Development of a New Class of Inhibitors for the Malarial Aspartic Protease Plasmepsin II Based on a Central 7-Azabicyclo[2.2.1]heptane Scaffold

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Dedicated to Professor *Andrea Vasella* on the occasion of his 60th birthday

Plasmepsin II (PMII), a malarial aspartic protease involved in the catabolism of hemoglobin in parasites of the genus *Plasmodium*, and renin, a human aspartic protease, share 35% sequence identity in their mature chains. Structures of 4-arylpiperidine inhibitors complexed to human renin were reported by *Roche* recently. The major conformational changes, compared to a structure of renin, with a peptidomimetic inhibitor were identified and subsequently modeled in a structure of PMII (*Fig. 1*). This distorted structure of PMII served as active-site model for a novel class of PMII inhibitors, according to a structure-based *de novo* design approach (*Fig. 2*). These newly designed inhibitors feature a rigid 7-azabicyclo[2.2.1]heptane scaffold, which, in its protonated form, is assumed to undergo ionic H-bonding with the two catalytic Asp residues at the active site of PMII. Two substituents depart from the scaffold for occupancy of either the S1/S3 or S2′-pocket and the hydrophobic flap pocket, newly created by the conformational changes in PMII. The inhibitors synthesized starting from *N*-Boc-protected 7-azabicyclo[2.2.1]hept-2-ene (**6**; *Schemes 1–5*) displayed up to single-digit micromolar activity (IC_{50} values) toward PMII and good selectivity towards renin. The clear structure–activity relationship (SAR; *Table*) provides strong validation of the proposed conformational changes in PMII and the occupancy of the resulting hydrophobic flap pocket by our new inhibitors.

1. Introduction. – Malaria, a life-threatening disease caused by parasites of the genus *Plasmodium*, kills each year more than one million people, and more than 500 millions clinical cases are annually registered [1]. The recent emergence of multi-drug-resistant strains of *Plasmodium falciparum*, the parasite that causes the deadliest form of malaria, demands the urgent development of new therapeutic agents with novel modes of action [2–7].

The malarial parasite undergoes a complicated life cycle, which requires stages both in a human host and a female *Anopheles* mosquito [8][9]. During its stay in the human body, the parasites infect erythrocytes and catabolize hemoglobin (Hb) to provide nutrients for its own growth and maturation, as well as for prevention of premature red

blood cell lysis that might occur were parasite growth not compensated by reduced host-cell volume [10]. Several proteinases have been isolated from acidic food vacuoles [11][12], where degradation processes take place. These enzymes are believed to play crucial roles in an ordered Hb degradation pathway. The most-recent studies suggest that plasmepsins I and II (PMI, EC 3.4.23.38, and PMII, EC 3.4.23.39) [13][14], two aspartic proteases, initiate the degradation process by cleaving Hb in a hinge region without known sequence variations. After the initial cut, unraveling of Hb is possible, thereby facilitating further proteolysis by plasmepsin IV (PMIV) [15], another aspartic protease, and a histo-aspartic protease (HAP) [16]. Falcipain-2 [17], a cystein protease, and falcilysin [18], a metallo-protease, should act further downstream, degrading large fragments to small peptides, which are thought to be transported into the cytoplasm for terminal degradation to amino acids [19]. Because degradation of Hb is vital for parasite survival, inhibition of this degradation pathway offers a valid approach for the development of new therapeutic agents.

Plasmepsin I and II have been identified as suitable targets for blocking this degradation process [20]. In fact, a variety of inhibitors of PMII have been described in recent years. They include statine- [21] and hydroxyethylamine-based [22] peptidomimetic inhibitors [23] generated by combinatorial-chemistry approaches, substrate analogs based on allophenylnorstatin [24] and mannitol scaffolds [25], and aminopiperidines discovered at *Actelion* by high-throughput-screening of large compound libraries [26]. In several lead-optimization cycles, activities of the latter compound class were improved to IC_{50} values (concentration of inhibitor at which 50% V_{max} is observed) in the single-digit nanomolar range. Selectivities over cathepsin D, the most closely related human aspartic protease, were higher than 1000-fold (for a review on PMII inhibitors, see [27]). The X-ray crystal structure of recombinant PMII complexed to pepstatin A, a nonspecific aspartic protease inhibitor, has been solved at 2.7-Å resolution [28]. Therefore, this enzyme was selected to serve as the structural matrix for an X-ray structure-based *de novo* design approach as already pursued by the ETH group in a variety of medicinal-chemistry projects [29–31].

High-throughput screening of the *Roche* compound library identified 3-substituted 4-arylpiperidines as novel inhibitors of the human aspartic proteinase renin (EC 3.4.23.15) [32]. The X-ray crystal structures of recombinant human renin complexed with several representatives of this new class of inhibitors have been determined, providing crucial structural information, which might be the basis of a novel paradigm for the inhibition of monomeric aspartic proteases. Binding of the 4-arylpiperidine derivatives, in their *N*-protonated form, to the two Asp residues of the catalytic dyad is accompanied by a major induced-fit adaptation around the active site of the enzyme. The long β-hairpin loop (flap), tightly covering the catalytic dyad when inhibited by a peptidomimetic inhibitor, is shifted into a more-open conformation, with several residues changing side-chain conformation. This structural rearrangement unlocks a new hydrophobic pocket that is occupied by the residue in position 4 of the piperidine scaffold. *Rich* and co-workers postulated recently a similar binding mode for piperidinium-based inhibitors of pepsin (EC 3.4.23.1), another human aspartic protease [33], hinting at the possibility that such conformational changes might also be operative in other eucaryotic aspartic proteases.

The remarkable interdomain flexibility of PMII observed by *Silva et al.* [28], as well as the sequence identity of 35% between mature renin and PMII, prompted us to hypothesize that an induced-fit adaptation as observed in renin might also be effective in PMII. Further evidence for the high conformational flexibility of PMII arose from the crystal structure of proplasmepsin II [34]. Also, some of the 3-substituted 4-arylpiperidines of the *Roche* group were reported in a patent to possess high antimalarial activity, presumably by inhibiting one of the plasmepsin enzymes [35].

The conformational changes observed in structures of human renin complexed to 4-arylpiperidine derivatives were introduced to an available crystal structure of PMII (PDB: 1SME), providing a new active-site matrix, which was subsequently exploited in our design strategy (*Fig. 1,a*). The modeled active site of this distorted PMII structure features three major binding pockets next to the catalytic dyad (*Fig. 1,b*) namely *i*) the large hydrophobic S1/S3 pocket (Phe120, Phe111, Met15), *ii*) the more-hydrophilic S2′ pocket (Leu131, Tyr192), and *iii*) the lipophilic flap pocket, narrow at its entry and spacious at its rear. The unlocking of the latter sub-site results after a cascade-like reaction, including a lifting of the flap and side-chain rearrangements of Leu73, Tyr75, and Trp39 (pepsin numbering), as well as the disruption of the H-bond between the latter two amino acids (*Fig. 1,b*).

With a modified structure of PMII, featuring conformational properties of a renin 4-arylpiperidine inhibitor complex and serving as active-site template, we designed two classes of nonpeptidic PMII inhibitors. Synthesis and *in vitro* evaluation of these new lead compounds, showing up to single-digit micromolar activities, are described in this and the following paper [36] (for a preliminary communication of parts of this work, see [37]).

2. Results and Discussion. – 2.1. *Design of the First Lead Structure.* With the *Roche*-in-house molecular-modeling program MOLOC [38], we identified 7-azabicyclo[2.2.1]-heptane as a suitable central scaffold for new PMII inhibitors (for antimalarial activity of some 8-azabicyclo[3.2.1]octane derivatives, see [35]). This bicyclus has a pK_a value of 10.8 [39] and should be fully protonated in the acidic vacuoles (estimated pH 5.0–5.4 [40]) where Hb degradation takes place. The protonated N-atom was expected to form two charge-re-inforced H-bonds to the Asp residues of the catalytic dyad, by analogy with the renin complexes of the 4-arylpiperidinium inhibitors from *Roche* [32].

To produce inhibitors with molecular weights not exceeding 500 [41], we decided to decorate the scaffold with two residues only, assuming that they should be pointing into the more hydrophobic S1/S3 and flap pockets, while leaving the less-hydrophobic S2′ pocket empty. Modeling suggested that C(2) and C(3) of the bicyclic scaffold would furnish suitable anchoring points for these substituents. Thus, compound (±)-**1** (*Fig. 2*) was designed as initial lead. In a PMII complex of (2*S*,3*R*)-**1**, the naphthyl moiety should occupy the S1/S3 pocket, establishing *Van der Waals* contacts with the side chains of Phe111, Phe120, and Met15 (for a review on sulfur–aromatic interactions, see [42]). The narrow entry of the flap pocket should be occupied by the benzyloxy moiety, establishing *Van der Waals* contacts with the side chains of Met75, Phe111, and Tyr77. The rather spacious lipophilic environment at the rear end of the flap pocket would be

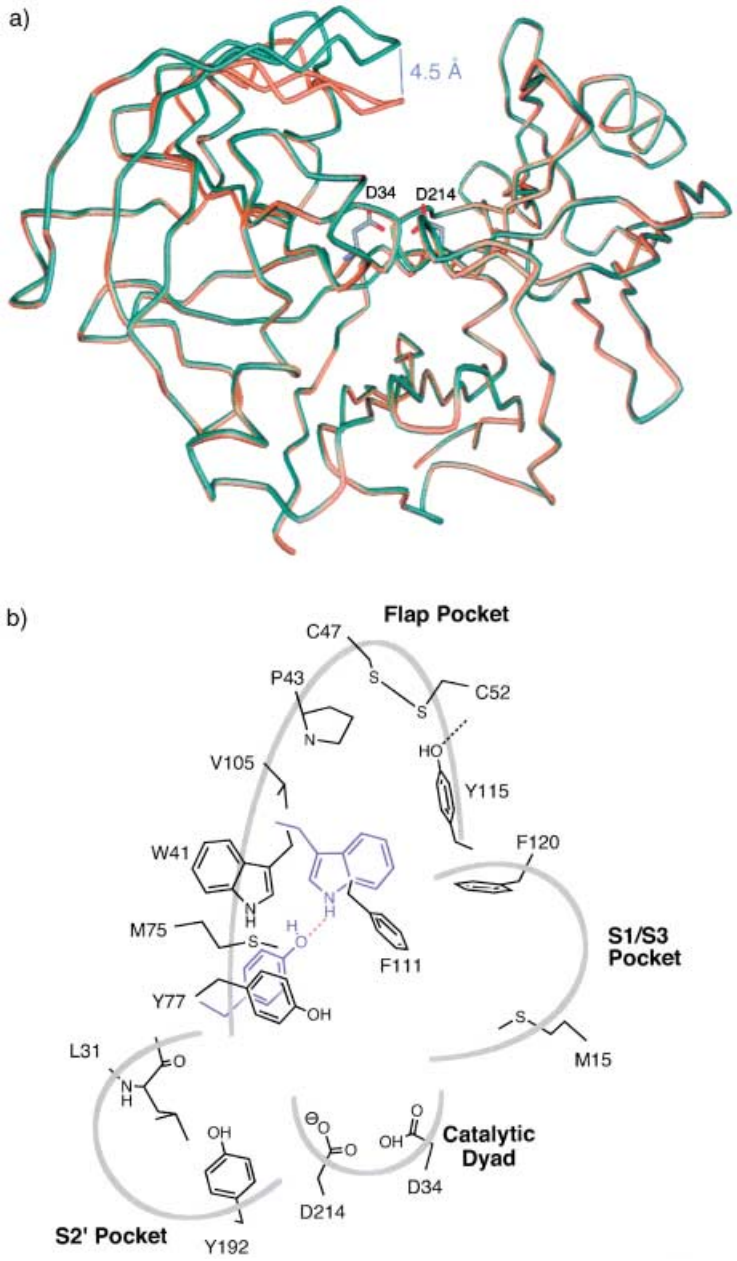
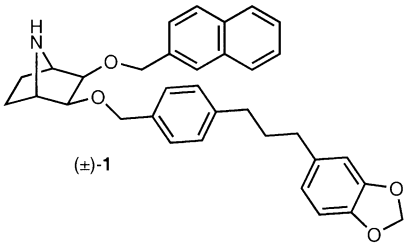


Fig. 1. *Structural basis for inhibitor design*. *a*) Superposition of the X-ray crystal structure of PMII (orange) with the modeled structure (green), where the flap has been moved away from the catalytic dyad, consisting of Asp34 and Asp214. *b*) Schematic representation of the active site of the modeled structure. Shown in blue is the original location of the H-bonded side chains of Trp41 and Tyr77 before the flap moves.



suitably filled by a piperonyl (=1,3-benzodioxol) ring sandwiched between the side chains of Val105 and Tyr115 and linked by a propyl chain to the *para*-position of the benzyloxy moiety.

