Asymmetric Synthesis and Enantioselectivity of Binding of 1-Aryl-1,2,3,4-tetrahydroisoquinolines at the *PCP* Site of the *NMDA* Receptor Complex☆

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A new method for the asymmetric synthesis of 1-substituted tetrahydroisoquinolines is presented. It is based on stereoselective addition reactions of organometallic compounds to the intermediate *N*-acyliminium ion **6**, which is provided with an *N*-acyl group as a chiral auxiliary. In addition reactions with organomagnesium and organozinc reagents diastereoselectivities from 70:30 to 95:5 (for **7**/**8**) were observed with the zinc reagents in general leading to markedly improved stereoselectivities. By catalytic hydrogenation of **7** and **8** and after removal of the chiral auxiliary the target compounds **11** and **12** were obtained. The enantiomerically pure **11c–g** and **12c–g** (ee > 99 %), 1-aryltetrahydroisoquinolines, were evaluated for their affinity to the *PCP* [1-(1-phenylcyclohexyl)piperidine] binding site of the *NMDA* (*N*-methyl *D*-aspartate) receptor. In each case the enantiomers **11** exhibited a higher affinity than those of **12**, with the potencies of the enantiomers differing by a factor of 4 (**11**/**12g**) to 27 (**11**/**12c**). The absolute configuration of the more potent enantiomers **11** is in accordance with the stereochemical requirement found for *FR 115427* (**3**) which is a close analogue.

Introduction

The *N*-methyl *D*-aspartate (*NMDA*) receptor is a subtype of the excitatory amino acid (*EAA*) receptors and has been implicated in many physiological and pathological events in the brain.[1]

Several binding sites have been characterized to control the activity of the *NMDA* receptor complex. One binding site, the *PCP* site is located within the ion channel (ion channel binding site) which is an integral part of the *NMDA* receptor. Agents that bind to this site always exhibit an antagonistic effect as the ion flux through the receptor channel is blocked.

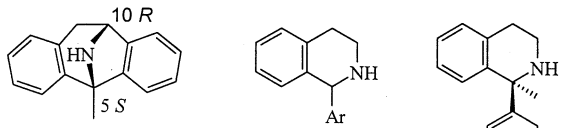
At present this site is a major target for the development of new drugs for the treatment of various neuronal disease states (e.g. Alzheimer′s disease, Parkinson′s disease)[2][3].

MK-801 (**1**) is a long-known high-affinity ligand (*PCP* site ligand) for the aforementioned binding site with a unique structure[4].

In 1989 N. Gray et al.[5] reported new ligands for the *PCP* binding site with the general structure **2**, which had been designed as flexible analogues of *MK-801* (**1**). For those compounds, however, it was found that their affinity for the *PCP* binding site is about three orders less in magnitude than that of *MK-801* ($IC_{50} \approx 2-5$ μM).

A few years later (1993) a research group at the Fujisawa Pharmaceutical Company presented the tetrahydroisoquinoline *rac*-**3** with a quaternary carbon atom at C-1 as a new and distinctly more potent ligand for the *PCP* binding site as compared to those of class **2**[6]. The enantiomers of **3** were found to exhibit a remarkable degree of stereoselectivity in binding with the (*S*) isomer being about hundred times more potent than the (*R*) form [(*S*)-*FR 115427*, K_i = 35.4 nM; (*R*)-*FR 115427*, K_i = 3756 nM]. In contrast to that the enantioselectivity of binding of *MK-801* is only moderate with K_i values of 3.57 nM and 16.0 nM for the (+)-(5*S*,10*R*) and the (−)-(5*R*,10*S*) isomers, respectively[6]. [The designation *MK-801* stands for the (+)-(5*S*,10*R*) enantiomer, whereas the (−)-(5*R*,10*S*) stereoisomer is termed as (−)-*MK-801*].

Scheme 1



1 *MK-801* **2** (*S*)-**3**

(Fr 115427 = (*S*)-**3**
Fr 115426 = (*R*)-**3**)

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Compound **3** and the isoquinolines **2** are flexible analogues of *MK-801* (**1**) that differ from the latter (**1**) mainly by the fact that a carbon−carbon bond between position 9a and 10 is missing.

With the structure of these compounds being closely related, their binding mode to the *PCP* receptor (of **2** and **3**) as compared to that of *MK-801* (**1**) might be very similiar, as well. In this case, also the enantioselectivity of the binding of the more flexible derivatives (**2** and **3**) should coincide with that of *MK-801* (**1**). That means the (*R*) stereoisomers of **2** and **3** should be more potent than the (*S*) enantiomers, as the former exhibit the same sense of chirality like *MK-801* (with respect to the chiral center at C-5, the change of the chiral descriptor is a result of the *CIP* rules).

The aim of the present study was to evaluate the 1-aryl-1,2,3,4-tetrahydroisoquinolines **2** for their enantioselectivity of binding to the *PCP* receptor and to establish whether the stereochemical requirements for the binding of **2** and *MK-801* (**1**) are indeed the same. The study of Gray et al. mentioned above had dealt only with racemic compounds.

When our study was already in progress[7], the absolute configuration of the more potent enantiomer of **3**, (*S*)-*FR115427*, was published (in 1996) to be (*S*) (at C-1), and is therefore opposite to that of **1** (at the chiral center at C-5)[8]. As this result was rather unexpected it became even more interesting to uncover whether this is true for compounds of type **2** as well.

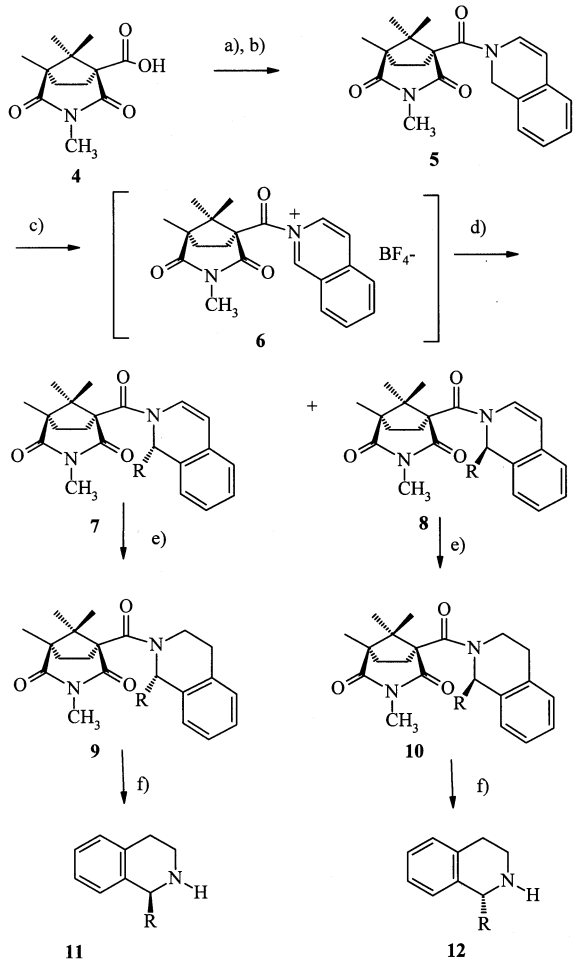
Results and Discussion

For the synthesis of the 1-aryl-1,2,3,4-tetrahydroisoquinolines **11/12c−f**, which we had selected as the target compounds, we employed a method termed as Asymmetric Electrophilic α-Amidoalkylation (AEαA)[9][10]. As a main feature for this type of reaction the desired stereocenter is formed by stereoselectively adding a suitable nucleophile to a chiral *N*-acyliminium ion. In a recent investigation concerning the asymmetric synthesis of 2-substituted piperidines we found that carboxylic acid **4** is a useful chiral auxiliary[11].

This auxiliary and related chiral auxiliaries are assumed to mediate their asymmetric induction by a precomplexation mechanism[11][12]. Thus, when an ambiphilic organometallic reagent is employed, it may coordinate to the chiral auxiliary. In the next step a ligand may be transferred to the iminium subunit, a process that of course proceeds preferentially to one side of the prochiral subunit as a result of the geometry of the formed complex. In the case of the amidoalkylation reactions of piperidines the complex **A** (Scheme 4) appears to be important for the asymmetric induction. According to the results of the present study, however, the geometry of the reactive intermediate may change depending on the nature of the nitrogen heterocycle. For the isoquinoline series reported herein a complex with a different geometry seems to be involved (see below).

The synthesis of the requisite amidoalkylation reagent **5** provided with **4** as a chiral auxiliary was accomplished according to a synthetic methodology, which was developed by Yamaguchi et al[13]. By treatment of the carboxylic acid

Scheme 2



a) $SOCl_2$, 60−65°C, 1.5 h; b) isoquinoline (**13**), Bu_3SnH, − 78°C → r.t.; c) $Ph_3C^+BF_4^-$, r.t., 16 h; d) method A: ArMgBr or CH_3MgBr, −78°C, 2.0−2.5 h; method B: $ZnCl_2$/ArMgBr or Et_2Zn or Me_2Zn, −78°C, 2.0−2.5 h; method C: only for R = Et, $AlEt_3$, −78°C, 2.0 h; e) **7/8a, c, d, f, g**: Pd/C, H_2, EtOH, r.t., 48 h; **7/8 e**: Pt/C, H_2, EtOAc/*n*-hexane, r.t., 48 h; f) $LiAlH_4$, Et_2O, 0°C, 30 h.

chloride of **4** with isoquinoline (**13**) and Bu_3SnH − as the trapping reagent for the intermediate *N*-acylisoquinolinium ion − compound **5** was obtained in high yield (73%).

Compound **5** proved to be a well-suited precursor for the generation of the *N*-acylisoquinolinium ion **6**. This conversion could be accomplished by hydrid abstraction with $Ph_3C^+BF_4^-$. According to TLC the oxidation (of **5** to **6**) was complete within a few hours. It should also be stated that this protocol does not suffer from any unfavorable equilibria, which often occur, when *N*-acyliminium ions are generated in a more direct manner: as for example by reaction of an imine or an unsaturated nitrogen heterocycle with an acid chloride[14].

In order to uncover the influence of the nature of the organometallic species on the stereoselectivity and the yield of the addition reactions to **6** Grignard and zinc reagents were employed as nucleophiles in each case. Except for the ethylation reaction in addition to the zinc an aluminum instead of a Grignard reagent was used (Table 1 entry b).

Table 1. Diastereoselectivities and yields in the preparation of compounds 7−12

	R	MR_x[a]	d.s.[b] **7/8**	Yield [%] **7** + **8**[c]	**7**[d]	**8**[d]	**9**[d]	**10**[d]	**11**[c]	**12**[c]
a)	CH_3	A	72.8:27.2	57	–	–	–	–	–	–
		B	84.8:15.2	43	34	6	–	–	–	–
b)	C_2H_5	B	89.2:10.8	–	–	–	–	–	–	–
		C	87.6:12.4	51	42	5	–	–	–	–
c)	Ph	A	80.4:19.6	82	51	13	93[e]	–	55	42
		B	95.2:4.8	77	–	–	–	–	–	–
d)	4-$H_3CO-C_6H_4$	A	72.0:28.0	84	56	19	90	88	52	43
		B	95.7:4.3	63	–	–	–	–	–	–
e)	4-$Cl-C_6H_4$	A	74.8:25.2	74	48	16	71	72	46	39
		B	96.2:3.8	41	–	–	–	–	–	–
f)	2-Thienyl	A	94.3:5.7	73	58	5	39	32	47	41
		B	82.5:17.5	41	–	–	–	–	–	–
g)	2-Naphthyl	A	68.1:31.9	88	53	24	76	72	34	31
		B	90.1:9.9	48	–	–	–	–	–	–

[a] Method A: addition of 2.0 equiv. ArMgBr or 2.25 equiv. CH_3MgBr (in THF or Et_2O) to a solution of **6** in CH_2Cl_2 at −78°C; Method B: 2.0 equiv. ArMgBr was pretreated with 1.2 equiv. $ZnCl_2$ (in Et_2O) and the resulting mixture was added to a solution of **6** in CH_2Cl_2 at −78°C; for entries a) and b) a solution of Me_2Zn (2.0 M in toluene, 20 equiv.) or Et_2Zn (0.86 M in *n*-hexane, 4 equiv.) was used; method C: addition of 4 equiv. Et_3Al (0.91 M in *n*-hexane) to a solution of **6** in CH_2Cl_2 at −78°C. − [b] Determined from the crude reaction product by HPLC. − [c] After flash chromatography. − [d] After preparative HPLC − [e] Total yield of **9c** + **10c**; preparative HPLC provided the pure isomers **9c** (63%) and **10c** (13%).

