A New Class of Inhibitors for the Metalloprotease Neprilysin Based on a Central Imidazole Scaffold

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Neprilysin (NEP; neutral endopeptidase EC 3.4.24.11) is a Zn^{II}-dependent, membrane-bound endopeptidase. NEP is widely distributed in the organs, particularly in the kidneys and lungs, and it is involved in the metabolism of a number of smaller regulatory peptides. Inhibition of NEP has been proposed as a potential target for analgesic and antihypertensive therapies. In this study, new nonpeptidic inhibitors of neprilysin ((±)-**1**, (±)-**43**, (±)-**45**, and (±)-**46**; *Table*) were designed, based on the X-ray crystal structure of NEP complexed to phosphoramidon (*Fig. 1*). They feature an imidazole ring as the central scaffold, acting as a peptide bond isoster to undergo H-bonding with the side chains of Asn542 and Arg717 (*Fig. 2*). The scaffold is decorated with a thiol group to ligate to the Zn^{II} ion and two aromatic residues to bind into the hydrophobic S1′ and S2′ pockets. The synthesis of the new inhibitors was approached by two routes (*Schemes 1–4* and *5–8*), with the second one involving a double directed *ortho*-metallation of the imidazole platform and a *Stille* cross-coupling, providing the desired target molecules as hydrochloride salts. In a fluorescence assay, inhibitors (±)-**1**, (±)-**43**, (±)-**45**, and (±)-**46** all exhibit IC_{50} values in the single-digit micromolar activity range (2–4 μM, *Table*), which validates the binding mode postulated by modeling. Useful guidelines for a next lead optimization cycle were obtained in several control runs.

1. Introduction. – Neprilysin (EC 3.4.24.11) is a mammalian, Zn^{II}-dependent, membrane-bound endopeptidase (type-II integral membrane protein), related to other mammalian metalloproteases such as the endothelin-converting enzymes (ECE-1 and ECE-2), KELL, and PEX [1][2]. It is involved in the metabolism of a number of regulatory peptides of the nervous, cardiovascular, inflammatory, and immune systems.

The enzyme was extracted for the first time in 1974 from rabbit kidney brush border [3]. It is found in various tissues, but most abundantly in the kidney [4]. Besides the wide distribution, it also has broad substrate specificity. The first substrates discovered were the pentapeptidic endorphins Leu- and Met-enkephalin and substance P [5][6]. Among numerous other substrates [4][7], the cardiovascular peptide ANP (atrial natriuretic peptide) is the most familiar [8]. Furthermore, NEP plays an important role in various cancers. The downregulation of NEP in the lung by cigarette smoke may be causally related to the development of small-cell carcinomas [9][10]. Recently, it has been reported that NEP degrades both amyloid β-peptides 1-40 and 1-42, which play a pivotal role in *Alzheimer*'s disease [11][12].

Since NEP cleaves ANP and enkephalins, it is a potential drug target. ANP reduces blood pressure by sodium excretion in the kidneys [8]. Selective NEP inhibitors are,

therefore, possible anti-hypertensive agents, either alone or in combination with selective ACE (angiotensin-converting enzyme) inhibitors or as dual NEP/ACE inhibitors, so called vasopeptidase inhibitors [13–16]. Enkephalins act as endogenous painkillers in the central nervous system by binding to μ- and δ-opiate receptors [17]. Blocking NEP by a selective inhibitor leads to enhanced enkephalin concentrations *in vitro* and to antinociceptic activity in mice [18]. This suggests that selective inhibitors of neprilysin can act as new analgesic therapeutics [4].

When the structure of the extracellular domain (residues 52–749) of human NEP complexed with the metalloprotease inhibitor phosphoramidon was solved by X-ray crystallography at 2.1-Å resolution (PDB: 1DMT) [19] (for some current structures, see [20]), we became interested in the development of novel nonpeptidic inhibitors of neprilysin by X-ray structure-based *de novo* design. This strategy has been successfully pursued in a variety of medicinal-chemistry projects in the *Diederich* group [21–23]. In addition to the therapeutic and basic pharmacological interest of the target, we were motivated to contribute to an enhanced understanding of the structural and molecular-recognition requirements for selective metalloprotease inhibition. As the intriguing ultimate target of this research program, we envision blocking NEP selectively and with high affinity without binding to the Zn^{II} ion.

Here, we report the synthesis and *in vitro* evaluation of the first generation of nonpeptidic neprilysin inhibitors based on a central imidazole scaffold. This scaffold is elegantly decorated using double directed-*ortho*-metallation strategies [24]. The first-generation ligands, which still contain a Zn^{II}-binding thiol ligand, show IC_{50} values in the low micromolar activity range (for a preliminary communication of parts of this work, see [25]; IC_{50}: concentration of inhibitor at which 50% V_{max} is observed). Their proposed binding mode is fully validated by the X-ray crystal-structure data reported in the following paper in this issue [26].

2. Results and Discussion. – 2.1. *Design of the Lead Structure.* The basis for the design of new inhibitors was the crystal structure of neprilysin complexed with phosphoramidon [19] (*Fig. 1*). We used the molecular modeling package MOLOC [27] to analyze the active site and to design our lead structure **1** featuring a 2,5-disubstituted 1*H*-imidazole as central scaffold (*Fig. 2*). Important features included in the design of **1** are: *i*) The central 1*H*-imidazole platform of the active, (1′*S*,1″*R*)-configured enantiomer should act as a peptide-bond isoster and anchor at the active site by forming H-bonds to Asn542 and Arg717. Both residues had been shown in site-directed mutagenesis studies to be important for substrate and ligand binding [28][29]. *ii*) An ethylsulfanyl residue departs from C(2) of the 1*H*-imidazole platform to coordinate to the Zn^{II} ion, ligated to the side chains of Glu646, His583, and His587 of the protein. *iii*) The two hydrophobic pockets S1′ and S2′ at the active site should be filled in an energetically beneficial way [30][31] by Ph rings attached by short linkers to the central scaffold. The S1′ pocket, defined by Phe106, Ile558, Phe563, Met579, Val580, Val692, and Trp693, is deep and can accommodate substituents as large as biphenyls [20][32]. The S2′ pocket, defined by the residues Arg102, Phe106, Arg110, Val541, and Trp693, is shallower and less specific than the S1′ pocket [33]. *iv*) We also hoped to gain additional affinity by engaging the NH_2 moiety of Asn542 in a H-bond with a MeO substituent at the (*R*)-configured C(1″) in **1**.

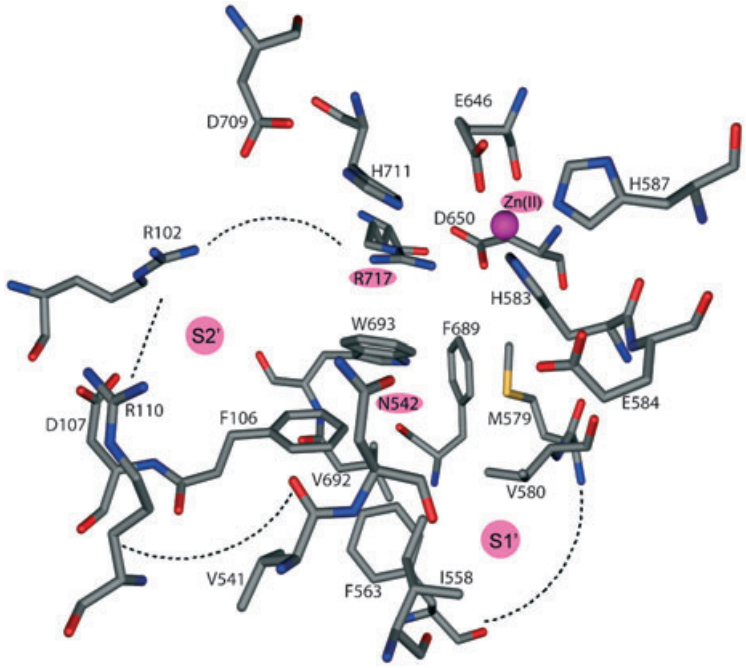


Fig. 1. *Analysis of the active site as revealed in the crystal structure of NEP complexed with phosphoramidon* [19]. Active site residues and catalytically active Zn^{II} ion are shown whereas phosphoramidon is removed. Important aspects for the design of the lead structure are highlighted in pink. Color code: grey: C-atom skeleton, red: O-atoms, blue: N-atoms, yellow: S-atoms, red sphere: Zn^{II} ion.

2.2. *Synthetic Approach towards Lead Structure (±)-***1** via *C_1-Homologation*. This synthetic route started from *N*-protected 1*H*-imidazole **2** obtained by protection of 1*H*-imidazole with the *N*,*N*-dimethylsulfamoyl group, which is *ortho*-directing and can be easily introduced and removed [34] (*Scheme 1*). Metallation of **2** with BuLi occurred selectively at C(2), and the following conversion with DMF afforded the 2-formylated 1*H*-imidazole **3** in high yield [35][36]. Benzyl-*Grignard* reagent, formed *in situ* from BnBr and Mg, was reacted with aldehyde **3** to give the racemic secondary alcohol (±)-**4**, which was protected as silyl ether (±)-**5** using (*t*-Bu)Me_2SiCl.

After selective *ortho*-metallation with *s*-BuLi at C(5) of (±)-**5**, reaction with DMF led to 5-formylated 1*H*-imidazole (±)-**6** (*Scheme 1*). Treatment of aldehyde (±)-**6** with a phenyl-*Grignard* reagent afforded a mixture of the diastereoisomeric pairs of enantiomers (±)-**7** and (±)-**8** in low yield only. An alternative and easier access to (±)-**7** and (±)-**8** was provided by treatment of (±)-**5** with *s*-BuLi and PhCHO. Separation of the diastereoisomers was possible by column chromatography: (±)-**7** and (±)-**8** were isolated in 37 and 28% yield, respectively, showing a slight diastereoselectivity (diastereoisomeric ratio dr 1.3 : 1) for the nucleophilic addition to PhCHO.

Methylation of the secondary OH groups of (±)-**7** and (±)-**8** to the methyl ethers (±)-**9** and (±)-**10**, respectively, was accomplished using NaH and MeI (*Scheme 2*). Deprotection of the (*t*-Bu)Me_2Si-protected OH groups of (±)-**7**, (±)-**8**, (±)-**9**, and (±)-

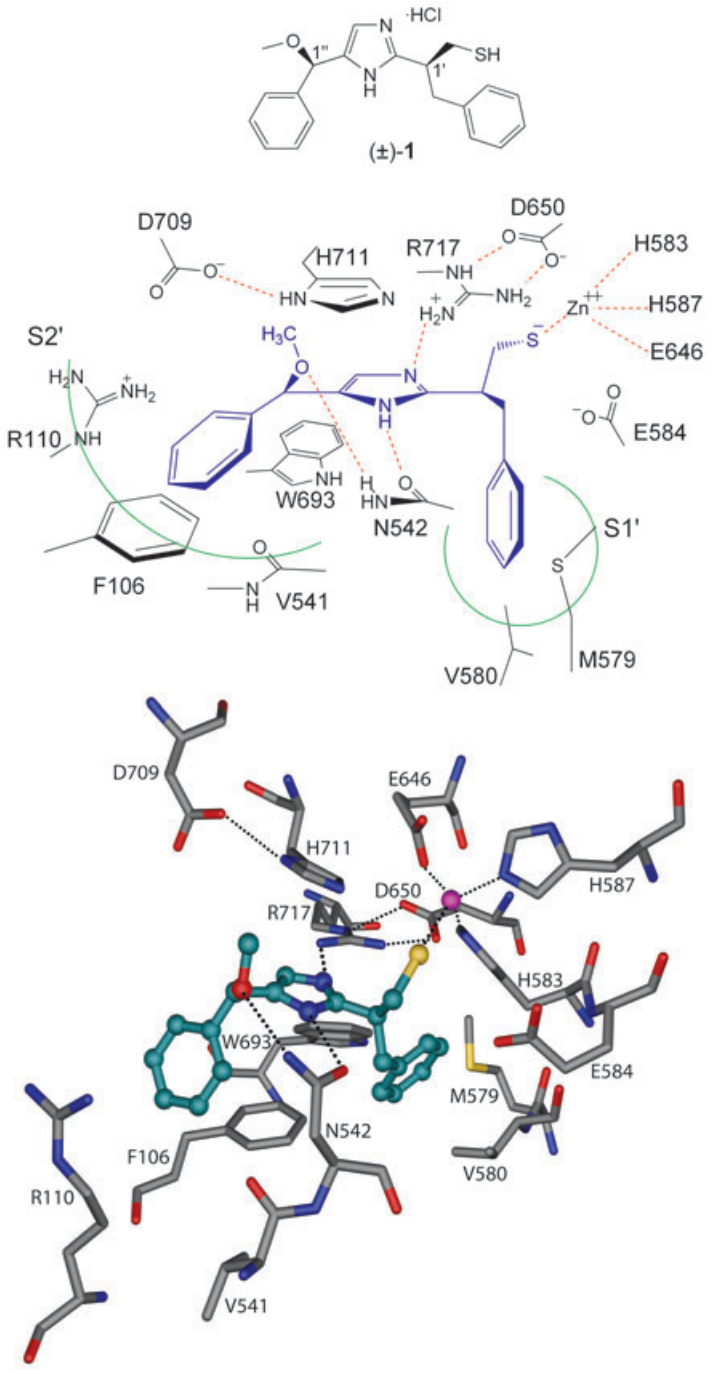
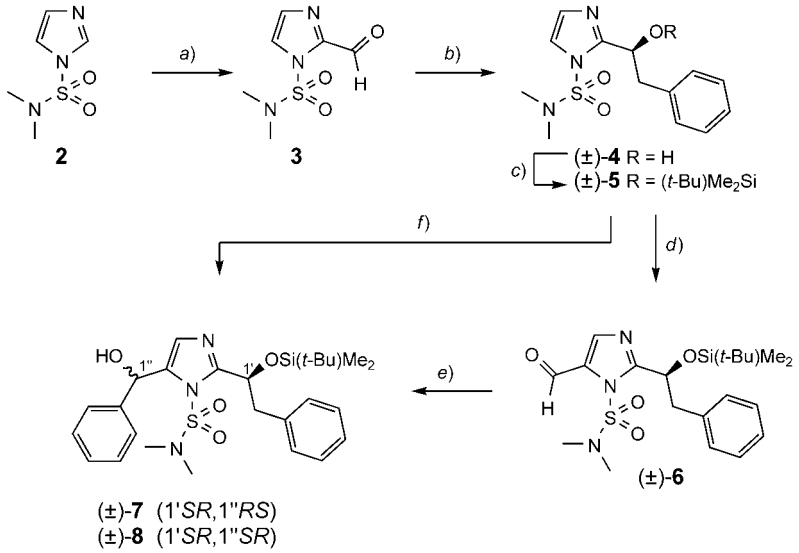


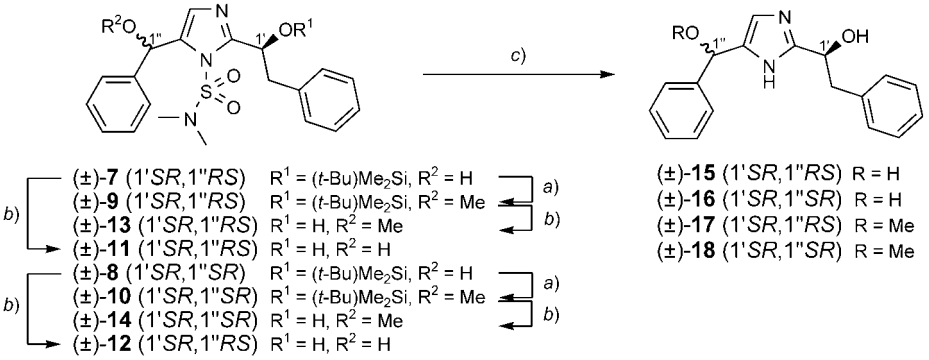
Fig. 2. *Lead structure* (±)-**1** (top) *and the proposed interactions of the active, (1'*S*,1''*R)*-configured enantiomer with the active-site residues of NEP in a schematic view* (middle), *and a molecular model* (bottom). H-Bonds and coordinative bonds to the Zn^{II} ion are shown as red and black dashed lines, respectively. Color code: see caption to *Fig. 1*; green: C-atom skeleton of the inhibitor.

Scheme 1. *Synthesis of Diastereoisomers* (±)-**7** *and* (±)-**8**



a) BuLi, DMF, THF, −78° → r.t.; 81%. *b*) Mg, BnBr, Et_2O, THF, r.t.; 57%. *c*) (*t*-Bu)Me_2SiCl, DMAP, CH_2Cl_2, 16 h, r.t.; 82%. *d*) *s*-BuLi, DMF, THF, −78°; 67%. *e*) PhMgBr, Et_2O, THF, 0° → r.t.; 11% (±)-**7**; 7% (±)-**8**. *f*) *s*-BuLi, PhCHO, THF, −78°; 28% (±)-**7**; 37% (±)-**8**. DMAP = 4-(dimethylamino)pyridine.

Scheme 2. *Synthesis of 2,5-Disubstituted Imidazoles* (±)-**15**–(±)-**18**



a) NaH, MeI, THF, 0° → r.t., 2 h; 82% (±)-**9**; 90% (±)-**10**. *b*) Bu_4NF, THF, r.t., 2.5 h; 76–86%. *c*) 4% HCl in EtOH, r.t., 3 h; 40–78%.

10 with Bu_4NF gave the corresponding secondary alcohols (±)-**11**, (±)-**12**, (±)-**13**, and (±)-**14**, respectively, in good yields. Crystals suitable for X-ray analysis of compound (±)-**14** were obtained by recrystallization from Et_2O (*Fig. 3*). This crystal structure led to the configurational assignment of the above-mentioned diastereoisomers.

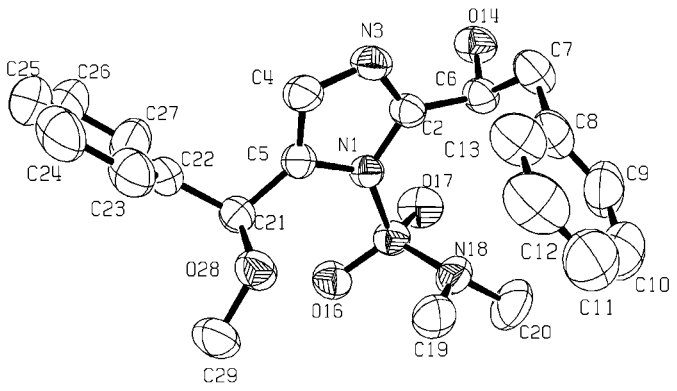


Fig. 3. *Crystal structure of (±)-***14**. The ORTEP representation is shown with atomic-displacement-parameter ellipsoids at 50% probability level. Arbitrary numbering.

