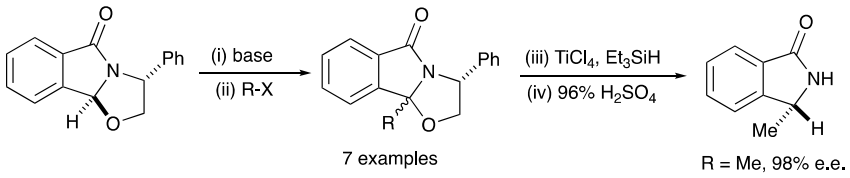
Graphical Abstract



A Novel and Highly Stereoselective Route for the Synthesis of Non-racemic 3-Substituted Isoindolin-1-one Targets

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Abstract

A new, versatile and highly stereoselective approach for the synthesis of non-racemic 3-substituted isoindolin-1-ones is described from a readily available chiral template. The potential of this new protocol is demonstrated through the synthesis of an enantiomerically enriched 3-alkyl N-*H* isoindolin-1-one target with an *e.e.* of 98%.

Keywords: Isoindolinone, *N*-Acyliminium, Stereoselective Synthesis

1. **Introduction**

The synthesis of non-racemic 3-substituted isoindolin-1-one targets remains an area of significant interest due to the wide range of biological activities exhibited by this class of compound. Typical examples of bioactive targets include compounds **1**-**3** (Figure 1). (*S*)-PD-172938, **1**, shows affinity for dopamine D_4 receptors,[1] whilst (*S*)-pagoclone, **2**, is known to display anxiolytic activity[2] and JM-1232, **3**, is a benzodiazepine receptor agonist also being investigated for the treatment of anxiety related conditions.[3] Selected biological activities of other, related, 3-substituted isoindolin-1-one derivatives include affinity for 5-HT receptors,[4] as inhibitors of the MDM2-p53 protein-protein interaction,[5] and as Kv1.5 ion channel blockers.[6]

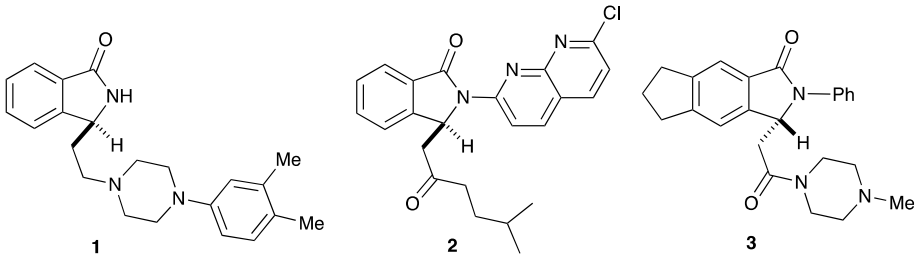
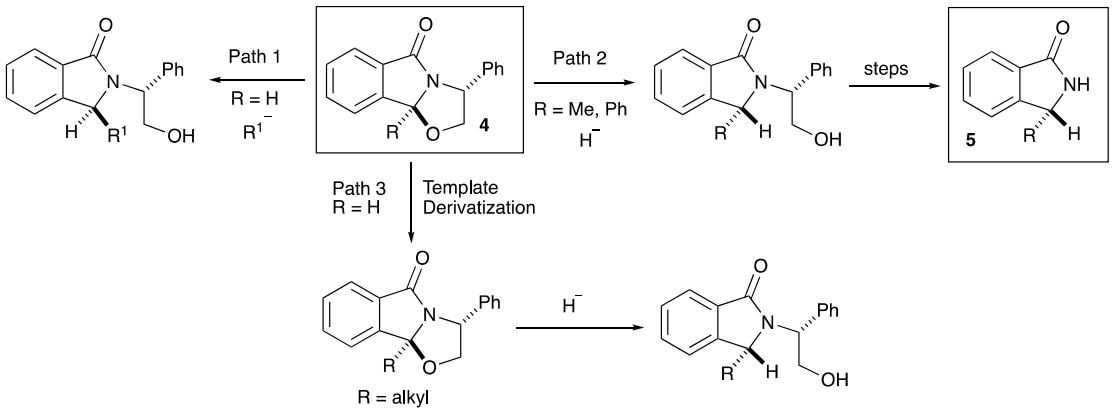


Figure 1. Biologically Active 3-Substituted Isoindolin-1-ones.

Deprotonation and subsequent benzylic *C*-alkylation of the parent isoindolinone template has been previously explored as a route to such targets in racemic form.[7] This approach has been extended to include chiral auxiliary based approaches for the asymmetric synthesis of non-racemic 3-substituted isoindolin-1-ones: for example in Couture's application of an aminoprolinol-derived template,[8] Royer's use of phenylglycinol,[9] and Comins' approach using TCC esters for control of asymmetric alkylation.[10]

In our own previous contribution to this area we pioneered the use of readily accessible Meyers-type tricyclic lactams, **4**, as versatile asymmetric building blocks, and reported the successful synthesis of non-racemic 3-alkyl and 3-aryl isoindolin-1-ones.[11] Appropriately substituted chiral templates, **4**, were used as novel *N*-acyliminium precursors which could be activated towards subsequent reaction with carbon nucleophiles (Scheme 1, path 1), or with hydride (Scheme 1, path 2) in order to deliver the desired 3-substituted isoindolin-1-one targets.

Although pathway 1 was found to suffer from low levels of product diastereoselectivity, we discovered that a complementary approach, pathway 2, delivered up to exclusive levels of product diastereoselectivity. We have also demonstrated two effective methods for removal of the phenylglycinol chiral auxiliary to deliver the corresponding enantio-enriched 3-alkyl and 3-aryl substituted N*H*-isoindolinones, **5**, with minimal loss of stereochemical integrity at the newly created chiral centre.[11]



Scheme 1. Approaches to Non-racemic 3-Substituted Isoindolin-1-one Targets Using a Tricyclic Lactam Template.

We were intrigued by the subsequent work from the aforementioned groups of Couture,[8] Royer[9] and Comins[10] which have each approached this challenge by generating an anion at the

benzylic position of suitably derivatized, non-racemic isoindolinone intermediates, followed by an asymmetric alkylation protocol - a complementary approach to our own routes.

