INTRAMOLECULAR CYCLIZATION WITH OXOCARBENIUM ION. SYNTHESIS OF 1-AZABICYCLO[3.3.1]NONENE AND [3.2.1]OCTENE DERIVATIVES

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Abstract: Hydroxy- and aryl-substituted 1-azabicyclo[3.3.1]nonene and [3.2.1]octene derivatives have been synthesized by the intramolecular cationic cyclization of 4-aryl-1,2,5,6-tetrahydropyridines bearing an acetal moiety in the nitrogen substituent. Factors governing the stereoselectivity of the ring closure step have been disclosed. Two compounds were resolved into the enantiomers and the absolute configuration of one of them was deduced from CD investigations. Among the new compounds substances with valuable antiamnesic effect have been found.

Among the 1-azabicycloalkane derivatives, substituted in position 3 or 4 by a group capable of forming hydrogen bonds, several highly potent muscarinic agonists were found, which might have potential as cognition enhancers in psychiatric disorders associated with dementia.[1] On the other hand the combination of the hydrogen bond-forming group of the above structures with an aryl moiety results generally in an affinity to the $5HT_3$ receptor and some representative antagonists of this group may be used as e.g. antiemetics, anxiolytic and memory enhancers.[2] Up till now practically no effort has been devoted to the synthesis of compounds, where an aryl group was directly attached to the 1-azabicyclic part of the molecule, distant from the bridgehead nitrogen atom

and in the proximity of the hydrogen bond-forming group, both of which were thought to be responsible for the receptor binding. Therefore, we decided to synthesize hydroxy and aryl substituted 1-azabicyclo[3.3.1]nonane and [3.2.1]octane derivatives, where the hydroxy group would serve as a hydrogen bond-forming moiety to assure the receptor binding or it may serve as starting point for further chemical transformations.

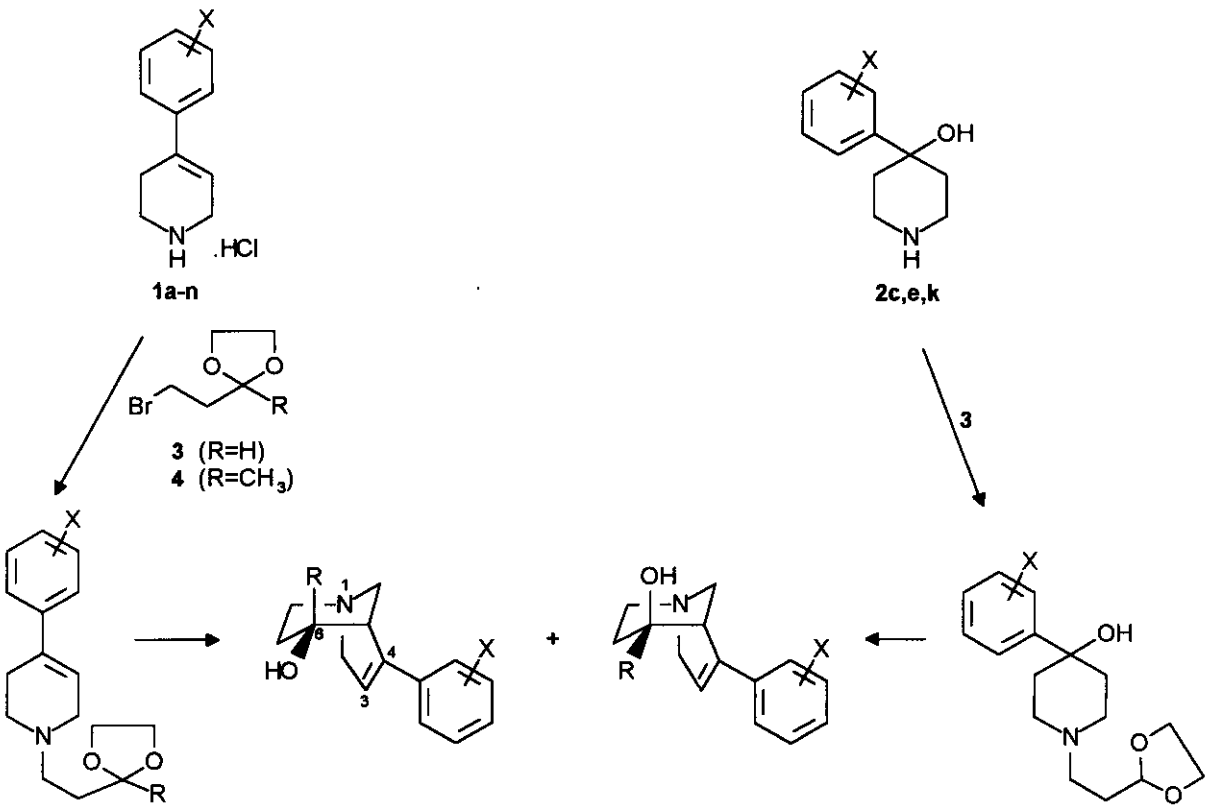
The 1-azabicyclo[3.3.1]nonane ring system, also called isogranatanine skeleton, was earlier synthesized e. g. by Dieckmann condensation[3] and intramolecular *N*-alkylation[4] as well as by intramolecular electrophylic cyclization of 1-allyl-1,2,5,6-tetrahydropyridine compounds in acidic medium, where a carbenium ion, resulting from an obvious protonation of the *N*-substituent, served as electrophile.[5] Our previous work showed that the same ring system can also be synthesized by Prins type intramolecular cyclization of an oxocarbenium ion, generated *in situ* from a carbonyl group.[6]

Whereas the methods mentioned above give only limited possibility to introduce functional groups into the azabicyclic ring system, we expected, that by applying the useful cationic ring closure strategy with oxocarbenium ions, generated from an acetal group,[7] the desired ring systems could be obtained. In the intramolecular cationic cyclizations with oxocarbenium ions isolated carbon-carbon double bonds,[8,9,11] triple bonds[9] and π-nucleophiles[10] are used as nucleophilic terminator. Only a limited number of examples has been reported, where a conjugated double bond was applied as a nucleophilic partner.[6,11,12]

We have found that aryl substituted 1,2,5,6-tetrahydropyridine derivatives (**5**) and (**9**), bearing a cyclic acetal ring in the side chain, treated with strong mineral acids, give isomeric mixtures of 1-azabicyclo[3.3.1]nonene derivatives (**6** + **7**) and (**10** + **11**), respectively (Scheme 1). From preparative point of view it was sometimes advantageous to perform the cyclization reaction from the carbinols (**8**). In the latter case a dehydration step obviously precedes the ring closure.

The starting compounds (**5**) and (**8**) were prepared from known 4-aryl-1,2,5,6-tetrahydropyridine hydrochlorides (**1**) or 4-aryl-4-hydroxypiperidine derivatives (**2**) by alkylation with 2-(2-bromoethyl)-1,3-dioxolane (**3**). To prepare the starting compounds (**9**), 2-(2-bromoethyl)-2-methyl-1,3-dioxolane (**4**) was used as alkylating agent. Generally **5**, **8**, and **9** were obtained as sufficiently pure raw products and were used in the cyclization reaction in most of the cases without further purification.

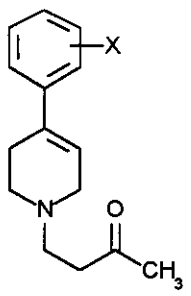
The products arising in the cyclisation reaction are racemates and the hydroxy group formed can occupy the equatorial = *endo*[13] (**6** and **10**) or the axial = *exo*[13] position (**7** and **11**). It was found that when substituent R was hydrogen, predominantly the **6** *endo*-hydroxy isomers are formed. The *endo-exo* ratio were in these cases



	a	b	c	d	e	f	g
X	H	3-Cl	4-Cl	3-F	4-F	2-CH_3	3-CH_3

	h	i	j	k	l	m
X	4-CH_3	3-CF_3	4-CF_3	2-OCH_3	4-OCH_3	4-SCH_3

	n
X	1-naphthyl instead of-C_6H_4-X



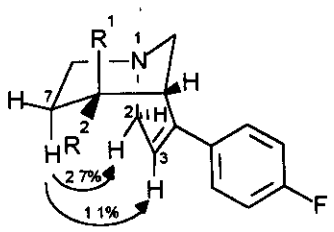
12a,c

Scheme 1

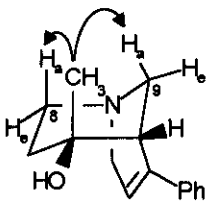
generally 9:1 or higher. Otherwise, with R = CH_3 substitution the *endo* and *exo* isomers were obtained in commensurable quantity, with higher excess of the *exo*-hydroxy isomers **(11)** only. In the latter reactions the cyclization products were always accompanied by oxo compounds **(12)**, which resulted in a parallel hydrolytic process of the starting acetals **(9)**. It was also established that compounds **(12)** are not intermediates of the cyclization process, because they could not be transformed into cyclized products under the same conditions.

The structure of compounds **(6)** and **(7)** were deduced by ^{1}H-nmr measurements on the corresponding ester derivatives. E.g. the 6-H of **13** (a propionate ester of **6e**) showed a signal at δ = 4,95 ppm with a *dt* multiplicity, corresponding to a diaxial and two axial-equatorial coupling (J_1 = 11.2 Hz, $J_2 = J_3$ = 4.9 Hz), supporting its axial position. Furthermore, the 6-H signal of the corresponding exo diastereomer **(14)** gave only a broad singlet at δ = 5.08 ppm, owing to the small J_{ee} coupling constants, supporting by this its equatorial position. To establish the unequivocal structure of **13**, the chair conformation of the piperidine ring in **13** was proven by NOE measurements as well, namely saturation of the 7-H_{axial} signal caused an 1.1% NOE on the signal of the 3-H_{vinyl} proton and a 2.7 % NOE on one of the 2-H signals, as is shown in the formula (Figure 1.).

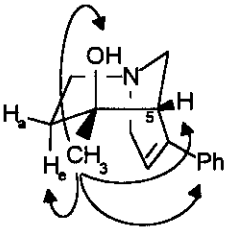
^{1}H-Nmr-NOE experiments were used to establish the position of the methyl group in **10** and **11** as well. Irradiation of the 6-CH_3 signal in **10a** caused NOE at the 8-H_{axial} and 9-H_{axial} proton signals, while saturation of the 6-CH_3 signal in **11a** resulted in NOE at the 5-H, 7-H_{axial} and phenyl signals as well as on the hydroxyl proton, as shown in Figure 1. This is in accordance with the axial position of the 6-CH_3 group in **10a**, while in the case of **11a** it takes the equatorial position.



13 (R_1=H, R_2=CH_3CH_2COO)
14 (R_1=CH_3CH_2COO, R_2=H)



10a

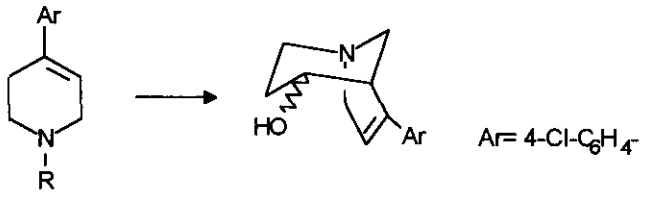


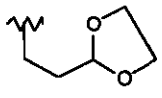
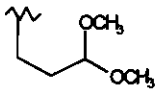
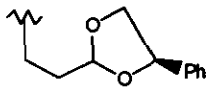
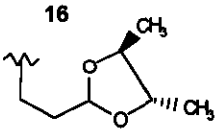
11a

Figure 1

We have also investigated the factors which influence the *endo/exo* product ratio in the stereoselective cyclization reaction of type **5** and related acetals. The results are summarized in the Table 1.

Table 1. Investigation of the Factors Governing the Product Ratio



R	acid/LA	T °C[a]	6c (*endo*)%[b]	7c (*exo*)%[b]
 **5c**	37% HCl	100	90	10
	18% HCl	100	89	10
	CF_3COOH	60	71	29
	CH_3SO_3H	25	94	6
	70% $HClO_4$	25	82	18
	70% $HClO_4$	80	38	61
 **15**	18% HCl	100	86	8
 **16**	24% HCl	100	86	8
	CF_3COOH	60	68	25
	$BF_3 . O(C_2H_5)_2$	40	-	-
 **17**	24% HCl	100	89	7

a) Temperature of the ring closure reaction. b) Determined by gc Temperature of termostate: isoterm at 200°C for 10 min, then upheating to 200-275°C with a speed of 5°C/min Temperature of injector/detector 295°C/295°C Concentration of sample 2 mg/1 ml DMSO, injected volume: 1µl R_T(**6c**):~7.77 min; R_T(**7c**).~8.09 min

It is seen from Table 1 that neither the structure of the acetal moiety nor the acid concentration, but rather the kind of acid influence the product ratio. It was also established that the formation of *endo* (equatorial)-hydroxy products is kinetically favoured and both the *endo-exo* mixture and the pure *endo* diastereomer could be isomerized into a mixture of **6** + **7**, where the *endo-exo* ratio is *ca.* 4:6. This isomerization reaction can be

executed by heating with 70% $HClO_4$ to 80°C for *ca.* 1 hour and made actually possible the preparation of **7c** and **7e** in reasonable quantity.

