Model Construction for the A – B – C Ring System of Lysergic Acid *via* *Vilsmeier – Haack*-Type Cyclization of 1*H*-Indole-4-propanoic Acid Derivatives

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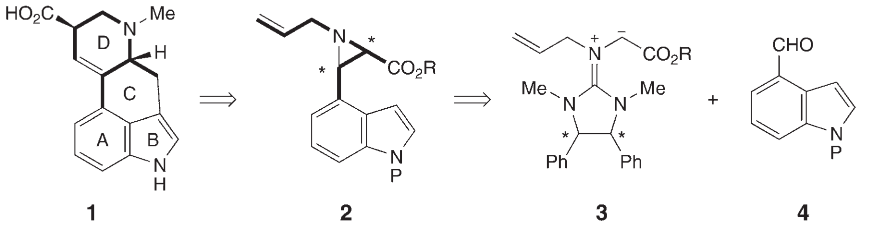
Vilsmeier – Haack-type cyclization of 1*H*-indole-4-propanoic acid derivatives was examined as model construction for the A – B – C ring system of lysergic acid (**1**). Smooth cyclization from the 4 position of 1*H*-indole to the 3 position was achieved by *Vilsmeier – Haack* reaction in the presence of K_2CO_3 in MeCN, and the best substrate was found to be the *N*,*N*-dimethylcarboxamide **9** (*Table 1*). The modified method can be successfully applied to an α-amino acid derivative protected with an *N*-acetyl function, *i.e.*, to **27** (*Table 2*); however, loss of optical purity was observed in the cyclization when a chiral substrate (*S*)-**27** was used (*Scheme 5*). On the other hand, the intramolecular *Pummerer* reaction of the corresponding sulfoxide **20** afforded an S-containing tricyclic system **22**, which was formed by a cyclization to the 5 position (*Scheme 3*).

1. Introduction. – Lysergic acid (**1**), a tetracyclic indole derivative with two stereogenic centers, is the core unit of ergot alkaloids showing wide spectra of biological activities [1] such as prolactin inhibition, anti-*Parkinsonian* effect, and depression of hypertension. The total synthesis of racemic **1** has been reported by nine research groups [2], and two groups have successfully achieved the asymmetric synthesis [3].

Recently, we have explored a novel aziridination from guanidinium ylides and aromatic (or unsaturated) aldehydes, applicable to asymmetric synthesis [4], and designed the atom-economical synthesis of bioactive N-containing compounds using the formed aziridine as a key synthetic intermediate. Our *retro*-synthetic strategy of lysergic acid (**1**) is shown in *Scheme 1*, in which all the C- and the N-units of the aziridine **2**, derived from guanidinium ylide **3** and 1*H*-indole-4-carboxaldehyde **4**, are incorporated in the lysergic acid structure during the synthesis. One of the key reactions is the construction of ring C *via* cyclization from the 4 position of the 1*H*-indole skeleton **2** to its 3-position. Such cyclizations had already been examined by four groups [2i][5], among which *Nedelec* and *Raincy* [5a] reported the application of the *Vilsmeier – Haack* reaction to 1*H*-indole-4-propanamide in their patent. Thus, we extensively examined the cyclization based on their methodology and, in this paper, describe experimental results obtained by using varieties of 1*H*-indole-4-propanoic acid derivatives.

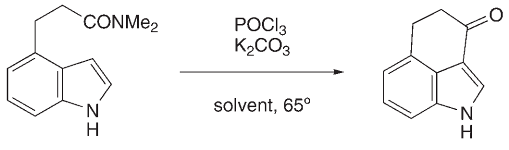
2. Results and Discussion. – 2.1. *Cyclizations with 1*H*-Indole-4-propanamides.* First we tried to trace the *Vilsmeier – Haack* reaction of *N*,*N*-dimethyl-1*H*-indole-4-

Scheme 1. retro-*Synthesis of Lysergic Acid* (**1**) *with Aziridine Derivative* **2** *as Key Intermediate*



propanamide (**9**) under the conditions reported in [5a]. The needed *N*,*N*-dimethylpropanamide **9** was prepared from the known *N*-Boc-1*H*-indole-4-carboxaldehyde **5** (Boc = (*tert*-butoxy)carbonyl) [6] in four steps *via* **6b**, **7b**, and **8** (*Scheme 2*) and subjected to the cyclization reaction with phosphoric trichloride ($POCl_3$) in THF at 65° for 6 h to give the desired product **10** in 38% yield (*Entry 1*, *Table 1*). Although no improvement was observed when $CHCl_3$ was used as solvent in place of THF (*Entry 2*), the use of MeCN resulted in the formation of **10** not only in higher yield but also with shorter reaction time (*Entry 3*). Some time ago, we have reported the efficiency of K_2CO_3 as an additive in the intramolecular *Friedel–Crafts* reaction of 2,4-diarylbutanoic acids using $POCl_3$ to give 2-aryl-3,4-dihydronaphthalen-1(2*H*)-one derivatives [7]. In the *Vilsmeier–Haack* reaction with **9**, addition of K_2CO_3 is also effective (*Entries 4–6*), and the best yield (74%) was achieved under the conditions shown in *Entry 5*.

Table 1. Vilsmeier–Haack *Reaction of* N,N-*Dimethyl-1*H-*indole-4-propanamide* (**9**)



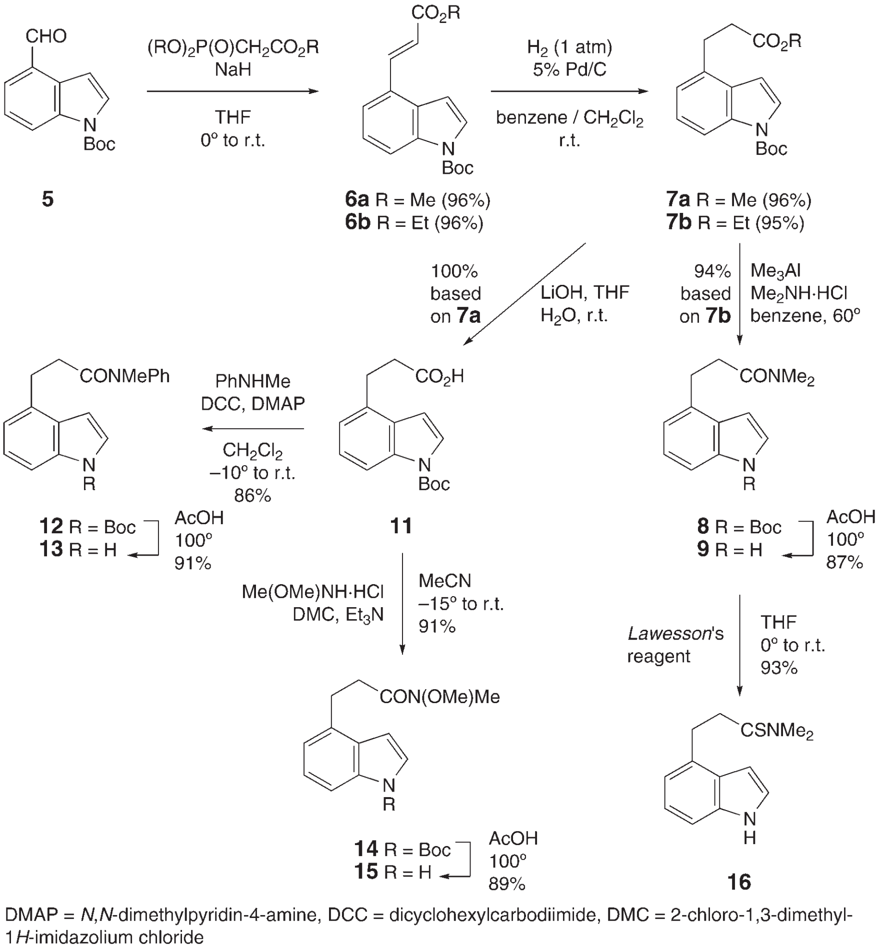
9 **10**

Entry	Solvent	$POCl_3$ [mol]	K_2CO_3 [mol]	Time [h]	Yield[a]) [%] of **10**
1	THF	6.3	none	6	38
2	$CHCl_3$	6.4	none	2	40
3	MeCN	6.3	none	2	58
4	MeCN	6.2	2.5	2	56
5	MeCN	3.6	2.7	3	74
6	MeCN	3.8	3.8	4	64

[a]) Non-optimized yield of isolated material.

Further trials for the *Vilsmeier–Haack* reaction by using different kinds of carboxamides, *i.e.*, *N*-methyl-*N*-phenyl-1*H*-indole-4-propanamide (**13**), *N*-methoxy-*N*-methyl-1*H*-indole-4-propanamide (**15**), and *N*,*N*-dimethyl-1*H*-indole-4-propanethioamide (**16**), which were prepared as shown in *Scheme 2* from **7a** *via* **11** and **12**, *via* **11** and **14**, and from **7b** *via* **8** and **9**, respectively, only resulted in the formation of complex mixtures.

Scheme 2. *Preparation of 1*H*-Indole-4-propanamides for the* Vilsmeier–Haack *Reaction*

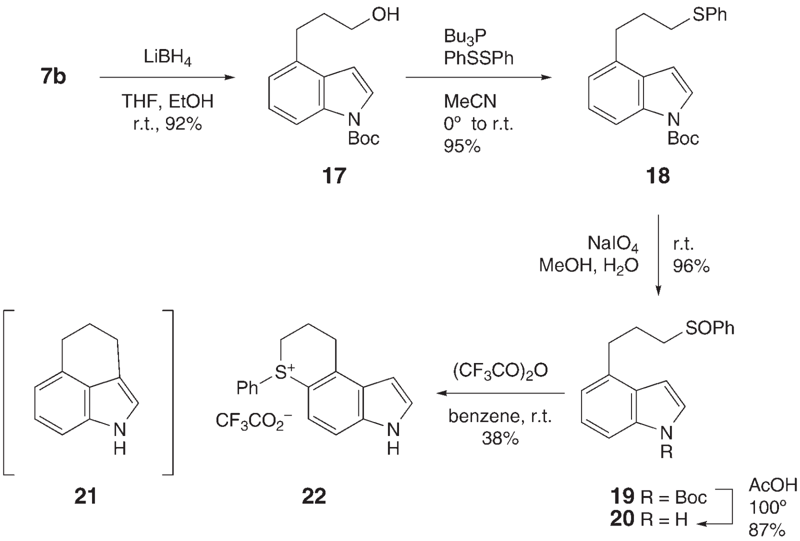


DMAP = *N*,*N*-dimethylpyridin-4-amine, DCC = dicyclohexylcarbodiimide, DMC = 2-chloro-1,3-dimethyl-1*H*-imidazolium chloride

Sano and co-workers [8] reported the acid-mediated cyclization of 2-(benzylamino)ethyl phenyl sulfoxide for the construction of the isoquinoline skeleton. Thus, we prepared the 3-(1*H*-indol-4-yl)propyl phenyl sulfoxide (**20**) from ethyl 1-Boc-1*H*-indole-4-propanoate **7b** in four steps *via* **17**–**19** and subjected it to a *Pummerer*-type cyclization under the reported conditions [8], with the objective to obtain the tricyclic compound **21** (*Scheme 3*). Although a reaction occurred, the product obtained was an S-containing tricyclic system **22**, which was formed in 38% yield by a cyclization to the 5 position of the 1*H*-indole skeleton. Comparable results dependent upon the substrates used were observed in the cyclization of other 4-substituted 1*H*-indoles.

