Structure-Based Design of Nonpeptidic Thrombin Inhibitors: Exploring the D-Pocket and the Oxyanion Hole

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Structure-activity relationships for new members of a class of nonpeptidic, low-molecular-weight inhibitors of thrombin, a key serine protease in the blood coagulation cascade, are described. These compounds, which originate from X-ray-structure-based design, feature a conformationally rigid, bi- or tricyclic core from which side chains diverge into the four major binding pockets (distal D, proximal P, recognition or specificity S1, and oxyanion hole O) at the thrombin active site (*Fig. 1*). Phenylamidinium is the side chain of choice for the S1 pocket, while the most active inhibitors orient an i-Pr group into the P-pocket (*Table 1*). The key step in the synthesis of the inhibitors is the construction of the central bi- or tricyclic scaffold by 1,3-dipolar cycloaddition of an *in situ* prepared azomethine ylide and an *N*-substituted maleimide (*Schemes 1–3*, and *8–10*). One series of compounds was designed to explore the binding features of the large hydrophobic D pocket. This pocket provides space for lipophilic residues as bulky as benzhydryl groups. A new strategy was developed, allowing introduction of these sterically demanding substituents very late in the synthesis (*Schemes 5* and *6*). Benzhydryl derivative (±)-**2** was found to be the most selective member (K_i (trypsin)/K_i (thrombin) = 1200) of this class of nonpeptidic thrombin inhibitors, while the 'dipiperonyl' analog (±)-**3** (K_i = 9 nM, 7.60-fold selectivity) displays the highest potency of all compounds prepared so far (*Table 1*). A second series of inhibitors features side chains designed to orient into the oxyanion hole and to undergo H-bonding with the backbone NH groups lining the catalytic site of the enzyme. Unfortunately, neither activity nor selectivity could be substantially improved by introduction of these substituents (*Table 2*). Presumably, the high degree of pre-organization and the rigidity of the tightly bound scaffolds prevents the new substituents from assuming a position that would allow favorable interactions in the oxyanion hole. However, the oxyanion hole and the S1′ pocket next to it were found to be capable of accommodating quite large groups, which leaves much room for further exploration.

1. Introduction. – Controlling the delicate balance of blood coagulation, which is responsible for vital hemostasis on the one side, but for undesired formation of blood clots within intact blood vessels (thrombosis) on the other, continues to be in the focus of pharmaceutical research, since thrombotic disorders are among the major causes of mortality in the developed world [1]. Thrombin is a trypsin-like serine protease and one of the key enzymes regulating blood coagulation. It catalyzes the conversion of the soluble blood constituent fibrinogen into insoluble and polymerizable fibrin and activates platelet aggregation, as well as enzymes within the coagulation cascade [2]. X-Ray crystal structures of thrombin-inhibitor complexes show a fairly rigid protein

with a number of well-defined binding pockets at the active site [3][4]. Not surprisingly, the central position of thrombin as a target in the blood coagulation process, the availability of structural information, and the rigidity of its active site have led to a significant number of structure-based-inhibitor design programs [5–8].

Fig. 1 shows inhibitor (+)-**1** ($K_i = 7$ nM, selectivity over trypsin K_i(trypsin)/K_i(thrombin) = 740) developed in our laboratory and its binding mode in the thrombin active site according to an X-ray crystal structure of the protein complex [9][10]. The thrombin active site features four pockets: The distal (D) pocket is a large hydrophobic pocket that preferentially accommodates lipophilic residues such as aromatic rings; it is occupied by a Phe side chain in the case of the natural substrate fibrinogen. The proximal (P) pocket binds small hydrophobic residues; in the complex with fibrinogen, this pocket is occupied by a Val side chain. The specificity pocket S1 features an Asp carboxylate at the bottom and prefers incorporation of a positively charged group; the natural substrate directs an Arg side chain into this pocket. Finally, the catalytic site with the oxyanion hole (O), lined with H-bond donor centers, is another potential pocket for occupation by parts of an inhibitor.

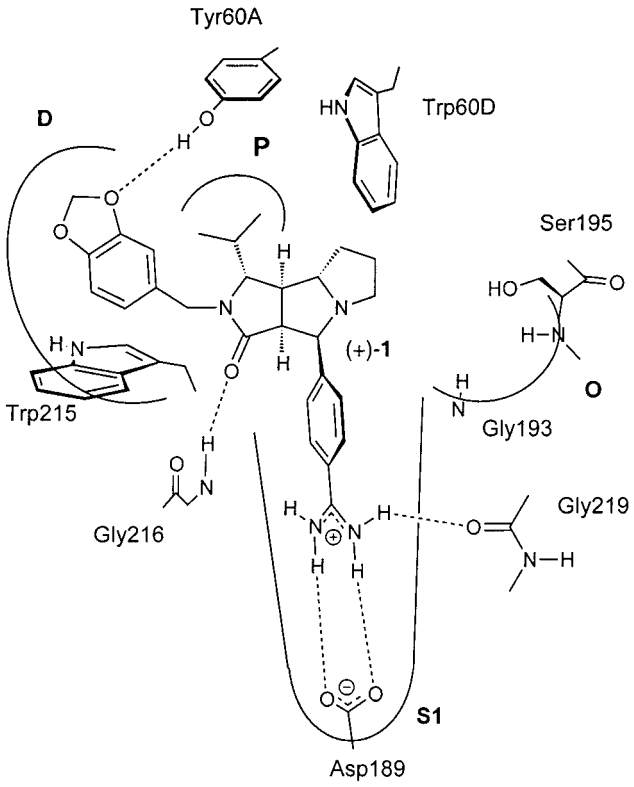


Fig. 1. *Inhibitor (+)-***1** *in the active site of thrombin* [10]. D = distal pocket, P = proximal pocket, S1 = specificity pocket, O = oxyanion hole.

Here, we describe our efforts to improve binding potency and specificity of our class of inhibitors (such as (+)-**1**; *Fig. 1*) [9–11] through modification of the substituent extending into the D-pocket and by anchoring new side chains to the central bi- and tricyclic scaffolds for reaching into the oxyanion hole (for a preliminary communication of parts of this work, see [12]; for some recent reports on thrombin inhibitors, see [13]).

2. Results and Discussion. – 2.1. *Optimization of the Substituent to Fill the D-Pocket.* 2.1.1. *Design.* The majority of synthetic low-molecular-weight thrombin inhibitors fill the large hydrophobic D-pocket with lipophilic residues, often Ph rings [5–8]. Quite a few of them employ even larger aromatic residues as D-pocket substituents. Within a series of peptidomimetic D-Phe–Pro–Arg-type inhibitors, it was discovered by researchers at *Merck* that a change from D-Phe to D-diphenylalanine ($H_2N-CH(CHPh_2)-CO_2H$) boosted the activity by as much as a factor of 160 (*Fig. 2*) [14]. Several other large lipophilic residues, even nonaromatic ones such as the dicyclohexylmethyl group could be easily placed into the D-pocket as well [15][16].

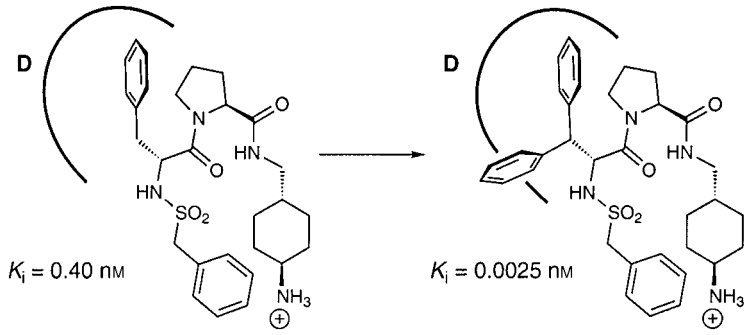


Fig. 2. *Thrombin inhibitors reported by the* Merck *group: increased activity upon changing from the benzyl to the benzhydryl group*

We had introduced the piperonyl (=(1,3-benzodioxol-5-yl)methyl) group as a D-pocket substituent in our inhibitors sich as (+)-**1**. Expecting a similar increase in affinity as reported in the *Merck* study, a second aromatic ring was to be introduced into our systems. Therefore, we planned the synthesis of the *N*-benzhydryl derivative (±)-**2** and, for comparison purposes, *N*-benzyl-substituted (±)-**3** (*Fig. 3*). The additional Ph ring (*a*) in (±)-**2** (*Fig. 3*) was predicted by computer modeling [17] to undergo aromatic edge-to-face interactions with the indole ring of Trp60D, which was expected to compensate for the loss of the H-bond between the piperonyl residue and Tyr60A in (+)-**1**. The second Ph ring (*b*) of the active enantiomer of (±)-**2** was predicted to adopt a location in the D-pocket similar to that of the piperonyl residue in (+)-**1**. As a difference, however, Ph ring *b* in (±)-**2** was expected to undergo parallel π-π stacking with the indole ring of Trp215, whereas the piperonyl residue in (+)-**1** prefers an edge-to-face orientation [9][10]. Finally, the active enantiomer of compound (±)-**4** combines the recognition features of both piperonyl and diarylmethyl residues.

2.1.2. *Synthesis.* Synthesis of the *N*-benzyl-substituted inhibitor (±)-**3** was accomplished according to the method used for (±)-**1** [10]. *N*-Benzylmaleimide (**5**) [18] was reacted in a 1,3-dipolar cycloaddition with the azomethine ylide [19], generated *in situ*

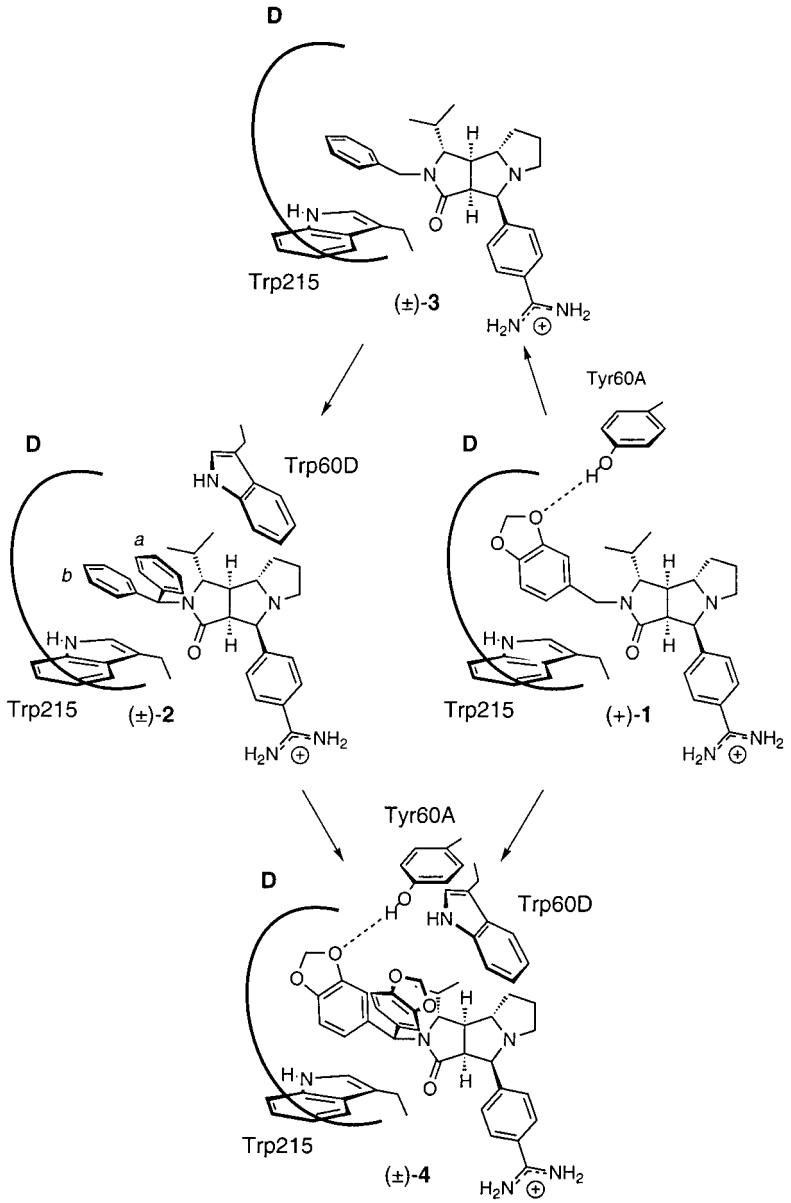
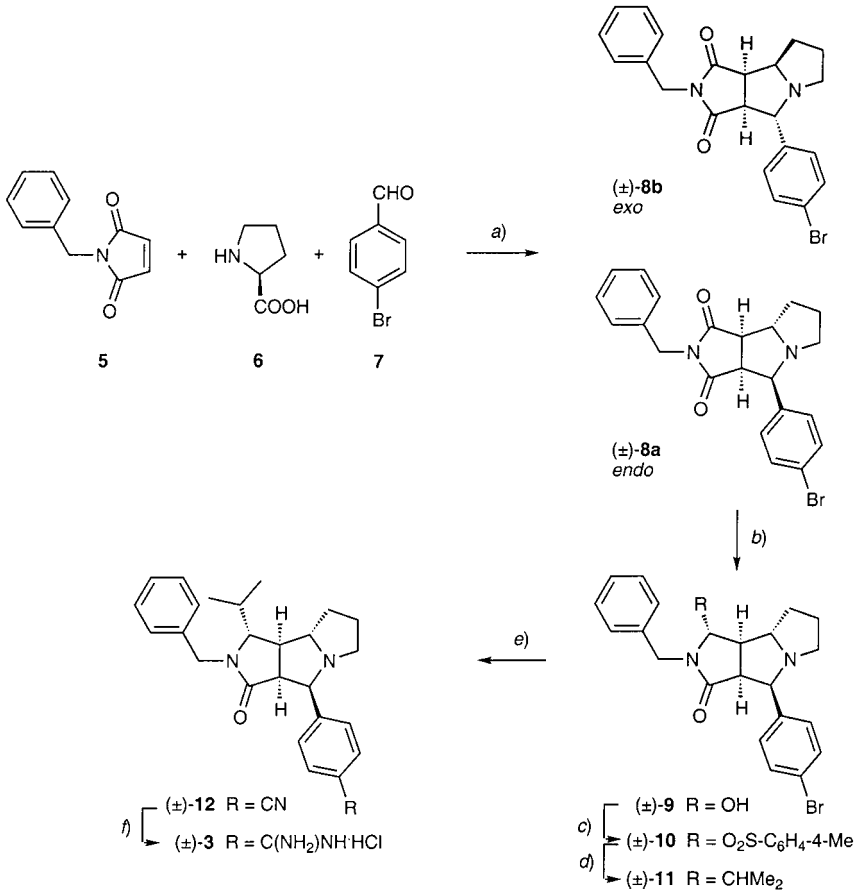


Fig. 3. *Large aromatic residues for filling the D-pocket at the thrombin active site.* The active enantiomers of compounds (±)-**2**, (±)-**3**, and (±)-**4** are shown.

from L-proline (**6**) and 4-bromobenzaldehyde (**7**), to yield nearly equal amounts of the desired *endo*-cycloadduct (±)-**8a** (42%) and the undesired *exo*-derivative (±)-**8b** (40%; *Scheme 1*). Regio- and stereoselective reduction (Li[Et_3BH], THF) of (±)-**8a** afforded hydroxy lactam (±)-**9**, which was converted to sulfone (±)-**10** [10]. Nucleophilic

Scheme 1. *Synthesis of the* N-*Benzylated Inhibitor* (±)-**3**



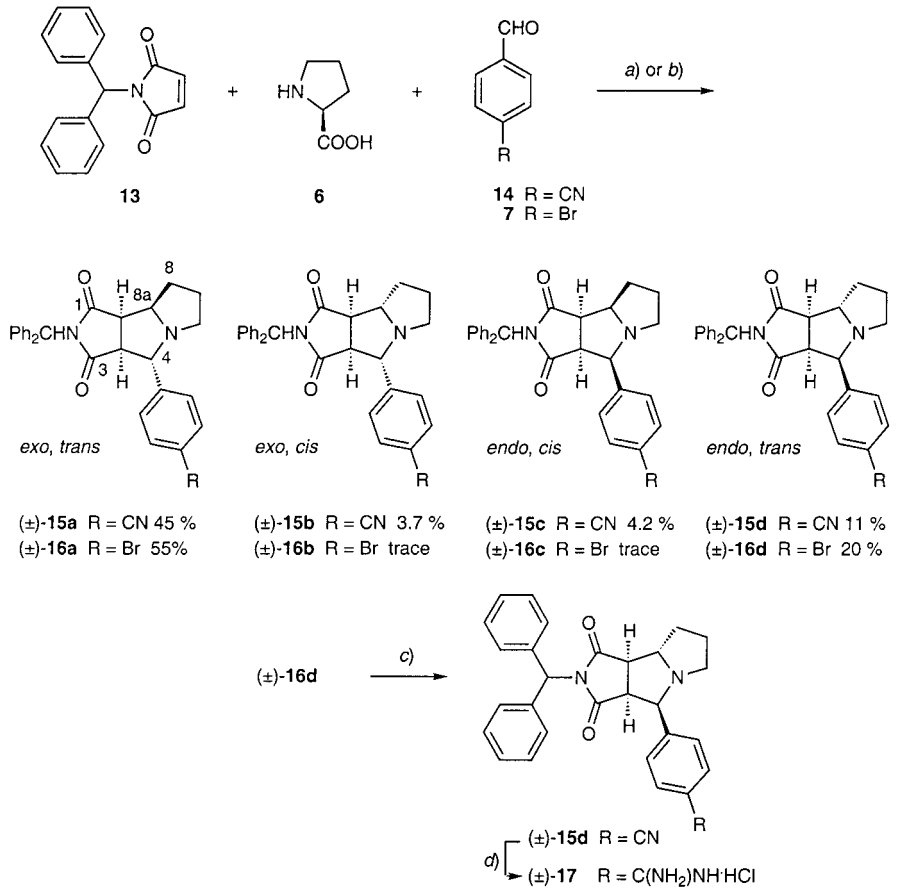
a) MeCN, Δ, 7 h; 42% ((±)-**8a**), 40% ((±)-**8b**). *b*) Li[Et_3BH], THF, −78°, 30 min. *c*) 4-Me−$C_6H_4SO_2H$, $CaCl_2$, CH_2Cl_2, r.t., 5 d; 74% (from (±)-**8a**). *d*) (i-Pr)MgCl, $ZnCl_2$, CH_2Cl_2, r.t., 23 h; 78%. *e*) CuCN, DMF, Δ, 10 h; 66%. *f*) 1. HCl (g), MeOH, $CHCl_3$, 4°, 3 d; 2. NH_3, MeOH, 65°, 3 h; 86%.

displacement of the arylsulfonyl group according to the protocol ($ZnCl_2$/i-PrMgCl) introduced by *Ley* and co-workers [20] gave – under retention of configuration – isopropyl derivative (±)-**11**. Finally, bromide/nitrile exchange to (±)-**12** and the *Pinner* reaction [21] provided target compound (±)-**3**.

The synthesis of *N*-benzhydryl derivative (±)-**2** was planned along a similar route (*Scheme 2*). The preparation of the required dipolarophile, *N*-benzhydrylmaleimide (**13**), required rather harsh conditions compared with the formation of derivatives with less bulky *N*-substituents such as **5**. Cycloaddition of **13** with the azomethine ylide formed from L-proline (**6**) and 4-formylbenzonitrile (**14**) also turned out to be more problematic than expected. For the first time in our thrombin-inhibitor project [9–11], all four possible diastereoisomers (±)-**15a–d** were formed in significant amounts

during the cycloaddition. Apparently, the steric bulk of the benzhydryl group reduces the reactivity of dipolarophile **13**, slowing down the cycloaddition considerably and allowing isomerization of the initially formed (*E*)-azomethine ylide [22] to the (*Z*)-configured 1,3-dipole, from which the *exo*,*cis* and *endo*,*cis*-isomers, (±)-**15b** and (±)-**15c**, respectively, arise (*endo*,*exo* refer to the orientation of the 4-cyanophenyl ring at C(4) with respect to the bicyclic perhydropyrrolo[3,4-*c*]pyrrole scaffold, and *cis*,*trans* to the position of this ring with respect to the configuration of C(8a) at the fusion of the two pentagons in the perhydropyrrolizine bicycle; for numbering, see *Scheme 2*). In cycloadditions with sterically less-hindered, highly reactive maleimides (such as **5**; *Scheme 1*), only the *exo*,*trans*- and *endo*,*trans*-diastereoisomers, resulting from addition of the (*E*)-configured 1,3-dipole, are obtained.

Scheme 2. *Cycloadditions with* N-*Benzhydrylmaleimide* (**13**) *and Synthesis of Inhibitor* (±)-**17**



a) R=CN: DMF, 80°, 3.5 h. *b*) R=Br: MeCN, Δ, 3.5 h. *c*) CuCN, DMF, Δ, 22 h; 45%. *d*) 1. HCl (g), MeOH, $CHCl_3$, 4°, 2 d; 2. NH_3, MeOH, 65°, 6 h; 35%.

Assignment of the correct relative configuration of the *trans*-isomers (±)-**15a** and (±)-**15d** was possible through comparison with the ^{1}H-NMR spectra of other pairs of *endo*/*exo*-cycloadducts such as (±)-**8a** and (±)-**8b**. An X-ray crystal-structure analysis (*Fig. 4*) of (±)-**15c** revealed its *endo,cis*-configuration; therefore, (±)-**15b** had to be the *exo,cis*-diastereoisomer.

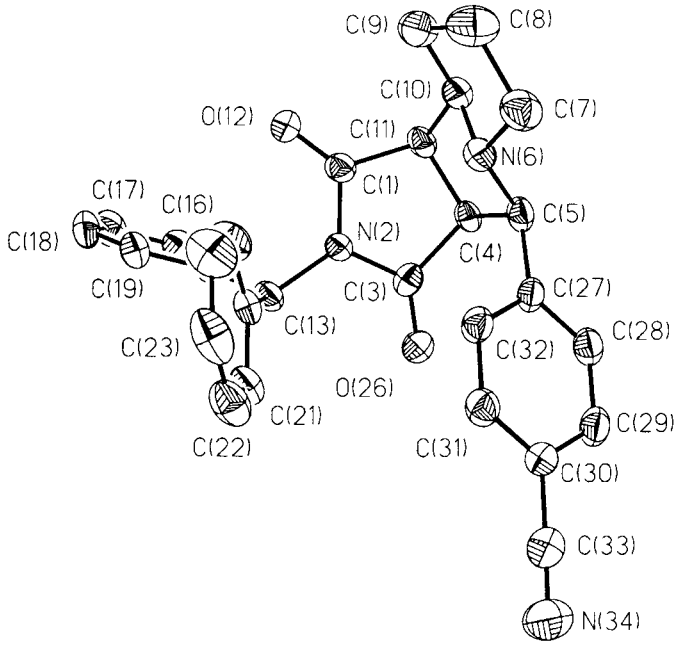


Fig. 4. *X-Ray crystal structure of* endo,cis-*(±)*-**15c**. Arbitrary numbering. Atomic displacement parameters obtained at 293 K are drawn at the 50% probability level.

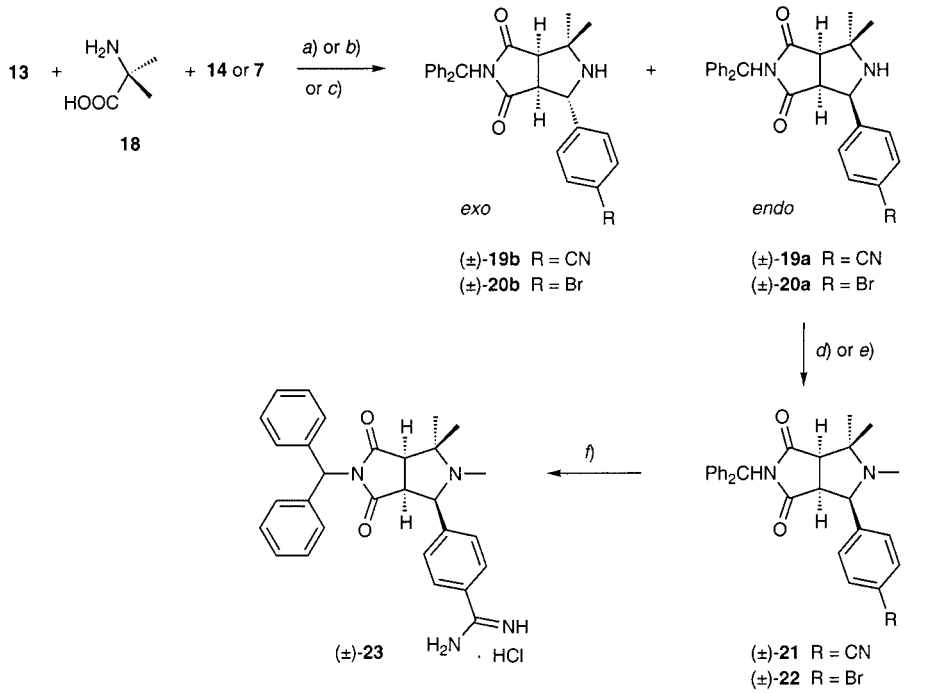
The use of 4-bromobenzaldehyde (**7**) instead of the benzonitrile **14** under optimized cycloaddition conditions allowed suppression of the formation of the two undesired isomers (±)-*exo,cis*-**16b** and (±)-*endo,cis*-**16c** (*Scheme 2*), which greatly facilitated workup and purification. The desired *endo,trans*-diastereoisomer (±)-**16d** was converted to carbonitrile (±)-**15d** and eventually to amidinium salt (±)-**17**.