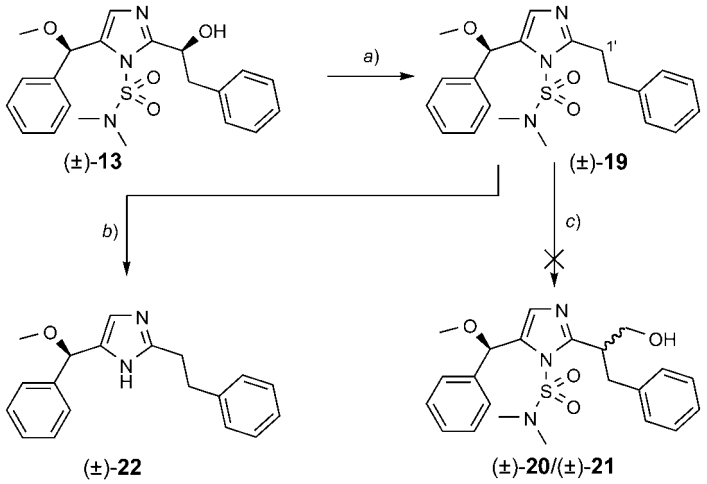
Removal of the sulfamoyl protecting group in (±)-**11**, (±)-**12**, (±)-**13**, and (±)-**14** in ethanolic HCl gave the corresponding 2,5-disubstituted 1*H*-imidazoles (±)-**15**, (±)-**16**, (±)-**17**, and (±)-**18**, respectively (*Scheme 2*).

We envisaged two possibilities for a C_1-homologation at C(1′): *i*) generation of a nucleophile at this position and attack at a C_1-electrophile, or *ii*) generation of an electrophile at C(1′), for instance, a carbonyl group and attack of a C_1-nucleophile. Following the first route, the secondary alcohol (±)-**13** was deoxygenated according to *Barton* and *McCombie* to give the phenethyl derivative (±)-**19** (*Scheme 3*) [37]. *Noyce et al*. showed that 1,2-dimethyl-1*H*-imidazole is not metallated in the imidazole ring, but at the 2-Me group [38]. This finding suggested that metallation of (±)-**19** could occur at C(1′), since both C(2) and C(5) in the heterocyclic nucleus are substituted. Unfortunately, application of BuLi, *s*-BuLi, *t*-BuLi, or $(i\text{-}Pr)_2NLi$ as base for deprotonation of (±)-**19**, followed by addition of *s*-trioxane, did not afford any of the desired diastereoisomers (±)-**20** and (±)-**21**. ^{1}H-NMR Measurements of probes quenched with D_2O indeed suggested that a regioselective deprotonation of (±)-**19** is quite difficult. Removal of the sulfamoyl group of (±)-**19** afforded (±)-**22**.

Oxidation of the secondary alcohol (±)-**13** to the corresponding ketone (±)-**23** was accomplished with *Dess–Martin* periodinane [39]. Several nucleophilic C_1-homologation procedures were subsequently explored. First, all attempts at conducting a *Darzens* glycidic ester synthesis [40] using various bases and α-halo esters under a variety of reaction conditions were unsuccessful, and none of the desired glycidic ester (±)-**24** was isolated (*Scheme 4*). A C_1-homologation by *Peterson* olefination [41] to provide vinyl derivative (±)-**25** failed just as the *Wittig* olefination [42], whereas the desired olefination was achieved with the *Tebbe* reagent [43], although in disappointingly low yield (9%; *Scheme 4*). The poor results of the nucleophilic C_1-homologation attempts are presumably due to the acidity of the benzylic H-atoms in α-position to the C=O group in (±)-**23**.

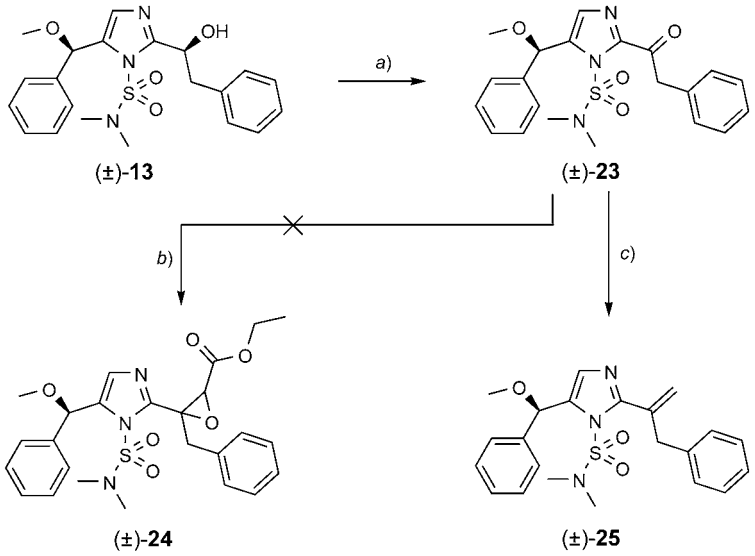
2.3. *Synthesis of Lead Structure (±)-***1** via Stille *Cross-Coupling*. Next, we envisaged a more direct approach to build up the 'right' part of the molecule *via* a *Stille* cross-coupling [44]. Stannylation of sulfamoyl-protected 1*H*-imidazole **2** at C(2) was

Scheme 3. *Attempted C_1-Homologation at C(1′)*



a) 1. NaH, CS_2, MeI, THF, 0° → r.t., 2.5 h; 2. Bu_3SnH, AIBN, PhH, 5 h, Δ; 85% over 2 steps. *b*) 4% HCl in EtOH, r.t., 3 h; 84%. *c*) BuLi, *s*-BuLi, *t*-BuLi, or $(i\text{-Pr})_2NLi$, *s*-trioxane. AIBN = 2,2′-azobis[isobutyronitrile].

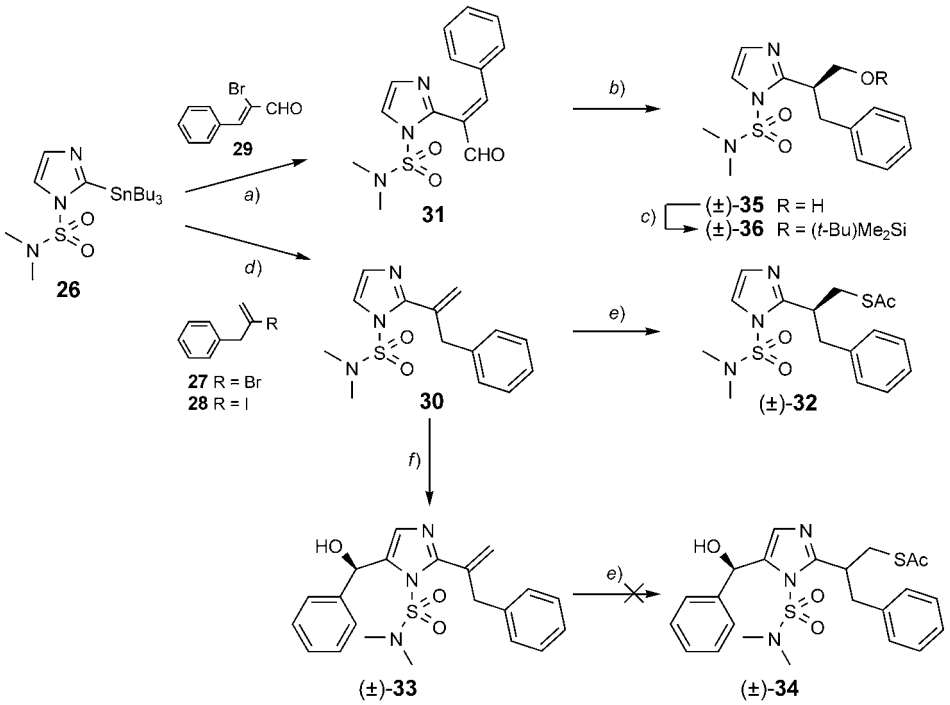
Scheme 4. *Synthesis of the Olefin (±)-***25**



a) *Dess–Martin* periodinane, CH_2Cl_2, r.t., 2.5 h; 47%. *b*) *t*-BuOK, $ClCH_2CO_2Et$, *t*-BuOH, r.t. *or* NaH, $ClCH_2CO_2Et$, THF, −10° → r.t., 2 h *or* $(i\text{-Pr})_2NLi$, $ClCH_2CO_2Et$, THF, −78° → r.t., 40 min *or* $(Me_3Si)_2NLi$, $ClCH_2CO_2Et$, THF, −78° → r.t., 3 h *or* NaH, $BrCH_2CO_2Et$, THF, −78° → r.t, 2 h *or* $(Me_3Si)_2NLi$, $BrCH_2CO_2Et$, THF, −78° → r.t., 3 h. *c*) *Tebbe* reagent, THF, PhMe, −78° → −20°, 125 min; 9%.

accomplished according to *Gutierrez et al.* by selective metallation, followed by reaction with Bu_3SnCl [45] (*Scheme 5*). The stannylated derivative **26** was then cross-coupled with halo-olefins **27**–**29** with $[PdCl_2(PPh_3)_2]$ (10 mol-%) as catalyst and a

Scheme 5. Stille *Cross-Couplings and Synthesis of Key Intermediate* (±)-**36** *on the Way to* (±)-**1**



a) [$PdCl_2(PPh_3)_2$], Ag_2O, DMF, 100°, 48 h; 50%. *b*) [$Pd(PPh_3)_4$], Bu_3SnH, AcOH, PhH, r.t., 14 h; 82%. *c*) (*t*-Bu)Me_2SiCl, DMAP, CH_2Cl_2, 16 h, r.t.; 79%. *d*) **27** or **28**, [$PdCl_2(PPh_3)_2$], Ag_2O, DMF, 100°, 48 h; 76% (from **27**) or 39% (from **28**). *e*) AIBN, AcSH, PhH, 100°, 4 h; 99%. *f*) *s*-BuLi, PhCHO, THF, −78°, 2 h; 31%.

stoichiometric amount of Ag_2O, which seems to be important for the acceleration of the reaction [45][46]. The couplings with **27** and **28**, respectively, yielded 2-vinyl-1*H*-imidazole **30**. It is noteworthy that the transformation gave better yields with bromide **27** than with iodide **28**. The cross-coupling with bromo aldehyde **29** gave **31** in moderate yields.

Radical addition of AcSH to the C=C bond of **30** using AIBN as initiator afforded thioester (±)-**32** in good yield. We assumed that the thioester group is not stable under the metallation conditions, so the substituent in 5-position of the 1*H*-imidazole core was introduced earlier, by *ortho*-metallation of **30**, followed by reaction with PhCHO to give (±)-**33**. The yield, however, was much lower than in similar reactions described above (*Scheme 1*). Radical addition of AcSH to (±)-**33** did not afford the desired thioester (±)-**34**, presumably because of decomposition of the benzylic alcohol moiety.

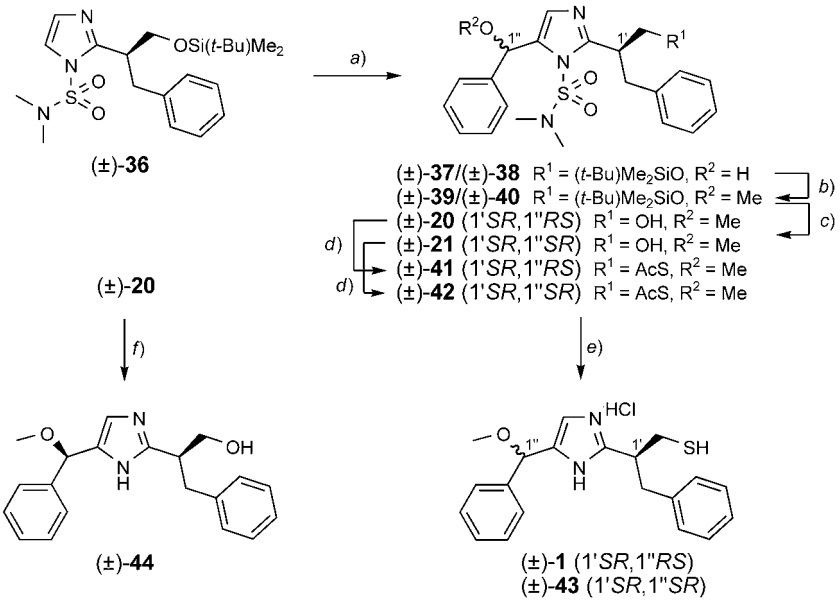
Since the synthesis starting from **30** was unsatisfactory, we continued on the way to (±)-**1** from α,β-unsaturated aldehyde **31**. We tried to reduce selectively the C=C bond to obtain the corresponding saturated aldehyde by Pd-catalyzed conjugate reduction with Bu_3SnH as hydride donor and AcOH as proton donor [47]. Surprisingly, addition of 2 equiv. of Bu_3SnH, 9 equiv. of AcOH, and [$Pd(PPh_3)_4$] (1 mol-%) as catalyst led to

the reduction of both C=C and C=O bonds to give the primary alcohol (±)-**35** (*Scheme 5*), which was subsequently converted into silyl ether (±)-**36**.

ortho-Metallation of (±)-**36** with *s*-BuLi, followed by addition to PhCHO afforded a mixture of the diastereoisomeric 1,2,5-trisubstituted 1*H*-imidazoles (±)-**37** and (±)-**38** (*Scheme 6*). This mixture was *O*-methylated to give, in almost quantitative yield, a mixture of (±)-**39** and (±)-**40**. Cleavage of the silyl ether moieties afforded the primary alcohols (±)-**20** and (±)-**21**, which were separated by column chromatography. The isolated yields of 62% ((±)-**20**) and 35% ((±)-**21**) reflect the diastereoselectivity (dr 1.8 : 1) for the nucleophilic addition to PhCHO. Conversion of (±)-**20** and (±)-**21** to the thioesters (±)-**41** and (±)-**42**, respectively, was accomplished in excellent yields by a *Mitsunobu* reaction [48]. The assignment of the diastereoisomers of this series was based on the X-ray analysis of crystals of (±)-**41** (*Fig. 4*). Thiol and imidazole deprotection in one step with NaOMe in MeOH under H_2 [49], followed by addition of CF_3COOH, and subsequent treatment of the crude product with methanolic HCl and purification by reverse-phase column chromatography afforded the hydrochloride salts of lead structure (±)-**1** and its diastereoisomer (±)-**43**, respectively (*Scheme 6*). Comparison compound (±)-**44** was obtained by removal of the sulfamoyl group of (±)-**20**.

2.4. *Synthesis of Inhibitors* (±)-**45** *and* (±)-**46**. Treatment of (±)-**36** with *s*-BuLi and naphthalene-2-carbaldehyde afforded the diastereoisomers (±)-**47** and (±)-**48**, which

Scheme 6. *Synthesis of the Potential Inhibitors (±)-***1**, *(±)-***43**, *and (±)-***44**



a) *s*-BuLi, PhCHO, THF, −78°, 2 h; 85%. *b*) NaH, MeI, THF, 0° → r.t., 2 h; 98%. *c*) Bu_4NF, THF, r.t., 2.5 h; 62% (±)-**20**; 35% (±)-21. *d*) DIAD, PPh_3, AcSH, THF, 0° → r.t., 3 h; 95% (±)-**41**; 93% (±)-**42**. *e*) 1. NaOMe, MeOH, r.t., 75 min then CF_3COOH, r.t., 105 min; 2. 0.1% HCl in MeOH, r.t., 5 min; 41% (±)-**1**; 43% (±)-**43** over 2 steps. *f*) 4% HCl in EtOH, r.t., 3 h; 82%. DIAD = Diisopropyl azodicarboxylate.