2.2. *Cyclizations with α-Amino-*N,N*-dimethyl-1*H*-indole-4-propanamides.* Next, the *Vilsmeier–Haack* reaction was applied to α-amino-*N*,*N*-dimethyl-1*H*-indole-4-propanamides with different kinds of *N*-protecting groups. The desired propanamides **27**

Scheme 3. *Preparation of 3-(1*H*-Indol-4-yl)propyl Phenyl Sulfoxide* (**20**) *and a Trial for a* Pummerer-*type Cyclization*

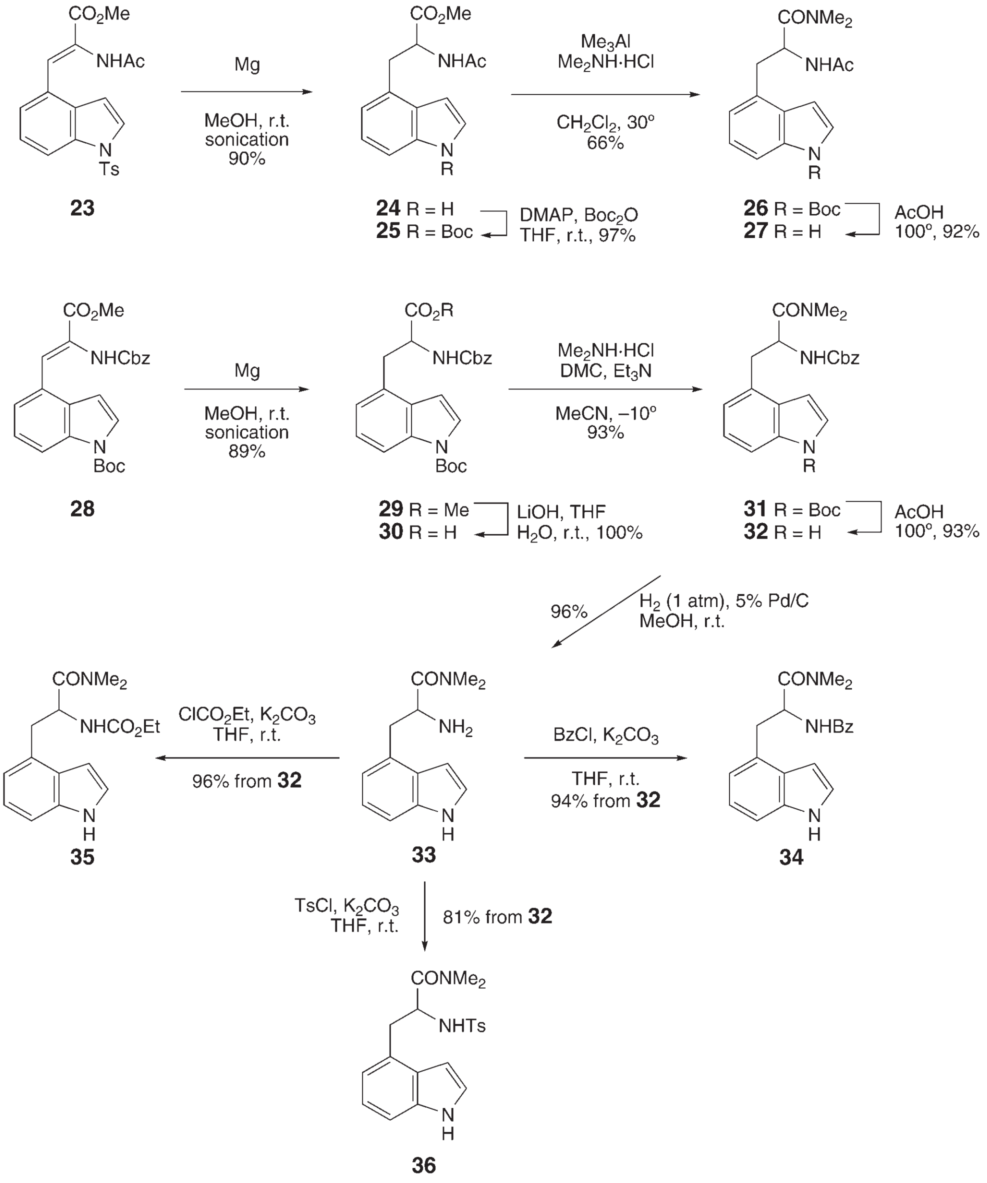


and **32**–**36** were prepared from the known methyl (2*Z*)-2-(acetylamino)-3-(1-tosyl-1*H*-indol-4-yl)prop-2-enoate (**23**) [9] *via* **24**–**26** and from the known methyl (2*Z*)-2-(Cbz-amino)-3-(1-Boc-1*H*-indol-4-yl)prop-2-enoate **28** [6] *via* **29**–**31**, as shown in *Scheme 4*. These propanamides were treated under the optimized *Vilsmeier*–*Haack* reaction conditions mentioned above (*Table 2*).

The desired *Vilsmeier*–*Haack* cyclization gave the amino ketone **37** (R = Ac) in 34% yield by using the (acetylamino)derivative **27** as a starting material (*Entry 1*, *Table 2*). Simple *N*-phosphorylation occurred when *N*-unprotected carboxamide **33** was used (*Entry 3*). However, replacement of the (acetylamino) by the (benzoylamino) group prevented the cyclization and, instead, hydrolysis of the carboxamide function occurred (*Entry 4*). The (ethoxycarbonyl)-protected **35** led to the cyclized product in 11% yield (*Entry 5*), whereas the reactions with the (benzyloxy)carbonylated and the tosylated derivatives **32** and **36**, respectively, resulted in the formation of a complex mixture (*Entries 2* and *6*).

Thus, as the desired cyclization was observed in the *Vilsmeier*–*Haack* reaction of α-(acetylamino)-*N*,*N*-dimethyl-1*H*-indole-4-propanamide (**27**), although not satisfactorily, we attempted to carry out the reaction with the corresponding optically active substrate. (2*S*)-Methyl 2-(Cbz-amino)-3-(1-Boc-1*H*-indol-4-yl)propanoate (*S*)-**29** with 99% ee was prepared by asymmetric hydrogenation of the *Wittig*–*Horner*–*Emmons* reaction product **28** according to the reported method [6]. Successive alkaline hydrolysis (→(*S*)-**30**), 2-chloro-1,3-dimethyl-1*H*-imidazolium chloride (DMC)-assisted amidation [10] with Me$_2$NH (→(*S*)-**31**), deprotection of the 1*H*-indole N-atom (→(*S*)-**32**), and displacement of the Cbz by the Ac function under reductive conditions afforded (*S*)-**27** in a total yield of 70% (*Scheme 5*). The high retention of optical activity during the reaction sequence was confirmed by the formation of 2-(Cbz-

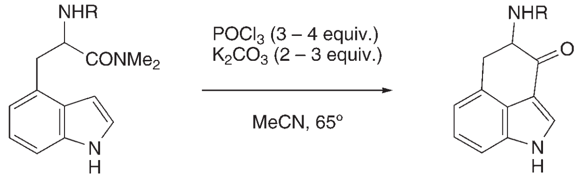
Scheme 4. *Preparation of Different 2-Amino-*N,N*-dimethyl-1*H*-indole-4-propanamides*



DMAP = *N,N*-dimethylpyridin-4-amine, DMC = 2-chloro-1,3-dimethyl-1*H*-imidazolium chloride

amino)-*N,N*-dimethyl-1*H*-indole-4-propanamide (*S*)-**32** with 99% ee. Unfortunately, racemization of (*S*)-**27** occurred in the *Vilsmeier–Haack* reaction to give the cyclized product (*S*)-**37** with only 4% ee.

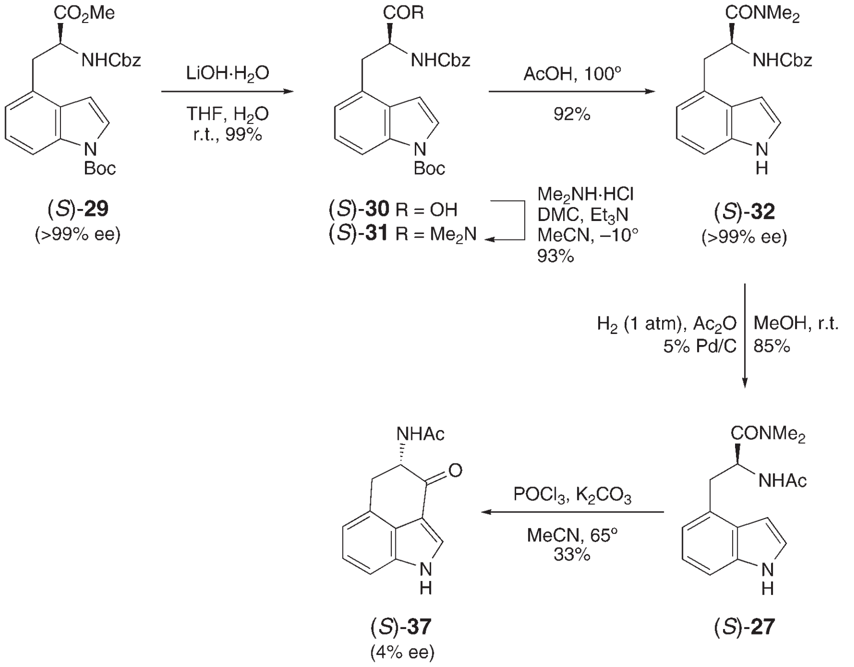
Table 2. Vilsmeier–Haack *Reaction of Different α-Amino-*N,N*-dimethyl-1*H*-indole-4-propanamides* **27** *and* **32**–**36**



27, **32** – **36** **37**

Entry	Substrate (R)	Time [h]	Results
1	**27** (Ac)	1	**37** (R = Ac) (34%)
2	**32** (Cbz)	3	complex mixture
3	**33** (H)	3	*N*-phosphorylation (44%)
4	**34** (Bz)	4	*C*-hydrolysis (36%)
5	**35** (CO_2Et)	4	**37** (R = CO_2Et) (11%)
6	**36** (Ts)	6	complex mixture

Scheme 5. *Preparation of Optically Active (α*S*)-α-(Acetylamino)-*N,N*-dimethyl-1*H*-indole-4-propanamide ((*S*)-**27**) and Subsequent* Vilsmeier–Haack *Reaction*



DMC = 2-chloro-1,3-dimethyl-1*H*-imidazolium chloride

3. Conclusions. – In summary, smooth cyclization from the 4 position of 1*H*-indole to the 3 position was achieved by the *Vilsmeier–Haack* reaction of *N,N*-dimethyl-1*H*-indole-4-propanamide (**9**) in the presence of K_2CO_3 in MeCN. The optimized conditions can be successfully applied to the α-amino acid derivative **27** *N*-protected by an acetyl function; however, the loss of optical purity was observed in the cyclization when the enantiomerically pure substrate (*S*)-**27** was used. On the other hand, the intramolecular *Pummerer* reaction of the corresponding sulfoxide **20** afforded a cyclized product at the 5 position but not at the 3 position.

