The first synthesis of promothiocin A

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The first total synthesis of the naturally occurring macrocyclic thiopeptide promothiocin A 1 is described.

Promothiocin A **1**, isolated from *Streptomyces* sp. SF2741, is a member of the thiopeptide family of antibiotics.[1] These natural products, which inhibit protein synthesis in bacteria, are characterised by their complex structure in which an array of heterocyclic rings is incorporated into a macrocyclic peptide framework. Despite the fascinating biological activity of the thiopeptide antibiotics, little synthetic work has been carried out to date, although the synthesis of the pyridine fragments of the micrococcins, sulfomycin and nosiheptide has been addressed,[2–5] and very recently micrococcin P has yielded to synthesis.[6] In continuation of our interest in the synthesis of heterocyclic natural products,[7] we now report the first total synthesis of promothiocin A **1**, thereby confirming the structure and stereochemistry.

The structure of promothiocin A **1** was established by NMR spectroscopy, although the stereochemistry of the natural product was not reported.[1] Therefore we have assumed that the three stereocentres result from natural amino acids (see Fig. 1) and could be incorporated from suitable derivatives of (*S*)-alanine and (*S*)-valine. The overall plan, indicated by the arrows in Fig. 1, was to form the macrocycle by two peptide coupling reactions (1 and 2), followed by introduction of the dehydroalanine side chain (3).

The starting point was the synthesis of the two oxazoles **2** and **3** from (*S*)-alanine and glycine, respectively. This was readily achieved using our previously published method;[8] thus rhodium(II) acetate catalysed reaction of the *N*-protected amino acid amides with methyl 2-diazo-3-oxobutanoate resulted in clean insertion of the metallocarbenoid into the amide N–H bond. Cyclodehydration of the resulting keto amides using the Wipf protocol (Ph_3P, I_2, Et_3N)[9] gave the required oxazoles **2** and **3** in 56 and 49% overall yield respectively (Scheme 1). The glycine derived oxazole **3** was deprotected to give the 2-aminomethyloxazole **4** for subsequent coupling, whereas the alanine derived oxazole **2** was converted into the oxazole-thiazole-pyridine fragment **5** using our previously developed method,[10] based on the Bohlmann–Rahtz pyridine synthesis.[11]

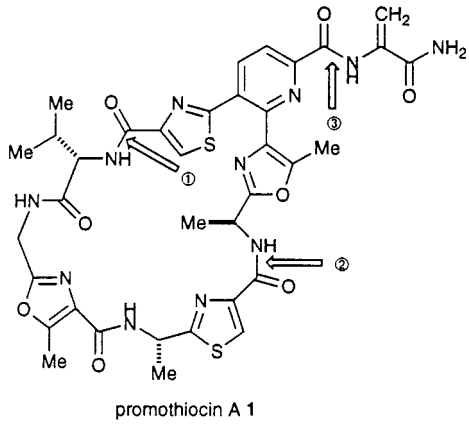
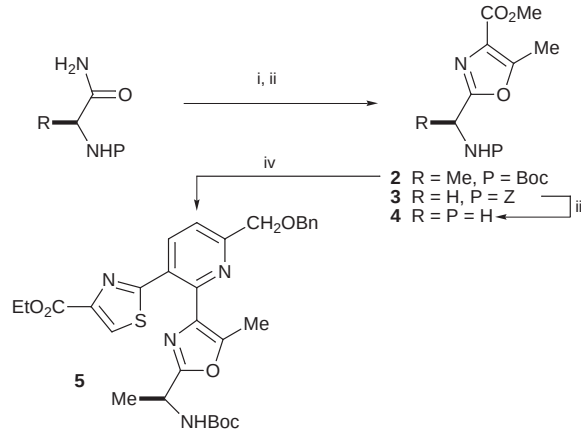
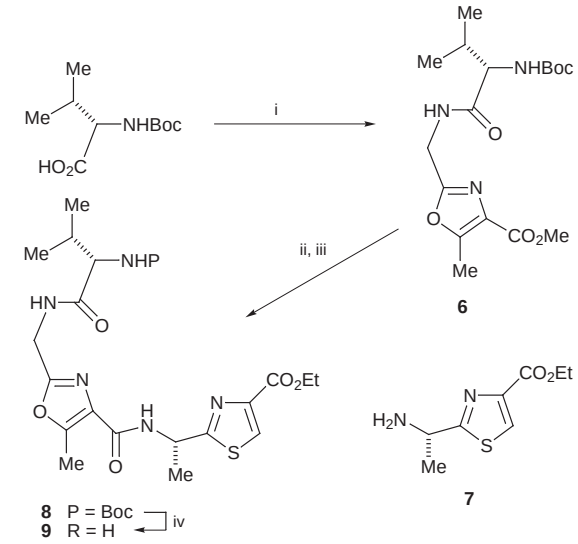


