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Mild and efficient syntheses of diverse isoindolinones from *ortho*-phthaldehydic acid methylthiomethyl ester

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ABSTRACT

A mild and efficient method for the synthesis of diverse isoindolinones from *o*-phthaldehydic acid methylthiomethyl ester and aliphatic/aromatic amines has been developed. A number of nucleophiles including a hydride ion were successfully added to the intermediate Schiff's base providing isoindolinones, with or without substitution at 3-position. Conditions have also been developed for amines with an integrated nucleophilic group to react in a diverse fashion either to give isoindolinones or tricyclic γ-lactams as single diastereoisomers in very good yield.

1. Introduction

Isoindolinone (2,3-dihydro-1*H*-isoindolin-1-one) **1** (Fig. 1) is a key structural feature found in many drugs of natural and synthetic origin.[1] For example, indoprofen **2**[2] is shown to have anti-inflammatory activities while deoxythalidomide **3**[3] is an inhibitor of tumor necrosis factor production and tricyclic γ-lactam **4**[4] is a non-nucleosidic HIV reverse transcriptase inhibitor. Isoindolinone derivatives are also known as 5-HT_{2C} antagonists,[5] and vasodilators.[6] Both (*R*)- and (*S*)-3-alkyl substituted isoindolinones have been shown to be valuable chiral auxiliaries.[7] The 3-position of isoindolinone ring system is generally regarded as a benzylic alcohol bioisotere liable to undergo metabolic oxidation, but on substitution, has shown to posses improved metabolic stability while retaining functionality.[8] Therefore, 3-substituted isoindolinones are also very important class of molecules. Beside biological activities, a class of isoindolinone was reported recently to have special fluorescent properties.[9] In addition, the isoindolinone skeleton frequently serves as an indispensable building block for the synthesis of many naturally occurring bioactive compounds.[10]

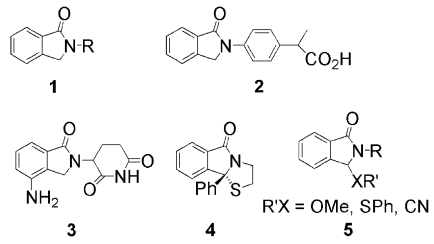

Figure 1. Few examples of isoindolinone moiety present in various drugs.

Consequently, the chemistry of isoindolinones has attracted much attention, and a number of synthetic strategies have been developed over the past few decades including conversion of lactones to lactams,[11] organometallic addition on imines and/or reduction of phthalimides,[12] amination and cyclization of 2-bromomethylbenzoyl esters,[13] palladium catalyzed carbonylation of amines or their derivatives,[14] base-induced reaction of 2-halogeno-*N*-(phosphorylmethyl)benzamide derivatives[15] or 2-hydroxymethylbenzamide derivatives,[16] and Parham-type cyclization of isolated benzyl-dicarbamates.[17]

Isoindolinones of type **5** with heteroatomic substituents at 3-position have also been designed to be potent inhibitors for DNA gyrase.[18a] Subsequently, they have been synthesized[18] in moderate to poor yields from *o*-phthaldehydic acid methyl ester by heating with an amine and nucleophiles such as thiophenoxide, methoxide, and HCN at elevated temperatures over a long period. Intramolecular variation of this reaction to provide tricyclic lactams **6** (Scheme 1) has also been achieved[19] by heating *o*-phthaldehydic acid with amino alcohols at elevated temperatures. These harsh conditions are required to improve the reactivity of intermediate zwitterionic acid **7** (Scheme 1) to undergo condensation with expulsion of a water

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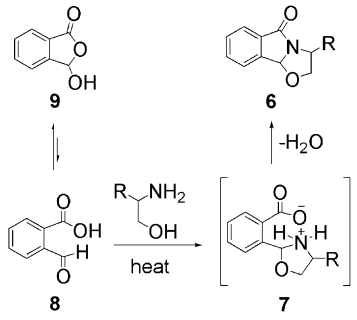
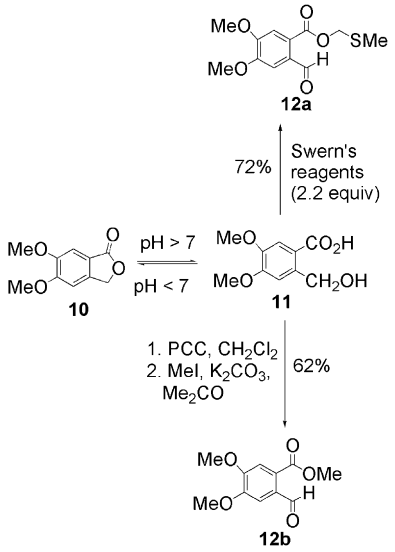
molecule. The other reason could be the slow rate of imine/imino acetal formation because *o*-phthaldehydic acid **8**→lactone **9** equilibrium favors the formation of later. To overcome these drawbacks, we have been studying a milder route. This can be achieved by tuned activation of the carboxylic acid group that would stop lactol formation and favor lactam formation. In this paper we describe our studies toward the syntheses of diverse isoindolinones from a *o*-phthaldehydic acid methylthiomethyl (MTM) ester, amines, and nucleophiles including a hydride ion (H^-) by a sequence of reactions in one-pot involving amination and lactamization.



Scheme 1. Reaction of *o*-phthaldehydic acid with amino alcohols via zwitterionic acid intermediate **7**.

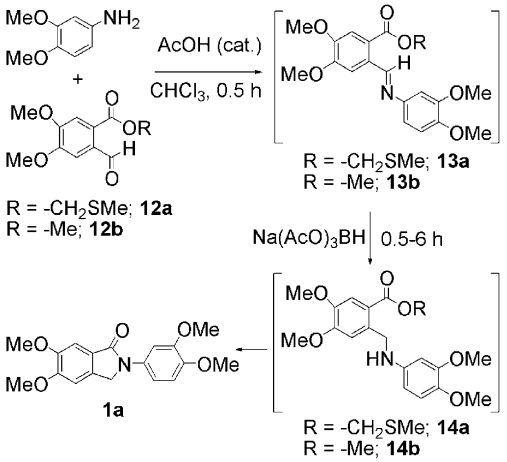
2. Results and discussion

We have recently reported[20] an efficient method for the synthesis of MTM esters from the corresponding acids under Swern oxidation conditions wherein substituted 2-hydroxymethyl benzoic acid[21]**11**, obtained from corresponding lactone **10**, gave methylthiomethyl-2-formyl-4,5-dimethoxy benzoate **12a** in 72% yield (Scheme 2). We anticipated that this ester would be ideal starting material for isoindolinone synthesis by carrying out a reductive amination on the aldehyde functionality, which would then undergo intramolecular cyclization with the MTM ester group. The MTM group has double advantages because it is known to be a moderately activating group for amidation of acids and also compatible with mild reducing agent[22] needed for reductive amination to give the lactam **1**.



Scheme 2. Preparation of MTM and methyl esters of 2-formyl-4,5-dimethoxybenzoic acid.

