A Concise and Flexible Diastereoselective Approach to Heteroring-Fused Isoindolinones

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Abstract: A variety of poly and diversely substituted isoindolinones fused with six-membered heterocyclic moieties has been readily assembled through a sequence involving metalation of N-chloroalkylated models, subsequent interception with appropriate electrophiles and ultimate intramolecular annulation reaction.

Key words: carbanions, fused-ring systems, lactams, metalation, cyclization

The isoindolinone ring system, which represents a conformationally constrained variant of the benzamide nucleus, is a ubiquitous structural feature of numerous naturally occurring alkaloids, and can be frequently recognized in the framework of structurally sophisticated drug candidates.[1] The benzolactam nucleus may serve as a linker for a variety of pharmacophores[2] and structural variations that act on the pharmacological profile of the models can be classified into two main categories. In most cases, bioactive isoindolinone-centered compounds naturally comprise a benzolactam unit with appropriate functionalities attached to the lactam nitrogen.[3] Alternatively, the isoindolinone ring can be fused with constitutionally diverse heterocyclic moieties, and this class of compounds has recently attracted considerable attention due to their profound physiological and chemotherapeutic properties.[4] The representative compounds **1**–**4** fall into this class of compounds (Figure 1). Thus, the tricyclic γ-lactams **1**, with heteroatomic substituents at the 3-position, have been studied as selective non-nucleosidic HIV reverse transcriptase inhibitors,[5] and **2** has also been shown to have a promising antibacterial activity.[6] The amino-derivative **3** was recently reported to be a potent and selective 5-HT_{2C} agonist as antiobesity agent,[7] and compound **4** was recently tested as a cognition modulator.[8] Consequently, interest in designing efficient synthetic procedures for the assembly of structurally and constitutionally diverse isoindolinone-centered models is an area of current investigation.[9] Organic chemists have at their disposal a great number of synthetic methods for the preparation of substituted isoindolinones,[10] but few flexible and general methods are available for the construction of highly heterofused models with structural variability.[4] In this regard, we have aimed to develop new and convergent approaches to rapidly achieve molecular complexity in a highly efficient manner. We have assumed that the presence of heteroatoms in the cyclic moieties embedded in the compact molecular framework could retain the bioactivity of the models and lead to a new generation of SAR studies.

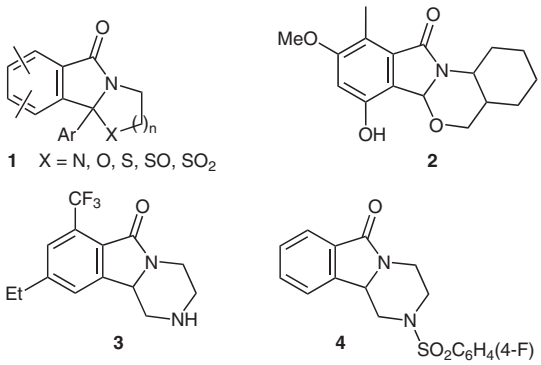

Figure 1 Bioactive isoindolinone-centered compounds

The present work originated from the following premises: (i) isoindolinones with hydroxyalkyl chains that may serve as a handle for further synthetic planning tethered on the lactam nitrogen, can be readily accessed through anionic cyclization of N-bromobenzylated carbamates;[11] (ii) isoindolinones have been successfully metalated at the benzylic position of the heteroring system thus allowing the connection of a range of electrophiles at the 3-position of the lactam ring.[12] Consequently, one could envisage triggering an intramolecular cyclization process by chemical manipulation of appropriate appendages connected to the lactam unit, which would give rise to tailor-made, architecturally diverse fused models.

The first facet of the synthesis was the elaboration of the N-hydroxylated isoindolinones **5a–d**. These parent compounds were readily obtained by capture of the lithiated species **6**, which were derived from the parent carbamates **7a–d** with an oxazolidinone (n = 1) acting as an internal electrophile. This technique provided the potential for direct construction of the isoindolinone template with concomitant connection of the required hydroxyalkyl appendage, thereby providing the N-functionalized models **5a–d** (Scheme 1).[11a]

