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An efficient lactamization of fimbrolides to novel 1,5-dihydropyrrol-2-ones

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Abstract—A new versatile method for the conversion of fimbrolides to the corresponding novel dihydropyrrol-2-ones is described. This new efficient lactamization protocol has the advantage of higher yields and can be used for the synthesis of a series of new dihydropyrrol-2-ones with interesting anti-bacterial properties.

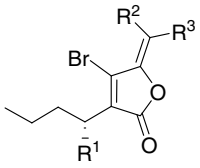
With the emergence of multi-resistant strains of bacteria, it is increasingly important to identify new therapeutic compounds with novel mechanisms of action to supplement existing anti-microbials. A key strategy is to target the various regulatory systems in bacteria that control the expression of virulence.

Bacteria utilize a rich lexicon of diffusible chemical signals to communicate both within and between species.[1] These chemical cues are used as a Quorum Sensing (QS) platform for a variety of signal detection and transduction mechanisms that are vital for processes such as bioluminescence, virulence factor expression and biofilm development.[2]

It is well understood that pathogenic bacteria rely on this system to control the expression of virulence.[3–5] One such system, found in the Gram-negative bacteria is the N-acylated homoserine lactone (AHL) system, which controls phenotypes such as biofilm formation.[2]

It has been shown that fimbrolides **1**, a novel class of marine natural products isolated from *Delisea pulchra*, act as antagonists that specifically inhibit the AHL-dependent phenotypes (swarming and bioluminescence) behaviour of *Serratia liquefaciens*.[4,6]

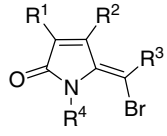
Ecological studies have found fimbrolides **1** to be effective in reducing the bacterial phenotype expression while having minimal effect on bacterial protein synthesis or growth. The potency of the fimbrolides has encouraged an interest in developing synthetic analogues of the parent fimbrolide as novel anti-bacterial agents.



	R^1	R^2	R^3
a	H	H	Br
b	OAc	H	Br
c	OH	H	Br
d	H	Br	Br
e	OAc	H	Cl

1

In view of the important biological properties of the fimbrolides, modifications on the basic scaffold of the ring may also bring significant changes in the antagonist activities, which have not been previously reported. A related structure to the fimbrolides is 1,5-dihydropyrrol-2-ones **2**.



R^1 = alkyl
R^2 = H, Br
R^3 = H, Br
R^4 = alkyl, aryl

2

Numerous methods for the synthesis of the pyrrol-2-ones have been reported;[7–9] however, these methods lack the halogenation pattern present in fimbrolides. Recently, synthesis of 3-butyl-5-bromomethylene-1,5-dihydropyrrol-2-one has been reported via halolactamization of allenamides with copper halides, in moderate

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yields.[10] The uniqueness of the bromination pattern on the ring and the presence of the bromomethylene group make this molecule more elusive to the common lactamization reactions that have been reported in the literature. Thus, the real challenge in synthesis lies in preserving the bromination pattern, critical for biological activity.

Here, we report a direct route to the 5-bromomethylene-dihydropyrrol-2-one ring system via an efficient lactone–lactam conversion. Significantly, this new approach maintains the unique bromination pattern of the molecule (Table 1).

Fimbrolides **3** (where R^1 is restricted to H, *n*-C_4H_9 or *n*-C_6H_{13}) were obtained via the sulfuric acid catalyzed cyclization of brominated 2-alkyl-levulinic acids.[11]

5-Hydroxy-1,5-dihydropyrrol-2-ones **4** were synthesized by dissolving fimbrolides **3** in CH_2Cl_2, cooling to 0 °C, and treating with excess amine (Scheme 1). Because of the many potential reactive sites on the fimbrolide molecules, the reaction temperature had to be closely regulated as alkylamine reactions must be performed in ice-cold conditions to control the regiospecificity of the amine reaction at C2. The reactions were completed within 2–3 h resulting in hydroxy-lactams **4a**–**i** as the only products (TLC monitoring) in good yields.

The ^1H NMR spectra of hydroxy-lactams **4a**–**i** exhibit a characteristic AB doublet for the CH_2Br protons at δ 3.30–3.60 ppm. A further ^1H–^{15}N HMBC experiment on compound **4b** showed a correlation of H3 with the nitrogen, thus confirming the presence of the lactam ring.

Reactions with aniline required heating at 80 °C for 24–48 h for completion and afforded two products in equal ratios (Scheme 2). The first product with the higher R_f value was phenyl-amino-methylene furanone **6** formed by a Michael-type addition across the methylene side chain of the fimbrolide.

