Synthesis of 4-aryl-1,7-dihydroxyalkane-2,6-diones under aldol reaction conditions

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Reactions of 3-hydroxyalkan-2-ones with (hetero)aromatic aldehydes under basic conditions lead to 4-aryl-1,7-dihydroxyalkane-2,6-diones. These products were also synthesized by dismutation of 4-aryl-1-hydroxyalk-3-ene-2-ones. The reactions proceed as tandem retro aldol reactions and the Michael addition.

Key words: α-hydroxy enones, α,β-enones, diketodiols, 1,5-diketones, aldol condensation, the Michael addition.

Crotonic condensation and the Michael addition involving aldehydes, ketones, 1,3-diketones, and CH acids represent the most powerful carbon—carbon bond forming reactions.[1] The intermediates synthesized *via* these reactions found application in the synthesis of phenols, five- and six-membered carbo- and heterocyclic compounds, polyketides, pharmaceutical agents, and other biologically active substances.[2] In the last decades, these transformations attract attention as efficient steps in the domino reactions[3] and enantioselective syntheses.[4]

Numerous examples of the synthesis of carbonyl compounds[4,5] (including 1,5-diketo derivatives[4e,5i]) *via* addition of either metal enolates (Li, Mg, Zn, Cu, Ba, *etc*.) or their *N*- and *S*-analogs, or their complexes to the Michael acceptors have been described. The reactions involving the metal derivatives are the most preferable; however, they have to be performed under an inert atmosphere in anhydrous solvents in the presence of expensive catalysts. Other synthetic conditions, namely, a direct addition of the generated *in situ* methyl ketones (in an enolate form) using pinacoline[6a,b] and hydroxyacetophenones in ionic liquid[6c] are also reported. Aqueous base catalysis is of interest from ecological and economical viewpoints and versatility,[7] but the reactions carried out under such conditions are reversible, proceed with low selectivity, and accompanied by the side reactions.

Earlier,[8] studying the aldol condensation of 3-hydroxyalkan-2-ones **1** with aldehydes we have found (Scheme 1) that this process is accompanied by side formation of symmetrical adduct **3** (7—9%) resulting from the condensation of two molecules of α-hydroxy ketone and one molecule of aldehyde. To the best of our knowledge, formation of such side products upon aldol condensations of hydroxy ketones[1] has not been described.

In continuation of our previous study,[8] in the present work we describe a new synthetic approach towards compounds **3** starting from 3-hydroxyalkan-2-ones **1a**,**b** and their arylidene derivatives **2a**—**f** on treatment with bases in aqueous alcoholic media (see Scheme 1).

To reveal the parameters responsible for this reaction direction, we evaluated the effects of the solvent, reagent ratio, nature of the base (NaOH, K_2CO_3, KOH, BuOK, *etc*.), and temperature on the example of the synthesis of compound **3b**.

All attempts to enable condensation under catalyst-free conditions or in the presence of weak bases failed and only the starting compounds were recovered. More strong bases, *e.g.*, KOH, NaOH, and anhydrous system NaOH—K_2CO_3—CH_2Cl_2 have found to be the more efficient catalysts. Note that in this case, alcohols (EtOH, Pr^iOH) are more preferable as the solvents than aprotic media (dioxane, DMF). The moderate yields of product **3b** were achieved in 1,2-dimethoxyethane. The prolongation of the reaction time to 40—50 h at 20 °C increases the yield of compound **3b** up to ~30%. The prolonged (15 h) reflux in alcohols results in complex mixtures. The best results were achieved under mild temperature conditions (~30—40 °C). Thus, the typical procedure involved the use of an equimolar amounts of compounds **1** and **2** in EtOH—Pr^iOH (1 : 2 v/v), and 50% aqueous NaOH (2 equiv.). The maintaining the reaction mixture at 33—38 °C for 7—10 days gives symmetric diketo diols **3a**—**f** in the preparative yields of 43—71% (see Experimental, method ***A***, and Table 1). Synthesis of dihydroxy diones **3b**,**g**,**h** could also be accomplished one-pot using a 1 : 2.5 mixture of aldehyde (benzaldehyde, furfural) and hydroxy ketone **1a**,**b** on treatment with 50% aqueous NaOH (method ***B***); however, in the lower yields.