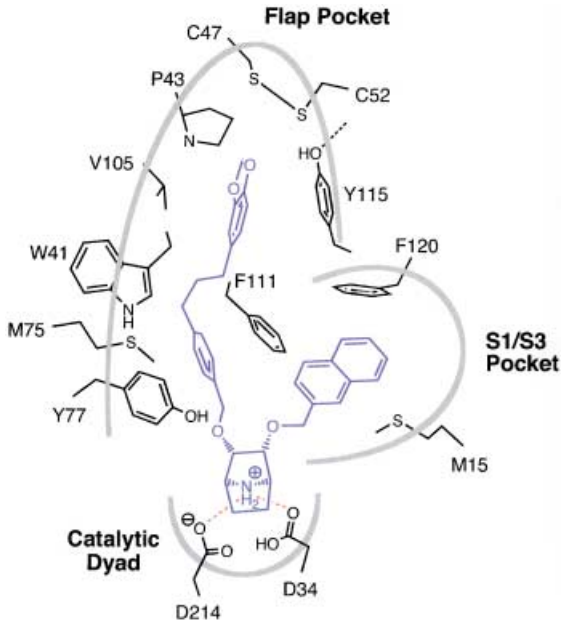
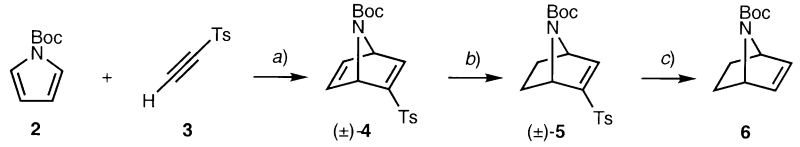


Fig. 2. *Representation of (2S,3R)-***1** *in the active site of the modeled structure of PMII*

2.2. *Synthesis of (±)-***1**. Synthesis of the lead compound started with the *Diels–Alder* reaction between *N*-Boc-protected 1*H*-pyrrole **2** [43] and alkyne **3** [44], furnishing (±)-**4** in 80% yield [45] (*Scheme 1*). Selective hydrogenation of the more electron-rich C=C bond under mild conditions provided (±)-**5** in quantitative yield. Desulfonylation of (±)-**5** with Na/Hg afforded **6** in acceptable yield (53%), by analogy with the work of *Liang et al.* [46]. However, the large excess of Na/Hg (20 equiv.) required for this one-step reductive cleavage of the Ts group prompted us to investigate an alternative route to **6**.

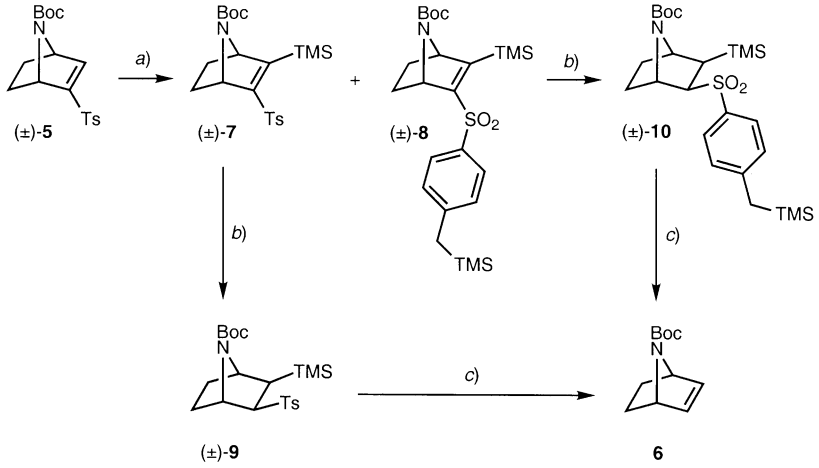
Scheme 1. *Synthesis of the Central Scaffold* **6**



a) 80°, 24 h; 80%. *b*) Ni_2B, EtOH, r.t., 3 h; 100%. *c*) Na/Hg (2.5%), Na_2HPO_4/NaH_2PO_4, AcOEt/*t*-BuOH, r.t., 24 h; 53%. Boc = (*tert*-butoxy)carbonyl.

The three-step desulfonylation described by *Kaufmann* and co-workers appeared to be a more suitable solution [47]. Initial hydrosilylation of (±)-**5**, reported to proceed in high yield, however, afforded (±)-**7** in 28% yield only. On the other hand, metallation (BuLi/TMEDA) followed by reaction with TMSCl gave (±)-**7** in 53% yield along with side product (±)-**8** (19%; *Scheme 2*). Hydrogenation of (±)-**7** and (±)-**8** with diimide, generated *in situ* from dipotassium azodicarboxylate, afforded with complete *endo*-selectivity (±)-**9** and (±)-**10** in 92 and 90% yield, respectively. Treatment of (±)-**9** or (±)-**10** with $Bu_4NF \cdot 3\,H_2O$ furnished **6** in 72 and 81% yield, respectively (*Scheme 2*).

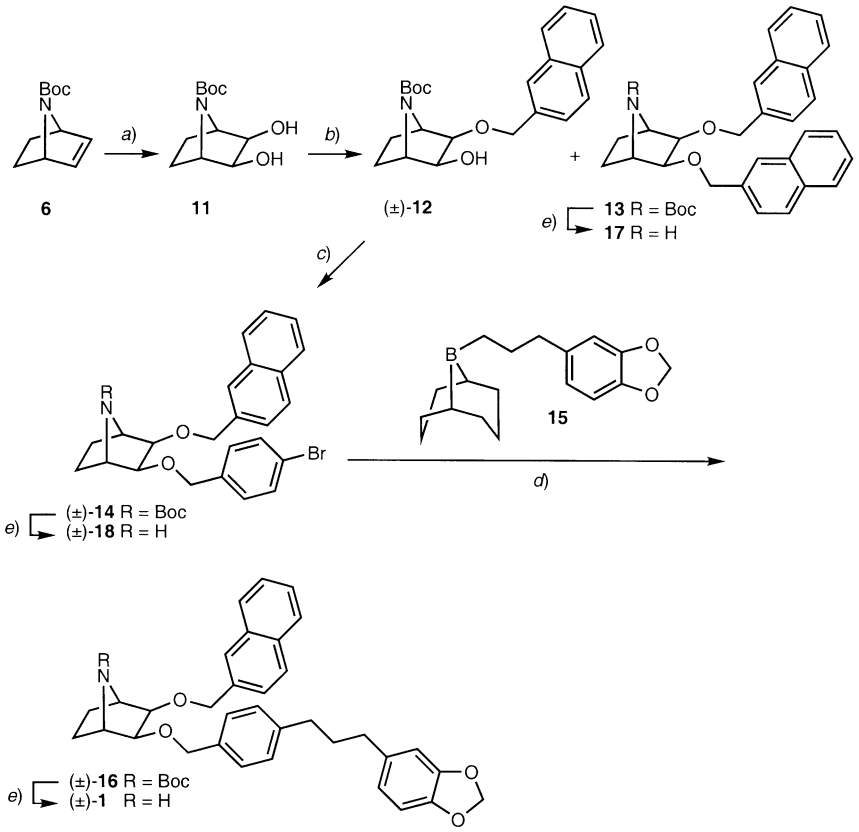
Scheme 2. *Alternative Route to* **6**



a) TMEDA, BuLi, TMSCl, THF, −78°, 1 h; 53% ((±)-**7**), 19% ((±)-**8**). *b*) N_2H_2, MeOH, r.t., 12 h – 6 d; 92% ((±)-**9**), 90% ((±)-**10**). *c*) $Bu_4NF \cdot 3\,H_2O$, THF, r.t., 12 h; 72 – 81%. TMEDA = *N,N,N′,N′*-Tetramethylethylenediamine; TMS = Me_3Si.

Dihydroxylation of **6** with OsO_4/NMO cleanly led to the *exo-cis*-diol **11** (100%) [48], and *Williamson* ether synthesis (2-(bromomethyl)naphthalene/NaH) provided mono-ether (±)-**12** (68%) together with di-ether **13** (16%) (*Scheme 3*). A second *Williamson* ether synthesis of (±)-**12** with 4-bromobenzyl bromide afforded (±)-**14** in 97% yield. Subsequent *Suzuki* cross-coupling with borane **15** produced (±)-**16** (49%), which was deprotected to the target compound (±)-**1** in 86% yield. For comparison, **13** and (±)-**14** were also deprotected, furnishing **17** and (±)-**18** in 60 and 89% yield, respectively.

Scheme 3. *Synthesis of (±)-***1**



a) NMO, OsO_4, $NaHCO_3$, H_2O/*t*-BuOH/THF, r.t., 2 d; 100%. *b*) 2-(Bromomethyl)naphthalene, NaH, THF, 0° → r.t., 1 d; 68% ((±)-**12**), 16% (**13**). *c*) 4-Bromobenzyl bromide, NaH, THF, 0° → r.t., 12 h; 97%. *d*) [$PdCl_2$(dppf)], MeONa, THF, Δ, 50 h; 49%. e) TFA, CH_2Cl_2, r.t., 30 min, 60–89%. NMO = 4-Methylmorpholine 4-oxide; dppf = 1,1′-bis(diphenylphosphino)ferrocene; TFA = trifluoroacetic acid.

2.3. *Biological Activity.* The *in vitro* activity of compounds (±)-**1**, **17**, and (±)-**18** toward PMII was determined in a fluorescence assay (*Table*; for details, see the *Exper. Part*). Target compound (±)-**1** (IC_{50} = 70 μM) was found to bind much better than **17** (700 μM) or (±)-**18** (> 1000 μM; limit of the assay). The shorter substituents of **17** and (±)-**18**, proposed to point into the flap pocket, probably leave the rear of this subsite unoccupied, leading to a substantial loss in activity. On the other hand, the affinity measured for (±)-**1** corroborated the suitability of the 7-azabicyclo[2.2.1]heptane scaffold for the development of more-potent inhibitors of PMII.

2.4. *Second-Generation Inhibitors.* Considering the binding data obtained with the first series of inhibitors, we intended to specifically occupy the rear of the flap pocket, which appeared to have a strong influence on biological activity. According to molecular modeling, the 1,3-benzothiazole residue, as seen in (±)-**19**, seemed to

Table. *Biological Activities of Designed Inhibitors of Plasmepsin II*

Inhibitor	IC_{50}				
	PMII[a]) [μM]	PMIV[b]) [μM]	CatD[c]) [μM]	CatE[d]) [μM]	Renin [μM]
(±)-**1**	70	n.d.[e])	n.d.	n.d.	n.d.
17	700	n.d.	n.d.	n.d.	n.d.
(±)-**18**	>1000	n.d.	n.d.	n.d.	n.d.
(±)-**19**	9	39	15	20	>100
(±)-**20**	10	61	16	35	>100
(−)-**19**	5	61	8	16	>100
(+)-**19**	4	61	12	25	>100

[a]) Plasmepsin II. [b]) Plasmepsin IV. [c]) Cathepsin D. [d]) Cathepsin E. [e]) Not determined.

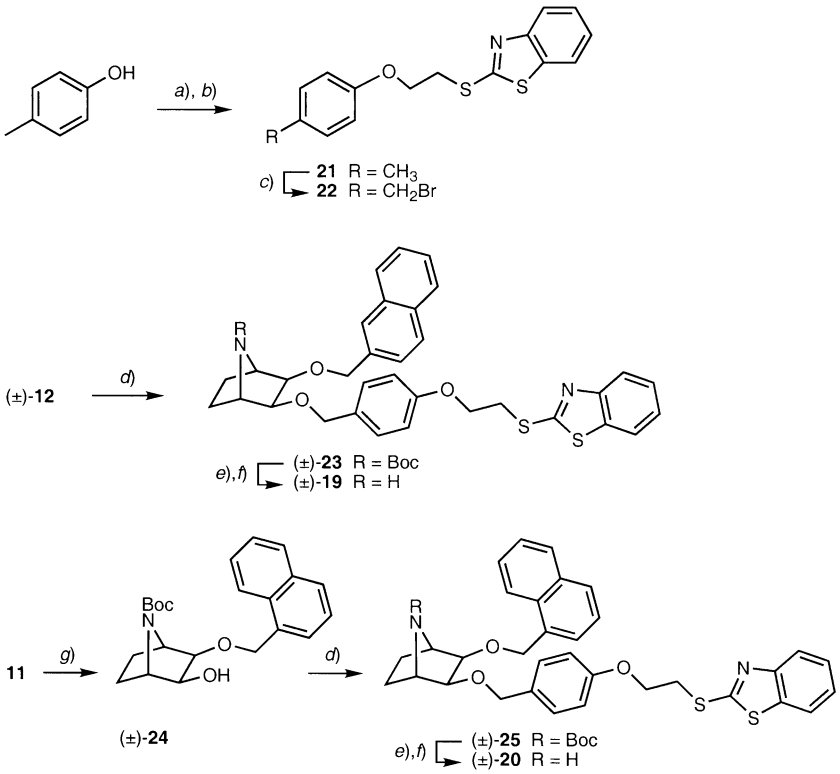
be superior over the 1,3-benzodioxole moiety (in (±)-**1**), thereby inverting the orientation of the heterocycle to present the benzene ring directly to the hydrophobic residues at the rear of the pocket. Furthermore, a different linker to the naphthyl substituent, possibly favoring its positioning in the S1/S3-pocket, was explored in (±)-**20**.

