

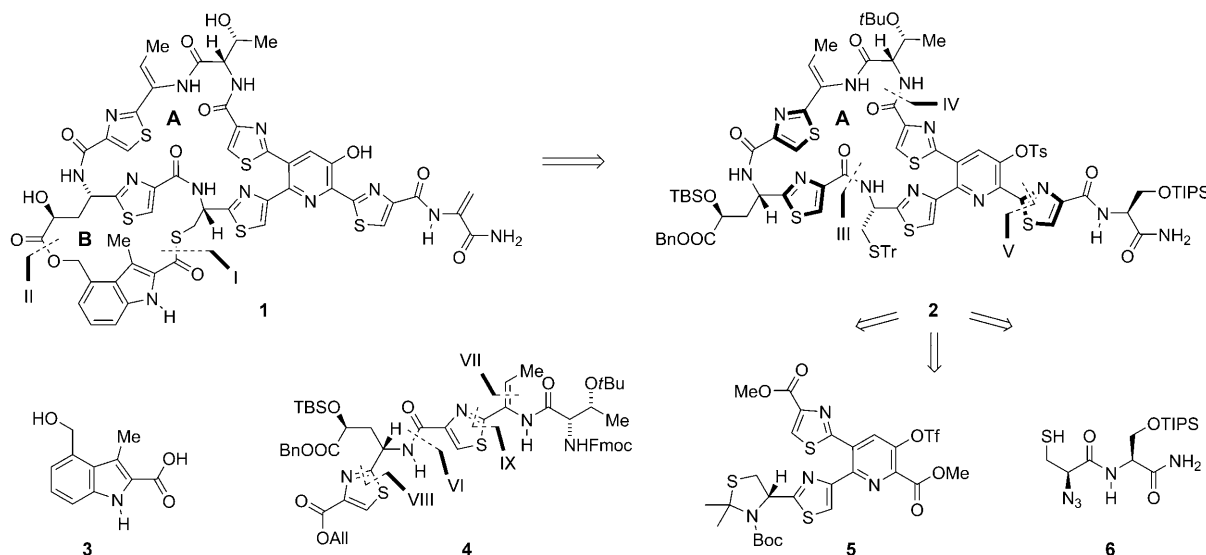
Aza-Wittig-Supported Synthesis of the A Ring of Nosiheptide**

Jin-Yong Lu, Matthias Riedrich, Martin Mikyna, and Hans-Dieter Arndt*

In the constant quest for lead molecules to combat infectious diseases,^[1] a promising class of natural products not used for human therapy are the thiopeptide antibiotics.^[2] These heterocycle-rich molecules are biosynthesized from linear ribosomal peptides^[3] and block the biosynthesis of the bacterial protein very efficiently.^[2,4] The bismacrocyclic nosiheptide (**1**; Scheme 1) stands out among them as having the highest potency against multidrug-resistant *S. aureus* (MRSA) strains.^[4d,5,6] Derivatives of **1** with improved biological properties have been identified,^[7] but most synthetic studies have focused on the preparation of small frag-

ments.^[8,9] Notably, a study on the thioester-containing B-ring of **1** was recently reported.^[10] Herein, we describe the synthesis of the fully functionalized A ring of **1** by using aza-Wittig transformations.^[11,12]

Nosiheptide (**1**) is distinguished from other thiopeptide natural products^[2] by an indolic acid macrothiolactone group which forms the smaller B ring ("southern hemisphere"),^[10] and by a peculiar 3-hydroxypyridine group in the larger A ring ("northern hemisphere").^[10] Retrosynthetic disconnection of the indole **3**^[8d] (I, II) and introduction of latent functionality and protecting groups leads to the A-ring



Scheme 1. Retrosynthetic analysis of nosiheptide (**1**) by thioesterifications (I/II), macrolactam formation (III/IV) and aza-Wittig ring closures (V, VIII, IX; rings in bold); Bn = benzyl, Boc = *tert*-butoxycarbonyl, Fmoc = 9-fluorenylmethyloxycarbonyl, TBS = *tert*-butyldimethylsilyl, TIPS = triisopropylsilyl, Tf = trifluoromethylsulfonyl, Tr = triphenylmethyl, Ts = 4-toluenesulfonyl.

