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PAPER

Addition of TMSCN to chiral ketimines derived from isatin. Synthesis of an oxindole-based peptidomimetic and a bioactive spirohydantoin†

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We investigated the Strecker-type reaction of isatin derived chiral ketimines with TMSCN in the presence of a Lewis acid. The desired α-amino nitriles have been obtained in good yields with moderate diastereoselectivity. Further elaboration of the cyanide group allowed the preparation of a new oxindole-based peptidomimetic and a pharmaceutically relevant spirohydantoin.

Introduction

The addition of cyanide ions to imines to give α-amino nitriles is a useful tool in synthetic organic chemistry. The α-amino nitrile products are versatile intermediates for the synthesis of a number of interesting molecules.[1] The cyano group[2] can be transformed into a primary amine[3] or aldehyde[4] (by reduction), ketone (by organometallic addition) or carboxylic acid (by hydrolysis). The latter transformation is involved in a classical α-amino acid synthesis, the Strecker[5] reaction, and has found important applications in the preparation of both natural and unnatural amino acids.[6] Moreover, the recognized value of enantiopure amino acids has stimulated a lot of efforts in designing asymmetric versions of the Strecker reaction.[7] Besides enantioselective catalytic methods, the use of chiral auxiliaries has generally been distinguished as a powerful tool in stereoselective synthesis. The utility of amines as chiral auxiliaries is of particular significance since many enantiopure amines are easily available from the chiral pool. Accordingly, chiral aldimines[8] and ketimines[9] have been exploited as substrates for the addition of cyanide ions.

In the course of our studies on new methodologies to access pharmaceutically relevant heterocyclic scaffolds,[10] we recently became interested in the asymmetric synthesis of quaternary 3-aminooxindoles.[11] The important oxindole moiety is found in many natural compounds having several biological activities, as evidenced in the cyclic peptide Celogentin K[12] and the spiro-oxindole alkaloids (–)-horsfiline[13] and spirotryprostatin.[14] Some important synthetic therapeutic agents also contain a 3-substituted-3-aminooxindole core, as the potent gastrin/CCK-B receptor antagonist AG-041R (**1**),[15] the vasopressin/V1b receptor antagonist SSR-149415 (**2**)[16] and the spirohydantoin (**3**) developed by AstraZeneca for potential use in the treatment of pain (Fig. 1).[17]

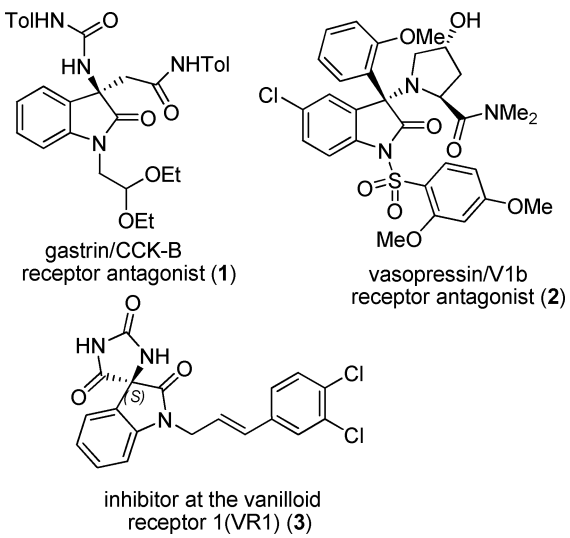

Fig. 1 Some important therapeutic agents containing a 3-substituted-3-aminooxindole core.

Despite the relevance of the quaternary 3-amino oxindole nucleus, the synthesis of 3-amino-3-cyano oxindole has received little attention.[18] Only very recently work from Zhou[19] described the use of a *Cinchona* based catalyst in the enantioselective organocatalytic addition of TMSCN to ketimines derived from isatin, however with moderate yields and enantioselectivities. In light of this, we decided to report here our auxiliary-based approach to the cyanide ion addition to chiral ketimines, obtained from isatin and chiral primary amines. As a preliminary demonstration of the versatility of 3-amino-3-cyano oxindoles, we also accomplished

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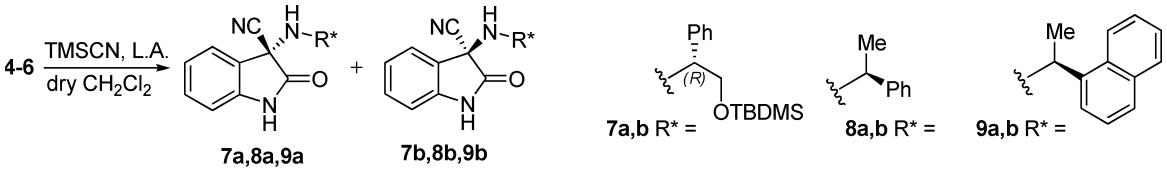
† Electronic supplementary information (ESI) available: General methods, copies of ^{1}H NMR and ^{13}C NMR spectra for compounds **4–6**, **7a**, **8a,b**, **9a,b**, **10a**, **10b**, **12**, **14**, **15a**, **16a**, **16b**, **17**, **19**, **20a,b**, **21a,b**, **3**. Crystallographic data for compound **10a**. CCDC reference numbers 816608. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c1ob05532a

Table 1 Addition of TMSCN to imines **4–6**



Entry	Imine	LA	TMSCN (eq)	Time (h)	Yield (%)	dr	Product
1	**4**	$MgBr_2$	1.5	22	49	65 : 35	**7a,b**
2	**4**	$MgBr_2$	3	5	78	67 : 33	**7a,b**
3[a]	**4**	$MgBr_2$	3	22	68	65 : 35	**7a,b**
4[b]	**4**	$MgBr_2$	3	22	51	66 : 34	**7a,b**
5	**4**	$MgBr_2$	5	20	*quant.*	74 : 26	**7a,b**
6	**4**	$BF_3{\cdot}Et_2O$	3	4	55	55 : 45	**7a,b**
7	**4**	$Yb(OTf)_3$	3	22	43	57 : 43	**7a,b**
8[c]	**4**	$Ti(iPrO)_4$	3	45	26	57 : 43	**7a,b**
9[c]	**4**	$ZnCl_2$	3	28	—	—	
10	**4**	TMSOTf	3	4	81	56 : 44	**7a,b**
11	**4**	$SnCl_4$	3	21	40	74 : 26	**7a,b**
12	**5**	$MgBr_2$	1.5	22	61	55 : 45	**8a,b**
13	**5**	$SnCl_4$	1.5	24	88	68 : 32	**8a,b**
14	**5**	$BF_3{\cdot}Et_2O$	1.5	24	32	62 : 38	**8a,b**
15	**5**	$ZnCl_2$	1.5	24	—	—	
16	**5**	—	1.5	22	71	53 : 47	**8a,b**
17	**6**	$MgBr_2$	3	24	80	46 : 54	**9a,b**
18	**6**	$SnCl_4$	3	22	68	61 : 39	**9a,b**

[a] $T = -30°$ C. [b] $T = -40$ °C. [c] $T = -20$ °C to rt.

the synthesis of a new oxindole-based quaternary amino acid and of the spirohydantoin **3**.

Results and discussion

We selected the chiral imines **4–6**, which were easily prepared by treating isatin with the proper enantiopure amine in dichloromethane with $MgSO_4$ as dehydrating agent (Fig. 2).

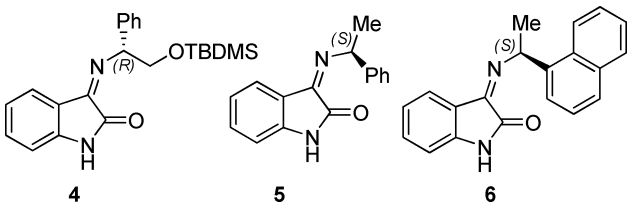


Fig. 2 Substrates for the addition of TMSCN.

