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# STEREOSELECTIVE SYNTHESIS OF 1-SUBSTITUTED 1,2,3,4-TETRA-HYDRO-β-CARBOLINES BY ASYMMETRIC ELECTROPHILIC α-AMIDOALKYLATION REACTIONS

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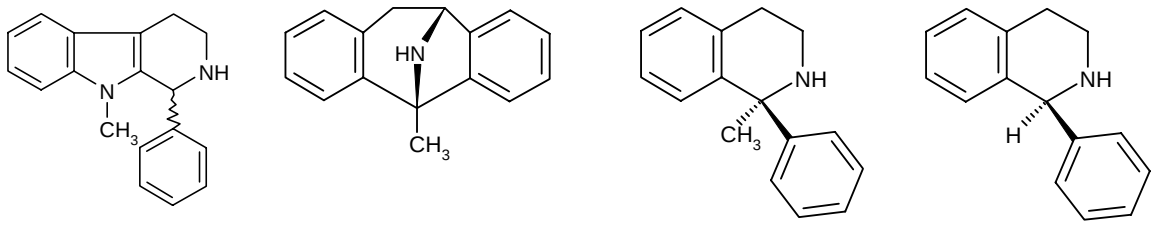
**Abstract** - An efficient procedure for the asymmetric synthesis of 1-substituted 1,2,3,4-tetrahydro-9-methyl-β-carbolines based on asymmetric electrophilic α-amidoalkylation reactions is described. Stereoselective addition of various organometallic reagents to a chiral *N*-acyl-β-carbolinium ion gave the corresponding 1-substituted 1,2-dihydro-β-carbolines in high yields and very good to excellent diastereomeric ratios. Catalytic hydrogenation followed by the removal of the chiral auxiliary *via* reductive cleavage of the amide bond proceeded with complete conservation of the absolute configuration at the newly created stereocenter leading to 1-substituted 1,2,3,4-tetrahydro-9-methyl-β-carboline derivatives in high yields. Their absolute stereochemistry was proven by X-Ray analysis. The 1-phenyl-substituted 1,2,3,4-tetrahydro-β-carbolines were evaluated for their affinity to the PCP binding site of the NMDA receptor.

## INTRODUCTION

The β-carboline and tetrahydro-β-carboline nuclei are structural units often found in natural products exhibiting interesting biological and pharmacological activities.[1] Tetrahydro-β-carbolines having a

substituent at the C1 position have proven to be valuable substrates for the synthesis of a wide variety of complex molecules including indole alkaloids and pharmaceuticals.[2] In the context of a study aimed at the development of new ion channel blockers targeting the PCP binding site of the NMDA receptor,[3] we reasoned that 1-aryl-substituted 1,2,3,4-tetrahydro-β-carbolines (**1d**) methylated at the nitrogen atom at 9-position can be regarded as structurally related to the known ion channel blockers MK-801 (**2**) and FR-115427 (**3**) (Scheme 1). The affinity of the (+)-enantiomer of MK-801 to the PCP binding site was reported to be seven times higher than that of the (-)-enantiomer.[4] In an earlier study undertaken by us it was discovered that the (*S*)-enantiomer of 1,2,3,4-tetrahydroisoquinoline (**4**) displays a distinctly higher potency at the PCP binding site than the (*R*)-enantiomer.[5] Thus, to evaluate C1-substituted 1,2,3,4-tetrahydro-β-carbolines as potential NMDA antagonists, it was of great interest to us to provide efficient access to these compounds in enantiopure form.




**1d** **2** (MK-801) (*S*)-**3** (FR-115427) (*S*)-**4**

Scheme 1

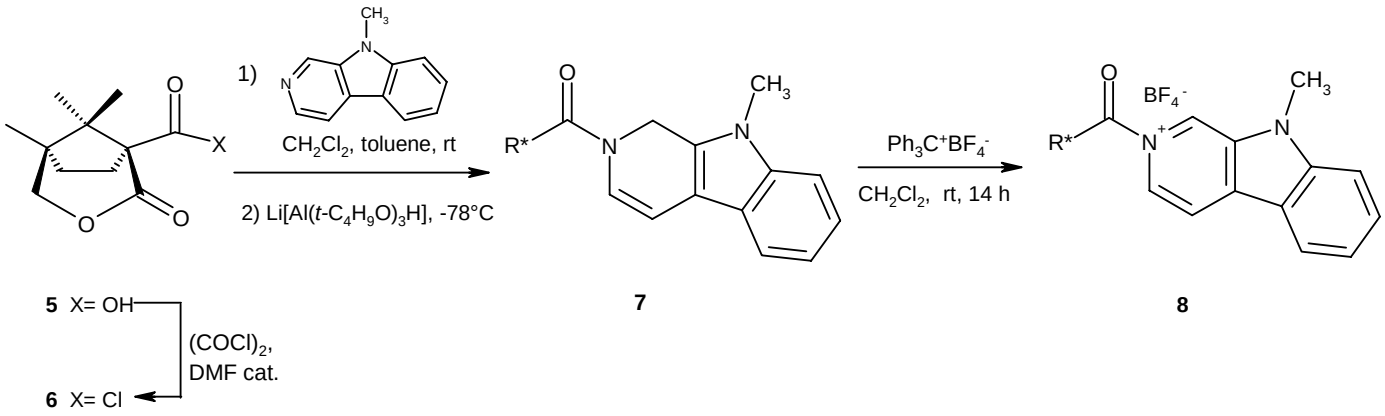
Various strategies for the stereoselective synthesis of C1-substituted tetrahydro-β-carbolines have been reported. Among these synthetic methodologies, variations of the Pictet-Spengler reaction facilitating the preparation of enantiopure compounds are one of the most extensively studied. They include "ex-chiral-pool" syntheses employing chiral aldehydes[6] or chiral tryptophan esters[7] and Pictet-Spengler reactions of tryptamine derivatives bearing a chiral auxiliary on the aminoethane nitrogen atom.[8] An enantioselective Pictet-Spengler reaction based on diisopinocampheylchloroborane as a chiral Lewis acid catalyst has been developed by Nakagawa.[9] The Bischler-Napieralski reaction of chiral tryptamine derivatives was shown to proceed diastereoselectively to afford C1-substituted 1,2,3,4-tetrahydro-ß-carboline derivatives, which were successfully used for the synthesis of various indole alkaloids.[10] A vinylogous Mannich reaction performed on a 3,4-dihydro-β-carboline derivative derived from D-tryptophan was reported to lead to the corresponding 1,2,3,4-tetrahydro-β-carboline in a highly diastereoselective manner.[11] Ohsawa developed an enantioselective synthesis based on the proline-catalyzed addition of ketones to 9-tosyl-3,4-dihydro-β-carboline.[12] Nakamura reported that allylzinc reagents reacted with 3,4-dihydro-β-carboline in the presence of a lithiated bisoxazoline ligand to give an allyl adduct in high enantiomeric excess.[13] The

transformation of racemic C1-substituted tetrahydro-β-carbolines into enantiopure compounds by oxidation and subsequent enantioselective hydrogenation using a chiral ruthenium catalyst has been published by Tietze.[14] Meyers developed an asymmetric method based on transforming 1,2,3,4-tetrahydro-β-carboline into a chiral formamidine followed by a diastereoselective deprotonation/alkylation sequence at C1.[15] In analogy, Quirion described a general stereospecific route *via* electrophilic attack at an α-aminoalkyl carbanion derived from the corresponding chiral 1,2,3,4-tetrahydro-β-carbolinecarboxylic acid amide derivative.[16] Even though the trapping reactions of *N*-acyliminium ions with nucleophiles represent a frequently used process in the construction of α-substituted nitrogen heterocycles,[17] to the best of our knowledge, investigations on the versatility of asymmetric reactions involving addition of nucleophiles to chiral *N*-acyl-β-carbolinium salts with the chirality residing in an N1-acyl group are very limited. To date, only Ohsawa described a method[18] featuring the generation of a chiral N1,N9-diacyl-β-carbolinium ion wherein the N1-acyl group is achiral and the N9 is provided with the chiral auxiliary. Trapping reactions of these intermediates with allyltributyltin or silylenolethers led to C1-substituted 1,2-dihydro-β-carbolines in high diastereoselectivities. Following reduction, the corresponding 1,2,3,4-tetrahydro-β-carbolines were obtained. In recent years, a major focus of our research was the stereoselective construction of α-substituted nitrogen heterocycles. We have developed a synthetic method termed by us as Asymmetric Electrophilic α-Amidoalkylation (AEαA ). It is based on trapping reactions of chiral *N*-acyliminium ions with the chirality residing in the *N*-acyl group with appropriate nucleophiles. Thus far, the concept has been proven successful for the asymmetric synthesis of piperidine, pyrrolidine, 1,2-dihydropyridine and 1,2,3,4-tetrahydroisoquinoline derivatives using the carboxylic acid (**5**) as chiral auxiliary.[19] In this paper we report that this method is also suitable to provide access to 1,2-dihydro-β-carbolines in a straightforward and stereoselective manner. Upon reduction and removal of the chiral auxiliary, enantiopure 1,2,3,4-tetrahydro-β-carbolines were readily obtained.

## RESULTS AND DISCUSSION

In analogy to a previously published route involving the generation of chiral tetrahydroisoquinolinium ions and subsequent asymmetric electrophilic α-amidoalkylation, we first synthesized the 1,2-dihydro-β-carboline (**7**) as a precursor for the requisite *N*-acyl-β-carbolinium salt. Compound (**7**) was obtained in good yield (69%) by the reaction of the chiral carboxylic acid chloride (**6**) with 9-methyl-β-carboline in a solvent mixture of $CH_2Cl_2$ and toluene at 0°C. This resulted in the formation of a heterogeneous mixture containing the corresponding *N*-acyliminium salt as a precipitate which upon treatment with Li[Al(*t*-$C_4H_9O)_3H$] at -78°C provided compound (**7**). In accordance with related systems previously published by

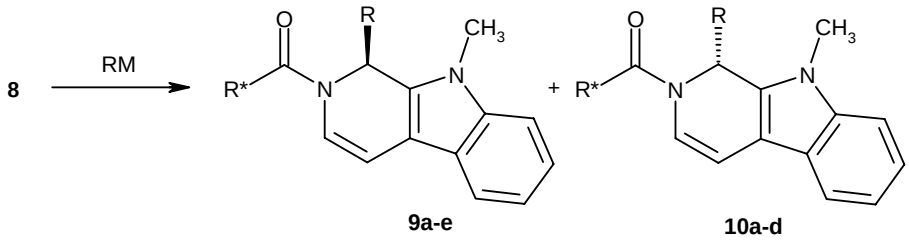
us, hydride abstraction accomplished using $Ph_3C^+BF_4^-$ led to the *N*-acyl-β-carbolinium ion (**8**). According to TLC the oxidation was complete within 14 hours at room temperature. Following precipitation induced by the addition of THF, *N*-acyl-α-carbolinium salt (**8**) was obtained as yellow crystals and could be fully characterized. Since the *N*-acyl-β-carbolinium ion is formed irreversibly and its generation does not suffer from any unfavorable equilibria, the presented reduction/oxidation reaction sequence is an improvement over direct procedures for the generation of *N*-acyliminium ions. [19d, 20]