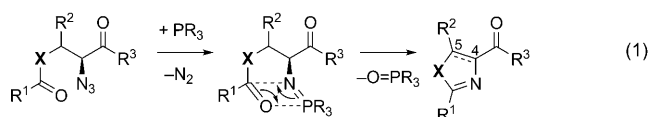
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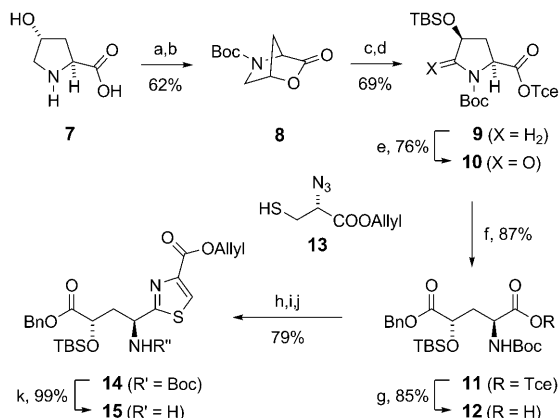
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scaffold **2** as a key synthetic target. We sought to disconnect the A ring into three fragments (III, IV, V): The thiazole segment **4**, the 3-hydroxypyridine core **5**, and the dipeptide side chain **6**. Compound **4** should be available from two smaller building blocks (VI), and elimination of a side chain could deliver the enamide (VII). We have shown before that 1-azadiene cycloadditions efficiently furnish functionalized 3-hydroxypyridines such as **5**.^[13] The dipeptide **6** is easily available.^[14] Overall, three aza-Wittig ring closures (V, VIII, IX) were planned for introducing the thiazole rings. In this synthesis design we planned to make ideal use of the mild aza-Wittig reaction, which is an acid- and base-free kinetic condensation reaction mediated by an intermediate imino-phosphorane [Eq. (1)].^[11,12] Liberal selection of the heteroatom (X = O, S, NR)^[12] as well as the degree of oxidation in the ring (4,5-H₂ or 4,5-Δ)^[12] would offer additional flexibility.



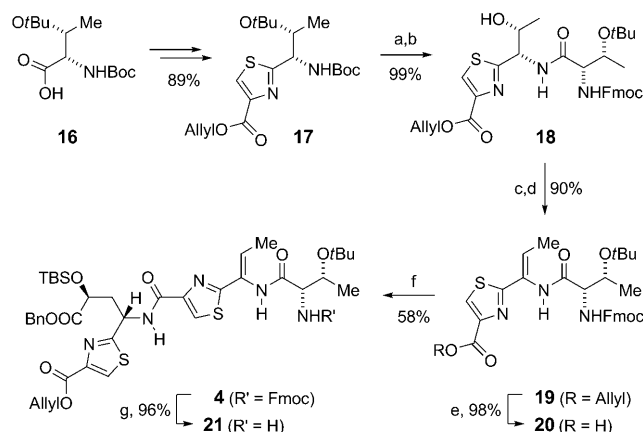
The synthesis began with *trans*-4-hydroxyproline **7** (Scheme 2), which was protected at the nitrogen atom by a Boc group and then transformed under Mitsunobu conditions^[15] into the crystalline bicyclic lactone **8** with an inverted



Scheme 2. Synthesis of thiazole amine **15**. Reagents and conditions: a) Boc_2O , 10% K_2CO_3 , 1,4-dioxane, $0 \rightarrow 20^\circ\text{C}$, 8 h; b) diisopropylazodicarboxylate (1.1 equiv), PPh_3 (1 equiv), THF, 0°C , 4 h; c) TceOH (4 equiv), NaH, THF, -78°C , 1 h; d) TBSCl, DMF, 20°C , 6 h; e) RuCl_3 (1 mol %), NaIO_4 (3 equiv), $\text{CCl}_4/\text{CH}_3\text{CN}/\text{H}_2\text{O}$ (1:9:15), 0°C , 8 h; f) BnOH , NaH, THF, -78°C ; g) Zn^0 , THF, NaH_2PO_4 (20 mM, pH 7.0), ultrasound, 16 h; h) EDC, HOBT, **13**, CH_2Cl_2 , 0°C , 2 h; i) PPh_3 , THF, $-20 \rightarrow 20^\circ\text{C}$, 4 h; j) BrCCl_3 , DBU, CH_2Cl_2 , 4 h; k) TFA/ CH_2Cl_2 , 1:2, 0°C , 30 min. DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, DMF = *N,N*-dimethylformamide, EDC = *N*-ethyl-*N'*-(3-dimethylaminopropyl)carbodiimide, HOBT = 1-hydroxybenzotriazole, Tce = trichloroethyl, THF = tetrahydrofuran, TFA = trifluoroacetic acid.

