Pergamon

Tetrahedron 58 (2002) 6757–6770

TETRAHEDRON

Generation of chiral *N*-acylpyridinium ions by means of silyl triflates and their diastereoselective trapping reactions: formation of *N*-acyldihydropyridines and *N*-acyldihydropyridones

Cornelia E. Hoesl, Markus Maurus, Jörg Pabel, Kurt Polborn and Klaus Th. Wanner*

Department Pharmazie, Zentrum für Pharmaforschung, LMU München, Butenandtstr. 5-13, D-81377 München, Germany

Received 27 December 2001; revised 1 March 2002; accepted 13 March 2002

Abstract—An efficient method for the generation of chiral *N*-acylpyridinium salts from various pyridines and a chiral acid chloride promoted by means of silyl triflates as additives is presented. The stereoselective addition of organometallic reagents to the intermediate chiral *N*-acylpyridinium ions led to α-substituted *N*-acyldihydropyridines and *N*-acyldihydropyridones in good yields, whereas no or minor amounts of products were obtained, when standard procedures without silyltriflates as additives were employed. Good diastereoselectivities were observed dependent on which pyridine or organometallic reagents were used. The removal of the chiral auxiliary proceeded smoothly either under basic or reductive reaction conditions.

1. Introduction

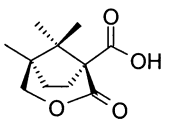
Electrophilic α-amidoalkylation, i.e. the reaction of a carbon nucleophile with an *N*-acyliminium ion, is one of the most intriguing principles for the synthesis of α-substituted amines due to simplicity and flexibility of this process. Especially *N*-acylpyridinium ions are frequently used as their trapping reactions with organometallic reagents provide substituted *N*-acyldihydropyridines and *N*-acyldihydropyridones,[1] which are valuable building blocks for the construction of various pyridine derivatives.[2] In the past, we established a chiral version of the electrophilic α-amidoalkylation methodology, by employing *N*-acyliminium ions that are provided with a chiral *N*-acyl group.[3] So far we have applied this method to the asymmetric construction of piperidine, pyrrolidine, isoquinoline and β-carboline derivatives. Comins made use of a related strategy in the asymmetric synthesis of piperidine alkaloids[4] by employing chiral pyridinium salts that are derived from 4-methoxy-3-(triisopropylsilyl)-pyridine and *trans*-2-(α-cumyl)cyclohexanol chloroformate or (−)-8-phenoxyphenylmenthol chloroformate. This approach, though attractive, is limited to pyridines provided with a bulky substituent at C-3 in order to reach a reasonable asymmetric induction. Streith[5] disclosed an alternative procedure where a bulky substituent may be omitted from the pyridine skeleton by employing a chiral auxiliary, where the asymmetric induction is assumed to arise from a chelate control mechanism.

In recent investigations, we successfully employed the bicyclolactonecarboxylic acid **1** (Scheme 1) as a chiral auxiliary for the *N*-acyliminium ion based asymmetric synthesis of pyrrolidine, piperidine, 1,2,3,4-tetrahydroisoquinoline and β-carboline derivatives.[6]

The chiral auxiliary **1** was designed to provide stereodifferentiation by a precomplexation mechanism.[6b] It was thought that ambiphilic organometallic reagents should at first coordinate to the lactone moiety whereupon a ligand from the complex thus formed may than be stereoselectively transferred to the prochiral iminium subunit. Encouraged by the results obtained with **1** so far, we decided to investigate whether **1** and the acid chloride **2** (Scheme 2), respectively, could be useful as a chiral auxiliary exhibiting reasonable asymmetric induction in the case of *N*-acyliminium ions derived from pyridine derivatives as well.

2. Results and discussion

Among the methods currently available for the formation of *N*-acylpyridinium ions, one of the most convenient and general approaches is the acylation of an appropriate pyridine with a suitable acid halide. However, this reaction is an equilibrium reaction and depending on the nature of



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Scheme 1.

Keywords: *N*-acyliminium ions; pyridines; amidoalkylation; silyl triflates; molecular structures; dienamide reduction.

* Corresponding author. Tel.: +49-89-2180-7249; fax: +49-89-2180-7247; e-mail: klaus.wanner@cup.uni-muenchen.de

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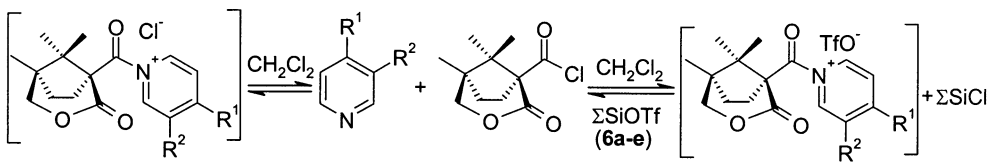
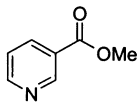
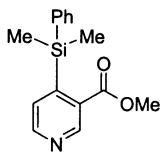
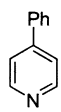
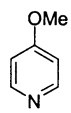
PII: S0040-4020(02)00675-0



Scheme 2.

Table 1. Amount of *N*-acylpyridinium ion formed by reaction of **3a–d** and **2** in the absence (**4a–d**) and in the presence of R_3SiOTf (**5a–d**) determined by ^1H NMR

Entry	ΣSiOTf				
	6	**3a**	**3b**	**3c**	**3d**
		4a	**4b**	**4c**	**4d**
1		0	0	0	0
		5a	**5b**	**5c**	**5d**
2	Me_3SiOTf (**6a**)	45	87	68/83[a]	85
3	iPr_3SiOTf (**6b**)	–	87	81/>95[a]	90
4	Et_3SiOTf (**6c**)	–	–	64	73
5	Ph_3SiOTf (**6d**)	–	–	62	–
6	$(MeO)_3SiOTf$ (**6e**)	–	–	62	–

Reaction temperature: 20°C; concentration for reactions: 0.1 M in CD_2Cl_2.
[a] Concentration for reactions: 0.2 M in CD_2Cl_2.

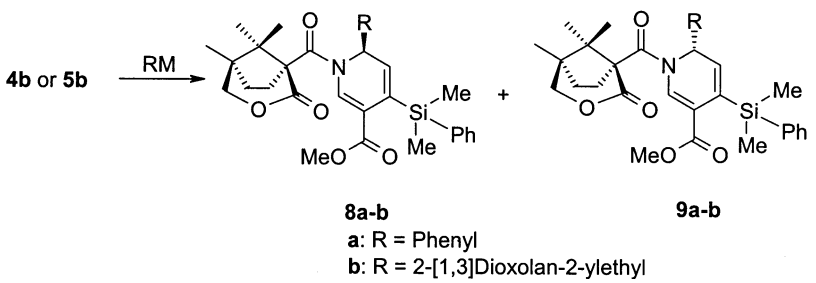
the reagents, the position of this equilibrium may be located either more on the side of the starting materials or of the products. Consequently, when the reactivity of the pyridine derivative or of the acid halide or of both is low, only a small amount of the corresponding *N*-acylpyridinium ions will form. As part of our initial studies, we treated the pyridines **3a–d** with acid chloride **2** in CH_2Cl_2 (Scheme 2). However, all attempts to trap the intermediate *N*-acyliminium ions with a suitable organometallic reagent (PhMgBr) remained more or less unsuccessful (Schemes 3 and 4 yield of *N*-acyldihydropyridine: 0–1%, Tables 2 and 3; Scheme 5 yield of *N*-acyldihydropyridone: 25%, Table 4). Subsequent investigations by ^1H NMR spectroscopy revealed that no detectable amounts of *N*-acylpyridinium salts **4a–d** had formed (see Table 1, entry 1). Recently, we have uncovered, that the amount of *N*-acyliminium ions, when formed by reaction of an azaaromatic with an acid chloride, is significantly raised by the addition of silyl triflates. This was demonstrated for pivaloyl chloride as a sterically demanding acid halide.[7] The formation of trialkylsilyl chlorides from trialkylsilyl triflates is thought to be the driving force for the observed shift of the equilibria towards the *N*-acylpyridinium salt. Of course, this method seemed also promising for the generation of the desired chiral *N*-acylpyridinium salts **5a–d** (Scheme 2), since the chiral auxiliary **2** is not much bulkier than pivaloyl chloride. Thus, various silyl triflates **6a–e** were investigated with respect to their potency regarding the formation of the *N*-acyliminium ions **5a–d** from the acyl chloride **2** and the respective pyridines **3a–d** (total conc.: 0.1 M in CD_2Cl_2). The extent of the *N*-acylpyridinium ion formation was determined by ^1H NMR spectroscopy. Indeed a significant shift towards the formation of the chiral *N*-acylpyridinium ion was observed, when trimethylsilyl triflate **6a** was applied. In the absence of trimethylsilyl triflate according to the ^1H NMR data no detectable amounts of the *N*-acyliminium ions **4a–d** (Table 1, entry 1) had formed. In contrast, when trimethylsilyl triflate was present, to our great delight 45–87% of the *N*-acyliminium salts **5a–d** (Table 1, entry 2, c=0.1 M) were found. The differences between the amounts of the various *N*-acyliminium ions **5a–d** formed might probably reflect the nucleophilicity of the pyridine derivatives **3a–d** employed. By using triisopropylsilyl triflate **6b** the amount of the *N*-acylpyridinium salts could be further improved for **5c** (from 68 to 81%) and for **5d** (from 85 to 90%) whereas for **5b** it remained unchanged (Table 1, entry 3). For **5a**, the effect of triisopropylsilyl triflate (**6b**) was not investigated as in the case of the corresponding *N*-acyliminium ion derived from pivaloyl chloride triisopropylsilyl triflate (**6b**) had been far less efficient as compared to trimethylsilyl triflate (**6a**).[7] For the pyridine derivatives **3c** and **3d** also the effect of triethylsilyl triflate (**6c**), triphenylsilyl triflate (**6d**) or trimethoxysilyl triflate (**6e**) was studied. Though the amount of *N*-acylpyridinium ion was heightened up to 62–64% (Table 1, entry 4–6) by these reagents, the aforementioned results were not as favorable as those seen with **6a** and **6b**. Further experiments with the pyridine **3c** revealed that the generation of the *N*-acylpyridinium ion may be influenced by the concentration of the solution as well. Thus, when the concentration

for the reaction was raised from 0.1 to 0.2 M, an increase of **5c** from 68 to 83% with trimethylsilyl triflate (**6a**) (Table 1, entry 2) and from 81 to >95% with triisopropylsilyl triflate (**6b**) (Table 1, entry 3) was observed. Besides their characterization by ^{1}H NMR spectroscopy the *N*-acylpyridinium ions **5a–d** were also identified by NO-experiments: in each case, irradiation of H-2 or H-6 of the pyridine nucleus lead to a significant NO effect for H-7′$_{endo}$ of the chiral acyl residue and vice versa.

Next, we turned our attention to trapping reactions of the above mentioned *N*-acyliminium ions. Of course, it was expected that the use of silyl triflates as additives besides having a positive effect on the *N*-acyliminium ion formation should also improve the yields of subsequent addition reactions. This was observed for related systems.[7] For the first experiments, the *N*-acyliminium ions **4a** and **5a** derived from the nicotinic acid derivative **3a** were used. In the absence of a silyl additive, all trapping reactions (at −78°C) failed, though various nucleophiles were employed (phenylmagnesium bromide, 2-[1,3]dioxolan-2-ylethylmagnesium bromide and methylmagnesium bromide), whereas in the presence of trimethylsilyl triflate the addition products were obtained in reasonable yields (24–50%). However, as the regioselectivity[8] for these reactions turned out to be low, all further attempts in this direction were abandoned.

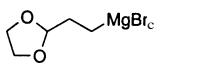
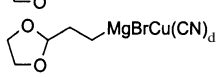
moderate yield of 26% for the addition product **8a/9a**, which was, however, heightened to 47%, when the heterocuprate PhCu(CN)MgBr was used. Also in the case of the 2-[1,3]dioxolan-2-ylethyl residue, the heterocuprate (Table 2, entry 5) delineated from 2-[1,3]dioxolan-2-ylethylmagnesium bromide gave a higher yield in the addition reaction to the *N*-acyliminium ion **5b** (62%) than the Grignard reagent itself (Table 2, entry 4, 41%). Except for the addition of the Grignard reagents no substantial asymmetric induction were observed. Thus, the addition reactions of the various cuprates shown in Table 2 were almost devoid of any asymmetric induction.

Similar to the results described above, attempts to trap the *N*-acyliminium ion **4c**, that might form under standard conditions when 4-phenylpyridine **3c** is treated with the acid chloride **2** (in the absence of a silyl triflate) did not give any significant success, independent from the Grignard reagent, that was employed (phenylmagnesium bromide or 2-[1,3]dioxolan-2-ylethylmagnesium bromide). However, when 1 equiv. of trimethylsilyl triflate was present the addition of phenylmagnesium bromide resulted in a yield of 63% for the dihydropyridines **10a/11a** (Table 3, compare entry 2 with entry 1). This yield (for **10a/11a**) was raised to 83%, when trimethylsilyl chloride formed during the generation of the *N*-acylpyridinium ion was removed and



Scheme 3.