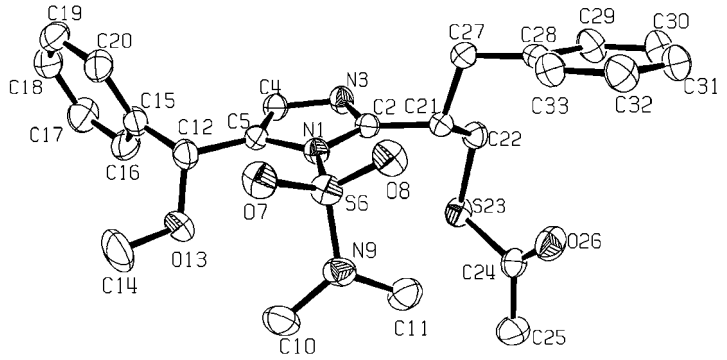
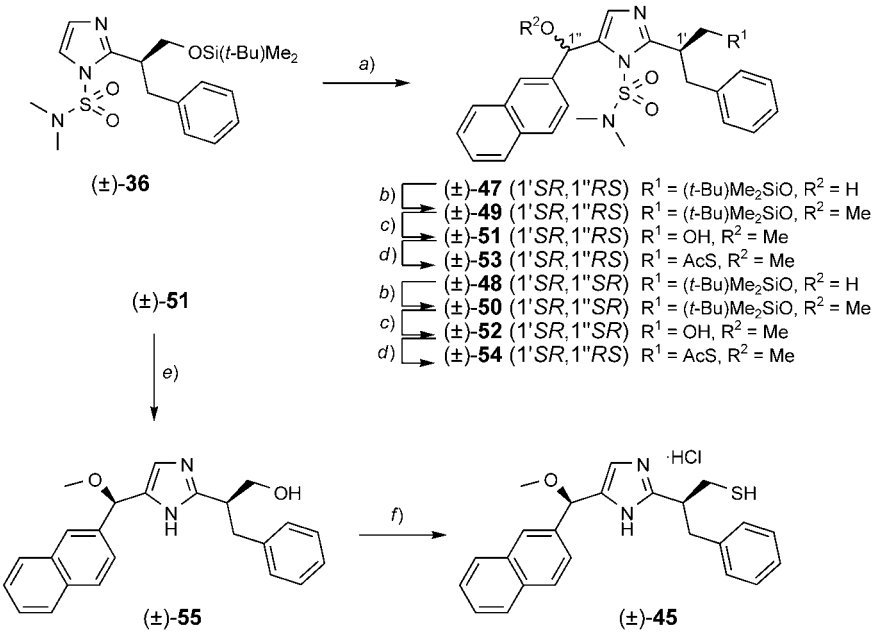


Fig. 4. *Crystal structure of (±)-***41**. The ORTEP representation is shown with atomic-displacement-parameter ellipsoids at 50% probability level. Arbitrary numbering.

were separated by column chromatography (*Scheme 7*). Methylation provided (±)-**49** and (±)-**50**, silyl deprotection gave (±)-**51** and (±)-**52**, and *Mitsunobu* reaction yielded (±)-**53** and (±)-**54**, respectively. The final one-step removal of the Ac and sulfamoyl protecting groups in (±)-**53** and (±)-**54** was not very successful, so the sulfamoyl group

Scheme 7. *Synthesis of Inhibitor (±)-***45**

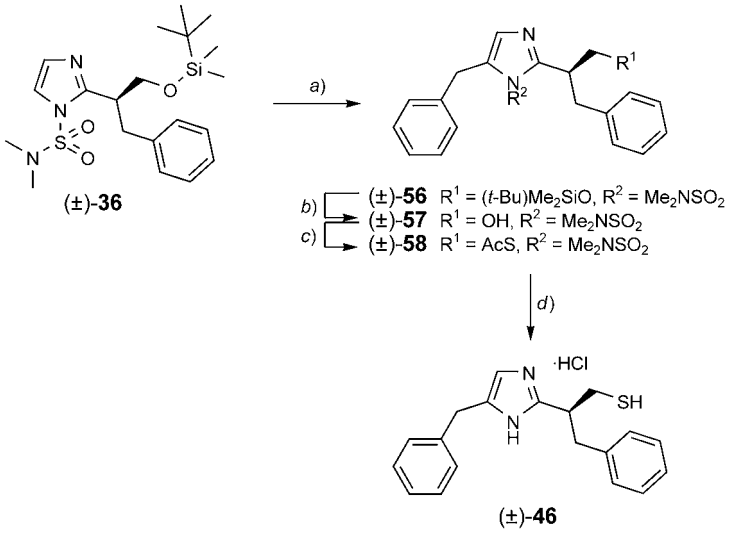


a) *s*-BuLi, 2-naphthalene-2-carbaldehyde, THF, −78°, 2 h; 56% (±)-**47**; 40% (±)-**48**. *b*) NaH, MeI, THF, 0° → r.t., 2 h; 94% (±)-**49**; 97% (±)-**50**. *c*) Bu_4NF, THF, r.t., 2.5 h; 80% (±)-**51**; 76% (±)-**52**. *d*) DIAD, PPh_3, AcSH, THF, 0° → r.t., 3 h; 83% (±)-**53**; 87% (±)-**54**. *e*) 4% HCl in EtOH, r.t., 3 h; 75%. *f*) 1. DIAD, PPh_3, AcSH, THF, 0° → r.t., 3 h; 2. NaOMe, MeOH, r.t., 75 min; 3. 0.1% HCl in MeOH, r.t., 5 min; 21% over 3 steps.

of (±)-**51** was cleaved to 1*H*-imidazole (±)-**55**. Subsequent *Mitsunobu* reaction with AcSH and cleavage of the Ac group afforded the desired inhibitor (±)-**45**, which was isolated as hydrochloride salt.

Treatment of (±)-**36** with *s*-BuLi and BnBr afforded (±)-**56**, which was deprotected to (±)-**57** and converted to (±)-**58** as described above (*Scheme 8*). The thioester moiety was cleaved with HCl in boiling MeOH. Under these conditions, the sulfamoyl group was also removed to yield (±)-**46**. Note that these conditions could not be used for double deprotection of (±)-**41**, (±)-**42**, (±)-**53**, or (±)-**54**, since these compounds decomposed. The pure hydrochloride salt (±)-**46** was obtained by treatment with HCl gas in $CHCl_3$ and purification by reverse-phase column chromatography.

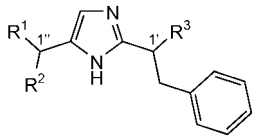
Scheme 8. *Synthesis of Inhibitor (±)-***46**



a) s-BuLi, BnBr, THF, $-78° \rightarrow$ r.t., 3.5 h; 67%. *b*) Bu_4NF, THF, r.t., 2.5 h; 81%. *c*) DIAD, PPh_3, AcSH, THF, $0° \rightarrow$ r.t., 3 h; 92%. *d*) 1. 4% HCl in MeOH, 70°, 4 h; 2. HCl (g), $CHCl_3$, r.t. 10 min; 46% over two steps. Bn = benzyl.

2.5. *Biological Activity.* The *in vitro* activity of compounds (±)-**15**, (±)-**16**, (±)-**17**, (±)-**18**, (±)-**22**, (±)-**44**, and the hydrochloride salts of (±)-**1**, (±)-**43**, (±)-**45**, and (±)-**46** towards neprilysin was determined in a fluorimetric assay (*Table*; for a description of the assay, see *Exper. Part*). In the active form of the ligands, the 1*H*-imidazole core is not protonated. Gratifyingly, our designed lead structure (±)-**1** ($IC_{50} = 2.0$ μM) shows a good binding affinity. This suggests that our proposed binding mode is correct, and that the 1*H*-imidazole core acts indeed as a peptide bond isoster. The similar activity of its diastereoisomeric analog (±)-**43** ($IC_{50} = 1.7$ μM) indicates that the predicted H-bond between the O-atom of the MeO group in (±)-**1** and the side-chain N–H of Asn542 is not effective. Indeed, the H-bond-accepting MeO group can be completely omitted without penalty as shown by the activity of (±)-**46** ($IC_{50} = 2.5$ μM), which lacks the MeO group and is about as active as (±)-**1** and (±)-**43**. The IC_{50} value of naphthyl derivative (±)-**45** ($IC_{50} = 3.6$ μM) is by a factor of 1.8 higher than the value measured

Table. *Activities of the New Imidazole-Based Inhibitors towards Neprilysin*



Inhibitor	R^1	R^2	R^3	Active enantiomer	IC_{50} [μM]
(±)-**15**	OH	Ph	OH	(1′*S*,1″*R*)	15[a])
(±)-**16**	OH	Ph	OH	(1′*S*,1″*S*)	18[a])
(±)-**17**	MeO	Ph	OH	(1′*S*,1″*R*)	24[a])
(±)-**18**	MeO	Ph	OH	(1′*S*,1″*S*)	17[a])
(±)-**22**	MeO	Ph	H	(1″*S*)	17[a])
(±)-**44**	MeO	Ph	CH_2OH	(1′*S*,1″*R*)	17[a])
(±)-**1**[b])	MeO	Ph	CH_2SH	(1′*S*,1″*R*)	2.0
(±)-**43**[b])	MeO	Ph	CH_2SH	(1′*S*,1″*S*)	1.7
(±)-**45**[b])	MeO	Np[c])	CH_2SH	(1′*S*,1″*R*)	3.6
(±)-**46**[b])	H	Ph	CH_2SH	(1′*S*)	2.5

[a]) % Inhibition at 100 μM inhibitor concentration. [b]) The hydrochloride salts were used in the assay; in the active ligand, the imidazole is not protonated. [c]) Np = Naphthalen-2-yl.

for lead compound (±)-**1**. This result indicates that no additional binding free enthalpy is gained upon introduction of a larger aromatic substituent in the S2′ pocket and confirms the assumption that this pocket is less well-defined and rather promiscuous [19][33].

The substitution of the sulfanylmethyl by a hydroxymethyl group as in (±)-**44** leads to a dramatic loss in activity. Similarly, the hydroxy derivatives (±)-**15**, (±)-**16**, (±)-**17**, and (±)-**18** were all inactive as was compound (±)-**22** lacking any vector for potential Zn^{II} binding. This clearly shows that, at the stage of the compounds resulting from the first design cycle, strong ligation to the metal ion by a thiol residue is required for biological activity.

3. Conclusions. – This paper describes the first generation of nonpeptidic inhibitors of the Zn^{II}-dependent membrane-bound endopeptidase neprilysin (NEP) resulting from X-ray-structure-based design. Their synthesis involves an elegant double directed *ortho*-metallation of an 1*H*-imidazole scaffold introduced as peptide-bond isoster. The first of the metallations is followed by a *Stille* cross-coupling, thereby providing another example for the versatile directed *ortho*-metallation-cross-coupling strategy, largely developed and recently reviewed by *Anctil* and *Snieckus* [50]. The IC_{50} values of the new inhibitors (±)-**1**, (±)-**43**, (±)-**45**, and (±)-**46**, determined by a fluorescence assay, are all in the lower micromolar range ($IC_{50} = 2-4$ μM). This suggests that the binding mode predicted by modeling is basically correct: the imidazole ring acts as peptide bond isoster, the two aromatic rings occupy the two hydrophobic S1′ and S2′ pockets, and the thiol vector ligates to the Zn^{II} ion. Control experiments show that, at this stage of lead development, thiol ligation to the Zn^{II} ion is absolutely required. The inactive compounds (±)-**15**, (±)-**16**, (±)-**17**, and (±)-**18** clearly do not bind with their OH group in the 1′-position to the Zn^{II} ion *via* the 'catalytic' H_2O acting as a bridging molecule. Presumably, the ligand exchange of the catalytically active H_2O at the Zn^{II} ion is too

fast to establish a stable inhibitor–H_2O–Zn^{II} complex. Contrary to the kinetically stable binding of Zn^{II} to the protein, the hydrolytic function of the enzyme requires a labile complexation of the active H_2O molecule [51]. Two additional results provide useful guidance for the next lead-optimization cycle: H-bonding to the side-chain N–H of Asn542 does not make a measurable contribution to the binding free enthalpy and can be omitted (see comparison (±)-**1**, (±)-**43**, and (±)-**46**). Also, occupancy of the wider, conformationally less-defined S2′ pocket by larger aromatic side chains does not enhance binding affinity. In summary, this project has again demonstrated the potential of structure-based *de novo* design as a powerful tool for nonpeptidic lead generation, complementing other strategies such as high-throughput screening. The activity of the first NEP inhibitor ((±)-**1**; $IC_{50} = 2$ μM) is well in the range of those of the first ligands prepared in other *de novo* design programs in our laboratory (thrombin: inhibition constant $K_i = 18$ μM [52], catechol *O*-methyltransferase: $IC_{50} = 6$ μM [53], *t*RNA guanine transglycosylase: $K_i = 100$ nM [54], and plasmepsin II: $K_i = 5$ μM [55]). These data suggest that single leads with inhibitory activities between $K_i \approx 20$ μM and 100 nM can be generated with great confidence by structure-based design, provided the target enzyme active site is conformationally well-defined and possesses pronounced concave/convex surfaces, which is the case for all five targets.

We thank the *ETH Research Council* and *F. Hoffmann-La Roche,* Basel, for generous support of this work, and Dr. *C. Thilgen* for help with the nomenclature.

Experimental Part

General. Solvents and reagents were of reagent-grade, purchased from commercial suppliers, and used without further purification unless otherwise stated. The following compounds were prepared according to literature procedures: **2** [34], **26** [45], **27** [56], **28** [57], and **29** [58]. THF was freshly distilled from sodium benzophenone ketyl, CH_2Cl_2 from CaH_2. Evaporation *in vacuo* was conducted at 30–70° and 600–15 mbar pressure. All products were dried under high vacuum (10^{-2} Torr) before anal. characterization. Column chromatography (CC): SiO_2-*60* (40–63 μm) and *RP-18* SiO_2 (40–63 μm) from *Fluka*, 0–0.4 bar pressure. TLC: SiO_2-*60* F_{254}, *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) or a soln. of $(NH_4)_6\,Mo_7O_{24}\cdot 6\,H_2O$ (20 g) and $Ce(SO_4)_2$ (0.4 g) in 10% aq. H_2SO_4 soln. (400 ml). M.p.: *Büchi B-540* melting-point apparatus; uncorrected. IR [cm^{-1}]: *Perkin-Elmer 1600-FT* or *Perkin-Elmer Spectrum BX* spectrometer. NMR (^1H and ^{13}C): *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: *Finnigan MAT TSQ 7000* spectrometer; HR-MALDI-MS: *IonSpec Ultima* (2,5-dihydroxybenzoic acid (DHB) or 2-{(2*E*)-3-[4-(*tert*-butyl)phenyl)]-2-methylprop-2-enylidene}malononitrile (DTCB) matrix). Elemental analyses were performed by the *Mikrolabor* at the *Laboratorium für Organische Chemie, ETH-Zürich*.

Biological Assay. The NEP assay was based on the method described by *Carvalho et al.* [59] with a minor difference in the substrate. The fluorescent substrate (ABZ-GGDFLRRVQEDDnp) contained an additional glutamine between the valine and the fluorescent group. Incubations (for 1 h at 37°) were carried out in 96-well microplates in triplicate at 4 to 6 concentrations ranging from 100 μm to 1 nm. IC_{50} Values were calculated after logit/log transformation of the percent inhibition data with a best-fit regression model. The inhibitors were tested for their fluorescence or quenching properties, and values were corrected accordingly. Thiorphan as reference compound gave an IC_{50} value of 7.0 ± 0.2 nM ($n = 6$) in this assay.

General Procedure for the Silylation of a OH Group with (t-*Bu*)*Me*$_2$*SiCl* (*GP 1*). To a soln. of the alcohol (1 equiv.) in dry CH_2Cl_2 (0.04M), (*t*-Bu)Me_2SiCl (1.5 equiv.) and DMAP (1.7 equiv.) were added, and the mixture was stirred for 16 h at r.t. After addition of Et_2O, and washing with H_2O and sat. aq. NaCl soln., the aq. phases were extracted (CH_2Cl_2), and the combined org. phases were dried ($MgSO_4$) and concentrated *in vacuo.*

*General Procedure for the Nucleophilic Addition of 5-Metallated 1*H-*Imidazoles to Aromatic Aldehydes* (*GP 2*). At −78°, *s*-BuLi (1.3M in cyclohexane, 1.2 equiv.) was added dropwise to a soln. of the 1,2-disubstituted

1*H*-imidazole (1 equiv.) in dry THF (0.06M), and the mixture was stirred for 30 min. The aldehyde (3 equiv.) was added, followed by stirring for 3 h at −78°. The reaction was quenched by addition of 1N HCl, and the mixture was neutralized with sat. aq. $NaHCO_3$ soln., and extracted (CH_2Cl_2). The org. phases were dried ($MgSO_4$) and concentrated *in vacuo*.

General Procedure for the Deprotection of a (t-*Bu*)*Me*$_2$*Si-Protected Hydroxy Group* (*GP 3*). To a soln of the silyl-protected compound (1 equiv.) in dry THF (0.07M), Bu_4NF (1M in THF, 2 equiv.) was added dropwise at r.t. The mixture was stirred for 2.5 h at r.t., and the reaction was quenched by addition of H_2O. After extraction (CH_2Cl_2), the org. phase was dried ($MgSO_4$) and concentrated *in vacuo*.

General Procedure for the Deprotection of a N-*Me*$_2$*NSO*$_2$*-Protected 1*H-*Imidazole* (*GP 4*). A soln. of the *N*-protected 1*H*-imidazole (1 equiv.) in 4% ethanolic HCl soln. (0.1M) was stirred for 3 h at r.t. The mixture was neutralized by addition of sat. aq. $NaHCO_3$ soln., extracted (CH_2Cl_2), and the org. phases were dried ($MgSO_4$), and the solvent was removed *in vacuo*.

General Procedure for the Methylation of a Hydroxy Group (*GP 5*). Pentane was added to NaH (2 equiv.) under N_2. After stirring for 10 min, the pentane was decanted, and the white solid was dried by streaming N_2. A soln. of the alcohol (1 equiv.) in dry THF was added to the solid at 0°. After stirring for 30 min at r.t., MeI (1.1 equiv.) was added at 0°, and the mixture was stirred for additional 2 h at r.t. The reaction was quenched with H_2O, the mixture was extracted (CH_2Cl_2), the org. phases were dried ($MgSO_4$), and the solvent was removed *in vacuo*.

General Procedure for the Substitution of a Hydroxy Group by AcSH Under Mitsunobu *Conditions* (*GP 6*). To a soln. of Ph_3P (1.5 equiv.) in dry THF (0.1M), DIAD (1.5 equiv.) was added at 0°, and the mixture was stirred for 30 min, whereas a white solid precipitated. A soln. of the alcohol (1 equiv.) in dry THF (0.16M) was added dropwise to the mixture, followed by addition of freshly distilled AcSH (2 equiv.). The mixture was stirred for 1 h at 0° and for 2 h at r.t. After addition of Et_2O, and washing with H_2O and sat. aq. NaCl soln., the aq. phases were extracted (CH_2Cl_2), and the combined org. phases were dried ($MgSO_4$) and concentrated *in vacuo*.

2-Formyl-N,N-*dimethyl-1*H-*imidazole-1-sulfonamide* (**3**). To a soln. of **2** (5.00 g, 29 mmol) in dry THF (150 ml), BuLi (1.6M in hexane, 21.4 ml, 34 mmol) was added slowly at −78°. After stirring for 5 min, DMF (10.5 ml, 137 mmol) was added, and the mixture was stirred for 30 min at −78° and 1 h at r.t. The mixture was poured into 2M HCl, neutralized with sat. aq. $NaHCO_3$ soln., and extracted (CH_2Cl_2). The org. phases were dried ($MgSO_4$) and concentrated *in vacuo*. The resulting residue was purified by CC (SiO_2; hexane/AcOEt 25:75) to give **3** (4.70 g, 81%). Yellowish powder. M.p. 91–92° ([31]: 92°). ^{1}H-NMR (300 MHz, $CDCl_3$): 3.01 (*s*, 6 H); 7.03 (*d*, *J* = 1.3, 1 H); 7.58 (*dd*, *J* = 1.3, 0.6, 1 H); 9.94 (*d*, *J* = 0.6, 1 H).