Scheme 2

Next, the asymmetric addition reaction to the *N*-acyl-β-carbolinium tetrafluoroborate (**8**) was investigated extensively. Grignard, lithium, aluminium and zinc reagents were employed as nucleophiles to study the influence of the nature of the organometallic species. The reactions were performed by adding four equivalents of the organometallic compounds (solution in ether or THF) to a solution of the chiral *N*-acyl-ß-carbolinium ion (**8**) in $CH_2Cl_2$ at -78 °C. The addition reaction of Grignard reagents proceeded in good yields (65-90%) as depicted in Table 1. However, diastereoselectivities were found to be only average (Entries 1, 2, and 5), with only the phenylation reaction being an exception (Entry 9). When phenylmagnesium bromide was employed, an excellent diastereoselectivity of *ds* ≥ 99.9/0.1 (Entry 9) has to be assumed, since, despite of an intensive search, no minor isomer (**10e**) could be detected. The ethylation reaction was chosen as model system to perform optimization studies regarding the addition of alkyl substituents. Using $(C_2H_5)_3Al$ a significant increase of the diastereoselectivity (*ds* = 93.2/6.8, Entry 3) was observed with a yield only slightly lower compared to the corresponding Grignard reagent. Employing $(C_2H_5)_2Zn$ the diastereoselectivity even rose to *ds* = 96.2/3.8 (Entry 4). A similar trend was observed for the butylation reaction with *n*-$C_4H_9MgBr$ providing a low (*ds* = 78.1/21.9, Entry 5) and (*n*-$C_4H_9)_2Zn$ a high diasteroselectivity (*ds* = 95.4/4.6, Entry 6). It is noteworthy that even the addition of the bulky *tert*-butyl substituent resulted in high yield (79%) and diastereoselectivity (*ds* = 93.9/6.1) using (*t*-$C_4H_9)_2Zn$ as nucleophile. Also of note is the successful addition of highly reactive *t*-$C_4H_9Li$. However, in

this case both the yield and the diastereoselectivity were low (Entry 7). The attempted addition reaction with $(CH_3)_2Zn$ and $(CH_3)_3Al$ to the desired 1-methyl products (**9a**) and (**10a**) failed even when the reaction was carried out using high excess of the reagents at elevated temperatures (refluxing THF). This indicates that these organometallic reagents are not sufficiently reactive. The observed influence of the organometallic reagent on the asymmetric electrophilic α-amidoalkylation reaction of the β-carbolinium ion (**8**) parallels the results previously reported for addition reactions to tetrahydroisoquinolinium ions with organozinc and organoaluminum compounds being more favorable than organomagnesium reagents with respect to high diastereoselectivities.




Scheme 3

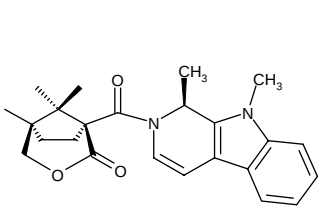
| Entry | Product | **RM** | d.s. | Yield [%] | | |
|---|---|---|---|---|---|---|
| | **9+10** | | **9/10** | **9+10** | **9** | **10** |
| 1 | **a** | $CH_3MgCl$[a] | 74.1/25.9 | 87 | 64 | 23 |
| 2 | **b** | $C_2H_5MgI(Et_2O)$[a] | 70.4/29.6 | 65 | 46 | 19 |
| 3 | | $(C_2H_5)_3Al$[a] | 93.2/6.8 | 62 | 58 | 4 |
| 4 | | $(C_2H_5)_2Zn$[b] | 96.2/3.8 | 60 | 58 | 2 |
| 5 | **c** | *n*-$C_4H_9MgBr$[a] | 78.1/21.9 | 89 | 70 | 19 |
| 6 | | $(n\text{-}C_4H_9)_2Zn$[a] | 95.4/4.6 | 82 | 79 | 4 |
| 7 | **d** | $(t\text{-}C_4H_9)Li$[a] | 65.1/34.9 | 44 | 29 | 15 |
| 8 | | $(t\text{-}C_4H_9)_2Zn$[a] | 93.9/6.1 | 79 | 74 | 5 |
| 9 | **e** | PhMgBr (THF)[a] | 99.9/<0.1 | - | 90 | - |

[a] 4 equiv., 1.5 h, -78 °C [b] 2 equiv. (the second equiv. was added after 1 h)

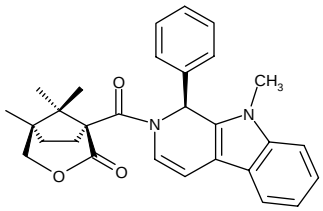
Table 1

The stereochemistry of the newly created stereocenter of the major diastereomers (**9a**) and (**9e**) obtained by methylation or phenylation, respectively, was established by X-Ray crystallography (Figure 1). In both cases, the configuration was found to be (*S*). The stereochemical assignment of the amidoalkylation

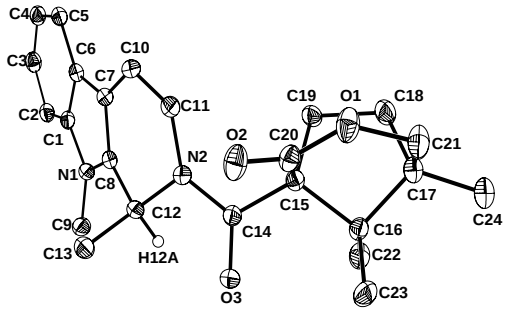
products (**9b-d**) and (**10b-d**), was delineated from a comparison of their $^1$H NMR spectral data with the $^1$H spectrum obtained for **9a** and **10a**. The spectra of the compounds (**9b-d**) formed predominantly were of high similarity to the spectrum of **9a**, as were the spectra of the minor isomer (**10b-d**) with the spectrum of the minor compound (**10a**). Therefore, it is reasonable to assume that the major diastereomers (**9b-d**) are (*S*)- and the minor isomers (**10b-d**) are (*R*)-configurated as well.




**9a**




**9e**



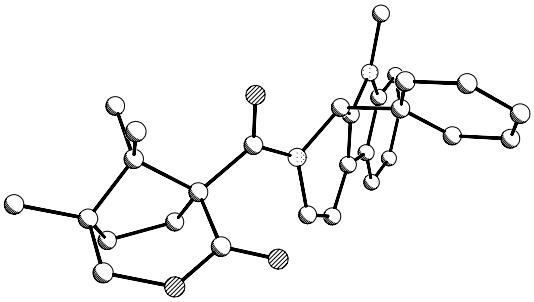
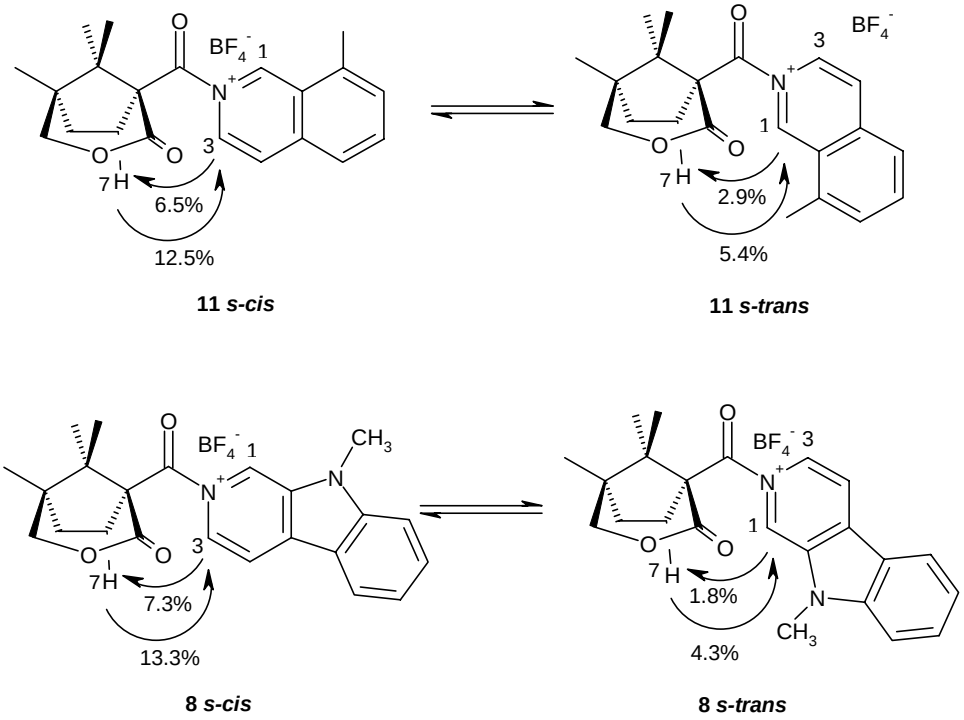



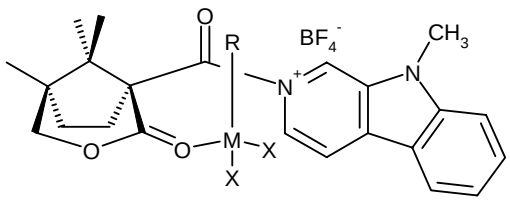
Figure 1

The addition of organometallic nucleophiles to the prochiral iminium subunit of **8** has occurred preferentially from the *si* face. In recent studies on the addition reaction to *N*-acylisoquinolinium ion (**11**) and related compounds, we observed the same sense of asymmetric induction. The auxiliary (**5**) is thought to cause asymmetric induction by a precomplexation mechanism. It involves the coordination of the lactone functionality to the metal ion of the organometallic reagent and the subsequent intramolecular transfer of a residue from the preorientated organic metal center to the iminium subunit.[4, 19] We previously proposed - based on NOE experiments - that the *s-cis* conformer of the *N*-acylisoquinolinium ion (**11**) predominates over the *s-trans* conformer. Furthermore, we suggested that the OC-NC subunit adopts a synperiplanar orientation with the dimethyl substituted 8'-carbon of the bicyclic ring system (for details see reference 19). Similarly, we performed NOE measurements on the *N*-acyl-β-carbolinium ion (**8**). The intensity of the interaction between 3H-7′H$_{endo}$ was three times higher than the NO effect observed for 1H-7′H$_{endo}$. Apart from these NO effects, no other significant NOE's between the H1 and H3 of the isocarbolinium moiety and the protons of the bicyclic lactone subunit were seen. This indicates that for

both, compound (**8**) and compound (**11**), a conformation predominates where the OC-NC is of *s-cis* orientation and is aligned synperiplanar with the dimethyl-substituted 8'-carbon of the bicyclic ring system. Accordingly, in analogy to the stereomodel for **11**, we suggest a mechanistic rationale based on structure (**12**) in Figure 2 for the asymmetric induction obtained by addition reactions to the *N*-acyl-β-carbolinium ion (**8**). This is, of course, in line with the configuration of the major diastereomers (**9a-e**)**,** which according to the proposed model must be formed by *si* face addition.




