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ASYMMETRIC SYNTHESIS OF 1-SUBSTITUTED 1,2,3,4-TETRAHYDROISOQUINOLINES BY ASYMMETRIC ELECTROPHILIC α–AMIDOALKYLATION REACTIONS

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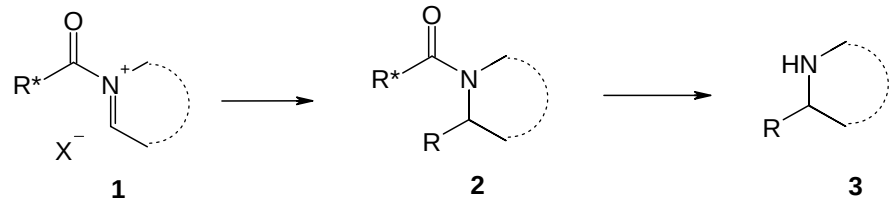
Abstract – An efficient method for the asymmetric synthesis of 1-substituted 1,2,3,4-tetrahydroisoquinolines *via* chiral *N*-acyliminium ions is presented. The *N*-acyl-1,2-dihydroisoquinolines (**8**) and (**9**) underwent smooth oxidation reactions with $Ph_3C^+BF_4^-$ to give the chiral *N*-acylisoquinolinium ions (**10**) and (**13**), respectively. Stereoselective addition of organomagnesium and organozinc compounds to intermediates (**10**) and (**13**) provided the corresponding 1-substituted *N*-acyl-1,2-dihydroisoquinolines (**11**/**12**) and (**14**/**15**) in good yields. The diastereoselectivity of these reactions appeared to be dependent on the structure of the *N*-acyliminium ion intermediates (**10**) and (**13**) and on the nature of the trapping reagent with the zinc reagents in general leading to markedly improved stereoselectivities. Pure diastereomers were obtained by preparative HPLC and readily transformed into enantiopure 1-substituted 1,2,3,4-tetrahydroisoquinolines by catalytic hydrogenation and reductive removal of the chiral auxiliary.

INTRODUCTION

Trapping reactions of *N*-acyliminium ions with nucleophiles represent a frequently used process in the construction of α-substituted amides displaying high versatility with respect to the *N*-acyliminium ions and the nucleophiles that may be employed.[1] Also various chiral variations have been realized so far giving

[#] Dedicated to Prof. H.-D. Stachel with the very best wishes on the occasion of his 75th birthday

rise to a significant extension of the scope of this powerful method, which is also termed electrophilic α-amidoalkylation reaction. Thereby broad applicability applies especially to those chiral processes where the *N*-acyliminium ions are part of an asymmetric synthesis relying on chiral auxiliaries.[2]



R*CO: Chiral auxiliary

Scheme 1

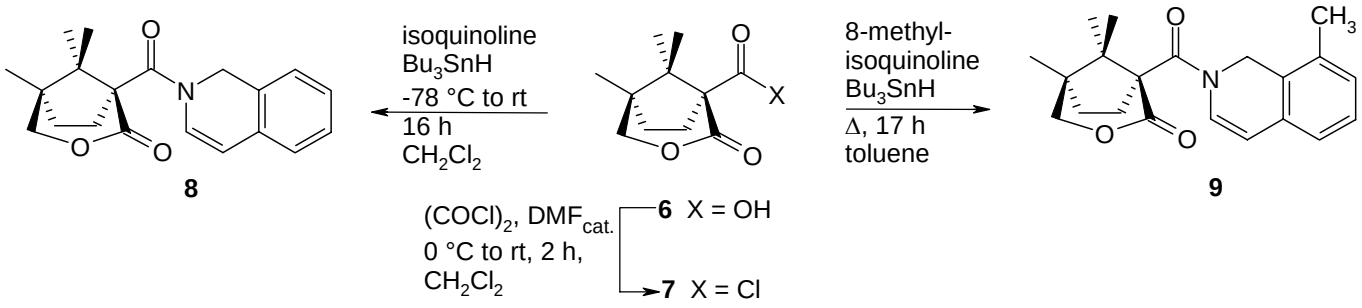
One such method developed by us features chiral *N*-acyliminium ions provided with a chiral *N*-acyl group serving as a chiral auxiliary. After removal of the latter the corresponding free amines are obtained, thus rendering the overall sequence an asymmetric synthesis for α-substituted amines (see Scheme 1). So far this method has been successfully applied to the asymmetric construction of piperidine, pyrrolidine, 1,2,3,4-tetrahydroisoquinoline and 1,2,3,4-tetrahydro-ß-carboline derivatives.[3]

Figure 1

In continuation with a project directed at the development of new ligands of the ion channel binding site of the NMDA receptor two series of enantiomerically pure 1,2,3,4-tetrahydroisoquinolines exhibiting an 1-arylsubstituent – **20** and **21** – were of great interest to us.[3h] *MK-801* (**4**) and *FR-115427* (**5**) are prototypic ligands of the aforementioned binding site of the *N*-methyl-*D*-aspartate (NMDA) receptor both displaying a high degree of enantioselectivity in binding.[4] In a former study performed by us the (*S*) stereoisomer (**20c**) was found to display a distinctly higher potency at the ion channel binding site of the NMDA receptor as compared to the (*R*) enantiomer. Up to then only the racemic mixture of **20c** had been characterized.[5] By being structurally closely related with compounds (**4**, **5** and **20c**) derivatives of series (**20**) and (**21**) appeared to be worth to be evaluated as ligands of this binding site. Of course, by taking into account the enantioselectivity in binding mentioned above it seemed reasonable to characterize these compounds in enantiomerically pure form. In this paper we wish to report our efforts directed towards the synthesis of derivatives (**20**) and (**21**) as potential ligands of the ion channel binding site of the NMDA receptor in enantiomerically pure form.[6] For the synthesis of the desired compounds we decided to employ the chiral *N*-acyliminium ions (**10**) and (**13**). The chiral auxiliary (**6**)[3c] present in **10** and **13** had been selected, as it had proven useful in many related systems.

RESULTS AND DISCUSSION

The synthesis of compounds (**8**) and (**9**) as precursors for the requisite *N*-acyliminium ions (**10**) and (**13**) provided with **6** as a chiral auxiliary was accomplished according to a synthetic methodology, which was developed by Yamaguchi *et al*.[7]



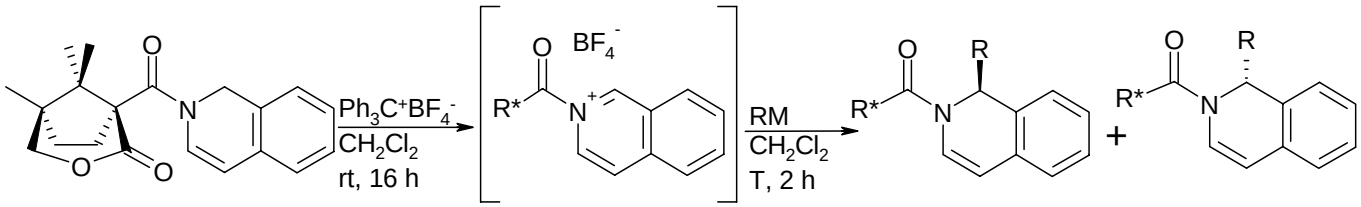
Scheme 2

By treatment of the carboxylic acid chloride (**7**) – derived from **6** – with isoquinoline and Bu_3SnH as a trapping reagent for the intermediate *N*-acylisoquinolinium ion the *N*-acyl-1,2-dihydroisoquinoline (**8**) was obtained in high yield (80 %). However, for 8-methylisoquinoline[8] the same transformation could be accomplished only when forcing conditions – heating the reaction mixture to reflux in toluene instead of stirring at room temperature in CH_2Cl_2 – were applied. Obviously, the 8-methyl group present in 8-methylisoquinoline must give rise to severe steric hindrance resulting in a significant drop of reactivity in this transformation reaction. But, fortunately, this lack in reactivity could be overcome by the modified reaction conditions providing **9** in a reasonable yield as well (71 %).

Compounds (**8**) and (**9**) proved to be well-suited precursors for the generation of the *N*-acylisoquinolinium ions (**10**) and (**13**), respectively. As for related systems[3h,9] the conversion could be efficiently effected by hydride abstraction with $Ph_3C^+BF_4^-$.[10] According to TLC the oxidation was almost complete within several hours at room temperature, but for convenience was always run overnight (16 h). The formation of the *N*-acylisoquinolinium ions could be verified unequivocally by NMR spectroscopic methods (see below). In both cases the *N*-acyliminium ions resulted in almost pure form from the oxidation step. Therefore, as there was no need for purification, the reaction mixtures obtained from the oxidation process (in CH_2Cl_2) were used without change for the subsequent trapping reactions. It should also be stated, that the generation of *N*-acyliminium ions according to this protocol is irreversible. Thus it does not suffer from any unfavorable equilibria, which often occur when *N*-acyliminium are generated more directly e.g. by reacting the corresponding imine or nitrogen heterocycle with an acid chloride.[11]

In order to determine the influence of the nature of the organometallic species on the result of the addition reactions to the *N*-acyliminium salts Grignard and zinc reagents were employed as nucleophiles in each case except for the methylation reaction. The methylation reaction of **10** with CH_3MgCl proceeded with good yield whereas the diastereoselectivity was far from being satisfying (*ds* **11a**/**12a** 60.6/39.4, see Table 1, Entry 1). The introduction of an ethyl group by means of C_2H_5MgBr led to a similar result the yield

being almost complete, while the asymmetric induction though it had increased was still poor (*ds* **11b**/**12b** 64.0/36.0, see Table 1, Entry 2). But when the ethylation reaction was performed with $(C_2H_5)_2Zn$ (1M in *n*-hexane) the diastereoselectivity rose to 87.7/12.3 and even to 92.7/7.3 when the zinc reagent had been pretreated with 5 equivalents of THF (see Table 1, Entries 3 and 4). With respect to our drug development program mentioned above derivatives with a phenyl-, a 2,6-dimethylphenyl- and a furan-2-yl group were of main interest. Addition reactions with the respective Grignard and zinc reagents (generated *in situ*) proceeded all with reasonable yields. For the addition of a phenyl and a furan-2-yl group the organozinc reagent led in both cases to a very pleasing diastereoselectivity which was also distinctly higher than the one observed with the Grignard reagent. Interestingly, for the addition of the 2,6- $(CH_3)_2C_6H_3$-moiety the opposite was true, the Grignard reagent giving rise to a high and the zinc compound to an insufficient diastereoselectivity (see Table 1, Entries 5-10).



8 **10** **11** **12**

Scheme 3

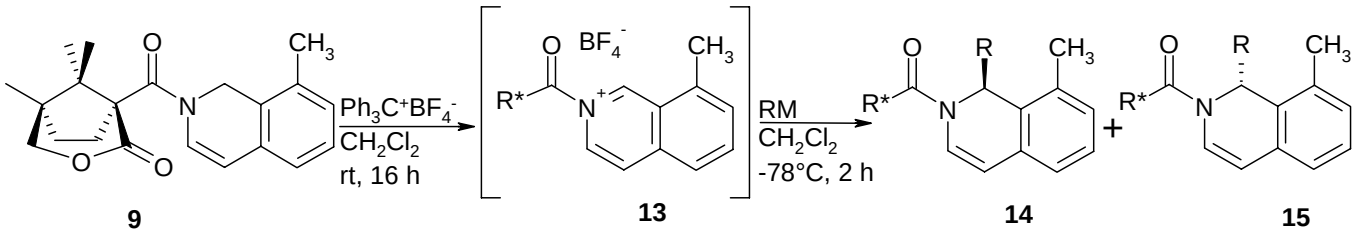
Table 1

Entry	Product 11+12	RM	Equiv.	T/ °C	Yield	*ds*[a] 11/12
1	**a**	CH_3MgCl[b]	10.0	-78	74 %	60.6/39.4
2	**b**	C_2H_5MgBr[c]	3.0	-78	98 %	64.0/36.0
3	**b**	$Zn(C_2H_5)_2$[d]	10.0	-78	80 %	87.7/12.3
4	**b**	$Zn(C_2H_5)_2$[d] + 5 equiv. THF	10.0	-78	75 %	92.7/7.3
5	**c**	PhMgCl[e]	3.0	-78	65 %	84.3/15.7
6	**c**	PhMgCl/$ZnCl_2$[f]	3.0	-90	74 %	97.0/3.0
7	**d**	2,6-$(CH_3)_2C_6H_3MgBr$[c]	3.0	-78	74 %	93.6/6.4
8	**d**	2,6-$(CH_3)_2C_6H_3MgBr/ZnCl_2$[g]	3.0	-78	66 %	65.5/34.5
9	**e**	Furan-2-yl MgBr[h]	3.0	-78	73 %	75.5/24.5
10	**e**	$(Furan\text{-}2\text{-}yl)_2Zn$[i]	3.0	-78	71 %	92.3/7.7

[a] Determined from the crude product by HPLC; [b] 3 M in THF; [c] 1.0 M in THF; [d] 1.0 M in *n*-hexane; [e] 25 % in THF; [f] from 1.8 mmol of PhMgCl (25 % in THF) and 0.9 mmol of $ZnCl_2$ (0.5 M in THF); [g] from 2 mmol of 2,6-$(CH_3)_2C_6H_3MgBr$ (1.0 M in THF) and 1 mmol of $ZnCl_2$ (1.3 M in THF); [h] preparation by treatment of 1.0 equiv. of furan with 1.0 equiv. of *s*-C_4H_9Li (1.3 M in cyclohexane) followed by 1.0 equiv. of $MgBr_2$; [i] preparation by treatment of 2.0 equiv. of furan with 2.0 equiv. of *s*-C_4H_9Li (1.3 M in cyclohexane) followed by 1.0 equiv. of $ZnCl_2$.

For the addition reactions to the *N*-acylisoquinolinium ion (**13**) a series of various aryl residues was selected which may be seen from Table 2. This time the nature of the organometallic reagents had only a minor influence on the outcome of the addition reaction. The addition of Grignard and zinc reagents proceeded both with high to excellent asymmetric induction with diastereoselectivities ranging from 91.1/8.9 to 98.8/1.2 (see Table 2). Furthermore, in every case also the yields were quite pleasing (from 59

to 95 %). Only the addition reactions performed with 2,6-$(CH_3)_2C_6H_3MgBr$ and 2,6-$(CH_3)_2C_6H_3MgBr/ZnCl_2$ appeared to be an exception. In case of the Grignard reagent the diastereoselectivity dropped to 63.9/36.1 whereas the corresponding zinc derivative did not react at all.



9 **13** **14** **15**

Scheme 4

Table 2

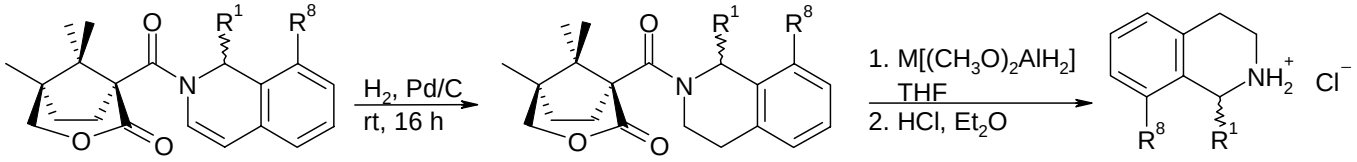
Entry	Product 14+15	RM	Equiv.	T/ °C	Yield	*ds*[a] 14/15
1	**a**	PhMgCl[b]	10.0	-78	95 %	98.1/1.9
2	**a**	$ZnPh_2$[c]	5.0	-78	59 %	98.8/1.2
3	**b**	2-$CH_3C_6H_4MgBr$[c]	3.0	-78	95 %	97.1/2.9
4	**b**	2-$CH_3C_6H_4MgBr/ZnCl_2$[d]	3.0	-78	91 %	93.3/6.7
5	**c**	2,6-$(CH_3)_2C_6H_3MgBr$[c]	3.0	-78	77 %	63.9/36.1
6	**c**	2,6-$(CH_3)_2C_6H_3MgBr/ZnCl_2$[e]	3.0	-78	0 %	-
7	**d**	Furan-2-ylMgBr[f]	3.0	-78	71 %	91.1/8.9
8	**d**	$(Furan\text{-}2\text{-}yl)_2Zn$[g]	3.0	-78	65 %	91.3/8.7

[a] Determined from the crude product by HPLC; [b] 25 % in THF; [c] 1.0 M in THF; [d] from 2 mmol of 2-$CH_3C_6H_4MgBr$ (1.0 M in THF) and 1 mmol of $ZnCl_2$ (1.3 M in THF); [e] from 2 mmol of 2,6-$(CH_3)_2C_6H_3MgBr$ (1.0 M in THF) and 1 mmol of $ZnCl_2$ (1.3 M in THF); [f] by treatment of 1.0 equiv. of furan with 1.0 equiv. of *s*-C_4H_9Li (1.3 M in cyclohexane) followed by 1.0 equiv. of $MgBr_2$; [g] by treatment of 2.0 equiv. of furan with 2.0 equiv. of *s*-C_4H_9 (1.3 M in cyclohexane) followed by 1.0 equiv. of $ZnCl_2$.

