Enantiomerically Pure Thrombin Inhibitors for Exploring the Molecular-Recognition Features of the Oxyanion Hole

by **Kaspar Schärer**, **Martin Morgenthaler**, **Paul Seiler**, and **François Diederich***

Laboratorium für Organische Chemie der Eidgenössischen Technischen Hochschule, ETH-Hönggerberg, HCI, CH-8093 Zürich (e-mail: diederich@org.chem.ethz.ch)

and

David W. Banner*, **Thomas Tschopp**, and **Ulrike Obst-Sander**

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

A new route *via* intermediate *pseudoenantiomers* was developed to synthesize racemic and enantiomerically pure new non-peptidic inhibitors of thrombin, a key serine protease in the blood-coagulation cascade. These ligands feature a conformationally rigid tricyclic core and are decorated with substituents to fill the major binding pockets (distal (D), proximal (P), selectivity (S1), and oxyanion hole) at the thrombin active site (*Fig. 1*). The key step in the preparation of the new inhibitors is the 1,3-dipolar cycloaddition between an optically active azomethine ylide, prepared *in situ* from L-(4*R*)-hydroxyproline and 4-bromobenzaldehyde, and *N*-piperonylmaleimide (*Scheme 1*). According to this protocol, tricyclic imide (compounds (±)-**15**-(±)-**18** and (+)-**21**) and lactam (compound (+)-**2**) inhibitors with OH or ether substituents at C(7) in the proline-derived pyrrolidine ring were synthesized to specifically explore the binding features of the oxyanion hole (*Schemes 2–4*). Biological assays (*Table*) showed that the polar oxyanion hole in thrombin is not suitable for the accommodation of bulky substituents of low polarity, thereby confirming previous findings. In contrast, tricyclic lactam (+)-**2** ($K_i = 9$ nM, K_i(trypsin)/K_i(thrombin) = 1055) and tricyclic imide (+)-**21** ($K_i = 36$ nM, K_i(trypsin)/K_i(thrombin) = 50) with OH-substituents at the (*R*)-configured C(7)-atom are among the most-potent and most-selective thrombin inhibitors in their respective classes, prepared today. While initial modeling predicted H-bonding between the OH group at C(7) in (+)-**2** and (+)-**21** with the H_2O molecule bound in the oxyanion hole (*Fig. 2*), the X-ray crystal structure of the complex of (+)-**21** (*Fig. 7,b*) revealed a different interaction for this group. The propionate side chain of Glu192 undergoes a conformational change, thereby re-orienting towards the OH group at C(7) under formation of a very short ionic H-bond (O–H···$^-$OOC; d(O···O) = 2.4 Å). The energetic contribution of this H-bond, however, is negligible, due to its location on the surface of the protein and the unfavorable conformation of the H-bonded propionate side chain.

1. Introduction. – The globular serine protease thrombin from the blood-coagulation cascade continues to be an important pharmaceutical target for the prevention and treatment of thrombotic disorders [1][2]. Early crystal structures revealed a well-defined active site [3][4], and, accordingly, structure-based design has been intensively applied to the generation of new inhibitors of this enzyme [5–7] (for some recent reports, see [8]). By a *de novo* design strategy, we developed a series of high-affinity inhibitors with a tricyclic core such as lactam (+)-**1** (*Fig. 1*; inhibitory constant $K_i = 7$ nM, selectivity over the digestive serine protease trypsin K_i(trypsin)/K_i(thrombin) = 740) and confirmed the binding modes of several derivatives at the thrombin active site by crystal-structure analysis [9][10]. This analysis revealed that the active site of thrombin has limited conformational flexibility, thereby making it an outstanding receptor for biological molecular-recognition studies [11]. As a result of

the rigidity of the active site, related ligands with functional-group mutations form complexes of similar geometry, allowing direct correlation of measured changes in the complexation free enthalpy with the contributions of individual ligand substituents. Previous investigations with this class of tricyclic inhibitors addressed in greater detail the molecular-recognition features of the spacious hydrophobic D-pocket (D: distal) [9a,b][10][12], the tight hydrophobic P-pocket (P: proximal) [9b][10], and the selectivity pocket S1 (*Fig. 1*) [9b]. Most recently, an extensive fluorine scan of these inhibitors was undertaken by systematically replacing one or more H-atoms with F-atoms to map the fluorophilicity/fluorophobicity of the thrombin active site [13]. In contrast, the molecular-recognition properties of the oxyanion hole remain rather unexplored [9b]. In particular, we were intrigued by the possibility to bind to the H_2O molecule found in the oxyanion hole in the crystal structure of (+)-**1**, H-bonded to the N–H residues of Gly193 and Ser195. Molecular modeling with MOLOC [14] suggested that substitution of the tricyclic core in position 7 (*Fig. 1*) with a H-bond donor center would be particularly suitable for bonding to the H_2O molecule. According to this analysis, the OH group at (*R*)-configured C(7) in inhibitor (+)-**2** could form a short intermolecular H-bond ($d(O\cdots O) = 2.9$ Å) to the bound H_2O molecule (*Fig. 2*). Here, we describe the synthesis and biological activity of a series of new tricyclic thrombin inhibitors bearing substituents of different size and polarity at C(7) to investigate the molecular-recognition properties of the oxyanion hole in thrombin.

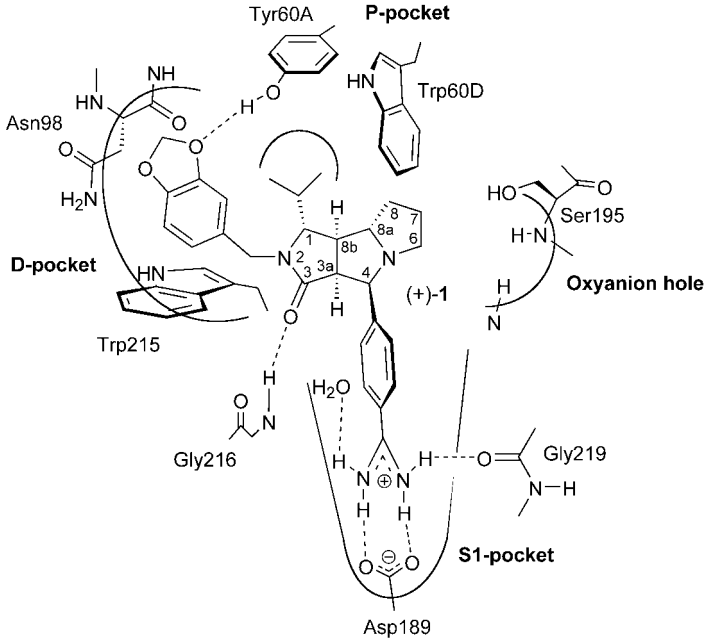


Fig. 1. *Inhibitor (+)-***1** *in the active site of thrombin, according to crystal-structure analysis* [9b][10]

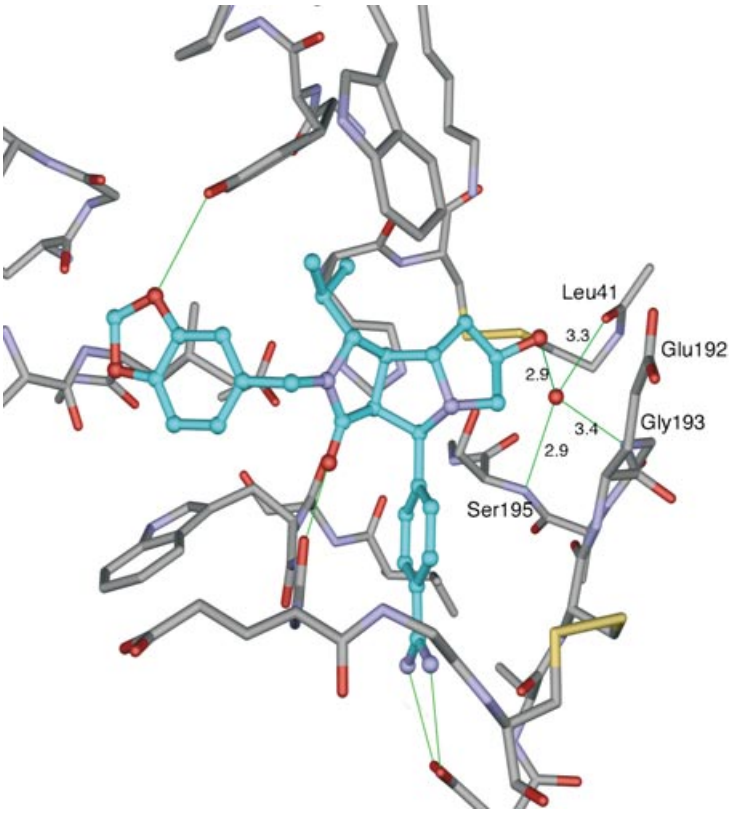
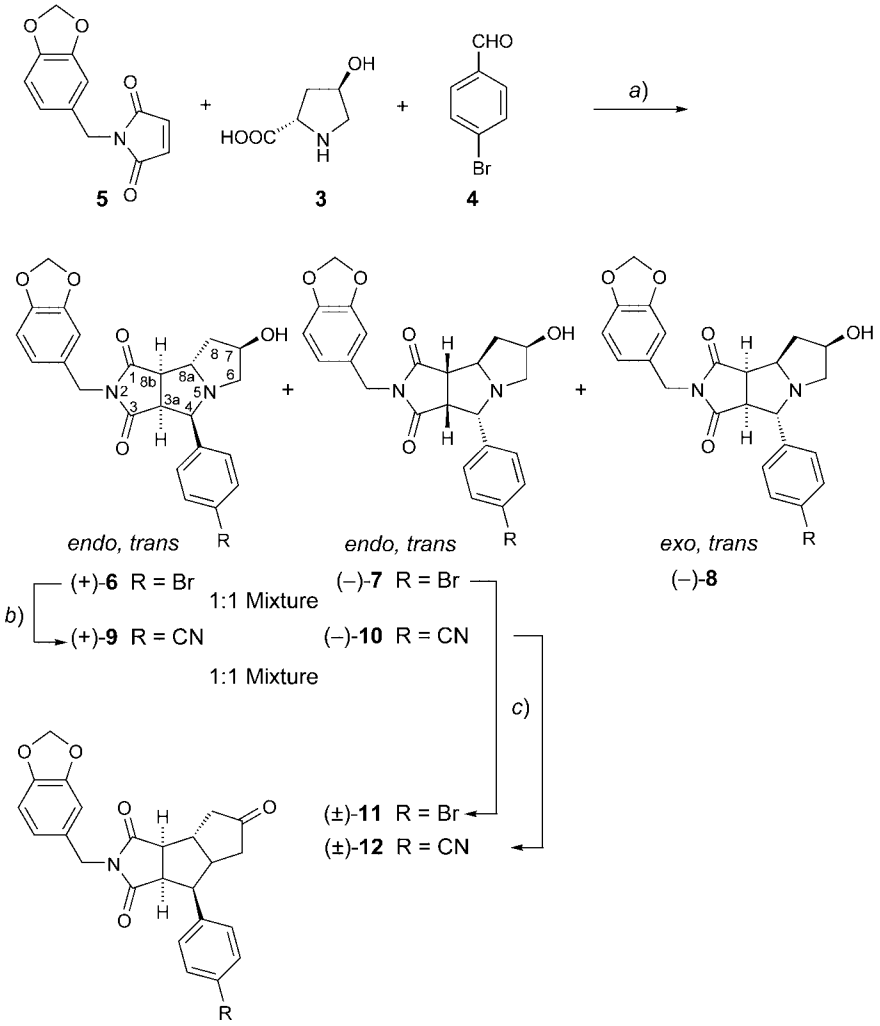


Fig. 2. *Molecular model of (+)-***2** *complexed to thrombin, showing the predicted H-bond to the H_2O molecule bound in the oxyanion hole.* This model was obtained starting from the crystal structure of (+)-**1** bound to thrombin, attachment of the OH group to (*R*)-configured C(7), and minimization of the inhibitor in the active site, while keeping the protein conformation with the bound H_2O molecule unchanged. Color code: C-skeleton of (+)-**2**: *cyan*, C-skeleton of the protein: *grey*, O-atoms: *red*, N-atoms: *blue*, S-atoms: *yellow*.

2. Results and Discussion. – 2.1. *Synthesis of Racemic Tricyclic Imide Inhibitors.* A series of tricyclic imide inhibitors was prepared starting with the 1,3-dipolar cycloaddition between the azomethine ylide, formed *in situ* from L-(4*R*)-hydroxyproline (**3**) and 4-bromobenzaldehyde (**4**), and *N*-piperonylmaleimide (**5**) in DMF [9][12][15] (*Scheme 1*). The desired *endo,trans*-derivatives (+)-**6** and (−)-**7** were obtained as an inseparable 1:1 mixture in 34% yield (for their separation, see *Sect. 2.2* below) together with *exo,trans*-isomer (−)-**8** as a major side product (35% yield; *exo* and *endo* refer to the orientation of the 4-bromophenyl substituent at C(4) with respect to the bicyclic perhydropyrrolo[3,4-*c*]pyrrole scaffold, and *cis* and *trans* to the position of this 4-bromophenyl ring with respect to the configuration of C(8a) at the fusion of the two pentagons in the perhydropyrrolizine bicycle). The *exo*-diastereoisomer (−)-**8** was separated by column chromatography, and its relative configuration was assigned on the basis of 1D-NOE difference ^{1}H-NMR spectra (NOE = nuclear *Overhauser* effect). As discussed in a preliminary way in a previous paper [12], the *endo*-diastereoisomers

Scheme 1. *Synthesis of the Ketones (±)-***11** *and (±)-***12**



a) DMF, 85°, 24 h; 17% of (+)-**6**, 17% of (−)-**7**, 35% of (−)-**8**. *b*) CuCN, DMF, Δ, 18 h; 39% of (+)-**9**, 39% of (−)-**10**. *c*) 1. Me_2SO, $(COCl)_2$, −60°, 30 min; 2. NEt_3, 0°, 3 h; 60% of (±)-**11**; 66% of (±)-**12**. DMF = Dimethylformamide.

(+)-**6** and (−)-**7** can be viewed as *pseudoenantiomers*, differing at only one stereogenic center (for pseudoenantiomerism in the cinchona alkaloid family, see [16]). They cannot be separated by column chromatography and crystallize together, forming a 1:1 mixed crystal whose crystal structure was solved [12], In fact, the two compounds (for the synthesis of the pure diastereoisomers, see *Sect. 2.2* below) even show optical rotational angles of opposite sign yet of identical magnitude: $[\alpha]_D^{25} = +169.4$ ($c = 1.00$, $CHCl_3$) for (+)-**6** and -169.4 ($c = 1.00$, $CHCl_3$) for (−)-**7**.

Br/CN Exchange starting from the 1:1 mixture of (+)-**6** and (−)-**7** provided the corresponding mixture of nitriles (+)-**9** and (−)-**10**. Again, separation by chromatography was not possible, and crystal-structure analysis revealed the formation of 1:1 mixed crystals (space group *P*1). In the crystal lattice, the two diastereoisomers are aligned pairwise and are related by a pseudo-inversion center (*Fig. 3*,*a*). Short intermolecular contacts include H-bonds between the OH group at C(7) (numbering adopted from *Scheme 1*) and the CN group (O···N distances: 3.01 and 3.20 Å, resp.; *Fig. 3*,*b*) as well as π-π stacking between parallel shifted piperonyl rings (shortest C···C distance: 3.67 Å; *Fig. 3*,*c*).88

In view of the inseparabilitity of the *pseudoenantiomeric* bromides (+)-**6**/(−)-**7** and nitriles (+)-**9**/(−)-**10**, the mixtures were transformed by *Swern* oxidation [17] into the racemic ketones (±)-**11** and (±)-**12**, respectively. The structures of (±)-**11** (*Fig. 4*,*a*) and (±)-**12** (*Fig. 4*,*b*), which crystallize both in the space group $P2_1/n$, were confirmed by crystal-structure analyses.

