Pergamon

Tetrahedron Vol. 50, No. 10, pp. 3113-3122, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4020/94 $6.00+0.00

0040-4020(94)E0048-X

Asymmetric Electrophilic α-Amidoalkylation - 10:[1] A new Camphorimide Derived Chiral Auxiliary for the Asymmetric Synthesis with N-Acyliminium Ions - Preparation of Aracemic[2] 2-Substituted Piperidines.

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Key Words: Asymmetric Synthesis; α-Amidoalkylation; 2-Substituted Piperidines; Precomplexation

Abstract: Compound **5** is a new α-amidoalkylation reagent for the asymmetric synthesis of 2-substituted piperidines. Its chiral auxiliary **3** is derived from camphoric acid and designed for an asymmetric induction mechanism featuring precomplexation as the decisive step for stereodifferentiation. Reagent **5** can smoothly be alkylated with various organometallic reagents after its activation by HCl-addition which presumably results in α-chloroamide **6**. Organozinc and organoaluminum compounds appear to give the best results with the highest diastereoselectivities being 97.8/2.2 for the ethylation (**7a/8a**), 87.7/12.3 for the methylation (**7b/8b**), 96.5/3.5 for the butylation (**7c/8c**) and 90.4/9.6 for the phenylation (**7d/8d**) of **5**. From the α-amidoalkylation products **7a-d** the corresponding optically active 2-substituted piperidinium chlorides **9a-d** can be obtained by removal of the chiral auxiliary which removal may be accomplished either through reduction with $LiAlH_4$ or by hydrolysis with KOH.

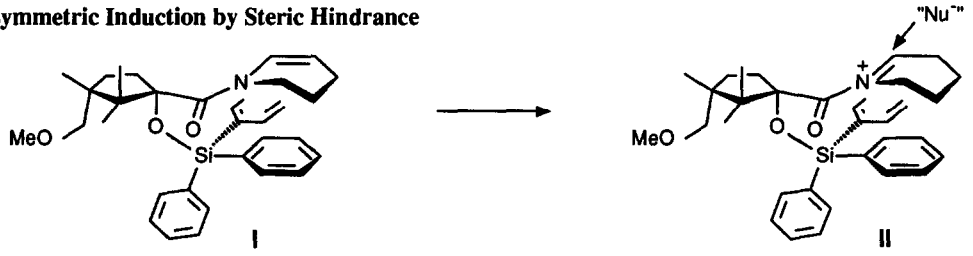
The preparation of 2-substituted piperidines in optically active form is an intensively studied object. This is at least in part due to the fact that this type of structure is common to several piperidine alkaloids and that such compounds may also serve as building blocks for the synthesis of more complex alkaloids.[3]

Among the methods currently available for the asymmetric synthesis of 2-substituted piperidines the most intriguing with regard to simplicity and flexibility, are those which allow the introduction of the 2-substituent in stereocontrolled manner. The chiral formamidine method developed by A. I. Meyers[4] represents an elegant example of an asymmetric synthesis along these lines. Another well established procedure is the CN(*R*,*S*) method of Husson[5] for the preparation of 2-substituted and 2,6-disubstituted piperidines having high enantiomeric purities. These methods differ fundamentally (with respect to charge) as in the former chiral carbanions and in the latter chiral iminium ions are involved.

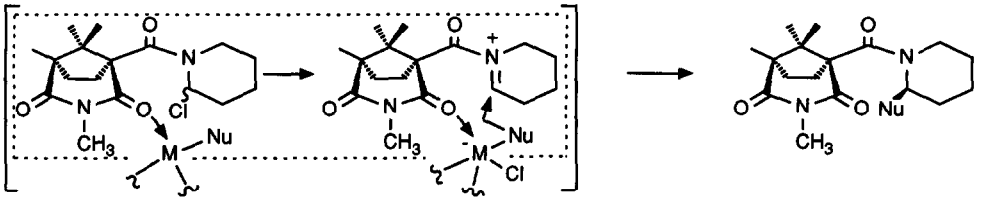
Some time ago we reported on a cationic type of asymmetric synthesis involving chiral N-acyliminium ions having an N-acyl group as chiral auxiliary which we have termed Asymmetric Electrophilic α-Amidoalkylation.[1] An optimized asymmetric electrophilic α-amidoalkylation reagent for the synthesis of chiral piperidines that has been developed by us is depicted in Scheme I. Enamides have proved to be useful precursors for the generation of N-acyliminium ions and amidoalkylation reactions with compound **I** proceed with high chemical yields and excellent diastereoselectivities[1] (d.s. ranging from 97/3 to >99.9/0.1). As can be seen from the stereomodel **II** that we have proposed for this reaction it is mainly steric hindrance that dictates the observed stereoselectivity by directing the approach of the nucleophile to the top face of the molecule.

We next turned to the question whether there might be an alternative strategy for achieving asymmetric induction. We considered the possibility of effecting stereodifferentiation by a precomplexation mechanism. For example, when an asymmetric reagent which features a chiral auxiliary equipped with a suitably oriented

Asymmetric Induction by Steric Hindrance



Asymmetric Induction by Precomplexation



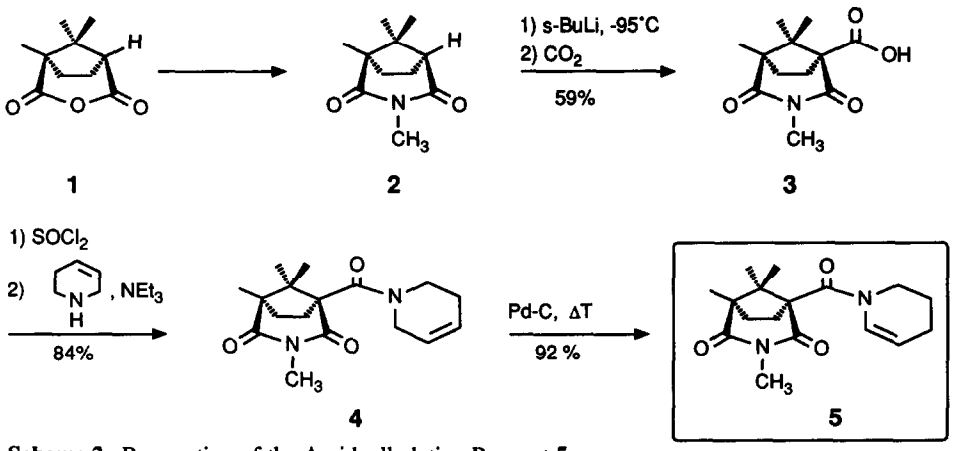
Scheme 1.

Lewis basic subsite is subjected to a reaction with a Lewis acidic organometallic reagent, most likely a complex would be formed first. Subsequently a substituent would probably be transferred from the complexed organometallic reagent to the prochiral carbon thus establishing the new stereocenter. In this case the geometry of the coordination complex would ultimately dictate the stereochemistry. This strategy would have the advantages that the chiral auxiliary could be smaller in size and that the conformational behavior of the acyliminium ion would become less important (e.g. with respect to the central OC-N=C - bond). In this paper we report the results of our studies directed toward this goal.

