Assembly of the Nosiheptide A-Ring: A Fruitful Lesson

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Abstract: The synthesis of a 28-membered thiopeptide macrocycle is described. Key steps are mild aza-Wittig thiazole ring closures, a scandium(III)-mediated regioselective ester hydrolysis, and a highly efficient macrolactam formation with its 3-hydroxypyridine nucleus orthogonally protected.

Key words: antibiotics, aza-Wittig reaction, heterocycles, natural products, macrocyclization, thiopeptides.

Nosiheptide (**1a**) is a secondary metabolite that was isolated in the early 1960s at the French pharma company Rhône Poulenc S.A. (now part of Sanofi S.A.) from *Streptomyces actuosus* 40037.[3] It is a member of the tetrasubstituted pyridine class of thiopeptide antibiotics[4,5] and shows strong activity in vitro against Gram-positive bacteria.[3b] Recently, nosiheptide was rediscovered in a marine bacterium and it was found to be exquisitely potent against clinically relevant MRSA strains, also in a mouse model.[6] Nosiheptide binds to the bacterial ribosome with sub-nM affinity at the thiostrepton binding site and inhibits protein biosynthesis by interference with elongation factor binding and translation processivity.[7]

The complete chemical structure of nosiheptide has been elucidated by chemical degradation,[8] NMR studies[9] and X-ray crystallography.[10] Studies on its biosynthesis revealed recently that the assembly of the amino acid components into an appropriate pre-peptide occurs from a template gene at the ribosome.[11] Extensive posttranslational modifications convert this regular α-peptide precursor chain into the unique thiopeptide bicyclic structure.[12]

Despite its extraordinary potency as an antibiotic, nosiheptide remains unused as a therapeutic, mainly due to its low solubility and modest chemical stability. It has, however, found applications in animal farming: The compound neither crosses the epithelium of the intestine nor broadly eradicates Gram-negative gut bacteria, but induces strong weight gain in farm animals when used as a feed additive in low doses.[4,13]

During the last decade, some molecules related to nosiheptide (**1a**) have been discovered.[14] The elementary scaffold of these compounds is represented by nocathiacin I (**1b**). Main differences are in the sugar scaffold and in diverse oxidative decorations of the core, rendering the nocathiacins considerably more complex. Importantly, the peculiar thiolactone is replaced by a more stable, regular lactone (likely arising from a Cys → Ser mutation).

Nonetheless, the less oxidized nosiheptide probably constitutes the minimal structural template within this compound class whereupon general synthetic exploration could be based. Its structure is composed of a tris(thiazolyl)pyridine core with an unusual 3-hydroxy group, a thiazole-containing peptide chain completing the larger ring A, and a 2,3,4-trisubstituted indole with a rare thioester linkage to form the smaller ring B. These unique structural features in a densely functionalized architecture make nosiheptide (**1a**) a rewarding target for synthesis development.

Although impressive achievements have been made in the field of thiopeptide antibiotics in terms of total synthesis,[4,5,15] reports on nosiheptide[16] and its congeners[17] remain mostly confined to building block preparation. Beyond these data, Moody et al. disclosed the synthesis of a model system for B-ring formation.[18] Our group has established a synthesis of the A-ring **2a**[19] by implementing novel aza-Wittig[20] and hetero-Diels–Alder chemistry.[21] In this feature article, we give an account of the full details of our unique approach to nosiheptide A-ring fragment **2a** including detours and unexpected results, which are instructive for further research in the area.

A retrosynthetic analysis of nosiheptide (**1a**, Scheme 1) suggested disconnecting the indole unit and opening the labile B-ring. Introduction of latent functionality and protecting groups led to the A-ring key intermediate **2a**,**b**. The indole **3** was envisioned to be constructed by a Reissert-type indole synthesis, and the methyl group could be installed by an sp^2–sp^3 coupling. The isolated A-ring could be disconnected into three fragments: the thiazolo peptide **4**, the 3-hydroxypyridine core **5**, and the side chain dipeptide **6**. The thiazole peptide **4a**,**b** could be united from two smaller intermediates, a glutamic acid derived thiazole and an enamide, by peptide coupling. Aza-Wittig reactions would enable the formation of the thiazoles under mild conditions. The 3-hydroxypyridine core **5** was to be accessed by employing a 1-azadiene hetero-Diels–Alder cycloaddition.[21] The side chain dipeptide could be prepared straightforwardly from amino acids.

The synthesis of indole ester **3** started from the known indole derivative **8** (Scheme 2), which was prepared from

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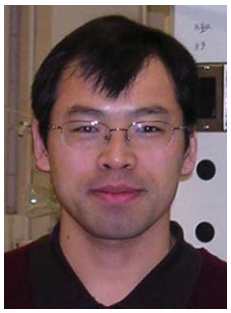
Biographical Sketches

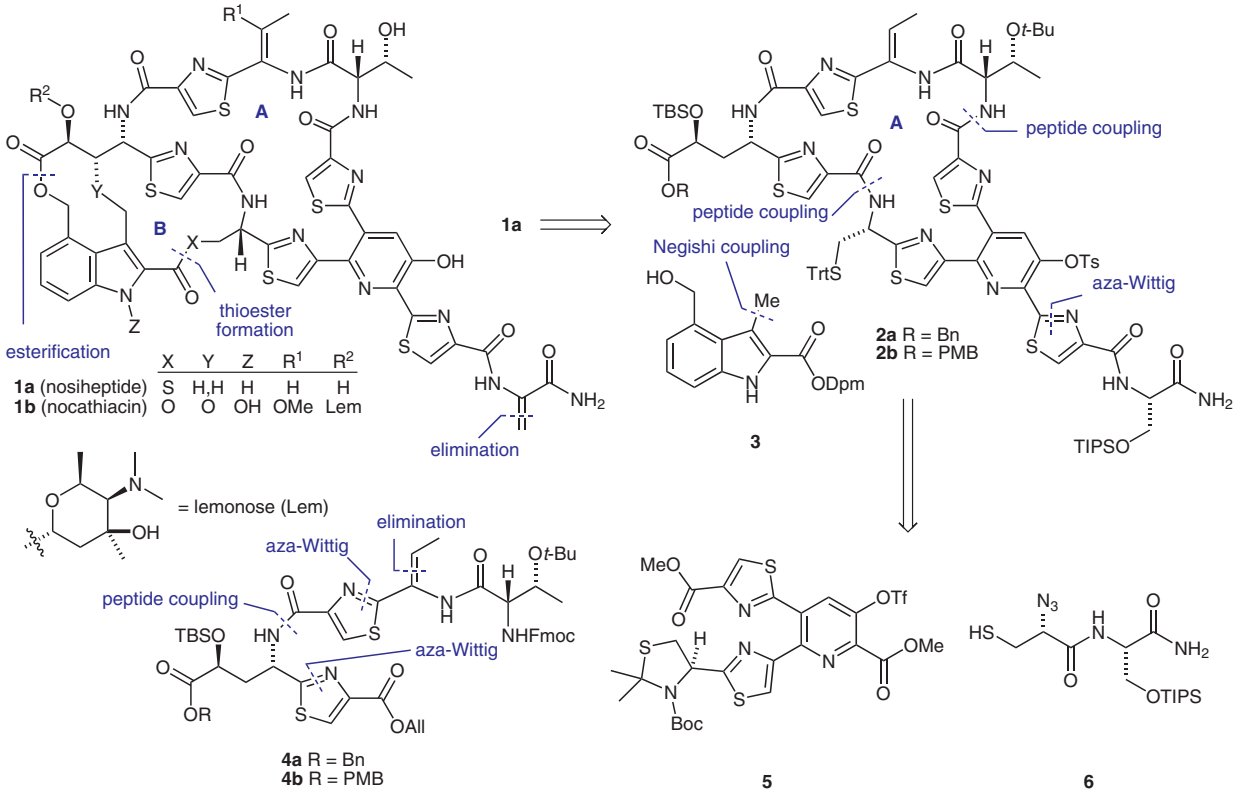


Dr. Jin-Yong Lu was born in Shandong, P. R. of China, in 1977 and studied chemistry at Liaocheng University and Nankai University, China. He completed his M. Sc. degree at Nankai with work on the mechanism of NAD(P)H model hydride transfer in the group of Prof. Dr. Xiao-Qing Zhu. In 2004 he moved to Dortmund to pursue doctoral studies with Prof. Dr. Hans-Dieter Arndt, where he concentrated on azadiene hetero-Diels–Alder reactions in natural product synthesis. After postdoctoral training at the University of Alberta (Edmonton, Canada) with Prof. Dr. Dennis G. Hall, he joined ChemRoutes Corporation at Edmonton in 2012, where he is currently employed as group leader in research and development of early stage drug discovery.

Dr. Matthias Riedrich was born in Singen, Germany, in 1978 and studied chemistry at the University of Konstanz, Germany. He completed his Diploma degree with work on the synthesis of cotylenin analogues in the group of Prof. Dr. Ulrich Groth. In 2004 he moved to Dortmund to carry out doctoral studies with Prof. Dr. Hans-Dieter Arndt, where he focused on the aza-Wittig reaction and its application to thiopeptide structures. After completing his Ph.D. degree he joined the group of Prof. Dr. Karl A. Scheidt at Northwestern University (Evanston, USA) to study NHC-catalyzed conjugate additions. Since 2010 he has been employed at Bayer CropScience, Monheim, Germany, where he currently holds a position as laboratory head in process research.