configuration (62%). Compound **8** was transesterified with TceOH, protected with a TBS group ($\rightarrow$ **9**, 69%), and regioselectively oxidized to lactam **10** (76%) using a catalytic amount of RuO_4 .^[16] Ring opening of **10** was achieved with NaOBn at low temperature (87%). The resulting orthogonally protected 4-hydroxyglutamate **11** was converted into acid **12** by reduction with Zn^0 . Thioester formation with azidothiol **13**,^[12] aza-Wittig ring closure with PPh_3 , and oxidation delivered building block **14** in excellent yield and purity (79%, d.r. > 98:2), which was swiftly converted into the labile amine **15** by removal of the protecting groups.

Furthermore, threonine **16** was converted into thiazole **17** by using an aza-Wittig reaction (89%; Scheme 3).^[12] Removal of the *t*Bu and Boc groups and subsequent selective chain extension at the nitrogen atom was carried out on Fmoc-protected Thr using EDC/HOBT ($\rightarrow$ **18**, 99%). We found that the crucial enamide could be cleanly installed by using the method developed by Grieco et al. ($\rightarrow$ **19**, 90%).^[17] In contrast, activation of the OH group (Ms, Ts) and elimination (DBU, DMAP) gave **19** with inferior results. Palladium-

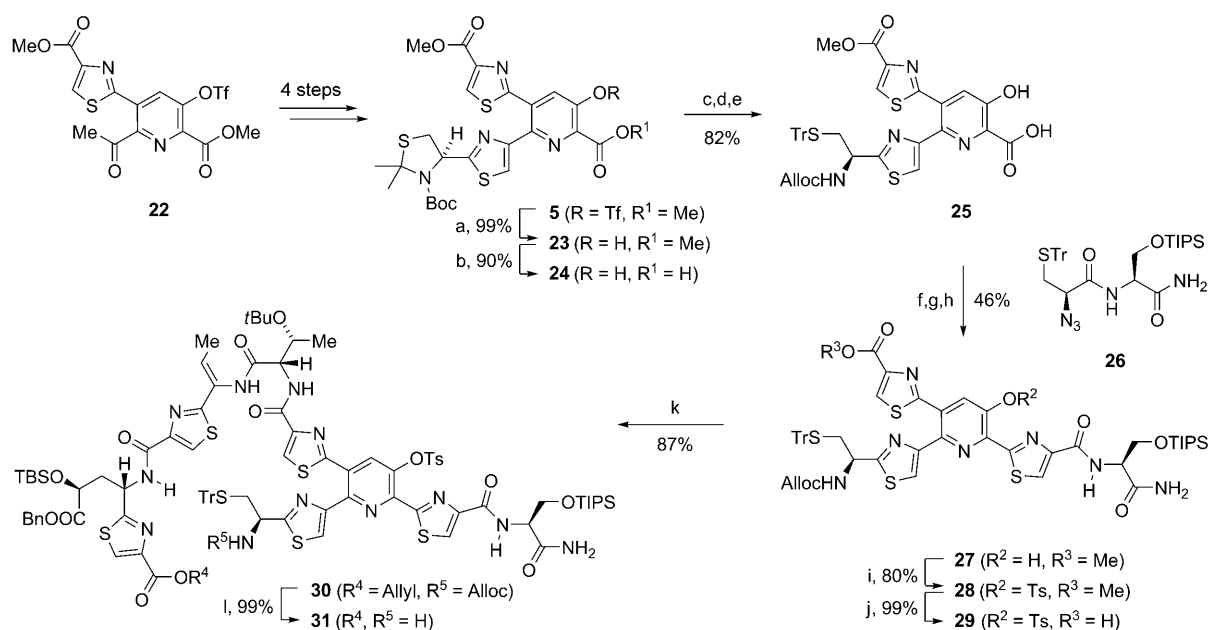


Scheme 3. Preparation of bithiazole peptide **21**. Reagents and conditions: a) TFA/ CH_2Cl_2 (1:1), $0 \rightarrow 20^\circ\text{C}$, 1 h; b) Fmoc(*t*Bu)ThrOH, EDC, HOBT, $\text{CH}_2\text{Cl}_2/\text{DMF}$ (10:1), $0 \rightarrow 20^\circ\text{C}$, 4 h; c) *o*- $\text{NO}_2\text{C}_6\text{H}_4\text{SeCN}$ (2 equiv), PBu_3 (2 equiv), CH_2Cl_2 , 20°C , 16 h; d) 1% H_2O_2 , 20°C , 30 min; e) $[\text{Pd}(\text{PPh}_3)_4]$, PhSiH_3 (2 equiv), CH_2Cl_2 , 20°C , 10 min; f) **15**, HOBT, EDC, $0 \rightarrow 20^\circ\text{C}$, 5 h; g) 1% DBU, 5% piperidine in CH_2Cl_2 , 0°C , 30 min; h) 50% TFA, $0 \rightarrow 20^\circ\text{C}$, 20 min.

mediated deallylation under neutral reaction conditions^[18] then provided acid **20**, which was coupled to amine **15** and delivered segment **4** (58%). Removal of the Fmoc group provided amine **21**, which was ready for extension (96%).

