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Stereoselective synthesis of highly functionalized thiopeptide thiazole fragments from uronic acid/cysteine condensation products: access to the core dipeptide of the thiazomycins and nocathiacins

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ABSTRACT

We present the stereoselective synthesis of various highly functionalized thiazole dipeptides that are found in thiopeptide antibiotics like thiazomycins and nocathiacins. The condensation of an uronic acid with L-cysteine methyl ester delivers along two different protocols the stereopure thiazolidine lactones or lactams on the multigram scale, respectively. Oxidation of the thiazolidine moiety to the thiazole and tailoring of the sugar chains yield the thiazole dipeptide as present in the core motif of the thiopeptide antibiotics, as well as its epimer and a homolog. The modular assembly of the potent natural products and their analogs relies on the synthetic accessibility of adequately protected building blocks of tailored absolute stereochemistry.

1. Introduction

Thiazoles add rigidity, hydrophobicity, and stability against enzymatic degradation to peptides, thus expanding their spectrum of biological activity.[1,2] Thiazole peptides undergo high-affinity interactions with proteins,[3] RNA,[4] DNA,[5,6] metal ions,[7] and cell membranes,[8] causing a highly selective mode of biological action.

The five-membered thiazole heterocycle is biosynthetically generated by cyclization of a cysteine side chain thiol and the adjacent N-terminal backbone amide. This process is carried out for ribosomally synthesized products by dedicated heterocyclases and oxidases, as well as non-ribosomally during the peptide chain assembly.[9,10] Many non-ribosomal thiazole-containing peptides have catched attention as potential cancer therapeutics, for example, acting as powerful inhibitors of cytokinesis[11,12] or tubulin polymerization.[13–15] Among the ribosomal products, the thiopeptides stand out as efficient inhibitors of bacterial protein biosynthesis, being promising therapeutic candidates for the treatment of infections caused by multiresistant bacteria.[16–18] Their structural complexity provides a significant challenge for chemical synthesis and is demonstrated by the fact that, in spite of the research effort spent in the past, only a small fraction of the more than 80 members of the thiopeptide class have so far succumbed to total synthesis.[19] Fig. 1 shows the structure of the nocathiacins and thiazomycins, which are among the most complex examples.[20–22] Their characteristic six-membered hydroxypyridine core and the highly functionalized thiazole dipeptide both serve as cross-linkers in a network of 10-, 15-, and 26-membered rings.[23] The central dipeptide can be seen as consisting of the amino acid dihydroxyglutamate (Dyg) and thiazole carboxylic acid (Thz). In order to indicate the backbone-rigidifying second linkage generated by the thiazole ring we suggest the use of the hyphen '<', resulting in the denotation Dyg<Thz for the dipeptide unit.[24]

Over the last years, the possibilities for the chemical synthesis of thiazoles have been significantly expanded. For example, modified reaction protocols of the classical Hantzsch procedure were developed and successfully used within the total synthesis of thiostrepton by Nicolaou et al.[25–28] Bach et al. employed C–C couplings of metalated thiazoles to access GE2270 and amythiamicin thiopeptides[29,30] while Dömling, Wessjohann et al. succeeded in the total synthesis of tubulysin peptides by using

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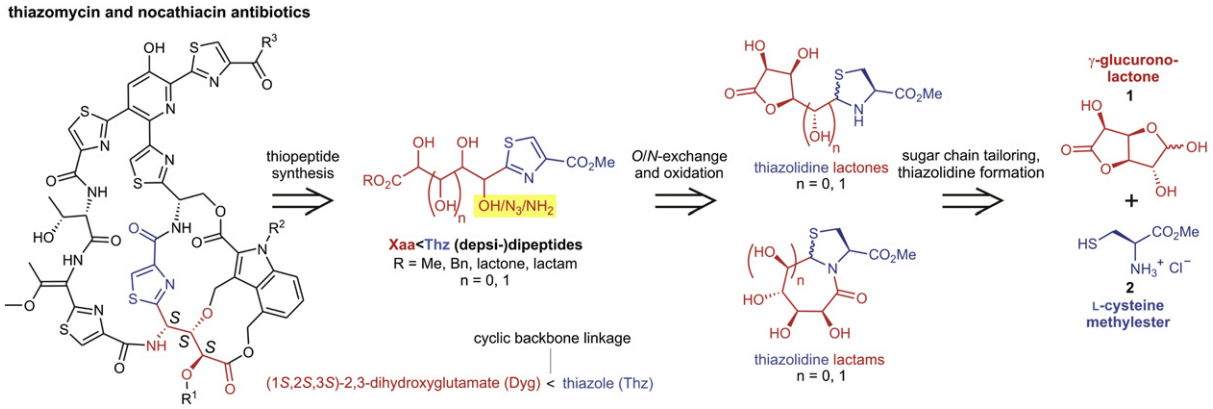


Fig. 1. Retrosynthetic analysis of the Dyg<Thz dipeptide as present in thiazomycin and nocathiacin antibiotics. The hyphen '<' stands for the inseparable linkage between dihydroxyglutamic acid (Dyg) and thiazole carboxylic acid (Thz). Depending on the reaction conditions, the condensation of γ-glucuronolactone **1** and L-cysteine methyl ester **2** yields either thiazolidine lactones as kinetic products or thiazolidine lactams as thermodynamic products. Both groups of compounds are precursors of Xaa<Thz dipeptides as they are found in thiopeptide antibiotics. R^1=amino sugar or H, R^2=OH or H, R^3=dehydroalanine (Dha) or NH_2.

a three-component coupling similar to the Passerini reaction.[31,32] Further synthetic strategies include the aza-Wittig reaction[33,34] and the activation of amino acid side chains[35,36] or amides[37,38] in pre-synthesized peptides, the latter also being applicable to solid-phase synthesis.[39]

In spite of the progress that was enabled by these methods, the access to stereopure thiazole dipeptides with highly functionalized side chains, as present in the nocathiacin and thiazomycin antibiotics, still remains a challenge. While a methodology has been presented for the synthesis and linkage of the hydroxyindole unit, no synthetic route has been established so far to the Dyg<Thz dipeptide core.[40] In order to develop an efficient synthetic route to hydroxylated thiazole dipeptides, we investigated an strategy based on a saccharide starting material and cysteine as the biomimetic thiazole precursor. Advantages are a minimum of protecting groups since we start from unprotected sugars and since we can avoid malodorous and toxic thioxylation reagents. The Dyg side chain in the Dyg<Thz unit has the stereochemistry of D-arabinurosamine (Fig. 1). This led us to the proposal that, instead of creating the stereocenters of the side chain by chemical synthesis, sugar-based starting materials are a versatile alternative.[41] The work presented here describes the stereoselective synthesis of the Dyg<Thz dipeptide as well as of other highly functionalized derivatives.

2. Results and discussion

2.1. Retrosynthetic analysis

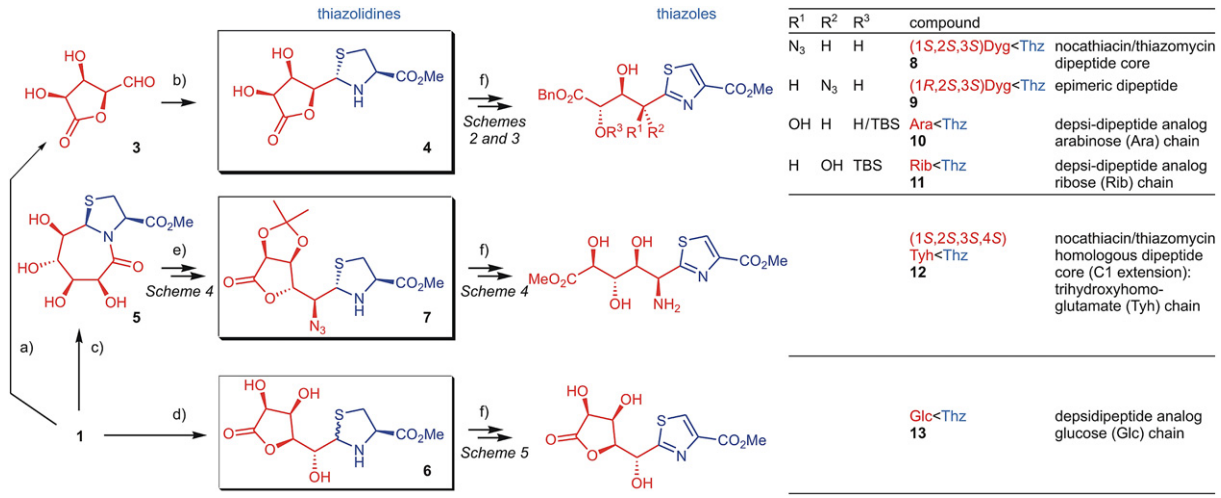
Fig. 1 shows the retrosynthetic analysis of the Dyg<Thz dipeptide. O/N-exchange of the hydroxyl group next to the aromatic thiazole ring of the depsidipeptide introduces the α-nitrogen functionality. The depsidipeptide is accessible from thiazolidine precursors by oxidation of the thiazolidine ring and tailoring of the sugar chain. Previous work published by our group describes the synthesis of the stereopure bicyclic thiazolidine lactams[42] as well as of the epimeric thiazolidine lactones,[43] which are directly accessible from condensation reactions of γ-glucuronolactone **1** and cysteine **2** without protecting groups. The thermodynamic products of such reactions are the thiazolidine lactams, which are constitutional isomers of the thiazolidine lactones obtained by kinetic control. Cyclic and bicyclic starting materials minimize the number of protection and steps while maximizing the chemo-, stereo-, and regioselectivity of the subsequent transformations like O/N-exchange and tailoring of the sugar chain.

2.2. Condensation variants and accessible thiazole units

The condensation of L-cysteine methyl ester with the uronolactones γ-glucuronolactone **1** or D-arabinuronolactone **3**, respectively, led to four different thiazolidines (**4**–**7**) on a multigram scale (Scheme 1), which are precursors of the Dyg<Thz dipeptide and derivatives thereof. Compound **3** was obtained from **1** by periodate diol cleavage (a) and directly subjected to condensation (b) with L-cysteine methyl ester, yielding thiazolidine **4**. Fig. 2 shows the crystal structure of **4**.[44] Schemes 2 and 3 describe subsequent transformations of **4** to the Dyg<Thz dipeptide core **8**, its α-epimer **9**, as well as to the depsidipeptide analogs **10** and **11**. The condensation of uronolactone **1** with L-cysteine along to two different reaction protocols affords two different products, which are either isolated by crystallization (c, thermodynamic product **5**) or precipitation (d, kinetic product **6**), respectively. Finally, Scheme 4 describes the transformation of bicyclic thiazolidine lactam **5** via thiazolidine **7** to the dipeptide **12** with a trihydroxyhomoglutamate (Tyh) side chain. Carrying out the condensation of lactone **1** at high concentrations led to precipitation of the kinetic product **6**, which was isolated in 56% yield by filtration (d). Scheme 5 outlines the three-step reaction sequence leading to the thiazole **13** with a D-*gluco* configured (Glc) polyol chain.

2.3. Stereoselective synthesis of both α-epimers of the Dyg < Thz dipeptide

The strategic bottleneck of a thiazole synthesis from a hydroxylated thiazolidine precursor is to carry out the oxidative dehydrogenation to the thiazole by avoiding or minimizing intramolecular N-acylation, diol cleavage, hydrolysis, benzylic oxidations, and other degradation reactions. Activated MnO_2 has by far been used most often as oxidant to generate thiazoles,[45,46] although it is known to generally reduce the yields due to these side reactions.[47–49] In order to make this oxidation applicable to the highly functionalized thiazolidine lactone **4**, its hydroxyl functions had to be protected appropriately, and silyl ethers proved sufficiently stable to the oxidation conditions. Reaction of the diol **4** with TES chloride and imidazole in DMF (a) yielded the bis(-triethylsilyl) (TES) ether **14** (Scheme 2), which as a crude product was directly subjected to oxidation with excess MnO_2 in toluene at 70 °C, yielding the desired TES-protected thiazole lactone **15** in 33% yield over two steps on a multigram scale (b). In order to access the α-position of the later amino acid side chain, the lactone was opened in the following step using benzyl alcohol as both reagent



R^1	R^2	R^3	compound	
N_3	H	H	(1*S*,2*S*,3*S*)Dyg<Thz **8**	nocathiacin/thiazomycin dipeptide core
H	N_3	H	(1*R*,2*S*,3*S*)Dyg<Thz **9**	epimeric dipeptide
OH	H	H/TBS	Ara<Thz **10**	depsi-dipeptide analog arabinose (Ara) chain
H	OH	TBS	Rib<Thz **11**	depsi-dipeptide analog ribose (Rib) chain
			(1*S*,2*S*,3*S*,4*S*) Tyh<Thz **12**	nocathiacin/thiazomycin homologous dipeptide core (C1 extension): trihydroxyhomo-glutamate (Tyh) chain
			Glc<Thz **13**	depsidipeptide analog glucose (Glc) chain

Scheme 1. Synthesis of the thiazolidine precursors and overview of succeeding synthetic routes leading to the various thiazole units. (a) $NaIO_4$ (1.0 equiv), phosphate buffer, 0 °C, 1 h; (b) L-CysOMe×HCl (1.0 equiv), MeOH/H_2O/pyridine=15:5:1, rt, 15 h, 53% over two steps; (c) L-CysOMe×HCl (1.0 equiv), H_2O/pyridine=10:1, rt, 4 days, 52%; (d) L-CysOMe×HCl (1.0 equiv), H_2O/pyridine=10:1, rt, 15 min, 56%; (e) O/N-exchange and lactam alcoholysis; (f) (de)protection steps, oxidation, sugar chain modifications, and/or O/N-exchange. Sugar chain configurations: Ara=D-*arabino*, Rib=D-*ribo*, Tyh=trihydroxyhomoglutamate, Glc=D-*gluco*.

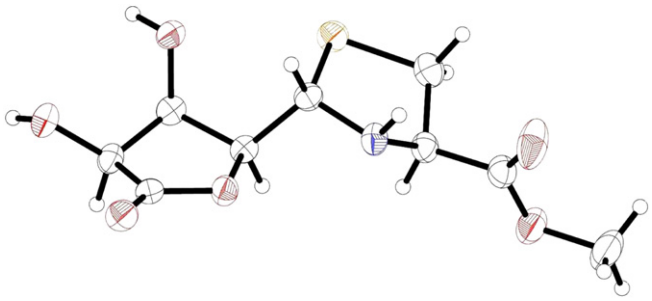
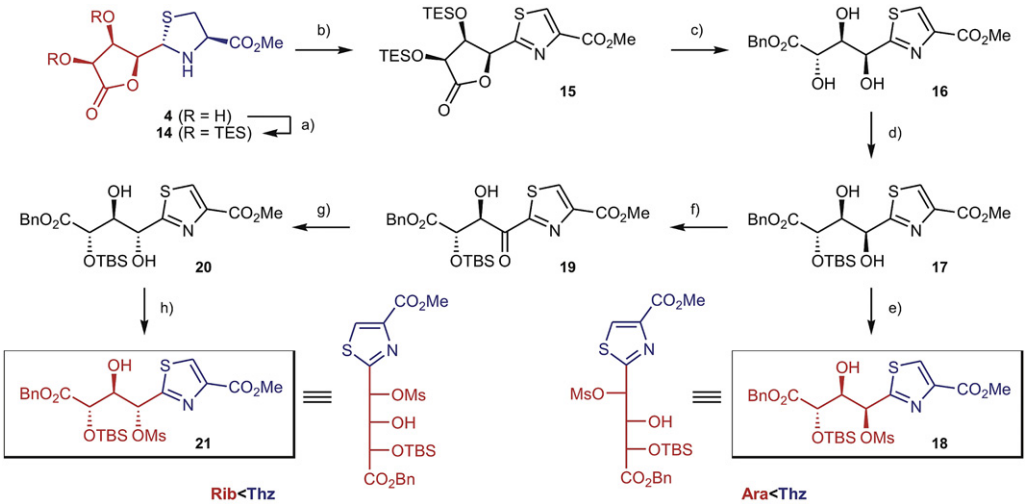


Fig. 2. Perspective drawing of X-ray structure of thiazolidine **4**.

