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Indolylglycines backbones in the synthesis of enantiopure 3,3-spiroindolenines, indolyl tetracyclic hemiaminals and 3-indolyl-maleimides frameworks

Jozef Markus,[a] Branislav Ferko,[a] Dušan Berkeš,*[a] Ján Moncol,[b] Ata Martin Lawson,[c] Mohamed Othman,[c] and Adam Daïch*[c]

‡ Dedicated to the memory of our colleague Prof. Dr. Ing. František Považanec who passed away in his hometown on 20 April 2017.

Abstract: This paper describes the synthesis of novel *N*-substituted 3-indolylglycines (3IGs), in high yields and optical purity via three-component Mannich reaction (3CR) of indole and free glyoxylic acid in the presence of primary and secondary aliphatic amines. By using this efficient approach, a series of racemic 3-indolylglycines (3IGs) as well as the optically pure (*S*)-3-indolylglycine ((*S*)-3IG) in multigram synthesis using (*R*-1-phenylethylamine ((*R*)-α-PEA) as chiral pool were synthetized. In parallel investigations, 3IGs were used as the starting material for the highly stereoselective synthesis of spiroindolenines bearing three controlled contiguous stereogenic centers. Despite our expectations, the *N*-chloroacetyl esters of 3IGs did not provide the expected spiroindolenine derivatives but led us to the discovery of a new methodology for the preparation of 3-indolylmaleimides (3IMs); compounds known for their broad range of important biological and fluorescence activities.

Introduction

Aza-heterocyclic systems probably constitute the largest and most varied family of organic compounds. The indole nuclei belonging to this family occupy a privileged place as the most frequent ring present in the bioactive natural compounds as well as the highest reliable source to provide new molecules with both pharmaceutical and industrial importance.[1] In particular, spirocyclic indolenines **1**, **2** and **3** (Figure 1)[2] are among the best studied classes, due to their therapeutic potential and versatility to act as precursors for other important heterocyclic systems including carbazoles, oxindoles and more.[3] Another important class of compounds bearing an indole subunit are bis-indolylmaleimides (BIMs) **4** and **5** (Figure 1)[4] which possess a broad range of biological potential,[5] not only as protein kinase inhibitors,[6] but also as promising agents in anticancer therapy.[7] In addition, representative of 3-indolylmaleimides (3IMs) subfamily such as compound **6** (SB-216763, Figure 1)[8] can be useful in modern optoelectronics because of its high fluorescence activity.[8]

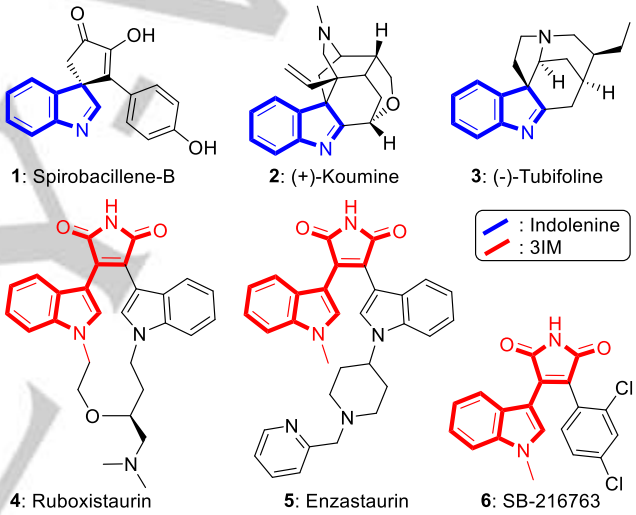

Figure 1. Examples of naturally occurring alkaloids such as spiroindolenines (**1,2,3**) and bis-indolylmaleimide (BIM; **4,5**) and unnatural 3-indolylmaleimide (3IM) derivative **6** (SB-216763).

Because of these interesting properties, the synthetic strategies for these compounds is a matter of interest. In this light, we present herein the strategy for the preparation of optically pure spiroindolenine derivatives, their tetracyclic hemiaminals and 3-indolylmaleimides (3IM) from enantiopure *N*-substituted 3-indolylglycines (3IGs).

3IGs have attracted great attention as nonproteinogenic acids and serve as important synthetic intermediates in drug development, natural products as well as peptide mimetics. Several synthetic approaches for the synthesis of 3IGs have been reported in recent years all based on the use of substituted indole.[9-13] They rely on a small number of strategies, based on asymmetric catalysis, chiral auxiliary-mediated induction[9-11,13] and racemic approaches[12] followed exclusively in the latter case by an enzymatic resolution.[12a]

However, only a few methods are capable to provide an efficient synthesis of highly enantioenriched α-3IGs. The most frequent synthetic approach used is the asymmetric Friedel-Crafts α-aminoalkylation using racemic glyoxylate imines and

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chiral Lewis or Brönsted acids (Routes IV, Figure 2).[9a-d] Sporadic approaches using chiral nitrones (Route II, Figure 2)[10] and an asymmetric oxidative heterocoupling reaction of a chiral nickel(II) complex (Route III, Figure 2)[11] with indoles (Is) as carba-nucleophiles were reported.

Furthermore, diastereoselective synthesis based on chiral imines can also be applied (Route I, Figure 2).[9e-g] A three-component aminoalkylation of indole moiety in greener racemic version using glyoxylic acid ((Route VI (R = H), Figure 2)[12e,13a] or in asymmetric version using chiral amine and ethyl glyoxylate (Routes VII and VIII (R = Et), Figure 2)[13b,c] were also reported. It is worth noting that implementation of chiral centre from chiral amines via diastereoselective approach is usually high and the enantiomeric purity of the ultimate 3IGs can be improved mostly via crystallization.[9] In parallel, an interesting 'four-step' sequence using a chiral *N*-Boc-oxazolidine-3-indole as a key reagent was also developed recently (Route V, Figure 2).[9h]

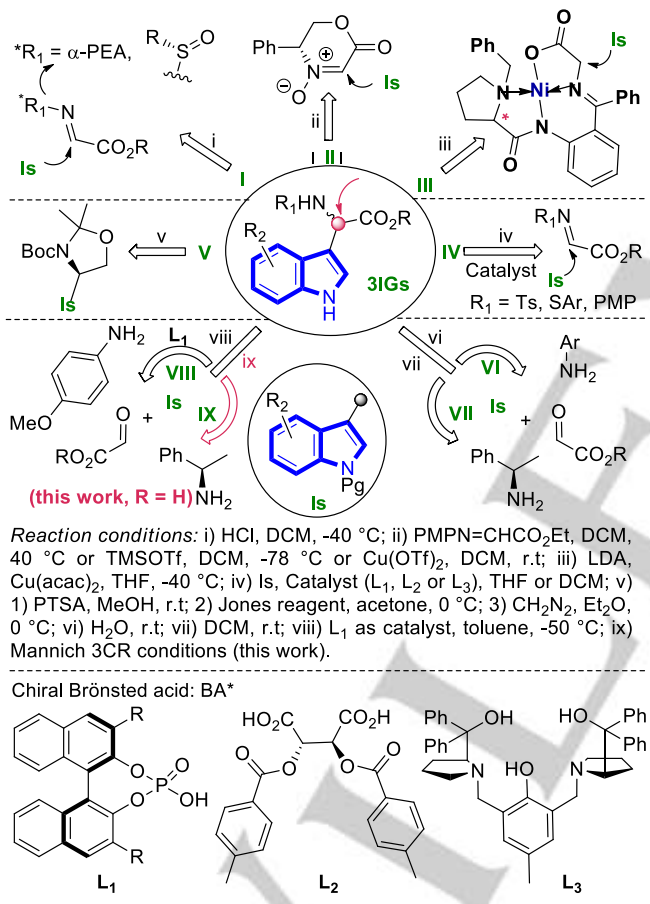


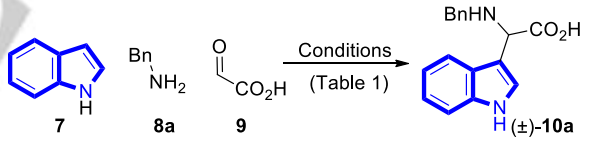
Figure 2. Classical methods used for the synthesis of *N*-substituted 3-indolylglycines (3IGs) (Routes I-VIII) and our Mannich's 3CR one (Route IX).

Based on both Mannich's 3CR type[13] and our contribution on the elaboration of conformationally constrained homophenyl-alanines using crystallization-induced asymmetric transformation (CIAT) technology,[14] in this contribution we report the direct three-component aminoalkylation (3CR) of indole moiety using glyoxylic acid hydrate and primary or secondary amines as starting materials (Route IX (R = H), Figure 2). To date, free glyoxylic acid utilization in indolylglycines synthesis is rare. The application of Petasis reaction[13b] is an successful example of such a transformation; however, the indolylboronic acids, often more difficult to obtain, are required as starting materials. Ghandi's recent work describes the synthesis of 3IGs,[13a] which uses water as solvent in greener context, though is limited only to primary amines. Thus, the Mannich's 3CR approach for the elaboration of enantiopure 3IGs, in which both primary and secondary amines are transferred under very mild reaction conditions in high optical purity is a matter of interest.

Results and Discussion

Our study was initiated by the synthesis of racemic α-3IGs by three-component Mannich type reaction of indole, free glyoxylic acid and amines. The optimization of the reaction conditions was accomplished through *N*-benzyl amine as a model substrate. Interestingly enough, when we examined the various reaction conditions including the molar scale, used solvent, reaction time and concentration for the reaction yield, the addition order of the reactant seemed to be an important factor. From these attempts, a significant improvement of the reaction yield, when indole (**7**) and benzyl amine (**8a**) were mixed first followed by addition of glyoxylic acid (**9**) with vigorous stirring was achieved. The optimized results are summarized in the Table 1.

Table 1. Optimization of the reaction conditions for the three-component Mannich type reaction (3CR) of indole (**7**), *N*-benzyl amine (**8a**) and free glyoxylic acid **9**.[a,b]



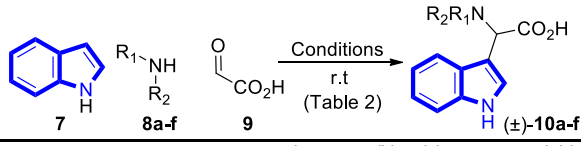
Entry	**7** (equiv.)	8a (equiv.)	9 (equiv.)	Solvent	C (M)	t (h)	Product **10a** Yield (%)[d]
1	1	1.5	1	EtOH	1.2	2	58
2	1	1.1	1	EtOH	0.7	2	44
3	1	1.1	1	*i*-PrOH	0.4	2	29
4	1	1.1	1	EtOH	0.7	2	68
5	1	2	1.5	EtOH	0.7	2	85
6	1	1.3	1.3	EtOH	0.5	2	90
7	1	1.3	1.2	MeOH	0.4	2	91
8	1	1.3	1.2	MeOH	0.4	2	91
9[c]	1	1.1	1.1	MeOH	0.25	1	92

[a] All reactions were performed at room temperature (25 °C). [b] Reactions were performed on 2 mmol scale. [c] Reaction was performed on 5 mmol scale. [d] Isolated yields

With the optimized reaction conditions in hand, we examined the scope of the Mannich's 3CR with a series of primary and secondary aliphatic amines as well as amino alcohol. As highlighted in Table 2, the production of the expected derivatives **10** is effective with yields ranging from 75% up to 93% and with the reaction times ranging from 1 hour up to 4 hours depending on the used amines. The Mannich's 3CR resulting products (±)-

10a-f are easily isolated from the reaction mixture by simple filtration as white solids. The series of racemic 3IGs obtained are summarized in Table 2.

Table 2. Mannich's 3CR type reaction leading to 3IGs derivatives (±)-**10a-f**, from indole (**7**), amine (**8a-f**) and free glyoxylic acid (**9**).

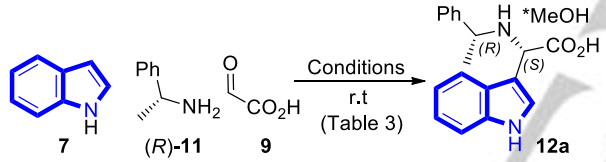


7 **8a-f** **9** (±)-**10a-f**

Entry	R_1 group	R_2 group	Solvent	t (h)	(±)-**10**	Yield (%)
1	Bn	H	MeOH	1	(±)-**10a**	92
2	Me	H	MeOH	2	(±)-**10b**	82
3	2-Ph$(CH_2)_2$	H	MeOH	1	(±)-**10c**	93
4	Allyl	H	EtOH	2	(±)-**10d**	88
5	2-hydroxyethyl	H	MeOH	2	(±)-**10e**	90
6	Bn	Me	MeOH	2	(±)-**10f**	75

Next, we examined various conditions for the preparation of optically pure (*S*)-3-indolylglycine ((*S*)-3IG). For this purpose, various reaction conditions were explored by using cost-effective (*R*)-phenylethylamine (**11**) ((*R*)-α-PEA) as chiral pool (Table 3).

Table 3. Optimization of the reaction conditions en-route to the preparation of pure (*S*)-3-indolylglycine ((*S*)-3IG) via the (*R*,*S*)-diastereomer **12a**.



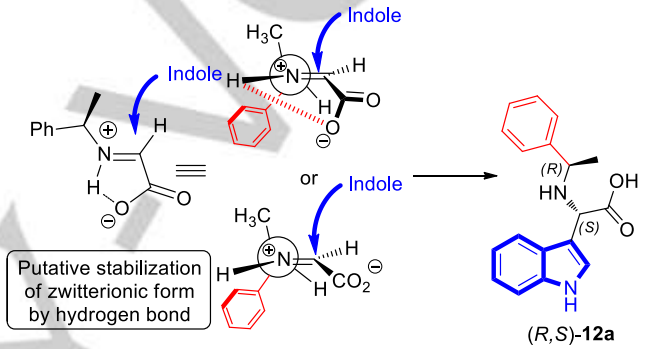
7 (*R*)-**11** **9** **12a**

Entry	**11** (equiv.)	**9** (equiv.)	Solvent	C (M)	t (h)	Yield(%)[h]	d.r[g]
1	1.3	1.2	EtOH	1.2	2	90[a]	62:38
2	1.1	1.1	MeOH	2	2	93[a]	67:33
3	1.1	1.1	THF	1	2	89[a]	78:22
4	1.1	1.1	THF	1	4[e]	92[a]	80:20
5	1.1	1.1	THF	0.3	4[f]	75[a]	82:18
6	1.1	1.1	Dioxane	0.25	2	87[a]	78:22
7	1.1	1.1	MeCN	025	2	56[b]	75:25
8	1.1	1.1	MeOH	1.3	2	95[c]	77:23
9	1.1	1.1	MeOH	0.8	2	63[d]	90:10
10	1.1	1.1	MeOH	0.7	1.5	60[d]	94:6
11	1.1	1.1	MeOH	0.7	1	58[d]	95:5
12	1.1	1.1	MeOH	0.5	1.5	52[d]	>99:1
13	1.1	1.1	MeOH	0.5	1.5	52[d]	>99:1

Reactions were carried using 1 equiv. of indole (**7**) at room temperature (25 °C) unless otherwise noted. Reactions were performed on 2 mmol scale (entries 1-7), 10 mmol (entries 8-11), 20 mmol (entry 12), 100 mmol (entry 13). [a] After evaporation of solvent, **12a** was isolated by trituration with Et_2O. [b] Product **12a** was isolated by simple filtration. [c] After evaporation of solvent, **12a** was isolated by trituration with acetonitrile. [d] Reaction mixture was seeded with crystals of pure diastereomer and **12a** was isolated by filtration from reaction mixture. [e] Reaction was carried out at -5 °C. [f] Reaction was carried out at -30 °C. [g] (*R*,*S*)-diastereomer **12a** : (*R*,*R*)-diastereomer **12b** ratio (HPLC). [h] Isolated yields

By using ethanol and methanol as the reaction solvent (entries 1,2, Table 3), the product **12a** was obtained in d.r. excess of 62:38 and 67:33 in favour of the (*R*,*S*)-diastereomer. With lowering the reaction temperature, no change was observed in the d.r. ratios while the reaction time increased. After the addition of the free glyoxylic acid (**9**) the reaction turned to homogeneous mixture (entries 1-6). Precise tuning of reaction conditions using methanol (entries 8-12) allowed us to isolate the major (*R*,*S*)-diastereomer in excellent diastereomeric purity (d.r > 99:1) by simple filtration of precipitated methanolic solvate from the reaction mixture (entries 12 and 13). In both cases, changing the quantity of the starting indole (**7**, 20 mmol up to 100 mmol) had no influence on either d.r ratio or reaction yield.

Moreover, the diastereoselective nucleophilic additions to the *N*-substituted chiral imines derived from glyoxylic acid were recently studied by Ender´s[15] and Sigh´s[16] groups. Based on this, a putative model of stereoinduction in the addition of indole to the zwitterionic intermediate was proposed (Scheme 1).



Scheme 1. Plausible mechanism leading to (*R*,*S*)-diastereomer **12a**.

The relative and absolute configuration of the new stereogenic centre was determined by X-ray. The suitable single crystal **12a·MeOH** for X-ray analysis was obtained by crystallization from the mixture of MeOH/Et_2O (Figure 3).[17]

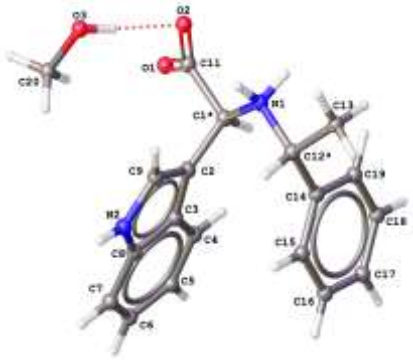
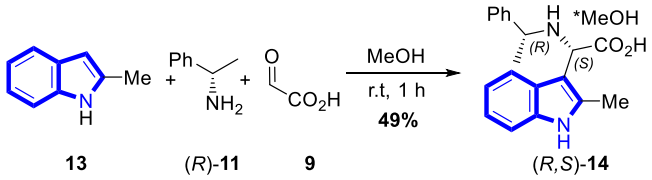


Figure 3. Molecular structure of the pure (*R*,*S*)-diastereomer **12a·MeOH** (salt form) which was used to provide pure (*S*)-3-indolylglycine ((*S*)-3IG) (**15**).

