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# A New Approach to the Synthesis of 3,6- and 5,6-Dialkyl Derivatives of 4-Hydroxy-2-pyrone. Synthesis of *rac*-Germicidin.

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*Abstract* : A new approach to the synthesis of 3,6- and 5,6-dialkyl-4-hydroxy-2-pyrones has been developed. The method includes the formation of acylated Meldrum's acids (5-(2-alkyl-3-oxoacyl)-2,2-dimethyl-1,3-dioxane-4,6-diones) followed by their thermal transformation. Introduction of 3-alkyl substituents was accomplished by acylation of 4-hydroxy-2-pyrones and ionic hydrogenation of the 3-acyl derivatives obtained. The effectiveness of this new approach has been demonstrated in the synthesis of *rac*-germicidin, an autoregulative germination inhibitor of *Streptomyces viridochromogenes* NRRL B-1551. 

## INTRODUCTION

Alkyl derivatives of 4-hydroxy-2-pyrone attract considerable attention because of their broad spectrum of chemical and biological properties. During the last few years a great number of 3-, 5- and 6-alkyl derivatives of 4-hydroxy-2-pyrone have been isolated from fungi, plants and molluscs. Syntheses of such complex natural 2-pyrones as verrucosodin,[1] citreoviridin,[2] asteltoxin,[3] citromontanin[4] and many others cover an extensive arsenal of chemical and biochemical methods of molecule transformation. The development of new methods for the construction of 2-pyrones with various alkyl substituents presents an interesting challenge.

Alkylation of the 4-hydroxy-6-methyl-2-pyrone dianion with alkyl halides[5] and aldol condensation of 4-methoxy derivatives with aldehydes[1,2b,3,4b,6] are the most widespread methods for introduction of substituents at position 6. Syntheses based upon the transformation of a C-6 methyl group to an aldehyde[4a,7] or bromomethyl[2a] are used less frequently.

Few methods to effect the introduction of alkyl substituents at position 3 have been developed and these tend to be low yielding. The best result has been obtained by direct alkylation of the anion of 4-hydroxy-6-methyl-2-pyrone with methyl iodide[9], where the yield of target product was only 16%. Reduction of the readily available 3-acetyl-4-hydroxy-6-methyl-2-pyrone **1** with borane-methyl sulphide complex[10] results in the formation of 3-ethyl derivative **2a** in low yield (23%). Catalytic hydrogenation of 3-acetylpyrone **1a** over palladium is not applicable for this purpose because $\Delta^5$-bond reduction is more facile leading to a 5,6-dihydro-2-pyrone.[11] Thus there is considerable deficiency in the methods for the synthesis of alkyl derivatives of 4-hydroxy-2-pyrone, especially with substituents at positions 3 and 5.

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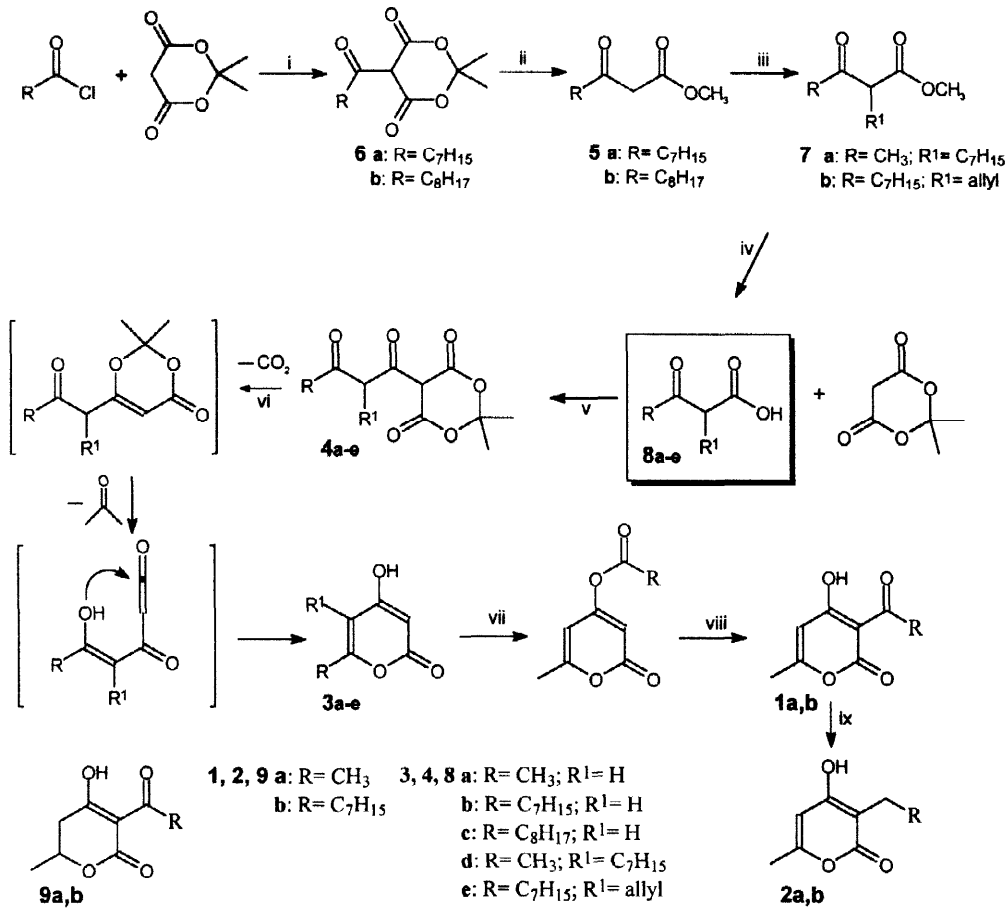
In the present paper we outline a new approach to 3,6- and 5,6-dialkyl-4-hydroxy-2-pyrones **2** and **3** that uses a thermolysis of acetoacylated Meldrum's acids as a key step for the construction of the 2-pyrone ring system.

