Rapid Assembly of the 1-Azabicyclo[3.1.0]hexane Skeleton of Ficellomycin

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Abstract: The 1-azabicyclo[3.1.0]hexane core of ficellomycin can be assembled in a concise manner by way of a double cyclisation reaction involving in situ generation of an NH aziridine and further intramolecular conjugate addition onto a dehydroamino ester.

Key words: antibiotics, aziridines, 1,2-azido alcohols, conjugate addition reactions, polymer supported triphenylphosphine

In 1976, Argoudelis et al. described the isolation of ficellomycin (**1**) from the culture broths of *Streptomyces ficellus*.[1] This natural product was shown to inhibit the in vitro growth of Gram positive bacteria and *Staphylococcus aureus* infections in mice. Little is known about its mode of action although there is evidence to suggest that it inhibits semiconservative DNA replication in bacteria.[2] In 1989, structure **1a** was proposed for this antibiotic by Kuo et al. based on a combination of NMR, mass spectrometry and derivatisation studies (Figure 1).[3] Most intriguingly ficellomycin contains a highly strained 1-azabicyclo[3.1.0]hexane ring system which has only been identified once before, in the anti-tumour agents azinomycin A and B.[4] Although it is known from degradation studies that the valine residue of ficellomycin possesses the *S*-configuration,[1] questions remained concerning the stereochemistry at the other asymmetric centres. The relative stereochemistry at C-3, C-5 and C-6 within the rigid bicycle was assigned by Kuo using ^{1}H-^{1}H coupling constants assuming a chair conformation. Armstrong and Zhao have revised the ring conformation to a boat and the relative stereochemistry at C-6 to **1b** based upon additional NMR experiments including NOE difference measurements.[5] On the basis of its unique chemical architecture, stereochemical ambiguities, and interesting antibiotic activity, ficellomycin is an attractive and challenging synthetic target. In this Letter, we describe preliminary studies aimed at accomplishing its total synthesis.

In considering synthetic approaches to ficellomycin, we felt that existing routes to 1-azabicyclo[3.1.0]hexanes were not well suited for the purpose.[6] Instead, we were drawn to the idea of using an intramolecular conjugate addition of an aziridine onto a dehydroamino acid derivative,[7] i.e. disconnection across the aziridine nitrogen/C-3 bond (ficellomycin numbering). Indeed, Zhao and Armstrong have undertaken exploratory studies to test the feasibility of this route to ficellomycin.[5] In seeking the most expedient route to this natural product, we were drawn to the idea of generating the NH aziridine in situ from the corresponding 1,2-azido alcohol using a phosphine induced Staudinger-type reaction, which might undergo spontaneous closure onto a suitably functionalised dehydroamino acid. The basic concept is illustrated in Scheme 1 with the C-5 amino substituent omitted. In this way, both rings of the natural product might be assembled in a single chemical transformation. This reaction establishes the stereochemistry at C-2 and C-3 in the resulting bicycles. Since the stereochemistry of ficellomycin at these stereocentres is uncertain (vide supra), the possibility of fine-tuning the cyclisation to provide access to any or all of the possible diastereomers is an additional attractive feature.

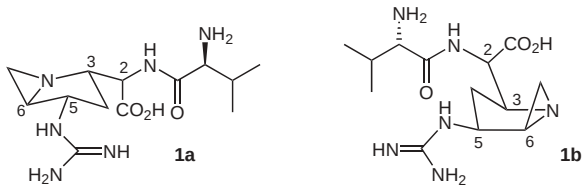
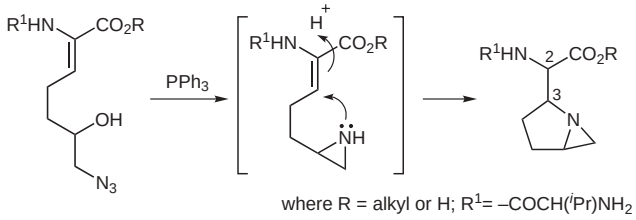


Figure 1 Structural proposals for ficellomycin



Scheme 1 Proposed double cyclisation to the ficellomycin skeleton

To explore these ideas, we embarked on the synthesis of a model substrate, namely 1,2-azido alcohol **2**. Reaction of commercially available phosphonate **3** with 4-pentenal[8] in the presence of DBN provided dehydroamino ester **4** in 79% yield as a single geometric isomer after column chromatography. Chemoselective epoxidation of diene **4** was achieved using excess *m*-chloroperoxybenzoic acid (*m*CPBA) providing epoxide **5** in 88% yield. Competitive oxidation of the alkene functionality of the dehydroamino