Starting from *p*-cresol, a sequence of nucleophilic substitutions furnished aryl ether **21**, which was brominated with NBS to afford **22** (*Scheme 4*). *Williamson* ether synthesis of **22** with (±)-**12** provided the protected inhibitor (±)-**23**. Subsequent *N*-Boc deprotection under standard conditions (TFA, CH_2Cl_2) yielded unexpected results. The desired removal of the Boc protecting group was accompanied by cleavage of the 4-alkoxy-substituted benzyl ether moiety. Selective Boc-group removal by the mild and selective method reported by *Nigam et al.* [49], with anhydrous $ZnBr_2$ in CH_2Cl_2, was not successful either. Finally, a two-step procedure led to target compound (±)-**19** under very mild conditions. Conversion of (±)-**23** to a moisture- and acid-sensitive (*tert*-butyl)dimethylsilyl carbamate [50], followed by immediate treatment of the crude product with F^-, provided (±)-**19** in 82% yield. By analogy, target compound (±)-**20** was prepared starting from **11**, *via* (±)-**24** and (±)-**25**.

Biological activity of the two new target compounds toward PMII and PMIV, as well as the three human aspartic proteases cathepsin D (CatD; EC 3.4.23.5), cathepsin E (CatE; EC 3.4.23.34), and renin, was determined in an automated assay (see *Exper. Part*). Inhibitors (±)-**19** and (±)-**20** exhibited IC_{50} values of 9 and 10 μM, respectively, thereby showing substantially enhanced activity compared with first-generation compound (±)-**1** (*Table*). Apparently, the spacious S1/S3 pocket can accommodate naphthyl residues in different orientations ((±)-**19** *vs.* (±)-**20**). Most importantly, a modeling-predicted increase in binding affinity upon better occupancy of the flap pocket was validated experimentally ((±)-**1** *vs.* (±)-**19**). This provides an encouraging boost for future modeling-driven lead-optimization cycles.

This second series of PMII inhibitors showed good selectivity towards renin, but poor selectivity with respect to CatD and CatE. These findings suggest that the latter two human aspartic proteases may also undergo induced-fit adaptations, thereby forming a flap pocket that can be occupied by the 1,3-benzothiazole residue of (±)-**19** and (±)-**20**.

Scheme 4. *Synthesis of (±)-***19** *and (±)-***20**



a) 1,2-Dibromoethane, NaOH, H_2O, Δ, 6 h; 98%. *b*) 2-Sulfanylbenzothiazole, NaH, DMF, 80°, 1 h; 90%. *c*) NBS, AIBN, $CHCl_3$, Δ, 4 h; 19%. *d*) **22**, NaH, THF, 0° → r.t., 16 h; 37–82%. *e*) TBDMSOTf, 2,6-lutidine, CH_2Cl_2, r.t., 30 min. *f*) Bu_4NF, THF, r.t., 1–2 h; 71–82% over 2 steps. *g*) 1-(Bromomethyl)naphthalene, NaH, THF, 0° → r.t., 15 h; 43%. NBS = *N*-Bromosuccinimide; AIBN = azobis(isobutyronitrile); TBDMS = (*tert*-butyl)dimethylsilyl; TfO = trifluoromethanesulfonate.

2.5. *Optical Resolution of (±)-***19**. Initial attempts to form esters of (−)-D-mandelic acid with alcohol (±)-**12** and to separate the mixture of diastereoisomers by column chromatography were unsuccessful. In contrast, esterification of (−)-camphanic acid with (±)-**12** furnished a mixture of diastereoisomers, which could be separated by column chromatography, to afford **26** and **27** (*Scheme 5*). The X-ray crystal structure of **26** was subsequently determined, which allowed the assignment of the absolute configuration to the two diastereoisomers (*Fig. 3*). Basic ester hydrolysis finally led to optically pure (+)-**12** and (−)-**12**, which were further processed according to the synthetic route described above (*Scheme 4*) to yield (+)-(2*S*,3*R*)-**19** and (−)-(2*R*,3*S*)-**19**, respectively.

Both antipodes displayed similar IC_{50} values ((−)-**19**: 5 μM and (+)-**19**: 4 μM; *Table*); they are within the uncertainty of the biological assay identical to the activity of racemate (±)-**19** (9 μM). This result leads us to conclude that either the spacious active site of PMII may undergo major conformational changes upon complexation of small

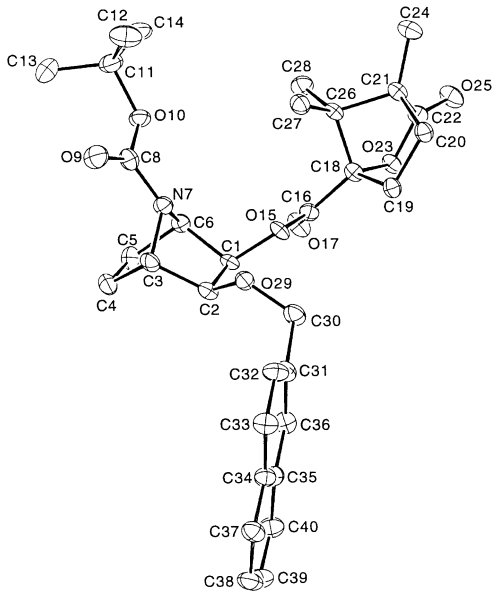


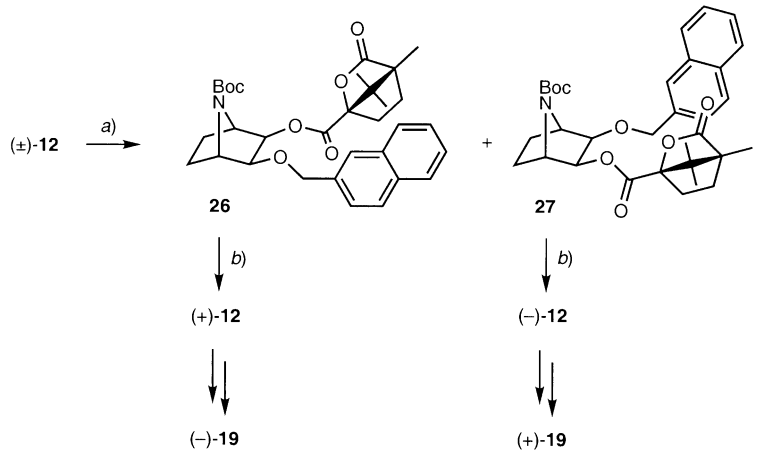
Fig. 3. *ORTEP Representation of* **26** *with vibrational ellipsoids shown at the 30% probability level.* Arbitrary numbering.

molecules or that hydrophobic inhibitors can sufficiently adapt to spatial conditions dictated by the enzyme active site. Both enantiomers can be fit into the active site of the modeled structure of PMII, with the 1,3-benzothiazole moiety apparently being located in the flap pocket in both cases. Consequently, the naphthyl moiety should be positioned either in the S1/S3 pocket for the first enantiomer, or in the S2′ subsite for the other antipode. Molecular modeling indeed suggests that the S1/S3 and S2′ pockets should both be able to accommodate the naphthyl residue.

3. Conclusions. – In this study on the rational development of plasmepsin II (PMII) inhibitors, we report a successful extension of our program on X-ray-structure-based design of nonpeptidic enzyme inhibitors. In previous work [29–31], the X-ray crystal structures of enzyme–inhibitor complexes were used unchanged for design purposes. In contrast, in this work, the crystal structure of PMII was adapted to a more-open conformation, based on observations made for the structurally related human aspartic protease renin and the 35% sequence identity between mature renin and PMII, respectively.

Based on this modified PMII structure, which features a new hydrophobic flap pocket, we designed a new class of inhibitors with promising biological activity. They feature a rigid 7-azabicyclo[2.2.1]heptane scaffold, which, in protonated form, is assumed to undergo ionic H-bonding with the two catalytic Asp residues at the active site of PMII. Optimization of the two inhibitor substituents, which are assumed to point into the flap pocket and the S1/S3 or S2′-pocket (depending on the enantiomer of the chiral inhibitors), led to (±)-**19**, which displayed an IC_{50} value of 9 μM.

Scheme 5. *Optical Resolution of* (±)-**19**



a) (−)-Camphanoyl chloride, Et_3N, CH_2Cl_2, r.t., 20 h; 38% (**26**), 30% (**27**). *b*) aq. KOH (3M), MeOH/CH_2Cl_2, r.t., 30 min; 74–98%.

The following lessons can be drawn: *i*) the observed SAR (*Table*) provides strong support for the proposed conformational changes in PMII, leading to the opening of a hydrophobic flap pocket. Correct occupancy of this pocket in terms of shape and electronic complementarity appears to be crucial; however, the nature of the substituents positioned in this area must be hydrophobic. In particular, complete occupation of this pocket seems absolutely necessary for good affinity as reflected by the strong loss of activity in **17** and (±)-**18** equipped with inadequate, short substituents. Further evidence for the binding free energy to be gained in this unlocked hydrophobic pocket was obtained from the significantly enhanced affinity displayed by (±)-**19** and (±)-**20** in comparison to (±)-**1**. Our proposal for a conformational rearrangement of the entire flap, as well as selected parts of the protein core in PMII, receives strong support from a yet-unpublished report on an X-ray crystal structure of a complex of PMII inhibited by a 4-arylpiperidine derivative from *Roche* [51]. *ii*) The naphthyl moieties seem to be accepted in a number of different conformations by the spacious S1/S3 pocket. The poor enantioselectivity observed with (−)-**19** and (+)-**19** can be explained by potential adaptations of the protein or incomplete filling of the protein pockets by these two molecules. These findings will certainly benefit future refinements of the molecular modeling in design and synthesis of new generations of more-potent and -selective PMII inhibitors.

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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: **2** [43], **3** [44], (±)-**4** [45], (±)-**5**, and **6** [46]. THF was freshly distilled from sodium benzophenone ketyl, CH_2Cl_2 from CaH_2. Evaporation *in vacuo* was conducted at H_2O aspirator pressure. 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; *Alox ICN Alumina B*, Act. II from *ICN Biochemicals*. TLC: SiO_2 *60* F_{245}, *Merck*, visualization by UV light at 254 nm or by staining with a soln. of $KMnO_4$ (3 g) and K_2CO_3 (20 g) in 5% aq. NaOH soln. (5 ml) and H_2O (300 ml). M.p.: *Büchi B540* melting point apparatus; uncorrected. Optical rotations: *Perkin-Elmer 241* polarimeter; 1-dm cell, $\lambda = 589$ nm (Na D-line). IR [cm^{-1}]: *Perkin-Elmer 1600-FT* spectrometer. NMR (^1H,^{13}C): *Varian Gemini-200, Varian Gemini-300*, or *Bruker AMX-500*; spectra were recorded at r.t. with solvent peak as reference. MS (*m*/*z* (%)): EI-MS: *VG-TRIBRID* spectrometer at 70 eV; ESI-MS: *Perkin-Elmer Sciex API III* spectrometer; HR-MALDI-MS: *IonSpec Ultima* (2,5-dihydroxybenzoic acid (DHB) matrix). Elemental analyses were performed by the *Mikrolabor* at the *Laboratorium für Organische Chemie, ETH Zürich*.

Biological Assays. The biological activities of (±)-**1**, **17**, and (±)-**18** were determined as follows: the FRET (fluorescence resonance energy transfer)-based assay used the quenched fluorogenic substrate 4-{[4-(dimethylamino)phenyl]azo}benzoic acid (DABCYL)-Arg-Leu-Glu-Arg-Thr-Phe-Leu-Ser-Phe-Pro-Thr-Thr-Asp-Arg-5-[(2-aminoethyl)amino]naphthalene-1-sulfonic acid (EDANS), whose peptide sequence is derived from the natural Hb processing site for PMII. Incubation of PMII with the fluorogenic substrate resulted in specific cleavage at the Phe–Leu bond and a time-dependent increase in fluorescence intensity that was linearly related to the extent of substrate hydrolysis. The standard conditions for hydrolysis at 37° were 20 mM AcONa, pH 4.7, containing activated PMII (2 ng; the Pro-PMII was prepared and purified as described by *Hill et al.* and was activated by incubation in 20 mM AcONa, pH 4.7, at r.t. for 60 min. [14]), 20 μM peptide (stock soln.: 5 mM in 50% Me_2SO) in a total volume of 100 μl on a microtiter plate (*Black ViewPlate*™, *Packard*). The hydrolysis of the substrate by PMII was monitored by measuring the fluorescence at $\lambda_{em} = 530$ nm and $\lambda_{em} = 360$ nm in a *Fluorescence Measurement System Millipore CytoFluor 2350* immediately after starting the reaction and after an incubation period of 7 h.