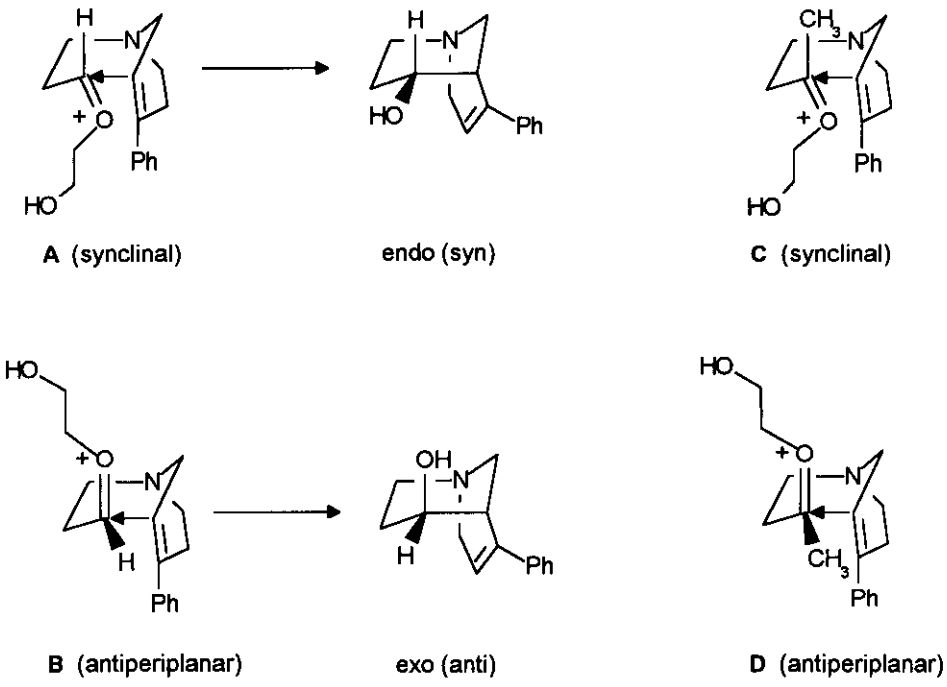
No ring closure reaction could be observed with Lewis acids as boron trifluoride etherate or dichlorobis(isopopoxy)titanium (the latter was prepared by equilibration of equivalent amount of titanium isopropoxide and titanium chloride in dichloromethane as solvent[14]). Stronger Lewis acids, which are often used to generate oxocarbenium ions from acetals,[15] could not be applied because of the precipitation, which in dichloromethane occurs due to complexation with the tertiary amine structure of compounds (**5-7**). In these multicomponent reaction mixtures only negligible amounts of **6** or **7** could be detected by tlc or gc methods.

Attempts were made to interpret the predominant formation of the *endo*-hydroxy isomers during the cyclization of compounds (**5**). We can presume that our cyclization process takes place *via* an oxocarbenium intermediate (Scheme 2.). It was shown in the literature that in cleavage reactions of acetals by a nucleophile in the presence of Lewis acid an oxocarbenium ion occurs.[16] In the case of our cyclization reactions the occurance of the oxocarbenium ion is even more likely, because acidic conditions are used.

During the cyclization reaction a synclinal (**A**) and an antiperiplanar (**B**) like transition state conformation of the oxocarbenium ion can be supposed leading to the formation of the *endo* (syn) and *exo* (anti) isomers, respectively. In this process a clear predominance of the synclinal transition state must lead to the preferred formation of the *endo* product. This finding is in accordance with the results of Denmark and coworkers, where simple unbranched aliphatic acetals of cyclohexenecarbaldehyde bearing an allylsilane moiety as a nucleophile were cyclized with trifluoroacetic acid and some simple Lewis acids. They also found a clear preference of the syn over the anti product and suggested a stereoelectronic effect in origin as explanation of this.[10b]

A possible explanation for the missing stereoselectivity with the R=CH_3 substituted **9a,c** acetals can be given by investigation of their analogous transition states: **C** and **D**. Owing to possible steric interference of the methyl group in **C** with the future methylene bridge, the transition state **D** seems more likely. In this case the stereoelectronic factors will probably be overcome by the steric effects and rather the formation of the *endo*-methyl isomers (**11**) is favoured.

Two chiral acetals (**16** and **17**; see Table 1) have also been synthesized and **16** was a suitable model to study whether a chirality transfer can occur during the ring closure process. Unfortunately, the products obtained from the acidic ring closure reactions of **16** showed no optical rotation. This lack of optical activity can also be regarded as an indirect evidence for the existence of an oxocarbenium ion, (similar to **A** or **B**) with an extended

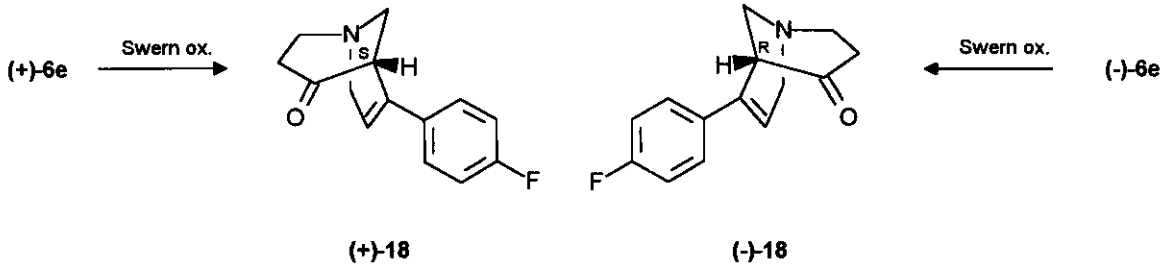


Scheme 2

linear structure, where the chiral center is at least in a 1,3 or 1,4 relationship to the reacting carbenium carbon. Therefore, it may have little or no influence on the cyclization itself. With a bicoordinate Lewis acid (like: $TiCl_4$ or $SnCl_4$) no reactions could be performed by the reasons mentioned before.

For the sake of more in depth biological investigations compound (**6e**) was resolved into the enantiomers by the fractional crystallization of the diastereomeric salt formed with optically active acid. (For details see Experimental).

To determine the absolute configuration of the enantiomers of **6e** by cd spectroscopy, both enantiomers were oxidized by Swern oxidation into the corresponding ketones ((+)-**18**) and ((-)-**18**) (Scheme 3).



Scheme 3

The octant rule[17] was used to determine the absolute configuration of the asymmetric center C-5.

(+)- and (-)-**18** are β-amino ketones, in which the carbonyl group interacts with the lone pair on the bridgehead nitrogen atom[18] (Figure 2a). In order to eliminate this interaction the enantiomers have been transformed into their salts by adding hydrochloride. The spectral change is shown in Figure 2b.

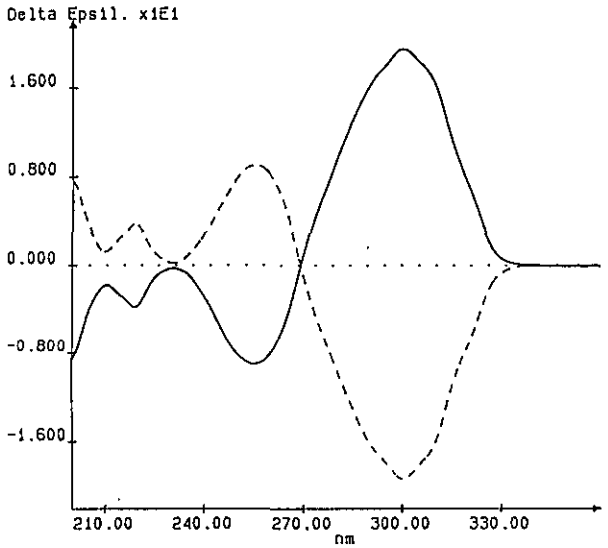


Figure 2a. Cd spectra of the enantiomers of β-amino ketones (free bases):— (+)-**18** and ···(-)**18**.

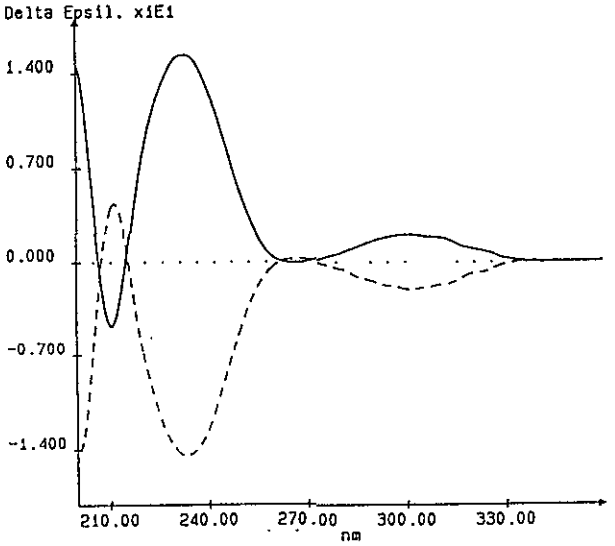


Figure 2b. Cd spectra of the enantiomers of β-amino ketone hydrochloride: — (+)-**18**·HCl and ··· (-)-**18**·HCl.

The first band near 300 nm which appears with decreased intensity in the spectrum of the protonated molecule comes from the n→π* transition of the carbonyl chromophore. Its sign is determined by the absolute configuration of the asymmetric center C-5. To apply the octant rule (Figure 3), the *R* and *S* enantiomeric forms of the molecule were suitably placed in the octant-diagram. As shown in Figure 4, the majority of the perturbing atoms of the *S* form are found in a positive sector. According to the rule the sign of the n→π* band of the ketone group has to be positive and the configuration of the asymmetric center C-5 of (+)-**18** is *S*. (Scheme 3.) (Contrary to the β-amino hydrochloride salts, the anti-octant effect is not valid for this molecule, since the nitrogen atom is lying in one of the symmetry planes.)

The rule for β,γ-unsaturated oxocompounds[19] has been also applied to determine the absolute configuration of asymmetric center C-5, since the carbonyl-chromophore is "homoconjugated" with the olefine group in enantiomers (**18**). This rule also predicts a positive sign of the nπ* band, in agreement with octant rule.

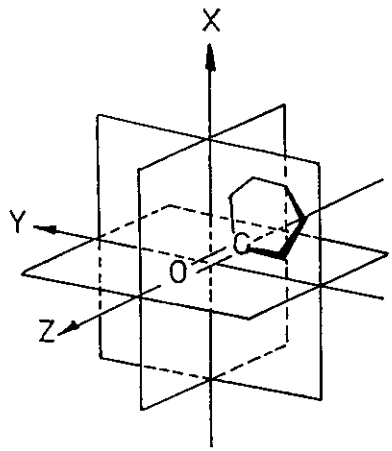


Figure 3. Placing of the cyclohexanone molecule in the octant-diagram as an example.

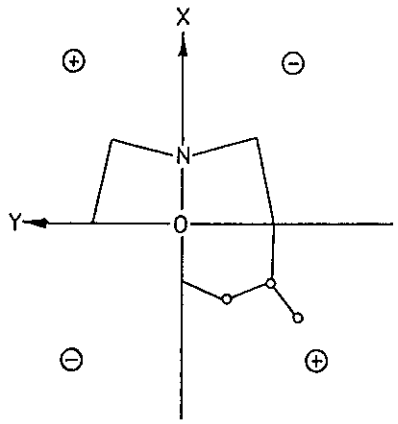


Figure 4. The sectors of the back quadrant with changing signs of the optical rotatory power.

