Natural Product Synthesis

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Total Synthesis of Nosiheptide

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Abstract: *Total synthesis of the bismacrocyclic thiopeptide antibiotic nosiheptide was achieved through the assembly of a fully functionalized linear precursor followed by consecutive macrocyclizations. Key features are a critical macrothiolactonization and a mild deprotection strategy for the 3-hydroxypyridine core. The natural product was identical to isolated authentic material in terms of spectral data and antibiotic activity.*

Thiopeptide antibiotics are highly potent and structurally complex secondary metabolites from soil bacteria (*Actinomycetes*),[1] and they are formed by ribosomal peptide biosynthesis.[2] Total syntheses have been reported for several examples of monomacrocyclic thiopeptide natural products,[3] as well as for the bismacrocyclic thiopeptides thiostrepton[4] and its close relative siomycin.[5] Other bismacrocyclic thiopeptide antibiotics have remained a challenge, notably the highly active "class e" scaffolds[1] of nosiheptide (**1**), nocathiacin (**2**–**5**), and glycothiohexide (**6**, Figure 1). Nosiheptide (**1**) contains a unique 3-hydroxypyridine core, several substituted thiazoles, a sterically hindered aromatic B-ring thiolactone, and an indolylmethyl ester, all embedded within a bismacrocyclic scaffold endowed with a pendant dehydroaminoacid side chain. The other congeners (**2**–**6**) feature an additional transannular bridge further dividing ring B, as well as oxidative modifications, methylations, and glycosidations. In the nocathiacins, one Cys residue is apparently exchanged for a Ser, as indicated by a sulfur-free B-ring macrolactone.

Nosiheptide (**1**) can be regarded as the structural prototype of the class e thiopeptide antibiotics.[6] It exerts exceptional antibiotic activity in vitro and in a mouse model against critical Gram-positive pathogens such as MRSA, VRE, or *Clostridium difficile*.[6c] Chiefly due to unfavorable physicochemical properties, it has been used previously only for applications in farm animals, mainly as a feed additive.[7] Previous synthetic work on nosiheptide has focused on building blocks and the development of synthetic methods.[8] The characteristic A-[9] and B-ring[10] systems have been synthesized in model studies. Herein, we report on a successful total synthesis of nosiheptide that was achieved by employing double macrocyclization of a fully functionalized linear precursor.

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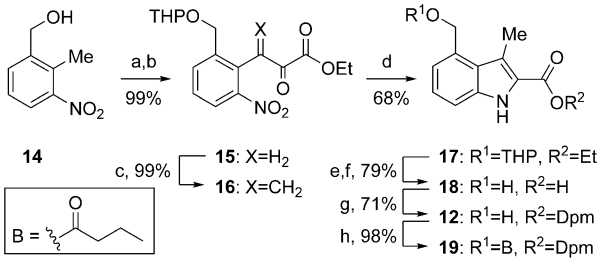
In designing a synthesis of nosiheptide, the electrophilic dehydroalanine (DHA) residue and thiol precursors of the potentially labile thioester were deemed incompatible (Figure 1). Therefore, the DHA residue was initially masked as a protected serine derivative (a). The thioester was traced back (b) to an ω-mercapto acid with acid-labile protection (Dpm, Tr). Further disconnections at strategic amide bonds (c/d) led to the fragments **7** and **8**, which feature sets of matching orthogonal protecting groups, guided by the successful macrolactamization precedence toward the A-ring model.[9] Introducing the indole ester into fragment **7** early seemed appropriate, since late-stage esterifications have been found to be problematic.[9] While the synthesis of hydroxypyridine **8** was known,[9b] fragment **7** was to be assembled from a thiazole peptide (**9**–**11**), hydroxymethyl indole **12**, and γ-lactam **13**.