The reactivity of the zinc reagent must obviously be too low for the sterically demanding 2,6-dimethylphenyl moiety being transferred from the organometallic center to the iminium subunit which itself suffers from severe steric hindrance arising from the 8-methyl group of the isoquinoline ring. According to the model for asymmetric induction proposed for the chiral auxiliary (**7**) (see below) the formation of a complex between the carbonyl function of the lactone moiety and the organometallic reagent is detrimental for the asymmetric addition reaction to occur. In support of this model the low diastereoselectivity observed for the addition of 2,6-dimethylphenylmagnesium bromide (to **13**) and the failure with the zinc derivative might indicate that in this case due to steric crowding this complex is not tight enough to give a reasonable asymmetric induction or is not formed at all.

As final compounds for the biological studies the pure enantiomers of the free 1,2,3,4-tetrahydro-isoquinolines (**20c,d**) and (**21a-c**) were needed. Thus, from the respective mixtures the major diastereomers were isolated by preparative HPLC and purified at least to > 99 %. In case of the phenyl adducts (**11c**/**12c**) and the 2,6-dimethylphenyl addition products (**14c**/**15c**) also the minor isomers were present in reasonable amounts in the crude reaction mixtures and, therefore, were isolated in pure form and included in the final transformation reactions as well. For general reasons, especially with the intention to

determine the sense of asymmetric induction for the addition of alkyl groups, also the tetrahydroisoquinoline (**20a**) seemed of interest. Thus, in addition to the aryl derivatives also compound (**11a**) was carried through the final sequence.



11a,c,d
12c
14a-c
15c

16a,c,d
17c
18a-c
19c

20a,c,d
(*ent*)-20c
21a-c
(*ent*)-21c

Scheme 5

Table 3

Entry	Educt	R^1	R^8	Configuration at C-1	Solvent	Yield	Product
1	**11a**	CH_3	H	*S*	CH_3OH	92 %	**16a**
2	**11c**	Ph	H	*S*	CH_3OH/C_2H_5OAc	78 %	**16c**
3	**11d**	2,6-$(CH_3)_2C_6H_3$	H	*R*	CH_3OH/C_2H_5OAc	78 %	**16d**
4	**12c**	Ph	H	*R*	CH_3OH/C_2H_5OAc	85 %	**17c**
5	**14a**	Ph	CH_3	*S*	CH_3OH	85 %	**18a**
6	**14b**	2-$CH_3C_6H_4$	CH_3	*S*	CH_3OH/C_2H_5OAc	64 %	**18b**
7	**14c**	2,6-$(CH_3)_2C_6H_3$	CH_3	*S*	CH_3OH/C_2H_5OAc	80 %	**18c**
8	**15c**	2,6-$(CH_3)_2C_6H_3$	CH_3	*R*	CH_3OH/C_2H_5OAc	83 %	**19c**

Table 4

Entry	Educt	R^1	R^8	Config. at C-1	Equiv	$M[(CH_3O)_2AlH_2]$[a)]	T/°C	t/h	Yield	Product
1	**16a**	CH_3	H	*S*	1.05	$Li[(CH_3O)_2AlH_2]$	–50	65	57 %	**20a**
2	**16c**	Ph	H	*S*	1.05	$Li[(CH_3O)_2AlH_2]$	–50	72	32 %	**20c**
3	**16d**	2,6-$(CH_3)_2C_6H_3$	H	*R*	3.0	$Na[(CH_3O)_2AlH_2]$	–30	96	51 %	**20d**
4	**17c**	Ph	H	*R*	1.05	$Li[(CH_3O)_2AlH_2]$	–50	72	35 %	**(*ent*)-20c**
5	**18a**	Ph	CH_3	*S*	1.05	$Li[(CH_3O)_2AlH_2]$	–50	19	17 %	**21a**
6	**18b**	2-$CH_3C_6H_4$	CH_3	*S*	3.0	$Na[(CH_3O)_2AlH_2]$	–30	90	47 %	**21b**
7	**18c**	2,6-$(CH_3)_2C_6H_3$	CH_3	*S*	2.0	$Na[(CH_3O)_2AlH_2]$	–30	90	34 %	**21c**
8	**19c**	2,6-$(CH_3)_2C_6H_3$	CH_3	*R*	3.0	$Na[(CH_3O)_2AlH_2]$	–30	90	56 %	**(*ent*)-21c**

[a)] 1.0 M in THF; from $MAlH_4$ (1.0 M in THF) by treatment with CH_3OH.

The hydrogenation of the pure diastereomers was performed under normal pressure in the presence of catalytic amounts of Pd-C which gave the required 1,2,3,4-tetrahydroisoquinoline derivatives in good yields (see Table 3).

The last step in our synthesis involved the removal of the chiral auxiliary. Strongly basic or acidic reaction conditions to accomplish the hydrolysis of the amide function had to be ruled out, as for related systems such attempts had either proceeded with epimerization or with decomposition of the starting material.[12] So far reductive cleavage procedures had always led to the best results with respect to the yield of the final

product. This was especially true when $Na[(CH_3O)_2AlH_2]$[3f] was employed but $Li[(CH_3O)_2AlH_2]$ had proven useful in may cases, too.[3d] Thus, a reductive procedure for the removal of the auxiliary employing either $Li[(CH_3O)_2AlH_2]$ or $Na[(CH_3O)_2AlH_2]$ was used here, as well, providing the final compounds listed in Table 4 in medium to good yields.

The configuration at the newly created stereocenter of compounds (**20c**, **21a**, **21b** and **21c**) was determined to be (*S*) in every case by X-Ray analyses carried out on the intermediates (**11c**, **14a**, **14b** and **14c**), respectively. The methyl derivative (**20a**) was identified to be of (*S*) configuration as well. In this case the assignment was accomplished by chiral column chromatography of the naphthamide of **20a** according to a known procedure for an authentic sample.[3h] Of course, as they are precursors of **20a**, compounds (**11a**) and (**16a**) must display (*S*) configuration at 1-position of the isoquinoline ring as well.

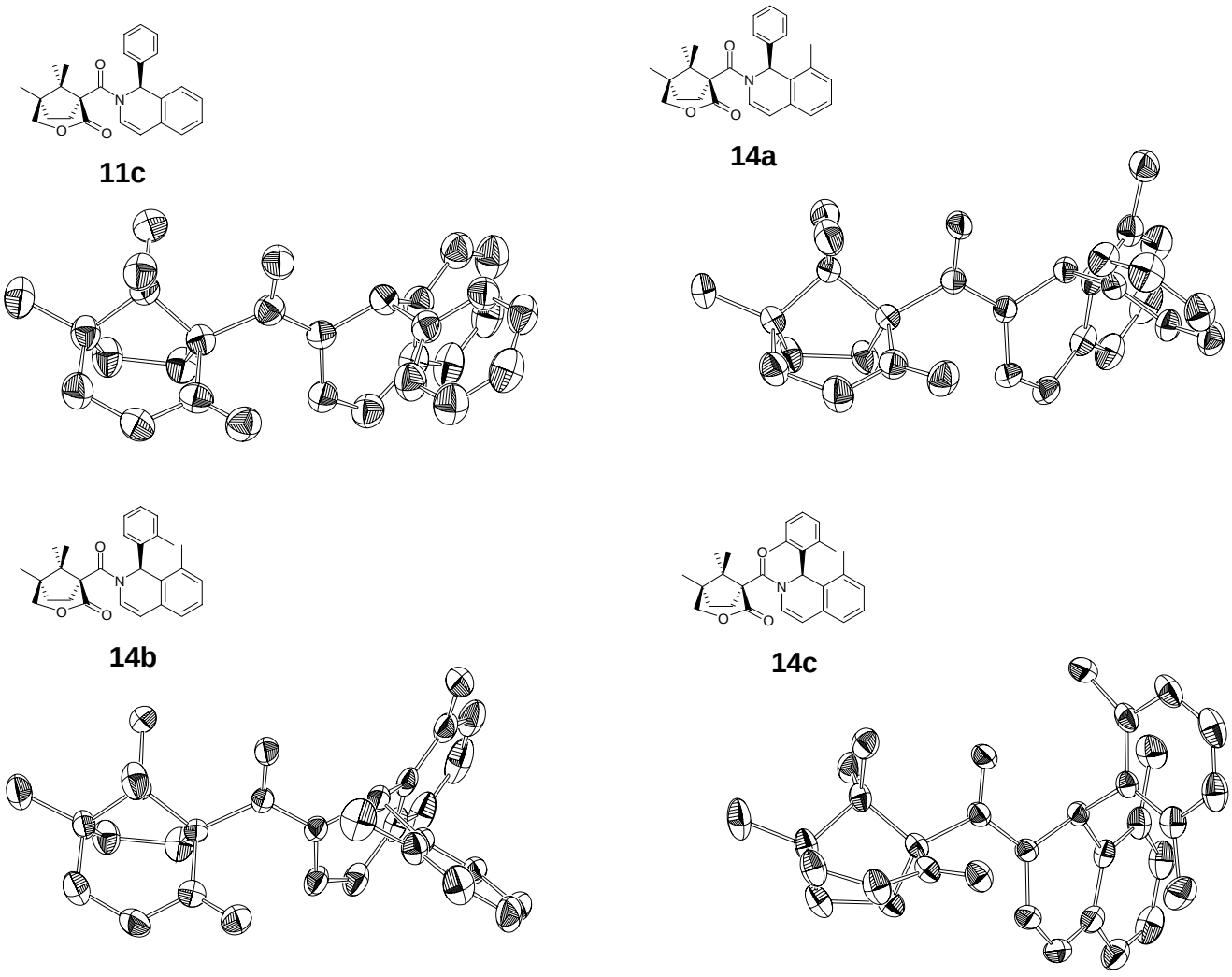


Figure 2

The stereochemistry of the addition products (**11**/**12b**, **11**/**12d**, **11**/**12e** and **14**/**15d**) became apparent from a comparison of their ^1H NMR spectra with those obtained for the amidoalkylation products (**11**/**12a**, **11**/**12c** and **14**/**15a-c**). The spectra of the major products (**11a-e**) and (**14a-d**), respectively, were of high similarity to each other and the same was true for the minor isomers (**12a-e**) and (**15a-d**). Thus, with the

configuration being known for **11a**, **11c** and **14a-c** to be (*S*) at the newly created stereocenter it can be concluded that this configuration applies to **11b**, **11d**, **11e** and **14d** as well and that the minor diastereomers (**12b**, **12d**, **12e** and **15d**) are of (*R*) configuration at this carbon.

According to the configuration observed for the addition products, the addition to the prochiral iminium subunit of **10** and **13** has proceeded preferentially from the *si* face, which is in accord with the results found for a closely related *N*-acylisoquinolinium ion provided with a similar chiral auxiliary.[3h]

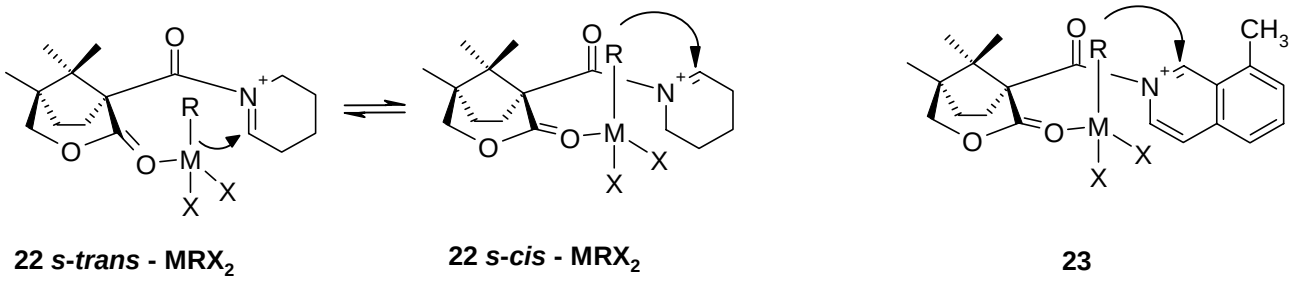


Figure 3

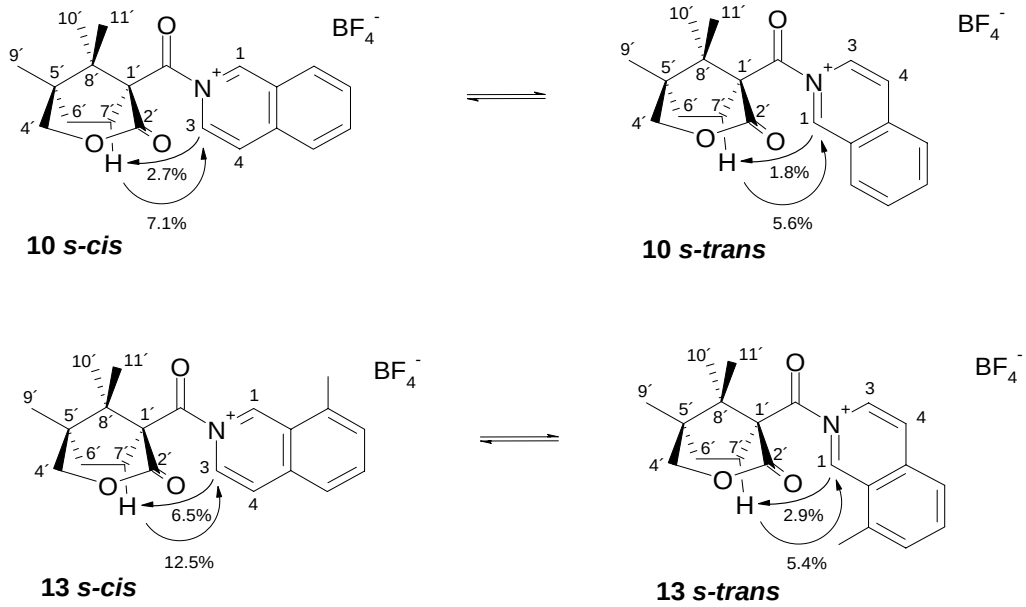


Figure 4

However, the opposite sense of asymmetric induction has been established for the *N*-acylpiperidinium salt (**22**) where as compared to **10** and **13** the isoquinolinium unit is replaced with a piperidinium moiety.[3c] According to the precomplexation mechanism proposed for this type of chiral auxiliary first a complex between the organometallic reagent and the carbonyl function of the chiral auxiliary is formed which formation is finally followed by an intramolecular transfer of a residue from the organometallic center to the iminium subunit. For **22** the conformations **22** ***s-trans*** and **22** ***s-cis*** (see Figure 3) are likely to predominate and, furthermore, to reflect the geometry of the transition states for the transfer reaction (see Figure 3 **22** ***s-trans*-MRX$_2$** and **22** ***s-cis*-MRX$_2$**). Steric interactions should be minimized when the

coplanar OC-NC subunit, which coplanarity is reasonable to assume for electronic reasons,[13] adopts an orientation where the CO group of the OC-NC subunit is synperiplanar with the dimethyl substituted 8'-carbon of the bicyclic ring system. In addition, **22 *s-trans*-MRX_2** and **22 *s-cis*-MRX_2** seem to be the only reasonable conformations where the donor and the acceptor site are close enough for a transfer reaction to occur. Actually, at first sight molecular models suggested that **22 *s-trans*-MRX_2** is the most favorable conformation with respect to the distance of the two reaction centers. However, a group transfer seems viable for **22 *s-cis*-MRX_2** as well, as a ring flip of the lactone ring may bring the metal center closer to the electrophilic carbon of the iminium moiety. Thus, the stereochemical outcome of the transfer reaction might at least to some extent be determined by the conformational behavior of the OC-NC subunit - *s-cis* versus *s-trans* - of the *N*-acyliminium salt in question. For **22** and related *N*-acylpiperidinium salts clear evidence for a predominance of the *s*-trans conformation of the OC-NC subunit has been provided, which may be rationalized by a minimization of steric interactions.[3c,14] As the same arguments are valid for a complex of **22** with an organometallic species as well it seems reasonable to assume, that also for **22-MRX_2** the *s*-trans conformation of the OC-NC subunit predominates (see Figure 3 **22 *s-trans*-MRX_2** and **22 *s-cis*-MRX_2**). Consequently, **22 *s-trans*-MRX_2** should reflect the transition state for the *N*-acylpiperidinium ion (**22**). In accord with the sense of asymmetric induction predicted by this model addition reactions to **22** proceed with *re* face selectivity.

