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Asymmetric Syntheses of Medicinally Important Isoindolinones, (*S*)-PD 172938, (*R*)-JM 1232 and Related Structures

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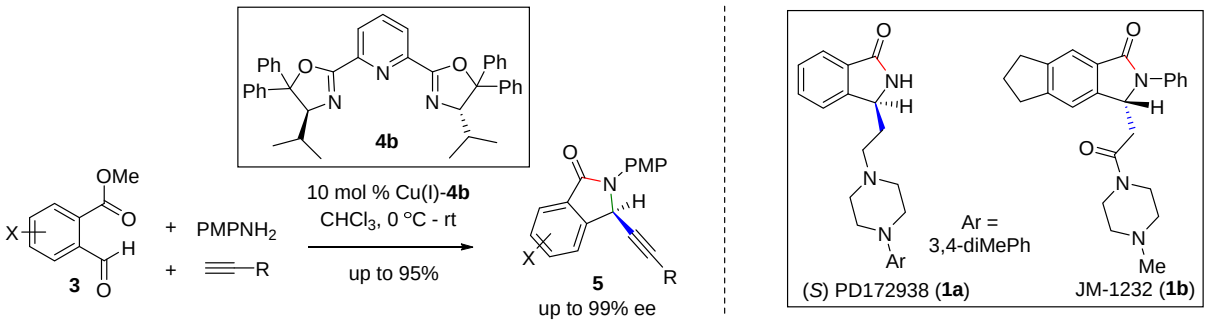
TOC GRAPHIC



ABSTRACT

A unified approach for the asymmetric syntheses of medicinally important isoindolinones (*S*)-PD 172938 and (*R*)-JM 1232 has been accomplished via a Cu(I)-PYBOX-diPh catalyzed highly enantioselective (up to 99% ee) alkynylation/lactamization sequence in one-pot fashion. The overall sequence involves one C-C and two C-N bond forming events in one-pot starting from inexpensive starting material in ambient reaction conditions.

INTRODUCTION

Isoindolinones are heterocyclic compounds (**1a-e**; Figure 1) having potential biological activities, such as anti-hypertensive,[1] anti-psychotic,[2] anti-inflammatory,[3] and anesthetic.[4] Some members of this class of heterocyclic scaffolds also display anti-ulcer,[5] vasodilatory,[6] anti-viral,[7] anti-leukemic properties,[8a] and platelet aggregation inhibitory[8b] activities. These are also found to induce dose-dependent p53-dependent gene transcription in MDM2-amplified SJSA human sarcoma cell lines.[9] In addition, isoindolinones are useful in the synthesis of various drugs[10] and complex natural products.[11] Since enantiomers interact differently with the biological system, therefore, intense research is going on to synthesize these biologically active isoindolinones in enantioenriched form. In fact, (*S*)-PD 172938 (**1a**) is reported as a potent dopamine D_4 ligand,[12] and (*R*)-JM 1232 (**1b**) is a benzodiazepine receptor agonists for the treatment of anxiety,[13] whereas **1c** is an inhibitor of the β-secretase enzyme for the treatment of Alzheimer's disease.[14]

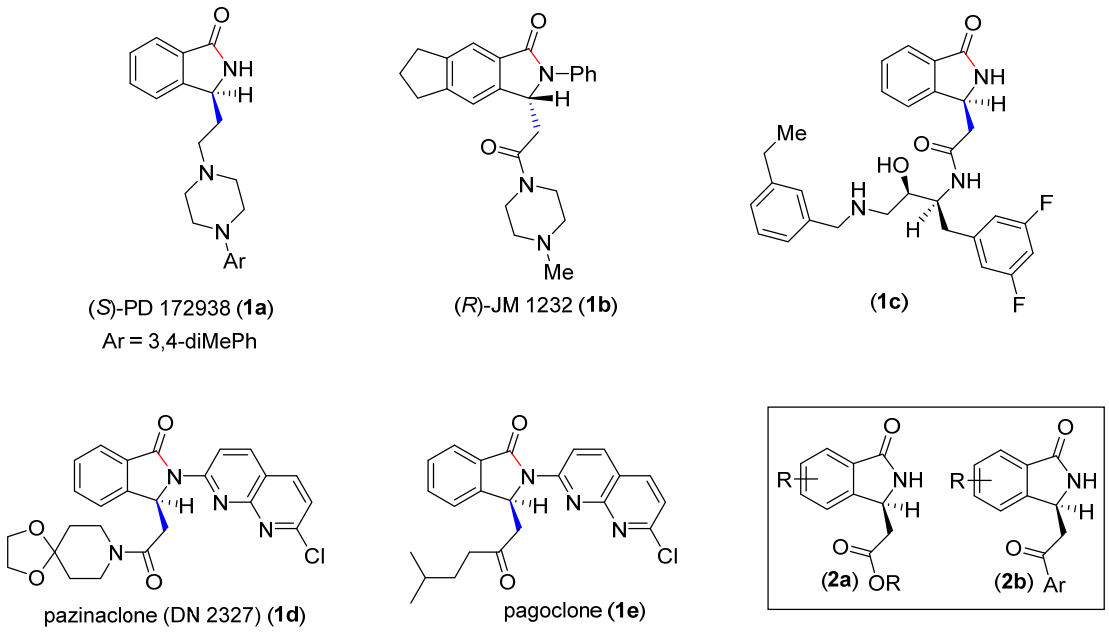
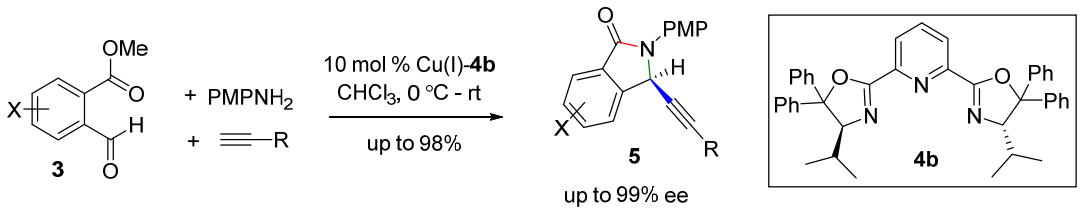


Figure 1. Selected enantioenriched isoindolinones.

Prominent approaches to this class of heterocyclics include Heck cyclization,[15] Diels-Alder approach,[16] domino three-component coupling-lactamization,[17] ring-closure of chiral hydrazones,[18] reactions of chiral acyliminium ion,[19a-b] allylation to chiral imines,[19c] aza-conjugate addition,[20a] and chiral appendage mediated carbanion method.[20b-c] Most of these syntheses involve a chiral auxiliary mediated diastereoselective approach and face limited substrate scope. Only a few enantioselective syntheses of isoindolinones are known in literature.[21-24] Towards this, transition-metal catalyzed processes include, Rh(I)-catalyzed arylation,[21a] Cu(I)-catalyzed tandem Michael-Mannich reaction,[21b] Pd(II)-catalyzed aza-Wacker type cyclization[21c] and organocatalytic syntheses include thio-urea catalyzed malonate addition,[22] our direct organocatalytic Mannich-lactamization,[23] and phase transfer catalyzed aza-Michael reactions.[24]



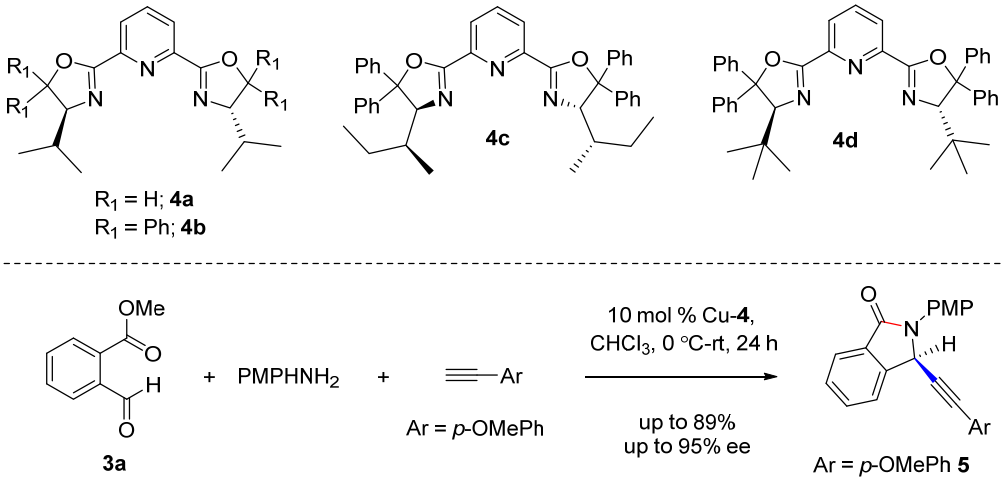
Scheme 1. Our report on domino enantioselective alkynylation/lactamization.

Towards this, we recently reported enantioselective synthesis of isoindolinones (>99% ee) *via* a Cu^{I}-^{i}Pr-pybox-diPh **4b** catalyzed alkynylation-lactamization cascade (Scheme 1).[25] We envisioned that one can achieve asymmetric syntheses of **1a-e** from a common enatioenriched isoindolinone **2a** via synthetic elaboration (Figure 1). Compound **2a** could be accessed from enantioenriched aryl ketone **2b** via a Baeyer-Villiger oxidation, which in turn could be synthesized from enantioenriched **5** following oxidative reaction (Scheme 2). Utilizing above strategy, herein, we report first unified approach for the asymmetric syntheses of medicinally important (*S*)-PD 172938, and (*R*)-JM 1232.

RESULTS AND DISCUSSION

At the outset, we studied several potential catalysts to ultimately identify the most efficient catalytic system (Table 1) to realize this transformation. As a model system *en route* to isoindolinone derivatives, we carried out Cu-(I)-catalyzed alkynylation/lactamization cascade with methyl 2-formyl benzoate (**3a**) in the presence of 10 mol % of Cu(I)-**4a-d** in chloroform at room temperature under inert atmosphere. Since *p*-methoxyphenyl group of $PMPNH_2$ can be cleaved under oxidative condition, we decided to us this as amine source. Also, to facilitate Baeyer-Villiger oxidation of compound **2b**, we choose *p*-methoxyphenylacetylene as terminal alkyne (Table 1).