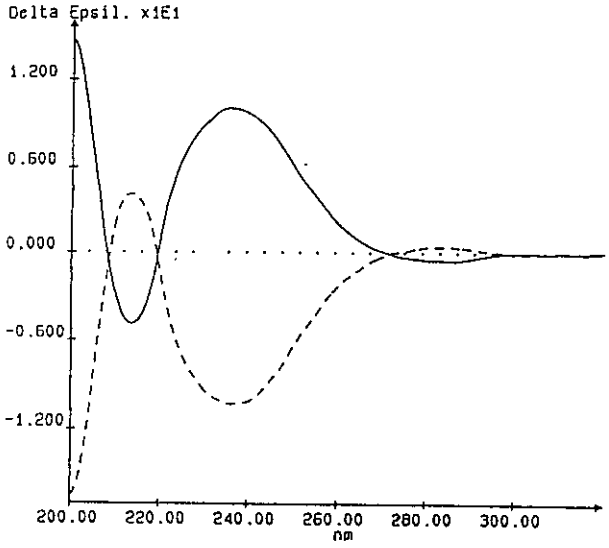


Figure 5a. Cd spectra of the enantiomers of alcohols: — (+)-6e and ··· (-)-6e

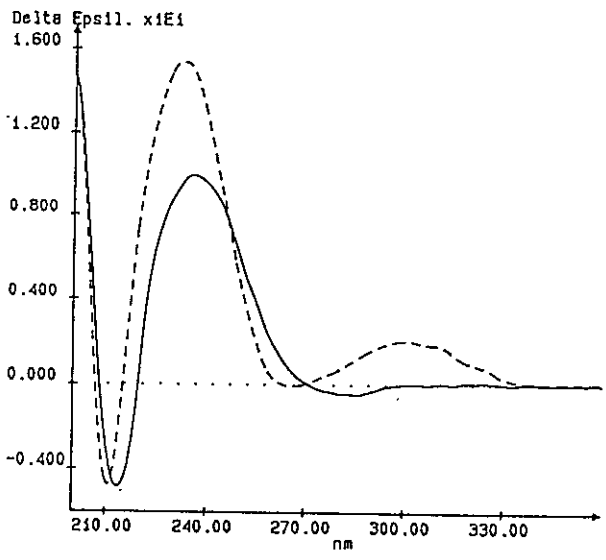


Figure 5b. Cd spectra of the alcohol (+)-6e — and of its corresponding ketone HCl: (+)-18·HCl ···

The cd spectrum of (+)-**18** contains two more characteristic bands: a strong positive band at 232 nm and a negative one at 210 nm. The first band is due to the electron transition ^1L_a of the aromatic chromophore, the second likely originates from the $\pi\rightarrow\pi^*$ transition of the noncoplanar styrol-like olefine-group. The cd spectra of the optically active alcohols (+)- and (-)-**6e** are shown in Figure 5a.

The spectra of the alcohols and of their corresponding ketone hydrochloride salts are very similar (Figure 5b) except for the longer wavelenghts, where the very weak L_b band appears, belonging to the first $\pi\rightarrow\pi^*$ transition of the substituted phenyl group, with an opposite sign to the band of $n\rightarrow\pi^*$ transition coming from the ketone group. This band is overlapped by the stronger band of carbonyl chromophore in the spectra of ketones.

Table 2. Cd Data of the β-Amino ketone hydrochloride Salts and Their Corresponding Alcohols.

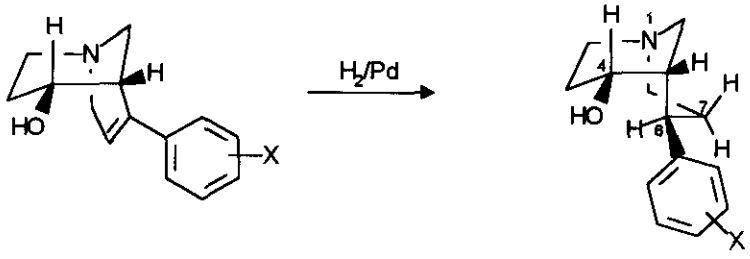
	nm	Δε		nm	Δε
(+)-18	301	2.03	**(+)-6e**	286	-0.49
	233	15.33		236	10.02
	211	-4.77		212	-4.83
(-)-18	301	-2.05	**(-)-6e**	284	0.41
	232	-14.44		236	-10.32
	211	4.35		213	4.04

Finally, summarising the results of cd measurements, we determined the absolute configuration of the optically active alcohols containing hydroxyl group in equatorial = *endo* position. Accordingly, the asymmetric centers of the enantiomer ((+)-**6e**) have configuration C-5(*S*) and C-6(*R*), towards (-)-**6e**: containing C-5(*R*) and C-6(*S*).

Compounds (**6**) also served as starting materials for further chemical transformations.[20] In the catalytic hydrogenations of compounds (**6**) with palladium-charcoal as catalyst, hydrogen addition occurred predominantly from the *endo* side, providing stereoselectively the 6-*exo*-phenyl-1-azabicyclononane derivatives (**19**) (Scheme 4). However a careful investigation of the mother liquor of **19a** showed the minor diastereomer in negligible quantity.

The *exo*-equatorial position of the phenyl substituent in **19a** was established by ^{1}H-nmr-NOE measurements because the multiplicity of the 6-H signal could not be determined owing to overlapping of signals in the simple

^{1}H-nmr spectrum. When the signal of the phenyl protons was saturated, 2.1% NOE was measured on the signal of the 7-H_{axial} as well as 2.5% NOE could be found on the 6-H signal and a *dt* multiplicity was established for the latter proton with coupling constants (J_1= 13.5 Hz, $J_2 = J_3$ = 3.5 Hz) corresponding to a diaxial and two axial-equatorial coupling. This is in accordance with an axial position for 6-H and an equatorial phenyl group as shown in Scheme 4.



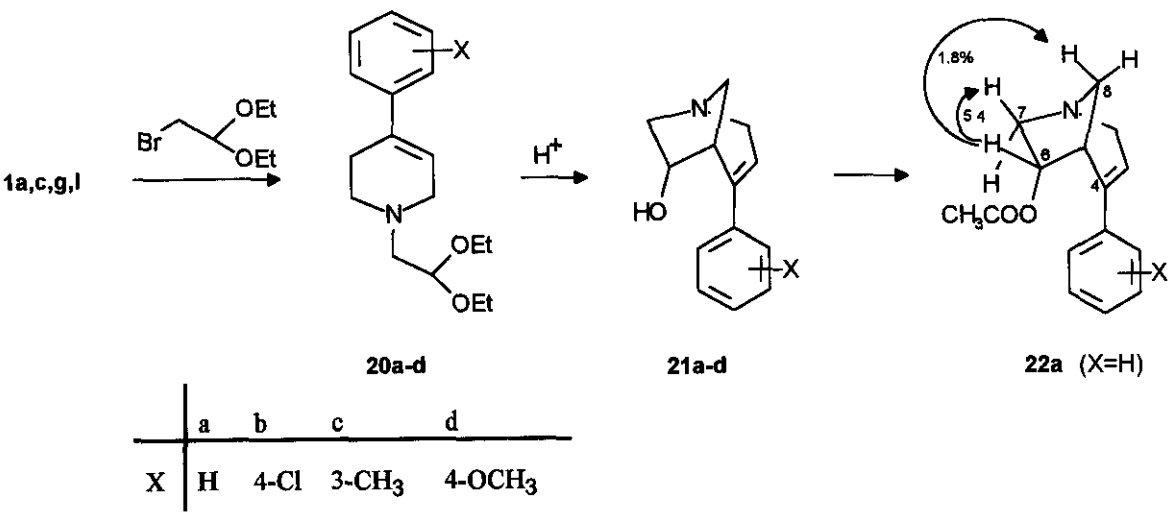
6a,e,g,h,j,k **19a,e,g,h,j,k**

	a	e	g	h	j	k
X	H	4-F	3-CH_3	4-CH_3	4-CF_3	2-OCH_3

Scheme 4

The succesful synthesis of 1-azabicyclo[3.3.1]nonene derivatives prompted us to synthesize their analogs with one carbon atom less: the corresponding 1-azabicyclo[3.2.1]octenes (Scheme 5.). As starting compounds for this ring closure reaction, **20a-d** acetals were prepared from the corresponding 4-phenyl-tetrahydropyridines by alkylation with bromoacetaldehyde diethyl acetal. By treating the acetals (**20a-d**) with mineral acid, the azabicyclooctenes (**21a-d**) were obtained and isolated with modest yield. The diastereomers with quasi-equatorial 6-*endo*-hydroxy group could be isolated only. In some cases from the multicomponent reaction mixture fractions containing ethoxy-substituted 1-azabicyclooctanes could be isolated in negligible amount and revealed by ^{1}H-nmr, but preparation of them was not attempted. These side products originate from the incomplete ether fission after the ring closure. In this respect the 1,3-dioxolane ring of compounds (**5**) and (**9**), as an oxocarbenium ion precursor, was of advantage, because in the ring closure reactions of **5** and **9** no ether type compounds (2-hydroxyethoxy-azabicyclononenes) could be found beside the expected products.

The *endo* position of the 6-hydroxy group in products (**21**) was established again by ^{1}H-nmr-NOE experiments



20a-d **21a-d** **22a** (X=H)

	a	b	c	d
X	H	4-Cl	3-CH_3	4-OCH_3

Scheme 5

on the corresponding esters. Thus, e.g. in the case of compound **(22a)** a saturation of the 6-H signal caused NOE on the vicinal 7-H and on one of the signals of the methylene bridge protons, as shown in Scheme 5.

Compounds **(6,7,10,11** and **21)** as well as some of their ester derivatives[20] were used for biological screening. Generally, only modest affinity to the muscarinic receptor was noticed, however, some of the compounds **(6b,6c,6e,13,19a)** showed very remarkable *in vivo* antiamnesic effect in the scopolamine- or electroshock-induced passive avoidance response in rats.[21] Therefore, this effect was attributed to the involvement of serotonergic mechanisms. Indeed, the most active substances were found to show a significant affinity to the $5HT_3$ receptor, although in some related tests they behave somewhat differently from the known $5HT_3$-receptor antagonists.[22] Compound **((+)-13)** (as hydrochloride with the code GYKI-46903) had been chosen for further investigation as a memory enhancer.[23, 30]

EXPERIMENTAL

Melting points: Boetius hot-stage microscope, uncorrected values. Ir spectra were measured in KBr with a Bruker IFS-85 spectrophotometer. Nmr spectra were recorded with a Bruker AC 250 instrument (^1H, 250 MHz; ^{13}C, 63 MHz) in deuterochloroform with tetramethylsilane as internal standard at T = 298 K. Other solvents are indicated. Column chromatography was performed on silica gel (Kieselgel 60, Merck). For analytical gc measurement the Chrompack 9000 GC equipment with flame ionization detector was used, with a

capillary column: 25 m × 0,32 mm, stationary face: CP Sil 5CB. For hplc a Waters Millipore LC System with a variable wavelenght detector at 254 nm was used. Cd was measured with a Jobin-Yoon dichrograph Mark VI. Pathlength of the cell was 0.05 cm. The concentrations of the solutions were about 1 mmol/l in 96% ethanol (Fluka).

General Procedure for the Synthesis of the Tetrahydropyridine Derivatives (5a-n) and (9a,c). 33.0 mmol of the appropriate 4-aryl-1,2,5,6-tetrahydropyridine hydrochloride (**1**) was mixed with 50 ml of DMF and 8.0 g (75 mmol) of Na_2CO_3. To the mixture was added droppwise over 30 min 7.21 g (39.8 mmol) of 2-(2-bromoethyl)-1,3-dioxolane (**3**) or 2-(2-bromoethyl)-2-methyl-1,3-dioxolane (**4**) and then it was heated at 80°C for 3 - 5 h. After the reaction was complete, the mixture was diluted with water and the product was separated or extracted. **5a,b,d,f,g,i,k,n** and **9a** were isolated as oils and were pure enough for the cyclization reaction.

4-(4-Chlorophenyl)-1-[3,3-(ethylenedioxy)propyl]-1,2,5,6-tetrahydropyridine (5c): mp 99-100°C (iPrOH); ir : 1642, 1140, 1034, 1100 cm^{-1}; ^{1}H-nmr δ 3.20 (br s, 2H), 3.93 (m, 4H), 5.02 (t, J = 7.0 Hz, 1H), 6.14 (br s, 1H). Anal. Calcd for $C_{16}H_{20}NO_2Cl$: C 65.41; H 6.86; N 4.77. Found : C 65.27; H 6.81; N 4.67.