Extensive NOE measurements revealed the gross conformational behaviour of **10** and **13**. Upon irradiation at the frequency of 7'-H_{endo} (for **10** and **13**) the signals in 1- and 3-position of the isoquinoline nucleus were significantly enhanced. Interestingly, the NO effect observed for the 3-position was distinctly stronger than the effect observed for the 1-position, which was true for both *N*-acyliminium ions, (**10**) and (**13**). When the signals corresponding to 1-H and 3-H of the isoquinoline nucleus of **10** and **13**, respectively, were excited distinct NO effects for 7'-H_{endo} arose. Interestingly, and in line with the former results the intensity of the interaction between 3-H-7'-H_{endo} was about twice as high as for 1-H-7'-H_{endo}. Actually, though every relevant proton of the chiral auxiliary and the isoquinoline nucleus (of **10** and **13**) was subjected to NOE measurements no further NO effects between the isoquinoline ring and the chiral auxiliary were observed, with one exception. For the *N*-acyliminium ion (**13**) excitation of the 10'-CH_3 and 11'-CH_3 group generated NO effects for the protons in 1- and 3-position of the isoquinoline nucleus, which were, however, very weak (10'-CH_3 $\Rightarrow$ 1-H: 0.5 %, 3-H: 0.2 %; 11'-CH_3 $\Rightarrow$ 1-H: 0.2 %, 3-H: 0.2 %). Consequently, the *N*-acyliminium ions (**10**) and (**13**) are thought to prefer a conformation where similar to **22** the carbonyl function of the OC-NC subunit is synperiplanar with the dimethyl substituted 8'-carbon of the chiral auxiliary. But, what is most important, now the *s-cis* conformation of the OC-NC subunit must predominate over the *s-trans* orientation. Thus, in contrast to *N*-acylpiperidinium salt (**22**) the *N*-acylisoquinolinium ions (**10**) and (**13**) prefer to adopt a *s-cis* orientation for the OC-NC subunit. This

feature, again provided the *N*-acylisoquinolinium ions (**10**) and (**13**) behave the same when attached to an organometallic reagent, may be considered as the main reason why addition reactions to the *N*-acylisoquinolinium ions (**10**) and (**13**) exhibit *si* face selectivity in contrast to addition reactions to the corresponding *N*-acylpiperidinium ions for which the opposite is true (*re* face selectivity). Thus, **23** is proposed as model for asymmetric induction for addition reactions to **10** and **13**.

In summary, asymmetric syntheses of 1-substituted 1,2,3,4-tetrahydroisoquinolines based on the employment of the chiral *N*-acyliminium ions (**10**) and (**13**) have been disclosed. The addition reactions to **10** and **13** proceeded with *si* face selectivity. Based on NO experiments performed with **10** and **13** the model for asymmetric induction **23** displayed in Figure 3 is proposed. The addition products (**11a**,**c**,**d**, **12c**, **14a-c** and **15c**) were used to prepare enantiopure 1-substituted 1,2,3,4-tetrahydroisoquinoline derivatives (**20a**,**c**,**d**, (*ent*)-**20c**, **21a-c** and (*ent*)-**21c**).

EXPERIMENTAL

All reactions were carried out in vacuum dried glassware under nitrogen atmosphere. All reagents were used as commercially available. $Ph_3C^+BF_4^-$ was obtained from Fluka or prepared following.[10] Solvents were dried and distilled prior to use. Benzene, cyclohexane, dioxane, $(C_2H_5)_2O$, *n*-hexane, *n*-pentane, THF and toluene were freshly distilled from sodium metal/benzophenone ketyl, CH_2Cl_2 from CaH_2, C_2H_5OH from sodium metal/diethyl phthalate and CH_3OH from Mg prior to use. Melting points were determined on a Büchi melting point apparatus no. 510 (Dr. Tottoli) and are uncorrected. IR spectra were recorded with a Perkin Elmer FT-IR spectrophotometer Paragon 1000 or 1600, and NMR spectra were obtained with a JEOL JNM-GX 400 spectrometer (400 MHz for ^1H, 100 MHz for ^{13}C) with TMS as internal standard. The NMR spectra were recalculated with NUTS, 2D version 4.35 or 5.097. MS spectra were recorded on a Hewlett Packard 5989 A with 59980 B particle beam LC/MS interface. CHN-analyses were determined with 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 (0.040–0.063 mm). Analytical HPLC: L-6000 or L-6200 pump, L-4000 or L-7400 UV/Vis detector, D-7500 or 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-Dihydroisoquinolin-2-yl)carbonyl]-5,8,8-trimethyl-3-oxabicyclo[3.2.1]octan-2-one (8).

To a solution of 4.069 g (19.17 mmol) of **6**[3c] in 38 mL of CH_2Cl_2 1.84 mL (21.09 mmol) of oxalyl chloride and 5 drops of DMF were added at 0 °C. The reaction mixture was stirred for 3 h and 15 min at rt before it was liberated from solvent and excess oxalyl chloride in vacuo. The residue thus obtained **7** was dissolved in 38 mL of CH_2Cl_2, the solution cooled to −78 °C and treated with 4.51 mL (38.34 mmol) of isoquinoline and 5.67 mL (21.09 mmol) of Bu_3SnH. Then the reaction mixture was allowed to slowly warm up to rt. After 16 h the reaction was quenched by addition of 40 mL of H_2O and the organic phase was successively washed with 2 M HCl (2×40 mL), 2 M NaOH (2×40 mL), H_2O (1x40 mL) and brine (1x40 mL), dried ($MgSO_4$) and concentrated in vacuo. The residue was washed with *n*-pentane until it was free of stannanes (according to TLC) and was finally purified by CC (C_2H_5OAc/*n*-hexane = 20/80) to yield 4.985 g (80 %) of colorless crystals, mp 164 °C. – TLC: R_f = 0.26 (C_2H_5OAc/*n*-hexane = 30/70). — $[\alpha]_D^{23}$ = +297 ° (c = 0.785 in $CHCl_3$). –^{1}H NMR (nitrobenzene-d_5, 140 °C): δ = 0.91 (s, 3 H, CH_3), 1.04 (s, 3 H, CH_3), 1.43 (s, 3 H, CH_3), 1.70–2.00 (m, 2 H, CH_2CH_2), 2.40–3.56 (m, 2 H, CH_2CH_2), 4.02 (d, J = 11.1 Hz, 1 H, CH_2O), 4.22 (d, J = 11.1 Hz, 1 H, CH_2O), 4.68 (d, J = 15.8 Hz, 1 H, NCH_2C_{ar}), 5.12 (d, J = 15.8 Hz, 1 H, NCH_2C_{ar}), 5.91 (d, J = 7.7 Hz, 1 H, $=CHC_{ar}$), 7.00–7.20 (m, 5 H, NCH=, H_{ar}). – IR (KBr): $\tilde{\nu}$ = 1722 cm^{-1}, 1657, 1627, 1573, 1458. – MS (70 eV); m/z (%): 325 (9) [M^+], 195 (2), 167 (3), 130 (100). – Anal. Calcd for $C_{20}H_{23}NO_3$: C, 73.82; H, 7.12; N, 4.30. Found: C, 73.81; H, 7.19; N, 4.24.

(1*S*,5*R*)-5,8,8-Trimethyl-1-[(8-methyl-1,2-dihydroisoquinolin-2-yl)carbonyl]-3-oxa-bicyclo[3.2.1]-octan-2-one (9).

To a solution of the acid chloride (**7**), that had been obtained according to the procedure described for **8** from 5.048 g (23.79 mmol) of **6**,[3c] in 100 mL of toluene under ice cooling 12.80 mL (47.57 mmol) of Bu_3SnH and 3.76 mL (26.25 mmol) of 8-methylisoquinoline[8] in 5 mL of toluene were added. After heating the mixture to reflux for 24 h the reaction was quenched by addition of 15 mL of H_2O. The organic phase was concentrated in vacuo. The residue was dissolved in 100 mL of CH_2Cl_2. The resulting solution was successively washed with 2 M HCl (3×70 mL), 2 M NaOH (3×70 mL) and brine (1x70 mL), dried ($MgSO_4$) and concentrated in vacuo. The product was washed with *n*-pentane until it was free of stannanes (according to TLC) and finally purified by CC (C_2H_5OAc/*n*-heptane = 20/80) to yield 5.730 mg (71 %) of colorless crystals, mp 146 °C (decomp). – TLC: R_f = 0.18 (C_2H_5OAc/*n*-heptane = 20/80). – $[\alpha]_D^{14}$ = +299 ° (c = 0.205 in $CHCl_3$). – ^{1}H NMR (nitrobenzene-d_5, 140 °C): δ = 0.91 (s, 3 H, CH_3), 1.05 (s, 3 H, CH_3), 1.43 (s, 3 H, CH_3), 1.72–1.99 (m, 2 H, CH_2CH_2), 2.21 (s, 3 H, $C_{ar}CH_3$), 2.38–2.54 (m, 2 H, CH_2CH_2), 4.01 (d, J = 11.1 Hz, 1 H, CH_2O), 4.21 (d, J = 11.1 Hz, 1 H, CH_2O), 4.59 (d, J = 16.2 Hz, 1 H, CH_2N), 5.18 (d, J = 16.2 Hz, 1 H, CH_2N), 5.83 (d, J = 7.7 Hz, 1 H, $=CHC_{ar}$), 6.87 (d, J = 7.3 Hz, 1 H, H_{ar}), 6.92–6.96 (m, 2 H, NCH=, H_{ar}), 7.05 (t, J = 7.7 Hz, 1 H, H_{ar}). – IR (KBr): $\tilde{\nu}$ = 1734 cm^{-1}, 1633, 1627, 1466, 1335. – MS (70 eV); m/z (%): 339 (10) [M^+], 195 (3), 167 (4), 144 (100). – Anal. Calcd for $C_{21}H_{25}NO_3$: C, 74.31; H, 7.42; N, 4.13. Found: C, 74.15; H, 7.68; N, 4.04.

General procedure for electrophiliç α-amidoalkylation reactions with 10 and 13 - GP1. To a solution of compound (**8**) or (**9**) in CH_2Cl_2 (0.16 M) 1.1 equiv. of $Ph_3C^+ BF_4^-$ (0.30 M in CH_2Cl_2) was added and the resulting mixture was stirred for 16 h at rt. After cooling to −78 °C and addition of the respective organometallic reagent it was stirred for 2 h. Then H_2O was added, the reaction mixture was warmed up to rt and 2 M HCl was added until the reaction mixture became clear. The aqueous layer was extracted with CH_2Cl_2 (4 ×), and the combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. The diastereoselectivity was determined by HPLC (from the crude product). The crude products were first purified by CC and the resulting mixtures finally separated by prep. HPLC.

2-[(1*S*,5*R*)-5,8,8-Trimethyl-2-oxo-3-oxabicyclo[3.2.1]octylcarbonyl]isoquinoliniumtetrafluoroborate (10).

To a solution of 199 mg (0.61 mmol) of **8** in 1.0 mL of CH_2Cl_2 1.1 equiv. of $Ph_3C^+ BF_4^-$ (0.7 M in CH_2Cl_2) was added. The mixture was stirred for 16 h at rt before it was concentrated in high vacuo. The solution obtained upon addition of 1.0 mL of CD_2Cl_2 to the resulting residue was used for NMR-experiments. – ^{1}H NMR (CD_2Cl_2, 20 °C): δ = 0.98 (s, 3 H, 9′-H), 1.16 (s, 3 H, 10′-H), 1.43 (s, 3 H, 11′-H), 1.95–2.09 (m, 2 H, 6′-H), 2.27 (ddd, J = 13.8/10.6/6.2 Hz, 1 H, 7′$_{exo}$-H), 2.67 (ddd, J = 13.9/8.9/5.8 Hz, 1 H, 7′$_{endo}$-H), 4.21 (d, J = 11.2 Hz, 1 H, 4′$_{endo}$-H), 4.29 (dd, J = 11.2/1.6 Hz, 1 H, 4′$_{exo}$-H), 8.06 (ddd, J = 8.4/6.6/1.6 Hz, 1 H, 7-H), 8.25 (d, J = 8.2 Hz, 1 H, 5-H), 8.29 (ddd, J = 8.4/6.6/1.2 Hz, 1 H, 6-H), 8.48 (d, J = 7.1 Hz, 1 H, 4-H), 8.69 (dd, J = 8.4/0.8 Hz, 1 H, 8-H), 8.89 (dd, J = 7.1/1.6 Hz, 1 H, 3-H), 10.08 (d, J = 1.4 Hz, 1 H, 1-H). – ^{13}C NMR (CD_2Cl_2, 20 °C): δ = 15.0 (9′-C), 18.5 (10′-C), 18.6 (11′-C), 30.3 (7′-C), 33.6 (6′-C), 44.0, 49.0, 69.0 (1′-C), 80.5 (4′-C), 126.4 (4-C), 127.3, 128.0 (5-C), 130.4 (3-C), 132.7 (7-C), 133.5 (8-C), 140.5, 140.7 (6-C), 147.5 (1-C), 169.6 (COO), 172.3 (CON).

(1*S*,5*R*)-5,8,8-Trimethyl-1-[(1*S*)-1-methyl-1,2-dihydroisoquinolin-2-yl)carbonyl]-3-oxabicyclo-[3.2.1]octan-2-one (11a) and (1*S*,5*R*)-5,8,8-Trimethyl-1-[(1*R*)-1-methyl-1,2-dihydroisoquinolin-2-yl-carbonyl]-3-oxabicyclo[3.2.1]octan-2-one (12a).

According to GP1 from 1.499 g (4.61 mmol) of **8** and 15.4 mL (46.2 mmol) of CH_3MgCl (3 M in THF). HPLC (C_2H_5OAc/*n*-heptane = 15/85; 2 mL/min): **11a**: t_{ret} = 8.1 min, 60.6 %; **12a**: t_{ret} = 12.2 min, 39.4 %. Purification by CC (C_2H_5OAc/*n*-heptane = 20/80) yielded 1.150 g (74 %) of a mixture of **11a** and **12a**. Pure diastereomers were obtained after prep. HPLC (C_2H_5OAc/*n*-heptane = 15/85; 15 mL/min).

11a: Colorless crystals, mp 216 °C. – TLC: R_f = 0.26 (C_2H_5OAc/*n*-heptane = 20/80). – $[\alpha]_D^{10}$ = +553 ° (*c* = 0.26 in $CHCl_3$). – ^{1}H NMR (nitrobenzene-d_5, 140 °C): δ = 0.89 (s, 3 H, CH_3), 1.05 (s, 3 H, CH_3), 1.39 (d, *J* = 6.6 Hz, 3 H, $CHCH_3$), 1.46 (s, 3 H, CH_3), 1.83–1.91 (m, 2 H, CH_2CH_2), 2.16–2.30 (m, 1 H, CH_2CH_2), 2.40–2.52 (m, 1 H, CH_2CH_2), 4.00 (d, *J* = 11.0 Hz, 1 H, CH_2O), 4.19 (d, *J* = 11.0 Hz, 1 H, CH_2O), 5.65–5.72 (m, 1 H, CH), 5.96 (d, *J* = 7.3 Hz, 1 H, =CHC_{ar}), 6.82 (d, *J* = 7.3 Hz, 1 H, NCH=), 7.05–7.21

(m, 4 H, H_{ar}). – IR (KBr): $\tilde{\nu}$ = 1722 cm^{-1}, 1660, 1627, 1457, 1331. – MS (70 eV); *m/z* (%): 339 (17) [M^+], 324 (57), 195 (100), 167 (34), 144 (19), 139 (41). – Anal. Calcd for $C_{21}H_{25}NO_3$:C, 74.31; H, 7.42; N, 4.13. Found: C, 74.24; H, 7.58; N 4.05.

12a: Colorless crystals. – TLC: R_f = 0.21 (C_2H_5OAc/*n*-hexane = 20/80). – ^1H NMR (nitrobenzene-d_5, 140 °C): δ = 0.88 (s, 3 H, CH_3), 0.94 (s, 3 H, CH_3), 1.27 (s, 3 H, CH_3), 1.37 (d, *J* = 6.6 Hz, 3 H, $CHCH_3$), 1.81–1.98 (m, 2 H, CH_2CH_2), 2.29–2.40 (m, 1 H, CH_2CH_2), 2.87–3.03 (m, 1 H, CH_2CH_2), 3.99 (d, *J* = 10.9 Hz, 1 H, CH_2O), 4.22 (d, *J* = 10.9 Hz, 1 H, CH_2O), 5.87 (d, *J* = 7.9 Hz, 1 H, =$CH C_{ar}$), 5.91 (q, *J* = 6.6 Hz, 1 H, CH), 6.90 (d, *J* = 7.9 Hz, 1 H, NCH=), 7.03–7.20 (m, 4 H, H_{ar}). – IR (KBr): $\tilde{\nu}$ = 1727 cm^{-1}, 1653, 1623, 1456, 1325. – MS (70 eV); *m/z* (%): 339 (26) [M^+], 324 (64), 195 (100), 167 (33), 144 (26), 139 (42).