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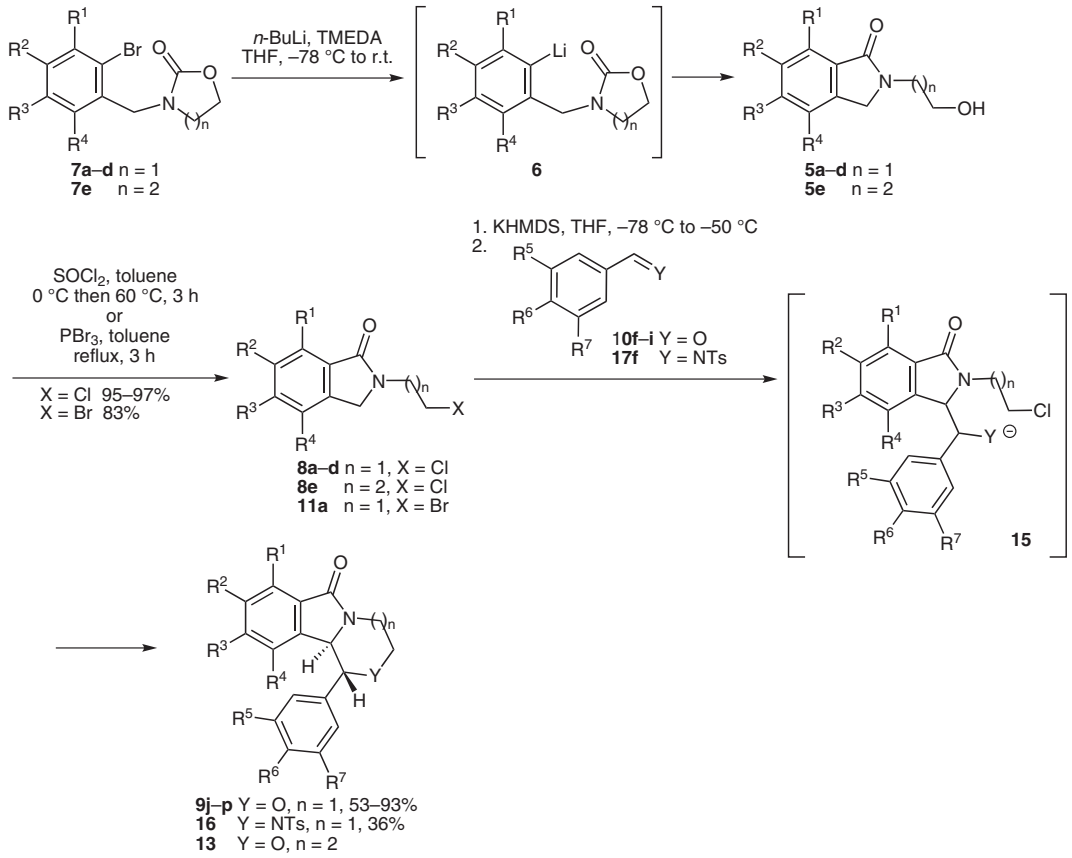

Scheme 1 Synthesis of fused isoindolinones

The next step was the conversion of the hydroxyalkyl tethered compounds **5a–d** into the corresponding chlorinated derivatives **8a–d**. This operation was readily and efficiently secured by treatment of **5a–d** with thionyl chloride (Scheme 1, Table 1, Table 2). With compounds **8a–d** in hand we were actually one step away from the target fused compounds **9j–p** since we envisioned that the subsequent third and fourth phases of the synthesis could be performed as a one-pot reaction. Compounds **8a–d** were smoothly deprotonated with potassium hexamethyldisylazide (KHMDS) at –78 °C and subsequently quenched with an array of unsaturated compounds **10f–h**

Table 1 Compounds **8a–e**, **9j–p**, **16** and **14** Prepared

Starting material													Fused isoindolinones
N-Chloroalkylisoindolinone **8**							Benzaldehyde **10** or benzaldimine **17**						**9**, **16**, **14**
	R^1	R^2	R^3	R^4	n	Yield (%)		R^5	R^6	R^7	Y		Yield (%)
8a	H	H	OMe	OMe	1	95	**10f**	H	H	H	O	**9j**	62
8b	OMe	OMe	H	H	1	93	**10f**	H	H	H	O	**9k**	64
8c	OMe	OMe	OMe	H	1	97	**10f**	H	H	H	O	**9l**	93
8c	OMe	OMe	OMe	H	1		**10g**	H	$MeSO_2$	H	O	**9m**	59
8d	H	OMe	OBn	H	1	97	**10h**	OMe	OMe	OMe	O	**9n**	56
8d	H	OMe	OBn	H	1		**10g**	H	$MeSO_2$	H	O	**9o**	53
	H	OMe	OH	H	1			H	$MeSO_2$	H	O	**9p**	58[a]
8a	H	H	OMe	OMe	1		**17f**	H	H	H	NTs	**16**	36
8e	H	OMe	OMe	H	2	83	**10i**	H	OMe	H	O	**14**	68[b]

[a] Compound **9p** was prepared by deprotection of the benzylated analogue **9o**.
[b] Primary adduct of condensation of anisaldehyde with lithiated isoindolinone; 50:50 mixture of diastereomers.

at –50 °C. Warming to 0 °C was followed by acidic aqueous work-up and, gratifyingly, conducting the reaction according to this procedure led to the complete consumption of the starting material and smoothly afforded the tricyclic lactams **9j–p** (Scheme 1, Table 1, Table 2).

It is worth mentioning that the decision to use chlorinated compounds was rewarded here. Indeed, we observed that treatment of the brominated analogue **11a** under the conditions described above did not lead to the target annulated compounds but led instead to the E2 elimination product **12** (Figure 2).

