A New Class of Inhibitors for the Malarial Aspartic Protease Plasmepsin II Based on a Central 11-Azatricyclo[6.2.1.$0^{2,7}$]undeca-2,4,6-triene Scaffold

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

A new class of nonpeptidic inhibitors of the malarial aspartic protease plasmepsin II (PMII) with up to single-digit micromolar activities (IC_{50} values) was developed by structure-based *de novo* design. The active-site matrix used in the design was based on an X-ray crystal structure of PMII, onto which the major conformational changes seen in the structure of renin upon complexation of 4-arylpiperidines – including the unlocking of a new hydrophobic (flap) pocket – were modeled. The sequence identity of 35% between mature renin and PMII had prompted us to hypothesize that an induced-fit adaptation around the active site as observed in renin might also be effective in PMII. The new inhibitors contain a central 11-azatricyclo[6.2.1.$0^{2,7}$]undeca-2(7),3,5-triene core, which, in protonated form, undergoes ionic H-bonding with the two catalytic Asp residues at the active site of PMII (*Figs. 1* and *2*). This tricyclic scaffold is readily prepared by a *Diels–Alder* reaction between an activated pyrrole and a benzyne species generated *in situ* (*Scheme 1*). Two substituents with naphthyl or 1,3-benzothiazole moieties are attached to the central core (*Schemes 1–4*) for accommodation in the hydrophobic flap and S1/S3 (or S2′, depending on the optical antipode of the inhibitor) pockets at the active site of the enzyme. The most-potent inhibitors (±)-**19a**–**19c** (IC_{50} 3–5 μM) and (±)-**23b** (2 μM) (*Table*) bear an additional Cl-atom on the 1,3-benzothiazole moiety to fully fill the rear of the flap pocket. Optimization of the linker between the tricyclic scaffold and the 1,3-benzothiazole moiety, based on detailed conformational analysis (*Figs. 3* and *4*), led to a further small increase in inhibitory strength. The new compounds were also tested against other aspartic proteases. They were found to be quite selective against renin, while the selectivity against cathepsin D and E, two other human aspartic proteases, is rather poor (*Table*). The detailed SARs established in this investigation provide a valuable basis for the design of the next generations of more-potent and -selective PMII inhibitors with potential application in a new antimalarial therapy.

1. Introduction. – In the preceding paper [1], we described a new class of inhibitors (*e.g.*, (±)-**1**; *Fig. 1*) of the malarial aspartic protease plasmepsin II (PMII) with a central 7-azabicyclo[2.2.1]heptane scaffold, featuring up to single-digit micromolar activities (IC_{50} values). The *de novo* design of these compounds was based on the X-ray crystal structure of PMII (PDB: 1SME) [2], in which conformational changes observed in structures of human renin complexed to 4-arylpiperidine inhibitors of *Roche* [3] had been introduced. The sequence identity of 35% between mature renin and PMII had

prompted us to hypothesize that an induced-fit adaptation around the active site as observed in renin might also be effective in PMII. In this conformational change, the long β-hairpin loop (flap) covering the catalytic dyad of PMII shifts to a more open conformation and thereby helps to unlock a new hydrophobic (flap) pocket.

The structure–activity relationships (SARs) observed with the novel inhibitors, indeed, provided strong support for the proposed conformational changes in PMII [1]. Thus, the 7-azabicyclo[2.2.1]heptane scaffold of (±)-**1** in protonated form is assumed to be involved in ionic H-bonding with the two catalytic Asp residues at the active site of PMII. The 1,3-benzothiazole moiety linked to the scaffold is assumed to occupy the newly created hydrophobic flap pocket, whereas the naphthyl residue points either into the spacious apolar S1/S3 pocket or the S2′ pocket (depending on the optical antipode of the inhibitor).

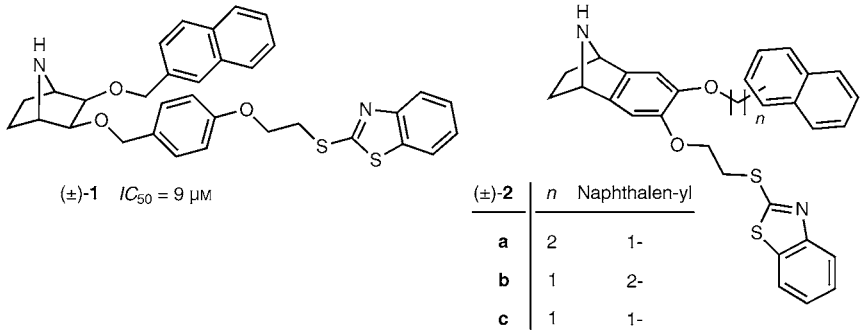


Fig. 1. *Examples of* de novo *designed inhibitors of the malarial enzyme Plasmepsin II (PMII)*

To further confirm this putative binding hypothesis, we used the active-site matrix in the distorted structure of PMII to design a second class of inhibitors such as (±)-**2a**–**2c**, featuring a more extended, rigid 11-azatricyclo[6.2.1.$0^{2,7}$]undeca-2(7),3,5-triene scaffold (*Fig. 1*). These compounds were expected, by molecular modeling (program *MOLOC* [4]), to adopt a binding mode similar to (±)-**1** (*Fig. 2*). Since the rigid central scaffold in (±)-**2a**–**2c** is more extended than in (±)-**1**, a shorter, less-flexible linker is required between central scaffold and 1,3-benzothiazole moiety. We expected the enhanced rigidity of the new inhibitors to result in higher binding affinities. Here, we describe the synthesis of this second class of designed PMII inhibitors, as well as *in vitro* binding studies, which provide strong support for the proposed binding mode (for a preliminary communication of parts of this work, see [5]).

2. Results and Discussion. – 2.1. *Synthesis of the First-Generation Inhibitors (±)-***2a**–**2c**. The synthetic route started with the dibenzyl protection of catechol, leading to diether **3**, which was selectively dibrominated affording **4** (*Scheme 1*) [6]. *Diels–Alder* reaction of protected 1*H*-pyrrole **5** [7] and a benzyne species, generated *in situ* from **4**, gave rise to the tricyclic scaffold **6** in acceptable yield. Hydrogenation afforded **7**, and a

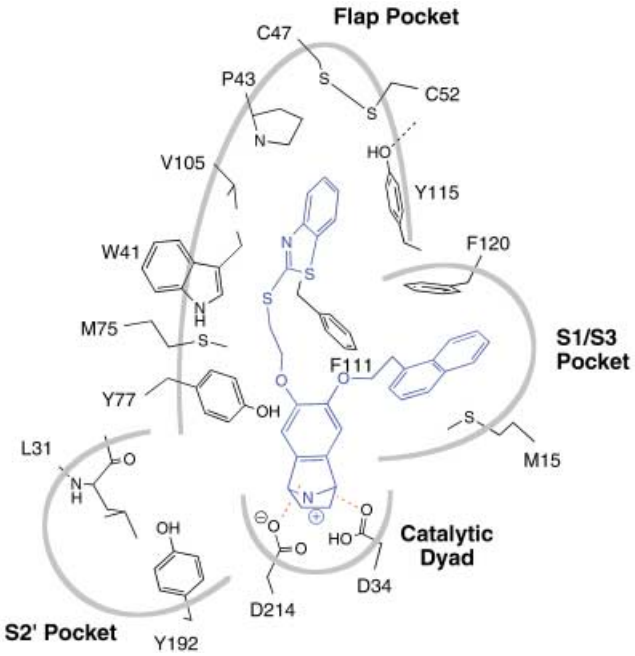
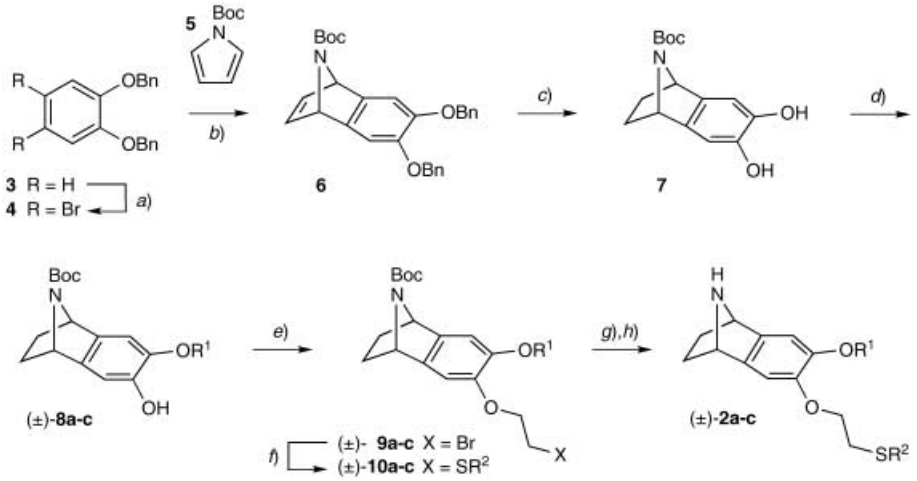


Fig. 2. *Representation of (1S,8*R*)-***2a*** in the active site of the modeled structure of plasmepsin II*

sequence of nucleophilic substitutions provided, *via* (±)-**8a**–**8c** and (±)-**9a**–**9c**, the protected inhibitors (±)-**10a**–**10c**. Final deprotection *via* intermediate formation of the (*tert*-butyl)dimethylsilyl carbamate, followed by cleavage under basic conditions, gave (±)-**2a**–**2c**. Optical resolution of (±)-**2a** was possible by preparative HPLC on a *Chiracel OD* column (absorbent: cellulose tris(3,5-dimethylphenyl carbamate), particle size: 20 μm, column dimensions: 20 × 250 mm, eluent: hexane/EtOH 1:1, flow rate: 6 ml/min, UV detection at 310 nm).

2.2. *Biological Activity of (±)-***2a**–**2c**. The *in vitro* activity of (±)-**2a**–**2c** against PMII, plasmepsin IV (PMIV), as well as three human aspartic proteases, cathepsin D (CatD), cathepsin E (CatE), and renin, was determined in automated assays (*Table*; for a detailed protocol, see [1]). The IC_{50} values (concentration of inhibitor at which 50% V_{max} is observed) provided evidence that the spacious S1/S3 pocket can accommodate naphthyl moieties in different orientations with similar affinities, thereby confirming observations made with our first series of inhibitors [1]. On the other hand, reduction of the length of the flexible linker between the 1,3-benzothiazole moiety and the tricyclic scaffold in (±)-**2a**–**2c** did not enhance the binding affinity compared to (±)-**1** (IC_{50} 9 μM). The results confirmed, however, the suitability of the new tricyclic central scaffold, which is prepared by a shorter and more-efficient route than the 7-azabicyclo[2.2.1]heptane core in (±)-**1**. The separated enantiomers of **2a** (of unknown absolute configuration) showed activities of 11 and 7 μM, respectively. This lack of enantioselectivity parallels the observations made for the two enantiomers of **1** (5 and 4 μM) [1]. As for **1** and *ent*-**1**, molecular modeling suggests that both enantiomers

Scheme 1. *Synthesis of Inhibitors* (±)-**2a**–**2c**.



a) Br_2, CH_2Cl_2, 0°, 30 min; 46%. *b*) *t*-BuLi, PhMe/hexane, −40° → r.t, 3 h; 65%. *c*) H_2, Pd/C (10%), MeCN, r.t., 3 h; 86%. *d*) R^1X, K_2CO_3, DMF, 60–80°, 12–18 h; 53–64% (X = Br, TsO). *e*) 1,2-Dibromoethane, KOH, Bu_4NOH, H_2O, 50°, 15 h; 92–100%. *f*) R^2SH, NaH, DMF, 80°, 1–2 h; 77–81%. *g*) (*t*-Bu)$Me_2SiOSO_2CF_3$, 2,6-lutidine, CH_2Cl_2, r.t., 30 min. *h*) Aq. K_2CO_3, THF/MeOH, r.t., 1 h; 55–71% (over two steps). Boc = (*tert*-butoxy)carbonyl; Ts = 4-toluenesulfonyl; Bn = benzyl. See *Fig. 1* for R^1 and R^2.

Table. *Biological Activity and Selectivity of the New Series of PMII Inhibitors*

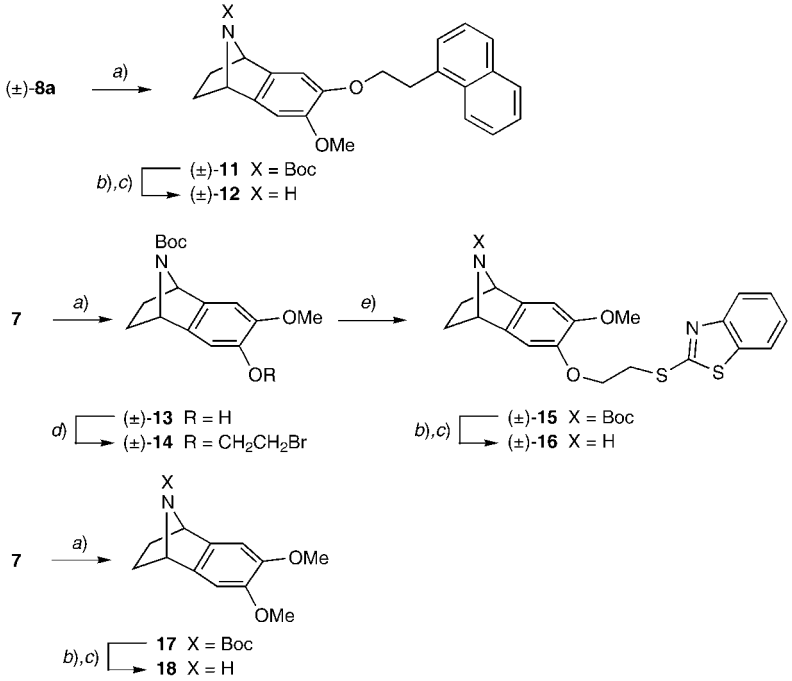
Inhibitor	IC_{50}				
	PII[a]) [μM]	PIV[b]) [μM]	Cat. D[c]) [μM]	Cat. E[d]) [μM]	Renin [μM]
(±)-**2a**	13	60	18	34	83
(±)-**2b**	10	85	23	42	81
(±)-**2c**	14	70	25	46	> 100
(±)-**12**	24	81	82	70	> 100
(±)-**16**	34	54	71	47	> 100
18	> 100	> 100	> 100	> 100	> 100
(±)-**19a**	3	15	12	6	> 100
(±)-**19b**	4	50	11	14	> 100
(±)-**19c**	5	17	12	7	> 100
(±)-**21**	79	n.d.[e])	n.d.	n.d.	n.d.
(±)-**23a**	4	33	12	9	93
(±)-**23b**	2	10	7	4	> 100

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

of **2a** can be fit into the active site of the modeled structure of PMII, with the 1,3-benzothiazole moiety occupying the flap pocket in both cases, and the naphthyl moiety positioned in either the S1/S3 or the S2′ pocket, depending on the antipode.