The biological activity of (±)-**19**, (±)-**20**, (+)-**19**, and (−)-**19** was determined in automated assays [37]. The proteolytic activities of plasmepsins II and IV, and cathepsins D and E were determined in a FRET-based assay with a substrate purchased from *Bachem* (# *M-2120*). Approx. 1 nM enzyme was incubated with 1 mM substrate at 37° in 50 mM AcONa (pH 5), 12.5% (*w*/*v*) glycerol, 0.1% (*w*/*v*) BSA (bovine serum albumin), and 10% Me_2SO. Enzyme activity was derived from the turnover rate of the substrate and monitored by the increase of the fluorescent signal over time. Fluorescence was determined with a *FLUOstar Galaxy* from *BMG* using excitation and emission filters of 355 and 520 nm. The proteolytic activity of renin was determined in two steps. Approx. 2 pM renin was incubated at 37° with 0.5 μM of a peptide substrate (*Bachem*, # *M-1120*), whose sequence is derived from the renin cleavage site in angiotensinogen. The assay buffer was PBS (phosphate-buffered saline; pH 7.4), 1 mM EDTA (ethylenediaminetetraacetic acid), 1 mM 8-hydroxyquinoline sulfate, 0.1% BSA, and 5% Me_2SO. Angiotensin 1 produced by renin was subsequently quantified with an enzyme immunoassay, by comparison with an angiotensin 1 standard curve. Test compounds were dissolved and diluted in 100% Me_2SO.

IC_{50} Values for some of the inhibitors in this and the following paper [36] were also determined by both methods; good agreement between the data was found.

tert-*Butyl 2-[(4-Methylphenyl)sulfonyl]-3-(trimethylsilyl)-7-azabicyclo[2.2.1]hept-2-ene-7-carboxylate* ((±)-**7**) *and* tert-*Butyl 2-(Trimethylsilyl)-3-({4-[(trimethylsilyl)methyl]phenyl}sulfonyl)-7-azabicyclo[2.2.1]hept-2-ene-7-carboxylate* ((±)-**8**). To a well-stirred soln. of TMEDA (0.70 ml, 4.64 mmol) in THF (30 ml), a freshly titrated soln. of BuLi in hexane (1.01M, 4.58 ml, 4.64 mmol) was added dropwise under Ar at −78°. A soln. of (±)-**5** (1.5 g, 4.29 mmol) in THF (9 ml) was then added at −78°. The mixture was stirred for 1 h, and freshly distilled TMSCl (0.59 ml, 5.15 mmol) was added at −70°. After warming to r.t., an equal volume of sat. aq. NH_4Cl soln. was added, leading to the formation of a white precipitate. After separation of the org. phase, the aq. phase was extracted with Et_2O (3×). The combined org. layers were washed with sat. aq. $NaHCO_3$ soln., dried ($MgSO_4$), and concentrated *in vacuo* to give a brown oil as crude product. CC (SiO_2; hexane/AcOEt 3:1) yielded (±)-**7** (961 mg, 53%) together with (±)-**8** (406 mg, 19%).

*Data of (±)-***7**: Yellow oil. IR ($CHCl_3$): 3019*w*, 1697*s*, 1595*w*, 1297*m*, 1145*s*, 840*m*. ^1H-NMR ($CDCl_3$, 300 MHz): 0.36 (*s*, 9 H); 1.21 (br. *s*, 9 H); 1.33–1.52 (*m*, 2 H); 1.87–2.02 (*m*, 2 H); 2.44 (*s*, 3 H); 4.68–4.70 (*m*, 1 H); 4.88 (br. *s*, 1 H); 7.35 (*d*, $J = 8.1$, 2 H); 7.80 (*d*, $J = 8.1$, 2 H). ^{13}C-NMR ($CDCl_3$, 75.5 MHz): 0.37; 21.64; 24.18 (2×); 27.85; 62.98; 66.86; 80.53; 128.15 (2×); 130.19 (2×); 137.63; 144.76; 153.11; 155.33; 161.58. HR-MALDI-MS (DHB): 444.1631 ($[M + Na]^+$, $C_{21}H_{31}NNaO_4SSi^+$; calc. 444.1641). Anal. calc. for $C_{21}H_{31}NO_4SSi$ (421.63): C 59.82, H 7.41, N 3.32; found: C 59.71, H 7.27, N 3.52.

Data of (±)-**8**: Pale-yellow solid. M.p. 87°. IR (KBr): 2944*s*, 1706*s*, 1583*w*, 1293*s*, 1270*s*, 1162*s*, 1150*s*, 844*s*. ^{1}H-NMR ($CDCl_3$, 300 MHz): 0.35 (*s*, 9 H); 0.43 (*s*, 9 H); 1.12–1.21 (*m*, 2 H); 1.33 (br. *s*, 9 H); 1.86–2.02 (*m*, 2 H); 2.42 (*s*, 2 H); 4.52–4.53 (*m*, 1 H); 4.92 (br. *s*, 1 H); 7.25–7.27 (*m*, 2 H); 7.57–7.60 (*m*, 2 H). ^{13}C-NMR ($CDCl_3$, 75.5 MHz): −0.40; 1.46; 21.72; 24.53 (2×); 28.06; 62.74; 66.79; 80.57; 129.64 (2×); 130.35; 137.57 (2×); 140.10; 142.69; 155.13; 160.93. HR-MALDI-MS (DHB): 516.2026 (100, $[M+Na]^+$, $C_{24}H_{39}NNaO_4SSi_2^+$; calc. 516.2036).

tert-*Butyl 2-[(4-Methylphenyl)sulfonyl]-3-(trimethylsilyl)-7-azabicyclo[2.2.1]heptane-7-carboxylate* ((±)-**9**). Freshly prepared dipotassium azodicarboxylate (1.02 g, 5.27 mmol) [52] was added to a stirred soln. of (±)-**7** (740 mg, 1.76 mmol) in anh. MeOH (18 ml) at 0°. The reduction was initiated by adding few drops of aq. AcOH (50%). The ice bath was removed, and the mixture was allowed to stir overnight. H_2O was added, and the mixture was extracted with Et_2O (3×). The combined org. phases were washed with H_2O (1×) and sat. aq. NaCl soln. (2×), dried ($MgSO_4$), and concentrated *in vacuo* to yield (±)-**9** (686 mg, 92%), which was used without further purification in the next step. An anal. sample was obtained by CC (SiO_2; hexane/AcOEt 3:1). White solid. M.p. 145°. IR (KBr): 2967*s*, 1700*s*, 1589*m*, 1283*s*, 1174*s*, 1133*s*, 850*s*. ^{1}H-NMR ($CDCl_3$, 300 MHz): 0.33 (*s*, 9 H); 1.41 (*s*, 9 H); 1.44–1.49 (*m*, 2 H); 1.75–1.85 (*m*, 2 H); 2.47 (*s*, 3 H); 2.60–2.69 (*m*, 1 H); 3.79 (br. *m*, 1 H); 3.86 (br. *s*, 1 H); 4.30 (br. *s*, 1 H); 7.38 (*d*, $J=8.5$, 2 H); 7.77 (*d*, $J=8.5$, 2 H). ^{13}C-NMR ($CDCl_3$, 75.5 MHz): 0.55; 13.90; 21.63; 23.51; 27.31; 28.23; 59.31; 62.40; 67.77; 80.49; 128.05 (2×); 130.28 (2×); 137.59; 144.88; 155.02. HR-MALDI-MS (DHB): 446.1788 ($[M+Na]^+$, $C_{21}H_{33}NNaO_4SSi^+$; calc. 446.1797).

tert-*Butyl 2-(Trimethylsilyl)-3-({4-[(trimethylsilyl)methyl]phenyl}sulfonyl)-7-azabicyclo[2.2.1]heptane-7-carboxylate* ((±)-**10**). Freshly prepared dipotassium azodicarboxylate (2.32 g, 11.94 mmol) was added to a stirred soln. of (±)-**8** (1.18 g, 2.39 mmol) in anh. MeOH (25 ml) at 0°. The reduction was initiated by adding few drops of 50% aq. AcOH soln. The mixture was stirred for 3 d at r.t., another portion of dipotassium azodicarboxylate (1.81 g, 9.31 mmol) and a few drops of a 50% aq. AcOH soln. were added, and the mixture was stirred for another 3 d. After addition of H_2O, the aq. phase was extracted with Et_2O (3×). The combined org. phases were washed with H_2O (1 × 100 ml) and sat. aq. NaCl soln. (2×), dried ($MgSO_4$), and concentrated *in vacuo* to yield (±)-**10** (1.06 g, 90%), which was used without further purification in the next step. An anal. sample was obtained by CC (SiO_2; hexane/AcOEt 3:1). White solid. M.p. 154°. IR (KBr): 2969*s*, 1708*s*, 1601*m*, 1289*s*, 1272*s*, 1179*s*, 1138*s*, 843*s*. ^{1}H-NMR ($CDCl_3$, 200 MHz): 0.34 (*s*, 9 H); 0.41 (*s*, 9 H); 1.38 (br. *s*, 9 H); 1.43–1.49 (*m*, 2 H); 1.77–1.83 (*m*, 2 H); 2.45 (*s*, 2 H); 2.84–2.90 (*m*, 1 H); 3.68–3.71 (*m*, 1 H); 3.80–3.87 (*m*, 1 H); 4.26–4.30 (*m*, 1 H); 7.36 (*d*, $J=7.4$, 2 H); 7.81 (*d*, $J=7.4$, 2 H). ^{13}C-NMR ($CDCl_3$, 75.5 MHz): 0.51; 1.57; 14.07; 21.73; 24.61 (2×); 28.17; 59.87; 64.12; 69.11; 80.51; 129.72 (2×); 130.46; 137.81 (2×); 142.83; 155.09. HR-MALDI-MS (DHB): 518.2182 ($[M+Na]^+$, $C_{24}H_{41}NNaO_4SSi_2^+$; calc. 518.2192).

tert-*Butyl 7-Azabicyclo[2.2.1]hept-2-ene-7-carboxylate* (**6**) [46]. *Procedure A:* To a stirred soln. of (±)-**9** (1.71 g, 4.04 mmol) in THF (210 ml), $Bu_4NF \cdot 3\ H_2O$ (7.64 g, 24.22 mmol) was added, and the mixture was stirred for 12 h at r.t under Ar. H_2O and pentane were added and, after separation of the org. phase, the aq. phase was extracted with Et_2O (2×). The combined org. layers were dried ($MgSO_4$) and concentrated *in vacuo* to yield a brown oil. CC (SiO_2; pentane/Et_2O 1:1) furnished **6** (642 mg, 81%). Colorless liquid. ^{1}H-NMR ($CDCl_3$, 200 MHz): 1.09–1.14 (*m*, 2 H); 1.44 (*s*, 9 H); 1.84–1.90 (*m*, 2 H); 4.68 (br. *s*, 2 H); 6.24 (br. *s*, 2 H).

Procedure B: To a stirred soln. of (±)-**10** (1.08 g, 2.17 mmol) in THF (126 ml), $Bu_4NF \cdot 3\ H_2O$ (7.64 g, 24.22 mmol) was added, and the mixture was stirred for 12 h at r.t under Ar. Workup as described for *Procedure A* afforded **6** (307 mg, 72%).

tert-*Butyl 2,3-Dihydroxy-7-azabicyclo[2.2.1]heptane-7-carboxylate* (**11**). A soln. of **6** (1.18 g, 6.04 mmol) in THF (9 ml), NMO (1.23 g, 9.08 mmol), and OsO_4 (0.6 ml of a 2.5% soln. in *t*-BuOH) were added in succession to a stirred soln. of $NaHCO_3$ (0.51 g, 6.04 mmol) in *t*-BuOH (48 ml) and H_2O (12 ml). After stirring at r.t. for 2 d under Ar, an aq. soln. of $NaHSO_4$ (10%, 25 ml) was added. Stirring was continued for 1 h, and AcOEt was added. After separation of the aq. phase, the org. phase was washed with sat. aq. NaCl soln., dried ($MgSO_4$), and concentrated *in vacuo* to yield **11** (1.38 g, 100%). Pale-yellow solid. M.p. 79°. IR ($CHCl_3$): 3432*w*, 3023*s*, 1676*m*, 1368*s*, 1208*s*, 1142*m*. ^{1}H-NMR ($CDCl_3$, 500 MHz): 1.27–1.32 (*m*, 2 H); 1.46 (*s*, 9 H); 1.65–1.71 (*m*, 2 H); 3.06 (br. *s*, 2 H); 3.80 (*s*, 2 H); 4.12 (*s*, 2 H). ^{13}C-NMR ($CDCl_3$, 75.5 MHz): 24.23 (2×); 28.18; 62.62 (2×); 74.85 (2×); 80.53; 158.10. EI-MS: 229 (M^+). Anal. calc. for $C_{11}H_{19}NO_4$ (229.28): C 57.63, H 8.35, N 6.11; found: C 57.42, H 8.21, N 6.06.

tert-*Butyl 2-Hydroxy-3-[(naphthalen-2-yl)methoxy]-7-azabicyclo[2.2.1]heptane-7-carboxylate* ((±)-**12**) *and* tert-*Butyl 2,3-Bis[(naphthalen-2-yl)methoxy]-7-azabicyclo[2.2.1]heptane-7-carboxylate* (**13**). To a stirred suspension of NaH (60% in oil, 96 mg, 2.40 mmol) in THF (4 ml) at 0°, **11** (500 mg, 2.18 mmol) in THF (6 ml) was added. A soln. of 2-(bromomethyl)naphthalene (530 mg, 2.40 mmol) in THF (20 ml) was added dropwise at 0°, and the mixture was stirred at r.t. for 1 d. MeOH was added, and the mixture was stirred for 1 h. After

removal of the solvent *in vacuo*, the residue was taken up in Et_2O and washed with H_2O (1 ×). Drying ($MgSO_4$) and concentration *in vacuo* gave a yellow oil, which was purified by CC (SiO_2; hexane/AcOEt 4:1) to afford (±)-**12** (545 mg, 68%) and **13** (177 mg, 16%).