Initially, indole derivative **12** was prepared from 3-nitro-2-methylbenzylalcohol (**14**, Scheme 1), which was *O*-THP-protected and *C*-acylated with diethyl oxalate[11] to give α-keto ester **15** (99% yield, two steps). Methenylation[12] gave nitroarylenone **16** (99%), which was reductively transformed into indole **17**. Incomplete reduction to the *N*-hydroxy indole[13] could be suppressed by employing optimized hydrogenation conditions. Then the ethyl ester was exchanged for an acid-labile Dpm group (→**18**→**12**, 56%).[9b] To test the stability of esters of **12** and to find suitable deprotection conditions, model butyrate **19** was investigated (Scheme 1). Indeed, standard conditions (TFA in CH_2Cl_2) led to unselective cleavage and steady loss of butyrate even at low TFA concentrations (1%). In the event, by using BF_3 in AcOH[14]



Scheme 1. Synthesis of indole **12**. Reagents and conditions: a) Dihydropyran (2 equiv), PPTS (0.1 equiv), 1,2-dichloroethane, 20°C, 18 h; b) NaH (3 equiv), diethyloxalate (6 equiv), DMF, 0°C→20°C, 18 h; c) dimethylmethylidene-iminium chloride (3 equiv), NEt_3 (3 equiv), 20°C, 13 h; d) cat. 10% Pd/C (10 wt%), 1–4 bar H_2, 4 Å molecular sieves (20 wt%), THF/*i*PrOH (1:1), 18 h; e) aq. NaOH (2.5 M, 3 equiv), EtOH, reflux, 30 min; f) AcOH (70%), 20°C, 18 h; g) diphenyldiazomethane, cat. TFA, THF, 60°C, 3 h; h) butyric anhydride (2 equiv), Et*N*i*Pr*$_2$ (4 equiv), DMAP (0.1 equiv), THF, 0°C→20°C, 13 h.

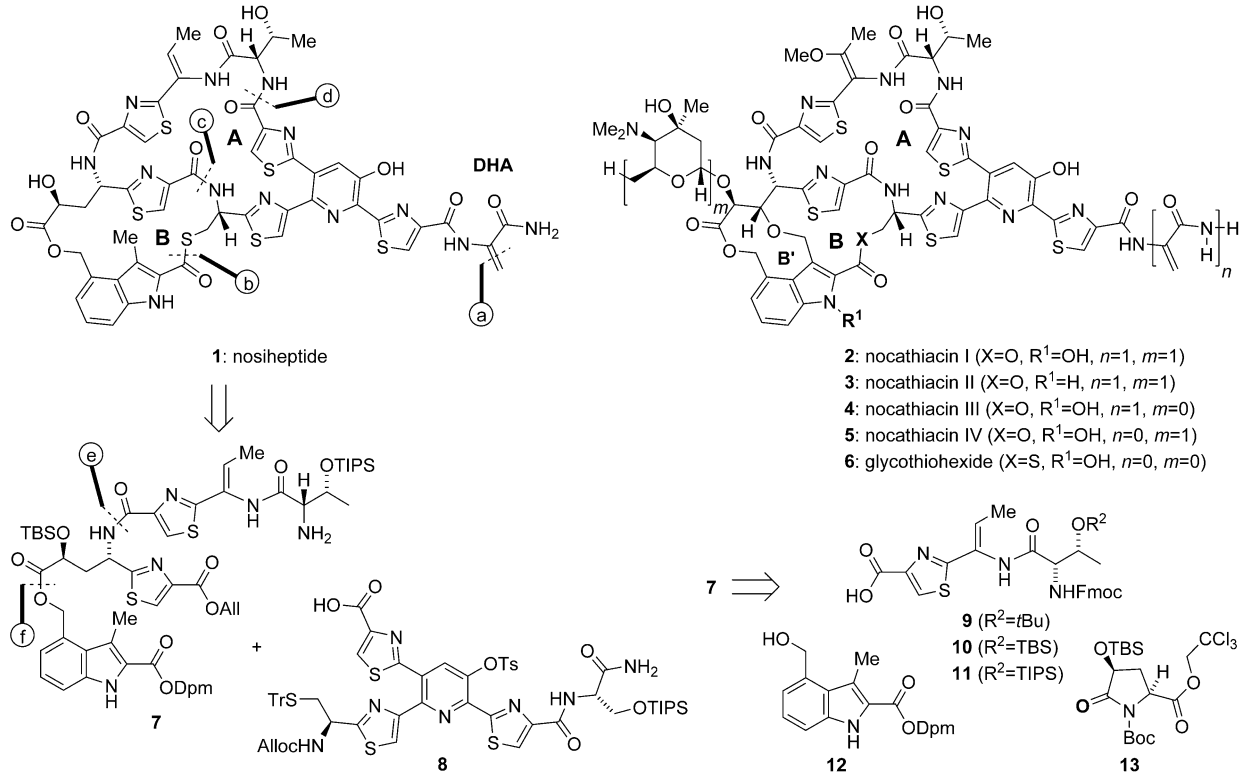
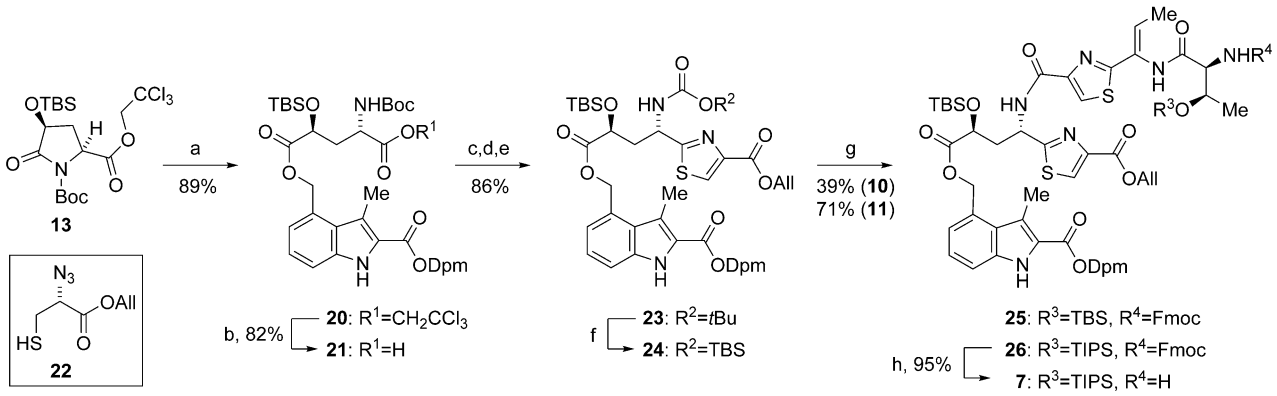


