Synthesis of 1-(2,6-Dihydroxyphenyl)-1-alkanones and Benzophenone by Aromatization of 2-Acyl-3-hydroxy-2-cyclohexene-1-ones with Mercuric Acetate

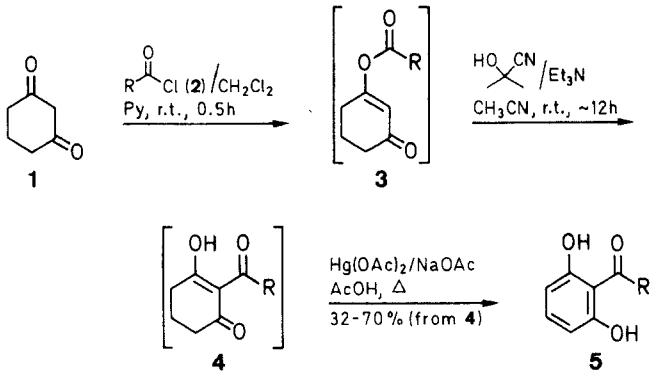
James E. Oliver,* Kenneth R. Wilzer, Rolland M. Waters
USDA-ARS, Agricultural Research Center, Beltsville, MD 20705, USA

1-(2,6-Dihydroxyphenyl)-1-alkanones, natural products identified from insects and from medicinal plants, are readily prepared from 1,3-cyclohexanedione and appropriate carboxylic acids. The final step involves aromatization using mercuric acetate.

We recently identified 1-(2,6-dihydroxyphenyl)-1-dodecanone, **(5a)** as a component of the setal exudate of immature andromeda lace bugs (*Stephanitis takeyai* Drake and Maa),[1] and also found that **5a** inhibited prostaglandin synthase in two *in vitro* systems.[2] Other investigators have reported 1-(2,6-dihydroxyphenyl)-ethanone homologs from medicinal plants including **5b** from *Myristica dactyloides*,[3] **5c** from the same plant[3] and also from *M. malabarica*,[4] and **5d** from *Horsfieldia glabra*[5] and from *Virola sebifera*.[6]

Unlike for their more common 2,4-dihydroxy counterparts,[7] general synthetic methods for 1-(2,6-dihydroxyphenyl)-1-alkanones are lacking, the *Organic Syntheses* procedure[8] for the latter evidently failing for homologs with long chain R groups.[9] A synthesis of **5c** from 2,6-dimethoxyphenylglyoxal has been reported,[10] and we earlier synthesized **5a** from methyl 2,6-dimethoxybenzoate.[11] In the latter case, demethylation was observed to occur in a stepwise fashion, with removal of the second methyl demanding particularly forcing conditions.

2-Acyl-3-hydroxy-2-cyclohexen-1-ones **4** are easily prepared following literature procedures. Reaction of 1,3-cyclohexanedione with an acid chloride **2** gives the enol ester **3**, which is rearranged to **4**.[1,12,13,22] The rearrangement of **4** to **5** can be achieved by heating with a (dialkylamino)pyridine[12] or by cyanide ion catalysis at room temperature.[13] Both steps proceed in high yield, thus compounds **4** are essentially as available as the corresponding precursor carboxylic acids (RCO_2H) of acid chlorides **2**. Being only one oxidation state removed, **4** would seem to comprise an attractive precursor of **5**. A conversion of **4** to **5** was reported that involved chlorination with *N*-chlorosuccinimide followed by rearrangement in hot dimethylformamide containing hydrochloric acid;[14] however, this sequence has been subject to side reactions.[15] A recent patent described aromatization of 2-



2–5	a	b	c	d	e
R	n-$C_{11}H_{23}$	n-$C_{13}H_{27}$	$(CH_2)_7CH_2Ph$	$(CH_2)_9CH_2Ph$	Ph