*2-[(1*RS*)-1-Hydroxy-2-phenylethyl]*-N,N-*dimethyl-1*H-*imidazole-1-sulfonamide* ((±)-**4**). Mg (1.01 g, 42 mmol) in Et_2O (10 ml) was slowly treated with BnBr (4.1 ml, 35 mmol). The resulting suspension was added to a soln. of **3** (4.70 g, 23 mmol) in THF (30 ml). After addition, the reaction was carefully quenched with sat. aq. NH_4Cl soln., and the mixture was extracted (CH_2Cl_2). The org. phases were dried ($MgSO_4$) and concentrated *in vacuo*. The resulting residue was purified by CC (SiO_2; AcOEt) to give (±)-**4** (3.87 g, 57%). Reddish powder. M.p. 72–73°. IR ($CHCl_3$): 3580, 3007, 1455, 1420, 1393, 1180, 1160. ^{1}H-NMR (300 MHz, $CDCl_3$): 2.84 (*s*, 6 H); 3.16 (*dd*, *J* = 13.7, 8.1, 1 H); 3.37 (*dd*, *J* = 13.7, 4.7, 1 H); 5.29 (*dd*, *J* = 8.1, 4.7, 1 H); 7.05 (*d*, *J* = 1.6, 1 H); 7.22–7.32 (*m*, Ph). ^{13}C-NMR (75 MHz, $CDCl_3$): 38.2; 43.1; 67.9; 119.9; 126.7; 127.6; 128.4; 129.6; 137.5; 150.5. EI-MS: 295.1 (1, M^+), 276.1 (16), 204.0 (63), 169.1 (44), 108.0 (100). Anal. calc. for $C_{13}H_{17}N_3O_3S$ (295.36): C 52.87, H 5.80, N 14.23; found: C 53.04, H 5.89, N 14.07.

*2-((1*RS*)-1-{[(*tert-*Butyl)(dimethyl)silyl]oxy}-2-phenylethyl)*-N,N-*dimethyl-1*H-*imidazole-1-sulfonamide* ((±)-**5**). *GP 1*, starting from (±)-**4** (10.50 g, 35.5 mmol), gave (±)-**5** (11.97 g, 82%) after purification through a plug (SiO_2; pentane/AcOEt 67:33) and recrystallization from Et_2O. Yellowish crystals. M.p. 70–72°. IR ($CHCl_3$): 2930, 2857, 1472, 1420, 1392, 1255, 1178, 1159. ^{1}H-NMR (300 MHz, $CDCl_3$): −0.15 (*s*, 3 H); −0.14 (*s*, 3 H); 0.77 (*s*, 9 H); 2.68 (*s*, 6 H); 3.06 (*dd*, *J* = 13,1, 7.8, 1 H); 3.35 (*dd*, *J* = 13.1, 5.9, 1 H); 5.37 (*dd*, *J* = 7.8, 5.9, 1 H); 7.08 (*d*, *J* = 1.6, 1 H); 7.16–7.24 (*m*, 6 H). ^{13}C-NMR (75 MHz, $CDCl_3$): −5.1; 18.2; 25.7; 37.9; 44.4; 69.1; 119.1; 126.4; 128.1; 128.2; 130.0; 138.1; 150.7. MALDI-MS (DHB): 432.2 (72, $[M+Na]^+$), 278.1 (63), 233.0 (12), 215.1 (12), 214.1 (100). MALDI-HR-MS (DHB): 432.1748 ($[M+Na]^+$, $C_{19}H_{31}N_3NaO_3SSi^+$; calc. 432.1748). Anal. calc. for $C_{19}H_{31}N_3O_3SSi$ (409.62): C 55.71, H 7.63, N 10.26, S 7.83; found C 55.97, H 7.64, N 10.25, S 7.76.

*2-((1*RS*)-1-{[(*tert-*Butyl)(dimethyl)silyl]oxy}-2-phenylethyl)-5-formyl*-N,N-*dimethyl-1*H-*imidazole-1-sulfonamide* ((±)-**6**). To a soln. of (±)-**5** (3.00 g, 7.32 mmol) in dry THF (50 ml), *s*-BuLi (1.3M in cyclohexane, 8.5 ml, 11 mmol) was slowly added at −78 °C. After stirring for 30 min, DMF (2.7 ml, 35 mmol) was added, and the mixture was stirred for 1 h at −78°. The mixture was poured into 1M HCl, neutralized with sat. aq. $NaHCO_3$ soln., and extracted (CH_2Cl_2). The org. phases were dried ($MgSO_4$) and concentrated *in vacuo*. The resulting residue was purified by CC (SiO_2; pentane/AcOEt 75:25) to give (±)-**6** (2.15 g, 67%). Colorless oil. IR

($CHCl_3$): 3436, 3015, 2956, 2861, 1692, 1671, 1543, 1471, 1394, 1260. ^{1}H-NMR (300 MHz, $CDCl_3$): −0.13 (*s*, 3 H); −0.10 (*s*, 3 H); 0.79 (*s*, 9 H); 2.72 (*s*, 6 H); 3.03 (*dd*, *J* = 13.1, 7.5, 1 H); 3.40 (*dd*, *J* = 13.1, 5.9, 1 H); 5.51 (*dd*, *J* = 7.5, 5.9, 1 H); 7.18–7.27 (*m*, 5 H); 7.89 (*s*, 1 H); 10.00 (*s*, 1 H). ^{13}C-NMR (75 MHz, $CDCl_3$): −5.1; 18.2; 25.7; 37.9; 44.4; 69.8; 126.7; 128.3; 128.3; 130.0; 137.4; 139.1; 157.5; 179.8. MALDI-MS (DHB): 460.2 (72, $[M + Na]^+$), 438.2 (14), 393.2 (11), 380.2 (24), 359.2 (21), 358.2 (100). MALDI-HR-MS (DHB): 460.1703 ($[M + Na]^+$, $C_{20}H_{31}N_3NaO_4SSi^+$; calc. 460.1697).

*2-((1*RS*)-1-[[(*tert-*Butyl)(dimethyl)silyl]oxy}-2-phenylethyl)-5-[(*SR*)-hydroxy(phenyl)methyl]-*N,N*-dimethyl-1*H*-imidazole-1-sulfonamide* ((±)-**7**) *and 2-((1*RS*)-1-[[(*tert-*Butyl)(dimethyl)silyl]oxy}-2-phenylethyl)-5-[(*RS*)-hydroxy(phenyl)methyl]-*N,N*-dimethyl-1*H*-imidazole-1-sulfonamide* ((±)-**8**). *GP 2*, starting from (±)-**5** (17.80 g, 43.45 mmol) and PhCHO, afforded (±)-**7** (6.23 g, 28%) and (±)-**8** (8.31 g, 37%) after purification by CC (SiO_2; pentane/AcOEt 75 : 25).

*Data of (±)-***7**: Colorless crystals. M.p. 127–128°. IR ($CHCl_3$): 3580, 2944, 1600, 1492, 1467, 1451, 1374, 1251, 1185, 1161, 1097. ^{1}H-NMR (300 MHz, $CDCl_3$): −0.12 (*s*, 6 H); 0.77 (*s*, 9 H); 2.61 (*s*, 6 H); 3.02 (*dd*, *J* = 13.1, 7.5, 1 H); 3.12 (*d*, *J* = 5.0, 1 H); 3.32 (*dd*, *J* = 13.1, 6.2, 1 H); 5.35 (*dd*, *J* = 7.5, 6.2, 1 H); 6.06 (*s*, 1 H); 6.60 (*s*, 1 H); 7.15–7.42 (*m*, 5 H); 7.31–7.43 (*m*, 5 H). ^{13}C-NMR (125 MHz, $CDCl_3$): −5.0; 18.2; 25.6; 37.5; 44.4; 67.7; 69.6; 126.4; 126.8; 128.1; 128.3; 129.8; 130.0; 136.5; 138.1; 140.4; 153.4 (1 arom. signal overlapping). MALDI-MS (DHB): 538.2 (30, $[M + Na]^+$), 516.2 (13, MH^+), 431.2 (13), 409.2 (17), 391.2 (34), 384.1 (25), 366.1 (100). MALDI-HR-MS (DHB): 538.2165 ($[M + Na]^+$, $C_{26}H_{37}N_3NaO_4SSi^+$; calc. 538.2166).

*Data of (±)-***8**: Colorless crystals. M.p. 127–128°. IR ($CHCl_3$): 3590, 2930, 2857, 1600, 1455, 1376, 1254, 1161, 1102. ^{1}H-NMR (300 MHz, $CDCl_3$): −0.17 (*s*, 3 H); −0.15 (*s*, 3 H); 0.76 (*s*, 9 H); 2.67 (*s*, 6 H); 3.00 (*dd*, *J* = 13.1, 8.0, 1 H); 3.32 (*dd*, *J* = 13.1, 5.3, 1 H); 5.33 (*dd*, *J* = 8.0, 5.3, 1 H); 6.10 (*s*, 1 H); 6.62 (*s*, 1 H); 7.18–7.27 (*m*, 5 H); 7.31–7.43 (*m*, 5 H). ^{13}C-NMR (125 MHz, $CDCl_3$): −5.1; 18.2; 25.7; 37.6; 44.6; 67.7; 69.9; 126.6; 126.8; 128.2; 128.4; 129.7; 130.0; 136.6; 138.1; 140.5; 153.5 (1 arom. signal overlapping). MALDI-MS (DHB): 538.2 (33, $[M + Na]^+$), 516.2 (20, MH^+), 431.2 (16), 409.2 (49), 391.2 (100). MALDI-HR-MS (DHB): 538.2168 ($[M + Na]^+$, $C_{26}H_{37}N_3NaO_4SSi^+$; calc. 538.2166). Anal. calc. for $C_{26}H_{37}N_3O_4SSi$ (515.74): C 60.55, H 7.23, N 8.15; found C 60.75, H 7.21, N 8.12.

*2-[(1*RS*)-1-Hydroxy-2-phenylethyl]-5-[(*SR*)-hydroxy(phenyl)methyl]-*N,N*-dimethyl-1*H*-imidazole-1-sulfonamide* ((±)-**11**). *GP 3*, starting from (±)-**7** (300 mg, 0.58 mmol), afforded (±)-**11** (177 mg, 76%) after purification by CC (SiO_2; AcOEt). White powder. M.p. 120°. IR ($CHCl_3$): 3587, 3009, 2966, 1717, 1604, 1495, 1454, 1420, 1387, 1262, 1161, 1098. ^{1}H-NMR (300 MHz, $CDCl_3$): 2.81 (*s*, 6 H); 3.10 (*dd*, *J* = 13.7, 7.8, 1 H); 3.35 (*dd*, *J* = 13.7, 5.0, 1 H); 5.24 (*m*, 1 H); 6.12 (*s*, 1 H); 6.58 (*s*, 1 H); 7.20–7.40 (*m*, 10 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 37.8; 43.3; 67.6; 68.4; 126.5; 126.6; 128.1; 128.2; 128.3; 128.9; 129.5; 136.7; 137.5; 140.6; 153.0. MALDI-MS (DHB): 424.1 (22, $[M + Na]^+$), 402.1 (48, MH^+), 317.1 (22), 304.1 (12), 295.1 (18), 277.1 (100). MALDI-HR-MS (DHB): 402.1491 (MH^+, $C_{20}H_{24}N_3O_4S^+$; calc. 402.1482).

*2-[(1*RS*)-1-Hydroxy-2-phenylethyl]-5-[(*SR*)-hydroxy(phenyl)methyl]-*N,N*-dimethyl-1*H*-imidazole-1-sulfonamide* ((±)-**12**). *GP 3*, starting from (±)-**8** (200 mg, 0.39 mmol), afforded (±)-**12** (135 mg, 86%) after purification by CC (SiO_2; AcOEt). White powder. M.p. 126°. IR ($CHCl_3$): 3582, 3020, 1602, 1495, 1454, 1419, 1383, 1323, 1274, 1162, 1099. ^{1}H-NMR (300 MHz, $CDCl_3$): 2.82 (*s*, 6 H); 3.06 (*dd*, *J* = 13.7, 8.4, 1 H); 3.33 (*dd*, *J* = 13.7, 4.7, 1 H); 5.26 (*m*, 1 H); 6.09 (*s*, 1 H); 6.48 (*s*, 1 H); 7.20–7.44 (*m*, 10 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 38.0; 43.8; 67.5; 68.7; 126.6; 126.7; 128.2; 128.3; 128.3; 129.2; 129.5; 137.0; 137.5; 139.7; 153.4. MALDI-MS (DHB): 402.1 (48, MH^+), 317.1 (7), 295.1 (13), 277.1 (100). MALDI-HR-MS (DHB): 402.1490 (MH^+, $C_{20}H_{24}N_3O_4S^+$; calc. 402.1482).

*(1*RS*)-1-[5-[(*SR*)-Hydroxy(phenyl)methyl]-1*H*-imidazol-2-yl]-2-phenylethanol* ((±)-**15**). *GP 4*, starting from (±)-**11** (100 mg, 0.25 mmol), gave (±)-**15** (39 mg, 53%) after purification by CC (SiO_2; CH_2Cl_2/MeOH 91 : 9). White powder. M.p. 167–168°. IR (KBr): 3238, 2678, 1947, 1558, 1491, 1452, 1315, 1222, 1194, 1080, 1066, 1024, 996. ^{1}H-NMR (300 MHz, CD_3OD): 3.02 (*dd*, *J* = 13.7, 7.2, 1 H); 3.14 (*dd*, *J* = 13.7, 5.9, 1 H); 4.87 (*m*, 1 H); 5.72 (*s*, 1 H); 6.69 (*s*, 1 H); 7.06–7.39 (*m*, 10 H). ^{13}C-NMR (75 MHz, CD_3OD): 43.9; 69.9; 71.2; 126.8; 127.5; 127.9; 128.7; 128.7; 130.1; 138.5; 144.2; 151.2 (2 arom. signals overlapping). MALDI-MS (DHB): 317.1 (30, $[M + Na]^+$), 309.2 (30), 295.1 (37, MH^+), 291.1 (13), 277.1 (100). MALDI-HR-MS (DHB): 295.1444 (MH^+, $C_{18}H_{19}N_2O_2^+$; calc. 295.1447).

*(1*RS*)-1-[5-[(*RS*)-Hydroxy(phenyl)methyl]-1*H*-imidazol-2-yl]-2-phenylethanol* ((±)-**16**). *GP 4*, starting from (±)-**12** (100 mg, 0.25 mmol), gave (±)-**16** (29 mg, 40%) after purification by CC (SiO_2; CH_2Cl_2/MeOH 91 : 9). White powder. M.p. 179–180°. IR (KBr): 3250, 2672, 1947, 1603, 1564, 1494, 1454, 1401, 1309, 1216, 1116, 1083, 995. ^{1}H-NMR (300 MHz, CD_3OD): 3.02 (*dd*, *J* = 13.5, 7.6, 1 H); 3.16 (*dd*, *J* = 13.5, 6.1, 1 H); 4.87 (*m*, 1 H); 5.73 (*s*, 1 H); 6.70 (*s*, 1 H); 7.08–7.40 (*m*, 10 H). ^{13}C-NMR (75 MHz, CD_3OD): 44.0; 69.9; 71.0; 127.0; 127.5; 128.1; 128.8; 130.2; 138.6; 144.2; 151.3 (3 arom. signals overlapping). MALDI-MS (DHB): 317.1 (22,

[M + Na]$^+$), 295.1 (21, MH$^+$), 277.1 (100). MALDI-HR-MS (DHB): 295.1454 (MH$^+$, $C_{18}H_{19}N_2O_2^+$; calc. 295.1447). Anal. calc. for $C_{18}H_{18}N_2O_2$ (294.35): C 73.45, H 6.16, N 9.52; found C 73.41, H 6.26, N 9.41.

*2-((1*RS*)-1-[[(*tert*-Butyl)(dimethyl)silyl]oxy]-2-phenylethyl)-5-[(*SR*)-methoxy(phenyl)methyl]-*N,N*-dimethyl-1*H*-imidazole-1-sulfonamide* ((±)-**9**). *GP 5*, starting from (±)-**7** (2.24 g, 4.34 mmol), afforded (±)-**9** (1.89 g, 82%) after purification by CC (SiO_2; pentane/AcOEt 80:20). Slightly yellow oil. IR ($CHCl_3$): 3019, 2929, 2856, 1454, 1380, 1214, 1101, 940. ^{1}H-NMR (300 MHz, $CDCl_3$): −0.22 (*s*, 3 H); −0.21 (*s*, 3 H); 0.74 (*s*, 9 H); 2.67 (*s*, 6 H); 2.93 (*dd*, *J* = 13.1, 8.4, 1 H); 3.29 (*dd*, *J* = 13.1, 4.4, 1 H); 3.34 (*s*, 3 H); 5.24 (*dd*, *J* = 8.4, 4.4, 1 H); 5.61 (*d*, *J* = 0.6, 1 H); 6.58 (*d*, *J* = 0.6, 1 H); 7.15–7.37 (*m*, 10 H). ^{13}C-NMR (75 MHz, $CDCl_3$) −5.4; 18.3; 25.7; 37.7; 44.8; 56.9; 70.2; 126.9; 127.9; 128.2; 128.3; 128.6; 129.8; 130.0; 134.4; 136.1; 138.4; 152.9 (1 aliph. signal under solvent peak). MALDI-MS (DHB): 552.2 (25, [M + Na]$^+$), 530.3 (6, MH$^+$), 391.2 (100), 366.1 (72), 259.1 (67). MALDI-HR-MS (DHB): 552.2328 ([M + Na]$^+$, $C_{27}H_{39}N_3NaO_4SSi^+$; calc. 552.2323).