Dipl. Chem. Kamil Philip Wojtas was born in Kwidzyn (Marienwerder), Poland, in 1984, but grew up in Kamen, Germany. He studied chemistry at TU Dortmund and completed his diploma degree with Prof. Dr. Martin Hiersemann for work on the synthesis of macrocyclic allyl vinyl ethers as model substrates for intramolecular Gostelli–Claisen rearrangements. In 2010, he joined the group of Prof. Dr. Hans-Dieter Arndt, where he is currently working toward his Ph.D. degree at the Friedrich-Schiller University, Jena, in the field of heterocyclic chemistry and synthetic methods development for the construction of thiopeptide antibiotic scaffolds.

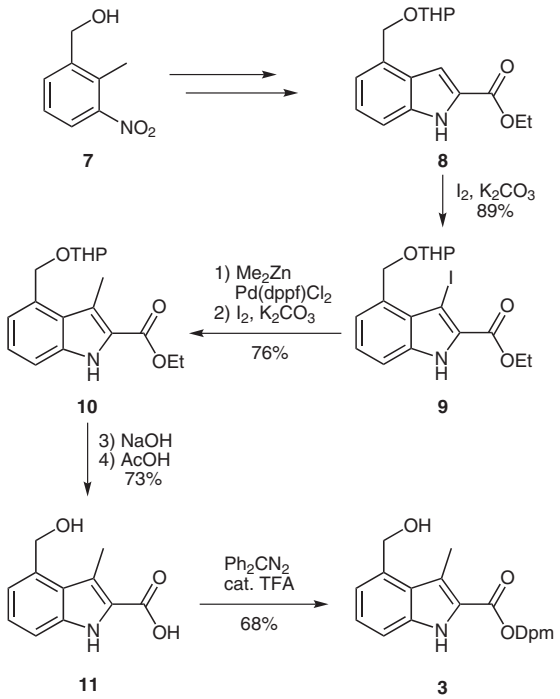
Prof. Dr. Hans-Dieter Arndt was born in Krefeld, Germany, in 1971. He studied chemistry at the Universities of Ulm, Marburg, LMU München, Germany, and at Imperial College, London, U.K. In 2002 he received his doctoral degree from the Humboldt-Universität zu Berlin with Prof. Dr. Ulrich Koert. After a postdoctoral appointment with Prof. Dr. Peter B. Dervan at the California Institute of Technology (Pasadena, USA) he became group leader at the MPI of Molecular Physiology and Emmy-Noether fellow at TU Dortmund in 2004. Since 2011 he has been full professor of organic chemistry at the Friedrich-Schiller-University, Jena, Germany. He is recipient of the ORCHEM Price 2010 and the DECHEMA natural products young investigator award. His current research interests encompass synthetic and functional studies of molecules as modulators of cellular processes and peptide-derived bioactive secondary metabolites and their targets.



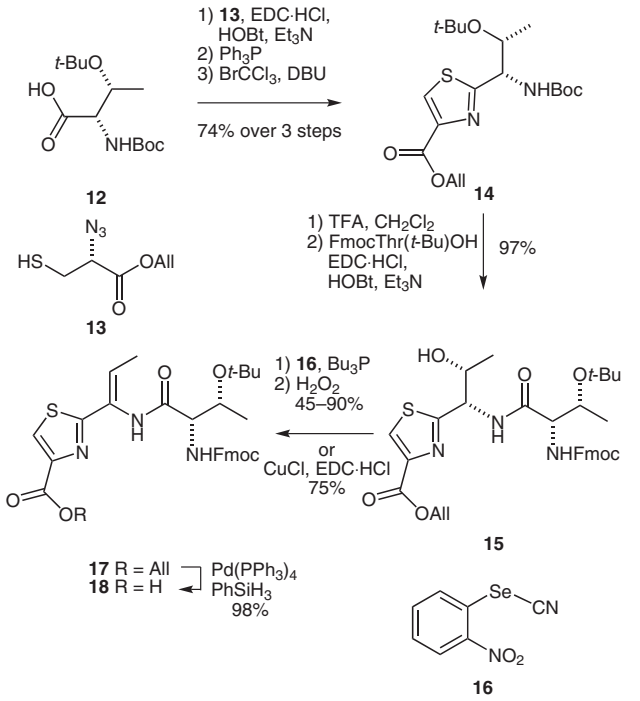
Scheme 1 Chemical structure of nosiheptide (**1a**) and nocathiacin I (**1b**) and retrosynthetic disconnection

nitrobenzyl alcohol **7**.[16b] We then found alkylation procedures reported for position 3 of indoles difficult to reproduce in this case.[17b] In response, we implemented more flexible sp^2 coupling chemistry. Direct iodination of indole **8** delivered 3-iodoindole **9** as the sole isolable product. Negishi coupling of 3-iodoindole **9** with dimethylzinc catalyzed by $Pd(dppf)Cl_2$ provided methylindole **10** together with some dehalogenated indole **8** in variable ratios (3:1–20:1) as an inseparable mixture.[22] Subjecting the mixture to iodination again allowed isolation of pure indole **10** and recycling of **8**. Deprotection of the THP ether, saponification, and introduction of the acid labile diphenylmethyl (Dpm) group[23] by using diphenyldiazomethane delivered indole **3** in reasonable yield.

To obtain peptide fragments **4a** or **4b**, respectively, first free thiol **13** and threonine-derived acid **12** were coupled to obtain a thioester that was converted into thiazole **14** by an aza-Wittig reaction and subsequent oxidation in excellent yield (Scheme 3). The *t*-Bu and Boc groups were then released under acidic conditions and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDC·HCl)/1-hydroxybenzotriazole (HOBT)-promoted amide formation provided dipeptide **15** with ease.



Scheme 2 Synthesis of indole fragment **3**



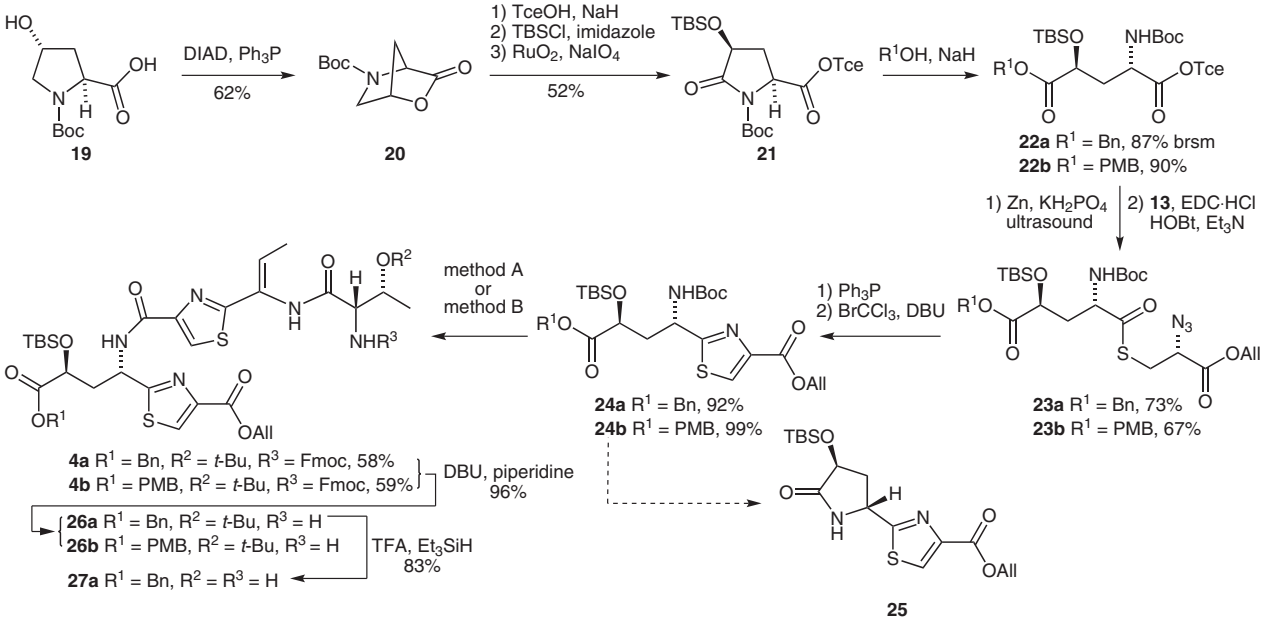
Scheme 3 Synthesis of thiazolyl acid **18**

Initial attempts to install the enamide function in **15** by activation of the OH group with Ms/Ts and base-mediated elimination (DBU/DMAP) to give enamide **17** met with mixed results. After careful experimentation, the dehydration was cleanly accomplished by employing Grieco's selenium-based elimination method.[24] However, in this case yields strongly depended on the quality of the reagent and reaction scale. It was found necessary to purify selenocyanate **16** by chromatography and to employ an excess of reagent (5–10 fold) to achieve reproducible results.

