Asymmetric Electrophilic α-Amidoalkylation, VII[1]:

Generation, Crystal Structure, and Trapping Reactions of a Chiral 6,7-Dimethoxy-1,2,3,4-tetrahydroisoquinoline Derived N-Acyliminium Ion

Klaus Th. Wanner[a] *, Ilona Praschak[a], and Ulrich Nagel[b]

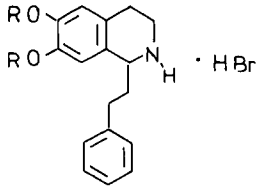
a) Institut für Pharmazie und Lebensmittelchemie der Universität München, Sophienstr. 10, 8000 München 2
b) Institut für Anorganische Chemie der Universität München, Meiserstr. 1, 8000 München 2

Received May 8, 1989

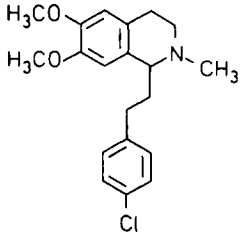
The camphanic acid amide **4** has efficiently been oxidized with triphenylcarbenium tetrafluoroborate (**3**) to yield the chiral N-acyliminium ion **1**. Trapping reactions of **1** with the silyl nucleophiles **7a-c** and **10a-f** proceeded with stereoselective bond formation, affording the diastereomers (R)-**8**/(S)-**9a-c** and (R)-**11**/(S)-**12a-f**, respectively, with diastereoselectivities of up to 93.9/6.1.
The amido ketones (R)-**8**/(S)-**9a-c** were employed in the synthesis of the secondary amines (R)-**16a-c**, (S)-**16a** and for the preparation of (-)-homolaudanosine (R)-**18**.
By X-ray crystallography the conformation of **1** in the crystal lattice was established and the preferred conformation of **1** in solution was elucidated by NOE experiments. Finally, the addition reaction of **7a** to the iminium ion **21** derived from menthyl carbamate **20** was investigated, which reaction, however, proceeded only with insignificant asymmetric induction.

Asymmetrische Elektrophile α-Amidoalkylierung, 7. Mitt.[1]: Erzeugung, Kristallstruktur und Abfangreaktionen eines chiralen von 6,7-Dimethoxy-1,2,3,4-tetrahydroisochinolin abgeleiteten N-Acyliminiumions

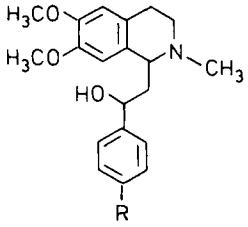
Aus dem Camphansäureamid **4** ließ sich durch Oxidation mit Triphenylcarbeniumtetrafluoroborat (**3**) sehr effizient das chirale N-Acyliminiumion **1** herstellen. Abfangreaktionen von **1** mit den Silylderivaten **7a-c** und **10a-f** verliefen stereoselektiv, die Diastereomeren (R)-**8**/(S)-**9a-c** bzw. (R)-**11**/(S)-**12a-f** wurden mit Diastereoselektivitäten bis zu 93.9/6.1 erhalten. Die Amidoketone (R)-**8**/(S)-**9a-c** wurden zur Synthese der sekundären Amine (R)-**16a-c**, (S)-**16a** und für die Darstellung von Homolaudanosin (R)-**18** herangezogen. Die Konformation von **1** im Kristallgitter wurde durch Röntgenstrukturanalyse bestimmt, und NOE-Experimente gestatteten Rückschlüsse auf die in Lösung vorherrschende Konformation. - Schließlich wurde noch die Additionsreaktion von **7a** an das Iminiumion **21**, das sich vom Menthylcarbamat **20** ableitet, untersucht, die jedoch ohne nennenswerte asymmetrische Induktion verlief.



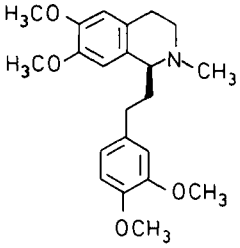
Ia R = H
Ib R = $COCH_3$



II



III R = Cl, NO_2



IV

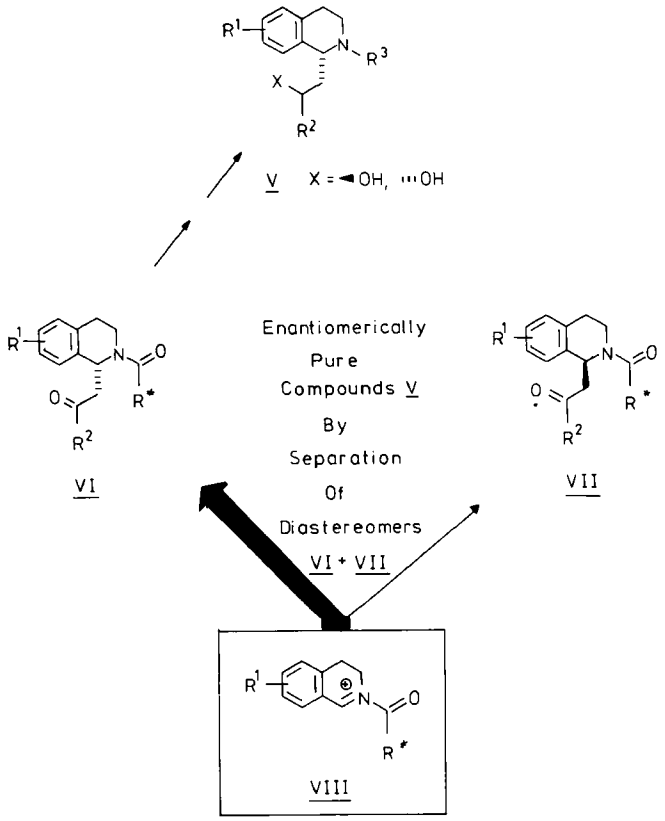
About 50 years ago some patents of the German Tropon-Werke[2] directed to the preparation of certain 1-arylalkyl substituted tetrahydroisoquinolines, such as, e.g. **Ia** and **Ib**, were published. This class of compounds attracted attention mainly since members thereof had been found to be analgetically active.

Two decades later a research group at Hoffmann-La Roche, stimulated by that results, developed a series of most interesting synthetic isoquinoline analgetics[3]. A typical representative is methopholine (**II**). From animal experiments with methopholine and related compounds it could be concluded that only the respective R-enantiomer is analgetically active. Furthermore, the Swiss group synthesized several analgetics which were far more active than methopholine, for example the aminoalcohols **III** that turned out, however, to be very addictive. It was shown that the analgetic activity strongly depends on the relative configuration of the two chiral centers in **III** (by a factor of 10 or more), although their relative configuration was not determined. Studies concerning the optically active isomers of **III** were not included either[3], the question as to the stereochemical requirements for the analgetic activity of compounds **III** so remaining unsettled.

Therefore, we launched a project which we expected to provide a general access to enantiomerically pure tetrahydroisoquinolines with a chiral center in position 1. In addition to the analgetically active compounds mentioned above some structurally closely related, naturally occuring substances, the phenethylisoquinoline alkaloids[4] caused our interest in this project. Recently isolated homolaudanosine[5]

 ©VCH Verlagsgesellschaft mbH, D-6940 Weinheim, 1990 0365-6233/90/0606-0335 $ 02.50/0

IV is a typical representative of those alkaloids. Therefore, it appeared very tempting to us to develop a new route to this type of compounds in enantiomerically pure form[6].



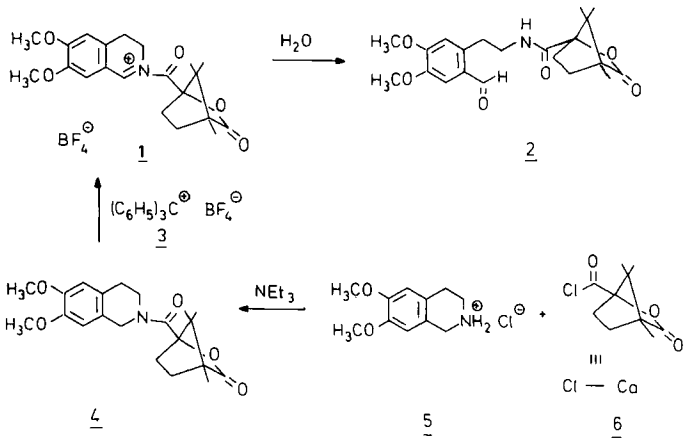
The Asymmetric Electrophilic α-Amidoalkylation (AEαA) is a general concept we have developed for the preparation of enantiomerically pure secondary amines with a chiral center in α position with respect to nitrogen and that we have already employed in the synthesis of pyrrolidines[7] and piperidines[8]. Electrophilic α-amidoalkylation involves the linkage of an amido alkyl group to another molecule via the α-carbon atom of an intermediate N-acyliminium ion (the electrophile). The key step of the AEαA is the diastereoselective trapping reaction of an acyliminium ion (e.g. **VIII**) by a nucleophile as outlined for isoquinolines in Scheme 2 (**VIII** → **VI** + **VII**), wherein a chiral acyl group (R^xCO) gives rise to the asymmetric induction. As a result one diastereomer should prevail. Provided a suitable nucleophile has been employed that diastereomer may be an α-amidoketone, e.g. **VI**. Eventually amines **V** (X=H) or aminoalkohols **V** (X=OH) can be obtained from **VI** by simple reduction and subsequent removal of the chiral auxiliary R^xCO. It should be stressed that this sequence reliably affords the final product in enantiomerically pure form if **VI** is employed in the form of a single diastereomer. That diastereomer can be obtained by conventional methods such as chromatography and crystallisation.

In this paper we wish to report in detail[9] the successfull implementation of the above concept in the synthesis of 1-phenyl-ethylamines V (X=H, R^2=Ar).

Generation of N-Camphanoyl-3,4-dihydroisoquinolinium Ion 1

We chose (-)-camphanic acid as chiral auxiliary since it can be regarded as configurationally stable. Considering the substitution of the analgesics mentioned above it appeared attractive to generate the acyliminium ion **1**.

For this purpose, amide **4** was prepared from the tetrahydro isoquinolinium chloride **5** and (-)-camphanic acid chloride (**6**) in 90.4% yield. A method frequently used for the conversion of tertiary amides to acyliminium ions involves the preparation of α-methoxyamides as synthetic intermediates by means of electrochemical oxidation[10]. Therefore, we subjected **4** dissolved in CH_3OH in the presence of the electrolyte $(CH_3)_4N^+BF_4^-$ to anodic oxidation. In this oxidation the starting material **4** was completely consumed within a few h but no defined product could be detected (TLC). Next we focused our attention on oxidations of amides by means of organic compounds.



As oxidation of a structurally related amide (amide nitrogen in benzylic position) with 2,3-dichloro-4,5-dicyano-p-benzoquinone[11] (DDQ) had been reported we treated **4** with DDQ as well (CH_2Cl_2, -78°C, 3 d). Indeed, upon aqueous work-up aldehyde **2** could be isolated in about 20% yield. The formation of **2** indicates that the acyliminium ion **1** had been formed, which upon addition of water underwent ring opening to give **2**. Finally we found that by using triphenylcarbenium tetrafluoroborate[12] (**3**) a complete and clean oxidation of **4** can be effected within 16 h, subsequent hydrolysis again leading to **2** (26.1% of pure material; the low yield is due to incomplete separation of **2** from a minor side product).

At the concentrations we usually employed in this oxidation reaction always a yellow precipitate occurred with increasing reaction time. As we assumed this precipitate to be the iminium ion **1**, it was subjected after recrystallisation to a single crystal X-ray analysis which unequivocally confirmed our assumption (for details on the X-ray analysis see below).

A series of trapping reactions of **1** with different nucleophiles is described below. For this purpose the crude reaction mixture resulting from the oxidation of **4** with **3** was used after having dissolved the precipitate by addition of some extra solvent.

Trapping Reactions of N-Camphanoyl-3,4-dihydroisoquinolinium Ion 1

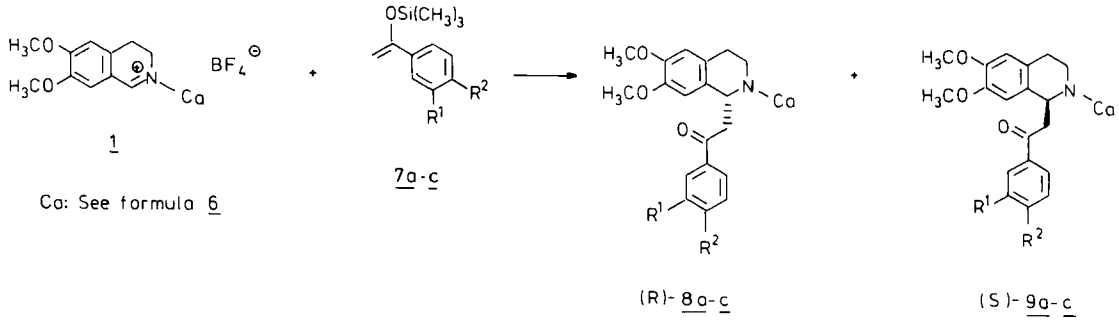


Table 1: Trapping reactions of N-camphanoyl-3,4-dihydroisoquinolinium ion **1** with silyl enol ethers **7a-c**.

	Silyl Enol Ether						Product	Yield [%]	(R)-8	Ratio	(S)-9
		R^1	R^2	equ.-$TiCl_4$	T [°C]	t [h]		(R)-8+(S)-9	δ_{H-1} [ppm][a]	(R)-8/(S)-9	δ_{H-1} [ppm][a]
1	**7a**	H	H	-	-78	2	**8a/9a**	-	6.03	79.7/20.3	6.17
2	"	"	"	-	-90	2	"	97.2	-	82.4/17.6	-
3	"	"	"	0.5	-78	2	"	-	-	80.2/19.8	-
4	"	"	"	1.0	-78	2	"	-	-	87.6/12.4	-
5	"	"	"	1.0	-93	3.5	"	-	-	88.8/11.2	-
6	"	"	"	1.5	-78	1.5	"	-	-	88.4/11.6	-
7	"	"	"	2.0	-78	3	"	-	-	90.3/ 9.7	-
8	"	"	"	2.5	-78	2	"	77.8	-	91.2/ 8.8[b]	-
9	"	"	"	3.0	-78	1.66	"	-	-	88.0/12.0	-
10	"	"	"	3.5	-78	2	"	-	-	86.5/13.5	-
11	**7b**	H	Cl	-	-78	18	**8b/9b**	98.9	5.98	85.2/14.8	6.12
12	"	"	"	2.5	-78	2	"	84.4	-	93.9/ 6.1	-
13	**7c**	OCH_3	OCH_3	-	-78	20	**8c/9c**	96.8	6.00	82.4/17.6	6.14

a) Signal of the major conformer recorded at 400 MHz.
b) The same experiment carried out on a larger scale resulted in a 91.9/8.1-ratio.

It is well known that acyliminium ions add silyl enol ethers to give amido ketones[13]. So does the chiral acyliminium ion **1** but, of course, stereoselectively. When silyl enol ether **7a** derived from acetophenone was added to a solution of **1** in CH_2Cl_2 (prepared without isolation of **1**) at -78°C the diastereomeric amido ketones (R)-**8a** and (S)-**9a** were formed in a quite reasonable 79.7/20.3-ratio (Table 1 entry 1; determined by HPLC). By lowering the temp. to -90°C this ratio slightly increased to 82.4/17.6 (Tabel 1 entry 2). The diastereomers (R)-**8a**/(S)-**9a** were obtained after flash chromatography on silica gel (they are inseparable although various solvents have been tried) in an excellent combined yield of 97.2 % based on amide **4**. The diastereomeric ratios reported for (R)-**8a**/(S)-**9a** were determined (as generally, if not stated otherwise) with the crude product (after aqueous work-up) by HPLC. For (R)-**8a**/(S)-**9a** as for all other diastereomeric mixtures that proved to be inseparable or only incompletely separable on silica gel ((R)-**8a-c**/(S)-**9a-c**, (R)-**11f**/(S)-**12f** a chiral stationary phase was employed. In addition, in the case of (R)-**8a**/(S)-**9a** (as for most of the mixtures inseparable on silica gel) we made use of a preparative chiral column in order to obtain the pure diastereomers in tractable amounts (see Table 1 and 2).

The ^{1}H-NMR-spectra of (R)-**8a** and (S)-**9a** recorded at 400 MHz each showed two sets of signals of different intensity. This phenomenon is well known with amides and is due to two different conformations (*E* and *Z*) caused by hindered rotation around the N-CO bond[14]. From the ^{1}H-NMR-spectra of (R)-**8a**, (S)-**9a** it can unambigously be concluded that these compounds have the constitution shown. The major isomer (R)-**8a** has been assigned R-configuration for the newly created chiral center by chemical conversion (see below). The proton attached to this stereogenic carbon (C-**1** of the isoquinoline nucleus) is very sensitive to its stereochemical environment. In the case of the major isomer, (R)-**8a**, it resonates at distinctly higher field (H-1; δ = 6.03 ppm; signal of the major conformer of the major isomer) as compared to the one of the minor isomer (H-1: δ = 6.17 ppm; major conformer of the minor isomer). This trend was observed for substituted compounds (R)-**8b-c**/(S)-**9b-c** as well (see Table 1).

It occurred to us that it might be possible even to increase the diastereoselectivities observed so far by addition of a *Lewis* acid. Addition of 0.5 equiv. of $TiCl_4$ to **1** prior to the addition of silyl enol ether did not afford a significant effect (compare Table 1, entry 3 to entry 1). However, upon

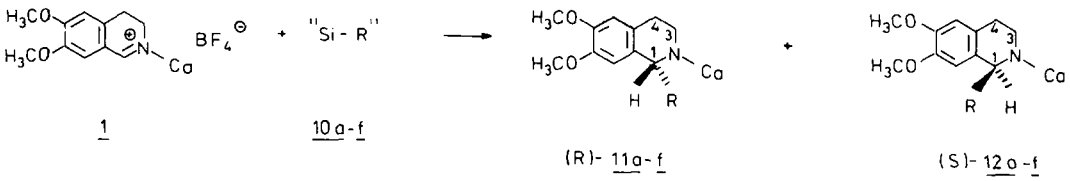
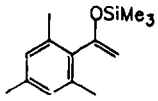
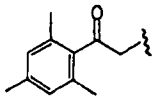
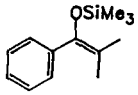
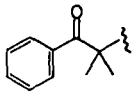
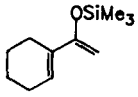
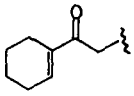
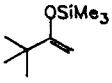
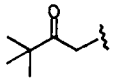
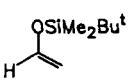
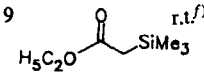
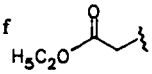


Table 2: Trapping reactions of N-camphanoyl-3,4-dihydroisoquinolinium ion **1** with silicon reagents **10a-f**.