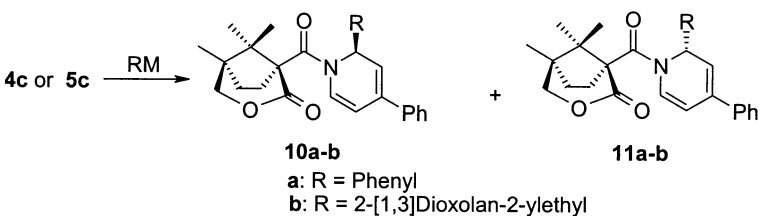
Table 2. Trapping reactions of *N*-acyl-4-dimethylphenylsilyl-3-methyloxycarbonylpyridinium salts in the absence (**4b**) and in the presence of Me_3SiOTf (**5b**)

Entry	Product **8**+**9**	Reagent	Additive	Time (h)[a]	Yield (%) **8**+**9**	d.s.[b] **8/9**
1	**a**	PhMgBr[c]	–	1	0	–
2	**a**	PhMgBr[c]	Me_3SiOTf	1	27	24.0/76.0
3	**a**	PhCu(CN)MgBr[d]	Me_3SiOTf	3	47	50.5/49.5
4	**b**		Me_3SiOTf	3	41	87.2/12.8
5	**b**		Me_3SiOTf	3	62	65.2/34.8

Concentration for all reactions: 0.1 M in CH_2Cl_2; alkylation temperature: −78°C.
[a] For amidoalkylation.
[b] Determined by HPLC from the crude reaction product.
[c] 3 equiv., 1.0 M in THF.
[d] 3 equiv., 0.17 M in THF prepared from 1 equiv. of CuCN and 1 equiv. of RMgBr.

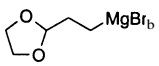
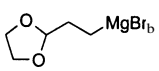
In case of the *N*-acyliminium ions **4b/5b** provided with a silyl blocking group in the 4-position of the pyridine nucleus trapping reactions proceeded with complete 1,6-regioselectivity. Here again, the addition of trimethylsilyl triflate was a prerequisite for the nucleophiles being successfully added to the intermediate *N*-acyliminium ions (e.g. Table 2, compare entry 1 with entry 2). But even in the presence of this additive phenylmagnesium bromide gave only a

the concentration was increased from 0.1 to 0.2 M prior to the trapping reaction (Table 3, entry 3). By employing *i*Pr$_3$SiOTf at *c*=0.1 M, a slight improvement of the yield as compared to the reaction with trimethylsilyl triflate was achieved (Table 3 compare entry 4 with entry 2). Finally, the best result with a yield amounting to 89% for **10a/11a** was obtained when the reaction with *i*Pr$_3$SiOTf as an additive was performed at a concentration of 0.2 M (Table



Scheme 4.

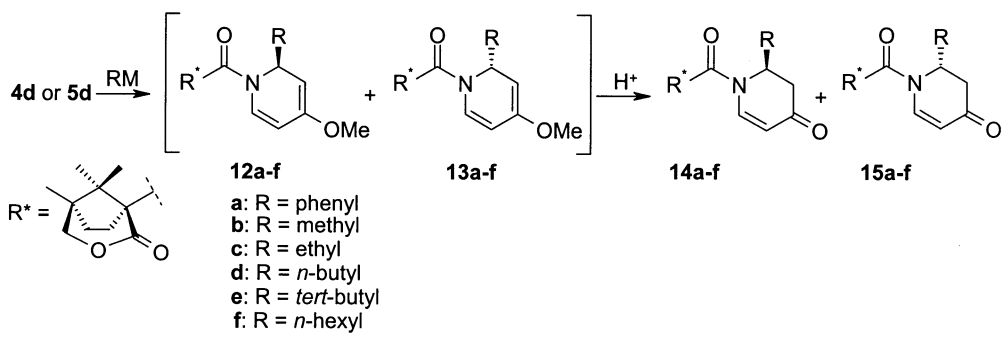
Table 3. Trapping reactions of *N*-acyl-4-phenylpyridinium salts in the absence (**4c**) and in the presence of R^3_3SiOTf (**5c**)

Entry	Product **10**+**11**	Reagent	Additive	Conc. (M)	Yield (%) **10**+**11**	d.s.[a] **10/11**
1	**a**	PhMgBr[b]	–	0.1	1	22/78
2	**a**	PhMgBr[b]	Me_3SiOTf	0.1	63	47/53
3	**a**	PhMgBr[b]	Me_3SiOTf	0.2/0.1[c]	83	38/62
4	**a**	PhMgBr[b]	iPr_3SiOTf	0.1	69	41/59
5	**a**	PhMgBr[b]	iPr_3SiOTf	0.2	89	38/62
6	**b**		Me_3SiOTf	0.1	25[d]	96/4[e]
7	**b**		Me_3SiOTf	0.2/0.1[c]	72[f]	93/7[e]

Alkylation time: 1 h, alkylation temperature: −78°C.
[a] Determined by HPLC from the crude reaction product.
[b] 3 equiv., 1.0 M in THF.
[c] Concentration for the generation of the *N*-acylpyridinium salt: 0.2 M in CH_2Cl_2, removal of the solvent and R^3_3SiCl after generation of the *N*-acylpyridinium triflate, concentration for the trapping reaction: 0.1 M in CH_2Cl_2.
[d] Alkylation time: 16 h.
[e] Determined by ^1H NMR from the crude reaction product.
[f] Alkylation time: 3 h.

3, entry 5). It should be noted that the same conditions had led to the highest amount of the *N*-acyliminium ion **5c** (>95%, Table 1, entry 3) as well. Besides also Et_3SiOTf, Ph_3SiOTf and $(MeO)_3SiOTf$ were employed in these reactions but appeared to be less efficient with respect to the yields of the addition products formed (~50%), except for Et_3SiOTf which led to a yield of 76% for **10a/11a**. However, for all addition reactions carried out with phenylmagnesium bromide as a nucleophile, the diastereoselectivities were only around 4/6 (except for Table 3, entry 1 with d.s.=to 22/78, yield 1%). In contrast, the addition of 2-[1,3]dioxolan-2-ylethyl magnesium bromide to **5c** gave both a high yield (at *c*=0.2 M after removal of Me_3SiCl, Table 3 entry 7) and a high diastereoselectivity (96/4 and 93/7, Table 3 entries 6 and 7), the latter being typical for addition reactions of this residue.

Finally, addition reactions of various organometallic reagents to the *N*-acylpyridinium salt **5d** were performed (Scheme 5). Again, a significant increase in yield was observed when trimethylsilyl triflate was present. In the case of phenylmagnesium bromide as nucleophile the yield rose from 25 to 64% (Table 4, compare entries 1 and 2). Therefore, trimethylsilyl triflate was employed for all other trapping reactions. The results of these reactions are summarized in Table 4. As it was more convenient to isolate the dihydropyridones **14a–f/15a–f**, which in contrast to **12a–f/13a–f** are stable compounds, the reaction mixtures were subjected to an acidic work up in order to convert the latter into the former. Addition reactions of alkylgrignard reagents to **5d** proceeded with good yields (40–76%) but were almost devoid of a reasonable stereoselection. This was true for the addition of phenylmagnesium bromide as well (Table 4, entry 2). Finally, organozinc reagents were found to give rise to reasonable diastereoselectivities and satisfying yields as well, on



Scheme 5.

Table 4. Trapping reactions of *N*-acyl-4-methoxypyridinium salts in the absence (**4d**) and in the presence (**5d**) of Me_3SiOTf

Entry	Product **14**+**15**	Reagent	Equiv.[a]	Additive	Temperature (°C)[b]	Time (h)[b]	Yield (%) **14**+**15**	d.s.[c] **14/15**
1	**a**	PhMgBr[d]	1.2	–	−78	1	25[e]	18/82
2	**a**	PhMgBr[d]	1.2	Me_3SiOTf	−78	1	64[e]	34/66
3	**a**	PhMgBr/$ZnCl_2$[f]+NMP	2.0	Me_3SiOTf	0	12	51[g]	73/27
4	**b**	$ZnMe_2$[h]+DMPU	2.0	Me_3SiOTf	0	14	56[e,i]	89/11
5	**c**	Et_2Zn[j]+NMP	2.0	Me_3SiOTf	−78→0°C	12	55[e,i]	82/18
6	**d**	(*n*-Butyl)$_2$Zn[k]+NMP	2.0	Me_3SiOTf	0	12	50[g]	83/17
7	**e**	(*tert*-Butyl)$_2$Zn[f]+NMP	2.0	Me_3SiOTf	0	12	28[g]	63/37
8	**f**	(*n*-Hexyl)$_2$Zn[k]+NMP	2.0	Me_3SiOTf	0	12	47[g]	85/15

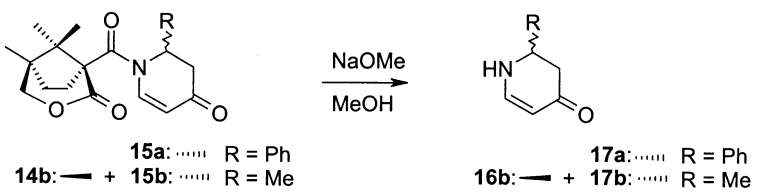
[a] Organometallic reagents.
[b] For amidoalkylation.
[c] Determined by HPLC from the crude reaction product.
[d] 1.0 M in THF.
[e] Concentration for the generation of the *N*-acypyridinium salt and for the trapping reaction: 0.1 M in CH_2Cl_2.
[f] 0.33 M, prepared from 1 equiv. $ZnCl_2$ (1.0 M in diethyl ether) and 2 equiv. PhMgBr (1.0 M in THF) or 2 equiv. *t*BuLi (1.0 M in pentane).
[g] Concentration for the generation of the *N*-acylpyridinium salt: 0.1 M in CH_2Cl_2, removal of the solvent and Me_3SiCl after the generation of the *N*-acylpyridinium triflate, concentration for the trapping reaction: 0.1 M in CH_2Cl_2+10% NMP.
[h] 2.0 M in toluene.
[i] Addition of 10% DMPU or NMP before alkylation.
[j] 1.0 M in hexane.
[k] 1.0 M in toluene.

condition that NMP or DMPU are used as cosolvents in order to increase the reactivity of the organometallic reagents.[9] The results for these addition reactions performed with various nucleophiles were all quite pleasing (except for the addition of a *tert*-butyl group) and may be seen from Table 4 (entries 3–8).

In the final step of the above described asymmetric syntheses the chiral auxiliary had to be removed, which was performed for some representative examples and furthermore also the stereochemistry of the newly created stereocenters had to be determined.

For the *N*-acyldihydropyridone **15a** the removal of the chiral auxiliary was easily accomplished by heating **15a** with NaOMe in methanol (Scheme 6) according to a procedure for related compounds[4c] providing **17a** in good yield (77%). The stereochemistry of **17a** resulted from a comparison of the optical rotation of **17a** with the literature value. For **17a** an optical rotation of $[\alpha]_D^{20}=+295.8°$ was found, indicating that this compound is of (*S*)-configuration (lit. value[4c] for (*S*): $[\alpha]_D^{20}=+332.3°$). Since the diastereomeric *N*-acyldihydropyridones **14b** and **15b** appeared to be inseparable a 85:15-mixture of **14b/15b** was subjected to the cleavage procedure with NaOMe in methanol. The optical rotation of the cleavage product **16b/17b** (yield: 63%) amounted to $[\alpha]_D^{20}=-320°$. In the literature[5] for the (*R*)-enantiomer **17b** a value of $[\alpha]_D^{20}=+495°$ is reported. Accordingly, the major enantiomer **16b** must posses (*S*)-stereochemistry, which of course must apply for the precursor **14b** as well [(*S*)-stereochemistry at C-2 of the dihydropyridone nucleus). The configuration of the newly created stereocenter of **14c–f** and **15c–f** was delineated from a comparison of their ^1H NMR data with those of **14b** and **15b**. The results are displayed in Table 5. Accordingly, whereas phenylmagnesium bromide exhibited *re* face selectivity, all organozinc reagents added to the *si* face of the *N*-acylpyridinium salt (the change of the stereochemical descriptor is only a result of the *CIP* rules).

The stereochemistry of the minor diastereomer **8a** [(*R*)-configuration)] obtained by phenylation of **5b** with a Grignard



Scheme 6.

Table 5. ^1H NMR correlation of **14c–f** with **14b** and **15c–f** with **15b** (in CD_2Cl_4)

R		H-2	H-4	H-6	H-5	Conf.		H-2	H-4	H-6	H-5	Conf.
Me	**14b**	4.87[a]	–	7.45	5.30	*S*	**15b**	5.05[a]	–	7.45	5.26	*R*
Et	**14c**	4.63[a]	–	7.39	5.22	*S*	**15c**	4.89	–	7.39	5.17	*R*
*n*Bu	**14d**	4.71[a]	–	7.39	5.23	*S*	**15d**	4.96[a]	–	7.39	5.17	*R*
*t*Bu[b]	**14e**	4.72[a]	–	7.47	5.24	*R*[c]	**15e**	4.99[a]	–	7.46	5.16	*S*[c]
n-Hexyl	**14f**	4.71[a]	–	7.39	5.22	*S*	**15f**	4.96[a]	–	7.38	5.17	*R*

[a] Average of multiplets.
[b] In nitrobenzene-d_5.
[c] Priority change is a result of the CIP rules.