In order to evaluate the impact of the nucleophile size on the reaction stereochemistry outcome, Mannich's 3CR was also carried out with 2-methylindole (**13**) as starting material. By analogy (Scheme 2), using standard conditions, the expected product **14** was isolated in similar 49% yield and in high d.r. (>99:1).



13 (*R*)-**11** 9 (*R,S*)-**14**

Scheme 2. Mannich's 3CR type reaction leading to 3IGs derivative **14** from 2-methylindole (**13**), (*R*)-α-PEA (**11**) and free glyoxylic acid (**9**).

The relative and absolute configuration of the new stereogenic centre in the pure product **14** was also determined by crystallographic analysis. The suitable single-crystal of **14·MeOH** for X-ray diffraction was obtained by crystallization from the mixture of MeOH/Et_2O (Figure 4).[18]

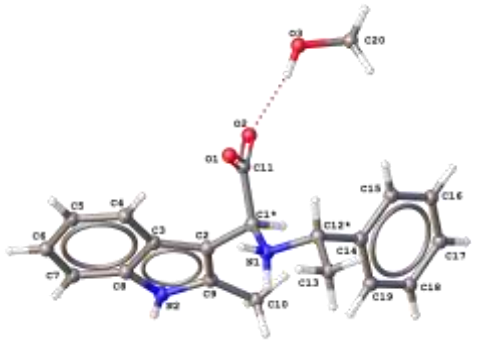
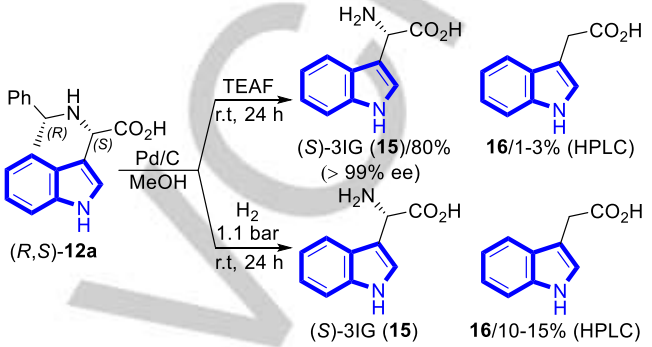


Figure 4. Molecular structure of the pure (*R,S*)-diastereomer **14·MeOH** isolated in the saltf form as MeOH solvate.

From the observations raised while verifying the literature, we found that simple route for the preparation of enantiomeric pure *N*-substituted 3IGs **12a** and **14** is still not a guarantee that these derivatives could be easily transferred to corresponding optically pure amino acids. There are several known protocols for the preparation of optically pure *N*-substituted 3IGs[9,13b,c] (see Figure 2 and corresponding comments along the text) but only a few of them describe how to remove the protecting group in order to isolate corresponding free amino acids.[9b,11] This important challenge was thoroughly investigated as a rare example by Hiemstra's group[9b] in one of his work dedicated to optically pure free amino acids. This concretely proceeded by deprotection of 2-nitrophenylsulfenyl or triphenylmethylsulfenyl group by cleavage of N-S linkage under acidic conditions (TFA in DCM) which turned out to be more complicated in the latter case.[9b] No *N*-debenzylation was discussed in these reports.

Standard conditions for *N*-debenzylation (e.g., Pd/C, MeOH, H_2 1.1 bar, r.t for 24 h)[19] leads to partial hydrogenlytic bond breaking of C-N of the amino acid fragment. This gives the 3-indolylacetic acid (**16**) as a side reaction product (estimated to 10-15% of the mixture by HPLC) which considerably complicates the isolation of the free amino acid (*S*)-3IG (**16**) (Scheme 3).

To overcome this problem, after numerous attempts we found the optimized conditions for the selective *N*-debenzylation using CTH (Catalytic Transfer Hydrogenation).[20] Simply by using TEAF (triethylammonium formate) as hydrogen source in combination with Pd/C in MeOH, we prepared the enantiomeric pure (*S*)-3IG (**15**) in 80% yield and high optical purity (>99.8% ee) (Scheme 3). This significantly decreased hydrogenolysis of the C-N bond of the amino acid (1-3%) and prevented racemization of the optically pure (*S*)-3IG (**15**).



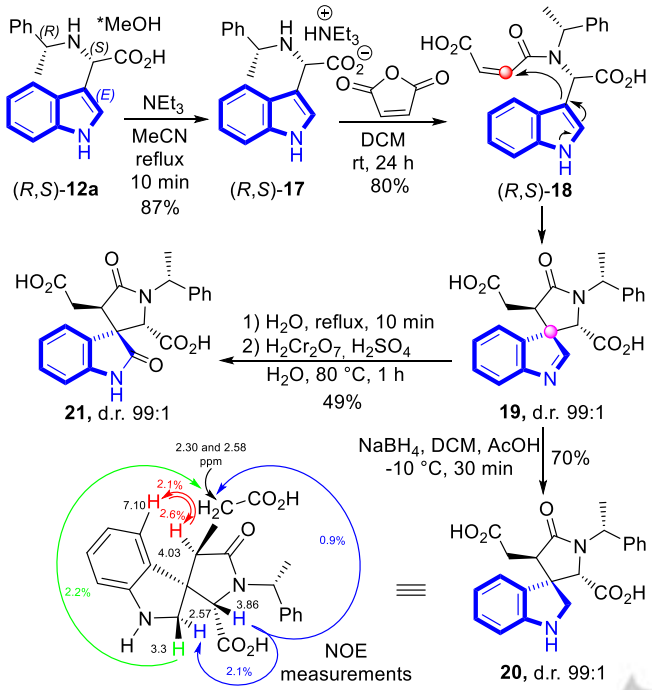
Scheme 3. Preparation of the enantiopure (*S*)-3IG (**15**) by highly selective *N*-debenzylation of (*R,S*)-diastereomer **12a**.

Subsequently, we established a practical two-step sequence consisting of a highly diastereoselective Mannich's 3CR and a highly chemoselective *N*-debenzylation to form optically pure amino acids via CTH on multigram scale. Next, we decided to demonstrate the high potential of the enantiopure (*S*)-3IG as starting material for the elaboration of three families of new compounds such as spiroindolenines, indolyl tetracyclic hemiaminals and 3IMs by exploring the well-known high nucleophilic reactivity of the indole C_3-position[1,21] towards both $C_{SP}{}^2$ and $C_{SP}{}^3$ electrophilic centers.

Thus having the suitable synthon **12a** for spirocyclization,[21] we examined the intramolecular Michael addition with maleic anhydride using indole nucleophilicity.[21] Initial acylation experiments were attempted starting from methanolic solvate of the 3-IG (*R,S*)-**12a**, but due to its low solubility, further optimization was necessary (Scheme 4). To resolve this problem, the methanolic solvate of 3-IG (*R,S*)-**12a**, was converted to the anhydrous triethylammonium salt which showed high solubility in DCM. The latter was hence easily acylated in this medium with the maleic anhydride forming the unstable *N*-acylated-3-IG **18**, which underwent spontaneous cyclization furnishing spirocyclic indolenine derivative **19** (Scheme 4).

Furthermore, the acylation and intramolecular Michael addition occured in one-pot, without isolation of unstable intermediate **18** whereas the pure spiroindolenine derivative **19** was isolated in 80% yield from (*R,S*)-**17**. This cascade reaction is highly stereoselective and only one stereoisomer of spirocyclic indolenine derivative **19** was confirmed by NMR and HPLC analysis of the reaction mixture (see SI Part). The absolute stereochemistry of the product (*R,S*)-**19** was determined from the structure of spirocyclic indoline **20**, which was prepared by the reduction of 3*H*-indole derivative **19** with $NaBH_4$ in the mixture of acetic acid and DCM 1:5 in 70% yield. Based on NMR measurements (gHMBC, gCOSY, NOESY and HSQC) the

absolute configuration on the new stereogenic centers was determined as (*2'S,3'S,4'R*) (Scheme 4).

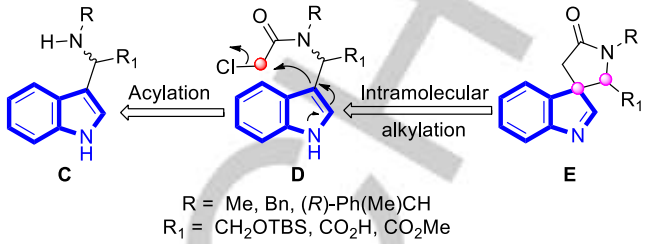


Scheme 4. Two-steps preparation from (*R,S*)-diastereomer **12a** of the optically pure spirocyclic indolenine derivative **19** and its reduction and oxidation into indoline and oxindole derivatives **20** and **21**, respectively.

Since the reduction of spiroindolenine **19** went smoothly, we persueded to test the oxidation reaction of the imine function of product (*R,S*)-**19** which would likely lead to enantiopure aza-spirannic compounds belonging to spiro-oxindole series.[23] This family of compounds is fundamental due to the great abundance of alkaloids bearing this pattern, with important biological activities including the inhibition of p53-MDM2 interaction useful in targeted cancer therapy.[24] For this perspective, the compound (*R,S*)-**19** was refluxed in water, forming a hemiaminal, followed by its oxidization with dichromic acid in the presence of sulfuric acid to provide spirooxindole derivative (*R,S*)-**21** in 49% yield (Scheme 4).

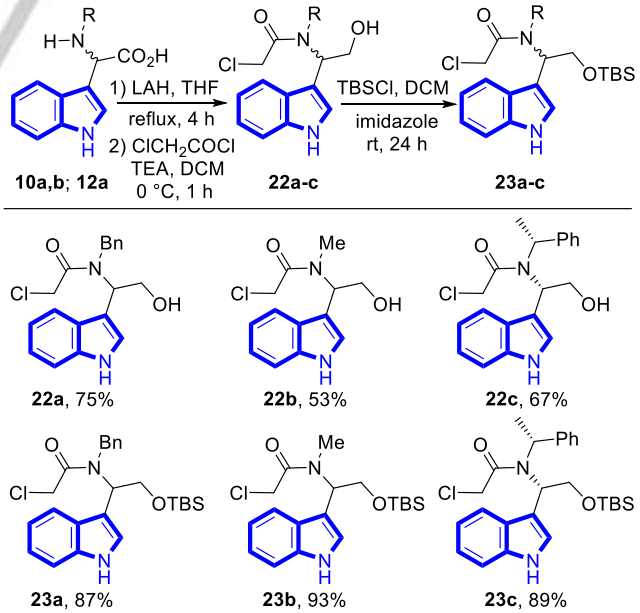
Having established the capacity of indole-3-branched containing substituents to provide cascade process in forming spirooxindole derivatives, we sought to demonstrate the potential of *N*-chloroacetyl derivative of 3-IGs as suitable substrates for intramolecular indole C_3 position-$C_{sp}{}^3$ alkylation to form the spiro moiety (Scheme 5).

It is noteworthy that, although intermediates D (Scheme 5) containing functionalized α-haloacetamides appear to be trivial substrates, intriguingly only a few of them were engaged in the intramolecular cyclization reactions. On the other hand, the papers devoted to them are all concerned with the synthesis of the indolic Aspidosperma alkaloids, such as (-)-Vindorosine[25] and more broadly the *Strychnos* alkaloids[26] which showed significant MDR reversal activity potentially important for cancer cell eradication.[27] The reactions proceeded as S_N2 alkylations by displacement of halide (Heathcock reaction) [26d] which is associated mostly with aza-Prins type cyclization.[25-27]



Scheme 5. Intramolecular alkylation of *N*-chloroacetyl-3-indolylglycines **D** into spiro-compounds **E**.

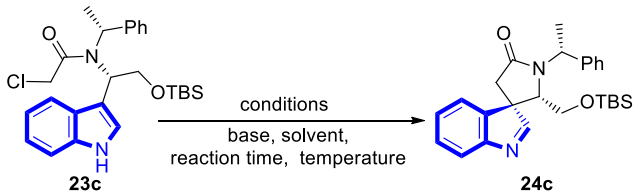
At the beginning, attempts with free amino acids **10a**, **10b** or enatiopure (*R,S*)-**12a** failed due to intramolecular nucleophile substitution of chloride with carboxylate anion and the following hydrolysis of six-membered ring lactone. To bypass this problem, we decided to prepare 3-indolylglycinols and use them as a starting substrates for desired spirocyclization. This is to measure the effect of the R group on the cyclization step as well as the stereochemistry outcome hoping to establish the generality and versatility of the process. Thus, reduction of prepared *N*-alkyl substituted 3-IGs **10a,b** and (*R,S*)-**12a** with LAH leads to the formation of 3-indolylglycinols which were used without further purification in the next step to form *N*-chloroacetyl-3-indolylglycinols **22a-c** in 53-75% yield (Scheme 6). To avoid the hypothetic undesired side reaction of chloride intramolecular substitution with alcohol, the latter free alcohols **22a-c** were protected with silyl protecting group to provide **23a-c** in 87% up to 93% yield.



Scheme 6. Synthesis of *N*-chloroacetyl-3-indolylglycinols **22a-c** and *N*-chloroacetyl-*O*-protected 3-indolylglycinols **23a-c**.

The reaction conditions for the base induced intramolecular alkylation of **23** with indole C_3-position were optimized using optically pure *N*-chloroacetyl-*O*-protected 3-indolylglycinol (**23c**).

Table 4. Optimization of the reaction conditions for spirocyclization of the enantiopure acetamide **23c** into **24c**.



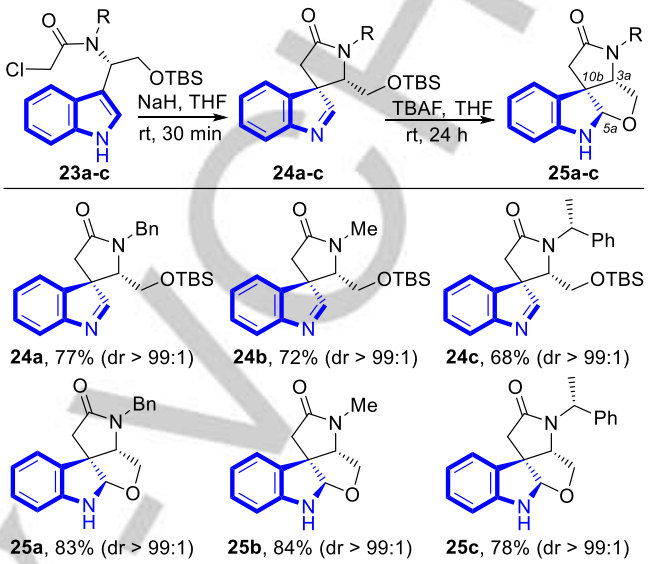
23c **24c**

Entry	Base	Base (Equiv.)	Solvent	t (h)	T (°C)	Yield(%)[b]
1	NaH	1.1	THF	0.5	rt	68
2	NaH	1.1	THF	1	0	68
3	NaH	1.1	Et_2O	0.5	rt	52
4	*t*-BuOK	1.5	THF	0.5	rt	53
5	*t*-BuOK	1.5	THF	0.5	0	52
6	*t*-BuOK	1.5	DMF	0.5	rt	8
7	NaHMDS	2	THF	0.5	rt	52
8	LiHMDS	2	THF	1	rt	44
9	K_2CO_3	5	MeCN	24	reflux	35
10	DBU	2	THF	24	rt	-[a]
11	LiOH	2	THF	24	rt	-[a]

[a] Only the decomposition of the reaction substrate was observed. [b] Isolated yields

The various reaction conditions were optimized including base, solvent, reaction time, temperature and the results are summarized in Table 4. From the latters, both the nature and the quantity relative to the substrate **23c** of the base seem to be pivotal for the successful reaction and NaH (1.1 equiv.) in dry THF at room temperature for 30 minutes (entry 1) seems to be the best formulation used (Table 4). Interestingly, the reaction failed with DBU (entry 10) and LiOH (entry 11) in THF at room temperature even with up to 2 equivalents of the base and the reaction time prolonged to 24 hours. It is noteworthy that the reaction is highly stereoselective and in all cases only one diastereomer of spirocylic product **24c** was observed. Related result with allyl group instead of CH_2OTBS was published by us recently using the same base in THF, but the d.r. of the spiroindolenine obtained was only of 91:9.[28] Furthermore, due to the high steric hindrance of *N*-chloroacetyl function and *O*-silyl protecting group configuration, the NMR spectrum of **24c** is a mixture of rotamers (see Supporting Information for details).

The optimized reaction conditions obtained for **24c** were applied in the synthesis of **24a,b** using racemic *N*-benzyl and *N*-methyl substituted derivatives **23a** and **23b**, respectively. The intramolecular alkylation occurs with high diastereoselectivity, whereas only one diastereomer from the reaction mixture was isolated (d.r. > 99:1). Moreover, deprotection of silyl group with TBAF at room temperature according to classical procedure from spiroindolenine derivatives **24a-c** afforded the free alcohol which underwent spontaneously an intramolecular cyclization to form the tetracyclic hemiaminals **25a-c** ranging from 78% to 84% yield. These results clearly demonstrate only very low impact of the *N*-substituted moiety on the spirocyclization profile but none on the stereochemistry reaction outcome. Finally, the relative configuration of new stereogenic center C_{5a} was determined to be *R* by NOESY NMR analysis and configuration on spirocyclic carbon C_{10b} was also confirmed to be *S* (see SI Part) as determined by X-ray analysis for product **25a** (Figure 5).