Experimental Part

General. Anh. THF and CH_2Cl_2 were purchased from *Wako* and *Kanto Chemicals*, resp. DMF, Et_3N, MeCN, benzene, and EtOH were distilled from CaH_2. MeOH was distilled from Mg turnings. Org. solns. obtained by extraction were dried over Na_2SO_4. Column chromatography (CC): silica gel *60* (spherical, 70–230 mesh) from *Kanto Chemicals.* M.p.: *Yanaco MP-S3* apparatus; uncorrected. $[\alpha]_D$: *Jasco P-1020.* IR Spectra: *Jasco FT/IR-300E* spectrophotometer; ATR = attenuated total reflexion; in cm^{-1}. NMR Spectra: $CDCl_3$ soln.; *Jeol JNM-ECP-400* (400 (^1H) and 100 (^{13}C) MHz) or *ALPHA-500* (500 (^1H) and 125 (^{13}C) MHz) instrument; $SiMe_4$ as an internal standard for ^1H, unless otherwise stated, and central resonance of $CDCl_3$ (δ 77.0) as an internal standard for ^{13}C; δ in ppm, *J* in Hz. MS: *Jeol GC*-Mate spectrometer with direct inlet for EI; *Jeol JMS-HX-110A* spectrometer with 3-nitrobenzyl alcohol as a matrix for HR-FAB; in *m/z* (rel. %).

*Methyl (2*E*)-3-{1-[(*tert*-Butoxy)carbonyl]-1*H*-indol-4-yl}prop-2-enoate* (**6a**). To a suspension of NaH (60%; 139 mg, 1.56 mmol) in dry THF (8 ml) under Ar was added dropwise methyl (dimethoxyphosphinyl)acetate (0.52 ml, 3.61 mmol) at 0°, and the mixture was stirred at r.t. for 1 h. Then, a soln. of **5** (519 mg, 2.12 mmol) in dry THF (8 ml) was added dropwise at 0°, the mixture was stirred at r.t. for 3 h, and the reaction was quenched with sat. aq. NH_4Cl soln. (3.5 ml). After the precipitate was dissolved in H_2O (4 ml), the mixture was stirred at r.t. for 10 min and extracted with hexane/AcOEt 2:1 (3 × 20 ml). The combined extract was washed with sat. aq. $NaHCO_3$ soln. (10 ml) and brine (12 ml), dried, and concentrated and the residue purified by CC (hexane/AcOEt 24:1 to 18:1): **6a** (615 mg, 96%). Colorless prisms. M.p. 103.5–104°. IR (ATR): 1722, 1703 (CO). ^1H-NMR (400 MHz): 1.68 (*s*, Me_3C); 3.84 (*s*, MeO); 6.57 (*d*, $J = 16.1$, H–C(2)); 6.85 (*d*, $J = 3.7$, arom. H); 7.33 (*dd*, $J = 8.0, 8.0$, arom. H); 7.50 (*d*, $J = 8.0$, arom. H); 7.69 (*d*, $J = 3.7$, arom. H); 8.07 (*d*, $J = 16.1$, H–C(3)); 8.22 (*d*, $J = 8.0$, arom. H). ^{13}C-NMR (125 MHz): 28.2; 51.8; 84.1; 105.1; 117.0; 118.5; 121.4; 124.3; 126.7; 127.1; 130.1; 135.6; 142.1; 149.5; 167.6. EI-MS: 302 (4, $[M + H]^+$), 301 (23, M^+), 245 (84), 201 (64), 170 (47), 115 (32), 57 (100). Anal. calc. for $C_{17}H_{19}NO_4$: C 67.76, H 6.36, N 4.65; found: C 67.66, H 6.32, N 4.54.

*Ethyl (2*E*)-3-{1-[(*tert*-Butoxy)carbonyl]-1*H*-indol-4-yl}prop-2-enoate* (**6b**). As described for **6a**, from **5**: **6b** (96%). Colorless prisms. M.p. 128.5–129°. IR (KBr): 1720, 1698 (CO). ^1H-NMR (400 MHz): 1.36 (*t*, $J = 7.1$, *Me*CH_2); 1.68 (*s*, Me_3C); 4.30 (*q*, $J = 7.1$, Me*C*H_2); 6.57 (*d*, $J = 15.9$, H–C(2)); 6.86 (*d*, $J = 3.7$, arom. H); 7.33 (*dd*, $J = 8.0, 8.0$, arom. H); 7.50 (*d*, $J = 8.0$, arom. H); 7.69 (*d*, $J = 3.7$, arom. H); 8.06 (*d*, $J = 15.9$, H–C(3)); 8.21 (*d*, $J = 8.0$, arom. H). ^{13}C-NMR (100 MHz): 14.4; 28.2; 60.5; 84.1; 105.2; 116.9; 119.0; 121.4; 124.3; 126.8; 127.0; 130.1; 135.7; 141.9; 149.5; 167.2. FAB-MS: 316 ($[M + H]^+$), 315 (M^+). Anal. calc. for $C_{18}H_{21}NO_4$: C 68.55, H 6.71, N 4.44; found: C 68.60, H 6.68, N 4.28.

*Methyl 1-[(*tert*-Butoxy)carbonyl]-1*H*-indole-4-propanoate* (**7a**). A mixture of **6a** (1.525 g, 5.06 mmol) in dry benzene (28 ml) and dry CH_2Cl_2 (14 ml) was hydrogenated over 5% Pd/C (410 mg) under H_2 at r.t. for 50 min. After removal of the catalyst by filteration through a *Celite*® pad followed by washing with AcOEt, the filtrate was evaporated. Purification of the residue by CC (hexane/AcOEt 20:1 to 17:1) afforded **7a** (1.472 g, 96%). Colorless oil. IR (ATR): 1735 (CO). ^1H-NMR (400 MHz): 1.67 (*s*, Me_3C); 2.71 (*t*, $J = 7.9$, $CH_2(\alpha)$); 3.20 (*t*, $J = 7.9$, $CH_2(\beta)$); 3.67 (*s*, MeO); 6.64 (*d*, $J = 3.7$, arom. H); 7.05 (*d*, $J = 7.7$, arom. H); 7.24 (*dd*, $J = 7.7, 7.7$, arom. H); 7.61 (*d*, $J = 3.7$, arom. H); 8.02 (*d*, $J = 7.7$, arom. H). ^{13}C-NMR (125 MHz): 28.2; 35.1; 51.6; 83.7; 105.2; 113.5; 122.0; 124.4; 125.7; 129.6; 132.8; 135.2; 149.8; 173.4. HR-FAB-MS: 303.1473 (M^+, $C_{17}H_{21}NO_4^+$; calc. 303.1471).

*Ethyl 1-[(*tert*-Butoxy)carbonyl]-1*H*-indole-4-propanoate* (**7b**). As described for **7a**, from **6b**: **7b** (95%). Colorless oil. IR (neat): 1735 (CO). ^{1}H-NMR (400 MHz): 1.24 (*t*, $J = 7.1$, *Me*CH$_2$); 1.67 (*s*, Me_3C); 2.69 (*t*, $J = 7.9$, CH$_2$(α)); 3.19 (*t*, $J = 7.9$, CH$_2$(β)); 4.13 (*q*, $J = 7.1$, MeC*H$_2$*); 6.64 (*d*, $J = 3.8$, arom. H); 7.06 (*d*, $J = 8.0$, arom. H); 7.24 (*dd*, $J = 8.0, 8.0$, arom. H); 7.60 (*d*, $J = 3.8$, arom. H); 8.02 (*d*, $J = 8.0$, arom. H). ^{13}C-NMR (100 MHz): 14.2; 28.1; 28.2; 35.3; 60.5; 83.7; 105.2; 113.4; 122.0; 124.4; 125.7; 129.6; 132.8; 135.2; 149.8; 173.0. HR-FAB-MS: 317.1629 (M^+, $C_{18}H_{23}NO_4^+$; calc. 317.1627).

*1-[(*tert*-Butoxy)carbonyl]-*N,N*-dimethyl-1*H*-indole-4-propanamide* (**8**). To a suspension of $Me_2NH \cdot HCl$ (268 mg, 3.29 mmol) in dry benzene (5.5 ml) under Ar was added dropwise at 0° 2M Me_3Al in heptane (1.6 ml, 3.20 mmol), and the mixture was stirred at r.t. for 1 h. Then a soln. of **7b** (504 mg, 1.59 mmol) in dry benzene (7 ml) was added at 0°. The mixture was stirred at 65° for 7 h, and the reaction was quenched with H_2O (8 ml) at 0°. After addition of 10% HCl aq. soln. (2.4 ml), the mixture was extracted with AcOEt (3 × 15 ml), the combined org. extract washed with sat. aq. $NaHCO_3$ soln. (10 ml) and brine (12 ml), dried, and concentrated, and the residue purified by CC (benzene/AcOEt 6 : 1 to 4 : 1): **8** (471 mg, 94%). Colorless oil. IR (neat): 1734, 1653 (CO). ^{1}H-NMR (400 MHz): 1.67 (*s*, Me_3C); 2.68 (*t*, $J = 7.9$, CH$_2$(α)); 2.86, 2.94 (each *s*, MeN); 3.22 (*t*, $J = 7.9$, CH$_2$(β)); 6.66 (*d*, $J = 3.7$, arom. H); 7.07 (*d*, $J = 7.1$, arom. H); 7.24 (*dd*, $J = 7.1, 7.7$, arom. H); 7.60 (*d*, $J = 3.7$, arom. H); 8.03 (*d*, $J = 7.7$, arom. H). ^{13}C-NMR (100 MHz): 28.1; 28.5; 34.4; 35.4; 37.1; 83.6; 105.3; 113.2; 122.1; 124.3; 125.6; 129.6; 133.7; 135.1; 149.7; 172.2. HR-FAB-MS: 317.1872 ($[M + H]^+$, $C_{18}H_{25}N_2O_3^+$; calc. 317.1865).