## RESULTS AND DISCUSSION

The most convenient method for synthesis of 4-hydroxy-6-methyl-2-pyrone **3a**[12] involves refluxing acetoacetyl Meldrum's acid **4a** in dioxane. This reaction proceeds through formation of an α-oxoketene as a key intermediate followed by its intramolecular addition to an enolic hydroxyl. Compound **4a** is readily obtained by the reaction of Meldrum's acid with diketene. Formally synthesis of 5,6-dialkyl-2-pyrones **3b-e** is reduced to formation of oxoacylderivatives **4b-e** of Meldrum's acid with the alkyl substituents preintroduced.




**Reagents**: i: 1) 2 eq. Py, $CHCl_3$, -20 °C, 2) 5% HCl; ii: MeOH reflux; iii: 1) MeONa in MeOH, 2) $R^1Br$; iv: 1) 1.1 eq. MeONa in MeOH, 2) 1 *N* HCl; v: 1) DCC, 0.3 eq. DMAP, $Et_3N$, $CH_2Cl_2$, 2) 5% HCl; vi: toluene reflux; vii and viii: 1 eq. RCOCl, *TFA* reflux; ix: $Et_3SiH$, TFA, 0.01 eq. $LiClO_4$

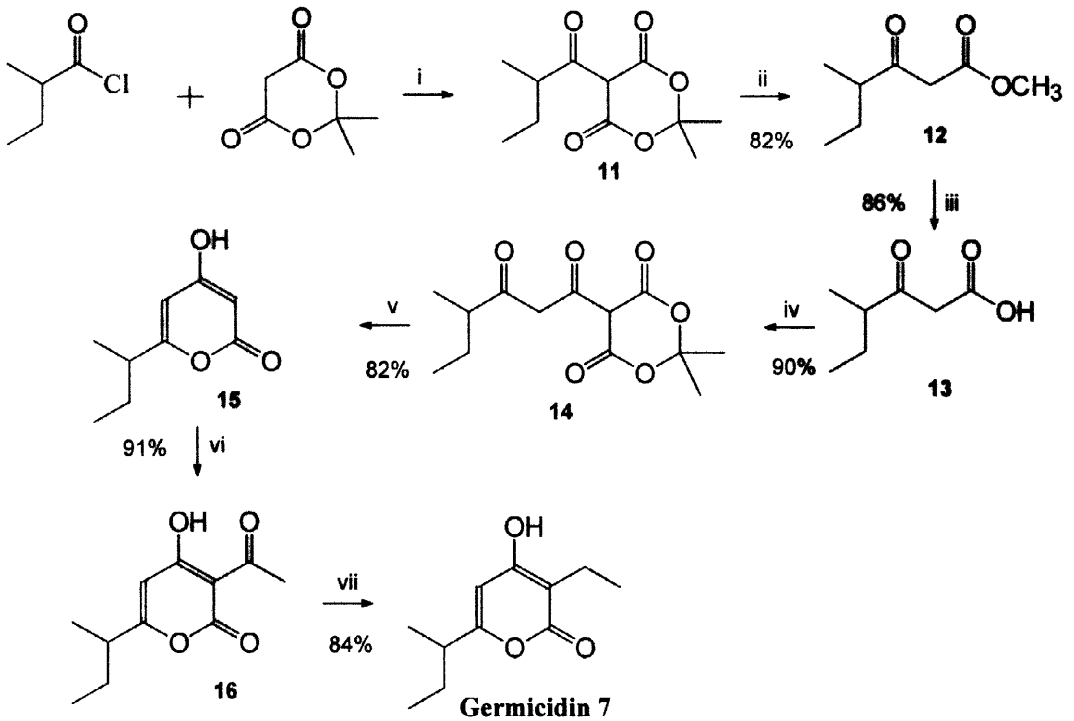
Introduction of an α-alkylsubstituent into acyclic β-dicarbonyl compounds such as esters **5** is a classic reaction.[13] There are several methods for the synthesis of β-oxoesters.[14] The most convenient and reliable one is based upon alcoholysis of a synthetic equivalent of a mixed diketene — acylated Meldrum's acid **6** — which is obtained in quantitative yield in mild conditions from commercially available reagents.[14a]

As we have supposed, methyl β-oxoesters **5** and **7** can be easily obtained according to standard methods and saponified by the action of alkali in almost quantitative yield to afford acids **8**. The method for the synthesis of acyl derivatives of Meldrum's acid **6** mentioned above is not applicable for obtaining the key precursors **4** because of instability of the β-oxoacid chlorides.[15] For this purpose we successfully applied the condensation of Meldrum's acid directly with β-oxoacids **8** by the action of dicyclohexylcarbodiimide (DCC)[16] in the presence of triethylamine and a catalytic amount of dimethylaminopyridine (DMAP). This resulted in formation in good yield of the key compounds **4** (qualitatively detected by an alcoholic $FeCl_3$ stain). Without additional purification compounds **4** thus obtained were refluxed in toluene for 5-15 h. After column chromatography, the target alkylpyrones **3a-e** were obtained in 46-91 % overall yield in 3 steps starting from β-oxoesters **5** and **7**. The yield of 5-allyl derivative **3e** was the lowest in part because of steric hindrances of substituents during recyclization. Another reason was the low purity of the oily product **8e** which could not be purified by recrystallization as for other β-oxoacids obtained in this manner.

The described method for the synthesis of 5,6-dialkyl-4-hydroxy-2-pyrones **3b-e** has a range of advantages in comparison with earlier ones. They proceed in good yields and under mild conditions (strong basic or acidic reagents and solvents that may cause undesirable transformations of substrates are not involved).