				Product	Yield [%]	(R)-11		Ratio	(S)-12	
Entry	"Si-R"	T [°C]	t [h]	11/12 R	(R)-11+(S)-12	Yield [%] (% de)	$\delta_{H\text{-}1}$ [ppm][a]	(R)-11/(S)-12	Yield [%] (% de)	$\delta_{H\text{-}1}$ [ppm][a]
1	 10a	-78	2	a 	34	10.8 (99.0)	6.13	58.7/41.3[b]	2.9 (96.0)	6.29
2	 10b	-78	2	b 	10	2.6 (>95.5)	6.35	61.1/38.9[b]	2.0 (99.0)	6.44
3	 10c	-95	1	c 	87.2	12.4 (98.1)	5.85	76.0/24.0[c]	2.2 (98.4)	6.02
4	 10d	-78	3	d 	-	-	5.90	80.7/19.3[b]	-	6.04
5	"	-95	3	" "	69.4	30.9	-	84.1/15.9[b]	-	-
6[d]	"	-78	3	" "	-	-	-	82.3/17.7[b]	-	-
7[d]	"	-95	4.5	" "	-	34.9 (>99.5)	-	82.1/17.9[b]	7.6 (85)	-
8	 10e	-19	6	e	39.1	-	5.87	9/1[e]	-	6.06
9	 10f	r.t.[f]	11d	f 	43.7	-	5.87	60.8/39.2[c]	-	6.01

a) Signal of the major conformer recorded at 400 MHz.
b) Determined by HPLC on SiO_2.
c) Determined by HPLC on a chiral stationary phase.
d) Addition of 1 equ. $TiCl_4$ prior to **10 d**.
e) Determined by 400 MHz - ^{1}H-NMR; signals of atropisomers were assigned by spectra taken at different temperatures.
f) Room temperature.

addition of 1.0 equiv. of $TiCl_4$ the diastereoselectivity rose to 87.6/12.4 (Table 1 entry 4).

As lowering the temp. to -93°C (Table 1 entry 5) had no remarkable effect on the diastereoselectivity, the following experiments were carried out at -78°C. With increasing amounts of $TiCl_4$ (in steps of 0.5 equiv.; after addition of 1.5 equiv. $TiCl_4$ the reaction mixture became a suspension) the diastereoselectivity gradually rose (Table 1, entries 6 and 7) until at 2.5 equiv of $TiCl_4$ the optimum (91.2/8.2 Table 1, entry 8) was reached (see also Table 1, entries 9 and 10). As evident from the experiment with 2.5 equiv. of $TiCl_4$ (Table 1, entry 8), the price for the higher selectivity is a decrease in yield (77.8% (R)-**8a** + (S)-**9a** after flash chromatography).

In order to get some information as to the reason for the stereoselectivity increasing effect of the *Lewis* acid, we treated a mixture of (R)-**8a**/(S)-**9a** of known composition (82.4/17.6) with 2.0 equiv. of $TiCl_4$ for 2 h at -78°C. After that time the (R)-**8a**/(S)-**9a** ratio had changed only insignificantly (82.7/17.3). Therefore, it is assumed that the action of the *Lewis* acid results from its influence on the addition step and is not due to the conversion of already formed diastereomers.

The results of the bond forming reactions with silyl enol ether **7b** and **7c** were similar to those obtained with **7a** (see Table 1, entry 11 to 13). For **7c** (Table 1, entry 13) the influence of $TiCl_4$ has not yet been investigated. Besides **7a-c** a variety of different silicon based nucleophiles has been employed in the addition reaction with the acyliminium ion **1**. Results are summarized in Table 2.

To our surprise silyl enol ethers **10a** and **10b** gave only very low diastereoselectivities (Table 2, entries 1 and 2) despite the fact that they are sterically much more demanding than the silyl enol ethers **7a-c** (Table 1). On the other hand, the steric hindrance led to a sharp drop in yield ((R)-**11a** + (S)-**12a**, (R)-**11b** + (S)-**12b**). The addition of silyl enol ether **10c** derived from acetyl cyclohexene again proceeded smoothly, resulting after 1 h at -95°C in a high conversion (according to TLC, the low yield of pure (R)-**11c** is due to incomplete separation) and a satisfactory diastereoselectivity (Table 2, entry 3). By employing silyl enol ether **10d** a (R)-**11d**/(S)-**12d** ratio of 80.7/19.3 and 84.1/15.9, respectively, was achieved (Table 2, entries 4 and 5) as a function of the temp. of the reaction mixture. Addition of one equiv. of $TiCl_4$ increased the ratio of the reaction at -78°C (Table 2, entries 4 and 6), whereas the opposite was true for the experiment at -95°C (Table 2, entries 5 and 7). At present we can not explain these results.

In the trapping reactions of **1**, enol ether **10e** and even more so the silane **10f** proved to be of low reactivity, requiring higher reaction temp. (Table 2, entries 8 and 9). Probably at least in part due to this the diastereoselectivity in case of the addition of **10f** was low (Table 2, entry 9).

The assignment of the absolute configuration of the newly produced stereogenic center to the major and minor diastereomers of the α-amidoalkylation reaction as given in Table 2 requires some comment. This assignment is only tentative since it is merely based on a phenomenon observed with the ^{1}H-NMR-chemical shift of the proton attached to the newly created stereogenic center. In the major isomers the proton at C-1 of the isoquinoline nucleus in each case resonates at higher field than the one of the minor isomer (Table 2; only signals of the major conformers have been considered). The compounds listed in Table 1 behave exactly the same; however, for those compounds the (R)-configuration of the major diastereomers has been established. Taking this into account, it is reasonable to assume that the major diastereomers of the α-amidoalkylation products listed in Table 2 belong to the (R)-series as well.

Structure Determination of N-Acyliminium Ion **1**

To verify the assumed structure of N-acyliminium ion **1**, a single crystal X-ray analysis at -90°C was conducted. The experimental details[15] of the X-ray structural determination are summarized in Table 3; atomic fractional coordinates can be taken from Table 4 and selected bond distances are given in Table 5.

Table 3: Experimental details of the X-ray structural determination of **1**[16].

Formula	$[C_{21}H_{26}NO_5]^+BF_4^- \cdot 1/2\ CH_2Cl_2$
Crystal system	monoclinic
Space group	$P2_1$
a [pm]	947.0 (7)
b [pm]	2 269.9 (9)
c [pm]	1 164.3 (5)
β [°]	111.79 (5)
V [nm^3]	2 324
Z	4 (two crystallographically independent molecules)
d calc [g cm^{-3}]	1.43
u (Mo-Kα) [cm^{-1}]	2.25
Diffractometer	Nicolet P3
Temperature	-90°C
Scan mode	ω, ±1.2°, $4 \leq \omega \leq 30°$ min^{-1}
Measured refl.	10496 (±h ±k ±l)
Independent refl.	7461
Observed refl. ($I > 2\sigma(I)$)	4703
No. of parameters	281
R	0.00771
R_w	0.00784

Two crystallographically independent pairs of molecules of **1** beside two molecules of CH_2Cl_2 from the recrystallisation solvent are present in the unit cell. A side view of two of these molecules **A** and **B**, one of each pair, is given in Figure 1 [15] (BF_4^--counter ion and CH_2Cl_2 are not shown).

From Figure 1 it is apparent that there is not a tremendous difference between molecules A and B. The conformation of the (C=O)-(N=C)- subunit is close to antiperiplanar, the torsion angles being -176.1° for **A** (C11-N1-C10-03) and -169.8° for **B** (C32-N2-C31-08) and this is among the most interesting findings. The carbonyl group is almost eclipsed with the bridging carbon (e.g. C-4 in **A**) of the camphanic

Table 4: Atomic fractional coordinates (x 10^4) and equivalent isotropic thermal parameters (pm^{-2} x 10^{-1}) for **1**

	x	y	z	U
C(1)	-151(9)	3772(4)	2693(7)	23(2)
C(2)	-2679(77)	3644(29)	1656(59)	27(17)
C(3)	-2192(8)	3517(3)	3082(7)	28(2)
C(4)	-598(8)	3238(3)	3314(7)	29(2)
C(5)	-687(80)	2629(33)	2663(63)	48(18)
C(6)	392(11)	3144(5)	4668(8)	49(3)
C(7)	-3323(10)	3181(4)	3472(8)	40(2)
C(8)	-1770(10)	4131(4)	3649(8)	40(2)
C(9)	-358(76)	4292(29)	3456(61)	26(17)
C(10)	1304(9)	3725(3)	2444(7)	29(2)
C(11)	722(10)	4582(4)	1072(7)	28(2)
C(12)	1142(9)	5010(3)	383(7)	29(2)
C(13)	28(33)	5409(12)	-358(23)	24(7)
C(14)	454(10)	5840(4)	-1004(7)	29(2)
C(15)	1986(9)	5871(3)	-923(7)	32(2)
C(16)	3065(9)	5469(3)	-192(7)	30(2)
C(17)	2664(8)	5047(3)	450(6)	27(2)
C(18)	3777(10)	4616(4)	1305(8)	32(2)
C(19)	3032(10)	4041(4)	1355(8)	33(2)
C(20)	-2039(10)	6264(4)	-1755(8)	45(2)
C(21)	3834(11)	6347(5)	-1577(9)	56(3)
O(1)	-3946(23)	3613(9)	907(18)	40(6)
O(2)	-1419(6)	3797(2)	1475(4)	25(1)
O(3)	2281(23)	3350(9)	2949(18)	39(5)
O(4)	-524(7)	6255(3)	-1766(5)	38(2)
O(5)	2264(6)	6302(2)	-1611(5)	42(1)
N(1)	1627(24)	4134(9)	1627(18)	28(5)
C(22)	-4412(9)	6526(4)	3886(7)	26(2)
C(23)	-6027(11)	6668(4)	4880(8)	37(2)
C(24)	-6769(11)	6827(4)	3540(8)	36(2)
C(25)	-5324(8)	7083(3)	3368(7)	28(2)
C(26)	-4705(11)	7637(4)	4124(8)	47(3)
C(27)	-5587(25)	7218(10)	1985(18)	38(6)
C(28)	-8149(10)	7216(4)	3235(8)	52(2)
C(29)	-7017(25)	6229(9)	2851(20)	35(5)
C(30)	-5366(22)	6030(9)	3071(18)	33(5)
C(31)	-2707(23)	6546(9)	4141(17)	29(5)
C(32)	-2078(9)	5648(3)	5431(7)	31(2)
C(33)	-1043(22)	5227(9)	6109(18)	33(5)
C(34)	-1497(23)	4780(8)	6789(16)	28(5)
C(35)	-479(10)	4371(4)	7451(8)	36(2)
C(36)	1018(24)	4365(10)	7428(19)	40(5)
C(37)	1441(16)	4775(5)	6736(11)	33(3)
C(38)	456(14)	5221(6)	6106(11)	27(3)
C(39)	821(10)	5658(4)	5300(7)	31(2)
C(40)	-37(15)	6226(6)	5246(12)	30(3)
C(41)	3481(16)	3898(7)	8138(13)	50(4)
C(42)	-2262(11)	3942(5)	8231(9)	50(3)
O(6)	-6483(10)	6679(4)	5714(8)	41(2)
O(7)	-4588(9)	6461(4)	5089(7)	30(2)
O(8)	-2204(10)	6906(4)	3628(8)	40(2)
O(9)	-756(7)	3941(3)	8160(5)	41(2)
O(10)	1923(10)	3933(4)	8088(8)	40(2)
N(2)	-1662(8)	6129(3)	4938(6)	29(2)
B(1)[a]	2308(4)	665(2)	8424(3)	40(3)
F(1)[a]	3171(4)	1146(1)	8986(3)	76(2)
F(2)[a]	2647(4)	502(2)	7418(3)	57(1)
F(3)[a]	2625(4)	205(1)	9251(3)	64(2)
F(4)[a]	791(3)	806(2)	8043(3)	80(2)
B(2)[a]	4267(1)	4661(1)	4990(1)	31(2)
F(5)[a]	2973(1)	4840(1)	4075(1)	71(2)
F(6)[a]	5359(2)	4566(2)	4519(2)	66(2)
F(7)[a]	4742(3)	5082(1)	5875(2)	75(2)
F(8)[a]	3999(2)	4155(1)	5492(3)	88(2)
Cl(1)[b]	3520(3)	2587(1)	198(2)	57(1)[c]
Cl(2)[b]	389(3)	2573(2)	29(2)	69(1)[c]
C(43)[b]	1614(10)	2487(5)	-800(8)	47(3)

a) Atomic coordinates of BF^4.

b) Atomic coordinates of CH_2Cl_2.

c) Equivalent isotropic U defined as one third of the trace of the orthogonalized U_{ij} tensor.

Table 5: Selected bond distances (pm) of **1**

C(1)-C(4)	154.8(12)	C(1)-C(9)	153.4(72)
C(1)-C(10)	151.4(13)	C(1)-O(2)	148.0(8)
C(2)-C(3)	157.6(66)	C(2)-O(1)	119.6(60)
C(2)-O(2)	133.2(79)	C(3)-C(4)	156.6(11)
C(3)-C(7)	151.5(13)	C(3)-C(8)	153.0(12
C(4)-C(5)	156.4(76)	C(4)-C(6)	152.1(11)
C(8)-C(9)	148.1(80)	C(10)-O(3)	123.4(21)
C(10)-N(1)	144.0(25)	C(11)-C(12)	140.8(12)
C(11)-N(1)	133.4(21)	C(12)-C(13)	141.4(27)
C(12)-C(17)	141.7(12)	C(13)-C(14)	138.2(32)
C(14)-C(15)	142.1(13)	C(14)-O(4)	138.6(9)
C(15)-C(16)	139.8(10)	C(15)-O(5)	134.9(10)
C(16)-C(17)	135.3(12)	C(17)-C(18)	150.9(10)
C(18)-C(19)	149.7(12)	C(19)-N(1)	149.3(27)
C(20)-O(4)	143.9(12)	C(21)-O(5)	147.6(13)
C(22)-C(25)	152.4(11)	C(22)-C(30)	153.1(20)
C(22)-C(31)	153.1(23)	C(22)-O(7)	147.8(13)
C(23)-C(24)	149.8(12)	C(23)-O(6)	120.0(15)
C(23)-O(7)	137.5(13)	C(24)-C(25)	156.7(14)
C(24)-C(28)	150.6(13)	C(24)-C(29)	154.9(23)
C(25)-C(26)	152.2(12)	C(25)-C(27)	156.6(23)
C(29)-C(30)	155.5(31)	C(31)-O(8)	120.7(25)
C(31)-N(2)	143.4(19)	C(32)-C(33)	138.6(20)
C(32)-N(2)	135.8(11)	C(33)-C(34)	144.8(30)
C(33)-C(38)	142.1(27)	C(34)-C(35)	135.3(20)
C(35)-C(36)	142.8(26)	C(35)-O(9)	136.6(12)
C(36)-C(37)	138.4(28)	C(36)-O(10)	134.1(22)
C(37)-C(38)	138.7(17)	C(38)-C(39)	149.2(17)
C(39)-C(40)	151.4(16)	C(40)-N(2)	146.2(15)
C(41)-O(10)	145.6(19)	C(42)-O(9)	145.9(13)
B(1)-F(1)	137.5(5)	B(1)-F(2)	137.5(5)
B(1)-F(3)	137.5(5)	B(1)-F(4)	137.5(5)
B(2)-F(5)	135.4(2)	B(2)-F(6)	135.5(3)
B(2)-F(7)	135.5(2)	B(2)-F(8)	135.4(3)
Cl(1)-C(43)	176.1(9)	Cl(2)-C(43)	177.4(12)

acid residue (see Figure 2, front view on **A**), and the carbon of the iminium subunit (e.g. C-11) is situated on the sterically less demanding face of the chiral auxiliary center, e.g. for **A** between O-2 and C-9.

This raises the question whether the asymmetric induction we had observed in our α-amidoalkylation reactions possibly originates from the above or from a related conformation, with O-2 and C-9 discriminating the two faces of the iminium subunit. However, the conformational preference in a crystal lattice can be distinctly different from that in solution. We expected ^{1}H-NMR-spectroscopy, including NOEDS, to provide some information regarding the preferred conformation of **1** in solution.

First, conventional ^{1}H-NMR-spectra of **1** in CD_2Cl_2 and $CDCl_3$ at room temp. were taken. The ^{1}H-NMR-spectra unfortunately showed not only the signals of **1** but also the signals of an unidentified compound present in minor amounts. The intensities of the signals arising from the unknown compound varied from sample to sample and also increased upon standing at room temp. (in a capped NMR tube). Therefore, in our opinion that compound results from the addition of H_2O to the iminium ion **1**, although we did our best to exclude moisture. The ^{1}H-NMR data for **1** were as expected (e.g.: 9.41 ppm, s, H-1; 7.51 ppm, s, H-8; 2.65 ppm, ddd, H-6'ax; 2.55 ppm, ddd, H-6'eq; the assignment is based on a combination of NOEDS and coupling constants) and did not change significantly upon cooling to -60°C ($CDCl_3$) and -90°C (CD_2Cl_2), respectively.

NOEDS experiments revealed that the axially positioned proton at C-6' (H-6'ax) gives rise to the signal at 2.65 ppm. Irradiation of the methyl groups of the camphanic acid moiety led to an enhancement of the signals at 1.85, 1.98, and 2.55 ppm but did not change the intensity of the signal at 2.65 ppm. By NOEDS experiments it was further found that irradiation of the proton attached to the iminium subunit (H-1) enhances both the signals of H-6'ax (δ = 2.65 ppm) and H-8, and that, conversely, irradiation of H-6'ax results in a clear enhancement of the signal of H-1 whereas the proton at C-3 of the isoquinoline ring remains unaffected.

Therefore, we now assume that in $CDCl_3$ solution a conformation similiar to that observed in the crystal lattice is the prevailing one.