Reductive amination of aromatic aldehyde and ketone is well known, which goes via Schiff's base formation. Amongst the plethora of reducing agents capable of reducing Schiff's base, borohydride based reagents such as sodium cyanoborohydride and sodium triacetoxyborohydride are frequently used. When aldehydic MTM ester **12a** was treated with 3,4-dimethoxyaniline (1.2 equiv) in the presence of catalytic amount of acetic acid (40 mol %), it provided the intermediate Schiff's base **13a**. This on treatment with sodium triacetoxyborohydride (1.5 equiv) underwent in situ reduction to intermediate amine **14a**, which on intramolecular lactamization directly gave the isoindolinone **1a** (Scheme 3). Amongst the various solvents we studied, chloroform gave the best result and the reaction proceeded well at room temperature (28 °C) to give the product **1a** in 90% yield. As mentioned earlier, isoindolinones of type **5** (Fig. 1) with heteroatom substituents at 3-position have been synthesized[18] from *o*-phthaldehydic acid methyl ester by heating with an amine and nucleophiles at elevated temperature. It was, therefore, necessary to check the efficiency of reductive amination–lactamization with the methyl ester substrate. We prepared methyl-2-formyl-4,5-dimethoxybenzoate **12b** from corresponding 2-hydroxymethyl benzoic acid **11** by pyridinium chlorochromate (PCC) oxidation followed by esterification with iodomethane[23] in the presence of base K_2CO_3 in 62% overall yield (Scheme 2). To compare the relative reactivity, MTM ester **12a** and methyl ester **12b** were separately reacted with 3,4-dimethoxy aniline (1.2 equiv) in the presence of catalytic amount of AcOH (40 mol %) in $CHCl_3$ (0.08 M) for 30 min. The resulting Schiff's bases **13a** and **13b** (Scheme 3) were then reacted with sodium triacetoxyborohydride (1.5 equiv) at room temperature (28 °C). We were gratified to note that the reaction of MTM ester **12a**→**1a** was complete within 30 min whereas the methyl ester **12b**→**1a** required 6 h for completion. The isolated yield of isoindolinone **1a** from the MTM ester **12a** was very good (90%) while from the methyl ester **12b** was 78%. Time dependent ^{1}H NMR experiment[24] at 25 °C also suggested that in case of MTM ester **12a**, the rate determining step is the reduction of the imine **13a** while the slowest step in case of methyl ester **12b** is the intramolecular lactamization of the intermediate benzylamine **14b**. It is worthwhile to note that the rate of lactamization of benzyl amine MTM ester **14a** is >50 times[24] faster than the corresponding methyl ester **14b**.



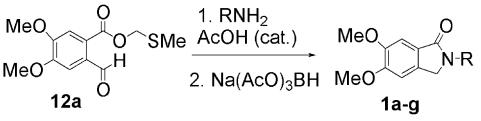
Scheme 3. Proposed mechanism for the preparation of isoindolinones from corresponding aniline and MTM/methyl esters **12a**/**12b** via reductive amination.

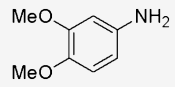
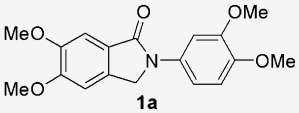
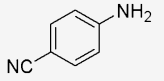
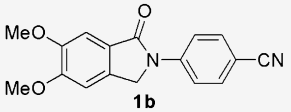
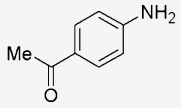
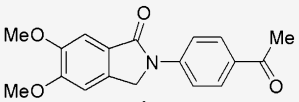
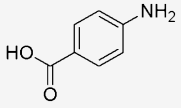
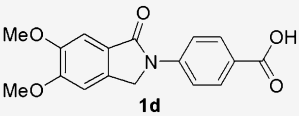
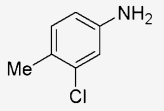
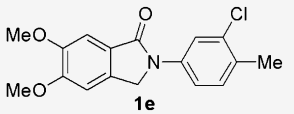
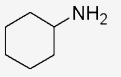
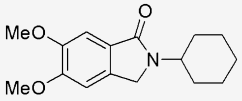
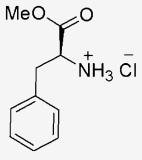
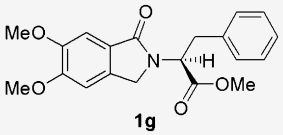
To establish the generality of the MTM ester mediated reductive amination–lactamization process, a few substituted anilines were reacted with the aldehyde MTM ester **12a** under reductive amination conditions in chloroform to give the

corresponding isoindolinones as shown in Table 1. In few cases with anilines having electron withdrawing substituents (Table 1, entries 2–5), the Schiff's base formation was very slow at room temperature hence required heating at 40 °C. The reaction is not restricted to aniline derivatives. Aliphatic amine such as cyclohexylamine or phenylalanine (Table 1, entries 6, 7) reacted at a much faster rate at room temperature to give the desired product in excellent yield.

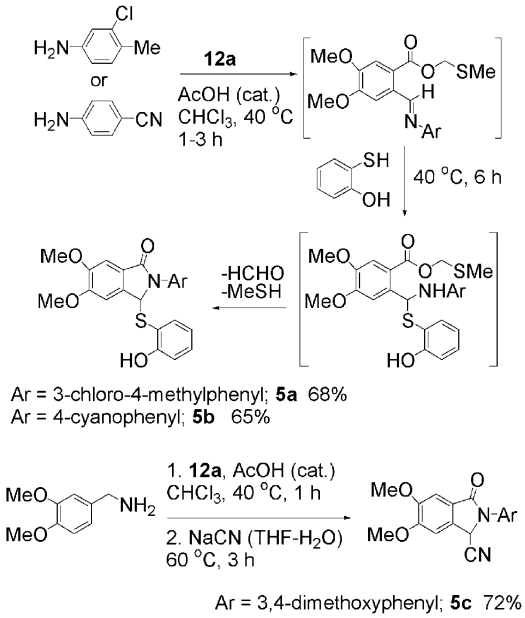
We next turned our attention to the synthesis of 3-heteroatom substituted isoindolinone derivatives. In the reductive amination–lactamization sequence as described above, the hydride (H^-) nucleophile added to the imine bond (C=N) of the Schiff's base **13a**. We were therefore curious to know if other nucleophiles can be engaged for this purpose. We first tried with a thiol nucleophile. Therefore, when a mixture of MTM ester **12a** and 3-chloro-4-methylaniline was stirred at 40 °C in the presence of catalytic amount of acetic acid in chloroform followed by addition of 2-mercaptophenol and heating at 40 °C for 1 h provided the 3-thioaryl substituted isoindolinone **5a** in moderate yield (Scheme 4). The reaction took place smoothly even with electronically deactivated 4-cyanoaniline to give 3-subsituted isoindolinone **5b**, although slightly longer (3 h) reaction time was needed. The cyanide ion (CN^-) also underwent smooth nucleophilic addition. When the Schiff's base was made by the reaction of MTM ester **12a** with 3,4-dimethoxybenzylamine at room temperature and reacted with aqueous-THF solution of sodium cyanide at 60 °C, it gave the 3-cyanosubsituted isoindolinone **5c** (Scheme 4) in good yield.

