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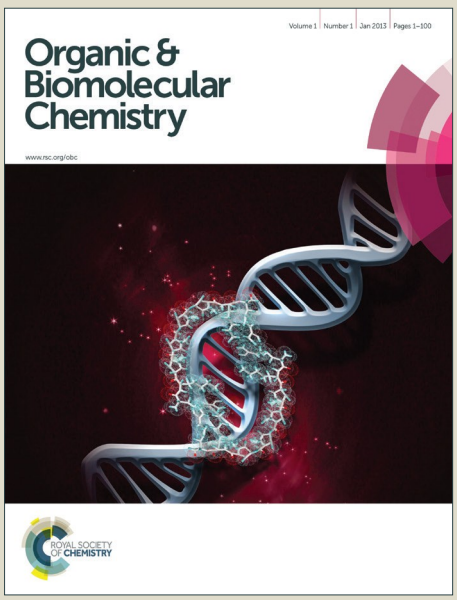

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ARTICLE TYPE

Total Synthesis of the Azolemycins

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The first total syntheses of newly isolated polyazole natural products azolemycins A-D, along with the synthesis of the tetra-oxazole non-natural analogue, are described.

Introduction

Azolemycins A-D are compounds recently isolated from the soil bacterium, *Streptomyces* sp. FXJ1.264, each existing as two geometric isomers.[1] A combination of mass spectrometry and 1D and 2D NMR spectrometry identified the structure as a modified heptapeptide, with four linked azoles and an *N*-terminal oxime. The major isolated azolemycins are the *N*-hydroxy derivative with the greater proportion as the *E*-oxime geometric isomer **1a**, named azolemycin A and the lesser proportion as the *Z*-geometric isomer **1b**, named azolemycin B. The minor isolated azolemycins differ only in containing an *N*-methoxy group and again were isolated as the *E*-isomer **2a** and the *Z*-isomer **2b** (azolemycins C and D respectively).

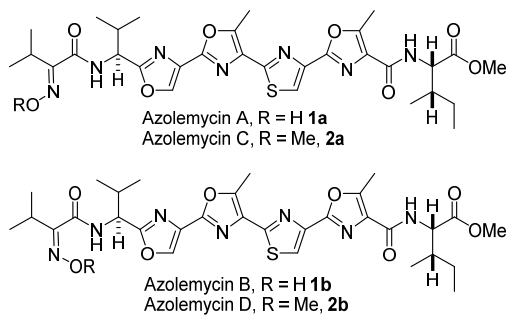


Figure 1 Azolemycins A-D.

The biosynthesis of the azolemycins has been described,[1] and is believed to involve the posttranslational modification of a ribosomally-biosynthesised 7 amino-acid precursor. The oxime functional group is believed to occur from a previously unknown posttranslational modification, apparently utilizing a flavin-dependent monooxygenase to catalyse the oxidation of an *N*-terminal valine residue to the corresponding amine.[1] Oxime-containing natural products are unusual, and those reported, including caerulomycin A, althiomycin, collismycin A and nocardicins A and B,[2] result from nonribosomal peptide synthesis.

Until the 1980s, very few thiazole and oxazole-containing natural products were known, but an increasing array have since been identified, particularly derived from marine sources.[3] These products range from single oxazoles and thiazoles to more complicated linked chains or macrocycles of concatenated azoles.

The combination of potent biological activity of many of these azole products and the exciting synthetic challenges they pose has made them extremely attractive targets for total syntheses,[4] and a wide range of reagents have been developed for to allow for this.[5]

Polyazoles, or polyazole-containing, natural products made by total synthesis range from the relatively simple linked bis- and triazole motifs, as found in the hennoxazoles,[6] muscorides,[7] bleomycins,[8] and myxothiazols,[9] to more complicated macrocyclic molecules such as the heptazole telomestatin, the related YM-216391, IB-01211 and more recently, plantazolicin.[10] [4b, 11]

Synthetic Strategy

Our chosen disconnection of the azolemycins involved a convergent synthesis, with late stage formation of the central thiazole, similar to the strategy used in the synthesis of YM-216391.[11a] The disconnection gave four distinct units: the isopropyl oxime **3**, the left-hand mixed bisoxazole fragment **4**, the right-hand methyl oxazole **5** and the isoleucine methyl ester **6** (figure 2).

