Synthesis of the 'Northern-Hemisphere' Fragments of the Thiopeptide Antibiotic Nosiheptide

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Dedicated to Professor Richard Heck in recognition of his outstanding contributions to organic synthesis

Abstract: The northern-hemisphere fragments **4** and **5** of the thiopeptide antibiotic nosiheptide have been synthesized from Boc-Glu-OBn **7** and Boc-Thr **12** in 21.8% and 16.8% overall yields, respectively.

Key words: thiazole, amino acids, heterocycles, antibiotics

The antibiotic nosiheptide **1** (RP9671), originally isolated from *Streptomyces actuous* 40037 in the early 1960s by French workers,[1,2] with its structure determined by chemical degradation[3] and X-ray crystallography,[4,5] is characterized by the presence of seven heterocyclic rings (five thiazoles, one indole, one pyridine) in a double macrocyclic array. Nosiheptide is a member of the thiopeptide antibiotics, a growing class of sulfur-rich modified cyclic peptides,[6] and has been subject of detailed biosynthetic studies which establish the origin of the heterocyclic rings from modification of the amino acid side-chains with cyclization.[7] Although none of the thiopeptides are used clinically as yet, nosiheptide is in commercial use as a feed additive to increase weight gain in poultry and pigs.[8,9]

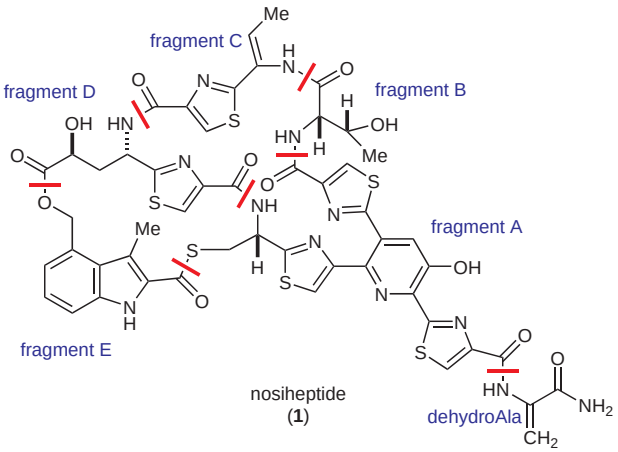

Figure 1

Nosiheptide has traditionally been regarded as comprising six fragments (Figure 1) – dehydroalanine and fragments A (2,3,5,6-tetrasubstituted pyridine), B (threonine), C (threonine–cysteine-derived propenylthiazole), D (modified glutamate) and E (2,3,4-trisubstituted indole). Although nosiheptide has yet to succumb to total synthesis, routes to various fragments have been described, including the indole fragment E,[10–12] the modified glutamate fragment D,[13–15] and the pyridine fragment A.[16,17] The synthesis of a potential precursor to the B-C-D-fragment has also been described,[14] although in many of these examples, the use of non-orthogonal protecting groups would appear to preclude their use in any total-synthesis campaign. In continuation of our interest in the synthesis of the thiopeptide antibiotics,[18–21] including nosiheptide,[12] we now report concise routes to the 'northern-hemisphere' fragments of the antibiotic.

Our overall plan for the synthesis of nosiheptide (**1**) is shown in Scheme 1, and involves formation of the macrolactone/thiolactone from a suitable indole **2**, previously synthesized in our laboratory,[12] and macrocyclic pyridine fragment **3**, which in turn could be derived from the 'northern-hemisphere' fragments **4** and **5** and the pyridine **6** by two amide couplings and one Pd-catalyzed biaryl formation (Scheme 1).

The modified glutamate **4**, corresponding to fragment D in the original analysis, has been synthesized on four previous occasions: from D-glucose (ca. 12 steps),[13] from (*S*)-2,2-dimethyl-1,3-dioxolane-4-acetaldehyde (10 steps, overall yield ca. 11%),[15] from (*S*)-pyroglutamic acid (11 steps, overall yield ca. 2%),[14] or from D-glyceraldehyde (11 steps, overall yield ca. 8%).[14] Our route that starts from commercially available *N*-Boc-glutamic acid benzyl ester **7** delivers the required fragment in just seven steps in an overall yield of 22%, and importantly, with orthogonal protecting groups on the two carboxyl, hydroxyl and amino groups (Scheme 2).