As was noted above, methods for introduction of 3-alkylsubstituents into the 4-hydroxy-2-pyrone cycle have been developed but give low yields. To address this problem, we applied a method proposed by us earlier[17,18] for obtaining α-alkylderivatives of different carbo- and heterocyclic β-dicarbonyl compounds. The method includes *O*-acylation of β-dicarbonyl compounds, *O*-*C*-isomerization of enol acylates obtained followed by regioselective hydrogenolysis of the oxo function in 3-acylsubstituent in the corresponding 3-acylderivatives **1** during ionic hydrogenation with the use of triethylsilane in *TFA* in the presence of Lewis acids. These processes usually proceed smoothly in excellent yield. However, in the case of 3-acyl-4-hydroxy-5,6-dihydropyrones **9**, the closest analogues of 3-acetyl-4-hydroxy-6-methyl-2-pyrones **1a**, the reaction of ionic hydrogenation was unsuccessful probably because of the instability of the lactone cycle in the strong acidic medium. In the case of 3-acyl-4-hydroxy-6-methyl-2-pyrones **1** the method proposed above resulted in formation of 3-alkyl derivatives **2** in overall yields of about 80% in a 3 step sequence starting from pyrones **3**.

The effectiveness of this new approach to the synthesis of 2-pyrone alkyl derivatives leads us to consider its application toward the germicidin **10**,[19] which was isolated from *Streptomyces viridochromogenes* NRRL B-1551 and shown to have an inhibitory effect on the germination of its own arthrospores at concentrations as low as 40 pg/mL; at higher concentrations germicidin inhibits porcine $Na^+/K^+$ activated ATPase and retards the germination of the cress *Lepidium sativum*.




**Reagents**: i: 1) 2 eq. Py, $CHCl_3$, -20 °C, 2) 5% HCl; ii: MeOH reflux; iii 1) 1.1 eq. MeONa in MeOH, 2) 1 *N* HCl; iv: 1) Meldrum's acid, DCC, 0.3 eq. DMAP, $Et_3N$, $CH_2Cl_2$, 2) 5% HCl; v: toluene reflux; vi: 1) $CH_3COOH$, DCC, 0.3 eq. DMAP, $Et_3N$, $CH_2Cl_2$, 2) 5% HCl; vii: $Et_3SiH$, TFA, 0.01 eq. $LiClO_4$

Reaction of the pyridinium salt of Meldrum's acid with 2-methylbutyric acid chloride followed by heating the tricarbonyl compound **11** thus obtained in methanol gave β-oxoester **12** in 82% overall yield. Hydrolysis of the latter resulted in β-oxoacid **13**. Meldrum's acid acylation by the action of DCC, triethylamine and a catalytic amount of DMAP gave tetracarbonyl compound **14**, which was converted into 6-*sec*-butyl-2-pyrone **15** on refluxing for 6 h in toluene. For the synthesis of 3-acetyl-2-pyrone **16** we used a *one pot* procedure involving the acylation of **15** by the action of acetic acid and DCC followed by *O*-*C*-isomerization with the use of DMAP and triethylamine. Ionic hydrogenation of 3-acetylpyrone **16** afforded racemic germicidin **10** in 84% yield.

Thus, total synthesis of *rac*-germicidin proceeds in 40% overall yield in 7 steps. *Rac*-germicidin obtained was isolated as an oil which crystallised on standing. Recrystallization of the product from ether-hexane afforded a white solid with melting point 95-97 °C. Spectral characteristics of the obtained product coincided with the literature data. The method proposed allows synthesis of germicidin in optically active form (natural product or its enantiomer). To date there is no information in the literature concerning the optical activity of the natural sample.

## EXPERIMENTAL

The $^1H$ NMR and $^{13}C$ NMR spectra were recorded on Brucker WM-360 and Brucker AC-200 spectrometers operating at 360 and 200 MHz for $^1H$ NMR and 50.33 MHz for $^{13}C$ NMR in $CDCl_3$. The chemical shifts of $^1H$

NMR signals δ are reported in ppm (TMS as internal standard, δ=0). Mass spectra (EI, 70 eV) were recorded on a Shimadzu apparatus (chromatograph GC-17A, mass-spectrometer QP-5000, gas - helium). IR spectra were recorded on UR-20 apparatus (KBr disks or liquid film). Melting points were determined on a Kofler apparatus and are uncorrected. Thin layer chromatography (TLC) was carried out on Silufol $UV_{254}$ plates coated with 0.2 mm layer of silica gel and UV visualisation. Column chromatography was performed using silica gel of 70-230 mesh ($CHCl_3$). Starting materials: Meldrum's acid,[20] 2,2-dimethyl-5-(3-oxobutyryl)-1,3-dioxane-4,6-dione **4a**,[12] 5,6-dihydro-4-hydroxy-2-pyrone[12] were obtained by standard procedures.

Acylation of Meldrum's acid. To a solution of Meldrum's acid (7.2 g, 0.05 mol) in $CHCl_3$ (100 mL) at -20 °C was added pyridine (8.85 mL, 0.11 mol) and dropwise carboxylic acid chloride (0.11 mol). After stirring for 1 h the mixture was acidified with 1N HCl (120 mL) and organic layer was washed with 1N HCl (50 mL) and dried over anhydrous $Na_2SO_4$. The solvent was evaporated *in vacuo* to give **6** as a yellowish oil. Products of acylation **6** obtained are not stable for additional purification and were used immediately in the next stage.

**2,2-Dimethyl-5-octanoyl-1,3-dioxane-4,6-dione (6a)**: $\delta_H$ (200 MHz, $CDCl_3$) 15.28 (1 H, br, OH), 3.05 (2 H, t, *J* 7.4 Hz, $C\underline{H}_2CO$), 1.71 (6 H, s, 2x$C\underline{H}_3C$), 1.12-1.45 (10 H, m, $(C\underline{H}_2)_5CH_3$), 0.88 (3 H, t, *J* 7.4 Hz, $C\underline{H}_3CH_2$); $\nu_{max}$(liquid film) 1025, 1160, 1205, 1410, 1580, 1665, 1715, 1745, 2860, 2930, 2960 $cm^{-1}$.

