Synthesis of Novel Nonpeptidic Thrombin Inhibitors

by **Ulrike Obst**, **Patrick Betschmann**, **Christian Lerner**, **Paul Seiler**, and **François Diederich***

Laboratorium für Organische Chemie der Eidgenössischen Technischen Hochschule, ETH-Zentrum, Universitätstrasse 16, CH-8092 Zürich

and **Volker Gramlich**

Laboratorium für Kristallographie der Eidgenössischen Technischen Hochschule, ETH-Zentrum, Sonneggstrasse 5, CH-8092 Zürich

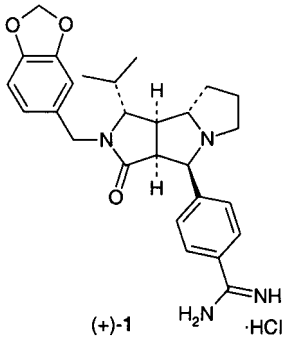
and **Lutz Weber**, **David W. Banner**, and **Peter Schönholzer**

Pharma Division, Präklinische Forschung, *F. Hoffmann-La Roche AG,* CH-4070 Basel

A novel class of nonpeptidic, active, and selective thrombin inhibitors has resulted from X-ray-structure-based design and subsequent improvement of the initial lead molecules. These inhibitors possess a bi- or tricyclic central core structure with attached side chains to reach the three binding pockets (selectivity S1 pocket, distal D pocket, and proximal P pocket) present in the active site of the enzyme. The key step in the preparation of these compounds is the 1,3-dipolar cycloaddition between an azomethine ylide, prepared *in situ* by the decarboxylative method from an aromatic aldehyde and an α-amino acid, with an *N*-substituted maleimide (*e.g.*, see *Schemes 1* and *2*). All potent inhibitors contain an amidinium residue in the side chain for incorporation into the S1 pocket, which was introduced in the last step of the synthesis by a *Pinner* reaction. The compounds were tested in biological assays for activity against thrombin and the related serine protease trypsin. The first-generation lead compounds (±)-**11** and (±)-**19** (*Scheme 1*) with a bicyclic central scaffold showed K_i values for thrombin inhibition of 18 μM and 0.67 μM, respectively. Conformationally more restricted second-generation analogs (*Scheme 2*) were more active ((±)-**22i**: $K_i = 90$ nM (*Table 1*)); yet the selectivity for thrombin over trypsin remained weak. In the third-generation compounds, a small lipophilic side chain for incorporation into the hydrophobic P pocket was introduced (*Schemes 7* and *8*). Since this pocket is present in thrombin but not in trypsin, an increase in binding affinity was accompanied by an increase in selectivity for thrombin over trypsin. The most selective inhibitor ($K_i = 13$ nM, 760-fold selectivity for thrombin over trypsin; *Table 2*) was (±)-**1** with an i-Pr group for incorporation into the P pocket. Optical resolution of (±)-**1** (*Scheme 9*) provided (+)-**1** with a K_i value of 7 nM and a 740-fold selectivity, whereas (−)-**1** was 800-fold less active ($K_i = 5.6$ μM, 21-fold selectivity). The absolute configuration of the stronger-binding enantiomer was assigned based on the X-ray crystal structure of the complex formed between thrombin and this inhibitor. Compound (+)-**1** mimics the natural thrombin substrate, fibrinogen, which binds to the enzyme with the Ph group of a phenylalanine (piperonyl in (+)-**1**) in the distal D pocket, with the i-Pr group of a valine (i-Pr in (+)-**1**) in the proximal P pocket, and with a guanidinium side chain of an arginine residue (phenylamidinium group in (+)-**1**) in the selectivity S1 pocket of thrombin. A series of analogs of (±)-**1** with the phenylamidinium group replaced by aromatic and aliphatic rings bearing OH or NH_2 groups (*Schemes 10–14*) were not effectively bound by thrombin. A number of X-ray crystal-structure analyses of free inhibitors confirmed the high degree of preorganization of these compounds in the unbound state. Since all inhibitors prefer similar modes of association with thrombin, detailed information on the strength of individual intermolecular bonding interactions and their incremental contribution to the overall free energy of complexation was generated in correlative binding and X-ray studies. The present study demonstrates that defined mutations in highly preorganized inhibitors provide an attractive alternative to site-directed mutagenesis in exploring molecular-recognition phenomena at enzyme active sites.

1. Introduction. – Thrombin is a trypsin-like serine protease that is central in the process of hemostasis and thrombosis. In the blood-coagulation cascade, it cleaves the protein fibrinogen after specific Arg residues to give polymerizable fibrin, which is a major constituent of blood clots. Moreover, thrombin is the main activator of platelet-aggregation and other coagulation factors [1][2]. It is therefore an important pharmaceutical target for prevention and treatment of thrombotic diseases. Natural inhibitors of the enzyme include the protein hirudin from the leech *Hirudo medicinalis*. Hirudin is currently the most active and selective thrombin inhibitor (inhibition constant $K_i = 0.27$ pM) [3]. In the past two decades, an intensive search for small, potentially orally bioavailable synthetic inhibitors has been conducted [4] (for recent reviews on thrombin inhibition, see [5]). X-Ray crystal structures of thrombin-inhibitor complexes show that the enzyme is a rather rigid protein with well-defined binding pockets in the active site [6][7], and, accordingly, structure-based design has been intensively applied to the development of new inhibitors. *Fig. 1* shows a small selection of potent synthetic thrombin inhibitors [6][8–15].

The active site of thrombin features three major binding pockets in addition to the catalytic site with the oxy-anion hole. This is schematically shown in *Fig. 2* for the complexation of the most potent inhibitor (+)-**1** ($K_i = 7$ nM) described in this report [16]. *i*) The specificity S1 pocket contains Asp 189 for interaction with Arg or Lys side



(+)-**1**

chains of peptidic substrates. *ii*) The large hydrophobic D pocket (D = distal to the catalytic site [7]) is preferentially occupied by aromatic rings that can undergo CH$\cdots\pi$ aromatic interactions with the indole ring of Trp 215. *iii*) An additional smaller P pocket (P = proximal) is positioned close to the catalytic site. This pocket is absent in trypsin; therefore, its filling with parts of an inhibitor not only enhances the binding affinity but also the selectivity for thrombin against trypsin. Other sub-binding sites (not shown in *Fig. 2*) whose occupancy by appropriate inhibitor moieties contributes to binding strength and selectivity were identified in recent work by researchers at *Merck* [17].

Among the compounds shown in *Fig. 1*, **2** [6] is an irreversible inhibitor that is attacked by Ser 195 of the catalytic triad (for the classification of thrombin inhibitors, see [4a]). Boronic acid **3** [8] is a so-called 'reversible covalent inhibitor' that reacts with Ser 195 to form a tetrahedral anionic adduct that resembles the transition state of peptide hydrolysis. All other compounds in *Fig. 1* are non-covalent inhibitors. Compounds **4**–**7** [9–12] bind with their positively charged side chains into the S1

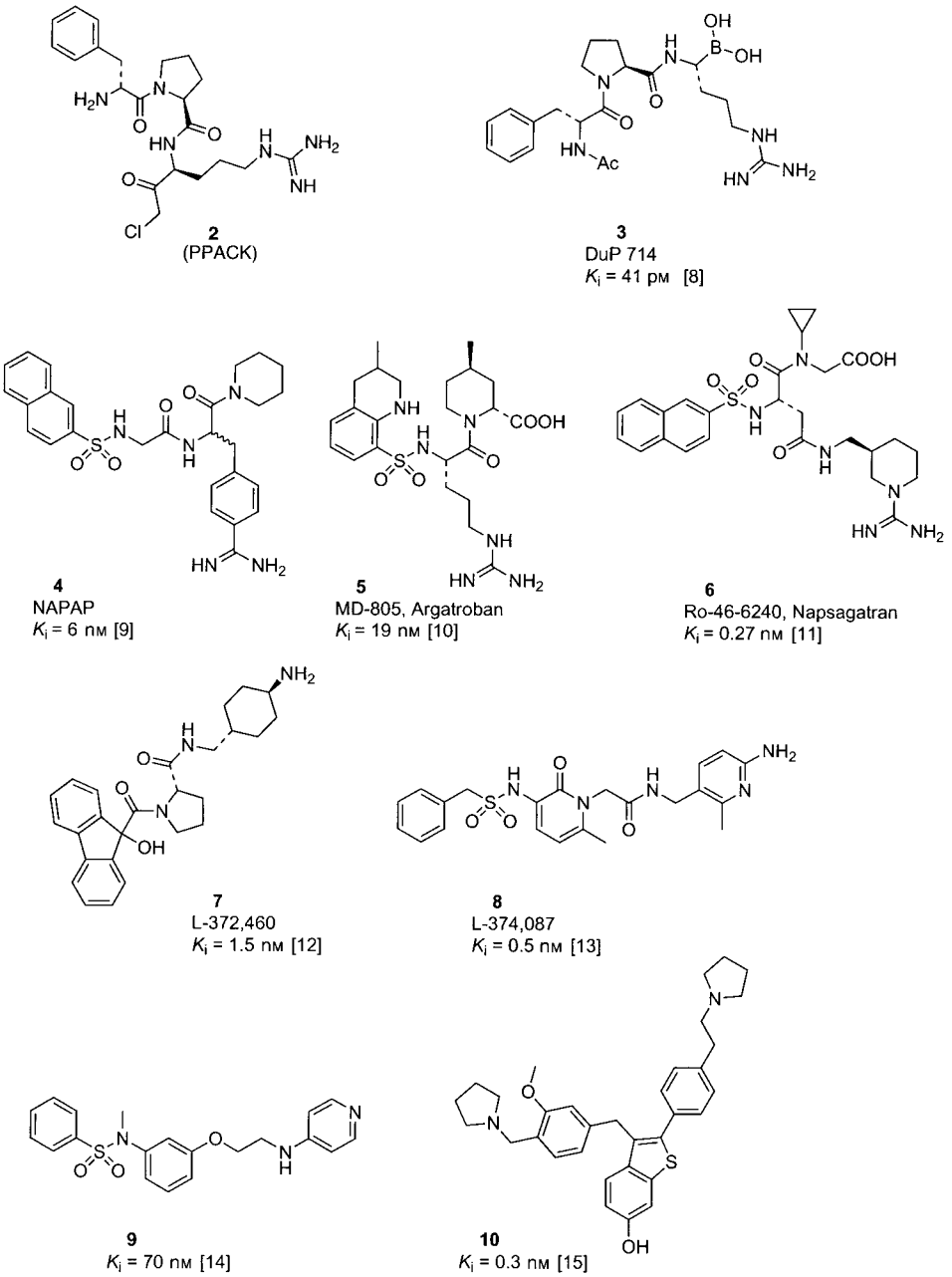


Fig. 1. *Examples of synthetic thrombin inhibitors.* Shown are also the K_i values for the inhibition of thrombin.

pocket. They all interact to different degrees with the D and P pockets of the enzyme and form H-bonds with Gly 216. Since positively charged aliphatic ammonium, guanidinium, or amidinium side chains tend to strongly limit the bioavailablity of

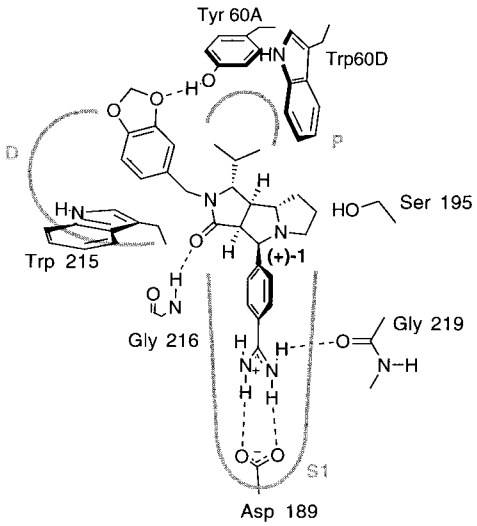


Fig. 2. *Schematic representation of the bonding interactions in the complex between (+)-***1** *and thrombin as revealed by X-ray crystal-structure analysis* [16]. S1 = specificity pocket; D = hydrophobic distal pocket; P = hydrophobic proximal pocket.

thrombin inhibitors, an intensive search for active compounds lacking such side chains has been conducted in several laboratories. The high affinity of compounds **8**–**10** [13–15] demonstrates that thrombin can be efficiently complexed by inhibitors that direct neutral groups, such as the 6-hydroxybenzo[*b*]thiophene residue in **10**, into the S1 pocket.

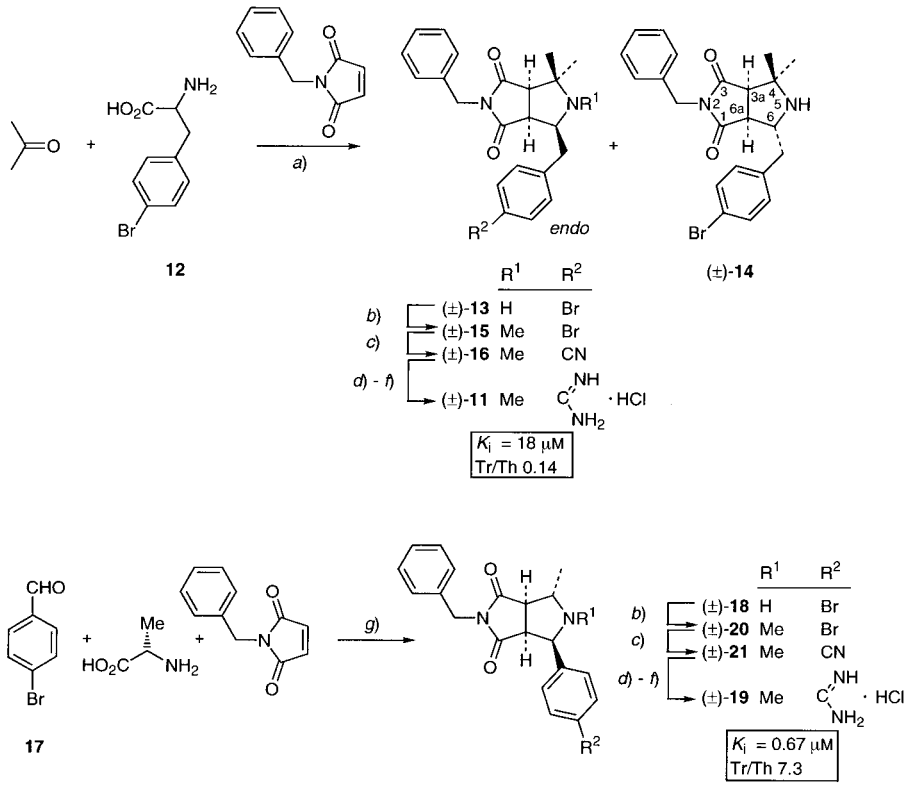
We started in 1993 a program aimed at the *de novo* structure-based design of novel nonpeptidic inhibitors of thrombin, featuring a central bi- or tricyclic (see (+)-**1** in *Fig. 2*) scaffold from which side chains are directed into the S1, D, and P pockets of the active site. The central scaffold (sometimes called a 'cyclic template' in medicinal chemistry, see [18]) is readily assembled by azomethine ylide 1,3-dipolar cycloaddition [19–21]. In two previous papers, we described in detail the design of these inhibitors and their biological affinity [16] [22]. The molecular-recognition characteristics of these compounds at the enzyme-active site were revealed in three X-ray crystal-structure analyses of thrombin-inhibitor complexes. Here, we describe the synthesis and structural characterization of this new class of thrombin inhibitors. We believe that their bi- and tricyclic scaffolds also represent attractive, multi-functional central platforms for inhibitors of other classes of enzymes. To provide a better structural appreciation of these new molecular shapes, the X-ray crystallographic characterization of several inhibitors or precursors, and their often quite intriguing crystal packing in the absence of thrombin are described. In new developments, we describe the synthesis and biological results for inhibitors, in which the phenylamidinium residue in **1** is replaced by a phenolic group or aliphatic or aromatic amines.

2. Results and Discussion. – 2.1. *Synthesis of First-Generation Inhibitors.* Using computer simulations, initially with the molecular-modeling program *Insight II* [23],

then in most parts of the work the *F. Hoffmann-La Roche* in-house program *MOLOC* [24], we identified (±)-**11** (*Scheme 1*) as our first target compound. It was anticipated that (±)-**11** would bind to the active site of thrombin in a way similar to (±)-**1** (*Fig. 1*), with the side chains that depart from the central scaffold filling the S1, P, and D pockets and Gly 216 of the enzyme, forming a H-bond to one of the imide O-atoms of the scaffold [22]. For the synthesis of (±)-**11** (*Scheme 1*), an azomethine ylide was generated *in situ* from 4-bromophenylalanine (**12**) and acetone under decarboxylation [20][21] (for a review, see [21c]) and then treated with *N*-benzylmaleimide to give the desired *endo*-adduct (±)-**13** besides *exo*-derivative (±)-**14**.

The *endo*-geometry of (±)-**13** was confirmed by an X-ray crystal-structure analysis (*Fig. 3*). The compound crystallized as a racemate in the space group $P2_1/n$, and the two enantiomers are arranged in an extended orientation to allow for efficient C–H···π aromatic interactions [25] between their aromatic termini. Additional stabilizing interactions are short C–H···O contacts (C···O distance 3.51 Å) between H–C(19) of one enantiomer and the imide O-atom O(9) of the second.

Scheme 1. Synthesis of First-Generation Inhibitors



a) PhMe, *Δ*, 68 h; 25% ((±)-**13**), 14% ((±)-**14**). *b*) HCHO, HCO_2H, 100°, 10 h; 81% ((±)-**15**), 96% ((±)-**20**). *c*) CuCN, DMF, *Δ*, 56 h; 63% ((±)-**16**), 85% ((±)-**21**). *d*) HCl (g), MeOH, 4°, 48 h. *e*) $NaHCO_3$. *f*) NH_4Cl, MeOH/H_2O, 65°, 3 h; 57% ((±)-**11**), 70% ((±)-**19**) (steps *d*)–*f*)). *g*) DMF, 90°, 7 h; 47%.

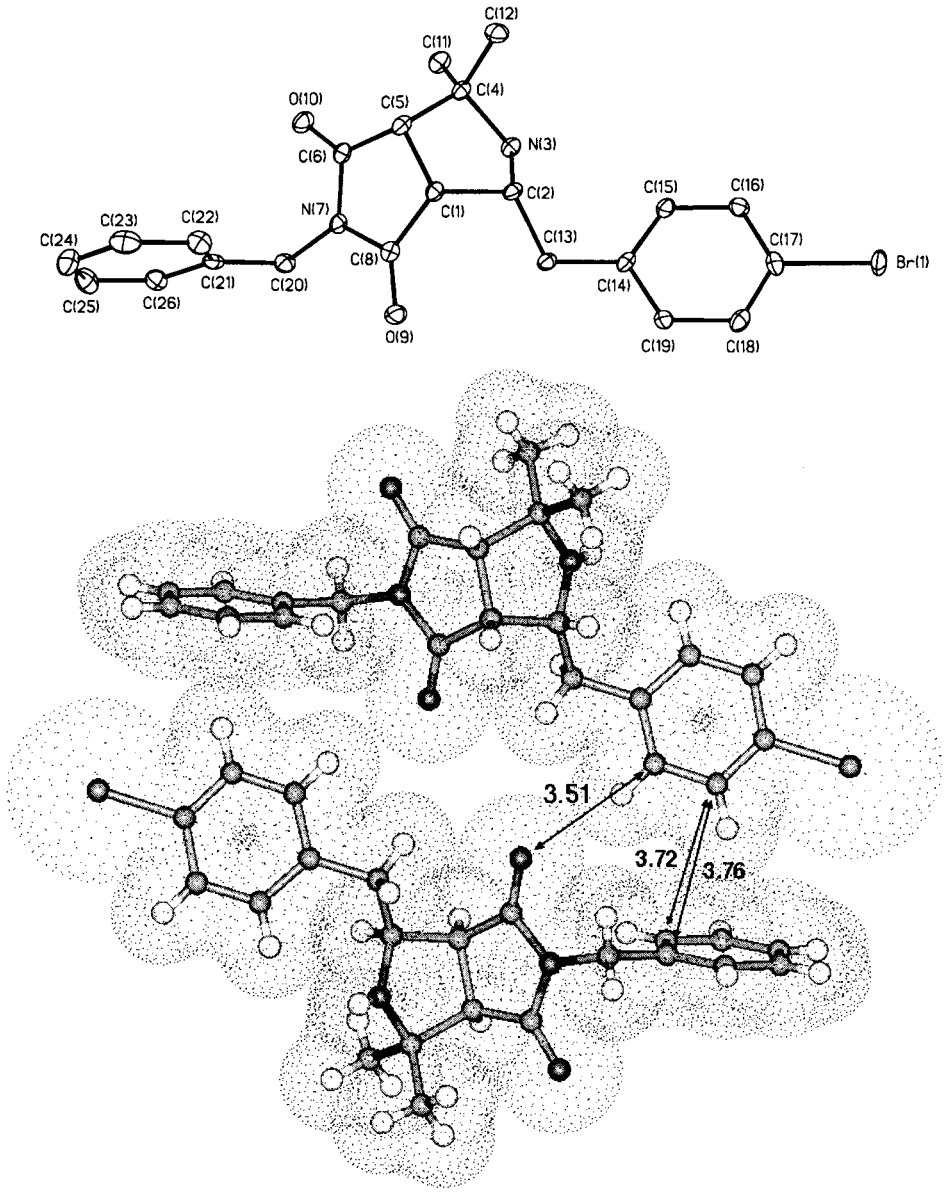


Fig. 3. *X-Ray crystal structure* (top) *and crystal packing* (bottom) *of (±)*-**13**. Arbitrary numbering. Atomic displacement parameters obtained at 100 K are drawn at the 30% probability level.

Eschweiler-Clarke methylation [26] of (±)-**13** gave (±)-**15**, and Br → CN exchange led to nitrile (±)-**16**. The conversion of nitrile (±)-**16** to the amidinium salt (±)-**11** was achieved with a *Pinner* reaction, using NH_4Cl to transform the intermediate imido-ester hydrochloride into the amidinium salt [27].

In a model reaction aimed at improving the yield of the 1,3-dipolar cycloaddition reaction, we prepared the azomethine-ylide intermediate starting from 4-bromobenzaldehyde (**17**) and L-alanine and obtained the *endo-trans*-cycloadduct (±)-**18** in 49% yield (*endo* refers to the orientation of the bromophenyl ring and *trans* to the position of this ring and the Me group on the pyrrolidine ring; *Scheme 1*). Compound (±)-**18** is formed from an *anti*-ylide through an *exo*-transition state. It is well-established that the 1,3-dipolar cycloadditions with highly reactive dipolarophiles (such as maleimides) and azomethine ylides generated by the decarboxylative method preferentially yield *trans*-substituted pyrrolidines *via* kinetically favored *anti*-ylides [21c] (see also *Sect. 2.2*). By the synthetic sequence described for (±)-**11**, aminidinium salt (±)-**19** was obtained *via* methylamine (±)-**20** and nitrile (±)-**21**. The latter compound crystallized as a racemate in the space group $P\bar{1}$. The X-ray crystal-structure analysis (*Fig. 4*) showed that this molecule adopts a more folded U-shape (compared to the more extended conformation of crystalline (±)-**13**), with the terminal aromatic rings participating in intramolecular C–H$\cdots\pi$ interactions (C(13)$\cdots$C(19) 3.67 Å; C(14)$\cdots$C(17) 3.73 Å).

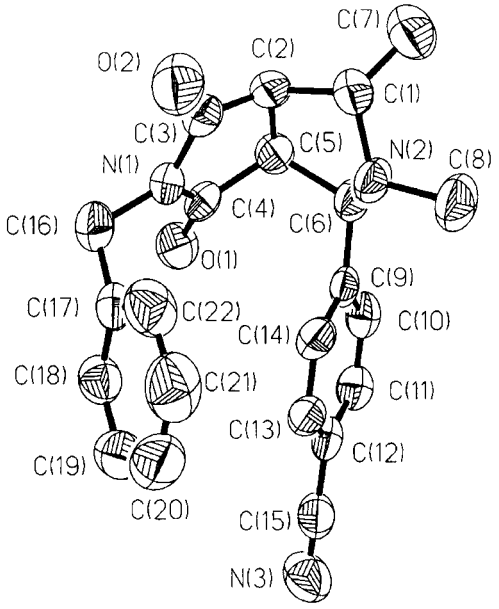


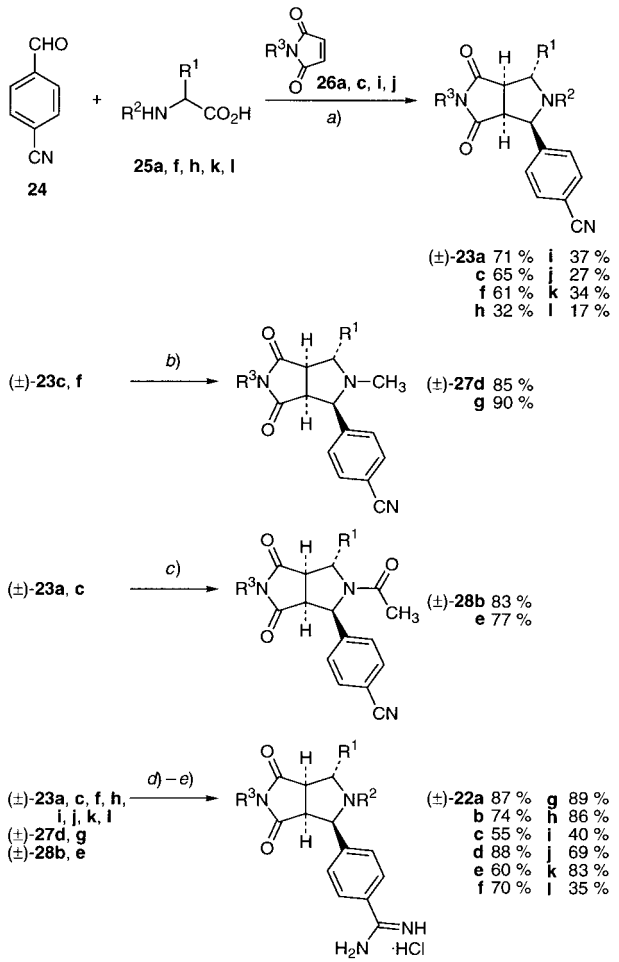
Fig. 4. *X-Ray crystal structure of (±)-***21**. Arbitrary numbering. Atomic displacement parameters obtained at 293 K are drawn at the 50% probability level.

Enzyme assays [11][22][27] gave for (±)-**11** a K_i value for thrombin inhibition of 18 μM and a selectivity for thrombin over trypsin Tr/Th (= [K_i(trypsin)/K_i(thrombin)]) of 0.14, whereas (±)-**19** showed a much higher affinity with $K_i = 0.67$ μM and also a better selectivity (Tr/Th = 7.3). Computer modeling revealed that (±)-**19**, with the phenylamidinium 'needle' directly attached to the bicyclic scaffold, had a much higher complementarity to the active site than (±)-**11**, with an extra CH_2 group between needle and scaffold. In particular, the modeling showed that only one enantiomer – with the same configuration at the stereogenic centers as in (+)-**1** – should be able to

occupy the active site (this was proven in later studies; see below). Based on these findings, more extensive structure-activity relationships were explored with a second inhibitor generation.

2.2. *Synthesis of Second-Generation Inhibitors.* At this stage of the study, we were interested in exploring changes in the substituents at the two N-atoms of the cyclic scaffold, as well as further expansions of this central platform by transformation into a tricyclic system. The synthesis of the phenylamidinium salts (±)-**22a**–**l** is shown in *Scheme 2*; the different residues R^1, R^2, and R^3 in (±)-**22a**–**l** and their precursors in the synthetic route are given in *Table 1* together with the biological activities [22]. The bicyclic scaffolds (±)-**23** were prepared by the azomethine ylide 1,3-dipolar cyclo-

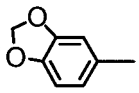
Scheme 2. *Synthesis of the* endo-trans-*Phenylamidinium Chlorides* (±)-**22a**–**l** *as Second-Generation Thrombin Inhibitors*



a) DMF, 80°, 5 h. *b*) HCHO, HCO_2H, 100°, 10 h. *c*) Ac_2O, pyridine, 0° → 20°, 2 h. *d*) HCl (g), MeOH, 4°, 24 h. *e*) NH_3, MeOH, 65°, 3 h. For the definition of residues R^1–R^3, see *Table 1*.

Table 1. *Activities of the Thrombin Inhibitors (±)-***22a–l** *and Selectivities with Respect to Trypsin* [22]

Inhibitor	R^1	R^2	R^3	K_i [μM]	Selectivity Tr/Th[a])
(±)-**22a**	Me	H	Bn	1.1	4.6
(±)-**22b**	Me	Ac	Bn	170	2.5
(±)-**22c**	Me	H	Bu	11	1.3
(±)-**22d**	Me	Me	Bu	2.9	7.6
(±)-**22e**	Me	Ac	Bu	160	2.3
(±)-**22f**	i-Bu	H	Bn	1.5	3.4
(±)-**22g**	i-Bu	Me	Bn	1.0	2.8
(±)-**22h**	$-(CH_2)_3-$		Bn	0.22	12
(±)-**22i**	$-(CH_2)_3-$		Piperonyl[b])	0.09	7.8
(±)-**22j**	$-(CH_2)_3-$		Cyclohexylmethyl	0.35	15
(±)-**22k**	$-(CH_2)_4-$		Bn	10	0.6
(±)-**22l**	$-CH_2SCH_2-$		Piperonyl	0.44	20

[a]) K_i(Trypsin)/K_i(Thrombin). [b]) Piperonyl (=(1,3-benzodioxol-5-yl)methyl) = 

addition starting from 4-formylbenzonitrile (**24**), commercial amino acids **25** (in either optically pure or racemic form), and maleimides **26**. The desired *endo-trans*-adducts (see *Sect. 2.1* for definitions of *endo* and *trans*) were obtained in 17–71% yield. Larger amounts of *exo-trans*-products were obtained in the cycloaddition reactions with the cyclic amino acids proline (**25h**), piperidine-2-carboxylic acid (**25k**), and thiazolidine-4-carboxylic acid (**25l**). The reduction of the *endo*-selectivity in the cycloadditions of azomethine ylides formed from aldehydes and *N*-substituted amino acids by the decarboxylation method had previously been noted in the literature [21c].

The *endo-trans*-geometry of the tricyclic cycloadduct (±)-**23h** obtained from proline (**25h**), 4-formylbenzonitrile (**24**), and *N*-benzylmaleimide (**26a**) was clearly established by X-ray crystal-structure analysis (*Fig. 5*). In the solid state, (±)-**23h** adopts a folded conformation resembling that observed in crystals of the bicyclic cycloadduct (±)-**21** (see *Fig. 4*).

Eschweiler-Clarke methylation afforded compounds (±)-**27**, whereas acylation with Ac_2O gave amides (±)-**28**. Starting from (±)-**23**, (±)-**27**, and (±)-**28**, the targeted amidinium salts were obtained by the *Pinner* reaction, this time using methanolic NH_3 to transform the intermediate imidoester hydrochloride into the amidinium salt. The amidinium salts (±)-**22a–l** were purified either by repeated dissolution in EtOH followed by fractional precipitation with Et_2O or by reversed-phase chromatography.

By the same methodology, some of the isolated *exo-trans*-cycloadducts (±)-**29i**, **j**, **k**, **l** were transformed into amidinium salts ((±)-**30i**, **k**, **l**) (*Scheme 3*).

Biological studies with the *endo*-derivatives (±)-**22a–l** (*Table 1*) provided the following results:

i) Compounds with a methylated N-atom ((±)-**22d**, **g** and also (±)-**19** (*Scheme 1*)) showed increased activity relative to the nonmethylated ones ((±)-**22a**, **c**, **f**), whereas a dramatic reduction in binding affinity was observed with acetylated compounds ((±)-**22b**, **e**). Although geometric differences cannot be completely excluded, we believe that the pyrrolidine N-atom is preferentially bound when protonated.

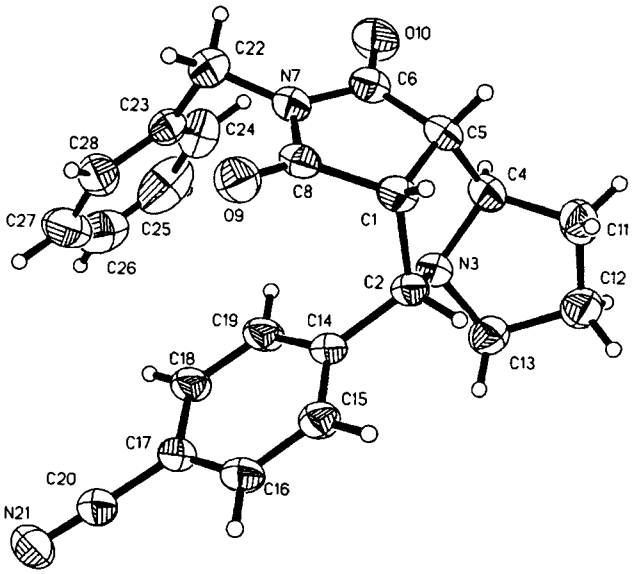
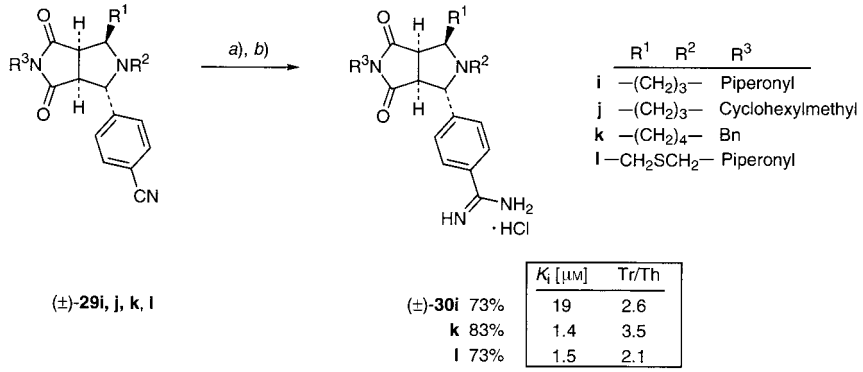


Fig. 5. *X-Ray crystal structure of* (±)-**23h**. Arbitrary numbering. Atomic displacement parameters obtained at 173 K are drawn at the 50% probability level.

Scheme 3. *Synthesis of the* exo-trans-*Phenylamidinium Salts* (±)-**30i**, **k**, **l**



	R^1	R^2	R^3
i	$-(CH_2)_3-$		Piperonyl
j	$-(CH_2)_3-$		Cyclohexylmethyl
k	$-(CH_2)_4-$		Bn
l	$-CH_2SCH_2-$		Piperonyl

(±)-**29i, j, k, l**

	K_i [μM]	Tr/Th
(±)-**30i** 73%	19	2.6
k 83%	1.4	3.5
l 73%	1.5	2.1

a) HCl (g), MeOH, 4°, 24–48 h. *b*) NH_3, MeOH, 65°, 3 h.

ii) The best affinities for thrombin (lowest K_i values) were achieved with the addition of a five-membered ring on the right side of the molecule ((±)-**22h**–**j**). A larger six-membered ring as in (±)-**22k** strongly reduces the inhibitory activity, probably because of the unfavorable displacement of a H_2O molecule localized in the oxy-anion hole close to Ser 195. Thus, the change from five- to six-membered ring fusion leads to a remarkably large, unfavorable change in binding free enthalpy of $\Delta(\Delta G)$ ((±)-**22h** → (±)-**22k**) = 2.2 kcal mol^{-1}. A fused thiazolidine ring (in (±)-**22l**) is probably also slightly too big (length of a C–S single bond: 1.82 Å, length of a C–C single bond: 1.53 Å [28]).

iii) Changes in the substituent R^3 (Bu, $PhCH_2$, cyclohexylmethyl) on the succinimide N-atom for incorporation of the D pocket have only a minor effect on the binding affinity. Interestingly, similar K_i values were measured for the benzyl- ((±)-**22h**) and the cyclohexylmethyl-substituted ((±)-**22j**) compounds, both of which presumably adopt an edge-to-face geometry with respect to Trp 215 in the D pocket. This finding suggests that specific electrostatic arene-arene C−H···π interactions in the complex of (±)-**22h** are not of particular importance; a result in good agreement with other recent findings [29]. The highest activity in the series was achieved with a (1,3-benzodioxol-5-yl)methyl (= piperonyl) substituent ((±)-**22i**; $K_i = 90$ nM).

The X-ray crystal structure of the complex between thrombin and (±)-**22i** at 1.9-Å resolution [22] confirmed the predictions from computer modeling (*Fig. 6*). Only the (3a*S*,4*R*,8a*S*,8b*R*)-enantiomer of the racemic mixture was found in the crystal structure, demonstrating a high degree of chiral recognition by the enzyme. The overall binding geometry is very similar to that shown for (+)-**1** in *Fig. 2*, with the large tricyclic scaffold occupying the middle of the active site and the S1 and D pockets being filled by the piperonyl and phenylamidinium residues, respectively. Whereas one imide C=O group undergoes H-bonding with Gly 216, the other one is found in the hydrophobic P pocket of the enzyme pointing onto the π-surface of Tyr 60A. Such an orthogonal orientation between C=O group and aromatic ring is quite disfavored (compared to the location of the C=O group in the plane of an aromatic ring), as had been shown by protein X-ray crystal-structure analyses [30]. Furthermore, the C=O group must become desolvated upon transfer from aqueous solution into the P pocket, which does not contain H-bond donors. This is energetically quite unfavorable, and C=O groups in the interior of proteins almost always (> 98%) participate in H-bonding interactions [31][32]. This loss in desolvation energy is not required for the binding of the inhibitor to trypsin, because it lacks the loop that forms the P pocket in thrombin. This could explain why

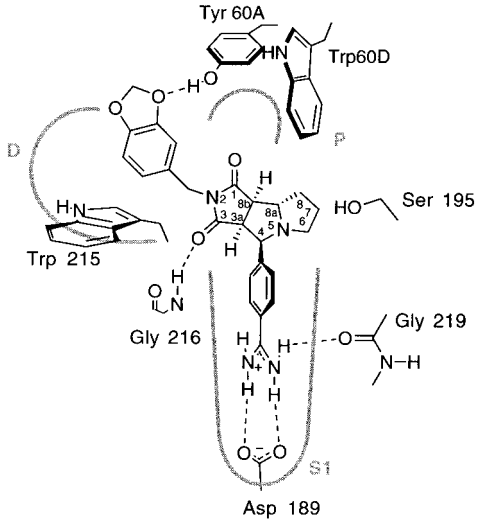


Fig. 6. *Schematic representation of the interactions of (3a*S*,4*R*,8a*S*,8b*R*)-***22i*** with thrombin, according to the X-ray crystal structure* [22]

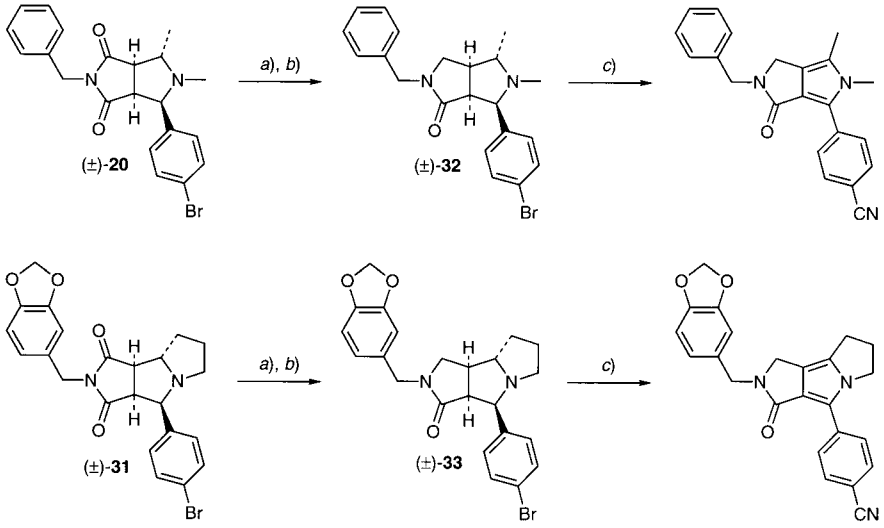
this second generation class of inhibitors is only slightly more selective (up to 20-fold; *Table 1*) for thrombin than for trypsin.

Whereas the *exo*-derivative (±)-**30i** ($K_i = 19$ μM) was a much weaker thrombin inhibitor than the *endo*-isomer (±)-**22i** ($K_i = 90$ nM), the opposite selectivity was observed for the pair of *endo/exo*-diastereoisomers (±)-**22k** and (±)-**30k** (*Table 1* and *Scheme 3*). Computer modeling was not of much help in proposing a satisfactory binding mode for the *exo*-isomers.

2.3. *Synthesis of Racemic Third-Generation Inhibitors with Strongly Enhanced Binding Selectivity for Thrombin over Trypsin*. Based on structure-activity data (*Sect. 2.2*), we had identified the unfavorable binding of the 'upper' imide C=O group into the hydrophobic P pocket as the origin of the weak selectivity of the second-generation inhibitors (see *Sect. 2.2*). Therefore, we targeted a new series of compounds in which this C=O group was either reduced to a CH_2 moiety or substituted by a suitably sized lipophilic group to fill the P pocket.

2.3.1. *Transformation of Imide into Lactam Inhibitors.* Initial attempts to reduce the imide to a γ-hydroxy lactam with $NaBH_4$ at pH 8–10, as described in the literature for succinimide [33], failed. Much more successful was the reduction to the γ-hydroxy lactam with $Li[Et_3BH]$ ('super hydride') [34]. Subsequent reduction to the corresponding lactam was readily accomplished with $Na[BH_3CN]$ in CF_3COOH. The latter reaction presumably involves protonation of the OH group and elimination to an acyliminium ion, and subsequent reduction to the lactam [35]. Starting from the bromo derivatives (±)-**20** and (±)-**31**, lactams (±)-**32** and (±)-**33**, respectively, could be prepared with a remarkably high regioselectivity (for reduction of the upper C=O group); however, the subsequent Br → CN exchange led to rapid aromatization of the pyrrolidine to a pyrrole ring (*Scheme 4*).