Commercially available (*S*)-1-phenylethylamine and (*S*)-1-(1-naphthyl)ethylamine were used, while *O*-TBDMS (*R*)-phenylglycinol was prepared according to the literature.[20] As expected, the products **4–6** were isolated as 1 : 1 *E*/*Z* mixtures at the C=N bond. The ketimines **4–6** were then reacted with TMSCN in the presence of different Lewis acids. We assumed that the Lewis acid could act both by blocking the *E* geometry of the imine, through the concurrent coordination of the imine nitrogen and the oxindole oxygen, and by activating the C=N bond to the nucleophilic addition of the cyanide ion. The reactions were carried out using 1.5 eq. of Lewis acid ($MgBr_2$, $BF_3{\cdot}Et_2O$, $Yb(OTf)_3$, $Ti(iPrO)_4$, $ZnCl_2$, TMSOTf and $SnCl_4$ were screened) and with different amounts of TMSCN. To improve the diastereoselectivity, the temperature was maintained at –20 °C.

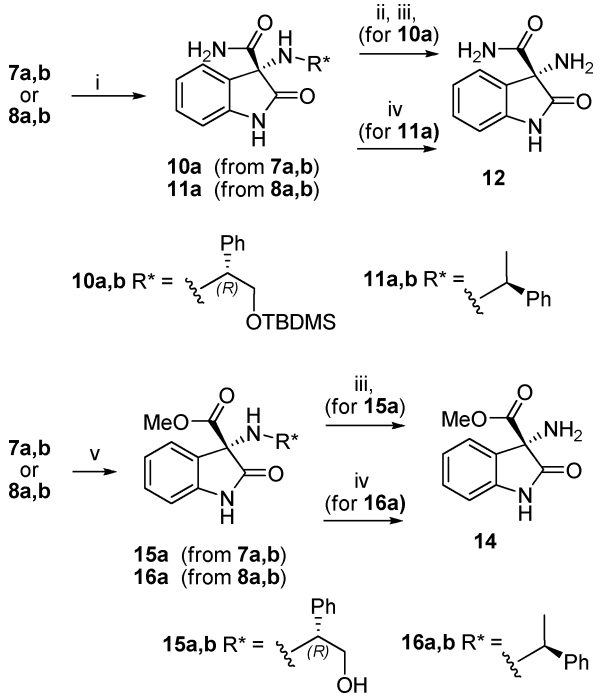
The results of this study are outlined in Table 1. The addition products **7–9** were obtained in moderate to good yields and in moderate diastereoisomeric ratios. The best performing Lewis acid was $SnCl_4$ which afforded a 74 : 26 dr (determined by ^{1}H NMR) on substrate **4** (entry 11) and 68 : 32 dr on **5** (entry 13). Quantitative yield and similar dr were obtained on **4** using $MgBr_2$ and a 5 fold excess of TMSCN (entry 5). Furthermore, imine **5** efficiently adds TMSCN even in the absence of a Lewis acid but with poor diastereoselectivity, revealing the importance of the metal coordination for the stereochemical outcome of the process. To our disappointment, the two diastereoisomers **a** and **b** of products **7–9** were not separable by standard column chromatography.

This prompted us to explore at once the reactivity of the cyano group, versatile precursor of other functionalities. We first studied its hydrolysis to the primary amide group. After testing different conditions, the amino nitriles **7a,b** (from entry 4) were conveniently converted into the desired diastereoisomeric amino amides **10a,b** by reaction with 30% H_2O_2 in acetone–1 N aq. Na_2CO_3 (2 : 1)[21] (Scheme 1, *vide infra* for determination of the shown configuration at the C3 stereocenter).

After facile separation by flash chromatography, the major amino amide diastereoisomer was crystallized from an *i*-Pr_2O–MeOH 9 : 1 mixture.

The X-ray diffraction of the obtained crystal established the absolute configuration at the quaternary stereocenter C3 corresponding to the product **10a**, which was attributed as 3*R* as the configuration on the phenylglycinol residue was known to be *R*. (Fig. 3).

The chiral auxiliary of **10a** was then removed by a standard two step procedure, consisting of the cleavage of the TBDMS protective group (4% HCl in ethanol) and the subsequent treatment of the resulting amino alcohol with $Pb(OAc)_4$, followed by



Scheme 1 Elaboration of the cyanide group.

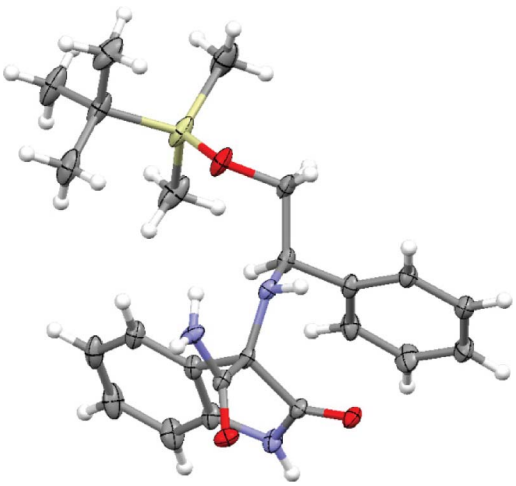
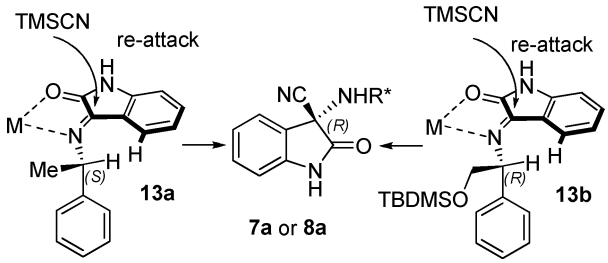


Fig. 3 Plot of the structure of compound **10a** as determined by X-ray crystallography. Atomic displacement parameters at 50% probability level.

addition of a 3 M HCl–dioxane solution, to cleanly afford compound **12**.

In the same way, amino nitriles **8a,b** were converted into the corresponding amino amides **11a,b** which could also be isolated separately. In this case, the cleavage of the chiral auxiliary from the major diastereoisomer was achieved by simple hydrogenation over $Pd(OH)_2/C$, obtaining **12** as the same (–) enantiomer already obtained from **10a**. Absolute configuration of the major diastereoisomer **11a** was consequently ascertained again as 3*R*.

These data allowed us to propose a possible mechanism for the addition of TMSCN to both ketimines **4** and **5**, according to Scheme 2. In our hypothesis, the coordination with the metal of the Lewis acid, stabilizes the *E* geometry of the imine, and the spatial arrangement of the chiral residue on the nitrogen

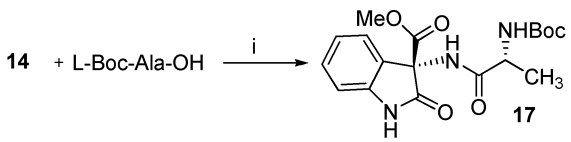


Scheme 2 Proposed mechanism for the addition of TMSCN to imines **4** and **5**.

atom is ruled by the steric hindrance with the aromatic H4 of oxindole (see structures **13a** and **13b**). In both cases, this results in a favored attack on the *re* face of the ketimine double bond, affording preferentially amino nitriles **7a** or **8a**.

The cyano group was also successfully converted into the corresponding methyl ester to address the synthesis of α,α-disubstituted amino esters, which are potentially useful as precursors of constrained quaternary amino acids. Thus treatment of **7a,b** and **8a,b** with saturated HCl–methanol afforded the desired methyl esters, as products **15a,b** and **16a,b**. Also in this case, the two diastereoisomers could easily be separated by chromatography. After removal of the chiral auxiliary as previously described from major diastereoisomers **15a** and **16a,** the amino ester **14** could be readily obtained.