In this present paper we describe a novel application of the "Meyers'" tricyclic lactams in an analogous anionic approach to the targets of interest (Scheme 1, path 3), which significantly extends our earlier work in this area by overcoming a number of potentially limiting factors, such as the lack of availability of appropriate ketoacid building blocks, and so allows for the preparation of a wider range of the intermediate templates, **4**.

2. Results and Discussion

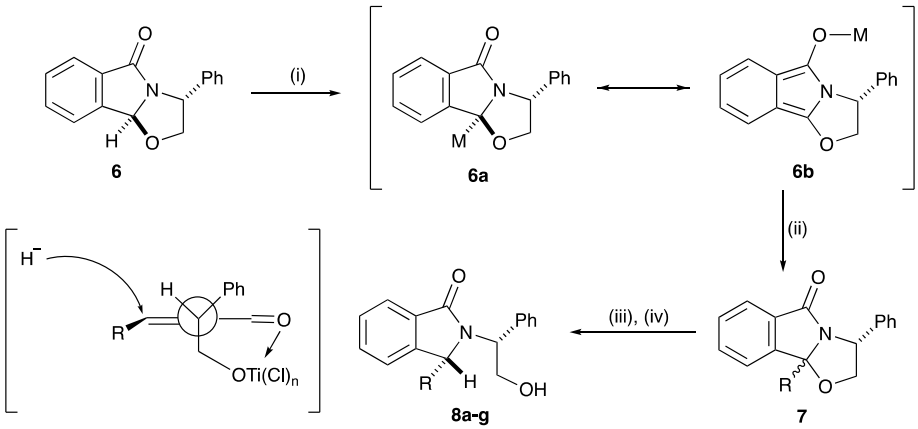
In the new approach described in this paper we have utilized the (*R*)-phenylglycinol derived template, **6**, readily prepared as previously described by us in 75% yield as a single diastereoisomer through Dean-Stark condensation of the commercially available enantiopure aminoalcohol with 2-carboxybenzaldeyde.[11]

In our exploratory work (Scheme 2), template **6** was deprotonated using 1.1 eq. of LHMDS at -78 ^{o}C in dry THF and the intermediate anion was then alkylated with 1.2 eq. MeI to generate the alkylated template **7** as a 1:1 mixture of diastereoisomers, as determined by 400 MHz ^{1}H-NMR spectroscopy on the crude reaction mixture (Step 1).

The lack of any diastereoselectivity observed in the synthesis of intermediate **7** is of no consequence to our ultimate goal, since the subsequent step of this new approach involves the generation of a planar *N*-acyliminium species on activation of **7**, where any stereochemistry that was established during the initial alkylation step would be lost. followed by the second stage of the process, a stereoselective reduction of the non-racemic *N*-acyliminium intermediate with a silane-based hydride reagent, which would be expected to induce high

levels of diastereoselectivity in the final product, based on our previous experience with these templates.[11]

Our results are presented in Table 1 for alkylation of template **6** using a representative range of alkyl halides. For allyl bromide, which gave the highest level of diastereoselectivity when using LiHMDS as the base, alternative bases were investigated due to the significance of the counterion on the diastereoisomeric product ratio in related studies.[9]



Scheme 2. (i) 1.1 eq. Base, THF, -78 ^{o}C; (ii) 1.2 eq. Alkyl halide, THF, -78 ^{o}C to R.T. (12 h), then H_3O^+; (iii) 1.5 eq. $TiCl_4$, DCM, -78 ^{o}C; (iv) 1.5 eq. Et_3SiH, THF, -78 ^{o}C to R.T.

Table 1. Diastereoselective Alkylation of Tricyclic Lactam, **6**.

Base	**Alkyl halide**	**Diastereoisomeric Ratio[a]**	**% conversion[a]**
LiHMDS	Me-I	50:50	50
LiHMDS	Benzyl-Br	75:25	94
LiHMDS	Allyl-Br	80:20	96
NaHMDS	Allyl-Br	90:10	50
KHMDS	Allyl-Br	86:14	57

[a]determined by 400 MHz ^{1}H-NMR spectroscopy on the crude reaction mixture.

As can be seen from Table 1, the highest level of diastereoselectivity achieved with allyl bromide as the electrophile was in the presence of sodium as the counterion, although this base (NaHMDS) gave the poorest conversion (50%) by 400 MHz ^{1}H NMR. A significantly higher conversion of 96% was achieved with LiHMDS. In examples where the conversion was observed to be low, the 400 MHz ^{1}H NMR spectra of the crude product mixture showed only the presence of non-alkylated starting material as a by-product. Variation of the number of equivalents of both base and alkyl halide did not improve the observed outcome.

As noted by Couture,[8] the deprotonated species **6a** may undergo delocalization to form the alternative extended enolate **6b**. It may be tempting to suggest that a preference for one enolate form over the other (**6a** : **6b**) in the presence of a given base may help to rationalize the observed diastereoselectivities of the alkylation step, although there may be other factors at

play and so we would prefer not to speculate further at this juncture, particularly as the stereoselective outcome of this initial alkylation reaction is of no consequence to the overall success of this new approach to the 3-substituted isonidolino-1-one targets.

We were pleased to find that reductive ring-opening of intermediate **7** using 1.5 eq. triethylsilane in the presence of 1.5 eq. $TiCl_4$ in dry DCM gave the desired 3-methyl isoindolino-1-one, **8a**, in 32% yield (over 2 steps) as a ≥95:5 mixture of diastereoisomers by ^{1}H NMR spectroscopy (Scheme 2, Table 2).

Access to compound **8a**, prepared by us in our previous research efforts,[11] allowed us to determine that the relative stereochemistry of the major diastereoisomer was as shown in Scheme 2, by comparison of ^{1}H NMR data. The observed stereochemical outcome can be rationalized by reference to our usual conformational model (Scheme 2).