Since preparation and purification of larger amounts of cycloadduct (±)-**16d** were tedious and low-yielding, this route seemed impractical for the synthesis of target molecule (±)-**2**, which would require several additional steps. Hence, it was decided to replace proline (**6**) by achiral α-aminoisobutyric acid (**18**) as the amine component in the azomethine ylide formation [10]. This would eliminate one stereogenic center in the cycloadducts, while ultimately leading to bicyclic inhibitors close in potency to their tricyclic congeners.

DMF had previously been used in the 1,3-dipolar cycloadditions since the desired *endo*-cycloadduct was always formed preferentially in this solvent [10]. While the reaction with *N*-benzhydrylmaleimide (**13**), α-aminoisobutyric acid (**18**), and 4-formylbenzonitrile in this environment also yielded a mixture of *endo* ((±)-**19a**, 35%) and *exo* ((±)-**19b**, 13%) cycloadducts, the corresponding conversion with 4-bromo-

benzaldehyde (**7**) turned out to be *exo*-selective ((±)-*endo*-**20a**: 20% and (±)-*exo*-**20b**: 51%; *Scheme 3*). Fortunately, this selectivity could be reversed by using less polar and higher-boiling solvents such as chlorobenzene, an observation that still warrants a good explanation. Both *endo*-cycloadducts (±)-**19a** and (±)-**20a** were *N*-methylated under *Eschweiler-Clarke* conditions [10][23] to yield (±)-**21** and (±)-**22**, respectively. Finally, carbonitrile (±)-**21** was converted to the corresponding amidinium salt (±)-**23**.

Scheme 3. *Synthesis of Inhibitor (±)-***23**



a) DMF, 80°, 12 h; 35% ((±)-**19a**), 13% ((±)-**19b**). *b*) DMF, 80°, 24 h; 20% ((±)-**20a**), 51% ((±)-**20b**). *c*) PhCl, Δ, 24 h; 53% ((±)-**20a**), 12% ((±)-**20b**). *d*) R=CN: HCHO, HCO_2H, Δ, 12 h; 71% ((±)-**21**). *e*) HCHO, HCO_2H, Δ, 6 h; 87% ((±)-**22**). *f*) from ((±)-**21**): 1. HCl (g), MeOH, $CHCl_3$, 4°, 2 d; 2. NH_3, MeOH, Δ, 6 h; 76%.

The relative configuration of (±)-*endo*-**19a** was confirmed by X-ray crystallography (*Fig. 5,a*). In the crystal packing (*Fig. 5,b*), the major interactions among enantiomers are both parallel-shifted π-π stacking as well as *edge-to-face* C−H···π interactions [24] between their aromatic rings. Another notable short contact (3.47 Å) is observed between the cyano N-atom and an aromatic benzhydryl C−H group. Since this C−H group is orthogonal to the C≡N bond, the contact is best viewed as a weak H-bond to the π-system of the CN group [25]. The cyanophenyl moieties of two enantiomers stack in an antiparallel way, thereby favorably compensating their local dipole moments.

Reduction of (±)-**22** was surprising in its unfavorable regioselectivity, as the major product was the undesired constitutional isomer (±)-**24** (55%), with the desired (±)-**25**

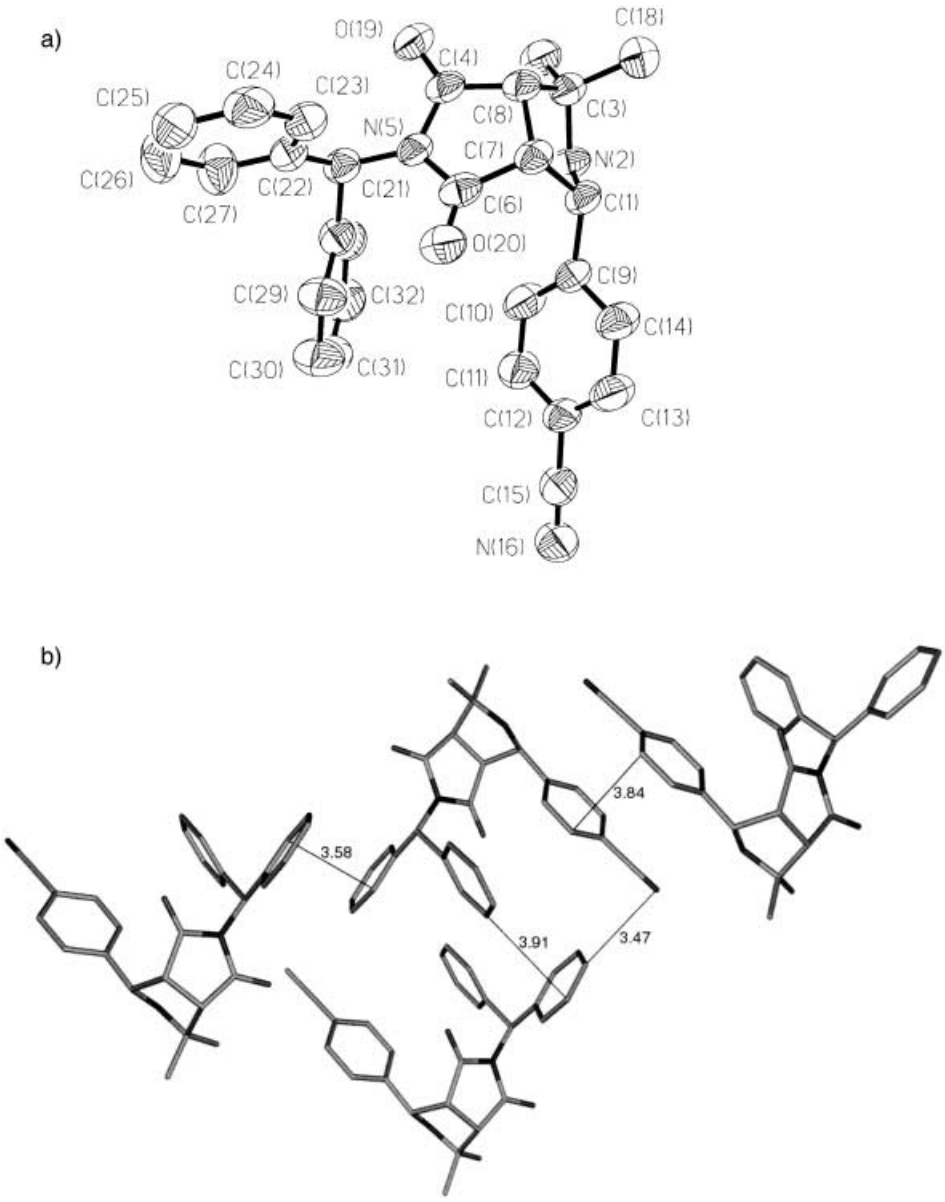
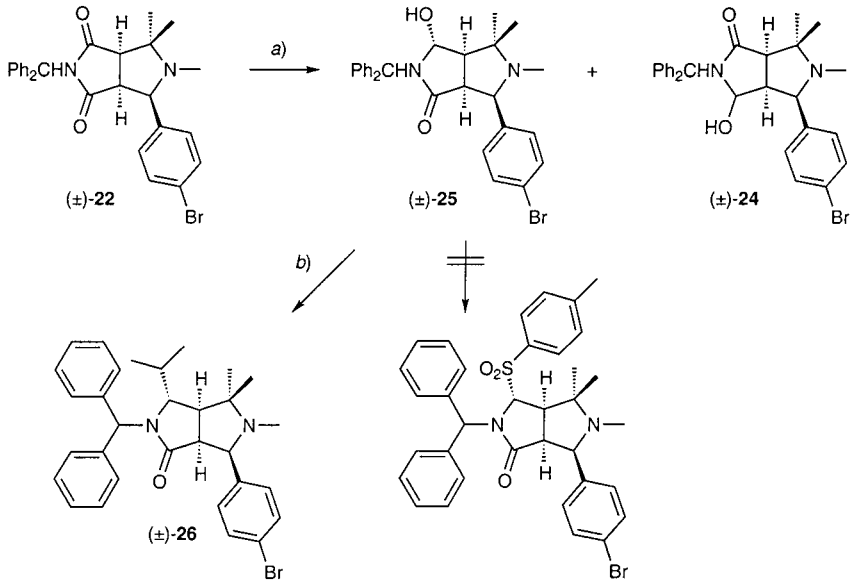


Fig. 5. a) *X-Ray crystal structure of carbonitrile (±)*-**19a**. Arbitrary numbering. Atomic displacement parameters obtained at 293 K are drawn at the 50% probability level. b) *Crystal packing of (±)*-**19**.

formed in only 31% yield (*Scheme 4*). Again, this was in sharp contrast to the reduction of *N*-benzyl (*Scheme 1*) or *N*-piperonyl derivatives [10], which all yielded predominately the desired regioisomer. The rather unexpected *exo*-orientation of the OH group in hydroxy lactam (±)-**25** was confirmed by X-ray crystallography (*Fig. 6*).

Scheme 4. *Introduction of the i-Pr Side Chain into (±)-**22***



a) Li[Et_3BH], CH_2Cl_2, 0°, 90 min; 55% ((±)-**24**), 31% ((±)-**25**). *b*) 1. Ac_2O, 4-(dimethylamino)pyridine (DMAP), r.t., 3 h; 2. i-PrMgCl, $ZnCl_2$, CH_2Cl_2, r.t., 15 h; 9%.

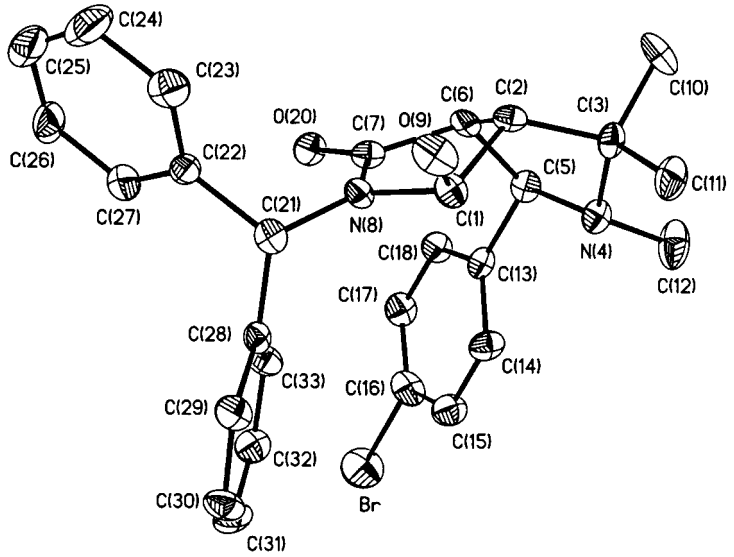


Fig. 6. *X-Ray crystal structure of hydroxy lactam (±)-**25***. Arbitrary numbering. Atomic displacement parameters obtained at 293 K are drawn at the 50% probability level.

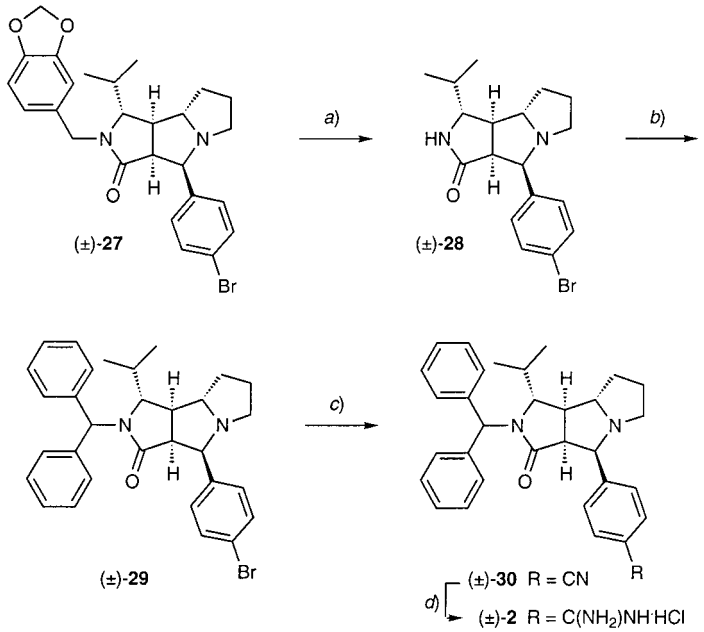
The subsequent introduction of the Ts group or less bulky sulfonyl groups into (±)-**25** failed, apparently due to steric hindrance by the benzhydryl residue. The use of AcO instead of sulfonyl as a leaving group for introducing the i-Pr side chain gave the desired lactam (±)-**26**; however, in very low yield at best.

The harsh conditions required for the preparation of maleimide **13**, the lack of diasteroselectivity in the cycloaddition (*Scheme 2*), the wrong regioselectivity in the imide reduction, and the failure to form the aryl sulfone from (±)-**25** (*Scheme 4*) are obviously due to the increased steric bulk of the benzhydryl compared with the benzyl or piperonyl group. It was, therefore, decided to follow a different strategy to prepare (±)-**2**. In this new route, the imide moiety in the tricyclic cycloadduct is *N*-protected, then the i-Pr side chain is introduced, followed by *N*-deprotection and introduction of the bulky benzhydryl residue late in the synthesis.

We chose the piperonyl group as *N*-protecting group, since the synthesis of the key intermediate lactam (±)-**27** had been established in our previous work [10]. Removal of the piperonyl group, however, proved to be quite challenging. Among the many published methods for *N*-dealkylating an amide or lactam [26], only the treatment with molten phosphoric acid or benzylic oxidation with CrO_3, followed by hydrolysis [27], gave isolable quantities of the desired *N*-unsubstituted lactam (±)-**28** (*Scheme 5*).

Successful *N*-re-alkylation of (±)-**28** required considerable experimentation as well. Deprotonation or activation of the lactam to improve its nucleophilicity in a

Scheme 5. *Synthesis of Inhibitor (±)-***2**

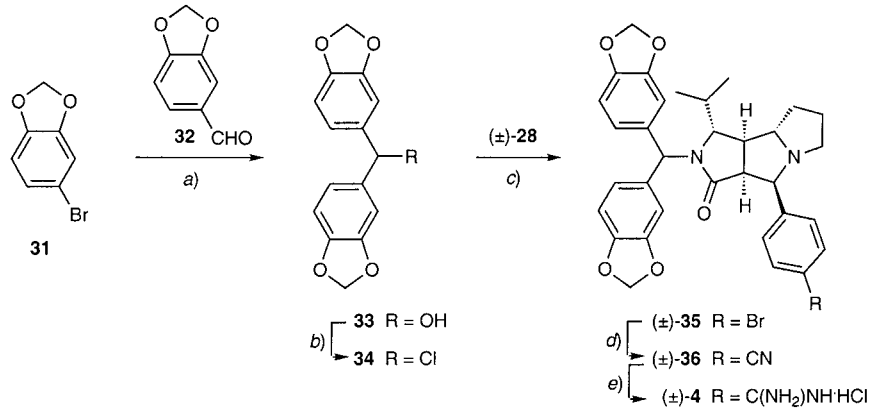


a) 1. H_3PO_4, PhOH, 150°, 1 h; 2. aq. NaOH soln., Δ, 1 h; 32%. *b*) Ph_2CHCl, $AgOSO_2CF_3$, CH_2Cl_2, sealed tube, 100°, 1 h; 65%. *c*) CuCN, DMF, Δ, 20 h; 40%. *d*) 1. HCl (g), MeOH, $CHCl_3$, 4°, 24 h; 2. NH_3, MeOH, 65°, 3.5 h; 42%.

substitution reaction with benzhydryl bromide produced only trace amounts of (±)-**29**, but the use of better electrophiles, such as diazodiphenylmethane and benzhydryl triflate [28], gave higher yields of (±)-**29** (*Scheme 5*). Bromide (±)-**29** was then converted to carbonitrile (±)-**30** and, finally, to amidinium salt (±)-**2**.

The synthesis of inhibitor (±)-**4** was performed according to a similar protocol (*Scheme 6*). Lithiation of 5-bromo-2*H*-benzo[*d*][1,3]dioxole (**31**) and addition to piperonal (**32**) gave the secondary alcohol **33**, which was converted to chloride **34** [29]. *N*-Alkylation of (±)-**28** with the triflate generated *in situ* from **34** provided lactam (±)-**35**, which was transformed into nitrile (±)-**36** and finally into target compound (±)-**4**.

Scheme 6. *Synthesis of Inhibitor (±)-***4**



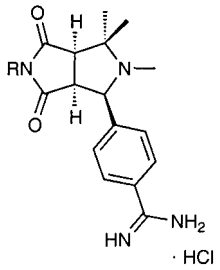
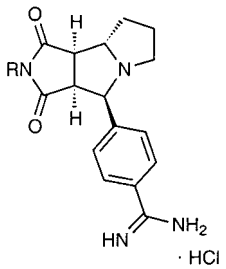
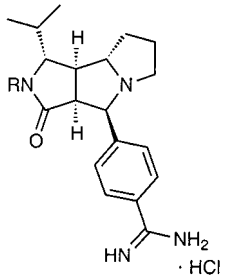
a) BuLi, −78°, 15 min; 98%. *b*) HCl (g), Et_2O, r.t., 2 h; 97%. *c*) $AgOSO_2CF_3$, CH_2Cl_2, sealed tube, 100°, 3 h; 44%. *d*) CuCN, DMF, Δ, 2 d; 52%; *e*) 1. HCl (g), MeOH, $CHCl_3$, 4°, 2 d; 2. NH_3, MeOH, 65°, 4 h; 54%.

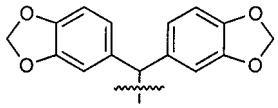
2.1.3. *Biological Activity.* All newly synthesized inhibitors were tested for their activity against thrombin, trypsin, and related enzymes (coagulation factors VIIa and Xa). Their potency was compared with that of some of the previously described, structurally related inhibitors (±)-**37**–(±)-**39** and (±)-**1** [10] (*Table 1*). In the series of imides with a bicyclic scaffold, the benzhydryl derivative (±)-**23** showed an inhibitory potency similar to that of the piperonyl analog (±)-**37**. Assuming similar overall enzyme-inhibitor binding geometries, the loss of the H-bond to Tyr60A (in the complex of (±)-**37**) is fully compensated for by the interactions gained by inclusion of the second Ph ring in the complex of (±)-**23**.

A comparison in the series of imides with a tricyclic scaffold ((±)-**38**, (±)-**39**, and (±)-**17**) also shows that the introduction of the benzhydryl moiety is as profitable for potency as the introduction of the piperonyl group. It is noteworthy, however, that undesired inhibition of trypsin by the benzhydryl derivative (±)-**17** is *ca.* six times weaker than by (±)-**39**. This is an indicator for the predicted interactions (see *Sect. 2.1.1*) between one of the Ph rings and the Tyr60A-Pro60B-Pro60C-Trp60D loop, which is unique to thrombin. Compound (±)-**17** is the most selective of all inhibitors with a C=O group occupying the P-pocket [10].

The same trend reappears in the tricyclic lactam series (±)-**1**–(±)-**4**. Although it is slightly less active than the piperonyl reference (±)-**1**, the benzhydryl derivative (±)-**2**

Table 1. *Activities of Thrombin Inhibitors and Selectivities with Respect to Trypsin*

Inhibitor	R	K_i [μM]		Selectivity[a])
		Thrombin	Trypsin	
				
(±)-**23**	Ph_2CH	0.61	1.1	1.8
(±)-**37**[b])	Piperonyl	0.5	1.1	2.2
				
(±)-**38**[b])	$PhCH_2$	0.22	2.6	12
(±)-**39**[b])	Piperonyl	0.09	0.7	7.8
(±)-**17**	Ph_2CH	0.11	4.8	44
				
(±)-**1**[b])	Piperonyl	0.013	9.9	760
(±)-**3**	$PhCH_2$	0.065	25	380
(±)-**2**	Ph_2CH	0.028	35	1200
(±)-**4**	dipip[c])	0.009	7.0	790

[a]) K_i(Trypsin)/K_i(Thrombin). [b]) From [10]. [c]) dipip = 

is the most selective so far within this family of nonpeptidic thrombin inhibitors. Finally, the 'dipiperonyl' inhibitor (±)-**4** displays only a very modest increase in activity and a small decrease in selectivity (as compared with (±)-**2**). With its biological data resembling those of the monopiperonyl derivative (±)-**1**, the second aryl ring seems ineffective.

2.2. *Reaching into the Oxyanion Hole.* 2.2.1. *Side Chains Attached to the Pyrrolidine N-Atom.* The negatively charged tetrahedral intermediates (and the corresponding transition states) formed during thrombin-catalyzed fibrinogen cleavage are stabilized by ionic H-bonding to NH residues of the peptidic enzyme backbone inside the so-called oxyanion hole. Placing a suitable substituent, which is capable of H-bonding with these groups, into this pocket could substantially increase binding strength of a thrombin inhibitor. In choosing such a substituent, it was our clear objective to avoid formation of a covalently binding inhibitor, which would contain an electrophilic residue that is attacked by Ser195 of the catalytic triade (for examples of 'covalent' thrombin inhibitors, see [8][30–35].

In a first approach, side chains designed to reach the oxyanion hole were attached to the pyrrolidine N-atom. The C=O groups of nonactivated carboxylate (±)-**37**, carboxylic acid (±)-**38**, and dione (±)-**39** (*Scheme 7*) were to serve as H-bond acceptors in the oxyanion hole. Cycloadduct (±)-**40**, originating from an azomethine ylide generated from α-aminoisobutyric acid (**18**), was alkylated with glyoxylic acid in a *Leuckart-Wallach* reaction [23], and the crude product was esterified with MeOH to give ester (±)-**41**, which was converted to (±)-**37** and, by hydrolysis, to (±)-**38** (*Scheme 7*). Another *Leuckart-Wallach* reaction with phenylglyoxal afforded (±)-**42** and, subsequently, target compound (±)-**39**.