A stereomodel that accounts for the observed asymmetric induction (Table 1) is proposed as given in Figure 4, wherein the CH_2-group facing the oxygen brings forth the stereodifferentiation[17]. In an analogous system with the

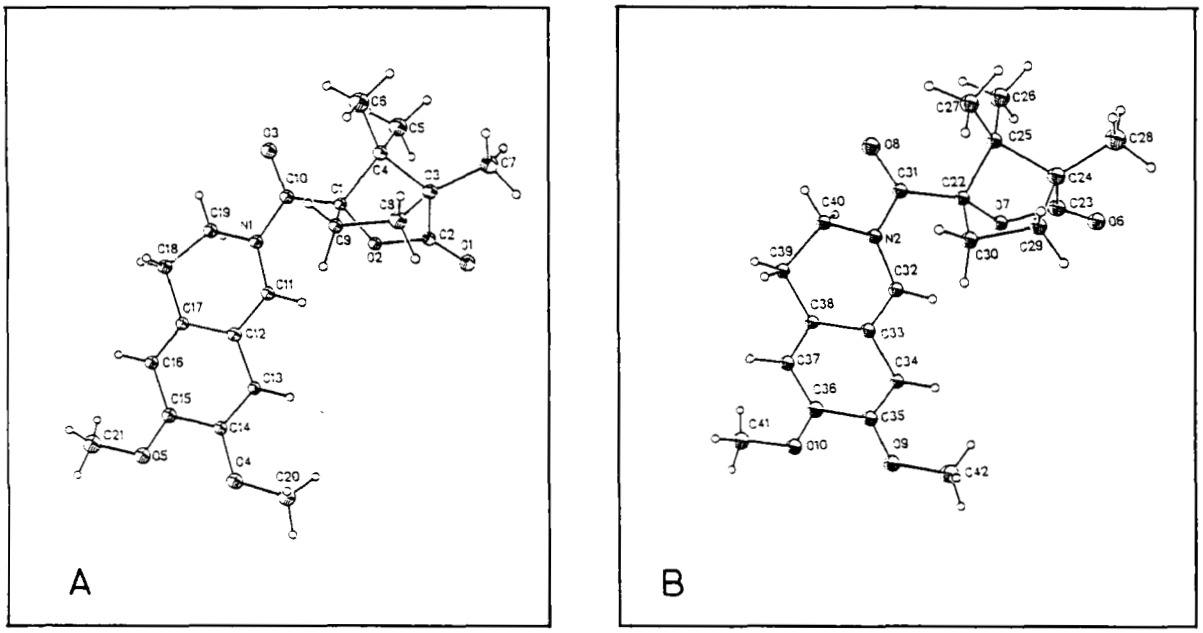


Figure 1: Perspective side view of molecules A and B of **1** (arbitrary atomic numbering, 20% probability of finding).

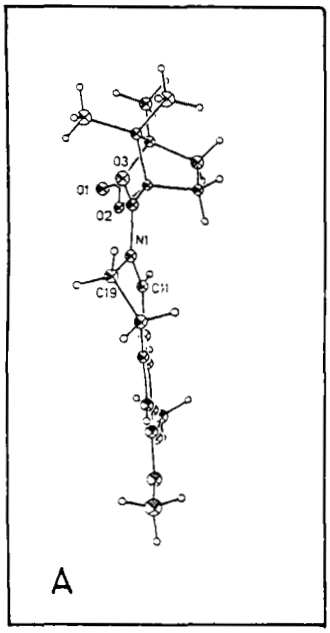


Figure 2: Perspective front view of molecule A of **1** (arbitrary atomic numbering, 20% probability of finding).

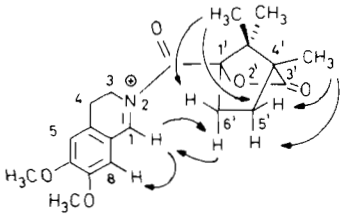


Figure 3: Nuclear Overhauser effects observed for **1**

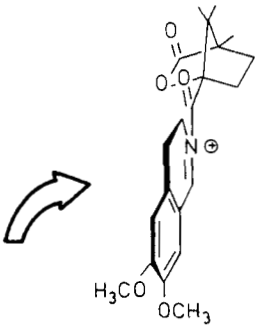
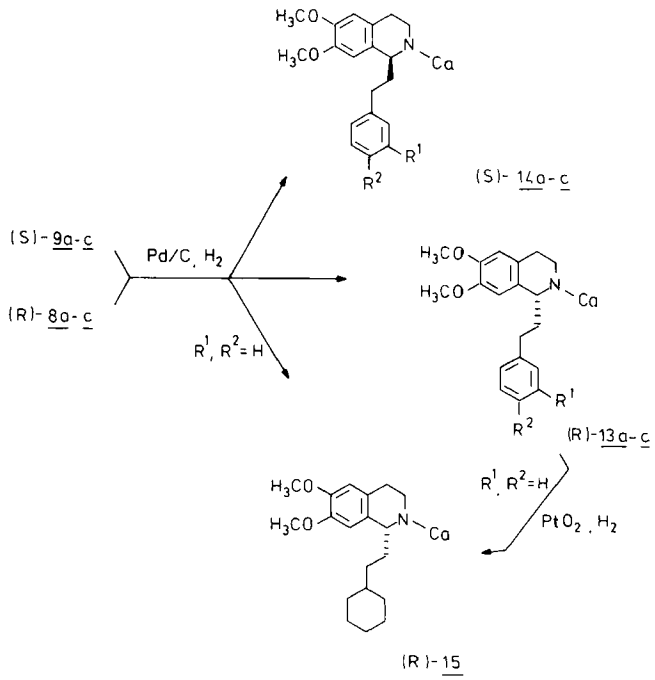


Figure 4: Stereomodel

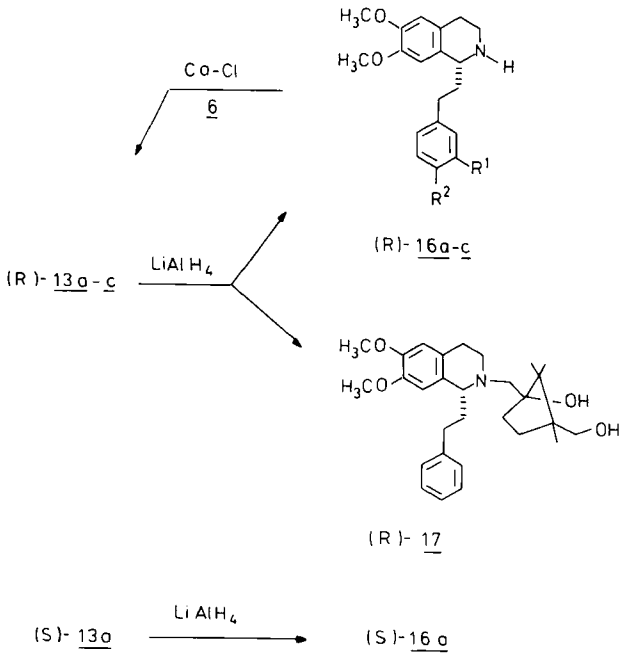
isoquinoline ring replaced by a tetrahydropyridine moiety we have found the opposite direction of asymmetric induction[18] when the reaction was performed with *Lewis* acids like $SnCl_4$ or $TiCl_4$. This is not in conflict with the model presented here, if one assumes that in those cases the *Lewis* acid (after taking up the leaving group $Cl^- \rightarrow$ e.g. $TiCl_5^-$ or $SnCl_5^-$) shields the front face of the piperidine ring by forming a complex with the O-CO-bridge (This has already been proposed by us as a rationale for the asymmetric induction observed for the piperdine system[8]). In **1** the counterion BF_4^- already has its maximum coordination number (in the piperidine system the BF_3Cl^- and $SbCl_6^-$ counterions caused a low but also reversed asymmetric induction[18] - as compared to $TiCl_5^-$ or $SnCl^5$ - that equals the one observed for **1**). Furthermore the iminium ion **1**, in contrast to that piperidine system, also has two methoxy groups available for the complexation of a *Lewis* acid.

1-(2-Phenylethyl)isoquinolines from Asymmetric α-Amidoalkylation Products

The mixtures of diastereomers (R)-**8**/(S)-**9a-c** obtained by the AEαA procedure after flash chromatography were employed in the synthesis of 1-substituted tetrahydroisoquinolines (R)-**16a-c** including the alkaloid homolaudanosine (R)-**18**, as described below. By hydrogenation in acetic acid/1% trifluoroacetic acid using Pd/C (10 % Pd) the amides (R)-**13**/(S)-**14a-c** were formed.



In contrast to the starting ketones, these diastereomers proved to be separable on silica gel. The yields of the major ((R)-**13**) and minor diastereomers ((S)-**14**) are listed in Table 6. As a result of overreduction in the case of the hydrogenation of (R)-**13a**/(S)-**14a** the cyclohexyl derivative (R)-**15** (7%) was isolated. The (R)-configuration of (R)-**15** has been established by hydrogenation of the pure diastereomer (R)-**13a**, which by use of PtO_2 as catalyst yielded (R)-**15** as well. Beside (R)-**15** no other cyclohexane derivatives have been isolated from the above mentioned hydrogenation reactions (of the diastereomeric mixtures), though it is our feeling that such derivatives might have been formed. The ratio of the diastereomers (R)-**13**/(S)-**14a-c** was found to be almost the same as the ratio for (R)-**8**/(S)-**9a-c** (Table 6), except for the compounds with a 4-chlorophenyl substituent (Table 6, entry 2). This might be due to a difference in the rate of a side reaction that occured during the hydrogenation of (R)-**8b**/(S)-**9b**. In addition to the carbonyl oxygen also the chlorine substituent had been eliminated to some extent (36%), and (R)-**13a**/(S)-**14a** were formed as side products. This side reaction also complicated the isolation of the chloro compound (R)-**13b** in pure form.



The next step involved the removal of the chiral auxiliary and was first attempted by means of LiOH in dioxane/H_2O (3/1, sealed tube, ~150°C), although without any noticeable success. Finally we found that amides (R)-**13a-c**, as also demonstrated in a single case ((S)-**13a**) for the (S)-series, can be cleaved by treatment with 2.5-5.0 mol. - equiv. of $LiAlH_4$ in THF (2-3 h, room temp.). The pure amines (R)-**16a-c** and (S)-**16a** were thus obtained in fairly good yields after flash chromatography (see Table 7).

Table 6: Compounds (R)-**13a-c**/(S)-**14a-c** from hydrogenation of (R)-**8a-c**/(S)-**9a-c**

	Substituents		Ratio		(R)-13		(S)-14	
Entry	R^1	R^2	(R)-8/(S)-9	(R)-13/(S)-14	Yield [%][a]	$[\alpha]_{578}$	Yield [%]	$[\alpha]_{578}$
1	a H	H	82.4/17.6	83.3/16.7	59.1	-119.6°	8.7	+121.2°
2	b H	Cl	85.2/14.8	90.1/ 9.9	5.3[b] 51.9[c]	-102.9°	-	-
3	c OCH_3	OCH_3	82.4/17.6	81.5/18.5	37.9	- 83.0°	-	-

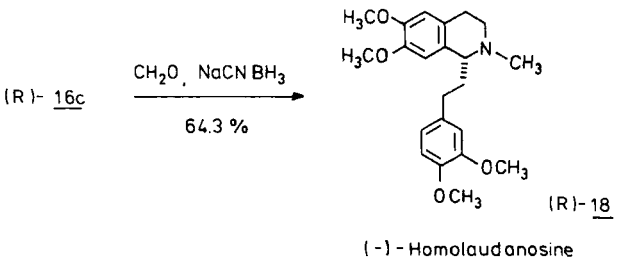
a) Pure compound according to HPLC.
b) Pure compound for analytical purposes only.
c) Hard to separate mixture of (R)-**13a** and (R)-**13b**

Table 7: Secondary amines (R)-**16a-c** and (S)-**16a**

Entry	Start. Comp. No.	Substituents R^1	R^2	Product No.	Yield [%]	$[\alpha]_{578}$
1	(R)-**13a**	H	H	(R)-**16a**	64.7	+25.5
2	(S)-**14a**	"	"	(S)-**16a**	63.0	-22.0
3	(R)-**13b**[a)]	H	Cl	(R)-**16b**	16.1[b)]	+12.4
4	(R)-**13c**	OCH_3	OCH_3	(R)-**16c**	77.0	+15.1

a) Contaminated with ~36% (R)-**13a**.
b) Contamination of starting material has not been taken into account.

This cleavage procedure is not completely devoid of side reactions. When applied to (R)-**13a** besides the secondary amine (R)-**16a** also the tertiary amine (R)-**17** was isolated (30.4%). It must be assumed that similar by-products have formed from (R)-**13b** and (R)-**13c** as well, although we could not isolate them. The lower yield of (R)-**16b** can be blamed on the fact that for convenience a mixture of (R)-**13b** and (R)-**13a** (obtained from hydrogenation, vide supra) had been employed as starting material. (R)-**16b** is an optically active derivative of the analgesic drug methopholine **II**[3)], mentioned in the introduction (methopholine I stands for the racemic compound). Its R-stereochemistry has been established by comparing the optical rotation ($[\alpha]_{578}$ = +12.4°, $[\alpha]_{546}$ = + 11.5°) with lit. values[19)] reported for authentic sample ((R)-**16b**: $[\alpha]_D$ = + 15°) which had been prepared from a precursor obtained by optical resolution. The R configuration of R-**16a** could be deduced from the product distribution that was observed after hydrogenation of (R)-**8b**/(S)-**9b**. Thereby, in addition to (R)-**13b**/(S)-**14b**, a mixture of (R)-**13a**/(S)-**14a** was formed (vide supra) wherein the predominant isomer was the same as in the product obtained directly from (R)-**8a**/(S)-**9a**, as verified by HPLC.



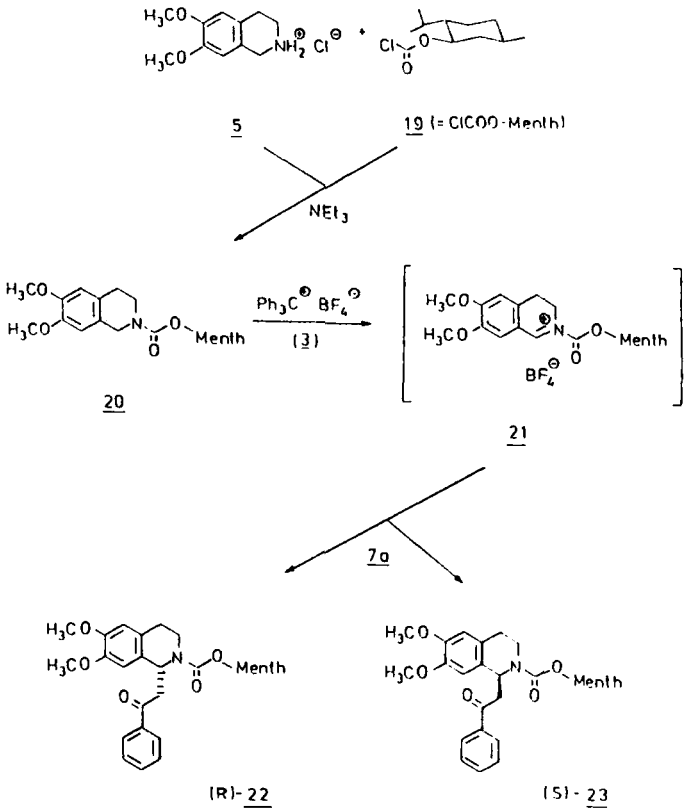
To complete the synthesis of (R)-homolaudanosine ((R)-**18**), (R)-**16c** was subjected to reductive N-methylation with $CH_2O/NaCNBH_3$ which, after aqueous work-up and flash chromatography, afforded (R)-**18** in 64.3% yield.

The optical rotation of the obtained product ($[\alpha]_{578}$ = -13.5°, EtOH), compared to that of the natural enantiomer[5)] ((S): $[\alpha]_D$ = + 11°, EtOH), indicated that our synthesis had resulted in (R)-homolaudanosine. Of course, also the stereochemistry of the precursors - including the α-amidoalkylation products - has been established herewith.

In order to determine the optical purity of the obtained secondary amines, a sample of (R)-**16a** was reconverted into the starting amide by treating it with (-)-camphanic acid chloride (**6**). HPLC revealed (R)-**13a** to be the prevailing compound, accompanied by trace amounts of a side product (<0.4 %) which possibly was (S)-**14a**. Therefore, the optical purity of the amines described herein ((R)-**16a-c**, (S)-**16a** and (R)-**18**) should be higher than at least 99 % (ee).

A Chiral Carbamate Derived Acyliminium Ion

As a logical extension of our work with chiral N-acyliminium ions derived from amides, we have studied the applicability of our concept to carbamate **20**. The synthesis of **20**, starting from the isoquinoline **5** and the chiral chloroformate **19**, was routine (yield 94.0%). When treated with $Ph_3C^+BF_4^-$, carbamate **20** was completely consumed within 16 h (TLC) and from the subsequent reaction with silyl enol ether **7a** (at -78°C) which yielded (R)-**22** and (S)-**23** it became evident that the acyliminium ion **21** had formed.



The diastereomers (R)-**22** and (S)-**23** were isolated in a combined yield of 78% by flash chromatography wherein they proved inseparable on silica gel. HPLC analysis with a chiral stationary phase revealed that the reaction had more or less been devoid of asymmetric induction ((R)-**22**/(S)-**23** ~ 1/1). Therefore, this synthetic sequence appeared unattractive to us and consequently has not been carried on further.

In summary, we have demonstrated that tetrahydroisoquinoline amide **4** can efficiently be oxidized with triphenylcarbenium tetrafluoroborate (**3**), yielding acyliminium ion **1**. Subsequent trapping reactions with silyl nucleophiles proceed with stereoselective bond formation, the resulting addition products being usefull intermediates in the

synthesis of chiral 1-substituted amines of high enantiomeric purity. By means of X-ray and ^{1}H-NMR studies light has been shed upon the conformational preference of acyliminium ion **1**. Currently we are engaged in the synthesis of isoquinoline derived 1,3-amino alcohols by applying the asymmetric α-amidoalkylation methodology presented herein.

We are greatly indebted to Prof. *F. Eiden* for his generous support and to Prof. *W. Beck* for providing the X-ray facilities. We thank Dr. *H. Lerche* for carrying out the NOE-experiments and Mr. *M. Steimann* for his help in performing the X-ray analysis.