Scheme 4. *Attempted Synthesis of Phenylamidinium Inhibitors with a Lactam Ring*



a) $Li[Et_3BH]$, THF, −78° → 0°, 20 min. *b*) $Na[BH_3CN]$, CF_3COOH, 20°, 1.5 h. *c*) CuCN, DMF, Δ.

To prevent aromatization, we introduced an additional Me group. 1,3-Dipolar cycloaddition gave (±)-**35**, and subsequent *N*-methylation yielded imide (±)-**34**. The introduction of the additional Me group in (±)-**34** (as compared to (±)-**20**), however, led to a loss in regioselectivity in the reduction of the imide moiety, giving the regioisomeric lactams (±)-**36** and (±)-**37** in 49% and 31% yield, respectively. Compounds (±)-**36** and (±)-**37** were separated by chromatography and transformed *via* nitriles (±)-**38** and (±)-**39** into the amidinium salts (±)-**40** and (±)-**41** (*Scheme 5*). For comparison purposes (see below), the phenylamidinium salt (±)-**42** was also prepared from (±)-**34** *via* (±)-**43**.

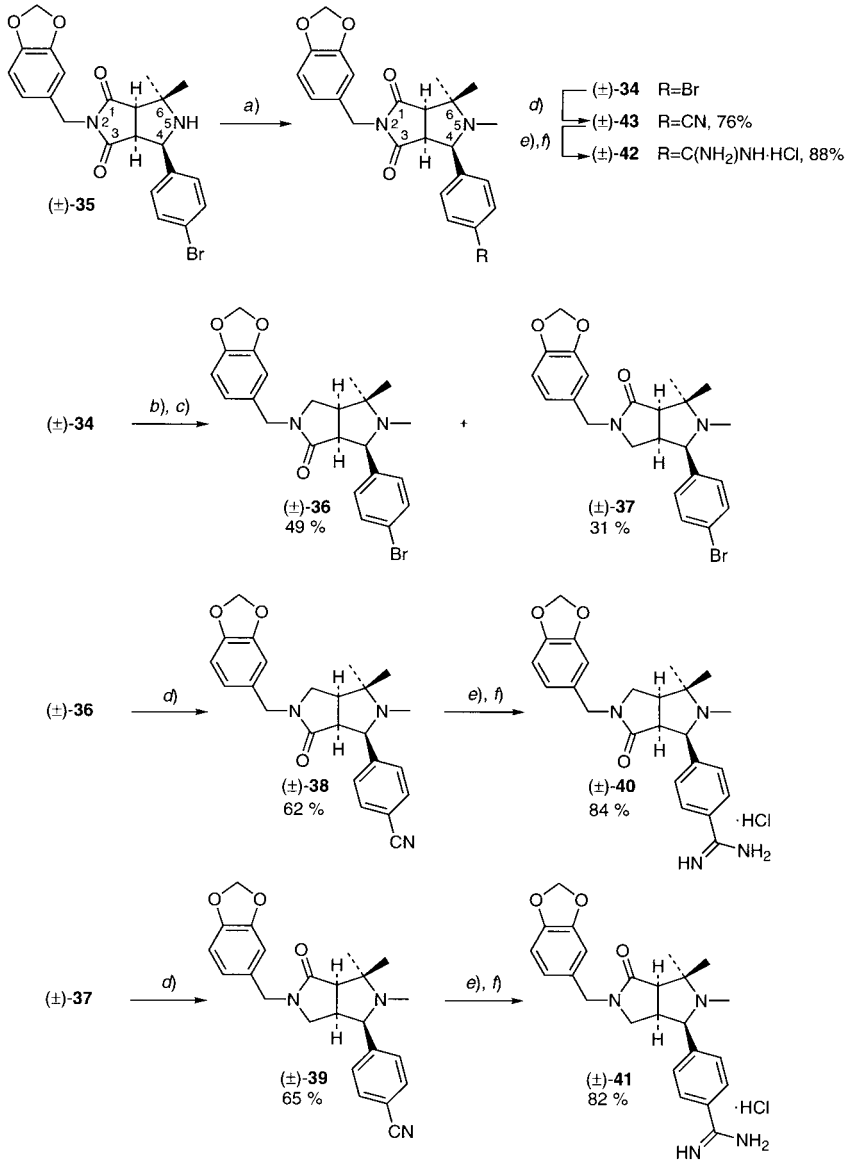
The constitution of lactam (±)-**38** was established by X-ray crystal-structure analysis (*Fig. 7,a*). A superimposition with the crystal structure of imide (±)-**21** (*Fig. 7,b*) showed that the conformation of the bicyclic scaffold does not change significantly upon reduction of the imide. Thus, differences in binding affinity between inhibitors containing imide and lactam scaffolds should mostly originate from the additional C=O group in the imide and not be due to structural changes in the bicyclic skeleton. Compound (±)-**38** crystallized as a racemate in the space group $P2_1/c$; the arrangement of the enantiomers in the crystal leads to a specific overlap of their piperonyl rings (*Fig. 7,c*), presumably as a result of favorable compensation of the C(aryl)−O dipoles.

2.3.2. *Preparation of Inhibitors with Lipophilic Residues for Incorporation into the P Pocket of Thrombin*. We first attempted the replacement of the upper imide C=O group in (±)-**34** by an alkyl group using a *Grignard* reagent (MeMgCl) [33b]. The crude product was subsequently reduced with $Na[BH_3CN]$ in CF_3COOH [36] to provide, in excellent yield and complete regioselectivity, the methylated lactam (±)-**44** (*Scheme 6*). This specific nucleophilic attack at the 'lower' C=O group of imide (±)-**34** is in contrast to the preferred reduction of the 'upper' C=O group with 'super hydride' (*Schemes 4* and *5*). This could suggest that the 'lower' imide C=O group is the intrinsically more reactive one, and that steric factors may be irrelevant in the attack of the small MeMgCl reagent. Lactam (±)-**44** was subsequently transformed *via* nitrile (±)-**45** into the amidinium salt (±)-**46**.

The configuration of (±)-**44** with the *endo*-Me group at C(6) was established by a nuclear *Overhauser* effect (NOE) observed between H−C(6) and H−C(3a) (300 MHz, $CDCl_3$). It is conceivable that addition of the *Grignard* reagent is followed by protonation of the resulting tertiary alcohol and elimination of H_2O to the acyliminium ion, which is then reduced from the sterically less hindered *exo*-face. *Grignard* addition to (±)-**20** with only one Me group near the 'upper' C=O group, followed by reduction, also provided the *endo*-methylated lactam. Utilization of MeLi instead of the *Grignard* reagent expectedly did not affect the stereochemical outcome of the transformation of (±)-**34**.

Since organometallic reagents preferentially added to the 'lower' imide C=O group, we turned to further transformations of γ-hydroxy lactam (±)-**47** (*Scheme 7*) in order to introduce the lipophilic residue for incorporation into the P pocket. Compound (±)-**47** was readily obtained as a mixture of a major and a minor configurational isomer (no assignment was made) by reduction of (±)-**34** with $Li[Et_3BH]$ (*Sect. 2.3.1*). Attempts to form the corresponding acyliminium ion with a *Lewis* acid ($BF_3 \cdot OEt_2$ [37], $SnCl_4$ [38], or CF_3COOH [39]) and to add allyl

Scheme 5. *Preparation of the Lactam Inhibitors* (±)-**40** and (±)-**41**



a) HCHO, HCO_2H, 100°, 10 h; 92%. *b*) Li[Et_3BH], THF, −78° → 0°, 1 h. *c*) Na[BH_3CN], CF_3COOH, 20°, 5 h. *d*) CuCN, DMF, Δ, 17–30 h. *e*) HCl (g), MeOH, 4°, 24 h. *f*) NH_3, MeOH, 65°, 3 h.

trimethylsilane to give the allyl-substituted lactam were unsuccessful. Similarly, transformation of (±)-**47** into the methanesulfonate and subsequent reaction with MeLi did not provide the methylated lactam.

Finally, hydroxy lactam (±)-**47** could be transformed in good yield with 4-toluenesulfinic acid in the presence of $CaCl_2$ into sulfone (±)-**48** (*Scheme 7*). Starting

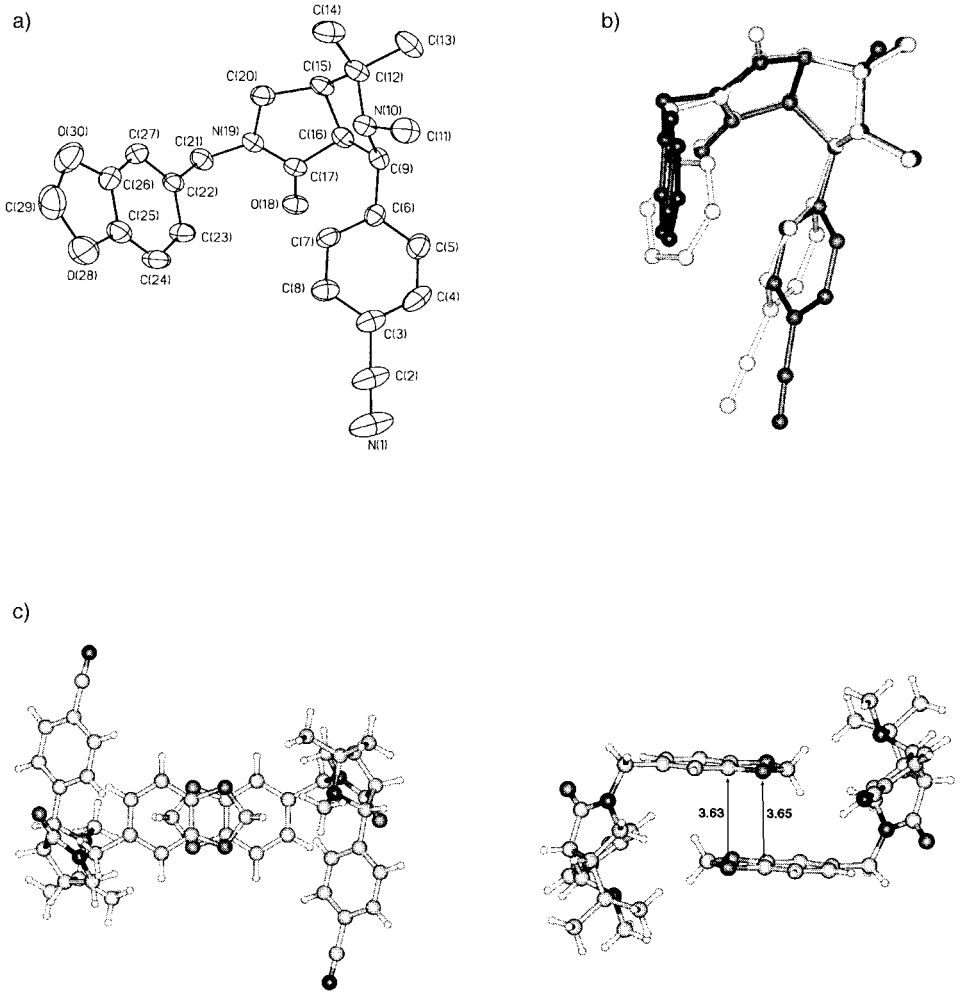
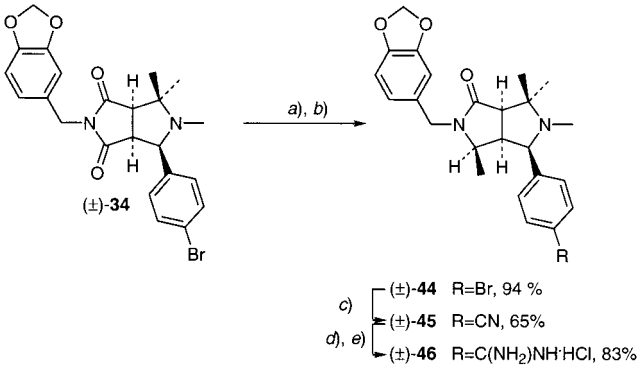


Fig. 7. a) *X-Ray crystal structure of* (±)-**38**. Arbitrary numbering. Atomic displacement parameters obtained at 295 K are drawn at the 30% probability level. b) *Superimposition of the X-ray crystal structures of* (±)-**38** *and* (±)-**21**. c) *View onto* (left) *and parallel* (right) *to the stacking piperonyl rings of the two enantiomers of* (±)-**38**.

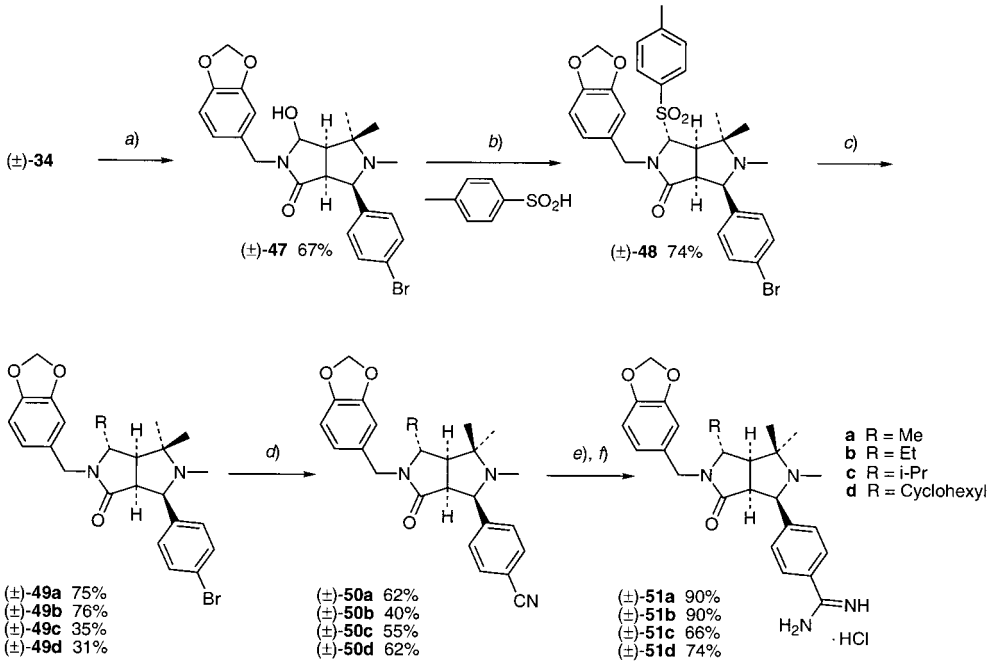
from this versatile intermediate, we took advantage of a protocol by *Ley* and co-workers [40], who described that the conversion of *Grignard* reagents with $ZnCl_2$ generates organometallic reagents suitable for the nucleophilic substitution of the arylsulfone group. The exact nature of the reagent is unknown; however, the presence of Mg salts is essential for the successful displacement of the sulfone by an alkyl residue. By this methodology, the alkylated derivatives (±)-**49a**–**d** were prepared in 75% (attack of primary alkyl groups) and 30–35% yield (attack of bulkier secondary alkyl groups). In each case, the reaction proceeded with retention of configuration, providing the *exo*-stereoisomer. The configuration at the newly created stereogenic center was readily established by NOE difference spectroscopy. A plausible explan-

Scheme 6. *Preparation of the Lactam Inhibitor* (±)-**46**



a) MeMgCl, THF, 20°, 13 h, *b*) Na[BH_3CN], MeOH, CF_3COOH, 20°, 2 h. *c*) CuCN, DMF, Δ, 30 h. *d*) HCl (g), MeOH, 4°, 24 h. *e*) NH_3, MeOH, 65°, 3.5 h.

Scheme 7. *Synthesis of the Alkylated Inhibitors* (±)-**51a**–**d**



a) Li[Et_3BH], THF, −78° → 0°, 2 h. *b*) CH_2Cl_2, $CaCl_2$, 20°, 19 h. *c*) $ZnCl_2$, RMgCl or RMgBr, CH_2Cl_2, 0° → 20°, 13–36 h. *d*) CuCN, DMF, Δ, 17–30 h. *e*) MeOH, HCl (g), $CHCl_3$, 4°, 24 h. *f*) NH_3, MeOH, 65°, 3.5 h.

ation for this stereochemical outcome involves the intermediate formation of the acyliminium salt, which is attacked from the *exo*-face. The alkylated derivatives (±)-**49a**–**d** were subsequently transformed into nitriles (±)-**50a**–**d** and eventually into the targeted amidinium salts (±)-**51a**–**d**.

Crystallization of amidinium salt (±)-**51c** from H_2O afforded crystals suitable for X-ray analysis. The compound crystallized as a racemate in the space group $P\bar{1}$ together with 1 equiv. of H_2O. Two similar conformers I and II – each in racemic form – were present in the crystal; they differed mainly in the orientation of their piperonyl rings (*Fig. 8*). The dihedral angle between the planes of the phenyl ring and the attached amidinium moiety amounted to 29° in both conformers.

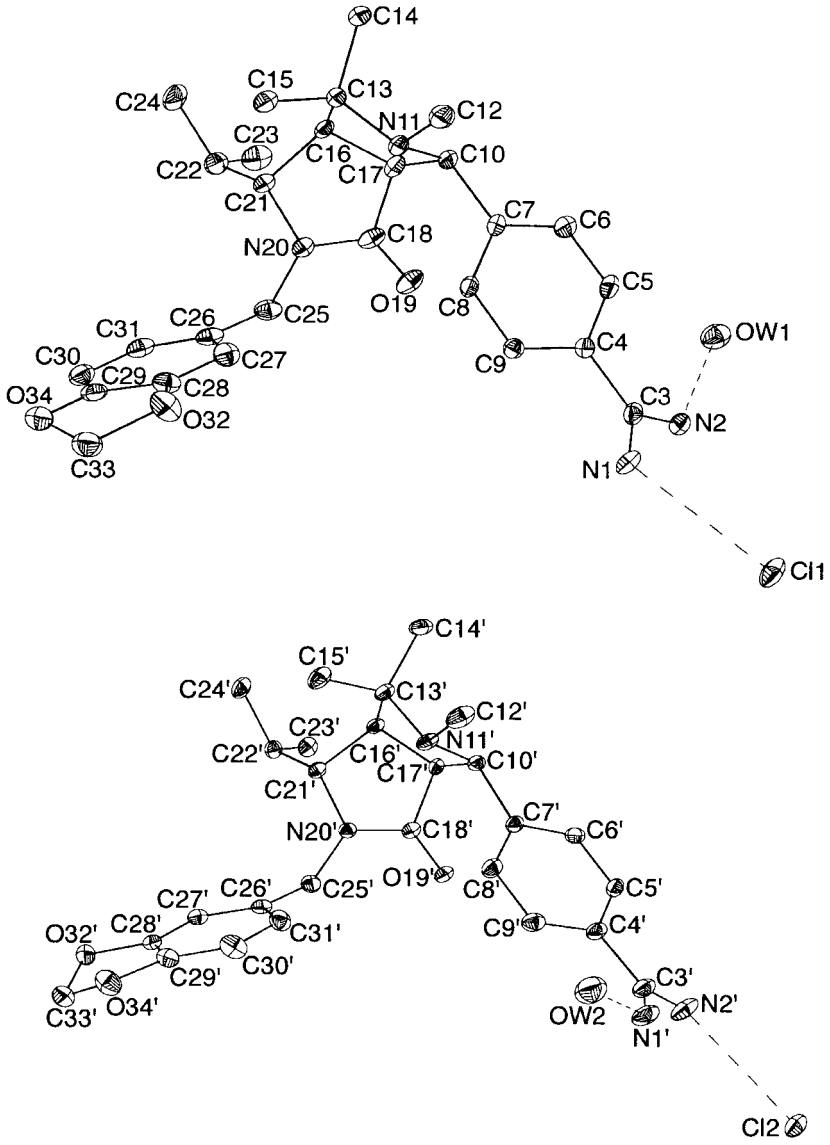


Fig. 8. *X-Ray crystal structure of (±)-***51c**. Shown are the two conformers I and II, each present in racemic form in the crystal. Arbitrary numbering. Atomic displacement parameters obtained at 295 K are drawn at the 30% probability level.

The crystal packing was quite complicated in view of the presence of two conformers. Basically, the piperonyl rings arrange in hydrophobic layers whereas the amidinium moieties form hydrophilic layers which also contain the Cl^- counterions and H_2O molecules (*Fig. 9*). A network of ionic H-bonds, involving the amidinium groups, the Cl^- counterion, the H_2O molecules, and the lactam C=O groups extends throughout the crystal.

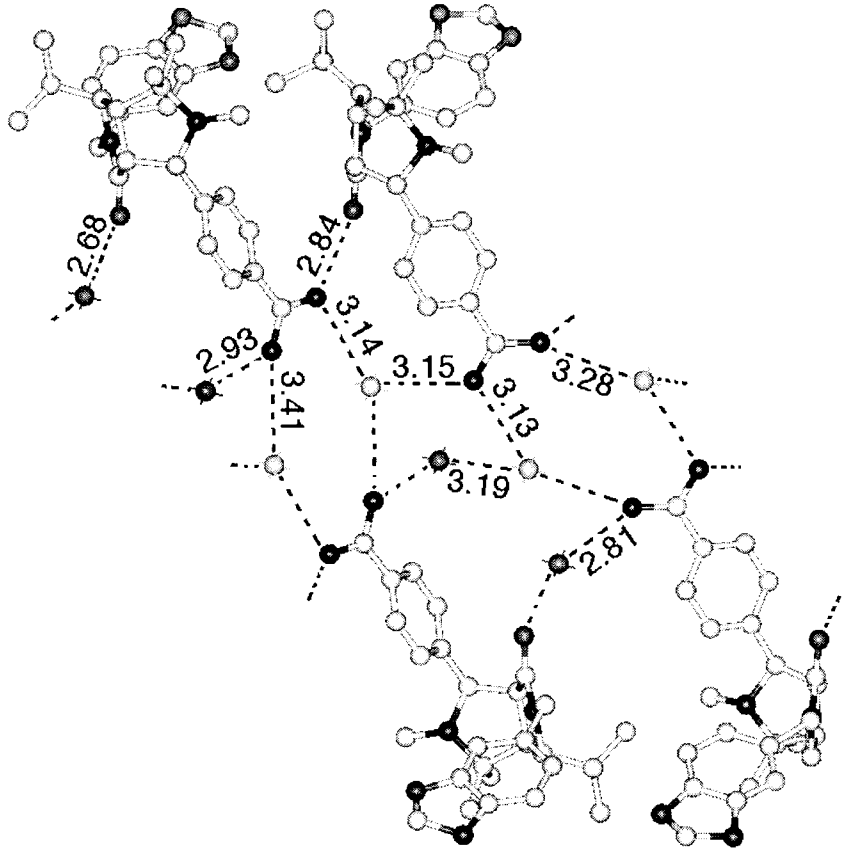
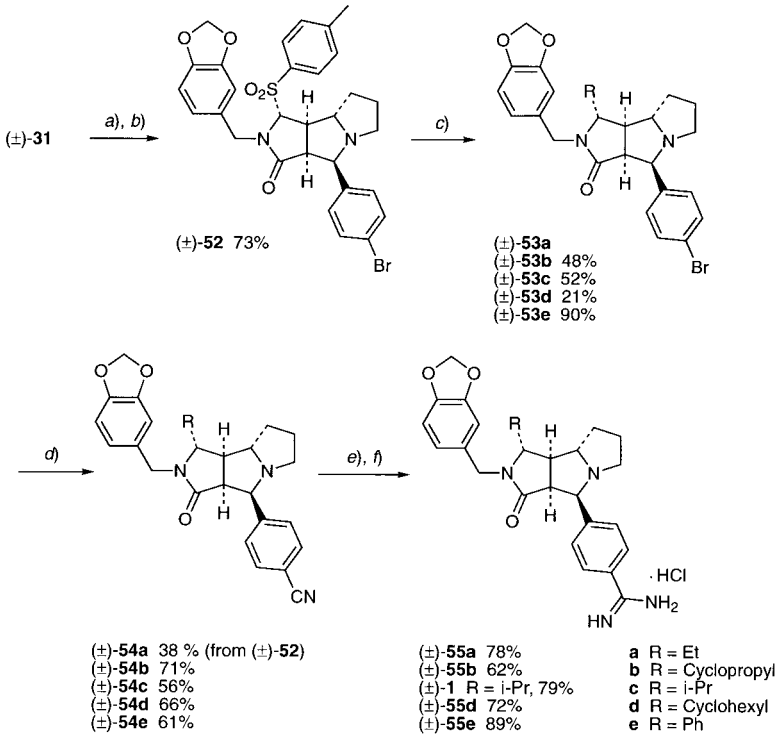


Fig. 9. *View onto the crystal packing of (±)-***51c** *featuring the H-bonding network within the hydrophilic layer.* The lighter spheres in the network are Cl^- ions, the darker ones are H_2O molecules. H-Bonding distances (X···Y) are given in Å.

We then turned to the substitution of the 'upper' imide C=O group by alkyl residues in the tricyclic, higher-affinity series. Reduction of (±)-**31** proceeded selectively, yielding only one of the four possible isomeric γ-hydroxy lactams, which was transformed directly – without further purification – into sulfone (±)-**52** (*Scheme 8*). Larger quantities of this compound are conveniently purified by simple washing of the crystalline crude product obtained after workup with AcOEt. In this solvent, (±)-**52** is quite insoluble, whereas the impurities dissolve readily. Lactams (±)-**53a**–**e** were formed from (±)-**52** with the corresponding *Grignard* reagents in the

Scheme 8. *Synthesis of Inhibitors* (±)-**55a**,**b**,**d**,**e** *and* **1** *with a Tricyclic Central Scaffold*



a) Li[Et_3BH], THF, $-78° \rightarrow 0°$, 30 min. *b*) 4-Toluenesulfinic acid, CH_2Cl_2, $CaCl_2$, 20°, 24 h. *c*) $ZnCl_2$, RMgCl or RMgBr, CH_2Cl_2, $0° \rightarrow 20°$, 13–36 h. *d*) CuCN, DMF, Δ, 17–30 h. *e*) MeOH, HCl (g), $CHCl_3$, 4°, 24 h. *f*) NH_3, MeOH, 65°, 3.5 h.

presence of $ZnCl_2$, with a particularly high yield (90%) being obtained with PhMgBr. The conversions with the larger *Grignard* reagents exclusively provided the *exo*-products (±)-**53b**–**e**, whereas conversion with EtMgBr afforded an isomeric mixture from which the desired *exo*-isomer could be separated only after conversion to the nitrile. Bromides (±)-**53a**–**e** were transformed without significant aromatization (see *Scheme 4*) into nitriles (±)-**54a**–**e** and finally to the amidinium salts (±)-**55a**,**b**,**d**,**e** and (±)-**1**. The *exo*-orientation of the i-Pr group in nitrile (±)-**54c** was supported by NOE difference spectroscopy; furthermore, this configuration was also confirmed for phenylamidinium salt (±)-**1** by the X-ray crystal structure of its complex with thrombin [16].

With their rigid bi- and tricyclic cores, these inhibitors are all highly preorganized for binding (as shown by the X-ray crystal structures and computer modeling), and it is reasonable to assume that they all prefer similar modes of association to thrombin. Measured changes in the binding free enthalpy were, therefore, expected to correlate directly with the bonding contributions of individual substituents of the inhibitors, thereby providing valuable information on the magnitudes of individual intermolecular interactions. The affinities of the lactam inhibitors for thrombin and the selectivities for thrombin over trypsin are given in *Table 2*.

Table 2. *Activities of the Lactam-Based Thrombin Inhibitors and Selectivities with Respect to Trypsin* [16]. The activities of the two imide inhibitors (±)-**42** and (±)-**22i** are given for comparison. Also shown is the stabilization or destabilization $\Delta\Delta G$ of the thrombin-inhibitor complex by replacement of one C=O group in the two imide inhibitors.

Inhibitor	K_i [μM]	Selectivity Tr/Th[a])	
			$\Delta\Delta G$[b])
(±)-**42**	0.5	2.2	
(±)-**41**	2.0	32	+0.8
(±)-**46**	9.2	4.3	+1.7
(±)-**40**	6.2	5	+1.5
(±)-**51a**	2.0	32	+0.8
(±)-**51b**	0.095	77	−1.0
(±)-**51c**	0.030	223	−1.7
(±)-**51d**	0.86	38	+0.3
			$\Delta\Delta G$[c])
(±)-**22i**	0.09	7.8	
(±)-**55a**	0.0081	210	−1.4
(±)-**55b**	0.010	230	−1.3
(±)-**1**	0.013	760	−1.1
(±)-**55d**	1.7	2.6	+1.7
(±)-**55e**	1.4	3.6	+1.6

[a]) K_i(Trypsin)/K_i(Thrombin). [b]) ΔG((±)-**42**) − ΔG(x); x: other inhibitors with a bicyclic core in *Table 2*. [c]) ΔG((±)-**22i**) − ΔG(x); x: other inhibitors with a tricyclic core in *Table 2*.

Inhibitors lacking the 'lower' C=O group ((±)-**41**, (±)-**46**) are less active than imide (±)-**42**, since they are unable to form a H-bond to the backbone NH of Gly 216 (see *Fig. 2*). A comparison between the inhibitory affinities of imide (±)-**42** and lactam (±)-**41** (*Table 2*) shows that this H-bond contributes only 0.8 kcal mol^{-1} to the overall binding free enthalpy. This comparison was validated by X-ray crystallography. The crystal structures of the thrombin complexes with (±)-**22i** and (±)-**41** (for details, see [16]) showed that the removal of the C=O group and, consequently, of the H-bond to Gly 216 did not induce a significant positional shift of the bicyclic core structure within the protein. In both structures, the inhibitors adopt a similar position in the active site, analogous to that shown for (±)-**1** in *Fig. 2*. The free energy increment assigned to this H-bond is in good agreement with data from *Fersht et al.* [41], who observed losses in binding free energy of 0.5 – 1.5 kcal mol^{-1} upon deleting uncharged H-bonds in enzyme-substrate complexes using site-directed mutagenesis (for a more indepth discussion of the weakness of this H-bond, see [16]). Lactam (±)-**46** (*Scheme 6*), with an *endo*-Me group at C(6) still showed some affinity towards thrombin and trypsin; a different binding mode can, however, not be ruled out.

A comparison of the affinities of (±)-**42** and (±)-**40** indicated, quite surprisingly, that the imide bound by 1.5 kcal mol^{-1} better than the lactam. Apparently, it is better to fill the hydrophobic P pocket with an imide C=O group – despite its polar character – than to leave it empty for solvation by H_2O. Introduction of an *exo*-Me group at C(4) in (±)-**51a** led to only a modest improvement (it was known from literature that a Me group does not sufficiently fill the P pocket [11]) in both binding affinity and selectivity,

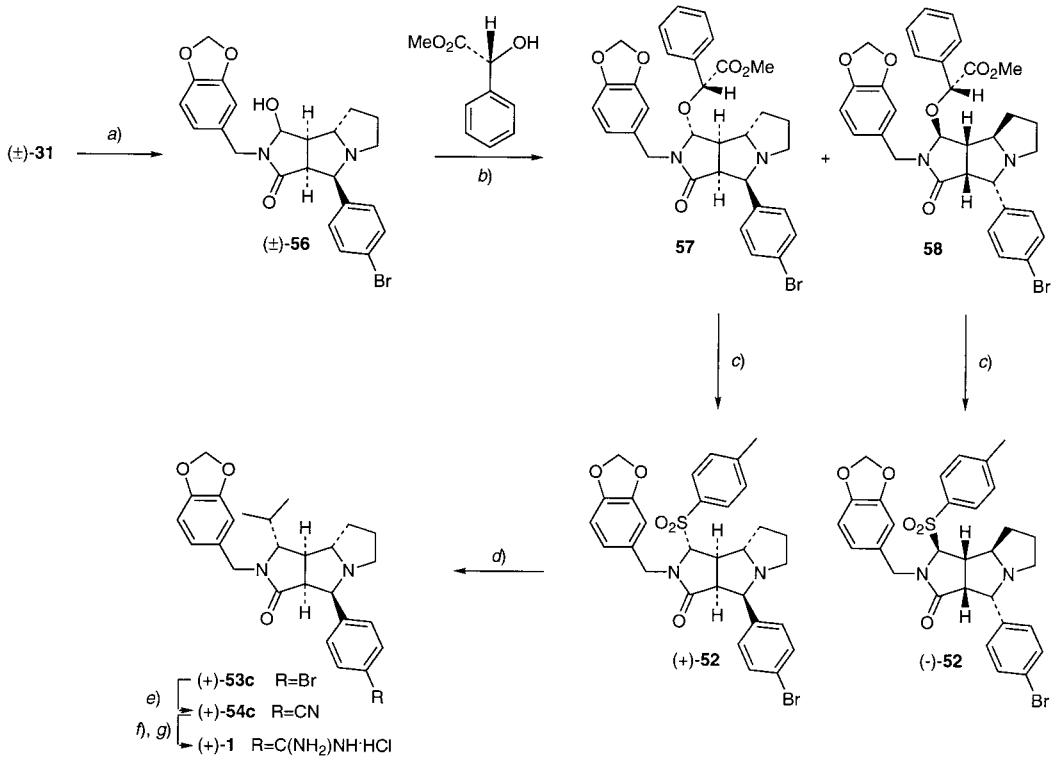
compared to lactam (±)-**40** (*Table 2*). A large improvement in both affinity and selectivity resulted from the introduction of an Et group and, in particular, an i-Pr group. With a K_i of 30 nM and a 223-fold higher affinity for thrombin over trypsin, (±)-**51c** was the most potent and most selective among the inhibitors with a bicyclic core. A cyclohexyl substituent ((±)-**51d**) is too large for optimal binding in the P pocket and binding affinity and selectivity decrease again.

The inhibitors with a tricyclic core structure are much more active and selective than those with a bicyclic one (*Table 2*). The three lactams with an *exo*-Et ((±)-**55a**), *exo*-cyclopropyl ((±)-**55b**), and an *exo*-(i-Pr) group ((±)-**1**) showed high binding affinities and selectivities. Compound (±)-**1** ($K_i = 13$ nM) displayed the highest selectivity for thrombin over trypsin (760-fold) and was only a very weak binder of the other coagulation factors Xa ($K_i = 140$ μM) and VIIa ($K_i > 500$ μM). It is noticeable that the natural thrombin substrate fibrinogen also binds to the P pocket with an i-Pr group of a valine residue. Cyclohexyl (in (±)-**55d**) and phenyl rings (in (±)-**55e**) are again too voluminous for energetically favorable incorporation into the P pocket. Obviously, the loop in thrombin that forms the P pocket is rather rigid and cannot adapt well to larger hydrophobic groups of the inhibitor. As mentioned in the introduction, the X-ray crystal structure of the complex between thrombin and (+)-**1** was solved, and the observed interactions between enzyme and inhibitors are schematically depicted in *Fig. 2*; for a detailed discussion of this crystal structure, the reader is referred to [16].

2.4. *Optical Resolution of (±)-***1**. In crystals obtained from thrombin and (±)-**1** (for the experimental protocol, see [16]), the (+)-(1*R*,3a*S*,4*R*,8a*S*,8b*R*)-enantiomer was found exclusively in the enzyme-active site. To quantify the degree of enantioselectivity in thrombin recognition, which had also been predicted by computer modeling, we carried out the optical resolution of this most selective inhibitor.

Initial attempts to resolve (±)-**1** by crystallization of diastereoisomeric salts formed with a diversity of non-racemic acids such as (+)-(1*S*)-camphor-10-sulfonic acid, (−)-D-mandelic acid, or (+)-L-tartaric acid and derivatives in a variety of solvents all failed. Attempts to form esters from hydroxy lactam (±)-**56** (*Scheme 9*) and acyl halides of some of the mentioned non-racemic acids and to separate the diastereoisomers by chromatography also remained unsuccessful, presumably due to the instability of the esters. In contrast, etherification of (±)-**56** was found to yield relatively stable products that could be chromatographed without decomposition. Thus, crude (±)-**56**, obtained by reduction of imide (±)-**31**, was treated with methyl (−)-D-mandelate in refluxing toluene in the presence of a catalytic amount of pyridinium toluene-4-sulfonate (PPTS) [42] and the resulting diastereoisomeric ethers **57** and **58** were separated by chromatography on SiO_2 (*Scheme 9*). Since these compounds decompose slowly on SiO_2, small quantities of intensely yellow-colored impurities, which eluted together with the separated diastereoisomers, were not completely removed. All attempts to obtain X-ray-quality crystals of **57** or **58** failed, which prevented a direct determination of their absolute configurations. Therefore, the ethers were directly converted with toluene-4-sulfinic acid into sulfones (+)-**52** and (−)-**52**, which are intermediates on the way to the amidinium salts (+)-**1** and (−)-**1**, respectively. Configurational assignments in *Scheme 9* were made based on the strongly different binding affinities of (+)-**1** and (−)-**1** (see below), and the assumption that the better-binding enantiomer is the one seen in the X-ray crystal structure (*Fig. 2*).

Scheme 9. *Synthesis of Optically Pure (+)-***1**



a) Li[Et_3BH], THF, $-78° \rightarrow 0°$, 30 min. *b*) PPTS, PhMe, Δ, 6 h; 61% (**57**), 64% (**58**), yields starting from (±)-**31**. *c*) Toluene-4-sulfinic acid, $CaCl_2$, CH_2Cl_2, 20°, 12 h; 91% ((+)-**52**), 79% ((−)-**52**). *d*) $Me_2CHMgBr$, $ZnCl_2$, CH_2Cl_2, 20°, 24 h. *e*) CuCN, DMF, Δ, 27 h, (51% from (+)-**52**). *f*) MeOH, HCl (g), $CHCl_3$, 4°, 24 h. *g*) NH_3, MeOH, 65°, 3.5 h (75% from (+)-**54c**). The synthesis of (−)-**1** from (−)-**52** followed the same protocol.

The purity of the non-racemic sulfones was determined by high performance liquid chromatography (HPLC) on a (*S,S*)-*Whelk-O-1* chiral stationary phase (CSP) [43] with AcOEt/hexane 1:1 as eluent (*Fig. 10*). Enantiomer (−)-**52** was found to be of high purity (> 99.5%), whereas (+)-**52** (96.5%) was substantially contaminated with its antipode (3.5%).

Since an enantiomeric purity of > 99:1 was required for meaningful biological assays at the stage of the amidinium salts, a further purification of (+)-**52** was necessary. This was achieved by addition of a small quantity of racemic (±)-**52** to a solution of (+)-**52** in AcOEt. Upon very slow addition of hexane, nearly pure racemate crystallized out, leaving the remaining (+)-**52** in solution with an enantiomeric purity higher than 99:1 (*Fig. 11*).

An in-depth insight into the high propensity of (±)-**52** to crystallize even in the presence of a large excess of the (+)-enantiomer, was provided by X-ray crystal-structure analysis. Sulfone (±)-**52** crystallized as a racemate in the space group $P2_1/c$ (*Fig. 12*). An analysis of the crystal lattice revealed a much larger amount of favorable contacts between opposite than between identical enantiomers. A double-layer

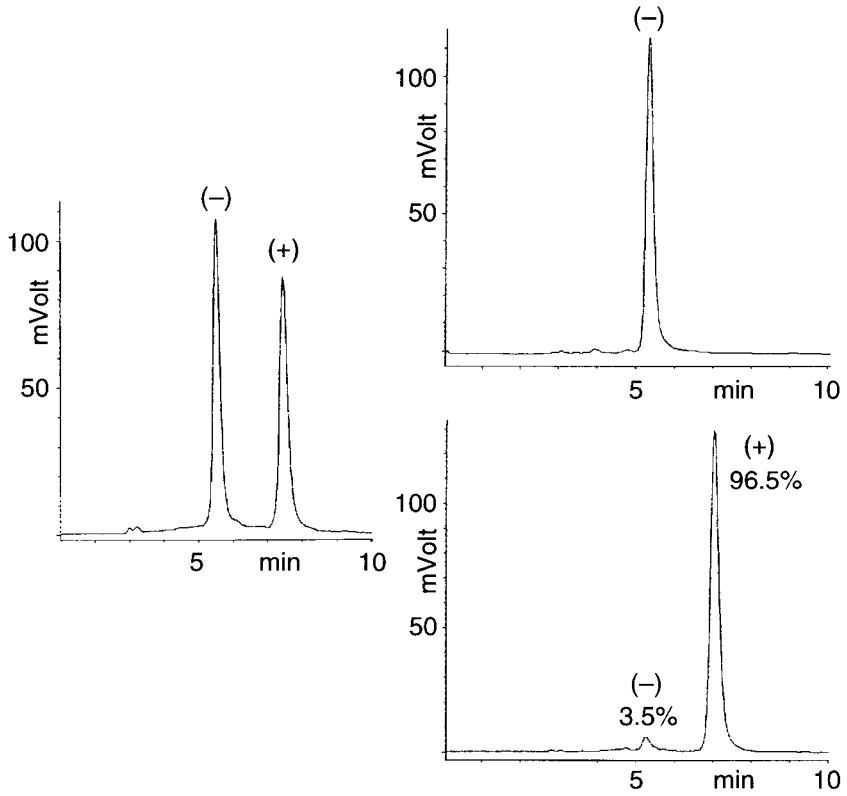


Fig. 10. *Analytical HPLC of sulfones (–)*-**52** (right top, $t_R = 5.5$ min) *and (+)*-**52** (right bottom, $t_R = 7.5$ min) *on a* (S,S)-Whelk-O-1 CSP. Eluent: AcOEt/hexane, flow rate 1 ml min^{-1}, detection at 254 nm; retention time of non-retained solute: $t_0 = 3.0$ min; separation factor $\alpha = (t_{R'} - t_0)/(t_R - t_0) = 1.8$. The chromatogram on the left corresponds to racemic (±)-**52**.

structure (*Fig. 13,a*) features segregated stacks of the (+)- and the (–)-enantiomer, with the Ts groups providing the boundaries of each double layer. In this layered structure, each molecule is surrounded by four molecules of opposite configuration (*Fig. 13,b*).

A closer analysis reveals the nature of the intermolecular contacts in the crystal lattice. *Fig. 14,a*, shows the segregated stacks of the enantiomers in a double layer. Between two identical enantiomers, aromatic C–H$\cdots\pi$ interactions exist between the Ts and the piperonyl groups, with distances between C-atoms of the two rings of 3.66 Å (C(33)$\cdots$C(23)) and 3.75 Å (C(14)$\cdots$C(22); (for the numbering, see *Fig. 12*). Between two opposite enantiomers, a very short C–H$\cdots\pi$ interaction (distance C(18)$\cdots$C(23): 3.45 Å) is observed between the methyl group of the Ts residue and the piperonyl group.