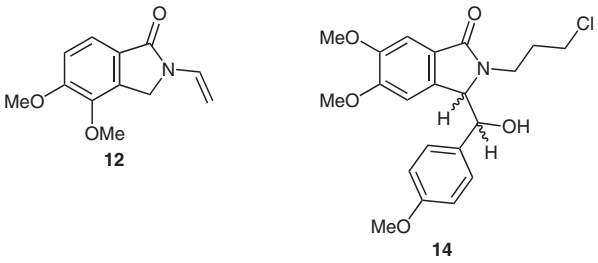

Figure 2 Unexpected products from the synthetic process

A representative series of compounds that have been prepared by this technique are presented in Table 1. It can be seen that this simple procedure affords very satisfactory yields of the previously unattainable benzo-fused lactams **9j–p**. The reaction conditions were found to be compatible with a broad range of substitution patterns within the environmentally diverse aromatic units.

Interestingly, the six-membered models **9j–p** were exclusively obtained as the *trans*-stereoisomers. To establish the stereochemistry at the 2-C and 19-C positions of the fused compounds **9j–p**, X-ray crystallographic analysis of **9j** was performed. The ORTEP view (Figure 3) provides direct evidence of the *trans*-configuration of these benzylic positions.

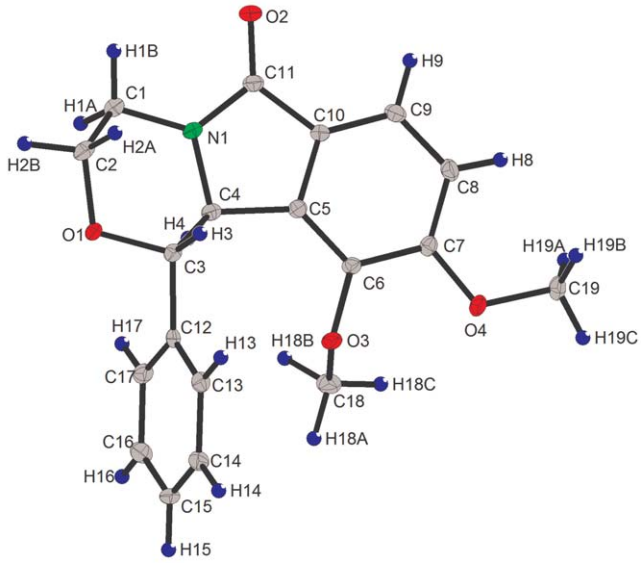

Figure 3 ORTEP view of the X-ray crystal structure of **9j**[13]

Unfortunately all attempts to synthesize the seven-membered analogues **13** by the same synthetic approach failed. Initially, exposure of **7e** (n = 2) to *n*-BuLi led efficiently to the hydroxyalkylated isoindolinones **5e**, and chlorination proceeded uneventfully to provide the halogenated compound **8e**. However, deprotonation of **8e** with KHMDS and interception of the transient lithiated species with *p*-anisaldehyde **10i** followed by standard work-up delivered exclusively the adduct **14** (Figure 2, Table 1, Table 2) as an equimolecular mixture of easily separable *erythro* and *threo* isomers. In order to force the annulation reaction of the primary adduct **14** and thus gain access to compounds that are structurally related to **12** through the intermediacy of **15**, variation of the solvent (THF, DMF), base (NaH, KH), temperature profile, and inclusion of anion modifiers (TMEDA, crown ether) were all assessed. Disappointingly, none of these operations met with success. However, the method did allow the assembly of oxygen- and nitrogen-containing, highly fused models, as exemplified by the synthesis of the piperazine-containing model **16** upon exposure of metalated isoindolinone **8b** to tosylimine **17f** (Scheme 1, Table 1, Table 2).

In summary, we have developed a rapid and convergent method with which to construct a variety of fused ring isoindolinones without the need for isolation and purification of the key intermediates. The notable advantages of this method are operational simplicity, mild reaction conditions, and ease of isolation of products, which display large molecular diversity and contain functional group characteristics of all the precursors. The flexible protocol developed in the present study paves the way for the construction of related isoindolinone derivatives for further biological studies.

Tetrahydrofuran (THF) was pre-dried with anhydrous Na_2SO_4 and distilled over sodium benzophenone ketyl under Ar before use. Toluene was distilled from CaH_2. Dry glassware was obtained by oven-drying and assembly under anhydrous Ar. The glassware was equipped with rubber septa and reagent transfer was performed using syringe techniques. For flash chromatography, Merck silica gel 60 (40–63 μm; 230–400 mesh ASTM) was used. Melting points were obtained with a Reichert–Thermopan apparatus and are not corrected. Elemental analyses were obtained with a Carlo–Erba CHNS-11110 instrument. NMR spectra were recorded with a Bruker AM 300 (300 MHz and 75 MHz, for ^1H and ^{13}C) instrument, with $CDCl_3$ as solvent and TMS as internal standard.

3-(5-Benzyloxy-2-bromo-4-methoxybenzyl)oxazolidin-2-one (7d)

Oxazolidinones **7a–c** and oxazinanone **7e** were prepared according to a previously reported procedure.[11a]

Following the same procedure, **7d** was readily assembled by condensation of oxazolidin-2-one and 1-benzyloxy-4-bromo-5-bromomethyl-2-methoxybenzene prepared by bromination of the corresponding benzyl alcohol[13] with PBr_3 in Et_2O.

Yield: 1.36 g (87%); colorless crystals; mp 82–83 °C.

