Construction of macrocyclic thiodepsipeptides: synthesis of a nosiheptide 'southern hemisphere' model system†

Marc C. Kimber and Christopher J. Moody*

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A 20-membered macrocyclic thiodepsipeptide has been synthesized as a model for the southern hemisphere of nosiheptide, the key steps being assembly of an acyclic precursor by amide coupling of indole and thiazole fragments followed by formation of the thiolactone in the macrocyclization step.

Nosiheptide **1**, a member of a class of thiopeptide antibiotics,[1,2] was originally isolated from *Streptomyces actuous* 40037 in the early 1960s.[3,4] Its structure was determined by a series of chemical degradation,[5] X-ray crystallographic[6,7] and ^{1}H and ^{13}C NMR studies,[8] and was shown to contain two macrocyclic regions incorporating seven heterocyclic rings—namely five thiazoles, one indole and one pyridine—that are thought to derive in Nature from modification of the amino acid side chains with cyclization.[9] Although active *in vitro*, nosiheptide **1** shows little *in vivo* activity,[4] and in common with other thiopeptide antibiotics is not used clinically as yet. However, it is in commercial use as a feed additive to increase weight gain in poultry and pigs.[10]

From a retrosynthetic point of view, nosiheptide **1** has traditionally been regarded as comprising six fragments, three in each 'hemisphere' (Fig. 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 yield to total synthesis, routes to various fragments have been described, including the pyridine fragment A,[11–13] the B–C fragment,[14] the modified glutamate fragment D,[14–17] and the indole E.[18–21] The synthesis of a potential precursor to the B–C–D-fragment of nosiheptide has also been described,[16] although in many of these examples, the use of non-orthogonal protecting groups would appear to preclude their use in any total synthesis campaign. Hence to date, there have been no reported syntheses of either of the two macrocyclic domains. In continuation of our interest in the synthesis of the thiopeptide antibiotics,[22,23] we now report the first synthesis of a 20-membered macrocyclic thiodepsipeptide **2**, a model for the southern hemisphere of nosiheptide **1**.

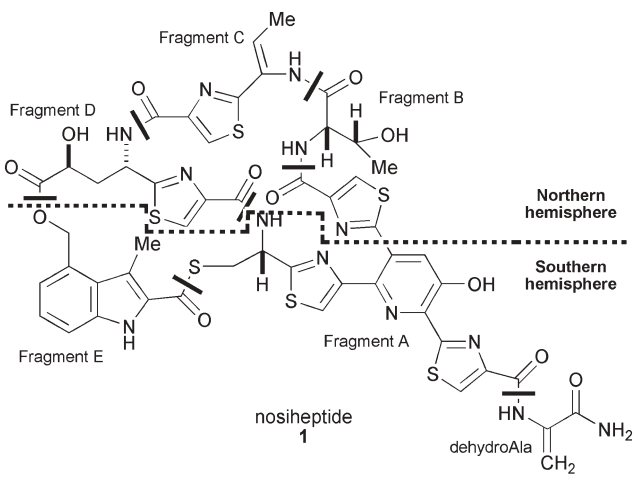

Fig. 1 Structure of the thiopeptide antibiotic nosiheptide.

Thiodepsipeptides occur rarely in Nature, a notable example being the anticancer, DNA-binding, macrocyclic thiodepsipeptide thiocoraline.[24,25] However, we regarded the thiolactone functionality as the key to the southern hemisphere macrocycle of nosiheptide. Hence we decided that this potentially labile thiolactone in the model macrocycle **2** should be formed last by cyclization of the thiol acid **3**, notwithstanding the fact that there is limited precedent for macrocyclizations involving thiolactone formation.[26–28] The overall retrosynthetic approach to the southern hemisphere model **2** is shown in Scheme 1, and involves sequential amide, ester and thioester bond formation between suitably protected fragments D, E and the A-fragment model.

The synthesis of the southern hemisphere model **2** began with construction of the thiazole derived from a modified glutamate residue (fragment D) that was assembled using methodology previously established in our laboratory.[14] Thus stereocontrolled hydroxylation of glutamate **4** under the Hanessian conditions[29] gave the 4-hydroxy glutamate, immediately converted into its TBS-ether, which after purification was obtained as a single diastereomer in 68% yield over the two steps. Hydrogenolysis of the benzyl ester was followed by conversion of the resulting acid into the amide **5**. Treatment of **5** with Lawesson's reagent gave the corresponding thioamide which underwent Hantzsch reaction with 3-bromopyruvic acid[30] giving the desired fragment **6** in an overall yield of 34% over six steps (Scheme 2).