Table 1
Synthesis of isoindolin-1-ones from MTM ester **12a** and amines[a]



Entry	Amine (1.2 equiv)	Product	Temp[b] (°C)	Yield[c] (%)
1		 **1a**	28[d]	90[e]
2		 **1b**	40[f]	79[g]
3		 **1c**	40[f]	88[g]
4		 **1d**	40[f]	96[h]
5		 **1e**	40[f]	85[h]
6		 **1f**	28[d]	88[e]
7		 **1g**	28[d]	75[e]

[a] The reactions were carried out in chloroform.
[b] Temperature for the formation of the Schiff's base.
[c] Yield of the isolated product after chromatography/crystallization.
[d] Schiff's base formation time 0.5 h.
[e] Reduction and cyclization time 0.5 h.
[f] Schiff's base formation time 2 h.
[g] Reduction and cyclization time 4 h.
[h] Reduction and cyclization time 6 h.

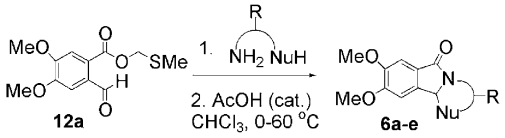


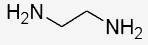
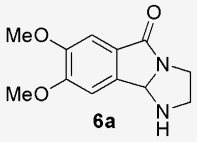
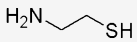
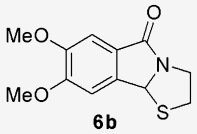
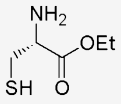
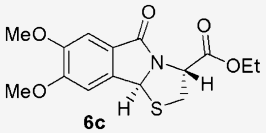
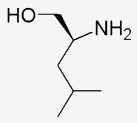
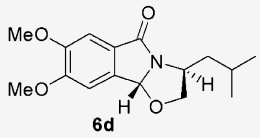
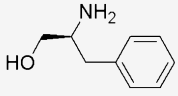
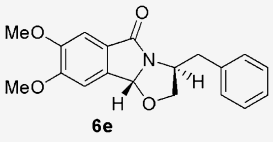
Scheme 4. Synthesis of 3-substituted isoindolinones using various nucleophiles.

We intended to apply our strategy with MTM ester **12a** and amines with an integrated nucleophile to make tricyclic lactams of type **6**. As mentioned earlier, synthesis of such lactams has been achieved[19,25] by heating *o*-phthaldehydic acid with amino alcohols at high temperatures over long time. When MTM ester **12a** was treated with 1,2-ethylenediamine (1.2 equiv) at room temperature, a clean reaction took place to give the tricyclic γ-lactam **6a** in excellent yield (Table 2, entry 1). Thiol containing nucleophiles viz. 2-aminothioethanol, (*R*)-cysteine ethyl ester (Table 2, entries 2 and 3) also gave the tricyclic heterocycles **6b** and **6c** with great ease at 0 °C. Interestingly, **6c** was formed as a single diastereoisomer only. Amino alcohols derived from chiral amino acids viz. (*S*)-leucinol and (*S*)-phenylalaninol also reacted intramolecularly to give the tricyclic lactams **6d** and **6e** (Table 2, entries 4 and 5) again as single diastereoisomers as confirmed by HPLC analyses as well as ^{1}H NMR of the crude products. Slightly higher temperature (60 °C) was required for these amino alcohols to drive the reaction to completion because of relatively lower nucleophilicity of the OH group compared to NH_2 or SH groups. The trans stereochemistry of the (*S*)-leucinol derived product **6d** (Table 2, entry 4) was confirmed from ^{1}H–^{1}H NOESY interactions.

The reaction of aldehyde **12a** with the amine containing an integrated nucleophile first forms the intermediate imine **15** (Scheme 5). Intramolecular addition of the nucleophilic group to the imine then results in the reversible formation of iminoacetals *trans*-**16** and *cis*-**16**. The exclusive formation[19a] of single diastereoisomeric tricyclic lactams **6** can be explained on the basis of easy ring formation for the thermodynamically favored trans

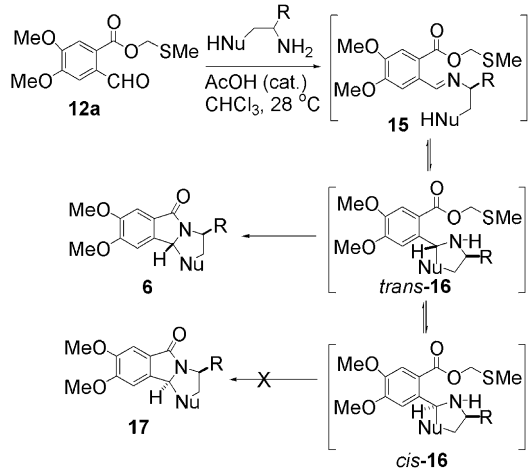
Table 2
Synthesis of tricyclic γ-lactams from MTM ester **12a** and amines integrated with nucleophiles[a]



Entry	Amine/ nucleophile (1.2 equiv)	Product	Temp (°C)/ time	Yield[b] (%)
1		 **6a**	28/1 h	94
2		 **6b**	0/2 h	92
3		 **6c**	0/3 h	79
4		 **6d**	60/4.5 h	86
5		 **6e**	60/4.5 h	80

[a] The reactions were carried out in chloroform.
[b] Yield of the isolated product after chromatography/crystallization.

product. The simple molecular model building shows that the trans-diastereoisomer **6** adopts a 'bowl-like' shape, with the bulky alkyl substituent disposed on the less hindered convex face of the fused 5,5-bicyclic system. On the other hand, the cis-diastereoisomer **17** where the alkyl substituent has to be disposed on the congested concave face won't allow a transition state conformation

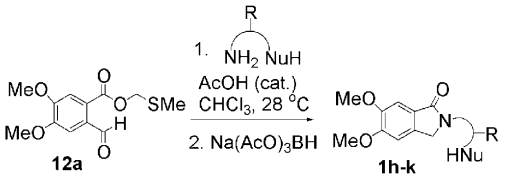


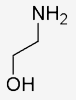
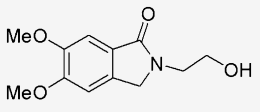
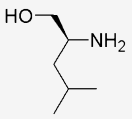
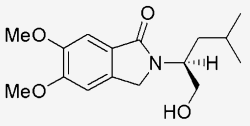
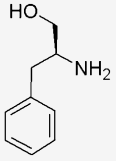
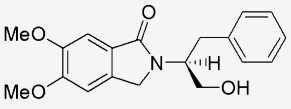
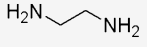
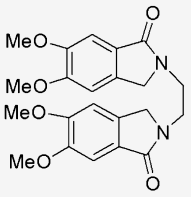
Scheme 5. Proposed synthetic steps for synthesis of tricyclic γ-lactams using amines with integrated nucleophiles.

where the reactive functional groups (–CO_2CH_2SMe and –NH–) can come closer. The reversibility of the iminoacetal *cis*-**16** to imine **15** then follows Curtin–Hammett principle thus channelizes iminoacetal *cis*-**16** to *trans*-**16** and finally to the trans product **6** (Scheme 5) as a single diastereoisomer.

