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Concise Total Synthesis of the Thiazolyl Peptide Antibiotic GE2270 A

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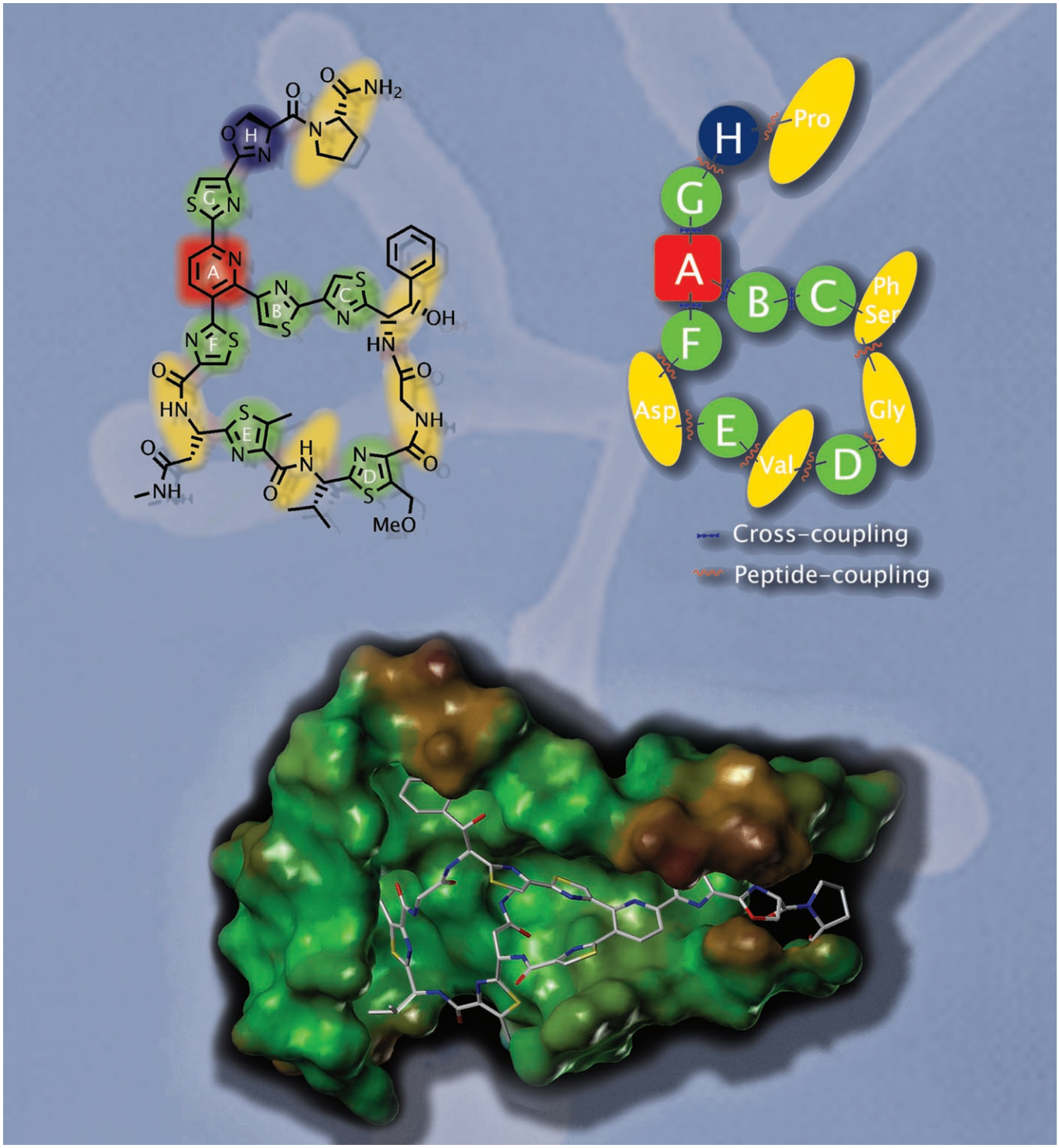
Dedicated to Professor Wolfgang A. Herrmann on the occasion of his 60th birthday



Abstract: The potent antibiotic thiazolylpeptide GE2270 A was synthesized starting from *N-tert*-butyloxycarbonyl protected valine in a longest linear sequence of 20 steps and with an overall yield of 4.8%. Key strategy was the assembly of the 2,3,6-trisubstituted pyridine core by consecutive cross-coupling reactions starting from 2,6-dibromo-3-iodopyridine. The complete Southern fragment was installed by Negishi cross-coupling of 3-zincated 2,6-dibromopyridine at the terminal 2-iodothiazole of a trithiazole (87%). The substituent at C-6 representing the Northern part of the molecule was introduced in form of the truncated *tert*-butyl 2-bromothiazole-4-carboxylate after metalation to a zinc reagent by another Negishi cross-coupling (48%). Decisive step of the whole sequence was the macrocyclization to a 29-membered macrolactam, which was conducted as an intramolecular Stille cross-coupling occurring at C-2 of the pyridine core and providing the desired product in 75% yield. The required stannane was obtained by amide bond formation (87%) between a complex dithiazole fragment representing the Eastern part of GE2270 A and a 3,6-disubstituted 2-bromopyridine. Final steps included attachment of a serine-proline amide dipeptide to the Northern part of the molecule (65%), formation of the oxazoline ring and silyl ether deprotection (55% overall).

Keywords: antibiotics · cross-coupling · macrocycles · natural products · total synthesis

Introduction

The increasing number of resistances observed in bacterial infections poses a significant clinical problem and becomes a growing threat for many patients suffering from these diseases. The search for antibiotics with new modes of action is of utmost importance. Unless new antibiotic drugs are found in the near future, mankind may soon be disarmed in its fight against infectious diseases.[1] In this context, the bacterial elongation factor EF-Tu[2] has been established as a validated drug target representing an ubiquitous enzyme essential for bacterial protein biosynthesis. It is significantly different from the human elongation factor eEF-1α guaranteeing desirable target specificity. Currently, four structurally different compound classes are known to inhibit EF-Tu efficiently, the prototypical examples being kirromycin, enacycloxin IIa, pulvomycin, and GE2270 A.[3] It has been shown that the binding sites of pulvomycin and GE2270 A are identical, whereas kirromycin and enacycloxin IIa possess different modes of action. GE2270 A and pulvomycin hinder the formation of the ternary complex between EF-Tu, guanosin triphosphate (GTP) and aminoacyl tRNA by binding to the domain 2 of the enzyme.[4]

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The GE2270 antibiotic GE2270 A is the longest known and best studied member of this compound class. It was isolated by Selva et al. from *Planobispora rosea* ATCC 53773 and its structure was reported in 1991.[5] Later several related compounds were reported, which were found in the same microorganism and which were named GE2270 factors E, D1, D2, C1, C2a, C2b, B1, B2, and T.[6] They differ from GE2270 in the substitution or in the binding pattern (single vs double bond) at the marked positions (-----, Figure 1). In addition there are other structurally related thiopeptides,[7] which also bear a central triply substituted pyridine fragment, for example, the amythiamicins,[8] thiostreptone,[9] or micrococcin P.[10]

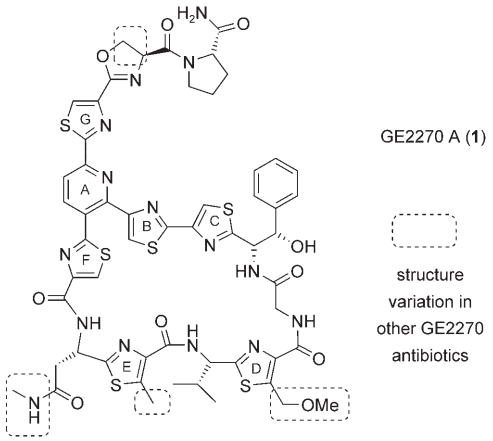
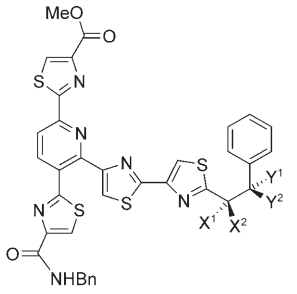


Figure 1. Structure of GE2270 A (**1**) and locations (-----) of structure variation in other GE2270 thiazolyl peptides.

The constitution and configuration of GE2270 A was elucidated by a combination of analytical and synthetic methods. In the initial assignment the thiazole units D and E were mistakenly interchanged.[5] The correction of this assignment was accompanied by proof for the absolute configuration of the valine-, asparagine-, serine- and proline-de-

rived moieties in the Northern and Southern part of the molecule.[11] The elusive configurational assignment for the phenylserine fragment in the Eastern section of GE2270 A (ring C) was initially based on crystallographic data of a 1:1 molar complex between *Escherichia coli* EF Tu-GDP (guanine nucleotide diphosphate) and GE2270 A (2.35 Å resolution).[4a] The assignment was certainly biased by the fact that most, if not all, phenylserines in natural products derived from bacteria had been shown to be *threo*-(2*S*,3*R*)-configured.[12] In the context of preliminary studies towards GE2270 A we prepared the two tetrathiazoles **2** [*threo*-(2*S*,3*R*)] and **3** [*erythro*-(2*R*,3*R*)] in enantiomerically and diastereomerically pure form[13] with the intention to compare their spectral data with the data of a degradation product of GE2270 A (Figure 2) earlier reported by Tavecchia et al.[11b]



2: X^1 = NHAc X^2 = H Y^1 = H Y^2 = OAc
3: X^1 = H X^2 = NHAc Y^1 = H Y^2 = OAc
ent-**3**: X^1 = NHAc X^2 = H Y^1 = OAc Y^2 = H

Figure 2. Structure of synthetically prepared diastereomeric tetrathiazoles **2** and **3** and of the degradation product *ent*-**3** obtained from GE2270 A.

Surprisingly, *threo*-compound **2** was not identical to the degradation product. Instead, compound **3** proved to be the enantiomer of the degradation product, to which structure *ent*-**3** could be unambiguously assigned. As a consequence, the *erythro*-(*S*,*S*)-configuration was also assigned to the stereogenic centers at the phenylserine-derived part of GE2270 A. The structural assignment was confirmed in 2006 when the structure of the ternary complex of *T. thermophilus* EF-Tu, guanylyl imino diphosphate (GDPNP) and GE2270 A was solved at 1.6 Å resolution.[4b,14]

The most notable synthetic strategy successfully implemented in the preparation of thiopeptides[15] is the biomimetic approach,[16] according to which the central pyridine core is built by a hetero-Diels–Alder reaction. This strategy has been beautifully applied by Moody et al. to the synthesis of amythiamicin D[17] and by Nicolaou et al. to the synthesis of thiostrepton.[18] In 2006, Nicolaou, Chen et al. used this strategy successfully to establish a synthesis of GE2270 A[19] and of another GE2270 factor, GE2270 T. Additional pyridine ring construction methods, which have been elegantly applied to the synthesis of thiopeptides, include the Bohlmann–Rahtz reaction,[20] as used by Moody et al. in the synthesis of promothiocin A,[21] and the condensation of a 1,5-diketone, as implemented by Ciufolini et al. in their synthesis of the Bycroft–Gowland structure of micrococcin P.[22] Kelly et al. employed a *N*-pivaloyl protected 2-amino-3-bromo-6-ethoxypyridine as a starting material for the synthesis of micrococcinic acid.[23] Substitution reactions at the pyridine were conducted by cross-coupling at the individual positions after appropriate activation. The Shin group has reported the synthesis of an advanced linear precursor of a diastereoisomer of GE2270 A, following a strategy that relies on the attachment of the thiazole rings successively to an appropriately functionalized pyridine core making extensive use of classical condensation reactions.[24,25]

Our own synthetic strategy to GE2270 A was based on a regioselective cross-coupling[26] at the central pyridine fragment (Figure 3).[27] Contrary to the above-mentioned cross-

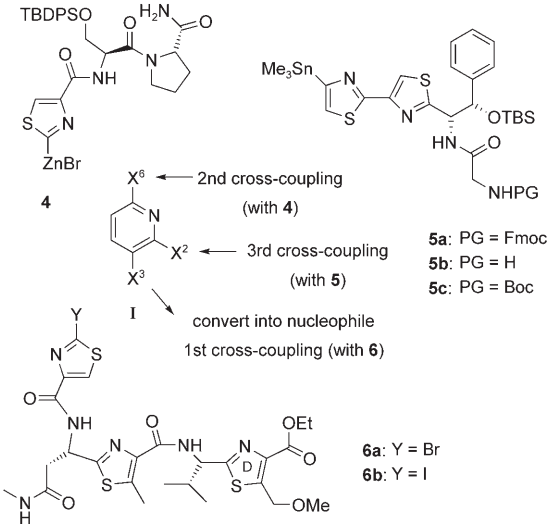


Figure 3. Synthetic plan of three consecutive cross-coupling reactions at a central pyridine core **I** with idealized coupling partners **4**–**6** indicated (PG = protecting group).

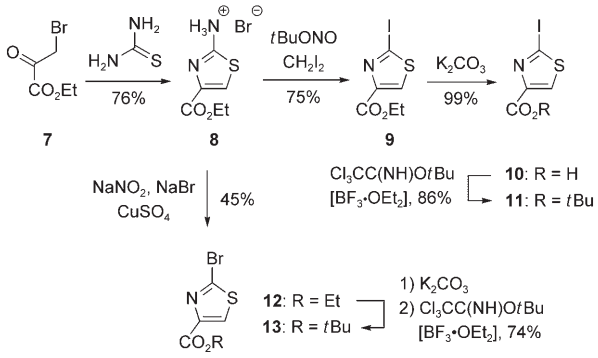
coupling strategy,[23] we planned to address the individual halogenated positions by a judicious choice of reagents, rather than to activate them successively. The propensity of 2,3,6-trihalogenated pyridine (**I**) for a regioselective metalation or a regioselective halogen–metal exchange was deduced from reactions[28] occurring on 2,3-dihalopyridines[29] or on 2,5-dihalopyridines.[29a,30] By this means, position C-3 of the central pyridine was to be initially addressed and converted into a nucleophile, which in turn should be cross-coupled (first cross-coupling) with an electrophilic building block **6**. The second cross-coupling was expected for steric reasons to occur at position C-6 of the pyridine[31] replacing substituent X^6 by an appropriate nucleophile **4** (TBDPS = *tert*-butyldiphenylsilyl). Eventually, the C–C bond formation at C-2 was to be conducted as a Stille cross-coupling[32] in line with our previous experience[33] that sterically encumbered heterocyclic ring positions with limited reactivity are best addressed by Stille or Suzuki cross-coupling reactions. For this cross-coupling we had originally projected the *N*-

tert-butyloxycarbonyl (Boc) protected Eastern fragment **5c** (TBS = *tert*-butyldimethylsilyl), which was in its deprotection scheme orthogonal to the other protecting groups. An alternative substrate with a base-labile protecting group was 9-fluorenylmethyloxycarbonyl (Fmoc) derivative **5a**. A macrolactamization occurring between the *N*-terminus of the glycine and the thiazole carboxylic acid D of the Southern fragment were planned to conclude the synthesis of the central skeleton of GE2270 A. Oxazoline ring closure and deprotection should in two final steps establish the target molecule.

It turned out that the retrosynthetic route as depicted in Figure 3 required modifications as the synthesis progessed. Introduction of the complete Northern fragment was impossible and a truncated analogue was used instead. More importantly, the third cross-coupling was conducted after the amide bond formation, which connects the Eastern fragment via the glycine to thiazole carboxylic acid D (Figure 3) in the Southern part. This modification, employing an intramolecular Stille cross-coupling for the macrocyclization, improved the synthetic efficiency by a factor of five. Details of our synthetic endeavor are given in this full account.[34]

Results and Discussion

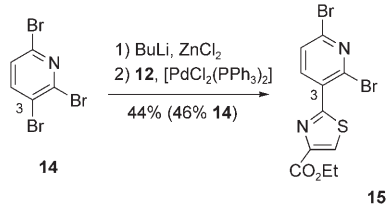
Preparation of thiazoles, pyridines, and cross-coupling studies at C-3: A series of thiazole-4-carboxylates was required either for implementation into the Northern fragment **4** or into the Southern fragment **6**. The readily available ethyl 2-aminothiazole-4-carboxylate (**8**),[35] which was prepared from pyruvate **7**, served as valuable intermediate which could after diazotation be converted into iodide **9** and bromide **12**[36] (Scheme 1). The free iodothiazolecarboxylic acid



Scheme 1. Synthesis of different 2-halothiazole-4-carboxylates.

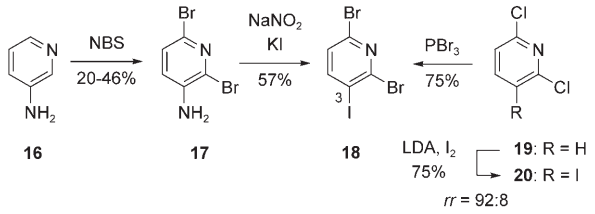
(**10**) was obtained by saponification and could easily be converted into the corresponding *tert*-butyl ester **11** by an acid-catalyzed *tert*-butylation. In a similar fashion the *tert*-butyl 2-bromothiazole-4-carboxylate (**13**) was prepared from ethyl ester **12**.

