Asymmetric Synthesis and Enantiospecificity of Binding of 2-(1,2,3,4-Tetrahydro-1-isoquinolyl)-ethanol Derivatives to μ and κ Receptors☆

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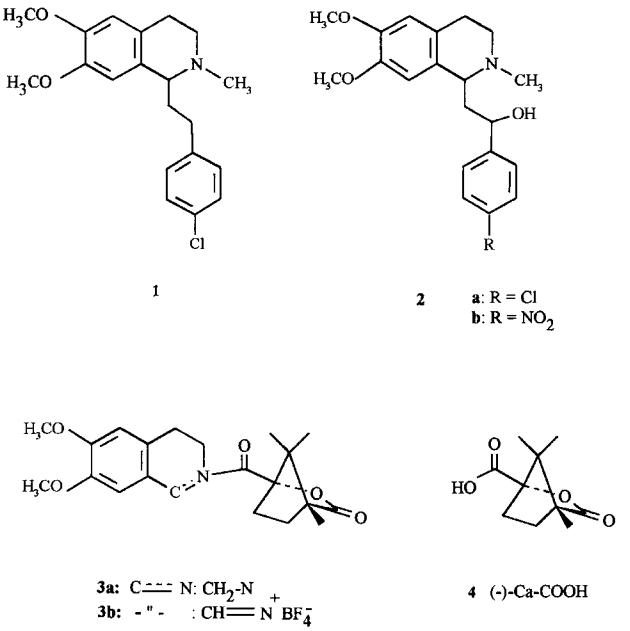
Summary

A number of 2-(1,2,3,4-tetrahydro-1-isoquinolyl)-ethanol derivatives 7a–e have been synthesized in diastereomerically and enantiomerically pure form and have been evaluated for their binding affinity at μ and κ opioid receptors. The amido ketones 5a–c and *ent*-5a–c, which were accessible by employing 3b and *ent*-3b for Asymmetric Electrophilic Amidoalkylation reactions, served as starting compounds. Upon reduction of 5a–c and *ent*-5a–c the amido alcohols *l*-6a–c, *u*-6a–c, *ent-l*-6a–c and *ent-u*-6a–c were obtained. Hydrolysis of these compounds yielded the secondary amino alcohols *l*-7a–c, *u*-7a–c, *ent-l*-7a–c and *ent-u*-7a–c and upon reductive methylation of *l*-7b–c, *u*-7b–c, *ent-l*-7b–c and *ent-u*-7b–c with CH_2O and $NaCNBH_3$ the tertiary amino alcohols *l*-7d–e, *u*-7d–e, *ent-l*-7d–e and *ent-u*-7d–e were obtained.

The binding affinities of the final compounds *l*-7a–e, *u*-7a–e, *ent-l*-7a–e and *ent-u*-7a–e at both the μ and the κ receptor were strongly dependent on their stereochemistry. In each case isomers exhibited higher affinity at the μ than at the κ receptor. For the secondary amino alcohols 7a–c the affinity at the μ receptor followed the stereochemical order *l*-7 > *ent-l*-7 > *ent-u*-7 > *u*-7 whereas for the tertiary amino alcohols the order *l*-7 > *u*-7 > *ent-l*-7 > *ent-u*-7 was found. The stereoisomers *l*-7d and *l*-7e of the tertiary amino alcohols were found to be the most active compounds the latter exhibiting a K_i value of 7.17 which is close to that of Morphine (K_i = 1.64). In an *in vivo* model, the Writhing Test, both compounds *l*-7d and *l*-7e displayed high analgetic activity.

Introduction

1-Arylalkyl-substituted tetrahydroisoquinolines may exhibit distinct analgetic activity, as was found by the German Company Tropon-Werke some 50 years ago[1]. About 20 years later an extensive investigation at Hoffmann-La Roche prompted by this finding led to the development of new highly potent centrally active analgesics[2]. These analgesics may be classified in two groups by chemical structure, both groups being closely related. The first group (group **I**) is comprised of 1,2,3,4-tetrahydroisoquinolines substituted with an arylethyl side chain in position 1 (see **1,** Scheme **1**). The second one (group **II**) differs from the former by an additional hydroxy function in that side chain (see **2a** and **2b**, Scheme **2**). The analgetic effectiveness of these compounds was mostly determined in animal models. The potency of compounds of group **I** was of the order of codeine and the degree of addictiveness exhibited by these compounds was found to be rather low and to be commensurate with their analgetic activity. The chloro derivative **1** was finally evaluated for its analgetic effectiveness in man. It was chosen, although not the most potent compound in this series, because its addictiveness had proved to be very low. The clinical trials revealed that compound **1** is a safe analgetic with a potency comparable to that of codeine. Yet this compound, named Methopholine (Versidyne^R, racemic compound), never did reach the market.



Scheme 1

For Methopholine (**1**) and some related compounds it has been shown that their analgetic activity resides exclusively in one enantiomer of a pair of enantiomeric compounds, with the active isomer having the (*R*)-configuration in each case.

The compounds of group **II** were studied exclusively as racemic mixtures. The analgetic activity of these compounds appeared to be strongly dependent on their relative stereochemistry.

This resulted in two diastereomeric series with different activity; however, the relative stereochemistry of these series has not been determined. Members of the more active series

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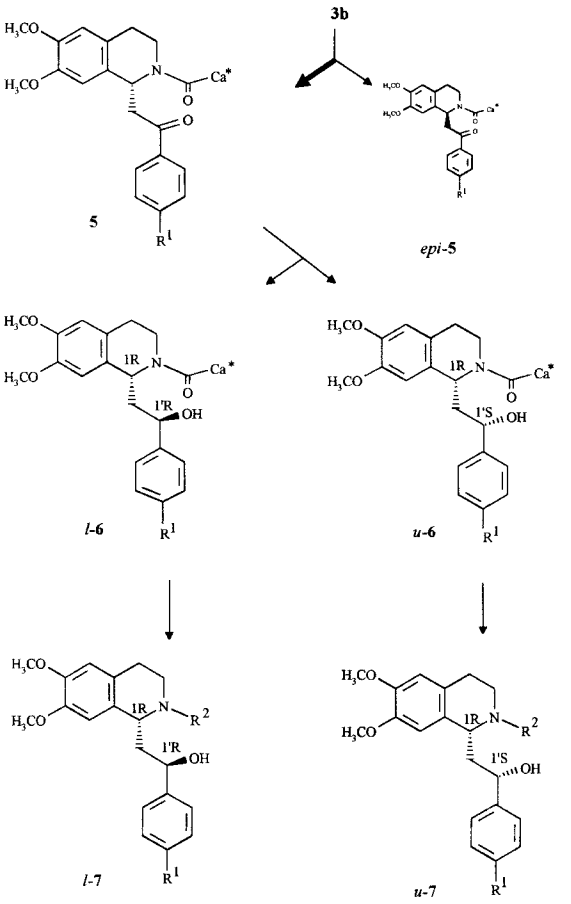
(as racemic compounds) were about ten times more active than those of the series with opposite relative stereochemistry. The more active isomers of this group of compounds (group **II**) were more potent than the corresponding drugs of group **I**. Thus, for example the analgetic activity exhibited by the more active isomer of the chloro derivative **2a** was of the same order as that of morphine and this was still surpassed by the nitro derivative **2b** which was even many times more active. In general, the pharmacological properties of these compounds (group **II**) were very similar to those of the arylalkyl tetrahydroisoquinolines (group **I**), with the exception that the higher degree of effectiveness exhibited by them was also accompanied by a higher physical dependence capacity.

On the basis of the results of the pharmacological studies it appears reasonable to assume that the drugs mentioned above mediate their pharmacological effect via interaction with opioid receptors. Three distinct opioid receptors have been well characterized, the μ, κ, and δ receptors [3]. It is well established that activation of each of these receptors can produce antinociceptive effects. However, these receptors differ widely with respect to their side effects, with physical dependence, respiratory depression, and constipation, for example, being associated with activation of the μ receptor[4]. The aim of the present study was to evaluate the oxygenated isoquinolines **2a** and a number of related compounds for their affinity and selectivity to μ and κ receptors by receptor binding studies, in order to confirm that these compounds are indeed opioid analgesics.

We employed enantiomerically pure compounds to examine the stereochemical requirements for the activity of these compounds and to determine whether these requirements are similar to those found for the compounds of group **I**.



a: R^1 = H, R^2 = H

b: R^1 = OCH_3, R^2 = H — CH_2=O, $NaCNBH_3$ → **d**: R^1 = OCH_3, R^2 = CH_3

c: R^1 = Cl, R^2 = H — CH_2=O, $NaCNBH_3$ → **e**: R^1 = Cl, R^2 = CH_3

Scheme 2

Chemistry

Recently we reported a method for the synthesis of 1-substituted 1,2,3,4-tetrahydroisoquinolines in enantiomerically pure form [5]. The key step of this method, which may be regarded as an Asymmetric Electrophilic α-Amidoalkylation (AEαA), comprises the stereoselective addition of an appropriate nucleophile to a chiral *N*-acyl-dihydroisoquinolinium ion. Thus, from the isoquinolinium ion **3b** – with (–)-camphanic acid (**4**) as chiral auxiliary – which is accessible from the corresponding amide **3a** by hydride abstraction with triphenylcarbenium tetrafluoroborate ($Ph_3C^+BF_4^-$) the corresponding amido ketones (e.g. **5**) could be obtained by addition of the appropriate silyl enol ethers. In the case of compounds **5a**/*epi*-**5a** and **5c**/*epi*-**5c** the diastereoselectivity amounted to >90/10 (ds) and liquid chromatography afforded the major isomers **5a** and **5c** in pure form[5].

For the biological studies we selected the amino alcohols **7a–e** which differ from each other only with respect to their substitution at the phenyl ring and at the amine nitrogen, and thus form a series of related compounds. These amino alcohols **7a–e** appeared to be easily accessible from the amido ketones **5a–c**. Two of these starting compounds, the amido ketones **5a** and **5c**, were available to us from the investigation mentioned above. The synthesis of **5b** was achieved in an analogous manner by employing the method developed for the first two compounds (see Experimental Part).

For reduction the amido ketones **5a** and **5b** were subjected to a catalytic hydrogenation over Pd on carbon which yielded the amido alcohols *l*-**6**/*u*-**6a** and *l*-**6**/*u*-**6b** as a mixture of diastereomers (see Table 1). In the case of **5c** a complete dehalogenation occurred when applying this catalytic procedure. Therefore in this case KBH_4 was used for hydrogenation, which indeed led to *l*-**6**/*u*-**6c**. In each case the resulting mixtures contained both diastereomers in reasonable amounts as these reactions proceeded with very low diastereoselectivities (see Table 1). However, this provided the opportunity to obtain both diastereomers in reasonable amounts from one and the same reaction product by separating the resulting mixtures. This separation was accomplished by flash chromatography and in each case the diastereomers were purified to at least 99.5% de.

For amido ketones related to **5** but exhibiting a pyrrolidine nucleus instead of an isoquinoline ring it had been found [6] that the reduction may result in rather high diastereoselectivi-

Table 1. Preparation of amido alcohols *l*-**6**/*u*-**6a-c** from **5a-c.**

start compd.	reaction conditions	ratio[a] *l*-**6**/*u*-**6**	yield [%][b] *l*-**6**	*u*-**6**
5a	H_2, Pd-C, MeOH, NH_3, r.t., 24 h	56/44	44	39
5b	H_2, Pd-C, MeOH, NH_3, r.t., 26 h	63/37	61	37
5c	KBH_4 (10 eq.), EtOH, r.t., 36 h	36/64	32	51

[a] Determined by HPLC

[b] After separation by prep. HPLC, de ≥ 99.5 %

Table 2. Diastereoselectivities in the reduction of **5a**

reaction conditions [a]				*l*-**6a**/*u*-**6a**	conversion [%]
1. $NaBH_4$ (2.8 eq.),	EtOH,	r.t.,	4 h	17/83	>99
2. KBH_4 (10 eq.),	EtOH,	r.t.,	36 h	32/68	>99
3. $LiAlH(O\text{-}^tBu)_3$ (3.2 eq.),	THF,	0°C,	1.25 h	13/87	98
4. $LiBH(s\text{-}Bu)_3$ (1.2 eq.),	THF,	–78 °C,	2 h	15/85	65
5. $LiBH(s\text{-}Bu)_3$ (1.2 eq.),	Toluene,	–78 °C,	3.5 h	37/63	76
6. $KBH(s\text{-}Bu)_3$ (1.2 eq.),	THF,	–78 °C,	2 h	11/89	80
7. DIBAlH (2 eq.),	THF,	–78 °C,	5 h	5/95	35
8. DIBAlH (2 eq.),	Toluene,	–78 °C,	5 h	6/94	75

[a] Reactions were run at concentrations from 0.02 to 0.07 [mol l^{-1}]

ties when the appropriate reducing agents are used and – even more interesting – that the direction of the asymmetric induction may be inverted by proper choice of the reducing agents, this being in accordance with the concept of chelate and non-chelate control [7].

