Studies on Thiopeptide Antibiotics: Synthesis of an Oxazole-Thiazole-Pyridine Fragment related to Promothiocin A

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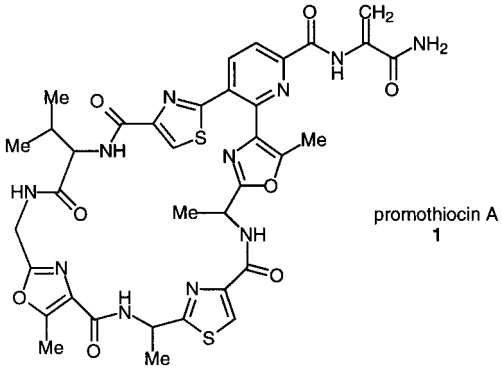
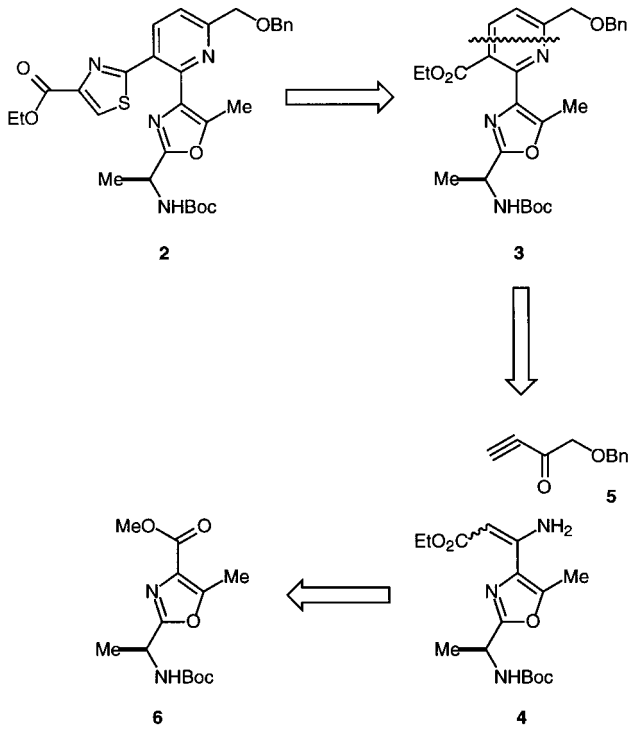
Promothiocin A **1**, isolated from *Streptomyces* sp. SF2741, is a member of the thiopeptide family of antibiotics.[1] These antibiotics, which inhibit protein synthesis in bacteria and induce the expression of various genes (of unknown function), are characterised by their complex structure in which an array of heterocyclic rings is incorporated into a macrocyclic peptide framework. Despite the fascinating biological activity of the thiopeptide antibiotics, very 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 recently,[2-5] as has the construction of some related pyridines.[6,7] In continuation of our interest in the synthesis of heterocyclic natural products,[8] we now report the synthesis of the oxazole-thiazole-pyridine **2**, which contains the required functionality for elaboration into promothiocin A **1**.