We chose a camphorimide derived carboxylic acid **3** as chiral auxiliary as it appeared to be easily accessible and meets the above criteria of containing a basic subsite of suitable orientation. The amidoalkylation reagent derived from **3** may form a complex as depicted in formula **III**. The amide moiety is believed to prefer an orientation with its nitrogen anti to the dimethyl substituted methano bridge of the chiral auxiliarxy thus minimizing steric interactions. And also for steric reasons, it is reasonable that the organometallic reagent is located in the lower part of the front face. Thus a group transferred from the metal center to an intermediate iminium ion **IV** formed by chloride abstraction most likely will add to the *re* face of the prochiral carbon (→ **V**).

The synthesis of the requisite amidoalkylation reagent and N-acyliminium ion precursor, i. e., the enamide **5**, is outlined in Scheme 2. Our synthesis started from the camphor imide **2** that is easily available from the anhydride **1**.[6] The conversion of **2** to **3** was effected by deprotonation with s-BuLi (1.05 equ.) at -95 °C and subsequent trapping of the formed carbanion with CO_2. The reaction proceeded smoothly at this temperature and after workup of the reaction mixture compound **3** was obtained in high yields (89%), the purity (» 95%) being sufficient for use in further reactions. A single recrystallization allowed the isolation of **3** in analytically pure form, although with a reduced yield of 59%. Metallation and carboxylation may also be carried out at higher temperatures (-78 °C) but the purity of the crude material is somewhat lower then (yield: 89%; purity ~ 95%).

The preparation of the amide **4** from **3** was accomplished by conventional methods involving activation of the carboxylic acid function of **3** with $SOCl_2$ and aminolysis of the acid chloride formed with 1,2,5,6-tetrahydropyridine (yield 84%). Finally the enamide **5** was prepared from **4** by an efficient double bond rearrangement using



Scheme 2. Preparation of the Amidoalkylation Reagent **5**

Pd-C[7] as catalyst (yield 92%).

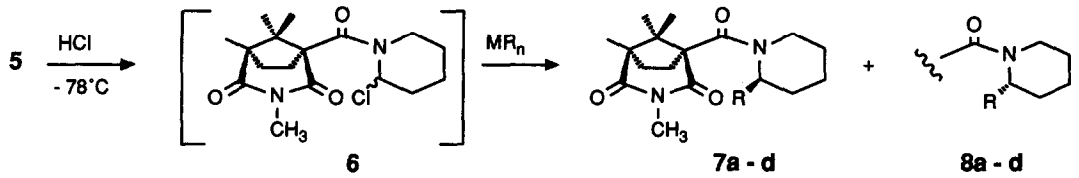
The ^{1}H-NMR (400 MHz, $CDCl_3$) spectrum of **5** recorded at ambient temperature exhibited extensive line broadening which was indicative of coalescence and the presence of **5** in the form of a mixture of conformers. By lowering the temperature to -20 °C the signals sharpened and the olefinic proton H-2, for example, gave rise to four different signals (δ = 6.18, 6.49, 6.99 and 7.23 ppm, ratio: 0.11/0.17/0.22/0.5). Carboxylic acid amides are well known to exist in two different conformations with respect to the amide bond[8,9a], thus leading to signal doubling. In the present case there obviously is a second dynamic process which most likely involves a ring inversion of the piperidine unit.[9]

Finally, also a high temperature spectrum (at +100 °C) of **5** was taken and at that temperature the coalescence point had clearly been surpassed (except for NCH_2) as the spectrum appeared to be sharp and showed only one set of signals for compound **5**. The most significant signals were those for the olefinic protons located at 6.97 ppm (H-2) and 4.92 ppm (H-3). This spectrum in addition provides unequivocal proof for the structure of **5**.

For the amidoalkylation reactions with enamide **5** we used the following procedure. First the enamide **5** was added to a solution of HCl in CH_2Cl_2 (at -78 °C) in order to generate an α-chloro amide as direct precursor for an N-acyliminium ion. After the subsequent removal of excessive HCl (in vacuo at -78 to -65°C) a solution of the respective organometallic compound was added. The results of these reactions are summarized in Tables 1-4.

The addition of diethylzinc (1.0 equ. in n-hexane, Table 1 entry 1) resulted in a straight forward reaction which afforded the ethylated products **7a** and **8a** with a d.s. of 91.5/8.5. Only a small amount of unreacted starting material **5** could be detected.[10] By using an excess of organometallic reagent an almost complete conversion could be effected (Table 1, entry 2). Even more important is the fact that by lowering the temperature to -95°C the d.s. increased to 95.0/5.0 (Table 1, entry 3). Triethylaluminum also gave a smooth conversion to **7a/8a** and in comparison to the use of diethylzinc a significant increase of the asymmetric induction to 94.9/5.1 at -78 °C (compare entries 4 and 1 in Table 1) and 97.8/2.2 at -95 °C (compare Table 1, entries 5 and 3) was observed.

Trialkylaluminum compounds as a rule show a tendency to exist as dimeric or oligomeric species in hydrocarbon solvents. However, with Lewis bases, e.g. diethyl ether, they react to form complexes that are monomeric.[11,12] With this in mind the amidoalkylation reaction (at -78 °C with Et_3Al) was additionally conducted under conditions comparable to the former ones, but with triethylaluminum which had been pretreated with 1.1 and 5.0 equ. diethyl ether, respectively. In these cases a slight but still significant increase in diastereoselectivity



Scheme 3.

occurred (see Table 1, entries 6 and 7). However, for the reaction at -95 °C (Table 1, entry 5) the diastereoselectivity remained unaffected by the addition of diethyl ether (1.0 equ.).

With diethylaluminum chloride the diastereoselectivity dropped to 91.0/9.0 (Table 1, entry 8). It even became as poor as 65.7/34.3 when the reaction was carried out by addition of $AlCl_3$ to first generate an N-acyliminium ion followed by adding triethyaluminum as trapping agent (see Table 1, entry 9). Ethylmagnesium bromide afforded a very disappointing result with respect to both conversion and diastereoselectivity. Most interestingly the reaction had proceeded with opposite asymmetric induction (see Table 1, entry 10).

On the basis of our theory one would expect the asymmetric induction to increase with increasing Lewis acidity of the organometallic reagent. This is in line with our findings that the aluminum reagents provided better diastereoselectivities than the zinc compounds (compare Table 1, entries 1 and 4 and entries 3 and 5). However, strong Lewis acids capable of accepting more than one electron pair might also give rise to chelate formation, the ß-dicarbonyl unit present in **6** (carbonyl at piperidine nitrogen and adjacent carbonyl of the imide unit) acting as bidentate ligand. The corresponding chelate is not to be expected to afford too high a degree of stereodifferentiation. Possibly the asymmetric induction is even opposite to that of the former complex where **6** plays the role of an unidentate ligand thus leading to a reduced diastereoselectivity of the overall reaction as well.