(1*S*,5*R*)-1-[(1*S*)-1-Ethyl-1,2-dihydroisoquinolin-2-ylcarbonyl]-5,8,8-trimethyl-3-oxa-bicyclo[3.2.1]octan-2-one (11b) and (1*S*,5*R*)-1-[(1*R*)1-Ethyl-1,2-dihydroisoquinolin-2-yl-carbonyl]-5,8,8-trimethyl-3-oxabicyclo[3.2.1]octan-2-one (12b).

A) According to GP1 from 0.594 g (1.83 mmol) of **8** and 5.50 mL (5.50 mmol) of $(C_2H_5)_2Zn$ (1.0 M in *n*-hexane). HPLC (C_2H_5OAc/*n*-heptane = 14/86; 2 mL/min): **11b**: t_{ret} = 8.1 min, 87.7 %; **12b**: t_{ret} = 13.7 min, 12.3 %. CC (C_2H_5OAc/*n*-heptane = 20/80) yielded 0.516 g (80 %) of a mixture of **11b** and **12b**. Pure diastereomers were obtained after prep. HPLC (C_2H_5OAc/*n*-heptane = 10/90; 12 mL/min).

11b: Colorless crystals, mp 129 °C. – TLC: R_f = 0.19 (C_2H_5OAc/*n*-heptane = 20/80). – $[\alpha]_D^{26}$ = +551 ° (*c* = 0.480 in $CHCl_3$). – ^1H NMR (nitrobenzene-d_5, 140 °C): δ = 0.88 (s, 3 H, CH_3), 0.93 (t, *J* = 7.3 Hz, 3 H, CH_2CH_3), 1.03 (s, 3 H, CH_3), 1.45 (s, 3 H, CH_3), 1.70–1.90 (m, 4 H, CH_2CH_3, CH_2CH_2), 2.10–2.25 (m, 1 H, CH_2CH_2), 2.40–2.55 (m, 1 H, CH_2CH_2), 3.99 (d, *J* = 10.7 Hz, 1 H, CH_2O), 4.18 (d, *J* = 10.7 Hz, 1 H, CH_2O), 5.50–5.55 (m, 1 H, CH), 5.97 (d, *J* = 7.3 Hz, 1 H, =$CH C_{ar}$), 6.84 (d, *J* = 7.3 Hz, 1 H, NCH=), 7.05–7.25 (m, 4 H, H_{ar}). – IR (KBr): $\tilde{\nu}$ = 1719 cm^{-1}, 1660, 1623, 1457, 1325. – MS (70 eV); *m/z* (%): 353 (3) [M^+], 324 (44), 195 (100), 167 (33), 139 (45). – Anal. Calcd for $C_{22}H_{27}NO_3$: C, 74.76; H, 7.70; N, 3.96. Found: C, 74.99; H, 7.66; N, 3.78.

12b: Colorless crystals – TLC: R_f = 0.13 (C_2H_5OAc/*n*-heptane = 20/80). – ^1H NMR (nitrobenzene-d_5 140 °C): δ = 0.83–0.98 (m, 9 H, 2 CH_3, CH_2CH_3), 1.26 (s, 3 H, CH_3), 1.71–1.96 (m, 4 H, CH_2CH_3, CH_2CH_2), 2.28–2.39 (m, 1 H, CH_2CH_2), 2.91–3.05 (m, 1 H, CH_2CH_2), 3.99 (d, *J* = 10.0 Hz, 1 H, CH_2O), 4.22 (d, *J* = 10.0 Hz, 1 H, CH_2O), 5.77–5.83 (m, 1 H, CH), 5.88 (d, *J* = 6.0 Hz, 1 H, =$CH C_{ar}$), 6.92 (d, *J* = 6.0 Hz, 1 H, NCH=), 7.02–7.22 (m, 4 H, H_{ar}). – IR (KBr): $\tilde{\nu}$ = 1716 cm^{-1}, 1655, 1619, 1456, 1323. – MS (70 eV); *m/z* (%): 353 (3) [M^+], 324 (41), 195 (100), 167 (35), 139 (45).

B) According to GP1 from 28.5 mg (0.088 mmol) of **8** and 1.24 mL (0.097 mmol) of a solution of $(C_2H_5)_2Zn$ [prep. from 2.0 mL $(C_2H_5)_2Zn$ (1.0 M in *n*-hexane) by addition of 0.81 mL of THF]. HPLC

(C_2H_5OAc/*n*-heptane = 14/86; 2 mL/min): **11b**: t_{ret} = 8.3 min, 92.7 %; **12b**: t_{ret} = 12.9 min, 7.3 %. CC (C_2H_5OAc/*n*-heptane = 20/80) yielded 23.2 mg (0.066 mmol, 75 %) of a mixture of **11b** and **12b**.

C) According to GP1 from 159 mg (0.49 mmol) of **8** und 1.46 mL (1.46 mmol) of C_2H_5MgBr (1.0 M in THF). HPLC (C_2H_5OAc/*n*-heptane = 15/85; 2 mL/min): **11b**: t_{ret} = 7.1 min, 64.0 %; **12b**: t_{ret} = 10.8 min, 36.0 %. CC (C_2H_5OAc/*n*-heptane = 20/80) yielded 169 mg (98 %) of a mixture of **11b** and **12b**.

(1*S*,5*R*)-5,8,8-Trimethyl-1-[(1*S*)-1-phenyl-1,2-dihydroisoquinolin-2-yl)carbonyl]-3-oxa-bicyclo[3.2.1]octan-2-one (11c) and (1*S*,5*R*)-5,8,8-Trimethyl-1-[(1*R*)-1-phenyl-1,2-dihydroisoquinolin-2-yl)carbonyl]-3-oxabicyclo[3.2.1]octan-2-one (12c).

A) According to GP1 from 0.253 g (0.78 mmol) of **8** and 1.23 mL (2.34 mmol) of PhMgCl (25 % in THF). HPLC (C_2H_5OAc/*n*-heptane = 15/85; 2 mL/min): **11c**: t_{ret} = 7.7 min, 84.3 %; **12c :** t_{ret} = 10.1 min, 15.7 %. CC (C_2H_5OAc/*n*-heptane = 20/80) yielded 201 mg (65 %) of a mixture of **11c** and **12c**. Pure diastereomeres were obtained by prep. – HPLC (C_2H_5OAc/*n*-heptane = 15/85; 15 mL/min) .

11c: Colorless crystals mp 186 °C. – TLC: R_f = 0.18 (C_2H_5OAc/*n*-heptane = 20/80). $[\alpha]_D^{14}$ = +423 ° (c = 0.270 in $CHCl_3$). – ^{1}H NMR (nitrobenzene-d_5, 140 °C): δ = 0.89 (s, 3 H, CH_3), 1.04 (s, 3 H, CH_3), 1.43 (s, 3 H, CH_3), 1.84–1.91 (m, 2 H, CH_2CH_2), 2.21–2.34 (m, 1 H, CH_2CH_2), 2.49–2.59 (m, 1 H, CH_2CH_2), 4.06 (d, J = 11.0 Hz, 1 H, CH_2O), 4.20 (dd, J = 11.0/0.9 Hz, 1 H, CH_2O), 6.01 (d, J = 7.8 Hz, 1 H, =CHC_{ar}), 6.84 (s, 1 H, CH), 7.01 (d, J = 7.8 Hz, 1 H, NCH=), 7.09–7.29 (m, 6 H, H_{ar}), 7.34 (d, J = 7.3 Hz, 1 H, H_{ar}), 7.56 (d, J = 7.8 Hz, 2 H, H_{ar}). – IR (KBr): $\tilde{\nu}$ = 1720 cm^{-1}, 1664, 1626, 1456, 1321. – MS (70 eV); m/z (%): 401 (15) [M^+], 324 (9), 206 (100), 195 (11), 167 (5). – Anal. Calcd for $C_{26}H_{27}NO_3$: C, 77.78; H, 6.78; N, 3.49. Found: C, 77.64; H, 6.86; N, 3.55.

12c: Colorless crystals. – TLC: R_f = 0.13 (C_2H_5OAc/*n*-heptane = 20/80). – ^{1}H NMR (nitrobenzene-d_5, 140 °C): δ = 0.87 (s, 6 H, 2 CH_3), 1.29 (s, 3 H, CH_3), 1.81–1.92 (m, 2 H, CH_2CH_2), 2.26–2.38 (m, 1 H, CH_2CH_2), 2.80–2.97 (m, 1 H, CH_2CH_2), 3.99 (d, J = 11.0 Hz, 1 H, CH_2O), 4.22 (d, J = 11.0 Hz, 1 H, CH_2O), 5.90 (d, J = 7.8 Hz, 1 H, =CHC_{ar}), 7.02–7.27 (m, 9 H, CH, NCH=, H_{ar}), 7.34–7.51 (m, 2 H, H_{ar}). – IR (KBr): $\tilde{\nu}$ = 1725 cm^{-1}, 1654, 1624, 1457, 1320. – MS (70 eV); m/z (%): 401 (28) [M^+], 324 (17), 206 (100), 195 (31), 167 (14), 139 (25).

B) According to GP1 from 40.9 mg (0.126 mmol) of **8** and 1.18 mL (0.378 mmol) of Ph_2Zn [(generated by mixing 1.0 mL of PhMgCl (25 % in THF) with 1.8 mL of $ZnCl_2$ (0.5 M in THF)]; reaction temp. –90 °C. HPLC (C_2H_5OAc/*n*-heptane = 15/85; 2 mL/min): **11c**: t_{ret} = 12.1 min, 97.0 %; **12c**: t_{ret} = 17.5 min, 3.0 %. CC (C_2H_5OAc/*n*-heptane = 20/80) yielded 37.6 mg (74 %) of a mixture of **11c** and **12c**.

(1*S*,5*R*)-1-[(1*R*)-1-(2,6-Dimethylphenyl)-1,2-dihydroisoquinolin-2-ylcarbonyl]-5,8,8-tri-methyl-3-oxabicyclo[3.2.1]octan-2-one (11d) and (1*S*,5*R*)-1-[(1*S*)-1-(2,6-Dimethylphenyl)-1,2-dihydroisoquinolin-2-ylcarbonyl]-5,8,8-trimethyl-3-oxabicyclo[3.2.1]octan-2-one (12d).

A) According to GP1 from 203 mg (0.62 mmol) of **8** und 1.87 mL (1.87 mmol) of 2,6-$(CH_3)_2C_6H_3MgBr$ (1.0 M in THF). HPLC (C_2H_5OAc/*n*-heptane = 15/85; 2 mL/min): **11d**: t_{ret} = 9.6 min, 6.4 %; **12d**: t_{ret} = 12.5 min, 93.6 %. CC (C_2H_5OAc/*n*-heptane = 20/80) yielded 197 mg (74 %) of a mixture of **11d** and **12d**. Pure diastereomers were obtained by prep. HPLC (C_2H_5OAc/*n*-heptane = 15/85; 12 mL/min).

11d: Colorless crystals, mp 132 °C. – TLC: R_f = 0.19 (C_2H_5OAc/*n*-heptane = 20/80). – $[\alpha]_D^{20}$ = +220 ° (*c* = 0.106 in $CHCl_3$). – ^1H NMR (nitrobenzene-d_5, 140 °C): δ = 0.85 (s, 3 H, CH_3), 0.87 (s, 3 H, CH_3), 1.25 (s, 3 H, CH_3), 1.78–1.94 (m, 2 H, CH_2CH_2), 2.40 (ddd, *J* = 14.6/9.0/6.0 Hz, 1 H, CH_2CH_2), 2.61 (s, 6 H, $C_{ar}CH_3$), 2.67 (ddd, *J* = 14.6/11.2/6.0 Hz, 1 H, CH_2CH_2), 3.95 (d, *J* = 11.0 Hz, 1 H, CH_2O), 4.16 (dd, *J* = 11.0/2.0 Hz, 1 H, CH_2O), 5.74 (d, *J* = 8.1 Hz, 1 H, =CHC_{ar}), 6.80 (d, *J* = 7.7, 1 H, H_{ar}), 6.88–6.98 (m, 6 H, CH, H_{ar}, =CHN), 7.00 (d, *J* = 7.4 Hz, 1 H, H_{ar}), 7.09 (t, *J* = 7.4 Hz, 1 H, H_{ar}). – IR (KBr): $\tilde{\nu}$ = 1733 cm^{-1}, 1668, 1634, 1314, 1234, 1213, 1124. – MS (70 eV); *m/z* (%): 429 (6) [M^+], 324 (7), 234 (100), 195 (21), 167 (14), 139 (14). – Anal. Calcd for $C_{28}H_{31}NO_3$: C, 78.29; H, 7.27; N, 3.26. Found: C, 78.19; H, 7.56; N, 3.06.

12d: Colorless crystals, – TLC: R_f = 0.23 (C_2H_5OAc/*n*-heptane = 20/80). – ^1H NMR (nitrobenzene-d_5, 140 °C): δ = 0.43 (s, 3 H, CH_3), 0.80 (s, 3 H, CH_3), 1.27 (s, 3 H, CH_3), 1.83–1.89 (m, 2 H, CH_2CH_2), 2.37–2.55 (m, 2 H, CH_2CH_2), 2.50 (s, 6 H, $C_{ar}CH_3$), 3.96 (d, *J* = 11.0 Hz, 1 H, CH_2O), 4.13 (dd, *J* = 11.0/1.5 Hz, 1 H, CH_2O), 5.63 (d, *J* = 8.4 Hz, 1 H, =CHC_{ar}), 6.63 (d, *J* = 7.4, 1 H, H_{ar}), 6.87 (td, *J* = 7.5/1.4 Hz, 1 H, H_{ar}), 6.91 (d, *J* = 8.4 Hz, 1 H, =CHN), 6.93–7.08 (m, 6 H, CH, H_{ar}). – IR (KBr): $\tilde{\nu}$ = 1722 cm^{-1}, 1673, 1637, 1472, 1455, 1304, 1282, 1219. – MS (70 eV); *m/z* (%): 429 (8) [M^+], 324 (10), 234 (100), 195 (32), 167 (14), 139 (17).

B) According to GP1 from 155 mg (0.475 mmol) of **8** and 3.96 mL (1.425 mmol) $(2,6\text{-}(CH_3)_2C_6H_3)_2Zn$ [generated by mixing 8.0 mL of 2,6-$(CH_3)_2C_6H_3MgBr$ (1.0 M in THF) and 3.15 mL of $ZnCl_2$ (1.27 M in THF)]. HPLC- (C_2H_5OAc/*n*-heptane = 15/85; 2 mL/min): **11d**: t_{ret} = 8.7 min, 34.5 %; **12d**: t_{ret} = 11.1 min, 65.5 %. CC (C_2H_5OAc/*n*-heptane = 20/80) yielded 134 mg (0.313 mmol, 66 %) of a mixture of **11d** and **12d**.

(1*S*,5*R*)-1-[(1*R*)-1-Furan-2-yl-1,2-dihydroisoquinolin-2-ylcarbonyl]-5,8,8-trimethyl-3-oxa-bicyclo[3.2.1]octan-2-one (11e) and (1*S*,5*R*)-1-[(1*S*)-1-Furan-2-yl-1,2-dihydroiso-quinolin-2-ylcarbonyl]-5,8,8-trimethyl-3-oxabicyclo[3.2.1]octan-2-one (12e).

A) According to GP1 from 1.477 g (4.54 mmol) of **8** and 26.0 mL of furan-2-yl MgBr prepared by treating of 1.10 mL of furan in 15.0 mL of THF at -20 °C with 11.6 mL of *s*-C_4H_9Li (1.3 M in cyclohexane) followed by 3.57 g of $MgBr_2$ (13.8 mmol)]. HPLC (C_2H_5OAc/*n*-heptane = 15/85; 2 mL/min): **11e**: t_{ret} = 13.1 min, 75.5 %; **12e**: t_{ret} = 18.6 min, 24.5 %. CC [$(C_2H_5)_2O$/CH_2Cl_2/*n*-heptane = 5/35/60)] yielded

1.305 g (73 %) of a mixture of **11e** and **12e**. Pure diastereomers were obtained by prep. HPLC (C_2H_5OAc/*n*-heptane = 20/80; 12 mL/min).