Scheme 4

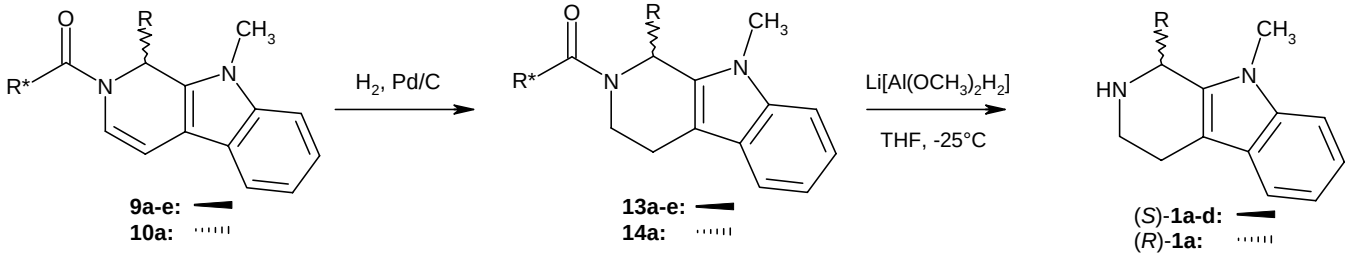



**12**

Figure 2 Model for asymmetric induction

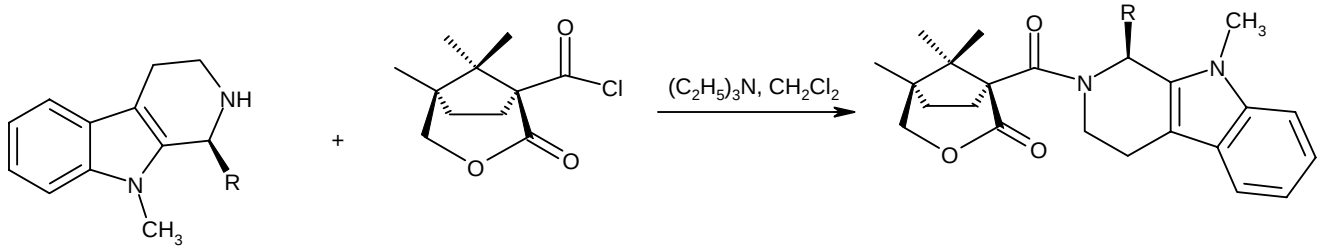
Since we planned to determine the binding affinities of the enantiopure 1,2,3,4-tetrahydro-β-carbolines (**1**) to the *PCP* binding site of the *NMDA* receptor, the *N*-acyl-1,2-dihydro-β-carbolines (**9**) and (**10**) had to be converted to their tetrahydro counterparts. First, the major diastereomers (**9a-e**) and the minor

diastereomer (**10a**), which was also accessible in a reasonable amount, were separated from the respective diastereomeric mixture by preparative HPLC and purified at least to > 99%. Hydrogenation of the $\Delta^{3,4}$ double bond using Pd/C as catalyst led to the required *N*-acyl-1,2,3,4-tetrahydro-β-carbolines (**13a-e**) and (**14a**) in excellent yields.[5, 21] The hydrogenation proceeded quantitatively at normal pressure and room temperature, except for the reduction of the *tert*-butyl derivative (**9d**) requiring a pressure of 3 bar.




Scheme 5

The chiral auxiliary can be easily removed by cleavage of the amide bond using $Li[(CH_3O)_2AlH_2]$ or $Na[(CH_3O)_2AlH_2]$ as reducing agents. In the present case, $Li[(CH_3O)_2AlH_2]$ was used which was employed at a reaction temperature of -25 °C to prevent the formation of tertiary amines as a result of overreduction. The products (**1**) were obtained in about 80% yield. Attempts to cleave the amide bond of compound (**13d**) bearing the bulky *tert*-butyl substituent in α-position failed under reducing as well as basic or acidic conditions.



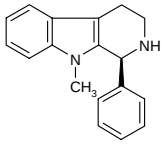
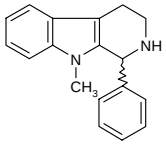
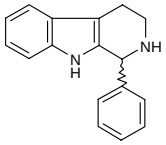
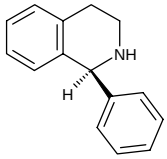

**(*S*)-1a**
**(*S*)-1e**

**6**

**13a**
**13e**

Scheme 6

In a representative experiment, the methyl derivative ((*S*)-**1a**) and the phenyl derivative ((*S*)-**1e**) were attached to the chiral auxiliary (Scheme 6) to investigate whether epimerization might have occurred during cleavage. The diastereomeric purity of the resulting amides was determined by analytical HPLC. As expected, only one peak was detected in both cases at the retention time of compounds (**13a**) and (**13e**) indicating that reductive removal of the chiral auxiliary had proceeded without epimerization.

| $K_i$ [μM][a] - [$^3$H]MK-801 | | | |
|---|---|---|---|
|  |  |  |  |
| (*S*)-**1d** | (*rac*)-**1d** | (*rac*)-**15** | **4** |
| 18.9±0.4 | 27.1±1.7 | 58.4±3.1 | 1.38±0.07 |

[a] Means±standard error of the mean from three independent experiments each carried out in triplicate.

Table 2

The enantiopure 1-aryl-1,2,3,4-tetrahydro-β-carboline ((*S*)-**1e**) was evaluated for its *in vitro* activity on the *PCP* binding site of the *NMDA* receptor. The binding affinity was determined by a radioligand binding assay on pig cortical brain membranes with [$^3$H]MK-801 as the specific ligand.[22] Due to excellent stereoselectivity the minor stereoisomer (*R*)-1-aryl-1,2,3,4-tetrahydro-β-carboline ((*R*)-**1e**) was not accessible by employing the herein presented synthetic route. Therefore, we decided to prepare the racemic mixture ((*rac*)-**1e**) to get an estimate of the receptor binding affinity of the (*R*)-configurated enantiomer ((*R*)-**1e**). We chose the (*rac*)-1-phenyl-1,2,3,4-tetrahydro-β-carboline ((*rac*)-**15**), which was easily prepared according to literature, as a precursor for the synthesis of (*rac*)-**1e**. To study the influence of the substituents on the indole nitrogen atom (methyl versus hydrogen), (*rac*)-**15** was also included in the biological study. As depicted in Table 2, the 1-aryl-1,2,3,4-tetrahydro-β-carbolines ((*S*)-**1e**, (*rac*)-**1e** and (*rac*)-**15**) were found to be less potent as compared to the structurally related 1-aryl-1,2,3,4-tetrahydroisoquinoline ((*S*)-**4**). The *N*-methyl derivatives ((*S*)-**1e**) and ((*rac*)-**1e**) showed greater affinity to the *PCP* binding site than compound ((*rac*)-**15**) lacking a methyl substituent on the indole nitrogen atom. In addition, it was observed that the enantiopure 1,2,3,4-tetrahydro-β-carboline ((*S*)-**1e**) displays enhanced binding affinity as compared to the racemic mixture ((*rac*)-**1e**). We therefore conclude that the (*R*)-enantiomer ((*R*)-**1e**) is less potent than the (*S*)-enantiomer ((*S*)-**1e**). This result corroborates our previous

report on the enantioselectivity of binding of 1-aryl-1,2,3,4-tetrahydroisoquinolines to the *PCP* binding site of the *NMDA* receptor.[19g]

In summary, we have realized the asymmetric synthesis of 1-substituted 1,2,3,4-tetrahydro-β-carbolines based on the employment of a chiral *N*-acyl-iminium ion (**8**) derived from 9-methyl-β-carboline. NOE experiments performed on the chiral *N*-acyl-β-carbolinium salt (**8**) support the recently published model for asymmetric induction by the chiral auxiliary (**5**). The addition reactions leading to the 1-substituted *N*-acyl-1,2-dihydro-β-carbolines (**9**) and (**10**) were found to occur from the *si* face of the *N*-acyl-β-carbolinium salt (**8**). The addition products (**9a-c**), (**9e**) and (**10a**) were transformed into the corresponding 1-substituted 1,2,3,4-tetrahydro-β-carbolines. The 1-phenyl derivative ((*S*)-**1e**) was biologically evaluated for its binding affinity to the PCP binding site of the NMDA receptor.

## EXPERIMENTAL

All reactions were carried out in vacuum dried glassware under nitrogen atmosphere. All reagents were used as commercially available. Solvents were dried and distilled prior to use. THF and toluene were freshly distilled from sodium metal/benzophenone ketyl, $CH_2Cl_2$ and DMF from $CaH_2$, and $CH_3OH$ from Mg. Melting points were determined on a Büchi melting point apparatus (no. 510 Dr. Tottoli or Linström) and are uncorrected. IR spectra were recorded with a Perkin Elmer FT-IR spectrophotometer IR 430, Paragon 1000 or Paragon 1600, and NMR spectra were obtained with a BRUKER AC 300 spectrometer (300 MHz for $^1H$) or JEOL JNM-GX 400 spectrometer (400 MHz for $^1H$) with TMS as internal standard. MS spectra were recorded on a Kratos MJ25RS, a Finnigan Match 7 or a Hewlett Packard 5989 A with 59980 B particle beam LC/MS interface. CHN-analyses were determined with an elemental analysator 340B or 340C (Perkin Elmer) or an elemental analysator Rapid (Heraeus). TLC: Merck 60 F-254. Column chromatography (CC) was performed as flash chromatography with silica gel Merck 60 F-254 (0.032–0.063 mm). Analytical HPLC: L-6200 pump, L-4250 UV/Vis detector, D-2500 Chromato Integrator (Merck-Hitachi), column: LiChroCart® with Lichrosorb® Si 60 cartridge (5 µm, 250x4 mm with precolumn 4x4 mm), (Merck). Preparative HPLC: L-6000 pump, L-4000 UV/Vis, D-2000 Chromato Integrator (Merck-Hitachi), column: Hibar RT LiChrosorb® Si 60 (7 µm, 250x25 mm) (Merck).

### (1*S*,5*R*)-1-[1,2-Dihydro-9-methylpyrido[3,4-*b*]indol-2-ylcarbonyl]-5,8,8-trimethyl-3-oxabicyclo[3.2.1]octan-2-one (7).

One drop of DMF was added to a slurry of **5**[19c] (72 mg, 0.34 mmol) in 1.5 mL of $CH_2Cl_2$. The slurry was cooled to 0 °C and oxalyl chloride (33 µL, 0.38 mmol) was added dropwise. The resulting mixture was

stirred for 30 min at rt. The solution was cooled to 0 °C and a solution of 9-methyl-β-carboline (60 mg, 0.33 mmol) in 2.00 mL of $CH_2Cl_2$ was added. Following addition of toluene (3.00 mL), the mixture was stirred for 1 h at rt and cooled to –78 °C. A solution of Li[Al(*t*-$C_4H_9O)_3H$] (346 mg, 1.36 mmol) in 3.00 mL of THF was added. After 30 min at –78 °C the reaction mixture was allowed to warm to rt. After 16 h the reaction was quenched by addition of water (2.00 mL). The resulting mixture was chromatographed on a small bed of silica (length ~ 3.50 cm, Ø ~ 5.00 cm) using $CH_2Cl_2/C_2H_5OAc$ = 4:1. Product (**7**) was obtained following evaporation of the solvents in vacuo. Yield: 77 mg (60%), colorless crystals, mp 155 °C ($C_2H_5OAc$). $[\alpha]_D^{25}$ = +112.5° (*c* = 0.8, $CH_2Cl_2$). $^1$H NMR ($CDCl_3$): δ = 0.85 (s, 3 H, $CH_3$), 0.95 (s, 3 H, $CH_3$), 1.15 (s, 3 H, $CH_3$), 1.70-1.80 (m, 2 H, $CH_2CH_2$), 2.05-2.15 (m, 1 H, $CH_2CH_2$), 2.50-2.55 (m, 1 H, $CH_2CH_2$), 3.66 (s, 3 H, $NCH_3$), 3.91 (d, *J* = 11.0 Hz, 1 H, $CH_2O$), 4.07 (d, *J* = 11.0 Hz, 1 H, $CH_2O$), 4.59 (d, *J* = 16.7 Hz, 1 H, $NCH_2$), 5.42 (d, *J* = 16.7 Hz, 1 H, $NCH_2$), 6.01 (d, *J* = 7.3 Hz, 1 H, NCH=C*H*), 6.43 (d, *J* = 7.3 Hz, 1 H, NC*H*=CH), 7.08 (t, *J* = 7.2 Hz, 1 H, $H_{ar}$), 7.20 (t, *J* = 7.2 Hz, 1 H, $H_{ar}$), 7.25 (d, *J* = 7.2 Hz, 1 H, $H_{ar}$), 7.47 (d, *J* = 7.2 Hz, 1 H, $H_{ar}$). IR (KBr): *v*= 2961 $cm^{-1}$, 1727, 1654, 1625, 1472. MS (70 eV); *m/z*: 378 ($M^+$), 183, 57. Anal. Calcd for $C_{23}H_{26}N_2O_3$: C, 72.99; H, 6.93; N, 7.40. Found: C, 73.45; H, 7.03; N, 6.84.