promothiocin A
1

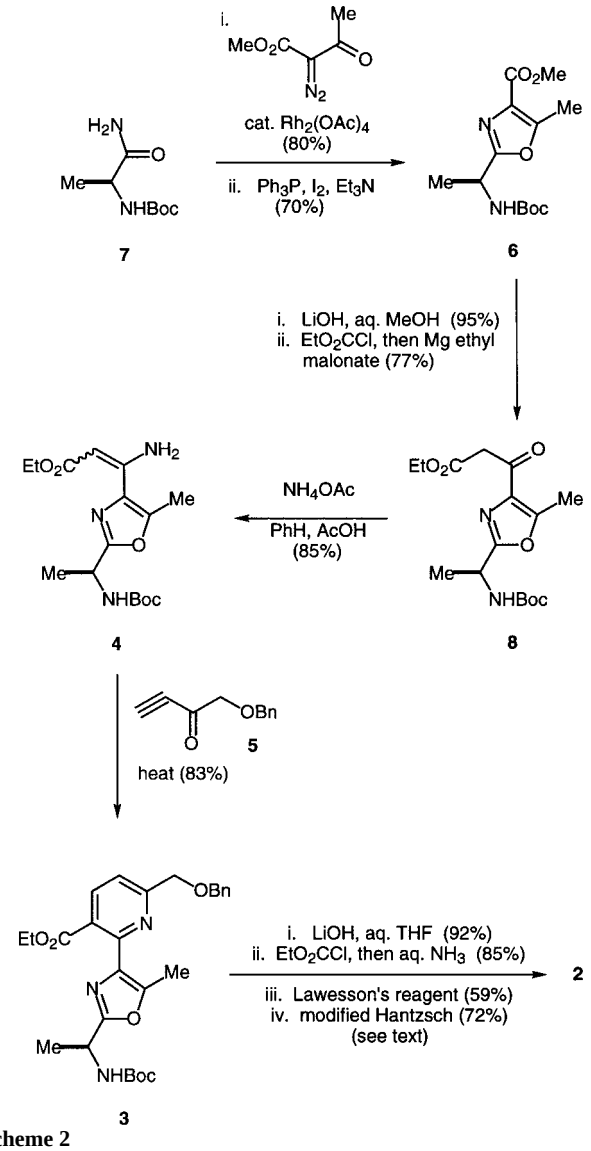
With the exception of Ciufolini's recent synthesis of the heterocyclic core of the micrococcins, in which the pyridine ring is assembled from two fragments which are combined to give a 1,5-diketone precursor for subsequent reaction with ammonia and dehydrogenation,[4] most approaches to related heterocycles rely on the stepwise modification of pre-formed pyridine rings. Our plan, outlined in Scheme 1, was to construct the pyridine **3** by reaction of the enamine **4** with the ynone **5**. This method of pyridine formation (enamine plus ynone), first reported by Bohlmann and Rahtz 40 years ago,[9] has found little or no use to date, and although it is related to the corresponding reactions with enones and hence to the well known Hantzsch pyridine synthesis, it has the considerable advantage in that the aromatic product is formed directly.



Scheme 1

Since the stereochemistry of the natural product was not reported, we have assumed that the stereocentres derive from "natural" L-aminoacids and therefore the synthesis of the pyridine **2** started from a derivative of L(S)-alanine. *N*-Boc-Alaninamide **7** was converted into the chiral oxazole **6** using our previously published method;[10] thus rhodium(II) catalysed reaction of **7** with methyl diazoacetoacetate resulted in clean insertion of the metallocarbenoid into the amide N-H bond (80%). Cyclodehydration of the resulting keto-amide using the Wipf protocol (Ph_3P, I_2, Et_3N)[11] gave the required oxazole **6** in 70% yield.[12,13] To prepare the required enamine **4** necessitated homologation of the oxazole ester **6** to the corresponding β-ketoester **8**; thus hydrolysis of the ester **6** (95%) was followed by mixed anhydride formation wth ethyl chloroformate, and reaction with magnesium ethyl malonate. This method was more effective than related procedures using imidazolide intermediates.[14] Reaction of **8** with ammonium acetate in benzene-acetic acid then gave the enamine **4** in 85% yield (Scheme 2),[15,16] although an increase in the amount of acetic acid and ammonium acetate over and above the literature conditions[15] was necessary for complete conversion. The key pyridine forming step was carried out by heating the enamine **4** with ynone **5**[17] in ethanol at 50 °C overnight to effect the initial conjugate addition, followed by removal of the solvent and heating the residue at 140 °C under vacuum to effect cyclisation. This resulted in a good yield of the desired pyridine **3**,[18] establishing for the first time that the Bohlmann-Rahtz method can be used for the synthesis of relatively complex pyridines.

With the pyridine-3-ester **3** in hand, the thiazole ring was elaborated using the modified Hantzsch reaction,[19] the standard procedure resulting in a complex mixture of products. Hydrolysis of the ester (92%), was followed by amide formation (85%), and conversion into the thioamide (59%) which was reacted with ethyl bromopyruvate and potassium hydrogen carbonate in THF at 0 °C followed by treatment with TFAA in the presence of 2,6-lutidine to give the oxazole-thiazole-pyridine **2**,[20] containing all the necessary functionality for elaboration into the natural product.



Scheme 2

Acknowledgements

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References and Notes

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(12) The rhodium(II) catalysed N-H insertion and subsequent cyclodehydration reactions were carried out as described in reference 10.

(13) (S)-Methyl 2-[1-(*tert*-Butoxycarbonyl)aminoethyl]oxazole-4-carboxylate **6**, mp 94-95 °C (from ether-light petroleum); $[\alpha]^{22}_D$= -44.0° (*c* 1.0 in $CHCl_3$); ν_{max} (KBr)/cm^{-1} 3357, 1719, 1689; δ_H (400 MHz; $CDCl_3$) 5.18 (1 H, bs, exch D_2O, NH), 4.92 (1 H, m, CH), 3.89 (3 H, s, MeO), 2.59 (3 H, s, Me), 1.51 (3 H, d, *J* 7.0, CHMe), and 1.42 (9 H, s, CMe_3); the optical purity was confirmed as >99% by HPLC on a chiral stationary phase (Chiralpak AD, hexane : 2-propanol, 9 : 1, 1.0 ml/min) by comparison with the racemate.