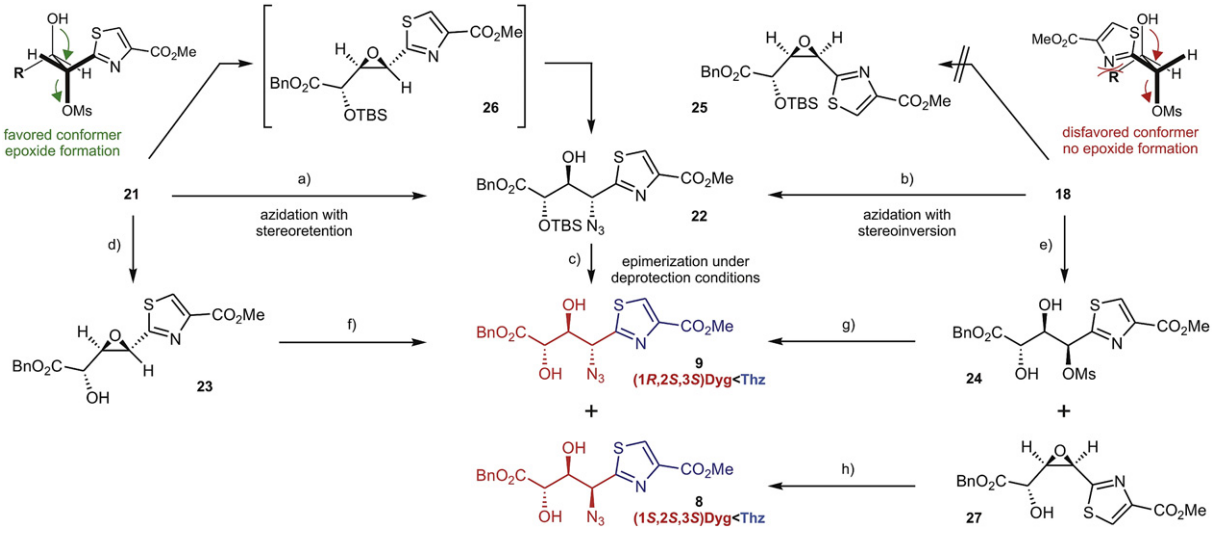
and solvent with 0.05 equiv of camphor sulfonic acid at 50 °C (c). Under these conditions, the thiazole triol **16** with orthogonally protected carboxyl functions precipitates from the reaction mixture and was isolated in good purity and in 81% yield by filtration.

With the D-*arabino* configuration of the triol chain, thiazole **16** already represents the 2-oxo analog of the naturally occuring (1*S*,2*S*,3*S*)Dyg<Thz core motif and was accessible from γ-glucuronolactone and L-cysteine methyl ester in five linear steps with 14.2% overall yield, yet on the multigram scale. The reaction sequence requires only one chromatographic purification (after the oxidation step) and no anhydrous solvents or inert gas. The desired nitrogen functionality at position 1 could not be installed with all three hydroxyl groups deprotected. Attempts to maintain the silyl ethers upon lactone opening (in this case, the more stable TBS group was chosen) were unsuccessful as protecting group migration occurred. However, the 3-hydroxyl function of the triol **16** was protected selectively as *tert*-butyldimethyl silyl (TBS) ether **17** in 74% yield (d). Treatment with mesyl chloride in pyridine finally allowed to selectively activate the 1-hydroxy function as mesylate **18** in 62% yield b.r.s.m. (e).

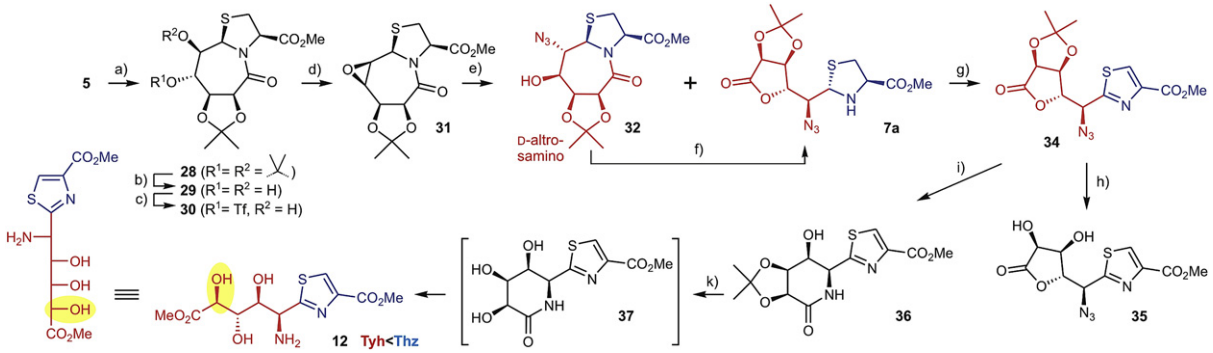
In addition to the selective activation, we also sought to selectively invert the stereocenter at position 1 in order to obtain both



Scheme 2. Synthesis of thiazole polyols with D-*ribo* (Rib) and D-*arabino* (Ara) configuration. The final products are also shown in the Fischer projection. (a) TESCl (2.4 equiv), imidazole (2.4 equiv), DMF, 0 °C to rt, 3 h; (b) MnO_2 (20+25 equiv), toluene, 70 °C, 36+43 h, 33% over two steps; (c) BnOH, CSA (0.05 equiv), 50 °C, 67 h, 81%; (d) TBSCl (1.2 equiv), imidazole (1.2 equiv), DMF, rt, 18 h, 74% (plus 16% starting material reisolated); (e) MsCl (1.0 equiv), anhydrous pyridine, 0 °C to rt, 13 h, 48% (plus 23% starting material and 20% dimesylate isolated); (f) IBX (5.0 equiv), EtOAc, 80 °C, 1.5 h, 29% (plus 53% starting material reisolated); (g) BF_3×Et_2O (2.2 equiv), Bu_3SnH (1.2+1.0 equiv), anhydrous THF, −78 °C to rt, 32 h, 75%, dr>99:1; (h) MsCl (1.5+1.0 equiv), DMAP (cat.), anhydrous pyridine, 0 °C to rt, 17 h, 73% (plus 25% dimesylate).

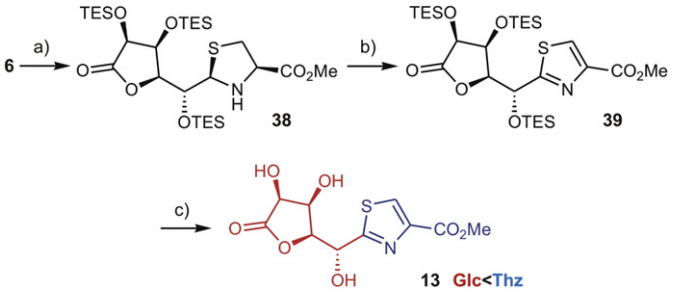


Scheme 3. O/N-exchange reactions and neighboring group effects in thiazole units with D-*ribo* (left) and D-*arabino* configuration (right). (a) NaN_3 (1.5+1.5 equiv), anhydrous DMF, 85 °C, 3.5 h; (b) NaN_3 (1.5 equiv), DMF (abs), 85 °C, 2.5 h, 19%; (c) H_2SiF_6 (2.0 equiv), acetonitrile, rt, 24 h, 13% of **8** and 12% of **9** (over two steps from **18**); (d) TBAF (1.3 equiv), anhydrous THF, 0 °C, 45 min, 42%; (e) TBAF (1.3 equiv), anhydrous THF, 0 °C, 1.5 h, 21%; of **24** and 23% of **27**; (f) NaN_3 (5.0 equiv), CSA (cat.), anhydrous DMF, 70 °C, 4 h, >95% conversion (NMR); (g) NaN_3 (3.0 equiv), anhydrous DMF, 85 °C, 2 h, 70%; (h) NaN_3 (5.0 equiv), DMSO, *p*-TosOH×H_2O (cat.), 70 °C, 9 h, >95% conversion (NMR), isolated yield 16%. R=CH(OTBS)–CO_2Bn.



Scheme 4. Synthetic route to a trihydroxyhomoglutamate(Tyh)<Thz dipeptide, which is a C_1-extended (yellow) nocathiacin and thiazomycin thiopeptide core with native stereochemistry. Its synthesis was accomplished by selective tailoring and subsequent alcoholysis of a D-*gluco* configured 7,5-bicyclic thiazolidin lactam scaffold. (a) DMP (10 equiv), *p*-TosOH×H_2O (cat.), DMF, 60 °C, 38 h, 93%; (b) *p*-TosOH×H_2O (cat.), MeOH, rt, 17 h, 67%; (c) Tf_2O (1.2 equiv), anhydrous CH_2Cl_2/pyridine=3:1, 0 °C to rt, 4.5 h, 94%; (d) DMF/NEt_3=14:1, 60 °C, 14 h, 81%; (e) NaN_3 (1.7 equiv), AcOH (1.7 equiv), DMF, 45–55 °C, 50 h, 39% of **7a** and 33% of **32**; (f) DMF/AcOH=130:1, 50 °C, 72 h, 33%; (g) MnO_2 (30 equiv), 70 °C, 20 h, 31% (plus 27% of starting material reisolated); (h) formic acid (60% in H_2O), 65 °C, 40 min, 69%; (i) Pd/C (5%, wet), H_2 (1 bar), EtOAc/MeOH=2:1, rt, 45 h, 88%; (k) *p*-TosOH×H_2O (cat.), MeOH, 50 °C, 66 h, 22%.

epimers of the Dyg<Thz dipeptide as well as of its depsidipeptide analog. Since $KMnO_4$, which had been successfully used for analogous oxidations of sugar substrates,[50] led to diol cleavage in the case of thiazole **17**, we investigated the use of IBX in EtOAc.[51] Under optimized reaction conditions (5.0 equiv IBX, 80 °C, 1.5 h), the extent of decomposition was minimized and 62% b.r.s.m. of the ketone **19** were obtained (f). Reduction with Bu_3SnH in the presence of BF_3×OEt_2[52] finally afforded the thiazole triol **20** with D-ribose (Rib) configuration in 75% yield and >99:1 diastereoselectivity (g). Analogously to the 1-epimeric triol **17**, **20** was subjected to selective activation of the 1-hydroxyl, yielding 73% of the mesylate **21** (h).



Scheme 5. Synthesis of the thiazole lactone **13** with D-*gluco* (Glc) configuration, applicable to the multigram scale. (a) TESCl (3.6 equiv), imidazole (3.6 equiv), anhydrous DMF, rt, 3 h; (b) MnO_2 (20 equiv), toluene, 70 °C, 28 h, then $BrCCl_3$ (3.0 equiv), DBU (3.0 equiv), toluene, rt, 14 h, 48% over three steps; (c) H_2SiF_6 (1.66 M in H_2O, 2.0 equiv), acetonitrile, 0 °C to rt, 4.5 h, 98%.

O/N-exchange reactions were investigated with both mesylates **18** and **21** (Scheme 3). Under identical reaction conditions (3.0 equiv NaN_3 in DMF at 85 °C) the same azide main product was obtained from both **21** (a) and **18** (b), respectively, which was later identified as azide **22**. As some TBS group migration had occurred, the silyl ethers were deprotected with hexafluoro silicic acid (c). However, this resulted in racemization of the stereocenter at position 1, yielding a 1:1 mixture of the Dyg<Thz epimers **8** and **9** in an overall yield of 25% over both steps. In order to overcome the low yields we decided to perform the azide exchange with TBS-deprotected substrates. The less steric congestion associated with the removal of the bulky TBS group had also significantly increased the yield of azide product in the total synthesis of the GE2270 thiopeptides.[53]

The products obtained for the TBS-deprotection of **18** and **21** also revealed the mechanism of azide introduction in dependence of the relative stereochemistry. In the case of mesylate **21**, the epoxide **23** was the only product obtained after treatment with TBAF in THF (d), while in contrast identical reaction conditions applied to mesylate **18** gave the diol **24** (e). The absence of epoxide **25** in the crude product after azide substitution of mesylate **18** (b) was ascribed to the steric congestion which is significantly lower in the case of mesylate **21** (Scheme 3). Consequently, the azide substitution in this case proceeded via formation of the TBS-protected epoxyalcohol **26** (a) and subsequent epoxide opening by the azide ion, resulting in retention of the configuration (double S_N2-type inversion) while in the case of the epimer **18** a direct S_N2 reaction inverts the stereocenter, affording the same product **22**.

The conversion of the TBS-deprotection products **23** and **24** with 5.0 equiv NaN_3 in DMF (catalytical amounts of CSA added in the case of the epoxide; (f) and (g)) supported the postulated reaction pathways, since the same azide **9** was obtained as the only product in 70% yield (g). Azide **9** is a protected derivative of the (1*R*,2*S*,3*S*) Dyg<Thz unit as present in the thiopeptides, with the amine and carboxylic function protected as azide and ester, respectively.

The key to the synthesis of the epimeric (1*S*,2*S*,3*S*)Dyg<Thz unit, which is, for example, present in thiazomycin, was the epoxyalcohol **27**, which could be separated from the mesylate diol **26** as a second product by silica gel chromatography after TBS cleavage of mesylate **18** (e). Upon treatment with NaN_3 (5.0 equiv) and *p*-TosOH (cat.) in DMSO at 70 °C (h), one product was isolated in 16% yield, which was identified as epimer **8**. The low yield can be ascribed to decomposition reactions like ester cleavage, as suggested from monitoring the reaction by HPLC and ^{1}H NMR. Although some of the reaction steps yet have to be optimized with respect to the isolated yields, this route allows the first stereoselective chemical access to Dyg<Thz dipeptides. Monitoring of the azide substitutions by NMR spectroscopy and analytical HPLC showed a >95% conversion in all cases and the lack of any azide/azide substitution reactions, which would give rise to epimerization under the applied conditions. Comparison of the optical rotations measured for all products shown in Schemes 2 and 3 revealed that, independently from the functionalization at position 2 and hydroxyl protection, all 1*S* configured substrates showed negative rotations while the 1*R* configuration always resulted in a positive rotation. These results are in accordance with the optical rotations observed for fully deprotected 2,3-dihydroxyglutamates.[54]

2.4. Stereoselective synthesis of a C1-extended Dyg < Thz homolog

Scheme 4 shows the conversion of D-*gluco* configuration of the uronic acid chain in lactam **5** to a D-altrosamino configuration in only five steps. The reaction sequence starts with the protection of all four hydroxyl functions as acetonides by treatment with DMP and *p*-TosOH in DMF at 60 °C, yielding the bis-acetonide **28** in 93% yield (a). After cleavage of the 8,9-acetonide using *p*-TosOH in MeOH at rt, the diol **29** was obtained in 67% yield (b) and activated regioselectively as triflate **30** in 94% yield with Tf_2O in a DCM/pyridine (c). Treatment with NEt_3 in DMF at 60 °C afforded epoxide **31** (81% yield), which was subsequently opened with NaN_3 in AcOH and DMF at temperatures between 45 and 55 °C (e). This reaction yielded two 1-hydroxyl azide main products, which were both further used because they can be converted from one form to the other.[55] Regioselective opening of the epoxide at position 9 in **31** yielded lactam **32**, a D-altrosamino configured sugar chain, in 33% yield. Compound **32** undergoes alcoholysis by attack of the 8-hydroxyl group, which opens the seven-membered lactam ring, thus forming the thiazolidine lactone **7a**, which was obtained in 39% yield after separation from lactam **32** by column chromatography. Fig. 3 shows the crystal structure of the analogously synthesized ethyl ester **7b**.[44] The yield of lactone **7a** was further increased by heating the lactam **32** in a DMF/AcOH mixture at 50 °C (f); however, since the lactone **7a** was formed reversibly, a mixture of **32** and **7a** was always obtained. The thiazolidine lactone **7a** was subsequently converted into a C-1 extended homolog of the Dyg<Thz dipeptide (Scheme 4). Again, the use of an excess of activated MnO_2 at 70 °C enabled the oxidation to the corresponding thiazole **34** (g); however, acetonitrile as solvent proved superior to toluene. Since the required harsh reaction conditions also resulted in a slow decomposition of the starting material as well as of the product, the best results were obtained by stopping the reaction at an early stage and to separate the formed thiazole from remaining starting material by column chromatography. This procedure afforded 42% b.r.s.m. of the thiazole **34**. A comparison of the scalar coupling parameters via NMR showed that the oxidation did not affect the stereopurity of the sugar chain. The acetonide in thiazole **34** was cleaved by treatment with aqueous formic acid at 65 °C, yielding 69% of the diol **35** (h).