*2-((1*RS*)-1-[[(*tert*-Butyl)(dimethyl)silyl]oxy]-2-phenylethyl)-5-[(*RS*)-methoxy(phenyl)methyl]-*N,N*-dimethyl-1*H*-imidazole-1-sulfonamide* ((±)-**10**). *GP 5*, starting from (±)-**8** (3.50 g, 6.79 mmol), afforded (±)-**10** (3.25 g, 90%) after purification by CC (SiO_2; pentane/AcOEt 80:20). Slightly yellow oil. IR ($CHCl_3$): 3017, 2929, 2857, 1454, 1380, 1218, 1086. ^{1}H-NMR (300 MHz, $CDCl_3$): −0.16 (*s*, 6 H); 0.75 (*s*, 9 H); 2.59 (*s*, 6 H); 3.03 (*dd*, *J* = 13.1, 7.5, 1 H); 3.33 (*s*, 3 H); 3.34 (*dd*, *J* = 13.1, 5.6, 1 H); 5.32 (*t*, *J* = 6.9, 1 H); 5.63 (*s*,1 H); 6.66 (*s*, 1 H); 7.15–7.39 (*m*, 10 H). ^{13}C-NMR (75 MHz, $CDCl_3$): −4.8; 18.3; 25.9; 37.5; 44.6; 57.0; 69.7; 76.9; 126.3; 127.7; 128.1; 128.2; 128.4; 129.5; 129.9; 134.5; 138.2; 138.7; 153.0. MALDI-MS (DHB): 552.2 (25, [M + Na]$^+$), 530.3 (7, MH$^+$), 391.2 (100), 366.1 (56), 259.1 (47). MALDI-HR-MS (DHB): 552.2327 ([M + Na]$^+$, $C_{27}H_{39}N_3NaO_4SSi^+$; calc. 552.2323).

*2-[(1*RS*)-1-Hydroxy-2-phenylethyl]-5-[(*SR*)-methoxy(phenyl)methyl]-*N,N*-dimethyl-1*H*-imidazole-1-sulfonamide* ((±)-**13**). *GP 3*, starting from (±)-**9** (3.25 g, 6.13 mmol), gave (±)-**13** (1.97 g, 77%) after purification by recrystallization from Et_2O. Colorless crystals. M.p. 151–152°. IR ($CHCl_3$): 3574; 3064; 2997; 2933; 2826; 1603; 1454; 1391; 1163; 1084; 970. ^{1}H-NMR (300 MHz, $CDCl_3$): 2.90 (*s*, 6 H); 3.01 (*dd*, *J* = 13.7, 8.4, 1 H); 3.29 (*dd*, *J* = 13.7, 4.0, 1 H); 3.34 (*s*, 3 H); 5.25–5.30 (*m*, 1 H); 5.64 (*d*, *J* = 0.9, 1 H); 6.50 (*d*, *J* = 0.9, 1 H); 7.17–7.41 (*m*, 10 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 38.2; 44.1; 56.9; 68.9; 76.1; 126.5; 127.5; 128.3; 128.4; 128.4; 129.2; 129.5; 134.9; 137.7; 138.4; 153.3. MALDI-MS (DHB): 438.2 (6, [M + Na]$^+$), 416.2 (28, MH$^+$), 277.1 (68), 242.3 (100). MALDI-HR-MS (DHB): 416.1642 (MH$^+$, $C_{21}H_{26}N_3O_4S^+$; calc. 416.1639).

*2-[(1*RS*)-1-Hydroxy-2-phenylethyl]-5-[(*RS*)-methoxy(phenyl)methyl]-*N,N*-dimethyl-1*H*-imidazole-1-sulfonamide* ((±)-**14**). *GP 3*, starting from (±)-**10** (1.76 g, 3.32 mmol), gave (±)-**14** (1.06 g, 77%) after purification by CC (SiO_2; pentane/AcOEt 50:50). Colorless crystals. M.p. 122°. IR ($CHCl_3$): 3577; 3025; 3012; 2933; 2826; 1604; 1454; 1385; 1162; 1084; 968. ^{1}H-NMR (300 MHz, $CDCl_3$): 2.68 (*s*, 6 H); 3.15 (*dd*, *J* = 13.7, 7.8, 1 H); 3.35 (*s*, 3 H); 3.42 (*dd*, *J* = 13.7, 5.6, 1 H); 5.21 (*t*, *J* = 6.5, 1 H); 5.63 (*d*, *J* = 0.9, 1 H); 6.62 (*d*, *J* = 0.9, 1 H); 7.18–7.40 (*m*, 10 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 37.69; 42.61; 57.04; 68.45; 77.17; 126.42; 127.60; 128.22; 128.32; 128.37; 129.17; 129.49; 134.86; 137.65; 138.24; 152.64. MALDI-MS (DHB): 438.1 (6, [M + Na]$^+$), 416.2 (28, MH$^+$), 331.1 (21), 318.1 (17), 277.1 (100), 259.1 (19). MALDI-HR-MS (DHB): 416.1641 (MH$^+$, $C_{21}H_{26}N_3O_4S^+$; calc. 416.1639). Anal. calc. for $C_{21}H_{25}N_3O_4S$ (415.51): C 60.70, H 6.06, N 10.11; found C 60.86, H 6.12, N 10.04. X-Ray: see *Fig. 3*.

*(1*RS*)-1-[5-[(*SR*)-Methoxy(phenyl)methyl]-1*H*-imidazol-2-yl]-2-phenylethanol* ((±)-**17**). *GP 4*, starting from (±)-**13** (150 mg, 0.36 mmol), afforded (±)-**17** (68 mg, 61%) after purification by CC (SiO_2; AcOEt/MeOH 99:1). White solid. M.p. 108–109°. IR (KBr): 3620, 3018, 2894, 1950, 1520, 1473, 1423, 1334, 1215. ^{1}H-NMR (300 MHz, CD_3OD): 3.03 (*dd*, *J* = 13.7, 7.5, 1 H); 3.15 (*dd*, *J* = 13.7, 6.2, 1 H); 3.30 (*s*, 3 H); 4.92 (*dd*, *J* = 6.8, 5.9, 1 H); 5.25 (*s*, 1 H); 6.65 (*s*, 1 H); 7.05–7.38 (*m*, 10 H). ^{13}C-NMR (75 MHz, CD_3OD): 44.0; 56.7; 69.9; 80.3; 118.1; 127.0; 127.9; 128.4; 128.8; 128.9; 130.2; 138.5; 139.2; 141.6; 151.6. MALDI-MS (DHB): 331.1 (8, [M + Na]$^+$), 309.2 (8, MH$^+$), 277.1 (100). MALDI-HR-MS (DHB): 309.1601 (MH$^+$, $C_{19}H_{21}N_2O_2^+$; calc. 309.1598).

*(1*RS*)-1-[5-[(*RS*)-Methoxy(phenyl)methyl]-1*H*-imidazol-2-yl]-2-phenylethanol* ((±)-**18**). *GP 4*, starting from (±)-**14** (300 mg, 0.72 mmol), afforded (±)-**18** (173 mg, 78%) after purification by CC (SiO_2; AcOEt/MeOH 99:1). White solid. M.p. 132–133°. IR ($CHCl_3$): 3683, 3620, 3018, 2976, 2895, 1521, 1476, 1424, 1216, 1047, 929. ^{1}H-NMR (300 MHz, $CDCl_3$): 2.96 (*dd*, *J* = 13.7, 8.4, 1 H); 3.29 (*dd*, *J* = 13.7, 4.4, 1 H); 3.32 (*s*, 3 H); 4.96 (*dd*, *J* = 8.4, 4.4, 1 H); 5.24 (*s*, 1 H); 6.58 (*s*, 1 H); 7.13–7.39 (*m*, 10 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 44.0; 56.7; 70.0; 80.3; 126.9; 127.9; 128.3; 128.8; 128.9; 130.2; 138.6; 141.6; 151.6 (2 arom. signals overlapping). MALDI-MS (DHB): 331.1 (20, [M + Na]$^+$), 309.2 (12, MH$^+$), 277.1 (100). MALDI-HR-MS (DHB): 331.1420 ([M + Na]$^+$, $C_{19}H_{20}N_2NaO_2^+$; calc. 331.1417).

*2-[(*RS*)-Methoxy(phenyl)methyl]-*N,N*-dimethyl-5-(2-phenylethyl)-1*H*-imidazole-1-sulfonamide* ((±)-**19**). NaH (60%, 0.144 g, 3.78 mmol) was suspended in pentane (10 ml) and stirred for 10 min. The solvent was decanted, and the solid was dried under a stream of N_2. A soln. of (±)-**13** (1.00 g, 2.41 mmol) in dry THF (12 ml)

was added at 0°, and the mixture was stirred for 45 min at r.t. After addition of CS_2 (0.32 ml, 5.29 mmol), the soln. turned yellow and was stirred for 30 min, then MeI (0.64 ml, 10.20 mmol) was added, whereupon the soln. turned red and was stirred for an additional h at r.t. The reaction was quenched with H_2O, the mixture was extracted (CH_2Cl_2), and the org. phases were dried ($MgSO_4$) and concentrated *in vacuo*. The obtained intermediate (yellow oil) was dried overnight and then dissolved in PhH (12 ml). Bu_3SnH (0.99 ml, 3.61 mmol) and AIBN (cat. amount) were added, and the soln. was heated to reflux for 5 h. After addition of CH_2Cl_2, the mixture was concentrated *in vacuo*. Purification by CC (SiO_2; pentane/AcOEt 75:25) gave (±)-**19** (818 mg, 85%). Colorless oil. IR ($CHCl_3$): 3014, 1731, 1454, 1383, 1223, 1160, 1084, 970. ^{1}H-NMR (300 MHz, $CDCl_3$): 2.81 (*s*, 6 H); 3.04–3.29 (*m*, 4 H); 3.35 (*s*, 3 H); 5.65 (*s*, 1 H); 6.46 (*s*, 1 H); 7.17–7.40 (*m*, 10 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 31.0; 31.6; 34.1; 37.9; 56.9; 126.1; 127.6; 128.2; 128.3; 128.8; 134.8; 138.5; 141.0; 151.0 (2 arom. signals overlapping). MALDI-MS (DHB): 422.2 (8, $[M+Na]^+$); 400.2 (34, MH^+); 315.2 (13); 262.2 (17); 261.1 (100). MALDI-HR-MS (DHB): 400.1787 (MH^+, $C_{21}H_{26}N_3O_3S^+$; calc. 400.1689).

*2-[(*RS*)-Methoxy(phenyl)methyl]-5-(2-phenylethyl)-1*H*-imidazole* ((±)-**22**). *GP 4*, starting from (±)-**19** (406 mg, 1.02 mmol), afforded (±)-**22** (250 mg, 84%) after purification by CC (SiO_2; AcOEt/MeOH 99:1). Slightly yellow oil. IR ($CHCl_3$): 3452, 3020, 2976, 1521, 1454, 1424, 1208, 1086, 1047, 928. ^{1}H-NMR (300 MHz, $CDCl_3$): 2.98 (*s*, 4 H); 3.32 (*s*, 3 H); 5.23 (*s*, 1 H); 6.50 (*s*, 1 H); 7.09–7.37 (*m*, 10 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 30.5; 34.6; 56.8; 79.0; 126.2; 126.9; 127.7; 128.2; 128.4; 140.0; 140.6; 147.8 (3 arom. signals overlapping). MALDI-MS (DHB): 551.3 (14), 331.2 (4, $[M+K]^+$), 321.2 (20), 315.1 (8, $[M+Na]^+$), 293.2 (4, MH^+), 261.1 (100). MALDI-HR-MS (DHB): 293.1651 (MH^+, $C_{19}H_{21}N_2O^+$; calc. 293.1648).

*2-[(*RS*)-Methoxy(phenyl)methyl]-*N,N*-dimethyl-5-(phenylacetyl)-1*H*-imidazole-1-sulfonamide* ((±)-**23**). To a soln. of (±)-**13** (1.00 g, 2.41 mmol) in CH_2Cl_2 (50 ml), *Dess–Martin* periodinane (15% soln. in CH_2Cl_2, 7.83 ml, 3.61 mmol) was added, and the mixture was stirred for 2.5 h at r.t. The reaction was quenched with H_2O, the mixture was extracted (CH_2Cl_2), and the org. phases were dried ($MgSO_4$) and concentrated *in vacuo*. Purification by CC (SiO_2; pentane/AcOEt 67:33) gave (±)-**23** (470 mg, 47%). Colorless needles. M.p. 89°. IR ($CHCl_3$): 3019, 2975, 2896, 1653, 1616, 1521, 1424, 1222, 1046, 929. ^{1}H-NMR (300 MHz, $CDCl_3$): 2.91 (*s*, 6 H); 3.35 (*s*, 3 H); 4.30 (*d*, *J* = 15.5, 1 H); 4.38 (*d*, *J* = 15.5, 1 H); 5.73 (*s*, 1 H); 6.57 (*s*, 1 H); 7.24–7.39 (*m*, 10 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 38.6; 47.4; 57.0; 77.2; 126.9; 127.9; 128.4; 128.5; 129.5; 129.8; 133.5; 135.2; 138.0; 139.3; 146.8; 196.4. MALDI-MS (DHB): 436.1 (4, $[M+Na]^+$), 414.2 (3, MH^+), 356.2 (22), 275.1 (100), 273.0 (37). MALDI-HR-MS (DHB): 436.1305 ($[M+Na]^+$, $C_{21}H_{23}N_3NaO_4S^+$; calc.: 436.1307). Anal. calc. for $C_{21}H_{23}N_3O_4S$ (413.49): C 61.00, H 5.61, N 10.16; found C 60.82, H 5.68, N 10.00.

*2-(1-Benzylethenyl)-5-[(*RS*)-methoxy(phenyl)methyl]-*N,N*-dimethyl-1*H*-imidazole-1-sulfonamide* ((±)-**25**). To a soln. of (±)-**23** (75 mg, 0.18 mmol) in THF (1.5 ml) at −78°, *Tebbe* reagent (0.5M in PhMe, 0.43 ml, 0.22 mmol) was added dropwise under Ar. After stirring for 45 min at −78°, the mixture was warmed to −20° and stirred for 80 min. After cooling to −50°, the reaction was quenched with 10% aq. KOH soln., CH_2Cl_2 was added at r.t., the mixture was filtered over *Celite*, and the solvent was removed *in vacuo*. Purification by CC (SiO_2; pentane/AcOEt 75:25) afforded (±)-**25** (7 mg, 9%). Yellowish oil. IR ($CHCl_3$): 3034, 3022, 2935, 1708, 1454, 1390, 1218, 1085. ^{1}H-NMR (300 MHz, $CDCl_3$): 2.70 (*s*, 6 H); 3.36 (*s*, 3 H); 3.71 (*d*, *J* = 15.9, 1 H); 3.81 (*d*, *J* = 15.9, 1 H); 5.19 (*s*, 1 H); 5.39 (*s*, 1 H); 5.67 (*s*, 1 H); 6.56 (*s*, 1 H); 7.18–7.42 (*m*, 10 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 37.8; 42.6; 56.8; 77.2; 120.3; 126.3; 127.5; 128.1; 128.2; 129.2; 129.5; 135.1; 137.8; 138.4; 140.6; 150.5 (1 arom. signal overlapping). MALDI-MS (DHB): 434.2 (3, $[M+Na]^+$), 412.2 (21, MH^+), 379.2 (28), 173.1 (100). MALDI-HR-MS (DHB): 412.1686 (MH^+, $C_{22}H_{26}N_3O_3S^+$; calc.: 412.1689).

*2-(1-Benzylethenyl)-*N,N*-dimethyl-1*H*-imidazole-1-sulfonamide* (**30**). A mixture of **27** (2.10 g, 10.66 mmol), **26** (8.36 g, 18 mmol), $[PdCl_2(PPh_3)_2]$ (748 mg, 1.06 mmol), and Ag_2O (2.47 g, 10.66 mmol) in DMF (25 ml) was degassed in the ultrasonic bath for 30 min under Ar. The mixture was the stirred for 2 d in a sealed tube at 100°. The solvent was removed *in vacuo*. The residue was suspended in CH_2Cl_2 and filtered over *Celite*. Purification by CC (SiO_2; pentane/AcOEt 67:33, then AcOEt) gave **30** (2.36 g, 76%). Yellow oil. IR ($CHCl_3$): 3162, 2970, 2475, 1948, 1863, 1721, 1602, 1529, 1496, 1454, 1420, 1393, 1281, 1178. ^{1}H-NMR (300 MHz, $CDCl_3$): 2.58 (*s*, 6 H); 3.84 (*s*, 2 H); 5.37 (*d*, *J* = 0.9, 1 H); 5.58 (*d*, *J* = 0.9, 1 H); 7.01 (*d*, *J* = 1.6, 1 H); 7.17–7.28 (*m*, 6 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 37.9; 42.9; 121.0; 121.2; 126.3; 127.3; 128.3; 129.4; 138.3; 139.1; 147.8. MALDI-MS (DHB): 314.1 (12, $[M+Na]^+$), 301.2 (12), 292.1 (60, MH^+), 273.0 (100). MALDI-HR-MS (DHB): 314.0941 ($[M+Na]^+$, $C_{14}H_{17}N_3NaO_2S^+$; calc. 314.0939).

*2-[(*E*)-1-Formyl-2-phenylethenyl]-*N,N*-dimethyl-1*H*-imidazole-1-sulfonamide* (**31**). A mixture of **29** (1.50 g, 6.23 mmol), **26** (3.25 g, 7 mmol), $[PdCl_2(PPh_3)_2]$ (490 mg, 0.71 mmol), and Ag_2O (1.62 g, 7.00 mmol) in DMF (25 ml) was degassed in the ultrasonic bath for 30 min under Ar. The mixture was the stirred for 2 d in a sealed tube at 100°. The solvent was removed *in vacuo*. The residue was suspended in CH_2Cl_2 and filtered over *Celite*. Purification by CC (SiO_2; pentane/AcOEt 67:33, then AcOEt) gave **31** (951 mg, 50%). Colorless

crystals. M.p. 131–132°. IR ($CHCl_3$): 3156, 2987, 2831, 2253, 1794, 1688, 1631, 1394, 1176. ^{1}H-NMR (300 MHz, $CDCl_3$): 2.72 (*s*, 6 H); 7.09 (*d*, *J* = 1.3, 1 H); 7.11–7.36 (*m*, 5 H); 7.43 (*d*, *J* = 1.3, 1 H); 7.70 (*s*, 1 H); 9.73 (*s*, 1 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 38.1; 120.1; 128.9; 129.5; 130.5; 131.5; 121.7; 132.8; 140.2; 154.1; 191.8. MALDI-MS (DHB): 328.1 (28.4, $[M + Na]^+$), 306.1 (88, MH^+), 273.0 (100). MALDI-HR-MS (DHB): 306.0908 (MH^+, $C_{14}H_{16}N_3O_3S^+$; calc. 306.0907).