1-[3,3-(Ethylenedioxy)propyl]-4-(4-fluorophenyl)-1,2,5,6-tetrahydropyridine (5e): mp 72-74°C (iPrOH); ^{1}H-nmr δ 1.95 (m, 2H), 3.12 (m, 2H), 2.50 - 3.75 (m, 6H), 3.81-4.05 (m, 4H), 4.95 (d, J = 5.9 Hz, 1H), 6.00 (br s, 1H), 6.98 (dd, J_1 =J_2 = 8.8 Hz, 2H), 7.32 (dd, J_1 = 8.8, J_2 = 5.9 Hz, 2H). Anal. Calcd for $C_{16}H_{20}NO_2F$: C 69.29; H 7.27; N 5.05. Found : C 68.57; H 7.23; N 5.06.

1-[3,3-(Ethylenedioxy)propyl]-4-(4-tolyl)-1,2,5,6-tetrahydropyridine (5h): mp 78-82°C (iPrOH); ^{1}H-nmr δ 1.95 (m, 2H), 2.33 (s, 3H), 2.55 (m, 2H), 2.62 (t, J = 7.8 Hz, 2H), 2.72 (t, J = 5.5 Hz, 2H), 3.15 (m, 2H), 3.80 - 4.05 (m, 4H), 4.95 (t, J = 4.6 Hz, 1H), 6.07 (m, 1H), 7.11 (d, J = 8.0 Hz, 2H), 7.29 (d, J = 8.0 Hz, 2H). Anal. Calcd for $C_{17}H_{23}NO_2$: C 74.69; H 8.48; N 5.12. Found: C 74.50; H 8.37; N 5.03.

1-[3,3-(Ethylenedioxy)propyl]-4-(4-trifluoromethylphenyl)-1,2,5,6-tetrahydropyridine (5j): mp 105-109°C (iPrOH); ^{1}H-nmr δ 1.96 (m, 2H), 2.58 (m, 2H), 2.64 (t, J = 7.8 Hz, 2H), 2.74 (t, J = 5.8 Hz, 2H), 3.22 (m, 2H), 3.80 - 4.05 (m, 4H), 4.97 (t, J = 4.8 Hz, 1H), 6.15 (m, 1H), 7.47 (d, J = 8.4 Hz, 2H), 7.57 (d, J = 8.4 Hz, 2H).

Anal. Calcd for $C_{17}H_{20}NO_2F_3$: C 62.37; H 6.16; N 17.41. Found: C 62.21; H 6.04; N 17.17.

1-[3,3-(Ethylenedioxy)propyl]-4-(4-methoxyphenyl)-1,2,5,6-tetrahydropyridine (5l) : mp 101-102°C (iPrOH); ^{1}H-nmr δ 1.92 (m, 2H), 2.40 - 2.80 (m, 6H), 3.15 (br s, 2H), 3.85 (s, 3H), 3.90 - 4.12 (m, 4H), 4.95 (t, J = 7.3 Hz, 1H), 5.90 (br s, 1H), 6.82 (d, J = 8.5 Hz, 2H), 7.30 (d, J = 8.5 Hz, 2H). Anal. Calcd for $C_{17}H_{23}NO_3$: C 70.56; H 8.01; N 4.84. Found: C 70.58; H 8.12; N 4.79.

1-[3,3-(Ethylenedioxy)propyl]-4-(4-methyltiophenyl)-1,2,5,6-tetrahydropyridine (5m): preparation of the appropriate starting compound (**1m**) is described in lit.[20] From this the general procedure was followed: mp 98-99°C (iPrOH); ^{1}H-nmr δ 2.48 (s, 3H), 3.15 (br s, 2H), 3.80 - 4.00 (m, 4H), 4.95 (t, J = 7.1 Hz, 1H), 7.18 (d, J = 8.4 Hz, 2H), 7.30 (d, J = 8.4 Hz, 2H).

1-[3,3-(Ethylenedioxy)butyl]-4-phenyl-1,2,5,6-tetrahydropyridine (9a) as (*E*)-2-Butenedioate (1:1): **9a** was isolated as oil and fumarate salt was prepared with equivalent fumaric acid in ethanol. mp 176°C (MeOH). Anal. Calcd for $C_{17}H_{23}NO_2 \cdot C_4H_4O_4$: C 64.76; H 6.99; N 3.60. Found: C 64.75; H 6.85; N 3.65.

4-(4-Chlorophenyl)-1-[3,3-(ethylenedioxy)butyl]-1,2,5,6-tetrahydropyridine (9c): mp 115-116°C (MeOH); ir: 2750 and 2710, 1648, 1162, 1082, 1065 cm^{-1}; ^{1}H-nmr δ 1.40 (s, 3H), 2.03 (m, 2H), 2.61 (m, 2H), 3.23 (m, 2H), 4.04 (br s, 4H), 6.20 (m, 1H). Anal. Calcd for $C_{17}H_{22}NO_2Cl$: C 66.33; H 7.20; N 4.55. Found: C 66.34; H 6.92; N 4.47.

General Procedure for the Synthesis of Alkylated Tetrahydropyridine Derivatives (8c,e,f,k). The procedure used corresponds essentially to the process which was applied in the synthesis of compounds (**5**) and (**9**).
4-(4-Chlorophenyl)-1-[3,3-(ethylenedioxy)propyl]-4-hydroxypiperidine (8c): mp 134-136°C (iPrOH); ^{1}H-nmr δ 1.55 (d, J = 12.9 Hz, 2H), 1.70 - 1.92 (m, 4H), 2.20 - 2.74 (m, 6H), 3.71 - 3.95 (m,4H), 4.85 (t, J = 7.1 Hz, 1H), 4.90 (OH, br s), 7.30 - 7.45 (d, J = 8.2 Hz, 4H). Anal. Calcd for $C_{16}H_{22}NO_3Cl$: C 61.63; H 7.11; N 4.49; Cl 11.37. Found: C 61.69; H 7,28; N 4.54; Cl 11.38.

1-[3,3-(Ethylenedioxy)propyl]-4-(4-fluorophenyl)-4-hydroxypiperidine (8e): mp 110-112°C (iPrOH); ^{1}H-

nmr δ 4.90 (t, J = 4.9 Hz, 1H), 7.00 (dd, $J_1 = J_2$ = 8.7 Hz, 2H), 7.34 (dd, J_1 = 8.7, J_2 = 5.7 Hz, 2H). Anal. Calcd for $C_{16}H_{22}NO_3F$: C 65.06; H 7.51; F 6.43. Found C 64.88; H 7.53; F 6.38.

1-[3,3-(Ethylenedioxy)propyl]-4-hydroxy-4-(2-tolyl)piperidine (8f): mp 204-205°C (iPrOH); ^{1}H-nmr δ 2.15 (d, J = 13.8 Hz, 2H), 2.27 (m, 2H), 2.60 (s, 3H), 2.74 (m, 2H), 3.05 (br s, 3H), 3.30 (br s, 4H), 3.80 - 4.05 (m, 4H), 4.95 (t, J = 7.1 Hz, 1H), 7.05 - 7.42 (m, 4H).

1-[3,3-(Ethylenedioxy)propyl]-4-hydroxy-4-(2-methoxyphenyl)piperidine (8k): partly crystallized oil; ^{1}H-nmr δ 3.50 (s, 3H), 4.72 (m, 1H), 5.45 (OH, br s), 6.47 (d, J = 8.8 Hz, 1H), 6.58 (dd, $J_1 = J_2$ = 8.8 Hz 1H), 6.85 (dd, $J_1 = J_2$ = 8.8 Hz, 1H), 7.47 (d, J_1 = 8.8 Hz, 1H). ^{13}C-nmr δ 68,1 (s, C-OH), 100.9 (d, O-CH-O).

General Procedure for the Synthesis of 1-Azabicyclo[3.3.1]non-3-ene Derivatives (6) and (7).

4-Aryl-1,2,5,6-tetrahydropyridine derivatives (**5a-n**) or the 4-aryl-4-hydroxypiperidine derivatives (**8c,e,f,k**) were dissolved in 5-8 fold amount of concentrated hydrochloric acid or in 10 fold amount of a 2:1 mixture of concentrated hydrochloric acid and water and refluxed for 3-6 h. The reaction mixtures were evaporated to dryness and the residues were mixed with acetone or a mixture of acetone and isopropanol, containing 5-10% of the latter, to produce crystalline products as hydrochloride salt. Latters were recystallized from ethanol or isopropanol to yield endo-hydroxy derivatives (**6a-n**). Further heating either of the crude or the pure products (**6c,e**) in 70% perchloric acid caused a partial isomerization to **7c,e**. Details are given later.

(±)-*endo*-6-Hydroxy-4-phenyl-1-azabicyclo[3.3.1]non-3-ene Hydrochloride (6a·HCl): mp 263-264°C (EtOH), yield 58%. ^{1}H-Nmr (DMSO-d_6) δ 1.75 (m, 2H), 3.10 - 3.54 (m, 5H) 3.73 (2-H; dd, J_1 = 18.7 Hz, J_2 = 3.2 Hz, 1H), 4.03 (2-H; dd, J_1 = 18.7 Hz, J_2 = 2,6 Hz, 1H), 4.02 (6-H; m, 1H), 4.97 (OH, br s), 6.28 (3-H; dd, J_1 = 3.2 Hz, J_2 = 2.6 Hz, 1H), 7.20 - 7.42 (m, 3H), 7.50 (d, J = 8.8 Hz, 2H). Anal. Calcd for $C_{14}H_{17}NO{\cdot}HCl$: C 66.79; H 7.20; N 5.56. Found: C 66.84; H 6.90; N 5.55.

(±)-*endo*-4-(3-Chlorophenyl)-6-hydroxy-1-azabicyclo[3.3.1]non-3-ene Hydrochloride (6b·HCl): mp 237-239°C (EtOH), overall yield: 47% (from **1b**). ^{1}H-Nmr (DMSO-d_6) δ 1.77 (7-H; m, 2H), 3.10 - 3.52 (m, 5H), 3.80 (2-H; dd, J_1 = 18.5 Hz, J_2 = 3.3 Hz, 1H), 4.02 (6-H; m, 1H), 4.07 (2-H; dd, J_1 = 18.5 Hz, J_2 = 2.6 Hz,

1H), 5.02 (OH, br s), 6.37 (3-H; dd, J_1 = 3.3 Hz, J_2 = 2.6 Hz, 1H), 7.21 - 7.50 (m, 3H) 7.60 (br s, 1H). Anal. Calcd for $C_{14}H_{16}NOCl{\cdot}HCl$: C 58.75; H 5.99; N 4.89. Found: C 58.70; H 5.92; N 4. 67.

(±)-*endo*-4-(4-Chlorophenyl)-6-hydroxy-1-azabicyclo[3.3.1]non-3-ene Hydrochloride (6c·HCl): mp 291-293°C (EtOH), yields: 69% (from **5c**) and 63% (from **8c**). ^{1}H-Nmr (DMSO-d_6) δ 1.75(m, 2H), 3.12 - 3.52 (m, 5H), 3.75 (2-H; dd, J_1 = 18.6 Hz, J_2 = 2.6 Hz, 1H) 4.05 (6-H; m, 1H), 4.07 (2-H, dd, J_1 = 18.6 J_2 = 2.6 Hz, 1H), 5.02 (OH, br s) 6.32 (3-H; dd, J_1 = 3.4 Hz, J_2 = 2.6 Hz, 1H), 7.38 and 7.57 (d, J = 9.5 Hz, 4H). Anal. Calcd for $C_{14}H_{16}NOCl{\cdot}HCl$: C 58.75; H 5.99; N 4.89. Found: C 58.70; H 5.99; N 4.91.

(±)-*endo*-4-(3-Fluorophenyl)-6-hydroxy-1-azabicyclo[3.3.1]non-3-ene (6d) as (*E*)-2-Butanedioate (2:1): The product prepared according to the general procedure could not be crystallized, therefore it was basified by a 10% solution of Na_2CO_3. After extraction and evaporation fumarate salt was prepared: mp 193-195°C (iPrOH), overall yield: 43% (from **1d**). ^{1}H-Nmr (DMSO-d_6) δ 1.62 (7-H; m, 2H), 2.90 - 3.33 (m, 4H), 3.52 and 4.03 (2-H; d, J = 18.5 Hz, 2H), 3.95 (6-H, m, 1H), 4.02 (OH, br s), 6.38 (3-H; br s, 1H), 6.50 (s, 2H, fumaric acid), 7.01 - 7.53 (m, 4H). Anal. Calcd for $C_{14}H_{16}NOF{\cdot}1/2\ C_4H_4O_4$: C 65.96; H 6.23; N 4.81. Found: C 65.14: H 6.28: N 4.26.