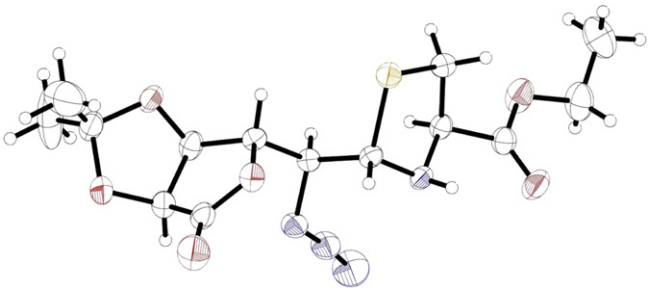


Fig. 3. Perspective drawing of X-ray structure of ethylester **7b**.

The azide **34** was hydrogenated under hydrogen atmosphere (1 bar) in the presence of Pd/C catalyst and the product isolated in 88% yield (i) was δ-lactam **36**, probably formed by intermediate aminolysis of the lactone. Lactam **36** resembles a precursor of Xaa–Yaa<Thz tripeptides, which can theoretically be obtained by cleavage of a C–C bond of the triol motif, providing the Xaa and Yaa side chains. By methanolysis of the lactam, however, it was possible to synthesize a Tyh<Thz dipeptide, which resembles a C-1 extended Dyg<Thz analog (extension highlighted in yellow, Scheme 4). Treatment of lactam **36** in acidified MeOH at elevated temperatures (k) led to the cleavage of the acetonide, providing the triol **37** as the only observed intermediate, and finally the lactam ring opened to form the methyl ester **12**. Although some optimization is required in order to increase the yield, for example, by using modern catalytic techniques for lactone alcoholysis, the reaction is simple to perform since the product **12** precipitates from the reaction mixture after neutralization, being isolated in 22% yield and in good purity by filtration from the reaction mixture containing mostly unreacted triol **37**.

2.5. Synthesis of a D-*gluco* configured thiazole polyol

The oxidation of the D-*gluco* configured analog was accomplished without affecting the stereopurity of the sugar side chain and in a protocol applicable to the multigram scale. The triol **6** was protected for the oxidation step by treatment with TESCl and imidazole (a), and the resulting TBS ether **38** was subjected to oxidation without purification (Scheme 5). Excess MnO_2 in toluene at 70 °C effected oxidation, however, it turned out that the thiazoline intermediate was formed quickly while the second

oxidation to the thiazole **39** proceeded very slowly. The long reaction times and decomposition made a different oxidation method necessary. The use of $BrCCl_3$ and DBU, which had been shown to effect clean oxidation of a range of partially unsaturated heterocycles,[56,57] proved successful in this case, too. The thiazolidine **38** was treated with MnO_2 until no more starting material was present, then the reaction mixture was cooled to rt, then $BrCCl_3$ and DBU were added. The thiazole lactone **39** was finally be isolated in 48% yield over three steps, and subsequent treatment with H_2SiF_6[58] afforded the thiazole triol **13** in 98% yield (c). X-ray crystallographic analysis (Fig. 4)[44] proved the stereopurity of the sugar chain.

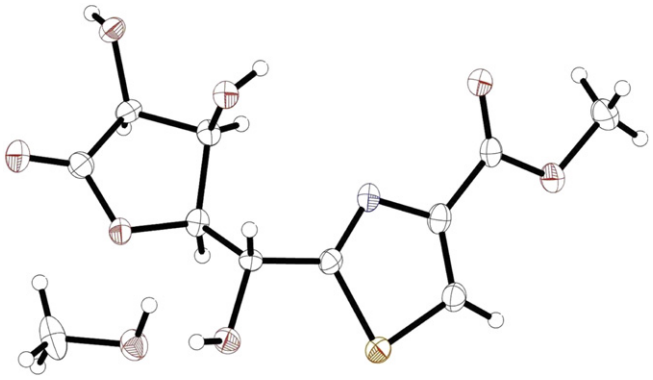


Fig. 4. Perspective drawing of X-ray structure of thiazole **13** including a MeOH molecule.

3. Conclusion

A strategy is presented for the stereoselective synthesis of highly functionalized Xaa<Thz depsidipeptides and dipeptides that rely on the condensation of an uronic acid and cysteine. Assembling the carbon skeleton already in the first step avoids tedious multi-step protection and deprotection protocols. The methods described above yield peptidic thiazole motifs that are present in thiopeptide antibiotics and that have not been available by other methods so far. This includes the Dyg<Thz unit, which is an essential core motif of the nocathiacin and thiazomycin antibiotics, as well as of its epimer and a C-1 extended homolog (Tyh<Thz). The synthetic protocols leading to the thiazole polyols are applicable to the multigram scale, and further work is underway to optimize the protocols leading to the thiazole peptides. In addition, we are also concerned with the condensation reactions of differently configured uronic acids, which are expected to further extend the library of available thiazole compounds.

4. Experimental section

4.1. General information

Reactions with substrates, reagents, and catalysts sensitive to oxygen and/or moisture were run under an atmosphere of nitrogen in flame-dried glassware. All purchased reagents were not further purified prior to use. Anhydrous DMF and anhydrous pyridine were purchased from *Acros* and not dried further. If no anhydrous DMF was required, peptide grade DMF (purchased from Iris Biotech) was used. All other solvents were dried and distilled according to standard protocols. The solvent mixtures are given in volume ratios (v/v). For the oxidation step from thiazolidines to thiazoles, MnO_2 purchased from Fluka (technical, activated, ≥90%) gave the best results.

Thin layer chromatography (TLC) monitoring of all reactions was carried out using analytical TLC plates coated with silica gel (60 F_{254}, Merck). Preparative column chromatography was carried out at room temperature (rt) with compressed air using flash silica gel (particle size 40–60 μm, Merck). For analytical HPLC characterizations of purified products, a Dionex system with diode array detection, a Dionex P680 dual gradient pump, auto sampler, and a reversed-phase Dionex Acclaim 120 (C-18, particle size 5 μm, pore diameter 120 Å, 4.6×150 mm) was used with a flow rate of 0.6 mL/min (acetonitrile in 0.06% TFA/H_2O) and varying gradients (specified for the respective substrate). ^1H and ^{13}C NMR spectra were recorded at 300 K on Bruker spectrometers (300–600 MHz). Chemical shifts δ are given in parts per million (ppm) and were determined from the center of the respective coupling pattern (s: singlet, d: doublet, dd: doublet of d, ddd: doublet of dd, t: triplet, pt: pseudotriplet, m: multiplet). Signals of diastereomeric protons, which could not be assigned pro*R*/*S* are assigned u (upfield) and d (downfield), respectively. The numbering of compounds is shown below.[59] The solvent signals were used as internal standard ($CDCl_3$: $\delta(^1H)$=7.26 ppm, $\delta(^{13}C)$=77.16 ppm; DMSO-d_6: $\delta(^1H)$=2.50 ppm, $\delta(^{13}C)$=39.52 ppm). ESI-HMRS measurements were performed on a LTQ-FT mass spectrometer (Thermo Fisher Scientific), and IR spectra were recorded on a Bruker IFS88 interferometer or a Bruker Alpha spectrometer. All optical rotation values were determined on a Perkin-Elmer 241 polarimeter (length of used vessel 1.0001 dm, values given in mL/mg dm). Melting points (mp) were recorded on a capillary melting point apparatus and are given uncorrected.

4.2. Synthesis procedures

*4.2.1. (2S,4R)-Methyl 2-[((2S,3R,4S)-dihydroxy-5-oxo-tetrahydrofuran-2-yl)]-thiazolidine-4-carboxylate (**4**).* To a solution of γ-glucuronolactone **1** (10.0 g, 56.8 mmol) in aq Na_2HPO_4 (0.05 M, 100 mL) at 0 °C $NaIO_4$ (16.6 g, 56.8 mmol) was added, the solution was vigorously stirred at 0 °C for 1 h and then diluted with MeOH (100 mL). After 30 min the precipitated salts were filtered and the filtrate was concentrated in vacuo to yield the crude aldehyde **3** as pale yellow oil. This was dissolved in MeOH/H_2O/pyridine=15:5:1 (90 mL), L-cysteine methyl ester hydrochloride **2** (9.77 g, 56.8 mmol) was added and the solution was stirred at rt for 15 h. The solution was filtered, the precipitate was washed with cold EtOH, and dried in vacuo to yield the first fraction of thiazolidine **4** as a colorless solid. Further product was isolated by concentration of the filtrate in vacuo, addition of EtOH (50 mL), and storage of the resulting suspension at 5 °C for 30 min. After filtration, washing of the precipitate with cold EtOH and drying in vacuo the combination of both fractions gave a 53% (7.93 g over two steps) overall yield of thiazolidine **4**. R_f (EtOAc) 0.26; mp 120 °C (decomposition); IR (KBr) 3434, 3270, 1763, 1733, 1437, 1358, 1323, 1290, 1228, 1183, 1141, 1118, 1022, 981, 967, 930, 897, 849, 829, 849, 829, 785, 771, 740, 723 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ 2.69 (dd, 1H, $^2J_{Thz-5-H^{proR}/Thz-5-H^{proS}}$=10.0 Hz, $^3J_{Thz-5-H^{proR}/Thz-4-H}$=8.2 Hz, Thz-5-$H^{proR}$), 3.11 (dd, 1H, $^2J_{Thz-5-H^{proS}/Thz-5-H^{proR}}$=10.0 Hz, $^3J_{Thz-5-H^{proS}/Thz-4-H}$=6.2 Hz, Thz-5-$H^{proS}$), 3.67 (dd, 1H, $^3J_{NH/Thz-2-H}$=7.8 Hz, $^3J_{NH/Thz-4-H}$=11.3 Hz, NH), 3.70 (s, 3H, CO_2CH_3), 3.93–3.98 (m, 1H, Thz-4-H), 4.13 (ddd, 1H, $^3J_{3-H/2-H}$=2.9 Hz, $^3J_{3-H/3-OH}$=4.2 Hz, $^3J_{3-H/4-H}$=4.6 Hz, 3-H), 4.24 (ddd, 1H, $^3J_{2-H/3-H}$=2.9 Hz, $^3J_{2-H/Thz-2-H}$=9.7 Hz, $^4J_{2-H/3-OH}$=0.9 Hz, 1-H), 4.40 (dd, 1H, $^3J_{4-H/3-H}$=4.6 Hz, $^3J_{4-H/4-OH}$=7.3 Hz, 4-H), 4.82 (dd, 1H,$^3J_{Thz-2-H/NH}$=7.8 Hz, $^3J_{Thz-2-H/2-H}$=9.7 Hz, Thz-2-H), 5.47 (dd, 1H, $^3J_{3-OH/3-H}$=4.2 Hz, $^4J_{3-OH/2-H}$=0.9 Hz, 3-OH), 5.87 (d, 1H,$^3J_{4-OH/4-H}$=7.3 Hz, 4-OH); ^{13}C NMR (125 MHz, DMSO-d_6): δ 36.1 (Thz-C-5), 52.1 (CO_2CH_3), 63.6 (Thz-C-

4), 67.4 (Thz-C-2), 69.7 (C-3), 70.8 (C-4), 80.1 (C-2), 171.1 (CO_2CH_3), 176.1 (C-5); $[\alpha]_D^{23}$ −107.6 (*c* 0.97, DMSO); ESI-HMRS found 286.0354 (calcd for $C_9H_{13}NO_6S+Na^+$ 286.0356). Suitable crystals for X-ray analysis were grown from a MeOH solution.[44]

*4.2.2. (3R,6S,7S,8S,9R,9aR)-Methyl octahydro-6,7,8,9-tetrahydroxy-5-oxothiazolo[3,2-a]azepine-3-carboxylate (**5**).* A solution of γ-glucuronolactone **1** (12.0 g, 68.1 mmol) and L-cysteine methyl ester hydrochloride **2** (11.6 g, 68.1 mmol) in H_2O/pyridine=9:1 (150 mL) was stirred at rt for 4 d. The solvents were removed in vacuo, the residue was dissolved in H_2O, and the solution was allowed to stand at rt in a crystallizing dish. After several days, the 7,5-bicycle **5** was isolated as colorless crystals (10.3 g, 52%); R_f (EtOAc/MeOH=10:1) 0.25; mp 117 °C; IR (KBr) 3371, 3303, 3257, 1715, 1651, 1436, 1371, 1340, 1231, 1180, 1110, 1073, 1010, 810 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ=3.27 (dd, 1H, $^2J_{2-H^u/2-H^d}$=11.0 Hz, $^3J_{2-H^u/3-H}$=7.2 Hz, 2-H^u), 3.31 (dd, 1H, $^2J_{2-H^d/2-H^u}$=11.0 Hz, $^3J_{2-H^d/3-H}$=7.8 Hz, 2-H^d), 3.54 (ddd, 1H, $^3J_{9-H/9-OH}$=10.9 Hz, $^3J_{9-H/8-H}$=3.6 Hz, $^4J_{9-H/7-H}$=1.4 Hz, 9-H), 3.64 (s, 3H, CO_2CH_3), 3.77–3.84 (m, 2H, 7-H, 8-H), 4.30 (d, 1H, $^3J_{9-OH/9-H}$=10.9 Hz, 9-OH), 4.51 (d, 1H, $^3J_{6-OH/6-H}$=6.6 Hz, 6-OH), 4.68 (d, 1H, $^3J_{6-H/6-OH}$=6.6 Hz, 6-H), 4.71 (pt, 1H, 3-H), 5.33 (d, 1H, $^3J_{7-OH/7-H}$=5.2 Hz, 7-OH), 5.42 (s, 1H, 9a-H), 5.64 (d, 1H,$^3J_{8-OH/8-H}$=3.4 Hz, 8-OH); ^{13}C NMR (75 MHz, DMSO-d_6): δ=31.4 (C-β), 52.2 (CO_2CH_3), 61.1 (C-9a), 64.0 (C-3), 69.3 (C-6), 70.1 (C-8), 76.1 (C-7), 77.0 (C-9), 170.5 (CO_2CH_3), 170.7 (C-5); $[\alpha]_D^{21}$ −63.6 (*c* 1.00, H_2O); ESI-HMRS found 316.0457 (calcd for $C_{10}H_{15}NO_7S+Na^+$ 316.0461).