Table 1. Optimization of domino Cu(I)-catalyzed enantioselective alkynylation/lactamization.



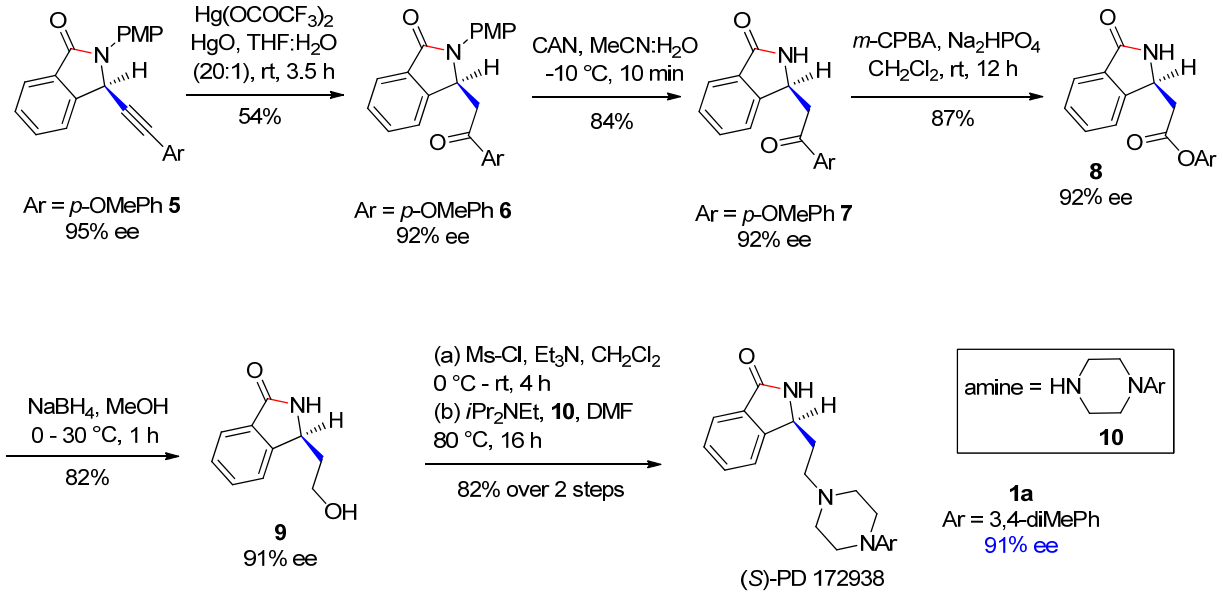
entry	metal salt	catalyst	solvent	Temp	Time	% yield[b]	ee

				°C	(h)		(%)[c]
1	$(CuOTf)_2$.PhMe	**4a**	$CHCl_3$	0 - 25	48	59	79
2	$(CuOTf)_2$.PhMe	**4b**	$CHCl_3$	0 - 25	24	92	99
3	$(CuOTf)_2$.PhMe	**4c**	$CHCl_3$	0 - 25	26	84	92
4	$(CuOTf)_2$.PhMe	**4d**	$CHCl_3$	0 - 25	25	90	85
5	CuI	**4b**	$CHCl_3$	0 - 25	48	00	00
6	$Cu(OTf)_2$	**4b**	$CHCl_3$	0 - 25	25	88	94
7	CuTC	**4b**	$CHCl_3$	0 - 25	48	00	00
8	$[Cu(CH_3CN)_4]BF_4$	**4b**	$CHCl_3$	0 - 25	26	90	94
9	$[Cu(CH_3CN)_4]PF_6$	**4b**	$CHCl_3$	0 - 25	26	85	93
10	$(CuOTf)_2$.PhH	**4b**	$CHCl_3$	0 - 25	25	83	92
11[e]	$(CuOTf)_2$.PhMe	**4b**	$CHCl_3$	0 - 25	36	89	95

[a] Unless otherwise stated all the reactions were performed with 1 equivalent of each aldehyde and *p*-anisidine, and 1.2 equivalent of 4-ethynylanisole (ratio of 1:1:1.2) under inert atmosphere. [b] isolated yields. [c] determined by chiral HPLC analysis. [d] decomposition of rest of the mass balance. [e] the reaction was carried out on 3.0 mmol scale (~0.5g scale).

Following extensive optimization, it was found that $(CuOTf)_2$.PhMe complex of PYBOX-**4a-d** afforded isoindolinone **5** in 59%, 92%, 84% and 90% of yields with 79%, 99%, 92% and 85% of ee, respectively (entries 1-4, table 1). Thus, it is quite clear that,

ligands with *gem*-diphenyl groups **4b-d** are superior over **4a**. Since ^{i}Pr-PYBOX-diPh (**4b**) is best ligand among all *gem*-diphenyl groups, further optimization with various Cu-catalysts were carried out using **4b**. Among various Cu(I)-complexes, $[Cu(CH_3CN)_4]BF_4$, $[Cu(CH_3CN)_4]PF_6$, and $(CuOTf)_2$.PhH afforded **5** in 94%, 93% and 92% ee, respectively, with 83-90% yields (entries 8-10), whereas Cu(I)I and Cu(I)TC-complexes of **4b** were found to be completely inactive catalysts (entries 5 and 7). Gratifyingly, Cu(II)-**4b** also afforded isoindolinone **5** in 94% enantioselectivity (entry 6). This method is attractive towards its utilization in organic synthesis because this catalytic system works without the use of any additives.

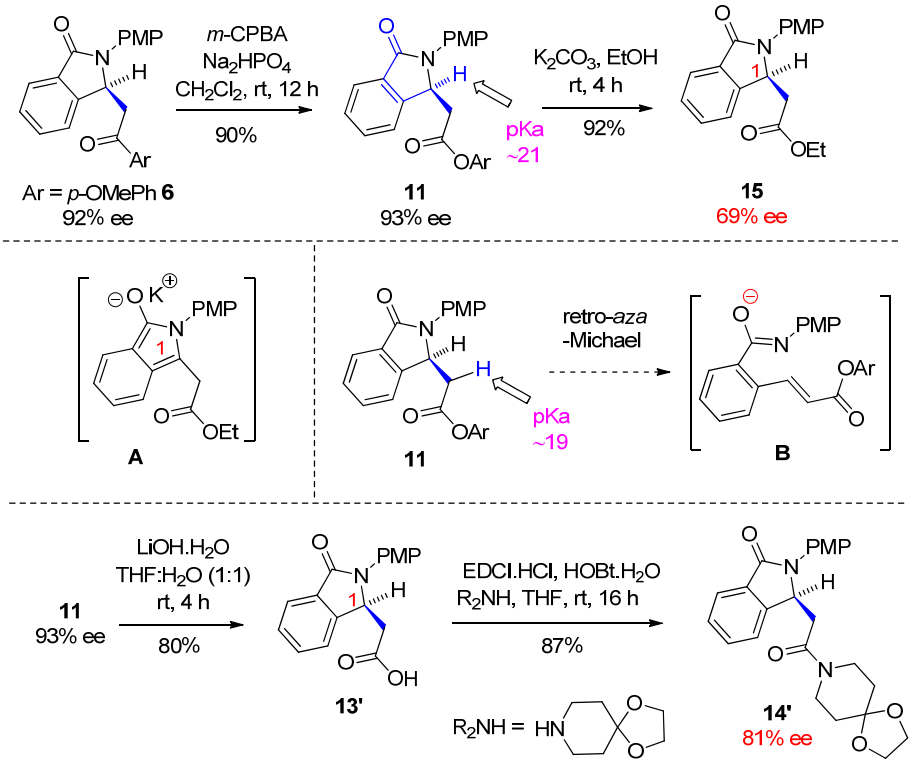


Scheme 2. Synthesis of (*S*)-PD 172938.

With enough quantity in hand, our effort was thereafter to elaborate compound **5** for synthesis of PD 172938 **1a** (Scheme 2). Towards this, we treated **5** with $Hg(OCOCF_3)_2$ in the presence of HgO[26] to affect hydration of alkyne functionality to afford aryl ketone **6** in 54% yield. The later was then treated with ceric(IV) ammonium nitrate (CAN) to furnish **7** in 84%

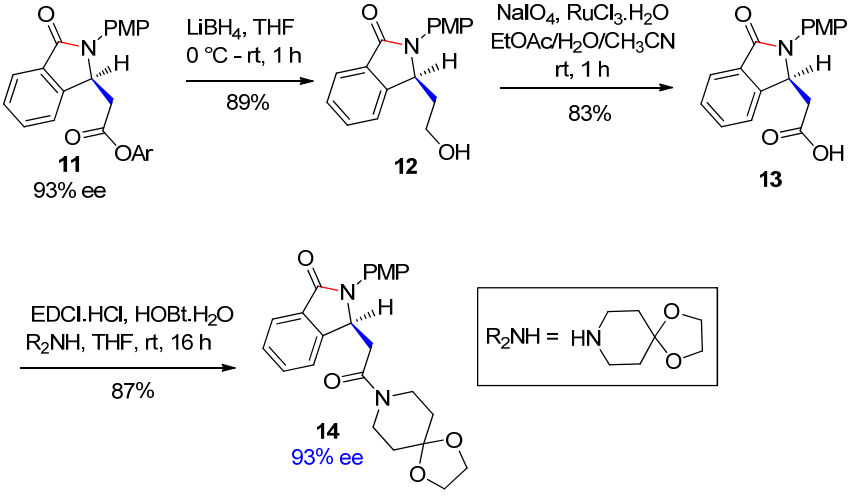
yield, which was then converted to aryl ester **8** in 87% yield via Baeyer-Villiger oxidation.[26] Then, ester **8** was reduced with $NaBH_4$ to get **9** in 82% yield (91% ee), which was followed by mesylation concomitant with *N*-alkylations with *N*-substituted piperazine to complete the synthesis of (*S*)-PD 172938 **1a** in 91% ee (See Supporting Information for HPLC traces).