β-Oxoesters **5** and **12**. Acylated products **6** and **11** (all quantity obtained in the previous stage) were refluxed for 2 h in methanol (80 mL) and after evaporation of solvent gave rise to almost pure β-oxoesters **5** and **12** as yellowish oils.

**Methyl 3-oxodecanoate (5a)**: Yield: 9.40 g (94%); b.p. $110_{1mm}$ °C; δH (200 MHz, $CDCl_3$) 12.02 (1 H x 0.1, s, O$\underline{H}$ enolic form), 3.74 (3 H, s, $OC\underline{H}_3$), 3.46 (2 H, s, $C\underline{H}_2CO_2Me$), 2.56 (2 H, t, *J* 7.4 Hz, $CH_2C\underline{H}_2CO$), 1.50-1.70 (2 H, br, $C\underline{H}_2CH_2CO$), 1.40-1.18 (8 H, br, $(C\underline{H}_2)_4CH_3$), 0.89 (3 H, t, *J* 7.3 Hz, $C\underline{H}_3CH_2$); $\nu_{max}$ (liquid film) 1160, 1245, 1330, 1415, 1450, 1640, 1730, 1760, 2865, 2940, 2965 $cm^{-1}$.

**Methyl 3-oxoundecanoate (5b)**: Yield: 9.84 g (94%); b.p. $112_{1mm}$ °C; $\delta_H$ (200 MHz, $CDCl_3$) 12.00 (1 H x 0.1, s, O$\underline{H}$ of enolic form), 3.75 (3 H, s, $OC\underline{H}_3$), 3.45 (2 H, s, $C\underline{H}_2CO_2Me$), 2.55 (2 H, t, *J* 7.4 Hz, $CH_2C\underline{H}_2CO$), 1.50-1.70 (2 H, br, $C\underline{H}_2CH_2CO$), 1.40-1.18 (10 H, br, $(C\underline{H}_2)_5CH_3$), 0.89 (3 H, t, *J* 7.3 Hz, $C\underline{H}_3CH_2$); $\nu_{max}$ (liquid film) 1160, 1245, 1330, 1410, 1450, 1645, 1730, 1760, 2865, 2940, 2965 $cm^{-1}$.

**Methyl 4-methyl-3-oxohexanoate (12)**: Yield: 6.5 g (82%); b.p. $95_{1mm}$ °C; $\delta_H$ (200 MHz, $CDCl_3$) 3.75 (3 H, s, $OC\underline{H}_3$), 3.50 (2 H, s, $C\underline{H}_2CO_2$), 2.58 (1 H, sxt, *J* 7 Hz, $C\underline{H}CH_3$), 1.72 (2 H, m, *J* 7.5 Hz, $C\underline{H}_2CH_3$), 1.15 (3 H, d, *J* 7 Hz, $CHC\underline{H}_3$), 0.93 (3 H, t, *J* 8 Hz, $CH_2C\underline{H}_3$).

Alkylation of β-oxoester **7** was conducted by a standard procedure.[13]

**Methyl 2-acetononanoate (7a)**: From ethyl acetoacetate (13 g, 0.1 mol) and 1-bromoheptane (18.8 g, 0.105 mol) with the use of Na (2.3 g, 0.1 mol) in MeOH (120 mL) was obtained the *title compound* **7a** (18.62 g, 87%) as a yellowish oil, b.p. $105_{1mm}$ °C; $\delta_H$ (200 MHz, $CDCl_3$) 3.66 (3 H, s, $OC\underline{H}_3$), 3.44 (1 H, t, *J* 7.3 Hz, C$\underline{H}$), 2.24 (3 H, s, $C\underline{H}_3CO$), 1.65-1.45 (2 H, m, $C\underline{H}_2CH$), 1.40-1.14 (10 H), 0.88 (3 H, t, *J* 7.5 Hz, $C\underline{H}_3CH_2$).

**Methyl 2-allyl-3-oxodecanoate (7b)**: From methyl 3-oxodecanoate **5a** (9.4 g, 0.047 mol) and allyl bromide (5.97 g, 0.049 mol) with the use of Na (1.08 g, 0.047 mol) in MeOH (50 mL) was obtained the *title compound* **7b** (9.59 g, 85%) as a yellowish oil, b.p. $125_{1mm}$ °C; $\delta_H$ (200 MHz, $CDCl_3$) 5.84-5.62 (1 H, m, =CH), 5.14 (1 H, br, $=CH_aH_b$), 5.03 (1 H, br, $=CH_aH_b$), 3.72 (3 H, s, $OCH_3$), 3.57 (1 H, t, *J* 7.2 Hz, $CHCH_2CH=$), 2.67-2.46 (4 H, 2t, $CH_2CH+CH_2CO$), 1.68 (2 H, br, $CH_2CH_2CO$), 1.40-1.15 (8 H, br, $(CH_2)_4CH_3$), 0.88 (3 H, t, *J* 7.4 Hz); $\nu_{max}$(liquid film) 925, 1005, 1140, 1180, 1205, 1240, 1275, 1350, 1450, 1470, 1650, 1730, 1760, 2865, 2940, 2965 $cm^{-1}$.