In the synthesis of tetrathiazoles **2** and **3** we had already conducted a regioselective metalation cross-coupling sequence starting from tribromide **14**.[13] The halogen–metal exchange was conducted with butyl lithium at −78 °C in Et_2O and after transmetalation with $ZnCl_2$ (0.5 M solution in THF) the Negishi cross-coupling[37] was performed using 5 mol % of $[PdCl_2(PPh_3)_2]$ as the catalyst. The yield of dibromide **15** was high if based on recovered starting material (Scheme 2). The fact that the cross-coupling remained incomplete with the pyridine being the limiting reagent was unsatisfactory, however. Yields were variable and depended on the metalation conditions. In addition, access to pure 2,3,6-tribromopyridine (**14**) according to the reported procedure[38] was tedious, because other bromopyridines were also formed and difficult to remove. We therefore decided to reinvestigate the reaction leading to ester **15** in an attempt to optimize the cross-coupling conditions.



Scheme 2. Synthesis of dithiazole **15** by metalation/Negishi cross-coupling.

It was shown that both the bromine–lithium (BuLi, Et_2O, −78 °C) and the bromine–magnesium (*i*PrMgBr, THF, 0 °C) exchange proceed completely. If the transmetalation to zinc ($ZnCl_2$ or $ZnBr_2$ in THF) was conducted after complete bromine–metal exchange, however, the Negishi cross-coupling did not go to completion under a variety of conditions neither with thiazolyl bromide **12** nor with iodide **9**. Direct cross-coupling of the magnesium compound (Kumada cross-coupling) was not feasible, either. Since we felt that an insufficient transmetalation may be responsible for the failure of the cross-coupling we attempted to prepare the zinc species by direct zincation.[39] Expectedly, the zincation (Zn, TMSCl, $BrCH_2CH_2Br$) occurred with high regioselectivity at the 3-position of tribromide **14** but it could not be driven to completion even under forcing conditions (DMA, 150 °C). In order to facilitate zincation we prepared 2,6-dibromo-3-iodopyridine (**18**, Scheme 3). The best regioselectivitity in its preparation was achieved if the bromination (NBS = *N*-bromosuccinimide) was conducted starting from commercially available 3-aminopyridine (**16**). Although we were not able to completely reproduce the yield (92 %) reported for this transformation[40] the method delivered reasonable amounts of regioisomerically pure 2,6-dibromopyridine **17**. The iodo-de-amination[41] was straightforward and gave the desired 2,6-dibromo-3-iodopyridine (**18**). The higher yielding method for its synthesis started from 2,6-dichloropyridine (**19**) but suffered from an incomplete regioselectivity in the deprotonation/iodination step.[42] The 3-iodo product **20** was after re-crystallization still contaminated with the 4-iodopyridine (regioisomeric ratio *rr* = 92:8). The bromo-de-chlorination[43] proceeded smoothly.

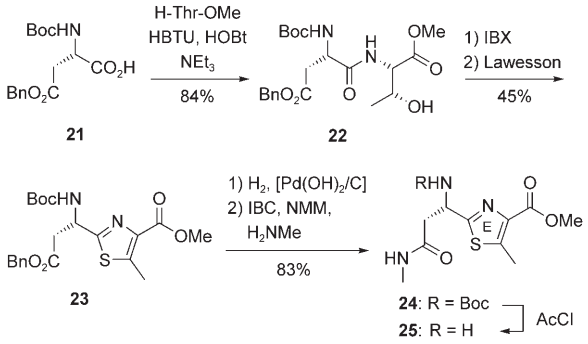


Scheme 3. Two approaches for the synthesis of the trihalogenated pyridine **18**.

We were pleased to find that the direct zincation of iodide **18** was feasible at room temperature upon addition of a THF solution of **18** to activated zinc[39] in DMA. The reaction was complete after 30 min as indicated by GC control of the hydrolysis products. The reaction could be conducted in THF/DMA mixtures up to a ratio of 2.5:1, which proved to be beneficial for the subsequent cross-coupling step.

Indeed, Negishi cross-coupling with bromide **12** gave reproducibly a yield of 60% if either $[PdCl_2(PPh_3)_2]$ or $[Pd_2(dba)_3]$/tfp [dba = dibenzylidenacetone, tfp = tri(2-furyl)phosphane] was used as the catalyst at 45°C. As the conversion was not complete we attempted to further improve the reaction by replacing the bromide **12** with the more reactive ethyl 2-iodothiazole-4-carboxylate (**9**). In this reaction, $[Pd_2(dba)_3]$/tfp turned out to be the superior catalyst as compared to $[PdCl_2(PPh_3)_2]$ with optimum yields of 87 versus 72%. Formation of the ligated Pd^0 species was indicated in the former case by a color change of the solution from red to grey. Since preliminary studies suggested that not only the 2-iodothiazole-4-carboxylates but also the corresponding secondary amides underwent the required cross-coupling reactions, we embarked on the synthesis of the complete Southern fragment with an iodide at the 2-position of thiazole ring F (compound **6b**, Figure 3).

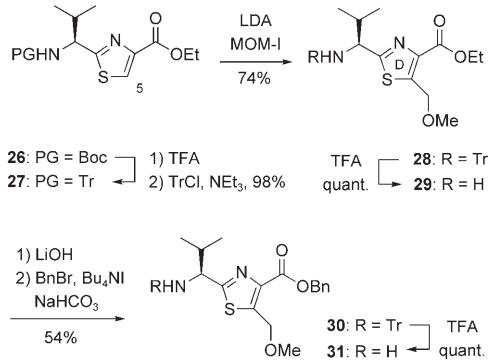
Synthesis of the Southern fragment: The trithiazole **6** invites amide bond formation reactions to link the individual thiazole fragments (rings D, E, F in Figure 1). Retrosynthetically, the two more complex thiazoles resulting from this consideration contain stereogenic centers derived from aspartate (ring E) and from valine (ring D). Amino and carboxyl termini require orthogonal protecting group strategies. We relied on the Gabriel thiazole synthesis[44] for the synthesis of thiazole **24** (Scheme 4).[45] Starting from *N*-Boc-protected monobenzylated amino acid **21**, dipeptide **22** was generated employing *O*-(benzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate (HBTU) in the presence of 1-hydroxybenzotriazole (HOBt) as the peptide coupling reagent. After oxidation with 2-iodoxybenzoic acid (IBX)[46] and treatment of the resulting ketone with the Lawesson reagent[47] the desired ring closure occurred uneventfully. The Lawesson reagent, however, led to significant sulfur impurities, which severely hampered the subsequent hydrogenolytic cleavage of the benzylester **23**.[48] While the impurities could be removed by repeated (up to ten times) chromatographic purification we found that we could circumvent this tedious procedure by washing an ethyl acetate solution of **23** with an aqueous $AgNO_3$ solution. After a single chromatographic purification step the ester **23** was sufficiently pure to undergo a high yielding hydrogenolysis to the free acid, which was converted into the primary amide **24** via the mixed anhydride generated with isobutyl chloroformate (IBC) and *N*-methylmorpholine (NMM). Hydrogen and Pearlman's catalyst $[Pd(OH)_2/C]$ proved in our hands to be superior reagents for the hydrogenolysis compared with other typically used reagent combinations, for example, H_2 [Pd], HCOOH [Pd/C], or cyclohexene [Pd/C]. In the amide formation step, an excess of methyl amine and prolonged reaction times (>1 h) should be avoided to suppress formation of the undesired diamide, which resulted from a reaction at the methyl ester. After Boc deprotection the enantiomeric purity (>95% *ee*) of the resulting amino acid **25** was assessed by the Mosher method.[49]



Scheme 4. Synthesis of the aspartate-derived thiazole **24**.

Attempts to obtain the methyl ester **24** or related esters by reaction of a thioamide derived from carboxylic acid **21** with an appropriate β-bromo-α-ketobutanoate were met with limited success. Best yields were in the range of 35–40%. Contrary to that, the same thioamide reacted nicely and cleanly (80–90%) with the corresponding α-pyruvates (i.e., β-bromo-α-ketopropanoates) indicating that the sterically more hindered secondary bromide is by far more difficult to substitute than a primary bromide. With these results in mind we decided to assemble the valine-derived thiazole **31**, also bearing a substituent at C-5, by a Hantzsch synthesis[50] with ethyl α-bromopyruvate and subsequent alkylation[51] at C-5 rather than by introducing the methoxymethyl group via the bromide in the thiazole forming step (Scheme 5). Indeed, Boc-protected thiazole **26** is literature known and was prepared from *N*-Boc-protected valine in four steps and 77% overall yield by the method earlier described by Meyers.[52] Attempted alkylation of thiazole **26** proceeded smoothly using three equivalents of LDA in the deprotonation step. It turned out, however, in a Mosher analysis conducted at a later stage of the synthesis that minor racemization had occurred during the alkylation (89% *ee*). This observation forced us to switch protecting groups and to convert the *N*-Boc protected amine **26** into its

N-trityl (Tr) protected analogue **27**. The bulkier protecting group shields the amine proton effectively and allowed deprotonation at C-5 with 1.1 equivalents of LDA. Methoxymethylation with methoxymethyl iodide (MOM-I) delivered product **28** in very good yield. The use of MOM-I was mandatory as methoxymethyl chloride (MOM-Cl) was too weak an electrophile to provide a significant conversion.

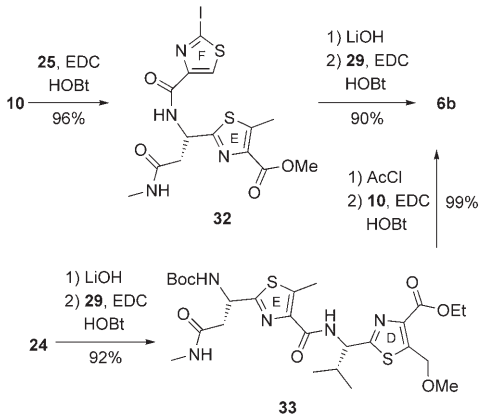


Scheme 5. Synthesis of the valine-derived thiazole **30**.

While the ethyl ester **28** was used for further synthetic elaboration, the synthesis of benzyl ester **30** is also shown in Scheme 5 because complete Mosher analysis was conducted with this compound (>95% *ee*). Since benzyl ester **30** was obtained from ethyl ester **28** the enantiomeric purity of this and any other precursor can be safely assumed. Deprotection of the trityl group (**28** → **29**, **30** → **31**) was straightforward with TFA (trifluoroacetic acid) in CH_2Cl_2 as the solvent and proceeded quantitatively. The possibility of further functionalization at C-5 was briefly evaluated because this option could be useful if different thiazole rings were to be introduced into ring D for structure–activity relationship studies. Indeed, iodination and stannylation reactions at C-5 of **27** were easily accomplished opening up different venues for further synthetic manipulations.

Having the three building blocks **10**, **24**/**25**, and **29** in hand we attempted their assembly to trithiazole **6b**. *N*-(3-Dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride (EDC)[53] turned out to be an excellent activating reagent to mediate the required amide bond formation in high yields. While both connection pathways, that is, F-E-D (**10**, **25** then **29**) or D-E-F (**24**, **29** then **10**) were feasible (Scheme 6) it turned out that the latter route was more reliable with regard to the stereochemical integrity of the asparagine-derived thiazole fragment.

After the straightforward amide-bond formation between **10** and **25** to dithiazole **32** the subsequent saponification led to a racemization at the stereogenic center in α-position of ring E as evident from the fact that the corresponding trithiazole was obtained as a mixture of two diastereoisomers in a ratio of 85:15. Attempts to suppress the racemization by applying other methods to the saponification reaction were not successful. Both Me_3SnOH ($C_2H_4Cl_2$, 80 °C)[54] and $KOSiMe_3$ (THF/CH_2Cl_2, RT)[55] led to racemization resulting



Scheme 6. Assembly of the Southern fragment **6b**.

in a diastereomeric ratio of 74:26 and 75:25, respectively, for product **6b**. The result is surprising in light of the fact that we found the saponification of methyl ester **24**—in agreement with literature precedence[17]—to proceed without any racemization. Presumably, the low solubility and as a consequence the heterogeneous saponification conditions are responsible for the undesired loss of stereochemical integrity. The saponification of ester **24** proceeds in a homogenous solution. An electronic factor exerted by the thiazolylacyl group is less likely as subsequent saponification reactions of the ethyl ester at thiazole D in products derived from **6b** proceeded racemization-free. Fortunately, the trithiazole formation of D-E-F (**24**, **29** then **10**) proceeded not only devoid of any racemization but delivered product **6b** in even higher yield than the other sequence. Intermediate **33** was Boc-deprotected with AcCl in MeOH and subsequently connected with the free acid **10** to provide the desired Southern fragment **6b**.

Linkage of the Southern and the Northern fragment to the pyridine core: Given the high density of functional groups in iodothiazole **6b** as compared to the model compound **9**, it was a pleasurable surprise to note that the previously developed cross-coupling conditions could be transferred to the reaction of zincated iodide **18** and the Southern fragment **6b**. Essentially no modifications were required to assemble the desired 3-substituted 2,6-dibromopyridine **34** (Figure 4). Zincated iodide **18** underwent a clean Negishi cross-coupling with iodide **6b** at 45 °C in a solvent mixture of THF/DMA using [$Pd_2(dba)_3$]/tfp (6 mol%) as the catalyst. The yield was high (87%) and the product **34** was obtained as a single diastereoisomer.

The next step according to our initial synthetic strategy (Figure 3) was to link the complete Northern fragment to the position C-6 of dibromopyridine **34**. Tripeptide **41** (Scheme 7) was targeted as an obvious precursor for zinc reagent **4**. The synthesis of this building block from carboxylic acid **33**, serine methyl ester hydrochloride (**36**)[56] and proline amide (**40**)[57] was straightforward although some time was spent optimizing the reaction conditions for the peptide

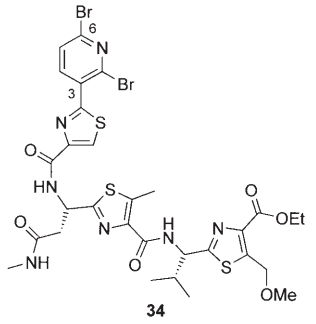
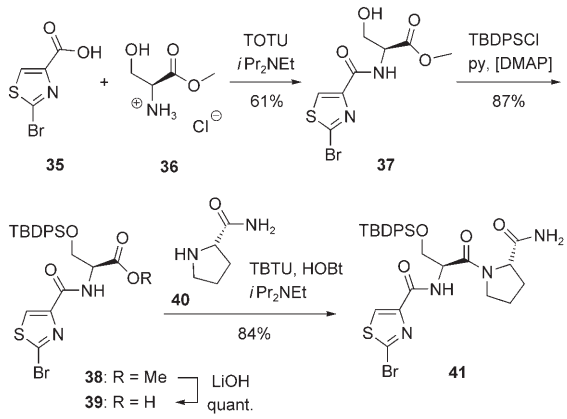


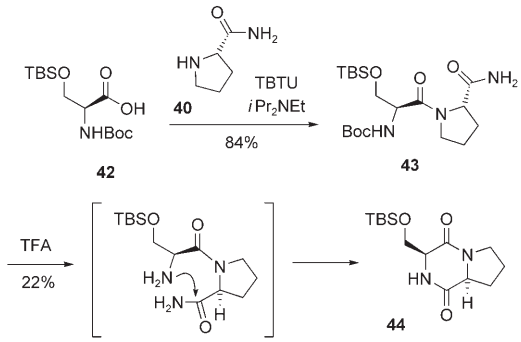
Figure 4. Structure of the key intermediate 2,6-dibromopyridine **34**.

coupling. Eventually, it was found that *O*-[(ethoxycarbonyl)-cyanomethylenamino]-*N*,*N*,*N*′,*N*′-tetramethyluronium tetrafluoroborate (TOTU)[58] was best suited to link thiazole carboxylic acid **35** and serine ester **36** to dipeptide **37** and that a reagent combination of *O*-(benzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate (TBTU) and 1-hydroxybenzotriazole (HOBt) was the best choice[59] to establish the amide bond between carboxylic acid **39** and proline amide (**40**) generating the desired tripeptide **41**. The intermediary steps, silyl protection (**37** → **38**, DMAP = *N*,*N*-dimethylaminopyridine) and saponification (**38** → **39**), proceeded smoothly in high yields.



Scheme 7. Synthesis of the Northern fragment **41**.

Attempts to prepare tripeptides such as **41** by performing the coupling in reversed order were hampered by the undesired diketopiperazine[60] formation of the dipeptides from serine and proline amide. As an example the dipeptide **43**, which was easily obtained from protected serine **42** and proline amide **40**,[59] could not be coupled under conventional conditions to thiazole carboxylic acid **35**. Upon attempted generation of the free amine, rapid cyclization to product **44** was observed prior to any peptide coupling. Even after prolonged stirring of the reaction mixture employed for deprotection the undesired diketopiperazine **44** could be isolated, albeit in low yield (Scheme 8). The situation was even worse if the deprotection was conducted under non-acidic conditions. The *N*-benzyloxycarbonyl protected analogue of *N*-Boc-dipeptide **43** was readily converted into diketopiperazine **44** upon hydrogenolysis (H_2, Pd/C in EtOH, 82% yield). We later found a solution to circumvent the cyclization reaction making use of the corresponding ammonium salt obtained after Boc deprotection (see below).