In another sequence, we carried out Baeyer-Villiger oxidation of arylketone **6** followed by trans-esterification to afford advanced intermediate for the synthesis of pazinaclone (DN 2327) **1d** (Scheme 3). However, we found that trans-esterification using K_2CO_3/EtOH afforded ethylester **15** in only 69% ee. We speculate that, since pKa of benzylic proton is ~21 (essentially vinylogous position: see blue portion of **11**), racemization could takes place *via* intermediate **A**. Another alternate racemization pathway would be retro-aza-Michael process to intermediate **B** (Scheme 3). A similar case was observed when saponification of **11** was carried out using $LiOH.H_2O$ to furnish carboxylic acid **13'**. When the later was coupled with 4-piperidone derivative, it afforded amide **14'** in 81% ee (See SI for HPLC traces).



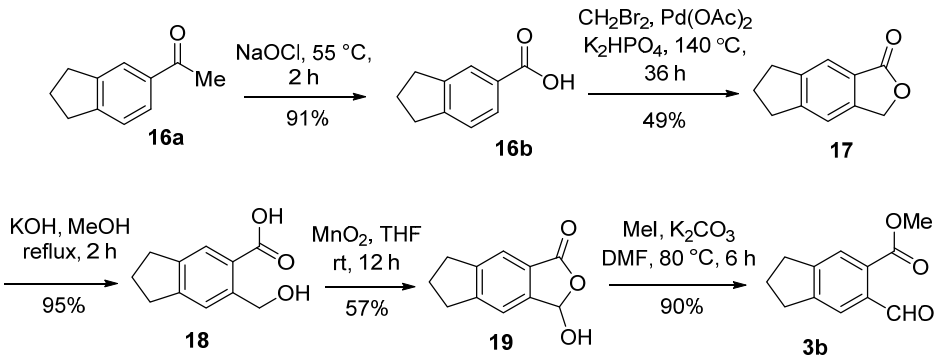
Scheme 3. Synthesis of advanced intermediate **14'**.

Thus, in an alternate strategy, arylester **11** (93% ee) was reduced to primary alcohol **12** and which was re-oxidized to carboxylic acid **13** in 74% overall yield (Scheme 4). Finally, **13** were coupled with 4-piperidone derivative to afford advanced intermediate amide **14** without the loss of any enantiopurity (Scheme 4).



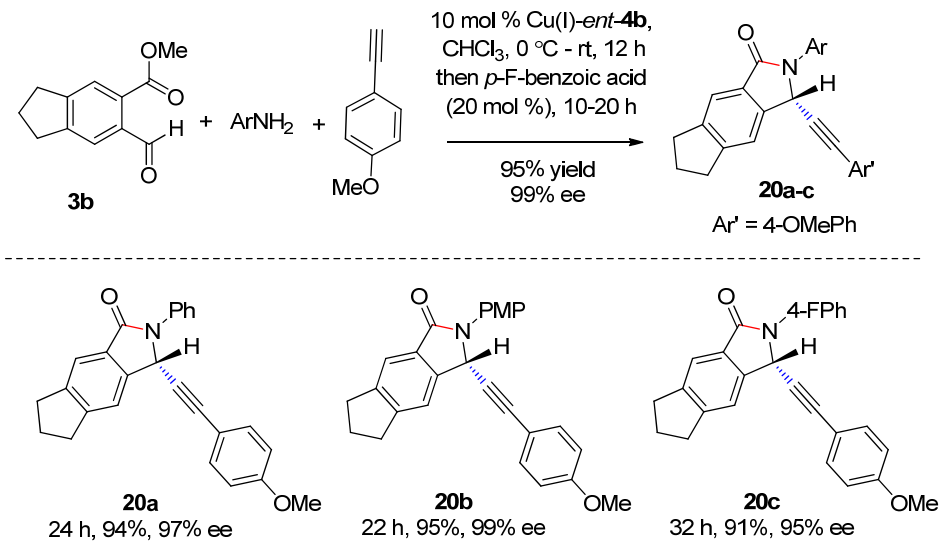
Scheme 4. Synthesis of advanced amide intermediate **14**.

Next, we targeted for the asymmetric syntheses of (*R*)-JM 1232 **1b** (Figure 1). Towards this, we synthesized *o*-formyl methylbenzoate **3b** from commercially available acetophenone **16a** in 5 steps (Scheme 5). First, **16a** was oxidized to benzoic acid **16b** in 91% yield, which was then converted to phthalide **17** by reaction with dibromomethane in the presence of $Pd(OAc)_2$.[27] The later afforded *o*-formyl methylbenzoate **3b** in 3 steps viz. saponification to form **18**, MnO_2-oxidation to afford **19** followed by reaction with MeI in presence of K_2CO_3 (Scheme 5).



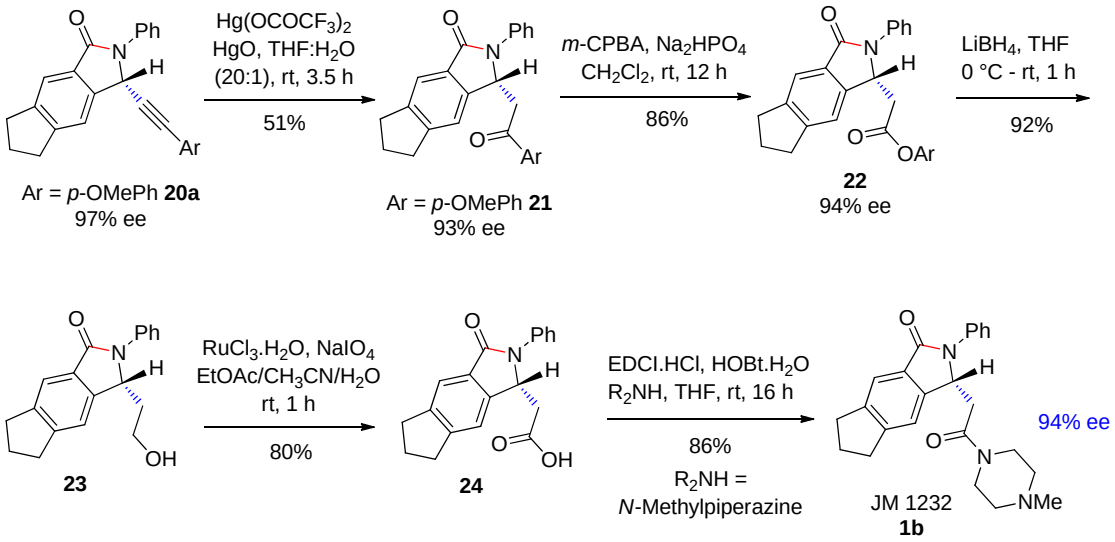
Scheme 5. Synthesis of o-formyl methylbenzoate **3b**.

Having *o*-formyl methylbenzoate **3b** in hand, we then carried out propargylation using ligand *ent*-**4b** to access isoindolinone **20** with *R*-stereochemistry (Scheme 6). Gratifyingly, we could able to use three aromatic amines with different electronic nature, such as aniline, *p*-methoxyaniline, and *p*-fluoroaniline in the presence of 4-ethynylanisole to afford isoindolinones **20a-c** in high yields with excellent enantioselectivities (up to 99% ee). However, all these cases 20 mol % *p*-fluorobenzoic acid was used as additive.[28]



Scheme 6. Substrate scope using *o*-formyl methylbenzoate **3b**.

We then synthesized aryl ester **22** from isoindolinone **20a** in two steps viz reactions using $Hg(OCOCF_3)_2$ in presence of HgO, and Baeyer-Villiger oxidation in 44% overall yields (Scheme 7). Aryl ester **22** was reduced with $LiBH_4$ followed by $RuCl_3$-catalyzed oxidation to afford carboxylic acid **24** (Scheme 7). Finally, amide coupling using *N*-methylpiperazine in the presence of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride salt (EDCI.HCl) afforded required (*R*)-JM 1232 (**1b**) in 94% ee (See Supporting Information for HPLC traces).



Scheme 7. Asymmetric synthesis of JM 1232 (**1b**).

CONCLUSIONS

In conclusion, we report asymmetric syntheses of medicinally important isoindolinones, (*S*)-PD 172938 (**1a**), and (*R*) JM 1232 (**1b**) via a highly enantioselective one-pot alkynylation-lactamization cascade. Important features of our strategy include: (1) the reactions do not require preformed imine equivalents; (2) the method is operationally simple and inexpensive; (3) excellent enantioselectivity (95% ee) has been achieved even using 0.5 g scale of **3a**. Further application of this strategy is under active investigation in our laboratory.

EXPERIMENTAL SECTION

Materials and Methods

Unless otherwise stated, reactions were performed in oven-dried glassware fitted with rubber septa and were stirred with Teflon-coated magnetic stirring bars. Liquid reagents and solvents were transferred *via* syringe using standard Schlenk techniques. Tetrahydrofuran (THF), diethyl ether (Et_2O), benzene and toluene were distilled over sodium/benzophenone ketyl. Dichloromethane (CH_2Cl_2), and chloroform ($CHCl_3$) were distilled over calcium hydride. All other solvents and reagents were used as received unless otherwise noted. Reaction temperatures above 25 °C refer to oil bath temperature. Thin layer chromatography was performed using silica gel 60 F-254 precoated plates (0.25 mm) and visualized by UV irradiation, 2,4-DNP stain and other stains. Silica gel of particle size 100-200 mesh was used for column chromatography. Melting points were recorded on a digital melting point

apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded 400 MHz, 500 MHz, and 700 MHz, spectrometers with ^{13}C operating frequencies of 100 MHz, 125 MHz, and 176 MHz respectively. Chemical shifts (δ) are reported in ppm relative to the residual solvent ($CDCl_3$) signal (δ = 7.24 ppm for ^{1}H NMR and δ = 77.0 ppm for ^{13}C NMR), (DMSO-d_6) signal (δ = 2.54 ppm for ^{1}H NMR and δ = 39.9 ppm for ^{13}C NMR) and (CD_3OD) signal (δ = 4.78 and 3.29 ppm for ^{1}H NMR and δ = 47.6 ppm for ^{13}C NMR). Data for ^{1}H NMR spectra are reported as follows: chemical shift (multiplicity, coupling constants and number of hydrogen). Abbreviations are as follows: s (singlet), d (doublet), t (triplet), q (quartet), quint (quintet), m (multiplet), br (broad), dd (doublet of doublets). IR spectra were recorded on a FT-IR system and are reported in frequency of absorption (cm^{-1}). Only selected IR absorbances are reported. High-Resolution Mass Spectrometry (HRMS) data was recorded on TOF-Q-II mass spectrometer using acetonitrile as solvent. Optical rotations were measured on a commercial automatic polarimeter. Enantiomeric excess was determined by chiral HPLC analysis using Chiralpak AD-H and Chiralpak IA columns.

