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An efficient synthesis of brominated 4-alkyl-2(5*H*)-furanones

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ABSTRACT

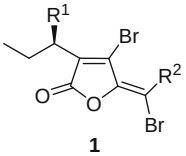
A versatile method for the synthesis of novel brominated 4-alkyl-2(5*H*)-furanones under mild reaction conditions is described. This synthetic strategy requires only one chromatographic separation over six steps and employs the cyclodehydration of brominated levulinic acid as the key transformation.

The indiscriminate overuse of conventional antibiotics to combat bacterial infection has resulted in the evolution of multidrug-resistant bacterial 'superbugs'.[1] New therapeutic compounds with novel modes of action are urgently needed to complement existing anti-microbial treatments.[2]

A new key strategy is to target the various intercellular chemical communication systems in bacteria known as 'quorum sensing'.[3] This regulatory platform mediates critical bacterial behaviour such as biofilm formation, swarming motility and the expression of virulence factors.[4]

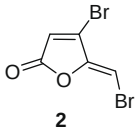
Naturally occurring halogenated furanones or fimbrolides **1** isolated from the marine alga *Delisea pulchra* were found to inhibit the *N*-acylhomoserine lactone (AHL)-mediated quorum sensing system employed by many pathogenic gram-negative bacterial species.[5] Synthetic fimbrolides such as **2** are potent antagonists of *Pseudomonas aeruginosa* virulence in vitro and in vivo.[6]

Importantly, these furanones were efficacious at non-bactericidal concentrations and therefore should not impose the same selective pressure as conventional antibiotics on bacteria to develop resistance. To date, over 200 analogues of furanones with different bromination patterns and alkyl chain lengths have been generated and evaluated for quorum sensing inhibitory activities.[7]



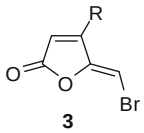
1

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



2

In continuation of our efforts to develop novel quorum sensing inhibitors based on fimbrolides,[8] we decided to target 4-substituted 2(5*H*)-furanones **3**,**4** to investigate their potential biological activities. Furanones **4** (R = alkyl) are close analogues of the natural fimbrolide **1a**, but with the 3-alkyl and 4-bromo substituents interchanged.



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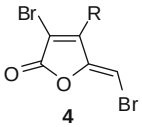

4

R = alkyl, phenyl, benzyl

Although various methodologies exist for the synthesis of 3-alkylfuranones similar to fimbrolide **1a**,[9,10] an equivalent method to furanones **3**,**4** has not previously been reported. 4-Alkyl-3-bromo-2(5*H*)-furanones unsubstituted at C5 have been prepared via bromination–dehydrobromination of 4-alkyl-2(5*H*)-furanones,[11] or

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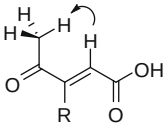
the regioselective Suzuki–Miyaura reaction of 3,4-dibromo-2(5*H*)-furanones.[12] The presence of the additional exocyclic bromomethylene moiety at C5 in furanones **3**,**4** makes these syntheses unsuitable. Here we describe a versatile and efficient method for the synthesis of novel fimbrolide analogues **3**,**4** employing the cyclodehydration of brominated levulinic acid as the key step.

The intermediate 4-oxoalkenoic acids **6a–h** were obtained from the acid-catalysed condensation of 2-alkanones **5** with glyoxylic acid (Scheme 1). In order to assess the generality of our methodology, and to provide potential SAR data on the 4-alkyl-substituted series of furanones, we used 2-alkanones with aliphatic side chains of different lengths ranging from methyl to *n*-decyl, as well as phenyl and benzyl-substituted alkanones.

The condensation reaction of 2-alkanones **5** occurs regioselectively at C3, and 4-oxoalkenoic acids **6a–h** are formed as the major products.[13] The minor products **7** resulting from condensation at C1 and pseudoacids **8** were also sometimes observed in low yields. In contrast, branched 2-alkanones react preferentially at the less hindered C1 position,[14] presumably due to kinetic factors. The *E*-stereochemistry for alkenoic acids **6** was established on the basis of NOE correlations of the olefinic proton to the terminal methyl group (Fig. 1).