Fig. 1 Promothiocin A **1** and proposed disconnections

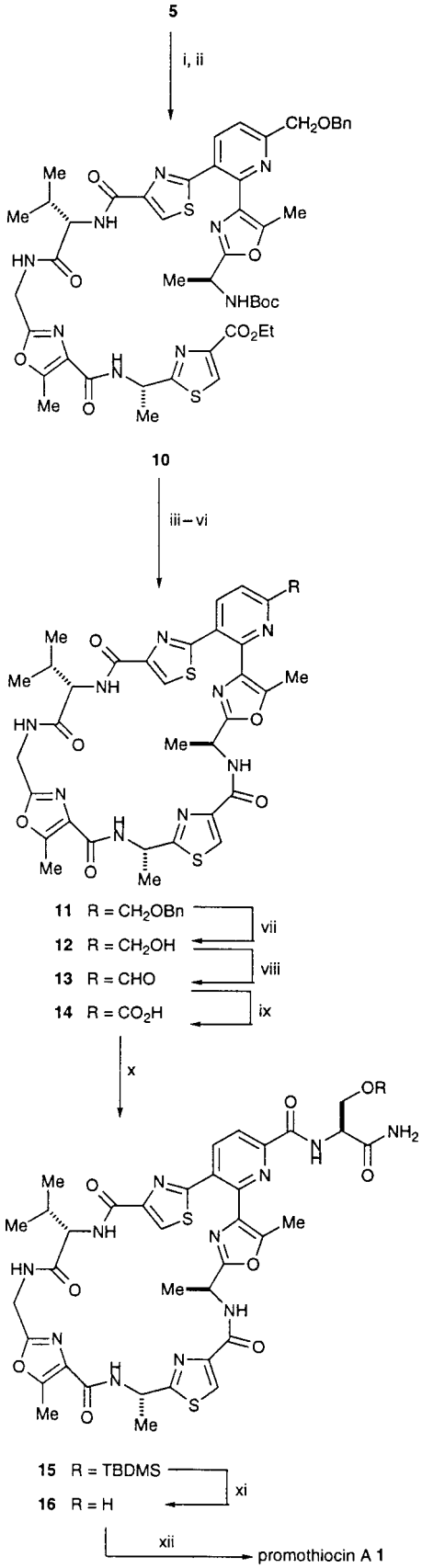


Scheme 1 *Reagents and conditions*: i, methyl 2-diazo-3-oxobutanoate cat. $Rh_2(OAc)_4$, $CHCl_3$, heat (80% for **2**, 76% for **3**); ii, Ph_3P, I_2, Et_3N, CH_2Cl_2 (70% for **2**, 64% for **3**); iii, H_2, Pd-C, MeOH (100%); iv, see ref. 10