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

Experimental Part

General procedures

Standard vacuum techniques were used in the handling of air sensitive materials. - Solvents were dried and kept under N_2 and freshly distilled before use. - Melting points are uncorrected: melting point apparatus according to Dr. *Totolli*. - ^{1}H-NMR spectra: 400 JNM-GX (Jeol), chemical shifts (δ), TMS as internal reference. - Mass spectra: CH 7 (Varian). - IR spectra: Acculab 6 (Beckman) and model 710B (Perkin Elmer). Liquids were run as films, solids as KBr pellets. - Optical rotation: Light electric polarimeter Zeiss, 0.5 dm cell. - Combustion analysis: CHN Rapid (Heraeus). - Column chromatography: Flash Chromatography. - Radial chromatography: Chromatotron (Harrison Research), Si 60. - HPLC: L-6000 pump (Merck Hitachi), UV-Detektor 440, 254 nm (Waters), Refractive Index Detector RID-6A (Shimadzu), Chromato-Integrator D-2000 (Merck Hitachi); Achiral column: LiChroCart^R, LiChroSorb^R Si60 cartridge (250 mm x 4 mm, Merck); precolumn: LiChroCart^R, LiChroSorb^R Si60 precolumn cartridge (25 x 4 mm, Merck). Chiral column: (R)-N-3,5-Dinitrobenzoylphenylglycin covalently bound (250 x 4 mm, Bakerbond^R DNBPG, J.T. Baker Chemicals); precolumn: see above achiral column. Prep. HPLC: HPLC pump 64 (Knauer, prep. head), spectrophotometric detector 8201 (Bischoff), integrator Datamodule (Waters); Achiral column: LiChroSorb^R Si60 7μ (250 x 20 mm, Bischoff); precolumn: LiChroSorb^R Si60 7μ (50 x 20 mm, Bischoff). Chiral column: (R)-N-3,5-Dinitrobenzoylphenylglycin covalently bound (250 x 22 mm, Chiral=Si100D-DNB Phgly, 5μ Serva).

6,7-Dimethoxy-2-[(1S,4R)-4,7,7-trimethyl-3-oxo-2-oxa-1-bicyclo[2.2.1]-heptylcarbonyl]-3,4-dihydroisoquinolinium-tetrafluoroborate (**1**)

To a stirred solution of 0.530 g (1.606 mmol) of **3** in 5 ml of CH_2Cl_2 0.500 g (1.339 mmol) of **4** in 6 ml of CH_2Cl_2 were added. The mixture was stirred overnight and then the yellow precipitate was filtered off under N_2 and recrystallized from CH_2Cl_2. Orange needles. For $C_{21}H_{26}BF_4NO_5$ x 1/3 CH_2Cl_2 (probably due to previous drying the amount of CH_2Cl_2 found by combustion analysis was smaller than that found by X-ray analysis) Calc. C 52.5 H 5.51 N 2.9 Found C 52.7 H 5.71 N 3.1. - 400 MHz - ^{1}H-NMR ($CDCl_3$; numbering according to Figure 3): 0.96 (s, 3H, CH_3), 1.09 (s, 3H, CH_3), 1.18 (s, 3H, CH_3), 1.85 (ddd, J = 4.6/9/13.5 Hz, 1H, H-5'ax), 1.98 (ddd, J = 4.7/10.5/13.5 Hz, 1H, H-5'eq), 2.55 (ddd, J = 4.6/10.5/14.3 Hz, 1H, H-6'eq), 2.65 (ddd, J = 4.7/9/14.3 Hz, 1H, H-6'ax), 3.18-3.35 (m, 2H, H-4), 3.91 (s, 3H, OCH_3), 4.08 (s, 3H, OCH_3), 4.12 (dt, partly obscured, J ~ 6.5/14 Hz, 1H, H-3), 4.31 (ddd, J = 5.5/6.5/14 Hz, 1H, H-3), 6.95 (s, 1H, H-5), 7.51 (s, 1H, H-8), 9.41 (s, 1H, H-1).

(1S,4R)-N-[2-(2-Formyl-4,5-dimethoxyphenyl)ethyl]-1-carbamoyl-4,7,7-trimethyl-2-oxa-bicyclo[2.2.1]heptan-3-one (**2**)

A CH_2Cl_2 suspension of **1**, obtained from 91 mg (0.244 mmol) of **4** as described for **1**, was treated with 2 ml of H_2O. After a few minutes the org. layer was washed with saturated NaCl-solution (3x), dried over $MgSO_4$ and evaporated to dryness under reduced pressure. The residue was purified by CC (n-hexane/ether = 1/9). Colorless crystals, m.p. 129-132°C, yield 24.8 mg (26.1%). - $C_{21}H_{27}NO_6$ (389.4) Calc. C 64.8 H 6.99 N 3.6 Found C 64.8 H 7.02 N 3.5. Mol.mass 389 (MS). - IR: 3400; 1785; 1670; 1600; 1510 cm^{-1}. - 400 MHz - ^{1}H-NMR ($CDCl_3$): 0.83 (s, 3H, CH_3), 1.08 (s, 6H, 2xCH_3), 1.66 (ddd, J ~ 4/9/13 Hz, 1H), 1.80-1.95 (m, 2H), 2.49 (ddd, ~ 4/11/13 Hz, 1H), 3.17 (ddd, J ~ 6/7/14 Hz, 1H), 3.26 (dt, J ~ 13.5/7 Hz, 1H), 3.5-3.63 (m, 2H), 3.92 (s, 3H, OCH_3), 3.94 (s, 3H, OCH_3), 6.67 (t, unresolved, 1H, NH), 6.73 (s, 1H, Ar-H), 7.32 (s, 1H, Ar-H), 10.10 (s, 1H, CHO).

(1S,4R)-1-(6,7-Dimethoxy-1,2,3,4-tetrahydro-2-isoquinolylcarbonyl)-4,7,7-trimethyl-2-oxa-bicyclo[2.2.1]heptan-3-one (**4**)

To a stirred suspension of 3.99 g (17.37 mmol) of **5** in 30 ml of CH_2Cl_2 at 0°C 5.76 ml (41.65 mmol) of NEt_3 were added, followed by 3.0 g (13.88 mmol) of **6**. After 15 min the mixture was allowed to warm to room temp. and stirred for 4 h. The mixture was consecutively washed with 0.05 M HCl (3x) and saturated NaCl-solution (3x) and dried over $MgSO_4$. The solvent was evaporated in vacuo and the residue was purified by CC (n-hexane/ethyl acetate = 6/4). Colorless crystals, m.p. 140-142°C, $[\alpha]_{546}$ = -21.0°, $[\alpha]_{578}$ = - 19.5° (c = 1.39, CH_3OH), yield 4.69 g (90.4 %). - $C_{21}H_{27}NO_5$ (373.5) Calc. C 67.5 H 7.28 N 3.7 Found C 67.8 H 7.20 N 3.6. Mol. mass 373 (MS). - IR: 2960; 1780; 1630; 1510 cm^{-1}. - 400 MHz - ^{1}H-NMR ($CDCl_3$): 0.99 (s, 0.4 x 3H, CH_3), 1.01 (s, 0.6 x 3H, CH_3), 1.11 (s, 3H, CH_3), 1.17 (s, 0.4 x 3H, CH_3), 1.19 (s, 0.6 x 3H, CH_3), 1.73 (ddd, J ~ 4/9/13 Hz, 1H), 1.88-1.98 (m, 1H), 2.00 (ddd, J ~ 4/9/13 Hz, 0.4 x 1H), 2.09 (ddd, J ~ 4/9/13 Hz, 0.6 x 1H), 2.38 (ddd, J ~ 4/11/13 Hz, 0.4 x 1H), 2.44 (ddd, J ~ 4/11/13 Hz, 0.6 x 1H), 2.73-2.79, 2.80-2.97 (2 x m, combined 2H), 3.54 (ddd, J = 4.4/8.5/12.9 Hz, 0.4 x 1H), 3.86, 3.87 (2 x s, combined 6H, 2 x OCH_3), 3.81-3.88 (m, 0.6 x 1H, signal overlapped by two s at 3.86 and 3.87), 4.07-4.14 (m, 1H), 4.58 (d, J ~ 16.9 Hz, 0.6 x 1H, NCH_2Ar), 4.76 (d, J ~ 16.9 Hz, 0.6 x 1H, NCH_2Ar), 4.81 (d, J ~ 16.9 Hz, 0.4 x 1H, NCH_2Ar), 4.92 (d, J ~ 16.9 Hz, 0.4 x 1H, NCH_2Ar), 6.60, 6.61 (2xs, comb. 2H, Ar-H). Ratio of atropisomers ~ 2:3.

*(1S,4R)-1-[(1R)-1,2,3,4-Tetrahydro-6,7-dimethoxy-1-(2-oxo-2-phenyl-1-ethyl)-2-isoquinolylcarbonyl]-4,7,7-trimethyl-2-oxa-bicyclo[2.2.1]heptan-3-one (R)-**8a** and (1S,4R)-1-[(1S)-1,2,3,4-Tetrahydro-6,7-dimethoxy-1-(2-oxo-2-phenyl-1-ethyl)-2-isoquinolylcarbonyl]-4,7,7-trimethyl-2-oxa-bicyclo[2.2.1]heptan-3-one (S)-**9a***

a) To a stirred solution of 2.30 g (6.97 mmol) of triphenylcarbenium tetrafluoroborate (**3**) in 30 ml of CH_2Cl_2 2.17 g (5.81 mmol) of **4** in 30 ml of CH_2Cl_2 were added. The resulting solution was stirred for 16 h at room temp. The yellow precipitate formed was dissolved by addition of 85 ml of CH_2Cl_2 and the solution was cooled to -78°C. A solution of 1.60 ml (14.53 mmol) of $TiCl_4$ in 0.85 ml of CH_2Cl_2 was added dropwise, followed by 1.34 g (6.98 mmol) of **7a** dissolved in 3.55 ml of CH_2Cl_2. The mixture was stirred for 1 h and 45 min at -78°C and then quenched by addition of 40 ml of H_2O. The org. layer was washed with saturated NaCl-solution (3x), dried over $MgSO_4$ and evaporated under reduced pressure. The residue was purified by CC (CH_2Cl_2/Et_2O = 97/3). A colorless solid containing (R)-**8a** and (S)-**9a** was obtained. The ratio of (R)-**8a**/(S)-(**9a**) was determined by HPLC (from the crude product; chiral column, n-hexane/isopropanol = 8/2): Table 1, entry 8. Yield 2.22 g (77.8 %). $C_{29}H_{33}NO_6$ (491.5) Calc. C 70.9 H 6.77 N 2.9 Found C 70.9 H 6.91 N 2.7. Mol. mass 491 (MS). - IR: 1790; 1680; 1640; 1510 cm^{-1}. - Separation of the diastereomers was effected by prep. HPLC (chiral column, n-hexane/isopropanol = 7:3). From a 86 mg sample ((R)-**8a**/(S)-**9a** = 91.2/8.8) 51 mg of (R)-**8a** (59.3 %; de>99.5 %) was obtained.

(R)-**8a**: Colorless crystals, m.p. 90-95°C, $[\alpha]_{546}$ = -165.3°, $[\alpha]_{578}$ = -144.4° (c = 0.72, CH_3OH). - 400 MHz - ^{1}H-NMR ($CDCl_3$): 0.92 (s, 0.7 x 3H, CH_3), 0.94 (s, 0.3 x 3H, CH_3), 1.06 (s, 0.3 x 3H, CH_3), 1.07 (s, 0.7 x 3H, CH_3), 1.12 (s, 0.7 x 3H, CH_3), 1.19 (s, 0.3 x 3H, CH_3), 1.68

(ddd, J ~ 4/9/13 Hz, 0.7 x 1H), 1.75 (ddd, partly obscured, J ~ 4/9/13 Hz, 0.3 x 1H), 1.87 (ddd, J ~ 4/11/13 Hz, 1H), 1.97 (ddd, J ~ 4/9/13 Hz, 0.7 x 1H), 2.05 (ddd, partly obscured, J ~ 4/9/13 Hz, 0.3 x 1H), 2.13 (ddd, J ~ 4/11/13 Hz, 0.7 x 1H), 2.24 (ddd, J ~ 4/11/13 Hz, 0.3 x 1H), 2.74 (dt, J ~ 16/3 Hz, 1H), 2.97-3.05 (m, partly obscured, 0.3 x 1H), 3.08 (ddd, J ~ 5/11/16 Hz, 0.7 x 1H), 3.28 (ddd, J ~ 4/11/12 Hz, 0.3 x 1H), 3.38-3.49 (m, 2H), 3.57 (ddd, J ~ 4/11/13 Hz, 0.7 x 1H), 3.74 (s, 0.3 x 3H, OCH_3), 3.78 (s, 0.7 x 3H, OCH_3), 3.84 (s, 0.3 x 3H, OCH_3), 3.85 (s, 0.7 x 3H, OCH_3), 4.46 (ddd, J ~ 3/5/13 Hz, 0.7 x 1H), 4.57 (ddd, unresolved, 0.3 x 1H), 6.03 (t, J = 6.6 Hz, 1H, NC<u>H</u>Ar), 6.60 (s, 1H, Ar-H), 6.69 (s, 0.7 x 1H, Ar-H), 6.81 (s, 0.3 x 1H, Ar-H), 7.44-7.59 (m, 3H, Ar-H), 7.97-8.00 (m, 2H, Ar-H). Ratio of atropisomers ~ 3/7.

(S)-**9a**: 400 MHz - ^{1}H-NMR ($CDCl_3$): 0.90 (s, 3H, CH_3), 1.07 (s, 3H, CH_3), 1.08 (s, 3H, CH_3), 1.65 (ddd, J ~ 4/9/13 Hz, 1H), 1.88 (ddd, J ~ 4/11/13 Hz, 1H), 1.97 (ddd, J ~ 4/9/13 Hz, 1H), 2.43 (ddd, J ~ 4/11/13 Hz, 1H), 2.78 (dt, J ~ 16/4 Hz, 1H), 2.92 (ddd, J ~ 5/11/16 Hz, 1H), 3.37 (dd, J = 5.6/14.9 Hz, 1H), 3.46 (dd, J = 7.2/14.9 Hz, 1H), 3.70 (ddd, J ~ 4/11/14 Hz, 1H), 3.80 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 4.56 (ddd, J ~ 4/5/14 Hz, 0.8 x 1H, $NC\underline{H}_2CH_2Ar$), 4.66 (ddd, J ~ 3/5/13 Hz, 0.2 x 1H, $NC\underline{H}_2CH_2Ar$), 6.18 (pseudo-t, J ~ 6.5 Hz, 0.8 x 1H, NC<u>H</u>Ar), 6.30 (dd, J ~ 5/7.7 Hz, 0.2 x 1H, NC<u>H</u>Ar), 6.59 (s, 1H, Ar-H), 6.70 (s, 1H, Ar-H), 7.44-7.49 (m, 2H, Ar-H), 7.55-7.59 (m, 1H, Ar-H), 7.96-7.99 (m, 2H, Ar-H). Ratio of atropisomers ~ 2/8.

The following experiments were preformed as described under a).

b) From 1.755 g (5.32 mmol) of **3**, 1.805 g (4.83 mmol) of **4** and 1.116 g (5.80 mmol) of **7a**. No $TiCl_4$, addition of **7a** at -90°C. Yield 2.309 g (97.2 %). Ratio (R)-**8a**/(S)-**9a**: Table 1 entry 2.

c) From 60 mg (0.181 mmol) of **3**, 61 mg (0.164 mmol) of **4** and 38 mg (0.197 mmol) of **7a**. No $TiCl_4$, addition of **7a** at -78°C. Ratio (R)-**8a**/(S)-**9a**: Table 1, entry 1.

d) From 87 mg (0.263 mmol) of **3**, 82 mg (0.219 mmol) of **4**, 21 mg (0.110 mmol) of $TiCl_4$ and 51 mg (0.263 mmol) of **7a**. Ratio (R)-**8a**/(S)-**9a**: Table 1, entry 3.

e) From 90 mg (0.271 mmol) of **3**, 92 mg (0.247 mmol) of **4**, 47 mg (0.247 mmol) of $TiCl_4$, 57 mg (0.296 mmol) of **7a**. Ratio (R)-**8a**/(S)-**9a**: Table 1, entry 4.

f) From 85 mg (0.256 mmol) of **3**, 80 mg (0.214 mmol) of **4**, 41 mg (0.214 mmol) of $TiCl_4$, 49.3 mg (0.256 mmol) of **7a**. Ratio (R)-**8a**/(S)-**9a**: Table 1, entry 5.

g) From 85 mg (0.257 mmol) of **3**, 80 mg (0.214 mmol) of **4**, 61 mg (0.322 mmol) of $TiCl_4$, 50 mg (0.257 mmol) of **7a**. Ratio (R)-**8a**/(S)-**9a**: Table 1, entry 6.

h) From 107 mg (0.325 mmol) of **3**, 101 mg (0.271 mmol) of **4**, 103 mg (0.543 mmol) of $TiCl_4$, 63 mg (0.325 mmol) of **7a**. Ratio (R)-**8a**/(S)-**9a**: Table 1, entry 7.

i) From 87 mg (0.265 mmol) of **3**, 82 mg (0.221 mmol) of **4**, 126 mg (0.662 mmol) of $TiCl_4$, 51 mg (0.265 mmol) of **7a**. Ratio (R)-**8a**/(S)-**9a**: Table 1, entry 9.

j) From 97 mg (0.295 mmol) of **3**, 92 mg (0.246 mmol) of **4**, 163 mg (0.860 mmol) of $TiCl_4$, 57 mg (0.295 mmol) of **7a**. Ratio (R)-**8a**/(S)-**9a**: Table 1, entry 10.

*(1S,4R)-1-{(1R)-1,2,3,4-Tetrahydro-6,7-dimethoxy-1-[2-(4-chlorophenyl)-2-oxo-1-ethyl]-2-isoquinolylcarbonyl}-4,7,7-trimethyl-2-oxa-bicyclo[2.2.1]-heptan-3-one (R)-**8b** and (1S, 4R)-1-{(1S)-1,2,3,4-Tetrahydro-6,7-dimethoxy-1-[2-(4-chlorophenyl-2-oxo-1-ethyl]-2-isoquinolylcarbonyl}-4,7,7-trimethyl-2-oxa-bicyclo[2.2.1]heptan-3-one (S)-**9b**.*

From 1.46 g (4.42 mmol) of **3**, 1.50 g (4.02 mmol) of **4** and 1.0 g (4.42 mmol) of **7b** as described for (R)-**8a**/(S)-**9a** a). Without $TiCl_4$; addition of **7b** at -78°C. Solvent for CC: n-hexane/ethyl acetate = 65/35. A colorless solid containing (R)-**8b** and (S)-**9b** was obtained. Yield 2.09 g (98.9 %). Ratio of (R)-**8b**/(S)-**9b** determined by HPLC (chiral column, n-hexane/isopropanol = 85/15): Table 1, entry 11. - $C_{29}H_{32}ClNO_6$ (526.0) Calc. C 66.2 H 6.13 N 2.7 Found C 66.1 H 6.34 N 2.5. Mol. mass 526 (MS). - IR: 1785; 1675; 1640; 1510 cm^{-1}. - Separation of the diastereomers was effected by prep. HPLC (chiral column, n-hexane/ethyl acetate = 7/3). From a 87 mg sample ((R)-**8b**/(S)-**9b** = 93.9/6.1) 60 mg of (R)-**8b** (70.0%; de>99.5%) and small amounts of (S)-**9b** were obtained.