2.3. *Role of the Substituents Attached to the Central Scaffold*. A new series of compounds was prepared to investigate in more detail the influence of the substituents decorating the central tricyclic scaffold. Methylation of the free OH group in (±)-**8a** gave (±)-**11**, which was deprotected to give (±)-**12** (*Scheme 2*). Monomethylation of **7** furnished (±)-**13**, which was transformed *via* (±)-**14** and (±)-**15** into target compound (±)-**16**. Finally, dimethylation of **7** provided **17** and, after deprotection, the desired dimethoxy ether **18**.

Scheme 2. *Synthesis of Methoxy Derivatives (±)-***12**, *(±)-***16**, *and* **18**



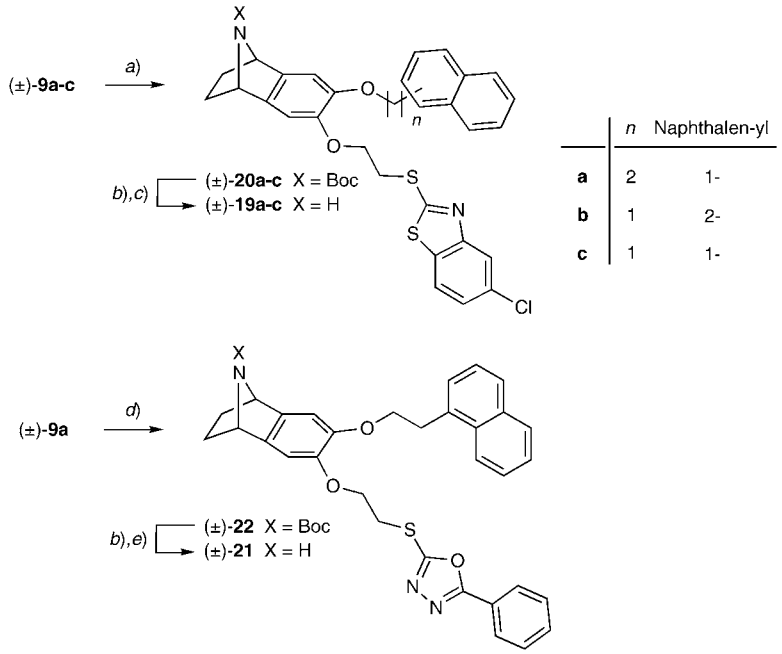
a) MeI, K_2CO_3, Me_2CO, 2.5 – 3 h, 40 – 60°; 66 – 98%. *b*) (*t*-Bu)$Me_2SiOSO_2CF_3$, 2,6-lutidine, CH_2Cl_2, r.t., 30 min. *c*) Aq. K_2CO_3, THF/MeOH, r.t., 1 h; 65 – 70% (over two steps). *d*) 1,2-Dibromoethane, KOH, Bu_4NOH, H_2O, 50°, 15 h; 100%. *e*) 2-sulfanyl-1,3-benzothiazole, NaH, DMF, 80°, 1 h; 71%.

As expected, the replacement of one of the large hydrophobic substituents by a MeO group led to a significant loss in biological activity against the tested plasmepsins and cathepsins (*Table*). Moreover, the dimethoxy derivative **18** loses all activity within the boundary of the assay. This finding confirms that binding of the protonated tricyclic 'needle' to the catalytic dyad is by far not sufficient to inhibit efficiently the activity of aspartic proteases. The comparable IC_{50} values of (±)-**12** (24 μM) and (±)-**16** (34 μM) might be rationalized in two different ways according to molecular modeling. The bonding interactions of the 1,3-benzothiazole moiety of (±)-**16** in the flap pocket and the naphthyl moiety of (±)-**12** in the S1/S3 pocket could be of similar strength. Alternatively, the single large substituent in both complexes may point into the flap pocket of PMII, thereby providing similar bonding interactions.

2.4. *Variation of the Substituent for Occupancy of the Flap Pocket.* Structure–activity relationships within the first class of PMII inhibitors ((±)-**1** and its derivatives) [1] had shown that appropriate occupancy of the rear of the flap pocket had a very large effect on biological activity. We are implicitly assuming that the protonated N-atom of the inhibitor is in close contact with the two catalytic Asp residues. Molecular-modeling examinations now suggested that a Cl-atom at C(5) of the 1,3-benzothiazole moiety in (±)-**2a**–**2c**, which occupies the flap pocket, could further enhance binding activity. The additional halogen atom appeared to fill space previously left empty, and could conceivably undergo favorable dispersion contacts with the highly polarizable disulfide bridge at the bottom of the pocket. Modeling also suggested that a 5-phenyl-2-sulfanyl-1,3,4-oxodiazole residue [8] would be well accommodated by the flap pocket.

In the synthesis of the new inhibitors, nucleophilic substitution of (±)-**9a**–**9c** with 5-chloro-2-sulfanyl-1,3-benzothiazole afforded (±)-**20a**–**20c**, and subsequent deprotection provided the chlorinated target compounds (±)-**19a**–**19c** (*Scheme 3*). Similarly, nucleophilic substitution of (±)-**9a** with 5-phenyl-2-sulfanyl-1,3,4-oxadiazole [8] gave (±)-**22**, which was deprotected to give (±)-**21** (*Scheme 3*).

Scheme 3. *Synthesis of Inhibitors (±)-***19a**–**19c** *and (±)-***21**



a) 5-Chloro-2-sulfanyl-1,3-benzothiazole, NaH, DMF, 80°, 12 h; 42–65%. *b*) (*t*-Bu)$Me_2SiOSO_2CF_3$, 2,6-lutidine, CH_2Cl_2, r.t., 30 min. *c*) Aq. K_2CO_3, THF/MeOH, r.t., 1 h; 59–69% (over two steps). *d*) 2-Mercapto-5-phenyl-1,3,4-oxadiazole, NaH, DMF, 80°, 2 h; 26%. *e*) Bu_4NF, THF, r.t., 1 h; 29% (steps *b* and *e*).

The introduction of the 5-phenyl-1,3,4-oxadiazole moiety in (±)-**21** for accommodation in the flap pocket did not lead to enhanced binding affinity (*Table*). Re-examination of the computer models of the predicted complex suggested that this

group might be too extended for fitting into the flap pocket of PMII, thus giving rise to repulsive *Van der Waals* contacts at the bottom of the pocket. On the other hand, the introduction of the Cl-atom at C(5) of the 1,3-benzothiazole moiety did enhance binding affinity as predicted by modeling. The chlorinated inhibitors showed a three- to fourfold increase in affinity with respect to their nonchlorinated analogues (*Table*). We consider this result as another strong evidence for the postulated binding mode of this new class of PMII inhibitors.

2.5. *Conformational Effects.* During modeling studies, we noticed that the preferred conformations adopted by the two ether substituents in inhibitors such as (±)-**2a**–**2c** or (±)-**19a**–**19c** were not optimal in the bound state. A search of the *Cambridge Structural Database* (*CSD*) clearly shows that the lowest-energy conformation of 1,2-dialkoxybenzene derivatives features both substituents splayed in the plane of the aromatic ring (conformation **A** of 1,2-dimethoxybenzene in *Fig. 3*; torsional angles $C(sp^2)-C(sp^2)-O-C(sp^3)=0^\circ$) [9]. In contrast, the corresponding torsional angles in (1*S*,8*R*)-**2a**, energy-minimized in the active site of PMII (*Fig. 2*), deviate by 22° (naphthyl substituent) and −136° (1,3-benzothiazole moiety) from planarity (schematically shown for conformation **B** of 1,2-dimethoxybenzene in *Fig. 3*). The latter large rotation out of planarity is required to orient the substituent into the flap pocket.

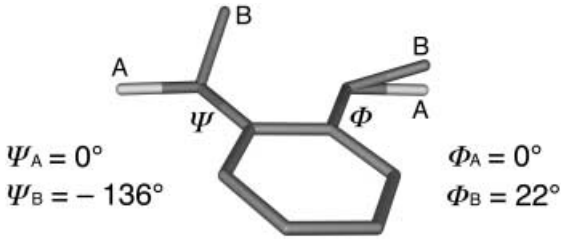


Fig. 3. *Conformational analysis of 1,2-dimethoxybenzene.* Conformer **A** has the lowest energy, while conformer **B** (a model for the geometry of (1*S*,8*R*)-**2a** optimized in the active site of PMII) is by *ca.* 2.2 kcal mol^{-1} higher in energy.

We subsequently undertook a conformational analysis to estimate the energetic costs in the gas phase associated with achieving the predicted conformation of (1*S*,8*R*)-**2a** in the active site of PMII. With the MacroModel software package and the MM2 force field [10], we calculated for 1,2-dimethoxybenzene (as model for bound (1*S*,8*R*)-**2a**) the energy while individually rotating the torsional angles Φ and Ψ (*Fig. 3*). The resulting *Ramachandran*-type plot expectedly revealed that the lowest-energy conformer corresponds to $\Phi=\Psi=0^\circ$, while the conformation with $\Phi=22^\circ$ and $\Psi=-136^\circ$ is by *ca.* 2.2 kcal/mol higher in energy. This increase in energy mostly results from the large Ψ angle.

Computational studies also suggested that replacement of the aryl ether O-atom in the linker to the 1,3-benzothiazole moiety by a CH_2 group should permit the resulting new inhibitors (±)-**23a** and **23b** (*Scheme 4*) to adopt a more-favorable conformation. This hypothesis was further validated by molecular-mechanics calculations, as described above, for model compound 2-ethylanisole (*Fig. 4*).

The calculated ideal conformation for 2-ethylanisole features the MeO group in the plane of the aromatic ring ($\Phi=0^\circ$) and the Et group twisted by *ca.* $\Psi=-95^\circ$ from

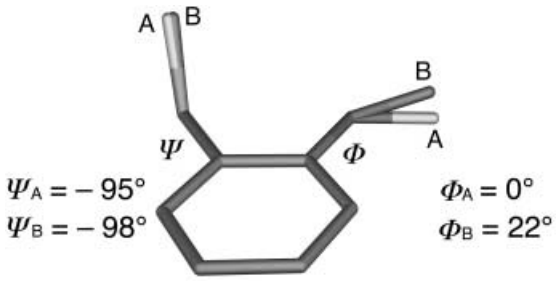


Fig. 4. *Conformational analysis of 2-ethylanisole.* The calculated lowest-energy conformation **A** closely resembles conformer **B**, a model for the geometry of inhibitor (1*S*,8*R*)-**23a** optimized in the active site of PMII.

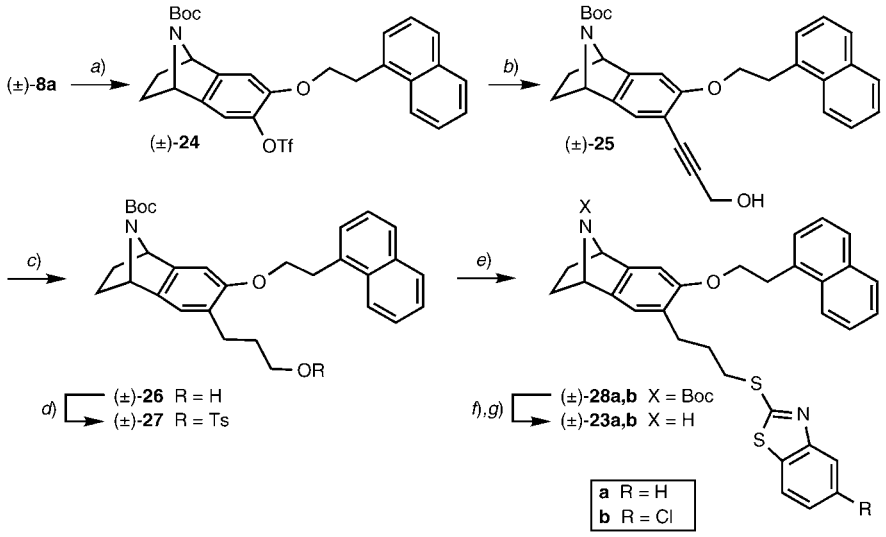
planarity (*Fig. 4*, conformer **A**). In parallel, (1*S*,8*R*)-**23a** was energy-minimized in the active site of PMII yielding $\Phi = 22°$ and $\Psi = -98°$. The conformation of 2-ethylanisole featuring the latter torsional angles (**B** in *Fig. 4*) is calculated to be only *ca.* 0.3 kcal/mol higher in energy. Free and PMII-bound (1*S*,8*R*)-**23a** are, thus, predicted to have similar conformational preferences; hence, we expected better binding affinity for this compound compared to the dialkoxy-substituted inhibitors, for which the calculations revealed a higher-energy geometry in the predicted bound than in the free state.

The synthesis of (±)-**23a** and **23b** started from (±)-**8a** that was transformed into aryl triflate (±)-**24**. *Sonogashira* cross-coupling [11] with propargyl aldehyde gave (±)-**25**, and reduction of the C≡C bond provided (±)-**26** that was converted into Ts derivative (±)-**27**. Nucleophilic substitution with either 2-sulfanyl-1,3-benzothiazole or 5-chloro-2-sulfanyl-1,3-benzothiazole afforded (±)-**28a** and **28b**, which were deprotected to give inhibitors (±)-**23a** and **23b**, respectively (*Scheme 4*).

The experimentally determined gain in binding affinity upon substitution of one of the ether O-atoms with a CH_2 group was less than expected based on the conformational analysis (*Table*). While (±)-**23a** (IC_{50} 4 μM) showed a desirable *ca.* threefold increase in affinity over (±)-**2a** (13 μM), the two chlorinated derivatives, (±)-**23b** (2 μM) and (±)-**19a** (3 μM), displayed activities against PMII that were nearly identical within the detection limit of the assay.