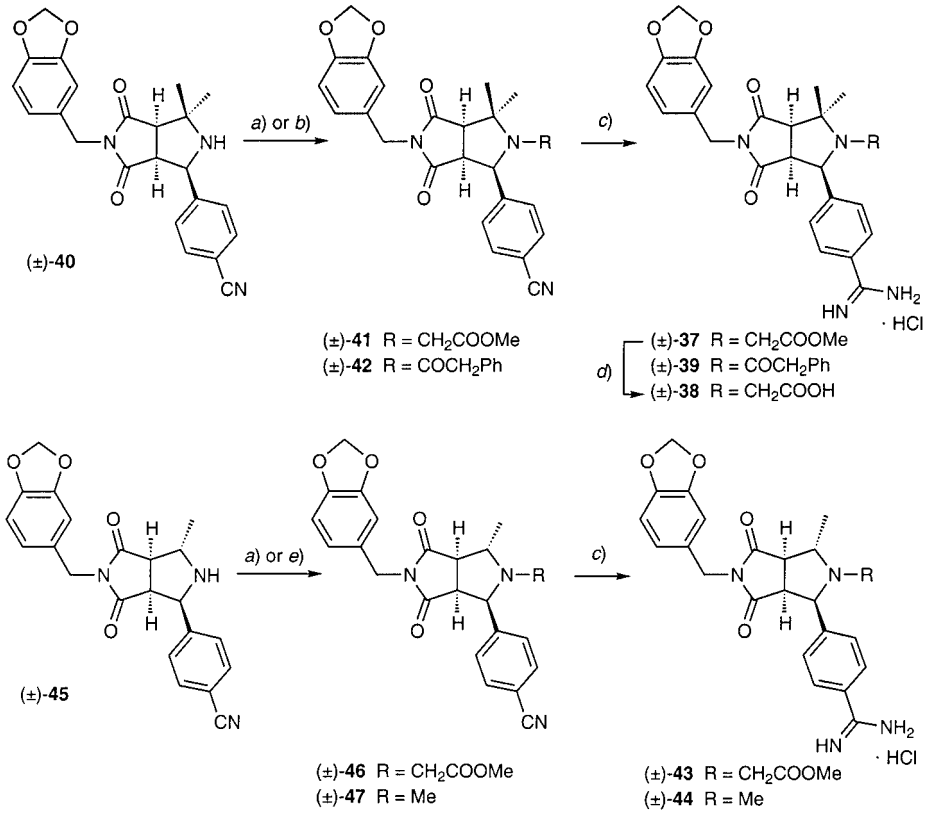
Inhibitor (±)-**43** with an ester side chain and, for comparison, (±)-**44** were also prepared, since the *endo*-Me group in (±)-**37**–(±)-**39** was suspected to conflict sterically with the indole ring of Trp60D [36]. Their syntheses started from cycloadduct (±)-**45** and proceeded in the usual way *via* (±)-**46** and (±)-**47**, respectively.

Compared with (±)-**48** [10], carboxylate (±)-**37** was only slightly more active but significantly more selective for thrombin over trypsin (*Table 2*). The corresponding carboxylic acid (±)-**38** and dione (±)-**39**, however, were bound much more weakly. Unfavorable complexation-induced desolvation of the carboxy group in (±)-**38** and steric hindrance of the Ph group in bound (±)-**39** are possible reasons for the loss of activity. The removal of the *endo*-Me group in inhibitors (±)-**43** and (±)-**44** did not provide much advantage in potency over the corresponding geminal dimethyl derivatives (±)-**48** and (±)-**37**, respectively. However, both inhibitors (±)-**43** and (±)-**44** were significantly more selective than (±)-**37** and (±)-**48**, respectively, which was rather unexpected.

It can be concluded from these biological results that the chosen *N*-substituents do not significantly benefit from new interactions within the oxyanion hole.

2.2.2. *Side Chains Attached to the C(1)-Atom of the Octahydropyrrolo[3,4-*c*]pyrrole Scaffold.* Molecular-modeling examinations indicated that the C(1)-atom of the octahydropyrrolo[3,4-*c*]pyrrole scaffold (for numbering, see *Fig. 7*) in our family of inhibitors would be another possible point of attachment for oxyanion-hole-binding substituents, such as propionate (in (±)-**49**) and hydroxamate (in (±)-**50**) (*Table 2*). *Fig. 7* depicts the binding mode predicted for the active enantiomer of hydroxamic acid

Scheme 7. *Synthesis of Inhibitors with a Side Chain at the Pyrrolidine N-Atom*

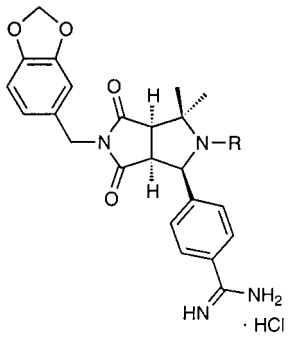
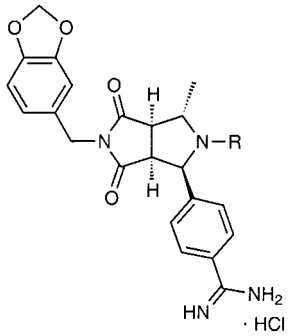
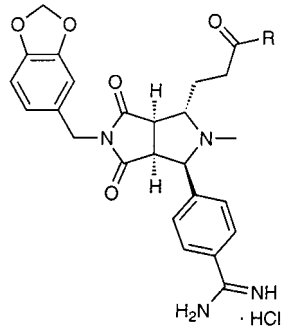


a) 1). $HCOCO_2H$, HCO_2H, Δ, 1 d; 2. MeOH, cat. H_2SO_4, Δ, 2 d; 40% ((±)-**41**), 48% ((±)-**46**). *b*) HCOCOPh, HCO_2H, 100°, 10 h; 22% ((±)-**42**). *c*) 1. HCl (g), MeOH, $CHCl_3$, 4°, 24 h; 2. NH_3, MeOH, 65°, 3.5 h; 75% ((±)-**37**); 97% ((±)-**39**); 37% ((±)-**43**); 56% ((±)-**44**). *d*) 3N HCl, Δ, 17 h; 36%. *e*) HCHO, HCO_2H, Δ, 20 h; 91% ((±)-**47**).

(±)-**50**. The modeling suggested for the hydroxamic acid residue of (±)-**50** to interact with both the NH group of Gly193 and the C=O group of Leu41. For the carboxy residue of (±)-**49**, both H-bonding to the NH group of Gly193 in the oxyanion hole and ion pairing with the side chain of Lys60F were predicted. Obviously, a compound such as (±)-**50** would hardly be a selective serine protease inhibitor, since hydroxamic acids are well-known metalloprotease inhibitors [37], but our objective was primarily to verify binding predictions based on modeling in an isolated *in vitro* test.

Our initial synthetic strategy towards inhibitors (±)-**49** and (±)-**50** started with the 1,3-dipolar cycloaddition between *N*-piperonylmaleimide (**51**) and the azomethine ylide formed from L-glutamine (**52**) and 4-formylbenzonitrile (**14**) to yield the desired bicyclic central scaffold. Its *exo*-propionamide side chain would be transformed into the desired carboxylic and hydroxamic acid residues afterwards. However, only one diastereoisomer of the desired cycloadduct (±)-**53** was isolated in poor yield (5.1%)

Table 2. *Activities of Thrombin Inhibitors with Side Chains Designed to Reach into the Oxyanion Hole and Selectivities with Respect to Trypsin*

Inhibitor	R	K_i [μM]		Selectivity[a])
		Thrombin	Trypsin	
				
(±)-**48**[b])	Me	0.5	1.1	2.2
(±)-**37**	CH_2COOMe	0.27	3.8	14
(±)-**38**	CH_2COOH	7.4	3.2	0.4
(±)-**39**	$COCH_2Ph$	5.1	32	6.3
				
(±)-**44**	Me	0.20	4.9	24.3
(±)-**43**	CH_2COOMe	0.53	19	36
				
(±)-**49**	OH	18	57	3.2
(±)-**58**	OMe	0.17	1.2	7.2
(±)-**50**	NHOH	0.43	5.0	11.6
(±)-**59**	$NHOCH_2Ph$	0.57	2.6	4.5

[a]) K_i(Trypsin)/K_i(Thrombin). [b]) From [10].

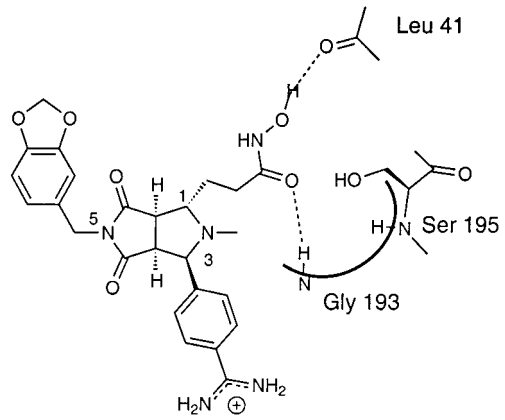
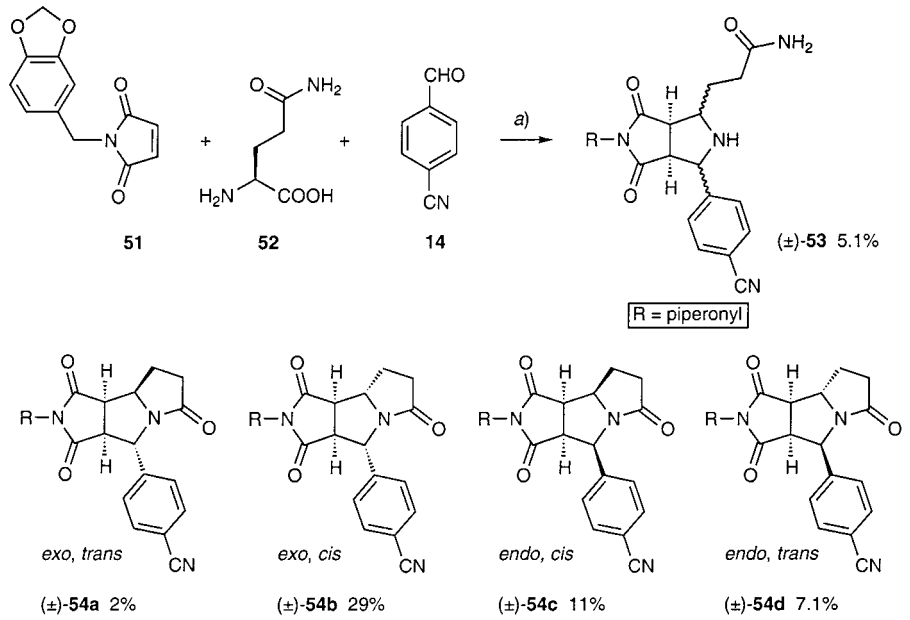


Fig. 7. *Schematic representation of the expected interactions between thrombin and the active enantiomer of hydroxamic acid (±)-***50**

with the major product fraction containing the four diastereoisomeric tricyclic lactams (±)-**54a**–**d** (total yield of 49.1%; *Scheme 8*). Although amide C=O groups are poor electrophiles, intramolecular attack by the secondary pyrrolidine N-atom had led to the formation of five-ring lactams. These lactams were probably formed after and not before the cycloaddition, since pyroglutamic acid, the intramolecular cyclization product of L-glutamine (**52**), would not form an azomethine ylide with aldehyde **14**.

Scheme 8. *1,3-Dipolar Cycloaddition with an Azomethine Ylide Formed from* L*-Glutamine*



a) PhCl, Δ, 45 h.

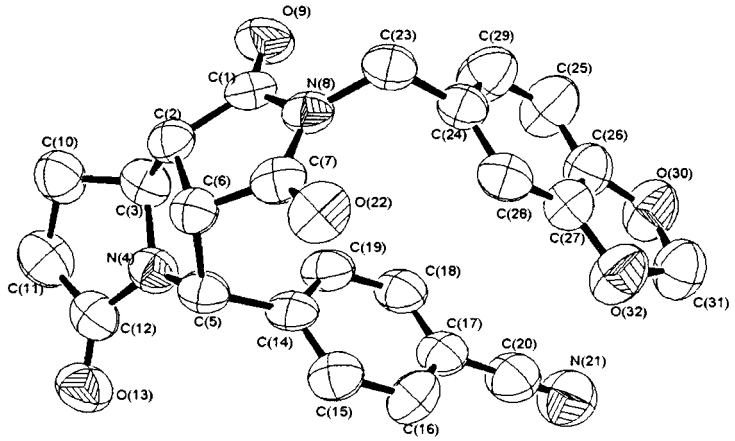


Fig. 8. *X-Ray crystal structure of lactam (±)-***54d**. Arbitrary numbering. Atomic displacement parameters obtained at 293 K are drawn at the 50% probability level.

The relative configurations of diastereoisomers (±)-**54a**–**d** were assigned on the basis of the 1D-NOE difference ^{1}H-NMR spectra; these assignments were further supported by the X-ray crystal structure of (±)-**54d** (*Fig. 8*). We decided not to proceed any further with these lactams, since an earlier study [11] had shown that *N*-acetylated pyrrolidine inhibitors of this type display strongly reduced activity.

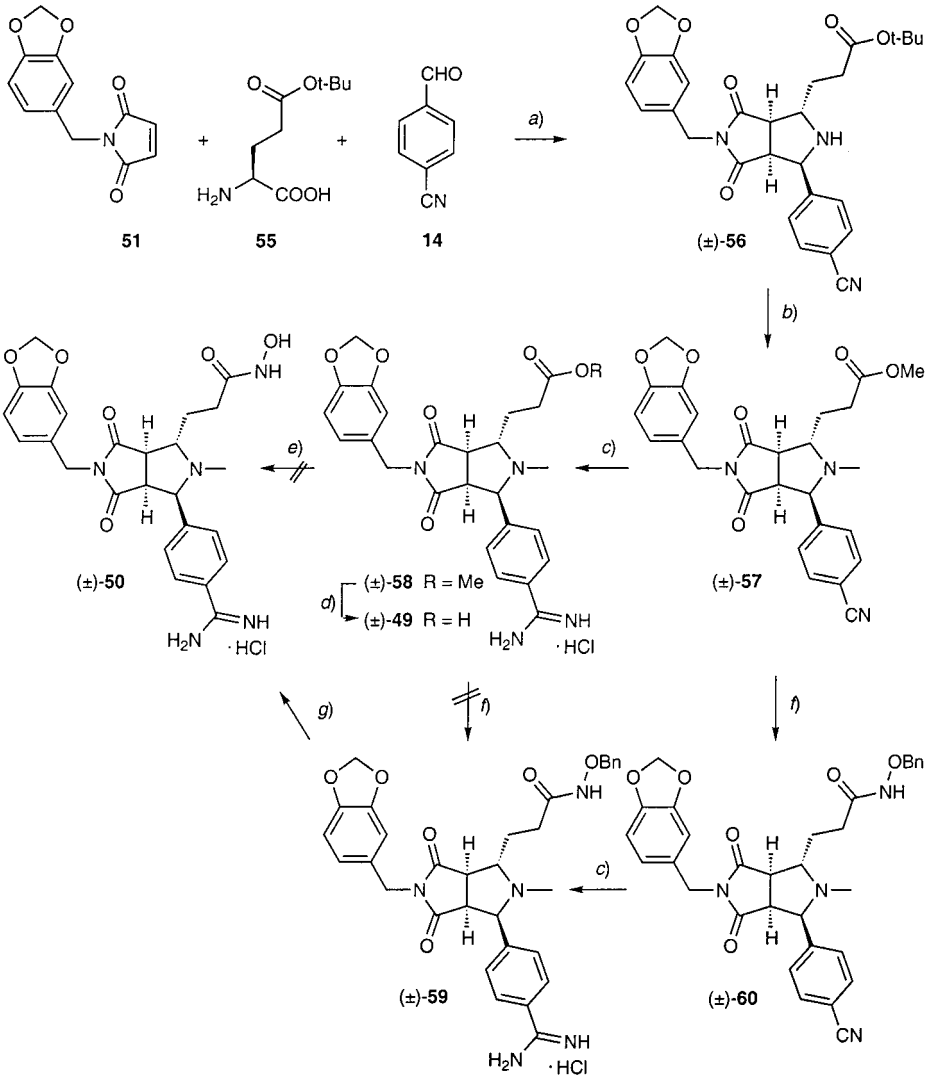
We finally succeeded in introducing the desired substituents by using L-glutamic acid derivative **55** with the side-chain carboxy group protected as *tert*-butyl ester [38]. Steric hindrance by the bulky ester residue prevented intramolecular lactamization effectively during the 1,3-dipolar cycloaddition. Under optimized conditions, cycloadduct (±)-**56** with the desired propionate side chain was obtained with a remarkable *endo,trans*-selectivity and in good yield (56%; *Scheme 9*). *N*-Methylation of (±)-**56** under *Eschweiler-Clarke* conditions also led to cleavage of the *tert*-butyl ester. The intermediate was, therefore, re-esterified with MeOH to give (±)-**57**, and *Pinner* reaction provided methyl propionate (±)-**58**. Hydrolysis gave the target carboxylic acid (±)-**49**.

Attempts to prepare hydroxamic acid (±)-**50** by reacting (±)-**58** with hydroxylamine hydrochloride [39] or by transforming the methyl ester into the Bn-protected precursor (±)-**59** failed. Fortunately, benzyloxy amide (±)-**60** could be prepared at the stage of the nitrile [40] and subsequently transformed into the amidinium salt (±)-**59**. Catalytic hydrogenolysis of the *O*-Bn group finally afforded hydroxamic acid (±)-**50** (*Scheme 9*) [37].

Biological studies showed propionic acid (±)-**49** to be the weakest of the inhibitors with the C(1) side chain (*Table 2*). A similar result had been obtained in the series of inhibitors with side chains departing from the pyrrolidine N-atom ((±)-**38**). Probably, no interaction in the oxyanion hole can compensate for the energy necessary to desolvate the carboxylate.

Ester (±)-**58** is slightly more active than hydroxamic acid (±)-**50** or Bn-protected (±)-**59**. Unfortunately, there is no supporting evidence that the side chain C=O groups

Scheme 9. *Synthesis of Inhibitors* (±)-**49** *and* (±)-**50**



a) MeCN, 90°, 16 h; 56%. *b*) 1. HCO_2H, CH_2O, 100°, 14 h; 2. MeOH, conc. H_2SO_4, Δ, 18 h; 76%. *c*) 1. HCl, MeOH, $CHCl_3$, 4°, 24 h; 2. NH_3, MeOH, 3 h, 65°; 54% ((±)-**58**); 21% ((±)-**59**). *d*) KOH, MeOH, r.t., 24 h; 74%. *e*) $NH_2OH \cdot HCl$, KOH, MeOH. *f*) Me_3Al, $BnONH_2 \cdot HCl$, CH_2Cl_2, r.t., 20 h, 24% ((±)-**60**). *g*) H_2, Pd/C, MeOH, r.t., 7 h; 99%.

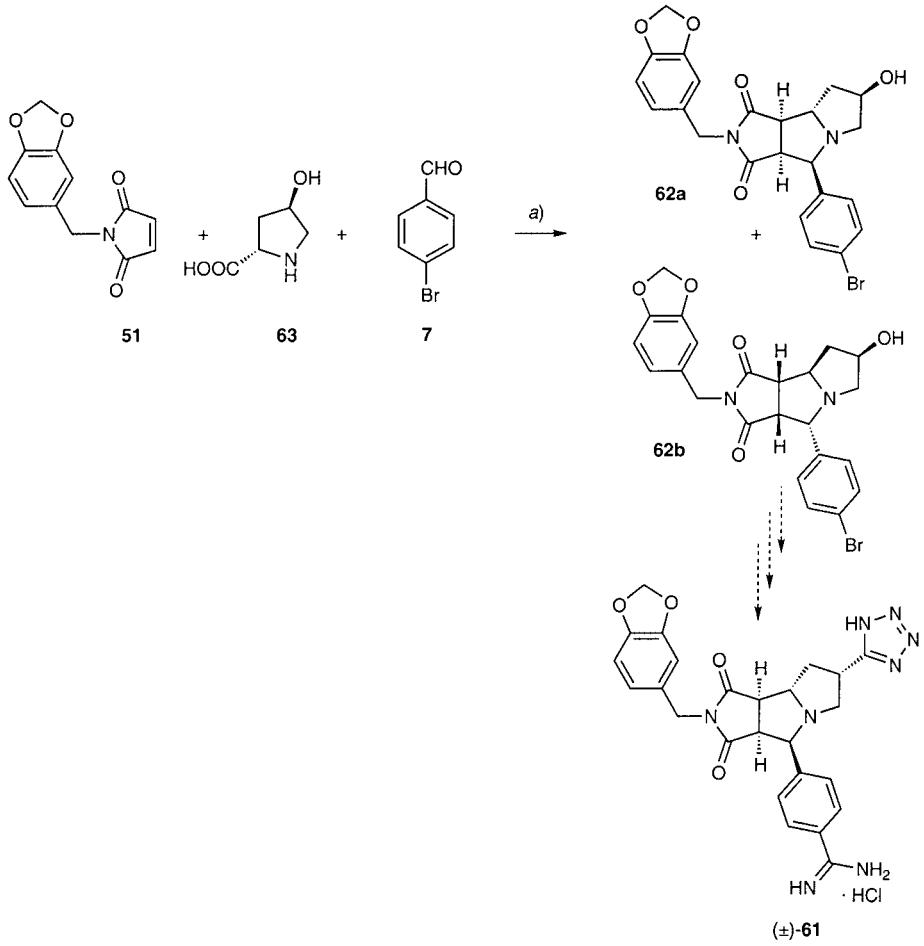
of these compounds actually participate in the predicted H-bonding in the oxyanion hole. It is possible that the conformational rigidity of the bicyclic scaffold prevents their optimal positioning in this newly targeted pocket.

2.2.3. *Side Chains Attached to the Tricyclic Scaffold: Preliminary Results.* Molecular-modeling studies indicated that a tetrazole ring, attached to the tricyclic scaffold in (±)-

61, could favorably interact at the catalytic site of thrombin. As a precursor to (±)-**61**, the tricyclic derivatives **62a** and **62b** were synthesized by 1,3-dipolar cycloaddition with L-(4*R*)-hydroxyproline (**63**; *Scheme 10*) as the amine component to form the azomethine ylide. The latter, formed *in situ*, is no longer C_S-symmetrical, as in the other cases reported in this study. With a C_1-symmetrical azomethine ylide, no racemates are formed in the cycloaddition, but up to eight different, optically active diastereoisomers are possible.

The reaction was carried out in MeCN or DMF, leading to only three diastereoisomers, including **62a** and **62b** (*Scheme 10*). The latter two could not yet be separated by chromatography; they even crystallize together, forming a mixed crystal, whose structure was solved by X-ray-analysis (*Fig. 9,a*). This behavior is reminiscent of

Scheme 10. *Synthesis of the Two Diastereoisomers* **62a** *and* **62b**



a) MeCN, 90°, 28 h; 14% (**62a**), 14% (**62b**).

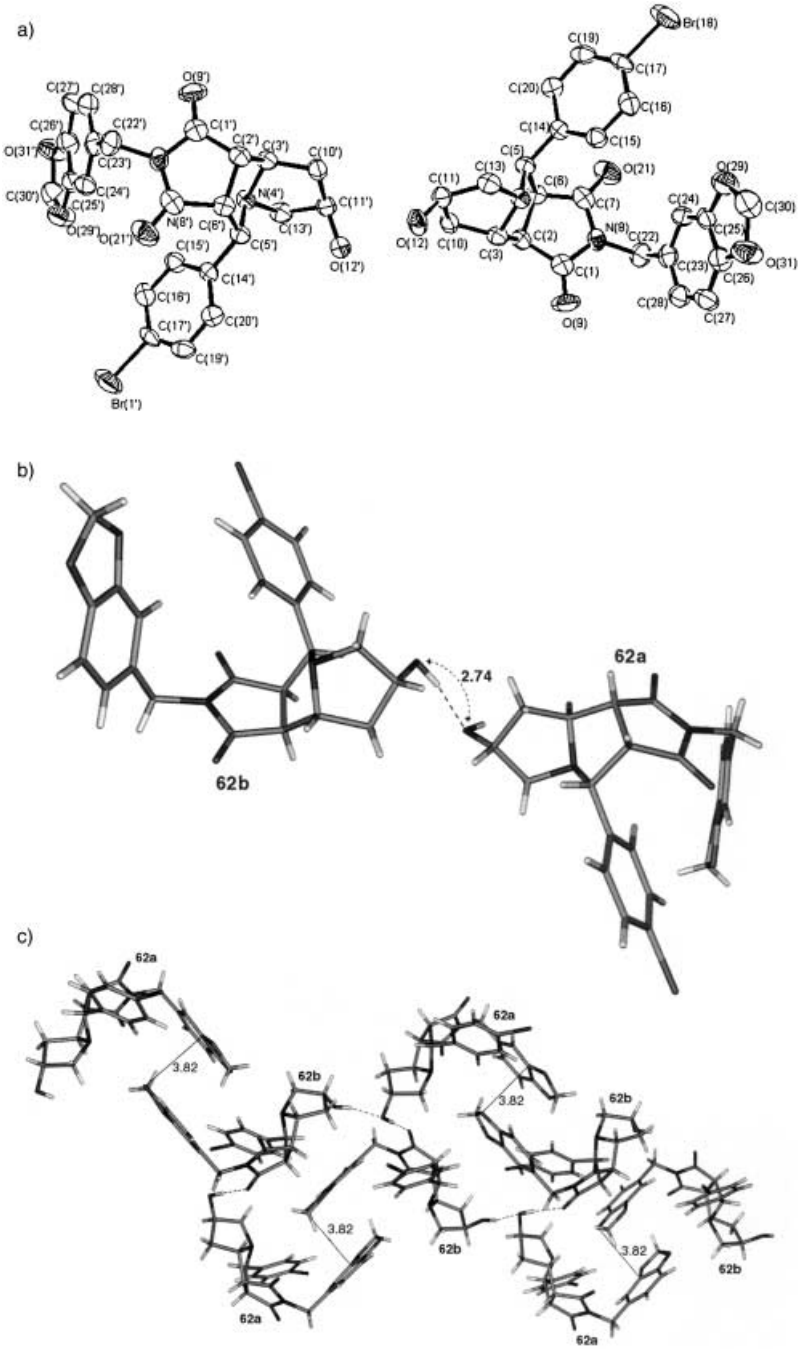


Fig. 9. a) *X-Ray crystal structure of hydroxy derivatives* **62a** *and* **62b**. Arbitrary numbering. Atomic displacement parameters obtained at 293 K are drawn at the 50% probability level. b) *H-Bonding between two diastereoisomers* **62a** *and* **62b** *in the crystal*. c) *View of the packing in the mixed crystal.* Distances in Å.

racemate formation by a pair of enantiomers, and we propose that the two diastereoisomers **62a** and **62b** can be viewed as *pseudoenantiomers*. Pseudoenantiomeric behavior is well-established for some members of the cinchona alkaloid family. Thus, quinine and quinidine (or cinchonine and cinchonidine) are pairs of diastereoisomers, but they usually behave like enantiomers when used as ligands in asymmetric catalysis or as components of chiral stationary phases [41][42].

