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Synthesis of the quorum sensing molecule Diffusible Signal Factor using the alkyne zipper reaction.

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ABSTRACT

The development of a concise synthesis of the quorum sensing molecule Diffusible Signal Factor is described. This route exploits an alkyne zipper reaction to form a key terminal alkyne intermediate. The chemistry outlined here may also be applied to the preparation of *cis*-unsaturated analogues of Diffusible Signal Factor.

Keywords:

Alkyne zipper reaction;

Diffusible signal factor;

Partial hydrogenation;

1. Introduction

Although bacterial infections have traditionally been treated with antibiotics, many organisms have developed or acquired mechanisms that render these drugs ineffective.^{1,2} This increased resistance, compounded by the limited development of new antimicrobial agents, poses a considerable threat to public health and has spurred researchers to investigate alternative strategies for disease control.^{3,4} These strategies include targeting the signaling pathways that control the synthesis of microbial virulence factors and approaches that improve the efficacy of existing antibiotics.^{5,6} For bacteria, cell-cell communication or quorum sensing (QS) has been proposed as one possible target for inhibition.^{7,8} Among the many families of QS molecules discovered to date, several strains of bacteria utilise Diffusible Signal Factor (DSF, **1**) for cell to cell communication (Figure 1).⁹ DSF is a *cis*-unsaturated long chain carboxylic acid, namely *cis*-11-methyl-2-dodecenoic acid. DSF was first identified in the *X. campestris*,¹⁰ and was subsequently discovered in other plant and human pathogens such as *Xanthomonas oryzae* pv. *oryzae*¹¹ and *S. maltophilia*.^{12,13}

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The presence of DSF is associated with multiple effects including increased biofilm production, greater virulence and antibiotics tolerance.¹⁴ The *cis*-unsaturated double bond is known to be critical for biological activity with the saturated derivative displaying significantly lower activity, while *trans*-DSF has little or no activity.¹⁵ This *cis*-unsaturated motif is also found in related QS molecules e.g. Burkholderia Diffusible Signal Factor (BDSF, **2**).¹⁶

DSF constitutes a useful probe in biological studies for understanding the role of QS in certain bacteria. Furthermore, derivatives of DSF could form the basis of future therapies for managing resistant bacterial infections. Herein we describe our efforts to find a concise synthesis of DSF. We outline our early approaches before discovering an efficient route which exploits the alkyne zipper reaction. Finally, we demonstrate the utility of this approach to the preparation of *cis*-unsaturated derivatives of DSF.

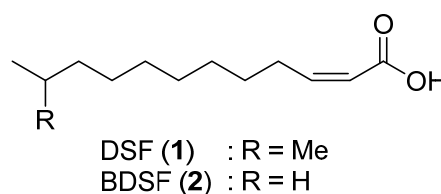
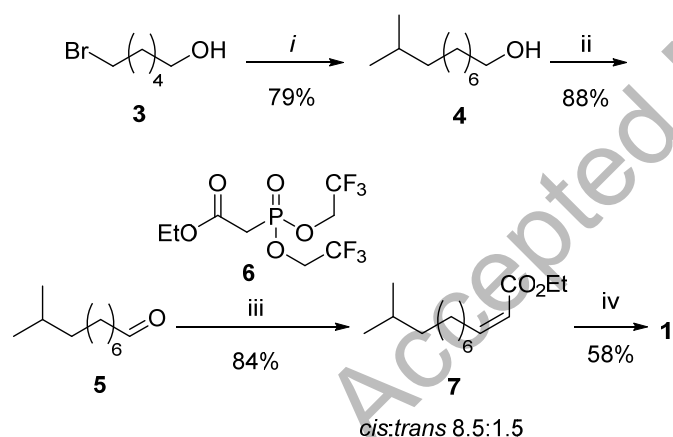


Figure 1. Quorum sensing molecules DSF and BDSF

2. Results and Discussion

The starting point for the synthesis of DSF involved a dilithium tetrachlorocuprate-mediated coupling of *iso*-pentyl magnesium bromide with 6-bromohexan-1-ol (**3**) to afford 9-methyldecan-1-ol (**4**) in 79% yield (Scheme 1). Dilithium tetrachlorocuprate is a copper catalyst which is soluble in organic solvents and improves the efficiency of halide substitutions with Grignard reagents.¹⁷ Subsequent Swern oxidation of **4** furnished aldehyde **5** in 88% yield. The next step involved a Horner-Emmons reaction to install the *cis*-unsaturated ester. Stabilised Horner-Emmons reagents typically furnish the *trans*-isomer as the major product. However, the fluorinated phosphonates developed by Still and Gennari bearing electron-withdrawing groups are *cis*-selective.¹⁸ Accordingly, addition of aldehyde **5** to a solution of **6** and sodium hydride in THF at 0 °C furnished α,β -unsaturated ester **7** in 84% overall yield as a mixture of isomers. The *cis*-unsaturated ester was predominant, formed in a ratio of 85:15. Careful separation of the products by column chromatography afforded *Z*-**7** exclusively, as confirmed by the smaller coupling of 11.5 Hz in its ¹H-NMR spectrum as compared to 15.7 Hz for the *trans*-isomer. Finally, hydrolysis of ethyl ester *Z*-**7** with lithium hydroxide in THF-MeOH-H₂O (2:1:1) at 0 °C for 16 h provided DSF (**1**) in 58% yield.