Figure 1. Chemical structures of class e thiopeptide natural products and retrosynthetic disconnection of nosiheptide. All = Allyl, Alloc = Allyloxycarbonyl, Boc = *tert*-Butyloxycarbonyl, DBU = 1,8-Diazabicyclo[5.4.0]undec-7-en, DMAP = Dimethylaminopyridine, Dpm = Diphenylmethyl, Fmoc = Fluorenylmethyloxycarbonyl, HATU = *O*-(7′-Azabenzotriazol-1′-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate, HOAt = 1-Hydroxy-7-azabenzotriazole, PPTS = Pyridinium 4-methylphenylsulfonate, PyAOP = (7-Azabenzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate, PyDOP = (3,4-Dihydro-4-oxo-1,2,3-benzotriazin-3-yl)oxytripyrrolidinophosphonium hexafluorophosphate, TBS = *tert*-Butyldimethylsilyl, TIPS = Triisopropylsilyl, Tr = Triphenylmethyl, Ts = 4-Methylphenylsulfonyl.

or by buffering TFA in anisole as a solvent,[15] selective cleavage of the Dpm group was achieved.

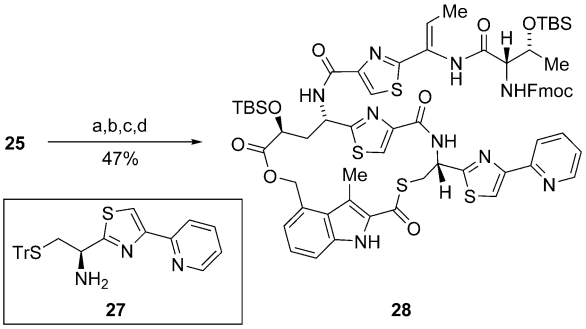
In order to incorporate the indole into the nosiheptide structure, alcohol **12** was acylated with activated lactam **13**[9] under carefully controlled basic conditions (89%, Scheme 2). Tce ester **20** was reductively deprotected (82% yield), and the resulting acid **21** was extended with azido thiol **22** and transformed into thiazole **23** by using an aza-Wittig ring closure and thiazoline oxidation (86%).[16] Liberation of the amino group in **23** proved challenging owing to the high acid sensitivity of the indolyl ester and a propensity for γ-butyrolactam formation. However, chemoselective conver-