The crystal lattice shows pairwise alignment of the two diastereoisomers with a short H-bond (O···O distance: 2.74 Å) between their OH groups (*Fig. 9,b*). H-Bonding between imide C=O and OH groups, as well as parallel-shifted π-π stacking, are additional intermolecular contacts seen in the crystal packing (*Fig. 9,c*). Conversion of these compounds to the desired tetrazole is now in progress.

3. Conclusions. – Consistent with literature reports, the D-pocket of the thrombin active site is capable of accommodating very large, lipophilic groups, providing high activity and selectivity (over trypsin; *Table 1*). Thus, the benzhydryl derivative (±)-**2** is the most selective member (K_i(trypsin)/K_i(thrombin) = 1200) of our class of non-peptidic thrombin inhibitors with a bicyclic or a tricyclic central scaffold, constructed by 1,3-dipolar cycloaddition of *in situ* prepared azomethine ylides to *N*-substituted maleimides. Also, the 'dipiperonyl' analog (±)-**4** (K_i = 9 nM, 760-fold selectivity) is the most potent inhibitor in this class prepared so far. In contrast to the findings within a series of peptidomimetic inhibitors reported by the *Merck* group (*Fig. 2*) [14], however, we did not observe a dramatic increase in binding upon changing the D-pocket substituent from a benzyl ((±)-**3**; K_i = 65 nM) to a benzhydryl group ((±)-**2**; K_i = 28 nM). Presumably, the rigid, phenylamidinium-substituted bi- and tricyclic central scaffolds do not allow the benzhydryl group to adopt the most favorable binding mode in the D-pocket. Additional, more in-depth exploration of the binding characteristics of the D-pocket is clearly warranted. Our new approach, which allows incorporation of the D-pocket substituent very late in the synthesis, should greatly facilitate such study.

Our first attempts to enhance binding potency and selectivity by directing a side chain of the inhibitor into the oxyanion hole for H-bonding to the backbone NH groups of the enzyme have not yet been very successful. The biological results (*Table 2*) do not provide evidence for additional noncovalent interactions being picked up at this site. Again, the high degree of preorganization and the rigidity of the central scaffold may not allow the new side chains to assume a position required to undergo the predicted interactions. However, the unexpectedly high residual activity of the large *N*-benzyloxyamide (±)-**59** (K_i = 570 nM) indicates that the catalytic site and its neighborhood, the S1′-pocket, are capable of accommodating quite large groups. This also leaves room for further exploration, which we will continue with the synthesis of tetrazole-substituted (±)-**61**.

Although we have experienced difficulties in successfully predicting and establishing new host-guest interactions in the thrombin active site, we continue to recognize structural information as a very useful piece of knowledge in guiding a medicinal-chemistry project.

This work was supported by *F. Hoffmann-La Roche AG*. We thank *David W. Banner* and *Allan D'Arcy* for protein X-ray crystallographic analyses and *Heidi Hoffmann Maiocchi*, *Pascale Blond*, and *Thomas Tschopp* for the measurement of enzyme inhibitor constants. We also thank *Holger Gohlke* for his contributions towards the design of some inhibitors described.

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: **5** [9][10], 4-toluenesulfinic acid [43], and (±)-**27** [10]. THF and Et_2O were freshly distilled from sodium benzophenone ketyl, CH_2Cl_2 from CaH_2. HCl Gas was dried with conc. H_2SO_4, NH_3 gas with KOH (s). Molecular sieves were activated at 10^{-2} Torr and 500°. Evaporation *in vacuo* was conducted at H_2O aspirator pressure. If not mentioned otherwise, all products were dried under high vacuum (10^{-2} Torr) before anal. characterization. Column chromatography (CC): SiO_2 *60* (40–63 μm) from *Fluka* or *Merck*, 0–0.4 bar pressure. TLC: SiO_2 *60* F_{245}, *Merck*, visualization by UV light at 245 nm. M.p.: *Büchi SMP 20* apparatus; uncorrected. IR Spectra [cm^{-1}]: *Perkin-Elmer 1600-FT* spectrometer. NMR spectra (^1H, ^{13}C, ^{19}F, NOE): *Varian Gemini-200*, *Varian Gemini-300*, and *Bruker AMX-500*, spectra were recorded at r.t. with solvent peak as reference. In some ^1H- and ^{13}C-NMR spectra ((±)-**2**, (±)-**4**, (±)-**16a**, (±)-**17**, (±)-**20b**, (±)-**21**, (±)-**23,** (±)-**30**, (±)-**38**, (±)-**39**, (±)-**42**, (±)-**43**, (±)-**49**, (±)-**50**, (±)-**60**, **62a**, **62b**), individual resonances overlap or are buried under the solvent peak. MS (*m*/*z* (%)): FAB: *VG-ZAB2-SEQ* (3-nitrobenzyl alcohol matrix); EI, DEI: *VG-TRIBRID* at 70 eV; MALDI: *IonSpec Ultima* (2,5-dihydroxybenzoic acid (DHB) matrix); 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*.

Determination of Inhibition Constants. The affinities of thrombin inhibitors were determined according to [44][45] (chromogenic substrate S-2238). An exhaustive protocol of the binding assay identical to the one used in this study is provided in [44].

General Procedure A for the 1,3-Dipolar Cycloaddition. A mixture of α-amino acid (1 mmol), 4-formylbenzonitrile, or 4-bromobenzaldehyde (1 mmol), and *N*-substituted maleimide (1 mmol) in MeCN (3 ml) was heated to 80° for 16–48 h. The solvent was evaporated *in vacuo*, and the residue was purified by CC (AcOEt/Et_3N 99:1 or hexane/AcOEt/Et_3N 59:40:1 or 33:66:1).

General Procedure B for the Eschweiler-Clarke *Methylation*. A mixture of cycloadduct (9 mmol), 85% aq. HCO_2O soln. (100 mmol), and 35% aq. HCHO soln. (36 mmol) was heated to 100° for 6–20 h. After cooling, sat. aq. $NaHCO_3$ soln. was added, and the mixture was extracted with CH_2Cl_2. The org. phase was dried (Na_2SO_4) and evaporated, and the residue was purified by CC (hexane/AcOEt/Et_3N 74:25:1 or 49.5:49.5:1).

General Procedure C for the Preparation of Amidinium Salts by the Pinner *Reaction*. Dry HCl 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). 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 was dissolved in EtOH, and the amidinium salt was slowly precipitated with Et_2O.

General Procedure D for the Conversion of an Aryl Bromide to the Corresponding Aryl Nitrile. A suspension of the aryl bromide (1 mmol) and CuCN (5 mmol) in DMF (5 ml, purged with Ar) was heated to reflux under Ar for 12–48 h. The solvent was partially removed, and CH_2Cl_2 and conc. aq. NH_4OH soln. were added. The mixture was stirred at r.t. for 1 h, the blue aq. phase removed, and the org. phase washed with conc. aq. NH_4OH soln. and H_2O. The combined aq. phases were extracted with CH_2Cl_2. The combined org. phases were dried (Na_2SO_4), the solvent removed *in vacuo*, and the resulting residue purified by CC (hexane/AcOEt/Et_3N 49.5:49.5:1 or 66:33:1 or CH_2Cl_2/Et_3N 99:1).

*(3a*SR,*4*RS,*8a*SR,*8b*RS*)- and (3a*SR,*4*SR,*8a*RS,*8b*RS*)-4-(4-Bromophenyl)-2,3,3a,4,5,6,7,8,8a,8b-decahydro-2-(phenylmethyl)-1*H*-pyrrolo[3,4-*a*]pyrrolizine-1,3-dione* ((±)-**8a** and (±)**8b**, resp.). *General Procedure A*, starting from **5**, **6**, and **7**, gave *endo*- and *exo*-adducts ((±)-**8a** and (±)-**8b**, resp.) adducts after CC (CH_2Cl_2/Et_3N 99:1).

Data of (±)-**8a**: 42%. Colorless solid. M.p. 172–175°. IR ($CHCl_3$): 3025, 3013, 2971, 1775, 1705, 1399, 1346, 1072, 1011. ^1H-NMR (300 MHz, $CDCl_3$): 1.61–1.82 (*m*, 2 H); 1.96–2.17 (*m*, 2 H); 2.58–2.67 (*m*, 1 H); 2.79–2.89 (*m*, 1 H); 3.27 (*d*, *J* = 8.1, 1 H); 3.46 (*dd*, *J* = 8.1, 8.6, 1 H); 3.77 (*dd*, *J* = 7.3, 9.8, 1 H); 4.01 (*d*, *J* = 8.6, 1 H); 4.53 (*s*, 1 H); 4.54 (*s*, 1 H); 7.07, 7.34 (*AA′BB′*, *J* = 8.4, 4 H); 7.26–7.30 (*m*, 5 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 23.4; 29.6; 42.6; 49.2; 50.6; 50.8; 68.0; 68.4; 121.8; 128.1; 128.8; 129.2; 130.0; 131.5; 136.0; 137.3; 175.4; 178.2. FAB-MS: 849.1 (2, M_2H^+), 425.0 (100, MH^+), 237.0 (17), 90.8 (8, $PhCH_2^+$). Anal. calc. for $C_{22}H_{21}BrN_2O_2$ (425.33): C 62.13, H 4.98, N 6.59, Br 18,79; found: C 62.00, H 5.05, N 6.59, Br 18.73.

Data of (±)-**8b**: 40%. Colorless crystals. M.p. 122–124° (MeOH). IR ($CHCl_3$): 2969, 1773, 1704, 1487, 1434, 1395, 1344, 1072, 1011. ^1H-NMR (300 MHz, $CDCl_3$): 1.50–1.60 (*m*, 1 H); 1.63–1.74 (*m*, 2 H); 1.88–1.97 (*m*, 1 H);

2.37–2.46 (*m*, 1 H); 2.88–2.96 (*m*, 1 H); 3.29 (*dd*, *J* = 5.7, 9.1, 1 H); 3.52 (*t*, *J* = 9.1, 1 H); 3.87 (*m*, 1 H); 4.05 (*d*, *J* = 5.7, 1 H); 4.65 (*s*, 2 H); 7.26–7.49 (*m*, 9 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 24.4; 26.3; 42.7; 48.0; 52.1; 55.6; 66.5; 69.2; 121.5; 128.4; 128.9; 128.9; 129.3; 132.0; 135.7; 141.5; 176.9; 178.0. FAB-MS: 849.0 (10, M_2H^+), 425.1 (100, MH^+), 237.0 (22), 90.8 (31, $PhCH_2^+$). Anal. calc. for $C_{22}H_{21}BrN_2O_2$ (425.33): C 62.13, H 4.98, N 6.59, Br 18.79; found: C 62.19, H 5.13, N 6.58, 18.65.

*(1*RS,*3a*SR,*4*RS,*8a*SR,*8b*RS*)-4-(4-Bromophenyl)-2,3,3a,4,5,6,7,8,8a,8b-decahydro-1-[(4-methylphenyl)sulfonyl]-2-(phenylmethyl)-1*H*-pyrrolo[3,4-*a*]pyrrolizin-3-one* ((±)-**10**). A 1M soln. of Li[Et_3BH] in THF (240 ml, 240 mmol) was added to (±)-**8a** (59.54 g, 140 mmol) in dry THF (500 ml) at −78° under Ar. After 30 min, the mixture was warmed to r.t., and sat. aq. $NaHCO_3$ soln. was added. Extraction with CH_2Cl_2, drying of the org. phase ($MgSO_4$), and evaporation *in vacuo* gave crude hydroxy lactam (±)-**9**. A CH_2Cl_2 soln. containing (±)-**9**, 4-toluenesulfinic acid (65.6 g, 420 mmol), and suspended H_2O-free, powdered $CaCl_2$ (46.6 g, 420 mmol) was stirred at r.t. for 5 d. Sat. aq. $NaHCO_3$ soln. was added, the extracted org. phase was washed several times with sat. aq. $NaHCO_3$ soln. and dried (Na_2SO_4), and the solvent was removed *in vacuo*. The crude sulfone (±)-**10** was purified by dissolution in a small amount of boiling AcOEt and subsequent precipitation. Redissolving in CH_2Cl_2 and evaporation of the solvent *in vacuo* removed traces of AcOEt to yield (±)-**10** (58.6 g, 74%). Colorless solid. M.p. 186–188°. IR ($CHCl_3$): 3018, 1712, 1487, 1400, 1318, 1303, 1135, 1082. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.53–1.71 (*m*, 2 H); 1.85–1.92 (*m*, 1 H); 1.94–2.05 (*m*, 1 H); 2.43–2.58 (*m*, 2 H); 2.48 (*s*, 3 H); 2.82–2.91 (*m*, 1 H); 2.96–2.99 (*m*, 1 H); 3.03–3.09 (*m*, 1 H); 3.91 (*d*, *J* = 6.5, 1 H); 4.08, 5.14 (*AB*, *J* = 14.8, 2 H); 4.30 (*s*, 1 H); 7.16–7.24 (*m*, 4 H); 7.29–7.43 (*m*, 7 H); 7.72 (*d*, *J* = 8.1, 2 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 21.9; 24.5; 31.8; 43.1; 45.2; 51.1; 51.9; 69.7; 71.3; 81.1; 121.1; 127.9; 128.5; 128.8; 129.4; 129.7; 130.5; 130.9; 132.3; 135.2; 137.2; 146.2; 172.6. DEI-MS: 565.1 (0.2, MH^+), 409.0 (18), 304.0 (25), 212.1 (52), 156.0 (20), 139.0 (40), 91.1 (100, $PhCH_2^+$). Anal. calc. for $C_{29}H_{29}BrN_2O_3S$ (565.53): C 61.59, H 5.17, N 4.95, S 5.67, Br 14.13; found: C 61.40, H 5.31, N 4.99, S 5.77, Br 14.12.

*(1*RS,*3a*SR,*4*RS,*8a*SR,*8b*RS*)-4-(4-Bromophenyl)-2,3,3a,4,5,6,7,8,8a,8b-decahydro-1-(1-methylethyl)-2-(phenylmethyl)-1*H*-pyrrolo[3,4-*a*]pyrrolizin-3-one* ((±)-**11**). (i-Pr)MgCl (89 ml of 2M soln. in THF/Et_2O, 188 mmol) was added to a soln. of $ZnCl_2$ (103 ml of 1M soln. in Et_2O, 103 mmol) in dry CH_2Cl_2 (400 ml) under Ar. After 30 min, a soln. of (±)-**10** (53.29 g, 94 mmol) in dry CH_2Cl_2 (400 ml) was slowly added while cooling with an ice bath. The mixture was stirred at r.t. for 23 h, then 1N HCl was added. After 15 min, the mixture was neutralized with sat. aq. $NaHCO_3$ soln. and extracted with CH_2Cl_2. The org. phase was dried (Na_2SO_4), the solvent was removed, and the product was purified by CC (hexane/AcOEt/Et_3N 66:33:1) to provide (±)-**11** (33.19 g, 78%). Colorless crystals. M.p. 135–138° (AcOEt). IR ($CHCl_3$): 3007, 2964, 1675, 1486, 1441, 1071, 835. ^{1}H-NMR (300 MHz, $CDCl_3$): 0.71 (*d*, *J* = 6.8, 3 H); 0.90 (*d*, *J* = 7.2, 3 H); 1.51–1.67 (*m*, 1 H); 1.68–1.78 (*m*, 1 H); 1.89–2.01 (*m*, 2 H); 2.03–2.14 (*m*, 1 H); 2.48 (*dt*, *J* = 2.8, 8.6, 1 H); 2.58–2.66 (*m*, 1 H); 2.89–2.98 (*m*, 1 H); 3.23–3.25 (*m*, 2 H); 3.31 (*dd*, *J* = 7.8, 8.6, 1 H); 3.79, 4.90 (*AB*, *J* = 15.3, 2 H); 4.09 (*d*, *J* = 7.8, 1 H); 7.15–7.18 (*m*, 2 H); 7.24–7.35 (*m*, 3 H); 7.31, 7.44 (*AA′BB′*, *J* = 8.4, 4 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 14.7; 18.5; 24.6; 28.0; 31.4; 41.5; 44.0; 52.5; 52.8; 67.3; 70.2; 73.2; 120.8; 127.3; 128.1; 128.5; 129.9; 130.9; 136.6; 138.8; 172.5. FAB-MS: 905.4 (2, M_2H^+),453.2 (100, MH^+), 297.2 (5), 237.1 (9), 90.8 (9, $PhCH_2^+$). Anal. calc. for $C_{25}H_{29}BrN_2O$ (453.43): C 66.22, H 6.45, N 6.18, Br 17.62; found: C 66.05, H 6.44, N 6.17, Br 17.63.

*4-[(1*RS,*3a*SR,*4*RS,*8a*SR,*8b*RS*)-1-(1-Methylethyl)-2,3,3a,4,5,6,7,8,8a,8b-decahydro-3-oxo-2-(phenylmethyl)-1*H*-pyrrolo[3,4-*a*]pyrrolizin-4-yl]benzonitrile* ((±)-**12**). *General Procedure D*, starting from (±)-**11**, afforded nitrile (±)-**12** in 66% yield. Colorless crystals. M.p. 143–146° (AcOEt). IR ($CHCl_3$): 3010, 2966, 2230, 1677, 1440, 1241, 844. ^{1}H-NMR (300 MHz, $CDCl_3$): 0.72 (*d*, *J* = 6.7, 3 H); 0.91 (*d*, *J* = 7.0, 3 H); 1.54–1.64 (*m*, 1 H); 1.70–1.80 (*m*, 1 H); 1.89–2.03 (*m*, 2 H); 2.09 (*dqq*, *J* = 3.4, 6.7, 7.0, 1 H); 2.49 (*dt*, *J* = 2.8, 8.4, 1 H); 2.54–2.63 (*m*, 1 H); 2.91–3.00 (*m*, 1 H); 3.22–3.29 (*m*, 2 H); 3.35 (*dd*, *J* = 7.8, 8.4, 1 H); 3.79, 4.88 (*AB*, *J* = 14.9, 2 H); 4.16 (*d*, *J* = 7.8, 1 H); 7.16–7.18 (*m*, 2 H); 7.25–7.36 (*m*, 3 H); 7.40, 7.60 (*AA′BB′*, *J* = 8.4, 4 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 14.9; 18.5; 24.7; 28.1; 31.5; 41.6; 44.0; 52.7; 53.1; 67.4; 70.7; 73.5; 110.8; 119.6; 127.6; 128.2; 128.8; 129.1; 131.8; 136.8; 146.1; 172.5. EI-MS: 799.2 (4, M_2H^+), 400.3 (100, MH^+), 184.2 (46), 90.8 (38, $PhCH_2^+$). Anal. calc. for $C_{26}H_{29}N_3O$ (399.54): C 78.16, H 7.32, N 10.52; found: C 78.12, H 7.41, N 10.46.

*4-[(1*RS,*3a*SR,*4*RS,*8a*SR,*8b*RS*)-1-(1-Methylethyl)-2,3,3a,4,5,6,7,8,8a,8b-decahydro-3-oxo-2-(phenylmethyl)-1*H*-pyrrolo[3,4-*a*]pyrrolizin-4-yl]benzamidine Hydrochloride* ((±-**3**). *General Procedure C*, starting from (±)-**12**, afforded (±)-**3** in 86% yield. Orange solid. M.p. 190–195°. IR ($CHCl_3$): 3281, 2967, 1672, 1614, 1493, 1448. ^{1}H-NMR (300 MHz, $(CD_3)_2SO$): 0.66 (*d*, *J* = 6.5, 3 H); 0.88 (*d*, *J* = 6.9, 3 H); 1.55–1.70 (*m*, 2 H); 1.86–1.97 (*m*, 2 H); 2.06–2.11 (*m*, 1 H); 2.42–2.51 (*m*, 1 H); 2.55 (*d*, *J* = 8.1, 1 H); 2.79–2.85 (*m*, 1 H); 3.16–3.19 (*m*, 2 H); 3.35–3.41 (*m*, 1 H); 3.87, 4.63 (*AB*, *J* = 14.9, 2 H); 4.20 (*d*, *J* = 7.2, 1 H); 7.20–7.39 (*m*, 5 H); 7.57, 7.78 (*AA′BB′*, *J* = 8.4, 4 H); 9.19 (br. *s*, 2 H), 9.37 (br. *s*, 2 H). ^{13}C-NMR (125 MHz, $(CD_3)_2SO$): 14.5; 18.0; 24.2; 27.4; 30.6; 40.6; 42.8; 52.0; 52.2; 66.7; 69.6; 73.0; 125.5; 127.0; 127.1; 127.6; 128.4; 128.6; 136.9; 147.3; 165.4; 171.6. DEI-

MS: 416.3 (30, M^+), 399.3 (17), 201.2 (49), 184.2 (100), 91.1 (23, $PhCH_2^+$). HR-EI-MS: 416.2588 (M^+, $C_{26}H_{32}N_4O$; calc. 416.2576).

*1-(Diphenylmethyl)-2,5-dihydro-1*H*-pyrrole-2,5-dione* (N-*Benzhydrylmaleimide*) (**13**). A soln. of benzhydrylamine (35.5 ml, 36.7 g, 200 mmol) in abs. Et_2O (50 ml) was slowly added to a vigorously stirred, ice-cold soln. of maleic anhydride (19.6 g, 200 mmol) in abs. Et_2O (300 ml). The insoluble maleamic acid was filtered off, repeatedly washed with Et_2O, and dried. It was then dissolved in Ac_2O (91.4 ml, 98.69 g, 965 mmol) together with AcONa (13.34 g, 193 mmol) and stirred for 1 h at 100°. After cooling to r.t., H_2O (300 ml) was added, and the mixture was stirred for 12 h. The resulting precipitate was filtered off and purified by CC (CH_2Cl_2) to give **13** (22.37, 42%). Colorless crystals. M.p. 139–141° (MeOH) ([46]: 147–151°). ^{1}H-NMR (300 MHz, $CDCl_3$): 6.52 (*s*, 1 H); 6.71 (*s*, 2 H); 7.27–7.38 (*m*, 10 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 57.8; 128.0; 128.7; 128.8; 134.5; 138.4; 170.7.

*4-[(3a*SR,*4*SR,*8a*RS,*8b*RS*)-, (3a*SR,*4*SR,*8a*SR,*8b*RS*)-, (3a*SR,*4*RS,*8a*RS,*8b*RS*)-, and (3a*SR,*4*RS,*8a*RS,*8b*RS*)-2-(Diphenylmethyl)-2,3,3a,4,5,6,7,8,8a,8b-decahydro-1,3-dioxo-1*H*-pyrrolo[3,4-*a*]pyrrolizin-4-yl]benzonitrile* ((±)-**15a**–**15d**, resp.). *General Procedure A*, starting from **6**, **13**, and **14** in DMF as the solvent, gave *exo,trans*-, *exo,cis*, *endo,cis*, and *endo,trans* adducts, (±)-**15a**–(±**15d**, resp., after CC (hexane/AcOEt/Et_3N 79:20:1, then CH_2Cl_2/Et_3N 99:1, then CH_2Cl_2/hexane/Et_3N 79:20:1).