Having established that this new approach to the synthesis of 3-substituted isoindolin-1-one targets had significant potential, we explored the application of a range of alkylating agents (Table 2). Based on the model study outlined in Table 1, we chose to use LiHMDS as the base, since this base gave highest conversions. Although the initial diastereoselectivity for alkylation of the template using LiHMDS was the lowest for those bases explored, this would be of no consequence to the formation of the desired non-racemic 3-substituted isoindolin-1-one targets with high levels of diastereoselectivity. The alkylated intermediate from Step 1 was not isolated during this reaction sequence, but instead was subjected to the reductive ring opening in Step 2.

Table 2. Template Derivatization and Diastereoselective Ring Opening.

Alkyl halide	**Step 1 conversion (%)[a]**	**diastereoisomeric ratio (step 1)[a]**	**product**	**diastereoisomeric ratio (step 2) [a]**	**yield (%)[b]**
methyl iodide	50	50:50	**8a**	≥95:5	32
ethyl iodide	81	50:50	**8b**	≥95:5	47
propyl iodide	78	66:34	**8c**	≥95:5	32
allyl bromide	96	80:20	**8d**	≥95:5	49
benzyl bromide	94	60:40	**8e**	≥95:5	35
2-fluorobenzyl bromide	94	83:17	**8f**	≥95:5	65
3-methoxybenzyl bromide	96	80:20	**8g**	≥95:5	61

[a] determined by 400 MHz ^{1}H NMR spectroscopy on the crude reaction mixture.

[b] overall isolated yield after 2 steps, following purification by flash column chromatography.

As can be seen from Table 2, alkylation of the parent template could be achieved with variable levels of diastereoselectivity at the intermediate stage of the synthetic sequence (Step 1). In all

cases, the reductive ring-opening of the intermediate proceeded to deliver excellent levels of product diastereoselectivity (Step 2) for all final target compounds. Although the overall yields of the desired products are only low to moderate, the yields quoted for products **8a-g** in Table 2 are over the two reaction steps from template **6**, following purification by column chromatography. In all cases, the major by-product of the two-step procedure was formation of the corresponding ring-opened product from the presence of unalkylated template **6** following Step 1, which was readily separable from the desired products by column chromatography.

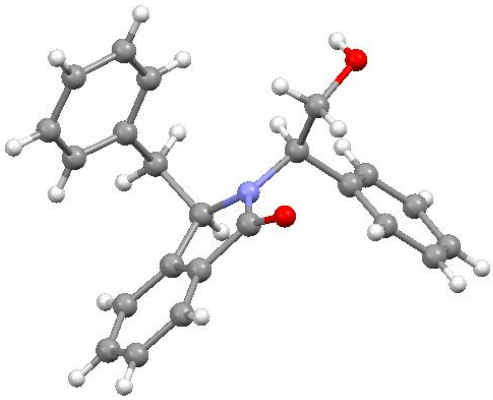


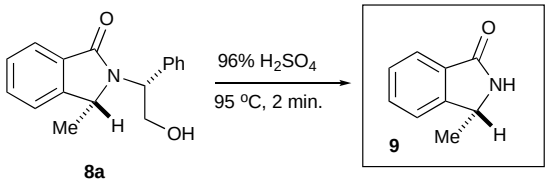
Figure 2. Single Crystal X-Ray Structure of Compound **8e**.

X-Ray crystal structures were obtained for the major diastereoisomers of products **8b**, **8d** and **8e**; with that of benzyl-substituted product **8e** shown in Figure 2. Interestingly, the relative stereochemistry of the allyl-substituted product **8d** is, as expected from our rationale, opposite to that observed when accessing the same compound *via* our alternative, complementary approach using a carbon-centred nucleophile (allyl trimethylsilane, Scheme 1, path 1), thus further supporting the conformational model that we have proposed to rationalize the stereochemical induction that is observed on ring opening of such tricyclic lactam substrates

(Scheme 2). The induced relative stereochemistry in the reaction sequence is governed by the approach of the corresponding nucleophile: hydride in this current study, but allyl in our previous work, thus leading to the observed opposite relative stereochemistry.[11]

One major advantage of our new approach, described herein, is the significant increase in product diastereoselectivity that can be achieved for a wider range of 3-position substituents: for example, allyl derivative **8d** was isolated as a ≥95:5 ratio of diastereoisomers using our new approach, whereas our previously reported methodology delivered this target compound with a diastereoisomeric ratio of only 2:1.[11]

In order to demonstrate the synthetic potential of this new methodology as a potential route to access enantiomerically enriched 3-substituted N*H*-isoindolin-1-one targets, we then subjected major diastereoisomer **8a** to our previously developed method for cleavage of the chiral auxiliary group (Scheme 3).[11] Thus, treatment of **8a** with 96% sulfuric acid over a reaction time of just 2 minutes at 95 ^{o}C gave a 38% yield of (*R*)-3-methyl isoindolino-1-one, **9**, with 98% *e.e.* (as determined by chiral HPLC).[12]



Scheme 3. Access to Enantiomerically Enriched 3-Substituted Isoindolin-1-one Target, **9**.

3. Conclusion

Our previously reported approach to the synthesis of non-racemic 3-substituted isoindolin-1-ones relied upon the availability of appropriate keto-acid substrates, which could be a limiting factor in the introduction of structural diversity to the chiral templates. Given the ready

availability of a wide range of alkylating agents, our new approach described herein now circumvents this issue, since it allows for the synthesis of an extended range of 3-substituted isoindolin-1-one targets from a common, readily available lactam template (**4**, R = H), itself accessed as a crystalline intermediate in high yield in one step from commercially available substrates. Further applications of this methodology in target synthesis are underway, and will be reported in due course.

4. Experimental

Materials and Methods

^{1}H and ^{13}C nuclear magnetic resonance (NMR) were measured on a Jeol eclipse 400 MHz spectrometer using $CDCl_3$, at 400 MHz for ^{1}H NMR and 100 MHz for ^{13}C NMR. Chemical shifts are quoted in ppm downfield from TMS; coupling constants (*J*) are quoted in Hertz (Hz). TMS was defined as 0 ppm in ^{1}H NMR and the residual chloroform triplet as 77.10 ppm in ^{13}C NMR. The following abbreviations were used in analysis; broad (br), singlet (s), doublet (d), triplet (t), quartet (q), double doublet (dd), doublet of doublet of doublets (ddd), doublet of triplets (dt) and multiplet (m). Mass spectra were obtained from the EPSRC National Mass Spectrometry Centre at Swansea University using electron spray ionisation (ES). Infra-red spectra were recorded in the range 4000-600 cm^{-1} using a Perkin Elmer spectrum 100 FT-IR spectrometer. Optical rotation measurements were obtained from a Bellingham and Stanley ADP440+ Polarimeter, at 24 ^{o}C, at a concentration of 0.5 g/100 ml^{-1}, with a cell length of 5cm. Melting points were measured on a Stuart SMP10 melting point apparatus.