**9-Methyl-2-[(1*S*,5*R*)-5,8,8-trimethyl-2-oxo-3-oxabicyclo[3.2.1]octylcarbonyl]pyrido[3,4-*b*]indolinium tetrafluoroborate (8).**

A solution of **7** (30 mg, 0.08 mmol) was added dropwise to a solution of $Ph_3C^+ BF_4^-$ (31 mg, 0.09 mmol) in 1.5 mL of $CH_2Cl_2$ at 0 °C. The mixture was stirred for 14 h at rt followed by evaporation of ~ 25% of the solvent in vacuo. THF (1.00 mL) was added and the mixture was stirred until a yellow solid precipitated (after ~ 20 min). Following the removal of the solution *via* cannula, the product was washed two times with 1.00 mL of THF and dried in vacuo. Yield: 28 mg (75%), yellow crystals, mp 133-134°C (THF/$CH_2Cl_2$). $[\alpha]_D^{25}$ = +39.6° (*c* = 2.0, $CH_2Cl_2$). UV/VIS ($CH_2Cl_2$): $\lambda_{max}$ (lg ε) = 431 nm (3.73), 335 (4.38), 285 (4.54). $^1$H NMR ($CDCl_3$): δ = 0.92 (s, 3 H, $CH_3$), 1.20 (s, 3 H, $CH_3$), 1.40 (s, 3 H, $CH_3$), 1.80-1.89 (m, 1 H, $CH_2CH_2$), 2.00-2.10 (m, 1 H, $CH_2CH_2$), 2.42 (t, *J* = 7.3 Hz, 2 H, $CH_2CH_2$), 4.12 (d, *J* = 11.1 Hz, 1 H, $CH_2O$), 4.16 (s, 3 H, $NCH_3$), 4.22 (d, *J* = 11.1 Hz, 1 H, $CH_2O$), 7.62 (d, *J* = 8.1 Hz, 1 H, NCC*H*CH), 7.84 (t, *J* = 8.1 Hz, 1 H, NCCHC*H*), 7.43 (t, *J* = 8.1 Hz, 1 H, NCCHCHC*H*), 8.22 (d, *J* = 8.1 Hz, 1 H, NCCHCHCHC*H*), 8.30 (d, *J* = 6.8 Hz, 1 H, NCHC*H*), 8.74 (d, *J* = 6.8 Hz, 1 H, NC*H*CH), 9.45 (s, 1 H, NC*H*C). IR: *v* = 1792 $cm^{-1}$, 1712, 1636, 1517, 1074. MS (70 eV); *m/z*: 377 (*N*-acyl-β-carbolinium ion), 362, 192, 182. Anal. Calcd for $C_{23}H_{25}N_2O_3BF_4$: C, 59.50; H, 5.43; N, 6.03; Found: C, 59.73; H, 5.50; N, 6.08.

**General procedure for electrophilic α-amidoalkylation reactions leading to compounds (9) and (10) (GP1).** A solution of **8** (28 mg, 0.06 mmol) in 2.00 mL of $CH_2Cl_2$ was cooled to -78 °C. A solution of the respective organometallic reagent (4 equiv.) was added dropwise. The mixture was stirred at -78 °C for 1.5 h. Following addition of 1.5 mL of water, the mixture was allowed to warm to rt, 5.00 mL of water were added and the aqueous layer was extracted four times with $CH_2Cl_2$ (5.00 mL for each extraction). The organic layers were dried over $Na_2SO_4$. Following evaporation of the solvent in vacuo, the crude product was purified by CC (petrol ether/$C_2H_5OAc$ = 4:1).

**(1*S*,5*R*)-1-[(1*S*)-1,2-Dihydro-1,9-dimethylpyrido[3,4-*b*]indolylcarbonyl]-5,8,8-trimethyl-3-oxa-bicyclo[3.2.1]octan-2-one (9a) and (1*S*,5*R*)-1-[(1*R*)-1,2-Dihydro-1,9-dimethylpyrido[3,4-*b*]indolylcarbonyl]-5,8,8-trimethyl-3-oxa-bicyclo[3.2.1]octan-2-one (10a).**

According to GP1. Yields and diastereoselectivities see Table 1. Analytical HLPC (*n*-heptane/$C_2H_5OAc$ = 8:2; 1 mL/min).

**9a**: Colorless crystals, mp 75 °C (*n*-heptane). $t_R$ = 20.2 min. $[\alpha]_D$ = +242° (*c* = 0.2, $CH_2Cl_2$). $^1$H NMR (400 MHz, $CDCl_3$): δ = 1.01 ppm (s, 3 H, $CH_3$), 1.25 (s, 3 H, $CH_3$), 1.35 (d, *J* = 6.4 Hz, 3 H, NCHC*H*$_3$), 1.42 (s, 3 H, $CH_3$), 1.81-1.85 (m, 2 H, $CH_2CH_2$), 2.10-2.18 (m, 1 H, $CH_2CH_2$), 2.57-2.64 (m, 1 H, $CH_2CH_2$), 3.73 (s, 3 H, $NCH_3$), 3.97 (d, *J* = 11.1 Hz, 1 H, $CH_2O$), 4.16 (d, *J* = 11.1 Hz, 1 H, $CH_2O$), 5.85 (q, *J* = 6.4 Hz, 1 H, NC*H*$CH_3$), 6.19 (d, *J* = 7.7 Hz, 1 H, NCH=C*H*), 6.40 (d, *J* = 7.70 Hz, 1 H, NC*H*=CH), 7.15 (t, *J* = 7.8 Hz, 1 H, $H_{ar}$), 7.22 (t, *J* = 7.8 Hz, 1 H, $H_{ar}$), 7.30 (d, *J* = 7.8 Hz, 1 H, $H_{ar}$), 7.55 (d, *J* = 7.8 Hz, 1 H, $H_{ar}$). IR (KBr): *v* = 2968 cm$^{-1}$, 2925, 1728, 1654, 1616, 1459, 1336, 1320, 1218, 1124, 816, 735. MS (70 eV); *m/z*: 392 ($M^+$), 377, 195, 167. Anal. Calcd for $C_{24}H_{28}N_2O_3$: C, 73.44; H, 7.19; N, 7.14. Found: C, 73.45; H, 7.18; N, 7.14.

**10a**: Colorless crystals, mp 112 °C (*n*-heptane). $t_R$ = 37.4 min. $[\alpha]_D$ = -52° (*c* = 0.2, $CH_2Cl_2$). $^1$H NMR (400 MHz, $CDCl_3$): δ = 0.71 ppm (s, 3 H, $CH_3$), 0.81 (s, 3 H, $CH_3$), 1.04 (s, 3 H, $CH_3$), 1.29 (d, *J* = 6.4 Hz, 3 H, NCHC*H*$_3$), 1.75-1.81 (m, 2 H, $CH_2CH_2$), 2.05-2.10 (m, 1 H, $CH_2CH_2$), 3.17 (dt, *J* = 8.1, 12.8 Hz, 1 H, $CH_2CH_2$), 3.67 (s, 3 H, $CH_3$), 3.90 (d, *J* = 11.1 Hz, 1 H, $CH_2O$), 4.15 (d, *J* = 11.1 Hz, 1 H, $CH_2O$), 6.04-6.06 (m, 2 H, NC*H*$CH_3$, NCH=C*H*), 6.31 (d, *J* = 7.6 Hz, 1 H, NC*H*=CH), 7.09 (t, *J* = 7.3 Hz, 1 H, $H_{ar}$), 7.15 (t, *J* = 7.3 Hz, 1 H, $H_{ar}$), 7.25 (d, *J* = 7.3 Hz, 1 H, $H_{ar}$), 7.51 (d, *J* = 7.3 Hz, 1 H, $H_{ar}$). IR (KBr): *v* = 1726 cm$^{-1}$, 1647, 1468, 1321, 1121, 743. MS (70 eV); *m/z*: 392 ($M^+$), 377, 195, 167.

**(1*S*,5*R*)-1-[(1*S*)-1-Ethyl-1,2-dihydro-9-methylpyrido[3,4-*b*]indolylcarbonyl]-5,8,8-trimethyl-3-oxabicyclo[3.2.1]octan-2-one (9b) and (1*S*,5*R*)-1-[(1*R*)-1-Ethyl-1,2-dihydro-9-methylpyrido[3,4-*b*]indolylcarbonyl]-5,8,8-trimethyl-3-oxabicyclo[3.2.1]octan-2-one (10b).**

According to GP1. Yields and diastereoselectivities see Table 1. Analytical HLPC (*n*-heptane/$C_2H_5OAc$ = 8:2; 2 mL/min).

**9b**: Colorless crystals, mp 70 °C (*n*-heptane). $t_R$ = 8.5 min. $[\alpha]_D$ = +72° (*c* = 1.0, $CH_2Cl_2$). $^1$H NMR (400 MHz, $CDCl_3$): δ = 0.81 ppm (s, 3 H, $CH_3$), 0.90 (t, *J* = 7.5 Hz, 3 H, $CH_2CH_3$), 0.94 (s, 3 H, $CH_3$), 1.33 (s, 3 H, $CH_3$), 1.70-1.78 (m, 4 H, $CH_2CH_3$, $CH_2CH_2$), 2.03-2.07 (m, 1 H, $CH_2CH_2$), 2.50-2.57 (m, 1 H, $CH_2CH_2$), 3.67 (s, 3 H, $NCH_3$), 3.89 (d, *J* = 10.7 Hz, 1 H, $CH_2O$), 4.08 (d, *J* = 10.7 Hz, 1 H, $CH_2O$), 5.74 (t, *J* = 6.6 Hz, 1 H, $NCHCH_2$), 6.13 (d, *J* = 7.3 Hz, 1 H, NCH=CH), 6.36 (d, *J* = 7.3 Hz, 1 H, NCH=CH), 7.10 (t, *J* = 7.9 Hz, 1 H, $H_{ar}$), 7.15 (t, *J* = 7.9 Hz, 1 H, $H_{ar}$), 7.24 (d, *J* = 7.9 Hz, 1 H, $H_{ar}$), 7.50 (d, *J* = 7.9 Hz, 1 H, $H_{ar}$). IR (KBr): $\nu$ = 2295 cm$^{-1}$, 1724, 1654, 1468, 1336, 1232, 1126, 1070, 737. MS (50 eV); *m/z*: 406 ($M^+$), 377, 195, 167. Anal. Calcd for $C_{25}H_{30}N_2O_3$: C, 73.86; H, 7.44; N, 6.89. Found: C, 73.62; H, 8.43; N, 6.11.

**10b**: Colorless crystals, mp 45 °C (*n*-heptane). $t_R$ = 14.3 min. $[\alpha]_D$ = -195° (*c* = 1.0, $CH_2Cl_2$). $^1$H NMR (400 MHz, $CDCl_3$): δ = 0.85 ppm (s, 3 H, $CH_3$), 0.93 (t, *J* = 7.3 Hz, 3 H, $CH_2CH_3$), 0.99 (s, 3 H, $CH_3$), 1.30 (s, 3 H, $CH_3$), 1.60-1.80 (m, 3 H, $CH_2CH_3$, $CH_2CH_2$), 2.00-2.10 (m, 2 H, $CH_2CH_2$), 3.05 (dd, *J* = 5.1, 10.2 Hz, 1 H, $CH_2CH_2$), 3.67 (s, 3 H, $NCH_3$), 3.89 (d, *J* = 10.7 Hz, 1 H, $CH_2O$), 4.14 (d, *J* = 10.7 Hz, 1 H, $CH_2O$), 6.10-6.12 (m, 2 H, $NCHCH_2$, NCH=CH), 6.45 (d, *J* = 7.3 Hz, 1 H, NCH=CH), 7.10 (t, *J* = 7.9 Hz, 1 H, $H_{ar}$), 7.15 (t, *J* = 7.9 Hz, 1 H, $H_{ar}$), 7.30 (d, *J* = 7.9 Hz, 1 H, $H_{ar}$), 7.55 (d, *J* = 7.9 Hz, 1 H, $H_{ar}$). IR (KBr): $\nu$ = 2294 cm$^{-1}$, 1725, 1650, 1465, 1339, 1240, 1124, 1074, 740. MS (70eV); *m/z* = 406 ($M^+$), 377, 195, 167, 139, 57.