Hydrolysis of β-oxoesters **5, 7 and 12**. β-Oxoester (0.05 mol), sodium methoxide (0.055 mol) in methanol (100 mL) and water (10 mL) were stirred for 8 h. The methanol was evaporated *in vacuo* and the residue was acidified with 1N HCl (65 mL) and extracted with dichloromethane (2x100 mL). Extract was dried over anhydrous $Na_2SO_4$ and the solvent evaporated *in vacuo*. Washing with cold hexane and drying *in vacuo* gave the product **8** or **13** as an oil or white solid. β-Oxoacids obtained are unstable [while standing at room temperature for a few days 2-acetononanoic acid is decarboxylated into **2-decanone**: $\delta_H$ (200 MHz, $CDCl_3$) 2.40 (2 H, t, *J* 7.5 Hz, $CH_2CO$), 2.18 (3 H, s, $CH_3CO$), 1.70-1.16 (10 H, br), 0.89 (3 H, t, *J* 7.5 Hz, $CH_3CH_2$); $\nu_{max}$(liquid film) 940, 1130, 1190, 1415, 1470, 1715 (sharp), 2865, 2935, 2960 $cm^{-1}$]. β-Oxoacids obtained needed no further purification and were used directly in the next step.

**Acetoacetic acid (8a)**: Yield 3.88 g (76%) as a yellowish oil; $\delta_H$ (200 MHz, $CDCl_3$) 10.35 (1 H, br, OH), 3.55 (2 H, s, $CH_2$), 2.31 (3 H, s, $CH_3$).

**3-Oxodecanoic acid (8b)**: Yield 8.93 g (96%) as a white solid, m.p. 78 °C (dec.)(hexane); $\delta_H$ (200 MHz, $CDCl_3$) 11.85 (1 H x 0.05, br, OH of enolic form), 9.00 (1 H, br, OH), 3.55 (2 H, s, $CH_2COOH$), 2.60 (2 H, t, *J* 7.4 Hz, $CH_2COCH_2$), 1.48 (2 H, m, $CH_2CH_2CO$), 1.45-1.20 (8 H, br, $(CH_2)_4CH_3$), 0.90 (3 H, t, *J* 7.3 Hz, $CH_3$).

**3-Oxoundecanoic acid (8c)**: Yield 9.52 g (95%) as a white solid, m.p. 80 °C (dec.)(hexane).

**2-Acetononanoic acid (8d)**: Yield 86.87 g (87%) as a white solid, m.p. 46 °C (dec.)(hexane); $\delta_H$ (200 MHz, $CDCl_3$) 12.00 (1 H, br, OH), 3.60 (1 H, s, CH), 2.25 (3 H, s, $CH_3CO$), 1.65-1.45 (2 H, m, $CH_2CH$), 1.40-1.15 (10 H), 0.90 (3 H, t, *J* 7.5 Hz, $CH_3CH_2$).

**2-Allyl-3-oxodecanoic acid (8e)**: Yield 8.36 g (74%) as a yellowish oil; $\delta_H$ (200 MHz, $CDCl_3$) 11.00 (1 H, br, OH), 5.90-5.60 (1 H, m, =CH), 5.07-4.93 (2 H, m, $=CH_2$), 3.55 (1 H, t, *J* 7.3 Hz, $CHCH_2CH=$), 2.60-2.25 (4 H, m, $CH_2CH+CH_2CO$), 1.68 (2 H, m, $CH_2CH_2CO$), 1.40-1.15 (8 H, br, $(CH_2)_4CH_3$), 0.88 (3 H, t, *J* 7.5 Hz, $CH_3$).

**4-Methyl-3-oxo-hexanoic acid (13)**: Yield 6.19 g (86%) as a yellowish oil.

Condensation of Meldrum's acid with β-oxyacids. A solution of β-oxyacid **8** or **13** (0.02 mol), triethylamine (2.78 mL, 0.02 mol), Meldrum's acid (2.88 g, 0.02 mol), 4-dimethylaminopyridine (0.61 g, 0.005 mol) and *N,N*-dicyclohexylcarbodiimide (4.33 g, 0.021 mol) in dichloromethane (80 mL) was stirred at room temperature for 6 h. The *N,N*-dicyclohexylurea was filtered off and washed with an additional portion of dichloromethane. The filtrate was acidified with 5% HCl (25 mL)and washed with brine (30 mL), dried over anhydrous $Na_2SO_4$ and the solvent evaporated *in vacuo* to give the product as an oil. Acylated Meldrum's acids

**4a-e** are unstable [while standing for a few days at room temperature **4a** is transformed into **3-carboxy-4-hydroxy-6-methyl-2-pyrone**: $\delta_H$ (200 MHz, $CDCl_3$) 14.03 (1 H, br, enolic OH), 12.67 (1 H, br, COOH), 6.21 (1 H, s, CH), 2.42 (3 H, s, $CH_3$); m.p. 123 °C (dec.)($Et_2O$)]. For this reason **4a-e** were used without purification in the next step.

**2,2-Dimethyl-5-(3-oxobutyryl)-1,3-dioxane-4,6-dione (4a)**: Yield 4.51 g (99%) as a white solid, m.p. 82-83 °C ($Et_2O$); $\delta_H$ (200 MHz, $CDCl_3$) 15.00 (1 H, br, OH), 4.18 (2 H, s, $CH_2$), 2.35 (3 H, s, $CH_3C$=O), 1.75 (6 H, s, $(CH_3)_2C$).

**2,2-Dimethyl-5-(3-oxodecanoyl)-1,3-dioxane-4,6-dione (4b)**: Yield 6.12 g (98%) as a yellowish oil; $\delta_H$ (200 MHz, $CDCl_3$) 15.00 (1 H, br, OH), 4.10 (2 H, s, O=C$CH_2$C=O), 2.44 (2 H, t, *J* 7.5 Hz, $CH_2CH_2CO$), 1.76 (6 H, s, $(CH_3)_2C$), 1.60 (2 H, m, $CH_2CH_2CO$), 1.45-1.15 (8 H, br, $(CH_2)_4CH_3$), 0.90 (3 H, t, *J* 7.4 Hz, $CH_3CH_2$).