^1H NMR (300 MHz, $CDCl_3$): δ = 3.28 (t, *J* = 8.0 Hz, 2 H, NCH_2), 3.89 (s, 3 H, OCH_3), 4.19 (t, *J* = 8.0 Hz, 2 H, CH_2O), 4.46 (s, 2 H, NCH_2), 5.15 (s, 2 H, CH_2Ph), 6.87 (s, 1 H, ArH), 7.03 (s, 1 H, ArH), 7.32–7.44 (m, 5 H, ArH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 44.0 (CH_2), 56.3 (CH_2), 56.3 (CH_3), 61.9 (CH_2), 70.0 (CH_2), 114.3 (C), 115.1 (CH), 115.7 (CH), 127.4 (2 × CH), 128.0 (C), 128.6 (2 × CH), 128.8 (CH), 136.5 (C), 147.6 (C), 149.9 (C), 158.5 (CO).

Anal. Calcd for $C_{18}H_{18}BrNO_4$: C, 55.12; H, 4.63; N, 3.57. Found: C, 55.36; H, 4.48; N, 3.84.

5-Benzyloxy-2-(2-hydroxyethyl)-6-methoxy-2,3-dihydro-1*H*-isoindol-1-one (5d)

N-Hydroxyalkylisoindolinones **5a–c** and **5e** were easily obtained by treatment of oxazolidinones **7a–c** and oxazinone **7e** with *n*-BuLi as previously described.[11a] The same procedure was applied to **7d** to furnish **5d** as light-fawn crystals after purification by flash column chromatography on silica gel (acetone–hexanes, 80:20).

Yield: 160 mg (51%); mp 176–177 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.70 (t, *J* = 5.0 Hz, 2 H, NCH_2), 3.87 (t, *J* = 5.0 Hz, 2 H, CH_2OH), 3.93 (s, 3 H, OCH_3), 4.35 (s, 2 H, NCH_2), 5.20 (s, 2 H, CH_2Ph), 6.88 (s, 1 H, ArH), 7.29 (s, 1 H, ArH), 7.32–7.46 (m, 5 H, ArH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 46.2 (CH_2), 51.3 (CH_2), 56.3 (CH_3), 61.7 (CH_2), 71.1 (CH_2), 105.5 (CH), 107.2 (CH), 125.1 (C), 127.1 (2 × CH), 128.1 (CH), 128.7 (2 × CH), 134.8 (C), 136.3 (C), 150.2 (C), 151.6 (C), 170.0 (CO).

Anal. Calcd for $C_{18}H_{19}NO_4$: C, 69.00; H, 6.11; N, 4.47. Found: C, 68.13; H, 5.89; N, 4.49.

N-(Chloroalkyl)isoindolinones 8a–e; General Procedure[14]

Thionyl chloride (400 mg, 3.4 mmol) was added dropwise to an ice–water cooled solution of *N*-hydroxyalkylisoindolinone **5a–e** (3.0 mmol) in toluene (50 mL). The reaction mixture was allowed to stand at r.t. for 4 h with occasional swirling and then heated at 60 °C for 3 h. The toluene and the excess thionyl chloride were removed by evaporation under vacuum and the hot residue was poured into hexanes (50 mL) to afford a brown solid. After filtration, the solid was dissolved in refluxing toluene. The solution was filtered hot and the hot filtrate was poured into hexanes (30 mL) with stirring. The precipitate was filtered, washed with hexanes and dried in a vacuum oven to afford **8a–e** as a light-fawn solid, which was used without further purification.

2-(2-Bromoethyl)-4,5-dimethoxy-2,3-dihydro-1*H*-isoindol-1-one (11a)

A mixture of a 2-(2-hydroxyethyl)-4,5-dimethoxy-2,3-dihydro-1*H*-isoindol-1-one (**5a**; 0.897 g, 3.00 mmol) and PBr_3 (570 mg, 0.20 mL, 2.10 mmol) in toluene (20 mL) was heated at reflux for 3 h. H_2O (20 mL) was added to the reaction mixture with stirring and the organic layer was separated, washed with aq 5% NaOH (2 × 5 mL), H_2O (5 mL) and then dried (K_2CO_3). The solvent was evaporated to afford the crude product, which was purified by flash column chromatography on silica gel (CH_2Cl_2–EtOAc, 50:50) to afford **11a** as colorless crystals (718 mg, 80%).