Reagents and solvents were purchased from Sigma-Aldrich, Acros Organics and Alfa Aesar, and were used without further purification. Anhydrous solvents (used where specified) were purchased from Sigma-Aldrich and used without further drying. Reactions were carried out

under a flow of nitrogen gas, where specified. Dry ice/acetone baths were used to cool reactions to -78℃.

The progress of the reactions was monitored by thin layer chromatography (TLC), using glass pre-coated silica gel plates (Merck) visualized by UV irradiation at a wavelength of 254 nm. Flash column chromatography was carried out on silica gel 60 (43-60 mesh) (Fluorochem).

(3*R*,9b*S*)-3-phenyl-2,3-dihydrooxazolo[2,3-a]isoindol-5(9b*H*)-one, (6).[11c]

(*R*)-Phenylglycinol, (5.00g, 36 mmol, 1 eq.) was heated with 2-carboxybenzaldehyde (6.02g, 40 mmol, 1.1 eq.) in toluene (300 mL) under Dean-Stark conditions for 48 hours. The crude reaction mixture was then evaporated to yield an oil, which was purified by flash column chromatography (50:50 Et_2O/petroleum ether (40-60)). Evaporation of the solvents under reduced pressure afforded a white crystalline solid. Yield: 75% (5.50 g); Mp: 117-119℃ (DCM/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 - 7.78 (m, 1H), 7.71 - 7.55 (m, 3H), 7.51 - 7.29 (m, 5H), 6.06 (s, 1H), 5.23 (t, *J* = 7.4 , 1H), 4.85 (dd, *J* = 7.4, 8.8, 1H), 4.17 (dd, *J* = 7.4, 8.8, 1H).

(*R*)-2-((*R*)-2-hydroxy-1-phenylethyl)-3-methylisoindolin-1-one, 8a.

Compound **6**, (1.00g, 3.96 mmol, 1.0 eq.) was dissolved in dry THF (15 mL, dry) under nitrogen and the solution cooled to -78℃. LiHMDS (1M in THF) (4.36 mL, 4.36 mmol, 1.1 eq.) was then added drop-wise and the resulting mixture stirred for 30 minutes. Methyl iodide (0.30 mL, 4.77 mmol, 1.2 eq.) was then added drop-wise and the solution was allowed to warm to room temperature overnight. Saturated NH_4Cl aq. (20mL) was then added to quench the reaction, and the reaction mixture was then further diluted with H_2O (20 mL). The mixture was

then extracted with 5 x 30 mL portions of Et_2O and the combined organic extracts were washed with 1 x 30 mL brine, dried over anhydrous $MgSO_4$, filtered and evaporated under reduced pressure to yield the crude product as a light brown oil which was used in the next step without any further purification. Analysis of the crude reaction mixture by ^1H NMR spectroscopy (400 MHz) confirmed a conversion of 50% of starting material in this synthetic step.

The crude product (1.06 g, 3.96 mmol, 1.0 eq.) was stirred in dry DCM (15 mL), under nitrogen and cooled to -78℃. $TiCl_4$ (1M in DCM) (5.94 mL, 5.94 mmol, 1.5 eq.) was added drop-wise to the solution and left to stir for 30 minutes at -78℃. Triethylsilane (0.95 mL, 5.94 mmol, 1.5 eq.) was added drop-wise to the mixture, which was then allowed to warm to room temperature overnight. The reaction was quenched by the addition of saturated NH_4Cl aq. (20 mL) and then diluted further with H_2O (20 mL). The mixture was extracted with 3 x 40 mL portions of DCM and the organic extracts combined and washed with 30 mL brine, dried over anhydrous $MgSO_4$, filtered and evaporated under reduced pressure to give a light brown residue. This was then purified by flash column chromatography (100% petroleum ether (40-60)) to afford a yellow oil. Yield: 32% (0.34 g); $[\alpha]_D$ = + 244 (*c* 0.5, 24 ^oC, DCM); ^1H NMR (400 MHz, $CDCl_3$) δ 7.88 (d, *J* = 7.4, 1H), 7.62 - 7.44 (m, 2H), 7.39 - 7.26 (m, 6H), 5.00 - 4.89 (m, 1H), 4.77 (dd, *J* = 3.4, 8.0, 1H), 4.53 - 4.43 (m, 1H), 4.34 (q, *J* = 6.7, 1H), 4.18 - 4.05 (m, 1H), 1.46 (d, *J* = 6.7, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.7, 147.1, 137.9, 132.1, 128.9, 128.4, 128.1, 127.3, 123.9, 122.0, 64.7, 62.5, 57.1, 18.4; ν_{max} (solid): 3333, 1658, 1469, 1404, 1353 cm^{-1}; HRMS (ESI, *m/z*): calcd. for $C_{17}H_{17}NO_2$ ($M + H^+$) 268.1332, found: 268.1334.

(*R*)-3-ethyl-2-((*R*)-2-hydroxy-1-phenylethyl)isoindolin-1-one, (8b).

Compound **6**, (0.50g, 1.98 mmol, 1.0 eq.) was dissolved in dry THF (15 mL) under nitrogen and the solution cooled to -78℃. LiHMDS (1M in THF) (2.18 mL, 2.18 mmol, 1.1 eq.) was added drop-wise and the resulting mixture stirred for 30 minutes. Ethyl iodide (0.19 mL, 2.39 mmol, 1.2 eq.) was then added drop-wise and the solution was allowed to warm to room temperature overnight. Saturated NH_4Cl aq. (15 mL) was then added to quench the reaction, which was then diluted further with H_2O (20 mL). The mixture was then extracted with 5 x 30 mL portions of Et_2O and the organic extracts were combined and washed with 1 x 30 mL brine, dried over anhydrous $MgSO_4$, filtered and evaporated to give the crude intermediate as an orange oil, which was used in the next step without any further purification. Analysis of the crude reaction mixture by ^1H NMR spectroscopy (400 MHz) confirmed a conversion of 81% of starting material in this synthetic step.

