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SYNTHESIS OF 2,4,5-TRISUBSTITUTED THIAZOLES WITH A 5-(*N*,*N*-DIMETHYLAMINOMETHYL) SUBSTITUENT

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Dedicated to Prof. Y. Kishi at the occasion of his 70th birthday

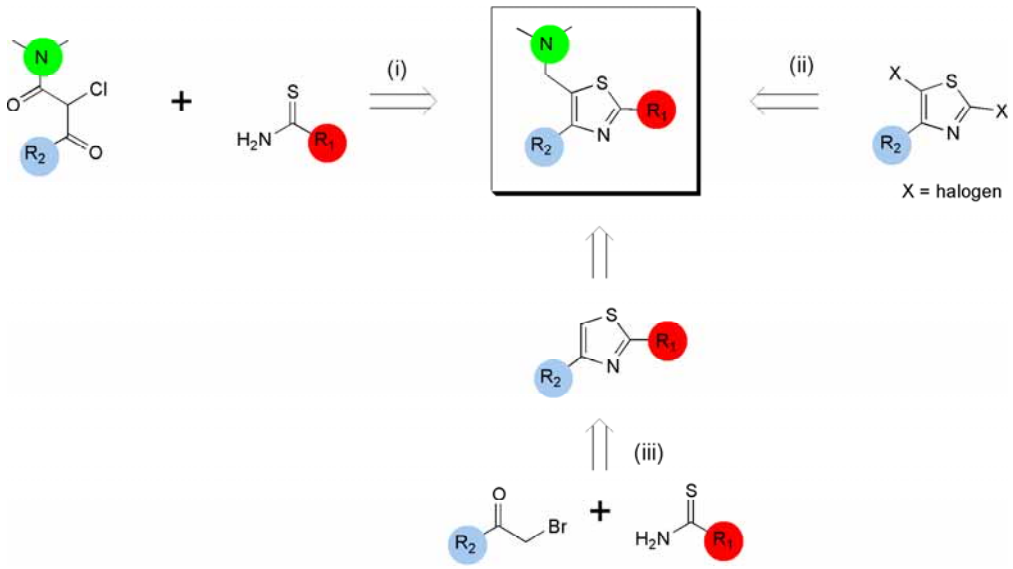
Abstract – We report synthetic strategies to 2,4,5-trisubstituted thiazoles with a *N*,*N*-dimethylaminomethyl residue at C(5). Three different routes to build up these scaffolds are described. Furthermore, we report a *retro*-Brook rearrangement of a thiazole derivative as well as an unusual cyclization leading to a highly substituted benzothiazole.

INTRODUCTION

Substituted thiazoles are ubiquitous structural motifs in medicinal chemistry and are also found in several natural products. During the course of our search for new small-molecule inhibitors for the enzyme trypanothione reductase,[1-3] an essential oxidoreductase present in trypanosomatids causing African sleeping sickness, *Chagas* disease or Leishmaniasis, we became interested in the development of 2,4,5-trisubstituted thiazole scaffolds bearing a *N*,*N*-dimethylaminomethyl group at C(5). While the decorated thiazoles were prepared with this objective, they could also serve as interesting starting points for hit generation in other medicinal chemistry projects.

Three different strategies were envisaged for the development of 2,4,5-trisubstituted thiazole scaffolds (Scheme 1): (i) assembly of the thiazole core by *Hantzsch*-type cyclization[4-6] of α-chloroketone and thioamide precursors incorporating the final substituents at C(2) and C(4) and a synthon for the

N,*N*-dimethylaminomethyl group at C(5), (ii) thiazole formation by *Hantzsch*-type cyclization of precursors bearing the final substituent (or an appropriate synthon) at C(4) and halogens at C(2) and C(5) to introduce the two residual substituents after cyclization, and (iii) cyclization to a disubstituted thiazole with substituents at C(2) and C(4), followed by introduction of the 5-(*N*,*N*-dimethylaminomethyl) group in the last step. Here we report the formation of 2,4,5-trisubstituted thiazoles by all three routes that are compared and critically discussed.

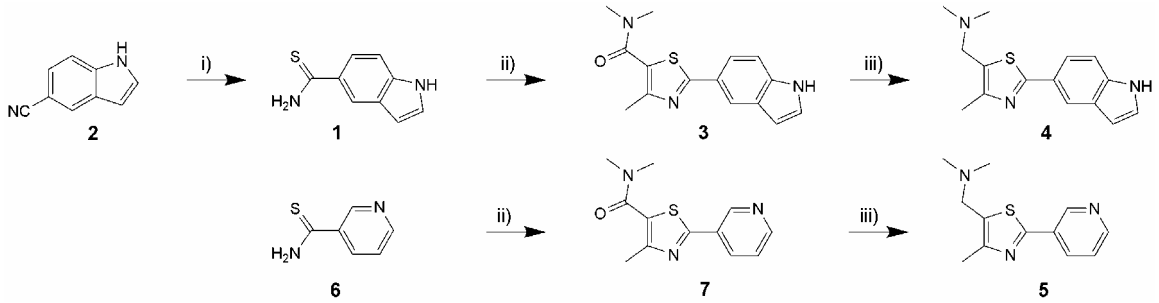


Scheme 1 Routes to 2,4,5-trisubstituted thiazoles.

RESULTS AND DISCUSSION

Route 1.

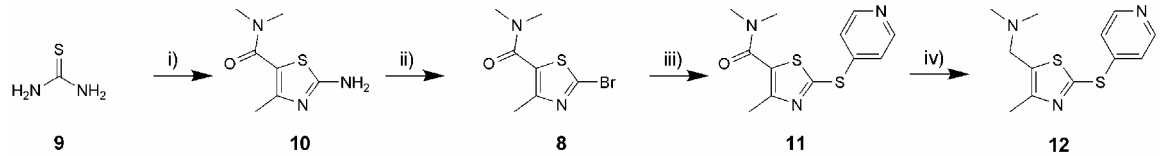
A first class of compounds of interest were 5-(*N*,*N*-dimethylaminomethyl)-substituted thiazoles bearing a methyl group at C(4) and an aromatic ring attached to C(2) either directly or *via* a thioether linkage. Thus, thioamide **1** was prepared from 5-bromoindole by Br/CN exchange[7] to give **2**, followed by conversion of the cyano group into the desired thioamide functionality by treatment with *O*,*O'*-diethyl hydrogen dithiophosphate(Scheme 2). Cyclization of **1** with *N*,*N*-dimethyl-2-chloroacetoacetamide provided trisubstituted thiazole **3** in good yield. Reduction of the amide group finally yielded the desired tertiary amine **4**. The pyridyl derivative **5** was obtained following a similar route. Condensation of commercially available thionicotinamide (**6**) with *N*,*N*-dimethyl-2-chloroacetoacetamide furnished thiazole **7** which was reduced with $LiAlH_4$ to give target compound **5**.



Reagents and conditions: i) *O,O*-Diethyl hydrogen dithiophosphate, CH_2Cl_2, rt, 35 h; 68%. ii) *N,N*-Dimethyl-2-chloroacetoacetamide, EtOH, 79 °C; 3.5–12 h; 68% (**3**), 59% (**6**). iii) $LiAlH_4$, THF, 67 °C, 30-40 min; 90% (**4**), 43% (**5**).

Scheme 2 Synthesis of 2,4,5-trisubstituted thiazoles **4** and **5** with a 5-*N,N*-dimethylaminomethyl substituent according to Strategy 1 (Scheme 1).

Only a few examples of cyclizations leading directly to 2-arylsulfanyl-substituted thiazoles are known[8,9]. In a modification of strategy 1 (Scheme 3), we developed a synthetic route that enables the introduction of an arylsulfanyl ligand at C(2) after the cyclization step, *via* nucleophilic aromatic substitution. For this purpose, 2-bromothiazole **8** was built by condensation of thiourea (**9**) with *N,N*-dimethyl-2-chloroacetoacetamide to give 2-aminothiazole **10**, followed by a *Sandmeyer* reaction. The bromide was subsequently substituted by a pyridin-4-ylsulfanyl residue, furnishing **11**, which was reduced to the target compound **12**. This route should be generally applicable and allow the production of other 2-arylsulfanylated thiazoles. Attempts to apply strategy 1 to the preparation of 2-aryl-5-(*N,N*-dialkylaminomethyl)thiazoles with a carboxylic group at C(4) however failed so far.



Reagents and conditions: i) *N,N*-Dimethyl-2-chloroacetoacetamide, EtOH, rt, 12 h; 93%. ii) $CuBr_2$, isoamylnitrite, MeCN, 0 °C, 2 h; 74%. iii) 4-Mercaptopyridine, NaH, MeCN, 0 °C → rt, 3.5 d; 66%. iv) $LiAlH_4$, THF, 0 °C → 67 °C, 14 h; 37%.

Scheme 3 Synthesis of 2-arylsulfanylthiazole **12**.

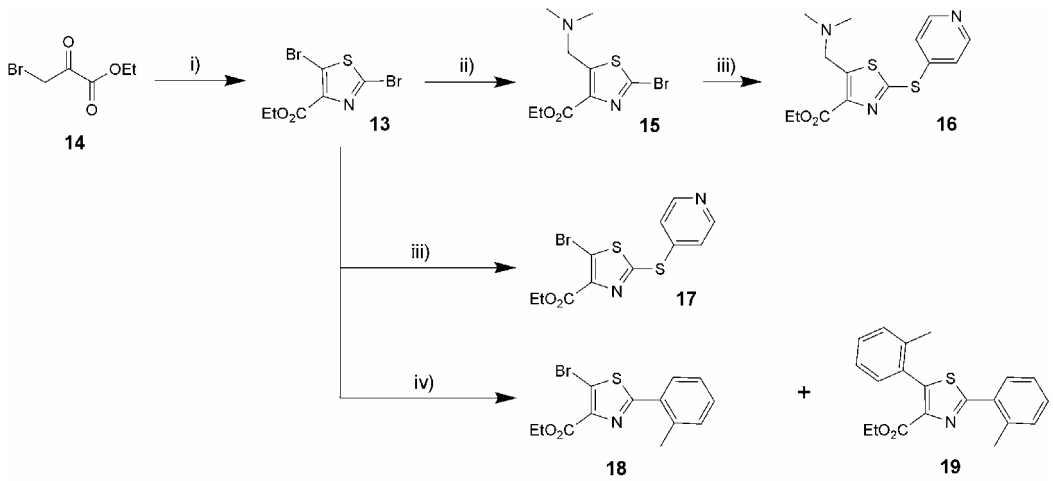
Route 2.

The limitations encountered in route 1, in particular with respect to the introduction of a carboxyl substituent at C(4) led us to change to strategy 2 (Scheme 1). The required ethyl 2,5-dibromothiazolecarboxylate (**13**) was synthesized according to a literature procedure[10] *via* cyclization of ethyl bromopyruvate (**14**) with thiourea (**9**), followed by NBS-mediated bromination of the formed

thiazole at C(5) and subsequent transformation of the 2-amino group into a second bromide substituent by a *Sandmeyer* reaction (Scheme 4).

Generally, bromides in position 2 of 2,5-dibromothiazoles are more readily displaced than in position 5.[11,12] When the dibromo derivative **13** was treated with a solution of *i*-PrMgCl, a reversed reactivity was obtained. Assisted by the chelation of the *Grignard* reagent with the neighboring ester group in position 4, the bromide at C(5) underwent a highly selective halogen/magnesium exchange.[13] The obtained metallated intermediate was reacted with *Eschenmoser* salt *in situ*, which furnished dimethylaminomethyl-substituted thiazole **15**. Subsequent S_NAr reaction with 4-mercaptopyridine led to ethyl thiazolecarboxylate **16.**

On the other hand, 2,5-dibromothiazole **13** can also be functionalized selectively at C(2) without touching the bromo substituent in position 5. Treatment with 4-mercaptopyridine under basic conditions gave exclusively the 2-sulfanylated derivative **17**. Alternatively, palladium-catalyzed *Suzuki* cross coupling reaction with 2-tolylboronic acid furnished the 2-*o*-tolylthiazole **18** in moderate yield, as well as traces of the doubly coupled product **19**, but no 2-bromo-5-*o*-tolylthiazole derivative.

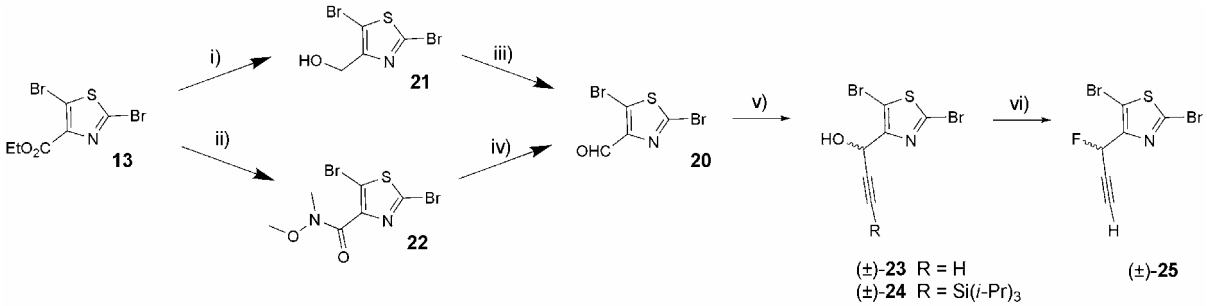


Reagents and conditions: i) a) $SC(NH_2)_2$, neat, 80 °C, 20 min; b) NBS, CH_2Cl_2, rt, 4 h; c) NaBr, $CuSO_4$, $NaNO_2$, H_2O, H_2SO_4, 0 °C, 14 h; 75% (3 steps). ii) *i*-PrMgCl, $CH_2NMe_2^+ I^-$, THF, –78 °C → 0 °C, 4 h; 66%. iii) 4-Mercaptopyridine, *n*-BuLi, THF, –78 °C → rt, 13-48 h; 31% (**16**), 33% (**17**). iv) 2-Tolylboronic acid, Cs_2CO_3, [$Pd(PPh_3)_4$], H_2O, DME, 80 °C, 15 h; 35% (**18**), 13% (**19**). NBS = *N*-bromosuccinimide. THF = tetrahydrofuran. DME = 1,2-dimethoxyethane.

Scheme 4 Selective halogen exchanges in 2,5-dibromothiazole derivative **13**.

To introduce alkyne substituents in position 4, thiazolecarboxylic ester **13** was transformed into aldehyde **20** (Scheme 5). Since the reduction of **13** with DIBALH could not be stopped at the stage of the aldehyde, even at –78 °C, the formed alcohol **21** was oxidized with *Dess-Martin* periodinane[14] to give **20**. Alternatively, the ester was transformed into *Weinreb* amide **22** by treatment with *N,O*-dimethylhydroxylamine and $AlMe_3$, and reduction[15] afforded **20** in good yield. When lithium

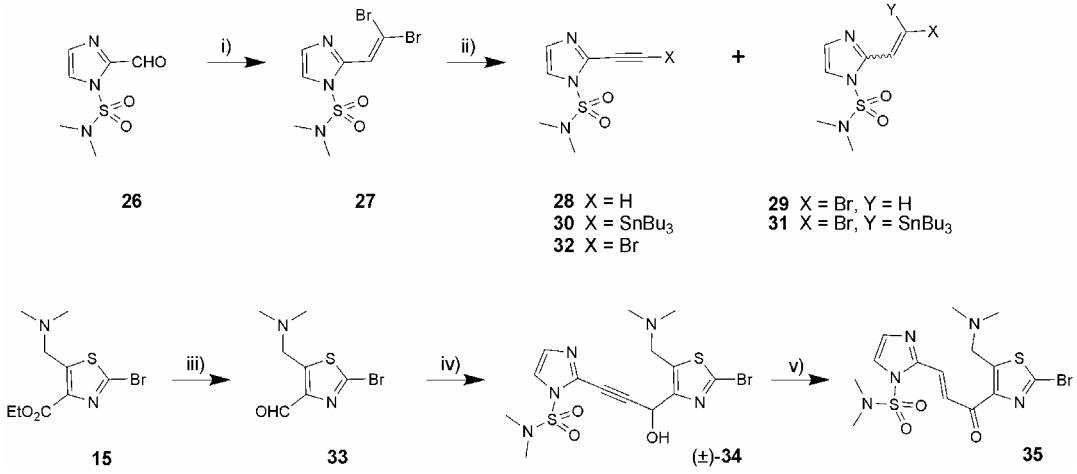
acetylide was reacted with **20**, propargyl alcohol (±)-**23** was obtained in good yield, while the *Grignard* reagent formed from bromo(triisopropylsilyl)acetylene[16] with *i*-PrMgCl afforded silyl-protected (±)-**24**. Treatment of (±)-**23** with DAST gave the propargylic fluoride (±)-**25**.



Reagents and conditions: i) DIBALH, CH_2Cl_2, –78 °C → rt, 17 h; 46%. ii) MeONHMe-HCl, $AlMe_3$, CH_2Cl_2, 0 °C → rt, 2.5 h; 93%. iii) *Dess-Martin* periodinane, CH_2Cl_2, 0 °C → rt, 9 h; 97%. iv) DIBALH, CH_2Cl_2, –78 °C, 2 h; 84%. v) HC≡C–Li, THF, 0 °C → rt, 2 h; 87% ((±)-**23**) or TIPS–C≡C–MgCl, 0 °C → rt, 2 h; 64% ((±)-**24**). vi) DAST, CH_2Cl_2, –78 °C, 1 h; 40%. DIBALH = diisobutylaluminum hydride. DAST = diethylaminosulfur trifluoride.