Table 2 Physical and Spectroscopic Data

Product	Mp (°C)	^{1}H NMR ($CDCl_3$/TMS): δ (ppm)	^{13}C NMR ($CDCl_3$/TMS): δ (ppm)
8a	89–90 (fawn crystals)	3.80 (t, *J* = 6.0 Hz, 2 H, CH_2Cl), 3.92–3.95 (m, 2 H, NCH_2), 4.95 (s, 3 H, OCH_3), 4.96 (s, 3 H, OCH_3), 4.59 (s, 2 H, $ArCH_2$), 7.04 (d, *J* = 8.3 Hz, 1 H, ArH), 7.57 (d, *J* = 8.3 Hz, 1 H, ArH)	42.8 (CH_2), 44.8 (CH_2), 49.2 (CH_2), 56.2 (CH_3), 60.4 (CH_3), 112.7 (CH), 119.6 (CH), 125.8 (C), 133.4 (C), 143.7 (C), 155.5 (C), 168.7 (CO)
8b	87–88 (light-fawn crystals)	3.74 (t, *J* = 5.8 Hz, 2 H, CH_2Cl), 3.84–3.88 (m, 5 H, OCH_3 and NCH_2), 4.03 (s, 3 H, OCH_3), 4.43 (s, 2 H, $ArCH_2$), 7.04–7.07 (m, 2 H, ArH)	46.2 (CH_2), 44.7 (CH_2), 50.5 (CH_3), 56.7 (CH_2), 62.5 (CH_3), 116.6 (CH), 117.8 (CH), 124.5 (C), 136.4 (C), 147.1 (C), 152.2 (C), 167.0 (CO)
8c	114–115[14]		
8d	160–161 (light-fawn crystals)	3.78 (t, *J* = 5.8 Hz, 2 H, CH_2Cl), 3.94 (t, *J* = 5.9 Hz, 2 H, NCH_2), 3.96 (s, 3 H, OCH_3), 4.45 (s, 2 H, $ArCH_2$), 5.24 (s, 2 H, CH_2Ph), 6.93 (s, 1 H, ArH), 7.34–7.47 (m, 6 H, ArH)	42.9 (CH_2), 44.7 (CH_2), 51.1 (CH_2), 56.3 (CH_3), 71.1 (CH_2), 105.7 (CH), 107.2 (CH), 124.9 (C), 127.1 (2 × CH), 128.1 (CH), 128.7 (2 × CH), 134.7 (C), 136.3 (C), 150.2 (C), 151.7 (C), 169.1 (CO)
8e	110–111[14]		
11a[a]	98–99 (colorless crystals)	3.63 (t, *J* = 6.3 Hz, 2 H, CH_2), 3.94 (s, 3 H, OCH_3), 3.95 (s, 3 H, OCH_3), 4.00 (t, *J* = 6.3 Hz, 2 H, CH_2), 4.57 (s, 2 H, NCH_2), 7.03 (d, *J* = 8.2 Hz, 1 H, ArH), 7.56 (d, *J* = 8.2 Hz, 1 H, ArH)	30.1 (CH_2), 44.7 (CH_2), 48.8 (CH_2), 56.2 (CH_3), 60.4 (CH_3), 112.7 (CH), 119.6 (CH), 125.7 (C), 133.3 (C), 143.4 (C), 154.9 (C), 168.4 (CO)
9j[a]	109–110 (colorless crystals)	2.99 (s, 3 H, OCH_3), 3.38 (td, *J* = 4.1, 12.6 Hz, 1 H, NCH_2), 3.54 (td, *J* = 3.1, 11.6 Hz, 1 H, NCH_2), 3.80 (s, 3 H, OCH_3), 3.86 (d, *J* = 9.2 Hz, 1 H, CHO), 4.09 (dd, *J* = 3.8, 11.1 Hz, 1 H, CH_2O), 4.43 (dd, *J* = 2.7, 12.9 Hz, 1 H CH_2O), 4.80 (d, *J* = 9.1 Hz, 1 H, CHN),.6.98 (d, *J* = 8.3 Hz, 1 H, ArH), 7.37–7.42 (m, 5 H, ArH), 7.58 (d, *J* = 8.3 Hz, 1 H, ArH).	40.1 (CH_2), 56.1 (CH_3), 59.6 (CH), 61.5 (CH_3), 66.9 (CH_2), 85.8 (CH), 113.4 (CH), 119.4 (CH), 126.4 (C), 128.0 (2 × CH), 128.5 (2 × CH), 128.8 (CH), 133.3 (C), 138.7 (C), 144.7 (C), 155.5 (C), 166.3 (CO)
9k[a]	124–125 (colorless crystals)	3.41 (td, *J* = 4.0, 12.6 Hz, 1 H, NCH_2), 3.58 (td, *J* = 3.2, 11.7 Hz, 1 H, NCH_2), 3.82 (s, 3 H, OCH_3), 3.84 (d, *J* = 9.3 Hz, 1 H, CHPh), 4.07 (s, 3 H, OCH_3), 4.15 (dd, *J* = 4.0, 11.3 Hz, 1 H, CH_2O), 4.40 (dd, *J* = 3.1, 13.2 Hz, 1 H, of CH_2O), 4.44 (d, *J* = 9.4 Hz, 1 H, CHN), 6.00 (d, *J* = 8.2 Hz, 1 H, ArH), 6.83 (d, *J* = 8.3 Hz, 1 H, ArH), 7.38–7.46 (m, 5 H, ArH)	39.7 (CH_2), 56.5 (CH_3), 61.5 (CH_3), 62.5 (CH), 67.1 (CH_2), 85.0 (CH), 115.5 (CH), 119.0 (CH), 125.0 (C), 128.2 (2 × CH), 128.8 (2 × CH), 129.3 (CH), 133.8 (C), 137.4 (C), 147.2 (C), 152.9 (C), 164.6 (CO)