Scheme 8. Diketopiperazine formation upon deprotection of dipeptide **43**.

The Negishi cross-coupling reactions of appropriately metalated Northern fragments to dibromide **34** turned out to be the most frustrating and most time consuming part of the whole total synthesis project. Metalation was facile using a direct reductive zincation method[39] or a bromine–lithium exchange reaction with subsequent transmetalation to zinc. The success of the metalation was indicated by complete hydro-de-halogenation after aqueous work-up. A host of different conditions for the Negishi cross-coupling was screened. In no instance, however, was a cross-coupling reaction to the electrophile **34** observed. Model electrophiles (e.g. 2-bromopyridine or dibromopyridine **15**) also failed to react in most cases. The only exception was the successful cross-coupling of zincated **41** with 2-bromopyridine in THF employing $[PdCl_2(PPh_3)_2]$ as the catalyst (63% yield). The success of this reaction led us to speculate that the high number of acidic protons in the substrate **34** and in the reagent may be responsible for the failure of the reaction. It was reasoned that an explanation for the exclusive isolation in all cases of the protodebrominated Northern fragment is that the relatively acidic amide protons quenched the organozinc intermediate before entering the Pd-catalytic cycle. Aiming to reduce the number of protons in the zinc reagent we prepared several analogues of compound **41**, which were metalated and subjected to Negishi cross-coupling conditions with dibromide **34**. A selection of these compounds **45**–**48** is shown in Figure 5, none of which, however, underwent the desired reaction. The modification of the catalyst (catalysts, that were employed, include among others $[Pd_2(dba)_3]$/tfp, $[Pd_2(dba)_3]/P(Cy)_3$, $[Pd(PPh_3)_4]$, $[PdCl_2(DPEphos)_2]$, $[Ni(dppe)Cl_2]$) resulted in no improvement.

In order to reduce the number of acidic protons even further we settled on the use of a zincated thiazole derived from ethyl 4-bromo-2-thiazole carboxylate (**12**, Scheme 1). The reagent had been previously employed in the cross-coupling with dibromide **15**[13] and it was therefore not surpris-

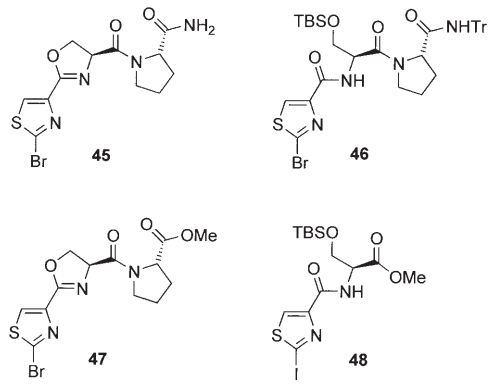
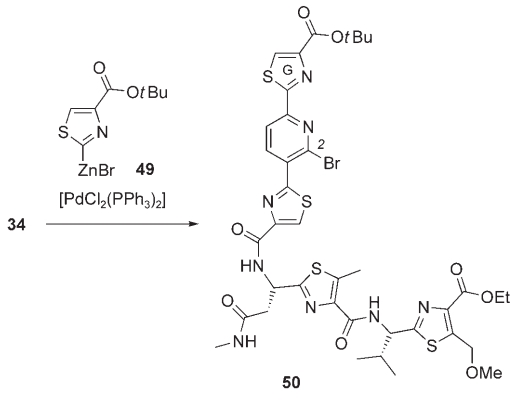


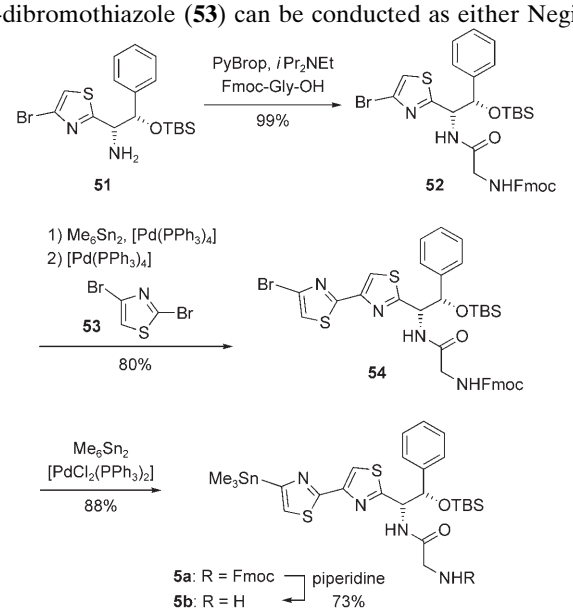
Figure 5. Various Northern fragments **45**–**48** tried in cross-coupling reactions.



Scheme 9. Synthesis of 2-bromopyridine **50** by regioselective Negishi cross-coupling.

ing that model reactions with 2,6-dibromopyridine were equally successful using $[Pd(PPh_3)_4]$ as the catalyst in a mixture of DMA and THF as the solvent. The reaction with dibromide **34** was unfortunately far away from being as clean and as reproducible as the test reaction. If a large excess of the zinc reagent was used (20 equiv) the desired coupling product could be obtained together with 50% of unreacted starting material. A separation of the product and the starting material by column chromatography was impossible. An important breakthrough was achieved, when the order of reagent addition was inverted. Previously, the organozinc compound, which was obtained by reductive metalation, had been added to a solution of the catalyst and dibromide **34** in an appropriate solvent. Now, the organozinc compound and the catalyst were stirred in a separate flask and a solution of dibromide **34** was slowly added. By this means, a more reproducible procedure was established, which allowed for further optimization. In the first place, the ethyl ester **12** was replaced by *tert*-butyl ester **13** as starting material, because the former compound did not provide the required protecting group orthogonality. Secondly, a catalyst screening was conducted, from which $[PdCl_2(PPh_3)_2]$ and $[PdCl_2(dppf)]$ emerged as best suited, whereas many other palladium catalyst failed to provide any cross-coupling reaction or resulted in rapid double substitution at C-6 and C-2. Catalyst loadings needed to be high to guarantee full conversion. Thirdly, the progress of the reaction was monitored with time. It was found that with 30 mol% of $[PdCl_2(PPh_3)_2]$ as the catalyst and with 8 equiv of zinc reagent **49** (Scheme 9) the reaction proceeded cleanly to the desired cross-coupling product **50** with a conversion of about 70% after three hours. After 3.5 h side products became visible with the doubly coupled (C-6 and C-2) being the most severe. As a consequence, it was recommendable to stop the reaction after three hours. The crude product yield was around 60% but triphenylphosphine oxide, which was one major impurity, could not be removed by flash chromatography. An HPLC separation (reversed phase: ODS-A, $MeCN/H_2O$ 70:30, 15 mL min^{-1}) was required to obtain material of sufficient analytical purity. For practical purposes, the material obtained after flash chromatography containing about 15–20% triphenylphosphine oxide was used in further reactions and the triphenylphosphine oxide was chromatographically removed at a later stage of the synthesis (see below).

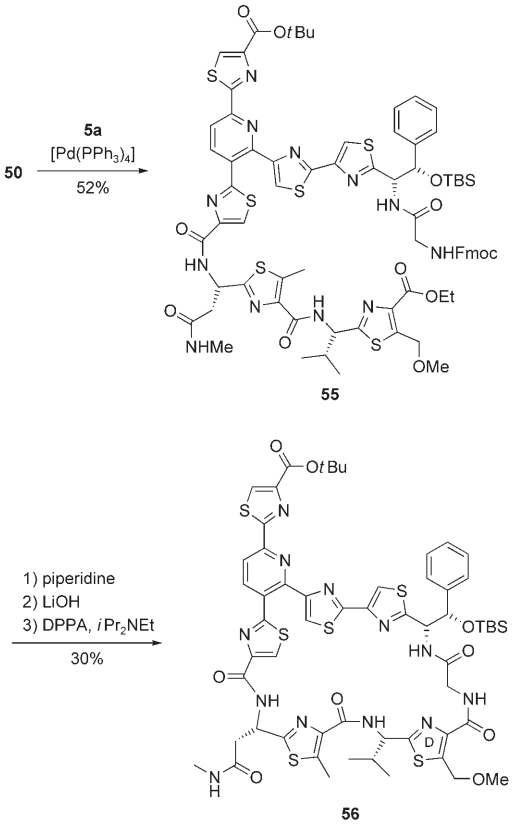
Assembly of the Eastern fragment and macrolactamization: With 2-bromopyridine **50** in hand we turned our interest to the remaining substitution reaction at the pyridine core (Scheme 10). The required Eastern fragment for cross-coupling at C-2 of **50** was prepared in close analogy to a method previously described.[61] Synthetic focus was put on the Fmoc-protected fragment **5a** instead of the Boc-fragment **5c** (Figure 3) because the introduction of the *tert*-butyl ester via thiazole G in **50** (Scheme 9) required the removal of the glycine *N*-protecting group under basic rather under acidic conditions. The known *O*-protected aminoalcohol **51** was coupled with Fmoc-protected glycine using bromotri(pyrrolidino)phosphonium hexafluorophosphate (PyBrop) as the coupling reagent. Earlier research in our group had established that regioselective cross-coupling reactions at 2,4-dibromothiazole (**53**) can be conducted as either Negishi



Scheme 10. Synthesis of the Eastern fragment **5b**.

or Stille cross-coupling reactions.[62] Given the propensity of the Fmoc group for basic cleavage we opted for a Stille cross-coupling in this case. To this end, bromide **52** was converted into the corresponding stannane by a Pd-catalyzed stannyl-de-bromination with hexamethylditin.[63] The latter intermediate was not isolated but directly coupled with dibromide **53** to yield the desired dithiazole[64] **54**. The stannyl-de-bromination reaction was repeated under similar conditions on this 4-bromodithiazole yielding the Eastern fragment **5a**, which could be deprotected to yield the free amine **5b**.

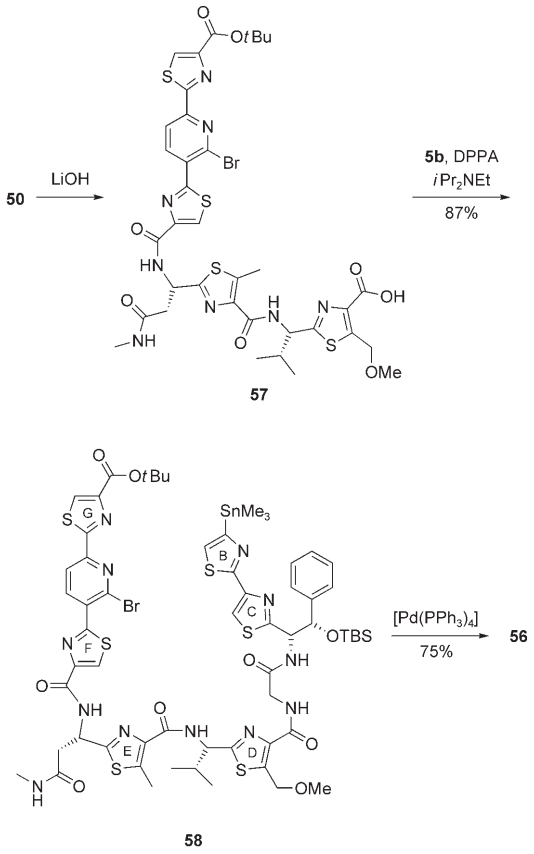
We were pleased to find that the final Stille cross-coupling of dithiazole **5a** at 2-bromopyridine **50** did not require much optimization. The use of standard conditions generally employed for the Stille coupling of 4-stannylated thiazoles (toluene, $[Pd(PPh_3)_4]$, 90 °C, 12–18 h) led to the predominant formation of the desired pyridine **55** in 52% yield (Scheme 11). It was found that in order to get full conversion, at least 1.6 equivalents of the eastern subunit **5a** were necessary. The use of a more polar solvent (dioxane) or additives (CuI) also led to the formation of the desired product but in lower yields. The deprotection of the Fmoc group in product **55** was not trivial. Standard conditions led to moderate yields (50–70%) and in some runs epimerization at an unidentified stereocenter occurred. However, the final key macrolactamization could be attempted once the corresponding carboxylic acid was released with LiOH. To our delight, the use of diphenylphosphoryl azide (DPPA) and Hünig's base in a diluted solution of the corresponding



Scheme 11. Macrocyclization by amide-bond formation.

amino acid generated the desired macrocycle **56** albeit in low yield (20–30% over three steps). Other peptide coupling reagents were also employed, leading to no conversion (PyBrop) or even lower yield (10%, HATU, HOAt). Our observations support the findings of Nicolaou, Chen et al. that the macrolactamization to the basic GE2270 skeleton was a low-yielding process.[19] Indeed, the macrolactamization in their synthesis of GE2270 A, which was conducted with pentafluorophenyl diphenylphosphinate (FDPP) as the coupling agent at the very same junction, had provided a yield of 30%. More significantly, they had found that macrolactamization reactions at the other possible amide bonds were even lower in yield or did not occur at all.

The apparent difficulties with the macrolactamization prompted us to explore a different perhaps even more elegant approach to the assembly of compound **56**. We fancied that the initial formation of the amide bond between the glycine part of **5b** and the thiazole carboxylic acid at ring D was feasible in an *inter*molecular fashion and the subsequent macrocyclization would possibly occur in a subsequent step by a Stille cross-coupling. It was decided to use the same set of reactions (DPPA-mediated peptide coupling and $[Pd(PPh_3)_4]$-catalyzed Stille coupling) but in the reverse order. The stability of the 4-stannylated thiazole was crucial, since it would have to remain inert towards a range of reaction conditions. Luckily, the Fmoc protection offered the advantage of being easily cleaved in the presence of an amine base. In the event, treatment of bisthiazole **5a** with piperidine in DMF followed by concentration of the reaction mixture in vacuo yielded the desired amine **5b**, ready to be trapped in the subsequent peptide-bond formation. Saponification of ester **50** to the free carboxylic acid **57** was straightforward and proceeded epimerization-free (Scheme 12). As in the intramolecular case, the reactant chosen for the amide-bond formation was DPPA and the macrocycle precursor **58** was obtained in 87% yield (two steps from the ethyl ester **50**). Amazingly, the yield in the intermolecular reaction exceeded that obtained in the macrolactamization attempts by a factor of almost three. The stage was set for the decisive step. This reaction would combine in a single synthetic operation two of the presumably most challenging tasks of the complete synthesis: the formation of the fully substituted pyridine core and the formation of the 29-membered macrocycle. To our delight, the conditions employed in the previous Stille coupling (that led to the acyclic precursor **55**) could be successfully adapted to the macrocyclization reaction. In order to avoid the formation of any polymers the substrate and the catalyst were stirred for three days in hot toluene (90 °C) under high dilution conditions ($c = 0.001$ M). The yield observed (75%) was excellent, taking into account the complexity of the process. Interestingly, the only product that could be isolated from this step was the macrocycle **56**, even in cases in which the starting material was contaminated with phosphine oxides or with isomers arising from the previous cross-coupling steps. The intramolecular Stille cross-coupling depicted in Scheme 12 is with regard to molecular size ($M_W = 1.54$ kDa) and function-

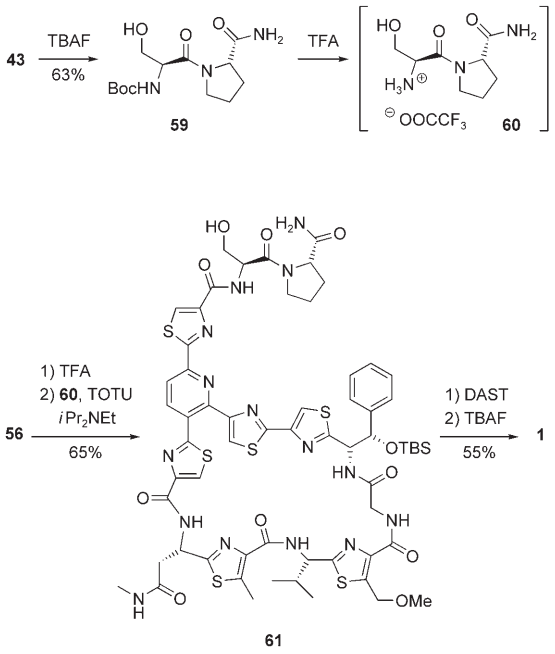


Scheme 12. Macrocyclization by Stille cross-coupling.

al group density one of the most complex reactions of this type ever conducted.[65] It appears, as if the thiazole rings B-F exerted a positive template effect for the cyclization and rather helped than hurt the desired reaction.[66] Nonetheless, the reaction is testimony to the immense synthetic potential of cross-coupling methodology, in general, and of the Stille cross-coupling, specifically.