The crude product (0.55 g, 1.98 mmol, 1.0 eq.) was stirred in dry DCM (10 mL), under nitrogen and cooled to -78℃. $TiCl_4$ (1M in DCM) (2.97 mL, 2.97 mmol, 1.5 eq.) was added drop-wise and the solution left to stir for 30 minutes at -78℃. Triethylsilane (0.47 mL, 2.97 mmol, 1.5 eq.) was added drop-wise to the mixture, which was then allowed to warm to room temperature overnight. The reaction was quenched by addition of saturated NH_4Cl aq. (20 mL) and the mixture further diluted with H_2O (20 mL). The mixture was then extracted with 3 x 30 mL portions of DCM and the combined organic extracts washed with 1 x 30 mL brine, dried over anhydrous $MgSO_4$, filtered and evaporated under reduced pressure to give a light brown residue which was purified by flash column chromatography (80:20 EtOAc/ petroleum ether (40-60)) to afford the target compound as a yellow crystalline solid. Yield: 47% (0.26 g); Mp: 101-104 ^{0}C (DCM/hexanes); $[\alpha]_D$ = + 180 (*c* 0.5, 24 ^{o}C, DCM); ν_{max} (solid): 3345, 2995, 2876, 1659, 1469, 1407, 1214 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.88 (d, *J* = 7.5, 1H), 7.62 - 7.40 (m, 2H), 7.38 - 7.26 (m, 6H), 7.38 - 7.21 (m, 1H), 5.07 - 4.99 (m, 1H), 4.62 (dd, *J* = 3.3, 8.0, 1H),

4.48 (dt, *J* = 7.9, 12.5, 1H), 4.40 (dd, *J* = 2.7, 5.1, 1H), 4.11 (ddd, *J* = 3.3, 7.0, 12.5, 1H), 2.13 - 1.90 (m, 2H), 0.55 (t, *J* = 7.4, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.4, 144.9, 138.0, 132.9, 132.0, 128.9, 128.4, 128.1, 127.3, 123.8, 122.0, 64.8, 62.8, 61.1, 22.9, 5.9; HRMS (ESI, *m/z*): calcd. for $C_{18}H_{19}NO_2$ ($M + H^+$) 282.1489, found 282.1489.

(*R*)-2-((*R*)-2-hydroxy-1-phenylethyl)-3-propylisoindolin-1-one, (8c).

Compound **6**, (0.50 g, 1.98 mmol, 1.0 eq.) was dissolved in dry THF, (15 mL), under nitrogen and the solution cooled to -78℃. LiHMDS (1M in THF) (2.18 mL, 2.18 mmol, 1.1 eq.) was then added drop-wise and the resulting mixture stirred for 30 minutes. 1-Iodopropane (0.23 mL, 2.39 mmol, 1.2 eq.) was then added drop-wise and the solution was allowed to warm to room temperature overnight. Saturated NH_4Cl aq. (15 mL) was then added to quench the reaction, which was then diluted further with H_2O (20 mL). The mixture was then extracted with 5 x 30 mL portions of Et_2O and the organic extracts were combined and washed with 1 x 30 mL brine, dried over anhydrous $MgSO_4$, filtered and evaporated under reduced pressure to give the crude intermediate as a light brown oil, which was used in the next step without any further purification. Analysis of the crude reaction mixture by ^{1}H NMR spectroscopy (400 MHz) confirmed a conversion of 78% of starting material in this synthetic step.

The crude product (0.58 g, 1.98 mmol, 1.0 eq.) was stirred in dry DCM (10 mL), under nitrogen and cooled to -78℃. $TiCl_4$ (1M in DCM) (2.97 mL, 2.97 mmol, 1.5 eq.) was added drop-wise and the solution left to stir for 30 minutes at -78℃. Triethylsilane (0.47 mL, 2.97 mmol, 1.5 eq.) was added drop-wise to the mixture, which was then allowed to warm to room temperature overnight. The reaction was quenched by addition of saturated NH_4Cl aq. (20mL) and the mixture further diluted with H_2O (20 mL). The mixture was then extracted with 3 x 30 mL portions of DCM and the combined organic extracts washed with 1 x 30 mL brine, dried over

anhydrous $MgSO_4$, filtered and evaporated under reduced pressure to give a light brown residue which was purified by flash column chromatography (80:20 EtOAc/ petroleum ether (40-60)) to afford the target compound as white crystalline solid. Yield: 32% (0.19 g); Mp: 149-151 ^{o}C (DCM/hexanes); $[\alpha]_D$ = + 132 [*c* 0.5, 24 ^{o}C, DCM]; ν_{max} (solid): 3300, 2998, 2875, 1660, 1413, 1305, 1216 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, *J* = 7.5, 1H), 7.61 - 7.42 (m, 2H), 7.38 - 7.15 (m, 6H), 5.08 - 4.94 (m, 1H), 4.66 (dd, *J* = 3.4, 8.0, 1H), 4.47 (dt, *J* = 7.9, 12.5, 1H), 4.42 - 4.31 (m, 1H), 4.09 (ddd, *J* = 3.4, 7.3, 12.4, 1H), 2.02 - 1.79 (m, 2H), 1.29 - 1.09 (m, 1H), 0.88 - 0.68 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.2, 145.4, 137.9, 132.5, 131.8, 128.8, 128.2, 127.9, 127.1, 123.7, 121.9, 64.7, 62.6, 60.5, 32.3, 15.1, 13.9; HRMS (ESI, *m/z*): calcd. for $C_{19}H_{21}NO_2$ (M + H^+) 296.1645, found 296.1644.

(*R*)-3-allyl-2-((*R*)-2-hydroxy-1-phenylethyl)isoindolin-1-one, (8d).