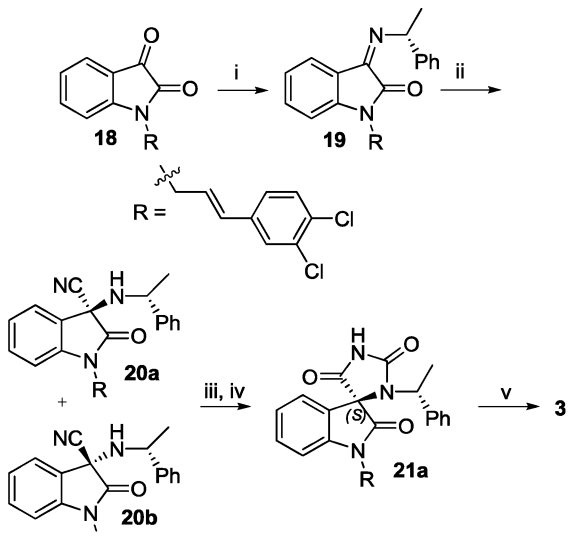
To verify the reactivity of the sterically hindered quaternary amino group of **14**, coupling with *N*-Boc-L-alanine using BopCl as a condensation agent was performed (Scheme 3). Orthogonally protected dipeptide mimetic **17** could be obtained in satisfactory yield.



Reagents and conditions. i) BopCl, TEA, CH_2Cl_2 0 °C to rt, 22 h, 53%.

Scheme 3 Synthesis of dipeptide **17**.

As a further demonstration of the high versatility of oxindole-based amino nitriles, we also investigated the conversion of **12** into a spirohydantoin derivative by reaction with different reagents (CDI, phosgene, triphosgene), but, to our disappointment, no useful results were obtained. We then changed our strategy to use hydantoin-based compounds and we focused our attention on the synthesis of **3**. This compound is presently synthesized as a racemic mixture by reaction of isatin **18** with ammonium carbonate and KCN (Bucherer–Bergs reaction) followed by resolution of enantiomers by means of chiral Simulated Moving Bed (SMB) chromatography.[22] At the present time, no stereoselective synthesis of **3** has been reported in the literature. The isatin derivative **18**, prepared according to the literature,[23] was converted into imine **19** (Scheme 4). Following our previous results, in order to obtain the correct stereochemistry of the final product **3**, this time (*R*)-1-phenylethylamine was used as the chiral auxiliary. Imine **19** was reacted with TMSCN to afford **20a,b** in a 71 : 29 diastereoisomeric ratio, again as an inseparable mixture.



Reagent and conditions: i) (*R*)-1-phenylethylamine, $MgSO_4$, THF, rt, overnight, 98%. ii) $SnCl_4$, TMSCN, CH_2Cl_2, -20 °C, 24 h, 88%. iii) CSI, CH_2Cl_2, rt, 15 min, then aq. 1M HCl rt to reflux, 2 h, 93%. iv) recrystallization from hexane/EtOAc or chromatographic separation from the minor diastereoisomer **21b**. v) MsOH toluene, reflux, 2 h, 93%.

Scheme 4 Synthesis of spirohydantoin **3**.

Reaction of **20a,b** with chlorosulfonyl isocyanate (CSI) in CH_2Cl_2, followed by refluxing in aqueous 1 M HCl, gave the spirohydantoin products **21a,b**. The pure major diastereoisomer **21a** could be obtained by recrystallization from hexane–EtOAc or, alternatively, by careful chromatographic separation with toluene–EtOAc 95 : 5 as eluent. In order to preserve the olefin functional group, the removal of the chiral auxiliary was performed by refluxing **21a** in toluene in the presence of MeOH.[24] The spirohydantoin **3** was obtained in quantitative yield. By comparison of its optical rotatory power with literature,[22] a 97% ee was determined and the *S* configuration at the quaternary stereocenter was assessed, thus confirming again our proposal on the mechanism of the TMSCN addition.

In conclusion, we have investigated the addition of TMSCN to chiral imines derived from isatin. The addition reactions proceeded with good yields and moderate diastereoselectivity. The versatility of the amino nitrile products has been demonstrated by synthesizing the new quaternary amino ester **14**, potentially useful in peptidomimetic chemistry, and by accomplishing the first stereoselective synthesis of the bioactive spirohydantoin **3**.

Experimental section

3-[(*R*)-2-(*tert*-Butyl-dimethyl-silanyloxy)-1-phenyl-ethylimino]-1,3-dihydro-indol-2-one 4. To a solution of isatin (643 mg, 4.37 mmol) in anhydrous CH_2Cl_2 (20 ml) at room temperature, $MgSO_4$ (4.2 g, 34.96 mmol, 8 equiv) and a solution of (*R*)-OTBDMS-phenylglycinol (1.1 g, 4.37 mmol, 1 equiv) in anhydrous CH_2Cl_2 (4 ml) were subsequently added. The reaction mixture was stirred at room temperature for five days. The solution was filtered through a pad of Celite and the solvent evaporated under reduced pressure affording the mixture of imine isomers (1.63 g, 98% yield). The product was used in the next reaction without any further purification. *Mixture of stereoisomers* (≈ 1 : 1) R_f = 0.37 (hexane–EtOAc, 7 : 3). $[\alpha]_D^{20}$ = −8.2 (*c* 0.65, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$, 1 : 1 mixture of isomers) δ 9.71 (br s, 0.5H) and 8.86 (br s, 0.5H), 7.86 (d, *J* = 7.7 Hz, 0.5H), 7.71 (d, *J* = 7.3 Hz, 0.5H), 7.63–7.20 (m, 6H), 7.10–7.00 (m, 1H), 6.97–6.93 (m, 0.5H), 6.83 (d, *J* = 7.8 Hz, 0.5H), 6.73–6.67 (m, 0.5H) and 5.55 (t, *J* = 6.7 Hz, 0.5H), 4.14 (d, *J* = 6.6 Hz, 1H) and 4.03–3.98 (m, 1H), 0.82 (s, 4.5H), 0.79 (s, 4.5H), 0.02 (s, 1.5H), −0.01 (s, 1.5H), −0.05 (s, 1.5H), −0.08 (s, 1.5H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.6 and 160.8, 155.0 and 153.3, 145.2 and 142.9, 141.1 and 140.2, 134.1 and 133.4, 129.6–127.2 (5C), 126.1 and 124.3, 123.9 and 123.7, 117.3, 113.4 and 112.0, 69.3 and 68.9, 68.4 and 64.8, 25.8 (3C), 18.3 and 18.2, −5.3 and −5 (2C). IR ($CHCl_3$) ν_{max} 3431, 1741, 1620 (cm^{-1}). HRMS (ESI) calcd for $C_{22}H_{28}N_2O_2Si$ 380.1920, found 380.1919.

3-[(*S*)-1-Phenyl-ethylimino]-1,3-dihydro-indol-2-one 5. To a solution of isatin (500 mg, 3.40 mmol) in dry CH_2Cl_2 (15 ml) at room temperature, $MgSO_4$ (3.3 g, 27.20 mmol, 8 equiv) and a solution of (*S*)-1-phenyl-ethylamine (520 mg, 3.40 mmol, 1 equiv) in dry CH_2Cl_2 (3 ml) were subsequently added. The reaction mixture was stirred at room temperature for five days. The solution was filtered through a pad of Celite and the solvent evaporated under reduced pressure affording the mixture of imine isomers **5** (833.5 mg, 98% yield). The product was used in the next reaction without any further purification. *Mixture of stereoisomers* (≈ 1 : 1). R_f = 0.57 (hexane–EtOAc, 1 : 1). $[\alpha]_D^{20}$ = −58.9 (*c* 0.25, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.71–9.31 (br s, 0.5H), 8.53 (br s, 0.5H), 7.72 (d, *J* = 7.6 Hz, 0.5H), 7.68 (d, *J* = 7.0 Hz, 0.5H), 7.56 (d, *J* = 7.0 Hz, 1H), 7.51 (d, *J* = 7.3 Hz, 1H), 7.39–7.21 (m, 4H), 7.07–7.01 (m, 1H), 6.96 (d, *J* = 7.6 Hz, 0.5H), 6.80 (d, *J* = 7.8 Hz, 0.5H), 6.59 (q, *J* = 6.6 Hz, 0.5H), 5.54 (q, *J* = 6.6 Hz, 0.5H), 1.75 (d, *J* = 6.4 Hz, 1.5H), 1.61 (d, *J* = 6.7 Hz, 1.5H). ^{13}C NMR (101 MHz, $CDCl_3$) δ = 166.2 and 160.9, 153.8 and 151.9, 145.7, 144.3 and 143.4, 133.7 and 132.9, 128.8–128.6 (3C), 127.4–126.8 (4C), 123.1 and 122.7, 122.8 and 116.9, 112.3 and 110.8, 61.8 and 58.5, 24.9 and 24.5. IR ($CHCl_3$) ν_{max} 3437, 1728, 1620 (cm^{-1}). HRMS (ESI) calcd for $C_{16}H_{14}N_2O$ 250.1106, found 250.1103.