The second eluted compound was the desired hydroxy-lactam **4a**. The structure of the former was established by an X-ray crystallographic analysis. Reaction of the natural fimbrolide **1b** (R^1 = OAc) with diethylamine has been previously reported to yield the similar 5-amino-methylene compound.[12]

The dehydration of 5-hydroxy-1,5-dihydropyrrol-2-ones **4** could be accomplished by several dehydrating agents such as sulfuric acid, phosphorus pentoxide or *p*-toluenesulfonic acid (*p*-TsOH).[13] It was found that *p*-TsOH gave the cleanest reactions and products **5a**–**i** were easily purified by chromatography and obtained in high yields (Scheme 1). The *Z*-isomer of the lactam was isolated from all reactions as shown by a comparison of the chemical shift of the methylene proton with that of the corresponding parent fimbrolide.

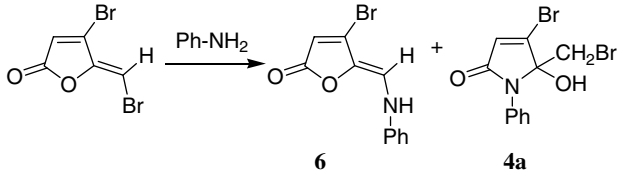
The formation of the hydroxy-lactam analogues could be explained by the reaction sequence presented in Scheme 3.

A molecule of amine could react at the carbonyl group followed by ring opening to form the amide intermediate **7**. Subsequent keto–enol tautomerism would yield the

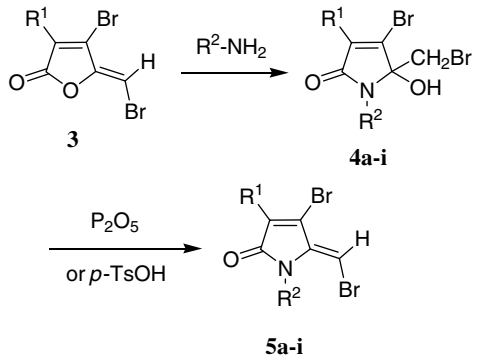
Table 1. Lactone–lactam conversion reaction of fimbrolides

	R^1	R^2	**4** Yield[a] (%)	**5** Yield[a] (%)
a	H	Ph	20	92
b	H	CH_2Ph	57	80
c	H	*n*-C_4H_9	39	43
d	*n*-C_4H_9	Ph	26	95
e	*n*-C_4H_9	CH_2Ph	73	98
f	*n*-C_4H_9	*n*-C_4H_9	80	82
g	*n*-C_6H_{13}	Ph	69	91
h	*n*-C_6H_{13}	CH_2Ph	85	89
i	*n*-C_6H_{13}	*n*-C_4H_9	82	79

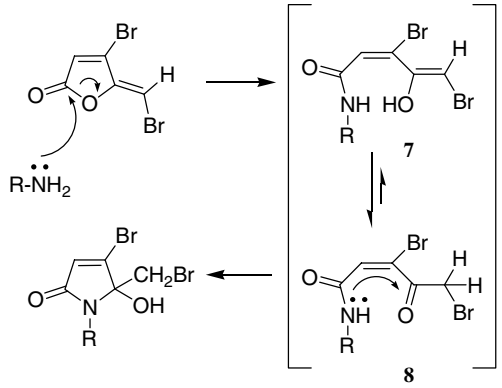
[a] Yield of isolated pure product.



Scheme 2.



Scheme 1.

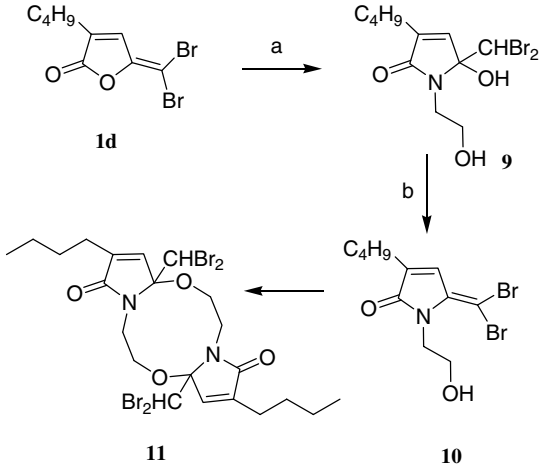


Scheme 3.

more stable keto tautomer **8**, and this intermediate would cyclize to generate the lactam ring.

In an attempt to prepare 1-(2-hydroxyethyl)-dihydropyrrol-2-one **9** by the reaction of ethanolamine with fimbrolide **1d**, formation of a dimeric structure containing a ten-membered heterocyclic ring **11**, was observed instead of the expected dibromomethylene lactam **10** (Scheme 4).

The structure of dimer **11** was consistent with NMR and mass spectroscopic data and confirmed by X-ray crystallographic analysis[14] (Fig. 1). It is likely that compound **11** was formed by the intermolecular nucleophilic attack of the pendant hydroxyl group of compound **10** on the C5 position of a second molecule.



Scheme 4. Reagents: (a) Ethanolamine/CH_2Cl_2, (b) treatment with P_2O_5.