Scheme 7. Synthesis of spiroindolenine derivatives **24a-c** and their tetracyclic hemiaminals **25a-c**.

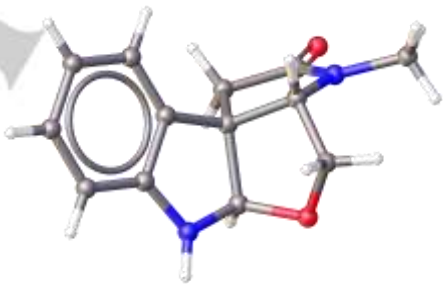
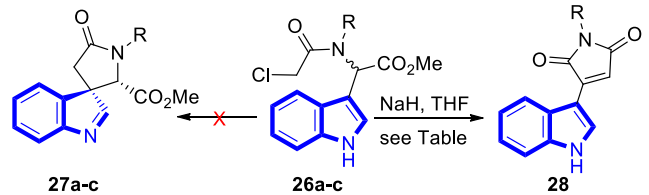


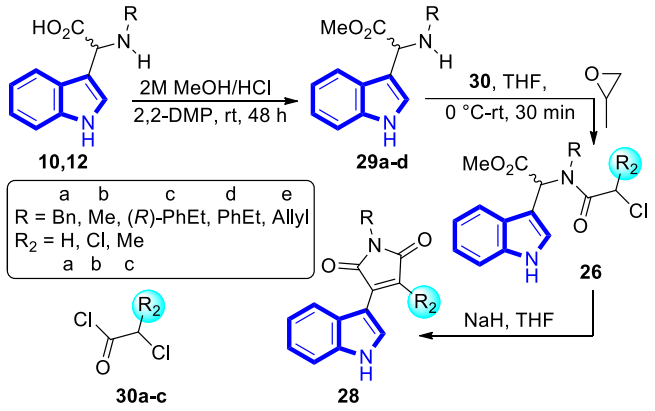
Figure 5. Molecular structure of **25b**.[29]

We next worked to establish the generality and versatility of the synthetic approach depicted in the Scheme 7 with *N*-chloroacetyl-3-indolylglycinols **22a-c** which proved to be suitable substrates for spirocyclization after alcohol protection. The behavior of *N*-chloroacetyl esters of 3-indolylglycines **26a-c** substituted by benzyl, methyl or chiral α-phenylethyl groups on the nitrogen amide atom were examined under the same cyclization conditions.



Scheme 8. Cyclization of *N*-chloroacetyl esters of 3-indolylglycines **26a-c** into the unexpected 3-indolylmaleimides **28**.

Despite our expectations, the methylesters of chloroacetyl indolylglycines **26a-c** under basic conditions did not provide the expected spiroindolenine derivatives **27a-c**. We were able to isolate unknown fluorescence compounds as major products in low yields under the reaction conditions for spirocyclization used above. Comparing their physical and chemical properties with pertinent literature, the structure of unknown products was determined to be 3-indolylmaleimides (3IMs) **28**, which possess a very interesting broad range of pharmacological and fluorescence activities (Scheme 8).[8,30]



Scheme 9. Cyclization of *N*-chloroacetyl esters of 3-indolylglycines **26a-c** into the unexpected 3-indolylmaleimides **28** starting from amino acids **10a-b**,**12a**.

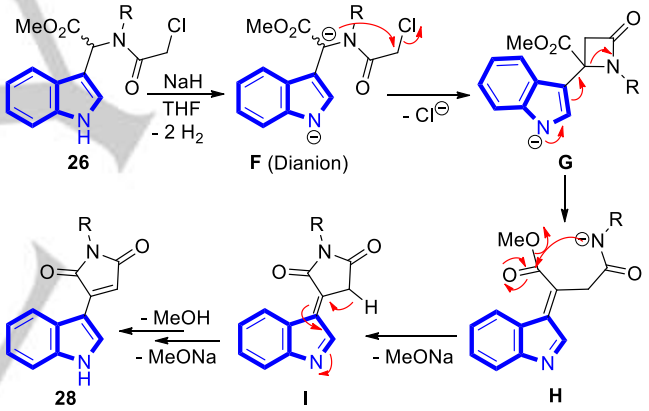
Table 5. Preparation of *N*-substituted 3IMs **28** *via* amino esters **29** and chloroacetamides **26**.

Entry	R	R_2	Yield (%) 29	Products **26** & **28**	Yield (%) **26**	Yield (%) **28**
1	Bn	H	73	aa	94	87
2	Me	H	53	ba	75	95
3	Me	Cl	-	bb	86	32
4	Me	Me	-	bc	87	55
5	(*R*)-PhEt[a]	H	86	ca	94	83
6	PhEt	H	75	da	80	79
7	Allyl	H	72	ea	70	73

[a] The reaction was realized in chiral series with commercially available (*R*)-α-PEA.

To the best of our knowledge, this approach for the synthesis of 3IMs **28** starting form chloroacetamide ester of type **26** is unprecedented in the published research. We thus decided to investigate and optimize the reaction conditions for this domino process. First, we had to find specific reaction conditions for successful esterification of 3IGs in racemic and chiral forms, respectively **10** and **12**, since these derivatives are very sensitive in acidic solution. For the preparation of methylesters of 3IGs **29** we used the mixture of methanolic HCl solution in combination with 2,2-dimethoxypropane which was carried out at rt (Scheme 9). The next step was the chloroacetylation of prepared methylesters of 3IGs **29** which was realized by analogy as for 3-indolylglycinols **22a-c** with chloroacetyl chloride and triethylamine. This method leads to the expected chloroacetylated esters of type **26** which were obtained in low yields due to isolation problems during the work-up. To overcome this problem, the use of an excess of propylene oxide as hydrogen chloride scavenger drastically improved the isolation and overall yields of the reaction. Finally, the optimization of reaction conditions for 3IMs was carried out with methyl acetate **26ba**.

To increase the reaction yields, we investigated the type and amount of the base in various polar aprotic solvents. Since the lower temperature did not seem to affect the overall yields of the reactions, all the reactions were performed at room temperature. When the reaction was carried out in DMF and dioxane instead of THF, only lower yields were observed. Among the various screening bases, NaH was the most effective and the further crucial parameter was its quantity. In fact, when the reaction was treated with 2.2 equiv. of NaH the 100% conversion was achieved in just 10 minutes and the overall yield after the purification of *N*-methyl 3IM **28ba** (Table 5, entry 2) was improved to 95%. Having established the optimal conditions, we thus generalized the new process by preparing five mono-substituted 3IMs in yields ranging from 73% up to 95%. Curiously, two 2-disubstituted 3IMs (Table 5, Entries 3 and 4) were formed with lower yields which did not exceed 32% (**28bb**) and 55% (**28bc**), respectively.



Scheme 10. Proposed mechanism of the base-mediated formation of 3IMs **28**.

Me-**b** Cl

Based on the precedent results, a plausible mechanism for the base-mediated ring-opening ring closure (RORC) of *N*-chloroacetyl esters of 3IGs **26** was proposed through the formation of β-lactam intermediate **G** (Scheme 10). This argument agrees with the González-Muniz group's investigations of similar base-assisted intramolecular alkylation of *N*-benzyl-*N*-chloroacetyl amino acid derivatives.[31] Thus formation of the dianion species **F**, from 3IGs **26** which required 2 equivalents of base, undergoes an intramolecular nucleophilic substitution to furnish the indol-3-yl β-lactam system **G** according to the reported observations. The shift of electron pairs of these unstable intermediates induces the opening of the β-lactam strained ring giving the corresponding intermediate **H**. This intermediate, after peptide coupling by addition/elimination process, delivers (**I**). The deprotonation/protonation under acid-base equilibrium of the latter furnishes ultimately the isolated product **28** containing both indole and maleimide rings.

Conclusions

In summary, we have developed a new three component Mannich type reaction of indole and glyoxylic acid in the presence of primary and secondary aliphatic amines in moderate to high yields. This provides a straightforward access to racemic *N*-substituted-3-indolylglycines in multigram scale. We also presented optically pure derivative of (*S*)-3-indolylglycine with cost effective (*R*)-1-phenylethylamine as chiral auxiliary which was successfully transformed to the enantiopure amino acid (*S*)-3-indolylglycine both in high yield and enantiomeric purity >99%ee.

The optically pure derivatives of (*S*)-3-indolylglycine were used as valuable platforms for the synthesis of more complex spirocyclic derivatives, such as substructures of the bioactive indole alkaloids including spiroindolenines, spirooxindoles and spirocyclic indolines. Three derivatives of indolyl tetracyclic hemiaminals were synthesized from *N*-chloroacetyl *O*-protected 3-indolyglycinols, whereas in all cases only one stereoisomer was observed. Finally, a novel approach for the preparation of compelling indolylmaleimides derivatives, the pivotal intermediates for pharmacological compounds, was described in only three steps from *N*-substituted-3-indolylglycines. Ultimately, we also proposed the plausible mechanism for cyclization of *N*-chloroacetyl esters of 3-indolyglycines to form maleimide ring through the formation of β-lactam intermediate.

Experimental Section

Crystallographic data: Data collection and cell refinement of 12a·MeOH, **14·MeOH** and **25b** were made by Stoe StadiVari diffractometer using HPAD detector Pilatus3R 300K microfocused source Xenocs Genix3D Cu HF. The structure were solved by program SUPERFLIP or SHELXT,[32] and refined by full-matrix least-squares procedures with CRYSTALS (ver. 14.61) or SHELXL (ver. 2018/3).[33] The structures were drawn using OLEX2 package.[34] Absolute structures were determined for **12a·MeOH** by Hooft method[35a] implemented in CRYSTALS (y = -0.09(8)),[35b] and for **14·MeOH** using Parsons[35c] and Hooft[35a] methods (x = 0.03(3), y = 0.06(3)). The molecule **25b** is full disordered in two stastical positions with occupancy factors 0.533(8) and 0.467(8) (See ESI). The disordered molecules are modeled using SAME instruction, and structure model has been refined using SHELXL's commands RIGU and EADP. Full crystallographic data have been deposited with the Cambridge Crystallographic Data Centre (CCDC n°: 1912329, 1912330 and 1912331). Copies of the data can be obtained free of charge at the following address: http://www.ccdc.cam

General Remarks: Most of the commercially available chemicals were purchased from Sigma-Aldrich, Alfa Aesar or from any other commercial sources with high purity and were used without further purification. All solvents were distilled before use. Thin layer chromatographic (TLC) studies were performed on pre-coated silica gel 60 F 254 on aluminum sheets (Merck KGaA). The compounds were visualized by UV fluorescence and by dipping the plates in an aqueous H_2SO_4 solution of cerium sulfate/ammonium molybdate followed by charring with a heat gun. Melting points were obtained using a Stuart SMP30 apparatus and are uncorrected. Optical rotations were measured with a JASCO P-2000 polarimeter and are given in units of 10^{-1} deg.cm^2.g^{-1}. ^{1}H (600 MHz and 300 MHz) and ^{13}C (150 MHz and 75 MHz) NMR spectra were obtained on a Varian Unity Inova 300 MHz (300 MHz for ^{1}H, 75 MHz for ^{13}C) or Varian 600 VNMRS (600 MHz for ^{1}H, 150 MHz for ^{13}C) spectrometers. Chemical shifts are cited with respect to Me_4Si as internal (^{1}H and ^{13}C) standard, or residual solvent peak. The chemical shifts are given in parts per million (ppm). High-resolution mass spectra (HRMS) were recorded on a Thermo Scientific Orbitrap Velos mass spectrometer with a heated electrospray ionisation (HESI) source. The mass spectrometer was operated with full scan (50–2000 amu) in positive or negative FT mode (at a resolution of 100000). The analyte was dissolved in MeOH and infused via syringe pump at a rate of 5 mL/min. The heated capillary was maintained at 275 °C with a source heater temperature of 50 °C, and the sheath, auxiliary and sweep gases were at 10, 5 and 0 units, respectively. The source voltage was set to 3.5 kV.

2-(Benzylamino)-2-(1*H*-indol-3-yl)acetic acid (10a). To the stirred solution of indole (590 mg; 5 mmol) and benzylamine (589 mg; 5.5 mmol) in 10 mL of methanol at 0 °C was added solution of glyoxylic acid monohydrate (506 mg; 5.5 mmol) dissolved in 10 mL of MeOH. The reaction mixture was stirred at room temperature for 1 hour. The precipitated product was filtered off, washed with MeOH and Et_2O and dried. The corresponding *2*-(benzylamino)-2-(1*H*-indol-3-yl)acetic acid (**10a**) was obtained as white solid (1.29 g, 92 %), m.p = 202-206 °C (lit.[13] m.p = 205-207 °C). ^{1}H NMR (300 MHz, NaOD/D_2O) δ = 7.58 (d, *J* = 7,8 Hz, 1H); 7.40 (d, *J* = 8.1 Hz, 1H); 7.25-7.0 (m, 8H); 4.40 (s, 1H); 3.63 (d, *J* = 12.8 Hz, 1H), 3.54 (d, *J* = 12.8 Hz, 1H). ^{13}C NMR (75 MHz, NaOD/D_2O) δ = 180.1, 139.0, 136.1, 128.6, 128.5, 127.2, 125.8, 124.0, 121.7, 119.2, 118.9, 113.3, 111.7, 58.9, 50.6. HRMS (HESI): m/z [M+H]$^+$ calculated for $C_{17}H_{17}N_2O_2$ (281.12900), found 281.12845.

2-(1*H*-Indol-3-yl)-2-(methylamino)acetic acid (10b). To the stirred solution of indole (5.9 g; 50 mmol) and methylamine (27.5 mL 2M/MeOH; 55 mmol) in 50 mL of MeOH at 0 °C was added solution of glyoxylic acid monohydrate (5.06 g; 55 mmol) dissolved in 50 mL of MeOH. The reaction mixture was stirred at room temperature for 2 hours. The precipitated product was filtered off, washed with MeOH and Et_2O and dried. The corresponding 2-(1*H*-indol-3-yl)-2-(methyl-amino)acetic acid (**10b**) was obtained as white solid (8.42 g, 82 %), m.p = 197-200 °C (lit.[13] m.p = 198-200 °C). ^{1}H NMR (300 MHz, NaOD/D_2O) δ = 7.74 (ddd, *J* = 7.8, 1.3, 0.8 Hz, 1H), 7.51 (ddd, *J* = 8.0, 1.3, 0.8 Hz, 1H), 7.32 (bs, 1H), 7.23 (ddd, *J* = 8.4, 7.1, 1.3 Hz, 1H), 7.16 (ddd, *J* = 8.3, 7.1, 1.3 Hz, 1H), 4.38 (d, *J* = 0.6 Hz, 1H), 2.33 (s, 3H). ^{13}C NMR (75 MHz, NaOD/D_2O) δ = 180.0, 136.1, 125.6, 124.0, 121.8, 119.3, 118.9, 112.9, 111.8, 61.5, 32.9. HRMS (HESI): m/z [M+H]$^+$ calculated for $C_{11}H_{13}N_2O_2$ (205.09770), found 205.09715.

2-(1*H*-Indol-3-yl)-2-(phenethylamino)acetic acid (10c). To the stirred solution of indole (1.18 g; 10 mmol) and phenylethylamine (1.332 g; 11 mmol) in 20 mL of methanol at 0 °C was added solution of glyoxylic acid monohydrate (1.01 g; 11 mmol) dissolved in 5 mL of MeOH. The reaction mixture was stirred at room temperature for 1 hour. The precipitated product was filtered off, washed with MeOH and Et_2O and dried. The corresponding 2-(1*H*-indol-3-yl)-2-(phenethyl-amino)acetic acid (**10c**) was obtained as white solid (2.74 g, 93 %), m.p = 209-211 °C. ^{1}H NMR (300 MHz, D_2O/NaOD): δ = 7.49 (d, *J* = 7.9 Hz, 1H), 7.32 (d, *J* = 8.1 Hz, 1H), 7.19 – 6.72 (m, 8H), 4.38 (s, 1H), 2.58 – 2.37 (m, 4H). ^{13}C NMR (75 MHz, D_2O/NaOD): δ = 179.9, 139.7, 136.1, 128.5, 128.4, 126.0, 125.8, 124.0, 121.6, 119.1, 118.8, 113.2, 111.7, 59.6, 47.5, 34.9. HRMS (HESI): m/z [M+H]$^+$ calculated for $C_{18}H_{18}N_2O_2$ (295.1446), found 295.1440.

2-(Allylamino)-2-(1*H*-indol-3-yl)acetic acid (10d). To the stirred solution of indole (1.18 g; 10 mmol) and allylamine (0.632 g; 11 mmol) in 30 mL of ethanol at 0 °C was added solution of glyoxylic acid monohydrate (1.01 g; 11 mmol) dissolved in 5 mL of EtOH. The reaction mixture was stirred at room temperature for 2 hours. The precipitated

product was filtered off, washed with EtOH and Et_2O and dried. The corresponding 2-(allylamino)-2-(1*H*-indol-3-yl)acetic acid (**10d**) was obtained as white solid (2.04 g, 88 %), m.p = 185-186 °C. ^{1}H NMR (300 MHz, D_2O/NaOD): δ = 7.83 – 7.65 (d, *J* = 7.9 Hz, 1H), 7.50 (d, *J* = 8.0 Hz, 1H), 7.32 (s, 1H) 7.30 – 7.10 (m, 2H), 5.94 (ddt, *J* = 16.5, 10.3, 6.2 Hz, 1H), 5.27 - 5.14 (m, 2H), 4.48 (s, 1H), 3.27 (ddt, *J* = 13.8, 6.0, 1.4 Hz, 1H), 3.16 (ddt, *J* = 13.8, 6.4, 1.3 Hz, 1H). ^{13}C NMR (75 MHz, D_2O/NaOD): δ = 179.3, 136.1, 134.3, 125.7, 124.4, 121.8, 119.3, 118.9, 117.9, 112.3, 111.8, 58.7, 49.2. HRMS (HESI): m/z $[M+H]^+$ calculated for $C_{13}H_{14}N_2O_2$ (231.1133), found 231.1129.