The reduction of ketone (±)-**11** in CH_2Cl_2 proceeded diastereoselectively to give alcohol (±)-**7** as the major product besides alcohol (±)-**6** as the minor one (*Scheme 2*). Correspondingly, reduction of (±)-**12** under the same conditions provided alcohol (±)-**10** as the major and (±)-**9** as the minor product. Model analysis suggested an explanation for the observed diastereoselectivity, showing that the *Re*-face of the trigonal centers (C(7)) in (3a*R*,4*S*,8a*R*,8b*S*)-**11**/**12** (and correspondingly the *Si*-face in (3a*S*,4*R*,8a*S*,8b*R*)-**11**/**12**) is sterically less hindered than the opposite face. Accordingly, by increasing the steric bulk of the reducting agents [18], the diastereoselectivity was enhanced (superhydride (Li[Et_3BH]) at −78°: diastereoisomeric ratio (dr) (±)**7**/(±)-**6** 77:23; *L-Selectride* (Li[(*sec*-Bu)$_3$BH] at −78°: dr 89:11; *LS-Selectride* (lithium trisiamylborohydride) at −95°: dr 95:5). The diastereoselectivity in the reduction of carbonitrile (±)-**12** was surprisingly lower, with the highest dr ((±)-**10**/(±)-**9**) 81:19 being obtained with *LS-Selectride* at −95°. *O*-Methylation and *O*-benzylation [19] provided methyl ether (±)-**13** and benzyl ether (±)-**14**, respectively, and the relative configurations assigned were confirmed by the crystal-structure analysis of (±)-**14**, which, surprisingly, crystallized with both enantiomers in the non-centrosymmetric space group $P2_12_12_1$ (*Fig. 5*).

The conversion of the carbonitriles (±)-**10**, (±)-**13**, and (±)-**14** to the phenylamidinium salts (±)-**15**, (±)-**16**, and (±)-**17**, respectively, was readily achieved with the *Pinner* reaction [20]. When this transformation was applied to carbonitrile (±)-**12**, the C=O group at C(7) was acetalized, thereby providing the phenylamidinium salt as the remarkably stable *O,O*-acetal (±)-**18**.

2.2. *Synthesis of Enantiomerically Pure Tricyclic Imide Inhibitors.* Whereas the 1:1 mixture of hydroxy derivatives (+)-**6** and (−)-**7** could not be separated, this was possible after (*t*-Bu)Me_2Si protection. The two silylated diastereoisomers (+)-**19** and (−)-**20** were isolated in pure form after column chromatography and subsequently transformed – by deprotection – into the pure *pseudoenantiomers* (+)-**6** and (−)-**7** (*Scheme 3*). Both compounds were converted to the enantiomerically pure carbonitriles (+)-**9** and (−)-**10**. *Pinner* reaction subsequently provided the phenylamidinium inhibitor (+)-**21**, which we hoped would bind to the H_2O molecule in the oxyanion hole of thrombin (*Fig. 2*) with its suitably positioned C(7)−OH group ((−)-**10** was not transformed into the corresponding amidinium salt).

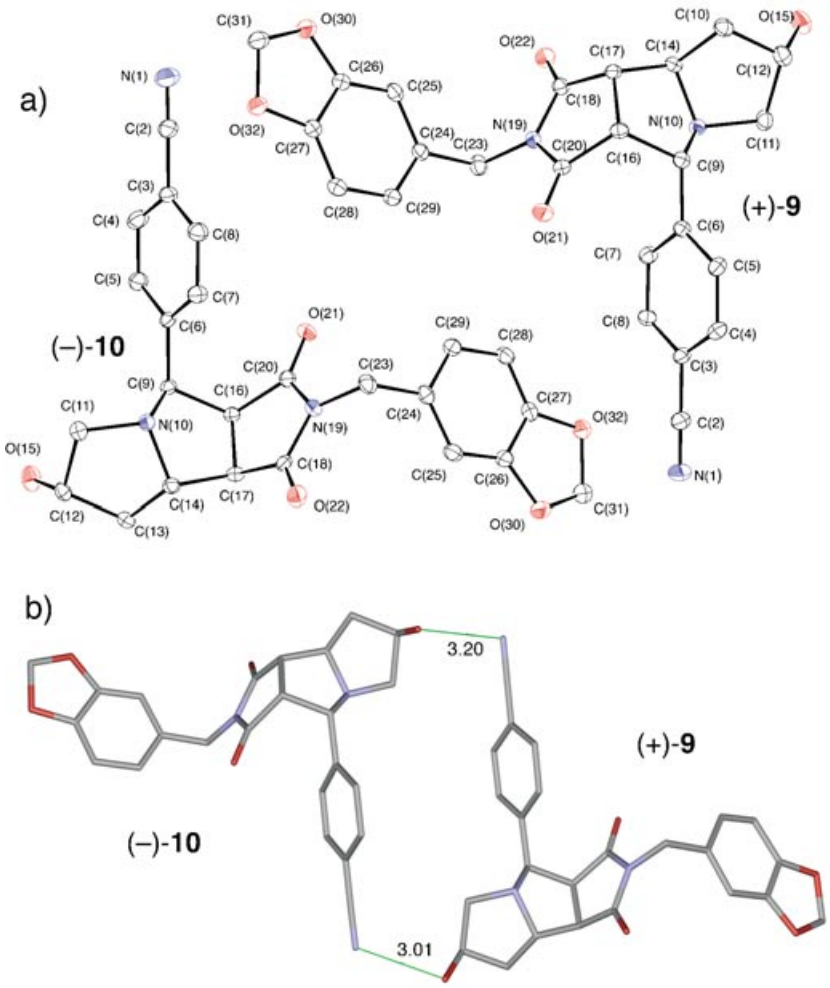


Fig. 3. *X-Ray crystal structure of a 1:1 mixed crystal of (+)-***9** *and (–)-***10**. a) *View on the pairwise alignment of the two diastereoisomers in the crystal lattice.* Arbitrary numbering. Atomic displacement parameters obtained at 173 K are drawn at the 50% probability level. b) *H-Bonding between the two diastereoisomers in the crystal*. Distances in Å. c) *π-π-Stacking observed in stacks of each diastereoisomer* (see next page). Color code: C-skeleton: *grey*, O-atoms: *red*, N-atoms: *blue.*

2.3. *Synthesis of an Optically Active, High-Affinity Tricyclic Lactam Inhibitor.* The preparation of the inhibitor (+)-**2**, with an i-Pr group to favorably fill the P-pocket [9–13], started from silyl-protected (+)-**19**, which was converted in a regio- and stereoselective reduction with superhydride (Li[Et_3BH]) to hydroxy lactam (+)-**22**, presumably bearing the OH group in *exo*-position as observed previously by X-ray analysis [12] (*Scheme 4*).

Silyl deprotection, followed by treatment of the resulting diol with 4-toluenesulfinic acid in the presence of $CaCl_2$, afforded sulfone (+)-**23**, probably by attack at an

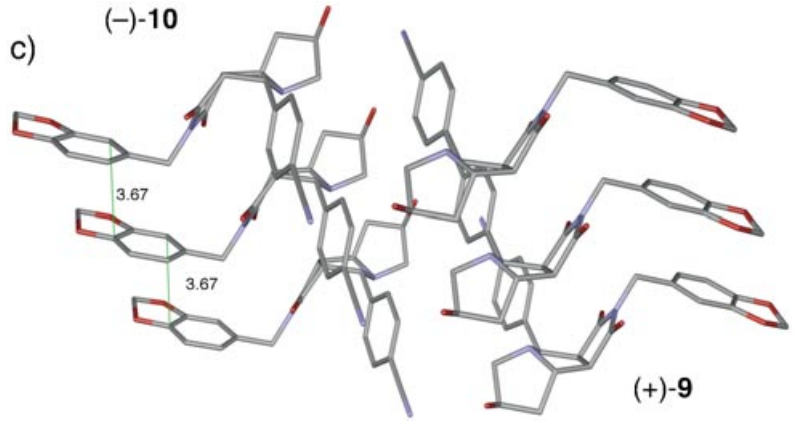


Fig. 3 (cont.)

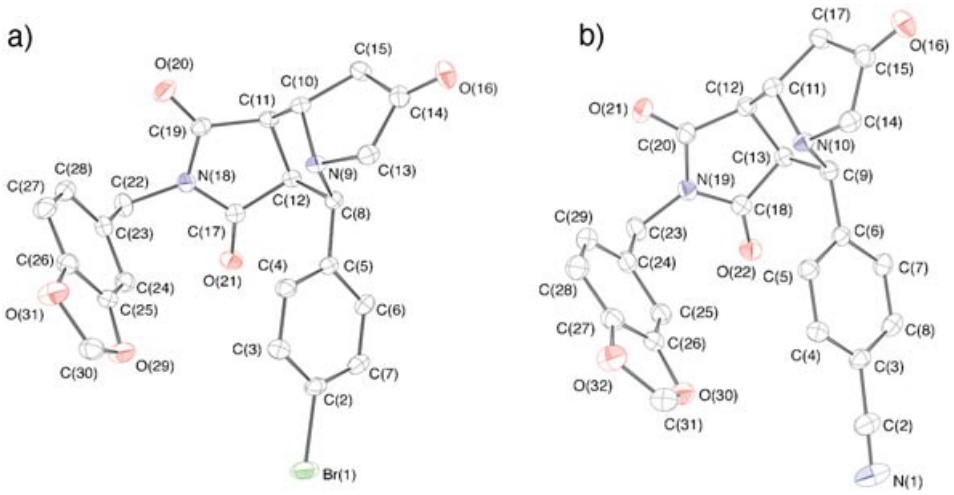
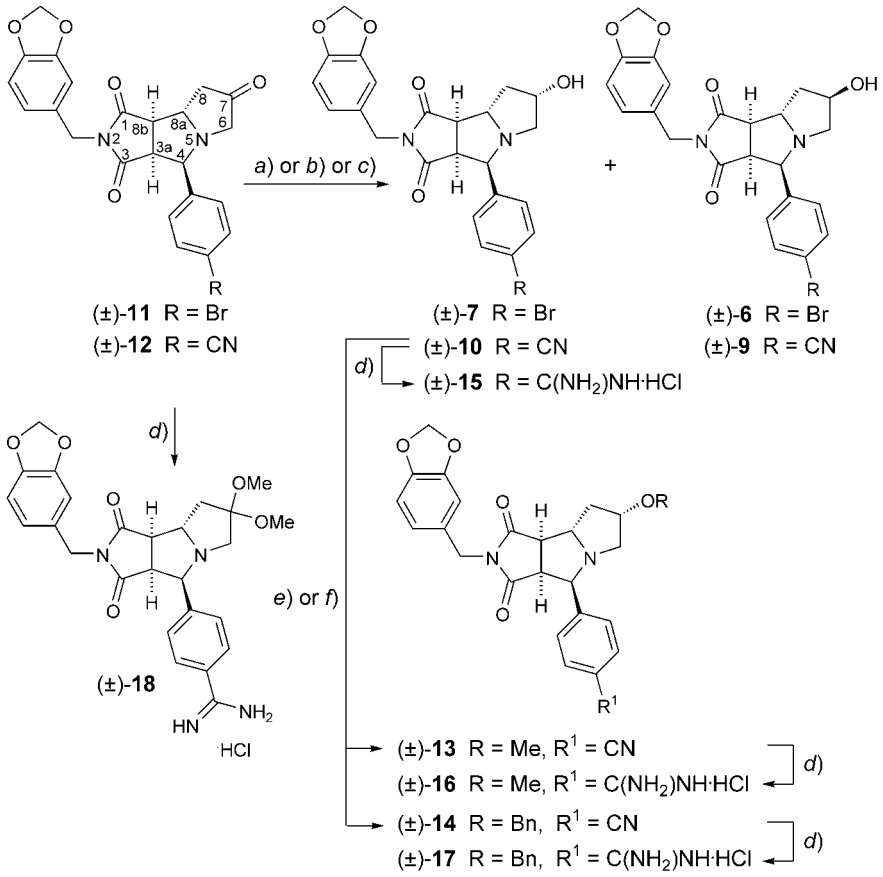


Fig. 4. *X-Ray crystal structures of bromide* (±)-**11** (left) *and nitrile* (±)-**12** (right). Arbitrary numbering. Atomic displacement parameters obtained at 223 K are drawn at the 50% probability level.

intermediately formed acyliminium ion from the less-hindered *exo*-face [9b]. Silyl protection provided (+)-**24**, and subsequent nucleophilic displacement of the arylsulfonyl group according to the protocol ($ZnCl_2$/i-PrMgCl) introduced by *Ley* and co-workers [21] gave – under retention of configuration resulting from attack of the intermediate acyliminium ion from the *exo*-face – the i-Pr derivative (+)-**25**. Silyl deprotection led to (+)-**26**, and X-ray crystal-structure analysis (space group $P2_12_12_1$) confirmed the predicted configuration (*Fig. 6*). The crystal packing shows a short intermolecular H-bond between the C(7)-OH (for numbering, see *Scheme 1*) and the lactam C=O groups of adjacent molecules ($d(O\cdots O) = 2.80$ Å). Br/CN Exchange

Scheme 2. *Synthesis of the Inhibitors (±)-***15** *to (±)-***18**



a) Li[Et_3BH], CH_2Cl_2, −78°, 2.5 h; 70% of (±)-**7**, dr (±)-**7**/(±)-**6** 77:23. *b*) *L-Selectride*, CH_2Cl_2, −78°, 2.5 h; 63% of (±)-**7**; dr 89:11. *c*) *LS-Selectride*, CH_2Cl_2, −78°, 2.5 h; 75% of (±)-**7**; dr 95:5 or *LS-Selectride*, CH_2Cl_2, −95°, 2.5 h; 79% of (±)-**7**; dr 95:5; 69% of (±)-**10**; dr (±)-**10**/(±)-**9** 81:19. *d*) 1. HCl (g), MeOH, $CHCl_3$, 4°, 24 h; 2. NH_3, MeOH, 65°, 3.5 h; 80% of (±)-**15**, 38% of (±)-**16**, 50% of (±)-**17**, 13% of (±)-**18**. *e*) NaH, [15]crown-5, MeI, THF, r.t., 3.5 h; 38% of (±)-**13**). *f*) NaH, [15]crown-5, BnBr, THF, r.t., 2 h; 70% of (±)-**14**. Bn = $PhCH_2$.

((+)-**26** → (+)-**27**) and *Pinner* reaction finally afforded target compound (+)-**2**. All attempted protocols avoiding the rather tedious silyl protection/deprotection steps in the synthesis of (+)-**2** were unsuccessful, providing much lower yields in the individual transformations.

2.4. *Biological Activity and Crystal-Structure Analysis of the Complex between Thrombin and Inhibitor* (±)-**21**. All newly synthesized inhibitors were tested for their activity against thrombin, trypsin, and related enzymes (coagulation factors VIIa and Xa) as previously described [22]. Their potencies were compared with those of the previously described, structurally related inhibitors (+)-**1** and (±)-**28**, lacking the substituent at C(7) [9].

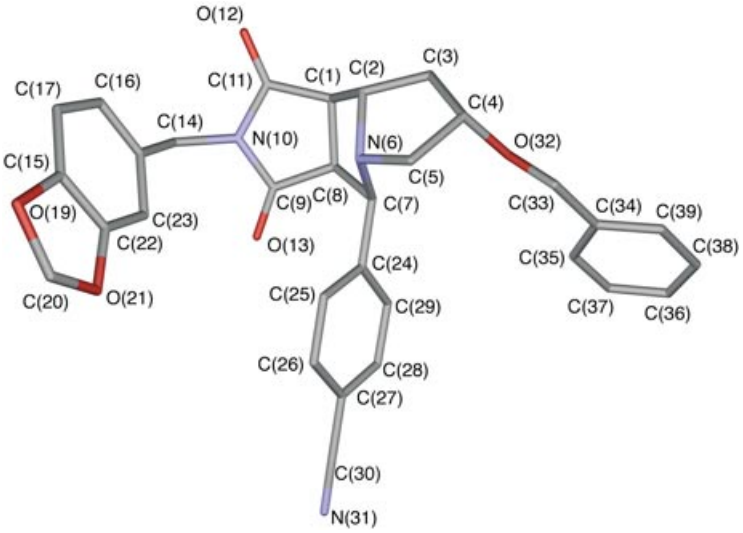


Fig. 5. *X-Ray crystal structure of the carbonitrile (±)-***14**. Arbitrary numbering. Atomic displacement parameters obtained at 222 K are drawn at the 50% probability level.