An alternative was found when employing EDC·HCl mediated dehydration in the presence of copper(I) chloride.[25] These conditions delivered the enamide **17** with no need for reagent purification. Apparently, the *Z*-configured thermodynamic product is formed here, in spite of a *syn*-elimination mechanism being operative. The *E*-configured enamide was identified as a minor byproduct only (LC-MS). The allyl ester protecting group was cleanly removed by using $Pd(PPh_3)_4$ in the presence of phenylsilane as a scavenger[26] to give acid **18**.

The synthesis continued with the preparation of thiazole **24a** (or respective **24b**) starting from *N*-Boc-4-hydroxy-L-proline (**19**, Scheme 4). Intramolecular lactonization with inversion of configuration by using a Mitsunobu reaction[27] gave crystalline bicyclic lactone **20** in 62% yield after recrystallization. Subsequent lactone opening with 2,2,2-trichloroethanol, trapping of the liberated hydroxy group with TBSCl, and ruthenium-mediated α-oxidation[28] selectively furnished lactam **21** in good yield. The activated lactam was then opened by treatment with NaOBn or NaOPMB at low temperature to provide the diester **22a** or **22b**, respectively. Both variants were explored because the benzyl ester was found to be difficult to cleave on advanced intermediates (*vide infra*).

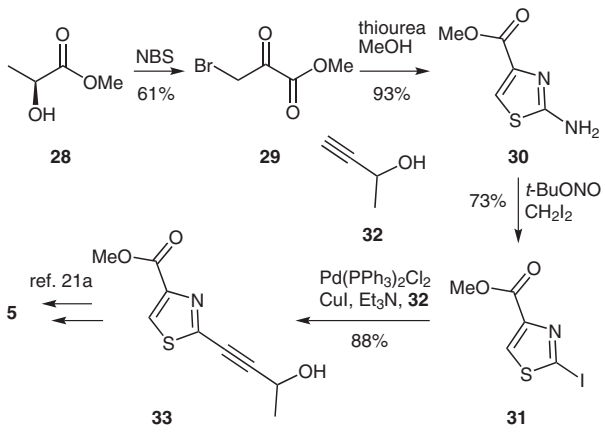
The 2,2,2-trichloroethylester was chemoselectively removed with zinc powder at pH 7. Acylation of thiol **13** provided the thioester **23a** (or respective **23b**) in good yield. After aza-Wittig ring closure and oxidation, thiazole **24a** (or **24b**) was obtained. In the case of **24a**, an immediate sequence of acidic Boc deprotection and EDC·HCl mediated coupling with thiazolyl acid **18** clean-



Scheme 4 *Reagents and conditions*: Method A for **24a**: (a) TFA/CH_2Cl_2 (1:2); (b) **18**, HOBt, EDC·HCl, Et_3N; Method B for **24b**: (a) TBSOTf; (b) **18**, HOAt, HATU, $NaHCO_3$.

ly delivered bisthiazole **4a**. Due to the lability of the PMB ester the conditions for the Boc deprotection of thiazole **24b** needed to be adjusted. TBSOTf was found to remove selectively the Boc group,[29] leaving the TBS and PMB groups untouched. Amide bond formation with thiazolyl acid **18** gave the bisthiazole **4b** in 59% yield. The moderate yields for both couplings could be explained by the formation of the five-membered ring lactam **25**, which was identified by MS as a major side product in the deprotection of **24**.[16h] The amine group was liberated efficiently with DBU in both cases to give **26a** or **26b**, respectively, ready for the coupling to the pyridine core fragment.

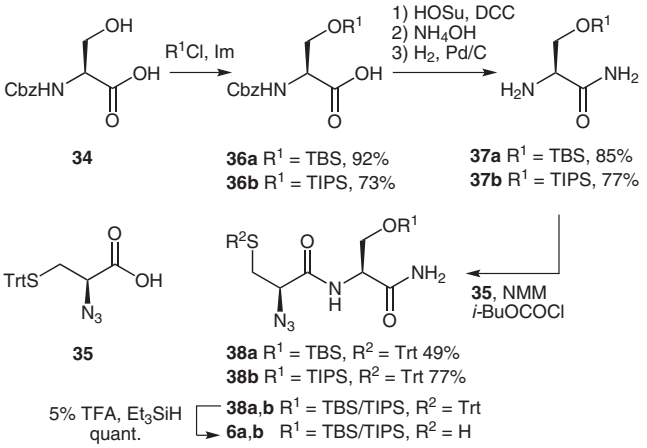
The synthesis of pyridine fragment **5** was reported previously starting from commercially available ethyl bromopyruvate.[21a] However, to render access to the necessary methyl ester containing building block more efficient and cost effective, some improvements to the previous route were developed (Scheme 5).



Scheme 5 Synthetic route to alkynylthiazole **33**

In order to access methyl bromopyruvate effectively, methyl L-lactate was oxidized and α-brominated with *N*-bromosuccinimide in carbon tetrachloride in one step.[30] We found this route superior to procedures starting from ethyl bromopyruvate[21a] or pyruvic acid.[31] Subsequently, a Hantzsch thiazole synthesis with thiourea gave 2-amiothiazole **30** after simple basic workup. It was found crucial to use methanol as the solvent to obtain high yields in this case.

Previously, dihalogenated products were difficult to suppress when using copper salts for the oxidative halogenation of aminothiazole **30**.[21a] It was then found that iodide **31** could be cleanly obtained after diazotization with *tert*-butyl nitrite and decomposition of the diazonium salt in situ in the presence of diiodomethane as a scavenger.[32] In the next step a Sonogashira coupling with 3-butyn-2-ol (**32**) gave alkynylthiazole **33** in good yield. All subsequent steps leading to pyridine fragment **5** were carried out according to the literature.[21a] The fully protected terminal dipeptide **6a** or **6b** was assembled starting from Cbz-protected serine (Scheme 6). Initially, TBS protection was planned for the serine side chain. Later it was found that its stability was not sufficient. In the first step the hydroxy function was protected as its silyl ether by modifying a reported procedure.[33] The L-serine derivatives were transformed to the corresponding terminal amides by using *N*,*N*′-dicyclohexylcarbodiimide facilitated coupling with *N*-hydroxysuccinimide, followed by exposure to aqueous ammonia. After hydrogenolysis of the Cbz group the free amine **37a** or **37b**, respectively, was coupled to azido acid **35** using isobutyl chloroformate and *N*-methylmorpholine as the base to activate the acid as a mixed anhydride.



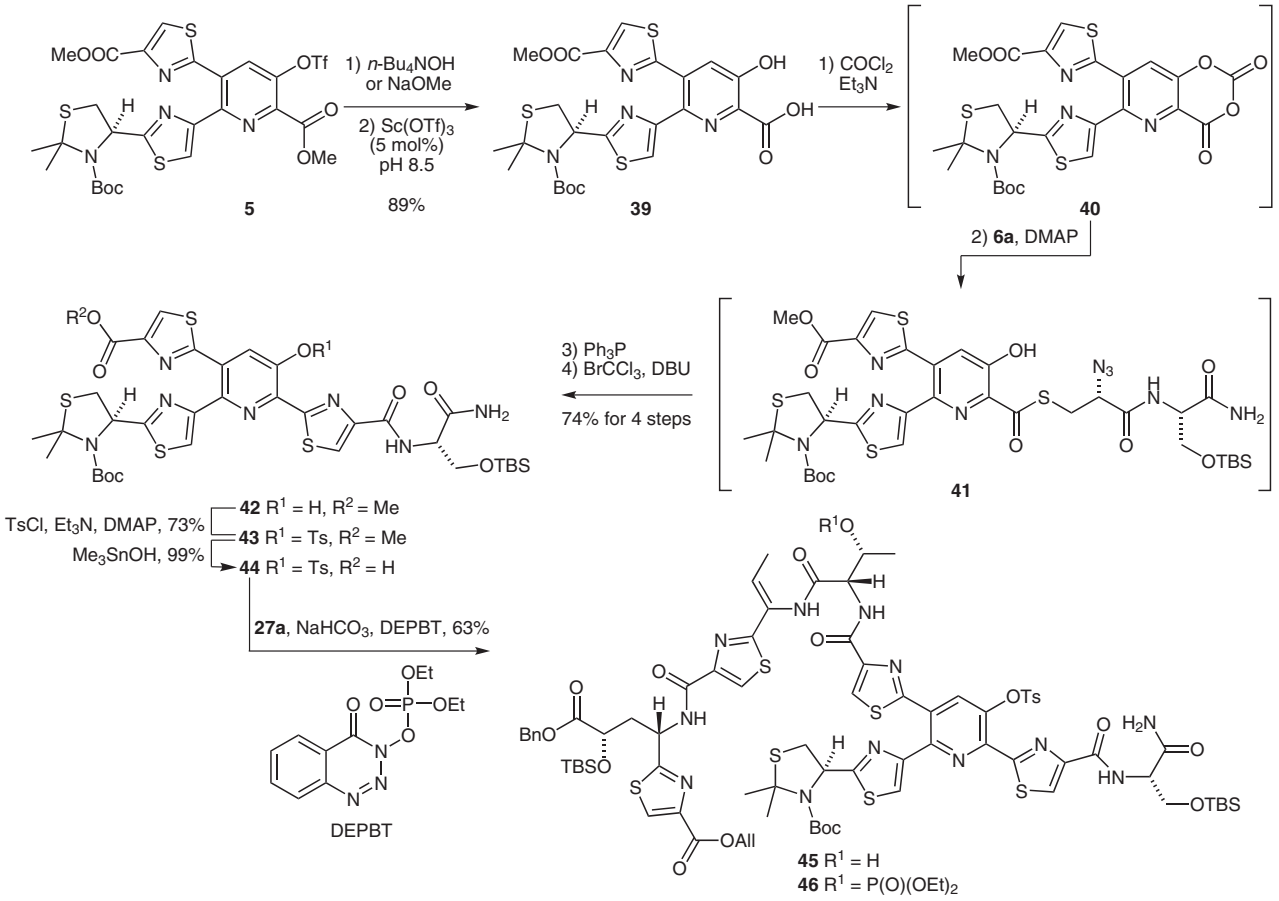
Scheme 6 Preparation of the tail dipeptide **6a** or **6b**