Table 2 Physical and Spectroscopic Data (continued)

Product	Mp (°C)	^{1}H NMR ($CDCl_3$/TMS): δ (ppm)	^{13}C NMR ($CDCl_3$/TMS): δ (ppm)
9l[a]	161–162 (yellow crystals)	3.43 (td, *J* = 4.5, 12.7 Hz, 1 H, NCH_2), 3.52 (s, 3 H, OCH_3), 3.61 (td, *J* = 2.8, 11.7 Hz, 1 H, NCH_2), 3.89 (d, *J* = 9.2 Hz, 1 H, CHN), 3.89 (s, 3 H, OCH_3), 4.14 (s, 3 H, OCH_3), 4.19 (dd, *J* = 4.0, 11.2, 1 H, CH_2O), 4.39–4.44 (m, 2 H: 1 H, CH_2O and 1 H CHPh), 5.53 (s, 1 H, ArH), 7.44–7.50 (m, 5 H, ArH)	39.5 (CH_2), 55.7 (CH_3), 61.4 (CH_3), 62.0 (CH_3), 62.6 (CH), 67.1 (CH_2), 85.0 (CH), 102.4 (CH), 117.5 (C), 128.3 (2 × CH), 128.6 (2 × CH), 129.4 (CH), 137.4 (C), 138.0 (C), 142.1 (C), 151.5 (C), 156.2 (C), 164.7 (CO)
9m[a]	213–215 (yellow crystals)	3.26 (s, 3 H, SO_2CH_3), 3.31–3.40 (m, 1 H, NCH_2), 3.43–3.53 (m, 1 H, NCH_2), 3.45 (s, 3 H, OCH_3), 3.70 (s, 3 H, OCH_3), 3.97 (s, 3 H, OCH_3), 4.10 (dd, *J* = 4.1, 10.3 Hz, 1 H, CH_2O), 4.12 (d, *J* = 9.3 Hz, 1 H, CHN), 4.17 (dd, *J* = 2.3, 13.1 Hz, 1 H, CH_2O), 4.56 (d, *J* = 9.2 Hz, 1 H, CH), 5.42 (s, 1 H, ArH), 7.75 (d, *J* = 8.3 Hz, 2 H, ArH), 8.06 (d, *J* = 8.3 Hz, 2 H, ArH)	39.1 (CH_2), 43.9 (CH_3), 55.9 (CH_3), 61.3 (CH_3), 61.4 (CH_3), 62.8 (CH), 66.8 (CH_2), 83.5 (CH), 102.8 (CH), 117.5 (C), 127.6 (2 × CH), 130.0 (2 × CH), 138.3 (C), 141.8 (C), 142.0 (C), 143.5 (C), 151.4 (C), 156.2 (C), 163.9 (CO)
9n[a]	211–212 (light-yellow crystals)	3.43 (td, *J* = 4.1, 12.6, 1 H, NCH_2), 3.58 (td, *J* = 2.9, 11.6 Hz, 1 H, NCH_2), 3.75 (d, *J* = 9.3 Hz, 1 H, CHO), 3.89 (s, 6 H, 2 × OCH_3), 3.92 (s, 3 H, OCH_3), 3.94 (s, 3 H, OCH_3), 4.17 (dd, *J* = 4.0, 11.3 Hz, 1 H, CH_2O), 4.36–4.41 (m, 2 H: 1 H, CHN and 1 H, CH_2O), 4.71 (d, *J* = 12.0 Hz, 1 H, CH_2Ph), 5.00 (d, *J* = 12.9 Hz, 1 H, CH_2Ph), 5.95 (s, 1 H, ArH), 6.62 (s, 2 H, ArH), 7.19–7.21 (m, 2 H, ArH), 7.26–7.32 (m, 3 H, ArH), 7.36 (s, 1 H, ArH)	39.8 (CH_2), 56.2 (3 × CH_3), 60.1 (CH_3), 62.0 (CH), 67.2 (CH_2), 71.0 (CH_2), 85.3 (CH), 105.5 (2 × CH), 108.2 (CH), 125.4 (C), 127.0 (2 × CH), 127.1 (CH), 128.1 (CH), 128.7 (2 × CH), 132.9 (C), 133.9 (C), 135.9 (C), 138.6 (C), 150.6 (C), 150.9 (C), 153.5 (2 × C), 166.6 (CO)
9o[a]	113–114 (light-yellow crystals)	3.09 (s, 3 H, SO_2CH_3), 3.43 (td, *J* = 3.7, 12.5 Hz, 1 H, NCH_2), 3.57 (td, *J* = 3.5, 11.4 Hz, 1 H, NCH_2), 3.92 (d, *J* = 9.1 Hz, 1 H, CHN), 3.96 (s, 3 H, OCH_3), 4.17 (dd, *J* = 3.4, 10.9 Hz, 1 H, CH_2O), 4.32 (d, *J* = 9.2 Hz, 1 H, CHO), 4.41 (d, *J* = 13.0 Hz, 1 H, CH_2O), 4.85 (d, *J* = 13.4 Hz, 1 H, CH_2Ph), 5.03 (d, *J* = 13.3 Hz, 1 H, CH_2Ph), 5.80 (s, 1 H, ArH), 7.14–7.24 (m, 2 H, ArH), 7.28–7.39 (m, 4 H, ArH), 7.56 (d, *J* = 8.2 Hz, 2 H, ArH), 7.99 (d, *J* = 8.2 Hz, 2 H, ArH)	39.8 (CH_2), 44.5 (CH_3), 56.3 (CH_3), 62.0 (CH), 67.0 (CH_2), 70.6 (CH_2), 83.9 (CH), 105.8 (CH), 125.5 (C), 126.4 (2 × CH), 126.9 (CH), 127.8 (2 × CH), 128.0 (2 × CH), 128.8 (2 × CH), 129.2 (CH), 133.2 (C), 135.8 (C), 141.3 (C), 143.5 (C), 150.8 (C), 150.9 (C), 066.4 (CO)