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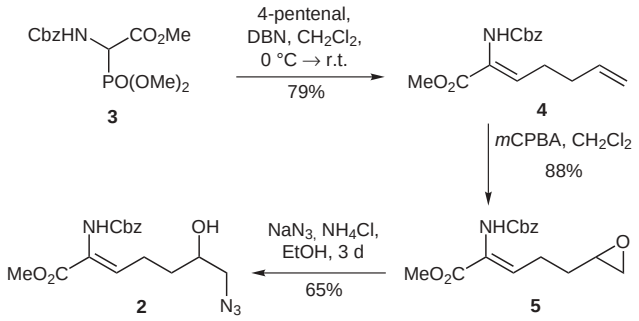
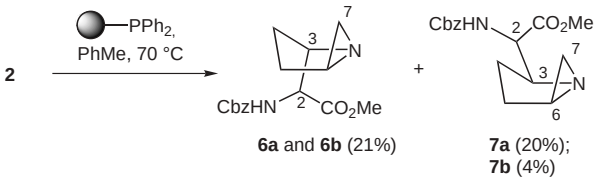
ester was not observed. At this juncture, it was possible to confirm the anticipated *Z*-stereochemistry[9] by NOE difference experiments, which produced strong reciprocal enhancements between the NH and allylic hydrogens (i.e. -C*H*$_2$CH=CN*H*CbzCO$_2$Me). Regioselective opening of epoxide **5** was achieved using sodium azide and ammonium chloride in ethanol. This provided azido alcohol **2** in three steps in 45% overall yield (Scheme 2).



Scheme 2

Several Staudinger-type conditions were examined for the cyclisation of azide **2** including variations in the nature of the phosphine (PPh_3 or PBu_3), solvent (toluene, acetonitrile or THF) and reaction temperature (r.t. or heating). It was rapidly established that heating azide **2** in acetonitrile at reflux with triphenylphosphine (1.6 equiv) for 24 hours led to the production of all four expected 1-azabicyclo[3.1.0]hexanes, namely **6a**,**b** and **7a**,**b**. However, the purification of these aziridines was hampered by the presence of excess triphenylphosphine and triphenylphosphine oxide in the reaction mixture. To overcome this problem, we resorted to the use of a polymer-supported variant of triphenyl phosphine, namely diphenylphosphinopolystyrene (ca 3 mmol/g, Fluka). As far as we are aware, supported phosphines have not been used previously for NH aziridine formation from 1,2-azido alcohols. Heating azide **2** with this supported phosphine (1.1 equiv) for 16 hours in toluene at 70 °C provided **6a**,**b** and **7a**,**b** devoid of phosphine contamination after filtration and evaporation (Scheme 3). The distinctive pattern of the aziridine hydrogens in the ^{1}H NMR spectrum made their identification straightforward. Integration of these signals revealed that only modest diastereoselectivity was observed (crude dr **6a**:**6b**:**7a**:**7b** = ca 3:1:5:1). These bicycles were quite stable and could be purified by chromatography on silica gel pretreated with triethylamine. The *anti*-diastereomers **6a** and **6b** (which are epimeric at C-2) were isolated in 21% yield as an inseparable 75:25 mixture. The more polar *syn*-diastereomers **7a** (20%) and **7b** (4%) were isolated as separated components. The reaction shows very modest preference for the production of the *syn*-diastereomers. All the bicycles have been fully characterised and the relative stereochemistry at the ring junction (C-3) solved by NMR methods.[10] Both *anti*-diastereomers **6a** and **6b** showed strong reciprocal NOE enhancements between H-3 and H-7$_{endo}$. In contrast,



Scheme 3

syn-diastereomers **7a** and **7b** showed NOE enhancements between H-2 and H-7$_{endo}$. At this juncture, we are unable to deduce the relative stereochemistry at C-2 in either the *syn*- or *anti*-diastereomers.

Whilst little stereoselectivity is observed in this model system, the suitability of this strategy for the assembly of 'ficellomycin-like' molecules has been demonstrated. The modest yield obtained for the key step (45% combined) is largely offset by the brevity of the approach. Ongoing studies are focused on examining whether greater stereocontrol can be achieved by the incorporation of the C-5 amino substituent and the (*S*)-valine residue into azido alcohol precursors, and to completing the total synthesis of ficellomycin.

Acknowledgment

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(8) Prepared by oxidation of of 4-penten-1-ol (PCC, CH_2Cl_2, 3 h, r.t.), which was used directly in the olefination reaction without purification.
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(10) **Selected Spectroscopic Data.** Compound **6a/b**: IR (neat): ν_{max} = 3334, 2951, 1713, 1498 cm^{-1}. ^{1}H NMR (400 MHz, C_6D_6): δ = 7.22–7.15 (2 H, m, ArH), 7.11–7.00 (3 H, m,