3-[(*R*)-1-Naphthalen-2-yl-ethylimino]-1,3-dihydro-indol-2-one 6. To a solution of isatin (500 mg, 3.40 mmol) in anhydrous CH_2Cl_2 (14 ml) at room temperature, $MgSO_4$ (3.3 g, 27.20 mmol, 8 equiv) and a solution of (*R*)-1-naphthalen-2-yl-ethylamine (546 µl, 3.40 mmol, 1 equiv) in anhydrous CH_2Cl_2 (3 ml) were subsequently added. The reaction mixture was stirred at room temperature for six days. The solution was filtered through a pad of Celite and the solvent removed *in vacuo* providing the mixture of imine isomers **6** (928 mg, 91% yield). The product was used in the next reaction without any further purification. *Mixture of diastereoisomers* (≈ 1 : 1) R_f = 0.40 (hexane–EtOAc, 7 : 3). $[\alpha]_D^{20}$ = −238.1 (*c* 0.62, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.11 (br s, 0.5 H), 9.10 (br s, 0.5 H), 8.31 (d, *J* = 9.1 Hz, 0.5 H), 8.15 (d, *J* = 9.1 Hz, 0.5 H), 8.01 (d, *J* = 9.0 Hz, 0.5 H), 7.85 (t, *J* = 8.7 Hz, 0.5 H),7.80–7.75 (m, 2 H), 7.72–7.26 (m, 6 H), 7.15–6.96 (m, 1,5 H), 6.90–6.72 (m, 1.5 H), 6.21 (q, *J* = 6.5 Hz, 0.5H), 5.42 (q, *J* = 6.5 Hz, 0.5H),1.93 (d, *J* = 6.5 Hz, 1.5H), 1.77 (d, *J* = 6.5 Hz, 1.5H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.3 and 161.8, 155.2 and 152.3, 147.2 and 143.8, 142.7 and 140.6, 138.2, 134.7, 134.2, 132.8 and 131.7 and 131.0, 128.8 and 128.2, 127.3 and 127.2, 126.9 and 126.7, 126.2 and 125.8, 123.9 and 123.7, 123.3 and 122.7,118.3 and 117.2, 113.3 and 112.4, 111.2, 58.8 and 55.5, 25.2 and 24.6. IR ($CHCl_3$) ν_{max} 3437, 1738,

1618 (cm^{-1}). HRMS (ESI) calcd for $C_{20}H_{16}N_2O$ 300.1263, found 300.1267.

Representative procedure for the addition of TMSCN to the imines 4–6. To a solution of the imine (0.26 mmol) in dry CH_2Cl_2 (2.5 ml) at –20 °C, was first added the Lewis acid (0.39 mmol, 1.5 equiv) and then, dropwise, TMSCN (50 µl, 42 mmol, 1.5 equiv). The reaction mixture was stirred at –20 °C for 22 h. The solution was then poured into a saturated aqueous solution of $NaHCO_3$ (8 ml). The aqueous layer was extracted with CH_2Cl_2 (3 × 4 ml) and the combined organic extracts were washed with water (15 ml), dried over Na_2SO_4, filtered and evaporated under reduced pressure. The mixture of isomers was recovered as a yellow oil, and could be used in the next reaction without any further purification.

3-[(*R*)-2-(*tert*-Butyl-dimethyl-silanyloxy)-1-phenyl-ethylamino]-2-oxo-2,3-dihydro-1*H*-indole-3-carbonitrile (7a,b). *Mixture of diastereoisomers* **7a,b** R_f = 0.32 (hexane–EtOAc, 7 : 3). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.62 (br s, 0.5H) and 8.48 (br s, 0.5H), 7.26–7.17 (m, 6H), 7.05 (d, J = 7.5 Hz, 0.5H) and 6.92 (d, J = 7.9 Hz, 0.5H), 6.83–6.70 (m, 1.5H), 6.58 (d, J = 7.2 Hz, 0.5H), 4.31 (dd, J = 9.2, 4.2 Hz, 0.5H) and 3.84 (dd, J = 8.7, 4.4 Hz, 0.5H), 3.73 (dd, J = 10.3, 4.3 Hz, 0.5H), 3.60 (dd, J = 10.3, 4.4 Hz, 0.5H), 3.57–3.45 (m, 1H), 2.21–2.02 (br s, 1H),0.96 (s, 4.5H) and 0.92 (s, 4.5H), 0.26 (s, 1.5H) and 0.09 (s, 1.5H), 0.07 (s, 1.5H) and 0.03 (s, 1.5H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.4 and 172.1, 140.5, 139.6, 130.9 and 130.7, 126.3 and 126.0, 123.3 and 123.0, 111.5 and 111.1, 128.2–127.3 (5C, Ph), 124.9, 116.5 and 115.7, 67.6 and 67.3, 61.8 and 61.1, 60.3, 25.9 (3C), 18.2, –5.3 (2C). IR ($CHCl_3$) ν_{max} 3431, 3288, 2249, 1743 (cm^{-1}). An analytical sample of the major diastereoisomer could be obtained by chromatographic separation. *Major diastereoisomer* **7a** R_f = 0.44 (hexane–EtOAc, 7 : 3). $[\alpha]_D^{20}$ = –40.2 (*c* 1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 (br s, 1H), 7.29–7.19 (m, 6H), 6.84 (d, J = 7.8 Hz, 1H), 6.75 (dt, J = 7.7, 1.0 Hz, 1H), 6.59 (d, J = 7.6 Hz, 1H), 4.40 (dd, J = 9.2, 4.3 Hz, 1H), 3.79 (dd, J = 10.3, 4.3 Hz, 1H), 3.57 (dd, J = 10.3, 9.3 Hz, 1H), 2.47–2.33 (br s, 1H), 0.97 (s, 9H), 0.14 (s, 3H), 0.11 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.7, 140.4, 139.6, 130.6, 128.3–128.0 (5C),126.5, 125.0, 123.0, 110.9, 115.6, 67.6, 62.0, 60.2, 25.9 (3C), 18.2, –5.3, –5.5. HRMS (ESI) calcd for $C_{23}H_{29}N_3O_2SiNa$ (MNa^+) 430.1921, found 430.1919.