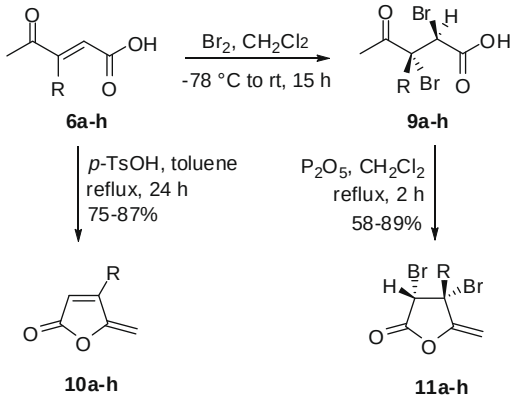
The key 3-alkyl-2,3-dibromolevulinic acids **9a–h** were prepared *via* bromination of 4-oxoalkenoic acids **6**. A range of dehydrating agents were investigated for the cyclodehydration of 4-oxoalkenoic acids **6** and brominated levulinic acids **9**, including phosphorus pentoxide, *p*-toluenesulfonic acid, silica gel, alumina, polyphosphoric acid, phosphoryl chloride, acetic anhydride, trifluoroacetic anhydride and triflic anhydride. Of these, *p*-toluenesulfonic acid was found to be the most efficient for the cyclisation of 4-oxoalkenoic acids **6** into the corresponding 5-methylene-4-alkylfuranones **10a–h**, while phosphorus pentoxide in dichloromethane gave the highest yields for the cyclisation of brominated acids **9** to dihydrofuranones **11a–h** (Scheme 2). In the latter case, a simple filtration sufficed to afford the corresponding dihydrofuranones **11a–h** in moderate to high yields and sufficient purity for use in the next step. This cyclodehydration reaction appears to be quite general and was repeated on a gram scale. Interestingly, during the bromination of alkenoic acids **6**, partial cyclisation of the alkenoic acids to the 5-hydroxy-5-methyl-4-alkylfuranones **8** was also observed. This product does not undergo bromination as the double bond is now in the ring. This compound can be dehydrated under acidic conditions to yield 5-methylene-4-alkylfuranones **10a–h**.

The dihydrofuranones **11** were dehydrobrominated by treatment with DBU to yield 5-methylene-2(5*H*)-furanones **12a–h**, as desbromo analogues of the target furanones **4**. We anticipated that these could be readily converted into the fimbrolide analogues **4**



6a-h

Figure 1. Key NOE correlation for (*E*)-alkenoic acids **6**.

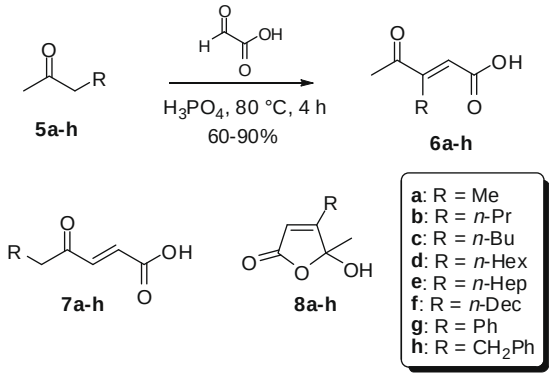


Scheme 2. Cyclodehydration reactions of acids **6a–h** and **9a–h**.[15]

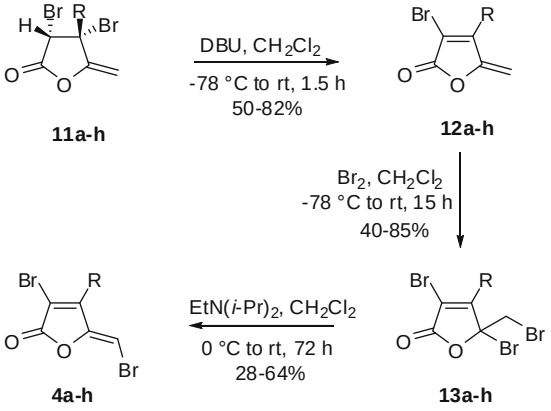
containing the 5-bromomethylene moiety by a standard bromination–dehydrobromination sequence (Scheme 3).

While the bromination of the 2(5*H*)-furanones **12** to the tribromo intermediates **13** proceeded smoothly, unexpected difficulties were encountered in the dehydrobromination step employing the previously used reagent such as DBU or DABCO. Fortunately, this was overcome by the use of *N*,*N*-diisopropylethylamine (Hünig's base) in dichloromethane to yield the target 4-alkyl-3-bromo-5-bromomethylene-2(5*H*)-furanones **4a–h**.[16] Similar bromination and dehydrobromination of the desbromo furanones **10** gave 4-alkyl-5-bromomethylene-2(5*H*)-furanones **3a–f**.[17] However, in this case dehydrobromination could be carried out with DBU in dichloromethane.