(±)-*endo*-4-(4-Fluorophenyl)-6-hydroxy-1-azabicyclo[3.3.1]non-3-ene Hydrochloride (6e·HCl): mp 216-218°C (EtOH), yields: 54% (from **5e**) and 86% (from **8e**). ^{1}H-Nmr (DMSO-d_6) δ 1.75 (7-H, m, 2H), 3.75 (2-H; dd, J_1 = 19.6 Hz, J_2 = 3.4 Hz, 1H), 4.05 (6-H; m, overlapping, 1H), 4.07 (2-H; dd, J_1 = 19.6 Hz, J_2 = 2.0 Hz, 1H), 5.05 (OH, br s), 6.25 (3-H; dd, J_1 = 3.4 Hz, J_2 = 2.0 Hz, 1H), 7.10 (dd, J_1 = J_2 = 9.3 Hz, 2H), 7.60 (dd, J_1 = 9.3 Hz, J_2 = 5.9 Hz, 2H), 11.50 (br. s, 1H). Anal. Calcd for $C_{14}H_{16}NOF{\cdot}HCl$: C 62.33; H 6.35; N 5.19. Found: C 62.38; H 6.38; N 5.08.

(±)-*endo*-6-Hydroxy-4-(2-tolyl)-1-azabicyclo[3.3.1]non-3-ene Hydrochloride (6f·HCl): mp 293-295°C (EtOH), yield: 41% (from **8f**). ^{1}H-Nmr (DMSO-d_6) δ 1.80 - 2.12 (m, 2H), 2.25 (s, 3H), 2.95 (br s, 1H), 3.15 - 3.41 (m, 4H), 3.80 (2-H; dd, J_1 = 18.8 Hz, J_2 = 3.3 Hz, 1H), and 4.00 (2-H; dd, J_1 = 18.8 Hz, J_2 = 2.4 Hz, 1H), 4.00 (m, 1H), 4.90 (OH, br s), 5.75 (3-H; dd, J_1 = 3.3 Hz, J_2 = 2.4 Hz, 1H), 7.13 (br s, 4H). Anal. Calcd for $C_{15}H_{19}NO{\cdot}HCl$: C 67.78; H 7.59; N 5.27. Found: C 67.56; H 7.64; N 5.20.

(±)-*endo*-6-Hydroxy-4-(3-tolyl)-1-azabicyclo[3.3.1]non-3-ene Hydrochloride (6g·HCl): mp 227-230°C (iPrOH), overall yield: 75% (from **1g**). ^{1}H-Nmr (DMSO-d_6) δ 1.75 (7-H, m, 2H), 2.29 (s, 3H), 3.12 - 3.55 (m, 5H), 3.72 (2-H; dd, J_1 = 18.5 Hz, J_2 = 3.3 Hz. 1H), and 4.05 (2-H; dd, J_1 = 18.5 Hz, J_2 = 2.6 Hz, 1H), 3.91 (6-H; m, 1H), 4.90 (OH, br s), 6.22 (3-H; dd, J_1 = 3.3 Hz, J_2 = 2.6 Hz, 1H), 7.05 (d, J = 7.0 Hz, 1H), 7.20 (dd, J_1 = J_2 = 7.0 Hz, 1H), 7.31 (d, J = 7.0 Hz, 1H), 7.33 (br s, 1H). Anal. Calcd for $C_{15}H_{19}NO$·HCl: C 67.78; H 7.59; N 5.27. Found: C 57.95; H 7.61; N 5.30.

(±)-*endo*-6-Hydroxy-4-(4-tolyl)-1-azabicyclo[3.3.1]non-3-ene Hydrochloride (6h·HCl): mp 253-257°C (iPrOH), yield: 60%. ^{1}H-Nmr (DMSO-d_6) δ 1.75 (7-H, m, 2H), 2.25 (s, 3H), 3.12 - 3.40 (m, 5H), 3.70 (2-H; dd, J_1 = 18.8 Hz, J_2 = 3.4 Hz, 1H), and 4.03 (2-H; J = 18.8 Hz, 1H, partly overlapped), 4.04 (6-H; m, 1H), 4.92 (OH, br s), 6.22 (3-H; dd, J = 3.4 Hz), 7.08 (d, J = 8.3 Hz, 2H), 7.43 (d, J = 8.3 Hz, 2H). Anal. Calcd for $C_{15}H_{19}NO$·HCl: C 67.78; H 7.59; N 5.27. Found: C 68.17; H 7.70; N 5.08.

(±)-*endo*-6-Hydroxy-4-(3-trifluoromethylphenyl)-1-azabicyclo[3.3.1]non-3-ene Hydrochloride (6i·HCl): mp 230-233°C (iPrOH), overall yield: 27% (from **1i**). ^{1}H-Nmr (DMSO-d_6) δ 1.83 (7-H, m, 2H), 3.10 - 3.54 (m, 5H), 3.80 (2-H; dd, J_1 = 18.7 Hz, J_2 = 3.2 Hz, 1H) and 4.10 (2-H; dd, J_1 = 18.7 Hz, J_2 = 2.5 Hz, 1H), 4.05 (6-H; m, 1H), 5.10 (OH, d, J = 4.8 Hz), 6.45 (3-H; dd, J_1 = 3.2 Hz, J_2 = 2.5Hz, 1H), 7.55 (m, 2H), 7.80 (m, 1H), 7.85 (br s, 1H). Anal. Calcd for $C_{15}H_{16}NOF_3$·HCl: C 56.34; H 5.36; N 4.38. Found: C 56.55; H 5.46; N 4.45.

(±)-*endo*-6-Hydroxy-4-(4-trifluoromethylphenyl)-1-azabicyclo[3.3.1]non-3-ene Hydrochloride (6j·HCl): mp 255°C (subl.) (EtOH), yield: 56%. ^{1}H-Nmr (DMSO-d_6) δ 1.80 (7-H, m, 2H), 3.10 - 3.75 (m, 5H), 3.85 (2-H; dd, J_1 = 18.6 Hz, J_2 = 3.2 Hz, 1H), and 4.10 (2-H; br d, J = 18.6 Hz, 1H), 4.05 (6-H; m, 1H), 5.00 (OH, br s), 6.45 (3-H; dd, J_1 = 3.2 Hz, J_2 = 2.4 Hz, 1H), 7.70 (d, J = 8.0 Hz, 2H). Anal. Calcd for $C_{15}H_{16}NOF_3$·HCl: C 56.34; H 5.36; F 17.83. Found: C 56.73; H 5.43; F 17.90.

(±)-*endo*-6-Hydroxy-4-(2-methoxyphenyl)-1-azabicyclo[3.3.1]non-3-ene Hydrochloride (6k·HCl): mp 263-268°C (EtOH), yield: 74% (from **8k**). ^{1}H-Nmr (DMSO-d_6) δ 1.85 (7-H, m, 2H), 3.15 - 4.15 (m, 6H), 3.75 (s, 3H), 3.92 (6-H; m, 1H), 4.05 (2-H; br d, J = 18.6 Hz, 1H), 5.85 (3-H; br s, 1-H), 6.90 (dd, J_1 = J_2 = 7.2 Hz,

1H), 6.90 (d, J = 7.2 Hz, 1H), 7.15 (d, J = 7.2 Hz, 1H), 7.25 (dd, $J_1 = J_2$ = 7.2 Hz, 1H). Anal. Calcd for $C_{15}H_{19}NO_2$·HCl: C 63.93; H 7.15; N 4.97. Found: C 63.84; H 7.17; N 4.94.

(±)-*endo*-6-Hydroxy-4-(4-methoxyphenyl)-1-azabicyclo[3.3.1]non-3-ene Hydrochloride (6l·HCl): mp 235-236°C (EtOH), yield: 43%. ^{1}H-Nmr (DMSO-d_6) δ 1.75 (7-H, m, 2H), 3.02 - 3.53 (m, 5H), 3.75 (2-H; d, J = 18.9 Hz, partly overlapping, 1H), 3.75 (s, 3H), 4.00 (2-H; d, J = 18.9 Hz, partly overlapping, 1H), 4.00 (6-H; m, 1H), 4.97 (OH, br s), 6.18 (br s, 1H), 6.90 (d, J = 8.8 Hz, 2H). Anal. Calcd for $C_{15}H_{19}NO_2$·HCl: C 63.93; H 7.15; N 4.97. Found: C 63.49; H 7.23; N 4.85.

(±)-*endo*-6-Hydroxy-4-(4-methylthiophenyl)-1-azabicyclo[3.3.1]non-3-ene Hydrochloride (6m·HCl): mp 222-225°C (EtOH), yield: 41%. ^{1}H-Nmr (DMSO-d_6) δ 1.80 (7-H, m, 2H), 2.45 (s, 3H), 3.15 - 3.55 (m, 5H), 3.75 (dd, J_1 = 18.8 Hz, J_2 = 3.2 Hz, 1H), and 4.05 (dd, J_1 = 18.8 Hz, J_2 = 2.6 Hz, 1H), 4.04 (6-H, m, 1H), 4.95 (OH, br s), 6.28 (3-H; dd, J_1 = 3.2 Hz, J_2 = 2.6 Hz, 1H), 7.18 (d, J = 8.8 Hz, 2H), 7.50 (s, J = 8.8 Hz, 2H). Anal. Calcd for $C_{15}H_{19}NOS$·HCl: C 60.49; H 6.77; N 4.70. Found: C 59.65; H 6.87; N 4.70.

(±)-*endo*-6-Hydroxy-4-(1-naphthyl)-1-azabicyclo[3.3.1]non-3-ene Hydrochloride (6n·HCl): mp 309-312°C (MeOH), overall yield: 65% (from **1n**). ^{1}H-Nmr (DMSO-d_6) δ 1.90 (7-H, d, J = 12.8 Hz, 1H), 2.10 (7-H, m, 1H), 3.15 (5-H; br s, 1H), 3.20 - 3.72 (m, 4H), 3.97 (m, 1H), 3.90 (2-H; dd, J_1 = 18.7 Hz, J_2 = 3.3 Hz, 1H), and 4.05 (2-H; dd, J_1 = 18.7 Hz, J_2 = 2.5 Hz, 1H), 4.75 (OH, m), 5.97 (3-H; dd, J_1 = 3.3 Hz, J_2 = 2.5 Hz, 1H), 7.30 - 7.52 (m, 4H), 7.72 - 8.03 (m, 3H). Anal. Calcd for $C_{18}H_{19}NO$·HCl: C 71.63; H 6.6.8; N 4.64. Found: C 71.36; H 6.77; N 4.54.

(±)-*exo*-4-(4-Chlorophenyl)-6-hydroxy-1-azabicyclo[3.3.1]non-3-ene (7c): 6.0 g of **6c** was dissolved in 20 ml of 70% perchloric acid and was heated at 80°C for 4 h. The gc analysis showed that 63% of the starting compound was isomerized. The mixture was poured into an excess of 10% sodium bicarbonate solution and extracted with ethyl acetate. After evaporation the residue (5.6 g) was chromatographed on a column packed with 600 g of silica gel. As eluent a mixture of benzene-methanol-triethylamine (800:200:4) was used. Following the unchanged isomer and an isomeric mixture a fraction consisting mainly of the exo isomer with R_F: 0,55, was collected, which gave after evaporation 1.82 g of a residue which was again chromatographed as above. After

evaporation of the fraction containing the pure exo isomer the crystallined residue was recrystallized from ethyl acetate to yield 0.40 g of **7c**, with mp 160-163°C. ^{1}H-Nmr δ 1.25 (7-H_e; br d, J = 14.0 Hz, 1H), 1.92 (7-H_a; dddd, $J_1 = J_2$ = 14.0 Hz, J_3 = 5.3 Hz, J_4 = 2.9 Hz, 1H), 2.42 (OH, br s), 2.55 (5-H; br s, 1H), 2.67 (9-H; d, J = 13.0 Hz, 1H), 2.72 (8-H_e; dd, J_1 = 14.0 Hz, J_2 = 5.3 Hz, 1H), 3.21 (2-H; dd, J_1 = 19.8 Hz, J_2 = 3.3 Hz, 1H), 3.35 (8-H_a; ddd, $J_1 = J_2$ = 14.0 Hz, J_3 = 3.7 Hz, 1H), 3.57 (9-H; d, J = 13.0 Hz, 1H), 3.83 (2-H; ddd, J_1 = 19.8 Hz, $J_2 = J_3$ = 2.0 Hz, 1H), 3.93 (6-H_e; br d, J = 2.3 Hz, 1H), 6.25 (3-H; dd, J_1 = 3.3 Hz, J_2 = 2.0 Hz, 1H), 7.27 (br s, 4H). Anal. Calcd for $C_{14}H_{16}NOCl$: C 67.33; H 6.46: N 5.61: Cl 14.20. Found: C 67.39; H 6.55; N 5.35; Cl 14.38.