*4.2.3. (2R/S,4R)-Methyl 2-[((R)-(2S,3R,4S)-3,4-dihydroxy-5-oxo-tetrahydrofuran-2-yl)(hydroxy)methyl]-thiazolidine-4-carboxylate (**6**).* γ-Glucuronolactone **1** (4.61 g, 26.2 mmol) and L-cysteine methyl ester hydrochloride **2** (4.50 g, 26.2 mmol) were dissolved in a minimum amount of H_2O/pyridine=10:1 so that a clear solution was obtained after 5 min (approx. 13 mL required). A voluminous precipitate formed within approx. 10 min and the mixture was subsequently cooled to 5 °C for 5 min. The product was filtered, washed with cold EtOH, and dried in vacuo to yield thiazolidine **6** as a colorless solid (4.39 g, 56%). ESI-HMRS found 316.0459 (calcd for $C_{10}H_{15}NO_7S+Na^+$ 316.0461). Major epimer (1*R*): R_f ($CHCl_3$/MeOH=9:1) 0.30; ^1H NMR (300 MHz, DMSO-d_6): δ 2.70 (pt, 1H, $^2J_{Thz-5-H^{proS}/Thz-5-H^{proR}}$=9.8 Hz, $^3J_{Thz-5-H^{proS}/Thz-4-H}$=9.8 Hz, Thz-5-H^{proS}), 2.89 (pt, 1H, $^3J_{NH/Thz-4-H}$=12.7 Hz, $^3J_{NH/Thz-2-H}$=12.7 Hz, NH), 3.22 (dd, 1H, $^2J_{Thz-5-H^{proR}/Thz-5-H^{proS}}$=9.8 Hz, $^3J_{Thz-5-H^{proR}/Thz-4-H}$=6.9 Hz, Thz-5-H^{proR}), 3.71 (s, 3H, CO_2CH_3), 3.84 (ddd, 1H, $^3J_{Thz-4-H/Thz-5-H^{proR}}$=6.9 Hz, $^3J_{Thz-4-H/Thz-5-H^{proS}}$=9.8 Hz, $^3J_{Thz-4-H/NH}$=12.7 Hz, Thz-4-H), 3.98 (ddd, 1H, $^3J_{Cx-H/Thz-2-H}$=1.1 Hz, $^3J_{Cx-H/Cx-OH}$=5.6 Hz, $^3J_{Cx-H/2-H}$=8.7 Hz, CX-H), 4.13 (m, 1H, 3-H), 4.32 (dd, 1H, $^3J_{2-H/3-H}$=2.7 Hz, $^3J_{2-H/3-H}$=8.7 Hz, 2-H), 4.51 (dd, 1H, $^3J_{4-H/5-H}$=4.5 Hz, $^3J_{4-H/4-OH}$=7.3 Hz, 4-H), 4.70 (dd, 1H,$^3J_{Thz-2-H/Cx-H}$=1.1 Hz, $^3J_{Thz-2-H/NH}$=12.7 Hz, Thz-2-H), 5.45 (d, 1H, $^3J_{3-OH/3-H}$=3.9 Hz, 3-OH), 5.85 (d, 1H,$^3J_{Cx-OH/Cx-H}$=5.6 Hz, CX-OH), 5.90 (d, 1H, $^3J_{4-OH/4-H}$=7.3 Hz, 4-OH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 37.0 (Thz-C-5), 52.3 (CO_2CH_3), 65.1 (Thz-C-4), 67.7 (C-X), 69.1 (C-3), 69.5 (Thz-C-2), 70.7 (C-4), 81.5 (C-2), 171.4 (CO_2CH_3), 176.0 (C-5). Minor epimer (1*S*): R_f ($CHCl_3$/MeOH=9:1) 0.18; ^1H NMR (300 MHz, DMSO-d_6): δ 2.94 (dd, 1H, $^2J_{Thz-5-H^{proR}/Thz-5-H^{proS}}$=10.3 Hz, $^3J_{Thz-5-H^{proR}/Thz-4-H}$=4.9 Hz, Thz-5-H^{proR}), 3.03 (dd, 1H, $^2J_{Thz-5-H^{proS}/Thz-5-H^{proR}}$=10.3 Hz, $^3J_{Thz-5-H^{proS}/Thz-4-H}$=6.8 Hz, Thz-5-H^{proS}), 3.64 (s, 3H, CO_2CH_3), 3.96 (dd, 1H, $^3J_{Cx-H/2-H}$=4.5 Hz, $^3J_{Cx-H/Cx-OH}$=5.9 Hz, CX-H), 4.11–4.19 (m, 2H, 2-H, 3-H), 4.38 (m, 1H, Thz-4-H), 4.55 (m, 1H, 4-H), 4.71 (br s, 1H, Thz-2-H), 5.52 (d, 1H, $^3J_{Cx-OH/Cx-H}$=5.9 Hz, CX-OH), 5.55 (d, 1H,$^3J_{3-OH/3-H}$=3.6 Hz, 3-OH), 5.88 (d, 1H, $^3J_{4-OH/4-H}$=7.4 Hz, 4-OH), NH signal invisible; ^{13}C NMR (75 MHz, DMSO-d_6): δ 36.7 (Thz-C-5), 52.0 (CO_2CH_3), 64.2 (Thz-C-4), 69.6 (C-X), 70.1 (Thz-C-2, C-3), 70.7 (C-4), 81.9 (C-2), 171.8 (CO_2CH_3), 175.9 (C-5).

*4.2.4. Methyl 2-[((2S,3R,4S)-bis[(triethylsilyl)oxy]-5-oxo-tetrahydrofuran-2-yl)]-thiazole-4-carboxylate (**15**).* Thiazolidine **4** (10.4 g, 39.6 mmol) and imidazole (6.47 g, 95.0 mmol) were dissolved in DMF (50 mL) in a nitrogen atmosphere at 0 °C. TESCl (16.5 mL, 95.0 mmol) was added over 3 min, the solution was stirred at 0 °C for 3 h, diluted with CH_2Cl_2 (200 mL), and 5% aq $NaHCO_3$ was added under vigorous stirring until complete solution of the precipitate. The layers were separated and the aqueous layer was extracted twice with CH_2Cl_2. The combined organic layers were dried with brine and over $MgSO_4$, filtered, and concentrated in vacuo to yield the thiazolidine **14** as yellow oil (R_f (toluene/EtOAc=2:1) 0.52). This was dissolved in toluene (250 mL), MnO_2 (68.8 g, 792 mmol) was added, the suspension was vigorously stirred at 70 °C for 36 h, filtered over Celite, and concentrated in vacuo. The resulting oil was again dissolved in toluene (200 mL), MnO_2 (51.6 g, 594 mmol) was added, and the suspension was vigorously stirred at 70 °C for 28 h. After cooling to rt, additional 34.4 g of MnO_2 (activated, Fluka; 396 mmol, 10 equiv) were added and stirring at 70 °C was continued for another 15 h. After filtration over Celite and concentration in vacuo, column chromatography (toluene/EtOAc=6:1 to 4:1) yielded thiazole **15** (6.30 g, 33% over two steps) as a pale yellow oil. R_f (toluene/EtOAc=2:1) 0.67; IR (film) 2954, 2912, 2877, 1811, 1732, 1485, 1458, 1436, 1413, 1379, 1345, 1327, 1216, 1184, 1131, 1097, 989, 941, 920, 843, 813, 784, 727, 683 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 0.32–0.45 (m, 6H, 3×SiCH_2CH$_3$), 0.73–0.80 (m, 15H, 3×SiCH_2CH$_3$ and 3×SiCH$_2$CH_3), 1.01 (t, 9H, ^3J=7.9 Hz, 3×SiCH$_2$CH_3), 3.96 (s, 3H, CO_2CH_3), 4.53 (d, 1H, $^3J_{4-H/3-H}$=3.9 Hz, 4-H), 4.71 (dd, 1H, $^3J_{3-H/2-H}$=2.7 Hz, $^3J_{3-H/2-H}$=3.9 Hz, 3-H), 5.71 (d, 1H, $^3J_{2-H/3-H}$=2.7 Hz, 2-H), 8.26 (s, 1H,Thz-5-H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 4.8, 4.9 (each SiCH_2CH$_3$), 6.6, 6.8 (each SiCH$_2$CH_3), 52.7 (CO_2CH_3), 73.0 (C-4), 74.1 (C-3), 79.3 (C-2), 129.0 (Thz-C-5), 146.5 (Thz-C-4), 161.8 (CO_2CH_3), 166.2 (Thz-C-2), 173.3 (C-5); $[\alpha]_D^{20}$ −46.6 (*c* 0.92, $CHCl_3$); ESI-HMRS found 510.1776 (calcd for $C_{21}H_{37}NO_6SSi_2+Na^+$ 510.1772).

*4.2.5. Methyl 2-[(1S,2R,3S)-3-(benzyloxycarbonyl)-1,2,3-trihydroxypropyl]-thiazole-4-carboxylate (**16**).* To a solution of lactone **15** (3.97 g, 8.14 mmol) in BnOH (20 mL) CSA (93 mg, 0.40 mmol) was added and the solution was stirred at 50 °C for 67 h during which a colorless solid precipitated. The mixture was cooled to rt and filtered, the precipitate was washed with toluene and dried in vacuo to afford the triol **16** (2.42 g, 81%) as a colorless solid. R_f (EtOAc/MeOH=5:1) 0.72; mp 104 °C; IR (KBr) 3427, 3237, 2960, 1712, 1495, 1389, 1318, 1294, 1232, 1200, 1124, 1090, 1045, 979, 914, 834, 726, 672, 648 cm^{-1}; ^1H NMR (600 MHz, DMSO-d_6): δ 3.82 (s, 3H, CO_2CH_3), 3.98–4.01 (m, 1H, 3-H), 4.16 (dd, 1H, $^3J_{3-H/3-OH}$=7.1 Hz, $^3J_{3-H/2-H}$=9.1 Hz, 3-H), 5.08 (d, 1H, $^3J_{2-OH/2-H}$=8.2 Hz, 2-OH), 5.08 (dd, 1H, $^3J_{1-H/2-H}$=1.4 Hz, $^3J_{1-H/1-OH}$=6.7 Hz, 1-H), 5.11 (d, 1H, ^2J=12.8 Hz, $CO_2CH_2Ph^u$), 5.16 (d, 1H, ^2J=12.8 Hz, $CO_2CH_2Ph^d$), 6.00 (d, 1H, $^3J_{3-OH/3-H}$=7.1 Hz, 3-OH), 6.30 (d, 1H,$^3J_{1-OH/1-H}$=6.7 Hz, 1-OH), 7.32–7.41 (m, 5H, CO_2CH_2Ph), 8.43 (s, 1H, Thz-5-H); ^{13}C NMR (150 MHz, DMSO-d_6): δ 51.8 (CO_2CH_3), 65.4 (CO_2CH_2Ph), 69.6 (C-1), 71.3 (C-3), 74.3 (C-2), 127.6, 127.8, 128.3 (each Bn-$CH_{arom.}$), 128.9 (Thz-C-5), 136.1 (Bn-$C_{arom., quart.}$), 145.4 (Thz-C-4), 161.5 (CO_2CH_3), 172.8 (C-4), 177.0 (Thz-C-2); $[\alpha]_D^{18}$ −23.3 (*c* 1.03, MeOH); ESI-HMRS found 390.0625 (calcd for $C_{16}H_{17}NO_7S+Na^+$ 390.0618).

*4.2.6. Methyl 2-[(1S,2R,3S)-3-(benzyloxycarbonyl)-1,2-dihydroxy-3-(tert-butyl-dimethylsilyloxy)-propyl]-thiazole-4-carboxylate (**17**).* To a solution of triol **16** (3.59 g, 9.77 mmol) and imidazole (1.77 g, 11.7 mmol) in DMF (24 mL) TBSCl (798 mg, 11.7 mmol) was added and the solution was stirred at rt for 18 h. After dilution with CH_2Cl_2

and 5% aq $NaHCO_3$ the layers were separated and the aqueous layer was extracted twice with CH_2Cl_2. The combined organic layers were dried with brine and over $MgSO_4$, filtered, and concentrated in vacuo. Column chromatography (toluene/EtOAc=4:1 to 3:1) afforded silyl ether **17** (3.49 g, 74%) as a colorless oil. R_f (EtOAc/toluene=1:1) 0.36; IR (film) 3446, 3118, 2954, 2930, 2887, 2857, 1724, 1486, 1461, 1435, 1389, 1348, 1326, 1251, 1170, 1099, 1049, 989, 837, 780, 750, 697 cm^{-1}; ^1H NMR (600 MHz, DMSO-d_6): δ −0.01, 0.06 (each s, 3H, $SiCH_3$), 0.83 (s, 9H, $SiC(CH_3)_3$), 3.82 (s, 3H, CO_2CH_3), 3.95 (ddd, 1H, $^3J_{2\text{-}H/1\text{-}H}$=1.9 Hz, $^3J_{2\text{-}H/2\text{-}OH}$=8.1 Hz, $^3J_{2\text{-}H/3\text{-}H}$=8.9 Hz, 2-H), 4.32 (d, 1H, $^3J_{3\text{-}H/2\text{-}H}$=8.9 Hz, 3-H), 4.98 (dd, 1H, $^3J_{1\text{-}H/2\text{-}H}$=1.9 Hz, $^3J_{1\text{-}H/1\text{-}OH}$=6.4 Hz, 1-H), 5.09 (d, 1H, ^2J=12.5 Hz, $CO_2CH_2Ph^u$), 5.16 (d, 1H, ^2J=12.5 Hz, $CO_2CH_2Ph^d$), 5.31 (d, 1H, $^3J_{2\text{-}OH/2\text{-}H}$=8.1 Hz, 2-OH), 6.33 (d, 1H, $^3J_{1\text{-}OH/1\text{-}H}$=6.4 Hz, 1-OH), 7.32–7.40 (m, 5H, CO_2CH_2Ph), 8.45 (s, 1H, Thz-5-H); ^{13}C NMR (150 MHz, DMSO-d_6): δ −4.8, −4.7 (each $SiCH_3$), 18.5 ($SiC(CH_3)_3$), 26.2 ($SiC(CH_3)_3$), 52.7 (CO_2CH_3), 66.5 (CO_2CH_2Ph), 70.3 (C-1), 73.3 (C-3), 75.4 (C-2), 128.0, 128.1, 128.3 (each Bn-$CH_{arom.}$), 129.7 (Thz-C-5), 135.7 (Bn-$C_{arom.,\ quart.}$), 146.3 (Thz-C-4), 162.2 (CO_2CH_3), 172.2 (C-4), 177.4 (Thz-C-2); $[\alpha]_D^{18}$ −45.5 (*c* 1.08, EtOH); ESI-HMRS found 504.1486 (calcd for $C_{22}H_{31}NO_7SSi+Na^+$ 504.1483).

*4.2.7. Methyl 2-[(1S,2R,3S)-3-(benzyloxycarbonyl)-1-methanesulfonyloxy-2-hydroxy-3-(tert-butyl-dimethylsilyloxy)-propyl]-thiazole-4-carboxylate (**18**).* A solution of diol **17** (988 mg, 2.05 mmol) in anhydrous pyridine (40 mL) was cooled to 0 °C in a nitrogen atmosphere. MsCl (159 μL, 2.05 mmol) was added and the solution was allowed to warm to rt under stirring. After 13 h the reaction was diluted with CH_2Cl_2, quenched with ice, and the layers were separated. The aqueous layer was extracted three times with CH_2Cl_2. The combined organic layers were dried with brine and over $MgSO_4$, filtered, and concentrated in vacuo. Column chromatography (toluene/EtOAc=5:1 to 4:1) afforded the mesylate **18** (547 mg, 48%) as a colorless oil. In addition, starting material **17** (225 mg, 23%) was reisolated. R_f (CH_2Cl_2/MeOH=35:1) 0.53; IR (film) 3472, 2953, 2931, 2857, 1725, 1472, 1435, 1359, 1250, 1217, 1174, 1120, 987, 963, 910, 836, 780, 752, 697 cm^{-1}; ^1H NMR (600 MHz, DMSO-d_6): δ −0.04, 0.05 (each s, 3H, $SiCH_3$), 0.84 (s, 9H, $SiC(CH_3)_3$), 3.15 (s, 3H, Ms-CH_3), 3.83 (s, 3H, CO_2CH_3), 4.16 (ddd, 1H, $^3J_{2\text{-}H/1\text{-}H}$=4.4 Hz, $^3J_{2\text{-}H/3\text{-}H}$=6.0 Hz, $^3J_{2\text{-}H/2\text{-}OH}$=7.0 Hz, 2-H), 4.32 (d, 1H, $^3J_{3\text{-}H/2\text{-}H}$=6.0 Hz, 3-H), 5.02 (d, 1H, ^2J=12.3 Hz, $CO_2CH_2Ph^u$), 5.07 (d, 1H, ^2J=12.3 Hz, $CO_2CH_2Ph^d$), 5.86 (d, 1H, $^3J_{1\text{-}H/2\text{-}H}$=4.4 Hz, 1-H), 6.39 (d, 1H, $^3J_{2\text{-}OH/2\text{-}H}$=7.0 Hz, 2-OH), 7.36–7.41 (m, 5H, CO_2CH_2Ph), 8.66 (s, 1H, Thz-H-5); ^{13}C NMR (150 MHz, DMSO-d_6): δ −5.4, −5.3 (each $SiCH_3$), 17.8 ($SiC(CH_3)_3$), 25.5 ($SiC(CH_3)_3$), 38.7 (Ms-CH_3), 52.1 (CO_2CH_3), 66.3 (CO_2CH_2Ph), 73.2 (C-3), 74.0 (C-2), 77.6 (C-1), 128.1, 128.3, 128.4 (each Bn-$CH_{arom.}$), 131.3 (Thz-C-5), 135.4 (Bn-$C_{arom.,\ quart.}$), 145.5 (Thz-C-4), 161.0 (CO_2CH_3), 165.5 (Thz-C-2), 170.3 (C-4); $[\alpha]_D^{18}$ −42.4 (*c* 1.04, $CHCl_3$); ESI-HMRS found 582.1263 (calcd for $C_{23}H_{33}NO_9S_2Si+Na^+$ 582.1258).