Several additional contacts exist between opposite enantiomers in adjacent double layers (*Fig. 14,b*). There is an aromatic C–H$\cdots\pi$ interaction (distance C(17)$\cdots$C(22): 3.72 Å) between Ts and piperonyl rings of opposite enantiomers in adjacent double layers. A remarkably short contact (distance 3.34 Å) is observed between the Ts

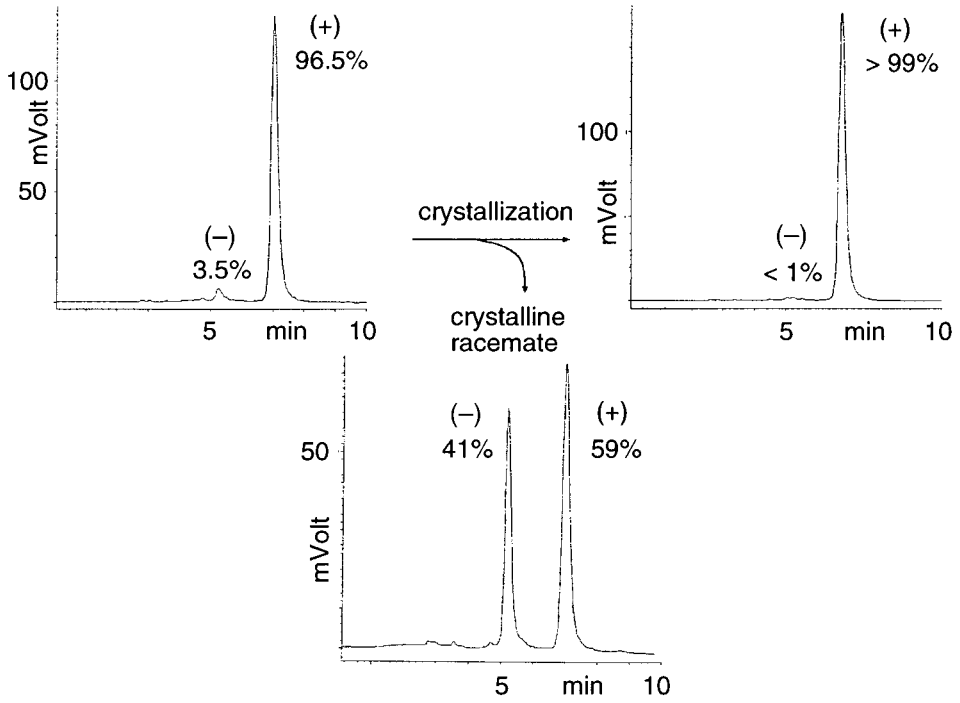


Fig. 11. *Analytical HPLC showing the purification of (+)-***52** *by crystallization of (±)-***2** *as an insoluble racemate.* For the conditions, see caption to *Fig. 10.*

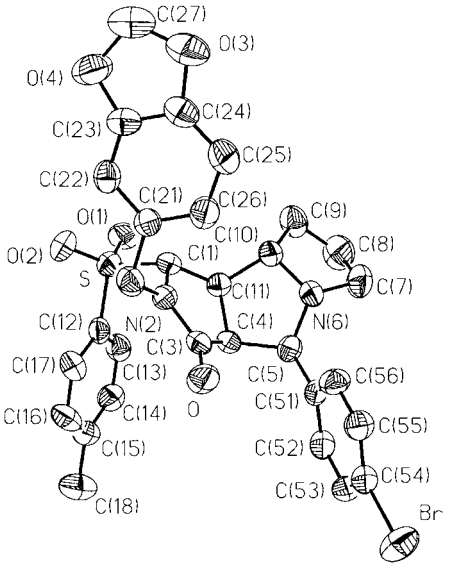


Fig. 12. *X-Ray crystal structure of (±)-***52**. Arbitrary numbering. Atomic displacement parameters obtained at 295 K are drawn at the 50% probability level.

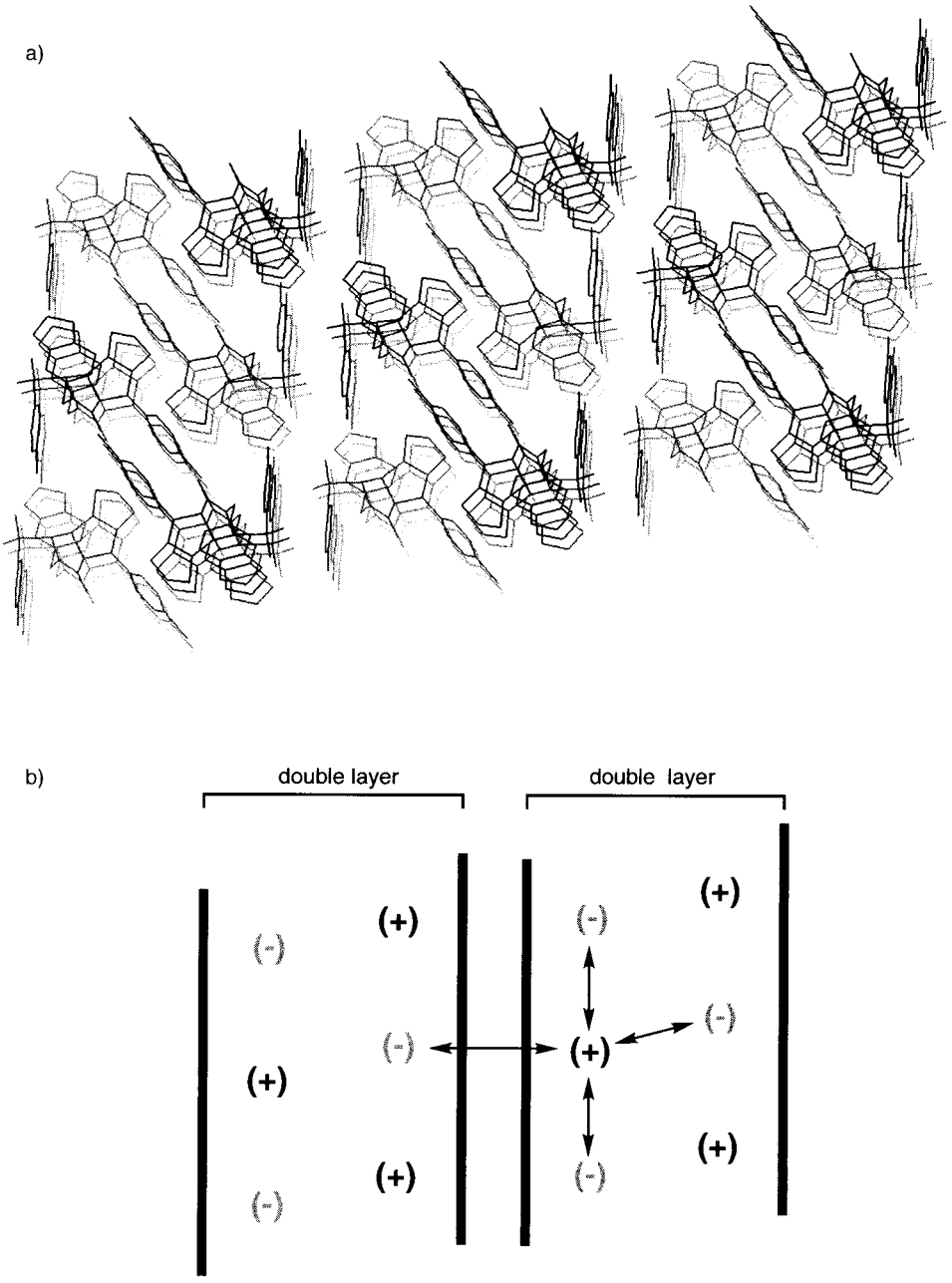


Fig. 13. a) *Crystal packing of (±)-***52**. The two enantiomers form segregated stacks (perpendicular to the paper plane) that arrange in a double-layer structure. The (+)-enantiomer is shown in darker shading. b) *Schematic representation of the contacts between opposite enantiomers in the crystal packing.*

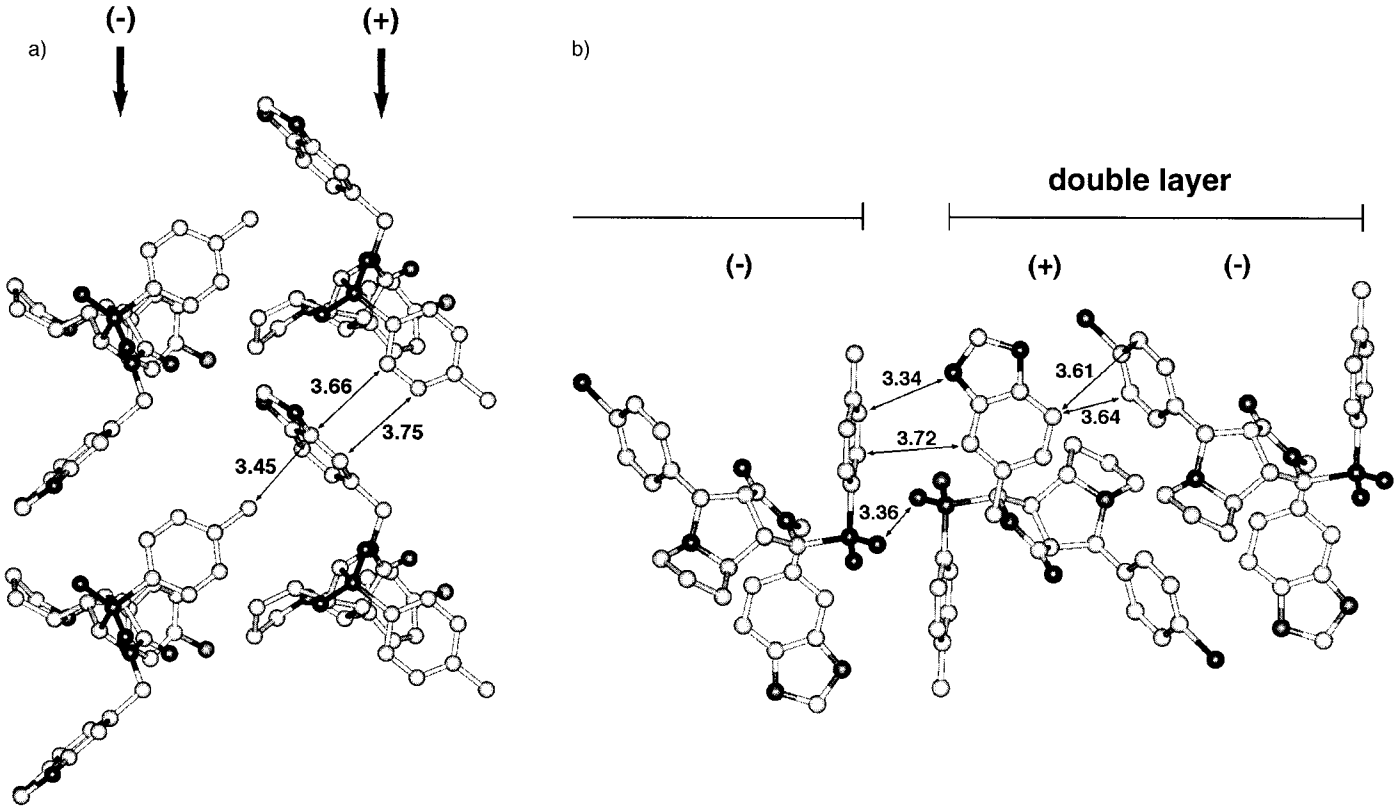


Fig. 14. a) *Intermolecular contacts in the segregated stacks of one double layer of the crystal packing of (±)-***52**. b) *Intermolecular contacts between opposite enantiomers of the same and of adjacent double layers.* View *a*) corresponds to a view from the left side onto the crystal packing shown in *Fig. 13,a*; view *b*) is identical to that in *Fig. 13,a*.

C-atom C(16) and the piperonyl O-atom O(4), and an additional contact (distance 3.36 Å) exists between O-atoms of the SO_2 moieties. Aromatic C–H$\cdots\pi$ interactions are also seen between bromophenyl and piperonyl rings of opposite enantiomers within a double layer (distances C(25)$\cdots$C(54): 3.61 Å and C(25)$\cdots$C(55): 3.64 Å).

Overall, these numerous contacts result in a very dense crystal packing with a remarkably high calculated density of 1.493 g cm^{-3}. This explains the high crystallization tendency of the racemate, and it can be assumed that a similarly favorable packing cannot be reached in crystals containing identical enantiomers.

The enantiomerically pure sulfones (+)-**52** and (−)-**52** were subsequently transformed into the amidinium salts (+)-**1** and (−)-**1**, respectively, by the route applied for the preparation of (±)-**1** (*Scheme 9*). Purification of the intermediate nitriles (+)-**53c** and (−)-**53c** proved to be more difficult than that for the synthesis of racemic material. An intensively yellow-colored impurity could not be separated by crystallization, but required filtration through neutral Al_2O_3 and activated charcoal. The amidinium salts were conveniently purified by chromatography (SiO_2; $CHCl_3$/MeOH 7:1).

Biological studies showed that the affinity of enantiomer (+)-**1** ($K_i = 7$ nM) to thrombin was nearly twice that of racemic (±)-**2** and showed a 740-fold selectivity for thrombin over trypsin. It was, therefore, 800 times more active than (−)-**1** ($K_i = 5.6$ μM, selectivity 21). There is little doubt that the more potent enantiomer is the one found in the crystal structure of the complex formed between thrombin and (±)-**1** and, consequently, the (1*R*,3a*S*,4*R*,8a*S*,8b*R*)-configuration is assigned to (+)-**1** (for the numbering, see *Fig. 6*).

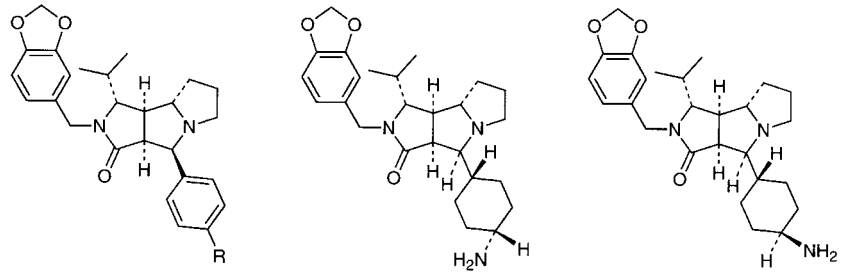
The enantioselectivity in the molecular recognition by thrombin has also been investigated in other studies. Racemic **4** ('NAPAP') gave a K_i value of 6 nM, the more active D-enantiomer a K_i value of 2.1 nM, whereas the L-enantiomer was 670 times less active (1.4 μM) [44], the extent of chiral recognition, therefore, being of similar magnitude as the one observed for **1** in this study.

2.5. *Substitution of the Phenylamidinium Side Chain.* The high affinity of inhibitors **8**–**10** (*Fig. 1*) demonstrates that an amidinium or guanidinium side chain is not necessary for efficient complexation to thrombin. Therefore, we decided to substitute the phenylamidinium side chain in the tricyclic inhibitor (±)-**1** by a series of other residues with a geometry complementary to the S1 pocket and undertook the preparation of compounds (±)-**59a**–**e**, (±)-**60**, and (±)-**61**.

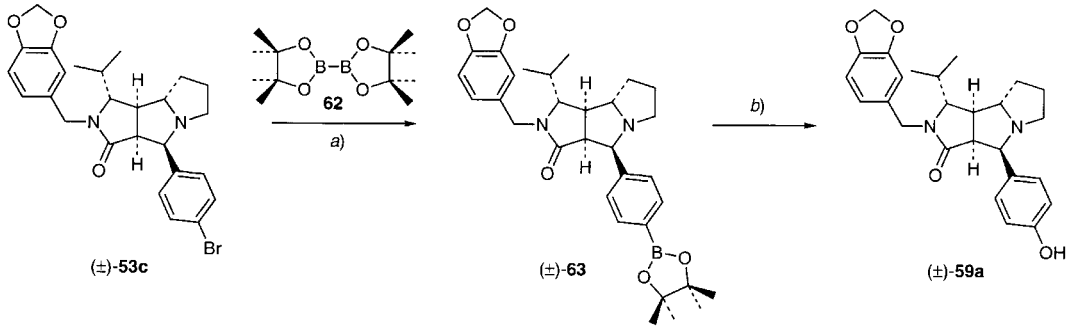
For the preparation of phenol (±)-**59a**, we took advantage of the recent advances in the Pd-catalyzed formation of bonds between aromatic C-atoms and heteroatoms [45–47]. Reaction of bromide (±)-**53c** with bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolanyl) (**62**) [48] in the presence of [$PdCl_2$ (dppf)] (dppf = 1,1-bis(diphenylphosphino)ferrocene) afforded crude boronic ester (±)-**63**, which was converted without further purification with H_2O_2 [49] to phenol (±)-**59a** (*Scheme 10*).

Carboxamide (±)-**59b** was readily obtained by partial hydrolysis of nitrile (±)-**54c** with H_2O_2 (*Scheme 11*). Also, the chemoselective reduction of (±)-**54c** with Li[Et_3BH] [50] afforded benzylamine (±)-**59c** in very high yield (93%).

The synthesis of acetamide (±)-**59d** started with the 1,3-dipolar cycloaddition using *N*-(4-formylphenyl)acetamide to give the *endo* ((±)-**64**) and *exo* ((±)-**65**) cycloadducts, and was completed *via* the sequence (±)-**64** → (±)-**66** → (±)-**67** → (±)-**59d** (*Scheme 12*). Subsequent acidic hydrolysis provided the aniline (±)-**59e**. Alternatively,

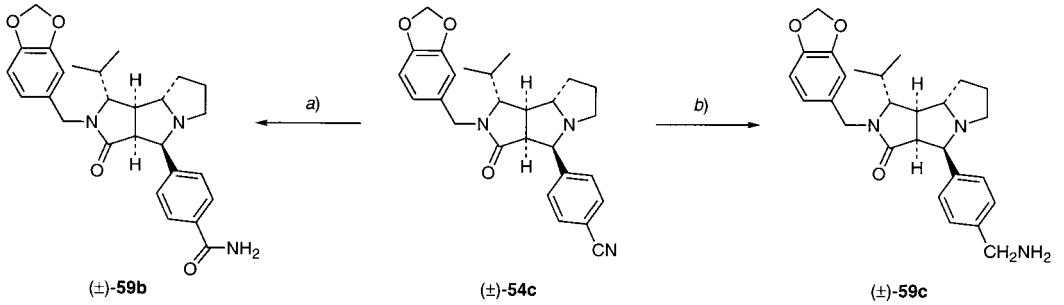


Scheme 10. *Synthesis of Phenol (±)-***59a**



a) [$PdCl_2$(dppf)], KOAc, Me_2SO, 80°, 12 h. *b*) H_2O_2, H_2O, Et_2O, 20°, 3 h; 48% (from (±)-**53c**).

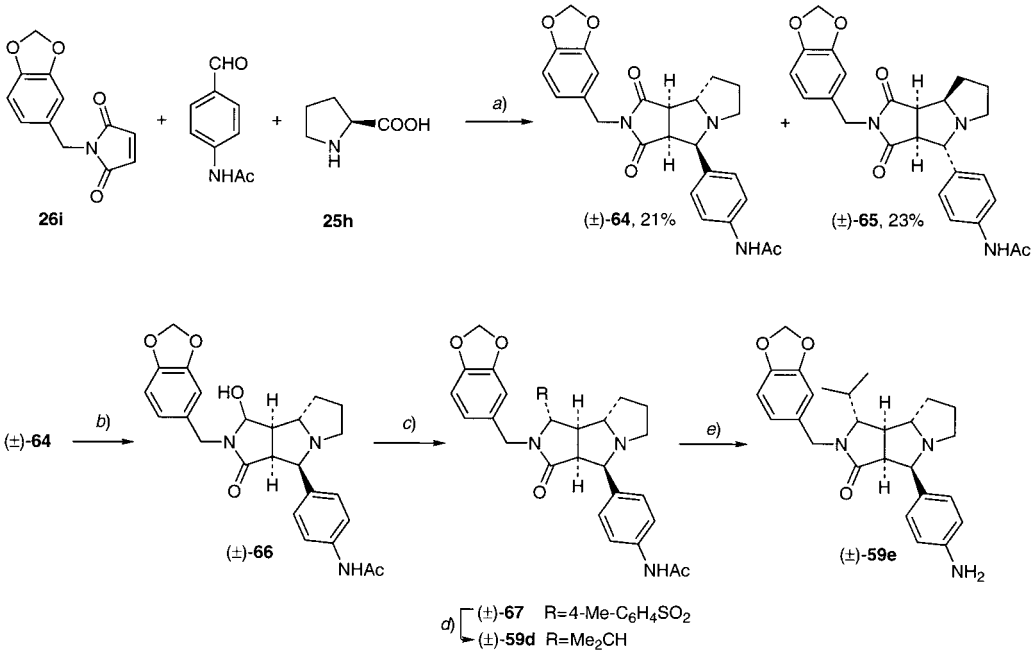
Scheme 11. *Synthesis of Carboxamide (±)-***59b** *and Benzylamine (±)-***59c**



a) 1. H_2O_2, KOH, Me_2CO, H_2O, 20°, 1 h; 2. $Na_2S_2O_3$, H_2O; 61%. *b*) Li[Et_3BH], CH_2Cl_2, −78°, 2 h; 93%.

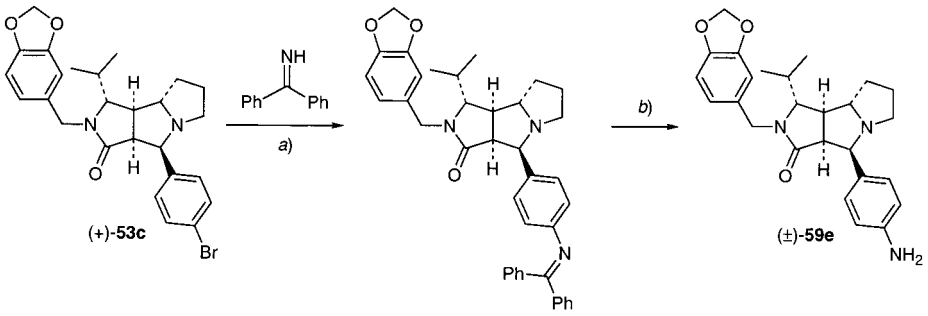
(±)-**59e** was prepared by Pd-catalyzed amination of bromide (±)-**53c** *via* imine intermediate (±)-**67** [51] (*Scheme 13*). Despite much experimentation and the application of other protocols [52], the yield of this conversion could not be raised above 17%.

Scheme 12. *Synthesis of Acetamide (±)-***59d** *and Aniline (±)-***59e**



a) MeCN, Δ, 14 h. *b*) Li[Et_3BH], CH_2Cl_2, −78°, 2 h; 96%. *c*) 4-Toluenesulfinic acid, $CaCl_2$, CH_2Cl_2, 20°, 3 d; 93%. *d*) $Me_2CHMgCl$, $ZnCl_2$, CH_2Cl_2, 20°, 40 h, 60%. *e*) 2N HCl, Δ, 16 h; 60%.

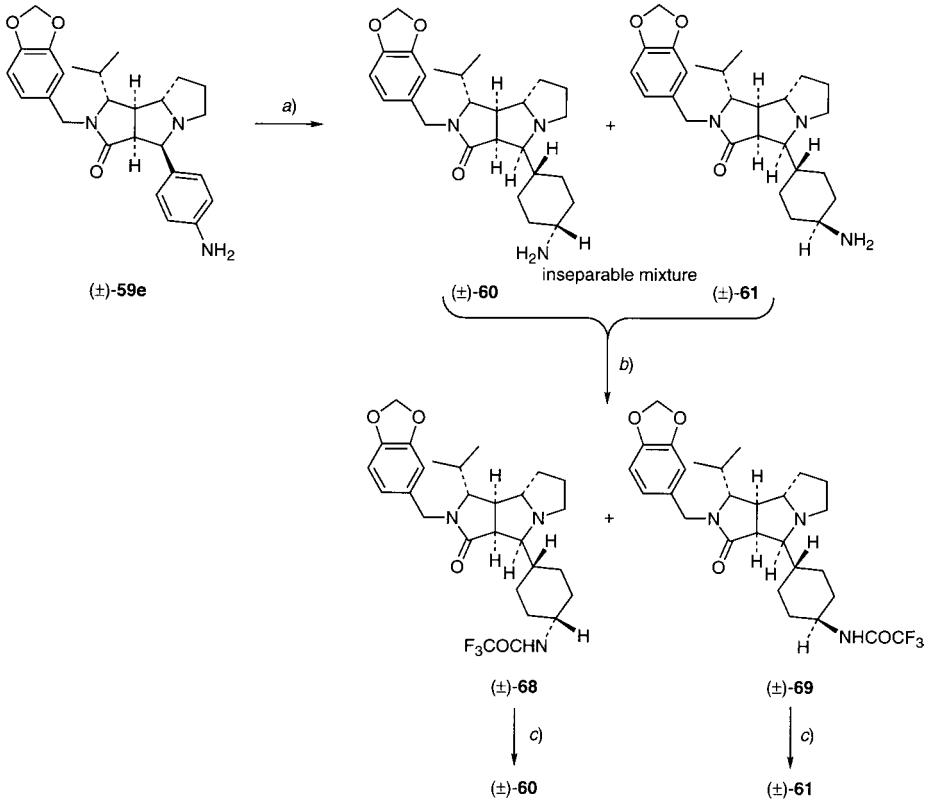
Scheme 13. *Alternative Synthesis of Aniline (±)-***59e**



a) [$Pd(OAc)_2$], (+)-(*R*)-2,2′-bis(diphenylphosphino)-1,1′-binaphthalene ((+)-(*R*)-BINAP), Cs_2CO_3, PhMe, 100°, 5 d. *b*) 2N HCl, THF, 20°, 30 min; 17% (from (±)-**53c**).

For the preparation of the *cis*- and *trans*-cyclohexylamines (±)-**60** and (±)-**61**, aniline (±)-**59e** was hydrogenated in the presence of PtO_2 as catalyst [53][54]. The reaction was highly chemoselective, since neither hydrogenolysis of the *N*-piperonyl residue nor hydrogenation of its aromatic ring were observed, and the mixture of (±)-**60** and (±)-**61** was obtained in 66% yield (*Scheme 14*). Separation of the two diastereoisomeric pairs of enantiomers, however, was exceedingly difficult. Similarly,

Scheme 14. *Synthesis of* cis- *and* trans-*Cyclohexylamines* (±)-**60** *and* (±)-**61**



a) H_2 (2 → 4 bar) PtO_2, 4 d; 67%. *b*) $(CF_3CO)_2O$, CH_2Cl_2, 20°, 2 h, then chromatography (SiO_2; CH_2Cl_2/MeOH 97:3); 25% (±**68**) and 32% ((±)-**69**). *c*) K_2CO_3, MeOH, H_2O, Δ, 3 h; 99% ((±)-**60**) and 68% ((±)-**61**).

attempts to separate an *N*-Boc-protected (Boc = (*tert*-butoxy)carbonyl) mixture of (±)-**60** and (±)-**61** ($(Boc)_2O$, Et_3N, MeOH; 93% [55]) remained unsuccessful. Eventually, the trifluoroacetamides (±)-**68** and (±)-**69** were prepared [56], which could be separated chromatographically by using a very large excess of SiO_2. Subsequent hydrolysis afforded the desired pure cyclohexylamines (±)-**60** and (±)-**61**.

The configuration of (±)-**60** and (±)-**61** was first assigned with the help of ^{1}H-NMR spectroscopy, including {^{1}H,^{1}H}-COSY-2D-NMR spectra. Eventually, crystals of trifluoroacetamide (±)-**69** suitable for X-ray analysis were obtained by diffusion of pentane vapors into a solution of the compound in $CHCl_3$. The compound crystallized as a racemate in the space group $P2_1/c$, and the X-ray crystal-structure analysis (*Fig. 15*,*a*) confirmed the *trans*-configuration, which had been predicted by the ^{1}H-NMR spectroscopic analysis. The crystal lattice shows a layered structure with two opposite enantiomers forming two H-bonds (N···O distance = 2.86 Å) between the N–H groups of their trifluoroacetamide moieties and the C=O groups of their pyrrolidone rings (*Fig. 15*,*b*).

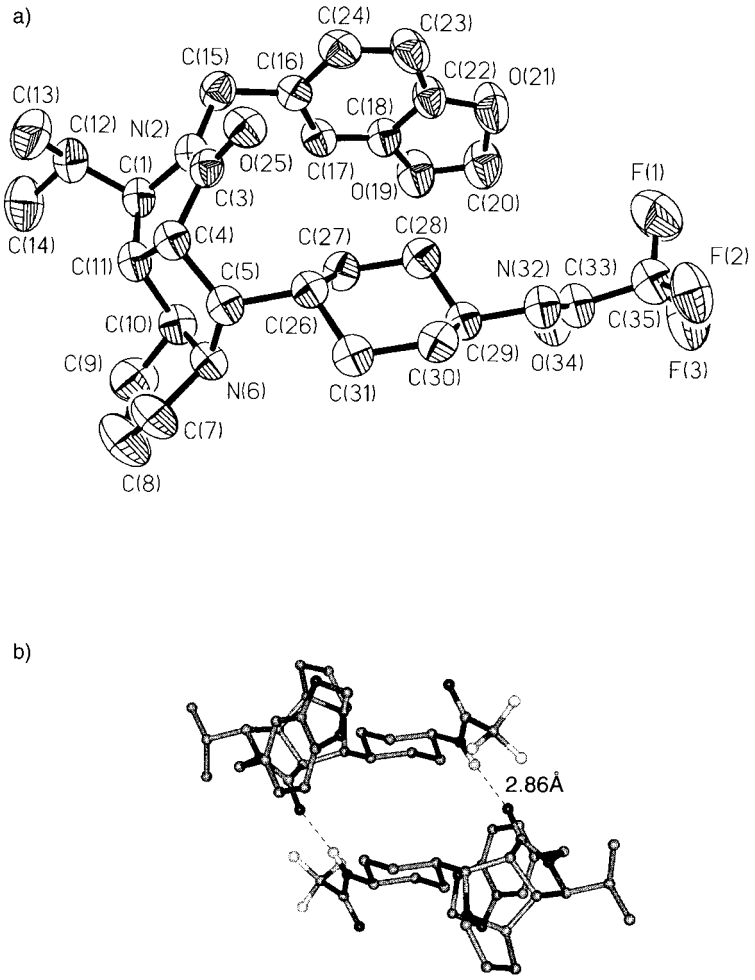


Fig. 15. a) *X-Ray crystal structure of (±)-***69**. Arbitrary numbering. Atomic displacement parameters obtained at 295 K are drawn at the 50% probability level. b) *H-Bonding between pairs of enantiomers in the crystal packing of (±)-***69** (distance N ··· O = 2.86 Å).

Biological studies showed that the substitution of the phenylamidinium moiety in (±)-**1** by other phenyl derivatives (in (±)-**59a – e**) or by cyclohexylamines (in (±)-**60** and (±)-**61**) dramatically reduced the inhibitory power for thrombin, as well as for other serine proteases. Within the limits of detection ($K_i \leq 68.3$ (trypsin), 35.1 (thrombin), 33.3 (plasmin), 62.0 (kallikrein), 76.4 (aPC), 69.4 (factor VII_a), 75.4 (factor X_a), 55.8 (factor XI_a)), none of these compounds showed any affinity for the mentioned serine proteases, except benzylamine (±)-**59c**, which inhibited thrombin with $K_i = 17.0$ μM. This came as quite a surprise, given that all these compounds – according to computer modeling – fit very well into the active site of thrombin and that other classes of inhibitors, which do not direct an amidinium or guanidium side chain into the S1 pocket, such as **7 – 10** (*Fig. 1*), were found to be efficient binders of thrombin.

Substitution of the amidinium group in (±)-**1** by a $CH_2NH_3^+$ group in (±)-**59c** (protonation of the benzylamine residue can be assumed under the conditions of the assay) raises the inhibitory constant more than 1000-fold. Since similar binding geometries of the two compounds in the active site of thrombin can be assumed, the difference in incremental free enthalpy contribution from the stronger salt bridge between Asp 189 and the amidinium residue of (±)-**1** and the weaker one with the primary ammonium group of (±)-**59c** amounts to more than 4 kcal mol^{-1}. We are, of course, aware of the limitations of such a comparison, which ignores any differences in (solvation) free enthalpy of the two inhibitors in the unbound state. The unsuccessful attempts of this study to substitute the phenylamidinium residue in (±)-**1** demonstrate that selective molecular-recognition processes are effective at the thrombin active site. Apparently, this selectivity is particularly strong if the inhibitors are conformationally rigid, as is the case for the compounds described in this work.

3. Conclusions. – In the past decade, methods of modern drug research have changed considerably. The availability of high-resolution X-ray structures of therapeutically relevant enzymes offers a unique opportunity for the *de novo* design of nonpeptidic inhibitors. In principle, it is possible to design novel inhibitors solely by careful analysis of the enzyme's binding site with respect to important enzyme-inhibitor interactions. This *molecular-recognition approach* can be considered as an alternative to the traditional screening methods for lead structure finding. Enzymes that are best suited for such a rational design approach are those with rigid, well-defined binding pockets in the active site. Thrombin, a trypsin-like serine protease, which is involved in the blood-coagulation process, meets these requirements.

A series of novel thrombin inhibitors was designed based on the knowledge of the three-dimensional structure of thrombin. They contain nonpeptidic, bi- or tricyclic core structures with attached side chains in order to reach the three main binding pockets present in the active site of the enzyme. The rigid scaffold was chosen to prevent a hydrophobic collapse of the side chains and preorganize the compounds for binding to thrombin. The key step in the synthesis of these inhibitors in racemic form is the 1,3-dipolar cycloaddition between *in situ* prepared azomethine ylides and *N*-substituted maleimides. Careful optimization of the side chains and enantiomer resolution led to a compound ((+)-**1**) with a K_i value of 7 nM for thrombin inhibition and an 800-fold selectivity for thrombin over trypsin. This potent and selective inhibitor can be considered to mimic the binding mode of the natural thrombin substrate fibrinogen. Fibrinogen binds with the Ph group of a phenylalanine (piperonyl in (+)-**1**) to the distal D pocket, with the i-Pr group of a valine (i-Pr in (+)-**1**) to the proximal P pocket, and with a guanidinium side chain of an arginine residue (phenylamidinium group in (+)-**1**) to the selectivity S1 pocket of thrombin.

Molecular recognition by thrombin was found to be highly selective. For high affinity and selectivity, the correct size and shape of the rigid central scaffold and the hydrophobic group penetrating the P pocket were of crucial importance. Furthermore, only a phenylamidinium side chain was found to be complementary to the S1 pocket with its buried aspartate side chain; aromatic and aliphatic rings bearing OH or NH_2 groups were not effectively bound in this pocket. We explain this remarkable selectivity, which contrasts with other findings in the recent literature, with the high

conformational rigidity of the new class of inhibitors. A good fit between a rigid active site (such as in thrombin) and a highly preorganized inhibitor seems to require a particularly high degree of stereoelectronic complementarity.

A larger number of X-ray crystal-structure analyses of free inhibitors are reported in this paper. These structural analyses confirmed the high degree of preorganization of these compounds in the unbound state: their central scaffolds with the side chains for incorporation into the three binding pockets adopt conformations nearly identical to those seen in X-ray crystal structures of complexes with thrombin [16][22]. Since all inhibitors prefer similar modes of association to thrombin, detailed information on the strength of individual intermolecular bonding interactions and their incremental contribution to the overall free enthalpy of complexation were generated in correlative binding and X-ray structural studies. Consequently, this study demonstrates that defined mutations in highly preorganized inhibitors provide an attractive alternative to site-directed mutagenesis in exploring molecular recognition phenomena at enzyme active sites.

Experimental Part

General. Solvents and reagents were reagent-grade, purchased from commercial suppliers, and used without further purification unless otherwise stated. The following compounds were prepared according to literature procedures: *4-bromophenylalanine* (**12**) [57], *N*-substituted maleimides [58], 4-toluenesulfinic acid [59], cyclopropylmagnesium bromide [60], and methyl (−)-D-mandelate [61]. THF and Et_2O were freshly distilled from sodium benzophenone ketyl, CH_2Cl_2 from CaH_2. Anh. Me_2SO over molecular sieves was purchased from *Fluka*. Evaporation *in vacuo* was conducted at H_2O-aspirator pressure. If not mentioned otherwise, all products were dried under high vacuum (0.05 Torr) before analytical characterization. Column chromatography (CC): SiO_2 *60* (230–400 mesh, 0.040–0.063 mm) from *Fluka*, *Merck*, or *Macherey-Nagel*. Flash chromatography (FC): SiO_2 *60* at 0.4 bar pressure or SiO_2 *H* at 1 bar pressure. Reversed-phase CC: *Lichroprep RP-18* (230–400 mesh, 0.040–0.063 mm) from *Merck*. TLC: SiO_2 *60* F_{245}, *Merck*, visualization by UV light at 245 mm or by staining with a soln. of $(NH_4)_6Mo_7O_{24}\cdot 6H_2O$ (20 g) and $Ce(SO_4)_2$ (0.4 g) in 10% aq. H_2SO_4 soln. (400 ml). M.p.: *Büchi SMP-20* or *B-540*; uncorrected. Optical rotations: *Perkin Elmer 241* polarimeter, 1-dm cell, $\lambda = 589$ nm (Na D-line). IR Spectra [cm^{-1}]: *Perkin-Elmer 1600-FT IR* or *Nicolet 7199-FT-IR* spectrometer, spectra in soln. were recorded in *IR-CHCl*$_3$ from *Fluka*. ^1H- and ^{13}C-NMR Spectra: *Bruker AC 250*, *WM-300*, *AMX 500*, and *Varian Gemini 300* or *200* at 296 K, with solvent peak as reference. In some ^1H- and ^{13}C-NMR spectra ((±)-**23j**, (±)-**29k**, (±)-**22a**, (±)-**22f**–**k**, (±)-**30k**, (±)-**42**, (±)-**55a**,**b**, (±)-**1**) resonances are buried under the solvent peak. MS (*m*/*z* (%)): EI: *VG TRIBRID* spectrometer at 70 eV; FAB: *VG ZAB2-SEQ* spectrometer with 3-nitrobenzyl alcohol (NOBA) as matrix; ESI: *Perkin-Elmer Sciex API III* spectrometer. Molecular ions (M^+) reported for phenylamidinium salts refer to the corresponding phenylamidine derivatives. Elemental analyses were performed by the *Mikrolabor* at the *Laboratorium für Organische Chemie, ETH-Zürich*. The nomenclature was generated with the computer programs *AUTONOM* (*Beilstein*) and *ACD-Name* (*ACD/Labs*).

Determination of Inhibition Constants. The affinity of thrombin inhibitors was determined according to [11][62] (chromogenic substrate S-2238). An exhaustive protocol of the binding assay identical to the one used in this study is provided in [11].

General Procedure A for the 1,3-Dipolar Cycloaddition. A mixture of α-amino acid (10 mmol), 4-formylbenzonitrile or 4-bromobenzaldehyde (10 mmol), and *N*-substituted maleimide (10 mmol) in DMF (30 ml) was heated to 80° for 5–16 h. The solvent was evaporated *in vacuo* and the residue purified by CC (SiO_2; hexane/AcOEt/Et_3N 49.5:4 9.5:1 or 66:33:1).

General Procedure B for the Eschweiler-Clarke *Methylation*. A mixture of cycloadduct (9 mmol), 85% aq. HCOOH soln. (90 mmol) and 35% aq. HCHO soln. (30 mmol) was heated to 100° for 6 h. After cooling, 1N NaOH (50 ml) was added, and the mixture was extracted with CH_2Cl_2 (4×). The org. phase was dried (Na_2SO_4) and evaporated, and the residue purified by CC (SiO_2; hexane/AcOEt/Et_3N 74:25:1).

General Procedure C for the N-*Acetylation*. To a soln. of cycloadduct (10 mmol) and pyridine (20 mmol) in MeCN (10 ml), Ac_2O was added dropwise under cooling with ice. The mixture was stirred for 1.5 h at 20°, then

poured into sat. aq. NaCl soln. and extracted with CH_2Cl_2. The org. layer was dried (Na_2SO_4), evaporated, and the residue was purified by CC (SiO_2; AcOEt/hexane 50:50).

General Procedure D for the Conversion of an Aryl Bromide to the Corresponding Aryl Nitrile. A suspension of the aryl bromide (5 mmol) and CuCN (20 mmol) in DMF (30 ml, purged with Ar) was heated to reflux under Ar for 17–30 h. The solvent was partially removed (20 ml), then CH_2Cl_2 (30 ml) and conc. aq. NH_4OH soln. (10 ml) were added. The mixture was stirred for 1 h at 20°, the blue aq. phase was removed, and the org. phase was washed with conc. aq. NH_4OH soln. (2×) and H_2O. The combined aq. phases were extracted with CH_2Cl_2, and the combined org. phase was dried (Na_2SO_4) and evaporated *in vacuo* to give a residue, which was purified by CC (SiO_2; hexane/AcOEt/Et_3N 49.5:49.5:1 or 66:33:1).

General Procedure E for the Preparation of Amidinium Salts by the Pinner *Reaction. Method A:* Dry HCl gas was bubbled at 0° for 10 min into a soln. of nitrile (2 mmol) in dry $CHCl_3$ (5 ml) and dry MeOH (1 ml). After storing at 4° for 24 h, Et_2O was added and the precipitate formed was collected by filtration and dried in high vacuum. $CHCl_3$ (20 ml) and 5% aq. $NaHCO_3$ soln. (8 ml) were added, the phases were rapidly separated, and the aq. layer was extracted with $CHCl_3$ (2×). The combined org. phases were dried (Na_2SO_4) and evaporated. The residue was dissolved in MeOH (7 ml), a soln. of NH_4Cl (150 mg) in H_2O (1.5 ml) was added, and the mixture was stirred for 3.5 h at 65°. After cooling, acetone was added to precipitate NH_4Cl, which was collected by filtration. The residue obtained by evaporation *in vacuo* was dissolved in EtOH, and the amidinium salt was slowly precipitated with Et_2O.