(±)-*exo*-4-(4-Fluorophenyl)-6-hydroxy-1-azabicyclo[3.3.1]non-3-ene (7e): The mother liquor obtained at the preparation of **6e**, was evaporated and the residue was converted to the base. 5.0 g of this base (endo-exo ratio of about 4:1) are heated with 25 ml of 70% perchloric acid at 80°C for 1 h. The solution was cooled, made alkaline with 5N NaOH, extracted with chloroform and evaporated. In the resulting base the ratio of endo-exo isomers amounts to about 2:3. 3.80 g of this isomer mixture were separated on a silica gel column using benzene-methanol (4:1) as eluant. Following the fractions containing the unchanged isomer and the mixture of both, **7e** was collected. Evaporation resulted 1.85 g of a crude product, which gave after recrystallization from ethyl acetate 1.40 g of **7e** with mp 133-137°C. [Hydrochloride salt (**7e**·HCl) had mp 220-224°C]. ^{1}H-Nmr δ 1.30 (7-H_e; br d, J = 13.8 Hz, 1H), 1.97 (7-H_a; dddd, $J_1 = J_2$ = 13.8 Hz, J_3 = 5.1 Hz, J_4 = 2.4 Hz, 1H), 2.56 (5-H; br s, 1H), 2.70 (9-H; d, J = 12.5 Hz, 1H), 2.76 (8-H_e; dd, J_1 = 13.7 Hz, J_2 = 5.1 Hz, 1H), 3.25 (2-H; dd, J_1 = 19.6 Hz, J_2 = 3.2 Hz, 1H), 3.42 (8-H_a; ddd, $J_1 = J_2$ = 13.8 Hz, J_3 = 3.6 Hz, 1H), 3.63 (9-H; d, J = 12.5 Hz, 1H), 3.85 (2-H; dd, J_1 = 19.6 Hz, J_2 = 2.3 Hz, 1H), 3.95 (6-H_e; br d, J = 2.4 Hz, 1H), 4.01 (OH; br s, 1H), 6.22 (3-H; dd, J_1 = 3.2 Hz, J_2 = 2.3 Hz, 1H), 7.00 (dd, $J_1 = J_2$ = 9.3 Hz, 2H), 7.40 (dd, J_1 = 9.3 Hz, J_2 = 5.9 Hz, 2H). Anal. Calcd for $C_{14}H_{16}NOF$·HCl: C 62.33; H 6.35; F 7.04. Found: C 62.38; H 6.70; F 7.10.

Ring Closure Reaction of 9a

10.0g of **9a** were added dropwise at constant stirring to 50 ml of 85% sulfuric acid at 90°C. After a reaction period of 24 h the mixture was poured into water and its pH was adjusted to 9 with solid NaOH. The product was extracted with ethyl acetate, the organic layer was washed and the solvent evaporated. The resulting residue was mixed with isopropyl ether and the crystalline product formed was filtered. Recrystallizing 2.3 g of this

crude product from ethyl acetate gave 2.0 g of **(±)-6-*exo*-hydroxy-6-*endo*-methyl-4-phenyl-1-azabicyclo[3.3.1]non-3-ene (11a)** with mp 179-182°C. ^{1}H-Nmr δ 0.82 (s, 3H), 1.17 (7-H_e; dd, J_1 = 13.7 Hz, J_2 = 3.4 Hz, 1H), 1.82 (7-H_a; ddd, $J_1 = J_2$ = 13.7 Hz, J_3 = 5.3 Hz, 1H), 2.65 (OH, br s), 2.75 (9-H; ddd, J_1 = 12.5 Hz, $J_2 = J_3$ = 2.0 Hz, 1H), 2.82 (8-H_e; dd, J_1 = 13.7 Hz, J_2 = 5.3 Hz, 1H), 3.22 (2-H; dd, J_1 = 19.7 Hz, J_2 = 3.0 Hz, 1H), 3.33 (8-H_a; ddd, $J_1 = J_2$ = 13.7 Hz, J_3 = 3.4 Hz, 1H), 3.65 (9-H; dd, J_1 = 12.5 Hz, J_2 = 2.0 Hz, 1H), 3.85 (2-H; ddd, J_1 = 19.7 Hz, $J_2 = J_3$ = 1.7 Hz, 1H), 6.00 (3-H; dd, J_1 = 3.0 Hz, J_2 = 1.7 Hz, 1H), 7.20 - 7.42 (m, 5H). Anal. Calcd for $C_{15}H_{19}NO$: C 78.56; H 8.35; N 6.14. Found: C 78.89; H 8.39; N 6.42.

The mother liquor, after filtering the above product, was evaporated and the 4.3 g oily residue were submitted to flash chromatography applying as eluant a 8:2 mixture of chloroform and methanol, containing 1 drop of triethylamine for each 20 ml of the mixture. A fraction collected with an approx. R_f: 0.75 gave after evaporation an oily substance. Treating this oil with hydrochloric acid in isopropanol-ether 0.54 g of **1-(3-oxobutyl)-4-phenyl-1,2,5,6-tetrahydropyridine hydrochloride (12a·HCl)** was isolated with mp 199-200°C (decomp.) Ir: 1711 cm^{-1}; ^{1}H-nmr (DMSO-d_6) δ 2.20 (s, 3H), 6.18 (br s, 1H), 7.20 - 7.53 (m, 5H). Anal. Calcd for $C_{15}H_{19}NO$·HCl: C 67.78; H 7.58: N 5.27. Found: C 67.50; H 7.60; N 5.26.

A further fraction having an R_f of about 0.6 provided after evaporation 0.46 g of an oily substance, which was (±)-4-methyl-6-phenyl-1-azabicyclo[3.3.1]nona-3,6-diene, but was not further characterized. Elution was continued and a fraction having an R_f value of about 0.2 was evaporated, giving a solid substance (0.54 g), which was recrystallized from isopropanol to provide 0.28 g of **(±)-6-*endo*-hydroxy-6-*exo*-methyl-4-phenyl-1-azabicyclo[3.3.1]non-3-ene (10a)** with mp 160-161°C. ^{1}H-Nmr δ 1.35 (7-H_e; d, J = 13.2 Hz, 1H), 1.39 (s, 3H), 1.76 (7-H_a; ddd, $J_1 = J_2$ = 13.2 Hz, J_3 = 6.4 Hz, 1H), 2.74 (5-H; br s, 1H), 2.90 - 3.05 (m, 3H), 3.10 (dd, J_1 = 13.7 Hz, J_2 = 1.5 Hz), 3.21 (2-H; dd, J_1 = 19.5 Hz, J_2 = 3.0 Hz, 1H), 3.83 (2-H; dd, J_1 = 19.5 Hz, J_2 = 1.8 Hz, 1H), 6.24 (3-H; dd, J_1 = 3.0 Hz, J_2 = 1.8 Hz, 1H), 7.22 (dd, $J_1 = J_2$ = 6.8 Hz, 1H), 7.33 (dd, $J_1 = J_2$ = 6.8 Hz, 2H), 7.43 (d, J = 6.8 Hz, 2H). Anal. Calcd for $C_{15}H_{19}NO$·HCl: C 67.78; H 7.58; N 5.27. Found C 67.50; H 7.60; N 5.26.

Ring Closure Reaction of 9c

6.64 g (21.5 mmol) of **9c** were dissolved in 26 ml of 85% sulfuric acid and the solution was left to stand at room temperature for 10 days. Then the mixture was poured over icewater and the pH was adjusted to 9 with solid NaOH. The precipitated product was extracted with ethyl acetate. After evaporation the crystalline residue

obtained was recrystallized from ethyl acetate to yield 2.81 g (50%) of **(±)-4-(4-chlorophenyl)-6-*exo*-hydroxy-6-*endo*-methyl-1-azabicyclo[3.3.1]non-3-ene (11c)** with mp 191-192°C. ^{1}H-Nmr δ 0.80 (s, 3H), 1.14 (7-H, d, J = 14.5 Hz, 1H), 1.80 (7-H, ddd, $J_1 = J_2$ = 14.5 Hz, J_3 = 3.8 Hz, 1H), 2.20 (OH, br s), 2.52 (5-H; br s, 1H), 2.83 (9-H, d, J = 14.3 Hz, 1H), 2.80 (8-H; partly overlapping, 1H), 3.25 (2-H, dd, J_1 = 19.8 Hz, J_2 = 3.2 Hz, 1H), 3.30 (8-H_a, ddd, $J_1 = J_2$= 14.5 Hz, J_3 = 2.9 Hz, 1H), 3.65 (9-H, d, J = 14.3 Hz, 1H), 3.95 (2-H, dd, J_1 = 19.8 Hz, J_2 = 2.3 Hz, 1H), 6.08 (dd, J_1 = 3.2 Hz, J_2 = 2.3 Hz, 1H), 7.20 (br s, 4H). Anal. Calcd for $C_{15}H_{18}NOCl$: C 68.30; H 6.88; N 5.31. Found: C 68.67; H 6.90; N 5.46.

The mother liquor obtained after filtering the above product was evaporated and chromatographed in the same way as described at the ring closure reaction of **9a** to isolate further products: 0.8 g of **4-(4-chlorophenyl)-1-(3-oxobutyl)-1,2,5,6-tetrahydropyridine (12c**; with R_f: 0.8), which was recrystallized from isopropyl ether: mp 96-97°C. Ir: 1700 cm^{-1}. Anal. Calcd for $C_{15}H_{18}NOCl$: C 68.30; H 6.88; N 5.31. Found: C 68.65; H 7.13; N 5.56. Further elution provided 0.44 g of **(±)-4-(4-chlorophenyl)-6-*endo*-hydroxy-6-*exo*-methyl-1-azabicyclo-[3.3.1]non-3-ene (10c)** with an approx. R_f: 0.2-0.3; mp 132-133°C (ethyl acetate). ^{1}H-Nmr δ 1.40 (s, 3H), 1.40 (7-H_e; overlapping), 1.77 (7-H_a; ddd, $J_1 = J_2$ = 14.3 Hz, J_3 = 3.7 Hz, 1H), 2.65 (5-H; br s, 1H), 2.85 - 2.95 (m, 3H), 3.08 (d, J = 14.6 Hz, 1H), 3.22 (dd, J_1 = 19.7 Hz, J_2 = 3.2 Hz, 1H), 3.82 (dd, J_1 = 19.7 Hz, J_2 = 2.3 Hz), 6.22 (dd, J_1 = 3.2 Hz, J_2 = 2.3 Hz, 1H), 7.28 (d, J = 8.8 Hz, 2H), 7.35 (d, J = 8.8 Hz, 2H). Anal. Calcd for $C_{15}H_{18}NOCl$: C 68.30; H 6.88; N 5.31. Found: C 67.81; H 6.59; N 5.27.

(±)-*endo*-4-(4-Fluorophenyl)-6-propionyloxy-1-azabicyclo[3.3.1]non-3-ene Hydrochloride (13·HCl): prepared from **6e** by acylation with propionic anhydride at 60°C for 8 h. Excess anhydride was decomposed with water and then it was evaporated to dryness. Treating the residue with hydrochloric acid in methanol provided **13** with 96% yield: mp 233-235°C (MeOH). Ir: 1732, 1603 cm^{-1}. ^{1}H-Nmr (DMSO-d_6) δ 0.60 (t, J = 7.4 Hz, 3H), 1.25 (m, 1H), 1.75 (m, 1H), 1.85 - 2.05 (m, 2H), 3.22 - 3.50 (m, 5H), 3.57 (d, J = 12.4 Hz), 3.65 (5-H; br s, 1H), 3.83 (dd, J_1 = 18.8 Hz, J_2 = 3.3 Hz, 1H), 4.15 (dd, J_1 = 18.8 Hz, J_2 = 2.6 Hz, 1H), 5.06 (6-H_a; m, 1H), 7.21 (dd, $J_1 = J_2$ = 8.9 Hz, 2H), 7.41 (dd, J_1 = 8.9 Hz, J_2 = 5.5 Hz, 2H), 11.60 (br s, 1H). Anal. Calcd for $C_{17}H_{20}NO_2F$·HCl: C 62.67; H 6.50; F 5.83. Found: C 62.74; H 6.62; F 5.76.