2-Oxo-3-((*S*)-1-phenylethylamino)indoline-3-carbonitrile. *Mixture of diastereoisomers* **8a,b** (≈ 3 : 2) R_f = 0.56 (hexane–EtOAc, 1 : 1) ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (br. s., 0.5 H), 7.80 (br. s., 0.5 H), 7.11–7.30 (m, 7 H), 6.96–7.01 (m, 0.5 H), 6.88–6.95 (m, 0.5 H), 6.85 (d, J = 7.8 Hz, 0.5 H), 6.81 (d, J = 8.1 Hz, 0.5 H), 4.24 (m, J = 6.3, 4.3 Hz, 0.5 H), 3.97 (m, J = 6.4, 3.1 Hz, 0.5 H), 2.54 (br s, 0.5 H), 2.50 (br s, 0.5 H), 1.45 (d, J = 6.7 Hz, 1.5 H), 1.42 (d, J = 6.7 Hz, 1.5 H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.3 and 172.1, 144.8 and 144.1, 140.7 and 140.5, 130.9, 128.3 (3C), 127.4 and 127.1, 126.9, 126.3 and 125.9, 124.7 and 124.4, 123.4 and 123.3, 116.4 and 116.2, 111.1, 60.0 and 59.7, 55.0 and 54.5, 25.2 and 25.0. IR ($CHCl_3$) ν_{max} 3437, 3208, 2249, 1730 (cm^{-1}). HRMS (ESI) calcd for $C_{17}H_{15}N_3O$ 277.1215 found 277.1219.

3-((*R*)-1-Naphthalen-2-yl-ethylamino)-2-oxo-2,3-dihydro-1*H*-indole-3-carbonitrile (9a,b). *Mixture of diastereoisomers* R_f = 0.17 (hexane–EtOAc, 7 : 3). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 (br s, 0.5 H), 8.10 (br s, 0.5 H), 8.06 (d, J = 9.1 Hz, 0.5 H), 7.96–8.01 (m, 0.5 H), 7.76–7.86 (m, 1 H), 7.61–7.71 (m, 1 H), 7.53 (d, J = 6.7 Hz, 0.5 H), 7.34–7.48 (m, 2 H), 7.26–7.32 (m, 2 H), 7.18 (td, J = 7.7, 1.2 Hz, 0.5 H), 7.04–7.12 (m, 1 H), 6.90 (d, J = 7.6 Hz, 0.5 H), 6.68–6.79 (m, 1.5 H), 5.17 (q, J = 6.7 Hz, 0.5 H), 4.83 (q, J = 6.5 Hz, 0.5 H), 2.52–3.34 (br s, 1 H), 1.65 (d, J = 6.7 Hz, 1.5 H), 1.61 (d, J = 6.7 Hz, 1.5 H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.3 and 171.8, 141.1 and 140.6, 139.2, 134.5, 131.4, 131.1 and 130.9, 129.5, 128.3, 126.7 (2C), 126.4 and 126.1, 125.9 (2C), 125.0 and 124.7, 123.9, 123.3 and 123.0, 117.1 and 116.9, 111.4 and 111.3, 60.6 and 60.3, 51.6 and 51.3, 25.7 and 25.5. IR ($CHCl_3$) ν_{max} 3428, 3215, 2242, 1732 (cm^{-1}). HRMS (ESI) calcd for $C_{21}H_{17}N_3O$ 327.1372 found 327.1373.

3-[(*R*)-2-(*tert*-Butyl-dimethyl-silanyloxy)-1-phenyl-ethylamino]-2-oxo-2,3-dihydro-1*H*-indole-3-carboxylic acid amide (10a,b). To a stirring solution of **7a,b** (827.39 mg, 2.03 mmol) in acetone (16.2 ml) was added a 1 N aqueous solution of Na_2CO_3 (6.9 ml, 3.45 mmol, 3.4 equiv) and dropwise 30% H_2O_2 (6.9 ml, 60.9 mmol, 30 equiv). The reaction mixture was stirred for 3 days at room temperature. The solvent was removed *in vacuo* and the resulting aqueous mixture was extracted with CH_2Cl_2 (3 × 20 ml). The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash chromatography (hexane–EtOAc, 3 : 7) provided compound **10a** (381.7 mg) and compound **10b** (282.2 mg) (77% overall yield). Crystals of **10a** suitable for X-ray analysis were obtained by slow evaporation at room temperature of a solution of **10a** in *i*Pr_2O/MeOH, 9 : 1. **10a**. R_f = 0.16 (hexane–EtOAc, 3 : 7). Mp 173–175 °C. $[\alpha]_D^{20}$ = –167.0 (*c* 1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (br s, 1H), 7.35 (d, J = 7.4 Hz, 1H), 7.27 (t, J = 7.2 Hz, 1H), 7.23–7.11 (m, 3H), 7.08 (t, J = 7.6 Hz, 1H), 6.98–6.92 (m, 2H), 6.73 (d, J = 7.7 Hz, 1H), 5.96 (br s, 2H), 3.84 (t, ^3J = 5.7 Hz, 1H), 3.75–3.69 (m, 2H), 1.26 (s, 1H), 0.90 (s, 9H), 0.02 (s, 3H), –0.01 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.4, 171.9, 142.4, 140.4, 130.5, 128.8–128.3 (5C), 127.3, 126.1, 123.1, 111.0, 70.7, 68.3, 61.0, 26.5 (3C), 18.9, –4.9 (2C). IR ($CHCl_3$) ν_{max} 3498, 3433, 1734, 1691 (cm^{-1}). HRMS (ESI) calcd for $C_{23}H_{31}N_3O_3SiNa$ (MNa^+) 448.2027, found 448.2028. **10b**. R_f = 0.28 (hexane–EtOAc, 3 : 7). $[\alpha]_D^{20}$ = –9.2 (*c* 1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.02 (br s, 1H), 7.13–7.08 (m, 3H), 7.07–6.99 (m, 3H), 6.76 (d, J = 7.8 Hz, 1H), 6.73–6.62 (m, 1H), 6.54 (t, J = 7.5 Hz, 1H), 6.31 (br s, 2H), 3.73–3.64 (m, 1H), 3.63–3.54 (m, 2H), 2.22 (s, 1H), 0.95 (s, 9H), 0.07 (s, 3H), 0.06 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.3, 172.2, 142.3, 130.1, 128.5–127.8 (6H), 127.1, 126.6, 122.7, 110.9, 72.0, 68.1, 61.9, 26.6 (3C), 19.0, –4.7, –4.9.

2-Oxo-3-((*S*)-1-phenyl-ethylamino)-2,3-dihydro-1*H*-indole-3-carboxylic acid amide (11a,b). To a stirring solution of **8a,b** (2.04 g, 7.36 mmol) in acetone (59 ml) was added an 1 N aqueous solution of Na_2CO_3 (25 ml, 12.51 mmol, 3.4 equiv) and dropwise 30% H_2O_2 (21.5 ml, 220.8 mmol, 30 equiv). The reaction mixture was stirred at room temperature for 3 days. The solvent was removed *in vacuo* and the resulting aqueous mixture was extracted with CH_2Cl_2 (3 × 30 ml). The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash chromatography (hexane–EtOAc, 1 : 9) afforded compound **11a** (783 mg) and compound **11b** (417 mg), (1.2 g, 55% overall yield). **11a**. R_f = 0.21 (hexane–EtOAc, 1 : 9). $[\alpha]_D^{20}$ = –274.6 (*c* 1, CH_3OH). ^{1}H NMR (400 MHz, CD_3OD. Exchangeable protons were not detected) δ 7.39 (d, J = 7.4 Hz, 1H), 7.30 (t, J = 7.6 Hz,

1H), 7.17–7.04 (m, 4H), 6.81 (d, J = 6.8 Hz, 2H), 6.73 (d, ^3J = 7.7 Hz, 1H), 3.77 (q, J = 6.6 Hz, 1H), 1.34 (d, J = 6.7 Hz, 3H). ^{13}C NMR (100 MHz, CD_3OD) δ 178.6, 173.5, 143.9, 143.5, 129.6, 127.5 (2C), 127.2, 126.7 (3C), 124.6, 121.8, 110.3, 71.0, 54.3, 23.6. IR ($CHCl_3$) ν_{max} 3500, 3431, 1734, 1689 (cm^{-1}). **11b**. R_f = 0.27 (hexane–EtOAc, 1 : 9). $[\alpha]_D^{20}$ = −31.6 (c 1, CH_3OH). ^{1}H NMR (400 MHz, CD_3OD. Exchangeable protons were not detected) δ 7.11–7.00 (m, 6H), 6.82 (d, J = 7.8 Hz, 1H), 6.72 (d, J = 7.4 Hz, 1H), 6.60 (t, J = 7.6 Hz, 1H), 3.52 (q, J = 6.7 Hz, 1H), 1.31 (d, J = 6.7 Hz, 3H). ^{13}C NMR (100 MHz, CD_3OD) δ 173.4 (2C), 146.9, 143.1, 129.7, 128.2 (2C), 127.7, 126.8 (3C), 125.8, 122.4, 110.5, 72.6, 55.1, 24.8. HRMS (ESI) calcd for $C_{17}H_{17}N_3O_2$ 295.1321, found 295.1320.