The enhanced diastereoselectivities observed in the reactions with triethylaluminum reagents pretreated with Et_2O can be rationalized by this model, too. Due to the presence of Et_2O the extent of chelate formation will be reduced thus making the corresponding reaction pathway less important. Alternatively it can be assumed that the presence of Et_2O leads to an increase in size of the reagent which in turn could give rise to a higher stereoselectivity. The low diastereoselectivities with Et_2AlCl and $AlCl_3/AlEt_3$ can also be explained by this model as the high Lewis acidities of these reagents will promote chelate formation.

Next we extended this reaction to organometallic reagents capable of transfering a methyl-, n-butyl-, or phenyl-group thereby obtaining the products **7/8b-d**. The experimental results are summarized in Tables 2 to 4. In comparison to the corresponding ethylation the methylation to **7b/8b** proceeded with somewhat lower diastereoselectivity. It is interesting to note that in this case under standard conditions (no solvent additives, -78 °C) the aluminum reagent $AlMe_3$ was surpassed by the zinc compound $ZnMe_2$ with respect to asymmetric induction (compare Table 2, entries 1 and 3). Again a significant increase in diastereoselectivity could be brought about by pretreating the organometallic reagent with Et_2O. Thus, in the case of $AlMe_3$ the diastereoselectivity could be raised from 71.7/28.9 to 83.5/16.5 upon addition of 5.0 equ. of Et_2O (compare Table 2, entries 3 and 4). The reaction with $ZnMe_2$ also was conducted at -95 °C, leading to a diastereoselectivity of 87.7/12.3 (see Table 2, entry 2).

For the butylation reaction of **6** the organometallic compounds shown in Table 3 were tested. With $AlBu_3$ a quite remarkable diastereoselectivity was reached (Table 3, entries 1-2) which is distinctively higher than that obtained with the corresponding methyl derivative ($AlMe_3$). The corresponding zinc reagent ($ZnBu_2$ prepared from $ZnCl_2$ and BuLi) also gave a quite reasonable diastereoselectivity (Table 3, entry 5), although somewhat lower than that obtained with the aluminum reagent. The copper and cer reagents tested appeared to be less suitable for

Table 1. Amidoalkylation of **5** to Ethylated Products **7a** and **8a**

a) R = Et reagent	equ.	T [°C]	d. s.[a] 7a / 8a	ratio: 7a + 8a / 5 [a]
1. Zn Et_2 [b]	1.0	- 78	91.5/ 8.5	98/ 2
2. "	3.0	"	91.9/ 8.1	~ 100/ 0
3. "	1.0	- 95	95.0/ 5.0	99/ 1
4. $AlEt_3$ [c]	1.1	- 78	94.9/ 5.1	~ 100/ 0
5. "	"	- 95	97.8/ 2.2	97/ 3
6. Al Et_3[c]/Et_2O (1.1 equ.)	"	- 78	96.0/ 4.0	99/ 1
7. " / " (5.0 ")	1.25	"	96.9/ 3.1	98/ 2
8. $AlEt_2Cl$ [d]	1.1	"	91.0/ 9.0	90/10
9. $AlCl_3$[e] (1.0 equ.)/$AlEt_3$	"	"	65.7/34.3	89/11
10. Et Mg Br [f]	1.2	"	36.0/64.0	59/41

[a] Determined by HPLC from the crude reaction product; [b] 0.86 M in n-hexane; [c] 1.0 M in n-hexane; [e] 1.0 M in nitrobenzene; [f] 2.0 M in THF.

Table 2. Amidoalkylation of **5** to Methylated Products **7b** and **8b**

b) R = Me reagent	equ.	T [°C]	d. s.[a] 7b / 8b	ratio: 7b + 8b / 5 [a]
1. Zn Me_2 [b]	1.25	- 78	83.5/16.5	> 95/5
2. "	"	- 95	87.7/12.3	> 95/5
3. $AlMe_3$ [c]	1.1	- 78	71.1/28.9	> 95/5
4. $AlMe_3$[d]/Et_2O(5.0 equ.)	1.25	- 78	83.5/16.5	> 95/5

[a] Determined by HPLC from the crude reaction product; [b] 2.0 M in toluene; [c] 1.0 M in toluene; [d] 2.0 M in hexane.

Table 3. Amidoalkylation of **5** to Butylated Products **7c** and **8c**

c) R = n-Bu reagent	equ.	T [°C]	d. s.[a] 7c / 8c	ratio: 7c + 8c / 5 [a]
1. Al(n-Bu)$_3$ [b]	1.25	- 78	96.5/ 3.5	> 95/5
2. "	"	- 96	95.9/ 4.1	> 9/1
3. LiCu(n-Bu)$_2$ [c]	1.5	- 78	46.0/54.0	> 95/5
4. $CeCl_3$/n-BuLi [d]	2.0	- 78 → r.t.	61.9/38.1	~ 1/1
5. $ZnCl_2$/n-BuLi [e](1.2/2.0 equ.)	1.25	- 78	(91/9 - 92/8)	> 95/5

[a] Determined by HPLC from the crude reaction product; [b] 0.25 M in n-hexane; [c] 1 mmol CuI in 2 ml Et_2O plus 2 mmol n-BuLi (1.6 M, n-hexane)at - 20°C; [d] 1 mmol $CeCl_3$ in 4.25 ml THF plus 1 mmol n-BuLi (1.6 M, n-hexane) at - 78°C; [e] 1.8 mmol $ZnCl_2$ (1.0 M, Et_2O) in 2.7 ml Et_2O plus 3 mmol n-BuLi (2.0 M, n-pentane) at r.t.

Table 4. Amidoalkylation of **5** to Phenylated Products **7d** and **8d**

d) R = Ph reagent	equ.	T [°C]	d. s.[a] 7d / 8d	ratio: 7d + 8d / 5 [a]
1. Ph Mg Br [b]	1.1	- 78	87.5/12.5	> 90/10
2. $ZnCl_2$/PhMgBr(1.0/2.0 equ.,Et_2O)	"	"	81.7/18.3	> 99/ 1
3. $ZnCl_2$/PhMgBr[c] (1.2/2.0 equ., Et_2O)	"	"	83.1/16.9	91/ 9
4. $ZnCl_2$/PhMgBr[d](1.2/2.0 equ., THF)	"	"	90.4/ 9.6	94/ 6

[a] Determined by HPLC from the crude reaction product; [b] 3.0 M in Et_2O; [c] 3 mmol PhMgBr (3.0 M, Et_2O) in 0.8 ml Et_2O plus 1.8 mmol $ZnCl_2$ (1.0 M, Et_2O) at r.t.; [d] 1.5 mmol PhMgBr (1.0 M, THF) in 4.5 ml THF plus 0.9 mmol $ZnCl_2$ at r.t..