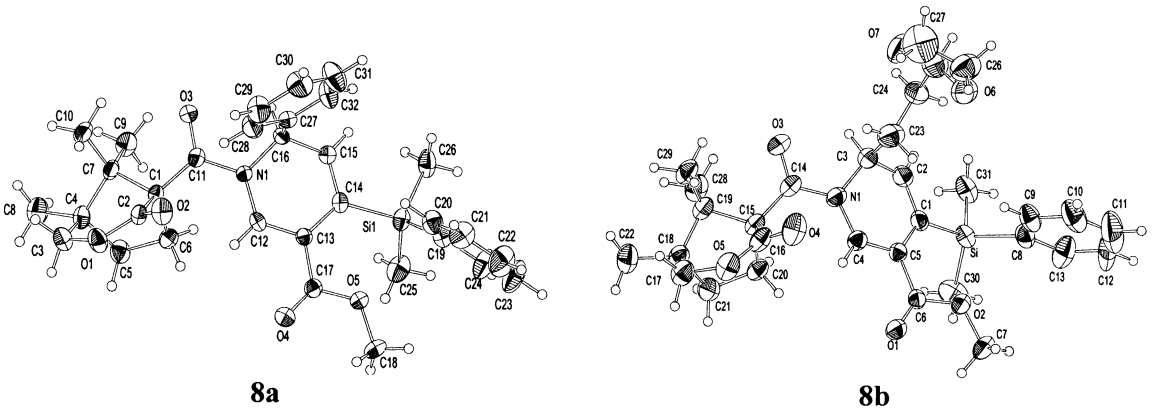
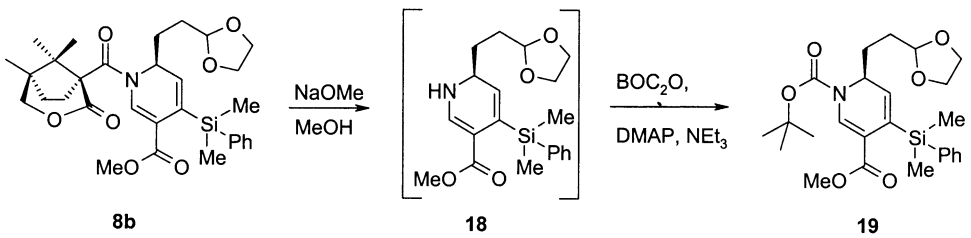


Figure 1.



Scheme 7.

reagent and of the major diastereomer **8b** [(*S*)-configuration)] resulting from the addition of 2-[1,3]-dioxolan-2-ylethylmagnesium bromide (to **5b**) was established by X-ray analyses (Fig. 1). Accordingly, the phenylgrignard had added preferentially from the *re* face and the alkylgrignard reagent from the *si* face.

The dihydropyridine **18** and the BOC-protected derivative **19** had been designed as chiral building blocks for an ongoing project directed towards the synthesis of new potentially bioactive compounds. Compound **18** was easily liberated from **8b** by heating the latter with NaOMe in methanol to 80°C. This also indicates that the above cleavage procedure so far only utilized for the cleavage of *N*-acyldihydropyridin-4(1*H*)-ones is suitable for the hydrolysis of *N*-acyl-3-methoxycarbonyl-1,6-dihydropyridines as well. The 1,6-dihydropyridine **18** appeared to be highly sensitive to air.[10] And, though it was handled with great care, it was always contaminated with small amounts of decomposition products like the respective pyridine. This problem was solved by protecting **18** with a BOC-group to give **19**. The protection was accomplished by Steglich's DMAP method[11] providing **19** in a total yield of 70% for both steps, the amide cleavage and the protection (based on **8b**) (Scheme 7).

The stereochemistry of the phenyl derivative **10a** (minor diastereomer) obtained from trapping reactions of the *N*-acyliminium salt **5c** was again established by X-ray analysis which showed that compound **10a** is of (*R*)-configuration (Fig. 2). The *N*-acyldihydropyridine **10b** was thought to be used for the preparation of the *N*-acyl-1,2,3,6-tetrahydropyridine **21** (Scheme 8) as an advanced intermediate for the construction of highly functionalized piperidine derivatives. First, conventional procedures were applied to reduce **10b** to the *N*-acyl-1,2,3,6-dihydropyridine derivative **20**, however, without any success. After some experimentation, it was found that the desired reduction

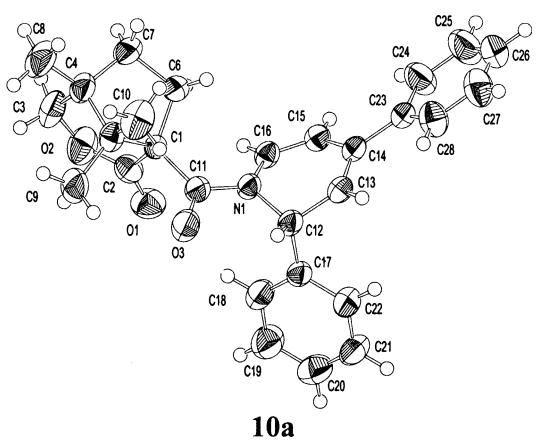


Figure 2.

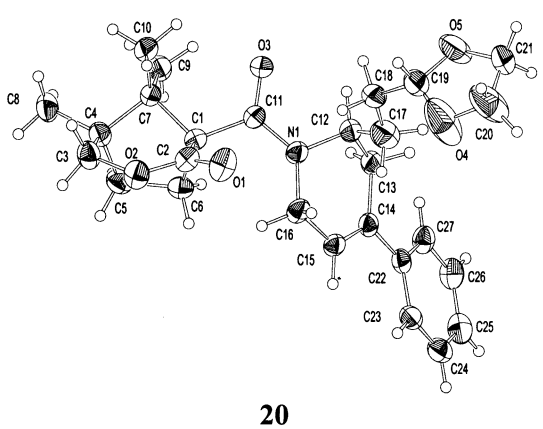
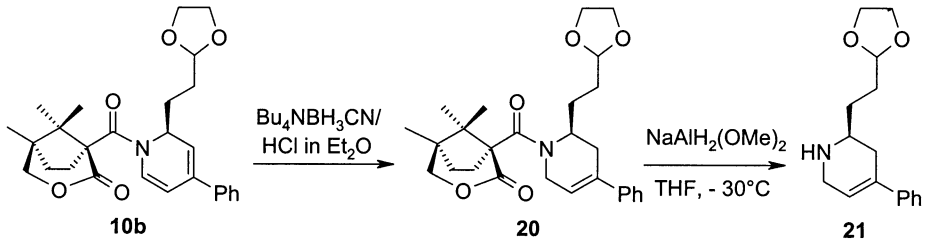


Figure 3.



Scheme 8.

may be best accomplished with tetrabutylammonium cyanoborohydride and when **10b** in a solution with the reducing agent (in CH_2Cl_2) is treated with HCl in Et_2O. This procedure was very efficient providing **20** with a yield of 78%. The final step, the removal of the chiral auxiliary from **20** was accomplished by a reductive cleavage of the amide bond employing $Na[AlH_2(OMe)_2]$ in THF at −25°C.[12] $Na[AlH_2(OMe)_2]$ appeared to be more efficient than $LiAlH_4$ which we had used earlier for the cleavage of amide bonds of related systems like *N*-acylpiperidines or *N*-acyl-1,2,3,4-tetrahydroisoquinolines.[13] At least, with 95% the yield for **21** was quite satisfying. Finally an X-ray analysis of **20** revealed that this compound exhibits (*S*)-configuration for the newly created stereocenter beneath the ring nitrogen (Fig. 3). Therefore, of course, the precursor **10b** and the product **21** must be of (*S*)-configuration at this position as well. According to these results, trapping reactions of **5c** with phenylmagnesium bromide exhibit *re* face selectivity whereas alkylation reactions proceed with opposite asymmetric induction (*si* face addition).

Thus, for the *N*-acyliminium salts **5c**–**d** presented in this paper addition reactions of phenylgrignard reagents occurred from the *re* face, whereas addition reactions of alkylgrignard reagents and of organozinc compounds proceeded with *si* face selectivity. At present, the reason for this change in the facial selectivity is unclear. Compared to the diastereoselectivities that had been achieved in former studies concerning the addition of organometallic reagents to closely related chiral *N*-acylpiperidinium ions (d.s.= >99/1, attack from the *re* face)[13a] and *N*-acylisoquinolinium ions (d.s.=96/4, attack from the *si* face)[13b] the diastereoselectivities of the present study with *N*-acylpyridinium ions are still to be improved.

3. Conclusion

In summary, we have developed an efficient methodology to generate chiral *N*-acylpyridinium ions in high amounts from the chiral acid chloride **2** and the pyridine derivatives **3a**–**d** based on trialkylsilyl triflates as additives. In addition, it has been demonstrated that also the yields for subsequent trapping reactions of the chiral *N*-acyliminium ions **5a**–**d** are improved by this procedure. The resulting α-substituted chiral *N*-acyldihydropyridines and *N*-acyldihydropyridones were obtained with reasonable diastereoselectivities. Addition reaction to the chiral *N*-acylpyridinium ions proceeded with *si* face selectivity, when alkylgrignard reagents or organozinc compounds were employed, whereas phenylgrignards led to a *re* face selectivity. Removal of the chiral auxiliary proceeded smoothly and in high yields by either employing NaOMe in methanol or $Na[AlH_2(OMe)_2]$ in THF. Furthermore, a new method for the regioselective reduction of acid-sensitive cyclic dienamides has been disclosed.

4. Experimental

4.1. General

All reactions were carried out in vacuum dried glassware sealed with rubber septa under nitrogen or argon atmosphere. All reagents were used as commercially available. The solvents were dried and distilled. Mp (uncorrected values): Büchi melting point apparatus no. 510 (Dr Tottoli). Optical rotations: Polarimeter 241 MC (Perkin–Elmer). IR: Perkin–Elmer FT-IR spectrophotometer Paragon 1000. ^{1}H NMR: JEOL JNMR-GX 400 spectrometer (400 MHz) with TMS as internal standard. MS spectra: Hewlett–Packard 5989 with 59980 B particle beam LC/MS interface. Elemental analysis: CHN Rapid (Heraeus). TLC: TLC plates Merck 60 F-254. Column chromatography (CC): Flash chromatography on silica gel (Merck 60 F-254, 0.040–0.063 mm). Analytical HPLC: L-6000 pump, L-4000 UV/Vis detector, D-7500 Chromato Integrator (Merck-Hitachi), column: LiChroCart® with Lichrospher® Si 60 cartridge (5 μm, 250×4 mm with precolumn 4×4 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, 250×25 mm) (Merck).

4.2. General procedure for the examination of the *N*-acyliminium ions by ^{1}H NMR (GP1)

Acid chloride **2** was prepared from 43 mg (0.2 mmol) of **1** in 1.4 ml of CH_2Cl_2, 18 μl (27 mg, 0.210 mmol, 1.05 equiv.) of oxalyl chloride and 2 μl of DMF at room temperature.[6b] After 3 h, the solvent was removed in vacuo. The remaining residue containing 0.2 mmol (1.0 equiv.) of acid chloride **2** was dissolved in 1 ml of CH_2Cl_2 and added to 0.2 mmol (1.0 equiv.) of the respective pyridine (0.2 or 0.4 M in CH_2Cl_2) followed by 36 μl (44 mg, 0.2 mmol, 1.0 equiv.) of trimethylsilyl triflate or 54 μl (61 mg, 0.2 mmol, 1.0 equiv.) of triisopropylsilyl triflate or 46 μl (52 mg, 0.2 mmol, 1.0 equiv.) of triethylsilyl triflate or 1.0 equiv. of triphenylsilyl triflate [prepared from 66 mg (0.22 mmol) of allyltriphenylsilane[14] in 1 ml of CD_2Cl_2 and 30 mg (17 μl, 0.2 mmol) of trifluoromethanesulfonic acid at 0°C, reaction time: 2 h] or 1.0 equiv. of trimethoxysilyl triflate [prepared from 30 mg (17 μl, 0.2 mmol) of allyltrimethoxysilane in 1 ml of CD_2Cl_2 and 30 mg (17 μl, 0.2 mmol) of trifluoromethanesulfonic acid at 0°C, reaction time: 2 h] after 5 min.

The resulting reaction mixture was allowed to equilibrate for 1 h before it was examined by ^{1}H NMR.

4.3. General procedure for α-amidoalkylation reactions (GP2)

For the preparation of **2**, carboxylic acid **1** (0.1 M in CH_2Cl_2) was treated with 1.05 equiv. of oxalyl chloride and a few drops of DMF at room temperature.[6b] After 3 h, the solvent was removed in vacuo and the residue (1 equiv. of **2**) was dissolved in CH_2Cl_2 (to give a concentration of 0.2 or 0.4 M) and added to the respective pyridine (0.2 or 0.4 M in CH_2Cl_2) followed by 1 equiv. of the silyl triflate after 5 min, when an additive was applied. Then the solution was stirred for 1 h at room temperature. Where indicated, the solvent and the trialkylsilylchloride were removed in vacuo and the residue was redissolved in CH_2Cl_2 (0.2 or 0.4 M). After cooling to the respective temperature for the alkylation reaction, the organometallic reagent was added dropwise and the reaction mixture was stirred for the time given. Then the reaction was quenched and the mixture worked up as indicated.

4.4. General procedure for the hydrolysis of *N*-acyldihydropyridines and *N*-acyldihydropyridones (GP3)

A solution of the *N*-acyldihydropyridine or *N*-acyldihydropyridone in MeOH was refluxed with NaOMe in MeOH. The reaction mixture was cooled to room temperature and worked up as indicated.