*Data of (±)-***12**: White solid. M.p. 117°. IR (KBr): 3504*s*, 3056*m*, 2972*s*, 1682*s*, 1507*m*, 1416*s*, 1361*s*, 1110*s*, 757*s*, 617*s*. ^{1}H-NMR ($CDCl_3$, 500 MHz): 1.17–1.27 (*m*, 2 H); 1.44 (*s*, 9 H); 1.67 (br. *s*, 2 H); 3.33 (br. *s*, 1 H); 3.60 (*d*, *J* = 6.2, 1 H); 3.84 (*dd*, *J* = 7.7, 6.2, 1 H); 4.11 (br. *s*, 1 H); 4.28 (br. *s*, 1 H); 4.79–4.81 (*m*, 2 H); 7.46–7.53 (*m*, 3 H); 7.79–7.87 (*m*, 4 H). ^{13}C-NMR ($CDCl_3$, 125 MHz): 24.08 (2 ×); 28.28; 58.17; 62.47; 72.62; 74.81; 79.78; 80.51; 125.74; 126.08; 126.24; 126.71; 127.72; 127.89; 128.35; 133.11; 133.21; 134.71; 156.34. HR-MALDI-MS (DHB): 392.1835 ($[M+Na]^+$, $C_{22}H_{27}NNaO_4^+$; calc. 392.1838). Anal. calc. for $C_{22}H_{27}NO_4$ (369.46): C 71.52, H 7.37, N 3.79; found: C 71.52, H 7.42, N 3.81.

Data of **13**: White solid. M.p. 131°. IR (KBr): 2972*s*, 1698*s*, 1600*w*, 1509*w*, 1355*s*, 1080*s*, 742*m*, 620*w*. ^{1}H-NMR ($CDCl_3$, 500 MHz): 1.18–1.30 (*m*, 2 H); 1.43 (*s*, 9 H); 1.64–1.73 (*m*, 2 H); 3.65 (*s*, 2 H); 4.26 (br. *s*, 1 H); 4.42 (br. *s*, 1 H); 4.82 (*s*, 4 H); 7.41–7.50 (*m*, 6 H); 7.68–7.82 (*m*, 8 H). ^{13}C-NMR ($CDCl_3$, 125 MHz): 24.08; 25.17; 28.31; 58.37; 59.75; 72.27 (2 ×); 79.59; 81.78; 82.35; 125.74 (2 ×); 125.97 (4 ×); 126.49 (2 ×); 127.65 (2 ×); 127.88 (2 ×); 128.00 (2 ×); 132.96 (2 ×); 133.25 (2 ×); 135.81 (2 ×); 156.21. HR-MALDI-MS (DHB): 532.2456 ($[M+Na]^+$, $C_{33}H_{35}NNaO_4^+$; calc. 532.2464). Anal. calc. for $C_{33}H_{35}NO_4$ (509.64): C 77.77, H 6.92, N 2.75; found: C 77.93, H 6.94, N 2.78.

tert-*Butyl (2*R,*3*S*)-2-Hydroxy-3-[(naphthalen-2-yl)methoxy]-7-azabicyclo[2.2.1]heptane-7-carboxylate* ((+)-**12**). To **26** (34 mg, 0.06 mmol) in MeOH (0.3 ml) and CH_2Cl_2 (0.1 ml), 3M KOH (0.1 ml, 0.30 mmol) was added. The mixture was stirred for 30 min, diluted with H_2O, and extracted with Et_2O (2 ×). The combined org. phases were dried ($MgSO_4$) and concentrated *in vacuo* to afford a colorless turbid oil. CC (SiO_2; hexane/AcOEt 2:1) yielded (+)-**12** (17 mg, 74%). Colorless oil. $[\alpha]_D^{24} = +25.5$ ($c = 0.85$, $CHCl_3$).

tert-*Butyl (2*S,*3*R*)-2-Hydroxy-3-[(naphthalen-2-yl)methoxy]-7-azabicyclo[2.2.1]heptane-7-carboxylate* ((−)-**12**). To **27** (66 mg, 0.12 mmol) in MeOH (0.7 ml) and CH_2Cl_2 (0.2 ml), 3M KOH (0.2 ml, 0.60 mmol) was added. Workup as described for (+)-**12** provided (−)-**12** (43 mg, 98%). Colorless oil. $[\alpha]_D^{24} = -19.3$ ($c = 0.7$, $CHCl_3$).

tert-*Butyl 2-[(4-Bromobenzyl)oxy]-3-[(naphthalen-2-yl)methoxy]-7-azabicyclo[2.2.1]heptane-7-carboxylate* ((±)-**14**). A soln. of (±)-**12** (100 mg, 0.27 mmol) in THF (0.7 ml) was added dropwise to a suspension of NaH (60% in oil, 12 mg, 0.29 mmol) in THF (2.2 ml) at 0°, and the mixture was stirred for 1 h at r.t. 4-Bromobenzyl bromide (73 mg, 0.29 mmol) in THF (0.5 ml) was added at 0°, and the mixture was stirred at r.t. for 12 h. MeOH was then added, and the mixture was stirred for 30 min. Concentration *in vacuo* yielded a white solid, which was taken up in Et_2O. Washing with H_2O (1 ×), drying ($MgSO_4$), and concentration *in vacuo* afforded (±)-**14** (140 mg, 97%). White solid. M.p. 126°. IR (KBr): 2970*s*, 1698*s*, 1354*s*, 1111*s*, 1079*s*, 862*m*, 751*m*, 620*m*. ^{1}H-NMR ($CDCl_3$, 500 MHz): 1.20–1.29 (*m*, 2 H); 1.42 (*s*, 9 H); 1.61–1.72 (*m*, 2 H); 3.60 (*d*, *J* = 5.7, 1 H); 3.65 (*d*, *J* = 5.7, 1 H); 4.19–4.28 (*m*, 1 H); 4.32–4.43 (*m*, 1 H); 4.60 (*s*, 2 H); 4.75 (*s*, 2 H); 7.22 (br. *s*, 2 H); 7.39 (br. *s*, 2 H); 7.45–7.49 (*m*, 3 H); 7.74–7.84 (*m*, 4 H). ^{13}C-NMR ($CDCl_3$, 125 MHz): 23.95; 25.14; 28.28; 58.45; 59.82; 71.42; 72.19; 79.61; 81.56; 82.19; 121.28; 125.81 (2 ×); 126.06; 126.45; 127.66; 127.83; 127.99; 129.35 (2 ×); 131.31 (2 ×); 132.94; 133.21; 135.65; 137.41; 156.08. HR-MALDI-MS (DHB): 560.1401 ($[M+Na]^+$, $C_{29}H_{32}BrNNaO_4^+$; calc. 560.1412).

tert-*Butyl 2-({4-[3-(1,3-Benzodioxol-5-yl)propyl]benzyl}oxy)-3-[(naphthalen-2-yl)methoxy]-7-azabicyclo[2.2.1]heptane-7-carboxylate* ((±)-(**16**)). A soln. of **15** in THF (0.37 ml, 0.17 mmol; prepared by stirring safrol (1 equiv.) and 0.5N 9-borabicyclo[3.3.1]nonane (9-BBN) (1 equiv.) in THF) was added to a degassed soln. of (±)-**14** (85 mg, 0.16 mmol), [$PdCl_2$(dppf)] (4 mg, 4 μmol), and NaOMe (23 mg, 0.43 mmol). The mixture was heated to reflux for 50 h, then H_2O was added. The aq. phase was extracted with Et_2O (2 ×), and the combined org. phases were washed with sat. aq. NaCl soln., dried ($MgSO_4$), and concentrated *in vacuo* to give a brown oil. CC (SiO_2; hexane/AcOEt 3:1) furnished (±)-**16** (48 mg, 49%). White solid. M.p. 146°. IR ($CHCl_3$): 2984*s*, 1686*s*, 1609*w*, 1516*m*, 1107*s*, 943*w*, 854*w*. ^{1}H-NMR ($CDCl_3$, 300 MHz): 1.15–1.19 (*m*, 2 H); 1.42 (*s*, 9 H); 1.60–1.68 (*m*, 2 H); 1.84–1.94 (*m*, 2 H); 2.53–2.64 (*m*, 4 H); 3.58 (*d*, *J* = 5.9, 1 H); 3.61 (*d*, *J* = 5.9, 1 H); 4.19–4.27 (*m*, 1 H); 4.32–4.40 (*m*, 1 H); 4.63 (*s*, 2 H); 4.79 (*s*, 2 H); 5.92 (*s*, 2 H); 6.63–6.74 (*m*, 3 H); 7.11 (*d*, *J* = 7.4, 2 H); 7.27 (*d*, *J* = 7.4, 2 H); 7.43–7.49 (*m*, 3 H); 7.73–7.82 (*m*, 4 H). ^{13}C-NMR ($CDCl_3$, 125 MHz): 23.95; 25.21; 28.29; 33.22; 34.98; 35.12; 58.52; 59.73; 72.20 (2 ×); 79.54; 81.54; 82.09; 100.70; 108.06; 108.86; 121.12; 125.70 (2 ×); 125.94; 126.46; 127.64; 127.85; 127.93; 128.25 (2 ×); 128.32 (2 ×); 132.93; 133.24; 135.67; 135.84; 136.13; 141.55; 145.52; 147.52; 156.19. HR-MALDI-MS (DHB): 644.2979 ($[M+Na]^+$, $C_{39}H_{43}NNaO_6^+$; calc. 644.2988).

2,3-Bis[(naphthalen-2-yl)methoxy]-7-azabicyclo[2.2.1]heptane (**17**). A soln. of **13** (52 mg, 0.10 mmol) and TFA (0.27 ml, 3.57 mmol) in CH_2Cl_2 (4 ml) was stirred for 30 min at r.t. under Ar. The crude TFA salt of **17**, obtained after evaporation *in vacuo*, was taken up in sat. aq. NaCl soln., and the pH of the soln. was adjusted to

10 with 10% aq. K_2CO_3 soln. The aq. phase was extracted with $CHCl_3$/i-PrOH 3:1 (2×). The combined org. phases were dried ($MgSO_4$) and concentrated *in vacuo* to yield a brown solid. CC (SiO_2; AcOEt/NEt_3 99:1) yielded **17** (25 mg, 60%). Colorless oil. IR ($CHCl_3$): 3289*w*, 2977*w*, 1602*w*, 1509*w*, 1101*s*. ^{1}H-NMR ($CDCl_3$, 300 MHz): 1.07–1.11 (*m*, 2 H); 1.61–1.65 (*m*, 2 H); 2.31 (br. *s*, 1 H); 3.60–3.62 (*m*, 2 H); 3.72 (*s*, 2 H); 4.79 (*s*, 4 H); 7.41–7.51 (*m*, 6 H); 7.67–7.86 (*m*, 8 H). ^{13}C-NMR ($CDCl_3$, 50 MHz): 24.02 (2×); 59.79 (2×); 72.56 (2×); 83.41 (2×); 125.92 (2×); 126.02 (2×); 126.11 (2×); 126.65 (2×); 127.73 (2×); 127.95 (2×); 128.21 (2×); 133.03 (2×); 133.35 (2×); 135.86 (2×). HR-MALDI-MS (DHB): 432.1923 ($[M+Na]^+$, $C_{28}H_{27}NNaO_2^+$; calc. 432.1939).

2-[(4-Bromobenzyl)oxy]-3-[(naphthalen-2-yl)methoxy]-7-azabicyclo[2.2.1]heptane ((±)-**18**). A soln. of (±)-**14** (100 mg, 0.19 mmol) and TFA (0.50 ml, 6.50 mmol) in CH_2Cl_2 (7.5 ml) was stirred for 30 min at r.t. under Ar. Workup as described for **17** provided (±)-**18** (72 mg, 89%). Colorless oil. IR ($CHCl_3$): 3292*w*, 2954*m*, 2512*w*, 1662*w*, 1595*w*, 1508*w*, 1103*s*, 1072*s*, 862*w*. ^{1}H-NMR ($CDCl_3$, 500 MHz): 1.08–1.13 (*m*, 2 H); 1.68–1.72 (*m*, 2 H); 3.02 (br. *s*, 1 H); 3.60–3.65 (*m*, 2 H); 3.65, 3.71 (*AB*, *J* = 5.5, 2 H); 4.53, 4.57 (*AB*, *J* = 11.8, 2 H); 4.71, 4.76 (*AB*, *J* = 11.9, 2 H); 7.20 (*d*, *J* = 8.3, 2 H); 7.41 (*d*, *J* = 8.3, 2 H); 7.39–7.50 (*m*, 3 H); 7.72–7.84 (*m*, 4 H). ^{13}C-NMR ($CDCl_3$, 125 MHz): 23.82; 23.92; 59.82; 60.06; 71.80; 72.57; 83.03; 83.29; 121.51; 125.80; 125.95; 126.18; 126.56; 127.68; 127.83; 128.15; 129.41 (2×); 131.46 (2×); 132.99; 133.22; 135.49; 137.24. HR-MALDI-MS (DHB): 460.0876 ($[M+Na]^+$, $C_{24}H_{24}NNaO_2^+$; calc. 460.0888).