3. Conclusions. – This study provides additional strong experimental support for the proposed [1] opening of a hydrophobic flap pocket induced by the complexation of nonpeptidic inhibitors at the active site of plasmepsin II. 11-Azatricyclo[6.2.1.$0^{2,7}$]undeca-2(7),3,5-triene was found to be a suitable central scaffold for inhibitors of plasmepsin II, as had been predicted by molecular modeling. However, SARs (*Table*) clearly showed that the H-bonding interactions of this core, in protonated form, with the catalytic dyad of the aspartic protease by themselves are by far not sufficient for generating binding affinity measurable by the applied automated *in vitro* assay (detection limit 100 μM). For single-digit micromolar activity, decoration of the scaffold with two substituents for accommodation into the hydrophobic flap and S1/S3 (or S2′, depending on the optical antipode of the inhibitor) pockets is required. In agreement with the previous study on inhibitors with a central 7-azabicyclo[2.2.1]heptane scaffold [1], full occupancy of the rear part of the flap pocket is particularly beneficial for

Scheme 4. *Synthesis of Inhibitors* (±)-**23a** *and* (±)-**23b**



a) $(CF_3SO_2)_2O$, pyridine, CH_2Cl_2, $-78°$, 2 h; 100%. *b*) Propargyl alcohol, piperidine, $[Pd(PPh_3)_4]$, sealed tube, 80°, 36 h; 57%. *c*) H_2, Pd/C (10%), MeOH, r.t., 12 h; 100%. *d*) TsCl, pyridine, CH_2Cl_2, $0° \rightarrow$ r.t., 90 min; 51%. *e*) 2-Mercapto-1,3-benzothiazole or 5-Chloro-2-mercapto-1,3-benzothiazole, NaH, DMF, r.t., 12 h; 52–72% *f*) (*t*-Bu)$Me_2SiOSO_2CF_3$, 2,6-lutidine, CH_2Cl_2, r.t., 30 min. *g*) Aq. K_2CO_3, THF/MeOH, r.t., 45 min; 67–75% (over two steps). Tf = trifluoromethanesulfonyl.

binding affinity. Thus, (±)-**19a**–**19c** (IC_{50} 3–5 μM) and (±)-**23b** (2 μM), with an additional Cl-atom on the 1,3-benzothiazole moiety to fully fill this pocket, are among the most potent in the entire series of inhibitors prepared. Optimization of the linker connecting the 1,3-benzothiazole moiety to the core led to additional improvement of the inhibitory potency ((±)-**2a** *vs.* (±)-**23a**), although to a lesser extent than was expected based on a detailed conformational analysis.

The inhibitors bearing two substituents display good selectivity towards renin, the first aspartic protease for which the major induced-fit adaptation including the unlocking of a new flap pocket had been unambiguously demonstrated by X-ray crystallography [3]. Our compounds show modest selectivity against plasmepsin IV and almost no selectivity towards cathepsins D and E. These results suggest that the conformational changes at the active site, predicted for plasmepsin II, are likely to be operative in the cathepsins as well.

Finally, the SARs established in this and the previous [1] investigation provide highly useful guidelines for structure-based design and synthesis of next generations of more-potent and -selective nonpeptidic inhibitors of plasmepsin II, potentially leading to new antimalarial therapies.

We are grateful to the *ETH Research Council* and *F. Hoffmann-La Roche* for support of the work done at the ETH. We thank Dr. *R. P. Moon* for helpful discussions and Dr. *C. Thilgen* for assistance with the nomenclature.

Experimental Part

General. See [1]. The following compounds were prepared according to literature procedures: **3** [6], **4** [6], and **5** [7]. Prep. HPLC: *Knauer HPLC* with HPLC pump *64*; chiral stationary phase: *Chiralcel OD* (particle size: 20 μm, column dimensions: 20 × 250 mm) from *Daicel Chemical Industries*.

Biological Assay. The automated assay described in [1] was used to determine the inhibitory activities.

General Procedure for the Williamson *Ether Synthesis, Reacting a Phenolic OH-Group with 1,2-Dibromoethane* (*Procedure A*). The phenol was dissolved in 1,2-dibromoethane, and solns. of Bu_4NOH (40% in H_2O) and KOH (40% in H_2O) were added. The mixture was heated to 50° for 15 h. After cooling to r.t., CH_2Cl_2 was added, and the soln. was washed with H_2O (2×) and sat. aq. NaCl soln. (1×). The org. phase was dried ($MgSO_4$), and the solvent was evaporated *in vacuo* to give an oily crude product.

General Procedure for the Nucleophilic Substitution of an Alkyl Bromide with 2-Sulfanyl-1,3-benzothiazole (*Procedure B*). To 2-sulfanyl-1,3-benzothiazole in dry DMF, NaH (60% in oil) was added, and the suspension was stirred for 15 min. The suspension was added to the alkyl bromide in dry DMF, and the mixture was heated to 80° for 1 h. After addition of H_2O and AcOEt, the aq. phase was separated, and the org. phase was washed with H_2O (2×) and sat. aq. NaCl soln. (1×), dried ($MgSO_4$), and concentrated *in vacuo* to afford a clear yellow oil, which was purified by CC (SiO_2; hexane/AcOEt 4:1) to yield a colorless oil.

General Procedure for the Conversion of the Boc Group into the Silyl Carbamate and Subsequent Cleavage to the Free Amine (*Procedure C*). To a well-stirred soln. of the *N*-Boc-protected derivative of the potential inhibitor in CH_2Cl_2, 2,6-lutidine and (*t*-Bu)$Me_2SiOSO_2CF_3$ (TBDMSOTf) were added, the latter dropwise. The yellow mixture was stirred for 30 min and then quenched with sat. aq. NH_4Cl soln. After phase separation, the aq. phase was extracted with Et_2O (3×). The combined org. layers were washed with sat. aq. NaCl soln. (1×) and H_2O (1×), dried ($MgSO_4$), and evaporated *in vacuo* to yield the silyl carbamate intermediate. This crude product was dissolved in THF/MeOH 2:5, and 1M K_2CO_3 was added. The mixture was stirred for 1 h at r.t. under Ar, and sat. aq. NH_4Cl soln. was added. The mixture was extracted with CH_2Cl_2 (2×) and the combined org. phases washed with sat. aq. NaCl soln. (1×), dried ($MgSO_4$), and evaporated *in vacuo*. The crude product was purified by CC (basic Al_2O_3, act. II; AcOEt/MeOH 6:1 → 10:1).

General Procedure for the Nucleophilic Substitution of an Alkyl Bromide with 5-Chloro-2-sulfanyl-1,3-benzothiazole (*Procedure D*). To 5-chloro-2-sulfanyl-1,3-benzothiazole in dry DMF, NaH (60% in oil) was added, and the suspension was stirred for 15 min at r.t., then added to a soln. of the alkyl bromide in dry DMF. The mixture was heated to 80° overnight, and after cooling to r.t., diluted with H_2O and AcOEt. The aq. phase was separated, and the org. phase was washed with H_2O (2×) and sat. aq. NaCl soln. (1×), dried ($MgSO_4$), and concentrated *in vacuo*. CC (hexane/AcOEt 5:1) furnished the pure compound as a yellow oil.

tert-*Butyl 4,5-Bis(benzyloxy)-11-azatricyclo[6.2.1.0^{2,7}]undeca-2(7),3,5,9-tetraene-11-carboxylate* (**6**). To a well-stirred soln. of **5** (1.87 g, 11.20 mmol) and **4** (1.50 g, 3.35 mmol) in PhMe (20 ml) at −40°, a soln. of *t*-BuLi (1.32M in hexane, 3.4 ml, 4.48 mmol) in hexane (freshly distilled from Na, 8 ml) was added portionwise. The mixture was kept at −40° for 1.5 h, then allowed to warm to r.t. during 1.5 h. MeOH (5 ml) was added, the mixture was stirred for 30 min, then washed with H_2O (2×), dried ($MgSO_4$), and concentrated *in vacuo* to yield a yellow-brown liquid. CC (SiO_2; hexane/AcOEt 3:1) gave **6** (330 mg, 65%). Pale-brown oil. IR (KBr): 2979*m*, 1700*s*, 1607*m*, 1456*s*, 1173*s*, 1087*s*. ^{1}H-NMR ($CDCl_3$, 300 MHz): 1.35 (*s*, 9 H); 5.09 (*s*, 4 H); 5.37 (br. *s*, 2 H); 6.98–7.00 (*m*, 4 H); 7.30–7.43 (*m*, 10 H). ^{13}C-NMR ($CDCl_3$, 75.5 MHz): 28.02; 66.24; 66.87; 72.27 (2×); 80.56; 111.29 (2×); 127.50 (4×); 127.87 (2×); 128.53 (4×); 137.53 (2×); 142.04; 142.61; 143.68 (2×); 146.12 (2×); 155.13. HR-MALDI-MS (DHB): 356.1645 ([*M*H − Boc]$^+$, $C_{24}H_{22}NO_2^+$; calc. 356.1651). Anal. calc. for $C_{29}H_{29}NO_4$ (455.55): C 76.46, H 6.42, N 3.07; found: C 76.33, H 6.53, N 3.13.

tert-*Butyl 4,5-Dihydroxy-11-azatricyclo[6.2.1.0^{2,7}]undeca-2(7),3,5-triene-11-carboxylate* (**7**). To a well-degassed soln. of **6** (3.57 g, 7.85 mmol) in MeCN (300 ml), Pd/C (10%, 2.49 g) was added. The mixture was degassed for 10 min, placed under H_2 (1 bar), and stirred for 3 h. The black slurry was filtered through a pad of *Celite*, which was washed several times with AcOEt, and the filtrate was concentrated *in vacuo* to furnish a dark-brown solid. CC (SiO_2; hexane/AcOEt/AcOH 50:49:1 → AcOEt/AcOH 100:1) afforded **7** (1.86 g, 86%). Pale-brown solid. M.p. >190° (dec.). IR (KBr): 3484*s*, 3230*s*, 2978*s*, 1674*s*, 1615*s*, 1464*s*, 1386*s*, 1159*s*, 1088*s*. ^{1}H-NMR ($CDCl_3$, 300 MHz): 1.21–1.26 (*m*, 2 H); 1.41 (*s*, 9 H); 2.05–2.07 (*m*, 2 H); 4.99 (*s*, 2 H); 6.76 (br. *s*, 2 H). ^{13}C-NMR ($CDCl_3$, 75.5 MHz): 27.23 (2×); 28.17; 61.11 (2×); 80.87; 107.60 (2×); 137.21 (2×); 142.29 (2×); 155.94. HR-MALDI-MS (DHB): 300.1205 ([*M* + Na]$^+$, $C_{15}H_{19}NNaO_4^+$; calc. 300.1212). Anal. calc. for $C_{15}H_{19}NO_4$ (277.32): C 64.97, H 6.91, N 5.05; found: C 64.97, H 6.94, N 5.02.

tert-*Butyl 4-Hydroxy-5-[2-(naphthalen-1-yl)ethoxy]-11-azatricyclo[6.2.1.0^{2,7}]undeca-2(7),3,5-triene-11-carboxylate* ((±)-**8a**). To **7** (223 mg, 0.81 mmol) in dry DMF (2.7 ml), K_2CO_3 (335 mg, 2.43 mmol) was added. After

heating to 60° for 1 h, 2-(naphthalen-1-yl)ethyl *p*-toluenesulfonate (263 mg, 0.81 mmol) in dry DMF (1.9 ml) was added. Heating was continued for 12 h, the soln. was cooled to r.t., and Et_2O added. The phases were separated, and the aq. phase was extracted with Et_2O (2×). The combined org. phases were washed with 1N HCl (2×), H_2O (2×), and sat. aq. NaCl soln (1×). The org. layers were dried ($MgSO_4$) and evaporated *in vacuo* to give a red-brown oil. CC (SiO_2; CH_2Cl_2/AcOEt 50:1) yielded (±)-**8a** (223 mg, 64%). Colorless foam. IR ($CHCl_3$): 3535*w*, 2983*w*, 2944*w*, 1693*s*, 1601*w*, 1488*m*, 1349*s*, 1272*s*, 1160*s*, 1084*m*. ^{1}H-NMR ($CDCl_3$, 300 MHz): 1.17–1.20 (*m*, 2 H); 1.38 (*s*, 9 H); 2.02–2.05 (*m*, 2 H); 3.58 (*t*, *J* = 6.8, 2 H); 4.31–4.40 (*m*, 2 H); 4.99 (br. *s*, 2 H); 5.35 (*s*, 1 H); 6.79 (br. *s*, 2 H); 7.41–7.60 (*m*, 4 H); 7.77–7.80 (*m*, 1 H); 7.88–7.91 (*m*, 1 H); 8.09–8.13 (*m*, 1 H). ^{13}C-NMR ($CDCl_3$, 75.5 MHz): 27.13 (2×); 28.11; 32.64; 60.97 (2×); 69.51; 79.88; 104.70; 107.08; 123.39; 125.65; 125.81; 126.33; 127.04; 127.68; 129.13; 132.25; 134.02; 134.15; 136.66; 138.19; 143.95; 144.44; 155.36. HR-MALDI-MS (DHB): 454.1986 ($[M+Na]^+$, $C_{27}H_{29}NNaO_4^+$; calc. 454.1994). Anal. calc. for $C_{27}H_{29}NO_4$ (431.53): C 75.15, H 6.77, N 3.25; found: C 75.00, H 6.83, N 3.06.

tert-*Butyl 4-Hydroxy-5-[(naphthalen-2-yl)methoxy]-11-azatricyclo[6.2.1.0^{2,7}]undeca-2(7),3,5-triene-11-carboxylate* ((±)-**8b**). To **7** (300 mg, 1.08 mmol) in dry DMF (4 ml), K_2CO_3 (448 mg, 3.24 mmol) was added. After heating to 60° for 1 h, 2-(bromomethyl)naphthalene (239 mg, 1.08 mmol) in dry DMF (3 ml) was added. The mixture was heated to 60° overnight, and, after cooling to r.t., H_2O was added. The mixture was rendered acidic by addition of 1N HCl and then extracted with Et_2O (4×). The combined org. phases were washed with sat. aq. NaCl soln. (1×), dried ($MgSO_4$), and concentrated *in vacuo* to give a brown oil. CC (SiO_2; hexane/AcOEt 7:1) provided (±)-**8b** (238 mg, 53%). Colorless foam. IR ($CHCl_3$): 3539*m*, 2981*m*, 2867*w*, 1693*s*, 1603*m*, 1487*s*, 1348*s*, 1272*s*, 1160*s*, 1082*s*. ^{1}H-NMR ($CDCl_3$, 300 MHz): 1.21–1.26 (*m*, 2 H); 1.39 (*s*, 9 H); 2.05–2.08 (*m*, 2 H); 5.03 (br. *s*, 2 H); 5.25 (*s*, 2 H); 5.63 (*s*, 1 H); 6.89 (br. *s*, 1 H); 6.94 (br. *s*, 1 H); 7.50–7.54 (*m*, 3 H); 7.84–7.90 (*m*, 4 H). ^{13}C-NMR ($CDCl_3$, 75.5 MHz): 27.05 (2×); 28.12; 61.05 (2×); 71.89; 79.91; 105.40; 107.29; 125.54; 126.46; 126.54; 126.90; 127.89; 128.08; 128.73; 133.35 (2×); 133.95; 136.80; 138.56; 144.19; 144.65; 155.44. HR-MALDI-MS (DHB): 440.1832 ($[M+Na]^+$, $C_{26}H_{27}NNaO_4^+$; calc. 440.1838).