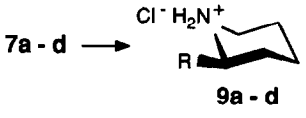
this purpose, affording very poor asymmetric inductions and, in addition, a low conversion in the case of the cer compound (see Table 3, entries 3 and 4).

The phenylation reaction of **6** with PhMgBr led to a satisfactory result with respect to both diastereoselectivity and conversion (see Table 4, entry 1). Diphenylzinc was also employed in this reaction. The best result was obtained with the zinc reagent prepared from $ZnCl_2$ and PhMgBr in a ratio of 1.2/2.0 in THF, the corresponding d.s. amounting to 90.4/9.6 (see Table 4, entry 4). The exchange of THF by Et_2O gave a reduced d.s. (Table 4, entry 3) and a further but less significant drop in d.s. was observed (in Et_2O) when shifting the ratio of the reactants from 1.2/2.0 to 1.0/2.0 (Table 4, entry 2). The latter effect might by caused by a change in the nature of the reactive species. The solvent effect is in line with that found for the former reactions (see Tables 1 and 2 for the change from CH_2Cl_2 to Et_2O) which emphasizes the necessity of avoiding an unfavorable chelate formation.

The removal of the chiral auxiliary could be accomplished best by cleaving the amide bond by a reductive procedure. $LiAlH_4$ turned out to be the reagent most suited for this reaction (1.1-1.5 equ. $LiAlH_4$, THF, room temperature), whereas other reducing agents like Red-Al^R, $LiEt_3BH$, $AlH(i\text{-}Bu)_2$ failed to afford any noticeable amounts of the desired amines **9a-d**. The amines **9a-c** were thus obtained in fairly good yields ranging from 75 to 81% (see Table 5, isolation as hydrochlorides). For convenience the amides **7a-c** had been subjected to this reaction with the diastereomeric purity indicated in Table 5.

Table 5. 2-Substituted Piperidines from Asymmetric α-Amidoalkylation Products

		starting material	product 9		
	R	7/8	yield [%]	$[\alpha]^{23}_D$	absol. conf.
a	Et	97.2/ 2.8	75	+ 3.86°	*R*
b	Me	83.5/16.5	81	+ 2.53°	*R*
c	Bu	96.5/ 3.5	79	+ 4.0°	*R*
d	Ph	91 / 9	76	+ 1.5°	*S*



Scheme 4.

The phenyl derivative **7d**, however could not be cleaved by this procedure. Eventually we found that the hydrolysis of these amides can also be effected by heating with KOH in ethylene glycol monomethyl ether, although at higher temperatures. For **7a** a temperature of 160 °C was just sufficient to generate the amine **9a** (yield 49%) whereas for **7d** a temperature of 175 °C even had to be applied (sealed tube for 7 days) for providing **9d** in a yield of 76%.

To check the integrity of the chiral center of **9d**, a sample of **9d** was reconverted to **7d** by treatment with the carboxylic acid chloride derived from **5**. A diasteromeric mixture of **7d/8d** = 6/4 was obtained, indicating that extensive racemization had occurred. Nevertheless this method seems to be a valuable alternative for the hydrolysis of configurationally stable compounds (e.g. **7a** → **9a**). The enantiomeric purity of the amines **9a-c** obtained according to the reductive cleavage procedure is equivalent to the diastereomeric purity of the starting materials **7/8a-c** since under the mild reaction conditions employed racemization can certainly be excluded.

The stereochemistry of compounds **9b-d** was established by comparison of their optical rotations with literature values. For **9b** an optical rotation of $[\alpha]^{23}_D = +2.53°$ was determined, indicating that this compound had (*R*)-configuration {lit. value[13] for (*S*): $[\alpha]^{15}_D = -4.2°$}. The value found also was in full agreement with that expected when taking into account the diasteromeric purity of the starting material **7b**. Compound **9c** turned out to be of (*R*)-stereochemistry as well. In this case the assignment had been based on the optical rotation of the free

amine of **9c** {$[\alpha]^{24}_D$ = - 6.8°} as the value for this compound (in contrast to that for the hydrochloride) is available in the literature {lit. value[14] for (*S*): $[\alpha]_D$ = + 7.5°}. The stereochemistry of **9a** was determined via its ß-naphthamide by HPLC (on a chiral column) according to a literature procedure[15] for an authentic material. This revealed **9a** to be present in the (*R*)-stereoisomeric form.

Although compound **9d** had been obtained in largely racemic form its optical rotation {$[\alpha]^{23}_D$= + 1.5°} was still sufficient to unequivocally establish its stereochemistry {lit. value[16] for (*R*): $[\alpha]_D$= - 9.6°}. It was found to be (*S*), **9d** being thus homochiral with respect to the former compounds. (The change in the descriptor is a consequence of the CIP-rules.) Of course, the stereochemistry of the precursors is automatically established by the above results.

From the results obtained it becomes clear that the organometallic compounds had consistently added themselves to the *re* face of the transient N-acyliminium ion. Although this does not prove our mechanistic working model of "asymmetric induction by precomplexation" the results described are in full agreement therewith.

EXPERIMENTAL

Melting points (uncorrected): Linström apparatus. - ^{1}H-NMR-spectra: WM 250 (Bruker), AC 300 (Bruker), JNM-GX 400 (Jeol), δ-scale (ppm), TMS int. stand., in several cases coalescence occurred and the signals were broadened and unresolved (unr.) and as a consequence thereof no exact integrals could be obtained. - Mass spectra: MI 25RS (Kratos), MAT-CH7 (Finnigan). - IR-spectra: spectral photometer 1420 (Perkin-Elmer), liquids were run as films, solids as KBr pellets. - Optical rotations: 241 MC polarimeter (Perkin-Elmer). - Combustion analysis: element analyzer 240 B and 240 C (Perkin-Elmer). - Solvents were dried and kept under nitrogen and were freshly distilled before use. Unless otherwise indicated, all reactions were carried out under a nitrogen atmosphere. - Flash chromatography: silicagel 60 (0.040 - 0.063 mm). - HPLC: chromatography pump L-6200 (Merck-Hitachi), UV-VIS detector L-4250, 254 nm (Merck-Hitachi), integrator D-2500 (Merck-Hitachi); LiChroCART^R, LiChrospher^R Si 60 5 µm, HPLC-cartridge (250 x 4 mm) and LiChroCART^R, LiChrospher^R Si 60 5 µm precolumn (4 x 4 mm). - Prep.-HPLC: chromatography pump L-6000, prep. pump head (Merck-Hitachi), UV-Detector L-4000, 254 nm (Merck-Hitachi), integrator D-2500 (Merck-Hitachi), HPLC-column Vertex, LiChrosorb^R Si 60 5 µm (250 x 20 mm), Vertex precolumn, LiChrosorb^R Si 60 5 µm (30 x 20 mm).

