Natural Products

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

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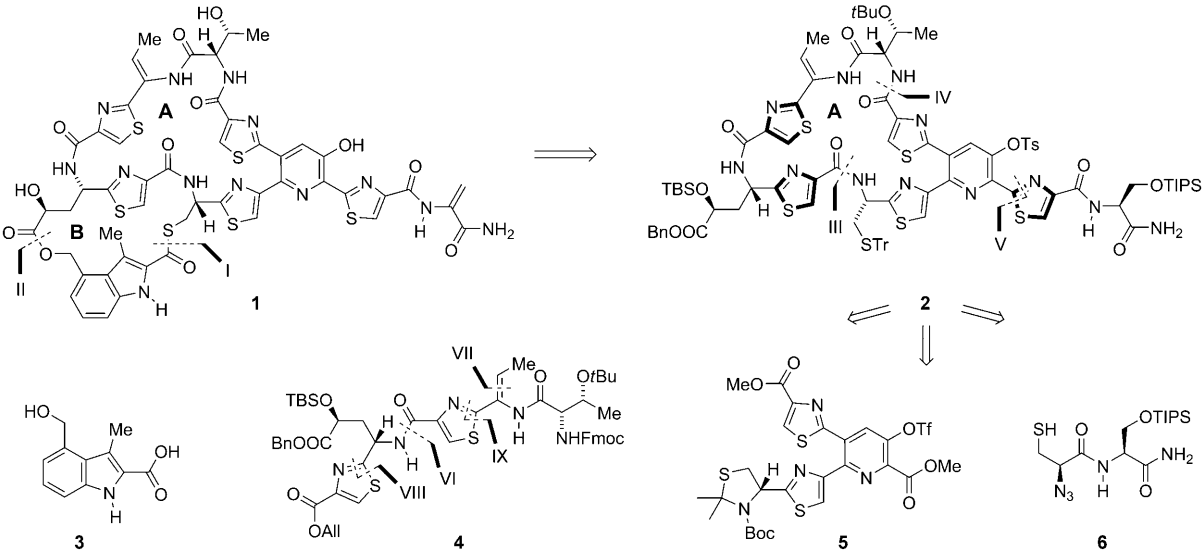
In the constant quest for lead molecules to combat infectious diseases,[1] a promising class of natural products not used for human therapy are the thiopeptide antibiotics.[2] These heterocycle-rich molecules are biosynthesized from linear ribosomal peptides[3] and block the biosynthesis of the bacterial 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 fragments.[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 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 iminophosphorane [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-H_2 or 4,5-Δ)[12] would offer additional flexibility.



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 = trifluormethylsulfonyl, Tr = triphenylmethyl, Ts = 4-toluenesulfonyl.

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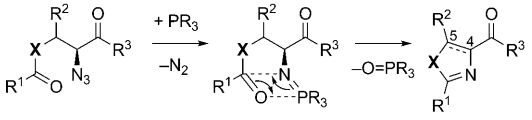
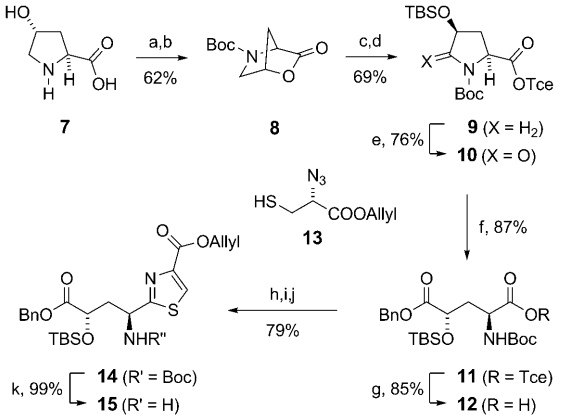


(1)