*4.2.8. Methyl 2-[(2R,3S)-3-(benzyloxycarbonyl)-1-oxo-2-hydroxy-3-(tert-butyl-dimethylsilyloxy)-propyl]-thiazole-4-carboxylate (**19**).* To a solution of the diol **17** (1.02 g, 2.12 mmol) in EtOAc (60 mL) was added IBX (2.97 g, 10.6 mmol) and the suspension was refluxed at 80 °C for 1.5 h under vigorous stirring. After cooling to rt, filtration over Celite, washing with EtOAc, and concentration in vacuo, column chromatography (toluene/EtOAc=5:1 to 3:1) afforded ketone **19** (294 mg, 29%) as pale yellow oil. In addition, starting material **17** (543 mg, 53%) was reisolated. R_f (toluene/EtOAc=3:1) 0.59; IR (KBr) 3485, 3113, 2954, 2930, 2887, 2857, 1726, 1697, 1492, 1336, 1250, 1216, 1186, 1140, 990, 938, 864, 837, 779, 748, 697 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 0.08, 0.12 (each s, 3H, $SiCH_3$), 0.88 (s, 9H, $SiC(CH_3)_3$), 3.92 (s, 3H, CO_2CH_3), 4.00 (br s, 1H, 2-OH), 5.12 (d, 1H, ^2J=12.1 Hz, $CO_2CH_2Ph^u$), 5.15 (d, 1H, $^3J_{3\text{-}H/2\text{-}H}$=2.5 Hz, 4-H), 5.22 (d, 1H, ^2J=12.1 Hz, $CO_2CH_2Ph^d$), 5.42 (br s, 1H, 2-H), 7.31–7.35 (m, 5H, CO_2CH_2Ph), 8.45 (s, 1H, Thz-5-H); ^{13}C NMR (150 MHz, $CDCl_3$): −5.3, −4.6 (each $SiCH_3$), 18.4 ($SiC(CH_3)_3$), 25.8 ($SiC(CH_3)_3$), 52.6 (CO_2CH_3), 67.5 (CO_2CH_2Ph), 76.0 (C-2), 78.4 (C-3), 128.5, 128.6, 128.7 (each Bn-$CH_{arom.}$), 133.7 (Thz-C-5), 135.4 (Bn-$C_{arom.,\ quart.}$), 148.6 (Thz-C-4), 161.0 (CO_2CH_3), 164.5 (Thz-C-2), 170.2 (C-4), 189.9 (C-1); $[\alpha]_D^{25}$ −8.6 (*c* 1.00, $CHCl_3$); ESI-HMRS found 502.1325 (calcd for $C_{22}H_{29}NO_7SSi+Na^+$ 502.1326).

*4.2.9. Methyl 2-[(1R,2R,3S)-3-(benzyloxycarbonyl)-1,2-dihydroxy-3-(tert-butyl-dimethylsilyloxy)-propyl]-thiazole-4-carboxylate (**20**).* A solution of ketone **19** (290 mg, 0.60 mmol) in 20 mL of anhydrous toluene in a nitrogen atmosphere was cooled to −78 °C. $BF_3\times OEt_2$ (89.5 μL, 0.73 mmol) was added dropwise and, after 7 min, Bu_3SnH (194 μL, 0.73 mmol) was added. The mixture was allowed to warm to 0 °C under stirring and, after 12 h, additional $BF_3\times OEt_2$ (73.5 μL, 0.60 mmol) and Bu_3SnH (158 μL, 0.60 mmol) were added. The solution was allowed to warm to rt under stirring, and after 20 h the reaction was subsequently quenched with 5% aq $NaHCO_3$ (15 mL) and vigorously stirred at rt for 4 h. The mixture was extracted three times with EtOAc, the combined organic layers were dried with brine and over $MgSO_4$, filtered, and concentrated in vacuo. Column chromatography (toluene/EtOAc=4:1 to 2:1) afforded the diol **20** (219 mg, 75%) as a colorless oil. R_f (toluene/EtOAc=3:1) 0.21; IR (film) 3446, 3118, 2953, 2928, 2895, 2856, 1724, 1486, 1461, 1435, 1388, 1346, 1326, 1248, 1214, 1145, 1099, 1072, 991, 837, 780, 751, 697 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 0.00, 0.08 (each s, 3H, $SiCH_3$), 0.83 (s, 9H, $SiC(CH_3)_3$), 3.81 (s, 3H, CO_2CH_3), 4.06 (ddd, 1H, $^3J_{2\text{-}H/1\text{-}H}$=4.2 Hz, $^3J_{2\text{-}H/2\text{-}OH}$=5.7 Hz, $^3J_{2\text{-}H/3\text{-}H}$=6.8 Hz, 2-H), 4.35 (d, 1H, $^3J_{3\text{-}H/2\text{-}H}$=6.8 Hz, 3-H), 4.99 (dd, 1H, $^3J_{1\text{-}H/2\text{-}H}$=4.2 Hz, $^3J_{1\text{-}H/1\text{-}OH}$=5.0 Hz, 1-H), 5.10 (s, 2H, CO_2CH_2Ph), 5.62 (d, 1H, $^3J_{2\text{-}OH/2\text{-}H}$=5.7 Hz, 2-OH), 6.48 (d, 1H, $^3J_{1\text{-}OH/1\text{-}H}$=5.0 Hz, 1-OH), 7.32–7.41 (m, 5H, CO_2CH_2Ph), 8.47 (s, 1H, Thz-5-H); ^{13}C NMR (100 MHz, DMSO-d_6): δ −5.3, −5.2 (each $SiCH_3$), 17.9 ($SiC(CH_3)_3$), 25.6 ($SiC(CH_3)_3$), 51.8 (CO_2CH_3), 65.7 (CO_2CH_2Ph), 70.3 (C-1), 73.3 (C-3), 75.6 (C-2), 128.0, 128.1, 128.3 (each Bn-$CH_{arom.}$), 129.2 (Thz-C-5), 135.8 (Bn-$C_{arom.,\ quart.}$), 145.0 (Thz-C-4), 161.4 (CO_2CH_3), 171.3 (C-4), 174.4 (Thz-C-2); $[\alpha]_D^{24}$ 16.0 (*c* 0.48, $CHCl_3$); ESI-HMRS found 504.1484 (calcd for $C_{22}H_{31}NO_7SSi+Na^+$ 504.1483).

*4.2.10. Methyl 2-[(1R,2R,3S)-3-(benzyloxycarbonyl)-1-methanesulfonyloxy-2-hydroxy-3-(tert-butyl-dimethylsilyloxy)-propyl]-thiazole-4-carboxylate (**21**).* A solution of diol **20** (195 mg, 405 μmol) and a catalytical amount of DMAP in anhydrous pyridine (6 mL) was cooled to 0 °C in a nitrogen atmosphere. MsCl (31.3 μL, 405 μmol) was added and the solution was allowed to warm to rt under stirring. After 14 h, the solution was cooled to 0 °C and more MsCl (15.7 μmol, 203 μmol) was added. After warming to rt and stirring for another 3 h the reaction was diluted with CH_2Cl_2, quenched with ice, and the layers were separated. The aqueous layer was extracted twice with CH_2Cl_2. The combined organic layers were dried with brine and over $MgSO_4$, filtered, and concentrated in vacuo. Column chromatography (toluene/EtOAc=5:1) afforded the mesylate **21** (165 mg, 73%) as a colorless oil. R_f (CH_2Cl_2/MeOH=35:1) 0.23; IR (film) 3463, 2954, 2930, 2857, 1727, 1462, 1435, 1412, 1361, 1249, 1216, 1175, 1099, 956, 836, 781, 751, 697 cm^{-1}; ^1H NMR (600 MHz, DMSO-d_6): δ −0.05, 0.05 (each s, 3H, $SiCH_3$), 0.84 (s, 9H, $SiC(CH_3)_3$), 3.16 (s, 3H, Ms-CH_3), 3.84 (s, 3H, CO_2CH_3), 4.16 (d, 1H, $^3J_{3\text{-}H/2\text{-}H}$=6.2 Hz, 3-H), 4.38 (m, 1H, 2-H), 5.11 (d, 1H, ^2J=12.3 Hz, $CO_2CH_2Ph^u$), 5.18 (d, 1H, ^2J=12.3 Hz, $CO_2CH_2Ph^d$), 5.87 (d, 1H, $^3J_{1\text{-}H/2\text{-}H}$=4.8 Hz, 1-H), 6.40 (d, 1H, $^3J_{2\text{-}OH/2\text{-}H}$=6.0 Hz, 2-OH), 7.35–7.42 (m, 5H, CO_2CH_2Ph), 8.65 (s, 1H, Thz-5-H); ^{13}C NMR (150 MHz, DMSO-d_6): δ −5.6, −5.4 (each $SiCH_3$), 17.8 ($SiC(CH_3)_3$), 25.5 ($SiC(CH_3)_3$), 38.3 (Ms-CH_3), 52.1 (CO_2CH_3), 66.3 (CO_2CH_2Ph), 73.4 (C-3), 73.5 (C-2), 77.7 (C-1), 128.2, 128.3, 128.4 (each Bn-$CH_{arom.}$), 131.2 (Thz-C-5),

135.4 (Bn-$C_{arom.,\ quart.}$), 145.2 (Thz-C-4), 161.0 (CO_2CH_3), 165.0 (Thz-C-2), 170.5 (C-4); $[\alpha]_D^{22}$ 26.5 (*c* 2.38, $CHCl_3$); ESI-HMRS found 582.1267 (calcd for $C_{23}H_{33}NO_9S_2Si+Na^+$ 582.1258).

*4.2.11. Methyl 2-[(1R,2R,3S)-3-(benzyloxycarbonyl)-1-azido-2-hydroxy-3-(tert-butyl-dimethylsilyloxy)-propyl]-thiazole-4-carboxylate (**22**).* NaN_3 (3.8 mg, 59.0 μmol) was added to a solution of the mesylate **18** (22 mg, 39.3 μmol) in anhydrous DMF (0.4 mL) in a nitrogen atmosphere and the mixture was stirred at 85 °C for 2.5 h. After cooling to rt and removal of the DMF in vacuo, CH_2Cl_2 and H_2O were added, the layers were separated, and the aqueous layer was extracted twice with CH_2Cl_2. The combined organic layers were dried with brine and over $MgSO_4$, filtered, and concentrated in vacuo. Column chromatography (toluene/EtOAc=6:1) yielded the azide **22** (2.4 mg, 10%) as a colorless oil, which is available from mesylate **21** along the same procedure. R_f (toluene/EtOAc=3:1) 0.58; ^{1}H NMR (500 MHz, DMSO-d_6): δ −0.05, 0.00 (each s, 3H, $SiCH_3$), 0.82 (s, 9H, $SiC(CH_3)_3$), 3.83 (s, 3H, CO_2CH_3), 4.24–4.27 (m, 2H, 2-H, 3-H), 5.03 (d, 1H, $^3J_{1\text{-}H/2\text{-}H}$=5.4 Hz, 1-H), 5.15 (s, 2H, CO_2CH_2Ph), 6.26 (d, 1H, $^3J_{2\text{-}OH/2\text{-}H}$=5.6 Hz, 2-OH), 7.33–7.41 (m, 5H, CO_2CH_2*Ph*), 8.58 (s, 1H, Thz-5-H); ^{13}C NMR (125 MHz, DMSO-d_6): δ −5.5, −5.5 (each $SiCH_3$), 17.6 ($SiC(CH_3)_3$), 25.2 ($SiC(CH_3)_3$), 51.7 (CO_2CH_3), 62.3 (C-1), 66.1 (CO_2CH_2Ph), 73.4, 73.7 (C-2, C-3), 127.9, 128.0, 128.1 (each Bn-$CH_{arom.}$), 130.4 (Thz-C-5), 135.5 (Bn-$C_{arom.,\ quart.}$), 145.0 (Thz-C-4), 160.9 (CO_2CH_3), 165.9 (Thz-C-2), 170.4 (C-4); $[\alpha]_D^{18}$ 6.0 (*c* 0.32, $CHCl_3$); ESI-HMRS found 529.1554 (calcd for $C_{22}H_{30}N_4O_6SSi+Na^+$ 529.1548).

*4.2.12. Methyl 2-[(1S,2R,3S)-3-(benzyloxycarbonyl)-1,2-epoxy-3-hydroxypropyl]-thiazole-4-carboxylate (**23**).* Mesylate **21** (121 mg, 156 μmol) was dissolved in anhydrous THF (10 mL) in a nitrogen atmosphere and cooled to 0 °C. TBAF (1.0 M in THF; 203 μL, 203 μmol) was added dropwise and the solution was stirred at 0 °C for 45 min. The reaction mixture was diluted with EtOAc and the THF was removed in vacuo. The remaining solution was washed twice with aq NaCl, dried with brine and over $MgSO_4$, filtered, and evaporated. Column chromatography (toluene/EtOAc=3:1) yielded the epoxide **23** (23 mg, 42%) as a colorless solid. R_f (EtOAc/toluene=1:1) 0.36; mp 89 °C; IR (KBr) 3478, 3111, 2958, 1732, 1715, 1496, 1455, 1440, 1392, 1274, 1237, 1205, 1124, 1093, 1028, 984, 933, 911, 882, 851, 753, 698 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ 3.84 (s, 3H, CO_2CH_3), 3.62 (dd, 1H, $^3J_{2\text{-}H/1\text{-}H}$=2.0 Hz, $^3J_{2\text{-}H/3\text{-}H}$=4.2 Hz, 2-H), 4.39 (dd, 1H, $^3J_{3\text{-}H/2\text{-}H}$=4.2 Hz, $^3J_{3\text{-}H/3\text{-}OH}$=6.5 Hz, 3-H), 4.45 (d, 1H, $^3J_{1\text{-}H/2\text{-}H}$=2.0 Hz, 1-H), 5.21 (s, 1H, CO_2CH_2Ph), 6.18 (d, 1H, $^3J_{3\text{-}OH/3\text{-}H}$=6.5 Hz, 3-OH), 7.33–7.37 (m, 5H, CO_2CH_2*Ph*), 8.56 (s, 1H, Thz-5-H); ^{13}C NMR (125 MHz, DMSO-d_6): δ=52.1 (CO_2CH_3), 52.2 (C-1), 66.1 (CO_2CH_2Ph), 62.4 (C-2), 68.8 (C-3), 127.8, 128.1, 128.4 (each Bn-$CH_{arom.}$), 129.7 (Thz-C-5), 135.7 (Bn-$C_{arom.,\ quart.}$), 146.0 (Thz-C-4), 160.9 (CO_2CH_3), 167.9 (Thz-C-2), 170.5 (C-4); $[\alpha]_D^{18}$ −0.7 (*c* 1.77, $CHCl_3$); ESI-HMRS found 372.0510 (calcd for $C_{16}H_{15}NO_6S+Na^+$ 372.0512).

