Simple synthesis of natural polyketides, 2-dodecanoyl-5-hydroxycyclohexane-1,3-dione and 2-dodecanoylresorcinol

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The title compounds were synthesised in two and three steps, respectively, starting from 5-hydroxycyclohexane-1,3-dione.

2-Dodecanoyl-5-hydroxycyclohexane-1,3-dione **1** was identified[1] as the major component of the secretions of *Stephanitis takeyai*. It was prepared by a complex multistage synthesis including the construction of the cyclohexane ring containing a phenyldimethylsilyl substituent as a masked hydroxy group.[2] The authors reported the easy aromatization of hydroxytriketone **1** due to the known succeptibility of β-hydroxyketones to dehydration.

Recently, we reported the first synthesis of 5-hydroxycyclohexane-1,3-dione **2**.[3] We have found that 5-hydroxydiketone **2** exists in solution mainly in the enolic form, and it takes part in reactions through its enol group. It gives little or no by-product aromatics in the absence of an acid. Based on this finding, we carried out a simple two-step synthesis of target compound **1** by the method developed earlier[4] for regioisomeric 2-acyl-4-hydroxycyclohexane-1,3-diones. Acylation of 5-hydroxydiketone **2** with dodecanoyl chloride proceeds regiospecifically, affording enolacylate **3**. The latter was then subjected to a smooth O–C isomerization into triketone **1**[†] under the CN$^-$ catalysis.

This method can be used as a general procedure for the synthesis of other 2-acyl-5-hydroxycyclohexane-1,3-diones. Moreover, these 5-hydroxyketones are the immediate synthetic precursors of natural bioactive 2-acylresorcinols.[5] Thus, hydroxytriketone **1** was entirely converted into 2-dodecanoylresorcinol **4**[‡] when treated with a mineral acid.

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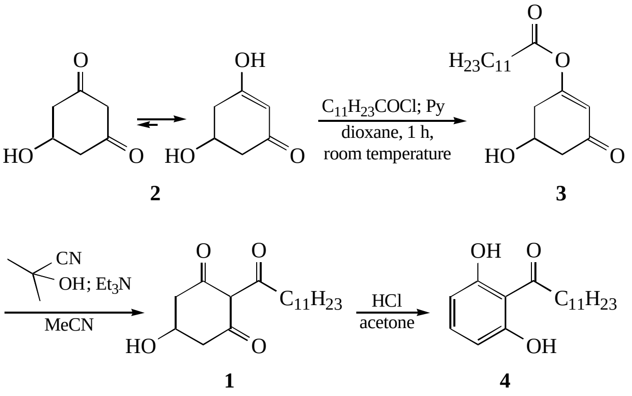

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[†] *2-Dodecanoyl-5-hydroxycyclohexane-1,3-dione* **1**. To a stirred solution of 0.39 g (3 mmol) of anhydrous 5-hydroxycyclohexane-1,3-dione **2** (mp 95–96 °C) and 0.25 ml (3.1 mmol) of pyridine in 30 ml of dioxane, 0.60 ml (2.5 mmol) of dodecanoyl chloride in 20 ml of dioxane was added dropwise, over 1 h at room temperature. The solvent was evaporated *in vacuo*, and 20 ml of $CHCl_3$ was added to the residue. The solution was washed with 0.2 M HCl, H_2O, brine, and then dried over $MgSO_4$. The crude product after solvent evaporation was recrystallised from hexane giving 0.71 g (92%) of 3-dodecanoyl-5-hydroxycyclohex-2-en-1-one **3**. Mp 43–44 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 0.88 (t, 3H, Me, *J* 6.5 Hz), 1.27 (m, 16H, 4′–11′-CH_2), 1.67 (m, 2H, 3′-CH_2), 2.48 (t, 2H, 2′-CH_2, *J* 7.5 Hz), 2.55 and 2.64 (2dd, 2H, 4,6-H_a, *J* 6.5 and 17 Hz), 2.70 (dd, 1H, 4- or 6-H_e, *J* 4 and 17 Hz), 2.88 (dd, 1H, 4- or 6-H_e, *J* 4 and 17 Hz), 4.43 (m, 1H, 5-H), 5.98 (s, 1H, 2-H). IR (KBr, ν/cm^{-1}): 3440 (br.), 1765, 1680, 1660, 1480, 1420, 1380, 1145, 1135, 1115, 1070.

To a solution of 0.17 g (0.55 mmol) of enolacylate **3** and 0.24 ml (2.5 mmol) of Et_3N in 30 ml of acetonitrile, 0.06 ml (0.6 mmol) of acetone cyanohydrin was added. The reaction mixture was allowed to stand for 3 h at room temperature, then the solvent was evaporated *in vacuo*, and the residue was worked up as above giving, after recrystallization from hexane, 0.16 g (94%) of 2-dodecanoyl-5-hydroxycyclohexane-1,3-dione **1**. Mp 55–56 °C. Physical and chemical characteristics of synthetic **1** are the same as those published.[2]

[‡] *2-Dodecanoylresorcinol* **4** was obtained by dehydration in an acid medium (2 drops of conc. HCl in 20 ml of acetone) of crude hydroxytriketone **1** synthesised as described above from 0.30 g (0.97 mmol) of enolacylate **3**. After completing the dehydration reaction (3 h, control by TLC), the solvent was evaporated. The residue was dissolved in $CHCl_3$, washed with H_2O and brine, dried over $MgSO_4$, and the solvent was evaporated giving, after recrystallization of the residue from hexane, 0.25 g (88%) of 2-dodecanoylresorcinol **4**. Mp 85–86 °C. Physical and chemical characteristics of synthetic **4** are the same as those published.[6]