tert-*Butyl 4-Hydroxy-5-[(naphthalen-1-yl)methoxy]-11-azatricyclo[6.2.1.0^{2,7}]undeca-2(7),3,5-triene-11-carboxylate* ((±)-**8c**). To **7** (100 mg, 0.36 mmol) in dry DMF (1.2 ml), K_2CO_3 (150 mg, 1.08 mmol) was added. After heating to 60° for 30 min, a soln. of 1-(bromomethyl)naphthalene (80 mg, 0.36 mmol) in dry DMF (0.9 ml) was added. After heating to 80° overnight and cooling to r.t., Et_2O (4 ml) and H_2O (2 ml) were added. The phases were separated, the aq. phase was extracted with Et_2O (1×), and the combined org. phases were washed with 1N HCl (2×), H_2O (2×), and sat. aq. NaCl soln. (1×). Drying ($MgSO_4$) and evaporation *in vacuo* left a brown oil. CC (SiO_2; hexane/AcOEt 5:1) afforded (±)-**8c** (88 mg, 58%). Colorless oil. IR ($CHCl_3$): 3539*w*, 2985*w*, 2872*w*, 1693*s*, 1601*w*, 1487*m*, 1349*s*, 1272*m*, 1160*s*, 1082*m*. ^{1}H-NMR ($CDCl_3$, 300 MHz): 1.24–1.28 (*m*, 2 H); 1.41 (*s*, 9 H); 2.07–2.09 (*m*, 2 H); 5.05 (br. *s*, 2 H); 5.29 (*s*, 1 H); 5.51 (*s*, 2 H); 6.87 (*s*, 1 H); 7.05 (*s*, 1 H); 7.45–7.57 (*m*, 4 H); 7.88–7.94 (*m*, 2 H); 8.02–8.05 (*m*, 1 H). ^{13}C-NMR ($CDCl_3$, 125 MHz): 27.16 (2×); 28.25; 60.79; 61.12; 70.38; 79.95; 105.33; 107.28; 123.46; 125.29; 126.11; 126.79; 127.19; 128.83; 129.53; 131.65; 131.78; 133.82; 136.68; 138.52; 144.07; 144.61; 155.28. HR-MALDI-MS (DHB): 440.1839 ($[M+Na]^+$, $C_{26}H_{27}NNaO_4^+$; calc. 440.1838).

tert-*Butyl 4-(2-Bromoethoxy)-5-[2-(naphthalen-1-yl)ethoxy]-11-azatricyclo[6.2.1.0^{2,7}]undeca-2(7),3,5-triene-11-carboxylate* ((±)-**9a**). *Procedure A* with (±)-**8a** (144 mg, 0.33 mmol), 1,2-dibromoethane (1.00 ml, 11.7 mmol), and aq. solns. of Bu_4NOH (0.14 ml, 0.22 mmol) and KOH (0.23 ml, 1.67 mmol): crude (±)-**9a** (164 mg, 92%), which was used without further purification. A sample was purified by CC (SiO_2; CH_2Cl_2/AcOEt 19:1) for anal. purposes. Colorless oil. IR ($CHCl_3$): 2964*s*, 2877*s*, 1693*s*, 1619*m*, 1474*s*, 1267*s*, 1160*s*, 1089*s*. ^{1}H-NMR ($CDCl_3$, 300 MHz): 1.19–1.22 (*m*, 2 H); 1.38 (*s*, 9 H); 2.04–2.06 (*m*, 2 H); 3.52 (*t*, *J* = 6.5, 2 H); 3.60 (*t*, *J* = 7.1, 2 H); 4.18 (*t*, *J* = 6.5, 2 H); 4.29–4.36 (*m*, 2 H); 4.99–5.02 (br. *m*, 2 H); 6.84 (*s*, 1 H); 6.89 (*s*, 1 H); 7.42–7.54 (*m*, 4 H); 7.75–7.78 (*m*, 1 H); 7.86–7.89 (*m*, 1 H); 8.09–8.11 (*m*, 1 H). ^{13}C-NMR ($CDCl_3$, 75.5 MHz): 26.83 (2×); 28.06; 29.37; 32.78; 61.01 (2×); 69.74; 70.32; 79.93; 107.42; 109.70; 123.61; 125.56; 125.60; 126.09; 127.22; 127.35; 128.89; 132.12; 133.92; 134.21; 138.03 (2×); 146.52; 148.30; 155.29. HR-MALDI-MS (DHB): 560.1405 (100, $[M+Na]^+$, $C_{29}H_{32}BrNNaO_4^+$; calc. 560.1412). Anal. calc. for $C_{29}H_{32}BrNO_4$ (538.48): C 64.69, H 5.99, N 2.60; found: C 64.90, H 5.91, N 2.75.

tert-*Butyl 4-(2-Bromoethoxy)-5-[(naphthalen-2-yl)methoxy]-11-azatricyclo[6.2.1.0^{2,7}]undeca-2(7),3,5-triene-11-carboxylate* ((±)-**9b**). *Procedure A* with (±)-**8b** (70 mg, 0.17 mmol), 1,2-dibromoethane (0.7 ml, 8.38 mmol), and aq. solns. of Bu_4NOH (0.08 ml, 0.12 mmol) and KOH (0.12 ml, 0.84 mmol): crude (±)-**9b** (88 mg, 100%), which was used without further purification. ^{1}H-NMR ($CDCl_3$, 200 MHz): 1.21–1.25 (*m*, 2 H); 1.37 (*s*, 9 H); 2.04–2.08 (*m*, 2 H); 3.64 (*t*, *J* = 6.4, 2 H); 4.34 (*t*, *J* = 6.4, 2 H); 4.99–5.04 (br. *m*, 2 H); 5.26 (*s*, 2 H); 6.93 (*s*, 1 H); 6.95 (*s*, 1 H); 7.46–7.58 (*m*, 3 H); 7.82–7.90 (*m*, 4 H).

tert-*Butyl 4-(2-Bromoethoxy)-5-[(naphthalen-1-yl)methoxy]-11-azatricyclo[6.2.1.0^{2,7}]undeca-2(7),3,5-triene-11-carboxylate* ((±)-**9c**). *Procedure A* with (±)-**8c** (77 mg, 0.18 mmol), 1,2-dibromoethane (0.8 ml, 9.22 mmol), and aq. solns. of Bu_4NOH (0.08 ml, 0.13 mmol) and KOH (0.13 ml, 0.92 mmol): crude (±)-**9c** (97 mg, 100%), which was used without further purification. ^{1}H-NMR ($CDCl_3$, 300 MHz): 1.18–1.26 (*m*, 2 H); 1.39 (*s*, 9 H); 2.04–2.08 (*m*, 2 H); 3.54 (*t*, *J* = 6.4, 2 H); 4.27 (*t*, *J* = 6.4, 2 H); 4.99–5.04 (br. *m*, 2 H); 5.53 (*s*, 2 H); 6.93 (*s*, 1 H); 6.99 (*s*, 1 H); 7.42–7.60 (*m*, 4 H); 7.83–7.91 (*m*, 2 H); 8.15–8.17 (*m*, 1 H).

tert-*Butyl 4-{2-[(1,3-Benzothiazol-2-yl)sulfanyl]ethoxy}-5-[2-(naphthalen-1-yl)ethoxy]-11-azatricyclo[6.2.1.0^{2,7}]undeca-2(7),3,5-triene-11-carboxylate* ((±)-**10a**). *Procedure B* with (±)-**9a** (200 mg, 0.37 mmol), NaH (60% in oil, 52 mg, 1.30 mmol), and 2-sulfanyl-1,3-benzothiazole (216 mg, 1.30 mmol) in dry DMF (2 ml): (±)-**10a** (178 mg, 77%). Colorless oil. IR ($CHCl_3$): 3007*m*, 2944*m*, 2878*w*, 1692*s*, 1598*m*, 1460*s*, 1428*s*, 1267*s*, 1160*s*, 1084*m*. ^{1}H-NMR ($CDCl_3$, 300 MHz): 1.19–1.23 (*m*, 2 H); 1.38 (*s*, 9 H); 2.00–2.08 (*m*, 2 H); 3.59 (*t*, *J* = 11.0, 2 H); 3.68 (*t*, *J* = 9.8, 2 H); 4.29–4.35 (*m*, 4 H); 4.96–5.04 (br. *m*, 2 H); 6.84 (*s*, 1 H); 6.98 (*s*, 1 H); 7.27–7.56 (*m*, 6 H); 7.72–7.91 (*m*, 4 H); 8.10–8.14 (*m*, 1 H). ^{13}C-NMR ($CDCl_3$, 75.5 MHz): 26.94 (2×); 28.11; 32.20; 32.81; 61.06 (2×); 68.46; 69.85; 79.99; 107.45; 108.65; 120.78; 121.53; 123.68; 123.86; 125.60 (2×); 126.12; 126.66; 127.24; 127.35; 128.89; 132.16; 133.94; 134.26; 135.43; 138.03; 138.87; 146.95; 147.93; 153.24; 155.34; 166.36. HR-MALDI-MS (DHB): 647.2010 ([*M* + Na]$^+$, $C_{36}H_{36}N_2NaO_4S_2^+$; calc. 647.2014). Anal. calc. for $C_{36}H_{36}N_2O_4S_2$ (624.82): C 69.20, H 5.81, N 4.48; found: C 69.32, H 5.84, N 4.33.

tert-*Butyl 4-{2-[(1,3-Benzothiazol-2-yl)sulfanyl]ethoxy}-5-[(naphthalen-2-yl)methoxy]-11-azatricyclo[6.2.1.0^{2,7}]undeca-2(7),3,5-triene-11-carboxylate* ((±)-**10b**). *Procedure B* with (±)-**9b** (83 mg, 0.16 mmol), NaH (60% in oil, 13 mg, 0.32 mmol), and 2-sulfanyl-1,3-benzothiazole (53 mg, 0.32 mmol) in dry DMF (1.2 ml): (±)-**10b** (80 mg, 81%). Pale-yellow oil. IR ($CHCl_3$): 2995*m*, 2882*m*, 1694*s*, 1600*w*, 1459*s*, 1428*s*, 1268*s*, 1160*s*, 1087*s*. ^{1}H-NMR ($CDCl_3$, 300 MHz): 1.20–1.24 (*m*, 2 H); 1.36 (*s*, 9 H); 2.02–2.10 (*m*, 2 H); 3.77 (*t*, *J* = 6.7, 2 H); 4.44 (*t*, *J* = 6.7, 2 H); 5.00–5.03 (br. *m*, 2 H); 5.25 (*s*, 2 H); 6.94 (*s*, 1 H); 7.03 (*s*, 1 H); 7.27–7.32 (*m*, 1 H); 7.39–7.49 (*m*, 4 H); 7.54–7.57 (*m*, 1 H); 7.73–7.75 (*m*, 1 H); 7.82–7.89 (*m*, 4 H). ^{13}C-NMR ($CDCl_3$, 75.5 MHz): 26.91 (2×); 28.12; 32.31; 61.10 (2×); 68.26; 72.07; 79.90; 108.14; 108.45; 120.96; 121.41; 124.23; 125.19; 125.88; 125.99; 126.05; 126.10; 127.62; 127.90; 128.17; 132.95; 133.19; 134.73; 135.28; 138.35 (2×); 147.23; 147.49; 153.02; 155.18; 166.08. HR-MALDI-MS (DHB): 633.1844 ([*M* + Na]$^+$, $C_{35}H_{34}N_2NaO_4S_2^+$; calc. 633.1858). Anal. calc. for $C_{35}H_{34}N_2O_4S_2$ (610.80): C 68.83, H 5.61, N 4.59; found: C 68.89, H 5.89, N 4.43.

tert-*Butyl 4-{2-[(1,3-Benzothiazol-2-yl)sulfanyl]ethoxy}-5-[(naphthalen-1-yl)methoxy]-11-azatricyclo[6.2.1.0^{2,7}]undeca-2(7),3,5-triene-11-carboxylate* ((±)-**10c**). *Procedure B* with (±)-**9c** (275 mg, 0.51 mmol), NaH (60% in oil, 82 mg, 2.04 mmol), and 2-sulfanyl-1,3-benzothiazole (341 mg, 2.04 mmol) in dry DMF (4.5 ml): (±)-**10c** (246 mg, 79%). Pale-yellow oil. IR ($CHCl_3$): 3005*w*, 2982*w*, 2872*w*, 1693*s*, 1600*w*, 1459*m*, 1428*s*, 1268*s*, 1161*s*, 1087*m*. ^{1}H-NMR ($CDCl_3$, 300 MHz): 1.21–1.24 (*m*, 2 H); 1.39 (*s*, 9 H); 2.01–2.07 (*m*, 2 H); 3.69 (*t*, *J* = 6.6, 2 H); 4.39 (*t*, *J* = 6.6, 2 H); 5.02–5.05 (*m*, 2 H); 5.53 (*s*, 2 H); 6.97 (*s*, 1 H); 7.03 (*s*, 1 H); 7.27–7.32 (*m*, 1 H); 7.39–7.60 (*m*, 5 H); 7.73–7.76 (*m*, 1 H); 7.81–7.90 (*m*, 3 H); 8.17–8.19 (*m*, 1 H). ^{13}C-NMR ($CDCl_3$, 125 MHz): 26.90 (2×); 28.23; 32.35; 61.19 (2×); 68.42; 70.99; 79.98; 108.38; 109.26; 121.01; 121.50; 123.92; 124.29; 125.30; 125.83; 126.05; 126.30; 126.44; 128.61; 128.81; 131.52; 132.68; 133.72; 135.37; 138.76 (2×); 147.70 (2×); 153.12; 155.22; 166.15. HR-MALDI-MS (DHB): 633.1858 ([*M* + Na]$^+$, $C_{35}H_{34}N_2NaO_4S_2^+$; calc. 633.1858).

4-{2-[(1,3-Benzothiazol-2-yl)sulfanyl]ethoxy}-5-[2-(naphthalen-1-yl)ethoxy]-11-azatricyclo[6.2.1.0^{2,7}]undeca-2(7),3,5-triene ((±)-**2a**). *Procedure C* with (±)-**10a** (77 mg, 0.12 mmol), CH_2Cl_2 (0.40 ml), 2,6-lutidine (29 µl, 0.25 mmol), TBDMSOTf (43 µl, 0.19 mmol), THF (0.4 ml), MeOH (0.9 ml), and 1M K_2CO_3 (0.26 ml, 0.26 mmol): (±)-**2a** (46 mg, 71%). Pale-yellow oil. IR ($CHCl_3$): 3422*w*, 2928*s*, 2855*m*, 1594*m*, 1428*s*, 1278*m*, 1089*s*. ^{1}H-NMR ($CDCl_3$, 300 MHz): 1.12–1.21 (*m*, 2 H); 1.73 (br. *s*, 1 H); 1.97–1.99 (*m*, 2 H); 3.60 (*t*, *J* = 7.2, 2 H); 3.68 (*t*, *J* = 6.6, 2 H); 4.30–4.34 (*m*, 4 H); 4.42–4.46 (br. *m*, 2 H); 6.81 (*s*, 1 H); 6.95 (*s*, 1 H); 7.27–7.33 (*m*, 1 H); 7.40–7.55 (*m*, 5 H); 7.72–7.77 (*m*, 2 H); 7.83–7.88 (*m*, 2 H); 8.09–8.12 (*m*, 1 H). ^{13}C-NMR ($CDCl_3$, 75.5 MHz): 26.52 (2×); 32.22; 32.88; 61.00 (2×); 68.49; 69.87; 107.26; 108.52; 121.07; 121.51; 123.70; 124.36; 125.60 (2×); 126.11 (2×); 127.24; 127.34; 128.89; 132.17; 133.94; 134.31; 135.44; 140.94; 141.75; 146.72; 147.71; 153.24; 166.36. HR-MALDI-MS (DHB): 547.1491 ([*M* + Na]$^+$, $C_{31}H_{28}N_2NaO_2S_2^+$; calc. 547.1490).