Starting materials such as **3a**,[25] **10** and **16b**[29] were prepared according to the literature known procedures.

Procedure for the synthesis of compound (3b):[25]

To a solution of compound **19** (1.5 mmol, 1.0 equiv) in dry DMF (4 mL) was added MeI (3.15 mmol, 2.1 equiv), and K_2CO_3 (1.5 mmol, 1.0 equiv) at RT. The reaction mixture was heated at 80 °C for 6 h. Upon completion of the reaction (monitored by TLC), the reaction mixture was quenched with water (25 mL) and the aqueous layer was extracted with EtOAc (3 × 40 mL). The combined organic layers were washed with 15 mL of saturated aqueous $Na_2S_2O_3$ solution followed by 15 mL of saturated aqueous $NaHCO_3$ solution. The organic

layer was then washed with 20 mL of brine solution, dried over anhydrous Na_2SO_4, concentrated *in vacuo*, and purified by silica gel column chromatography to afford pure ester **3b** as a pale yellow solid (275.7 mg, 90%).

Methyl 6-formyl-2,3-dihydro-1*H*-indene-5-carboxylate (3b): 275.7 mg, 90% Yield of (**3b**) as pale yellow solid. R_f = 0.45 (15% EtOAc in hexanes); **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 10.54 (s, 1H), 7.77 (brs, 2H), 3.92 (s, 3H), 2.96 (t, *J* = 7.5 Hz, 4H), 2.12 (quint, *J* = 7.5 Hz, 2H); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ 192.3, 167.2, 150.3, 149.4, 135.8, 130.7, 126.3, 124.2, 52.6, 32.9, 32.7, 25.2; **IR** (film) υ_{max} 2953, 2904, 1716, 1688, 1434, 1273, 1119, 1037, 773 cm^{-1}; **HRMS** (ESI) m/z 227.0697 $[M+Na]^+$; calculated for $[C_{12}H_{12}O_3 + Na]^+$: 227.0679; **MP** 39-41 °C.

General procedure for Cu(I)-catalyzed Alkynylation-lactamization cascade:[25]

Large Scale:

A solution of a ligand **4b** (*S,S*)-^{i}Pr-PyBOX-DiPh (0.3 mmol, 10 mol %) and $(CuOTf)_2$.PhMe complex (0.3 mmol, 10 mol %) in dry chloroform (30 mL) was stirred at 0 °C for 45 min under nitrogen atmosphere. An aldehyde **3a** (3.0 mmol) and *p*-anisidine (3.0mmol) were added and the whole mixture was stirred for additional 45 min followed by addition of 4-ethynylanisole (3.6 mmol) at the same temperature. The reaction mixture was gradually allowed to warm up to 25 ºC. After completion of the reaction (monitoring by TLC), the mixture was concentrated *in vacuo* and purified over silica gel by column chromatography (EtOAc/hexane) affording product **5** in 986.3 mg, 89% yield and 95% ee.

Procedure for the synthesis of compound (6):[26]

To a solution of compound **5** (1.5 mmol, 1.0 equiv) in wet THF (60 mL, THF/H_2O, 20:1, v/v) was added red HgO (1.2 mmol, 0.8 equiv) and mercuric trifluoroacetate (0.6 mmol, 0.4 equiv). The reaction mixture was stirred for 3.5 h at RT before quenched with saturated aqueous Na_2S solution (25 mL) at 0 °C. After stirring for another 20 minutes, saturated aqueous $NaHCO_3$ solution (25 mL) was added. After filtration through Celite, the aqueous phase was then extracted with EtOAc (3 × 40 mL). The combined organic layers were washed with water and brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was purified by silica gel chromatography to give aryl ketone **6** as orange solid (313.8 mg, 54% yield).

(+)-2-(4-Methoxyphenyl)-3-(2-(4-methoxyphenyl)-2-oxoethyl)isoindolin-1-one (6): 313.8 mg, 54% Yield of (**6**) as orange solid. R_f = 0.36 (40% EtOAc in hexanes); **^{1}H-NMR** (500 MHz, $CDCl_3$) δ 7.94-7.96 (m, 1H), 7.85 (d, *J* = 8.9 Hz, 2H), 7.49-7.53 (m, 5H), 6.97 (d, *J* = 8.9 Hz, 2H), 6.90 (d, *J* = 8.9 Hz, 2H), 5.90 (dd, *J* = 9.6, 3.2 Hz, 1H), 3.86 (s, 3H), 3.83 (s, 3H), 3.45 (dd, *J* = 17.4, 3.2, 1H), 3.14 (dd, *J* = 17.4, 9.6 Hz, 1H); **^{13}C-NMR** (125 MHz, $CDCl_3$) δ 196.1, 166.9, 163.9, 157.6, 145.4, 132.1, 131.9, 130.4, 129.6, 129.5, 128.6, 125.3, 123.9, 123.2, 114.6, 113.9, 57.6, 55.5, 55.4, 41.5; **IR** (film) υ_{max} 2933, 1691, 1599, 1512, 1250, 1171, 1030, 758 cm^{-1}; **HRMS** (ESI) m/z 388.1551 $[M+H]^+$; calculated for $[C_{24}H_{21}NO_4 + H]^+$: 388.1543; **MP** 52-54 °C; Enantiomeric excess was determined *via* HPLC analysis using a Chiralpak AD-H column; solvent: hexane/2-propanol =65/35; flow rate: 1.0 mL/min; detection: at 254nm): t_R minor = 18.79 min, t_R major = 33.35 min. $[\alpha]_D^{25.0}$ = +166.5 (*c* = 0.4, $CHCl_3$, for 92% ee).

Procedure for the synthesis of compound (7):[17b]

The compound **6** (0.58 mmol, 1.0 equiv) was dissolved in CH_3CN (10 mL) and cooled at −10 °C using ice-salt mixture. An aqueous solution of CAN (2.5 equiv, 1.45 mmol dissolved in 5.0 mL H_2O) was added dropwise, and stirred for 10 min at the same temperature. Upon completion of the reaction (monitored by TLC), the reaction mixture was quenched with saturated aqueous solution of $NaHCO_3$, and extracted with EtOAc (3 x 20 mL). The organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography using EtOAc/hexane as eluent to afford compound **7** as brown solid (137.0 mg, 84% yield).

(−)-3-(2-(4-Methoxyphenyl)-2-oxoethyl)isoindolin-1-one (7): 137.0 mg, 84% Yield of (**7**) as brown solid. R_f = 0.31 (60% EtOAc in hexanes); **^{1}H-NMR** (500 MHz, $CDCl_3$) δ 7.94 (d, *J* = 8.9 Hz, 2H), 7.89 (d, *J* = 7.5 Hz, 1H), 7.61 (td, *J* = 7.5, 1.1 Hz, 1H), 7.49-7.53 (m, 2H), 6.99 (brs, 1H), 6.95 (d, *J* = 8.9 Hz, 2H), 5.15 (dd, *J* = 10.2, 3.0 Hz, 1H), 3.89 (s, 3H), 3.68 (dd, *J* = 17.8, 3.3 Hz, 1H), 3.07 (dd, *J* = 17.8, 10.2 Hz, 1H); **^{13}C-NMR** (125 MHz, $CDCl_3$) δ 196.3, 169.9, 164.1, 146.7, 132.0, 131.9, 130.4, 129.2, 128.5, 124.1, 122.4, 113.9, 55.6, 52.6, 43.7; **IR** (film) υ_{max} 3379, 2909, 1694, 1670, 1600, 1360, 1262, 1170, 768 cm^{-1}; **HRMS** (ESI) m/z 282.1106 $[M+H]^+$; calculated for $[C_{17}H_{15}NO_3 + H]^+$: 282.1125; **MP** 148-150 °C; Enantiomeric excess was determined *via* HPLC analysis using a Chiralpak AD-H column; solvent: hexane/2-propanol =50/50; flow rate: 1.0 mL/min; detection: at 254nm): t_R minor = 8.49 min, t_R major = 12.18 min. $[\alpha]_D^{25.0}$ = –126.7 (*c* = 0.34, $CHCl_3$, for 92% ee).

Procedure for the synthesis of compound (8):[26]

To a solution of compound **7** (0.4 mmol, 1.0 equiv) in CH_2Cl_2 (5 mL) was added Na_2HPO_4 (4.8 mmol, 12.0 equiv) and *m*-CPBA (2.4 mmol, 6.0 equiv). The reaction mixture was then stirred under Ar atmosphere at room temperature for 12 h before it was quenched by 20 mL

of saturated aqueous $Na_2S_2O_3$ solution. After stirred vigorously for 30 min, 20 mL of saturated aqueous $NaHCO_3$ solution was added and extracted with CH_2Cl_2 (3 × 30 mL). The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was purified by column chromatography using EtOAc/hexane as eluent to afford compound **8** as pale yellow solid (103.5 mg, 87% yield).

4-Methoxyphenyl (–)-2-(3-oxoisoindolin-1-yl)acetate (8): 103.5 mg, 87% Yield of (**8**) as pale yellow solid. R_f = 0.38 (60% EtOAc in hexanes); **^{1}H-NMR** (500 MHz, $CDCl_3$) δ 7.91 (d, *J* = 7.6 Hz, 1H), 7.63 (td, *J* = 7.5, 1.1 Hz, 1H), 7.54 (t, *J* = 7.4 Hz, 1H), 7.51 (dd, *J* = 7.6, 0.8 Hz, 1H), 7.16 (brs, 1H), 7.03-7.07 (m, 2H), 6.91-6.95 (m, 2H), 5.06 (dd, *J* = 10.1, 3.7 Hz, 1H), 3.82 (s, 3H), 3.27 (dd, *J* = 17.2, 3.8 Hz, 1H), 2.77 (dd, *J* = 17.2, 10.1 Hz, 1H); **^{13}C-NMR** (125 MHz, $CDCl_3$) δ 170.23, 170.21, 157.6, 145.7, 143.7, 132.2, 131.8, 128.8, 124.2, 122.4, 122.1, 114.6, 55.6, 52.7, 39.7; **IR** (film) υ_{max} 3244, 2920, 1750, 1697, 1505, 1192, 1140, 752 cm^{-1}; **HRMS** (ESI) m/z 298.1092 $[M+H]^+$; calculated for $[C_{17}H_{15}NO_4 + H]^+$: 298.1074; **MP** 138-140 °C; Enantiomeric excess was determined *via* HPLC analysis using a Chiralpak AD-H column; solvent: hexane/2-propanol =70/30; flow rate: 1.0 mL/min; detection: at 254nm): t_R minor = 11.73 min, t_R major = 14.18 min. $[\alpha]_D^{25.0} = -102.9$ (*c* = 0.58, $CHCl_3$, for 92% ee).