The thiol **6** could be released easily by acidic cleavage of the trityl group. However, the free thiol decomposed on silica gel and upon storage for more than a few hours. Therefore, it was always freshly prepared and immediately submitted to thioester formation.

In proceeding with the synthetic assembly it was necessary to saponify the methyl ester located at the pyridine ring in compound **5** (Scheme 7) regioselectively. In contrast to our expectation, selectivity could not be achieved by typical base-mediated saponification (LiOH, NH_4OH, pH 8.5–10). In order to render this transformation regioselective, we sought to engage the phenolic hydroxy substituent of the pyridine ring.

It was found that the triflate protecting group could be removed either with sodium methoxide or tetrabutylammonium hydroxide. After careful experimentation it was then found, that scandium(III) triflate induced hydrolysis conditions led to regioselective deprotection under very mild conditions with excellent yield, furnishing the free acid **39**. Activation of the carboxylic acid by forming a cyclic mixed anhydride **40** with phosgene and treatment with in situ prepared thiol **6a** provided thioester **41**. After immediate ring closure of the crude thioester by an intramolecular aza-Wittig reaction and oxidation, the tris(thiazolyl)pyridine **42** was obtained in very good yield (74% for 4 steps).

With this advanced intermediate in hand the fragment union with **26a** was addressed next. The methyl ester on



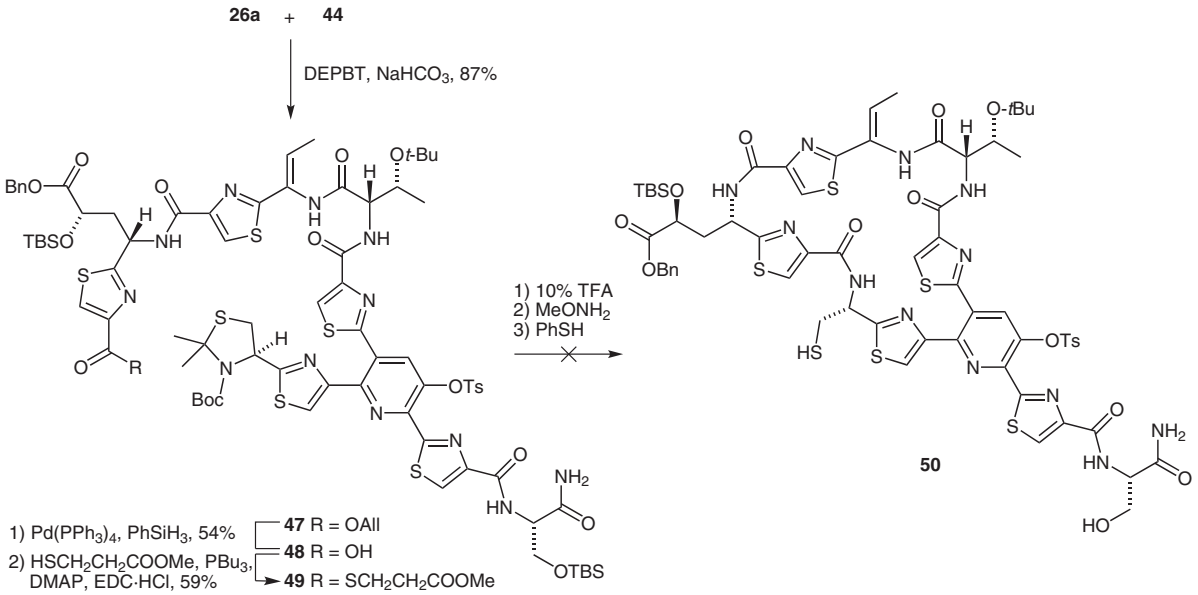
Scheme 7 Preparation of macrolactam precursor **45**

the thiazole ring in **42** could be cleaved with excess of lithium hydroxide. However, a variety of coupling attempts did not meet with success. To reduce the steric hindrance on the threonine residue in **26a**, the *tert*-butyl group was removed to give **27a**. This allowed coupling of the two fragments, but the purification proved to be very challenging even when preparative HPLC was used for chromatography. Intense investigations revealed that protection of the phenolic 3-hydroxy group in **42** was crucial for the success of the fragment union. After screening several alternative protective groups (R^1 = MOM, PMB, Bn, and mesitylsulfonyl), the Ts group was found to be suited to further investigations for the reasons of ease of introduction and stability. For ester cleavage, trimethyltin hydroxide[34] was found to be the only efficient reagent to give **44**. Among all the screened coupling reagents, 3-[(diethoxyphosphoryl)oxy]-1,2,3-benzotriazin-4(3*H*)-one (DEPBT)[35] was the most efficient, delivering amide **45** in good yield. A phosphorylated side product was observed as well, which most likely originates from a side reaction of DEPBT with the hydroxy group on the threonine residue **46**.[36]

Further experimentation revealed that DEPBT could even couple the amine **26a** with its 2′-hydroxy group *tert*-butyl protected to form the macrolactam precursor **47** with excellent yield (Scheme 8), if the 3′-hydroxy group in the core remained protected.

At this stage, its chemical structure featuring an N-terminal Cys-derived residue tempted us to explore ring closure of the nosiheptide A-ring by using a mild, native chemical ligation reaction of a C-terminal thioester.[37] Consequently, palladium(0)-catalyzed deallylation to give **48** and thioester formation were employed to convert allyl ester **47** into thioester **49**. Trifluoroacetic acid mediated removal of the Boc group and the ketal cleavage were then performed following a reported procedure.[38] However, no formation of macrocyclization product **50** could be observed upon neutralization of the reaction mixture, neither in the crude nor after work-up. Modifying the ligation conditions likewise did not meet with success.[39] Detailed analysis indicated firstly that the primary TBS ether was more labile than the Boc group. The secondary TBS ether and *tert*-butyl group were then consecutively cleaved when increasing the concentration of acid. However, the thiazolidine ketal that had been instrumental to suppress building block racemization remained intact under all of these conditions.

The unexpected stability of the thiazolidine coerced us to address its removal at an earlier stage. First pyridine **43** was chosen as a model substrate. Screening of deprotection conditions revealed that the primary TBS ether was cleaved every time prior to Boc and ketal group (Table 1), regardless of the method used. Trifluoroacetic acid cleav-

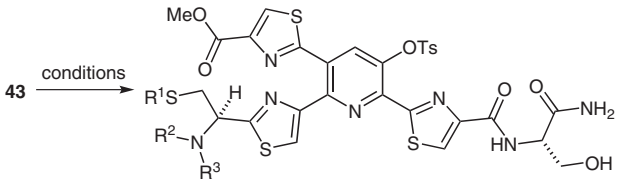


Scheme 8 Native chemical ligation approach to nosiheptide A-ring

age at low temperature gave alcohol **51** as the major product (entry 1). Elevation of the reaction temperature led to the fully deprotected pyridine **53** (entry 2). Interestingly, in the absence of any scavenger, the ketal could not be released even with higher concentrations of trifluoroacetic acid (entry 3). Changing the scavenger and low trifluoroacetic acid concentration resulted in a complex mixture (entry 4). Associating Lewis acids with trifluoroacetic acid[40] did not improve the low selectivity (entry 5 and 6). *tert*-Butyldimethylsilyl triflate[29] was not able to release the Boc group in this case (entry 7). In mildly acidic medium the TBS ether was cleaved selectively (entry 8 and 9), as well under one-electron oxidation conditions (entry 10), presumably mediated by the Lewis acidity of ceric ammonium nitrate. The combination of chlorotrimethylsilane and phenol[41] (entry 11) cleanly liberated the Boc group and the ketal group giving **53**; however, the large excess of phenol was exceedingly difficult to remove. Trials of orthogonal re-functionalization of pyridine **53** proved to be inefficient as a result of poor chemoselectivity.