Scheme 5 Synthesis of propargyl derivatives (±)-**23** to (±)-**25**.

Computer modeling suggested that a central 2,4,5-trisubstituted thiazole bearing a propargylic vector with an attached imidazole in position 4 would hold promise as trypanothione reductase inhibitors. Therefore, we developed a synthesis of a suitable alkynylated imidazole for attack at a thiazole-4-carbaldehyde (Scheme 6).



Reagents and conditions: i) CBr_4, PPh_3, CH_2Cl_2, 0 °C → rt, 4 h; 95%. ii) a) *n*-BuLi, THF, –78 °C → 0 °C, 2 h; 57% (**28**), 26% (**29**); b) *n*-BuLi, *n*-Bu_3SnCl, THF, – 78 °C → rt, 4 h; 40% (**30**), 34% (**31**); c) NaH, THF, 0 °C → rt, 14 h; 79% (**32**). iii) DIBALH, CH_2Cl_2, –78 °C, 2 h; 69%. iv) **32**, *i*-PrMgCl, THF, –78 °C → rt, 5 h; 58%. v) $CDCl_3$, rt, 5 d; quant.

Scheme 6 Synthesis of a 2,4,5-trisubstituted thiazole with an alkynylated imidazole-substituent in position 4.

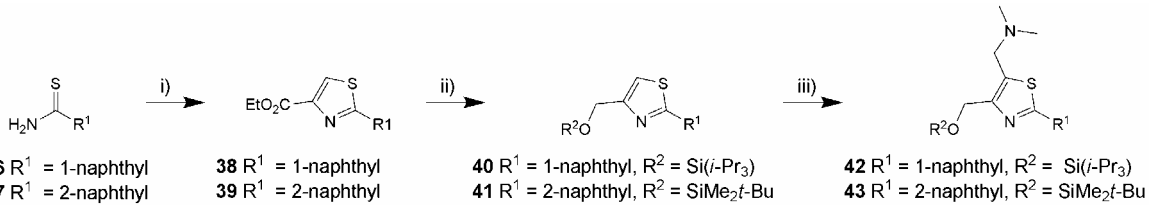
Starting from the protected imidazole-2-carbaldehyde **26**,[17] *Corey-Fuchs* dibromoolefination[18] afforded the dibromoalkene **27** which was treated with *n*-BuLi (2 equivalents) to yield, after aqueous workup, the terminal alkyne **28** besides minor amounts of mono-brominated olefin **29**. When the lithium acetylide, obtained in the reaction of **27** with *n*-BuLi, was quenched with tris(*n*-butyl)stannylchloride, the stannylated derivative **30** was formed in moderate yield besides stannylated olefin **31**, indicating that the dehydrobromination preceeding the quenching with the electrophile was not complete.

We also prepared mono-brominated alkyne **32** by dehydrobromination of dibromoalkene **27**. Both the use of *t*-BuOK in *i*-PrOH/THF 2:1 at 0 °C and LHMDS in THF at –78 °C led only to decomposition of the starting material. The recently reported elimination[19] with DBU in Me_2SO at rt provided **32** in only 23% yield. Use of one equivalent of *n*-BuLi in THF (–78 °C → rt) increased the yield to 57%, but the best results (79% yield) were obtained with NaH as a base while stirring overnight (0 °C → rt).

For the attachment of bromoalkynylated imidazole **32** to the thiazole core, ester **15** was reduced to aldehyde **33**. In contrast to the conversion of dibromothiazole **13** (Scheme 5) the reduction of ester **15** with DIBALH (1 equivalent, –78 °C) could be stopped at the stage of the aldehyde and no alcohol was formed under these conditions. Br/Mg exchange of **32** was achieved by treatment with *i*-PrMgCl and the generated nucleophile reacted *in situ* with aldehyde **33** to yield the propargylic alcohol (±)-**34**. This compound underwent a rearrangement to enone **35** in solution. In previous work, such transformations have been described mediated by catalytic amounts of palladium acetate[20,21] or by simple stirring at high temperatures in the presence of triethylamine.[22] Most probably, the *N*,*N*-dimethylamino group acts as an intramolecular base to trigger the rearrangement of propargylic alcohol (±)-**34** to the chalcone-like structure **35**, so that no external reagent is needed for this transformation.

Route 3.

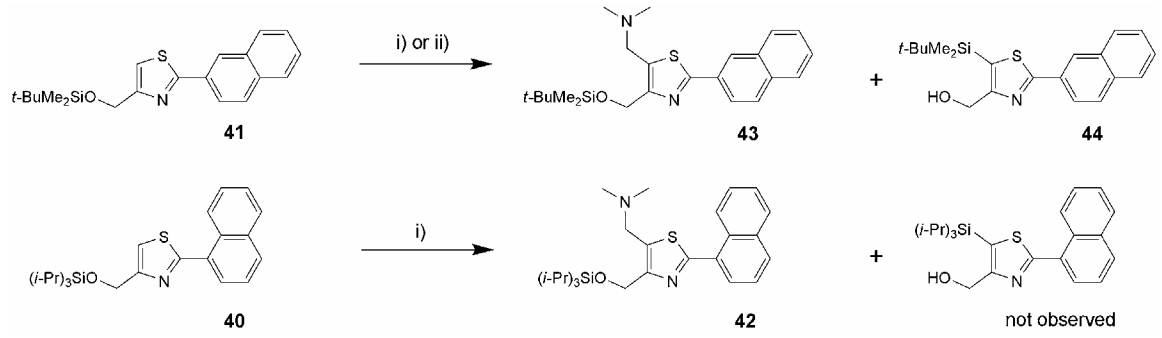
According to the third strategy, the *N*,*N*-dimethylaminomethyl group is introduced late into a 2,4-disubstituted thiazole having either the final substituents or synthons thereof in place. Starting from naphthalene-1- or 2-carbothioamide **36** and **37**, the thiazole core was built up by condensation with ethyl bromopyruvate (**14**) yielding the 2,4-disubstituted thiazoles **38** and **39**, respectively (Scheme 7). Reduction of the ester group and silyl-protection of the obtained alcohol afforded the naphthyl derivatives **40** and **41**, respectively. Lithiation at position 5 of the thiazole ring, followed by addition of *Eschenmoser* salt afforded the desired tertiary amines **42** and **43**.



Reagents and conditions: i) Ethyl bromopyruvate, EtOH, 79 °C, 30–90 min, 83% (**38**), 85% (**39**). ii) a). DIBALH, CH_2Cl_2, –10 °C → rt, 2 h; b) TIPSCl, imidazole, CH_2Cl_2, rt, 15 h; 67% (**40**) or TBDMSCl, DMAP CH_2Cl_2, rt, 16 h; 94% (**41**). iii) a) *n*-BuLi, THF, –78 °C, 10 min; b) $CH_2NMe_2^+ I^-$, –78 °C → rt, 6 h; 80% (**42**), 62% (**43**). DMAP = 4-(dimethylamino)pyridine, TBDMS = *tert*-butyldimethylsilyl, TIPS = triisopropylsilyl.

Scheme 7 Introduction of the 5-*N*,*N*-dimethylaminomethyl substituent into 2,4-disubstituted thiazoles.

In the case of the conversion of the TBDMS protected alcohol **41**, a noteworthy amount of 5-(*tert*-butyldimethylsilanyl)thiazole **44** was isolated after treatment with *n*-BuLi (Scheme 8). Obviously, the TBDMS group had migrated from the alcohol O-atom to the thiazole C(5)-atom under the basic conditions. By allowing the mixture to warm to 0 °C before *Eschenmoser* salt was added, the silylated thiazole **44** was isolated in 72% yield as the major product. Migrations of TBDMS groups are well known to occur between OH-groups of nucleosides.[23,24] When the migration occurs from the hydroxyl group to C-atoms under basic conditions, it is known as the retro-*Brook* rearrangement.[25] While it has been observed for thiophene and furan derivatives[26-28] and was recently applied to the synthesis of sesquiterpenoids[29], it has to the best of our knowledge not been reported for thiazole derivatives.

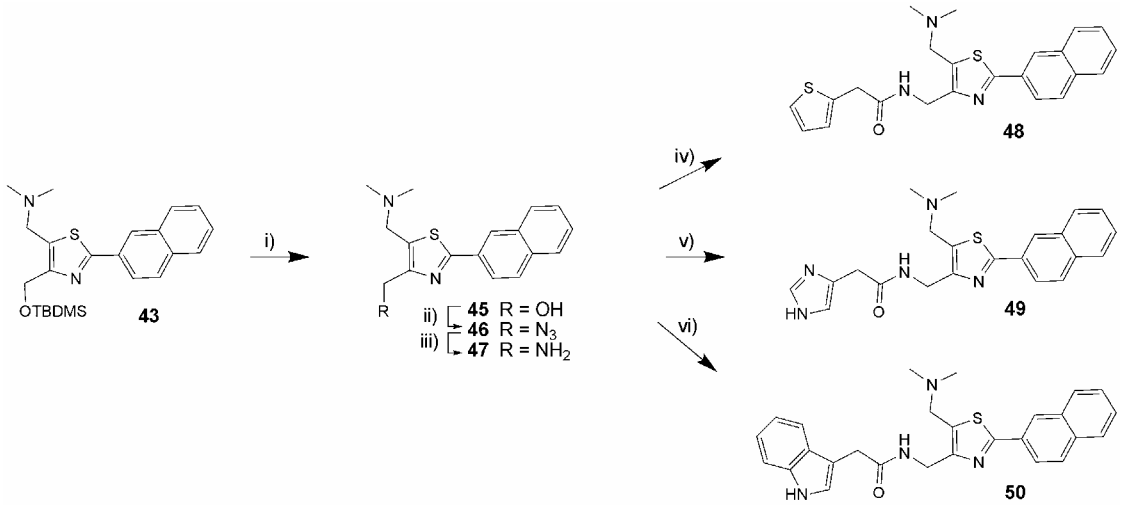


Reagents and conditions: i) a) *n*-BuLi, THF, –78 °C, 10 min; b) $CH_2NMe_2^+ I^-$, –78 °C → rt, 6 h; 62% (**43**), 14% (**44**), 80% (**42**). ii) b) *n*-BuLi, THF, –78 °C → rt, 1 h; b) $CH_2NMe_2^+ I^-$, 15 h; 7% (**43**), 72% (**44**).

Scheme 8 Retro-*Brook* rearrangement of TBDMS protected alcohol **41**.

In studies of the migration of silyl protecting groups between HO groups of nucleosides, it was shown that TIPS groups are more stable than TBDMS groups.[30] This is also the case for our system: lithiation of TIPS-protected **40** yielded exclusively the desired (5-*N*,*N*-dimethylaminomethyl) derivative **42** and no rearranged 5-(triisopropylsilanyl)thiazole.

To introduce heteroarylacetamide moieties in position 4 of the thiazole core, silylether **43** was cleaved, furnishing alcohol **45** (Scheme 9). *Mitsunobu*-like reaction[31] with diphenylphosphoryl azide and DBU afforded azide **46** which was converted into the primary amine **47** in a *Staudinger* reaction. Subsequent amide coupling reactions with crude **47** afforded the heteroarylacetamides **48**-**50**.



Reagents and conditions: i) *n*-Bu_4NF, THF, rt, 3 h; 99%. ii) Diphenylphosphoryl azide, DBU, THF, 0 °C → rt, 2 h. iii) PMe_3, H_2O, THF, rt, 16 h; iv) Thiophene-2-acetyl chloride, *i*-$PrNEt_2$, CH_2Cl_2, –78 °C → rt, 3 d; 35% (3 steps). v) 1*H*-imidazol-4-ylacetic acid hydrochloride, CDI, $(i\text{-Pr})_2NEt$, DMF, THF, rt, 23 h; 67% (3 steps). vi) Indole-3-acetic acid, CDI, THF, rt, 18 h; 46% (3 steps). DBU = 1,3-diazabicyclo[5.4.0]undecane. CDI = *N*,*N*-carbonyldiimidazole. DMF = dimethylformamide.

Scheme 9 Synthesis of heteroarylacetamides **48**-**50**.

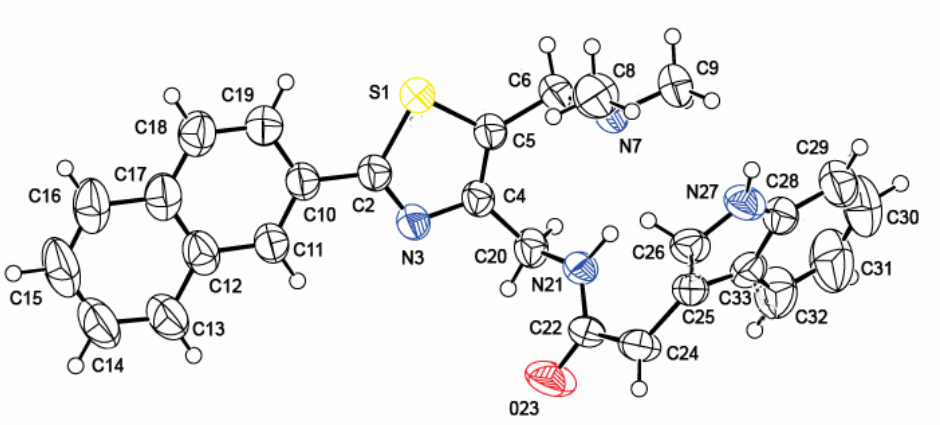
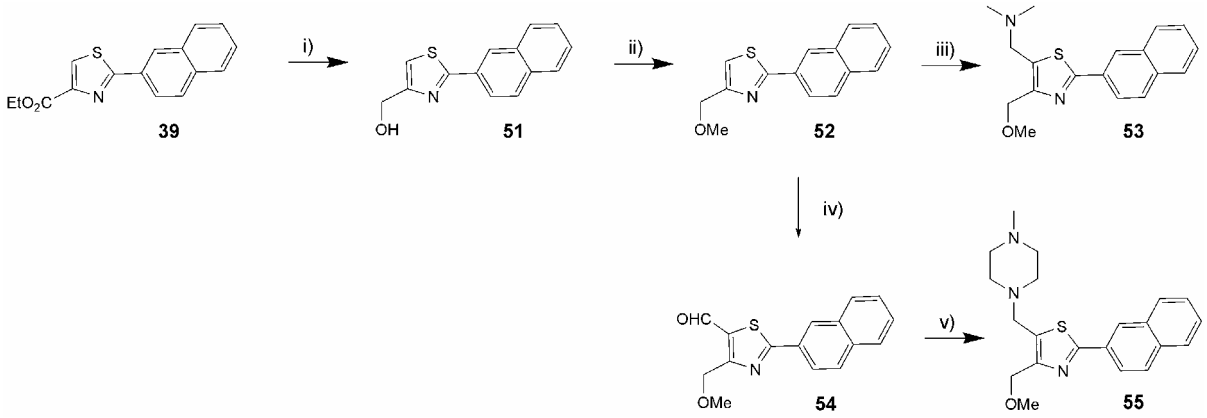


Figure 1 Crystal structure of indole derivative **50**. The ORTEP representation is shwon with atomic displacement parameter ellipsoids at the 50% probability level. Arbitrary numbering.

The structure of crystals of **50** obtained from MeCN was elucidated by X-ray analysis (Figure 1). The compound crystallizes in the triclinic space group $P\bar{1}$ with two symmetrically independent molecules related by a pseudo, non-crystallographic inversion centre.

Besides the intramolecular hydrogen bonds N(7)···N(21) (3.01/3.07 Å) each independent molecule forms a H-bond chain N(27)···O(23)' by a translation of the molecule along the crystallographic a-axis (2.80/2.78Å), which also leads to a partially parallel stacking of the naphthalene ring (Ring-plane distance 3.76/3.67Å). Closest contact between the two molecules occurs between C(11) and C(26)'of the naphthalene and indole ring (3.43/3.52Å) where the ring planes adopt a 30° inclined conformation.

Reduction of ester **39**, followed by the methylation of the resulting alcohol **51,** furnished the methoxy derivative **52** (Scheme 10). Lithiation and subsequent addition of *Eschenmoser* salt gave the desired tertiary amine **53** in moderate yield.