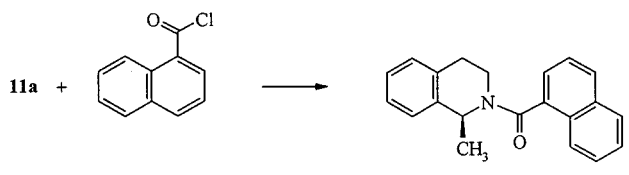
For the methylation reactions of **6** both the stereoselectivities and the yields (total yield of **7** and **8**) were low (see Table 1), regardless whether the Grignard or the zinc reagent had been used and also despite the fact that in the case of the zinc reagent a large excess had been employed (20 equivalents). The ethylation reactions, which were performed with $ZnEt_2$ and $AlEt_3$, proceeded with a higher stereoselectivity than those in the above-mentioned methylation process. As a result the asymmetric induction was in the range of 90:10. These results compare well to those found for a related system derived from a piperidinium ion where the ethylation reactions proceeded with higher diastereoselectivies as well[11].

The arylation reactions of **6** proceeded quite smoothly, no matter whether organomagnesium or organozinc compounds were used, even though the reactions differed in yields (**7** + **8**) and even more significantly in stereoselectivities (d.s. **7/8**, see Table 1). Thus, as a general trend for the magnesium reagents higher yields but lower diastereoselectivities (in the range of 80:20) were found, whereas for the zinc reagents the opposite was true. In the case of the latter reagent the stereoselectivity reached 95:5 (**7/8**, see Table 1). As a single exception from this general trend, however, the results of the addition of the 2-thienyl group were exactly contrary to those mentioned above.

The reaction products that were obtained by the addition of the Grignard reagent were well suited to give access to both enantiomers of the final compounds (**11** and **12**), as due to the lower diastereoselectivity both diastereomers **7** and **8** were present in reasonable amounts. As final compounds for the biological studies the enantiomers **11c−g** and **12c−g** were needed and with respect to the stereochemical assignment (see below), the methyl derivative **11a** was of major interest. Thus, the respective mixtures were separated by preparative HPLC and the diastereomers (**7** and **8**) were purified at least to > 99% de in each case. In the next step these diastereomers were subjected to catalytic hydrogenation to give the tetrahydro derivatives **9** and **10**. In the case of the phenyl derivative **7c/8c** this synthetic sequence was reversed, which means the HPLC separation was carried out after the hydrogenation had been performed. The last step in our synthesis was the removal of the chiral auxiliary and was accomplished by a reductive procedure with $LiAlH_4$ providing the final compounds **11** and **12** in medium yields (see Table 1). Of course, as a result of this procedure the chiral auxiliary could not be recovered.

The stereochemistry of the compound (*S*)-**11c** was established to be (*S*) by an X-ray analysis performed on the intermediate **7c**[15]. Thereby it became also apparent that the stereochemical assignment for (*S*)-**11c** given in literature is incorrect and has to be revised[10b].

Scheme 3



14 **15**

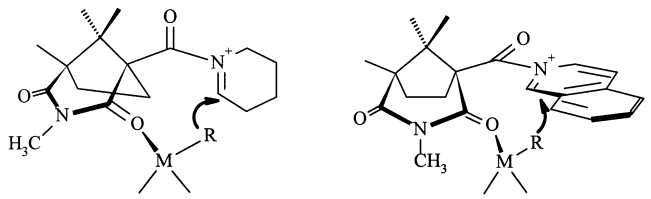
The methyl derivative (*S*)-**11a** was identified to be of (*S*) configuration as well. This assignment has been accomplished by chiral column chromatography of the α-

naphthamide **15** (see Scheme 3) of (*S*)-**11a**[16] which was identical with an analysis performed already earlier by Pirkle et al.[17] for an authentic sample.

The stereochemistry of the remaining compounds **11b**, **11d−g**, **12b** and **12d−g** became apparent from the ^{1}H-NMR spectra of the amidoalkylation products. The spectra of the major diastereomers were of high similarity to each other and the same was true for the minor isomers. Thus, with the stereochemistry being known for (*S*)-**11a** and (*S*)-**11c** to be (*S*) it can be concluded that this stereochemistry applies for **11b**, **11d−g** as well, and that their enantiomers **12b** and **12d−g** are of (*R*) configuration[18].

As a result of the diastereomeric purity of the amidoalkylation products employed in subsequent reactions (de > 99%) the enantiomeric purity of the obtained amines **11c−g** and **12c−g** should be at least 99% (ee). This assumption was verified by reconverting a sample of **11c** to **9c** (with the acid chloride of **4**) which resulted in a product (**9c**) with a diastereomeric purity > 99% (de)

Scheme 4



Complex **A** Complex **B**

According to the above-mentioned results regarding the stereochemistry of the isoquinolines the asymmetric induction in the case of the isoquinolines is opposite to that one which was found for a closely related system with the same chiral auxiliary where the isoquinoline subunit is replaced by a piperidine ring[11][12] (see Scheme 4, **A**). At present the reason for this change of the stereoselectivity in the addition reaction from the *re* to the *si* face is not clear. The stereochemical outcome may be rationalized by the transition state **B** (Scheme 4) where the isoquinolinium substructure is located between the imide function and the dimethylmethano bridge of the chiral auxiliary. For the planar isoquinolinium system this conformation is possibly more easily accessible than this would be the case for the partially saturated and thus sterically more demanding piperidine ring. Although this model is supported by the results of some preliminary force-field calculations, further investigations will have to be awaited in order to verify this assumption.

Biological Test Results

The amines **11c−g** and **12c−g** were evaluated for their in vitro activity on the *PCP* site of the *NMDA* receptor by a radioreceptor assay.

The binding affinities were determined for the water-soluble hydrochloride salts (of **11c−g** and **12c−g**) at rat forebrain membranes with [^{3}H]*MK-801* as a specific ligand.

As reference compounds *PCP*, *MK-801* and *(−)-MK-801* were used. As depicted in Table 2 the binding affinities were strongly dependent on the stereochemistry. For each pair of enantiomers the isomer **11** with (*S*) configuration[18] was more potent than its counterpart **12**. The potencies differed by a factor of at least 4 for **11/12g** to 27 for **11/12c** as the maximum. Thereby the potencies of these compounds are in a range that is in good agreement with the values that have been reported for the racemic substances[5]. However, the order of the potencies e.g. for the more active enantiomers is different from that which was found for the racemates. This does at least partly originate from the fact that the pairs of enantiomers differ markedly in their enantioselectivities of binding. Also some of those differences in binding affinities are very small, and therefore not meaningful.

It is interesting to note that the stereochemical requirement for the binding which was found for the amines **11** and **12** with the isomers **11** exerting the higher biological activities is in accord with the stereochemical behavior found at Fujisawa for the 1-methyl derivative *FR 115427* [(*S*)-**3** more potent than (*R*)-**3**]. Thus, not only the Fujisawa compound *FR 115427* but also the isoquinolines **11/12** exhi-

Table 2. Affinity of **11** and **12** for the *PCP* site of the *NMDA* receptor and for the σ-binding site

	Ar	*PCP* − K_i [μM] **11**	**12**	σ − K_i [μM] **11**	**12**
c)	Ph	1.38 ± 0.07	37.9 ± 5.4	16.3 ± 0.3	12.0 ± 0.4
d)	4-$H_3CO-C_6H_4$	1.84 ± 0.12	31.8 ± 4.6	9.45 ± 0.76	10.7 ± 0.6
e)	4-$Cl-C_6H_4$	3.18 ± 0.19	23.5 ± 2.1	10.3 ± 0.2	7.82 ± 0.24
f)	2-Thienyl	1.22 ± 0.03	27.1 ± 0.4	18.9 ± 0.7	18.5 ± 1.6
g)	2-Naphthyl	6.79 ± 0.41	25.4 ± 1.9	13.8 ± 0.2	9.22 ± 0.32
	PCP	0.109 ± 0.012		2.01 ± 0.08	
	MK-801	0.00436 ± 0.00024			
	(−)-*MK-801*	0.0215 ± 0.0020			
	R-(+)-*3-PPP*			0.0879 ± 0.0037	
	S-(−)-*3-PPP*			0.302 ± 0.025	
	Haloperidol			0.0085 ± 0.0020	
	(+)-*SKF 10,047*				

bit a stereochemical behavior that is opposite to that of *MK-801* (**1**). Thereby the eudismic ratio measured for the isomers **11** and **12** ranging from 4 to 27 is lower than that reported for **3** (eudismic ratio = 100) but with a single exception (**11/12g**, eudismic ratio = 4) higher than that of *MK-801* (**1**, eudismic ratio = 5).

Many *NMDA* antagonists, particularly those acting as *PCP* site ligands, produce psychotomimetic-type activity in animals[19]. It is still under debate whether this unfavorable side effects might arise by an activation of σ receptors[20]. For the racemic compounds of **11/12** it is known that they are ligands for the σ-binding sites as well, and that their binding affinities are in the same range as those for the *PCP* site[5]. As these compounds exhibit a distinct enantioselectivity of binding to the *PCP* site it seemed reasonable to evaluate their stereochemical behavior with respect to the σ-binding sites, as well. Especially with respect to the receptor selectivity, which is for the racemic compounds (**11/12**) almost negligible, the pure enantiomers are possibly more favorable. The assays were performed with a synaptosomal membrane fraction of guinea pig brain using [^{3}H]*DTG* as a radioligand. The binding affinities found were low, especially when compared to those of the reference compounds (see Table 2), but they were in the range of those reported for the racemic compounds[5]. But remarkably, for each pair of enantiomers **11** and **12** the binding potencies are either almost equal or slightly in favor of **12**.

This is in marked contrast to the binding affinities for the *PCP* site where in each case the enantiomers **11** are the more potent compounds. Thus, the enantiomers **11** exhibit a higher affinity for the *PCP* receptor combined with a higher receptor selectivity, according to which result further developments in this area should certainly take the enantiomerically pure compounds into account.

Conclusion

In summary, we have developed a new method for the asymmetric synthesis of 1-substituted tetrahydroisoquinolines based on the employment of the chiral *N*-acyliminium ion **6**. Addition reactions to **6** proceeded with *si* selectivity which may be rationalized by the transition state given in Scheme 4 **B**. The addition products were used to prepare a series of pairs of enantiomeric 1-aryl-substituted tetrahydroisoquinolines (**11** and **12**). *PCP* site binding studies showed the effect of the absolute configuration on the binding affinity. In each case the enantiomers **11** were more potent than their stereochemical counterparts **12** with the selectivities being in the range of 4 to 27. According to these results the stereochemical requirement for binding of **11/12** corresponds to the enantioselectivity of the binding reported for *FR 115427* whereas it is opposite to that of *MK 801*.

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Experimental Section

General Remarks: Standard vacuum techniques were used in the handling of air-sensitive materials. Solvents were dried and kept under N_2 and freshly distilled before use. − M.p.s (uncorrected): Apparatus according to Dr. Tottoli. − ^{1}H NMR spectra: AC 300 and WM 250 (Bruker), chemical shifts (δ), TMS as internal reference. − Mass spectra: SMCH 7 (Varian). − IR spectra: Acculab 6 (Beckman), and IR 430 (Perkin Elmer). Liquids were run as films, solids as KBr pellets. − Optical rotations: Light electric polarimeter Zeiss, 0.5-dm cell and 241 MC Polarimeter (Perkin Elmer); T = 20°C. − Combustion analysis: CHN Rapid (Heraeus), Elemental Analyser 340 B and 340 C (Perkin Elmer). − Column chromatography: Flash chromatography (silica gel 60, 0.40−0.063). − HPLC: L-6200 Intelligent-Pump, L-4250 UV-VIS, D-2500 Chromato-Integrator (Merck Hitachi); column: LiChroCart^R, LiChroSorb^R Si 60 cartridge (250 mm × 4 mm, Merck); precolumn: LiChroCart^R, LiChroSorb^R Si 60 precolumn cartridge (25 × 4 mm, Merck). Preparative HPLC: L-6000 Pump, L-4000 UV-VIS, D-2500 Chromato-Integrator (Merck Hitachi); LiChroSorb^R Si 60 5μ (250 × 20 mm); precolumn: LiChroSorb^R Si 60 5μ (30 × 20 mm).