4-{2-[(1,3-Benzothiazol-2-yl)sulfanyl]ethoxy}-5-[(naphthalen-2-yl)methoxy]-11-azatricyclo[6.2.1.0^{2,7}]undeca-2(7),3,5-triene ((±)-**2b**). *Procedure C* with (±)-**10b** (110 mg, 0.18 mmol), CH_2Cl_2 (0.5 ml), 2,6-lutidine (42 µl, 0.36 mmol), TBDMSOTf (67 µl, 0.27 mmol), THF (0.45 ml), MeOH (1.2 ml), and 1M K_2CO_3 (0.36 ml, 0.36 mmol): (±)-**2b** (65 mg, 71%). Pale-yellow oil. IR (neat): 3400*m*, 2979*s*, 2872*m*, 1603*m*, 1428*s*, 1280*s*, 1088*s*. ^{1}H-NMR ($CDCl_3$, 300 MHz): 1.16–1.20 (*m*, 2 H); 1.68 (br. *s*, 1 H); 1.97–1.99 (*m*, 2 H); 3.77 (*t*, *J* = 6.6, 2 H); 4.42–4.48 (*m*, 4 H); 5.25 (*s*, 2 H); 6.90 (*s*, 1 H); 7.00 (*s*, 1 H); 7.26–7.32 (*m*, 1 H); 7.39–7.49 (*m*, 4 H); 7.55–7.58 (*m*, 1 H); 7.72–7.75 (*m*, 1 H); 7.81–7.90 (*m*, 4 H). ^{13}C-NMR ($CDCl_3$, 75.5 MHz): 26.51 (2×); 32.35; 60.98 (2×);

68.30; 72.07; 108.00; 108.24; 120.96; 121.38; 124.23; 125.20; 125.88; 125.99; 126.07 (2×); 127.64; 127.90; 128.17; 132.93; 133.21; 134.82; 135.28; 140.84; 141.02; 147.04; 147.36; 153.02; 166.13. HR-MALDI-MS (DHB): 533.1333 ($[M+Na]^+$, $C_{30}H_{26}N_2NaO_2S_2^+$; calc. 533.1334).

4-{2-[(1,3-Benzothiazol-2-yl)sulfanyl]ethoxy}-5-[(naphthalen-1-yl)methoxy]-11-azatricyclo[6.2.1.0^{2,7}]undeca-2(7),3,5-triene ((±)-**2c**). *Procedure C* with (±)-**10c** (250 mg, 0.41 mmol), CH_2Cl_2 (1.2 ml), 2,6-lutidine (95 µl, 0.82 mmol), TBDMSOTf (141 µl, 0.61 mmol), THF (1.2 ml), MeOH (2.7 ml), and 1M K_2CO_3 (0.82 ml, 0.82 mmol): (±)-**2c** (114 mg, 55%). Pale-yellow oil. IR (neat): 3392*m*, 2962*s*, 2874*m*, 1593*w*, 1428*s*, 1278*s*, 1195*m*, 1088*s*. ^{1}H-NMR ($CDCl_3$, 300 MHz): 1.17–1.21 (*m*, 2 H); 1.83 (br. *s*, 1 H); 1.97–2.00 (*m*, 2 H); 3.69 (*t*, *J* = 6.7, 2 H); 4.38 (*t*, *J* = 6.7, 2 H); 4.44–4.48 (*m*, 2 H); 5.52 (*s*, 2 H); 6.94 (*s*, 1 H); 6.99 (*s*, 1 H); 7.26–7.32 (*m*, 1 H); 7.38–7.61 (*m*, 5 H); 7.72–7.75 (*m*, 1 H); 7.81–7.89 (*m*, 3 H); 8.17–8.20 (*m*, 1 H). ^{13}C-NMR ($CDCl_3$, 75.5 MHz): 26.70 (2×); 32.28; 61.08; 61.14; 68.44; 70.95; 108.26; 108.99; 121.07; 121.51; 123.97; 124.34; 125.38; 125.88; 126.11; 126.33; 126.45; 128.68; 128.82; 131.59; 132.90; 133.79; 135.44; 142.22; 142.29; 147.38 (2x); 153.24; 166.36. HR-MALDI-MS (DHB): 533.1319 ($[M+Na]^+$, $C_{30}H_{26}N_2NaO_2S_2^+$; calc. 533.1334).

tert-*Butyl 4-Methoxy-5-[2-(naphthalen-1-yl)ethoxy]-11-azatricyclo[6.2.1.0^{2,7}]undeca-2(7),3,5-triene-11-carboxylate* ((±)-**11**). To (±)-**8a** (100 mg, 0.23 mmol) and K_2CO_3 (480 mg, 3.48 mmol) in dry Me_2CO (2 ml), MeI (38 µl, 0.51 mmol) was added. The mixture was heated to 40° for 2.5 h. After cooling to r.t., the mixture was filtered, and the salts were washed with Me_2CO and $CHCl_3$. The filtrate was concentrated *in vacuo*, the residue was dissolved in $CHCl_3$, and the resulting soln. was washed with sat. aq. NaCl soln. (1×). Drying ($MgSO_4$) and evaporation *in vacuo* gave an oily crude product. CC (SiO_2; $CH_2Cl_2 \rightarrow CH_2Cl_2$/AcOEt 50:1) yielded pure (±)-**11** (91 mg, 89%). Colorless oil. IR ($CHCl_3$): 3007*s*, 2981*s*, 2876*m*, 1694*s*, 1597*m*, 1492*s*, 1267*s*, 1160*s*, 1090*s*. ^{1}H-NMR ($CDCl_3$, 300 MHz): 1.19–1.22 (*m*, 2 H); 1.39 (*s*, 9 H); 1.98–2.09 (*m*, 2 H); 3.63 (*t*, *J* = 7.7, 2 H); 3.85 (*s*, 3 H); 4.28–4.35 (*m*, 2 H); 4.99–5.04 (br. *m*, 2 H); 6.83 (*s*, 1 H); 6.88 (*s*, 1 H); 7.42–7.53 (*m*, 4 H); 7.75–7.78 (*m*, 1 H); 7.86–7.89 (*m*, 1 H); 8.10–8.12 (*m*, 1 H). ^{13}C-NMR ($CDCl_3$, 75.5 MHz): 26.99 (2×); 28.12; 32.88; 56.40; 61.18 (2×); 69.70; 79.91; 105.14; 106.69; 123.73; 125.65; 125.69; 126.17; 127.17; 127.42; 128.90; 132.22; 133.97; 134.10; 137.43; 138.12; 146.99; 148.33; 155.39. HR-MALDI-MS (DHB): 468.2145 ($[M+Na]^+$, $C_{28}H_{31}NNaO_4^+$; calc. 468.2151). Anal. calc. for $C_{28}H_{31}NO_4$ (445.56): C 75.48, H 7.01, N 3.14; found: C 75.59, H 6.91, N 3.05.

4-Methoxy-5-[2-(naphthalen-1-yl)ethoxy]-11-azatricyclo[6.2.1.0^{2,7}]undeca-2(7),3,5-triene ((±)-**12**). *Procedure C* with (±)-**11** (32 mg, 72 µmol), CH_2Cl_2 (0.20 ml), 2,6-lutidine (16 µl, 144 µmol), TBDMSOTf (24 µl, 108 µmol), THF (0.1 ml), MeOH (0.25 ml), and 1M K_2CO_3 (0.07 ml, 72 µmol): (±)-**12** (16 mg, 67%). Pale-yellow oil. IR (neat): 3400*m*, 2947*m*, 2868*w*, 1596*w*, 1492*m*, 1280*m*, 1090*s*. ^{1}H-NMR ($CDCl_3$, 300 MHz): 1.16–1.20 (*m*, 2 H); 1.98–2.01 (*m*, 2 H); 2.37 (br. *s*, 1 H); 3.63 (*t*, *J* = 7.8, 2 H); 3.85 (*s*, 3 H); 4.29–4.34 (*m*, 2 H); 4.44 (*d*, *J* = 3.6, 1 H); 4.50 (*d*, *J* = 3.6, 1 H); 6.80 (*s*, 1 H); 6.84 (*s*, 1 H); 7.39–7.55 (*m*, 4 H); 7.75–7.78 (*m*, 1 H); 7.85–7.89 (*m*, 1 H); 8.09–8.13 (*m*, 1 H). ^{13}C-NMR ($CDCl_3$, 75.5 MHz): 26.78 (2×); 32.99; 56.47; 61.15; 61.23; 69.69; 104.86; 106.40; 123.65; 125.55; 125.59; 126.05; 127.07; 127.30; 128.81; 132.11; 133.85; 134.01; 140.39; 140.84; 146.55; 147.88. HR-MALDI-MS (DHB): 368.1623 ($[M+Na]^+$, $C_{23}H_{23}NNaO_2^+$; calc. 368.1627).

tert-*Butyl 4-Hydroxy-5-methoxy-11-azatricyclo[6.2.1.0^{2,7}]undeca-2(7),3,5-triene-11-carboxylate* ((±)-**13**). To **7** (70 mg, 0.25 mmol) and K_2CO_3 (523 mg, 3.79 mmol) in dry Me_2CO (2 ml), MeI (19 µl, 0.20 mmol) was added, and the mixture was heated to 60° for 3 h. After cooling to r.t., the soln. was filtered, and the salts were washed with $CHCl_3$. After concentration of the filtrate *in vacuo*, the residue was dissolved in $CHCl_3$ and the resulting soln. was washed with sat. aq. NaCl soln. (1×). Drying ($MgSO_4$) and evaporation *in vacuo* gave a red oil. CC (SiO_2; hexane/AcOEt 3:1) yielded (±)-**13** (58 mg, 98%). Pale-yellow oil. IR ($CHCl_3$): 3539*m*, 3007*s*, 2980*s*, 2874*w*, 1693*s*, 1602*m*, 1490*s*, 1272*s*, 1160*s*, 1094*s*. ^{1}H-NMR ($CDCl_3$, 300 MHz): 1.22–1.24 (*m*, 2 H); 1.39 (*s*, 9 H); 2.04–2.07 (*m*, 2 H); 3.87 (*s*, 3 H); 5.03 (*s*, 2 H); 5.55 (*s*, 1 H); 6.83 (*s*, 1 H); 6.85 (*s*, 1 H). ^{13}C-NMR ($CDCl_3$, 75.5 MHz): 26.97 (2×); 28.14; 56.24; 61.10 (2×); 79.91; 103.70; 107.01; 136.75; 137.98; 144.29; 144.94; 155.44. HR-MALDI-MS (DHB): 314.1366 ($[M+Na]^+$, $C_{16}H_{21}NNaO_4^+$; calc. 314.1369). Anal. calc. for $C_{16}H_{21}NO_4$ (291.35): C 65.96, H 7.26, N 4.81; found: C 66.01, H 7.45, N 4.52.

tert-*Butyl 4-(2-Bromoethoxy)-5-methoxy-11-azatricyclo[6.2.1.0^{2,7}]undeca-2(7),3,5-triene-11-carboxylate* ((±)-**14**). *Procedure A* with (±)-**13** (50 mg, 0.17 mmol), 1,2-dibromoethane (0.7 ml, 8.52 mmol), and aq. solns. of Bu_4NOH (80 µl, 0.12 mmol) and KOH (0.12 ml, 0.86 mmol): crude (±)-**14** (68 mg, 100%) as a pale-yellow oil, which was used without further purification. ^{1}H-NMR ($CDCl_3$, 300 MHz): 1.23–1.25 (*m*, 2 H); 1.40 (*s*, 9 H); 2.06–2.09 (*m*, 2 H); 3.63 (*t*, *J* = 6.6, 2 H); 3.5 (*s*, 3 H); 4.27–4.32 (*m*, 2 H); 5.02 (br. *m*, 2 H); 6.88 (*s*, 1 H); 6.89 (*s*, 1 H).

tert-*Butyl 4-{2-[(1,3-Benzothiazol-2-yl)sulfanyl]ethoxy}-5-methoxy-11-azatricyclo[6.2.1.0^{2,7}]undeca-2(7),3,5-triene-11-carboxylate* ((±)-**15**). *Procedure B* with (±)-**14** (67 mg, 0.17 mmol), NaH (60% in oil, 14 mg, 0.34 mmol), and 2-sulfanyl-1,3-benzothiazole (57 mg, 0.34 mmol) in dry DMF (1.2 ml): (±)-**15** (59 mg,

71%). Yellow oil. IR ($CHCl_3$): 2954*m*, 2929*m*, 2872*w*, 1693*m*, 1595*w*, 1463*m*, 1428*s*, 1267*s*, 1160*m*, 1086*m*. ^{1}H-NMR ($CDCl_3$, 300 MHz): 1.23–1.25 (*m*, 2 H); 1.39 (*s*, 9 H); 2.06–2.09 (*m*, 2 H); 3.73 (*t*, *J* = 6.9, 2 H); 3.83 (*s*, 3 H); 4.41 (*t*, *J* = 6.9, 2 H); 5.05 (br. *s*, 2 H); 6.84 (*s*, 1 H); 6.98 (*s*, 1 H); 7.28–7.45 (*m*, 2 H); 7.74–7.78 (*m*, 1 H); 7.86–7.89 (*m*, 1 H). ^{13}C-NMR ($CDCl_3$, 75.5 MHz): 27.14 (2×); 28.30; 32.09; 56.52; 61.36 (2×); 68.33; 80.13; 105.37; 107.76; 121.29; 121.76; 124.59; 126.34; 135.69; 137.63; 138.73; 146.59; 148.73; 153.42; 155.54; 166.38. HR-MALDI-MS (DHB): 507.1386 ($[M+Na]^+$, $C_{25}H_{28}N_2NaO_4S_2^+$; calc. 507.1388).