Although we have previously reported a synthesis of the indole fragment of nosiheptide,[20] we have developed an improved method that utilizes, as the key step, the novel palladium mediated Suzuki coupling of trimethylboroxine[31] to a 3-bromoindole. The route began with a classical Reissert synthesis starting from the THP-ether of commercially available 2-methyl-3-nitrobenzyl alcohol **7** to give, after reductive cyclization, the known indole-2-carboxylate **8**.[19] Regioselective C-3 bromination proceeded smoothly with NBS in THF, and introduction of the methyl group at C-3 of the indole was achieved *via* palladium catalyzed coupling with trimethylboroxine to provide the indole **9** in a good yield of 78%. Owing to the presence of an ester link in our

School of Chemistry, University of Nottingham, University Park, Nottingham, UK NG7 2RD. E-mail: c.j.moody@nottingham.ac.uk; Fax: +44 115 951 3564

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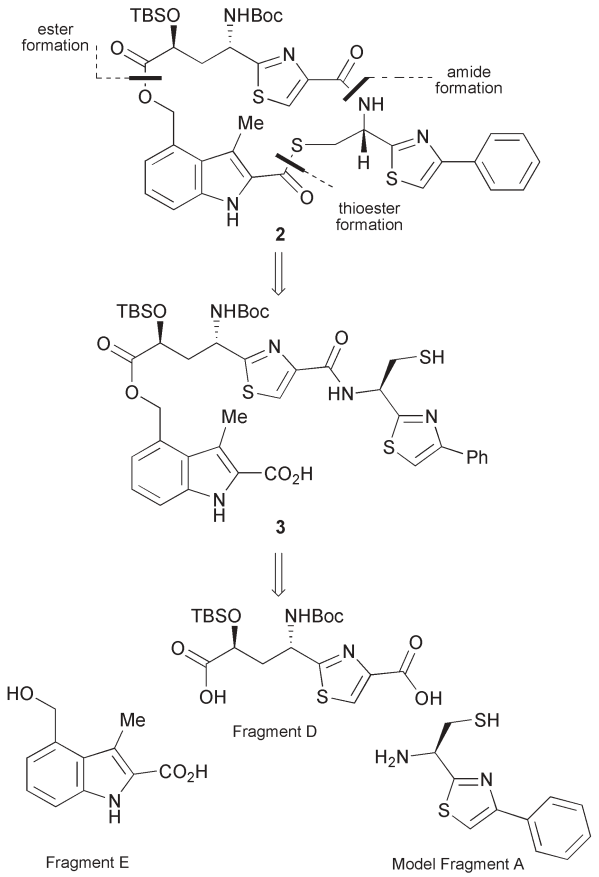
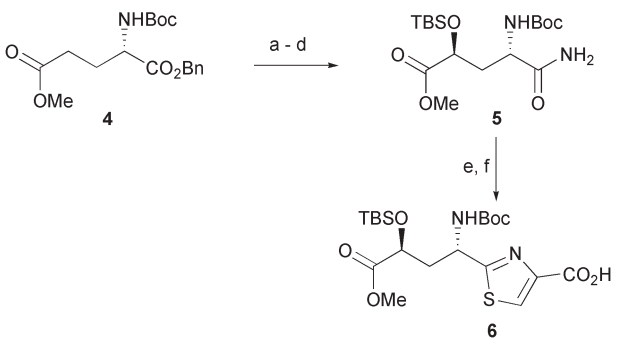