Conclusion of the synthesis and analytical data: With the macrocycle **56** in hand, only one amide bond remained to be formed. The hydrolysis of the *tert*-butyl ester proceeded smoothly upon addition of TFA in CH_2Cl_2, without affecting the remaining silyl ether. It was anticipated that the key issue in the final peptide coupling would not be the choice of coupling reagent but the handling of the dipeptide **43** (Scheme 8) and analogues thereof. It is well known that unprotected serine-proline fragments react in an intramolecular fashion to form diketopiperazines (Scheme 8).[60] One possible detour would be to build up the remaining fragment stepwise attaching first the serine to the free thiazole carboxylic acid and then the proline amide.[19] We reasoned, however, that the diketopiperazine formation could be halted by having a Boc protecting group at the serine nitrogen, since the acidic conditions employed for the deprotection would generate the corresponding ammonium salt, which in turn cyclizes only slowly to the diketopiperazine (see above). As there was no need for serine to be *O*-protected in this event, the TBS group was removed to produce the monoprotected dipeptide **59**, which was further *N*-deprotected with TFA to produce the ammonium salt **60** (Scheme 13).

Upon mixing this freshly generated ammonium salt with



Scheme 13. Final steps of the total synthesis of GE2270 A (**1**).

the coupling reagent TOTU and the free carboxylic acid in DMF and adding in immediate succession an excess of base, we could efficiently generate the desired amide **61** in very short reaction times. With this procedure, which reveals the serine amine in the presence of the coupling reagent and the acid, we exploit the higher reaction rate of the peptide coupling step versus the diketopiperazine formation.[67] For the oxazoline formation we made use of *N*,*N*-(diethylamino)sulfur trifluoride (DAST), a reagent that has become very popular[68] for the formation of different heterocycles in total synthesis. It offers several advantages, for example, the convenient handling of the reagent and the high reactivity (which allows the reaction to be carried out at low temperatures). With the limited amounts of substrate we had in hand there was very little room for reaction optimization. The first experiments were conducted with a previously prepared 0.1 M stock solution. However, the result from these tests was the almost complete recovery of the starting hydroxyamide **61**. This behavior was initially attributed to the common difficulties associated with the reactions that are carried in such a small scale (ca. 1 μmol). Some unsuccessful tests with Burgess reagent led us back to the more selective DAST. To our delight, when a large excess of DAST (20–30 equiv) was added to a solution of **61** in CH_2Cl_2 at −78 °C total conversion to the desired oxazoline was observed. With the oxazoline in hand, only the deprotection of the phenylserine alcohol remained to be done. The experience we had accumulated during the project in the handling of

the TBS protecting group (both in the introduction and removal of silyl ethers at that position in intermediates in the *erythro* and *threo* series) indicated that a basic fluoride source (such as TBAF) would be suitable to affect the desired desilylation. This transformation could be also carried out in acidic or neutral media although requiring longer reaction times. In the event, treatment of a solution of the silyl ether in THF with TBAF (2.5 equiv) yielded after one hour a sample containing GE2270 A (**1**). Unfortunately, our target molecule was accompanied by considerable amounts of tetrabutylammonium impurities derived from the desilylating reagent. This problem that has been often faced by others in the deprotection leading to very polar compounds[69] and could in our hands only be circumvented by the use of HPLC. While this additional purification step lowered the combined yield in the final two steps to 55% it did deliver material of satisfying analytical purity.

The identity of the synthetic material and the natural product was based on the comparison of NMR data. The presence of many isolated protons and longer sequences of carbon atoms without any attached protons make extensive delay times (10 s) a requirement to obtain ^{1}H and ^{13}C NMR spectra of reasonable quality. As an example the single protons at H-5 of thiazole rings B and C would deliver a ^{1}H NMR integration of only 0.5 if normal delay times of 1 s were used. In Table 1 the ^{13}C NMR data are collected for our final product as compared to the data previously reported by Selva et al.[5b] and by Tavecchia et al.[11b] for the natural product. Assignments are given for the pyridine ring A, for the thiazole rings B–G, for the oxazoline ring H, and for the amino acid derived fragments proline (Pro), phenylserine (Phe) and glycine (Gly). Assignments which can be mutually interchanged are marked. The fit of the ^{13}C NMR data is excellent with the ^{1}H NMR data also perfectly matching the reported values.

Table 1. ^{13}C NMR data of natural and synthetic GE2270 A in comparison.

Ring	Assignment	Selva et al.[a][5b]	Tavecchia et al.[b][11b]	This work[c]
E:	C5-CH_3	11.8	11.7	11.9
D:	$CH(CH_3)(CH_3)$	17.9	17.7	17.8
D:	$CH(CH_3)(CH_3)$	18.4	18.2	18.4
Pro:	C-4	24.1	24.0	24.1
E:	$NHCH_3$	25.7	25.6	25.7
Pro:	C-3	29.6	29.5	29.6
D:	$CH(CH_3)_2$	33.9	33.8	33.9
E:	$CH_2CONHCH_3$	37.6	37.4	37.4
Gly:	CH_2	41.1	41.0	41.0
Pro:	C-5	46.9	46.8	46.9
E:	CH	48.1	47.9	47.9
D:	CH	55.3	55.2	55.2
	CH(NHGly)	58.1	58.0	58.0
D:	CH_2OCH_3	58.5	58.4	58.5
Pro:	C-2	60.0	59.9	60.0
D:	CH_2OCH_3	67.2	67.1	67.3
H:	C-4	67.9	67.7	67.8
H:	C-5	69.3	69.2	69.3
	PhCHOH	73.8	73.6	73.7
C:	C-5	116.3	116.1	116.3
A:	C-5	118.5	118.4	118.5
B:	C-5	122.9	122.9	123.0
F:	C-5*	126.5	126.5	126.6
Phe:	C-2, C-6*	126.5	126.6	126.9
Phe:	C-4	127.5	126.6	127.5
A:	C-3	127.6	127.4	127.6
Phe:	C-3, C-5	127.8	127.4	127.8
G:	C-5	128.5	127.7	128.6
E:	C-5	139.4	139.3	139.3
D:	C-5	141.0	140.8	140.7
A:	C-4	141.6	141.1	141.2
Phe:	C-1	141.6	141.5	141.7
E:	C-4	142.0	141.9	141.9
D:	C-4	143.5	143.5	143.6
G:	C-4	144.7	144.5	144.6
C:	C-4	146.7	146.7	146.7
F:	C-4	149.4	149.2	149.3
A:	C-2[#]	150.1	149.9	150.0
A:	C-6[#]	150.3	150.1	150.2
B:	C-4	153.3	153.2	153.2
H:	C-2	159.2	159.1	159.2
D:	CO	160.2	160.0	160.1
B:	C-2	160.4	160.2	160.3
F:	CO	161.1	161.0	161.0
E:	CO	161.3	161.1	161.2
F:	C-2	164.7	164.5	164.6
D:	C-2	165.7	165.4	165.4
H:	CO	167.7	167.6	167.6
G:	CO	168.1	168.0	168.1
E:	CO	168.3	168.2	168.3
Gly:	CO	169.4	169.3	169.4
E:	$CONHCH_3$	169.7	169.6	169.6
C:	C-2	170.9	170.2	171.0
Pro:	$CONH_2$	173.5	173.4	173.5

[a] [D_6]DMSO, 125 MHz, 33 °C. [b] [D_6]DMSO, 125 MHz, 35 °C. [c] [D_6]DMSO, 150 MHz, 25 °C.

Conclusion

In summary, a concise and convergent synthesis of the thiazolylpeptide GE2270 A was achieved, which proceeds with an overall yield of 4.8% along the longest linear sequence starting from *N*-Boc protected valine (20 steps). The single most remarkable reaction step is the facile macrocyclic ring closure to a 29-membered ring by an intramolecular Stille cross-coupling reaction (75% yield). The step completes the assembly of elaborated fragments to a central pyridine core employing regioselective cross-coupling and metalation reactions. The strategy allows a facile variation of all sites in the macrocycle and may therefore be valuable for the synthesis of GE2270 A analogues. In addition, the modular approach opens a venue to replace the thiazoles by other hetero- and homocyclic rings and it should allow an increase of the notoriously low hydrophilicity of the compound. Previous experiments in this area[70] were limited to the Northern fragment, because it was the only part of the molecule, which could be semisynthetically addressed. The concise synthesis we have developed should therefore be a good starting point for evaluating the chemical genetics of the GE2270 family of antibiotics.

Experimental Section

General: All reactions involving water-sensitive chemicals were carried out in flame-dried glassware with magnetic stirring under argon. Tetrahydrofuran (THF), diethyl ether (Et_2O) and 1,2-dimethoxyethane (DME) were distilled from sodium immediately prior to use. Dichloromethane, triethylamine, pyridine and diisopropylethylamine were distilled from calcium hydride. All other chemicals were either commercially available or prepared according to the cited references. TLC: Merck glass sheets (0.25 mm silica gel 60, F_{254}), eluent given in brackets. Detection was performed by UV or coloration with cerium ammonium molybdate (CAM) or $KMnO_4$. ^1H and ^{13}C NMR spectra were recorded at ambient temperature unless otherwise indicated. Chemical shifts are reported relative to tetramethylsilane as internal standard. Apparent multiplets which occur as a result of the accidental equality of coupling constants of magnetically nonequivalent protons are marked as virtual (virt.). Flash chromatography was performed on silica gel 60 (Merck, 230–400 mesh) (ca. 50 g for 1 g of material to be separated) with the indicated eluent. Common solvents for chromatography [pentane (P), ethyl acetate (EtOAc), diethyl ether (Et_2O), dichloromethane (CH_2Cl_2)] were distilled prior to use. The preparation and analytical data of compounds **5b**, **20**, **30**, **32**, **37**–**39**, **41**–**44**, **55** are reported in the Supporting Information. ^{13}C NMR spectra of all new compounds are also presented in the Supporting Information.

2-Iodothiazole-4-carboxylic acid ethyl ester (9)

Synthesis of 2-aminothiazole-4-carboxylic acid ethyl ester: A mixture of thiourea (1.78 g, 23.4 mmol) and ethyl 3-bromopyruvate (**7**) (2.94 mL, 4.56 mmol, 21.0 mmol) was heated to 100 °C for 1 h. After cooling down to room temperature the crude product was washed with acetone (20 mL) and dried in vacuo to give 2-aminothiazole-4-carboxylic acid ethyl ester hydrobromide (**8**) (4.02 g, 15.9 mmol, 76 %). To obtain the 2-aminothiazole-4-carboxylic acid ethyl ester the hydrobromide salt **8** was dissolved in CH_2Cl_2 and washed with saturated aq. $NaHCO_3$, dried (Na_2SO_4) and the solvent removed in vacuo.

*2-Iodothiazole-4-carboxylic acid ethyl ester (**9**)*: To a stirred solution of 2-aminothiazole-4-carboxylic acid ethyl ester (344 mg, 2.00 mmol) in THF (4 mL) at 0 °C was added consecutively diiodomethane (0.8 mL, 2.66 g, 10.0 mmol) and slowly *tert*-butylnitrite (1.00 mL, 0.87 g, 8.40 mmol). The reaction mixture was allowed to reach room temperature and the stirring was continued for 2.5 h. The mixture was concentrated in vacuo and the residue was dissolved in EtOAc (150 mL), washed with saturated aq. $NaHCO_3$ (50 mL) and saturated brine (50 mL), dried (Na_2SO_4) and the solvents were removed in vacuo. The crude product was purified by flash chromatography (P/Et_2O 3:1) to yield the desired compound **9** (426 mg, 1.50 mmol, 75 %) as a colorless solid. M.p. 82 °C; R_f = 0.31 (P/Et_2O 3:1); ^1H NMR (360 MHz, $CDCl_3$): δ = 8.13 (s, 1H; H-5), 4.43 (q, ^3J = 7.1 Hz, 2H; CH_2CH$_3$), 1.41 ppm (t, ^3J = 7.1 Hz, 3H; CH$_2$CH_3); ^{13}C NMR ($CDCl_3$, 90 MHz): δ = 160.0, 149.6, 133.4, 101.3, 62.0, 14.5 ppm; IR (KBr): $\tilde{\nu}$ = 3128 (w), 2979 (w), 2360 (s), 2341 (m), 1708 (s), 1500 (m), 1404 (m), 1304 (m), 1234 (s), 1021 (m), 988 (m), 752 (w) cm^{-1}; HRMS (EI): *m*/*z*: calcd for $C_6H_6NO_2SI$: 282.9164 [M^+], found 282.9163.

2-Iodothiazole-4-carboxylic acid (10): 2-Iodothiazole-4-carboxylic acid ethyl ester (**9**) (2.04 g, 7.20 mmol) was dissolved in MeOH (20 mL) and H_2O (5 mL). Potassium carbonate (9.90 g, 72.0 mmol) was added and the stirring was continued for 3 h at room temperature. The reaction mixture was partitioned between H_2O (150 mL) and CH_2Cl_2 (100 mL). The aqueous layer was acidified to pH ≈1 with 3 N HCl solution. The aqueous layer was extracted with CH_2Cl_2/THF (10:1, 3×100 mL). The combined organic layers were dried (Na_2SO_4) and concentrated to yield the carboxylic acid **10** (1.82 g, 7.10 mmol, 99 %) as a colorless solid. M.p. 180 °C (decomposition); ^1H NMR (360 MHz, $CDCl_3$, CD_3OD): δ = 8.05 ppm (s, 1H; H-5); ^{13}C NMR (90 MHz, $CDCl_3$, CD_3OD): δ = 161.3, 149.6, 133.6, 101.7 ppm; IR (KBr): $\tilde{\nu}$ = 3095 (s), 1672 (s), 1484 (w), 1433 (m), 1319 (w), 1228 (m), 1112 (w), 985 (s), 739 (w) cm^{-1}; HRMS (EI): *m*/*z*: calcd for $C_4H_2NO_2SI$: 254.8851 [M^+], found 254.8852.

2-Iodothiazole-4-carboxylic acid *tert*-butyl ester (11): To a stirred solution of **10** in CH_2Cl_2 (5 mL) and THF (3 mL) was added *tert*-butyl 2,2,2-trichloroacetimidate (424 mg, 1.94 mmol) and boron trifluoride diethyletherate (15.0 μL, 17.0 mg, 122 μmol). The reaction mixture was stirred for 16 h at room temperature. The reaction was quenched by the slow addition of saturated aq. $NaHCO_3$ (50 mL). After 20 min the aqueous layer was extracted with EtOAc (2×100 mL), and the combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by flash chromatography (P/Et_2O 4:1) to yield the title compound **11** (223 mg, 0.72 mmol, 86 %) as a colorless solid. M.p. 88 °C; R_f = 0.61 (P/Et_2O 3:1); ^1H NMR (360 MHz, $CDCl_3$): δ = 8.00 (s, 1H; H-5), 1.60 ppm [s, 9H; C(CH_3)$_3$]; ^{13}C NMR (90 MHz, $CDCl_3$): δ = 159.1, 151.0, 132.5, 100.9, 82.8, 28.3 ppm; IR (KBr): $\tilde{\nu}$ = 3126 (w), 2969 (w), 1709 (s), 1496 (m), 1393 (s), 1365 (m), 1314 (m), 1250 (s), 1160 (m), 1088 (w), 979 (m), 869 (w), 844 (w), 797 (w), 749 (m) cm^{-1}; HRMS (EI): *m*/*z*: calcd for $C_8H_{10}NO_2SI$: 310.9477 [M^+], found 310.9480.

2-Bromothiazole-4-carboxylic acid ethyl ester (12):[36] To a stirred solution of **8** (7.98 g, 31.5 mmol), $CuSO_4 \cdot 5H_2O$ (15.7 g, 63.1 mmol) and NaBr (13.0 g, 126 mmol) in 50 % H_2SO_4 (90 mL) at −10 °C was added a precooled solution of $NaNO_2$ (2.61 mg, 37.8 mmol) in H_2O (25 mL) dropwise. The mixture was stirred for 1 h at −5 °C and 2 h at room temperature and then water (120 mL) was added. The aqueous layer was extracted with CH_2Cl_2 (5×80 mL) and the combined organic extracts were washed with 5 % aq. $NaHCO_3$ (80 mL) and saturated aq. NaCl (40 mL) and dried (Na_2SO_4). The solvent was removed in vacuo and the residue was purified by flash chromatography (P/Et_2O 3:1) to yield the desired ethyl ester **12** (3.35 g, 14.2 mmol, 45 %) as a colorless solid. M.p. 70 °C; R_f = 0.28 (P/Et_2O 3:1) ; ^1H NMR (360 MHz, $CDCl_3$): δ = 8.11 (s, 1H; H-5), 4.42 (q, ^3J = 7.1 Hz, 2H; CH_2CH$_3$), 1.40 ppm (t, ^3J = 7.1 Hz, 3H; CH$_2$CH_3); ^{13}C NMR (90 MHz, $CDCl_3$): δ = 160.3, 147.5, 136.9, 130.9, 62.0, 14.4 ppm.

2-Bromothiazole-4-carboxylic acid *tert*-butyl ester (13)

Saponification: Ethyl ester **12** (3.25 g, 13.8 mmol) was dissolved in MeOH (40 mL) and H_2O (10 mL). Potassium carbonate (19.0 g, 138 mmol) was added and the stirring was continued for 3 h at room temperature. The reaction mixture was partitioned between H_2O (300 mL) and CH_2Cl_2 (200 mL). The aqueous layer was acidified to pH ≈1 with 3 N HCl solution. The aqueous layer was extracted with CH_2Cl_2/THF (10:1, 3×250 mL). The combined organic layers were dried (Na_2SO_4) and concentrated to yield the carboxylic acid **35** (2.88 g, 13.8 mmol, 99 %) as a colorless solid.