(1S,5R)-1-(1,2-Dihydro-2-isoquinolylcarbonyl)-3,5,8,8-tetramethyl-3-azabicyclo[3.2.1]octane-2,4-dione (**5**): 5.205 g (21.7 mmol) of **4**[11] was added to 7.1 ml (97.8 mmol, 4.5 equiv.) of thionyl chloride under ice-cooling and the resulting mixture was warmed to 60−65°C for 90 min. After removal of excess thionyl chloride in vacuo, the acid chloride was dissolved in 14 ml of CH_2Cl_2 and added dropwise to a solution (cooled to −78°C) of 2.31 g (21.75 mmol) of isoquinoline and 5.75 ml (21.75 mmol) of Bu_3SnH in 80 ml of CH_2Cl_2. After 140 min, the reaction was quenched by addition of 10 ml of H_2O and the mixture was warmed to room temp. The organic phase was washed with 2 N HCl (2 ×) and with brine (2 ×). After drying ($MgSO_4$) and evaporation of the solvent in vacuo, **5** was obtained by flash chromatography (*n*-hexane/EtOAc = 85:15). Colorless crystals, m.p. 115°C, yield 5.58 g (73%). − $[\alpha]_D$ = +34 (c = 1.01 in CH_3OH). − IR: $\tilde{\nu}$ = 1722 cm^{-1}, 1672, 1623. − ^{1}H NMR (250 MHz, [D_5]nitrobenzene, 393 K): δ = 1.08 (s, 3 H, CH_3), 1.29 (s, 3 H, CH_3), 1.30 (s, 3 H, CH_3), 1.95 (t, J = 8 Hz, 2 H, CH_2), 2.37−2.49 (m, 1 H, CH_2), 2.59−2.71 (m, 1 H, CH_2), 3.23 (s, 3 H, NCH_3), 4.72 (d, J = 15.7 Hz, 1 H, NCH_2), 5.12 (d, J = 15.7 Hz, 1 H, NCH_2), 5.91 (d, J = 7.9 Hz, 1 H, N-C=CH), 7.00−7.20 (m, 5 H, N-CH=, aromatic H). − MS (70 eV); *m/z*: 352 [M^+], 222, 167, 130, 109. − $C_{21}H_{24}N_2O_3$ (352.4): calcd. C 71.60, H 6.86, N 7.95; found C 71.7, H 7.04, N 8.16.

General Procedure I (GP I) for Electrophilic α-Amidoalkylations with **5**: To **5** a solution of $Ph_3C^+BF_4^-$ (0.14 M in CH_2Cl_2) was added and the resulting mixture was stirred overnight at room temp. After cooling to −78°C and addition of the organometallic reagent [method A) organomagnesium, B) organo zinc, C) organo aluminium reagent] it was stirred for 2.5 h. Then 1 ml of H_2O was added and the reaction mixture was warmed to room temp. The aqueous layer was extracted with CH_2Cl_2 (4 ×), and the combined extracts were dried ($MgSO_4$) and concentrated in vacuo. The diastereomeric ratio of the reaction was determined by HPLC (from the crude product). The crude products were purified by flash chromatography to yield **7a−g/8a−g** as a mixture of diastereomers. The pure diastereomers were obtained by preparative HPLC.

(1S,5R)-1-[(S)-1,2-Dihydro-1-methyl-2-isoquinolylcarbonyl]-3,5,8,8-tetramethyl-3-azabicyclo[3.2.1]octane-2,4-dione (**7a**) *and (1S,5R)-1-[(R)-1,2-Dihydro-1-methyl-2-isoquinolylcarbonyl]-3,5,8,8-tetramethyl-3-azabicyclo[3.2.1]octane-2,4-dione* (**8a**): A) According to GP I from 184.7 mg (0.52 mmol) of **5**, 4.0 ml (0.56 mmol, 0.14 M in CH_2Cl_2) of $Ph_3C^+BF_4^-$ and 0.39 ml (1.17 mmol,

3.0 M in Et_2O) of MeMgBr; yield 108.4 mg (57%); **7a/8a** = 72.8:27.2. − B) According to GP I from 252.3 mg (0.716 mmol) of **5**, 5.2 ml (0.72 mmol, 0.14 M in CH_2Cl_2) of $Ph_3C^+BF_4^-$ and 7.16 ml of Me_2Zn (2.0 M in toluene, 20 equiv.). The crude product (**7a/8a** = 84.8:15.2, *n*-hexane/Et_2O = 80:20, 1.0 ml/min) was purified by flash chromatography (*n*-hexane/Et_2O = 75:25) to give 112.8 mg (43%) of colorless crystals. Preparative HPLC (*n*-hexane/Et_2O = 75:25, 9.0 ml/min) of a sample of 84.7 mg yielded 66.9 mg (34%) of **7a** and 11.9 mg (6%) of **8a**.

7a: Colorless crystals, m.p. 195°C. − $[\alpha]_D$ = +602 (*c* = 1.02 in CH_2Cl_2). − IR: $\tilde{\nu}$ = 1721 cm^{-1}, 1671, 1622. − ^1H NMR (300 MHz, $CDCl_3$): δ = 1.03 (s, 3 H, CH_3), 1.22 (s, 3 H, CH_3), 1.28 (s, 3 H, CH_3), 1.38 (d, *J* = 6.6 Hz, 3 H, CHC*H*$_3$), 1.88 (t, *J* = 7.6 Hz, 2 H, CH_2), 2.26−2.42 (m, 2 H, CH_2), 3.15 (s, 3 H, NCH_3), 5.56 (q, *J* = 6.6 Hz, 1 H, C*H*CH_3), 5.93 (d, *J* = 7.7 Hz, 1 H, NC=CH), 6.59 (d, *J* = 7.7 Hz, 1 H, NCH=), 7.07−7.12 (m, 2 H, aromatic H), 7.17−7.22 (m, 2 H, aromatic H). − MS (70 eV); *m/z*: 366 [M^+], 351, 222, 194, 137, 109. − $C_{22}H_{26}N_2O_3$ (366.4): calcd. C 72.10, H 7.15, N 7.65; found C 72.2, H 7.15, N 7.48.

8a: Colorless crystals. − ^1H NMR (300 MHz, $CDCl_3$): δ = 0.83 (s, 3 H, CH_3), 1.01 (s, 3 H, CH_3), 1.19 (s, 3 H, CH_3), 1.37 (d, *J* = 6.5 Hz, 3 H, CHC*H*$_3$), 1.83−2.24 (m, 3 H, CH_2), 3.23 (s, 3 H, NCH_3), 3.37 (ddd, *J* = 6/11/15, 1 H, CH_2), 5.79 (q, *J* = 6.5 Hz, 1 H, C*H*CH_3, partially covered), 5.82 (d, *J* = 7.8 Hz, 1 H, NC=CH), 6.38 (d, *J* = 7.8 Hz, 1 H, NCH=), 7.04−7.12 (m, 2 H, aromatic H), 7.19−7.21 (m, 2 H, aromatic H). − MS (70 eV); *m/z*: 366 [M^+], 351, 222, 194, 137, 109.

(1S,5R)-1-[(S)-1-Ethyl-1,2-dihydro-2-isoquinolylcarbonyl]-3,5,8,8-tetramethyl-3-azabicyclo[3.2.1]octane-2,4-dione (**7b**) *and (1S,5R)-1-[(R)-1-Ethyl-1,2-dihydro-2-isoquinolylcarbonyl]-3,5,8,8-tetramethyl-3-azabicyclo[3.2.1]octane-2,4-dione* (**8b**): C) According to GP I from 32.4 mg (0.092 mmol) of **5**, 0.65 ml (0.091 mmol, 0.14 M in CH_2Cl_2) of $Ph_3C^+BF_4^-$ and 0.37 ml (0.41 mmol, 0.91 M in hexane) of Et_3Al, reaction time 2 h. The crude product (**7b/8b** = 87.6:12.4, *n*-hexane/EtOAc = 82:18, 1.0 ml/min) was purified by flash chromatography (*n*-hexane/EtOAc = 82:18) to give 17.8 mg (51%) of colorless crystals. Preparative HPLC (*n*-hexane/EtOAc = 75:25, 10.5 ml/min) yielded 14.8 mg (42%) of **7b** and 1.8 mg (3%) of **8b**.

7b: Colorless crystals, m.p. 83°C. − $[\alpha]_D$ = +58 (*c* = 0.50 in CH_3OH). − IR: $\tilde{\nu}$ = 1721 cm^{-1}, 1672, 1622. − ^1H NMR (300 MHz, $CDCl_3$): δ = 0.92 (t, *J* = 7.5 Hz, 3 H, CH_2CH_3), 1.02 (s, 3 H, CH_3), 1.22 (s, 3 H, CH_3), 1.27 (s, 3 H, CH_3), 1.78 (dq, *J* = 7.3/7.5 Hz, 2 H, C*H*$_2$CH$_3$), 1.87 (t, *J* = 7.7 Hz, 2 H, CH_2), 2.23−2.45 (m, 2 H, CH_2), 3.16 (s, 3 H, NCH_3), 5.37 (t, *J* = 7.3 Hz, 1 H, NCH), 5.94 (d, *J* = 7.6 Hz, 1 H, NC=CH), 6.62 (d, *J* = 7.6 Hz, 1 H, NCH=), 7.10 (d, *J* = 7.2 Hz, 2 H, aromatic H), 7.17−7.24 (m, 2 H, aromatic H). − MS (70 eV); *m/z*: 380 [M^+] 351, 222, 137, 109. − $C_{23}H_{28}N_2O_3$ (380.5): calcd. C 72.54, H 7.42, N 7.36; found C 72.8, H 7.62, N 7.61.

8b: Colorless crystals. − IR: $\tilde{\nu}$ = 1721 cm^{-1}, 1672, 1622. − ^1H NMR (300 MHz, $CDCl_3$): δ = 0.81 (s, 3 H, CH_3), 0.91 (t, *J* = 7.5 Hz, 3 H, CH_2CH_3), 0.99 (s, 3 H, CH_3), 1.18 (s, 3 H, CH_3), 1.76 (dq, *J* = 7/7.5 Hz, 2 H, C*H*$_2$CH$_3$), 1.81−1.95 (m, 3 H, CH_2), 3.23 (s, 3 H, NCH_3), 3.38 (ddd, *J* = 6/11/15 Hz, 1 H, CH_2), 5.65 (t, *J* = 7 Hz, 1 H, NC*H*), 5.83 (d, *J* = 7.8 Hz, 1 H, NC=CH), 6.42 (d, *J* = 7.8 Hz, 1 H, NCH=), 7.05−7.22 (m, 4 H, aromatic H). − MS (70 eV); *m/z*: 380 [M^+], 351, 222, 137, 109.

B) According to GP I from 56.7 mg (0.16 mmol) of **5**, 1.15 ml (0.16 mmol, 0.14 M in CH_2Cl_2) of $Ph_3C^+BF_4^-$ and 0.75 ml (0.64 mmol, 0.86 M in hexane) of Et_2Zn; **7b/8b** = 89.2:10.8.

(1S,5R)-1-[(S)-1,2-Dihydro-1-phenyl-2-isoquinolylcarbonyl]-3,5,8,8-tetramethyl-3-azabicyclo[3.2.1]octane-2,4-dione (**7c**) *and (1S,5R)-1-[(R)-1,2-Dihydro-1-phenyl-2-isoquinolylcarbonyl]-3,5,8,8-tetramethyl-3-azabicyclo[3.2.1]octane-2,4-dione* (**8c**): A) According to GP I from 1.00 g (2.86 mmol) of **5**, 20.7 ml (2.90 mmol, 0.14 M in CH_2Cl_2) of $Ph_3C^+BF_4^-$ and 5.72 ml (5.72 mmol, 1.0 M in THF) of PhMgBr; reaction time 2 h. The crude product (**7c/8c** = 80.4:19.6, *n*-hexane/Et_2O = 80:20, 1.0 ml/min) was purified by flash chromatography (*n*-hexane/Et_2O = 65:35) to give 1.0 g (82%) of colorless crystals. Preparative HPLC (*n*-hexane/Et_2O = 80:20, 10.5 ml/min) of a sample of 206.5 mg yielded 129.3 mg (51%) of **7c** and 32.7 mg (13%) of **8c**.