Table. Compounds **5a–e** Prepared

Product	Yield[a] (%)	mp (°C)	Molecular Formula or Lit. mp (°C)	IR (CCl_4) ν(cm^{-1})	^{1}H-NMR ($CDCl_3$/TMS) δ, J(Hz)	MS (70 eV) m/z (%)
5a	54	86–88	$C_{18}H_{28}O_3$ (292.4)	3596, 1634, 1453, 1234, 1037	0.88 (t, 3H, J = 6.3), 1.0–1.5 (m, ≅16H), 1.67 (m, 2H), 3.12 (t, 2H, J = 7.8), 6.39 (d, 2H, J = 8.1), 7.22 (t, 1H, J = 8.1), 9.51 (br s, 2H)	292 (M^+, 6), 274 (6), 189 (11), 165 (23), 152 (26), 138 (8), 137 (100), 123 (5), 81 (7), 55 (7)
5b	70	93–94	91–91.5[3]	3595, 1634, 1453, 1235, 1037	0.88 (t, 3H, J = 6.9), 1.0–1.5 (m, ≅20H), 1.70 (m, 2H, J ≅ 7), 3.16 (t, 2H, J = 7.2), 6.39 (d, 2H, J = 8.1), 7.22 (t, 1H, J = 8.1), 9.52 (br s, 2H)	320 (M^+, 6), 302 (9), 189 (12), 165 (22), 152 (26), 138 (6), 137 (100), 123 (5), 81 (7), 55 (10)
5c	68	78–79	80–82[3]	3595, 1633, 1453, 1234, 1036	1.33 (br s, ≅8H), 1.5–1.75 (m, 4H), 2.60 (t, 2H, J = 8.1), 3.11 (t, 2H, J = 7.5), 6.38 (d, 2H, J = 8.1), 7.12–7.30 (m, ≅6H), 9.53 (br s, 2H)	326 (M^+, 6), 308 (7), 189 (6), 165 (22), 152 (21), 138 (7), 137 (100), 123 (5), 91 (23), 81 (6), 55 (6)
5d	32	62–64	69–71[5]	3595, 1635, 1453, 1234, 1037	1.29 (br s, ≅20H), 1.5–1.75 (m, 4H), 2.59 (t, 2H, J = 7.8), 3.12 (t, 2H, J = 7.5), 6.38 (d, 2H, J = 8.2), 7.12–7.31 (m, ≅6H), 9.50 (br s, 2H)	354 (M^+, 5), 189 (10), 165 (25), 152 (22), 138 (5), 137 (100), 91 (25), 55 (6)
5e	45	132–135	135[21]	3550, 1632, 1456, 1328, 1187	6.49 (d, 2H, J = 8.1), 7.32 (t, 1H, J = 8.1), 7.51 (t, 2H, J = 8.1), 7.61 (t, 1H, J = 8.1), 7.72 (d, 2H, J = 8.1), 8.18 (br s, 2H)	214 (M^+, 48), 213 (100), 139 (6), 137 (30), 136 (10), 108 (10), 107 (5), 105 (11), 81 (6), 77 (34), 51 (19)

[a] Yield based on **4**.

acetyl-3-hydroxy-2-cyclohexen-1-one with palladium-on-carbon in xylene at 175°C,[16] but in general we found compounds **4a** and **4b** to be surprisingly resistant to dehydrogenation, and the following reagents/conditions were all ineffective in attempted conversion of **4** to **5**: cupric bromide/lithium bromide in refluxing acetonitrile,[17,18] 2,3-dichloro-5,6-dicyano-1,4-benzoquinone in refluxing dioxane, dimethylformamide, or collidine, pyridinum hydrobromide dibromide in acetic acid or dimethylformamide, palladium chloride in refluxing *tert*-butyl alcohol,[19] palladium chloride in acetic anhydride, palladium on carbon in refluxing decalin containing 1-decene,[20] and lead (IV) acetate in refluxing benzene.

Cleaver et al[21] investigated aromatization of 5-alkyl-1,3-cyclohexanediones, and reported some success with mercuric acetate in a refluxing mixture of dioxane and acetic acid. Although these conditions were not satisfactory when applied to **4a**, they were encouraging in that several percent conversion of **4a** to **5a** was achieved, and we subsequently observed that when **4a** was heated in acetic acid containing an excess of mercuric acetate and sodium acetate a clear solution resulted, but soon thereafter a tan solid separated. This material was too insoluble to permit purification or NMR analysis; decomposition with aqueous hydrochloric acid regenerated **4a**. However, continued heating of the original mixture resulted in the development of a brown color, gradual dissolution of the solid, and separation of metallic mercury. Workup at this point provided the desired 1-(2,6-dihydroxyphenyl)-1-dodecanone **(5a)**, identical to the natural product isolated from *S. takeyai*.[1] Application of the same procedure to **4b–4d** provided the plant-derived compounds **5b–5d**, respectively, and as a further test of generality, the benzoyl derivative **4e** was converted to the benzophenone **(5e)**.[23] Although not quantitative, the yields reported in the Table are of purified materials, and the availability of precursors makes this a practical and covenient route to the title compounds.

