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Mendeleev Commun., 1995, 5(6), 224–226
Mendeleev Communications

A Novel Approach to the Synthesis of Malabaricones and Related Polyketides

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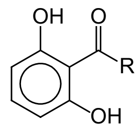
Starting from 4-hydroxycyclohexan-1,3-dione, a three-step synthesis of natural long-chain 2-acyl-1,3-dihydroxybenzenes is described.

The structural fragment of 2-acylresorcinols of general formula **1** (R = hydrocarbon residue of saturated, mono- and polyunsaturated and aromatic-containing fatty acids) appears as a part of various natural bioactive compounds mainly isolated from plants.[1] The most interesting properties of these compounds are inhibition of PGH-synthase[2a] and protein kinase C,[2b] antiulcerogenic,[2c] antitumour,[2d,e] antiviral[2f,g] and fungicidal[2h] activities.

It is known that Friedel–Crafts acylation of 1,3-dihydroxybenzenes affords isomeric 4-acyl derivatives,[3] so 2-acylresorcinols **1** should be prepared by other ways.[4–6] However, such methods do not include preparation of the long-chain derivatives[4,5] or require rigid conditions[6a,b] and multistage operations.[6c,d]

We present here a novel approach to the synthesis of natural 2-acylresorcinols and their analogues using as



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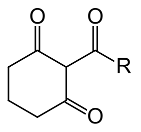

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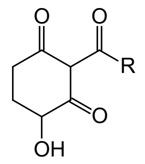

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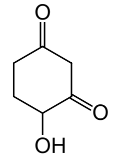

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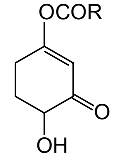

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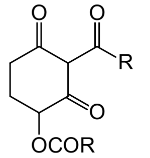

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a $R = C_{11}H_{13}$
b $R = C_{13}H_{27}$
c $R = (CH_2)_8Ph$

examples Malabaricone A **1c** isolated earlier from Myristicaceous plants,[6c] as well as 2-lauroyl- and 2-myristoylresorcinols **1a** and **1b**, respectively (occurring in plants and animals[1c,d,7a]), starting from the corresponding 2-acyl-4-hydroxycyclohexan-1,3-diones **3a**–**c**.[†] These hydroxytriketones **3a**–**c** have been prepared on a preparative scale from a readily available key synthon, 4-hydroxycyclohexan-1,3-dione **4**.[8a,b] Selective *O*-acylation of the dione **4** gave mono-enolacylate **5**, which underwent further *O-C*-isomerisation into the target hydroxytriketone **3** following acetone cyanohydrine catalysis.[8a,c] The synthesis of 2-dodecanoyl-4-hydroxycyclohexan-1,3-dione **3a** has been described recently,[8a] and here we present the syntheses of 2-tetradecanoyl- and 2-(ω-phenylnonanoyl)-4-hydroxycyclohexan-1,3-diones **3b** and **3c**, respestively. ω-Phenylnonanoic acid required for the synthesis of **3c** has been prepared from hydrocinnamic acid by carbon chain elongation according to a modified procedure.[9]

One could expect an easy aromatization of 2-acyl-4-hydroxycyclohexan-1,3-diones **3** into 2-acylresorcinols **1** as a result of simple dehydration. In fact, authors[7b] have reported the aromatization of homologous hydroxytriketone **3** [R = $(CH_2)_{10}Ph$] isolated from the fruits of Virola sebifera and V.elongata (Myristicaceae) when attempting its acetylation. However, our experience with various hydroxytriketones **3** and the data from their mass-spectra including literature data[10] for the same naturally-derived compounds (in general: weak intensity of peaks corresponding to $M^+ - 18$) strongly suggests the relative stability of such molecules towards dehydration. Also, it is known that α-hydroxyketones are not readily dehydrated.

We have tried acid-catalysed aromatization (*p*-TsOH, TFA and also heating in neat TFA) of compound **3a** without success. Moreover, acetylation of hydroxytriketone **3a** ($Ac_2O + Py$) and subsequent treatment of the reaction mixture with methanolic HCl resulted in a 4-acetoxy derivative of compound **3a** (instead of 2-acyl resorcinol **1**[7b]), which was also resistant to aromatization.