9p[a]	174–175 (colorless crystals)	3.29 (s, 3 H, SO_2CH_3), 3.39–3.47 (m, 2 H, NCH_2), 3.82 (s, 3 H, OCH_3), 4.04–4.07 (m, 2 H: 1 H, CH_2O and 1 H, CHN), 4.16–4.20 (m, 1 H, CH_2O), 4.64 (d, *J* = 9.1 Hz, 1 H, CHO), 5.78 (s, 1 H, ArH), 7.21 (s, 1 H, ArH), 7.74 (d, *J* = 8.2 Hz, 2 H, ArH), 8.04 (d, *J* = 8.2 Hz, 2 H, ArH), 9.73 (s, 1 H, OH)	43.5 (CH_3), 55.7 (CH_3), 56.0 (CH_2), 60.4 (CH), 66.4 (CH_2), 83.1 (CH), 105.7 (CH), 109.7 (CH), 123.4 (C), 127.2 (2 × CH), 129.3 (2 × CH), 134.3 (C),141.1 (C), 143.3 (C), 148.7 (C), 149.8 (C), 165.5 (CO)
16[a]	200–201 (yellow crystals)	2.33 (s, 3 H, CH_3), 3.21 (td, *J* = 4.0, 12.6 Hz, 1 H, NCH_2), 3.37 (td, *J* = 4.3, 12.6 Hz, 1 H, NCH_2), 3.77 (s, 3 H, OCH_3), 3.78–3.83 (m, 4 H: 3 H, OCH_3 and 1 H, CH_2NSO_2), 4.02 (s, 3 H, OCH_3), 4.48 (dd, *J* = 3.4, 12.9 Hz, 1 H, CH_2NSO_2), 4.84 (d, *J* = 5.3 Hz, 1 H, CHN), 5.65 (d, *J* = 5.5 Hz, 1 H, CHPh), 6.49 (s, 1 H, ArH), 6.96–7.03 (m, 4 H, ArH), 7.07–7.10 (m, 3 H, ArH), 7.41–7.44 (m, 2 H, ArH)	21.4 (CH_3), 38.3 (CH_2), 39.7 (CH_2), 56.3 (CH_3), 58.5 (CH_3), 59. 7 (CH), 61.4 (CH_3), 62.5 (CH), 101.6 (CH), 117.4 (C), 126.4 (CH), 127.2 (2 × CH), 128.3 (2 × CH), 128.7 (2 × CH), 129.4 (2 × CH),.34.0 (C), 136.0 (C), 138.8 (C), 141.8 (C), 143.5 (C), 151.4 (C), 157.1 (C), 165.4 (CO)
erythro-**14**[a,b]	85–86 (white crystals)	2.08–2.51 (m, 2 H, CH_2), 3.49–3.62 (m, 4 H: 1 H, NCH_2 and 2 H, CH_2 and 1 H, OH), 3.65 (s, 3 H, OCH_3), 3.83 (s, 3 H, OCH_3), 3.86 (s, 3 H, OCH_3), 4.10 (m, 1 H, NCH_2), 4.74 (d, *J* = 2.9 Hz, 1 H, CHN), 5.37 (s, 1 H, CHO), 6.01 (s, 1 H, ArH), 6.94 (d, *J* = 8.5 Hz, 2 H, ArH), 7.10 (s, 1 H, ArH), 7.32 (d, *J* = 8.5 Hz, 2 H, ArH)	31.1 (CH_2), 38.4 (CH_2), 42.6 (CH_2), 55.4 (CH_3), 55.8 (CH_3), 55.9 (CH_3), 65.7 (CH), 71.0 (CH), 105.0 (CH), 106.2 (CH), 113.8 (2 × CH), 125.3 (C), 127.3 (2 × CH), 131.6 (C), 134.9 (C), 149.8 (C), 151.5 (C), 159.3 (C), 169.8 (CO)
threo-**14**[a,b]	95–96 (white crystals)	2.04–2.31 (m, 2 H, CH_2), 2.82 (br s, 1 H, OH), 3.51–4.00 (m, 3 H: 1 H, NCH_2 and 2 H, CH_2), 3.68 (s, 3 H, OCH_3), 3.76 (s, 3 H, OCH_3), 3.87 (s, 3 H, OCH_3), 4.06 (m, 1 H, CH_2N), 4.72 (d, *J* = 6.4 Hz, 1 H, CHN), 4.82 (d, *J* = 6.4 Hz, 1 H, CHO), 6.21 (s, 1 H, ArH), 6.80 (d, *J* = 8.5 Hz, 2 H, ArH), 7.08 (d, *J* = 8.5 Hz, 2 H, ArH), 7.14 (s, 1 H, ArH)	31.3 (CH_2), 40.0 (CH_2), 42.6 (CH_2), 55.3 (CH_3), 55.8 (CH_3), 56.0 (CH_3), 64.5 (CH), 76.4 (CH), 104.6 (CH), 106.7 (CH), 113.6 (2 × CH), 125.0 (C), 128.3 (2 × CH), 132.1 (C), 135.4 (C), 149.7 (C), 151.4 (C), 159.7 (C), 169.3 (CO)