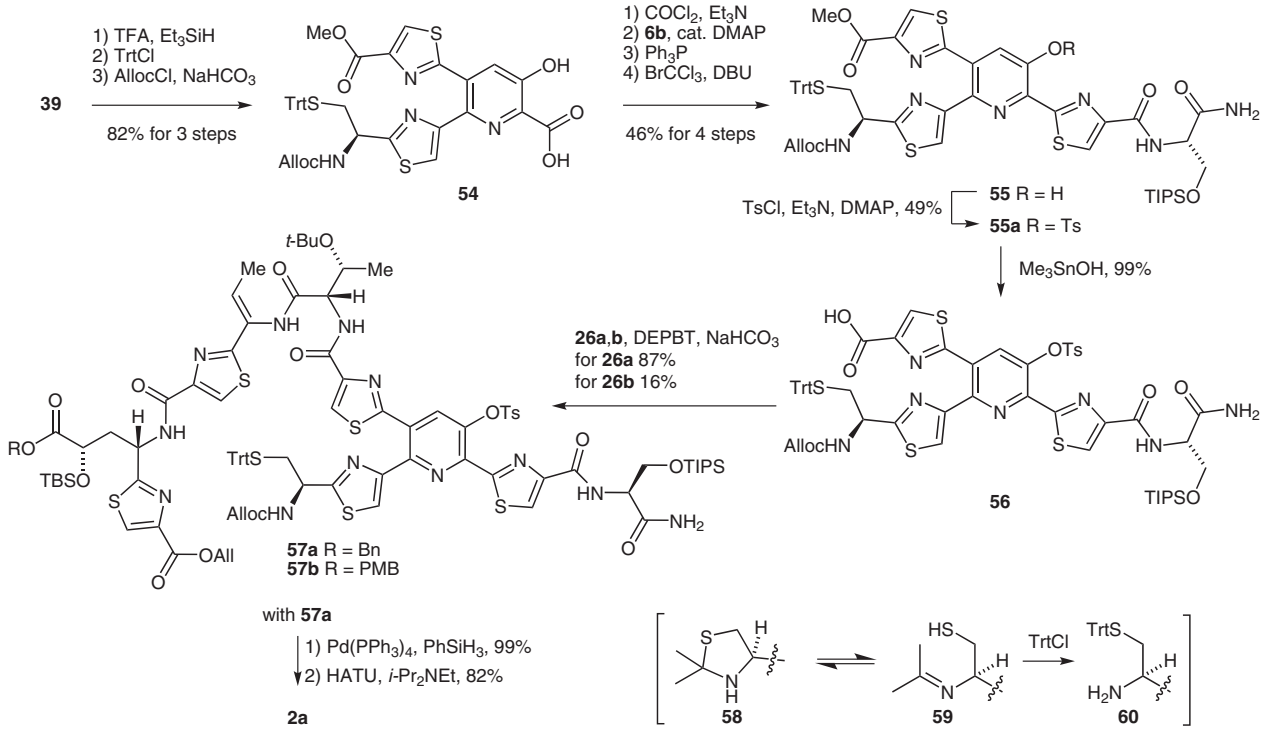
This setback forced us to adjust the synthetic plan at an earlier stage. Hence, the ketal was removed from acid **39** and the free amine and thiol functionalities were reprotected (Scheme 9). High concentration of trifluoroacetic acid assisted with silane scavenger to quench *t*-Bu cations was employed to deprotect the Boc and ketal groups. The Boc group was liberated after 30 minutes; however, the ketal group could not be removed even after excessive reaction time. It was then found that after exposing the crude product to S-tritylation conditions, the free amine could be isolated in pure form. We hypothesize that equilibration of thiazolidine **58** and its imine form **59** keeps the ketal bound to the aminothiol fragment. From the latter the free thiol might be trapped by trityl cation, driving the conversion and facilitating amine cleavage.

Table 1 Ketal Deprotection



Entry	Conditions	Major products
1	10% TFA–CH_2Cl_2, Et_3SiH, 0 °C, 2 h	**51**
2	20% TFA–CH_2Cl_2, Et_3SiH, r.t., 2 h	**53**
3	40% TFA–CH_2Cl_2, r.t.	**52**
4	5% TFA–CH_2Cl_2, $PhSiH_3$	**51** + **52** + **53**
5	$Hg(OOCCF_3)_2$, TFA, $PhSiH_3$, CH_2Cl_2	**51** + **52** + **53**
6	$AgBF_4$, TFA, anisole, CH_2Cl_2	**51** + **52** + **53**
7	TBSOTf, 2,6-lutidine, CH_2Cl_2	no conversion
8	PTSA, MeOH	**51**
9	HCl, 1,4-dioxane	**51**
10	CAN, MeCN	**51**
11	TMSCl, PhOH (3 M), CH_2Cl_2	**53**

Orthogonal protection of the amine as the allylcarbamate gave carboxylic acid **54** in excellent yield over three steps. Following the same procedure as for pyridine **42**, hy-



Scheme 9 Synthesis of nosiheptide A-ring **2a**

droxypyridine **55** was prepared featuring the more stable TIPS protection. Protection of the phenolic hydroxy group and liberation of the methyl ester furnished free acid **56**, which was coupled to the amine **26a** or **26b** by DEPBT-mediated peptide coupling. In case of **26a** the A-ring precursor was obtained in very good yield (87%). Much to our surprise the yield was considerably lower in case of PMB ester **26b** (16%, after preparative HPLC), not allowing to pursue its further elaboration.

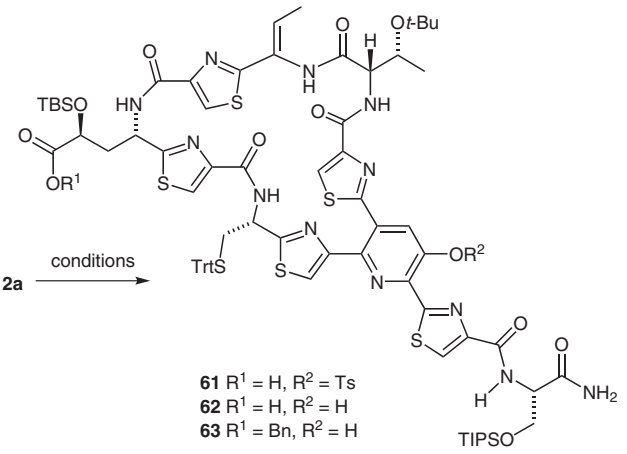
The allyl-based protecting groups could be cleaved cleanly with $Pd(PPh_3)_4$ and phenylsilane. It was found that slow addition of the ω-amino carboxylic acid in nonpolar solvent to a solution of coupling reagents gave the best and most consistent results. HATU-mediated macrolactam formation provided the nosiheptide A-ring **2a** with high efficiency (82%). These data indicated a favorable conformational preorganization in the ω-amino carboxylic acid cyclization precursor.[19]

With the A-ring **2a** in hand, the challenge of the B-ring was to be assembled next. For this purpose the benzyl ester needed to be removed in order to couple indolyl alcohol **3** to acid **61**. Representative results are summarized in Table 2. Unfortunately, no benzyl group liberation was observed varying the palladium source and scavenger[42] (entries 1–3). Stronger reductive conditions or oxidative cleavage with *N*-bromosuccinimide[43] led to decomposition of the starting material (entries 4 and 5).

No conversion was observed by applying 2,3-dichloro-5,6-dicyano-1,4-benzoquinone,[44] even at elevated temperature and prolonged reaction time (entry 6). The same was observed when Lewis acids[45] were employed (entries 7 and 8). Application of strong Lewis acid[46] decomposed the starting material (entry 9). Trimethyltin hydroxide removed selectively the sulfonate group (entry 10). Bases such as 1,4-diazabicyclo[2.2.2]octane[47] did not give any conversion at ambient temperature, but decomposed the A-ring **2a** at higher temperature (entry 11). Milder basic conditions could not remove any protecting group (entry 12), sodium hydroxide in mixed solvents cleanly cleaved the benzyl and tosyl group simultaneously (entry 13). Unfortunately, activation of the acid **62** under various conditions for ester formation with indole alcohol **3** did not meet with success. Apparently, the free 3-hydroxy group at the pyridine nucleus precludes proper acylation reactions.

In conclusion, we presented an efficient synthesis to the fully functionalized A-ring of nosiheptide **2a**. Aza-Wittig ring closures allowed the installation of challenging thiopeptide functionality, including peptide azoles. Furthermore, we developed highly efficient macrolactam formation conditions, a novel scandium(III)-mediated regioselective ester hydrolysis, and manipulation strategies for the nosiheptide A-ring featuring the unique 3-hydroxypyridine core. En route, an optimized protecting group strategy evolved. However, a sufficiently robust and orthogonal protecting group for the unique 3-hydroxypyridine needs to be developed to successfully complete a total synthesis of nosiheptide. These results will prove highly valuable for synthetic work of thiopeptides and guide future research directions in our laboratory.