The lower valine-oxazole-thiazole fragment **9** was obtained as shown in Scheme 2. Thus *N*-Boc-valine was coupled to the aminomethyloxazole **4** in high yield by mixed anhydride methodology using isobutyl chloroformate and *N*-methylmorpholine (NMM) to give the oxazole **6**. The alanine derived thiazole **7** was obtained from the known *N*-Boc derivative, prepared using the modified Hantzsch reaction,[12] the standard conditions leading to extensive racemisation, and coupled to the carboxylic acid derived by hydrolysis of the ester **6** to give the valine-oxazole-thiazole **8** in excellent yield (Scheme 2). Finally



Scheme 2 *Reagents and conditions*: i, Bu^iO_2CCl, NMM, THF, then **4** (87%); ii, LiOH, aq. THF (93%); iii, Bu^iO_2CCl, NMM, THF then **7** (84%); iv, AcCl, EtOH (100%)



Scheme 3 *Reagents and conditions*: i, LiOH, aq. THF (94%); ii, Bu^iO_2CCl, NMM, THF, then **9** (69%); iii, LiOH, aq. THF (97%); iv, C_6F_5OH, EDCI, CH_2Cl_2 (100%); v, 4 M HCl in dioxane, then aq. $KHCO_3$; vi, Et_3N, $CHCl_3$ (55% over 2 steps); vii, $BCl_3{\cdot}SMe_2$, CH_2Cl_2 (39%); viii, IBX, DMSO (81%); ix, $NaClO_2$, KH_2PO_4, 2-methylbut-2-ene, aq. Bu^tOH (70%); x, *O*-TBDMS-serinamide, EDCI, CH_2Cl_2 (50%); xi, TBAF, THF (57%); xii, MsCl, Et_3N, CH_2Cl_2, then Et_3N (59%)

deprotection of the *N*-terminal Boc group with ethanolic HCl gave the free amine **9** for subsequent coupling.

The coupling of the lower and upper fragments of the promothiocin macrocycle was achieved using mixed anhydride methodology (Scheme 3). Hydrolysis of the ester group in the oxazole-thiazole-pyridine **5** was followed by activation with isobutyl chloroformate/NMM and coupling with the amine **9** to give the terminally protected 'linear peptide' **10** in good yield. Although there are several methods available for macrolactamisation, we have found the Schmidt protocol,[13] used in our recent synthesis of nostocyclamide,[7] to be particularly reliable. Hence the ester group in **10** was hydrolysed and converted into the corresponding pentafluorophenyl ester by coupling with pentafluorophenol in the presence of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI). The pentafluorophenyl ester was not purified but underwent deprotection at the *N*-terminus on treatment with HCl in dioxane. Work-up and treatment with triethylamine resulted in lactamisation to give the promothiocin macrocycle **11** in 55% yield. The synthesis was completed by elaboration of the dehydroalaninamide side chain, although these final steps proved far from trivial. Deprotection of the benzyl ether to give the pyridine-2-methanol derivative **12** was followed by conversion to the aldehyde **13** using *o*-iodoxybenzoic acid (IBX) in DMSO,[14] and further oxidation with sodium chlorite[15] to give the desired acid **14**. Coupling of the acid **14** with the *tert*-butyldimethylsilyl ether of (*S*)-serinamide using EDCI gave the amide **15**; deprotection of the serine side-chain with TBAF was followed by dehydration (MsCl, Et_3N) to give promothiocin A **1** (Scheme 3). The synthetic material had 400 MHz ^1H and 100 MHz ^{13}C NMR spectra identical to those reported for the natural product,[1] and its specific rotation of $[\alpha]_D^{23}$ + 87.3 (*c* 0.34, $CHCl_3$–MeOH, 1 : 1) [lit.,[1] +79.2 (*c* 0.69, $CHCl_3$–MeOH, 1 : 1)] strongly implies that the natural product does indeed have the stereochemistry indicated in Fig. 1. Thus we have completed the first total synthesis of the thiopeptide promothiocin A **1**, and established the stereostructure of the natural product.

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Notes and References

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