Several conclusions can be drawn from the data summarized in the *Table:*

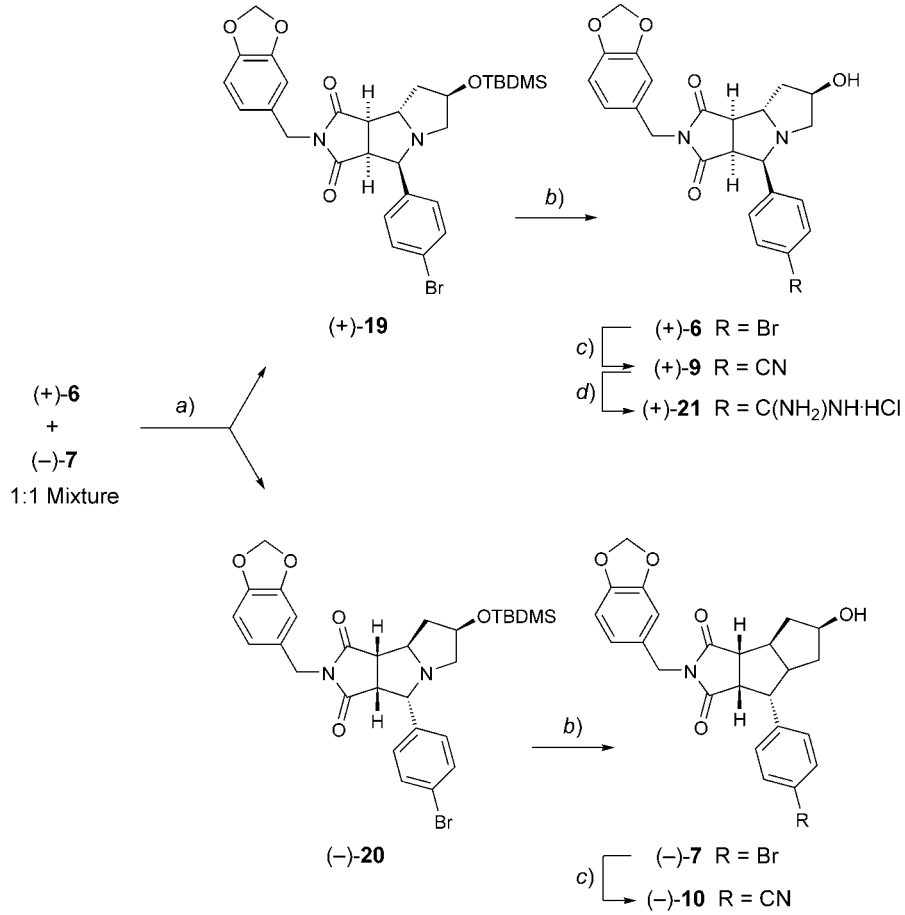
i) The affinity for thrombin is not much altered by the introduction of an OH group at C(7): ligands (+)-**1** (without OH; $K_i = 7$ nM) and (+)-**2** (with OH; $K_i = 9$ nM) display similar activity, and the introduction of the OH group does also not increase the activity at the stage of the imide derivatives ((+)-**21** *vs.* (±)-**28**). The comparison of (±)-**15** ($K_i = 100$ nM) with (+)-**21** ($K_i = 36$ nM) shows that the configuration at C(7) does not play a significant role (similar to (+)-**21**, only the (3a*S*,4*R*,8a*S*,8b*R*)-configured enantiomer of (±)-**15** is active [9].

ii) Introduction of less-polar substituents at C(7) (MeO and BnO in (±)-**16** (K_i 710 nM) and (±)-**17** ($K_i = 1100$ nM), resp.) reduces the activity by a factor of 7–11 as compared with (±)-**15**. The similar activity displayed by (±)-**18** ($K_i = 720$ nM) could suggest that the *O,O*-acetal might actually be stable under the conditions of the assay: a higher activity would be expected for the free ketone.

iii) The introduction of the OH substituents at C(7) increases the selectivity for thrombin over trypsin in both the tricyclic imide and lactam classes of inhibitors. Thus, (+)-**2** is not only one of the most potent thrombin inhibitors in the tricyclic lactam class [9–13], but at K_i(trypsin)/K_i(thrombin) = 1055, it is also one of the most-selective ones. On the other hand, introduction of a larger, less-polar BnO substituent at C(7) lowers not only the binding affinity but also the selectivity ((±)-**17**; $K_i = 1100$ nM, K_i(trypsin)/K_i(thrombin) = 3.6). None of the inhibitors showed any affinity for other serine proteases in the blood-coagulation cascade below the threshold (69 μM) of the assay.

We had started this project with the modeling-supported hypothesis that the OH group at C(7) of the inhibitors could bind to a H_2O molecule bound in the oxyanion hole of thrombin (such a H_2O molecule is not only seen in the complex of (+)-**1** (*Fig. 2*) but also in the complex of (±)-**28** [9a]). To verify this proposal, the X-ray crystal

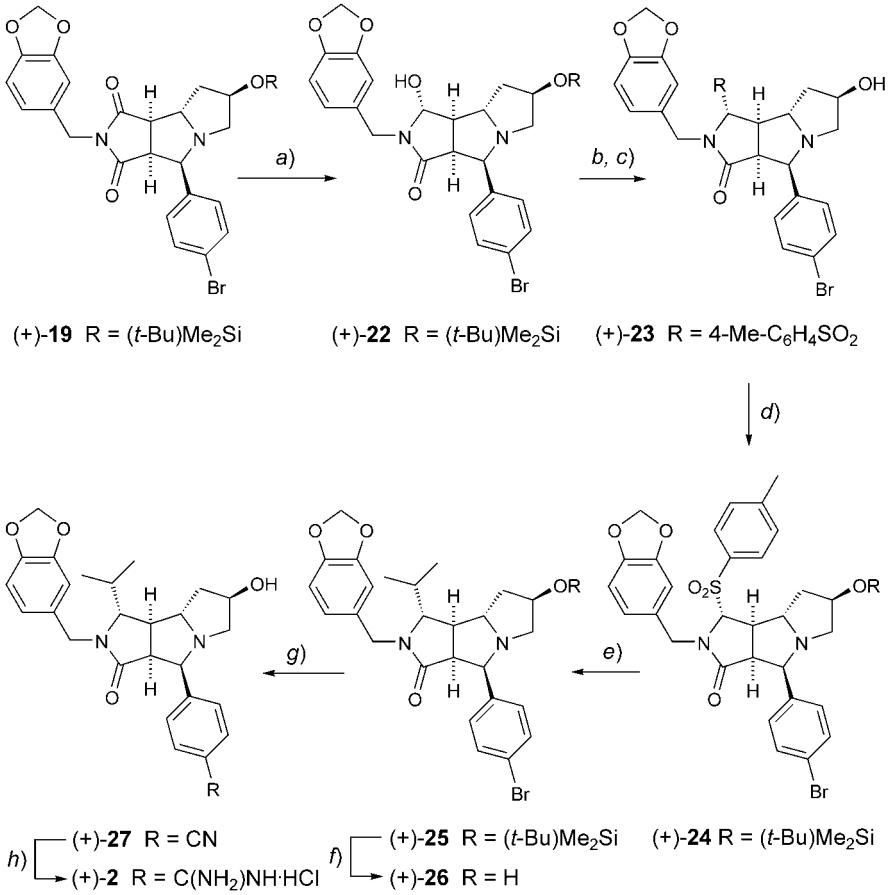
Scheme 3. *Synthesis of the Inhibitor (+)-***21**



a) *t*-Bu)Me_2SiCl, DMAP, CH_2Cl_2, 25°, 16 h; 43% of (+)-**19**); 43% of (−)-**20**. *b*) Bu_4NF, THF, r.t., 1.5 h; 69% of (+)-**6**, 72% of (−)-**7**. *c*) CuCN, DMF, Δ, 18 h; 55% of (+)-**9**; 45% of (−)-**10**. *d*) 1. HCl (g), MeOH, $CHCl_3$, 4°, 24 h; 2. NH_3, MeOH, 65°, 3.5 h; 55%. DMAP = 4-(Dimethylamino)pyridine.

structure of (+)-**21** bound to thrombin was solved at a 1.54-Å resolution. A superimposition of the crystal structures of the complexes of thrombin with (+)-**21** and (+)-**1** (or (±)-**28**, not shown [9a]) proved a nearly identical binding mode for the two inhibitors (*Fig. 7,a*). The conformation of the surrounding protein was also similar with one notable exception. The propionate side chain of Glu192, which, in the complex of (+)-**1** (and in the predicted binding mode for (+)-**2** and (+)-**21**; *Fig. 2*), was pointing away from the proline-derived pyrrolidine ring, is now oriented towards the OH group at C(7) under formation of a very short ionic H-bond (O−H···$^-$OOC; d(O···O) = 2.4 Å; *Fig. 7,b*). An intermolecular interaction between the OH group in (+)-**21** and the H_2O molecule in the oxyanion hole is not observed (measured O···O distance: 4.6 Å). Clearly, the molecular modeling, which did not take into account possible

Scheme 4. *Synthesis of the Inhibitor (+)-***2**



a) Li[Et_3BH], THF, $-78°$, 15 min; 94%. *b*) Bu_4NF, THF, r.t., 1 h. *c*) 4-Me-$C_6H_4SO_2H$, $CaCl_2$, CH_2Cl_2, r.t., 2 d; 75% over 2 steps. *d*) (*t*-Bu)Me_2SiCl, DMAP, CH_2Cl_2, 25°, 16 h; 87%. *e*) (i-Pr)MgCl, $ZnCl_2$, CH_2Cl_2, r.t., 16 h; 79%. *f*) Bu_4NF, THF, r.t., 1 h; 75%. *g*) CuCN, DMF, Δ, 18 h; 55%. *h*) 1. HCl (g), MeOH, $CHCl_3$, 4°, 24 h; 2. NH_3, MeOH, 65°, 3.5 h; 60%.

conformational changes of the protein, such as the move of the Glu192 side chain, was too crude.

Although the ionic H-bond between the OH group of the ligand and the carboxylate of Glu192 is very short ($d(O\cdots O) = 2.4$ Å), the gain in free enthalpy resulting from this additional intermolecular interaction is negligible, as shown by the comparison of the K_i values of (±)-**28** (without OH group) and (+)-**21** (with OH group). Two factors account for the absence of a significant energetic contribution of this short ionic H-bond. First, the conformation of the free propionate side chain (*antiplanar* torsional angle $\theta(C(\alpha)-C-C-C(O_2)) = 168°$) is energetically more favorable than the conformation of the H-bonded one (*gauche* torsional angle $\theta(C(\alpha)-C-C-C(O_2)) = 61°$). Second, the observed H-bonding occurs rather at the

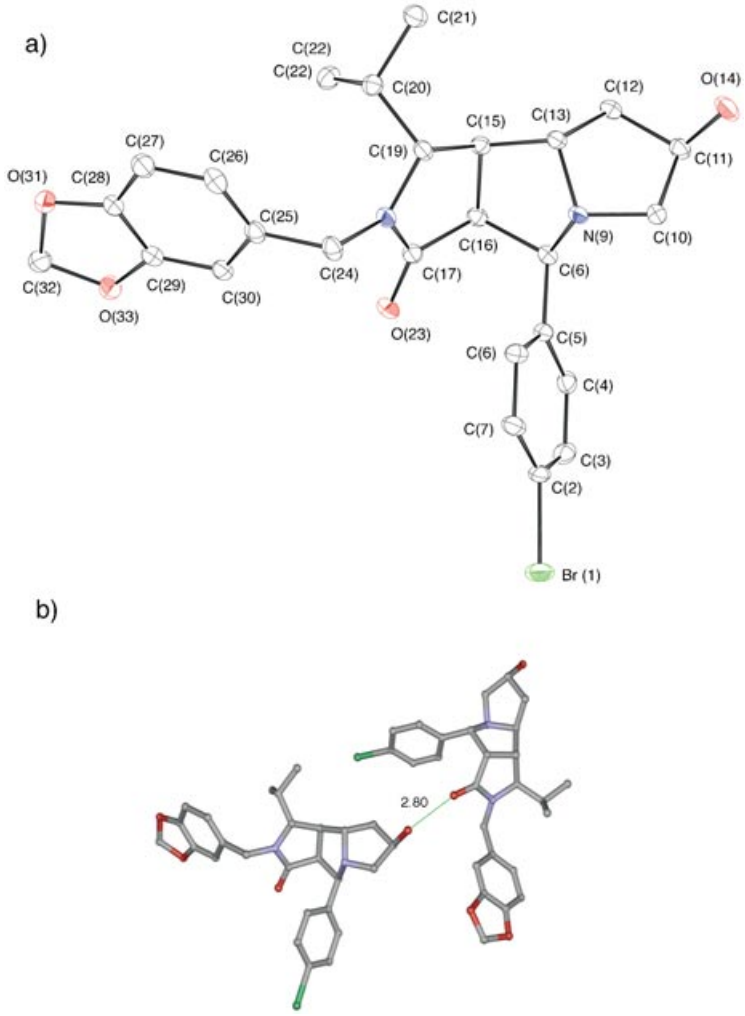


Fig. 6. a) *X-Ray crystal structure of (+)-***26**. Arbitrary numbering. Atomic displacement parameters obtained at 163 K are drawn at the 50% probability level. b) *Crystal packing of (+)-***26**. Distance in Å. Color code: see caption to *Fig. 3*; Br-atoms: *green*.

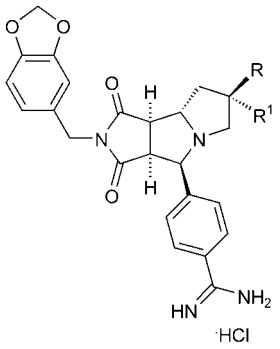
surface of the protein, meaning that the carboxylate of Glu192 exchanges favorable H-bonds to surrounding H_2O molecules for the intermolecular H-bond to the ligand.

3. Conclusions. – A new synthesis to enantiomerically pure thrombin inhibitors *via* intermediate *pseudoenantiomers* was developed. This synthesis starts with the 1,3-dipolar cycloaddition of the azomethine ylide, formed *in situ* from L-(4*R*)-hydroxyproline and 4-bromobenzaldehyde, and *N*-piperonylmaleimide, and provided access to (+)-**2**, one of the most-potent and most-selective tricyclic lactam inhibitors of thrombin prepared today ($K_i = 9$ nM, K_i(trypsin)/K_i(thrombin) = 1055). While the initial model-

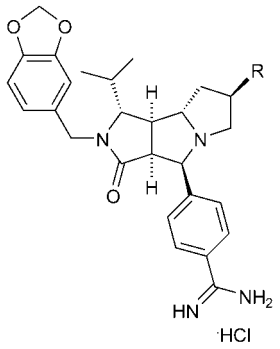
Table. *Activities of the New Tricyclic Thrombin Inhibitors and Selectivities with Respect to Trypsin*

Inhibitor	K_i [nM][a])	Selectivity[b])
(±)-**28**[c])[d])	90	7.8
(+)-**1**[c])	7	760
(+)-**2**	9	1055
(±)-**15**[d])	100	33
(±)-**16**[d])	710	35
(±)-**17**[d])	1100	3.6
(±)-**18**[d])	720	32
(+)-**21**	36	50

[a]) The uncertainty of the measured K_i values is ±20%. [b]) K_i(trypsin)/K_i(thrombin). [c]) From [9b]. [d]) Only the (3a*S*,4*R*,8a*S*,8b*R*)-configured enantiomer is bound, as determined from the crystal-structure analysis [9].