Data of (±)-**15a**: 45%. Colorless oil. ^{1}H-NMR (200 MHz, $CDCl_3$): 1.52–1.76 (*m*, 3 H); 1.87–2.00 (*m*, 1 H); 2.36–2.49 (*m*, 1 H); 2.92–3.04 (*m*, 1 H); 3.34 (*dd*, *J* = 9.1, 5.4, 1 H); 3.57 (*dd*, *J* = 9.1, 8.7, 1 H); 3.92 (*m*, 1 H); 4.22 (*d*, *J* = 5.4, 1 H); 6.57 (*s*, 1 H); 7.29–7.38 (*m*, 10 H); 7.64 (*s*, 4 H). FAB-MS: 448.2 (100, MH^+), 167.1 (71, $PhCH_2^+$).

Data of (±)-**15b**: 3.7%. Colorless oil. ^{1}H-NMR (200 MHz, $CDCl_3$): 1.94–1.98 (*m*, 3 H); 2.17–2.31 (*m*, 2 H); 2.49–2.59 (*m*, 1 H); 3.32 (*dd*, *J* = 9.5, 7.1, 1 H); 3.54 (*m*, 1 H); 3.77 (*dd*, *J* = 9.5, 8.3, 1 H); 4.29 (*d*, *J* = 8.3, 1 H); 6.52 (*s*, 1 H); 7.32–7.33 (*m*, 10 H); 7.66, 7.74 (*AA′BB′*, *J* = 8.3, 4 H). FAB-MS: 448.2 (100, MH^+), 167.1 (24, Ph_2CH^+), 149.0 (55).

Data of (±)-**15c**: 4.2%. Colorless crystals. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.83–2.00 (*m*, 3 H); 2.04–2.14 (*m*, 1 H); 2.17–2.28 (*m*, 1 H); 2.82 (*dt*, *J* = 8.4, 2.2, 1 H); 2.90–2.97 (*m*, 1 H); 3.14–3.18 (*m*, 1 H); 3.65–3.66 (*m*, 2 H); 6.43 (*s*, 1 H); 7.13, 7.42 (*AA′BB′*, *J* = 8.4, 4 H); 7.26–7.36 (*m*, 10 H). FAB-MS: 448.2 (83, MH^+), 391.2 (100), 167.1 (43, Ph_2CH^+), 149.0 (55). X-Ray: see *Fig. 4*.

Data of (±)-**15d**: 11%. Colorless oil. IR ($CHCl_3$): 3056, 2944, 2226, 1774, 1708, 1605, 1497, 1451, 1360, 1113, 1077. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.61–1.88 (*m*, 2 H); 1.98–2.20 (*m*, 2 H); 2.59–2.67 (*m*, 1 H); 2.89–2.98 (*m*, 1 H); 3.33 (*d*, *J* = 8.2, 1 H); 3.55 (*dd*, *J* = 8.6, 8.2, 1 H); 3.84 (*dd*, *J* = 9.7, 7.5, 1 H); 4.13 (*d*, *J* = 8.6, 1 H); 6.41 (*s*, 1 H); 7.21–7.34 (*m*, 12 H); 7.45 (*d*, *J* = 8.4, 2 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 23.5; 29.7; 49.0; 50.3; 51.0; 58.7; 68.4; 68.8; 111.6; 119.2; 128.0; 128.1; 128.5; 128.6; 128.6; 129.1; 129.3; 132.1; 137.5; 137.7; 143.8; 175.0; 177.9. FAB-MS: 448.2 (100, MH^+), 167.1 (53, Ph_2CH^+). HR-FAB-MS: 448.2032 (MH^+, $C_{29}H_{25}N_3O_2$; calc. 448.2025).

An alternative synthesis of (±)-**15d** according to *General Procedure D*, starting from (±)-**16d**, afforded nitrile (±)-**15d** in 45% yield.

*(3a*SR,*4*SR,*8a*RS,*8b*RS*)- and (3a*SR,*4*RS,*8a*RS,*8b*RS*)-4-(4-Bromophenyl)-2,3,3a,4,5,6,7,8,8a,8b-decahydro-2-(diphenylmethyl)-1*H*-pyrrolo[3,4-*a*]pyrrolizine-1,3-dione* ((±)-**16a** and (±)-**16d**, resp.). *General Procedure A*, starting from **6**, **7**, and **13**, gave *exo,trans*- and *endo,trans* adducts, (±)-**16a** and (±)-**16d**, resp., after CC (CH_2Cl_2/Et_3N 99:1).

Data of (±)-**16a**: 55%. Oil. IR ($CHCl_3$): 2968, 1708, 1487, 1384, 1359, 1172, 1074, 1011. ^{1}H-NMR (200 MHz, $CDCl_3$): 1.46–1.74 (*m*, 3 H); 1.85–1.97 (*m*, 1 H); 2.37–2.50 (*m*, 1 H); 2.89–3.04 (*m*, 1 H); 3.35 (*dd*, *J* = 9.1, 5.4, 1 H); 3.57 (*dd*, *J* = 9.6, 8.7, 1 H); 3.85–3.97 (*m*, 1 H); 4.12 (*d*, *J* = 5.0, 1 H); 6.56 (*s*, 1 H); 7.28–7.38 (*m*, 12 H); 7.45–7.50 (*m*, 2 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 24.5; 26.2; 47.8; 52.2; 55.5; 58.8; 66.8; 69.4; 121.5; 128.2; 128.6; 128.7; 128.7; 128.9; 129.0; 131.9; 137.5; 141.5; 176.8; 177.9. FAB-MS: 501.1 (100, MH^+), 167.1 (74, Ph_2CH^+). HR-FAB-MS: 501.1185 (MH^+, $C_{28}H_{26}N_2O_2$; calc. 501.1178).

Data of (±)-**16d**: 20%. Colorless crystals. M.p. 171–173° (MeOH). IR (KBr): 2958, 1705, 1486, 1384, 1367, 1172, 1078, 1009, 698. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.64–1.83 (*m*, 2 H); 1.99–2.14 (*m*, 2 H); 2.62–2.69 (*m*, 1 H); 2.86–2.95 (*m*, 1 H); 3.29 (*d*, *J* = 8.1, 1 H); 3.49 (*t*, *J* = 8.4, 1 H); 3.80 (*m*, 1 H); 4.04 (*d*, *J* = 8.7, 1 H); 6.42 (*s*, 1 H); 7.11 (*d*, *J* = 8.1, 2 H); 7.26–7.33 (*m*, 12 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 23.4; 29.6; 49.0; 50.3; 50.9; 58.6; 68.3; 68.6; 121.7; 127.8; 128.0; 128.5; 128.5; 128.7; 129.3; 130.0; 131.5; 137.1; 137.7; 137.8; 175.2; 178.2. FAB-MS: 1001.0 (3, M_2H^+), 501.1 (100, MH^+), 167.1 (56, Ph_2CH^+). Anal. calc. for $C_{28}H_{25}BrN_2O_2$ (501.43): C 67.07, H 5.03, N 5.59, Br 15.94; found: C 67.03, H 5.11, N 5.60, Br 16.05.

*4-[(3a*SR,*4*RS,*8a*SR,*8b*RS*)-2-(Diphenylmethyl)-2,3,3a,4,5,6,7,8,8a,8b-decohydro-1,3-dioxo-1*H*-pyrrolo[3,4-*a*]pyrrolizin-4-yl]benzamidine Hydrochloride* ((±)-**17**). *General Procedure C*, starting from (±)-**15d**, afforded amidinium salt (±)-**17** after CC (CH_2Cl_2/MeOH 95:5, 90:10) in 35% yield. Yellowish solid. Dec.

$>165°$. IR ($CHCl_3$): 1708, 1676, 1588, 1366, 909. ^{1}H-NMR (300 MHz, $(CD_3)_2SO$): 1.69–1.72 (*m*, 2 H); 1.98 (*m*, 2 H); 2.66–2.84 (*m*, 2 H); 3.49–3.61 (*m*, 2 H); 3.80 (*t*, *J* = 8.4, 1 H); 4.25 (*d*, *J* = 8.7, 1 H); 6.28 (*s*, 1 H); 7.13–7.19 (*m*, 4 H); 7.29–7.39 (*m*, 6 H); 7.43, 7.67 (*AA′BB′*, *J* = 8.4, 4 H); 8.99 (*s*, 4 H). ^{13}C-NMR (125 MHz, $(CD_3)SO$): 23.0; 29.0; 48.3; 50.0; 50.4; 57.4; 67.5; 67.7; 126.6; 127.4; 127.5; 128.1; 128.1; 128.2; 128.4; 128.6; 137.6; 137.6; 145.3; 165.1; 175.2; 177.0. FAB-MS: 465.2 (100, MH^+), 338.3 (38). HR-FAB-MS: 465.2285 (MH^+, $C_{29}H_{29}N_4O_2$; calc. 465.2291).

*4-[(1*RS*,3a*RS*,6a*SR*)-5-(Diphenylmethyl)-1,2,3,3a,4,5,6,6a-octahydro-3,3-dimethyl-4,6-dioxopyrrolo[3,4-c]pyrrol-1-yl]benzonitrile* ((±)-**19a**). *General Procedure A*, starting from **13**, **14**, and **18** in DMF as the solvent, yielded 35% of (±)-**19a** after CC (hexane/Et_2O/Et_3N 40 : 59 : 1). Colorless crystals. M.p. 170–172° (MeOH). IR ($CHCl_3$): 3320, 2966, 2226, 1698, 1382, 1358, 871, 612. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.39 (*s*, 3 H); 1.46 (*s*, 3 H); 2.92 (*d*, *J* = 7.8, 1 H); 3.45 (*dd*, *J* = 7.8, 8.1, 1 H); 4.77 (*d*, *J* = 8.1, 1 H); 6.40 (*s*, 1 H); 7.23–7.36 (*m*, 12 H); 7.44–7.47 (*m*, 2 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 26.5; 28.4; 49.9; 53.4; 58.6; 60.6; 61.2; 111.7; 119.1; 128.0 (2 ×); 128.4; 128.5; 128.6; 128.7; 129.2; 132.1; 137.6; 137.7; 144.1; 174.9; 176.0. FAB-MS: 871.6 (13, M_2H^+), 436.3 (100, MH^+), 420.2 (26). Anal. calc. for $C_{28}H_{25}N_3O_2$ (435.53): C 77.22, H 5.79, N 9.65; found: C 77.21, H 5.68, N 9.60. X-Ray: see *Fig. 5*. A small amount (13%) of the (1*SR*,3a*RS*,6a*SR*)-cycloadduct (±)-**19b** was also formed.

*(3a*RS*,6*RS*,6a*SR*)- and (3a*RS*,6*SR*,6a*SR*)-6-(4-Bromophenyl)-2-(diphenylmethyl)-1,2,3,3a,4,5,6,6a-octahydro-4,4-dimethylpyrrolo[3,4-c]pyrrole-1,3-dione* ((±)-**20a** and (±)-**20b**, resp.). *General Procedure A*, starting from **7**, **13**, and **18**, was applied in PhCl as the solvent. Addition of MeOH to the crude isolated mixture of diastereoisomers led to crystallization of the *endo*-isomer (±)-**20a**, which was purified by CC (Et_2O/Et_3N 99 : 1). The remaining *exo*-isomer (±)-**20b** was purified by CC (hexane/Et_2O/Et_3N 66 : 33 : 1).

Data of (±)-**20a**: 53%. Colorless crystals. M.p. 191–193° (MeOH). IR ($CHCl_3$): 2966, 1770, 1699, 1486, 1364, 1195, 1008, 699. ^{1}H-NMR (200 MHz, $CDCl_3$): 1.38 (*s*, 3 H); 1.45 (*s*, 3 H); 2.89 (*d*, *J* = 7.9, 1 H); 3.41 (*dd*, *J* = 7.9, 7.9, 1 H); 4.71 (*d*, *J* = 7.9, 1 H); 6.43 (*s*, 1 H); 7.11 (*d*, *J* = 8.3, 2 H); 7.26–7.34 (*m*, 12 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 26.4; 28.7; 49.9; 53.5; 58.4; 60.3; 61.0; 121.5; 127.6; 127.7; 128.2; 128.3; 128.5; 129.0; 129.0; 131.2; 137.1; 137.5; 137.6; 174.8; 175.9. FAB-MS: 977.3 (2, M_2H^+), 489.2 (100, MH^+), 391.3 (16), 167.1 (54, Ph_2CH^+). Anal. calc. for $C_{27}H_{25}BrN_2O_2$ (489.41): C 66.26, H 5.15, N 5.72, Br 16.33; found: C 66.15, H 5.15, N 5.69, Br 16.42.

Data of (±)-**21b**: 12%. Colorless foam. M.p. 70–80° (MeOH). IR ($CHCl_3$): 2965, 1771, 1704, 1488, 1355, 1170, 698. ^{1}H-NMR (200 MHz, $CDCl_3$): 1.03 (*s*, 3 H); 1.46 (*s*, 3 H); 3.16 (*d*, *J* = 9.6, 1 H); 3.33 (*dd*, *J* = 9.5, 6.6, 1 H); 4.51 (*d*, *J* = 6.6, 1 H); 6.55 (*s*, 1 H); 7.33–7.46 (*m*, 14 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 23.0; 30.5; 54.8; 55.7; 58.6; 61.5; 62.2; 121.3; 127.8; 127.9; 128.3; 128.3; 128.4; 128.5; 128.8; 131.6; 137.4; 141.0; 175.8; 177.4. FAB-MS: 489.1 (100, MH^+), 338.3 (40), 289.1 (51). Anal. calc. for $C_{27}H_{25}BrN_2O_2$ (489.41): C 66.26, H 5.15, N 5.72, Br 16.33; found: C 66.25, H 5.24, N 5.72, Br 16.23.

*4-[(1*RS*,3a*RS*,6a*SR*)-5-(Diphenylmethyl)-1,2,3,3a,4,5,6,6a-octahydro-2,3,3-trimethyl-4,6-dioxopyrrolo[3,4-c]pyrrol-1-yl]benzonitrile* ((±)-**21**). *General Procedure B*, starting from (±)-**19a**, afforded tertiary amine (±)-**21** in 71% yield. Colorless crystals. M.p. 219–222° (MeOH/Et_2O). IR (KBr): 2974, 2225, 1768, 1701, 1364, 1191, 1172, 837, 700. ^{1}H-NMR (200 MHz, $CDCl_3$): 1.12 (*s*, 3 H); 1.48 (*s*, 3 H); 2.00 (*s*, 3 H); 2.94 (*d*, *J* = 8.3, 1 H); 3.43–3.48 (*m*, 1 H); 4.00 (*d*, *J* = 9.1, 1 H); 6.36 (*s*, 1 H); 7.11–7.36 (*m*, 14 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 18.9; 24.4; 32.2; 48.3; 53.8; 58.6; 63.4; 68.8; 111.7; 119.1; 128.0; 128.1; 128.5; 128.7; 129.1; 129.5; 132.3; 137.6; 137.9; 143.6; 175.2; 176.1. DEI-MS: 449.2 (0.4, M^+),434.2 (40), 167.1 (100, Ph_2CH^+). Anal. calc. for $C_{29}H_{27}N_3O_2$ (449.56): C 77.48, H 6.05, N 9.35; found: C 77.43, H 6.02, N 9.29.

*(3a*RS*,6*RS*,6a*SR*)-6-(4-Bromophenyl)-2-(diphenylmethyl)-1,2,3,3a,4,5,6,6a-octahydro-4,4,5-trimethylpyrrolo[3,4-c]pyrrol-1,3-dione* ((±)-**22**). *General Procedure B*, starting from (±)-**20a**, afforded tertiary amine (±)-**22** in 87% yield. Colorless crystals. M.p. 227–231° (AcOEt). IR (KBr): 2969, 1692, 1602, 1484, 1365, 1190, 1006, 699. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.10 (*s*, 3 H); 1.45 (*s*, 3 H); 1.98 (*s*, 3 H); 2.89 (*d*, *J* = 8.1, 1 H); 3.38 (*dd*, *J* = 9.0, 8.1, 1 H); 3.91 (*d*, *J* = 9.0, 1 H); 6.38 (*s*, 1 H); 6.92 (*d*, *J* = 7.5, 2 H); 7.20–7.36 (*m*, 12 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 18.8; 24.5; 32.2; 48.3; 53.8; 58.5; 63.1; 68.6; 121.7; 127.9; 128.0; 128.5; 128.6; 128.7; 129.5; 130.0; 131.6; 136.9; 137.7; 138.0; 175.4; 176.3. EI-MS: 502.2 (1, M^+), 487.1 (74), 167.2 (100, Ph_2CH^+). Anal. calc. for $C_{28}H_{27}BrN_2O_2$ (503.44): C 66.80, H 5.41, N 5.56, Br 15.87; found: C 66.60, H 5.40, N 5.51, Br 15.99.

*4-[(1*RS*,3a*RS*,6a*SR*)-5-(Diphenylmethyl)-1,2,3,3a,4,5,6,6a-octahydro-2,3,3-trimethyl-4,6-dioxopyrrolo[3,4-c]pyrrol-1-yl]benzamidine Hydrochloride* ((±)-**23**). *General Procedure C*, starting from (±)-**21**, afforded amidinium salt (±)-**23** in 76% yield. Yellowish solid. M.p. 200–202°. IR (KBr): 3059, 1705, 1491, 1359, 1194, 843, 700, 613. ^{1}H-NMR (200 MHz, $(CD_3)_2SO$): 1.09 (*s*, 3 H); 1.29 (*s*, 3 H); 1.89 (*s*, 3 H); 3.16 (*d*, *J* = 7.9, 1 H); 3.63–3.71 (*m*, 1 H); 4.13 (*d*, *J* = 8.7, 1 H); 6.26 (*s*, 1 H); 7.17–7.39 (*m*, 12 H); 7.64 (*d*, *J* = 7.9, 2 H); 9.20 (*s*, 2 H); 9.34 (*s*, 2 H). ^{13}C-NMR (75 MHz, $(CD_3)_2SO$): 18.6; 24.2; 32.1; 48.0; 53.2; 56.0; 62.5; 67.8; 126.5; 127.5; 127.5; 128.1;

128.1; 128.2; 128.5; 137.6; 137.7; 144.9; 165.2; 175.1; 179.9. FAB-MS: 933.5 (3, M_2H^+), 467.3 (100, MH^+). HR-FAB-MS: 467.2453 (MH^+, $C_{29}H_{31}N_4O_2$; calc. 467.2447).

*(3*RS*,3a*RS*,6*RS*,6a*SR*)-6-(4-Bromophenyl)-2-(diphenylmethyl)-1,2,3,3a,4,5,6,6a-octahydro-3-hydroxy-4,4,5-trimethylpyrrolo[3,4-*c*]pyrrol-1-one* ((±)-**25**) *and (3a*SR*,4*RS*,6a*RS*)-4-(4-Bromophenyl)-2-(diphenylmethyl)-1,2,3,3a,4,5,6,6a-octahydro-3-hydroxy-5,6,6-trimethylpyrrolo[3,4-*c*]pyrrol-1-one* ((±)-**24**). A 1M soln. of Li[Et_3BH] in THF (24 ml, 24 mmol) was added to (±)-**22** (6.04 g, 12 mmol) in dry CH_2Cl_2 (100 ml) at 0° under Ar. After 90 min, the mixture was warmed to r.t. and 1N NaOH was added. Separation of the phases, extraction of the aq. phase with CH_2Cl_2, drying of the combined org. phases (Na_2SO_4), evaporation *in vacuo*, and CC (CH_2Cl_2/AcOEt/Et_3N 97:2:1) gave a mixture of (±)-**25** and (±)-**24**.

*Data of (±)-***25**: 1.91 g (31%). Colorless crystals. Dec. >215° (AcOEt). IR (KBr): 3167, 2960, 1659, 1485, 1448, 1244, 1205, 1111, 1077, 1009, 820, 699. ^{1}H-NMR (200 MHz, $CDCl_3$): 1.04 (*s*, 3 H); 1.20 (*s*, 3 H); 1.98 (*s*, 3 H); 2.41 (*dd*, *J* = 8.7, 4.6, 1 H); 3.39 (*dd*, *J* = 10.0, 8.7, 1 H); 3.84 (*d*, *J* = 10.0, 1 H); 5.06 (*m*, 1 H); 6.12 (*s*, 1 H); 7.07 (*d*, *J* = 8.3, 2 H); 7.22–7.27 (*m*, 8 H); 7.40–7.45 (*m*, 4 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 18.3; 22.5; 32.1; 49.2; 57.6; 59.5; 61.1; 69.0; 84.2; 111.2; 121.5; 127.3; 128.0; 128.4; 128.4; 129.0; 130.2; 131.6; 138.0; 138.5; 140.3; 171.7. EI-MS: 504.2 (0.1, M^+); 289.1 (11), 262.0 (14), 196.0 (14), 167.1 (100, Ph_2CH^+). Anal. calc. for $C_{28}H_{29}BrN_2O_2$ (505.46): C 66.54, H 5.78, N 5.54, Br 15.81; found: C 66.53, H 5.83, N 5.49, Br 15.68. X-Ray: see *Fig. 6*.

*Data of (±)-***24**: 3.33 g (55%). Colorless crystals. Dec. >230° (AcOEt). IR (KBr): 3411, 1654, 1444, 1389, 1256, 1044, 811, 700. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.07 (*s*, 3 H); 1.43 (*s*, 3 H); 2.03 (*s*, 3 H); 2.83 (*dd*, *J* = 8.7, 8.7, 1 H); 2.94 (*d*, *J* = 8.7, 1 H); 3.84 (*d*, *J* = 8.4, 1 H); 4.20 (*s*, 1 H); 6.17 (*s*, 1 H); 7.02–7.32 (*m*, 14 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 19.5; 23.9; 32.4; 48.4; 54.1; 60.8; 63.1; 68.4; 82.6; 121.1; 127.6; 128.0; 128.5; 128.7; 128.8; 129.3; 129.9; 131.9; 138.4; 138.6; 139.7; 174.0. EI-MS: 503.1 (1, $[M-H]^+$), 489.1 (12), 167.1 (100, Ph_2CH^+). Anal. calc. for $C_{28}H_{29}BrN_2O_2$ (505.46): C 66.54, H 5.78, N 5.54, Br 15.81; found: C 66.64, H 5.84, N 5.55, Br 15.93.

*(3*RS*,3a*SR*,6*RS*,6a*SR*)-6-(4-Bromophenyl)-2-(diphenylmethyl)-1,2,3,3a,4,5,6,6a-octahydro-4,4,5-trimethyl-3-(1-methylethyl)pyrrolo[3,4-*c*]pyrrol-1-one* ((±)-**26**). Ac_2O (0.09 ml, 102 mg) was added to (±)-**25** (101 mg, 0.2 mmol) and DMAP (122 mg, 1 mmol) in CH_2Cl_2 (2 ml) at −20°. After stirring for 3 h at r.t., the solvent was removed *in vacuo*, and the residue was purified by CC (hexane/AcOEt/Et_3N 89:10:1) and washed with Et_2O to yield acetoxylactam intermediate (57 mg, 52%). Colorless crystals. Dec. >145° (hexane/AcOEt). IR ($CHCl_3$): 3008, 1707, 1600, 1482, 1405, 1364, 1005. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.03 (*s*, 3 H); 1.31 (*s*, 3 H); 1.59 (*s*, 3 H); 2.00 (*s*, 3 H); 2.42 (*dd*, *J* = 8.7, 1.9, 1 H); 3.31 (*dd*, *J* = 8.7, 8.4, 1 H); 3.84 (*d*, *J* = 8.4, 1 H); 6.14 (*s*, 1 H); 6.33 (*d*, *J* = 1.9, 1 H); 7.00 (*d*, *J* = 8.4, 2 H); 7.20–7.41 (*m*, 12 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 19.3; 20.8; 23.7; 32.2; 48.7; 54.6; 60.3; 61.9; 69.1; 85.3; 111.2; 127.5; 128.0; 128.3; 128.7; 129.1; 129.4; 130.3; 131.3; 137.3; 138.6; 139.1; 169.8; 173.3. FAB-MS: 547.6 (100, MH^+), 531.9 (76), 471.5 (50). Anal. calc. for $C_{30}H_{31}BrN_2O_3$ (547.49): C 65.81, H 5.71, N 5.12, Br 14.59; found: C 65.90, H 5.92, N 5.13, Br 14.43.