**2,2-Dimethyl-5-(3-oxoundecanoyl)-1,3-dioxane-4,6-dione (4c)**: Yield 6.26 g (96%) as a yellowish oil; $\delta_H$ (200 MHz, $CDCl_3$) 15.00 (1 H, br, OH), 4.15 (2 H, s, O=C$CH_2$C=O), 2.45 (2 H, t, *J* 7.5 Hz, $CH_2CH_2CO$), 1.75 (6 H, s, $(CH_3)_2C$), 1.62 (2 H, m, $CH_2CH_2CO$), 1.48-1.15 (10H, br, $(CH_2)_5CH_3$), 0.89 (3 H, t, *J* 7.4 Hz, $CH_3CH_2$).

**5-(2-Acetononanoyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (4d)**: Yield 6.06 g (93%) as a yellowish oil; $\delta_H$ (200 MHz, $CDCl_3$) 15.00 (1 H, br, OH), 4.12 (1 H, s, $CHCH_2$), 2.36 (3 H, s, $CH_3CO$), 1.75 (6 H, s, $(CH_3)_2C$), 1.62 (2 H, m, $CH_2CH$), 1.45-1.15 (10 H, br, $(CH_2)_5CH_3$), 0.90 (3 H, t, *J* 7.4 Hz, $CH_3CH_2$).

**5-(2-Allyl-3-oxodecanoyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (4e)**: Yield 6.12 g (87%) as a yellowish oil; $\delta_H$ (200 MHz, $CDCl_3$) 15.60 (1 H, br, OH), 5.90-5.65 (1 H, m, =CH), 5.15-4.90 (3 H, m, $CH_2$= + $CHCH_2CH$=), 2.65-2.22 (4 H, m, =$CHCH_2$ + $CH_2CO$), 1.80 (6 H, s, $(CH_3)_2C$), 1.68 (2 H, m, $CH_2CH_2CO$), 1.45-1.15 (8 H, br, $(CH_2)_4CH_3$), 0.90 (3 H, t, *J* 7.5 Hz, $CH_3CH_2$).

**2,2-Dimethyl-5-(4-methyl-3-oxohexanoyl)-1,3-dioxane (14)**: Yield 5.39 g (90%) as a yellowish oil; $\delta_H$ (200 MHz, $CDCl_3$) 15.60 (1 H, br, OH), 3.54 (2 H, s, $CH_2CO_2$), 2.58 (1 H, m, $CHCH_3$), 1.75 (6 H, s, $(CH_3)_2C$), 1.70 (2 H, m, *J* 7.5 Hz, $CH_2CH_3$), 1.15 (3 H, d, *J* 7 Hz, $CHCH_3$), 0.92 (3 H, t, *J* 8 Hz, $CH_2CH_3$).

Formation of 2-pyrone cycle (recyclization and decarboxylation). Acylated Meldrum's acids **4** (0.02 mol) were dissolved in absolute toluene (80 mL) and refluxed for 5-15 h (reaction was monitored by TLC). Toluene was evaporated *in vacuo* and the residue was purified by column chromatography ($CHCl_3$).

**4-Hydroxy-6-methyl-2-pyrone (3a)**: Yield 1.92 g (76%), m.p 189 °C (toluene)[12].

**6-Heptyl-4-hydroxy-2-pyrone (3b)**: Yield: 4.07 g (97%), m.p. 63-64 °C ($Et_2O$); $\nu_{max}$(KBr): 1250, 1500, 1570, 1620, 1695, 2865, 2930, 2960 $cm^{-1}$. $\delta_H$ (200 MHz $CDCl_3$) 6.00 (1 H, s, =CH=), 5.62 (1 H, d, *J* 2 Hz, =CHCO), 2.48 (2 H, t, *J* 7.5 Hz, =$CCH_2$), 1.63 (2 H, m, =$CCH_2CH_2$), 1.44-1.10 (8 H, br, $(CH_2)_4CH_3$), 0.89 (3 H, t, *J* 7.5 Hz, $CH_3$), OH signal is not observed. $C_{12}H_{18}O_3$ (210.28): calc. C, 68.54; H, 8.63. Found: C, 68.75; H, 8.60.

**4-Hydroxy-6-octyl-2-pyrone (3c)**: Yield: 4.28 g (95%), m.p. 57-59 °C ($Et_2O$); $\nu_{max}$(KBr) 1250, 1500, 1570, 1620, 1695, 2865, 2930, 2960 $cm^{-1}$. $\delta_H$ (200 MHz, $CDCl_3$) 6.00 (1 H, s, =CH=), 5.62 (1 H, d, *J* 2 Hz, =CHCO

), 2.50 (2 H, t, *J* 7.5 Hz, =CC$\underline{H}_2$), 1.65 (2 H, m, =CCH$_2$C$\underline{H}_2$), 1.50-1.10 (10 H, br, (C$\underline{H}_2$)$_5$CH$_3$), 0.90 (3 H, t, *J* 7.5 Hz, C$\underline{H}_3$), O$\underline{H}$ signal is not observed. $C_{13}H_{20}O_3$ (224.30): calc. C, 69.61; H, 8.99. Found: C, 69.65; H, 9.00.

**5-Heptyl-4-hydroxy-6-methyl-2-pyrone (3d)**: Yield: 4.25 g (95%), m.p. 85 °C; $\nu_{max}$(KBr) 1260, 1300, 1470, 1540, 1580, 1630, 1655, 1735, 2855, 2930, 2970 cm$^{-1}$. $\delta_H$ (200 MHz, $CDCl_3$) 5.68 (1 H, s, =C$\underline{H}$CO), 2.37 (2 H, t, *J* 7.3 Hz, CH$_2$C=), 2.25 (3 H, s, CH$_3$C=), 1.45 (2 H, C$\underline{H}_2$CH$_2$C=), 1.29 (8 H, br), 0.88 (3 H, t, *J* 7.5 Hz, C$\underline{H}_3$CH$_2$), O$\underline{H}$ signal is not observed. $C_{13}H_{20}O_3$ (224.30): calc. C, 69.61; H, 8.99. Found: C, 69.65; H, 8.95.