(±)-**15** R = H, R^1 = OH
(±)-**16** R = H, R^1 = MeO
(±)-**17** R = H, R^1 = BnO
(±)-**18** R = R^1 = MeO
(+)-**21** R = OH, R^1 = H
(±)-**28** R = R^1 = H



(+)-**1** R = H
(+)-**2** R = OH

ing predicted H-bonding between the OH group at C(7) in (+)-**2** and the tricyclic imide analog (+)-**21** with the H_2O molecule that is seen in the oxyanion hole of several thrombin complexes (*e.g.*, of (+)-**1** and (±)-**28**), the X-ray crystal structure of the complex of (+)-**21** (K_i = 36 nM, K_i(trypsin)/K_i(thrombin) = 50) revealed a different, more-favorable internal solvation of this OH group by the enzyme. It was found that the propionate side chain of Glu192 undergoes a conformational change, thereby re-orienting towards the OH group at C(7) under formation of a very short ionic H-bond (O–H···$^-$OOC; d(O···O) = 2.4 Å). The incremental free-enthalpy contribution of this very short, ionic H-bond is negligible as shown by the comparison of the K_i values for (±)-**28** (without OH group) and with K_i (+)-**21** (with OH group). This can be explained by the less-favorable conformation of the H-bonded propionate side chain of Glu192 and by its location close to the solvated surface of the protein. Investigations with a series of inhibitors featuring bulkier, less-polar substituents at C(7) confirmed

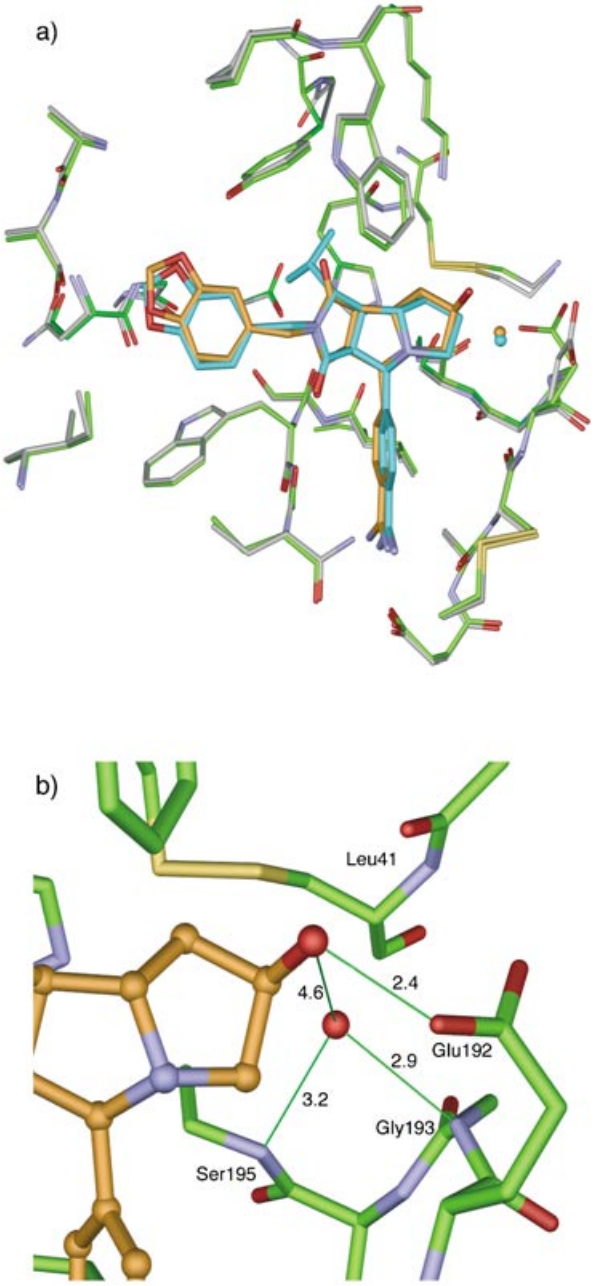


Fig. 7. a) *Inhibitors (+)*-**1** [9b][10] *and (+)*-**21** *in the active site of thrombin as revealed by crystal-structure analyses.* Color code: C-skeleton of (+)-**1**: *cyan*, C-skeleton of (+)-**21**: *golden*, C-skeleton of thrombin in the complex of (+)-**1**: *grey*, C-skeleton of thrombin in the complex of (+)-**21**: *green*, O-atoms: *red*, N-atoms: *blue*, S-atoms: *yellow*. The H_2O molecules in the oxyanion hole are shown in the color of the corresponding enzyme. b) *Binding mode of inhibitor (+)*-**21** *in the oxyanion hole as revealed in the crystal structure.* Distances in Å.

our previous findings [12] that the polar oxyanion hole of thrombin is not an appropriate site to accommodate such groups.

We thank *F. Hoffmann-La Roche*, *Chugai Pharmaceuticals*, and the *ETH Research Council* for support of this work. We thank *Olivier Kuster* for the measurement of enzyme inhibitor constants and Dr. *Joerg Benz* and *Martine Stihle* for help in the crystal preparation.

Experimental Part

General. Solvents and reagents were reagent-grade, purchased from commercial suppliers, and used without further purification unless otherwise stated. The following compounds were prepared according to literature procedures: 4-toluenesulfinic acid [23] and the 1:1 mixture of *pseudoenantiomers* (+)-**6**/(−)-**7** [12]. THF was freshly distilled from sodium benzophenone ketyl, CH_2Cl_2 from CaH_2. HCl Gas was dried with conc. H_2SO_4. 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* (230–400 mesh, 0.040–0.063 mm) from *Fluka*. TLC: SiO_2-*60* F_{245}, *Merck;* visualization by UV light at 245 nm. M.p.: *Büchi SMP 20* apparatus; uncorrected. Optical rotations: *Perkin-Elmer 241* polarimeter, 1-dm cell, $\lambda = 589$ nm (Na D-line). IR Spectra [cm^{-1}]: *Perkin-Elmer 1600-FTIR* spectrometer. NMR Spectra (^1H, ^{13}C, NOE): *Varian Gemini-300*, *Varian Gemini-400*, and *Bruker AMX-500*; spectra were recorded at r.t. with solvent peak as reference. In some ^1H- and ^{13}C-NMR spectra (compounds (−)-**7**, (+)-**9**, (±)-**18**, (+)-**19**, (+)-**22**, (+)-**24**, and (+)-**25**), individual resonances overlap or are buried under the solvent peak. High-resolution (HR) MALDI mass spectra (HR-MS): *IonSpec Ultima*, 2,5-dihydroxybenzoic acid (DHB) as 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 [22][24] (chromogenic substrate S-2238). An exhaustive protocol of the binding assay used in this study is provided in [24].

General Procedure for the 1,3-Dipolar Cycloaddition (*GP 1*). A mixture of α-amino acid (1 mmol), 4-bromobenzaldehyde (1 mmol), and *N*-piperonylmaleimide (1 mmol) in DMF (3 ml) was heated to 120° for 16–48 h. The solvent was evaporated *in vacuo* and the residue purified by CC (AcOEt or AcOEt/hexane 70:30 or 50:50).

General Procedure for the Preparation of Amidinium Salts by the Pinner *Reaction* (*GP 2*). Dry HCl gas was bubbled at 0° for 10 min into a soln. of the nitrile (2 mmol) in dry $CHCl_3$ (5 ml) and dry MeOH (1 ml). The mixture was stored at 4° for 24 h, then Et_2O was added. The precipitate formed was isolated by filtration, dried in high vacuum, and redissolved in MeOH (5 ml). A methanolic soln. of NH_3 was slowly added until the NH_3 odor persisted; then, the mixture was stirred for 3.5 h at 65°. After cooling, NH_4Cl was precipitated with acetone and removed by filtration. The solvent was evaporated *in vacuo*, the residue was dissolved in EtOH, and the amidinium salt was slowly precipitated with Et_2O and purified by CC (CH_2Cl_2/MeOH 91:9).

General Procedure for the Conversion of an Aryl Bromide to the Corresponding Arene-Carbonitrile (*GP 3*). A suspension of the aryl bromide (1 mmol) and CuCN (4 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 was removed, and the org. phase was washed with conc. aq. NH_4OH soln. and H_2O. The combined aq. phases were extracted with CH_2Cl_2, dried ($MgSO_4$), and evaporated *in vacuo* to give a residue that was purified by CC (hexane/AcOEt/ 50:50 or 25:75).

General Procedure for the Silylation of a OH Group with (t-*Bu*)*Me*$_2$*SiCl* (*GP 4*). To a soln. of cycloadduct (10 mmol) and DMAP (17 mmol) in CH_2Cl_2 (16 ml), (*t*-Bu)Me_2SiCl (15 mmol) was added at r.t. under Ar. The mixture was stirred for 18 h at 20°, then poured into sat. aq. $NaHCO_3$ soln. and extracted with CH_2Cl_2. The combined org. phases were dried ($MgSO_4$), the solvent was removed *in vacuo*, and the resulting residue was purified by CC (pentane/AcOEt 75:25).

General Procedure for the Deprotection of a (t-*Bu*)*Me*$_2$*Si-Protected Hydroxy Group* (*GP 5*). To a soln. of the silyl-protected compound (3.3 mmol) in dry THF (36 ml), Bu_4NF (8 mmol; as soln. in THF) was added dropwise under cooling with ice. The mixture was stirred for 1 h at 20°, then poured into sat. aq. NaCl soln. and extracted with CH_2Cl_2. The combined org. phases were dried ($MgSO_4$), the solvent was removed *in vacuo*, and the resulting residue was purified by CC (pentane/AcOEt 50:50).

*(3a*S*,4*R*,7*R*,8a*S*,8b*R*)-, (3a*R*,4*S*,7*R*,8a*R*,8b*S*)-, and (3a*S*,4*S*,7*R*,8a*R*,8b*R*)-2-[(Benzo[1,3]dioxol-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* ((+)-

6, (−)-**7**, and (−)-**8**). *GP 1*, starting from **3**, **4**, and **5**, gave *endo*-adducts (+)-**6**/(−)-**7** as a 1:1 mixture in 34% yield, which precipitated from AcOEt or MeOH as mixed crystals. In addition, the *exo*-adduct (+)-**8** was formed in 35% yield.

*Synthesis of (+)-***6** *and (−)-***7**. *GP 5*, starting from (+)-**19**, afforded (+)-**6** in 69% yield and, starting from (+)-**20**, gave (−)-**7** in 72% yield.

*Synthesis of (±)-***7**. A 1M soln. of *LS-Selectride* (3.6 ml, 3.6 mmol) in THF was added to a soln. of (±)-**11** (1.0 g, 2.07 mmol) in dry CH_2Cl_2 (10 ml) at −95° under Ar. The mixture was stirred for 2 h at −95°, then warmed to 0°, neutralized with sat. aq. $NaHCO_3$ soln., and extracted with CH_2Cl_2. The combined org. phases were dried ($MgSO_4$), the solvent was removed *in vacuo*, and the resulting residue was purified by CC (pentane/EtOAc 50:50) to give (±)-**7** (804 mg; 79% as a 95:5 mixture with (±)-**6**).

*Data of (+)-***6**: Colorless solid. M.p. 178°. $[\alpha]_D^{25} = +169.4$ ($c = 1.00$, $CHCl_3$). IR ($CHCl_3$): 3609, 3007, 2931, 1774, 1705, 1607, 1503, 1489, 1446, 1399, 1342, 1090, 1042, 1011. ^{1}H-NMR (400 MHz, $CDCl_3$): 1.88–1.96 (*m*, 2 H); 2.06 (*dd*, *J* = 6.4, 12.7, 1 H); 2.77 (*dd*, *J* = 2.9, 13.7, 1 H); 2.94 (*dd*, *J* = 6.1, 13.7, 1 H); 3.25 (*d*, *J* = 8.3, 1 H); 3.44 (*dd*, *J* = 8.3, 8.6, 1 H); 3.97 (*d*, *J* = 8.6, 1 H); 4.10 (*dd*, *J* = 6.4, 12.7, 1 H); 4.41 (*s*, 2 H); 4.56–4.59 (*m*, 1 H); 5.93, 5.95 (*AB*, *J* = 1.4, 2 H); 6.70–6.78 (*m*, 3 H); 7.06, 7.37 (*AA′BB′*, *J* = 8.4, 4 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 39.9; 42.2; 48.4; 50.4; 61.3; 65.8; 69.9; 72.4; 101.1; 108.1; 109.5; 121.7; 122.6; 129.3; 129.7; 131.3; 136.6; 147.2; 147.6; 174.8; 177.5. MALDI-HR-MS: 485.0703 (*M*H$^+$, $C_{23}H_{22}BrN_2O_5^+$; calc. 485.0712). Anal. calc. for $C_{23}H_{21}BrN_2O_5$ (485.33): C 56.92, H 4.36, N 5.77; found: C 56.97, H 4.36, N 5.91.

*Data of (±)-***7**: Colorless solid. M.p. 202°.

*Data of (−)-***7**: Colorless solid. M.p. 174°. $[\alpha]_D^{25} = -169.4$ ($c = 1.00$, $CHCl_3$). IR ($CHCl_3$): 3613, 3007, 1774, 1704, 1606, 1503, 1446, 1399, 1342, 1098, 1043. ^{1}H-NMR (400 MHz, $CDCl_3$): 1.69 (br. *s*, 1 H); 1.76–1.83 (*m*, 1 H); 2.51–2.58 (*m*, 1 H); 2.66 (*d*, *J* = 14.0, 1 H); 2.98 (*dd*, *J* = 6.1, 14.0, 1 H); 3.22 (*d*, *J* = 8.3, 1 H); 3.55 (*dd*, *J* = 8.3, 8.7, 1 H); 3.80 (*dd*, *J* = 8.7, 8.9, 1 H); 4.40 (*s*, 2 H); 4.54–4.58 (*m*, 1 H); 4.69 (*d*, *J* = 8.7, 1 H); 5.93, 5.95 (*AB*, *J* = 1.4, 2 H); 6.69–6.80 (*m*, 3 H); 7.07, 7.37 (*AA′BB′*, *J* = 8.3, 4 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 40.7; 42.2; 49.6; 50.3; 60.2; 67.2; 68.8; 74.8; 101.0; 108.1; 109.5; 121.5; 122.6; 129.3; 131.2; 136.9; 147.2; 147.6; 175.1; 177.7. MALDI-HR-MS: 485.0702 (*M*H$^+$, $C_{23}H_{22}BrN_2O_5^+$; calc. 485.0712). Anal. calc. for $C_{23}H_{21}BrN_2O_5$ (485.33): C 56.92, H 4.36, N 5.77; found: C 56.92, H 4.44, N 5.82.

*Data of (−)-***8**: Colorless solid. M.p. 87°. $[\alpha]_D^{25} = -48.0$ ($c = 0.50$, $CHCl_3$). IR ($CHCl_3$): 3613, 2975, 1703, 1489, 1446, 1394, 1248, 1042. ^{1}H-NMR (400 MHz, $CDCl_3$): 1.78–1.85 (*m*, 1 H); 1.90 (br. *s*, 1 H); 1.96 (*dd*, *J* = 6.7, 14.1, 1 H); 2.63 (*dd*, *J* = 5.3, 12.3, 1 H); 2.86 (*dd*, *J* = 1.1, 12.3, 1 H); 3.29 (*dd*, *J* = 5.5, 9.1, 1 H); 3.52 (*dd*, *J* = 9.1, 9.1, 1 H); 4.03 (*d*, *J* = 5.5, 1 H); 4.09–4.18 (*m*, 1 H); 4.26–4.29 (*m*, 1 H); 4.53 (*s*, 2 H); 5.93 (*s*, 2 H); 6.74 (*d*, *J* = 7.7, 1 H); 6.89 (*d*, *J* = 7.7, 2 H); 7.34, 7.47 (*AA′BB′*, *J* = 7.6, 4 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 36.7; 42.4; 47.7; 55.7; 61.4; 64.4; 69.5; 72.7; 101.2; 108.3; 109.5; 121.4; 122.8; 128.5; 129.1; 131.8; 140.8; 147.5; 147.8; 176.4; 177.3. MALDI-HR-MS: 485.0711 (*M*H$^+$, $C_{23}H_{22}BrN_2O_5^+$; calc. 485.0712). Anal. calc. for $C_{23}H_{21}BrN_2O_5$ (485.33): C 56.92, H 4.36, N 5.77; found: C 57.04, H 4.48, N 5.55.