4-{2-[(1,3-Benzothiazol-2-yl)sulfanyl]ethoxy}-5-methoxy-11-azatricyclo[6.2.1.0^{2,7}]undeca-2(7),3,5-triene ((±)-**16**). *Procedure C* with (±)-**15** (54 mg, 96 μmol), CH_2Cl_2 (0.3 ml), 2,6-lutidine (26 μl, 223 μmol), TBDMSOTf (39 μl, 167 μmol), THF (0.3 ml), MeOH (0.8 ml), and 1M K_2CO_3 (0.22 ml, 225 μmol): (±)-**16** (28 mg, 65%). Colorless oil. IR (neat): 3375*w*, 2945*m*, 2868*w*, 1592*w*, 1461*s*, 1428*s*, 1280*s*, 1090*s*. ^{1}H-NMR ($CDCl_3$, 300 MHz): 1.19–1.21 (*m*, 2 H); 1.58 (br. *s*, 1 H); 1.98–2.04 (*m*, 2 H); 3.75 (*t*, *J* = 7.0, 2 H); 3.84 (*s*, 3 H); 4.41 (*t*, *J* = 7.0, 2 H); 4.49 (br. *s*, 2 H); 6.84 (*s*, 1 H); 7.01 (*s*, 1 H); 7.27–7.34 (*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 ($CDCl_3$, 50.3 MHz): 26.39; 26.44; 31.96; 56.36; 61.03; 61.10; 68.07; 104.93; 107.20; 121.01; 121.43; 124.31; 126.04; 135.34; 139.11; 140.23; 146.25; 148.32; 153.04; 166.02. HR-MALDI-MS (DHB): 407.0854 ($[M+Na]^+$; $C_{20}H_{20}N_2NaO_2S_2^+$; calc. 407.0864).

tert-*Butyl 4,5-Dimethoxy-11-azatricyclo[6.2.1.0^{2,7}]undeca-2(7),3,5-triene-11-carboxylate* (**17**). To **7** (40 mg, 0.14 mmol) and K_2CO_3 (299 mg, 2.16 mmol) in dry Me_2CO (1 ml), MeI (40 μl, 0.43 mmol) was added and the mixture heated to 60° for 3 h. After cooling to r.t., the soln. was filtered, and the salts were washed with $CHCl_3$. The filtrate was concentrated *in vacuo*, the residue was dissolved in $CHCl_3$, and the resulting soln. was washed with sat. aq. NaCl soln. Drying ($MgSO_4$) and evaporation *in vacuo* afforded a dark-brown oil. CC (SiO_2; hexane/AcOEt 3:1) yielded **17** (29 mg, 66%). Pale-yellow oil. IR ($CHCl_3$): 2982*m*, 2874*w*, 2836*w*, 1694*s*, 1615*w*, 1466*s*, 1267*s*, 1160*s*, 1090*s*. ^{1}H-NMR ($CDCl_3$, 300 MHz): 1.21–1.24 (*m*, 2 H); 1.39 (*s*, 9 H); 2.05–2.08 (*m*, 2 H); 3.85 (*s*, 6 H); 5.04 (*s*, 2 H); 6.85 (*s*, 2 H). ^{13}C-NMR ($CDCl_3$, 75.5 MHz): 26.99 (2×); 28.09; 56.14 (2×); 61.19 (2×); 79.88; 104.43 (2×); 137.33 (2×); 147.74 (2×); 155.39. HR-MALDI-MS (DHB): 328.1519 ($[M+Na]^+$, $C_{17}H_{23}NNaO_4^+$; calc. 328.1525). Anal. calc. for $C_{17}H_{23}NO_4$ (305.37): C 66.86, H 7.59, N 4.59; found: C 66.77, H 7.65, N 4.42.

4,5-Dimethoxy-11-azatricyclo[6.2.1.0^{2,7}]undeca-2(7),3,5-triene (**18**). *Procedure C* with **17** (29 mg, 95 μmol), CH_2Cl_2 (0.20 ml), 2,6-lutidine (22 μl, 190 μmol), TBDMSOTf (33 μl, 142 μmol), THF (0.25 ml), MeOH (0.70 ml), and 1M K_2CO_3 (0.20 ml, 200 μmol): **18** (14 mg, 70%). Colorless oil. IR ($CHCl_3$): 3549*w*, 2933*m*, 2851*m*, 1602*s*, 1283*m*, 1091*s*. ^{1}H-NMR ($CDCl_3$, 300 MHz): 1.16–1.22 (*m*, 2 H); 1.75 (br. *s*, 1 H); 1.99–2.04 (*m*, 2 H); 3.86 (*s*, 6 H); 4.49–4.50 (*m*, 2 H); 6.83 (*s*, 2 H). ^{13}C-NMR ($CDCl_3$, 75.5 MHz): 26.77 (2×); 56.21 (2×); 61.26 (2×); 104.29 (2×); 140.60 (2×); 147.47 (2×). HR-MALDI-MS (DHB): 228.0994 ($[M+Na]^+$; $C_{12}H_{15}NNaO_2^+$; calc. 228.1001).

tert-*Butyl 4-{2-[(5-Chloro-1,3-benzothiazol-2-yl)sulfanyl]ethoxy}-5-[2-(naphthalen-1-yl)ethoxy]-11-azatricyclo[6.2.1.0^{2,7}]undeca-2(7),3,5-triene-11-carboxylate* ((±)-**20a**). *Procedure D* with 5-chloro-2-sulfanyl-1,3-benzothiazole (89 mg, 0.44 mmol), NaH (60% in oil, 18 mg, 0.44 mmol), and (±)-**9a** (60 mg, 0.11 mmol) in dry DMF (1.0 ml): (±)-**20a** (31 mg, 42%). Pale-yellow oil. IR ($CHCl_3$): 3008*m*, 2872*w*, 1696*s*, 1597*w*, 1458*m*, 1430*s*, 1267*s*, 1160*s*, 1089*m*. ^{1}H-NMR ($CDCl_3$, 300 MHz): 1.19–1.21 (*m*, 2 H); 1.38 (*s*, 9 H); 2.03–2.07 (*m*, 2 H); 3.58 (*t*, *J* = 7.2, 2 H); 3.66 (*t*, *J* = 6.6, 2 H); 4.28–4.35 (*m*, 4 H); 5.00–5.02 (*m*, 2 H); 6.85 (*s*, 1 H); 6.95 (*s*, 1 H); 7.25–7.28 (*m*, 1 H); 7.41–7.53 (*m*, 4 H); 7.62–7.65 (*m*, 1 H); 7.74–7.77 (*m*, 1 H); 7.83–7.88 (*m*, 2 H); 8.07–8.10 (*m*, 1 H). ^{13}C-NMR ($CDCl_3$, 50.3 MHz): 26.97 (2×); 28.11; 32.40; 32.87; 61.13 (2×); 68.49; 69.86; 79.98; 107.51; 108.84; 121.44; 121.67; 123.67; 124.68; 125.63 (2×); 126.11; 127.22; 127.38; 128.90; 132.18; 132.24; 133.67; 133.95; 134.27; 138.11; 139.06, 146.94; 148.01; 154.05; 155.35; 168.71. HR-MALDI-MS (DHB): 681.1622 ($[M+Na]^+$, $C_{36}H_{35}ClN_2NaO_4S_2^+$; calc. 681.1625).

tert-*Butyl 4-{2-[(5-Chloro-1,3-benzothiazol-2-yl)sulfanyl]ethoxy}-5-[(naphthalen-2-yl)methoxy]-11-azatricyclo[6.2.1.0^{2,7}]undeca-2(7),3,5-triene-11-carboxylate* ((±)-**20b**). *Procedure D* with 5-chloro-2-sulfanyl-1,3-benzothiazole (576 mg, 2.86 mmol), NaH (60% in oil, 115 mg, 2.86 mmol), and (±)-**9b** (299 mg, 0.72 mmol) in dry DMF (4.5 ml): (±)-**20b** (232 mg, 50%). Pale-yellow oil. IR ($CHCl_3$): 2983*m*, 1694*s*, 1597*w*, 1457*m*, 1431*s*, 1368*s*, 1160*s*, 1109*s*, 1087*m*. ^{1}H-NMR ($CDCl_3$, 300 MHz): 1.18–1.26 (*m*, 2 H); 1.36 (*s*, 9 H); 2.03–2.09 (*m*, 2 H); 3.77 (*t*, *J* = 6.3, 2 H); 4.43 (*t*, *J* = 6.3, 2 H); 4.99–5.06 (*m*, 2 H); 5.25 (*s*, 2 H); 6.94 (*s*, 1 H); 7.00 (*s*, 1 H); 7.22–7.28 (*m*, 1 H); 7.46–7.49 (*m*, 2 H); 7.53–7.56 (*m*, 1 H); 7.60–7.63 (*m*, 1 H); 7.80–7.88 (*m*, 5 H). ^{13}C-NMR ($CDCl_3$, 75.5 MHz): 26.81 (2×); 27.99; 32.26; 60.86 (2×); 67.87; 71.71; 79.76; 107.81; 107.93; 120.86; 121.18; 124.12; 124.86; 125.54; 125.70; 125.80; 127.23; 127.50; 127.76; 131.61; 132.53; 132.75; 133.07; 134.16; 137.89; 138.17; 146.67; 147.08; 153.32; 154.80; 167.99. HR-MALDI-MS (DHB): 667.1467 (100, $[M+Na]^+$, $C_{35}H_{33}ClN_2NaO_4S_2^+$; calc. 667.1468).

tert-*Butyl 4-[2-[(5-Chloro-1,3-benzothiazol-2-yl)sulfanyl]ethoxy]-5-[(naphthalen-1-yl)methoxy]-11-azatricyclo[6.2.1.0^{2,7}]undeca-2(7),3,5-triene-11-carboxylate* ((±)-**20c**). *Procedure D* with 5-chloro-2-sulfanyl-1,3-benzothiazole (77 mg, 0.38 mmol), NaH (60% in oil, 15 mg, 0.38 mmol), and (±)-**9c** (67 mg, 0.13 mmol) in dry DMF (1.3 ml): (±)-**20c** (54 mg, 65%). Pale-yellow oil. IR ($CHCl_3$): 3008*m*, 1694*s*, 1587*w*, 1458*s*, 1431*s*, 1368*s*, 1160*s*, 1109*s*. ^{1}H-NMR ($CDCl_3$, 300 MHz): 1.21–1.28 (*m*, 2 H); 1.38 (*s*, 9 H); 2.03–2.10 (*m*, 2 H); 3.67 (*t*, *J* = 6.3, 2 H); 4.36 (*t*, *J* = 6.3, 2 H); 5.00–5.05 (*m*, 2 H); 5.52 (*s*, 2 H); 6.97–7.01 (*m*, 2 H); 7.24–7.29 (*m*, 1 H); 7.40–7.59 (*m*, 4 H); 7.61–7.64 (*m*, 1 H); 7.81–7.89 (*m*, 3 H); 8.15–8.18 (*m*, 1 H). ^{13}C-NMR ($CDCl_3$, 75.5 MHz): 26.91 (2×); 28.17; 32.40; 61.10 (2×); 68.28; 70.82; 79.95; 108.39; 109.02; 121.28; 121.54; 123.81; 124.52; 125.23; 125.78; 126.23; 126.36; 126.56; 128.77; 131.43; 132.02; 132.54; 133.48; 133.63; 138.69 (2×); 147.57 (2×); 153.80; 155.18; 168.46. HR-MALDI-MS (DHB): 667.1473 ([*M* + Na]$^+$, $C_{35}H_{33}ClN_2NaO_4S_2^+$; calc. 667.1468).

4-[2-[(5-Chloro-1,3-benzothiazol-2-yl)sulfanyl]ethoxy]-5-[2-(naphthalen-1-yl)ethoxy]-11-azatricyclo[6.2.1.0^{2,7}]undeca-2(7),3,5-triene ((±)-**19a**). *Procedure C* with (±)-**20a** (60 mg, 0.09 mmol), CH_2Cl_2 (0.5 ml), 2,6-lutidine (21 µl, 0.18 mmol), TBDMSOTf (32 µl, 0.14 mmol), THF (0.3 ml), MeOH (0.7 ml), and 1M K_2CO_3 (0.18 ml, 0.18 mmol): (±)-**19a** (35 mg, 69%). Pale-yellow oil. IR ($CHCl_3$): 3422*w*, 3000*m*, 2951*m*, 2878*m*, 1600*m*, 1431*s*, 1272*m*, 1089*s*. ^{1}H-NMR ($CDCl_3$, 300 MHz): 1.20–1.24 (*m*, 2 H); 1.99 (br. *s*, 1 H); 2.04–2.10 (*m*, 2 H); 3.58 (*t*, *J* = 7.2, 2 H); 3.67 (*t*, *J* = 6.5, 2 H); 4.28–4.35 (*m*, 4 H); 4.55–4.58 (*m*, 2 H); 6.82 (*s*, 1 H); 6.93 (*s*, 1 H); 7.25–7.28 (*m*, 1 H); 7.39–7.55 (*m*, 4 H); 7.62–7.65 (*m*, 1 H); 7.72–7.77 (*m*, 1 H); 7.83–7.88 (*m*, 2 H); 8.09–8.12 (*m*, 1 H). ^{13}C-NMR ($CDCl_3$, 75.5 MHz): 26.79 (2×); 32.44; 32.91; 61.10; 61.16; 68.56; 69.92; 107.31; 108.71; 121.41; 121.67; 123.67; 124.68; 125.60 (2×); 126.08; 127.19; 127.35; 128.90; 132.17; 133.70; 133.95; 134.33; 141.54; 142.49; 146.55; 147.67; 154.05; 155.28; 168.78. HR-MALDI-MS (DHB): 581.1103 ([*M* + Na]$^+$, $C_{31}H_{27}ClN_2NaO_2S_2^+$; calc. 581.1100).

4-[2-[(5-Chloro-1,3-benzothiazol-2-yl)sulfanyl]ethoxy]-5-[(naphthalen-2-yl)methoxy]-11-azatricyclo[6.2.1.0^{2,7}]undeca-2(7),3,5-triene ((±)-**19b**). *Procedure C* with (±)-**20b** (230 mg, 0.36 mmol), CH_2Cl_2 (1.2 ml), 2,6-lutidine (83 µl, 0.71 mmol), TBDMSOTf (123 µl, 0.54 mmol), THF (1.0 ml), MeOH (2.5 ml), and 1M K_2CO_3 (0.71 ml, 0.71 mmol): (±)-**19b** (194 mg, 59%). Pale-yellow oil. IR ($CHCl_3$): 3194*w*, 2953*w*, 1459*m*, 1431*m*, 1323*m*, 1279*w*, 1087*m*. ^{1}H-NMR ($CDCl_3$, 300 MHz): 1.16–1.21 (*m*, 2 H); 1.68 (br. *s*, 1 H); 1.97–2.02 (*m*, 2 H); 3.77 (*t*, *J* = 6.5, 2 H); 4.43 (*t*, *J* = 6.5, 2 H); 4.43–4.49 (*m*, 2 H); 5.25 (*s*, 2 H); 6.91 (*s*, 1 H); 6.98 (*s*, 1 H); 7.24–7.28 (*m*, 1 H); 7.46–7.49 (*m*, 2 H); 7.54–7.57 (*m*, 1 H); 7.60–7.63 (*m*, 1 H); 7.81–7.89 (*m*, 5 H). ^{13}C-NMR ($CDCl_3$, 75.5 MHz): 26.77 (2×); 32.56; 61.02 (2×); 68.24; 71.99; 108.00; 108.02; 121.09; 121.38; 124.35; 125.03; 125.73; 125.88; 125.92; 127.49; 127.71; 127.99; 131.84; 132.75; 133.02; 133.30; 134.67; 141.45; 141.78; 146.59; 147.06; 153.57; 168.27. HR-MALDI-MS (DHB): 567.0938 (100, [*M* + Na]$^+$, $C_{30}H_{25}ClN_2NaO_2S_2^+$; calc. 567.0944).