Procedure for the synthesis of compound (9):[31]

A solution of aryl ester **8** (0.3 mmol, 1.0 equiv) in MeOH (10 mL) was cooled to 0 °C using ice-water mixture. The reaction mixture was charged with portion wise addition of $NaBH_4$ (20.0 equiv) at the same temperature. The reaction mixture was then stirred for 1 h at 30 °C. Upon completion of the reaction (monitored by TLC), the reaction mixture was quenched with 10 mL of saturated aqueous NH_4Cl solution and the solvent was removed *in vacuo*. The resulting aqueous solution was extracted with EtOAc (5 x 20 mL). The combined organic

layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by small pad of silica gel column chromatography using MeOH/EtOAc as eluent to afford compound **9** as colorless viscous gel (43.6 mg, 82% yield).

(–)-3-(2-Hydroxyethyl)isoindolin-1-one (9): 43.6 mg, 82% Yield of (**9**) as colorless viscous gel. R_f = 0.38 (5% MeOH in EtOAc); **^{1}H-NMR** (400 MHz, DMSO-d_6) δ 8.68 (brs, 1H), 7.56-7.64 (m, 3H), 7.43-7.49 (m, 1H), 4.69 (t, *J* = 5.0 Hz, 1H), 4.63 (dd, *J* = 8.6, 4.0 Hz, 1H), 3.52-3.63 (m, 2H), 2.00-2.08 (m, 1H), 1.49-1.58 (m, 1H); **^{13}C-NMR** (125 MHz, $CDCl_3$) δ 171.3, 147.9, 131.9, 131.6, 128.2, 123.8, 122.4, 60.3, 55.8, 37.1; **IR** (film) υ_{max} 3279, 2925, 1681, 1418, 1368, 1054, 739 cm^{-1}; **HRMS** (ESI) m/z 178.0889 $[M+H]^+$; calculated for $[C_{10}H_{11}NO_2 + H]^+$: 178.0863; Enantiomeric excess was determined *via* HPLC analysis using a Chiralpak AD-H column; solvent: hexane/2-propanol =90/10; flow rate: 0.5 mL/min; detection: at 254nm): t_R major = 32.13 min, t_R minor = 34.14 min. $[\alpha]_D^{25.0}$ = –115.3 (*c* = 0.30, $CHCl_3$, for 91% ee).

Procedure for the synthesis of compound (*S*)-PD 172938 (1a):[12]

Step-I:

To a solution of alcohol **9** (0.2 mmol, 1.0 equiv) in CH_2Cl_2 (6 mL) was cooled to 0 °C using ice-water bath. Et_3N (0.6 mmol, 3.0 equiv) was added to the reaction mixture followed by dropwise addition of methanesulfonyl chloride (0.24 mmol, 1.2 equiv). The reaction mixture was stirred for 4 h at room temperature. Once the starting material was completely consumed, it was diluted with CH_2Cl_2. The diluted reaction mixture was washed with 1 N HCl (2 mL). The organic layer was dried over anhydrous Na_2SO_4 and filtered through Celite to get the crude product which was used for the next step without further purification.

Step-II:

A DMF (4 mL) solution of the above product (0.2 mmol, 1.0 equiv), 1-(3,4-dimethylphenyl)piperazine, **10** (0.2 mmol, 1.0 equiv), and *N*,*N*-diisopropylethylamine (0.6 mmol, 3.0 equiv) was stirred for 16 h at 80 °C. Once starting material completely consumed (monitored by TLC), the volatile component was removed *in vacuo*. The residue was partitioned between EtOAc and water, and the organic layer was washed with water and brine, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The resulting crude material was purified by silica gel column chromatography using the solvent system MeOH/EtOAc/NH_4OH to afford the title compound **1a** as an off-white solid (57.3 mg, 82% over two steps).

(–)-3-(2-(4-(3,4-Dimethylphenyl)piperazin-1-yl)ethyl)isoindolin-1-one (1a): 57.3 mg, 82% Yield (over 2 steps) of (**1a**) as off-white solid. R_f = 0.28 (5% MeOH/CH_2Cl_2); **^{1}H-NMR** (700 MHz, $CDCl_3$) δ 7.88 (d, *J* = 7.6 Hz, 1H), 7.59 (td, *J* = 7.5, 1.0 Hz, 1H), 7.49 (t, *J* = 7.4 Hz, 1H), 7.50 (dd, *J* = 7.6, 0.6 Hz, 1H), 7.35 (brs, 1H), 7.05 (d, *J* = 8.2 Hz, 1H), 6.78 (d, *J* = 2.4 Hz, 1H), 6.72 (dd, *J* = 8.2, 2.6 Hz, 1H), 4.66 (dd, *J* = 10.0, 2.9 Hz, 1H), 3.18-3.24 (m, 4H), 2.71-2.75 (m, 3H), 2.64 (dt, *J* = 12.5, 4.9 Hz, 1H), 2.56-2.59 (m, 2H), 2.26 (s, 3H), 2.21 (s, 3H), 2.15-2.19 (m, 1H), 1.75-1.80 (m, 1H); **^{13}C-NMR** (125 MHz, $CDCl_3$) δ 170.1, 149.5, 147.5, 137.1, 132.0, 131.7, 130.1, 128.3, 128.2, 123.9, 122.2, 118.3, 114.0, 57.2, 56.7, 53.4, 49.8, 31.3, 20.2, 18.8; **IR** (film) υ_{max} 3227, 2923, 2853, 1693, 1614, 1506, 1356, 1139, 1003 cm^{-1}; **HRMS** (ESI) m/z 350.2242 $[M+H]^+$; calculated for $[C_{22}H_{27}N_3O + H]^+$: 350.2227; **MP** 133-135 °C; Enantiomeric excess was determined *via* HPLC analysis using a Chiralpak AD-H column; solvent: hexane/2-propanol =75/25; flow rate: 1.0 mL/min; detection: at 254nm): t_R minor = 8.98 min, t_R major = 11.04 min. $[\alpha]_D^{25.0}$ = –44.2 (*c* = 0.90, $CHCl_3$, for 91% ee).

4-Methoxyphenyl (+)-2-(2-(4-methoxyphenyl)-3-oxoisoindolin-1-yl)acetate (11): 217.8 mg, 90% Yield of (**11**) as pale yellow solid. R_f = 0.37 (40% EtOAc in hexanes); **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.93 (d, *J* = 7.4 Hz, 1H), 7.51-7.60 (m, 3H), 7.44 (d, *J* = 8.8 Hz, 2H), 6.98 (d, *J* = 8.8 Hz, 2H), 6.82 (d, *J* = 9.0 Hz, 2H), 6.76 (d, *J* = 9.0 Hz, 2H), 5.55 (dd, *J* = 7.4, 4.5 Hz, 1H), 3.82 (s, 3H), 3.76 (s, 3H), 3.10 (dd, *J* = 16.1, 4.4 Hz, 1H), 2.77 (dd, *J* = 16.1, 7.7 Hz, 1H); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ 169.2, 166.9, 158.1, 157.5, 143.9, 143.6, 132.2, 132.1, 129.1, 129.0, 126.3, 124.3, 122.6, 122.0, 114.7, 114.5, 58.2, 55.6, 55.5, 37.7; **IR** (film) υ_{max} 2927, 1751, 1694, 1509, 1388, 1299, 1248, 1192, 1135, 1031, 758 cm^{-1}; **HRMS** (ESI) m/z 404.1520 $[M+H]^+$; calculated for $[C_{24}H_{21}NO_5 + H]^+$: 404.1492; **MP** 116-118 °C; Enantiomeric excess was determined *via* HPLC analysis using a Chiralpak AD-H column; solvent: hexane/2-propanol =65/35; flow rate: 1.0 mL/min; detection: at 254nm): t_R minor = 20.75 min, t_R major = 25.83 min. $[\alpha]_D^{25.0}$ = +52.4 (*c* = 0.34, $CHCl_3$, for 93% ee).

Procedure for the synthesis of compound (12):

A solution of aryl ester **11** (0.4 mmol, 1.0 equiv) in freshly distilled THF (6 mL) was cooled to 0 °C using ice-water mixture. The reaction mixture was charged with portion wise addition of $LiBH_4$ (5.0 equiv) at the same temperature. The reaction mixture was gradually allowed to stir at room temperature for 1 h. Upon completion of the reaction (monitored by TLC), the reaction mixture was quenched with 10 mL of saturated aqueous NH_4Cl solution and the solvent was removed *in vacuo*. The resulting aqueous solution was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by short pad of silica gel column chromatography using EtOAc/hexane as eluent to afford compound **12** as pale yellow solid (100.8 mg, 89% yield).