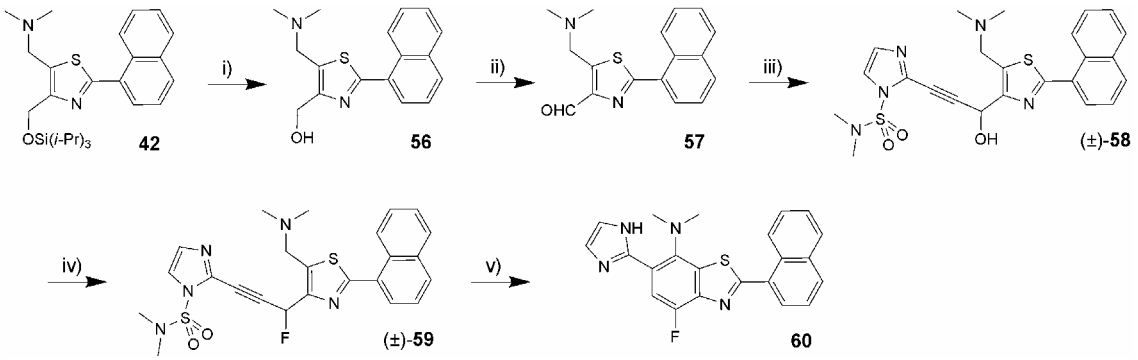


Reagents and conditions: i) DIBALH, CH_2Cl_2, –10 °C → rt, 4 h; 98%. ii)a) NaH, THF, 0 °C → rt, 40 min; b) MeI, 0 °C → rt, 5 h; 88%. iii) a) *n*-BuLi, THF, –78 °C, 10 min; b) $CH_2NMe_2^+ I^-$, –78 °C → rt, 5 h; 25%. iv) a) *n*-BuLi, THF, –78 °C → 0 °C, 20 min; b) DMF, –78 °C → rt, 2 h; 61%. v) *N*-Methylpiperazine, $NaBH(OAc)_3$, molecular sieves (4Å), CH_2Cl_2, 0 °C → rt, 21 h; 57%.

Scheme 10 Synthesis of piperazine derivative **55** by reductive amination.

Reductive amination of an aldehyde constitutes an alternative, general pathway for the introduction of the tertiary amine at C(5). As an example, 5-lithiated thiazole **52** was treated with DMF furnishing aldehyde **54**, which reacted with *N*-methylpiperazine in the presence of $NaBH(OAc)_3$ as the reducing agent to yield amine **55**.

For the introduction of the ethinylimidazole moiety in position 4 of 1-naphthyl-substituted thiazole **42**, the silyl ether was cleaved and the resulting alcohol **56** oxidized to aldehyde **57** (Scheme 11). Br/Li exchange on bromoacetylene **32** with *n*-BuLi generated the acetylide that was reacted *in situ* with aldehyde **57** giving access to propargylic alcohol (±)-**58**.



i) *n*-Bu_4NF, THF, rt, 1.5 h; 93%. ii) PyridineSO_3, Me_2SO, rt, 4 h, 75%. iii) *n*-BuLi, **32**, THF, –78 °C → rt, 70 min; 69%. iv) DAST, CH_2Cl_2, –78 °C, 1 h; 28%. v) NaOMe, MeOH, 4 h; 77%.

Scheme 11 Cyclization to the highly decorated benzothiazole **60**.

Treatment with DAST provided fluoride (±)-**59** in poor yield. When this compound was subjected to basic conditions, an interesting, unexpected cyclization to the highly substituted benzothiazole **60** occurred in high (77%) yield (Scheme 11). In the same reaction, the sulfamoyl protecting group was cleaved to furnish the unprotected imidazole moiety. Mechanism and scope of this cyclization are now under further investigation.

CONCLUSIONS

Three different routes are used to synthesize 2,4,5-trisubstituted thiazoles that were designed as potential inhibitors for the enzyme trypanothione reductase. While a number of specific derivatives were prepared as part of the target-oriented synthetic project, much of the methodology reported in this paper is applicable for a broader, more general decoration of the thiazole scaffold, thereby providing a diversity of compounds with the potential to serve as hits in various medicinal chemistry projects. In addition to the exploration of the three different strategies towards the target molecules, highlights in this work have been the first observation of the retro-*Brook*-rearrangement in thiazole chemistry and an unusual cyclization leading to a highly decorated benzothiazole scaffold. Mechanism and scope of the latter cyclization are being further explored.

EXPERIMENTAL

Solvents and reagents were of reagent-grade, purchased from commercial suppliers, and used without further purification unless otherwise stated. THF was freshly distilled from sodium benzophenone ketyl, CH_2Cl_2 from CaH_2. Evaporation *in vacuo* was conducted at 30–70 °C and 600–15 mbar pressure. Products were dried under high vacuum (10^{-2} Torr) before analytical characterization. Column chromatography: SiO_2-*60* (40–63 μm) from *Fluka*, 0-0.4 bar pressure. TLC: SiO_2-*60* F_{254}, *Merck*, visualization under UV light at 254 nm or staining with a solution of $KMnO_4$ (3 g) and K_2CO_3 (20 g) in

5% aqueous NaOH solution (5 mL) and H_2O (300 mL). Melting points (mp): *Büchi B-450* melting-point apparatus, uncorrected. IR: *Perkin-Elmer 1600-FT* spectrometer. NMR: *Varian Gemini-300* spectrometer; spectra were recorded at rt with solvent peak as reference. MS (m/z; %): EI-MS: *VG-TRIBID* spectrometer at 70 eV; ESI-MS: *Finnigan MAT TSQ TSQ 7000* spectrometer; MALDI-MS: *IonSpec Ultima* (2.5 dihydroxybenzoic acid (DHB) matrix or stated). Elemental analyses were performed by the *Mikrolabor* at the *Laboratorium für Organische Chemie, ETH Zürich*.

General procedure for cyclizations with *N,N*-dimethyl-2-chloroacetoacetamide (GP 1)

The thioamide compound (1 equivalent) and *N,N*-dimethyl-2-chloroacetoacetamide (1 equivalent) were heated to reflux in EtOH. Addition of saturated aqueous $NaHCO_3$ solution and extraction with AcOEt were followed by drying the organic phase with $MgSO_4$ and concentration under reduced pressure.

General procedure for the reduction of amides (GP 2)

The amide compound (1 equivalent) was dissolved in THF, and $LiAlH_4$ (1 M solution in THF, 3 equivalents) was dropped into the solution which was heated to reflux. After addition of MeOH at rt, the mixture was poured into a saturated aqueous $NaHCO_3$ solution and extracted with CH_2Cl_2. The organic phases were dried ($MgSO_4$) and concentrated under reduced pressure.

General procedure for the S_NAr reaction with 4-mercaptopyridine (GP 3)

4-Mercaptopyridine (1.1 equivalents) was dissolved in THF and cooled to –78 °C, then *n*-BuLi (1.6 M in hexane, 1 equivalent) was added. After 10 min, the solution was slowly transferred to the corresponding bromide (1 equivalent) dissolved in THF (15 mL). The mixture was allowed to warm to rt. Saturated aqueous NH_4Cl solution was added and the resulting mixture extracted with CH_2Cl_2/*i*-PrOH 67:33. The organic phase was dried ($MgSO_4$) and concentrated *in vacuo*.

General procedure for the replacement of an hydroxyl group by a fluorine (GP 4)

The propargylic alcohol (1 equivalent) was dissolved in CH_2Cl_2 and cooled to –78 °C, then DAST (1.1 equivalents) was added. The mixture was stirred at this temperature before it was poured into a mixture of saturated aqueous $NaHCO_3$ solution and ice. The solution was extracted with CH_2Cl_2 and the organic phase dried ($MgSO_4$) and concentrated *in vacuo*.

General procedure for the cyclization of a thioamide to a thiazole (GP 5)

The thioamide (1 equivalent) was dissolved in EtOH and ethyl bromopyruvate (**14**) (1.2 equivalents) was added. The mixture was heated to reflux for 30 min, allowed to cool to rt, and poured into saturated

aqueous $NaHCO_3$ solution This mixture was extracted with AcOEt, and the combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo.*

General procedure for the lithiation and subsequent attack on *Eschenmoser* salt (GP 6)

The thiazole (1 equivalent) was dissolved in THF and cooled to –78 °C. Then, *n*-BuLi (1.6 M in hexane, 1.1 equivalents) was slowly added and the mixture stirred for 5–10 min at –78 °C. The solution was transferred within 20 min *via* a cannula to a suspension of *Eschenmoser* salt (2 equivalents) in THF that was cooled to –78 °C. The mixture was stirred for 6 h while it was allowed to reach rt. After addition of saturated aqueous $NaHCO_3$ solution followed by H_2O, the mixture was extracted with AcOEt. The organic layers were dried ($MgSO_4$) and the solvent evaporated under reduced pressure.

General procedure for the deprotection of silyl-protected alcohols (GP 7)

The silyl ether (1 equivalent) was dissolved in THF, and *n*-Bu_4NF (1 M in THF, 1.2 equivalents) was added. The resulting solution was stirred for 3 h, before saturated aqueous solutions of NH_4Cl and Na_2CO_3 were added. After extraction with CH_2Cl_2/*i*-PrOH 67:33, the combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo*.

General procedure for the reduction of azides (GP 8)

The azide (1 equivalent) was dissolved in THF, and PMe_3 (1 M in THF, 1.5 equivalents), followed by H_2O and NaOH (1.5 equivalents) were added. The mixture was stirred for 22 h at rt or for 3 h at 50 °C before the solvent was removed under reduced pressure to give the crude amine.

General procedure for the coupling of primary amines with carboxylic acids (GP 9)

The acid (1 equivalent) was dissolved in THF, CDI (1 equivalent) was added and the resulting mixture stirred for 3 h at rt. A solution of the raw amine (1 equivalent) in THF was slowly dropped to the solution with the activated acid. The mixture was stirred for 20 h at rt before the solvent was removed under reduced pressure. Re-dissolving the residue in CH_2Cl_2/*i*-PrOH 67:33, washing with saturated aqueous $NaHCO_3$ solution, and extraction of the aqueous layer with CH_2Cl_2/*i*-PrOH 2:1 were followed by drying ($MgSO_4$) of the combined organic phases and concentrating *in vacuo*.

1*H*-Indole-5-carbothioamide (1)

Nitrile **2** (75 mg, 0.52 mmol) was dissolved in CH_2Cl_2 (5 mL) and *O*,*O*'-diethyl hydrogen dithiophosphate (0.20 mL, 1.05 mmol) added to the solution that was stirred for 15 h. As the conversion was not complete, additional *O*,*O*'-diethyl hydrogen dithiophosphate (0.50 mL, 2.66 mmol) was added and the

mixture stirred for another 20 h. The mixture was diluted by addition of EtOAc, washed with a saturated aqueous NaCl solution, and the aqueous phases extracted (EtOAc). The combined organic phases were dried ($MgSO_4$) and the residue purified by column chromatography (CC) (SiO_2; pentane/AcOEt 66:34 → 50:50) to give **1** as a yellow solid. Yield: 62 mg (68%). Mp: 163–164 °C. IR (neat): υ 3391, 3141, 2509, 2342, 1607, 1511, 1470, 1344, 1317, 1245, 890, 816, 765, 728, 678 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 6.54–6.55 (m, 1H); 7.30 (dd, J = 3.0, 2.8 Hz, 1H); 7.35 (d, J = 8.6 Hz, 1H); 7.79 (dd, J = 8.6, 1.8 Hz, 1H); 8.24 (d, J = 2.1 Hz, 1H); 10.79 (s, 1H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 103.8, 111.3, 121.5, 122.5, 127.2, 128.6, 131.8, 139.5, 204.2. EI-MS: 178.1 (39), 177.1 (59), 176.0 (37, M^+); 160.0 (16), 144.1 (54), 143.1 (100), 142.1 (100), 116.1 (40), 115.0 (51), 114.0 (22), 90.0 (12), 89.0 (22), 88.0 (17). EI-HRMS: 176.0403 (M^+, $C_9H_8N_2S^+$, calcd 176.0404).

1*H*-Indole-5-carbonitrile (2)

DMF (20 mL) was degassed in an ultrasonic bath for 20 min under Ar. 5-Bromoindole (0.95 g, 4.85 mmol) and CuCN (1.74 g, 19.38 mmol) were added and the mixture heated to reflux for 20 h. The solvent was evaporated under reduced pressure and the residue suspended in CH_2Cl_2. Concentrated aqueous ammonia was added and the mixture stirred for 1 h until it became a clear solution. Extraction (CH_2Cl_2), followed by drying of the organic phase ($MgSO_4$) and concentration *in vacuo* afforded a brownish residue. Purification by CC (SiO_2; hexane/AcOEt 75:25) afforded **2** as a white solid. Yield: 0.61 g (88%). Mp: 105 °C (Lit.,[32]: 104–106 °C). IR (neat): υ 3396, 2915, 2223, 1662, 1608, 1468, 1415, 1345, 1321, 1220, 1087, 885, 810, 739, 624 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 6.63–6.65 (m, 1H); 7.34–7.36 (m, 1H); 7.41–7.49 (m, 2H); 8.00 (s, 1H); 8.70 (brs 1H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 102.7, 103.4, 111.9, 120.7, 124.8, 126.3, 136.3, 137.5, 137.3. EI-MS: 143.1 (10), 142.1 (100, M^+); 115.0 (39), 114.0 (16). EI-HRMS: 142.0524 (M^+, $C_9H_6N^+$, calcd 142.0531).

2-(1*H*-Indol-5-yl)-*N*,*N*,4-trimethyl-1,3-thiazole-5-carboxamide (3)

GP 1, starting from **1** (40 mg, 227 μM), gave **3** after CC (SiO_2; pentane/AcOEt 50:50) as a colorless solid. Yield: 61 mg (94%). Mp: 159 °C. IR (neat): υ 3236, 1601, 1480, 1434, 1396, 1327, 1165, 1076, 885, 766, 734. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 2.48 (s, 3H); 3.10 (s, 6H); 6.55–6.57 (m, 1H); 7.18–7.20 (m, 1H); 7.35 (d, J = 8.4 Hz, 1H); 7.72 (dd, J = 8.4, 1.5 Hz, 1H); 8.19 (d, J = 1.5 Hz, 1H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 16.7, 103.1, 111.6, 119.4, 120.6, 123.1, 124.8, 125.7, 127.9, 137.1, 152.2, 164.3, 169.6 (2 aromatic signals hidden). MALDI-MS: 308.1 (10, $[M+Na]^+$); 287.1 (12), 286.1 (100, $[M+H]^+$); 241.0 (19). MALDI-HRMS: 286.1004 ($[M+H]^+$, $C_{15}H_{16}N_3OS^+$, calcd 286.1009).

1-[2-(1*H*-Indol-5-yl)-4-methyl-1,3-thiazol-5-yl]-*N*,*N*-dimethylmethanamine (4)

GP 2, starting from **3** (40 mg, 0.14 mmol), afforded **4** as red crystals after CC (SiO_2; CH_2Cl_2/MeOH 90:10). Yield: 34 mg (90%). Mp: 161 °C. IR (neat): υ 3079, 2938, 2821, 2358, 1662, 1418, 1325, 1234, 1096, 860, 829, 749 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 2.32 (s, 6H); 2.44 (s, 3H); 3.59 (s, 2H); 6.58–6.60 (m, 1H); 7.22 (dd, J = 3.6, 2.7 Hz, 1H); 7.38 (dd, J = 8.0, 0.8 Hz, 1H); 7.77 (dd, J = 8.0, 1.8 Hz, 1H); 8.20 (dd, J = 1.5, 0.8, Hz 1H); 8.53 (brs, 1H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 15.5, 45.2, 55.1, 103.4, 111.3, 119.0, 120.7, 125.2, 126.1, 128.0, 128.1, 136.6, 149.7, 167.5. MALDI-MS: 273.1 (15), 272.1 (100, $[M+H]^+$); 270.1 (47, $[M-H]^+$); 227.1 (33), 136.1 (8). MALDI-HRMS: 272.1211 ($[M+H]^+$, $C_{15}H_{17}N_3S^+$, calcd 272.1216).

***N*,*N*-Dimethyl-1-(4-methyl-2-pyridin-3-yl-1,3-thiazol-5-yl)methanamine (5)**

GP 2, starting from **7** (1.00 g, 4.04 mmol), gave **5** as a colorless oil after CC (SiO_2; CH_2Cl_2/MeOH 90:10). Yield: 0.40 g (43%). IR (neat): υ 3233, 2943, 2819, 2772, 1601, 1438, 1355, 1327, 1256, 1023, 765, 730, 704 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 2.27 (s, 3H); 2.41 (s, 6H); 3.57 (s, 2H); 7.33 (ddd, J = 8.1, 4.6, 0.8 Hz, 1H); 8.15 (ddd, J = 8.1, 2.7, 1.6 Hz, 1H); 8.58 (dd, J = 4.6, 1.6 Hz, 1H); 9.08 (dd, J = 2.7, 0.8 Hz, 1H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 15.3, 45.2, 55.0, 119.8, 123.7, 133.3, 139.5, 147.4, 150.3, 162.2 (1 signal missing). MALDI-MS: 250.1 (74, *N*-oxide); 249.1 (19), 234.1 (100, $[M+H]^+$); 233.1 (20), 232.1 (59), 189.1 (83). MALDI-HRMS: 234.1056 ($[M+H]^+$, $C_{13}H_{15}N_3S^+$, calcd 234.1059).