*4-[(3a*S*,4*R*,7*R*,8a*S*,8b*R*)- and (3a*R*,4*S*,7*R*,8a*R*,8b*S*)-2-[(Benzo[1,3]dioxol-5-yl)methyl]-1,3-dioxo-2,3,3a,4,5,6,7,8,8a,8b-decahydro-7-hydroxy-1*H*-pyrrolo[3,4-*a*]pyrrolizin-4-yl]benzonitrile* ((+)-**9** and (−)-**10**). *GP 3*, starting from a 1:1 mixture of (+)-**6**/(−)-**7**, afforded (+)-**9** and (−)-**10** as a 1:1 mixture, which precipitated from MeOH as 1:1 mixed crystals in 78% yield. Starting from (+)-**6**, (+)-**9** was obtained in 55% yield. Starting from (−)-**7**, (−)-**10** was isolated in 45% yield.

*Data of (+)-***9**: Colorless solid. M.p. 202°. $[\alpha]_D^{25} = +147.4$ ($c = 0.83$, $CHCl_3$). IR ($CHCl_3$): 3612, 3008, 2230, 1774, 1705, 1609, 1490, 1399, 1342, 1171, 1098, 1042. ^{1}H-NMR (400 MHz, $CDCl_3$): 1.90–1.96 (*m*, 1 H); 2.00–2.13 (*m*, 2 H); 2.84 (*dd*, *J* = 2.9, 13.6, 1 H); 2.87–2.95 (*m*, 1 H); 3.29 (*d*, *J* = 8.3, 1 H); 3.52 (*dd*, *J* = 8.3, 8.6, 1 H); 4.08 (*d*, *J* = 8.6, 1 H); 4.11–4.16 (*m*, 1 H); 4.39 (*s*, 2 H); 4.60 (*m*, 1 H); 5.96 (*m*, 2 H); 6.70–6.77 (*m*, 3); 7.30–7.33 (*m*, 2 H); 7.49–7.54 (*m*, 2 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 40.1; 42.3; 48.5; 50.5; 61.5; 66.0; 69.0; 72.4; 108.2; 111.6; 118.9; 128.8; 129.3; 131.9; 132.0; 143.8; 147.3; 147.4; 147.7; 174.6; 177.3. MALDI-HR-MS: 432.1550 (*M*H$^+$, $C_{24}H_{22}N_3O_5^+$; calc. 432.1559). Anal. calc. for $C_{24}H_{21}N_3O_5$ (431.44): C 66.81, H 4.91, N 9.74; found: C 66.83, H 4.94, N 9.67.

*Data of (−)-***10**: Colorless solid. M.p. 189°. $[\alpha]_D^{25} = -178.3$ ($c = 0.83$, $CHCl_3$). IR ($CHCl_3$): 3612, 3008, 2230, 1774, 1705, 1609, 1490, 1399, 1342, 1171, 1098, 1042. ^{1}H-NMR (400 MHz, $CDCl_3$): 1.79–1.87 (*m*, 1 H); 1.99 (br. *s*, 1 H); 2.56–2.63 (*m*, 1 H); 2.67 (*d*, *J* = 13.9, 1 H); 3.02 (*dd*, *J* = 5.9, 13.9, 1 H); 3.37 (*d*, *J* = 8.3, 1 H); 3.63 (*dd*, *J* = 8.3, 8.7, 1 H); 3.85 (*dd*, *J* = 8.3, 8.8, 1 H); 4.40 (*s*, 2 H); 4.58–4.61 (*m*, 1 H); 4.82 (*d*, *J* = 8.7, 1 H); 5.94, 5.96 (*AB*, *J* = 1.4, 2 H); 6.70–6.77 (*m*, 3 H); 7.32 (*m*, 2 H); 7.51 (*m*, 2 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 40.9; 42.3; 49.8; 50.4; 60.3; 67.4; 70.0; 74.8; 101.2; 108.1; 109.5; 111.4; 119.0; 122.6; 128.8; 128.8; 129.3; 131.9; 143.8; 147.7; 174.9; 177.5. MALDI-HR-MS: 432.1550 (*M*H$^+$, $C_{24}H_{22}N_3O_5^+$; calc. 432.1559). Anal. calc. for $C_{24}H_{21}N_3O_5$ (431.44): C 66.81, H 4.91, N 9.74; found: C 66.71, H 5.00, N 9.60.

*(3a*SR,*4*RS,*8a*SR,*8b*RS*)-2-[(Benzo[1,3]dioxol-5-yl)methyl]-4-(4-bromophenyl)-2,3,3a,4,5,6,7,8,8a,8b)-decahydro-1*H-*pyrrolo[3,4-*a*]pyrrolizine-1,3,7-trione* ((±)-**11**). Me_2SO (2.34 ml, 2.58 g, 33 mmol) was added to a soln. of $(COCl)_2$ (1.41 ml, 2.09 g, 16.5 mmol) in dry CH_2Cl_2 (50 ml) at −78° under Ar. After 15 min, a 1:1 mixture of (+)-**6**/(−)-**7** (4 g, 8.24 mmol) was added and, after 30 min, Et_3N (8 ml, 5.84 g, 57.7 mmol), and the mixture was warmed to 0° and stirred for 2 h. The mixture was diluted with AcOEt (150 ml) and extracted with sat. aq. $NaHCO_3$ soln. The combined org. phases were dried ($MgSO_4$), the solvent was removed *in vacuo*, and the resulting residue purified by CC (AcOEt/pentane 66:34) to give (±)-**11** (2.37 g, 60%). Colorless solid. M.p. 169°. IR ($CHCl_3$): 3005, 1750, 1707, 1503, 1490, 1446, 1400, 1343, 1041, 1010, 929. ^{1}H-NMR (400 MHz, $CDCl_3$): 2.33 (*dd*, *J* = 11.0, 18.4, 1 H); 2.61 (*dd*, *J* = 7.2, 18.4, 1 H); 2.88 (*d*, *J* = 18.7, 1 H); 3.17 (*d*, *J* = 18.7, 1 H); 3.39 (*d*, *J* = 8.3, 1 H); 3.55 (*dd*, *J* = 8.3, 8.7, 1 H); 4.08 (*d*, *J* = 8.7, 1 H); 4.30 (*dd*, *J* = 7.2, 11.0, 1 H); 4.47 (*s*, 2 H); 5.97 (*s*, 2 H); 6.73–6.82 (*m*, 3 H); 7.02, 7.38 (*AA′BB′*, *J* = 8.4, 4 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 40.9; 44.1; 50.4; 51.3; 60.6; 64.7; 69.6; 100.0; 106.7; 108.1; 120.2; 120.6; 126.7; 127.2; 129.0; 132.3; 144.0; 144.3; 169.5; 172.0; 209.2. MALDI-HR-MS: 483.0546 (MH^+, $C_{23}H_{20}BrN_2O_5^+$; calc. 483.0556). Anal. calc. for $C_{23}H_{19}BrN_2O_5$ (483.31): C 57.16, H 3.96, N 5.80; found: C 57.13, H 4.08, N 5.67.

*4{(3a*SR,*4*RS,*8a*SR,*8b*RS*)-2-[(Benzo[1,3]dioxol-5-yl)methyl]-1,3,7-trioxodecahydro-1*H-*pyrrolo[3,4-*a*]pyrrolizin-4-yl}benzonitrile* ((±)-**12**). Me_2SO (10.6 ml, 9.38 g, 148 mmol) was added to a soln. of $(COCl)_2$ (6.4 ml, 9.38 g, 74.2 mmol) in dry CH_2Cl_2 (190 ml) at −78°. After 15 min, a 1:1 mixture of (+)-**9**/(−)-**10** (16 g, 37.1 mmol) was added and, after 30 min, Et_3N (36 ml, 26.28 g, 259 mmol), and the mixture was warmed to 0° and stirred for 2 h under Ar. The mixture was diluted with AcOEt (500 ml) and extracted with sat. aq. $NaHCO_3$ soln. The combined org. phases were dried ($MgSO_4$), the solvent was removed *in vacuo*, and the resulting residue was purified by CC (AcOEt/pentane 75:25) to give (±)-**12** (10.50 g, 66%). Colorless solid. M.p. 192°. IR ($CHCl_3$): 3473, 3007, 2900, 2231, 1751, 1708, 1609, 1504, 1490, 1399, 1041. ^{1}H-NMR (400 MHz, $CDCl_3$): 2.35 (*dd*, *J* = 11.0, 18.4, 1 H); 2.65 (*dd*, *J* = 7.2, 18.4, 1 H); 2.86 (*d*, *J* = 18.7, 1 H); 3.21 (*d*, *J* = 18.7, 1 H); 3.44 (*d*, *J* = 8.3, 1 H); 3.63 (*dd*, *J* = 8.3, 8.7, 1 H); 4.20 (*d*, *J* = 8.7, 1 H); 4.34 (*dd*, *J* = 7.2, 11.0, 1 H); 4.38, 4.45 (*AB*, *J* = 6.6, 2 H); 5.97, 5.99 (*AB*, *J* = 1.4, 2 H); 6.73–6.81 (*m*, 3 H); 7.27, 7.54 (*AA′BB′*, *J* = 7.5, 4 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 39.2; 42.6; 49.1; 50.1; 59.8; 64.3; 69.3; 101.2; 108.2; 109.6; 112.3; 118.6; 122.8; 128.8; 129.1; 132.2; 141.6; 147.5; 147.7; 174.0; 176.5; 215.2. MALDI-HR-MS: 430.1402 (MH^+, $C_{24}H_{20}N_3O_5^+$; calc. 430.1403). Anal. calc. for $C_{24}H_{19}N_3O_5$ (429.42): C 67.13, H 4.46, N 9.79; found: C 67.13, H 4.65, N 9.71.

*4-{(3a*SR,*4*RS,*7*SR,*8a*SR,*8b*RS*)-2-[(Benzo[1,3]dioxol-5-yl)methyl]-2,3,3a,4,5,6,7,8,8a,8b-decahydro-7-methoxy-1,3-dioxo-1*H-*pyrrolo[3,4-*a*]pyrrolizin-4-yl}benzonitrile* ((±)-**13**). A suspension of NaH (63 mg, 1.75 mmol) and (±)-**10** (500 mg, 1.16 mmol) in dry THF (5 ml) was stirred for 10 min. After addition of [15]crown-5 (0.41 ml, 2.09 mmol), the soln. was stirred for another 10 min and MeI (0.11 ml, 1.75 mmol) was added. The soln. was stirred at r.t. for 3 h, and subsequently treated with sat. aq. NH_4Cl soln. The aq. phase was removed and extracted with AcOEt. The combined org. phases were dried ($MgSO_4$), the solvent was removed *in vacuo*, and the resulting residue was purified by CC (AcOEt/pentane 67:33) to yield (±)-**13** (196 mg, 38%). Colorless solid. M.p. 169°. IR ($CHCl_3$): 3008, 2972, 2230, 1705, 1608, 1503, 1490, 1446, 1369, 1342, 1100, 1042. ^{1}H-NMR (400 MHz, $CDCl_3$): 1.76–1.83 (*m*, 1 H); 2.50–2.58 (*m*, 1 H); 2.76 (*d*, *J* = 14.0, 1 H); 2.91 (*dd*, *J* = 6.0, 14.0, 1 H); 3.22 (*s*, 3 H); 3.34 (*d*, *J* = 8.3, 1 H); 3.58 (*dd*, *J* = 8.3, 8.7, 1 H); 3.84 (*dd*, *J* = 8.3, 9.9, 1 H); 4.00–4.05 (*m*, 1 H); 4.40 (*s*, 2 H); 4.66 (*dd*, *J* = 8.7, 1 H); 5.96 (*d*, *J* = 1.4, 2 H); 6.70–6.78 (*m*, 3 H); 7.31, 7.52 (*AA′BB′*, *J* = 8.3, 4 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 38.1; 42.3; 49.7; 50.3; 56.7; 57.3; 67.1; 68.6; 84.0; 101.2; 108.1; 109.6; 111.5; 119.0; 122.6; 128.9; 129.3; 131.9; 143.7; 147.4; 147.7; 174.9; 177.4. MALDI-HR-MS: 446.1707 (MH^+, $C_{25}H_{24}N_3O_5^+$; calc. 446.1716). Anal. calc. for $C_{25}H_{23}N_3O_5$ (445.47): C 67.41, H 5.20, N 9.43; found: C 67.40, H 5.29, N 9.35.

*4-{(3a*SR,*4*RS,*7*SR,*8a*SR,*8b*RS*)-2-[(Benzo[1,3]dioxol-5-yl)methyl]-7-(benzyloxy)-2,3,3a,4,5,6,7,8,8a,8b-decahydro-1,3-dioxo-1*H-*pyrrolo[3,4-*a*]pyrrolizin-4-yl}benzonitrile* ((±)-**14**). A suspension of NaH (63 mg, 1.75 mmol) and (±)-**10** (500 mg, 1.16 mmol) in dry THF (5 ml) was stirred for 10 min. After addition of [15]crown-5 (0.41 ml, 2.09 mmol), the soln. was stirred for 10 min and BnBr (0.69 ml, 5.79 mmol) was added. The soln. was stirred at r.t. for 2 h, and treated with sat. aq. NH_4Cl soln. The aq. phase was separated and extracted with AcOEt. The combined org. phases were dried ($MgSO_4$), the solvent was removed *in vacuo*, and the resulting residue was purified by CC (AcOEt/pentane 50:50) to yield (±)-**14** (421 mg, 70%). Colorless solid. M.p. 151°. IR ($CHCl_3$): 3007, 2929, 2230, 1774, 1705, 1609, 1503, 1490, 1446, 1399, 1343, 1100, 1042. ^{1}H-NMR (400 MHz, $CDCl_3$): 1.85–1.92 (*m*, 1 H); 2.53–2.60 (*m*, 1 H); 2.83 (*d*, *J* = 13.9, 1 H); 2.92 (*dd*, *J* = 5.8, 13.9, 1 H); 3.34 (*d*, *J* = 8.3, 1 H); 3.57 (*dd*, *J* = 8.3, 8.7, 1 H); 3.84 (*dd*, *J* = 8.3, 9.6, 1 H); 4.22–4.26 (*m*, 1 H); 4.34–4.44 (*m*, 4 H); 4.75 (*d*, *J* = 8.7, 1 H); 5.95 (*d*, *J* = 1.4, 2 H); 6.70–6.77 (*m*, 3 H); 7.26–7.34 (*m*, 5 H); 7.22, 7.52 (*AA′BB′*, *J* = 7.3, 4 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 38.4; 42.3; 49.7; 50.3; 56.9; 67.1; 68.6; 71.8; 81.8; 101.2; 108.1; 109.6; 111.5; 118.9; 122.6; 127.6; 127.8; 128.3; 128.5; 128.9; 129.3; 131.9; 132.2; 137.8; 143.7; 147.3; 147.7; 174.9; 177.4.

MALDI-HR-MS: 522.2019 (MH^+, $C_{31}H_{28}N_3O_5^+$; calc. 522.2029). Anal. calc. for $C_{31}H_{27}N_3O_5$ (521.56): C 71.39, H 5.22, N 8.06; found: C 71.18, H 5.47, N 8.07.