ArH), 5.87 (0.75 H, d, *J* = 8.5 Hz, NH), 5.73 (0.25 H, d, *J* = 8.0 Hz, NH), 5.14–4.98 (2 H, m, CH_2Ph), 4.48 (0.25 H, dd, *J* = 8.5, 3.8 Hz, H-2), 4.40–4.33 (0.75 H, m, H-2), 3.41 (0.25 H, dd, *J* = 8.5, 3.5 Hz, H-3), 3.33 (0.75 H, s, CH_3O), 3.29 (2.25 H, s, CH_3O), 2.95 (0.75 H, t, *J* = 7.5 Hz, H-3), 2.02–1.98 (0.75 H, m, H-6), 1.91–1.85 (0.25 H, m, H-6), 1.61–1.43 (3 H, m, 2 × H-5, H-4), 1.31 (0.75 H, d, *J* = 5.2 Hz, H-7_{exo}), 1.29 (0.25 H, d, *J* = 5.5 Hz, H-7_{exo}), 1.18–0.88 (1 H, m, H-4), 0.56 (0.75 H, d, *J* = 3.3 Hz, H-7_{endo}), 0.53 (0.25 H, d, *J* = 3.5 Hz, H-7_{endo}). ^{13}C NMR (100 MHz, C_6D_6): δ = 172.0 (CH_3OCO), 171.4 (CH_3OCO), 157.0 (NHCOO), 156.2 (NHCOO), 137.2 (ArC), 128.5–128.4 (ArCH), 67.1 (CH_2), 67.0 (CH_2), 66.9 (C-3), 66.0 (C-3), 59.9 (C-2), 58.1 (C-2), 51.9 (CH_3O), 51.7 (CH_3O), 41.0 (C-6), 40.0 (C-6), 28.2 (C-7), 28.0 (C-7), 26.1 (C-5), 25.0 (C-5), 24.3 (C-4), 22.6 (C-4). MS (ES^+): *m/z* = 305 [MH^+], 261, 91. HRMS (ES^+): *m/z* calcd for $C_{16}H_{21}N_2O_4$: 305.1496; found: 305.1493 [MH^+]. Compound **7a**: IR (neat): ν_{max} = 3319, 3172, 2947, 1712, 1527, 1435 cm^{-1}. ^{1}H NMR (400 MHz, C_6D_6): δ = 7.22–7.18 (2 H, m, ArH), 7.11–7.01 (3 H, m, ArH), 5.99 (1 H, d, *J* = 9.0 Hz, NH), 5.09 (1 H, d, *J* = 12.3 Hz, C*H*HPh), 5.01 (1 H, d, *J* = 12.3 Hz, CH*H*Ph), 4.54 (1 H, t, *J* = 8.4 Hz, H-2), 3.33 (3 H, s, CH_3O), 3.21–3.14 (1 H, m, H-3), 2.07–2.02 (1 H, m, H-6), 1.59–1.52 (1 H, m, H-5), 1.43–1.33 (1 H, m, H-5′), 1.26 (1 H, d, *J* = 4.8 Hz, H-7_{exo}), 1.20–1.05 (2 H, m, H-4), 0.99 (1 H, d, *J* = 2.0 Hz, H-7_{endo}). ^{13}C NMR (100 MHz, C_6D_6): δ = 172.2 (CH_3OCO), 156.2 (NHCOO), 137.2 (ArC), 128.4–128.3 (ArCH), 67.0 (CH_2Ph), 65.4 (C-3), 56.8 (C-2), 51.7 (CH_3O), 38.7 (C-6), 26.0 (C-5), 23.1 (C-7), 22.2 (C-4). MS (ES^+): *m/z* = 305 [MH^+], 91. HRMS (ES^+): *m/z* calcd for $C_{16}H_{21}N_2O_4$: 305.1496; found: 305.1492 [MH^+]. Anal. Calcd for $C_{16}H_{20}NO_4$: C, 63.14; H, 6.62; N, 9.20%. Found: C, 63.10; H, 6.65; N, 8.80%. Compound **7b**: IR (neat): ν_{max} = 3368, 3181, 2948, 1710, 1499 cm^{-1}. ^{1}H NMR (400 MHz, C_6D_6): δ = 7.22–7.16 (3 H, m, ArH and NH), 7.11–6.99 (3 H, m, ArH), 5.08 (1 H, d, *J* = 12.0 Hz, C*H*HPh), 5.03 (1 H, d, *J* = 12.0 Hz, CH*H*Ph), 4.33 (1 H, dd, *J* = 8.8, 6.6 Hz, H-2), 3.38–3.29 (4 H, m, CH_3O and H-3), 2.15–2.09 (1 H, m, H-6), 1.51 (1 H, dd, *J* = 13.0, 8.0 Hz, H-5), 1.44–1.34 (1 H, m, H-5′), 1.22 (1 H, d, *J* = 5.0 Hz, H-7_{exo}), 1.18–1.09 (1 H, m, H-4), 1.05–0.96 (1 H, m, H-4′), 0.93 (1 H, m, H-7_{endo}). ^{13}C NMR (100 MHz, C_6D_6): δ = 172.0 (CH_3OCO), 156.6 (NHCOO), 137.3 (ArC), 128.5–128.2 (ArCH), 70.0 (CH_2Ph), 63.7 (C-3), 57.7 (C-2), 51.8 (CH_3O), 38.8 (C-6), 26.2 (C-5), 22.8 (C-7), 22.5 (C-4). MS (ES^+): *m/z* = 305 [MH^+], 261, 91. HRMS (ES^+): m/z calcd for $C_{16}H_{21}N_2O_4$: 305.1496; found: 305.1496 [MH^+].