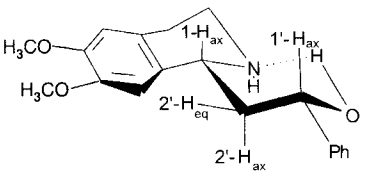
We thus hypothesized that this might be possible in the present case. We were pleased to find that the diastereoselectivities obtained were in the range of 5/95 when DIBAlH (Table 2, entries 7 and 8), which may be regarded as one of the most typical reagents for reductions under non-chelate control, was used. The use of the borohydrides $LiBH(s\text{-}Bu)_3$ and $KBH(s\text{-}Bu)_3$ resulted in an asymmetric induction of the same direction. This is in agreement with the study[6] mentioned above. However, from the results of that study we had expected that the diastereoselectivities of the latter reductions would be higher than those for the DIBAlH reaction, but the opposite was true. Finally we were surprised to find that the use of $LiAlH(O\text{-}^tBu)_3$ which is a reducing agent capable of reductions under chelate-control did not lead to the expected inversion of the diastereoselectivity (Table 2 entry 3); while the stereoselectivity was quite high the same stereoisomer as in the case of the former reagents for non-chelate control prevailed. Thus all reducing agents including $NaBH_4$ and KBH_4 also used for this purpose (the former giving higher stereoselectivities, see Table 2 entry 1) led to *l*-**6a** as the predominant stereoisomer.

The next step in our synthesis was the removal of the chiral auxiliary and could be effected very efficiently be treating the amido alcohols *l*-**6a–c** and *u*-**6a–c** with KOH in MeOH for several days. In the case of *u*-**6a–c** the cleavage occurred already at room temperature whereas for *l*-**6a–c** the temperature had to be raised to 40 °C in order to induce the reaction. Higher temperatures turned out to be unsuitable as they resulted in extensive decomposition. Although under these conditions it took several days to complete hydrolysis, the yields of the amino alcohols *l*-**7a–c** and *u*-**7a–c** were found to be quite satisfactory (see Table 3 and 4). Finally, for the synthesis of the tertiary amino alcohols *l*-**7d–e** and *u*-**7d–e** the compounds *l*-**7b–c** and *u*-**7b–c** were subjected to a reductive *N*-methylation with $CH_2O/NaCNBH_3$ which after aqueous workup afforded *l*-**7d–e** and *u*-**7d–e** in yields of 75 to 93%.

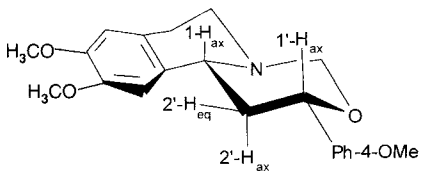
The major isomers of the amidoalkylation reaction **5a** and **5c** have been assigned the *(R)*-configuration for the chiral center at C-1 of the isoquinoline ring[5]. Of course, the chiral centers at C-1 of the isoquinoline rings of the subsequent products described in this paper must then also be of *(R)*-configuration.

with respect to the values of chemical shifts and coupling constants for the protons of the ethyl side chain and the proton at C-1. The values of these coupling constants present clear evidence that a pseudo-cycle with a chair conformation displaying the protons 1-H_{ax} and 1′-H_{ax} in axial positions had formed. Thus the compounds *u*-**7a–c** may be assigned the

Table 3. Yields and selected ^{1}H-NMR data of *u*-**7** and *u*-**8**



u-**7a**

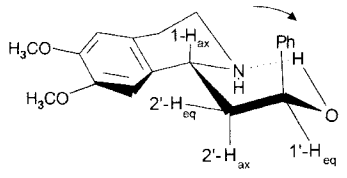


u-**8**

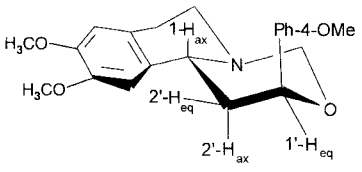
		J_{vic} [Hz]			
compound	yield [%]	1-H_{ax}/2′-H_{ax}	1-H_{ax}/2′-H_{eq}	1′-H_{ax} /2′-H_{ax}	1′-H_{ax}/2′-H_{eq}
u-**8**[a]	–	11.5	3	11.5	3
u-**7a**[b]	80	11.5	2.5	10.5	2.5
u-**7b**[b]	70	11.5	2.5	10.5	2.5
u-**7c**[b]	87	11.5	2.5	10.5	2.5

[a] The synthesis was performed by treating *u*-**7b** with CH_2O in Et_2O (r.t., 17 h); the compound was characterized by ^{1}H-NMR only.
[b] From *u*-**6** by hydrolysis with 0.5 N KOH in CH_3OH (+10 % H_2O, r.t., 4–6 d).

Table 4. Yields and selected ^{1}H-NMR data of *l*-**7** and *l*-**8**



l-**7a**



l-**8**

		J_{vic} [Hz]			
compound	yield [%]	1-H_{ax}/2′-H_{ax}	1-H_{ax}/2′-H_{eq}	1′-H_{eq}/2′-H_{ax}	1′-H_{eq}/2′-H_{eq}
l-**8**[a]	–	11	3	5.5	3
l-**7a**[b]	89	7.3[c]	3[c]	7.7[d]	3[d]
l-**7b**[b]	71	7.3[c]	2.5[c]	7.7[d]	2.5[d]
l-**7c**[b]	91	7.3[c]	3.0[d]	7.7[d]	3.0[d]

a) The synthesis was performed by treating *l*-**7b** with CH_2O in Et_2O; the compound was characterized by ^{1}H-NMR only.
[b] From *l*-**6** by hydrolysis with 0.5 *N* KOH in CH_3OH at 40°C (11–14 d).
[c], [d] Assignment may be reversed.

The relative stereochemistry of the amino alcohols *l*-**7a–c** and *u*-**7a–c** was established by ^{1}H-NMR studies. 1,3-Amino alcohols tend to form an intramolecular H-bond between the amine nitrogen and the hydroxyl group, thus giving rise to the formation of a six-membered pseudo-cycle adopting a chair conformation (see Fig. *l*-**7a** and *u*-**7a** in Tables 3 and 4)[8]. In the case of *u*-**7a–c** the ^{1}H-NMR spectra were quite similar

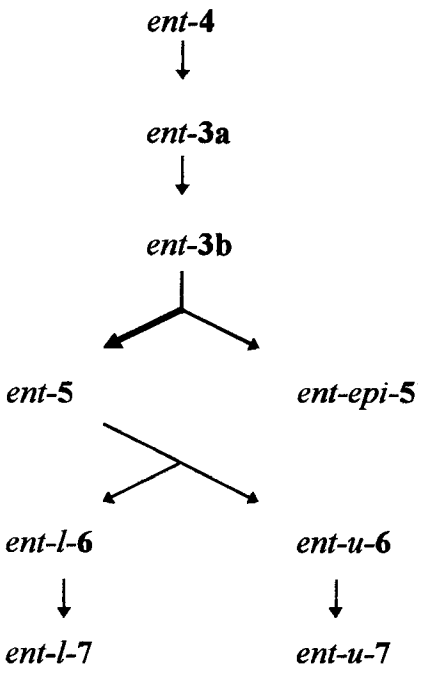
u-configuration and finally their absolute stereochemistry can be determined by taking into account the absolute configuration assigned to C-1 of the isoquinoline ring.

The above stereochemical assignment was further verified by a comparative ^{1}H-NMR study of the 1,3-oxazines *u*-**8** and *l*-**8**. The synthesis of these compounds was accomplished by subjecting the amino alcohols *u*-**7b** and *l*-**7b** to a condensation

reaction with CH_2O[9]. According to the ^{1}H-NMR spectra the 1,3-oxazine ring adopts a chair conformation in both compounds. For *u*-**8** the protons at C-1 and C-1′ are both in axial positions whereas for *l*-**8** only the proton at C-1 occupies the axial position, the proton at C-1′ being in equatorial position. This is in full agreement with the above stereochemical assignment based on the ^{1}H-NMR spectra of the amino alcohols *u*-**7a–c**. It is further interesting to note that the ^{1}H-NMR spectrum of *u*-**8** is very similar to those of the amino alcohols *u*-**7a–c**, thus confirming that the latter indeed exist (in $CDCl_3$) in the presumed pseudo-cyclic conformation.

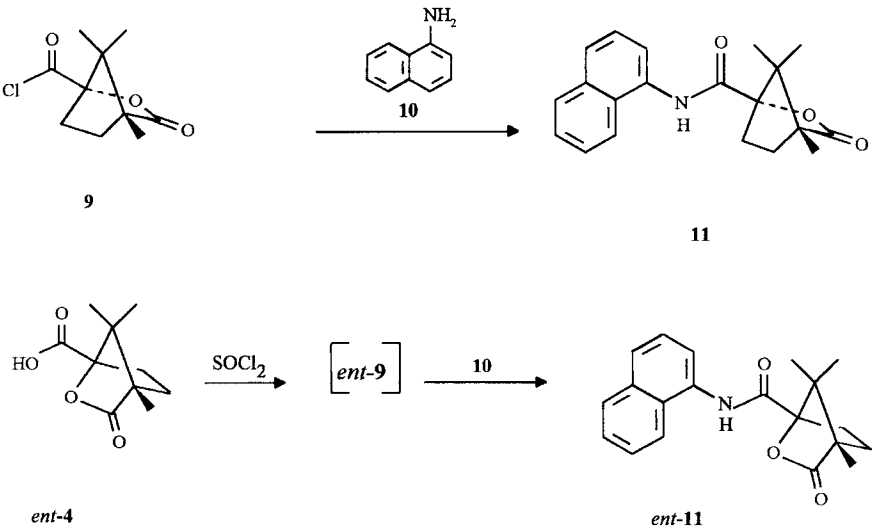
The fact that the amino alcohols *l*-**7a–c** are diastereomeric with respect to *u*-**7a–c** with the only difference being the configuration at the hydroxyl bearing carbon allows unambiguous determination of the stereochemistry of this group of compounds. Of course, the *l*-configuration of these compounds is apparent from the stereochemistry also found for *l*-**8** (see above). However, in contrast to the ^{1}H-NMR spectra of *u*-**7a–c** those of the amino alcohols *l*-**7a–c** were not very informative. The spectra of the amino alcohols *l*-**7a–c** again were very similar (see Table 4) a phenomenon already observed for *u*-**7a–c** and indicating their stereochemical relationship, but the spectra (of *l*-**7a–c**) were distinctly different from the ^{1}H-NMR spectrum of *l*-**8**, especially with respect to the coupling constants for the protons attached to C-1, C-2′ and C-1′. The values of these coupling constants indicate that no pseudo-cycle (hydrogen bridge) with a regular chair conformation is formed. The chair conformation must either be strongly distorted or free non-cyclic conformations may have gained increased importance[10] (for *l*-**7a–c**). This phenomenon is most likely due to the fact that for *l*-**7a–c** a regular chair conformation would suffer from severe 1,3-diaxial steric interactions (see Fig. *l*-**7a** in Table 4).