(1R,5R)-3,5,8,8-Tetramethyl-2,4-dioxo-3-azabicyclo[3.2.1]octane-1-carboxylic acid **3**

To a solution of 3.905 g (20.0 mmol) of **2**[6] in 30 ml of THF at -95 °C was added 15.0 ml (21.0 mmol) of 1.4 M sec-butyllithium (hexane). After stirring for 5 min at -95 °C, small pieces of dry ice (~ 3 g) were added and the reaction mixture was kept at this temperature for 1 h before quenching with H_2O (~ 3 ml). After having been adjusted to pH ~ 9 with 0.5 N NaOH the aqueous layer (pH ~ 9) was washed several times with Et_2O. Then the aqueous layer was acidified with solid $NaHSO_4$ and extracted with CH_2Cl_2. The combined CH_2Cl_2 layers were dried ($MgSO_4$) and the solvent was evaporated in vacuo. Recrystallization of the residue (4.265 g, 89%) from EtOAc/cyclohexane (5/3) gave **3** as colorless crystals (2.916 g, 59%).
M.p. 204°C, $[\alpha]^{24}_D$ = + 2.1 (c = 1.04, EtOH), $[\alpha]^{20}_{546}$ = - 2.5°, $[\alpha]^{20}_{578}$ = 2.1° (c = 0.93, EtOH). - $C_{12}H_{17}NO_4$ (239.3) calc. C 60.24 H 7.16 N 5.85 found C 60.04 H 7.42 N 5.86 Mol.-mass 239 (ms). - IR: 3150, 3100, 1740, 1710, 1674, 1549 cm^{-1}. - 300 MHz-^{1}H-NMR ($CDCl_3$): 1.01 (s, 3 H, CH_3), 1.13 (s, 3 H, CH_3), 1.24 (s, 3 H, CH_3), 1.85 - 2.00 (m, 2 H, C$\underline{H_2}$CH$_2$), 2.07 (ddd, J = 5/9.4/14.5 Hz, 1 H, HC$\underline{H}$CH$_2$), 2.68 (ddd, J = 6/10.5/14.5 Hz, 1 H, $\underline{H}$CHCH$_2$), 3.13 (s, 3 H, NCH$_3$) 10.77 (s, 1 H, OH).

(1R,5S)-1,3,8,8-Tetramethyl-5-(1,2,3,6-tetrahydro-1-pyridylcarbonyl)-3-azabicyclo[3.2.1]octan-2,4-dione **4**

A quantity of 1.914 g (8.0 mmol) of **3** was refluxed for 90 min in 3.2 ml of thionyl chloride. Then the reagent was evaporated in vacuo and the residue was dissolved in 8.0 ml of CH_2Cl_2. To this solution at 0 °C were added 3.4 ml (24.0 mmol) of NEt_3 and 0.88 ml (9.6 mmol) of 1,2,3,6-tetrahydropyridine. The resulting suspension was stirred at room temp. for 16 h. Then 20 ml of CH_2Cl_2 was added and the organic layer was washed several times with 0.5 N HCl. The CH_2Cl_2 layer was dried ($MgSO_4$) and concentrated. The oily residue was purified by flash chromatography (n-hexane/EtOAc = 7/3) to afford **4** (2.041 g, 84%) as colorless crystals.
M.p. 125°C, $[\alpha]^{20}_{546}$ = + 87.2°, $[\alpha]^{20}_{578}$ = + 76.1° (c = 1.23, EtOH). - $C_{17}H_{24}N_2O_3$ (304.4) calc. C 67.08 H 7.95 N 9.20 found C 66.90 H 8.24 N 9.12 Mol.-mass 304 (ms). - IR: 3032, 1717, 1671, 1628 cm^{-1}. - 250 MHz-^{1}H-NMR (110°C) (toluene-d_8): 1.07 (s, 3 H, CH_3), 1.28 (s, 3 H, CH_3), 1.30 (s, 3 H, CH_3), 1.71 (m, 2 H, CH_2), 2.03 (m, 2 H, CH_2), 2.22 (m, 2 H, CH_2), 3.18 (s, 3 H, NCH_3), 3.29 (m, 1 H, NC$\underline{H_2}$CH$_2$), 3.85-3.96 (m, 2 H, NC$\underline{H_2}$CH$_2$ and NC$\underline{H_2}$CH=C), 4.14 (m, 1 H, NC$\underline{H_2}$CH=C), 5.61 (m, 1 H, CH=H), 5.80 (m, 1 H, CH=H).

(1R,5S)-1,3,8,8-Tetramethyl-5-(1,2,3,4-tetrahydro-1-pyridylcarbonyl)-3-azabicyclo[3.2.1]octan-2,4-dione **5**

A mixture of 609 mg (2.0 mmol) **4**, 30 mg Pd-C (10% Pd) and 2 ml THF/NEt_3 (8/2) was heated at 120 °C for 6 h in a sealed tube. After filtration, the solvent was evaporated under reduced pressure and the residue was purified by flash chromatography (n-hexane/Et_2O = 1/1) to give **5** (563 mg, 92%) as a colorless oil. $[\alpha]^{24}_D$ = + 148.9° (c = 1.20, EtOH), $[\alpha]^{20}_{546}$ = + 188.8°, $[\alpha]^{20}_{578}$ = + 162.5° (c = 1.07, EtOH). - $C_{17}H_{24}N_2O_3$ (304.4) calc. C 67.08 H 7.95 N 9.20 found C 66.97 H 8.21 N 9.00 Mol.-mass 304 (ms). - IR: 1722, 1672, 1635 cm^{-1}. - 250 MHz-^{1}H-NMR (100°C) (toluene-d_8): 1.05 (s, 3 H, CH_3), 1.28 (s, 3 H, CH_3), 1.32 (s, 3 H, CH_3), 1.69 (m, 2 H CH_2), 1.78 (m, 2 H, CH_2), 1.99 (m, 2 H, CH_2), 2.10 (m, 1 H, CH_2), 2.4-2.7 (m, unr., 1 H, CH_2), 3.18 (s, 3 H, NCH_3), 3.35-3.60 (m, unr., 1 H, NCH_2), 3.85-4.10 (m, unr., 1 H, NCH_2), 4.92 (ddd, J = 3.8/4.2/8.4 Hz, 1 H, NC=CH), 6.97 (d, J = 8.4 Hz, 1 H, NCH=C). - 400 MHz-^{1}H-NMR (-20°C) ($CDCl_3$ olefinic protons only): 4.84 (ddd, J = 3.7/4.4/8.5 Hz, 0.22 H, NC=CH), 4.89 (ddd, J = 3.7/4.4/8.5 Hz, 0.5 H, NC=CH), 5.14 (m, 0.17 H, NC=CH), 5.18 (m, 0.11 H, NC=CH), 6.18 (d, J = 8.5 Hz, 0.22 H, NCH=C), 6.49 (d, J = 8.5 Hz, 0.5 H, NCH=C), 6.99 (d, J = 8.1 Hz, 0.17 H, NCH=C), 7.23 (d, J ~ 8 Hz, 0.11 H, NCH=C). - Ratio of rotamers and ring conformers, respectively: ~ 0.11/ 0.17/ 0.22/ 0.5.