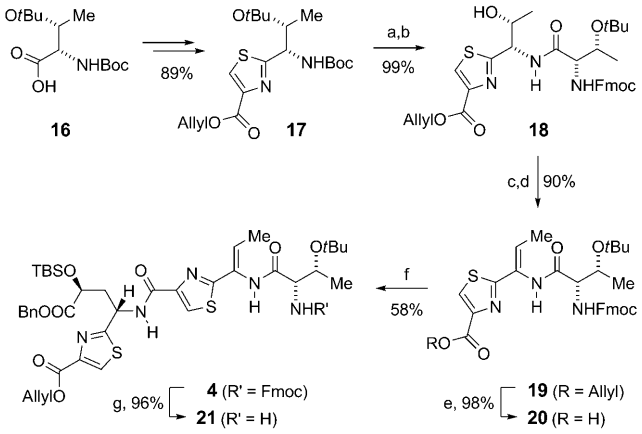
The synthesis began with *trans*-4-hydroxyproline **7** (Scheme 2), which was protected at the nitrogen atom by a Boc group and then transformed under Mitsunobu conditions[15] into the crystalline bicyclic lactone **8** with an inverted



Scheme 2. Synthesis of thiazole amine **15**. Reagents and conditions: a) Boc_2O, 10% K_2CO_3, 1,4-dioxane, 0→20°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), $CCl_4/CH_3CN/H_2O$ (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→20°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 (→**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 (→**18**, 99%). We found that the crucial enamide could be cleanly installed by using the method developed by Grieco et al. (→**19**, 90%).[17] In contrast, activation of the OH group (Ms, Ts) and elimination (DBU, DMAP) gave **19** with inferior results. Palladium-