The synthesis of the amino alcohols *ent-l*-**7a–e** and *ent-u*-**7a–e**, the enantiomers of *l*-**7a–e** and



Scheme 3

u-**7a–e**, was accomplished by a synthetic sequence completely enantiomorphic to that described above (for *l*-**7a–e** and *u*-**7a–e**). By employing (+)-camphanic acid *ent*-**4** as a chiral auxiliary the enantiomeric amidoalkylation reagent *ent*-**3b** (via *ent*-**3a**) was prepared which served as the key compound in this sequence. The synthetic results for the



Chiral HPLC (Pirkle-Column, (*R*)-DNBPG): **11** : ee > 99.5 %
ent-**11** : ee ≥ 99.5 %

Scheme 4

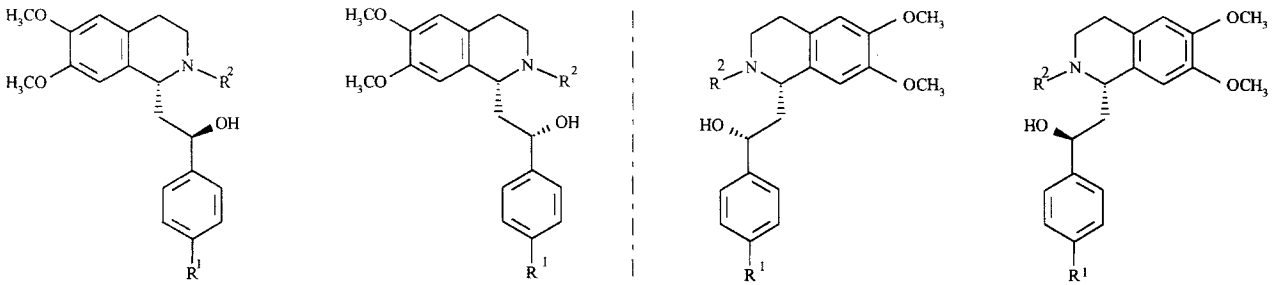
preparation of *ent*-**4** and for all subsequent reactions compare well to those found for the original series and are presented below in the Experimental Part. The numbering of these compounds is given in Scheme 3.

The enantiomeric purity of the obtained amines is a direct result of both the diastereomeric purity of the synthetic intermediates (e.g. *l*-**6**) employed in subsequent reactions (in each case those intermediates had been purified to de > 99.5%) and the enantiomeric purity of the chiral auxiliaries (**9** and *ent*-**4**) used for the preparation of the amidoalkylation reagents **3a** and *ent*-**3a**. Therefore we checked the enantiomeric purity of commercial samples of **9** (the acid chloride of **4**, which is commercially available) and *ent*-**4** employed in this study.

This analysis was performed by chiral chromatography with a Pirkle column ((*R*)-DNBPG). In order to obtain separable enantiomers, **9** and *ent*-**4** had to be converted into their naphthamides **11** and *ent*-**11**, respectively (see Scheme 4). The latter could be separated on a Pirkle column. The analysis revealed **11** to be free of any trace of its enantiomeric compound (within the limits of detection) whereas *ent*-**11** was contaminated with 0.2% of the optical isomer **11**. Therefore, the enantiomeric purity of the amines described here (*l*-**7**, *u*-**7**, *ent-l*-**7** and *ent-u*-**7**) should be higher than 99% (ee) since both the enantiomeric purity (ee) of the chiral auxiliaries and the diastereomeric purity (de) of the synthetic intermediates were at least 99.5%.

Results and Discussion of Biological Activities

Final compounds (Table 5) were evaluated for *in vitro* activity on μ and κ opioid receptors by radioreceptor binding assays. All compounds were used in the form of hydrochloride salts and were water soluble. The binding affinities were determined at crude bovine striatal membranes with ^{3}H-DAMGO and ^{3}H-U-69,593 as specific ligands for the μ and the κ opioid receptors, respectively. Morphine, Naloxone, Tramadol and U-50,488 were used as reference compounds (see Table 5).



Scheme 5

Table 5. Affinities of amino alcohols **7a–e** in radioligand bindings assays at bovine striatal μ and κ opioid receptors

				K_i:mean (±SEM, nM)				
	R^1	R^2		*l*-**7**	*u*-**7**	*ent-u*-**7**	*ent-l*-**7**	*l*-**7** / *ent-l*-**7** / *u*-**7** /*ent-u*-**7**
a	H	H	μ	*1920* (± 110)	27300 (*n* = 1)	19900 (±800)	8280 (±1400)	1 / 4.3 / 14.2 / 10.4
			κ	*12700* (± 600)	> 100000	94100 (*n* = 1)	24500 (±2800)	1 / 1.9 / 7.9 / 7.4
b	OCH_3	H	μ	*715* (± 60)	10800 (±2200)	5790 (± 760)	2210 (± 680)	1 / 3.1 / 15.1 / 8.1
			κ	*12030* (±1640)	55500 (*n* = 1)	47900 (*n* = 1)	55900 (*n* = 1)	1 / 4.6 / 4.6 / 4.0
c	Cl	H	μ	*255* (±24)	6680 (± 290)	2630 (± 50)	924 (± 107)	1 / 3.6 / 26.2 / 10.3
			κ	*4110* (± 440)	36300 (*n* = 1)	44100 (*n* = 1)	26500 (± 2970)	1 / 6.4 / 8.8 / 10.7
d	OCH_3	CH_3	μ	*59.5* (± 2.0)	327 (± 1)	21600 (*n* = 1)	2730 (± 850)	1 / 46 / 5.6 / 363
			κ	*459* (± 38)	2050 (± 340)	39500 (*n* = 1)	21200 (±2800)	1 / 46 / 4.5 / 86
e	Cl	CH_3	μ	*7.17* (± 0.78)	108 (± 8)	2670 (± 140)	502 (± 25)	1 / **70** / 15.1 / **372**
			κ	*63.6* (± 3.6)	442 (± 40)	23400 (± 2100)	8230 (± 720)	1 / 129 / 6.9 / 368
Morphine			μ	1.64 (± 0.26)	κ 111 (± 12)			
Naloxone			μ	1.30 (± 0.05)	κ 6.11 (± 0.97)			
Tramadol			μ	1690 (± 210)	κ 51000 (± 3700)			
U-50,488			μ	–	κ 1.44 (± 0.025)			

Table 6. Analgetic activity of amino alcohols **7d-e** in Writhing Test

			ED_{50} (mg/kg in mice)								
	R^1	R^2	*l*-**7**		*u*-**7**		*ent-u*-**7**		*ent-l*-**7**	*l*-**7** / *ent-l*-**7** / *u*-**7** / *ent-u*-**7**
d	OCH_3	CH_3	3.9	(2.6–5.9)	10.0	(4.0–25.0)	12.5	(8.1–19.4)	17.0 (5.3–54.4)	1 / 4.4 / 2.6 / 3.2
e	Cl	CH_3	1.7	(1.2–2.4)	10.2	(4.4–23.7)	22.0	(6.9–70.4)	100 (15.9–630)	1 / 59 / 6 / 12.9
Morphine			0.60	(0.38–0.96)						
U – 50,488			4.7	(3.0–7.4)						
Tramadol			8.4	(4.3–16.5)						

As depicted in Table 5, the binding affinity of the amino alcohols **7a–e** for both the μ and κ opioid receptor was strongly dependent on the stereochemistry. The stereoisomers with the highest binding affinities with regard to both the μ and κ receptor all exhibited the (*R,R*)-configuration (*l*-**7a–e**). One may consider the amino alcohols to belong to two subsets of compounds, subset I with **7a–c** and subset II with **7d–e** with a secondary and a tertiary amino function, respectively. As regards the μ receptor, the stereoisomers *l*-**7a–c**, the isomers of subset I with the highest activity, exhibit binding affinities that are far lower than that of Morphine but which are still in the range or even better than that of Tramadol. The affinity of these and all other isomeric compounds increases in the order *l*-**7a** to *l*-**7c** with the substituents at the phenyl ring changing from "H" to OCH_3 to Cl. It is most interesting to note that, regarding the μ receptor, the stereochemical order of binding affinities for all compounds (of subset I) is as follows: *l*-**7** > *ent-l*-**7** > *ent-u*-**7** > *u*-**7**. In addition the ratios of these binding affinities are also very similar (≈ 1/4/14/10). The stereoisomers with *l*-configuration, *l*-**7** and *ent-l*-**7**, exhibit higher affinities than those with *u*-stereochemistry (*ent-u*-**7** and *u*-**7**). Thus the binding affinity is above all determined by the relative stereochemistry (*l* better than *u*). The absolute configuration is of minor importance, the (*R*)-configuration being more advantageous than the (*S*)-configuration at C-1′ (C-OH). Regarding the κ receptor, much lower affinities are found for **7a–c**. Furthermore, except for the fact that the stereoisomers *l*-**7** are the most active ones, no clearcut gradation is seen for the other stereoisomers.

The μ receptor affinity displayed by the tertiary amines **7d–e** (subset II) was found to be much higher than that of the former compounds. The potencies of the stereoisomers, for both the chloro and the methoxy derivatives **7d** and **7e**, decreased in the order *l*-**7** > *u*-**7** > *ent-l*-**7** > *ent-u*-**7**. This order differed from that of the former compounds and in addition the differences in potencies of the stereoisomers were much more pronounced (see Table 5). Thus for example *l*-**7e**, the most potent amino alcohol with a K_i value (7.17 nM) close to that of Morphine (1.64 nM), exhibited an enantioselectivity of binding of 1/70. This was still surpassed by the stereoselectivity of binding of the same compound to the κ receptor: 1/129. One may speculate that in these cases the enantioselectivities begin to be leveled off by the limited enantiomeric purity of the compounds (ee > 99%).

Besides the enantioselectivity also the diastereoselectivity of binding of these compounds deserves special mention, the corresponding values being in the range of 1/370 (!). From these data it becomes apparent that for the tertiary amines **7d–e** the binding affinity is controlled above all by the absolute configuration at C-1 of the isoquinoline ring which must be *R* for high affinities (*l*-**7** and u-**7**). The relative configuration is of only minor importance (*l* better than *u*).

For the κ opioid receptors, lower affinities were found as compared to those for the μ receptor, the stereochemical trend being the same for both receptors, however.

The amino alcohols **7d–e** were evaluated for their analgetic activity in an *in vivo* study, the Writhing Test[11]. Compounds **7a–c** were omitted from this investigation as in a preceding screening according to Irwin[11] they appeared to be devoid of CNS activity typical for analgesics (in doses up to 100/kg). As can be seen from the data shown in Table 6 the compounds are potent analgesics, which so far is in agreement with the results of the *in vitro* study. However, the methoxy and the chloro series exhibited no or only small differences in activity with *ent-l*-**7** being the only exception. As in the *in vitro* studies the highest activity is seen for *l*-**7d** and *l*-**7e** (see Table 6). For the latter compound (*l*-**7e**) the activity is close to that of Morphine. However, the stereochemical order of activity does not parallel that of the *in vitro* study and the differences are far less pronounced. The reason for this remains unclear, but it has to be kept in mind that the accuracy of the *in vivo* data (especially the ED_{50}-values of the modestly effective compounds) seems to be rather low. From the results of this study it may be concluded that of the two series of diastereomeric amino alcohols reported by Hoffmann-La Roche the one exerting higher analgetic activity must have been of *l*-configuration. Furthermore it is interesting to note that the most active isomers of the amino alcohols (*l*-**7**) exhibit the (*R*)-configuration at C-1 (of the isoquinoline ring), which is in agreement with the stereochemical requirement found at Hoffmann-La Roche for the arylalkyl isoquinolines (e.g. **1**).

Conclusion

We have prepared a number of secondary and tertiary amino alcohols of differing absolute stereochemistry at the two stereogenic centers. μ and κ opioid receptor binding studies showed the effect of the configuration on the affinity. All compounds under investigation exhibited a distinct selectivity for the μ receptor. The stereoisomers showing the highest potencies were all of the (*R,R*)-configuration (*l*-**7**). For **7a–c** the activity of the stereoisomers followed the order *l*-**7** > *ent-l*-**7** > *ent-u*-**7** > *u*-**7** whereas for **7d–e** the order *l*-**7** > *u*-**7** > *ent-l*-**7** > *ent-u*-**7** was found. The most active compound *l*-**7e**

exhibited a K_i of 7.17 (±0.78 nM), which is close to that of Morphine (K_i: 1.64 ± 0.26 nM).

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Experimental Part

General procedures

Our basic laboratory procedures and methods of HPLC analysis have all been previously reported in detail[5].