*N,N-Dimethyl-1*H*-indole-4-propanamide* (**9**). A soln. of **8** (707 mg, 2.23 mmol) in AcOH (29 ml, 507 mmol) was stirred at 100° for 22 h, and the solvent was evaporated. The residue was purified by CC (benzene/AcOEt 4 : 1 to 2 : 1): **9** (420 mg, 87%). Colorless prisms. M.p. 117 – 118° ([5a]: 117 – 118°). IR (ATR): 3208 (NH), 1631 (CO). ^{1}H-NMR (400 MHz, CD$_3$OD): 2.75 (*t*, $J = 7.8$, CH$_2$(α)); 2.78, 2.87 (each *s*, MeN); 3.16 (*t*, $J = 7.8$, CH$_2$(β)); 6.50 (*dd*, $J = 3.1, 0.9$, arom. H); 6.83 (*dd*, $J = 7.6, 0.9$, arom. H); 7.01 (*dd*, $J = 7.6, 7.6$, arom. H); 7.21 (*d*, $J = 3.1$, arom. H); 7.23 (*d*, $J = 7.6$, arom. H). ^{13}C-NMR (100 MHz, CD$_3$OD): 29.1; 34.5; 35.5; 37.2; 100.7; 109.3; 119.1; 122.1; 123.9; 127.1; 133.5; 135.8; 172.8. FAB-MS: 217 ($[M + H]^+$), 216 (M^+). HR-FAB-MS: 216.1249 (M^+, $C_{13}H_{16}N_2O^+$; calc. 216.1263).

*1-[(*tert*-Butoxy)carbonyl]-1*H*-indole-4-propanoic Acid* (**11**). A mixture of **7a** (157 mg, 0.518 mmol) and $LiOH \cdot H_2O$ (330 mg, 7.87 mmol) in THF (2.4 ml) and H_2O (2.4 ml) was stirred at r.t. for 5 h, acidified with 6N aq. HCl (pH 2), and extracted with AcOEt (3 × 9 ml). The combined extract was washed with brine (5 ml), dried, and concentrated and the residue purified by CC (hexane/AcOEt 10 : 1 to 10 : 3): **11** (150 mg, 100%). Colorless prisms. M.p. 131.5 – 132°. IR (ATR): 3200 – 2600 (OH); 1726, 1693 (CO). ^{1}H-NMR (400 MHz): 1.67 (*s*, Me_3C); 2.77 (*t*, $J = 7.9$, CH$_2$(α)); 3.21 (*t*, $J = 7.9$, CH$_2$(β)); 6.64 (*d*, $J = 3.8$, arom. H); 7.07 (*d*, $J = 7.8$, arom. H); 7.25 (*dd*, $J = 7.8, 7.8$, arom. H); 7.61 (*d*, $J = 3.8$, arom. H); 8.03 (*d*, $J = 7.8$, arom. H). ^{13}C-NMR (125 MHz): 27.8; 28.0; 34.9; 83.7; 105.1; 113.6; 122.0; 124.4; 125.8; 129.5; 132.3; 135.2; 149.7; 178.9. FAB-MS: 290 ($[M + H]^+$), 289 (M^+). Anal. calc. for $C_{16}H_{19}NO_4$: C 66.42, H 6.62, N 4.84; found: C 66.37, H 6.63, N 4.73.

*1-[(*tert*-Butoxy)carbonyl]-*N*-methyl-*N*-phenyl-1*H*-indole-4-propanamide* (**12**). A mixture of **11** (100 mg, 0.346 mmol), *N*-methylbenzenamine (75 µl, 0.692 mmol), DCC (142 mg, 0.688 mmol), and DMAP (11 mg, 90.0 µmol) in CH_2Cl_2 (2.5 ml) was stirred at r.t. for 6 h, and the reaction was quenched with sat. aq. NH_4Cl soln. (3 ml). Then the precipitates were dissolved with H_2O (3 ml). The mixture was extracted with CH_2Cl_2 (2 × 12 ml), the combined extract washed with brine (6 ml), dried, and concentrated, and the residue purified by CC (hexane/AcOEt 5 : 1 to 3 : 1): **12** (112 mg, 86%). Colorless oil. IR (ATR): 1724, 1649 (CO). ^{1}H-NMR (400 MHz): 1.67 (*s*, Me_3C); 2.44 (*t*, $J = 7.8$, CH$_2$(α)); 3.14 (*t*, $J = 7.8$, CH$_2$(β)); 3.25 (*s*, MeN); 6.40 (*d*, $J = 3.7$, arom. H); 6.91 (*d*, $J = 7.6$, arom. H); 6.97 (*d*, $J = 7.0$, 2 arom. H); 7.17 (*dd*, $J = 7.6, 7.6$, arom. H); 7.27 – 7.33 (*m*, 3 arom. H); 7.51 (*d*, $J = 3.7$, arom. H); 7.97 (*d*, $J = 7.6$, arom. H). ^{13}C-NMR (125 MHz): 28.2; 29.1; 35.2; 37.4; 83.6; 105.3; 113.2; 122.3; 124.3; 125.5; 127.3; 127.7; 129.6; 129.7; 133.5; 135.1; 144.0; 149.8; 172.4. HR-FAB-MS: 379.2023 ($[M + H]^+$, $C_{23}H_{27}N_2O_3^+$; calc. 379.2022).

*N-Methyl-N-phenyl-1*H*-indole-4-propanamide* (**13**). A soln. of **12** (398 mg, 1.05 mmol) in AcOH (13.2 ml, 231 mmol) was stirred at 100° for 12 h, and the solvent was evaporated. The residue was dissolved with AcOEt (25 ml), the org. soln. washed with 5N NaOH (3 ml) and brine (7 ml), dried, and concentrated, and the residue purified by CC (hexane/AcOEt 3 : 1 to 2 : 1): **13** (266 mg, 91%). Yellow oil. IR (ATR): 3282 (NH), 1633 (CO). ^{1}H-NMR (400 MHz): 2.51 (*t*, $J = 8.1$, CH$_2$(α)); 3.20 (*t*, $J = 8.1$,

$CH_2(\beta)$); 3.27 (*s*, MeN); 6.36 (br. *s*, arom. H); 6.80 (*d*, $J = 7.6$, arom. H); 7.01 (*d*, $J = 7.1$, 2 arom. H); 7.06 (*dd*, $J = 7.6$, 7.6, arom. H); 7.13 (*dd*, $J = 2.7$, 2.6, arom. H); 7.23 (*d*, $J = 7.6$, arom. H); 7.27–7.33 (*m*, 3 arom. H); 8.15 (br. *s*, NH). ^{13}C-NMR (100 MHz): 29.6; 35.1; 37.4; 100.8; 109.1; 119.1; 122.1; 123.6; 127.1; 127.3; 127.6; 129.6; 133.3; 135.7; 144.1; 172.8. HR-FAB-MS: 279.1498 ($[M + H]^+$, $C_{18}H_{19}N_2O^+$; calc. 279.1497).

*1-[(*tert*-Butoxy)carbonyl]-*N*-methoxy-*N*-methyl-1*H*-indole-4-propanamide* (**14**). To a soln. of **11** (399 mg, 1.38 mmol), *N*,*O*-dimethylhydroxylamine hydrochloride (385 mg, 3.95 mmol), and Et_3N (1.6 ml, 11.5 mmol) in dry MeCN (10.3 ml) was added a soln. of 1M 2-chloro-1,3-dimethyl-1*H*-imidazolium chloride (DMC) in CH_2Cl_2 (3.20 ml, 3.20 mmol) over 20 min at −15°. The mixture was stirred at −10° for 4 h and then at 0° for 1 h. The reaction was quenched with sat. aq. K_2CO_3 soln. (10 ml). Then the precipitate was dissolved with H_2O (10 ml), the mixture extracted with AcOEt (2 × 30 ml), the combined extract washed with brine (15 ml), dried, and concentrated, and the residue purified by CC (benzene/AcOEt 10:1): **14** (417 mg, 91%). Colorless oil. IR (ATR): 1732, 1662 (CO). ^1H-NMR (400 MHz): 1.67 (*s*, Me_3C); 2.81 (*t*, $J = 8.0$, $CH_2(\alpha)$); 3.18 (*s*, MeN); 3.20 (*t*, $J = 8.0$, $CH_2(\beta)$); 3.57 (*s*, MeO); 6.67 (*d*, $J = 3.8$, arom. H); 7.09 (*d*, $J = 7.8$, arom. H); 7.24 (*dd*, $J = 7.8$, 7.8, arom. H); 7.60 (*d*, $J = 3.8$, arom. H); 8.01 (*d*, $J = 7.8$, arom. H). ^{13}C-NMR (100 MHz): 27.9; 28.2; 32.2; 33.2; 61.2; 83.7; 105.4; 113.3; 122.2; 124.4; 125.6; 129.6; 133.6; 135.2; 149.8; 173.8. HR-FAB-MS: 333.1798 ($[M + H]^+$, $C_{18}H_{25}N_2O_4^+$; calc. 333.1814).

*N-Methoxy-N-methyl-1*H*-indole-4-propanamide* (**15**). A soln. of **14** (84 mg, 0.254 mmol) in AcOH (3.2 ml, 56.0 mmol) was stirred at 100° for 21 h, and the solvent was evaporated. The residue was purified by CC (benzene/AcOEt 8:1 to 4:1): **15** (53 mg, 89%). Yellow oil. IR (ATR): 3400–3286 (NH), 1637 (CO). ^1H-NMR (400 MHz): 2.87 (*t*, $J = 8.1$, $CH_2(\alpha)$); 3.20 (*s*, MeN); 3.26 (*t*, $J = 8.1$, $CH_2(\beta)$); 3.58 (*s*, MeO); 6.63 (*ddd*, $J = 3.0$, 2.2, 1.1, arom. H); 6.98 (*dd*, $J = 7.6$, 1.1, arom. H); 7.14 (*dd*, $J = 7.6$, 7.6, arom. H); 7.22 (*dd*, $J = 3.0$, 2.8, arom. H); 7.28 (*dd*, $J = 7.6$, 1.1, arom. H); 8.20 (br. *s*, NH). ^{13}C-NMR (100 MHz): 28.4; 32.2; 33.0; 61.2; 100.9; 109.2; 119.1; 122.2; 123.8; 127.1; 133.4; 135.8; 174.2. HR-FAB-MS: 233.1283 ($[M + H]^+$, $C_{13}H_{17}N_2O_2^+$; calc. 233.1290).