***N*,*N*,4-Trimethyl-2-pyridin-3-yl-1,3-thiazole-5-carboxamide (7)**

GP 1, starting from thionicotinamide (**6**) (1.50 g, 10.86 mmol), afforded **7** after CC (SiO_2; hexane/AcOEt 67:33) as a yellow solid. Yield: 1.58 g (59%). Mp: 63–64 °C. IR (neat): υ 2927, 2361, 1617, 1395, 1257, 1066, 1002, 734, 702, 668 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 2.50 (s, 3H); 3.11 (s, 6H); 7.38 (ddd, J = 8.1, 4.6, 1.2 Hz, 1H); 8.19 (ddd, J = 8.1, 2.3, 1.6 Hz, 1H); 8.55 (dd, J = 4.6, 1.6 Hz, 1H); 9.12 (dd, J = 2.3, 0.8 Hz, 1H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 16.6, 35.4, 123.7, 125.5, 129.0, 133.5, 147.5, 151.0, 152.9, 163.3, 163.8. MALDI-MS: 249.1 (7), 248.1 (100, $[M+H]^+$); 124.0 (6). MALDI-HRMS: 248.0848 ($[M+H]^+$, $C_{12}H_{13}N_3OS^+$, calcd 248.0852). *Anal.* Calcd for $C_{12}H_{13}N_3OS$ (247.317): C, 58.28; H, 5.30; N, 16.99. Found: C, 58.17; H, 5.43; N, 17.16.

2-Bromo-*N*,*N*,4-trimethyl-1,3-thiazole-5-carboxamide (8)

$CuBr_2$ (0.40g, 1.8 mmol) and isoamyl nitrite (0.31 mL, 2.3 mmol) were added to a suspension of amine **10** (0.28 mg, 1.5 mmol) in CH_3CN (10 mL) at 0 °C, and the mixture was stirred at this temperature for 2 h. The solvent was evaporated under reduced pressure and the residue dissolved again in AcOEt and washed with saturated aqueous NaCl solution. The aqueous phase was extracted with AcOEt, and the combined

organic phases were dried ($MgSO_4$) and concentrated *in vacuo* to provide **8** as a pale yellow oil after CC (SiO_2; AcOEt). Yield: 0.28 g (74%). IR (neat): υ 2923, 1626, 1394, 1061, 1033, 1004 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 2.41 (s, 3H); 3.07 (s, 6H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 16.7, 36.3, 38.5, 129.0, 136.2, 152.2, 162.6. EI-MS: 250.0 (34), 248.0 (33, M^+); 206.0 (100), 204.0 (96), 169.0 (95), 72.0 (34). EI-HRMS: 247.9610 (M^+, $C_7H_9BrN_2OS^+$, calcd 247.9619).

2-Amino-*N*,*N*,4-trimethyl-1,3-thiazole-5-carboxamide (10)

GP 1, starting from thiourea (**9**) (7.61 g, 0.10 mol), gave a residue that was dissolved in H_2O. The pH was adjusted to 7 by addition of Na_2CO_3, the resulting suspension filtered, and the residue washed with Et_2O to furnish **10** as a white solid. Yield: 17.20 g (93%). Mp: 237 °C (Lit.,[33]: 236–238 °C). IR (neat): υ 3264, 3096, 2467, 2278, 1589, 1495, 1375, 1305, 1072, 736 cm^{-1}. ^{1}H-NMR (300 MHz, CD_3OD): δ 2.16 (s, 3H); 3.06 (s, 6H). ^{13}C-NMR (75 MHz, CD_3OD): δ 15.4, 36.8, 111.5, 149.4, 165.6, 170.1. EI-MS: 185.1 (36, M^+); 141.0 (100), 145.1 (25), 114.1 (12), 72.0 (17). EI-HRMS: 185.0616 (M^+, $C_7H_{11}N_3OS^+$, calcd 185.0623).

***N*,*N*,4-Trimethyl-2-(pyridin-4-ylthio)-1,3-thiazole-5-carboxyamide (11)**

NaH (60% dispersion in mineral oil, 0.12 g, 3.0 mmol), followed by thiazole **8** (0.37 g, 2.0 mmol) was added at 0 °C to a solution of 4-mercaptopyridine (0.21 g, 1.8 mmol) in CH_3CN (10 mL). After stirring for 3.5 d at rt, the solvent was evaporated under reduced pressure, leaving a residue that was dissolved in CH_2Cl_2 and washed with saturated aqueous $NaHCO_3$ solution and H_2O. The aqueous phases were extracted with CH_2Cl_2 and the combined organic phases dried ($MgSO_4$) and concentrated *in vacuo*. CC (SiO_2; AcOEt/EtOH 100:0 → 70:30) provided **11** as a pale yellow oil. Yield: 0.33 g (66%). IR (neat): υ 3033, 2922, 1626, 1567, 1393, 1063, 805, 701 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 2.49 (s, 3H); 3.08 (s, 6H); 7.37 (d, J = 4.8 Hz, 2H); 8.52 (d, J = 4.8 Hz, 2H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 16.7, 36.0, 39.1, 123.4, 129.8, 146.5, 149.4, 153.7, 156.9, 162.8. ESI-MS: 282.1 (37), 281.1 (33), 280.1 (100, $[M+H]^+$); 140.0 (16). ESI-HRMS: 280.0569 ($[M+H]^+$, $C_{12}H_{14}N_3OS_2^+$, calcd 280.0578).

***N*,*N*-Dimethyl-1-[4-methyl-2-(pyridin-4-ylthio)-1,3-thiazol-5-yl]methanamine (12)**

GP 2, staring from **11** (0.17 g, 0.61 mmol), afforded **12** after CC (SiO_2; AcOEt) as a yellow oil. Yield: 60 mg (37%). IR (neat): υ 3031, 2933, 2921, 1543, 1387, 1301, 1298, 1174, 946 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 2.25 (s, 6H); 2.39 (s, 3H); 3.52 (s, 2H); 7.15 (dd, J = 4.5, 1.5 Hz, 2H); 8.41 (dd, J = 4.5, 1.5 Hz, 2H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 15.4, 45.3, 55.1, 122.0, 136.1, 146.5, 149.6, 151.0, 153.3. ESI-MS: 257.1 (15), 266.1 (100, $[M+H]^+$); 221.0 (69). ESI-HRMS: 266.0785 ($[M+H]^+$, $C_{13}H_{15}N_3S_2^+$, calcd 266.0786).

Ethyl 2-bromo-5-[(dimethylamine)methyl]-1,3-thiazole-4-carboxyate (15)

Dibromothiazole **13** (2.00 g, 6.35 mmol) was dissolved in THF (120 mL) and cooled to –78 °C, then *i*-PrMgCl (2 M in THF, 3.5 mL, 6.99 mmol) added dropwise. After stirring for 15 min, the deep red solution was transferred at –60 °C to a suspension of *Eschenmoser* salt (2.35 g, 12.70 mmol) in THF (60 mL) and slowly warmed to 0 °C. After 4 h, 1 M aqueous HCl was added and the mixture further extracted with 1 M aqueous HCl. The combined aqueous phases were neutralized by addition of saturated aqueous Na_2CO_3 solution and extracted with CH_2Cl_2/*i*-PrOH 67:33. The combined organic phases were dried ($MgSO_4$), and the solvent was removed under reduced pressure. Amine **15** was obtained as a yellow oil after CC (SiO_2; hexane/AcOEt 75:25). Yield: 1.22 g (66%). IR (neat): υ 2979, 2825, 2777, 1734, 1707, 1445, 1366, 1317, 1199, 1156, 1021, 785, 763 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.39 (t, J = 7.2 Hz, 3H), 2.35 (s, 6H), 3.97 (s, 2H,), 4.39 (q, J = 7.2 Hz, 2H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 14.5, 46.0, 56.7, 61.6, 135.2, 140.1, 155.6, 161.1. EI-MS: 294.0 (7), 292.0 (7, M^+); 247.9 (35), 245.9 (32), 219.9 (23), 139.0 (100), 114.0 (46). EI-HRMS: 291.9877 (M^+, $C_9H_{13}N_2O_2BrS^+$, calcd 291.9881). *Anal.* Calcd for $C_9H_{13}N_2O_2BrS$ (293.18): C, 36.87; H, 4.47; N, 9.55. Found: C, 37.07; H, 4.57; N, 9.29.

Ethyl 5-[(dimethylamino)methyl]-2-(pyridin-4-ylthio)-1,3-thiazole-4-carboxylate (16)

GP 3, starting from **15** (0.11 g, 0.38 mmol) gave **16** after CC (SiO_2; hexane/AcOEt 60:40 → 0:100) as a pale yellow oil. Yield: 37 mg (31%). IR (neat): υ 2976, 2942, 2823, 2776, 2359, 2341, 1707, 1570, 1405, 1320, 1206, 1028, 631 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.39 (t, J = 7.2 Hz, 3H); 2.32 (s, 6H); 3.99 (s, 2H); 4.39 (q, J = 7.2 Hz, 2H); 7.24 (dd, J = 4.6, 1.5 Hz, 2H); 8.48 (dd, J = 4.6, 1.5 Hz, 2H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 14.4, 46.0, 56.8, 61.5, 123.2, 141.5, 144.9, 149.9, 155.6, 156.5, 161.5. MALDI-MS (3-HPA (3-hydroxypicolinic acid)): 326.1 (8), 325.1 (13), 324.1 (100, $[M+H]^+$); 322.1 (19), 279.0 (23). MALDI-HRMS (3-HPA) 324.0829 ($[M+H]^+$), $C_{14}H_{18}N_3O_2S_2^+$, calcd: 324.0835).

Ethyl 5-bromo-2-(pyridin-4-ylthio)-1,3-thiazole-4-carboxylate (17)

GP 3, starting from **13** (1.50 g, 4.13 mmol), afforded **17** as a yellow solid after CC (SiO_2; hexane/AcOEt 75:25 → 50:50). Yield: 0.45 g (33 %). Mp: 101 °C. IR (neat): υ 2919, 2849, 1714, 1622, 1568, 1403, 1295, 1194, 1008, 977, 807 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.34 (t, J = 7.2 Hz**,** 3H), 4.39 (q, J = 7.2 Hz, 2H), 7.32 (dd, J = 4.6, 1.6 Hz, 2H), 8.57 (dd, J = 4.6, 1.6 Hz, 2H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 14.3, 62.1, 99.8, 123.8, 124.8, 144.2, 145.4, 150.5, 160.0. EI-MS: 294.0 (7), 292.0 (7, M^+); 247.9 (35), 245.9 (32), 219.9 (23), 139.0 (100), 114.0 (46). EI-HRMS: 291.9877 (M^+, $C_9H_{13}N_2O_2BrS^+$, calcd 291.9881).

Ethyl 5-bromo-2-(2-methylphenyl)-1,3-thiazole-4-carboxyate (18) and ethyl 2,5-bis(2-methylphenyl)-1,3-thiazole-4-carboxylate (19)

Dibromide **13** (1.17 g, 3.70 mmol) was mixed with 2-tolylboronic acid (0.5 g, 3.68 mmol) and Cs_2CO_3 (6.03 g, 18.5 mmol) in DME (30 mL). H_2O (2.5 mL) was added and the suspension degassed in the ultrasonic bath for 20 min under Ar. $[Pd(PPh_3)_4]$ (0.17 g, 0.15 mmol) was added and the mixture stirred for 15 h at 80 °C. The solution was allowed to cool to rt and saturated aqueous solutions of NH_4Cl and $NaHCO_3$ were added and the mixture extracted with AcOEt and CH_2Cl_2. The organic phases were dried ($MgSO_4$), and the solvent was removed under reduced pressure to give, after CC (SiO_2; hexane/AcOEt 90:10) **18** and **19**. **18**: pale yellow oil. Yield: 0.40 g (35%). IR (neat): υ 2975, 1719, 1473, 1302, 1229, 1199, 1033, 1010, 761, 632 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.44 (t, J = 7.1 Hz**,** 3H), 2.56 (s, 3H), 4.45 (q, J = 7.1 Hz**,** 2H), 7.26–7.33 (m, 3H), 7.63 (d, J = 7.8 Hz, 1H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 14.5, 21.3, 61.8, 116.9, 126.2, 129.8, 130.3, 131.4, 131.7, 136.7, 143.5, 161.0, 167.3. EI-MS: 327.0 (95), 325.0 (92, M^+); 281.9 (13), 279.9 (13), 252.9 (100), 250.9 (97), 218.0 (55), 172.0 (26). EI-HRMS: 324.9766 (M^+, $C_{13}H_{12}NO_2BrS^+$, calcd 324.9772).

19: colorless oil. Yield: 0.154 g (13%). IR (neat): υ 2979, 2359, 2342, 1719, 1474, 1444, 1324, 1185, 1026, 753, 668, 633 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.03 (t, J = 7.2 Hz, 3H); 2.17 (s, 3H); 2.56 (s, 3H); 4.13 (q, J = 7.2 Hz, 2H); 7.14–7.27 (m, 7H); 7.70 (d, J = 7.5 Hz, 1H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 14.0, 20.3, 21.6, 61.1, 125.4, 126.1, 129.1, 129.7, 129.8, 129.9, 130.0, 130.0, 130.3, 131.4, 126.6, 127.2, 142.2, 145.5, 161.7, 166.1. EI-MS: 337.1 (18, M^+); 327.0 (23), 325.0 (22), 314.8 (25), 286.8 (20), 280.9 (21), 271.8 (25), 267.8 (24), 244.8 (28), 236.0 (26), 235.0 (43), 225.9 (47), 198.9 (42), 174.0 (62), 147.0 (38), 29.0 (100). EI-HRMS: 337.1132 (M^+, $C_{20}H_{19}NO_2S$, calcd 337.1137).

2,5-Dibromo-1,3-thiazole-4-carbaldehyde (20)

Starting from alcohol **21**:

Alcohol **21** (335 mg, 1.23 mmol) was dissolved in CH_2Cl_2 (20 mL) and cooled to 0 °C, when *Dess-Martin* periodinane (15 weight%, in CH_2Cl_2, 3.15 mL, 1.47 mmol) was added and the mixture stirred for 3 h while allowing warming to rt. The reaction was stopped by addition of saturated aqueous NaCl solution and extracted with CH_2Cl_2. The organic phase was dried ($MgSO_4$) and concentrated *in vacuo*. CC (SiO_2; hexane/AcOEt 75:25) afforded **20** as a white solid. Yield: 323 mg (97%).

Starting from Weinreb *amide* **22**:

Amide **22** (0.17 g, 0.50 mmol) was dissolved in CH_2Cl_2 (10 mL) and cooled to –78 °C, before DIBALH (1 M in CH_2Cl_2, 0.80 mL, 0.80 mmol) was dropped to the solution. The mixture was stirred at this temperature for 2 h before MeOH was carefully added, followed by AcOEt. The solution was further diluted with H_2O and extracted with CH_2Cl_2. The combined organic phases were dried ($MgSO_4$) and the

solvent evaporated under reduced pressure to give, after CC (SiO_2, hexane/AcOEt 67:33), aldehyde **20**. Yield: 0.12 g (84%). Mp: 100 °C. IR (neat): υ 3373, 2921, 2839, 2749, 1738, 1693, 1464, 1427, 1249, 1042, 1012, 946, 693 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 9.95 (s, 1H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 120.8, 137.1, 149.5, 181.5. EI-MS: 272.8 (37), 270.8 (72), 268.8 (35, M^+); 191.9 (100), 189.9 (99), 163.9 (17), 161.9 (15), 136.9 (17), 134.9 (15). EI-HRMS: 268.8144 (M^+, $C_4HNOBr_2S^+$, calcd 268.8146). *Anal.* Calcd for C_4HNOBr_2S (270.93): C, 17.73; H, 0.37; N, 5.17. Found: C, 17.71; H, 0.36; N, 5.25.

(2,5-Dibromo-1,3-thiazol-4-yl)methanol (21)

Ester **13** (1.00g, 3.18 mmol) was dissolved in CH_2Cl_2 (10 mL) and cooled to –78 °C. Then, DIBALH (1 M in CH_2Cl_2, 5.0 mL, 5.00 mmol) was added slowly. After stirring for 2 h at this temperature, TLC analysis showed that the reaction had partially delivered alcohol **21** while ester **13** was still present. Additional DIBALH (1 M in CH_2Cl_2, 4.0 mL, 4.00 mmol) was added and the mixture stirred for 15 h at rt. Addition of a solution of potassium sodium tartrate, extraction with AcOEt and CH_2Cl_2, drying of the combined organic phases ($MgSO_4$), and concentration under reduced pressure provided **21** after CC (SiO_2; hexane/AcOEt 80:20). Yield: 0.40 g (46%). Mp: 84 °C. IR (neat): υ 3308, 2938, 2809, 1721, 1517, 1517, 1414, 1046, 1011, 969, 732 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 3.52 (t, J = 6.3 Hz, 1H); 4.64 (d, J = 6.3 Hz, 2H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 58.1, 107.7, 135.7, 154.4. EI-MS: 274.8 (27), 273.8 (16), 272.8 (52), 271.8 (27), 270.8 (27, M^+); 245.8 (53), 243.8 (100), 241.8 (50), 193.9 (35), 11.9 (36), 87.0 (14). EI-HRMS: 270.8295 (M^+, $C_4H_3NOBr_2S^+$, calcd 270.8302).