The synthesis of the enantiomeric compounds *ent*-**3**, *ent*-**5**, *ent-epi*-**5**, *ent-l*-**6**, *ent-u*-**6**, *ent-l*-**7** and *ent-u*-**7**, was accomplished by synthetic procedures corresponding to those for their images, except that they were enantiomorphic. Therefore the experimental procedure is given for only one of two enantiomers. As in each case the spectroscopic data (IR, ^{1}H-NMR, ^{13}C-NMR, MS) of enantiomeric compounds were identical with each other, these data are also given for only one of two enantiomers.

*(1S,4R)-1-{(1R)-1,2,3,4-Tetrahydro-6,7-dimethoxy-1-[2-(4-methoxyphenyl)-2-oxo-1-ethyl]-2-isoquinolylcarbonyl}-4,7,7-trimethyl-2-oxa-bicyclo[2.2.1]heptan-3-one (***5b***) and (1S,4R)-1-{(1S)-1,2,3,4-Tetrahydro-6,7-dimethoxy-1-[2-(4-methoxyphenyl)-2-oxo-1-ethyl]-2-isoquinolylcarbonyl}-4,7,7-trimethyl-2-oxa-bicyclo[2.2.1]heptan-3-one (epi-***5b***)*

The synthesis was accomplished in analogy to the procedure employed for the preparation of **5a**/*epi*-**5a**[5].

2.55 g (7.72 mmol) of Ph_3C^+ BF_4^- in 30 ml of CH_2Cl_2; 2.31 g (6.17 mmol) of **3a** in 30 ml of CH_2Cl_2; 1.70 ml (15.4 mmol) of $TiCl_4$ in 1.0 ml of CH_2Cl_2; 1.58 g (7.41 mmol) 4-methoxy-1-(1-trimethylsilyloxyethenyl)-benzene in 1.5 ml of CH_2Cl_2; reaction time: 2 h at –78 °C.

A colorless solid containing **5b** and *epi*-**5b** was obtained after flash chromatography in a yield of 1.96 g (61 %). The ratio of **5b**/*epi*-**5b** was determined by HPLC (from the crude product; chiral column, *n*-hexane:isopropanol = 75:25): 88.5/11.5.

Anal. ($C_{30}H_{35}NO_7$).– IR: 1790 cm^{-1}, 1675, 1640, 1600.– MS; *m/z* = 521 (M^+).– Separation of the diastereomers was effected by prep. HPLC (chiral column, *n*-hexane:EtOAc:isopropanol = 75:19:6). From a sample of 82 mg (**5b**/*epi*-**5b** 88.5/11.5) 40 mg of **5b** (de > 99.5%) and 7 mg (0.4%) of *epi*-**5b** (de ≈ 82%) were obtained.

5b: Colorless crystals, mp. 91–93 °C.– $[\alpha]_{546} = -155.6°$, $[\alpha]_{578} = -137.4°$ (*c* = 0.50 in CH_3OH).– Anal. ($C_{30}H_{35}NO_7$).– 400 MHz ^{1}H-NMR ($CDCl_3$):0.93 (s, 0.8 × 3H, CH_3), 0.96 (s, 0.2 × 3H, CH_3), 1.07 (s, 0.2 × 3H, CH_3), 1.08 (s, 0.8 × 3H, CH_3), 1.14 (s, 0.8 × 3H), 1.20 (s, 0.2 × 3H, CH_3), 1.70 (ddd, *J* ≈ 4/9/13 Hz, 1H), 1.89 (ddd, *J* ≈ 4/11/13 Hz, 1H), 2.01 (ddd, *J* ≈ 4/9/13 Hz, 1H), 2.20 (ddd, *J* ≈ 4/11/13 Hz, 1H), 2.73 (dt, *J* ≈ 16/2.6 Hz, 1H), 2.95–3.05 (m, 0.2 × 1H), 3.08 (ddd, *J* ≈ 5/11/16 Hz, 0.8 × 1H), 3.35 (dd, *J* ≈ 6.6/14 Hz, 1H), 3.40 (dd, *J* ≈ 6.6/14 Hz, 1H), 3.52–3.59 (m, 1H), 3.72 (s, 0.2 × 3H, OCH_3), 3.77 (s, 0.8 × 3H, OCH_3), 3.83 (s, 0.2 × 3 H, OCH_3), 3.84 (s, 0.8 × 3H, OCH_3), 3.86 (s, 0.2 × 3H, OCH_3), 3.87 (s, 0.8 × 3H, OCH_3), 4.46 (ddd, *J* ≈ 2/5/13 Hz, 0.8 × 1H, NC*H*$_2$CH$_2$Ar), 4.55–4.62 (m, 0.2 × 1H, NC*H*$_2$CH$_2$Ar), 6.03 (t, *J* ≈ 6.6 Hz, 1H, NC*H*Ar), 6.58 (s, 0.2 × 1H, aromatic H), 6.59 (s, 0.8 × 1H, aromatic H), 6.65 (s, 0.8 × 1H, aromatic H), 6.75 (s, 0.2 × 1H, aromatic H). 6.92–6.96 (m, 2H, aromatic H), 7.97–8.01 (m, 2H, aromatic H). Ratio of atropisomers ≈ 2:8.

epi-**5b**: 400 MHz ^{1}H-NMR ($CDCl_3$): 0.89 (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), 1.97 (ddd, *J* ≈ 4/9/13 Hz, 1H), 2.43 (ddd, *J* ≈ 4/11/13 Hz, 1H), 2.78 (dt, *J* ≈ 16/3 Hz, 1H), 2.91 (ddd, *J* ≈ 5/11/16 Hz, 1H), 3.29 (dd, *J* ≈ 6/14 Hz, 1H), 3.42 (dd, *J* ≈ 7/14 Hz, 1H), 3.64–3.71 (m, 1H), 3.79 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 4.56 (ddd, *J* ≈ 3/5/14 Hz, 0.8 × 1H, NC*H*$_2$CH$_2$Ar), 4.62–4.68 (m, 0.2 × 1H, NC*H*$_2$CH$_2$Ar), 6.16 (t, *J* ≈ 6.6 Hz, 0.8 × 1H, NC*H*Ar), 6.22–6.28 (m, 0.2 × 1H, NC*H*Ar), 6.58 (s, 1H, aromatic H), 6.68 (s, 1H, aromatic H), 6.91–6.96 (m, 2H, aromatic H), 7.91–7.99 (m, 2H, aromatic H), ratio of atropisomers ≈ 2:8. Signals of the minor atropisomer that could not be assigned unequivocally have been omitted.

*(1R,4S)-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 (ent-***5a***) and (1R,4S)-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 (ent-epi-***5a***)*

Preparation according to the procedure reported for **5a**/*epi*-**5a**[5] from 2.5 g (6.61 mmol) of *ent*-**3a**. Yield (*ent*-**5a** + *ent-epi*-**5a**), 2.61 g (80 %). Separation by prep. HPLC (chiral column, *n*-hexane:EtOAc = 62.5:37.5) yielded *ent*-**5a** and *ent-epi*-**5a.**

ent-**5a:** Colorless crystals, mp. 90–93 °C.– $[\alpha]_{546}$ = + 161.9°, $[\alpha]_{578}$ = + 139.7° (*c* = 0.32 in CH_3OH).– Anal. ($C_{29}H_{33}NO_6$).

ent-epi-**5a**: Characterization only by ^{1}H-NMR.

*(1R,4S)-1-{(1S)-1,2,3,4-Tetrahydro-6,7-dimethoxy-1-[2-(4-methoxyphenyl)-2-oxo-1-ethyl]-2-isoquinolylcarbonyl}-4,7,7-trimethyl-2-oxa-bicyclo[2.2.1]heptan-3-one (ent-***5b***) and (1R,4S)-1-{(1R)-1,2,3,4-Tetrahydro-6,7-dimethoxy-1-[2-(4-methoxyphenyl)-2-oxo-1-ethyl]-2-isoquinolylcarbonyl}-4,7,7-trimethyl-2-oxa-bicyclo[2.2.1]heptan-3-one (ent-epi-***5b***)*

Preparation according to the procedure described for **5b**/*epi*-**5b** from 2.32 g (6.21 mmol) of *ent*-**3a**. Yield (*ent*-**5b** *ent-epi*-**5b**), 2.15 g (66 %).

ent-**5b**: Colorless crystals, mp 91–93 °C.– $[\alpha]_{546}$ = + 155.3°, $[\alpha]_{578}$ = + 139.5° (*c* = 0.38 in CH_3OH).– Anal. ($C_{30}H_{35}NO_7$).

ent-epi-**5b**: Characterization only by ^{1}H-NMR.

*(1R,4S)-1-{(1S)-1-[2-(4-Chlorophenyl)-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 (ent-***5c***) and (1R, 4S)-1-{(1R)-1-[2-(4-Chlorophenyl)-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 (ent-epi-***5c***)*

Preparation according to the procedure reported for **5c**/*epi*-**5c**[5] from 2.26 g (6.06 mmol) of *ent*-**3a**. Yield (*ent*-**5c** + *ent-epi*-**5c**), 2.13 g (67 %).

ent-**5c**: Colorless Crystals, mp 97–98 °C.– $[\alpha]_{546}$ = + 165.0°, $[\alpha]_{578}$ = + 145.0° (*c* = 0.60 in CH_3OH).– Anal. ($C_{29}H_{32}ClNO_6$).

ent-epi-**5c**: Characterization only by ^{1}H-NMR.

*(1S,4R)-1-{(1R)-1,2,3,4-Tetrahydro-1-[(2R)-2-hydroxy-2-phenylethyl]-6,7-dimethoxy-2-isoquinolylcarbonyl}-4,7,7-trimethyl-2-oxa-bicyclo-[2.2.1]heptan-3-one (l-***6a***) and (1S,4R)-1-{(1R)-1,2,3,4-Tetrahydro-1-[(2S)-2-hydroxy-2-phenylethyl]-6,7-dimethoxy-2-isoquinolylcarbonyl}-4,7,7-trimethyl-2-oxa-bicyclo-[2.2.1]heptan-3-one (u-***6a***)*

To a solution of 0.50 g (1.01 mmol) of **5a** in 25ml of CH_3OH were added 40 drops of NH_3 (25 %) and 50 mg of Pd/C and the resulting mixture was hydrogenated at room temp. at 1 bar for 26 h. The mixture was then separated from the catalyst by filtration, dried over $MgSO_4$ and evaporated under reduced pressure. The resulting residue containing *l*-**6a**/*u*-**6a** in a ratio of 56/44 (determined by HPLC; SiO_2; CH_2Cl_2:Et_2O = 92:8) was fractionated by flash-chromatography (CH_2Cl_2:Et_2O = 95:5).

l-**6a**: Colorless crystals, mp 198–199 °C, yield 223 mg (44 %, de > 99.5%).– $[\alpha]_{546}$ = –116.7°, $[\alpha]_{578}$ = –105.5° (*c* = 0.36 in CH_2Cl_2).– Anal. ($C_{29}H_{35}NO_6$).– IR: ν = 3500–3300 cm^{-1}, 1780, 1610.– 400 MHz ^{1}H-NMR ($CDCl_3$):0.99 (s, 3H, CH_3), 1.12 (s, 3H, CH_3), 1.24 (s, 3H, CH_3), 1.79 (ddd, *J* ≈ 4/9/13 Hz, 1H), 2.00 (ddd, *J* ≈ 4/11/13 Hz, 1H), 2.11–2.27 (m, 3H), 2.44 (ddd, *J* ≈ 4/11/13 Hz, 1H), 2.70 (dd, *J* ≈ 3/16 Hz, 1H), 3.20 (ddd, *J* ≈ 5/13/16 Hz, 1H), 3.39 (dt, *J* ≈ 3/13 Hz, 1H), 3.82 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), 4.49 (dt, *J* ≈ 3/11 Hz, 1H), 4.56 (dd, *J* ≈ 5/13 Hz, 1H, NC*H*$_2$CH$_2$Ar), 5.21 (d, *J* ≈ 3Hz, 1H, OH), 5.69 (dd, *J* ≈ 3/11 Hz, 1H, NC*H*Ar), 6.58 (s, 2H, aromatic H), 7.23–7.41 (m, 5H, aromatic H). Signals of minor atropisomers of very low intensity.– MS; *m/z* = 493 [M^+].