7c: Colorless crystals, m.p. 244°C. − $[\alpha]_D$ = +450 (*c* = 0.50 in CH_2Cl_2). − IR: $\tilde{\nu}$ = 1721 cm^{-1}, 1669, 1622. − ^1H NMR (300 MHz, $CDCl_3$): δ = 1.06 (s, 3 H, CH_3), 1.23 (s, 3 H, CH_3), 1.28 (s, 3 H, CH_3), 1.89 (pseudo-t, *J* = 7.7 Hz, 2 H, CH_2), 2.34 (ddd, *J* = 7/8/15 Hz, 1 H, CH_2), 2.46 (ddd, *J* = 7/8/15 Hz, 1 H, CH_2), 3.17 (s, 3 H, NCH_3), 5.95 (d, *J* = 7.6 Hz, 1 H, NC=CH), 6.65 (s, 1 H, NCH), 6.76 (d, *J* = 7.6 Hz, 1 H, NCH=), 7.11−7.38 (m, 9 H, aromatic H). − MS (70 eV); *m/z*: 428 [M^+], 351, 222, 137, 109. − $C_{27}H_{28}N_2O_3$ (428.5): calcd. C 75.68, H 6.59, N 6.54; found C 75.7, H 6.80, N 6.36.

8c: Colorless crystals, m.p. 194°C. − $[\alpha]_D$ = −326 (*c* = 0.58 in CH_2Cl_2). − IR: $\tilde{\nu}$ = 1721 cm^{-1}, 1669, 1622. − ^1H NMR (300 MHz, $CDCl_3$): δ = 0.84 (s, 3 H, CH_3), 1.03 (s, 0.8 × 3 H, CH_3), 1.19 (s, 3 H, CH_3), 1.25 (s, 0.2 × 3 H, CH_3), 1.78−1.92 (m, 2 H, CH_2), 1.96−2.06 (m, 0.8 × 1 H, CH_2), 2.17−2.28 (m, 0.2 × 1 H, CH_2), 2.39−2.50 (m, 0.2 × 1 H, CH_2), 3.09 (s, 0.2 × 3 H, NCH_3), 3.23 (s, 0.8 × 3 H, NCH_3), 3.40 (ddd, *J* = 6/10/15 Hz, 0.8 × 1 H, CH_2), 5.75 (d, *J* = 7.8 Hz, 0.2 × 1 H, NC=CH), 5.86 (d, *J* = 7.8 Hz, 0.8 × 1 H, NC=CH), 6.60 (d, *J* = 7.8 Hz, 0.8 × 1 H, NCH=), 6.76 (d, *J* = 7.8 Hz, 0.2 × 1 H, NCH=), 6.88 (s, 0.8 × 1 H, NCH), 7.01 (s, 0.2 × 1 H, NCH), 7.07−7.34 (m, 9 H, aromatic H); ratio of rotamers = 8:2. − MS (70 eV); *m/z*: 428 [M^+], 351, 222, 137, 109. − $C_{27}H_{28}N_2O_3$ (428.5): calcd. C 75.68, H 6.59, N 6.54; found C 75.8, H 6.75, N 6.37.

B) According to GP I from 46.4 mg (0.13 mmol) of **5**, 1.0 ml (0.14 mmol, 0.14 M in CH_2Cl_2) of $Ph_3C^+BF_4^-$ and an organozinc reagent, which was produced by adding 0.15 ml (0.15 mmol, 1.0 M in Et_2O) of $ZnCl_2$ to 1.0 ml (0.25 mmol, 0.25 M in THF) of PhMgBr and by stirring the resulting mixture for 30 min at room temp.; yield: 37.3 mg (77%); **7c/8c** = 95:5.

(1S,5R)-1-[(S)-1,2-Dihydro-1-(4-methoxyphenyl)-2-isoquinolylcarbonyl]-3,5,8,8-tetramethyl-3-azabicyclo[3.2.1]octane-2,4-dione (**7d**) *and (1S,5R)-1-[(R)-1,2-Dihydro-1-(4-methoxyphenyl)-2-isoquinolylcarbonyl]-3,5,8,8-tetramethyl-3-azabicyclo[3.2.1]octane-2,4-dione* (**8d**): A) According to GP I from 1.164 g (3.30 mmol) of **5**, 25.3 ml (3.55 mmol, 0.14 M in CH_2Cl_2) of $Ph_3C^+BF_4^-$ and 11.0 ml (6.60 mmol, 0.6 M in THF) of 4-$H_3CO-C_6H_4-MgBr$. The crude product (**7d/8d** = 72:28, *n*-hexane/Et_2O = 80:20, 2.5 ml/min) was purified by flash chromatography (*n*-hexane/EtOAc = 80:20) to give 1.51 g (84%) of colorless crystals. Preparative HPLC (*n*-hexane/Et_2O = 75:25, 9.5 ml/min) yielded 849 mg (56%) of **7d** and 287 mg (19%) of **8d**.

7d: Colorless crystals, m.p. 218°C. − $[\alpha]_D$ = +257 (*c* = 0.13 in CH_2Cl_2). − IR: $\tilde{\nu}$ = 1720 cm^{-1}, 1671, 1621, 1506, 1322. − ^1H NMR (300 MHz, $CDCl_3$): δ = 1.06 (s, 3 H, CH_3), 1.23 (s, 3 H, CH_3), 1.29 (s, 3 H, CH_3), 1.89 (pseudo t, *J* = 7.6 Hz, 2 H, CH_2), 2.33 (ddd, *J* = 7/8/15 Hz, 1 H, CH_2), 2.44 (ddd, *J* = 7/8/15 Hz, 1 H, CH_2), 3.16 (s, 3 H, N-CH_3), 3.73 (s, 3 H, OCH_3), 5.96 (d, *J* = 7.5 Hz, 1 H, NC=CH), 6.61 (s, 1 H, NCH), 6.71 (d, *J* = 7.5 Hz,

1 H, NCH=), 6.79 (d, J = 8.7 Hz, 2 H, aromatic H), 7.11−7.14 (m, 1 H, aromatic H), 7.23−7.30 (m, 5 H, aromatic H). − MS (70 eV); *m/z*: 458 [M^+], 351, 236, 137, 109. − $C_{28}H_{30}N_2O_4$ (458.5): calcd. C 73.34, H 6.59, N 6.11; found C 73.1, H 6.77, N 6.36.

8d: Colorless crystals, m.p. 139°C. − $[\alpha]_D$ = −394 (c = 1.1 in CH_2Cl_2). − IR: $\tilde{\nu}$ = 1721 cm^{-1}, 1669, 1622, 1507, 1320. − ^1H NMR (300 MHz, $CDCl_3$): δ = 0.85 (s, 0.8 × 3 H, CH_3), 0.91 (s, 0.2 × 3 H, CH_3), 1.03 (s, 0.8 × 3 H, CH_3), 1.20 (s, 3 H, CH_3), 1.26 (s, 0.2 × 3 H, CH_3), 1.80−2.06 (m, 2 H + 0.8 × 1 H, CH_2), 2.17−2.24 (m, 0.2 × 1 H, CH_2), 2.36−2.47 (m, 0.2 × 1 H, CH_2), 3.10 (s, 0.2 × 3 H, NCH_3), 3.22 (s, 0.8 × 1 H, NCH_3), 3.38 (ddd, J = 6/11/15 Hz, 0.8 × 1 H, CH_2), 3.73 (s, 1 H, OCH_3), 5.76 (d, J = 7.8 Hz, 0.2 × 1 H, NC=CH), 5.87 (d, J = 7.8 Hz, 0.8 × 1 H, NC=CH), 6.56 (d, J = 7.8 Hz, 0.8 × 1 H, NCH=), 6.73−6.83 (m, 2 H + 0.2 × 1 H, NCH=, aromatic H), 6.85 (s, 0.8 × 1 H, NCH), 7.00 (s, 0.2 × 1 H, NCH), 7.10−7.27 (m, 6 H, aromatic H); ratio of rotamers ≈ 8:2. − MS (70 eV); *m/z*: 458 [M^+], 351, 236, 137, 109. − $C_{28}H_{30}N_2O_4$ (458.5): calcd. C 73.3, H 6.59, N 6.11; found C 73.2, H 6.65, N 5.99.

B) According to GP I from 61.8 mg (0.175 mmol) of **5**, 1.3 ml (0.18 mmol, 0.14 M in CH_2Cl_2) of $Ph_3C^+BF_4^-$ and an organozinc reagent, which was produced by adding 0.21 ml (0.21 mmol, 1.0 M in Et_2O) of $ZnCl_2$ to 1.60 ml (0.36 mmol, 0.225 M in THF) of 4-$H_3CO-C_6H_4-$MgBr and by stirring the resulting mixture for 30 min at room temp.; yield: 50.5 mg (63%); **7d/8d =** 95:5.

(1S,5R)-1-[(S)-1-(4-Chlorophenyl)-1,2-dihydro-2-isoquinolylcarbonyl]-3,5,8,8-tetramethyl-3-azabicyclo[3.2.1]octane-2,4-dione (**7e**) *and (1S,5R)-1-[(R)-1-(4-Chlorophenyl)-1,2-dihydro-2-isoquinolylcarbonyl]-3,5,8,8-tetramethyl-3-azabicyclo[3.2.1]octane-2,4-dione* (**8e**): A) According to GPI from 1.168 g (3.31 mmol) of **5** , 25.3 ml (3.54 mmol, 0.14 M in CH_2Cl_2) of $Ph_3C^+BF_4^-$ and 6.63 ml (6.63 mmol, 1.0 M in Et_2O) of 4-Cl−C_6H_4−MgBr. The crude product (**7e/8e** = 74.8:25.2, *n*-hexane/EtOAc = 80:20, 1.0 ml/min) was purified by flash chromatography (*n*-hexane/EtOAc = 80:20) to give 1.137 g (74%) as colorless crystals. Preparative HPLC (*n*-hexane/Et_2O = 75:25, 9.5 ml/min) yielded 735 mg (48%) of **7e** and 245 mg (16%) of **8e**.

7e: Colorless crystals, m.p. 195°C. − $[\alpha]^{24}{}_D$ = +458 (c = 0.51 in CH_2Cl_2). − IR: $\tilde{\nu}$ = 1721 cm^{-1}, 1669, 1622. − ^1H NMR (300 MHz, $CDCl_3$): δ = 1.05 (s, 3 H, CH_3), 1.23 (s, 3 H, CH_3), 1.28 (s, 3 H, CH_3), 1.89 (pseudo-t, J = 7.6 Hz, 2 H, CH_2), 2.36 (ddd, J = 7/8/15 Hz, 1 H, CH_2), 2.41 (ddd, J = 7/8/15 Hz, 1 H, CH_2), 3.17 (s, 3 H, NCH_3), 5.96 (d, J = 7.6 Hz, 1 H, NC=CH), 6.61 (s, 1 H, NCH), 6.76 (dd, J = 7.6/1.6 Hz, 1 H, NCH=), 7.14−7.33 (m, 8 H). − MS (70 eV); *m/z*: 462 [M^+], 351, 240, 137, 109. − $C_{27}H_{27}ClN_2O_3$ (462.95): calcd. C 70.05, H 5.88, N 6.05; found C 70.0, H 6.11, N 5.76.