*4.2.13. Methyl 2-[((1S,2R,3S)-3-(benzyloxycarbonyl)-1-methanesulfonyloxy-2,3-dihydroxybutyl-dimethylsilyloxy)-propyl]-thiazole-4-carboxylate (**24**).* A solution of the mesylate **18** (220 mg, 393 μmol) in anhydrous THF (25 mL) was cooled to 0 °C in a nitrogen atmosphere. TBAF (1.0 M in THF; 511 μL, 511 μmol) was added dropwise and the mixture was stirred at 0 °C for 1.5 h. After removal of the solvent under reduced pressure at 30 °C the residue was subjected to column chromatography (EtOAc/toluene=1:1), which yielded the mesylate **24** (36 mg, 21%) as pale yellow oil. R_f (EtOAc/toluene=1:1) 0.15; IR (film) 3435, 3117, 3029, 2955, 1722, 1496, 1485, 1455, 1435, 1351, 1217, 1174, 1095, 964, 908, 854, 812, 787, 751, 734, 697 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.27 (s, 3H, Ms-CH_3), 3.84 (s, 3H, CO_2CH_3), 4.08–4.13 (m, 2H, 2-H, 3-H), 5.12 (d, 1H, ^2J=12.6 Hz, $CO_2CH_2Ph^u$), 5.16 (d, 1H, ^2J=12.6 Hz, $CO_2CH_2Ph^d$), 5.99 (d, 1H, $^3J_{1\text{-}H/2\text{-}H}$=1.0 Hz, 1-H), 6.04, 6.39 (each br s, 1H, 2-OH, 3-OH), 7.35–7.42 (m, 5H, CO_2CH_2*Ph*), 8.61 (s, 1H, Thz-5-H); ^{13}C NMR (100 MHz, DMSO-d_6): δ=38.1 (Ms-CH_3), 52.1 (CO_2CH_3), 65.9 (CO_2CH_2Ph), 71.0 (C-1), 73.2 (C-2), 78.6 (C-3), 127.9, 128.2, 128.4 (each Bn-$CH_{arom.}$), 130.5 (Thz-C-5), 135.8 (Bn-$C_{arom.,\ quart.}$), 145.3 (Thz-C-4), 161.0 (CO_2CH_3), 167.7 (Thz-C-2), 171.9 (C-4); $[\alpha]_D^{19}$ −27.9 (*c* 1.54, $CHCl_3$); ESI-HMRS found 468.0398 (calcd for $C_{17}H_{19}N_4O_9S_2+Na^+$ 468.0393).

*4.2.14. Methyl 2-[(1R,2R,3S)-3-(benzyloxycarbonyl)-1,2-epoxy-3-hydroxypropyl]-thiazole-4-carboxylate (**27**).* The epoxide **27** was obtained as a second product (16 mg, 26%) after TBS cleavage of mesylate **18** (Section 4.2.7) as colorless solid. R_f (EtOAc/toluene=1:1) 0.30; mp 101 °C; IR (neat) 3237, 3130, 3102, 2956, 2926, 1725, 1495, 1455, 1436, 1322, 1289, 1261, 1242, 1229, 1193, 1096, 1083, 1071, 981, 921, 882, 837, 759, 744, 696 cm^{-1}; ^{1}H NMR (600 MHz, DMSO-d_6): δ 3.84 (s, 3H, CO_2CH_3), 3.59 (dd, 1H, $^3J_{2\text{-}H/1\text{-}H}$=4.0 Hz, $^3J_{2\text{-}H/3\text{-}H}$=8.5 Hz, 2-H), 3.93 (dd, 1H, $^3J_{3\text{-}H/3\text{-}OH}$=6.5 Hz, $^3J_{3\text{-}H/2\text{-}H}$=8.5 Hz, 3-H), 4.62 (d, 1H, $^3J_{1\text{-}H/2\text{-}H}$=4.0 Hz, 1-H), 5.21 (d, 1H, ^2J=12.7 Hz, $CO_2CH_2Ph^u$), 5.25 (d, 1H, ^2J=12.7 Hz, $CO_2CH_2Ph^d$), 6.11 (d, 1H, $^3J_{3\text{-}OH/3\text{-}H}$=6.5 Hz, 3-OH), 7.33–7.42 (m, 5H, CO_2CH_2*Ph*), 8.58 (s, 1H, Thz-5-H); ^{13}C NMR (150 MHz, DMSO-d_6): δ 52.1 (CO_2CH_3), 53.8 (C-1), 59.0 (C-2), 66.0 (CO_2CH_2Ph), 67.5 (C-3), 127.1, 128.1, 128.4 (each Bn-$CH_{arom.}$), 129.6 (Thz-C-5), 135.8 (Bn-$C_{arom.,\ quart.}$), 146.4 (Thz-C-4), 160.9 (CO_2CH_3), 165.3 (Thz-C-2), 171.3 (C-4); $[\alpha]_D^{13}$ 68.5 (*c* 1.14, $CHCl_3$); ESI-HMRS found 372.0509 (calcd for $C_{16}H_{15}NO_6S+Na^+$ 372.0512).

*4.2.15. Methyl 2-[(1S,2S,3S)-3-(benzyloxycarbonyl)-1-azido-2,3-dihydroxypropyl]-thiazole-4-carboxylate (**8**).* A solution of epoxide **27** (17 mg, 48.7 μmol), NaN_3 (16 mg, 244 μmol), and a catalytical amount of *p*-TosOH×H_2O in DMSO (1.0 mL) was stirred at 70 °C for 9 h in a nitrogen atmosphere. After cooling to rt and addition of H_2O and CH_2Cl_2 the layers were separated and the aqueous layer was extracted three times with CH_2Cl_2. The combined organic layers were dried with brine and over $MgSO_4$, filtered, and concentrated in vacuo. Column chromatography (toluene/EtOAc=2:1) yielded the azide **8** (3.0 mg, 16%) as a pale yellow oil. NMR monitoring of the reaction in DMSO-d_6 showed a >90% conversion after 13.5 h under identical conditions. R_f (EtOAc/toluene=3:2) 0.41; IR (film) 3436, 3116, 3012, 2954, 2925, 2108, 1723, 1625, 1498, 1456, 1435, 1319, 1214, 1095, 986, 918, 864, 828, 783, 748, 697 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ 3.83 (s, 3H, CO_2CH_3), 4.16 (dd, 1H, $^3J_{3\text{-}H/2\text{-}H}$=2.9 Hz, $^3J_{3\text{-}H/3\text{-}OH}$=6.9 Hz, 3-H), 4.25 (dpt, 1H, $^3J_{2\text{-}H/3\text{-}H}$=2.9 Hz, $^3J_{2\text{-}H/1\text{-}H}$=7.3 Hz, $^3J_{2\text{-}H/2\text{-}OH}$=7.3 Hz, 2-H), 5.11 (d, 1H, $^3J_{1\text{-}H/2\text{-}H}$=7.3 Hz, 1-H), 5.13 (d, 1H, ^2J=12.6 Hz, $CO_2CH_2Ph^u$), 5.17 (d, 1H, ^2J=12.6 Hz, $CO_2CH_2Ph^d$), 5.58 (d, 1H, $^3J_{3\text{-}OH/3\text{-}H}$=6.9 Hz, 3-OH), 6.04 (d, 1H, $^3J_{2\text{-}OH/2\text{-}H}$=7.3 Hz, 2-OH), 7.35–7.40 (m, 5H, CO_2CH_2*Ph*), 8.56 (s, 1H, Thz-5-H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 52.1 (CO_2CH_3), 63.1 (C-1), 65.9 (CO_2CH_2Ph), 71.2 (C-3), 74.4 (C-2), 127.8, 128.0, 128.4 (each Bn-$CH_{arom.}$), 130.3 (Thz-C-5), 135.9 (Bn-$C_{arom.,\ quart.}$), 145.7 (Thz-C-4), 161.0 (CO_2CH_3), 167.1 (Thz-C-2), 171.8 (C-4); $[\alpha]_D^{21}$ −30.9 (*c* 0.28, $CHCl_3$); ESI-HMRS found 415.0688 (calcd for $C_{16}H_{16}N_4O_6S+Na^+$ 415.0683).

*4.2.16. Methyl 2-[(1R,2S,3S)-3-(benzyloxycarbonyl)-1-azido-2,3-dihydroxypropyl]-thiazole-4-carboxylate (**9**).*

(a) *from epoxide* **23**: A solution of epoxide **23** (19 mg, 54.4 μmol), NaN_3 (18 mg, 272 μmol), and a catalytical amount of CSA in anhydrous DMF (2.0 mL) was stirred at 85 °C for 4 h in a nitrogen atmosphere. After cooling to rt and neutralization with NEt_3 the DMF was removed in vacuo. EtOAc and H_2O were added, the layers were separated, and the aqueous layer was extracted three times with EtOAc. The combined organic layers were dried with brine and over $MgSO_4$, filtered, and

concentrated in vacuo to obtain the crude product as a pale yellow oil. NMR monitoring of the reaction with DMSO-d_6 instead of anhydrous DMF as solvent showed a >90% conversion after 3.5 h under otherwise identical conditions.

(b) *from mesylate* **24**: A solution of mesylate **24** (76 mg, 171 μmol) and NaN_3 (33 mg, 513 μmol) in anhydrous DMF (6.5 mL) was stirred at 85 °C for 2 h in a nitrogen atmosphere. After cooling to rt and removal of the DMF in vacuo, EtOAc and H_2O were added, the layers were separated, and the aqueous layer was extracted three times with EtOAc. The combined organic layers were dried with brine and over $MgSO_4$, filtered, and concentrated in vacuo to obtain the crude product as a pale yellow oil. Column chromatography (EtOAc/toluene=1:1) yielded the azide **9** (120 μmol, 70%) as a pale yellow oil. R_f (EtOAc/toluene=3:2) 0.31; IR (film) 3435, 3115, 2954, 2925, 2854, 2108, 1724, 1482, 1456, 1435, 1324, 1216, 1095, 989, 915, 854, 753, 697 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 3.83 (s, 3H, CO_2CH_3), 3.99–4.03 (m, 1H, 3-H), 4.18–4.22 (m, 1H, 2-H), 5.11 (d, 1H, ^2J=12.6 Hz, $CO_2CH_2Ph^u$), 5.16 (d, 1H, ^2J=12.6 Hz, $CO_2CH_2Ph^d$), 5.17 (d, 1H, $^3J_{1\text{-}H/2\text{-}H}$=4.8 Hz, 1-H), 6.06 (d, 1H, $^3J_{3\text{-}OH/3\text{-}H}$=6.2 Hz, 3-OH), 6.28 (d, 1H, $^3J_{2\text{-}OH/2\text{-}H}$=6.2 Hz, 2-OH), 7.34–7.39 (m, 5H, CO_2CH_2*Ph*), 8.58 (s, 1H, Thz-5-H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 52.7 (CO_2CH_3), 62.6 (C-1), 68.2 (CO_2CH_2Ph), 71.9 (C-3), 75.0 (C-2), 128.8 (Thz-C-5), 128.8, 128.9, 128.9 (each Bn-$CH_{arom.}$), 134.8 (Bn-$C_{arom.,\ quart.}$), 147.1 (Thz-C-4), 161.5 (CO_2CH_3), 168.8 (Thz-C-2), 171.8 (C-4); $[\alpha]_D^{21}$ 10.5 (*c* 0.26, $CHCl_3$); ESI-HMRS found 415.0689 (calcd for $C_{16}H_{16}N_4O_6S+Na^+$ 415.0683).

*4.2.17. (9aR)H-bis-(6S,7S)-(8S,9R)-O-Isopropylidene-5-oxo-octahydro-thiazolo[3,2-a]azepine-(3R)-carboxylic acid methyl ester (**28**).* To a solution of the tetraol **5** (12.0 g, 40.9 mmol) in anhydrous DMF (120 mL) under a nitrogen atmosphere were added DMP (50.3 mL, 409 mmol) and a catalytic amount of *p*-TosOH×H_2O. The solution was stirred at 60 °C for 38 h, cooled to rt, neutralized by addition of NEt_3, and concentrated in vacuo. Column chromatography (EtOAc/toluene/NEt_3 300:50:1) yielded the bis-acetonide **28** as colorless powder (14.19 g, 93%). R_f (EtOAc/toluene=4:1) 0.54; mp 224 °C; IR (KBr) 2985, 2939, 2888, 1752, 1647, 1372, 1302, 1213, 1165, 1076, 998, 851 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 1.34 (s, 3H, isopr-CH_3), 1.38 (s, 6H, 2×isopr-CH_3), 1.44 (s, 3H, isopr-CH_3), 3.09 (dd, 1H, $^2J_{2-H^u/2-H^d}$=12.3 Hz, $^3J_{2-H^u/3-H}$=1.8 Hz, 2-H^u), 3.26 (dd, 1H, $^2J_{2-H^d/2-H^u}$=12.3 Hz, $^3J_{2-H^d/3-H}$=7.3 Hz, 2-H^d), 3.65 (s, 3H, CO_2CH_3), 4.29 (dd, 1H, $^3J_{9\text{-}H/9a\text{-}H}$=7.1 Hz, $^3J_{9\text{-}H/8\text{-}H}$=9.4 Hz, 9-H), 4.36 (dd, 1H, $^3J_{7\text{-}H/6\text{-}H}$=5.9 Hz, $^3J_{7\text{-}H/8\text{-}H}$=8.2 Hz, 7-H), 4.52 (dd, 1H, $^3J_{8\text{-}H/7\text{-}H}$=8.2 Hz, $^3J_{8\text{-}H/9\text{-}H}$=9.4 Hz, 8-H), 4.78 (dd, 1H, $^3J_{3-H/2-H^u}$=1.8 Hz, $^3J_{3-H/2-H^d}$=7.3 Hz, 3-H), 4.84 (d, 1H, $^3J_{6\text{-}H/7\text{-}H}$=5.9 Hz, 6-H), 5.46 (d, 1H, $^3J_{9a\text{-}H/9\text{-}H}$=7.1 Hz, 9a-H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 26.2, 26.2, 26.9, 27.0 (each isopr-CH_3), 30.6 (C-2), 52.2 (CO_2CH_3), 62.0 (C-9a), 63.5 (C-3), 73.5 (C-9), 75.1 (C-6), 75.3 (C-8), 76.9 (C-7), 111.8, 111.9 (each isopr-$C_{quart.}$), 166.4, 170.1 (CO_2CH_3, C-5); $[\alpha]_D^{23}$ 57.1 (*c* 1.02, $CHCl_3$); ESI-HMRS found 396.1089 (calcd for $C_{16}H_{23}NO_7S+Na^+$ 396.1087).