Further, it was found that 4-hydroxytriketones **3** undergo aromatization into the corresponding 2-acylresorcinols **1** upon heating in a mixture (Ac_2O–AcOH = 1:1) in the presence of an equimolar amount of 98% H_2SO_4 (the reaction did not proceed upon heating in a mixture of AcOH–H_2SO_4 or Ac_2O–AcOH). The target compounds **1** were obtained by acid hydrolysis of the resulting acetates in total yield 60–70% from triketones **3**. Their spectral data were identical with those from the literature.[6b,c] It is worth mentioning that such aromatization conditions were used earlier[11] for the *oxidation* of some substituted cyclohexan-1,3-diones to the corresponding 1,3-dihydroxybenzene diacetates. In our case both the starting compounds **3** and the target acylresorcinols **1** have *the same oxidation state*, so the aromatization of **3** would have to occur through a dehydration step under the above-mentioned conditions.

All compounds synthesized gave satisfactory analytical and ^1H NMR, IR and mass spectral data.

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[†] 2-*Tetradecanoyl*-4-*hydroxycyclohexan*-1,3-*dione* **3b**. To a solution of 15.5 mmol (30% excess) of diketone **4** in a mixture of 50 ml THF and 1 ml Py was added a solution of 11.5 mmol of tetradecanoyl chloride in 10 ml of THF, dropwise during 0.5 h. The reaction mixture was stirred for 0.5 h, then the solution was filtered and solvent evaporated *in vacuo*, and to the residue was added 50 ml benzene. The resulting solution was filtered again and the solvent was evaporated *in vacuo*. To the residue was added a mixture of 80 ml acetonitrile, 4 ml Et_3N and 0.8 ml acetone cyanohydrine. The resulting mixture was allowed to stand for 2 h at room temperature, then evaporated to dryness *in vacuo*. To the residue were added 20 ml ether and 1 ml 1 M H_2SO_4. The organic layer was separated and the aqueous phase extracted with ether (2 × 20 ml). The combined ethereal extracts were dried over $MgSO_4$ and the solvent was evaporated. The residue was crystallized from MeOH giving 0.67 g of 4-tetradecanoyloxy triketone **6b**, m.p. 61–62 °C. Subsequent crystallization of the mother solution from aqueous MeOH gave 1.0 g (29%) of 4-hydroxytriketone **3b**, m.p. 56–57 °C (MeOH–hexane). An additional 0.35 g (10%) of **3b** were obtained after basic hydrolysis (alcoholic KOH) of the ester **6b** with subsequent extraction and crystallization as described above.

2-(ω-*Phenylnonanoyl*)-4-*hydroxycyclohexan*-1,3-*dione* **3c** was obtained using the same procedure in 34% yield, m.p. 44 °C (ether).

2-*Tetradecanoylresorcinol* **1b**. 2-Tetradecanoyl-4-hydroxycyclohexan-1,3-dione **3b** (300 mg, 0.89 mmol) was dissolved in 2 ml Ac_2O and 2 ml AcOH. After the addition of 2 drops of 98% H_2SO_4, the mixture was refluxed for 1 h under Ar, then poured into 20 ml water at 0 °C. After being stirred for 0.5 h the mixture was extracted with ether (3 × 15 ml). The combined ethereal extracts were washed with brine, dried over $MgSO_4$ and the solvent was evaporated *in vacuo*. The residue (0.3 g) was further dissolved in 4 ml MeOH, and to the solution 2 drops of AcCl were added in an inert atmosphere whilst shaking the flask. The resulting solution was allowed to stand for 0.5 h and then refluxed for 20 min under Ar. The residue (0.27 g) after solvent evaporation was crystallized from aqueous MeOH, affording 200 mg (70%) of 2-tetradecanoylresorcinol **1b**, m.p. 93–94 °C.

2-(ω-*Phenylnonanoyl*)*resorcinol* [*Malabaricone A*] **1c** was obtained using the same procedure from 0.66 g (1.9 mmol) of triketone **3c**, yield 0.40 g (60%), m.p. 79–80 °C (hexane–ether).

2-*Dodecanoylresorcinol* **1a** was obtained from 2-dodecanoyl-4-hydroxycyclohexan-1,3-dione **3a**,[8a] yield 64%, m.p. 85 °C.

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Received: Moscow, 21st June 1995
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