At this stage, we were keen to see if we can make 3-unsubstituted isoindolinones with amines containing a nucleophilic substituent under reductive amination conditions. We were delighted to note that when MTM ester **12a** was treated with ethanolamine at room temperature followed by sodium triacetoxyborohydride, a clean reaction took place to give the 3-unsubstituted isoindolinone **1h** in good yield (Table 3, entry 1). Similarly, (*S*)-leucinol and (*S*)-phenylalaninol also gave the desired products **1i** and **1j**, respectively. Amines with another amino substituent such as ethylene diamine gave an interesting product **1k** due to reaction with two molecules of **12a** at 0 °C. The formation of the dimer **1k** even took place in the presence of excess of ethylene diamine. The optimized conditions were to use 2 equiv of MTM ester **12a** per diamine that gave **1k** in excellent yield (Table 3, entry 4). It is imperative to mention that for the ethylene diamine case, low temperature (0 °C) is critical. Above this, variable amount of **6a** formation was observed.

Table 3
Synthesis of 3-unsubstituted isoindolinones from MTM ester **12a** and amines containing a nucleophilic substituent[a]



Entry	Amine	Product	Temp[b] (°C)	Yield[c] (%)
1		 **1h**	28[d]	78[e]
2		 **1i**	28[f]	74[g]
3		 **1j**	28[f]	74[h]
4		 **1k**	0[d]	56[e,i]

[a] The reactions were carried out in chloroform.
[b] Temperature for the formation of the Schiff's base.
[c] Yield of the isolated product after chromatography/crystallization.
[d] Schiff's base formation time 15 min.
[e] Reduction time 2 h.
[f] Schiff's base formation time 0.5 h.
[g] Reduction time 3 h.
[h] Reduction time 4 h.
[i] Yield 94% when 2 equiv of MTM ester **12a** was used.

3. Conclusion

We have developed a new, mild, and efficient method for the synthesis of diversely substituted isoindolinones based on readily available precursors. The synthetic potential of this method is further demonstrated by the synthesis of 3-unsubstituted isoindolinones and fused tricyclic γ-lactams as single diastereoisomers in very good yield.

4. Experimental section

4.1. Materials and methods

All reactions were performed in oven-dried (120 °C) or flame-dried glass apparatus under dry N_2 or argon atmosphere. Solvents were obtained from commercial sources and purified further by distillation before use. Reagents were purchased from Aldrich/Fluka and used as such. The column chromatography was performed on silica gel (200–300 mesh). ^{1}H NMR and ^{13}C NMR spectra were recorded with Bruker 200/300 MHz spectrometers. ^{1}H–^{1}H NOESY spectra were recorded with Bruker 500 MHz spectrometer. Spectra were referenced to residual chloroform (δ 7.25 ppm, ^{1}H; 77.16 ppm, ^{13}C). High resolution mass spectra were recorded at with Bruker Daltonics Micro TOF-Q spectrometer (ESI, N_2). Melting points (mp) were determined on a LABINDIA melting range apparatus MR-VIS and are uncorrected. Optical rotations were taken relative to sucrose on Perkin Elmer 341 Polarimeter. Methyl 2-formyl-4,5-dimethoxybenzoate **12b** was prepared following the literature procedure.[23]

4.2. Methylthiomethyl-2-formyl-4,5-dimethoxybenzoate (12a)

A solution of DMSO (8.5 mL, 120.6 mmol) in dichloromethane (150 mL) was added drop-wise to a stirred solution of oxalyl chloride (7.2 mL, 83 mmol) in dichloromethane (150 mL) at −60 to −65 °C under nitrogen. After 5 min, solid 2-(hydroxymethyl)-4,5-dimethoxybenzoic acid[21] (8.0 g, 37.7 mmol) was added to the reaction mixture and stirring was continued for 15 min. Triethylamine (26.0 mL, 188.5 mmol) was added drop-wise to the reaction mixture and was allowed to attain room temperature. The reaction mixture was diluted with dichloromethane (250 mL), washed with water (100 mL) and with brine (75 mL). The organic extract was dried over anhydrous sodium sulfate and evaporated under reduced pressure. The residue was purified by silica gel column chromatography (10% EtOAc/hexane) to give **12a** (7.3 g, 72%) as solid. Mp 90–92 °C; δ_H (300 MHz, $CDCl_3$) 10.68 (1H, s, CHO), 7.53 (1H, s, Ar), 7.49 (1H, s, Ar), 5.46 (2H, s, –OC*H*$_2$SMe), 4.02 (3H, s, OMe), 4.01 (3H, s, OMe), 2.35 (3H, s, SMe); δ_C (75 MHz, $CDCl_3$) 191.0, 165.5, 152.4, 152.2, 131.4, 125.6, 112.6, 109.7, 69.8, 56.4, 56.3, 15.9; *m*/*z* (ESI): 271 $[M+H]^+$.

4.3. Methyl 2-formyl-4,5-dimethoxybenzoate (12b)

Solid 2-(hydroxymethyl)-4,5-dimethoxybenzoic acid[21] (0.5 g, 2.35 mmol) was added to a stirred suspension of pyridinium chlorochromate (PCC) (0.8 g, 3.7 mmol) in dichloromethane (10 mL) at room temperature. After 1 h, the reaction mixture was diluted with ether and the reaction mixture was passed through a Celite column. The eluent was evaporated to give the crude aldehydic acid (0.360 g, 73%) as an unstable material. Following the literature procedure,[23] a solution of this acid (0.360 g, 1.7 mmol) and iodomethane (0.2 mL, 3.2 mmol) in acetone (6 mL) was stirred over anhydrous potassium carbonate (0.71 g, 5.1 mmol) at room temperature over 3 h. The reaction mixture was filtered and the filtrate was evaporated under reduced pressure. The residue was dissolved in ether and washed with water. The organic extract was dried over anhydrous sodium sulfate and evaporated under reduced pressure. The residue was purified by silica gel column chromatography (10% EtOAc/hexane) to give **12b** (0.325 g, 85%; 62% overall) as solid. Mp 99–101 °C; δ_H (300 MHz, $CDCl_3$) 10.67 (1H, s), 7.53 (1H, s), 7.48 (1H, s), 4.02 (3H, s), 4.01 (3H, s), 3.99 (3H, s); δ_C (75 MHz, $CDCl_3$) 191.4, 166.5, 152.6, 152.2, 131.5, 126.2, 112.8, 109.8, 56.6, 56.5, 52.8; *m*/*z* (ESI): 247 $[M+Na]^+$.

4.4. General procedure I. Preparation of isoindolin-1-one (1a–1g)

In a typical procedure, the amine (2.4 mmol) was added to a solution of MTM ester **12a** (0.541 g, 2.0 mmol) in chloroform (25 mL) under N_2 atmosphere. Acetic acid (0.05 mL, 0.85 mmol) was added to the reaction mixture and stirred at 28 °C/40 °C for 0.5–2 h followed by addition of sodium triacetoxyborohyride (0.636 g, 3.0 mmol). After 0.5–6 h at 28 °C, the reaction mixture was quenched with water (25 mL) and extracted with chloroform (100 mL). The combined extract was washed with water (50 mL) and with brine (50 mL), dried (Na_2SO_4) and evaporated. The residue was purified by silica gel column chromatography (20% EtOAc/hexane)/crystallization to give pure **1a**–**1g**.