Thus glutamate **7** was esterified using methyl chloroformate,[22] and then subjected to the excellent Hanessian protocol for the stereocontrolled hydroxylation of the glutamate dianion, formed upon treatment with LiHMDS (2 equiv), with the Davis oxaziridine.[23,24] The resulting 4-hydroxy compound was not purified, but immediately converted into its TBS-ether **9**, which after purification was obtained as a single diastereomer in 60% yield over

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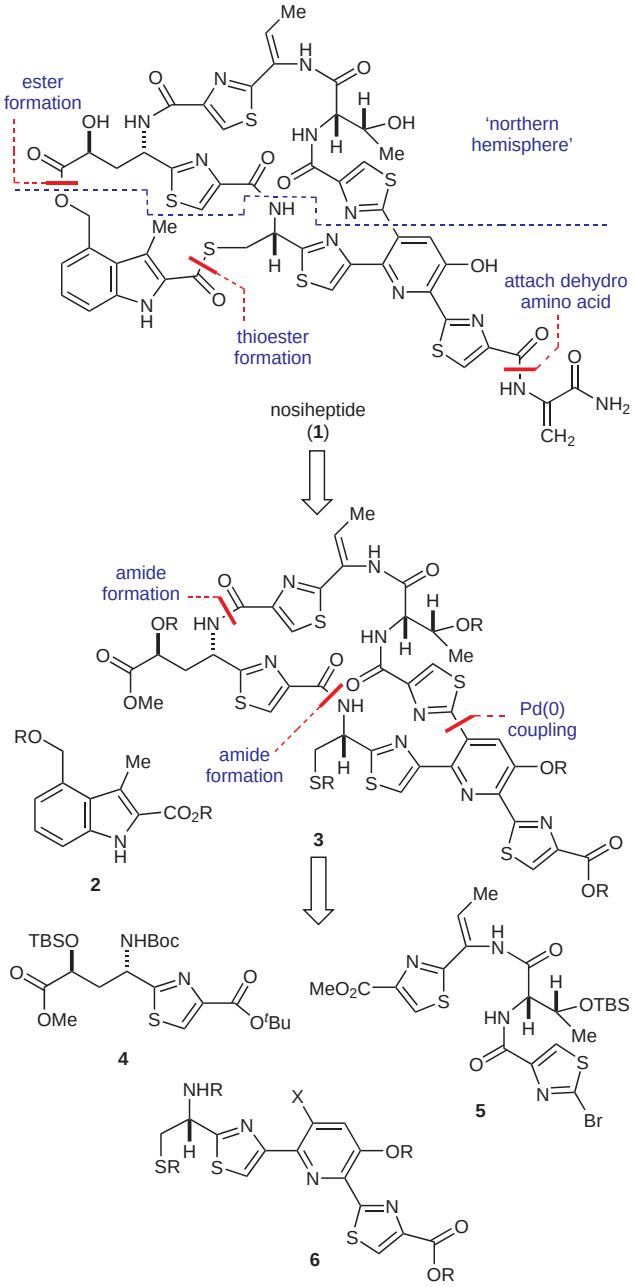
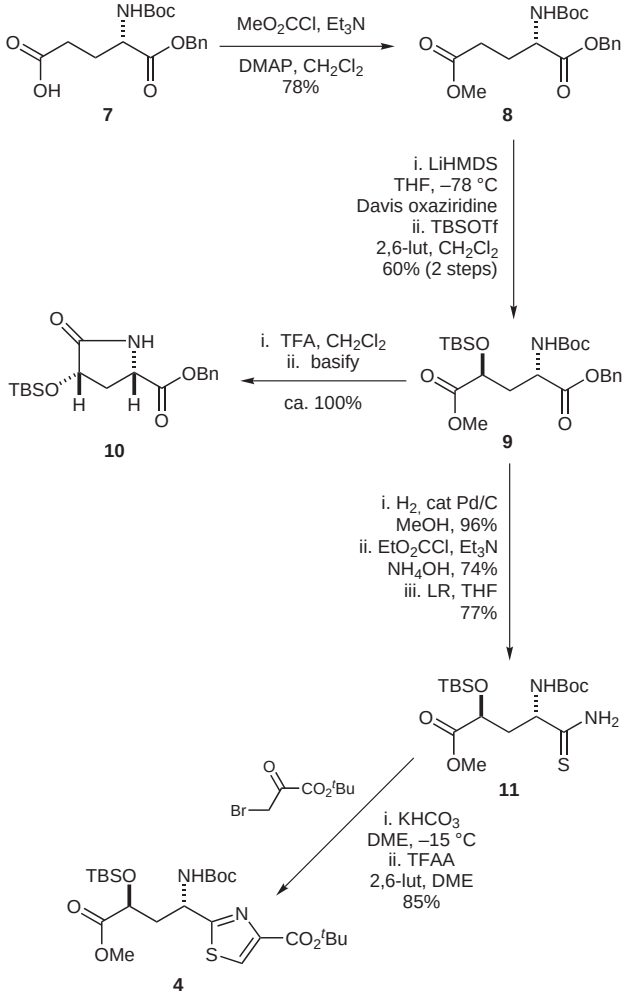