2-({4-[3-(1,3-Benzodioxol-5-yl)propyl]benzyl}oxy)-3-[(naphthalen-2-yl)methoxy]-7-azabicyclo[2.2.1]heptane ((±)-**1**). A soln. of (±)-**16** (45 mg, 0.07 mmol) and TFA (0.20 ml, 2.6 mmol) in CH_2Cl_2 (3 ml) was stirred for 30 min at r.t. under Ar. Workup as described for **17** followed by CC (SiO_2; AcOEt/NEt_3 99:1) yielded (±)-**1** (32 mg, 86%). Colorless oil. IR ($CHCl_3$): 3250*w*, 2928*m*, 2476*w*, 1666*w*, 1605*w*, 1504*m*, 1099*s*, 933*w*, 860*w*. ^{1}H-NMR ($CDCl_3$, 500 MHz): 1.09–1.13 (*m*, 2 H); 1.72–1.74 (*m*, 2 H); 1.89 (*m*, 2 H); 2.56 (*t*, *J* = 7.7, 2 H); 2.61 (*t*, *J* = 7.8, 2 H); 3.00 (br. *s*, 1 H); 3.64–3.67 (*m*, 2 H); 3.67, 3.70 (*AB*, *J* = 5.5, 2 H); 4.59, 4.60 (*AB*, *J* = 11.9, 2 H); 4.73, 4.74 (*AB*, *J* = 11.9, 2 H); 5.92 (*s*, 2 H); 6.61–6.73 (*m*, 3 H); 7.12 (*d*, *J* = 7.9, 2 H); 7.26 (*d*, *J* = 7.9, 2 H); 7.42–7.47 (*m*, 3 H); 7.74–7.82 (*m*, 4 H). ^{13}C-NMR ($CDCl_3$, 125 MHz): 23.69; 23.74; 33.20; 34.98; 35.13; 60.08; 60.15; 72.47; 72.59; 82.76; 82.79; 100.71; 108.07; 108.84; 121.11; 125.87; 125.90; 126.07; 126.61; 127.66; 127.86; 128.05 (2×); 128.12; 128.47 (2×); 132.99; 133.23; 135.43; 135.55; 136.07; 141.84; 145.54; 147.53. HR-MALDI-MS (DHB): 544.2450 ($[M+Na]^+$, $C_{34}H_{35}NNaO_4^+$; calc. 544.2464).

2-{[2-(4-Methylphenoxy)ethyl]sulfanyl}-1,3-benzothiazole (**21**). NaH (60% in oil, 240 mg, 6.0 mmol) was added to a soln. of 1-(2-bromoethoxy)-4-methylbenzene (1.19 g, 5.4 mmol) [53] and 2-sulfanyl-1,3-benzothiazole (1.00 g, 6.0 mmol) in dry DMF (13 ml), and the yellow mixture was heated to 80° for 1 h. H_2O was added, and the turbid soln. was extracted with Et_2O (2×). The combined org. phases were washed with sat. aq. NaCl soln. and H_2O, dried ($MgSO_4$), and concentrated *in vacuo* to furnish a yellow solid. CC (SiO_2; hexane/AcOEt 21:4) yielded **21** (1.48 g, 90%). Pale-yellow solid. M.p. 64°. IR ($CHCl_3$): 3005*w*, 2923*w*, 2872*w*, 1610*w*, 1511*s*, 1463*m*, 1429*s*, 1303*w*, 1292*w*, 1240*s*, 1174*w*, 1072*w*, 1026*w*, 998*w*, 822*w*. ^{1}H-NMR ($CDCl_3$, 300 MHz): 2.29 (*s*, 3 H); 3.74 (*t*, *J* = 6.6, 2 H); 4.36 (*t*, *J* = 6.6, 2 H); 6.86–6.89 (*m*, 2 H); 7.08–7.12 (*m*, 2 H); 7.28–7.33 (*m*, 1 H); 7.40–7.46 (*m*, 1 H); 7.75–7.78 (*m*, 1 H); 7.86–7.89 (*m*, 1 H). ^{13}C-NMR ($CDCl_3$, 50 MHz): 20.37; 32.14; 66.49; 114.68 (2×); 121.09; 121.60; 124.40; 126.11; 130.02 (2×); 130.52; 135.22; 153.22; 156.33; 166.20. HR-MALDI-MS (DHB): 302.0670 (MH^+, $C_{16}H_{16}NOS_2^+$; calc. 302.0673). Anal. calc. for $C_{16}H_{15}NOS_2$ (301.43): C 63.75, H 5.02, N 4.65; found: C 63.78, H 5.04, N 4.60.

2-({2-[4-(Bromomethyl)phenoxy]ethyl}sulfanyl)-1,3-benzothiazole (**22**). A dried flask was charged with **21** (416 mg, 1.44 mmol) in dry $CHCl_3$ (6 ml), freshly recrystallized NBS (274 mg, 1.54 mmol), and AIBN (1.6 mg, 0.01 mmol). The mixture was heated to reflux for 4 h, then cooled to r.t. and filtered. The filtrate was washed with 0.5M $NaHCO_3$ and H_2O, dried ($MgSO_4$), and evaporated *in vacuo* to provide a light-yellow solid. CC (SiO_2; hexane/AcOEt 7:1) yielded **22** (103 mg, 19%). White solid. M.p. 105°. IR ($CHCl_3$): 1610*s*, 1512*s*, 1456*s*, 1428*s*, 1306*m*, 998*s*. ^{1}H-NMR ($CDCl_3$, 300 MHz): 3.75 (*t*, *J* = 6.7, 2 H); 4.39 (*t*, *J* = 6.7, 2 H); 4.50 (*s*, 2 H); 6.94–6.96 (*m*, 2 H); 7.29–7.35 (*m*, 3 H); 7.42–7.46 (*m*, 1 H); 7.75–7.78 (*m*, 1 H); 7.86–7.89 (*m*, 1 H). ^{13}C-NMR ($CDCl_3$, 75.5 MHz): 31.88; 33.69; 66.44; 115.07 (2×); 121.14; 121.62; 124.50; 126.20; 130.60 (3×); 135.49; 153.17; 158.61; 166.02. HR-MALDI-MS (DHB): 379.9778 (MH^+, $C_{16}H_{15}BrNOS_2^+$; calc. 379.9778). Anal. calc. for $C_{16}H_{14}NOS_2Br$ (380.33): C 50.53, H 3.71, N 3.68; found: C 50.46, H 3.88, N 3.65.

tert-*Butyl 2-[{4-[2-[(1,3-Benzothiazol-2-yl)sulfanyl]ethoxy}benzyl)oxy]-3-[(naphthalen-2-yl)methoxy]-7-azabicyclo[2.2.1]heptane-7-carboxylate* ((±)-**23**). A soln. of (±)-**12** (111 mg, 0.3 mmol) in THF (3 ml) was added to NaH (60% in oil, 16 mg, 0.39 mmol) at 0° under Ar. After stirring for 30 min at 0°, **22** (120 mg, 0.3 mmol) in THF (1.5 ml) was added dropwise. After 16 h at r.t., MeOH was added, and the mixture was stirred for 15 min. The residue obtained by evaporation *in vacuo* was taken up in Et_2O, and the soln. was washed with H_2O, dried ($MgSO_4$), and concentrated *in vacuo* to give a white solid. CC (SiO_2; CH_2Cl_2/AcOEt 199:1 → 19:1)

provided (±)-**23** (75 mg, 37%). Viscous colorless oil. IR ($CHCl_3$): 2951*w*, 2882*w*, 1694*s*, 1611*m*, 1511*m*, 1463*m*, 1429*m*, 1367*s*, 1324*m*, 1174*m*, 1148*s*, 1123*m*, 1082*m*, 997*m*, 890*w*, 859*w*. ^{1}H-NMR ($CDCl_3$, 300 MHz): 1.15–1.17 (br. *m*, 2 H); 1.41 (*s*, 9 H); 1.62–1.64 (br. *m*, 2 H); 3.57, 3.61 (*AB*, $J = 5.7$, 2 H); 3.74 (*t*, $J = 6.5$, 2 H); 4.13–4.24 (br. *m*, 1 H); 4.34–4.38 (br. *m*, 3 H); 4.59 (br. *s*, 2 H); 4.78 (br. *s*, 2 H); 6.88–6.91 (*m*, 2 H); 7.25–7.33 (*m*, 3 H); 7.39–7.49 (*m*, 4 H); 7.74–7.82 (*m*, 5 H); 7.86–7.89 (*m*, 1 H). ^{13}C-NMR ($CDCl_3$, 75.5 MHz): 23.91; 24.85; 28.17; 31.79; 58.31; 59.67; 66.34; 71.69; 72.16; 79.51; 81.81 (2×); 114.52 (2×); 121.09; 121.58; 124.42; 125.80 (2×); 126.04; 126.15; 126.58; 127.71; 127.93; 128.03; 129.57 (2×); 131.01; 133.00; 133.31; 135.44; 135.89; 153.19; 156.35; 158.00; 166.12. HR-MALDI-MS (DHB): 691.2268 (22, $[M + Na]^+$, $C_{38}H_{40}N_2NaO_5S_2^+$; calc. 691.2276). Anal. calc. for $C_{38}H_{40}N_2O_5S_2$ (668.88): C 68.24, H 6.03, N 4.19; found: C 68.09, H 6.12, N 4.12.

tert-*Butyl (2*R,*3*S*)-2-[(4-[2-[(1,3-Benzothiazol-2-yl)sulfanyl]ethoxy}benzyl)oxy]-3-[(naphthalen-2-yl)-methoxy]-7-azabicyclo[2.2.1]heptane-7-carboxylate* ((−)-**23**). $[\alpha]_D^{24} = -2.0$ ($c = 0.75$, $CHCl_3$).

tert-*Butyl (2*S,*3*R*)-2-[(4-[2-[(1,3-benzothiazol-2-yl)sulfanyl]ethoxy}benzyl)oxy]-3-[(naphthalen-2-yl)-methoxy]-7-azabicyclo[2.2.1]heptane-7-carboxylate* ((+)-**23**). $[\alpha]_D^{24} = +1.9$ ($c = 0.75$, $CHCl_3$).

2-[(2-{4-[({3-[(Naphthalen-2-yl)methoxy]-7-azabicyclo [2.2.1]hept-2-yl}oxy)methyl]phenoxy}ethyl)sulfanyl]-1,3-benzothiazole ((±)-**19**). To (±)-**23** (50 mg, 0.08 mmol) in CH_2Cl_2 (140 µl), 2,6-lutidine (17 µl, 0.15 mmol) and TBDMSOTf (26 µl, 0.11 mmol) were added, and the mixture was stirred for 30 min. Sat. aq. NH_4Cl soln. was added, and the mixture was extracted with Et_2O (2×). The combined org. layers were washed with sat. aq. NaCl soln. and H_2O, dried ($MgSO_4$), and evaporated *in vacuo* to yield a turbid yellow oil. This oil was dissolved in THF (135 µl), Bu_4NF (1M in THF, 132 µl, 0.13 mmol) was added, and the mixture was stirred at r.t. for 1 h under Ar. Sat. aq. NH_4Cl soln. was added, and the mixture was extracted with $CHCl_3$ (3×). The combined org. layers were washed with sat. aq. NaCl soln., dried ($MgSO_4$), and evaporated *in vacuo* to afford a turbid yellow oil. CC (basic Al_2O_3, act. II; AcOEt/MeOH 25:1) yielded (±)-**19**. Pale-yellow oil (38 mg, 82% over 2 steps). IR ($CHCl_3$): 2971*m*, 1601*w*, 1527*w*, 1458*w*, 1425*m*, 1253*s*, 1091*s*, 1021*s*. ^{1}H-NMR ($CDCl_3$, 300 MHz): 1.03–1.09 (*m*, 2 H); 1.58–1.64 (*m*, 2 H); 1.93 (br. *s*, 1 H); 3.53–3.58 (*m*, 2 H), 3.64, 3.68 (*AB*, $J = 5.3$, 2 H); 3.75 (*t*, $J = 6.6$, 2 H); 4.36 (*t*, $J = 6.6$, 2 H); 4.56 (*s*, 2 H); 4.75 (*s*, 2 H); 6.87–6.92 (*m*, 2 H); 7.26–7.33 (*m*, 3 H); 7.38–7.48 (*m*, 4 H); 7.74–7.89 (*m*, 6 H). ^{13}C-NMR ($CDCl_3$, 75.5 MHz): 23.54 (2×); 31.99; 59.69 (2×); 66.39; 72.08; 72.50; 82.63; 82.84; 114.67 (2×); 121.12; 121.61; 124.46; 125.96; 125.99; 126.17 (2×); 126.70; 127.76; 127.97; 128.21; 129.63 (2×); 130.85; 133.08; 133.32; 135.47; 135.67; 153.21; 158.16; 166.12. HR-MALDI-MS (DHB): 591.1740 ($[M + Na]^+$, $C_{33}H_{32}N_2NaO_3S_2^+$; calc. 591.1752).