*4.4.1. 2-(3,4-Dimethoxyphenyl)-5,6-dimethoxyisoindolin-1-one (**1a**).* Yield: 0.59 g, 90%; R_f (50% EtOAc/hexane) 0.32; solid, mp 171–173 °C; δ_H (300 MHz, $CDCl_3$) 7.83 (1H, d, *J*=2.1 Hz, Ar), 7.35 (1H, s, Ar), 6.99 (1H, dd, *J*=2.1, 8.7 Hz, Ar), 6.96 (1H, s, Ar), 6.88 (1H, d, *J*=8.7 Hz, Ar), 4.74 (2H, s, NCH_2–), 3.97 (3H, s, OMe), 3.96 (3H, s, OMe), 3.94 (3H, s, OMe), 3.89 (3H, s, OMe); δ_C (75 MHz, $CDCl_3$) 167.8, 153.2, 150.1, 149.3, 146.0, 133.9, 133.6, 125.7, 111.4, 111.0, 105.5, 104.8 (2C), 56.4, 56.4, 56.2, 56.1, 51.0; HRMS (ESI): MH^+, found 330.1311. $C_{18}H_{20}NO_5$ requires 330.1336.

This compound was also prepared from **12b** and 3,4-dimethoxyaniline as follows. 3,4-Dimethoxyaniline (0.368 g, 2.4 mmol) was added to a solution of methyl ester **12b** (0.448 g, 2.0 mmol) in chloroform (25 mL) under N_2 atmosphere. Acetic acid (0.05 mL, 0.85 mmol) was added to the reaction mixture and stirred at 28 °C for 0.5 h followed by addition of sodium triacetoxyborohyride (0.636 g, 3.0 mmol). After 6 h at 28 °C, the reaction mixture was quenched with water (25 mL) and extracted with chloroform (100 mL). The combined extract was washed with water (50 mL) and with brine (50 mL), dried (Na_2SO_4) and evaporated. The residue was purified by silica gel column chromatography (20% EtOAc/hexane) to give pure **1a** (0.515 g, 78%).

*4.4.2. 4-(5,6-Dimethoxy-1-oxoisoindolin-2-yl)benzonitrile (**1b**).* Yield: 0.464 g, 79%; R_f (50% EtOAc/hexane) 0.35; solid, mp 238–239 °C; δ_H (300 MHz, $CDCl_3$) 8.00 (2H, d, *J*=8.7 Hz, Ar), 7.68 (2H, d, *J*=8.7 Hz, Ar), 7.34 (1H, s, Ar), 6.97 (1H, s, Ar), 4.77 (2H, s, NCH_2–), 3.96 (3H, s, OMe), 3.98 (3H, s, OMe); δ_C (75 MHz, $CDCl_3$) 168.4, 154.2, 150.4, 143.7, 133.9, 133.5 (2C), 124.8, 119.1, 118.3 (2C), 106.6, 105.7, 104.7, 56.5, 50.0, 29.8; HRMS (ESI): MH^+, found 295.1082. $C_{17}H_{15}N_2O_3$ requires 295.1077.

*4.4.3. 2-(4-Acetylphenyl)-5,6-dimethoxyisoindolinon-1-one (**1c**).* Yield: 0.545 g, 88%; R_f (2% MeOH/$CHCl_3$) 0.35; solid, mp 245–247 °C; δ_H (300 MHz, $CDCl_3$) 7.94–8.02 (4H, m, Ar), 7.33 (1H, s, Ar), 6.96 (1H, s, Ar), 4.78 (2H, s, NCH_2–), 3.98 (3H, s, OMe), 3.96 (3H, s, OMe), 2.59 (3H, s, MeCO); δ_C (75 MHz, $CDCl_3$) 197.1, 168.2, 153.9, 150.3, 144.1, 134.0, 132.4, 129.9 (2C), 125.1, 117.8 (2C), 105.6, 104.7, 56.5, 56.4, 50.2, 26.6; HRMS (ESI): MH^+, found 312.1225. $C_{18}H_{18}NO_4$ requires 312.1230.

*4.4.4. 4-(5,6-Dimethoxy-1-oxoisoindolin-2-yl) benzoic acid (**1d**).* Yield: 0.601 g, 96%; R_f (5% MeOH/$CHCl_3$) 0.21; solid, mp 315–318 °C (decomp.); δ_H (300 MHz, $CDCl_3$) 12.77 (1H, s, CO_2H), 7.94–8.02 (4H,

m, Ar), 7.23 (1H, s, Ar), 7.22 (1H, s, Ar), 4.92 (2H, s, NCH_2–), 3.87 (3H, s, OMe), 3.83 (3H, s, OMe); δ_C (75 MHz, $CDCl_3$) 167.9, 167.5, 153.98, 150.2, 144.2, 135.5, 131.0 (2C), 125.8, 124.4, 118.3 (2C), 106.3, 105.6, 56.7, 56.4, 50.4; HRMS (ESI): MH^+, found 314.1032. $C_{17}H_{16}NO_5$ requires 314.1023.

*4.4.5. 2-(3-Chloro-4-methylphenyl)-5,6-dimethoxyisoindolin-1-one (**1e**).* Yield: 0.541 g, 85%; R_f (50% EtOAc/hexane) 0.23; Solid, mp 212–214 °C; δ_H (300 MHz, $CDCl_3$) 7.81 (1H, d, J=2.1 Hz, Ar), 7.67 (1H, dd, J=2.1, 8.4 Hz, Ar), 7.32 (1H, s, Ar), 7.23 (1H, d, J=8.4 Hz, Ar), 6.94 (1H, s, Ar), 4.69 (2H, s, NCH_2–), 3.97 (3H, s, OMe), 3.95 (3H, s, OMe), 2.35 (3H, s, Me); δ_C (75 MHz, $CDCl_3$) 167.8, 153.5, 150.2, 138.7, 134.8, 133.9, 131.6, 131.3, 125.3, 119.5, 117.4, 105.6, 104.7, 56.4 (2C), 50.4, 19.6; HRMS (ESI): MH^+, found 318.0873. $C_{17}H_{17}ClNO_3$ requires 318.0891.

*4.4.6. 2-Cyclohexyl-5,6-dimethoxyisoindolin-1-one (**1f**).* Yield: 0.487 g, 88%; R_f (50% EtOAc/hexane) 0.14; Solid, mp 136–138 °C; δ_H (300 MHz, $CDCl_3$) 7.31 (1H, s, Ar), 6.91 (1H, s, Ar), 4.26 (2H, s, NCH_2-), 4.17–4.21 (1H, m, NCH), 3.93 (6H, s, 2×OMe), 1.84–1.86 (4H, m, cyclohexyl), 1.67–1.74 (1H, m, cyclohexyl), 1.38–1.53 (4H, m, cyclohexyl), 1.16–1.21 (1H, m, cyclohexyl); δ_C (75 MHz, $CDCl_3$) 167.7, 151.8, 149.1, 134.3, 125.2, 104.8, 104.5, 55.8 (2C), 50.1, 45.2, 31.1 (2C), 25.2 (3C); HRMS (ESI): MH^+, found 276.1611. $C_{16}H_{22}NO_3$ requires 276.1594.