**5-Allyl-6-heptyl-2-pyrone (3e)**: Yield: 3.57 g (71%), m.p. 38-39 °C; $\nu_{max}$(KBr) 1265, 1315, 1510, 1590, 1665, 1730, 2865, 2940, 2970 cm$^{-1}$. $\delta_H$ (200 MHz, $CDCl_3$) 5.87 (1 H, m, C$\underline{H}$CH$_2$), 5.71 (1 H, s, =C$\underline{H}$C=O), 5.07 (1 H, s, CH=CH$_a\underline{H}_b$), 5.00 (1 H, d, *J* 6.5 Hz, CH=CH$_a\underline{H}_b$), 3.18 (2 H, d, *J* 5.5 Hz, CH$_2$=CHC$\underline{H}_2$), 2.52 (2 H, t, *J* 6.5 Hz, =CC$\underline{H}_2$CH$_2$), 1.64 (2 H, m, =CCH$_2$C$\underline{H}_2$), 1.41-1.14 (8H, br, (C$\underline{H}_2$)$_4$CH$_3$), 0.89 (3 H, t, *J* 7.5 Hz, C$\underline{H}_3$), O$\underline{H}$ signal is not observed; $\delta_C$ (50.33 MHz, $CDCl_3$) and DEPT 172.2 (C), 167.6 (C), 164.1 (C), 134.8 (CH), 115.5 (CH$_2$), 110.7 (C), 89.9 (CH), 31.6 (CH$_2$), 30.8 (CH$_2$), 29.2 (CH$_2$), 28.9 (CH$_2$), 27.9 (CH$_2$), 27.3 (CH$_2$), 22.5 (CH$_2$), 14.0 (CH$_3$). $C_{15}H_{22}O_3$ (250.34): calc. C, 71.97; H, 8.86. Found: C, 72.05; H, 8.95.

**6-(2-Butyl)-4-hydroxy-2-pyrone (15)**: Yield: 2.76 g (82%) as a colourless oil; $\nu_{max}$(liquid film) 1245, 1445, 1575, 1630, 1670, 1700, 2880, 2940, 2970 cm$^{-1}$; $\delta_H$ (200 MHz, $CDCl_3$) 6.00 (1 H, d, *J* 2 Hz, BuC=C$\underline{H}$), 5.60 (1 H, d, *J* 2 Hz, =C$\underline{H}$CO), 2.50 (1 H, m, C$\underline{H}$CH$_3$), 1.80-1.45 (2 H, m, C$\underline{H}_2$CH$_3$), 1.20 (3 H, d, *J* 6.5 Hz, CHC$\underline{H}_3$), 0.90 (3 H, t, *J* 7.3 Hz, C$\underline{H}_3$CH$_2$), O$\underline{H}$ signal is not observed. $C_9H_{12}O_3$ (168.19): calc. C, 64.27; H, 7.19. Found: C, 64.50; H, 7.15.

Acylation of 4-hydroxy-6-methyl-2-pyrone **3a** and 5,6-dihydro-4-hydroxy-6-methyl-2-pyrone: 2-Pyrone (0.01 mol) and acetyl or octanoyl chloride (0.01 mol) were refluxed in trifluoroacetic acid (10 mL) for about 5 h (until HCl evolution ceased). TFA was evaporated *in vacuo* and the residue was dissolved in ether (150 mL) and washed with brine (2x50mL) and dried over anhydrous $Na_2SO_4$. The crude product obtained after evaporation of solvent was purified by column chromatography ($CHCl_3$).

**4-Hydroxy-6-methyl-3-octanoyl-2-pyrone (1b)**: Yield: 2.17 g (86%), m.p. 63-64 °C ($Et_2O$); $\nu_{max}$(KBr) 1000, 1345, 1365, 1455, 1565 br, 1615, 1650, 1730 br, 2855, 2930, 2970 cm$^{-1}$; $\delta_H$ (200 MHz, $CDCl_3$) 16.90 (1 H, br, O$\underline{H}$), 5.93 (1 H, s, =C$\underline{H}$), 3.10 (2 H, t, *J* 7.5 Hz, C$\underline{H}_2$CO), 2.28 (3 H, s, =CC$\underline{H}_3$), 1.67 (2 H, m, C$\underline{H}_2$CH$_2$CO), 1.45-1.20 (8 H, br, (C$\underline{H}_2$)$_4$CH$_3$), 0.90 (3 H, t, *J* 7.5 Hz, C$\underline{H}_3$CH$_2$). $C_{14}H_{20}O_4$ (252.31): calc. C, 66.64; H, 7.99. Found: C, 66.51; H, 7.97.

**3-Acetyl-5,6-dihydro-4-hydroxy-6-methyl-2-pyrone (9a)**: Yield 1.40 g (82%), m.p. 94 °C ($Et_2O$);[11a] $\delta_H$ (200 MHz, $CDCl_3$) 17.90 (1 H, br, O$\underline{H}$), 4.50 (1 H, m, C$\underline{H}$), 2.68 (2 H, m, C$\underline{H}_2$CH), 2.63 (3 H, s, C$\underline{H}_3$C=O), 1.47 (3 H, d, *J* 6.8 Hz, C$\underline{H}_3$CH).