2-(2-Hydroxyethylamino)-2-(1*H*-indol-3-yl)acetic acid (10e). To the stirred solution of indole (590 mg; 5 mmol) and ethanolamine (336 mg; 5.5 mmol) in 10 mL of MeOH at 0 °C was added solution of glyoxylic acid monohydrate (506 mg; 5.5 mmol) dissolved in 10 mL of MeOH. The reaction mixture was stirred at room temperature for 2 hours. The precipitated product was filtered off, washed with MeOH and Et_2O and dried. The corresponding 2-(2-hydroxyethylamino)-2-(1*H*-indol-3-yl)acetic acid (**10e**) was obtained as white solid (1.05 g, 90 %), m.p = 180-183 °C. ^{1}H NMR (300 MHz, D_2O/NaOD): δ = 7.76 – 7.72 (m, 1H), 7.50 – 7.45 (m, 1H), 7.32 (s, 1H), 7.26 – 7.10 (m, 2H), 4.47 (d, *J* = 0.5 Hz, 1H), 3.74 – 3.58 (m, 2H), 2.82 – 2.55 (m, 2H). ^{13}C NMR (75 MHz, D_2O/NaOD): δ = 180.3, 136.1, 125.7, 123.9, 121.8, 119.2, 118.9, 113.4, 111.8, 60.5, 60.0, 48.5. HRMS (HESI): m/z $[M+H]^+$ calculated for $C_{12}H_{15}N_2O_3$ (235.10827), found 235.10772.

2-(benzyl(methyl)amino)-2-(1H-indol-3-yl)acetic (10f). To the stirred solution of indole (590 mg; 5 mmol) and *N*-methylbenzylamine (667 mg; 5.5 mmol) in 10 ml of methanol at 0°C was added solution of glyoxylic acid monohydrate (506 mg; 5.5 mmol) dissolved in 10 ml of methanol. The reaction mixture was stirred at RT for 1 hour. The precipitated product was filtered off, washed with methanol and diethyl ether and dried. The corresponding 2-(benzyl(methyl)amino)-2-(1H-indol-3-yl)acetic (11f). was obtained as white solid (1.10 g, 75 %), m.p = 184-189 °C. ^{1}H NMR (300 MHz, D_2O/NaOD): δ = 7.73 (d, *J* = 7.8 Hz, 1H), 7.49 (d, *J* = 8.0 Hz, 1H), 7.42 (s, 1H), 7.38 – 7.09 (m, 7H), 4.33 (s, 1H), 3.72 (d, *J* = 12.8 Hz, 1H), 3.55 (d, *J* = 12.7 Hz, 1H), 2.15 (s, 3H)^{13}C NMR (75 MHz, D_2O/NaOD): δ = 177.4, 135.5, 133.6, 127.8, 125.9, 124.9, 124.8, 123.1, 119.4, 117.0, 109.5, 109.3, 64.6, 56.0, 36.7. HRMS (HESI): m/z $[M+H]^+$ calculated for $C_{18}H_{19}N_2O_2$ (295.14410), found 295.14420

(*S*)-2-(1H-Indol-3-yl)-2-(((*R*)-1-phenylethyl)amino)acetic acid (12a). To the stirred solution of indole (11.7 g; 100 mmol) and (*R*)-α-phenylethylamine (13.4 g; 110 mmol) in 100 mL of MeOH at 0 °C was added solution of glyoxylic acid monohydrate (10.3 g; 110 mmol) dissolved in 100 mL of MeOH. After 10 minutes the reaction mixture was seeded with crystals of the pure (*R*,*S*)-diastereomer and stirred at room temperature for 1.5 hour. The precipitated product was filtered off, washed with MeOH (50 mL) and Et_2O (50 mL) and dried. The corresponding (*S*)-2-(1*H*-indol-3-yl)-2-(((*R*)-1-phenylethyl)amino)acetic acid (**12a**) was obtained as white solid (17 g, 52 %; d.r 99:1), m.p = 150-152 °C. $[\alpha]_D^{25}$ = +96° (MeOH c 0.2). ^{1}H NMR (300 MHz, NaOD/D_2O) δ = 7.49 (d, *J* = 7.9 Hz, 1H), 7.39 (d, *J* = 8.1 Hz, 1H), 7.31 – 7.08 (m, 7H), 7.01 (t, *J* = 7.5 Hz, 1H), 4.30 (s, 1H), 3.57 (q, *J* = 6.6 Hz, 1H), 1.22 (d, *J* = 6.7 Hz, 3H). ^{13}C NMR (75 MHz, NaOD/D_2O) δ = 180.0, 144.3, 136.1, 128.6, 127.2, 126.9, 125.9, 124.2, 121.6, 119.0, 118.9, 113.1, 111.7, 54.6, 48.7, 22.1. HRMS (HESI): m/z $[M+H]^+$ calculated for $C_{19}H_{22}N_2O_3$ (295.14465), found 295.14410. HPLC: column WATERS SPHERISORB ODS1, 250x4.6 mm, 5 µm; mobile fase: MeCN/H_2O 2:7 (1% TEA, 1% H_3PO_4); flow: 1.0mL/min; detection UV 210 nm; major (*R*,*S*)-diastereomer t = 12.6 min; minor (*R,R*)-diastereomer t = 10.9 min.

(*R*)-2-(1*H*-Indol-3-yl)-2-(((*R*)-1-phenylethyl)amino)acetic acid (12b). To the residue filtrate of the reaction **12a** was added Et_2O (200 mL) and the reaction mixture was left to sit for 1 hour at room temperature. The precipitated product was filtered off and dissolved in MeOH (200 mL). Insoluble residue was filtered off and to the filtrate was added Et_2O (200 mL) and mixture was left to sit for 1 hour. The corresponding (*R*)-2-(1*H*-indol-3-yl)-2-(((*R*)-1-phenylethyl)amino)acetic acid (**12b**) were obtained by filtration as white crystals (3.5 g, 11%; d.r 99:1), m.p = 157-159 °C. $[\alpha]_D^{25}$ = -77° (MeOH c 0.34). ^{1}H NMR (300 MHz, NaOD/D_2O) δ = 7.44 – 7.29 (m, 7H), 7.18 (s, 1H), 7.14 (t, *J* = 7.6 Hz, 1H), 7.02 (t, *J* = 7.5 Hz, 1H), 4.17 (s, 1H), 3.83 (q, *J* = 6.5 Hz, 1H), 1.33 (d, *J* = 6.6 Hz, 3H).^{13}C NMR (75 MHz, NaOD/D_2O) δ = 180.5, 144.0, 135.9, 128.7, 127.5, 127.3, 125.9, 123.4, 121.7, 119.1, 118.6, 113.6, 111.6, 56.2, 48.7, 22.7.

(*S*)-2-(2-Methyl-1*H*-indol-3-yl)-2-(((*R*)-1-phenylethyl)amino)acetic acid (14). To the stirred solution of 2-methylindole (655 mg; 5 mmol) and (*R*)-α-phenylethylamine (667 mg; 5.5 mmol) in 50 mL of MeOH at 0 °C was added solution of glyoxylic acid monohydrate (506 g; 5.5 mmol) dissolved in 25 mL of MeOH. After 10 minutes the reaction mixture was seeded with crystals of the pure (*R*,*S*)-diastereomer and stirred at room temperature for 1 hour. The precipitated product was filtered off, washed with MeOH, Et_2O and dried. The corresponding (*S*)-2-(2-methyl-1*H*-indol-3-yl)-2-(((*R*)-1-phenylethyl)amino)acetic acid (**14**) was obtained as white solid (759 mg, 49 %; d.r 99:1), m.p = 147-149 °C. $[\alpha]_D^{25}$ = +88° (MeOH c 0.2). ^{1}H NMR (600 MHz, NaOD/D_2O) δ = 7.63 (bd, *J* = 7.8 Hz, 1H), 7.34 (bd, *J* = 7.9 Hz, 1H), 7.24 (m, 2H), 7.18 (m, 1H), 7.11 (m, 1H), 7.09 – 7.03 (m, 3H), 4.29 (s, 1H), 3.46 (q, *J* = 6.6 Hz, 1H), 1.91 (s, 3H), 1.18 (d, *J* = 6.7 Hz, 3H).^{13}C NMR (151 MHz, NaOD/D_2O) δ = 182.6, 147.4, 138.3, 138.1, 131.5, 129.9, 129.8, 123.5, 121.9, 121.3, 113.8, 111.2, 59.6, 26.4, 13.4. HPLC: column WATERS SPHERISORB ODS1, 250x4.6 mm, 5 µm; mobile fase: MeCN/H_2O 2:7 (1% TEA, 1% H_3PO_4); flow: 1.0mL/min; detection UV 210 nm; major (*S,R*)-diastereomer t = 13.9 min; minor (*R,R*)-diastereomer t = 11.2 min. HRMS (HESI): m/z $[M+H]^+$ calculated for $C_{19}H_{21}N_2O_2$ (309.15975), found 309.16036.

(*S*)-2-Amino-2-(1*H*-indol-3-yl)acetic acid (15). The acid **12a** (6.53 g; 20 mmol) was dissolved in dry methanol (300 mL) and TEAF (6.48 g; 15 mmol). To the suspension was added 10% Pd/C (1.31 g; 20 wt%) and the reaction mixture was stirred under athmosphere of Argon for 24 h at room temperature. The catalyst was filtered off and washed with hot MeOH (200 mL). The filtrate was reduced to the approximately 50 mL and was sonicated for about 10 minutes. The mixture was left to sit for 24 h in freezer and the precipitated product was filtered off, washed with MeOH, Et_2O and dried. The corresponding (*S*)-2-amino-2-(1*H*-indol-3-yl)acetic acid (**15**) was obtained as white solid (3.06 g, 80 %; ee 99.8%), m.p = 199-202 °C, $[\alpha]_D^{25}$ = +109° (H_2O c 0.2). ^{1}H NMR (300 MHz, NaOD/D_2O) δ = 7.69 (d, *J* = 7.9 Hz, 1H), 7.46 (d, *J* = 8.1 Hz, 1H), 7.27 (s, 1H), 7.20 (t, *J* = 7.5 Hz, 1H), 7.12 (t, *J* = 7.4 Hz, 1H), 4.60 (s, 1H). ^{13}C NMR (75 MHz, NaOD/D_2O) δ = 181.7, 136.2, 125.2, 123.4, 121.8, 119.2, 118.9, 115.8, 111.8, 53.0. HRMS (HESI): m/z $[M+H]^+$ calculated for $C_{10}H_{10}N_2O_2$ (191.08205), found 191.08148. HPLC: column CROWNPAK CR (+) fy Daicel Chem. Ind. Ltd. 150x4 mm; Mobile phase: aqueous solution of HClO4 (pH 2.0)/methanol = 1000/15; flow: 1.2 mL/min, detection UV 210 nm; (*R*)-enantiomer t_R = 9.2 min. (*S*)-enantiomer t_R = 17.8 min.

Triethylammonium (*S*)-2-(1*H*-indol-3-yl)-2-(((*R*)-1-phenylethyl)amino) acetate (17). The acid **12a** (3.26 g; 10 mmol) was dissolved in acetonitrile (50 mL). To the suspension was added TEA (10 mL) and the reaction mixture was refluxed for 10 minutes. The hot mixture was filtered off and left to slowly crystallize at room temperature approximately for 30 minutes. After cooling at room temperature, the reaction mixture was left to sit in the freezer for 12 hours. The precipitated crystals were filtered off, washed with dry Et_2O and dried. The corresponding triethylammonium (*S*)-2-(1*H*-indol-3-yl)-2-(((*R*)-1-phenylethyl)amino) acetate (**17**) were obtained as crystals (3.45 g, 87 %), m.p = 134-136 °C, $[\alpha]_D^{25}$ =

+72°(MeOH c 0.2). ^{1}H NMR (300 MHz, D_2O) δ = 7.59 (d, *J* = 7.9 Hz, 1H), 7.49 (d, *J* = 8.1 Hz, 1H), 7.45 – 7.18 (m, 7H), 7.12 (t, *J* = 7.5 Hz, 1H), 4.45 (s, 1H), 3.76 (q, *J* = 6.7 Hz, 1H), 3.05 (q, *J* = 7.3 Hz, 6H), 1.37 (d, *J* = 6.7 Hz, 3H), 1.20 (t, *J* = 7.3 Hz, 9H).^{13}C NMR (75 MHz, D_2O) δ = 182.1, 146.5, 139.0, 131.6, 130.4, 129.9, 128.7, 127.4, 124.7, 122.1, 121.9, 115.3, 114.7, 60.4, 57.9, 49.3, 24.5, 11.1. HRMS (HESI): m/z $[M+H]^+$ calculated for $C_{24}H_{33}N_3O_2$ (396.26510), found 396.26455.

(2'*S*,3*R*,4'*R*)-4'-(Carboxymethyl)-5'-oxo-1'-((*R*)-1-phenylethyl)spiro-[indole-3,3'-pyrrolidine]-2'-carboxylic acid (19). **17** (791 mg; 2 mmol) was dissolved in DCM (10 mL). Subsequently was added maleic anhydride (216 mg; 2.2 mmol) and the reaction mixture was stirred at room temperature for 24 hours. The DCM was evaporated, and the residue was purified by column chromatography (DCM/AcOH 5:1). The product was isolated as a yellowish solid (630 mg, 80%, d.r 99:1), m.p = 141-143 °C, $[\alpha]_D^{25}$ = +187° (EtOAc c 0.2). ^{1}H NMR (600 MHz, DMSO) δ = 12.54 (s, 1H), 7.88 (s, 1H), 7.54 (d, *J* = 7.5 Hz, 1H), 7.45 – 7.36 (m, 5H), 7.36 – 7.30 (m, 2H), 7.27 (t, *J* = 7.2 Hz, 1H), 5.45 (q, *J* = 6.9 Hz, 1H), 3.81 – 3.78 (m, 1H), 3.36 (s, 1H), 2.36 (dd, *J* = 16.4, 7.6 Hz, 1H), 1.46 (m, 4H).^{13}C NMR (151 MHz, DMSO) δ = 172.9, 172.6, 171.5, 155.7, 139.7, 133.4, 129.3, 128.7, 127.8, 127.2, 126.7, 123.5, 120.8, 62.5, 58.0, 50.2, 42.9, 29.8, 16.1. HRMS (HESI): m/z $[M+H]^+$ calculated for $C_{22}H_{20}N_2O_5$ (393.14505), found 393.14450.

(2'*S*,3*S*,4'*R*)-4'-(Carboxymethyl)-5'-oxo-1'-((*R*)-1-phenylethyl)spiro-[indoline-3,3'-pyrrolidine]-2'-carboxylic acid (20). The carboxylic acid **19** (500 mg; 1.26 mmol) was dissolved in DCM (20 mL) and AcOH (2 mL). The mixture was cooled down to -10 °C and during 10 minutes was added $NaBH_4$ (95 mg; 2.52 mmol) portionwise. The reaction mixture was stirred for 30 minutes at -10 °C and then was quenched with water (8 mL). The DCM was evaporated and the precipitated product was filtered off and washed with water (5 mL). The product was isolated as a white solid (350 mg, 70%, d.r 99:1), m.p = 258-262 °C, $[\alpha]_D^{25}$ = +118° (MeOH c 0.2). ^{1}H NMR (600 MHz, $CD_3OD/CDCl_3$) δ = 7.41 – 7.30 (m, 5H), 7.10 (d, *J* = 7.5 Hz, 1H), 7.03 (t, *J* = 7.4 Hz, 1H), 6.67 (t, *J* = 7.4 Hz, 1H), 6.60 (d, *J* = 7.8 Hz, 1H), 5.54 (q, *J* = 7.2 Hz, 1H), 4.03 (dd, *J* = 7.4, 6.1 Hz, 1H), 3.86 (s, 1H), 3.31 (d, J = 10 Hz, 1H), 2.63 – 2.54 (m, 2H), 2.30 (dd, *J* = 16.2, 5.8 Hz, 1H), 1.49 (d, *J* = 7.3 Hz, 3H). ^{13}C NMR (151 MHz, $CD_3OD/CDCl_3$) δ = 176.6, 175.0, 173.8, 153.8, 140.6, 130.4, 129.8, 129.1, 128.3, 126.7, 124.8, 119.8, 111.4, 64.8, 56.3, 55.7, 51.5, 44.0, 31.3, 16.3. HRMS (HESI): m/z $[M+H]^+$ calculated for $C_{22}H_{22}N_2O_5$ (395.16070), found 395.16015.

(2'*S*,3*R*,4'*R*)-4'-(Carboxymethyl)-2,5'-dioxo-1'-((*R*)-1-phenylethyl)-spiro[indoline-3,3'-pyrrolidine]-2'-carboxylic acid (21). The carboxylic acid **19** (200 mg; 0.51 mmol) was mixed with water (30 mL) and the result mixture was refluxed for about 10 minutes until the formation of clear solution. The reaction mixture then was placed to the oil bath (heated to 80 °C) and 0.0001 M solution of H_2SO_4 was added (10 mL). After 10 minutes the solution of 0.0001 M H_2CrO_4 was added in small portions during 5-10 minutes. After 1 hour the reaction mixture was cooled down and was extracted with EtOAc (4x25 mL). The collected extracts were dry under anhydrous $MgSO_4$, evaporated and the residue was purified by column chromatography (DCM/AcOH 10:1) yielding colourless solid (102 mg, 49%, d.r 99:1), m.p = 156-159 °C, $[\alpha]_D^{25}$ = -10.4°(EtOAc c 0.2). ^{1}H NMR (600 MHz, DMSO) δ = 12.35 (s, 2H), 10.61 (s, 1H), 7.42 – 7.25 (m, 5H), 7.22 (t, *J* = 7.6 Hz, 1H), 7.16 (d, *J* = 7.4 Hz, 1H), 6.96 (t, *J* = 7.5 Hz, 1H), 6.81 (d, *J* = 7.6 Hz, 1H), 5.29 (q, *J* = 7.0 Hz, 1H), 3.69 (s, 1H), 3.59 (t, *J* = 6.5 Hz, 1H), 2.55 – 2.41 (m, 1H), 1.85 (dd, *J* = 16.1, 6.1 Hz, 1H), 1.45 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (151 MHz, DMSO) δ = 176.3, 172.6, 172.0, 171.3, 142.5, 139.2, 129.3, 128.1, 127.6, 127.4, 124.9, 124.2, 121.9, 109.7, 62.3, 52.8, 50.8, 44.2, 30.4, 17.0. HRMS (HESI): m/z $[M+H]^+$ calculated for $C_{22}H_{20}N_2O_6$ (409.13996), found 409.13941.