(±) -*exo*-4-(4-Fluorophenyl)-6-propionyloxy-1-azabicyclo[3.3.1]non-3-ene Hydrochloride (14·HCl): Prepared from **7e** analogously to **13**; mp 174-179°C (MeOH). ^{1}H-Nmr (DMSO-d_6) δ 1.10 (t, J = 7.5 Hz, 3H),

1.77 (d, J = 14.6 Hz, 1H), 2.10 (m, 1H), 2.42 (m, 2H), 3.15 (d, J = 12.7 Hz, 1H), 3.21 - 3.33 (m, 5H), 3.53 (d, J = 12.7 Hz, 1H), 3.90 (dd, J_1 = 18.5 Hz, J_2 = 3.2 Hz, 1H), 4.20 (dd, J_1 = 18.5 Hz, J_2 = 2.5 Hz, 1H), 6.47 (dd, J_1 = 3.2 Hz, J_2 = 2.5 Hz, 1H), 7.28 (dd, $J_1 = J_2$ = 8.9 Hz, 2H), 7.70 (dd, J_1 = 8.9 Hz, J_2 = 5.5 Hz, 2H), 11.32 (br s, 1H). Anal. Calcd for $C_{17}H_{20}NO_2F{\cdot}HCl$: C 62.67; H 6.50; F 5.83. Found: C 61.89; H 6.41; F 5.86.

1-(3,3-Dimethoxypropyl)-4-(4-chlorophenyl)-1,2,5,6-tetrahydropyridine (15): The base was liberated from **1c** and 2.30 g (10 mmol) of this base were dissolved in 20 ml of DMF. To this solution 2.12 g (20 mmol) of Na_2CO_3 were given and during vigirous stirring 2.30 g (12.6 mmol) of 3-bromopropionaldehyde dimethyl acetal were added dropwise. The reaction mixture was stirred at 70°C for 5 h and finally poured into water. Extraction with dichloromethane and evaporation of the extract gave 2.16 g of a partly crystallized oil, which was chromatographed on silica gel with chloroform-methanol (95:5). After evaporating the solvent 1.71 g (58%) of a semi-crystalline product was isolated. Anal. Calcd for $C_{16}H_{22}NO_2Cl$: C 64.96; H 7.50; N 4.74. Found: C 65.10; H 7.82; N 4,55.

(4*S*)-2-[1-[4-(-Chlorophenyl)-1,2,5,6-tetrahydropyridyl]-ethyl]-4-phenyl-1,3-dioxolane (16): On the analogy of a lit.[25] synthesis of **3** (4*S*)-2-(2-bromoethyl)-4-phenyl-1,3-dioxolane was prepared from (*S*)-(+)-phenyl-1,2-ethanediol.[26] The product showed signs of decomposition during distillation at $bp_{0.4\text{-}0.6}$:118-130°C, therefore chromatography was used to isolate the pure bromocompound (silica gel, eluent: chloroform-hexane (7:3). Anal. Calcd for $C_{11}H_{13}O_2Br$: Br 31.08. Found: Br 30.99.)

Using (4*S*)-2-(2-bromoethyl)-4-phenyl-1,3-dioxolane and **1c**, the procedure as described for **15**, was used to prepare compound (**16**): mp 64-67°C; $[\alpha]_D$: -44.8° (c=1, ethanol). According to the nmr spectrum the product is a nearly 1:1 mixture of the cis-trans isomers. ^{1}H-Nmr δ CH(O)(O): 5.21 (t, J = 4.8 Hz) and 5.39 (t, J = 4.8 Hz). Anal. Calcd for $C_{22}H_{24}NO_2Cl$: C 71.43; H 6.54; N 3.79. Found: C 69.87; H 6.21; N 3.43.

(4*R*,5*R*)-2-[1-[4-(-Chlorophenyl)-1,2,5,6-tetrahydropyridyl]ethyl]-4,5-dimethyl-1,3-dioxolane (17): (4*R*,5*R*)-2-(2-Bromoethyl)-1,3-dioxolane was prepared from (2*R*,3*R*)-(-)-2.3 butanediol on the analogy of a lit procedure.[25] $Bp_{0.4\text{-}0.8}$: 44-48°C; yield:72%. Anal. Calcd for $C_7H_{13}O_2Br$: Br 38.22. Found: Br 38.30. Using this bromo-compound as alkylating agent for **1c**, the procedure as described for **15**, was used to prepare **17**: mp 76-78°C; yield: 76%. $[\alpha]_D$: -8.25° (c=1, ethanol). ^{1}H-Nmr δ 1.22 (d, J = 5.9 Hz, 3H), 1.30 (d, J = 5.9 Hz,

3H), 3.60 (m, 2H), 5.33 (t, J = 4.8 Hz, 1H), 6.05 (m, 1H), 7.26 (d, J = 8.9 Hz, 2H), 7.30 (d, J = 8.9 Hz, 2H). Anal. Calcd for $C_{18}H_{24}NO_2Cl$: C 67.17; H 7.52; N 4.35. Found: C 66.84; H 7.50; N 4.20.

Resolution of 6e

32.66 g (140 mmol) of **6e** was dissolved in 330 ml of 96% ethanol. To this solution 15.76 g (70 mmol) of (*R,R*)-(+)-tartaric acid monoanilide,[27] dissolved in 96% ethanol (150 ml), were added dropwise at 45°C over 15-20 min. The solution was stirred overnight at room temperature and the separated salt was filtered and washed with 15 ml of icecold isopropanol and two times with 125 ml of ether to give 21.57 g of a product with mp 194-198°C ($[\alpha]_D$: +135.9°, c=1, methanol) This salt was dissolved in 220 ml of 90% ethanol by warming and was stirred with slow cooling to room temperature overnight. The separated crystals were washed with cold isopropanol (5 ml) and ether (2×12 ml) to yield 16 g of a salt with mp 196-199°C ($[\alpha]_D$: +150.7°, c=1, methanol). This salt was dissolved in 80 ml of water at 65°C and 15 ml of 5N KOH solution were added dropwise. From the solution crystals were separated during cooling to room temperature and the suspension was stored at 0-5°C overnight. Filtering gave 7.73 g of **(+)-6e** with mp 153-156°C; $[\alpha]_D$: +148.8° (c=1, methanol). Enantiomeric purity was determined by chiral hplc method[28] (Column: Chiralcell OF, mobile phase: hexane-isopropanol-diethylamine, 80:20:0,1) and the enantiomeric excess was better than 99% ee.

(-)-6e was prepared from the mother liquor of the tartaric-anilid salt. The solution was evaporated and the residue was stirred with 280 ml of water and 8 ml of 5N KOH. Crystals were separated, which were filtered and recrystallized twice from ethyl acetate yielding 5.70 g of **(-)-6e** with mp 156-159°C; $[\alpha]_D$: -154,0° (c=1, MeOH). The enantiomeric excess was better than 99% ee, the enantiomeric purity was determined as for **(+)-6e**.

(5*R*)-(-)-4-(4-Fluorophenyl)-1-azabicyclo[3.3.1]non-3-en-6-one [(-)-18]: The solution of 2.25 ml (25.8 mmol) of oxalyl chloride in dichloromethane (16 ml) was cooled to -60°C and a solution of 3.6 ml (51.3 mmol) of DMSO in dichloromethane (9 ml) was added with stirring. After 30 min the solution of 4.20 g (18 mmol) of **(-)-6e** ($[\alpha]_D$: -154°, c=1, methanol) in dichloromethane (34 ml) was added dropwise and stirring was continued for 2 h at -60°C. The reaction mixture was quenched with 15 ml of triethylamine and washed with brine and dried. After evaporation of the solvent, the residue was flash-chromatographed using chloroform methanol 95:5 as eluant. The resinous product was recrystallized from hexane to give 2.43 g (58%) of the title ketone with mp 73-74°C; $[\alpha]_D$: -521.2° (c=1, methanol). Ir (film): 1703 cm^{-1}. ^{1}H-Nmr δ 2.20 (7-H; dd, J_1 = 14.2 Hz, J_2 = 3.9

Hz, 1H), 2.83 (7-H; ddd, J_1 = 14.2 Hz, J_2 = 12.2 Hz, J_3 = 7.8 Hz, 1H), 3.15-3.45 (m, 5H), 3.52 (2-H; dd, J_1 = 19.9 Hz, J_2 = 3.4 Hz, 1H), 4.08 (2-H; dd, J_1 = 19.9 Hz, J_2 = 2.2 Hz, 1H), 6.34 (3-H; dd, J_1 = 3.4 Hz, J_2 = 2.2 Hz, 1H), 7.00 (dd, J_1 = J_2 = 8.8 Hz, 2H), 7.40 (dd, J_1 = 8.8 Hz, J_2 = 5.4 Hz, 2H). Anal. Calcd for $C_{14}H_{14}NOF$: C 72.71; H 6.10; N 6.06. Found: C 72.82; H 6.22; N 5.96.

(5*S*)-(+)-4-(4-Fluorophenyl)-1-azabicyclo[3.3.1]non-3-en-6-one [(+)-18]: Prepared from (+)-**6e** as described for (-)-**18**; mp 72-73°C (hexane); $[\alpha]_D$: +515.5° (c=1, methanol).

General Procedure for the Hydrogenation of Compounds (6e,g,h,j,k).

The starting compound was dissolved in a 1:1 mixture of methylene chloride and ethanol and using about 0.10 g of 10% palladium charcoal for 5 mmol of the corresponding compound (**6**), they were submitted to hydrogenolysis. When the uptake of the calculated amount of hydrogen gas was completed (5-8 h), catalyst was filtered and the filtrate was evaporated. Products were prepared as hydrochloride salts or the corredponding base was liberated and they were recrystallized.

(±)-*exo*-6-Phenyl-1-azabicyclo[3.3.1]nonan-4-(*endo*)-ol Hydrochloride (19a·HCl): mp 284-285°C (MeOH), yield: 67%. ^{1}H-Nmr (DMSO-d_6) δ 1.90 (m, 2H), 2.15 (m, 1H), 2.55 (br s, 1H), 2.70 (m, 1H), 3.10 - 3.63 (m, 7H), 4.00 (6-H_a; m, 1H), 4.25 (OH, br s), 7.12 - 7.43 (m, 5H). Anal. Calcd for $C_{14}H_{19}NO{\cdot}HCl$: C 66.26; H 7.94; N 5.52. Found: C 66.40; H 8.10; N 5.53.

(±)-*exo*-6-(4-Fluorophenyl)-1-azabicyclo[3.3.1]nonan-4-(*endo*)-ol (19e): mp 173-175°C (iPrOH), yield: 72%. ^{1}H-Nmr δ 1.65 - 1.95 (m, 3H), 2.25 (5-H; br s, 1H), 2.45 (m, 1H), 2.95 (d, J = 10.5 Hz, 1H), 2.9 - 3.35 (m, 6H), 3.97 (4-H_a; m, 1H), 7.00 (dd, J_1 = J_2 = 8.9 Hz, 2H), 7.35 (dd, J_1 = 8.9 Hz, J_2 = 5.5 Hz, 2H). Anal. Calcd for $C_{14}H_{18}NOF$: C 71.46; H 7.71. Found: C 71.35; H 7.49.

(±)-*exo*-6-(3-Tolyl)-1-azabicyclo[3.3.1]nonan-4-(*endo*)-ol (19g): mp 153-157°C (iPrOH), yield: 83%. ^{1}H-Nmr δ 1.70 (6-H_a; ddd, J_1 = 13.7 Hz, J_2 = J_3 = 5.1 Hz, 1H), 1.90 (m, 2H), 2.33 (5-H; br s, 1H), 2.36 (s, 3H), 2.55 (m, 1H), 2.86 (d, J = 12.6 Hz, 1H), 2.91 - 3.32 (m, 6H), 3.95 (4-H_a; m, 1H), 7.05 (d, J = 7.2 Hz, 1H), 7.15 (m, 2H), 7.26 (dd, J_1 = J_2 = 7.2 Hz, 1H). Anal. Calcd for $C_{15}H_{21}NO$: C 77.88; H 9.15; N 6.06. Found: C 78.04; H

9.35; N 6.07.