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(16) (S)-Ethyl 3-Amino-3-{2-[1-(*tert*-butoxycarbonyl)aminoethyl]-oxazol-4-yl}propenoate **4**, colourless needles, mp 103-104 °C (from ether-light petroleum); $[\alpha]^{22}_D$ = -60.5° (*c* 1.1 in $CHCl_3$); ν_{max} (KBr)/cm^{-1} 3455, 3351, 1681, 1669; δ_H (400 MHz; $CDCl_3$) 6.92 (2 H, bs, exch D_2O, NH_2), 5.09 (1 H, bs, exch D_2O, NH), 4.89 (1 H, m, CHMe), 4.83 (1 H, m, CH), 4.16 (2 H, q, *J* 7.1, CH_2Me), 2.49 (3 H, s, Me), 1.51 (3 H, d, *J* 7.0, CHMe), 1.45 (9 H, s, CMe_3), and 1.29 (3 H, t, *J* 7.1, CH_2Me).

(17) Prepared by addition of ethynylmagnesium bromide to benzyloxyacetaldehyde in THF (86%), followed by oxidation to the ketone with *o*-iodoxybenzoic acid (IBX) in DMSO (89%). For oxidations with IBX, see: Frigerio, M.; Santagostino, M. *Tetrahedron Lett.* **1994**, *35*, 8019.

(18) (S)-Ethyl 2-{2-[1-(*tert*-Butoxycarbonyl)aminoethyl]oxazol-4-yl}-6-(benzyloxy)methylpyridine-3-carboxylate **3**, pale yellow foam; $[\alpha]^{22}_D$ = -21.4° (*c* 0.6 in $CHCl_3$); ν_{max} ($CHCl_3$)/cm^{-1} 3442, 1715; δ_H (400 MHz; $CDCl_3$) 7.96 (1 H, d, *J* 8.0, 4-H), 7.48 (1 H, d, *J* 8.0, 5-H), 7.41-7.27 (5 H, m, ArH), 5.23 (1 H, d, *J* 7.2, exch D_2O, NH), 4.94 (1 H, m, CH), 4.72 (2 H, s, PyCH_2), 4.66 (2 H, s, PhCH_2), 4.31 (2 H, q, *J* 7.1, CH_2Me), 2.56 (3 H, s, Me), 1.52 (3 H, d, *J* 6.9, CHMe), 1.45 (9 H, s, CMe_3), and 1.28 (3 H, t, *J* 7.1, CH_2Me).

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(20) (S)-2-{2-[1-(*tert*-Butoxycarbonyl)aminoethyl]oxazol-4-yl}-3-(4-ethoxycarbonylthiazol-2-yl)-6-(benzyloxy)methylpyridine **2**, pale yellow oil; $[\alpha]^{23}_D$ = -26.8° (*c* 1.3 in $CHCl_3$); ν_{max} ($CHCl_3$)/cm^{-1} 3437, 1715; δ_H (400 MHz; $CDCl_3$) 8.35 (1 H, d, *J* 8.1, 4-H), 8.17 (1 H, s, SCH), 7.61 (1 H, d, *J* 8.1, 5-H), 7.41-7.26 (5 H, m, ArH), 5.09 (1 H, bs, exch D_2O, NH), 4.89 (1 H, m, CH), 4.76 (2 H, s, PyCH_2), 4.67 (2 H, s, PhCH_2), 4.42 (2 H, q, *J* 7.2, CH_2Me), 2.26 (3 H, s, Me), 1.46 (3 H, d, *J* 6.8, CHMe), 1.43 (9 H, s, CMe_3), and 1.40 (3 H, t, *J* 7.2, CH_2Me); δ_C (100.6 MHz; $CDCl_3$) 165.4 (C), 162.9 (C), 161.3 (C), 160.2 (C), 154.9 (C), 154.8 (C), 148.6 (C), 147.1 (C), 138.9 (CH), 137.7 (C), 132.6 (C), 128.9 (CH), 128.5 (CH), 127.9 (CH), 127.8 (CH), 127.6 (C), 120.2 (CH), 79.8 (C), 73.1 (CH_2), 72.7 (CH_2), 61.5 (CH_2), 44.7 (CH), 28.3 (Me), 20.3 (Me), 14.3 (Me), and 11.1 (Me).