Esterification: To a stirred solution of 2-bromothiazole-4-carboxylic acid (**35**) (2.88 g, 13.8 mmol) in CH_2Cl_2 (80 mL) and THF (48 mL) was added *tert*-butyl 2,2,2-trichloroacetimidate (6.06 g, 27.7 mmol) and boron trifluoride diethyletherate (250 μL, 288 mg, 2.00 mol). The reaction mixture was stirred for 16 h at room temperature. The reaction was quenched by the slow addition of saturated aq. $NaHCO_3$ (150 mL). After 20 min the aqueous layer was extracted with EtOAc (2×250 mL), and the combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by flash chromatography (P/Et_2O 4:1) to yield the title compound **13** (2.70 mg, 10.2 mmol, 74 %) as a colorless solid. M.p. 100 °C; R_f = 0.52 (P/Et_2O 3:1); ^1H NMR (360 MHz, $CDCl_3$): δ = 7.98 (s, 1H; H-5), 1.56 ppm [s, 9H; C(CH_3)$_3$]; ^{13}C NMR (90 MHz, $CDCl_3$): δ = 159.1, 148.5, 136.4, 130.0, 82.7, 28.0 ppm; HRMS (EI): *m*/*z*: calcd for $C_8H_{10}BrNO_2S$: 262.9616 [M^+], found 262.9621.

3-Amino-2,6-dibromopyridine (17):[40] To a stirred suspension of 3-aminopyridine (**16**) (133 mg, 1.40 mmol) in CCl_4 (7.5 mL) was added *N*-bromosuccinimide (503 mg, 2.8 mmol). The reaction mixture was stirred in darkness for 2 h at room temperature. Silica gel, CH_2Cl_2 (15 mL), THF (15 mL) and triethylamine (3 mL) were added to the mixture and concentrated in vacuo. The residue was purified by flash chromatography (P/EtOAc 4:1 and 1 % triethylamine) to give the title compound **17** (164 mg, 0.65 mmol, 46 %) as a colorless solid. The yield was varying between 20 and 46 %. Polymerisation occurred as a side reaction. R_f = 0.29 (P/EtOAc 5:1); ^1H NMR (360 MHz, $CDCl_3$): δ = 7.20 (d, ^3J = 8.2 Hz, 1H; H-4), 6.90 (d, ^3J = 8.2 Hz, 1H; H-5), 4.15 ppm (br s, 2H; NH_2); ^{13}C NMR ($CDCl_3$, 90 MHz): δ = 141.3, 127.7, 127.4, 126.6, 124.4 ppm.

2,6-Dibromo-3-iodopyridine (18)

Synthesis from **17**: Compound **17** (916 mg, 3.64 mmol) was suspended in 6 N H_2SO_4 (6 mL). A solution of sodium nitrite (376 mg, 5.50 mmol) in H_2O (1.5 mL) was added dropwise at 0 °C. After 20 min a solution of po-

tassium iodide (1.33 g, 8 mmol) in H_2O (3 mL) was added and the reaction mixture was allowed to reach room temperature. The stirring was continued for 20 min and potassium carbonate was added until a pH 10 was reached. The aqueous layer was extracted with EtOAc (2×150 mL) and the combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo. The residue was purified with flash chromatography (P/Et_2O 40:1) to give a brown solid. A second purification by flash chromatography (P/Et_2O 40:1) yielded the desired compound **18** (750 mg, 2.06 mmol, 57%) as a colorless solid. M.p. 84°C; R_f=0.55 (P/Et_2O 20:1); ^{1}H NMR (360 MHz, $CDCl_3$): δ=7.89 (d, ^3J=8.1 Hz, 1H; H-4), 7.18 ppm (d, ^3J= 8.1 Hz, 1H; H-5); ^{13}C NMR (90 MHz, $CDCl_3$): δ=149.9, 147.5, 140.1, 128.1, 98.2 ppm; IR (KBr): $\tilde{\nu}$=3094 (m), 2360 (m), 1518 (s), 1390 (s), 1309 (s), 1100 (m), 995 (s), 824 (m), 764 (m), 646 (w) cm^{-1}; HRMS (EI): *m*/*z*: calcd for $C_5H_2NBr_2I$: 360.7599 [M^+], found 360.7598.

(*S*,*S*)-2-(3-Benzyloxycarbonyl-2-*tert*-butoxycarbonylaminopropionylamino)-3-hydroxybutyric acid methylester (22): To a stirred solution of (*S*)-*N*-α-(*tert*-butyloxycarbonyl)-aspartic acid β-benzyl ester (**21**) (8.88 g, 27.5 mmol) in DMF (120 mL) at −25°C was added a solution of the (*S*)-threonine methyl ester hydrochloride (H-Thr-OMe) (5.60 g, 33.0 mmol) in DMF (14 mL), HBTU (12.5 g, 33.0 mmol) and HOBt (5.18 g, 33.0 mmol), followed by the slow addition of triethylamine (14 mL, 10.2 g, 0.10 mol) over 2 h. The stirring was continued for 16 h while the mixture was allowed to warm to room temperature. The solvent was removed in vacuo and the residue dissolved in EtOAc (500 mL). The resulting solution was washed with saturated aq. NH_4Cl (250 mL), saturated aq. $NaHCO_3$ (250 mL), saturated brine (250 mL) and dried (Na_2SO_4). After the solvent was removed the crude product was purified by flash chromatography (P/EtOAc 1:1) to yield the dipeptide **22** (10.1 g, 23.1 mmol, 84%) as a white foam. M.p. 48°C; R_f=0.20 (P/EtOAc 1:1); = −15.0 (*c*=1.00 in CH_3CN); ^{1}H NMR (360 MHz, $CDCl_3$): δ=7.40–7.30 (m, 5H; Aryl-H), 7.20 (d, ^3J=8.9 Hz, 1H; NH), 5.70 (brs, 1H; NH), 5.16 (d, ^2J=12.3 Hz, 1H; PhCH*H*), 5.12 (d, ^2J=12.3 Hz, 1H; PhC*H*H), 4.57–4.54 (m, 2H; C*H*CO_2CH_3, C*H*NHBoc), 4.32–4.30 (m, 1H; C*H*CH_3OH), 3.74 (s, 3H; CO_2CH_3), 3.06 (dd, ^2J=17.1, ^3J=4.9 Hz, 1H; CH*H*CO_2Bn), 2.78 (dd, ^2J=17.1, ^3J=5.8 Hz, 1H; C*H*HCO_2Bn), 1.45 [s, 9H; C(CH_3)$_3$], 1.19 ppm (d, ^3J=6.4 Hz, 3H; CHC*H*$_3$OH); ^{13}C NMR (90 MHz, $CDCl_3$): δ=171.8, 171.3, 171.1, 155.6, 135.5, 128.7, 128.5, 128.4, 80.8, 68.3, 67.1, 57.6, 52.7, 51.0, 36.3, 28.4, 20.0 ppm; IR (KBr): $\tilde{\nu}$=3354 (m), 2978 (w), 1738 (s), 1715 (s), 1673 (s), 1537 (s), 1519 (s), 1504 (s), 1455 (w), 1367 (m), 1164 (s), 1023 (w), 860 (w), 736 (w), 698 (w) cm^{-1}; HRMS (EI): *m*/*z*: calcd for $C_{19}H_{26}N_2O_7$: 394.1740 [$M-C_2H_4O^+$], found 394.1742.

(*S*)-2-(2-Benzyloxycarbonyl-1-*tert*-butoxycarbonylaminoethyl)-5-methylthiazole-4-carboxylic acid methyl ester (23)

Oxidation to the amidoketone: IBX (14.2 g, 50.7 mmol) was added at room temperature to a stirred solution of dipeptide **22** (10.3 g, 23.5 mmol) in MeCN (150 mL). The reaction mixture was heated to reflux for 3.5 h. After cooling to room temperature, the reaction was filtered filtered through Celite and washed with EtOAc (200 mL). The solvents were removed in vacuo.

Thiazole synthesis: The crude amidoketone was dissolved in THF (240 mL) and Lawesson's reagent (14.3 g, 35.4 mmol) was added. The reaction mixture was heated to reflux for 5 h and then cooled to room temperature. The mixture was diluted with EtOAc (500 mL) and washed with water (200 mL), saturated aq. NH_4Cl (200 mL), saturated aq. $NaHCO_3$ (200 mL) and saturated brine (200 mL). The organic layer was dried (Na_2SO_4) and the solvents removed in vacuo. The crude product was purified by flash chromatography (P/EtOAc 3:1) to give a yellow solid. This residue was dissolved in EtOAc (400 mL) and washed with 5% aq. $AgNO_3$ (4×100 mL) and dried (Na_2SO_4). The mixture was concentrated in vacuo and purified by flash chromatography (P/EtOAc 3:1) to yield the desired thiazole **23** (4.59 g, 10.6 mmol, 45%) as a white foam. R_f=0.49 (P/EtOAc 2:1); $[\alpha]_D^{20}$=−29.2 (*c*=1.00 in MeCN); ^{1}H NMR (360 MHz, $CDCl_3$): δ=7.40–7.25 (m, 5H; Aryl-H), 5.96–5.93 (m, 1H; NH), 5.31–5.29 (m, 1H; CH), 5.09 (s, 2H; $PhCH_2$), 3.90 (s, 3H; CO_2CH_3), 3.35–3.30 (m, 1H; CH*H*CO_2Bn), 3.03 (dd, ^2J=16.8, ^3J= 5.4 Hz, 1H; C*H*HCO_2Bn), 2.71 (s, 3H; CH_3), 1.45 ppm [s, 9H; C(CH_3)$_3$]; ^{13}C NMR (90 MHz, $CDCl_3$): δ=171.0, 168.1, 162.9, 155.1, 145.5, 141.0, 135.5, 128.7, 128.5, 128.3, 80.6, 66.8, 55.7, 49.4, 38.6, 28.4, 13.3 ppm; IR (KBr): $\tilde{\nu}$=3345 (w), 2976 (w), 1715 (s), 1498 (w), 1333 (w), 1224 (w), 1167 (m) cm^{-1}; HRMS (EI) calcd for $C_{21}H_{26}N_2O_6S$: 434.1511 [M^+], found 434.1514.

2-(1-*tert*-Butoxycarbonylamino-2-methylcarbamoylethyl)-5-methylthiazole-4-carboxylic acid methyl ester (24)

Hydrogenolysis: $Pd(OH)_2$ on carbon (200 mg, 7 mol%) was added to a solution of thiazole **23** (829 mg, 1.91 mmol) in MeOH (20 mL). The atmosphere in the reaction vessel was changed to hydrogen (1 atm) and stirred at 60°C for 16 h. After cooling to room temperature, the reaction mixture was filtered through Celite and washed with MeOH (20 mL). The combined organic layer was concentrated in vacuo to yield the crude acid as a colorless solid.

Reaction with methylamine: To a stirred solution of the above carboxylic acid in THF (15 mL) at −25°C was added *N*-methylmorpholine (210 μL, 193 mg, 1.91 mmol) followed by isobutyl chloroformiate (210 μL, 193 mg, 1.91 mmol). After 10 min aq. methylamine (40%; 178 μL, 2.30 mmol) was added and the stirring was continued for 1 h while the mixture was allowed to warm to room temperature. The mixture was concentrated in vacuo and the crude product was dissolved in EtOAc (300 mL). The organic layer was washed with saturated aq. NH_4Cl (100 mL), saturated brine (100 mL), dried (Na_2SO_4) and concentrated in vacuo. Purification by flash chromatography (EtOAC) yielded the title compound **24** (567 mg, 1.59 mmol, 83%) as a colorless solid. R_f=0.33 (EtOAc); $[\alpha]_D^{20}$= −35.9 (*c*=0.10 in MeCN), ^{1}H NMR (360 MHz, $CDCl_3$): δ=6.62–6.60 (m, 1H; NH), 6.19 (brs, 1H; NH), 5.18–5.13 (m, 1H; CH), 3.84 (s, 3H; CO_2CH_3), 3.08–3.04 (m, 1H; CH*H*CO_2NHCH$_3$), 2.80 (dd, ^2J=15.1, ^3J= 4.9 Hz, 1H; C*H*HCO$_2$NHCH$_3$), 2.66–2.64 (m, 6H, CH_3; NHC*H*$_3$), 1.40 ppm [s, 9H; C(C*H*$_3$)$_3$]; ^{13}C NMR (90 MHz, $CDCl_3$): δ=170.9, 169.5, 162.9, 155.4, 145.3, 140.9, 80.2, 52.0, 50.1, 39.2, 28.4, 26.2, 13.2 ppm; IR (KBr): $\tilde{\nu}$=3334 (s), 2352 (m), 1704 (s), 1673 (s), 1649 (s), 1547 (w), 1519 (s), 1328 (m), 1223 (m), 1162 (m), 1055 (m), 852 (w) cm^{-1}; HRMS (EI): *m*/*z*: calcd for $C_{15}H_{23}N_3O_5S$: 357.1358 [M^+], found 357.1359.

(*S*)-2-[2-Methyl-1-(tritylamino)propyl]-thiazole-4-carboxylic acid ethyl ester (27)

Boc deprotection: Trifluoroacetic acid (4 mL) was added at room temperature to a stirred solution of thiazole **26** (1 g, 3.05 mmol) in CH_2Cl_2 (20 mL). After 90 min the reaction mixture was concentrated in vacuo and then azeotroped with toluene (3×10 mL) to give the corresponding ammonium salt as a white solid. This material was used without further purification.

Tritylation: The above ammonium salt was dissolved in DMF (10 mL) and then trityl chloride (850 mg, 3.05 mmol) and triethylamine (1.10 mL, 799 mg, 7.89 mmol) were sequentially added. The reaction mixture was stirred for 16 h at room temperature and concentrated in vacuo. The resulting residue was partitioned between EtOAc (200 mL) and saturated aq. $NaHCO_3$ (100 mL). The organic layer was dried (Na_2SO_4) and the solvent removed in vacuo. Purification by flash chromatography (P/Et_2O 4:1 and 0.5% triethylamine) yielded the title compound **27** (1.41 g, 2.99 mmol, 98%) as a white foam. M.p. 52°C; R_f=0.40 (P/Et_2O 5:1); $[\alpha]_D^{20}$=−70.5 (*c*=1.00 in MeCN); ^{1}H NMR (360 MHz, $CDCl_3$): δ=7.89 (s, 1H; H-5), 7.43–7.39 (m, 6H; Aryl-H), 7.21–7.11 (m, 9H; Aryl-H), 4.43–4.33 (m, 2H; CH_2CH_3), 4.17 (dd, ^3J=6.5, ^3J=4.1 Hz, 1H; CH), 2.87 (d, ^3J=6.5 Hz, 1H; NH), 1.71–1.67 [m, 1H; C*H*(CH_3)$_2$], 1.38 (t, ^3J= 7.1 Hz, 3H; CH_2CH_3), 0.86 [d, ^3J=6.8 Hz, 3H; CH(CH_3)(C*H*$_3$)], 0.76 ppm [d, ^3J=6.8 Hz, 3H; CH(C*H*$_3$)(CH_3)]; ^{13}C NMR (90 MHz, $CDCl_3$): δ=176.7, 161.8, 145.9, 129.2, 128.0, 127.9, 127.5, 126.7, 72.2, 61.2, 60.4, 34.7, 20.2, 16.9, 14.5 ppm; IR (KBr): $\tilde{\nu}$=3101 (m), 2959 (m), 1732 (s), 1491 (w), 1445 (w), 1205 (s), 1111 (w), 1027 (w), 902 (w), 832 (w), 750 (w), 711 (m) cm^{-1}; HRMS (EI): *m*/*z*: calcd for $C_{26}H_{23}N_2O_2S$: 427.1480 [M^+], found 427.1473.