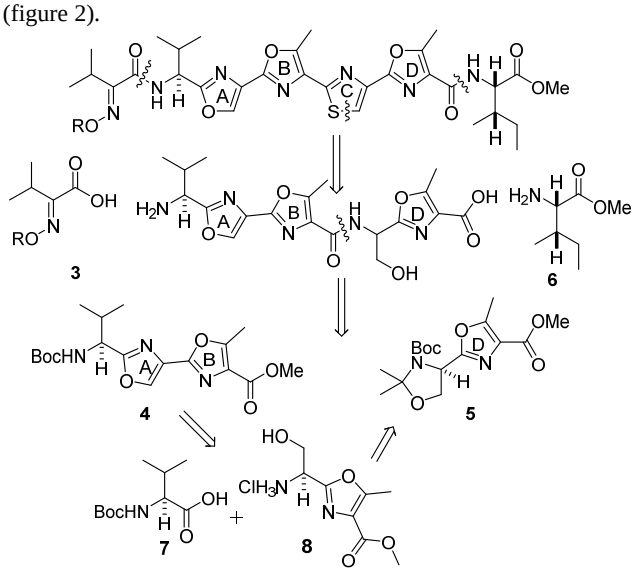
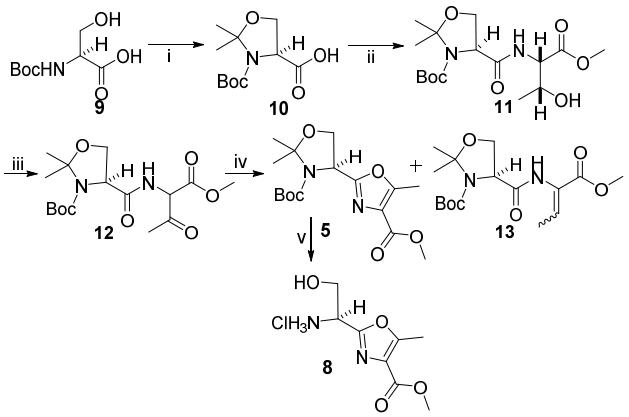


Figure 2 Preliminary disconnections for the synthesis of azolemycin A

As we planned to synthesise the thiazole from serine, the tetraazole core could be divided into two repeating serine-threonine dimers, corresponding to a common threonine derived oxazole **5**. We therefore further disconnected the AB unit **4** into

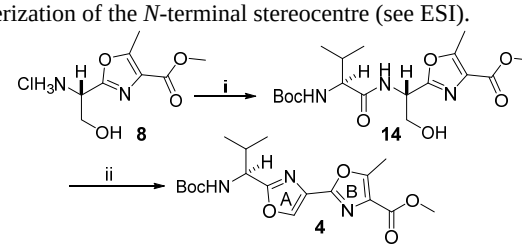
oxazole **8** and Boc-L-valine, **7** (figure 2). The protected oxazole building block **5** was synthesised from the diprotected Boc-serine acetonide **10**. An HOBt/EDCI peptide coupling gave the threonine dipeptide **11** in excellent yields. Oxidation of the threonine residue using the Parikh-Doering conditions,[12] and cyclodehydration using $PPh_3/I_2/NEt_3$, as described by Wipf,[7c] gave the oxazole **5** (scheme 1). In some reaction batches some unreacted alcohol **11** was carried through, with ketone **12**, to the cyclodehydration step. In these cases, the elimination product **13** was obtained and this was extremely difficult to separate from oxazole **5**. We therefore performed a Sharpless dihydroxylation on the mixture of alkene **13** and oxazole **5**.[13] This chemoselective procedure did not affect the oxazole but, as predicted, a simple aqueous work-up afforded only the clean oxazole **5**. We propose that the alkene **13** formed an unstable diol that decomposed to give two non-isolated water soluble products, an amide and a keto-ester.