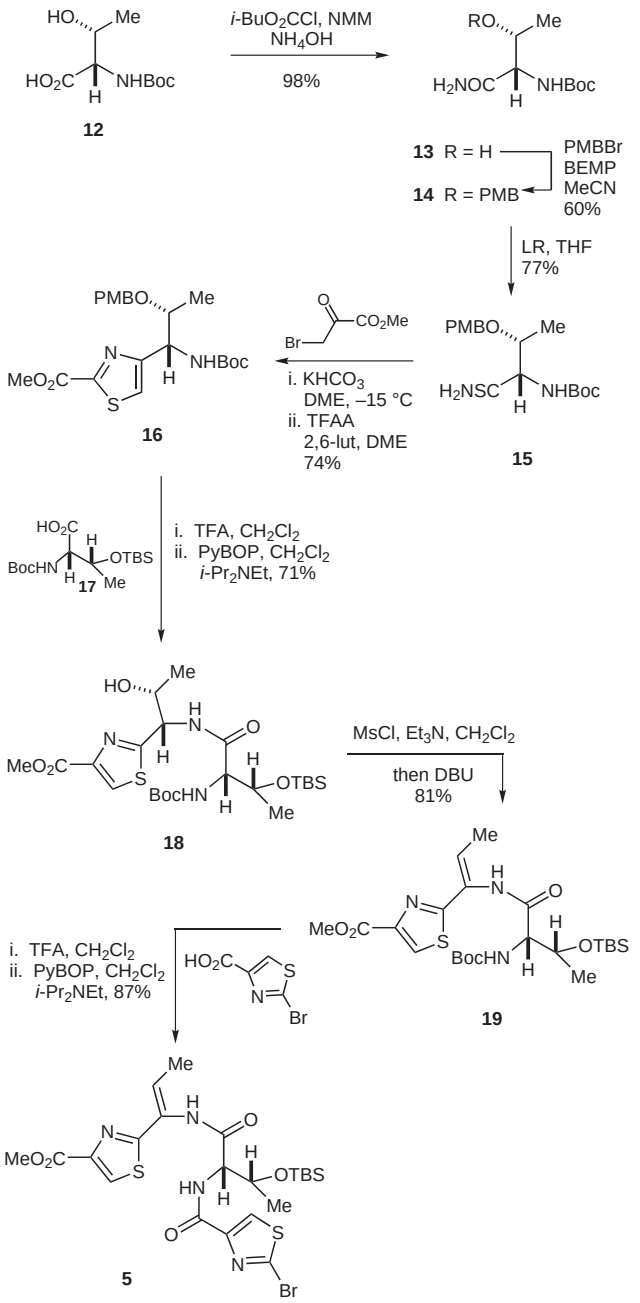
Scheme 1

the two steps.[25] That the hydroxyl group had indeed been introduced with the desired *S*-stereochemistry was confirmed by removal of the Boc protecting group under acidic conditions, basification and cyclization to the pyroglutamate derivative **10**. NMR studies on compound **10** established that the hydrogens at C-2 and C-4 are *syn* to each other. In order to complete the synthesis, the benzyl ester in glutamate **9** was removed by hydrogenolysis, and the resulting acid converted into the thioamide **11** by treatment of the corresponding carboxamide with Lawesson's reagent (LR). Finally, Hantzsch reaction with *tert*-butyl bromopyruvate,[26] under the modified conditions to prevent racemization,[27] gave the orthogonally protected glutamate fragment **4** (Scheme 2).[28,29]



Scheme 2 LR = Lawesson's reagent

The synthesis of fragment **5** started with *N*-Boc-threonine **12**, readily converted into the known carboxamide **13** in good yield (Scheme 3). Protection of the hydroxyl group as its 4-methoxybenzyl (PMB) ether **14** using 2-*tert*-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine (BEMP) as base, was followed by conversion into the thioamide **15** and Hantzsch reaction with methyl bromopyruvate to give the thiazole **16**.[30] Treatment of **16** with TFA in dichloromethane cleaved both Boc and PMB protecting groups, and the resulting amine trifluoroacetate salt was coupled to *N*-Boc-*O*-*tert*-butyldimethylsilylthreonine (**17**)[31] to give the dipeptide **18**. The unprotected threonine side-chain underwent dehydration upon treatment with methanesulfonyl chloride and triethylamine, followed by DBU[32] to give