[a] Satisfactory microanalyses were obtained: C ±0.25, H ±0.27, N ±0.29.
[b] MS (ESI+): *m*/*z* (%) = 408 (39), 407 (22), 406 (100) $[M + Na]^+$.

1-Aryl-1,3,4,10b-tetrahydro[1,4]oxazino[3,4-*a*]isoindol-6-ones (9j–p) and 7,8,9-Trimethoxy-1-phenyl-2-toluene-4-sulfonyl-1,3,4,10b-tetrahydro-2*H*-pyrazino[2,1-*a*]isoindol-6-one (16); General Procedure

A colorless solution of halogenated isoindolinone **8a–e** or **11a** (1.00 mmol) in anhydrous THF (25 mL) was cooled to –78 °C and a solution of KHMDS (0.5 M in toluene, 2.20 mL, 1.10 mmol) was added dropwise. The colored (orange/red for **8a–d** or greenish for **8e**) mixture was stirred and allowed to warm from –78 °C to –50 °C over a 30 min period under stirring and a solution of aldehyde **10f–i** or tosylimine **17f**[15] (1.10 mmol) in THF (15 mL) was subsequently added. The mixture was allowed to warm to r.t. over 30 min, then poured into aq sat. NH_4Cl (5 mL) diluted with H_2O (10 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 30 mL) and the organic layers were combined, washed with H_2O (2 × 10 mL), dried (Na_2SO_4) and concentrated under reduced pressure. Purification by flash column chromatography on silica gel (hexanes–EtOAc, 50:50→25:75) afforded the target products **9j–o** or **16**.

The diastereomers *erythro*-**14** and *threo*-**14** were separated by flash column chromatography on silica gel (CH_2Cl_2–acetone, 90:10).

Compound **9p** was prepared by deprotection of benzylated precursor **9o** under standard conditions. A mixture of oxazinoindolinone **9o** (0.240 g, 0.5 mmol) and 10% Pd/C (15 mg) in MeOH (20 mL) was stirred under a H_2 atmosphere for 12 h. The reaction mixture was filtered through a Celite pad and the filtrate was evaporated to yield the debenzylated product **9p** as colorless crystals (0.113 g, 58%).

4,5-Dimethoxy-2-vinyl-2,3-dihydro-1*H*-isoindol-1-one (12)

Compound **12** was obtained by exposure of brominated isoindolinone **11a** (300 mg) to *n*-BuLi as described in General Procedure.

Yield: 169 mg (77%); colorless crystals; mp 86–89 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.90 (s, 3 H, OCH_3), 3.92 (s, 3 H, OCH_3), 4.43–4.46 (m, 3 H: 2 H, CH_2N and 1 H, $=CH_2$), 4.56 (dd, *J* = 0.8, 16.0 Hz, 1 H, $=CH_2$), 6.97 (d, *J* = 8.3 Hz, 1 H, ArH), 7.25 (dd, *J* = 9.2, 16.1 Hz, 1 H, NCH=), 7.51 (d, *J* = 8.3 Hz, 1 H, ArH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 45.3 (CH_2), 56.2 (CH_3), 60.4 (CH_3), 93.0 (CH_2), 112.9 (CH), 120.1 (CH), 125.3 (C), 129.2 (CH), 132.8 (C), 143.5 (C), 155.6 (C), 166.6 (CO).

Anal. Calcd for $C_{12}H_{13}NO_3$: C, 65.74; H, 5.98; N, 6.39. Found: C, 65.52; H, 6.10; N, 6.41.

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(13) Selected X-ray crystallographic data for **9j**: Empirical formula: $C_{19}H_{19}NO_4$; *M*r = 325.35 g·mol^{-1}; *F*(000) = 688; white crystal; *D* = 1.353 g·cm^{-3}; μ(Mo K$_\alpha$) = 0.095; monoclinic; P21/n; *a* = 5.56820 (10) Å, *b* = 8.60050 (10) Å, *c* = 33.3710 (6) Å; α = 90.00, β = 91.8710 (10), γ = 90.00; *V* = 1597.26 (4) Å^3; Z = 4; T = 100 K. Further details of the X-ray structure data are available on request from the Cambridge Crystallographic Data Centre (CCDC 791641)

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