(+)-3-(2-Hydroxyethyl)-2-(4-methoxyphenyl)isoindolin-1-one (12): 100.8 mg, 89% Yield of (**12**) as pale yellow solid. R_f = 0.29 (60% EtOAc in hexanes); **^{1}H-NMR** (500 MHz, $CDCl_3$) δ 7.93 (d, *J* = 7.5 Hz, 1H), 7.62 (td, *J* = 7.6, 1.1 Hz, 1H), 7.57 (d, *J* = 6.8 Hz, 1H), 7.53 (d, *J* = 7.4 z, 1H), 7.45-7.48 (m, 2H), 6.97-7.00 (m, 2H), 5.31 (dd, *J* = 6.1, 4.2 Hz, 1H), 3.85 (s, 3H), 3.47-3.56 (m, 2H), 2.20-2.27 (m, 1H), 2.04-2.10 (m, 1H), 1.74 (brs, 1H); **^{13}C-NMR** (125 MHz, $CDCl_3$) δ 167.2, 157.6, 144.6, 132.2, 131.9, 129.8, 128.5, 125.5, 124.2, 122.5, 114.5, 58.9, 58.0, 55.5, 34.4; **IR** (film) υ_{max} 3398, 2920, 1670, 1512, 1395, 1247, 1036, 771 cm^{-1}; **HRMS** (ESI) m/z 284.1282 $[M+H]^+$; calculated for $[C_{17}H_{17}NO_3 + H]^+$: 284.1281; **MP** 137-139 °C; Enantiomeric excess was determined *via* HPLC analysis using a Chiralpak AD-H column; solvent: hexane/2-propanol =85/15; flow rate: 1.0 mL/min; detection: at 254nm): t_R minor = 31.69 min, t_R major = 36.81 min. $[\alpha]_D^{25.0}$ = +25.0 (*c* = 0.28, $CHCl_3$, for 93% ee).

Procedure for the synthesis of compound (13):

Method A: Oxidation of primary alcohol[32]

To a solution of alcohol **12** (0.2 mmol, 1.0 equiv) in CH_3CN/EtOAc/H_2O (7 mL, 2:2:3, v/v/v) were added $NaIO_4$ (0.82 mmol, 4.1 equiv) and $RuCl_3.H_2O$ (5 mol %) sequentially. The reaction mixture was then allowed to stir at RT for 1 h. Upon completion of the reaction (monitored by TLC), the reaction mixture was filtered through Celite to remove insoluble solids. The aqueous layer was then extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was purified by small pad of silica gel column chromatography using MeOH/EtOAc as eluent to afford compound **13** as white solid (49.4 mg, 83% yield).

Method B: Aryl ester hydrolysis using $LiOH.H_2O$[33]

The aryl ester **11** (0.2 mmol, 1.0 equiv) was dissolved in THF/H_2O (4 mL, 1:1, v/v) and LiOH.H_2O (1.0 mmol, 5.0 equiv) was added. The reaction mixture was stirred at room temperature for 3 h. Upon completion of the reaction (monitored by TLC), the reaction mixture was neutralized with 1 N HCl and extracted with EtOAc (3 X 15 mL). The solvent was removed *in vacuo*. The residue was purified by short pad of silica gel column chromatography using MeOH/EtOAc as eluent to afford compound **13** as white solid (47.6 mg, 80% yield).

(+)-2-(2-(4-Methoxyphenyl)-3-oxoisoindolin-1-yl)acetic acid (13): **Method A**: 49.4 mg, 83% Yield of (**13**) as white solid. R_f = 0.28 (10% MeOH in EtOAc); **^{1}H-NMR** (400 MHz, CD_3OD) δ 7.80 (d, *J* = 7.5 Hz, 1H), 7.70 (d, *J* = 7.5 Hz, 1H), 7.62 (t, *J* = 7.3 Hz, 1H), 7.52 (t, *J* = 7.4 Hz, 1H), 7.43 (d, *J* = 8.8 Hz, 2H), 7.01 (d, *J* = 8.8 Hz, 2H), 5.53 (dd, *J* = 8.4, 3.7 Hz, 1H), 3.81 (s, 3H), 2.83 (dd, *J* = 15.8, 3.6 Hz, 1H), 2.33 (dd, *J* = 13.9, 9.5 Hz, 1H); **^{13}C-NMR** (125 MHz, CD_3OD) δ 167.9, 158.4, 145.7, 132.0, 131.3, 128.9, 128.3, 126.4, 123.0, 122.9, 114.1, 59.6, 54.5, 38.4; **IR** (film) υ_{max} 2920, 1644, 1513, 1394, 1248, 1157, 758 cm^{-1}; **HRMS** (ESI) m/z 298.1077 $[M+H]^+$; calculated for $[C_{17}H_{15}NO_4 + H]^+$: 298.1074; **MP** 175-177 °C; $[\alpha]_D^{25.0}$ = +25.3 (*c* = 0.45, $CHCl_3$).

Procedure for the synthesis of compound (14):[13]

To a solution of an acid **13** (0.1 mmol, 1.0 equiv), 1,4-dioxa-8-azaspiro[4.5]decane (0.1 mmol, 1.0 equiv), *N*-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride (0.1 mmol, 1.0 equiv) and 1-hydroxybenzotriazole monohydrate (0.1 mmol, 1.0 equiv) in freshly distilled THF (5 ml) were allowed to stir at RT for 16 h. The solvent was then concentrated under reduced pressure. The residue was redissolved in EtOAc (15 mL) and H_2O (10 mL) and the organic layer was separated. The aqueous layer was extracted thrice with EtOAc (3 x

15 mL). The combined organic layers were then washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography using EtOAc/hexane as eluent to afford compound **14** as white solid (36.8 mg, 87% yield).

(+)-2-(4-Methoxyphenyl)-3-(2-oxo-2-(1,4-dioxa-8-azaspiro[4.5]decan-8-yl)ethyl)isoindolin-1-one (14): 36.8 mg, 87% Yield of (**14**) as white solid. R_f = 0.42 (80% EtOAc in hexanes); **^{1}H-NMR** (500 MHz, $CDCl_3$) δ 7.92 (d, *J* = 7.4 Hz, 1H), 7.63 (d, *J* = 7.5 Hz, 1H), 7.57 (t, *J* = 7.4 Hz, 1H), 7.50-7.53 (m, 3H), 6.99 (d, *J* = 8.9 Hz, 2H), 5.80 (dd, *J* = 9.3, 3.5 Hz, 1H), 3.92-3.98 (m, 4H), 3.84 (s, 3H), 3.74-3.79 (m, 1H), 3.67-3.72 (m, 1H), 3.27-3.36 (m, 2H), 2.89 (dd, *J* = 15.9, 3.6 Hz, 1H), 2.44 (dd, *J* = 15.9, 9.4 Hz, 1H), 1.63-1.71 (m, 2H), 1.51 (t, *J* = 5.7 Hz, 2H); **^{13}C-NMR** (125 MHz, $CDCl_3$) δ 167.9, 166.8, 157.5, 145.3, 132.1, 131.8, 129.4, 128.6, 125.1, 123.9, 123.2, 114.5, 106.6, 64.5, 58.4, 55.5, 43.5, 40.0, 36.4, 35.4, 34.7; **IR** (film) υ_{max} 2920, 1750, 1697, 1505, 1192, 1140, 752 cm^{-1}; **HRMS** (ESI) m/z 423.1919 $[M+H]^+$; calculated for $[C_{24}H_{26}N_2O_5 + H]^+$: 423.1914; **MP** 153-155 °C; Enantiomeric excess was determined *via* HPLC analysis using a Chiralpak AD-H column; solvent: hexane/2-propanol =65/35; flow rate: 1.0 mL/min; detection: at 254nm): t_R minor = 14.89 min, t_R major = 24.68 min. $[\alpha]_D^{25.0}$ = +97.1 (*c* = 0.31, $CHCl_3$, for 93% ee).

Procedure for the synthesis of compound (15):[26]

To a solution of aryl ester **11** (0.2 mmol, 1.0 equiv) in EtOH was added K_2CO_3 (0.6 mmol, 3.0 equiv). The reaction mixture was stirred at room temperature for 4 h. Solvent was removed and it was purified by silica gel coumn chromatography (hexanes/ethyl acetate as eluent) to afford ethyl ester **15** as a colorless viscous gel (59.9 mg, 92% yield).

Ethyl (+)-2-(2-(4-methoxyphenyl)-3-oxoisoindolin-1-yl)acetate (15): 59.9 mg, 92% Yield of (**15**) as colorless viscous gel. R_f = 0.44 (40% EtOAc in hexanes); **^{1}H-NMR** (500 MHz, $CDCl_3$) δ 7.95 (d, *J* = 7.9 Hz, 1H), 7.60 (t, *J* = 7.3 Hz, 1H), 7.53-7.59 (m, 2H), 7.45 (d, *J* = 8.9 Hz, 2H), 7.00 (d, *J* = 8.9 Hz, 2H), 5.50 (dd, *J* = 8.1, 4.4 Hz, 1H), 4.04-4.13 (m, 2H), 3.85 (s, 3H), 2.90 (dd, *J* = 16.1, 4.4 Hz, 1H), 2.54 (dd, *J* = 16.0, 8.2 Hz, 1H), 1.18 (t, *J* = 7.1 Hz, 3H); **^{13}C-NMR** (125 MHz, $CDCl_3$) δ 170.4, 166.9, 157.9, 144.3, 132.1, 132.0, 129.2, 128.8, 126.1, 124.2, 122.5, 114.6, 61.0, 58.2, 55.5, 37.8, 14.0; **IR** (film) υ_{max} 2920, 1732, 1693, 1513, 1389, 1248, 1177, 1034, 758 cm^{-1}; **HRMS** (ESI) m/z 326.1411 $[M+H]^+$; calculated for $[C_{19}H_{19}NO_4 + H]^+$: 326.1387; Enantiomeric excess was determined *via* HPLC analysis using a Chiralpak AD-H column; solvent: hexane/2-propanol =65/35; flow rate: 1.0 mL/min; detection: at 254nm): t_R minor = 10.61 min, t_R major = 12.86 min. $[\alpha]_D^{25.0}$ = +44.5 (*c* = 0.35, $CHCl_3$, for 69% ee).

Procedure for the synthesis of compound (17):[27]

A 50 mL round bottom sealed flask equipped with a magnetic stir bar was charged with $Pd(OAc)_2$ (1 mmol, 0.1 equiv) followed by K_2HPO_4 (30 mmol, 3.0 equiv), 2,3-dihydro-1*H*-indene-5-carboxylic acid (10 mmol, 1.0 equiv), and CH_2Br_2 (25 mL). The reaction tube was sealed with a Teflon tube and was stirred at 140 °C for 36 h, after which it was filtered through a small pad of Celite. The filtrate was concentrated *in vacuo* and the residue was purified by silica gel column chromatography (CH_2Cl_2/hexane as eluent) to give the corresponding product **17** as a white solid (853.6 mg, 49% yield).