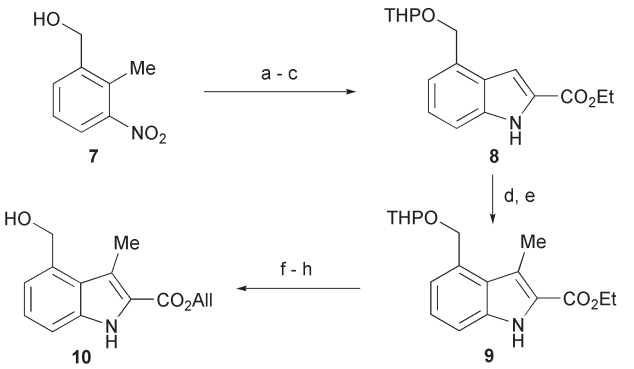
Scheme 1



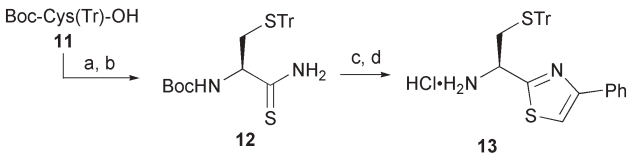
Scheme 2 *Reagents and conditions*: (a) LHMDS, 2-benzenesulfonyl-3-phenyloxaziridine, THF, −78 °C; (b) TBSCl, imidazole, DMF (68% over 2 steps); (c) H_2, Pd–C (10%), MeOH; (d) EtO_2CCl, Et_3N, THF then NH_4OH (30% aq.) (88% over 2 steps); (e) Lawesson's reagent, THF; (f) 3-bromopyruvic acid, EtOH, $CaCO_3$ (57% over 2 steps).

proposed cyclization precursor **3**, we required an indole fragment with an orthogonally protected carboxylate at C-2, and we elected to use an allyl group since it can be removed under non-hydrolytic conditions.[32] Hence, simple saponification of **9** to the free acid was followed by DCC-mediated coupling with allyl alcohol, and final deprotection of the THP group to reveal the desired indole fragment **10** in eight steps and an overall yield of 38% (Scheme 3).

The model thiazole fragment A was synthesized in four steps (Scheme 4). Commercial *N*-Boc-*S*-tritylcysteine **11** was converted into the corresponding amide *via* the formation of the mixed



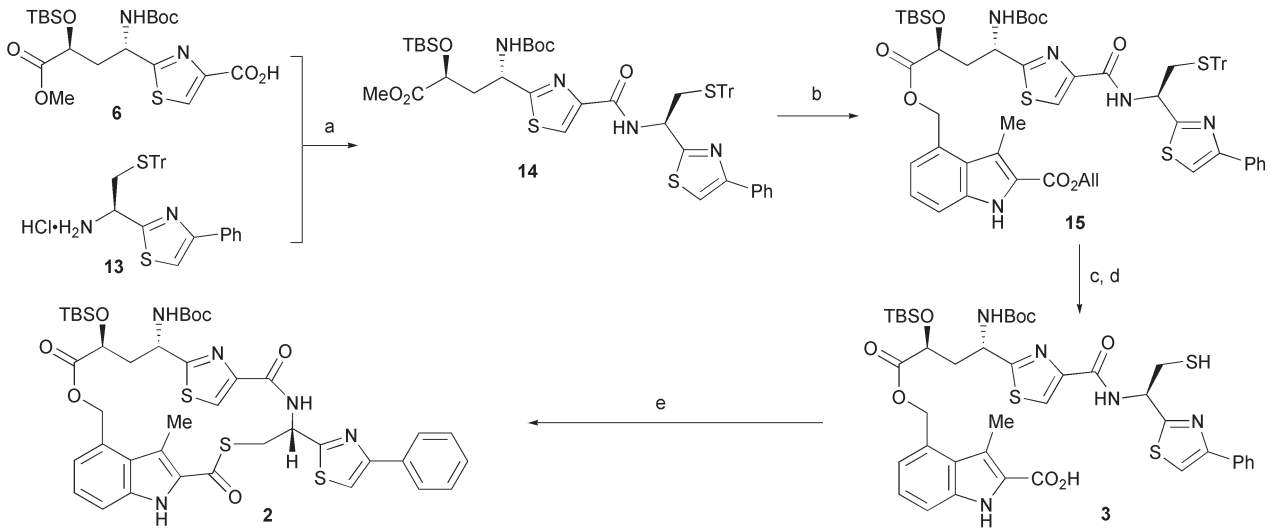
Scheme 3 *Reagents and conditions*: (a) dihydropyran, TsOH, DCM (91%); (b) NaH, DMF, diethyl oxalate (87%); (c) H_2, Pd–C (10%), EtOH (98%); (d) NBS, THF (96%); (e) trimethylboroxine, $Pd(PPh_3)_4$, K_2CO_3, dioxane (78%); (f) LiOH, MeOH, THF, H_2O (2 : 2 : 1) (96%); (g) DCC, allyl alcohol, CH_2Cl_2, DMAP (79%); (h) EtOH, PPTS (87%).