2,5-Dibromo-*N*-methoxy-*N*-methyl-1,3-thiazole-4-carboxamide (22)

Ester **13** (1.00 g, 3.18 mmol) was dissolved in CH_2Cl_2 (10 mL) and cooled to 0 °C before $AlMe_3$ (2 M in toluene, 3.95 mL, 7.94 mmol) was slowly added. The mixture was stirred at this temperature for 20 min and for 20 min at rt. By the means of a cannula, MeONHMe·HCl (0.78 g, 7.94 mmol) in CH_2Cl_2 (7 mL) was slowly added to the mixture which was again cooled to 0 °C. After stirring for 30 min at this temperature, the mixture was allowed to warm to rt and stirred for additional 2 h. The reaction was stopped by careful addition of 2 M aqueous HCl. After addition of saturated aqueous NaCl solution and extraction with AcOEt, followed by the drying of the organic phase with $MgSO_4$ and concentration under reduced pressure, **22** was obtained after purification by CC (SiO_2, hexane/AcOEt 67:33). Yield: 0.98 g (93%). IR (neat): υ 2933, 1653, 1507, 1425, 1176, 1099, 1020, 986, 633 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 3.33 (s, 3H); 3.72 (s, 3H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 32.7, 61.9, 111.5, 135.0, 147.5, 162.2. EI-MS: 329.9 (6), 327.9 (3, M^+); 298.8 (9), 286.8 (5), 271.8 (55), 269.8 (100), 267.8 (53), 241.8 (14), 82.0 (18). EI-HRMS: 327.8510 (M^+, $C_6H_6N_2O_2Br_2S^+$, calcd 327.8517).

1-(2,5-Dibromo-1,3-thiazol-4-yl)prop-2-yn-1-ol ((±)-23)

Aldehyde **20** (0.20 g, 0.74 mmol) was dissolved in THF (15 mL), when ethynylmagnesium bromide (0.5 M in THF, 1.8 mL, 0.87 mmol) was dropped to the solution at 0 °C. After stirring for 30 min, the mixture was allowed to warm to rt and stirred for additional 2 h. Saturated aqueous solutions of NH_4Cl and $NaHCO_3$ were added, and the mixture was extracted with AcOEt and CH_2Cl_2. The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo*, and CC (SiO_2; hexane/AcOEt = 100:0 → 67:33) afforded (±)-**23** as colorless crystals. Yield: 0.19 mg (87%). Mp: 64–65 °C. IR (neat): υ 3263, 2917, 2109, 1618, 1516, 1412, 1058, 1031, 964, 766, 658 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 2.64 (d, J = 2.1 Hz, 1H); 2.97 (d, J = 8.9 Hz, 1H); 5.52 (dd, J = 8.9, 2.1 Hz, 1H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 58.4, 74.9, 81.0, 107.5, 136.3, 152.8. EI-MS: 298.8 (24), 296.8 (46), 294.8 (22, M^+); 269.8 (30), 267.8 (44), 265.8 (21), 243.8 (100), 241.8 (51), 217.9 (20), 215.9 (22), 189.9 (27), 124.9 (19), 122.9 (19), 109.0 (21), 93.0 (23), 83.0 (22), 82.0 (35). EI-HRMS: 294.8298 (M^+, $C_6H_3NOBr_2S^+$, calcd 294.8302).

1-(2,5-Dibromo-1,3-thiazol-4-yl)-3-(triisopropylsiliyl)prop-2-yn-1-ol ((±)-24)

Bromoethynyltriisopropylsilane (0.168 g, 0.62 mmol) was dissolved in THF (20 mL) and cooled to –78 °C. *i*-PrMgCl (2 M in THF) was dropped to the solution which was stirred 30 min, before aldehyde **20** (0.222 g, 0.85 mmol) dissolved in THF (7 mL) was added at 0 °C. The mixture was stirred for 1 h at 0 °C and 4 h at rt. Addition of saturated aqueous solutions of $NaHCO_3$ and $NaHCO_3$, extraction with AcOEt and CH_2Cl_2, drying with $MgSO_4$, concentration *in vacuo*, and purification by CC (SiO_2; hexane/AcOEt 67:33) afforded (±)-**24** as a colorless oil. Yield: 180 mg (64%). IR (neat): υ 3292, 2940, 2864, 1464, 1413, 1382, 1061, 1043, 991, 880, 769, 659, 676, 642 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.05 (s, 21H); 3.08 (d, J = 8.9 Hz, 1H), 5.52 (d, J = 8.9 Hz, 1H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 11.1, 18.6, 59.2, 88.4, 104.1, 106.7, 135.4, 153.5. EI-MS: 453.0 (12), 451.0 (5, M^+); 411.9 (53), 410.0 (100), 407.9 (49), 367.8 (11), 287.9 (10), 285.9 (11), 177.0 (20), 138.9 (26). EI-HRMS: 450.9633 (M^+, $C_{15}H_{23}NOBr_2SSi^+$, calcd 450.9636).

2,5-Dibromo-4-(1-fluoroprop-2-yn-1-yl)-1,3-thiazole ((±)-25)

GP 4, starting from (±)-**23** (50 mg, 0.17 mmol), gave (±)-**25** as a brown oil after CC (SiO_2; hexane/AcOEt 80:20). Yield: 20 mg (40%). IR (neat): υ 3292, 2940, 2864, 2124, 1684, 1512, 1419, 1039, 991, 767, 642 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 2.91 (dd, J = 5.4, 2.3 Hz, 1H); 6.18 (dd, J = 46.4, 2.3 Hz, 1H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 74.4, 76.7, 79.9, 111.8, 136.4 (CHF signal not visible). EI-MS: 300.8 (36), 298.8 (67), 296.8 (33, M^+); 219.9 (100), 204.0 (96), 217.9 (100), 113.0 (79). EI-HRMS: 296.8252 (M^+, $C_6H_2NBr_2FS^+$, calcd 296.8259).

2-(2,2-Dibromovinyl)-*N*,*N*-dimethyl-1*H*-imidazole-1-sulfonamide (27)

Aldehyde **26**[17] (1.02 g, 5.0 mmol) was dissolved in CH_2Cl_2 (30 mL) and cooled to 0 °C, then CBr_4 (4.97 g, 15.0 mmol), followed by PPh_3 (3.93 g, 15.0 mmol), was added. The mixture was stirred for 2 h at this temperature and for 2 h at rt. Pentane (20 mL) was added and the resulting suspension filtered. The filtrate was concentrated under reduced pressure and purified by CC (SiO_2; pentane/AcOEt 50:50) to yield **27** as white crystals. Yield: 1.70 g (95%). Mp: 89–90 °C. IR (neat): υ 3162, 3113, 3076, 1595, 1514, 1452, 1377, 1184, 1151, 1110, 962, 734, 620 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 2.87 (s, 6H); 7.19 (d, J = 1.5 Hz, 1H); 7.33 (d, J = 1.5 Hz, 1H); 7.85 (s, 1H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 38.4, 97.1, 129.4, 124.6, 128.9, 142.0. MALDI-MS (DHB tl): 361.9 (8), 359.9 (15), 357.9 (7, $[M+H]^+$); 327.0 (5), 325.0 (6) 279.1 (23), 274.0 (15) 273.0 (100, Matrix); 252.9 (10). MALDI-HRMS (DHB tl): 357.8856 ($[M+H]^+$, $C_7H_{10}N_3O_2Br_2S^+$, calcd 357.8860). *Anal.* Calcd for $C_7H_9N_3O_2Br_2S$ (359.04): C, 23.42; H, 2.53; N, 11.70; O, 8.91; S, 8.93; Br, 44.5. Found: C, 23.61; H, 2.37; N, 11.52; O, 8.99; S, 9.00; Br, 44.31.

2-Ethynyl-*N*,*N*-dimethyl-1*H*-imidazole-1-sulfonamide (28) and
2-[(*E*)-2-bromovinyl]-*N*,*N*-dimethyl-1*H*-imidazole-1-sulfonamide (29)

Dibromide **27** (0.20 g, 0.56 mmol) was dissolved in THF (20 mL) and cooled to –78 °C. At this point, *n*-BuLi (*ca.* 1.6 M in hexane, 0.75 mL, 1.23 mmol) was slowly dropped to the solution which was stirred for 2 h. The mixture was allowed to reach rt and 1 M aqueous HCl (2 mL) was added. Dilution with H_2O, followed by washing with saturated aqueous NaCl solution, extraction of the aqueous phases with CH_2Cl_2, drying of the combined organic phases with $MgSO_4$ and concentration *in vacuo* afforded **28** and **29** after CC (SiO_2; pentane/AcOEt 50:50). **28**: brown solid. Yield: 63 mg (57%). Mp: 56–57 °C. IR (neat): υ 2957, 2928, 1724, 1634, 1275, 1118, 1071, 610 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 2.95 (s, 6H); 3.41 (s, 1H); 7.04 (d, J = 1.5 Hz, 1H); 7.31 (d, J = 1.5 Hz, 1H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 38.8, 73.0, 82.9, 121.4, 129.3, 171.3. EI-MS: 199.0 (4, M^+); 169.0 (5), 131.0 (21), 119.0 (15), 108.0 (10), 100.0 (7), 69.0 (68), 44.0 (4). EI-HRMS: 199.0417 (M^+, $C_7H_9N_3O_2S^+$, calcd 199.0416).

29: white solid. Yield: 40 mg (26%). Mp: 109 °C. IR (neat): 3166, 3087, 2926, 2359, 1594, 1458, 1379, 1155, 1102, 936, 730. ^{1}H-NMR (300 MHz, $CDCl_3$): 2.87 (s, 6H); 7.04 (d, J = 1.5, 1H); 7.29 (d, J = 1.5, 1H), 7.39–7.52 (m, 2H). ^{13}C-NMR (75 MHz, $CDCl_3$): 38.4, 115.3, 120.3, 123.9, 128.7 (1 aromatic signal not visible). EI-MS: 281.0 (17), 279.0 (19, M^+), 200.1 (12), 173.0 (18), 171.0 (17), 136.1 (28), 108.0 (100), 92.0 (60). EI-HRMS: 278.9673 (M^+, $C_7H_{10}N_3O_2BrS^+$, calcd 278.9677).

_N,N_-Dimethyl-2-[(tributylstannanyl)ethynyl]-1_H_-imidazole-1-sulfonamide (30) and 2-[(_Z_)-2-bromo-2-(tributylstannanyl)vinyl]-_N,N_-dimethyl-1_H_-imidazole-1-sulfonamide (31)

Dibromide **27** (0.5 g, 1.39 mmol) was dissolved in THF (50 mL) and cooled to –78 °C. *n*-BuLi (1.6 M in hexane, 1.9 mL, 3.06 mmol) was slowly dropped to the solution. The mixture was stirred at this temperature for 15 min. *n*-Bu_3SnCl (0.38 mL, 1.39 mmol) was dropped to the dark red mixture which was stirred for 1 h at –78 °C and for 3 h at rt. The solvent was evaporated under reduced pressure and the residue dissolved in CH_2Cl_2 and washed with saturated aqueous $NaHCO_3$ solution. The aqueous phase was extracted with CH_2Cl_2, and the combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. Purification by CC (SiO_2; pentane/AcOEt 80:20) afforded **30** and **31**. **30**: green oil. Yield: 0.27g (40%). IR (neat): υ 3724, 2955, 2922, 2360, 2120, 1510, 1392, 1167 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 0.90 (t, J = 7.5 Hz, 9H); 1.05–1.63 (m, 18H); 2.95 (s, 6H); 6.99 (d, J = 1.2 Hz, 1H); 7.26–7.27 (m, 1H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 11.5, 13.8, 27.2, 29.0, 38.9, 120.6, 128.8, 168.0, 177.0 (1 aromatic signal not visible).

31: green oil. Yield: 0.27g (34%). IR (neat): 2954, 2919, 2852, 2324, 1457, 1394, 1182, 1157, 967, 728. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 0.82–1.54 (m, 27H); 2.86 (s, 6H); 6.91 (d, J = 1.5 Hz, 1H); 7.28 (d, J = 1.5 Hz, 1H); 8.09 (s, 1H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 13.8, 27.3, 27.4, 29.0, 38.4, 120.2, 127.5, 132.4, 145.3, 145.8.

2-(Bromoethynyl)-_N,N_-dimethyl-1_H_-imidazole-1-sulfonamide (32)

Dibromide **27** (1.68 g, 4.68 mmol) was dissolved in THF (60 mL), and NaH (~60 weight% in mineral oil, 0.22 g, 5.62 mmol) was added. After stirring for 15 h, H_2O was added and the mixture extracted with AcOEt. The organic phase was dried ($MgSO_4$) and concentrated under reduced pressure. CC (SiO_2; hexane/AcOEt 60:40 → 50:50) gave **32** as a white solid. Yield: 1.03 g (79%). Mp: 100 °C. IR (neat): υ 3158, 2970, 2192, 1738, 1390, 1158, 1167, 965, 727 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 2.93 (s, 6H); 7.00 (d, J = 1.4 Hz, 1H); 7.28 (d, J = 1.3 Hz, 1H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 38.6, 57.6, 70.0, 121.0, 128.9, 129.3. EI-MS: 279.0 (11), 177.0 (11, M^+), 206.9 (6), 173.0 (5), 171.0 (9), 108.0 (100), 92.0 (9). EI-HRMS: 276.9518 (M^+, $C_7H_8N_3O_2BrS^+$, calcd 276.9521). *Anal*. Calcd for $C_7H_8N_3O_2BrS$ (278.13): C, 30.23; H, 2.90; N, 15.11. Found: C, 30.51; H, 3.09; N, 14.92.

2-Bromo-5-[(dimethylamine)methyl]-1,3-thiazole-4-carbaldehyde (33)

Ester **15** (91 mg, 0.31 mmol) was dissolved in CH_2Cl_2 (10 mL) and cooled to –78 °C, then DIBALH (1 M in CH_2Cl_2, 0.37 mL, 0.37 mmol) was dropped to the solution that was stirred at this temperature for 2 h. After addition of MeOH (1 mL), followed by AcOEt (5 mL), the mixture was allowed to warm to rt, further diluted with AcOEt, and washed with saturated aqueous $NaHCO_3$ solution. The aqueous phases

were extracted with CH_2Cl_2 and the combined organic phases dried ($MgSO_4$) and evaporated under reduced pressure. Purification by CC (SiO; hexane/AcOEt 67:33) provided **33** as pale yellow oil. Yield: 53 mg (69%). IR (neat): υ 2945, 2825, 2778, 1691, 1519, 1443, 1339, 1203, 1030, 842, 722, 657 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 2.35 (s, 6H); 4.00 (s, 2H); 10.01 (s, 1H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 46.1, 56.0, 136.0, 148.2, 155.8, 185.6. EI-MS: 250.0 (28); 248.0 (20, M^+); 235.0 (22), 233.0 (19), 205.9 (15), 203.9 (15), 169.0 (14), 131.0 (18), 119.0 (24), 110.1 (100), 69.0 (38), 58.0 (40). EI-HRMS: 247.9617 (M^+, $C_7H_9N_2OBrS^+$, calcd 247.9619).

2-(3-{2-Bromo-5-[(dimethylamino)methyl]-1,3-thiazol-4-yl}-3-hydroxyprop-1-yn-1-yl)-*N*,*N*-dimethyl-1*H*-imidazole-1-sulfonamide ((±)-34)

Bromoacetylene **32** (98 mg, 0.35 mmol) was dissolved in THF (5 mL) and cooled to –78 °C, then *i*-PrMgCl (2 M in THF, 0.18 mL, 0.35 mmol) was slowly added dropwise. The mixture was allowed to warm to 0 °C and transferred by means of a cannula to aldehyde **33** (134 mg, 0.54 mmol) that was dissolved in THF (10 mL) and cooled to –78 °C. This mixture was allowed to warm to rt and stirred for a total of 5 h, before saturated aqueous $NaHCO_3$ solution was added. The mixture was extracted with Et_2O and CH_2Cl_2 and the separated organic phases dried ($MgSO_4$) and concentrated under reduced pressure. Alcohol (±)-**34** was obtained as pale yellow oil after purification by CC (SiO_2; AcOEt/MeOH 90:10). Yield: 92 mg (58%). IR (neat): υ 3645, 3136, 2988, 2341, 1502, 1435, 1326, 1176, 1143, 1103, 1002, 953, 836, 734, 664 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 2.32 (s, 6H); 2.90 (s, 6H); 3.36 (d, J = 14.3 Hz, 1H); 4.07 (d, J = 14.3 Hz, 1H); 5.76 (s, 1H); 7.00 (d, J = 1.5 Hz, 1H); 7.28 (d, J = 1.5 Hz, 1H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 38.5, 44.5, 53.1, 60.7, 73.8, 92.9, 121.1, 128.7, 129.5, 132.2, 135.2, 153.3. MALDI-MS (3-HPA): 472.0 (7), 470.0 (6, ($[M+Na]^+$); 451.0 (17), 450.0 (100), 449.0 (13), 448.0 (72, $[M+H]^+$); 405.0 (13), 403.0 (13), 341.0 (35), 339.0 (34). MALDI-HRMS (3-HPA) 448.0101 (72, $[M+H]^+$, $C_{14}H_{19}N_5O_3BrS_2^+$, calcd: 448.0107).