Electrophilic α-Amidoalkylation - General Procedure

At - 78°C HCl gas was passed into CH_2Cl_2 (2 ml) and after 20 min a solution of the enamide **5** (0.5 mmol) in CH_2Cl_2 (2 ml) was added dropwise under vigorous stirring. HCl introduction was not interrupted during the addition and continued for 20 min after the addition of **5** was complete. Excess HCl was stripped off in vacuo at - 78°C (60 min) and then a solution of the organometallic reagent (0.55 mmol) was added dropwise. The reaction mixture was stirred for 90 min at - 78°C and finally quenched with H_2O (~ 10 ml). The aqueous layer was extracted several times with CH_2Cl_2 and the combined organic layers were dried ($MgSO_4$) and concentrated. The diastereoselectivity (d.s.) of the reaction was determined by HPLC from the resulting residue. The crude products were purified by flash chromatography (silica gel) to yield a mixture of the diastereomers **7a-d/8a-d**. Pure diastereomers were obtained by prep. HPLC.

(1S,5R)-1-[(R)-2-Ethyl-1-piperidylcarbonyl]-3,5,8,8-tetramethyl-3-azabicyclo[3.2.1]octan-2,4-dione (***R***)-**7a** and *(1S,5R)-1-[(S)-2-Ethyl-1-piperidylcarbonyl]-3,5,8,8-tetramethyl-3-azabicyclo[3.2.1]octan-2,4-dione* (***S***)-**8a**

Obtained by following the above general procedure from 152.2 mg (0.5 mmol) **5** and 600 µl 0.91 M $AlEt_3$ (in n-hexane, 0.55 mmol). Flash chromatography (n-hexane/EtOAc = 85/15) afforded a mixture of **7a/8a** (94.9/5.1, 99.4 mg, 59%). Prep. HPLC (n-hexane/EtOAc = 85/15, 12.0 ml/min) yielded **7a** (86.4 mg, 52%) and **8a** (4.1 mg, 3%).

(***R***)-**7a**: Colorless crystals, m.p. 90-92°C, $[\alpha]^{20}_{546}$ = + 44.9°, $[\alpha]^{20}_{578}$ = + 39.3° (c = 1.01 EtOH). - $C_{19}H_{30}N_2O_3$ (334.4) calc. C 68.23 H 9.04 N 8.38 found C 68.48 H 9.30 N 8.43 Mol.-mass 334 (ms). - IR: 1717, 1674, 1620 cm^{-1}. - 300 MHz-^{1}H-NMR ($CDCl_3$): 0.82 (t, J = 7.3 Hz, 0.55 x 3 H, CH_2CH_3), 0.93 (s, 0.45 x 3 H, CH_3), 0.97 (t, J = 7.4 Hz, 0.45 x 3 H, CH_2CH_3), 1.07 (s, 3 H, CH_3), 1.22 (s, 0.45 x 3 H, CH_3), 1.23 (s, 0.55 x 3 H, CH_3), 1.24 (s, 0.55 x 3 H, CH_3), 1.34-1.43 (m, 1 H, CH_2CH_3), 1.53-1.97 (m, 9.54 H, CH_2), 2.29-2.45 (m, 0.55 x 2 H, CH_2), 2.95-3.05 (m, 1.45 H, NCH_2), 3.11 (s, 0.55 x 3 H, NCH_3), 3.15 (s, 0.45 x 3 H, NCH_3), 3.34-3.46 (m, 0.45 H, CH_2), 3.61 (d, J = 12.6Hz, 0.55 H, NCH_2), 4.77 (m, 1 H, NCH). - Ratio of rotamers: ~ 0.45/0.55.

(***S***)-**8a**: Colorless crystals, Mol.-mass 334 (ms). - 300 MHz-^{1}H-NMR ($CDCl_3$): 0.90 (t, J = 7.4 Hz, 0.5 x 3 H, CH_2CH_3), 0.91 (s, 0.5 x 3 H, CH_3), 0.98 (t, J = 7.4 Hz, 0.5 x 3 H, CH_2CH_3), 1.03 (s, 0.5 x 3 H, CH_3), 1.13 (s, 0.5 x 3 H, CH_3), 1.21 (s, 0.5 x 3 H, CH_3), 1.23 (s, 3 H, CH_3), 1.35-2.0 (m, 10.5 H, CH_2), 2.25-2.5 (m, 1 H, CH_2), 3.1 (s, 0.5 x 3 H, NCH_3), 3.15 (s, 0.5 x 3 H, NCH_3), 3.3-3.45 (m, 0.5 H, CH_2), 2.55-2.75, 2.95-3.1, 3.5-3.7, 4.3-4.5, 4.85-4.95 (5 x m, unr., combined 3 H, NCH and NCH_2). - Ratio of rotamers: ~ 0.5/0.5.

d.s. according to HPLC (n-hexane/EtOAc = 9/1, 1.0 ml/min): (***R***)-**7a** (30.1 min)/ (***S***)-**8a** (33.7 min) = 94.9/5.1.

(1R,5S)-1,3,8,8-Tetramethyl-5-[(R)-2-methyl-1-piperidylcarbonyl]-3-azabicyclo[3.2.1]octan-2,4-dione (***R***)-**7b** and *(1R,5S)-1,3,8,8-Tetramethyl-5-[(S)-2-methyl-1-piperidylcarbonyl]-3-azabicyclo[3.2.1]octan-2,4-dione* (***S***)-**8b**

Obtained by following the above general procedure from 304.4 mg (1.0 mmol) **5** and 1.22 ml 1.03 M $AlMe_3/Et_2O$ (5.0 equ.) (in n-hexane, 1.25 mmol). Flash chromatography (n-hexane/EtOAc = 85/15) afforded a mixture of **7b/8b** (83.5/16.5, 198.9 mg, 62%). Prep. HPLC (n-hexane/EtOAc = 80/20, 10.5 ml/min) yielded **7b** (153.8 mg, 48%) and **8b** (29.7 mg, 9%).

(***R***)-**7b**: Colorless crystals, m.p. 113-114°C, $[\alpha]^{20}_{546}$ = + 6.2°, $[\alpha]^{20}_{578}$ = + 5.6° (c = 0.77, EtOH). - $C_{18}H_{28}N_2O_3$ (320.4) calc. C 67.47 H 8.81 N 8.74 found C 67.58 H 9.09 N 8.84 Mol.-mass 320 (ms). - IR: 1719, 1672, 1628 cm^{-1}. - 300 MHz-^{1}H-NMR ($CDCl_3$): 0.92 (s, 0.5 x 3 H, CH_3) 1.07 (s, 0.5 x 3 H, CH_3), 1.08 (s, 0.5 x 3 H, CH_3), 1.15-1.3 (several singlets and doublets superimposed, combined 8.5 H, CH_3 and $NCHCH_3$ and CH_2), 1.5-2.0 (m, 7.5 H, CH_2), 2.15-2.45 (m, unr., 0.5 x 2 H, CH_2), 3.10 (s, 0.5 x 3 H, NCH_3), 3.14 (s, 0.5 x 3 H, NCH_3), 3.3-3.45 (m, 0.5 H, CH_2), 2.95-3.3, 3.5-3.7, 4.85-5.1 (3 x m, unr., comb. 3 H, NCH NCH_2).- Ratio of rotamers: ~ 0.5/0.5.