4.4.1. 3-Methyloxycarbonyl-1-[(1*S*,5*R*)-5,8,8-trimethyl-2-oxo-3-oxabicyclo[3.2.1]octylcarbonyl]pyridinium trifluoromethanesulfonate (5a). Preparation according to GP1 from 27 mg (0.2 mmol, 1.0 equiv.) of pyridine **3a**.

^{1}H NMR (CD_2Cl_2): δ (ppm)=0.99 (s, 3H, CH_3), 1.15 (s, 3H, CH_3), 1.41 (s, 3H, CH_3), 1.80–1.92 (m, 1H, 6′), 2.03–2.13 (m, 1H, 6′), 2.44–2.55 (m, 1H, $7'_{exo}$), 2.54–2.67 (m, 1H, $7'_{endo}$), 4.20 (d, *J*=11.1 Hz, 1H, OCH_2), 4.28 (dd, *J*=11.1, 1.7 Hz, 1H, OCH_2), 4.07 (s, 3H, $COOCH_3$), 8.39 (dd, *J*=8.3, 5.8 Hz, 1H, NCHC*H*CH), 9.22 (d, 1H, *J*=8.3 Hz, NCHCHC*H*), 9.47 (d, *J*=5.8 Hz, 1H, N=C*H*CHCH), 9.64 (s, 1H, NC*H*=C).

4.4.2. 4-(Dimethylphenylsilyl)-3-methyloxycarbonyl-1-[(1*S*,5*R*)-5,8,8-trimethyl-2-oxo-3-oxabicyclo[3.2.1]octylcarbonyl]pyridinium trifluoromethanesulfonate (5b). Preparation according to GP1 from 54 mg (0.2 mmol, 1.0 equiv.) pyridine **3b**.

^{1}H NMR (CD_2Cl_2): δ (ppm)=0.75 (s, 6H, 2×CH_3Si), 0.90 (s, 3H, CH_3), 1.14 (s, 3H, CH_3), 1.39 (s, 3H, CH_3), 1.92–2.02 (m, 2H, 6′), 2.40–2.48 (m, 1H, $7'_{endo}$), 2.61–2.73 (m, 1H, $7'_{exo}$), 3.88 (s, 3H, $COOCH_3$), 4.18 (d, *J*=11.0 Hz, 1H, OCH_2), 4.26 (d, *J*=11.0 Hz, 1H, OCH_2), 7.35–7.56 (m, 5H, $H_{arom.}$), 8.19 (d, *J*=6.0 Hz, 1H, N=CHC*H*), 9.11 (d, *J*=6.0 Hz, 1H, N=C*H*CH), 9.49 (s, 1H, NC*H*=C).

4.4.3. 4-Phenyl-1-[(1*S*,5*R*)-5,8,8-trimethyl-2-oxo-3-oxabicyclo[3.2.1]octylcarbonyl]pyridinium trifluoromethanesulfonate (5c). Preparation according to GP1 from 31 mg (0.2 mmol, 1.00 equiv.) of pyridine **3c**.

^{1}H NMR (CD_2Cl_2): δ (ppm)=0.95 (s, 3H, CH_3), 1.09 (s, 3H, CH_3), 1.37 (s, 3H, CH_3), 1.95–2.06 (m, 2H, 6′), 2.35 (ddd, *J*=14, 11.6, 5.4 Hz, 1H, $7'_{exo}$), 2.69 (ddd, *J*=14, 9.2, 5.4 Hz, 1H, $7'_{endo}$), 4.15 (d, *J*=11.1 Hz, 1H, 4′), 4.23 (dd, *J*=11.1, 1.5 Hz, 1H, 4′), 7.56–7.71 (m, 3H, $C_6H_{5,meta,para}$), 7.94–8.02 (m, 2H, $C_6H_{5,ortho}$), 8.42–8.51 (m, 2H, NCH=C*H*), 9.20–9.27 (m, 2H, NC*H*).

4.4.4. 4-Methoxy-1-[(1*S*,5*R*)-5,8,8-trimethyl-2-oxo-3-oxabicyclo[3.2.1]octylcarbonyl]pyridinium trifluoromethanesulfonate (5d). Preparation according to GP1 from 22 mg (0.20 mmol, 1.0 equiv.) of pyridine **3d**.

^{1}H NMR (CD_2Cl_2): δ (ppm)=0.91 (s, 3H, CH_3), 1.02 (s, 3H, CH_3), 1.31 (s, 3H, CH_3), 1.79–2.04 (m, 2H, 6′), 2.28–2.37 (m, 1H, 7′), 2.50–2.57 (m, 1H, 7′), 4.11 (d, *J*=11.6 Hz, 1H, OCH_2), 4.19 (d, *J*=11.6 Hz, 1H, OCH_2), 4.20 (s, 3H, OCH_3), 7.49 (d, *J*=8.0 Hz, 2H, NCH=C*H*), 8.93 (d, *J*=8.0 Hz, 2H, NC*H*).

4.4.5. Methyl (*R*)-4-(dimethylphenylsilyl)-6-phenyl-1-[(1*S*,5*R*)-5,8,8-trimethyl-2-oxo-3-oxabicyclo[3.2.1]octylcarbonyl]-1,6-dihydropyridine-3-carboxylate (8a) and methyl (*S*)-4-(dimethylphenylsilyl)-6-phenyl-1-[(1*S*,5*R*)-5,8,8-trimethyl-2-oxo-3-oxabicyclo[3.2.1]octylcarbonyl]-1,6-dihydropyridine-3-carboxylate (9a). The reaction was performed according to GP2. Preparation of **2** from 106 mg (0.50 mmol) of **1**[6b] in 3.75 ml of CH_2Cl_2, 44 μl (66 mg, 0.52 mmol, 1.03 equiv.) of oxalyl chloride and 2 μl of DMF. Generation of **5b** from **2** in 2.5 ml of CH_2Cl_2, 136 mg (0.50 mmol, 1.00 equiv.) of **3b** in 2.5 ml of CH_2Cl_2 and 90 μl (111 mg, 0.50 mmol, 1.00 equiv.) of TMSOTf. Arylation with 1.5 ml (1.50 mmol, 3.0 equiv.) of phenylmagnesium bromide (1.0 M in THF); arylation temperature −78°C; arylation time 1 h; quenching at −78°C with phosphate buffer (pH=7, *c*=1.0 M). The reaction mixture was extracted with CH_2Cl_2. The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo. Purification by CC (*n*-heptane/EtOAc=70:30) afforded 73 mg (27%) of a mixture of **8a** and **9a**. Separation of the diastereomers by preparative HPLC (*n*-heptane/EtOAc=80:20; 10.5 ml/min) yielded 17 mg (6%) of **8a** and 55 mg (20%) of **9a**. Analytical HPLC (*n*-heptane/EtOAc=80:20; 1.0 ml/min): d.s. (**8a**/**9a**)=24.0/76.0; **8a**: t_R=22.6 min; **9a**: t_R=25.7 min.

Compound **8a**. Colorless crystals, mp 168°C. TLC: R_f=0.25 (*n*-heptane/EtOAc=70:30). $[\alpha]_D^{20}$=+49.3° (*c*=0.29, CH_2Cl_2). IR (KBr): $\tilde{\nu}$ (cm^{-1})=1714, 1684, 1598, 1551, 1225, 808, 766, 695. ^{1}H NMR (nitrobenzene-d_5, 140°C): δ (ppm)=0.55 (s, 3H, $SiCH_3$), 0.56 (s, 3H, $SiCH_3$), 0.89 (s, 3H, CH_3), 1.01 (s, 3H, CH_3), 1.39 (s, 3H, CH_3), 1.84–2.01 (m, 2H, CH_2CH_2), 2.47–2.58 (m, 1H, CH_2CH_2), 2.59–2.69 (m, 1H, CH_2CH_2), 3.53 (s, 3H, $COOCH_3$), 3.99 (d, *J*=10.9 Hz, 1H, OCH_2), 4.19 (d, *J*=10.9 Hz, 1H, OCH_2), 5.18 (d, *J*=6.2 Hz, 1H, *H*CPh), 6.49 (d, *J*=6.2 Hz, 1H, NCHPhC*H*), 7.15–7.33 (m, 6H, $H_{arom.}$), 7.58–7.62 (m, 4H, $H_{arom.}$), 8.19 (s, 1H, NC*H*=C). MS (CI, CH_5^+); *m*/*z* (%): 544 [M^++1] (2), 512 (1), 466 (16), 195 (1). $C_{32}H_{37}NO_5Si$ (543.73): calcd C 70.69, H 6.86, N 2.58; found C 70.51, H 6.97, N 2.71.

Compound **9a**. Colorless crystals, mp 76–78°C. TLC: R_f=0.25 (*n*-heptane/EtOAc=70:30). $[\alpha]_D^{20}$=−292.4° (*c*=

0.73, CH_2Cl_2). IR (KBr): $\tilde{\nu}$ (cm^{-1})=1727, 1681, 1605, 1562, 1219, 816, 699. ^1H NMR (nitrobenzene-d_5, 140°C): δ (ppm)=0.54 (s, 3H, $SiCH_3$), 0.55 (s, 3H, $SiCH_3$), 0.89 (s, 6H, 2×CH_3), 1.34 (s, 3H, CH_3), 1.85–1.94 (m, 2H, CH_2CH_2), 2.37–2.48 (m, 1H, CH_2CH_2), 2.70–2.83 (m, 1H, CH_2CH_2), 3.56 (s, 3H, $COOCH_3$), 3.98 (d, J=10.9 Hz, 1H, OCH_2), 4.22 (d, J=10.9 Hz, 1H, OCH_2), 6.31 (d, J=5.7 Hz, 1H, *H*CPh), 6.35 (d, J=5.7 Hz, 1H, NCHPhC*H*), 7.15–7.35 (m, 6H, $H_{arom.}$), 7.54–7.63 (m, 4H, $H_{arom.}$), 8.19 (s, 1H, NC*H*=C). MS (CI, CH_5^+); *m*/*z* (%): 544 [M^++1] (2), 512 (1), 466 (14), 195 (1). $C_{32}H_{37}NO_5Si$ (543.73): calcd C 70.69, H 6.86, N 2.58; found C 70.44, H 7.07, N 2.62.

4.4.6. Methyl (*S*)-4-(dimethylphenylsilyl)-6-(2-[1,3]dioxolan-2-ylethyl)-1-[(1*S*,5*R*)-5,8,8-trimethyl-2-oxo-3-oxabicyclo[3.2.1]octylcarbonyl]-1,6-dihydropyridine-3-carboxylate (8b) and methyl (*R*)-4-(dimethylphenylsilyl)-6-(2-[1,3]dioxolan-2-ylethyl)-1-[(1*S*,5*R*)-5,8,8-trimethyl-2-oxo-3-oxabicyclo[3.2.1]octylcarbonyl]-1,6-dihydropyridine-3-carboxylate (9b). The reaction was performed according to GP2. Preparation of **2** from 408 mg (1.50 mmol) of **1**[6b] in 7.5 ml of CH_2Cl_2, 135 μl (203 mg, 1.60 mmol, 1.06 equiv.) of oxalyl chloride and 2 μl of DMF. Generation of **5b** from **2** in 7.5 ml of CH_2Cl_2, 318 mg (1.50 mmol, 1.0 equiv.) of **3b** in 7.5 ml of CH_2Cl_2, 272 μl (335 mg, 1.50 mmol, 1.0 equiv.) of TMSOTf. Alkylation with 4.5 ml (4.50 mmol, 3.0 equiv.) of 2-([1,3]dioxolan-2-yl)ethylmagnesium bromide (1.0 M in THF); alkylation temperature −78°C; alkylation time 3 h; quenching at −78°C with phosphate buffer (pH=7, c=1.0 M). Work up as described for the preparation of **8a** and **9a**. Purification by CC (*n*-heptane/EtOAc=50:50) afforded 350 mg (41%) of a mixture of **8b** and **9b**. Separation of the diastereomers by preparative HPLC (*n*-heptane/EtOAc=70:30; 12.0 ml/min) yielded 315 mg (37%) of **8b** and 35 mg (4%) of **9b**. Analytical HPLC (*n*-heptane/EtOAc=70:30; 1.5 ml/min): d.s. (**8b/9b**)=87.2/12.8; **8b**: t_R=11.1 min; **9b**: t_R=16.2 min.

Compound **8b**. Colorless crystals, mp 150°C. TLC: R_f=0.28 (*n*-heptane/EtOAc=50:50). $[\alpha]_D^{20}$=+496.7° (c=0.39, CH_2Cl_2). IR (KBr): $\tilde{\nu}$ (cm^{-1})=1728, 1677, 1601, 1556, 1221, 815, 702. ^1H NMR (nitrobenzene-d_5, 140°C): δ (ppm)=0.56 (s, 6H, 2×$SiCH_3$), 0.90 (s, 3H, CH_3), 1.06 (s, 3H, CH_3), 1.43 (s, 3H, CH_3), 1.83–2.01 (m, 6H, CH_2CH_2, CH_2CH_2), 2.36–2.48 (m, 2H, CH_2CH_2), 3.56 (s, 3H, $COOCH_3$), 3.73–3.82 (m, 2H, OCH_2CH_2O), 3.84–3.94 (m, 2H, OCH_2CH_2O), 3.99 (d, J=10.9 Hz, 1H, OCH_2), 4.19 (d, J=10.9 Hz, 1H, OCH_2), 4.87–4.91 (m, 1H, OCHO), 5.10–5.16 (m, 1H, NC*H*CH), 6.31 (d, J=5.8 Hz, 1H, NCHC*H*), 7.29–7.37 (m, 3H, $H_{arom.}$), 7.61–7.66 (m, 2H, $H_{arom.}$), 8.03 (s, 1H, NC*H*=C). MS (70 eV); *m*/*z* (%): 567 [M^+] (149), 552 (43), 466 (69), 372 (108), 195 (113). $C_{31}H_{41}NO_7Si$ (567.65): calcd C 65.59, H 7.28, N 2.47; found C 65.32, H 7.54, N 2.44.