Table 2 Debenzylation Trials[a]



61 R^1 = H, R^2 = Ts
62 R^1 = H, R^2 = H
63 R^1 = Bn, R^2 = H

Entry	Conditions	Result
1	$Pd(OAc)_2$, Et_3SiH, Et_3N, CH_2Cl_2, r.t.	decomposition
2	Pd black, HCO_2NH_4, EtOH, r.t.	no conversion
3	$Pd(OH)_2$, hexa-1,4-diene, EtOH, r.t.	no conversion
4	Raney Ni, H_2, EtOH, r.t.	decomposition
5	NBS, AIBN, CCl_4, reflux	decomposition
6	DDQ, 1,4-dioxane, 80 °C	no conversion
7	LiBr, Et_3N, THF, r.t.	no conversion
8	$AlCl_3$, anisole, CH_2Cl_2, –70 °C >–20 °C	no conversion
9	TMSCl, NaI, MeCN, r.t.	decomposition
10	Me_3SnOH, DCE, 80 °C	**63**
11	DABCO, toluene, 130 °C	decomposition
12	K_2CO_3, THF–H_2O, r.t.	no conversion
13	NaOH, MeOH–CH_2Cl_2, r.t.	**62**

[a] All reactions were performed on small scale (1 mg) under the conditions indicated with monitoring (TLC, LC-ESI-MS, MALDI-TOF) for 48 h or until conversion was complete.

All solvents, if not purchased in suitable purity or dryness, were distilled. Deionized water was used for all experiments. Thin-layer chromatography (TLC) was carried out on Merck precoated silica gel plates (60F-254) using ultraviolet light irradiation at 254 nm or $KMnO_4$ solution as staining reagent. Silica gel chromatography was performed using silica gel from J. T. Baker or Merck (particle size 40–60 μm) under approximately 0.5 bar pressure. ^1H and ^{13}C NMR spectra were recorded using a Varian Mercury 400 spectrometer. Fourier transform infrared spectroscopy (FT-IR) spectra were measured in a Bruker vector 22 with a diffuse reflectance head A527 from Spectra Tech (KBr as matrix) or a Shimadzu IRAffinity 1. Melting points were determined in a Büchi melting point B-540 apparatus in open capillaries (uncorrected). Electrospray mass spectrometric analyses (ESI-MS) were performed on a Finnigan LCQ spectrometer coupled to an Agilent 1100 HPLC system. Computed molecular masses were obtained using the software ChemDraw Ultra (CambridgeSoft Corporation) or Xcalibur. Optical rotations were measured in a Schmidt + Haensch Polartronic HH8 polarimeter at 589 nm. Concentrations are given in g/100 mL solvent. PE = light petroleum ether.[48]

General Procedure for Amide Bond Formation with EDC/HOBt (GP1)
Amine and carboxylic acid were dissolved in CH_2Cl_2 (0.1 M) and cooled to 0 °C, HOBt (1.5 equiv) and Et_3N (1.5 equiv, 3 equiv per amine hydrochloride) were added and stirred for 15 min, EDC·HCl (1.25 equiv) was added. The reaction mixture was slowly warmed to r.t. and stirred until conversion was complete (TLC monitoring).

General Procedure for Aza-Wittig Ring Closure (GP2)
The thioester was dissolved in anhyd THF (50 mM) and cooled to –20 °C. Ph_3P (1.5 equiv) in THF (0.5 M) was added dropwise and the reaction mixture was stirred until gas evolution ceased. The cooling bath was removed and the reaction mixture was then stirred at 40 °C (TLC monitoring). The solvent was removed and the resulting residue was purified by column chromatography (silica gel) to give the thiazoline.

General Procedure for Oxidation with DBU/$BrCCl_3$ (GP3)
Thiazoline was dissolved in anhyd CH_2Cl_2 (50 mM) and cooled to –20 °C. DBU (2.1 equiv) was added and the reaction mixture was stirred for 5 min. $BrCCl_3$ (1.05 equiv) was added dropwise and slowly warmed to r.t. (TLC monitoring). Aq HCl (0.1 N, 10 mL) was added and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic phase was dried with $MgSO_4$ and concentrated. Purification by column chromatography (silica gel) furnished the azole.

Alkenylthiazole 17
Procedure A: 2-Nitrophenyl selenocyanate (**16**, 571 mg, 2.5 mmol) was added to alcohol **15** (781 mg, 1.3 mmol) in THF at r.t., Bu_3P (0.64 mL, 2.5 mmol) was added dropwise and the mixture was stirred for 16 h. 35% H_2O_2 (0.5 mL) was added to the mixture and stirred for a further 30 min. The mixture was diluted with EtOAc (300 mL), and washed with phosphate buffer (pH 3.0, 50 mL) and brine (50 mL). The organic layer was dried ($MgSO_4$) and concentrated. Purification twice by column chromatography (silica gel, A: 100 g, PE–EtOAc, 4:1; B: 75 g, $CHCl_3$–MeOH, 40:1) gave **17** (680 mg, 1.1 mmol, 90%) as a dark yellow foam.

Procedure B: Freshly prepared CuCl (9.6 mg, 96.5 μmol) was added to a stirred soln of alcohol **15** (50 mg, 80.4 μmol) and EDC·HCl (31 mg, 160.8 μmol) in CH_2Cl_2 (500 μL) and DMF (20 μL). The mixture was stirred for 20 h and concentrated, and the residue was taken up in pH 3 buffer (15 mL) and extracted with EtOAc (3 × 15 mL). The combined organic fractions were dried (Na_2SO_4) and concentrated. Purification by column chromatography (silica gel, 10 g, PE–EtOAc, 2:1) gave **17** (36 mg, 60.3 μmol, 75%) as a colorless foam.

$[\alpha]_D^{20}$ +4.8 (*c* 1.0, $CHCl_3$); R_f = 0.30 (PE–EtOAc, 2:1).

IR (KBr): 3301 (br m), 2977 (m), 1716 (s), 1696 (s), 1505 (s), 1495 (s), 1451 (m), 1228 (s), 856 (s), 742 cm^{-1} (s).

^1H NMR (400 MHz, $CDCl_3$): δ = 1.21 (d, *J* = 6.4 Hz, 3 H, H4″), 1.34 [s, 9 H, $OC(CH_3)_3$], 1.86 (d, *J* = 7.2 Hz, 3 H, H3′), 4.23 (t, *J* = 7.1 Hz, 1 H, Fmoc), 4.29 (dd, *J* = 4.2, 6.3 Hz, 1 H, H3″), 4.41 (m, 3 H, Fmoc, H2″), 4.84 (d, *J* = 5.8 Hz, 2 H, $CH_2CH{=}CH_2$), 5.28 (dd, *J* = 1.3, 10.4 Hz, 1 H, CH=CH*H*), 5.40 (dd, *J* = 1.5, 17.2 Hz, 1 H, CH=C*H*H), 6.03 (m, 2 H, NH, C*H*=CH_2), 6.60 (q, *J* = 7.1 Hz, 6.4. 1 H, H2′), 7.61 (d, *J* = 7.4 Hz, 2 H, Fmoc), 7.44–7.27 (m, 4 H, Fmoc), 7.76 (d, *J* = 7.3 Hz, 2 H, Fmoc), 8.09 (s, 1 H, H5), 8.75 (s, 1 H, NH).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 14.4, 17.2, 28.4, 47.4, 59.2, 66.1, 67.0, 67.2, 76.3, 119.0, 120.2, 125.3, 126.3, 127.3, 127.9, 128.4, 132.1, 141.5, 143.9, 144.1, 147.3, 156.3, 161.1, 167.4, 168.3.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{33}H_{38}N_3O_6S$: 604.2476; found: 604.2472.

Azido Thioester 23a

Freshly activated Zn powder[49] (2.0 g, 30.7 mmol) was added to diester **22a** (515 mg, 0.86 mmol) in THF (35 mL) and 1 M KH_2PO_4 (5 mL) was added. The mixture was sonicated for 16 h, filtered on a sintered filter and concentrated to remove all THF. The aqueous phase was dissolved in 5% citric acid soln and extracted with Et_2O (3 × 50 mL). The combined organic phases were washed with sat. NaCl (30 mL) and dried ($MgSO_4$). Concentration and purification by column chromatography (silica gel, 50 g, $CHCl_3$–MeOH, 15:1) gave the acid (341 mg, 0.73 mmol, 85%) as a colorless gum.

$[\alpha]_D^{20}$ –25.7 (*c* 1.0, $CHCl_3$); R_f = 0.25 ($CHCl_3$–MeOH, 12:1).

IR (KBr): 2957 (w), 2858 (w), 1731 (s), 1715 (s), 1505 (m), 1394 (m), 1368 (m), 1166 (s), 840 cm^{-1} (s).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.02 [s, 3 H, $Si(CH_3)_2$], 0.88 [s, 9 H, $SiC(CH_3)_3$], 1.42 [s, 9 H, $CO_2C(CH_3)_3$], 2.23–2.09 (m, 1 H, H3), 2.30 (dd, *J* = 6.8, 14.5 Hz, 1 H, H3), 4.46–4.33 (m, 2 H, H2, H4), 5.15 (s, 2 H, CH_2Ph), 5.46 (d, *J* = 7.2 Hz, 1 H, NH), 7.40–7.30 (m, 5 H, Ph).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = –5.4, –4.9, 18.3, 25.9, 28.5, 36.0, 51.2, 67.2, 69.8, 80.6, 128.7, 128.8, 135.4, 156.3, 172.9, 176.6.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{23}H_{37}NO_7SiNa$: 490.2232; found: 490.2227.