**(1*S*,5*R*)-1-[(1*S*)-1-Butyl-1,2-dihydro-9-methylpyrido[3,4-*b*]indolylcarbonyl]-5,8,8-trimethyl-3-oxabicyclo[3.2.1]octan-2-one (9c) and (1*S*,5*R*)-1-[(1*R*)-1-Butyl-1,2-dihydro-9-methylpyrido[3,4-*b*]indolylcarbonyl]-5,8,8-trimethyl-3-oxabicyclo[3.2.1]octan-2-one (10c).**

According to GP1. Yields and diastereoselectivities see Table 1. Analytical HLPC (*n*-heptane/$C_2H_5OAc$ = 8:2; 1 mL/min).

**9c**: Colorless crystals, mp 65 °C (*n*-heptane). $t_R$ = 7.2 min. $[\alpha]_D$ = -211° (*c* = 0.3, $CH_2Cl_2$). $^1$H NMR (400 MHz, $CDCl_3$): δ = 0.76 ppm (t, *J* = 7.0 Hz, 3 H, $CH_3$), 0.81 (s, 3 H, $CH_3$), 0.92 (s, 3 H, $CH_3$), 1.16-1.27 (m, 7 H, $CH_3$, 2 x $CH_2$), 1.65-1.87 (m, 4 H, 2 x $CH_2$), 1.98-2.05 (m, 1 H, $CH_2$), 2.45-2.56 (m, 1 H, $CH_2$), 3.66 (s, 3 H, $NCH_3$), 3.88 (d, *J* = 11.1 Hz, 1 H, $CH_2O$), 4.07 (d, *J* = 11.1 Hz, 1 H, $CH_2O$), 5.76 (t, *J* = 6.5 Hz, 1 H, $NCHCH_2$), 6.14 (d, *J* = 7.3 Hz, 1 H, NCH=CH), 6.36 (d, *J* = 7.3 Hz, 1 H, NCH=CH), 7.09 (t, *J* = 8.1 Hz, 1 H, $H_{ar}$), 7.15 (t, *J* = 8.1 Hz, 1 H, $H_{ar}$), 7.30 (d, *J* = 8.1 Hz, 1 H, $H_{ar}$), 7.54 (d, *J* = 8.1 Hz, 1 H, $H_{ar}$). IR (KBr): $\nu$ = 2957 cm$^{-1}$, 2927, 1732, 1654, 1468, 1334, 1218, 1124, 738. MS (70 eV); *m/z*: 434

($M^+$), 377, 195, 167, 139. Anal. Calcd for $C_{27}H_{34}N_2O_3$: C, 74.62; H, 7.89; N, 6.45. Found: C, 74.69; H, 7.93; N, 6.53.

**10c**: Colorless oil. $t_R$ = 10.4 min. $[\alpha]_D$ = -11° (*c* = 1.0, $CH_2Cl_2$). $^1$H NMR (400 MHz, $CDCl_3$): δ = 0.75 ppm (s, 3 H, $CH_3$), 0.81-0.99 (m, 12 H, 2 x $CH_3$, 3 x $CH_2$), 1.26 (s, 3 H, $CH_3$), 1.65-1.80 (m, 2 H, $CH_2$), 2.05-2.10 (m, 1 H, $CH_2$), 3.23 (dt, *J* = 5.2, 11.3 Hz, 1 H, $CH_2$), 3.74 (s, 3 H, $NCH_3$), 3.95 (d, *J* = 11.1 Hz, 1 H, $CH_2O$), 4.20 (d, *J* = 11.1 Hz, 1 H, $CH_2O$), 6.13-6.16 (m, 2 H, NC*H*$CH_2$, NCH=C*H*), 6.41 (d, *J* = 7.3 Hz, 1 H, NC*H*=CH), 7.16 (t, *J* = 7.4 Hz, 1 H, $H_{ar}$), 7.22 (t, *J* = 7.4 Hz, 1 H, $H_{ar}$), 7.33 (d, *J* = 7.4 Hz, 1 H, $H_{ar}$), 7.54 (d, *J* = 7.4 Hz, 1 H, $H_{ar}$). IR (KBr): *v* = 2955 $cm^{-1}$, 1738, 1652, 1468, 1340, 1217, 1110, 740. MS (CI); *m/z*: 435 (M+1), 391, 239, 149.

**(1*S*,5*R*)-1-[(1*S*)-1-*tert*-Butyl-1,2-dihydro-9-methylpyrido[3,4-*b*]indolylcarbonyl]-5,8,8-trimethyl-3-oxabicyclo[3.2.1]octan-2-one (9d) and (1*S*,5*R*)-1-[(1*R*)-1-*tert*-Butyl-1,2-dihydro-9-methylpyrido[3,4-*b*]indolylcarbonyl]-5,8,8-trimethyl-3-oxabicyclo[3.2.1]octan-2-one (10d).**

According GP1. Yields and diastereoselectivities see Table 1. Analytical HLPC (*n*-heptane/$C_2H_5OAc$ = 8:2; 2 mL/min).

**9d**: Colorless crystals, mp 95 °C (*n*-heptane). $t_R$ = 9.8 min. $[\alpha]_D$ = +329° (*c* = 0.2, $CH_2Cl_2$). $^1$H NMR (400 MHz, $CDCl_3$): δ = 0.86 ppm (s, 3 H, $CH_3$), 0.98 (s, 3 H, $CH_3$), 1.03 (s, 9 H, *t*-$C_4H_9$), 1.37 (s, 3 H, $CH_3$), 1.77 (t, *J* = 8.5 Hz, 2 H, $CH_2CH_2$), 1.97 (dt, *J* = 10.2, 8.5 Hz, 1 H, $CH_2CH_2$), 2.58 (dt, *J* = 10.2, 8.5 Hz, 1 H, $CH_2CH_2$), 3.75 (s, 3 H, $NCH_3$), 3.94 (d, *J* = 11.1 Hz, 1 H, $CH_2O$), 4.13 (d, *J* = 11. 1 Hz, 1 H, $CH_2O$), 5.81 (s, 1 H, NC*H*$CH_2$), 6.23 (d, *J* = 7.3 Hz, 1 H, NCH=C*H*), 6.51 (d, *J* = 7.3 Hz, 1 H, NC*H*=CH), 7.14 (t, *J* = 7.1 Hz, 1 H, $H_{ar}$), 7.20 (t, *J* = 7.1 Hz, 1 H, $H_{ar}$), 7.33 (d, *J* = 7.1 Hz, 1 H, $H_{ar}$), 7.59 (d, *J* = 7.1 Hz, 1 H, $H_{ar}$). IR (KBr): $\tilde{\nu}$ = 2958 $cm^{-1}$, 1734, 1654, 1617, 1468, 1317, 738. MS (CI); *m/z*: 435 (M+1), 377. Anal. Calcd for $C_{27}H_{34}N_2O_3$: C, 74.62; H, 7.89; N, 6.45. Found: C, 74.44; H, 7.58; N, 6.16.

**10d**: Colorless crystals, mp 107 °C (*n*-heptane). $t_R$ = 13.1 min. $[\alpha]_D$ = -282° (*c* = 0.1, $CH_2Cl_2$). $^1$H NMR (400 MHz, $CDCl_3$): δ = 0.61 ppm (s, 3 H, $CH_3$), 0.78 (s, 3 H, $CH_3$), 0.87 (s, 3 H, $CH_3$), 0.94 (s, 9 H, *t*-$C_4H_9$), 1.65-1.78 (m, 2 H, $CH_2CH_2$), 2.00-2.09 (m, 1 H, $CH_2CH_2$), 3.20 (dt, *J* = 5.1, 11.4 Hz, 1 H, $CH_2CH_2$), 3.70 (s, 3 H, $CH_3$), 3.89 (d, *J* = 11.1 Hz, 1 H, $CH_2O$), 4.10 ( d, *J* = 11.1. Hz, 1 H, $CH_2O$), 6.08-6.10 (m, 2 H, NC*H*$CH_2$, NCH=C*H*), 6.42 (d, *J* = 7.7 Hz, 1 H, NC*H*=CH), 7.10-7.30 (m, 3 H, $H_{ar}$), 7.53 (d, *J* = 7.2 Hz, 1 H, $H_{ar}$). IR (KBr): *v* = 2953 $cm^{-1}$, 1738, 1650, 1615, 1450, 1320, 740. MS (CI); *m/z*: 435 (M+1).

**(1*S*,5*R*)-1-[(1*S*)-1,2-Dihydro-9-methyl-1-phenylpyrido[3,4-*b*]indolylcarbonyl]-5,8,8-trimethyl-3-oxabicyclo[3.2.1]octan-2-one (9e).**

According to GP1. Yields and diastereoselectivities see Table 1. Analytical HLPC (*n*-heptane/$C_2H_5OAc$ = 9:1; 2 mL/min).

**9e**: Colorless crystals, mp 238 °C (*n*-heptane). $t_R$ = 31.2 min. $[\alpha]_D$ = +605° (*c* = 0.2, $CH_2Cl_2$). $^1H$ NMR (400 MHz, $CDCl_3$): δ = 0.82 ppm (s, 3 H, $CH_3$), 0.98 (s, 3 H, $CH_3$), 1.35 (s, 3 H, $CH_3$), 1.76-1.78 (m, 2 H, $CH_2CH_2$), 2.05-2.13 (m, 1 H, $CH_2CH_2$), 2.53-2.61 (m, 1 H, $CH_2CH_2$), 3.61 (s, 3 H, $NCH_3$), 3.88 (d, *J* = 11.1 Hz, 1 H, $OCH_2$), 4.07 (d, *J* = 11.1 Hz, 1 H, $OCH_2$), 6.20 (d, *J* = 7.3 Hz, 1 H, NCH=C*H*), 6.37 (d, *J* = 7.3, 1 H, NC*H*=CH), 6.89 (s, 1 H, NC*H*C), 7.09-7.18 (m, 8 H, $H_{ar}$), 7.56 (d, *J* = 8.1 Hz, 1 H, $H_{ar}$). IR (KBr): *v* = 3447 $cm^{-1}$, 2925, 1727, 1654, 1472, 1329, 1228, 734. MS (70 eV); *m/z*: 454 ($M^+$), 377, 259, 244, 195. Anal. Calcd for $C_{29}H_{30}N_2O_3$: C, 76.63; H, 6.62; N, 6.16. Found: C, 76.43; H, 6.63; N, 6.07.

**General procedure for the hydrogenation of 9 and 10 leading to 13 and 14 (GP2).**

Compound (**9**) or (**10**) (1.00 mmol), respectively, was dissolved in anhydrous $CH_3OH$ (35.0 mL). Whenever the compound was poorly soluble in $CH_3OH$, a small amount of anhydrous $C_2H_5OAc$ was added. Pd/C (400 mg, 10% Pd, oxidized form, Merck) was added for each mmol of **9** or **10**. The vessel was flushed with $H_2$ and a balloon filled with $H_2$ was put on the vessel. The reaction mixture was stirred under $H_2$ atmosphere at normal pressure and at rt for 14 h (for **9**/**10d**: 3 bar, 5 days). The mixture was filtered followed by thorough washes with $CH_2Cl_2$ and evaporation of the solvent in vacuo. Purification by CC (petrol ether/$C_2H_5OAc$ = 7:3). The reaction proceeded quantitatively in each case.