11e: Colorless crystals, mp 169 °C. – TLC: R_f = 0.17 (C_2H_5OAc/*n*-heptane = 20/80). $[\alpha]_D^{20}$ = +418 ° (c = 0.190 in $CHCl_3$). – ^1H NMR (nitrobenzene-d_5, 140 °C): δ = 0.89 (s, 3 H, CH_3), 1.06 (s, 3 H, CH_3), 1.43 (s, 3 H, CH_3), 1.82–1.95 (m, 2 H, CH_2CH_2), 2.25–2.39 (m, 1 H, CH_2CH_2), 2.47–2.56 (m, 1 H, CH_2CH_2), 4.00 (d, J = 11.0 Hz, 1 H, CH_2O), 4.19 (dd, J = 11.0/1.6 Hz, 1 H, CH_2O), 6.01 (d, J = 7.8 Hz, 1 H, =CHC_{ar}), 6.19 (dd, J = 3.2/1.8 Hz, 1 H, H_{ar}), 6.34 (d, J = 3.2 Hz, 1 H, H_{ar}), 6.83 (s, 1 H, CH), 6.98 (dd, J = 7.8/1.0 Hz, 1 H, NCH=), 7.13 (dd, J = 7.2/1.4 Hz, 1 H, H_{ar}), 7.17–7.28 (m, 3 H, H_{ar}), 7.33 (d, J = 7.3 Hz, 1 H, H_{ar}). – IR (KBr): $\tilde{\nu}$ = 1732 cm^{-1}, 1665, 1628, 1341, 1322, 1228. – MS (CI); m/z (%): 392 (54) [M + H^+], 324 (92), 196 (100), 195 (39), 167 (15). – Anal. Calcd for $C_{24}H_{25}NO_4$: C, 73.64; H, 6.44; N, 3.58. Found: C, 73.64; H, 6.49; N, 3.53.

12e: Colorless crystals, mp 195 °C. – TLC: R_f = 0.14 (C_2H_5OAc/*n*-heptane = 20/80). $[\alpha]_D^{20}$ = –357 ° (c = 0.190 in $CHCl_3$). – ^1H NMR (nitrobenzene-d_5, 140 °C): δ = 0.90 (s, 3 H, CH_3), 0.99 (s, 3 H, CH_3), 1.32 (s, 3 H, CH_3), 1.67–2.00 (m, 2 H, CH_2CH_2), 2.31–2.41 (m, 1 H, CH_2CH_2), 2.84–2.98 (m, 1 H, CH_2CH_2), 4.00 (d, J = 11.0 Hz, 1 H, CH_2O), 4.23 (dd, J = 11.0/2.2 Hz, 1 H, CH_2O), 5.90 (d, J = 7.8 Hz, 1 H, =CHC_{ar}), 6.16–6.19 (m, 1 H, H_{ar}), 6.22 (dd, J = 3.2/1.8 Hz, 1 H, H_{ar}), 7.00 (d, J = 7.8 Hz, 1 H, NCH=), 7.09–7.13 (m, 2 H, H_{ar}), 7.16–7.26 (m, 2 H, H_{ar}), 7.29 (d, J = 7.4 Hz, 1 H, H_{ar}), 7.38 (s, 1 H, CH). – IR (KBr): $\tilde{\nu}$ = 1715 cm^{-1}, 1662, 1625, 1457, 1340, 1320, 1215. – MS (70 eV); m/z (%): 391 (12) [M^+], 195 (100), 167 (11), 139 (14). – Anal. Calcd for $C_{24}H_{25}NO_4$: C, 73.64; H, 6.44; N, 3.58. Found: C, 73.69; H, 6.49; N, 3.48.

B) According to GP1 from 1.516 g (4.66 mmol) of **8** and 46.6 mL (9.32 mmol) of (Furan-2-yl)$_2$Zn [prepared by mixing 1.45 mL of furan in , 15.4 mL of THF at – 20 °C with, 15.4 mL of *s*-C_4H_9Li (1.3 M in cyclohexane) followed by 20.0 mL of $ZnCl_2$ (0.5 M in THF)]. HPLC (C_2H_5OAc/*n*-heptane = 15/85; 2 mL/min): **11e**: t_{ret} = 13.0 min, 92.3 %; **12e**: t_{ret} = 18.5 min, 7.7 %. CC (C_2H_5OAc/*n*-heptane = 20/60) yielded 1.290 g (71 %) of a mixture of **11e** and **12e**.

8-Methyl-2-[(1*S*,5*R*)-5,8,8-trimethyl-2-oxo-3-oxabicyclo[3.2.1]octylcarbonyl]isoquinolinium tetrafluoroborate (13).

To a solution of 100 mg (0.29 mmol) of **9** in 1.8 mL of CH_2Cl_2 1.1 equiv. of $Ph_3C^+ BF_4^-$ (0.3 M in CH_2Cl_2) was added. The mixture was stirred for 16 h at rt before it was concentrated in high-vacuo. The solution obtained upon addition of 1.0 mL of CD_2Cl_2 to the resulting residue was used for NMR-experiments. – ^1H NMR (CD_2Cl_2, 20 °C): δ = 0.99 (s, 3 H, 9′-H), 1.18 (s, 3 H, 10′-H), 1.44 (s, 3 H, 11′-H), 1.95–2.11 (m, 2 H, 6′-H), 2.40 (ddd, *J* = 13.9/11.7/5.0 Hz, 1 H, 7′$_{exo}$-H), 2.56 (ddd, *J* = 14.0/9.5/5.4 Hz, 1 H, 7′$_{endo}$-H), 2.95 (s, 3 H, 9-H), 4.22 (d, *J* = 11.4 Hz, 1 H, 4′$_{endo}$-H), 4.29 (dd, *J* = 11.3/2.1 Hz, 1 H, 4′$_{exo}$-H), 7.85 (dt, *J* = 7.2/1.0 Hz, 1 H, 7-H), 8.07 (d, *J* = 8.2 Hz, 1 H, 5-H), 8.16 (dd, *J* = 8.3/7.2 Hz, 1 H, 6-H), 8.39 (d, *J* = 7.1

Hz, 1 H, 4-H), 8.84 (dd, *J* = 7.0/1.6 Hz, 1 H, 3-H), 9.99 (d, *J* = 0.7 Hz, 1 H, 1-H). – ^{13}C NMR (CD_2Cl_2, 20 °C): δ = 15.1 (9′-C), 18.5 (9-C), 18.6 (10′-C), 18.8 (11′-C), 30.6 (7′-C), 33.9 (6′-C), 44.1, 49.1, 68.9 (1′-*C*), 80.6 (4′-C), 126.0 (5-C), 126.2 (4-C), 126.9, 130.3 (3-C), 133.2 (7-C), 140.7 (6-C), 141.3, 142.7, 144.3 (1-C), 169.4 (COO), 172.3 (CON).

(1*S*,5*R*)-5,8,8-Trimethyl-1-[(1*S*)-8-methyl-1-phenyl-1,2-dihydroisoquinolin-2-ylcarbonyl]-3-oxabicyclo[3.2.1]octan-2-one (14a) and (1*S*,5*R*)-5,8,8-Trimethyl-1-[(1*R*)-8-methyl-1-phenyl-1,2-dihydroisoquinolin-2-ylcarbonyl]-3-oxabicyclo[3.2.1]octan-2-one (15a).

A) According to GP1 from 223 mg (0.66 mmol) of **9** and 3.65 mL (6.57 mmol) of PhMgCl (25 % in THF). HPLC (C_2H_5OAc/*n*-heptane = 14/86; 2 mL/min): **14a**: t_{ret} = 12.2 min, 98.1 %; **15a**: t_{ret} = 17.8 min, 1.9 %. CC (C_2H_5OAc/*n*-heptane = 20/80) yielded 0.259 g (95 %) of a mixture of **14a** and **15a**. Pure diastereomers were obtained by prep. HPLC (C_2H_5OAc/*n*-heptane = 15/85; 15 mL/min).

14a: Colorless crystals, mp 220 °C. – TLC: R_f = 0.20 (C_2H_5OAc/*n*-heptane = 20/80). $[\alpha]_D^{20}$ = +410 ° (*c* = 0.450 in $CHCl_3$). – ^{1}H NMR (nitrobenzene-d_5, 140 °C): δ = 0.89 (s, 3 H, CH_3), 1.03 (s, 3 H, CH_3), 1.22–1.30 (m, 2 H, CH_2CH_2), 1.45 (s, 3 H, CH_3), 1.85–1.89 (m, 1 H, CH_2CH_2), 2.29 (s, 3 H, $C_{ar}CH_3$), 2.44–2.55 (m, 1 H, CH_2CH_2), 3.99 (d, *J* = 10.8 Hz, 1 H, CH_2O), 4.19 (d, *J* = 10.8 Hz, 1 H, CH_2O), 6.03 (d, *J* = 7.2 Hz, 1 H, =CHC_{ar}), 6.85 (d, *J* = 7.2 Hz, 1 H, NCH=), 7.04–7.10 (m, 2 H, CH, H_{ar}), 7.15–7.23 (m, 5 H, H_{ar}), 7.42–7.47 (m, 2 H, H_{ar}). – IR (KBr): $\tilde{\nu}$ = 1727 cm^{-1}, 1657, 1625, 1466, 1320, 1221. – MS (70 eV); *m/z* (%): 415 (73) [M^+], 338 (100), 220 (54), 195 (66), 167 (24). – Anal. Calcd for $C_{27}H_{29}NO_3$: C, 78.04; H, 7.03; N, 3.37. Found: C, 78.10; H, 7.12; N, 3.22.

15a: Colorless crystals. – TLC: R_f = 0.14 (C_2H_5OAc/*n*-heptane = 20/80). – ^{1}H NMR (nitrobenzene-d_5, 140 °C): δ = 0.88 (s, 3 H, CH_3), 0.95 (s, 3 H, CH_3), 1.29 (s, 3 H, CH_3), 1.79–1.94 (m, 2 H, CH_2CH_2), 2.24 (s, 3 H, $C_{ar}CH_3$), 2.26–2.38 (m, 1.5H, CH_2CH_2), 2.70–2.90 (m, 0.5H, CH_2CH_2), 3.97 (d, *J* = 11.3 Hz, 1 H, CH_2O), 4.21 (d, *J* = 11.3 Hz, 1 H, CH_2O), 5.94 (d, *J* = 7.8 Hz, 1 H, =CHC_{ar}), 6.90 (d, *J* = 7.8 Hz, 1h NCH=), 7.00–7.06 (m, 2 H, CH, H_{ar}), 7.14–7.29 (m, 4 H, H_{ar}), 7.36–7.42 (m, 3 H, H_{ar}). – IR (KBr): $\tilde{\nu}$ = 1729 cm^{-1}, 1653, 1624, 1470, 1319. – MS (70 eV); *m/z* (%): 415 (63) [M^+], 338 (100), 220 (55), 195 (93), 167 (39), 139 (42).

B) According to GP1 from 25.5 mg (0.075 mmol) of **9** and 0.38 mL (0.38 mmol) of Ph_2Zn (1.0 M in THF). HPLC (C_2H_5OAc/*n*-heptane = 15/85; 2 mL/min): **14a**: t_{ret} = 10.7 min, 98.8 %; **15a**: t_{ret} = 15.6 min, 1.2 %. CC (C_2H_5OAc/*n*-heptane = 20/80) yielded 18.2 mg (59 %) of a mixture of **14a** and **15a**.

(1*S*,5*R*)-5,8,8-Trimethyl-1-[(1*S*)-8-methyl-1-(2-methylphenyl)-1,2-dihydroisoquinolin-2-yl-carbonyl]-3-oxabicyclo[3.2.1]octan-2-one (14b) and (1*S*,5*R*)-5,8,8-Trimethyl-1-[(1*R*)-8-methyl-1-(2-methylphenyl)-1,2-dihydroisoquinolin-2-ylcarbonyl]-3-oxabicyclo[3.2.1]octan-2-one (15b).

A) According to GP1 from 1.569 g (4.60 mmol) of **9** and 13.8 mL (13.80 mmol) of 2-$CH_3C_6H_4MgBr$ (1 M in THF). HPLC (C_2H_5OAc/*n*-heptane = 15/85; 2 mL/min): **14b**: t_{ret} = 8.2 min, 97.1 %; **15b**: t_{ret} = 12.2 min, 2.9 %. CC (C_2H_5OAc/*n*-heptane = 20/80) yielded 1.872 g (95 %) of a mixture of **14b** and **15b**. Pure diastereomers were obtained by prep. HPLC (C_2H_5OAc/*n*-heptane = 15/85; 15 mL/min).

14b: Colorless crystals, mp 211 °C. – TLC: R_f = 0.25 (C_2H_5OAc/*n*-heptane = 20/80). $[\alpha]_D^{20}$ = +616 ° (*c* = 0.115 in $CHCl_3$). – ^{1}H NMR (nitrobenzene-d_5, 140 °C): δ = 0.84 (s, 3 H, CH_3), 0.91 (br s, 3 H, CH_3), 1.33 (s, 3 H, CH_3), 1.74–1.90 (m, 2 H, CH_2CH_2), 2.15 (s, 3 H, $C_{ar}CH_3$), 2.36–2.52 (m, 2 H, CH_2CH_2), 2.85 (s, 3 H, $C_{ar}CH_3$), 3.93 (d, *J* = 11.1 Hz, 1 H, CH_2O), 4.15 (d, *J* = 11.1 Hz, 1 H, CH_2O), 6.12 (br d, *J* = 6.5 Hz, 1 H, =CHC_{ar}), 6.82 (d, *J* = 7.9 Hz, 1 H, H_{ar}), 6.89–7.14 (m, 6 H, NCH=, H_{ar}) 7.24 (s, 1 H, CH), 7.38 (d, *J* = 7.9 Hz, 1 H, H_{ar}). – IR (KBr): $\tilde{\nu}$ = 1727 cm^{-1}, 1654, 1624, 1464, 1344, 1310, 1219. – MS (70 eV); *m/z* (%): 429 (58) [M^+], 338 (100), 234 (51), 195 (75), 167 (28), 139 (28). – Anal. Calcd for $C_{28}H_{31}NO_3$: C, 78.29; H, 7.27; N, 3.26 . Found: C, 78.10; H, 7.49; N, 3.24.

15b: Colorless crystals. – TLC: R_f = 0.20 (C_2H_5OAc/*n*-heptane = 20/80). – ^{1}H NMR (nitrobenzene-d_5, 140 °C): δ = 0.84 (s, 3 H, CH_3), 0.87 (s, 3 H, CH_3), 1.34 (s, 3 H, CH_3), 1.75–1.92 (m, 2 H, CH_2CH_2), 2.11 (s, 3 H, $C_{ar}CH_3$), 2.27–2.41 (m, 1 H, CH_2CH_2), 2.41–2.55 (m, 1 H, CH_2CH_2), 2.73 (s, 3 H, $C_{ar}CH_3$), 3.94 (d, *J* = 10.7 Hz, 1 H, CH_2O), 4.14 (d, *J* = 10.7 Hz, 1 H, CH_2O), 5.99 (d, *J* = 7.4 Hz, 1 H, =CHC_{ar}), 6.81 (d, *J* = 7.4 Hz, 1 H, NCH=), 6.89–7.16 (m, 6 H, H_{ar}) 7.25 (dd, *J* = 7.8/1.1 Hz, 1 H, H_{ar}), 7.42 (s, 1 H, CH). – IR (KBr): $\tilde{\nu}$ = 1727 cm^{-1}, 1664, 1636, 1466, 1311. – MS (70 eV); *m/z* (%): 429 (23) [M^+], 338 (71), 234 (67), 195 (100), 167 (42), 139 (41).

B) According to GP1 from 171 mg (0.50 mmol) of **9** and 4.16 mL (1.50 mmol) of $(2\text{-}CH_3C_6H_4)_2Zn$ [prepared by 4.00 mL of 2-$CH_3C_6H_4MgBr$ (1 M in THF) with 1.57 mL of $ZnCl_2$ (1.27 M in THF)]. HPLC (C_2H_5OAc/*n*-heptane = 15/85; 2 mL/min): **14b**: t_{ret} = 8.7 min, 93.3 %; **15b**: t_{ret} = 11.9 min, 6.7 %. CC (C_2H_5OAc/*n*-heptane = 20/80) yielded 195 mg (0.45 mmol, 91 %) of a mixture of **14b** and **15b**.