Scheme 2. Synthesis of the indole-thiazole building block. Reagents and conditions: a) **12** (0.5 equiv), NaH (1.25 equiv), THF, −78°C, 2 h (98% b.r.s.m.); b) Zn (36 equiv), 1 M KH_2PO_4, THF, 45°C, ultrasound, 10 h (95% b.r.s.m.); c) **22** (1.5 equiv), PyAOP (1.2 equiv), $EtNiPr_2$ (2.5 equiv), 0°C→20°C, 3 h; d) PPh_3 (1.5 equiv), THF, −20°C→20°C, 2 h; then 40°C, 14 h; e) DBU (2.1 equiv), $BrCCl_3$ (1.05 equiv), CH_2Cl_2, −20°C, 1 h; f) TBSOTf (11 equiv), 2,6-lutidine (22 equiv), CH_2Cl_2, 0°C→20°C; g) **10** or **11** (1 equiv), HATU (1.4 equiv), HOAt (6.5 equiv), $NaHCO_3$ (3 equiv), THF, 0°C→20°C, 48 h; h) DBU (5% in CH_2Cl_2), −20°C, 5 min. b.r.s.m. = based on recovered starting material.

sion of the Boc group into a silyl carbamate was achieved by using TBSOTf.[17] We found that TBS carbamate **24** could be directly coupled to thiazole acid fragments **10** or **11** (see the Supporting Information) by using HATU/HOAt and solid $NaHCO_3$, which apparently releases the amine from the TBS carbamate slowly in situ. Coupling products could thereby be obtained in good yields (39–71%). Interestingly we found that silyl-protected threonine residues induced sensitivity to *E*/*Z* isomerization of the enamine double bond under basic conditions, while the *N*-acyl enamine had been rather inert in building blocks featuring a *t*Bu protecting group.[9] This feature was more prominent with larger groups (TIPS > TBS ⩾ tBu). An excess of DBU at low temperature was found to be optimal to cleanly achieve Fmoc cleavage (→**7**, 95%).

Closure of the B-ring assembly was then tested after Pd-mediated deallylation[18] of ester **25** (Scheme 3). Coupling of amine **27** to the resulting acid led to an amide that had to be Tr- and Dpm-deprotected. Under acidic conditions, partial cleavage of the indolyl ester and/or loss of the TBS groups became apparent. However, TFA in anisole gave clean conversion into an ω-mercapto carboxylic acid that was consecutively cyclized to thiolactone **28** in 66% yield. These experiments validated the protecting-group strategy and set the stage for completion of the synthesis. Notably, it was found that the TBS group on the threonine residue was rather labile toward acids and fluoride, therefore, the more stable TIPS derivative was subsequently used instead.



Scheme 3. Completion of the fully equipped B-ring model. Reagents and conditions: a) $[Pd(PPh_3)_4]$ (20 mol%), $PhSiH_3$ (8.6 equiv), THF, 0°C, 20 min, 93%; b) PyBOP (2.1 equiv), $EtNiPr_2$ (2.5 equiv), **27** (1.5 equiv), DMF, 0°C→20°C, 16 h, 77%; c) anisole/TFA/Et_3SiH (8:5:4), −25°C→0°C, 24 h; d) PyAOP (1.2 equiv), $EtNiPr_2$ (2.2 equiv), THF, 0°C, 15 min, 20°C, 1 h, 66%.