Scheme 4 *Reagents and conditions*: (a) EtO_2CCl, Et_3N, THF then NH_4OH (98%); (b) Lawesson's reagent, THF (93%); (c) 2′-bromoacetophenone, EtOH (78%); (d) 4 M HCl in dioxane (75%).

anhydride with subsequent treatment with aqueous ammonia. Conversion into the thioamide **12** was achieved by treatment with Lawesson's reagent, and thiazole formation was accomplished by treatment of **12** with 2′-bromoacetophenone in ethanol in a good yield of 78%. A final acid mediated deprotection gave the desired model fragment **13** as the HCl salt in 75% yield (Scheme 4).

PyBOP® promoted amide formation between fragments **6** and **13** gave the bis-thiazole **14** in 81% yield and with no racemization, as indicated by ^{13}C NMR spectroscopy of the product. Saponification of **14** gave the corresponding acid, coupling of which with indole **10** was attempted using a variety of methods, including Mitsunobu, EDCI, and modified Yamaguchi conditions, but only gave the desired ester **15** in yields of up to 40%. However, esterification using DCC and a catalytic amount of DMAP did deliver the desired ester **15** although significant amounts of the unreactive *N*-acylurea by-product were also recovered. Satisfyingly, upon addition of HOAt to the reaction mixture, the urea by-product was not observed, and the desired ester **15** could be obtained in 69% yield over the two steps from the ester **14** (Scheme 5). The free acid at the 2-position of the indole ring of **15** was revealed by standard palladium catalyzed allyl deprotection with morpholine as the scavenger yielding the acid in 93% yield. Deprotection of the trityl protected cysteine sulfur was accomplished *via* a modified one-pot silver(I) protocol.[33] Hence, treatment of the protected thiol with $AgNO_3$ in the presence of pyridine in methanol at 0 °C cleanly gave the silver thiolate. Quenching of the reaction mixture with 2-mercaptoethanol then revealed the free thiol acid **3** in a yield of 75%. Finally, cyclization to the thiolactone **2** was achieved using DCC or PyBOP® mediated coupling in high dilution conditions (*ca.* 0.01 M), yielding the southern hemisphere model **2** in 52% and 47% yield



Scheme 5 *Reagents and conditions*: (a) PyBOP®, CH_2Cl_2, DIPEA (81%); (b) (i) LiOH, THF, MeOH, H_2O (2 : 2 : 1), (ii) **10**, DCC, DMAP, HOAt, CH_2Cl_2 (69% over 2 steps); (c) $Pd(OAc)_2$ (10 mol%), PPh_3, THF, morpholine (93%); (d) $AgNO_3$, pyridine, MeOH, 30 min, 0 °C, then $HSCH_2CH_2OH$ (10 equiv.), rt (75%); (e) *Method A*. DCC (1.2 equiv.), THF (0.01 M), 1 h, then DMAP (1.2 equiv.), 16 h (52%); *Method B*. PyBOP® (1.2 equiv.), DIPEA (2.0 equiv.), THF (0.01 M), 16 h (47%).

respectively. The spectroscopic data for the macrocycle **2** show, *inter alia*, a signal at 182.8 ppm in its ^{13}C NMR spectrum characteristic of a thiolactone (*cf.* the thiolactone carbon in nosiheptide at 181.3 ppm[8]). Hence, the synthesis of the macrocyclic thiodepsipeptide model southern hemisphere for nosiheptide was completed in an overall yield of 9.6% with a longest linear sequence of 13 steps.

In conclusion, the strategy of successive amide, ester and thioester bond formation between orthogonally protected dicarboxylate, hydroxy-acid and amino-thiol fragments has proved to be a viable and robust route towards the lower 20-membered macrocyclic array of nosiheptide **1**. The methodology establishes, for the first time, that macrocyclic thiodepsipeptides can be accessed by formation of the thioester bond in the macrocyclization step, and paves the way for a synthesis of nosiheptide itself.

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