u-**6a**: Colorless crystals, mp 100–102 °C, yield 194 mg (39%, de > 99.5%).– $[\alpha]_{546}$ = –131.4°, $[\alpha]_{578}$ = –111.4° (*c* = 0.35 in CH_2Cl_2).– Anal. ($C_{29}H_{35}NO_6$).– IR: ν = 3540–3380 cm^{-1}, 1790, 1640. – 400 MHz ^{1}H-NMR ($CDCl_3$): 0.92 (s, 0.85 × 3H, CH_3), 1.04 (s, 0.15 × 3H, CH_3), 1.06 (s, 0.85 × 3H, CH_3), 1.14 (s, 0.15 × 3H, CH_3), 1.18 (s, 0.85 × 3H, CH_3), 1.24 (s, 0.15 × 3H, CH_3), 1.61–1.74 (m, 2H), 1.82–1.89 (m,1H), 1.94–2.01 (m, 1H), 2.34 (dt, *J* ≈ 4/15 Hz, 1H), 2.46 (ddd, *J* ≈ 6.5/8/15 Hz, 1H), 2.66 (dt, *J* ≈ 4/16 Hz, 1H), 3.09 (ddd, *J* ≈ 4/11/16 Hz, 1H), 3.36 (ddd, *J* ≈ 4/11/13 Hz, 1H), 3.85, 3.86 (2 × s, 1.7 × 3H, OCH_3), 3.88, 3.89 (2 × s, 0.3 × 3H, OCH_3), 4.13 (dd, *J* ≈ 4/13 Hz, 1H, NC*H*$_2$CH$_2$Ar), 4.41 (d, *J* ≈ 6.5 Hz, 1H, OH), 5.05 (pseudo-q, *J* ≈ 6.5 Hz, 1H, C*H*OH), 5.60 (dd, *J* ≈ 4/8 Hz, 1H, NC*H*Ar), 6.58 (s, 1H, aromatic H), 6.66 (s, 0.85 × 1H, aromatic H), 6.90 (s, 0.15 × 1H, aromatic H), 7.22–7.52 (m, 5H, aromatic H), ratio of atropisomers ≈ 15:85.– MS; *m/z* = 493 [M^+].

*(1S,4R)-1-{(1R)-1,2,3,4-Tetrahydro-1-[(2R)-2-hydroxy-2-(4-methoxyphenyl)-ethyl]-6,7-dimethoxy-2-isoquinolylcarbonyl}-4,7,7-trimethyl-2-oxa-bicyclo[2.2.1]heptan-3-one (l-***6b***) and (1S,4R)-1-{(1R)-1,2,3,4-Tetrahydro-1-[(2S)-2-hydroxy-2-(4-methoxyphenyl)-ethyl]-6,7-dimethoxy-2-isoquinolylcarbonyl}-4,7,7-trimethyl-2-oxa-bicyclo[2.2.1]heptan-3-one (u-***6b***)*

To a solution of 501 mg (0.96 mmol) of **5b** in 25 ml of CH_3OH were added 40 drops of NH_3 (25%) and 52 mg of Pd/C (10% Pd) and the resulting mixture was hydrogenated at room temp. at 1.1 bar for 26 h. The mixture was then separated from the catalyst by filtration, dried over $MgSO_4$ and evaporated under reduced pressure.The resulting residue containing *l*-**6b**/*u*-**6b** in a ratio of 62.5 / 37.5 (determined by HPLC; SiO_2; *n*-hexane:EtOAc = 7:3) was fractionated by flash chromatography (*n*-hexane:EtOAc = 6:4).

l-**6b**: Colorless crystals, mp 102–105 °C, yield 1.87 g (61%, de > 99.5%).– $[\alpha]_{546}$ = –106.5°, $[\alpha]_{578}$ = –96.1° (*c* = 0.39 in CH_2Cl_2).– Anal. ($C_{30}H_{37}NO_7$).– IR: ν = 3600–3300 cm^{-1} 1790, 1610.– 400 MHz ^{1}H-NMR ($CDCl_3$): 0.99 (s, 3H, CH_3), 1.12 (s, 3H, CH_3), 1.24 (s, 3H, CH_3), 1.79 (ddd, *J* ≈ 4/9/13 Hz, 1H), 2.00 (ddd, *J* ≈ 4/11/13 Hz, 1H), 2.10–2.24 (m, 3H), 2.44 (ddd, *J* ≈ 4/11/13 Hz, 1H), 2.70 (dd, *J* ≈ 2/16 Hz, 1H), 3.19 (ddd, *J* ≈ 5/13/16 Hz, 1H), 3.37 (dt, *J* ≈ 3/13 Hz, 1H), 3.79 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), 4.44 (dt, *J* ≈ 10/3 Hz, 1H), 4.54 (dd, *J* ≈ 5/13 Hz, 1H, NC*H*$_2$CH$_2$Ar), 5.15 (d, *J* ≈ 3 Hz, 1H), 5.68 (dd, *J* ≈ 3/12 Hz, 1H), 6.57 (s, 1H, aromatic H), 6.59 (s, 1H, aromatic H), 6.87 (d, *J* ≈ 8.5 Hz, 2H, aromatic H), 7.32 (d, *J* ≈ 8.5 Hz, 2H, aromatic H). Signals of minor atropisomer of very low intensity.– MS; *m/z* = 523 [M^+].

u-**6b**: Colorless crystals, mp 92–95 °C, yield 1.14 g (37 %, de > 99.5%).– $[\alpha]_{546}$ = –117.9°, $[\alpha]_{578}$ = –102.6° (*c* = 0.39 in CH_2Cl_2).– Anal.($C_{30}H_{37}NO_7$).– IR: ν = 3600–3300 cm^{-1}, 1790, 1640.– 400 MHz ^{1}H-NMR ($CDCl_3$): 0.93 (s, 0.85 × 3H, CH_3), 1.05 (s, 0.15 × 3H, CH_3), 1.07 (s, 0.85 × 3H, CH_3), 1.14 (s, 0.15 × 3H, CH_3), 1.20 (s, 0.85 × 3H, CH_3), 1.24 (s, 0.15 × 3H, CH_3), 1.65–1.70 (m, 1H), 1.80–1.92 (m, 2H), 2.06–2.12 (m, 1H), 2.27 (dt, *J* ≈ 15/4 Hz, 1H), 2.37–2.45 (m, 1H), 2.66 (dt, *J* ≈ 16/3 Hz, 1H), 3.10 (ddd, *J* ≈ 5/12/16 Hz, 1H), 3.39 (ddd, *J* ≈ 3/12/13 Hz, 1H), 3.79, 3.847, 3.851, 3.877, 3.884 (5 × s, combined 9H, 3× OCH_3), 4.10 (d, *J* ≈ 6.4 Hz, 1H), 4.20 (dd, *J* ≈ 5/13 Hz, 0.85 × 1H, NC*H*$_2$CH$_2$Ar), 4.34–4.40 (m, 0.15 × 1H, NC*H*$_2$CH$_2$Ar), 4.75–4.83 (m, 0.15 × 1H), 5.01 (pseudo-q, *J* ≈ 5 Hz, 0.85 × 1H), 5.59 (dd, *J* ≈ 4/8 Hz, 1H, NC*H*Ar), 6.58 (s, 1H, aromatic H), 6.63 (s, 0.85 × 1H, aromatic H), 6.65 (s, 0.15 × 1H, aromatic H), 6.85–6.89 (m, 2H, aromatic H), 7.28–7.33 (m, 2H, aromatic H), ratio of atropisomers ≈ 85:15.– MS; *m/z* = 523 [M^+].

*(1S,4R)-1-{(1R)-1,2,3,4-Tetrahydro-1-[(2R)-2-hydroxy-2-(4-chlorophenyl)-ethyl]-6,7-dimethoxy-2-isoquinolylcarbonyl}-4,7,7-trimethyl-2-oxa-bicyclo[2.2.1]heptan-3-one (l-***6c***) and (1S,4R)-1-{(1R)-1,2,3,4-Tetrahydro-1-[(2S)-2-hydroxy-2-(4-chloro phenyl)- ethyl]-6,7-dimethoxy-2-isoquinolylcarbonyl}-4,7,7-trimethyl-2-oxa-bicyclo[2.2.1]heptan-3-one (u-***6c***)*

A solution of 301 mg (0.57 mmol) of **5c** in 13 ml of EtOH was cooled with an ice bath and treated with 308 mg (5.7 mmol) of KBH_4. The resulting mixture was then stirred for 36 h at room temp. After cooling to 0° C 5 ml of 2 N HCl was added. The mixture was allowed to warm to room temp. whereafter it was concentrated under reduced pressure. The resulting residue was extracted with CH_2Cl_2 (4×). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The resulting residue containing (*l*-**6c**/*u*-**6c**) in a ratio of 35.8/64.2 (determined by HPLC, SiO_2 ; *n*-hexane: EtOAc = 75:25) was separated by flash chromatography (CH_2Cl_2:Et_2O = 92:8).

l-**6c**: Colorless crystals, mp 188–190 °C, yield 97 mg (32 %, de > 99.5 %).– $[\alpha]_{546}$ = –108.6°, $[\alpha]_{578}$ = –94.3° (*c* = 0.35 in CH_2Cl_2).– Anal. ($C_{29}H_{34}ClNO_6$).– IR: ν = 3440 cm^{-1}, 1790, 1610.– 400 MHz ^{1}H-NMR ($CDCl_3$): 0.98 (s, 3H, CH_3), 1.12 (s, 3H, CH_3), 1.24 (s, 3H, CH_3), 1.79 (ddd, *J* ≈ 4/9/13 Hz, 1H), 2.00 (ddd, *J* ≈ 4/11/13 Hz, 1H), 2.05–2.12 (m, 1H), 2.17–2.24 (m, 2H), 2.44 (ddd, *J* ≈ 4/11/13 Hz, 1H), 2.71 (dd, *J* ≈ 3/16 Hz, 1H), 3.20 (ddd, *J* ≈ 5/13/16 Hz, 1H), 3.38 (dt, *J* ≈ 4/12.5 Hz, 1H), 3.82 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3), 4.45 (dt, *J* ≈ 11/3 Hz, 1H), 4.56 (dd, *J* ≈ 5/13 Hz, 1H, NC*H*$_2$CH$_2$Ar), 5.29 (d, *J* ≈ 3 Hz, 1H), 5.66 (dd, *J* ≈ 3/12 Hz, 1H NC*H*Ar), 6.56 (s, 1H, aromatic H), 6.57 (s, 1H, aromatic H), 7.29–7.39 (m, 4H, aromatic H). Signals of minor atropisomer of very low intensity.– MS; *m/z* = 528 [M^+].

u-**6c**: Colorless crystals, mp 103–105 °C, yield 152 mg (51 %, de > 99.5 %).– $[\alpha]_{546}$ = –103.6°, $[\alpha]_{578}$ = –94.0° (*c* = 0.42 in CH_2Cl_2).– Anal.($C_{29}H_{34}ClNO_6$).– IR: ν = 3620–3250 cm^{-1}, 1790, 1640.– 400 MHz ^{1}H-NMR ($CDCl_3$): 0.92 (s, 0.8 × 3H, CH_3), 1.04 (s, 0.2 × 3H, CH_3), 1.07 (s, 0.8 × 3H, CH_3), 1.14 (s, 0.2 × 3H, CH_3), 1.19 (s, 0.8 × 3H, CH_3), 1.21 (s, 0.2 × 3H, CH_3), 1.67 (ddd, *J* ≈ 4/9/13 Hz, 1H), 1.75–1.81 (m, 1H), 1.86–1.93 (m, 1H), 2.03 (ddd, *J* ≈ 4/11/13 Hz, 1H), 2.30 (dt, *J* ≈ 15/5 Hz, 1H), 2.39 (dt, *J* ≈ 15/8 Hz, 1H), 2.66 (dt, *J* ≈ 16/3 Hz, 1H), 3.10 (ddd, *J* ≈ 5/11/16 Hz, 1H), 3.35 (ddd, *J* ≈ 4/11/13 Hz, 1H), 3.85 (s, 0.8 × 3H, OCH_3), 3.86 (s, 0.8 × 3H, OCH_3), 3.879 (s, 0.2 × 3H, OCH_3), 3.886 (s, 0.2 × 3H, OCH_3), 4.17 (dd, *J* ≈ 4/13 Hz, 1H, NC*H*$_2$CH$_2$Ar), 4.50 (d, *J* ≈ 6.6 Hz, 1H), 5.03 (pseudo-q, *J* ≈ 6.6 Hz, 1H), 5.57 (dd, *J* ≈ 5/8 Hz, 1H, NC*H*Ar), 6.58, 6.63, 6.66 (3 × s, combined 2H, aromatic H), 7.26–7.36 (m, 4H, aromatic H), ratio of atropisomers ≈ 2:8.– MS; *m/z* = 528 [M^+].