2-[(1*E*)-3-{2-Bromo-5-[(dimethylamino)methyl]-1,3-thiazol-4-yl}-3-oxoprop-1-en-1-yl]-*N*,*N*-dimethyl-1*H*-imidazole-1-sulfonamide (35)

A solution of (±)-**34** in $CDCl_3$ showed quantitative rearrangement within 5 d to enone **35**. IR (neat): υ 3675, 2984, 2778, 2359, 2341, 1663, 1606, 1505, 1441, 1376, 1188, 1155, 1105, 1037, 1006, 731, 668 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 2.37 (s, 6H); 2.90 (s, 6H); 4.04 (s, 2H); 7.21 (d, J = 1.3 Hz, 1H); 7.45 (d, J = 1.3 Hz, 1H); 8.11 (d, J = 15.6 Hz, 1H); 8.25 (d, J = 15.6 Hz, 1H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 38.4, 46.1, 57.2, 122.4, 128.5, 129.3, 129.7, 134.1, 143.8, 147.4, 156.6, 193.1. MALDI-MS (3-HPA): 450.0 (29), 449.0 (47), 448.0 (100, $[M+H]^+$); 447.0 (40, M^+); 405.0 (20), 403.0 (21), 368.1 (13). MALDI-HRMS (3-HPA): 447.0013 (M^+, $C_{14}H_{19}N_5O_3BrS_2^+$, calcd: 447.0034).

Ethyl 2-(1-naphthyl)-1,3-thiazole-4-carboxylate (38)

GP 5, starting from 1-naphthylthioamide (**36**) (0.84 g, 4.46 mmol), gave **38** as a pale yellow solid after CC (SiO_2; hexane/AcOEt 80:20). Yield: 1.05 g (83%). Mp: 62 °C. IR (neat): υ 2982, 1729, 1480, 1369, 1237, 1205, 1087, 1021, 803, 753, 632 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.45 (t, J = 7.2 Hz, 3H); 4.48 (q, J = 7.2 Hz, 2H); 7.49–7.63 (m, 3H); 7.81 (dd, J = 7.2, 1.2 Hz, 1H); 7.89 (dd, J = 6.9, 1.5 Hz, 1H); 7.96 (d, J = 8.4 Hz, 1H); 8.30 (d, J = 0.9 Hz, 1H), 8.72 (dd, J = 8.7, 1.5 Hz, 1H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 14.6, 61.4, 124.8, 125.5, 126.5, 127.6, 128.0, 128.3, 128.8, 130.0, 130.5, 130.9, 133.8, 147.9, 161.5, 167.9. EI-MS: 284.1 (21), 283.1 (M^+,100); 282.1 (38), 255.0 (18), 254.0 (89), 211.0 (31), 171.0 (24), 153.1 (31), 127.1 (20), 126.1 (14). EI-HRMS: 283.0663 (M^+, $C_{16}H_{13}NO_2S^+$, calcd 283.0662). *Anal. Calcd* for $C_{11}H_9NS$ (187.26): C, 70.55; H, 4.84; N, 7.48. Found: C, 70.65; H, 5.05; N, 7.45.

Ethyl 2-(2-naphthyl)-1,3-thiazole-4-carboxylate (39)

GP 5, starting from 2-naphthylthioamide (**37**) (5.47 g, 29.2 mmol), gave **39** as a yellow solid after CC (SiO_2; hexane/AcOEt 85:15 → 0:100). Yield: 7.06 g (85%). Mp: 78 °C (Lit.[34]: 79–80 °C). IR (neat): υ 3134, 3052, 2981, 2926, 2892, 1724, 1599, 1477, 1449, 1364, 1333, 1214, 1096, 1032, 1000, 973, 950, 926, 894, 884, 866, 838, 789, 762, 739, 659 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 1.46 (t, J = 7.1 Hz, 3H); 4.48 (q, J = 7.1 Hz, 2H); 7.51–7.57 (m, 2H); 7.86–7.96 (m, 3H); 8.11 (dd, J = 8.5, 1.8 Hz, 1H); 8.20 (s, 1H); 8.52 (s, 1H). ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 14.4, 61.5, 124.1, 126.7, 126.9, 127.1, 127.3, 127.8, 128.7, 128.8, 130.1, 133.1, 134.3, 148.2, 161.5, 168.9. EI-MS: 285.1 (5), 284.1 (16), 283.1 (85, M^+); 238.0 (17), 212.0 (15), 211.0 (100), 171.0 (51), 155.1 (16), 154.1 (11), 153.1 (32), 127.1 (30), 126.0 (11). EI-HRMS: 283.0660 (M^+, $C_{16}H_{13}NO_2S^+$, calcd 283.0662).

2-(1-Naphthyl)-4-{[(triisopropylsilyl)oxy]methyl}-1,3-thiazole (40)

Ester **38** (4.80 g, 16.9 mmol) was dissolved in CH_2Cl_2 (150 mL) and cooled to –10 °C, then DIBALH (1 M in CH_2Cl_2, 45.0 mL, 45.0 mmol) was slowly added dropwise. The mixture was stirred for 10 min at this temperature and for 2 h at rt, then saturated aqueous solutions of NH_4Cl and NaCl were added. After extraction with AcOEt, the organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. This raw solid product was utilized without further purification in the next step. Yield: 3.93 g (96%). Mp: 96 °C. IR (neat): υ 3258, 3070, 1738, 1634, 1506, 1387, 1201, 1103, 1033, 777 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 3.41 (brs, 1H); 4.86 (s, 2H); 7.23 (d, J = 0.9 Hz, 1H); 7.47–7.58 (m, 3H); 7.76 (d, J = 7.2 Hz, 1H); 7.88–7.94 (m, 2H); 8.67 (dd, J = 7.5, 1.8 Hz, 1H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 61.0, 115.3, 124.9, 125.5, 126.2, 127.2, 128.2, 128.4, 130.3, 130.5, 133.8, 157.0, 167.7 (1 aromatic signal hidden). MALDI-MS (3-HPA): 243.1 (13), 242.1 (100, $[M+H]^+$); 240.1 (6), 225.1 (8), 224.1 (76). MALDI-HRMS: 242.0634 ($[M+H]^+$, $C_{14}H_{11}NOS$, calcd 242.0639). The raw alcohol (3.13 g, 13.0 mmol) was dissolved in CH_2Cl_2

(100 mL) together with imidazole (1.77 g, 26.0 mmol). TIPSCl (2.5 mL, 14.4 mmol) was added dropwise and the mixture stirred for 15 h. Addition of saturated aqueous NH_4Cl solution, dilution with H_2O, extraction with CH_2Cl_2 and AcOEt, drying of the combined organic phases with $MgSO_4$, concentration under reduced pressure and CC (SiO_2, hexane/AcOEt 90:10) afforded **40** as a colorless oil. Yield: 3.45 g (67%). IR (neat): υ 2941, 2864, 1462, 1135, 1110, 1070, 882, 684, 632 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.06–1.29 (m, 21H); 5.15 (d, J = 1.2 Hz, 2H); 7.38 (d, J = 1.2 Hz, 1H); 7.49–7.58 (m, 3H); 7.80 (dd, J = 6.3, 1.2 Hz, 1H); 7.88–7.94 (m, 2H); 8.76–8.79 (m, 1H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 12.4, 18.1, 63.1, 114.0, 124.9, 125.7, 126.2, 127.1, 128.2, 128.3, 130.1, 130.4, 130.9, 133.9, 158.3, 167.2. MALDI-MS (3-HPA): 447.1 (12), 420.1 (9, $[M+Na]^+$); 399.2 (8), 398.2 (30, $[M+H]^+$); 355.1 (29), 354.1 (100), 224.1 (52). MALDI-HRMS: 398.1973 ($[M+H]^+$, $C_{24}H_{31}NOSSi^+$, calcd 398.1968).

4-({[*tert*-Butyl(dimethyl)silyl]oxy}methyl)-2-(2-naphthyl)-1,3-thiazole (41)

Ester **39** (912 mg, 3.22 mmol) was dissolved in CH_2Cl_2 (200 ml) and cooled to –10 °C. DIBALH (1 M in CH_2Cl_2, 16.0 mL, 16.0 mmol) was added and the mixture stirred for 30 min at –10 °C and for 4 h at rt. After addition of saturated aqueous NH_4Cl solution, the mixture was stirred for 30 min. Dilution with H_2O, extraction with CH_2Cl_2, drying of the combined organic phases with $MgSO_4$, and concentration under reduced pressure gave a residue which was dissolved in dry CH_2Cl_2. DMAP (1.31 g, 10.7 mmol) and TBDMSCl (1.01 g, 6.70 mmol) were added, and the resulting solution was stirred for 16 h. The mixture was washed with saturated aqueous NH_4Cl solution, the aqueous phases were extracted with CH_2Cl_2, and the combined organic phases dried ($MgSO_4$) and concentrated *in vacuo*. CC (SiO_2; hexane/AcOEt 85:15) afforded **41** as pale yellow oil. Yield: 1.07 g (94%). IR (neat): υ 3134, 3054, 2953, 2927, 2893, 2855, 1718, 1600, 1522, 1471, 1460, 1431, 1387, 1361, 1335, 1253, 1214, 1186, 1136, 1096, 1029, 1001, 950, 928, 833, 817, 776, 739, 668, 660 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 0.18 (s, 6H); 1.00 (s, 9H); 4.99 (d, J = 1.2 Hz, 2H); 1.24 (t, J = 1.2 Hz, 1H); 7.49–7.54 (m, 2H); 7.82–7.95 (m, 3H); 8.05 (dd, J = 8.6, 1.5 Hz, 1H); 8.42 (d, J = 1.5 Hz, 1H). ^{13}C-NMR ($CDCl_3$, 75 MHz): δ -5.3, 18.4, 25.9, 62.5, 113.5, 124.0, 125.7, 126.7, 126.9, 127.8, 128.6, 128.7, 131.1, 133.2, 134.0, 158.5, 168.2. MALDI-MS: 358.1 (5), 257.2 (24), 356.1 (100, $[M+H]^+$); 224.1 (42), 178.1 (8). MALDI-HRMS: 356.1494 ($[M+H]^+$, $C_{20}H_{26}NOSSi^+$, calcd 356.1499).

***N*,*N*-Dimethyl-1-[2-(1-naphthyl)-4-{[(triisopropylsilyl)oxy]methyl}-1,3-thiazol-5-yl]methanamine (42)**

GP 6, starting from thiazole **40** (2.50 g, 6.29 mmol), gave **42** as a yellow oil after CC (SiO_2; hexane/AcOEt 67:33). Yield: 2.28 g (80%). IR (neat): υ 2942, 2864, 1455, 1099, 1068, 1023, 882, 799, 773, 682, 634 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.12–1.30 (m, 21H); 2.39 (s, 6H); 3.88 (s, 2H); 5.04 (s, 2H);

7.50–7.56 (m, 3H); 7.81 (dd, J = 7.2, 0.9 Hz, 1H); 7.87–7.92 (m, 2H); 8.91 (dd, J = 6.9, 2.7 Hz, 1H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 12.2, 18.2, 45.5, 55.0, 60.9, 109.8, 124.9, 126.1, 126.9, 128.1, 128.1, 129.9, 120.4, 120.9, 133.9, 134.6, 152.6, 165.1. MALDI-MS (3-HPA): 477.2 (11, $[M+Na]^+$); 455.3 (16, $[M+H]^+$); 454.2 (19), 453.2 (61, $[M-H]^+$); 411.2 (28), 369.1 (26), 368.1 (100), 238.1 (19). MALDI-HRMS: 453.2327 ($[M-H]^+$, $C_{26}H_{37}N_2OSSi^+$, calcd 453.2395).

1-[4-({[*tert*-Butyl(dimethyl)silyl]oxy}methyl)-2-(2-naphthyl)-1,3-thiazol-5-yl]-*N*,*N*-dimethylmethanamine (43)

GP 6, starting from thiazole **41** (0.60 g, 1.69 mmol), gave **43** as a yellow solid after CC (SiO_2; hexane/AcOEt 85:15 → 65:35). Yield: 434 mg (62%). Mp: 64 °C. IR (neat): υ 3736, 3691, 3650, 3630, 3048, 2964, 2928, 2856, 2823, 2779, 1598, 1540, 1506, 1472, 1455, 1383, 1354, 1257, 1151, 1126, 1065, 1038, 1025, 998, 978, 941, 923, 886, 853, 836, 776, 752, 683, 668, 654 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 0.16 (s, 6H); 0.95 (s, 9H); 2.35 (s, 6H); 3.77 (s, 2H); 4.89 (s, 2H); 7.48–7.53 (m, 2H); 7.81–7.93 (m, 3H); 8.03 (dd, J = 8.6, 1.6 Hz, 1H); 8.38 (d, J = 1.6 Hz, 1H). ^{13}C-NMR ($CDCl_3$, 75 MHz): δ -5.10, 18.5, 26.0, 45.5, 55.0, 60.4, 123.9, 125.6, 126.6, 126.8, 127.8, 128.5, 128.6, 131.3, 133.3, 134.0, 134.6, 152.7, 165.8. MALDI-MS: 413.2 (9), 412.2 (33), 411.2 (100, $[M-H]^+$); 369.2 (10), 368.1 (44), 312.1 (22), 238.1 (6), 102.8 (3). MALDI-HRMS: 411.1913 ($[M-H]^+$, $C_{23}H_{31}N_2OSSi^+$, calcd 411.1921). *Anal.* Calcd for $C_{23}H_{32}N_2OSiS$ (412.67): C, 66.94; H, 7.82; N, 6.79. Found: C, 67.08; H, 7.84; N, 6.80.

{5-[*tert*-Butyl(dimethyl)silyl]-2-(2-naphthyl)-1,3-thiazol-4-yl}methanol (44)

GP 6, starting from thiazole **41** (0.89 g, 2.50 mmol), but stirring the mixture after deprotonation for 30 min at –78 °C and for 30 min at 0 °C, gave **44** as a yellow solid together with **43** (85 mg, 7%) after CC (SiO_2; hexane/AcOEt 83:17 → 67:33). Yield: 0.51 g (72%). Mp: 91–92 °C. IR (neat): υ 3365, 2951, 2925, 2853, 1597, 1495, 1469, 1460, 1386, 1358, 1273, 1250, 1205, 1184, 1126, 1066, 1030, 1007, 992, 976, 935, 894, 861, 829, 819, 808, 772, 746, 677, 657 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 0.41 (s, 6H); 0.98 (s, 9H); 3.09 (t, J = 5.7 Hz, 1H); 4.81 (d, J = 5.7 Hz, 2H); 7.49–7.55 (m, 2H); 7.82–7.94 (m, 3H); 8.07 (dd, J = 8.5; 1.8 Hz, 1H); 8.45 (s, 1H). ^{13}C-NMR ($CDCl_3$, 75 MHz): δ -3.7, 17.7, 26.4, 61.3, 124.0, 125.1, 126.0, 126.6, 126.9, 127.7, 128.5, 128.6, 130.4, 133.1, 134.0, 162.6, 171.7. MALDI-MS: 412.2 (10), 378.1 (8), 357.2 (14), 356.1 (67, $[M+H]^+$); 283.1 (22), 282.1 (100), 178.1 (8), 141.0 (8). MALDI-HRMS: 356.1492 ($[M+H]^+$, $C_{20}H_{26}NOSSi^+$, calcd: 356.1499).

{5-[(Dimethylamino)methyl]-2-(2-naphthyl)-1,3-thiazol-4-yl}methanol (45)

GP 7, starting from silyl ether **43** (434 mg, 1.05 mmol), gave **45** as a pale yellow solid after CC (SiO_2; AcOEt/MeOH 90:10). Yield: 311 mg (99%). Mp: 76–77 °C. IR (neat): υ 3059, 2974, 2944, 2868,

2830, 2792, 1599, 1534, 1503, 1462, 1426, 1361, 1282, 1249, 1229, 1175, 1154, 1130, 1097, 1058, 1033, 1004, 992, 960, 944, 932, 881, 852, 833, 822, 757, 746, 710, 693, 656 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 2.34 (s, 6H); 3.67 (s, 2H); 4.87 (s, 2H); 5.78 (s, 1H); 7.46–7.53 (m, 2H); 7.81–7.92 (m, 3H); 7.99 (dd, J = 8.6, 1.5 Hz, 1H); 8.36 (d, J = 1.5 Hz, 1H). ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 44.8, 54.3, 60.7, 123.8, 125.7, 126.8, 126.9, 127.8, 128.6, 128.7, 130.1, 130.8, 133.2, 134.0, 155.7, 165.1. MALDI-MS: 531.1 (12), 461.1 (27), 361.0 (6), 331.1 (10), 321.1 (7), 299.1 (12), 298.1 (25), 297.1 (100, $[M-H]^+$); 281.1 (7), 256.3 (10), 254.1 (26), 252.0 (18), 242.3 (18), 238.1 (37), 226.1 (31), 148.6 (13). MALDI-HRMS: 297.1057 ($[M-H]^+$, $C_{17}H_{17}N_2OS^+$, calcd 297.1055).