8e: Colorless crystals, m.p. 134°C, $[\alpha]^{24}{}_D$ = −376 (c = 0.635 in CH_2Cl_2). − IR: $\tilde{\nu}$ = 1724 cm^{-1}, 1671, 1622. − ^1H NMR (300 MHz, $CDCl_3$): δ = 0.85 (s, 0.9 × 3 H, CH_3), 0.90 (s, 0.1 × 3 H, CH_3), 1.03 (s, 0.9 × 3 H, CH_3), 1.20 (s, 3 H, CH_3), 1.26 (s, 0.1 × 3 H, CH_3), 1.80−2.06 (m, 2 H + 0.9 × 1 H, CH_2), 2.19−2.26 (m, 0.1 × 1 H, CH_2), 2.42−2.49 (m, 0.1 × 1 H, CH_2), 3.10 (s, 0.1 × 3 H, NCH_3), 3.23 (s, 0.9 × 3 H, NCH_3), 3.37 (ddd, J = 6/11/15 Hz, 0.9 × 1 H, CH_2), 5.76 (d, J = 8 Hz, 0.1 × 1 H, NC=CH), 5.87 (d, J = 7.8 Hz, 0.9 × 1 H, NC=CH), 6.56 (d, J = 7.8 Hz, 0.9 × 1 H, NCH=), 6.76 (d, J = 8 Hz, 0.1 × 1 H, NCH=), 6.84 (s, 0.9 × 1 H, NCH), 7.00−7.28 (m, 8 H + 0.1 × 1 H, aromatic H, NCH); ratio of rotamers = 9:1. − MS (70 eV); *m/z*: 462 [M^+], 351, 240, 137, 109. − $C_{27}H_{27}ClN_2O_3$ (462.95): calcd. C 70.05, H 5.88, N 6.05; found C 70.0, H 6.13, N 5.89.

B) According to GP I from 99.9 mg (0.283 mmol) of **5**, 2.15 ml (0.30 mmol, 0.14 M in CH_2Cl_2) of $Ph_3C^+BF_4^-$ and an organozinc reagent, which was produced by adding 0.34 ml (0.34 mmol, 1.0 M in Et_2O) of $ZnCl_2$ to 2.27 ml (0.57 mmol, 0.25 M in THF) of 4-Cl−C_6H_4−MgBr and by stirring the mixture for 30 min at room temp.; yield: 53.7 mg (41%); **7e/8e** = 96:4.

(1S,5R)-1-[(R)-1,2-Dihydro-1-(thien-2-yl)-2-isoquinolylcarbonyl]-3,5,8,8-tetramethyl-3-azabicyclo[3.2.1]octane-2,4-dione (**7f**) *and (1S,5R)-1-[(S)-1,2-Dihydro-1-(thien-2-yl)-2-isoquinolylcarbonyl]-3,5,8,8-tetramethyl-3-azabicyclo[3.2.1]octane-2,4-dione* (**8f**): A) According to GP I from 1.047 g (2.97 mmol) of **5**, 22.7 ml (3.18 mmol, 0.14 M in CH_2Cl_2) of $Ph_3C^+BF_4^-$ and 8.0 ml (6.0 mmol, 0.75 M in THF) of 2-thienyl−MgBr. The crude product (**7f/8f** = 94:6, *n*-hexane/Et_2O = 80:20, 1.0 ml/min) was purified by flash chromatography (*n*-hexane/Et_2O = 70:30) to give 0.939 g (73%) of colorless crystals. Preparative HPLC (*n*-hexane/Et_2O = 75:25, 9.5 ml/min) yielded 784 mg (58%) of **7f** and 65 mg (5%) of **8f**.

7f: Colorless crystals, m.p. 195°C (dec.). − $[\alpha]^{24}{}_D$ = +372 (c = 1.125 in CH_2Cl_2). − IR: $\tilde{\nu}$ = 1722 cm^{-1}, 1666, 1621, 1320. − ^1H NMR (300 MHz, $CDCl_3$): δ = 1.06 (s, 3 H, CH_3), 1.23 (s, 3 H, CH_3), 1.31 (s, 3 H, CH_3), 1.88 (pseudo-t, J = 8 Hz, 2 H, CH_2), 2.33 (ddd, J = 7/8/14 Hz, 1 H, CH_2), 2.43 (ddd, J = 7/8/14 Hz, 1 H, CH_2), 3.15 (s, 3 H, NCH_3), 6.00 (d, J = 7.6 Hz, 1 H, NC=CH), 6.65 (d, J = 7.6 Hz, 1 H, NCH=), 6.77 (d, J = 3.5 Hz, 1 H, thienyl), 6.80 (s, 1 H, NCH), 6.83 (dd, J = 3.5/4.9 Hz, 1 H, thienyl), 7.14−7.17 (m, 2 H, aromatic H), 7.25−7.35 (m , 3 H, aromatic H). − MS (70 eV); *m/z*: 434 [M^+], 351, 222, 137, 109. − $C_{25}H_{26}N_2O_3S$ (434.5): calcd. C 69.10, H 6.03, N 6.45; found C 69.3, H 6.03, N 6.54.

8f: Colorless crystals, m.p. 193°C. − $[\alpha]^{24}{}_D$ = −397 (c = 0.96 in CH_2Cl_2). − IR: $\tilde{\nu}$ = 2970 cm^{-1}, 1721, 1670, 1622, 1319. − ^1H NMR (300 MHz, $CDCl_3$): δ = 0.86 (s, 0.85 × 3 H, CH_3), 1.02 (s, 3 H, CH_3), 1.20 (s, 3 H + 0.15 × 3 H, CH_3), 1.85−2.11 (m, 2 H + 0.85 × 1 H, CH_2), 2.43 (s, br., 0.3 × 1 H, CH_2), 3.10 (s, 0.15 × 3 H, NCH_3), 3.21 (s, 0.85 × 3 H, NCH_3), 3.41 (ddd, J = 6/11/15 Hz, 0.85 × 1 H, CH_2), 5.85 (s, br., 0.15 × 1 H, NC=CH, partially covered), 5.92 (d, J = 7.7 Hz, 0.85 × 1 H, NC=CH), 6.50 (d, J = 7.7 Hz, 0.85 × 1 H, NCH=), 6.60 (s, br., 0.15 × 1 H, NCH=), 6.78−6.85 (m, 2 H, aromatic H), 7.06 (s, 0.85 × 1 H, NCH), 7.14 (d, J = 5 Hz, 2 H, aromatic H), 7.22−7.29 (m , 3 H + 0.15 × 1 H, aromatic H, NCH); ratio of rotamers ≈ 15:85. − MS (70 eV); *m/z*: 434 [M^+], 351, 222, 137, 109. − $C_{25}H_{26}N_2O_3S$ (434.5): calcd. C 69.10, H 6.03, N 6.45; found C 68.9, H 6.18, N 6.48.

B) According to GP I from 50.5 mg (0.143 mmol) of **5**, 1.10 ml (0.154 mmol, 0.14 M in CH_2Cl_2) of $Ph_3C^+BF_4^-$ and an organozinc reagent, which was produced by adding 0.17 ml (0.17 mmol, 1.0 M in Et_2O) $ZnCl_2$ to 1.45 ml (0.29 mmol, 0.20 M in THF) of 2-thienyl−MgBr and by stirring the resulting mixture for 30 min at room temp.; yield: 25.5 mg (41%); **7f/8f** = 82.5:17.5.

(1S,5R)-1-[(S)-1,2-Dihydro-1-(2-naphthyl)-2-isoquinolylcarbonyl]-3,5,8,8-tetramethyl-3-azabicyclo[3.2.1]octane-2,4-dione (**7g**) *and (1S,5R)-1-[(R)-1,2-Dihydro-1-(2-naphthyl)-2-isoquinolylcarbonyl]-3,5,8,8-tetramethyl-3-azabicyclo[3.2.1]octane-2,4-dione* (**8g**): A) According to GPI from 0.900 g (2.55 mmol) of **5**, 19.2 ml (2.72 mmol, 0.14 M in $CHCl_2$) of $Ph_3C^+BF_4^-$ and 5.10 ml (5.10 mmol, 1.0 M in THF) of 2-naphthyl−MgBr. The crude product (**7g/8g** = 68.1:31.9, *n*-hexane/Et_2O = 80:20, 2.5 ml/min) was purified by flash chromatography (*n*-hexane/EtOAc = 80:20) to give 1.074 g (88%) of colorless crystals. Preparative HPLC (*n*-hexane/Et_2O = 70:30, 9.0 ml/min) yielded 647 mg (53%) of **7g** and 293 mg (24%) of **8g**.

7g: Colorless crystals, m.p. 215°C. − $[\alpha]_D$ = +435 (*c* = 1.105 in CH_2Cl_2). − IR: $\tilde{\nu}$ = 1720 cm^{-1}, 1665, 1622. − ^1H NMR (300 MHz, $CDCl_3$): δ = 1.08 (s, 3 H, CH_3), 1.24 (s, 3 H, CH_3), 1.29 (s, 3 H, CH_3), 1.90 (pseudo t, *J* = 7.7 Hz, 2 H, CH_2), 2.38 (ddd, *J* = 7/8/15 Hz, 1 H, CH_2), 2.47 (ddd, *J* = 7/8/15 Hz, 1 H, CH_2), 3.18 (s, 3 H, NCH_3), 5.97 (d, *J* = 7.8 Hz, 1 H, NC=CH), 6.80 (d, *J* = 7.8 Hz, 1 H, NCH=, partially overlapped), 6.81 (s, 1 H, NCH), 7.13−7.16 (m, 1 H, aromatic H), 7.28−7.33 (m, 2 H, aromatic H), 7.37−7.45 (m, 3 H, aromatic H), 7.62 (dd, *J* = 2/9 Hz, 1 H, aromatic H), 7.67 (s, 1 H, aromatic H), 7.72−7.77 (m, 3 H, aromatic H). − MS (70 eV); *m/z*: 478 [M^+], 351, 256, 222, 194, 137, 109. − $C_{31}H_{30}N_2O_3$ (478.6): calcd. C 77.80, H 6.32, N 5.85; found C 77.8, H 6.44, N 5.68.

8g: Colorless crystals, m.p. 115°C. − $[\alpha]_D$ = −328 (*c* = 1.08 in CH_2Cl_2). − IR: $\tilde{\nu}$ = 2966 cm^{-1}, 1721, 1669, 1622. − ^1H NMR (300 MHz, $CDCl_3$): δ = 0.80 (s, 0.15 × 3 H, CH_3), 0.87 (s, 0.85 × 3 H, CH_3), 1.05 (s, 0.85 × 3 H, CH_3), 1.16 (s, 0,15 × 3 H, CH_3), 1.20 (s, 3 H, CH_3), 1.83−1.92 (m, 1 H + 0.85 × 1 H, CH_2), 1.98−2.07 (m, 1 H, CH_2), 2.16−2.27 (m, 0.15 × 1 H, CH_2), 2.40−2.50 (m, 0.15 × 1 H, CH_2), 3.10 (s, 0.15 × 3 H, NCH_3), 3.24 (s, 0.85 × 3 H, NCH_3), 3.40 (ddd, *J* = 6/11/16 Hz, 0.85 × 1 H, CH_2), 5.79 (d, *J* = 8 Hz, 0.15 × 1 H, NC=CH), 5.89 (d, *J* = 7.8 Hz, 0.85 × 1 H, NC=CH), 6.64 (d, *J* = 7.8 Hz, 0.85 × 1 H, NCH=), 6.79 (d, *J* = 8 Hz, 0.15 × 1 H, NCH=), 7.04 (s, 0.85 × 1 H, NCH), 7.10−7.13 (m, 0.85 × 2 H, aromatic H), 7.20 (s, 0.15 × 1 H, NCH), 7.25 (dd, *J* = 3.6/7.3 Hz, 2 H, aromatic H), 7.38−7.46 (m, 2 H + 0.15 × 2 H, aromatic H), 7.55−7.58 (m, 0.85 × 1 H, aromatic H), 7.64 (s, 0.15 × 1 H), 7.69 (s, 0.85 × 1 H), 7.69−7.77 (m, 3 H + 0.15 × 1 H, aromatic H); ratio of rotamers ≈ 15:85. − MS (70 eV); *m/z*: 478 [M^+], 351, 256, 222, 194, 137, 109. − $C_{31}H_{30}N_2O_3$ (478.6): calcd. C 77.80, H 6.32, N 5.85; found C 77.5, H 6.53, N 5.97.

B) According to GP I from 65.6 mg (0.186 mmol) of **5**, 1.40 ml (0.196 mmol, 0.14 M in CH_2Cl_2) of $Ph_3C^+BF_4^-$ and an organozinc reagent, which was produced by adding 0.22 ml (0.22 mmol, 1.0 M in Et_2O) of $ZnCl_2$ to 1.53 ml (0.38 mmol, 0.25 M in THF) of 2-naphthyl−MgBr and by stirring the resulting mixture for 30 min at room temp.; yield: 42.7 mg (48%); **7g/8g** = 90.1:9.9.