Compound **6**, (1.00 g, 3.96 mmol, 1.0 eq.) was dissolved in dry THF, (15 mL), under nitrogen and the solution cooled to -78℃. LiHMDS (1M in THF) (4.36 mL, 4.36 mmol, 1.1 eq.) was then added drop-wise and the resulting mixture stirred for 30 minutes. Allyl bromide (0.41 mL, 4.77 mmol, 1.2 eq.) was then added drop-wise and the solution was allowed to warm to room temperature overnight. Saturated NH_4Cl aq. (15mL) was then added to quench the reaction, which was then diluted further with H_2O (20 mL). The mixture was then extracted with 5 x 30 mL portions of Et_2O and the organic extracts were combined and washed with 1 x 30 mL brine, dried over anhydrous $MgSO_4$, filtered and evaporated under reduced pressure to give the crude intermediate as an orange oil, which was used in the next step without any further purification. Analysis of the crude reaction mixture by ^{1}H NMR spectroscopy (400 MHz) confirmed a conversion of 96% of starting material in this synthetic step.

The crude product (1.15 g, 3.96 mmol, 1.0 eq.) was stirred in dry DCM (10 mL), under nitrogen and cooled to -78℃. $TiCl_4$ (1M in DCM) (5.94 mL, 5.94 mmol, 1.5 eq.) was added drop-wise and the solution left to stir for 30 minutes at -78℃. Triethylsilane (0.95 mL, 5.94 mmol, 1.5 eq.) was added drop-wise to the mixture, which was then allowed to warm to room temperature overnight. The reaction was quenched by addition of saturated NH_4Cl aq. (20mL) and the mixture further diluted with H_2O (20 mL). The mixture was then extracted with 3 x 30 mL portions of DCM and the combined organic extracts washed with 1 x 30 mL brine, dried over anhydrous $MgSO_4$, filtered and evaporated under reduced pressure to give a light brown residue which was purified by flash column chromatography (80:20 EtOAc/ petroleum ether (40-60)) to afford the target compound as a yellow solid. Yield: 49% (0.57 g); Mp: 109-112 ^{o}C (DCM/hexanes); $[\alpha]_D$ = + 104 (*c* 0.5, 24 ^{o}C, DCM); ν_{max} (solid): 3381, 2924, 1725, 1646, 1406 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, *J* = 7.4, 1H), 7.60 - 7.44 (m, 2H), 7.41 - 7.21 (m, 6H), 5.56 - 5.15 (m, 1H), 5.12 - 4.96 (m, 3H), 4.74 (dd, *J* = 3.2, 7.7, 1H), 4.49 - 4.36 (m, 2H), 4.13 (m, 1H), 2.80 - 2.48 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.1, 144.8, 137.8, 132.3, 131.8, 130.4, 128.8, 128.3, 127.9, 127.1, 123.7, 122.2, 119.7, 64.5, 62.6, 59.9, 34.9; HRMS (ESI, *m/z*): calcd. for $C_{19}H_{19}NO_2$ ($M + H^+$) 294.1489, found 294.1490.

(*R*)-3-benzyl-2-((*R*)-2-hydroxy-1-phenylethyl)isoindolin-1-one, (8e).

Compound **6**, (0.50 g, 1.98 mmol, 1.0 eq.) was dissolved in dry THF, (15 mL), under nitrogen and the solution cooled to -78℃. LiHMDS (1M in THF) (2.18 mL, 2.18 mmol, 1.1 eq.) was then added drop-wise and the resulting mixture stirred for 30 minutes. Benzyl bromide (0.31 mL, 2.39 mmol, 1.2 eq.) was then added drop-wise and the solution was allowed to warm to room temperature overnight. Saturated NH_4Cl aq. (15mL) was then added to quench the reaction, which was then diluted further with H_2O (20 mL). The mixture was then extracted

with 5 x 30 mL portions of Et_2O and the organic extracts were combined and washed with 1 x 30 mL brine, dried over anhydrous $MgSO_4$, filtered and evaporated under reduced pressure to give the crude intermediate as a light orange solid, which was used in the next step without any further purification. Analysis of the crude reaction mixture by ^1H NMR spectroscopy (400 MHz) confirmed a conversion of 94% of starting material in this synthetic step.

The crude product (0.68 g, 1.98 mmol, 1.0 eq.) was stirred in dry DCM (10 mL), under nitrogen and cooled to -78℃. $TiCl_4$ (1M in DCM) (2.97 mL, 2.97 mmol, 1.5 eq.) was added drop-wise and the solution left to stir for 30 minutes at -78℃. Triethylsilane (0.47 mL, 2.97 mmol, 1.5 eq.) was added drop-wise to the mixture, which was then allowed to warm to room temperature overnight. The reaction was quenched by addition of saturated NH_4Cl aq. (20mL) and the mixture further diluted with H_2O (20 mL). The mixture was then extracted with 3 x 30 mL portions of DCM and the combined organic extracts washed with 1 x 30 mL brine, dried over anhydrous $MgSO_4$, filtered and evaporated under reduced pressure to give a light brown residue which was purified by flash column chromatography (80:20 EtOAc/ petroleum ether (40-60)) to afford the target compound as a white crystalline solid. Yield: 35% (0.24 g); Mp: 174-177 ℃ (EtOAc/hexanes); $[\alpha]_D$ = + 124 (*c* 0.5, 24 ^oC, DCM); ν_{max} (solid): 3380, 2924, 2885, 1649, 1408 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.84 - 7.74 (m, 1H), 7.51 - 7.14 (m, 10H), 6.98 - 6.91 (m, 2H), 6.88 - 6.78 (m, 1H), 5.10 - 4.95 (m, 1H), 4.87 (dd, *J* = 3.4, 7.8, 1H), 4.54 (dd, *J* = 4.5, 7.8, 1H), 4.46 (dt, *J* = 7.7, 12.5, 1H 1H), 4.09 (ddd, *J* = 3.3, 6.9, 12.4, 1H), 3.37 (dd, *J* = 4.4, 13.9, 1H), 2.88 (dd, *J* = 7.8, 13.8, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.9, 144.9, 137.9, 135.4, 132.0, 131.4, 129.4, 128.9, 128.4, 128.3, 128.0, 127.1, 127.1, 123.7, 122.8, 64.6, 63.1, 61.7, 38.1; HRMS (ESI, *m/z*): calcd. for $C_{23}H_{21}NO_2$ ($M + H^+$) 344.1645, found 344.1643.