(1*S*,5*R*)-1-[(1*S*)-1-(2,6-Dimethylphenyl)-8-methyl-1,2-dihydroisoquinolin-2-ylcarbonyl]-5,8,8-trimethyl-3-oxabicyclo[3.2.1]octan-2-one (14c) and (1*S*,5*R*)-1-[(1*R*)-(2,6-dimethylphenyl)-8-methyl-1,2-dihydroisoquinolin-2-ylcarbonyl]-5,8,8-trimethyl-3-oxabicyclo[3.2.1]octan-2-one (15c).

According to GP1 from 200 mg (0.59 mmol) of **14** and 1.76 mL of 2,6-$(CH_3)_2C_6H_3MgBr$ (1.0 M in THF). HPLC (C_2H_5OAc/*n*-heptane = 15/85; 2 mL/min): **14c**: t_{ret} = 7.1 min, 36.1 %; **15c**: t_{ret} = 9.8 min, 63.9 %. CC (C_2H_5OAc/*n*-heptane = 20/80) yielded 202 mg (77 %) of a mixture of **14c** and **15c**. Pure diastereomers were obtained by prep. HPLC (C_2H_5OAc/*n*-heptane = 15/85; 12 mL/min).

14c: Colorless crystals, mp 255 °C. – TLC: R_f = 0.19 (C_2H_5OAc/*n*-heptane = 20/80). $[\alpha]_D^{25}$ = +308 ° (*c* = 0.105 in $CHCl_3$). – ^{1}H NMR (nitrobenzene-d_5, 140 °C): δ = 0.69 (s, 3 H, CH_3), 0.84 (s, 3 H, CH_3), 1.26 (s, 3 H, CH_3), 1.78–1.86 (m, 2 H, CH_2CH_2), 1.97 (s, 3 H, $C_{ar}CH_3$), 2.30–2.39 (m, 1 H, CH_2CH_2), 2.62 (s, 6 H,

2 $C_{ar}CH_3$), 2.68–2.78 (m, 1 H, CH_2CH_2), 3.94 (d, J = 11.5 Hz, 1 H, CH_2O), 4.18 (d, J = 11.5 Hz, 1 H, CH_2O), 5.81 (d, J = 7.6 Hz, 1 H, =CHC_{ar}), 6.83 (d, J = 7.5 Hz, 1 H, H_{ar}), 6.87 (d, J = 7.8 Hz, 1 H, H_{ar}), 6.89 (d, J = 7.6 Hz, 1 H, NCH=), 6.91–6.99 (m, 3 H, H_{ar}), 7.00 (s, 1 H, CH), 7.06 (t, J = 7.5 Hz, 1 H, H_{ar}).– IR (KBr): $\tilde{\nu}$ = 1726 cm^{-1}, 1682, 1644, 1466, 1315, 1211. – MS (70 eV); *m/z* (%): 443 (42) [M^+], 338 (100), 248 (24), 195 (31), 167 (5), 139 (3). – Anal. Calcd for $C_{29}H_{33}NO_3$: C, 78.52; H, 7.50; N, 3.16. Found: C, 78.43; H, 7.60; N, 3.16.

15c: Colorless crystals, mp 230 °C. – TLC: R_f = 0.23 (C_2H_5OAc/*n*-heptane = 20/80). $[\alpha]_D^{25}$ = +13.0 ° (*c* = 0.11 in $CHCl_3$). – ^{1}H NMR (nitrobenzene-d_5, 140 °C): δ = 0.29 (s, 3 H, CH_3), 0.77 (s, 3 H, CH_3), 1.31 (s, 3 H, CH_3), 1.67–1.88 (m, 2 H, CH_2CH_2), 1.85 (s, 3 H, $C_{ar}CH_3$), 2.12–2.24 (m, 1 H, CH_2CH_2), 2.40–2.63 (m, 1 H, CH_2CH_2), 2.54 (br s, 6 H, 2 $C_{ar}CH_3$), 3.94 (d, J = 11.1 Hz, 1 H, CH_2O), 4.12 (dd, J = 11.1/2.3 Hz, 1 H, CH_2O), 5.60 (d, J = 8.0 Hz, 1 H, =CHC_{ar}), 6.74–6.80 (m, 2 H, =CHN, CH, H_{ar}), 6.88–7.03 (m, 6 H, =CHN, CH, H_{ar}). – IR (KBr): $\tilde{\nu}$ = 1719 cm^{-1}, 1679, 1647, 1467, 1303, 1282, 1217. – MS (70 eV); *m/z* (%): 443 (42) [M^+], 338 (100), 248 (24), 195 (31), 167 (5), 139 (3). – Anal. Calcd for $C_{29}H_{33}NO_3$: C, 78.52; H, 7.50; N, 3.16. Found: C, 78.34; H, 7.76; N, 3.08.

(1*S*,5*R*)-1-[(1*R*)-1-Furan-2-yl-8-methyl-1,2-dihydroisoquinolin-2-ylcarbonyl]-5,8,8-trimethyl-3-oxabicyclo[3.2.1]octan-2-one (14d) and (1*S*,5*R*)-1-[(1*S*)-1-Furan-2-yl-8-methyl-1,2-dihydroisoquinolin-2-ylcarbonyl]-5,8,8-trimethyl-3-oxabicyclo[3.2.1]octan-2-one (15d).

A) According to GP1 from 1.314 g (3.87 mmol) of **9** and 21.1 mL of furan-2-ylMgBr [prepared by treating 1.10 mL of furan in 15.0 mL of THF with 11.6 mL of *s*-C_4H_9Li (1.3 M in cyclohexane) at 20 °C followed by 3.57 g of $MgBr_2$ (13.8 mmol)]. HPLC (C_2H_5OAc/*n*-heptane = 15/85; 2 mL/min): **14d**: t_{ret} = 11.2 min, 91.1 %; **15d**: t_{ret} = 15.9 min, 8.9 %. CC [$(C_2H_5)_2O$/*n*-heptane = 40/60)] yielded 1.118 g (71 %) of a mixture of **14d** and **15d**. Pure diastereomers were obtained by prep. HPLC (C_2H_5OAc/*n*-heptane = 20/80; 12 mL/min) .

14d: Colorless crystals, mp 119 °C. – TLC: R_f = 0.13 (C_2H_5OAc/*n*-heptane = 20/80). $[\alpha]_D^{20}$ = +408 ° (*c* = 0.130 in $CHCl_3$). – ^{1}H NMR (nitrobenzene-d_5, 140 °C): δ = 0.90 (s, 3 H, CH_3), 1.08 (s, 3 H, CH_3), 1.45 (s, 3 H, CH_3), 1.71–1.96 (m, 2 H, CH_2CH_2), 2.27–2.56 (m, 2 H, CH_2CH_2), 2.38 (s, 3 H, $C_{ar}CH_3$), 4.00 (d, J = 10.9 Hz, 1 H, CH_2O), 4.20 (dd, J = 10.9/0.9 Hz, 1 H, CH_2O), 6.03 (d, J = 7.7 Hz, 1 H, =CHC_{ar}), 6.22 (dd, J = 3.2/1.8 Hz, 1 H, H_{ar}), 6.29 (d, J = 3.0 Hz, 1 H, H_{ar}), 6.92 (dd, J = 7.7/0.9 Hz, 1 H, =CHN), 7.01 (d, J = 7.4 Hz, 1 H, H_{ar}), 7.04 (d, J = 7.4 Hz, 1 H, H_{ar}), 7.16 (7, J = 7.4 Hz, 1 H, H_{ar}), 7.17 (s, 1 H, CH), 7.20–7.22 (m, 1 H, H_{ar}). – IR (KBr): $\tilde{\nu}$ = 1717 cm^{-1}, 1664, 1467, 1347, 1321, 1220. – MS (CI); *m/z* (%): 406 (100) [$M + H^+$], 338 (29), 210 (58), 195 (27). – Anal. Calcd for $C_{25}H_{27}NO_4$: C, 74.05; H, 6.71; N, 3.45. Found: C, 73.93; H, 7.00; N, 3.28.

15d: Colorless crystals. – TLC: R_f = 0.09 (C_2H_5OAc/*n*-heptane = 20/80). – ^{1}H NMR (nitrobenzene-d_5, 140 °C): δ = 0.89 (s, 3 H, CH_3), 1.02 (s, 3 H, CH_3), 1.32 (s, 3 H, CH_3), 1.83–1.99 (m, 2 H, CH_2CH_2), 2.26–2.42 (m, 1 H, CH_2CH_2), 2.33 (s, 3 H, $C_{ar}CH_3$), 2.77–2.94 (m, 1 H, CH_2CH_2), 3.99 (d, *J* = 11.1 Hz, 1 H, CH_2O), 4.21 (dd, *J* = 11.1/2.2 Hz, 1 H, CH_2O), 5.92 (d, *J* = 7.9 Hz, 1 H, =CHC_{ar}), 6.06–6.10 (m, 1 H, H_{ar}), 6.22 (dd, *J* = 3.3/1.9 Hz, 1 H, H_{ar}), 6.94 (d, *J* = 7.9 Hz, 1 H, NCH=), 6.97 (d, *J* = 7.6 Hz, 1 H, H_{ar}), 7.02 (d, *J* = 7.6 Hz, 1 H, H_{ar}), 7.14 (t, *J* = 7.6 Hz, 1 H, H_{ar}), 7.23–7.25 (m, 1 H, H_{ar}), 7.44 (s, 1 H, CH). – IR (KBr): $\tilde{\nu}$ = 1717 cm^{-1}, 1664, 1632, 1319, 1214. – MS (CI); *m/z* (%): 406 (100) [M + H$^+$], 338 (30), 210 (8), 195 (7).

B) According to GP1 from 97.3 mg (0.285 mmol) of **9** and 4.23 mL of (furan-2-yl)$_2$Zn [prepared by treating 1.45 mL (20.0 mmol) of furan in 15.4 mL of THF with 15.4 mL of *s*-C_4H_9Li (1.3 M in cyclohexane) at -20 °C followed by 20.0 mL of $ZnCl_2$ (0.5 M in THF)]. HPLC (C_2H_5OAc/*n*-heptane = 15/85; 2 mL/min): **14d**: t_{ret} = 13.4 min, 91.3 %; **15d**: t_{ret} = 18.9 min, 8.7 %. CC (C_2H_5OAc/*n*-heptane = 20/60) yielded 74.7 mg (65 %) of a mixture of **14d** and **15d**.

General procedure for the hydrogenation of 1,2-dihydroisoquinolines (11a,c,d, 12c, 14a-c and 15c – GP2).

To a solution of the respective compound Pd/C (10 % Pd) was added and the resulting mixture was hydrogenated under normal pressure with stirring for 24 h at rt. Then the mixture was filtered and concentrated in vacuo.

(1*S*,5*R*)-5,8,8-Trimethyl-1-[(1*S*)-1-methyl-1,2,3,4-tetrahydroisoquinolin-2-ylcarbonyl]-3-oxabicyclo[3.2.1]octan-2-one (16a).

According to GP2: 84 mg (0.248 mmol) **11a**, 25 mL of CH_3OH (analytical reagent grade), 15 mg of Pd/C. Colorless crystals, mp 188 °C, yield 78 mg (92 %). – $[\alpha]_D^{14}$ = +135 ° (*c* = 0.475 in $CHCl_3$). – ^{1}H NMR (nitrobenzene-d_5, 140 °C): δ = 0.90 (s, 3 H, CH_3), 1.09 (s, 3 H, CH_3), 1.37 (s, 3 H, CH_3), 1.54 (d, *J* = 6.6 Hz, 3 H, CHC*H*$_3$), 1.83–2.03 (m, 2 H, CH_2), 2.31–2.47 (m, 1 H, CH_2), 2.59–2.80 (m, 2 H, CH_2), 3.00–3.14 (m, 1 H, CH_2), 3.39 (dt, *J* = 12.8/3.7 Hz, 1 H, CH_2), 3.97 (d, *J* = 11.1 Hz, 1 H, CH_2O), 4.05 (d, *J* = 11.1 Hz, 1 H, CH_2), 4.19 (d, *J* = 11.1 Hz, 1 H, CH_2O), 5.48–5.57 (m, 1 H, CH), 7.04–7.17 (m, 4 H, H_{ar}). – IR (KBr): $\tilde{\nu}$ = 1725 cm^{-1}, 1640, 1416. – MS (70 eV); *m/z* (%): 341 (2) [M$^+$], 326 (16), 195 (5), 146 (100). – Anal. Calcd for $C_{21}H_{27}NO_3$: C, 73.87; H, 7.97; N, 4.10. Found: C, 73.79; H, 8.06; N, 4.10.

(1*S*,5*R*)-5,8,8-Trimethyl-1-[(1*S*)-1-phenyl-1,2,3,4-tetrahydroisoquinolin-2-yl-carbonyl]-3-oxabicyclo[3.2.1]octan-2-one (16c).

According to GP2: 237 mg (0.59 mmol) of **11c**, 10 mL of CH_3OH/C_2H_5OAc (1/1), 236 mg of Pd/C. Colorless crystals, mp 167 °C, yield 187 mg (78 %). – HPLC: t_{ret} = 15.85 min (C_2H_5OAc/*n*-heptane = 15/85; 2 mL/min). – $[\alpha]_D^{26}$ = +142 ° (*c* = 0.260 in $CHCl_3$). – ^{1}H NMR (nitrobenzene-d_5, 140 °C): δ = 0.87

(s, 3 H, CH_3), 1.00 (s, 3 H, CH_3), 1.25 (s, 3 H, CH_3), 1.80–2.15 (m, 2 H, CH_2), 2.24–2.40 (m, 1 H, CH_2), 2.62–2.95 (m, 2 H, CH_2), 3.15–3.27 (m, 1 H, CH_2), 3.52–3.61 (m, 1 H, CH_2), 3.84–3.92 (m, 1 H, CH_2), 3.94 (d, J = 11.3 Hz, 1 H, CH_2O), 4.18 (d, J = 11.3 Hz, 1 H, CH_2O), 6.97 (s, 1 H, CH), 7.04–7.29 (m, 7 H, H_{ar}), 7.41–7.50 (m, 2 H, H_{ar}). – IR (KBr): $\tilde{\nu}$ = 1724 cm^{-1}, 1618, 1420, 1261. – MS (CI); *m/z* (%): 404 (53) [M + H^+]. – Anal. Calcd for $C_{26}H_{29}NO_3$: C, 77.39; H, 7.24; N, 3.47. Found: C, 77.24; H, 7.27; N, 3.60.

(1*S*,5*R*)-5,8,8-Trimethyl-1-[(1*R*)-1-phenyl-1,2,3,4-tetrahydroisoquinolin-2-yl-carbonyl]-3-oxabicyclo[3.2.1]octan-2-one (17c).

According to GP2: 227 mg (0.57 mmol) of **12c**, 10 mL of CH_3OH/C_2H_5OAc (1/1), 227 mg of Pd/C. Colorless crystals, mp 174 °C, yield 194 mg (0.48 mmol, 85 %). – HPLC: t_{ret} = 10.18 min (C_2H_5OAc/*n*-heptane = 15/85; 2 mL/min). – $[\alpha]_D^{20}$ = –123 ° (*c* = 0.265 in $CHCl_3$). – ^{1}H NMR (nitrobenzene-d_5, 140 °C): δ = 0.87 (s, 3 H, CH_3), 1.09 (s, 3 H, CH_3), 1.43 (s, 3 H, CH_3), 1.74–1.96 (m, 2 H, CH_2), 2.14–2.31 (m, 1 H, CH_2), 2.35–2.45 (m, 1 H, CH_2), 2.77 (brd, J = 16.1 Hz, 1 H, CH_2), 3.24–3.35 (m, 1 H, CH_2), 3.39–3.49 (m, 1 H, CH_2), 3.92–4.01 (m, 1 H, CH_2), 3.96 (d, J = 10.7 Hz, 1 H, CH_2O), 4.15 (d, J = 10.7 Hz, 1 H, CH_2O), 6.99 (s, 1 H, CH), 7.04 (d, J = 7.4 Hz, 1 H, H_{ar}), 7.09–7.32 (m, 8 H, H_{ar}). – IR (KBr): $\tilde{\nu}$ = 1727 cm^{-1}, 1629, 1412, 1226. – MS (CI); *m/z* (%): 404 (53) [M + H^+]. – Anal. Calcd for $C_{26}H_{29}NO_3$: C, 77.39; H, 7.24; N, 3.47. Found: C, 77.17; H, 7.18; N, 3.76.

(1*S*,5*R*)-1-[(1*R*)-1-(2,6-Dimethylphenyl)-1,2,3,4-tetrahydroisoquinolin-2-yl-carbonyl]-5,8,8-trimethyl-3-oxabicyclo[3.2.1]octan-2-one (16d).

