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Synthesis of racemic germicidin

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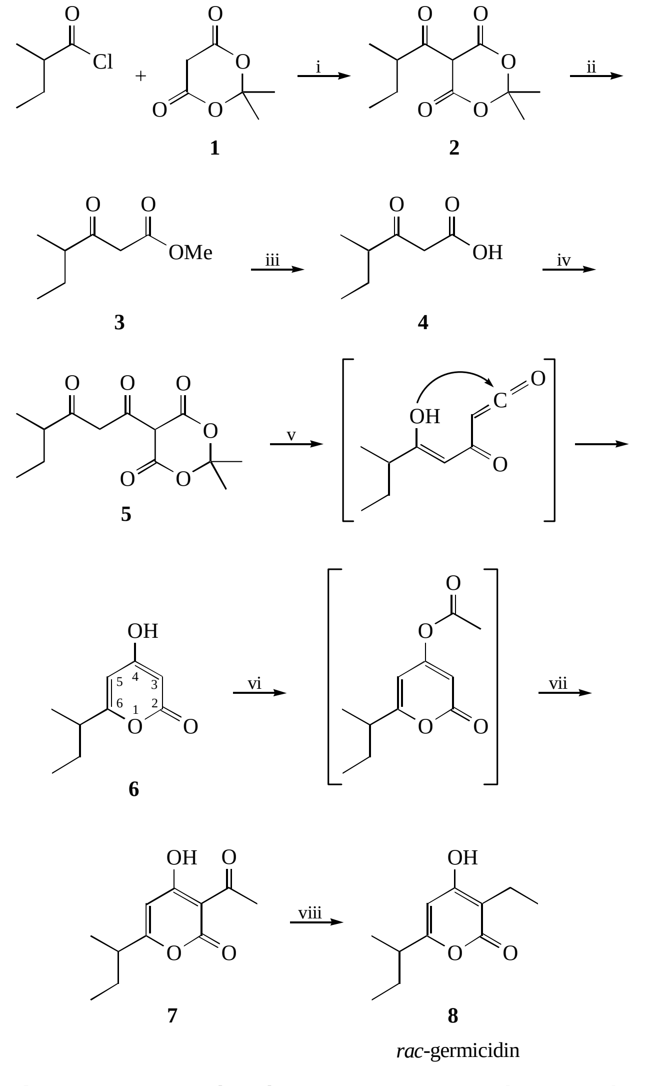
The seven-step synthesis of racemic germicidin in 40% overall yield has been accomplished for the first time.

Alkyl derivatives of 4-hydroxy-2-pyrone attract considerable attention because of a broad spectrum of their chemical and biological properties. In recent years, a great number of 3-, 5- and 6-alkyl derivatives of 4-hydroxy-2-pyrone have been isolated from different fungi, plants and molluscs. In the synthesis of complex natural 2-pyrones such as verrucosidin,[1] cytreoviridin,[2] asteltoxin,[3] cytreomontanin[4] *etc.*, a wide variety of chemical methods and biosynthetic approaches to the molecular transformations were used.

In this paper, we describe the first total synthesis of racemic germicidin **8** (a 3,6-dialkyl derivative of 4-hydroxy-2-pyrone). Germicidin was isolated from *Streptomices viridochromogenes* NRRL B-1551, and it exhibited an inhibitory effect on the germination of arthrospores of its own producer (at a concentration of 40 pg ml^{-1}).[5]



Scheme 1 *Reagents and conditions*: i, 2 equiv. Py, $CHCl_3$, –20 °C, then 5% HCl; ii, MeOH, reflux; iii, MeONa/MeOH, H_2O, 5–10 °C, then 1 M HCl; iv, Meldrum's acid, DCC, 0.3 equiv. DMAP, Et_3N, CH_2Cl_2, then 5% HCl; v, toluene, 6 h, reflux; vi, AcOH, DCC, Et_3N, CH_2Cl_2; vii, 0.3 equiv. DMAP, Et_3N, CH_2Cl_2, then 10% HCl; vii, 3 equiv. Et_3SiH, TFA, cat. amount $LiClO_4$.