While this route did provide access to DSF, it is not without its drawbacks. Chief among these is the limited selectivity of the Horner-Emmons reaction which produces both the *cis*- and *trans*-unsaturated esters. This is further aggravated by the difficulty in separating these isomers. Additionally, Horner-Emmons reagent **6** is relatively expensive. For these reasons, we sought out an alternative route to DSF which avoided these obstacles.

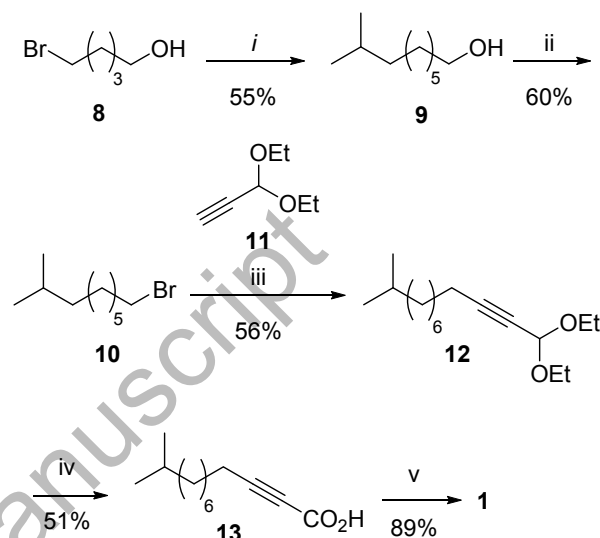


Scheme 1. i. *iso*-Pentyl bromide/Mg then Li₂CuCl₄ (cat.), THF, 0 °C, 2 h; ii. Oxalyl chloride, DMSO, Et₃N, CH₂Cl₂, -78 °C, 2 h; iii. NaH, THF, 0 °C to -78 °C, 1.5 h; iv. LiOH, THF, MeOH, H₂O, 0 °C to r.t., 16 h.

This alternative approach is outlined in Scheme 2. Branched alcohol **9** was prepared *via* a copper-mediated coupling as before. An Appel reaction with **9** furnished bromide **10** in 60% yield. Lithiation of 3,3-diethoxy-1-propyne (**11**), followed by addition of **10**, afforded acetal **12**. Acidic hydrolysis of **12** revealed an unstable aldehyde which was oxidised *in situ* under Pinnick conditions to produce propargyl acid **13** in 51% overall yield. Partial hydrogenation of the acetylenic bond required careful optimisation so as to avoid over-reduction to the alkane or isomerisation. Conjugation with the carbonyl group reduces the reactivity of the triple bond. Use of Lindlar's catalyst in a 60 PSI hydrogen atmosphere furnished DSF (**1**) in 89% yield exclusively as the *Z*-isomer. While this approach was much improved

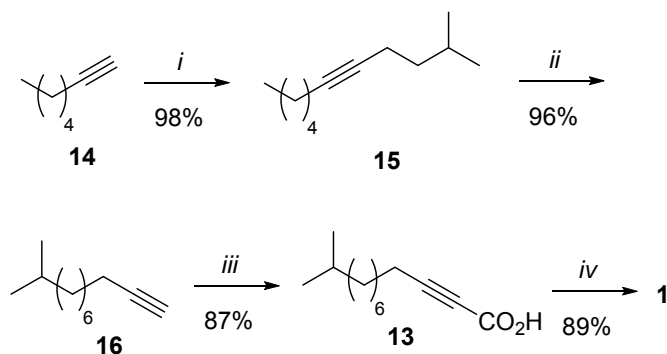
compared to the original route, some issues remained. Chief among these was the hydrolysis/oxidation step, which proved capricious and was not amenable to scale up.