*4-[(3a*SR*,4*RS*,7*SR*,8a*SR*,8*bRS*)-2-[(Benzo[1,3]dioxol-5-yl)methyl]-2,3,3a,4,5,6,7,8,8a,8b-decahydro-7-hydroxy-1,3-dioxo-1*H*-pyrrolo[3,4-*a*]pyrrolizin-4-yl}benzamidine Hydrochloride* ((±)-**15**). *GP 2*, starting from (±)-**10**, afforded (±)-**15** in 80% yield. Yellowish solid. M.p. 175°. IR ($CHCl_3$): 3502, 2972, 1704, 1503, 1490, 1446, 1399, 1242. ^{1}H-NMR (400 MHz, $(CD_3)_2SO$): 1.72–1.79 (*m*, 1 H); 2.35–2.42 (*m*, 2 H); 2.90 (*m*, 1 H); 3.34 (*s*, 1 H); 3.51 (*d*, *J* = 8.4, 1 H); 3.61 (*dd*, *J* = 7.9, 10.3, 1 H); 3.84 (*dd*, *J* = 8.4, 8.6, 1 H); 4.31–4.38 (*m*, 2 H); 4.81 (*d*, *J* = 8.6, 1 H); 5.06–5.18 (*m*, 1 H); 6.01 (*s*, 2 H); 6.63–6.70 (*m*, 2 H); 6.87 (*d*, *J* = 8.0, 1 H); 7.44, 7.74 (*AA′BB′*, *J* = 8.4, 4 H); 9.31 (*s*, 4 H). ^{13}C-NMR (100 MHz, $(CD_3)_2SO$): 47.8; 48.5; 48.8; 50.1; 59.6; 66.7; 68.1; 72.8; 100.9; 108.0; 108.1; 121.0; 126.3; 127.4; 128.5; 129.6; 145.5; 146.4; 147.1; 165.4; 175.3; 178.0. MALDI-HR-MS: 449.1825 (MH^+, $C_{24}H_{25}ClN_4O_5^+$; calc. 449.1825).

*4-[(3a*SR*,4*RS*,7*SR*,8a*SR*,8b*RS*)-2-[(Benzo[1,3]dioxol-5-yl)methyl]-2,3,3a,4,5,6,7,8,8a,8b-decahydro-7-methoxy-1,3-dioxo-1*H*-pyrrolo[3,4-*a*]pyrrolizin-4-yl}benzamidine Hydrochloride* ((±)-**16**). *GP 2*, starting from (±)-**13**, afforded (±)-**16** in 38% yield. Yellowish solid. M.p. >155° (dec.). IR ($CHCl_3$): 2972, 1774, 1704, 1506, 1486, 1444, 1399, 1246. ^{1}H-NMR (400 MHz, $(CD_3)_2SO$): 1.77–1.84 (*m*, 1 H); 2.40–2.48 (*m*, 1 H); 2.50–2.55 (*m*, 1 H); 2.90 (*dd*, *J* = 6.4, 11.1, 1 H); 3.13 (*s*, 3 H); 3.52 (*d*, *J* = 8.2, 1 H); 3.66 (*dd*, *J* = 8.2, 9.6, 1 H); 3.84 (*dd*, *J* = 8.2, 11.1, 1 H); 4.02 (*m*, 1 H); 4.85, 4.75 (*AB*, *J* = 14.7, 2 H); 4.62 (*d*, *J* = 9.6, 1 H); 6.02 (*s*, 2 H); 6.64–6.69 (*m*, 2 H); 6.88 (*d*, *J* = 7.9, 1 H); 7.43, 7.75 (*AA′BB′*, *J* = 8.5, 4 H); 9.34 (*s*, 4 H). ^{13}C-NMR (100 MHz, $(CD_3)_2SO$): 36.9; 48.7; 50.0; 56.0; 62.7; 66.6; 67.7; 83.4; 101.0; 108.0; 108.1; 121.0; 126.4; 127.3; 127.5; 128.5; 129.6; 145.1; 146.5; 147.1; 165.3; 175.2; 177.9. MALDI-HR-MS: 463.1980 (MH^+, $C_{25}H_{27}N_4O_5^+$; calc. 463.1982).

*4-[(3a*SR*,4*RS*,7*SR*,8a*SR*,8b*RS*)-2-[(Benzo[1,3]dioxol-5-yl)methyl]-7-(benzyloxy)-2,3,3a,4,5,6,7,8,8a,8b-decahydro-1,3-dioxo-1*H*-pyrrolo[3,4-*a*]pyrrolizin-4-yl}benzamidine Hydrochloride* ((±)-**17**). *GP 2*, starting from (±)-**14**, afforded (±)-**17** in 50% yield. Yellowish solid. M.p. 148°. IR ($CHCl_3$): 2972, 1705, 1501, 1494, 1439, 1399, 1240. ^{1}H-NMR (400 MHz, $(CD_3)_2SO$): 1.88–1.95 (*m*, 1 H); 2.46–2.51 (*m*, 1 H); 2.63 (*d*, *J* = 12.8, 1 H); 2.92 (*dd*, *J* = 5.8, 12.8, 1 H); 3.38, 3.40 (*AB*, *J* = 2.5, 2 H); 3.54 (*d*, *J* = 7.8, 1 H); 3.67 (*dd*, *J* = 7.8, 9.7, 1 H); 3.87 (*dd*, *J* = 8.6, 9.7, 1 H); 4.22 (*dd*, *J* = 5.8, 12.8, 1 H); 4.33 (*s*, 2 H); 4.74 (*d*, *J* = 8.6, 1 H); 6.02 (*s*, 2 H); 6.65–6.69 (*m*, 2 H); 6.88 (*d*, *J* = 7.9, 1 H); 7.25–7.35 (*m*, 5 H); 7.42, 7.76 (*AA′BB′*, *J* = 8.5, 4 H); 9.40 (*s*, 4 H). ^{13}C-NMR (100 MHz, $(CD_3)_2SO$): 37.2; 48.7; 50.1; 56.2; 62.7; 66.6; 67.7; 70.7; 81.4; 101.0; 108.0; 108.1; 121.0; 126.4; 127.2; 127.3; 127.5; 128.1; 128.5; 129.6; 138.2; 145.2; 146.5; 147.1; 165.3; 175.3; 177.9. MALDI-HR-MS: 539.2284 (MH^+, $C_{31}H_{31}N_4O_5^+$; calc. 539.2295).

*4-[(3a*SR*,4*RS*,7*SR*,8a*SR*,8b*RS*)-2-[(Benzo[1,3]dioxol-5-yl)methyl]-2,3,3a,4,5,6,7,8,8a,8b-decahydro-7,7-dimethoxy-1,3-dioxo-1*H*-pyrrolo[3,4-*a*]pyrrolizin-4-yl}benzamidine Hydrochloride* ((±)-**18**). *GP* 2, starting from (±)-**12**, afforded (±)-**18** in 13% yield. Yellowish solid. M.p. >156° (dec.). IR ($CHCl_3$): 2972, 1771, 1707, 1502, 1489, 1444, 1399, 1238. ^{1}H-NMR (400 MHz, $(CD_3)_2SO$): 2.11 (*dd*, *J* = 11.2, 13.3, 1 H); 2.26 (*d*, *J* = 13.3, 1 H); 2.49–2.51 (*m*, 1 H); 2.57 (*d*, *J* = 13.3, 1 H); 2.91 (*d*, *J* = 13.3, 1 H); 3.08 (*s*, 6 H); 3.48 (*d*, *J* = 8.7, 1 H); 3.78–3.86 (*m*, 1 H); 4.33 (*d*, *J* = 6.6, 2 H); 4.57 (*d*, *J* = 8.7, 1 H); 6.02 (*s*, 2 H); 6.64–6.69 (*m*, 2 H); 6.87–6.89 (*m*, 1 H); 7.41, 7.72 (*AA′BB′*, *J* = 8.5, 4 H); 9.26 (*s*, 4 H). ^{13}C-NMR (100 MHz, $(CD_3)_2SO$): 48.4; 48.9; 49.7; 50.0; 58.5; 64.8; 65.5; 67.7; 101.0; 108.0; 108.1; 112.7; 121.1; 126.6; 127.5; 128.5; 129.6; 144.8; 146.5; 147.1; 165.3; 175.1; 177.7. MALDI-HR-MS: 493.2098 (MH^+, $C_{26}H_{29}N_4O_6^+$; calc. 493.2087).

*(3a*S*,4*R*,7*R*,8a*S*,8b*R*)- and (3a*R*,4*S*,7*R*,8a*R*,8b*S*)-2-[(Benzo[1,3]dioxol-5-yl)methyl]-4-(4-bromophenyl)-7-[(*tert*-butyl)dimethylsilyloxy]-2,3,3a,4,5,6,7,8,8a,8b-decahydro-1*H*-pyrrolo[3,4-*a*]pyrrolizin-1,3-dione* ((+)-**19**) *and* (−)-**20**). *GP 4*, starting from a 1:1 mixture of (+)-**6** and (−)-**7**, afforded (+)-**19** (43% yield) and (−)-**20** (43% yield).

Data of (+)-**19**: Colorless solid. M.p. 81°. $[\alpha]_D^{25} = +112.1$ (*c* = 1.00, $CHCl_3$). IR ($CHCl_3$): 3684, 2929, 2856, 1774, 1704, 1602, 1503, 1489, 1446, 1400, 1369, 1342, 1097, 1042. ^{1}H-NMR (400 MHz, $CDCl_3$): −0.01 (*s*, 3 H); 0.02 (*s*, 3 H); 0.85 (*s*, 9 H); 1.82–1.90 (*m*, 1 H); 2.01 (*dd*, *J* = 6.4, 12.9, 1 H); 2.74 (*dd*, *J* = 3.1, 13.4, 1 H); 2.89 (*dd*, *J* = 6.1, 13.4, 1 H); 3.23 (*dd*, *J* = 8.5, 8.5, 1 H); 3.41 (*dd*, *J* = 8.5, 8.5, 1 H); 3.93 (*d*, *J* = 8.5, 1 H); 4.09 (*dd*, *J* = 8.7, 8.8, 1 H); 4.43 (*s*, 2 H); 4.50–4.53 (*m*, 1 H); 5.94, 5.96 (*AB*, *J* = 1.4, 2 H); 6.70–6.80 (*m*, 3 H); 7.07, 7.38 (*AA′BB′*, *J* = 8.4, 4 H). ^{13}C-NMR (100 MHz, $CDCl_3$): −4.9; −4.8; +18.0; 25.8; 40.1; 42.2; 48.3; 50.4; 61.9; 65.9; 72.7; 101.1; 108.1; 109.6; 121.7; 122.6; 129.4; 131.3; 136.8; 147.2; 147.6; 174.9; 177.6. MALDI-HR-MS: 599.1566 (MH^+, $C_{29}H_{36}BrN_2O_5Si^+$; calc. 599.1577). Anal. calc. for $C_{29}H_{35}BrN_2O_5Si$ (599.59): C 58.09, H 5.88, N 4.67; found: C 58.19, H 6.02, N 4.59.

Data of (−)-**20**: Colorless solid. M.p. 79°. $[\alpha]_D^{25} = -116.7$ (*c* = 1.00, $CHCl_3$). IR ($CHCl_3$): 3684, 3007, 2928, 2856, 1773, 1704, 1602, 1503, 1490, 1446, 1399, 1370, 1342, 1098, 1043, 1010. ^{1}H-NMR (400 MHz, $CDCl_3$): −0.04 (*s*, 3 H); 0.02 (*s*, 3 H); 0.85 (*s*, 9 H); 1.73–1.79 (*m*, 1 H); 2.46–2.53 (*m*, 1 H); 2.62 (*d*, *J* = 13.6, 1 H); 2.91 (*dd*, *J* = 6.1, 13.4, 1 H); 3.31 (*d*, *J* = 8.6, 1 H); 3.55 (*dd*, *J* = 8.6, 8.6, 1 H); 3.79 (*dd*, *J* = 8.6, 8.6, 1 H); 4.41 (*s*, 2 H);

4.42–4.47 (*m*, 1 H); 4.71 (*d*, *J* = 8.6, 1 H); 5.94, 5.96 (*AB*, *J* = 1.4, 2 H); 6.70–6.79 (*m*, 3 H); 7.04, 7.35 (*AA′BB′*, *J* = 8.4, 4 H). ^{13}C-NMR (100 MHz, $CDCl_3$): −5.0; −4.9; 17.8; 25.7; 41.7; 42.2; 49.9; 50.4; 60.6; 67.1; 68.8; 75.0; 101.1; 108.1; 109.6; 121.5; 122.6; 129.4; 129.8; 131.2; 137.2; 147.2; 147.6; 175.2; 177.8. MALDI-HR-MS: 599.1566 (*M*H$^+$, $C_{29}H_{36}BrN_2O_5Si^+$; calc. 599.1577). Anal. calc. for $C_{29}H_{35}BrN_2O_5Si$ (599.59): C 58.09, H 5.88, N 4.67; found: C 58.22, H 5.75, N 4.62.

*4-[(3a*S*,4*R*,7*R*,8a*S*,8b*R*)-2-[(Benzo[1,3]dioxol-5-yl)methyl]-2,3,3a,4,5,6,7,8,8a,8b-decahydro-7-hydroxy-1,3-dioxo-1*H*-pyrrolo[3,4-*a*]pyrrolizin-4-yl]benzamidine Hydrochloride* ((+)-**21**). *GP 2*, starting from (+)-**9**, afforded (+)-**21** in 55% yield. Yellowish solid. M.p. >230° (dec.). $[\alpha]_D^{25} = +108.9$ (*c* = 0.43, $CHCl_3$). IR ($CHCl_3$): 3502, 2972, 1704, 1503, 1490, 1446, 1399, 1242. ^{1}H-NMR (400 MHz, $(CD_3)_2SO$): 1.72–1.79 (*m*, 1 H); 2.35–2.42 (*m*, 2 H); 2.90 (*m*, 1 H); 3.34 (*s*, 1 H); 3.51 (*d*, *J* = 8.4, 1 H); 3.61 (*dd*, *J* = 7.9, 10.3, 1 H); 3.84 (*dd*, *J* = 8.4, 8.6, 1 H); 4.31–4.38 (*m*, 2 H); 4.81 (*d*, *J* = 8.6, 1 H); 5.06–5.18 (*m*, 1 H); 6.01 (*s*, 2 H); 6.63–6.70 (*m*, 2 H); 6.87 (*d*, *J* = 8.0, 1 H); 7.44, 7.74 (*AA′BB′*, *J* = 8.4, 4 H); 9.31 (*s*, 4 H). ^{13}C-NMR (100 MHz, $(CD_3)_2SO$): 47.8; 48.5; 48.8; 50.1; 59.6; 66.7; 68.1; 72.8; 100.9; 108.0; 108.1; 121.0; 126.3; 127.4; 128.5; 129.6; 145.5; 146.4; 147.1; 165.4; 175.3; 178.0. MALDI-HR-MS: 449.1825 (*M*H$^+$, $C_{24}H_{25}N_4O_5^+$; Ber. 449.1825).

*(3a*S*,4*R*,7*R*,8a*S*,8b*S*)-2-[(1,3-Benzodioxol-5-yl)methyl]-4-(4-bromophenyl)-7-[*tert*-butyldimethylsilyloxy]-2,3,3a,4,5,6,7,8,8a,8b-decahydro-1-hydroxy-1*H*-pyrrolo[3,4-*a*]pyrrolizin-3-one* ((+)-**22**). A 1M soln. of Li[Et_3BH] in THF (2.83 ml, 2.83 mmol) was added to (+)-**19** (1.00 g, 1.66 mmol) in dry THF (6 ml) at −78° under Ar. After 30 min, the mixture was warmed to r.t., neutralized with sat. aq. $NaHCO_3$ soln., and extracted with CH_2Cl_2. The org. phase was dried ($MgSO_4$), the solvent removed, and the residue purified by CC (AcOEt/pentane 50:50, then 80:20) to yield (+)-**22** (939 mg, 94%). Colorless solid. M.p. 78–80° (MeOH). $[\alpha]_D^{25} = +55$ (*c* = 1.00 $CHCl_3$). IR ($CHCl_3$): 3351, 2928, 1673, 1503, 1443, 1243, 1187. ^{1}H-NMR (400 MHz, $CDCl_3$): 0.02 (*d*, *J* = 9.1, 6 H); 0.86 (*s*, 9 H); 1.80–1.92 (*m*, 3 H); 2.81 (*dd*, *J* = 3.6, 13.5, 1 H); 3.00 (*dd*, *J* = 7.1, 8.5, 1 H); 3.07 (*dd*, *J* = 6.3, 13.5, 1 H); 3.31 (*dd*, *J* = 8.5, 10.3, 1 H); 3.76 (*d*, *J* = 10.3, 1 H); 3.88 (*dd*, *J* = 6.7, 11.1, 1 H); 4.03 (*d*, *J* = 14.5, 1 H); 4.44 (*d*, *J* = 14.5, 1 H); 4.61–6.63 (*m*, 1 H); 4.98 (*d*, *J* = 7.1, 1 H); 5.92, 5.93 (*AB*, *J* = 1.5, 2 H); 6.71–6.72 (*m*, 3 H); 7.14, 7.42 (*AA′BB′*, *J* = 7.3, 4 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 18.0; 25.8; 38.2; 43.8; 49.8; 62.1; 64.0; 68.6; 72.7; 76.7; 82.3; 101.0; 108.0; 109.2; 121.7; 122.1; 129.6; 130.6; 131.4; 136.5; 146.9; 147.7; 171.5. MALDI-HR-MS: 600.1600 (*M*H$^+$, $C_{29}H_{38}BrN_2O_5Si^+$; calc. 600.1655).