**(1*S*,5*R*)-1-[(1*S*)-1,2,3,4-Tetrahydro-1,9-dimethylpyrido[3,4-*b*]indolylcarbonyl]-5,8,8-trimethyl-3-oxabicyclo[3.2.1]octan-2-one (13a).**

According to GP2. Analytical HLPC (*n*-heptane/$C_2H_5OAc$ = 85:15; 1 mL/min).

Colorless crystals, mp 82 °C (*n*-heptane). $t_R$ = 31.1 min. $[\alpha]_D$ = +18° (*c* = 1.0, $CH_2Cl_2$). $^1H$ NMR (400 MHz, $d^5$-nitrobenzene, 120 °C): δ = 0.92 ppm (s, 3 H, $CH_3$), 1.13 (s, 3 H, $CH_3$), 1.42 (s, 3 H, $CH_3$), 1.59 (d, *J* = 6.3 Hz, 3 H, NCHC*H*$_3$), 1.94-2.07 (m, 3 H, $CH_2$), 2.38-2.64 (m, 1 H, $CH_2$), 2.70 (d, *J* = 14.6 Hz, 1 H, $CH_2$), 2.84-3.13 (m, 1 H, $CH_2$), 3.48 (dt, *J* = 12.4, 3.8 Hz, 1 H, $CH_2$), 3.58 (s, 3 H, $NCH_3$), 4.02 (d, *J* = 11.2 Hz, 1 H, $CH_2O$), 4.15-4.28 (m, 2 H, $CH_2$, $CH_2O$), 5.60-5.76 (br, 1 H, N*CH*$CH_3$), 7.09-7.15 (t, 1 H, $H_{ar}$), 7.17-7.28 (m, 2 H, $H_{ar}$), 7.43-7.47 (m, 1 H, $H_{ar}$). IR (KBr): *v* = 2924 $cm^{-1}$, 1729, 1636, 1472, 1414, 1121, 1072, 1023, 741. MS (70 eV); *m/z*: 394 ($M^+$), 397, 199. Anal. Calcd for $C_{24}H_{30}N_2O_3$: C, 73.07; H, 7.66; N, 7.10. Found: C, 72.77; H, 7.81; N, 7.25.

**(1*S*,5*R*)-1-[(1*R*)-1,2,3,4-Tetrahydro-1,9-dimethylpyrido[3,4-*b*]indolylcarbonyl]-5,8,8-trimethyl-3-oxabicyclo[3.2.1]octan-2-one (14a).**

According to GP2. Analytical HLPC (*n*-heptane/$C_2H_5OAc$ = 85:15; 1 mL/min).

Colorless crystals, $t_R$ = 39.4 min. $[\alpha]_D$ = –11° (*c* = 1.0, $CH_2Cl_2$). $^1H$ NMR (400 MHz, nitrobenzene-$d^5$, 120 °C): δ = 0.93 ppm (s, 3 H, $CH_3$), 1.13 (s, 3 H, $CH_3$), 1.43 (s, 3 H, $CH_3$), 1.52 (d, *J* = 6.3 Hz, 3 H, NCHC*H*$_3$), 1.80-1.95 (m, 4 H, $CH_2$), 2.40-2.58 (m, 1 H, $CH_2$), 2.75 (dt, *J* = 14.6, 3.3 Hz, 1 H, $CH_2$), 3.04-3.16 (m, 1 H, $CH_2$), 3.51 (dt, *J* = 12.8, 3.6 Hz, 1 H, $CH_2$), 3.59 (s, 3 H, $NCH_3$), 4.02 (d, *J* = 11.2 Hz, 1 H, $CH_2O$), 4.14-4.26 (m, 2 H, $CH_2$, $CH_2O$), 5.98 (q, *J* = 6.3 Hz, 1 H, N*CH*$CH_3$), 7.08 (t, *J* = 6.4 Hz, 1 H, $H_{ar}$), 7.16-7.19 (m, 2 H, $H_{ar}$), 7.44 (d, *J* = 6.4 Hz, 1 H, $H_{ar}$ ). IR (KBr): *v* = 2928 $cm^{-1}$, 1725, 1637, 1472, 1414, 1121, 1070, 1032, 740. MS (70 eV); *m/z*: 394 ($M^+$), 379, 199. Anal. Calcd for $C_{24}H_{30}N_2O_3$: C, 73.07; H, 7.66; N, 7.10. Found: C, 73.10; H, 8.08; N, 6.95.

**(1*S*,5*R*)-1-[(1*S*)-1-Ethyl-1,2,3,4-tetrahydro-9-methylpyrido[3,4-*b*]indolylcarbonyl]-5,8,8-trimethyl-3-oxabicyclo[3.2.1]octan-2-one (13b).**

According to GP2. Colorless crystals, mp 75 °C (*n*-heptane). $t_R$ = 28.5 min (*n*-heptane/$C_2H_5OAc$ = 85:15; 1 mL/min). $[\alpha]_D$ = + 41° (*c* = 0.4, $CH_2Cl_2$). $^1H$ NMR (400 MHz, nitrobenzene-$d^5$, 130 °C): δ = 0.92 ppm (s, 3 H, $CH_3$), 1.13 (s, 3 H, $CH_3$), 1.21 (t, *J* = 7.2 Hz, 3 H, $CH_2C$*H*$_3$), 1.43 (s, 3 H, $CH_3$), 2.01-2.10 (m, 5 H, $CH_2$), 2.45-2.55 (m, 1 H, $CH_2$), 2.71 (dt, *J* = 2.8, 11.2 Hz, 1 H, $CH_2$), 3.00-3.09 (m, 1 H, $CH_2$), 3.55-3.66 (m, 4 H, $NCH_3$, $CH_2$), 4.01 (d, *J* = 11.1 Hz, 1 H, $CH_2O$), 4.16 (dt, *J* = 3.2, 11.2 Hz, 1 H, $CH_2$), 4.21 (d, *J* = 11.1 Hz, 1 H, $CH_2O$), 5.86-5.91 (m, 1 H, NC*H*$CH_2$), 7.09 (t, *J* = 6.6 Hz, 1 H, $H_{ar}$), 7.20-7.28 (m, 2 H, $H_{ar}$), 7.46 (d, *J* = 7.2 Hz, 1 H, $H_{ar}$). IR (KBr): *v* = 2926 $cm^{-1}$, 1733, 1636, 1471, 1412, 1377, 1227, 1070, 1022, 740. MS (70 eV); *m/z*: 408 ($M^+$), 379, 195, 167. Anal. Calcd for $C_{25}H_{32}N_2O_3$: C, 73.50; H, 7.89; N, 6.86. Found: C, 73.81; H, 8.05; N, 6.41.

**(1*S*,5*R*)-1-[(1*S*)-1-Butyl-1,2,3,4-tetrahydro-9-methylpyrido[3,4-*b*]indolylcarbonyl]-5,8,8-trimethyl-3-oxabicyclo[3.2.1]octan-2-one (13c).**

According to GP2. Colorless crystals, mp 88 °C (*n*-heptane). $t_R$ = 25.3 min (*n*-heptane/$C_2H_5OAc$ = 85:15; 1 mL/min). $[\alpha]_D$ = +30° (*c* = 0.3, $CH_2Cl_2$). $^1H$ NMR (400 MHz, $CDCl_3$): δ = 0.70-0.82 ppm (m, 9 H, 3 x $CH_3$), 1.21-1.32 (m, 6 H, $CH_2$), 1.35 (s, 3 H, $CH_3$), 1.72-1.82 (m, 4 H, $CH_2$), 2.18 (dt, *J* = 3.2, 11.2 Hz, 0.2 x 1 H, $CH_2$), 2.48-2.57 (m, 0.8 x 1 H, $CH_2$), 2.63 (dd, *J* = 10.8, 2.5 Hz, 0.2 x 1 H, $CH_2$), 2.65-2.71 (m, 0.8 x 1 H, $CH_2$), 3.25 (dt, *J* = 11.2, 3.7 Hz, 0.2 x 1 H, $CH_2$), 3.45-3.53 (m, 0.8 x 2 H and 0.2 x 1 H, $CH_2$), 3.59 (s, 0.2 x 3 H, $NCH_3$), 3.61 (s, 0.8 x 3 H, $NCH_3$), 3.85 (d, *J* = 11.1 Hz, 0.2 x 1 H, $CH_2O$), 3.89 (d, *J* = 11.1 Hz, 0.8 x 1 H , $CH_2O$), 3.95 (d, *J* = 11.1 Hz, 0.2 x 1 H, $CH_2O$), 4.07 (d, *J* = 11.1. Hz, 0.8 x 1 H, $CH_2O$), 5.68-5.70 (m, 0.8 x 1 H, NC*H*$CH_2$), 6.06-6.08 (m, 0.2 x 1 H, NC*H*$CH_2$), 6.99-7.04 (m, 1 H, $H_{ar}$), 7.10 (t, *J* = 8.2 Hz, 1 H, $H_{ar}$), 7.18-7.21 (m, 1 H, $H_{ar}$), 7.36 (d, *J* = 7.8 Hz, 1 H, $H_{ar}$); ratio of rotamers: 8:2.

IR (KBr): $\nu$ = 2957 $cm^{-1}$, 1739, 1636, 1469, 1412, 1214, 1120, 1074, 1023, 740. MS (70 eV); *m/z*: 436 ($M^+$), 379, 167. Anal. Calcd for $C_{27}H_{36}N_2O_3$: C, 74.28; H, 8.31; N, 6.42. Found: C, 74.22; H, 8.69; N, 5.00.

**(1*S*,5*R*)-1-[(1*S*)-1-*tert*-Butyl-1,2,3,4-tetrahydro-9-methylpyrido[3,4-*b*]indolylcarbonyl]-5,8,8-trimethyl-3-oxabicyclo[3.2.1]octan-2-one (13d).**

According to GP2 (3 bar, 5 days). Colorless crystals, mp 27 °C (*n*-heptane). $t_R$ = 20.1 min (*n*-heptane/$C_2H_5OAc$ = 85:15; 1 mL/min). $[\alpha]_D$ = +23° (*c* = 0.3, $CH_2Cl_2$). $^1H$ NMR (400 MHz, $CDCl_3$): δ = 0.86 ppm (s, 0.75 x 3 H, $CH_3$), 0.94 ppm (s, 0.25 x 3 H, $CH_3$), 0.98 (s, 0.25 x 3 H, $CH_3$), 1.01 (s, 0.75 x 3 H, $CH_3$), 1.10 (s, 0.25 x 9 H, $CH_3$), 1.15 (s, 0.75 x 9H, $CH_3$), 1.31 (s, 0.25 x 3 H, $CH_3$), 1.34 (s, 0.75 x 3 H, $CH_3$), 1.80-1.95 (m, 2 H, $CH_2$), 2.12-2.17 (m, 1 H, $CH_2$), 2.50-2.61 (m, 1 H, $CH_2$), 2.73-2.99 (m, 1 H, $CH_2$), 3.21-3.37 (m, 1 H, $CH_2$), 3.62 (s, 0.25 x 3 H, $NCH_3$), 3.65 (s, 0.75 x 3 H, $NCH_3$), 3.75-3.81 (m, 1 H, $CH_2$), 3.95 (d, *J* = 11.1 Hz, 0.75 x 1 H, $CH_2O$), 4.05 (d, *J* = 11.1 Hz, 0.25 x 1 H, $CH_2O$), 4.12 (d, *J* = 11.1 Hz, 0.75 x 1 H, $CH_2O$), 4.21 (d, *J* = 11.1 Hz, 0.25 H, $CH_2O$), 5.60 (s, 0.75 H, NC*H*C), 5.98 (s, 0.25 H, NC*H*C), 7.05-7.20 (m, 2 H, $H_{ar}$), 7.31 (d, *J* = 8.1 Hz, 1 H, $H_{ar}$), 7.47 (d, *J* = 8.1 Hz, 1 H, $H_{ar}$); ratio of rotamers:75:25. IR (KBr): $\nu$ = 2924 $cm^{-1}$, 1739, 1636, 1472, 1217, 1121, 1062, 1014, 834, 741. MS (CI); *m/z*: 437 ($M^+$+1), 379, 202, 149. Anal. Calcd for $C_{27}H_{36}N_2O_3$: C, 74.28; H, 8.31; N, 6.42. Found: C, 74.51; H, 8.42; N, 6.96.