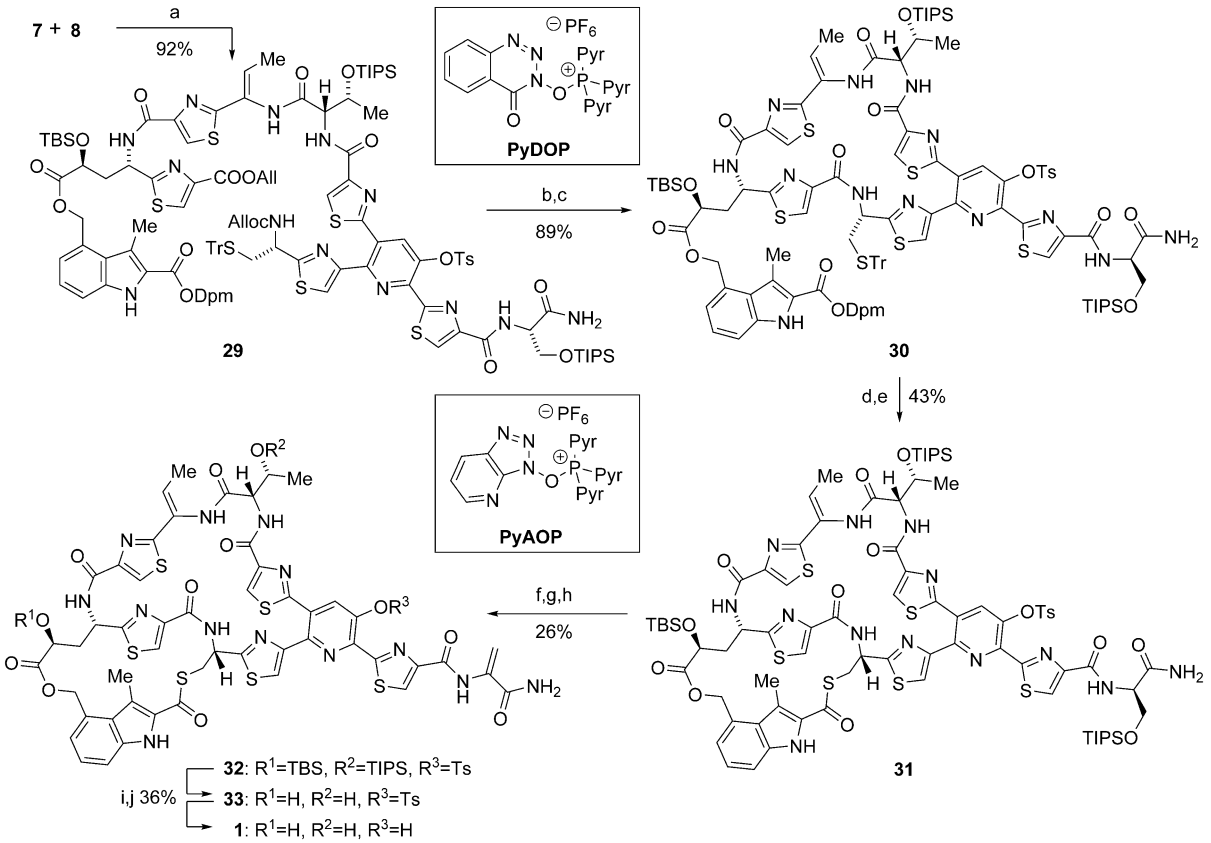
Amine **7** had now to be coupled with acid **8** to obtain the fully assembled linear precursor **29** (Scheme 4). During these experiments, we found that the Ts protection of the hydroxypyridine was partially cleaved when HOBt or HOAt were used in excess. After screening coupling reagents, clean conversion and an excellent coupling yield of 93% were achieved by using PyDOP.[19] Pd-mediated Alloc and allyl deprotection and consecutive macrocyclization of the A-ring by using HATU under highly dilute conditions were successful. Substrate **30** then was cleanly *S*-detritylated and *O*-Dpm-deprotected by applying the conditions established earlier. The annelated macrothiolactone B-ring was effectively formed with PyAOP in THF (→**31**, 43%).

In order to install the terminal DHA residue, the primary TIPS ether on scaffold **31** was selectively removed by using aqueous HF. For the dehydration of the terminal serine amide, a variety of conditions and reagents (e.g., TsCl/DMAP, Tf_2O, PPh_3/CCl_4, Cu^ICl/EDCI) were tested to induce elimination. Concomitantly, dehydration of the terminal amide (nitrile formation), Ts-deprotection, and/or 3-hydroxypyridine refunctionalization were frequently observed. To our delight, *O*-sulfonylation of the monodesilylated compound could be selectively achieved by using MsCl and 2,6-lutidine. Carefully monitored treatment with DBU then induced elimination to generate the crucial DHA residue (→**32**, ca. 70%, 35% after preparative HPLC). Further desilylation was then realized by using $Et_3N{\cdot}3HF$. The concluding cleavage of the *O*-Ts group was then achieved by exposing compound **33** to a solution of HOBT in DMF in the presence of base. Notably, the Ts group was removed cleanly without compromising the thioester bond. Synthetic nosiheptide (**1**) was then purified by employing preparative TLC (ca. 65%) followed by preparative HPLC (36% yield over two steps).