General Procedure II (GP II) for the Hydrogenation of Compounds **7** *and* **8**: To a solution of the respective compound (**7** or **8**) Pd/C (10% Pd; in the case of **7e** and **8e** Pt/C was used) was added and the resulting mixture was hydrogenated under stirring for 48 h under normal pressure. Then the mixture was filtered, concentrated in vacuo, and purified by preparative HPLC.

(1S,5R)-1-[(S)-1,2,3,4-Tetrahydro-1-phenyl-2-isoquinolylcarbonyl]-3,5,8,8-tetramethyl-3-azabicyclo[3.2.1]octane-2,4-dione (**9c**) *and (1S,5R)-1-[(R)-1,2,3,4-Tetrahydro-1-phenyl-2-isoquinolylcarbonyl]-3,5,8,8-tetramethyl-3-azabicyclo[3.2.1]octane-2,4-dione* (**10c**): According to GP II from 785.5 mg (1.833 mmol) of **7c/8c** (**7c/8c =** 80:20) and 860 mg of Pd/C in 100 ml of EtOH. The isomeric mixture obtained (732.2 mg, 93%) was separated by preparative HPLC (*n*-hexane/EtOAc = 80:20, 8.0 ml:min) to yield 494 mg (63%) of **9c** and 103 mg (13%) of **10c**.

9c: Colorless crystals, m.p. 235°C. − $[\alpha]_D$ = +121 (*c* = 0.935 in CH_2Cl_2). − IR: $\tilde{\nu}$ = 2943 cm^{-1}, 1720, 1671, 1630. − ^1H NMR (300 MHz, $CDCl_3$): δ = 0.74 (s, 0.5 × 3 H, CH_3), 0.78 (s, 0.5 × 3 H, CH_3), 1.13 (s, 0.5 × 3 H, CH_3), 1.16 (s, 0.5 × 3 H, CH_3), 1.24 (s, 0.5 × 3 H, CH_3), 1.28 (s, 0.5 × 3 H, CH_3), 1.81−1.94 (m, 2.5 H, CH_2), 2.45 (t, *J* = 7.5 Hz, 1 H, CH_2), 2.63−2.67 (m, 0.5 H, CH_2), 2.77−2.82 (m, 0.5 H, CH_2), 2.94−2.99 (m, 0.5 H, CH_2), 3.11 (s, 0.5 × 3 H, NCH_3), 3.18 (s, 0.5 × 3 H, *n*-CH_3), 3.38−3.55 (m, 2.5 H, CH_2), 3.70−3.74 (m, 0.5 H, CH_2), 6.82 (s, 0.5 H, NCH), 6.99 (d, *J* = 7.6 Hz, 0.5 H, aromatic H), 7.12−7.16 (m, 1 H, aromatic H), 7.13 (s, 0.5 H, NCH, partially covered), 7.19−7.36 (m, 7.5 H, aromatic H); ratio of rotamers = 1:1. − MS (70 eV); *m/z*: 430 [M^+], 353, 222, 208, 137, 109. − $C_{27}H_{28}N_2O_3$ (430.5): calcd. C 75.32, H 7.02, N 6.51; found C 75.5, H 7.27, N 6.34.

10c: Colorless crystals, m.p. 148°C. − $[\alpha]_D$ = -81 (*c* = 1.045 in CH_2Cl_2). − IR: $\tilde{\nu}$ = 2965 cm^{-1}, 1720, 1667, 1622. − ^1H NMR (300 MHz, $CDCl_3$): δ = 0.91 (s, 0.3 × 3 H, CH_3), 1.07 (s, 0.7 × 3 H, CH_3), 1.10 (s, 0.3 × 3 H, CH_3), 1.23 (s, 3 H, CH_3), 1.24 (s, 0.7 × 3 H, CH_3), 1.79−1.95 (m, 2 H + 0.3 × 1 H, CH_2), 2.13 (ddd, *J* = 5/9/15 Hz, 0.7 × 1 H, CH_2), 2.37 (ddd, *J* = 6/9/15 Hz, 0.7 × 1 H, CH_2), 2.73−2.87 (m, 1 H, CH_2), 2.95−3.06 (m, 0.3 × 1 H, CH_2, partially covered), 3.11 (s, 0.7 × 3 H, NCH_3), 3.13 (s, 0.3 × 3 H, NCH_3), 3.27−3.50 (m, 2 H + 0.3 × 1 H, CH_2), 3.85−3.89 (m, 0.7 × 1 H, CH_2), 7.01−7.04 (m, 2 H + 0.3 × 1 H), 7.13−7.27 (m, 7 H + 0.7 × 1 H), ratio of rotamers ≈ 7:3. − MS (70 eV); *m/z*: 430 [M^+], 353, 222, 208, 137, 109. − $C_{27}H_{28}N_2O_3$ (430.5): calcd. C 75.32, H 7.02, N 6.51; found C 75.3, H 7.08, N 6.34.

(1S,5R)-1-[(S)-1,2,3,4-Tetrahydro-1-(4-methoxyphenyl)-2-isoquinolylcarbonyl]-3,5,8,8-tetramethyl-3-azabicyclo[3.2.1]octane-2,4-dione (**9d**): According to GP II from 753.8 mg (1.644 mmol) of **7d** with 876 mg of Pd/C and 30 ml of EtOH. Preparative HPLC (*n*-hexane/EtOAc = 75:25, 8.9 ml/min) yielded 683.0 mg (90%) of **9d** as colorless crystals, m.p. 237°C. − $[\alpha]_D$ = +140 (c = 1.01 in CH_2Cl_2). − IR: $\tilde{\nu}$ = 2951 cm^{-1}, 1721, 1672, 1627. − ^1H NMR (300 MHz, $CDCl_3$): δ = 0.75 (s, 0.5 × 3 H, CH_3), 0.79 (s, 0.5 × 3 H, CH_3), 1.13 (s, 0.5 × 3 H, CH_3), 1.16 (s, 0.5 × 3 H, CH_3), 1.24 (s, 0.5 × 3 H, CH_3), 1.28 (s, 0.5 × 3 H, CH_3), 1.84−1.94 (m, 2.5 H, CH_2), 2.45 (t, *J* = 7.5 Hz, 1 H, CH_2), 2.61−2.65 (m, 0.5 H, CH_2), 2.76−2.82 (m, 0.5 H, CH_2), 2.95−3.05 (m, 0.5 H, CH_2), 3.10 (s, 0.5 × 3 H, NCH_3), 3.18 (s, 0.5 × 3 H, NCH_3), 3.36−3.55 (m, 2.5 H, CH_2), 3.68−3.74 (m, 0.5 H, CH_2, partially covered), 3.76 (s, 0.5 × 3 H, OCH_3), 3.77 (s, 0.5 × 3 H, OCH_3), 6.77−6.83 (m, 2.5 H), 6.98 (d, *J* = 7.7 Hz, 0.5 H, aromatic H), 7.09−7.26 (m, 6 H); ratio of rotamers ≈ 1:1. − MS (70 eV); *m/z*: 460 [M^+], 445, 431, 353, 238, 222, 137, 109. − $C_{28}H_{32}N_2O_4$ (460.5): calcd. C 73.02, H 7.00, N 6.08; found C 73.1, H 7.01, N 6.15.

(1S,5R)-1-[(R)-1,2,3,4-Tetrahydro-1-(4-methoxyphenyl)-2-isoquinolylcarbonyl]-3,5,8,8-tetramethyl-3-azabicyclo[3.2.1]octane-2,4-dione (**10d**): According to GP II from 263.2 mg (0.574 mmol) of **8d** with 406 mg of Pd/C and 10 ml of EtOH. Preparative HPLC (*n*-hexane/EtOAc = 75:25, 8.0 ml/min) yielded 231.8 mg (88%) of **10d** as colorless crystals, m.p. 174°C. − $[\alpha]_D$ = −89 (*c* = 3.0 in CH_2Cl_2). − IR: $\tilde{\nu}$ = 2942 cm^{-1}, 1721, 1671, 1630. − ^1H NMR (300 MHz, $CDCl_3$): δ = 0.91 (s, 0.2 × 3 H, CH_3), 1.09 (s, 3 H, CH_3), 1.23 (s, 0.8 × 3 H, CH_3), 1.24 (s, 3 H, CH_3), 1.78−1.95 (m, 2 H + 0.2 × 1 H, CH_2), 2.11 (ddd, *J* = 5/9/14 Hz, 0.8 × 1 H, CH_2), 2.36 (ddd, *J* = 6/9/14 Hz, 0.8 × 1 H, CH_2), 2.71−2.87 (m, 0.8 × 1 H, CH_2), 2.87−3.03 (m, 0.2 × 2 H, CH_2, partially covered), 3.10 (s, 0.8 × 3 H, NCH_3), 3.12 (s, 0.2 × 3 H, NCH_3), 3.19−3.54 (m, 2 H + 0.2 × 1 H, CH_2), 3.77 (s, 3 H, OCH_3), 3.75−3.85 (m, 0.8 × 1 H, CH_2, partially covered), 6.78−6.80 (m, 2 H), 6.98−7.07 (m, 3 H), 7.11−7.23 (m, 4 H); ratio of rotamers ≈ 8:2. − MS (70 eV); *m/z*: 460 [M^+], 445, 431, 353, 238, 137, 109. − $C_{28}H_{32}N_2O_4$ (460.5): calcd. C 73.02, H 7.00, N 6.08; found C 73.0, H 7.04, N 6.11.

(1S,5R)-1-[(S)-1-(4-Chlorophenyl)-1,2,3,4-tetrahydro-2-isoquinolylcarbonyl]-3,5,8,8-tetramethyl-3-azabicyclo[3.2.1]octane-2,4-dione (**9e**): According to GP II from 629.1 mg (1.359 mmol) of **7e** with 381 mg of Pt/C in 35 ml of *n*-hexane/EtOAc (70:30). Preparative HPLC (*n*-hexane/EtOAc = 80:20, 8.0 ml/min) yielded 449.0 mg (71%) of **9e** as colorless crystals, m.p. 230°C. − $[\alpha]_D$ =

+127 (c = 1.165 in CH_2Cl_2). − IR: $\tilde{\nu}$ = 2942 cm^{-1}, 1719, 1671, 1629. − ^1H NMR (300 MHz, $CDCl_3$): δ = 0.73 (s, 0.4 × 3 H, CH_3), 0.80 (s, 0.4 × 3 H, CH_3), 1.12 (s, 0.6 × 3 H, CH_3), 1.17 (s, 0.4 × 3 H, CH_3), 1.24 (s, 0.6 × 3 H, CH_3), 1.27 (s, 0.6 × 3 H, CH_3), 1.80−2.01 (m, 2 H + 0.4 × 1 H, CH_2), 2.45 (t, J = 7.5 Hz, 0.6 × 2 H, CH_2), 2.61−2.67 (m, 0.4 × 1 H, CH_2), 2.76−2.82 (m, 0.6 × 1 H, CH_2), 2.93−3.05 (m, 0.6 × 1 H, CH_2), 3.11 (s, 0.6 × 3 H, NCH_3), 3.18 (s, 0.4 × 3 H, NCH_3), 3.29−3.55 (m, 1 H + 1.2 × 1 H, CH_2), 3.70−3.75 (m, 0.6 × 1 H, CH_2), 6.76 (s, 0.6 × 1 H, NCH), 6.95 (d, J = 7.8 Hz, 0.4 × 1 H, aromatic H), 7.08 (s, 0.4 × 1 H, NCH), 7.14−7.28 (m, 7 H + 0.6 × 1 H, aromatic H); ratio of rotamers ≈ 6:4. − MS (70 eV); m/z: 464 [M^+], 353, 242, 137, 109. − $C_{27}H_{29}ClN_2O_3$ (464.95): calcd. C 69.74, H 6.29, N 6.03; found C 69.9, H 6.30, N 6.05.