*4.4.7. (S)-Methyl-2-(5,6-dimethoxy-1-oxoindolin-2-yl)-3-phenylpropanoate (**1g**).* Yield: 0.53 g, 75%; R_f (50% EtOAc/hexane) 0.34; Solid, mp 138–139 °C; $[\alpha]_D^{20}$ −72.17 (*c* 2.3, $CHCl_3$); δ_H (300 MHz, $CDCl_3$) 7.35 (1H, s, Ar), 7.22–7.14 (5H, m, Ph), 6.86 (1H, s, Ar), 5.36 (1H, dd, J=5.7, 10.5 Hz, $PhCH_2CH$), 4.42 (1H, d, J=16.2 Hz, NCH_aH_b), 4.26 (1H, d, J=16.2 Hz, NCH_aH_b), 3.91 (3H, s, OMe), 3.90 (3H, s, OMe), 3.71 (3H, s, CO_2Me), 3.47 (1H, dd, J=5.7, 14.7 Hz, $PhCH_aH_b$), 3.17 (1H, dd, J=10.5, 14.7 Hz, $PhCH_aH_b$); δ_C (75 MHz, $CDCl_3$) 171.1, 168.8, 152.3, 149.2, 136.0, 134.9, 128.2 (2C), 128.1 (2C), 126.5, 123.6, 105.0, 104.5, 55.7 (2C), 54.2, 51.9, 46.8, 35.4; HRMS (ESI): MH^+, found 356.1478. $C_{20}H_{22}NO_5$ requires 356.1492.

4.5. General procedure II. Preparation of 3-substituted isoindolinones (5a and 5b)

In a typical procedure, the required amine (2.4 mmol) was added to a solution of MTM ester **12a** (0.541 g, 2.0 mmol) in chloroform (25 mL) under N_2 atmosphere. Acetic acid (0.05 mL, 0.85 mmol) was added to the reaction mixture and stirred at 40 °C for 1–3 h followed by addition of the required thiol (3.0 mmol). After 6 h at 40 °C, the reaction mixture was quenched with water (25 mL) and extracted with chloroform (100 mL). The combined extract was washed with water (50 mL) and with brine (50 mL), dried (Na_2SO_4), and evaporated. The residue was purified by silica gel column chromatography (EtOAc/hexane) to give pure **5a** and **5b**.

*4.5.1. 2-(3-Chloro-4-methyl-phenyl)-3-(2-hydroxy-phenylsulfanyl)-5,6-dimethoxy-2,3-dihydro-isoindol-1-one (**5a**).* Yield: 0.601 g, 68%; R_f (5% MeOH/$CHCl_3$) 0.45; solid, mp 169–171 °C; δ_H (300 MHz, $CDCl_3$) 7.62 (1H, d, J=1.5 Hz, Ar), 7.47 (1H, dd, J=1.5, 8.4 Hz, Ar), 7.31 (1H, d, J=8.4 Hz, Ar), 7.15 (1H, d, J=7.8 Hz, Ar), 7.13 (1H, s, Ar), 7.06 (1H, s, Ar), 6.84 (1H, d, J=7.5 Hz, Ar), 6.75 (1H, d, J=8.1 Hz, Ar), 6.62 (1H, t, J=7.5 Hz, Ar), 6.15 (1H, s, OH), 6.03 (1H, s, S*CH*N), 4.00 (3H, s, OMe), 3.89 (3H, s, OMe), 2.40 (3H, s, Me); δ_C (75 MHz, $CDCl_3$) 166.4, 157.8, 153.6, 150.8, 136.7, 135.4, 135.3, 134.8, 133.3, 132.6, 131.3, 124.0, 123.2, 121.1, 120.6, 115.3, 112.3, 105.3, 105.1, 66.7, 56.6, 56.4, 19.8; HRMS (ESI): MH^+, found 442.0846. $C_{23}H_{21}ClNO_4S$ requires 442.0874.

*4.5.2. 4-[1-(2-Hydroxy-phenylsulfanyl)-5,6-dimethoxy-3-oxo-1,3-dihydro-isoindol-2-yl]-benzonitrile (**5b**).* Yield: 0.544 g, 65%; R_f (5% MeOH/$CHCl_3$) 0.48; solid, mp 192–197 °C; δ_H (300 MHz, $CDCl_3$): 7.87 (2H, d, J=8.4 Hz, Ar), 7.75 (2H, d, J=8.4 Hz, Ar), 7.16 (1H, t, J=7.5 Hz, Ar), 7.12 (1H, s, Ar), 7.09 (1H, s, Ar), 6.75–6.71 (2H, m, Ar), 6.61 (1H, t, J=7.5 Hz, Ar), 6.23 (1H, s, OH), 5.89 (1H, s, SCHN), 4.03 (3H, s, OMe), 3.91 (3H, s, oMe); δ_C (75 MHz, $CDCl_3$) 166.6, 157.9, 154.2, 151.1, 140.8, 136.7, 135.4, 133.2 (2C), 132.9, 123.5, 121.7 (2C), 120.7, 118.9, 115.4, 111.5, 108.0, 105.1 (2C), 65.7, 56.7, 56.5; HRMS (ESI): MH^+, found 419.1019. $C_{23}H_{19}N_2O_4S$ requires 419.1060.

*4.5.3. 2-(3,4-Dimethoxybenzyl)-5,6-dimethoxy-3-oxoisoindoline-1-carbonitrile (**5c**).* 3,4-Dimethoxy benzylamine (0.198 g, 1.2 mmol) was added to a solution of MTM ester **12a** (0.27 g, 1.0 mmol) in chloroform (10 mL) under N_2 atmosphere. Acetic acid (25 μL, 0.42 mmol) was added to the reaction mixture and stirred at 28 °C for 1 h. The reaction mixture was concentrated under reduced pressure and a solution of NaCN (0.059 g, 1.2 mmol) in 1/1 THF/H_2O (30 mL) was added into it. After 3 h at 60 °C, THF was evaporated under reduced pressure and the reaction mixture was quenched with dil HCl (0.3 M, 10 mL). The mixture was extracted with chloroform (150 mL) and the extract was washed with water (50 mL) and with brine (50 mL), dried (Na_2SO_4), and evaporated. The residue was purified by silica gel column chromatography (40% EtOAc/hexane) to give pure **5c** (0.265 g, 72%) as solid; R_f (5% MeOH/$CHCl_3$) 0.51; mp 127–129 °C; δ_H (300 MHz, $CDCl_3$) 7.32 (1H, s, Ar), 7.28 (1H, s, Ar), 6.92 (2H, d, J=8.1 Hz, Ar), 6.82 (1H, dd, J=1.8, 8.1 Hz, Ar), 5.65 (1H, s, CHCN), 4.89 (1H, d, J=15.0 Hz, $ArCH_aH_b$), 4.44 (1H, d, J=15.3 Hz, $ArCH_aH_b$), 3.90 (3H, s, OMe), 3.85 (3H, s, OMe), 3.72 (3H, s, OMe), 3.71 (3H, s, OMe); δ_C (75 MHz, $CDCl_3$) 166.9, 153.3, 150.8, 148.9, 148.5, 131.2, 128.5, 122.7, 120.4, 116.3, 111.9 (2C), 106.1, 105.4, 56.2, 56.0, 55.5, 55.5, 49.1, 44.8; HRMS (ESI): MNa^+, found 391.1247. $C_{20}H_{20}N_2O_5Na$ requires 391.1264.