4-[2-[(5-Chloro-1,3-benzothiazol-2-yl)sulfanyl]ethoxy]-5-[(naphthalen-1-yl)methoxy]-11-azatricyclo[6.2.1.0^{2,7}]undeca-2(7),3,5-triene ((±)-**19c**). *Procedure C* with (±)-**20c** (60 mg, 0.09 mmol), CH_2Cl_2 (0.2 ml), 2,6-lutidine (22 µl, 0.19 mmol), TBDMSOTf (32 µl, 0.14 mmol), THF (0.3 ml), MeOH (0.75 ml), and 1M K_2CO_3 (0.18 ml, 0.18 mmol): (±)-**19c** (32 mg, 63%). Pale-yellow oil. IR ($CHCl_3$): 3018*s*, 1430*m*, 1322*w*, 1089*w*, 1004*w*. ^{1}H-NMR ($CDCl_3$, 300 MHz): 1.16–1.21 (*m*, 2 H); 1.87 (*s*, 1 H); 1.98–2.02 (*m*, 2 H); 3.68 (*t*, *J* = 6.4, 2 H); 4.37 (*t*, *J* = 6.4, 2 H); 4.46–4.50 (br. *m*, 2 H); 5.52 (*s*, 2 H); 6.96 (*s*, 1 H); 6.97 (*s*, 1 H); 7.24–7.28 (*m*, 1 H); 7.41–7.59 (*m*, 4 H); 7.61–7.64 (*m*, 1 H); 7.81–7.89 (*m*, 3 H); 8.15–8.18 (*m*, 1 H). ^{13}C-NMR ($CDCl_3$, 75.5 MHz): 26.73 (2×); 32.49; 61.13 (2×); 68.41; 70.90; 108.31; 108.81; 121.35; 121.59; 123.87; 124.58; 125.29; 125.81; 126.27; 126.36; 128.61; 128.79; 131.47; 132.72 (2×); 133.55; 133.69; 141.93 (2×); 147.22; 147.38; 153.87; 168.54. HR-MALDI-MS (DHB): 567.0942 (100, [*M* + Na]$^+$, $C_{30}H_{25}ClN_2NaO_2S_2^+$; calc. 567.0944).

tert-*Butyl 4-[2-(Naphthalen-1-yl)ethoxy]-5-[2-[(5-phenyl-1,3,4-oxadiazol-2-yl)sulfanyl]ethoxy]-11-azatricyclo[6.2.1.0^{2,7}]undeca-2(7),3,5-triene-11-carboxylate* ((±)-**22**). To (±)-**9a** (73 mg, 169 µmol) in dry DMF (0.7 ml), a suspension of NaH (60% in oil, 20 mg, 507 µmol) and 5-phenyl-2-sulfanyl-1,3,4-oxadiazole (90 mg, 507 µmol) in dry DMF (0.5 ml), which has been stirred for 15 min, was added. The mixture was heated to 80° for 2 h. After addition of H_2O and AcOEt, the phases were separated. The org. phase was washed with sat. aq. NaCl soln. (1×) and H_2O (2×), dried ($MgSO_4$), and evaporated *in vacuo* to afford a turbid-orange oil. CC (SiO_2; hexane/AcOEt 5:1) gave (±)-**22** (28 mg, 26%). Yellow oil. IR (neat): 2953*m*, 1696*s*, 1472*s*, 1265*m*, 1159*s*, 1080*m*. ^{1}H-NMR ($CDCl_3$, 300 MHz): 1.18–1.21 (*m*, 2 H); 1.38 (*s*, 9 H); 2.01–2.05 (*m*, 2 H); 3.56–3.62 (*m*, 4 H); 4.26–4.35 (*m*, 4 H); 4.99–5.01 (*m*, 2 H); 6.84 (*s*, 1 H); 6.91 (*s*, 1 H); 7.40–7.55 (*m*, 7 H); 7.74–7.77 (*m*, 1 H); 7.85–7.87 (*m*, 1 H); 7.97–8.01 (*m*, 2 H); 8.08–8.11 (*m*, 1 H). ^{13}C-NMR ($CDCl_3$, 75.5 MHz): 26.91 (2×); 28.21; 31.97; 32.91; 60.98 (2×); 68.28; 69.75; 79.96; 107.27; 108.97; 123.61 (2×); 125.52; 125.55; 126.05; 126.65 (2×); 127.17; 127.30; 128.82; 129.02 (2×); 131.65; 132.07; 133.84; 134.16; 138.01 (2×); 146.57; 147.94; 155.18; 164.11; 165.89. HR-MALDI-MS (DHB): 658.2349 ([*M* + Na]$^+$, $C_{37}H_{37}N_3NaO_5S^+$; calc. 658.2352).

4-[2-(Naphthalen-1-yl)ethoxy]-5-[2-[(5-phenyl-1,3,4-oxadiazol-2-yl)sulfanyl]ethoxy]-11-azatricyclo[6.2.1.0^{2,7}]undeca-2(7),3,5-triene ((±)-**21**). To a well-stirred soln. of (±)-**22** (28 mg, 43 µmol) in CH_2Cl_2 (90 µl), 2,6-lutidine

(10 µl, 88 µmol) and TBDMSOTf (15 µl, 66 µmol) were added, the latter dropwise. The yellow mixture was stirred for 30 min and then quenched with sat. aq. NH_4Cl soln. After phase separation, the aq. phase was extracted with Et_2O (3×). The combined org. layers were washed with sat. aq. NaCl soln. (1×) and H_2O (1×), dried ($MgSO_4$), and evaporated *in vacuo* to yield the silyl carbamate intermediate. This crude product was dissolved in THF (80 µl), and Bu_4NF (1M in THF, 59 µl) was added. The mixture was stirred at r.t. for 1 h, then the reaction was quenched with sat. aq. NH_4Cl soln. After five extractions with $CHCl_3$, the combined org. layers were washed with sat. aq. NaCl soln. (1×), dried ($MgSO_4$), and evaporated *in vacuo*. CC (basic Al_2O_3, act. II; AcOEt/MeOH 6:1) furnished (±)-**21** (6 mg, 29%). Pale-yellow oil. IR ($CHCl_3$): 2976*m*, 1466*s*, 1370*m*, 1265*m*, 1192*w*, 1163*s*, 1104*m*. ^{1}H-NMR ($CDCl_3$, 300 MHz): 1.14–1.16 (*m*, 2 H); 1.95–1.97 (*m*, 2 H); 2.00 (br. *s*, 1 H); 3.55–3.62 (*m*, 4 H); 4.28–4.34 (*m*, 4 H); 4.41–4.45 (*m*, 2 H); 6.80 (*s*, 1 H); 6.88 (*s*, 1 H); 7.39–7.54 (*m*, 7 H); 7.73–7.76 (*m*, 1 H); 7.84–7.87 (*m*, 1 H); 7.97–8.00 (*m*, 2 H); 8.08–8.11 (*m*, 1 H). ^{13}C-NMR ($CDCl_3$, 75.5 MHz): 26.67; 26.73; 31.92; 32.89; 61.05; 61.14; 68.38; 69.83; 107.19; 108.97; 123.66; 123.71; 125.64 (2×); 126.12; 126.74 (2×); 127.24; 127.37; 128.92; 129.12 (2×); 131.75; 132.19; 133.97; 134.34; 141.54; 142.74; 146.36; 147.77; 164.32; 166.05. HR-MALDI-MS (DHB): 558.1827 ($[M+Na]^+$, $C_{32}H_{29}N_3NaO_3S^+$; calc. 558.1828).

tert-*Butyl 4-[2-(Naphthalen-1-yl)ethoxy]-5-{[(trifluoromethyl)sulfonyl]oxy}-11-azatricyclo[6.2.1.0^{2,7}]undeca-2(7),3,5-triene-11-carboxylate* ((±)-**24**). To (±)-**8a** (200 mg, 0.46 mmol) and pyridine (117 µl, 1.45 mmol) in CH_2Cl_2 (2 ml) at −78°, Tf_2O (0.13 ml, 0.75 mmol) was added, and the mixture was stirred at −78° for 2 h. H_2O was added, and the soln. was allowed to warm to r.t. The mixture was extracted with CH_2Cl_2 (3×), and the combined org. phases were washed with sat. aq. NaCl soln. (1×), dried ($MgSO_4$), and evaporated *in vacuo* to give an orange oil. CC (SiO_2, hexane/AcOEt 5:1) yielded (±)-**24** (261 mg, 100%). Colorless foam. IR ($CHCl_3$): 2983*m*, 2867*w*, 1697*s*, 1607*w*, 1472*m*, 1345*s*, 1277*s*, 1160*s*, 1068*s*. ^{1}H-NMR ($CDCl_3$, 300 MHz): 1.21–1.26 (*m*, 2 H); 1.38 (*s*, 9 H); 2.06–2.11 (*m*, 2 H); 3.64 (*t*, *J* = 11.0, 2 H); 4.31–4.40 (*m*, 2 H); 5.01–5.05 (*m*, 2 H); 6.90 (*s*, 1 H); 7.10 (*s*, 1 H); 7.39–7.59 (*m*, 4 H); 7.76–7.79 (*m*, 1 H); 7.86–7.91 (*m*, 1 H); 8.05–8.10 (*m*, 1 H). ^{13}C-NMR ($CDCl_3$, 75.5 MHz): 26.22; 26.75; 28.04; 32.55; 60.72; 61.13; 69.65; 80.45; 106.74; 114.20; 120.99; 123.42; 125.72 (2×); 126.35; 127.64 (2×); 129.02; 131.98; 133.35; 134.00; 137.11; 137.56; 146.04; 149.66; 155.16. HR-MALDI-MS (DHB): 586.1487 ($[M+Na]^+$, $C_{28}H_{28}F_3NNaO_6S^+$; calc. 586.1487). Anal. calc. for $C_{28}H_{28}F_3NO_6S$ (563.59): C 59.67, H 5.01, N 2.49; found: C 59.82, H 5.19, N 2.50.

tert-*Butyl 4-(3-Hydroxyprop-1-ynyl)-5-[2-(naphthalen-1-yl)ethoxy]-11-azatricyclo[6.2.1.0^{2,7}]undeca-2(7),3,5-triene-11-carboxylate* ((±)-**25**). To a well-degassed soln. of (±)-**24** (180 mg, 0.32 mmol) in piperidine (0.7 ml), $[Pd(PPh_3)_4]$ (10 mg, 0.01 mmol) and a well-degassed soln. of propargyl alcohol (95 µl, 1.59 mmol) in piperidine (0.5 ml) were added. The mixture was stirred to 80° for 36 h in a sealed tube. After cooling to r.t., sat. aq. NH_4Cl soln. was added, and the mixture was extracted with Et_2O (3×). The combined org. phases were dried ($MgSO_4$) and evaporated *in vacuo* to afford a brown crude product. CC (basic Al_2O_3, act. II; hexane/Me_2CO 3:1 → AcOEt) gave (±)-**25** (86 mg, 57%). Colorless, slightly turbid oil. IR ($CHCl_3$): 3478*w*, 2967*m*, 2867*w*, 2356*w*, 1694*s*, 1600*w*, 1461*m*, 1274*m*, 1160*s*. ^{1}H-NMR ($CDCl_3$, 300 MHz): 1.20–1.23 (*m*, 2 H); 1.38 (*s*, 9 H); 1.59 (br. *s*, 1 H); 2.05–2.08 (*m*, 2 H); 3.62 (*t*, *J* = 7.1, 2 H); 4.31–4.39 (*m*, 2 H); 4.48–4.50 (*m*, 2 H); 5.01 (br. *s*, 2 H); 6.80 (*s*, 1 H); 7.23 (*s*, 1 H); 7.41–7.57 (*m*, 4 H); 7.76–7.79 (*m*, 1 H); 7.86–7.90 (*m*, 1 H); 8.10–8.12 (*m*, 1 H). ^{13}C-NMR ($CDCl_3$, 75.5 MHz): 26.47; 27.05; 28.09: 32.65; 51.81; 60.56; 61.35; 69.17; 80.19; 82.44; 90.92; 105.06; 109.57; 123.63; 124.42; 125.60; 125.69; 126.19; 127.46; 127.50; 128.99; 132.16; 133.97; 134.08; 137.29; 147.37; 155.37; 159.03. HR-MALDI-MS (DHB): 492.2150 ($[M+Na]^+$, $C_{30}H_{31}NNaO_4^+$; calc. 492.2151). Anal. calc. for $C_{30}H_{31}NO_4$ (469.58): C 76.73, H 6.65, N 2.98; found: C 76.68, H 6.51, N 3.00.

tert-*Butyl 4-(3-Hydroxypropyl)-5-[2-(naphthalen-1-yl)ethoxy]-11-azatricyclo[6.2.1.0^{2,7}]undeca-2(7),3,5-triene-11-carboxylate* ((±)-**26**). To a well-degassed soln. of (±)-**25** (197 mg, 0.42 mmol) in MeOH (9 ml), Pd/C (10%, 99 mg) was added. The mixture was stirred at r.t. for 12 h under H_2 (1 bar). The black slurry was filtered through a pad of *Celite*, which was rinsed several times with MeOH. The combined filtrates were concentrated *in vacuo* to furnish (±)-**26** (200 mg, 100%) as a colorless oil, which was used without further purification. IR ($CHCl_3$): 3491*w*, 3007*m*, 2955*m*, 2876*m*, 1692*s*, 1475*m*, 1257*s*, 1161*s*, 1083*s*. ^{1}H-NMR ($CDCl_3$, 300 MHz): 1.23–1.26 (*m*, 2 H); 1.38 (*s*, 9 H); 1.50–1.76 (br. *m*, 3 H); 2.02–2.07 (*m*, 2 H); 2.51–2.58 (*m*, 2 H); 3.50 (*t*, *J* = 6.2, 2 H); 3.58 (*t*, *J* = 6.8, 2 H); 4.24–4.40 (*m*, 2 H); 5.01 (br. *s*, 2 H); 6.78 (*s*, 1 H); 6.98 (*s*, 1 H); 7.42–7.55 (*m*, 4 H); 7.75–7.79 (*m*, 1 H); 7.86–7.90 (*m*, 1 H); 8.08–8.12 (*m*, 1 H). ^{13}C-NMR ($CDCl_3$, 50.3 MHz): 26.11; 26.71; 27.16; 28.14: 32.81; 32.91; 60.75; 61.25; 62.02; 68.56; 79.86; 104.08; 121.29; 123.63; 125.57; 125.67; 126.14; 127.25; 127.41; 127.79; 128.94; 132.14; 133.98; 134.33; 137.35; 144.11; 155.29; 155.35. HR-MALDI-MS (DHB): 496.2455 ($[M+Na]^+$, $C_{30}H_{35}NNaO_4^+$; calc. 496.2464).