3,5,6,7-tetrahydro-1*H*-indeno[5,6-*c*]furan-1-one (17): 853.6 mg, 49% Yield of (**17**) as white solid. R_f = 0.5 (70% CH_2Cl_2 in hexanes); **^{1}H-NMR** (500 MHz, $CDCl_3$) δ 7.71 (s, 1H), 7.30 (s, 1H), 5.25 (s, 2H), 3.00 (q, *J* = 7.7 Hz, 4H), 2.17 (quint, *J* = 7.4 Hz, 2H); **^{13}C-NMR**

(125 MHz, $CDCl_3$) δ 171.4, 152.3, 146.0, 145.6, 124.1, 121.0, 117.6, 69.4, 33.0, 33.2, 25.8; **IR** (film) υ_{max} 2922, 2847, 1746, 1641, 1451, 1012, 771 cm^{-1}; **HRMS** (ESI) m/z 175.0769 $[M+H]^+$; calculated for $[C_{11}H_{10}O_2 + H]^+$: 175.0754; **MP** 116-118 °C.

Procedure for the synthesis of compound (18):[30]

To a solution of compound **17** (3.6 mmol, 1.0 equiv) in an aqueous solution of MeOH (85%, 20 mL) was added KOH pellets (5.4 mmol, 1.5 equiv). The reaction mixture was refluxed for 2 h. After cooling to room temperature, the reaction mixture was concentrated *in vacuo* to remove MeOH, and the residue was diluted with H_2O (10 mL). The mixture was then neutralized to pH 4-5 by addition of a solution of $KHSO_4$ (1 M). The formed solid was filtrated, and washed with water (3 x 5 mL) to give product **18** as a white solid (657.3 mg, 95% yield).

6-(Hydroxymethyl)-2,3-dihydro-1*H*-indene-5-carboxylic acid (18): 657.3 mg, 95% Yield of (**18**) as white solid. R_f = 0.2 (60% EtOAc in hexanes); **^{1}H-NMR** (500 MHz, DMSO-d_6) δ 7.71 (s, 1H), 7.55 (s, 1H), 4.79 (s, 2H), 3.38 (brs, 1H), 2.85-2.91 (m, 4H), 2.03 (quint, J = 7.4 Hz, 2H); **^{13}C-NMR** (125 MHz, DMSO-d_6) δ 169.1, 148.7, 143.3, 142.2, 126.7, 126.4, 123.2, 61.8, 33.0, 32.2, 25.4; **IR** (film) υ_{max} 3292, 2946, 1687, 1413, 1254, 1042, 803 cm^{-1}; **HRMS** (ESI) m/z 215.0670 $[M+Na]^+$; calculated for $[C_{11}H_{12}O_3 + Na]^+$: 215.0679; **MP** 134-136 °C.

Procedure for the synthesis of compound (19):[30]

To a solution of compound **18** (3.0 mmol, 1.0 equiv) in dry THF (50 mL) were added Celite (600 mg), and active MnO_2 (60 mmol, 20.0 equiv) sequentially. The reaction mixture was stirred at room temperature for 12 h. Upon completion of the reaction (monitored by TLC),

the reaction was filtered through small pad of Celite, and the filtrate was concentrated. The residue was purified by a silica gel chromatography (EtOAc/Hexane) to give product **19** as a white solid (325.2 mg, 57% yield).

3-Hydroxy-3,5,6,7-tetrahydro-1*H*-indeno[5,6-*c*]furan-1-one (19): 325.2 mg, 57% Yield of (**19**) as white solid. R_f = 0.5 (50% EtOAc in hexanes); **^{1}H-NMR** (500 MHz, DMSO-d_6) δ 8.04 (s, 1H), 7.61 (s, 1H), 7.47 (s, 1H), 6.57 (s, 1H), 2.92-2.98 (m, 4H), 2.09 (quint, *J* = 7.5 Hz, 2H); **^{13}C-NMR** (125 MHz, DMSO-d_6) δ 169.0, 152.4, 147.5, 147.0, 125.5, 120.3, 119.7, 98.2, 32.9, 32.2, 25.8; **IR** (film) υ_{max} 3362, 2952, 2844, 1744, 1619, 1436, 1152, 1083, 927 cm^{-1}; **HRMS** (ESI) m/z 213.0520 $[M+Na]^+$; calculated for $[C_{11}H_{10}O_3 + Na]^+$: 213.0522; **MP** 101-103 °C.

Procedure for the synthesis of compounds (20a-c):

A solution of a ligand *ent*-**4b** (*R*,*R*)-^{i}Pr-PyBOX-DiPh (0.03 mmol, 10 mol %) and $(CuOTf)_2$.PhMe complex (0.03 mmol, 10 mol %) in dry chloroform (3 mL) was stirred at 0 °C for 20 min under nitrogen atmosphere. An aldehyde **3b** (0.3 mmol) and aromatic amine (0.3 mmol) were added and the whole mixture was stirred for additional 30 min followed by addition of alkyne (0.36 mmol) at the same temperature. The reaction mixture was gradually allowed to warm up to 25 ºC. After stirring for 12 h, 20 mol % of *p*-fluorobenzoic acid was added to the reaction mixture and allowed to stir for another 10-20 h for the completion of lactamization step. The mixture was concentrated *in vacuo* and purified over silica gel by column chromatography (EtOAc/hexane as eluent) affording products **20a-c** in upto 95% yield and upto 99% enantioselectivities.

(–)-3-((4-Methoxyphenyl)ethynyl)-2-phenyl-3,5,6,7-tetrahydrocyclopenta[*f*]isoindol-1(2*H*)-one (20a): 107.0 mg, 94% Yield of (**20a**) as white solid. R_f = 0.3 (15% EtOAc in hexanes); **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.85 (d, *J* = 7.7 Hz, 2H), 7.73 (s, 1H), 7.50 (s, 1H), 7.43 (t, *J* = 8.0 Hz, 2H), 7.17-7.24 (m, 3H), 6.75 (d, *J* = 8.8 Hz, 2H), 5.92 (s, 1H), 3.75 (s, 3H), 3.00 (dd, *J* = 16.1, 8.0 Hz, 4H), 2.15 (quint, *J* = 7.4 Hz, 2H); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ 167.0, 159.9, 150.3, 145.9, 140.7, 138.0, 133.3, 130.1, 128.9, 124.9, 121.9, 119.7, 118.7, 114.0, 113.8, 85.8, 82.6, 55.2, 53.0, 33.1, 32.4, 25.7; **IR** (film) υ_{max} 2924, 2851, 2120, 1700, 1603, 1508, 1448, 1359, 1250, 1031, 772 cm^{-1}; **HRMS** (ESI) m/z 402.1459 $[M+Na]^+$; calculated for $[C_{26}H_{21}NO_2 + Na]^+$: 402.1465; **MP** 175-177 °C; Enantiomeric excess was determined *via* HPLC analysis using a Chiralpak IA column; solvent: hexane/2-propanol =80/20; flow rate: 1.0 mL/min; detection: at 254nm): t_R minor = 12.64 min, t_R major = 19.70 min. $[\alpha]_D^{25.0}$ = –7.8 (*c* = 0.50, $CHCl_3$, for 97% ee).

(–)-2-(4-Methoxyphenyl)-3-((4-methoxyphenyl)ethynyl)-3,5,6,7-tetrahydrocyclopenta[*f*]isoindol-1(2*H*)-one (20b): 116.7 mg, 95% Yield of (**20b**) as white solid. R_f = 0.28 (20% EtOAc in hexanes); **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.71 (s, 1H), 7.67 (d, *J* = 9.1 Hz, 2H), 7.48 (s, 1H), 7.23 (d, *J* = 8.8 Hz, 2H), 6.96 (d, *J* = 9.1 Hz, 2H), 6.75 (d, *J* = 8.8 Hz, 2H), 5.83 (s, 1H), 3.80 (s, 3H), 3.75 (s, 3H), 2.98 (dd, *J* = 15.3, 7.6 Hz, 4H), 2.14 (quint, *J* = 7.4 Hz, 2H); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ 166.9, 159.9, 157.3, 150.1, 145.8, 140.8, 133.3, 131.0, 130.1, 124.5, 119.6, 118.7, 114.2, 114.1, 133.9, 85.8, 82.8, 55.4, 55.3, 53.7, 33.1, 32.5, 25.8; **IR** (film) υ_{max} 2954, 2095, 1693, 1605, 1510, 1249, 1032, 773 cm^{-1}; **HRMS** (ESI) m/z 432.1575 $[M+Na]^+$; calculated for $[C_{27}H_{23}NO_3 + Na]^+$: 432.1570; **MP** 168-170 °C; Enantiomeric excess was determined *via* HPLC analysis using a Chiralpak IA column; solvent: hexane/2-propanol =80/20; flow rate: 1.0 mL/min; detection: at 254nm): t_R minor = 22.09 min, t_R major = 41.71 min. $[\alpha]_D^{25.0}$ = –27.4 (*c* = 0.35, $CHCl_3$, for 99% ee).

(–)-2-(4-Fluorophenyl)-3-((4-methoxyphenyl)ethynyl)-3,5,6,7-tetrahydrocyclopenta[*f*]isoindol-1(2*H*)-one (20c): 108.5 mg, 91% Yield of (**20c**) as white solid. R_f = 0.32 (15% EtOAc in hexanes); **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.75-7.79 (m, 2H), 7.72 (s, 1H), 7.49 (s, 1H), 7.23 (d, *J* = 8.8 Hz, 2H), 7.12 (t, *J* = 8.7 Hz, 2H), 6.76 (d, *J* = 8.8 Hz, 2H), 5.87 (s, 1H), 3.76 (s, 3H), 3.00 (dd, *J* = 16.5, 7.8 Hz, 4H), 2.15 (quint, *J* = 7.5 Hz, 2H); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ 166.9, 160.0 (d, *J* = 243.1 Hz), 160.0, 150.5, 146.0, 140.7, 134.1 (d, *J* = 2.8 Hz), 133.3, 129.9, 124.1 (d, *J* = 8.0 Hz), 119.7, 118.8, 115.6 (d, *J* = 22.3 Hz), 113.9, 113.8, 86.1, 82.4, 55.3, 53.4, 33.1, 32.4, 25.8; **IR** (film) υ_{max} 2952, 2101, 1688, 1607, 1509, 1365, 1250, 1156 cm^{-1}; **HRMS** (ESI) m/z 420.1351 $[M+Na]^+$; calculated for $[C_{26}H_{20}FNO_2 + Na]^+$: 420.1370; **MP** 150-152 °C; Enantiomeric excess was determined *via* HPLC analysis using a Chiralpak IA column; solvent: hexane/2-propanol =80/20; flow rate: 1.0 mL/min; detection: at 254nm): t_R minor = 13.62 min, t_R major = 27.36 min. $[\alpha]_D^{25.0}$ = –8.1 (*c* = 0.49, $CHCl_3$, for 95% ee).