The hydroxyproline core was elaborated by a hetero-Diels–Alder cycloaddition.^[13] The regiochemistry was unequivocally established by X-ray crystal structure analysis of ketone **22**,^[14] which was then converted into bithiazolyl pyridine **5** by a racemization-free Hantzsch annelation (Scheme 4).^[13a] The hydrolysis of diester **5** initially proved nonselective under a variety of reaction conditions. We found, however, that catalytic amounts of $\text{Sc}(\text{OTf})_3$ ^[19] removed the methyl ester group on the pyridine ring selectively if a free hydroxy group at C3 was present (**23** $\rightarrow$ **24**).^[20] The synthesis was initially carried on with the mandatory^[13a] Boc-protected thioaminal group, but all attempts to unmask the cysteine residue at a later stage in the synthesis were unsuccessful. Therefore, the thioaminal **24** had to be cleaved at this stage. The free thiol was captured with TrCl, and an Alloc group was introduced on the nitrogen atom ($\rightarrow$ **25**, 82%).

To install the side chain, the hydroxy acid **25** was activated with phosgene and treated with peptide thiol **6**, which was prepared in situ from the stable peptide **26** (5% TFA, quant.). Immediate aza-Wittig ring closure gave the thiazoline, which was directly oxidized to the *tris*-thiazolyl pyridine **27** (46%, over 4 steps). Protection of the hydroxy group at C3 using a sulfonate group had to be carefully controlled ($\rightarrow$ **28**, 80% based on recovered starting material), then acid **29** was released using Me_3SnOH .^[21] Coupling of **29** to amine **21** proved challenging under many reaction conditions, but reliable transformation into **30** was achieved with DEPBT as the activating reagent (87%; 47% after preparative HPLC).^[22] Parallel removal of the allyl-based protecting groups could then be cleanly achieved—despite the sulfur-rich substrate **30**—with $\text{Pd}^0/\text{PhSiH}_3$ under neutral reaction conditions (99%).