Anal. Calcd for $C_{23}H_{37}NO_7Si$: C 59.1; H 8.0; N 3.0. Found: C 58.8; H 8.0; N 2.6.

Et_3SiH (0.52 mL, 3.3 mmol) was added to allyl (*R*)-2-azido-3-(tritylthio)propanoate (1.29 g, 3.0 mmol) in CH_2Cl_2–TFA (20 mL, 9:1) and the mixture was stirred for 10 min at r.t. The volatiles were removed, and co-evaporated with toluene under high vacuum. The resulting free thiol was dissolved in CH_2Cl_2, treated with glutamic acid prepared above (1.18 g, 2.5 mmol), HOBt (574 mg, 3.8 mmol), Et_3N (0.52 mL, 3.8 mmol), and EDC·HCl (600 mg, 3.1 mmol) following GP1. Purification by column chromatography (silica gel, 150 g, PE–EtOAc, 9:1) gave **23a** (1.36 g, 2.1 mmol, 86%) as a colorless oil.

$[\alpha]_D^{20}$ –53.5 (*c* 2.0, $CHCl_3$); R_f = 0.50 (PE–EtOAc, 2:1).

IR (KBr): 3366 (br m), 3068 (w), 2931 (s), 2118 (s), 1505 (m), 1457 (m), 1392 (m), 1169 (m), 840 (s), 783 cm^{-1} (s).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.02, 0.04 [s, 3 H, $Si(CH_3)_2$], 0.90 [s, 9 H, $SiC(CH_3)_3$], 1.45 [s, 9 H, $CO_2C(CH_3)_3$], 2.32–2.00 (m, 2 H, H3′), 3.17 (dd, *J* = 7.9, 13.9 Hz, 1 H, CH*H*S), 3.35 (dd, *J* = 5.4, 13.8 Hz, 1 H, C*H*HS), 4.06 (dd, *J* = 5.4, 7.9 Hz, 1 H, CHN_3), 4.37 (dd, *J* = 3.0, 8.9 Hz, 1 H, H2′), 4.46 (td, *J* = 3.8, 8.7 Hz, 1 H, H4), 4.76–4.62 (m, 2 H, $CH_2CH{=}CH_2$), 5.14 (s, 2 H, CH_2Ph), 5.43–5.22 (m, 2 H, $CH{=}CH_2$), 5.55 (d, *J* = 7.9 Hz, 1 H, NH), 5.92 (ddt, *J* = 5.8, 10.4, 16.2 Hz, 1 H, $CH{=}CH_2$), 7.40–7.30 (m, 5 H, Ph).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = –5.3, –4.8, 18.3, 25.9, 28.5, 30.3, 36.5, 58.4, 61.5, 66.9, 67.3, 69.7, 80.7, 119.7, 128.8, 131.3, 135.4, 155.3, 168.4, 172.6, 200.8.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{29}H_{45}N_4O_8SSi$: 637.2722; found: 637.2719.

Thiazole 24a

The crude thiazoline was obtained by GP2 from thioester **23a** (859 mg, 1.3 mmol) and Ph_3P (530 mg, 2.0 mmol). After removal of the volatiles, the residue was oxidized with DBU (0.6 mL, 4.0 mmol) and $BrCCl_3$ (0.2 mL, 2.0 mmol) following GP3. Purification by column chromatography (silica gel, 150 g, PE–EtOAc, 6:1) gave **24a** (735 mg, 1.2 mmol, 92%) as a colorless oil.

$[\alpha]_D^{20}$ –33.4 (*c* 1.0, $CHCl_3$); R_f = 0.27 (PE–EtOAc, 4:1).

IR (KBr): 3355 (w), 3093 (w), 2931 (m), 2858 (w), 1715 (s), 1505 (m), 1367 (m), 1174 (m), 840 cm^{-1} (s).

^{1}H NMR (400 MHz, $CDCl_3$): δ = –0.02, 0.00 [s, 3 H, $Si(CH_3)_2$], 0.89 [s, 9 H, $SiC(CH_3)_3$], 1.42 [s, 9 H, $CO_2C(CH_3)_3$], 2.45 (dd, *J* = 4.7, 8.3 Hz, 2 H, H2′), 4.43 (dd, *J* = 4.1, 8.2 Hz, 1 H, H3′), 4.83 (dt, *J* = 1.3, 5.8 Hz, 2 H, $CH_2CH{=}CH_2$), 5.23–5.05 (m, 3 H, H1′, CH_2Ph), 5.28 (dq, *J* = 1.2, 10.4 Hz, 1 H, CH=CH*H*), 5.39 (dq, *J* = 1.5, 17.2 Hz, 1 H, CH=C*H*H), 5.81 (d, *J* = 7.8 Hz, 1 H, NH), 6.01 (ddt, *J* = 5.8, 10.4, 16.2 Hz, 1 H, $CH{=}CH_2$), 7.42–7.29 (m, 5 H, Ph).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = –5.3, –4.8, 18.3, 25.9, 28.5, 38.9, 50.5, 66.1, 67.2, 69.8, 80.4, 119.0, 127.9, 128.7, 128.8, 132.1, 135.4, 147.2, 155.3, 161.1, 172.8, 174.2.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{29}H_{43}N_2O_7SSi$: 591.2555; found: 591.2551.

Bisthiazole 4a

N-Boc-protected amine **24a** (325 mg, 0.55 mmol) was dissolved in CH_2Cl_2–TFA (5 mL, 7:3) with stirring for 1 h. Toluene was added and co-evaporated under high vacuum to completely remove TFA (2 × 10 mL). Amide formation following GP1 with the crude amine, carboxylic acid **18** (281 mg, 0.52 mmol), HOBt (120 mg, 0.78 mmol), Et_3N (0.11 mL, 0.78 mmol), and EDC·HCl (125 mg, 0.65 mmol) followed by after column chromatography purification (silica gel, 30 g, PE–EtOAc, 4:1) gave **4a** (312 mg, 0.30 mmol, 58%) as a colorless foam.

$[\alpha]_D^{20}$ +3.6 (*c* 1.0, $CHCl_3$); R_f = 0.19 (PE–EtOAc, 2:1).

IR (KBr): 3387 (br w), 2976 (m), 2857 (m), 1726 (s), 1696 (s), 1532 (m), 1488 (s), 1228 (s), 813 (s), 758 cm^{-1} (m).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.00, 0.01 [s, 3 H, $Si(CH_3)_2$], 0.89 [s, 9 H, $SiC(CH_3)_3$], 1.20 (d, *J* = 6.4 Hz, 3 H, H4‴), 1.35 [s, 9 H, $OC(CH_3)_3$], 1.88 (d, *J* = 7.2 Hz, 3 H, H3‴), 2.78–2.61 (m, 2 H, H2′), 4.32–4.23 (m, 2 H, H3‴, Fmoc-CH), 4.47–4.41 (m, 3 H, Fmoc-CH2, H2‴), 4.49 (dd, *J* = 4.6, 8.1 Hz, 1 H, H3′), 4.85 (dt, *J* = 1.4, 5.8 Hz, 2 H, $CH_2CH{=}CH_2$), 5.09 (d, *J* = 12.1 Hz, 1 H, CH*H*Ph), 5.14 (d, *J* = 12.1 Hz, 1 H, C*H*HPh), 5.30 (dq, *J* = 1.2, 10.4 Hz, 1 H, CH=CH*H*), 5.41 (dq, *J* = 1.5, 17.2 Hz, 1 H, CH=C*H*H), 5.75 (td, *J* = 5.1, 8.9 Hz, 1 H, H1′), 6.04–5.98 (m, 2 H, $CH{=}CH_2$, Fmoc-NH), 6.70 (q, *J* = 7.1 Hz, 1 H, H2‴), 7.38–7.29 (m, 7 H, Fmoc, Ph), 7.42 (t, *J* = 7.5 Hz, 2 H, Fmoc), 7.62 (d, *J* = 7.3 Hz, 2 H, Fmoc), 7.78 (d, *J* = 7.5 Hz, 2 H, Fmoc), 7.95 (d, *J* = 8.8 Hz, 1 H, 1′-NH), 8.06 (s, 1 H, H5″), 8.12 (s, 1 H, H5), 8.67 (s, 1 H, 1‴-NH).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = –5.2, –4.8, 14.3, 17.2, 18.4, 25.9, 28.5, 39.3, 47.4, 47.9, 59.1, 66.1, 67.0, 67.2, 67.3, 69.5, 76.4, 119.0, 120.2, 123.8, 125.3, 126.6, 127.3, 128.0, 128.1, 128.3, 128.6, 128.8, 132.1, 135.5, 141.6, 143.9, 147.0, 149.7, 156.3, 160.9, 161.1, 167.2, 168.4, 171.9, 173.0.

HRMS (ESI): *m*/*z* $[M + H]^+$calcd for $C_{54}H_{66}N_5O_{10}S_2Si$: 1036.4015; found: 1036.4031.