***N*-Benzyl-2-chloro-*N*-(2-hydroxy-1-(1*H*-indol-3-yl)ethyl)acetamide (22a)**. To the suspension of LAH (3.6 g; 93.5 mmol) in THF (100 mL) was added **10a** (5 g; 17.8 mmol) under virgous stirring and the reaction mixture was refluxed for 4 hours. After completion of the reaction, the mixture was cooled down (ice-bath) and was slowly quenched with 5N solution of KOH (20 mL). The formed clear layer was separated, and the residue was washed several times with Et_2O. The collected organic layers were dried over anhydrous $MgSO_4$, filtered off and evaporated yielding a crude product (4.3 g; 91%) which was used to the next step without further purification. To the solution of crude product (4.13 g; 15.5 mmol) and TEA (3.24 mL; 23.25 mmol) in DCM (60 mL) at 0 °C was slowly added the solution of chloracetylchloride (1.35 mL; 17.05 mmol) in DCM (15 mL). The reaction mixture was stirred for 1 hour at 0 °C and then was quenched with saturated solution of $NaHCO_3$ and extracted with EtOAc (2x75 mL). The collected organic layers were dried over anhydrous $MgSO_4$, filtered off, evaporated and the residue was purified by column chromatography (EtOAc/DCM 2:3) yielding a product as a colourless solid (3.98 g, 75%), m.p = 112-117 °C. ^{1}H NMR (600 MHz, DMSO)-Major rotamer δ =11.10 (s, 1H), 7.57 (d, *J* = 7.9 Hz, 1H), 7.38 – 7.32 (m, 2H), 7.12 – 7.06 (m, 2H), 7.05 – 6.98 (m, 3H), 6.91 – 6.87 (m, 2H), 5.38 (dd, *J* = 8.6, 5.0 Hz, 1H), 5.24 (t, *J* = 5.1 Hz, 1H-OH), 5.04 (d, *J* = 13.4 Hz, 1H), 4.60 (d, *J* = 13.3 Hz, 1H), 4.38 (m, 1H), 4.19 (d, *J* = 15.6 Hz, 1H), 3.93 – 3.86 (m, 2H). ^{13}C NMR (151 MHz, DMSO)-Major rotamer δ = 167.1, 138.8, 136.0, 127.4, 126.8, 126.6, 125.8, 124.3, 119.0, 118.7, 111.5, 109.6, 61.3, 56.3, 45.3, 43.1. ^{1}H NMR (600 MHz, DMSO)-Minor rotamer δ =11.02 (s, 1H), 7.51 (d, *J* = 7.8 Hz, 1H), 7.38 – 7.30 (m, 2H), 7.17 – 7.13 (m, 3H), 7.05 – 6.97 (m, 4H), 6.16 (dd, *J* = 8.1, 5.8 Hz, 1H), 4.93 (t, *J* = 5.5 Hz, 1H-OH), 4.46 (d, *J* = 17.9 Hz, 1H), 4.41 (m, 1H), 4.08 (d, *J* = 13.9 Hz, 1H), 4.04 (d, *J* = 13.9 Hz, 1H), 3.89 – 3.79 (m, 2H). ^{13}C NMR (151 MHz, DMSO)-Minor rotamer δ = 166.9, 138.5, 135.9, 128.3, 126.9, 126.5, 126.0, 121.4, 118.9, 118.6, 111.5, 110.7, 60.8, 52.6, 46.0, 43.1. HRMS (HESI): m/z $[M+H]^+$ calculated for $C_{19}H_{20}ClN_2O_2$ (343.12133), found 343.12093.

2-Chloro-*N*-(2-hydroxy-1-(1*H*-indol-3-yl)ethyl)-*N*-methylacetamide (22b). Following the analogy as for **22a**, from reduction of carboxylic acid **10b,** crude substrate (4.3 g; 22.6 mmol) delivered compound **22b** and was purified by column chromatography (EtOAc/MeOH 20:1) yielding a product as a white solid (3.19 g, 53%), m.p = 146-147 °C. ^{1}H NMR (600 MHz, DMSO)-Major rotamer δ =11.05 (s, 1H), 7.45 (d, *J* = 7.9 Hz, 1H), 7.40 – 7.34 (m, 2H), 7.13 – 7.06 (m, 1H), 6.98 – 6.95 (m, 1H), 5.97 (dd, *J* = 8.8, 5.4 Hz, 1H), 4.84 (t, *J* = 5.7 Hz, 1H-OH), 4.45 (d, *J* = 13.5 Hz, 1H), 4.35 (d, *J* = 13.5 Hz, 1H), 3.97 – 3.89 (m, 2H), 2.70 (s, 3H). ^{13}C NMR (151 MHz, DMSO)-Major rotamer δ =166.1, 136.0, 126.7, 123.7, 121.4, 118.8, 118.7, 111.4, 110.6, 59.9, 51.3, 43.0, 28.9. ^{1}H NMR (600 MHz, DMSO)-Minor rotamer δ =11.15 (s, 1H), 7.50 (d, *J* = 7.9 Hz, 1H), 7.40 – 7.34 (m, 2H), 7.13 – 7.06 (m, 1H), 7.02 – 6.99 (m, 1H), 5.24 (dd, *J* = 8.7, 4.9 Hz, 1H), 5.21 (t, *J* = 5.5 Hz, 1H-OH), 4.91 (d, *J* = 13.4 Hz, 1H), 4.50 (d, *J* = 13.3 Hz, 1H), 3.88 – 3.81 (m, 2H), 2.53 (s, 3H). ^{13}C NMR (151 MHz, DMSO)-Minor rotamer δ =166.6, 136.2, 126.2, 123.7, 121.4, 119.0, 118.7, 111.6, 109.8, 60.1, 55.8, 42.8, 27.9. HRMS (HESI): m/z $[M+H]^+$ calculated for $C_{13}H_{16}ClN_2O_2$ (267.09003), found 267.08954.

2-Chloro-*N*-((*S*)-2-hydroxy-1-(1*H*-indol-3-yl)ethyl)-*N*-((*R*)-1-phenyl-ethyl)acetamide (22c). Following the analogy as for **22a**, from reduction of carboxylic acid **12a,** crude substrate (2.24 g; 8 mmol) delivered compound **22c** and was purified by column chromatography (Hexanes/EtOAc 2:1) yielding a product as a white solid (1.91 g, 67%), m.p = 161-162 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.45 (bs, 1H), 7.53 (d, *J* = 7.8 Hz, 1H), 7.32 (d, *J* = 8.0 Hz, 1H), 7.24 (m, 2H), 7.20 – 7.03 (m, 5H), 6.93 (d, *J* = 2.4 Hz, 1H), 5.00 (q, *J* = 7.1 Hz, 1H), 4.91 (t, *J* = 3.8 Hz, 1H), 4.43 (d, *J* = 16.6 Hz, 1H), 4.29 (d, *J* = 16.6 Hz, 1H), 4.03 – 3.92 (m, 2H), 1.69 (d, *J* = 7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 167.6, 141.0, 136.2, 128.0, 127.3, 127.1, 125.6, 123.9, 122.4, 119.9, 118.5, 113.1,

111.6, 69.8, 68.8, 56.5, 53.2, 18.3. HRMS (HESI): m/z $[M+H]^+$ calculated for $C_{20}H_{22}ClN_2O_2$ (357.13698), found 357.13638.

***N*-Benzyl-*N*-(2-((tert-butyldimethylsilyl)oxy)-1-(1*H*-indol-3-yl)ethyl)-2-chloroacetamide (23a)**. To the solution of **22a** (3.7 g; 10.8 mmol) and imidazole (1.1 g; 16.1 mmol) in DCM (120 mL) at room temperature was added solution of TBSCl (2.43 g; 16.1 mmol). The reaction mixture was stirred for 24 hours and after completition was dilluted with water and extracted with DCM. The collected organic layers were dried over anhydrous $MgSO_4$, filtered off and evaporated resulting crude product which was purified by column chromatography (Et_2O/Hexane 1:4). The product was isolated as a colourless solid (4.32 g, 87 %), m.p = 131-137 °C. ^{1}H NMR (600 MHz, DMSO)-Major rotamer δ =11.16 (s, 1H), 7.57 (d, *J* = 8.0 Hz, 1H), 7.44 (d, *J* = 2.2 Hz, 1H), 7.38 – 7.33 (m, 1H), 7.18 – 6.88 (m, 7H), 5.50 (dd, *J* = 9.4, 4.1 Hz, 1H), 5.05 (d, *J* = 13.6 Hz, 1H), 4.65 (d, *J* = 13.5 Hz, 1H), 4.51 – 4.41 (m, 1H), 4.16 – 3.97 (m, 3H), 0.90 (s, 9H), 0.08 (s, 3H), 0.02 (s, 3H). ^{13}C NMR (151 MHz, DMSO) - Major rotamer δ =167.1, 138.9, 136.0, 127.5, 126.7, 126.4, 126.0, 124.3, 121.5, 119.0, 118.7, 111.5, 109.0, 62.7, 55.8, 45.1, 43.3, 25.7, 17.8, -5.7, -5.7. ^{1}H NMR (600 MHz, DMSO)-Minor rotamer δ = 11.06 (s, 1H), 7.51 (d, *J* = 7.9 Hz, 1H), 7.40 (d, *J* = 1.9 Hz, 1H), 7.38 – 7.33 (m, 1H), 7.18 – 6.88 (m, 7H), 6.19 (dd, *J* = 8.6, 4.9 Hz, 1H), 4.53 – 4.38 (m, 2H), 4.21 – 3.92 (m, 4H), 0.87 (s, 9H), 0.07 (s, 6H). ^{13}C NMR (151 MHz, DMSO) - Minor rotamer δ =166.9, 138.4, 136.0, 128.2, 126.8, 126.8, 126.0, 124.2, 121.5, 119.0, 118.5, 111.5, 110.2, 62.3, 52.3, 46.1, 42.9, 25.7, 17.8, -5.5, -5.5. HRMS (HESI): m/z $[M+H]^+$ calculated for $C_{25}H_{34}ClN_2O_2Si$ (457.20781), found 457.20740.

***N*-(2-((Tert-butyldimethylsilyl)oxy)-1-(1*H*-indol-3-yl)ethyl)-2-chloro-*N*-methylacetamide (23b)**. Following the analogy as for **23a**, substrate **22b** (797 mg; 2.99 mmol) delivered compound **23b** and was purified by column chromatography (Et_2O/Hexane 1:3) yielding a product as a colourless solid (1.06 g, 93%), m.p = 155-156 °C. ^{1}H NMR (600 MHz, DMSO)-Major rotamer δ =11.08 (bs, 1H), 7.44 (d, *J* = 8.0 Hz, 1H), 7.41 (d, *J* = 2.0 Hz, 1H), 7.36 (d, *J* = 8.1 Hz, 1H), 7.10 (m, 1H), 6.97 (t, *J* = 7.5 Hz, 1H), 6.00 (dd, *J* = 8.7, 5.1 Hz, 1H), 4.39 (d, *J* = 13.3 Hz, 1H), 4.35 (d, *J* = 13.3 Hz, 1H), 4.14 – 4.07 (m, 1H), 4.00 (dd, *J* = 10.8, 5.2 Hz, 1H), 2.72 (s, 3H), 0.87 (s, 9H), 0.09 (s, 3H), 0.08 (s, 3H). ^{13}C NMR (151 MHz, DMSO)-Major rotamer δ =166.1, 136.0, 126.7, 123.8, 121.4, 118.9, 118.6, 111.4, 110.1, 61.5, 50.8, 42.7, 29.2, 25.8, 17.8, -5.4, -5.5. ^{1}H NMR (600 MHz, DMSO)-Minor rotamer δ =11.20 (bs, 1H), 7.51 (d, *J* = 7.9 Hz, 1H), 7.42 (d, *J* = 2.2 Hz, 1H), 7.39 (d, *J* = 8.1 Hz, 1H), 7.10 (m, 1H), 7.01 (t, *J* = 7.5 Hz, 1H), 5.35 (dd, *J* = 8.9, 4.6 Hz, 1H), 4.90 (d, *J* = 13.5 Hz, 1H), 4.49 (d, *J* = 13.5 Hz, 1H), 4.15 – 4.07 (m, 2H), 2.51 (s, 3H), 0.88 (s, 9H), 0.11 (s, 3H), 0.08 (s, 3H). ^{13}C NMR (151 MHz, DMSO)-Minor rotamer δ =166.6, 136.1, 126.1, 123.8, 121.5, 119.0, 118.7, 111.6, 109.1, 61.6, 55.2, 43.0, 27.8, 25.7, 17.8, -5.6, -5.6. HRMS (HESI): m/z $[M+H]^+$ calculated for $C_{19}H_{30}ClN_2O_2Si$ (381.17651), found 381.17592.

***N*-((*S*)-2-((Tert-butyldimethylsilyl)oxy)-1-(1*H*-indol-3-yl)ethyl)-2-chloro-*N*-((*R*)-1-phenylethyl)acetamide (23c)**. Following the analogy as for **23a**, substrate (762 mg; 2 mmol) delivered compound **23c** and was purified by column chromatography (Et_2O/Hexane 1:2) yielding a product as a colourless solid (1.25 g, 89%), m.p = 90-96 °C. ^{1}H NMR (600 MHz, DMSO) (mixture of rotamers) δ = 11.19 (bs, 1H-NH, major), 10.97 (bs, 1H-NH-minor), 7.70 (m 1H), 7.60 (m, 1H), 7.40 (m, 3H), 7.15 – 6.62 (m, 12H), 5.48 (m, 1H-CH-Ind), 5.01 (m, 1H-CH-Ph, minor), 4.96 (d, *J* = 13.7 Hz, 1H-CH_2-Cl), 4.62 (m, 1H-CH-Ph, major), 4.56 (d, *J* = 13.7 Hz, 1H-CH_2-Cl), 4.39 (m, 2H-CH_2-OTBS), 4.00 (m, 2H-CH_2-OTBS), 1.79 (m, 3H-CH_3-CH, minor), 1.74 (d, *J* = 5.9 Hz, 3H-CH_3-CH, major), 0.92 (s, 9H-Si-*terc*-butyl, major), 0.89 (s, 9H-Si-*terc*-butyl, minor), 0.17 (s, 3H-Si-CH_3, major), 0.15 (s, 3H-Si-CH_3-major), 0.09 (m, 6H-Si-CH_3x2, minor). ^{13}C NMR (151 MHz, DMSO) (mixture of rotamers) δ =166.7(C=O, minor), 165.2(C=O, major), 142.1, 141.5, 135.8, 135.4, 128.0, 127.1, 126.9, 126.7, 126.1, 126.0, 125.3, 125.0, 124.5, 121.5, 121.3, 119.0, 118.9, 118.8, 118.5, 111.5, 111.3, 110.5, 109.1, 62.2(CH_2-OTBS, major/minor), 55.9(CH-Ind, major/minor), 52.6(CH-Ph, minor), 51.5(CH-Ph, major), 44.4(CH_2-Cl, major), 43.0(CH_2-Cl, minor), 25.7, 18.9, 17.8, 17.7, 17.3, -5.5, -5.6. HRMS (HESI): m/z $[M+H]^+$ calculated for $C_{26}H_{36}ClN_2O_2Si$ (471.22346), found 471.22281.

(2'*S*,3*S*)-1'-Benzyl-2'-(((tert-butyldimethylsilyl)oxy)methyl)spiro-[indole-3,3'-pyrrolidin]-5'-one (24a). To the solution of **23a** (914 mg; 2 mmol) in THF (10 mL) was added sodium hydride (60% dispersion in mineral oil 120 mg; 3 mmol) portionwise. The reaction mixture was stirred for 30 minutes and after completition the solvent was evaporated. The resulting crude product was purified by column chromatography (DCM/EtOAc 2:1). The product was isolated as a colourless solid (648 mg, 77 %, d.r 99:1), m.p = 75-81 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ = 8.29 (s, 1H), 7.57 (d, *J* = 7.7 Hz, 1H), 7.37 – 7.32 (m, 4H), 7.31 – 7.26 (m, 2H), 7.10 (td, *J* = 7.5, 0.7 Hz, 1H), 7.02 (ddd, *J* = 7.5, 1.1, 0.6 Hz, 1H), 5.21 (d, *J* = 14.6 Hz, 1H), 3.99 (d, *J* = 14.6 Hz, 1H), 3.89 (dd, *J* = 11.6, 2.7 Hz, 1H), 3.53 (dd, *J* = 11.6, 1.9 Hz, 1H), 3.45 (t, *J* = 2.2 Hz, 1H), 3.25 (dd, *J* = 16.6, 0.9 Hz, 1H), 2.29 (d, *J* = 16.6 Hz, 1H), 0.95 (s, 9H), 0.11 (s, 3H), 0.09 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ = 173.2, 172.8, 153.9, 143.0, 136.0, 128.8, 128.7, 128.5, 128.0, 126.9, 121.3, 120.5, 63.9, 61.6, 58.6, 44.8, 36.9, 25.8, 18.0, -5.6. HRMS (HESI): m/z $[M+H]^+$ calculated for $C_{25}H_{33}N_2O_2Si$ (421.23113), found 421.23044.