(***S***)-**8b**: Colorless crystals, Mol.-mass 320 (ms). - 300 MHz-^{1}H-NMR ($CDCl_3$): 0.87-1.27 (several singlets and doublets superimposed, combined 12 H, CH_3 and $NCHCH_3$), 1.4-2.05 (m, 8.5 H, CH_2), 2.36 (m, unr., 1 H, CH_2), 3.09 (s, 0.5 x 3 H, NCH_3), 3.15 (s, 0.5 x 3 H, NCH_3), 3.35-3.45 (m, 0.5 H, CH_2), 2.69, 3.0-3.2, 3.56, 4.02,

4.3-4.45, 4.62, 5.13 (7 x m, unr., comb. 3 H, NCH NCH_2). - Ratio of rotamers: ~ 0.5/0.5.
d.s. according to HPLC (n-hexane/EtOAc = 9/1, 1.25 ml/min): **(*S*)-8b** (44.2 min)/**(*R*)-7b** (52.1 min) = 16.5/83.5.

(1S,5R)-1-[(R)-2-Butyl-1-piperidylcarbonyl]-3,5,8,8-tetramethyl-3-azabicyclo[3.2.1]octan-2,4-dione **(*R*)-7c** and *(1S,5R)-1-[(S)-2-Butyl-1-piperidylcarbonyl]-3,5,8,8-tetramethyl-3-azabicyclo[3.2.1]octan-2,4-dione* **(*S*)-8c**

Obtained by following the above general procedure from 152.2 mg (0.5 mmol) **5** and 1.56 ml 0.4 M Al(n-Bu)$_3$ (in pentane/hexane = 3/1, 0.625 mmol). Flash chromatography (n-hexane/EtOAc = 85/15) afforded a mixture of **7c/8c** (96.5/3.5, 104.6 mg, 58%). Prep. HPLC (n-hexane/EtOAc = 85/15, 10.5 ml/min) yielded **7c** (94.2 mg, 52%) and **8c** (3.1 mg, 2%).
(*R*)-7c: Colorless crystals, m.p. 90-91°C, $[\alpha]^{20}_{546}$ = + 53.6, $[\alpha]^{20}_{578}$ = + 45.2, (c = 0.465, EtOH). - $C_{21}H_{34}N_2O_3$ (362.5) calc. C 69.58 H 9.45 N 7.73 found C 69.77 H 9.69 N. 7.76 Mol.-mass 362 (ms). - IR: 1721, 1674, 1628 cm^{-1}. - 300 MHz-^{1}H-NMR ($CDCl_3$): 0.87 (t, J = 7.2 Hz, 0.55 x 3 H, CH_2CH_3), 0.91 (t, J = 7.2 Hz, 0.45 x 3 H, CH_2CH_3), 0.92 (s, 0.45 x 3 H, CH_3), 1.07 (s, 3 H, CH_3), 1.22 (s, 0.45 x 3 H, CH_3), 1.23 (s, 0.55 x 3 H, CH_3), 1.24 (s, 0.55 x 3 H, CH_3) 1.14-1.45 (m, 5 H, CH_2), 1.50-2.00 (m, 9.55 H, CH_2), 2.27 (ddd, J = 5.0/10.6/14.0 Hz, 0.55 H, CH_2CH_2, chiral auxiliary), 2.40 (ddd, J = 5.9/9.5/14.0 Hz, 0.55 H, CH_2CH_2, chiral auxiliary), 2.96-3.06 (m, 1.45 H, NCH_2), 3.11 (s, 0.55 x 3 H, NCH_3), 3.15 (s, 0.45 x 3 H, NCH_3), 3.34-3.46 (m, 0.45 H, CH_2), 3.60 (d, J = 12.4 Hz, 0.55 H, NCH_2), 4.81 (m, 1 H, NCH). - Ratio of rotamers: ~ 0.45/0.55.
(*S*)-8c:Colorless oil, Mol.-mass 362 (ms). - 300 MHz-^{1}H-NMR ($CDCl_3$): 0.89 (t, J = 7.2 Hz, 0.5 x 3 H, CH_2CH_3), 0.90 (s, 0.5 x 3 H, CH_3), 0.90 (t, partially covered, 0.5 x 3 H, CH_2CH_3), 1.03 (s, 0.5 x 3 H, CH_3), 1.13 (s, 0.5 x 3 H, CH_3), 1.21 (s, 3 H, CH_3), 1.23 (s, 0.5 x 3 H, CH_3), 1.25-2.0 (m, 14.5 H, CH_2), 2.28-2.48 (m, 1 H, CH_2), 3.09 (s, 0.5 x 3 H, NCH_3), 3.15 (s, 0.5 x 3 H, NCH_3), 3.3-3.46 (m, 0.5 H, CH_2), 2.6-2.73, 2.94-3.13, 3.5-3.6, 3.65-3.77, 4.3-4.42, 4.44-4.54, 4.93-5.03 (7 x m, unr., combined 3 H, NCH and NCH_2). - Ratio of rotamers: ~ 0.5/0.5.
d.s. according to HPLC (n-hexane/EtOAc = 9/1, 1.4 ml/min): **(*R*)-7c** (17.6 min)/**(*S*)-8c** (22.2 min) = 96.5/3.5.