Compound **9b**. Colorless crystals, mp 68°C. TLC: R_f=0.28 (*n*-heptane/EtOAc=50:50). $[\alpha]_D^{20}$=−342.6° (c=0.31, CH_2Cl_2). IR (KBr): $\tilde{\nu}$ (cm^{-1})=1726, 1672, 1602, 1556, 1231, 816, 704. ^1H NMR (nitrobenzene-d_5, 140°C): δ (ppm)=0.55 (s, 6H, 2×$SiCH_3$), 0.92 (s, 3H, CH_3), 1.01 (s, 3H, CH_3), 1.32 (s, 3H, CH_3), 1.78–1.99 (m, 6H, CH_2CH_2, CH_2CH_2), 2.36–2.48 (m, 1H, CH_2CH_2), 2.87–2.99 (m, 1H, CH_2CH_2), 3.53 (s, 3H, $COOCH_3$), 3.74–3.83 (m, 2H, OCH_2CH_2O), 3.86–3.92 (m, 2H, OCH_2CH_2O), 4.00 (d, J=10.9 Hz, 1H, OCH_2), 4.23 (d, J=10.9 Hz, 1H, OCH_2), 4.87–4.91 (m, 1H, OCHO), 5.32–5.39 (m, 1H, NC*H*CH_2), 6.22 (d, J=5.7 Hz, 1H, NCHC*H*), 7.27–7.37 (m, 3H, $H_{arom.}$), 7.59–7.66 (m, 2H, $H_{arom.}$), 8.06 (s, 1H, NC*H*=C). MS (CI, CH_5^+); *m*/*z* (%): 568 [M^++1] (50), 466 (13), 372 (110), 195 (91), 167 (192), 139 (77). $C_{31}H_{41}NO_7Si$ (567.65): calcd C 65.59, H 7.28, N 2.47; found C 65.46, H 7.42, N 2.47.

4.4.7. (1*S*,5*R*)-1-[(2*R*)-2,4-Diphenyl-1,2-dihydropyridylcarbonyl]-5,8,8-trimethyl-3-oxabicyclo[3.2.1]octan-2-one (10a) and (1*S*,5*R*)-1-[(2*S*)-2,4-diphenyl-1,2-dihydropyridylcarbonyl]-5,8,8-trimethyl-3-oxabicyclo[3.2.1]octan-2-one (11a). The reaction was performed according to GP2. Generation of **5c** as described for the preparation of **8a** and **9a** with 78 mg (0.50 mmol, 1.0 equiv.) of **3c**. The solvent and TMSCl were removed in vacuo. The residue was dissolved in 5 ml of CH_2Cl_2. Arylation with 1.5 ml (1.50 mmol, 3.0 equiv.) of phenylmagnesium bromide (1.0 M in THF); arylation temperature −78°C; arylation time 1 h; quenching at −78°C with phosphate buffer (pH=7, c=1.0 M). The reaction mixture was extracted with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. Purification by CC (*n*-heptane/EtOAc=75:25) afforded 177 mg (83%) of a mixture of **10a** and **11a**. Separation of the diastereomers by preparative HPLC (*n*-heptane/EtOAc=85:15; 15.0 ml/min). Analytical HPLC (*n*-heptane/EtOAc=80:20; 1.0 ml/min): d.s. (**10a/11a**)=38.3/61.7; **10a**: t_R=15.8 min; **11a**: t_R=19.7 min.

Compound **10a**. Colorless crystals, mp 198–202°C. TLC: R_f=0.34 (*n*-heptane/EtOAc=60:40). $[\alpha]_D^{20}$=+615.8° (c=0.5, CH_2Cl_2). IR (KBr): $\tilde{\nu}$ (cm^{-1})=2957, 1730, 1634, 759, 730, 701. ^1H NMR ($C_2D_2Cl_4$, 120°C): δ (ppm)=0.93 (s, 6H, CH_3), 1.37 (s, 3H, CH_3), 1.81–2.06 (m, 3H, CH_2CH_2), 2.29–2.62 (m, 1H, CH_2CH_2), 3.98 (d, J=11.0 Hz, 1H, OCH_2), 4.17 (dd, J=11.0, 1.9 Hz, 1H, OCH_2), 5.76 (d, J=7.8 Hz, 1H, NCH=C*H*), 6.21 (d_{br}, J=6.1 Hz, 1H, NC*H*Ph), 6.26 (d, J=6.1 Hz, 1H, NCHPhC*H*), 6.86 (d, J=7.8 Hz, 1H, NC*H*=CH), 7.22–7.40 (m, 6H, $H_{arom.}$), 7.43–7.48 (m, 2H, $H_{arom.}$), 7.50–7.55 (m, 2H, $H_{arom.}$). MS (70 eV); *m*/*z* (%): 427 (2) [M^+], 350 (8), 232 (100), 195 (32), 167 (16), 139 (16). $C_{28}H_{29}NO_3$ (427.54): calcd C 78.66, H 6.84, N 3.28; found C 78.49, H 7.07, N 3.22.

Compound **11a**. Colorless crystals, mp 87–90°C. TLC: R_f=0.29 (*n*-heptane/EtOAc=60:40). $[\alpha]_D^{20}$=−300.0° (c=0.05, CH_2Cl_2). IR (KBr): $\tilde{\nu}$ (cm^{-1})=2965, 1728, 1651. ^1H NMR ($C_2D_2Cl_4$, 140°C): δ (ppm)=0.86 (s, 3H, CH_3), 0.92 (s, 3H, CH_3), 1.28 (s, 3H, CH_3), 1.79–1.97 (m, 2H, CH_2CH_2), 2.17–2.35 (m, 1H, CH_2CH_2), 2.58–3.10 (m, 1H, CH_2CH_2), 3.97 (d, J=11.1 Hz, 1H, OCH_2), 4.20 (d, J=11.1 Hz, 1H, OCH_2), 5.65 (d, J=7.4 Hz, 1H, NCH=C*H*), 6.05–6.15 (m, 1H, NC*H*Ph), 6.43 (d, J=5.2 Hz, 1H, NCHPhC*H*), 6.86 (d, J=7.4 Hz, 1H, NC*H*=CH), 7.20–7.55 (m, 10H, $H_{arom.}$). MS (70 eV); *m*/*z* (%): 427 (5) [M^+], 350 (14), 232 (100), 195 (33), 167 (15). $C_{28}H_{29}NO_3$ (427.54): calcd C 78.66, H 6.84, N 3.28; found C 78.89, H 6.92, N 2.98.

4.4.8. (1*S*,5*R*)-1-[(2*S*)-2-(2-[1,3]Dioxolan-2-ylethyl)-4-phenyl-1,2-dihydropyridylcarbonyl]-5,8,8-trimethyl-3-oxabicyclo[3.2.1]octan-2-one (10b) and (1*S*,5*R*)-1-[(2*R*)-2-(2-[1,3]dioxolan-2-ylethyl)-4-phenyl-1,2-dihydropyridylcarbonyl]-5,8,8-trimethyl-3-oxabicyclo[3.2.1]octan-2-one (11b). The reaction was performed according to GP2. Preparation of **2** from 848 mg (4.0 mmol) of **1**[6] in 28 ml of CH_2Cl_2, 360 μl (533 mg, 4.2 mmol, 1.05 equiv.) of oxalyl chloride and 6 μl of DMF. Generation of **5c** from **2** in 10 ml of CH_2Cl_2, 620 mg (4.00 mmol, 1.0 equiv.) of **3c** in 10 ml of CH_2Cl_2, 724 μl (890 mg, 4.0 mmol, 1.0 equiv.) of TMSOTf. The solvent and TMSCl were removed in vacuo. The residue was dissolved in 40 ml of CH_2Cl_2. Alkylation with 12 ml (12.0 mmol, 3.0 equiv.) of 2-([1,3]dioxolan-2-yl)-ethylmagnesium bromide (1.0 M in THF); alkylation temperature −78°C; alkylation time 3 h; quenching at −78°C with phosphate buffer (pH=7, c=1.0 M). Work up as described for the preparation of **10a** and **11a**. Purification by CC (iPr$_2$O/EtOAc=90:10) afforded 1.298 g (72%) of **10b** (R_f=0.23). The fraction containing **11b** was washed with isohexane and the residue was purified by preparative HPLC (isohexane/EtOAc=70:30; 12.0 ml/min). The diastereoselectivity for **10b/11b** was determined by ^{1}H NMR from the crude product: d.s. (**10b/11b**)=93/7.

Compound **10b**. Colorless crystals, mp 55–60°C. TLC: R_f=0.23 (iPr$_2$O/EtOAc=90:10). $[\alpha]_D^{20}$=+160.0° (c=0.4, CH_2Cl_2). IR (KBr): $\tilde{\nu}$ (cm^{-1})=2953, 1725, 1643, 1412. ^{1}H NMR ($CDCl_3$): δ (ppm)=0.89 (s, 3H, CH_3), 1.03 (s, 3H, CH_3), 1.38 (s, 3H, CH_3), 1.77–1.98 (m, 6H, CH_2CH_2, CH_2CH_2), 2.18 (ddd, J=14.2, 11.8, 4.8 Hz, 1H, CH_2CH_2), 2.53 (ddd, J=14.2, 8.9, 5.7 Hz, 1H, CH_2CH_2), 3.79–3.84 (m, 2H, OCH_2CH_2O), 3.91–3.95 (m, 2H, OCH_2CH_2O), 3.97 (d, J=11.0 Hz, 1H, OCH_2), 4.14 (dd, J=11.0, 2.2 Hz, 1H, OCH_2), 4.89 (t, J=4.5 Hz, 1H, OCHO), 5.06–5.12 (m, 1H, NC*H*RCH), 5.76 (dd, J=7.6, 1.7 Hz, 1H, NCH=C*H*), 6.03 (dd, J=6.2, 1.7 Hz, 1H, NCHRC*H*), 6.68 (d, J=7.6 Hz, 1H, NC*H*=CH), 7.26–7.43 (m, 5H, $H_{arom.}$). MS (70 eV); m/z (%): 451 (1) [M$^+$], 350 (65), 195 (100), 167 (38), 139 (36). $C_{27}H_{33}NO_5$ (451.56): calcd C 71.82, H 7.37, N 3.10; found C 71.80, H 7.63, N 2.86.

Compound **11b**. Colorless crystals, mp 120–128°C. TLC: R_f=0.15 (iPr$_2$O/EtOAc=90:10). $[\alpha]_D^{20}$=−130.5° (c=0.8, CH_2Cl_2). IR (KBr): $\tilde{\nu}$ (cm^{-1})=2958, 2885, 1728, 1654, 1637, 1321. ^{1}H NMR ($CDCl_3$): δ (ppm)=0.81 (s, 3H, CH_3), 0.89 (s, 3H, CH_3), 1.12 (s, 3H, CH_3), 1.71–1.92 (m, 6H, CH_2CH_2, CH_2CH_2), 2.09 (ddd, J=14.7, 9.7, 4.7 Hz, 1H, CH_2CH_2), 3.20 (ddd, J=14.7, 12.7, 6.1 Hz, 1H, CH_2CH_2), 3.78–3.86 (m, 2H, OCH_2CH_2O), 3.89–3.99 (m, 3H, OCH_2CH_2O, OCH_2), 4.14 (d, J=11.3 Hz, 1H, OCH_2), 4.86–4.91 (m, 1H, OCHO), 5.32–5.40 (m, 1H, NC*H*RCH), 5.69 (d, J=7.9 Hz, 1H, NCH=C*H*), 6.00 (d, J=6.0 Hz, 1H, NCHRC*H*), 6.65 (d, J=7.9 Hz, 1H, NC*H*=CH), 7.25–7.42 (m, 5H, $H_{arom.}$). MS (70 eV); m/z (%): 451 (1) [M$^+$], 350 (65), 195 (100), 167 (38), 139 (36). $C_{27}H_{33}NO_5$ (451.56): calcd C 71.82, H 7.37, N 3.10; found C 71.92, H 7.42, N 3.00.