Method B: Dry HCl was bubbled at 0° for 10 min into a soln. of the nitrile (2 mmol) in dry $CHCl_3$ (5 ml) and dry MeOH (1 ml). The mixture was stored at 4° for 24 h, then Et_2O was added. The precipitate formed was isolated by filtration, dried in high vacuum, and redissolved in MeOH (5 ml). A methanolic soln. of NH_3 was slowly added until the NH_3 odor persisted, then the mixture was stirred for 3.5 h at 65°. After cooling, NH_4Cl was precipitated with acetone and removed by filtration. The solvent was evaporated *in vacuo*, the residue dissolved in EtOH, and the amidinium salt was slowly precipitated with Et_2O.

General Procedure F for the Substitution of a Ts Group by an Alkyl or Aryl Residue. To a soln. of $ZnCl_2$ (4.40 mmol; as soln. in Et_2O or THF) in dry CH_2Cl_2 (20 ml), a soln. of *Grignard* reagent (8.00 mmol) in Et_2O or THF was added and the mixture stirred under Ar for 30 min. A soln. of sulfone (4.00 mmol) in dry CH_2Cl_2 (20 ml) was slowly added under ice cooling, and the mixture was stirred for 13–36 h. After addition of 1M HCl, the mixture was neutralized with aq. $NaHCO_3$ soln. and extracted with CH_2Cl_2. The org. phase was dried (Na_2SO_4), the solvent was evaporated *in vacuo*, and the residue was purified by CC (SiO_2; hexane/AcOEt/Et_3N 49.5:49.5:1 or 66:33:1).

*(3a*RS*,6*SR*,6a*SR*)-2-Benzyl-6-(4-bromobenzyl)-4,4-dimethyl-3a,4,5,6-tetrahydro-1*H*,3*H*-pyrrolo[3,4-*c*]pyrrole-1,3-dione* ((±)-**13**) *and (3a*RS*,6*RS*,6a*SR*)-2-Benzyl-6-(4-bromobenzyl)-4,4-dimethyl-3a,4,5,6-tetrahydro-1*H*,3*H*-pyrrolo[3,4-*c*]pyrrole-1,3-dione* ((±)-**14**). A mixture of *4-bromophenylalanine* (**12**) (8.83 g, 36.2 mmol), acetone (4.74 g, 81.7 mmol), and *N*-benzylmaleimide (7.00 g, 37.43 mmol) in PhMe (140 ml) and activated molecular sieves (4 Å) was heated to reflux for 68 h. The solvent was evaporated *in vacuo*, and the residue was purified by CC (SiO_2; hexane/AcOEt/Et_3N 49.5:49.5:1). (±)-**13**: Yield: 3.88 g (25%). Colorless oil which crystallized overnight after addition of a small quantity of MeOH to give colorless needles. M.p. 142–143°. IR (KBr): 1763, 1687, 1488, 1423, 1396, 1337, 1174. ^{1}H-NMR (200 MHz, $CDCl_3$): 1.20 (*s*, 3 H); 1.24 (*s*, 3 H); 2.49 (*dd*, *J* = 9.7, 14.4, 1 H); 2.89 (*d*, *J* = 8.8, 1 H); 3.24 (*m*, 2 H); 3.64 (*m*, 1 H); 4.67 (*s*, 2 H); 7.15 (*d*, *J* = 8.3, 2 H); 7.35 (*m*, 7 H). ^{13}C-NMR (50 MHz, $CDCl_3$): 26.3; 29.1; 37.2; 42.4; 48.9; 54.8; 59.4; 60.6; 120.2; 127.9; 128.5; 128.9; 130.7; 131.8; 135.9; 138.7; 176.2; 176.4. FAB-MS: 427.1 (58, MH^+), 257.1 (66, $[M - BrC_6H_4CH_2]^+$), 240.0 (8), 90.9 (58, $[C_7H_7]^+$). Anal. calc. for $C_{22}H_{23}BrN_2O$ (427.34): C 61.83, H 5.42, Br 18.70, N 6.56, O 7.49; found: C 61.71, H 5.32, Br 18.53, N 6.57, O 7.74. X-ray analysis: see *Fig. 3*.

*Data of (±)-***13**: Yield: 2.12 g (14%). Colorless oil. ^{1}H-NMR (200 MHz, $CDCl_3$): 0.89 (*s*, 3 H); 1.36 (*s*, 3 H); 2.77 (*dd*, *J* = 8.3, 13.7, 1 H); 3.05 (*m*, 3 H); 3.58 (*m*, 1 H); 4.59 (*s*, 2 H); 7.13 (*d*, *J* = 8.3, 2 H); 7.33 (*m*, 7 H). FAB-MS: 427.1 (88, MH^+), 257.1 (89, $[M - BrC_6H_4CH_2]^+$), 91.0 (100, $[C_7H_7]^+$).

*(3a*RS*,6*SR*,6a*SR*)-2-Benzyl-6-(4-bromobenzyl)-4,4,5-trimethyl-3a,4,5,6-tetrahydro-1*H*,3*H*-pyrrolo[3,4-*c*]pyrrole-1,3-dione* ((±)-**15**). *General Procedure B*, starting from (±)-**13** gave (±)-**15** in 81% yield. Yellowish oil. IR ($CHCl_3$): 1701, 1488, 1433, 1400, 1348. ^{1}H-NMR (200 MH7, $CDCl_3$): 1.01 (*s*, 3 H); 1.21 (*s*, 3 H); 2.16 (*s*, 3 H); 2.73 (*m*, 2 H); 3.04 (*m*, 3 H); 4.63 (*s*, 2 H); 7.35 (*m*, 9 H). ^{13}C-NMR (50 MHz, $CDCl_3$): 19.1; 24.5; 32.3; 33.9; 42.0; 45.5; 52.9; 62.6; 65.3; 119.7; 127.4; 128.1; 128.3; 131.0; 135.5; 138.5; 176.1; two peaks missing due to signal overlap. FAB-MS: 440.9 (40, MH^+), 271.0 (100, $[M - BrC_6H_4CH_2]^+$), 110.0 (26), 90.9 (42, $[C_7H_7]^+$).

*(1*SR*,3a*RS*,6a*SR*)-4-[(5-Benzyl-2,3,3-trimethyl-4,6-dioxoperhydropyrrolo[3,4-*c*]pyrrol-1-yl)methyl]benzonitrile (*(±)-**16**). *General Procedure D*, starting from (±)-**15** gave (±)-**16** in 63% yield. Yellowish oil. IR ($CHCl_3$): 2230, 1701, 1608, 1506, 1433, 1399, 1348. ^{1}H-NMR (200 MHz, $CDCl_3$): 1.01 (*s*, 3 H); 1.21 (*s*, 3 H); 2.15 (*s*, 3 H);

2.73 (*d*, *J* = 7.7, 1 H); 3.05 (*m*, 4 H); 4.61 (*s*, 2 H); 7.30 (*m*, 5 H); 7.57 (*s*, 4 H). ^{13}C-NMR (50 MHz, $CDCl_3$): 19.6; 24.9; 32.7; 35.3; 42.5; 45.9; 53.3; 63.2; 65.4; 110.3; 119.4; 128.1; 128.7; 128.9; 130.6; 132.4; 136.1; 145.8; 176.7; one peak missing due to signal overlap. FAB-MS: 388.2 (58, MH$^+$), 271.1 (100, $[M - CNC_6H_4CH_2]^+$), 91.0 (42).

*(1*S*R,3a*R*S,6a*S*R)-4-[(5-Benzyl-2,3,3-trimethyl-4,6-dioxoperhydropyrrolo[3,4-c]pyrrol-1-yl)methyl]benzamidine Hydrochloride* ((±)-**11**). *General Procedure E* (*Method A*), starting from (±)-**16** afforded (±)-**11** in 57% yield. Yellowish powder. M.p. 205–207°. IR (KBr): 1770, 1701, 1672, 1612, 1540, 1493, 1430, 1398, 1343, 1180. ^{1}H-NMR (250 MHz, $(CD_3)_2SO$): 0.98 (*s*, 3 H); 1.10 (*s*, 3 H); 2.07 (*s*, 3 H); 3.04 (*m*, 5 H); 4.53 (*s*, 2 H); 7.26 (*m*, 5 H); 7.67, 7.79 (*AA′BB′*, *J* = 8.3, 4 H); 9.18 (*s*, 2 H); 9.35 (*s*, 2 H). ^{13}C-NMR (62.5 MHz, $(CD_3)_2SO$): 19.2; 24.6; 32.3; 34.7; 41.3; 45.6; 53.0; 62.2; 63.9; 125.3; 127.2; 127.3; 127.8; 128.4; 129.6; 136.1; 146.7; 165.5; 176.5; 176.8. ESI-MS: 405.4 (100, MH$^+$). HR-DEI-MS: 405.2267 (MH$^+$, $C_{24}H_{29}N_4O_2$; calc. 405.2290).

*(3a*S*R,4*R*S,6*S*R,6a*R*S)-2-Benzyl-4-(4-bromophenyl)-6-methyl-3a,4,5,6-tetrahydro-1*H*,3*H*-pyrrolo[3,4-c]pyrrole-1,3-dione* ((±)-**18**). *General Procedure A*, starting from **17**, alanine, and *N*-benzylmaleimide gave (±)-**18** in 47% yield. Colorless crystals. M.p. 170–172° ($CHCl_3$/MeOH). IR (KBr): 3317, 1698, 1397, 1349, 1170. ^{1}H-NMR (200 MHz, $CDCl_3$): 1.31 (*d*, *J* = 6.7, 3 H); 2.99 (*d*, *J* = 10.9, 1 H); 3.37 (*m*, 1 H); 4.07 (*q*, *J* = 6.6, 1 H); 4.48, 4.56 (*AB*, *J* = 14.0, 2 H); 4.67 (*d*, *J* = 8.7, 1 H); 6.96, 7.27 (*AA′BB′*, *J* = 8.5, 4 H); 7.31 (*m*, 5 H). ^{13}C-NMR (50 MHz, $CDCl_3$): 21.0; 42.7; 49.2; 52.9; 55.9; 61.3; 121.9; 128.3; 128.9; 129.3; 129.4; 131.6; 136.4; 137.5; 175.6; 178.6. FAB-MS: 799.0 (10), 399.0 (100, MH$^+$), 210.9 (29), 90.9 (61, $[C_7H_7]^+$). Anal. calc. for $C_{20}H_{19}BrN_2O_2$ (399.29): C 60.16, H 4.80, Br 20.01, N 7.02, O 8.01; found: C 60.14, H 4.76, Br 19.84, N 7.04, O 8.11.

*(3a*S*R,4*R*S,6*S*R,6a*R*S)-2-Benzyl-4-(4-bromophenyl)-5,6-dimethyl-3a,4,5,6-tetrahydro-1*H*,3*H*-pyrrolo[3,4-c]pyrrole-1,3-dione* ((±)-**20**). *General Procedure B*, starting from (±)-**18** gave (±)-**20** in 96% yield. Colorless crystals. M.p. 166–168° (AcOEt/hexane). IR (KBr): 1705, 1397, 1342. ^{1}H-NMR (200 MHz, $CDCl_3$): 1.13 (*d*, *J* = 6.7, 3 H); 2.04 (*s*, 3 H); 2.95 (*d*, *J* = 7.8, 1 H); 3.40 (*m*, 1 H); 3.93 (*m*, 2 H); 4.47, 4.55 (*AB*, *J* = 13.8, 2 H); 6.81, 7.21 (*AA′BB′*, *J* = 8.4, 4 H); 7.33 (*m*, 5 H). ^{13}C-NMR (50 MHz, $CDCl_3$): 11.7; 34.8; 42.8; 50.0; 52.0; 60.8; 67.1; 121.9; 128.3; 128.9; 129.8; 129.9; 131.8; 136.1; 136.5; 175.9; 178.8. FAB-MS: 827.1 (3), 413.1 (100, MH$^+$), 397.1 (31, $[M - CH_3]^+$), 91.0 (46, $[C_7H_7]^+$). Anal. calc. for $C_{21}H_{21}BrN_2O_2$ (413.31): C 61.03, H 5.12, Br 19.33, N 6.78, O 7.74; found: C 61.07, H 5.09, Br 19.27, N 6.78, O 7.78.

*(1*R*S,3*S*R,3a*R*S,6a*S*R)-4-(5-Benzyl-2,3-dimethyl-4,6-dioxoperhydropyrrolo[3,4-c]pyrrol-1-yl)benzonitrile* ((±)-**21**). *General Procedure D*, starting from (±)-**20** gave (±)-**21** in 85% yield. Colorless crystals. M.p. 188–190° (AcOEt). IR (KBr): 2225, 1702, 1399, 1346. ^{1}H-NMR (200 MHz, $CDCl_3$): 1.16 (*d*, *J* = 6.7, 3 H); 2.05 (*s*, 3 H); 2.99 (*d*, *J* = 7.9, 1 H); 3.44 (*m*, 1 H); 3.99 (*m*, 2 H); 4.41, 4.58 (*AB*, *J* = 13.8, 2 H); 7.02 (*d*, *J* = 8.3, 2 H); 7.34 (*m*, 7 H). ^{13}C-NMR (50 MHz, $CDCl_3$): 11.8; 34.8; 42.9; 50.1; 52.1; 61.0; 67.3; 111.9; 119.2; 128.4; 128.9; 129.8; 129.9; 132.5; 136.0; 143.1; 175.6; 178.5. FAB-MS: 359.7 (100, MH$^+$), 343.7 (41, $[M - CH_3]^+$), 106.8 (37), 90.8 (56, $[C_7H_7]^+$). Anal. calc. for $C_{22}H_{21}N_3O_2$ (359.43): C 73.52, H 5.89, N 11.69, O 8.90; found: C 73.00, H 5.89, N 11.69, O 8.91. X-Ray analysis: see *Fig. 4*.

*(1*R*S,3*S*R,3a*R*S,6a*S*R)-4-(5-Benzyl-2,3-dimethyl-4,6-dioxoperhydropyrrolo[3,4-c]pyrrol-1-yl)benzamidine Hydrochloride* ((±)-**19**). *General Procedure E* (*Method A*), starting from (±)-**21** afforded (±)-**19** in 70% yield. Colorless powder. M.p. 201–203°. IR (KBr): 1705, 1671, 1613, 1488, 1400, 1348. ^{1}H-NMR (250 MHz, $(CD_3)SO$): 1.11 (*d*, *J* = 6.7, 3 H); 1.97 (*s*, 3 H); 3.20 (*d*, *J* = 7.9, 1 H); 3.66 (*m*, 1 H); 3.77 (*q*, *J* = 6.7, 1 H); 4.16 (*d*, *J* = 8.4, 1 H); 4.42 (*m*, 2 H); 7.22 (*m*, 4 H); 7.35 (*m*, 3 H); 7.69 (*d*, *J* = 8.4, 2 H); 9.36 (*s*, 2 H); 9.47 (*s*, 2 H). ^{13}C-NMR (62.5 MHz, $(CD_3)_2SO$): 11.5; 34.5; 41.7; 49.7; 51.3; 60.3; 66.2; 126.7; 127.6; 127.7; 128.2; 128.4; 128.6; 136.0; 144.5; 165.4; 175.6; 178.5. ESI-MS: 377.4 (100, MH$^+$).

*(1*R*S,3*S*R,3a*R*S,6a*S*R)-4-(5-Benzyl-3-methyl-4,6-dioxooctahydropyrrolo[3,4-c]pyrrol-1-yl)benzonitrile* ((±)-**23a**). *General Procedure A*, starting from **24**, **25a**, and **26a** gave (±)-**23a** in 71% yield. Colorless crystals (MeOH). M.p. 169–170°. IR (KBr): 3315, 2220, 1696, 1432, 1399, 1347, 1173. ^{1}H-NMR (250 MHz, $(CD_3)_2SO$): 1.22 (*d*, *J* = 6.6, 3 H); 3.12 (*d*, *J* = 7.9, 2 H); 3.60 (*m*, 1 H); 3.78 (*q*, *J* = 6.7, 1 H); 4.38 (*s*, 2 H); 4.79 (*d*, *J* = 8.5, 1 H); 7.15 (*m*, 2 H); 7.31 (*m*, 3 H); 7.38, 7.60 (*AA′BB′*, *J* = 8.3, 4 H). ^{13}C-NMR (62.5 MHz, $(CD_3)_2SO$: 20.1; 41.4; 49.0; 52.4; 55.3; 60.3; 109.5; 119.0; 127.4; 127.6; 128.3; 128.5; 131.4; 136.0; 145.7; 175.6; 178.6. ESI-MS: 346.3 (45, MH$^+$), 279.3 (26), 267.2 (18), 199.3 (13), 171.4 (23), 158.2 (28), 149.2 (25), 134.1 (17). Anal. calc. for $C_{21}H_{19}N_3O_2$ (345.40): C 73.03, H 5.54, N 12.17; found: C 72.78, H 5.57, N 12.08.

*(1*R*S,3*S*R,3a*R*S,6a*S*R)-4-(5-Butyl-3-methyl-4,6-dioxooctahydropyrrolo[3,4-c]pyrrol-1-yl)benzonitrile* ((±)-**23c**). *General Procedure A*, starting from **24**, **25a**, and **26c** afforded (±)-**23c** in 65% yield. Yellowish oil. IR ($CHCl_3$): 3255, 2210, 1764, 1700, 1600, 1402, 1374, 1345, 1192. ^{1}H-NMR (250 MHz, $(CD_3)_2SO$): 0.83 (*t*, *J* = 7.2, 3 H); 1.21 (*m*, 4 H); 1.21 (*d*, *J* = 6.7, 3 H); 3.02 (*m*, 2 H); 3.18 (*t*, *J* = 6.7, 2 H); 3.52 (*m*, 1 H); 3.76 (*q*, *J* = 6.7, 1 H); 4.78 (*m*, 1 H); 7.48, 7.73 (*AA′BB′*, *J* = 8.3, 4 H). ^{13}C-NMR (62.5 MHz, $(CD_3)_2SO$): 13.4; 19.3; 20.1; 29.2; 37.6; 49.0; 52.3; 55.3; 60.3; 109.6; 119.0; 128.4; 131.5; 145.9; 175.7; 178.7. EI-MS: 311 (12, M^+), 296 (9, $[M - Me]^+$), 183 (8), 169 (13), 158 (100).

*(1*RS,*3*SR,*3a*RS,*6a*SR*)-4-[5-Benzyl-3-(2-methylpropyl)-4,6-dioxooctahydropyrrolo[3,4-*c*]pyrrol-1-yl]benzonitrile* ((±)-**23f**). *General Procedure A*, starting from **24**, **25f**, and **26a** provided (±)-**23f** in 61% yield. Colorless prisms. M.p. 152–153° (MeOH). IR (KBr): 3323, 2227, 1773, 1699, 1435, 1399, 1345, 1173. ^{1}H-NMR (250 MHz, $(CD_3)_2SO$): 0.94 (*m*, 6 H); 1.41 (*m*, 2 H); 1.71 (*m*, 1 H); 3.04 (*d*, *J* = 4.9, 1 H); 3.17 (*d*, *J* = 7.7, 1 H); 3.56 (*t*, *J* = 8.1, 1 H); 3.65 (*m*, 1 H); 4.38 (*s*, 2 H); 4.71 (*m*, 1 H); 7.14 (*m*, 2 H); 7.30 (*m*, 3 H); 7.37, 7.60 (*AA′BB′*, *J* = 8.2, 4 H). ^{13}C-NMR (62.5 MHz, $(CD_3)_2SO$): 22.3; 22.5; 24.5; 41.5; 42.0; 49.2; 51.0; 58.2; 60.7; 109.5; 119.0; 127.4; 127.7; 128.3; 128.4; 131.4; 136.0; 145.6; 175.6; 178.8. EI-MS: 387 (4, M^+), 330 (100, $[M - Me_2CHCH_2]^+$), 169 (48), 91 (57). Anal. calc. for $C_{24}H_{25}N_3O_2$ (387.48): C 74.39, H 6.50, N 10.84; found: C 74.11, H 6.40, N 10.80.

*(3a*SR,*4*RS,*8a*SR,*8b*RS*)-4-(2-Benzyl-1,3-dioxoperhydropyrrolo[3,4-*a*]pyrrolizin-4-yl)benzonitrile* ((±)-**23h**). *General Procedure A*, starting from **24**, **25h**, and **26a** gave (±)-**23h** in 32% yield. Colorless crystals. M.p. 191–193° (MeOH). IR (KBr): 2225, 1773, 1705, 1607, 1398, 1347, 1313, 1174. ^{1}H-NMR (250 MHz, $(CD_3)_2SO$): 1.67 (*m*, 2 H); 1.98 (*m*, 2 H); 2.46 (*m*, 1 H); 2.75 (*m*, 1 H); 3.47 (*d*, *J* = 8.0, 1 H); 3.57 (*m*, 1 H); 3.76 (*t*, *J* = 8.4, 1 H); 4.22 (*d*, *J* = 8.8, 1 H); 4.41 (*s*, 2 H); 7.15 (*d*, *J* = 7.3, 2 H); 7.35 (*m*, 3 H); 7.40, 7.65 (*AA′BB′*, *J* = 8.1, 4 H). ^{13}C-NMR (62.5 MHz, $(CD_3)_2SO$): 23.2; 29.2; 41.6; 48.8; 50.4; 50.6; 67.4; 67.7; 109.0; 119.1; 127.6; 127.7; 128.5; 129.2; 131.7; 136.1; 145.1; 175.5; 178.3. EI-MS: 371 (7, M^+), 184 (100), 156 (11), 91 (12, $[C_7H_7]^+$). Anal. calc. for $C_{23}H_{21}N_3O_2$ (371.44): C 74.37, H 5.70, N 11.31; found: C 74.15, H 5.76, N 11.23. X-Ray analysis: see *Fig. 5*.

*(3a*SR,*4*RS,*8a*SR,*8b*RS*)-4-[2-[(1,3-Benzodioxol-5-yl)methyl]-1,3-dioxoperhydropyrrolo[3,4-*a*]pyrrolizin-4-yl]benzonitrile* ((±)-**23i**) *and (3a*SR,*4*SR,*8a*RS,*8b*RS*)-4-[2-[(1,3-Benzodioxol-5-yl)methyl]-1,3-dioxoperhydropyrrolo[3,4-*a*]pyrrolizin-4-yl]benzonitrile* ((±)-**29i**). *General Procedure A*, starting from **24**, **25h**, and **26i** gave pure *endo*- and *exo*-adducts.

endo-*Adduct* (±)-**23i**: 37% yield. Colorless needles. M.p. 176–179° (MeOH). IR (KBr): 2230, 1699, 1402, 1398, 1343, 1249, 1166, 1038. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.67 (*m*, 1 H); 1.79 (*m*, 1 H); 1.97 (*m*, 1 H); 2.15 (*m*, 1 H); 2.60 (*m*, 1 H); 2.87 (*m*, 1 H); 3.29 (*d*, *J* = 8.4, 1 H); 3.52 (*t*, *J* = 8.4, 1 H); 3.78 (*m*, 1 H); 4.10 (*d*, *J* = 8.7); 4.42 (*s*, 2 H); 5.98 (*m*, 2 H); 6.76 (*m*, 3 H); 8.09, 8.40 (*AA′BB′*, *J* = 8.3, 4 H). ^{13}C-NMR (62.5 MHz, $(CD_3)_2SO$): 23.0; 29.0; 41.2; 48.7; 50.2; 50.4; 67.2; 67.5; 101.0; 108.1; 108.3; 109.8; 119.0; 121.2; 129.0; 129.8; 131.6; 145.0; 146.6; 147.2; 175.3; 178.1. ESI-MS: 416.4 (100, MH^+), 289.4 (15), 277.3 (55), 267.3 (24). Anal. calc. for $C_{24}H_{21}N_3O_4$ (415.45): C 69.39, H 5.10, N 10.11; found: C 69.22, H 5.13, N 9.96.

exo-*Adduct* (±)-**29i**: 50% yield. Yellowish foam. M.p. 61–63°. IR (KBr) 2226, 1772, 1701, 1493, 1396, 1340, 1247, 1168, 1037. ^{1}H-NMR (250 MHz, $(CD_3)_2SO$): 1.63 (*m*, 4 H); 2.39 (*m*, 1 H); 2.81 (*m*, 1 H); 3.43 (*dd*, *J* = 8.7, 6.1, 1 H); 3.68 (*m*, 1 H); 3.76 (*m*, 1 H); 4.13 (*d*, *J* = 6.0, 1 H); 4.48 (*s*, 2 H); 5.99 (*s*, 2 H); 6.83 (*m*, 3 H); 7.63, 7.83 (*AA′BB′*, *J* = 8.3, 4 H). ^{13}C-NMR (62.5 MHz, $(CD_3)_2SO$): 24.0; 26.0; 41.5; 47.5; 51.4; 54.9; 65.5; 68.2; 101.0; 108.2; 108.5; 110.0; 118.8; 121.6; 128.0; 129.6; 132.4; 146.6; 147.2; 148.4; 176.7; 177.6. ESI-MS: 416.4 (100, MH^+).

*(3a*SR,*4*RS,*8a*SR,*8b*RS*)-4-[2-(Cyclohexylmethyl)-1,3-dioxoperhydropyrrolo[3,4-*a*]pyrrolizin-4-yl]benzonitrile* ((±)-**23j**) *and (3a*SR,*4*SR,*8a*RS,*8b*RS*)-4-[2-(Cyclohexylmethyl)-1,3-dioxoperhydropyrrolo[3,4-*a*]pyrrolizin-4-yl]benzonitrile* ((±)-**29j**). *General Procedure A*, starting from **24**, **25h**, and **26j** gave pure *endo*- and *exo*-adducts.

endo-*Adduct* (±)-**23j**: 27% yield. Colorless crystals. M.p. 119–122° (AcOEt/hexane). IR (KBr): 2226, 1773, 1701, 1608, 1401, 1359. ^{1}H-NMR (250 MHz, $(CD_3)_2SO$): 0.82 (*m*, 2 H); 1.12 (*m*, 3 H); 1.57 (*m*, 8 H); 1.99 (*m*, 2 H); 2.79 (*m*, 1 H); 3.05 (*d*, *J* = 6.3, 2 H); 3.40 (*d*, *J* = 8.1, 1 H); 3.57 (*m*, 1 H); 3.69 (*t*, *J* = 8.3, 1 H); 4.23 (*d*, *J* = 8.8, 1 H); 7.49, 7.75 (*AA′BB′*, *J* = 8.2, 4 H). ^{13}C-NMR (62.5 MHz, $(CD_3)_2SO$): 23.1; 25.1; 25.8; 29.1; 30.0; 35.6; 43.9; 48.6; 50.1; 50.5; 67.2; 67.6; 109.8; 119.0; 128.9; 131.6; 145.2; 175.6; two peaks missing due to signal overlap. ESI-MS: 378.4 (100, MH^+). Anal. calc. for $C_{23}H_{27}N_3O_2$ (377.49) with 1.68% $C_4H_8O_2$: C 72.87, H 7.24, N 10.95; found: C 72.82, H 7.24, N 10.98.

exo-*Adduct* (±)-**29j**: 37% yield. Yellowish oil. IR (KBr): 2228, 1773, 1700, 1608, 1398, 1360. ^{1}H-NMR (250 MHz, $(CD_3)_2SO$): 0.92 (*m*, 2 H); 1.19 (*m*, 3 H); 1.61 (*m*, 8 H); 1.85 (*m*, 2 H); 2.83 (*m*, 1 H); 3.08 (*m*, 1 H); 3.22 (*d*, *J* = 6.7, 2 H); 3.39 (*d*, *J* = 6.6, 1 H); 3.68 (*t*, *J* = 6.6, 1 H); 3.78 (*m*, 1 H); 4.07 (*d*, *J* = 6.5, 1 H); 7.64, 7.84 (*AA′BB′*, *J* = 8.2, 4 H). ^{13}C-NMR (62.5 MHz, $(CD_3)_2SO$): 24.2; 25.1; 25.8; 26.4; 30.3; 30.4; 35.9; 44.2; 45.5; 47.3; 51.3; 54.7; 65.4; 68.4; 110.0; 118.8; 128.1; 132.4; 148.5; 177.0; 177.9. ESI-MS: 378.4 (100, MH^+).

*(3a*SR,*4*RS,*9a*SR,*9b*RS*)-4-(2-Benzyl-1,3-dioxoperhydropyrrolo[3,4-*c*]indolizin-4-yl)benzonitrile* ((±)-**23k**) *and (3a*SR,*4*SR,*9a*RS,*9b*RS*)-4-(2-Benzyl-1,3-dioxoperhydropyrrolo[3,4-*c*]indolizin-4-yl)benzonitrile* ((±)-**29k**). *General Procedure A*, starting from **24**, **25k**, and **26a** gave pure *endo*- and *exo*-adducts.

endo-*Adduct* (±)-**23k**: 34% yield. Colorless prisms. M.p. 165–167° (MeOH). IR (KBr): 2225, 1773, 1704, 1429, 1399, 1342. ^{1}H-NMR (250 MHz, $(CD_3)_2SO$): 1.03 (*m*, 1 H); 1.46 (*m*, 4 H); 1.79 (*m*, 1 H); 2.39 (*m*, 1 H); 2.68 (*m*, 1 H); 3.11 (*d*, *J* = 8.0, 1 H); 3.62 (*m*, 2 H); 4.40 (*s*, 2 H); 4.72 (*d*, *J* = 9.2, 1 H); 7.20 (*m*, 4 H); 7.33 (*m*, 3 H); 7.56 (*d*, *J* = 8.1, 2 H). ^{13}C-NMR (62.5 MHz, $(CD_3)_2SO$): 17.4; 24.0; 25.1; 41.7; 44.4; 49.0; 50.4; 61.4;

61.6; 110.0; 118.8; 127.5; 128.1; 128.4; 129.0; 131.8; 136.0; 144.2; 175.7; 178.4. ESI-MS: 386.4 (100, MH$^+$). Anal. calc. for $C_{24}H_{23}N_3O_2$ (385.47): C 74.78, H 6.01, N 10.90; found: C 74.51, H 6.05, N 10.76.

exo-*Adduct* (±)-**29k**: 46% yield. Colorless prisms. M.p. 153–154° (MeOH). IR (KBr): 2228, 1775, 1703, 1429, 1400, 1341. ^{1}H-NMR (250 MHz, $(CD_3)_2SO$): 0.89 (*m*, 2 H); 1.22 (*m*, 1 H); 1.40 (*m*, 2 H); 1.58 (*m*, 1 H); 1.81 (*m*, 1 H); 2.61 (*m*, 1 H); 2.92 (*m*, 1 H); 3.57 (*d*, J = 7.8, 1 H); 3.77 (*t*, J = 8.1, 1 H); 4.63 (*m*, 3 H); 7.30 (*m*, 5 H); 7.47, 7.86 (*AA′BB′*, J = 8.1, 4 H). ^{13}C-NMR (62.5 MHz, $(CD_3)_2SO$): 23.6; 24.6; 28.8; 41.4; 47.8; 49.2; 58.9; 67.5; 110.6; 118.7; 126.9; 127.3; 128.4; 129.7; 131.9; 135.9; 141.6; 176.4; 178.4. ESI-MS: 386.4 (100, MH$^+$). Anal. calc. for $C_{24}H_{23}N_3O_2$ (385.47): C 74.78, H 6.01, N 10.90; found: C 74.51, H 6.02, N 10.74.

*(5*RS*,5a*SR*,8a*RS*,8b*SR*)-4-{7-[(1,3-Benzodioxol-5-yl)methyl]-6,8-dioxoperhydropyrrolo[3′,4′:3,4]pyrrolo-[1,2-c]thiazol-5-yl}benzonitrile* ((±)-**23l**) *and (5*SR*,5a*SR*,8a*RS*,8b*RS*)-4-{7-[(1,3-Benzodioxol-5-yl)methyl]-6,8-dioxoperhydropyrrolo[3′,4′:3,4]pyrrolo[1,2-c]thiazol-5-yl}benzonitrile* ((±)-**29l**). *General Procedure A*, starting from **24**, **25l**, and **26i** gave pure *endo*- and *exo*-adducts.

endo-*Adduct* (±)-**23l**: 17% yield. Colorless crystals. M.p. 183–184° (MeOH). IR (KBr): 2229, 1774, 1704, 1608, 1489, 1445, 1397, 1369, 1339, 1248, 1167, 1034. ^{1}H-NMR (250 MHz, $(CD_3)_2SO$): 2.80 (*t*, J = 10.0, 1 H); 3.23 (*m*, 1 H); 3.61 (*d*, J = 7.9, 1 H); 3.70, 4.18 (*AB*, J = 10.1, 2 H); 3.83 (*m*, 2 H); 4.52 (*d*, J = 9.2, 1 H); 4.33 (*s*, 2 H); 6.04 (*s*, 2 H); 6.67 (*m*, 2 H); 6.90 (*d*, J = 8.5, 1 H); 7.33, 7.67 (*AA′BB′*, J = 8.0, 4 H). ^{13}C-NMR (62.5 MHz, $(CD_3)_2SO$): 34.3; 41.4; 48.5; 49.4; 56.6; 64.5; 70.8; 101.1; 108.2; 108.6; 110.3; 118.8; 121.6; 128.9; 129.7; 131.9; 143.4; 146.7; 147.2; 174.9; 177.1. FAB-MS: 472 (25, $[M+K]^+$), 456 (54, $[M+Na]^+$), 434 (100, MH$^+$). Anal. calc. for $C_{23}H_{19}N_3O_4S$ (433.48): C 63.73, H 4.42, N 9.69; S 7.40; found: C 63.58, H 4.50, N 9.36, S 7.40.

exo-*Adduct* (±)-**29l**: 50% yield. Colorless needles. M.p. 142–143° (MeOH). IR (KBr): 2228, 1775, 1706, 1608, 1494, 1446, 1398, 1371, 1343, 1248, 1170, 1038. ^{1}H-NMR (250 MHz, $(CD_3)_2SO$): 2.21 (*m*, 1 H); 2.91 (*m*, 1 H); 3.48 (*m*, 1 H); 3.77, 4.11 (*AB*, J = 10.3, 2 H); 3.85 (*d*, J = 8.4, 1 H); 4.02 (*m*, 2 H); 4.47 (*s*, 2 H); 5.99 (*s*, 2 H); 6.83 (*m*, 3 H); 7.65, 7.89 (*AA′BB′*, J = 8.3, 4 H). ^{13}C-NMR (62.5 MHz, $(CD_3)_2SO$): 31.7; 41.6; 46.6; 53.7; 55.8; 64.7; 68.9; 101.0; 108.1; 108.5; 110.8; 118.7; 121.5; 128.7; 129.7; 132.7; 146.1; 146.7; 147.4; 175.5; 176.5. ESI-MS: 434.2 (100, MH$^+$). Anal. calc. for $C_{23}H_{19}N_3O_4S$ (433.48): C 63.73, H 4.42, N 9.69, S 7.40; found: C 63.44, H 4.35, N 9.43, S 7.34.

*(1*RS*,3*SR*,3a*RS*,6a*SR*)-4-(5-Butyl-2,3-dimethyl-4,6-dioxoperhydropyrrolo[3,4-c]pyrrol-1-yl)benzonitrile* ((±)-**27d**). *General Procedure B*, starting from (±)-**23c** gave (±)-**27d** in 85% yield. Colorless oil. IR ($CHCl_3$): 2227, 1775, 1702, 1600, 1503, 1437, 1401, 1372, 1347, 1194. ^{1}H-NMR (250 MHz, $(CD_3)_2SO$): 0.87 (*t*, J = 6.9, 3 H); 1.10 (*d*, J = 6.6, 3 H); 1.24 (*m*, 4 H); 2.03 (*s*, 3 H); 3.11 (*d*, J = 7.8, 1 H); 3.20 (*t*, J = 6.6, 2 H); 3.58 (*m*, 1 H); 3.75 (*q*, J = 6.6, 1 H); 4.15 (*d*, J = 9.1, 1 H); 7.36, 7.76 (*AA′BB′*, J = 8.0, 4 H). ^{13}C-NMR (62.5 MHz, $(CD_3)_2SO$): 11.5; 13.4; 19.5; 29.3; 34.4; 37.8; 49.6; 51.2; 60.2; 66.1; 110.1; 118.8; 128.9; 132.0; 144.2; 175.7; 178.6. EI-MS: 325 (8, M^+), 310 (95, $[M-Me]^+$), 223 (10), 183 (24), 171 (40), 157 (10), 70 (15), 56 (17, $[C_4H_8]^+$), 43 (100, $[C_3H_7]^+$). Anal. calc. for $C_{19}H_{23}N_3O_2$ (325.41): C 70.13, H 7.12, N 12.91; found: C 69.84, H 7.18, N 12.83.

*(1*RS*,3*SR*,3a*RS*,6a*SR*)-4-[5-Benzyl-2-methyl-3-(2-methylpropyl)-4,6-dioxoperhydropyrrolo[3,4-c]pyrrol-1-yl]benzonitrile* ((±)-**27g**). *General Procedure B*, starting from (±)-**23f** gave (±)-**27g** in 90% yield. Colorless needles. M.p. 173–174° (MeOH). IR (KBr): 2221, 1772, 1705, 1430, 1399, 1344, 1153. ^{1}H-NMR (250 MHz, $(CD_3)_2SO$): 0.98 (*m*, 6 H); 1.37 (*m*, 2 H); 1.67 (*m*, 1 H); 1.98 (*s*, 3 H); 3.30 (*d*, J = 7.9, 1 H); 3.60 (*m*, 2 H); 4.10 (*d*, J = 9.0, 1 H); 4.40 (*s*, 2 H); 7.14, 7.54 (*AA′BB′*, J = 8.1, 4 H); 7.19 (*m*, 2 H); 7.35 (*m*, 3 H). ^{13}C-NMR (62.5 MHz, $(CD_3)_2SO$): 21.0; 23.9; 25.0; 32.1; 34.2; 41.7; 48.9; 50.0; 63.5; 66.8; 110.0; 118.5; 127.6; 128.3; 128.4; 128.9; 131.8; 136.0; 144.0; 175.6; 178.8. ESI-MS: 402.5 (100, MH$^+$). Anal. calc. for $C_{25}H_{27}N_3O_2$ (401.51): C 74.79, H 6.78, N 10.47; found: C 74.57, H 6.88, N 10.41.

*(1*RS*,3*SR*,3a*RS*,6a*SR*)-4-(2-Acetyl-5-benzyl-3-methyl-4,6-dioxoperhydropyrrolo[3,4-c]pyrrol-1-yl)benzonitrile* ((±)-**28b**). *General Procedure C*, starting from (±)-**23a** gave (±)-**28b** in 83% yield. Colorless solid. M.p. 107–109° (AcOEt/pentane). IR (KBr): 2228, 1710, 1653, 1432, 1390, 1343, 1166. ^{1}H-NMR (250 MHz, $(CD_3)_2SO$): 1.38 (*m*, 3 H); 1.43, 2.06 (2*s*, 3 H); 3.53 (*m*, 1 H); 4.08 (*m*, 3 H); 4.66, 4.73 (2*q*, J = 6.4, 1 H); 5.33, 5.63 (2*d*, J = 10.5, 1 H); 7.00 (*m*, 4 H); 7.39 (*m*, 5 H); two conformers. ^{13}C-NMR (62.5 MHz, $(CD_3)_2SO$): 20.2; 21.5; 22.7; 23.5; 41.7; 47.6; 49.3; 51.4; 52.8; 55.0; 55.5; 61.4; 62.3; 109.3; 110.6; 118.5; 127.0 (br.); 127.5; 128.3; 131.5; 132.3; 135.3; 144.1; 169.5; 169.7; 173.9; 174.1; 177.1; two conformers. EI-MS: 387 (72, M^+), 344 (35, $[M-COCH_3]^+$), 320 (28), 254 (18), 183 (16), 169 (17), 158 (53), 91 (86), 43 (100, $[COCH_3]^+$). Anal. calc. for $C_{23}H_{21}N_3O_3$ (387.44) with 2.59% $C_4H_8O_2$: C 70.87, H 5.56, N 10.57; found: C 70.88, H 5.62, N 10.68.

*(1*RS*,3*SR*,3a*RS*,6a*SR*)-4-(2-Acetyl-5-butyl-3-methyl-4,6-dioxoperhydropyrrolo[3,4-c]pyrrol-1-yl)benzonitrile* ((±)-**28e**). *General Procedure C*, starting from (±)-**23c** afforded (±)-**28e** in 77% yield. Colorless solid. M.p. 140–141° (AcOEt). IR (KBr): 2232, 1779, 1705, 1636, 1506, 1434, 1387, 1353. ^{1}H-NMR (250 MHz, $(CD_3)_2SO$): 0.74 (*m*, 3 H); 1.01 (*m*, 4 H); 1.39 (*t*, J = 5.9, 3 H); 1.50, 2.08 (2*s*, 3 H); 2.91 (*m*, 2 H); 3.43 (*m*, 1 H); 3.96, 4.14 (2*m*, 1 H); 4.62, 4.72 (2*q*, J = 6.5, 1 H); 5.37, 5.68 (2*d*, J = 10.9, 1 H); 7.14 (br. *m*, 2 H); 7.66, 7.81 (*d*, J =

8.5, 2 H); two conformers. ^{13}C-NMR (62.5 MHz, $(CD_3)_2SO$): 13.4; 19.5; 20.4; 21.7; 22.7; 23.4; 28.7; 28.9; 37.7; 37.9; 47.6; 49.3; 51.4; 52.8; 54.9; 55.3; 61.5; 62.5; 109.5; 110.8; 118.4; 118.8; 127 (br.); 131.7; 132.5; 144.4; 144.6; 169.3; 169.6; 174.0; 174.3; 177.0; two conformers. ESI-MS: 354.3 (100, MH$^+$), 158.1 (30). Anal. calc. for $C_{20}H_{23}N_3O_3$ (353.42): C 67.97, H 6.56, 11.89; found: C 67.70, H 6.59, N 11.88.