(1R,5S)-1,3,8,8-Tetramethyl-5-[(S)-2-phenyl-1-piperidylcarbonyl]-3-azabicyclo[3.2.1]octan-2,4-dione **(*S*)-7d** and *(1R,5S)-1,3,8,8-Tetramethyl-5-[(R)-2-phenyl-1-piperidylcarbonyl]-3-azabicyclo[3.2.1]octan-2,4-dione* **(*R*)-8d**

Obtained by following the above general procedure from 152.4 mg (0.5 mmol) **5** and 4.808 ml (0.625 mmol) of a organozinc reagent generated by treating 1.5 ml 1 M PhMgBr (in THF, 1.5 mmol) in 4.5 ml THF at room temp. with 0.9 ml 1 M $ZnCl_2$ (in Et_2O, 0.9 mmol). Flash chromatography (n-hexane/EtOAc = 80/20) afforded a mixture of **7d/8d** (90.5/9.5) contaminated with ~ 5% **5** (90.5/9.5) (116.2 mg, 61%). Prep. HPLC (n-hexane/EtOAc = 85/15, 10.5 ml/min) yielded **7d** (94.9 mg, 50%) and **8d** (9.7 mg, 5%).
(*S*)-7d: Colorless crystals, m.p. 153-155 °C, $[\alpha]^{20}_{546}$ = - 25.4°, $[\alpha]^{20}_{578}$ = - 22.1° (c = 0.55, EtOH). - $C_{23}H_{30}N_2O_3$ (382.5) calc. C 72.22 H 7.91 N 7.32 found C 72.02 H 7.73 N 7.61 Mol.-mass 382 (ms). - IR: 3050, 1720, 1670, 1625 cm^{-1}. - 300 MHz-^{1}H-NMR ($CDCl_3$): 0.99, 1.14, 1.16, 1.25, 1.26, 1.28 (6 x s, combined 9 H, CH_3), 1.4-1.75 (m, 4 H, CH_2), 1.77-2.13 (m, 3.45 H, CH_2), 2.36-2.56 (m, 2 H, CH_2), 2.92 (dt, J = 2/12 Hz, 0.55 H, NCH_2), 3.07-3.17 (m, covered by NCH_3 signal, 0.45 H, NCH_2), 3.13 (s, 0.45 x 3 H, NCH_3), 3.20 (s, 0.55 x 3 H, NCH_3), 3.25 (d, J = 12 Hz, 0.55 H, NCH_2), 3.4-3.55 (m, 0.55 H, CH_2), 3.67 (d, J= 12 Hz, 0.45 H, NCH_2), 6.00 (s, 0.45 H, NCH), 6.10 (s, 0.55 H, NCH), 7.18-7.26 (m, 2 H, C_6H_5), 7.33-7.42 (m, 2 H, C_6H_5), 7.48 (d, 8 Hz, 1 H, C_6H_5). - Ratio of rotamers: ~ 0.45/0.55.
(*R*)-8d: Colorless crystals, Mol.-mass 382 (ms). - 300 MHz-^{1}H-NMR ($CDCl_3$): 1.03-1.28 (several signals superimposed, combined 9 H, CH_3), 1.44-2.13 (m, 7.5 H, CH_2), 2.17-2.55 (m, 2 H, CH_2), 3.12, 3.15, 3.17 (3 x s, combined 3 H, NCH_3), 3.37-3.52 (m, 0.5 H, CH_2), 2.69-2.82, 2.89-3.0, 3.02-3.25, 3.6-3.73, 4.46-4.56 (5 x m, combined 2 H, NCH_2), 5.11, 5.79, 6.13 (3 x s, comb. 1 H, NCH), 7.2-7.47 (m, 5 H, C_6H_5). - Ratio of rotamers: ~ 0.5/0.5.
d.s. according to HPLC (n-hexane/EtOAc = 9/1, 1.25 ml/min): **(*R*)-8d** (32.7 min)/**(*S*)-7d** (37.0 min) = 9.6/90.4.

Reductive Cleavage of the Amide Bond - General Procedure

To a solution of 1.0 mmol of **7a-c/8a-c** in 5 ml of THF at room temp. was added 1.5 ml (1.5 mmol) of 1.0 M $LiAlH_4$ (THF). After stirring for 6 h at room temp. the reaction was quenched with 5 ml H_2O. The aqueous layer was acidified with dilute HCl and washed several times with Et_2O. Then conc. NaOH was added and the alkaline aqueous layer was extracted several times with Et_2O. The combined organic layers from the alkaline extractions were concentrated after dropwise addition of 1 ml 12 N HCl. The resulting crystalline residue was extracted with 20 ml CH_2Cl_2 and subsequent filtration and evaporation of the solvent yielded the hydrochlorides **9a-c**. Recrystallisation gave the pure hydrochlorides **9a-c**.

(R)-2-Ethylpiperidinium chloride **(*R*)-9a**

a) Obtained by following the above general procedure from 84.5 mg (0.253 mmol) **7a/8a** (97.2/2.8). Recrystallization from EtOH yielded 28.2 mg (75%) **9a**. Colorless needles, m.p. 180-182°C, (lit.[17]: 181-182°C), $[\alpha]^{23}_D$ = + 3.86°, (c = 1.06, EtOH). b) Obtained in analogy to the synthesis of **(*S*)-9d** by heating **(*R*)-9a** (104 mg, 0.31 mmol) in 3 ml 3 M KOH (in $CH_3OCH_2CH_2OH$) at 160°C for 7 days.

(R)-2-Methylpiperidinium chloride **(*R*)-9b**

Obtained by following the above general procedure from 94.7 mg (0.295 mmol) **7b/8b** (83.5/16.5). Recrys-

tallization from EtOH yielded 32.2 mg (81%) **9b**.
Colorless needles, m.p. 188- 190°C, (lit.[18]: 190°C), $[\alpha]^{23}_D$ = + 2.53°, (c = 1.12, EtOH); lit.[13]: (*S*)-2-methylpiperidine-HCl: $[\alpha]^{15}_D$ = - 4.2°, (c = 6.9, EtOH).

(R)-2-Butylpiperidinium chloride (*R*)-**9c**

Obtained by following the above general procedure from 72.5 mg (0.2 mmol) **7c/8c** (96.5/3.5). Recrystallization from EtOH yielded 27.9 mg (79%) **9c**.
Colorless needles, m.p. 178-180°C, (lit.[19]: racemic compound: 181-182°C), $[\alpha]^{23}_D$ = + 4.0, (c = 0.365, EtOH), free base: $[\alpha]^{24}_D$ = - 6.8 (c = 0.33, EtOH 95%); lit.[14]: (*S*)-2-n-butylpiperidine: $[\alpha]_D$ = +7.5° (c = 0.2 - 2.0, EtOH 95%).

(S)-2-Phenylpiperidinium chloride (*S*)-**9d**

A total of 153 mg (0.4 mmol) of **7d/8d** (91/9) in 4 ml 3 M KOH ($MeOCH_2CH_2OH$) was heated in a steel tube at 175°C for 7 days . The aqueous layer was adjusted to pH ~ 2 by addition of dilute HCl and finally washed several times with Et_2O. Then conc. NaOH was added and the alkaline aqueous layer was extracted with Et_2O a few times. After dropwise addition of 0.5 ml 12 N HCl the combined organic layers from the alkaline extraction were concentrated. The resulting crystalline residue was extracted with 10 ml CH_2Cl_2 and subsequent filtration and evaporation of the solvent yielded the hydrochloride **9d** (60.3 mg, 76%).
Colorless crystals, m.p. 192-193°C, (lit.[16]: 194-195°C), $[\alpha]^{23}_D$ = + 1.5° (c = 1.675, MeOH); lit.[16]: (*R*)-2-phenylpiperidine-HCl: $[\alpha]_D$ = -9.6° (MeOH).

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

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(*Received in Germany* 22 *July* 1993; *accepted* 11 *January* 1994)