Scheme 1 (i) Dimethoxypropane, TsOH.H_2O, CH_2Cl_2, 40 °C, 2 h, 80 %; (ii) l-Thr.OMe.HCl, EDCI, cat. HOBt, EtOH, 0 °C to rt, 18 h, 84 %; (iii) SO_3.pyr, DMSO, $^iPr_2EtN$, CH_2Cl_2, 0 °C, 3 h; (iv) PPh_3, I_2, NEt_3, CH_2Cl_2, 0 °C to rt, 18 h, 32 % over 2 steps; (v) AcCl, MeOH, rt, 18h, quant

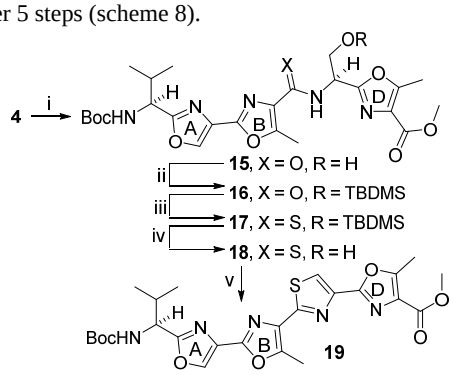
The right hand AB unit was formed from the tripeptide **14**, which was made by coupling Boc-valine **7** to the deblocked oxazole-amine **8** (scheme 2). The serine residue was then cyclodehydrated using DAST to give the crude oxazoline, as described by Williams *et al.* in their synthesis of (-)-hennoxazole A.[6a]. Attempts to oxidise this using standard conditions (e.g. $BrCCl_3$ and DBU,[5f] or $BrCCl_3$, CCl_4 and pyridine[14]) were unsuccessful, presumably due to the unactivated nature of the oxazoline. Though oxidations of this type of relatively unactivated oxazoline are not common in the literature, examples do exist which use either MnO_2 or NiO_2,[5i, 11c, 11d] which are assumed to follow a similar mechanism.[15] Despite being a widely used oxidising agent, many procedures do not state the provenance or preparation method of MnO_2, and the method of preparation has been shown to have a significant effect on the oxidative ability of the reagent.[16] Yokokawa and Shiori have reported that chemical manganese dioxide (CMD), manufactured for the production of dry batteries, is a superior oxidising agent than MnO_2 prepared by other methods.[17] We therefore investigated a method of producing activated MnO_2 proposed by Ball, Goodwin and Morton, where an aqueous solution of potassium permanganate is reacted with manganese sulfate in neutral medium to give a precipitate of MnO_2.[18] The MnO_2 is then activated as required by azeotropic drying with toluene, as described by Goldman.[19] This provides a source of MnO_2 presumably similar in composition to the CMD, and indeed a similar technique using benzene-dried CMD was successfully exploited by Shiori and Yokokawa for the synthesis of a variety of thiazole-containing natural products. [20]

The oxazoline was treated with an excess of the freshly activated MnO_2 and, on completion, the residual MnO_2 was reduced using aqueous SO_2. A simple aqueous work-up and silica chromatography gave the clean bisoxazole **4** in 27 % yield over two steps. It is likely that loss of the *N*-terminal Boc group during the reduction of the MnO_2 cause the low yield for this step, and a more resilient protecting group would undoubtedly have improved the yield. As this step provided us with sufficient material to complete the synthesis however, we did not attempt to optimise it further. One major concern was retaining the stereointegrity of the *N*-terminal valine during oxazole synthesis. Previous work within the group had identified isoleucine as a useful residue to detect epimerization by ^1H NMR in similar reactions. Boc-Ile-Ser-OMe was used as a model compound for oxazole, and we were encouraged to see no apparent epimerization of the *N*-terminal stereocentre (see ESI).



Scheme 2 (i) **7**, EDCI, cat. HOBt, NMM, EtOH, rt, 18 h, 88 %; (ii) DAST, CH_2Cl_2, -78 °C to rt 2 h; then MnO_2, toluene, 110 °C, 6 h, 27 %.