(i-Pr)MgCl (0.2 ml of 2M soln. in Et_2O, 0.4 mmol) was added to $ZnCl_2$ (0.44 ml of 0.5M soln. in Et_2O, 0.22 mmol) in dry CH_2Cl_2 (1 ml) under Ar. After 1 h, a soln. of the acetoxylactam (109.5 mg, 0.2 mmol) in dry CH_2Cl_2 (1 ml) was slowly added while cooling with an ice bath. After stirring at r.t. for 15 h, 1N HCl was added, and, 15 min later, the mixture was neutralized with sat. aq. $NaHCO_3$ soln. and extracted with CH_2Cl_2. The org. phase was dried (Na_2SO_4), the solvent was removed, and the product was purified by CC (hexane/AcOEt/Et_3N 79:20:1, then 66:33:1) to yield (±)-**26** (17.6 g, 17%; 9% based on (±)-**25**). Colorless oil. IR ($CHCl_3$): 3027, 2968, 1678, 1492, 1451, 1395, 1072, 1011, 831. ^{1}H-NMR (300 MHz, $CDCl_3$): 0.55 (*d*, *J* = 6.8, 3 H); 0.75 (*d*, *J* = 6.8, 3 H); 1.02 (*s*, 3 H); 1.12 (*s*, 3 H); 1.65 (*dsept.*, *J* = 6.8, 2.8, 1 H); 1.99 (*s*, 3 H); 2.20 (*dd*, *J* = 9.3, 2.3, 1 H); 3.11 (*dd*, *J* = 9.3, 7.8, 1 H); 3.73 (*dd*, *J* = 2.8, 2.3, 1 H); 3.82 (*d*, *J* = 7.8, 1 H); 6.00 (*s*, 1 H); 6.97 (*d*, *J* = 8.7, 2 H); 7.22 (*m*, 10 H); 7.46–7.49 (*m*, 2 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 14.5; 18.9; 20.4; 24.9; 29.7; 32.7; 45.3; 50.6; 62.2; 62.7; 64.8; 69.7; 120.7; 127.2; 127.5; 127.9; 128.3; 129.0; 129.6; 130.5; 130.6; 137.6; 138.9; 140.0; 172.7. FAB-MS: 531.1 (100, MH^+), 515.0 (60), 167.1 (51, Ph_2CH^+). HR-MALDI-MS: 529.1849 ($[M-H]^+$, $C_{31}H_{34}BrN_2O$; calc. 529.1855).

*(1*RS*,3a*SR*,4*RS*,8a*SR*,8b*SR*)-4-(4-Bromophenyl)-2,3,3a,4,5,6,7,8,8a,8b-decahydro-1-(1-methylethyl)-1*H*-pyrrolo[3,4-*a*]pyrrolizin-3-one* ((±)-**28**). A mixture of (±)-**27** (379 mg, 0.76 mmol), phenol (120 mg, 1.28 mmol), and orthophosphoric acid (3.73 g, 38 mmol) was homogenized with CH_2Cl_2 (5 ml) and then stirred at 150° for 1 h. After cooling to r.t., H_2O was added, and the mixture was extracted with Et_2O. The combined org. phases were extracted with H_2O. The combined aq. phases were rendered alkaline with NaOH, heated to reflux for 1 h, and extracted with CH_2Cl_2. The combined org. phases were dried (Na_2SO_4), and the solvent was evaporated *in vacuo*. The brownish residue was washed with AcOEt and purified by CC (hexane/AcOEt/Et_3N 49.5:49.5:1) to afford (±)-**28** (90 mg, 32%). Colorless crystals. M.p. 191–193° (hexane/AcOEt)). IR ($CHCl_3$): 3436, 3018, 2965, 1694, 1486, 1072, 1010. ^{1}H-NMR (300 MHz, $CDCl_3$): 0.84 (*d*, *J* = 6.9, 3 H); 0.89

(*d*, *J* = 6.5, 3 H); 1.48–1-63 (*m*, 2 H); 1.71–1.83 (*m*, 1 H); 1.94–2.08 (*m*, 2 H); 2.59 (*ddd*, *J* = 8.7, 3.9, 1.6, 1 H); 2.64–2.70 (*m*, 1 H); 2.87–2.97 (*m*, 1 H); 3.20 (*t*, *J* = 8.7, 1 H); 3.20 (*dd*, *J* = 6.5, 3.9, 1 H); 3.37–3.43 (*m*, 1 H); 3.96 (*d*, *J* = 8.7, 1 H); 6.64 (*s*, 1 H); 7.29, 7.42 (*AA′BB′*, *J* = 8.6, 4 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 18.3; 18.3; 24.1; 30.4; 34.0; 47.5; 51.9; 52.0; 66.2; 69.5; 72.9; 120.9; 130.0; 131.0; 139.1; 175.7. FAB-MS: 363.2 (94, MH^+), 239.1 (7), 167.2 (9), 149.1 (100), 115.0 (16). HR-FAB-MS: 363.1078 (MH^+, $C_{18}H_{24}BrN_2O$; calc. 363.1072).

*(1*RS,*3a*SR,*4*RS,*8a*SR,*8b*RS*)-4-(4-Bromophenyl)-2-(diphenylmethyl)-2,3,3a,4,5,6,7,8,8a,8b-decahydro-1-(1-methylethyl)-1*H*-pyrrolo[3,4-*a*]pyrrolizin-3-one* ((±)-**29**). Benzhydryl chloride (0.36 ml, 811 mg, 2 mmol) was added to a suspension of (±)-**28** (727 mg, 2 mmol) and $AgOSO_2CF_3$ (514 mg, 2 mmol) in a sealed tube. A gray precipitate formed instantly. After stirring at 100° for 1 h and cooling to r.t., sat. aq. $NaHCO_3$ soln. was added, and the mixture was extracted with CH_2Cl_2. The org. phase was dried (Na_2SO_4), the solvent was removed *in vacuo*, and the residue was purified by CC (hexane/AcOEt/Et_3N 82.5 : 16.5 : 1) to yield (±)-**29** (693 mg, 65%). Yellowish oil. IR ($CHCl_3$): 3028, 2966, 1681, 1590, 1487, 1410, 1073, 1011. ^{1}H-NMR (300 MHz, $CDCl_3$): 0.63 (*d*, *J* = 6.5, 3 H); 0.75 (*d*, *J* = 6.9, 3 H); 1.43–1.51 (*m*, 1 H); 1.56–1.68 (*m*, 1 H); 1.71–1.82 (*m*, 1 H); 1.89–2.07 (*m*, 2 H); 2.46 (*dd*, *J* = 3.3, 7.7, 1 H); 2.56–2.66 (*m*, 1 H); 2.94–3.03 (*m*, 1 H); 3.29 (*dd*, *J* = 6.9, 7.7, 1 H); 3.34–3.39 (*m*, 2 H); 4.07 (*d*, *J* = 6.9, 1 H); 6.14 (*s*, 1 H); 7.23–7.41 (*m*, 14 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 15.1; 19.0; 24.9; 29.8; 32.0; 41.9; 52.5; 53.6; 61.5; 69.5; 71.0; 73.7; 120.8; 127.5; 127.6; 128.4; 128.5; 129.2; 129.3; 130.2; 131.0; 138.7; 139.5; 140.1; 173.1. FAB-MS: 529.1 (100, MH^+); 167.1 (45, Ph_2CH^+). HR-FAB-MS: 527.1699 ([$M-H$]$^+$, $C_{31}H_{32}BrN_2O$; calc. 527.1698).

*4-[(1*RS,*3a*SR,*4*RS,*8a*SR,*8b*RS*)-2-(Diphenylmethyl)-2,3,3a,4,5,6,7,8,8a,8b-decahydro-1-(1-methylethyl)-3-oxo-1*H*-pyrrolo[3,4-*a*]pyrrolizin-4-yl]benzonitrile* ((±)-**30**). *General Procedure D*, starting from (±)-**29**, afforded (±)-**30** in 40% yield. Yellowish oil. IR ($CHCl_3$): 3020, 2966, 2229, 1677, 1610, 1497, 1415. ^{1}H-NMR (300 MHz, $CDCl_3$): 0.63 (*d*, *J* = 6.6, 3 H); 0.76 (*d*, *J* = 6.6, 3 H); 1.40–1.60 (*m*, 1 H); 1.50–2.09 (*m*, 4 H); 2.46–2.65 (*m*, 2 H); 2.95–3.08 (*m*, 1 H); 3.32–3.45 (*m*, 3 H); 4.15 (*d*, *J* = 6.6, 1 H); 6.07 (*s*, 1 H); 7.19–7.38 (*m*, 10 H); 7.46, 7.51 (*AA′BB′*, *J* = 8.5, 4 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 15.1; 18.9; 25.0; 29.8; 32.0; 42.0; 52.7; 53.8; 61.7; 69.8; 71.3; 73.9; 110.6; 119.7; 127.6; 127.6; 128.4; 128.5; 129.1; 129.2; 131.7; 139.4; 139.9; 145.8; 172.8. FAB-MS: 951.5 (10, M_2H^+), 476.3 (100, MH^+), 167.1 (82, Ph_2CH^+). HR-FAB-MS: 476.2704 (MH^+, $C_{32}H_{34}N_3O$; calc. 476.2702).

*4-[(1*RS,*3a*SR,*4*RS,*8a*SR,*8b*RS*)-2-(Diphenylmethyl)-2,3,3a,4,5,6,7,8,8a,8b-decahydro-1-(1-methylethyl)-3-oxo-1*H*-pyrrolo[3,4-*a*]pyrrolizin-4-yl]benzamidine Hydrochloride* ((±)-**2**). *General Procedure C*, starting from (±)-**30**, afforded amidinium salt (±)-**2** in 42% yield. Yellowish solid. Dec. > 175°. IR ($CHCl_3$): 2968, 1675, 1614, 1494, 1448. ^{1}H-NMR (300 MHz, $(CD_3)_2SO$): 0.59 (*d*, *J* = 6.9, 3 H); 0.81 (*d*, *J* = 6.9, 3 H); 1.60–1.74 (*m*, 2 H); 1.86–2.04 (*m*, 3 H); 2.41–2.56 (*m*, 2 H); 2.83–2.96 (*m*, 1 H); 3.32–3.46 (*m*, 1 H); 3.50–3.59 (*m*, 1 H); 3.62–3.65 (*m*, 1 H); 4.19 (*d*, *J* = 6.2, 1 H); 5.79 (*s*, 1 H); 7.18–7.35 (*m*, 10 H); 7.52, 7.64 (*AA′BB′*, *J* = 8.4, 4 H); 9.02 (br. *s*, 2 H); 9.19 (br. *s*, 2 H). ^{13}C-NMR (125 MHz, CD_3OD): 15.6; 19.2; 26.0; 31.2; 32.6; 43.1; 54.1; 55.4; 63.8; 71.8; 72.5; 75.6; 127.9; 128.3; 128.7; 128.7; 129.4; 129.4; 129.8; 130.2; 130.4; 140.9; 141.0; 168.3; 174.6. FAB-MS: 985.3 (7, M_2H^+), 493.1 (100, MH^+), 167.1 (26, Ph_2CH^+). HR-FAB-MS: 493.2966 (MH^+, $C_{32}H_{37}N_4O$; calc. 493.2967).

(1,3-benzodioxol-5-yl)-1,3-benzodioxole-5-methanol (**33**). A soln. of **31** (7.41 ml, 12.06 g, 60 mmol) in dry THF (100 ml) was treated at −78° with 1.6M BuLi in hexane (38.6 ml, 61.8 mmol) and, after 5 min, with a soln. of **32** (9.01 g, 60 mmol) in dry THF (10 ml). After 10 min, MeOH (10 ml) was added, and, after warming to r.t., the solvent was removed *in vacuo*. The residue was redissolved in CH_2Cl_2 and extracted with sat. aq. $NaHCO_3$ soln. The org. phase was dried (Na_2SO_4), and the solvent was removed to yield **33** (16.07 g, 98%). Colorless solid. M.p. 82–85°. IR ($CHCl_3$): 3601, 3023, 2892, 1504, 1487, 1443, 1243, 1041, 934. ^{1}H-NMR (300 MHz, $CDCl_3$): 2.24 (*d*, *J* = 3.1, 1 H); 5.66 (*d*, *J* = 3.1, 1 H); 5.93, 5.93 (*AB*, *J* = 1.6, 4 H); 6.74–6.77 (*m*, 2 H); 6.82–6.85 (*m*, 4 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 75.8; 101.1; 107.0; 108.1; 119.8; 138.0; 147.0; 147.8. MALDI-MS: 273.0 (10, MH^+), 255.1 (100). Anal. calc. for $C_{15}H_{12}O_5$ (272.26): C 66.17, H 4.44; found: C 66.00, H 4.60.

*(1*RS,*3a*SR,*4*RS,*8a*SR,*8b*RS*)-4-(4-Bromophenyl)-2-[di(1,3-benzodioxol-5-yl)methyl]-2,3,3a,4,5,6,7,8,8a,8b-decahydro-1-(1-methylethyl)-1*H*-pyrrolo[3,4-*a*]pyrrolizin-3-one* ((±)-**35**). A soln. of **33** (599 mg, 2.2 mmol) in Et_2O (10 ml) was stirred for 2 h under HCl atmosphere. After a quick extraction with sat. aq. $NaHCO_3$ soln., the org. phase was dried (Na_2SO_4), and the solvent was removed *in vacuo*. The resulting crude diarylmethyl chloride **34** (618 mg, 97%) was redissolved in CH_2Cl_2 (20 ml) and added to a suspension of (±)-**28** (691 mg, 1.9 mmol) and $AgOSO_2CF_3$ (489 mg, 1.9 mmol) in CH_2Cl_2 (20 ml) in a sealed tube. A gray precipitate formed instantly. After stirring at 100° for 3 h and cooling to r.t., sat. aq. $NaHCO_3$ soln. was added, and the mixture was extracted with CH_2Cl_2. The org. phase was dried (Na_2SO_4), the solvent was removed *in vacuo*, and the residue was purified by CC (hexane/AcOEt/Et_3N 79 : 20 : 1) to yield (±)-**35** (520 mg, 44%) besides recovered starting material (±)-**28** (259 mg, 38%). Yellowish crystals. M.p. 191–193° (hexane/AcOEt). IR ($CHCl_3$): 3012, 1676,

1504, 1488, 1442, 1247, 1042, 937. ^{1}H-NMR (300 MHz, $CDCl_3$): 0.62 (*d*, *J* = 6.9, 3 H); 0.80 (*d*, *J* = 7.2, 3 H); 1.54–1.68 (*m*, 2 H); 1.70–1.82 (*m*, 1 H); 1.89–2.08 (*m*, 2 H); 2.47 (*dd*, *J* = 8.1, 2.2, 1 H); 2.58–2.66 (*m*, 1 H); 2.94–3.03 (*m*, 1 H); 3.25 (*dd*, *J* = 8.1, 6.7, 1 H); 3.34–3.42 (*m*, 2 H); 4.05 (*d*, *J* = 6.7, 1 H); 5.83 (*s*, 1 H); 5.94 (*s*, 2 H); 5.95 (*s*, 2 H); 6.66–6.78 (*m*, 4 H); 6.81–6.85 (*m*, 1 H); 6.95 (*d*, *J* = 1.6, 1 H); 7.23, 7.35 (*AB*, *J* = 8.4, 4 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 15.0; 19.0; 24.7; 29.9; 31.8; 41.6; 52.2; 53.5; 61.4; 70.0; 70.9; 73.8; 101.2; 101.2; 108.0; 108.1; 109.6; 109.8; 120.8; 122.3; 122.5; 130.1; 131.0; 133.7; 134.1; 138.5; 147.0; 147.1; 147.8; 148.0; 172.9. MALDI-MS: 639.1 (24, $[M+Na]^+$), 617.2 (11, MH^+), 255.1 (100, [di(benzodioxolyl)methyl]$^+$). MALDI-HR-MS: 639.1465 ($[M+Na]^+$, $C_{33}H_{33}BrN_2NaO_5$; calc. 639.1471). Anal. calc. for $C_{33}H_{33}BrN_2O_5$ (617.54): C 64.18, H 5.39, N 4.54, Br 12.94; found: C 64.27, H 5.58, 4.25; Br 13.07.

*2-[(1*RS*,3a*SR*,4*RS*,8a*SR*,8b*RS*)-Di(1,3-benzodioxol-5-yl)methyl]-2,3,3a,4,5,6,7,8,8a,8b-decahydro-1-(1-methylethyl)3-oxo-1*H*-pyrrolo[3,4-*a*]pyrrolizin-4-yl]benzonitrile* ((±)-**36**). *General Procedure D*, starting from (±)-**35**, afforded (±)-**36** in 52% yield. Yellowish oil. IR ($CHCl_3$): 2965, 2882, 2226, 1686, 1504, 1489, 1442, 1247, 1042, 936. ^{1}H-NMR (300 MHz, $CDCl_3$): 0.63 (*d*, *J* = 6.9, 3 H); 0.81 (*d*, *J* = 6.9, 3 H); 1.55–1.67 (*m*, 2 H); 1.73–1.82 (*m*, 1 H); 1.86–2.09 (*m*, 2 H); 2.49 (*dd*, *J* = 7.8, 2.8, 1 H); 2.54–2.63 (*m*, 1 H); 2.97–3.07 (*m*, 1 H); 3.33 (*dd*, = 7.8, 7.2, 1 H); 3.38–3.43 (*m*, 2 H); 4.15 (*d*, *J* = 7.2, 1 H); 5.77 (*s*, 1 H); 5.93 (*s*, 2 H); 5.95 (*s*, 2 H); 6.63–6.74 (*m*, 4 H); 6.78–6.81 (*m*, 1 H); 6.91 (*d*, *J* = 1.6, 1 H); 7.46, 7.51 (*AB*, *J* = 8.2, 4 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 15.0; 19.0; 24.8; 29.8; 31.8; 41.6; 52.3; 53.7; 61.4; 70.1; 71.0; 73.8; 101.1; 101.1; 107.8; 107.9; 109.3; 109.5; 110.4; 119.5; 122.0; 122.1; 128.8; 131.5; 133.4; 133.6; 145.4; 146.8; 146.9; 147.6; 147.7; 172.4. MALDI-MS: 586.2 (100, $[M+Na]^+$), 562.2 (9, MH^+), 255.1 (66, [di(benzodioxolyl)methyl]$^+$). HR-MALDI-MS: 586.2310 ($[M+Na]^+$, $C_{34}H_{33}N_3NaO_5$; calc. 586.2312).

*4-[(1*RS*,3a*SR*,4*RS*,8a*SR*,8b*RS*)-2-[Di(1,3-benzodioxol-5-yl)methyl]-2,3,3a,4,5,6,7,8,8a,8b-decahydro-1-(1-methylethyl)-3-oxo-1*H*-pyrrolo[3,4-*a*]pyrrolizin-4-yl]benzamidine Hydrochloride* ((±)-**4**). *General Procedure C*, starting from (±)-**36**, afforded (±)-**4** in 54% yield. Yellowish solid. Dec. > 200°. IR ($CHCl_3$): 3020, 2966, 1675, 1504, 1489, 1442, 1247, 1041, 936. ^{1}H-NMR (300 MHz, $CD_3)_2SO$): 0.55 (*d*, *J* = 6.9, 3 H); 0.85 (*d*, *J* = 6.9, 3 H); 1.61–1.73 (*m*, 2 H); 1.78–2.02 (*m*, 3 H); 2.42–2.55 (*m*, 2 H); 2.87–2.95 (*m*, 1 H); 3.30–3.37 (*m*, 1 H); 3.39–3.43 (*m*, 1 H); 3.50–3.51 (*m*, 1 H); 4.18 (*d*, *J* = 6.5, 1 H); 5.55 (*s*, 1 H); 5.97 (*s*, 2 H); 6.03, 6.04 (*AB*, *J* = 0.9, 2 H); 6.52 (*dd*, *J* = 8.1, 1.2, 1 H); 6.74–6.85 (*m*, 4 H); 6.93 (*d*, *J* = 1.6, 1 H); 7.52, 7.65 (*AA′BB′*, *J* = 8.4, 4 H); 8.65 (br. *s*, 4 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 15.5; 19.1; 25.4; 29.8; 32.3; 42.0; 52.8; 54.1; 61.9; 70.0; 70.9; 73.6; 101.2; 101.4; 107.8; 108.1; 108.6; 108.8; 121.4; 121.9; 125.3; 127.9; 128.3; 132.5; 146.3; 146.7; 147.1; 147.6; 147.9; 165.3; 173.1. MALDI-MS: 603.2 (38, $[M+Na]^+$), 581.2 (14, MH^+), 255.1 (100, [di(benzodioxolyl)methyl]$^+$). HR-MALDI-MS: 581.2766 (MH^+, $C_{34}H_{37}N_4O_5$; calc. 581.2764).

*(1*RS*,3a*RS*,6a*SR*)-4-{5-[(1,3-Benzodioxol-5-yl)methyl]-1,2,3,3a,4,5,6,6a-octahydro-3,3-dimethyl-4,6-dioxo-1*H*-pyrrolo[3,4-*c*]pyrrol-1-yl]benzonitrile* ((±)-**40**). *General Procedure A*, starting from **14**, **18**, and **51**, gave (±)-**40** in 34% yield. Colorless solid. M.p. 172–173° (MeOH). IR (KBr): 2230, 1770, 1698, 1608, 1490, 1443, 1400, 1369, 326, 1249, 1170, 1099, 1034. ^{1}H-NMR (200 MHz, $CDCl_3$): 1.37 (*s*, 3 H); 1.43 (*s*, 3 H); 1.50 (*s*, 1 H); 2.89 (*d*, *J* = 7.9, 1 H); 3.45 (*m*, 1 H); 4.38, 4.45 (*AB*, *J* = 13.9, 2 H); 4.75 (*d*, *J* = 8.7, 1 H); 5.96, 5.99 (*AB*, *J* = 1.2, 2 H); 6.74, 6.79 (*AB*, *J* = 7.9, 2 H); 6.77 (*s*, 1 H); 7.32, 7.53 (*AA′BB′*, *J* = 8.3, 4 H). ^{13}C-NMR (50 MHz, $CDCl_3$): 26.3; 28.8; 42.1; 50.2; 53.8; 60.4; 61.0; 101.3; 108.3; 109.7; 111.8; 119.1; 122.7; 128.4; 129.9; 132.0; 144.1; 147.5; 147.9; 175.0; 176.0. FAB-MS: 807.2 (23, M_2H^+), 404.1 (100, MH^+), 388.1 (11, $[M-Me]^+$). Anal. calc. for $C_{23}H_{21}N_3O_4$ (403.44): C 68.47, H 5.25, N 10.42; found: C 68.32, H 5.30, N 10.55.

*Methyl (3*RS*,3a*SR*,6a*RS*)-{5-[(1,3-Benzodioxol-5-yl)methyl]-3-(4-cyanophenyl)-1,2,3,3a,4,5,6,6a-octahydro-1,1-dimethyl-4,6-dioxopyrrolo[3,4-*c*]pyrrol-2-yl}acetate* ((±)-**41**). HCO_2H (1.73 g, 37.5 mmol), glyoxylic acid monohydrate (0.83 g, 9.0 mmol), and (±)-**40** (3.03 g, 7.5 mmol) were mixed at 0° and then heated to reflux for 24 h. The solvent was evaporated *in vacuo*, and the residue was redissolved in MeOH (11.5 ml). Conc. H_2SO_4 (0.15 g) was added, and the mixture was stirred at 90° for 48 h. After cooling, sat. aq. $NaHCO_3$ soln. was added, and the mixture was extracted with CH_2Cl_2. The org. phase was dried (Na_2SO_4), evaporated, and the residue was purified by CC (hexane/AcOEt/Et_3N 66 : 33 : 1, then 49.5 : 49.5 : 1) to give (±)-**41** (1.42 g, 40%). Colorless solid. M.p. 134–136° (MeOH). IR (KBr): 2229, 1763, 1730, 1702, 1610, 1508, 1488, 1444, 1400, 1372, 1326, 1247, 1175, 1034. ^{1}H-NMR (200 MHz, $CDCl_3$): 1.17 (*s*, 3 H); 1.46 (*s*, 3 H); 2.92 (*d*, *J* = 7.9, 1 H); 3.04, 3.16 (*AB*, *J* = 17.2, 2 H); 3.40 (*dd*, *J* = 7.9, 9.1, 1 H); 3.55 (*s*, 3 H); 4.34, 4.48 (*AB*, *J* = 13.9, 2 H); 4.63 (*d*, *J* = 9.1, 1 H); 5.97, 6.01 (*AB*, *J* = 1.25, 2 H); 6.81 (*m*, 3 H); 7.21, 7.44 (*AA′BB′*, *J* = 7.9, 4 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 21.2; 24.2; 42.2; 46.5; 48.2; 51.8; 54.1; 63.4; 66.2; 101.4; 108.4; 110.0; 112.2; 119.0; 123.0; 129.5; 129.7; 132.3; 142.8; 147.6; 147.9; 172.1; 175.0; 175.8. FAB-MS: 951.3 (9, $[M_2H]^+$), 476.1 (100, MH^+), 416.1 (34), 402.1 (20), 135.1 (69, [piperonyl]$^+$). Anal. calc. for $C_{26}H_{25}N_3O_6$ (475.50): C 65.68, H 5.30, N 8.84; found: C 65.70, H 5.29, N 8.80.