According to GP2: 90 mg (0.210 mmol) of **11d**, 10 mL of CH_3OH/C_2H_5OAc (1/1), 69 mg of Pd/C. Colorless crystals, mp 270 °C, yield 70 mg (78 %). – TLC: R_f = 0.14 (C_2H_5OAc/*n*-heptane = 20/80). – $[\alpha]_D^{25}$ = +20.8 (*c* = 0.159 in $CHCl_3$). – ^{1}H NMR (nitrobenzene-d_5, 140 °C): δ = 0.65 (s, 3 H, CH_3), 0.83 (s, 3 H, CH_3), 1.29 (s, 3 H, CH_3), 1.76 (t, J = 8.2 Hz, 2 H, CH_2), 2.08–2.17 (m, 1 H, CH_2), 2.43 (s, 6 H, $C_{ar}CH_3$), 2.86 (d, J = 15.8 Hz, 1 H, CH_2), 2.97–3.07 (m, 1 H, CH_2), 3.12–3.22 (m, 1 H, CH_2), 3.53–3.62 (m, 1 H, CH_2), 3.93 (d, J = 10.9 Hz, 1 H, CH_2O), 4.14–4.21 (m, 1 H, CH_2), 4.24 (d, J = 10.9 Hz, 1 H, CH_2O), 6.57 (s, 1 H, CH), 6.65 (d, J = 7.9 Hz, 1 H, H_{ar}), 6.98–7.05 (m, 3 H, H_{ar}), 7.05–7.11 (m, 1 H, H_{ar}), 7.12–7.21 (m, 2 H, H_{ar}). – IR (KBr): $\tilde{\nu}$ =1727 cm^{-1}, 1628, 1383, 1211. – MS (70 eV); *m/z* (%): 431 (1) [M^+], 326 (1), 236 (100), 195 (3), 167 (2). – Anal. Calcd for $C_{28}H_{33}NO_3$: C, 77.93; H, 7.71; N, 3.25. Found C, 77.85; H, 7.84; N 3.21.

(1*S*,5*R*)-5,8,8-Trimethyl-1-[(1*S*)-8-methyl-1-phenyl-1,2,3,4-tetrahydroisoquinolin-2-ylcarbonyl]-3-oxabicyclo[3.2.1]octan-2-one (18a).

According to GP2: 110 mg (0.27 mmol) of **14a**, 30 mL of CH_3OH, 36 mg of Pd/C. Colorless crystals, mp 223 °C, yield 95 mg (85 %). – $[\alpha]_D^{20}$ = +205 ° (*c* = 0.425 in $CHCl_3$). – ^{1}H NMR (nitrobenzene-d_5, 140 °C):

δ = 0.89 (s, 3 H, CH_3), 1.06 (s, 3 H, CH_3), 1.23 (s, 3 H, CH_3), 1.85–1.90 (m, 1 H, CH_2), 1.91–2.01 (m, 1 H, CH_2), 2.06 (s, 3 H, $C_{ar}CH_3$), 2.23–2.40 (m, 1 H, CH_2), 2.73 (d, *J* = 16.0 Hz, 1 H, CH_2), 2.79–3.05 (m, 1 H, CH_2), 3.21–3.36 (m, 1 H, CH_2), 3.40–3.50 (m, 1 H, CH_2), 3.76–3.85 (m, 1 H, CH_2), 3.95 (d, *J* = 11.0 Hz, 1 H, CH_2O), 4.19 (d, *J* = 11.0 Hz, 1 H, CH_2O), 6.98 (d, *J* = 7.6 Hz, 1 H, $CH_{ar}CH_{ar}CH_{ar}$), 7.06 (d, *J* = 7.6 Hz, 1 H, $CH_{ar}CH_{ar}CH_{ar}$), 7.15 (t, *J* = 7.6 Hz, 1 H, $CH_{ar}CH_{ar}CH_{ar}$), 7.20–7.29 (m, 4 H, H_{ar}, CH), 7.33–7.39 (m, 2 H, H_{ar}, CH). – IR (KBr): $\tilde{\nu}$ = 1727 cm^{-1}, 1617, 1418, 1210. – MS (CI); *m/z* (%): 418 (73) [M + H^+], 340 (1), 222 (27). – Anal. Calcd for $C_{27}H_{31}NO_3$: C, 77.67; H, 7.48; N, 3.35. Found: C, 77.59; H, 7.81; N, 3.10.

(1*S*,5*R*)-5,8,8-Trimethyl-1-[(1*S*)-8-methyl-1-tol-2-yl-1,2,3,4-tetrahydroisoquinolin-2-ylcarbonyl]-3-oxabicyclo[3.2.1]octan-2-one (18b).

According to GP2: 113 mg (0.26 mmol) of **14b**, 10 mL of CH_3OH/C_2H_5OAc (1/1), 113 mg of Pd/C. Colorless crystals, mp 258 °C, yield 72 mg (64 %). – TLC: R_f = 0.15 [$(C_2H_5)_2O$/*n*-heptane = 40/60)]. – HPLC: t_{ret} = 9.50 min [$(C_2H_5)_2O$/*n*-heptane = 40/60; 2 mL/min)]. – $[\alpha]_D^{25}$ = +277 ° (*c* = 0.103 in $CHCl_3$). – ^{1}H NMR (nitrobenzene-d_5, 140 °C): δ = 0.86 (s, 3 H, CH_3), 0.97 (s, 3 H, CH_3), 1.13 (s, 3 H, CH_3), 1.77–1.97 (m, 2 H, CH_2), 2.00 (s, 3 H, $C_{ar}CH_3$), 2.15–2.27 (m, 1 H, CH_2), 2.69 (s, 3 H, $C_{ar}CH_3$), 2.73–2.82 (m, 1 H, CH_2), 2.91–3.08 (m, 1 H, CH_2), 3.40–3.51 (m, 1 H, CH_2), 3.55–3.65 (m, 1 H, CH_2), 3.75–3.83 (m, 1 H, CH_2), 3.91 (d, *J* = 10.9 Hz, 1 H, CH_2O), 4.18 (d, *J* = 10.9 Hz, 1 H, CH_2O), 6.86 (d, *J* =7.9 Hz, 1 H, H_{ar}), 6.90 (d, *J* =6.7 Hz, 1 H, H_{ar}), 6.98 (t, *J* =7.7 Hz, 1 H, H_{ar}), 7.03–7.12 (m, 3 H, H_{ar}), 7.22 (d, *J* =7.3 Hz, 1 H, H_{ar}), 7.47 (s, 1 H, CH). – IR (KBr): $\tilde{\nu}$ = 1724 cm^{-1}, 1620, 1467, 1409, 1313, 1210, 1120. – MS (CI); *m/z* (%): 432 (38) [M + H^+], 340 (1), 236 (7), 221 (21), 212 (100). – Anal. Calcd for $C_{28}H_{33}NO_3$: C, 77.93; H, 7.71; N, 3.25. Found: C, 77.85; H, 7.75; N, 3.29.

(1*S*,5*R*)-1-[(1*S*)-1-(2,6-Dimethylphenyl)-8-methyl-1,2,3,4-tetrahydroisoquinolin-2-ylcarbonyl]-5,8,8-trimethyl-3-oxabicyclo[3.2.1]octan-2-one (18c).

According to GP2: 134 mg (0.30 mmol) of **14c**, 15 mL of CH_3OH/C_2H_5OAc (1/1), 120 mg of Pd/C. Colorless crystals, mp 246 °C, yield 108 mg (80 %). – TLC: R_f = 0.18 (C_2H_5OAc/*n*-heptane = 20/80). – $[\alpha]_D^{25}$ = +332 ° (*c* = 0.065 in $CHCl_3$). – ^{1}H NMR (nitrobenzene-d_5, 140 °C): δ = 0.85 (s, 3 H, CH_3), 0.92 (s, 3 H, CH_3), 1.10 (s, 3 H, CH_3), 1.77–1.93 (m, 2 H, CH_2), 2.01 (s, 3 H, $C_{ar}CH_3$), 2.14–2.49 (m, 7 H, CH_2, $C_{ar}CH_3$), 2.73–2.82 (m, 1 H, CH_2), 3.03–3.13 (m, 1 H, CH_2), 3.56–3.72 (m, 2 H, CH_2), 3.81–3.91 (m, 1 H, CH_2), 3.91 (d, *J* = 10.7 Hz, 1 H, CH_2O), 4.18 (dd, *J* = 10.7/1.3 Hz, 1 H, CH_2O), 6.89–7.10 (m, 6 H, CH, H_{ar}), 7.45–7.51 (m, 1 H, CH, H_{ar}). – IR (KBr): $\tilde{\nu}$ =1732 cm^{-1}, 1633, 1462. – MS (CI); *m/z* (%): 446 (100) [M + H], 340 (42), 250 (21), 195 (5), 167 (14). – Anal. Calcd for $C_{29}H_{35}NO_3$: C, 78.17; H, 7.92; N, 3.14. Found: C, 77.94; H, 8.17; N, 3.13.

(1*S*,5*R*)-1-[(1*R*)-1-(2,6-dimethylphenyl)-8-methyl-1,2,3,4-tetrahydroisoquinolin-2-yl-

carbonyl]-5,8,8-trimethyl-3-oxabicyclo[3.2.1]octan-2-one (19c).

According to GP2: 140 mg (0.32 mmol) of **15c**, 10 mL of CH_3OH/C_2H_5OAc (1/1), 146 mg of Pd/C. Colorless crystals, mp 180 °C, yield 116 mg (83 %). – TLC: R_f = 0.21 (C_2H_5OAc/*n*-heptane, 20/80). – $[\alpha]_D^{25}$ = –149 ° (c = 0.125 in $CHCl_3$). – ^{1}H NMR (nitrobenzene-d_5, 140 °C): δ = 0.87 (s, 3H, CH_3), 1.11 (s, 3H, CH_3), 1.25 (br s, 3H, CH_3), 1.42 (s, 3H, CH_3), 1.76 - 1.93 (m, 2H, CH_2), 1.99 (s, 3H, CH_3), 2.04 - 2.13 (m, 1H, CH_2), 2.16 (br s, 3H, CH_3, 2.39 - 2.49 (m, 1H, CH_2), 2.80 (dd, *J* = 16.8/4.9 Hz, 1H, CH_2), 3.48 - 3.57 (m, 1H, CH_2), 3.77 - 3.88 (m, 1H, CH_2), 3.90 - 3.95 (m, 1H, CH_2), 3.96 (d, *J* = 10.9 Hz, 1H, CH_2O), 4.12 (dd, *J* = 10.9/2.2 Hz, 1H, CH_2O), 6.87 - 7.11 (m, 6H, CH, H_{ar}), 7.15 (s, 1H, CH). – IR (KBr): $\tilde{\nu}$ = 1725 cm^{-1}, 1643, 1468, 1405, 1219. – MS (CI): *m/z* (%): 446 (100) [M+H$^+$], 340 (36), 250 (22), 195 (8), 167 (3). – Anal. Calcd for $C_{29}H_{35}NO_3$: C, 78.17; H, 7.92; N, 3.14. Found: C, 78.09; H, 8.07; N, 3.07.

General procedure for the reductive removal of the chiral auxiliary – GP3.

To a solution of the respective *N*-acyl-1,2,3,4-tetrahydroisoquinoline in THF (0.5 M) either 1.05 equiv. of $Li[(CH_3O)_2AlH_2]$ (1.0 M in THF) or 2.0 equiv. of $Na[(CH_3O)_2AlH_2]$ (1.0 M in THF) were added dropwise at –50 °C or at –30 °C. The reaction mixture was kept at the current temperature for the time given before it was quenched by the addition of CH_3OH. After warming up to rt and addition of 2 M HCl the reaction mixture was first washed with $(C_2H_5)_2O$ (4 ×). Then after basification with 2 M NaOH it was extracted with $(C_2H_5)_2O$ (4 ×). The combined organic layers obtained from the extraction under basic conditions were dried ($MgSO_4$) and concentrated in vacuo. Purification of the crude product by CC (C_2H_5OAc/*n*-heptane = 20/80 + 2 % $C_2H_5(CH_3)_2N$) provided the free amine. For the preparation of the corresponding hydrochloride the free amine was dissolved in $(C_2H_5)_2O$ and HCl was passed into the solution. Immediately thereafter, excessive HCl and solvent were removed in vacuo.

(1*S*)-1-Methyl-1,2,3,4-tetrahydroisoquinoline (20a).

According to GP3: 0.600 g (1.76 mmol) of **16a**, 1.85 mL (1.85 mmol) of $Li[(CH_3O)_2AlH_2]$, 65 h at –50 °C. The combined organic layers containing the free amine were directly, after having been dried over $MgSO_4$, treated with HCl. After evaporation the hydrochloride of **16a** was obtained.

Colorless crystals, mp 214 °C (lit.,[15] 208 °C), 184 mg (57 %). – TLC R_f = 0.09 (C_2H_5OAc/*n*-heptane = 20/80 + 2 % $C_2H_5(CH_3)_2N$). – $[\alpha]_D^{20}$ = –66.7 ° (*c* = 0.075 in $CHCl_3$) [lit.[16] $[\alpha]_D^{23}$ = –44 (*c* = 1.24 in C_2H_5OH)].

(1*S*)-1-Phenyl-1,2,3,4-tetrahydroisoquinoline (20c).

According to GP3: 98 mg (0.244 mmol) of **16c**, 256 µL (0.256 mmol) of $Li[(CH_3O)_2AlH_2]$, 72 h at –50 °C. **20c**: Colorless crystals, 16 mg (32 %). – $[\alpha]_D^{20}$ = +12.7 ° (*c* = 0.465 in $CHCl_3$) [lit.,[17] $[\alpha]_D$ = +12.3 ° (*c* = 0.57 in CH_2Cl_2)].

20c-HCl: Colorless crystals, mp 169 °C. – TLC: R_f = 0.20 (C_2H_5OAc/*n*-heptane = 20/80 + 2 % $C_2H_5(CH_3)_2N$). – $[\alpha]_D^{20}$ = +32.0 ° (*c* = 0.125 in $CHCl_3$). – ^1H NMR ($CDCl_3$, 20 °C): δ = 2.96–3.11 (m, 2 H, CH_2), 3.17–3.27 (m, 1 H, CH_2), 3.28–3.38 (m, 1 H, CH_2), 5.42 (s, 1 H, CH), 6.78 (d, *J* = 7.8 Hz, 1 H, H_{ar}), 7.14 (t, *J* = 7.5 Hz, 1 H, H_{ar}), 7.19 (d, *J* = 7.7 Hz, 1 H, H_{ar}), 7.22–7.29 (m, 1 H, H_{ar}), 7.39 (s, 5 H, H_{ar}), 9.88 (br. s, 1 H, NH_2^+), 10.72 (br s, 1 H, NH_2^+). – IR (KBr): $\tilde{\nu}$ = 3456 cm^{-1}, 2921, 2748, 1496, 1456, 1420. – MS (CI); *m/z* (%): 210 (100) [M – HCl + H^+]. – Anal. Calcd for $C_{15}H_{16}NCl$: C, 73.31; H, 6.56; N, 5.70. Found: C, 73.31; H, 6.66; N, 5.60.

(1*R*)-1-Phenyl-1,2,3,4-tetrahydroisoquinoline ((*ent*)-20c).

According to GP3: 103 mg (0.25 mmol) of **17c**, 0.267 mL (0.267 mmol) $Li[(CH_3O)_2AlH_2]$, 72 h at –50 °C. **(*ent*)-20c**: Colorless crystals, 18 mg (35 %).

(*ent*)-20c-HCl: Colorless crystals, mp 189 °C. – TLC : R_f = 0.20 (C_2H_5OAc/*n*-heptane = 20/80 + 2 % $C_2H_5(CH_3)_2N$). – $[\alpha]_D^{20}$ = –30.0 ° (*c* = 0.120 in $CHCl_3$). – ^1H NMR ($CDCl_3$, 20 °C): δ = 2.96–3.11 (m, 2 H, CH_2), 3.17–3.27 (m, 1 H, CH_2), 3.28–3.38 (m, 1 H, CH_2), 5.42 (s, 1 H, CH), 6.78 (d, *J* = 7.5 Hz, 1 H, H_{ar}), 7.14 (t, *J* = 7.5 Hz, 1 H, H_{ar}), 7.19 (d, *J* = 7.5 Hz, 1 H, H_{ar}), 7.22–7.29 (m, 1 H, H_{ar}), 7.39 (s, 5 H, H_{ar}), 9.88 (br s, 1 H, NH_2^+), 10.72 (br s, 1 H, NH_2^+). – IR (KBr): $\tilde{\nu}$ = 3435 cm^{-1}, 2918, 2738, 1493, 1453, 1413. – MS (CI); *m/z* (%): 210 (100) [M – HCl + H^+]. – Anal. Calcd for $C_{15}H_{16}NCl$: C, 73.31; H, 6.56; N, 5.70. Found: C, 73.45; H, 6.67; N, 5.45.