(2'*S*,3*S*)-2'-(((Tert-butyldimethylsilyl)oxy)methyl)-1'-methylspiro-[indole-3,3'-pyrrolidin]-5'-one (24b). Following the analogy as for **24a**, substrate **23b** (1.7 g; 4.4 mmol) delivered compound **24b** and was purified by column chromatography (DCM/EtOAc 1:1) yielding a product as a colourless solid (1.1 g, 72%, d.r 99:1), m.p = 106-108 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ = 8.31 (s, 1H), 7.64 (d, *J* = 7.7 Hz, 1H), 7.38 (td, *J* = 7.6, 1.2 Hz, 1H), 7.34 (d, *J* = 7.4 Hz, 1H), 7.29 – 7.24 (m, 1H), 3.88 (dd, *J* = 11.6, 2.6 Hz, 1H), 3.60 (dd, *J* = 11.6, 2.2 Hz, 1H), 3.54 (t, *J* = 2.3 Hz, 1H), 3.14 (d, *J* = 16.5 Hz, 1H), 2.99 (s, 3H), 2.29 (d, *J* = 16.5 Hz, 1H), 0.92 (s, 9H), 0.11 (s, 3H), 0.08 (s, 3H)^{13}C NMR (151 MHz, $CDCl_3$) δ = 173.3, 173.0, 154.0, 143.0, 128.7, 127.2, 121.5, 120.5, 67.0, 61.6, 58.91, 36.7, 28.1, 25.7, 18.0, -5.6. HRMS (HESI): m/z $[M+H]^+$ calculated for $C_{19}H_{29}N_2O_2Si$ (345.19983), found 345.19871.

(2'*S*,3*S*)-2'-(((Tert-butyldimethylsilyl)oxy)methyl)-1'-((*R*)-1-phenylethyl)spiro[indole-3,3'-pyrrolidin]-5'-one (24c). Following the analogy as for **24a**, substrate **23c** (942.2 mg; 2 mmol) delivered compound **24c** and was purified by column chromatography (Et_2O/Hexane 2:1) yielding a product as a colourless solid (590 mg, 68%, d.r 99:1), m.p = 143-145 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.22 (s, 1H), 7.54 (d, *J* = 7.7 Hz, 1H), 7.45 – 7.39 (m, 2H), 7.37 – 7.23 (m, 4H), 7.09 (t, *J* = 7.5 Hz, 1H), 6.96 (d, *J* = 8.0 Hz, 1H), 5.58 (q, *J* = 7.2 Hz, 1H), 3.87 (dd, *J* = 11.4, 3.0 Hz, 1H), 3.55 (dd, *J* = 11.4, 1.7 Hz, 1H), 3.36 (d, *J* = 16.3 Hz, 1H), 3.27 (dd, *J* = 2.9, 1.7 Hz, 1H), 2.16 (d, *J* = 16.3 Hz, 1H), 1.72 (d, *J* = 7.3 Hz, 3H), 0.96 (s, 9H), 0.10 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 172.9, 172.9, 153.6, 143.3, 138.9, 128.8, 128.3, 128.1, 127.8, 126.8, 121.2, 120.4, 64.8, 63.9, 59.3, 51.9, 37.2, 25.7, 18.0, 17.8, -5.7. HRMS (HESI): m/z $[M+H]^+$ calculated for $C_{26}H_{35}N_2O_2Si$ (435.24678), found 435.24579.

(3a*S*,5a*R*,10b*S*)-3-benzyl-3a,4,5a,6-tetrahydro-1H-pyrrolo[3',2':3,4]furo[2,3-b]indol-2(3*H*)-one (25a). To the solution of **24a** (421 mg; 1 mmol) in THF (5 mL) was added TBAF (379 mg, 1.2 mmol) and the reaction mixture was stirred for 24 hours at room temperature. After completition of the reaction the solvent was evaporated, and the resulting crude product was purified by column chromatography (EtOAc/Hexane 1:1). The product was obtained as a colourless crystals (254 mg, 83 %, d.r 99:1), m.p = 145-148 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.37 – 7.30 (m, 2H), 7.30 – 7.23 (m, 3H), 7.07 (ddd, *J* = 7.8, 7.5, 1.3 Hz, 1H), 7.04 (dddd, *J* = 7.5, 1.3. 0.7, 0.6 Hz,

1H), 6.74 (td, *J* = 7.5, 0.9 Hz, 1H), 6.57 (dd, *J* = 7.8 Hz, 1H), 5.71 (d, *J* = 3.3 Hz, 1H), 4.99 (d, *J* = 15.2 Hz, 1H), 4.70 (d, *J* = 2.9 Hz, 1H), 4.15 (d, *J* = 15.1 Hz, 1H), 4.01 (d, *J* = 10.6 Hz, 1H), 3.83 (d, *J* = 3.4 Hz, 1H), 3.57 (dd, *J* = 10.8, 3.4 Hz, 1H), 3.03 (d, *J* = 17.9 Hz, 1H), 2.87 (d, *J* = 17.9 Hz, 1H).^{13}C NMR (151 MHz, $CDCl_3$) δ= 172.5, 149.3, 135.7, 129.1, 128.9, 128.0, 127.9, 127.8, 123.5, 119.2, 108.6, 102.0, 70.3, 66.4, 56.7, 45.0, 42.1. HRMS (HESI): m/z $[M+H]^+$ calculated for $C_{19}H_{19}N_2O_2$ (307.14465), found 307.14402

(3a*S*,5a*R*,10b*S*)-3-methyl-3a,4,5a,6-tetrahydro-1*H*-pyrrolo[3',2':3,4]-furo[2,3-b]indol-2(3*H*)-one (25b). Following the analogy as for **25a**, substrate **24b** (318.83 mg; 0.925 mmol) delivered compound **25b** and was purified by column chromatography (Et_2O/EtOAc 1:1) yielding a product as a colourless crystals (179 mg, 84%, d.r 99:1), m.p = 224-227 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ = 7.15 – 7.09 (m, 2H), 6.79 (td, *J* = 7.5, 0.9 Hz, 1H), 6.61 (d, *J* = 7.7 Hz, 1H), 5.69 (s, 1H), 4.69 (s, 1H), 4.09 (d, *J* = 10.6 Hz, 1H), 3.91 (d, *J* = 3.3 Hz, 1H), 3.71 (dd, *J* = 10.6, 3.4 Hz, 1H), 2.98 (d, *J* = 17.8 Hz, 1H), 2.89 (s, 3H), 2.79 (d, *J* = 17.8 Hz, 1H).^{13}C NMR (151 MHz, $CDCl_3$) δ= 172.4, 149.4, 129.2, 128.0, 123.6, 119.3, 108.7, 102.1, 72.7, 66.5, 56.8, 42.1, 27.9. HRMS (HESI): m/z $[M+H]^+$ calculated for $C_{13}H_{15}N_2O_2$ (231.11335), found 231.11271.

(3a*R*,5a*S*,10b*R*)-3-((*R*)-1-Phenylethyl)-3a,4,5a,6-tetrahydro-1*H*-pyrrolo[3',2':3,4]furo[2,3-*b*]indol-2(3*H*)-one (25c). Following the analogy as for **25a**, substrate **24c** (434.65 mg; 1 mmol) delivered compound **25c** and was purified by column chromatography (Et_2O/Hexane 2:1→100:0→ Et_2O/AcOEt 2:1) yielding a product as a colourless crystals (251 mg, 78%, d.r 99:1), m.p = 163-166 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.39 – 7.23 (m, 5H), 7.05 (t, *J* = 7.7 Hz, 1H), 6.94 (d, *J* = 7.5 Hz, 1H), 6.72 (t, *J* = 7.5 Hz, 1H), 6.55 (d, *J* = 7.7 Hz, 1H), 5.63 (d, *J* = 3.0 Hz, 1H), 5.51 (q, *J* = 7.2 Hz, 1H), 4.69 (s, 1H), 3.96 (d, *J* = 10.3 Hz, 1H), 3.64 (d, *J* = 4.0 Hz,1H), 3.56 (dd, *J* = 10.3, 4.0 Hz, 1H), 2.94 (d, *J* = 17.9 Hz, 1H), 2.85 (d, *J* = 17.9 Hz, 1H), 1.67 (d, *J* = 7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ= 172.6, 149.0, 138.6, 128.9, 128.8, 128.7, 127.8, 127.4, 123.3, 119.3, 108.7, 101.7, 69.7, 68.9, 56.5, 51.1, 42.2, 18.0. HRMS (HESI): m/z $[M+H]^+$ calculated for $C_{20}H_{21}N_2O_2$ (321.16030), found 321.15967.

Methyl 2-(1*H*-indol-3-yl)-2-(methylamino)acetate (29b). The acid **10b** (11.5 g; 56.3 mmol) was dissolved in a mixture of 2M HCl/MeOH (200 mL) and 2,2-dimethoxypropane (200 mL). The reaction mixture was stirred at room temperature for 48 hours. The reaction mixture was evaporated under reduced pressure and the residue was extracted with a mixture of saturated $NaHCO_3$ (50 mL) and DCM (2x100 mL). The combined extracts were dried over $MgSO_4$, filtered off and evaporated in vacuum. The residue was purified by flash chromatography (EtOAc/MeOH 100%→10:1→5:1). The corresponding methyl 2-(1*H*-indol-3-yl)-2-(methylamino)acetate (**29a**) was obtained as white solid (7.3 g, 60 %), m.p = 76-79 °C. ^{1}H NMR (300 MHz, $CDCl_3$)**:** δ = 8.69 (s, 1H), 7.74 (d, *J* = 7.5 Hz, 1H), 7.31 (d, *J* = 7.7 Hz, 1H), 7.23 – 7.08 (m, 3H), 4.62 (s, 1H), 3.71 (s, 3H), 2.49 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$)**:** δ= 173.9, 136.3, 125.9, 123.0, 122.3, 119.9, 119.1, 112.7, 111.4, 60.1, 52.1, 34.6. HRMS (HESI): m/z $[M+H]^+$ calculated for $C_{12}H_{14}N_2O_2$ (219.1133), found 219.1127.

Methyl 2-(benzylamino)-2-(1*H*-indol-3-yl)acetate (29a). Following the analogy as for **29b**, substrate **10a** (3.52 g; 12.56 mmol) delivered compound **29a** and was purified by flash chromatography (EtOAc/hexane 1:2). The corresponding methyl 2-(benzylamino)-2-(1*H*-indol-3-yl)acetate (**29b**) was obtained as white solid (2.7 g, 73 %), m.p = 90-91 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.28 (bs, 1H), 7.80 – 7.57 (m, 1H), 7.38 – 7.27 (m, 6H), 7.24 – 7.11 (m, 3H), 4.72 (d, *J* = 0.5 Hz, 1H), 3.84 (d, *J* = 13.1, 1H), 3.79 (d, *J* = 13.1, 1H), 3.69 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 174.0, 139.7, 136.4, 128.4, 128.4, 127.1, 126.0, 123.0, 122.4, 120.0, 119.4, 113.1, 111.4, 57.4, 52.1, 51.6. HRMS (HESI): m/z $[M+H]^+$ calculated for $C_{18}H_{18}N_2O_2$ (295.1446), found 295.14471.

Methyl 2-(1*H*-indol-3-yl)-2-(((*R*)-1-phenylethyl)amino)acetate (29c). Following the analogy as for **29b**, substrate **12a** (589 mg; 2 mmol) delivered compound **29c** and was purified by flash chromatography (EtOAc/ hexane 1:4). The corresponding methyl 2-(1*H*-indol-3-yl)-2-(((*R*)-1-phenylethyl)amino)acetate (**29c**) was obtained as yellowish oil (580 mg, 94 %), $[\alpha]_D^{25}$ = -114° (MeOH, c = 0,2). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.20 (s, 1H), 7.67 (d, *J* = 7.9 Hz, 1H), 7.38 – 7.24 (m, 6H), 7.23 – 7.16 (m, 1H), 7.12 (m, 1H), 7.05 (d, *J* = 2.4 Hz, 1H), 4.55 (s, 1H), 3.71 (q, *J* = 6.6 Hz, 1H), 3.59 (s, 3H), 1.34 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.8, 144.8, 136.4, 128.4, 127.1, 127.0, 126.0, 123.4, 122.4, 119.9, 119.5, 113.1, 111.3, 55.8, 55.1, 52.1, 24.3. HRMS (HESI): m/z $[M+H]^+$ calculated for $C_{19}H_{20}N_2O_2$ (309.1603), found 309.15984.

Methyl 2-(1*H*-indol-3-yl)-2-(phenethylamino)acetate (29d). Following the analogy as for **29b**, substrate **10c** (4.47 g; 15.18 mmol) delivered compound **29d** and was purified by flash chromatography (EtOAc 100 %). The corresponding methyl 2-(1*H*-indol-3-yl)-2-(phenethylamino)acetate (**29d**) was obtained as white solid (3.51 g, 75 %), m.p = 98-100 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.20 (s, 1H), 7.68 (d, *J* = 7.9 Hz, 1H), 7.34 (d, *J* = 8.1 Hz, 1H), 7.29 – 7.24 (m, 2H), 7.19 (m, 4H), 7.15 – 7.09 (m, 2H), 4.73 (s, 1H), 3.68 (s, 3H), 2.97 – 2.79 (m, 4H). ^{13}C NMR (151 MHz, $CDCl_3$): δ = 173.9, 139.8, 136.3, 128.7, 128.4, 126.2, 126.0, 122.8, 122.4, 120.0, 119.4, 113.2, 111.3, 58.5, 52.1, 49.2, 36.5. HRMS (HESI): m/z $[M+H]^+$ calculated for $C_{19}H_{20}N_2O_2$ (309.1603), found 309.15962.

Methyl 2-(allylamino)-2-(1*H*-indol-3-yl)acetate (29e). Following the analogy as for **29b**, substrate **10d** (2.3 g; 10 mmol) delivered compound **29e** and was purified by flash chromatography (EtOAc/hexane 1:1). The corresponding methyl 2-(allylamino)-2-(1*H*-indol-3-yl)acetate (**29e**) was obtained as white solid (1.76 g, 72 %), m.p = 91-95 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.39 (s, 1H), 7.75 (d, *J* = 7.9 Hz, 1H), 7.34 (d, *J* = 8.1 Hz, 1H), 7.22 – 7.11 (m, 3H), 5.93 (ddt, *J* = 16.5, 10.3, 6.1 Hz, 1H), 5.20 (dd, *J* = 17.2, 1.5 Hz, 1H), 5.13 (dd, *J* = 10.2, 1.1 Hz, 1H), 4.75 (s, 1H), 3.71 (s, 3H), 3.32 (dd, *J* = 13.8, 6.0 Hz, 1H), 3.27 (dd, *J* = 13.8 Hz, 6.0 Hz, 1H), 2.06 (bs, 1H). ^{13}C NMR (151 MHz, $CDCl_3$): δ = 174.0, 136.3, 136.2, 126.0, 122.9, 122.4, 120.0, 119.3, 116.7, 113.1, 111.4, 57.3, 52.1, 50.4. HRMS (HESI): m/z $[M+H]^+$ calculated for $C_{14}H_{16}N_2O_2$ (245.1290), found 245.12835.

Methyl 2-(2-chloro-*N*-methylacetamido)-2-(1*H*-indol-3-yl)acetate (26ba). To the mixture of methyl 2-(1*H*-indol-3-yl)-2-(methylamino)acetate (**29b**) (411.5 mg; 1.88 mmol) and propylene oxide (1.64. g; 28.2 mmol) in THF (15 mL) at 0 °C was added chloracetyl chloride (233.6 mg; 2.07 mmol) in THF (5 mL). The reaction mixture was stirred at room temperature for 30 minutes and concentrated under reduced pressure. The residue was extracted with DCM and $NaHCO_3$ (aq.), dried over $MgSO_4$, filtered off and evaporated under vacuum. The crude product was purified by flash chromatography (EtOAc/hexane 1:2→1:1→2:1). The corresponding methyl 2-(2-chloro-N-methyl-acetamido)-2-(1*H*-indol-3-yl)acetate (**26ba**) was obtained as white solid (415.6 mg, 75%), m.p = 128-130 °C. ^{1}H NMR ($CDCl_3$): δ = 8.77 (bs, 1H), 7.50 (d, *J* = 7.9 Hz, 1H), 7.41 (d, *J* = 8.1 Hz, 1H), 7.29 – 7.17 (m, 2H), 7.14 (t, *J* = 7.5 Hz, 1H), 6.65 (s, 1H), 4.21 (d, *J* = 12.9, 1H), 4.16 (d, *J* = 12.9, 1H), 3.77 (s, 3H), 2.89 (s, 3H). ^{13}C NMR ($CDCl_3$): δ = 171.0, 167.3, 136.2, 126.4, 125.0, 122.8, 120.5, 118.6, 111.6, 108.1, 54.1, 52.4, 41.8, 31.7. HRMS (HESI): m/z $[M+H]^+$ calculated for $C_{14}H_{15}ClN_2O_3$ (295.08495), found 295.08446

Methyl 2-(*N*-benzyl-2-chloroacetamido)-2-(1*H*-indol-3-yl)acetate (26aa). Following the analogy as for **26ba**, substrate **29a** (294.35 mg; 1 mmol) delivered compound **26aa** and the crude product was purified by

flash chromatography (DCM/EtOAc 100%→20:1→10:1). The corresponding methyl 2-(*N*-benzyl-2-chloroacetamido)-2-(1*H*-indol-3-yl)acetate (**26aa**) was obtained as white solid (351 mg, 94 %), m.p = 121-122 °C. ^{1}H NMR ($CDCl_3$): δ = 8.47 (bs, 1H), 7.60 (d, *J* = 7.9 Hz, 1H), 7.34 (d, *J* = 8.2 Hz, 1H), 7.24 – 7.08 (m, 6H), 6.95 (m, 2H), 6.49 (s, 1H), 4.63 (d, *J* = 18.0 Hz, 1H), 4.59 (d, *J* = 17.6 Hz, 1H), 4.05 (d, *J* = 13.2 Hz, 1H), 3.95 (d, *J* = 13.2 Hz, 1H), 3.73 (s, 3H). ^{13}C NMR ($CDCl_3$): δ = 171.1, 168.2, 137.0, 136.0, 128.6, 127.3, 126.8, 126.0, 125.7, 122.9, 120.7, 118.7, 111.6, 107.8, 55.2, 52.5, 48.9, 42.3. HRMS (HESI): m/z $[M+H]^+$ calculated for $C_{20}H_{19}ClN_2O_3$ (371.11625), found 371.11596.