the desired *Z*-alkene **19** in good yield, the stereochemistry of the double bond being confirmed by NOE studies. Finally, selective removal of the *N*-Boc-group in TFA–dichloromethane was followed by coupling to 2-bromothiazole-4-carboxylic acid[33] to give the complete fragment **5**[34] (Scheme 3) in an overall yield of 16.8% over the nine steps.



Scheme 3 NMM = *N*-methylmorpholine; LR = Lawesson's reagent

In summary, we have developed concise routes to thiazoles **4** and **5** that together comprise the complete northern hemisphere of nosiheptide, with appropriate orthogonal protecting groups for further elaboration to the natural product.

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(25) **Analytical Data of (*S*,*S*)-1-Benzyl-5-methyl 2-*tert*-butoxycarbonylamino-4-*tert*-butyldimethylsiloxy Pentanedioate (9).**
^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.40–7.26 (5 H, br s, ArH), 5.30 (1 H, d, *J* = 8.3 Hz, N*H*), 5.22 (1 H, d, *J* = 12.4 Hz, C*H*HPh), 5.11 (1 H, d, *J* = 12.4 Hz, CH*H*Ph), 4.47 (1 H, m, C*H*NH), 4.28 (1 H, m, CHOSi), 3.70 (3 H, s, OMe), 2.28–2.09 (2 H, m, 3-CH_2), 1.42 (9 H, s, CMe_3), 0.91 (9 H, s, CMe_3), 0.04 (3 H, s, Me), 0.03 (3 H, s, Me). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.8 (C), 172.5 (C), 155.9 (C), 135.9 (C), 129.3 (CH), 128.8 (CH), 128.6 (CH), 80.2 (C), 69.9 (CH), 67.5 (CH_2), 52.5 (Me), 51.5 (CH), 36.7 (CH_2), 28.7 (Me), 26.1 (Me), 18.6 (C), –3.18 (Me).
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(28) It is established that Boc-groups can be deprotected in the presence of *tert*-butyl esters (for an example, see ref. 21) and of *tert*-butyldimethylsilyl ethers (cf. deprotection of compound **19**).