*(1*RS*,3a*RS*,6a*SR*)-4-{5-[(1,3-Benzodioxol-5-yl)methyl]-1,2,3,3a,4,5,6,6a-octahydro-3,3-dimethyl-4,6-dioxo-2-(2-oxo-2-phenylethyl)pyrrolo[3,4-*c*]pyrrol-1-yl}benzonitrile* ((±)-**42**). HCO_2H (4.6 g, 100 mmol), phenyl-

glyoxal monohydrate (3.65 g, 24 mmol), and (±)-**40** (8.07 g, 20 mmol) were mixed at 0° and then stirred for 10 h at 100°. After cooling, sat. aq. $NaHCO_3$ soln. was added, and the mixture was extracted with CH_2Cl_2. The org. phase was dried (Na_2SO_4), evaporated, and the residue was purified by CC (hexane/AcOEt/Et_3N 49.5 : 49.5 : 1) to give (±)-**42** (2.25 g, 22%). Colorless solid. M.p. 176–177° (hexane/AcOEt). IR (KBr): 2222, 1767, 1699, 1608, 1597, 1503, 1491, 1446, 1399, 1344, 1310, 1246, 1172, 1040. ^{1}H-NMR (200 MHz, $CDCl_3$): 1.25 (*s*, 3 H); 1.52 (*s*, 3 H); 2.99 (*d*, *J* = 8.3, 1 H); 3.48 (*m*, 1 H); 3.63, 3.92 (*AB*, *J* = 17.4, 2 H); 4.38, 4.52 (*AB*, *J* = 13.9, 2 H); 4.74 (*d*, *J* = 9.1, 1 H); 6.00, 6.03 (*AB*, *J* = 1.2, 2 H); 6.80–6.92 (*m*, 3 H); 7.15 (*d*, *J* = 8.3, 2 H); 7.31–7.58 (*m*, 3 H); 7.36, 7.70 (*AA′BB′*, *J* = 7.1, 4 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 21.8; 24.7; 42.2; 48.5; 51.6; 54.2; 63.9; 67.1; 101.4; 108.5; 110.1; 112.1; 119.0; 123.0; 127.9; 128.8; 129.7; 132.2; 133.5; 136.0; 142.9; 147.6; 147.9; 175.2; 175.9; 197.8. FAB-MS: 1043.4 (7, M_2H^+), 522.2 (100, MH^+), 416.2 (59), 135.0 (47 [piperonyl]$^+$). Anal. calc. for $C_{31}H_{27}N_3O_5$ (521.56): C 71.39, H 5.22, N 8.06; found: C 71.40, H 5.39, N 8.17.

*Methyl (3*RS,*3a*SR,*6a*RS*)-(3-{4-[Amino(imino)methyl]phenyl}-5-[(1,3-benzodioxol-5-yl)methyl]-1,2,3,3a,4,5,6,6a-octahydro-1,1-dimethyl-4,6-dioxopyrrolo[3,4-*c*]pyrrol-2-yl)acetate Hydrochloride* ((±)-**37**). *General Procedure C*, starting from (±)-**41**, gave (±)-**37** in 97% yield. Slightly pink foam. M.p. >143° (dec.). IR (KBr): 1704, 1675, 1614, 1539, 1490, 1445, 1400, 1370, 1342, 1248, 1172, 1102, 1036. ^{1}H-NMR (200 MHz, $(CD_3)_2SO$): 1.14 (*s*, 3 H); 1.32 (*s*, 3 H); 2.85, 3.33 (*AB*, *J* = 17.0, 2 H); 3.12 (*d*, *J* = 8.3, 1 H); 3.46 (*s*, 3 H); 3.60 (*m*, 1 H); 4.35 (*s*, 2 H); 4.54 (*d*, *J* = 8.7, 1 H); 6.06 (*s*, 2 H); 6.76 (*s*, 1 H); 6.77 (*m*, 2 H); 7.36, 7.65 (*AA′BB′*, *J* = 7.7, 4 H); 9.26 (br., 4 H). ^{13}C-NMR (75 MHz, $(CD_3)_2SO$): 19.9; 24.0; 41.0; 47.2; 48.1; 51.3; 53.6; 62.8; 66.4; 101.1; 108.2; 108.5; 121.3; 126.9; 127.6 (2×); 129.9; 144.7; 146.7; 147.4; 165.4; 172.0; 175.3; 176.2. DEI-MS: 492.3 (10, M^+), 477.2 (15, $[M-Me]^+$), 433.3 (12), 416.2 (28), 402.2 (14), 135.1 (100, [piperonyl]$^+$). HR-DEI-MS: 492.2005 (M^+, $C_{26}H_{28}N_4O_6$, calc. 492.2002).

*(3*RS,*3a*SR,*6a*RS*)-(3-{4-[Amino(imino)methyl]phenyl}-5-[(1,3-benzodioxol-5-yl)methyl]-1,2,3,3a,4,5,6,6a-octahydro-1,1-dimethyl-4,6-dioxopyrrolo[3,4-*c*]pyrrol-2-yl)acetic Acid Hydrochloride* ((±)-**38**). Ester (±)-**37** (793 mg, 1.5 mmol) was dissolved in 3N HCl (5 ml, 15 mmol) and stirred for 15 h at 100°. After cooling, the mixture was evaporated and dried under high vacuum. The residue was redissolved twice in EtOH and precipitated with Et_2O to give 721 mg (93%) crude product, from which 270 mg were further purified by CC (*RP18*-SiO_2; H_2O, then H_2O/MeOH 2 : 1, then 1 : 1) to give (±)-**38** (99.6 mg, 36%). Yellowish crystals. M.p. >170° (dec.). IR (KBr): 1771, 1698, 1617, 1490, 1445, 1402, 1248, 1172, 1036. ^{1}H-NMR (200 MHz, $(CD_3)_2SO$): 1.16 (*s*, 3 H); 1.34 (*s*, 3 H); 2.76, 3.14 (*AB*, *J* = 17.2, 2 H); 3.10 (*d*, *J* = 7.9, 1 H); 3.59 (*m*, 1 H); 4.35 (*s*, 2 H); 4.60 (*d*, *J* = 8.7, 1 H); 6.03 (*s*, 2 H); 6.77 (*s*, 1 H); 6.79, 6.90 (*AB*, *J* = 7.5, 2 H); 7.45, 7.61 (*AA′BB′*, *J* = 7.7, 4 H); 9.10 (br. *s*, 2 H); 9.60 (br. *s*, 2 H). ^{13}C-NMR (300 MHz, $(CD_3)_2SO$): 19.9; 24.0; 41.0; 46.6; 48.1; 53.6; 62.6; 65.9; 101.1; 108.2; 108.3; 120.9; 126.8; 127.6; 129.8; 145.0; 146.6; 147.4; 165.5; 173.1; 175.4; 176.3. FAB-MS: 479.2 (100, MH^+), 433.2 (7). Anal. calc. for $C_{25}H_{26}N_4O_6 \cdot HCl$ (514.96): C 58.31, H 5.28, N 10.88, Cl 6.88; found: C 58.58, H 5.25, N 11.02, Cl 7.18.

*(1*RS,*3a*RS,*6a*SR*)-4-[5-[(1,3-Benzodioxol-5-yl)methyl]-1,2,3,3a,4,5,6,6a-oxtahydro-3,3-dimethyl-4,6-dioxo-2-(2-oxo-2-phenylethyl)pyrrolo[3,4-*c*]pyrrol-1-yl]benzamidine Hydrochloride* ((±)-**39**). *General Procedure C*, starting from (±)-**42** gave (±)-**39** in 75% yield. Yellowish solid. M.p. 166°. IR (KBr): 1772, 1702, 1675, 1613, 1539, 1490, 1446, 1399, 1247, 1172, 1037. ^{1}H-NMR (200 MHz, $(CD_3)_2SO$): 1.17 (*s*, 3 H); 1.24 (*s*, 3 H); 3.10 (*d*, *J* = 7.9, 1 H); 3.59 (*m*, 1 H); 3.53, 4.09 (*AB*, *J* = 18.3, 2 H); 4.32 (*s*, 2 H); 4.61 (*d*, *J* = 9.1, 1 H); 6.02 (*m*, 2 H); 6.76 (*d*, *J* = 1.24, 1 H); 6.81, 6.92 (*AB*, *J* = 7.9, 2 H); 7.31–7.58 (*m*, 5 H); 7.37, 7.75 (*AA′BB′*, *J* = 7.1, 4 H); 9.03 (br. *s*, 2 H); 9.21 (br. *s*, 2 H). ^{13}C-NMR (50 MHz, $(CD_3)_2SO$): 18.2; 22.5; 46.5; 50.2; 52.0; 61.2; 65.0; 99.3; 106.4; 106.7; 119.4; 124.9; 125.7; 126.0; 126.9; 127.5; 128.0; 131.4; 134.0; 143.3; 144.9; 145.6; 163.5; 173.7; 174.5; 195.9. FAB-MS: 1077.4 (20, M_2H^+), 539.1 (100, MH^+), 433.1 (14), 135.0 (14, [piperonyl]$^+$).

*4-[(1*RS,*3*SR,*3a*RS,*6a*SR*)-5-[(1,3-Benzodioxol-5-yl)methyl]-1,2,3,3a,4,5,6,6a-octahydro-3-methyl-4,6-dioxopyrrolo[3,4-*c*]pyrrol-1-yl]benzonitrile* ((±)-**45**). *General Procedure A*, starting from (±)-alanine, **14**, and **19**, gave (±)-**45** in 38% yield. Colorless crystals. M.p. 175–178° (MeOH). IR ($CHCl_3$): 2968, 2230, 1708, 1495, 1404, 1048, 941. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.32 (*d*, *J* = 6.5, 3 H); 1.60 (*s*, 1 H); 3.00 (*d*, *J* = 7.8, 1 H); 3.42 (*dd*, *J* = 8.7, 7.8, 1 H); 4.06 (*q*, *J* = 6.5, 1 H); 4.36, 4.42 (*AB*, *J* = 13.8, 2 H); 4.80 (*d*, *J* = 8.7, 1 H); 5.95, 5.99 (*AB*, *J* = 1.4, 2 H); 6.71–6.78 (*m*, 3 H); 7.24, 7.47 (*AB*, *J* = 8.2, 4 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 20.8; 42.3; 49.0; 52.4; 55.7; 61.1; 101.2; 108.1; 109.7; 111.5; 118.9; 122.7; 128.1; 129.5; 131.9; 143.8; 147.3; 147.6; 175.0; 177.9. FAB-MS: 390.1 (100, MH^+), 135.0 (46, [piperonyl]$^+$). Anal. calc. for $C_{22}H_{19}N_3O_4$ (389.41): C 67.86, H 4.92, N 10.79; found: C 67.70, H 4.98, N 10.80.

*Methyl 2-{(1*RS,*3*SR,*3a*RS,*6a*SR*)-5-[(1,3-Benzodioxol-5-yl)methyl]-1-(4-cyanophenyl)-1,2,3,3a,4,5,6,6a-octahydro-3-methyl-4,6-dioxopyrrolo[3,4-*c*]pyrrol-2-yl}acetate* ((±)-**46**). A soln. of (±)-**45** (779 mg, 2 mmol) and glyoxylic acid monohydrate (276 mg, 3 mmol) in HCO_2H (0.38 ml, 460 mg, 10 mmol) was heated to reflux for 24 h. The solvent was evaporated, the residue was redissolved in MeOH (5 ml), and H_2SO_4 (0.08 ml) was

added. The mixture was heated to reflux for 48 h. After neutralization with sat. aq. $NaHCO_3$ soln., the mixture was extracted with CH_2Cl_2. The org. phase was dried (Na_2SO_4), and the residue was purified by CC (hexane/AcOEt/Et_3N 49.5:49.5:1) to give (±)-**46** (447 mg, 48%). Colorless crystals. M.p. 139–141° (MeOH). IR ($CHCl_3$): 3028, 2231, 1737, 1706, 1504, 1491, 1446, 1399, 1165, 1041. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.17 (*d*, *J* = 6.8, 3 H); 3.01 (*d*, *J* = 8.1, 1 H); 3.11, 3.14 (*AB*, *J* = 16.8, 2 H); 3.41–3.47 (*m*, 1 H); 3.65 (*s*, 3 H); 4.19 (*q*, *J* = 6.8, 1 H); 4.35, 4.49 (*AB*, *J* = 14.2, 2 H); 4.48 (*d*, *J* = 8.4, 1 H); 5.97, 6.01 (*AB*, *J* = 1.2, 2 H); 6.74–6.85 (*m*, 3 H); 7.09, 7.42 (*AB*, *J* = 8.4, 4 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 13.0; 42.5; 48.1; 49.1; 51.8; 51.9; 58.3; 65.2; 101.4; 108.4; 110.2; 112.3; 118.9; 123.2; 129.1; 129.7; 132.5; 142.3; 147.7; 147.9; 170.8; 175.3; 177.8. FAB-MS: 462.0 (100, *M*H$^+$), 402.0 (73), 388 (27), 135.0 (26, [piperonyl]$^+$). Anal. calc. for $C_{25}H_{23}N_3O_6$ (461.47): C 65.07, H 5.02, N 9.11; found: C 65.04, H 5.21, N 9.27.

*4-{(1*RS,*3*SR,*3a*RS,*6a*SR*)-5-[(1,3-Benzodioxol-5-yl)methyl]-1,2,3,3a,4,5,6,6a-octahydro-2,3-dimethyl-4,6-dioxopyrrolo[3,4-*c*]pyrrol-1-yl}benzonitrile* ((±)-**47**). *General Procedure B*, starting from (±)-**45**, gave (±)-**47** in 91% yield. Colorless crystals. M.p. 190–192° (hexane/AcOEt). IR ($CHCl_3$): 3028, 2231, 1703, 1491, 1400, 1039. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.15 (*d*, *J* = 6.8, 3 H); 2.06 (*s*, 3 H); 2.96 (*d*, *J* = 7.8, 1 H); 3.44 (*dd*, *J* = 9.0, 7.8, 1 H); 3.96 (*q*, *J* = 6.8, 1 H); 4.02 (*d*, *J* = 9.0, 1 H); 4.34, 4.43 (*AB*, *J* = 14.0, 2 H); 5.97, 6.01 (*AB*, *J* = 1.2, 2 H); 6.73–6.82 (*m*, 3 H); 7.08, 7.43 (*AB*, *J* = 8.2, 4 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 11.7; 34.7; 42.4; 49.9; 51.8; 60.7; 67.1; 101.2; 108.1; 110.2; 111.6; 118.9; 123.1; 128.7; 129.4; 132.1; 142.8; 147.4; 147.6; 175.2; 178.0. FAB-MS: 404.1 (71, *M*H$^+$), 402.0 (100), 135.0 (31, [piperonyl]$^+$). Anal. calc. for $C_{23}H_{21}N_3O_4$ (389.41): C 68.47, H 5.25, N 10.42; found: C 68.27, H 5.49, N 10.42.

*Methyl 2-((1*RS,*3*SR,*3a*RS,*6a*SR*)-1-{4-[Amino(imino)methyl]phenyl}-5-[(1,3-benzodioxol-5-yl)methyl]-1,2,3,3a,4,5,6,6a-octahydro-3-methyl-4,6-dioxopyrrolo[3,4-*c*]pyrrol-2-yl)acetate* ((±)-**43**). *General Procedure C*, starting from (±)-**46**, gave (±)-**43** in 37%. Yellowish solid. M.p. >90° (dec.). IR ($CHCl_3$): 2971, 1705, 1491, 1446, 1400, 1040. ^{1}H-NMR (300 MHz, $(CD_3)_2SO$): 1.10 (*d*, *J* = 6.8, 3 H); 2.85–2.96 (*m*, 1 H); 3.14, 3.23 (*m*, 2 H); 3.54 (*s*, 3 H); 3.62 (*dd*, *J* = 9.0, 8.1, 1 H); 4.01 (*q*, *J* = 6.8, 1 H); 4.33 (*s*, 2 H); 4.46 (*d*, *J* = 9.0, 1 H); 6.02, 6.03 (*AB*, *J* = 0.9, 2 H); 6.69–6.74 (*m*, 2 H); 6.82–6.89 (*m*, 1 H); 7.23, 7.61 (*AB*, *J* = 7.9, 4 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 12.7; 42.4; 48.2; 49.2; 51.7; 52.0; 58.1; 65.2; 101.4; 108.6; 109.8; 123.0; 127.4; 128.4; 129.5; 143.9; 147.5; 147.7; 166.2; 170.9; 176.3; 178.0. FAB-MS: 479.1 (100, *M*H$^+$), 391.2 (15), 329.0 (13). HR-FAB-MS: 479.1931 (*M*H$^+$, $C_{25}H_{27}N_4O_6$; calc. 479.1931).

*4-{(1*RS,*3*SR,*3a*RS,*6a*SR*)-5-[(1,3-Benzodioxol-5-yl)methyl]-1,2,3,3a,4,5,6,6a-octahydro-2,3-dimethyl-4,6-dioxopyrrolo[3,4-*c*]pyrrol-1-yl}benzamidine Hydrochloride* ((±)-**44**). *General Procedure C*, starting from (±)-**47**, gave (±)-**44** in 56% yield. Yellowish solid. M.p. >150° (dec.). IR ($CHCl_3$): 2972, 1704, 1491, 1446, 1401, 1041. ^{1}H-NMR (300 MHz, CD_3OD): 1.18 (*d*, *J* = 6.8, 3 H); 2.07 (*s*, 3 H); 3.13 (*d*, *J* = 8.1, 1 H); 3.61 (*dd*, *J* = 9.3, 8.1, 1 H); 3.88 (*q*, *J* = 6.8, 1 H); 4.18 (*d*, *J* = 9.3, 1 H); 4.33, 4.42 (*AB*, *J* = 14.2, 2 H); 5.96, 5.99 (*AB*, *J* = 1.1, 2 H); 6.71–6.79 (*m*, 3 H); 7.22, 7.56 (*AB*, *J* = 8.1, 4 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 11.7; 34.7; 42.3; 50.0; 51.8; 60.7; 66.8; 101.2; 108.4; 109.9; 123.0; 126.8; 128.0; 129.1; 129.3; 144.5; 147.3; 147.4; 166.0; 176.2; 178.1. FAB-MS: 421.1 (100, *M*H$^+$), 253.2 (68), 135.0 (43, [piperonyl]$^+$). HR-FAB-MS: 421.1870 (*M*H$^+$, $C_{23}H_{25}N_4O_4$; calc. 421.1876).

*4-[(3a*SR,*4*SR,*8a*RS,*8b*RS*)-, (3a*SR,*4*SR,*8a*SR,*8b*RS*)-, (3a*SR,*4*RS,*8a*RS,*8b*RS*)-, and (3a*SR,*4*RS,*8a*SR,*8b*RS*)-2-[(1,3-Benzodioxol-5-yl)methyl]-2,3,3a,4,5,6,7,8,8a,8b-decahydro-1,3,6-trioxo-1*H*-pyrrolo[3,4-*a*]pyrrolizin-4yl]benzonitrile* ((±)-**54a**–**54d**, resp.). *General Procedure A*, starting from **14**, **51**, and **52**, gave (±)-**54b** and (±)-**54d**.

*Data of (±)-***54b**: 34 mg (8%). Yellow foam. M.p. 98–100°. IR ($CHCl_3$): 3028, 2400, 2232, 1710, 1504, 1431. ^{1}H-NMR (300 MHz, $CDCl_3$): 2.04–2.16 (*m*, 1 H); 2.51–2.64 (*m*, 3 H); 3.27 (*dd*, *J* = 9.0, 8.1, 1 H); 3.52 (*dd*, *J* = 9.0, 4.2, 1 H); 3.92–4.02 (*m*, 1 H); 4.56 (*s*, 2 H); 4.78 (*d*, *J* = 4.2, 1 H); 5.94 (*s*, 2 H); 6.72–6.76 (*m*, 1 H); 6.84–6.87 (*m*, 2 H); 7.39, 7.66 (*AA′BB′*, *J* = 8.4, 4 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 28.1; 36.1; 42.7; 48.6; 58.8; 58.9; 65.8; 101.4; 108.7; 109.5; 112.5; 118.6; 122.9; 127.9; 128.4; 133.1; 143.0; 147.9; 148.2; 170.4; 174.3; 175.3. FAB-MS: 859.2 (2, M_2H$^+$); 460.1 (42), 430.1 (100, *M*H$^+$), 374.1 (49), 338.3 (14). HR-FAB-MS: 430.1402 (*M*H$^+$, $C_{24}H_{20}N_3O_5$; calc. 430.1403).

*Data of (±)-***54d**: 100 mg (23%). Colorless Crystals. M.p. 183–186° (AcOEt). IR ($CHCl_3$): 3011, 2233, 1779, 1711, 1610, 1491, 1447, 1390, 1342, 1249. ^{1}H-NMR (300 MHz, $CDCl_3$): 2.00–2.06 (*m*, 1 H); 2.46–2.56 (*m*, 1 H); 2.69–2.82 (*m*, 2 H); 3.31 (*dd*, *J* = 9.7, 5.0, 1 H); 4.00 (*dd*, *J* = 10.0, 9.7, 1 H); 4.21, 4.27 (*AB*, *J* = 13.8, 2 H); 4.57–4.60 (*m*, 1 H); 5.56 (*d*, *J* = 10.0, 1 H); 5.99, 6.07 (*AB*, *J* = 0.6, 2 H); 6.36 (*s*, 1 H); 6.58 (*dd*, *J* = 7.8, 1.6, 1 H); 6.66 (*d*, *J* = 7.8, 1 H); 7.09, 7.36 (*AA′BB′*, *J* = 8.4, 4 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 29.4; 33.3; 42.3; 52.0; 52.9; 58.4; 63.2; 101.4; 108.1; 109.2; 112.0; 118.3; 122.7; 127.5; 128.4; 132.0; 141.2; 147.5; 147.6; 172.6; 174.8; 175.3. FAB-MS: 858.9 (10, M_2H$^+$), 430.2 (100, *M*H$^+$); 338.3 (8), 135.0 (75, [piperonyl]$^+$). Anal. calc. for $C_{24}H_{19}N_3O_5$ (429.43): C 67.13, H 4.46, N 9.79; found: C 66.95, H 4.71, N 9.80. X-Ray: see *Fig. 8*.

Using PhCl as a solvent gave (±)-**54b** (29%) and (±)-**54d** (7.1%) besides (±)-**54a** and (±)-**54c**.

Data of (±)-**54a**: 2%. Yellow solid. M.p. >180° (dec.). IR ($CHCl_3$): 3006, 2233, 1709, 1490, 1398, 1041. ^{1}H-NMR (300 MHz, $CHCl_3$): 2.04–2.38 (*m*, 3 H); 2.53–2.69 (*m*, 1 H); 3.36 (*dd*, *J* = 8.3, 7.9, 1 H); 3.61 (*dd*, *J* = 7.9, 2.1, 1 H); 4.32–4.42 (*m*, 1 H); 4.52, 4.65 (*AB*, *J* = 13.7, 2 H); 5.63 (*d*, *J* = 2.1, 1 H); 5.96 (*s*, 2 H); 6.74–6.85 (*m*, 3 H); 7.45, 7.69 (*AA′BB′*, *J* = 8.4, 4 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 20.3; 32.0; 42.9; 47.2; 55.2; 59.4; 61.6; 101.3; 108.5; 109.2; 112.0; 118.3; 122.4; 126.4; 128.7; 132.9; 144.3; 147.6; 147.9; 174.5; 175.0; 175.7. FAB-MS: 461.1 (87), 431.0 (100, MH^+), 339.0 (35). HR-FAB-MS: 430.1405 (MH^+, $C_{24}H_{19}N_3O_5$; calc. 430.1403).