It is known that the chemical shift value for the exocyclic olefinic proton in 5-bromomethylene-2(5*H*)-furanones is characteristic for either the (*Z*)-isomer (typically δ 6.24 ppm) or the (*E*)-isomer (typically δ 6.57 ppm).[18] Thus the (*Z*)-stereochemistry of the products was confirmed by the chemical shifts of that proton, which occurred in the range δ 6.22–6.25 ppm for furanones **4a–h**. The preference for the (*Z*)-isomer is expected because the alkyl chain at C4 discourages the formation of the transition state lead-



Scheme 1. Synthesis of 4-oxoalkenoic acids **6a–h**.



Scheme 3. Synthesis of furanones **4a–h**.

ing to the (*E*)-isomer, due to steric clashes with the exocyclic bromine atom.

The levulinic acids and the 4-alkyl-2(5*H*)-furanones were mostly obtained as colourless, pale yellow or pale brown oils. An aqueous work-up or filtration was sufficient for all intermediate reactions and column chromatography was only used after the final step to isolate furanone products **4a–h**. The final products have a tendency to polymerise while standing, even in cold storage, however they were stable enough to be purified and fully characterised. All products gave satisfactory ^{1}H and ^{13}C NMR spectra and HRMS values.

In summary, we have described a versatile and efficient method for the synthesis of novel brominated 4-alkyl-2(5*H*)-furanones. This methodology utilises simple starting materials and reagents, mild reaction conditions and requires only one chromatographic purification over six steps. Further studies on the chemistry and biological activity of these fimbrolide derivatives are being conducted in our laboratory.