*(1R,4S)-1-{(1S)-1,2,3,4-Tetrahydro-1-[(2S)-2-hydroxy-2-phenylethyl]-6,7-dimethoxy-2-isoquinolylcarbonyl}-4,7,7-trimethyl-2-oxa-bicyclo-[2.2.1]heptan-3-one (ent-l-***6a***) and (1R,4S)-1-{(1S)-1,2,3,4-Tetrahydro-1-[(2R)-2-hydroxy-2-phenylethyl]-6,7-dimethoxy-2-isoquinolylcarbonyl}-4,7,7-trimethyl-2-oxa-bicyclo[2.2.1]heptan-3-one (ent-u-***6a***)*

From 300 mg (0.61 mmol) of *ent*-**5a**.

ent-l-**6a**: Colorless crystals, mp 200–201 °C, yield 151 mg (50 %, de > 99.5%).– $[\alpha]_{546}$ = + 124.3°, $[\alpha]_{578}$ = + 106.3° (*c* = 0.56 in CH_2Cl_2).– Anal. ($C_{29}H_{35}NO_6$).

ent-u-**6a**: Colorless crystals, mp 93–97 °C, yield 119 mg (39%, de > 99.5%).– $[\alpha]_{546}$ = + 128.9°, $[\alpha]_{578}$ = + 111.1° (*c* = 0.23 in CH_2Cl_2). – Anal. ($C_{29}H_{35}NO_6$).

*(1R,4S)-1-{(1S)-1,2,3,4-Tetrahydro-1-[(2S)-2-hydroxy-2-(4-methoxyphenyl)-ethyl]-6,7-dimethoxy-2-isoquinolylcarbonyl}-4,7,7-trimethyl-2-oxa-bicyclo[2.2.1]heptan-3-one (ent-l-***6b***) and (1R,4S)-1-{(1S)-1,2,3,4-Tetrahydro-1-[(2R)-2-hydroxy-2-(4-methoxyphenyl)-ethyl]-6,7-dimethoxy-2-isoquinoylcarbonyl}-4,7,7-trimethyl-2-oxa-bicyclo[2.2.1]heptan-3-one (ent-u-***6b***)*

From 0.60 g (1.15 mmol) of *ent*-**5b**.

ent-l-**6b**: Colorless crystals, mp 103–105 °C, yield 1.76 g (58%, de > 99.5%).– $[\alpha]_{546}$ = + 108.8°, $[\alpha]_{578}$ = + 97.1° (*c* = 0.34 in CH_2Cl_2).– Anal. ($C_{30}H_{37}NO_7$).

ent-u-**6b**: Colorless crystals, mp 93–96 °C, yield 1.04 g (35%, de > 99.5%).– $[\alpha]_{546}$ = + 118.8°, $[\alpha]_{578}$ = + 103.1° (*c* = 0.32 in CH_2Cl_2).– Anal. ($C_{30}H_{37}NO_7$).

*(1R,4S)-1-{(1S)-1,2,3,4-Tetrahydro-1-[(2S)-2-hydroxy-2-(4-chlorophenyl)-ethyl]-6,7-dimethoxy-2-isoquinolylcarbonyl}-4,7,7-trimethyl-2-oxa-bicyclo[2.2.1]heptan-3-one (ent-l-***6c***) and (1R,4S)-1-{(1S)-1,2,3,4-Tetrahydro-1-[(2R)-2-hydroxy-2-(4-chloro-phenyl)-ethyl]-6,7-dimethoxy-2-isoquinolylcarbonyl}-4,7,7-trimethyl-2-oxa-bicyclo[2.2.1]heptan-3-one (ent-u-***6c***)*

From 502 g (0.96 mmol) of *ent*-**5c**.

ent-l-**6c**: Colorless crystals, mp 188–190 °C, yield 160 mg (32%, de > 99.5%).– $[\alpha]_{546}$ = + 108.3°, $[\alpha]_{578}$ = + 95.8° (*c* = 0.24 in CH_2Cl_2).– Anal. ($C_{29}H_{34}Cl\,NO_6$).

ent-u-**6c**: Colorless crystals, mp 102–104 °C, yield 275 mg (55%, de > 99.5%).– $[\alpha]_{546}$ = + 103.6°, $[\alpha]_{578}$ = + 96.4° (*c* = 0.28 in CH_2Cl_2).– Anal. ($C_{29}H_{34}Cl\,NO_6$).

Preparation of the Aminoalcohols **7** *by Hydrolytic Cleavage of the Amide Bond – General Procedure*

To 1.0 mmol of *u*-**6**/*l*-**6** was added 12 ml of 0.5 N KOH (in CH_3OH for *l*-**7**; in CH_3OH:H_2O = 9:1 for *u*-**7**) and the resulting mixture was stirred at room temp. in the case of *u*-**6** and at 40 °C for *l*-**6**, respectively, for the time specified. Then the solvent was evaporated *in vacuo* the resulting residue was dissolved in saturated NaCl-solution and the mixture thus obtained was acidified by addition of 2 N HCl. The aqueous solution was washed with Et_2O (3×), made basic by addition of solid KOH and finally extracted with CH_2Cl_2 (5×). The combined CH_2Cl_2 solutions were consecutively washed with 0.01 N KOH (3×) and with saturated NaCl-solution, dried over $MgSO_4$ and evaporated *in vacuo* to give the amino alcohol as a solid residue.

*(1R)-1-Phenyl-2-[(1R)-1,2,3,4-tetrahydro-6,7-dimethoxy-1-isoquinolyl]-ethanol (l-***7a***)*

Preparation according to the above general procedure from 299 mg (0.61 mmol) of *l*-**6a**; reaction time 14 d. Colorless crystals, mp 111 °C, yield 170 mg (89%).– $[\alpha]_{546}$ = + 2.2°, $[\alpha]_{578}$ = + 4.4° (*c* = 0.46 in CH_2Cl_2).– Anal. ($C_{19}H_{23}NO_3$).– IR: ν = 3300 cm^{-1}, 3260–3100, 1610.– 400 MHz ^{1}H-NMR ($CDCl_3$): 2.02 (ddd, *J* ≈ 3/7.7/15 Hz, 1H), 2.38 (ddd, *J* ≈ 3/7.3/15 Hz, 1H), 2.63 (dt, *J* ≈ 15/5 Hz, 1H), 2.86–2.93 (m, 1H), 3.01 (ddd, *J* ≈ 4/8/12 Hz, 1H), 3.27 (dt, *J* ≈ 12/5.5 Hz, 1H), 3.82 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 4.26 (dd, *J* ≈ 3/7.3 Hz, 1H), 4.86 (dd, *J* ≈ 3/7.7 Hz, 1H), 6.46 (s, 1H, aromatic H), 6.59 (s, 1H, aromatic H), 7.22–7.25, 7.32–7.39 (2× m, combined 5H, aromatic H), OH and NH could not be detected.– MS; *m/z* = 313 [M^+].

*(1R)-1-(4-Methoxyphenyl)-2-[(1R)-1,2,3,4-tetrahydro-6,7-dimethoxy-1-isoquinolyl]-ethanol (l-***7b***)*

Preparation according to the above general procedure from 557 mg (1.063 mmol) of *l*-**6b**, reaction time 12 d.

Colorless crystals, mp 132–133 °C, yield 258 mg (71%).– $[\alpha]_{546}$ = –26.2°, $[\alpha]_{578}$ = –19.7° (*c* = 0.31 in CH_2Cl_2).– Anal. ($C_{20}H_{25}NO_3$).– IR: ν = 3280 cm^{-1}, 3240, 1610.– 400 MHz ^{1}H-NMR ($CDCl_3$): 2.01 (ddd, *J* ≈ 2.5/7.7/15 Hz, 1H), 2.34 (ddd, *J* ≈ 2.5/7.3/15 Hz, 1H), 2.62 (dt, *J* ≈ 15/5 Hz, 1H), 2.90 (ddd, *J* ≈ 5/8/15 Hz, 1H), 3.00 (ddd, *J* ≈ 5/8/12.5 Hz, 1H), 3.27 (dt, *J* ≈ 12.5/5 Hz, 1H), 3.80 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 4.28 (dd, *J* ≈ 2.5/7.3 Hz, 1H), 4.81 (dd, *J* ≈ 2.5/7.7 Hz, 1H), 6.46 (s, 1H, aromatic H), 6.59 (s, 1H, aromatic H), 6.87–6.90 (m, 2H, aromatic H), 7.27–7.30 (m, 2H, aromatic H), OH and NH could not be detected.– MS; *m/z* = 343 [M^+].

*(1R)-1-(4-Chlorophenyl)-2-[(1R)-1,2,3,4-tetrahydro-6,7-dimethoxy-1-isoquinolyl]-ethanol (l-***7c***)*

Preparation according to the above general procedure from 504 mg (0.95 mmol) of *l*-**6c**; reaction time 11 d.

Colorless crystals, mp 152–154 °C, yield 301 mg (91%).– $[\alpha]_{546}$ = –47.4°, $[\alpha]_{578}$ = –36.8° (*c* = 0.38 in CH_2Cl_2).– Anal. ($C_{19}H_{22}ClNO_3$).– IR: ν = 3250 cm^{-1}, 3220–3050, 1610.– 400 MHz ^{1}H-NMR ($CDCl_3$): 1.96 (ddd, *J* ≈ 3/7.7/15 Hz, 1H), 2.35 (ddd, *J* ≈ 3/7.3/15 Hz, 1H), 2.63 (dt, *J* ≈ 16/5 Hz, 1H), 2.86–2.93 (m, 1H) 3.01 (ddd, *J* ≈ 5/8/12 Hz, 1H), 3.26 (dt, *J* ≈ 12/5 Hz, 1H), 3.83 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 4.25 (dd, *J* ≈ 3/7.3 Hz, 1H,), 4.82 (dd, *J* ≈ 3/7.7 Hz, 1H), 6.44 (s, 1H, aromatic H), 6.60 (s, 1H, aromatic H), 7.29–7.33 (m, 4H, aromatic H), OH and NH could not be detected.– MS: *m/z* = 347 [M^+].

*(1S)-1-Phenyl-2-[(1R)-1,2,3,4-tetrahydro-6,7-dimethoxy-1-isoquinolyl]-ethanol (u-***7a***)*

Preparation according to the above general procedure from 202 mg (0.40 mmol) of *u*-**6a**; reaction time 6 d.

Colorless crystals, mp 53–55 °C, 101 mg (80%).– $[\alpha]_{546}$ = –72.1°, $[\alpha]_{578}$ = –62.3° (*c* = 0.31 in CH_2Cl_2).– Anal. ($C_{19}H_{23}NO_3$).– IR: ν = 3500–3360 cm^{-1}, 3310, 1610.– 400 MHz ^{1}H-NMR ($CDCl_3$): 1.95 (dt, *J* ≈ 14.5/2.5 Hz, 1H), 2.06 (ddd, *J* ≈ 10.5/11.5/14.5, Hz 1H), 2.65 (ddd, *J* ≈ 3/5/16 Hz, 1H), 2.74 (ddd, *J* ≈ 6/10/16 Hz, 1H), 3.21 (m, 2H), 3.82 (s, 3H, OCH_3) 3.84 (s, 3H, OCH_3), 4.26 (dd, *J* ≈ 2.5/11.5 Hz, 1H,), 5.08 (dd, *J* ≈ 2.5/10.5 Hz, 1H), 6.51 (s, 1H, aromatic H), 6.55 (s, 1H, aromatic H), 7.23–7.27, 7.32–7.36, 7.42–7.51 (3 × m, combined 5H, aromatic H), OH and NH could not be detected.– MS; *m/z* = 313 [M^+].