(±)-*exo*-6-(4-Tolyl)-1-azabicyclo[3.3.1]nonan-4-(*endo*)-ol (19h): mp 124-126°C (iPrOH), yield: 55%. ^{1}H-Nmr (DMSO-d_6) δ 1.60 (m, 2H), 1.90 (m, 1H), 2.15 (5-H; br s, 1H), 2.32 (s, 3H), 2.42 (m, 1H), 2.75 (d, J = 13.8 Hz, 1H), 2.80 - 3.24 (m, 6H), 3.55 (OH, br s), 3.90 (4-H_a; m, 1H), 7.03 (d, J = 8.3 Hz, 2H), 7.20 (d, J = 8.3 Hz, 2H). Anal. Calcd for $C_{15}H_{21}NO$: C 77.88; H 9.15; N 6.06. Found: C 77.98; H 9.26; N 6.13

(±)-*exo*-6-(4-Trifluoromethylphenyl)-1-azabicyclo[3.3.1]nonan-4-(*endo*)-ol Hydrochloride (19j·HCl): mp 299-303°C (EtOH), yield: 74%. ^{1}H-Nmr (DMSO-d_6) δ 1.81-2.33 (m, 3H), 2.60 (5-H; br s, 1H), 2.80 (m, 1H), 3.15-3.65 (m, 7H), 4.10 (4-H_a; m, 1H), 4.55 (OH; br s), 7.52 (d, J = 8.1 Hz, 2H), 7.60 (d, J = 8.1 Hz, 2H). Anal. Calcd for $C_{15}H_{18}NOF_3$·HCl: C 55.99; H 5.95; F 17.71. Found: C 56.08; H 6.19; F 17.75.

(±)-*exo*-6-(2-Methoxyphenyl)-1-azabicyclo[3.3.1]nonan-4-(*endo*)-ol Hydrochloride (19k·HCl): mp 258-263° (iPrOH); yield: 73%. ^{1}H-Nmr (DMSO-d_6) δ 1.68 (m, 1H), 1.85 (m, 1H), 2.15 (m, 1H), 2.50 (br s, overlapping with the signal of DMSO-d_6), 2.80 (m, 1H), 3.02 - 3.80 (m, 7H), 3.80 (s, 3H), 3.96 (4-H_a; m, 1H), 6.84 (d, J = 8.1 Hz, 1H), 6.93 (d, J = 8.1 Hz), 7.15 (dd, $J_1 = J_2$ = 8.1 Hz, 1H), 7.28 (d, J = 8.1 Hz). Anal. Calcd for $C_{15}H_{21}NO_2$. HCl: C 63.48; H 7.82; N 4.94. Found: C 63.60; H 7.82; N 5.07.

(±)-*endo*-6-Hydroxy-4-phenyl-1-azabicyclo[3.2.1]oct-3-ene Hydrochloride (21a·HCl): 9.78 g (50.0 mmol) of **1a** was reacted in 130 ml of DMF, in the presence of 10.6 g of Na_2CO_3, with 11.3 g (55.0 mmol) of bromoacetaldehyde diethyl acetal at 80°C for 16 h. The reaction mixture was poured into water and the product was extracted with ethyl acetate. Evaporation of the organic layer yielded 13.7 g of an oily residue consisting mainly of **1-(2,2-diethoxy-ethyl)-4-phenyl-1,2,5,6-tetrahydropyridine (20a)**. 11.3 g of this intermediate were refluxed with 100 ml of 18% hydrochloride acid for 4 h, then the reaction mixture was evaporated to dryness and the residue was mixed with acetone. The crude product (6.7 g) was recrystallized first from ethanol then from isopropanol to yield 3.2 g (34% overall yield) of the product with mp 228-230°C. ^{1}H-Nmr (DMSO-d_6) δ 2.90 (ddd, J_1 = 13.3 Hz, $J_2 = J_3$ = 3.3 Hz, 1H), 3.22 - 3.51 (m, 3H), 3.75 - 3.95 (m, 2H), 4.25 (2-H; dd, J_1 = 18.9 Hz, J_2 = 2.5 Hz, 1H), 4.82 (6-H; m, 1H), 5.63 (OH, d, J = 3.0 Hz), 6.05 (3-H; dd, J_1 = 3.3 Hz, J_2 = 2,5 Hz, 1H), 7.20 - 7.42 (m, 3H), 7.55 (d, J = 8.3 Hz, 2H). Anal. Calcd for $C_{13}H_{15}NO$·HCl: C 65.68; H 6.78; N 5.89. Found: C 64.92; H 6.91; N 5.41.

(±)-*endo*-4-(4-Chlorophenyl)-6-hydroxy-1-azabicyclo[3.2.1]oct-3-ene (21b): Starting from 11.43 g (50.0 mmol) of **1c** and 11.30 g (55.2 mmol) of bromoacetaldehyde diethyl acetal the same procedure was used, as described for **20a** and so 15.6 g of crude **4-(4-chlorophenyl)-1-(2,2-diethoxy-ethyl)-1,2,5,6-tetrahydropyridine (20b)** was prepared as a resinous product. This intermediate was added under constant stirring to 230 ml of 85% sulfuric acid at room temperature. Stirring was continued for 2 h then the reaction mixture was poured on ice and its pH was adjusted with sodium hydroxide to *9*. The product was extracted with ethyl acetate and after evaporating the organic layer the residue was submitted to flash chromatography (eluant: mixture of benzene-methanol-triethylamine 2:1:0.1). The main fraction obtained at an R_f of about 0.3 (7.2 g) was recrystallized from ethyl methyl ketone to yield 4.42 g (37% overall yield) of the product with mp 145-148°C. ^{1}H-Nmr δ 2.45 (6-H; ddd, J_1 = 13.2 Hz, $J_2 = J_3$ =3.5 Hz, 1H), 2.70 (OH, br s), 2.85 - 3.05 (m, 3H), 3 30 (2-H; dd, J_1 = 18.9 Hz, J_2 = 3.3 Hz, 1H), 3.44 (6-H; dd, J_1 = 13.2 Hz, J_2 = 8.3 Hz, 1H), 3.90 (dd, J_1 = 18.9 Hz, J_2 = 2.4 Hz, 1H), 4,75 (5-H; m, 1H), 6.00 (3-H; dd, J_1 = 3.3 Hz, J_2 = 2.4 Hz, 1H), 7.30 (d, J = 9.4 Hz, 2H), 7.40 (d, J = 9.4 Hz, 2H). Anal. Calcd for $C_{13}H_{14}NOCl$: C 66.24; H 5.99; N 5.94. Found: C 66.14; H 6.11; N 5.90.

(±)-*endo*-6-Hydroxy-4-(3-tolyl)-1-azabicyclo[3.2.1]oct-3-ene Hydrochloride (21c·HCl): 9.0 g (43 mmol) of **1g** and 10.3 g (50 mmol) of bromoacetaldehyde diethyl acetal were used to prepare the intermediate **1-(2,2-diethoxyethyl)-4-(3-tolyl)-1,2,5,6-tetrahydropyridine (20c)** in the same way as described for **20a**. The crude product was purified by flash chromatography (eluant: benzene-methanol-triethylamine, 95:5:0.1). After evaporation of the solvent of the main fraction, the resulting oil was dissolved in 30 ml of 24% HCl and stirred at room temperature for 20 h. The reaction mixture was poured on ice and the pH of the mixture was adjusted with sodium hydroxide to 9. The product was extracted with ether and after evaporation, it was recrystallized from ethyl acetate to yield 2.70 g of **21c** with mp 145-149°C. Overall yield: 48%. ^{1}H-Nmr δ 2.34 (s, 3H), 2.43 (ddd, J_1 = 13.3 Hz, $J_2 = J_3$ = 3.0 Hz, 1H), 2.88 (dd, J_1 = 9.5, J_2 = 3.0 Hz, 1H). 2.92 (dd, J_1 = 9.5 Hz, J_2 = 3.0 Hz, 1H), 3.00 (dd, J_1 = 6.1 Hz, J_2 = 3.0 Hz, 1H), 3.05 (OH; br s), 3.27 (2-H; dd, J_1 = 19.0 Hz, J_2 = 2.9 Hz, 1H), 3.40 (dd, J_1 = 13.3 Hz, J_2 = 8.2 Hz, 1H), 3.85 (2-H; dd, J_1 = 19.0 Hz, J_2 = 2.4 Hz, 1H), 4.72 (6-H; m, 1H), 5.92 (3-H; dd, J_1 = 2.9 Hz, J_2 = 2.4 Hz, 1H), 7.05 (d, J = 8.0 Hz, 1H), 7.25 (m, 3H). Anal. Calcd for $C_{14}H_{17}NO$: C 78.10; H 7.96; N 6.51. Found: C 78.20; H 8.09; N 6.36.

(±)-*endo*-6-Hydroxy-4-(4-methoxyphenyl)-1-azabicyclo[3.2.1]oct-3-ene Hydrochloride (21d·HCl): The

intermediate (**20d**) was prepared from 3.54 g (14.4 mmol) of **11** and 3.3 g (16 mmol) of bromoacetaldehyde diethyl acetal according to the procedure described for **20a**. Crude **20d** (4.6 g in form of an oil) was treated with 50 ml of 24% HCl at room temperature for 2 h. The reaction mixture was evaporated and the residue was recrystallized from ethanol to yield 1.58 g of the product with mp 265-267°C. Overall yield: 57%. ^{1}H-Nmr (DMSO-d_6) δ 2.86 (ddd, J_1 = 12.7 Hz, J_2 = 5.9 Hz, J_3 = 1.5 Hz, 1H), 3.20 - 3.53 (m, 3H), 3.75 - 3.95 (m, 2H), 3.75 (s, 3H), 4.20 (2-H; br d, J = 17.1 Hz, 1H), 4.83 (6-H; m, 1H), 5.65 (OH; d, J = 5.4 Hz), 5.92 (3-H; br s, 1H), 6.91 (d, J = 8.8 Hz, 2H), 7.45 (d, J = 8.8 Hz, 2H). Anal. Calcd for $C_{14}H_{17}NO_2$·HCl: C 62.80; H 6.78; N 5.23. Found: C 62.72; H 6.75; N 5.23.

(±)-*endo*-6-Acetoxy-4-phenyl-1-azabicyclo[3.2.1]oct-3-ene Hydrochloride (22a·HCl): prepared from **21a** by acetylation with acetic anhydride in a mixture of pyridine and dichloroethane at reflux temperature. The product was isolated as base and converted into the hydrochloride salt by hydrochloric acid in ether: mp 178-180°C (iPrOH). ^{1}H-Nmr (spectrum was taken with the base) δ 1.62 (s, 3H), 3.18 (7-H; ddd, J_1 = 13.3 Hz J_2 = J_3 = 3.3 Hz, 1H), 3.53 (d, J = 10.8 Hz, 1H), 3.70 (m, 2H), 4.00 (2-H; dd, J_1 = 18.8 Hz, J_2 = 2.6 Hz, 1H), 4.40 (7-H; dd, J_1 = 13,3 Hz, J_2 = 8.6 Hz, 1H), 4.50 (2-H; dd, J_1 = 18.8 Hz, J_2 = 2.6 Hz, 1H), 5.60 (6-H; m, 1H), 6.00 (3-H; dd, J_1 = 3.2 Hz, J_2 = 2.6 Hz, 1H), 7.30 (br s, 5H). Anal. Calcd for $C_{15}H_{17}NO_2$·HCl: C 64.40; H 6.48; N 5.01. Found: C 64.08; H 6.50 N 4.93.

Summary of the Main Biological Effects.

The most active compounds (**6b, 6c, 6e 13, 19a**) showed minimal effective doses of 0.62, 2.50, 0.62, 0.16 and 0.62 mg/kg (p.o.) in the scopolamine- and electroshock-induced passive avoidance test[21] in rats, respectively. With the enantiomers of **13** an enantioselectivity was found in the above tests and the more active (+)-**13** (as hydrochloride with code GYKI-46903) was selected as candidate for further developments. GYKI-46903 significantly reversed the scopolamine (0.5 mg/kg i.p.) or electroshock-induced impairment of passive avoidance response in rats. The dose-response curve was of an inverted U-shape in the dose range of 0.04-0.16 mg/kg p.o. in both tests. The effect on spatial working memory was examined in the radial arm maze test.[29] GYKI-46903 (0.04-0-32 mg/kg i.p.) revesed the scopolamine (1 mg/kg i.p.)-induced increase in errors. GYKI-46903 had also a benefitial effect on the time-related forgetting in a step-down passive avoidance test without applying any memory disrupting intervention.[23,30]

Effects of the compound was investigated on 5-HT_3-receptors and compared with ondansetron, a prototypical 5-HT_3 antagonist, in peripheral organs in vitro and in vivo, and in receptor binding assay to membrane prepared from rat cerebral cortex. The results of these experiments indicate that GYKI-46903 is a noncompetitive antagonist at the 5-HT_3 receptor.[22] Taking into consideration of its memory improving activity, we conclude that GYKI-46903 may have a unique pharmacological profile.

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Received, 1st November, 1994