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A Novel Convenient Route to the Naturally Occurring 3-Oxoacyl-L-Homoserinelactones and Related Bacterial Autoinducers.

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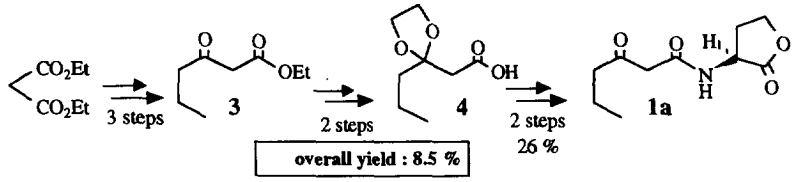
Abstract : The naturally occurring 3-oxohexanoyl-L-homoserinelactone (**1a**), a bacterial autoinducer, has been prepared in 47 % overall yield by condensing stable 3-oxohexanoic acid (**2**), prepared by hydrolysis from the corresponding ester (**3**), with L-homoserinelactone using hydroxybenzotriazole (HOBT) and dicyclohexylcarbodiimide (DCC) in non-aqueous media.

Analogues of homoserinelactone (HSL) have recently been shown to have a major role in cell-cell communication.[1] HSLs are produced during the normal growth of many Gram-negative bacteria, and at high cell densities, reach a threshold concentration for bacterial detection. This leads to global regulation of a variety of physiological processes.[1,2] HSLs isolated to date are : **(1a)**,[3,4] **(1b)**,[5] **(1c)**[6] and **(1d)**[7] (Scheme 2). Most microbiological studies to date have isolated HSLs from batch fermentation but there is a need for a rapid, simple synthetic method, versatile to allow for ready synthesis of variants.

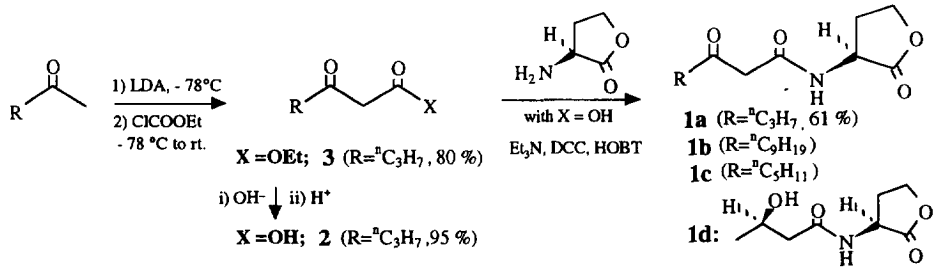
There are currently three reported syntheses of N-substituted-L-homoserinelactones of the autoinducer classes. The first reported, for N-(3-oxohexanoyl)-L-homoserinelactone **(1a)**, gave the racemate and it was not possible to calculate the overall yield.[3] A range of analogues has been reported using either carbodiimide or acyl chloride activation of the protected 3-ketoacid. The chirally pure product was synthesized (Scheme 1), in 26 % yield for the two steps from the ethylene glycol ketal of 3-oxohexanoic acid **4**, using a water-soluble carbodiimide.[6] Recently, N-(3-oxododecanoyl)-L-homoserinelactone **(1b)** was synthesized similarly.[5] In these routes β-ketoethylester **3** was prepared (three steps) from diethyl malonate [8] and the 3-oxo function ketal-protected (Scheme 1).

Scheme 1



We now report a route to this family of homoserinelactone autoinducers (Scheme 2) which avoids the need for these protection and deprotection steps.

Scheme 2



Previous studies differ from the synthetic route in Scheme 2 mainly in starting with diethyl malonate, 3-oxoprotection and an aqueous environment for condensation of the 3-oxoacid with L-homoserine lactone. We have found that by using hydroxybenzotriazole and dicyclohexylcarbodiimide in nonaqueous media there is no need to protect the 3-oxo site, leading to an improved overall yield with fewer steps. Ethyl 3-oxohexanoate **3** was condensed with ethyl chloroformate by means of lithium diisopropylamide in 80 % yield and base hydrolysis of this to the free acid **2** was carried out in 95 % yield. Although the β-ketoacid **2** has been reported as unstable at room temperature,[9] the spectral data for **2** were entirely consistent with the β-ketoacid structure. Finally, 3-oxo-N-(tetrahydro-2-oxo-3-furanyl)hexanamide (**1a**) was prepared in 61 % yield by reaction of **2** with L-homoserinelactone in dry dichloromethane with activation by DCC and HOBT.

In conclusion, a new, short, high-yielding route to the biologically interesting and useful synthetic N-(3-oxohexanoyl)-L-homoserinelactone (**1a**) has been developed. This synthetic methodology is clearly readily applicable to other analogues.

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