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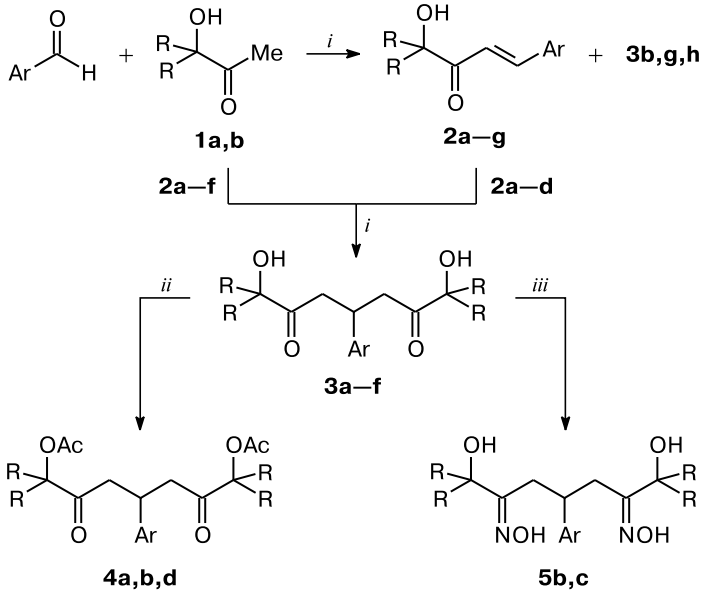
Scheme 1



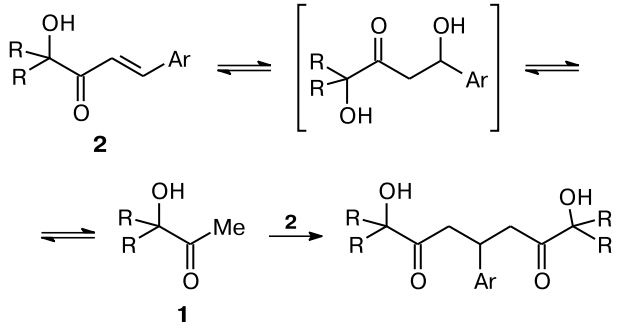
1: R = Me (**a**); R + R = $(CH_2)_5$ (**b**)
2—5: Ar = Ph, R = Me (**a**); Ar = Ph, R + R = $(CH_2)_5$ (**b**); Ar = 4-MeC_6H_4, R + R = $(CH_2)_5$ (**c**); Ar = 4-$MeOC_6H_4$, R + R = $(CH_2)_5$ (**d**); Ar = 3,4,5-$(MeO)_3C_6H_2$, R + R = $(CH_2)_5$ (**e**); Ar = 4-$MeOC_6H_5$, R = Me (**f**); Ar = 4-$Me_2NC_6H_5$, R = Me (**g**); Ar = 2-furyl, R = Me (**h**)

Reagents and conditions: *i*. 50% aqueous NaOH, EtOH—Pr^iOH (1 : 2), 33—38 °C, 7—8 days; *ii*. Ac_2O, CH_2Cl_2, DMAP; *iii*. $NH_2OH \cdot HCl$, 50% aqueous NaOH, 40 °C.

On the examples of enones **2a—d,f**, we found that the treatment of hydroxy-substituted α,β-enones with strong bases leads to symmetric diketo diols **3a—d,f** (method ***C***, Scheme 2). Apparently, the reaction proceeds following a retro aldol mechanism: destruction of enones **2** produces methyl ketone **1**, which reacts further as a CH nucleophile with the unreacted enone.

At the same time, the complete conversion of α,β-enones **2** and surprisingly high yields (>80%) of diketo diols **3** achieved in this transformation can result from one step reaction **2** + **2** → **3** realized due to the coordination by intermolecular hydrogen bonding between the hydroxy group and the carboxyl oxygen. Apparently, the electronic effects do not play an important role in this reaction; however, the detailed mechanism is still unclear. Similar dismutation in a chalcone series has not been described to date.

Scheme 2



Synthesized diketo diols **3a—i** are either oily substances (**3a**,**g—i**) or powders (**3b—d**,**f**). Structures of compounds **3** were confirmed by microanalysis data, NMR spectroscopy, mass spectrometry, and chemical transformations.