Key to our revised route was an alkyne zipper reaction (Scheme 3).¹⁹ This reaction results in the isomerisation of an internal alkyne to the corresponding terminal alkyne.²⁰⁻²³ Other groups have successfully adopted a similar approach in their syntheses of natural products.^{24, 25} The alkyne zipper reaction works best with a strong base, such as 1,3-diaminopropane, which is typically generated *in situ* from 1,3-diaminopropane.²⁶



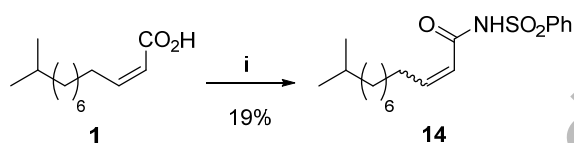
Scheme 2. i. *iso*-Pentyl bromide/Mg then Li₂CuCl₄ (cat.), 0 °C to r.t., 15 h; ii. CBr₄, PPh₃, CH₂Cl₂, 0-10 °C, 2 h; iii. **11**, *n*-BuLi (2.7M), THF then **10**, DMSO, -50 °C to r.t., 16 h; iv. TFA, CH₂Cl₂, -10 °C, 3 h then NaOCl₂, 30% H₂O₂, Na₂HPO₄, CH₃CN, 0 °C to r.t., 3 h; v. H₂ (60 PSI), Pd-Pb, CH₂Cl₂, r.t., 48 h.

Treatment of 1-hexyne (**14**) with *n*-butyllithium in HMPA generated an acetylide which was alkylated with 4-bromo-2-methyl butane at 0 °C. The next step required the isomerisation of internal alkyne **15** using the alkyne zipper reaction. Fortuitously, our initial choice of *n*-butyllithium, potassium *tert*-butoxide and 1,3-diaminopropane in tetrahydrofuran proved highly effective for this transformation. Accordingly, **15** was converted to terminal alkyne **16** in 96% yield. Evidence for the successful isomerisation to the target compound was found in the ¹H-NMR spectrum with the appearance of a 1H triplet at 1.93 ppm. Homologation of the alkyne to the corresponding carboxylic acid was achieved by deprotonation of **16** followed by addition of gaseous carbon dioxide which gave **13** in 87% yield. Finally, partial hydrogenation of **13** produced DSF (**1**).



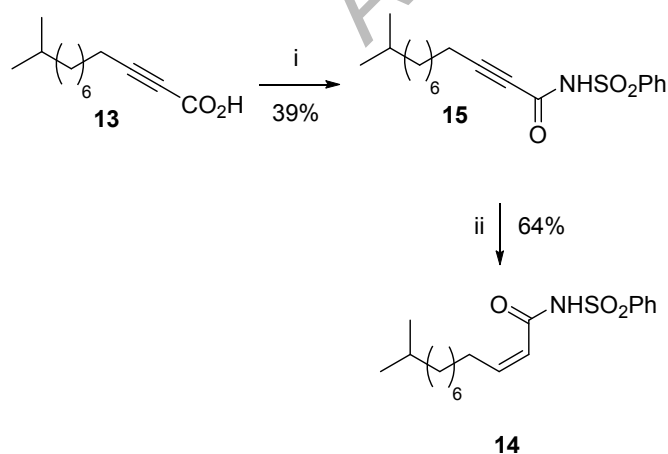
Scheme 3. i. *n*-BuLi, NaI, HMPA, THF then 1-bromo-3-methylbutane -20 °C to 0 °C; ii. *n*-BuLi, KOtBu, 1,3-diaminopropane, THF; iii. *n*-BuLi, then CO_{2(g)}, THF; iv. H₂ (60 PSI), Pd-Pb, CH₂Cl₂, r.t., 48 h.

In an effort to generate analogues of DSF, we investigated the coupling of **1** with a suitable sulfonamide. While a large number of examples exist for the coupling of *trans*-unsaturated carboxylic acids, similar examples of successful couplings of *cis*-unsaturated carboxylic acids are limited. When we attempted the EDCI-mediated coupling of **1** with benzenesulfonamide, the reaction was accompanied by isomerisation of the double bond (Scheme 4). This tendency of *cis*-unsaturated carboxylic acids to readily isomerise has previously been noted.²⁷ Separation of these isomers is often difficult due to their tendency to co-elute.



Scheme 4. i. PhSO₂NH₂, EDCI, DMAP, CH₂Cl₂, 25 °C, 16 h.

An alternative approach which avoids these issues is to start with carboxylic acid **13** which undergoes EDCI coupling with benzenesulfonamide to afford **15** in 39% yield (Scheme 5). Partial hydrogenation with Lindlar's catalyst afforded sulfonamide **14** in 64% yield exclusively as the *cis*-isomer.



Scheme 5. i. PhSO₂NH₂, EDCI, DMAP, CH₂Cl₂, 25 °C, 16 h; ii. H₂ (60 PSI), Pd-Pb, CH₂Cl₂, r.t., 16 h.

3. Conclusion

DSF plays an important role in cell-to-cell communication among various strains of bacteria and is an attractive synthetic target. We have outlined the development of a concise synthetic route to this molecule which exploits the alkyne zipper reaction followed by a partial hydrogenation to furnish DSF as a single isomer. This route also provides ready access to *cis*-unsaturated derivatives of DSF.

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Supplementary Data

Experimental procedures and compound characterization is provided in the electronic supplementary information.

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