(29) **Synthesis of (*S*,*S*)-*tert*-Butyl 2-[(1-*tert*-butoxycarbonylamino-3-*tert*-butyldimethylsiloxy-3-methoxycarbonyl)propyl]thiazole-4-carboxylate (4).**
To a solution of (*S*,*S*)-2-*tert*-butoxycarbonylamino-4-*tert*-butyldimethylsiloxy-4-methoxycarbonyl-thiobutanamide (**11**, 1.20 g, 2.95 mmol) and *tert*-butyl bromopyruvate (2.30 g, 10.33 mmol) in 1,2-dimethoxyethane (42 mL) at –30 °C was added $KHCO_3$ (1.18 g, 11.80 mmol). The mixture was stirred at –10 °C for 6 h. The colorless solid was filtered off and washed with 1,2-dimethoxyethane. The filtrate was concentrated in vacuo. The mixture was diluted in 1,2-dimethoxyethane (42 mL) and cooled at –30 °C before addition of TFAA (1.24 mL, 8.85 mmol) and 2,6-lutidine (2.06 mL, 17.70 mmol). The mixture was stirred overnight at –20 °C. The mixture was partitioned between EtOAc and brine, the organic layer separated and concentrated in vacuo. The crude product was purified by flash chromatography (EtOAc–light PE, 1:5) to give the title compound (1.33 g, 85%) as a colorless sticky solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.93 (1 H, s, H-4), 5.77 (1 H, d, *J* = 8.1 Hz, N*H*Boc), 5.15 (1 H, m, CHOSi), 4.42 (1 H, m, C*H*NH), 3.70 (3 H, s, OMe), 2.51–2.40 (2 H, m, CH_2), 1.57 (9 H, s, CMe_3), 1.42 (9 H, s, CMe_3), 0.91 (9 H, s, CMe_3), 0.05 (3 H, s, Me), 0.01 (3 H, s, Me). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.8 (2 × C), 160.8 (C), 155.6 (C), 149.0 (C), 126.9 (CH), 82.3 (C), 80.5 (C), 69.9 (CH), 52.5 (CH), 50.5 (Me), 39.1 (CH_2), 28.7 (Me), 28.6 (Me), 26.1 (Me), 18.5 (C), –4.6 (Me), –5.1 (Me). MS (FI): *m/z* = 531 (14) [MH^+], 473 (100), 418 (8), 417 (32), 132 (38), 57 (84).

(30) **Synthesis of Methyl 2-[(*S*)-1-(*tert*-Butoxycarbonylamino)-(*R*)-2-(4-methoxybenzyloxy)propyl]thiazole-4-carboxylate (16).**
To a solution of *N*-*tert*-butoxycarbonyl-*O*-(4-methoxybenzyl)thiothreoninamide (**15**, 1.60 g, 4.51 mmol) in 1,2-dimethoxyethane (31 mL) was added at 0 °C methyl bromopyruvate (1.68 mL, 15.80 mmol) and $KHCO_3$ (1.80 g, 18.04 mmol). The mixture was stirred 1 h at 0 °C before addition of TFAA (1.89 mL, 13.53 mmol) and 2,6-lutidine (3.15 mL, 27.06 mmol) at the same temperature. The mixture was stirred 2 h at 0 °C. The mixture was diluted in EtOAc and washed with brine. The organic layer was dried over Na_2SO_4 and concentrated in vacuo. The crude product was purified by flash chromatography (light PE–EtOAc, 2:1 to 1:2) to give the title compound (1.46 g, 74%) as a yellow-brown oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.09 (1 H, s, H-4), 6.95 (2 H, d, *J* = 8.6 Hz, ArH), 6.75 (2 H, d, *J* = 8.6 Hz, ArH), 5.70 (1 H, d, *J* = 8.7 Hz, N*H*Boc), 5.00 (1 H, d, *J* = 8.5 Hz, C*H*NH), 4.39 (1 H, d, *J* = 11.3 Hz, C*H*HPh), 4.31 (1 H, m, CH*H*Me), 4.14 (1 H, d, *J* = 11.1 Hz, C*H*Ph), 3.93 (3 H, s, OMe), 3.76 (3 H, s, OMe), 1.46 (9 H, s, CMe_3), 1.27 (3 H, d, *J* = 6.2 Hz, Me). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 175.0 (C), 162.3 (C), 159.6 (C), 156.1 (C), 147.3 (C), 130.1 (C), 129.8 (CH), 127.8 (CH), 114.0 (CH), 80.8 (C), 76.0 (CH), 71.5 (CH_2), 58.1 (CH), 55.6 (Me), 52.8 (Me), 28.7 (Me), 16.9 (Me).