**(1*S*,5*R*)-1-[(1*S*)-1,2,3,4-Tetrahydro-9-methyl-1-phenylpyrido[3,4-*b*]indolylcarbonyl]-5,8,8-trimethyl-3-oxabicyclo[3.2.1]octan-2-one (13e).**

According to GP2. Colorless crystals, mp 250 °C (*n*-heptane). $t_R$ = 26.1 min (*n*-heptane/$C_2H_5OAc$ = 85:15; 1 mL/min). $[\alpha]_D$ = +153° (*c* = 1.0, $CH_2Cl_2$). $^1H$ NMR (400 MHz, nitrobenzene-$d^5$, 130 °C): δ = 0.95 ppm (s, 3 H, $CH_3$), 1.10-1.15 (m, 1 H, $CH_2$), 1.20-1.35 (m, 7 H, 2 x $CH_3$ and 1 x $CH_2$), 1.95-2.01 (m, 1 H, $CH_2$), 2.40-2.45 (m, 2 H, $CH_2$), 2.76 (dd, *J* = 10.5, 1.5 Hz, 1 H, $CH_2$), 3.15-3.20 (m, 1 H, $CH_2$), 3.35 (s, 3 H, $NCH_3$), 3.45 (dt, *J* = 10.5, 3.2 Hz, 1 H, $CH_2$), 3.96 (d, *J* = 11.1 Hz, 1 H, $CH_2O$), 4.21 (d, *J* = 11.1 Hz, 1 H, $CH_2O$), 7.10-7.25 (m, 8 H, NC*H*C, $H_{ar}$), 7.47 (d, *J* = 7.2 Hz, 1 H, $H_{ar}$), 7.55 (d, *J* = 7.2 Hz, 1 H, $H_{ar}$). IR (KBr): $\nu$ = 2936 $cm^{-1}$, 1727, 1626, 1469, 1409, 1116, 1021, 754. MS (70 eV); *m/z*: 456, 430, 262, 232, 149. Anal. Calcd for $C_{29}H_{32}N_2O_3$: C, 76.29; H, 7.06; N, 6.14. Found: C, 76.20; H, 7.17; N, 6.38.

**General procedure for the reductive removal of the chiral auxiliary (GP3).**

$LiAlH_4$ (2.5 equiv., 1.00 M in $(C_2H_5)_2O$) was added to $CH_3OH$ (5 equiv., 1.00 M in THF). The resulting mixture was added dropwise to a solution of the respective *N*-acyl-1,2,3,4-tetrahydro-β-carboline (1

equiv., 0.04 M in THF) at -25 °C. Following 24 h stirring, the reaction was quenched by the addition of $CH_3OH$ (10 equiv.). The mixture was allowed to warm to rt. The mixture was diluted with $H_2O$, acidified with 1.00 M $HCl_{aqu}$ to pH 1 and the aqueous layer was extracted 3 times with $CH_2Cl_2$. The pH of the aqueous layer was brought to pH 8 with $Na_2CO_{3(s)}$ and 1.00 M $NaOH_{aqu}$. The aqueous layer was extracted 3 times with $CH_2Cl_2$. The resulting organic layers were dried over $MgSO_4$ and concentrated in vacuo. Purification by CC ($C_2H_5OAc/CH_3OH/C_2H_5(CH_3)_2N$ = 100:10:1).

**(*S*)-1,9-Dimethyl-1,2,3,4-tetrahydropyrido[3,4-*b*]indole ((*S*)-1a).** According to GP3. Yield: 80%. Colorless crystals, mp 105 °C. $[\alpha]_D$ = +10.2° ($C_2H_5OAc$) (*c* = 1.0, $CHCl_3$). $^1$H NMR (400 MHz, $CDCl_3$): δ = 1.43 ppm (d, *J* = 6.8 Hz, 3 H, CHC*H*$_3$), 1.75 (s, 1 H, NH), 2.66 (t, *J* = 5.6 Hz, 2 H, $NHCH_2CH_2$), 3.06 (td, *J* = 5.6, 13.3 Hz, 1 H, $NHCH_2CH_2$), 3.16 (td, *J* = 5.6, 13.3 Hz, 1 H, $CH_2$, $NHCH_2CH_2$), 3.57 (s, 3 H, $NCH_3$), 4.16 (q, *J* = 6.8 Hz, 1 H, $NCHCH_3$), 7.04 (t, *J* = 6.8 Hz, 1 H, NCCCHC*H*), 7.12 (t, *J* = 6.8 Hz, 1 H, NCCHC*H*), 7.24 (d, *J* = 6.8 Hz, NCC*H*), 7.42 (d, *J* = 6.8 Hz, 1 H, NCCC*H*). IR (KBr): *v* = 2971 cm$^{-1}$, 1470, 1377, 1260, 1184, 800, 739. MS (70 eV); *m/z*: 200 ($M^+$), 185. Anal. Calcd for $C_{13}H_{16}N_2$: C, 77.97; H, 8.05; N, 13.98. Found: C, 77.88; H, 8.19; N, 13.94. The analytical data ($^1$H NMR, IR and MS) are in accordance with literature.

**(*R*)-1,9-Dimethyl-1,2,3,4-tetrahydropyrido[3,4-*b*]indole ((*R*)-1a).** According to GP3. Yield: 76%. Colorless crystals. $[\alpha]_D$ = -10.8° (*c* = 1.0, $CHCl_3$). Anal. Calcd for $C_{13}H_{16}N_2$: C, 77.97; H, 8.05; N, 13.98. Found: C, 77.83; H, 8.18; N, 13.99. The spectral ($^1$H NMR, IR, and MS) data were identical with those of (*S*)-**1a**.

**(*S*)-1-Ethyl-9-methyl-1,2,3,4-tetrahydropyrido[3,4-*b*]indole ((S)-1b).** According to GP3. Yield: 62%. Colorless crystals, mp 102 °C ($C_2H_5OAc$). $[\alpha]_D$ = -13.2° (*c* = 1.0, $CHCl_3$). $^1$H NMR (400 MHz, $CDCl_3$): δ = 0.95 ppm (t, *J* = 6.1 Hz, 2 H, $NCHCH_2CH_3$), 1.36-1.40 (m, 2 H, $NCHCH_2CH_3$), 1.80 (s, 1 H, NH), 2.69 (m, 2 H, $NCH_2CH_2$), 3.10 (td, *J* = 4.6, 13.4 Hz, 1 H, $NHCH_2CH_2$), 3.15 (td, *J* = 7.1, 13.4 Hz, 1 H, $NHCH_2CH_2$), 3.35 (s, 3 H, $NCH_3$), 4.11 (t, *J* = 7.1 Hz, 1 H, $NHCHCH_2$), 7.08 (t, *J* = 7.2 Hz, 1 H, $H_{ar}$), 7.13 (t, *J* = 7.2 Hz, 1 H, $H_{ar}$), 7.26 (d, *J* = 7.2 Hz, 1 H, $H_{ar}$), 7.42 (d, *J* = 7.2 Hz, 1 H, $H_{ar}$). IR (KBr): *v* = 2972 cm$^{-1}$, 1455, 1305, 1163, 1100, 738. MS (70 eV): *m/z* = 214 ($M^+$), 199. Anal. Calcd for $C_{14}H_{18}N_2$: C, 78.46; H, 8.47; N, 13.07. Found: C, 78.50; H, 8.69; N, 12.82.

**(*S*)-1-Butyl-9-methyl-1,2,3,4-tetrahydropyrido[3,4-*b*]indole ((*S*)-1c).** According to GP3. Yield: 81%. Colorless crystals, mp 82 °C ($C_2H_5OAc$). $[\alpha]_D$ = -4.6° (*c* = 1.0, $CHCl_3$). $^1$H NMR (400 MHz, $CDCl_3$): δ =

0.94 ppm (t, $J$ = 7.1 Hz, 3 H, $CH_3$), 1.36-1.57 (m, 4 H, $CH_2$, NH), 1.63-1.70 (m, 2 H, $CH_2$), 2.65-2.78 (m, 3 H, $CH_2$, $NHCH_2CH_2$), 3.05 (td, $J$ = 6.9, 13.2 Hz 1 H, $NHCH_2CH_2$), 3.31 (td, $J$ = 5.2, 13.2 Hz, 1 H, $NHCH_2CH_2$), 3.45 (s, 3 H, $NCH_3$), 4.05-4.07 (m, 1 H, $NHCHCH_2$), 7.09 (t, $J$ = 7.9 Hz, 1 H, $H_{ar}$), 7.15 (t, $J$ = 7.9 Hz, 1 H, $H_{ar}$), 7.31 (d, $J$ = 7.9 Hz, 1 H, $H_{ar}$), 7.48 (d, $J$ = 7.9 Hz, 1 H, $H_{ar}$). IR (KBr): $\nu$ = 2960 $cm^{-1}$, 2931, 1472, 1456, 1368, 1323, 1170, 1098, 739. MS (70 eV); *m/z*: 242 (M+), 227. Anal. Calcd for $C_{16}H_{22}N_2$: C, 79.29; H, 9.15; N, 11.56. Found: C, 79.09; H, 9.46; N, 11.46.

**(*S*)-9-Methyl-1-phenyl-1,2,3,4-tetrahydropyrido[3,4-*b*]indole ((*S*)-1e).** According to GP3. Yield: 80%. Colorless crystals, mp 77 °C ($C_2H_5OAc$). $[\alpha]_D$ = -86° ($c$ = 1.0, $CHCl_3$). $^1H$ NMR (400 MHz, $CDCl_3$): δ = 1.75 ppm (s, 1 H, NH), 2.68-2.89 (m, 2 H, $NCH_2CH_2$), 3.03-3.15 (m, 2 H, $NCH_2CH_2$), 3.26 (s, 3 H, $CH_3$), 5.24 (s, 1 H, NHC*H*), 7.13-7.35 (m, 8 H, $H_{ar}$), 7.58 (d, $J$ = 7.2 Hz, 1 H, $H_{ar}$). IR (KBr): $\nu$ = 2920 $cm^{-1}$, 1457, 1350, 1310, 1171, 740. MS (70 eV); *m/z*: 262 ($M^+$), 232, 217, 185. Anal. Calcd for $C_{18}H_{18}N_2$: C, 82.41; H, 6.92; N, 10.67. Found: C, 82.78; H, 7.12; N, 10.45.

**X-Ray analyses**

*Crystal data for* **9a**. $C_{24}H_{28}N_2O_3$, $M$=392.48, orthorhombic, space group $P2_12_12_1$, $a$=6.9559(4) Å, $b$=11.5318(7) Å, $c$=25.1755(16) Å, volume 2019.4(2) $Å^3$, $Z$=4, $D_c$=1.291 mg $m^{-3}$, $\mu$=0.118 $mm^{-1}$, crystal dimensions 0.40x0.30x0.20 mm, $F$(000) 840, $T$=193(2) K, $2\Theta$=3.24° to 58.08°. 11659 reflections measured, independent reflections 4074 [$R_{int}$=0.0376], min. and max. transmission coefficient 0.8879 and 0.6889, $R1$=0.0429, $wR2$=0.0831 for all 4074 reflections with $I>2\sigma(I)$ and $R1$=0.0692, $wR2$=0.0913 for all reflections and 374 refined parameters. Final electron density 0.169 and -0.201 $eÅ^{-3}$, $S$=1.034, absolute structure parameter 0.3(13).