*N,N-Dimethyl-1*H*-indole-4-propanethioamide* (**16**). A mixture of **9** (128 mg, 0.592 mmol) and *Lawesson*'s reagent (167 mg, 0.413 mmol) in THF (1.8 ml) was stirred at r.t. for 24 h. After addition of MeOH (2.5 ml), the mixture was stirred at r.t. for 5 min, and the reaction was quenched with sat. aq. NH_4Cl soln. (2 ml) followed by H_2O (3 ml). The mixture was extracted with AcOEt (2 × 13 ml), the combined extract washed with brine (6 ml), dried, and concentrated, and the residue purified by CC (benzene/AcOEt 1:0 to 20:1): **16** (127 mg, 93%). Colorless plates. M.p. 89.5–90.5°. IR (ATR): 3400–3200 (NH), 1522 (CS). ^1H-NMR (400 MHz): 3.05, 3.46 (each *s*, MeN); 3.21 (*dd*, $J = 10.3$, 8.4, $CH_2(\alpha)$); 3.41 (*dd*, $J = 10.3$, 8.4, $CH_2(\beta)$); 6.67 (*ddd*, $J = 3.1$, 2.2, 0.9, arom. H); 6.97 (*d*, $J = 7.6$, arom. H); 7.13 (*dd*, $J = 7.6$, 7.6, arom. H); 7.23 (*dd*, $J = 3.1$, 2.6, arom. H); 7.29 (*dd*, $J = 7.6$, 0.9, arom. H); 8.20 (br. *s*, NH). ^{13}C-NMR (100 MHz): 33.5; 41.6; 44.2; 44.6; 100.9; 109.5; 119.3; 122.2; 124.0; 127.2; 132.8; 135.7; 203.7. HR-FAB-MS: 232.1047 (M^+, $C_{13}H_{16}N_2S$; calc. 232.1034).

Intramolecular Vilsmeier–Haack *Reaction of Amide* **9** (*Entry 1*, *Table 1*): *4,5-Dihydrobenz[*cd*]indol-3(1*H*)-one* (**10**). A soln. of **9** (45 mg, 0.209 mmol), K_2CO_3 (75 mg, 0.546 mmol), and $POCl_3$ (70 µl, 0.751 mmol) in dry MeCN (0.6 ml) was stirred at 65° for 3 h. Then the reaction was quenched with H_2O (3 ml) and the mixture washed with AcOEt (2 × 4 ml). After the aq. soln. was basified with 5N NaOH to pH 12, the mixture was extracted with AcOEt (3 × 11 ml), the combined extract washed with brine (10 ml), dried, and concentrated, and the residue purified by CC (benzene/AcOEt 7:1 to 9:2): **10** (27 mg, 74%). Yellow prisms. M.p. 183.5–184° ([5a]: 184°). IR (ATR): 3500–3250 (NH), 1650 (CO). ^1H-NMR (500 MHz): 2.90 (*t*, $J = 7.0$, $CH_2(5)$); 3.37 (*t*, $J = 7.0$, $CH_2(4)$); 7.11 (*dd*, $J = 7.5$, 0.9, arom. H); 7.25 (*dd*, $J = 7.5$, 7.5, arom. H); 7.31 (*dd*, $J = 7.5$, 0.9, arom. H); 7.75 (*d*, $J = 2.7$, arom. H); 9.09 (br. *s*, NH). ^{13}C-NMR (125 MHz): 27.7; 39.9; 109.2; 114.3; 118.5; 123.8; 124.3; 129.1; 129.3; 133.6; 194.5. HR-FAB-MS: 172.0770 ($[M + H]^+$, $C_{11}H_{10}NO^+$; calc. 172.0762).

*1-[(*tert*-Butoxy)carbonyl]-1*H*-indole-4-propanol* (**17**). A mixture of **7b** (209 mg, 0.66 mmol) and $LiBH_4$ (95%, 34.3 mg, 1.50 mmol) in dry THF (3.2 ml) and EtOH (0.8 ml) under Ar was stirred at r.t. for 1.5 h. Then the reaction was quenched with sat. aq. NH_4Cl soln. (5 ml) and H_2O (2 ml) at 0°, the mixture extracted with AcOEt (3 × 10 ml), the combined extract washed with brine (5 ml), dried, and concentrated, and the residue purified by CC (hexane/AcOEt 9:2): **17** (167 mg, 92%). Colorless oil. IR (neat): 3368 (OH), 1735 (CO). ^{1}H-NMR (400 MHz): 1.67 (*s*, Me_3C); 1.72 (br. *s*, OH); 2.00 (*tt*, $J = 7.6$, 6.4, $CH_2(\beta)$); 2.96 (*t*, $J = 7.6$, $CH_2(\gamma)$); 3.68 (*t*, $J = 6.4$, $CH_2(\alpha)$); 6.64 (*dd*, $J = 3.7$, 0.7, arom. H); 7.06 (*dd*, $J = 7.7$, 0.7, arom. H); 7.23 (*dd*, $J = 7.7$, 7.7, arom. H); 7.59 (*d*, $J = 3.7$, arom. H); 8.00 (*d*, $J = 7.7$, arom. H). ^{13}C-NMR (100 MHz): 28.2; 29.1; 33.5; 62.3; 83.6; 105.4; 113.0; 122.2; 124.3; 125.5; 129.7; 134.2; 135.1; 149.8. HR-FAB-MS: 275.1540 (M^+, $C_{16}H_{21}NO_3^+$; calc. 275.1522).

*3-{1-[(*tert*-Butoxy)carbonyl]-1*H*-indol-4-yl}propyl Phenyl Sulfide* (*=1-[(*tert*-Butoxy)carbonyl]-4-[3-(phenylthio)propyl]-1*H*-indole*; **18**). To an ice-cooled mixture of **17** (116 mg, 0.423 mmol) and PhSSPh (185 mg, 0.848 mmol) in dry MeCN (3.5 ml) under Ar was added Bu_3P (0.21 ml, 0.843 mmol), and the mixture was stirred at r.t. for 1 h. Then the reaction was quenched with 5% aq. NaOH soln. (3.5 ml) at 0°, the mixture extracted with Et_2O (3 × 8 ml), the combined extract washed with 10% aq. HCl soln. (2.7 ml), sat. aq. $NaHCO_3$ soln. (2 × 6 ml), and brine (2 × 5 ml), dried, and concentrated, and the residue purified by CC (hexane/AcOEt 120 : 1 to 110 : 1): **18** (147 mg, 95%). Colorless oil. IR (neat): 1735 (CO). ^{1}H-NMR (400 MHz): 1.67 (*s*, Me_3C); 2.04 (*tt*, $J = 7.3$, 7.3, $CH_2(\beta)$); 2.94 (*t*, $J = 7.3$, $CH_2(\gamma)$); 3.00 (*t*, $J = 7.3$, $CH_2(\alpha)$); 6.59 (*dd*, $J = 3.7$, 0.9, arom. H); 7.03 (*dif. d*, $J = 7.8$, arom. H); 7.16 (*m*, arom. H); 7.23 – 7.31 (*m*, 5 arom. H); 7.57 (*d*, $J = 3.7$, arom. H); 8.00 (*d*, $J = 7.8$, arom. H). ^{13}C-NMR (100 MHz): 28.2; 29.9; 31.7; 33.0; 83.6; 105.3; 113.1; 122.4; 124.3; 125.5; 125.8; 128.8; 129.0; 129.7; 133.6; 135.1; 136.5; 149.7. HR-FAB-MS: 367.1596 (M^+, $C_{22}H_{25}NO_2S^+$; calc. 367.1606).

*3-{1-[(*tert*-Butoxy)carbonyl]-1*H*-indol-4-yl}propyl Phenyl Sulfoxide* (*=1-[(*tert*-Butoxy)carbonyl]-4-[3-(phenylsulfinyl)propyl]-1*H*-indole*; **19**). A mixture of **18** (265 mg, 0.721 mmol) and $NaIO_4$ (237 mg, 1.11 mmol) in MeOH (5.5 ml) and H_2O (1.1 ml) was stirred at r.t. for 7 h. Then the reaction was quenched with H_2O (10 ml), the mixture extracted with AcOEt (3 × 13 ml), the combined extract washed with sat. aq. $NaHCO_3$ soln. (5 ml) and brine (2 × 5 ml), dried, and concentrated, and the residue purified by CC (hexane/AcOEt 7 : 2): **19** (266 mg, 96%). Colorless oil. IR (neat): 1735 (CO). ^{1}H-NMR (400 MHz): 1.67 (*s*, Me_3C); 2.04, 2.20 (each *dtt*, $J = 15.2$, 7.6, 7.6, $CH_2(\beta)$); 2.79 (*t*, $J = 7.6$, $CH_2(\gamma)$); 2.99 (*t*, $J = 7.6$, $CH_2(\alpha)$); 6.56 (*d*, $J = 3.9$, arom. H); 6.99 (*d*, $J = 7.9$, arom. H); 7.22 (*dd*, $J = 7.9$, 7.9, arom. H); 7.46 – 7.51 (*m*, 3 arom. H); 7.55 – 7.59 (*m*, 2 arom. H); 8.01 (*d*, $J = 7.9$, arom. H). ^{13}C-NMR (100 MHz): 22.9; 28.1; 31.5; 56.2; 83.7; 105.1; 113.4; 122.3; 123.9; 124.2; 125.6; 129.1; 129.6; 130.8; 132.6; 135.1; 143.7; 149.6. HR-FAB-MS: 384.1632 ($[M + H]^+$, $C_{22}H_{26}NO_3S^+$; calc. 384.1633).

*3-(1*H*-Indol-4-yl)propyl Phenyl Sulfoxide* (*=4-[3-(Phenylsulfinyl)propyl]-1*H*-indole*; **20**). A soln. of **19** (138 mg, 0.36 mmol) in AcOH (4.5 ml, 78.7 mmol) was stirred at 100° for 19 h, and the solvent was evaporated. Then, the residue was dissolved with AcOEt (20 ml), the org. soln. washed with sat. aq. $NaHCO_3$ soln. (8 ml) and brine (9 ml), dried, and concentrated, and the residue purified by CC (hexane/AcOEt 3 : 1 to 2 : 1): **20** (88 mg, 87%). Yellow oil. IR (neat): 3400 – 3160 (NH). ^{1}H-NMR (400 MHz): 2.10 (*dtt*, $J = 13.9$, 7.5, 7.5, $CH_2(\beta)$); 2.83 (*t*, $J = 7.5$, $CH_2(\gamma)$); 3.05 (*t*, $J = 7.5$, $CH_2(\alpha)$); 6.53 (*ddd*, $J = 2.9$, 2.0, 0.9, arom. H); 6.88 (*dd*, $J = 7.4$, 0.9, arom. H); 7.11 (*dd*, $J = 7.4$, 7.4, arom. H); 7.20 (*dd*, $J = 2.9$, 2.7, arom. H); 7.27 (*d*, $J = 7.4$, arom. H); 7.46 – 7.52 (*m*, 3 arom. H); 7.55 – 7.59 (*m*, 3 arom. H); 8.23 (br. *s*, NH). ^{13}C-NMR (100 MHz): 22.7; 31.9; 56.5; 100.3; 109.5; 119.0; 121.7; 123.9; 124.0; 127.0; 129.1; 130.8; 132.2; 135.8; 143.5. HR-FAB-MS: 284.1117 ($[M + H]^+$, $C_{17}H_{18}NOS^+$; calc. 284.1109).