(–)-3-(2-(4-Methoxyphenyl)-2-oxoethyl)-2-phenyl-3,5,6,7-tetrahydrocyclopenta[*f*]isoindol-1(2*H*)-one (21): 141.9 mg, 51% Yield of (**21**) as yellow solid. R_f = 0.32 (30% EtOAc in hexanes); **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.82 (d, *J* = 8.9 Hz, 2H), 7.71 (s, 1H), 7.63 (d, *J* = 7.6 Hz, 2H), 7.39 (t, *J* = 7.9 Hz, 2H), 7.29 (s, 1H), 7.16 (t, *J* = 7.4 Hz, 1H), 6.86 (d, *J* = 8.9 Hz, 2H), 5.89 (dd, *J* = 9.6, 2.3 Hz, 1H), 3.81 (s, 3H), 3.43 (d, *J* = 17.6, 2.7 Hz, 1H), 3.11 (dd, *J* = 17.6, 9.8 Hz, 1H), 2.81-2.96 (m, 4H), 2.02-2.14 (m, 2H); **^{13}C-NMR** (125 MHz, $CDCl_3$) δ 196.2, 167.2, 163.9, 149.9, 145.2, 144.2, 137.0, 130.4, 130.2, 129.5, 129.2, 125.2, 122.9, 119.6, 118.9, 113.8, 56.5, 55.5, 41.8, 33.1, 32.4, 25.7; **IR** (film) υ_{max} 2923, 2845, 1696, 1673, 1599, 1494, 1374, 1261, 1169, 758 cm^{-1}; **HRMS** (ESI) m/z 398.1769 $[M+H]^+$; calculated for $[C_{26}H_{23}NO_3 + H]^+$: 398.1751; **MP** 149-151 °C;

Enantiomeric excess was determined *via* HPLC analysis using a Chiralpak AD-H column; solvent: hexane/2-propanol =70/30; flow rate: 1.0 mL/min; detection: at 254nm): t_R major = 16.04 min, t_R minor = 18.64 min. $[\alpha]_D^{25.0} = -69.7$ (c = 0.33, $CHCl_3$, for 93% ee).

4-Methoxyphenyl (–)-2-(3-oxo-2-phenyl-1,2,3,5,6,7-hexahydrocyclopenta[*f*]isoindol-1-yl)acetate (**22**): 106.7 mg, 86% Yield of (**22**) as white solid. R_f = 0.35 (30% EtOAc in hexanes); **^{1}H-NMR** (400 MHz, $CDCl_3$) δ 7.75 (s, 1H), 7.59 (d, J = 7.7 Hz, 2H), 7.45 (t, J = 7.9 Hz, 2H), 7.41 (s, 1H), 7.23-7.27 (m, 1H), 6.80-6.86 (m, 4H), 5.60 (dd, J = 8.8, 4.0 Hz, 1H), 3.77 (s, 3H), 3.15 (dd, J = 16.2, 4.0 Hz, 1H), 2.98 (t, J = 7.4 Hz, 4H), 2.74 (dd, J = 16.1, 8.2 Hz, 1H), 2.15 (quint, J = 7.4 Hz, 2H); **^{13}C-NMR** (100 MHz, $CDCl_3$) δ 169.5, 167.1, 157.5, 150.0, 145.7, 143.7, 142.7, 136.7, 130.5, 129.3, 125.8, 123.9, 122.1, 119.9, 118.4, 114.5, 57.1, 55.6, 38.0, 33.1, 32.4, 25.7; **IR** (film) υ_{max} 2921, 2851, 1751, 1698, 1504, 1378, 1246, 1192, 1034 cm^{-1}; **HRMS** (ESI) m/z 414.1724 $[M+H]^+$; calculated for $[C_{26}H_{23}NO_4 + H]^+$: 414.1700; **MP** 150-152 °C; Enantiomeric excess was determined *via* HPLC analysis using a Chiralpak IA column; solvent: hexane/2-propanol =80/20; flow rate: 1.0 mL/min; detection: at 254nm): t_R major = 29.48 min, t_R minor = 33.18 min. $[\alpha]_D^{25.0} = -51.2$ (c = 0.21, $CHCl_3$, for 94% ee).

(–)-3-(2-Hydroxyethyl)-2-phenyl-3,5,6,7-tetrahydrocyclopenta[*f*]isoindol-1(2*H*)-one (23): 67.5 mg, 92% Yield of (**23**) as white solid. R_f = 0.3 (50% EtOAc in hexanes); **^{1}H-NMR** (700 MHz, $CDCl_3$) δ 7.74 (s, 1H), 7.57-7.59 (m, 2H), 7.42-7.45 (m, 2H), 7.39 (s, 1H), 7.23 (tt, J = 7.4, 1.0 Hz, 1H), 5.34 (dd, J = 6.2, 3.8 Hz, 1H), 3.45-3.52 (m, 2H), 2.97-3.04 (m, 4H), 2.20-2.25 (m, 1H), 2.15-2.19 (m, 2H), 2.04-2.09 (m, 1H), 1.84 (brs, 1H); **^{13}C-NMR** (176 MHz, $CDCl_3$) δ 167.5, 149.8, 145.2, 143.3, 137.2, 130.5, 129.1, 125.4, 123.4, 119.8, 118.3, 58.1, 57.9, 34.3, 33.1, 32.4, 25.8; **IR** (film) υ_{max} 3393, 2922, 2851, 1671, 1495, 1388, 1050, 763

cm^{-1}; **HRMS** (ESI) m/z 294.1507 $[M+H]^+$; calculated for $[C_{19}H_{19}NO_2 + H]^+$: 294.1489; **MP** 122-124 °C; Enantiomeric excess was determined *via* HPLC analysis using a Chiralpak AD-H column; solvent: hexane/2-propanol =75/25; flow rate: 1.0 mL/min; detection: at 254nm): t_R minor = 11.63 min, t_R major = 15.31 min. $[\alpha]_D^{25.0} = -24.2$ (c = 0.22, $CHCl_3$, for 93% ee).

(*R*)-2-(3-Oxo-2-phenyl-1,2,3,5,6,7-hexahydrocyclopenta[*f*]isoindol-1-yl)acetic acid (24)[13]: **Method A-** 49.2 mg, 80% Yield of (**24**) as white solid. R_f = 0.34 (10% MeOH in EtOAc); **^{1}H-NMR** (400 MHz, CD_3OD) δ 7.63 (s, 1H), 7.54 (d, J = 7.5 Hz, 2H), 7.44-7.48 (m, 3H), 7.28 (t, J = 7.4 Hz, 1H), 5.57 (dd, J = 7.6, 3.8 Hz, 1H), 2.99 (dd, J = 13.4, 6.9 Hz, 4H), 2.88 (dd, J = 16.2, 3.9 Hz, 1H), 2.50 (dd, J = 16.2, 7.7 Hz, 1H), 2.14 (quint, J = 7.4 Hz, 2H); **^{13}C-NMR** (100 MHz, DMSO-d_6) δ 171.5, 166.7, 149.6, 145.2, 143.9, 137.3, 130.6, 129.3, 125.6, 123.9, 119.2, 119.0, 57.0, 36.7, 32.9, 32.3, 25.8; **IR** (film) υ_{max} 2924, 1677, 1384, 1249, 1169, 763 cm^{-1}; **HRMS** (ESI) m/z 308.1298 $[M+H]^+$; calculated for $[C_{19}H_{17}NO_3 + H]^+$: 308.1281; **MP** 198-200 °C.

(–)-3-(2-(4-Methylpiperazin-1-yl)-2-oxoethyl)-2-phenyl-3,5,6,7-tetrahydrocyclopenta[*f*]isoindol-1(2*H*)-one (1b)[13]: 33.5 mg, 86% Yield of (**1b**) as white solid. R_f = 0.48 (10% MeOH in CH_2Cl_2); **^{1}H-NMR** (500 MHz, $CDCl_3$) δ 7.74 (s, 1H), 7.65 (d, J = 7.8 Hz, 2H), 7.43-7.46 (m, 3H), 7.22 (t, J = 7.4 Hz, 1H), 5.81 (dd, J = 9.2, 3.3 Hz, 1H), 3.63-3.73 (m, 2H), 3.19-3.30 (m, 2H), 2.99 (t, J = 7.4 Hz, 4H), 2.89 (dd, J = 15.9, 3.4 Hz, 1H), 2.37-2.45 (m, 3H), 2.27 (s, 3H), 2.22 (t, J = 4.9 Hz, 2H), 2.12-2.18 (m, 2H); **^{13}C-NMR** (125 MHz, $CDCl_3$) δ 168.3, 167.1, 149.9, 145.3, 144.0, 136.9, 130.1, 129.1, 125.2, 122.9, 119.6, 119.1, 57.4, 54.8, 54.5, 45.9, 45.3, 41.6, 36.6, 33.1, 32.4, 25.7; **IR** (film) υ_{max} 2937, 1694, 1638, 1450, 1376, 1291, 1141, 1001, 849, 758 cm^{-1}; **HRMS** (ESI) m/z 390.2206 $[M+H]^+$; calculated for $[C_{24}H_{27}N_3O_2 + H]^+$: 390.2176; Enantiomeric excess was determined

via HPLC analysis using a Chiralpak IA column; solvent: hexane/2-propanol =70/30; flow rate: 1.0 mL/min; detection: at 254nm): t_R major = 13.19 min, t_R minor = 22.06 min. $[\alpha]_D^{25.0}$ = −51.9 (*c* = 0.35, $CHCl_3$, for 94% ee).

ASSOCIATED CONTENT

Supporting Information

Copies of ^1H, ^{13}C NMR spectra, and HPLC chromatograms for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org

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Notes

The authors declare no competing financial interest.

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