(*S*)-5-Methoxymethyl-2-[2-methyl-1-(tritylamino)propyl]-thiazole-4-carboxylic acid ethyl ester (28): Diisopropylamine (0.30 mL, 215 mg, 2.12 mmol) was added at −78°C to a stirred solution of *n*BuLi (0.85 mL, 2.13 mmol, 2.50 M in hexane) in THF (20 mL). After 10 min a precooled (−78°C) solution of thiazole **27** (912 mg, 1.94 mmol) in THF (9 mL) was added rapidly by syringe. 10 min later iodomethoxymethane (0.50 mL, 1.02 g, 5.90 mmol) was added and the stirring was continued at −78°C for 5 min. The reaction mixture was quenched by addition of saturated

aq. NH_4Cl (10 mL). The mixture was diluted with EtOAc (250 mL) and washed with saturated aq. $NaHCO_3$ (100 mL) and saturated brine (100 mL). The organic layer was dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by flash chromatography (P/Et_2O = 4:1 and 0.5% triethylamine) to yield the title compound **28** (739 mg, 1.44 mmol, 74%) as white foam. R_f = 0.30 (P/Et_2O 4:1); $[\alpha]_D^{20}$ = −80.5(*c*=1.00 in MeCN); ^{1}H NMR (360 MHz, $CDCl_3$): δ = 7.43–7.39 (m, 6H; Aryl-H), 7.21–7.11 (m, 9H; Aryl-H), 4.94 (d, ^2J = 14.8 Hz, 1H; CH_2OCH$_3$), 4.87 (d, ^2J = 14.8 Hz, 1H; CH_2OCH$_3$), 4.46–4.30 (m, 2H; *CH*$_2$CH$_3$), 4.12 (dd, ^3J = 6.7, ^3J = 3.9 Hz, 1H; CH), 3.46 (s, 3H; CH$_2$OCH_3), 2.76 (d, ^3J = 6.7 Hz; NH), 1.60–1.49 [m, 1H; C*H*(CH$_3$)$_2$], 1.38 (t, ^3J = 7.0 Hz, 3H; CH$_2$*CH*$_3$), 0.86 [d, ^3J = 6.9 Hz, 3H; CH(CH$_3$)(CH_3)], 0.75 ppm [d, ^3J = 6.9 Hz, 3H; CH(CH_3)(CH$_3$)]; ^{13}C NMR (90 MHz, $CDCl_3$): δ = 174.1, 162.7, 147.9, 146.0, 139.0, 129.1, 127.9, 126.6, 72.3, 68.8, 61.1, 60.4, 59.2, 34.6, 20.1, 16.8, 14.6 ppm; IR (KBr): $\tilde{\nu}$ = 2960 (m), 2932 (w), 1707 (s), 1487 (m), 1446 (w), 1320 (m), 1212 (s), 1087 (m), 1066 (w), 902 (w), 765 (w), 708 (m) cm^{-1}; HRMS (EI): *m*/*z*: calcd for $C_{28}H_{27}N_2O_3S$: 471.1742 [$M-C_3H_7^+$], found 471.1745.

Bisthiazole 33

*Saponification of methyl ester **24***: Aq. lithium hydroxide solution (1 M; 5.00 mL, 5.00 mmol) was added to a solution of methyl ester **24** (515 mg, 1.44 mmol) in methanol (25 mL) at 0°C. The reaction mixture was stirred at room temperature for 16 h, concentrated in vacuo and the crude solid was partitioned between EtOAc (20 mL) and H_2O (75 mL). The aqueous layer was acidified with aq. HCl (2 N) to pH ≈3 and extracted with EtOAc (3×75 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo to yield the carboxylic acid. The material was used without further purification.

Trityl deprotection: To a stirred solution of thiazole **28** (739 mg, 1.44 mmol) in CH_2Cl_2 (22.5 mL) at room temperature was added trifluoroacetic acid (4.5 mL). After 20 min the reaction mixture was diluted with $CHCl_3$ (20 mL) and concentrated in vacuo. The residue was dissolved in $CHCl_3$ (150 mL) and washed with saturated aq. $NaHCO_3$ (50 mL). The aqueous layer was extracted with $CHCl_3$ (2×30 mL). The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo to yield the crude amine **29**. This material was used without further purification.

Peptide coupling: The above carboxylic acid and amine **29** were dissolved in DMF (20 mL). The solution was cooled to −10°C and HOBt hydrate (621 mg, 4.30 mmol) was added. This was stirred for 20 min at −10°C before EDC (330 mg, 1.70 mmol) was added. The mixture was allowed to warm to room temperature and stirred for 16 h. The solvent was removed in vacuo and the residue dissolved in EtOAc (350 mL) and washed with 10% citric acid (100 mL), saturated aq. $NaHCO_3$ (100 mL), saturated brine (50 mL), dried (Na_2SO_4) and concentrated in vacuo. Purification by flash chromatography (EtOAc) provided the bisthiazole **33** (788 mg, 1.32 mmol, 92%) as a white foam. R_f = 0.54 (EtAOc); $[\alpha]_D^{20}$ = −57.1 (*c*= 1.00 in $CHCl_3$), ^{1}H NMR (360 MHz, $CDCl_3$): δ = 8.37 (d, ^3J = 8.6 Hz, 1H; NH), 6.65 (d, ^3J = 8.5 Hz, 1H; N*H*Boc), 6.46 (brs, 1H; N*H*CH$_3$), 5.27–5.21 (m, 2H; C*H*iPr, C*H*NHBoc), 4.92 (s, 2H; CH_2OCH$_3$), 4.40 (q, ^3J= 7.1 Hz, 2H; CH_2CH$_3$), 3.49 (s, 3H; CH$_2$OCH_3), 3.11 (dd, ^2J = 14.6, ^3J= 3.1 Hz, 1H; CH*H*CONHCH$_3$), 2.81 (dd, ^2J = 14.6, ^3J = 4.6 Hz, 1H; C*H*HCONHCH$_3$), 2.74 (s, 3H; CH$_3$), 2.58 (d, ^3J = 4.4 Hz, 3H; NHCH_3), 2.43–2.33 [m, 1H; C*H*(CH$_3$)$_2$], 1.46 [s, 9H; C(CH$_3$)$_3$], 1.40 (t, ^3J = 7.1 Hz, 3H; CH$_2$CH_3), 0.98 [d, ^3J = 6.8 Hz, 3H; CH(CH$_3$)(CH_3)], 0.97 ppm [d, ^3J = 6.8 Hz, 3H; CH(CH_3)(CH$_3$)]; ^{13}C NMR (90 MHz, $CDCl_3$): δ = 171.2, 168.7, 168.3, 162.3, 162.2, 155.5, 148.3, 142.0, 142.0, 139.4, 80.2, 68.8, 61.7, 59.4, 56.2, 50.1, 39.2, 34.2, 28.5, 26.2, 19.3, 18.1, 14.5, 12.7 ppm; IR (KBr): $\tilde{\nu}$ = 3353 (s), 2976 (m), 2933 (m), 1715 (s), 1681 (s), 1651 (s), 1556 (m), 1504 (m), 1371 (m), 1334 (w), 1210 (w), 1164 (m), 1103 (w), 1026 (w), 863 (w), 736 (m) cm^{-1}; HRMS (ESI): *m*/*z*: calcd for $C_{26}H_{40}O_7N_5S_2$: 598.2364 [M+H$^+$], found 598.2362.

Tristhiazole 6b

*Boc deprotection of bisthiazole **33***: Acetyl chloride (0.90 mL, 1.00 g, 12.7 mmol) was added dropwise to EtOH (9.00 mL) at 0°C. Next, bisthiazole **33** (768 mg, 1.28 mmol) was added and the reaction mixture was allowed to warm to room temperature and the stirring was continued for 16 h. The solvent was removed in vacuo and the residue was dissolved in CH_2Cl_2 (250 mL), washed with saturated aq. $NaHCO_3$ (75 mL), dried (Na_2SO_4) and concentrated in vacuo to yield the crude amine. The material was used without further purification.

Peptide coupling: The above amine and compound **10** (328 mg, 1.29 mmol) were dissolved in DMF (18 mL). The solution was cooled to −10°C and HOBt hydrate (555 mg, 3.90 mmol) was added. This was stirred for 20 min at −10°C before EDC (295 mg, 1.54 mmol) was added. The mixture was allowed to warm to room temperature and stirred for 16 h. The solvent was removed in vacuo and the residue dissolved in EtOAc (350 mL) and washed with 10% citric acid (100 mL), saturated aq. $NaHCO_3$ (100 mL), saturated brine (50 mL), dried (Na_2SO_4) and concentrated in vacuo. Purification by flash chromatography (EtOAc) provided the tristhiazole **6b** (942 mg, 1.28 mmol, 99%) as a white foam. R_f = 0.44 (EtOAc); $[\alpha]_D^{20}$ = −43.2 (*c*= 1.00 in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.90 (d, ^3J = 8.9 Hz, 1H; NH), 8.52 (d, ^3J = 8.6 Hz, 1H; N*H*CH*i*Pr), 8.13 (s, 1H; CH^F), 6.69 (brq, ^3J = 4.6 Hz, 1H; E: N*H*CH$_3$), 5.85–5.78 (m, 1H; E: C*H*CH$_2$), 5.26 (dd, ^3J = 8.6, ^3J = 5.5 Hz, 1H; C*H*iPr), 4.94 (s, 2H; CH_2OCH$_3$), 4.43 (q, ^3J = 7.0 Hz, 2H; CH_2CH$_3$), 3.51 (s, 3H; CH$_2$OCH_3), 3.20 (dd, ^2J = 14.7, ^3J = 4.4 Hz, 1H; CH*H*CONHCH$_3$), 2.99 (dd, ^2J = 14.7, ^3J = 6.2 Hz, 1H; C*H*HCONHCH$_3$), 2.74 (s, 3H; CH$_3$), 2.66 (d, ^3J = 4.6 Hz, 3H; NHCH_3), 2.47–2.37 [m, 1H; C*H*(CH$_3$)$_2$], 1.42 (t, ^3J = 7.0 Hz, 3H; CH$_2$CH_3), 1.01 [d, ^3J = 6.8 Hz, 3H; CH(CH$_3$)(CH_3)], 0.98 ppm [d, ^3J = 6.8 Hz, 3H; CH(CH_3)(CH$_3$)]; ^{13}C NMR (90 MHz, $CDCl_3$): δ = 170.9, 168.5, 166.1, 162.2, 162.2, 159.3, 151.7, 148.3, 142.3, 141.9, 139.4, 130.4, 100.7, 68.8, 61.7, 59.4, 56.3, 48.6, 39.1, 34.2, 26.4, 19.2, 18.1, 14.5, 12.6 ppm; IR (KBr): $\tilde{\nu}$ = 3372 (m), 2963 (w), 2929 (w), 1711 (m), 1667 (s), 1653 (s), 1541 (s), 1488 (m), 1404 (w), 1370 (w), 1331 (w), 1211 (m), 1096 (w), 981 (w), 732 (w) cm^{-1}; HRMS (EI): *m*/*z*: calcd for $C_{25}H_{31}O_6N_6IS_3$: 734.0506 [M^+], found 734.0500.

2,6-Dibromopyridine 34

Zincation: DMA (1.9 mL) and 1,2-dibromoethane (33.0 μL, 72.0 mg, 383 μmol L) were added to a flame dried flask charged with zinc dust (227 mg, 3.47 mmol). The zinc suspension was shortly heated with a heat gun until evolution of ethylene occurred and then allowed to reach 25°C. This procedure was repeated three times. TMSCl (112 μL, 96.0 mg, 0.88 mmol) was added neat and the reaction mixture was stirred for 5 min. 2,6-Dibromo-3-iodopyridine (**18**) (596 mg, 1.64 mmol) dissolved in 5 mL THF was added. The stirring was continued for 30 min at 25°C, then the zinc dust was allowed to settle (30 min).

Negishi cross-coupling: The supernatant liquid containing the zincated dibromo pyridine was added to a solution of trithiazole **6b** (424 mg, 0.58 mmol), [Pd(dba)$_2$] (21.0 mg, 36.5 μmol, 6 mol%), TFP (17.0 mg, 73.0 μmol, 12 mol%) in 4.2 mL THF. The reaction mixture was stirred for 12 h at 45°C. After quenching with saturated aq. NH_4Cl (50 mL), the aqueous layer was extracted with EtOAc (3×50 mL). The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo. The crude product was purified by flash chromatography (EtOAc) to yield the desired product **34** (426 mg, 0.51 mmol, 87%) as a pale yellow solid. M.p. 86–89°C; R_f = 0.39 (EtOAc); $[\alpha]_D^{20}$ = −30.6 (*c*= 1.00 in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.42 (d, ^3J = 8.8 Hz, 1H; NH), 8.50 (d, ^3J = 8.2 Hz, 2H; N*H*CH*i*Pr, CH^{py}), 8.36 (s, 1H; CH^F), 7.59 (d, ^3J = 8.2 Hz, 1H; CH^{py}), 6.66 (d, ^3J = 4.5 Hz, 1H; N*H*CH$_3$), 5.83–5.79 (m, 1H; C*H*CH$_2$), 5.26 (dd, ^3J = 8.2, ^3J = 5.4 Hz, 1H; C*H*iPr), 4.94 (s, 2H; CH_2OCH$_3$), 4.42 (q, ^3J= 7.0 Hz, 2H; CH_2CH$_3$), 3.51 (s, 3H; CH$_2$OCH_3), 3.30 (dd, ^2J = 14.8, ^3J= 4.2 Hz, 1H; CH*H*CONHCH$_3$), 2.94 (dd, ^2J = 14.8, ^3J = 5.2 Hz, 1H; C*H*HCONHCH$_3$), 2.73 (s, 3H; CH$_3$), 2.62 (d, ^3J = 4.5 Hz, 3H; NHCH_3), 2.44–2.39 [m, 1H; C*H*(CH$_3$)$_2$], 1.42 (t, ^3J = 7.0 Hz, 3H; CH$_2$CH_3), 1.00 [d, ^3J = 6.8 Hz, 3H; CH(CH$_3$)(CH_3)], 0.98 ppm [d, ^3J = 6.8 Hz, 3H; CH-(CH_3)(CH$_3$)]; ^{13}C NMR (90 MHz, $CDCl_3$): δ = 171.3, 168.6, 166.5, 162.2, 162.2, 162.0, 160.6, 149.8, 148.4, 142.3, 142.1, 141.4, 141.3, 139.2, 139.0, 130.3, 127.8, 126.3, 68.8, 61.8, 59.4, 56.2, 48.7, 38.9, 34.3, 26.3, 19.2, 18.1, 14.5, 12.7 ppm; IR (KBr): $\tilde{\nu}$ = 3366 (m), 2969 (m), 2929 (w), 1711 (m), 1667 (s), 1535 (s), 1485 (m), 1406 (w), 1370 (w), 1331 (m), 1267 (w), 1208 (m), 1110 (m), 1071 (w), 735 (m) cm^{-1}; HRMS (EI): *m*/*z*: calcd for $C_{30}H_{32}O_6N_7Br_2S_3$: 841.0021 [$M^+$], found 840.9987.

2-Bromopyridine 50

Zincation of tert-*butyl ester **13***: DMA (1 mL) and 1,2-dibromoethane (10.0 μL, 22.0 mg, 116 μmol) were added to a flame dried flask charged

with zinc dust (66.0 mg, 1.00 mmol). The zinc suspension was shortly heated with a heat gun until evolution of ethylene occurred and then allowed to reach 25 °C. This procedure was repeated three times. Trimethylsilyl chloride (TMSCl) (27.0 μL, 23.0 mg, 213 μmol) was added neat and the reaction mixture was stirred for 5 min. *tert*-Butyl ester **13** (85.0 mg, 0.32 mmol) dissolved in 0.5 mL DMA was added. The stirring was continued for 30 min at 25 °C, then the zinc dust was allowed to settle (30 min).

Negishi cross-coupling: The supernatant liquid containing the zinc organyl **49** was transferred to a flask containing $[PdCl_2(PPh_3)_2]$ (8.30 mg, 12.0 μmol, 30 mol %). To this mixture a solution of pyridine **34** (33.7 mg, 40.0 μmol) in DMA (0.5 mL) was added dropwise over 10 min at 45 °C. The stirring was continued at 45 °C for 3.5 h. The reaction mixture was partitioned between saturated aq. NH_4Cl (10 mL) and EtOAc (3× 25 mL). The combined extracts were dried (Na_2SO_4) and concentrated in vacuo. Purification by flash chromatography (EtOAc) afforded a yellow foam (22 mg) containing the desired pyridine **50** (18.2 mg, 19.2 μmol, 48 %, colorless film) together with triphenylphosphine oxide (3.80 mg). Separation of the oxidated ligand from compound **50** was performed by reverse phase HPLC (RP, ODS-A, MeCN/H_2O 70:30, 15 mL min^{-1}). R_f = 0.47 (EtOAc); $[\alpha]_D^{20} = -23.5$ (c = 1.00 in $CHCl_3$); ^{1}H NMR (360 MHz, $CDCl_3$): δ = 9.34 (d, ^3J = 8.9 Hz, 1H; NH), 8.73 (d, ^3J = 8.2 Hz, 1H; CH^{py}), 8.51 (d, ^3J = 8.6 Hz, 1H; N*H*CH*i*Pr), 8.39 (d, ^{3}J = 8.2 Hz, 1H; CH^{py}), 8.37 (s, 1H; CH^F), 8.20 (s, 1H; CH^A), 6.69 (br q, ^3J = 4.8 Hz, 1H; N*H*CH_3), 5.88–5.82 (m, 1H; C*H*CH_2), 5.27 (dd, ^3J = 8.6, ^3J = 5.3 Hz, 1H; C*H*i*Pr*), 4.94 (s, 2H; C*H*$_2$OCH$_3$), 4.43 (q, ^3J = 7.0 Hz, 2H; C*H*$_2$CH$_3$), 3.51 (s, 3H; CH_2OCH_3), 3.27 (dd, ^2J = 14.8, ^3J = 4.2 Hz, 1H; CH*H*CONHCH$_3$), 3.01 (dd, ^2J = 14.8, ^3J = 5.8 Hz, 1H; C*H*HCONHCH$_3$), 2.74 (s, 3H; CH_3), 2.66 (d, ^3J = 4.8 Hz, 3H; NHC*H*$_3$), 2.45–2.35 [m, 1H; C*H*$(CH_3)_2$], 1.63 [s, 9H; $C(CH_3)_3$], 1.42 (t, ^3J = 7.0 Hz, 3H; CH_2CH_3), 1.01 [d, ^3J = 7.3 Hz, 3H; $CH(CH_3)(CH_3)$], 0.99 ppm [d, ^{3}J = 7.3 Hz, 3H; $CH(CH_3)(CH_3)$]; ^{13}C NMR (90 MHz, $CDCl_3$): δ = 171.2, 168.5, 166.8, 166.4, 162.4, 162.3, 162.2, 160.6, 160.4, 151.4, 150.2, 149.8, 148.5, 142.4, 142.0, 140.8, 139.6, 139.4, 131.7, 129.9, 126.4, 119.4, 82.6, 68.9, 61.8, 59.5, 56.2, 48.6, 38.9, 34.4, 28.3, 26.4, 19.2, 18.1, 14.6, 12.7 ppm; IR (KBr): $\tilde{\nu}$ = 3389 (s), 2965 (w), 2924 (w), 1713 (m), 1666 (s), 1537 (m), 1482 (m), 1369 (w), 1337 (m), 1267 (w), 1254 (w), 1158 (w), 1100 (w), 1020 (w) cm^{-1}; HRMS (ESI): m/z: calcd for $C_{38}H_{44}O_8N_8BrS_4$: 947.1343 [M+H$^+$], found 947.1337.