Table 1. Synthesis of 4-aryl-1,7-dihydroalkane-2,6-diones **3**

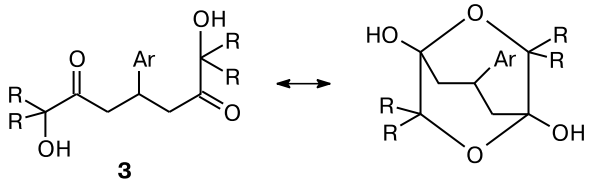
Compound	M.p./°C	Yield (%)[a]	δ_{CH-Ar}
3a	Oil[b]	63	3.82 (q)
3b	141—142	71	3.51 (q)
3c	126	43	3.86 (q)
3d	117—118	59	3.45 (q)
3e	Glassy substance	47	3.49 (virtual t)
3f	92—93	57	3.54 (q)
3i[c]	Oil	17[d]	3.54 (q)

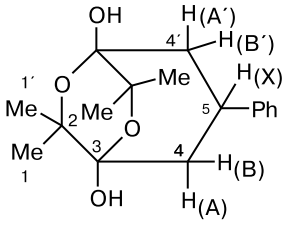
[a] Isolated yield based on α,β-enones (method ***A***).
[b] A 1 : 7 mixture of tautomers.
[c] Reaction of hydroxy ketone **1a** with hydroxy enone **2b** (see Scheme 4).
[d] Dione **3b** formed along with compound **3i**.

The characteristic feature of ^{1}H NMR spectra of compounds **3** is two non-equivalent AABBX spin systems formed by the CH_2 and CH protons of the linear fragment. The signals of both AABBX spin systems appear in the δ 2.8—3.1 range (J_{AB} = 17.9—18.2 Hz) with the intensity ratio of 4 : 1.

With the aim of detailed study of chemical transformations of the functional groups of compounds **3**, we synthesized diketo diacetates **4a**,**b**,**f** and the corresponding dioximes **5b**,**c** (see Scheme 1). Transformations of compounds **3** into derivatives **4**, **5** were monitored by ^{1}H NMR showing the OAc and =NOH protons signals, respectively. Therefore, compounds **3** were found to be prone of skeleton intramolecular CO-heterocyclization involving the OH and C=O groups of either the same or both fragments (Scheme 3). This ring—chain tautomerism already takes place in the reaction mixture leading to the certain difficulties, for instance, in the isolation of the individual tautomers. Thus, distillation of the reaction mixture obtained in the reaction of **1a** with **2a** affords inseparable mixture (~88 : 12) of linear diketo diol **3a** and cyclic compound with the likely structure of bis(hemiketal) **6a**. Similar heterocyclizations are known for several hydroxy carbonyl derivatives.[9]

Scheme 3





6a

The obtained spectral data indicate the presence of bis(hemiketal) structure. The chemical shifts of the methylene group protons ($H_{(AA'BB')}$) exhibiting a noticeable upfield shift for **6a** (δ 1.7—1.9) as compared with **3a** (δ 2.8—3.1) are the most characteristic. The structure of the bicyclic compound **6a** was confirmed by 2D NMR experiments (^{1}H—^{1}H COSY, ^{1}H—^{13}C HSQC, and HMBC). Cyclic carbon atoms were determined from the correlation peaks between the protons and the quaternary carbon atoms resonating at δ 103.1, which is indicative of its bonding to the oxygen atoms. HMBC spectrum exhibits the correlation peaks of the H(1) and H(1′) methyl protons with the C(3) atom and the H(4) and H(4′) methylene protons with the C(3) atom. The other signals were attributed using the data of the 2D NMR experiments (Table 2).

Table 2. ^{1}H and ^{13}C NMR ($CDCl_3$) spectral data of bicyclic compound **6a**

Atom	^{1}H NMR (δ, *J*/Hz)	^{13}C NMR (δ)	HMBC*
1	1.36 (s, 6 H)	15.7	C(2), C(3)
1′	1.53 (s, 6 H)	18.3	C(2), C(3)
2	—	85.1	—
3	—	103.1	—
4, 4′	1.75, 1.90 (both dd, ABX system, J_{AB} = 15.0, J_{AX} = 12.1, J_{BX} = 11.0)	38.7	C(3), C(5)
5	3.23 (m)	36.5	—
Ph	7.14—7.27	125.8—128.8, 144.1	—

* Correlations between protons and carbon atoms in the HMBC NMR experiment.

