2,3-Dihydro-5-methoxy-1*H*-isoindol-1-one (1b). Yield 51%; white solid; mp 160–161 °C (lit.:[29] 161–162 °C); ^{1}H NMR (δ_H): 3.81 (s, 3H, OCH_3), 4.30 (s, 2H, CH_2), 7.00 (d, J=8.3 Hz, 1H, aromatic H), 7.10 (s, 1H, aromatic H), 7.57 (d, J=8.3 Hz, 1H, aromatic H), 8.35 (br s, 1H, NH) ppm; ^{13}C NMR (δ_C): 45.2 (CH_2), 56.0 (CH_3), 108.4 (CH), 115.2 (CH), 124.5 (CH), 125.5 (C), 147.0 (C), 162.6 (C), 170.4 (CO) ppm.

4.1.3.3. 6,7-Dihydro-1,3-8*H*-dioxolo[4,5-*e*]isoindol-8-one (1c). Yield 52%; white solid; mp 258–259 °C; ^{1}H NMR (δ_H): 4.28 (s, 2H, CH_2), 6.14 (s, 2H, OCH_2O), 6.95 (d, J=7.6 Hz, 1H, aromatic H), 7.11 (d, J=7.6 Hz, 1H, aromatic H), 8.45 (br s, 1H, NH) ppm; ^{13}C NMR (δ_C): 45.3 (CH_2), 102.6 (OCH_2O), 111.6 (CH), 113.4 (C), 116.3 (CH), 137.9 (C), 143.3 (C), 147.9 (C), 167.9 (CO) ppm. Anal. calcd for $C_9H_7NO_3$ (177.0): C, 61.02; H, 3.98; N, 7.91%. Found: C, 60.78; H, 4.09; N, 7.93%.

4.1.3.4. 2,3-Dihydro-7-benzyloxy-6-methoxy-1*H*-isoindol-1-one (1d). Yield 64%; white solid; mp 95–96 °C; ^{1}H NMR (δ_H): 3.85 (s, 3H, OCH_3), 4.36 (s, 2H, CH_2), 5.35 (s, 2H, CH_2), 7.08–7.11 (m, 2H, aromatic H), 7.27–7.38 (m, 3H, aromatic H), 7.59–7.63 (m, 2H, aromatic H), 7.84 (br s, 1H, NH) ppm; ^{13}C NMR (δ_C): 44.7 (CH_2), 56.8 (CH_3), 76.5 (CH_2), 117.1 (CH), 118.3 (CH), 124.9 (C), 127.9 (CH), 128.2 (2×CH), 128.7 (2×CH), 137.2 (C), 137.6 (C), 146.1 (C), 152.4 (C), 170.1 (CO) ppm. Anal. calcd for $C_{16}H_{15}NO_3$ (269.1): C, 71.36; H, 5.61; N, 5.20%. Found: C, 71.33; H, 5.41; N, 5.16%.

4.1.3.5. 2,3-Dihydro-1*H*-benzo[*e*]isoindol-1-one (1e). Yield 65%; white solid; mp 189–190 °C; ^{1}H NMR (δ_H): 4.75 (s, 2H, CH_2), 7.64–7.72 (m, 3H, aromatic H), 7.98–8.05 (m, 3H, aromatic H), 8.67 (br s, 1H, NH) ppm; ^{13}C NMR (δ_C): 44.7 (CH_2), 119.9 (CH), 124.2 (CH), 127.6 (CH), 128.2 (CH), 128.4 (C), 128.9 (CH), 129.2 (CH), 130.3 (C), 134.8 (C), 143.8 (C), 171.1 (CO) ppm. Anal. calcd for $C_{12}H_9NO$ (183.1): C, 78.67; H, 4.95; N, 7.65%. Found: C, 78.84; H, 4.81; N, 7.66%.

4.1.3.6. 4-Phenyl-2,3-dihydro-1*H*-benzo[*f*]isoindol-1-one (14). Yield 63%; mp 277–279 °C (lit.:[30] 268–269.5 °C); ^{1}H NMR (δ_H): 4.27 (s, 2H, CH_2), 7.44–7.58 (m, 7H, aromatic H), 7.65 (d, J=7.8 Hz, 1H, aromatic H), 8.20 (d, J=7.6 Hz, 1H, aromatic H), 8.37 (s, 1H, aromatic H), 8.75 (br s, 1H, NH) ppm; ^{13}C NMR (δ_C): 44.8 (CH_2), 123.1 (CH), 125.6 (CH), 126.4 (CH), 128.2 (CH), 128.5 (CH), 129.3 (2×CH), 130.1 (2×CH), 130.2 (CH), 130.9 (C), 133.35 (C), 133.4 (C), 134.6 (C), 136.6 (C), 137.8 (C), 170.0 (CO) ppm.

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