{(*S*,*S*)-[1-(4-Bromothiazol-2-yl)-2-(*tert*-butyldimethylsilanyloxy)-2-phenylethylcarbamoyl]-methyl}-carbamic acid 9*H*-fluoren-9-ylmethyl ester (52): PyBrOP (472 mg, 1.02 mmol) and diisopropylamine (442 μL, 2.55 mmol) was added at 0 °C to a stirred solution of amine **51** (350 mg, 0.85 mmol) and Fmoc-Gly-OH (303 mg, 1.02 mmol) in CH_2Cl_2 (15 mL). After 4 h at 0 °C, the reaction mixture was quenched by the addition of saturated aq. $NaHCO_3$ solution (20 mL). The biphasic mixture was extracted with CH_2Cl_2 (3×20 mL), the combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo. Purification by flash chromatography (P/EtOAc 7:3) yielded **52** (583 mg, 0.84 mmol, 99 %) as a glassy solid. R_f = 0.25 (P/EtOAc 7:3); $[\alpha]_D^{20} = +0.70$ (c = 0.90 in $CHCl_3$); ^{1}H NMR (360 MHz, $CDCl_3$): δ = 7.77 (d, ^3J = 7.5 Hz, 2H), 7.63–7.56 (m, 2H), 7.44–7.37 (m, 2H), 7.35–7.21 (m, 7H), 7.10 (s, 1H), 6.90 (d, ^3J = 8.6 Hz, 1H), 5.49 (dd, ^3J = 8.8 Hz, 6.4 Hz, 1H), 5.43 (br s, 1H), 5.12 (d, ^3J = 6.4 Hz, 1H), 4.40 (d, ^3J = 7.5 Hz, 2H), 4.26–4.17 (m, 1H), 3.88–3.78 (m, 1H), 3.73 (dd, ^3J = 17.0 Hz, 5.5 Hz, 1H), 0.81 (s, 9H), −0.09 (s, 3H), −0.21 ppm (s, 3H); ^{13}C NMR (90 MHz, $CDCl_3$): δ = 168.4, 168.1, 156.3, 143.7, 141.2, 139.8, 128.2, 127.7, 127.1, 127.0, 126.7, 125.0, 124.5, 119.7, 117.0, 76.5, 67.2, 60.3, 57.3, 47.0, 44.3, 25.5, 17.9, −4.9, −5.5 ppm; IR (neat): $\tilde{\nu}$ = 3308 (m), 3064 (w), 2953 (s), 2928 (m), 2856 (m), 1737 (s), 1712 (s), 1258 (m), 1100 (m), 838 (m) cm^{-1}; HRMS (ESI): m/z: calcd for $C_{34}H_{38}N_3O_4SSiBr$: 692.1608 [M+H$^+$], found 692.1607; MS (ESI): m/z (%): 694/692 (100/90) [M+H$^+$], 415 (42).

{(*S*,*S*)-[1-(4-Bromo-[2,4′]bithiazolyl-2′-yl)-2-(*tert*-butyldimethylsilanyloxy)-2-phenylethylcarbamoyl]-methyl}-carbamic acid 9*H*-fluoren-9-ylmethyl ester (54): Hexamethylditin (336 μL, 1.60 mmol) was added to a stirred solution of thiazole **52** (280 mg, 0.40 mmol) and $[Pd(PPh_3)_4]$ (46.2 mg, 0.04 mmol, 10 mol %) in toluene (5 mL). The reaction mixture was stirred for 2 h at 85 °C, allowed to reach room temperature and then concentrated to ca. 1 mL. Purification by flash chromatography (P/EtOAc 7:3) gave white solid that was dissolved in toluene (6 mL). After the addition of 2,4-dibromothiazole (**53**) (180 mg, 0.74 mmol) and $[Pd(PPh_3)_4]$ (52.0 mg, 45 μmol) the resulting mixture was stirred for 10 h at 90 °C. Saturated aq. $NaHCO_3$ solution (20 mL) was added, the biphasic mixture was extracted with EtOAc (3×20 mL), the combined organic extracts were dried ($MgSO_4$) and concentrated in vacuo. Purification by flash chromatography (P/EtOAc 7:3) yielded bithiazole **54** (248 mg, 0.32 mmol, 80 %) as a glassy solid. R_f = 0.32 (P/EtOAc 7:3); $[\alpha]_D^{20} = -3.90$ (c = 1.00 in $CHCl_3$); ^{1}H NMR (360 MHz, $CDCl_3$): δ = 7.87 (s, 1H), 7.78 (d. ^3J = 7.5 Hz, 2H), 7.58 (br s, 2H), 7.44–7.38 (m, 2H), 7.35–7.23 (m, 7H), 7.14 (s, 1H), 7.00 (d, ^3J = 8.4 Hz, 1H), 5.54 (dd, ^3J = 8.4 Hz, 5.0 Hz, 1H), 5.34 (br s, 1H), 5.22 (d, ^3J = 5.0 Hz, 1H), 4.48–4.37 (m, 1H), 4.23 (br s, 1H), 4.00–3.91 (m, 1H), 3.84 (dd, ^3J = 16.6 Hz, 5.5 Hz, 1H), 0.87 (s, 9H), 0.00 (s, 3H), −0.17 ppm (s, 3H); ^{13}C NMR (90 MHz, $CDCl_3$): δ = 168.1, 167.1, 163.2, 156.4, 147.4, 143.6, 141.3, 139.7, 128.2, 127.8, 127.1, 126.6, 125.9, 125.0, 120.0, 117.4, 117.0, 76.1, 67.4, 60.3, 57.6, 47.0, 44.6, 25.7, 18.0, −4.8, −5.4 ppm; IR (neat): ν = 3308 (s), 2926 (s), 2854 (s), 1715 (s), 1674, 1506 (s), 1450 (s), 1250 (s), 1099 (s), 1071 (m), 838 (m), 778 (m) cm^{-1}; MS (LC/ESI): m/z (%): 777/775 (40/30) [M+H$^+$], 506 (92), 492 (100).

{(*S*,*S*)-[2-(*tert*-Butyldimethylsilanyloxy)-2-phenyl-1-(4-trimethylstannanyl-[2,4′]bithiazolyl-2′-yl)-ethylcarbamoyl]-methyl}-carbamic acid 9*H*-fluoren-9-ylmethyl ester (5a): To a stirred solution of bithiazole **54** (119 mg, 153 μmol) in degassed dioxane (4.5 mL) was added hexamethylditin (157 μL, 0.76 mmol) followed by $[PdCl_2(PPh_3)_2]$ (23.4 mg, 20 mol %). The resulting dark brown solution was stirred for 6 h at 90 °C, allowed to reach room temperature and concentrated under reduced pressure. Purification by flash chromatography (P/EtOAc 8:2→1:1) afforded bisthiazole **5a** (116 mg, 135 μmol, 88 %) as a glassy solid. R_f = 0.34 (P/EtOAc 7:3); ^{1}H NMR (360 MHz, $CDCl_3$): δ = 7.87 (s, 1H; C: H-5), 7.78 (d, ^3J = 7.5 Hz, 2H), 7.58 (br s, 2H), 7.44–7.38 (m, 2H), 7.35–7.23 (m, 7H), 7.14 (s, 1H), 7.00 (d, ^3J = 8.4 Hz, 1H), 5.54 (dd, ^3J = 8.4, ^3J = 5.0 Hz, 1H; CH-Gly), 5.34 (br s, 1H), 5.22 (d, ^3J = 5.0 Hz, 1H; C*H*OTBS), 4.48–4.37 (m, 1H), 4.23 (br s, 1H), 4.00–3.91 (m, 1H), 3.84 (dd, ^3J = 16.6, ^3J = 5.5 Hz, 1H), 0.84 [s, 9H; $OSi(CH_3)_2C(CH_3)_3$], 0.39 [s, 9H; $Sn(CH_3)_3$], 0.01 [s, 3H; $Si(CH_3)(CH_3)$], −0.18 ppm [s, 3H; $Si(CH_3)(CH_3)$].

Carboxylic acid 57: Aq. lithium hydroxide solution (1 M; 1 mL, 1.00 mmol) was added to a solution of the ethyl ester **50** (92.0 mg, 97.9 μmol) in *t*BuOH (2 mL) and THF (1 mL) at room temperature. The reaction mixture was stirred at room temperature for 1 h, concentrated in vacuo and the crude solid was dissolved in H_2O (10 mL). The aqueous layer was acidified with aq. HCl (2 N) to pH ≈3 and extracted with $CHCl_3$ (2×25 mL) and EtOAc (2×25 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo to yield the carboxylic acid **57** (92.0 mg, 97.9 μmol, 100 %.) as a colorless solid. $[\alpha]_D^{20} = +30.3$ (c = 0.50 in CH_3OH); ^{1}H NMR (360 MHz, CD_3OD, 37 °C): δ = 8.72 (d, ^3J = 8.2 Hz, 1H; CH^{py}), 8.42 (s, 1H; CH^F), 8.35 (s. 1H; CH^A), 8.22 (d, ^3J = 8.2 Hz, 1H; CH^{py}), 5.82 (virt. t, ^3J = 5.8 Hz, 1H; C*H*CH_2), 5.13 (d, ^3J = 6.7 Hz, 1H; C*H*i*Pr*), 4.93 (s, 2H; C*H*$_2$OCH$_3$), 3.44 (s, 3H; CH_2OCH_3), 3.22–3.09 (m, 2H; C*H*$_2$CONHCH$_3$), 2.71–2.69 (m, 6H; NHC*H*$_3$, CH_3), 2.48–2.34 [m, 1H; C*H*$(CH_3)_2$], 1.62 [s, 9H; $C(CH_3)_3$], 1.01 [d, ^3J = 6.7 Hz, 3H; $CH(CH_3)(CH_3)$], 0.97 ppm [d, ^3J = 6.7 Hz, 3H; $CH(CH_3)(CH_3)$]; ^{13}C NMR (90 MHz, CD_3OD, 37 °C): δ = 173.1, 170.5, 168.1, 168.0, 164.5, 164.0, 163.7, 162.5, 161.8, 152.4, 150.9, 150.5, 149.2, 143.9, 142.8, 142.1, 141.6, 140.5, 132.8, 131.7, 128.0, 120.0, 83.6, 69.4, 59.4, 57.6, 50.0, 39.9, 34.5, 28.5, 26.5, 19.9, 18.7, 12.7 ppm; IR (KBr): $\tilde{\nu}$ = 3324 (s), 3109 (m), 2967 (m), 2923 (m), 1717 (s), 1673 (s), 1651 (s), 1536 (s), 1489 (m), 1418 (w), 1347 (w), 1253 (m), 1229 (m), 1160 (s), 1097 (m), 1017 (m), 993 (w), 935 (w) cm^{-1}; HRMS (ESI): m/z: calcd for $C_{36}H_{38}O_8N_8BrS_4$: 917.0873 [M−H$^+$], found 917.0869.

Organostannane 58: Carboxylic acid **57** (21.0 mg, 23.0 μmol) and the amine **5b** (16.0 mg, 25.0 μmol) were dissolved in DMF (2 mL) and cooled to 0 °C. To this mixture diisopropylethylamine (14.5 μL, 11 mg, 85 μmol) and DPPA (9.00 μL, 11.5 mg, 41.8 μmol) were consecutively added. The reaction mixture was allowed to reach room temperature over 16 h and then partitioned between CH_2Cl_2 (10 mL) and saturated aq. NH_4Cl (15 mL). The aqueous layer was extracted with CH_2Cl_2 (2× 25 mL), the combined organic extracts were dried (Na_2SO_4) and concen-

trated in vacuo. Purification by flash chromatography (P/EtOAc 1:3) gave the bromopyridine **58** (30.8 mg, 20.0 μmol, 87%) as a colorless oil. R_f=0.35 (P/EtOAc 1:3); $[\alpha]_D^{20}$=−16.4 (c=1.00 in $CHCl_3$); ^{1}H NMR (360 MHz, $CDCl_3$): δ=9.61 (d, ^3J=8.8 Hz, 1H; NH), 8.75 (d, ^3J=8.1 Hz, 1H; CH^{py}), 8.40 (d, ^3J=8.1 Hz, 1H; CH^{py}), 8.34 (s, 1H; CH^F), 8.21 (s, 1H; CH^A), 8.11 (d, ^3J=9.2 Hz, 1H; N*H*CH*i*Pr), 7.95 (t, ^3J=5.6 Hz, 1H; NH), 7.86 (s, 1H; CH^C), 7.36 (s, 1H; CH^B), 7.24–7.16 (m, 5H; CH^{ph}), 7.12 (d, ^3J=8.5 Hz, 1H; NH), 6.59 (br q, ^3J=4.6 Hz, 1H; N*H*CH_3), 5.80–5.73 (m, 1H; C*H*CH_2), 5.48 (dd, ^3J=8.5, ^3J=5.4 Hz, 1H; C*H*CHOTBS), 5.28 (dd, ^3J=9.2, ^3J=5.6 Hz, 1H; C*H*i*Pr*), 5.19 (d, ^3J=5.4 Hz, 1H; C*H*OTBS), 5.06 (s, 2H; C*H*$_2$OCH$_3$), 4.22 (dd, ^2J=16.6, ^3J=6.4 Hz, 1H; CH*H*), 4.00 (dd, ^2J=16.6, ^3J=4.8 Hz, 1H; C*H*H), 3.48 (s, 3H; CH_2OCH_3), 3.18 (dd, ^2J=15.7, ^3J=4.4 Hz, 1H; CH*H*CONHCH$_3$), 2.94 (dd, ^2J=15.7, ^3J=4.7 Hz, 1H; C*H*HCONHCH$_3$), 2.75 (s, 3H; CH_3), 2.65 (d, ^3J=4.6 Hz, 3H; NHC*H*$_3$), 2.37–2.26 [m, 1H; C*H*$(CH_3)_2$], 1.64 [s, 9H; $C(CH_3)_3$], 0.96 [d, ^3J=6.9 Hz, 3H; $CH(CH_3)(CH_3)$], 0.96 [d, ^3J=6.9 Hz, 3H; $CH(CH_3)(CH_3)$], 0.80 [s, 9H; $Si(CH_3)_2C(CH_3)_3$], 0.37 [s, 9H; $Sn(CH_3)_3$], −0.05 [s, 3H; $Si(CH_3)(CH_3)$], −0.22 ppm [s, 3H; $Si(CH_3)(CH_3)$],; ^{13}C NMR (90 MHz, $CDCl_3$): δ=171.1, 168.6, 168.3, 167.0, 166.8, 166.7, 163.3, 162.5, 162.4, 162.2, 161.3, 160.8, 160.4, 151.4, 150.3, 149.9, 149.4, 144.7, 142.2, 142.2, 141.1, 140.8, 139.9, 139.6, 131.7, 129.9, 128.4, 128.3, 126.7, 126.5, 126.3, 119.5, 116.1, 82.5, 76.4, 68.3, 59.3, 58.0, 55.6, 48.7, 43.0, 38.5, 34.3, 28.3, 26.3, 25.8, 19.3, 18.2, 18.0, 12.8, −4.7, −5.2, −8.7 ppm; IR (KBr): $\tilde{\nu}$=3382 (s), 2960 (w), 2926 (m), 2853 (w), 1666 (s), 1651 (s), 1538 (m), 1504 (m), 1368 (w), 1252 (w), 1159 (w), 1101 (w), 1071 (w), 1017 (w), 838 (w), 777 (w) cm^{-1}; HRMS (ESI): m/z: calcd for $C_{61}H_{76}O_9N_{12}BrS_6SiSn$: 1539.2153 [$M$+H$^+$], found 1539.2104.