*(1*RS,*3*SR,*3a*RS,*6a*SR*)-4-(5-Benzyl-3-methyl-4,6-dioxoperhydropyrrolo[3,4-*c*]pyrrol-1-yl)benzamidine Hydrochloride* ((±)-**22a**). *General Procedure E* (method A), starting from (±)-**23a** gave (±)-**22a** in 87% yield. Colorless powder. M.p. 188–191°. IR (KBr): 1701, 1674, 1613, 1540, 1491, 1399, 1345, 1175. ^{1}H-NMR (250 MHz, $(CD_3)_2SO$): 1.24 (d, J = 6.6, 3 H); 3.03 (br. m, 1 H); 3.14 (d, J = 7.7, 1 H); 3.63 (m, 1 H); 3.78 (q, J = 6.7, 1 H); 4.36, 4.44 (AB, J = 15.0, 2 H); 4.81 (br. m, 1 H); 7.17 (m, 2 H); 7.31 (m, 3 H); 7.44, 7.70 ($AA'BB'$, J = 8.3, 4 H); 9.21 (s, 2 H); 9.38 (s, 2 H). ^{13}C-NMR (62.5 MHz, $(CD_3)_2SO$): 20.1; 41.4; 49.1; 52.3; 55.4; 60.4; 126.2; 127.3; 127.5; 128.1; 128.3; 136.0; 145.9; 165.3; 175.6; 178.6. ESI-MS: 363.4 (100, MH$^+$) HR-DEI-MS: 362.1722 (M^+, $C_{21}H_{22}N_4O_2$; calc. 362.1743).

*(1*RS,*3*SR,*3a*RS,*6a*SR*)-4-(2-Acetyl-5-benzyl-3-methyl-4,6-dioxoperhydropyrrolo[3,4-*c*]pyrrol-1-yl)benzamidine Hydrochloride* ((±)-**22b**). *General Procedure E* (*Method A*), starting from (±)-**28b** gave (±)-**22b** in 74% yield. Hygroscopic, colorless solid. M.p. 204–208° (acetone). IR (KBr): 1785, 1710, 1677, 1625, 1489, 1392, 1343, 1166. ^{1}H-NMR (250 MHz, $(CD_3)_2SO$): 1.38 (m, 3 H); 1.48, 2.06 (2s, 3 H); 3.58 (m, 1 H); 4.07 (m, 3 H); 4.75 (m, 1 H); 5.39, 5.72 (2d, J = 10.4, 1 H); 7.08 (m, 4 H); 7.23 (m, 3 H); 7.63 (m, 2 H); 9.45 (br. m, 4 H); two conformers. ^{13}C-NMR (62.5 MHz, $(CD_3)_2SO$): 20.2; 21.6; 22.7; 23.5; 41.5; 41.7; 47.8; 49.5; 51.4; 52.9; 55.0; 55.4; 61.5; 62.4; 125.9; 127.1; 127.4; 127.5; 127.9; 128.0; 128.3; 135.2; 135.3; 144.8; 144.9; 165.0; 165.3; 169.4; 169.5; 174.0; 174.2; 177.1; 177.2; two conformers. ESI-MS: 405 (100, MH$^+$). Anal. calc. for $C_{23}H_{24}N_4O_3 \cdot$HCl (440.93) with 3.92% CH_3COCH_3: C 62.63, H 5.90, N 12.21, Cl 7.73; found: C 62.06, H 5.85, N 12.07, Cl 7.84.

*(1*RS,*3*SR,*3a*RS,*6a*SR*)-4-(5-Butyl-3-methyl-4,6-dioxoperhydropyrrolo[3,4-*c*]pyrrol-1-yl)benzamidine Hydrochloride* ((±)-**22c**). *General Procedure E* (*Method A*), starting from (±)-**23c** gave (±)-**22c** in 55% yield. Colorless solid. M.p. > 180° (dec.). IR (KBr): 1768, 1696, 1671, 1612, 1402. ^{1}H-NMR (250 MHz, $(CD_3)_2SO$): 0.84 (t, J = 7.1, 3 H); 1.22 (m, 7 H); 3.07 (d, J = 7.6, 1 H); 3.19 (t, J = 6.8, 2 H); 3.55 (m, 1 H); 3.77 (m, 1 H); 4.81 (m, 1 H); 7.52, 7.78 ($AA'BB'$, J = 8.2, 4 H); 9.19 (s, 2 H); 9.38 (s, 2 H). ^{13}C-NMR (62.5 MHz, $(CD_3)_2SO$): 13.5; 19.4; 20.0; 29.2; 37.7; 49.0; 52.3; 55.4; 60.3; 126.2; 127.3; 128.0; 145.5 (br.); 165.3; 175.7; 178.6. ESI-MS: 329.4 (100, MH$^+$).

*(1*RS,*3*SR,*3a*RS,*6a*SR*)-4-(5-Butyl-2,3-dimethyl-4,6-dioxoperhydropyrrolo[3,4-*c*]pyrrol-1-yl)benzamidine Hydrochloride* ((±)-**22d**). *General Procedure E* (*Method A*), starting from (±)-**27d** gave (±)-**22d** in 88% yield. Colorless powder. M.p. 171–176°. IR (KBr): 1773, 1702, 1671, 1614, 1538, 1488, 1401. ^{1}H-NMR (250 MHz, $(CD_3)_2SO$): 0.88 (t, J = 7.1, 3 H); 1.10 (d, J = 6.8, 3 H); 1.27 (m, 4 H); 1.98 (s, 3 H); 3.12 (d, J = 7.9, 1 H); 3.22 (m, 2 H); 3.58 (m, 1 H); 3.75 (q, J = 6.7, 1 H); 4.16 (d, J = 9.0, 1 H); 7.38, 7.78 ($AA'BB'$, J = 6.7, 4 H); 9.13 (m, 4 H). ^{13}C-NMR (62.5 MHz, $(CD_3)_2SO$): 11.5; 13.5; 19.5; 29.3; 34.5; 37.8; 49.6; 51.2; 60.2; 66.1; 126.7; 127.8; 128.5; 144.7; 165.3; 175.8; 178.6. ESI-MS: 343.4 (100, MH$^+$).

*(1*RS,*3*SR,*3a*RS,*6a*SR*)-4-(2-Acetyl-5-butyl-3-methyl-4,6-dioxoperhydropyrrolo[3,4-*c*]pyrrol-1-yl)benzamidine Hydrochloride* ((±)-**22e**). *General Procedure E* (*Method A*), starting from (±)-**28e** afforded (±)-**22e** in 60% yield. Colorless powder. M.p. 203–206°. IR (KBr): 1706, 1675, 1633, 1486. 1397. ^{1}H-NMR (250 MHz, $(CD_3)_2SO$): 0.76 (m, 3 H); 1.05 (m, 4 H); 1.40 (t, J = 5.4, 3 H); 1.51, 2.08 (2s, 3 H); 2.87 (m, 2 H); 3.45 (m, 1 H); 3.99, 4.15 (2m, 1 H); 4.66, 4.74 (2q, J = 5.7, 1 H); 5.39, 5.69 (2d, J = 10.4, 1 H); 7.16 (br. m, 2 H); 7.70, 7.83 (2d, J = 8.5, 2 H); 9.18, 9.27 (2s, 2 H); 9.35, 9.41 (2s, 2 H); two conformers. ^{13}C-NMR (62.5 MHz, $(CD_3)_2SO$): 13.4; 19.5; 20.4; 21.8; 22.8; 23.4; 28.5; 28.8; 37.8; 47.6; 49.4; 51.4; 52.8; 54.8; 55.2; 61.5; 62.5; 126.0; 127.2; 127.5; 128.3; 145.1; 164.9; 165.2; 169.5; 174.1; 174.4; 177.1; two conformers. ESI-MS: 371.4 (100, MH$^+$).

*(1*RS,*3*SR,*3a*RS,*6a*SR*)-4-[5-Benzyl-3-(2-methylpropyl)-4,6-dioxoperhydropyrrolo[3,4-*c*]pyrrol-1-yl]benzamidine Hydrochloride* ((±)-**22f**). *General Procedure E* (*Method B*), starting from (±)-**23f** gave (±)-**22f** in 70% yield. Colorless foam. M.p. 152–157°. IR (KBr): 1771, 1702, 1675, 1613, 1491, 1402, 1343. ^{1}H-NMR (250 MHz, $(CD_3)_2SO$): 0.93 (m, 6 H); 1.42 (m, 2 H); 1.70 (m, 1 H); 3.08 (br. m, 1 H); 3.21 (d, J = 7.7, 1 H); 3.62 (m, 2 H); 4.40 (m, 2 H); 4.74 (m, 1 H); 7.16 (m, 2 H); 7.31 (m, 3 H); 7.45, 7.72 ($AA'BB'$, J = 8.3, 4 H); 9.35 (br. m, 4 H). ^{13}C-NMR (62.5 MHz, $(CD_3)_2SO$): 22.4; 22.5; 24.6; 41.5; 42.0; 49.3; 51.0; 58.2; 60.8; 126.1; 127.3; 127.4; 127.5; 128.1; 128.3; 136.0; 165.3; 175.7; 178.8. ESI-MS: 405.4 (100, MH$^+$), 315.4 (26). HR-DEI-MS: 404.2216 (M^+, $C_{24}H_{28}N_4O_2$; calc. 404.2212).

*(1*RS,*3*SR,*3a*RS,*6a*SR*)-4-[5-Benzyl-2-methyl-3-(2-methylpropyl)-4,6-dioxoperhydropyrrolo[3,4-*c*]pyrrol-1-yl]benzamidine Hydrochloride* ((±)-**22g**). *General Procedure E* (*Method B*), starting from (±)-**27g** gave (±)-**22g** in 89% yield. Colorless foam. M.p. 157–162°. IR (KBr): 1772, 1703, 1678, 1613, 1538, 1489, 1402, 1345. ^{1}H-NMR (250 MHz, $(CD_3)_2SO$): 0.98 (m, 6 H); 1.38 (m, 2 H); 1.68 (m, 1 H); 1.98 (s, 3 H); 3.31 (d, J = 7.9, 1 H); 3.62 (m, 2 H); 4.14 (d, J = 10.0, 1 H); 4.43 (m, 2 H); 7.23 (m, 4 H); 7.34 (m, 3 H); 7.64 (d, J = 8.0, 2 H); 9.20

(br. *s*, 2 H); 9.4 (br. *s*, 2 H). ^{13}C-NMR (62.5 MHz, $(CD_3)_2SO$): 21.0; 23.9; 25.0; 31.9; 34.3; 41.4; 48.5; 49.7; 63.4; 66.7; 126.7; 127.7; 128.1; 128.4; 136.0; 144.5; 165.4; 175.7; 178.9. ESI-MS: 419.5 (100, MH$^+$). HR-DEI-MS: 418.2335 (M^+, $C_{25}H_{30}N_4O_2$; calc. 418.2369).

*(3a*SR,*4*RS,*8a*SR,*8b*RS*)-4-(2-Benzyl-1,3-dioxoperhydropyrrolo[3,4-*a*]pyrrolizin-4-yl)benzamidine Hydrochloride* ((±)-**22h**). *General Procedure E* (*Method A*), starting from (±)-**23h** gave (±)-**22h** in 86% yield. Colorless solid. M.p. 202–205°. IR (KBr): 1775, 1708, 1671, 1613, 1537, 1490, 1400, 1345. ^{1}H-NMR (250 MHz, $(CD_3)_2SO$): 1.69 (*m*, 2 H); 2.00 (*m*, 2 H); 2.77 (*m*, 1 H); 3.48 (*d*, J = 8.0, 1 H); 3.57 (*m*, 1 H); 3.78 (*t*, J = 8.3, 1 H); 4.23 (*d*, J = 8.7, 1 H); 4.43 (*s*, 2 H); 7.17 (*d*, J = 6.7, 2 H); 7.32 (*m*, 3 H); 7.45 (*d*, J = 8.1, 2 H); 7.72 (br. *m*, 2 H); 9.17 (br. *s*, 2 H); 9.36 (*s*, 2 H). ^{13}C-NMR (62.5 MHz, $(CD_3)_2SO$): 23.0; 29.0; 41.4; 48.6; 50.4; 67.3; 67.5; 126.5; 127.5; 128.4; 128.7; 136.0; 145.5; 165.4; 175.4; 178.2; one peak missing due to signal overlap. ESI-MS: 389.4 (100, MH$^+$), 309.4 (20), 195.4 (58), 158.2 (40). HR-DEI-MS: 388.1892 (M^+, $C_{23}H_{24}N_4O_2$; calc. 388.1899).

*(3a*SR,*4*RS,*8a*SR,*8b*RS*)-4-{2-[(1,3-Benzodioxol-5-yl)methyl]-1,3-dioxoperhydropyrrolo[3,4-*a*]pyrrolizin-4-yl}benzamidine Hydrochloride* ((±)-**22i**). *General Procedure E* (*Method A*), starting from (±)-**23i** gave (±)-**22i** in 40% yield. Colorless powder. M.p. 177–181°. IR (KBr): 1773, 1701, 1678, 1613, 1489, 1445, 1402, 1343, 1248, 1173, 1037. ^{1}H-NMR (250 MHz, $(CD_3)_2SO$): 1.68 (*m*, 2 H); 1.98 (*m*, 2 H); 2.77 (*m*, 1 H); 3.47 (*d*, J = 7.8, 1 H); 3.56 (*m*, 1 H); 3.76 (*t*, J = 8.3, 1 H); 4.22 (*d*, J = 8.5, 1 H); 4.33 (*s*, 2 H); 6.02 (*s*, 2 H); 6.67, 6.88 (*AB*, J = 7.8, 2 H); 6.70 (*s*, 1 H); 7.44, 7.71 (*AA′BB′*, J = 8.2, 4 H); 9.08 (*s*, 2 H); 9.38 (*s*, 2 H). ^{13}C-NMR (62.5 MHz, $(CD_3)_2SO$): 23.0; 29.0; 41.2; 48.6; 50.3; 67.4; 67.5; 101.0; 108.1; 108.2; 121.2; 126.5; 127.5; 128.7; 129.7; 145.6; 146.6; 147.2; 165.4; 175.4; 178.1; one peak missing due to signal overlap. ESI-MS: 433.4 (100, MH$^+$). Anal. calc. for $C_{24}H_{24}N_4O_4 \cdot$ HCl (468.94): C 61.47, H 5.37, N 11.95, Cl 7.56; found: C 60.96, H 5.41, N 11.90, Cl 8.35.

*(3a*SR,*4*RS,*8a*SR,*8b*RS*)-4-[2-(Cyclohexylmethyl)-1,3-dioxoperhydropyrrolo[3,4-*a*]pyrrolizin-4-yl]benzamidine Hydrochloride* ((±)-**22j**). *General Procedure E* (*Method B*), starting from (±)-**23j** afforded (±)-**22j** in 69% yield. Yellowish solid. M.p. 104–110°. IR (KBr): 1773, 1700, 1680, 1613, 1488, 1402, 1358. ^{1}H-NMR (250 MHz, $(CD_3)_2SO$): 0.83 (*m*, 2 H); 1.14 (*m*, 3 H); 1.56 (*m*, 8 H); 2.00 (*m*, 2 H); 2.78 (*m*, 1 H); 3.07 (*d*, J = 6.9, 2 H); 3.38 (br. *m*, 1 H); 3.57 (*m*, 1 H); 3.70 (*t*, J = 8.3, 1 H); 4.23 (*d*, J = 8.8, 1 H); 7.51, 7.79 (*AA′BB′*, J = 8.1, 4 H); 9.19 (*s*, 2 H); 9.38 (*s*, 2 H). ^{13}C-NMR (62.5 MHz, $(CD_3)_2SO$): 18.5; 23.1; 25.1; 25.8; 29.0; 30.0; 35.6; 43.9; 48.5; 50.1; 50.5; 56.0; 67.4; 67.7; 126.5; 127.5; 128.6; 145.7; 165.3; 175.7; 178.6. ESI-MS: 395.4 (100, MH$^+$). HR-DEI-MS: 394.2373 (M^+, $C_{23}H_{30}N_4O_2$; calc. 394.2369).

*(3a*SR,*4*RS,*9a*SR,*9b*RS*)-4-(2-Benzyl-1,3-dioxoperhydropyrrolo[3,4-*c*]indolizin-4-yl)benzamidine Hydrochloride* ((±)-**22k**). *General Procedure E* (*Method B*), starting from (±)-**23k** gave (±)-**22k** in 83% yield. Colorless foam. M.p. 248–250°. IR (KBr): 1771, 1694, 1675, 1613, 1431, 1400, 1342. ^{1}H-NMR (250 MHz, $(CD_3)_2SO$): 1.03 (*m*, 1 H); 1.46 (*m*, 4 H); 1.78 (*m*, 1 H); 2.38 (*m*, 1 H); 2.68 (*m*, 1 H); 3.13 (*d*, J = 7.9, 1 H); 3.61 (*m*, 2 H); 4.39, 4.47 (*AB*, J = 14.7, 2 H); 4.75 (*d*, J = 9.0, 1 H); 7.24 (*m*, 7 H); 7.67 (*d*, J = 8.2, 2 H); 8.85 (br. *m*, 4 H). ^{13}C-NMR (62.5 MHz, $(CD_3)_2SO$): 17.4; 24.0; 25.0; 41.7; 44.4; 49.1; 50.3; 61.4; 61.6; 126.7; 127.5; 127.7; 128.0; 128.4; 136.0; 144.7; 165.4; 175.8; 178.5. ESI-MS: 403.4 (100, MH$^+$). HR-DEI-MS: 402.2071 (M^+, $C_{24}H_{26}N_4O_2$; calc. 402.2056).

*(5*RS,*5a*SR,*8a*RS,*8b*SR*)-4-{7-[(1,3-Benzodioxol-5-yl)methyl]-6,8-dioxoperhydropyrrolo[3′,4′:3,4]pyrrolo-[1,2-*c*]thiazol-5-yl}benzamidine Hydrochloride* ((±)-**22l**). *General Procedure E* (*Method B*), starting from (±)-**23l** afforded (±)-**22l** in 35% yield after CC (*RP18*, gradient H_2O/MeOH). Colorless Solid. M.p. 226–229°, >245° (dec). IR (KBr): 1771, 1703, 1675, 1614, 1490, 1446, 1403, 1344, 1250, 1176, 1036. ^{1}H-NMR (250 MHz, $(CD_3)_2SO$): 2.82 (*t*, J = 10.1, 1 H); 3.25 (*m*, 1 H); 3.64 (*m*, 2 H); 3.84 (*m*, 2 H); 4.19 (*d*, J = 10.1, 1 H); 4.27 (*d*, J = 9.2, 1 H); 4.35 (*s*, 2 H); 6.04 (*s*, 2 H); 6.70 (*m*, 2 H); 6.91 (*d*, J = 7.7, 1 H); 7.36, 7.71 (*AA′BB′*, J = 8.0, 4 H); 9.25 (*s*, 4 H). ^{13}C-NMR (62.5 MHz, $(CD_3)_2SO$): 34.3, 41.4; 48.4; 49.5; 56.6; 64.6; 70.8; 101.1; 108.2; 108.6; 121.5; 127.2; 127.8; 128.6; 129.6; 143.8; 146.6; 147.2; 165.2; 174.9; 177.1. ESI-MS: 451 (100, MH$^+$). Anal. calc. for $C_{23}H_{22}N_4O_4S \cdot$ HCl (486.97): C 56.73, H 4.76, N 11.51, S 6.58, Cl 7.28; found: C 56.91, H 4.80, N 11.48, S 6.60, Cl 7.31.

*(3a*SR,*4*SR,*8a*RS,*8b*RS*)-4-{2-[(1,3-Benzodioxol-5-yl)methyl]-1,3-dioxoperhydropyrrolo[3,4-*a*]pyrrolizin-4-yl}benzamidine Hydrochloride* ((±)-**30i**). *General Procedure E* (*Method A*), starting from (±)-**29i** gave (±)-**30i** in 73% yield. Colorless foam. M.p. 195–200°. IR (KBr): 1773, 1701, 1678, 1612, 1489, 1402, 1247, 1169, 1037. ^{1}H-NMR (250 MHz, $(CD_3)_2SO$): 1.39 (*m*, 2 H); 1.75 (*m*, 2 H); 2.39 (*m*, 1 H); 2.80 (*m*, 1 H); 3.41 (*m*, 1 H); 3.72 (*m*, 2 H); 4.10 (*d*, J = 6.0, 1 H); 4.47 (*s*, 2 H); 6.00 (*s*, 2 H); 6.84 (*m*, 3 H); 7.65, 7.83 (*AA′BB′*, J = 8.3, 4 H); 8.48 (br. *m*, 4 H). ^{13}C-NMR (62.5 MHz, $(CD_3)_2SO$): 24.0; 26.0; 41.5; 47.5; 51.2; 54.9; 65.5; 68.2; 101.0; 108.2; 108.5; 121.5; 126.7; 127.6; 128.3; 129.6; 146.6; 147.1; 148.7; 165.5; 176.7; 177.5. ESI-MS: 433.5 (100, MH$^+$).

*(3a*SR,*4*SR,*9a*RS,*9b*RS*)-4-(2-Benzyl-1,3-dioxoperhydropyrrolo[3,4-*c*]indolizin-4-yl)benzamidine Hydrochloride* ((±)-**30k**). *General Procedure E* (*Method A*), starting from (±)-**29k** gave (±)-**30k** in 83% yield. Colorless foam. M.p. >295°. IR (KBr): 1772, 1702, 1675, 1613, 1430, 1401, 1343, 1184. ^{1}H-NMR (250 MHz,

$(CD_3)_2SO$): 0.88 (*m*, 2 H); 1.22 (*m*, 1 H); 1.41 (*m*, 2 H); 1.61 (*m*, 1 H); 1.82 (*m*, 1 H); 2.62 (*m*, 1 H); 2.94 (*m*, 1 H); 3.57 (*d*, *J* = 7.8, 1 H); 3.84 (*t*, *J* = 8.0, 1 H); 4.64 (*m*, 3 H); 7.31 (*m*, 5 H); 7.51, 7.87 (*AA′BB′*, *J* = 8.1, 4 H); 9.30 (*s*, 2 H); 9.47 (*s*, 2 H). ^{13}C-NMR (62.5 MHz, $(CD_3)_2SO$): 23.7; 24.6; 28.3; 41.4; 47.8; 49.3; 59.0; 67.5; 126.9; 127.2; 127.3; 127.9; 128.4; 129.2; 136.0; 142.1; 165.3; 176.4; 178.5 (one signal under the solvent residual peak). ESI-MS: 403.4 (100, MH$^+$).

*(5*SR*,5a*SR*,8a*RS*,8b*RS*)-4-{7-[(1,3-Benzodioxol-5-yl)methyl]-6,8-dioxoperhydropyrrolo[3′,4′:3,4]pyrrolo-[1,2-c]thiazol-5-yl}benzamidine Hydrochloride* ((±)-**30l**). *General Procedure E* (*Method B*), starting from (±)-**29l** gave (±)-**30l** in 73% yield. Colorless foam. M.p. 182–188°. IR (KBr): 1777, 1704, 1679, 1614, 1489, 1445, 1400, 1248, 1172, 1037. ^{1}H-NMR (250 MHz, $(CD_3)_2SO$): 2.22 (*m*, 1 H); 2.93 (*m*, 1 H); 3.50 (*m*, 1 H); 3.74, 4.12 (*AB*, *J* = 10.2, 2 H); 3.85 (*d*, *J* = 8.5, 1 H); 4.06 (*m*, 2 H); 4.48 (*s*, 2 H); 6.00 (*s*, 2 H); 6.83 (*m*, 3 H); 7.67, 7.91 (*AA′BB′*, *J* = 8.3, 4 H); 9.36 (*s*, 2 H); 9.50 (*s*, 2 H). ^{13}C-NMR (62.5 MHz, $(CD_3)_2SO$): 31.7; 41.6; 46.7; 53.9; 55.7; 64.7; 69.0; 101.0; 108.2; 108.4; 121.4; 127.7; 128.2; 128.6; 129.7; 146.4; 146.7; 147.3; 165.5; 175.5; 176.5. ESI-MS: 451 (100, MH$^+$).

*3a*SR*,4*RS*,8a*SR*,8b*RS*)-2-[(1,3-Benzodioxol-5-yl)methyl]-4-(4-bromophenyl)perhydropyrrolo[3,4-*a*]pyrroli-zine-1,3-dione* ((±)-**31**). *General Procedure A*, starting from **17**, **26i**, and **25h** gave (±)-**31** in 20% yield after CC (SiO_2; CH_2Cl_2/MeOH 99:1). Colorless crystals. M.p. 134–136° (MeOH). IR (KBr): 1772, 1700, 1604, 1490, 1445, 1399, 1346, 1248, 1172, 1034. ^{1}H-NMR (200 MHz, $CDCl_3$): 1.71 (*m*, 2 H); 2.06 (*m*, 2 H); 2.61 (*m*, 1 H); 2.83 (*m*, 1 H); 3.26 (*d*, *J* = 8.3, 1 H); 3.46 (*t*, *J* = 8.4, 1 H); 3.75 (*m*, 1 H); 4.01 (*d*, *J* = 8.7, 1 H); 4.43 (*s*, 2 H); 5.97 (*m*, 2 H); 6.75 (*m*, 3 H); 7.09, 7.38 (*AA′BB′*, *J* = 8.4, 4 H). ^{13}C-NMR (50 MHz, $CDCl_3$): 23.6; 29.8; 42.5; 49.3; 50.7; 51.0; 68.1; 68.5; 101.4; 108.4; 109.9; 121.9; 123.0; 129.8; 130.1; 131.6; 137.4; 147.6; 148.0; 175.5; 178.3. FAB-MS: 938.8 (4), 469.1 (100, M^+), 237.0 (38), 135.1 (91, [Piperonyl]$^+$). Anal. calc. for $C_{23}H_{21}BrN_2O_4$ (469.33): C 58.86, H 4.51, Br 17.02, N 5.97; found: C 58.73, H 4.45, Br 16.81, N 5.87.

*(3a*SR*,4*RS*,6a*RS*)-2-[(1,3-Benzodioxol-5-yl)methyl]-4-(4-bromophenyl)-6,6-dimethyl-3a,4,5,6-tetrahydro-1*H*,3*H*-pyrrolo[3,4-*c*]pyrrole-1,3-dione* ((±)-**35**). *General Procedure A*, starting from **17**, α-aminoisobutyric acid, and **26i** gave (±)-**35** in 48% yield. Colorless platelets. M.p. 149–150° (AcOEt/hexane). IR (KBr): 1763, 1697, 1500, 1430, 1400, 1335, 1245, 1170, 1040. ^{1}H-NMR (200 MHz, $CDCl_3$): 1.33 (*s*, 3 H); 1.41 (*s*, 3 H); 2.84 (*d*, *J* = 7.8, 1 H); 3.35 (*m*, 1 H); 4.38, 4.43 (*AB*, *J* = 13.9, 2 H); 4.66 (*d*, *J* = 8.3, 1 H); 5.94 (*m*, 2 H); 6.75 (*m*, 3 H); 7.05, 7.34 (*AA′BB′*, *J* = 8.4, 4 H). ^{13}C-NMR (50 MHz, $CDCl_3$): 26.0; 28.4; 41.7; 49.9; 53.6; 59.9; 60.6; 100.8; 107.8; 109.3; 121.3; 122.3; 128.8; 129.5; 130.9; 137.0; 146.9; 147.3; 174.7; 175.7. FAB-MS: 915.3 (3, M_2H$^+$), 457.1 (67, M^+), 225.0 (40), 135.0 (100, [Piperonyl]$^+$), 91 (45). Anal. calc. for $C_{22}H_{21}BrN_2O_4$ (457.32): C 57.78, H 4.63, Br 17.47, N 6.13; found: C 57.73, H 4.59, Br 17.34, N 6.04.

As a side product, the exo-diastereoisomer *(3a*SR*,4*SR*,6a*RS*)-2-[(1,3-benzodioxol-5-yl)methyl]-4-(4-bromophenyl)-6,6-dimethyl-3a,4,5,6-tetrahydro-1*H*,3*H*-pyrrolo[3,4-*c*]pyrrole-1,3-dione* was obtained in 34% yield. Colorless crystals. M.p. 139–140° (MeOH). IR (KBr): 1764, 1698, 1491, 1444, 1374, 1338, 1249, 1167, 1038. ^{1}H-NMR (200 MHz, $CDCl_3$): 1.02 (*s*, 3 H); 1.44 (*s*, 3 H); 3.07 (*d*, *J* = 9.6, 1 H); 3.22 (*m*, 1 H); 4.43 (*d*, *J* = 6.6, 1 H); 4.51 (*s*, 2 H); 5.90 (*s*, 2 H); 6.70 (*d*, *J* = 8.4, 1 H); 6.88 (*m*, 2 H); 7.43 (*s*, 4 H). ^{13}C-NMR (50 MHz, $CDCl_3$): 23.1; 30.7; 42.4; 55.3; 56.2; 61.5; 62.1; 101.4; 108.6; 109.9; 121.6; 123.1; 128.7; 129.9; 132.0; 141.5; 147.7; 148.1; 176.2; 177.8. FAB-MS: 915.3 (2, M_2H$^+$), 457.1 (59, M^+), 225.0 (19), 135.1 (100, [Piperonyl]$^+$). Anal. calc. for $C_{22}H_{21}BrN_2O_4$ (457.32): C 57.78, H 4.63, Br 17.47, N 6.13; found: C 57.93, H 4.82, Br 17.44, N 6.06.

*(3a*SR*,4*RS*,6a*RS*)-2-[(1,3-Benzodioxol-5-yl)methyl]-4-(4-bromophenyl)-5,6,6-trimethyl-3a,4,5,6-tetrahydro-1*H*,3*H*-pyrrolo[3,4-*c*]pyrrole-1,3-dione* ((±)-**34**). *General Procedure B*, starting from (±)-**35** gave (±)-**34** in 92% yield. Colorless prisms. M.p. 109–111° (MeOH). IR (KBr): 1763, 1698, 1487, 1444, 1396, 1369, 1327, 1248, 1165, 1039. ^{1}H-NMR (200 MHz, $CDCl_3$): 1.08 (*s*, 3 H); 1.44 (*s*, 3 H); 1.94 (*s*, 3 H); 2.86 (*d*, *J* = 7.9, 1 H); 3.33 (*m*, 1 H); 3.88 (*d*, *J* = 9.2, 1 H); 4.38 (*d*, *J* = 6.6, 2 H); 5.96 (*m*, 2 H); 6.76 (*m*, 3 H); 6.91, 7.29 (*AA′BB′*, *J* = 8.1, 4 H). ^{13}C-NMR (50 MHz, $CDCl_3$): 18.8; 24.4; 32.2; 42.2; 48.5; 54.4; 63.0; 68.6; 101.4; 108.4; 110.3; 121.9; 123.3; 130.1; 131.7; 137.3; 147.6; 148.0; 175.6; 176.5; one peak missing due to signal overlap. FAB-MS: 941.0 (1, M_2H$^+$), 471.0 (71, MH$^+$), 470.0 (21, M^+), 469.0 (42), 455.0 (54, [$M - CH_3$]$^+$), 135.0 (100, [Piperonyl]$^+$). Anal. calc. for $C_{23}H_{23}BrN_2O_4$ (471.35): C 58.61, H 4.92, Br 16.95, N 5.94; found: C 58.63, H 4.91, Br 16.67, N 5.91.

*(1*RS*,3a*RS*,6a*SR*)-4-{5-[(1,3-Benzodioxol-5-yl)methyl]-2,3,3-trimethyl-4,6-dioxoperhydropyrrolo[3,4-*c*]pyr-rol-1-yl}benzonitrile* ((±)-**43**). *General Procedure D*, starting from (±)-**34** gave (±)-**43** in 76% yield. Colorless prisms. M.p. 133–134° (MeOH). IR (KBr): 2227, 1764, 1697, 1605, 1487, 1442, 1400, 1370, 1326, 1247, 1174, 1038. ^{1}H-NMR (200 MHz, $CDCl_3$): 1.10 (*s*, 3 H); 1.44 (*s*, 3 H); 1.94 (*s*, 3 H); 2.89 (*d*, *J* = 8.0, 1 H); 3.37 (*m*, 1 H); 3.96 (*d*, *J* = 9.3, 1 H); 4.30, 4.42 (*AB*, *J* = 13.8, 2 H); 5.98 (*m*, 2 H); 6.75 (*m*, 3 H); 7.13, 7.44 (*AA′BB′*, *J* = 8.0, 4 H). ^{13}C-NMR (50 MHz, $CDCl_3$): 18.5; 23.9; 31.8; 41.7; 48.0; 53.9; 62.7; 68.2; 100.9; 107.8; 109.6; 111.3; 118.6; 122.6; 128.5; 129.3; 131.7; 143.2; 147.0; 147.3; 174.6; 175.5. FAB-MS: 835.3 (3, M_2H$^+$), 418.2 (100, MH$^+$), 417.2 (52,

M^+), 402.2 (21, [M – Me]$^+$), 135.0 (87, [Piperonyl]$^+$). Anal. calc. for $C_{24}H_{23}N_3O_4$ (417.46): C 69.05, H 5.55, N 10.07; found: C 68.97, H 5.67, N 10.02.

*(1*RS*,3a*RS*,6a*S*)-4-[5-[(1,3-Benzodioxol-5-yl)methyl]-2,3,3-trimethyl-4,6-dioxoperhydropyrrolo[3,4-*c*]pyrrol-1-yl}benzamidine Hydrochloride* ((±)-**42**). *General Procedure E* (*Method B*), starting from (±)-**43** gave (±)-**42** in 88% yield. Colorless solid. M.p. 191–194°. IR (KBr): 1766, 1698, 1676, 1612, 1490, 1445, 1401, 1247, 1176, 1038. ^{1}H-NMR (200 MHz, $(CD_3)_2SO$): 1.03 (*s*, 3 H); 1.28 (*s*, 3 H); 1.83 (*s*, 3 H); 3.04 (*d*, *J* = 8.0, 1 H); 3.55 (*m*, 1 H); 4.05 (*d*, *J* = 9.1, 1 H); 4.30 (*s*, 2 H); 6.00 (*s*, 2 H); 6.65 (*m*, 2 H); 6.86 (*d*, *J* = 8.6, 1 H); 7.22, 7.62 (*AA′BB′*, *J* = 7.8, 4 H); 9.24 (br. *m*, 4 H). ^{13}C-NMR (50 MHz, $(CD_3)_2SO$): 18.6; 24.2; 32.1; 48.3; 53.9; 62.5; 67.8; 101.3; 108.4; 108.8; 121.7; 126.9; 127.9; 128.9; 130.2; 145.4; 146.9; 147.4; 165.7; 175.5; 176.5. ESI-MS: 435.2 (100, MH$^+$). HR-DEI-MS: 434.1984 (M^+, $C_{24}H_{26}N_4O_4$; calc. 434.1954).

*(3a*RS*,6*RS*,6a*SR*)-2-[(1,3-Benzodioxol-5-yl)methyl]-6-(4-bromophenyl)-4,4,5-trimethyl-2,3,3a,4,5,6-hexahydro-1*H*-pyrrolo[3,4-*c*]pyrrol-1-one* ((±)-**36**) and *(3a*SR*,4*RS*,6a*RS*)-2-[(1,3-Benzodioxol-5-yl)methyl]-4-(4-bromophenyl)-5,6,6-trimethyl-2,3,3a,4,5,6-hexahydro-1*H*-pyrrolo[3,4-*c*]pyrrol-1-one* ((±)-**37**). A 1M soln. of Li[Et_3BH] (14.45 ml, 14.45 mmol) was added at –78° under Ar to a soln. of (±)-**34** (4.00 g, 8.5 mmol) in dry THF (30 ml). The mixture was stirred at –78° for 1 h, then warmed to 0°. Sat. aq. $NaHCO_3$ soln. (10 ml) and 30% aq. H_2O_2 soln. were added sequentially, the mixture was stirred for 1 h at 0°, and THF was evaporated. The aq. phase was extracted with $CHCl_3$, then the org. phase was dried (Na_2SO_4) and evaporated *in vacuo*. The residue was dissolved in CF_3COOH (7 ml), and Na[$CNBH_3$] (1.07 g, 17 mmol) was carefully added. The mixture was stirred for 5 h at 20°, then H_2O (30 ml) was added followed by neutralization with 1N NaOH. The mixture was exhaustively extracted with CH_2Cl_2, the combined org. phases were dried (Na_2SO_4) and evaporated *in vacuo*, and the residue was purified by CC (SiO_2; hexane/AcOEt/Et_3N 49.5 : 49.5 : 1).

*Data of (±)-***36**: Yield: 1.90 g (49%). Colorless oil. IR ($CHCl_3$): 1677, 1504, 1490, 1445, 1367, 1246, 1042. ^{1}H-NMR (200 MHz, $CDCl_3$): 1.00 (*s*, 3 H); 1.14 (*s*, 3 H); 1.98 (*s*, 3 H); 2.60 (*m*, 1 H); 3.18 (*m*, 2 H); 3.38 (*m*, 1 H); 3.83 (*d*, *J* = 10.0, 1 H); 3.95, 4.26 (*AB*, *J* = 14.3, 2 H); 6.00 (*m*, 2 H); 6.61 (*m*, 2 H); 6.76 (*d*, *J* = 8.3, 1 H); 7.08, 7.40 (*AA′BB′*, *J* = 8.2, 4 H). ^{13}C-NMR (50 MHz, $CDCl_3$): 18.4; 22.5; 32.3; 46.7; 47.6; 48.5; 50.1; 61.5; 69.6; 101.4; 108.4; 109.7; 121.4; 122.5; 130.2; 130.3; 130.5; 131.6; 139.0; 148.2; 173.2. FAB-MS: 457.0 (83, MH$^+$), 441.0 (34, [M – Me]$^+$), 135.0 (100, [Piperonyl]$^+$).

*Data of (±)-***37**: Yield 1.19 g (31%). Colorless needles. M.p. 80–82° ($CHCl_3$/hexane). IR (KBr): 1677, 1486, 1448, 1375, 1317, 1244, 1040. ^{1}H-NMR (200 MHz, $CDCl_3$): 1.08 (*s*, 3 H); 1.43 (*s*, 3 H); 2.00 (*s*, 3 H); 2.52 (*dd*, *J* = 3.0, 10.1, 1 H); 2.68 (*d*, *J* = 8.6, 1 H); 2.76 (*m*, 1 H); 2.89 (*ddd*, *J* = 2.9, 8.2, 16.4, 1 H); 3.79 (*d*, *J* = 7.9, 1 H); 4.16 (*s*, 2 H); 5.96 (*s*, 2 H); 6.63 (*m*, 3 H); 7.02, 7.33 (*AA′BB′*, *J* = 8.4, 4 H). ^{13}C-NMR (50 MHz, $CDCl_3$): 19.7; 23.7; 32.3; 37.8; 46.1; 46.4; 55.4; 62.7; 69.4; 100.8; 107.8; 108.7; 120.5; 121.6; 129.5; 120.0; 131.0; 138.5; 146.7; 147.5; 173.2. FAB-MS: 915.2 (2), 457.1 (93, MH$^+$), 441.1 (68, [M – Me]$^+$), 135.0 (100, [Piperonyl]$^+$).

*(1*RS*,3a*RS*,6a*SR*)-4-[5-[(1,3-Benzodioxol-5-yl)methyl]-2,3,3-trimethyl-6-oxoperhydropyrrolo[3,4-*c*]pyrrol-1-yl}benzonitrile* ((±)-**38**). *General Procedure D*, starting from (±)-**36** gave (±)-**38** in 62% yield. Colorless needles. M.p. 109–111° (Et_2O). IR (KBr): 2224, 1681, 1490, 1431, 1252, 1041. ^{1}H-NMR (200 MHz, $CDCl_3$): 1.02 (*s*, 3 H); 1.15 (*s*, 3 H); 1.98 (*s*, 3 H); 2.63 (*m*, 1 H); 3.20 (*m*, 2 H); 3.38 (*m*, 1 H); 3.87, 4.27 (*AB*, *J* = 14.3, 2 H); 3.91 (*d*, *J* = 10.2, 1 H); 5.99 (*dd*, *J* = 1.4, 11.5, 2 H); 6.50 (*d*, *J* = 1.7, 1 H); 6.57 (*dd*, *J* = 1.7, 7.9, 1 H); 6.74 (*d*, *J* = 7.9, 1 H); 7.31, 7.55 (*AA′BB′*, *J* = 8.2, 4 H). ^{13}C-NMR (50 MHz, $CDCl_3$): 18.1; 22.0; 31.8; 46.2; 47.1; 48.0; 49.7; 61.3; 69.2; 100.9; 107.7; 109.1; 110.8; 118.9; 121.7; 128.5 (br.); 129.8; 131.7; 144.9; 146.9; 147.6; 171.9. FAB-MS: 807.3 (9, M_2H$^+$), 404.2 (100, MH$^+$), 388.2 (58, [M – Me]$^+$), 135.0 (86, [Piperonyl]$^+$). Anal. calc. for $C_{24}H_{25}N_3O_3$ (403.48): C 71.44, H 6.25, N 10.41; found: C 71.48, H 6.30, N 10.33. X-Ray analysis: see *Fig. 7*.

*(1*RS*,3a*RS*,6a*SR*)-4-[5-[(1,3-Benzodioxol-5-yl)methyl]-2,3,3-trimethyl-6-oxoperhydropyrrolo[3,4-*c*]pyrrol-1-yl}benzamidine Hydrochloride* ((±)-**40**). *General Procedure E* (*Method B*), starting from (±)-**38** gave (±)-**40** in 84% yield. Colorless foam. M.p. 176–180°. IR (KBr): 1667 (br.), 1613, 1538, 1489, 1443, 1405, 1369, 1280, 1245, 1205, 1037. ^{1}H-NMR (200 MHz, $(CD_3)_2SO$): 0.94 (*s*, 3 H); 1.10 (*s*, 3 H); 1.84 (*s*, 3 H); 2.63 (*m*, 1 H); 3.25 (*m*, 3 H); 3.89 (*m*, 2 H); 4.11 (*d*, *J* = 14.1, 1 H); 5.99 (*m*, 2 H); 6.56 (*s*, 1 H); 6.60, 6.85 (*AB*, *J* = 7.8, 2 H); 7.28, 7.70 (*AA′BB′*, *J* = 8.0, 4 H); 8.59 (br. *m*, 4 H). ^{13}C-NMR (50 MHz, $(CD_3)_2SO$): 18.1; 22.0; 32.1; 45.3; 46.6; 47.7; 49.4; 61.4; 69.1; 101.2; 108.3; 109.1; 121.9; 126.5; 127.8; 129.1; 130.7; 146.8; 147.2; 147.6; 165.8; 172.0. FAB-MS: 841.2 (5, (M_2H$^+$), 421.1 (100, MH$^+$). HR-DEI-MS: 420.2140 (M^+, $C_{24}H_{28}N_4O_3$; calc. 420.2161).