*4.2.18. (9aR)H-(6S,7S)-Dihydroxy-(8S,9R)-O-isopropylidene-5-oxo-octahydro-thiazolo[3,2-a]azepine-(3R)-carboxylic acid methyl ester (**29**).* To a solution of bis-acetonide **28** (14.2 g, 38.0 mmol) in MeOH (150 mL) was added a catalytic amount of *p*-TosOH×H_2O and the solution was stirred at rt for 17 h during which a fraction of the product crystallized from the reaction mixture. This was isolated by filtration, washed with cold MeOH, and dried in vacuo. The filtrate was neutralized by addition of NEt_3 and adsorbed on Celite by removal of the solvent in vacuo. Column chromatography (CH_2Cl_2/MeOH=10:1) yielded the second fraction of product, resulting in an overall yield of monoacetonide **29** (8.54 g, 67%) as a colorless solid. R_f (CH_2Cl_2/MeOH=10:1) 0.58; mp 207 °C; IR (KBr) 3503, 3434, 3000, 2936, 2897, 1754, 1650, 1434, 1204, 1170, 1143, 1081, 1068, 1034, 1007, 829 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 1.32, 1.38 (each s, 3H, isopr-CH_3), 3.26 (dd, 1H, $^2J_{2-H^u/2-H^d}$=10.7 Hz, $^3J_{2-H^u/3-H}$=8.8 Hz, 2-H^u), 3.26 (dd, 1H, $^2J_{2-H^d/2-H^u}$=10.7 Hz, $^3J_{2-H^d/3-H}$=7.6 Hz, 2-H^d), 3.33–3.39 (m, 1H, 9-H), 3.55 (ddd, 1H, $^3J_{8\text{-}H/8\text{-}OH}$=5.4 Hz, $^3J_{8\text{-}H/9\text{-}H}$=7.3 Hz, $^3J_{8\text{-}H/7\text{-}H}$=9.9 Hz, 8-H), 3.63 (s, 3H, CO_2CH_3), 4.24 (dd, 1H, $^3J_{7\text{-}H/6\text{-}H}$=8.0 Hz, $^3J_{7\text{-}H/8\text{-}H}$=9.8 Hz, 7-H), 4.50 (dd, 1H, $^3J_{3-H/2-H^d}$=7.6 Hz, $^3J_{3-H/2-H^u}$=8.8 Hz, 3-H), 5.01 (d, 1H, $^3J_{6\text{-}H/7\text{-}H}$=8.0 Hz, 6-H), 5.24 (d, 1H, $^3J_{9a\text{-}H/9\text{-}H}$=3.2 Hz, 9a-H), 5.32(pt, 2H, 8-OH, 9-OH); ^{13}C NMR (75 MHz, DMSO-d_6): δ 24.7, 26.9 (each isopr-CH_3), 32.4 (C-2), 52.0 (CO_2CH_3), 62.3 (C-3), 62.4 (C-9a), 74.6 (C-8), 74.8 (C-9), 75.0 (C-6), 76.8 (C-7), 108.6, (isopr-$C_{quart.}$), 165.8, 169.6 (CO_2CH_3, C-5); $[\alpha]_D^{22}$ −95.4 (*c* 0.95, DMSO); ESI-HMRS found 356.0767 (calcd for $C_{13}H_{19}NO_7S+Na^+$ 356.0774).

*4.2.19. (9aR)H-(6S,7R)-O-Isopropylidene (8S)-trifuoromethanesulfonyl-(9R)-hydroxy-5-oxo-octahydro-thiazolo[3,2-a]azepine-(3R)-carboxylic acid methyl ester (**30**).* A solution of the diol **29** (8.24 g, 24.7 mmol) in anhydrous CH_2Cl_2/DMF=3:1 (160 mL) was cooled to 0 °C under a nitrogen atmosphere. Tf_2O (4.98 mL, 32.1 mmol) was added dropwise over 15 min and the solution was stirred at 0 °C for 1 h and at rt for 3.5 h. The reaction was quenched with 170 mL of ice, the layers were separated and the aqueous layer was extracted twice with CH_2Cl_2. The combined organic layers were dried with brine and over $MgSO_4$, filtered, and concentrated in vacuo. A fraction of the product was isolated by filtration after addition of EtOAc/toluene=2:1 and the filtrate was subjected to column chromatography (EtOAc/toluene=2:1), yielding the triflate **30** as yellow solid (10.9 g, 94%). R_f (EtOAc/toluene 10:1) 0.59; mp 85 °C; IR (neat) 3328, 2992, 2950, 1747, 1661, 1436, 1411, 1397, 1376, 1352, 1329, 1246, 1199, 1141, 1069, 954, 888 cm^{-1}; ^1H NMR (600 MHz, DMSO-d_6): δ 1.35, 1.36 (each s, 3H, isopr-CH_3), 3.30 (dd, 1H, $^2J_{2-H^u/2-H^d}$=10.9 Hz, $^3J_{2-H^u/3-H}$=8.9 Hz, 2-H^u), 3.37 (dd, 1H, $^2J_{2-H^d/2-H^u}$=10.9 Hz, $^3J_{2-H^d/3-H}$=7.3 Hz, 2-H^d), 3.63 (s, 3H, CO_2CH_3), 3.91 (dd, 1H, $^3J_{9\text{-}H/9a\text{-}H}$=3.2 Hz, $^3J_{9\text{-}H/8\text{-}H}$=7.8 Hz, 9-H), 4.64 (dd, 1H, $^3J_{3-H/2-H^d}$=7.3 Hz, $^3J_{3-H/2-H^u}$=8.9 Hz, 3-H), 4.74 (dd, 1H, $^3J_{7\text{-}H/6\text{-}H}$=8.2 Hz, $^3J_{7\text{-}H/8\text{-}H}$=10.5 Hz, 7-H), 4.94 (dd, 1H, $^3J_{8\text{-}H/9\text{-}H}$=7.8 Hz, $^3J_{8\text{-}H/7\text{-}H}$=10.5 Hz, 8-H), 5.28 (d, 1H, $^3J_{6\text{-}H/7\text{-}H}$=8.2 Hz, 6-H), 5.30 (d, 1H, $^3J_{9a\text{-}H/9\text{-}H}$=3.2 Hz, 9a-H), 6.33 (br s, 1H, 9-OH); ^{13}C NMR (125 MHz, DMSO-d_6): δ 25.0, 26.1 (each isopr-CH_3), 32.1 (C-2), 52.1 (CO_2CH_3), 61.9 (C-9a), 62.2 (C-3), 71.2 (C-9), 72.7 (C-7), 75.3 (C-6), 92.2 (C-8), 110.2 (isopr-$C_{quart.}$), 164.4, 169.2 (CO_2CH_3, C-5); $[\alpha]_D^{20}$ −78.5 (*c* 1.00, $CHCl_3$); ESI-HMRS found 488.0269 (calcd for $C_{14}H_{18}F_3NO_9S+Na^+$ 488.0267).

*4.2.20. (9aR)H-(6S,7R)-O-Isopropylidene-(8R,9R)-epoxy-(9R)-5-oxo-octahydro-thiazolo[3,2-a]azepine-(3R)-carboxylic acid methyl ester (**31**).* Triflate **30** (10.8 g, 23.2 mmol) was dissolved in DMF (300 mL), NEt_3 (21 mL) was added and the mixture was stirred at 60 °C for 27 h. After cooling to rt and concentrated in vacuo, EtOAc/toluene=1:1 (50 mL) were added, the resulting suspension was stored in the fridge overnight, and filtered. The precipitate was washed with cold toluene and dried in vacuo to yield the epoxide **31** (5.95 g, 81%) as colorless powder. R_f (EtOAc/toluene=7:1) 0.31; mp 189 °C; IR (neat) 2992, 2976, 2949, 2926, 2866, 1766, 1655, 1430, 1371, 1334, 1281, 1242, 1225, 1199, 1170, 1058, 1016, 952, 906, 888, 863, 842, 809, 798, 784, 724, 713 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ 1.33, 1.42 (each s, 3H, isopr-CH_3), 3.11 (dd, 1H, $^2J_{2-H^u/2-H^d}$=11.8 Hz, $^3J_{2-H^u/3-H}$=3.5 Hz, 2-H^u), 3.22 (dd, 1H, $^2J_{2-H^d/2-H^u}$=11.8 Hz, $^3J_{2-H^d/3-H}$=6.7 Hz, 2-H^d), 3.33 (d, 1H, $^3J_{9\text{-}H/8\text{-}H}$=4.4 Hz, 9-H), 3.42 (dd, 1H, $^3J_{8\text{-}H/7\text{-}H}$=3.0 Hz, $^3J_{8\text{-}H/9\text{-}H}$=4.4 Hz, 8-H), 3.62 (s, 3H, CO_2CH_3), 4.56 (dd, 1H, $^3J_{7\text{-}H/8\text{-}H}$=3.0 Hz, $^3J_{7\text{-}H/6\text{-}H}$=6.5 Hz, 7-H), 4.74 (dd, 1H, $^3J_{3-H/2-H^u}$=3.5 Hz, $^3J_{3-H/2-H^d}$=6.7 Hz, 3-H), 4.68 (d, 1H, $^3J_{6\text{-}H/7\text{-}H}$=6.5 Hz, 6-H), 4.74 (dd, 1H, $^3J_{3-H/2-H^u}$=3.5 Hz, $^3J_{3-H/2-H^d}$=6.7 Hz, 3-H), 5.53 (s, 1H, 9a-H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 25.8, 26.9 (each isopr-CH_3),

31.4 (C-2), 51.5 (C-8), 51.8 (CO_2CH_3), 54.7 (C-9), 56.2 (C-9a), 63.3 (C-3), 73.6 (C-6), 73.7 (C-7), 108.3 (isopr-$C_{quart.}$), 166.8, 169.1 (CO_2CH_3, C-5); $[\alpha]_D^{23}$ −70.7 (*c* 1.00, $CHCl_3$); ESI-HMRS found 338.0671 (calcd for $C_{13}H_{17}NO_6S+Na^+$ 338.0669).

*4.2.21. (2S,4R)-Methyl 2-[(S)-azido((3aS,4S,6aS)-2,2-dimethyl-6-oxotetrahydrofuro[3,4-d][1,3]dioxol-4-yl)methyl]-thiazolidine-4-carboxylate (**7a**).*

(a) *from epoxide* **31**: Epoxide **31** (2.66 g, 8.44 mmol) and NaN_3 (950 mg, 14.3 mmol) were dissolved in DMF/AcOH=130:1 (38 mL). The mixture was stirred at 45 °C for 23 h, then at 50 °C for 4 h, and at 55 °C for 47 h. After cooling to rt, the solution was neutralized with NEt_3 and concentrated in vacuo. EtOAc (200 mL) and H_2O (50 mL) were added and the layers were separated. The aqueous layer was extracted with EtOAc and the combined organic layers were dried with brine and over $MgSO_4$, filtered, and concentrated in vacuo. Column chromatography (EtOAc/toluene=1:1) yielded the thiazolidine lactone **7a** as a colorless solid (1.17 g, 39%). After complete elution of **7a** the other species were obtained by elution with pure EtOAc, which yielded the reaction intermediate **32** as yellow foam (1.45 g, 33%).[52] This was recycled to yield further thiazolidine lactone **7a** as described in the following.

(b) *from intermediate* **32**: The thiazolidine lactam **32** (1.76 g, 4.91 mmol) was dissolved in DMF/AcOH=130:1 (38 mL) and the mixture was stirred at 50 °C for 72 h. The subsequent workup and purification were performed as described for method (a), yielding the thiazolidine lactone **7a** as a colorless solid (587 mg, 33%). R_f (EtOAc/toluene=7:1) 0.83; mp 175 °C; IR (neat) 3323, 3296, 2115, 1786, 1735, 1381, 1349, 1294, 1269, 1216, 1176, 1145, 1017, 993, 967, 945, 923, 864, 785, 764 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 1.38, 1.45 (each s, 3H, isopr-CH_3), 2.94 (dd, 1H, $^2J_{Thz-5-H^u/Thz-5-H^d}$=10.6 Hz, $^3J_{Thz-5-H^u/Thz-4-H}$=8.5 Hz, Thz-5-H^u), 3.09 (br s, 1H, NH), 3.34 (dd, 1H, $^2J_{Thz-5-H^d/Thz-5-H^u}$=10.6 Hz, $^3J_{Thz-5-H^d/Thz-4-H}$=6.4 Hz, Thz-5-H^d), 3.48 (dd, 1H, $^3J_{CN_3-H/2-H}$=1.7 Hz, $^3J_{CN_3-H/Thz-2-H}$=9.6 Hz, CN_3-H), 3.81 (s, 3H, CO_2CH_3), 3.95 (dd, 1H, $^3J_{Thz-4-H/Thz-5-H^d}$=6.4 Hz, $^3J_{Thz-4-H/Thz-5-H^u}$=8.5 Hz, Thz-4-H), 4.66 (d, 1H, $^3J_{3-H/4-H}$=5.8 Hz, 3-H), 4.77 (d, 1H, $^3J_{2-H/CN_3-H}$=1.7 Hz, 2-H), 4.86 (d, 1H, $^3J_{4-H/3-H}$=5.8 Hz, 4-H), 4.98 (d, 1H, $^3J_{Thz-2-H/CN_3-H}$=9.6 Hz, Thz-2-H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 25.7, 26.8 (each isopr-CH_3), 38.3 (Thz-C-5), 53.0 (CO_2CH_3), 63.6 (Thz-C-4), 66.3 (C-N_3), 69.6 (Thz-C-2), 75.0 (C-4), 79.0 (C-3), 81.1 (C-2), 113.8 (isopr-$C_{quart.}$), 171.1 (CO_2CH_3), 173.5 (C-5); $[\alpha]_D^{22}$ −78.5 (*c* 1.08, $CHCl_3$); ESI-HMRS found 381.0840 (calcd for $C_{13}H_{18}N_4O_6S+Na^+$ 381.0839). Suitable crystals for X-ray analysis were grown from a EtOAc/petrol ether solution.[44]

*4.2.22. (9aR)H-(6S,7R)-O-Isopropylidene-(8S)-hydroxy-(9S)-azido-5-oxo-octahydro-thiazolo[3,2-a]azepine-(3R)-carboxylic acid methyl ester (**32**).* The thiazolidine lactam **32** occurs as intermediate in the formation of the thiazolidine lactone **7a** as described in Section 4.2.21. When the flash chromatographic purification was carried out with EtOAc/toluene=2:1 to 5:1 to 9:1 the pure compound was isolated as colorless foam. R_f (EtOAc/toluene=7:1) 0.41; IR (neat) 3431, 2961, 2108, 1732, 1669, 1410, 1376, 1356, 1258, 1206, 1169, 1095, 1072, 1020, 973, 932, 911, 876, 855, 797, 734 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 1.30, 1.41 (each s, 3H, isopr-CH_3), 3.21 (dd, 1H, $^2J_{2-H^u/2-H^d}$=11.7 Hz, $^3J_{2-H^u/3-H}$=5.1 Hz, 2-H^u), 3.37 (dd, 1H, $^2J_{2-H^d/2-H^u}$=11.7 Hz, $^3J_{2-H^d/3-H}$=7.0 Hz, 2-H^d), 3.67 (s, 3H, CO_2CH_3), 4.00 (dd, 1H, $^3J_{9-H/8-H}$=1.3 Hz, $^3J_{9-H/9a-H}$=10.4 Hz, 9-H), 4.07 (m, 1H, 8-H), 4.47 (dd, 1H, $^3J_{7-H/8-H}$=1.7 Hz, $^3J_{7-H/6-H}$=8.8 Hz, 7-H), 4.86 (dd, 1H, $^3J_{3-H/2-H^u}$=5.1 Hz, $^3J_{3-H/2-H^d}$=7.0 Hz, 3-H), 4.96 (d, 1H, $^3J_{6-H/7-H}$=8.8 Hz, 6-H), 4.99 (d, 1H, $^3J_{9a-H/9-H}$=10.4 Hz, 9a-H), 5.05 (d, $^3J_{8-O-H/8-H}$=4.9 Hz, 8-OH); ^{13}C NMR (150 MHz, DMSO-d_6): δ 23.6, 25.6 (each isopr-CH_3), 31.0 (C-2), 52.4 (CO_2CH_3), 61.8 (C-9a), 62.0 (C-3), 67.3 (C-9), 71.3 (C-8), 74.2 (C-6), 74.6 (C-7), 107.9 (isopr-$C_{quart.}$), 166.6 (C-5), 170.6 (CO_2CH_3); $[\alpha]_D^{24}$ 3.3 (*c* 1.16, $CHCl_3$); ESI-HMRS found 381.0842 (calcd for $C_{13}H_{18}N_4O_6S+Na^+$ 381.0839).