4.6. General procedure III. Preparation of tricyclic γ-lactams (6a–6e)

In a typical procedure, the required nucleophile attached amine (2.4 mmol) was added to a solution of MTM ester **12a** (0.541 g, 2.0 mmol) in chloroform (25 mL) under N_2 atmosphere. Acetic acid (0.05 mL, 0.85 mmol) was added to the reaction mixture and stirred at 0–28 °C for 1–3 h. In the case of (*S*)-leucinol and (*S*)-phenylalaninol, the reaction mixture was refluxed at 60 °C for 4–5 h. The reaction mixture was quenched with water (25 mL) and extracted with chloroform (100 mL). The combined extract was washed with water (50 mL) and with brine (50 mL), dried (Na_2SO_4), and evaporated. The residue was purified by silica gel column chromatography (EtOAc/hexane) to give pure **6a–6e**.

*4.6.1. 7,8-Dimethoxy-[1,2,3,9b]-tetrahydro-imidazo-[2,1-a]-isoindol-5-one (**6a**).* Yield: 0.44 g, 94%; R_f (5% MeOH/$CHCl_3$) 0.23; solid, mp 212–217 °C; δ_H (300 MHz, $CDCl_3$) 7.24 (1H, s, Ar), 7.08 (1H, s, Ar), 5.24 (1H, s, NCHN), 3.95 (3H, s, OMe), 3.93 (3H, s, OMe), 3.72–3.62 (1H, m, NCH_aH_b), 3.59–3.54 (1H, m, NCH_aH_b), 3.51–3.42 (1H, m, $NHCH_aH_b$), 3.34–3.28 (1H, m, $NHCH_aH_b$), 2.16 (1H, s, NH); δ_C (75 MHz, $CDCl_3$) 166.1, 146.0, 143.9, 129.9, 119.1, 98.7, 98.6, 71.9, 49.2 (2C), 44.4, 35.8; HRMS (ESI): MH^+, found 235.1089. $C_{12}H_{15}N_2O_3$ requires 235.1077.

*4.6.2. 7,8-Dimethoxy-2,3-dihydrothiazolo[2,3-a]isoindol-5(9bH)-one (**6b**).* Yield: 0.462 g, 92%; R_f (50%EtOAc/hexane) 0.20; solid, mp 123–128 °C; δ_H (300 MHz, DMSO-d_6) 7.26 (1H, s, Ar), 7.16 (1H, s, Ar), 5.92 (1H, s, SCHN), 4.17–4.09 (1H, m, NCH_aH_b), 3.85 (3H, s, OMe), 3.83 (3H, s, OMe), 3.44–3.33 (3H, m, NCH_2, NCH_aH_b); δ_C (75 MHz, DMSO-d_6) 171.2, 153.6, 150.6, 139.9, 122.8, 107.0, 105.8, 66.1, 56.5,

56.3, 44.9, 36.5; HRMS (ESI): MH^+, found 252.0689. $C_{12}H_{14}NO_3S$ requires 252.0689.

*4.6.3. (3R)-Ethyl 7,8-dimethoxy-5-oxo-[2,3,5,9b]-tetrahydrothiazolo-[2,3-a]-isoindole-3-carboxylate (**6c**).* Yield: 0.51 g, 79%; R_f (50% EtOAc/hexane) 0.26; Thick gum; $[\alpha]_D^{27}$ −259.1 (*c* 1.02, $CHCl_3$); δ_H (300 MHz, $CDCl_3$) 7.28 (1H, s, Ar), 6.95 (1H, s, Ar), 6.03 (1H, s, SCHN), 5.23 (1H, dd, *J*=4.5, 6.9 Hz, NCHCO), 4.33 (1H, dd, *J*=1.5, 7.2 Hz, SCH_aH_b), 4.28 (1H, dd, *J*=1.5, 7.2 Hz, SCH_aH_b), 3.99 (3H, s, OMe), 3.95 (3H, s, OMe), 3.62 (2H, q, *J*=7.2 Hz, CO_2CH_2Me), 1.33 (3H, t, *J*=7.2 Hz, CO_2CH_2Me); δ_C (75 MHz, $CDCl_3$) 171.2, 170.3, 154.0, 150.8, 139.5, 122.7, 106.0, 105.3, 66.4, 62.2, 58.1, 56.5, 56.4, 39.7, 14.3; HRMS (ESI): MNa^+, found 346.0715. $C_{15}H_{17}NO_5SNa$ requires 346.0720.

*4.6.4. (3S)-3-Isobutyl-7,8-dimethoxy-2,3-dihydro-9bH-oxazolo[2,3-a]isoindol-5-one (**6d**).* Yield: 0.5 g, 86%; R_f (50% EtOAc/hexane) 0.32; solid, mp 102–104.5 °C; $[\alpha]_D^{24}$ +63.5 (*c* 0.95, $CHCl_3$); δ_H (300 MHz, $CDCl_3$) 7.23 (1H, s, Ar), 7.07 (1H, s, Ar), 5.81 (1H, s, OCHN), 4.45 (1H, dd, *J*=6.9, 8.4 Hz, OCH_aCH_b), 4.21–4.16 (1H, m, NCH), 3.97 (3H, s, OMe), 3.95 (3H, s, OMe), 3.84 (1H, dd, *J*=6.3, 8.4 Hz, OCH_aCH_b), 1.89–1.84 (1H, m, Me_2CH), 1.74–1.65 (1H, m, $NCHCH_aCH_b$), 1.42–1.33 (1H, m, $NCHCH_aCH_b$), 1.08 (3H, d, *J*=6.3 Hz, *Me*CH), 1.01 (3H, d, *J*=6.6 Hz, *Me*CH); δ_C (75 MHz, $CDCl_3$) 174.7, 153.9, 151.8, 136.8, 126.0, 106.3, 106.2, 90.8, 56.8, 56.8, 54.1 (2C), 44.1, 26.2, 23.6, 22.7; HRMS (ESI): MNa^+, found 314.1354. $C_{16}H_{20}NO_4$ Na requires 314.1363.

*4.6.5. (3S)-3-Benzyl-7,8-dimethoxy-2,3-dihydro-9bH-oxazolo[2,3-a]isoindol-5-one (**6e**).* Yield: 0.522 g, 80%; R_f (50% EtOAc/hexane) 0.31; solid, mp 184–186 °C; $[\alpha]_D^{23}$ +61.8 (*c* 1.03, $CHCl_3$); δ_H (300 MHz, $CDCl_3$) 7.36–7.27 (5H, m, Ph), 7.25 (1H, s, Ar),7.05 (1H, s, Ar), 5.72 (1H, s, OCHN), 4.49–4.41 (1H, m, NCH), 4.31 (1H, dd, *J*=6.9, 8.7 Hz, OCH_aH_b), 4.00 (1H, dd, *J*=6.0, 8.7 Hz, OCH_aH_b), 3.97 (3H, s, OMe), 3.95 (3H, s, OMe), 3.20 (1H, dd, *J*=5.4, 13.8 Hz, $PhCH_aH_b$), 2.98 (1H, dd, *J*=8.1, 13.8 Hz, $PhCH_aH_b$); δ_C (75 MHz, $CDCl_3$): 174.7, 154.0, 151.8, 137.5, 137.0, 130.0 (2C), 129.1 (2C), 127.3, 125.9, 106.3, 106.2, 91.3, 75.4, 56.8 (2C), 56.0, 40.3; HRMS (ESI): MNa^+, found 348.1213. $C_{19}H_{19}NO_4$ Na requires 348.1206.