*(1*RS*,3a*RS*,6a*SR*)-4-[5-[(1,3-Benzodioxol-5-yl)methyl]-2,3,3-trimethyl-4-oxoperhydropyrrolo[3,4-*c*]pyrrol-1-yl}benzonitrile* ((±)-**39**). *General Procedure D*, starting from (±)-**37** gave (±)-**39** in 65% yield. Colorless needles. M.p. 125–127° (Et_2O). IR (KBr): 1682, 1604, 1498, 1448, 1428, 1376, 1246, 1224, 1037. ^{1}H-NMR (200 MHz, $CDCl_3$): 1.10 (*s*, 3 H); 1.46 (*s*, 3 H); 2.01 (*s*, 3 H); 2.38 (*dd*, *J* = 2.7, 10.3, 1 H); 2.71 (*d*, *J* = 9.0, 1 H); 2.78 (*m*, 1 H); 2.99 (*ddd*, *J* = 2.7, 8.4, 16.9, 1 H); 3.88 (*d*, *J* = 8.3, 1 H); 4.06, 4.21 (*AB*, *J* = 14.3, 2 H); 5.98 (*s*, 2 H); 6.58 (*m*, 2 H); 6.71 (*d*, *J* = 8.3, 1 H); 7.26, 7.48 (*AA′BB′*, *J* = 8.3, 4 H). ^{13}C-NMR (50 MHz, $CDCl_3$): 20.2; 24.0; 32.9;

38.1; 46.6; 46.8; 55.9; 63.4; 70.3; 101.5; 107.4; 108.5; 109.3; 111.3; 122.3; 129.2; 130.5; 132.4; 145.9; 147.4; 148.1; 173.7. FAB-MS: 404.2 (61, MH$^+$), 388.2 (58, [M – Me]$^+$), 173.2 (39), 135.1 (100, [Piperonyl]$^+$). Anal. calc. for $C_{24}H_{25}N_3O_3$ (403.48): C 71.44, H 6.25, N 10.41; found: C 71.32, H 6.29, N 10.32.

*(1*RS,*3a*RS,*6*SR*)-4-[5-[(1,3-Benzodioxol-5-yl)methyl]-2,3,3-trimethyl-4-oxoperhydropyrrolo[3,4-c]pyrrol-1-yl]benzamidine Hydrochloride* ((±)-**41**). *General Procedure E* (*Method B*), starting from (±)-**39** gave (±)-**41** in 82% yield. Colorless foam. M.p. 180–185°. IR (KBr): 1661, 1612, 1538, 1490, 1443, 1366, 1298, 1245, 1037. ^{1}H-NMR (200 MHz, $(CD_3)_2SO$): 1.05 (*s*, 3 H); 1.33 (*s*, 3 H); 1.96 (*s*, 3 H); 2.32 (*dd*, J = 2.7, 10.2, 1 H); 2.68 (*d*, J = 8.7, 1 H); 2.77 (*m*, 1 H); 3.08 (*m*, 1 H); 3.96 (*d*, J = 7.9, 1 H); 4.01, 4.15 (*AB*, J = 16.3, 2 H); 6.01 (*m*, 2 H); 6.58, 6.82 (*AB*, J = 7.9, 2 H); 6.63 (*s*, 1 H); 7.34, 7.71 (*AA′BB′*, J = 8.1, 4 H); 9.27 (br. *m*, 4 H). ^{13}C-NMR (75 MHz, $(CD_3)_2SO$): 19.8; 23.7; 32.4; 37.3; 45.1; 46.1; 54.8; 62.5; 69.1; 100.9; 108.0; 108.2; 121.2; 126.3; 127.8; 128.2; 130.4; 146.2; 146.3; 147.1; 165.3; 172.5. DEI-MS: 420.3 (1, M^+), 405.3 (20, [M – Me]$^+$), 388.2 (8), 135.1 (100, [Piperonyl]$^+$). HR-DEI-MS: 420.2171 (M^+, $C_{24}H_{28}N_4O_3$; calc. 420.2161).

*(3*RS,*3a*SR,*4*RS,*6a*RS*)-2-[(1,3-Benzodioxol-5-yl)methyl]-4-(4-bromophenyl)-3,5,6,6-tetramethyl-2,3,3a,4,5,6-hexahydro-1*H*-pyrrolo[3,4-c]pyrrol-1-one* ((±)-**44**). A 3M soln. of MeMgCl (3.08 ml, 9.24 mmol) in THF was added *via* syringe at 20° to a soln. of (±)-**34** (1.98 g, 4.2 mmol) in dry THF (20 ml), and the mixture was stirred for 13 h. After hydrolysis with 1M HCl, the soln. was neutralized and extracted with CH_2Cl_2. The org. phase was dried (Na_2SO_4) and evaporated *in vacuo*. The residue was dissolved in MeOH (20 ml), and Na[BH_3CN] (264 mg, 4.2 mmol) and a trace of methyl orange were added. CF_3COOH was added dropwise to the stirred soln. until the color changed to red. Stirring was continued for 2 h, while CF_3COOH was added at regular intervals to maintain the red color of the soln. Neutralization with 1N NaOH, evaporation of MeOH, and extraction of the residue with CH_2Cl_2 afforded an org. phase which was dried (Na_2SO_4) and evaporated *in vacuo* to give a residue, which was purified by CC (SiO_2; hexane/AcOEt/Et_3N 66 : 33 : 1) to give (±)-**44** (1.86 g, 94%). Colorless crystals. M.p. 142–143°. ($CHCl_3$/hexane). IR (KBr): 1688, 1505, 1490, 1408, 1238, 1032. ^{1}H-NMR (200 MHz, $CDCl_3$): 0.37 (*d*, 7.2, 3 H); 1.06 (*s*, 3 H); 1.56 (*s*, 3 H); 1.98 (*s*, 3 H); 2.59 (*d*, J = 7.6, 1 H); 3.00 (*ddd*, J = 5.9, 7.6, 9.5, 1 H); 3.48 (*m*, 1 H); 3.59, 4.79 (*AB*, J = 14.7, 2 H); 3.74 (*d*, J = 9.5, 1 H); 5.92 (*s*, 2 H); 6.64 (*m*, 3 H); 7.20, 7.35 (*AA′BB′*, J = 8.5, 4 H). ^{13}C-NMR (50 MHz, $CDCl_3$): 14.7; 19.8; 23.3; 32.5; 43.7; 43.9; 54.2; 57.1; 61.9; 69.6; 101.3; 108.4; 109.0, 121.3; 121.8; 131.2; 131.4; 131.7; 140.7; 147.2; 148.1; 175.4. FAB-MS: 471.1 (100, MH$^+$), 455.0 (68, [M – Me]$^+$), 135.0 (36, [Piperonyl]$^+$). Anal. calc. for $C_{24}H_{27}BrN_2O_3$ (471.39): C 61.15, H 5.77, N 5.94, Br 16.95; found: C 61.22, H 5.83, N 6.00, Br 17.16.

*(1*RS,*3a*RS,*6*RS,*6a*SR*)-4-[5-[(1,3-Benzodioxol-5-yl)methyl]-2,3,3,6-tetramethyl-4-oxoperhydropyrrolo[3,4-c]pyrrol-1-yl]benzonitrile* ((±)-**45**). *General Procedure D*, starting from (±)-**44** gave (±)-**45** in 65% yield. Colorless prisms. M.p. 173–174° (AcOEt). IR (KBr): 2225, 1686, 1504, 1490, 1415, 1240, 1034. ^{1}H-NMR (200 MHz, $CDCl_3$): 0.30 (*d*, J = 7.2, 3 H); 1.06 (*s*, 3 H); 1.56 (*s*, 3 H); 1.96 (*s*, 3 H); 2.61 (*d*, J = 7.5, 1 H); 3.05 (*ddd*, J = 6.0, 7.5, 9.5, 1 H); 3.48 (*dq*, J = 7.1, 5.9, 1 H); 3.60, 4.71 (*AB*, J = 14.8, 2 H); 3.82 (*d*, J = 9.5, 1 H); 5.91 (*s*, 2 H); 6.62 (*m*, 3 H); 7.44, 7.49 (*AA′BB′*, J = 8.5, 4 H). ^{13}C-NMR (50 MHz, $CDCl_3$): 14.4; 19.5; 22.7; 32.1; 43.3; 43.7; 53.6, 56.5; 61.6; 69.4; 100.7; 107.8; 108.4; 110.8; 118.6; 121.1; 130.1; 130.3; 131.4; 146.5; 147.0; 147.5; 175.6. FAB-MS: 835.3 (3, M_2H$^+$), 418.1 (97, MH$^+$), 402.1 (100, [M – Me]$^+$). Anal. calc. for $C_{25}H_{27}N_3O_3$ (417.51): C 71.92, H 6.52, N 10.06; found: C 71.86, H 6.77, N 10.01.

*(1*RS,*3a*RS,*6*RS,*6a*SR*)-4-[5-[(1,3-Benzodioxol-5-yl)methyl]-2,3,3,6-tetramethyl-4-oxoperhydropyrrolo[3,4-c]pyrrol-1-yl]benzamidine Hydrochloride* ((±)-**46**). *General Procedure E* (*Method B*), starting from (±)-**45** gave (±)-**46** in 83% yield. Colorless solid. M.p. 215–220°. IR (KBr): 1677, 1612, 1490, 1444, 1409, 1243, 1037. ^{1}H-NMR (300 MHz, $(CD_3)_2SO$): 0.20 (*d*, J = 7.2, 3 H); 1.00 (*s*, 3 H); 1.42 (*s*, 3 H); 1.88 (*s*, 3 H); 2.65 (*d*, J = 7.8, 1 H); 3.13 (*m*, 1 H); 3.40 (*m*, 1 H); 3.59, 4.53 (*AB*, J = 14.9, 2 H); 3.86 (*d*, J = 9.3, 1 H); 5.95 (*m*, 2 H); 6.56, 6.77 (*AB*, J = 7.9, 2 H); 6.63 (*s*, 1 H); 7.46, 7.67 (*AA′BB′*, J = 8.3, 4 H); 9.08 (br. *s*, 2 H); 9.32 (br. *s*, 2 H). ^{13}C-NMR (75 MHz, $(CD_3)_2SO$): 14.1; 19.5; 22.9; 32.3; 42.5; 43.1; 53.2; 56.0; 61.4; 68.9; 101.0; 108.2; 121.1; 126.7; 127.7; 129.9; 131.1; 146.4; 147.4; 148.3; 165.6; 174.4; one peak missing due to signal overlap. FAB-MS: 435.2 (100, MH$^+$), 419.2 (21), 289.1 (34). HR-DEI-MS: 434.2313 (M^+, $C_{25}H_{30}N_4O_3$; calc. 434.2318).

*(3a*RS,*6*RS,*6a*SR*)-2-[(1,3-Benzodioxol-5-yl)methyl]-6-(4-bromophenyl)-3-hydroxy-4,4,5-trimethyl-2,3,3a,4,5,6-hexahydro-1*H*-pyrrolo[3,4-c]pyrrol-1-one* ((±)-**47**). A 1M soln. of Li[Et_3BH] (30.65 ml, 30.65 mmol) in THF was added under Ar to a soln. of (±)-**34** (8.49 g, 18.0 mmol) in dry THF (60 ml) at –78°. The mixture was stirred for 2 h at –78°, then warmed to 0°. A sat. aq. $NaHCO_3$ soln. (20 ml) and 30% aq. H_2O_2 soln. (6 ml) were added sequentially, and the mixture was stirred for 1 h at 0°. After evaporation of THF, the aq. phase was extracted with CH_2Cl_2, and the org. phase was dried (Na_2SO_4). Evaporation *in vacuo* and CC (SiO_2; CH_2Cl_2/CH_3OH 98 : 2) gave (±)-**47** in 67% yield. Colorless needles. M.p. 158–159° (Et_2O). IR (KBr): 1693, 1493, 1446, 1368, 1231, 1196, 1039, 1010. ^{1}H-NMR (200 MHz, $CDCl_3$): 1.04 (*s*, 3 H); 1.47 (*s*, 3 H); 2.09 (*s*, 3 H); 2.52 (*dd*, J = 6.2, 8.0, 1 H); 3.26 (*dd*, J = 8.0, 10.5, 1 H); 3.81 (*d*, J = 10.5, 1 H); 4.00, 4.49 (*AB*, J = 14.6, 2 H); 4.99 (br. *m*, 1 H);

5.93 (*s*, 2 H); 6.70 (*s*, 3 H); 6.89 (br. *m*, 1 H); 7.15, 7.43 (*AA′BB′*, *J* = 8.6, 4 H). ^{13}C-NMR (50 MHz, $CDCl_3$): 18.3; 21.6; 31.8; 43.6; 48.6; 50.0; 62.9; 67.5; 80.9; 101.3; 108.4; 109.5; 122.3; 131.1; 131.3; 131.5; 132.0; 136.4; 147.3; 148.1; 172.9. FAB-MS: 947.4 (4), 473.2 (76, MH^+), 457.2 (61, $[M - Me]^+$), 135.0 (100, [Piperonyl]$^+$). Anal. calc. for $C_{23}H_{25}BrN_2O_4$ (473.37): C 58.36, H 5.32, N 5.92, Br 16.88; found: C 58.35, H 5.10, N 6.07, Br 16.67.

A mixture of other isomers (2.22 g, 26%) was isolated as a side product.

*(3*RS*,3a*SR*,6*RS*,6a*SR*)-2-[(1,3-Benzodioxol-5-yl)methyl]-6-(4-bromophenyl)-4,4,5-trimethyl-3-(toluene-4-sulfonyl)-2,3,3a,4,5,6-hexahydro-1*H*-pyrrolo[3,4-*c*]pyrrol-1-one* (±)-**48**. A mixture of 4-toluenesulfinic acid (5.49 g, 35.2 mmol) and dry powdered $CaCl_2$ (3.91 g, 35.2 mmol) in dry CH_2Cl_2 (60 ml) was stirred for 10 min under Ar, after which a soln. of (±)-**47** (5.55 g, 11.7 mmol) in CH_2Cl_2 (20 ml) was added. After stirring for 19 h, sat. aq. $NaHCO_3$ soln. was added, and the mixture was extracted with CH_2Cl_2. The org. phase was washed thoroughly with sat. aq. $NaHCO_3$ soln. (4×), dried (Na_2SO_4), and evaporated *in vacuo*. The residue was purified by CC (SiO_2; hexane/AcOEt/Et_3N 74:25:1) to give (±)-**48** (5.29 g, 74%). Colorless prisms. M.p. 172–173° (AcOEt/hexane). IR (KBr): 1710, 1597, 1491, 1446, 1393, 1301, 1248, 1134, 1037. ^{1}H-NMR (200 MHz, $CDCl_3$): 1.00 (*s*, 6 H); 1.89 (*s*, 3 H); 2.42 (*m*, 1 H); 2.46 (*s*, 3 H); 2.71 (*dd*, *J* = 2.1, 9.3, 1 H); 3.70 (*d*, *J* = 8.0, 1 H); 4.34, 4.94 (*AB*, *J* = 14.5, 2 H); 4.67 (*d*, *J* = 2.0, 1 H); 6.01 (*m*, 2 H); 6.81 (*m*, 3 H); 6.94, 7.39 (*AA′BB′*, *J* = 8.4, 4 H); 7.37, 7.68 (*AA′BB′*, *J* = 8.1, 4 H). ^{13}C-NMR (50 MHz, $CDCl_3$): 19.7; 21.5; 24.0; 32.1; 44.7; 46.9; 47.8; 62.3; 68.8; 78.1; 100.9; 108.0; 109.6; 121.0; 122.6; 128.6; 129.2; 129.9; 130.0; 130.7; 131.4; 136.2; 145.7; 147.1; 147.6; 172.3. FAB-MS: 1223.3 (1), 1067.2 (1), 611.0 (30, MH^+), 455.1 (62, $[M - MeC_6H_4SO_2]^+$), 135.0 (100, [Piperonyl]$^+$). Anal. calc. for $C_{30}H_{31}BrN_2O_5S$ (611.56): C 58.92, H 5.11, N 4.58, Br 13.08, S 5.24; found: C 58.75, H 5.25, N 4.50, Br 13.02, S 5.38.

*(3*RS*,3a*SR*,6*RS*,6a*SR*)-2-[(1,3-Benzodioxol-5-yl)methyl]-6-(4-bromophenyl)-3,4,4,5-tetramethyl-2,3,3a,4,5,6-hexahydro-1*H*-pyrrolo[3,4-*c*]pyrrol-1-one* ((±)-**49a**). *General Procedure F*, starting from (±)-**48** gave (±)-**49a** in 75% yield. Colorless solid. M.p. 142–144° (toluene). IR (KBr): 1685, 1492, 1443, 1418, 1363, 1249, 1038. ^{1}H-NMR (200 MHz, $CDCl_3$): 1.00 (*s*, 3 H); 1.17 (*s*, 3 H); 1.25 (*d*, *J* = 6.3, 3 H); 1.96 (*s*, 3 H); 2.09 (*dd*, *J* = 7.1, 8.9, 1 H); 3.23 (*m*, 1 H); 3.63 (*m*, 1 H); 3.68, 4.59 (*AB*, *J* = 14.6, 2 H); 3.81 (*d*, *J* = 10.2, 1 H); 5.98, 6.02 (*AB*, *J* = 1.4, 2 H); 6.57 (*m*, 2 H); 6.74 (*d*, *J* = 8.3, 1 H); 7.06, 7.39 (*AA′BB′*, *J* = 8.3, 4 H). ^{13}C-NMR (50 MHz, $CDCl_3$): 18.3; 20.3; 22.1; 31.8; 43.0; 49.3; 53.9; 55.7; 61.2; 68.9; 100.8; 107.6; 109.4; 120.7; 121.7; 129.8; 130.2; 131.0; 138.1; 146.6; 147.4; 172.2. FAB-MS: 943.3 (6), 471.3 (82, MH^+), 455.2 (45, $[M - Me]^+$), 135.0 (100, [Piperonyl]$^+$). Anal. calc. for $C_{24}H_{27}BrN_2O_3$ (471.39): C 61.15, H 5.77, N 5.94, Br 16.95; found: C 61.17, H 5.96, N 5.98, Br 16.67.

*(3*RS*,3a*SR*,6*RS*,6a*SR*)-2-[(1,3-Benzodioxol-5-yl)methyl]-6-(4-bromophenyl)-3-ethyl-4,4,5-trimethyl-2,3,3a,4,5,6-hexahydro-1*H*-pyrrolo[3,4-*c*]pyrrol-1-one* ((±)-**49b**). *General Procedure F*, starting from (±)-**48** gave (±)-**49b** in 76% yield. Colorless needles. M.p. 156–157° ($CHCl_3$/hexane). IR (KBr): 1683, 1504, 1492, 1428, 1363, 1257, 1243, 1038. ^{1}H-NMR (200 MHz, $CDCl_3$): 0.80 (*t*, *J* = 7.4, 3 H); 1.01 (*s*, 3 H); 1.14 (*s*, 3 H); 1.59 (*m*, 1 H); 1.81 (*m*, 1 H); 1.94 (*s*, 3 H); 2.30 (*dd*, *J* = 6.5, 9.2, 1 H); 3.19 (*m*, 1 H); 3.56, 4.65 (*AB*, *J* = 14.6, 2 H); 3.68 (*m*, 1 H); 3.80 (*d*, *J* = 10.0, 1 H); 5.99, 6.03 (*AB*, *J* = 1.3, 2 H); 6.62 (*m*, 2 H); 6.75 (*d*, *J* = 7.5, 1 H); 7.04, 7.37 (*AA′BB′*, *J* = 8.4, 4 H). ^{13}C-NMR (50 MHz, $CDCl_3$): 6.4; 18.5; 22.6; 23.5; 31.9; 43.4; 49.3; 49.5; 57.4; 61.6; 69.1; 100.8; 107.6; 109.5; 120.6; 121.9; 129.9; 130.2; 130.9; 138.0; 146.6; 147.4; 172.7. FAB-MS: 971.3 (5), 485.1 (68, MH^+), 135.0 (100, [Piperonyl]$^+$). Anal. calc. for $C_{25}H_{29}BrN_2O_3$ (485.42): C 61.86, H 6.02, N 5.77, Br 16.46; found: C 61.69, H 6.21, N 5.71, Br 16.20.

*(3*RS*,3a*SR*,6*RS*,6a*SR*)-2-[(1,3-Benzodioxol-5-yl)methyl]-6-(4-bromophenyl)-3-isopropyl-4,4,5-trimethyl-2,3,3a,4,5,6-hexahydro-1*H*-pyrrolo[3,4-*c*]pyrrol-1-one* ((±)-**49c**). *General Procedure F*, starting from (±)-**48** gave (±)-**49c** in 35% yield. Colorless needles. M.p. 146–147° ($CHCl_3$/hexane). IR (KBr): 1682, 1504, 1492, 1431, 1362, 1285, 1246, 1038. ^{1}H-NMR (200 MHz, $CDCl_3$): 0.69 (*d*, *J* = 6.8, 3 H); 0.90 (*d*, *J* = 7.0, 3 H); 1.01 (*s*, 3 H); 1.10 (*s*, 3 H); 1.96 (*s*, 3 H); 2.13 (*m*, 1 H); 2.21 (*dd*, *J* = 3.6, 9.6, 1 H); 3.11 (*m*, 1 H); 3.54 (*m*, 1 H); 3.63, 4.75 (*AB*, *J* = 14.7, 2 H); 3.82 (*d*, *J* = 8.7, 1 H); 5.97, 6.00 (*AB*, *J* = 1.4, 2 H); 6.72 (*m*, 3 H); 7.11, 7.41 (*AA′BB′*, *J* = 8.4, 4 H). ^{13}C-NMR (50 MHz, $CDCl_3$): 14.4; 18.2; 19.4; 24.1; 27.7; 32.2; 43.4; 45.2; 49.9; 61.1; 62.3; 69.1; 100.8; 107.7; 108.9; 120.7; 121.3; 130.0; 130.1; 130.7; 137.9; 146.6; 147.5; 172.1. FAB-MS: 999.2 (2), 499.2 (78, MH^+), 135.1 (100, [Piperonyl]$^+$). Anal. calc. for $C_{26}H_{31}BrN_2O_3$ (499.45): C 62.53, H 6.26, N 5.61, Br 16.00; found: C 62.37, H 6.38, N 5.56, Br 15.80.

*(3*RS*,3a*SR*,6*RS*,6a*SR*)-2-[(1,3-Benzodioxol-5-yl)methyl]-6-(4-bromophenyl)-3-cyclohexyl-4,4,5-trimethyl-2,3,3a,4,5,6-hexahydro-1*H*-pyrrolo[3,4-*c*]pyrrol-1-one* ((±)-**49d**). *General Procedure F*, starting from (±)-**48** gave (±)-**49d** in 31% yield after CC (SiO_2; CH_2Cl_2/MeOH 98:2). Colorless crystals. M.p. 148–149° ($CHCl_3$/hexane). IR (KBr): 1684, 1489, 1444, 1244, 1039. ^{1}H-NMR (200 MHz, $CDCl_3$): 1.11 (*m*, 6 H); 1.01 (*s*, 3 H); 1.08 (*s*, 3 H); 1.51 (*m*, 1 H); 1.73 (*m*, 4 H); 1.95 (*s*, 3 H); 2.29 (*dd*, *J* = 3.5, 9.7, 1 H); 3.10 (*m*, 1 H); 3.53 (*t*, *J* = 3.3, 1 H); 3.66, 4.70 (*AB*, *J* = 14.7, 2 H); 3.80 (*d*, *J* = 8.7, 1 H); 5.97, 6.00 (*AB*, *J* = 1.3, 2 H); 6.75 (*m*, 3 H); 7.10, 7.39 (*AA′BB′*, *J* = 8.4, 4 H). ^{13}C-NMR (50 MHz, $CDCl_3$): 19.7; 24.4; 25.0; 26.0; 26.5; 29.3; 32.5; 38.9; 43.8; 46.5; 50.1;

61.4; 62.6; 69.4; 101.1; 108.0; 109.2; 121.0; 121.7; 130.3; 130.5; 131.0; 138.2; 146.8; 147.8; 172.5; one peak missing due to signal overlap. FAB-MS: 1079.9 (4), 539.4 (100, MH$^+$), 523.4 (61, [M – Me]$^+$), 135.0 (41, [Piperonyl]$^+$). Anal. calc. for $C_{29}H_{35}BrN_2O_3$ (539.51): C 64.56, H 6.54, N 5.19, Br 14.81; found: C 64.52, H 6.57, N 5.32, Br 14.90.

*(1*RS*,3a*SR*,4*RS*,6a*SR*)-4-{5-[(1,3-Benzodioxol-5-yl)methyl]-2,3,3,4-tetramethyl-6-oxoperhydropyrrolo[3,4-c]pyrrol-1-yl}benzonitrile* ((±)-**50a**). *General Procedure D*, starting from (±)-**49a** gave (±)-**50a** in 62% yield. Colorless crystals. M.p. 165–166° (AcOEt/Et$_2$O). IR (KBr): 2225, 1678, 1504, 1491, 1444, 1428, 1364, 1249, 1038. ^{1}H-NMR (200 MHz, $CDCl_3$): 1.02 (*s*, 3 H); 1.18 (*s*, 3 H); 1.26 (*d*, J = 6.3, 3 H); 1.96 (*s*, 3 H); 2.12 (*dd*, J = 7.1, 8.9, 1 H); 3.26 (*m*, 1 H); 3.62 (*m*, 1 H); 3.64, 4.56 (*AB*, J = 14.6, 2 H); 3.89 (*d*, J = 10.2, 1 H); 5.97, 6.05 (*AB*, J = 1.4, 2 H); 6.44 (*d*, J = 1.6, 1 H); 6.55 (*dd*, J = 1.7, 7.9, 1 H); 6.73 (*d*, J = 7.8, 1 H); 7.28, 7.54 (*AA′BB′*, J = 8.3, 4 H). ^{13}C-NMR (50 MHz, $CDCl_3$): 18.4; 20.2; 22.1; 31.9; 42.9; 49.4; 53.8; 55.7; 61.5; 69.1; 100.9; 107.5; 109.4; 110.7; 119.0; 121.6; 128.8; 130.0; 131.7; 144.7; 146.7; 147.5; 171.8. FAB-MS: 835.3 (20, M_2H$^+$), 418.2 (100, MH$^+$), 403.1 (52), 135.0 (40, [Piperonyl]$^+$). Anal. calc. for $C_{25}H_{27}N_3O_3$ (417.51): C 71.92, H 6.52, N 10.06; found: C 72.02, H 6.74, N 10.02.

*(1*RS*,3a*SR*,4*RS*,6a*SR*)-4-{5-[(1,3-Benzodioxol-5-yl)methyl]-4-ethyl-2,3,3-trimethyl-6-oxoperhydropyrrolo-[3,4-c]pyrrol-1-yl}benzonitrile* ((±)-**50b**). *General Procedure D*, starting from (±)-**49b** gave (±)-**50b** in 40% yield. Colorless needles. M.p. 188–190° (AcOEt). IR (KBr): 2222, 1677, 1607, 1504, 1492, 1434, 1364, 1256, 1243, 1037. ^{1}H-NMR (200 MHz, $CDCl_3$): 0.80 (*t*, J = 7.4, 3 H); 1.02 (*s*, 3 H); 1.15 (*s*, 3 H); 1.62 (*m*, 1 H); 1.81 (*m*, 1 H); 1.94 (*s*, 3 H); 2.32 (*dd*, J = 6.4, 9.2, 1 H); 3.23 (*m*, 1 H); 3.51, 4.61 (*AB*, J = 14.6, 2 H); 3.68 (*m*, 1 H); 3.88 (*d*, J = 10.0, 1 H); 5.97, 6.05 (*AB*, J = 1.3, 2 H); 6.53 (*d*, J = 1.6, 1 H); 6.58 (*dd*, J = 7.8, 1.6, 1 H); 6.74 (*d*, J = 7.8, 1 H); 7.26, 7.52 (*AA′BB′*, J = 8.3, 4 H). ^{13}C-NMR (50 MHz, $CDCl_3$): 6.4; 18.7; 22.5; 23.4; 31.9; 43.3; 49.4; 49.5; 57.3; 61.8; 69.3; 100.9; 107.6; 109.5; 110.6; 119.0; 121.7; 128.9; 130.0; 131.6; 144.7; 146.7; 147.5; 172.3. FAB-MS: 863.3 (9), 432.2 (100, MH$^+$), 416.2 (72, [M – Me]$^+$), 135.0 (99, [Piperonyl]$^+$). Anal. calc. for $C_{26}H_{29}N_3O_3$ (431.53): C 72.37, H 6.77, N 9.74, O 11.12; found: C 72.22, H 6.93, N 9.67, O 11.02.

*(1*RS*,3a*SR*,4*RS*,6a*SR*)-4-{5-[(1,3-Benzodioxol-5-yl)methyl]-4-isopropyl-2,3,3-trimethyl-6-oxoperhydropyrrolo[3,4-c]pyrrol-1-yl}benzonitrile* ((±)-**50c**). *General Procedure D*, starting from (±)-**49c** gave (±)-**50c** in 55% yield. Colorless prisms. M.p. 160–162° (AcOEt). IR (KBr): 2225, 1674, 1610, 1492, 1446, 1378, 1244, 1036. ^{1}H-NMR (200 MHz, $CDCl_3$): 0.69 (*d*, J = 6.7, 3 H); 0.91 (*d*, J = 7.0, 3 H); 1.04 (*s*, 3 H); 1.11 (*s*, 3 H); 1.97 (*s*, 3 H); 2.16 (*m*, 1 H); 2.24 (*dd*, J = 3.5, 9.7, 1 H); 3.17 (*m*, 1 H); 3.55 (*m*, 1 H); 3.64, 4.69 (*AB*, J = 15.1, 2 H); 3.91 (*d*, J = 8.7, 1 H); 5.98, 6.02 (*AB*, J = 0.9, 2 H); 6.73 (*m*, 3 H); 7.34, 7.57 (*AA′BB′*, J = 8.1, 4 H). ^{13}C-NMR (50 MHz, $CDCl_3$): 14.4; 18.2; 19.6; 24.0; 27.7; 32.3; 43.4; 45.2; 50.1; 61.2; 62.6; 68.3; 100.8; 107.8; 108.8; 110.6; 119.1; 121.3; 129.0; 130.0; 131.4; 144.8; 146.7; 147.6; 171.8. FAB-MS: 891.4 (13, M_2H$^+$), 446.2 (100, MH$^+$), 430.2 (63, [M – Me]$^+$), 135.0 (62, [Piperonyl]$^+$). Anal. calc. for $C_{27}H_{31}N_3O_3$ (445.56): C 72.78, H 7.01, N 9.43; found: C 72.69, H 7.24, N 9.35.

*(1*RS*,3a*SR*,4*RS*,6a*SR*)-4-{5-[(1,3-Benzodioxol-5-yl)methyl]-4-cyclohexyl-2,3,3-trimethyl-6-oxoperhydropyrrolo[3,4-c]pyrrol-1-yl}benzonitrile* ((±)-**50d**). *General Procedure D*, starting from (±)-**49d** gave (±)-**50d** in 62% yield. Colorless needles. M.p. 114–116° ($CHCl_3$/hexane). IR (KBr): 2226, 1669, 1488, 1445, 1370, 1241, 1040. ^{1}H-NMR (200 MHz, $CDCl_3$): 1.12 (*m*, 6 H); 1.03 (*s*, 3 H); 1.09 (*s*, 3 H); 1.61 (*m*, 1 H); 1.73 (*m*, 4 H); 1.95 (*s*, 3 H); 2.31 (*dd*, J = 3.4, 9.6, 1 H); 3.14 (*m*, 1 H); 3.54 (*m*, 1 H); 3.64, 4.67 (*AB*, J = 14.9, 2 H); 3.89 (*d*, J = 8.7, 1 H); 5.97, 6.01 (*AB*, J = 1.2, 2 H); 6.71 (*m*, 2 H); 6.78 (*d*, J = 7.5, 1 H); 7.32, 7.56 (*AA′BB′*, J = 8.2, 4 H). ^{13}C-NMR (50 MHz, $CDCl_3$): 19.6; 24.0; 24.7; 25.7; 26.2; 29.0; 32.2; 38.5; 43.5; 46.3; 50.0; 61.1; 62.6; 69.3; 100.8; 107.7; 108.9; 110.6; 119.1; 121.3; 129.0; 130.1; 131.4; 144.8; 146.6; 147.5; 171.8; one peak missing due to signal overlap. FAB-MS: 971.4 (6, M_2H$^+$), 486.2 (93, MH$^+$), 484.2 (40), 135.0 (100, [Piperonyl]$^+$). Anal. calc. for $C_{30}H_{35}N_3O_3$ (485.62): C 74.20, H 7.26, N 8.65; found: C 73.94, H 7.26, N 8.74.

*(1*RS*,3a*SR*,4*RS*,6a*SR*)-4-{5-[(1,3-Benzodioxol-5-yl)methyl]-2,3,3,4-tetramethyl-6-oxoperhydropyrrolo[3,4-c]pyrrol-1-yl}benzamidine Hydrochloride* ((±)-**51a**). *General Procedure E* (*Method B*), starting from (±)-**50a** afforded (±)-**51a** in 90% yield. Colorless foam. M.p. > 190° (dec.). IR (KBr): 1682, 1651, 1614, 1491, 1443, 1382, 1368, 1245, 1035. ^{1}H-NMR (200 MHz, $(CD_3)_2SO$): 0.99 (*s*, 3 H); 1.13 (*s*, 3 H); 1.20 (*d*, J = 6.2, 3 H); 1.87 (*s*, 3 H); 2.16 (*m*, 1 H); 3.27 (*m*, 1 H); 3.57 (*m*, 1 H); 3.78, 4.32 (*AB*, J = 14.9, 2 H); 3.92 (*d*, J = 10.3, 1 H); 6.04 (*m*, 2 H); 6.57 (*d*, J = 1.5, 1 H); 6.64 (*dd*, J = 1.5, 7.8, 1 H); 6.89 (*d*, J = 7.8, 1 H); 7.31, 7.72 (*AA′BB′*, J = 8.0, 4 H); 9.24 (br. *m*, 4 H). ^{13}C-NMR (75 MHz, $(CD_3)_2SO$): 18.2; 20.3; 21.9; 31.9; 42.6; 48.9; 53.8; 54.9; 61.3; 68.7; 100.9; 107.9; 108.9; 121.5; 126.1; 127.4; 128.8; 130.8; 146.2; 146.5; 147.0; 165.3; 171.5. DEI-MS: 435.3 (8, MH$^+$), 434.3 (6, M^+), 419.2 (12, [M – Me]$^+$), 214.2 (22), 197.1 (12), 135.1 (99, [Piperonyl]$^+$), 83.1 (100). HR-DEI-MS: 434.2337 (M^+, $C_{25}H_{30}N_4O_3$; calc. 434.2318).

*(1*RS*,3a*SR*,4*RS*,6a*SR*)-4-{5-[(1,3-Benzodioxol-5-yl)methyl]-4-ethyl-2,3,3-trimethyl-6-oxoperhydropyrrolo-[3,4-c]pyrrol-1-yl}benzamidine Hydrochloride* ((±)-**51b**). *General Procedure E* (*Method B*), starting from (±)-**50b** gave (±)-**51b** in 90% yield. Colorless foam. M.p. > 270° (dec.). IR (KBr): 1691, 1670, 1614, 1495, 1440, 1261,

1240, 1028. ^{1}H-NMR (200 MHz, $(CD_3)_2SO$): 0.70 (t, $J=7.0$, 3 H); 0.99 (s, 3 H); 1.10 (s, 3 H); 1.57 (m, 1 H); 1.75 (m, 1 H); 1.86 (s, 3 H); 2.32 (dd, $J=6.0$, 9.0, 1 H); 3.23 (m, 1 H); 3.62 (m, 2 H); 3.93 (d, $J=9.8$, 1 H); 4.39 (d, $J=14.5$, 1 H); 6.05 (m, 2 H); 6.68 (m, 2 H); 6.91 (d, $J=7.8$, 1 H); 7.30, 7.72 ($AA'BB'$, $J=8.2$, 4 H); 9.22 (s, 2 H); 9.38 (s, 2 H). ^{13}C-NMR (50 MHz, $(CD_3)_2SO$): 6.8; 18.7; 22.6; 23.7; 32.2; 43.1; 49.3; 57.6; 62.1; 69.2; 101.2; 108.2; 109.4; 122.1; 126.4; 127.7; 129.3; 131.0; 146.7; 146.8; 147.4; 165.9; 172.3; one peak missing due to signal overlap. DEI-MS: 448.3 (47, M^+), 433.3 (100, $[M-Me]^+$), 214.2 (33), 135.1 (44, [Piperonyl]$^+$). HE-DEI-MS: 448.2461 (M^+, $C_{26}H_{32}N_4O_3$; calc. 448.2474).

*(1*RS*,3a*SR*,4*RS*,6a*SR*)-4-[5-[(1,3-Benzodioxol-5-yl)methyl]-4-isopropyl-2,3,3-trimethyl-6-oxoperhydropyrrolo[3,4-*c*]pyrrol-1-yl}benzamidine Hydrochloride* ((±)-**51c**). *General Procedure E* (*Method B*), starting from (±)-**50c**; gave (±)-**51c** in 66% yield. Colorless foam. M.p. > 250° (dec.). IR (KBr): 1654, 1611, 1493, 1445, 1247, 1038. ^{1}H-NMR (200 MHz, $(CD_3)_2SO$): 0.62 (d, $J=6.7$, 3 H); 0.87 (d, $J=6.7$, 3 H); 1.02 (s, 3 H); 1.06 (s, 3 H); 1.90 (s, 3 H); 2.15 (m, 1 H); 2.26 (dd, $J=2.8$, 9.6, 1 H); 3.19 (m, 1 H); 3.48 (m, 1 H); 3.72, 4.52 (AB, $J=14.9$, 2 H); 3.98 (d, $J=8.4$, 1 H); 6.05 (m, 2 H); 6.80 (m, 2 H); 6.94 (d, $J=7.8$, 1 H); 7.39, 7.74 ($AA'BB'$, $J=8.3$, 4 H); 9.12 (s, 2 H); 9.35 (s, 2 H). ^{13}C-NMR (50 MHz, $(CD_3)_2SO$): 13.9; 17.7; 19.2; 23.7; 27.0; 32.1; 42.3; 44.3; 49.4; 60.4; 62.1; 68.6; 100.6; 107.8; 108.1; 120.9; 125.7; 126.8; 128.7; 130.2; 145.9; 146.1; 146.9; 165.0; 171.1. DEI-MS: 462.3 (33, M^+), 447.2 (100, $[M-Me]^+$), 430.3 (21), 214.2 (30), 135.1 (67, [Piperonyl]$^+$). HR-DEI-MS: 462.2633 (M^+, $C_{27}H_{34}N_4O_3$; calc. 462.2631). X-Ray analysis: see *Figs. 8* and *9*.

*(1*RS*,3a*SR*,4*RS*,6a*SR*)-4-[5-[(1,3-Benzodioxol-5-yl)methyl]-4-cyclohexyl-2,3,3-trimethyl-6-oxoperhydropyrrolo[3,4-*c*]pyrrol-1-yl}benzamidine Hydrochloride* ((±)-**51d**). *General Procedure E* (*Method B*), starting from (±)-**50d** afforded (±)-**51d** in 74% yield. Colorless foam. M.p. 195–199°. IR (KBr): 1667, 1611, 1490, 1443, 1366, 1246, 1036. ^{1}H-NMR (200 MHz, $(CD_3)_2SO$): 1.05 (m, 5 H); 1.00 (s, 3 H); 1.05 (s, 3 H); 1.41 (m, 2 H); 1.69 (m, 4 H); 1.86 (s, 3 H); 2.29 (m, 1 H); 3.14 (m, 1 H); 3.46 (m, 1 H); 3.72, 4.45 (AB, $J=14.9$, 2 H); 3.93 (d, $J=8.3$, 1 H); 6.01 (m, 2 H); 6.78 (m, 2 H); 6.91 (d, $J=7.5$, 1 H); 7.35, 7.73 ($AA'BB'$, $J=8.3$, 4 H); 9.1 (br. s, 2 H); 9.37 (br. s, 2 H). ^{13}C-NMR (50 MHz, $(CD_3)_2SO$): 17.7; 22.3; 22.6; 23.6; 24.2; 26.7; 30.1; 36.2; 41.1; 44.0; 48.0; 59.1; 60.8; 67.2; 99.3; 106.4; 106.8; 119.7; 124.3; 125.6; 127.4; 129.1; 144.7; 144.9; 145.7; 163.9; 170.0; one peak missing due to signal overlap. DEI-MS: 502.2 (11, M^+), 487.2 (42), 214.1 (38), 135 (100, [Piperonyl]$^+$). HR-DEI-MS: 502.2969 (M^+, $C_{30}H_{38}N_4O_3$; calc. 502.2944).