Pummerer-*Type Cyclization of Sulfoxide* **20**: *3,7,8,9-Tetrahydro-6-phenylthiopyrano[3,2-*e*]indolium Trifluoroacetate* (**22**). A soln. of **20** (45 mg, 0.159 mmol) and $(CF_3CO)_2O$ (70 µl, 0.496 mmol) in dry benzene (3.0 ml) was stirred at r.t. for 1 h, and the solvent was evaporated. Purification of the residue by prep. TLC ($CHCl_3$/MeOH 10 : 3) gave **22** (23 mg, 38%). Light red prisms. M.p. 133.5 – 134.5°. IR (KBr): 1684 (CO). ^{1}H-NMR (500 MHz, CD_3OD): 2.15, 2.48 (2*m*, H−C(5)); 3.32, 3.59 (2*m*, $CH_2(4)$); 3.93, 4.20 (2*m*, $CH_2(6)$); 6.84 (*d*, $J = 3.2$, arom. H); 7.33 (*d*, $J = 8.5$, arom. H); 7.54 (*m*, 2 arom. H); 7.59 (*d*, $J = 3.2$, arom. H); 7.64 (*m*, 2 arom. H); 7.69 (*m*, 2 arom. H). ^{13}C-NMR (125 MHz, CD_3OD): 15.9; 24.9; 42.0; 101.9; 112.7; 124.4; 125.2; 128.8; 128.9; 130.1; 130.8; 131.3; 131.9; 133.7; 134.0; 139.4; 162.9. HR-FAB-MS: 266.1022 (M^+, $C_{17}H_{16}NS^+$; calc. 266.1003).

*Methyl α-(Acetylamino)-1*H*-indole-4-propanoate* [6] (**24**). A mixture of **23** (483 mg, 1.17 mmol) and Mg turnings (249 mg, 10.2 mmol) in dry MeOH (16.0 ml) under Ar was stirred at r.t. for 2 h with sonication. Then the reaction was quenched with sat. aq. NH_4Cl soln. (9.0 ml) followd by H_2O (9.0 ml) and AcOEt (5.0 ml). The mixture was extracted with AcOEt (3 × 40 ml), the combined extract washed with sat. aq. $NaHCO_3$ soln. (20 ml) and brine (30 ml), dried, and concentrated, and the residue purified by CC (benzene/AcOEt 3 : 1 to 2 : 1): **24** (274 mg, 90%). Yellow oil. IR (ATR): 3288 (NH); 1736, 1653

(CO). ^{1}H-NMR (400 MHz): 1.93 (*s*, MeCO); 3.38 (*dd*, $J = 13.9, 5.6$, 1 H–C(β)); 3.46 (*dd*, $J = 13.9, 5.9$, 1 H–C(β)); 3.70 (*s*, MeO); 5.00 (*ddd*, $J = 8.0, 5.9, 5.6$, H–C(α)); 5.92 (*d*, $J = 8.0$, NH); 6.57 (*ddd*, $J = 3.2, 2.2, 1.1$, arom. H); 6.83 (*d*, $J = 7.2$, arom. H); 7.12 (*dd*, $J = 7.2, 7.2$, arom. H); 7.23 (*dd*, $J = 3.2, 2.5$, arom. H); 7.32 (*d*, $J = 7.2$, arom. H); 8.24 (br. *s*, NH). EI-MS: 261 (20, $[M + \mathrm{H}]^+$), 260 (100, M^+), 201 (100), 170 (65), 159 (51), 131 (100), 130 (100).

*Methyl α-(Acetylamino)-1-[(*tert*-butoxy)carbonyl]-1*H*-indole-4-propanoate* [6] (**25**). A soln. of **24** (266 mg, 1.02 mmol), DMAP (14 mg, 0.112 mmol), and (Boc)$_2$O (281 mg, 1.29 mmol) in dry THF (7.5 ml) under Ar was stirred at r.t. for 1 h, and the solvent was evaporated. The residue was purified by CC (benzene/AcOEt 4 : 1 to 2 : 1): **25** (357 mg, 97%). Colorless oil. IR (ATR): 3379 (NH); 1732, 1657 (CO). ^{1}H-NMR (400 MHz): 1.67 (*s*, Me$_3$C); 1.95 (*s*, MeCO); 3.35 (*dd*, $J = 13.9, 5.2$, 1 H–C(β)); 3.41 (*dd*, $J = 13.9, 6.0$, 1 H–C(β)); 3.69 (*s*, MeO); 4.97 (*ddd*, $J = 6.8, 6.0, 5.2$, H–C(α)); 5.93 (*d*, $J = 6.8$, NH); 6.61 (*dd*, $J = 3.8, 0.5$, arom. H); 6.93 (*dd*, $J = 7.8, 7.8$, arom. H); 7.23 (*d*, $J = 7.8$, arom. H); 7.60 (*d*, $J = 3.8$, arom. H); 8.07 (*dd*, $J = 7.8$, arom. H). FAB-MS: 361 ($[M + \mathrm{H}]^+$), 360 (M^+).

*α-(Acetylamino)-1-[(*tert*-butoxy)carbonyl]-*N,N*-dimethyl-1*H*-indole-4-propanamide* (**26**). Under Ar, 2M Me$_3$Al in heptane (2.2 ml, 4.40 mmol) was added dropwise to a soln. of Me$_2$NH·HCl (136 mg, 1.67 mmol) in dry CH$_2$Cl$_2$ (3.0 ml) at 0°, and the mixture was stirred at r.t. for 1 h. After addition of a soln. of **25** (305 mg, 0.85 mmol) in dry CH$_2$Cl$_2$ (4.5 ml) at 0°, the mixture was stirred at 30° for 26 h, and the reaction was quenched with sat. aq. NH$_4$Cl soln. (8.0 ml) at 0°, followed by H$_2$O (5.0 ml) and 10% aq. HCl soln. (2.4 ml). The mixture was extracted with CH$_2$Cl$_2$ (3 × 25 ml), the combined extract washed with sat. aq. NaHCO$_3$ soln. (15 ml) and brine (25 ml), dried, and concentrated, and the residue purified by CC (AcOEt/EtOH 1 : 0 to 12 : 1): **26** (207 mg, 66%). Colorless oil. IR (ATR): 3294 (NH); 1732, 1630 (CO). ^{1}H-NMR (500 MHz): 1.68 (*s*, Me$_3$C); 2.01 (*s*, MeCO); 2.27, 2.76 (2*s*, MeN); 3.13 (*dd*, $J = 13.0, 9.8$, 1 H–C(β)); 3.37 (*dd*, $J = 13.0, 4.4$, 1 H–C(β)); 5.23 (*ddd*, $J = 9.8, 7.9, 4.4$, H–C(α)); 6.57 (*d*, $J = 7.9$, NH); 6.83 (*d*, $J = 3.7$, arom. H); 7.01 (*d*, $J = 7.6$, arom. H); 7.22 (*dd*, $J = 7.6, 7.6$, arom. H); 7.60 (*d*, $J = 3.7$, arom. H); 8.05 (*d*, $J = 7.6$, arom. H). ^{13}C-NMR (125 MHz): 23.3; 28.2; 35.5; 36.7; 37.7; 49.8; 83.8; 105.5; 114.1; 123.6; 124.3; 126.0; 128.6; 130.6; 135.1; 149.7; 169.4; 171.3. HR-FAB-MS: 374.2082 ($[M + \mathrm{H}]^+$, $\mathrm{C_{20}H_{28}N_3O_4^+}$; calc. 374.2080).

*α-(Acetylamino)-*N,N*-dimethyl-1*H*-indole-4-propanamide* (**27**). A soln. of **26** (217 mg, 0.582 mmol) in AcOH (7 ml, 122.4 mmol) was stirred at 100° for 22 h, and the solvent was evaporated. The residue was purified by CC (AcOEt/EtOH 1 : 0 to 9 : 1, followed by 4 : 1): **27** (147 mg, 92%). Yellow prisms. M.p. 176–177°. IR (ATR): 3300–3200 (NH), 1620 (CO). ^{1}H-NMR (400 MHz, (D$_6$)DMSO): 1.78 (*s*, MeCO); 2.57, 2.67 (2*s*, MeN); 3.00 (*dd*, $J = 13.3, 6.9$, 1 H–C(β)); 3.11 (*dd*, $J = 13.3, 7.8$, 1 H–C(β)); 5.05 (*ddd*, $J = 8.4, 7.8, 6.9$, H–C(α)); 6.53 (br. *s*, arom. H); 6.77 (*d*, $J = 7.6$, arom. H); 6.96 (*dd*, $J = 7.6, 7.6$, arom. H); 7.23 (*d*, $J = 7.6$, arom. H); 7.31 (*dd*, $J = 2.9, 2.6$, arom. H); 8.30 (*d*, $J = 8.4$, NH); 11.1 (br. *s*, NH). ^{13}C-NMR (125 MHz, (D$_6$)DMSO): 22.3; 35.0; 36.2; 36.3; 48.8; 99.3; 109.9; 119.2; 120.7; 124.9; 127.4; 128.6; 135.6; 168.7; 171.2. HR-FAB-MS: 274.1547 ($[M + \mathrm{H}]^+$, $\mathrm{C_{15}H_{19}N_3O_2^+}$; calc. 274.1556).