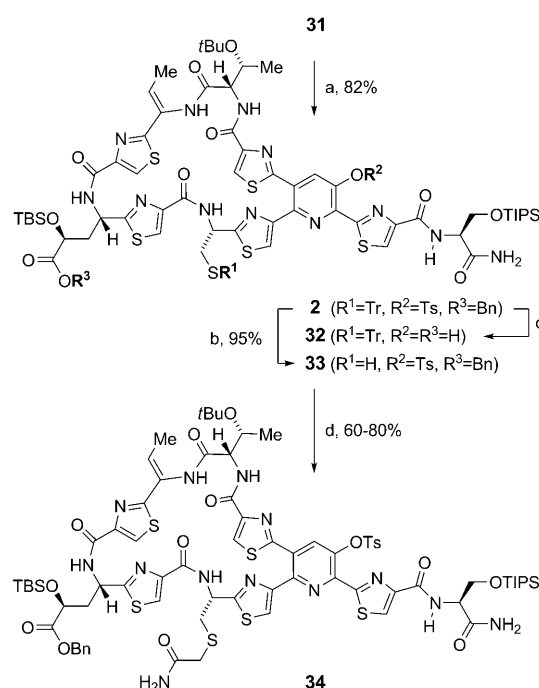


Scheme 4. Synthesis of peptide **31**. Reagents and conditions: a) (Bu₄N)OH (2 equiv), 1,4-dioxane, 20°C, 5 min; b) Sc(OTf)₃ (5 mol%), 1,4-dioxane/H₂O (3:1), pH 8.5, 60°C, 8 h; c) TFA/CH₂Cl₂/Et₃SiH (13:13:1), 20°C, 30 min; d) TrCl, DMF, 20°C, 14 h; e) AllocCl, NaHCO₃, THF/H₂O (5:1); f) COCl₂ (20% in toluene, 1.1 equiv), NEt₃, THF, -40°C, 2 h; then **6** (1.2 equiv), DMAP (0.1 equiv); g) PPh₃, THF, -20→40°C, 20 h; h) BrCCl₃, DBU, CH₂Cl₂, -20→20°C, 2 h; i) TsCl, NEt₃, DMAP (0.1 equiv), CH₂Cl₂, 0°C, 2 h; j) Me₃SnOH (9 equiv), 1,2-dichloroethane, 80°C, 4 h; k) DEPBT (3 equiv), NaHCO₃ (10 equiv), THF, **21**, 20°C, 19 h; l) PhSiH₃, [Pd(PPh₃)₄], CH₂Cl₂. Alloc = allyloxycarbonyl, DEPBT = 3-(diethoxyphosphoryloxy)-1,2,3-benzotriazin-4(3H)-one, DMAP = 4-dimethylaminopyridine.

The stage was now set for formation of the macrolactam (Scheme 5). In the event, HATU proved to be a superb mediator of this ring-closing reaction,^[23] but excess HOAt had to be minimized to avoid the formation of side products. The slow addition of amino acid **31** in nonpolar solvent gave the best results and consistently delivered the fully functionalized A ring **2** in excellent yield (82%; 56% after preparative HPLC). Notably, other cyclization strategies were less productive (data not shown), thus suggesting a very favorable conformational preorganization of **31**.

Preliminary deprotection studies of **2** showed that the thiol group could be cleanly unmasked (→**33**; Scheme 5). Alkylation delivered the stable thioether **34**. The silyl and *t*Bu groups could be removed under standard reaction conditions (HF/pyridine, 30% TFA), with removal of the TIPS group being the most labile. Removal of the TFA-stable Ts group was achieved in parallel to base-mediated cleavage of the Bn ester group (**32**). These results indicate that the A-ring scaffold **2** is suited well for access to nosiheptide (**1**) and its derivatives.

In summary, an efficient synthesis to the fully functionalized A Ring of nosiheptide (**1**) was presented. En route we have demonstrated that aza-Wittig ring closures allow challenging thiopeptide functionality to be mastered. A novel Sc^{III}-mediated regioselective ester hydrolysis, highly efficient formation of a macrolactam, and manipulation strategies for the A ring featuring the unique 3-hydroxypyridine nucleus have been developed. These results will prove highly valuable for the efficient synthesis of thiopeptides such as nosiheptide,^[5,7] and thus facilitate their further exploration.



Scheme 5. Manipulation of the A ring **2**. Reagents and conditions: a) HATU, Et₃NiPr₂, CH₂Cl₂/DMF (18:1), slow addition of **31** (0.8 mM final concentration); b) Et₃SiH, TFA/CH₂Cl₂ (1:19); c) NaOH (0.35 M) in CH₂Cl₂/MeOH (1:3); d) ICH₂CONH₂, DMF. HOAt = 1-hydroxy-7-azabenzotriazole, HATU = O-(7'-azabenzotriazol-1'-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate.

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