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(34) **Synthesis of Methyl 2-{(*S*)-1-[2-(2-Bromothiazole-4-carbonylamino)-(*R*)-3-(*tert*-butyldimethylsiloxy)butanoylamino]-(*Z*)-propenyl}thiazole-4-carboxylate (5).**
To a stirred solution of methyl 2-{(*S*)-1-[(*S*)-2-*tert*-butoxycarbonylamino-(*R*)-3-(*tert*-butyldimethylsiloxy)butanoylamino]-(*Z*)-propenyl}thiazole-4-carboxylate (**19**, 482 mg, 0.94 mmol) in CH_2Cl_2 (13 mL) was added TFA (1.74 mL, 23.46 mmol). The mixture was stirred 30 min at 20 °C. The solvent was removed in vacuo and the residue was azeotroped with toluene. To the crude thiazole amine trifluoroacetate and 2-bromo-4-thiazolecarboxylic acid (254 mg, 1.22 mmol) in CH_2Cl_2 (12 mL) at 0 °C was added PyBOP (587 mg, 1.13 mmol) and *N*,*N*-diisopropylethylamine (0.80 mL, 4.70 mmol). The mixture was stirred 15 min at 0 °C and then overnight at r.t. The solvent was removed in vacuo. The mixture was partitioned between EtOAc and sat. solution of $NaHCO_3$. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated. The crude product was purified by flash chromatography (light PE–EtOAc, 1:1 to 1:2) to give the title compound (496 mg, 87%) as a colorless solid, mp 69–73 °C; $[\alpha]_D^{25}$ +24.0 (*c* 0.5, $CHCl_3$). HRMS: *m/z* calcd for $C_{22}H_{31}BrN_4O_5S_2Si$ + H: 603.0767; found: 603.0768. IR (CH_2Cl_2): ν_{max} = 3387, 3294, 2954, 2930, 2856, 1727, 1670, 1536, 1473, 1432, 1244, 1215, 1094, 1014, 838, 779 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.41 (1 H, br s, N*H*), 8.22 (1 H, d, *J* = 6.4 Hz, N*H*), 8.07 (2 H, s, 2 × H-4), 6.66 (1 H, q, *J* = 7.1 Hz, =C=C*H*), 4.71 (1 H, dd, *J* = 6.4, 3.8 Hz, C*H*NH), 4.57 (1 H, m, C*H*OSi), 3.92 (3 H, s, OMe), 1.85 (3 H, d, *J* = 7.1 Hz, =CMe), 1.31 (3 H, d, *J* = 6.4 Hz, CH*Me*), 0.92 (9 H, s, CMe_3), 0.22 (3 H, s, Me), 0.18 (3 H, s, Me). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 168.3 (C), 167.8 (C), 162.0 (C), 160.5 (C), 149.6 (C), 147.2 (C), 136.6 (C), 128.1 (CH), 127.7 (CH), 127.4 (CH), 68.1 (CH), 58.8 (CH), 52.8 (Me), 26.2 (Me), 19.1 (Me), 18.3 (C), 14.7 (Me), –4.3 (Me), –4.6 (Me); one quaternary C unobserved. MS (CI): *m/z* = 605/603 (95) [MH^+], 587 (15), 525 (13), 199 (33), 133 (21), 115 (14).