(*R*)-3-Amino-2-oxo-2,3-dihydro-1*H*-indole-3-carboxylic acid amide 12

Synthesis of 12 from 10a. **10a** (80 mg, 0.19 mmol) was dissolved in a 4% solution of HCl in EtOH (2.7 ml). The reaction mixture was allowed to stir at room temperature for 3 h. The solution was neutralized with a saturated aqueous solution of $NaHCO_3$ and then the solvent was removed *in vacuo*. The aqueous layer was extracted with AcOEt (2 × 5 ml). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure providing the alcohol intermediate (41.2 mg, 70% yield). R_f = 0.22 (EtOAc–MeOH, 9.5 : 0.5). $[\alpha]_D^{20}$ = −257.1 (c 1, CH_3OH). ^{1}H NMR (400 MHz, CD_3OD. Exchangeable protons were not detected) δ 7.39 (dd, J = 7.5, 0.6 Hz, 1H), 7.31 (dt, J = 7.7, 1.3 Hz, 1H), 7.21–7.08 (m, H, 3H), 6.83 (dd, J = 8.0, 1.4 Hz, 2H), 6.75 (d, J = 7.6 Hz, 1H), 3.73–3.65 (m, 2H), 3.47 (dd, J = 15.3, 8.7 Hz, 1H). ^{13}C NMR (100 MHz, CD_3OD) δ 178.7 (2C), 143.4, 139.8, 129.6, 125.0, 121.8, 110.3, 127.5–127.2 (5C), 126.9, 70.7, 66.2, 60.9. To a solution of the alcohol intermediate (26.5 mg, 0.09 mmol) in 0.9 ml of CH_2Cl_2–MeOH, 1 : 1, at 0 °C, was added $Pb(OAc)_4$ (39.9 mg, 0.09 mmol, 1 equiv). The mixture was stirred at room temperature for 1 h. A 3 M solution of HCl in dioxane (0.6 ml) was added and the mixture was stirred at room temperature for 16 h. The solution was then basified to pH 8–9 by the addition of solid Na_2CO_3. The aqueous layer was extracted with EtOAc (3 × 2 ml). The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure yielding **12** (11.9 mg, 69% yield).

Synthesis of 12 from 11a. To a solution of **11a** (223.6 mg, 0.76 mmol) in dry MeOH (7.6 ml), 20% $Pd(OH)_2/C$ (45 mg) was added and the reaction mixture was stirred at room temperature under hydrogen atmosphere for 3 days. The suspension was then filtered through a pad of Celite and the residue washed with MeOH (3 × 8 ml). The solvent was evaporated *in vacuo* to obtain **12** (145.0 mg, 98%).

12. R_f = 0.46 (EtOAc/MeOH, 9.5 : 0.5). $[\alpha]_D^{20}$ = −72.4 (c 0.5, CH_3OH). ^{1}H NMR (400 MHz, CD_3OD. Exchangeable protons were not detected) δ 7.35 (d, J = 7.5 Hz, 1H), 7.30 (dt, J = 7.7, 1.2 Hz, 1H), 7.06 (dt, J = 7.6, 0.8 Hz, 1H), 6.95 (d, J = 7.8 Hz, 1H). ^{13}C NMR (100 MHz, CD_3OD) δ 174.1 (2C), 143.3, 131.2, 130.2, 124.0, 123.0, 110.8, 70.8. IR ($CHCl_3$) ν_{max} 3435, 3338, 3226, 1724, 1616 (cm^{-1}). HRMS (ESI) calcd for $C_9H_9N_3O_2$ 191.0695, found 191.0695.

(*S*)-3-Amino-2-oxo-2,3-dihydro-1*H*-indole-3-carboxylic acid methyl ester 14

Synthesis of 14 from 15a. To a solution of **15a** (98 mg, 0.31 mmol) in 3.1 ml of CH_2Cl_2–MeOH 1 : 1, at 0 °C, was added $Pb(OAc)_4$ (137.4 mg, 0.31 mmol, 1 equiv). The mixture was stirred at room temperature for 17 h. A 3 M solution of HCl in dioxane was added (2 ml) and the mixture was stirred at room temperature for 3 days. The solution was then basified to pH 8–9 by the addition of solid Na_2CO_3. The aqueous layer was extracted with AcOEt (3 × 7 ml). The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (hexane–EtOAc, 1.5 : 8.5) giving **14** (38.4 mg, 60% yield).

Synthesis of 14 from 16a. To a solution of **16a** (164.8 mg, 0.53 mmol) in dry MeOH (5.3 ml), 20% $Pd(OH)_2/C$ (35 mg) was added and the reaction mixture was stirred at room temperature under hydrogen atmosphere for 6 days. The suspension was then filtered through a pad of Celite and the residue washed with EtOAc (3 × 6 ml). The solvent was evaporated *in vacuo* providing **14** (107 mg, 98% yield).

14. R_f = 0.25 (hexane–EtOAc, 3 : 7). $[\alpha]_D^{20}$ = −113.8 (c 0.7, CH_3OH). ^{1}H NMR (400 MHz, CD_3OD. Exchangeable protons were not detected) δ 7.33–7.25 (m, 2H), 7.02 (t, J = 7.6 Hz, 1H), 6.93 (d, J = 7.6 Hz, 1H), 3.66 (s, 3H). ^{13}C NMR (100 MHz, CD_3OD) δ 178.5, 172.0, 144.2, 131.5, 130.1, 125.1, 124.2, 111.8, 61.3, 53.9. IR ($CHCl_3$) ν_{max} 3433, 3211, 1747, 1620 (cm^{-1}). HRMS (ESI) calcd for $C_{10}H_{10}N_2O_3$ 206.0691, found 206.0690.

3-((*R*)-2-Hydroxy-1-phenyl-ethylamino)-2-oxo-2,3-dihydro-1*H*-indole-3-carboxylic acid methyl ester (15a,b). **7a,b** (112 mg, 0.27 mmol) was dissolved in dry MeOH (3.5 ml) and cooled to 0 °C. HCl gas was then slowly bubbled through the solution for 15 min. The resulting dark red solution was then left to stir at room temperature for 22 h. Excess HCl was removed bubbling N_2 into the solution. After dilution with water (3.5 ml), the solution was neutralized by the addition of a saturated aqueous solution of $NaHCO_3$ and then the solvent removed *in vacuo*. The aqueous layer was extracted with CH_2Cl_2 (3 × 3.5 ml) and the organic layer obtained was dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash chromatography (hexane–EtOAc, 6 : 4) yielded compound **15a** (35.1 mg) and compound **15b** (24.8 mg) (68% overall yield). **15a**. R_f = 0.27 (hexane–EtOAc, 3 : 7). $[\alpha]_D^{20}$ = −136.7 (c 1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.31 (br s, 1 H), 7.39–7.30 (m, 2H), 7.21–7.16 (m, 3H), 7.12 (m, 1H), 7.14–7.08 (m, 2H), 6.83 (d, J = 7.6 Hz, 1H), 3.79–3.74 (m, 1H), 3.72–3.63 (m, 1H), 3.65 (s, 3H), 3.58–3.52 (m, 1H), 2.67–2.51 (br s 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.7, 169.3, 141.9, 139.1, 130.3, 125.0, 123.0, 110.7, 128.1–128.0 (5C), 125.8, 70.8, 66.5, 60.1, 53.5. IR ($CHCl_3$) ν_{max} 3433, 3330, 1747, 1620 (cm^{-1}). HRMS (ESI) calcd for $C_{18}H_{18}N_2O_4$ 326.1267 found 326.1263.