Methyl 2-(*N*-allyl-2-chloroacetamido)-2-(1*H*-indol-3-yl)acetate (26ea). Following the analogy as for **26ba**, substrate **29e** (2.12 g; 8.7 mmol) delivered compound **26ea** and the crude product was purified by flash chromatography (EtOAc/hexane 1:1). The corresponding methyl 2-(*N*-allyl-2-chloroacetamido)-2-(1*H*-indol-3-yl)acetate (**26ea**) was obtained as a white solid (1.95 g, 70 %), m.p = 95-96 °C. ^{1}H NMR ($CDCl_3$) δ = 8.75 (bs, 1H), 7.54 (d, *J* = 7.9 Hz, 1H), 7.41 (d, *J* = 8.1 Hz, 1H), (m, 1H), 7.26 – 7.19 (m, 2H), 7.14 (ddd, *J* = 8.0, 7.1, 1.1 Hz, 1H), 6.51 (s, 1H), 5.63 – 5.30 (m, 1H), 5.05 – 4.90 (m, 2H), 4.19 (s, 2H), 3.98 – 3.93 (m, 2H), 3.75 (s, 3H). ^{13}C NMR ($CDCl_3$) δ = 171.2, 167.9, 136.1, 134.1, 126.6, 125.5, 122.9, 120.6, 118.6, 116.8, 111.7, 107.9, 54.7, 52.5, 47.7, 42.0. HRMS (HESI): m/z $[M+H]^+$ calculated for $C_{16}H_{17}ClN_2O_3$ (321.10060), found 321.10033.

3-(1*H*-Indol-3-yl)-1-methyl-1*H*-pyrrole-2,5-dione (28ba). To the mixture of methyl 2-(2-chloro-*N*-methylacetamido)-2-(1*H*-indol-3-yl)acetate (**26ba**) (295 mg; 1 mmol) in THF (5 mL) was added NaH (80 mg; 2.2 mmol; 60 % dispersion in mineral oil) and the reaction mixture was stirred at room temperature for 10 minutes. The reaction was quenched by diluting with $NaHCO_3$ (0.5 ml) and DCM (20 mL), dried over $MgSO_4$, filtered off and evaporated under vacuum. The crude product was triturated with EtOAc (5 mL) and the corresponding 3-(1*H*-indol-3-yl)-1-methyl-1*H*-pyrrole-2,5-dione (**26aa**) was obtained as yellow crystalline solid by filtration (215 mg, 95%), m.p = 194-197 °C, (lit.[33] m.p = 195-196 °C). ^{1}H NMR (DMSO)**:** δ = 12.03 (bs, 1H), 8.39 (s, 1H), 7.96 (d, *J* = 7.3 Hz, 1H), 7.52 (d, *J* = 7.4 Hz, 1H), 7.30-7.15 (m, 2H), 6.85 (s, 1H), 2.92 (s, 3H). ^{13}C NMR (DMSO)**:** δ= 172.0, 171.6, 139.0, 136.7, 131.0, 125.5, 123.1, 121.5, 120.4, 114.1, 112.6, 105.5, 23.4. HRMS (HESI): m/z $[M+H]^+$ calculated for $C_{13}H_{10}N_2O_2$ (227.08205), found 227.08147.

3-Chloro-4-(1H-indol-3-yl)-1-methyl-1H-pyrrole-2,5-dione (28bb). To the mixture of **methyl 2-(1*H*-indol-3-yl)-2-(methylamino)acetate (29b)** (2.48 g; 11.4 mmol) and propylene oxide (9.9 g; 171 mmol) in THF (91 mL) at 0 °C was added dichloroacetyl chloride (1.85 g; 12.54 mmol) in THF (30 mL). The reaction mixture was stirred at room temperature for 30 minutes and concentrated under reduced pressure. The residue was extracted with DCM and $NaHCO_3$ (aq.), dried over $MgSO_4$, filtered off and evaporated under vacuum. The residue was triturated with hexane (25 mL) and Et_2O (5 mL) and the precipitated product was filtered off, washed with hexane (10 mL) and Et_2O (2 mL). The crude product methyl 2-(2,2-dichloro-*N*-methylacetamido)-2-(1*H*-indol-3-yl)acetate (**26bb**) (3.26 g, 86 %), m.p = 157-159 °C, was obtained as pale-yellow solid and it was used without further purification to the next step. HRMS (HESI): m/z $[M+H]^+$ calculated for $C_{14}H_{14}Cl_2N_2O_3$ (329.04597), found 329.04576. **26bb** (323.5 mg; 0.98 mmol) was dissolved in THF (5 ml) and NaH (86 mg; 2.12 mmol; 60 % dispersion in mineral oil) was added and reaction mixture was stirred at RT for 10 minutes. The reaction was quenched by diluting with $NaHCO_3$ (0.5 ml) and DCM (20 mL), dried over $MgSO_4$, filtered off and evaporated under vacuum. The crude product was purified by flash chromatography (DCM 100 %). The corresponding 3-chloro-4-(1*H*-indol-3-yl)-1-methyl-1*H*-pyrrole-2,5-dione (**28bb**) was obtained as yellow crystalline solid (82 mg, 32 %) m.p = 204-206 °C**,** (lit.[34] m.p = 207°C). ^{1}H NMR (DMSO) δ = 12.15 (bs, 1H), 8.08 (d, *J* = 3.0 Hz, 1H), 7.93 (dd, *J* = 7.8, 0.7 Hz, 1H), 7.56 – 7.49 (m, 1H), 7.23 (ddd, *J* = 8.1, 7.1, 1.1, 1H), 7.16 (ddd, *J* = 8.1, 7.1, 1.1, 1H), 3.00 (s, 3H). ^{13}C NMR (DMSO) δ = 168.6, 166.1, 136.5, 133.4, 131.3, 124.6, 122.6, 122.0, 121.6, 120.6, 112.4, 103.3, 24.4. HRMS (HESI): m/z $[M+H]^+$ calculated for $C_{13}H_9ClN_2O_2$ (261.04308), found 261.04265.

3-(1*H*-Indol-3-yl)-1,4-dimethyl-1*H*-pyrrole-2,5-dione (28bc).To the mixture of **methyl 2-(1*H*-indol-3-yl)-2-(methylamino)acetate (29b)** (1 g; 4.58 mmol) and propylene oxide (3.99 g; 69 mmol) in THF (37 mL) at 0 °C was added 2-chloropropionyl chloride (640 mg; 5.03 mmol) in THF (12 mL). The reaction mixture was stirred at room temperature for 30 minutes and concentrated under reduced pressure. The residue was extracted with DCM and $NaHCO_3$ (aq.), dried over $MgSO_4$, filtered off and evaporated under vacuum. The residue was triturated with hexane (15 mL) and Et_2O (2 mL) and the precipitated product was filtered off, washed with hexane (10 mL) and Et_2O (2 mL). The crude product methyl 2-(2-chloro-*N*-methylpropanamido)-2-(1*H*-indol-3-yl)acetate (**26bc**) (1.23 g, 87 %), m.p = 163-167 °C, was obtained as pale-yellow solid and it was used without further purification to the next step. HRMS (HESI): m/z $[M+H]^+$ calculated for $C_{15}H_{17}ClN_2O_3$ (309.10060), found 309.10070. **26bc** (308.76 mg; 1 mmol) was dissolved in THF (5 ml) and NaH (88 mg; 2.2 mmol; 60 % dispersion in mineral oil) was added and reaction mixture was stirred at RT for 10 minutes. The reaction was quenched by diluting with $NaHCO_3$ (0.5 ml) and DCM (20 mL), dried over $MgSO_4$, filtered off and evaporated under vacuum. The crude product was purified by flash chromatography (DCM 100 %). The corresponding 3-(1*H*-indol-3-yl)-1,4-dimethyl-1*H*-pyrrole-2,5-dione (**28bc**) was obtained as yellow crystalline solid (132 mg, 55 %) m.p = 174-176 °C. ^{1}H NMR (DMSO) δ = 11.85 (bs, 1H), 7.75 (d, *J* = 2.7 Hz, 1H), 7.67 (d, *J* = 7.7 Hz, 1H), 7.52-7.45 (m, 1H), 7.19 (ddd, *J* = 8.2, 7.1, 1.2 Hz, 1H), 7.10 (ddd, *J* = 8.1, 7.1, 1.2 Hz, 1H), 2.96 (s, 3H), 2.11 (s, 3H). ^{13}C NMR (DMSO) δ 172.4, 171.2, 136.3, 133.6, 130.4, 129.0, 125.3, 122.1, 120.8, 120.0, 112.1, 104.5, 23.7, 10.6. HRMS (HESI): m/z $[M+H]^+$ calculated for $C_{14}H_{12}N_2O_2$ (241.09770), found 241.09711.

1-Benzyl-3-(1*H*-indol-3-yl)-1*H*-pyrrole-2,5-dione (28aa). Following the analogy as for **28ba**, substrate **26aa** (501.8 mg; 1.35 mmol) delivered compound **28aa** and the crude product was purified by flash chromatography (EtOAc/hexane 1:2). The corresponding *1*-benzyl-3-(1*H*-indol-3-yl)-1*H*-pyrrole-2,5-dione (**28aa**) was obtained as yellow crystalline solid (315 mg, 77 %) m.p = 166-170 °C. ^{1}H NMR (DMSO) δ 12.09 (bs, 1H), 8.41 (bs, 1H), 7.99 (d, *J* = 7.6 Hz, 1H), 7.53 (d, *J* = 7.5 Hz, 1H), 7.40 – 7.11 (m, 7H), 6.94 (s, 1H), 4.66 (s, 2H). ^{13}C NMR (DMSO) δ 171.6, 171.3, 139.0, 137.1, 136.7, 131.3, 128.6, 127.3, 127.3, 125.5, 123.1, 121.6, 120.5, 113.9, 112.6, 105.5, 40.5. HRMS (HESI): m/z $[M+H]^+$ calculated for $C_{19}H_{14}N_2O_2$ (303.11335), found 303.11290.

(*R*)-3-(1*H*-Indol-3-yl)-1-(1-phenylethyl)-1*H*-pyrrole-2,5-dione (28ca).To the mixture of **methyl 2-(1*H*-indol-3-yl)-2-(((*R*)-1-phenylethyl)amino) acetate (29c)** (1.87 g; 6.1 mmol) and propylene oxide (5.3 g; 91.5 mmol) in THF (50 mL) at 0 °C was added chloracetyl chloride (758 mg; 6.71 mmol) in THF (16 mL). The reaction mixture was stirred at room temperature for 30 minutes and concentrated under reduced pressure. The residue was extracted with DCM and $NaHCO_3$ (aq.), dried over $MgSO_4$, filtered off and evaporated under vacuum. The crude product was triturated with hexane (25 mL) and Et_2O (5 mL) and the precipitated product was filtered off, washed with hexane (10 mL) and Et_2O (2 mL). The raw product methyl 2-(2-chloro-*N*-((*R*)-1-phenylethyl)acetamido)-2-(1*H*-indol-3-yl)acetate (**26ca**) (2.196 g, 94 %), m.p = 114.4-119 °C, $[\alpha]_D^{25}$ = -89 ° (MeOH, c = 0,3) was obtained as a pale-yellow solid and it was used without further purification to the next step. HRMS (HESI): m/z $[M+H]^+$ calculated for $C_{21}H_{21}ClN_2O_3$ (385.13190), found 385.13168. **26ca** (360.4 mg; 0.94 mmol) was dissolved in THF (4.7 ml) and NaH (83 mg; 2.07 mmol; 60 % dispersion in mineral oil) was added and reaction

mixture was stirred at RT for 10 minutes. The reaction was quenched by diluting with $NaHCO_3$ (0.5 ml) and DCM (20 mL), dried over $MgSO_4$, filtered off and evaporated under vacuum. The crude product was purified by flash chromatography (DCM 100 %). The corresponding (*R*)-3-(1*H*-indol-3-yl)-1-(1-phenylethyl)-1*H*-pyrrole-2,5-dione (**28ca**) was obtained as yellow crystalline solid (237mg, 83 %) m.p = 162-164 °C, $[\alpha]_D^{25}$ = -9,5 ° (MeOH, c = 0,3). ^{1}H NMR ($CDCl_3$) δ = 8.67 (bs, 1H), 8.38 (d, *J* = 2.9 Hz, 1H), 7.79 – 7.72 (m, 2H), 7.49 (m, 2H), 7.45 – 7.39 (m, 1H), 7.38 – 7.22 (m, 6H), 6.60 (s, 1H), 5.46 (q, *J* = 7.3 Hz, 1H), 1.89 (d, *J* = 7.3 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ = 172.0, 171.6, 140.7, 138.9, 136.2, 130.1, 128.5, 127.5, 127.2, 125.8, 123.7, 122.2, 120.2, 115.6, 112.0, 106.8, 49.2, 17.7. HRMS (HESI): m/z $[M+H]^+$ calculated for $C_{20}H_{16}N_2O_2$ (317.12900), found 317.12839.

3-(1*H*-Indol-3-yl)-1-phenethyl-1*H*-pyrrole-2,5-dione (28da). To the mixture of methyl 2-(1H-indol-3-yl)-2-(phenethylamino)acetate (**29d**) (1.06 g; 3.44 mmol) and propylene oxide (3. g; 51.6 mmol) in THF (28 mL) at 0 °C was added chloracetyl chloride (429 mg; 3.8 mmol) in THF (9 mL). The reaction mixture was stirred at room temperature for 30 minutes and concentrated under reduced pressure. The residue was extracted with DCM and $NaHCO_3$ (aq.), dried over $MgSO_4$, filtered off and evaporated under vacuum. The crude product was triturated with hexane (15 mL) and Et_2O (2 mL) and the precipitated product was filtered off, washed with hexane (10 mL) and Et_2O (2 mL). The corresponding methyl 2-(2-chloro-*N*-phenethylacetamido)-2-(1*H*-indol-3-yl)acetate (**26da**) was obtained as white solid (1.06 g, 80%). m.p = 142-144 °C. HRMS (HESI): m/z $[M+H]^+$ calculated for $C_{21}H_{21}ClN_2O_3$ (385.13190), found 385.13164. **26da** (384.86 mg; 1 mmol) was dissolved in THF (5 ml) and NaH (88 mg; 2.2 mmol; 60 % dispersion in mineral oil) was added and reaction mixture was stirred at RT for 10 minutes. The reaction was quenched by diluting with $NaHCO_3$ (0.5 ml) and DCM (20 mL), dried over $MgSO_4$, filtered off and evaporated under vacuum. The crude product was purified by flash chromatography (DCM 100 %). The corresponding 3-(1*H*-indol-3-yl)-1-phenethyl-1*H*-pyrrole-2,5-dione (**28da**) was obtained as yellow crystalline solid (250 mg, 79 %) m.p = 139-142 °C. ^{1}H NMR (DMSO) δ 12.05 (bs, 1H), 8.37 (s, 1H), 7.96 (d, *J* = 7.4 Hz, 1H), 7.53 (d, *J* = 7.4 Hz, 1H), 7.34 – 7.06 (m, 7H), 6.84 (s, 1H), 3.70 (t, *J* = 7.3 Hz, 2H), 2.88 (t, *J* = 7.3 Hz, 2H). ^{13}C NMR (DMSO) δ 171.7, 171.3, 138.8, 138.4, 136.7, 131.1, 128.7, 128.4, 126.4, 125.5, 123.1, 121.5, 120.4, 113.9, 112.6, 105.4, 38.5, 33.9. HRMS (HESI): m/z $[M+H]^+$ calculated for $C_{20}H_{16}N_2O_2$ (317.12900), found 317.12816.

1-Allyl-3-(1*H*-indol-3-yl)-1*H*-pyrrole-2,5-dione (28ea). Following the analogy as for **28ba**, substrate **26ea** (352.85 mg; 1.1 mmol) delivered compound **28ea** and the crude product was purified by flash chromatography (DCM 100 %). The corresponding 1-allyl-3-(1*H*-indol-3-yl)-1*H*-pyrrole-2,5-dione (**28ea**) was obtained as yellow crystalline solid (196.5 mg, 73 %) m.p = 154-155 °C. ^{1}H NMR (DMSO) δ = 12.06 (bs, 1H), 8.40 (d, *J* = 2.6 Hz, 1H), 8.00 (d, *J* = 7.5 Hz, 1H), 7.53 (d, *J* = 7.5 Hz, 1H), 7.35 – 7.09 (m, 2H), 6.93 (s, 1H), 5.92 – 5.78 (m, 1H), 5.17 – 5.04 (m, 2H), 4.12 – 4.06 (m, 2H). ^{13}C NMR (DMSO) δ = 171.4, 171.1, 138.9, 136.7, 132.9, 131.2, 125.5, 123.1, 121.5, 120.4, 116.0, 113.9, 112.6, 105.5, 39.2. HRMS (HESI): m/z $[M+H]^+$ calculated for $C_{15}H_{12}N_2O_2$ (253.09770), found 253.09721.