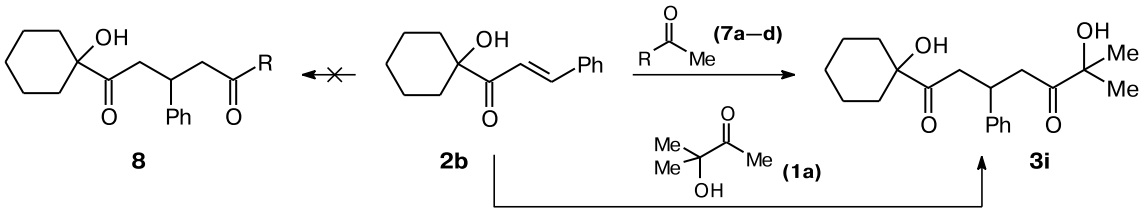
Tautomeric equilibrium **3** ↔ **6** is strongly shifted towards acyclic form **3** and the content of bicyclic compound **6** in the reaction mixtures of **3a**,**c**,**e**,**g**,**h** or in the mother liquors obtained by recrystallization of hydroxy diones **3b**,**d**,**f** is not exceeded 5—14%. Similar stability of the diketo diol form we have found earlier for acetate derivatives **4a**,**b** formed after two-three acylations of the residues obtained after isolation of solid diketo diols **3a**,**b**. No *O*-acylation of hemiketal hydroxy groups of compounds **6a** and **6b** was observed.

To evaluate the scope of synthetic applicability of this method, we tested methyl ketones **7a**—**d** of aliphatic, aromatic, and heterocyclic series in the reaction with **2b** under standard conditions (see Experimental, method ***A***) (Scheme 4).

In all cases, only symmetrical diketo diol **3b** (26—30%) was obtained; Michael addition of methyl ketones **7a**—**d** to give compounds **8** does not occur. Even the use of 5-fold excess of pinacoline **7a** does not affect the reaction direction. Similar transformation of non-symmetrical hydroxy components, *i.e.*, **1a** + **2b** and **1b** + **2a**, lead to hardly separable mixtures of two related diketo diols **3b**, **3i** and **3a**, **3i**, respectively. Despite the low yields of non-symmetrical diketo diol **3i**, electron spray ionization mass spectra of these mixtures reveal the molecular ion peak $[M + Na]^+$ with *m*/*z* 315, 355, and 395 thus confirming the formation of compounds **3a**, **3i**, and **3b**, respectively.

In summary, we elaborated simple and versatile procedures towards novel 4-aryl-1,7-dihydroxyalkane-2,6-diones and studied their structures and chemical properties. These compounds are prone to ring—chain tautomerism.

Scheme 4



7, 8: R = Bu^t (**a**), 4-HOC_6H_4 (b), 2-adamantyl (**c**), 3-pyridyl (**d**)

The obtained data widen the scope of unusual applications of aldol transformations. The described reactions are experimentally simple and open wide prospects to the design of *N*-, *O*-, and *S*-heterocycles and for the screening of new pharmacologically valuable chemotypes.

Experimental

^1H and ^{13}C NMR spectra were run on Bruker DRX-500 (500.13 (^1H) MHz) and Bruker AM-300 (300 (^1H) and 75.5 (^{13}C) MHz) instruments in $CDCl_3$ and DMSO-d_6 relative to Me_4Si as an internal standard. Electron impact mass spectra were recorded on a Kratos MS-30 spectrometer, electrospray ionization mass spectra were obtained with a Bruker micrOTOF 11 instrument. IR spectra were recorded with a Bruker spectrophotometer neat for oily substances and in the KBr pellets for solids. Melting points were measured with a Boetius apparatus (Germany) and are uncorrected. The reaction course was monitored by TLC using precoated Silufol (UV-254) plates, the spots of the compounds were visualized in the iodine chamber. The column chromatography was performed on Merck Silica gel 60, elution with hexane—ethyl acetate (0—12%) or hexane—CH_2Cl_2 (0—15%). Commercially available reagents were purchased from Khimmed (Russia), Aldrich, and Lancaster. Unsaturated ketones **2a—f** were synthesized by the known procedure,[8] compound **2g** was first synthesized in the present work.

Synthesis of diketo diols 3. Method *A* (using methyl ketones as the starting material). To a solution of the corresponding α,β-enone **2** (2 mmol) in EtOH—Pr^iOH (12—15 mL, 1 : 2 v/v) containing 50% aqueous NaOH (0.4 g), methyl ketone **1a**,**b** or **7a—d** (2.2 mmol) was added to produce a nearly homogeneous solution. The mixture was maintained at 30—38 °C for 7—10 days. The conversion of enone **2** was over 94% (TLC data). Compounds **3b—d**,**f** were isolated as follows: the reaction mixture was diluted with 1.5—2-fold excess of water, acidified with 1 *M* HCl, the resulting precipitate was collected by filtration, repeatedly washed with water with additives of EtOH—EtOAc (2—4%), dried on air, and recrystallized from hexane—EtOAc (3—10%). To isolate compounds **3a**,**e**,**i**, the reaction mixture was diluted with brine (15 mL) and 2 *M* HCl (5 mL), extracted with benzene—ethyl acetate (3×20 mL), the organic layer was successively washed with 1 *M* HCl and brine, dried with $MgSO_4$, filtered through a 2 cm silica gel pad, the solvent was removed *in vacuo*, the residue was dried under vacuum (1—2 Torr) at 160 °C, and vacuum distilled using microscale technique. Yields and some physicochemical properties of compounds **3a—f** are given in Table 1.