*Methyl α-{[(Benzyloxy)carbonyl]amino}-1-[(*tert*-butoxy)carbonyl]-1*H*-indole-4-propanoate* [6] (**29**). Under Ar, a mixture of **28** (180 mg, 0.400 mmol) and Mg turnings (62 mg, 2.55 mmol) in dry MeOH (5.1 ml) was stirred for 2 h at r.t. with sonication. After further addition of Mg turnings (21 mg, 0.864 mmol), the mixture was stirred at r.t. for 1 h under the same conditions. The reaction was quenched with sat. aq. NH$_4$Cl soln. (4.0 ml), H$_2$O (4.0 ml), and 4% aq. HCl soln. (1.5 ml), the mixture extracted with AcOEt (20 ml, 2 × 14 ml), the combined extract washed with sat. aq. NaHCO$_3$ soln. (7 ml) and brine (7 ml), dried, and concentrated, and the residue purified by CC (hexane/AcOEt 7 : 1): **29** (161 mg, 89%). Colorless oil. IR (ATR): 3348 (NH), 1728 (CO). ^{1}H-NMR (400 MHz, CD$_3$OD): 1.67 (*s*, Me$_3$C); 3.18 (*dd*, $J = 13.9, 8.8$, 1 H–C(β)); 3.39 (*dd*, $J = 13.9, 5.7$, 1 H–C(β)); 3.66 (*s*, MeO); 4.53 (*dd*, $J = 8.8, 5.7$, H–C(α)); 4.97, 5.02 (2*d*, $J = 12.2$, PhCH_2); 6.69 (*dd*, $J = 3.8$, arom. H); 7.03 (*d*, $J = 7.8$, arom. H); 7.19 (*dd*, $J = 7.8, 7.8$, arom. H); 7.22–7.33 (*m*, 5 arom. H); 7.58 (*d*, $J = 3.8$, arom. H); 8.01 (*d*, $J = 7.8$, arom. H). EI-MS: 453 (16, $[M + \mathrm{H}]^+$), 452 (55, M^+), 396 (25), 245 (100), 220 (28), 201 (91), 174 (94), 130 (100), 91 (100), 57 (92).

*α-{[(Benzyloxy)carbonyl]amino}-1-[(*tert*-butoxy)carbonyl]-1*H*-indole-4-propanoic Acid* (**30**). A mixture of **29** (369 mg, 0.816 mmol) and LiOH·H$_2$O (481 mg, 11.5 mmol) in THF (4.1 ml) and H$_2$O (4.1 ml) was stirred at r.t. for 1 h, and the reaction was quenched with 6N aq. HCl (→ pH 2). The mixture was extracted with AcOEt (20 ml, 2 × 15 ml), the combined extract washed with brine (10 ml), dried, and concentrated, and the residue purified by CC (hexane/AcOEt 4 : 1 to 3 : 1): **30** (360 mg, quant.). Colorless oil. IR (ATR): 3400–2800 (OH), 1726 (CO). ^{1}H-NMR (400 MHz): 1.67 (*s*, Me_3C); 3.35 (*dd*, $J = 13.9$, 6.3, 1 H−C(β)); 3.48 (*dd*, $J = 13.9$, 5.9, 1 H−C(β)); 4.77 (*ddd*, $J = 8.2$, 6.3, 5.9, H−C(α)); 5.08, 5.11 (2*d*, $J = 12.2$, PhCH_2); 5.19 (*d*, $J = 8.2$, NH); 6.61 (*d*, $J = 3.7$, arom. H); 7.00 (*d*, $J = 7.8$, arom. H); 7.22 (*dd*, $J = 7.8$, 7.8, arom. H); 7.29–7.38 (*m*, 5 arom. H); 7.55 (*d*, $J = 3.7$, arom. H); 8.07 (*d*, $J = 7.8$, arom. H). ^{13}C-NMR (125 MHz): 28.2; 35.1; 54.5; 67.1; 83.8; 105.1; 114.4; 123.5; 124.4; 126.1; 127.8; 128.1; 128.2; 128.5; 130.5; 135.3; 136.1; 149.7; 155.8; 175.7. HR-FAB-MS: 438.1758 (M^+, $C_{24}H_{26}N_2O_6$; calc. 438.1791).

*α-{[(Benzyloxy)carbonyl]amino}-1-[(*tert*-butoxy)carbonyl]-*N,N*-dimethyl-1*H*-indole-4-propanamide* (**31**). To an ice-cooled soln. of **30** (171 mg, 0.391 mmol) and $Me_2NH_2 \cdot HCl$ (88 mg, 1.08 mmol) in dry MeCN (3.4 ml) was added Et_3N (0.55 ml, 3.95 mmol) over 5 min, and the mixture was cooled to −15°. To the soln. was added 1M DMC in CH_2Cl_2 (1.10 ml, 1.10 mmol) over 10 min. The mixture was stirred at −10° for 1.5 h and then at 0° for 1.5 h, and the reaction was quenched with sat. aq. $NaHCO_3$ soln. (4 ml). Then the prepicitate was dissolved with H_2O (3.0 ml), the mixture extracted with AcOEt (3 × 13 ml), the combined extract washed with sat. aq. K_2CO_3 soln. (4 ml) and brine (7 ml), dried, and concentrated, and the residue purified by CC (hexane/AcOEt 4 : 1 to 3 : 1): **31** (170 mg, 93%). Colorless oil. IR (ATR): 3273 (NH); 1726, 1637 (CO). ^{1}H-NMR (400 MHz): 1.68 (*s*, Me_3C); 2.26, 2.75 (each *s*, MeN); 3.16 (*dd*, $J = 13.0$, 9.8, 1 H−C(β)); 3.37 (*dd*, $J = 13.0$, 4.8, 1 H−C(β)); 4.97 (*ddd*, $J = 9.8$, 8.2, 4.8, H−C(α)); 5.12 (*s*, PhCH_2); 5.84 (*d*, $J = 8.2$, NH); 6.79 (*d*, $J = 3.5$, arom. H); 7.02 (*d*, $J = 7.7$, arom. H); 7.22 (*dd*, $J = 7.7$, 7.7, arom. H); 7.29–7.36 (*m*, 5 arom. H); 7.59 (*d*, $J = 3.5$, arom. H); 8.05 (*d*, $J = 7.7$, arom. H). ^{13}C-NMR (125 MHz): 28.2; 35.1; 36.7; 38.0; 51.3; 66.8; 83.8; 105.4; 114.1; 123.6; 124.3; 126.0; 127.0; 128.0; 128.1; 128.5; 130.5; 135.1; 136.4; 149.7; 155.7; 171.2. HR-FAB-MS: 466.2338 (M^+, $C_{26}H_{32}N_3O_5^+$; calc. 466.2342).

*α-{[(Benzyloxy)carbonyl]amino}-*N,N*-dimethyl-1*H*-indole-4-propanamide* (**32**). A soln. of **31** (268 mg, 0.576 mmol) in AcOH (6.6 ml, 115 mmol) was stirred at 100° for 16 h, and the solvent was evaporated. The residue was purified by CC (hexane/AcOEt 2 : 1 to 3 : 2): **32** (196 mg, 93%). Yellow oil. IR (ATR): 3292 (NH); 1703, 1630 (CO). ^{1}H-NMR (400 MHz): 2.21, 2.73 (2*s*, MeN); 3.19 (*dd*, $J = 12.8$, 9.9, 1 H−C(β)); 3.42 (*dd*, $J = 12.8$, 4.9, 1 H−C(β)); 5.06 (*ddd*, $J = 9.9$, 8.2, 4.9, H−C(α)); 5.12 (*s*, PhCH_2); 5.85 (*d*, $J = 8.2$, NH); 6.75 (br. *s*, arom. H); 6.90 (*d*, $J = 7.5$, arom. H); 7.09 (*dd*, $J = 7.5$, 7.5, arom. H); 7.22 (*dd*, $J = 2.7$, 2.7, arom. H); 7.29 (*d*, $J = 7.5$, arom. H); 7.31–7.37 (*m*, 3 arom. H); 8.22 (br. *s*, NH). ^{13}C-NMR (125 MHz): 35.5; 36.6; 38.5; 51.2; 66.7; 100.8; 110.1; 120.5; 121.8; 124.3; 127.9; 128.0; 128.1; 128.5; 128.6; 135.7; 136.5; 155.7; 171.7. HR-FAB-MS: 366.1812 ($[M + H]^+$, $C_{21}H_{24}N_3O_3^+$; calc. 366.1818).

*α-Amino-*N,N*-dimethyl-1*H*-indole-4-propanamide* (**33**). A mixture of **32** (132 mg, 0.361 mmol) and 5% Pd/C (27.4 mg) in MeOH (3.0 ml) was stirred at r.t. for 2 h under H_2 (1 atm). After filtration, the filtrate was evaporated. The residue was purified by CC ($CHCl_3$/MeOH 30 : 1 to 8 : 1): **33** (80 mg, 96%). Yellow oil. IR (ATR): 3600–3100 (NH), 1620 (CO). ^{1}H-NMR (400 MHz): 2.60, 2.86 (each *s*, MeN); 3.09 (*dd*, $J = 13.2$, 7.5, 1 H−C(β)); 3.22 (*dd*, $J = 13.2$, 7.0, 1 H−C(β)); 4.12 (*dd*, $J = 7.5$, 7.0, H−C(α)); 6.60 (*ddd*, $J = 3.1$, 2.2, 0.9, arom. H); 6.94 (*dd*, $J = 7.6$, 0.9, arom. H); 7.13 (*dd*, $J = 7.6$, 7.6, arom. H); 7.23 (*dd*, $J = 3.1$, 2.7, arom. H); 7.30 (*d*, $J = 7.6$, arom. H); 8.29 (br. *s*, NH). ^{13}C-NMR (125 MHz): 35.7; 36.6; 40.8; 52.0; 100.8; 109.7; 120.5; 122.1; 124.1; 127.8; 129.8; 135.8; 175.0. HR-FAB-MS: 232.1460 ($[M + H]^+$, $C_{13}H_{18}N_3O^+$; calc. 232.1450).

*α-(Benzoylamino)-*N,N*-dimethyl-1*H*-indole-4-propanamide* (**34**). A soln. of **32** (110 mg, 0.301 mmol) and 5% Pd/C (23.5 mg) in MeOH (2.4 ml) was stirred at r.t. for 2.5 h under H_2 (1 atm). After filtration, the filtrate was evaporated. The residue was dissolved in dry THF (2.5 ml), and K_2CO_3 (252 mg, 1.82 mmol) and benzoyl chloride (60 μl, 0.517 mmol) were added at 0°. After being stirred at r.t. for 1 h, the reaction was quenched with H_2O (3 ml). The mixture was extracted with AcOEt (3 × 6 ml), the combined extract washed with sat. aq. $NaHCO_3$ soln. (5 ml) and brine (7 ml), dried, and concentrated, and the residue was purified by CC (hexane/AcOEt 1 : 1): **34** (95 mg, 94% over 2 steps). Colorless prisms. M.p. 197–198°. IR (ATR): 3350–3250 (NH), 1620 (CO). ^{1}H-NMR (500 MHz, (D_6)DMSO): 2.74, 2.77 (each *s*, MeN); 3.20 (*dd*, $J = 13.4$, 7.7, 1 H−C(β)); 3.26 (*dd*, $J = 13.4$, 7.0, 1 H−C(β)); 5.21 (*dd*, $J = 7.7$, 7.0, H−C(α)); 6.60 (*m*, arom. H); 6.91 (*d*, $J = 7.6$, arom. H); 6.97 (*dd*, $J = 7.6$, 7.6, arom. H); 7.23 (*d*, $J = 7.6$, arom. H); 7.32 (*dd*, $J = 2.7$, 2.7, arom. H); 7.43 (*dd*, $J = 7.4$, 7.4, 2 arom. H); 7.51 (*dd*, $J = 7.4$, 1.5, arom. H); 7.84 (*dd*, $J = 7.4$, 1.5, 2 arom. H); 8.74 (*d*, $J = 7.9$, NH); 11.07 (br. *s*, NH). ^{13}C-NMR (125 MHz, (D_6)DMSO): 35.2; 35.3; 36.4; 49.9; 99.3; 109.9; 119.5; 120.7; 124.9; 127.5 (C × 3); 128.1; 128.9; 131.3; 133.8; 135.7; 165.8; 171.3. HR-FAB-MS: 336.1685 ([M + H]$^+$, $C_{20}H_{22}N_3O_2^+$; calc. 336.1712).