*2-[(2-{(2*R,*3*S*)-4-[({3-[(Naphthalen-2-yl)methoxy]-7-azabicyclo[2.2.1]hept-2-yl}oxy)methyl]phenoxy}ethyl)-sulfanyl]-1,3-benzothiazole* ((−)-**19**). $[\alpha]_D^{24} = -2.6$ ($c = 0.3$, $CHCl_3$).

*2-[(2-{(2*S,*3*R*)-4-[({3-[(Naphthalen-2-yl)methoxy]-7-azabicyclo[2.2.1]hept-2-yl}oxy)methyl]phenoxy}ethyl)-sulfanyl]-1,3-benzothiazole* ((+)-**19**). $[\alpha]_D^{24} = +2.4$ ($c = 0.9$, $CHCl_3$).

tert-*Butyl 2-Hydroxy-3-[(naphthalen-1-yl)methoxy]-7-azabicyclo[2.2.1]heptane-7-carboxylate* ((±)-**24**. A soln. of **11** (500 mg, 2.18 mmol) in THF (6 ml) was added at 0° to a suspension of NaH (60% in oil, 96 mg, 2.40 mmol) in THF (4 ml), and the mixture was stirred at 0° for 15 min. A soln. of 1-(bromomethyl)naphthalene (530 mg, 2.40 mmol) in THF (20 ml) was added dropwise, and the mixture was stirred for 15 h at r.t. under Ar. After addition of MeOH, stirring was continued for 20 min. Evaporation *in vacuo* gave a residue, which was taken up in Et_2O. The soln. was washed with H_2O, dried ($MgSO_4$), and concentrated *in vacuo* to give an oil. CC (SiO_2; hexane/AcOEt 4:1) yielded (±)-**24** (371 mg, 43%). Colorless oil. IR ($CHCl_3$): 3517*w*, 3008*m*, 2980*m*, 2872*w*, 1693*s*, 1390*s*, 1368*s*, 1257*w*, 1171*m*, 1143*s*, 1113*m*, 1071*m*, 1020*w*, 905*w*, 889*w*. ^{1}H-NMR ($CDCl_3$, 300 MHz): 1.15–1.24 (*m*, 2 H); 1.42 (*s*, 9 H); 1.61–1.73 (*m*, 2 H); 3.27 (*m*, 1 H); 3.63 (*m*, 1 H); 3.83 (*m*, 1 H); 4.04–4.18 (*m*, 1 H); 4.21–4.37 (*m*, 1 H); 5.03–5.12 (*m*, 2 H); 7.42–7.58 (*m*, 4 H); 7.82–7.89 (*m*, 2 H); 8.10–8.14 (*m*, 1 H). ^{13}C-NMR ($CDCl_3$, 50 MHz): 23.94; 24.27; 28.14; 58.72; 62.49; 70.94; 74.84; 79.73; 80.52; 123.95; 125.22; 126.02; 126.59; 126.81; 128.65; 129.09; 131.76; 132.81; 133.82; 156.46. HR-MALDI-MS (DHB): 392.1837 ($[M + Na]^+$, $C_{22}H_{27}NNaO_4^+$; calc. 392.1838). Anal. calc. for $C_{22}H_{27}NO_4$ (369.46): C 71.52, H 7.37, N 3.79; found: C 71.50, H 7.34, N 3.81.

tert-*Butyl 2-[(4-[2-[(1,3-Benzothiazol-2-yl)sulfanyl]ethoxy}benzyl)oxy]-3-[(naphthalen-1-yl)methoxy]-7-azabicyclo[2.2.1]heptane-7-carboxylate* ((±)-**25**). A mixture of (±)-**24** (150 mg, 0.41 mmol), NaH (60% in oil, 25 mg, 0.62 mmol), and THF (3 ml) in a dried flask was stirred for 45 min at 0° under Ar, then a soln. of **22** (500 mg, 1.31 mmol) was added dropwise. After stirring at r.t. for 16 h, MeOH was added, and stirring was continued for 15 min. Evaporation *in vacuo* left a residue, which was taken up in Et_2O (30 ml) and washed with H_2O (2×), dried ($MgSO_4$), and concentrated *in vacuo* to afford a turbid yellow oil. CC (SiO_2; hexane/AcOEt 3:1) provided (±)-**25** (226 mg, 82%). Colorless oil. IR ($CHCl_3$): 3009*m*, 2951*w*, 1694*s*, 1610*w*, 1511*m*, 1464*m*, 1428*m*, 1368*s*, 1324*w*, 1240*m*, 1174*m*, 1148*s*, 1087*m*, 999*m*. ^{1}H-NMR ($CDCl_3$, 300 MHz): 1.13–1.16 (*m*, 2 H); 1.42 (*s*, 9 H); 1.61–1.74 (*m*, 2 H); 3.53, 3.59 (*AB*, $J = 6.2$, 2 H); 3.74 (*t*, $J = 6.4$, 2 H); 4.12–4.24 (*m*, 1 H);

4.29–4.40 (*m*, 1 H); 4.36 (*t*, *J* = 6.4, 2 H); 4.50–4.53 (*m*, 2 H); 5.06 (br. *s*, 2 H); 6.85–6.87 (*m*, 2 H); 7.13–7.25 (*m*, 2 H); 7.28–7.34 (*m*, 1 H); 7.37–7.49 (*m*, 5 H); 7.75–7.89 (*m*, 4 H); 8.15–8.19 (*m*, 1 H). ^{13}C-NMR ($CDCl_3$, 50 MHz): 24.46 (2×); 28.21; 32.05; 59.67 (2×); 66.40; 70.40; 71.67; 79.51; 81.44 (2×); 114.52 (2×); 121.09; 121.60; 124.43; 124.52; 125.19; 125.79; 126.17 (2×); 126.75; 128.46; 128.55; 129.51 (2×); 131.06; 131.89; 133.79 (2×); 135.48; 153.22; 156.33; 157.95; 166.11. HR-MALDI-MS (DHB): 691.2270 ($[M+Na]^+$, $C_{38}H_{40}N_2NaO_5S_2^+$; calc. 691.2276).

2-[(2-{4-[({3-[(Naphthalen-1-yl)methoxy]-7-azabicyclo[2.2.1]hept-2-yl}oxy)methyl]phenoxy}ethyl)sulfanyl]-1,3-benzothiazole ((±)-**20**). To (±)-**24** (182 mg, 0.27 mmol) in CH_2Cl_2 (0.5 ml), 2,6-lutidine (63 µl, 0.54 mmol) and TBDMSOTf (94 µl, 0.41 mmol) were added, and the mixture was stirred for 30 min. After addition of sat. aq. soln. of NH_4Cl, the mixture was extracted with Et_2O. The combined org. layers were washed with sat. aq. NaCl soln. and H_2O, dried ($MgSO_4$), and evaporated to give a turbid yellow oil. This oil was dissolved in THF (0.5 ml), Bu_4NF (1M in THF, 0.38 ml, 0.38 mmol) was added, and the mixture was stirred at r.t. for 2 h. After addition of sat. aq. NH_4Cl soln., extraction with $CHCl_3$ (3×), washing the combined org. layers with sat. aq. NaCl soln., drying ($MgSO_4$), and evaporation *in vacuo* afforded a turbid yellow oil. CC (basic Al_2O_3, act. II; AcOEt/MeOH 25:1) provided (±)-**20** (110 mg, 71%). Pale-yellow oil. IR ($CHCl_3$): 2962*m*, 1610*w*, 1513*w*, 1462*w*, 1431*w*, 1261*s*, 1097*s*, 1015*s*. ^{1}H-NMR ($CDCl_3$, 300 MHz): 1.04–1.13 (*m*, 2 H); 1.79–2.14 (*m*, 3 H); 3.57–3.60 (*m*, 2 H); 3.64, 3.70 (*AB*, *J* = 5.4, 2 H); 3.74 (*t*, *J* = 6.6, 2 H); 4.36 (*t*, *J* = 6.6, 2 H); 4.50 (*s*, 2 H); 5.00, 5.06 (*AB*, *J* = 11.7, 2 H); 6.86–6.89 (*m*, 2 H); 7.18–7.21 (*m*, 2 H); 7.28–7.33 (*m*, 1 H); 7.37–7.49 (*m*, 5 H); 7.75–7.89 (*m*, 4 H); 8.14–8.16 (*m*, 1 H). ^{13}C-NMR ($CDCl_3$, 75.5 MHz): 23.55; 23.66; 31.99; 58.13; 60.35; 66.39; 70.92; 72.00; 82.74; 82.94; 114.65 (2×); 121.12; 121.60; 124.39; 124.45; 125.24; 125.87; 126.17; 126.26; 126.81; 128.53; 128.74; 129.63 (2×); 130.84; 131.91; 133.72; 133.83; 135.47; 153.20; 158.12; 166.11. HR-MALDI-MS (DHB): 591.1745 (43, $[M+Na]^+$, $C_{33}H_{32}N_2NaO_5S_2^+$; calc. 591.1752).

tert-*Butyl (2S,3R)-2-[(Naphthalen-2-yl)methoxy]-3-({[(1S,4R)-4,7,7-trimethyl-3-oxo-2-oxabicyclo[2.2.1]-hept-1-yl]carbonyl}oxy)-7-azabicyclo[2.2.1]heptane-7-carboxylate* (**26**) *and* tert-*Butyl (2R,3S)-2-[(Naphthalen-2-yl)methoxy]-3-({[(1S,4R)-4,7,7-trimethyl-3-oxo-2-oxabicyclo[2.2.1]hept-1-yl]carbonyl}oxy)-7-azabicyclo[2.2.1]heptane-7-carboxylate* (**27**). To (±)-**12** (200 mg, 0.54 mmol) in CH_2Cl_2 (2 ml) at 0°, Et_3N (0.15 ml, 1.08 mmol) and (−)-camphanoyl chloride (132 mg, 0.61 mmol) in CH_2Cl_2 (0.8 ml) were added, and the mixture was stirred for 20 h at r.t. CH_2Cl_2 and H_2O were added, and the separated org. phase was washed with 2N HCl (2×), 1M $NaHCO_3$ (10 ml), and sat. aq. NaCl soln (2×). Drying ($MgSO_4$) and concentration *in vacuo* afforded a cloudy oil. CC (SiO_2; PhMe/AcOEt 2:1) yielded **26** (111 mg, 38%) and **27** (90 mg, 30%).

Data of **26**: White solid. M.p. 166°. IR (KBr): 2967*m*, 1789*s*, 1739*s*, 1694*s*, 1383*s*, 1261*s*, 1083*s*. ^{1}H-NMR ($CDCl_3$, 300 MHz): 0.86–1.06 (*m*, 9 H); 1.23–1.28 (*m*, 2 H); 1.35–1.44 (*m*, 10 H); 1.62–1.82 (*m*, 4 H); 2.21–2.30 (*m*, 1 H); 3.82–3.83 (*m*, 1 H); 4.23–4.42 (br. *s*, 2 H); 4.60–4.64 (*m*, 1 H); 4.73–4.76 (*m*, 1 H); 4.82–4.91 (br. *s*, 1 H); 7.44–7.49 (*m*, 3 H); 7.77–7.84 (*m*, 4 H). ^{13}C-NMR ($CDCl_3$, 75.5 MHz): 9.70; 16.70; 16.93; 24.37 (2×); 28.35; 28.95; 30.70; 54.11; 55.00; 58.48 (2×); 72.83 (2×); 79.87; 81.92; 91.55; 126.24; 126.41; 126.48; 127.19; 127.94; 128.18; 128.41; 133.36; 133.42; 135.10; 155.10; 167.56; 178.50. ESI-MS: 588 (15, $[M+K]^+$), 572 (100, $[M+Na]^+$), 567 (16, $[M+NH_4]^+$). X-Ray: see *Fig 3*.

Data of **27**: White solid. M.p. 141°. IR (KBr): 2961*m*, 1787*s*, 1751*s*, 1702*s*, 1390*s*, 1170*s*, 1087*s*. ^{1}H-NMR ($CDCl_3$, 300 MHz): 0.78 (br. *s*, 3 H); 0.94 (br. *s*, 3 H); 1.00 (br. *s*, 3 H); 1.22–1.25 (*m*, 2 H); 1.43–1.48 (*m*, 10 H); 1.73–1.79 (*m*, 4 H); 2.38–2.46 (*m*, 1 H); 3.81–3.83 (*m*, 1 H); 4.25–4.38 (br. *s*, 2 H); 4.53–4.86 (*m*, 3 H); 7.45–7.49 (*m*, 3 H); 7.77–7.84 (*m*, 4 H). ^{13}C-NMR ($CDCl_3$, 75.5 MHz): 9.65; 16.30; 16.46; 24.50 (2×); 28.45; 28.97; 30.89; 54.08; 54.90; 58.45 (2×); 72.51 (2×); 79.93; 81.44; 91.37; 126.24; 126.43 (2×); 127.26; 127.94; 128.15; 128.41; 133.34; 133.44; 135.06; 154.86; 167.50; 178.56. HR-MALDI-MS (DHB): 572.2614 ($[M+Na]^+$, $C_{32}H_{39}NNaO_7^+$; calc. 572.2624).