Macrocycle 56

Stille macrocylisation: To a stirred solution of bromopyridine **58** (24.0 mg, 15.6 μmol) in degassed toluene (15.5 mL) was added $[Pd(PPh_3)_4]$ (4.00 mg, 3.50 μmol, 22 mol%) and the resulting solution was heated to 85°C for 35 h. The reaction mixture was concentrated in vacuo to 0.5 mL and purified by flash chromatography (CH_2Cl_2/MeOH 98:2) to yield the macrolide **56** (15.2 mg, 11.7 μmol, 75%) as a pale yellow solid together with triphenylphoshine oxide. R_f=0.34 (P/EtOAc 1:3); $[\alpha]_D^{20}$=+46.6 (c=0.55 in $CHCl_3$); ^{1}H NMR (360 MHz, $CDCl_3$): δ=8.89 (d, ^3J=9.2 Hz, 1H; N*H*CHCH$_2$), 8.73 (d, ^3J=7.8 Hz, 1H; N*H*CH*i*Pr), 8.37 (d, ^3J=8.2 Hz, 1H; CH^{py}), 8.35 (s, 1H; CH^F), 8.19 (s, 1H; CH^A), 8.14 (s, 1H; CH^B), 8.10 (d, ^3J=8.1 Hz, 1H; CH^{py}), 7.76 (dd, J=9.4 Hz, J=3.4 Hz, 1H; CH_2NH), 7.23 (s, 1H; CH^C), 7.18–7.14 (m, 3H; CH^{ph}), 7.04–6.98 (m, 2H; CH^{ph}), 6.74–6.68 (br q, ^3J=4.8 Hz, 1H; N*H*CH_3), 6.67 (d, ^3J=7.0 Hz, 1H; NH), 5.42 (dd, ^3J=7.0, ^3J=4.1 Hz, 1H; C*H*CHOTBS), 5.39–5.33 (m, 1H; C*H*CH_2), 5.18 (dd, ^3J=7.8, ^3J=4.4 Hz, 1H; C*H*i*Pr*), 5.14–5.05 (m, 3H; C*H*$_2$OCH$_3$, C*H*OTBS), 4.87 (dd, ^2J=17.2, ^3J=9.4 Hz, 1H; CH*H*NH), 3.79 (dd, ^2J=17.2, ^3J=3.4 Hz, 1H; C*H*HNH), 3.50 (s, 3H; CH_2OCH_3), 2.64 (s, 3H; CH_3), 2.64–2.60 (m, 1H; CH*H*CONHCH$_3$), 2.59 (d, ^3J=4.8 Hz, 3H; NHC*H*$_3$), 2.32–2.18 [m, 1H; C*H*$(CH_3)_2$], 1.65 [s, 9H; $C(CH_3)_3$], 1.02–0.83 [m, 16H; $CH(CH_3)_2$, $Si(CH_3)_2C(CH_3)_3$, C*H*HCONHCH$_3$], 0.11 [s, 3H; $Si(CH_3)(CH_3)$], −0.17 ppm [s, 3H; $Si(CH_3)(CH_3)$]; ^{13}C NMR (90 MHz, $CDCl_3$): δ=169.5, 168.7, 168.6, 168.0, 167.9, 166.0, 165.1, 162.6, 162.1, 161.2, 160.6, 160.1, 154.4, 150.9, 150.4, 150.1, 148.3, 145.1, 142.4, 140.6, 140.4, 140.3, 138.5, 132.2, 129.5, 128.7, 128.4, 127.7, 126.3, 125.2, 123.2, 118.8, 115.4, 82.4, 76.3, 68.2, 59.3, 56.1, 53.5, 48.2, 41.3, 38.2, 34.6, 28.4, 26.4, 25.9, 18.5, 18.4, 18.1, 12.4, −4.3, −5.2 ppm; IR (film): $\tilde{\nu}$=3350 (m), 2929 (s), 2855 (m), 1727 (s), 1666 (s), 1555 (s), 1493 (s), 1454 (s), 1367 (m), 1254 (m), 1162 (m), 1103 (m), 701 (s) cm^{-1}; HRMS (ESI): m/z: calcd for $C_{58}H_{67}N_{12}O_9S_6Si$: 1295.3242 [$M$+H$^+$], found 1295.3241.

(*S*,*S*)-[2-(2-Carbamoylpyrrolidin-1-yl)-1-hydroxymethyl-2-oxoethyl]-carbamic acid *tert*-butyl ester (59): Tetrabutylammonium fluoride (TBAF) (1 M in THF, 220 μL, 0.22 mmol) was added at 0°C to a stirred solution of TBS-ether **43** (77.0 mg, 0.19 mmol) in THF (3 mL). After 30 min the reaction mixture was allowed to reach room temperature and the stirring was continued for 1 h. The reaction mixture was partitioned between $CHCl_3$ (10 mL) and saturated aq. NH_4Cl (3 mL) and the aqueous layer was extracted with $CHCl_3$ (3×10 mL). The combined organic extracts were dried (Na_2SO_4), concentrated in vacuo and purified by flash chromatography (EtOAc/MeOH 95:5) to yield the desired dipetide **59** (35.0 mg, 0.12 mmol, 63%) as a colorless foam. R_f=0.21 (EtOAc/MeOH 9:1); $[\alpha]_D^{20}$=−40.4 (c=1.00 in $CHCl_3$); ^{1}H NMR (360 MHz, CD_3OD): δ=4.56–4.46 (m, 2H; C*H*CH$_2$O, C*H*CONH$_2$), 3.85–3.67 (m, 4H; C*H*$_2$OH, NCH$_2$), 2.28–2.18 (m, 1H; CH$_2$CH*H*), 2.05–1.96 (m, 3H; Pro: C*H*$_2$C*H*H), 1.44 ppm [s, 9H; $C(CH_3)_3$]; ^{13}C NMR (90 MHz, CD_3OD): δ=177.1, 172.6, 157.8, 80.8, 63.4, 61.6, 55.4, 47.0, 30.7, 28.7, 25.7 ppm; IR (neat): $\tilde{\nu}$=3333 (s), 2979 (s), 1651 (s), 1519 (m), 1454 (m), 1367 (m), 1266 (m), 1167 (m), 1062 (w), 736 (m) cm^{-1}; HRMS (EI): m/z: calcd for $C_{13}H_{23}N_3O_5$: 301.1637 [M^+], found 301.1626.

Hydroxyamide 61

Boc deprotection of tert-*butyl ester* ***56***: Trifluoroacetic acid (0.4 mL) was added at room temperature to a stirred solution of the macrocyle **56** (13.5 mg, 10.4 μmol) in CH_2Cl_2 (2 mL). After 3 h the reaction mixture was concentrated in vacuo and then azetroped with toluene (3×5 mL) to give the corresponding ammonium salt as a colorless solid. This material was used in the subsequent peptide coupling without further purification.

Deprotection of dipeptide ***59***: Trifluoroacetic acid (0.2 mL) was added at room temperature to a stirred solution of the dipeptide **59** (17.0 mg, 56.4 μmol) in CH_2Cl_2 (2 mL). After 2 h the reaction mixture was concentrated in vacuo and then azetroped with toluene (3×5 mL) to give the corresponding ammonium salt **60** as a colorless solid. This material was used in the subsequent peptide coupling without further purification.

Peptide coupling: To a mixture of TOTU (5.90 mg, 18.0 μmol) and the ammonium salt **60** was added a solution of the above carboxylic acid in DMF (1.2 mL) and immediately after diisopropylethylamine (20.0 μL, 15.0 mg, 117 μmol). After 2 h the mixture was warmed to room temperature and the stirring was continued for 3 h. The mixture was partitioned between pH 5.5 buffer (3 mL) and $CHCl_3$ (5×10 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo. Purification by flash chromatography (CH_2Cl_2/MeOH 92:8) yielded the β-hydroxy amide **61** (9.60 mg, 6.80 μmol, 65%) as a colorless oil. The desired compound **61** was accompanied by an impurity derived from the coupling reagent. Further purification of the alcohol **61** by reverse phase HPLC was not successful. R_f=0.12 (CH_2Cl_2/MeOH 9:1); $[\alpha]_D^{20}$=+122.0 (c=0.25 in MeOH); ^{1}H NMR (600 MHz, CD_3OD): δ=9.06 (d, ^3J=8.5 Hz, 1H; NH), 8.98 (d, ^3J=8.1 Hz, 1H; NH), 8.91 (d, ^3J=7.8 Hz, 1H; NH), 8.80 (br q, ^3J=4.2 Hz, 1H; N*H*CH$_3$), 8.71 (d, ^3J=7.6 Hz, 1H; N*H*CH*i*Pr), 8.50 (s, 1H; CH^F), 8.41 (s, 1H; CH^A), 8.40 (d, ^3J=8.1 Hz, 1H; CH^{py}), 8.33 (d, ^3J=8.1 Hz, 1H; CH^{py}), 8.25 (s, 1H; CH^B), 7.64 (br s, 1H; NH), 7.50 (d, ^3J=7.3 Hz, 2H; CH^{ph}), 7.47 (s, 1H; CH^C), 7.42 (virt. t, ^3J=7.3 Hz, 2H; CH^{ph}), 7.38 (d, ^3J=7.1 Hz, 1H; CH^{ph}), 5.48–5.44 (m, 1H; C*H*CH_2OH), 5.32–5.30 (m, 1H; C*H*CH$_2$), 5.17 (dd, ^3J=7.6, ^3J=4.8 Hz, 1H; C*H*i*Pr*), 4.99–4.92 (m, 3H; C*H*HOH, C*H*$_2$OCH$_3$), 4.59–4.54 (m, 1H; CH*H*OH), 4.39–4.30 (m, 1H; CH*H*NH), 4.07–4.04 (m, 1H; C*H*CONH$_2$), 3.99–3.89 (m, 2H; NCH$_2$), 3.76 (dd, ^2J=16.8, ^3J=3.7 Hz, 1H; C*H*HNH), 3.46 (s, 3H; CH_2OCH_3), 2.76–2.72 (m, 1H; CH*H*CONHCH$_3$), 2.65 (s, 3H; CH_3), 2.62 (d, ^3J=4.2 Hz, 3H; NHC*H*$_3$), 2.36–2.26 [m, 1H; C*H*$(CH_3)_2$)], 2.26–2.18 (m, 1H; CH$_2$CH*H*), 2.12–1.99 (m, 3H; C*H*$_2$C*H*H), 1.37–1.34 (m, 1H; C*H*HCONHCH$_3$), 0.98 [d, ^3J=6.8 Hz, 3H; $CH(CH_3)(CH_3)$], 0.89 [d, ^3J=6.7 Hz, 3H; $CH(CH_3)(CH_3)$], 0.64 [s, 9H; $Si(CH_3)_2C(CH_3)_3$], −0.21 [s, 3H; $Si(CH_3)(CH_3)$], −0.37 ppm [s, 3H; $Si(CH_3)(CH_3)$]; ^{13}C NMR (90 MHz, CD_3OD): δ=177.2, 173.8, 172.1, 171.2, 169.7, 169.4, 166.7, 166.6, 164.1, 164.0, 163.4, 162.8, 162.7, 161.8, 155.4, 152.0, 151.6, 150.5, 149.5, 146.5, 143.3, 143.3, 142.4, 142.2, 142.0, 141.7, 129.6, 129.1, 128.6, 128.4, 127.7, 127.3, 124.2, 119.9, 117.0, 78.5, 69.0, 63.2, 61.7, 60.4, 59.4, 57.3, 54.6, 49.7, 46.2, 41.9, 39.1, 35.8, 30.9, 26.8, 26.0, 25.9, 18.7, 18.7, 18.6, 12.5, −4.6, −5.4, ppm; IR (neat): $\tilde{\nu}$=3382 (s), 2960 (m), 2926 (m), 1667 (s), 1651 (s), 1538 (m), 1504 (m), 1368 (w), 1252 (m), 1159 (w), 1101 (m), 838 (w), 778 (w) cm^{-1}; HRMS (ESI): m/z: calcd for $C_{63}H_{72}N_{14}O_{11}S_6SiK$: 1459.3236 [$M$+K$^+$], found 1459.3265.

GE2270 A (1)

Oxazoline formation: DAST (9.70 μL, 11.8 mg, 73.0 μmol) was added at −78°C to a stirred solution of β-hydroxy amide **61** (4.00 mg, 2.80 μmol) in CH_2Cl_2 (0.8 mL). After 1 h, anhydrous potassium carbonate (18.0 mg, 0.13 mmol) was added and the resulting white slurry was allowed to reach room temperature. The reaction was poured into saturated aq. $NaHCO_3$ (5 mL) and the biphasic mixture was extracted with CH_2Cl_2 (5×10 mL). The combined organic extracts were dried (Na_2SO_4) and con-

centrated in vacuo to afford crude oxazoline (5 mg) as a colorless oil. *TBS deprotection.* The crude oxazoline was dissolved in THF (1.5 mL) at 0 °C and TBAF (1 M in THF, 9 μL, 9 μmol) was added. After 2 h the reaction mixture was concentrated and purified by reverse phase HPLC (RP, ODS-A, MeCN/H_2O 20:80 → 100:0, 30 min, 15 mL min^{-1}) to afford GE2270 A (**1**) (2.1 mg, 1.6 μmol, 57 %) as a colorless solid. HPLC purification was necessary to free the natural product from the TBAF derived side product. R_f = 0.11 (CH_2Cl_2/MeOH = 9:1); $[\alpha]_D^{20}$ = +71.4 (c = 0.15 in $CHCl_3$); ^{1}H NMR (750 MHz, [D_6]DMSO, 25 °C): δ = 9.02 [d, ^3J = 7.8 Hz, 1H; N*H*CHCHOH], 8.71–8.66 (m, 2H; 2 × NH), 8.61 (s, 1H; CH^F), 8.55 (s, 1H; CH^A), 8.46–8.42 (m, 1H; CH_2NH), 8.43 (d, ^3J = 8.1 Hz, 1H; CH^{py}), 8.30 (s, 1H; CH^B), 8.28 (d, ^3J = 8.1 Hz, 1H; CH^{py}), 7.40–7.36 (m, 2H; CONH*H*, N*H*CH_3), 7.36 (s, 1H; CH^C), 7.33–7.31 (m, 2H; CH^{ph}), 7.29 (virt. t, ^3J = 7.5 Hz, 2H; CH^{ph}), 7.26–7.22 (m, 1H; CH^{ph}), 6.96 (s, 1H; CON*H*H), 6.03 (d, ^3J = 4.5 Hz, 1H; OH), 5.30 (virt. td, ^3J = 8.6, ^3J = 3.7 Hz, 1H; C*H*CH_2), 5.26–5.22 (m, 2H; OCH_2CH, C*H*CHOH), 5.20 (dd, ^3J = 8.1, ^3J = 4.8 Hz, 1H; C*H*CH*i*Pr), 5.02–4.96 (m, 3H; CH_2OCH_3, C*H*OH), 4.81 (virt t, $^{2/3}J$ = 7.6 Hz, 1H; OCH*H*CH), 4.57 (dd, $^{2/3}J$ = 9.7 Hz, $^{2/3}J$ = 7.9 Hz, 1H; OC*H*HCH), 4.27 (dd, ^2J = 17.0, ^3J = 8.2 Hz, 1H; CH*H*NH), 4.24 (dd, ^3J = 8.7, ^3J = 3.6 Hz, 1H; C*H*$CONH_2$), 3.99–3.95 (m, 1H; NCH*H*), 3.86–3.81 (m, 1H; NC*H*H), 3.79 (dd, ^2J = 17.0, ^3J = 3.8 Hz, 1H; C*H*HNH), 3.39 (s, 3H; CH_2OCH_3), 2.72 (dd, ^2J = 16.1, ^3J = 3.7 Hz, 1H; CH*H*$CONHCH_3$), 2.59 (s, 3H; CH_3), 2.48 (d, ^3J = 4.6 Hz, 3H; $NHCH_3$), 2.21–2.10 (m, 2H; C*H*$(CH_3)_2$, CH_2CH*H*), 1.99–1.86 (m, 3H; CH_2C*H*H), 1.36–1.28 (m, 1H; C*H*H$CONHCH_3$), 0.88 [d, ^3J = 6.8 Hz, 3H; $CH(CH_3)(CH_3)$], 0.85 ppm [d, ^3J = 6.8 Hz, 3H; $CH(CH_3)(CH_3)$]; ^{13}C NMR (150 MHz, [D_6]DMSO, 25 °C): δ = 173.5, 171.0, 169.6, 169.4, 168.3, 168.1, 167.6, 165.4, 164.6, 161.2, 161.0, 160.3, 160.1, 159.2, 153.2, 150.2, 150.0, 149.3, 146.7, 144.6, 143.6, 141.9, 141.7, 141.2, 140.7, 139.3, 128.6, 127.8, 127.6, 127.5, 126.9, 126.6, 123.0, 118.5, 116.3, 73.7, 69.3, 67.8, 67.3, 60.0, 58.5, 58.0, 55.2, 47.9, 46.9, 41.0, 37.4, 33.9, 29.6, 25.7, 24.1, 18.4, 17.8, 11.9 ppm; IR (neat): $\tilde{\nu}$ = 3351 (bs), 2960 (m), 2942 (s), 1659 (s), 1443 (m), 1225 (w), 1159 (w), 1094 (m), 750 (m) cm^{-1}; HRMS (ESI): m/z: calcd for $C_{56}H_{56}N_{15}O_{10}S_6$: 1290.2659 [$M$+H$^+$], found 1290.2664.

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