S-*((2*RS*)-2-[1-[(Dimethylamino)sulfonyl]-1*H*-imidazol-2-yl]-3-phenylpropyl) Ethanethioate* ((±)-**32**). To a soln. of **30** (291 mg, 1.00 mmol) in PhH (2 ml), AIBN (20 mg, 0.13 mmol) and freshly distilled AcSH (0.26 ml, 5.00 mmol) were added. The mixture was heated to reflux for 4 h. The solvent was removed *in vacuo*, and purification by CC (SiO_2; pentane/AcOEt 67:33, then AcOEt) afforded (±)-**32** (365 mg, 99%). Colorless oil. IR ($CHCl_3$): 3020, 1948, 1883, 1709, 1690, 1607, 1535, 1455, 1419, 1392, 1276, 1179, 1150, 1104. ^{1}H-NMR (300 MHz, $CDCl_3$): 2.27 (*s*, 3 H); 2.61 (*s*, 6 H); 2.93 (*dd*, *J* = 13.7, 6.7, 1 H); 3.22 (*dd*, *J* = 13.4, 8.4, 1 H); 3.31 (*dd*, *J* = 13.7, 8.4, 1 H); 3.36 (*dd*, *J* = 13.4, 5.6, 1 H); 3.81 (*m*, 1 H); 7.03 (*d*, *J* = 1.6, 1 H); 7.12–7.24 (*m*, 6 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 30.6; 33.3; 37.7; 40.3; 40.7; 119.6; 126.4; 127.4; 128.2; 129.2; 138.7; 149.9; 195.1. MALDI-MS (DHB): 390.1 (25, $[M + Na]^+$), 368.1 (100, MH^+). MALDI-HR-MS (DHB): 368.1100 (MH^+, $C_{16}H_{22}N_3O_3S_2^+$; calc. 368.1103).

*2-(1-Benzylethenyl)-5-[(*RS*)-hydroxy(phenyl)methyl]-*N,N*-dimethyl-1*H*-imidazole-1-sulfonamide* ((±)-**33**). *GP 2*, starting from **30** (291 mg, 1.0 mmol) and PhCHO, afforded (±)-**33** (125 mg, 31%) after purification by CC (SiO_2; pentane/AcOEt 60:40). Colorless oil. IR ($CHCl_3$): 3017, 2927, 2854, 1683, 1602, 1495, 1455, 1362, 1262, 1160, 1011, 959. ^{1}H-NMR (300 MHz, $CDCl_3$): 2.68 (*s*, 6 H); 3.33 (br. *s*, 1 H); 3.75 (*d*, *J* = 16.0, 1 H); 3.82 (*d*, *J* = 16.0, 1 H); 5.27 (*d*, *J* = 0.9, 1 H); 5.45 (*d*, *J* = 0.9, 1 H); 6.12 (*s*, 1 H); 6.48 (*s*, 1 H); 7.18–7.45 (*m*, 10 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 37.8; 42.7; 67.8; 120.7; 126.5; 127.9; 128.1; 128.2; 129.4; 129.5; 137.1; 137.8; 140.2; 150.5 (1 arom. signal overlapping). MALDI-MS (DHB): 427.3 (51), 420.1 (4, $[M + Na]^+$), 398.2 (27, MH^+), 380.1 (6), 313.1 (8), 291.2 (24), 273.1 (100). MALDI-HR-MS (DHB): 398.1540 (MH^+, $C_{21}H_{24}N_3O_3S^+$; calc. 398.1538).

*2-[(1*RS*)-1-Benzyl-2-hydroxyethyl]-*N,N*-dimethyl-1*H*-imidazole-1-sulfonamide* ((±)-**35**). To a suspension of **31** (500 mg, 1.64 mmol) in PhH (15 ml), AcOH (0.8 ml, 13.10 mmol) and $[Pd(PPh_3)_4]$ (18.5 mg, 0.016 mmol) were added. Subsequently, Bu_3SnH (0.83 ml, 3.36 mmol) was added dropwise, and the mixture was stirred for 14 h at r.t. After addition of CH_2Cl_2, the mixture was poured into ice-H_2O and neutralized with $NaHCO_3$. The org. phase was washed with sat. aq. NaCl soln., and the combined aq. phases were extracted (CH_2Cl_2). The combined org. phases were dried ($MgSO_4$) and concentrated *in vacuo*. Purification by CC (SiO_2; AcOEt) afforded (±)-**35** (412 mg, 82%). Slightly yellow oil. IR ($CHCl_3$): 3607, 3402, 3019, 2929, 2857, 1472, 1391, 1207, 899. ^{1}H-NMR (300 MHz, $CDCl_3$): 2.73 (*s*, 6 H); 3.01 (*dd*, *J* = 13.1, 9.0, 1 H); 3.18 (*dd*, *J* = 13.1, 5.9, 1 H); 3.48 (br. *s*, 1 H); 3.60–3.67 (*m*, 1 H); 3.81 (*s*, 2 H); 7.02 (*d*, *J* = 1.6, 1 H); 7.15–7.27 (*m*, 6 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 37.3; 38.0; 42.5; 63.2; 119.4; 126.2; 127.2; 128.3; 128.9; 129.2; 139.3. MALDI-MS (DHB): 332.1 (16, $[M + Na]^+$), 310.1 (100, MH^+), 279.1 (27). MALDI-HR-MS (DHB): 310.1215 (MH^+, $C_{14}H_{20}N_3O_3S^+$; calc. 310.1220).

*2-((1*RS*)-1-Benzyl-2-{[(*tert*-butyl)(dimethyl)silyl]oxy}ethyl)-*N,N*-dimethyl-1*H*-imidazole-1-sulfonamide* ((±)-**36**). *GP 1*, starting from (±)-**35** (620 mg, 2.00 mmol), afforded (±)-**36** (673 mg, 79%) after purification by CC (SiO_2; pentane/AcOEt 25:75). Slightly yellow oil. IR ($CHCl_3$): 3019, 2929, 2857, 1472, 1391, 1207, 899. ^{1}H-NMR (300 MHz, $CDCl_3$): −0.01 (*s*, 3 H); −0.07 (*s*, 3 H); 0.85 (*s*, 9 H); 2.51 (*s*, 6 H); 3.06 (*dd*, *J* = 13.1, 5.0, 1 H); 3.18 (*dd*, *J* = 13.1, 8.1, 1 H); 3.66–3.76 (*m*, 2 H); 3.93–4.00 (*m*, 1 H); 7.03 (*d*, *J* = 1.9, 1 H); 7.12–7.18 (*m*, 6 H). ^{13}C-NMR (75 MHz, $CDCl_3$): −5.3; 25.8; 26.0; 37.3; 37.7; 44.3; 65.9; 119.7; 126.0; 127.2; 128.1; 129.2; 140.2; 149.7. MALDI-MS (DHB): 446.2 (17, $[M + Na]^+$), 424.2 (100, MH^+), 360.2 (13), 317.2 (32). MALDI-HR-MS (DHB): 424.2074 (MH^+, $C_{20}H_{34}N_3O_3SSi^+$; calc. 424.2085).

*2-((1*RS*)-1-Benzyl-2-{[(*tert*-butyl)(dimethyl)silyl]oxy}ethyl)-5-[(*SR*)-hydroxy(phenyl)methyl]-*N,N*-dimethyl-1*H*-imidazole-1-sulfonamide* ((±)-**37**) *and 2-((1*RS*)-1-Benzyl-2-{[(*tert*-butyl)(dimethyl)silyl]oxy}ethyl)-5-[(*RS*)-hydroxy(phenyl)methyl]-*N,N*-dimethyl-1*H*-imidazole-1-sulfonamide* ((±)-**38**). *GP 2*, starting from (±)-**36** (460 mg, 1.09 mmol), afforded a mixture of diastereoisomers (±)-**37** and (±)-**38** (ratio *ca.* 2:1, total 490 mg, 85%) after purification by CC (SiO_2; pentane/AcOEt 75:25). Colorless crystals. M.p. 142–143°. IR ($CHCl_3$): 3688, 3587, 3029, 2959, 2928, 2857, 1603, 1495, 1454, 1261, 1101. ^{1}H-NMR (300 MHz, $CDCl_3$): −0.01 (*s*, 3 H); 0.01 (*s*, 3 H); 0.03 (*s*, 3 H); 0.04 (*s*, 3 H); 0.85 (*s*, 9 H); 0.88 (*s*, 9 H); 2.41 (*s*, 6 H); 2.54 (*s*, 6 H); 3.02–3.23 (*m*, 3 H + 3 H); 3.61–3.74 (*m*, 2 H + 2 H); 3.94–4.01 (*m*, 1 H + 1 H); 6.02–6.07 (*m*, 1 H + 1 H); 6.48 (*s*, 1 H); 6.54 (*s*, 1 H); 7.11–7.42 (*m*, 10 H + 10 H). ^{13}C-NMR (75 MHz, $CDCl_3$): −5.2; 18.4; 26.0; 37.1; 37.3; 37.7; 44.9; 45.2; 65.8; 66.1; 67.6; 67.9; 125.9; 126.6; 126.7; 127.9; 128.1; 128.2; 129.0; 129.1; 129.2; 136.5; 140.3; 140.5; 144.1; 151.2; 152.3; 155.0 (4 aliph. and 6 arom. signals overlapping). MALDI-MS (DHB): 532.5 (2, $[M + Na]^+$), 530.3 (21, MH^+), 445.2 (11), 123.3 (17), 406.4 (29), 44 (100). MALDI-HR-MS (DHB): 530.2492 (MH^+,

$C_{27}H_{40}N_3O_4SSi^+$; calc. 530.2503). Anal. calc. for $C_{27}H_{39}N_3O_4SSi$ (529.77): C 61.21, H 7.42, N 7.93; found C 61.11, H 7.57, N 7.97.

*2-((1*RS*)-1-Benzyl-2-{[(*tert*-butyl)(dimethyl)silyl]oxy}ethyl)-5-[(*SR*)-methoxy(phenyl)methyl]-*N,N*-dimethyl-1*H*-imidazole-1-sulfonamide* ((±)-**39**) *and 2-((1*RS*)-1-Benzyl-2-{[(*tert*-butyl)(dimethyl)silyl]oxy}ethyl)-5-[(*RS*)-methoxy(phenyl)methyl]-*N,N*-dimethyl-1*H*-imidazole-1-sulfonamide* ((±)-**40**). *GP 5*, starting from a mixture of (±)-**37** and (±)-**38** (ratio *ca.* 2:1, 490 mg, 0.93 mmol), afforded a mixture of (±)-**39** and (±)-**40** (ratio *ca.* 2:1, 492 mg, 98%). Yellow oil. IR ($CHCl_3$): 3020, 2955, 2930, 2857, 1454, 1382, 1216, 1102. ^{1}H-NMR (300 MHz, $CDCl_3$): −0.01 (*s*, 6 H); 0.02 (*s*, 6 H); 0.85 (*s*, 9 H); 0.87 (*s*, 9 H); 2.44 (*s*, 6 H); 2.47 (*s*, 6 H); 2.95–3.24 (*m*, 2 H + 2 H); 3.30 (*s*, 3 H); 3.35 (*s*, 3 H); 3.56–3.77 (*m*, 2 H + 2 H); 3.89–4.03 (*m*, 1 H + 1 H); 5.60 (*s*, 1 H,); 5.60 (*s*, 1 H); 6.47 (*d*, *J* = 0.9, 1 H); 6.63 (*d*, *J* = 0.9, 1 H); 7.01–7.49 (*m*, 10 H + 10 H). ^{13}C-NMR (75 MHz, $CDCl_3$): −5.2; 18.3; 25.7; 25.9; 37.0; 37.2; 37.9; 44.8; 45.3; 56.8; 57.0; 65.8; 66.0; 67.3; 125.9; 127.6; 127.8; 128.0; 128.1; 128.2; 128.6; 129.0; 129.1; 129.2; 134.2; 134.6; 138.6; 138.9; 140.2; 140.7; 151.8; 152.4 (4 arom. and 4 aliph. signals overlapping). MALDI-MS (DHB): 544.3 (13, *M*H$^+$), 465.3 (11), 419.3 (27), 406.3 (28), 405.2 (100). MALDI-HR-MS (DHB): 544.2667 (*M*H$^+$, $C_{28}H_{42}N_3O_4SSi^+$; calc. 544.2660).

*2-[(1*RS*)-1-Benzyl-2-hydroxyethyl]-5-[(*SR*)-methoxy(phenyl)methyl]-*N,N*-dimethyl-1*H*-imidazole-1-sulfonamide* ((±)-**20**) *and 2-[(1*RS*)-1-Benzyl-2-hydroxyethyl]-5-[(*RS*)-methoxy(phenyl)methyl]-*N,N*-dimethyl-1*H*-imidazole-1-sulfonamide* ((±)-**21**). *GP 3*, starting from a mixture of (±)-**39** and (±)-**40** (ratio *ca.* 2:1, 450 mg, 0.83 mmol), afforded (±)-**20** (220 mg, 62%) and (±)-**21** (123 mg, 35%) after purification and separation by CC (SiO_2; pentane/AcOEt 50:50).

*Data of (±)-***20**: Colorless crystals. M.p. 127–128°. IR ($CHCl_3$): 3402, 3010, 2933, 1454, 1387, 1161, 1085. ^{1}H-NMR (300 MHz, $CDCl_3$): 2.77 (*d*, *J* = 0.9, 6 H); 2.96 (*dd*, *J* = 13.1, 9.7, 1 H); 3.13 (*dd*, *J* = 13.1, 5.0, 1 H); 3.35 (*s*, 3 H); 3.51–3.57 (*m*, 1 H); 3.68–3.79 (*m*, 2 H); 5.65 (*s*, 1 H); 6.48 (*s*, 1 H); 7.15–7.40 (*m*, 10 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 37.4; 37.8; 43.0; 56.9; 62.7; 126.2; 127.6; 128.2; 128.3; 129.0; 129.2; 134.4; 138.4; 139.4; 153.6 (1 aliph. signal under solvent peak, 1 arom. signal overlapping). MALDI-MS (DHB): 452.2 (25, [*M* + Na$^+$]), 430.2 (72, *M*H$^+$), 345.2 (16), 291.2 (100), 273.0 (11). MALDI-HR-MS (DHB): 430.1797 (*M*H$^+$, $C_{22}H_{28}N_3O_4S^+$; calc. 430.1801).

*Data of (±)-***21**: Colorless crystals. M.p. 126–127°. IR ($CHCl_3$): 3421, 3031, 2933, 1454, 1381, 1162, 1086. ^{1}H-NMR (300 MHz, $CDCl_3$): 2.60 (*s*, 6 H); 3.02 (*dd*, *J* = 13.2, 7.6, 1 H); 3.22 (*dd*, *J* = 13.2, 7.0, 1 H); 3.32 (*s*, 3 H); 3.58–3.63 (*m*, 1 H); 3.76–3.84 (*m*, 2 H); 5.62 (*d*, *J* = 0.9, 1 H); 6.47 (*d*, *J* = 0.9, 1 H); 7.16–7.41 (*m*, 10 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 37.4; 37.5; 43.2; 56.9; 63.7; 77.0; 126.2; 127.6; 128.2; 128.3; 128.3; 129.1; 129.1; 134.7; 138.3; 139.6; 153.1. MALDI-MS (DHB): 452.2 (25, [*M* + Na]$^+$), 430.2 (64, *M*H$^+$), 345.2 (15), 291.2 (100), 273.0 (10). MALDI-HR-MS (DHB): 430.1793 (*M*H$^+$, $C_{22}H_{28}N_3O_4S^+$; calc. 430.1801).

S-*((2*RS*)-2-[1-[(Dimethylamino)sulfonyl]-5-[(*SR*)-methoxy(phenyl)methyl]-1*H*-imidazol-2-yl]-3-phenylpropyl) Ethanethioate* ((±)-**41**). *GP 6*, starting from (±)-**20** (100 mg, 0.23 mmol), afforded (±)-**41** (109 mg, 95%) after purification by CC (SiO_2; CH_2Cl_2/AcOEt 83:17). Colorless crystals. M.p. 119–120°. IR ($CHCl_3$): 3014, 2935, 2825, 1727, 1690, 1456, 1380, 1221, 1159. ^{1}H-NMR (300 MHz, $CDCl_3$): 2.25 (*s*, 3 H); 2.63 (*s*, 6 H); 2.80 (*dd*, *J* = 13.1, 7.8, 1 H); 3.25–3.32 (*m*, 3 H); 3.36 (*s*, 3 H); 3.72–3.76 (*m*, 1 H); 5.63 (*s*, 1 H); 6.57 (*s*, 1 H); 7.14–7.36 (*m*, 10 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 30.6; 32.9; 37.4; 41.0; 41.3; 57.0; 126.3; 127.6; 128.2; 128.2; 129.2; 124.5; 128.6; 138.6; 138.7; 152.7; 195.1 (1 aliph. and 1 arom. signal overlapping). MALDI-MS (DHB): 210.2 (40, [*M* + Na]$^+$), 488.2 (53, *M*H$^+$), 403.2 (26), 273.1 (100). MALDI-HR-MS (DHB): 488.1667 (*M*H$^+$, $C_{24}H_{30}N_3O_4S_2^+$; calc. 488.1672). Anal. calc. for $C_{24}H_{29}N_3O_4S_2$ (487.64): C 59.11, H 5.99, N 8.62; found C 59.16, H 6.13, N 8.65. X-Ray: see *Fig. 4*.

S-*((2*RS*)-2-[1-[(Dimethylamino)sulfonyl]-5-[(*SR*)-methoxy(phenyl)methyl]-1*H*-imidazol-2-yl]-3-phenylpropyl) Ethanethioate* ((±)-**42**). *GP 6*, starting from (±)-**21** (90 mg, 0.210 mmol), afforded (±)-**42** (95 mg, 93%) after purification by CC (SiO_2; pentane/AcOEt 50:50). Slightly yellow oil. IR ($CHCl_3$): 3014, 2933, 2826, 1952, 1727, 1690, 1454, 1381, 1217, 1161. ^{1}H-NMR (300 MHz, $CDCl_3$): 2.27 (*s*, 3 H); 2.51 (*s*, 6 H); 2.90 (*dd*, *J* = 13.4, 6.2, 1 H); 3.14–3.36 (*m*, 3 H); 3.31 (*s*, 3 H); 3.70–3.77 (*m*, 1 H); 5.61 (*s*, 1 H); 6.51 (*s*, 1 H); 7.12–7.42 (*m*, 10 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 30.6; 33.6; 37.2; 40.4; 41.1; 56.7; 76.7; 126.3; 127.3; 128.1; 128.2; 129.2; 134.8; 138.5; 139.1; 152.4; 195.0 (2 arom. signals overlapping). MALDI-MS (DHB): 510.1 (28, [*M* + Na]$^+$), 488.2 (55, *M*H$^+$), 350.1 (21), 349.1 (100). MALDI-HR-MS (DHB): 488.1660 (*M*H$^+$, $C_{24}H_{30}N_3O_4S_2^+$; calc. 488.1672).