*(1*S*,3a*S*,4*R*,7*R*,8a*S*,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-[(4-methylphenyl)sulfonyl]-1*H*-pyrrolo[3,4-*a*]pyrrolizin-3-one* ((+)-**23**). *GP 5,* starting from (+)-**22**, afforded the hydroxy intermediate in 94% yield without further purification. A mixture of 4-toluenesulfinic acid (69.2 mg, 0.44 mmol) and dry powdered $CaCl_2$ (49.2 mg, 0.44 mmol) in dry CH_2Cl_2 (0.8 ml) was stirred for 10 min under Ar, and a soln. of the hydroxy intermediate (80 mg, 0.16 mmol) in CH_2Cl_2 (0.4 ml) was added. After stirring for 19 h, sat. aq. $NaHCO_3$ soln. was added, and the mixture was extracted with CH_2Cl_2. The org. phase was dried ($MgSO_4$) and evaporated *in vacuo*. The residue was purified by CC (AcOEt/hexane 50:50) to yield (+)-**23** (82 mg, 80%). Yellow solid. M.p. 108–110° (AcOEt). $[\alpha]_D^{25} = +209$ (*c* = 1.00, $CHCl_3$). IR ($CHCl_3$): 3421, 2923, 1705, 1595, 1503, 1488, 1445, 1400, 1372, 1292. ^{1}H-NMR (400 MHz, $CDCl_3$): 1.67–1.74 (*m*, 1 H); 1.95 (*dd*, *J* = 6.1, 13.5, 1 H); 1.98 (*s*, 1 H); 2.42 (*s*, 3 H); 2.52 (*t*, *J* = 6.9, 1 H); 2.71 (*dd*, *J* = 5.3, 13.1, 1 H); 2.82 (*dd*, *J* = 1.9, 13.0, 1 H); 2.96 (*dd*, *J* = 3.4, 7.7, 1 H); 3.34–3.39 (*m*, 1 H); 3.81–3.85 (*m*, 2 H); 4.29 (*s*, 1 H); 4.43 (*t*, *J* = 5.3, 1 H); 4.94 (*d*, *J* = 14.7, 1 H); 5.90, 5.92 (*AB*, *J* = 1.4, 2 H); 6.56–6.72 (*m*, 3 H); 7.09 (*d*, *J* = 6.7, 2 H); 7.32–7.37 (*m*, 4 H); 7.65 (*d*, *J* = 8.3, 2 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 21.8; 40.9; 42.1; 45.1; 51.4; 61.5; 69.3; 70.7; 73.2; 80.9; 101.2; 108.4; 108.7; 121.3; 122.0; 128.7; 129.4; 129.6; 130.5; 131.0; 132.5; 136.6; 146.2; 147.4; 148.2; 172.3. MALDI-HR-MS: 627.0986 (*M*H$^+$, $C_{30}H_{30}BrN_2O_6S^+$; calc. 627.0988).

*(1*R*,3a*S*,4*R*,7*R*,8a*S*,8b*R*)-2-[(1,3-Benzodioxol-5-yl)methyl]-4-(4-bromophenyl)-7-[(*tert*-butyl)dimethylsilyloxy]-2,3,3a,4,5,6,7,8,8a,8b-decahydro-1-[(4-methylphenyl)sulfonyl]-1*H*-pyrrolo[3,4-*a*]pyrrolizin-3-one* ((+)-**24**). *GP 4*, starting from (+)-**23**, afforded (+)-**24** in 87% yield. Yellow foam. M.p. 109–101° (AcOEt). $[\alpha]_D^{25} = +171$ (*c* = 1.00, $CHCl_3$). IR ($CHCl_3$): 2929, 2359, 1711, 1503, 1488, 1398, 1302, 1134. ^{1}H-NMR (400 MHz, $CDCl_3$): −0.06 (*s*, 6 H); 0.79 (*s*, 9 H); 1.61–1.69 (*m*, 1 H); 1.87 (*dd*, *J* = 6.0, 13.0, 1 H); 2.42 (*s*, 3 H); 2.45 (*t*, *J* = 6.5, 1 H); 2.64 (*dd*, *J* = 2.3, 12.8, 1 H); 2.75 (*dd*, *J* = 2.3, 12.8, 1 H); 2.96 (*dd*, *J* = 3.1, 7.6, 1 H); 3.33–3.37 (*m*, 1 H); 3.78 (*d*, *J* = 6.5, 1 H); 3.83 (*d*, *J* = 15.1, 1 H); 4.32 (*s*, 1 H); 4.34–4.37 (*m*, 1 H); 4.96 (*d*, *J* = 15.1, 1 H); 5.91 (*s*, 2 H); 6.58–6.64 (*m*, 2 H); 6.71 (*d*, *J* = 7.9, 1 H); 7.10 (*d*, *J* = 8.3, 2 H); 7.32–7.37 (*m*, 4 H); 7.65 (*d*, *J* = 8.3, 2 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 18.0; 21.8; 25.8; 41.4; 41.9; 45.0; 51.3; 61.8; 69.5; 70.6; 73.3; 81.1; 101.1; 108.4; 108.7; 121.2; 121.8; 128.8; 129.4; 129.7; 130.5; 131.0; 132.5; 136.8; 146.2; 147.4; 148.2; 172.4. MALDI-HR-MS: 739.1863 (*M*H$^+$, $C_{36}H_{44}BrN_2O_6SSi^+$; calc. 739.1873).

*(1*S*,3a*S*,4*S*,7*R*,8a*S*,8b*S*)-2-[(1,3-Benzodioxol-5-yl)methyl]-4-(4-bromophenyl)-7-[(*tert*-butyl)dimethylsilyloxy]-2,3,3a,4,5,6,7,8,8a,8b-decahydro-1-(1-methylethyl)-1*H*-pyrrolo[3,4-*a*]pyrrolizin-3-one* ((+)-**25**). (i-Pr)MgCl (1.35 ml of a 2M soln. in THF/Et_2O, 2.7 mmol) was added to a soln. of $ZnCl_2$ (1.48 ml of 1M soln in Et_2O,

1.48 mmol) in dry CH_2Cl_2 (6 ml) under Ar. After 30 min, a soln. of (+)-**25** (1 g, 1.35 mmol) in dry CH_2Cl_2 (6.5 ml) was slowly added at 0°. The mixture was stirred at r.t. for 23 h, then 1N HCl was added. After 5 min, the mixture was neutralized with sat. aq. $NaHCO_3$ soln. and extracted with CH_2Cl_2. The org. phase was dried ($MgSO_4$), the solvent was removed, and the product was purified by CC (AcOEt/hexane 50:50) to yield (+)-**26** (668 mg, 79%). Colorless solid. M.p. 63–65° (AcOEt). $[\alpha]_D^{25} = +183$ ($c = 1.00$, $CHCl_3$). IR ($CHCl_3$): 2955, 1685, 1487, 1441, 1371, 1094, 1070, 1038, 1009. ^{1}H-NMR (400 MHz, $CDCl_3$): −0.04 (*s*, 6 H); 0.64 (*d*, *J* = 6.9, 3 H); 0.80 (*s*, 9 H); 0.87 (*d*, *J* = 6.9, 3 H); 1.67–1.74 (*m*, 1 H); 1.82 (*dd*, *J* = 6.3, 13.0, 1 H); 2.00–2.11 (*m*, 1 H); 2.39–2.43 (*m*, 1 H); 2.74–2.83 (*m*, 2 H); 3.17 (*t*, *J* = 8.1, 1 H); 3.24 (*t*, *J* = 3.9, 1 H); 3.45–3.50 (*m*, 1 H); 3.64 (*d*, *J* = 14.9, 1 H); 3.90 (*d*, *J* = 7.6, 1 H); 4.42–4.45 (*m*, 1 H); 4.73 (*d*, *J* = 14.9, 1 H); 5.89, 5.91 (*AB*, *J* = 1.5, 2 H); 6.60 (*dd*, *J* = 1.6, 7.9, 1 H); 6.65–6.67 (*m*, 2 H); 7.22, 7.39 (*AA′BB′*, *J* = 8.4, 4 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 14.7; 18.1; 18.5; 25.9; 28.0; 40.3; 41.2; 43.8; 52.7; 62.2; 67.3; 71.0; 71.2; 73.3; 101.0; 108.1; 108.7; 120.9; 121.2; 130.0; 130.4; 131.0; 138.3; 146.9; 148.0; 172.3. MALDI-HR-MS: 627.2256 (*M*H$^+$, $C_{32}H_{44}BrN_2O_4Si^+$; calc. 627.2254).

*(1*R*,3a*S*,4*R*,7*R*,8a*S*,8b*R*)-2-[(1,3-Benzodioxol-5-yl)methyl]-4-(4-bromophenyl)-2,3,3a,4,5,6,7,8,8a,8b-decahydro-7-hydroxy-1-(1-methylethyl)-1*H*-pyrrolo[3,4-a]pyrrolizin-3-one* ((+)-**26**). *GP 5*, starting from (+)-**25**, afforded (+)-**26** in 75% yield. Colorless crystals. M.p. 153–155° (MeCN). $[\alpha]_D^{25} = +208$ ($c = 1.00$, $CHCl_3$). IR ($CHCl_3$): 2928, 2360, 1682, 1503, 1488, 1442, 1371. ^{1}H-NMR (400 MHz, $CDCl_3$): 0.70 (*d*, *J* = 6.8, 3 H); 0.91 (*d*, *J* = 6.9, 3 H); 1.71 (*s*, 1 H); 1.78–1.84 (*m*, 1 H); 2.00 (*ddd*, *J* = 1.3, 6.1, 13.4, 1 H); 2.05–2.12 (*m*, 1 H); 2.47–2.50 (*m*, 1 H); 2.89–2.90 (*m*, 2 H); 3.25–3.31 (*m*, 2 H); 3.54–3.59 (*m*, 1 H); 3.68 (*d*, *J* = 14.9, 1 H); 4.03 (*d*, *J* = 7.7, 1 H); 4.55 (*s*, 1 H); 4.88 (*d*, *J* = 14.9, 1 H); 5.95, 5.97 (*AB*, *J* = 1.4, 2 H); 6.59 (*dd*, *J* = 1.7, 7.9, 1 H); 6.67 (*d*, *J* = 1.7, 1 H); 6.73 (*d*, *J* = 7.9; 1 H); 7.26, 7.44 (*AA′BB′*, *J* = 8.3, 4 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 14.7; 18.5; 27.9; 40.7; 40.8; 43.8; 53.0; 62.2; 67.2; 71.1; 71.2; 73.4; 101.0; 108.1; 108.7; 121.0; 121.3; 129.9; 130.3; 131.0; 138.2; 146.9; 147.9; 172.1. MALDI-HR-MS: 513.1390 (*M*H$^+$, $C_{26}H_{30}BrN_2O_4^+$; calc. 513.1389). Anal. calc. for $C_{26}H_{29}BrN_2O_4$ (513.42): C 60.82, H 5.69, N 5.46; found: C 60.86, H 5.72, N 5.33.

*4-[(1*S*,3a*S*,4*S*,7*R*,8a*S*,8b*S)-2-[(1,3-Benzodioxol-5-yl)methyl]-2,3,3a,4,5,6,7,8,8a,8b-decahydro-7-hydroxy-1-(1-methylethyl)-3-oxo-1*H*-pyrrolo[3,4-a]pyrrolizin-4-yl]benzonitrile* ((+)-**27**). *GP 3*, starting from (+)-**26**, afforded (+)-**27** in 55% yield. Grey solid. M.p. 76°. $[\alpha]_D^{25} = +285$ ($c = 0.50$, $CHCl_3$). IR ($CHCl_3$): 3472, 2961, 2236, 1681, 1608, 1501, 1486, 1441, 1239, 1039. ^{1}H-NMR (400 MHz, $CDCl_3$): 0.71 (*d*, *J* = 6.8, 3 H); 0.92 (*d*, *J* = 6.9, 3 H); 1.63 (*s*, 1 H); 1.76–1.84 (*m*, 1 H); 2.01–2.12 (*m*, 2 H); 2.49–2.53 (*m*, 1 H); 2.86 (*dd*, *J* = 5.3, 12.8, 1 H); 2.95 (*dd*, *J* = 2.1, 12.8, 1 H); 3.26 (*t*, *J* = 3.0, 1 H); 3.36 (*t*, *J* = 8.2, 1 H); 3.57–3.62 (*m*, 1 H); 3.67 (*d*, *J* = 15.1, 1 H); 4.13 (*d*, *J* = 7.7, 1 H); 4.58 (*s*, 1 H); 4.76 (*d*, *J* = 15.1, 1 H); 5.96, 5.98 (*AB*, *J* = 1.4, 2 H); 6.60–6.62 (*m*, 2 H); 6.73 (*d*, *J* = 8.3, 1 H); 7.50, 7.61 (*AA′BB′*, *J* = 8.2, 4 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 14.8; 18.5; 28.0; 40.8; 40.8; 43.8; 53.2; 62.3; 67.1; 71.3; 71.5; 73.5; 101.1; 108.1; 108.5; 110.9; 119.3; 121.3; 128.8; 130.2; 131.7; 145.1; 147.0; 148.0; 171.8. MALDI-HR-MS: 460.2229 (*M*H$^+$, $C_{27}H_{30}N_3O_4^+$; calc. 460.2236).

*4-[(1*S*,3a*S*,4*S*,7*R*,8a*S*,8b*S)-2-[(1,3-Benzodioxol-5-yl)methyl]-2,3,3a,4,5,6,7,8,8a,8b-decahydro-7-hydroxy-1-(1-methylethyl)-3-oxo-1*H*-pyrrolo[3,4-a]pyrrolizin-4-yl]benzamidine Hydrochloride* ((+)-**2**). *GP 2*, starting from (+)-**27**, afforded (+)-**2** in 60% yield. Yellowish powder. M.p. >200° (dec.). $[\alpha]_D^{25} = +211$ ($c = 0.45$, $CHCl_3$). IR (neat): 3276, 2961, 2359, 1667, 1539, 1489, 1441, 1373, 1242. ^{1}H-NMR (300 MHz, CD_3OD): 0.74 (*d*, *J* = 6.9, 3 H); 0.97 (*d*, *J* = 6.9, 3 H); 1.91–1.96 (*m*, 2 H); 2.16–2.22 (*m*, 1 H); 2.66–2.71 (*m*, 1 H); 2.80–2.86 (*m*, 2 H); 3.36 (*t*, *J* = 2.8, 1 H); 3.45 (*t*, *J* = 7.6, 1 H); 3.55–3.63 (*m*, 1 H); 3.82 (*d*, *J* = 14.9, 1 H); 4.27 (*d*, *J* = 7.6, 1 H); 4.49–4.52 (*m*, 1 H); 4.65 (*d*, *J* = 14.9, 1 H); 5.94, 5.96 (*AB*, *J* = 1.2, 2 H); 6.72–6.80 (*m*, 3 H); 7.61, 7.72 (*AA′BB′*, *J* = 8.2, 4 H). ^{13}C-NMR (75 MHz, CD_3OD): 14.7; 18.4; 29.0; 41.0; 41.2; 44.4; 54.7; 62.5; 69.3; 72.3; 73.0; 73.5; 102.3; 108.9; 109.2; 122.4; 127.6; 128.1; 130.1; 131.1; 148.1; 148.4; 149.2; 168.3; 174.4. MALDI-HR-MS: 477.2490 (*M*H$^+$, $C_{27}H_{33}N_4O_5^+$; calc. 477.2502).