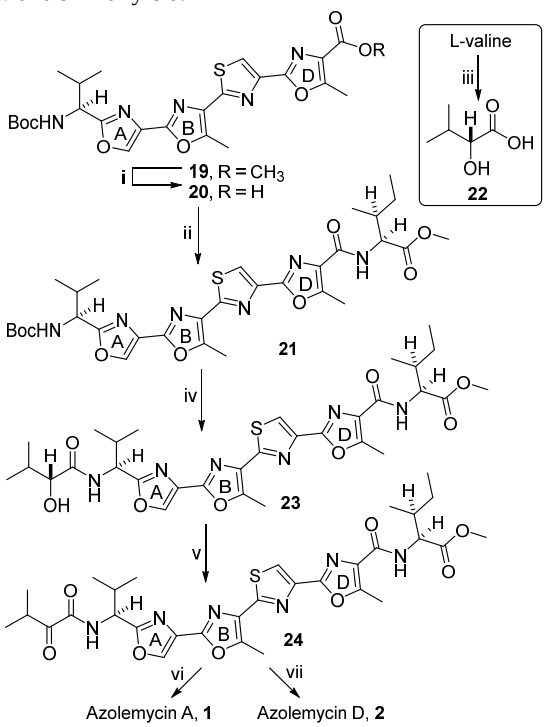
Methyl ester **4** was hydrolysed, and the resulting acid underwent an EDCI/HOBt coupling with amine **8** to give the pentapeptide, **15**. Protection of the pendant alcohol to give **16** was required to prevent beta-elimination during the formation of the thioamide, which was achieved in excellent yields with Lawesson's reagent to give **17**. Deprotection of the alcohol provided **18**, which underwent for a further DAST mediated cyclodehydration to give the crude thiazoline. This was oxidised using $BrCCl_3$, CCl_4 and pyridine to give thiazole **19** in a 27 % yield over 5 steps (scheme 8).



Scheme 3 (i) LiOH, H_2O, THF, rt, 4h, 99%; then **8**, EDCI, cat. HOBt, NMM, EtOH, rt, 18 h, 73 %; (ii) TBDMSCl, imidazole, DMF, 0 °C, 3 h, 83 %; (ii) Lawesson's reagent, toluene, THF, 110 °C, 44 h, 81 %; (iii) TBAF, THF, 0 °C, 1 h, 99 %; (iv) DAST,

CH_2Cl_2, -78 °C to rt 1.5 h; then DBU, pyr., CCl_4, MeCN, 0 °C to rt, 18 h, 58 % over 2 steps.

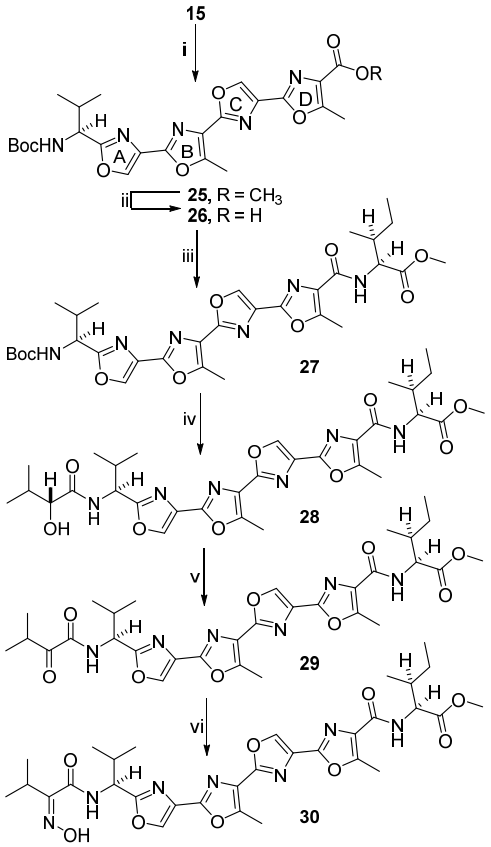
With the synthesis of the four azoles achieved, the completion of the natural products could be attempted. Saponification of the methyl ester **19** was more difficult than expected due to its low solubility, but long reaction times, high dilution and a mixture of solvents provided the hydrolysis product **20**, which was readily coupled to isoleucine methyl ester to give the hexapeptide **21**. Removal of the Boc-protecting group allowed coupling 2-hydroxy-3-methylbutyric acid **22,** made from L-valine according to the method of Bauer and Gajewiak,[21] to give alcohol **23**. This alcohol was oxidised to the ketone **24** which was reacted with hydroxylamine to give azolemycin A, **1a** (scheme 4; 21 steps, 16 steps longest linear sequence, with an overall yield of 0.3 %). Reaction of ketone **24** with methoxyamine gave azolemycin D, **2b**, with a similar yield.



Scheme 4, MeOH, THF, CH_2Cl_2, H_2O, rt, 26 h, 92 %; (ii) L-Ile-OMe.HCl, EDCI, cat. HOBt, NMM, EtOH, rt, 18 h, 84 %; (iii) $NaNO_2$, H_2SO_4, H_2O, 0 °C to rt, 18 h, 31 %; (iv)a) MeOH, AcCl,rt, 2 h; b) **22**, EDCI, cat. HOBt, NMM, EtOH, 0 °C to rt, 18 h, 90 % over 2 steps; (v) SO_3.pyr., NEt_3.DMSO, CH_2Cl_2, 0 °C, 3 h, 65 %; (vi) NH_2OH.HCl, pyridine, MeOH, CH_2Cl_2, rt, 24 h, 58 %; (vii) NH_2OMe.HCl, pyridine, MeOH, CH_2Cl_2, rt, 4h, 62 %.