*(1S)-1-(4-Methoxyphenyl)-2-[(1R)-1,2,3,4-tetrahydro-6,7-dimethoxy-1-isoquinolyl]-ethanol (u-***7b***)*

Preparation according to the above general procedure from 512 mg (0.98 mmol) of *u*-**6b**; reaction time 6 d.

Colorless crystals, mp 152–154 °C, yield 292 mg (87%).– $[\alpha]_{546}$ = –65.6°, $[\alpha]_{578}$ = –56.3° (*c* = 0.32 in CH_2Cl_2).– Anal. ($C_{20}H_{25}NO_4$).– IR: ν = 3310 cm^{-1}, 3200–3400, 1610.– 400 MHz ^{1}H-NMR ($CDCl_3$): 1.92 (dt, *J* ≈ 15/2.5 Hz, 1H), 2.06 (ddd, *J* ≈ 10.5/11.5/15 Hz, 1H), 2.65 (ddd, *J* ≈ 3/5/16 Hz, 1H), 2.74 (ddd, *J* ≈ 6/10/16 Hz, 1H), 3.16 (ddd, *J* ≈ 3/6/14 Hz, 1H,), 3.23 (ddd, *J* ≈ 5/10/14 Hz, 1H), 3.80 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3), 3.84 (s, 3H OCH_3), 4.24 (dd, *J* ≈ 2.5/11.5 Hz, 1H), 5.03 (dd, *J* ≈ 2.5/10.5 Hz, 1H), 6.51 (s, 1H, aromatic H), 6.55 (s, 1H, aromatic H), 6.86–6.90 (m, 2H, aromatic H), 7.33–7.37 (m, 2H, aromatic H), OH and NH could not be detected.– MS; *m/z* = 343 [M^+].

*(1S)-1-(4-Chlorophenyl)-2-[(1R)-1,2,3,4-tetrahydro-6,7-dimethoxy-1-isoquinolyl]-ethanol (u-***7c***)*

Preparation according to the above general procedure from 490 mg (0.93 mmol) of *u*-**6c**; reaction time 4 d.

Colorless crystals, mp 154–156 °C, yield 227 mg (70%).– $[\alpha]_{546}$ = –58.1°, $[\alpha]_{578}$ = –51.6° (*c* = 0.31 in CH_2Cl_2).– Anal. ($C_{19}H_{22}ClNO_3$).– IR: ν = 3300 cm^{-1}, 3200–3020, 1610.– 400 MHz ^{1}H-NMR ($CDCl_3$): 1.91 (dt, *J* ≈ 15/2.5 Hz, 1H), 2.01 (ddd, *J* ≈ 10.5/11.5/15 Hz, 1H), 2.66 (dt, *J* ≈ 16/4 Hz, 1H), 2.75 (ddd, *J* ≈ 6.5/10/16 Hz, 1H), 3.14–3.26 (m, 2H), 3.83 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), 4.26 (dd, *J* ≈ 2.5/11.5 Hz, 1H), 5.06 (dd, *J* ≈ 2.5/10.5 Hz, 1H), 6.50 (s, 1H, aromatic H), 6.56 (s, 1H, aromatic H), 7.29–7.38 (m, 4H, aromatic H), OH and NH could not be detected.– MS; *m/z* = 347 [M^+].

*(1S)-1-Phenyl-2-[(1S)-1,2,3,4-tetrahydro-6,7-dimethoxy-1-isoquinolyl]-ethanol (ent-l-***7a***)*

Preparation from 554 mg (1.12 mmol) of *ent-l*-**6a**.

Colorless crystals, mp 113 °C, yield 318 mg (91 %).– $[\alpha]_{546}$ = –1.3°, $[\alpha]_{578}$ = –2.5° (*c* = 0.79 in CH_2Cl_2). – Anal. ($C_{19}H_{23}NO_3$).

*(1S)-1-(4-Methoxyphenyl)-2-[(1S)-1,2,3,4-tetrahydro-6,7-dimethoxy-1-isoquinolyl]-ethanol (ent-l-***7b***)*

Preparation from 609 mg (1.16 mmol) of *ent-l*-**6b**.

Colorless crystals, mp 131–132 °C, yield 361 mg (91%).– $[\alpha]_{546}$ = +26.4°, $[\alpha]_{578}$ = + 20.6° (*c* = 0.34 in CH_2Cl_2).– Anal. ($C_{20}H_{25}NO_4$).

*(1S)-1-(4-Chlorophenyl)-2-[(1S)-1,2,3,4-tetrahydro-6,7-dimethoxy-1-isoquinolyl]-ethanol (ent-l-***7c***)*

Preparation from 504 mg (0.96 mmol) of *ent-l*-**6c**.

Colorless crystals mp 152–153 °C, yield 266 mg (80%).– $[\alpha]_{546}$ = +47.6°, $[\alpha]_{578}$ = + 38.1° (*c* = 0.32 in CH_2Cl_2). Anal. ($C_{19}H_{22}Cl\,NO_3$).

*(1R)-1-Phenyl-2-[(1S)-1,2,3,4-tetrahydro-6,7-dimethoxy-1-isoquinolyl]-ethanol (ent-u-***7a***)*

Preparation from 447 mg (0.91 mmol) of *ent-u*-**6a**.

Colorless crystals mp 51–54 °C, yield 259 mg (91%).– $[\alpha]_{546}$ = +73.8°, $[\alpha]_{578}$ = + 64.6° (*c* = 0.33 in CH_2Cl_2).– Anal. ($C_{19}H_{23}NO_3$).

*(1R)-1-(4-Methoxyphenyl)-2-[(1S)-1,2,3,4-tetrahydro-6,7-dimethoxy-1-isoquinolyl]-ethanol (ent-u-***7b***)*

Preparation from 451 mg (0.86 mmol) of *ent-u-***6b**.

Colorless crystals 151–153 °C, yield 189 mg (64.8%).– $[\alpha]_{546}$ = +65.6°, $[\alpha]_{578}$ = + 58.2° (*c* = 0.28 in CH_2Cl_2).– Anal. ($C_{20}H_{25}NO_4$).

*(1R)-1-(4-Chlorophenyl)-2-[(1S)-1,2,3,4-tetrahydro-6,7-dimethoxy-1-isoquinolyl]-ethanol (ent-u-***7c***)*

Preparation from 670 mg (1.27 mmol) of *ent-u-***6c**.

Colorless crystals, mp 154 °C, yield 303 mg (69%), $[\alpha]_{546}$ = +57.1°, $[\alpha]_{578}$ = + 51.4° (*c* = 0.35 in CH_2Cl_2).– Anal. ($C_{19}H_{22}ClNO_3$).

*(1R)-1-(4-Methoxyphenyl)-2-[(1R)-1,2,3,4-tetrahydro-6,7-dimethoxy-2-methyl-1-isoquinolyl]-ethanol (l-***7d***).*

From 23 mg (0.67 mmol) of *l-***7b** in 3.5 ml of CH_3OH, 0.15 ml CH_2O solution (37%) and 120 mg (1.91 mmol) of $NaCNBH_3$ as described for *l-***7e**.

Colorless crystals, mp 95–97 °C, yield 21 mg (88 %).– $[\alpha]_{546}$ = +29.3°, $[\alpha]_{578}$ = +29.7° (*c* = 0.3 in CH_2Cl_2).– Anal. ($C_{21}H_{27}NO_4$).– IR: ν = 3400–3100 cm^{-1}, 1610, 1516.– 400 MHz ^{1}H-NMR ($CDCl_3$): 1.55 (s, broad, 1H), 2.11 (ddd, *J* = 2.5/6/15 Hz, 1H), 2.20 (ddd, *J* = 3/8/15 Hz, 1H), 2.51 (s, 3H, NCH_3), 2.57 – 2.72 (m, 2H), 2.87–2.97 (m, 1H), 3.17 (dt, *J* = 12/5 Hz, 1H), 3.63–3.68 (m, 1H), 3.78 (s, 3H, OCH_3), 3.80 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 4.59 (dd, *J* = 2.5/8 Hz, 1H), 6.42 (s, 1H, aromatic H) 6.58 (s, 1H, aromatic H), 6.85 (d, *J* = 8 Hz, 2H, aromatic H), 7.28 (d, *J* = 8 Hz, 2H, aromatic H).– MS; *m/z* = 357 [M^+].

*(1S)-1-(4-Methoxyphenyl)-2-[(1R)-1,2,3,4-tetrahydro-6,7-dimethoxy-2-methyl-1-isoquinolyl]-ethanol (u-***7d***)*

From 171 mg (0.50 mmol) of *u-***7b** in 5.0 ml of CH_3OH, 0.2 ml of CH_2O-solution (37%) and 155 mg (2.46 mmol) of $NaCNBH_3$ as described for *l-***7e**; flash chromatography (Et_2O:Me_2EtN = 95:5).

Colorless crystals, mp 110–111 °C; yield 147 mg (82 %).– $[\alpha]_{546}$ = –7.1°, $[\alpha]_{578}$ = –5.8° (*c* = 0.38 in CH_2Cl_2).– Anal. ($C_{21}H_{27}NO_4$).– IR: ν = 3400–3100 cm^{-1}, 1611, 1518.– 400 MHz ^{1}H-NMR ($CDCl_3$):1.60 (s, broad, 1H), 1.82 (dt, *J* = 15/2 Hz, 1H), 2.06 (dt, *J* = 15/11 Hz, 1H), 2.42–2.46 (m, 1H), 2.55 (s, 3H, NCH_3), 2.89–3.02 (m, 2H), 3.40–3.51 (m, 1H), 3.78 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), 3.80–3.90 (partly obscured, 1H), 5.02 (dd, *J* = 2/11 Hz, 1H), 6.49 (s, 1H, aromatic H), 6.55 (s, 1H, aromatic H), 6.87 (d, *J* = 8.5 Hz, 2H, aromatic H), 7.33 (d, *J* = 8.5 Hz, 2H, aromatic H).– MS; *m/z* = 357 [M^+].

*(1S)-1-(4-Methoxyphenyl)-2-[(1S)-1,2,3,4-tetrahydro-6,7-dimethoxy-2-methyl-1-isoquinolyl]-ethanol (ent-l-***7d***)*

From 162 mg (0.47 mmol) of *ent-l-***7b** as described for *l-***7d**.

Colorless crystals, mp 92–96 °C, yield 156 mg (93 %).– $[\alpha]_{546}$ = –28.2°, $[\alpha]_{578}$ = –26.5° (*c* = 0.36 in CH_2Cl_2).– Anal. ($C_{21}H_{27}NO_4$).

*(1R)-1-(4-Methoxyphenyl)-2-[(1S]-1,2,3,4-tetrahydro-6,7-dimethoxy-2-methyl-1-isoquinolyl]-ethanol (ent-u-***7d***)*

From 64 mg (0.19 mmol) of *ent-u-***7b** as described for *u-***7d**.

Colorless crystals, mp 107–111 °C, yield 59 mg (89%).– $[\alpha]_{546}$ = +5°, $[\alpha]_{578}$ = +4.2° (*c* = 0.5 in CH_2Cl_2).– Anal. ($C_{21}H_{27}NO_4$).

*(1R)-1-(4-Chlorophenyl)-2-[(1R)-1,2,3,4-tetrahydro-6,7-dimethoxy-2-methyl-1-isoquinolyl]-ethanol (l-***7e***)*

To a solution of 177 mg (0.51 mmol) of *l-***7c** in 5 ml of CH_3OH 0.21 ml of HCHO solution (37%) and 160 mg (2.54 mmol) of $NaCNBH_3$ were added and the resulting mixture was stirred at room temp. for 24 h, the pH being periodically adjusted to 5–7 by addition of HOAc. The solvent was evaporated *in vacuo*. The resulting residue was dissolved in saturated NaCl solution and the resulting solution was made basic by addition of KOH. The aqueous phase was extracted with CH_2Cl_2 (5×). The combined organic layers were dried over $MgSO_4$, evaporated *in vacuo* and the resulting residue was purified by flash chromatography (Et_2O:Me_2EtN = 9:1).