(R)-**8b**: 400 MHz - ^{1}H-NMR ($CDCl_3$): 0.92 (s, 0.75 x 3H, CH_3), 0.94 (s, 0.25 x 3H, CH_3), 1.06 (s, 0.25 x 3H, CH_3), 1.08 (s, 0.75 x 3H, CH_3), 1.12 (s, 0.75 x 3H, CH_3), 1.20 (s, 0.25 x 3H, CH_3), 1.71 (ddd, J ~ 4/9/13 Hz, 1H), 1.91 (ddd, J ~ 4/11/13 Hz, 1H), 2.02 (ddd, J ~ 4/9/13 Hz, 1H), 2.19 (ddd, J ~ 4/11/13 Hz, 1H), 2.74 (dt, J ~ 16/3.6 Hz, 1H), 2.95-3.05 (m, partly obscured, 0.25 x 1H), 3.08 (ddd, J ~ 5/11/16 Hz, 0.75 x 1H), 3.34 (dd, J ~ 6.8/14 Hz, 1H), 3.43 (dd, J ~ 6.8/14 Hz, 1H), 3.55 (ddd, J ~ 3.6/11/13 Hz, 1H), 3.74 (s, 0.25 x 3H, OCH_3), 3.79 (s, 0.75 x 3H, OCH_3), 3.84 (s, 0.25 x 3H, OCH_3), 3.85 (s, 0.75 x 3H, OCH_3), 4.46 (ddd, J ~ 3/5/13 Hz, 0.75 x 1H, $NC\underline{H}_2CH_2Ar$), 4.56 (ddd, J ~ 3/5/13 Hz, 0.25 x 1H, $NC\underline{H}_2CH_2Ar$), 5.98 (t, J ~ 6.8 Hz, 1H, NC<u>H</u>Ar), 6.60 (s, 1H, Ar-H), 6.65 (s, 0.75 x 1H, Ar-H), 6.76 (s, 0.25 x 1H, Ar-H), 7.43-7.47 (m, 2H, Ar-H), 7.90-7.96 (m, 2H, Ar-H). Ratio of atropisomers ~ 75/25.

(S)-**9b**: 400 MHz - ^{1}H-NMR ($CDCl_3$): 0.94 (s, 3H, CH_3), 1.07 (s, 3H, CH_3), 1.10 (s, 3H, CH_3), 1.66 (ddd, J ~ 4/9/13 Hz, 1H), 1.87 (ddd, J ~ 4/11/13 Hz, 1H), 1.97 (ddd, J ~ 4/9/13 Hz, 1H); 2.42 (ddd, J ~ 4/11/13 Hz, 1H), 2.77 (dt, J ~ 16/3 Hz, 1H), 2.92 (ddd, J ~ 5/11/16 Hz, 1H), 3.37 (m, 2H), 3.68 (ddd, J ~ 3/11/14 Hz, 1H), 3.81 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 4.54 (ddd, J ~ 3/5/14 Hz, 1H, $NC\underline{H}_2CH_2Ar$), 6.12 (t, J ~ 6.5 Hz, 0.85 x 1H, NC<u>H</u>Ar), 6.23-6.28 (m, 0.15 x 1H, NC<u>H</u>Ar), 6.60 (s, 1H, Ar-H), 6.67 (s, 1H, Ar-H), 7.42-7.46 (m, 2H, Ar-H), 7.88-7.94 (m, 2H, Ar-H). Ratio of atropisomers ~ 85/15.

*(1S, 4R)-1-{(1R)-1,2,3,4-Tetrahydro-6,7-dimethoxy-1-[2-(3,4-dimethoxyphenyl)-2-oxo-1-ethyl]-2-isoquinolylcarbonyl}-4,7,7-trimethyl-2-oxa-bicyclo[2.2.1]heptan-3-one (R)-**8c** and (1S, 4R)-1-{(1S)-1,2,3,4-Tetrahydro-6,7-dimethoxy-1-[2-(3,4-dimethoxyphenyl)-2-oxo-1-ethyl]-2-isoquinolylcarbonyl]-4,7,7-trimethyl-2-oxa-bicyclo[2.2.1]heptan-3-one (S)-**9c***

From 1.79 g (5.42 mmol) of **3**, 1.83 g (4.90 mmol) of **4** and 1.54 g (6.08 mmol) of **7c** as described for (R)-**8a**/(S)-**9a** a). Without $TiCl_4$; addition of **7c** at -78°C, 20 h reaction time. A mixture of (R)-**8c**/(S)-**9c** was obtained as a colorless solid after CC (n-hexane/ethyl acetate = 1/1). Yield 2.61 g (96.8%). Ratio of (R)-**8c**/(S)-**9c** determined by HPLC (chiral column, n-hexane/isopropanol = 60/40): Table 1, entry 12. - $C_{31}H_{37}NO_8$ (551.6) Calc. C 67.5 H 6.76 N 2.5 Found C 67.5 H 6.80 N 2.5. Mol. mass 551 (MS). - IR: 1790; 1670; 1640; 1520 cm^{-1}. The diastereomers were separable by prep. HPLC (chiral column, n-hexane/ethyl acetate = 1/1). From a 87 mg sample ((R)-**8c**/(S)-**9c** = 82.4/17.6) 50 mg (R)-**8c** (57.1%; de>99.5 %) and minute amounts of (S)-**9c** were obtained.

(R)-**8c**: 400 MHz - ^{1}H-NMR ($CDCl_3$): 0.94 (s, 0.75 x 3H, CH_3), 0.95 (s, 0.25 x 3H, CH_3), 1.07 (s, 0.25 x 3H, CH_3), 1.08 (s, 0.75 x 3H, CH_3), 1.14 (s, 0.75 x 3H, CH_3), 1.20 (s, 0.25 x 3H, CH_3), 1.70 (ddd, J ~ 4/9/13 Hz, 1H), 1.90 (ddd, J ~ 4/11/13 Hz, 1H), 2.00 (ddd, J ~ 4/9/13 Hz, 1H), 2.20 (ddd, J ~ 4/11/13 Hz, 1H), 2.75 (dt, J ~ 16/3 Hz, 1H), 3.07 (ddd, J ~ 5/11/16 Hz, 1H), 3.33 (dd, J = 6.5/14 Hz, 1H), 3.44 (dd, J = 6.5/14 Hz, 1H), 3.56 (ddd, J ~ 3/11/13 Hz, 1H), 3.72 (s, 0.25 x 3H, OCH_3), 3.76 (s, 0.75 x 3H, OCH_3), 3.83 (s, 0.25 x 3H, OCH_3), 3.85 (s, 0.75 x 3H, OCH_3), 3.92 (s, 0.25 x 6H, OCH_3), 3.94 (s, 0.25 x 6H, OCH_3), 3.96 (s, 1.5 x 6H, OCH_3), 4.46 (ddd, J ~ 3/5/13 Hz, 0.75 x 1H, $NC\underline{H}_2CH_2Ar$), 4.59 (ddd, J=3/5/13 Hz, 0.25 x 1H, $NC\underline{H}_2CH_2Ar$), 6.00 (t, J = 6.5 Hz, 1H, NC<u>H</u>Ar), 6.59, 6.60, 6.73 (3xs, combined 2H, Ar-H), 6.88-6.93 (m, 1H, Ar-H), 7.55-7.68 (m, 2H, Ar-H). Ratio of atropisomers ~ 25/75.

(S)-**9c**: 400 MHz - ^{1}H-NMR ($CDCl_3$): 0.86 (s, 3H, CH_3), 1.07 (s, 3H, CH_3), 1.08 (s, 3H, CH_3), 1.66 (ddd, J ~ 4/9/13 Hz, 1H), 1.87 (ddd, J ~ 4/11/13 Hz, 1H), 1.98 (ddd, J ~ 4/9/13 Hz, 1H), 2.40 (ddd, J ~ 4/11/13 Hz, 1H), 2.78 (dt, J ~ 16/4 Hz, 1H), 2.91 (ddd, J ~ 5/11/16 Hz, 1H), 3.23 (dd, J ~ 7/14.3 Hz, 1H), 3.48 (dd, J ~ 7/14.3 Hz, 1H), 3.66-3.73 (m, 1H), 3.80,

3.85, 3.94, 3.95 (4xs, combined 12H, 4 x OCH_3), 4.57 (ddd, J ~ 4/5/13 Hz, 1H, $NC\underline{H}_2CH_2Ar$), 6.14 (t, J ~ 7 Hz, 1H, $NC\underline{H}Ar$), 6.59 (s, 1H, Ar-H), 6.66 (s, 1H, Ar-H), 6.91-6.93 (m, 1H, Ar-H), 7.52-7.67 (m, 2H, Ar-H). Signals of minor atropisomer of very low intensity.

*(1S, 4R)-1-{(1R)-1,2,3,4-Tetrahydro-6,7-dimethoxy-1-[2-(2,4,6-trimethylphenyl)-2-oxo-1-ethyl]-2-isoquinolylcarbonyl}-4,7,7-trimethyl-2-oxa-bicyclo[2.2.1]heptan-3-one (R)-***11a** *and (1S, 4R)-1-{(1S)-1,2,3,4-Tetrahydro-6,7-dimethoxy-1-[2-(2,4,6-trimethylphenyl)-2-oxo-1-ethyl]-2-isoquinolylcarbonyl}-4,7,7-trimethyl-2-oxa-bicyclo[2.2.1]heptan-3-one (S)-***12a**

From 567 mg (1.72 mmol) of **3** in 10 ml of CH_2Cl_2, 535 mg (1.43 mmol) of **4** in 10 ml of CH_2Cl_2 (dilution with 15 ml of CH_2Cl_2 prior to addition of **10a**) and 672 mg (2.86 mmol) of **10a** (in 0.4 ml of CH_2Cl_2) as described for (R)-**8a**/(S)-**9a**, but without $TiCl_4$. Addition of **10a** at -78°C, 2 h reaction time. After aqueous work-up a crude product containing (R)-**11a**/(S)-**12a** was obtained. Ratio of (R)-**11a**/(S)-**12a** determined by HPLC (SiO_2, n-hexane/Et_2O = 6/4, 2.0 ml/min, major isomer 15.3 min, minor isomer 18.3 min; ratio: Table 2, entry 1). Pure diastereomers were obtained after CC (n-hexane/Et_2O = 6/4).

Major isomer: Colorless crystals, m.p. 155-157°C, $[\alpha]_{546}$ = -94.0°, $[\alpha]_{578}$ = -82.1° (c = 0.67, CH_3OH), yield 83 mg (10.8%, de≥99.3%). - $C_{32}H_{39}NO_6$ (533.7). Calc. C 72.0 H 7.37 N 2.6 Found C. 72.1 H 7.39 N 2.5 Mol. mass 533 (MS). - IR: 1785; 1700; 1635; 1510 cm^{-1}. - 400 MHz - ^{1}H-NMR ($CDCl_3$): 0.98 (s, 0.65 x 3H, CH_3), 1.01 (s, 0.35 x 3H, CH_3), 1.10 (s, 3H, CH_3), 1.21 (s, 0.65 x 3H, CH_3), 1.22 (s, 0.35 x 3H, CH_3), 1.72 (ddd, J ~ 4/9/13 Hz, 1H), 1.80-1.97 (m, 2H), 2.08 (s, 3H, Ar-CH_3), 2.11 (s, 3H, Ar-CH_3), 2.24 (s, 0.35 x 3H, Ar-CH_3), 2.25 (s, 0.65 x 3H, Ar-CH_3), 2.36 (ddd, J ~ 4/11/13 Hz, 1H), 2.67-2.75 (m, 1H), 2.93-3.15 (m), 3.12 (dd, J ~ 4/18 Hz, 2.93-3.12 combined 2H), 3.26 (dd, J ~ 7.5/18 Hz, 1H combined with a signal obscured), 3.39-3.50 (m, 1H), 3.83 (s, 0.65 x 3H, OCH_3), 3.85 (s, 0.35 x 3H, OCH_3), 3.86 (s, 0.65 x 3H, OCH_3), 3.87 (s, 0.35 x 3H, OCH_3), 4.39-4.44 (m, 1H, $NC\underline{H}_2CH_2Ar$), 6.13 (dd, J ~ 4/7.5 Hz, signal of minor atropisomer obscured, 1H, $NC\underline{H}Ar$), 6.60 (s, 0.65 x 1H, Ar-H), 6.61 (s, 0.35 x 1H, Ar-H), 6.78, 6.79 (2 x s, combined 2H, Ar-H), 6.99 (s, 0.65 x 1H, Ar-H), 7.16 (s, 0.35 x 1H, Ar-H). Ratio of atropisomers ~ 35/65.

Minor isomer: Colorless crystals, yield 22 mg (2.9%, de=96.0%). - $C_{32}H_{39}NO_6$ (533.7) Calc. C 72.0 H 7.37 N 2.6 Found C 72.1 H 7.40 N 2.5. Mol. mass 533 (MS) - IR: 1785; 1700; 1640; 1510 cm^{-1}. - 400 MHz - ^{1}H-NMR ($CDCl_3$): 1.04 (s, 3H, CH_3), 1.11 (s, 3H, CH_3), 1.18 (s, 3H, CH_3), 1.70 (ddd, J ~ 4/9/13 Hz, 1H), 1.92 (ddd, J ~ 4/11/13 Hz, 1H), 2.03 (ddd, J ~ 4/9/13 Hz, 1H), 2.07, 2.12 (2 x s, combined 6H, Ar-CH_3), 2.25 (s, 3H, Ar-CH_3), 2.46 (ddd, J ~ 4/11/13 Hz, 1H), 2.73 (dt, J ~ 16/4 Hz, 1H), 2.88 (ddd, J ~ 5/11/16 Hz, 1H), 3.11-3.20 (m, 2H), 3.60 (ddd, J ~ 4/11/14 Hz, 1H), 3.84 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 4.47 (dt, J ~ 14/5 Hz, 1H, $NC\underline{H}_2CH_2Ar$), 6.29 (t, J ~ 5.5 Hz, 1H, $NC\underline{H}Ar$), 6.58 (s, 1H, Ar-H), 6.79 (s, 2H, Ar-H), 6.69 (s, 1H, Ar-H). Signals of minor atropisomer of very low intensity.

*(1S, 4R)-[(1R)-1,2,3,4-Tetryhydro-6,7-dimethoxy-1-(1,1-dimethyl-2-oxo-2-phenyl-1-ethyl)-2-isoquinolylcarbonyl]-4,7,7-trimethyl-2-oxa-bicyclo-[2.2.1]heptan-3-one (R)-***11b** *and (1S,4R)-[(1S)-1,2,3,4-Tetrahydro-6,7-dimethoxy-1-(1,1-dimethyl-2-oxo-2-phenyl-1-ethyl)-2-isoquinolylcarbonyl]-4,7,7-trimethyl-2-oxa-bicyclo-[2.2.1]heptan-3-one (S)-***12b**

From 436 mg (1.32 mmol) of **3** in 8 ml of CH_2Cl_2, 411 mg (1.10 mmol) of **4** in 8 ml of CH_2Cl_2 (dilution with 14 ml of CH_2Cl_2 prior to addition of **10b**) and 364 mg (1.65 mmol) of **10b** (in 0.2 ml of CH_2Cl_2) as described for (R)-**8a**/(S)-**9a**, but without $TiCl_4$. Addition of **10b** at -78°C, reaction time 2 h. After aqueous work-up a crude product containing (R)-**11b**/(S)-**12b** was obtained. Ratio of (R)-**11b**/(S)-**12b** determined by HPLC (SiO_2, n-hexane/ethyl acetate = 75/25, 2.0 ml/min, minor isomer 7.0 min, major isomer 10.4 min; ratio: Table 2, entry 2). Pure diastereomers were obtained after CC (n-hexane/ethyl acetate = 75/25).

Major isomer: Colorless crystals, yield 15 mg (2.6%, de=95.5%). - $C_{31}H_{37}NO_6$ (519.6). Mol. mass 519 (MS). - IR: 1790; 1680; 1650; 1510 cm^{-1}. - 400 MHz - ^{1}H-NMR ($CDCl_3$): 1.03 (s, 3H, CH_3), 1.12 (s, 3H, CH_3), 1.19 (s, 3H, CH_3), 1.23 (s, 3H, CH_3), 1.40 (s, 3H, CH_3), 1.73 (ddd, J ~ 4/9/13 Hz, 1H), 1.90-1.97 (m, 1H), 2.04 (ddd, J ~ 4/9/13 Hz, 1H), 2.41 (ddd, J ~ 4/11/13 Hz, 1H), 2.78-2.85 (m, 2H), 3.63 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3), 3.74-3.90 (m, 1H, partly obscured), 4.61 (ddd, unresolved, J ~ 2/5/14 Hz, 1H, $NC\underline{H}_2CH_2Ar$), 6.35 (s, 1H), 6.55 (s, 1H), 6.72 (s, 1H), 7.44-7.52 (m, 3H, Ar-H), 8.02-8.04 (m, 2H, Ar-H). Signals of minor atropisomer of very low intensity.

Minor isomer: Colorless crystals, m.p. 174-177°C, $[\alpha]_{546}$ = -56.6°, $[\alpha]_{578}$ = -50.0° (c=0.2, CH_2Cl_2), yield 11 mg (2.0%, de=99.0%). - $C_{31}H_{37}NO_6$ (519.6). Calc. C 71.7 H 7.18 N 2.7 Found C 71.6 H 7.29 N 2.8 Mol. mass 519 (MS). - IR: 1780; 1670; 1640; 1520 cm^{-1}. - 400 MHz - ^{1}H-NMR ($CDCl_3$): 0.98 (s, 3H, CH_3), 1.08 (s, 3H, CH_3), 1.14 (s, 3H, CH_3), 1.31 (s, 3H, CH_3), 1.36 (s, 3H, CH_3), 1.69 (ddd, J ~ 4/9/13 Hz, 1H), 1.86 (ddd, J~ 4/11/13 Hz, 1H), 2.01-2.11 (m, 2H), 2.72 (dd, J ~ 3.5/17 Hz, 1H), 3.05 (ddd, J ~ 7/12/17 Hz, 1H), 3.69 (s, 3H, OCH_3), 3.65-3.75 (1H, signal obscured), 3.84 (s, 3H, OCH_3), 4.50 (dd, J ~ 7/14 Hz, 1H, $NC\underline{H}_2CH_2Ar$), 6.44 (s, 1H), 6.51 (s, 1H), 6.57 (s, 1H), 7.41-7.52 (m, 3H, H-3/4 phenyl), 7.98-8.00 (m, 2H, H-2 phenyl).