Melting points were recorded on a Kofler hot stage apparatus and are corrected. Mass spectra were obtained from a Finnigan model 4510 GC/MS equipped with a DB-1 (J&W Scientific) fused silica column (i.d. 30 m × 0.32 mm). Electron ionization spectra were collected at 70 eV and a source block temperature of 150°. The ^{1}H-NMR spectra were obtained using a General Electric QE-300 NMR spectrometer. Elemental analyses were performed by Galbraith Laboratories, Knoxville, TN. Mention of a proprietary product does not imply endorsement by the U.S. Dept. of Agriculture.

Enol esters **3a–e** and hydroxyenones **4a–e** are known compounds and were prepared according to prcedures reported in references 12 and 13, respectively. The crude products were identified spectroscopically and found to be pure enough for the next step and used without further purification. While the procedures are partly from a patent, general methods for the preparation of **3** and **4** are given below.

2-Acyl-3-hydroxy-2-cyclohexen-1-ones 4a–e; General Procedure:

3-Acyloxy-2-cyclohexen-1-ones **3a–e**: A solution of an acid chloride **2** (5 mmol) in CH_2Cl_2 (5 mL) is added dropwise to a stirred solution of cyclohexane-1,3-dione (**1**; 0.56 g, 5 mmol) and pyridine (0.44 g, 5.5 mmol) in CH_2Cl_2 (10 mL). After stirring for 0.5 h at r.t. most of the CH_2Cl_2 is stripped *in vacuo* and the residue is partitioned between Et_2O/hexane (1:1) and cold, dil HCl. The organic phase is washed with H_2O, sat. aq $NaHCO_3$, dried ($MgSO_4$) and concentrated *in vacuo*.

Conversion of **3a–e** *to* **4a–e**: The crude product **3** from the above reaction is dissolved in CH_3CN (15 mL) and treated with Et_3N (1 mL) and acetone cyanohydrin (40 μL).[13] The mixture is allowed to stand overnight at r.t. and the reaction is monitored by GC or TLC to ensure completion (**3e** and **4e** proved difficult to resolve on some GC columns) and the solvent is removed *in vacuo*. The products **4a–e** are obtained by partitioning between Et_2O/hexane (1:1) and water. The organic phase is washed with dil HCl and H_2O, dried ($MgSO_4$) and concentrated *in vacuo*. Purification can be achieved by flash chromatography (hexane and EtOAc), but the crude products are frequently satisfactory for the next step. Yields are typially 85% from the precursor carboxylic acid (RCO_2H).

1-(2,6-Dihydroxyphenyl)-1-dodecanone (5a); Typical Procedure:

A mixture of **4a** (0.59 g, 2 mmol), $Hg(OAc)_2$ (1.92 g, 6 mmol), and anhydrous NaOAc (0.5 g, 6 mmol) in AcOH (5 mL) is heated (bath temperature 120–125°C) under a short path distillation head (only a few drops of AcOH actually distill out). A clear solution gives way to a voluminous precipitate; heating is continued until this material has entirely redissolved, metallic mercury has separated, and a dark brown solution results (usually 2–3 h). After cooling, 1 N HCl (10 mL) is added, and the mixture is stirred 0.5 h (or briefly heated to boiling). EtOAc (10–15 mL) is added and the entire mixture is filtered through a pad of Celite. Hexane/EtOAc (3:1) is used for rinsing the Celite and for subsequent extraction of the aqueous phase. After thorough partitioning, the combined organic phases are rinsed with ca. 20 mL each H_2O, 5% aq. $NaHSO_3$, 5% $NaHCO_3$, and again with H_2O. After drying ($MgSO_4$), the brown or amber solution is filtered through neutral alumina (~15 g), which is subsequently rinsed with several portions of EtOAc. The nearly colorless filtrate is concentrated *in vacuo* to give **5a** (0.55 g), which is purified by crystallization *from* hexane or by flash chromatography on silica gel (10–20% EtOAc in hexane) to give pure **5a**; yield: 0.32 g (54%); mp 86–88°C.

$C_{18}H_{28}O_3$	calc.	C 73.93	H 9.65
(292.4)	found	73.91	9.76

We are grateful to W.R. Lusby and D.J. Harrison for mass spectra.

Received: 9 April 1990; revised: 13 July 1990

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