Acylation of Meldrum's acid by 2-methylbutyric acid chloride[6] in the presence of pyridine followed by methanolysis of acyl derivative **2** gave rise to methyl ester **3** in 82% overall yield. Dropwise addition of water to a solution of **3** and sodium methylate (1:1 equiv.) in methanol at 5–10 °C and acidification with 1 M HCl led to 4-methyl-3-oxohexanoic acid **4**, which was further used for the acylation of Meldrum's acid in order to obtain tetracarbonyl compound **5**, the key precursor for the synthesis of 6-*sec*-butyl-4-hydroxy-2-pyrone **6**. Due to the instability of 3-oxocarboxylic acid chlorides[7] we used a modified procedure which consists in acylation of Meldrum's acid by acid **4** under the action of *N*,*N*′-dicyclohexylcarbodiimide (DCC) and a catalytic amount of 4-*N*,*N*-dimethylaminopyridine (DMAP). The ring system of 4-hydroxy-2-pyrone **6** was formed by thermal cyclization of tetracarbonyl compound **5** at reflux with toluene. In this case, the *sec*-butyl substituent at the 6-position was introduced at the stage of pyrone cycle formation. After chromatographic purification, the target 6-*sec*-butylpyrone **6**[†] was obtained in 82% overall yield on a basis of starting methyl ester **3**.

The last step in the synthesis of germicidin includes the introduction of an ethyl substituent at the 3-position in the cycle of compound **6**.

Methods for , ′-alkylation of cyclic -dicarbonyl compounds in general and 4-hydroxy-2-pyrones in particular have been developed insufficiently. Direct alkylation of the 4-hydroxy-6-methyl-2-pyrone anion by methyl iodide[8] resulted in the formation of the target product only in 16% yield. The reduction of readily available 3-acetyl-4-hydroxy-6-methyl-2-pyrone (dehydroacetic acid) with a borane–methyl sulfide complex[9] resulted in the formation of the 3-ethyl derivative in low yield (23%). Catalytic hydrogenation of 3-acetylpyrones over palladium is also unusable for our purpose, because in this case the ^{5}-bond is primarily reduced.[10] This fact results in the formation of 5,6-dihydro-2-pyrone ring.

The introduction of the 3-ethyl substituent into 6-*sec*-butylpyrone **6** was carried out by the previously suggested procedure.[11,12] The procedure includes the preparation of the corresponding , ′-tricarbonyl compounds followed by the reduction of the oxo-function of acyl substituents by ionic hydrogenation.

3-Acetylpyrone **7**[‡] was obtained by one-pot acetylation of pyrone **6** by acetic acid in the presence of DCC. The intermediate enolacylate was isomerised *in situ* under the action of DMAP, and 3-acetyl-6-(2-butyl)-4-hydroxy-2-pyrone **7** was obtained in 91% yield as an oil. Its reduction by triethylsilane in trifluoroacetic acid in the presence of a catalytic amount of $LiClO_4$ gives rise to racemic germicidin **8** in 84% yield as an oily product, which crystallises on standing. Recrystallisation from diethyl ether–hexane resulted in the crystalline product with mp 95–97 °C. Spectral characteristics of the compound obtained[§]

[†] *Spectroscopic data for* **6**: ^{1}H NMR, δ: 6.00 (d, 1H, *J* 2 Hz), 5.60 (d, 1H, *J* 2 Hz), 2.50 (m, 1H), 1.45–1.80 (m, 2H), 1.20 (d, 3H, *J* 6.5 Hz), 0.90 (t, 3H, *J* 7.3 Hz). IR (ν/cm^{-1}): 1245, 1445, 1575, 1630, 1670, 1700, 2880, 2940, 2970.

[‡] *Spectroscopic data for* **7**: ^{1}H NMR, δ: 16.70 (s, 1H, OH), 5.93 (s, 1H), 2.70 (s, 3H), 2.53 (m, 1H), 1.50–1.90 (m, 2H), 1.25 (d, 3H, *J* 7 Hz), 0.92 (t, 3H, *J* 7.4 Hz). IR (ν/cm^{-1}): 1400, 1455, 1580, 1655, 1765, 2890, 2945, 2980.

are in good agreement with the literature data for the natural product.[5]

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[§] *Spectroscopic data for racemic germicidin* **8**: ^{1}H NMR, δ: 6.22 (s, 1H), 2.48 (s + q, 2H + 1H, *J* 7.4 Hz), 1.24–1. 75 (m, 2H), 1.20 (d, 3H, *J* 6.7 Hz), 1.11 (t, 3H, *J* 7.5 Hz), 0.89 (t, 3H, *J* 7.5 Hz). ^{13}C NMR and DEPT, δ: 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 (Me, *J* 125 Hz), 16.4 (CH_2, *J* 125 Hz), 12.4 (Me, *J* 125 Hz), 11.6 (Me, *J* 125 Hz). MS, *m*/*z*: 196 [M$^+$]. IR (ν/cm^{-1}): 1160, 1285, 1430, 1595, 1680, 2885, 2945, 2980.