X-Ray Crystal Structure of **26**. Crystals were grown by slow diffusion of hexane into a soln. of **26** in CH_2Cl_2. X-Ray crystal data for $C_{32}H_{39}NO_7$ (M_r 549.64): orthorhombic space group $P2_12_12_1$ (No. 19), $D_c = 1.254$ g/cm^{-3}, $Z = 4$, $a = 6.326(1)$, $b = 11.317(1)$, $c = 40.658(5)$ Å, $V = 2910.8(6)$ Å^3, CuK_α radiation, $\lambda = 1.5418$ Å, $2.17° \leq \theta \leq 49.92°$, 1785 unique reflections, $T = 183$ K, crystal size *ca.* $0.1 \times 0.05 \times 0.05$ mm. The structure was solved by direct methods (SIR92) [54] and refined by full-matrix least-squares analysis (SHELXL-97) [55], using an isotropic extinction correction and $w = 1/(\sigma^2(F_o^2)) + (0.070P)^2 + 0.075P)$, where $P = (F_o^2 + 2F_c^2)/3$. All heavy atoms were refined anisotropically, H-atoms isotropically, whereby H-positions are based on stereochemical considerations. Final $R(F) = 0.0351$, $wR(F^2) = 0.0976$ for 401 parameters and 1628 reflections with $I > 2\sigma(I)$.

Crystallographic data (excluding structure factors) for **26** have been deposited with the *Cambridge Crystallographic Data Centre* as deposition No. CCDC-201544. 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).

REFERENCES

[1] U. Weiss, *Nature* **2002**, *415*, 669.
[2] C. Hopkins Sibley, J. E. Hyde, P. F. G. Sims, C. V. Plowe, J. G. Kublin, E. K. Mberu, A. F. Cowman, P. A. Winstanley, W. M. Watkins, A. M. Nzila, *Trends Parasitol.* **2001**, *17*, 582.
[3] A. Bell, *Curr. Opin. Anti-infect. Invest. Drugs* **2000**, *2*, 63.
[4] P. J. Rosenthal, 'Antimalarial Chemotherapy: Mechanisms of Action, Resistance, and New Directions in Drug Discovery', Humana Press, New Jersey, 2001.
[5] P. M. S. Chauhan, S. K. Srivastava, *Curr. Med. Chem.* **2001**, *8*, 1535.
[6] M. Frédérich, J.-M. Dogné, L. Angenot, P. DeMol, *Curr. Med. Chem.* **2002**, *9*, 1435.
[7] R. G. Ridley, *Nature* **2002**, *415*, 686.
[8] L. H. Miller, M. F. Good, G. Milon, *Science* **1994**, *264*, 1878.
[9] A. Robert, O. Dechy-Cabaret, J. Cazelles, B. Meunier, *Acc. Chem. Res.* **2002**, *35*, 167.
[10] S. E. Francis, D. J. Sullivan, D. E. Goldberg, *Annu. Rev. Microbiol.* **1997**, *51*, 97.
[11] R. Banerjee, J. Liu, W. Beatty, L. Pelosof, M. Klemba, D. E. Goldberg, *Proc. Natl. Acad. Sci. U.S.A.* **2002**, *99*, 990.
[12] G. H. Coombs, D. E. Goldberg, M. Klemba, C. Berry, J. Kay, J. C. Mottram, *Trends Parasitol.* **2001**, *17*, 532.
[13] R. P. Moon, L. Tyas, U. Certa, K. Rupp, D. Bur, C. Jacquet, H. Matile, H. Loetscher, F. Grueninger-Leitch, J. Kay, B. M. Dunn, C. Berry, R. G. Ridley, *Eur. J. Biochem.* **1997**, *244*, 552.
[14] J. Hill, L. Tyas, L. H. Phylip, J. Kay, B. M. Dunn, C. Berry, *FEBS Lett.* **1994**, *352*, 155.
[15] D. M. Wyatt, C. Berry, *FEBS Lett.* **2002**, *513*, 159.
[16] C. Berry, M. J. Humphreys, P. Matharu, R. Granger, P. Horrocks, R. P. Moon, U. Certa, R. G. Ridley, D. Bur, J. Kay, *FEBS Lett.* **1999**, *447*, 149.
[17] B. R. Shenai, P. S. Sijwali, A. Singh, P. J. Rosenthal, *J. Biol. Chem.* **2000**, *275*, 29000.
[18] K. K. Eggleson, K. L. Duffin, D. E. Goldberg, *J. Biol. Chem.* **1999**, *274*, 32411.
[19] K. A. Kolakovich, I. Y. Gluzman, K. L. Duffin, D. E. Goldberg, *Mol. Biochem. Parasitol.* **1997**, *87*, 123.
[20] R. P. Moon, D. Bur, H. Loetscher, A. D'Arcy, L. Tyas, C. Oefner, F. Grueninger-Leitch, D. Mona, K. Rupp, A. Dorn, H. Matile, U. Certa, C. Berry, J. Kay, R. G. Ridley, *Adv. Exp. Med. Biol.* **1998**, *436*, 397.
[21] C. D. Carroll, H. Patel, T. O. Johnson, T. Guo, M. Orlowski, Z.-M. He, C. L. Cavallaro, J. Guo, A. Oksman, I. Y. Gluzman, J. Conelly, D. Chelsky, D. E. Goldberg, R. E. Rolle, *Bioorg. Med. Chem. Lett.* **1998**, *8*, 2315; C. D. Carroll, T. O. Johnson, S. Tao, G. Lauri, M. Orlowski, I. Y. Gluzman, D. E. Goldberg, R. E. Dolle, *Bioorg. Med. Chem. Lett.* **1998**, *8*, 3203.
[22] T. S. Haque, A. G. Skillman, C. E. Lee, H. Habashita, I. Y. Gluzman, T. J. A. Ewing, D. E. Goldberg, I. D. Kuntz, J. A. Ellman, *J. Med. Chem.* **1999**, *42*, 1428; D. J. Maly, L. Huang, J. A. Ellman, *ChemBioChem* **2002**, *3*, 16.
[23] S. Jiang, S. T. Prigge, L. Wei, Y.-E. Gao, T. H. Hudson, L. Gerena, J. B. Dame, D. E. Kyle, *Antimicrob. Agents Chemother.* **2001**, *45*, 2577.
[24] A. Negami, I. Luque, T. Rimura, Y. Kiso, E. Freire, *Biochemistry* **2002**, *41*, 2273.
[25] K. Ersmark, I. Feierberg, S. Bjelic, J. Hulten, J. Aqvist, A. Hallberg, *Drugs Future (Suppl. A: XXIIth Int. Symp. Med. Chem.)* **2002**, *27*, 231.
[26] C. Boss, S. Richard, T. Weller, C. Binkert, S. Meyer, P. Strickner, D. Bur, W. Fischli, BOSS-9 Symposium Namur, Belgium 2002, Poster TH 046; C. Boss, W. Fischli, S. Meyer, S. Richard-Bildstein, T. Weller, *Actelion Pharmaceuticals Ltd.* 2002, WO-00224649; C. Boss, W. Fischli, S. Meyer, S. Richard-Bildstein, T. Weller, *Actelion Pharmaceuticals Ltd.* 2002, WO-00238534.
[27] C. Boss, S. Richard-Bildstein, T. Weller, W. Fischli, S. Meyer, C. Binkert, *Curr. Med. Chem.* **2003**, *10*, 883.
[28] A. M. Silva, A. Y. Lee, S. V. Gulnik, P. Majer, J. Collins, T. N. Bhat, P. J. Collins, R. E. Cachau, K. E. Luker, I. Y. Gluzman, S. E. Francis, A. Oksman, D. E. Goldberg, J. W. Erickson, *Proc. Natl. Acad. Sci. U.S.A.* **1996**, *93*, 10034.
[29] U. Obst, V. Gramlich, F. Diederich, L. Weber, D. W. Banner, *Angew. Chem.* **1995**, *107*, 1874; *Angew. Chem., Int. Ed.* **1995**, *34*, 1739; U. Obst, D. W. Banner, L. Weber, F. Diederich, *Chem. Biol.* **1997**, *4*, 287; 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; P. Betschmann, S. Sahli, F. Diederich, U. Obst, V. Gramlich, *Helv. Chim. Acta* **2002**, *85*, 1210.
[30] B. Masjost, P. Ballmer, E. Borroni, G. Zürcher, F. K. Winkler, R. Jakob-Roetne, F. Diederich, *Chem. – Eur. J.* **2000**, *6*, 971; C. Lerner, A. Ruf, V. Gramlich, B. Masjost, G. Zürcher, R. Jakob-Roetne, E. Borroni, F. Diederich, *Angew. Chem.* **2001**, *113*, 4164; *Angew. Chem., Int. Ed.* **2001**, *40*, 4040; C. Lerner, B. Masjost, A. Ruf, V. Gramlich, R. Jakob-Roetne, G. Zürcher, E. Borroni, F. Diederich, *OrgBioChem* **2003**, *1*, 42.

[31] E. A. Meyer, R. Brenk, R. K. Castellano, M. Furler, G. Klebe, F. Diederich, *ChemBioChem* **2002**, *3*, 250.
[32] C. Oefner, A. Binggeli, V. Breu, D. Bur, J.-P. Clozel, A. D'Arcy, A. Dorn, W. Fischli, F. Grüninger, R. Güller, G. Hirth, H. P. Maerki, S. Mathews, M. Müller, R. G. Ridley, H. Stadler, E. Vieira, M. Wilhelm, F. K. Winkler, W. Wostl, *Chem. Biol.* **1999**, *6*, 127.
[33] M. G. Bursavich, D. H. Rich, *Org. Lett.* **2001**, *3*, 2625; M. G. Bursavich, C. W. West, D. H. Rich, *Org. Lett.* **2001**, *3*, 2317.
[34] N. Khazanovich Bernstein, M. M. Cherny, H. Loetscher, R. G. Ridley, M. N. G. James, *Nat. Struct. Biol.* **1999**, *6*, 32.
[35] D. Bur, W. Fischli, H. Matile, R. G. Ridley, W. Wostl, *F. Hoffman-La Roche Ltd.*, 1999, WO-09912532.
[36] D. A. Carcache, S. R. Hörtner, A. Bertogg, F. Diederich, A. Dorn, H. P. Märki, C. Binkert, D. Bur, *Helv. Chim. Acta* **2003**, *86*, 2192.
[37] D. A. Carcache, S. R. Hörtner, A. Bertogg, C. Binkert, D. Bur, H. P. Märki, A. Dorn, F. Diederich, *ChemBioChem* **2002**, *3*, 1137.
[38] P. R. Gerber, K. Müller, *J. Comput.-Aided Mol. Design* **1995**, *9*, 251.
[39] R. R. Fraser, R. B. Swingle, *Can. J. Chem.* **1970**, *48*, 2065.
[40] A. Yayon, Z. I. Cabantchik, H. Ginsburg, *EMBO J.* **1984**, *3*, 2695.
[41] C. A. Lipinski, F. Lombardo, B. W. Dominy, P. J. Feeney, *Adv. Drug Deliv. Rev.* **1997**, *23*, 3.
[42] E. A. Meyer, R. K. Castellano, F. Diederich, *Angew. Chem.* **2003**, *115*, 1244; *Angew. Chem., Int. Ed.* **2003**, *42*, 1210.
[43] L. Grehn, U. Ragnarsson, *Angew. Chem.* **1984**, *96*, 291; *Angew. Chem., Int. Ed.* **1984**, *23*, 296.
[44] Z. Chen, M. L. Trudell, *Synth. Commun.* **1994**, *24*, 3149.
[45] H.-J. Altenbach, B. Blech, J. A. Marco, E. Vogel, *Angew. Chem.* **1982**, *94*, 789; *Angew. Chem., Int. Ed.* **1982**, *21*, 778.
[46] F. Liang, H. A. Navarro, P. Abraham, P. Kotian, Y.-S. Ding, J. Fowler, N. Volkow, M. J. Kuhar, F. Ivy Carroll, *J. Med. Chem.* **1997**, *40*, 2293.
[47] A. Otten, J. C. Namyslo, M. Stoermer, D. E. Kaufmann, *Eur. J. Org. Chem.* **1998**, 1997.
[48] R. Leung-Toung, Y. Liu, J. M. Muchowski, Y.-L. Wu, *J. Org. Chem.* **1998**, *63*, 3235.
[49] S. C. Nigam, A. Mann, M. Taddei, C.-G. Wermuth, *Synth. Commun.* **1989**, *19*, 3139.
[50] M. Sakaitani, Y. Ohfune, *J. Org. Chem.* **1990**, *55*, 870.
[51] J. Yuvaniyama, Department of Biochemistry, Mahidol University, Bangkok, Thailand, personal communication.
[52] J. T. Groves, K. W. Ma, *J. Am. Chem. Soc.* **1977**, *99*, 4076.
[53] A. R. Goldfarb, R. R. Renshaw, *J. Am. Chem. Soc.* **1941**, *63*, 2280.
[54] A. Altomare, G. Cascarano, C. Giacovazzo, A. Guagliardi, M. Burla, G. Polidori, M. Camalli, *J. Appl. Crystallogr.* **1994**, *27*, 435.
[55] G. M. Sheldrick, 'SHELXL-97 Program for the Refinement of Crystal Structures', University of Göttingen, Germany, 1997.

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