*(2*RS*)-2-[5-[(*SR*)-Methoxy(phenyl)methyl]-1*H*-imidazol-2-yl]-3-phenylpropan-1-ol* ((±)-**44**). *GP 4*, starting from (±)-**20** (90 mg, 0.21 mmol), afforded (±)-**44** (55 mg, 82%) after purification by CC (SiO_2; AcOEt/MeOH 95:5). Colorless oil. IR ($CHCl_3$): 3440, 3007, 2932, 1951, 1813, 1720, 1603, 1583, 1496, 1454, 1085. ^{1}H-NMR (300 MHz, $CDCl_3$): 2.91 (*dd*, *J* = 13.4, 8.4, 1 H); 3.01 (*dd*, *J* = 13.4, 7.2, 1 H); 3.04–3.13 (*m*, 1 H); 3.29 (*s*, 3 H); 3.70 (*dd*, *J* = 10.9, 5.6, 1 H); 3.76 (*dd*, *J* = 10.9, 3.7, 1 H); 5.22 (*s*, 1 H); 6.46 (*s*, 1 H); 7.03–7.37 (*m*, 10 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 37.4; 42.8; 56.9; 63.3; 79.4; 126.5; 127.3; 128.0; 128.6; 128.7; 129.2; 139.5; 140.3;

150.4 (2 arom. signals overlapping). MALDI-MS (DHB): 345.2 (10, $[M + Na]^+$), 323.2 (12, MH^+), 291.2 (100). MALDI-HR-MS (DHB): 323.1753 (MH^+, $C_{20}H_{23}N_2O_2^+$; calc. 323.1760).

*2-[(1*RS*)-1-Benzyl-2-sulfanylethyl]-5-[(*SR*)-methoxy(phenyl)methyl]-1*H*-imidazol-3-ium Chloride* ((±)-**1**). A suspension of MeONa (108 mg, 2.00 mmol) in MeOH (10 ml) was degassed in an ultrasonic bath for 30 min under Ar and for 10 min under H_2. A soln. of (±)-**41** (100 mg, 0.20 mmol) in MeOH (10 ml), degassed for 30 min under Ar, was added to the suspension, and the mixture was stirred for 75 min at r.t. CF_3COOH (0.46 ml, 6.00 mmol) was added, and stirring was continued for 105 min. After addition of CH_2Cl_2 (80 ml), the mixture was washed with dil. aq. $NaHCO_3$ soln. The aq. phases were extracted (CH_2Cl_2), and the combined org. phases were dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by CC (SiO_2; AcOEt/MeOH 99:1), the resulting product was dissolved in 0.1% methanolic HCl soln., and the solvent was removed *in vacuo*. The residue was purified 3 times by reversed-phase CC (*RP-18* SiO_2; 0.1% aq. HCl soln./MeCN 67:33) to give (±)-**1** (31 mg, 41%). Colorless oil. IR ($CHCl_3$): 2958, 2868, 2728, 2638, 1729, 1635, 1604, 1493, 1454, 1379. ^{1}H-NMR (500 MHz, $CDCl_3$): 1.55 (br. *s*, 1 H); 2.91 (*dd*, *J* = 13.7, 4.9, 1 H); 3.12–3.16 (*m*, 1 H); 3.19 (*dd*, *J* = 13.8, 8.2, 1 H); 3.27 (*s*, 3 H); 3.32 (*dd*, *J* = 13.8, 7.9, 1 H); 3.89–3.95 (*m*, 1 H); 5.34 (*s*, 1 H); 6.60 (*s*, 1 H); 7.08–7.16 (*m*, 5 H); 7.29–7.34 (*m*, 5 H); 14.40 (br. *s*, 2 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 27.1; 39.0; 43.6; 57.1; 76.3; 115.6; 126.9; 127.1; 128.7; 128.8; 128.9; 128.9; 134.5; 136.9; 137.4; 149.0. MALDI-MS (DHB): 361.1 (5, $[M + Na]^+$), 339.2 (15, MH^+), 321.1 (13), 307.1 (100). MALDI-HR-MS (DHB): 339.1523 (MH^+, $C_{20}H_{23}N_2OS^+$; calc. 339.1526).

*2-[(1*RS*)-1-Benzyl-2-sulfanylethyl]-5-[(*RS*)-methoxy(phenyl)methyl]-1*H*-imidazol-3-ium Chloride* ((±)-**43**). Analogous procedure as for (±)-**1**, starting from (±)-**42** (70 mg, 0.14 mmol), afforded (±)-**43** (23 mg, 43%). Colorless oil. IR ($CHCl_3$): 2958, 2868, 2728, 2639, 1729, 1634, 1603, 1494, 1455, 1379. ^{1}H-NMR (500 MHz, $CDCl_3$): 1.56 (br. *s*, 1 H); 2.91 (*dd*, *J* = 14.0, 5.0, 1 H); 3.10–3.15 (*m*, 1 H); 3.17 (*dd*, *J* = 13.8, 8.0, 1 H); 3.26 (*s*, 3 H); 3.29 (*dd*, *J* = 13.8, 6.1, 1 H); 3.86–3.92 (*m*, 1 H); 5.36 (*s*, 1 H); 6.62 (*s*, 1 H); 7.08–7.17 (*m*, 5 H); 7.30–7.35 (*m*, 5 H); 14.40 (br. *s*, 2 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 27.0; 39.0; 43.6; 57.1; 76.4; 115.5; 126.9; 127.1; 128.7; 128.8; 128.9; 128.9; 134.5; 136.7; 137.5; 148.9. MALDI-MS (DHB): 361.1 (11, $[M + Na]^+$), 341.1 (19), 339.2 (17, MH^+), 321.1 (7), 307.1 (100). MALDI-HR-MS (DHB): 361.1344 ($[M + Na]^+$, $C_{20}H_{22}N_2NaOS^+$; calc. 361.1351).

*2-((1*RS*)-1-Benzyl-2-{[(*tert*-butyl)(dimethyl)silyl]oxy}ethyl)-5-[(*SR*)-hydroxy(naphthalen-2-yl)methyl]-*N,N*-dimethyl-1*H*-imidazole-1-sulfonamide ((±)-**47**) and 2-((1*RS*)-1-Benzyl-2-{[(*tert*-butyl)(dimethyl)silyl]oxy}-ethyl)-5-[(*RS*)-hydroxy(naphthalen-2-yl)methyl]-N,N-dimethyl-1*H*-imidazole-1-sulfonamide ((±)-**48**)*. *GP 2*, starting from (±)-**36** (0.500 g, 1.180 mmol) and naphthalene-2-carbaldehyde, afforded (±)-**47** (269 mg, 39%), (±)-**48** (157 mg, 23%), and a mixture of (±)-**47** and (±)-**48** (231 mg, 34%) after purification by CC (SiO_2; pentane/AcOEt 84:16).

*Data of (±)-***47**: White solid. M.p. 160–161°. IR ($CHCl_3$): 3590, 3062, 2956, 2930, 2885, 2857, 1720, 1603, 1568, 1509, 1495, 1472, 1463, 1454, 1418, 1377. ^{1}H-NMR (300 MHz, $CDCl_3$): −0.01 (*s*, 3 H); 0.01 (*s*, 3 H); 0.90 (*t*, *J* = 2.8, 9 H); 2.43 (*s*, 6 H); 3.10 (*dd*, *J* = 13.1, 4.8, 1 H); 3.20 (*dd*, *J* = 13.1, 8.4, 1 H); 3.33 (*d*, *J* = 4.9, 1 H); 3.62–3.77 (*m*, 2 H); 3.92–4.00 (*m*, 1 H); 6.20 (*d*, *J* = 4.9, 1 H); 6.54 (*d*, *J* = 0.6, 1 H); 7.09–7.23 (*m*, 5 H); 7.42–7.54 (*m*, 3 H); 7.83–7.91 (*m*, 4 H). ^{13}C-NMR (75 MHz, $CDCl_3$): −5.2; 18.4; 26.0; 37.2; 37.3; 45.2; 66.1; 68.0; 124.9; 125.6; 126.0; 126.1; 126.2; 127.6; 127.9; 128.0; 128.1; 129.1; 129.2; 133.0; 133.0; 136.4; 137.8; 140.5; 152.3. MALDI-MS (DHB): 602.3 (26, $[M + Na]^+$), 580.3 (25, MH^+), 562.3 (10), 495.3 (22), 473.3 (8), 455.3 (100). MALDI-HR-MS (DHB): 580.2665 (MH^+, $C_{31}H_{42}N_3O_4SSi^+$; calc. 580.2660). Anal. calc. for $C_{31}H_{41}N_3O_4SSi$ (579.83): C 64.22, H 7.13, N 7.25; found C 64.18, H 7.29, N 7.38.

*Data of (±)-***48**: White solid. M.p. 163–164°. IR ($CHCl_3$): 3590, 3062, 2956, 2929, 2885, 2857, 1720, 1603, 1568, 1509, 1495, 1472, 1463, 1454, 1418, 1375. ^{1}H-NMR (300 MHz, $CDCl_3$): 0.04 (*s*, 3 H); 0.05 (*s*, 3 H); 0.84 (*t*, *J* = 2.9, 9 H); 2.56 (*s*, 6 H); 3.03 (*dd*, *J* = 13.2, 5.5, 1 H); 3.16 (*dd*, *J* = 13.2, 7.6, 1 H); 3.33 (*d*, *J* = 5.0, 1 H); 3.64–3.72 (*m*, 2 H); 3.91–3.97 (*m*, 1 H); 6.24 (*d*, *J* = 5.0, 1 H); 6.47 (*d*, *J* = 0.6, 1 H); 7.12–7.25 (*m*, 5 H); 7.42–7.52 (*m*, 3 H); 7.82–7.87 (*m*, 3 H); 7.96 (*s*, 1 H). ^{13}C-NMR (75 MHz, $CDCl_3$): −5.2; 18.4; 26.0; 37.4; 37.7; 45.0; 65.8; 67.6; 124.8; 125.3; 126.1; 126.2; 127.6; 127.8; 128.1; 128.2; 129.2; 129.3; 132.9; 133.0; 136.4; 137.7; 140.2; 152.5 (1 arom. signal overlapping). MALDI-MS (DHB): 580.3 (1, MH^+), 562.3 (6), 455.3 (100). MALDI-HR-MS (DHB): 580.2668 (MH^+, $C_{31}H_{42}N_3O_4SSi^+$; calc. 580.2660).

*2-((1*RS*)-1-Benzyl-2-{[(*tert*-butyl)(dimethyl)silyl]oxy}ethyl)-5-[(*SR*)-methoxy(naphthalen-2-yl)methyl]-N,N-dimethyl-1*H*-imidazole-1-sulfonamide* ((±)-**49**). *GP 5*, starting from (±)-**47** (269 mg, 0.464 mmol), afforded (±)-*49* (260 mg, 94%) after purification by CC (SiO_2; pentane/AcOEt 80:20). Colorless oil. IR ($CHCl_3$): 3687, 3062, 3022, 3019, 3016, 2955, 2929, 2857, 1603, 1496, 1472, 1463, 1454, 1419. ^{1}H-NMR (300 MHz, $CDCl_3$): −0.02 (*s*, 3 H); 0.01 (*s*, 3 H); 0.84 (*t*, *J* = 3.0, 9 H); 2.52 (*s*, 6 H); 2.96 (*dd*, *J* = 13.1, 6.1, 1 H); 3.14 (*dd*, *J* = 13.1, 7.2, 1 H); 3.38 (*s*, 3 H); 3.65–3.74 (*m*, 2 H); 3.98–4.02 (*m*, 1 H); 5.78 (*s*, 1 H); 6.63 (*d*, *J* = 0.9, 1 H); 7.09–7.21 (*m*, 5 H); 7.45–7.53 (*m*, 3 H); 7.81–7.86 (*m*, 4 H). ^{13}C-NMR (75 MHz, $CDCl_3$): −5.2; 18.4; 26.0; 37.4;

37.9; 44.8; 57.1; 65.7; 77.2; 125.5; 125.9; 126.1; 126.9; 127.6; 127.9; 128.1; 128.9; 129.1; 132.9; 133.1; 134.2; 136.3; 140.2; 152.5 (2 arom. signals overlapping). MALDI-MS (DHB): 616.3 (3, $[M + Na]^+$), 594.3 (19, MH$^+$), 455.3 (100). MALDI-HR-MS (DHB): 594.2823 (MH$^+$, $C_{32}H_{44}N_3O_4SSi^+$; calc. 594.2816).

*2-((1*RS*)-1-Benzyl-2-{[(*tert*-butyl)(dimethyl)silyl]oxy}ethyl)-5-[(*SR*)-methoxy(naphthalen-2-yl)methyl]-*N,N*-dimethyl-1*H*-imidazole-1-sulfonamide* ((±)-**50**). *GP 5*, starting from (±)-**48** (150 mg, 0.259 mmol), afforded (±)-**50** (149 mg, 97%) after purification by CC (SiO_2; pentane/AcOEt 80:20). Colorless solid. IR ($CHCl_3$): 3687, 3062, 3022, 3016, 2955, 2929, 2857, 1603, 1496, 1472, 1463, 1454, 1419, 1381. ^{1}H-NMR (300 MHz, $CDCl_3$): 0.00 (*s*, 6 H); 0.84 (*t*, *J* = 3.0, 9 H); 2.45 (*s*, 6 H); 3.17–3.21 (*m*, 2 H); 3.33 (*s*, 3 H); 3.57–3.66 (*m*, 2 H); 3.89–3.94 (*m*, 1 H); 5.78 (*s*, 1 H); 6.49 (*d*, *J* = 0.9, 1 H); 7.07–7.25 (*m*, 5 H); 7.48–7.53 (*m*, 3 H); 7.83–7.88 (*m*, 4 H). ^{13}C-NMR (75 MHz, $CDCl_3$): −5.2; 18.3; 26.0; 37.1; 45.5; 56.9; 66.0; 125.5; 125.9; 126.1; 126.6; 127.6; 128.0; 128.1; 128.2; 129.3; 133.1; 133.2; 134.6; 136.1; 140.8; 151.9 (2 aliph. and 2 arom. signals overlapping). MALDI-MS (DHB): 616.3 (3, $[M + Na]^+$), 594.3 (19, MH$^+$), 455.3 (100). MALDI-HR-MS (DHB): 594.2823 (MH$^+$, $C_{32}H_{44}N_3O_4SSi^+$; calc. 594.2816).

*2-[(1*RS*)-1-Benzyl-2-hydroxyethyl]-5-[(*SR*)-methoxy(naphthalen-2-yl)methyl]-*N,N*-dimethyl-1*H*-imidazole-1-sulfonamide* ((±)-**51**). *GP 3*, starting from (±)-**49** (260 mg, 0.438 mmol), afforded (±)-**51** (168 mg, 80%) after purification by CC (SiO_2; pentane/AcOEt 25:75). Colorless oil. IR ($CHCl_3$): 3679, 3387, 3027, 2935, 2824, 1603, 1497, 1454, 1419, 1382, 1161. ^{1}H-NMR (300 MHz, $CDCl_3$): 2.82 (*s*, 6 H); 2.96 (*dd*, *J* = 13.1, 10.0, 1 H); 3.13 (*dd*, *J* = 13.1, 4.8, 1 H); 3.40 (*s*, 3 H); 3.52–3.60 (*m*, 1 H); 3.70–3.80 (*m*, 3 H); 5.83 (*s*, 1 H); 6.48 (*d*, *J* = 0.9, 1 H); 7.16–7.30 (*m*, 5 H); 7.49–7.54 (*m*, 3 H); 7.84–7.90 (*m*, 4 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 37.5; 38.1; 43.2; 57.1; 62.9; 76.9; 125.6; 126.5; 127.0; 127.9; 128.2; 128.5; 128.6; 129.5; 133.3; 133.5; 134.6; 136.2; 139.7; 154.0 (3 arom. signals overlapping). MALDI-MS (DHB): 502.2 (16, $[M + Na]^+$), 480.2 (34, MH$^+$), 395.2 (18), 341.2 (100). MALDI-HR-MS (DHB): 480.1958 (MH$^+$, $C_{26}H_{30}N_3O_4S^+$; calc. 480.1952).

*2-[(1*RS*)-1-Benzyl-2-hydroxyethyl]-5-[(*RS*)-methoxy(naphthalen-2-yl)methyl]-*N,N*-dimethyl-1*H*-imidazole-1-sulfonamide* ((±)-**52**). *GP 3*, starting from (±)-**50** (149 mg, 0.251 mmol), afforded (±)-**52** (91 mg, 76%) after purification by CC (SiO_2; pentane/AcOEt 33:66). Colorless solid. M.p. 64°. IR ($CHCl_3$): 3681, 3416, 3023, 3016, 2931, 2823, 2398, 2360, 1602, 1497, 1454, 1379, 1224. ^{1}H-NMR (300 MHz, $CDCl_3$): 2.61 (*s*, 6 H); 3.04 (*dd*, *J* = 13.1, 7.5, 1 H); 3.25 (*dd*, *J* = 13.1, 7.5, 1 H); 3.37 (*s*, 3 H); 3.40 (*s*, 1 H); 3.61–3.66 (*m*, 1 H); 3.79 (br. *s*, 2 H); 5.81 (*s*, 1 H); 6.49 (*s*, 1 H); 7.17–7.30 (*m*, 5 H); 7.49–7.54 (*m*, 3 H); 7.86–7.90 (*m*, 4 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 37.5; 37.7; 43.5; 57.1; 64.1; 76.8; 125.6; 126.5; 127.0; 127.9; 128.3; 128.5; 128.6; 129.5; 129.6; 133.3; 133.5; 135.0; 136.1; 140.0; 153.4 (2 arom. signals overlapping). MALDI-MS (DHB): 502.2 (17, $[M + Na]^+$), 480.2 (31, MH$^+$), 395.2 (21), 341.2 (100). MALDI-HR-MS (DHB): 480.1956 (MH$^+$, $C_{26}H_{30}N_3O_4S^+$, calc. 480.1952). Anal. calc. for $C_{26}H_{29}N_3O_4S$ (479.59): C 65.11, H 6.09, N 8.76; found C 65.17, H 6.16, N 8.72.