Benzyl Ester 57a

The free amine **26a** (32 mg, 39 μmol) was added to the stirred soln of free acid **56** (64 mg, 52 μmol), DEPBT (74 mg, 0.25 mmol) and $NaHCO_3$ (40 mg, 0.48 mmol) in anhyd THF (0.5 mL), the mixture was stirred for 19 h at r.t. (TLC monitoring). The mixture was diluted with pH 7.0 phosphate buffer (20 mL) and extracted with CH_2Cl_2 (3 × 30 mL), and the combined organic layers were dried (Na_2SO_4) and concentrated. Purification by column chromatography (silica gel, 20 g, CH_2Cl_2–MeOH, 50:1) gave the coupling product **57a** (69 mg, 34 μmol, 87%) of as a colorless glass, suitable for further elaboration. Rigorous purification by preparative HPLC gave the coupling product (37.7 mg, 19 μmol, 47%) as a colorless glass.

$[\alpha]_D^{20}$ +4.8 (*c* 0.8, $CHCl_3$); R_f = 0.59 (CH_2Cl_2–MeOH, 10:1).

^{1}H NMR (400 MHz, CD_3OD): δ = –0.05 (s, 3 H, TBS), –0.03 (s, 3 H, TBS), 0.85 (s, 9 H, TBS), 1.08, 1.10 (21 H, TIPS), 1.26 (t, *J* = 4.6 Hz, 3 H, CH_3), 1.32 (s, 9 H, *t*-Bu), 1.90 (d, *J* = 7.2 Hz, 3 H, CH_3), 2.29 (s, 3 H, CH_3), 2.65 (dd, *J* = 8.0, 5.2 Hz, 3 H, CH, CH_2), 2.73 (dd, *J* = 9.0, 5.6 Hz, 1 H, CH), 4.15 (dd, *J* = 5.2 Hz, 1 H, CH_2),

4.24 (dd, J = 4.7 Hz, 1 H, CH_2), 4.37 (dd, J = 4.7, 1.7 Hz, 1 H, CH), 4.52 (dd, J = 5.3, 2.9 Hz, 4 H, 2 $CH_2CH{=}CH_2$), 4.69 (dd, J = 4.6, 3.3 Hz, 1 H, CH), 4.74 (dd, J = 8.2, 3.0 Hz, 1 H, CH), 4.79 (d, J = 5.4 Hz, 2 H, CH_2), 5.09 (s, 2 H, CH_2Ph), 5.17 (d, J = 10.3 Hz, 1 H, $CH_2CH{=}CH_2$), 5.25 (d, J = 10.6 Hz, 1 H, $CH_2CH{=}CH_2$), 5.30 (d, J = 17.9 Hz, 1 H, $CH_2CH{=}CH_2$), 5.38 (dd, J = 17.2, 1.4 Hz, 1 H, $CH_2CH{=}CH_2$), 5.69 (dd, J = 5.7, 3.1 Hz, 1 H, CH), 5.87–5.92 (m, 1 H, $CH_2CH{=}CH_2$), 5.98–6.05 (m, 1 H, $CH_2CH{=}CH_2$), 6.80 (dd, J = 7.3 Hz, 1 H, $CHCH_3$), 7.15–7.34 (m, 22 H, trityl, Ph, tosyl), 7.69 (d, J = 8.1 Hz, 2 H, tosyl), 7.99 (s, 1 H, CH), 8.11 (s, 1 H, CH), 8.18 (s, 1 H, CH), 8.25 (s, 1 H, CH), 8.28 (s, 1 H, CH), 8.32 (s, 1 H, CH), 8.49 (d, J = 8.0 Hz, 1 H, NH).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = –5.4, –5.1, 1.0, 11.8, 14.05, 14.09, 14.11, 14.14, 17.92, 17.94, 21.6, 25.7, 28.3, 29.7, 36.81, 36.82, 39.0, 47.7, 52.0, 54.7, 63.5, 65.89, 65.93, 66.4, 66.9, 67.5, 69.3, 117.9, 118.8, 122.1, 123.5, 126.1, 126.4, 126.9, 127.2, 127.5, 127.69, 127.74, 127.9, 128.09, 128.15, 128.2, 128.4, 128.5, 128.6, 129.5, 129.7, 130.1, 131.8, 132.6, 133.1, 133.66, 133.67, 133.71, 135.3, 135.6, 135.68, 135.70, 137.7, 141.9, 144.26, 144.32, 146.0, 146.8, 148.96, 148.99, 149.6, 151.4, 151.76, 151.78, 156.8, 160.6, 160.8, 161.1, 164.6, 171.7, 172.8.

HRMS (ESI): m/z [M + 2 H]$^{2+}$ calcd for $C_{99}H_{118}N_{12}O_{17}S_7Si_2$: 1013.3155; found: 1013.3174.

Nosiheptide A-Ring 2a

$Pd(PPh_3)_4$ (2.1 mg, 1.8 μmol) in anhyd CH_2Cl_2 (400 μL) was added to a soln of pyridine **57a** (17.9 mg, 8.8 μmol) and $PhSiH_3$ (6 μL, 45 μmol) in anhyd CH_2Cl_2 (3 mL) at r.t. The resulting mixture was stirred for 10 min (TLC monitoring). Toluene (3 mL) was added to the mixture. The solvents and volatiles were removed under reduced pressure. Purification by column chromatography (silica gel, 8 g, CH_2Cl_2–MeOH, 20:1) gave the amino acid (16.7 mg, 8.8 μmol, 99%) as a yellow resin. The amino acid was not stable upon storage and had to be used immediately for further transformations.

R_f = 0.2 (CH_2Cl_2–MeOH, 10:1).

HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{92}H_{109}N_{12}O_{15}S_7Si_2$: 1901.5713; found: 1901.5721.

The amino acid so obtained (29.0 mg, 15.0 μmol) was dissolved in CH_2Cl_2 (2 mL) and added dropwise by syringe pump to HATU (11.6 mg, 30.0 μmol) and i-Pr_2NEt (10 μL, 61 μmol) in CH_2Cl_2 (15 mL) and DMF (1.0 mL) at r.t. over a period of 2 h. Stirring was continued for a further 10 h. The reaction was diluted with phosphate buffer (pH 7.0, 15 mL) and EtOAc (150 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were washed with sat. NaCl soln (15 mL), dried (Na_2SO_4), and concentrated. Purification by column chromatography (silica gel, 10 g, CH_2Cl_2–MeOH, 100:1 to 20:1) yielded macrolactam **2a** (23.6 mg, 13.0 μmol, 82%) as a colorless resin. Purification by preparative HPLC of another batch prepared from amino acid (16.7 mg) gave **2a** (9.2 mg, 4.9 μmol, 56%) as a colorless resin.

$[\alpha]_D^{20}$ +27.3 (c 0.15, $CHCl_3$); R_f = 0.56 (CH_2Cl_2–MeOH, 10:1).

IR (KBr): 3447 (br), 2923 (s), 2361 (s), 1699 (s), 1654 (s), 1647 (s), 1570 (s), 1523 (s), 1458 (s), 1104 (s), 799 cm^{-1} (s).

^{1}H NMR (400MHz, DMSO): δ = –0.07 (s, 3 H, TBS), –0.01 (s, 3 H, TBS), 0.81 (s, 9 H, TBS), 1.01, 1.02 (21 H, TIPS), 1.23 (s, 9 H, t-Bu), 1.33 (d, J = 6.1 Hz, 3 H, CH_3), 1.79 (d, J = 6.9 Hz, 3 H, $CHCH_3$), 2.00 (dd, J = 7.8 Hz, 2 H, CH_2), 2.29 (d, J = 6.6 Hz, 3 H, CH_3), 2.29 (s, 3 H, CH_3), 2.91 (dd, J = 6.6 Hz, 1 H, CH), 4.01–4.10 (m, 2 H, CH_2), 4.22 (dd, J = 5.5 Hz, 1 H, CH), 4.39 (dd, J = 5.9 Hz, 1 H, CH), 4.52 (dd, J = 10.0 Hz, 1 H, CH), 4.61 (d, J = 4.5 Hz, 1 H, CH), 4.81 (t, J = 7.4 Hz, 1 H, CH), 5.54 (t, J = 7.0 Hz, 1 H, CH), 6.45 (dd, J = 6.9 Hz, 1 H, $CHCH_3$), 7.21–7.31 (m, 22 H, trityl, Ph, tosyl), 7.61 (s, 2 H, CH_2Ph), 7.68 (d, J = 8.5 Hz, 1 H, NH), 7.70 (d, J = 8.6 Hz, 2 H, tosyl), 7.79 (d, J = 6.5 Hz, 1 H, NH), 7.97 (d, J = 8.4 Hz, 2 H, 2 NH), 8.10 (s, 1 H, CH), 8.21 (s, 2 H, 2 CH), 8.24 (s, 2 H, 2 CH), 8.31 (s, 1 H, NH), 8.42 (s, 1 H, CH), 9.17 (s, 1 H, NH_2), 9.68 (s, 1 H, NH_2).

HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{92}H_{107}N_{12}O_{14}S_7Si_2$: 1883.5608; found: 1883.5611.

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