(1S,5R)-1-[(R)-1-(4-Chlorophenyl)-1,2,3,4-tetrahydro-2-isoquinolylcarbonyl]-3,5,8,8-tetramethyl-3-azabicyclo[3.2.1]octane-2,4-dione (**10e**): According to GP II from 172.1 mg (0.372 mmol) of **7e** with 219 mg of Pt/C in 12 ml of *n*-hexane/EtOAc (70:30). Preparative HPLC (*n*-hexane/Et_2O = 70:30, 8.0 ml/min) yielded 124.5 mg (72%) of **10e** as colorless crystals, m.p. 149°C. − $[\alpha]_D$ = −84 (c = 1.175 in CH_2Cl_2). − IR: $\tilde{\nu}$ = 2966 cm^{-1}, 1719, 1671, 1640.− ^1H NMR (300 MHz, $CDCl_3$): δ = 0.91 (s, 0.25 × 3 H, CH_3), 1.05 (s, 0.75 × 3 H, CH_3), 1.10 (s, 0.25 × 3 H, CH_3), 1.23 (s, 3 H, CH_3), 1.24 (s, 0.75 × 3 H, CH_3), 1.80−1.97 (m, 2 H + 0.25 × 1 H, CH_2), 2.10 (ddd, J = 5/9/14 Hz, 0.75 × 1 H, CH_2), 2.37 (ddd, J = 6/9/14 Hz, 0.75 × 1 H, CH_2), 2.73−2.84 (m, 1 H, CH_2), 2.87−2.93 (m, 0.25 × 1 H, CH_2), 3.11 (s, 0.75 × 3 H, NCH_3), 3.13 (s, 0.25 × 3 H, NCH_3), 3.23−3.45 (m, 2 H + 0.25 × 1 H, CH_2), 3.88−3.91 (m, 0.75 × 1 H, CH_2), 6.96−6.99 (m, 1 H + 0.75 × 1 H), 7.08−7.26 (m, 7 H + 0.25 × 1 H); ratio of rotamers ≈ 75:25. − MS (70eV); m/z: 464 [M^+], 353, 242, 137, 109. − $C_{27}H_{29}ClN_2O_3$ (464.95): calcd. C 69.74, H 6.29, N 6.03; found C 69.6, H 6.30, N 6.07.

(1S,5R)-1-[(R)-1,2,3,4-Tetrahydro-1-(2-thienyl)-2-isoquinolylcarbonyl]-3,5,8,8-tetramethyl-3-azabicyclo[3.2.1]octane-2,4-dione (**9f**): According to GP II from 512.3 mg (1.173 mmol) of **7f** with 5.23 g of Pd/C in 60 ml of EtOH, reaction time 4 d. Preparative HPLC (*n*-hexane/EtOAc = 80:20, 8.0 ml/min) yielded 200.9 mg (39%) of **9f** as colorless crystals, m.p. 201°C. − $[\alpha]_D$ = +185 (c = 1.195 in CH_2Cl_2). − IR: $\tilde{\nu}$ = 2937 cm^{-1}, 1720, 1672, 1634. − ^1H NMR (300 MHz, $CDCl_3$): δ = 0.88 (s, 0.4 × 3 H, CH_3), 0.91 (s, 0.4 × 3 H, CH_3), 1.12 (s, 0.6 × 3 H, CH_3), 1.19 (s, 0.4 × 3 H, CH_3), 1.24 (s, 0.6 × 3 H, CH_3), 1.29 (s, 0.6 × 3 H, CH_3), 1.83−1.97 (m, 2 H + 0.4 × 1 H, CH_2), 2.46 (t, J = 7.4 Hz, 1.2 × 1 H, CH_2), 2.60−2.65 (m, 0.4 × 1 H, CH_2), 2.77−2.83 (m, 0.6 × 1 H, CH_2), 2.97−3.06 (m, 1 H, CH_2, partially covered), 3.10 (s, 0.6 × 3 H, NCH_3), 3.19 (s, 0.4 × 3 H, NCH_3), 3.35−3.56 (m, 1 H + 0.4 × 2 H, CH_2), 3.76−3.82 (m, 0.6 × 1 H, CH_2), 6.76−6.80 (m, 1 H + 0.4 × 1 H), 6.87−6.90 (m, 1 H), 7.14−7.26 (m, 5 H + 0.6 × 1 H, aromatic H); ratio of rotamers ≈ 6:4. − MS (70 eV); m/z: 436 [M^+], 408, 353, 242, 214, 137, 109. − $C_{25}H_{28}N_2O_3S$ (436.6): calcd. C 68.78, H 6.46, N 6.42; found C 68.9, H 6.37, N 6.37.

(1S,5R)-1-[(S)-1,2,3,4-Tetrahydro-1-(2-thienyl)-2-isoquinolylcarbonyl]-3,5,8,8-tetramethyl-3-azabicyclo[3.2.1]octane-2,4-dione (**10f**): According to GP II from 53.8 mg (0.124 mmol) of **8f** with 61.8 mg of Pd/C in 15 ml of EtOH, reaction time 4 d. Preparative HPLC (*n*-hexane/EtOAc = 80:20, 8.0 ml/min) yielded 17.3 mg (32%) of **10f** as colorless crystals, m.p. 189°C. − $[\alpha]^{20}_D$ = −89 (c = 1.115 in CH_2Cl_2). − IR: $\tilde{\nu}$ = 2967 cm^{-1}, 1720, 1672, 1631. − ^1H NMR (300 MHz, $CDCl_3$): δ = 0.93 (s, 0.25 × 3 H, CH_3), 1.14 (s, 0.25 × 3 H, CH_3), 1.18 (s, 0.75 × 3 H, CH_3), 1.25 (s, 3 H + 0.75 × 3 H, CH_3), 1.81−1.97 (m, 2 H + 0.25 × 1 H, CH_2), 2.23−2.44 (m, 1.5 × 1 H, CH_2), 2.71−2.88 (m, 1 H, CH_2), 2.96−3.08 (m, 0.25 × 1 H, CH_2, partially covered), 3.12 (s, 3 H, NCH_3), 3.30−3.49 (m, 2 H + 0.25 × 1 H, CH_2), 3.91 (s, br., 0.75 × 1 H, CH_2), 6.66 (s, br., 0.75 × 1 H), 6.78 (m, 0.25 × 1 H), 6.84−6.88 (m, 1 H), 7.10−7.22 (m, 6 H); ratio of rotamers ≈ 75:25. − MS (70 eV); m/z: 436 [M^+], 408, 353, 242, 214, 137, 109. − $C_{25}H_{28}N_2O_3S$ (436.6): calcd. C 68.78, H 6.46, N 6.42; found C 68.9, H 6.36, N 6.48.

(1S,5R)-1-[(S)-1,2,3,4-Tetrahydro-1-(2-naphthyl)-2-isoquinolylcarbonyl]-3,5,8,8-tetramethyl-3-azabicyclo[3.2.1]octane-2,4-dione (**9g**): According to GP II from 412.3 mg (0.862 mmol) of **7g** with 585 mg of Pd/C in 80 ml of EtOH. Preparative HPLC (*n*-hexane/EtOAc = 80:20, 8.0 ml/min) yielded 314.1 mg (76%) of **9g** as colorless crystals, m.p. 223°C. − $[\alpha]_D$ = −121 (c = 0.98 in CH_2Cl_2). − IR: $\tilde{\nu}$ = 2969 cm^{-1}, 1719, 1670, 1628. − ^1H NMR (300 MHz, $CDCl_3$): δ = 0.74 (s, 0.5 × 3 H, CH_3), 0.76 (s, 0.5 × 3 H, CH_3), 1.14 (s, 0.5 × 3 H, CH_3), 1.15 (s, 0.5 × 3 H, CH_3), 1.25 (s, 0.5 × 3 H, CH_3), 1.30 (s, 0.5 × 3 H, CH_3), 1.86−1.95 (m, 2.5 H, CH_2), 2.47 (t, J = 7.4 Hz, 1 H, CH_2), 2.66−2.70 (m, 0.5 H, CH_2), 2.81−2.86 (m, 0.5 H, CH_2), 2.97−3.06 (m, 0.5 H, CH_2, partially covered), 3.10 (s, 0.5 × 3 H, NCH_3), 3.18 (s, 0.5 × 3 H, NCH_3), 3.41−3.51 (m, 2 H, CH_2), 3.55−3.62 (m, 0.5 H, CH_2), 3.72−3.75 (m, 0.5 H, CH_2), 6.99−7.05 (m, 1 H), 7.12−7.19 (m, 0.5 × 1 H, aromatic H), 7.23−7.31 (m, 3 H), 7.40−7.46 (m, 2 H, aromatic H), 7.51−7.56 (m, 2 H, aromatic H), 7.71−7.84 (m, 3.5 H, aromatic H); ratio of rotamers ≈ 1:1. − MS (70 eV); m/z: 480 [M^+], 353, 258, 242, 137, 109. − $C_{31}H_{32}N_2O_3$ (480.6): calcd. C 77.47, H 6.71, N 5.83; found C 77.4, H 7.06, N 5.68.

(1S,5R)-1-[(R)-1,2,3,4-Tetrahydro-1-(2-naphthyl)-2-isoquinolylcarbonyl]-3,5,8,8-tetramethyl-3-azabicyclo[3.2.1]octane-2,4-dione (**10g**): According to GP II from 209.1 mg (0.437 mmol) of **8g** with 218 mg of Pd/C in 50 ml of EtOH. Preparative HPLC (*n*-hexane/EtOAc = 80:20, 8.0 ml/min) yielded 151.2 mg (72%) of **10g** as colorless crystals, m.p. 120°C. − $[\alpha]_D$ = −118 (c = 1.105 in CH_2Cl_2). − IR: $\tilde{\nu}$ = 2938 cm^{-1}, 1720, 1671, 1631. − ^1H NMR (300 MHz, $CDCl_3$): δ = 0.93 (s, 0.2 × 3 H, CH_3), 1.10 (s, 0.8 × 3 H, CH_3), 1.12 (s, 0.2 × 3 H, CH_3), 1.22 (s, 0.8 × 3 H, CH_3), 1.26 (s, 3 H, CH_3), 1.81−1.95 (m, 2 H + 0.2 × 1 H, CH_2), 2.09 (ddd, J = 6/9/14 Hz, 0.8 × 1 H, CH_2), 2.35 (ddd, J = 6/9/15 Hz, 0.8 × 1 H, CH_2), 2.77−2.92 (m, 1 H, CH_2), 2.98−3.21 (m, 0.2 × 1 H, CH_2, partially covered), 3.11 (s, 3 H, NCH_3), 3.23−3.49 (m, 2 H + 0.2 × 1 H, CH_2), 3.74−3.96 (m, 0.8 × 1 H, CH_2), 7.06 (d, J = 7.6 Hz, 0.8 × 1 H, aromatic H), 7.18−7.27 (m, 4 H), 7.36 (d, J = 8 Hz, 0.8 × 1 H, aromatic H), 7.41−7.50 (m, 3 H + 0.2 × 1 H, aromatic H), 7.57 (d, J = 8 Hz, 0.2 × 1 H, aromatic H), 7.69−7.82 (m, 3 H, aromatic H); ratio of rotamers ≈ 8:2. − MS (70 V); m/z: 480 [M^+], 353, 258, 242, 137, 109. − $C_{31}H_{32}N_2O_3$ (480.6): calcd. C 77.47, H 6.71, N 5.83; found C 77.4, H 6.69, N 5.79.

General Procedure III (GP III) for the Removal of the Chiral Auxiliary: To a solution of the respective compound (**9** or **10**) in Et_2O 4 equiv. of $LiAlH_4$ (1.0 M in Et_2O) were added at 0°C and the resulting mixture was stirred for 48 h. After cooling to −78°C and dropwise addition of CH_3OH/Et_2O (1:4), the mixture was allowed to warm to room temp. Then 1 N NaOH was added and the alkaline aqueous layer was extracted with Et_2O several times. The combined layers were dried ($MgSO_4$) and concentrated in vacuo. The pure amines were obtained by flash chromatography (*n*-hexane/EtOAc/$NEtMe_2$ = 78:20:2). As in each case the spectroscopic data (IR, ^1H NMR, MS) of enantiomeric compounds were identical with each other, these data are given for only one of two enantiomers.