tert-*Butyl 4-(3-{(4-Methylphenyl)sulfonyl]oxy}propyl)-5-{2-[(naphthalen-1-yl)ethoxy]}-11-azatricyclo[6.2.1.0^{2,7}]undeca-2(7),3,5-triene-11-carboxylate* ((±)-**27**). To (±)-**26** (200 mg, 0.42 mmol) and pyridine (0.28 ml, 3.44 mmol) in CH_2Cl_2 (0.85 ml) at 0°, TsCl (245 mg, 1.27 mmol) was added, and the mixture was stirred

for 90 min. 1N HCl was added, and the soln. was extracted with CH_2Cl_2 (3×). The combined org. phases were dried ($MgSO_4$) and evaporated *in vacuo* to produce a beige oil. CC (basic Al_2O_3, act. II; hexane/acetone 5:1 → 1:1) furnished (±)-**27** (136 mg, 51%). Colorless oil. IR ($CHCl_3$): 3025*m*, 2956*m*, 2874*w*, 1692*s*, 1624*w*, 1598*w*, 1474*w*, 1367*s*, 1258*m*, 1176*s*, 1110*m*. ^{1}H-NMR ($CDCl_3$, 300 MHz): 1.17–1.19 (*m*, 2 H); 1.40 (*s*, 9 H); 1.69–1.76 (*m*, 2 H); 2.02–2.05 (*m*, 2 H); 2.44–2.52 (*m*, 5 H); 3.53 (*t*, *J* = 6.9, 2 H); 3.90 (*t*, *J* = 6.2, 2 H); 4.22–4.31 (*m*, 2 H); 4.96–4.99 (*m*, 2 H); 6.74 (*s*, 1 H); 6.78 (*s*, 1 H); 7.32–7.55 (*m*, 6 H); 7.72–7.80 (*m*, 3 H); 7.83–7.88 (*m*, 1 H); 8.06–8.11 (*m*, 1 H). ^{13}C-NMR ($CDCl_3$, 75.5 MHz): 21.72; 26.57; 27.01; 27.03; 28.30; 28.88; 32.87; 61.21; 62.44; 68.24; 70.14; 79.87; 103.67; 121.14; 123.44; 125.36; 125.46; 125.90; 126.24; 127.06; 127.18; 127.77 (2×); 128.74; 129.68 (2×); 131.89; 133.14; 133.70; 134.25; 136.66; 144.11; 144.45; 154.91; 155.07. HR-MALDI-MS (DHB): 650.2549 ($[M+Na]^+$, $C_{37}H_{41}NNaO_6S^+$; calc. 650.2552).

tert-*Butyl 4-{3-[(1,3-Benzothiazol-2-yl)sulfanyl]propyl}-5-[2-(naphthalen-1-yl)ethoxy]-11-azatricyclo[6.2.1.0^{2,7}]undeca-2(7),3,5-triene-11-carboxylate* ((±)-**28a**). To (±)-**27** (136 mg, 0.22 mmol) in dry DMF (0.5 ml), a suspension of NaH (60% in oil, 15 mg, 0.37 mmol) and 2-sulfanyl-1,3-benzothiazole (62 mg, 0.37 mmol) in dry DMF (1.3 ml), which had been stirred for 15 min, was added. The mixture was stirred at r.t. overnight, and H_2O and AcOEt were added. After phase separation, the aq. phase was extracted with AcOEt (3×). The combined org. phases were washed with sat. aq. NaCl soln. (1×) and H_2O (1×), dried ($MgSO_4$), and evaporated *in vacuo* to afford a brown oil. CC (SiO_2; hexane/AcOEt 5:1) yielded (±)-**28a** (100 mg, 72%). Yellow oil. IR ($CHCl_3$): 3023*s*, 1692*m*, 1463*m*, 1427*m*, 1414*m*, 1368*m*, 1319*m*, 1256*m*, 1219*s*, 1160*m*, 1080*w*. ^{1}H-NMR ($CDCl_3$, 300 MHz): 1.20–1.22 (*m*, 2 H); 1.38 (*s*, 9 H); 1.91–1.97 (*m*, 2 H); 2.03–2.06 (*m*, 2 H); 2.61–2.73 (*m*, 2 H); 3.21 (*t*, *J* = 7.4, 2 H); 3.56 (*t*, *J* = 6.9, 2 H); 4.22–4.32 (*m*, 2 H); 5.02 (br. *s*, 2 H); 6.77 (*s*, 1 H); 6.99 (*s*, 1 H); 7.25–7.52 (*m*, 6 H); 7.72–7.75 (*m*, 2 H); 7.85–7.88 (*m*, 2 H); 8.08–8.10 (*m*, 1 H). ^{13}C-NMR ($CDCl_3$, 75.5 MHz): 26.88 (2×); 28.21; 29.39; 29.53; 32.88; 33.19; 61.26 (2×); 68.39; 79.85; 103.81; 120.88; 121.21; 121.44; 123.56; 125.49; 125.55; 125.97; 126.02; 126.96; 127.19; 127.30; 128.85; 132.06; 133.85; 134.42; 135.13; 136.91; 144.19; 153.38; 153.75; 155.16; 155.32; 167.41. HR-MALDI-MS (DHB): 645.2217 ($[M+Na]^+$, $C_{37}H_{38}N_2NaO_3S_2^+$; calc. 645.2222).

tert-*Butyl 4-{3-[(5-Chloro-1,3-benzothiazol-2-yl)sulfanyl]propyl}-5-[2-(naphthalen-1-yl)ethoxy]-11-azatricyclo[6.2.1.0^{2,7}]undeca-2(7),3,5-triene-11-carboxylate* ((±)-**28b**). To 5-chloro-2-sulfanyl-1,3-benzothiazole (113 mg, 0.56 mmol) in dry DMF (2 ml), NaH (60% in oil, 23 mg, 0.56 mmol) was added, and the suspension was stirred for 15 min. Half of the suspension was added to (±)-**27** (208 mg, 0.33 mmol) in dry DMF (0.75 ml) Afer stirring at r.t. for 5 h, the other half of the suspension was added. The mixture was stirred overnight, then H_2O and AcOEt were added. After phase separation, the aq. phase was extracted with AcOEt (3×). The combined org. phases were washed with sat. aq. NaCl soln. (1×) and H_2O (1×), dried ($MgSO_4$), and evaporated *in vacuo* to afford a brown oil. CC (SiO_2; hexane/AcOEt 5:1) furnished (±)-**28b** (115 mg, 52%). Yellow oil. IR ($CHCl_3$): 3014*s*, 1692*w*, 1508*w*, 1428*w*, 1366*w*, 1228*s*, 1155*w*, 1073*w*. ^{1}H-NMR ($CDCl_3$, 300 MHz): 1.18–1.23 (*m*, 2 H); 1.39 (*s*, 9 H); 1.88–1.98 (*m*, 2 H); 2.06 (*m*, 2 H); 2.60–2.72 (*m*, 2 H); 3.17 (*t*, *J* = 7.2, 2 H); 3.56 (*t*, *J* = 6.8, 2 H); 4.23–4.32 (*m*, 2 H); 5.03 (br. *s*, 2 H); 6.77 (*s*, 1 H); 6.98 (*s*, 1 H); 7.20–7.26 (*m*, 1 H); 7.41–7.54 (*m*, 4 H); 7.60–7.63 (*m*, 1 H); 7.73–7.77 (*m*, 1 H); 7.82–7.87 (*m*, 2 H); 8.06–8.10 (*m*, 1 H). ^{13}C-NMR ($CDCl_3$, 50.3 MHz): 26.78; 27.23; 28.18; 29.32; 29.48; 32.84; 33.16; 60.72; 61.32; 68.46; 79.89; 104.02; 121.32; 121.44; 121.57; 123.67; 124.49; 125.57; 125.63; 126.11; 127.03; 127.22; 127.41; 128.97; 132.17 (2×); 133.51; 134.01; 134.52; 137.16; 144.43; 154.36; 155.32; 155.51; 164.65. HR-MALDI-MS (DHB): 679.1826 ($[M+Na]^+$, $C_{37}H_{37}ClN_2NaO_3S_2^+$; calc. 679.1832).

4-{3-[(1,3-benzothiazol-2-yl)sulfanyl]propyl}-5-[2-(naphthalen-1-yl)ethoxy]-11-azatricyclo[6.2.1.0^{2,7}]undeca-2(7),3,5-triene ((±)-**23a**). *Procedure C* with (±)-**28a** (57 mg, 0.09 mmol), CH_2Cl_2 (0.5 ml), 2,6-lutidine (21 µl, 0.18 mmol), TBDMSOTf (32 µl, 0.14 mmol), THF (0.3 ml), MeOH (0.7 ml), and 1M K_2CO_3 (0.19 ml, 0.19 mmol): (±)-**23a** (33 mg, 67%). Pale-yellow oil. IR ($CHCl_3$): 2986*m*, 1458*m*, 1426*m*, 1306*w*, 1254*m*, 1224*s*, 1212*m*, 1082*m*, 1024*w*. ^{1}H-NMR ($CDCl_3$, 300 MHz): 1.17–1.21 (*m*, 2 H); 1.91–2.02 (*m*, 4 H); 2.50 (br. *s*, 1 H); 2.50–2.73 (*m*, 2 H); 3.23 (*t*, *J* = 7.4, 2 H); 3.57 (*t*, *J* = 6.8, 2 H); 4.27–4.32 (*m*, 2 H); 4.47 (br. *s*, 2 H); 6.74 (*s*, 1 H); 6.96 (*s*, 1 H); 7.25–7.30 (*m*, 1 H); 7.37–7.55 (*m*, 5 H); 7.72–7.77 (*m*, 2 H); 7.84–7.87 (*m*, 2 H); 8.08–8.11 (*m*, 1 H). ^{13}C-NMR ($CDCl_3$, 75.5 MHz): 26.60; 26.95; 29.54; 29.69; 30.02; 33.34; 60.63; 61.36; 68.43; 103.66; 120.81; 120.96; 121.34; 123.50; 123.98; 125.40; 125.45; 125.90 (2×); 126.52; 127.10; 127.20; 128.76; 131.96; 133.74; 134.33; 135.02; 139.77; 147.19; 153.23; 155.01; 167.26. HR-MALDI-MS (DHB): 545.1697 ($[M+Na]^+$, $C_{32}H_{30}N_2NaOS_2^+$; calc. 545.1697).

4-{3-[(5-Chloro-1,3-benzothiazol-2-yl)sulfanyl]propyl}-5-[2-(naphthalen-1-yl)ethoxy]-11-azatricyclo[6.2.1.0^{2,7}]undeca-2(7),3,5-triene ((±)-**23b**). *Procedure C* with (±)-**28b** (60 mg, 0.09 mmol), CH_2Cl_2 (0.5 ml), 2,6-lutidine (22 µl, 0.18 mmol), TBDMSOTf (32 µl, 0.14 mmol), THF (0.3 ml), MeOH (0.7 ml), and 1M K_2CO_3 (0.18 ml, 0.18 mmol): (±)-**23b** (38 mg, 75%). Pale-yellow oil. IR ($CHCl_3$): 3023*s*, 1428*m*, 1296*w*, 1255*w*, 1219*s*, 1188*w*,

1146*w*, 1072*w*, 1001*w*. ^{1}H-NMR ($CDCl_3$, 300 MHz): 1.18–1.20 (*m*, 2 H); 1.91–2.04 (*m*, 4 H); 2.60–2.70 (*m*, 2 H); 3.21 (*t*, *J* = 7.2, 2 H); 3.56 (*t*, *J* = 6.8, 2 H); 4.26–4.31 (*m*, 2 H); 4.50 (br. *s*, 2 H); 6.75 (*s*, 1 H); 6.96 (*s*, 1 H); 7.22–7.26 (*m*, 1 H); 7.41–7.52 (*m*, 4 H); 7.60–7.63 (*m*, 1 H); 7.73–7.77 (*m*, 1 H); 7.82–7.87 (*m*, 2 H); 8.06–8.09 (*m*, 1 H). ^{13}C-NMR ($CDCl_3$, 75.5 MHz): 26.43; 26.78; 29.46; 29.70; 32.98; 33.32; 60.59; 61.31; 68.41; 103.73; 121.07; 121.20; 121.39; 123.45; 124.29; 125.38; 125.46; 125.92; 126.71; 127.06; 127.22; 128.77; 131.93 (2×); 133.24; 133.74; 134.26; 139.10; 141.84; 154.02; 155.16; 169.48. HR-MALDI-MS (DHB): 579.1308 ($[M+Na]^+$, $C_{32}H_{29}ClN_2NaOS_2^+$; calc. 579.1307).

REFERENCES

[1] D. A. Carcache, S. R. Hörtner, P. Seiler, F. Diederich, A. Dorn, H. P. Märki, C. Binkert, D. Bur, *Helv. Chim. Acta* **2003**, *86*, 2173.

[2] 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.

[3] 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. Märki, S. Mathews, M. Müller, R. G. Ridley, H. Stadler, E. Vieira, M. Wilhelm, F. K. Winkler, W. Wostl, *Chem. Biol.* **1999**, *6*, 127.

[4] P. R. Gerber, K. Müller, *J. Comput.-Aided Mol. Design* **1995**, *9*, 251.

[5] D. A. Carcache, S. R. Hörtner, A. Bertogg, C. Binkert, D. Bur, H. P. Märki, A. Dorn, F. Diederich, *ChemBioChem* **2002**, *3*, 1137.

[6] M. Hu, N. Brasseur, S. Z. Yildiz, J. E. van Lier, C. C. Leznoff, *J. Med. Chem.* **1998**, *41*, 1789.

[7] L. Grehn, U. Ragnarsson, *Angew. Chem.* **1984**, *96*, 291; *Angew. Chem., Int. Ed.* **1984**, *23*, 296.

[8] R. W. Young, K. H. Wood, *J. Am. Chem. Soc.* **1955**, *77*, 400.

[9] F. H. Allen, O. Kennard, *Chemical Design Automation News* **1993**, *8*, 31.

[10] F. Mohamadi, N. G. J. Richards, W. C. Guida, R. Liskamp, M. Lipton, C. Caufield, G. Chang, T. Hendrickson, W. C. Still, *J. Comput. Chem.* **1990**, *11*, 440.

[11] K. Sonogashira, in 'Metal-catalyzed Cross-coupling Reactions', Eds. F. Diederich, P. J. Stang, Wiley-VCH, Weinheim, 1998, p. 203–230.

Received February 5, 2003