*(1*RS*,3a*SR*,4*RS*,8a*SR*,8b*RS*)-2-[(1,3-Benzodioxol-5-yl)methyl]-4-(4-bromophenyl)-1-(toluene-4-sulfonyl)-perhydropyrrolo[3,4-*a*]pyrrolizin-3-one* ((±)-**52**). A 1M soln. of Li[Et_3BH] (7.87 ml, 7.87 mmol) in THF was added under Ar at −78° to a soln. of (±)-**31** (2.18 g, 4.63 mmol) in dry THF (20 ml). The mixture was stirred for 30 min at −78°, then warmed to 0°. A sat. $NaHCO_3$ soln. (5 ml) and 30% aq. H_2O_2 soln. (1.5 ml) were added sequentially, and the mixture was stirred for 1 h at 0°. After evaporation of THF, the aq. phase was extracted with CH_2Cl_2 and the resulting org. phase was dried (Na_2SO_4) and evaporated *in vacuo*. 4-Toluenesulfinic acid (2.17 g, 13.9 mmol), powdered $CaCl_2$ (1.54 g, 13.9 mmol), and CH_2Cl_2 (40 ml) were added to the residue, and the mixture was stirred under Ar for 24 h. After addition of sat. aq. $NaHCO_3$ soln., the mixture was extracted with CH_2Cl_2, and the org. phase was exhaustively washed with sat. aq. $NaHCO_3$ soln. (4×), dried (Na_2SO_4), and evaporated. CC (SiO_2; hexane/AcOEt/Et_3N 74:25:1) provided (±)-**52** (2.06 g, 73%). Colorless prisms. M.p. 199–201° (AcOEt). IR (KBr). 1717, 1490, 1446, 1393, 1301, 1250, 1136, 1084, 1038. ^{1}H-NMR (200 MHz, $CDCl_3$): 1.63 (m, 2 H); 1.99 (m, 2 H); 2.52 (m, 2 H); 2.47 (s, 3 H); 2.83 (m,1 H); 3.02 (m, 2 H); 3.90 (d, $J=6.3$, 1 H); 3.98, 5.03 (AB, $J=14.8$, 2 H); 4.33 (s, 1 H); 5.97, 5.99 (AB, $J=1.4$, 2 H); 6.72 (m, 3 H); 7.16, 7.41 ($AA'BB'$, $J=8.4$, 4 H); 7.39, 7.71 ($AA'BB'$, $J=8.1$, 4 H). ^{13}C-NMR (50 MHz, $CDCl_3$): 21.6; 24.1; 31.5; 42.7; 44.7; 50.8; 51.4; 69.3; 71.0; 80.7; 100.9; 108.0; 108.4; 120.8; 121.8; 128.6; 129.1; 129.4; 130.2; 130.6; 132.0; 136.8; 145.9; 147.0; 147.8; 172.3. FAB-MS: 1218.8 (4), 609.0 (100, MH$^+$), 453.0 (81), 135.0 (86, [Piperonyl]$^+$). Anal. calc. for $C_{30}H_{29}BrN_2O_5S$ (609.54): C 59.12, H 4.80, Br 13.11, N 4.60, S 5.26; found: C 58.95, H 4.88, Br 12.82, N 4.52, S 5.27. X-Ray analysis: see *Figs. 12–14*.

*(1*RS*,3a*SR*,4*RS*,8a*SR*,8b*RS*)-2-[(1,3-Benzodioxol-5-yl)methyl]-4-(4-bromophenyl)-1-cyclopropylperhydropyrrolo[3,4-*a*]pyrrolizin-3-one* ((±)-**53b**). *General Procedure F*, starting from (±)-**52** provided (±)-**53b** in 48% yield. Yellowish oil. IR ($CHCl_3$): 1677, 1490, 1445, 1246, 1042. ^{1}H-NMR (200 MHz, $CDCl_3$): 0.10 (m, 1 H); 0.22 (m, 1 H); 0.48 (m, 1 H); 0.66 (m, 2 H); 1.66 (m, 2 H); 1.98 (m, 2 H); 2.58 (m, 3 H); 2.88 (m, 1 H); 3.23 (m, 1 H); 3.41 (m, 1 H); 3.98, 4.79 (AB, $J=14.9$, 2 H); 4.05 (d, $J=8.3$, 1 H); 5.94, 5.96 (AB, $J=1.4$, 2 H); 6.55, 6.71 (AB, $J=7.9$, 2 H); 6.61 (s, 1 H); 7.28, 7.44 ($AA'BB'$, $J=8.6$, 4 H). ^{13}C-NMR (50 MHz, $CDCl_3$): −0.2; 5.4; 14.9; 24.2; 30.8; 43.6; 48.2; 51.5; 52.0; 67.5; 69.5; 71.8; 100.7; 107.6; 108.3; 120.6; 120.8; 129.7; 130.6; 130.7; 138.5; 146.4; 147.5; 171.9. FAB-MS: 991.3 (16), 495.2 (100, MH$^+$).

*(1*RS*,3a*SR*,4*RS*,8a*SR*,8b*RS*)-2-[(1,3-Benzodioxol-5-yl)methyl]-4-(4-bromophenyl)-1-isopropylperhydropyrrolo[3,4-*a*]pyrrolizin-3-one* ((±)-**53c**). *General Procedure F*, starting from (±)-**52** gave (±)-**53c** in 52% yield. Yellowish oil. IR ($CHCl_3$): 1735, 1686, 1488, 1443, 1243, 1037. ^{1}H-NMR (200 MHz, $CDCl_3$): 0.70 (d, $J=6.8$, 3 H);

0.91 (*d*, *J* = 6.9, 3 H); 1.65 (*m*, 2 H); 2.02 (*m*, 3 H); 2.48 (*dt*, *J* = 8.7, 2.8, 1 H); 2.61 (*m*, 1 H); 2.90 (*m*, 1 H); 3.22 (*m*, 3 H); 3.67, 4.79 (*AB*, *J* = 14.9, 2 H); 4.05 (*d*, *J* = 8.1, 1 H); 5.97 (*m*, 2 H); 6.68 (*m*, 3 H); 7.28, 7.44 (*AA′BB′*, *J* = 8.2, 4 H). ^{13}C-NMR (50 MHz, $CDCl_3$): 14.4; 18.2; 24.2; 27.6; 30.9; 41.0; 43.4; 52.0; 52.4; 66.9; 69.8; 72.9; 100.7; 107.8; 108.4; 120.5; 121.0; 129.6; 130.2; 130.6; 138.5; 146.6; 147.6; 172.2. FAB-MS: 995.1 (3), 497.1 (100, *M*H$^+$).

*(1*RS*,3a*SR*,4*RS*,8a*SR*,8b*RS*)-2-[(1,3-Benzodioxol-5-yl)methyl]-4-(4-bromophenyl)-1-cyclohexylperhydropyrrolo[3,4-*a*]pyrrolizin-3-one* ((±)-**53d**). *General Procedure F*, starting from (±)-**52** afforded (±)-**53d** in 21% yield. Colorless needles. M.p. 143–146° ($CHCl_3$/hexane). IR (KBr): 1684, 1501, 1488, 1444, 1248, 1040. ^{1}H-NMR (200 MHz, $CDCl_3$): 1.31 (*m*, 13 H); 1.92 (*m*, 2 H); 2.55 (*m*, 2 H); 2.90 (*m*, 1 H); 3.21 (*m*, 2 H); 3.25 (*m*, 1 H); 3.72, 4.75 (*AB*, *J* = 14.9, 2 H); 4.04 (*d*, *J* = 8.2, 1 H); 5.95, 5.97 (*AB*, *J* = 1.3, 2 H); 6.63 (*dd*, *J* = 1.6, 4.2, 1 H); 6.74 (*m*, 2 H); 7.27, 7.43 (*AA′BB′*, *J* = 8.4, 4 H). ^{13}C-NMR (50 MHz, $CDCl_3$): 24.3; 25.3; 25.6; 26.1; 26.3; 28.9; 31.0; 38.5; 42.3; 43.5; 52.0; 52.5; 66.6; 69.9; 72.8; 100.7; 107.7; 108.4; 120.4; 121.0; 129.6; 130.3; 130.6; 138.5; 146.5; 147.6; 172.2. FAB-MS: 1074.9 (9), 536.9 (100, *M*H$^+$), 135.0 (32, [Piperonyl]$^+$). Anal. calc. for $C_{29}H_{33}BrN_2O_3$ (537.50): C 64.80, H 6.19, N 5.21, Br 14.87; found: C 64.20, H 6.16, N 5.03, Br 14.56.

*(1*SR*,3a*SR*,4*RS*,8a*SR*,8b*RS*)-2-[(1,3-Benzodioxol-5-yl)methyl]-4-(4-bromophenyl)-1-phenylperhydropyrrolo[3,4-*a*]pyrrolizin-3-one* ((±)-**53e**). *General Procedure F*, starting from (±)-**52** gave (±)-**53e** in 90% yield. Colorless needles. M.p. 158–160° (hexane/AcOEt). IR (KBr): 1671, 1491, 1447, 1248, 1035. ^{1}H-NMR (200 MHz, $CDCl_3$): 1.49 (*m*, 1 H); 1.71 (*m*, 1 H); 1.93 (*m*, 2 H); 2.63 (*m*, 2 H); 2.90 (*m*, 1 H); 3.27, 4.83 (*AB*, *J* = 14.3, 2 H); 3.41 (*ddd*, *J* = 2.0, 6.8, 8.8, 1 H); 3.51 (*m*, 1 H); 4.04 (*d*, *J* = 8.6, 1 H); 4.30 (*d*, *J* = 3.8, 1 H); 5.96, 5.99 (*AB*, *J* = 1.4, 2 H); 6.35 (*dd*, *J* = 1.6, 7.9, 1 H); 6.52 (*d*, *J* = 1.6, 1 H); 6.69 (*d*, *J* = 7.8, 1 H); 7.13 (*m*, 2 H); 7.37 (*m*, 7 H). ^{13}C-NMR (50 MHz, $CDCl_3$): 24.1; 30.4; 43.7; 51.0; 51.3; 51.8; 66.7; 69.6; 71.1; 100.7; 107.7; 109.0; 120.7; 121.8; 126.5; 127.9; 128.9; 129.7; 129.8; 130.7; 138.3; 140.4; 146.6; 147.5; 172.4. FAB-MS: 531.1 (100, *M*H$^+$), 237.0 (31), 135.0 (78, [Piperonyl]$^+$). Anal. calc. for $C_{29}H_{27}BrN_2O_3$ (531.45): C 65.54, H 5.12, N 5.27, Br 15.04; found: C 65.67, H 5.11, N 5.37, Br 15.31.

*(1*RS*,3a*SR*,4*RS*,8a*SR*,8b*RS*)-4-[2-[(1,3-Benzodioxol-5-yl)methyl]-1-ethyl-3-oxoperhydropyrrolo[3,4-*a*]pyrrolizin-4-yl]benzonitrile* ((±)-**54a**). To $ZnCl_2$ (5.92 ml, 5.92 mmol; 1M soln. in Et_2O) in dry CH_2Cl_2 (15 ml), a 2M soln. of EtMgCl in THF was added, and the mixture was stirred for 30 min under Ar. A soln. of (±)-**52a** (3.0 g, 4.93 mmol) in CH_2Cl_2 (15 ml) was added slowly, and the mixture was stirred for 16 h at 20°. After addition of 1M HCl and neutralization with sat. aq. $NaHCO_3$ soln., the mixture was extracted with CH_2Cl_2, the resulting org. phase was dried (Na_2SO_4) and evaporated *in vacuo*. CC (SiO_2; hexane/AcOEt/Et_3N 66 : 33 : 1) gave 1.69 g (71%) of a yellowish oil consisting of two isomers. This crude product was combined with CuCN (1.25 g, 14 mmol) and DMF (35 ml, purged with Ar), and the mixture was heated to reflux for 28 h. After partial evaporation of DMF (*ca.* 20 ml), CH_2Cl_2 (30 ml) and conc. aq. NH_4OH soln. (10 ml) were added, and the mixture was vigorously stirred for 1 h. The blue aq. phase was removed, and the org. phase was washed with sat. aq. NH_4OH soln. (2×) and H_2O. Evaporation *in vacuo* and CC (SiO_2; hexane/AcOEt/Et_3N 49.5 : 49.5 : 1) provided (±)-**54a** (0.805 g, 38% from (±)-**52**. Colorless prisms. M.p. 150–151° (AcOEt). IR (KBr): 2219, 1681, 1491, 1445, 1246, 1041. ^{1}H-NMR (200 MHz, $CDCl_3$): 0.85 (*t*, *J* = 7.4, 3 H); 1.41 (*m*, 1 H); 1.55 (*m*, 1 H); 1.72 (*m*, 2 H); 1.98 (*m*, 2 H); 2.47 (*dt*, *J* = 2.9, 8.5, 1 H); 2.58 (*m*, 1 H); 2.92 (*m*, 1 H); 3.25 (*m*, 2 H); 3.39 (*m*, 1 H); 3.68, 4.73 (*AB*, *J* = 14.9, 2 H); 4.14 (*d*, *J* = 7.9, 1 H); 5.95, 5.98 (*AB*, *J* = 1.5, 2 H); 6.60 (*m*, 2 H); 6.73 (*d*, *J* = 8.4, 1 H); 7.52, 7.60 (*AA′BB′*, *J* = 8.4, 4 H). ^{13}C-NMR (50 MHz, $CDCl_3$): 8.3; 24.4; 25.1; 31.1; 43.4; 46.2; 52.1; 52.2; 62.7; 70.0; 72.1; 100.8; 107.7; 108.3; 110.3; 119.1; 120.9; 128.6; 130.1; 131.4; 145.5; 146.6; 147.7; 171.6. FAB-MS: 859.5 (14, M_2H$^+$), 430.3 (100, *M*H$^+$), 135.1 (18, [Piperonyl]$^+$). Anal. calc. for $C_{26}H_{27}N_3O_3$ (429.52): C 72.71, H 6.34, N 9.78; found: C 72.72, H 6.40, N 9.80.

*(1*RS*,3a*SR*,4*RS*,8a*SR*,8b*RS*)-4-[2-[(1,3-Benzodioxol-5-yl)-methyl]-1-cyclopropyl-3-oxoperhydropyrrolo-[3,4-*a*]pyrrolizin-4-yl]benzonitrile* ((±)-**54b**). *General Procedure D*, starting from (±)-**53b** gave (±)-**54b** in 71% yield. Colorless prisms. M.p. 120–122° (AcOEt). IR (KBr): 2229, 1685, 1492, 1421, 1243, 1037. ^{1}H-NMR (200 MHz, $CDCl_3$): 0.10 (*m*, 1 H); 0.25 (*m*, 1 H); 0.48 (*m*, 1 H); 0.68 (*m*, 2 H); 1.65 (*m*, 2 H); 1.98 (*m*, 2 H); 2.58 (*m*, 3 H); 2.91 (*m*, 1 H); 3.24 (*m*, 1 H); 3.47 (*m*, 1 H); 3.95, 4.77 (*AB*, *J* = 14.9, 2 H); 4.14 (*d*, *J* = 8.1, 1 H); 5.93, 5.97 (*AB*, *J* = 1.5, 2 H); 6.52 (*s*, 1 H); 6.57, 6.70 (*AB*, *J* = 7.8, 2 H); 7.52, 7.60 (*AA′BB′*, *J* = 8.4, 4 H). ^{13}C-NMR (50 MHz, $CDCl_3$): −0.2; 5.4; 14.8; 24.3; 30.9; 43.6; 48.2; 51.7; 52.2; 67.4; 69.8; 71.9; 100.8; 107.6; 108.1; 110.4; 119.1; 120.8; 128.6; 130.4; 131.4; 145.5; 146.5; 147.6; 171.6. FAB-MS: 883.4 (4, M_2H$^+$), 442.2 (100, *M*H$^+$), 184.1 (40). Anal. calc. for $C_{27}H_{27}N_3O_3$ (441.53): C 73.45, H 6.16, N 9.52; found: C 73.53, H 6.24, N 9.44.

*(1*RS*,3a*SR*,4*RS*,8a*SR*,8b*RS*)-4-[2-[(1,3-Benzodioxol-5-yl)methyl]-1-isopropyl-3-oxoperhydropyrrolo[3,4-*a*]-pyrrolizin-4-yl]benzonitrile* ((±)-**54c**). *General Procedure D*, starting from (±)-**53c** gave (±)-**54c** in 56% yield. Colorless needles. M.p. 152–153° (EtOH). IR (KBr): 1685, 1502, 1490, 1444, 1246, 1042. ^{1}H-NMR (200 MHz, $CDCl_3$): 0.71 (*d*, *J* = 6.8, 3 H); 0.92 (*d*, *J* = 6.9, 3 H); 1.65 (*m*, 2 H); 2.01 (*m*, 3 H); 2.49 (*dt*, *J* = 8.7, 2.8, 1 H); 2.58

(*m*, 1 H); 2.92 (*m*, 1 H); 3.21 (*m*, 2 H); 3.34 (*m*, 1 H); 3.65, 4.77 (*AB*, *J* = 14.9, 2 H); 4.14 (*d*, *J* = 7.9, 1 H); 5.95, 5.98 (*AB*, *J* = 1.4, 2 H); 6.61 (*m*, 2 H); 6.73 (*d*, *J* = 8.4, 1 H); 7.52, 7.60 (*AA′BB′*, *J* = 8.3, 4 H). ^{13}C-NMR (50 MHz, $CDCl_3$): 14.5; 18.2; 24.3; 27.6; 31.0; 41.1; 43.4; 52.2; 52.6; 66.8; 70.1; 73.0; 100.8; 107.8; 108.3; 110.3; 119.1; 121.0; 128.6; 130.0; 131.4; 145.5; 146.6; 147.7; 171.9. FAB-MS: 887.7 (4, M_2H^+), 444.3 (100, MH^+), 184.1 (36), 135.0 (64, [Piperonyl]$^+$). Anal. calc. for $C_{27}H_{29}N_3O_3$ (443.54): C 73.11, H 6.59, N 9.47; found: C 72.94, H 6.48, N 9.37.

*(1*RS*,3a*SR*,4*RS*,8a*SR*,8b*RS*)-4-[2-[(1,3-Benzodioxol-5-yl)methyl]-1-cyclohexyl-3-oxoperhydropyrrolo[3,4-*a*]pyrrolizin-4-yl]benzonitrile* ((±)-**54d**). *General Procedure D*, starting from (±)-**53d** provided (±)-**54d** in 66% yield. Colorless needles. M.p. 204–207° (AcOEt/hexane). IR (KBr): 2224, 1673, 1491, 1449, 1245, 1036. ^{1}H-NMR (200 MHz, $CDCl_3$): 0.85 (*m*, 1 H); 1.11 (*m*, 3 H); 1.58 (*m*, 9 H); 1.97 (*m*, 2 H); 2.55 (*m*, 2 H); 2.92 (*m*, 1 H); 3.19 (*m*, 2 H); 3.31 (*m*, 1 H); 3.70, 4.74 (*AB*, *J* = 14.9, 2 H); 4.13 (*d*, *J* = 7.4, 1 H); 5.95, 5.98 (*AB*, *J* = 1.4, 2 H); 6.68 (*m*, 3 H); 7.51, 7.60 (*AA′BB′*, *J* = 8.4, 4 H). ^{13}C-NMR (50 MHz, $CDCl_3$): 24.5; 25.4; 25.6; 26.1; 26.2; 28.9; 31.1; 38.4; 42.5; 43.5; 52.3; 52.7; 66.5; 70.3; 72.9; 100.8; 107.8; 108.3; 110.3; 119.1; 121.0; 128.6; 130.2; 131.3; 145.5; 146.6; 147.6; 172.2. FAB-MS: 967.3 (2, M_2H^+), 484.2 (100, MH^+), 135.0 (67, [Piperonyl]$^+$). Anal. calc. for $C_{30}H_{33}N_3O_3$ (483.61): C 74.51, H 6.88, N 8.69; found: C 74.60, H 6.91, N 8.68.

*(1*SR*,3a*SR*,4*RS*,8a*SR*,8b*RS*)-4-[2-[(1,3-Benzodioxol-5-yl)-methyl]-3-oxo-1-phenylperhydropyrrolo[3,4-*a*]-pyrrolizin-4-yl]benzonitrile* ((±)-**54e**). *General Procedure D*, starting from (±)-**53e** afforded (±)-**54e** in 61% yield. Colorless prisms. M.p. 154–156° (AcOEt). IR (KBr): 2224, 1688, 1488, 1443, 1244, 1031. ^{1}H-NMR (200 MHz, $CDCl_3$): 1.49 (*m*, 1 H); 1.75 (*m*, 1 H); 1.92 (*m*, 2 H); 2.62 (*m*, 2 H); 2.94 (*m*, 1 H); 3.26, 4.79 (*AB*, *J* = 14.5, 2 H); 3.43 (*ddd*, *J* = 2.1, 6.7, 8.8, 1 H); 3.57 (*m*, 1 H); 4.13 (*d*, *J* = 8.3, 1 H); 4.29 (*d*, *J* = 3.7, 1 H); 5.96, 6.01 (*AB*, *J* = 1.2, 2 H); 6.36 (*dd*, *J* = 1.5, 7.9, 1 H); 6.47 (*d*, *J* = 1.5, 1 H); 6.69 (*d*, *J* = 7.8, 1 H); 7.13 (*dd*, *J* = 1.9, 7.5, 2 H); 7.36 (*m*, 3 H); 7.53, 7.62 (*AA′BB′*, *J* = 8.3, 4 H). ^{13}C-NMR (50 MHz, $CDCl_3$): 24.2; 30.6; 43.7; 51.0; 51.5; 52.0; 66.5; 69.9; 71.4; 100.8; 107.7; 108.8; 110.5; 119.1; 121.6; 126.4; 128.0; 128.8; 128.9; 129.6; 131.5; 140.1; 145.3; 146.7; 147.6; 172.1. FAB-MS: 955.3 (7, M_2H^+), 478.1 (100, MH^+), 184.1 (31), 135.0 (61, [Piperonyl]$^+$). Anal. calc. for $C_{30}H_{27}N_3O_3$ (477.56): C 75.45, H 5.70, N 8.80; found: C 75.49, H 5.80, N 8.80.

*(1*SR*,3a*SR*,4*RS*,8a*SR*,8b*RS*)-4-[2-[(1,3-Benzodioxol-5-yl)methyl]-1-ethyl-3-oxoperhydropyrrolo[3,4-*a*]pyr-rolizin-4-yl]benzamidine Hydrochloride* ((±)-**55a**). *General Procedure E* (*Method B*), starting from (±)-**54a** gave (±)-**55a** in 78% yield. Colorless solid. M.p. 195–199°. IR (KBr): 1667, 1612, 1490, 1442, 1243, 1036. ^{1}H-NMR (200 MHz, $(CD_3)_2SO$): 0.78 (*t*, *J* = 7.2, 3 H); 1.35 (*m*, 2 H); 1.62 (*m*, 2 H); 1.91 (*m*, 2 H); 2.42 (*m*, 1 H); 2.80 (*m*, 1 H); 3.28 (*m*, 2 H); 3.42 (*m*, 1 H); 3.79, 4.49 (*AB*, *J* = 15.2, 2 H); 4.17 (*d*, *J* = 7.5, 1 H); 6.02 (*m*, 2 H); 6.70 (*m*, 2 H); 6.88 (*d*, *J* = 7.8, 1 H); 7.54, 7.76 (*AA′BB′*, *J* = 8.3, 4 H); 9.21 (br. *m*, 4 H). ^{13}C-NMR (50 MHz, $(CD_3)_2SO$): 8.0; 23.9; 24.4; 30.4; 42.2; 45.1; 51.3; 51.6; 62.2; 69.2; 71.8; 100.5; 107.6; 107.8; 120.5; 125.3; 126.7; 128.3; 130.5; 145.9; 147.0; 147.0; 165.1; 171.0. DEI-MS: 446.3 (22, M^+), 201.2 (64), 184.1 (45), 135.1 (100, [Piperonyl]$^+$). HR-DEI-MS: 446.2315 (M^+, $C_{26}H_{30}N_4O_3$; calc. 446.2318).

*(1*RS*,3a*SR*,4*RS*,8a*SR*,8b*RS*)-4-[2-[(1,3-Benzodioxol-5-yl)methyl]-1-cyclopropyl-3-oxoperhydropyrrolo[3,4-*a*]pyrrolizin-4-yl]benzamidine Hydrochloride* ((±)-**55b**). *General Procedure E* (*Method B*), starting from (±)-**54b** gave (±)-**55b** in 62% yield. Colorless solid. M.p. > 165° (dec.). IR (KBr): 1670, 1612, 1490, 1443, 1244, 1036. ^{1}H-NMR (200 MHz, $(CD_3)_2SO$): 0.18 (*m*, 2 H); 0.42 (*m*, 1 H); 0.62 (*m*, 1 H); 0.78 (*m*, 1 H); 1.62 (*m*, 2 H); 1.95 (*m*, 2 H); 2.66 (*m*, 1 H); 2.82 (*m*, 1 H); 3.22 (*m*, 1 H); 3.54 (*m*, 1 H); 3.98, 4.53 (*AB*, *J* = 15.1, 2 H); 4.18 (*d*, *J* = 7.2, 1 H); 6.00 (*m*, 2 H); 6.64 (*m*, 2 H); 6.86 (*d*, *J* = 8.3, 1 H); 7.56, 7.74 (*AA′BB′*, *J* = 8.0, 4 H); 9.04 (*s*, 2 H); 9.32 (*s*, 2 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 0.5; 5.8; 14.8; 25.3; 31.9; 44.3; 47.6; 52.1; 52.6; 67.6; 70.4; 72.5; 101.1; 108.0; 108.4; 121.0; 125.1; 128.3; 130.2; 145.6; 145.9; 148.0; 165.9; 172.1; one peak missing due to signal overlap. DEI-MS: 458.2 (23, M^+), 441.2 (10), 201.2 (54), 184.1 (75), 135.1 (100, [Piperonyl]$^+$). HR-DEI-MS: 458.2285 (M^+, $C_{27}H_{30}N_4O_3$; calc. 458.2318).

*(1*RS*,3a*SR*,4*RS*,8a*SR*,8b*RS*)-4-[2-[(1,3-Benzodioxol-5-yl)methyl]-1-isopropyl-3-oxoperhydropyrrolo[3,4-*a*]-pyrrolizin-4-yl]benzamidine Hydrochloride* ((±)-**1**). *General Procedure E* (*Method B*), starting from (±)-**54c** provided (±)-**1** in 79% yield. Colorless solid. M.p. 210–215°. IR (KBr): 1668, 1612, 1539, 1490, 1443, 1407, 1244, 1097, 1037. ^{1}H-NMR (200 MHz, $(CD_3)_2SO$): 0.65 (*d*, *J* = 6.4, 3 H); 0.89 (*d*, *J* = 6.7, 3 H); 1.63 (*m*, 2 H); 1.90 (*m*, 2 H); 2.09 (*m*, 1 H); 2.50 (*m*, 2 H); 2.82 (*m*, 1 H); 3.17 (*m*, 2 H); 3.36 (*m*, 1 H); 3.77, 4.53 (*AB*, *J* = 14.9, 2 H); 4.18 (*d*, *J* = 7.5, 1 H); 6.02 (*m*, 2 H); 6.70, 6.89 (*AB*, *J* = 7.9, 2 H); 6.74 (*s*, 1 H); 7.56, 7.76 (*AA′BB′*, *J* = 8.3, 4 H); 9.13 (*s*, 2 H); 9.34 (*s*, 2 H). ^{13}C-NMR (50 MHz, $(CD_3)_2SO$): 14.7; 18.2; 24.3; 27.6; 30.7; 42.8; 52.1; 52.5; 66.9; 69.9; 73.3; 101.2; 108.3; 108.4; 121.3; 126.0; 127.4; 129.0; 131.1; 146.6; 147.7; 165.9; 172.0; one peak missing due to signal overlap. DEI-MS: 460.2 (33, M^+), 201.1 (84), 184.1 (37), 172.1 (23), 135.0 (100, [Piperonyl]$^+$). HR-DEI-MS: 460.2488 (M^+, $C_{27}H_{32}N_4O_3$; calc. 460.2474).

*(1*RS*,3a*SR*,4*RS*,8a*SR*,8b*RS*)-4-[2-[(1,3-Benzodioxol-5-yl)methyl]-1-cyclohexyl-3-oxoperhydropyrrolo[3,4-*a*]pyrrolizin-4-yl]benzamidine Hydrochloride* ((±)-**55d**). *General Procedure E* (*Method B*), starting from (±)-

54d gave (±)-**55d** in 72% yield. Colorless solid. M.p. 219–224°. IR (KBr): 1668, 1612, 1490, 1443, 1244, 1037. ^{1}H-NMR (200 MHz, $(CD_3)_2SO$): 0.95 (*m*, 1 H); 1.18 (*m*, 3 H); 1.60 (*m*, 9 H); 1.92 (*m*, 2 H); 2.55 (*m*, 2 H); 2.83 (*m*, 1 H); 3.18 (*m*, 2 H); 3.38 (*m*, 1 H); 3.82, 4.48 (*AB*, *J* = 14.9, 2 H); 4.17 (*d*, *J* = 7.2, 1 H); 6.01 (*m*, 2 H); 6.73 (*m*, 2 H); 6.88 (*d*, *J* = 7.8, 1 H); 7.54, 7.75 (*AA′BB′*, *J* = 8.3, 4 H); 9.12 (br. *s*, 2 H); 9.34 (br. *s*, 2 H). ^{13}C-NMR (50 MHz, $(CD_3)_2SO$): 24.3; 25.0; 25.3; 25.8; 26.0; 28.3; 30.7; 37.9; 41.9; 42.7; 52.0; 52.2; 66.4; 70.0; 72.9; 100.8; 107.9; 108.0; 120.9; 125.6; 127.0; 128.5; 130.9; 146.2; 147.2; 147.3; 165.4; 171.5. DEI-MS: 500.2 (18, M^+), 483.1 (6), 349.1 (5), 201.1 (77), 184.1 (75), 135.1 (100, [Piperonyl]$^+$). HR-DEI-MS: 500.2784 (M^+, $C_{30}H_{36}N_4O_3$; calc. 500.2787).

*(1*SR*,3a*SR*,4*RS*,8a*SR*,8b*RS*)-4-[2-[(1,3-Benzodioxol-5-yl)methyl]-3-oxo-1-phenylperhydropyrrolo[3,4-*a*]pyrrolizin-4-yl]benzamidine Hydrochloride* ((±)-**55e**). *General Procedure E* (*Method B*), starting from (±)-**54e** afforded (±)-**55e** in 89% yield. Colorless powder. M.p. > 195° (dec.). IR (KBr): 1670, 1612, 1489, 1443, 1244, 1036. ^{1}H-NMR (200 MHz, $(CD_3)_2SO$): 1.55 (*m*, 2 H); 1.88 (*m*, 2 H); 2.62 (*m*, 1 H); 2.82 (*m*, 1 H); 3.27, 4.58 (*AB*, *J* = 14.8, 2 H); 3.38 (*m*, 1 H); 3.66 (*m*, 1 H); 4.20 (*d*, *J* = 7.7, 1 H); 4.33 (*d*, *J* = 2.2, 1 H); 6.03 (*m*, 2 H); 6.50 (*dd*, *J* = 1.4, 9.4, 1 H); 6.55 (*s*, 1 H); 6.87 (*d*, *J* = 7.8, 1 H); 7.20 (*dd*, *J* = 1.6, 7.8, 2 H); 7.37 (*m*, 3 H); 7.58, 7.81 (*AA′BB′*, *J* = 8.2, 4 H); 9.05 (br. *m*, 4 H). ^{13}C-NMR (50 MHz, $(CD_3)_2SO$): 24.4; 30.7; 43.4; 50.5; 51.3; 52.0; 66.0; 69.6; 71.9; 101.2; 108.3; 108.4; 121.3; 126.1; 126.8; 127.5; 128.2; 129.0; 129.3; 130.4; 141.3; 146.7; 147.4; 147.7; 165.9; 172.2. DEI-MS: 494.2 (18, M^+), 477.2 (14), 342.2 (7), 201.2 (49), 184.1 (100), 135.1 (74, [Piperonyl]$^+$). HR-DEI-MS: 494.2321 (M^+, $C_{30}H_{30}N_4O_3$; calc. 494.2318).

*Methyl (*R*)-{(1*R*,3a*S*,4*R*,8a*S*,8b*R*)-2-[(1,3-Benzodioxol-5-yl)methyl]-4-(4-bromophenyl)-3-oxoperhydropyrrolo[3,4-*a*]pyrrolizin-1-yloxy}phenylacetate* (**57**) *and Methyl (*R*)-{(1*S*,3a*R*,4*S*,8a*R*,8b*S*)-2-[(1,3-Benzodioxol-5-yl)methyl]-4-(bromophenyl)-3-oxoperhydropyrrolo[3,4-*a*]pyrrolizin-1-yloxy}phenylacetate* (**58**). A 1M soln. of Li[Et_3BH] (48.5 ml, 48.5 mmol) in THF was added at −78° under Ar to a soln. of (±)-**31** (13.41 g, 28.5 mmol) in THF (80 ml), and the mixture was stirred at −78° for 30 min. After warming to 0°, sat. aq. $NaHCO_3$ soln. (15 ml) and 30% aq. H_2O_2 soln. (5 ml) were added sequentially, and the mixture was stirred for 1 h at 0°. The aq. phase formed by evaporation of THF was extracted with CH_2Cl_2, and the resulting org. phase was dried (Na_2SO_4) and evaporated *in vacuo*. The residue was dissolved together with methyl (−)-D-mandelate (14.2 g, 85.5 mmol) in PhMe (250) under slight warming. PPTS (0.3 g, 1.2 mmol) was added, and the mixture was heated to reflux for 6 h, while H_2O was removed azeotropically. The solvent was evaporated *in vacuo*, the residue dissolved in CH_2Cl_2, and the resulting soln. washed with sat. aq. $NaHCO_3$ soln. The org. phase was dried (Na_2SO_4) and evaporated *in vacuo*, and CC (SiO_2; hexane/AcOEt 66.5 : 33.5) provided **57** and **58**, which were used in the next conversion without further purification.

Data of **57**: Yield: 5.34 g (61%). Yellowish foam. IR (KBr): 1748, 1701, 1490, 1446, 1247. ^{1}H-NMR (200 MHz, $CDCl_3$): 1.68 (*m*, 2 H); 2.01 (*m*, 2 H); 2.62 (*m*, 1 H); 2.87 (*m*, 1 H); 2.96 (*m*, 1 H); 3.26 (*m*, 1 H); 3.47 (*m*, 1 H); 3.73 (*s*, 3 H); 3.76, 4.72 (*AB*, *J* = 14.3, 2 H); 4.04 (*d*, *J* = 7.5, 1 H); 4.70 (*s*, 1 H); 4.89 (*s*, 1 H); 5.96, 5.99 (*AB*, *J* = 1.2, 2 H); 6.46 (*dd*, *J* = 1.2, 7.9, 1 H); 6.57 (*d*, *J* = 1.7, 1 H); 6.70 (*d*, *J* = 7.9, 1 H); 7.27, 7.47 (*AA′BB′*, *J* = 8.5; 4 H); 7.41 (*s*, 5 H). ^{13}C-NMR (50 MHz, $CDCl_3$): 24.0; 30.8; 43.1; 48.1; 51.1; 51.5; 52.3; 69.1; 69.7; 78.9; 93.1; 100.7; 107.7; 108.3; 120.7; 121.1; 127.0; 128.6; 128.8; 129.6; 129.7; 130.7; 135.5; 137.7; 146.7; 147.6; 170.7; 172.0. FAB-MS: 1239.1 (10 M_2H^+), 619.0 (100, MH^+), 460.0 (22).

Data of **58**: Yield: 5.61 g (64%). Yellowish foam IR (KBr). 1751, 1702, 1490, 1446, 1247. ^{1}H-NMR (200 MHz, $CDCl_3$): 1.40 (*m*, 1 H); 1.65 (*m*, 2 H); 1.90 (*m*, 1 H); 2.57 (*m*, 2 H); 2.82 (*m*, 1 H); 3.02 (*m*, 1 H); 3.38 (*m*, 1 H); 3.75 (*s*, 3 H); 3.96 (*d*, *J* = 7.5, 1 H); 4.04, 4.73 (*AB*, *J* = 14.9, 2 H); 4.73 (*s*, 1 H); 4.89 (*s*, 1 H); 6.01 (*m*, 2 H); 6.78 (*m*, 3 H); 7.23 (*d*, *J* = 8.3, 2 H); 7.45 (*m*, 7 H). ^{13}C-NMR (50 MHz, $CDCl_3$): 23.9; 30.6; 43.1; 47.9; 51.0; 51.4; 52.3; 69.0; 69.3; 77.9; 92.7; 100.7; 107.8; 108.6; 120.8; 121.3; 127.1; 128.6; 128.8; 129.6; 130.2; 130.7; 135.8; 137.6; 146.6; 147.6; 170.3; 171.8. FAB-MS: 1239.3 (3, M_2H^+), 619.2 (100, MH^+), 460.1 (7), 307.1 (18), 154.1 (49).

*(1*R*,3a*S*,4*R*,8a*S*,8b*R*)-2-[(1,3-Benzodioxol-5-yl)methyl]-4-(4-bromophenyl)-1-[(4-methylphenyl)sulfonyl]-perhydropyrrolo[3,4-*a*]pyrrolizin-3-one* ((+)-**52**) *and (1*S*,3a*R*,4*S*,8a*R*,8b*S*)-2-[(1,3-Benzodioxol-5-yl)methyl]-4-(4-bromophenyl)-1-[(4-methylphenyl)sulfonyl]perhydropyrrolo[3,4-*a*]pyrrolizin-3-one* ((−)-**52**). A soln. of **57** or **58** in CH_2Cl_2 was added to a suspension of 4-toluenesulfinic acid (3 equiv.) and finely powdered $CaCl_2$ (3 equiv.) in CH_2Cl_2, and the mixture was stirred under Ar for 12 h. After addition of sat. aq. $NaHCO_3$ soln, the mixture was extracted with CH_2Cl_2, and the resulting org. phase was thoroughly washed with sat. aq. $NaHCO_3$ soln. (4 ×), dried (Na_2SO_4), and evaporated. CC (SiO_2, hexane/AcOEt/Et_3N 74 : 25 : 1) gave (−)-**52** in > 99.5% enantiomeric purity (anal. HPLC, see *Fig. 10*) and (+)-**52** in 96.5% enantiomeric purity. Upon slow addition of hexane to a soln. of (+)-**52** in AcOEt, racemate (±)-**52** crystallized, and evaporation of the mother liquor afforded (+)-**52** with > 99% enantiomeric purity (anal. HPLC, see *Fig. 11*). (+)-**52**: Yield: 91%. Colorless foam.

M.p. 94–95°. $[\alpha]_D^{25} = +243$ ($c = 1.00$, $CHCl_3$). (−)-**52**: Yield: 79%. Colorless foam. M.p. 94–97°. $[\alpha]_D^{25} = -237$ ($c = 1.00$, $CHCl_3$).

*(1*R*,3a*S*,4*R*,8a*S*,8b*R*)-4-{2-[(1,3-Benzodioxol-5-yl)-methyl]-1-isopropyl-3-oxoperhydropyrrolo[3,4-*a*]pyrrolizin-4-yl}benzonitrile* ((+)-**54c**) *and (1*S*,3a*R*,4*S*,8a*R*,8b*S*)-4-{2-[(1,3-Benzodioxol-5-yl)methyl]-1-isopropyl-3-oxoperhydropyrrolo[3,4-*a*]pyrrolizin-4-yl}benzonitrile* ((−)-**54c**). A soln. of $Me_2CHMgBr$ in Et_2O (2 equiv.) was added under Ar at 20° to a soln. of $ZnCl_2$ (1.2 equiv, in Et_2O) in CH_2Cl_2, and the mixture was stirred for 30 min. A soln. of (+)-**52** or (−)-**52** (1 equiv.) in dry CH_2Cl_2 (5 ml/mmol) was slowly added under ice cooling, and the mixture was stirred for 24 h. After addition of 1M HCl and neutralization with sat. aq. $NaHCO_3$ soln., the mixture was extracted with CH_2Cl_2. The org. phase was dried (Na_2SO_4) and evaporated *in vacuo*, leaving a yellow oil. CuCN (4 equiv.) and DMF (6 ml/mmol, purged with Ar) were added, and the mixture was heated to reflux for 27 h under Ar. The solvent was partially evaporated *in vacuo*, and CH_2Cl_2 and conc. aq. NH_4OH soln. were added. After vigorous stirring for 1 h, the blue aq. phase was removed, and the org. phase was washed with sat. aq. NH_4OH soln. (2×) and H_2O. The combined aq. phases were extracted with CH_2Cl_2, and the combined org. phases were dried (Na_2SO_4) and evaporated *in vacuo*. CC (first SiO_2, hexane/AcOEt/Et_3N 74:25:1, then neutral Al_2O_3; hexane/AcOEt/Et_3N 49.5:49.5:1) and filtration over activated charcoal yielded (+)-**54c** and (−)-**54c**, resp. (+)-**54c**: Yield: 51%. Colorless foam. M.p. 63–65°. $[\alpha]_D^{25} = +366$ ($c = 0.75$, $CHCl_3$). (−)-**54c**: Yield: 50%. Colorless foam. M.p. 63–65°. $[\alpha]_D^{25} = -366$ ($c = 0.73$, $CHCl_3$).

*(1*R*,3a*S*,4*R*,8a*S*,8b*R*)-4-{2-[(1,3-Benzodioxol-5-yl)methyl]-1-isopropyl-3-oxoperhydropyrrolo[3,4-*a*]pyrrolizin-4-yl}benzamidine Hydrochloride* ((+)-**1**) *and (1*S*,3a*R*,4*S*,8a*R*,8b*S*)-4-{2-[(1,3-Benzodioxol-5-yl)methyl]-1-isopropyl-3-oxoperhydropyrrolo[3,4-*a*]pyrrolizin-4-yl}benzamidine Hydrochloride* ((−)-**1**). Preparation from (+)-**54c** and (−)-**54c**, resp., as described for (±)-**1**; purification by CC (SiO_2, $CHCl_3$/MeOH 88:12). (+)-**1**: Yield: 75%. Colorless foam. M.p. > 150° (dec.). $[\alpha]_D^{25} = +142$ ($c = 1.00$, $CHCl_3$). (−)-**1**: Yield: 73%. Colorless foam. M.p. > 150° (dec.). $[\alpha]_D^{25} - 145$ ($c = 0.99$, $CHCl_3$).