(*R*)-3-(2-fluorobenzyl)-2-((*R*)-2-hydroxy-1-phenylethyl)isoindolin-1-one, (8f).

Compound **6**, (0.50 g, 1.98 mmol, 1.0 eq.) was dissolved in dry THF, (15 mL), under nitrogen and the solution cooled to -78℃. LiHMDS (1M in THF) (2.18 mL, 2.18 mmol, 1.1 eq.) was then added drop-wise and the resulting mixture stirred for 30 minutes. 2-Fluorobenzyl bromide (0.29 mL, 2.39 mmol, 1.2 eq.) was then added drop-wise and the solution was allowed to warm to room temperature overnight. Saturated NH_4Cl aq. (15mL) was then added to quench the reaction, which was then diluted further with H_2O (20 mL). The mixture was then extracted with 5 x 30 mL portions of Et_2O and the organic extracts were combined and washed with 1 x 30 mL brine, dried over anhydrous $MgSO_4$, filtered and evaporated under reduced pressure to give the crude intermediate as a light orange oil, which was used in the next step without any further purification. Analysis of the crude reaction mixture by ^1H NMR spectroscopy (400 MHz) confirmed a conversion of 94% of starting material in this synthetic step.

The crude product (0.71 g, 1.98 mmol, 1.0 eq.) was stirred in dry DCM (10 mL), under nitrogen and cooled to -78℃. $TiCl_4$ (1M in DCM) (2.97 mL, 2.97 mmol, 1.5 eq.) was added drop-wise and the solution left to stir for 30 minutes at -78℃. Triethylsilane (0.47 mL, 2.97 mmol, 1.5 eq.) was added drop-wise to the mixture, which was then allowed to warm to room temperature overnight. The reaction was quenched by addition of saturated NH_4Cl aq. (20 mL) and the mixture further diluted with H_2O (20 mL). The mixture was then extracted with 3 x 30 mL portions of DCM and the combined organic extracts washed with 1 x 30 mL brine, dried over anhydrous $MgSO_4$, filtered and evaporated under reduced pressure to give a light brown residue which was purified by flash column chromatography (70:30 EtOAc/ petroleum ether (40-60)) to afford the target compound as an off-white crystalline solid. Yield: 65% (0.465 g); Mp: 140-143℃ (EtOAc/hexanes); $[\alpha]_D$ = + 152 (*c* 0.5, 24 ^oC, DCM); ν_{max} (solid): 3313, 2871, 1657, 1491, 1230 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.85 - 7.77 (m, 1H), 7.50 - 6.88 (m, 12H), 4.96 - 4.82 (m, 2H), 4.59 (dd, *J* = 4.3, 7.7, 1H), 4.48 (dt, *J* = 7.8, 12.5, 1H), 4.13 (ddd, *J* = 3.4, 7.0,

12.5, 1H), 3.43 (dd, *J* = 4.2, 14.0, 1H), 2.93 (dd, *J* = 7.7, 14.0, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.0, 161.2 (d, $^1J_{C\text{-}F}$ = 245.4 Hz), 144.9, 137.9, 132.1, 131.7 (d, $^3J_{C\text{-}F}$ = 4.8 Hz), 131.5, 129.1 (d, $^2J_{C\text{-}F}$ = 7.7 Hz), 128.9, 128.4, 128.0, 127.2, 124.0 (d, $^3J_{C\text{-}F}$ = 3.8 Hz), 123.8, 122.8, 122.7 (d, $^4J_{C\text{-}F}$ = 15.3 Hz), 115.4 (d, $^2J_{C\text{-}F}$ = 22.0 Hz), 64.6, 63.0, 60.5, 31.6; HRMS (ESI, *m/z*): calcd. for $C_{23}H_{20}FNO_2$ (M + H^+) 362.1551 found, 362.1550.

(*R*)-2-((*R*)-2-hydroxy-1-phenylethyl)-3-(3-methoxybenzyl)isoindolin-1-one, (8g).

Compound **6**, (0.50 g, 1.98 mmol, 1.0 eq.) was dissolved in dry THF, (15 mL), under nitrogen and the solution cooled to -78℃. LiHMDS (1M in THF) (2.18 mL, 2.18 mmol, 1.1 eq.) was then added drop-wise and the resulting mixture stirred for 30 minutes. 3-Methoxybenzyl bromide (0.33 mL, 2.39 mmol, 1.2 eq.) was then added drop-wise and the solution was allowed to warm to room temperature overnight. Saturated NH_4Cl aq. (15mL) was then added to quench the reaction, which was then diluted further with H_2O (20 mL). The mixture was then extracted with 5 x 30 mL portions of Et_2O and the organic extracts were combined and washed with 1 x 30 mL brine, dried over anhydrous $MgSO_4$, filtered and evaporated under reduced pressure to give the crude intermediate as a light orange oil, which was used in the next step without any further purification. Analysis of the crude reaction mixture by ^{1}H NMR spectroscopy (400 MHz) confirmed a conversion of 96% of starting material in this synthetic step.