15b. R_f = 0.32 (hexane–EtOAc, 3 : 7).^{1}H NMR (300 MHz, $CDCl_3$) δ 8.08 (br s, 1 H), 7.42–7.27 (m, 3H), 7.26–7.19 (m, 2H), 7.15 (dt, J = 7.6, 1.5 Hz, 1H), 6.87 (dd, J = 7.6, 1.4 Hz, 1H), 6.77–6.65 (m, 2H), 3.74–3.57 (m, 3H). 3.64 (s, 3H), 2.78–2.59 (br s 2H).

2-Oxo-3-((*S*)-1-phenyl-ethylamino)-2,3-dihydro-1*H*-indole-3-carboxylic acid methyl ester (16a,b)

8a,b (1.08 g, 3.89 mmol) was dissolved in dry MeOH (30 ml) and cooled to 0 °C. HCl gas was then slowly bubbled through the solution for 45 min. The resulting dark red solution was then left to stir at room temperature for 16 h. Excess HCl was removed by bubbling N_2 into the solution. After dilution with water (30 ml), the solution was neutralized by the addition of solid Na_2CO_3 and then the solvent removed *in vacuo*. The aqueous layer was extracted with CH_2Cl_2 (3 × 30 ml) and the organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash chromatography (hexane–EtOAc, 6.5 : 3.5) allowed a partial separation of compound **16a** (332.2 mg) and compound **16b** (319.5 mg) as a light yellow solid (651.7 mg, 54% overall yield). **16a**. R_f = 0.39 (hexane–EtOAc, 1 : 1). $[\alpha]_D^{20}$ = −150.3 (*c* 1.3, CH_3OH). ^{1}H NMR (400 MHz, CD_3OD. Exchangeable protons were not detected) δ 7.35–7.27 (m, 2H), 7.19–7.04 (m, 4H), 6.92 (dd, *J* = 7.7, 1.3 Hz, 2H), 6.76 (d, *J* = 7.9 Hz, 1H), 3.75 (q, *J* = 6.6 Hz, 1H), 3.62 (s, 3H), 1.27 (d, *J* = 6.7 Hz, 3H). ^{13}C NMR (100 MHz, CD_3OD) δ 176.2, 169.7, 143.5, 143.1, 129.8, 127.5–126.9 (5C), 126.3, 124.4, 121.9, 110.3, 70.5, 54.0, 52.3, 23.6. IR ($CHCl_3$) ν_{max} 3433, 3338, 1747, 1618 (cm^{-1}). HRMS (ESI) calcd for $C_{18}H_{18}N_2O_3$ 310.1317 found 310.1319.

16b. R_f = 0.43 (hexane–EtOAc, 1 : 1). $[\alpha]_D^{20}$ = −63.8 (*c* 1.2, CH_3OH). ^{1}H NMR (400 MHz, CD_3OD. Exchangeable protons were not detected) δ7.12–6.96 (m, 6H), 6.81 (dd, *J* = 7.5, 0.7 Hz, 1H), 6.76 (d, *J* = 7.7 Hz, 1H), 6.69 (dt, *J* = 7.6,1.0 Hz, 1H), 3.64 (s, 3H), 3.64 (q, *J* = 6.6 Hz, 1H), 1.31 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR (100 MHz, CD_3OD) δ 176.5, 169.3, 145.3, 142.1, 129.2, 124.8, 122.0, 109.9, 127.5–126.3 (5C), 126.8, 71.4, 54.2, 52.3, 23.9.

(*S*)-3-(*R*)-2-*tert*-Butoxycarbonylamino-propionylamino)-2-oxo-2,3-dihydro-1*H*-indole-3-carboxylic acid methyl ester 17. **14a** (68.4 mg, 0.33 mmol) was dissolved in dry CH_2Cl_2 (2 ml) at 0 °C. Dry Et_3N (51 µl, 0.37 mmol, 1.1 equiv) and BopCl (127.3 mg, 0.50 mmol, 1.5 equiv) were added and the reaction mixture was stirred at 0 °C for 40 min. Keeping the mixture at 0 °C, a solution of Boc-Ala-OH (62.4 mg, 0.33 mmol, 1 equiv) in dry CH_2Cl_2 (2 ml) and dry Et_3N (51 µl, 0.37 mmol, 1.1 equiv) was slowly added. The reaction mixture was allowed to warm to room temperature and stirred for 22 h. The reaction was quenched with H_2O (4 ml) and the organic layer was washed with 1 M HCl (2 × 4 ml), saturated aqueous solution of $NaHCO_3$ (2 × 4 ml) and water (4 ml), dried over Na_2SO_4, filtered and the solvent removed *in vacuo*. Purification by flash chromatography (hexane–EtOAc, 1 : 1) afforded compound **17** (66 mg, 53% yield). R_f = 0.48 (hexane–EtOAc, 3 : 7). $[\alpha]_D^{29}$ = −31.0 (*c* 0.72, CH_3OH). ^{1}H NMR (400 MHz, CD_3OD. Exchangeable protons were not detected) δ 7.30 (dt, *J* = 8.0, *J* = 1.3 Hz, 1H), 7.13 (d, *J* = 7.3 Hz, 1H), 7.01 (dt, *J* = 7.6, 0.9 Hz, 1H), 6.93 (d, *J* = 7.8 Hz, 1H), 4.13 (q, *J* = 7.2 Hz, 1H), 3.73 (s, 3H), 1.51 (s, 9H), 1.29 (d, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, CD_3OD) δ 173.1 (2C), 167.3, 157.2, 143.1, 129.7, 126.9, 122.4 (2C), 110.1, 79.6, 66.0, 53.0, 50.0, 27.3 (3C), 16.4. IR ($CHCl_3$) ν_{max} 3525, 3348, 1748, 1718, 1604 (cm^{-1}). HRMS (ESI) calcd for $C_{18}H_{23}N_3O_6$ 377.1587, found 377.1589.

1-[(*E*)-3-(3,4-Dichloro-phenyl)-allyl]-3-[(*S*)-1-phenyl-ethyl-imino]-1,3-dihydro-indol-2-one 19. To a solution of **18** (2 g, 6.02 mmol) in dry THF (20 ml) was first added at room temperature $MgSO_4$ (5.8 g, 48.16 mmol, 8 equiv) and then a solution of (*S*)-phenyl-ethylamine (922.5 mg, 6.02 mmol, 1 equiv) in dry THF (20 ml). The reaction mixture was stirred at room temperature overnight. The reaction mixture was filtered through a pad of Celite and the solvent removed *in vacuo* affording the mixture of imine isomers **19** (2.57 g, 98% yield). *Mixture of diastereoisomers* (≈ 3 : 1) $[\alpha]_D^{25}$ = −142.0 (*c* 1.5, $CHCl_3$) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (d, *J* = 7.7 Hz, 0.25H), 7.64 (d, *J* = 7.7 Hz, 0.75H), 7.51 (d,^{3}*J* = 7.7 Hz, 1.5H), 7.46 (d, *J* = 7.7 Hz, 0.5H), 7.34–7.22 (m, 5H), 7.20–7.14 (m, 1H), 7.09–6.95 (m, 2H), 6.81 (d, *J* = 7.7 Hz, 0.25H), 6.72 (d, *J* = 7.7 Hz, 0.75H), 6.57 (q, *J* = 6.2 Hz, 0.75H), 6.43 (d, *J* = 16.1 Hz, 1H), 6.12 (dt, *J* = 16.1, 6.2 Hz, 1H), 5.49 (q, *J* = 6.2 Hz, 0.25H), 4.47 (d, *J* = 6.2 Hz, 0.5), 4.41 (*J* = 6.2 Hz, 1.5H), 1.69 (d, *J* = 6.2 Hz, 0.75H), 1.55 (d, *J* = 6.2 Hz, 2.25H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.2 and 158.1, 151.0 and 150.9, 145.7 and 145.4, 144.5 and 144.4, 136.3 and 136.1, 133.1 and 132.7, 132.5, 131.6, 130.8 and 130.4, 128.3 and 128.2 (3C), 126.9 and 126.5 (4C), 125.5, 124.6, 123.1 and 122.9, 122.4, 121.9, 109.8 and 108.8, 61.5 and 58.5, 41.6 and 41.2, 24.8 and 24.6. IR ($CHCl_3$) ν_{max} 3419, 1733, 1624 (cm^{-1}). HRMS (ESI) calcd for $C_{25}H_{20}Cl_2N_2O$ 434.0953, found 434.0951.