4.4.9. (*R*)-2-Phenyl-1-[(1*S*,5*R*)-5,8,8-trimethyl-2-oxo-3-oxabicyclo[3.2.1]octan-1-yl-carbonyl]-2,3-dihydropyridin-4(1*H*)-one (14a) and (*S*)-2-phenyl-1-[(1*S*,5*R*)-5,8,8-trimethyl-2-oxo-3-oxabicyclo-[3.2.1]octan-1-yl-carbonyl]-2,3-dihydropyridin-4(1*H*)-one (15a). Generation of **5d** as described for the preparation of **8a** and **9a** with 54 mg (0.50 mmol, 1.0 equiv.) of **3d**. The solvent and TMSCl were removed in vacuo. The residue was dissolved in 5 ml of CH_2Cl_2 and 0.5 ml of NMP. Arylation with 3.0 ml (1.0 mmol, 2.0 equiv.) of diphenylzinc [0.33 M, preparation from 1 equiv. $ZnCl_2$ (1.0 M in diethyl ether) and 2 equiv. PhMgBr (1.0 M in THF)]; arylation temperature 0°C; arylation time 12 h; quenching at −78°C with 2 M HCl. The reaction mixture was extracted with Et_2O. The combined organic layers were washed with saturated aqueous $NaHCO_3$, dried ($MgSO_4$) and concentrated in vacuo. Purification by CC (EtOAc/iPr$_2$O=60:40) afforded 94 mg (51%) of a mixture of **14a** and **15a**. Separation of the diastereomers by preparative HPLC (n-heptane/EtOAc=60:40; 13.5 ml/min). Analytical HPLC (n-heptane/EtOAc=60:40; 2.0 ml/min): d.s. (**14a/15a**)=73/27; **14a**: t_R=18.0 min; **15a**: t_R=21.8 min.

Compound **14a**. Colorless crystals, mp 184–186°C. TLC: R_f=0.32 (EtOAc/iPr$_2$O=60:40). IR (KBr): $\tilde{\nu}$ (cm^{-1})=1722, 1673, 1595. ^{1}H NMR ($C_2D_2Cl_4$, 120°C): δ (ppm)=0.90 (s, 3H, CH_3), 1.00 (s, 3H, CH_3), 1.31 (s, 3H, CH_3), 1.85–1.95 (m, 2H, CH_2CH_2), 2.32–2.40 (m, 2H, CH_2CH_2), 2.90 (d, J=16.5 Hz, 1H, CH_2CO), 3.05 (dd, J=16.5, 6.4 Hz, 1H, CH_2CO), 3.95 (d, J=11.1 Hz, 1H, OCH_2), 4.14 (d, J=11.1 Hz, 1H, OCH_2), 5.26 (d, J=8.6 Hz, 1H, COCH=), 5.87 (d, J=6.4 Hz, 1H, NCH), 7.21–7.29 (m, 5H, $H_{arom.}$), 7.66 (d, J=8.6 Hz, 1H, NCH=). MS (70 eV); m/z (%): 367 (2) [M$^+$], 195 (50), 172 (100). HRM (70 eV) for $C_{22}H_{25}NO_2$: calcd 367.1784; found 367.1771 (M$^+$).

Compound **15a**. Colorless crystals, mp 190–192°C. TLC: R_f=0.32 (EtOAc/iPr$_2$O=60:40). $[\alpha]_D^{20}$=−91° (c=0.3, CH_2Cl_2). IR (KBr): $\tilde{\nu}$ (cm^{-1})=1716, 1672, 1603. ^{1}H NMR ($C_2D_2Cl_4$, 120°C): δ (ppm)=0.86 (s, 3H, CH_3), 0.89 (s, 3H, CH_3), 1.25 (s, 3H, CH_3), 1.79–1.92 (m, 2H, CH_2CH_2), 2.23–2.30 (m, 1H, CH_2CH_2), 2.61–2.75 (m, 1H, CH_2CH_2), 2.85 (d, J=16.6 Hz, 1H, CH_2CO), 3.03 (dd, J=16.6, 6 Hz, 1H, CH_2CO), 3.95 (d, J=11.1 Hz, 1H, OCH_2), 4.15 (dd, J=11.1, 2.1 Hz, 1H, OCH_2), 5.23 (d, J=8.0 Hz, 1H, COCH=), 6.05 (d, J=6 Hz, 1H, NCH), 7.19–7.29 (m, 5H, $H_{arom.}$), 7.58 (d, J=8.0 Hz, 1H, NCH=). MS (70 eV); m/z (%): 367 (2) [M$^+$], 195 (36), 172 (100). $C_{22}H_{25}NO_4$ (367.44): calcd C 71.91, H 6.86, N 3.81; found C 71.69, H 7.06, N 3.85.

4.4.10. (*S*)-2-Methyl-1-[(1*S*,5*R*)-5,8,8-trimethyl-2-oxo-3-oxabicyclo[3.2.1]octan-1-yl-carbonyl]-2,3-dihydropyridin-4(1*H*)-one (14b) and (*R*)-2-methyl-1-[(1*S*,5*R*)-5,8,8-trimethyl-2-oxo-3-oxabicyclo-[3.2.1]octan-1-yl-carbonyl]-2,3-dihydropyridin-4(1*H*)-one (15b). Generation of **5d** as described for the preparation of **8a** and **9a** with 54 mg (0.50 mmol, 1.0 equiv.) of **3d**. Addition of 0.5 ml of DMPU before alkylation with 0.5 ml (1.0 mmol, 2 equiv.) of dimethylzinc (2.0 M in toluene); alkylation temperature 0°C; alkylation time 14 h; quenching with 2 M HCl. Work up as described for the preparation of **14a** and **15a**. Purification by CC (EtOAc/iPr$_2$O=65:35) afforded 86 mg (56%) of a mixture of **14b** and **15b** (R_f=0.30). Analytical HPLC (n-heptane/dioxane=85:15; 2.0 ml/min): d.s. (**14b/15b**)=89/11; **14b**: t_R=28.9 min; **15b**: t_R=34.1 min.

Compounds **14b** and **15b**. Colorless crystals. TLC: R_f=0.30 (EtOAc/*i* Pr_2O=65:35). IR (KBr): $\tilde{\nu}$ (cm^{-1})=1721, 1667, 1592. ^1H NMR ($C_2D_2Cl_4$, 120°C) for a ~1/1-mixture of **14b/15b**: δ (ppm)=0.95 (s, 3H, CH_3), 0.99 (s, 0.5×3H, CH_3), 1.06 (s, 0.5×3H, CH_3), 1.28 (s, 0.5×3H, CH_3), 1.30 (d, *J*=6.2 Hz, 0.5×1H, CH_3), 1.33 (d, *J*=6.2 Hz, 0.5×1H, CH_3), 1.37 (s, 0.5×3H, CH_3), 1.82–2.05 (m, 2H, CH_2CH_2), 2.25–2.45 (m, 3H), 2.77–2.87 (m, 1H, CH_2CO), 3.99 (d, *J*=11.0 Hz, 1H, OCH_2), 4.18 (d, *J*=11.0 Hz, 1H, OCH_2), 4.82–4.93 (m, NCH, 0.5×1H, **14b**), 5.01–5.11 (m, NCH, 0.5×1H, **15b**), 5.26 (d, *J*=7.8 Hz, =CHCO, 0.5×1H, **15b**), 5.30 (d, *J*=7.8 Hz, 0.5×1H, =CHCO, **14b**), 7.45 (d, *J*=7.8 Hz, 1H, NCH=). MS (CI, CH_5^+); *m*/*z* (%): 306 (100) [M+1]. $C_{17}H_{23}NO_4$ (305.37): calcd C 66.87, H 7.59, N 4.58; found C 66.93, H 7.79, N 4.32.

4.4.11. (*S*)-2-Ethyl-1-[(1*S*,5*R*)-5,8,8-trimethyl-2-oxo-3-oxabicyclo[3.2.1]octan-1-yl-carbonyl]-2,3-dihydropyridin-4(1*H*)-one (14c) and (*R*)-2-ethyl-1-[(1*S*,5*R*)-5,8,8-trimethyl-2-oxo-3-oxabicyclo-[3.2.1]octan-1-ylcarbonyl]-2,3-dihydropyridin-4(1*H*)-one (15c). Generation of **5d** as described for the preparation of **8a** and **9a** with 54 mg (0.5 mmol, 1.0 equiv.) of **3d**. Addition of 0.5 ml of NMP before alkylation with 1.0 ml (1.0 mmol, 2.0 equiv.) of diethylzinc (1.0 M in hexane); alkylation temperature −78°C. The reaction mixture was warmed to 0°C and stirred for 12 h. Quenching with 2 M HCl. Work up as described for the preparation of **14a** and **15a**. Purification by CC (EtOAc/*i* Pr_2O=60:40) afforded 88 mg (55%) of a mixture of **14c** and **15c**. Separation of the diastereomers by preparative HPLC (CH_2Cl_2/Et_2O=94:4; 13.5 ml/min). Analytical HPLC (CH_2Cl_2/Et_2O=97:3, 2.0 ml/min): d.s. (**14c/15c**)=82/18; **14c**: t_R=37.5 min; **15c**: t_R=43.0 min.

Compound **14c**. Colorless crystals, mp 202°C. TLC: R_f=0.35 (EtOAc/*i* Pr_2O=60:40). $[\alpha]_D^{20}$=+318.4° (*c*=0.55, CH_2Cl_2). IR (KBr): $\tilde{\nu}$ (cm^{-1})=1721, 1669, 1593. ^1H NMR ($C_2D_2Cl_4$, 120°C): δ (ppm)=0.88–0.93 (m, 6H, $H_{coal.}$, 2×CH_3), 1.01 (s, 3H, CH_3), 1.31 (s, 3H, CH_3), 1.62–1.98 (m, 4H, $H_{coal.}$, C$H_2$$CH_3$, CH_2CH_2), 2.20–2.40 (m, 2H, $H_{coal.}$, CH_2CH_2), 2.50 (d, *J*=11.3 Hz, 1H, CH_2CO), 2.67 (dd, *J*=11.3, 5.1 Hz, 1H, CH_2CO), 3.92 (d, *J*=11.5 Hz, 1H, OCH_2), 4.12 (d, *J*=11.5 Hz, 1H, OCH_2), 4.59–4.67 (m, 1H, NCH), 5.22 (d, *J*=8.4 Hz, 1H, COCH=), 7.39 (d, *J*=8.4 Hz, 1H, NCH=). MS (70 eV); *m*/*z* (%): 319 (39) [M^+], 195 (100). HRM (70 eV) for $C_{18}H_{25}NO_4$: calcd 319.1784; found 319.1784 (M^+).

Compound **15c**. Colorless crystals, mp 135–138°C. TLC: R_f=0.35 (EtOAc/*i* Pr_2O=60:40). $[\alpha]_D^{20}$=−113° (*c*=0.7, CH_2Cl_2). IR (KBr): $\tilde{\nu}$ (cm^{-1})=1724, 1662, 1591. ^1H NMR ($C_2D_2Cl_4$, 120°C): δ (ppm)=0.89 (s, 3H, CH_3), 0.89 (t, *J*=7.5 Hz, 3H, CH_2CH_3), 0.94 (s, 3H, CH_3), 1.22 (s, 3H, CH_3), 1.63–1.69 (m, 2H, C$H_2$$CH_3$), 1.82–1.90 (m, 2H, CH_2CH_2), 2.14–2.36 (m, 1H, CH_2CH_2), 2.45 (d, *J*=16.6 Hz, 1H, CH_2CO), 2.71 (dd, *J*=16.6, 5.9 Hz, 1H, CH_2CO), 2.63–2.78 (m, 1H, CH_2CH_2), 3.93 (d, *J*=11.1 Hz, 1H, OCH_2), 4.13 (d, *J*=11.1 Hz, 1H, OCH_2), 4.85–4.93 (m, 1H, NCH), 5.17 (d, *J*=8.5 Hz, 1H, COCH=), 7.38 (d, *J*=8.5 Hz, 1H, NCH=). MS (70 eV); *m*/*z* (%): 319 (36) [M^+], 195 (100). C_{18} H_{25} NO_4 (319.40): calcd C 67.69, H 7.89, N 4.38; found C 67.83, H 7.97, N 4.20.

4.4.12. (*S*)-2-*n*-Butyl-1-[(1*S*,5*R*)-5,8,8-trimethyl-2-oxo-3-oxabicyclo[3.2.1]octan-1-yl-carbonyl]-2,3-dihydropyridin-4(1*H*)-one (14d) and (*R*)-2-*n*-butyl-1-[(1*S*,5*R*)-5,8,8-trimethyl-2-oxo-3-oxabicyclo[3.2.1]octan-1-yl-carbonyl]-2,3-dihydropyridin-4(1*H*)-one (15d). Generation of **5d** as described for the preparation of **8a** and **9a** with 54 mg (0.5 mmol, 1.0 equiv.) of pyridine **3d**. The solvent and TMSCl were removed in vacuo. The residue was dissolved in 5 ml CH_2Cl_2 and 0.5 ml NMP. Alkylation with 1.0 ml (1.0 mmol, 2.0 equiv.) of di-*n*-buthylzinc (1.0 M in toluene); alkylation temperature 0°C; alkylation time 12 h; quenching with 2 M HCl. Work up as described for the preparation of **14a** and **15a**. Purification by CC (EtOAc/*i* Pr_2O=50:50) afforded 87 mg (50%) of a mixture of **14d** and **15d**. Separation of the diastereomers by preparative HPLC (*n*-heptane/CH_2Cl_2/dioxane=75:25:4; 13.5 ml/min). Analytical HPLC (*n*-heptane/dioxane=87.5:12.5, 2.0 ml/min): d.s. (**14d/15d**)=83/17; **14d**: t_R=25.5 min; **15d**: t_R=29.3 min.