*Crystal data for* **9e**. $C_{29}H_{30}N_2O_3$, $M$=454.55, monoclinic, space group $P2_1$, $a$=7.4796(2) Å, $b$=10.1096(1) Å, $c$=15.8532(2) Å, volume 1185.23(4) $Å^3$, $Z$=2, $D_c$=1.274 mg $m^{-3}$, $\mu$=0.083 $mm^{-1}$, crystal dimensions 0.45x0.11x0.05 mm, $F$(000) 484, $T$=193 K, $2\Theta$=4.80° to 57.04°. 6205 reflections measured, independent reflections 3504 [$R_{int}$=0.0379], $R1$=0.0834, $wR2$=0.1524 for all 3504 reflections with $I>2\sigma(I)$ and $R1$=0.0912, $wR2$=0.1552 for all reflections and 311 refined parameters. Final electron density 0.265 and -0.263 $eÅ^{-3}$, $S$=1.377, absolute structure parameter -1(3).

All data sets were collected on a Siemens P4 diffractometer equipped with a LT2device and a CCD area detector; Mo Kα radiation, graphite monochromator. Single crystals were covered with perfluoroether oil

and mounted on the tip of a glass fibre. Data were collected in the hemisphere mode implemented in the program SMART.[23] Data reduction was performed with the program SAINT. The SHELX97[24] program was used for structure solution and refinement. All non-hydrogen atoms were refined anisotropically, and the hydrogen atoms were included in the final refinement as a riding model on placing them on calculated positions. Crystal and data collection parameters, relevant structure refinement parameters, atomic coordinates for the non-hydrogen atoms, positional and isotropic displacement coefficients for hydrogen atoms, a list of anisotropic displacement coefficients for the non-hydrogen atoms and a full list of bond distances and bond angles have been deposited with the Cambridge Crystallographic Data Center. The data will be sent on quoting the CCDCnumbers 251682 (e-mail: deposit@ccdc.cam.ac.uk)

**Radioreceptor Assay**

The binding assay was performed as described previously. $K_i$ values for test compounds were calculated from competition experiments with at least six concentrations of test compounds, by the use of InPlot 4.0 (GraphPad Software, San Diego, CA). Data are expressed as means ± standard error of the means (SEM) of three experiments, each carried out in triplicate.

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**REFERENCES**

1 (a) R. E. Schultes, *Science*, 1969, **163**, 245; (b) J. R. F. Allen, O. Beck, S. Borg, and R. Skroeder, *Eur. J. Mass Spectrom. Biochem. Med. Envir. Res.*, 1980, **1**, 171; (c) H. Rommelspacher, S. Strauss, and J. Lindemann, *FEBS Lett.*, 1980, **109**, 209; (d) A. Agarwal, S. K. Agarwal, S. N. Singh, N. Fatma, and R. K. Chatterjee, *Bioorg. Med. Chem. Lett.*, 1996, **6**, 225; (e) S. K. Rabindran, H. He, M. Singh, E. Brown, K. I. Collins, T. Annable, and L. M. Greenberger, *Cancer Res.*, 1998, **58**, 5850; (f) J. E. Audia, D. A. Evrard, G. R. Murdoch, J. J. Droste, J. S. Nissen, K. W. Schenck, P. Fludzinski, V. L. Lucaites, D. L. Nelson, and M. L. Cohen, *J. Med. Chem.*, 1996, **39**, 2773; (g) L.-M. Yang, C.-F. Chen, and K.-H. Lee, *Bioorg. Med. Chem. Lett.*, 1995, **5**, 465.

2 (a) Z. Czarnocki, D. B. MacLean, and W. A. Szarek, *Can. J. Chem.*, 1986, **64**, 2205; (b) L. F. Tietze, Y. Zhou, and E. Töpken, *Eur. J. Org. Chem.*, 2000, 2247; (c) D. L. Comins and S. O'Conner, 'Advances in Heterocyclic Chemistry,' Vol 44, ed. by A. R. Katrizky, Academic Press, San Diego, 1988, p. 199.

3 (a) K. Williams, C. Romano, M. A. Dichter, and P. B. Molinoff, *Life Sci.*, 1991, **48**, 469; (b) C. J. McBain and M. L. Mayer, *Physiol Rev.*, 1994, **74**, 723.

4 E. H. F. Wong, J. A Kemp, T. Priestley, A. R. Woodruff, and L. L. Iversen, *Proc. Natl. Acad. Sci. USA*, 1986, **83**, 7104.

5 M. Ludwig, K. Polborn, and K. T. Wanner, *Heterocycles*, 2003, **61**, 299.
6 (a) Z. Czarnocki, D. B. MacLean, and W. A. Szarek, *Bull. Soc. Chim. Belg.*, 1986, **95**, 749; (b) P. Melnyk, P. Ducrot, and C. Thal, *Tetrahedron*, 1993, **49**, 8589.
7 (a) F. Ungemach, M. DiPierro, R. Weber, and J. M. Cook, *J. Org. Chem.*, 1981, **46**, 164; (b) X. Fu and J. M. Cook, *J. Org. Chem.,* 1993, **58**, 661; (c) H. Akimoto, K. Okamura, M. Yui, T. Shioiri, M. Kuramoto, Y. Kikugawa, and S.-I. Yamada, *Chem. Pharm. Bull.*, 1974, **22**, 2614; (d) P. D. Bailey, S. P. Hollinshead, N. R. McLay, K. Morgan, S. J. Palmer, S. N. Prince, C. D. Reynolds, and S. D. Woods, *J. Chem. Soc., Perkin Trans. 1*, 1993, 431; (e) N. De La Figuera, M. T. Garcia-Lopez, I. Rozas, and R. Gonzalez-Muniz, *J. Chem. Soc., Chem. Commun.*, 1994, **5**, 613; (f) G. Massiot and T. Mulumba, *J. Chem. Soc., Chem. Commun.*, 1983,1147; (g) S. Peng and E. Winterfeldt, *Liebigs Ann. Chem.*, 1990, 313.
8 (a) H. Waldmann, G. Schmidt, M. Jansen, and J. Geb, *Tetrahedron*, 1994, **34**, 2402; (b) G. Schmidt, H. Waldmann, H. Henke, and M. Burkard, *Chem. Eur. J.*, 1996, **2**, 1566; (c) M. S. Reddy and J. M. Cook, *Tetrahedron Lett.*, 1994, **35**, 5413; (d) T. Soe, T. Kawate, N. Fukui, and M. Nakagawa, *Tetrahedron Lett.*, 1995, **36**, 1875; (e) R. Tsuji, M. Nakagawa, and A. Nishida, *Tetrahedron Asymmetry*, 2003, **14**, 177; (f) C. Gremmen, B. Willemse, M. J. Wanner, and G.-J. Koomen, *Org. Lett.*, 2000, **2**, 1955.
9 T. Kawate, H. Yamada, T. Soe, and M. Nakagawa, *Tetrahedron Asymmetry*, 1996, **7**, 1249.
10 (a) J. Aubé, S. Gosh, and M. Tanol, *J. Am. Chem. Soc.*, 1994, **116**, 9009; (b) B. Danieli, G. Lesma, M. Mauro, G. Palmisano, and D. Passerella, *J. Org. Chem.*, 1995, **60**, 2506; (c) D. Desmaeele, K. Mekouar, and J. d'Angelo, *J. Org. Chem.*, 1997, **62**, 3890; (d) T. Fujii, M. Ohba, T. Tachinami, and T. Ohashi, *Chem. Pharm. Bull.*, 1991, **39**, 75; (e) S. Hatakeyama, K. Saijo, and S. Takano, *Tetrahedron Lett.*, 1985, **26**, 865.
11 S. F. Martin, K. X. Chen, and C. T. Eary, *Org. Lett.*, 1999, **1**, 79.
12 T. Itoh, M. Yokoya, K. Miyauchi, K. Nagata, and A. Ohsawa, *Org. Lett.*, 2003, **5**, 4301.
13 M. Nakamura, A. Hirai, and E. Nakamura, *J. Am. Chem. Soc.*, 1996, **118**, 8489.
14 L. F. Tietze, Y. Zhou, and E. Töpken, *Eur. J. Org. Chem.*, 2000, 2247.
15 (a) A. I. Meyers, D. B. Miller, and F. H. White, *J. Am. Chem. Soc.*, 1988, **110**, 4778; (b) A. I. Meyers, T. Shoda, and M. F. Loewe, *J. Org. Chem.*, 1986, **51**, 3108; (c) M. F. Loewe and A. I. Meyers, *Tetrahedron Lett.*, 1985, **26**, 3291.
16 S. Adam, X. Pannecoucke, J.-C. Combret, and J.-C. Quirion, *J. Org. Chem.*, 2001, **66**, 8744.
17 W. N. Speckamp and M. J. Moolenaar, *Tetrahedron*, 2000, **56**, 3817.
18 (a) T. Itoh, Y. Matsuya, Y. Enomoto, K. Nagata, M. Miyakzaki, and A. Ohsawa, *Synlett*, 1999, **11**, 1799; (b) T. Itoh, Y. Matsuya, Y. Enomoto, and A. Ohsawa, *Tetrahedron*, 2001, **57**, 7277; (c) T. Itoh, N. Kazuhiro, Y. Masashi, M. Michiko, I. Sachiko, M. Yuji, E. Yasuko, and A. Ohsawa, *Synlett*, 2002, **6**, 1005; (d) T. Itoh, M. Miyazaki, S. Ikeda, K. Nagata, M. Yokoya, Y. Matsuya, Y. Enomoto, and A. Ohsawa, *Tetrahedron*, 2003, **59**, 3527; (e) T. Itoh, M. Miyazaki, K. Nagata, M. Yokoya, S. Nakamura, and A. Ohsawa, *Heterocycles*, 2002, **58**, 115.
19 (a) K. Th. Wanner and A. Kärtner, *Heterocycles*, 1987, **26**, 921; (b) G. Hoefner, G. Fuelep, and K. Th. Wanner, WO00140645, 2000; (c) K. Th. Wanner and F. F. Paintner, *Liebigs Ann. Chem*., 1996, 1941; (d) J. Pabel, C. E. Hösl, M. Maurus, M. Ege, and K. Th. Wanner, *J. Org. Chem*., 2000, **65**, 9272; (e) R. Kammler, K. Polborn, and K. Th. Wanner, *Tetrahedron*, 2003, **59**, 3359; (f) C. E. Hoesl, M. Maurus, J. Pabel, K. Polborn, and K. Th. Wanner, *Tetrahedron*, 2002, **58**, 6757; (g) K. Th. Wanner, H. Beer, G. Höfner, and M. Ludwig, *Eur. J. Org. Chem*., 1998, 2019.
20 W. N. Speckamp and H. Hiemstra, *Tetrahedron*, 1985, **41**, 4367.
21 J. L. Bennasar, E. Zulaica, B. A. Sufi, and J. Bosch, *Tetrahedron*, 1996, **52**, 8601.
22 G. Höfner and K. Th. Wanner, *J. Recept. Signal Transduct. Res*., 1996, **16**, 297.
23 Siemens Industrial Automation, Madison, Version 49 (1997). 5.0 and 5.1 (1995)
24 SHELX97 programm, G. W. Sheldrick, University of Göttingen, 1997.