The crude product (0.74 g, 1.98 mmol, 1.0 eq.) was stirred in dry DCM (10 mL), under nitrogen and cooled to -78℃. $TiCl_4$ (1M in DCM) (2.97 mL, 2.97 mmol, 1.5 eq.) was added drop-wise and the solution left to stir for 30 minutes at -78℃. Triethylsilane (0.47 mL, 2.97 mmol, 1.5 eq.) was added drop-wise to the mixture, which was then allowed to warm to room temperature overnight. The reaction was quenched by addition of saturated NH_4Cl aq. (20 mL) and the mixture further diluted with H_2O (20 mL). The mixture was then extracted with 3 x 30 mL

portions of DCM and the combined organic extracts washed with 1 x 30 mL brine, dried over anhydrous $MgSO_4$, filtered and evaporated under reduced pressure to give a light brown residue which was purified by flash column chromatography (70:30 EtOAc/ petroleum ether (40-60)) to afford the target compound as an off-white crystalline solid. Yield: 61% (0.45 g); Mp: 94-96℃ (EtOAc/hexanes); $[\alpha]_D$ = + 40 (*c* 0.5, 24 ^oC, DCM); ν_{max} (solid): 2868, 1715, 1616, 1361, 1311 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.84 - 7.76 (m, 1H), 7.49 - 7.40 (m, 2H), 7.38 - 7.28 (m, 3H), 7.27 - 7.20 (m, 2H), 7.14 (t, *J* = 7.9, 1H), 6.96 - 6.88 (m, 1H), 6.76 (dd, *J* = 2.0, 8.2, 1H), 6.56 (d, *J* = 7.5, 1H), 6.45 - 6.39 (m, 1H), 5.07 - 5.00 (m, 1H), 4.85 (dd, *J* = 3.1, 7.8 , 1H), 4.54 (dd, *J* = 4.4, 7.7, 1H), 4.45 (dt, *J* = 7.7, 12.5, 1H), 4.08 (ddd, *J* = 3.3, 7.2, 12.4, 1H), 3.68 (s, 3H), 3.34 (dd, *J* = 4.3, 13.9, 1H), 2.86 (dd, *J* = 7.8, 14.0, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.9, 159.5, 145.0, 137.9, 136.9, 132.1, 131.5, 129.4, 128.9, 128.3, 128.0, 127.2, 123.7, 122.8, 121.8, 114.8, 112.7, 64.6, 63.1, 61.6, 55.1, 38.1; HRMS (ESI, *m/z*): calcd. for $C_{24}H_{23}NO_3$ ($M + H^+$) 374.1751 found, 374.1749.

(*R*)-3-methylisoindolin-1-one, (9).[11c]

(*R*)-2-((*R*)-2-hydroxy-1-phenylethyl)-3-methylisoindolin-1-one, **8a**, (0.05g, 0.20 mmol, 1.0 eq.) was dissolved in conc. H_2SO_4 (96%, 2 mL) in a test tube. This was then immediately heated for two minutes over a steam bath, then cooled to room temperature. Cold H_2O (20 mL) was then added and the mixture extracted using 3 x 20mL portions of DCM. The combined organic extracts were dried over anhydrous $MgSO_4$, filtered and evaporated under reduced pressure to obtain a pale yellow oil. The crude product was then purified using preparative layer chromatography eluting with 80:20 EtOAc/ petroleum ether (40-60), to obtain the product as a clear, colourless oil. Yield: 38% (0.011 g); ^1H NMR (400 MHz, $CDCl_3$) δ 7.89 - 7.77 (m, 1H), 7.63 - 7.52 (m, 1H), 7.52 - 7.39 (m, 2H), 4.70 (q, *J* = 6.5, 1H), 1.51 (d, *J* = 6.7, 3H).

Enantiomeric excess (e.e) was determined independently by Reach Separations Ltd., (BioCity Nottingham, NG1 1GF). Analysis was carried out using a chiral stationary phase, Chiralpak IC column, 4.6mm x 250mm, 5μm, (Daicel Chemical Industries, Ltd., Tokyo, Japan). The isocratic mobile phase comprised of 20:80 MeOH:CO_2 (0.2% v/v NH_3). The flow rate of the mobile phase was 4.0 mL min^{-1}. A detector wavelength of 210-400nm was utilised. The column temperature was maintained at 40 ^oC and the injection volume was 1.0 μL. Under these conditions the enantiomeric excess of compound **9** was found to be 98 %, when compared to a racemic sample.

X-Ray Crystallography.

Suitable crystals were obtained by slow evaporation in ether/petrol (40-60 ^OC). Diffraction data (Mo-K_α) were collected on a Rigaku Oxford Diffraction Excalibur diffractometer at T = 150-158 K using graphite-monochromated Mo-Kα radiation. The structures were solved and refined using the SHELXS-2016 and SHELXL-2016 programs.[13]

8b, R = ethyl, *Crystal data*: $C_{18}H_{16}NO_2$, M_r = 281.34 g mol^{-1}, orthorhombic, $P2_12_12_1$, a = 6.3679(2), b =7.1844(2), c = 32.8776(12) Å, V = 1504.14(9) $Å^3$, T = 150 K, Z = 4, $R[F^2 > 2\sigma(F^2)]$ = 0.048 for 2711 reflections with $I > 2\sigma(I)$, $wR(F^2)$ = 0.093 for all 3135 independent data, GOF = 1.045, 192 refined parameters.

8d, R = allyl, *Crystal data*: $C_{19}H_{19}NO_2$, M_r = 293.35 g mol^{-1}, orthorhombic, $P2_12_12_1$, a = 9.4566(4), b =9.6198(3), c = 16.9868(7) Å, V = 1545.30(10) $Å^3$, T = 158 K, Z = 4, $R[F^2 > 2\sigma(F^2)]$ = 0.042 for 3072 reflections with $I > 2\sigma(I)$, $wR(F^2)$ = 0.090 for all 3364 independent data, GOF = 1.083, 208 refined parameters.

8e, R = benzyl, *Crystal data*: $C_{23}H_{21}NO_2$, M_r = 343.41 g mol^{-1}, orthorhombic, $P2_12_12_1$, a = 8.6454(3), b =10.5715(3), c = 20.1931(6) Å, V = 1845.55(10) $Å^3$, T = 150 K, Z = 4, $R[F^2 >$

$2\sigma(F^2)]$ = 0.053 for 3401 reflections with $I > 2\sigma(I)$, $wR(F^2)$ = 0.097 for all 3860 independent data, GOF = 1.104, 239 refined parameters.

The crystallographic data are deposited as CCDC 1583682, 1878667-1878668. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via via www.ccdc.cam.ac.uk/data_request/cif.

Conflicts of interest

There are no conflicts of interest to declare.

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13. G. M. Sheldrick, http://shelx.uni-ac.gwdg.de/SHELX/, University of Göttingen, Germany.

Supplementary Information available: NMR (1H and 13C) spectra for compounds: **6**, **8a-g**, **9**.