Acknowledgements

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References and notes

1. Livermore, D. *Clin. Infect. Dis.* **2003**, *36*, S11–S23.
2. Alanis, A. *Arch. Med. Res.* **2005**, *36*, 697–705.
3. Ni, N.; Li, M.; Wang, J.; Wang, B. *Med. Res. Rev.* **2009**, *29*, 65–124.
4. Miller, M.; Bassler, B. *Annu. Rev. Microbiol.* **2001**, *55*, 165–199.
5. Givskov, M.; de Nys, R.; Manefield, M.; Gram, L.; Maximilien, R.; Eberl, L.; Molin, S.; Steinberg, P. D.; Kjelleberg, S. *J. Bacteriol.* **1996**, *178*, 6618–6622.
6. Hentzer, M.; Wu, H.; Anderson, J.; Riedel, K.; Rasmussen, T.; Bagge, N.; Kumar, N.; Schembri, M.; Song, Z.; Kristoffersen, P.; Manefield, M.; Costerton, J.; Molin, S.; Eberl, L.; Steinberg, P.; Kjelleberg, S.; Hoiby, N.; Givskov, M. *J. EMBO* **2003**, *22*, 3803–3815.
7. deNys, R.; Givskov, M.; Kumar, N.; Kjelleberg, S.; Steinberg, P.. In *Antifouling Compounds*; Fusetani, N., Clare, A., Eds.; Springer: Berlin, Heidelberg, 2006; Vol. 2, pp 55–85.
8. Goh, W. K.; Iskander, G.; Black, D. StC.; Kumar, N. *Tetrahedron Lett.* **2007**, *48*, 2287–2290.
9. Manny, A. J.; Kjelleberg, S.; Kumar, N.; de Nys, R.; Read, R. W.; Steinberg, P. *Tetrahedron* **1997**, *53*, 15813–15826.
10. Caine, D.; Ukachukwu, V. C. *J. Org. Chem.* **1985**, *50*, 2195–2198.
11. Grossmann, G.; Poncioni, M.; Bornand, M.; Jolivet, B.; Neuburger, M.; Séquin, U. *Tetrahedron* **2003**, *59*, 3237–3251.
12. Bellina, F.; Anselmi, C.; Rossi, R. *Tetrahedron Lett.* **2001**, *42*, 3851–3854.
13. Scheffold, R.; Dubs, P. *Helv. Chim. Acta* **1967**, *50*, 798–808.
14. Zhang, R.; Chan, D.; Jessica, S.; Iskander, G.; Black, D. StC.; Kumar, N. *ARKIVOC* **2009**, *5*, 102–115.
15. *Representative procedure for compound* **11d**: To a solution of acid **9d** (0.052 mol) in dry dichloromethane (25 mL) were added phosphorus pentoxide (0.156 mol) and a few crystals of hydroquinone, and the mixture was refluxed for 2 h. The solution was cooled, filtered through a bed of Celite–silica and evaporated under reduced pressure to afford a mixture of diastereomers of furanone **11d** as a pale yellow oil (89%). ^{1}H NMR ($CDCl_3$): δ 0.92 (3H, t, J = 7.1 Hz, CH_3), 1.33–1.35 (6H, m, CH_2), 1.76 (2H, m, CH_2), 2.23–2.25 (2H, m, CH_2), 4.62 and 4.66 (1H, each s, H3), 4.87 and 5.03 (1H, each d, J = 3.2 Hz, $=CH_a$), 4.88 and 5.05 (1H, each d, J = 3.2 Hz, $=CH_b$); IR (KBr): ν_{max} 2956, 2930, 2859, 1787, 1767, 1650, 1605, 1460, 1378, 1268, 1239, 1166, 1109, 969, 931, 890 cm^{-1}. UV–vis (MeOH): λ_{max} 258 nm (ε 14,800 $cm^{-1}M^{-1}$).
16. *Representative procedure for compound* **4d**: To a stirred solution of furanone **13d** (0.05 mol) in dry dichloromethane (100 mL) at 0 °C was added a solution of *N*,*N*-diisopropylethylamine (0.17 mol) in dry dichloromethane (20 mL). The mixture was allowed to warm to room temperature and was further stirred for 72 h. The reaction mixture was washed successively with 2 M HCl (30 mL) and brine (30 mL), and the organic extract was dried over Na_2SO_4 and evaporated under reduced pressure. Purification by column chromatography on silica gel (25% dichloromethane/light petroleum) gave furanone **4d** (R_f 0.90) as a pale yellow oil (55%). ^{1}H NMR ($CDCl_3$): δ 0.90 (3H, t, J = 7.2 Hz, CH_3), 1.33 (6H, m, CH_2), 1.61 (2H, m, CH_2), 2.52 (2H, t, J = 7.9 Hz, CH_2), 6.22 (1H, s, CHBr). ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.9 (CH_3), 22.3, 26.1, 28.2, 29.0, 31.2 ($5CH_2$), 90.5 (CHBr), 117.7, 151.4, 153.5, 163.5 (C=O). IR (KBr): ν_{max} 3092, 2955, 2928, 2857, 1786, 1679, 1636, 1595, 1465, 1364, 1301, 1219, 1183, 1050, 982, 914, 840, 765, 750 cm^{-1}. UV–vis (MeOH) λ_{max}: 290 nm (ε 5650 $cm^{-1}M^{-1}$). MS (EI): *m*/*z* (%) 340 (M, $^{81}Br_2$, 20) 338 (M, ^{81}Br, ^{79}Br, 40), 336 (M, $^{79}Br_2$, 20), 270 (20), 268 (40), 266 (20), 259 (44), 257 (44), 215 (30), 213 (30), 189 (100), 187 (100), 178 (30), 176 (30), 159 (30), 149 (40), 135 (70), 121 (80). HRMS (+ESI): $C_{11}H_{15}{}^{79}Br_2O_2$ $[M+H]^+$ requires 336.9439, found 336.9414.
17. *Representative data for compound* **3a**: Pale yellow oil (50%). ^{1}H NMR ($CDCl_3$): δ 2.11 (3H, s, CH_3), 5.98 (1H, s, H3), 6.02 (1H, s, CHBr). ^{13}C NMR (75 MHz, $CDCl_3$): δ 12.2 (CH_3), 89.8 (CHBr), 117.9, 153.6, 154.0, 168.0 (C=O). IR (Nujol): ν_{max} 2950, 2920, 2850, 1765, 1590, 1460, 1380, 1230, 1020, 910, 850, 750, 720 cm^{-1}. HRMS (+ESI): $C_6H_5{}^{79}BrO_2$ $[M+Na]^+$ requires 210.9371, found 210.9370.
18. Beechan, C.; Sims, J. *Tetrahedron Lett.* **1979**, *19*, 1649–1652.