**5,6-Dihydro-4-hydroxy-6-methyl-3-octanoyl-2-pyrone (9b)**: Yield: 1.98 g (78%), m.p. 31 °C ($Et_2O$); $\nu_{max}$(KBr) 960, 1060, 1460 br, 1555 br, 1700, 2850, 2930, 2970 cm$^{-1}$; $\delta_H$ (200 MHz, $CDCl_3$) 17.95 (1 H, br, O$\underline{H}$), 4.51 (1 H, m, C$\underline{H}$CH$_3$), 3.03 (2 H, t, *J* 7.5 Hz, CH$_2$CO), 2.78 (2 H, m, CH$_2$C$\underline{H}$), 1.68 (2 H, m,

$CH_2CH_2CO$), 1.52 (3 H, d, *J* 6 Hz, $CH_3CH$), 1.40-1.20 (8 H, br, $(CH_2)_4CH_3$), 0.88 (3 H, t, *J* 7.5 Hz, $CH_3CH_2$). $C_{14}H_{22}O_4$ (254.32): calc. C, 66.12; H, 8.72. Found: C, 66.24; H, 8.73.

**3-Acetyl-6-*sec*-butyl-4-hydroxy-2-pyrone (16)**: A solution of pyrone **15** (0.002 mol, 0.408 g), triethylamine (0.278 mL, 0.002 mol) acetic acid (0.115 mL, 0.002 mol), 4-dimethylaminopiridine (0.061 g, 0.0005 mol) and N,N-dicyclohexylcarbodiimide (0.433 g, 0.0021 mol) in dichloromethane (80 mL) was stirred at room temperature for 6 h. The N,N-dicyclohexylurea was filtered and washed with dichloromethane. The filtrate was acidified with 5 mL of 5% HCl and washed with brine (100 mL), dried over anhydrous $Na_2SO_4$ and the solvent evaporated *in vacuo* to give the product **16** as oil. Yield 0.382 g (91%). $\nu_{max}$(liquid film) 1400, 1455, 1580, 1655, 1765, 2890, 2945, 2980 $cm^{-1}$; $\delta_H$ (200 MHz, $CDCl_3$) 16.70 (1 H, s, OH), 5.93 (1 H, s, =CH), 2.70 (3 H, s, $CH_3CO$), 2,53 (1 H, m, CHC=), 1.90-1.50 (2 H, m, $CH_2CH_3$), 1.25 (3 H, d, *J* 7 Hz, $CH_3CH$), 0.92 (3 H, t, *J* 7.4 Hz, $CH_3CH_2$). $C_{11}H_{14}O_4$ (210.23): calc. C, 62.85; H, 6.71. Found: C, 62.70; H, 6.65.

Ionic hydrogenation of β-tricarbonyl compounds **3a,b** and **16**: 3-Acyl-2-pyrone (0.002 mol), triethylsilane (1.29 mL, 0.008 mol) and $LiClO_4$ (0.002 g, 0.00002 mol) were dissolved in TFA (15 mL) and stirred at room temperature for about 4 h (reaction was monitored by TLC). The solvent was evaporated *in vacuo* and the residue was purified by column chromatography ($CHCl_3$).

**3-Ethyl-4-hydroxy-6-methyl-2-pyrone (2a)**: Yield: 0.265 g (85%). M.p. 187 °C ($Et_2O$). $\delta_H$ (200 MHz, $CDCl_3$) 6.00 (1 H, s, =CH), 2.48 (2 H, q, *J* 7.4 Hz, $=CCH_2$), 2.26 (3 H, s, $=CCH_3$), 1.11 (3 H, t, *J* 7.5 Hz, $CH_3CH_2C=$), OH signal is not observed. $\nu_{max}$ (KBr) 1000, 1145, 1290, 1390, 1415, 1455, 1590, 1645, 1685, 2660 br, 2940, 2980 $cm^{-1}$.

**4-Hydroxy-6-methyl-3-octyl-2-pyrone (2b)**: Yield: 0.42 g (88%), m.p. 100-102 °C. $\delta_H$ (200 MHz, $CDCl_3$) 6.00 (1 H, s, =CH), 2.39 (2 H, t, *J* 7.5 Hz, $=CCH_2$), 2.26 (3 H, s, $=CCH_3$), 1.66 (2 H, m, $=CCH_2CH_2$), 1.45-1.20 (8 H, br, $(CH_2)_4CH_3$), 0.90 (3 H, t, *J* 7.5 Hz, $CH_3CH_2$), OH signal is not observed; $\nu_{max}$(KBr) 1000, 1130, 1185, 1250, 1300, 1370, 1405, 1450, 1575, 1595 sh, 1640 br, 1670, 2660 br, 2860, 2930, 2960 $cm^{-1}$.

**6-(2-Butyl)-4-hydroxy-3-ethyl-2-pyrone (racemic germicidin) (10)**: Yield: 0.337 g (86%), m.p. 95-97 °C ($Et_2O$-hexane); $\delta_H$ (200 MHz, $CDCl_3$) 6.22 (1 H, s, =CH), 2.48 [(2 H, q, *J* 7.4 Hz, $=CCH_2$)+(1 H, m, $CHCH_3$)], 1.75-1.24 (2 H, m, $CHCH_2$), 1.20 (3 H, d, *J* 6.7 Hz, $CH_3CH$), 1.11 (3 H, t, *J* 7.5 Hz, $CH_3CH_2C=$), 0.89 (3 H, t, *J* 7.5 Hz, $CH_3CH_2CH$), OH signal is not observed; $\delta_C$ (50.33 MHz, $CDCl_3$) and DEPT 169.6 (C ), 168.8 (C ), 168.0 (C ), 105.0 (C ), 100.9 (CH, *J* 169 Hz), 39.8 (CH, *J* 125 Hz), 27.5 ($CH_2$, *J* 125 Hz), 17.7 ($CH_3$, *J* 125 Hz), 16.4 ($CH_2$, *J* 125 Hz), 12.4 ($CH_3$, *J* 125 Hz), 11.6 ($CH_3$, *J* 125 Hz); *m/z* [$M^+$] = 196; $\nu_{max}$(KBr) 1160, 1285, 1430, 1595, 1680, 2885, 2945, 2980 $cm^{-1}$. $C_{11}H_{16}O_3$ (196.25): calc. C, 67.32; H, 8.22. Found: C, 67.20; H, 8.25.

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