1-[4-(Azidomethyl)-2-(2-naphthyl)-1,3-thiazol-5-yl]-*N*,*N*-dimethylmethanamine (46)

Diphenylphosphoryl azide (0.24 ml, 1.1 mmol) was added to a solution of **45** (235 mg, 0.79 mmol) in THF (10 mL) that was cooled to 0 °C. After 5 min, DBU (0.14 mL, 0.94 mmol) was dropped to the mixture which was stirred at 0 °C for 45 min and at rt for 100 min. H_2O (10 mL) was added and the resulting mixture extracted with AcOEt. The organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. The major impurities were removed by CC (SiO_2, AcOEt) to yield the raw azide **46** as a colorless oil. IR (neat): υ 2989, 2169, 2133, 2093, 2019, 1646, 1592, 1545, 1487, 1453, 1384, 1357, 1255, 1225, 1207, 1161, 1127, 1080, 1070, 1024, 1009, 992, 945, 910, 888, 857, 822, 811, 776, 766, 743, 722, 691, 662, 619 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 2.34 (s, 6H); 3.67 (s, 2H); 4.50 (s, 2H); 7.49–7.55 (m, 2H); 7.82–7.94 (m, 3H); 8.04 (dd, J = 8.6, 1.6 Hz, 1H); 8.40 (d, J = 1.6 Hz, 1H). ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 45.4, 47.8, 54.9, 123.6, 125.7, 126.6, 126.9, 127.7, 128.45, 128.6, 129.6, 130.6, 133.0, 133.9, 148.0, 166.8. MALDI-MS: 531.1 (11), 486.1 (13), 374.1 (5), 331.1 (8), 326.1 (16), 324.1 (26, $[M+H]^+$); 323.1 (5), 322.1 (5), 296.1 (13), 294.1 (20), 282.1 (16), 281.1 (100), 277.1 (6), 253.1 (6), 251.0 (22), 238.1 (59). MALDI-HRMS: 324.1283 ($[M+H]^+$, $C_{17}H_{18}N_5S^+$, calcd 324.1277).

***N*-({5-[(Dimethylamino)methyl]-2-(2-naphthyl)-1,3-thiazol-4-yl}methyl)-2-(2-thienyl)acetamide (48)**

GP 8, starting from azide **46** (197 mg), gave the crude amine **47** as a brown oil. This was dissolved in CH_2Cl_2 (10 mL), then *Huenig* base (0.35 mL, 2.0 mmol) was added and the mixture cooled to –78 °C. At this temperature, 2-thiophenacetyl chloride (0.1 mL, 0.8 mmol) in CH_2Cl_2 (5 mL) was slowly dropped to the solution over 5 min. The mixture was allowed to warm to rt and stirred for 68 h. After addition of saturated aqueous $NaHCO_3$ solution, the aqueous layer was extracted with CH_2Cl_2, the combined organic phases were dried ($MgSO_4$) and the solvent removed under reduced pressure. Amide **48** was isolated as a pale brown solid after CC (SiO_2; hexane/AcOEt/MeOH 85:15:0 → 0:90:10). Yield: 117 mg (35% over 3 steps). Mp: 153 °C. IR (neat): υ 3276, 3049, 2972, 2940, 2851, 2812, 2766, 1683, 1634, 1598, 1538, 1486, 1455, 1429, 1412, 1373, 1354, 1285, 1256, 1225, 1188, 1172, 1149, 1125, 1094, 1075, 1038, 1017,

988, 938, 877, 848, 841, 818, 772, 748, 731, 689, 654, 632 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 2.29 (s, 6H); 3.64 (s, 2H); 3.84 (s, 2H); 4.54 (d, J = 5.0 Hz, 2H); 6.94 (s, 1H); 7.00 (dd, J = 3.5, 1.2 Hz, 1H); 7.04 (dd, J = 5.1, 3.5 Hz, 1H); 7.28 (dd, J = 5.1, 1.2 Hz, 1H); 7.50–7.56 (m, 2H); 7.83–7.90 (m, 3H); 7.93 (dd, J = 8.6, 1.1 Hz, 1H); 8.30 (s, 1H). ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 37.4, 38.2, 45.1, 54.4, 123.6, 125.4, 125.5, 126.7, 126.9, 127.2, 127.3, 127.7, 128.5, 128.6, 130.7, 132.7, 133.1, 133.9, 136.1, 149.4, 166.4, 169.5. MALDI-MS: 702.2 (4), 444.1 (9), 424.1 (6), 422.1 (100, $[M+H]^+$); 421.1 (11), 420.1 (39), 378.1 (11), 377.1 (47), 253.1 (4), 211.1 (5). MALDI-HRMS: 422.1348 ($[M+H]^+$, $C_{23}H_{24}N_3OS_2^+$, calcd 422.1355).

_N_-({5-[(Dimethylamino)methyl]-2-(2-naphthyl)-1,3-thiazol-4-yl}methyl)-2-(1_H_-imidazol-4-yl)acetamide (49)

GP 8, starting from azide **46**, gave the crude amine **47** as a brown oil. 1*H*-Imidazol-4-ylacetic acid hydrochloride (152 mg, 0.93 mmol) was dissolved in THF (10 mL) and DMF (10 mL) and converted into the free acid using *Huenig* base (0.18 mL, 1.0 mmol). This solution was used following GP 9 with part of the crude amine **47** (775 mg, 0.93 mmol) to furnish **49** as a brown oil after CC (SiO_2; AcOEt/MeOH 85:15). Yield: 270 mg (67% over 3 steps). IR (neat): υ 2972, 2819, 2774, 1651, 1538, 1488, 1455, 1428, 1355, 1256, 1154, 1126, 1086, 1022, 938, 906, 858, 815, 747, 690, 662, 621 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 2.27 (s, 6H); 3.58 (s, 2H); 3.61 (s, 2H); 4.53 (d, J = 5.1 Hz, 2H); 6.86 (s, 1H); 7.46–7.52 (m, 2H); 7.56 (d, J = 1.0 Hz, 1H); 7.75–7.91 (m, 4H); 7.95 (dd, J = 8.6, 1.7 Hz, 1H); 8.31 (d, J = 1.7 Hz, 1H). ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 35.5, 38.5, 45.4, 54.8, 117.3, 124.1, 126.0, 127.1, 127.4, 128.2, 128.9, 129.0, 131.2, 132.5, 133.2, 133.6, 134.4, 135.9, 150.2, 166.9, 171.0. MALDI-MS: 788.3 (7), 746.2 (14), 745.2 (20), 723.2 (9), 615.2 (6), 444.1 (7), 429.2 (9), 428.2 (28), 407.2 (36), 406.2 (100, $[M+H]^+$); 404.2 (18), 362.1 (22), 361.1 (73), 359.1 (32), 344.1 (18), 253.1 (13), 203.1 (6). MALDI-HRMS: 406.1688 ($[M+H]^+$, $C_{22}H_{24}N_5OS^+$, calcd 406.1696).

_N_-({5-[(Dimethylamino)methyl]-2-(2-naphthyl)-1,3-thiazol-4-yl}methyl)-2-(1_H_-indol-3-yl)acetamide (50)

GP 8, starting from azide **46**, gave the crude amine **47** as a brown oil, a part of which (777 mg, 0.94 mmol) was used following GP 9 with indole-3-acetic acid to furnish **50** as pale brown crystals after CC (SiO_2; AcOEt/MeOH 85:15). Yield: 506 mg (46% over 3 steps). Mp: 150 °C. IR (neat): υ 3241, 3053, 2975, 2821, 2774, 2358, 1651, 1590, 1515, 1488, 1455, 1428, 1319, 1274, 1228, 1179, 1161, 1126, 1098, 1071, 1025, 985, 945, 911, 896, 860, 817, 742, 690, 847 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 2.22 (s, 6H); 3.62 (s, 2H); 3.79 (s, 2H); 4.50 (d, J = 4.9 Hz, 2H); 6.78 (t, J = 4.9 Hz, 1H); 7.07–7.14 (m, 2H); 7.21 (td, J = 7.6, 1.1 Hz, 1H); 7.40 (dt, J = 8.1, 0.8 Hz, 1H); 7.49–7.54 (m, 2H); 7.57 (d, J = 7.8 Hz, 1H); 7.73 (dd, J = 8.6, 1.6 Hz, 1H); 7.82–7.89 (m, 3H); 8.18 (d, J = 1.6 Hz, 1H); 8.33 (s, 1H). ^{13}C-NMR ($CDCl_3$, 75 MHz):

δ 33.4, 38.0, 45.1, 54.5, 109.0, 111.3, 118.8, 120.0, 120.6, 120.7, 122.5, 123.7, 125.6, 126.7, 126.9, 127.8, 128.6, 129.3, 130.9, 132.7, 133.2, 134.0, 136.5, 149.8, 166.4, 171.3. MALDI-MS: 843.3 (7), 669.2 (5), 477.2 (16), 456.2 (44), 455.2 (100, $[M+H]^+$); 454.2 (23), 453.2 (51), 411.1 (26), 410.1 (62), 362.0 (14), 351.1 (13), 346.1 (62), 325.1 (14), 324.1 (94), 227.6 (5). MALDI-HRMS: 455.1892 ($[M+H]^+$, $C_{27}H_{27}N_4OS^+$, calcd 455.1900). *Anal.* Calcd for $C_{27}H_{26}N_4OS$ (454.59): C, 71.34; H, 5.76; N, 12.32. Found: C, 71.06; H, 6.00; N, 12.35.

[2-(2-Naphthyl)-1,3-thiazol-4-yl]methanol (51)

Ester **39** (1.6 g, 5.6 mmol) was dissolved in CH_2Cl_2 (50 mL) and cooled to –10 °C, then DIBALH (1 M in CH_2Cl_2, 15.0 mL, 15.0 mmol) was slowly added dropwise. The mixture was stirred for 10 min at this temperature and for 4 h at rt. Addition of saturated aqueous solutions of NH_4Cl and NaCl, extraction with AcOEt, drying of the combined organic layers with $MgSO_4$, and concentration *in vacuo*, followed by CC (SiO_2; hexane/AcOEt 50:50) yielded **51** as a white solid. Yield: 1.37 g (98%). Mp: 123 °C. IR (neat): υ 3181, 2908, 2855, 1524, 1429, 1348, 1277, 1126, 1032, 1002, 861, 821, 756, 724 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 2.86 (brs, 1H); 4.87 (d, J = 0.6 Hz, 2H); 7.22 (s, 1H); 7.49–7.54 (m, 2H); 7.82–7.92 (m, 3H); 8.00 (dd, J = 8.7, 2.1 Hz, 1H); 8.41 (s, 1H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 61.2, 114.6, 132.8, 125.9, 126.7, 126.9, 127.7, 128.5, 128.6, 130.6, 133.1, 134.0, 157.2, 168.7. MALDI-MS: 243.1 (12), 242.1 (100, $[M+H]^+$); 224.1 (29). MALDI-HRMS: 242.0630 ($[M+H]^+$, $C_{14}H_{12}NOS^+$, calcd 242.0634). *Anal.* Calcd for $C_{14}H_{11}NOS$ (241.31): C, 69.68; H, 4.59; N, 5.80. Found: C, 69.68; H, 4.78; N, 5.73.

4-(Methoxymethyl)-2-(2-naphthyl)-1,3-thiazole (52)

NaH (60 weight%, in mineral oil, 0.11 g, 2.8 mmol) was suspended in pentane (2 mL) and stirred for 2 min. The solvent was decanted and the solid dried under a stream of N_2. The solid was suspended in THF (30 mL) and cooled to 0 °C. Alcohol **51** (0.34 g, 1.39 mmol) in THF (20 mL) was added slowly by the means of a cannula. After stirring for 10 min at 0 °C and 20 min at rt, the mixture was again cooled to 0 °C and MeI (95 μL, 1.53 mmol) was added dropwise. After stirring for 20 min at 0 °C, the mixture was allowed to warm to rt and stirred for 5 h. Addition of H_2O and diluting with AcOEt were followed by washing with saturated aqueous solutions of $NaHCO_3$ and NaCl. The combined aqueous phases were extracted with AcOEt, dried ($MgSO_4$), and concentrated under reduced pressure. CC (SiO_2; hexane/AcOEt 91:9 → 50:50) gave **52** as a white solid. Yield: 0.31 g (88%). Mp: 53 °C. IR (neat): υ 3122, 2985, 2918, 2872, 2807, 1598, 1527, 1443, 1275, 1198, 1108, 1003, 856, 815 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 3.53 (s, 3H); 4.68 (d, J = 0.6 Hz, 2H); 7.50–7.55 (m, 2H); 7.83–7.94 (m, 3H); 8.06 (dd, J = 8.4, 1.5 Hz, 1H); 8.45 (d, J = 1.5 Hz, 1H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 58.8, 70.6, 115.8, 124.0, 125.9, 126.6, 126.9, 127.7, 128.5, 128.6, 130.8, 133.1, 134.0, 154.8, 168.4. MALDI-MS: 257.1 (6), 256.1 (45, $[M+H]^+$);

224.1 (100), 217.1 (6), 184.0 (7). MALDI-HRMS: 256.0795 ([M+H]$^+$, $C_{15}H_{14}NOS^+$, calcd 256.0791). *Anal.* Calcd for $C_{15}H_{13}NOS$ (255.34): C, 70.56; H, 5.13; N, 5.49. Found: C, 70.57; H, 5.16; N, 5.37.

1-[4-(Methoxymethyl)-2-(2-naphthyl)-1,3-thiazol-5-yl]-*N*,*N*-dimethylmethanamine (53)

GP 6, starting from methyl ether **52** (50 mg, 196 μmol), followed by CC (SiO_2; hexane/AcOEt 25:75 → 0:100) gave **53** as a white solid besides recovered starting material **52** (35 mg, 70%). Yield: 15 mg (25%). Mp: 55 °C. IR (neat): υ 2980, 2922, 2818, 2769, 2361, 1597, 1450, 1353, 1125, 1090, 1021, 998, 853, 743 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 2.36 (s, 6H); 3.47 (s, 3H); 3.75 (s, 2H); 4.62 (s, 2H); 7.48–7.53 (m, 2H); 7.81–7.91 (m, 3H); 8.03 (dd, J = 8.7, 1.8 Hz, 1H); 8.41 (d, J = 0.9 Hz, 1H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 58.8, 70.6, 115.8, 124.0, 125.9, 126.6, 126.9, 127.7, 128.5, 128.6, 130.8, 133.1, 134.0, 154.8, 168.4 (2 signals missing). MALDI-MS: 611.2 (100), 314.1 (11) 313.1 (62, [M+H]$^+$); 312.1 (11), 311.1 (56), 268.1 (69), 238.1 (49). MALDI-HRMS: 313.1367 ([M+H]$^+$, $C_{18}H_{20}N_2OS^+$, calcd 313.1369).

4-(Methoxymethyl)-2-(2-naphthyl)-1,3-thiazole-5-carbaldehyde (54)

Methyl ether **52** (0.13 g, 0.52 mmol) was dissolved in THF (20 mL) and cooled to –78 °C, then, *n*-BuLi (1.6 M in hexane, 0.49 mL, 0.78 mmol) was added dropwise and the solution stirred for 20 min at 0 °C. At –78 °C, DMF (0.20 mL, 2.58 mmol) was added and the mixture stirred for 1 h at –78 °C and 1 h at rt. After addition of 1 M aqueous HCl and saturated aqueous $NaHCO_3$ solution, the mixture was extracted with AcOEt. The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo* to give, after CC (SiO_2; hexane/AcOEt 91:09), aldehyde **54**. Yield: 88 mg (61%). Mp: 111 °C. IR (neat): υ 2910, 2821, 1663, 1375, 1322, 1237, 1095, 1002, 948, 861, 829, 750, 673 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 3.57 (s, 3H); 4.96 (s, 2 H); 7.54–7.58 (m, 2H); 7.86–7.97 (m, 3H); 8.05 (dd, J = 8.7, 1.8 Hz, 1H); 8.54 (d, J = 1.8 Hz, 1H); 10.35 (s, 1H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 59.1, 70.3, 123.7, 126.9, 127.2, 127.7, 128.8, 128.8, 129.7, 132.8, 134.6, 135.3, 161.1, 173.4, 183.2 (1 aromatic signal hidden). MALDI-MS: 367.0 (48), 345.0 (52), 285.1 (12), 284.1 (80, [M+H]$^+$); 235.1 (100), 233.1 (60), 200.0 (36), 189.1 (58). MALDI-HRMS: 284.0737 ([M+H]$^+$, $C_{16}H_{13}NO_2S^+$, calcd 284.0740).

1-{[4-(Methoxymethyl)-2-(2-naphthyl)-1,3-thiazol-5-yl]methyl}-4-methylpiperazine (55)

N-Methylpiperazine (25 μL, 0.220 mmol) was added at 0 °C to molecular sieves (4Å) and $NaBH(OAc)_3$ (46 mg, 0.212 mmol) in CH_2Cl_2 (10 mL). After stirring for 5 min, aldehyde **54** (30 mg, 0.106 mmol) was added in one portion and the mixture stirred for 1 h at 0 °C and 20 h at rt. After addition of 0.5 M aqueous HCl and dilution with AcOEt, the organic phase was extracted with 0.5 M aqueous HCl. The combined aqueous phases were rendered basic by addition of Na_2CO_3 and extracted with CH_2Cl_2/*i*-PrOH 67:33. The combined organic phases were dried ($MgSO_4$), and the solvent was removed under reduced pressure.