Although mass spectrometry and optical rotation measurements of the final product **1** indicated structural identity, we found the NMR spectra of nosiheptide to be quite dependent on solvent mixture, water content, and pH. To exclude ambiguities, a comparison with original material was pursued. The natural product was isolated for this purpose from a commercial feeding additive containing nosiheptide ("1% premix") by following published procedures.[20] Comparison of HPLC, NMR, and LC–MS data for the synthetic compound **1** with those for the synthesized material unequivocally confirmed structural identity (see the Supporting Information).

Moreover, an initial activity evaluation in inhibition-zone tests showed that the isolated and synthetic material similarly inhibited the growth of *Streptomyces coelicolor*, with apparent minimum inhibitory concentration (MIC) values of 0.3 μM in each case (see the Supporting Information). This result demonstrates that nosiheptide also displays potent antibacterial activity against soil bacteria, very close relatives and congeners of the producer *S. actuosus*. Surprisingly, *O*-tosylation of the hydroxypyridine core is not tolerated, since compound **33** did not display any appreciable antibacterial activity. These results are currently being further investigated with pathogenic bacteria.

In conclusion, a viable total synthesis of the bicyclic thiopeptide antibiotic nosiheptide was developed that enables access to unique class e thiopeptide scaffolds. Key features are an optimized macrocyclization precursor setup and an advanced protecting-group strategy adapted to the specific liabilities of the nosiheptide structure. Since this synthesis allows the exchange of building blocks, we anticipate that a deeper chemical biology profiling of this highly potent and structurally surprising antibiotic by chemical synthesis will now be possible.



Scheme 4. Completion of the synthesis. Reagents and conditions: a) PyDOP (2 equiv), $EtNiPr_2$ (2.2 equiv), THF, 0 °C, 15 min, 20 °C, 2 h; b) $[Pd(PPh_3)_4]$ (20 mol%), $PhSiH_3$ (20 equiv), THF, 0 °C, 30 min; c) HATU (5 equiv), $EtNiPr_2$ (30 equiv), THF, 0 °C, 15 h; d) anisole/TFA/Et_3SiH (8:5:4), −20 °C, 30 min; then 0 °C, 4 h; e) PyAOP (1.2 equiv), $EtNiPr_2$ (2.3 equiv), THF, 0 °C, 15 min, then 20 °C, 15 h; f) CH_3CN/conc. HF (24:1), 0 °C, 25 h, 75% (90% b.r.s.m.); g) methanesulfonyl chloride (100 equiv), 2,6-lutidine/CH_2Cl_2 (1:10), 0 °C→20 °C, 0.5 h; h) DBU (2% in CH_2Cl_2), −78 °C→−35 °C, 4.5 h (35%, two steps); i) $Et_3N\times3HF$/THF (1:9), 0 °C→20 °C, 27 h; j) HOBt (10 equiv), $EtNiPr_2$ (7 equiv), DMF, 0 °C → 20 °C, 1.5 h. Pyr = pyrrolidine-1-yl.

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Keywords: antibiotics · heterocycles · macrocycles · peptides · total synthesis

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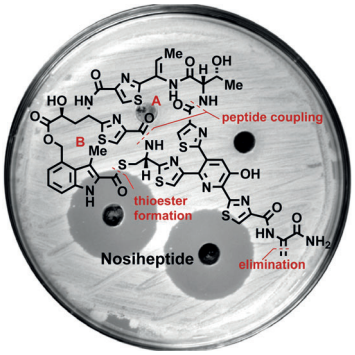
Communications

Natural Product Synthesis

K. P. Wojtas, M. Riedrich, J.-Y. Lu, P. Winter, T. Winkler, S. Walter, H.-D. Arndt* _____ ■■■■–■■■■

Total Synthesis of Nosiheptide



Each ring is different: A total synthesis of the bismacrocyclic thiopetide antibiotic nosiheptide was achieved through the assembly of a fully functionalized linear precursor, followed by consecutive macrocyclizations. Key to success were the late-stage formation of a dehydroalanine residue and finely tuned deprotection of the hydroxypyridine core. The synthesis product was identical to the natural material in terms of structure and function.