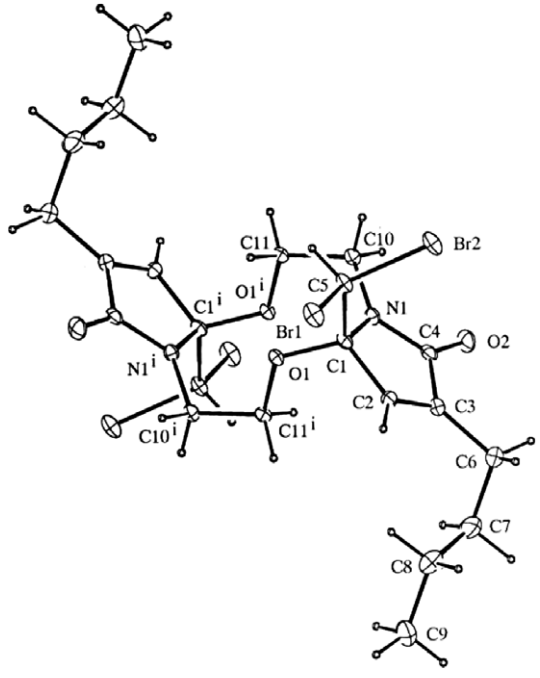


Figure 1. ORTEP diagram of **11**.

All reported products were characterized by ^1H and ^{13}C NMR, IR spectra, mass spectra and elemental analyses, and several by X-ray crystallographic analysis.

In conclusion, an efficient sequential lactamization of fimbrolides to the corresponding dihydropyrrol-2-ones has been developed. This reaction scheme generates a new series of N-substituted dihydropyrrol-2-one derivatives, which show potent Quorum Sensing antagonist activity in Gram-negative bacteria.

Acknowledgements

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13. *Representative procedure for* **5**: Fimbrolides **3** (2.0 mmol) were dissolved in CH_2Cl_2 (10 mL) and the solution was cooled to 0 °C. The amine (10.0 mmol, 5 equiv) in CH_2Cl_2 (10 mL) was added dropwise to the solution and the reaction mixture was maintained at 0 °C for 3 h. The reaction mixture was quenched with hydrochloric acid (2 M) and the dichloromethane layer washed with a saturated aqueous sodium bicarbonate solution followed by brine. The organic phase was dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. Flash

column chromatography provided intermediate **4**, which together with *p*-TsOH (0.3 mmol equiv) was dissolved in dry $CHCl_3$ and refluxed for 2 h. The mixture was concentrated in vacuo and purified by flash chromatography to give dihydropyrrol-2-one derivatives **5a**–**i**. Compound **5h**: Yellow oil; ^{1}H NMR: δ 0.87 (m, 3H, CH_3), 1.31 (m, 6H, $3\times CH_2$), 1.56 (m, 2H, CH_2), 2.43 (m, 2H, CH_2), 5.27 (s, 2H, NCH_2), 6.21 (s, 1H, CHBr), 7.13–7.32 (m, 5H, H_{aryl}); ^{13}C NMR: 13.9 (CH_3), 22.4 (CH_2), 25.4 (CH_2), 27.2 (CH_2), 28.9 (CH_2), 31.3 (CH_2), 43.9 (NCH_2), 90.5 (CHBr), 126.2 (2C) (CH_{aryl}), 126.6 (C), 127.0 (CH_{aryl}), 128.4 (2C) (CH_{aryl}), 135.6 (C), 137.5 (C), 138.6 (C), 169.2 (C=O); IR: (Nujol, ν, cm^{-1}): 3081, 3029, 1705, 1624, 1453, 1432, 1354, 1152, 882, 721, 695; HRMS (M+Na in ESI): *m*/*z* 449.985299 (M+Na; calcd for $C_{18}H_{21}Br_2NONa$, *m*/*z* 449.986188).

14. Crystal data for **11**: $C_{22}H_{30}Br_4N_2O_4$, colourless, crystal dimension $0.34\times0.14\times0.14$ mm, triclinic, space group $P\bar{1}$, $a = 6.731(4)$ Å, $b = 10.461(5)$ Å, $c = 11.759(6)$ Å, $\alpha = 83.27(3)°$, $\beta = 75.38(3)°$, $\gamma = 82.24(3)°$, $V = 790.9(5)$ Å^3, $M_r = 788.2$, $Z = 1$, $D_c = 1.65$ Mg/m^3, $\lambda = 0.71073$ Å, $\mu(\text{Mo K}_\alpha) = 5.077$ mm^{-1}, $F(000) = 392$, $2° < \theta < 23°$, $R = 0.047$, $wR = 0.057$, $S = 1.74$, largest difference in peak and hole: 0.71 and -1.13 e/Å^3. Crystallographic data for the structure of **11** reported in this paper have been deposited with the Cambridge Crystallograpic Data Centre as Supplementary Publication No. CCDC-629740.