Colorless crystals, mp 70–73 °C, yield 158 mg (86%).– $[\alpha]_{546}$ = +8.5°, $[\alpha]_{578}$ = + 10.7° (*c* = 0.27 in CH_2Cl_2).– Anal. ($C_{20}H_{24}ClNO_3$).– IR: ν = 3500–3100 cm^{-1}, 1610.– 400 MHz ^{1}H-NMR ($CDCl_3$): 1.56 (s, broad, 1H), 2.10–2.22 (m, 2H), 2.52 (s, 3H, NCH_3), 2.60–2.73 (m, 2H), 2.90–2.97 (m, 1H), 3.19 (dt, *J* ≈ 12/5 Hz, 1H), 3.65–3.68 (m, 1H), 3.82 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 4.62 (dd, *J* ≈ 3/8 Hz, 1H), 6.43 (s, 1H, aromatic H), 6.60 (s, 1H, aromatic H), 7.24–7.31 (m, 4H, aromatic H).– MS; *m/z* = 361 [M^+].

*(1S)-1-(4-Chlorophenyl)-2-[(1R)-1,2,3,4-tetrahydro-6,7-dimethoxy-2-methyl-1-isoquinolyl]-ethanol (u-***7e***)*

From 166 mg (0.48 mmol) of *u-***7c** in 5 ml of CH_3OH, 0.2 ml of HCHO-solution (37%) and 150 mg (2.38 mmol) of $NaCNBH_3$ as described for *l-***7d**. Reaction time 21 h. The product obtained after aqueous work-up was dissolved in Et_2O. Solid KOH was added and the mixture was stirred for 1 h at room temp. Subsequent filtration and evaporation of the solvent in vacuo yielded *u-***7e**.

Colorless crystals, mp. 51–54 °C, yield 129 mg (75%).– $[\alpha]_{546}$ = +1.7°, $[\alpha]_{578}$ = + 2.2° (*c* = 0.23 in CH_2Cl_2).– Anal. $C_{20}H_{24}ClNO_3$.– IR: ν = 3400–3100 cm^{-1}, 1610.– 400 MHz ^{1}H-NMR ($CDCl_3$): 1.56 (s, broad, 1H), 1.82 (dt, *J* ≈ 15/2 Hz, 1H), 2.00 (dt, *J* ≈ 15/11 Hz, 1H), 2.39–2.45 (m, 1H), 2.56 (s, 3H, NCH_3), 2.91–3.01 (m, 2H), 3.40–3.46 (m, 1H), 3.83 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), 3.83–3.86 (dd, partly obscured, 1H), 5.04 (dd, *J* ≈ 2/11 Hz, 1H), 6.49 (s, 1H, aromatic H), 6.55 (s, 1H, aromatic H), 7.27–7.36 (m, 4H, aromatic H).– MS; *m/z* = 361 [M^+].

*(1S)-1-(4-Chlorophenyl)-2-[(1S)-1,2,3,4-tetrahydro-6,7-dimethoxy-2-methyl-1-isoquinolyl]-ethanol (ent-l-***7e***)*

From 167 mg (0.480 mmol) of *ent-l-***7c** as described for *l-***7e**.

Colorless crystals, mp 69–73 °C, yield 140 mg (81%).– $[\alpha]_{546}$ = –11.2°, $[\alpha]_{578}$ = –11.7 (*c* = 1.0 in CH_2Cl_2).– Anal. ($C_{20}H_{24}ClNO_3$).

*(1R)-1-(4-Chlorophenyl)-2-[(1S)-1,2,3,4-tetrahydro-6,7-dimethoxy-2-methyl-1-isoquinolyl]-ethanol (ent-u-***7e***)*

From 184 mg (0.53 mmol) of *ent-u-***7c** as described for *u-***7e**.

Colorless crystals, mp 50–53 °C, yield 173 mg (90%).– $[\alpha]_{546}$ = –1.8°, $[\alpha]_{578}$ = –2.0° (*c* = 0.5 in CH_2Cl_2).– Anal. ($C_{20}H_{24}Cl\,NO_3$).

*(2S,11bR)-1,6,7,11b-Tetrahydro-9,10-dimethoxy-2-(4-methoxyphenyl)-2H-[1,3]-oxazino[4,3-a]-isoquinoline (u-***8***)*

To a solution of 1.1 mg (0.003 mmol) of *u-***7b** in 0.1 ml of Et_2O was added 5µl of H_2CO solution (37%) and the mixture was stirred for 17 h at room temp. The solvent was evaporated *in vacuo* and the residue was dissolved in CH_2Cl_2 and washed with H_2O (5×). The organic layer was dried over $MgSO_4$ and after filtration concentrated *in vacuo*.– 400 MHz ^{1}H-NMR ($CDCl_3$): 1.81 (dt, *J* ≈ 13.7/3 Hz, 1H), 2.00 (dt, *J* ≈ 13.7/11.5 Hz, 1H), 2.71 (dt, *J* ≈ 15/4 Hz, 1H), 2.82–2.96 (m, 2H), 3.36 (dt, *J* ≈ 4/11 Hz, 1H), 3.72 (s, 3H, OCH_3), 3.75 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3), 4.06 (dd, *J* ≈ 3/11.5 Hz, 1H), 4.56 (dd, *J* ≈ 3/11.5 Hz, 1H), 4.67 (d, *J* ≈ 10 Hz, 1H), 4.72 (d, *J* ≈ 10 Hz, 1H), 6.53 (s, 1H, aromatic H), 6.61 (s, 1H, aromatic H), 6.85–6.89 (m, 2H, aromatic H) 7.30–7.33 (m, 2H, aromatic H).

*(2R,11bR)-1,6,7,11b-Tetrahydro-9,10-dimethoxy-2-(4-methoxyphenyl)-2H-[1,3]-oxazino[4,3-a]-isoquinoline (l-***8***)*

From 1.5 mg (0.004 mmol) of *l-***7b** as described for *u-***8**.

400 MHz-^{1}H-NMR ($CDCl_3$): 2.21 (dt, *J* ≈ 14/3 Hz, 1H), 2.48 (ddd, *J* ≈ 5.5/11/14 Hz, 1H), 2.70–2.85 (m, 3H), 3.39–3.46 (m, 1H), 3.78 (s, 3H, OCH_3), 3.79 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3) 4.09 (dd, *J* ≈ 3/11 Hz, 1H), 4.29 (d, *J* ≈ 10 Hz, 1H), 4.56 (d, *J* ≈ 10 Hz, 1H), 5.00 (dd, *J* ≈ 3/5.5 Hz, 1H), 6.50 (s, 1H, aromatic H), 6.55 (s, 1H, aromatic H), 6.90–6.93 (m, 2H, aromatic H), 7.36–7.39 (m, 2H, aromatic H).

(1S,4R)-N-Naphthyl-4,7,7-trimethyl-3-oxo-2-oxa-bicyclo[2.2.1]heptane-1-carboxamide (**11**)

To a solution of 207 mg (1.45 mmol) of **10** in 2.5 ml of CH_2Cl_2 were added 0.2 ml (1.45 mmol) of NEt_3 and 250 mg (1.16 mmol) of **9** in 2.5 ml of CH_2Cl_2. The mixture was stirred for 15 h at room temp. Thereafter the mixture was diluted with 50 ml of CH_2Cl_2 washed consecutively with 0.05 N HCl (3×), and saturated NaCl-solution (3×), dried over $MgSO_4$ and evaporated *in vacuo*.The resulting residue was purified by flash chromatography (*n*-hexane:CH_2Cl_2 = 1:9). The enantiomeric purity of the material was determined by chiral HPLC (chiral column, *n*-hexane:isopropanol = 96:4). No trace of the enantiomeric compound *ent*-**11** could be detected, the enantiomeric purity thus being at least > 99.5%.

Colorless crystals, mp 171–172 °C, yield 320 mg (85%).– $[\alpha]_{546}$ = +7.8°, $[\alpha]_{578}$ = + 6.7° (*c* = 0.65 in CH_2Cl_2).– Anal. ($C_{20}H_{21}NO_3$).– IR: ν = 3375 cm^{-1}, 1780, 1680.– 400 MHz ^{1}H-NMR ($CDCl_3$): 1.10 (s, 3H, CH_3), 1.19 (s, 3H, CH_3), 1.21 (s, 3H, CH_3), 1.81 (ddd, *J* ≈ 4/9/13 Hz, 1H), 2.02–2.16 (m, 2H), 2.69 (ddd, *J* ≈ 4/11/13 Hz, 1H), 7.48–7.59 (m, 3H, aromatic H), 7.73 (d, *J* ≈ 8 Hz, 1H, aromatic H), 7.84–7.90 (m, 2H, aromatic H), 8.05 (d, *J* ≈ 8 Hz, 1H, aromatic H), 8.60 (s, broad, 1H, NH).

*(1R,4S)-N-Naphthyl-4,7,7-trimethyl-3-oxo-2-oxa-bicyclo[2.2.1]heptane-1-carboxamide (ent-***11***)*

To 250 mg (1.26 mmol) of *ent*-**4** was added 1 ml of $SOCl_2$ and the resulting mixture was heated for 3h to 60°C. After cooling excess reagent was evaporated *in vacuo*. The acid chloride thus obtained was transformed to *ent*-**11** according to the procedure described for **11**. Determination of the enantiomeric purity by chiral HPLC indicated the material to be contaminated with ≈ 0.2 % of **11** (⇒ee ≥ 99.5 %).– Colorless crystals, mp 171 °C, yield 208 mg (51%).– $[\alpha]_{546}$ = – 5.9°, $[\alpha]_{578}$ = – 5.5° (*c* = 0.80 in CH_2Cl_2).

Opioid Binding to Bovine Striatal Membranes

[^{3}H]-DAMGO and [^{3}H]-U-69,593 binding to bovine striatal membranes was performed according to standard radioligand binding assays[12,13], which were slightly modified as described below. Bovine striata from the local slaughterhouse were homogenized with a potter (PotterS Braun, 1200 rpm, 10 up-and-down strokes) in 10 volumes of cold 0.32 M sucrose and centrifuged at 1000g for 10 min at 4 °C. The supernatant was centrifuged at 48000g for 20 min at 4 °C. The resulting pellets were resuspended in 10 volumes of 50 mM Tris HCl pH 7.5 of the original wet weight and centrifuged at 39000g for 20 min at 4 °C. The pellets were resuspended again in the same volume of 50 mM Tris HCl pH 7.5, incubated for 30 min at 37 °C and centrifuged at 39000g for 20 min at 4 °C. The membranes were resuspended with 50 mM Tris HCl pH 7.5 to obtain a protein concentration of 3 mg/mL (estimated by the method of Bradford[14] using bovine serum albumin as standard) and subsequently frozen in liquid nitrogen.

At the day of the assay membranes were thawed and aliquots of about 1500 µg protein were incubated in the presence of the compound tested, 1 nM [^{3}H]-U-69,593 (1753 GBq/mmol DuPont NEN), 5 mM $MgCl_2$ and 50 mM Tris HCl pH 7.5 in a total volume of 1 mL at 20 °C for 1 h. [^{3}H]-DAMGO (2052.5 GBq/mmol DuPont NEN) binding was assayed in the same way with aliquots of 200 µg/ml protein and additionally 100 µM phenylmethanesulfonyl fluoride. The incubation was terminated by rapid filtration through presoaked Whatman GF/C filters (0.25 % polyethyleneimine for [^{3}H]-U-69,593;50 mM Tris,HCl pH 7.5 for [^{3}H]-DAMGO) using a Brandel M-24R cell harvester. After washing four times with 2 mL of cold 50 mM Tris-HCl pH 7.5, bound radioactivity trapped on the filters was counted in 3 mL rotiszint eco plus using a Canberra Packard TriCarb 1600 liquid scintillation counter. Non-specific binding was determined in the presence of 1µM Naloxon for [^{3}H]-DAMGO and 1 µM U-50,488 for [^{3}H]-U-69,593.

K_i values for test compounds were calculated from competition experiments with at least 6 concentrations of test compounds using InPlot 4.0 (GraphPad). K_D-values used in the Cheng and Prusoff[15] equation were determined in saturation experiments as 1.13 nM for [^{3}H]-DAMGO and 1.18 nM for [^{3}H]-U-69,593, respectively. If not stated otherwise, data are expressed as mean ± SEM of three independent experiments, each carried out in triplicate.

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☆ Dedicated to Professor F. Eiden on the occasion of his 70th birthday.

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