Compound **14d**. Colorless crystals, mp 130–132°C. TLC: R_f=0.33 (EtOAc/*i* Pr_2O=50:50). $[\alpha]_D^{20}$=+268° (*c*=0.2, CH_2Cl_2). IR (KBr): $\tilde{\nu}$ (cm^{-1})=1727, 1670, 1593. ^1H NMR ($C_2D_2Cl_4$, 120°C): δ (ppm)=0.86–0.89 (m, 6H, CH_2CH_3, CH_3), 1.02 (s, 3H, CH_3), 1.27–1.47 (m, 7H, CH_3, CH_2CH_2), 1.65–1.70 (m, 2H, CH_2CH_2), 1.80–1.97 (m, 2H, CH_2CH_2), 2.31–2.35 (m, 2H, CH_2CH_2), 2.46 (d, *J*=16.7 Hz, 1H, CH_2CO), 2.68 (dd, *J*=16.7, 6.1 Hz, 1H, CH_2CO), 3.92 (d, *J*=11.0 Hz, 1H, OCH_2), 4.12 (dd, *J*=11.0, 2.2 Hz, 1H, OCH_2), 4.68–4.74 (m, 1H, NCH), 5.22 (d, *J*=8.3 Hz, 1H, COCH=), 7.39 (d, *J*=8.3 Hz, 1H, NCH=). MS (70 eV); *m*/*z* (%): 347 (14) [M^+], 290 (25), 195 (100).

Compound **15d**. Colorless crystals, mp 135–138°C. TLC: R_f=0.33 (EtOAc/*i* Pr_2O=50:50). $[\alpha]_D^{20}$=−120.5° (*c*=0.95, CH_2Cl_2). IR (KBr): $\tilde{\nu}$ (cm^{-1})=1727, 1667, 1592. ^1H NMR ($C_2D_2Cl_4$, 120°C): δ (ppm)=0.85–0.90 (m, 6H, CH_3, CH_2CH_3), 0.95 (s, 3H, CH_3), 1.23–1.39 (m, 7H, CH_2CH_2, CH_3), 1.60–1.65 (m, 2H, CH_2CH_2), 1.80–1.95 (m, 2H, CH_2CH_2), 2.23–2.30 (m, 1H, CH_2CH_2), 2.44 (d, *J*=16.6 Hz, 1H, CH_2CO), 2.71 (dd, *J*=16.6, 6.7 Hz, 1H, CH_2CO), 2.61–2.81 (m, 1H, CH_2CH_2), 3.93 (d, *J*=11.2 Hz, 1H, OCH_2), 4.14 (dd, *J*=11.2, 2.2 Hz, 1H, OCH_2), 4.93–4.99 (m, 1H, NCH), 5.17 (d, *J*=8.5 Hz, COCH=), 7.39 (d, *J*=8.5 Hz, NCH=). MS (70 eV); *m*/*z* (%): 347 (15) [M^+], 290 (25), 195 (100). $C_{20}H_{29}NO_4$ (347.45): calcd C 69.14, H 8.41, N 4.03; found C 69.19, H 8.41, N 3.96.

4.4.13. (*R*)-2-*tert*-Butyl-1-[(1*S*,5*R*)-5,8,8-trimethyl-2-oxo-3-oxabicyclo[3.2.1]octan-1-yl-carbonyl]-2,3-dihydropyridin-4(1*H*)-one (14e) and (*S*)-2-*tert*-butyl-1-[(1*S*,5*R*)-5,8,8-trimethyl-2-oxo-3-oxabicyclo-[3.2.1]octan-1-yl-carbonyl]-2,3-dihydropyridin-4(1*H*)-one (15e). Preparation as described for **14d** and **15d**. Alkylation with 3.0 ml (1.0 mmol, 2.0 equiv.) of di-*tert*-butylzinc [0.33 M, preparation from 1 equiv. $ZnCl_2$ (1.0 M in diethyl ether) and 2 equiv. *t*BuLi (1.0 M in pentane)]. Purification by CC (EtOAc/*i* Pr_2O=50:50) afforded 48 mg (28%) of a mixture of **14e** and **15e**. Separation of the diastereomers by preparative HPLC (*n*-heptane/dioxane=85:15; 13.5 ml/min). Analytical HPLC (*n*-heptane/dioxane=85:15, 2.0 ml/

min): d.s. (**14e/15e**)=63/37; **14e**: t_R=14.6 min; **15e**: t_R=19.8 min.

Compound **14e**. Colorless crystals, mp 231–232°C. TLC: R_f=0.35 (EtOAc/*i*Pr$_2$O=50:50). $[\alpha]_D^{20}$=+241.3° (*c*=0.93, CH_2Cl_2). IR (KBr): $\tilde{\nu}$ (cm^{-1})=1718, 1669, 1603. ^1H NMR ($C_2D_2Cl_4$, 120°C): δ (ppm)=0.89 (s, 3H, CH_3), 0.99 (s, 9H, *t*Bu), 1.05 (s, 3H, CH_3), 1.31 (s, 3H, CH_3), 1.81–1.96 (m, 2H, CH_2CH_2), 2.26–2.35 (m, 2H, CH_2CH_2), 2.64–2.74 (m, 2H, CH_2CO), 3.91 (d, *J*=11.1 Hz, 1H, OCH_2), 4.11 (d, *J*=11.1 Hz, 1H, OCH_2), 4.70–4.74 (m, 1H, NCH), 5.22–5.26 (m, 1H, COCH=), 7.47 (d, *J*=7.9 Hz, 1H, NCH=). MS (70 eV); *m*/*z* (%): 347 (2) [M^+], 195 (34). HRM (70 eV) for $C_{20}H_{29}NO_4$: calcd 347.2096; found 347.2085 (M^+).

Compound **15e**. Colorless crystals, mp 219–220°C. TLC: R_f=0.35 (EtOAc/*i*Pr$_2$O=50:50). $[\alpha]_D^{20}$=−107.5° (*c*=0.8, CH_2Cl_2). IR (KBr): $\tilde{\nu}$ (cm^{-1})=1721, 1664, 1597. ^1H NMR ($C_2D_2Cl_4$, 120°C): δ (ppm)=0.90 (s, 3H, CH_3), 0.93 (s, 9H, *t*Bu), 0.99 (s, 3H, CH_3), 1.25 (s, 3H, CH_3), 1.82–1.96 (m, 2H, CH_2CH_2), 2.27–2.48 (m, 2H, $H_{coal.}$, CH_2CH_2), 2.65–2.76 (m, 2H, CH_2CO), 3.94 (d, *J*=11.1 Hz, 1H, OCH_2), 4.13 (d, *J*=11.1 Hz, 1H, OCH_2), 4.98–5.00 (m, 1H, NCH), 5.16 (d, *J*=8.5 Hz, 1H, COCH=), 7.46 (d, *J*=8.5 Hz, 1H, NCH=). MS (70 eV); *m*/*z* (%): 347 (5) [M^+], 195 (100). $C_{20}H_{29}NO_4$ (347.45) calcd C 69.14, H 8.41, N 4.03; found C 69.06, H 8.64, N 3.89.

4.4.14. (*S*)-2-*n*-Hexyl-1-[(1*S*,5*R*)-5,8,8-trimethyl-2-oxo-3-oxabicyclo[3.2.1]octan-1-ylcarbonyl]-2,3-dihydropyridin-4(1*H*)-one (14f) and (*R*)-2-*n*-hexyl-1-[(1*S*,5*R*)-5,8,8-trimethyl-2-oxo-3-oxabicyclo-[3.2.1]octan-1-yl-carbonyl]-2,3-dihydropyridin-4(1*H*)-one (15f). Preparation as described for **14d** and **15d**. Alkylation with 1.0 ml (1.0 mmol, 2.0 equiv.) of di-*n*-hexylzinc (1.0 M in toluene). Purification by CC (EtOAc/*i*Pr$_2$O=40:60) afforded 88 mg (47%) of a mixture of **14f** and **15f**. Separation of the diastereomers by preparative HPLC (*n*-heptane/CH_2Cl_2/dioxane=75:25:4; 13.5 ml/min). Analytical HPLC (*n*-heptane/dioxane=87.5:12.5, 2.0 ml/min): d.s. (**14f/15f**)=85/15; **14f**: t_R=21.2 min; **15f**: t_R=23.9 min.

Compound **14f**. Colorless crystals, mp 126–129°C. TLC: R_f=0.33 (EtOAc/*i*Pr$_2$O=40:60). $[\alpha]_D^{20}$=+232.4° (*c*=0.25, CH_2Cl_2). IR (KBr): $\tilde{\nu}$ (cm^{-1})=1718, 1667, 1592. ^1H NMR ($C_2D_2Cl_4$, 120°C): δ (ppm)=0.85–0.89 (m, 6H, CH_2CH_3, CH_3), 1.02 (s, 3H, CH_3), 1.27–1.36 (m, 11H, CH_3, CH_2CH_2), 1.65–1.68 (m, 2H, CH_2CH_2), 1.80–1.97 (m, 2H, CH_2CH_2), 2.31–2.35 (m, 2H, CH_2CH_2), 2.45 (d, *J*=16.7 Hz, 1H, CH_2CO), 2.68 (dd, *J*=16.7, 6.1 Hz, 1H, CH_2CO), 3.92 (d, *J*=11.1 Hz, 1H, OCH_2), 4.12 (dd, *J*=11.1, 2.4 Hz, 1H, OCH_2), 4.68–4.73 (m, 1H, NCH), 5.22 (d, *J*=8.2 Hz, 1H, COCH=), 7.39 (d, *J*=8.2 Hz, 1H, NCH=). MS (70 eV); *m*/*z* (%): 375 (6) [M^+], 290 (25), 195 (100). HRM (70eV) for $C_{22}H_{33}NO_4$: calcd 337.2410; found 375.2415 (M^+).

Compound **15f**. Colorless oil. TLC: R_f=0.33 (EtOAc/*i*Pr$_2$O=40:60). $[\alpha]_D^{20}$=−100.3° (*c*=0.8, CH_2Cl_2). IR (film): $\tilde{\nu}$ (cm^{-1})=1731, 1668, 1593. ^1H NMR ($C_2D_2Cl_4$, 120°C): δ (ppm)=0.85–0.90 (m, 6H, CH_2CH_3, CH_3), 0.95 (s, 3H, CH_3), 1.23–1.38 (m, 11H, CH_3, CH_2CH_2), 1.57–1.67 (m, 2H, CH_2CH_2), 1.80–1.94 (m, 2H, CH_2CH_2), 2.23–2.29 (m, 1H, CH_2CH_2), 2.44 (d, *J*=16.6 Hz, 1H, CH_2CO), 2.68–2.74 (m, 2H, CH_2CH_2, CH_2CO), 3.93 (d, *J*=11.1 Hz, 1H, OCH_2), 4.13 (d, *J*=11.1 Hz, 1H, OCH_2), 4.95–4.97 (m, 1H, NCH), 5.17 (d, *J*=8.3 Hz, 1H, COCH=), 7.38 (d, *J*=8.3 Hz, 1H, NCH=). MS (70 eV); *m*/*z* (%): 375 (7) [M^+], 290 (23), 195 (100). $C_{22}H_{33}NO_4$ (375.51): calcd C 70.37, H 8.86, N 3.73; found C 70.51, H 8.92, N 3.64.

4.4.15. (*S*)-2-Phenyl-2,3-dihydropyridin-4(1*H*)-one (17a). Preparation according to GP3 from 127 mg (0.35 mmol) of **15a** in 3.5 ml MeOH with 0.5 ml of a NaOMe solution (2.0 M in MeOH); reaction time: 12 h. The reaction mixture was cooled to room temperature, the solvent was removed in vacuo and the residue was dissolved in water and diethyl ether. The water layer was extracted with Et_2O, the combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated in vacuo. Purification by CC (CH_2Cl_2/MeOH=95:5) yielded 46 mg (77%) of **17a**.

Colorless crystals, mp 102–104°C. TLC: R_f=0.41 (CH_2Cl_2/MeOH=95:5). $[\alpha]_D^{20}$=+295.8° (*c*=0.56, EtOH); {Ref. 4c: $[\alpha]_D^{20}$=+332.3° (*c*=2.42, EtOH)}.

4.4.16. (*S*)-2-Methyl-2,3-dihydropyridin-4(1*H*)-one (16b, es 85:15). Preparation according to GP3 from 170 mg (0.56 mmol) of **14b** and **15b** (85:15) in 5.6 ml MeOH with 2.0 ml of a NaOMe solution (1.0 M in MeOH); reaction time: 12 h. Work up as given for the preparation of **17a**. Purification by CC (CH_2Cl_2/MeOH=95:5) yielded 41 mg (63%) of **16b** (es 85:15).

Colorless crystals. $[\alpha]_D^{20}$=−329° (*c*=2.05, $CHCl_3$).

4.4.17. Methyl (*S*)-4-(dimethylphenylsilyl)-6-(2-[1,3]-dioxolan-2-ylethyl)-1,6-dihydropyridin-3-carboxylate (18). Preparation according to GP3 from 77 mg (0.136 mmol) of **8b** in 2 ml $MeOH_{abs.}$ and 1 ml (3.5 M in MeOH); reaction time: 18 h. After addition of phosphate buffer (pH 7.0, *c*=1.0 M) the reaction mixture was extracted with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. Purification by CC (Et_2O/$NMeEt_2$=96:4) yielded 46 mg (90%) of **18** (contaminated with traces of pyridine formed by oxidation on air).