CC (SiO_2; AcOEt/MeOH 90:10) yielded **55** as a colorless oil. Yield: 22 mg (57%). IR (neat): υ 2932, 2794, 2359, 1454, 1345, 1291, 1160, 1143, 1096, 1009, 815, 746 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 2.30 (s, 3H); 2.47-2.62 (m, 8H); 3.46 (s, 3H); 3.79 (s, 2H); 4.61 (s, 2H); 7.49–7.52 (m, 2H); 7.82–7.90 (m, 3H); 8.02 (dd, J = 8.4, 1.8 Hz, 1H); 8.39 (d, J = 1.8 Hz, 1H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 46.0, 53.0, 53.7, 55.1, 58.4, 68.1, 124.0, 125.7, 126.7, 126.9, 127.8, 128.6, 131.1, 133.2, 134.0, 135.4, 150.5, 167.8 (1 aromatic signal hidden). MALDI-MS: 390.2 (25), 368.2 (48, $[M+H]^+$); 367.1 (22), 366.2 (100, $[M-H]^+$); 268.1 (46), 238.1 (66). MALDI-HRMS: 366.1630 ($[M+H]^+$, $C_{21}H_{24}N_3OS^+$, calcd 366.1635).

{5-[(Dimethylamino)methyl]-2-(1-naphthyl)-1,3-thiazol-4-yl}methanol (56)

GP 7, starting from silyl ether **42** (645 mg, 1.42 mmol), gave **56** as a yellow oil after CC (SiO_2; AcOEt/MeOH 90:10). Yield: 393 mg (93%). IR (neat): υ 3251 (*br*), 3069, 2907, 1506, 1387, 1235, 1103, 1034, 980, 809, 797, 778, 649 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 2.36 (s, 6H); 3.71 (s, 2H); 4.94 (s, 2H); 5.89 (s, 1H); 7.48–7.61 (m, 3H); 7.77 (dd, J = 7.2, 1.2 Hz, 1H); 7.85–7.94 (m, 2H); 8.89 (d, J = 7.8 Hz, 1H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 44.8, 54.0, 60.6, 124.9, 125.8, 126.3, 127.3, 128.3, 128.3, 130.3, 130.4, 130.5, 130.8, 133.9, 155.3, 164.3. MALDI-MS: 299.1 (22, $[M+H]^+$); 297.1 (6), 254.1 (20), 243.3 (11), 242.3 (100, $[NBu_4]^+$). MALDI-HRMS: 299.1218 ($[M+H]^+$, $C_{17}H_{19}N_2OS^+$, calcd 299.1213).

5-[(Dimethylamino)methyl]-2-(1-naphthyl)-1,3-thiazole-4-carbaldehyde (57)

Alcohol **56** (1.10 g, 3.67 mmol) was dissolved in Me_2SO (120 mL), and pyridine·SO_3 (purity: >45%, 2.60 g, *ca.* 7.34 mmol) was added in small portions. After stirring for 4 h, saturated aqueous $NaHCO_3$ solution was added and the mixture further diluted with H_2O. The mixture was extracted with AcOEt and CH_2Cl_2, and the combined organic phases were washed with an aqueous solution of NH_4Cl, dried ($MgSO_4$) and concentrated under reduced pressure to give, after CC (SiO_2; pentane/AcOEt/NEt_3 33:66:1), **57** as yellow oil. Yield: 0.82 g (75%). IR (neat): υ 3046, 2941, 2821, 2773, 1687, 1508, 1454, 1339, 1263, 1167, 1100, 1027, 798, 772 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 2.42 (s, 6H); 4.16 (s, 2H); 7.50–7.98 (m, 3H); 7.82 (dd, J = 7.1, 1.1 Hz, 1H); 7.83–7.98 (m, 2H); 8.86 (dd, J = 8.6, 1.1 Hz, 1H); 10.30 (s, 1H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 46.0, 55.7, 124.9, 125.4, 126.4, 127.5, 128.4, 128.6, 129.8, 130.1, 130.8, 133.9, 149.1, 150.9, 166.1, 186.9. MALDI-MS: 548.1 (15), 530.1 (12), 503.1 (25), 324.1 (12), 319.1 (19), 318.1 (10), 298.1 (21), 297.1 (90, $[M+H]^+$); 296.1 (12), 295.1 (100, $[M-H]^+$); 254.1 (13), 252.1 (67), 238.1 (11). MALDI-HRMS: 295.0901 ($[M-H]^+$, $C_{17}H_{16}N_2OS^+$, calcd 295.0900). *Anal.* Calcd for $C_{17}H_{16}N_2OS$ (296.39): C, 68.89; H, 5.44; N, 9.45. Found: C, 68.66; H, 5.59; N, 9.48.

2-(3-{5-[(Dimethylamino)methyl]-2-(1-naphthyl)-1,3-thiazol-4-yl}-3-hydroxyprop-1-yn-1-yl)-*N*,*N*-dimethyl-1*H*-imidazole-1-sulfonamide ((±)-58)

Bromide **32** (0.10 g, 0.34 mmol) was dissolved in THF (16 mL) and cooled to –78 °C, then *n*-BuLi (1.6 M in hexane, 0.21 mL, 0.34 mmol) was slowly added dropwise. After stirring for 10 min at –78 °C, aldehyde **57** (94 mg, 0.34 mmol) in THF (5 mL) was slowly dropped into the mixture *via* a cannula. The reaction was stirred for 1 h at –78 °C, then saturated aqueous solutions of NH_4Cl and $NaHCO_3$ were added. The mixture was extracted with CH_2Cl_2/*i*-PrOH 67:33, and the combined organic solvents were dried ($MgSO_4$) and concentrated *in vacuo*. CC (SiO_2, AcOEt/MeOH/NEt_3 100:0:0 → 97:2:1, then Al_2O_3, act. 3, AcOEt/hexane/MeOH 75:25:0 → 95:0:5) gave (±)-**58** as a yellow oil. Yield: 115 mg (%). IR (neat): υ 2824, 2780, 1510, 1455, 1390, 1161, 969, 802, 774, 725 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 2.42 (s, 6H); 2.90 (s, 6H); 3.50 (d, J = 14.1 Hz, 1H); 4.35 (d, J = 14.1 Hz, 1H); 6.02 (s, 1H); 7.04 (d, J = 1.5 Hz, 1H); 7.32 (d, J = 1.5 Hz, 1H); 7.48–7.60 (m, 3H); 7.76 (dd, J = 7.2, 1.2 Hz, 1H); 7.87–7.91 (m, 2H); 8.80 (dd, J = 8.1, 0.9 Hz, 1H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 38.6, 44.7, 53.4, 61.3, 73.6, 93.8, 121.0, 124.9, 125.7, 126.3, 127.4, 128.2, 128.3, 128.9, 129.7, 130.0, 130.2, 130.4, 131.7, 133.8, 153.8, 163.8. MALDI-MS: 518.1 (17), 497.2 (30), 496.2 (100, $[M+H]^+$); 494.1 (25), 478.1 (11), 452.1 (10), 451.1 (43), 388.1 (14), 342.1 (17). MALDI-HRMS: 496.1464 ($[M+H]^+$, $C_{24}H_{26}N_5O_3S_2^+$, calcd 496.1472).

2-(3-{5-[(Dimethylamino)methyl]-2-(1-naphthyl)-1,3-thiazol-4-yl}-3-fluoroprop-1-yn-1-yl)-*N*,*N*-dimethyl-1*H*-imidazole-1-sulfonamide ((±)-59)

GP 4, starting from alcohol (±)-**58** (85 mg, 172 μmol), gave (±)-**59** as a yellow oil after CC (SiO_2; AcOEt/MeOH/NEt_3 99:0.5:0.5). Yield: 24 mg (28 %). IR (neat): υ 2923, 2855, 2776, 2360, 1510, 1455, 1392, 1172, 1023, 938, 801, 774, 726 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 2.39 (s, 6H); 2.90 (s, 6H); 3.89–3.92 (m, 2H); 6.71 (d, J = 46.5 Hz, 1H); 7.10 (d, J = 1.5 Hz, 1H); 7.36 (d, J = 1.5 Hz, 1H); 7.48–7.59 (m, 3H); 7.80 (dd, J = 7.2, 1.2 Hz, 1H); 7.88–7.95 (m, 2H); 8.86 (dd, J = 8.1, 1.2 Hz, 1H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 38.6, 45.6, 54.8, 78.8, 88.1, 121.5, 124.9, 125.8, 126.3, 127.4, 128.2, 128.4, 128.8, 129.3, 130.2, 130.5, 133.8, 139.7, 146.1, 146.4, 166.3 (1 signal missing). MALDI-MS: 512.2 (36), 499.2 (17), 498.1 (60, $[M+H]^+$); 494.1 (37), 482.1 (41), 478.1 (100), 476.1 (14), 165.1 (24), 464.1 (96), 462.1 (16), 453.1 (55), 435.1 (31), 355.1 (28). MALDI-HRMS: 498.1420 ($[M+H]^+$, $C_{24}H_{25}N_5O_2FS_2^+$, calcd 498.1428).

4-Fluoro-6-(1*H*-imidazol-2-yl)-*N*,*N*-dimethyl-2-(1-naphthyl)-1,3-benzothiazol-7-amine (60)

Alkyne (±)-**59** (20 mg, 40 μmol) was dissolved in MeOH (5 mL), NaOMe (0.5 N in MeOH, 3.0 mL, 1.5 mmol) slowly added, and the mixture stirred for 4 h. Addition of saturated aqueous NH_4Cl solution, dilution with H_2O, extraction with CH_2Cl_2, and CC (SiO_2; hexane/AcOEt/NEt_3 44.5: 44.5:1) provided **60**

as a colorless oil. Yield: 12 mg (77%). IR (neat): υ 3060, 2930, 2849, 1668, 1418, 1387, 1174, 1152, 1097, 960, 774, 722 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 2.63 (s, 6H); 7.18 (d, J = 1.7 Hz, 1H); 7.51 (d, J = 1.7 Hz, 1H); 7.55–7.70 (m, 4H); 7.93–8.04 (m, 3H); 8.15 (dd, J = 1.6, 0.9 Hz, 1H); 9.04 (dd, J = 8.7, 0.9 Hz, 1H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 38.0, 114.5 (d, J = 20.3 Hz); 119.5 (d, J = 4.2 Hz); 122.5, 125.0, 125.8, 126.8, 128.1 (d, J = 4.6 Hz); 128.4, 128.5, 130.0, 130.5, 131.9, 134.1, 127.6 (d, J = 4.0 Hz); 143.7 (d, J = 13.5 Hz); 146.2, 155.1 (d, J = 258.3 Hz); 170.3 (2 arom. signals masked). ^{19}F-NMR (282 MHz, $CDCl_3$): -120.5 (d, J = 11.6 Hz). MALDI-MS: 414.2 (18), 390.1 (10), 389.1 (52, $[M+H]^+$); 387.1 (11), 360.1 (13), 346.1 (51), 345.1 (21), 344.1 (100), 343.2 (14), 317.1 (21), 303.0 (19), 277.1 (13). MALDI-HRMS: 389.1225 ($[M+H]^+$, $C_{22}H_{17}N_4FS^+$, calcd 389.1231).

Crystal structure determination of 50

Crystal data at 298 K for $C_{27}H_{26}N_4OS$ (M_r = 454.596): triclinic, space group *P1*, D_c = 1.252 g cm^{-3}, Z = 4, a = 8.2397(2) Å, b = 12.4931 (3) Å, c = 23.9699 (6) Å, V = 2411.30 (10) $Å^3$. *Bruker-Nonius Kappa-CCD* diffractometer, MoK_α radiation, λ = 0.71073 Å. A pale brown colored crystal (linear dimensions *ca.* 0.32 x 0.16 x 0.08 mm) was obtained by cooling of a saturated solution of **50** in CH_3CN. The crystal was solved by direct methods (SIR97)[35] and refined by full-matrix least-squares analysis (SHELXL-97)[36], using $1/[\sigma^2(I_o)+(I_o+I_c)^2/900]$. All heavy atoms of **50** were refined anisotropically, the H-atom parameters were not refined. Final $R(F)$ = 0.0727, $wR(F^2)$ = 0.1960 for 595 parameters and 5572 reflections with $I > 2\sigma(I)$ and 1.00° < θ < 25.35°.

Crystallographic data (excluding structure factors) for the structure have been deposited with the *Cambridge Crystallographic Data Centre* as deposition No. CCDC 626354. Copies of the data can be obtained, free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html or on application to the *CCDC*, 12 Union Road, Cambridge CB2 1EZ UK (fax: +44(1223)336033; e-mail:deposit@ccdc.cam.ac.uk).

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REFERENCES

1. R. L. Krauth-Siegel and G. H. Coombs, *Parasitol. Toda*y, 1999, **15**, 404.
2. A. H. Fairlamb, P. Blackburn, P. Ulrich, B. T. Chait, and A. Cerami, *Science*, 1985, **227**, 1485.
3. T. J. Benson, J. H. McKie, J. Garforth, A. Borges, A. H. Fairlamb, and K. T. Douglas, *Biochem. J*., 1992, **286**, 9.
4. Z. P. Xia and C. D. Smith, *J. Org. Chem*., 2001, **66**, 3459.

5. R. A. Hughes, S. P. Thompson, L. Alcaraz, and C. J. Moody, *J. Am. Chem. Soc*., 2005, **127**, 15644.
6. J. Guo, G. A. Erickson, R. N. Fitzgerald, R. T. Matsuoka, S. W. Rafferty, M. J. Sharp, B. R. Sickles, and J. C. Wisowaty, *J. Org. Chem*., 2006, **71**, 8302.
7. J. Zanon, A. Klapars, and S. L. Buchwald, *J. Am. Chem. Soc*., 2003, **125**, 2890.
8. R. H. Prager, M. R. Taylor, and C. M. Williams, *J. Chem. Soc., Perkin Trans. 1*, 1997, 2673.
9. R. Maeda, E. Ohsuqi, T. Fujioka, and K. Hirose, *Chem. Pharm. Bull*., 1983, **31**, 3770.
10. F. Al-Obeidi and J. F. Okonya, *Tetrahedron Lett*., 2002, **43**, 7051.
11. Y. G. Gu, M. Weitzberg, R. F. Clark, X. Xu, Q. Li, T. Zhang, T. M. Hansen, G. Liu, Z. Xin, X. Wang, R. Wang, T. McNally, H. Camp, B. A. Beutel, and H. L. Sham, *J. Med. Chem*., 2006, **49**, 3770.
12. A. Dondoni, M. Fogagnolo, A. Medici, and E. Negrini, *Synthesis,* 1987, 185.
13. M. Abarbri, J. Thibonnet, L. Bérillion, F. Dehmel, M. Rottländer, and P. Knochel, *J. Org. Chem.*, 2000, **65**, 4618.
14. D. B. Dess and J. C. Martin, *J. Am. Chem. Soc*., 1991, **113**, 7277.
15. S. Nahm and S. M. Weinreb, *Tetrahedron Lett*., 1981, **22**, 3815.
16. Y. Rubin, S. S. Lin, C. B. Knobler, J. Anthony, A. M. Boldi, and F. Diederich, *J. Am. Chem. Soc*., 1991, **113**, 6943.
17. J.-W. Kim, S. M. Abdelaal, L. Bauer, and N. E. Heimer, *J. Heterocycl. Chem.,* 1995, **41**, 611.
18. E. J. Corey and P. L. Fuchs, *Tetrahedron Lett.,* 1972, **13**, 3769.
19. V. Ratovelomanana, Y. Rollin, C. Gebehenne, C. Gosmini, and J. Perichon, *Tetrahedron Lett*., 1994, **35**, 4777.
20. J. S. Mahanty, M. De, P. Das, and N. G. Kundu, *Tetrahedron*, 1997, **53**, 13397.
21. Z.-X. Jiang and F.-L. Qing, *J. Fluorine Chem.,* 2003, **123**, 57.
22. A. Coelho, E. Sotelo, and E. Raviña, *Tetrahedron*, 2003, **59**, 2477.
23. R. W. Friesen and A. K. Daljeet, *Tetrahedron Lett*., 1990, **31**, 6133.
24. K. K. Ogilvie and D. W. Entwistle, *Carbohyd. Res.*, 1981, **89**, 201.
25. G. A. Gornowicz and R. West, *J. Am. Chem. Soc*., 1968, **90**, 4478.
26. E. Bures, P. G. Spinazze, G. Beese, I. R. Hunt, C. Rogers, and B. A. Keay, *J. Org. Chem*., 1997, **62**, 8741.
27. E. J. Bures and B. A. Keay, *Tetrahedron Lett.,* 1987, **28**, 5965.
28. E. J. Bures and B. A. Keay, *Tetrahedron Lett.*, 1988, **29**, 1247.
29. L. H. Mace, M. Sundaram Shanmugham, J. D. White, and M. G. B. Drew, *Org. Biomol. Chem*., 2006, **4**, 1020.
30. F. Seela and T. Fröhlich, *Helv. Chim. Acta*, 1994, **77**, 399.

31. A. S. Thompson, G. R. Humphrey, A. M. DeMarco, D. J. Mathre, and E. J. J. Grabowski, *J. Org. Chem*., 1993, **58**, 5886.
32. H. Singer and W. Shive, *J. Org. Chem*., 1955, **20**, 1458.
33. W. A. Harrison and M. Kulka, 1973, US 3725427.
34. A. Benkö and I. Rotaru, *Monatsh. Chem*., 1975, **106**, 1027.
35. A. Altomare, M. C. Burla, M. Camalli, G. L. Cascarano, C. Giacovazzo, A. Guagliardi, A. G. G. Moliterni, and R. Spagna, *J. Appl. Crystallogr*., 1999, **32**, 115.
36. G. M. Sheldrick, 1997. *SHELXL*97. Program for the Refinement of Crystal Structures. University of Göttingen, Germany.