*α-[(Ethoxycarbonyl)amino]-*N,N*-dimethyl-1*H*-indole-4-propanamide* (**35**). A soln. of **32** (60 mg, 0.164 mmol) and 5% Pd/C (12 mg) in MeOH (1.5 ml) was stirred at r.t. for 2.5 h under H_2 (1 atm). After filtration, the filtrate was evaporated. The residue was dissolved in dry THF (1.4 ml), and K_2CO_3 (74.5 mg, 0.539 mmol) and ethyl carbonochloridate (35 μl, 0.366 mmol) were added at 0°. After being stirred at r.t. for 0.5 h, the reaction was quenched with H_2O (3 ml). The mixture was extracted with AcOEt (3 × 7 ml), the combined extract washed with brine (4 ml), dried, and evaporated, and the residue purified by CC (hexane/AcOEt 3:1 to 1:1): **35** (48 mg, 96% over 2 steps). Colorless oil. IR (ATR): 3294 (NH); 1697, 1632 (CO). ^{1}H-NMR (400 MHz): 1.25 (t, J = 7.1, *Me*CH$_2$); 2.21, 2.73 (each s, MeN); 3.18 (dd, J = 13.0, 9.7, 1 H−C(β)); 3.41 (dd, J = 13.0, 4.9, 1 H−C(β)); 4.13 (q, J = 7.1, MeCH_2); 5.04 (ddd, J = 9.7, 8.4, 4.9, H−C(α)); 5.72 (d, J = 8.4, NH); 6.75 (br. s, arom. H); 6.90 (d, J = 7.6, arom. H); 7.09 (dd, J = 7.6, 7.6, arom. H); 7.22 (dd, J = 2.7, 2.7, arom. H); 7.29 (d, J = 7.6, arom. H); 8.31 (br. s, NH). ^{13}C-NMR (125 MHz): 14.6; 35.5; 36.6; 38.5; 51.0; 60.9; 101.0; 110.0; 120.5; 122.0; 124.2; 128.0; 128.4; 135.6; 156.0; 171.8. HR-FAB-MS: 304.1672 ([M + H]$^+$, $C_{16}H_{21}N_3O_3^+$; calc. 304.1661).

N,N*-Dimethyl-α-{[(4-methylphenyl)sulfonyl]amino}-1*H*-indole-4-propanamide* (**36**). A mixture of **32** (110 mg, 0.301 mmol) and 5% Pd/C (24.7 mg) in MeOH (2.4 ml) was stirred at r.t. for 2 h under H_2 (1 atm), and the catalyst was filtered off. After concentration of the filtrate, the residue was dissolved in dry THF (2.7 ml) and, to the soln. at 0° was added K_2CO_3 (189.5 mg, 1.37 mmol) and TsCl (90 mg, 0.472 mmol). The mixture was stirred at r.t. for 3 h, and the reaction was quenched with H_2O (3 ml). The mixture was extracted with AcOEt (3 × 7 ml), the combined extract washed with sat. aq. $NaHCO_3$ soln. (5 ml) and brine (7 ml), dried, and evaporated, and the residue purified by CC ($CHCl_3$/MeOH 35:1): **36** (93 mg, 81% over 2 steps). Light green prisms. M.p. 223–224°. IR (ATR): 3500–3200 (NH), 1620 (CO). ^{1}H-NMR (500 MHz, (D_6)DMSO): 2.24, 2.38 (2s, MeN); 2.34 (s, MeC); 2.88 (dd, J = 13.0, 5.8, 1 H−C(β)); 3.02 (dd, J = 13.0, 8.9, 1 H−C(β)); 4.44 (dd, J = 8.9, 5.8, H−C(α)); 6.20 (br. s, arom. H); 6.64 (d, J = 7.6, arom. H); 6.92 (dd, J = 7.6, 7.6, arom. H); 7.22 (d, J = 7.6, arom. H); 7.27–7.29 (m, 3 arom. H); 7.57 (d, J = 8.2, 2 arom. H); 8.15 (br. s, NH); 11.05 (br. s, NH). ^{13}C-NMR (125 MHz, (D_6)DMSO): 20.9; 34.9; 36.0; 36.8; 51.9; 98.7; 110.1; 119.4; 120.7; 125.0; 126.4; 127.2; 127.4; 129.1; 135.6; 138.1; 142.4; 169.9. HR-FAB-MS: 386.1526 ([M + H]$^+$, $C_{20}H_{24}N_3O_3S^+$; calc. 386.1538).

Intramolecular Vilsmeier–Haack *Reaction of Amide* **27** (*Entry 1*, *Table 2*): N*-(1,3,4,5-Tetrahydro-3-oxobenz[*cd*]indol-4-yl)acetamide* (**37**). A suspension of **27** (40 mg, 0.146 mmol), K_2CO_3 (53 mg, 0.383 mmol), and $POCl_3$ (53 μl, 0.569 mmol) in dry MeCN (0.65 ml) was stirred at 65° for 1 h, and the reaction was quenched with H_2O (3 ml). The aq. soln. was washed with AcOEt (2 × 6 ml), basified with 5N NaOH to pH 12, and extracted with AcOEt (3 × 12 ml). The combined extract was washed with brine (6 ml), dried, and concentrated, and the residue purified by CC (benzene/AcOEt 1:1 to 0:1): **37** (11.5 mg, 34%). Yellow prisms. M.p. 231.5–232°. IR (ATR): 3294 (NH); 1650, 1620 (CO). ^{1}H-NMR (500 MHz, (D_6)acetone): 2.02 (s, MeCO); 3.20 (dd, J = 15.8, 12.2, 1 H−C(5)); 3.68 (dd, J = 15.8, 6.6, 1 H−C(5)); 4.90 (ddd, J = 12.2, 6.6, 5.2, H−C(4)); 7.06 (d, J = 7.6, arom. H); 7.21 (dd, J = 7.6, 7.6, arom. H); 7.37 (d, J = 7.6, arom. H); 7.44 (br. s, NH); 7.88 (d, J = 2.4, arom. H); 11.30 (br. s, NH). ^{13}C-NMR (125 MHz, (D_6)acetone): 22.9; 35.4; 57.3; 110.8; 113.6; 119.1; 124.7; 125.9; 128.6; 129.7; 134.8; 170.4; 190.2. HR-FAB-MS: 229.0989 ([M + H]$^+$, $C_{13}H_{12}N_2O_2^+$; calc. 229.0977).

*Methyl (α*S*)-α-{[(Benzyloxy)carbonyl]amino}-1-[(*tert*-butoxy)carbonyl]-1*H*-indole-4-propanoate* [6] ((S)-**29**). (S)-**29** was prepared by asymmetric hydrogenation of **28** according to [6]. $[\alpha]_D^{24} = -15.5$ ($c = 0.5$, MeOH) ([6]: $[\alpha]_D^{25} = -13.4$ ($c = 0.685$, MeOH)). Chiral HPLC (*Daicel Chiralcel OD-H*, hexane/^{i}PrOH 24:1, 1 ml/min, 254 nm): t_R 25.5 (S; 99% ee) and 27.9 min (R).

*(α*S*)-α-{[(Benzyloxy)carbonyl]amino}-1-[(*tert*-butoxy)carbonyl]-1*H*-indole-4-propanoic Acid* ((S)-**30**). As described for racemic **30**, from (S)-**29**: (S)-**30**. $[\alpha]_D^{25} = +32.5$ ($c = 0.67$, $CHCl_3$).

*(α*S*)-α-{[(Benzyloxy)carbonyl]amino}-1-[(*tert*-butoxy)carbonyl]-*N,N*-dimethyl-1*H*-indole-4-propanamide* ((S)-**31**). As described for racemic **31**, from (S)-**30**: (S)-**31**. $[\alpha]_D^{24} = +24.9$ ($c = 0.56$, $CHCl_3$).

*(α*S*)-α-{[(Benzyloxy)carbonyl]amino}-*N,N*-dimethyl-1*H*-indole-4-propanamide* ((S)-**32**). As described for racemic **32**, from (S)-**31**: (S)-**32**. $[\alpha]_D^{24} = +38.2$ ($c = 0.56$, $CHCl_3$). Chiral HPLC (*Daicel Chiralcel OJ-H*, hexane/^{i}PrOH 9:1, 0.7 ml/min, 230 nm): t_R 57.5 (S; 99% ee) and 64.4 min (R).

*(α*S*)-α-(Acetylamino)-*N,N*-dimethyl-1*H*-indole-4-propanamide* ((*S*)-**27**). A mixture of (*S*)-**32** (164 mg, 0.449 mmol), 5% Pd/C (49.0 mg), and Ac_2O (0.300 ml, 3.17 mmol) in MeOH (3.7 ml) was stirred at r.t. for 5.5 h under H_2 (1 atm). After removal of the catalyst by filtration, the filtrate was concentrated. The residue was purified by CC (AcOEt/EtOH 1 : 0 to 20 : 1): (*S*)-**27** (105 mg, 85%). Light orange prisms. M.p. 174–175°. $[\alpha]_D^{24} = +84.0$ ($c = 0.43$, MeOH).

Intramolecular Vilsmeier–Haack *Reaction of* (*S*)-**27**: N*-[(4*S*)-1,3,4,5-Tetrahydro-3-oxobenz[*cd*]indol-4-yl]acetamide* ((*S*)-**37**). As described for racemic **37**, from (*S*)-**27**: (*S*)-**37**. M.p. 231.4–232.3°. $[\alpha]_D^{20} = -3.1$ ($c = 0.22$, MeOH). Chiral HPLC (*Daicel Chiralpak AD-H*, hexane/EtOH 4 : 1, 0.7 ml/min, 247 nm): t_R 16.8 (*S:* 4% ee) and 19.7 min (*R*).

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