Data of (±)-**54c**: 11%: Red foam. M.p. 95–105°. IR ($CHCl_3$): 3009, 2232, 1778, 1709, 1611, 1504, 1490, 1446, 1395, 1370, 1343, 1249. ^{1}H-NMR (300 MHz, $CDCl_3$): 2.33–2.44 (*m*, 2 H); 2.57–2.66 (*m*, 2 H); 3.32 (*dd*, *J* = 7.8, 7.6, 1 H); 3.87 (*dd*, *J* = 10.0, 7.8, 1 H); 4.33–4.37 (*m*, 1 H); 4.31, 4.42 (*AB*, *J* = 13.7, 2 H); 4.86 (*d*, *J* = 10.0, 1 H); 5.99, 6.07 (*AB*, *J* = 1.3, 2 H); 6.72–6.80 (*m*, 3 H); 6.94, 7.37 (*AA′BB′*, *J* = 8.4, 4 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 22.7; 36.7; 42.7; 45.1; 54.8; 58.9; 63.8; 101.6; 108.5; 110.3; 112.4; 118.8; 123.4; 128.5; 129.0; 132.2; 138.0; 148.0; 148.1; 170.9; 173.3; 174.4. FAB-MS: 859.1 (11, M_2H^+), 430.0 (100, MH^+), 338.2 (16), 135.0 (42, [piperonyl]$^+$). Anal. calc. for $C_{24}H_{19}N_3O_5$ (429.43): C 67.13, H 4.46, N 9.79; found: C 66.95, H 4.71, N 9.80.

*5-(*tert-*Butyl)* L-*Glutamate* (**55**) [38]. Pd/C (10%, 39 mg) was added to 5-(*tert*-butyl) *N*-carbobenzyloxy-L-glutamate (338 mg, 1 mmol) in MeOH (5 ml). The mixture was stirred for 24 h under H_2 (1 atm). The suspension was filtered through *Celite* and the solvent evaporated *in vacuo*. The residue was redissolved in warm MeOH and precipitated with Et_2O to give **55** (195 mg, 96%). Colorless solid. M.p. 185° (MeOH/Et_2O) ([38]: 186–187°). ^{1}H-NMR (300 MHz, CD_3OD): 1.45 (*s*, 9 H); 2.02–2.11 (*m*, 2 H); 2.42–2.48 (*m*, 2 H); 3.58 (*t*, *J* = 6.0, 1 H).

tert-*Butyl 3-{(1*SR,*3*RS,*3a*SR,*6a*RS*)-5-[(1,3-Benzodioxol-5-yl)methyl]-3-(4-cyanophenyl)-1,2,3,3a,4,5,6,6a-octahydro-4,6-dioxopyrrolo[3,4-*c*]pyrrol-1-yl}propanoate* ((±)-**56**). *General Procedure A*, starting from **14**, **51**, and **55**, gave (±)-**56** in 56% yield. Yellow Solid. M.p. 50–55° (hexane/AcOEt). IR ($CHCl_3$): 3010, 2231, 1776, 1706, 1610, 1490, 1447, 1395, 1369, 1248. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.42 (*s*, 9 H); 1.84–1.91 (*m*, 2 H); 2.33 (*dd*, *J* = 7.5, 7.2, 2 H); 3.05 (*d*, *J* = 7.8, 1 H); 3.40 (*dd*, *J* = 8.4, 7.8, 1 H); 3.83 (*t*, *J* = 7.5, 1 H); 4.34, 4.43 (*AB*, *J* = 14.0, 2 H); 4.72 (*d*, *J* = 8.4, 1 H); 5.95, 5.99 (*AB*, *J* = 1.2, 2 H); 6.71–6.78 (*m*, 3 H); 7.21, 7.46 (*AA′BB′*, *J* = 8.4, 4 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 28.0; 28.8; 32.7; 42.3; 49.0; 51.3; 60.3; 61.2; 81.0; 101.2; 108.1; 109.7; 111.6; 118.8; 122.8; 128.0; 129.5; 131.9; 143.5; 147.4; 147.6; 172.2; 174.9; 177.6. FAB-MS: 1007.2 (6, M_2H^+); 504.1 (76, MH^+), 448.0 (100), 135.0 (50, [piperonyl]$^+$). Anal. calc. for $C_{28}H_{29}N_3O_6$ (503.55): C 66.79, H 5.80, N 8.34; found: C 66.61, H 5.98, N 8.16.

Two other diastereoisomers were isolated in 14 and 18% yield, resp.

*Methyl 3-{(1*SR,*3*RS,*3a*SR,*6a*RS*)-5-[(1,3-Benzodioxol-5-yl)methyl]-3-(4-cyanophenyl)-1,2,3,3a,4,5,6,6a-octahydro-2-methyl-4,6-dioxopyrrolo[3,4-*c*]pyrrol-1-yl}propanoate* ((±)-**57**). A suspension of (±)-**56** (50 mg, 0.1 mmol), 98% aq. HCO_2H soln. (0.4 ml, 480 mg, 10.4 mmol), and 35% aq. HCHO soln. (0.05 ml, 0.6 mmol) was heated to 100° for 14 h. After cooling, sat. aq. $NaHCO_3$ soln. was added, and the mixture was extracted with CH_2Cl_2. The org. phase was dried (Na_2SO_4) and evaporated *in vacuo*. The residue was suspended in MeOH (1.2 ml), and conc. H_2SO_4 (2.6 ml) was added. The suspension was heated to reflux for 18 h. After cooling, the mixture was neutralized with sat. aq. $NaHCO_3$ soln. and extracted with CH_2Cl_2. The org. phase was dried (Na_2SO_4), concentrated *in vacuo*, and the residue was purified by CC (hexane/AcOEt/Et_3N 49.5 : 49.5 : 1) to give (±)-**57** (36 mg, 76%). Colorless solid. M.p. 105–110° (AcOEt). IR ($CHCl_3$): 3029, 2953, 2231, 1706, 1491, 1447, 1399, 1344, 1249. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.54–1.62 (*m*, 2 H); 2.13 (*s*, 3 H); 2.44 (*dd*, *J* = 7.8, 7.5, 2 H); 3.03 (*d*, *J* = 8.0, 1 H); 3.45 (*dd*, *J* = 9.1, 8.0, 1 H); 3.69 (*d*, *J* = 8.4, 1 H); 3.72 (*s*, 3 H); 4.06 (*d*, *J* = 9.1, 1 H); 4.34, 4.44 (*AB*, *J* = 14.0, 2 H); 5.97, 6.02 (*AB*, *J* = 1.3, 2 H); 6.74–6.83 (*m*, 3 H); 7.06, 7.43 (*AA′BB′*, *J* = 8.4, 4 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 20.1; 31.0; 34.6; 42.6; 49.2; 50.1; 52.0; 65.4; 67.7; 101.4; 108.4; 110.4; 112.0; 119.0; 123.4; 128.9; 129.6; 132.4; 142.8; 147.7; 147.9; 173.6; 175.3; 178.1. FAB-MS: 475.9 (100, MH^+), 388.0 (70), 135.0 (52, [piperonyl]$^+$). Anal. calc. for $C_{26}H_{25}N_3O_6$ (475.51): C 65.68, H 5.30, N 8.84; found: C 65.73, H 5.49, N 8.76.

*Methyl 3-((1*SR,*3*RS,*3a*SR,*6a*RS*)-3-{4-[Amino(imino)methyl]phenyl}-5-[(1,3-benzodioxol-5-yl)methyl]-1,2,3,3a,4,5,6,6a-octahydro-2-methyl-4,6-dioxopyrrolo[3,4-*c*]pyrrol-1-yl)propanoate Hydrochloride* ((±)-**58**). *General Procedure C*, starting from (±)-**57**, gave (±)-**58** in 54% yield. Colorless solid. M.p. 105–110°. IR ($CHCl_3$): 2972, 1704, 1615, 1503, 1490, 1446, 1400, 1369, 1247. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.51–1.66 (*m*, 2 H); 2.06 (*s*, 3 H); 2.41 (*dd*, *J* = 7.5, 7.4, 2 H); 3.04 (*d*, *J* = 7.8, 1 H); 3.45 (*dd*, *J* = 8.4, 7.8, 1 H); 3.64 (*dd*, *J* = 8.7, 2.5, 1 H); 3.71 (*s*, 3 H); 4.09 (*d*, *J* = 8.4, 1 H); 4.34, 4.40 (*AB*, *J* = 14.0, 2 H); 5.92 (*s*, 1 H); 6.02 (*s*, 1 H); 6.62 (*s*, 1 H); 6.74–6.80 (*m*, 2 H); 7.16, 7.72 (*AA′BB′*, *J* = 7.8, 4 H); 8.84 (br. *s*, 4 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 20.0; 30.9; 34.5; 42.5; 49.1; 50.1; 51.8; 65.4; 67.4; 101.2; 108.5; 110.0; 114.0; 123.1; 126.9; 127.9; 129.1; 129.3; 144.4; 147.4; 166.1; 173.2; 175.9; 177.7. FAB-MS: 985.2 (2, M_2H^+), 630.2 (11), 493.0 (100, MH^+), 338.1 (9). HR-FAB-MS: 493.2083 (MH^+, $C_{26}H_{29}N_4O_6$; calc. 493.2087).

*3-[(1*SR,*3*RS,*3a*SR,*6a*RS*)-3-[4-[Amino(imino)methyl]phenyl]-5-[(1,3-benzodioxol-5-yl)methyl]-1,2,3,3a,4,5,6,6a-octahydro-2-methyl-4,6-dioxopyrrolo[3,4-*c*]pyrrol-1-yl]propanoic Acid Hydrochloride* ((±)-**49**). Methyl ester (±)-**58** was dissolved in methanolic 2M KOH soln. and stirred for 24 h. The mixture was acidified to pH 0 with 1N HCl and evaporated *in vacuo*. The residue was suspended in EtOH, the precipitated KCl filtered off, and the filtrate concentrated *in vacuo*. The crude product was redissolved in very little EtOH and precipitated with Et_2O to provide (±)-**49** (36 mg, 74%). Colorless solid. M.p. >170° (dec.). IR (KBr): 3070, 1724, 1679, 1491, 1445, 1251, 1036. ^{1}H-NMR (200 MHz, CD_3OD): 1.47–1.67 (*m*, 2 H); 2.44–2.55 (*m*, 2 H); 2.78 (*s*, 3 H); 3.72–3.82 (*m*, 2 H); 3.90–3.97 (*m*, 1 H); 4.12 (*d*, *J* = 6.5, 1 H); 4.17, 4.19 (*AB*, *J* = 7.2, 2 H); 5.91, 5.92 (*AB*, *J* = 0.9, 2 H); 6.53 (*d*, *J* = 7.8, 1 H); 6.65 (*d*, *J* = 7.8, 2 H); 7.66, 7.81 (*AA′BB′*, *J* = 8.4, 4 H). ^{13}C-NMR (75 MHz, CD_3OD): 26.2; 30.4; 36.5; 43.9; 51.7; 52.9; 65.8; 73.0; 102.7; 109.2; 122.7; 130.1; 130.2; 130.9; 133.3; 137.4; 148.5; 149.3; 167.7; 171.7; 172.5; 175.9. FAB-MS: 525.0 (65), 497.0 (98), 477.9 (100, M^+), 338.2 (19). HR-FAB-MS: 479.1932 (MH^+, $C_{25}H_{27}N_4O_6$; calc. 479.1930).

*3-[(1*SR,*3*RS,*3a*SR,*6a*RS*)-5-[(1,3-Benzodioxol-5-yl)methyl]-3-(4-cyanophenyl)-1,2,3,3a,4,5,6,6a-octahydro-2-methyl-4,6-dioxopyrrolo[3,4-*c*]pyrrol-1-yl]-*N*-(benzyloxy)propanamide* ((±)-**60**). A 2M soln. of $AlMe_3$ in PhMe (0.25 ml, 0.5 mmol) was slowly added to a suspension of $BnONH_2 \cdot HCl$ (78 mg, 0.5 mmol) in dry CH_2Cl_2 (1 ml) at 0°. After stirring the mixture for 1 h at r.t., (±)-**57** (130 mg, 0.27 mmol) in dry CH_2Cl_2 (1 ml) was added at 0°, and the resulting soln. was stirred at r.t. for 20 h. Subsequently, 2N HCl was added carefully, followed by neutralization with sat. aq. $NaHCO_3$ soln. and extraction with CH_2Cl_2. The org. phase was dried (Na_2SO_4) and evaporated *in vacuo*. The crude product was purified by CC (hexane/AcOEt/Et_3N 25:74:1) to afford (±)-**60** (36 mg, 24%). Colorless Solid. M.p. 170–175°. IR ($CHCl_3$): 3005, 2231, 1705, 1504, 1493, 1447, 1400, 1371. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.53–1.65 (*m*, 2 H); 2.07–2.15 (*m*, 2 H); 2.09 (*s*, 3 H); 2.95 (*d*, *J* = 7.8, 1 H); 3.40 (*dd*, *J* = 8.1, 7.8, 1 H); 3.60 (*m*, 1 H); 4.05 (*d*, *J* = 8.1, 1 H); 4.33, 4.42 (*AB*, *J* = 13.7, 2 H); 4.93 (*s*, 2 H); 5.96, 6.01 (*AB*, *J* = 0.9, 2 H); 6.73–6.80 (*m*, 3 H); 7.05, 7.43 (*AA′BB′*, *J* = 8.1, 4 H); 7.33–7.42 (*m*, 5 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 18.7; 29.5; 34.1; 42.0; 48.6; 49.6; 65.1; 67.2; 100.8; 107.7; 109.7; 111.3; 118.4; 122.7; 128.2; 128.9; 131.7; 142.2; 147.2; 174.7; 177.6. FAB-MS: 1133.2 (1, M_2H^+), 567.1 (100, MH^+), 459.1 (37), 135.0 (35, [piperonyl]$^+$). HR-FAB-MS: 567.2242 (MH^+, $C_{32}H_{31}N_4O_6$; calc. 567.2243).

*3-((1*SR,*3*RS,*3a*SR,*6a*RS*)-3-[4-[Amino(imino)methyl]phenyl]-5-[(1,3-benzodioxol-5-yl)methyl]-1,2,3,3a,4,5,6,6a-octahydro-2-methyl-4,6-dioxopyrrolo[3,4-*c*]pyrrol-1-yl)-*N*-(benzyloxy)propanamide Hydrochloride* ((±)-**59**). *General Procedure C*, starting from (±)-**60**, gave (±)-**59** in 21% yield. Colorless solid. M.p. 90–100°. IR (KBr): 3146, 1772, 1700, 1490, 1446, 1402, 1371, 1340, 1248. ^{1}H-NMR (300 MHz, CD_3OD): 1.54–1.65 (*m*, 1 H); 2.09 (*s*, 3 H); 2.12–2.20 (*m*, 3 H); 3.16 (*d*, *J* = 8.1, 1 H); 3.53–3.61 (*m*, 2 H); 4.17 (*d*, *J* = 9.3, 1 H); 4.33, 4.44 (*AB*, *J* = 14.0, 2 H); 4.89 (*s*, 2 H); 5.95, 5.98 (*AB*, *J* = 0.9, 2 H); 6.72–6.80 (*m*, 3 H); 7.19, 7.54 (*AA′BB′*, *J* = 7.8, 4 H); 7.31–7.33 (*m*, 3 H); 7.46–7.47 (*m*, 2 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 21.4; 30.7; 34.9; 43.3; 50.6; 51.7; 67.0; 68.9; 79.2; 102.8; 109.3; 110.8; 111.1; 124.2; 129.2; 129.7; 129.8; 130.5; 130.7; 131.5; 137.4; 146.3; 149.1; 149.3; 168.8; 172.4; 178.0; 180.7. FAB-MS: 1167.0 (2, M_2H^+), 584.2 (100, MH^+), 476.2 (9), 397.1 (8). HR-FAB-MS: 584.2509 (MH^+, $C_{32}H_{34}N_5O_6$; calc. 584.2509).

Additionally, ester (±)-**58** was isolated in 31% yield.

*3-((1*SR,*3*RS,*3a*SR,*6a*RS*)-3-[4-[Amino(imino)methyl]phenyl]-5-[(1,3-benzodioxol-5-yl)methyl]-1,2,3,3a,4,5,6,6a-octahydro-2-methyl-4,6-dioxopyrrolo[3,4-*c*]pyrrol-1-yl)-*N*-hydroxypropanamide Hydrochloride* ((±)-**50**) Amide (±)-**59** (50 mg, 0.08 mmol) was dissolved in MeOH (1 ml), and Pd/C (10%, 5 mg) was added. The mixture was stirred under H_2 (1 atm) for 7 h at r.t., filtered over *Celite*, and evaporated *in vacuo* to give (±)-**50** (44 mg, 99%). Colorless solid. M.p. >160° (dec.). IR (KBr): 3385, 1772, 1700, 1540, 1490, 1446, 1403, 1371, 1342, 1248. ^{1}H-NMR (300 MHz, CD_3OD): 1.55–1.72 (*m*, 1 H); 2.12 (*s*, 3 H); 2.13–2.31 (*m*, 3 H); 3.26–3.30 (*m*, 1 H); 3.61–3.64 (*m*, 2 H); 4.19 (*d*, *J* = 9.0, 1 H); 4.33, 4.43 (*AB*, *J* = 14.0, 2 H); 5.95, 5.98 (*AB*, *J* = 0.9, 2 H); 6.71 (*s*, 1 H); 6.78 (*s*, 2 H); 7.20, 7.56 (*AA′BB′*, *J* = 7.8, 4 H). ^{13}C-NMR (75 MHz, CD_3OD): 21.4; 30.6; 34.9; 43.2; 50.5; 51.6; 67.0; 68.8; 102.6; 109.1; 110.0; 110.9; 124.0; 128.9; 130.3; 131.3; 146.0; 148.8; 149.1; 168.8; 177.6; 180.5. FAB-MS: 987.2 (2, M_2H^+), 494.0 (100, MH^+), 358.0 (21), 328.9 (35). HR-FAB-MS: 494.2031 (MH^+, $C_{25}H_{28}N_5O_6$; calc. 494.2040).

*(3a*S,*4*R,*7*R,*8a*S,*8b*R*)- and (3a*R,*4*S,*7*R,*8a*R,*8b*S*)-2-[(1,3-Benzodioxol-5-yl)methyl]-4-(4-bromophenyl)-2,3,3a,4,5,6,7,8,8a,8b-decahydro-7-hydroxy-1*H*-pyrrolo[3,4-*a*]pyrrolizin-1,3-dione* (**62b**). *General Procedure A*, starting from **7**, **51**, and **63**, gave **62a**/**62b** as a 1:1 mixture, which precipitated from AcOEt as mixed crystals. An additional isomer was obtained with 24% yield.

Data of **62a**/**62b**: Yield: 137 mg (28%). Reddish crystals. M.p. 160°. IR ($CHCl_3$): 3039, 1705, 1504, 1490, 1446, 1400, 1343. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.58–1.60 (*m*, 1 H); 1.77–1.98 (*m*, 3 H); 2.04–2.12 (*m*, 1 H); 2.53–2.62 (*m*, 1 H); 2.68 (*d*, *J* = 14.0, 1 H); 2.78 (*dd*, *J* = 13.7, 2.8, 1 H); 2.93–3.03 (*m*, 2 H); 3.25 (*d*, *J* = 8.1, 1 H); 3.33 (*dd*, *J* = 8.1, 0.9, 1 H); 3.46 (*dd*, *J* = 8.7, 8.1, 1 H); 3.57 (*dd*, *J* = 9.0, 8.1, 1 H); 3.82 (*dd*, *J* = 9.3, 8.1, 1 H);

3.97 (d, J = 8.7, 1 H); 4.08–4.14 (m, 1 H); 4.42–4.43 (m, 4 H); 4.60 (br. s, 2 H); 4.71 (d, J = 9.0, 1 H); 5.95–5.97 (m, 4 H); 6.70–6.80 (m, 6 H); 7.06–7.10 (m, 4 H); 7.35–7.41 (m, 4 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 40.1; 40.8; 42.3; 48.5; 49.7; 50.4; 50.5; 60.3; 61.5; 66.0; 67.4; 68.9; 70.1; 72.7; 75.0; 101.3; 108.3; 109.8; 121.8; 122.0; 122.9; 129.7; 129.9; 130.1; 131.5; 131.6; 136.9; 137.2; 147.6; 147.9; 175.5; 177.9. FAB-MS: 970.1 (7, M_2H^+), 484.5 (100, M^+), 338.0 (6), 135.0 (34, [piperonyl]$^+$). Anal. calc. for $C_{23}H_{21}BrN_2O_5$ (485.34): C 56.92, H 4.36, N 5.77, Br 16.46; found: C 57.01, H 4.46, N 5.57, Br 16.48. X-Ray: see *Fig. 10*.

X-Ray Crystal Structures. Compound (±)-**15c**. X-Ray crystal data for $C_{29}H_{25}N_3O_2$ (M_r 447.52): monoclinic space group $P2_1/c$, D_c = 1.273 g cm^{-3}, Z = 4, a = 15.258(8), b = 16.407(11), c = 9.394(4) Å, β = 96.87(4)°, V = 2335(2) Å^3, MoK_α radiation, λ = 0.7107 Å, 1.83° ≤ θ ≤ 20.04°, 2191 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 $R(F)$ = 0.0332, $wR(F^2)$ = 0.0668 for 308 parameters and 1304 reflections with $I > 2\sigma(I)$. *Cambridge Crystallographic Data Centre* Deposition No. CCDC-177643.

Compound (±)-**19a**. X-Ray crystal data for $C_{28}H_{25}N_3O_2$ (M_r 453.5): triclinic space group $P\bar{1}$, D_c = 1.238 g cm^{-3}, Z = 2, a = 10.524(9), b = 10.644(13), c = 11.127(7) Å, α = 109.90(8), β = 92.83(6), γ = 92.69(9)°, V = 1168(2) Å^3, CuK_α radiation, λ = 1.5418 Å, 4.22° ≤ 2θ ≤ 50.00°, 2392 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 $R(F)$ = 0.0648, $wR(F^2)$ = 0.1797 for 301 parameters and 2111 reflections with $I > 2\sigma(I)$. *Cambridge Crystallographic Data Centre* Deposition No. CCDC-177644.

Compound (±)-**25**. X-Ray crystal data for $C_{28}H_{29}BrN_2O_2$ (M_r 505.44): orthorhombic space group *Pbca*, D_c = 1.376 g cm^{-3}, Z = 8, a = 12.204(5), b = 17.055(13), c = 23.45(2) Å, V = 4881(6) Å^3, MoK_α radiation, λ = 0.7107 Å, 1.74° ≤ θ ≤ 20.05°, 2269 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 $R(F)$ = 0.0359, $wR(F^2)$ = 0.0670 for 299 parameters and 944 reflections with $I > 2\sigma(I)$. *Cambridge Crystallographic Data Centre* Deposition No. CCDC-177645.

Compound (±)-**54d**. X-Ray crystal data for $C_{24}H_{19}N_3O_5$ (M_r 429.42): monoclinic space group $P2_1/c$, D_c = 1.379 g cm^{-3}, Z = 4, a = 11.748(10), b = 23.23(3), c = 7.593(8) Å, β = 93.82(8)°, V = 2068(4) Å^3, CuK_α radiation, λ = 1.5418 Å, 3.77° ≤ θ ≤ 50.00°, 2107 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 $R(F)$ = 0.0664, $wR(F^2)$ = 0.1661 for 290 parameters and 1322 reflections with $I > 2\sigma(I)$. *Cambridge Crystallographic Data Centre* Deposition No. CCDC-177646.

Mixed Crystal of **62a** *and* **62b**. X-Ray crystal data for $C_{23}H_{21}BrN_2O_5 \cdot C_{23}H_{21}BrN_2O_5$ (M_r 970.66): monoclinic space group $P2_1$, D_c = 1.583 g cm^{-3}, Z = 2, a = 10.744(10), b = 17.476(12), c = 10.856(8) Å, β = 92.30(7)°, V = 2037(3) Å^3, MoK_α radiation, λ = 0.7107 Å, 1.88° ≤ θ ≤ 20.04°, 2003 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 $R(F)$ = 0.0341, $wR(F^2)$ = 0.0660 for 385 parameters and 1255 reflections with $I > 2\sigma(I)$. *Cambridge Crystallographic Data Centre* Deposition No. CCDC-177647.

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) 336033; e-mail: deposit@ccdc.cam.ac.uk).

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Received January 30, 2002