(S)-1,2,3,4-Tetrahydro-1-phenylisoquinoline (**11c**)[15]: According to GP III from 533.7 mg (1.24 mmol) of **9c**, in 180 ml of Et_2O with

5.0 ml (5.0 mmol) of $LiAlH_4$. Flash chromatography (*n*-hexane/EtOAc/$NEtMe_2$ = 78:20:2) yielded 142.1 mg (55%) of colorless crystals, m.p. 81°C. − $[\alpha]_D$ = +12.3 (*c* = 0.57 in CH_2Cl_2). − IR: $\tilde{\nu}$ = 3253 cm^{-1}, 1488, 1449, 743, 700. − ^1H NMR (300 MHz, $CDCl_3$): δ = 1.83 (s, 1 H, NH), 2.79−2.88 (m, 1 H, NCH_2CH_2), 2.99−3.14 (m, 2 H, NCH_2CH_2), 3.23−3.31 (m, 1 H, NCH_2CH_2), 5.10 (s, 1 H, NCH), 6.75 (d, *J* = 7.6 Hz, 1 H, aromatic H), 7.00−7.07 (m, 1 H, aromatic H), 7.10−7.20 (m, 2 H, aromatic H), 7.25−7.40 (m, 5 H, aromatic H). − MS (70 eV); *m*/*z*: 209 [M^+], 179, 132. − $C_{15}H_{15}N$ (209.3): calcd. C 86.08, H 7.22, N 6.69; found C 86.0, H 7.30, N 6.64.

(R)-1,2,3,4-Tetrahydro-1-phenylisoquinoline (**12c**): According to GP III from 395.0 mg (0.917 mmol) of **10c** in 100 ml of Et_2O with 3.7 ml (3.7 mmol) of $LiAlH_4$. Flash chromatography yielded 79.8 mg (42%) of colorless crystals, m.p. 79°C. − $[\alpha]_D$ = −12.3 (*c* = 1.55 in CH_2Cl_2). − $C_{15}H_{15}N$ (209.3): calcd. C 86.08, H 7.22, N 6.69; found C 85.8, H 7.24, N 6.63.

(S)-1,2,3,4-Tetrahydro-1-(4-methoxyphenyl)isoquinoline (**11d**): According to GP III from 517.0 mg (1.123 mmol) **9d** in 150 ml Et_2O with 4.5 ml (4.5 mmol) $LiAlH_4$. Flash chromatography yielded 139.2 mg (52%) of colorless crystals, m.p. 83°C. − $[\alpha]_D$ = +50 (*c* = 0.86 in CH_2Cl_2). − IR: $\tilde{\nu}$ = 1503 cm^{-1}, 1447, 1246, 1030, 744. − ^1H NMR (300 MHz, $CDCl_3$): δ = 1.67 (s, 1 H, NH), 2.78−2.87 (m, 1 H, NCH_2CH_2), 2.98−3.13 (m, 2 H, NCH_2CH_2), 3.22−3.31 (m, 1 H, NCH_2CH_2), 3.80 (s, 3 H, OCH_3), 5.06 (s, 1 H, NCH), 6.76 (d, *J* = 7.7 Hz, 1 H, aromatic H), 6.85 (pseudo-d, *J* = 8.7 Hz, 2 H, C_6H_4OMe), 7.00−7.08 (m, 1 H, aromatic H), 7.12−7.16 (m, 2 H, aromatic H), 7.18 (pseudo-d, *J* = 8.7 Hz, 2 H, C_6H_4OMe). − MS (70 eV); *m*/*z*: 239 [M^+], 209, 179, 132. − $C_{16}H_{17}NO$ (239.3): calcd. C 80.30, H 7.16, N 5.85; found C 80.3, H 7.37, N 6.05.

(R)-1,2,3,4-Tetrahydro-1-(4-methoxyphenyl)isoquinoline (**12d**): According to GP III 205.2 mg (0.445 mmol) from **10d** in 80 ml of Et_2O with 1.78 ml (1.78 mmol) of $LiAlH_4$. Flash chromatography yielded 45.8 mg (43%) of colorless crystals, m.p. 82°C. − $[\alpha]_D$ = −53 (*c* = 1.45 in CH_2Cl_2). − $C_{16}H_{17}NO$ (239.3): calcd. C 80.30, H 7.16, N 5.85; found C 80.6, H 7.24, N 5.98.

(S)-1-(4-Chlorophenyl)-1,2,3,4-tetrahydroisoquinoline (**11e**): According to GP III 464.1 mg (1.00 mmol) of **9e** in 170 ml of Et_2O with 4.0 ml (4.0 mmol) of $LiAlH_4$. Flash chromatography yielded 112.3 mg (46%) of colorless crystals, m.p. 106°C. − $[\alpha]_D$ = +36 (*c* = 0.915 in CH_2Cl_2). − IR: $\tilde{\nu}$ = 3239 cm^{-1}, 1488, 1086, 811, 741. − ^1H NMR (300 MHz, $CDCl_3$): δ = 1.71 (s, 1 H, NH), 2.78−2.87 (m, 1 H, NCH_2CH_2), 2.98−3.14 (m, 2 H, NCH_2CH_2), 3.21−3.29 (m, 1 H, NCH_2CH_2), 5.08 (s, 1 H, NCH), 6.71 (d, *J* = 7.7 Hz, 1 H, aromatic H), 7.00−7.08 (m, 1 H, aromatic H), 7.13−7.17 (m, 2 H, aromatic H), 7.20 (pseudo-d, *J* = 8.5 Hz, C_6H_4Cl), 7.29 (pseudo-d, *J* = 8.5 Hz, 2 H, C_6H_4Cl). − MS (70 eV); *m*/*z*: 243 [M^+], 179, 132. − $C_{15}H_{14}ClN$ (243.75): calcd. C 73.92, H 5.79, N 5.75; found C 73.8, H 5.83, N 5.80.

(R)-1-(4-Chlorphenyl)-1,2,3,4-tetrahydroisoquinoline (**12e**): According to GP III from 210.5 mg (0.455 mmol) of **10e** in 80 ml of Et_2O with 1.81 ml (1.81 mmol) of $LiAlH_4$. Flash chromatography yielded 43.1 mg (39%) of colorless crystals, m.p. 107°C. − $[\alpha]_D$ = −36 (*c* = 1.1 in CH_2Cl_2). − $C_{15}H_{14}ClN$ (243.75): calcd. C 73.92, H 5.79, N 5.75; found C 74.0, H 5.84, N 5.69.

(R)-1,2,3,4-Tetrahydro-1-(2-thienyl)isoquinoline (**11f**): According to GP III from 398.8 mg (0.913 mmol) of **9f** in 130 ml of Et_2O with 3.65 ml (3.65 mmol) of $LiAlH_4$. Flash chromatography yielded 92.1 mg (47%) of colorless crystals, m.p. 115°C. − $[\alpha]_D$ = −18 (*c* = 3.59 in CH_2Cl_2). − IR: $\tilde{\nu}$ = 1487 cm^{-1}, 1451, 1431, 1361, 1306, 1285. − ^1H NMR (300 MHz, $CDCl_3$): δ = 1.75 (s, 1 H, NH), 2.84 (dt, *J* = 6/16 Hz, 1 H, NCH_2CH_2), 2.95 (dt, *J* = 6/16 Hz, 1 H, NCH_2CH_2), 3.10 (ddd, *J* = 5.4/6.6/12 Hz, 1 H, NCH_2CH_2), 3.27 (ddd, *J* = 5.4/6.6/12 Hz, 1 H, NCH_2CH_2), 5.41 (s, 1 H, NCH), 6.85−7.05 (m, 3 H, aromatic H), 7.08−7.20 (m, 3 H, aromatic H), 7.23−7.26 (m, 1 H, aromatic H). − MS (70 eV); *m*/*z*: 215 [M^+], 185, 132. − $C_{13}H_{13}NS$ (215.4): calcd. C 72.52, H 6.08, N 6.51; found C 72.5, H 6.17, N 6.48.

(S)-1,2,3,4-Tetrahydro-1-(2-thienyl)isoquinoline (**12f**): According to GP III from 381.4 mg (0.87 mmol) of **10f** in 125 ml of Et_2O with 3.50 ml (3.50 mmol) of $LiAlH_4$. Flash chromatography yielded 76.2 mg (41%) of colorless crystals, m.p. 115°C. − $[\alpha]_D$ = +17.9 (*c* = 1.85 in CH_2Cl_2). − $C_{13}H_{13}NS$ (215.4): calcd. C 72.52, H 6.08, N 6.51; found C 72.5, H 6.19, N 6.51.

(S)-1,2,3,4-Tetrahydro-1-(2-naphthyl)isoquinoline (**11g**): According to GP III from 434.6 mg (0.904 mmol) of **9g** in 120 ml of Et_2O with 3.6 ml (3.6 mmol) of $LiAlH_4$. Flash chromatography yielded 80.3 mg (34%) of colorless crystals, m.p. 98°C. − $[\alpha]_D$ = +121 (*c* = 1.97 in CH_2Cl_2). − IR: $\tilde{\nu}$ = 1488 cm^{-1}, 1449, 1121, 818, 742. − ^1H NMR (300 MHz, $CDCl_3$): δ = 1.99 (s, 1 H, NH), 2.81−2.90 (m, 1 H, NCH_2CH_2), 3.05−3.18 (m, 2 H, NCH_2CH_2), 3.26−3.34 (m, 1 H, NCH_2CH_2), 5.25 (s, 1 H, NCH), 6.76 (d, *J* = 7.7 Hz, 1 H, aromatic H), 6.99−7.04 (m, 1 H, aromatic H), 7.12−7.19 (m, 2 H, aromatic H), 7.37−7.48 (m, 3 H, aromatic H), 7.72 (s, 1 H, aromatic H), 7.77−7.83 (m, 3 H, aromatic H). − MS (70 eV); *m*/*z*: 259 [M^+], 229, 132. − $C_{19}H_{17}N$ (259.3): calcd. C 87.99, H 6.61, N 5.40; found C 87.8, H 6.68, N 5.39.

(R)-1,2,3,4-Tetrahydro-1-(2-naphthyl)isoquinoline (**12g**): According to GP III from 387.9 mg (0.81 mmol) of **10g** in 110 ml of Et_2O with 3.23 ml (3.23 mmol) of $LiAlH_4$. Flash chromatography yielded 65.2 mg (31%) of colorless crystals, m.p. 96°C. − $[\alpha]_D$ = −123 (*c* = 1.77 in CH_2Cl_2). − $C_{19}H_{17}N$ (259.3): calcd. C 87.99, H 6.61, N 5.40; found C 87.9, H 6.75, N 5.42.

Determination of the Absolute Configuration of (1S,5R)-1-[(S)-1,2-Dihydro-1-methyl-2-isoquinolylcarbonyl]-3,5,8,8-tetramethyl-3-azabicyclo[3.2.1]octane-2,4-dione (**7a**): According to GP II a sample of **7a** was subjected to catalytical hydrogenation (in MeOH) to afford **9a**. In the next step the crude product was subjected GP III to remove the chiral auxiliary. Then the free amine **11a** that was obtained was dissolved in Et_2O and treated with HCl gas. The resulting crystalline hydrochloride (of **11a**) was transformed to the corresponding naphthamide **15** by addition of 2 N NaOH and α-naphthoyl chloride (**14**). The absolute configuration was determined by HPLC on a "Pirkle column"[17] (BAKERBOND Chiral Phase™ DNBPG (covalent) 5 μm, 250 × 4.6 mm; precolumn LiChroCART®, LiChrospher® Si 60 5 μm 4 × 4 mm, *n*-heptane/2-propanol = 90:10, 0.75 ml/min). The retention time of the test compound was found to be 19.42 min. This result compared with the retention times obtained for authentic racemic material (16.91 min and 19.42 min) revealed **11a** and its precursors (**9a** and **7a**) to be of (*S*) stereochemistry at 1-position of the isoquinoline ring.

[^{3}H]MK-801 and [^{3}H]DTG Binding: [^{3}H]*MK-801* binding to rat brain membranes as well as [^{3}H]*DTG* binding to guinea pig brain membranes was performed according to standard radioligand binding assays[21][22]. K_i values for test compounds were calculated from competition experiments with at least 6 concentrations of test compounds using InPlot 4.0 (GraphPad Software, San Diego, CA). K_D values used in the Cheng Prusoff[23] equation were determined in saturation experiments as 4.55 ± 0.57 nM for [^{3}H]*MK-801* and 45.0 ± 2.57 nM for [^{3}H]*DTG*, respectively. If not stated otherwise, data are expressed as means ± SEM of three independent experiments, each carried out in triplicates.

[☆] Dedicated to Prof. *M. H. Zenk* with best wishes on the occasion of his 65th birthday.

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