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[1] a) M. Bandini, A. Eichholzer, *Angew. Chem. Int. Ed.* **2009**, *48*, 9608–9644; b) M. Ishikura, T. Abe, T. Choshi, S. Hibino, *Nat. Prod. Rep.* **2013**, *30*, 694–752; c) H. Gao, Q.-L. Xu, M. Yousufuddin, D. H. Ess, L. Kürti, *Angew. Chem. Int. Ed.* **2014**, *53*, 2701–2705 and the references cited therein.

[2] a) H. J. Knölker, K. R. Reddy, *Chem. Rev.* **2002**, *102*, 4303–4427; b) A. W. Schmidt, K. R. Reddy, H.-J. Knölker, *Chem. Rev.* **2012**, *112*, 3193–3328; c) J. Bariwal, L. G. Voskressensky, E. V. Van der Eycken, *Chem. Soc. Rev*. **2018**, *47*, 3831–3848.

[3] a) M. E. Welsch, S. A. Snyder, B. R. Stockwell, *Curr. Opin. Chem. Biol.* **2010**, *14*, 347–361; b) C.-X. Zhuo, W. Zhang, S.-L. You, *Angew. Chem. Int. Ed.* **2012**, *51*, 12662–12686; c) C. Zheng, S.-L. You, *Nat. Prod. Rep.* **2019**, https://doi. 10.1039/c8np00098k.

[4] For interesting examples, see: a) P. D. Davis, C. H. Hill, E. Keech, G. Lawton, J. S. Nixon, A. D. Sedgwick, J. Wadsworth, D. Westmacott, S. E. Wilkinson, *FEBS Lett.* **1989**, *259*, 61–63; b) G. W. Gribble, S. J. Berthel, in *Studies in Natural Product Chemistry* (Ed.: Atta-ur-Rahman), Elsevier, Amsterdam, **1993**, vol. 12, pp. 365–409; c) M. Gaßel, C. B. Breitenlechner, N. König, H. Huber, R. A. Engh, D. Bossemeyer, *J. Biol. Chem.* **2004**, *279*, 23679–23690 ; d) L. Bouissane, J. P. Sestelo, L. A. Sarandeses, *Org. Lett.* **2009**, *11*, 1285–1288; e) Y.-L. An, Z.-H. Yang, H.-H. Zhang, S.-Y. Zhao, *Org. Lett.* **2016**, *18*, 152–155.

[5] a) K. Dodo, M. Katoh, T. Shimizu, M. Takahashi, M. Sodeoka, *Bioorg. Med. Chem. Lett.* **2005**, *15*, 3114–3118; b) S. Mahboobi, E. Eichhorn, A. Popp, A. Sellmer, S. Elz, U. Möllmann, *Eur.J. Med. Chem.* **2006**, *41*, 176–191; c) C. Peifer, T. Stoiber, E. Unger, F. Totzke, C. Schächtele, D. Marmé, R. Brenk, G. Klebe, D. Schollmeyer, G. Dannhardt, *J. Med. Chem.* **2006,** *49,* 1271–1281; d) D. E. Levy, D.-X. Wang, Q. Lu, Z. Chen, J. Perumattam, Y.-J. Xu, A. Liclican, J. Higaki, H. Dong, M. Laney, B. Mavunkel, S. Dugar, *Bioorg. Med. Chem. Lett.* **2008**, *18*, 2390–2394; e) M. E. McDonnell, H. Bian, J. Wrobel, G. R. Smith, S. Liang, H. Ma, A. B. Reitz, *Bioorg. Med. Chem. Lett.* **2014**, *24*, 1116–1121; f) E. Pereira, A. Youssef, M. El-Ghozzi, D. Avignant, J. Bain, M. Prudhomme, F. Anizon, P. Moreau, *Tetrahedron Lett.* **2014**, *55*, 834-–837.

[6] a) M. F. Denning, Y. Wang, B. J. Nickoloff, T. Wrone-Smith, *J. Biol. Chem.* **1998**, *273*, 29995–30002; b) A. Basu, *Mol. Pharmacol.* **1998**, *53*, 105–111; c) D. Brehmer, K. Godl, B. Zech, J. Wissing, H. Daub, *Mol. Cell. Proteomics* **2004**, *3*, 490–500; d) G. Szanda, P. Koncz, A. Rajki, A. Spät, *Cell Calcium* **2008**, *43*, 250–259.

[7] a) G. H. Zhu, B. C. Y. Wong, M. C. Eggo, S. T. Yuen, K. C. Lai, S. K. Lam, *Dig. Dis. Sci.* **1999**, *44*, 2020–2026; b) Z. Han, P. Pantazis, T. S. Lange, J. H. Wyche, E. A. Hendrickson, *Cell Death Differ.* **2000**, *7*, 521–530; c) R. T. Snowden, X. M. Sun, M. J. S. Dyer, G. M. Cohen, *Leukemia* **2003**, *17*, 1981–1989; d) B. Pajak, A. Turowska, A. Orzechowski, B. Gajkowska, *Apoptosis* **2008**, *13*, 509–522.

[8] a) C.-W. Chiu, T. J. Chow, C.-H. Chuen, H.-M. Lin, Y.-T. Tao, *Chem. Mater.* **2003**, *15,* 4527–4532; b) M. Nakazono, S. Nanbu, A. Uesaki, R. Kuwano, M. Kashiwabara, K. Zaitsu, *Org. Lett.* **2007**, *9*, 3583–3586; c)

M. Nakazono, A. Jinguji, S. Nanbu, R. Kuwano, Z. Zheng, K. Saita, Y. Oshikawa, Y. Mikuni, T. Murakami, Y. Zhao, S. Sasaki, K. Zaitsu, *Phys. Chem. Chem. Phys.* **2010**, *12*, 9783–9793; d) Y. S. Lee, Z. Lin, Y. Y. Chen, C. Y. Liu, T. J. Chow, *Org. Electron.* **2010**, *11*, 604–612; e) A. C. Schmöle, A. Brennführer, G. Karapetyan, R. Jaster, A. Pews-Davtyan, R. Hübner, S. Ortinau, M. Beller, A. Rolfs, M. J. Frech, *Bioorg. Med. Chem.* **2010**, *18*, 6785–6795.

[9] a) M. Johannsen, *Chem. Commun.* **1999**, 2233–2234; b) M. J. Wanner, P. Hauwert, H. E. Schoemaker, R. D. de Gelder, J. H. Van Maarseveen, H. Hiemstra, *Eur. J. Org. Chem.* **2008**, 180–185; c) H. Ube, S. Fukuchi, M. Terada, *Tetrahedron: Asymmetry* **2010**, *21*, 1203–1205; d) X.-W. Wang, Y.-Z. Hua, M.-C. Wang, *J. Org. Chem.* **2016**, *81*, 9227–9234; e) B. Jiang, Z.-G. Huang, *Synthesis* **2005**, 2198–2204; f) T. Andreassen, L. K. Hansen, O. R. Gautun, *Eur. J. Org. Chem.* **2008**, 4871–4876; g) D.-U. Ji, M.-H. Xu, *Chem. Commun.* **2010**, *46*, 1550–1552; h) K. Goswami, I. Duttagupta, S. Sinha, *J. Org. Chem.* **2012**, *77*, 7081–7085.

[10] M. L. Murat-Onana, C. Berini, J.-N. Denis, J.-F. Poisson, F. Minassian, N. Pelloux- Léon, *Eur. J. Org. Chem.* **2014**, 3773–3776.

[11] D. Lin, J. Wang, X. Zhang, S. Zhou, J. Lian, H. Jiang, H. Liu, *Chem. Commun.* **2013**, *49*, 2575–2577.

[12] a) A. Janczuk, W. Zhang, W. Xie, S. Lou, J.-P. Cheng, P. G. Wang, *Tetrahedron Lett.* **2002**, *43*, 4271–4274; b) N. Sakai, J. Asano, Y. Shimano, T. Konakahara, *Tetrahedron* **2008**, *64*, 9208–9215; c) K. Goswami, I. Duttagupta, S. Sinha, *J. Org. Chem.* **2012**, *77*, 7081–7085; d) Z. Xu, X. Yu, X. Feng, M. Bao, *Beilstein J. Org. Chem.* **2012,** *8,* 1564–1568; e) Li, J.-T.; Sun, S.-F.; Sun, M.-X. *Ultrason. Sonochem.* **2011**, *18*, 42-44; f) Xie, L.-H.; Cheng, J.; Luo, Z.-W.; Lu, G. *Tetrahedron Lett.*, **2018**, *59*, 457-461.

[13] For Mannich's 3CR type in this area, see: a) M. Ghandi, A. Taheri, *Molecules* **2009**, *14*, 1056–1061; b) B. Jiang, C.-G. Yang, H.-H. Gu, *Tetrahedron Lett.* **2001**, *42*, 2545-–2547; c) Q. Kang, Z.-A. Zhao, S.-L. You, *Tetrahedron* **2009**, *65*, 1603–1607.

[14] A. Kolarovič, D. Berkeš, P. Baran, F. Považanec, *Tetrahedron Lett.* **2005**, *46*, 975–978 and the refrences cited therein.

[15] D. Enders, M. Seppelt, T. Beck, *Adv. Synth. Catal.* **2010,** *352*, 1413–1418.

[16] N. Singh, R. D. Anand, S. Trehan, *Tetrahedron Lett.* **2004,** *45*, 2911–2913.

[17] Crystal Data for $C_{19}H_{22}N_2O_3$ (**12a·MeOH**) (*M* =326.40 g/mol): monoclinic, space group $P2_1$ (no. 4), a = 11.1461(2) Å, b = 6.29540(10) Å, c = 12.2120(2) Å, β = 101.096(2)°, *V* = 840.89(3) Å^3, *Z* = 2, *T* = 100 K, μ(Cu Kα) = 0.709 mm^{-1}, D_{calc} = 1.289 g/cm^3, 34703 reflections measured (7.38° ≤ 2Θ ≤ 143.04°), 2897 unique (R_{int} = 0.0135, R_{sigma} = 0.0051) which were used in all calculations. The final R_1 was 0.0315 (I>2.0σ(I)) and wR_2 was 0.0810 (all data). CCDC no. 1912329.

[18] Crystal Data for $C_{20}H_{24}N_2O_3$ (**14·MeOH**) (*M* =340.41 g/mol): orthorhombic, space group $P2_12_12_1$ (no. 19), a = 8.5965(3) Å, b = 10.2518(2) Å, c = 21.7025(5) Å, *V* = 1912.8963(9) Å^3, *Z* = 4, *T* = 295 K, μ(Cu Kα) = 0.642 mm^{-1}, D_{calc} = 1.182 g/cm^3, 107332 reflections measured (8.148° ≤ 2Θ ≤ 143.238°), 3713 unique (R_{int} = 0.0269, R_{sigma} = 0.0108) which were used in all calculations. The final R_1 was 0.0325 (I>2.0σ(I)) and wR_2 was 0.0905 (all data). CCDC no. 1912330.

[19] See for example, see: C. Cheng, J. Sun, L. Xing, J. Xu, X. Wang, Y. Hu, *J. Org. Chem.* **2009**, *74*, 5671–5674 and the references cited therein.

[20] a) S. Ram, L. D. Spicer, *Tetrahedron Lett.* **1987**, *28*, 515–516; b) M. J. Tike, V. V. Mahajani, *Chem. Eng. J.*, **2006**, *123*, 31–41; c) S. N. Narendra Babu, G. R. Srinivasa, D. C. Santhosh, D. Channe Gowda, *J. Chem. Res.* **2004**, 66-67.

[21] For recent review on spirocyclization, see: J. Bariwal, L. G. Voskressensky, E. V. Van der Eycken, *Chem. Soc. Rev.* **2018**, 47, 3831–3848.

[22] For example, see: S. Lakhdar, M. Westermaier, F. Terrier, R. Goumont, T. Boubaker, A. R. Ofial, H. Mayr, *J. Org. Chem.* **2006**, *71*, 9088–9095.

[23] For general review on spiro-oxindole compounds, see: a) A. Ding, M. Meazza, H. Guo, J. W. Yang, R. Rios, *Chem. Soc. Rev.* **2018**, *47*, 5946–5996; b) M. J. James, P. O'Brien, R. J. K. Taylor, W. P. Unsworth, *Chem. Eur. J.* **2016**, *22*, 2856–2881; c) J. M. Smith, J. Moreno, B. W. Boal, N. K. Garg, *Angew. Chem. Int. Ed.* **2015**, *54*, 400–412; d) C. Tsukano, Y. Takemoto, *Heterocycles* **2014**, *89*, 2271–2302; e) E. M. Carreira, T. C. Fessard, *Chem. Rev.* **2014**, *114*, 8257–8322.

[24] For recent examples, see: a) A. K. Gupta, M. Bharadwaj, A. Kumar, R. Mehrotra, *Top. Curr. Chem.* **2017**, *375*, 3. https://doi.org/10.1007/s41061-016-0089-0; b) C. Sheng, G. Dong, Z. Miao, W. Zhang, W. Wang, *Chem. Soc. Rev.* **2015**, *44*, 8238–8259.

[25] W. Chen, X.-D. Yang, W.-Y. Tan, X.-Y. Zhang, X.-L. Liao, H. Zhang, *Angew. Chem. Int. Ed.* **2017**, *56*, 12327–12331.

[26] a) C. N. Teijaro, S. Zhao, P. Kokkonda, R. B. Andrade, *Org. Lett.* **2015**, *47*, 1547–1556; b) G. Sirasani, R. B. Andrade, *Org. Lett.* **2011**, *13*, 4736–4737; c) G. Sirasani, T. Paul, W. Jr. Dougherty, S. Kassel, R. B. Andrade, *J. Org. Chem.* **2010**, *75*, 3529–3532; d) G. Sirasani, R. B. Andrade, *Org. Lett.* **2009**, *11*, 2085–2088.

[27] S. Munagala, G. Sirasani, P. Kokkonda, M. Phadke, N. Krynetskaia, P. Lu, F. J. Sharom, S. Chaudhury, M. D. M. Abdulhameed, G. Tawa, A. Wallqvist, R. Martinez, W. Childers, M. Abou-Gharbia, E. Krynetskiy, R. B. Andrade, *Bioorg. Med. Chem.* **2014**, *22*, 1148–1155.

[28] M. Šoral, J. Markus, J. Doháňošová, S. Šoralová, D. Dvoranová, A. Chyba, J. Moncol, D. Berkeš, T. Liptaj, *J. Mol. Struct.* **2017**, *1128*, 230–238.

[29] Crystal Data for $C_{13}H_{14}N_2O_2$ (**25b**) (*M* =230.26 g/mol): monoclinic, space group $P2_1/c$ (no. 14), a = 11.2021(4) Å, b = 7.1357(3) Å, c = 13.7312(6) Å, β = 99.688(3)°, *V* = 1081.95(8) Å^3, *Z* = 4, *T* = 100 K, μ(Cu Kα) = 0.788 mm^{-1}, D_{calc} = 1.414 g/cm^3, 14722 reflections measured (8.006° ≤ 2Θ ≤ 143.356°), 2079 unique (R_{int} = 0.0597, R_{sigma} = 0.0538) which were used in all calculations. The final R_1 was 0.0401 (I>2.0σ(I)) and wR_2 was 0.0965 (all data). CCDC no. 1912331.

[30] For recent review, see: T. Janosik, A. Rannug, U. Rannug, N. Wahlström, J. Slätt, J. Bergman, *Chem. Rev.* **2018**, *118*, 9058–9128.

[31] G. Gerona-Navarro, M. A. Bonache, R. Herranz, M. T. García-López, R. González-Muñiz, *Synlett* **2000**, *9*, 1249–1252.

[32] a) L. Palatinus, G. Chapuis, *J. Appl. Crystallogr.* **2007**, *40*, 786–790; b) G. M. Sheldrick, *Acta Crystallogr.* **2015**, *A71*, 3–8.

[33] a) P. W. Betteridge, J. R. Carruthers, R. I. Copper, K. Prout, D. Watkin, J. *J. Appl. Crystallogr.* **2003**, *36*, 1487–1487; b) G. M. Sheldrick, *Acta Crystallogr.* **2015**, *C71*, 3-8.

[34] O. Dolomanov, L. J. Bourhis, R. I. Gildea, J. A. K. Howard, *J. Appl. Crystallogr.* **2009**, *42*, 339–341.

[35] a) R. W. W. Hooft, L. H. Straver, A. L. Spek, *J. Appl. Crystallogr.* **2008**, *41*, 96–103; b) R. I. Cooper, D. J. Watkin, H. D. Flack, *Acta Crystallogr.* **2016**, *C72*, 261–267; c) S. Parsons, H. D. Flack, T. Wagner, *Acta Crystallogr.* **2013**, *B69*, 249–259.

[36] J. Bergman, E. Desarbre, E. Koch, *Tetrahedron* **1999**, *55*, 2363–2370.

[37] D. S. Cochin, M. I. Tranchepain, *Org. Biomol. Chem.* **2009**, *7*, 706–716.

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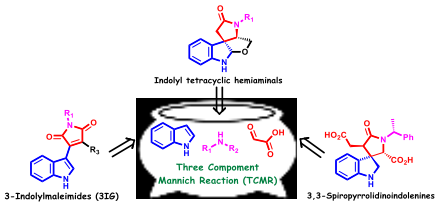

A series of racemic and enantiopure 3-indolylglycines (3IGs), in high yields and optical purity were reported *via* the simple and efficacious Mannich's 3CR of indole, free glyoxylic acid and primary or secondary aliphatic amines. A multigram synthesis using (*R*)-PEA as chiral auxiliary was realized and the resulting 3IGs were used to provide enantiopure 3,3-spiroindolenines, indolyl tetracyclic hemiaminals and 3-indolylmaleimides in an unexpected pathway.

Spiroindolenine Systems

J. Markus, B. Ferko, D. Berkeš, J. Moncol, A. M. Lawson, M. Othman, and A. Daïch**

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Indolylglycines backbones in the synthesis of enantiopure 3,3-spiroindolenines, indolyl tetracyclic hemiaminals and 3-indolyl-maleimides frameworks