S-*((2*RS*)-2-[1-[(Dimethylamino)sulfonyl]-5-[(*SR*)-methoxy(naphthalen-2-yl)methyl]-1*H*-imidazol-2-yl]-3-phenylpropyl) Ethanethioate* ((±)-**53**). *GP 6*, starting from (±)-**51** (168 mg, 0.350 mmol), gave (±)-**53** (156 mg, 83%) after purification by CC (pentane/AcOEt 80:20). Yellow oil. IR ($CHCl_3$): 3058, 3031, 3026, 3020, 3010, 2987, 2938, 2825, 1690, 1615, 1571, 1496, 1454, 1418, 1370. ^{1}H-NMR (300 MHz, $CDCl_3$): 2.24 (*s*, 3 H); 2.61 (*s*, 6 H); 2.79 (*dd*, *J* = 13.4, 8.1, 1 H); 3.20–3.33 (*m*, 3 H); 3.39 (*s*, 3 H); 3.70–3.80 (*m*, 1 H); 5.80 (*s*, 1 H); 6.57 (*d*, *J* = 0.9, 1 H); 7.12–7.26 (*m*, 5 H); 7.46–7.52 (*m*, 3 H); 7.80–7.87 (*m*, 4 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 30.6; 32.8; 37.6; 41.1; 41.4; 57.0; 69.9; 125.4; 126.2; 126.4; 126.8; 127.6; 128.0; 128.1; 128.2; 129.2; 133.0; 133.2; 134.5; 136.0; 138.7; 152.8; 156.4; 195.2 (1 arom. signal overlapping). MALDI-MS (DHB): 560.2 (30, $[M + Na]^+$), 538.2 (23, MH$^+$), 453.2 (37), 399.2 (100), 323.2 (27). MALDI-HR-MS (DHB): 560.1643 ($[M + Na]^+$, $C_{28}H_{31}N_3NaO_4S_2^+$; calc. 560.1648).

S-*((2*RS*)-2-[1-[(Dimethylamino)sulfonyl]-5-[(*RS*)-methoxy(naphthalen-2-yl)methyl]-1*H*-imidazol-2-yl]-3-phenylpropyl) Ethanethioate* ((±)-**54**). *GP 6*, starting from (±)-**52** (0.091 g, 0.190 mmol), gave (±)-**54** (89 mg, 87%) after purification by CC (SiO_2; pentane/AcOEt 75:25). Yellowish oil. IR ($CHCl_3$): 3061, 3031, 3019, 3010, 2987, 2937, 2825, 1690, 1602, 1571, 1496, 1454, 1418, 1380. ^{1}H-NMR (300 MHz, $CDCl_3$): 2.26 (*s*, 3 H); 2.52 (*s*, 6 H); 2.92 (*dd*, *J* = 13.4, 6.2, 1 H); 3.23 (*dd*, *J* = 13.4, 7.5, 1 H); 3.29–3.35 (*m*, 2 H); 3.36 (*s*, 3 H); 3.73–3.80 (*m*, 1 H); 5.80 (*s*, 1 H); 6.55 (*d*, *J* = 0.9, 1 H); 7.13–7.29 (*m*, 5 H); 7.48–7.54 (*m*, 3 H); 7.84–7.89 (*m*, 4 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 30.7; 33.8; 37.4; 40.4; 41.1; 57.1; 77.0; 125.7; 126.5; 126.6; 127.0; 127.9; 128.3; 128.4; 128.6; 129.5; 129.6; 133.3; 133.5; 135.0; 136.3; 139.5; 152.8; 195.5 (1 arom. signal overlapping). MALDI-MS (DHB): 560.2 (29, $[M + Na]^+$), 538.2 (25, MH$^+$), 453.2 (35), 399.2 (100), 323.2 (36). MALDI-HR-MS (DHB): 560.1642 ($[M + Na]^+$, $C_{28}H_{31}N_3NaO_4S_2^+$; calc. 560.1648).

*(2*RS*)-2-[5-[(*SR*)-Methoxy(naphthalen-2-yl)methyl]-1*H*-imidazol-2-yl]-3-phenylpropan-1-ol* ((±)-**55**). *GP 4*, starting from (±)-**51** (261 mg, 0.54 mmol), afforded (±)-**55** (151 mg, 75%) after purification by CC (SiO_2; AcOEt/MeOH/NEt_3 97:2:1). Colorless oil. IR ($CHCl_3$): 3440, 3014, 2936, 2829, 1955, 1888, 1818, 1600, 1497, 1452, 1323, 1080, 1018. ^{1}H-NMR (300 MHz, $CDCl_3$): 2.95 (*dd*, *J* = 13.4, 8.1, 1 H); 3.03 (*dd*, *J* = 13.4, 7.5,

1 H); 3.09–3.15 (*m*, 1 H); 3.37 (*s*, 3 H); 3.77 (*dd*, *J* = 10.6, 5.6, 1 H); 3.87 (*dd*, *J* = 10.6, 3.4, 1 H); 5.40 (*s*, 1 H); 6.56 (*s*, 1 H); 7.10–7.25 (*m*, 5 H); 7.45–7.51 (*m*, 3 H); 7.80–7.85 (*m*, 4 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 37.4; 42.6; 56.9; 63.7; 77.2; 124.9; 125.8; 125.9; 126.1; 126.4; 127.6; 127.9; 128.2; 128.6; 128.9; 133.0; 133.1; 137.5; 139.2; 149.9 (2 arom. signals overlapping). MALDI-MS (DHB): 401.2 (10), 395.2 (20, $[M + Na]^+$), 373.2 (7, MH^+), 341.2 (100, $[M - MeO]^+$). MALDI-HR-MS (DHB): 373.1906 (MH^+, $C_{24}H_{25}N_2O_2^+$; calc. 373.1910).

*2-[(1*RS*)-1-Benzyl-2-sulfanylethyl]-5-[(*SR*)-methoxy(naphthalen-2-yl)methyl]-1*H*-imidazol-3-ium Chloride* ((±)-**45**). *GP 6*, starting from (±)-**55** (70 mg, 0.19 mmol), afforded an Ac-protected intermediate that was purified by CC (SiO_2; CH_2Cl_2/AcOEt 60:40). The purified intermediate was dissolved in MeOH (4 ml), and the soln. was degassed under Ar for 30 min. The soln. was added to a suspension of MeONa (63 mg, 1.16 mmol) in MeOH (4 ml) that was degassed for 30 min under Ar and for 10 min under H_2. The mixture was stirred for 2 h at r.t. After addition of sat. aq. NH_4Cl soln. and extraction (CH_2Cl_2), the org. phases were dried ($MgSO_4$) and concentrated *in vacuo*. The residue was immediately purified by CC (SiO_2; AcOEt). The resulting product was dissolved in 0.1% methanolic HCl soln., and the solvent was removed *in vacuo*. Purification by reversed-phase CC (*RP-18* SiO_2; 0.1% aq. HCl soln./MeCN 67:33) gave ((±)-**45** (17 mg, 21% over 2 steps). White solid. M.p. 80–81°. IR ($CHCl_3$): 3675, 3064, 2969, 2829, 2700, 1812, 1756, 1715, 1631, 1600, 1544, 1497, 1457, 1334, 1088. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.53 (*t*, *J* = 9.1, 1 H); 2.84–2.93 (*m*, 1 H); 3.06–3.18 (*m*, 2 H); 3.24–3.33 (*m*, 1 H); 3.26 (*s*, 3 H); 3.85–3.95 (*m*, 1 H); 5.47 (*s*, 1 H); 6.60 (*s*, 1 H); 6.98–7.13 (*m*, 5 H); 7.24–7.48 (*m*, 3 H); 7.71–7.82 (*m*, 4 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 27.2; 39.0; 43.6; 57.2; 76.4; 115.4; 124.0; 126.4; 126.5; 126.7; 126.8; 127.6; 128.0; 128.5; 128.7; 128.8; 132.9; 133.3; 134.2; 134.5; 136.8; 148.9. MALDI-MS (DHB): 411.2 (5, $[M + Na]^+$), 389.2 (5, MH^+), 357.1 (100, $[M - MeO]^+$). MALDI-HR-MS (DHB): 389.1683 (MH^+, $C_{24}H_{25}N_2OS^+$; calc. 389.1682).

*5-Benzyl-2-((1*RS*)-1-benzyl-2-{[(*tert*-butyl)(dimethyl)silyl]oxy}ethyl)-*N,N*-dimethyl-1*H*-imidazole-1-sulfonamide* ((±)-**56**). At −78°, *s*-BuLi (1.3M in cyclohexane, 1.1 ml, 1.42 mmol) was added dropwise to a soln. of (±)-**36** (0.5 g, 1.18 mmol) in dry THF (30 ml), and the mixture was stirred for 30 min. BnBr (0.42 ml, 3.54 mmol) was added, followed by stirring for 2 h at −78° and for 1 h at r.t. The reaction was quenched by addition of 1N aq. HCl soln., and the mixture was neutralized with sat. aq. $NaHCO_3$ soln. and extracted (CH_2Cl_2). The org. phases were dried ($MgSO_4$) and concentrated *in vacuo*. Purification by CC (SiO_2; pentane/AcOEt 80:20) afforded (±)-**56** (407 mg, 67%). Yellow oil. IR ($CHCl_3$): 3693, 3328, 3064, 3033, 3010, 2956, 2929, 1949, 1603, 1495, 1472, 1454, 1377. ^{1}H-NMR (300 MHz, $CDCl_3$): 0.01 (*s*, 3 H); 0.02 (*s*, 3 H); 0.87 (*s*, 9 H); 2.33 (*s*, 6 H); 3.07 (*dd*, *J* = 13.0, 5.3, 1 H); 3.17 (*dd*, *J* = 13.0, 8.4, 1 H); 3.69–3.79 (*m*, 2 H); 3.98 (*m*, 1 H); 4.02 (*d*, *J* = 16.5, 1 H); 4.09 (*d*, *J* = 16.5, 1 H); 6.59 (*s*, 1 H); 7.10–7.32 (*m*, 10 H). ^{13}C-NMR (75 MHz, $CDCl_3$): −5.2; 26.1; 26.5; 32.6; 37.2; 37.8; 45.1; 66.2; 125.7; 126.2; 126.8; 128.4; 128.6; 129.1; 129.6; 132.6; 138.3; 140.8; 152.1. MALDI-MS (DHB): 536.3 (15, $[M + Na]^+$), 514.3 (100, MH^+), 497.3 (38), 407.3 (55). MALDI-HR-MS (DHB): 514.2559 (MH^+, $C_{27}H_{40}N_3O_3SSi^+$; calc. 514.2554).

*5-Benzyl-2-[(1*RS*)-1-benzyl-2-hydroxyethyl]-*N,N*-dimethyl-1*H*-imidazole-1-sulfonamide* ((±)-**57**). *GP 3*, starting from (±)-**56** (0.407 g, 0.79 mmol), afforded (±)-**57** (257 mg, 81%) after purification by CC (SiO_2; pentane/AcOEt 33:67). Colorless oil. IR ($CHCl_3$): 3394, 3008, 2993, 2883, 1950, 1877, 1810, 1733, 1604, 1577, 1496, 1454, 1379.. ^{1}H-NMR (300 MHz, $CDCl_3$): 2.57 (*s*, 6 H); 3.06 (*dd*, *J* = 13.1, 8.8, 1 H); 3.18 (*dd*, *J* = 13.1, 5.9, 1 H); 3.61–3.74 (*m*, 2 H); 3.77–3.80 (*m*, 2 H); 4.08 (*t*, *J* = 17.7, 2 H); 6.51 (*t*, *J* = 1.2, 1 H); 7.17–7.35 (*m*, 10 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 28.9; 32.5; 37.7; 43.3; 63.4; 126.5; 127.0; 128.2; 128.6; 128.7; 129.1; 129.6; 132.8; 137.7; 139.9; 153.4. MALDI-MS (DHB): 422.2 (20, $[M + Na]^+$), 400.2 (100, MH^+), 355.1 (36), 293.2 (62). MALDI-HR-MS (DHB): 400.1692 (MH^+, $C_{21}H_{26}N_3O_3S^+$; calc. 400.1689).

*S-((2*RS*)-2-{5-Benzyl-1-[(dimethylamino)sulfonyl]-1*H*-imidazol-2-yl}-3-phenylpropyl) Ethanethioate* ((±)-**58**). *GP 6*, starting from (±)-**57** (0.132 g, 0.330 mmol), afforded (±)-**58** (139 mg, 92%) after purification by CC (SiO_2; pentane/AcOEt 75:25). Colorless oil. IR ($CHCl_3$): 3688, 3065, 3030, 3023, 3010, 2972, 2360, 1951, 1690, 1378, 1226, 1220.. ^{1}H-NMR (300 MHz, $CDCl_3$): 2.26 (*s*, 3 H); 2.41 (*s*, 6 H); 2.90 (*dd*, *J* = 13.1, 6.9, 1 H); 3.24 (*dd*, *J* = 13.4, 8.4, 1 H); 3.29 (*dd*, *J* = 13.4, 7.8, 1 H); 3.35 (*dd*, *J* = 13.1, 5.6, 1 H); 3.83–3.92 (*m*, 1 H); 4.06 (*s*, 2 H); 6.58 (*s*, *J* = 0.9, 1 H); 7.13–7.33 (*m*, 10 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 30.6; 32.3; 33.4; 37.1; 41.0; 41.1; 126.3; 126.5; 128.2; 128.2; 128.3; 128.6; 129.2; 132.5; 137.7; 139.0; 152.1; 195.1. MALDI-MS (DHB): 480.1 (13, $[M + Na]^+$), 458.2 (78, MH^+), 351.2 (100). MALDI-HR-MS (DHB): 458.1571 (MH^+, $C_{23}H_{28}N_3O_3S_2^+$; calc. 458.1567).

*5-Benzyl-2-[(1*RS*)-1-benzyl-2-sulfanylethyl]-1*H*-imidazol-3-ium Chloride* ((±)-**46**). To a soln. of (±)-**58** (80 mg, 0.175 mmol) in MeOH (5 ml), conc. aq. HCl soln. (37%, 0.5 ml) was added, and the mixture was heated to reflux for 4 h. After cooling to r.t., CH_2Cl_2 (15 ml) was added, and the mixture was washed with dil. aq. $NaHCO_3$ soln. The aq. phases were extracted (CH_2Cl_2), and the combined org. phases were dried ($MgSO_4$) and concentrated *in vacuo*. Purification by CC (SiO_2; AcOEt/MeOH 99:1) gave a product, which was dissolved in

$CHCl_3$. HCl (g) was bubbled through the soln. for 10 min. Concentration *in vacuo* and purification by reversed-phase CC (*RP-18* SiO_2; 0.1% aq. HCl soln./MeCN 67:33) gave (±)-**46** (15 mg, 46%). Colorless solid. M.p. 53–54°. IR ($CHCl_3$): 3089, 3066, 2971, 2862, 2786, 2720, 2654, 1951, 1636, 1604, 1496, 1455. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.50 (*t*, *J* = 8.4, 1 H); 2.88–2.98 (*m*, 1 H); 3.06–3.24 (*m*, 2 H); 3.32 (*dd*, *J* = 13.7, 7.2, 1 H); 3.85 (br. *s*, 1 H); 3.94 (*s*, 2 H); 6.52 (*s*, 1 H); 7.10–7.26 (*m*, 10 H); 14.19 (br. *s*, 1 H); 14.48 (br. *s*, 1 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 27.6; 31.0; 40.1; 46.2; 116.8; 127.7; 127.8; 129.0; 129.2; 129.4; 129.5; 133.7; 137.6; 138.0; 149.3. MALDI-MS (DHB): 309.1 (100, MH^+). MALDI-HR-MS (DHB): 309.1422 (MH^+, $C_{19}H_{21}N_2S^+$; calc. 309.1420).

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

Compound (±)-**14**. Crystal data at 293(2) K for $C_{21}H_{25}N_3O_4S$ (M_r 415.50): monoclinic, space group *P*2(1)/*c*, $D_c = 1.268$ g cm^{-3}, $Z = 4$, $a = 9.787(2)$, $b = 19.841(3)$, $c = 11.365(3)$ Å, $\beta = 99.56(2)°$, $V = 2176.3(8)$ Å^3. *Enraf Nonius CAD-4* diffractometer with CuK_α radiation (graphite monochromator, $\lambda = 1.54184$ Å). The structure was solved by direct methods (SIR97) [60]. The non-H-atoms were refined anisotropically (SHELXL-97) [61]. The H-atoms were calculated at idealized positions and refined with constrained isotropic displacement parameters. The H(O) atom was located from a difference *Fourier* map and refined isotropically. Final $R(F) = 0.0433$, $wR(F^2) = 0.1522$ for 266 parameters, 0 restraints, and 3276 reflections with $I > 2\sigma(I)$ and $4.46 < \theta < 66.94°$. Deposition No. CCDC-256717.

Compound (±)-**41**. Crystal data at 202 K for $C_{24}H_{29}N_3O_4S_2$ (M_r 487.64): triclinic, space group $P\bar{1}$, $D_c = 1.324$ g cm^{-3}, $Z = 2$, $a = 9.3213(2)$, $b = 11.5643(2)$, $c = 12.1363(2)$ Å, $\alpha = 83.9220(8)°$, $\beta = 74.6721(8)°$, $\gamma = 76.0488(7)°$, $V = 1223.23(4)$ Å^3. *Bruker-Nonius Kappa CCD* diffractometer, MoK_α radiation, $\lambda = 0.71073$. The structure was solved by direct methods (SIR97) [60]. The non-H-atoms were refined anisotropically (SHELXL-97) [61]. The H-atoms were calculated at idealized positions and refined with constrained isotropic displacement parameters. Final $R(F) = 0.067$, $wR(F^2) = 0.161$ for 414 parameters, 0 restraints, and 5810 reflections with $I > 2\sigma(I)$ and $0.10 < \theta < 28.70°$. Deposition No. CCDC-256718.

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