The ^{1}H NMR spectra of the two synthesized natural products correlate well with the spectra of the naturally derived molecules. However, while the naturally derived azolemycins were isolated separately as both the *E*- and *Z*- oxime isomers, a separation was not possible for the synthesized product, **1**. The synthetic product consisted mainly of the *E*-oxime **1a** (azolemycin A), with only traces of the *Z*-isomer **1b** (azolemycin B), based on the valine α-CH peaks in ^{1}H NMR spectra. In contrast, the synthetic *N*-methoxy azolemycins, **2**, were obtained as primarily the *Z*-geometric oxime isomer (azolemycin D), but in $CDCl_3$ showed near complete conversion to the *E*-isomer (azolemycin C) in around 5 days.

To extend this project, the synthesis of an azolemycin-like tetra-oxazole natural product analogue **30** was attempted. It was envisaged that any activity shown by the natural product azolemycin A could be compared with this tetraoxazole equivalent to observe the requirement, if any, for the C-ring thiazole. The synthesis of **30** was achieved in a straightforward fashion by cyclisation and oxidation of serine-derived precursor **15**, forming the C-ring oxazole (scheme 10). This internal oxazole was formed with comparative ease compared to the *N*-terminal oxazole A in the bisoxazole fragment **4**. This supports our hypothesis that, while an adjacent electron withdrawing group at the 4-position is important for the oxidation of oxazolines, the reaction will still proceed in excellent yields if the forming benefits from conjugation at the 2- and 4-positions with neighbouring azoles.



Scheme 5 (i) DAST, CH_2Cl_2 then DBU, pyr., CCl_4, MeCN, 0 °C to rt, 72 h, 89 %; (ii) LiOH, H_2O, THF, CH_2Cl_2, 67%; (iii) L-Ile-OMe.HCl, EDCI, cat. HOBt, NMM, EtOH, 0 °C to rt, 18 h, 54 %; (iv) MeOH, AcCl, rt, 2 h; then **22**, EDCI, cat. HOBt, NMM, EtOH, 0 °C to rt, 18 h, 62 %; (v) SO_3.pyr., NEt_3.DMSO, CH_2Cl_2, 0 °C, 6 h, 72 %; (vi) NH_2OH.HCl, pyridine, MeOH, $CHCl_3$, rt, 18h, 33 %.

NMR spectrometry suggests that oxime **30** was formed as a mixture with the *Z*-isomer as the major isomer, with the major peak in the 1H spectrum for the CH adjacent to the oxime at 3.00 ppm, and the minor peak at 3.49 ppm (compare with 3.50 ppm for *E*-**1a**, 3.00 ppm for *Z*-**1b**). Comparison of the ^{13}C NMR spectra of the tetraoxazole **30** with the equivalent synthesized azolemycin A **1** showed some distinctive differences. As well as the obvious shift of the peak corresponding to *C*32 from 120.2 ppm in **1** to 138.31 ppm in **30**, the peaks corresponding to the other carbons of azole C, and those immediately surrounding it,

were shifted significantly. In particular, in the thiazole **1** the peak corresponding to B ring carbon *C11*, occurs at 130.9 ppm, but in the oxazole **30** the *C11* peak appears at 125.7 ppm. This large difference in chemical shift may facilitate the identification of the relative positions of oxazoles and thiazoles in new polyazole natural products.

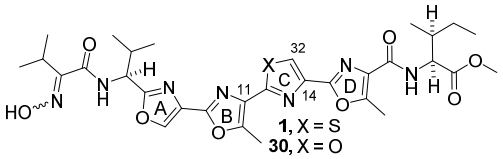


Figure 5 Numbering for azolemycin A, **1** and tetraoxazole **30**.

These syntheses produced azolemycin A and C and the tetraoxazole analogue **30,** for initial biological testing.[1] We are continuing assays in this area.

Acknowledgements

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Notes and references

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† Electronic Supplementary Information (ESI) available: synthesis details and NMR spectra. See DOI: 10.1039/b000000x/

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