*(1S, 4R)-1-[(1R)-1-(2-Cyclohex-1-enyl-2-oxo-1-ethyl)-1,2,3,4-tetrahydro-6,7-dimethoxy-2-isoquinolylcarbonyl]-4,7,7-trimethyl-2-oxa-bicyclo-[2.2.1]heptan-3-one (R)-***11c** *and (1S, 4R)-1-[(1S)-1-(2-Cyclohex-1-enyl-2-oxo-1-ethyl)-1,2,3,4-tetrahydro-6,7-dimethoxy-2-isoquinolylcarbonyl]-4,7,7-trimethyl-2-oxa-bicyclo-[2.2.1]heptan-3-one (S)-***12c**

From 321 mg (0.972 mmol) of **3** in 5 ml of CH_2Cl_2, 303 mg (0.810 mmol) of **4** in 5 ml of CH_2Cl_2 (12 ml of CH_2Cl_2 for dilution prior to addition of **10c**) and 191 mg (0.972 mmol) of **10c** (in 0.1 ml of CH_2Cl_2) as described for (R)-**8a**/(S)-**9a** a), but without $TiCl_4$. Addition of **10c** at -95°C, reaction time 1 h. After aqueous work-up a crude product containing (R)-**11c**/(S)-**12c** was obtained. Ratio of (R)-**11c**/(S)-**12c** determined by HPLC (chiral column, n-hexane/isopropanol = 85/15, 2.0 ml/min, major isomer 15.3 min, minor isomer 18.3 min; ratio: Table 2, entry 3). Pure diastereomers were obtained after repeated CC (n-hexane/ethyl ether = 45/55, the retention of the minor isomer is stronger).

Major isomer: Colorless crystals, m.p. 142-143°C, $[\alpha]_{546}$ = -172.9°, $[\alpha]_{578}$ = -150.5° (c=1.07, CH_3OH), yield 50 mg (12.4%, de ≥ 98%). - $C_{29}H_{37}NO_6$ (495.6) Calc. C 70.3 H 7.52 N 2.8 Found C 70.3 H 7.53 N 2.8 Mol. mass 495 (MS). - IR: 1780; 1650; 1635; 1510 cm^{-1}. - 400 MHz - ^{1}H-NMR ($CDCl_3$): 0.94 (s, 0.8 x 3H, CH_3), 0.98 (s, 0.2 x 3H, CH_3), 1.07 (s, 0.2 x 3H, CH_3), 1.08 (s, 0.8 x 3H, CH_3), 1.17 (s, 0.8 x 3H, CH_3), 1.19 (s, 0.2 x 3H, CH_3), 1.56-1.64 (m, 4H), 1.72 (ddd, J ~ 4/9/13 Hz, 1H), 1.91 (ddd, J ~ 4/11/13 Hz, 1H), 2.10 (ddd, J ~ 4/9/13 Hz, 1H), 2.20-2.31 (m, 4H), 2.34 (ddd, J ~ 4/11/13 Hz, 1H), 2.69 (dt, J ~ 16/3 Hz, 1H), 2.93 (dd, J ~ 7/13.9 Hz, 1H), 3.06 (ddd, J ~ 5/11.7/16 Hz, 1H), 3.23 (dd, J ~ 7/13.9 Hz, 1H), 3.50 (ddd, J ~ 3/11.7/13 Hz, 1H), 3.814 (s, 0.2 x 3H, OCH_3), 3.832 (s, 0.8 x 3H, OCH_3), 3.838 (s, 0.2 x 3H, OCH_3), 3.844 (s, 0.8 x 3H, OCH_3), 4.43 (dddd, J ~ 1/3/5/13 Hz, 0.8 x 1H, $NC\underline{H}_2CH_2Ar$, origin of long range coupling could not be ascertained), 4.51 (dddd, J ~ 1/3/5/13 Hz, 0.2 x 1H, $NC\underline{H}_2CH_2Ar$, origin of long range coupling not ascertained), 5.85 (t, J ~ 7 Hz, 1H, $NC\underline{H}Ar$), 6.58 (s, 0.2 x 1H, Ar-H), 6.58 (s, 0.8 x 1H, Ar-H), 6.65 (s, 0.8 x 1H, Ar-H), 6.82 (s, 0.2 x 1H, Ar-H), 6.90 (t, unresolved, 0.2 x 1H, H-alkene), 6.94 (t, unresolved, 0.8 x 1H, H-alkene). Ratio of atropisomers ~ 2/8.

Minor isomer: Colorless crystals, yield 9 mg (2.2%, de=98.4%). - $C_{29}H_{37}NO_6$ (495.6). Mol. mass 495 (MS) - IR: 1780; 1660; 1640; 1510 cm^{-1}. - 400 MHz - ^{1}H-NMR ($CDCl_3$): 1.04 (s, 0.8 x 3H, CH_3), 1.08 (s, 0.2 x 3H, CH_3), 1.09 (s, 0.2 x 3H, CH_3), 1.10 (s, 0.8 x 3H, CH_3), 1.11 (s, 0.8 x 3H, CH_3), 1.20 (s, 0.2 x 3H, CH_3), 1.56-1.70 (m, 5H), 1.88 (ddd, J ~ 4/11/13 Hz, 1H), 1.98 (ddd, J ~ 4/9/13 Hz, 1H), 2.23-2.27 (m, 4H), 2.45

(ddd, J ~ 4/11/13 Hz, 1H), 2.73 (dt, J ~ 16/3 Hz, 1H), 2.89 (ddd, J ~ 5/11/16 Hz, 1H), 3.03 (dd, J ~ 5.8/14.5 Hz, 1H), 3.10 (dd, J ~ 7.5/14.5 Hz, 1H), 3.60 (ddd, J ~ 3/11/14 Hz, 1H), 3.83, 3.84 (2 x s, combined 6H, 2 x OCH_3), 4.54 (ddd, J ~ 3/5/14 Hz, 0.8 x 1H, $NC\underline{H}_2CH_2Ar$), 4.62 (ddd, unresolved, 0.2 x 1H, $NC\underline{H}_2CH_2Ar$), 6.02 (pseudo t, J ~ 6-7 Hz, 0.8 x 1H, NC<u>H</u>Ar), 6.10 (m, 0.2 x 1H, NC<u>H</u>Ar), 6.57 (s, 1H, Ar-H), 6.67 (s, 1H, Ar-H), 6.84 (t, unresolved, 0.2 x 1H, H-alkene), 6.90 (t, unresolved, 0.8 x 1H, H-alkene). Ratio of atropisomers ~ 2/8.

*(1S, 4R)-1-[(1R)-1-(3,3-Dimethyl-2-oxo-1-butyl)-1,2,3,4-tetrahydro-6,7-dimethoxy-2-isoquinolylcarbonyl]-4,7,7-trimethyl-2-oxa-bicyclo[2.2.1]-heptan-3-one (R)-***11d** *and*
*(1S, 4R)-1-[(1S)-1-(3,3-Dimethyl-2-oxo-1-butyl)-1,2,3,4-tetrahydro-6,7-dimethoxy-2-isoquinolylcarbonyl]-4,7,7-trimethyl-2-oxa-bicyclo[2.2.1]-heptan-3-one (S)-***12d**

a) From 110 mg (0.333 mmol) of **3** in 1.5 ml of CH_2Cl_2, 104 mg (0.277 mmol) of **4** in 1.5 ml of CH_2Cl_2 (4 ml of CH_2Cl_2 for dilution prior to addition of **10d**) and 57 mg (0.333 mmol) of **10d** (in 0.15 ml of CH_2Cl_2) as described for (R)-**8a**/(S)-**9a** a). For reaction conditions and ratio of diastereomers (determined from the crude product by HPLC: SiO_2, n-hexane/ethyl ether = 6/4, 2.0 ml/min, major isomer 14.2 min, minor isomer 17.0 min): Table 2, entry 4.

b) From 1.23 g (3.72 mmol) of **3** in 18 ml of CH_2Cl_2, 1.16 g (3.10 mmol) of **4** in 18 ml of CH_2Cl_2 (40 ml of CH_2Cl_2 for dilution prior to addition of **10d**) and 642 mg (3.72 mmol) of **10d** (in 1 ml of CH_2Cl_2) as described under a) according Table 2, entry 5. The major isomer was obtained in a yield of 30.9% after CC.

c) From 85 mg (0.258 mmol) of **3** in 1.5 ml of CH_2Cl_2, 80 mg (0.215 mmol) of **4** in 1.5 ml of CH_2Cl_2 (3 ml of CH_2Cl_2 for dilution prior to addition of **10d**), 41 mg (0.215 mmol) of $TiCl_4$ and 45 mg (0.258 mmol) of **10d** (in 0.15 ml of CH_2Cl_2) as described under a) according Table 2, entry 6.

d) From 92 mg (0.278 mmol) of **3** in 1.7 ml of CH_2Cl_2, 87 mg (0.232 mmol) of **4** in 1.7 ml of CH_2Cl_2 (2 ml of CH_2Cl_2 for dilution prior to addition of **10d**), 44 mg (0.232 mmol) of $TiCl_4$ and 48 mg (0.278 mmol) of **10d** (in 0.15 ml of CH_2Cl_2) as described under a) according Table 2, entry 7.
Pure diastereomers were obtained after CC (n-hexane/ethyl ether = 4/6).
Major isomer: Colorless crystals, m.p. 143-144°C, $[\alpha]_{546}$ = -145.9°, $[\alpha]_{578}$ = -127.1° (c=0.42, CH_3OH), yield 38 mg (34.9%, de > 99.5%). - $C_{27}H_{37}NO_6$ (471.6) Calc. C 68.8 H 7.91 N 3.0 Found C 68.7 H 7.71 N 3.0. Mol. mass 471 (MS). - IR: 1780; 1690; 1630; 1520 cm^{-1}. - 400 MHz - ^{1}H-NMR ($CDCl_3$): 0.95 (s, 0.75 x 3H, CH_3), 0.98 (s, 0.25 x 3H, CH_3), 1.06 (s, 0.25 x 3H, CH_3), 1.09 (s, 0.75 x 3H, CH_3), 1.13 (s, 9H, $C(CH_3)_3$), 1.18 (s, 0.75 x 3H, CH_3), 1.19 (s, 0.25 x 3H, CH_3), 1.72 (ddd, J ~ 4/9/13 Hz, 1H), 1.92 (ddd, J ~ 4/11/13 Hz, 1H), 2.12 (ddd, J ~ 4/9/13 Hz, 1H), 2.38 (ddd, J ~ 4/11/13 Hz, 1H), 2.66-2.75 (m, 2H), 3.00-3.16 (m, 2H), 3.49 (ddd, J ~ 4/11/13 Hz, 1H), 3.80, 3.82, 3.84 (3 x s, combined 6H, 2x OCH_3), 4.46 (ddd, J ~ 3/6/13 Hz, 0.75 x 1H, $NC\underline{H}_2CH_2Ar$), 4.50-4.55 (m, 0.25 x 1H, $NC\underline{H}_2CH_2Ar$), 5.80-5.85 (m, 0.25 x 1H, NC<u>H</u>Ar), 5.90 (t, J ~ 6.5 Hz, 0.75 x 1H, NC<u>H</u>Ar), 6.58 (s, 1H, Ar-H), 6.65 (s, 0.75 x 1H, Ar-H), 6.92 (s, 0.25 x 1H, Ar-H). Ratio of atropisomers ~ 25/75.
Minor isomer: Colorless crystals, 8 mg (7.6%; de=85%). - $C_{27}H_{37}NO_6$ (471.6) Mol. mass 471 (MS). - IR: 1790; 1710; 1640; 1520 cm^{-1}. - 400 MHz - ^{1}H-NMR ($CDCl_3$): 1.07, 1.08, 1.11, 1.13, 1.14 (5 x s, combined 18H, 6 x CH_3), 1.66 (ddd, J ~ 4/9/13 Hz, 1H), 1.91 (ddd, J ~ 4/11/13 Hz, 1H), 1.99 (ddd, J ~ 4/9/13 Hz, 1H), 2.45 (ddd, J ~ 4/11/13 Hz, 1H), 2.74 (dt, J ~ 16/4 Hz, 1H), 2.84-2.99 (m, 3H), 3.60 (ddd, J ~ 4/11/14 Hz, 1H), 3.79, 3.82, 3.84 (3 x s, combined 6H, 2 x OCH_3), 4.51 (ddd, J ~ 3/4/14 Hz, 0.75 x 1H, $NC\underline{H}_2CH_2Ar$), 4.57-4.64 (m, 0.25 x 1H, $NC\underline{H}_2CH_2Ar$), 6.07 (t, J ~ 6.5 Hz, 1H, NC<u>H</u>Ar), 6.57 (s, 1H, Ar-H), 6.66 (s, 1H, Ar-H). Ratio of atropisomers ~ 75/25.

*(1S, 4R)-1-[(1R)-1,2,3,4-Tetrahydro-6,7-dimethoxy-1-(2-oxo-1-ethyl)-2-isoquinolylcarbonyl]-4,7,7-trimethyl-2-oxa-bicyclo[2.2.1]heptan-3-one (R)-***11e** *and (1S, 4R)-1-[(1S)-1,2,3,4-Tetrahydro-6,7-dimethoxy-1-(2-oxo-1-ethyl)-2-isoquinolylcarbonyl]-4,7,7-trimethyl-2-oxa-bicyclo-[2.2.1]heptan-3-one (S)-***12e**

From 96 mg (0.290 mmol) of **3** in 1.5 ml of CH_2Cl_2, 90 mg (0.242 mmol) of **4** in 1.5 ml of CH_2Cl_2 (3 ml of CH_2Cl_2 for dilution prior to addition of **10e**) and 46 mg (0.290 mmol) of **10e** as described for (R)-**8a**/(S)-**9a** a), but without $TiCl_4$. Addition of **10e** at -19°C, reaction time 6 h. After aqueous work-up and CC (SiO_2, n-hexane/ethyl acetate = 7/3) a mixture of (R)-**11e**/(S)-**12e** was obtained. As the diastereomers were inseparable on SiO_2, the ratio of (R)-**11e**/(S)-**12e** was determined from a purified sample by ^{1}H-NMR: Table 2, entry 8. 400 MHz - ^{1}H-NMR ($CDCl_2CDCl_2$, mixture of diastereomers): 0.93, 0.96, 0.99, 1.07, 1.09, 1.16, 1.18, 1.24 (8 x s, combined 9H, 3 x CH_3), 1.66-1.72 (m, 1H), 1.87-1.97 (m, 1H), 2.00-2.12 (m, 1H), 2.21-2.33 (m, 1H), 2.64-3.09 (m, 4H), 3.33-3.42 (m, 1H), 3.820, 3.824 (2 x s, comb. 6H, 2 x OCH_3), 4.40-4.50, 4.50-4.57, 4.57-4.65 (3 x m, comb. 1H, NCH_2), 5.78 (t, J = 6 Hz), 5.87 (dd, J = 4/9 Hz), 6.06 (dd, J = 4/10 Hz, 5.78-6.06 comb. 1H, NCH), 6.58, 6.59, 6.66 (3 x s, comb. 2H, Ar-H), 9.79 (dd, J = 2/4 Hz). 9.82 (dd, J = 2/4 Hz), 9.91 (t, J = 2 Hz, 9.79-9.91 comb. 1H, CHO). The signals reported arise from configurational and rotational isomers.

*(1S, 4R)-1-[(1R)-1-(2-Ethoxy-2-oxo-1-ethyl)-1,2,3,4-tetrahydro-6,7-dimethoxy-2-isoquinolylcarbonyl]-4,7,7-trimethyl-2-oxa-bicyclo[2.2.1]-heptan-3-one (R)-***11f** *and (1S, 4R)-1-[(1S)-1-(2-Ethoxy-2-oxo-1-ethyl)-1,2,3,4-tetrahydro-6,7-dimethoxy-2-isoquinolylcarbonyl]-4,7,7-trimethyl-2-oxa-bicyclo[2.2.1]heptan-3-one(S)-***12f**

From 98 mg (0.295 mmol) of **3** in 1.5 ml of CH_2Cl_2, 92 mg (0.246 mmol) of **4** in 1.5 ml of CH_2Cl_2 (3.5 ml of CH_2Cl_2 for dilution prior to addition of **10f**) and 394 mg (2.46 mmol) of **10f** as described for (R)-**8a**/(S)-**9a** a), but without $TiCl_4$. Addition of **10f** at room temp., reaction time 11 days. After aqueous work-up and CC (n-hexane/ethyl ether = 1/1) a mixture of diastereomers was obtained. The isomers were inseparable on SiO_2. The ratio (R)-**11f**/(S)-**12f** was determined on a chiral column by HPLC from the crude product (n-hexane/isopropanol = 8/2, 2.0 ml/min, major isomer 7.7 min, minor isomer 10.4 min; ratio: Table 2, entry 9). The physical data given below refer to the mixture of diastereomers obtained: Colorless crystals $[\alpha]_{546}$ = -9.6°, $[\alpha]_{578}$ = -9.6° (c=0.41, CH_3OH). - m.p. 60-67°C, yield 50 mg (43.8 %). - $C_{25}H_{33}NO_7$ (459.5) Calc. C 65.3 H 7.23 N 3.1 Found C 65.3 H 7.04 N 3.2. Mol. mass 459 (MS). - IR: 1785; 1730; 1640; 1510 cm^{-1}. For analytical purpose a sample of (R)-**11f**/(S)-**12f** was separated on a chiral column (n-hexane/isopropanol = 7/3; order of elution: 1. major isomer; 2. minor isomer).

Major isomer: 400 MHz - ^{1}H-NMR ($CDCl_3$): 0.96 (s, 0.8 x 3H, CH_3), 1.01 (s, 0.2 x 3H, CH_3), 1.09 (s, 3H, CH_3), 1.19 (s; 0.8 x 3H, CH_3), 1.21 (s, 0.2 x 3H, CH_3), 1.28 (t, J = 7.2 Hz, 3H, $CH_2C\underline{H}_3$), 1.74 (ddd, J ~ 4/9/13 Hz, 1H), 1.93 (ddd, J ~ 4/11/13 Hz, 1H), 2.14 (ddd, J ~ 4/9/13 Hz, 1H), 2.36 (ddd, J ~ 4/11/13 Hz, 1H), 2.66-2.70 (m, 1H), 2.71-2.80 (m, 0.8 x 2H), 2.87-2.91 (m, 0.2 x 2H), 3.08 (ddd, J ~ 4/11/16 Hz, 1H), 3.47 (ddd, J ~ 4/11/13 Hz, 1H), 3.84, 3.85 (2 x s, combined 6H, 2 x OCH_3), 4.12 (q, J = 7.2 Hz, 2H, $C\underline{H}_2CH_3$), 4.48 (dd, unresolved, J ~ 4/13 Hz, 0.8 x 1H; $NC\underline{H}_2CH_2Ar$), 4.55-4.62 (m, 0.2 x 1H, $NC\underline{H}_2CH_2Ar$), 5.72 (t, unresolved, 0.2 x 1H, NC<u>H</u>Ar), 5.87 (pseudo t, J ~ 6 and 8 Hz, respectively, 0.8 x 1H, NC<u>H</u>Ar), 6.59 (s, 1H, Ar-H), 6.67 (s, 0.8 x 1H, Ar-H), 6.80 (s, 0.2 x 1H, Ar-H). Ratio of atropisomers ~ 2/8.