*(1*RS*,3a*SR*,4*RS*,8a*SR*,8b*RS*)-2-[(1,3-Benzodioxol-5-yl)methyl]-4-(4-hydroxyphenyl)-1-(1-methylethyl)perhydropyrrolo[3,4-*a*]pyrrolizin-3-one* ((±)-**59a**). A mixture of (±)-**53c** (995 mg, 2 mmol), **62** (559 mg, 2.2 mmol), [$PdCl_2$(dppf)] (44 mg, 0.05 mmol), and AcOK (588 mg, 6 mmol) in dry, degassed Me_2SO was heated for 12 h to 80° in a sealed tube. The mixture was diluted with H_2O and extracted with PhMe (3×). The combined org. phases were washed with H_2O (3×), dried (Na_2SO_4), and evaporated *in vacuo* to yield crude (±)-**63**. The crude product (995 mg, 2 mmol) was dissolved in Et_2O (3 ml), and 10% aq. H_2O_2 soln. (1.5 ml, 204 mg, 6 mmol) was added under stirring. After 15 min, additional aq. H_2O_2 soln. (1 ml, 136 mg, 4 mmol) was added, and, after 3 h, the mixture was diluted with H_2O and extracted with CH_2Cl_2. The org. phase was washed with 10% aq. $FeSO_4 \cdot (NH_4)_2SO_4$ soln. (2×) until the yellow color remained. Drying (Na_2SO_4) and evaporation, followed by CC (SiO_2; AcOEt/Et_3N 99:1) afforded (±)-**59a** (421 mg, 48%). Colorless crystals. M.p. 194–195° (AcOEt). IR ($CHCl_3$): 3267, 3006, 2965, 1667, 1615, 1514, 1504, 1490, 1444, 1042. ^{1}H-NMR (200 MHz, $CDCl_3$): 0.73 (*d*, $J = 6.6$, 3 H); 0.93 (*d*, $J = 7.1$, 3 H); 1.63 (*m*, 2 H); 1.93 (*m*, 2 H); 2.16 (*dqq*, $J = 3.3, 6.6, 7.1$, 1 H); 2.53 (*ddd*, $J = 2.1, 3.3, 9.1$, 1 H); 2.68 (*m*, 1 H); 2.86 (*m*, 1 H); 3.28 (*m*, 3 H); 3.71, 4.89 (*AB*, $J = 14.9$, 2 H); 4.01 (*d*, $J = 8.3$, 1 H); 5.96, 5.98 (*AB*, $J = 1.5$, 2 H); 6.56, 7.15 (*AA′BB′*, $J = 8.5$, 4 H); 6.71 (*dd*, $J = 1.5, 7.9$, 1 H); 6.77 (*d*, $J = 7.9$, 1 H); 6.81 (*d*, $J = 1.5$, 1 H); 7.94 (br. *s*, 1 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 14.4; 18.4; 24.0; 27.7; 30.5; 40.7; 43.9; 51.7; 52.8; 67.6; 69.9; 73.0; 101.0; 108.1; 109.1; 115.3; 121.7; 129.0; 129.3; 130.1; 147.0; 147.9; 156.2; 173.9. FAB-MS: 869.9 (5, M_2H^+), 435.5 (100, MH^+), 341.4 (6), 175.3 (8), 135.1 (13, [Piperonyl]$^+$). Anal. calc. for $C_{26}H_{30}N_2O_4$ (434.53): C 71.87, H 6.96, N 6.45; found: C 71.75, H 6.91, N 6.45.

*(1*RS*,3a*SR*,4*RS*,8a*SR*,8b*RS*)-4-{-2-[(1,3-Benzodioxol-5-yl)methyl]-1-(1-methylethyl)-3-oxoperhydropyrrolo[3,4-*a*]pyrrolizin-4-yl}benzamide* ((±)-**59b**). A 30% aq. H_2O_2 soln. (2.3 ml, 765 mg, 22 mmol) was added dropwise to (±)-**54c** (200 mg, 0.45 mmol) and KOH (38 mg, 0.68 mmol) in acetone (5 ml) and H_2O (1 ml), causing a slight warming of the mixture. After stirring for 1 h, sat. aq. $Na_2S_2O_3$ soln. was added, and the acetone was evaporated *in vacuo*. After addition of sat. aq. $NaHCO_3$ soln., the mixture was extracted with CH_2Cl_2. The org. phase was dried (Na_2SO_4) and evaporated, and CC (SiO_2; AcOEt/Et_3N 99:1) gave (±)-**59b** (127 mg, 61%). Colorless solid. M.p. 151–154° (AcOEt). IR ($CHCl_3$): 3528, 3414, 3009, 2965, 1674, 1612, 1588, 1504, 1490, 1444, 1372, 1042. ^{1}H-NMR (300 MHz, $CDCl_3$): 0.71 (*d*, $J = 6.9$, 3 H); 0.92 (*d*, $J = 6.9$, 3 H); 1.59 (*m*, 1 H); 1.74 (*m*, 1 H); 1.97 (*m*, 2 H); 2.09 (*d'sept.'*, $J = 3.4, 6.9$, 1 H); 2.49 (*d't'*, $J = 2.8, 8.6$, 1 H); 2.62 (*m*, 1 H); 2.96 (*m*, 1 H); 3.28 (*m*, 2 H); 3.35 (*m*, 1 H); 3.68, 4.76 (*AB*, $J = 14.9$, 2 H); 4.16 (*d*, $J = 7.8$, 1 H); 5.82 (br. *m*, 1 H); 5.94, 5.97 (*AB*, $J = 1.2$, 2 H); 6.38 (br. *m*, 1 H); 6.63 (*dd*, $J = 1.6, 7.9$, 1 H); 6.66 (*s*, 1 H); 6.73 (*d*, $J = 7.9$, 1 H); 7.47, 7.76 (*AA′BB′*, $J = 8.2$, 4 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 14.7; 18.5; 24.5; 27.9; 31.1; 41.3; 43.7; 52.3; 52.8; 67.2; 70.3; 73.3; 101.0; 108.1; 108.8; 121.4; 127.1; 128.4; 130.4; 132.2; 144.1; 146.9; 147.9; 169.9; 172.5. FAB-MS: 923.4 (25, M_2H^+), 462.1 (100, MH^+), 202.1 (38), 135.0 (78, [Piperonyl]$^+$). HR-FAB-MS: 462.2394 (MH^+, $C_{27}H_{32}N_3O_4$; calc. 462.2393).

*(1*RS*,3a*SR*,4*RS*,8a*SR*,8b*RS*)-4-[4-(Aminomethyl)phenyl]-2-[(1,3-benzodioxol-5-yl)methyl]-1-(1-methylethyl)perhydropyrrolo[3,4-*a*]pyrrolizin-3-one* ((±)-**59c**). A 1M soln. of Li[Et_3BH] in THF (5.2 ml, 5.2 mmol) was added dropwise at −78° under Ar to (±)-**54c** (580 mg, 1.31 mmol) in dry CH_2Cl_2 (6 ml). After stirring under Ar for 2 h at −78°, CH_2Cl_2 (50 ml) was added, and the mixture was extracted with 1M HCl. The aq. phase was made basic with 1N NaOH and extracted with CH_2Cl_2. The org. phase was dried (Na_2SO_4), and the residue obtained by evaporation *in vacuo* was purified by CC (SiO_2; CH_2Cl_2/MeOH/Et_3N 92:7:1) to give (±)-**59c** (545 mg, 93%). Yellowish foam. M.p. 75–80°. IR ($CHCl_3$): 3003, 2950, 2876, 2358, 1671, 1492, 1444, 1133, 1043, 0.32. ^{1}H-NMR (300 MHz, $CDCl_3$): 0.71 (*d*, *J* = 6.9, 3 H); 0.92 (*d*, *J* = 6.9, 3 H); 1.64 (*m*, 4 H); 2.04 (*m*, 3 H); 2.49 (*dt*, *J* = 9.0, 2.8. 1 H); 2.67 (*m*, 1 H); 2.94 (*m*, 1 H); 3.28 (*m*, 3 H); 3.68, 4.79 (*AB*, *J* = 15.1, 2 H); 3.85 (*s*, 2 H); 4.30 (*d*, *J* = 8.1, 1 H); 5.95, 5.97 (*AB*, *J* = 1.4, 2 H); 6.64 (*dd*, *J* = 8.4, 1.6, 1 H); 6.65 (br. *m*, 1 H); 6.73 (*d*, *J* = 8.4, 1 H); 7.27, 7.62 (*AA′BB′*, *J* = 7.6, 4 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 14.7; 18.5; 24.4; 27.9; 32.1; 41.3; 43.7; 46.1; 52.3; 52.8; 67.2; 70.3; 73.3; 101.0; 108.0; 108.8; 121.3; 126.9; 128.4; 130.5; 138.4; 146.8; 147.9; 172.8; one peak missing due to signal overlap. FAB-MS: 895.6 (9, M_2H^+), 448.3 (100, MH^+), 188.2 (29), 135.0 (74, [Piperonyl]$^+$). HR-FAB-MS: 446.2444 ([$M-H$]$^+$, $C_{27}H_{32}N_3O_3$; calc. 446.2443).

*(3a*SR*,4*RS*,8a*SR*,8b*RS*)*-N-*(4-{2-[(1,3-Benzodioxol-5-yl)methyl]-1,3-dioxoperhydropyrrolo[3,4-*a*]pyrrolizin-4-yl}phenyl)ethanamide* ((±)-**64**) *and (3a*SR*,4*SR*,8a*RS*,8b*RS*)*-N-*(4-{-2-[(1,3-Benzodioxol-5-yl)methyl]-1,3-dioxoperhydropyrrolo[3,4-*a*]pyrrolizin-4-yl}phenyl)ethanamide* ((±)-**65**). A mixture of *N*-(4-formylphenyl)ethanamide (538 mg, 3.3 mmol), **25h** (380 mg, 3.3 mmol), and **26i** (694 mg, 3 mmol) in MeCN (5 ml) was heated to reflux for 14 h. Filtration, followed by removal of the solvent, left a residue, which was purified by CC (SiO_2; hexane/AcOEt/Et_3N 49.5:49.5:1 until complete elution of (±)-**64**, then AcOEt/Et_3N 99:1).

*Data of (±)-***64**: Yield: 285 mg (21%). Colorless solid. M.p. 213–214° (AcOEt). IR ($CHCl_3$): 2967, 1706, 1517, 1489, 1444, 1400, 1372, 1344, 1039, 928. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.67 (*m*, 2 H); 2.05 (*m*, 2 H); 2.16 (*s*, 3 H); 2.67 (*m*, 1 H); 2.84 (*m*, 1 H); 3.25 (*d*, *J* = 7.8, 1 H); 3.46 (*t*, *J* = 8.7, 1 H); 3.75 (*dd*, *J* = 9.9, 7.5, 1 H); 4.03 (*d*, *J* = 8.7, 1 H); 4.43, 4.45 (*AB*, *J* = 14.0, 2 H); 5.94, 5.95 (*AB*, *J* = 1.4, 2 H); 6.71 (*d*, *J* = 6.4, 1 H); 6.80 (*dd*, *J* = 6.4, 2.0, 1 H); 6.81 (br. *s*, 1 H); 7.17, 7.40 (*AA′BB′*, *J* = 8.4, 4 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 23.3; 24.6; 29.6; 42.3; 49.1; 50.7; 67.9; 68.5; 101.3; 108.3; 109.7; 119.8; 122.8; 128.9; 129.8; 133.9; 137.7; 147.5; 147.9; 168.5; 175.8; 178.4; one peak missing due to signal overlap. FAB-MS: 895.5 (8, M_2H^+), 448.2 (100, MH^+), 216.2 (21). Anal. calc. for $C_{25}H_{25}N_3O_5$ (447.49): C 67.10, H 5.63, N 9.39; found: C 67.11, H 5.75, N 9.39.

*Data of (±)-***65**: Yield: 315 mg (23%). Colorless foam. M.p. 80–85°. IR ($CHCl_3$): 3683, 3620, 3436, 3028, 2400, 1702, 1518, 1491, 1396, 1043, 929. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.56 (*m*, 1 H); 1.72 (*m*, 2 H); 1.96 (*m*, 1 H); 2.15 (*s*, 3 H); 2.44 (*m*, 1 H); 2.92 (*m*, 1 H); 3.31 (*dd*, *J* = 9.0, 5.6, 1 H); 3.51 (*t*, *J* = 8.7, 1 H); 3.87 (*dd*, *J* = 16.0, 7.6, 1 H); 4.05 (*d*, *J* = 5.9, 1 H); 4.54 (*s*, 2 H); 5.93 (*s*, 2 H); 6.73 (*d*, *J* = 7.5, 1 H); 6.89 (*dd*, *J* = 7.5, 1.9, 1 H); 6.90 (br. *s*, 1 H); 7.39, 7.46 (*AA′BB′*, *J* = 8.6, 4 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 24.3; 24.5; 26.2; 42.3; 47.9; 51.9; 55.5; 66.3; 69.1; 101.1; 108.3; 109.6; 120.2; 122.8; 127.5; 129.2; 137.2; 137.9; 147.4; 147.7; 168.4; 176.8; 177.8. FAB-MS: 895.9 (15, M_2H^+), 448.3 (100, MH^+), 216.2 (10), 135.0 (13, [Piperonyl]$^+$). HR-FAB-MS: 448.1869 (MH^+, $C_{25}H_{26}N_3O_5$; calc. 448.1872).

*(3a*SR*,4*RS*,8a*SR*,8b*RS*)*-N-*(4-{2-[(1,3-Benzodioxol-5-yl)methyl]-1-hydroxy-3-oxoperhydropyrrolo[3,4-*a*]pyrrolizin-4-yl}phenyl)ethanamide* ((±)-**66**). A 1M soln. of Li[Et_3BH] in THF (7.8 ml, 7.8 mmol) was added slowly under Ar at −78° to a soln. of (±)-**64** (3.5 g, 7.8 mmol) in dry CH_2Cl_2 (50 ml), and the mixture was stirred for 2 h at −78°, then warmed to 0°. After addition of sat. aq. $NaHCO_3$ soln. (50 ml), the mixture was stirred for 25 min at 0°. The phases were separated, and the aq. phase was extracted with CH_2Cl_2. The combined org. phases were dried (Na_2SO_4) and evaporated *in vacuo*, and the residue was purified by CC (SiO_2; CH_2Cl_2/CH_3OH/Et_3N 95:4:1) to give (±)-**66** (3.4 g, 96%). Colorless foam. M.p. 125°. IR ($CHCl_3$): 3438, 3324, 2972, 1683, 1602, 1512, 1440, 1412, 1370, 1307, 1127, 1041, 937. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.59 (*m*, 1 H); 1.84 (*m*, 2 H); 2.05 (*s*, 3 H); 2.08 (*m*, 1 H); 2.73 (*m*, 1 H); 2.86 (*m*, 1 H); 3.02 (*t*, *J* = 7.8, 1 H); 3.33 (*t*, *J* = 9.3, 1 H); 3.48 (*dd*, *J* = 10.9, 6.9, 1 H); 3.82 (*d*, *J* = 10.0, 1 H); 4.04, 4.55 (*AB*, *J* = 14.6, 2 H); 4.97 (*d*, *J* = 6.9, 1 H); 5.45 (br. *m*, 1 H); 5.90 (*s*, 2 H); 6.66 (*m*, 3 H); 7.15, 7.39 (*AA′BB′*, *J* = 8.4, 4 H); 8.34 (*s*, 1 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 23.1; 24.4; 27.0; 44.1; 46.2; 50.3; 50.7; 66.1; 66.9; 82.2; 101.2; 108.3; 109.2; 120.0; 122.2; 128.6; 130.7; 133.1; 138.4; 147.3; 148.1; 169.1; 172.8. FAB-MS: 899.2 (12, M_2H^+), 450.3 (100, MH^+), 363.2 (14), 216.2 (12), 135.1 (70, [Piperonyl]$^+$). HR-FAB-MS: 448.1873 ([$M-H$]$^+$, $C_{25}H_{26}N_3O_5$, calc. 448.1872).

*(3a*SR*,4*RS*,8a*SR*,8b*RS*)*-N-*(4-{2-[(1,3-Benzodioxol-5-yl)methyl]-1-[(4-methylphenyl)sulfonyl]-3-oxoperhydropyrrolo[3,4-*a*]pyrrolizin-4-yl}phenyl)ethanamide* ((±)-**67**). Dry powdered $CaCl_2$ (4.1 g, 37 mmol) was added to 4-toluenesulfinic acid (4.0 g, 25.9 mmol) in dry CH_2Cl_2 (15 ml), and the suspension was stirred for 10 min under Ar. A soln. of (±)-**66** (3.32 g, 7.4 mmol) in dry CH_2Cl_2 (15 ml) was added, and the mixture was stirred for 2 d at 20°. Since the conversion was not complete (TLC), additional 4-toluenesulfinic acid (4.0 g, 25.9 mmol) and $CaCl_2$ (4.1 g, 37 mmol) were added, and stirring was continued for 1 d. The mixture was washed

with sat. aq. $NaHCO_3$ soln. (4×), and the combined aq. phases were extracted with CH_2Cl_2. The combined org. phases were dried (Na_2SO_4), and evaporation *in vacuo* produced a residue, which was purified by CC (SiO_2; CH_2Cl_2/MeOH/Et_3N 95:4:1) to provide (±)-**67** (3.87 g, 93%). Yellow foam. M.p. 130–135°. IR ($CHCl_3$): 1702, 1517, 1504, 1491, 1447, 1407, 1372, 1314, 1135. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.62 (*m*, 2 H); 1.92 (*m*, 2 H); 1.93 (*s*, 3 H); 2.45 (*m*, 1 H); 2.47 (*s*, 3 H); 2.57 (*m*, 1 H); 2.84 (*m*, 1 H); 2.98 (*dd*, *J* = 7.6, 3.0, 1 H); 3.08 (*m*, 1 H); 3.91 (*d*, *J* = 6.2, 1 H); 4.03, 5.05 (*AB*, *J* = 14.8, 2 H); 4.36 (*s*, 1 H); 5.96, 5.98 (*AB*, *J* = 1.6, 2 H); 6.71 (*dd*, *J* = 8.1, 1.3, 1 H); 6.78 (br. *s*, 1 H); 6.79 (*d*, *J* = 8.1, 1 H); 7.17, 7.32 (*AA′BB′*, *J* = 8.6, 4 H); 7.38, 7.72 (*AA′BB′*, *J* = 8.1, 4 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 21.8; 24.3; 24.4; 31.7; 42.8; 45.2; 51.4; 51.5; 69.7; 71.5; 81.4; 101.4; 108.6; 108.9; 119.7; 122.2; 128.4; 129.1; 129.7; 130.7; 132.6; 133.4; 137.7; 146.4; 147.6; 148.5; 168.5; 173.4. FAB-MS: 1175.6 (12, M_2H^+), 588.3 (100, MH^+), 432.3 (54, $[M - MeC_6H_4SO_2)^+$), 135.0 (92, [Piperonyl]$^+$). HR-FAB-MS: 588.2167 (MH^+, $C_{32}H_{34}N_3O_6S$; calc. 588.2168).

*(1*RS*,3a*SR*,4*RS*,8a*SR*,8b*RS*)-*N*-(4-{2-[(1,3-Benzodioxol-5-yl)methyl]-1-(1-methylethyl)-3-oxoperhydropyrrolo[3,4-*a*]pyrrolizin-4-yl}phenyl)ethanamide* ((±)-**59d**). *General Procedure F*, starting from (±)-**67** yielded (±)-**59d** (60%) after CC (SiO_2, AcOEt/Et_3N 99:1). Colorless solid. M.p. 173–174° (Et_2O). IR ($CHCl_3$): 1673, 1601, 1601, 1516, 1503, 1486, 1443, 1409, 1367, 1307, 1129, 1043, 932. ^{1}H-NMR (300 MHz, $CDCl_3$): 0.71 (*d*, *J* = 6.9, 3 H); 0.92 (*d*, *J* = 7.2, 3 H); 1.64 (*m*, 2 H); 1.95 (*m*, 2 H); 2.00 (*s*, 3 H); 2.09 (*m*, 1 H); 2.49 (*dt*, *J* = 8.7, 2.7, 1 H); 2.64 (*m*, 1 H); 2.88 (*m*, 1 H); 3.25 (*m*, 3 H); 3.72, 4.83 (*AB*, *J* = 15.1, 2 H); 4.07 (*d*, *J* = 7.5, 1 H); 5.93, 5.95 (*AB*, *J* = 1.4, 2 H); 6.69 (*dd*, *J* = 8.1, 1.5, 1 H); 6.75 (*d*, *J* = 1.5, 1 H); 6.76 (*d*, *J* = 8.1, 1 H); 7.27, 7.36 (*AA′BB′*, *J* = 8.4, 4 H); 7.9 (*s*, 1 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 14.7; 18.4; 24.3; 24.4; 28.0; 31.0; 40.9; 43.7; 52.0; 53.0; 67.5; 70.0; 73.3; 101.0; 108.2; 108.6; 119.6; 121.3; 128.3; 130.4; 134.6; 137.4; 146.9; 147.9; 168.4; 172.9. FAB-MS: 951.9 (7, M_2H^+), 476.5 (100, MH^+), 432.4 (11), 216.2 (12), 135.1 (11, [Piperonyl]$^+$). Anal. calc. for $C_{28}H_{33}N_3O_4$ (475.59). C 70.71, H 6.99, N 8.84; found: C 70.67, H 6.92, N 8.85.

*(1*RS*,3a*SR*,4*RS*,8a*SR*,8b*RS*)-4-(4-Aminophenyl)-2-[(1,3-benzodioxol-5-yl)methyl]-1-(1-methylethyl)perhydropyrrolo[3,4-*a*]pyrrolizin-3-one* ((±)-**59e**). *Method A:* A suspension of (±)-**59d** (618 mg, 1.3 mmol) in 2N HCl (100 ml) was stirred for 16 h at reflux. After cooling, the clear yellowish soln. was carefully neutralized with solid $NaHCO_3$, then extracted with CH_2Cl_2. The aq. phase was dried (Na_2SO_4), and evaporation *in vacuo* left a residue, which was purified by CC (SiO_2; CH_2Cl_2/MeOH/Et_3N 97:2:1) to give (±)-**59e** (341 mg, 60%). Colorless foam. M.p. 80–85°. IR ($CHCl_3$): 3001, 2966, 1672, 1619, 1514, 1479, 1444, 1041, 931. ^{1}H-NMR (300 MHz, $CDCl_3$): 0.70 (*d*, *J* = 6.9, 3 H); 0.90 (*d*, *J* = 7.2, 3 H); 1.66 (*m*, 2 H); 2.04 (*m*, 3 H); 2.46 (*dt*, *J* = 9.3, 3.0, 1 H); 2.69 (*m*, 1 H); 2.91 (*m*, 1 H); 3.24 (*m*, 3 H); 3.58 (br. *s*, 2 H); 3.68, 4.81 (*AB*, *J* = 14.9, 2 H); 4.02 (*d*, *J* = 7.8, 1 H); 5.95, 5.97 (*AB*, *J* = 1.4, 2 H); 6.63 (*dd*, *J* = 8.0, 1.5, 1 H); 6.68 (*m*, 2 H); 6.68, 7.18 (*AA′BB′*, *J* = 8.6, 4 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 14.6; 18.5; 24.3; 27.8; 31.0; 41.3; 43.7; 52.2; 52.7; 67.2; 70.1; 73.0; 101.0; 108.0; 109.0; 115.0; 121.4; 129.1; 129.6; 130.7; 145.3; 146.8; 147.8; 173.0. FAB-MS: 867.8 (22, M_2H^+), 434.5 (100, MH^+), 341.4 (52), 174.3 (27), 135.1 (37, [Piperonyl]$^+$). Anal. calc. for $C_{26}H_{31}N_3O_3$ (433.55): C 72.03, H 7.21, N 9.69; found: C 72.14, H 7.32, N 9.44.

Method B: To a carefully degassed mixture of (±)-**53c** (995 mg, 2 mmol), (+)-(*R*)-BINAP (93 mg, 0.1 mmol), and Cs_2CO_3 (997 mg, 3 mmol, dried at 500° in high vacuum) in PhMe, [Pd(OAc)$_2$] (22 mg, 0.1 mmol) and benzophenone imine (0.4 ml, 434 mg, 2.4 mmol) were added. The mixture was stirred under Ar for 5 d at 100° in a sealed tube. The residue obtained by evaporation *in vacuo* was dissolved in THF (20 ml), and 2N HCl (3 ml) was added. After stirring for 30 min, hexane (30 ml) and AcOEt (15 ml) were added, and the mixture was extracted with 0.5N HCl. The aq. phase was made basic with 1N NaOH and extracted with CH_2Cl_2. The org. phase was dried (Na_2SO_4), and the residue obtained by evaporation *in vacuo* was purified by CC (SiO_2; AcOEt/Et_3N 99:1) to give (±)-**59e** (146 mg, 17%).

*(1*RS*,3a*SR*,4*RS*,8a*SR*,8b*RS*)*-N-(cis-*4-{2-[(1,3-Benzodioxol-5-yl)methyl]-1-(1-methylethyl)-3-oxoperhydropyrrolo[3,4-*a*]pyrrolizin-4-yl}cyclohexyl)-2,2,2-trifluorethanamide* ((±)-**68**) *and (1*RS*,3a*SR*,4*RS*,8a*SR*,8b*RS*)*-N-(trans-*4-{2-[(1,3-Benzodioxol-5-yl)methyl]-1-(1-methylethyl)-3-oxoperhydropyrrolo[3,4-*a*]pyrrolizin-4-yl}cyclohexyl)-2,2,2-trifluorethanamide* ((±)-**69**). A mixture of (±)-**59e** (870 mg, 2.1 mmol) and PtO_2 (100 mg, 0.4 mmol) in AcOH (50 ml) was hydrogenated for 2 d at 2 bar H_2, then 2 d at 4 bar H_2. The catalyst was removed by filtration, and the solvent was evaporated *in vacuo*. After addition of sat. aq. $NaHCO_3$ soln. (100 ml), the mixture was extracted with CH_2Cl_2. The org. phase was dried (Na_2SO_4) and evaporated *in vacuo* to yield 720 mg of crude product. CC (100 g SiO_2-*H*; CH_2Cl_2/MeOH/Et_3N 92:7:1) of 500 mg of the crude product afforded a mixture of (±)-**60** and (±)-**61** (428 mg, 67%). To a soln. of this mixture (300 g, 0.68 mmol) in dry CH_2Cl_2 (5 ml), $(CF_3CO)_2O$ (1 ml, 1.51 g, 7.19 mmol) was added, and the soln. was stirred for 2 h at 20°. Evaporation *in vacuo* and CC (100 g of SiO_2: CH_2Cl_2/MeOH 97:3) afforded the separated diastereoisomers.

*Data of (±)-***68**: Yield: 92 mg (25%). Colorless foam. M.p. 60–65°. IR ($CHCl_3$): 3442, 3284, 2962, 2873, 2258, 1716, 1671, 1531, 1504, 1490, 1444, 1373, 1166, 1042, 934. ^{1}H-NMR (500 MHz, $CDCl_3$): 0.73 (*d*, *J* = 6.9,

3 H); 0.90 (*d*, *J* = 6.9, 3 H); 1.27 (*m*, 1 H); 1.48 (*m*, 1 H); 1.81 (*m*, 10 H); 2.07 (*m*, 2 H); 2.15 (*t*, *J* = 7.4, 1 H); 2.61 (*dt*, *J* = 10.3, 5.5, 1 H); 2.87 (*t*, *J* = 7.0, 1 H); 2.95 (*m*, 1 H); 3.08 (*m*, 2 H); 3.17 (*t*, *J* = 8.0, 1 H); 3.80, 4.89 (*AB*, *J* = 14.5, 2 H); 4.31 (*d*, *J* = 7.3, 1 H); 5.94, 5.95 (*AB*, *J* = 1.4, 2 H); 6.70 (*dd*, *J* = 7.9, 1.6, 1 H); 6.74 (*d*, *J* = 7.9, 1 H); 6.75 (*d*, *J* = 1.6, 1 H); 7.34 (br. *m*, 1 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 15.3; 18.6; 23.2; 24.7; 25.0; 27.9; 29.3; 29.5; 31.0; 38.1; 42.4; 44.1; 45.6; 49.8; 55.5; 65.7; 72.6; 73.7; 101.1; 108.3; 108.8; 116.2 (*d*, *J* = 288.1); 121.6; 130.2; 147.0; 148.0; 156.6 (*d*, *J* = 36.6); 173.9. ^{19}F-NMR (282 MHz, $CDCl_3$): −75.7. FAB-MS: 536.3 (100, *M*H$^+$), 498.4 (20), 341.2 (17), 132.9 (51). Anal. calc. for $C_{28}H_{36}N_3O_4F_3$ (535.61): C 62.79, H 6.77, N 7.85, F 10.64; found: C 62.76, H 6.94, N 7.69, F 10.35.

Data of (±)-**69**: Yield: 118 mg (32%). Colorless needles. M.p. 192–193° (Et_2O). IR ($CHCl_3$): 3422, 2956, 2878, 1717, 1672, 1533, 1500, 1483, 1439, 1244, 1167, 1044, 933. ^{1}H-NMR (300 MHz, $CDCl_3$): 0.74 (*d*, *J* = 6.9, 3 H); 0.88 (*d*, *J* = 6.9, 3 H); 1.09 (*m*, 2 H); 1.38 (*m*, 3 H); 1.81 (*m*, 7 H); 2.10 (*m*, 2 H); 2.31 (*m*, 1 H); 2.55 (*dt*, *J* = 10.6, 6.2, 1 H); 2.69 (*dd*, *J* = 9.3, 7.3, 1 H); 2.93 (*d*, *J* = 3.4, 1 H); 3.05 (*m*, 2 H); 3.17 (*t*, *J* = 7.3, 1 H); 3.74, 4.91 (*AB*, *J* = 14.6, 2 H); 3.77 (*m*, 1 H); 5.94 (*s*, 2 H); 6.34 (*d*, *J* = 8.1, 1 H); 6.68 (*dd*, *J* = 8.1, 1.6, 1 H); 6.74 (*m*, 2 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 15.7; 18.7; 25.4; 27.8; 30.1; 30.4; 31.3; 31.9; 32.2; 39.2; 43.5; 43.8; 49.6; 49.9; 58.1; 64.5; 72.1; 76.0; 101.1; 108.3; 108.8; 115.9 (*d*, *J* = 288.1); 121.7; 130.2; 147.0; 147.9; 156.4 (*d*, *J* = 36.6); 173.1. ^{19}F-NMR (282 MHz, $CDCl_3$): −76.0. FAB-MS: 536.1 (100, *M*H$^+$), 498.4 (6), 341.1 (18), 132.9 (13). Anal. calc. for $C_{28}H_{36}N_3O_4F_3$ (535.61): C 62.79, H 6.77, N 7.85; found: C 62.58, H 6.79, N 7.78. X-Ray analysis: see *Fig. 15*.

*(1*RS*,3a*SR*,4*RS*,8a*SR*,8b*RS*)-4-(*cis*-4-Aminocyclohexyl)-2-[(1,3-benzodioxol-5-yl)methyl]-1-(1-methylethyl)perhydropyrrolo[3,4-*a*]pyrrolizin-3-one* ((±)-**60**). A mixture of (±)-**68** (44 mg, 0.1 mmol) and K_2CO_3 (50 mg, 0.36 mmol) in MeOH (10 ml) and H_2O (2 ml) was heated to reflux for 3 h. After evaporation, sat. aq. $NaHCO_3$ soln. (25 ml) was added, and the mixture was extracted with CH_2Cl_2. The org. phase was dried (Na_2SO_4), and evaporation *in vacuo* yielded (±)-**60** (44 mg, 99%). Colorless foam. M.p. 60–65°. IR ($CHCl_3$): 2956, 2922, 1668, 1506, 1483, 1444, 1372, 1128, 1094, 1044, 933. ^{1}H-NMR (300 MHz, $CDCl_3$): 0.74 (*d*, *J* = 6.9, 3 H); 0.88 (*d*, *J* = 6.5, 3 H); 1.66 (*m*, 12 H); 2.09 (*m*, 3 H); 2.59 (*dt*, *J* = 10.3, 5.8, 1 H); 2.84 (*t*, *J* = 1 H); 2.93 (*d*, *J* = 2.5, 1 H); 3.07 (*m*, 3 H); 3.18 (*t*, *J* = 7.7, 1 H); 3.75, 3.91 (*AB*, *J* = 14.8, 2 H); 5.93 (*s*, 2 H); 6.71 (*m*, 3 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 15.7; 18.7; 25.4; 25.5; 25.5; 27.9; 31.3; 32.6; 32.7; 39.2; 43.6; 43.9; 46.3; 49.9; 58.0; 64.7; 72.3; 75.3; 101.2; 108.4; 109.1; 121.9; 130.6; 147.2; 148.2; 173.6. FAB-MS: 440.2 (100, *M*H$^+$), 341.1 (51), 135.0 (16, [Piperonyl]$^+$). HR-FAB-MS: 440.2912 (*M*H$^+$, $C_{26}H_{38}N_3O_3$; calc. 440.2913).

*(1*RS*,3a*SR*,4*RS*,8a*SR*,8b*RS*)-4-(*trans*-4-Aminocyclohexyl)-2-[(1,3-benzodioxol-5-yl)methyl]-1-(1-methylethyl)perhydropyrrolo[3,4-*a*]pyrrolizin-3-one* ((±)-**61**). Compound (±)-**69** was hydrolyzed as described above for (±)-**68** to give (±)-**61** (30 mg, 68%). Colorless solid. M.p. 60–65°. IR ($CHCl_3$): 2956, 2922, 1672, 1506, 1483, 1433, 1372, 1117, 1094, 1033, 933. ^{1}H-NMR (300 MHz, $CDCl_3$): 0.75 (*d*, *J* = 6.9, 3 H); 0.87 (*d*, *J* = 6.9, 3 H); 1.45 (*m*, 12 H); 2.07 (*m*, 2 H); 2.22 (*m*, 1 H); 2.55 (*m*, 2 H); 2.66 (*t*, *J* = 8.1, 1 H); 2.92 (*d*, *J* = 3.1, 1 H); 3.06 (*m*, 2 H); 3.17 (*t*, *J* = 7.5, 1 H); 3.76, 3.91 (*AB*, *J* = 14.6, 2 H); 5.94 (*s*, 2 H); 6.72 (*m*, 3 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 15.7; 18.7; 25.4; 27.9; 30.8; 31.1; 31.4; 36.6; 36.9; 39.5; 43.6; 43.9; 50.1; 51.1; 58.2; 64.6; 72.3; 76.6; 101.2; 108.5; 109.1; 121.9; 130.6; 147.3; 148.3; 173.5. FAB-MS: 440.2 (100, *M*H$^+$), 423.2 (26), 341.1 (83), 135.0 (30, [Piperonyl]$^+$). HR-FAB-MS: 440.2915 (*M*H$^+$, $C_{26}H_{38}N_3O_3$; calc. 440.2913).

*X-Ray Crystal Structures. Compound (±)-***13**. Crystals were grown by slow diffusion (2 weeks) of hexane into a soln. of (±)-**13** in $CHCl_3$. X-Ray crystal data for $C_{22}H_{23}BrN_2O_2$ (M_r = 427.3): monoclinic space group $P2_1/n$ (No. 14), D_c = 1.5 g cm^{-3}, Z = 4, a = 12.190(2), b = 6.960(1), c = 22.747(5) Å, β = 100.95(3)°, V = 1894.8(6) Å^3, MoK_α radiation, λ = 0.7107 Å, 1.8° ≤ θ ≤ 27.0°, 3950 unique reflections, T = 100 K. The structure was solved by direct methods (SHELXS 86) and refined by full-matrix least-squares analysis (SHELXL 97) using an isotropic extinction correction and an exponentially modified weight factor r = 5 Å^2. All heavy atoms were refined anisotropically, H-atoms isotropically; H-positions are based on stereochemical considerations. Final $R(F)$ = 0.038, $wR(F^2)$ = 0.091 for 268 parameters and 2518 reflections with $I > 3\sigma(I)$. *Cambridge Crystallographic Data Centre* deposition No. CCDC-137389.

*Compound (±)-***21**. Crystals were grown by slow evaporation of a solution of (±)-**21** in AcOEt. X-Ray crystal data for $C_{22}H_{21}N_3O_2$ (M_r = 359.4): triclinic space group $P\bar{1}$, D_c = 1.269 g cm^{-3}, Z = 2, a = 9.352(8), b = 10.004(7), c = 10.882(9) Å, α = 95.55(6), β = 94.39(7), γ = 110.73(7)°, V = 941.0(13) Å^3, MoK_α radiation, λ = 0.71070 Å, 3° ≤ 2θ ≤ 40.0°, 1783 unique reflections, T = 293 K. The structure was solved by direct methods (SHELXS 86) and refined by full-matrix least-squares analysis (SHELXTL Plus (VMS)). All heavy atoms were refined anisotropically, H-atoms isotropically using a riding model; H-positions are based on stereochemical considerations. Final $R(F)$ = 0.0471, $wR(F)$ = 0.0422 for 244 parameters and 1365 reflections with $F > 4\sigma(F)$. *Cambridge Crystallographic Data Centre* deposition No. CCDC-137556.

Compound (±)-**23h**. Crystals were grown from a soln. of (±)-**23h** in MeOH. X-Ray crystal data for $C_{23}H_{21}N_3O_2$ (M_r = 371.43): triclinic space group $P\bar{1}$, D_c = 1.310 g cm^{-3}, Z = 4, a = 10.810(2), b = 11.138(2), c = 16.153(3) Å, α = 84.29(3), β = 84.33(3), γ = 77.40(3)°, V = 1882.6(6) Å^3, MoK_α radiation, λ = 0.71070 Å, 1.27° ≤ θ ≤ 25.0°, 6557 unique reflections, T = 173 K. The structure was solved by direct methods (SHELXS 86) and refined by full-matrix least-squares analysis (SHELXTL PLUS (VMS)). All heavy atoms were refined anisotropically, H-atoms isotropically; H-positions are based on stereochemical considerations. Final $R(F)$ = 0.0623, $wR(F^2)$ = 0.1781 for 505 parameters and 6545 reflections with $I > 2\sigma(I)$. *Cambridge Crystallographic Data Centre* deposition No. CCDC-138096.

Compound (±)-**38**. Crystals were grown from a soln. of (±)-**38** in Et_2O. X-Ray crystal data for $C_{24}H_{25}N_3O_3$ (M_r = 403.5): monoclinic space group $P2_1/c$ (No. 14), D_c = 1.27 g cm^{-3}, Z = 4, a = 10.605(4), b = 20.953(5), c = 10.036(3) Å, β = 108.93(2)°, V = 2109(1) Å^3, MoK_α radiation, λ = 0.7107 Å, 1.9° ≤ θ ≤ 22.0°, 2447 unique reflections, T = 295 K. The structure was solved by direct methods (SHELXS 86) and refined by full-matrix least-squares analysis (SHELXL 97) using an isotropic extinction correction and an exponentially modified weight factor r = 6 Å^2. All heavy atoms were refined anisotropically, H-atoms isotropically; H-positions are based on stereochemical considerations. Final $R(F)$ = 0.034, $wR(F^2)$ = 0.084 for 297 parameters and 1980 reflections with $I > 3\sigma(I)$. *Cambridge Crystallographic Data Centre* deposition No. CCDC-137390.

Compound (±)-**51c**. Crystals were grown from a soln. of (±)-**51c** in H_2O. X-Ray crystal data for $C_{27}H_{35}ClN_4O_3 \cdot H_2O$) ($M_r$ = 517.06): triclinic space group $P\bar{1}$ (No. 2), D_c = 1.28 g cm^{-3}, Z = 4, a = 11.854(1), b = 15.464(2), c = 15.881(2) Å, α = 79.26(1), β = 76.75(1), γ = 73.14(1)°, V = 2689(1) Å^3, CuK_α radiation, λ = 1.5418 Å, 2.9° ≤ θ ≤ 55.0°, 6762 unique reflections, T = 140 K. The structure was solved by direct methods (SHELXS 86) and refined by full-matrix least-squares analysis (SHELXL 97) using an isotropic extinction correction and an exponentially modified weight factor r = 6 Å. All heavy atoms were refined anisotropically, H-atoms isotropically; H-positions are based on stereochemical considerations. Final $R(F)$ = 0.049, $wR(F^2)$ = 0.122 for 720 parameters and 5307 reflections with $FI > 3\sigma(I)$. *Cambridge Crystallographic Data Centre* deposition No. CCDC-137391.

Compound (±)-**52**. Crystals were grown from a soln. of (±)-**52** in AcOEt. X-Ray crystal data for $C_{30}H_{29}BrN_2O_5S$ (M_r = 609.5): monoclinic space group $P2_1/c$, D_c = 1.493 g cm^{-3}, Z = 4, a = 16.507(8), b = 10.123(5), c = 16.842(10) Å, β = 105.58(4)°, V = 2711(2) Å^3, CuK_α radiation, λ = 1.54178 Å, 3° ≤ 2θ ≤ 100.0°, 2782 unique reflections, T = 293 K. The structure was solved by direct methods (SHELXS 86) and refined by full-matrix least-squares analysis (SHELXTL PLUS (VMS)). All heavy atoms were refined anisotropically, H-atoms isotropically using a riding model; H-positions are based on stereochemical considerations. Final $R(F)$ = 0.037, $wR(F^2)$ = 0.102 for 383 parameters and 2782 reflections with $I > 4\sigma(I)$. *Cambridge Crystallographic Data Centre* deposition No. CCDC-137489.

Compound (±)-**69**. Crystals were grown by slow diffusion of pentane into a soln. of (±)-**69** in $CHCl_3$. X-Ray crystal data for $C_{28}H_{36}F_3N_3O_4$ (M_r = 535.60): monoclinic space group $P2_1/c$, D_c = 1.338 g cm^{-3}, Z = 4, a = 10.204(9), b = 10.776(9), c = 24.19(2) Å, β = 90.97(7)°, V = 2660(4) Å^3, CuK_α radiation, λ = 1.54178 A, 3.65° ≤ θ ≤ 47.49°, 2438 unique reflections, T = 293 K. The structure was solved by direct methods (SHELXS 86) and refined by full-matrix least-squares analysis (SHELXTL PLUS (VMS)). All heavy atoms were refined anisotropically, H-atoms isotropically; H-positions are based on stereochemical considerations. Final $R(F)$ = 0.0546, $wR(F^2)$ = 0.1340 for 344 parameters and 2438 reflections with $I > 2\sigma(I)$. *Cambridge Crystallographic Data Centre* deposition No. CCDC-137588.

Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the *Cambridge Crystallographic Data Centre*. Copies of the data can be obtained, free of charge, on application to the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44(1223)336 033; e-mail: deposit@ccdc.cam.ac.uk).

This work was supported by *F. Hoffmann-La Roche AG* and by a *Kekulé* doctoral fellowship (to *U. O.*) from the *Fonds der Chemischen Industrie* (Germany). We thank *Heidi Hoffmann Maiocchi*, *Pascale Blond*, and *Thomas Tschopp* for the measurement of enzyme-inhibitor constants.

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Received January 28, 2000