(1*R*)-1-(2,6-Dimethylphenyl)-1,2,3,4-tetrahydroisoquinoline (20d).

According to GP3: 114 mg (0.26 mmol) of **16d**, 0.53 mL (0.79 mmol) of $Na[(CH_3O)_2AlH_2]$, 96 h at –30 °C. **20d**: Colorless crystals, 32 mg (51 %).

20d-HCl: Colorless crystals, mp 192 °C. – TLC: R_f = 0.27 (C_2H_5OAc/*n*-heptane = 10/90 + 2 % $C_2H_5(CH_3)_2N$). – $[\alpha]_D^{20}$ = +46.1 ° (*c* = 0.088 in $CHCl_3$). – ^1H NMR ($CDCl_3$, 20 °C): δ = 1.95 (s, 3 H, CH_3), 2.68 (s, 3 H, CH_3), 2.75 (brd, *J* = 17.2 Hz, 1 H, CH_2), 2.98 (td, *J* = 12.5/3.8 Hz, 1 H, CH_2), 3.19 (dd, *J* = 12.3/5.0 Hz, 1 H, CH_2), 3.42 (ddd, *J* = 17.3/12.7/5.3 Hz, 1 H, CH_2), 5.87 (s, 1 H, CH), 6.66 (d, *J* = 7.9 Hz, 1 H, H_{ar}), 7.00 (d, *J* = 7.9 Hz, 1 H, H_{ar}), 7.09 (t, *J* = 7.5 Hz, 1 H, H_{ar}), 7.12 (d, *J* = 7.6 Hz, 1 H, H_{ar}), 7.14 (d, *J* = 7.6 Hz, 1 H, H_{ar}), 7.17–7.23 (m, 2 H, H_{ar}), 8.97 (br s, 1 H, NH_2^+), 10.73 (br s, 1 H, NH_2^+). – IR (KBr): $\tilde{\nu}$ = 3425 cm^{-1}, 2920, 1591, 1455. – MS (CI); *m/z* (%): 238 (100) [M – HCl + H^+], 132 (18). – $C_{17}H_{20}NCl$: C, 74.57; H, 7.36; N, 5.12. Found: C, 74.61; H, 7.55; N, 4.90.

(1*S*)-8-Methyl-1-phenyl-1,2,3,4-tetrahydroisoquinoline (21a).

According to GP3: 0.653 g (1.56 mmol) of **18a**, 1.64 mL (1.64 mmol) of $Li[(CH_3O)_2AlH_2]$, 18 h at –50 °C. **21a**: Colorless crystals, mp 68 °C, 61 mg (17 %). – TLC: R_f = 0.13 (C_2H_5OAc/*n*-heptane = 20/80 + 2 % $C_2H_5(CH_3)_2N$). – $[\alpha]_D^{20}$ = +16.0 ° (*c* = 0.430 in $CHCl_3$). – ^1H NMR ($CDCl_3$, 20 °C): δ = 1.87 (br s, 1 H,

NH), 1.90 (s, 3 H, CH_3), 2.76–2.85 (m, 1 H, CH_2), 2.87–3.05 (m, 3 H, CH_2), 5.19 (s, 1 H, CH), 6.94–7.01 (m, 1 H, H_{ar}), 7.04–7.19 (m, 4 H, H_{ar}), 7.21–7.34 (m, 3 H, H_{ar}). – IR (KBr): $\tilde{\nu}$ = 1450 cm^{-1}, 1256, 1114, 1028. – MS (CI); *m/z* (%): 224 (100) [M + H^+]. – Anal. Calcd for $C_{16}H_{17}N$: C, 86.05; H, 7.67; N, 6.27. Found: C, 85.96; H, 7.80; N, 6.23.

21a-HCl: Colorless crystals, mp 121 °C. – TLC: R_f = 0.13 (C_2H_5OAc/*n*-heptane = 20/80 + 2 % $C_2H_5(CH_3)_2N$). – $[\alpha]_D^{20}$ = +56.0 ° (*c* = 0.125 in $CHCl_3$). – ^1H NMR ($CDCl_3$, 20 °C): δ = 1.91 (s, 3 H, CH_3), 3.00–3.08 (m, 1 H, CH_2), 3.10–3.20 (m, 1 H, CH_2), 3.25–3.33 (m, 1 H, CH_2), 3.45–3.56 (m, 1 H, CH_2), 5.77 (s, 1 H, CH), 7.03 (d, *J* = 7.6 Hz, 1 H, H_{ar}), 7.10 (d, *J* = 7.6 Hz, 1 H, H_{ar}), 7.23 (t, *J* = 7.6 Hz, 1 H, H_{ar}), 7.26–7.37 (m, 5 H, C_6H_5), 9.99 (br s, 1 H, NH_2^+), 10.61 (br s, 1 H, NH_2^+). – IR (KBr): $\tilde{\nu}$ = 3425 cm^{-1}, 2940, 2730, 1582, 1455. – MS (CI); *m/z* (%): 224 (100) [M – HCl + H^+], 146 (6). – Anal. Calcd for $C_{16}H_{18}NCl$: C, 73.98; H, 6.98; N, 5.39. Found: C, 73.74; H, 7.25; N, 5.36.

(1*S*)-8-Methyl-1-(2-methylphenyl)-1,2,3,4-tetrahydroisoquinoline (21b).

According to GP3: 224 mg (0.52 mmol) of **18b,** 1.55 mL (1.55 mmol) of $Na[(CH_3O)_2AlH_2]$, 90 h at –30 °C. **21b**: Colorless crystals, mp 82 °C, 58 mg (47 %). – TLC: R_f = 0.19 (C_2H_5OAc/*n*-heptane = 20/80 + 2 % $C_2H_5(CH_3)_2N$). $[\alpha]_D^{20}$ = +75.0 ° (*c* = 0.096 in $CHCl_3$). – ^1H NMR ($CDCl_3$, 20 °C): δ = 1.71 (br s, 1 H, NH), 1.81 (s, 3 H, CH_3), 2.56 (s, 3 H, CH_3), 2.83 (dd, *J* = 12.7/3.6 Hz, 1 H, CH_2), 2.89–3.05 (m, 3 H, CH_2), 5.37 (s, 1 H, CH), 6.57 (dd, *J* = 7.7/0.9 Hz, 1 H, H_{ar}), 6.95 (d, *J* = 7.3 Hz, 1 H, H_{ar}), 6.98 (dd, *J* = 7.5/0.9 Hz, 1 H, H_{ar}), 7.05 (d, *J* = 7.4 Hz, 1 H, H_{ar}), 7.12 (t, *J* = 7.5 Hz, 1 H, H_{ar}), 7.13 (t, *J* = 7.5 Hz, 1 H, H_{ar}), 7.22 (dd, *J* = 7.4/0.7 Hz, 1 H, H_{ar}). – IR (KBr): $\tilde{\nu}$ = 1460 cm^{-1}, 1118. – MS (CI); *m/z* (%): 238 (100) [M + H^+]. – Anal. Calcd for $C_{17}H_{19}N$: C, 86.03; H, 8.07; N, 5.90. Found: C, 86.06; H, 8.22; N, 5.72.

21b-HCl: TLC: R_f = 0.19 (C_2H_5OAc/*n*-heptane = 20/80 + 2 % $C_2H_5(CH_3)_2N$). – ^1H NMR ($CDCl_3$, 20 °C): δ = 1.79 (s, 3 H, CH_3), 2.74 (s, 3 H, CH_3), 3.13 (dd, *J* = 15.9/3.8 Hz, 1 H, CH_2), 3.18–3.35 (m, 2 H, CH_2), 3.41 (ddd, *J* = 16.5/9.9/6.7 Hz, 1 H, CH_2), 5.82 (s, 1 H, CH), 6.68 (d, *J* = 7.6 Hz, 1 H, H_{ar}), 6.99 (d, *J* = 7.4 Hz, 1 H, H_{ar}), 7.05 (td, *J* = 7.4/1.4 Hz, 1 H, H_{ar}), 7.09 (d, *J* = 7.9 Hz, 1 H, H_{ar}), 7.21 (t, *J* = 7.6 Hz, 1 H, H_{ar}), 7.22–7.29 (m, 2 H, H_{ar}), 9.61 (br s, 1 H, NH_2^+), 10.55 (br s, 1 H, NH_2^+). – IR (KBr): $\tilde{\nu}$ = 2918 cm^{-1}, 1576, 1463, 1109. – MS (CI); *m/z* (%): 238 (100) [M – HCl + H^+]. – Anal. Calcd for $C_{17}H_{20}NCl$: C, 74.57; H, 7.36; N, 5.12. Found: C, 74.61; H, 7.97; N, 4.48.

(1*S*)-1-(2,6-Dimethylphenyl)-8-methyl-1,2,3,4-tetrahydroisoquinoline (21c).

According to GP3: 112 mg (0.25 mmol) of **18c**, 0.50 mL (0.50 mmol) of $Na[(CH_3O)_2AlH_2]$, 96 h at –30 °C. **21c**: Colorless crystals, 21 mg (34%).

21c-HCl: Colorless crystals, mp 135 °C. – TLC: R_f = 0.34 (C_2H_5OAc/*n*-heptane = 20/80 + 2 % $C_2H_5(CH_3)_2N$). – $[\alpha]_D^{20}$ = +106 ° (*c* = 0.067 in $CHCl_3$). – ^1H NMR ($CDCl_3$, 20 °C): δ = 1.68 (s, 3 H, CH_3),

1.79 (s, 3 H, CH_3), 2.77 (s, 3 H, CH_3), 2.73–2.82 (m, 1 H, CH_2), 2.84–2.96 (m, 1 H, CH_2), 3.14–3.23 (m, 1 H, CH_2), 3.40–3.50 (m, 1 H, CH_2), 5.82 (dd, J = 8.9/5.8 Hz, 1 H, H_{ar}), 6.93–6.98 (m, 2 H, H_{ar}), 7.01 (d, J = 7.4 Hz, 1 H, H_{ar}), 7.09–7.20 (m, 3 H, CH, H_{ar}), 9.23 (br s, 1 H, NH_2^+), 10.73 (br s, 1 H, NH_2^+). – IR (KBr): $\tilde{\nu}$ = 3428 cm^{-1}, 2931, 1589, 1467. – MS (CI); *m/z* (%): 252 (100) [M – HCl + H^+], 146 (16). – Anal. Calcd for $C_{18}H_{22}NCl$: C, 75.11; H, 7.70; N, 4.87. Found: C, 75.08; H, 7.92; N, 4.68.

(1*R*)-1-(2,6-Dimethylphenyl)-8-methyl-1,2,3,4-tetrahydroisoquinoline ((*ent*)-21c).

According to GP3: 121 mg (0.27 mmol) of **19c**, 0.81 mL (0.81 mmol) of $Na[(CH_3O)_2AlH_2]$, 96 h at –30 °C. **(*ent*)-21c**: Colorless crystals, 44 mg (56 %).

(*ent*)-21c-HCl: Colorless crystals, mp 140 °C. – TLC: R_f = 0.21 (C_2H_5OAc/*n*-heptane = 20/80 + 2 % $C_2H_5(CH_3)_2N$). – $[\alpha]_D^{20}$ = –52.0 ° (*c* = 0.098 in $CHCl_3$). – ^1H NMR ($CDCl_3$, 20 °C): δ = 1.66 (s, 3 H, CH_3), 1.77 (s, 3 H, CH_3), 2.66–2.92 (m, 2 H, CH_2), 2.76 (s, 3 H, CH_3), 3.04–3.16 (m, 1 H, CH_2), 3.36–3.50 (m, 1 H, CH_2), 5.75–5.83 (m, 1 H, CH), 6.92–6.98 (m, 2 H, H_{ar}), 7.00 (d, J = 7.7 Hz, 1 H, H_{ar}), 7.08–7.21 (m, 3 H, H_{ar}), 9.22 (br s, 1 H, NH_2^+), 10.54 (br s, 1 H, NH_2^+). – IR (KBr): $\tilde{\nu}$ = 3429 cm^{-1}, 2924, 2763, 1589, 1467. – MS (CI); *m/z* (%): 252 (100) [M – HCl + H^+], 146 (30). – Anal. Calcd for $C_{18}H_{22}NCl$: C, 75.11; H, 7.70; N, 4.87. Found: C, 75.06; H, 7.97; N, 4.65.

X-Ray analyses

The data sets for **11c** and **14a** were collected on a Siemens R3m/V diffractometer with CuKα radiation (λ = 1.54178 Å) and for **14b** and **14c** on a Nonius MACH3 diffractometer with MoKα radiation (λ = 0.71069 Å). The structures were solved by direct methodes using SHELXS-86[18] and refined by full matrix least squares on F2 by SHELXL-93.[19] The molecular views were realized by ZORTEP.[20] Crystal and data collections parameters were deposited with the Cambridge Crystallographic Data Center. The data will be sent on quoting the respective CCDC number (email: deposit@ccdc.cam.ac.uk).

Crystal data for 11c: $C_{26}H_{27}NO_3$, M = 401.5, orthorhombic, space group $P2_12_12_1$, a = 9.840 (6), b = 12.534(8), c = 17.433(12) Å, volume = 2150(2) $Å^3$, Z = 4, D_c = 1.240 Mgm^{-3}, μ = 0.640 mm^{-1}, crystal dimensions .3x.3x.3 mm, *F(000)* = 856, T = 295(2) K, θ = 4.34 – 57.02°. 1683 reflections measured, unique reflections 1683 [R_{int} = 0.0], *R1* = 0.0493, *wR2* = 0.1257 for all 1412 reflections with I>2σ(I) and *R1* = 0.0599, *wR2* = 0.1376 for all reflections and 275 refined parameters. Final electron density 0.134 and –0.130 e $Å^{-3}$, S = 1.027, absolute structure parameter –0.62 (67), known due to a known substituent.

CCDC 212931

Crystal data for 14a: $C_{27}H_{29}NO_3$, M = 415.5, orthorhombic, space group $P2_12_12_1$, a = 8.214(2), b = 13.867(3), c = 19.640(6) Å, volume = 2237.1(10) $Å^3$, Z = 4, D_c = 1.234 Mgm^{-3}, μ = 0.631 mm^{-1}, crystal dimensions .25x.25x.50 mm, *F(000)* = 888, T = 295(2) K, θ = 3.90 – 56.97°. 1748 reflections measured, unique reflections 1748 [R_{int} = 0.0], *R1* = 0.0411, *wR2* = 0.1017 for all 1585 reflections with I>2σ(I) and

R1 = 0.0470, *wR2* = 0.1079 for all reflections and 285 refined parameters. Final electron density 0.131 and –0.121 e Å^{-3}, S = 1.061, absolute structure parameter –1.25 (56), known due to a known substituent. CCDC 212932

Crystal data for 14b: $C_{28}H_{31}NO_3$, *M* = 429.5, orthorhombic, space group $P2_12_12_1$, *a* = 8.613(3), *b* = 13.902(5), *c* = 19.627(7) Å, volume = 2350.1(14) Å^3, Z = 4, D_c = 1.214 Mgm^{-3}, μ = 0.078 mm^{-1}, crystal dimensions .13x.13x.50 mm, *F(000)* = 920, *T* = 295(2) K, θ = 2.54 – 21.98°. 3228 reflections measured, unique reflections 2866 [R_{int} = 0.0239], *R1* = 0.0545, *wR2* = 0.1192 for all 2126 reflections with I>2σ(I) and *R1* = 0.0805, *wR2* = 0.1534 for all reflections and 294 refined parameters. Final electron density 0.120 and –0.146 e Å^{-3}, *S* = 1.180, absolute structure parameter –3.40 (302), known due to a known substituent. CCDC 212933

Crystal data for 14c: $C_{29}H_{33}NO_3$, *M* = 443.6, orthorhombic, space group $P2_12_12_1$, *a* = 12.0991(14), *b* = 13.1587(10), *c* = 15.261(2) Å, volume = 2429.7(4) Å^3, Z = 4, D_c = 1.213 Mgm^{-3}, μ = 0.078 mm^{-1}, crystal dimensions .40x.47x.57 mm, *F(000)* = 952, *T* = 295(2) K, θ = 2.65 – 23.98°. 4174 reflections measured, unique reflections 3801 [R_{int} = 0.0113], *R1* = 0.0347, *wR2* = 0.0853 for all 3233 reflections with I>2σ(I) and *R1* = 0.0456, *wR2* = 0.0953 for all reflections and 305 refined parameters. Final electron density 0.142 and –0.113 e Å^{-3}, *S* = 1.057, absolute structure parameter –0.19 (143), known due to a known substituent. CCDC 212934

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