Minor isomers: 400 MHz - ^{1}H-NMR ($CDCl_3$): 1.07 (s, 3H, CH_3), 1.12 (s, 6H, 2 x CH_3), 1.28 (t, J ~ 7 Hz, 3H, $CH_2C\underline{H}_3$), 1.67 (ddd, J ~ 4/9/13 Hz, 1H), 1.90 (ddd, J ~ 4/11/13 Hz, 1H), 1.99 (ddd, J ~ 4/9/13 Hz, 1H), 2.50 (ddd, J ~ 4/11/13 Hz, 1H), 2.71-2.87 (m, 3H), 2.92 (ddd, J ~ 5/11.5/16 Hz, 1H), 3.55 (ddd, J ~ 4/11.5/14 Hz, 1H), 3.84, 3.85 (2 x s, combined 6H, 2 x OCH_3), 4.12 (pseudo dq, J ~ 1/7 Hz, ABX_3 pattern, 2H, $C\underline{H}_2CH_3$), 4.60

(ddd, J ~ 4/5/14 Hz, 1H, NC$\underline{H}_2$CH$_2$Ar), 6.01 (t, J ~ 7 Hz, 1H, NC$\underline{H}$Ar), 6.58 (s, 1H, Ar-H), 6.68 (s, 1H, Ar-H). Because of their low intensity the signals of the minor atropisomer have been omitted.

*Hydrogenation of Amido Ketones (R)-**8**/(S)-**9***

*(1S, 4R)-1-[(1R)-1,2,3,4-Tetrahydro-6,7-dimethoxy-1-(2-phenyl-1-ethyl)-2-isoquinolylcarbonyl]-4,7,7-trimethyl-2-oxa-bicyclo[2.2.1]heptan-3-one (R)-**13a**, (1S, 4R)-1-{(1S)-1,2,3,4-Tetrahydro-6,7-dimethoxy-1-(2-phenyl-1-ethyl)-2-isoquinolylcarbonyl}-4,7,7-trimethyl-2-oxa-bicyclo[2.2.1]heptan-3-one (S)-**14a** and (1S,4R)-1-[(1R)-1-(2-Cyclohexyl-1-ethyl)-1,2,3,4-tetrahydro-6,7-dimethoxy-isoquinolylcarbonyl]-4,7,7-trimethyl-2-oxa-bicyclo[2.2.1]heptan-3-one (R)-**15***

To a solution of 1.50 g (3.05 mmol) of a mixture of diastereomers of (R)-**8a**/(S)-**9a** (82.4/17.6) in 50 ml of glacial acetic acid, CF_3CO_2H (0.5 ml) and Pd/C (632 mg, 10% Pd) were added. The mixture was hydrogenated at room temp. at 3 bar for 24 h. Pd/C was filtered off and the filtrate concentrated in vacuo. The residue was dissolved in ethyl ether. The etheral solution was washed with saturated NaCl-solution (3x), dried over $MgSO_4$ and the solvent was evaporated in vacuo. The residue containing (R)-**13a**/(S)-**14a** (ratio determined by HPLC on SiO_2 with n-hexane/ethyl acetate = 7/3: Table 4, entry 1) was separated by repeated column and radial chromatography (n-hexane/ethyl acetate = 7/3). Thereby also (R)-**15** was obtained (order of elution: 1. (R)-**15** 2. (R)-**13a** 3. (S)-**14a**).

(R)-**13a**: Colorless crystals, m.p. 163-164°C, $[\alpha]_{546}$ = -140.2°, $[\alpha]_{578}$ = -119.6° (c=0.54, CH_3OH), yield 861 mg (59.1%, de>99.5%). - $C_{29}H_{35}NO_5$ (477.6) Calc. C 72.9 H 7.38 N 2.9 Found C 72.9 H 7.29 N 3.0 Mol.mass 477 (MS). - IR: 1785; 1640; 1510 cm^{-1}. - 400 MHz - ^{1}H-NMR ($CDCl_3$): 0.98 (s, 0.7 x 3H, CH_3), 1.07 (s, 0.3 x 3H, CH_3), 1.10 (s, 0.7 x 3H, CH_3), 1.12 (s, 0.3 x 3H, CH_3), 1.23 (s, 0.7 x 3H, CH_3), 1.24 (s, 0.3 x 3H, CH_3), 1.75 (ddd, J ~ 4/9/13 Hz, 1H), 1.83-2.02 (m, 1H), 2.09-2.19 (m, 3H), 2.38 (ddd, J ~ 4/11/13 Hz, 1H), 2.59-2.72 (m, 2H), 2.84 (ddd, J ~ 5/11/14 Hz, 0.7 x 1H), 2.95-3.00 (m, 0.3 x 1H), 3.11 (ddd, J ~ 5/12/16 Hz, 1H), 3.19 (ddd, J ~ 5/12/13 Hz, 0.3 x 1H), 3.48 (ddd, J ~ 4/12/13 Hz, 0.7 x 1H, NC$\underline{H}_2$CH$_2$Ar), 3.83, 3.84, 3.86 (3 x s, comb. 6H, 2 x OCH_3), 4.47 (dd, J ~ 5/13 Hz, 0.7 x 1H, NC$\underline{H}_2$CH$_2$Ar), 4.50-4.55 (m, 0.3 x 1H, NC$\underline{H}_2$CH$_2$Ar), 5.45 (t, J ~ 7 Hz, 0.3 x 1H, NC$\underline{H}$Ar), 5.65 (dd, J ~ 5/9 Hz, 0.7 x 1H, NC$\underline{H}$Ar), 6.56 (s, 0.3 x 2H, Ar-H), 6.58 (s, 0.7 x 2H, Ar-H), 7.14-7.29 (m, 5H, C_6H_5). Ratio of atropisomers ~ 3/7.

(S)-**14a**: Colorless crystals, m.p. 152-154°C, $[\alpha]_{546}$ = +134.6°, $[\alpha]_{578}$ = +121.2° (c=0.52, CH_3OH), yield 127 mg (8.7%, de>99.5%). - $C_{29}H_{35}NO_5$ (477.6) Calc. C 72.9 H 7.38 N 2.9 Found C 72.8 H 7.36 N 2.9. Mol.mass 477 (MS). - IR: 1780; 1620; 1510 cm^{-1}. - 400 MHz - ^{1}H-NMR ($CDCl_3$): 1.09 (s, 3H, CH_3), 1.13 (s, 3H, CH_3), 1.19 (s, 3H, CH_3), 1.73 (ddd, J ~ 4/9/13 Hz, 1H), 1.94 (ddd, J ~ 4/11/13 Hz, 1H), 2.02-2.19 (m, 3H), 2.46 (ddd, J ~ 4/11/13 Hz, 1H), 2.63 (ddd, J ~ 5/11/13 Hz, 1H), 2.71-2.77 (m, 2H), 2.90 (ddd, J ~ 5/12/16.5 Hz, 1H), 3.57 (ddd, J ~ 4/12/14 Hz, 1H, NC$\underline{H}_2$CH$_2$Ar), 3.82 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), 4.64 (dd, J ~ 5/14 Hz, 1H, NC$\underline{H}_2$CH$_2$Ar), 5.74 (dd, J ~ 5/9.9 Hz, 1H, NC$\underline{H}$Ar), 6.55, 6.56, 6.59 (3 x s, combined 2H, Ar-H), 7.16-7.20 (m, 3H, H-2/4 C_6H_5), 7.21-7.30 (m, 2H, H-3, C_6H_5). Because of their low intensity the signals of the minor atropisomer have been omitted.

(R)-**15**: Colorless crystals, m.p. 180-182°C, $[\alpha]_{546}$ = -130.1°, $[\alpha]_{578}$ = -112.6° (c=0.51, CH_3OH), yield 103 mg (7.0 %). - $C_{29}H_{41}NO_5$ (483.7) Calc. C 72.0 H 8.54 N 2.9 Found C 72.1 H 8.53 N 2.8. Mol. mass 483 (MS). - IR: 1780; 1640; 1520 cm^{-1}. - 400 MHz - ^{1}H-NMR ($CDCl_3$): 0.88-0.93 (m, 2H), 0.96 (s, 3H, CH_3), 1.10 (s, 3H, CH_3), 1.21 (s, 3H, CH_3), 1.13-1.28 (m, partly obscured, 5H), 1.34-1.42 (m, 1H), 1.66-1.86 (m), 1.95 (ddd, J ~ 4/11/13 Hz), 2.13 (ddd, J ~ 4/9/13 Hz), 2.39 (ddd, J ~ 4/11/13 Hz, 1.66-2.39 combined 11H), 2.65-2.69 (m, 1H), 2.88-3.18 (m), 3.40 (ddd, J ~ 4/11/13 Hz, 2.88-3.40 combined 2H), 3.84, 3.85, 3.87 (3 x s, combined 6H, 2 x OCH_3), 4.44 (dd, J ~ 5/13 Hz, 0.75 x 1H, NC$\underline{H}_2$CH$_2$Ar), 4.52 (dd, J ~ 5/13 Hz, 0.25 x 1H, NC$\underline{H}_2$CH$_2$Ar), 5.31 (t, J ~ 7 Hz, 0.25 x 1H, NC$\underline{H}$Ar), 5.49 (t, J ~ 7.3 Hz, 0.75 x 1H, NC$\underline{H}$Ar), 6.57, 6.58 (2 x s, combined 2H, Ar-H). Ratio of atropisomers ~ 25/75.

Hydrogenation of (R)-**13a** (10 mg, 0.021 mmol) with PtO_2 (16 mg) in CH_3OH/HCl (2.2 ml, 10/1) followed by usual work-up yielded a product that was identical with (R)-**15** according to 400 MHz - ^{1}H-NMR-spectrum and TLC.

*(1S, 4R)-1-{(1R)-1-[2-(4-Chlorophenyl)-1-ethyl]-1,2,3,4-tetrahydro-6,7-dimethoxy-2-isoquinolylcarbonyl}-4,7,7-trimethyl-2-oxa-bicyclo[2.2.1]-heptan-3-one (R)-**13b** and (1S, 4R)-1-{(1S)-1-[2-(4-Chlorophenyl)-1-ethyl]-1,2,3,4-tetrahydro-6,7-dimethoxy-2-isoquinolylcarbonyl}-4,7,7-trimethyl-2-oxa-bicyclo[2.2.1]heptan-3-one (S)-**14b***

From 1.0 g (1.90 mmol) of (R)-**8b**/(S)-**9b** (85.2/14.8) as described for (R)-**13a**/(S)-**14a**. Time of hydrogenation 44 h. The crude product contained a mixture of diastereomers (R)-**13b** and (S)-**14b** contaminated with a mixture of (R)-**13a** and (S)-**14a**. The portion composed of (R)-**13a** + (S)-**14a** amounted to about one third of the whole product. The ratio of (R)-**13a**/(S)-**14a** was determined as 94.4/5.6 by HPLC. Ratio of (R)-**13b**/(S)-**14b** (determined by HPLC on SiO_2, n-hexane/ethyl ether = 85/15): Table 4, entry 2. The subsequent CC (n-hexane/ethyl acetate = 7/3) resulted in only incomplete separation. 52 mg (5.32 %, de>99.5%) of (R)-**13b** (used for analytical purposes only), 8 mg (0.8 %) of (S)-**14b** and 505 mg (51.86%) of a mixture of (R)-**13a**/(R)-**13b** (~ 33/66) were obtained.

(R)-**13b**: Colorless crystals, m.p. 77-80°C, $[\alpha]_{546}$ = -114.3°, $[\alpha]_{578}$ = -102.9° (c=0.17, CH_3OH). - $C_{29}H_{34}ClNO_5$ (512.0) Calc. C 68.0 H 6.69 N 2.7 Found C 68.1 H 6.79 N 2.8. Mol.mass 512 (MS). - IR: 1790; 1640; 1520 cm^{-1}. - 400 MHz - ^{1}H-NMR: 0.97 (s, 0.7 x 3H, CH_3), 1.06 (s, 0.3 x 3H, CH_3), 1.10 (s, 0.7 x 3H, CH_3), 1.12 (s, 0.3 x 3H, CH_3), 1.22 (s, 0.7 x 3H, CH_3), 1.23 (s, 0.3 x 3H, CH_3), 1.70-1.78 (m, 1H), 1.81-1.99 (m, 1H), 2.02-2.17 (m, 3H), 2.38 (ddd, J ~ 4/11/13 Hz, 1H), 2.55-2.71 (m), 2.80 (ddd, J ~ 5/11/14 Hz), 2.91-3.23 (m), 3.47 (dt, J ~ 4/13 Hz, 2.55-3.47 comb. 5H), 3.83 (s, 0.7 x 3H, OCH_3), 3.84 (s, 3H, OCH_3), 3.86 (s, 0.3 x 3H, OCH_3), 4.48 (dd, J ~ 5/13 Hz, 1H, NC$\underline{H}_2$CH$_2$Ar), 5.41 (t, J ~ 7 Hz, 0.3 x 1H, NC$\underline{H}$Ar), 5.61 (dd, J ~ 5/9 Hz, 0.7 x 1H, NC$\underline{H}$Ar), 6.53 (s, 0.7 x 1H, Ar-H), 6.56 (s, 0.3 x 1H, Ar-H), 6.58 (s, 0.7 x 1H, Ar-H), 6.59 (s, 0.3 x 1H, Ar-H), 7.12-7.25 (m, 4H, C_6H_4-Cl). Ratio of atropisomers ~ 3/7.

(S)-**14b**: Colorless crystals. - 400 MHz - ^{1}H-NMR ($CDCl_3$): 1.09 (s, 3H, CH_3), 1.13 (s, 3H, CH_3), 1.19 (s, 3H, CH_3), 1.73 (ddd, J ~ 4/9/13 Hz, 1H), 1.94 (ddd, J ~ 4/11/13 Hz, 1H), 1.98-2.19 (m, 3H), 2.44 (ddd, J ~ 4/11/13 Hz, 1H), 2.54-2.76 (m, 3H), 2.85-2.92 (m, 1H), 3.51-3.60 (m, 1H), 3.82, 3.83 (2 x s, combined 6H, 2 x OCH_3), 4.62 (dd, J ~ 5/14 Hz, 1H, NC$\underline{H}_2$CH$_2$Ar), 5.71 (dd, J ~ 4/10 Hz, 1H, NCHAr), 6.52, 6.56 (2 x s, combined 2H, Ar-H), 7.12-7.35 (m, 4H, -C_6H_4Cl). The signals of the minor atropisomer have been omitted.

*(1S, 4R)-1-{(1R)-1,2,3,4-Tetrahydro-6,7-dimethoxy-1-[2-(3,4-dimethoxyphenyl)-1-ethyl]-2-isoquinolylcarbonyl}-4,7,7-trimethyl-2-oxa-bicyclo-[2.2.1]heptan-3-one (R)-**13c** and (1S, 4R)-1-{(1S)-1,2,3,4-Tetrahydro-6,7-dimethoxy-1-[2-(3,4-dimethoxyphenyl)-1-ethyl]-2-isoquinolylcarbonyl}-4,7,7-trimethyl-2-oxa-bicyclo-[2.2.1]heptan-3-one (S)-**14c***

From 1.25 g (2.26 mmol) of (R)-**8c**/(S)-**9c** (82.4/17.6) as described for (R)-**13a**/(S)-**14a**. Time of hydrogenation 16 h. The diastereomeric ratio was determined from the crude product by HPLC (SiO_2, n-hexane/Et_2O = 40/60; Ratio of (R)-**13c**/(S)-**14c**: Table 4, entry 3). Separation of the diastereomers could be effected by CC (n-hexane/ethyl ether = 3/7; (S)-**14c** being retained more strongly).

(R)-**13c**: Colorless crystals, $[\alpha]_{546}$ = -94.3°, $[\alpha]_{578}$ = -83.0° (c=0.27, CH_3OH), m.p. 79-84°C, yield 330 mg (27.1 %). - $C_{31}H_{39}NO_7$ (537.6) Calc. C 69.3 H 7.31 N 2.61 Found C 69.3 H 7.40 N 2.7. Mol. mass 537 (MS) - IR: 1785; 1640; 1510 cm^{-1}. - 400 MHz - ^{1}H-NMR ($CDCl_3$): 0.98 (s, 0.7 x 3H, CH_3), 1.06 (s, 0.3 x 3H, CH_3), 1.10 (s, 0.7 x 3H, CH_3), 1.12 (s, 0.3 x

3H, CH_3), 1.22 (s, 0.7 x 3H, CH_3), 1.23 (s, 0.3 x 3H, CH_3), 1.74 (ddd, J ~ 4/9/13 Hz, 1H), 1.83-1.90 (m, 0.3 x 1H), 1.95 (ddd, J ~ 4/11/13 Hz 0.7 x 1H), 2.03-2.23 (m, 3H), 2.39 (ddd, J ~ 4/11/13 Hz, 1H), 2.59 (ddd, J ~ 5/11/14 Hz), 2.66-2.73 (m), 2.77 (ddd, J ~ 5/11/14 Hz), 2.85-2.91 (m, 2.59-2.91 combined 3H), 3.00 (ddd, J ~ 5/11/16 Hz, 0.3 x 1H), 3.11 (ddd, J ~ 5/11/16 Hz, 0.7 x 1H), 3.22 (ddd, J ~ 4/11.5/13 Hz, 0.3 x 1H), 3.49 (ddd, J ~ 4/11.5/13 Hz, 0.7 x 1H), 3.82, 3.83, 3.84, 3.85, 3.86, 3.87 (6 x s, combined 12H, 4 x OCH_3), 4.47 (dd, J ~ 5/13 Hz, 0.7 x 1H, NCH_2CH_2Ar), 4.53 (ddd, partly obscured, 0.3 x 1H, NCH_2CH_2Ar), 5.41 (t, J ~ 7 Hz, 0.3 x 1H, NCHAr), 5.63 (dd, J ~ 5/9 Hz, 0.7 x 1H, NCHAr), 6.55 (s, 0.7 x 1H, Ar-H), 6.59 (s, 1H, Ar-H), 6.60 (s, 0.3 x 1H, Ar-H), 6.72-6.80 (m, 3H, -$C_6H_3(OMe)_2$). Ratio of atropisomers ~ 3/7.