*4.2.23. Methyl 2-[(S)-azido((3aS,4S,6aS)-2,2-dimethyl-6-oxotetrahydrofuro[3,4-d][1,3]dioxol-4-yl)methyl]-thiazole-4-carboxylate (**34**).* To a solution of thiazolidine **7a** (661 mg, 1.84 mmol) in acetonitrile (40 mL) was added MnO_2 (4.81 mg, 55.3 mmol), the suspension was stirred vigorously at 70 °C for 20 h, filtered over Celite, and concentrated in vacuo. The residue was dissolved in EtOAc/toluene=2:1, adsorbed on Celite, and subjected to column chromatography (EtOAc/toluene=5:1 to 3:1) to yield the thiazole **34** (203 mg, 31%) as pale yellow solid. In addition, starting material **7a** was also isolated (179 mg, 27%). R_f (toluene/EtOAc=5:1) 0.16; mp 142 °C; IR (KBr) 3098, 2990, 2114, 1790, 1717, 1474, 1377, 1346, 1276, 1244, 1223, 1210, 1166, 1103, 1084, 1065, 1032, 991, 980, 964, 947, 928, 913, 864, 780 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 1.41, 1.46 (each s, 3H, isopr-CH_3), 3.98 (s, 3H, CO_2CH_3), 4.87–4.88 (m, 2H, 2-H, 3-H), 4.96 (d, 1H, $^3J_{4-H/3-H}$=5.8 Hz, 4-H), 5.35 (d, 1H, $^3J_{CN_3-H/2-H}$=2.6 Hz, CN_3-H), 8.30 (s, 1H, Thz-5-H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 25.7, 26.7 (each isopr-CH_3), 52.8 (CO_2CH_3), 63.5 (C-N_3), 75.2 (C-4), 78.8 (C-3), 82.2 (C-2), 109.9 (isopr-$C_{quart.}$), 129.9 (Thz-C-5), 147.1 (Thz-C-4), 161.4 (CO_2CH_3), 164.9 (Thz-C-2), 173.1 (C-5); $[\alpha]_D^{20}$ −103.8 (*c* 0.99, $CHCl_3$); ESI-HMRS found 377.0527 (calcd for $C_{13}H_{14}N_4O_6S+Na^+$ 377.0526).

*4.2.24. Methyl 2-[((S)-azido(2S,3R,4S)-3,4-dihydroxy-5-oxo-tetrahydrofuran-2-yl)methyl]-thiazole-4-carboxylate (**35**).* A solution of the acetonide **34** (110 mg, 0.31 mmol) in 60% HCOOH in H_2O (11 mL) was stirred at 65 °C for 40 min. Upon completion of the reaction the mixture was cooled to rt and the solvent was removed in vacuo. Column chromatography (EtOAc/MeOH=5:1) yielded the diol **35** (67 mg, 69%) as colorless solid. R_f (EtOAc/MeOH=5:1) 0.23; IR (neat) 3365, 3117, 2956, 2111, 1781, 1716, 1480, 1435, 1323, 1221, 1132, 1061, 979, 956, 922, 905, 863, 843, 757 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 3.84 (s, 3H, CO_2CH_3), 4.29 (dd, 1H, $^3J_{3-H/2-H}$=1.2 Hz, $^3J_{3-H/4-H}$=5.5 Hz, 3-H), 4.57 (d, 1H, $^3J_{4-H/3-H}$=5.5 Hz, 4-H), 4.60 (dd, 1H, $^3J_{2-H/3-H}$=1.2 Hz, $^3J_{2-H/CN_3-H}$=6.2 Hz, 2-H), 5.75 (d, 1H, $^3J_{CN_3-H/2-H}$=6.2 Hz, CN_3-H), 8.63 (s, 1H, Thz-5-H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 52.6 (CO_2CH_3), 61.9 (C-N_3), 68.4 (C-4), 69.1 (C-3), 85.5 (C-2), 131.0 (Thz-C-5), 146.2 (Thz-C-4), 161.5 (CO_2CH_3), 166.4 (Thz-C-2), 175.7 (C-5); $[\alpha]_D^{21}$ −98.8 (*c* 0.60, $CHCl_3$); ESI-HMRS found 337.0207 (calcd for $C_{10}H_{10}N_4O_6S+Na^+$ 337.0213).

*4.2.25. Methyl 2-[(2S,3S,4S,5S)-3-hydroxy-4,5-O-isopropylidene-6-oxo-piperidin-2-yl]-thiazole-4-carboxylate (**36**).* Azide **34** (203 mg, 0.57 mmol) was dissolved in EtOAc/MeOH=2:1 (15 mL), Pd/C (400 mg; 5%, wet, Degussa) was added and the mixture was stirred at rt for 45 h in a H_2 atmosphere at 1 bar. During this time period the H_2 atmosphere was renewed twice. After filtration over a Celite column and concentration in vacuo the lactam **36** was obtained as a pale yellow solid (165 mg, 88%) and used without further purification. R_f ($CHCl_3$/MeOH=9:1) 0.36; ^1H NMR (600 MHz, DMSO-d_6): δ 1.44 (s, 3H, isopr-CH_3^{proR}), 1.51 (s, 3H, isopr-CH_3^{proS}), 3.95 (CO_2CH_3), 4.36 (m, 1H, 3-H), 4.64–4.65 (m, 2H, 4-H, 5-H), 5.03 (m, 1H, 2-H), 6.39 (br s, 1H, CONH), 8.24 (s, 1H, Thz-5-H); ^{13}C NMR (150 MHz, DMSO-d_6): δ 24.4 (isopr-CH_3^{proR}), 26.0 (isopr-CH_3^{proS}), 52.7 (CO_2CH_3), 55.5 (C-2), 66.3 (C-3), 72.2 (C-5), 74.6 (C-4), 111.4 (isopr-$C_{quart.}$), 129.3 (Thz-C-5), 146.4 (Thz-C-4), 161.5 (CO_2CH_3), 167.4 (Thz-C-2), 168.8 (C-6); ESI-HMRS found 351.0621 (calcd for $C_{13}H_{16}N_2O_6S+Na^+$ 351.0621).

*4.2.26. Methyl 2-[(1S,2S,3S,4S)-4-(methoxycarbonyl)-1-amino-2,3,4-trihydroxybutyl]-thiazole-4-carboxylate (**12**).* To a solution of the lactam **36** (115 mg, 0.35 mmol) in MeOH (15 mL) was added

a catalytical amount of *p*-TosOH×H_2O and the mixture was stirred at 60 °C for 7 h. After cooling to rt the mixture was neutralized with NEt_3 upon which amine **12** precipitated, and filtration and drying in vacuo yielded the first product fraction (14.2 mg, 13%) as colorless powder. The residue obtained upon concentration of the filtrate in vacuo consisted of the starting material **36** and the triol intermediate **37** (R_f (EtOAc/MeOH=5:1) 0.19) in a 60:40 ratio. This was dissolved in MeOH (4 mL), a catalytical amount of *p*-TosOH×H_2O was added, and the mixture was stirred at 50 °C for 18 h. After cooling to rt and neutralization with NEt_3 a second product fraction was isolated upon filtration (10.0 mg, 8.9%) as colorless powder. This resulted in an overall 22% yield of amine **12** (24.2 mg). R_f (EtOAc/MeOH=5:1) 0.09; mp 168 °C; IR (neat) 3419, 3341, 3275, 3118, 1741, 1719, 1713, 1495, 1468, 1433, 1396, 1346, 1318, 1265, 1240, 1205, 1166, 1115, 1084, 1071, 1043, 995, 973, 946, 908, 871, 847, 827, 773 cm^{-1}; ^1H NMR (600 MHz, DMSO-d_6): δ 2.28 (br s, 2H, NH_2), 3.61 (s, 3H, 5-CO_2CH_3), 3.82 (m, 4H, 4-H, Thz-CO_2CH_3), 4.21 (ddd, 1H, ^3J=1.6 Hz, $^3J_{2\text{-H}/2\text{-OH}}$=6.9 Hz, ^3J=8.9 Hz, 2-H), 4.27–4.29 (m, 2H, 1-H, 4-H), 4.82 (d, 1H, $^3J_{2\text{-OH}/2\text{-H}}$=6.9 Hz, 2-OH), 5.26 (d, 1H, $^3J_{3\text{-OH}/3\text{-H}}$=6.1 Hz, 3-OH), 5.41 (d, 1H, $^3J_{4\text{-OH}/4\text{-H}}$=6.0 Hz, 4-OH), 8.35 (s, 1H, Thz-5-H); ^{13}C NMR (150 MHz, DMSO-d_6): δ 51.1 (6-CO_2CH_3), 51.7 (Thz-CO_2CH_3), 54.0 (C-1), 72.0 (C-4), 72.5 (C-2), 73.3 (C-3), 128.8 (Thz-C-5), 145.6 (Thz-C-4), 161.6 (Thz-CO_2CH_3), 172.6 (C-5), 180.2 (Thz-C-2); $[\alpha]_D^{30}$ −42.3 (*c* 0.37, DMSO); ESI-HMRS found 343.0570 (calcd for $C_{11}H_{16}N_2O_7S$+Na^+ 343.0570).

*4.2.27. Methyl 2-[((R)-(2S,3S,4S)-5-oxo-3,4-bis(triethylsilyloxy)-tetrahydrofuran-2-yl)(triethylsilyloxy)methyl]-thiazole-4-carboxylate (**39**).* To a solution of thiazolidine **6** (6.64 g, 22.6 mmol) and imidazole (5.55 g, 81.5 mmol) in 14 mL of DMF TESCl (13.7 mL, 81.5 mmol) was slowly added. The solution was stirred at rt for 3 h, diluted with CH_2Cl_2 (500 mL) and 5% aq $NaHCO_3$ (40 mL), the layers were separated, and the aqueous layer was extracted once with CH_2Cl_2. The combined organic layers were dried with brine and over $MgSO_4$, filtered, and concentrated in vacuo. The resulting pale yellow oil (crude thiazolidine **38**, R_f (toluene/EtOAc=7:1) 0.47) was dissolved in toluene (200 mL), MnO_2 (39.4 g, 453 mmol) was added, and the suspension was vigorously stirred for 28 h at 70 °C. Upon complete consumption of the starting material the solution was cooled to rt, $BrCCl_3$ (6.69 mL, 67.8 mmol) and DBU (10.1 mL, 67.8 mmol) were added and the suspension was stirred at rt until no thiazoline intermediate was visible any more by TLC (R_f (toluene/EtOAc=7:1) 0.55). After filtration over Celite, the suspension was extracted once with satd $NaHCO_3$ and once with satd NH_4Cl, dried with brine and over $MgSO_4$, and concentrated in vacuo. Purification by column chromatography (CH_2Cl_2/pentane=4:1) yielded the thiazole **39** (6.91 g, 48%) as a colorless oil. R_f (toluene/EtOAc=7:1) 0.61; ^1H NMR (500 MHz, $CDCl_3$): δ 0.73–0.78 (m, 18H, 9×Si$CH_2$$CH_3$), 0.90 (t, 9H, *J*=8.0 Hz, 3×SiCH$_2$$CH_3$), 0.97–1.01 (m, 18H, 6× SiCH$_2$$CH_3$), 3.91 (s, 3H, CO_2CH_3), 4.28 (dd, 1H, $^3J_{2\text{-H}/3\text{-H}}$=2.2 Hz, $^3J_{2\text{-H}/\text{Cx-H}}$=9.1 Hz, 2-H), 4.36 (d, 1H, $^3J_{4\text{-H}/3\text{-H}}$=3.8 Hz, 4-H), 4.76 (dd, 1H, $^3J_{3\text{-H}/2\text{-H}}$=2.2 Hz, $^3J_{3\text{-H}/4\text{-H}}$=3.8 Hz, 3-H), 5.42 (d, 1H,$^3J_{\text{Cx-H}/2\text{-H}}$=9.1 Hz, CX-H), 8.18 (s, 1H, Thz-5-H); ^{13}C NMR (125 MHz, $CDCl_3$): δ=4.9, 5.1, 5.2 (each Si$CH_2$$CH_3$), 6.8, 6.8, 6.9 (each Si$CH_2$$CH_3$), 52.3 ($CO_2CH_3$), 70.5 (C-X), 72.8 (C-3), 73.5 (C-4), 81.7 (C-1), 128.4 (Thz-C-5), 147.3 (Thz-C-4), 162.0 (CO_2CH_3), 172.5 (Thz-C-2), 174.2 (C-5); IR (film) 2954, 2911, 2877, 1803, 1727, 1458, 1414, 1239, 1207, 1135, 1004, 987, 947, 892, 855, 830, 787, 725 cm^{-1}; $[\alpha]_D^{20}$ −8.9 (*c* 2.40, $CHCl_3$); $[\alpha]_D^{20}$ −8.9 (*c* 2.4, $CHCl_3$); ESI-HMRS found 654.2744 (calcd for $C_{28}H_{53}NO_7SSi_3$+Na^+ 654.2743).

*4.2.28. Methyl 2-[(R)-((2S,3S,4S)-3,4-dihydroxy-5-oxo-tetrahydrofuran-2-yl)(hydroxy)methyl]-thiazole-4-carboxylate (**13**).* To a solution of thiazole **13** (2.08 g, 3.29 mmol) in acetonitrile (35 mL) at 0 °C, H_2SiF_6 (1.66 M in H_2O; 3.96 mL) was added and the solution was stirred at 0 °C for 2.5 h and then at rt for 2 h. Solid $NaHCO_3$ was added in small portions until the solution reached pH 6, and solid $MgSO_4$ (20 g) was subsequently added. The mixture was filtered over Celite and the residue was washed with acetonitrile (100 mL). The filtrate was concentrated in vacuo to yield the thiazole triol **13** (933 mg, 98%) as a colorless solid. R_f (EtOAc/MeOH=5:1) 0.77; mp 105 °C; IR (KBr) 3380, 3097, 1795, 1780, 1718, 1683, 1477, 1417, 1362, 1254, 1220, 1164, 1136, 1114, 1089, 1001, 992, 955, 858, 780, 769, 729 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 3.83 (s, 3H, CO_2CH_3), 4.29–4.32 (m, 1H, 3-H), 4.55 (dd, 1H, $^3J_{4\text{-H}/3\text{-H}}$=4.6 Hz, $^3J_{4\text{-H}/4\text{-OH}}$=7.4 Hz, 4-H), 4.61 (dd, 1H, $^3J_{2\text{-H}/3\text{-H}}$=2.9 Hz, $^3J_{2\text{-H}/3\text{-H}}$=7.9 Hz, 2-H), 5.15 (dd, 1H, $^3J_{\text{Cx-H}/\text{Cx-OH}}$=5.7 Hz, $^3J_{\text{Cx-H}/2\text{-H}}$=7.9 Hz, CX-H), 5.52 (d, 1H, $^3J_{3\text{-OH}/3\text{-H}}$=3.8 Hz, 3-OH), 5.91 (d, 1H, $^3J_{4\text{-OH}/4\text{-H}}$=7.4 Hz, 4-OH), 6.57 (d, 1H, $^3J_{\text{Cx-OH}/\text{Cx-H}}$=5.7 Hz, CX-OH), 8.57 (s, 1H, Thz-5-H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 52.0 (CO_2CH_3), 68.5 (C-X), 69.7 (C-3), 70.4 (C-4), 80.9 (C-2), 129.7 (Thz-C-5), 145.5 (Thz-C-4), 161.2 (CO_2CH_3), 172.0 (Thz-C-2), 175.8 (C-5); $[\alpha]_D^{24}$ 73.3 (*c* 0.84, DMSO); ESI-HMRS found 312.0146 (calcd for $C_{10}H_{11}NO_7S$+Na^+ 312.0148). Suitable crystals for X-ray analysis were grown from a MeOH solution.[44]

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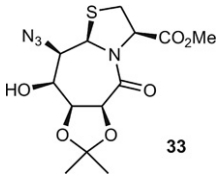

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