1-[(*E*)-3-(3,4-Dichloro-phenyl)-allyl]-2-oxo-3-((*S*)-1-phenyl-ethylamino)-2,3-dihydro-1*H*-indole-3-carbonitrile (20a,b). To a solution of **19** (1 g, 2.30 mmol) in anhydrous CH_2Cl_2 (25 ml), at −20 °C, was first added $SnCl_4$ (633 µl, 3.45 mmol, 1.5 equiv) and then dropwise TMSCN (863 µl, 6.90 mmol, 3 equiv). The reaction mixture was stirred at −20 °C for 24 h. The solution was then poured into a saturated aqueous solution of $NaHCO_3$ (25 ml). The aqueous layer was extracted with CH_2Cl_2 (3 × 50 ml), and the combined organic extracts were washed with water, dried over Na_2SO_4, filtered and evaporated under reduced pressure delivering **20** (936 mg, 88% yield). *Mixture of diastereoisomers* (65 : 35) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46–7.03 (m, 10H), 7.03–6.93 (m, 1H), 6.84 (d, *J* = 12.4 Hz, 0.4H), 6.78 (d, *J* = 12.4 Hz, 0.6H), 6.60–6.39 (m, 1H), 6.18 (dt, *J* = 16.7, 9.2 Hz, 0.4H), 6.01 (dt, *J* = 16.7, 9.2 Hz, 0.6H), 4.50 (dd, *J* = 9.2, 2.7 Hz, 1.2H), 4.36–3.97 (m, 1.8H), 2.64 (d, *J* = 3.9 Hz, 0.6H), 2.59 (d, *J* = 3.9 Hz, 0.4H), 1.46 (d, *J* = 11.0 Hz, 1.8H), 1.43 (d, *J* = 11.0 Hz, 1.2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.6 and 169.5, 144.3 and 143.5, 142.2 and 141.9, 135.8 and 135.7, 132.5 and 132.4, 131.5 and 131.4, 131.0 and 130.8, 130.7 and 130.6, 130.3 and 130.2, 128.2 and 128.1, 128.0, 127.9 and 127.8, 127.2 and 127.0, 126.7 and 126.6, 126.2, 125.8 and 125.6, 125.5 and 125.4, 123.8 and 123.6, 123.4 and 123.2, 123.3, 116.3 and 116.2, 109.6 and 109.5, 59.1 and 58.8, 54.7 and 54.2, 42.0, 25.1 and 24.9. IR ($CHCl_3$) ν_{max} 3425, 2246, 1736 (cm^{-1}). HRMS (ESI) calcd for $C_{26}H_{21}Cl_2N_3O$ 461.1062, found 461.1066.

1′-[(2*E*)-3-(3,4-dichlorophenyl)prop-2-en-1-yl]-1*H*,3-[(*S*)-1-phenyl-ethyl]spiro[imidazolidine-4,3′-indole]-2,2′,5(1′*H*)-trione (21a,b). To a solution of **20a,b** (900 mg, 1.95 mmol) in dry CH_2Cl_2 (23 ml) was added CSI(276 mg, 1.95 mmol, 1 equiv). The reaction mixture was stirred at room temperature for 15 min, then concentrated *in vacuo*. After addition of 18 ml of 1 N HCl, the suspension was stirred for 15 min at room temperature, followed by heating to reflux for 2 h. Once the mixture cooled to room temperature, the solid was filtered, washed with water and dried affording product **21a,b** in 93% yield. Crystallization (hexane–EtOAc, 95 : 5) and purification by flash chromatography (toluene–EtOAc, 95 : 5) allowed a partial separation of the major

diastereoisomer **21a**. *Mixture of diastereoisomers* (≈ 3 : 1) ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.40 (br s, 1H), 7.51–7.02 (m, 10H), 6.95–6.73 (m, 2H), 6.62 (d, J = 16.3 Hz, 0.75H), 6.49 (d, J = 16.3 Hz, 0.25H), 6.20 (dt, J = 16.3, 4.7 Hz, 0.75H), 6.45 (dt, J = 16.3, 4.7 Hz, 0.25H), 5.40 (q, J = 6.2 Hz, 0.75H), 5.15 (q, J = 6.2 Hz, 0.25H), 4.63 (dd, J = 15.5, 4.7 Hz, 0.75H), 4.39 (dd, J = 15.5, 4.7 Hz, 0.75H), 4.34 (dd, J = 15.5, 4.7 Hz, 0.25H), 3.88 (dd, J = 15.5, 4.7 Hz, 0.25H), 1.71 (d, J = 6.2 Hz, 0.75H), 1.66 (d, J = 6.2 Hz, 2.25H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.9, 168.4 and 168.3, 156.4 and 156.3, 143.0, 139.3, 136.9, 136.1, 132.7, 131.7, 131.0, 130.7, 130.5, 129.2, 128.2 (2C), 128.0 (2C), 127.9, 127.7, 125.8 and 124.9, 123.4 and 123.3, 122.5, 109.6, 60.4, 54.0 and 52.7, 42.2 and 42.0, 17.8 and 14.1. IR ($CHCl_3$) ν_{max} 3442, 1729, 1633 (cm^{-1}). HRMS (ESI) calcd for $C_{27}H_{21}Cl_2N_3O_3$ 505.0960, found 505.0962.

1′-[(2*E*)-3-(3,4-Dichlorophenyl)prop-2-en-1-yl]-2*H*,5*H*-spiro-[imidazolidine-4,3′-indole]-2,2′,5(1′*H*)-trione (3). To a solution of **21a** (120 mg, 0.24 mmol) in dry toluene (3 ml) was added MsOH (31 µl, 0.48 mmol, 2 equiv). The mixture was refluxed for 24 h. The reaction mixture was then cooled to room temperature, washed with a saturated aqueous solution of $NaHCO_3$ (2 × 5 ml) and with water (5 ml), dried over Na_2SO_4, filtered and evaporated under reduced pressure yielding **3** (90 mg, 93% yield). $[\alpha]_D^{25}$ = +16.2 (*c* 0.5, CH_3OH, lit +16.8, see ref. 22). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.50 (br s, 1H), 8.70 (br s, 1H), 7.68–7.63 (m, 1H), 7.56 (d, J = 7.7 Hz, 1H), 7.47–7.36 (m, 3H), 7.19–7.10 (m, 2H), 6.53 (d, J = 15.8 Hz, 1H), 6.44 (dt, J = 15.8, 3.8 Hz, 1H), 4.54 (d, J = 4.1 Hz, 2H) ^{13}C NMR (101 MHz, DMSO-d_6) δ 170.8, 170.6, 157.6, 143.4, 136.8, 131.5, 130.8 (2C), 130.0, 128.8, 128.1, 126.4, 125.4, 124.8, 124.2, 123.5, 110.1, 69.2, 41.5. IR ($CHCl_3$) ν_{max} 3440, 3330, 1797, 1734, 1702 (cm^{-1}). HRMS (ESI) calcd for $C_{19}H_{13}Cl_2N_3O_3$ 401.0334, found 401.0333.

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