(S)-**14c** (only minute amounts from CC): 400 MHz - ^{1}H-NMR ($CDCl_3$): 1.10 (s, 3H, CH_3), 1.13 (s, 3H, CH_3), 1.20 (s, 3H, CH_3), 1.73 (ddd, J ~ 4/9/13 Hz, 1H), 1.94 (ddd, J ~ 4/11/13 Hz, 1H), 2.01-2.16 (m, 3H), 2.45 (ddd, J ~ 4/11/13 Hz, 1H), 2.54-2.77 (m, 3H), 2.89 (ddd, J ~ 6/12/17 Hz, 1H), 3.59 (ddd, J ~ 4/12/14.5 Hz, 1H), 3.82, 3.84, 3.85, 3.88 (4 x s, combined 12H, 4 x OCH_3). 4.62 (dd, unresolved, 1H, NCH_2CH_2Ar), 5.73 (dd, J ~ 4.4/10.2 Hz, 1H, NCHAr), 6.54 (s, 1H, Ar-H), 6.56 (s, 1H, Ar-H), 6.71-6.81 (m, 3H, -C_6H_3 $(OMe)_2$). The signals of the minor atropisomer have been omitted.

*Secondary Amines (R)-***16a-c** *and (S)-***16a**

*(1R)-1,2,3,4-Tetrahydro-6,7-dimethoxy-1-(2-phenyl-1-ethyl)isoquinoline (R)-***16a** *and (1S, 3R)-1-[(1R)-1,2,3,4-Tetrahydro-6,7-dimethoxy-1-(2-phenyl-1-ethyl)-2-isoquinolyl-methyl]-3-hydroxymethyl-2,2,3-trimethyl-1-cyclopentanol (R)-***17**

303 mg (0.633 mmol) of (R)-**13a** were dissolved in 15 ml of THF. At room temp. 2.16 ml of a solution of $LiAlH_4$ (1M in THF) was added slowly. The mixture was stirred for 3 h and then quenched with water (6 ml). Then it was concentrated in vacuo and acidified with 2N HCl. The aqueous layer was extracted once with ethyl ether and the org. extract was discharged. After the water phase had been made alkaline by NaOH it was extracted with ethyl ether (3x). The org. layers were dried ($MgSO_4$) and the solvent was evaporated in vacuo. From the residue (R)-**16a** and (R)-**17a** were obtained by CC (SiO_2, ethyl ether/NEt_3 = 95/5; order of elution: 1. (R)-**17a** 2. (R)-**16a**.

(R)-**16a**: Colorless oil, $[\alpha]_{546}$ = +26.8°, $[\alpha]_{578}$ = +25.5° (c=0.75, CH_3OH), yield 121 mg (64.5%). - $C_{19}H_{23}NO_2$ (297.4) Calc. C 76.7 H 7.79 N 4.7 Found C 76.6 H 7.96 N 4.8. Mol.mass 297 (MS). - IR: 3330; 2940; 1510 cm^{-1}. - 400 MHz - ^{1}H-NMR: 1.89 (s, broad, 1H, NH), 1.99-2.17 (m, 2H), 2.64-2.88 (m, 4H), 3.00 (ddd, J = 5.1/7.3/12.5 Hz, 1H, NCH_2CH_2Ar), 3.25 (dt, J = 12.5/5.5 Hz, 1H, NCH_2CH_2Ar), 3.82, 3.84 (2 x s, combined 6H, 2 x OCH_3), 3.96 (dd, J = 3.3/8.8 Hz, 1H, NCHAr), 6.57 (s, 2H, Ar-H), 7.17-7.31 (m, 5H, -C_6H_5).

(R)-**17**: Colorless crystals, m.p. 51-56°C, $[\alpha]_{546}$ = -32.9°, $[\alpha]_{578}$ = -27.4° (c=0.37, CH_2Cl_2), yield 90 mg (30.4%). - $C_{29}H_{41}NO_4$ (467.6) Calc. C 72.3 H 8.16 N 2.9 Found C 72.1 H 8.41 N 2.9 Mol.mass 467 (MS). - IR: 3550-3200; 2950; 1520 cm^{-1}. - 400 MHz - ^{1}H-NMR: 0.68 (s, 3H, CH_3), 0.83 (s, 3H, CH_3), 0.88 (s, 3H, CH_3), 1.46 (ddd, J ~ 4/10/13 Hz, 1H), 1.75-1.87 (m, 2H), 1.89-2.00 (m, 1H), 2.02-2.12 (m, 1H), 2.15-2.23 (m, 1H), 2.42-2.59 (m, 3H), 2.64-2.78 (m, 1H), 2.81-2.98 (m, 3H), 3.11 (dd, J ~ 9/11 Hz, 1H), 3.39 (dt, J ~ 13/4 Hz, 1H), 3.58-3.64 (m, 2H), 3.84, 3.85 (2 x s, combined 6H, 2 x OCH_3), 5.53-5.57 (m, 2H), 6.49 (s, 1H, Ar-H), 6.58 (s, 1H, Ar-H), 7.16-7.31 (m, 5H, -C_6H_5).

*(1S)-1,2,3,4-Tetrahydro-6,7-dimethoxy-1-(2-phenyl-1-ethyl)isoquinoline (S)-***16a**

The same procedure as described for the synthesis of (R)-**16a** was applied for the reductive cleavage of (S)-**14a** (44 mg, 0.091 mmol) with $LiAlH_4$ (0.31 ml M solution). (S)-**16a** was isolated as a colorless oil. - $[\alpha]_{546}$ = -24.5°, $[\alpha]_{578}$ = -22.0° (c=0.77, CH_3OH), yield 17 mg (63.0%). NMR-, IR- and MS-data correspond to those observed for (R)-**16a**.

*(1R)-1-[2-(4-Chlorophenyl)-1-ethyl]-1,2,3,4-tetrahydro-6,7-dimethoxy-isoquinoline (R)-***16b**

From a mixture of (R)-**13a**/(R)-**13b** (200 mg, 0.391 mmol based on (R)-**13b**) and 2.0 ml of a M $LiAlH_4$ solution as described for (R)-**16a**. Separation of (R)-**16b** from the accompanying (R)-**16a** (which had also been formed) was accomplished by CC (ethyl ether/NEt_3 = 98/2; (R)-**16b** being retained more strongly). Colorless oil, $[\alpha]_{546}$ = +11.5°, $[\alpha]_{578}$ = +12.4° (c=1.05, CH_3OH) [ref.[19]]: $[\alpha]_D$ = +12.3° (c=0.25)], yield 21 mg (16.1%). - 400 MHz - ^{1}H-NMR ($CDCl_3$): 1.60 (s, broad, 1H, NH), 1.95-2.09 (m, 2H), 2.62-2.83 (m, 4H), 2.99 (ddd, J ~ 5/7/12 Hz, 1H, NCH_2CH_2Ar), 3.22 (dt, J ~ 12.5/5.5 Hz, 1H, NCH_2CH_2Ar), 3.82, 3.84 (2 x s, combined 6H, 2 x OCH_3), 3.93 (dd, J = 3.3/8.8 Hz, 1H, NCHAr), 6.55 (s, 1H, Ar-H), 6.57 (s, 1H, Ar-H), 7.13-7.17, 7.23-7.29 (2 x m, combined 4H, -C_6H_4Cl).

*(1R)-1,2,3,4-Tetrahydro-6,7-dimethoxy-1-[2-(3,4-dimethoxyphenyl)-1-ethyl]-isoquinoline (R)-***16c**

From 190 mg (0.353 mmol) of (R)-**13c** in 4 ml of THF and 1.13 ml of a M $LiAlH_4$ solution as described for (R)-**16a**. Reaction time 2 h. Purification by CC (ethyl ether/$EtMe_2N$ = 9/1). Colorless oil, $[\alpha]_{546}$ = +13.5°, $[\alpha]_{578}$ = +15.1° (c=0.59, CH_3OH), yield 97 mg (77.0 %). - $C_{21}H_{27}NO_4$ (357.4) Calc. C 70.6 H 7.61 N 3.9 Found C 70.4 H 7.72 N 4.1. Mol.mass 357 (MS). - IR: 3320; 2940; 1510 cm^{-1}. - 400 MHz - ^{1}H-NMR ($CDCl_3$): 1.63 (s, broad, 1H, NH), 1.96-2.15 (m, 2H), 2.63-2.82 (m, 4H), 2.99 (ddd, J ~ 5/7/12.5 Hz, 1H, NCH_2CH_2Ar), 3.24 (dt, J ~ 12.5/5 Hz, 1H, NCH_2CH_2Ar), 3.82, 3.84, 3.85, 3.86 (4 x s, combined 12H, 4 x OCH_3), 3.95 (dd, J ~ 3/8.8 Hz, 1H, NCHAr), 6.57, 6.58 (2 x s, combined 2H, 2 x Ar-H), 6.76-6.81 (m, 3H, -C_6H_3 $(OMe)_2$).

*(1R)-1,2,3,4-Tetrahydro-6,7-dimethoxy-1-[2-(3,4-dimethoxyphenyl)-1-ethyl]-2-methylisoquinoline (R)-***18**

28 mg (0.079 mmol) of (R)-**16c** were dissolved in 5.8 ml of CH_3OH. At room temp. and under stirring, 32 µl of a H_2CO solution (37%) and 25 mg (0.396 mmol) of $NaCNBH_3$ were added. The reaction mixture was adjusted to pH 5-7 by repeated addition of acetic acid. After 19 h the solvent was evaporated in vacuo and 0.8 ml of N NaOH were added. The aqueous phase was saturated with NaCl and then extracted with ethyl ether (3x). The combined org. layers were dried over $MgSO_4$ and concentrated in vacuo. The product was purified by CC (ethyl ether/NEt_3 = 9/1). Colorless oil, $[\alpha]_{546}$ = -20.2°, $[\alpha]_{578}$ = -13.5° (c=0.89, C_2H_5OH), [ref.[5]] (S)-**18**: $[\alpha]_D$ = +11° (c=0.21, C_2H_5OH)]. - The ^{1}H-NMR-data correspond to those reported[5] for (R)-**18**.

(1R, 3R, 4S)-3-Menthyl-(1,2,3,4-tetrahydro-6,7-dimethoxy-2-isoquinoline carboxylate) **20**

To a suspension of 800 mg (3.48 mmol) of **5** in 15 ml of CH_2Cl_2 1.057 g (10.45 mmol) of NEt_3 were added at room temp. followed (after cooling to 0°C) by the addition of 914 mg (4.18 mmol) of **19**. After 15 min the mixture was allowed to warm to room temp. and stirring was continued for 3.5 h. The reaction mixture was washed with 0.05 M HCl (3x) and saturated NaCl-solution (3x) and dried over $MgSO_4$. The solvent was evaporated in vacuo and the residue purified by CC (n-hexane/ethyl ether = 1/1). Colorless oil, $[\alpha]_{546}$ = -72.5°, $[\alpha]_{578}$ = -63.7° (c=0.91, CH_3OH), yield 1.23 g (94.0%). - $C_{22}H_{33}NO_4$ (375.5) Calc. C 70.4 H 8.86 N 3.7 Found C 70.4 H 8.87 N 3.7. Mol.mass 375 (MS). - IR: 1690; 1520 cm^{-1}. - 400 MHz - ^{1}H-NMR ($CDCl_3$): 0.78 (d, J ~ 7 Hz, 3H), 0.89 (d, J ~ 7 Hz, 3H), 0.90 (d, J ~ 7 Hz, 3H), 0.85-0.92 (m, signal obscured, 1H), 0.92-1.15, 1.20-1.30, 1.38-1.55, 1.65-1.72 (4 x m, combined 7H), 1.90-1.96 (m, 1H), 2.06-2.12 (m,

1H), 2.76 (s, broad, 2H), 3.65-3.70 (m, 1H), 3.85 (s, 6H, 2 x OCH_3), 4.55 (pseudo s, 2H), 4.61 (dt, J = 4/10 Hz, 1H), 6.60, 6.62 (2 x s, 2H, Ar-H). Only one set of signals has been observed.

*(1R, 3R, 4S)-3-Menthyl-[(1R)-1,2,3,4-tetrahydro-6,7-dimethoxy-1-(2-oxo-2-phenyl-1-ethyl)-2-isoquinoline carboxylate] (R)-**22** and (1R, 3R, 4S)-3-Menthyl-[(1S)-1,2,3,4-tetrahydro-6,7-dimethoxy-1-(2-oxo-2-phenyl-1-ethyl)-2-isoquinoline carboxylate] (S)-**23***

To a stirred solution of 63 mg (0.191 mmol) of **3** in 1.5 ml of CH_2Cl_2 60 mg (0.160 mmol) of **20** (in 1.5 ml of CH_2Cl_2) were added. After stirring for 16 h at room temp. the mixture was cooled to -78°C and 37 mg (0.190 mmol) of **7a** were added. Then stirring was continued for 3 h at -78°C whereafter the mixture was quenched with 3 ml of H_2O. The org. phase was washed with saturated NaCl-solution (3x), dried over $MgSO_4$ and the solvent was evaporated in vacuo. The diastereomers (R)-**22**/(S)-**23** proved to be inseparable on SiO_2 and were obtained as a mixture after CC (SiO_2, n-hexane/ethyl ether = 1/1). HPLC-analysis of the crude product revealed a diastereomeric ratio of about 1/1 (chiral column, n-hexane/isopropanol = 9/1; incomplete peak separation). Colorless crystals, m.p. 42-54°C, yield 62 mg (78.0%). - $C_{30}H_{39}NO_5$ (493.6) Calc. C 73.0 H 7.96 N 2.8 Found C 73.2 H 7.75 N 2.8. Mol.mass 493 (MS). - IR: 1690; 1670; 1520 cm^{-1}. For analytical purposes a sample of (R)-**22**/(S)-**23** was separated by prep. HPLC on a chiral column (n-hexane/isopropanol = 9/1).

Isomer 1 (being retained less strongly): 400 MHz - ^{1}H-NMR ($CDCl_3$): 0.63-1.10 (m, 11H), 1.20-1.50 (m, 3H), 1.64-2.17 (m, 4H), 2.72-2.92 (m, 2H), 3.22-3.60 (m, 3H); 3.75, 3.84 (2 x s, combined 6H, 2 x OCH_3), 3.86-3.95, 4.10-4.20 (2 x m, combined 1H), 4.48-4.60 (m, 1H), 5.65-5.80 (m, 1H), 6.61, 6.66 (2 x s, combined 2H, Ar-H), 7.44-7.57 (m, 3H, Ar-H), 7.91-8.01 (m, 2H, Ar-H). The signals reported arise from rotational isomers that are present in about equal amounts.

Isomer 2: 400 MHz - ^{1}H-NMR ($CDCl_3$): 0.62-1.00 (m, 11H), 1.20-1.43 (m, 3H), 1.59-2.05 (m, 4H), 2.72-2.92 (m, 2H), 3.24-3.50 (m, 3H), 3.75, 3.78, 3.84, 3.85 (4 x s, combined 6H, 2 x OCH_3), 3.90-4.00, 4.10-4.20 (2 x m, combined 1H), 4.49-4.55 (m, 1H), 5.68-5.74 (m, 1H), 6.59-6.70 (m, 2H, Ar-H), 7.45-7.58 (m, 3H, Ar-H), 7.91-8.02 (m, 2H, Ar-H). The signals reported arise from rotational isomers that are present in about equal amounts.

References and Footnotes

1 Part VI: K. Th. Wanner and I. Praschak, Heterocycles *29*, 29 (1989).

2 a) F. Külz and C. Schöpf, D.R.P. 726 173, C.A. *37*, 6277 (1943);
b) F. Külz, D.R.P. 728 326, C.A. *37*, 6675 (1943);
c) F. Külz, D.R.P. 732 502, C.A. *38*, 753 (1944).

3 A. Brossi, H. Besendorf, L.A. Pirk, and A. Rheiner: "Isoquinoline Analgetics". In: Analgetics, Medicinal Chemistry (G. deStevens, ed.), Vol. 5, p. 281, Academic Press, London 1965.

4 T. Kametani and M. Koizumi: "Phenethylisoquinoline Alkaloids". In: The alkaloids (R. Manske, ed.) Vol. XIV, p. 265, Academic Press, London 1979.

5 A.J. Aledesanmi, Ch. J. Kelley, and J.D. Ceasy, J. Nat. Prod. *46*, 127 (1983).

6 For a survey of the presently available methods see: J.M.P. Huber and D. Seebach, Helv. Chim. Acta *70*, 1944 (1987). See also: M. Yamato, K. Hashigaki, s. Ishikawa, and N. Qais, Tetrahedron Lett. *29*, 6949 (1988).

7 K. Th. Wanner and G. Höfner, Arch. Pharm. (Weinheim) *322*, 99 (1989).

8 K. Th. Wanner, A. Kärtner, and E. Wadenstorfer, Heterocycles *27*, 2549 (1988) and references cited therein.

9 For a short communication see reference[1].

10 T. Shono: "Electroorganic Chemistry as a New Tool in Organic Synthesis", p. 63, Springer-Verlag, Berlin 1984.

11 M. Onda, K. Yuasa, and J. Okada, Chem. Pharm. Bull. *22*, 2365 (1974).

12 For similar oxidation reactions utilizing triphenylcarbenium perchlorate see: T.V. Stupnikova, A.K. Sheinkman, L.A. Rybenko, and N.A. Klynev, Khim. Geterotsikl. Soedin. 1978, 251; C.A. *88*, 190638b (1978).

13 H.E. Zaugg, Synthesis *1984*, 181.

14 P.D. Palasz, J.H.P. Utley, and J.D. Hardstone, J. Chem. Soc. Perkin Trans. II, *1984*, 807.

15 Further details of the crystal structure investigation are available on request from the Fachinformationszentrum Energie, Physik, Mathematik GmbH, D-7514 Eggenstein-Leopoldshofen 2, on quoting the depository number CSD 53835, the names of the authors and the journal citation.

16 The structure was solved by use of SHELXS 86 and refined with SHELXTL 4.1. Hydrogen atom positions were calculated for idealized geometry with $U_H = 1.2 \times U_C$; R = 0.077, $R_W = 0.00784$, g = 0.0007, $w = 1/(\sigma^2 (F_o) + g \times F_o^2)$. All atomic positions except those for the tetrafluoroborate anion have been refined without restrictions. The tetrafluoroborate anion has been refined for an idealized tetrahedral geometry.

17 This could be the result of steric hindrance or of stereoelectronic factors as well.

18 K.Th. Wanner and A. Kärtner, Arch. Pharm. (Weinheim) *320*, 1253 (1987).

19 A. Brossi and F. Burkhardt, Helv. Chim. Acta *44*, 1558 (1961).

20 The separation of diastereomers via a menthyl derived carbamate in a related pyrrolidine system also failed: T. Nagasaka, H. Yamamoto, H. Hayashi, M. Watanabe, and F. Hamaguchi, Heterocycles *29*, 155 (1989).

[Ph690]