4.7. General procedure IV. Preparation of isoindolin-1-one (1h–1k)

In a typical procedure, the amine (2.4 mmol) was added to a solution of MTM ester **12a** (0.541 g, 2.0 mmol) in chloroform (25 mL) under N_2 atmosphere. Acetic acid (0.05 mL, 0.85 mmol) was added to the reaction mixture and stirred at 0–28 °C for 15–30 min followed by addition of sodium triacetoxyborohyride (0.636 g, 3.0 mmol). After 2–4 h at room temperature, the reaction mixture was quenched with water (25 mL) and extracted with chloroform (100 mL). The combined extract was washed with water (50 mL) and with brine (50 mL), dried (Na_2SO_4), and evaporated. The residue was purified by silica gel column chromatography (10% EtOAc/hexane) to give pure **1h**–**1k**.

*4.7.1. 2-(2-Hydroxyethyl)-5,6-dimethoxyisoindolin-1-one (**1h**).* Yield: 0.37 g, 78%; R_f (50% EtOAc/hexane) 0.21; solid, mp 147–152 °C; δ_H (300 MHz, $CDCl_3$) 7.32 (1H, s, Ar), 6.92 (1H, s, Ar), 4.44 (2H, s, $ArCH_2N$), 3.96 (3H, s, OMe), 3.95 (3H, s, OMe), 3.92 (2H, t, *J*=4.8 Hz, CH_2OH), 3.77 (2H, t, *J*=4.8 Hz, CH_2CH_2N), 3.21 (1H, br s, OH); δ_C (75 MHz, $CDCl_3$) 169.6, 152.1, 149.2, 134.6, 124.3, 104.7, 104.4, 61.4, 55.7 (2C), 51.0, 45.9; HRMS (ESI): MH^+, found 238.1080. $C_{12}H_{16}NO_4$ requires 238.1074.

*4.7.2. (S)-2-(1-Hydroxy-4-methylpentan-2-yl)-5,6-dimethoxyisoindolin-1-one (**1i**).* Yield: 0.435 g, 74%; R_f (5% MeOH/$CHCl_3$) 0.28; solid, mp 135–138 °C; $[\alpha]_D^{20}$ −18.2 (*c* 2.0, $CHCl_3$); δ_H (300 MHz, $CDCl_3$) 7.28 (1H, s, Ar), 6.89 (1H, s, Ar), 4.44–4.40 (1H, m, NCH), 4.37 (1H, d, *J*=16.8 Hz, $ArCH_aH_bN$), 4.24 (1H, d, *J*=16.8 Hz, $ArCH_aH_bN$), 3.93 (3H, s, OMe), 3.92 (3H, s, OMe), 3.83 (1H, dd, *J*=3.9, 11.4 Hz, CH_aH_bOH), 3.75–3.68 (1H, dd, *J*=3.9, 11.4 Hz, CH_aH_bOH), 2.86 (1H, s, OH), 1.60–1.69 (1H, m, Me_2CH), 1.40–1.57 (2H, m, Me_2CHCH_2), 0.96 (3H, d, *J*=6.0 Hz, *Me*CH), 0.92 (3H, d, *J*=6.3 Hz, *Me*CH); δ_C (75 MHz, $CDCl_3$) 170.2, 152.6, 149.7, 135.1, 125.1, 105.4, 105.0, 64.8, 56.3 (2C), 52.7, 47.0, 38.2, 25.0, 23.4, 22.2; HRMS (ESI): MH^+, found 294.1711. $C_{16}H_{24}NO_4$ requires 294.1700.

*4.7.3. (S)-2-(1-Hydroxy-3-phenylpropan-2-yl)-5,6-dimethoxyisoindolin-1-one (**1j**).* Yield: 0.485 g, 74%; R_f (5% MeOH/$CHCl_3$) 0.30; solid, mp 163–165 °C; $[\alpha]_D^{20}$ −113.4 (*c* 2.0, $CHCl_3$); δ_H (300 MHz, $CDCl_3$) 7.23–7.13 (5H, m, Ph), 7.11 (1H, s, Ar), 7.06 (1H, s, Ar), 4.90 (1H, t, *J*=5.4 Hz, OH), 4.49–4.39 (1H, m, NCH), 4.32 (1H, d, *J*=17.4 Hz, $ArCH_aH_bN$), 4.23 (1H, d, *J*=17.4 Hz, $ArCH_aH_bN$), 3.79 (3H, s, OMe), 3.76 (3H, s, OMe), 3.66–3.56 (2H, m, CH_2OH), 3.01–2.83 (2H, m, $PhCH_2$); δ_C (75 MHz, $CDCl_3$) 167.8, 152.0, 149.1, 138.7, 135.3, 128.7 (2C), 128.2 (2C), 126.1, 124.5, 106.0, 104.7, 62.0, 55.8, 55.7, 54.4, 46.4, 34.9; HRMS (ESI): MH^+, found 328.1524. $C_{19}H_{22}NO_4$ requires 328.1543.

*4.7.4. 2,2′-(Ethane-1,2-diyl)bis(5,6-dimethoxyisoindolin-1-one) (**1k**).* Yield: 0.231 g, 56%; R_f (5% MeOH/$CHCl_3$) 0.25; solid, mp 265.5–273 °C; δ_H (300 MHz, $CDCl_3$) 7.19 (2H, s, Ar), 6.92 (2H, s, Ar), 4.44 (4H, s, $ArCH_2N$), 3.94 (4H, s, CCH_2CH_2N), 3.92 (6H, s, 2×OMe), 3.89 (6H, s, 2×OMe); δ_C (75 MHz, $CDCl_3$) 168.8 (2C), 152.1 (2C), 149.1 (2C), 134.6 (2C), 123.9 (2C), 104.7 (4C), 55.7 (4C), 49.1 (2C), 39.9 (2C); HRMS (ESI): MH^+, found 413.1723. $C_{22}H_{25}N_2O_6$ requires 413.1707. This compound was also prepared using 2 equiv of MTM ester **12a** as follows. Ethylenediamine (125 μL, 2 mmol) was added to a solution of MTM ester **12a** (1.08 g, 4.0 mmol) in chloroform (40 mL) under N_2 atmosphere. Acetic acid (0.1 mL, 1.7 mmol) was added to the reaction mixture and stirred at 0 °C for 30 min followed by addition of sodium triacetoxyborohyride (1.28 g, 6.0 mmol). After 2 h at room temperature, the reaction mixture was quenched with water (25 mL) and extracted with chloroform (150 mL). The combined extract was washed with water (50 mL) and with brine (50 mL), dried (Na_2SO_4), and evaporated. The residue was purified by silica gel column chromatography (30% EtOAc/hexane) to give pure **1k** (0.775 g, 94%).

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Supplementary data

Copies of ^1H and ^{13}C of all new products, 2D-NOESY of **6d**, **6e**, and the study of the rate of formation of **1a** from **12a**/**12b** by ^1H NMR are provided. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2010.01.070.

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