Colorless oil. TLC: R_f=0.23 (Et_2O/$NMeEt_2$=96:4). ^1H NMR ($CDCl_3$): δ (ppm)=0.34 (s, 6H, $Si(CH_3)_2$), 1.48–1.63 (m, 2H, CH_2CH_2CH), 1.64–1.80 (m, 2H, CH_2CH_2CH), 3.36 (s, 3H, $COOCH_3$), 3.76–3.86 (m, 2H, OCH_2CH_2O), 3.86–3.97 (m, 2H, OCH_2CH_2O), 4.13 (td, *J*=5.6, 4.4 Hz, 1H, NCHCH), 4.83 (t, 1H, *J*=4.6 Hz, 1H, OCHO), 5.25 (d, *J*=4.4 Hz, 1H, NCHCH), 7.23–7.55 (m, 6H, $H_{arom.}$, NHCH=C).

4.4.18. Methyl (*S*)-1-*tert*-butyloxycarbonyl-4-(dimethylphenylsilyl)-6-(2-[1,3]dioxolan-2-ylethyl)-1,6-dihydropyridine-3-carboxylate (19). Preparation of **18** was accomplished as described above from 1.725 g (3.038 mmol) **8b** in 22 ml $MeOH_{abs.}$ with 15.19 ml of a NaOMe solution (1.0 M in MeOH). To **18** in 6.8 ml THF 492 μl (359 mg, 3.549 mmol, 1.17 equiv.) of NEt_3, 2.312 g (10.593 mmol, 3.49 equiv.) of Boc_2O and 434 mg (3.552 mmol, 1.17 equiv.) of DMAP were added followed by phosphate buffer (pH 7, *c*=1.0 M) after 3 days. The

reaction mixture was extracted with CH_2Cl_2, dried (Na_2SO_4) and concentrated in vacuo. Purification by CC (petrolether/Et_2O=75:25) yielded 1.189 g (70%) of **19**.

Colorless oil. TLC: R_f=0.21 (petrolether/Et_2O=75:25). $[\alpha]_D^{20}$=+394.3° (c=0.30, CH_2Cl_2). IR (film): $\tilde{\nu}$ (cm^{-1})= 1707, 1608, 1560, 1242, 1154, 814, 767, 702. ^1H NMR ($C_2D_2Cl_4$, 120°C): δ (ppm)=0.41 (s, 3H, $SiCH_3$), 0.43 (s, 3H, $SiCH_3$), 1.52 (s, 9H, *t* Bu), 1.55–1.76 (m, 4H, CH_2CH_2), 3.52 (s, 3H, $COOCH_3$), 3.72–3.82 (m, 2H, OCH_2CH_2O), 3.83–3.93 (m, 2H, OCH_2CH_2O), 4.68 (q, J=5.7 Hz, 1H, NC*H*CH), 4.82 (t, J=4.4 Hz, 1H, OCHO), 5.78 (d, J= 5.7 Hz, 1H, NCHC*H*), 7.24–7.31 (m, 3H, $H_{arom.}$), 7.44–7.50 (m, 2H, $H_{arom.}$), 7.82 (s, 1H, NC*H*=C). MS (CI, CH_5^+); *m/z* (%): 474 (11) [M^++1], 396 (100), 374 (14), 340 (47). $C_{25}H_{35}NO_6Si$ (473.64): calcd C 63.40, H 7.44, N 2.96; found. C 63.33, H 7.53, N 2.88.

4.4.19. (1*S*,5*R*)-1-[(2*S*)-2-(2-[1,3]Dioxolan-2-ylethyl)-4-phenyl-1,2,3,6-tetrahydro-1-pyridylcarbonyl]-5,8,8-trimethyl-3-oxabicyclo[3.2.1]octan-2-one (20). 864 mg (3.06 mmol, 1.15 equiv.) of tetrabutylammonium cyanoborohydride was added to 1.201 g (2.66 mmol) of **10b** in 21 ml of CH_2Cl_2 followed by 2.66 ml (2.93 mmol) of HCl (1.1 M in diethyl ether). After 30 min, phosphate buffer (pH=7, c=1.0) was added. The reaction mixture was extracted with CH_2Cl_2, dried ($MgSO_4$) and concentrated in vacuo. Purification by CC (i Pr_2O/Et_2O=73:27) yielded 940 mg (78%) of **20**.

Colorless crystals, mp 60–66°C. TLC: R_f=0.12 (*n*-heptane/EtOAc=60:40). $[\alpha]_D^{20}$=−3.1° (c=0.2, CH_2Cl_2). IR (KBr): $\tilde{\nu}$ (cm^{-1})=2957, 1729, 1630, 1409, 1218, 1122, 1067, 1022, 750, 697. ^1H NMR (nitrobenzene-d_5, 140°C): δ (ppm)=0.92 (s, 3H, CH_3), 1.15 (s, 3H, CH_3), 1.43 (s, 3H, CH_3), 1.76–2.07 (m, 6H, CH_2CH_2, CH_2CH_2CH), 2.43–2.55 (m, 1H, CH_2CH_2), 2.50 (d_{br}, J=16.7 Hz, 1H, NCHRCH_2), 2.59–2.74 (m, 1H, CH_2CH_2), 2.95 (d_{br}, J= 16.7 Hz, 1H, NCHRCH_2), 3.76–3.84 (m, 2H, OCH_2CH_2O), 3.84–3.96 (m, 3H, OCH_2CH_2O, NCH_2), 3.99 (d, J= 11.1 Hz, 1H, CH_2O), 4.21 (d, J=11.1 Hz, 1H, CH_2O), 4. 96 (d, J=18.8 Hz, 1H, NCH_2), 4.83–4.92 (m, 1H, NCHPh), 4.93–4.99 (m, 1H, OCHO), 6.07 (s_{large}, 1H, NCH_2CH), 7.21–7.27 (m, 1H, $H_{arom.}$), 7.32 (t, J=7.3 Hz, 2H, $H_{arom.}$), 7.40 (d, J=7.3 Hz, 2H, $H_{arom.}$). MS (CI, CH_5^+); *m/z* (%): 454 (56) [M^++1], 392 (32), 324 (100), 258 (68), 243 (30). $C_{27}H_{35}NO_5$ (453.58): calcd C 71.49, H 7.78, N 3.09; found. C 71.32, H 7.79, N 3.28.

4.4.20. (2*S*)-2-(2-[1,3]Dioxolan-2-ylethyl)-4-phenyl-1,2,3,6-tetrahydropyridine (21). 1.0 ml (1.0 mmol) of a $NaAlH_4$ solution (1.0 M in THF) and 81 μl (2.0 mmol) of $MeOH_{abs.}$ have been stirred for 30 min. 674 μl (0.67 mmol) of the resulting $NaAlH_2(OMe)_2$ solution (1.0 M in THF) was added to 170 mg (0.37 mmol) of **20** in 4 ml THF at −25°C. After 18 h the reaction mixture was quenched with phosphate buffer (pH=7, c=1.0 M), extracted with CH_2Cl_2, dried ($MgSO_4$) and concentrated in vacuo. Purification by CC (i Pr_2O/Et_2O=80:20+4% NMe_2Et) yielded 91 mg (95%) of **21**.

Colorless crystals, mp 72–75°C. TLC: R_f=0.30 (*n*-hep tane/EtOAc=60:40+5% NMe_2Et). $[\alpha]_D^{20}$=+203° (c=0.38, CH_2Cl_2). IR (KBr): $\tilde{\nu}$ (cm^{-1})=2914, 2884, 1471, 1445, 1408, 1378, 1320, 1146, 1117, 1027, 997, 961. ^1H NMR ($CDCl_3$): δ (ppm)=1.67–1.70 (m, 2H, CH_2CH_2), 1.80–1.88 (m, 2H, CH_2CH_2), 2.14–2.24 (m, 1H, NCHCH_2), 2.48 (d_{br}, J=16.7 Hz, 1H, NCHCH_2), 2.86 (dtd, J=10.0, 6.8, 4.0 Hz, 1H, NCH), 3.51–3.54 (m, 2H, NCH_2), 3.86–3.89 (m, 2H, OCH_2CH_2O), 3.97–3.99 (m, 2H, OCH_2CH_2O), 4.92 (t, J=4.7 Hz, 1H, OCHO), 6.12 (s_{br}, 1H, NCH_2CH), 7.20–7.35 (m, 3H, $H_{arom.}$), 7.36–7.41 (m, 2H, $H_{arom.}$). MS (CI, CH_5^+); *m/z* (%): 260 (100) [M^++1]. $C_{16}H_{21}NO_2$ (259.35): calcd C 74.10, H 8.16, N 5.40; found. C 73.85, H 8.18, N 5.28.

4.5. X-Ray analyses

Crystal data for **8a**. $C_{32}H_{37}NO_5Si$, M=543.72, orthorhombic, space group $P2_12_12_1$, a=8.9299(10) Å, b= 15.123(2) Å, c=22.156(3) Å,volume 2992.1(7) Å^3, Z=4, D_c=1.207 mg −m^3, μ=0.118 mm^{-1}, crystal dimensions 0.47×0.20×0.13 mm^3, F(000) 1160, T=295(2) K, Θ=2.28° to 23.99°. 5298 reflections measured, unique reflections 4687 [R_{int}=0.0386], min. and max. transmission coefficient 0.9665 and 0.9999, $R1$=0.0640, $wR2$=0.1349 for all 3017 reflections with $I>2\sigma(I)$ and $R1$=0.1074, $wR2$=0.1595 for all reflections and 358 refined parameters. Final electron density 0.169 and −0.170 e Å^{-3}, S=1.154, absolute structure parameter 0.1(3).

Crystal data for **8b**. $C_{31}H_{41}NO_7Si$, M=567.74, orthorhombic, space group $P2_12_12_1$, a=9.037(2) Å, b= 14.976(2) Å, c=22.927(4) Å, volume 3103.1(8) Å^3, Z=4, D_c=1.215 mg m^{-3}, μ=0.121 mm^{-1}, crystal dimensions 0.53×0.43×0.23 mm^3, F(000) 1216, T=295(2) K, Θ= 2.24° to 23.96°. 4732 reflections measured, unique reflections 4082 [R_{int}=0.0204], min. and max. transmission coefficient 0.9176 and 0.9989, $R1$=0.0501, $wR2$=0.1213 for all 3285 reflections with $I>2\sigma(I)$ and $R1$=0.0665, $wR2$=0.1333 for all reflections and 407 refined parameters and 95 restraints. Final electron density 0.315 and −0.164 e Å^{-3}, S=1.099, absolute structure parameter 0.1(2).

Crystal data for **10a**. $C_{28}H_{29}NO_3$, M=427.52, orthor hombic, space group $P2_12_12_1$, a=10.035(2) Å, b= 13.524(2) Å, c=16.958(2) Å, volume 2301(4) Å^3, Z=4, D_c=1.234 mg m^{-3}, μ=0.079 mm^{-1}, crystal dimensions 0.53×0.33×0.10 mm^3, F(000) 912, T=295(2) K, Θ=2.36° to 23.98°. 4085 reflections measured, unique reflections 3584 [R_{int}=0.0149], min. and max. transmission coefficient 0.9694 and 0.9995, $R1$=0.0423, $wR2$=0.0952 for all 2877 reflections with $I>2\sigma(I)$ and $R1$=0.0606, $wR2$= 0.1072 for all reflections and 293 refined parameters. Final electron density 0.132 and −0.120 e Å^{-3}, S=1.146, extinction coefficient 0.0086(11), absolute structure parameter −2(2).

Crystal data for **20**. C_{27} $H_{35}NO_5$, M=453.56, monoclinic, space group $P2_1$, a=6.6546(8) Å, b=18.192(2) Å A, c= 9.948(2) Å, β=91.819(12)°, volume 1203.7(3) Å^3, Z=2, D_c=1.251 mg m^{-3}, μ=0.085 mm^{-1}, crystal dimensions 0.47×0.27×0.20 mm^3, F(000) 488, T=295(2) K, Θ=2.24° to 23.97°. 4126 reflections measured, unique reflections 3773 [R_{int}=0.0154], min. and max. transmission coefficient

0.9746 and 1.0000, $R1$=0.0376, $wR2$=0.1096 for all 3226 reflections with $I>2\sigma(I)$ and $R1$=0.0484, $wR2$=0.1189 for all reflections and 368 refined parameters and 17 restraints. Final electron density 0.140 and −0.134 e Å^{-3}, S=1.119, extinction coefficient 0.015(3), absolute structure parameter −1.2(15).

All data sets were collected on a Nonius MACH3 kappa diffractometer with Mo K_α radiation (λ=0.71073 Å). The structures were solved by direct methods using SHELXS-86[15] and refined by full matrix least squares on F2 by SHELXL-93.[16] The molecular views were realised by ZORTEP.[17]

Crystal and data collection parameters, relevant structure refinement parameters, atomic coordinates for the non-hydrogen atoms, positional and isotropic displacement coefficients for hydrogen atoms, a list of anisotropic displacement coefficients for the non-hydrogen atoms and a full list of bond distances and bond angles have been deposited with the Cambridge Crystallographic Data Center. The data will be sent on quoting the CCDC-numbers 177107-177110 (e-mail: deposit@ccdc.cam.ac.uk)

Acknowledgments

Financial support of this work by the Deutsche Forschungsgemeinschaft, the Fonds der Chemischen Industrie and the BMBF is gratefully acknowledged.

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