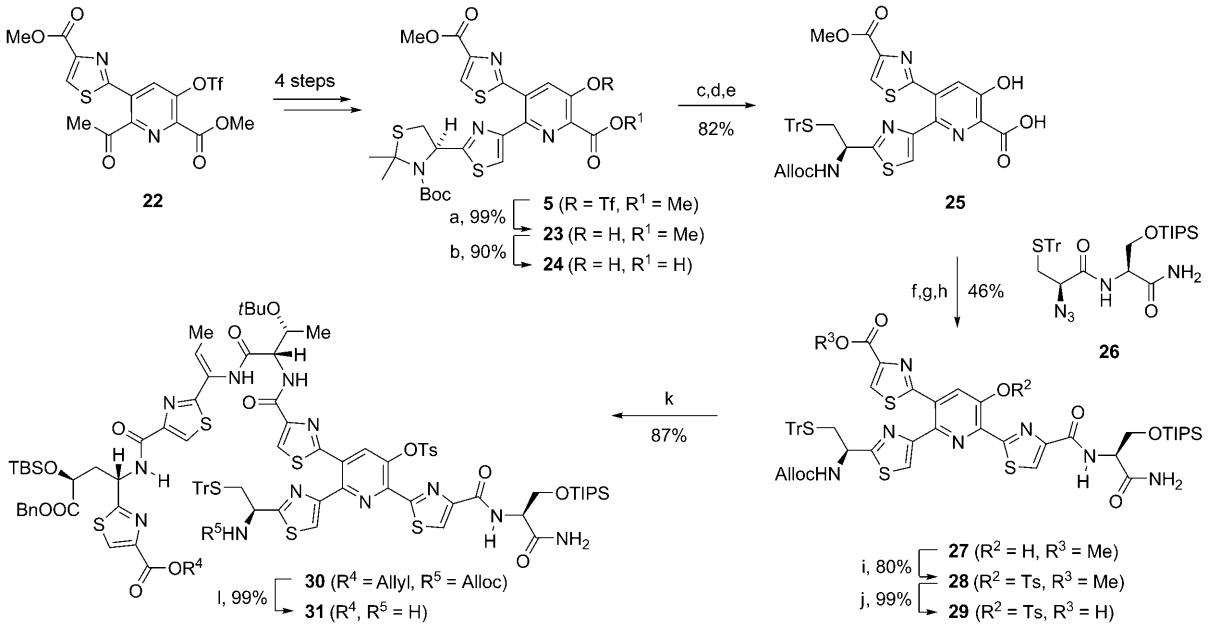


Scheme 3. Preparation of bisthiazole peptide **21**. Reagents and conditions: a) TFA/CH_2Cl_2 (1:1), 0→20°C, 1 h; b) Fmoc(*t*Bu)ThrOH, EDC, HOBt, CH_2Cl_2/DMF (10:1), 0→20°C, 4 h; c) *o*-$NO_2C_6H_4SeCN$ (2 equiv), PBu_3 (2 equiv), CH_2Cl_2, 20°C, 16 h; d) 1% H_2O_2, 20°C, 30 min; e) $[Pd(PPh_3)_4]$, $PhSiH_3$ (2 equiv), CH_2Cl_2, 20°C, 10 min; f) **15**, HOBt, EDC, 0→20°C, 5 h; g) 1% DBU, 5% piperidine in CH_2Cl_2, 0°C, 30 min; h) 50% TFA, 0→20°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 hydroxypyridine 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 bisthiazolyl 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 $Sc(OTf)_3$[19] removed the methyl ester group on the pyridine ring selectively if a free hydroxy group at C3 was present (**23**→**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 (→**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 (→**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 $Pd^0/PhSiH_3$ under neutral reaction conditions (99%).

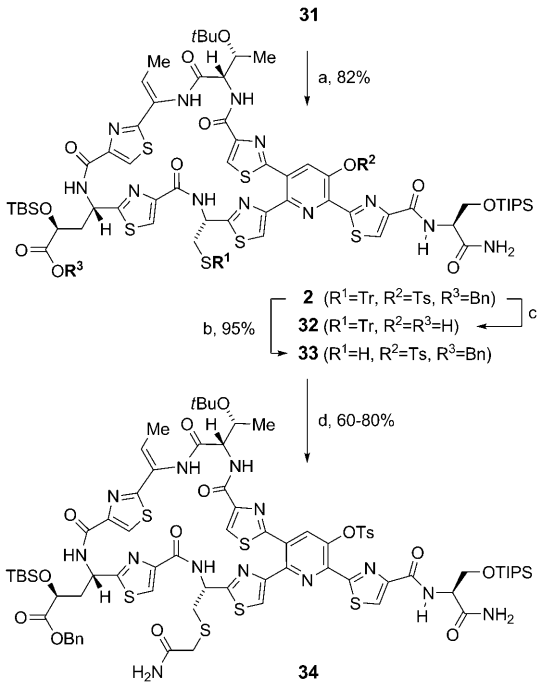


Scheme 4. Synthesis of peptide **31**. Reagents and conditions: a) $(Bu_4N)OH$ (2 equiv), 1,4-dioxane, 20 °C, 5 min; b) $Sc(OTf)_3$ (5 mol%), 1,4-dioxane/H_2O (3:1), pH 8.5, 60 °C, 8 h; c) TFA/CH_2Cl_2/Et_3SiH (13:13:1), 20 °C, 30 min; d) TrCl, DMF, 20 °C, 14 h; e) AllocCl, $NaHCO_3$, THF/H_2O (5:1); f) $COCl_2$ (20% in toluene, 1.1 equiv), NEt_3, THF, −40 °C, 2 h; then **6** (1.2 equiv), DMAP (0.1 equiv); g) PPh_3, THF, −20→40 °C, 20 h; h) $BrCCl_3$, DBU, CH_2Cl_2, −20→20 °C, 2 h; i) TsCl, NEt_3, DMAP (0.1 equiv), CH_2Cl_2, 0 °C, 2 h; j) Me_3SnOH (9 equiv), 1,2-dichloroethane, 80 °C, 4 h; k) DEPBT (3 equiv), $NaHCO_3$ (10 equiv), THF, **21**, 20 °C, 19 h; l) $PhSiH_3$, $[Pd(PPh_3)_4]$, CH_2Cl_2. Alloc = allyloxycarbonyl, DEPBT = 3-(diethoxyphosphoryloxy)-1,2,3-benzotriazin-4(3*H*)-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, $EtN(iPr)_2$, CH_2Cl_2/DMF (18:1), slow addition of **31** (0.8 mM final concentration); b) Et_3SiH, TFA/CH_2Cl_2 (1:19); c) NaOH (0.35 M) in CH_2Cl_2/MeOH (1:3); d) ICH_2CONH_2, DMF. HOAt = 1-hydroxy-7-azabenzotriazole, HATU = *O*-(7′-azabenzotriazol-1′-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate.

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