X-Ray Crystal Structures. Copies of the data can be obtained free of charge on application to *Cambridge Crystallographic Data Centre* (*CCDC*), 12 Union Road, Cambridge CB21EZ, UK (fax: (+44)1223-336-033; e-mail: deposit@ccdc.cam.ac.uk.

*Mixed Crystal of (+)-***9** *and (−)-***10**. Crystal data at 173(2) K for $C_{24}H_{21}N_3O_5 \cdot C_{24}H_{21}N_3O_5$ (M_r 862.88): triclinic, space group *P*1, $D_c = 1.450$ g cm^{-3}, $Z = 1$, $a = 4.7947(1)$, $b = 14.9058(3)$, $c = 15.1606(9)$ Å, $\alpha = 111.174(1)$, $\beta = 94.024(1)$, $\gamma = 99.021(1)°$, $V = 988.36(4)$ Å^3. *Bruker-Nonius Kappa-CCD* diffractometer, MoK_α radiation, $\lambda = 0.7107$, linear crystal dimensions *ca.* 0.15 × 0.12 × 0.10 mm. The structure was solved by direct methods (SIR97) [25] and refined by full-matrix least-squares analysis (SHELXL-97) [26], using an isotropic extinction correction. All heavy atoms were refined anisotropically, H-atoms isotropically, whereby H-positions are based on stereochemical considerations. Final $R(F) = 0.0402$, $wR(F^2) = 0.0980$ for 620 parameters, 3 restraints, and 6971 reflections with $I > 2\sigma(I)$ and $2.91 < \theta < 27.48°$. Deposition No. CCDC-238291.

Compound (±)-**11**. Crystal data at 223(2) K for $C_{23}H_{19}BrN_2O_5$ (M_r 483.31): monoclinic, space group *P*2(1)/n, $D_c = 1.598$ g cm^{-3}, $Z = 4$, $a = 10.6776(2)$, $b = 17.0057(3)$, $c = 11.0834(2)$ Å, $\beta = 93.550(1)°$, $V = 2008.66(6)$ Å^3.

Bruker-Nonius Kappa-CCD diffractometer, Mo$K\alpha$ radiation, $\lambda = 0.7107$, linear crystal dimensions *ca.* $0.20 \times 0.20 \times 0.20$ mm. The structure was solved by direct methods (SIR97) and refined by full-matrix least-squares analysis (SHELXL-97), using an isotropic extinction correction. All heavy atoms were refined anisotropically, H-atoms isotropically, whereby H-positions are based on stereochemical considerations. Final $R(F) = 0.0348$, $wR(F^2) = 0.0839$ for 300 parameters, 0 restraints, and 3649 reflections with $I > 2\sigma(I)$ and $3.51 < \theta < 27.48°$. Deposition No. CCDC-238289.

Compound (±)-**12**. Crystal data at 223(2) K for $C_{24}H_{19}N_3O_5$ (M_r 429.42): monoclinic, space group $P2(1)/n$, $D_c = 1.423$ g cm^{-3}, $Z = 4$, $a = 10.7504(4)$, $b = 16.9363(9)$, $c = 11.0123(5)$ Å, $\beta = 92.045(2)°$, $V = 2003.75(16)$ Å^3. *Bruker-Nonius Kappa-CCD* diffractometer, MoK_α radiation, $\lambda = 0.7107$, linear crystal dimensions *ca.* $0.20 \times 0.20 \times 0.18$ mm. The structure was solved by direct methods (SIR97) and refined by full-matrix least-squares analysis (SHELXL-97). All heavy atoms were refined anisotropically, H-atoms isotropically, whereby H-positions are based on stereochemical considerations. Final $R(F) = 0.0590$, $wR(F^2) = 0.1312$ for 309 parameters, 0 restraints, and 3562 reflections with $I > 2\sigma(I)$ and $1.17 < \theta < 28.70°$. Deposition No. CCDC-238290.

Compound (±)-**14**. Crystal data at 222 K for $C_{31}H_{27}N_3O_5$ (M_r 521.573): orthorhombic, space group $P2_12_12_1$, $D_c = 1.302$ g cm^{-3}, $Z = 8$, $a = 13.6217(2)$, $b = 17.3424(2)$, $c = 22.5267(4)$ Å, $V = 5321.55(14)$ Å^3. *Bruker-Nonius Kappa-CCD* diffractometer, MoK_α radiation, $\lambda = 0.7107$. The structure was solved by direct methods (SIR97) and refined by full-matrix least-squares analysis (SHELXL-97), using an isotropic extinction correction. All heavy atoms were refined anisotropically, H-atoms isotropically, whereby H-positions are based on stereochemical considerations. Final $R(F) = 0.0590$, $wR(F^2) = 0.1455$ for 707 parameters, and 9532 reflections with $I > 2\sigma(I)$ and $2.70 < \theta < 27.39°$. Deposition No. CCDC-238293.

Compound (+)-**26**. Crystal data at 163(2) K for $C_{26}H_{29}N_2O_4Br$ (M_r 513.42): orthorhombic, space group $P2_12_12_1$, $D_c = 1.496$ g cm^{-3}, $Z = 4$, $a = 5.1744(1)$, $b = 18.7267(3)$, $c = 23.5221(5)$ Å, $V = 2279.28(7)$ Å^3. *Bruker-Nonius Kappa-CCD* diffractometer, MoK_α radiation, $\lambda = 0.7107$, linear crystal dimensions *ca.* $0.25 \times 0.23 \times 0.20$ mm. The structure was solved by direct methods (SIR97) and refined by full-matrix least-squares analysis (SHELXL-97), using an isotropic extinction correction. All heavy atoms were refined anisotropically, H-atoms isotropically, whereby H-positions are based on stereochemical considerations. Final $R(F) = 0.0405$, $wR(F^2) = 0.0946$ for 328 parameters and 4738 reflections with $I > 2\sigma(I)$ and $1.39 < \theta < 27.50°$. Deposition No. CCDC-238292.

X-Ray Crystal Structure of the Complex of Thrombin with (+)-**21**. Crystals of human α-thrombin in complex with (+)-**21** were prepared and analyzed as described in [13a], except that the crystal-to-detector distance was 100 mm, and 678 frames were collected. Unit-cell dimensions were $a = 70.9$ Å, $b = 71.4$ Å, $c = 72.4$ Å, and $\beta = 100.4°$. For 306195 observations of 43087 reflections to 1.54-Å resolution, the merging R factor on intensities was 3.9% and in the outermost data shell (1.54 Å – 1.63 Å) was 21.6% with $I/\sigma I = 27.0$ overall and 8.56 in the outermost shell. Due to ice rings, which had to be eliminated, data completeness was not optimal, being 82.2% overall and 83.9% in the outermost shell. Structure 1oyt.pdb was taken as starting model for the non-inhibitor atoms, and the new structure was refined to final overall crystallographic R factors of 18.1 (working) and 20.9% (free), with values in the outer shell of 21.6 and 22.3% resp., for 2296 protein atoms, 35 inhibitor atoms, one Na^+ ion, one Ca^{++} ion, and 408 H_2O molecules. The inhibitor density is very clear, refined temp. factors for the inhibitor range from 14 Å^2 (amidinium moiety) to 22 Å^2. The coordinates have been deposited in the *Protein Data Bank* as 1vzq.pdb.

REFERENCES

[1] M. F. Scully, in 'Essays in Biochemistry', Ed. K. F. Tipton, Portland Press, London, 1992, pp. 17 – 36.
[2] B. Furie, B. C. Furie, *Cell* **1988**, *53*, 505.
[3] W. Bode, I. Mayr, U. Baumann, R. Huber, S. R. Stone, J. Hofsteenge, *EMBO J.* **1989**, *8*, 3467.
[4] D. W. Banner, P. Hadváry, *J. Biol. Chem.* **1991**, *266*, 20085.
[5] H. Kubinyi, *Pharm. unserer Zeit* **1998**, *27*, 158.
[6] A. M. Naylor-Olson, P. E. J. Sanderson, *Curr. Med. Chem.* **1998**, *5*, 289.
[7] V. Pavone, G. De Simone, F. Nastri, S. Galdiero, N. Staiono, A. Lombardi, C. Pedone, *Biol. Chem.* **1998**, *179*, 987.
[8] K. Menear, *Curr. Med. Chem.* **1998**, *5*, 457; J. W. Nilsson, I. Kvarnström, D. Musil, I. Nilsson, B. Samulesson, *J. Med. Chem.* **2003**, *46*, 3985; N. H. Hauel, H. Nar, H. Priepke, U. Ries, J.-M. Strassen, W. Wienen, *J. Med. Chem.* **2002**, *45*, 1757; S. Lévesque, Y. St.-Denis, B. Bachand, P. Préville, L. Leblond, P. D. Winocour, J. J. Edmunds, J. R. Rubin, M. A. Siddiqui, *Bioorg. Med. Chem. Lett.* **2001**, *11*, 3161; S. Chackalamannil, D.

Doller, K. Eagen, M. Czarniecki, H.-S. Ahn, C. J. Foster, G. Boykow, *Bioorg. Med. Chem. Lett.* **2001**, *11*, 2851; S. Hanessian, E. Therrien, K. Granberg, I. Nilsson, *Bioorg. Med. Chem. Lett*. **2002**, *12*, 2907; J. Z. Ho, T. S. Gibson, J. E. Semple, *Bioorg. Med. Chem. Lett*. **2002**, *12*, 743; I. Pechik, J. Madrazo, M. W. Mosesson, I. Hernandez, G. L. Gilliland, L. Medved, *Proc. Natl. Acad. Sci. U.S.A*. **2004**, *101*, 2718; S. Chackalamannil, D. Doller, K. Eagen, M. Czarniecki, H.-S. Ahn. C. J. Foster, G. Boykow, *Bioorg. Med. Chem. Lett*. **2001**, *11*, 2851; P. E. J. Sanderson, M. G. Stanton, B. D. Dorsey, T. A. Lyle, C. McDonough, W. M. Sanders, K. L. Savage, A. M. Naylor-Olsen, J. A. Krueger, S. D. Lewis, B. J. Lucas, J. J. Lynch, Y. Yan, *Bioorg. Med. Chem. Lett*. **2003**, *13*, 795; K. Lee, C. W. Park, W.-H. Jung, H. D. Park, S. H. Lee, K. H. Chung, S. K. Park, O. H. Kwon, M. Kang, D.-H. Park, S. K. Lee, E. E. Kim, S. K. Yoon, A. Kim, *J. Med. Chem*. **2003**, *46*, 3612; Y. St-Denis, S. Lévesque, B. Bachand, J. J. Edmunds, L. Leblond, P. Préville, M. Tarazi, P. D. Wincour, M. Arshad Siddiqui, *Bioorg. Med. Chem. Lett*. **2002**, *12*, 1181.

[9] a) U. Obst, V. Grammlich, F. Diederich, L. Weber, D. W. Banner, *Angew. Chem*. **1995**, *107*, 1874; *Angew. Chem*., *Int. Ed*. **1995**, *34*, 1739; b) U. Obst, P. Betschmann, C. Lerner, P. Seiler, F. Diederich, V. Gramlich, L. Weber, D. W. Banner, P. Schönholzer, *Helv. Chim. Acta* **2000**, *83*, 855; c) P. Betschmann, C. Lerner, S. Sahli, U. Obst, F. Diederich, *Chimia* **2000**, *54*, 633.

[10] U. Obst, D. W. Banner, L. Weber, F. Diederich, *Chem. Biol.* **1997**, *4*, 287.

[11] F. Hof, F. Diederich, *Chem. Commun.* **2004**, 477.

[12] P. Betschmann, S. Sahli, F. Diederich, U. Obst, V. Gramlich, *Helv. Chim. Acta* **2002**, *85*, 1210.

[13] a) J. A. Olsen, D. W. Banner, P. Seiler, U. Obst Sander, A. D'Arcy, M. Stihle, K. Müller, F. Diederich, *Angew. Chem*. **2003**, *115*, 2611; *Angew. Chem.*, *Int. Ed.* **2003**, *115*, 2507; b) J. A. Olsen, D. W. Banner, P. Seiler, B. Wagner, T. Tschopp, U. Obst-Sander, M. Kansy, K. Müller, F. Diederich, *ChemBioChem.* **2004**, *5*, 666; c) J. Olsen, P. Seiler, B. Wagner, T. Tschopp, H. Fischer, U. Obst-Sander, D. W. Banner, M. Kansy, K. Müller, F. Diederich, *Org. Biomol. Chem.* **2004**, *2*, 1339.

[14] P. R. Gerber, K. Müller, *J. Comput.-Aided Mol. Design* **1995**, *9*, 251; Gerber Molecular Design (http:www.moloc.ch).

[15] R. Huisgen, *J. Org. Chem.* **1976**, *41*, 403; R. Grigg, J. Idle, P. McMeekin, D. Vipond, *J. Chem. Soc., Chem. Commun.* **1987**, 49; O. Tsuge, S. Kanemasa, *Adv. Heterocycl. Chem.* **1989**, *45*, 231.

[16] G. D. H. Dijkstra, R. M. Kellogg, H. Wynberg, *J. Org. Chem.* **1990**, *55*, 6121; M. Lämmerhofer, N. M. Maier, W. Lindner, *Am. Lab.* **1998**, *30(8)*, 71; G. Chelucci, N. Culeddu, A. Saba, R. Valenti, *Tetrahedron: Asymmetry* **1999**, *10*, 3537; R. M. Pearlstein, B. K. Blackburn, W. M. Davis, K. B. Sharpless, *Angew. Chem.* **1990**, *102*, 710; *Angew. Chem., Int. Ed.* **1990**, *29*, 639.

[17] S. Tsutsumi, T. Okongi, S. Shibahara, S. Ohuchi, E. Hatsushiba, A. A. Patchett, B. G. Christensen, *J. Med. Chem*. **1994**, *37*, 3492.

[18] D. L. Boger, 'Modern Organic Synthesis', TSRI Press, San Diego, 1999, pp. 97 – 112.

[19] H. C. Aspinall, N. Greeves, W.-M. Lee, E. G. McIver, P. M. Smith, *Tetrahedron Lett*. **1997**, *38*, 4679.

[20] G. Wagner, I. Wunderlich, *Pharmazie* **1977**, *32*, 76; A. Pinner, F. Klein, *Ber. Dtsch. Chem. Ges.* **1877**, *10*, 1889.

[21] D. S. Brown, P. Charreau, T. Hansson, S. V. Ley, *Tetrahedron* **1991**, *47*, 1311.

[22] K. Hilpert, J. Ackermann, D. W. Banner, A. Gast, K. Gubernator, P. Hadvary, L. Labler, K. Moller, G. Schmid, T. B. Tschopp, H. van de Waterbeemd, *J. Med. Chem*. **1994**, *37*, 3889.

[23] L. F. Tietze, T. Eicher, 'Reaktionen und Synthesen im organisch-chemischen Praktikum', Thieme, Stuttgart, 1991, pp. 73 – 74.

[24] R. Lottenberg, J. A. Hall, M. Blinder, E. P. Binder, C. M. Jackson, *Biochim. Biophys. Acta* **1983**, *742*, 539.

[25] A. Altomare, G. Cascarano, C. Giacovazzo, A. Guagliardi, M. Burla, G. Polidori, M. Camalli, *J. Appl. Crystallogr*. **1994**, *27*, 435.

[26] G. M. Sheldrick, 'SHELX-97, program for the refinement of crystal structures', University of Göttingen, Germany, 1997.

Received June 3, 2004