Method *B* (reaction of methyl ketones 1 with (het)arylaldehydes). To a solution of the corresponding methyl ketone **1a**,**b** (5 mmol) in EtOH—Pr^iOH (15—20 mL, 1 : 2 v/v), ArCHO (Ar = Ph, 4-$Me_2NC_6H_5$, 2-furyl) (2.1 mmol) and 50% aqueous NaOH (0.2 g) were added to produce a nearly homogenous mixture. The reaction mixture was maintained at 30—38 °C for 10 days with occasional stirring using rotary evaporator. The reaction mixture was diluted with brine (15 mL), extracted with benzene—ethyl acetate (3×20 mL), dried with $MgSO_4$. The subsequent work up similar to method *A* produced compounds **3b**,**d**,**g**,**h**.

Method *C* (from hydroxy enones). A solution of hydroxy enone **2a—d**,**f** (2 mmol) in EtOH—Pr^iOH (15 mL) containing 50% aqueous NaOH (0.4 g, 5 mmol) was maintained at 33—38 °C for 10 days. The reaction mixture was diluted with water and worked up as described in method *A* to afford compounds **3a—d**,**f**.

2,8-Dihydroxy-2,8-dimethyl-5-phenylnonane-3,7-dione (3a) was synthesized as a ~88 : 12 mixture with cyclic hemiketal **6a**, pasty liquid, b.p. >250 °C (1 Torr, microscale distillation). Total yield 63% (method *A*), 68% (method *C*). IR, ν/cm^{-1}: 3469 sh., 3392, 1709. ^1H NMR (300 MHz, $CDCl_3$), δ (selected signals): 1.17, 1.29 (both s, 6 H each, Me); 2.92, 2.99 (both ABX system, 2 H each, CH_2, J_{AB} = 18.0 Hz, J_{AX} = 6.0 Hz, J_{BX} = 6.7 Hz); 3.82 (q, 1 H, CH, J = 7.0 Hz); 7.15—7.32 (m, 5 H, Ph). ^{13}C NMR ($CDCl_3$), δ: 25.94, 26.01, 35.92 (CH), 41.53, 76.21, 127.02, 127.22, 128.44, 143.21, 212.87 (C=O). MS (ESI): for both flows resolved by HPLC with τ_{ret} = 27.80 min and τ_{ret} = 26.64 min (without structure attribution): m/z 315 $[M + Na]^+$.

1,5-Dihydroxy-6,6,8,8-tetramethyl-3-phenyl-7,9-dioxabicyclo[3.2.2]nonane (6a) was synthesized by method *A* in the mixture with compound **3a**. Content 12%. ^1H and ^{13}C NMR spectral data are given in Table 2.

Bis(1-hydroxycyclohexyl)-3-phenylpentane-1,5-dione (3b) was synthesized in 71% yield by method *A* from methyl ketone **1a**; m.p. 141—142 °C (EtOAc); m.p. 140—141 °C (Pr^iOH—EtOH (3—4%)). Found (%): C, 74.13; H, 8.52. $C_{23}H_{32}O_4$. Calculated (%): C, 74.16; H, 8.66. IR, ν/cm^{-1}: 3417 br., 1702. ^1H NMR (300 MHz, DMSO-d_6), δ: 1.12, 1.18—1.62 (both m, 4 H and 16 H, CH_2); 2.84, 3.04 (both ABX system, 2 H each, CH_2, J_{AB} = 18.0 Hz, J_{AX} = 6.1 Hz, J_{BX} = 7.6 Hz); 3.51 (q, 1 H, CH, J = 6.7 Hz); 4.98 (s, 2 H, OH); 7.11 (m, 1 H, Ph); 7.20 (s, 4 H, Ph). ^{13}C NMR (DMSO-d_6), δ: 20.50, 20.64, 24.90, 32.63, 32.73, 42.00, 76.87, 125.72, 127.37, 127.85. 145.01, 214.18. MS (EI), m/z (I_{rel} (%)): 274 (47), 256 (18), 228 (10), 197 (20), 177 (50), 176 (100), 142 (50), 132 (28), 131 (47), 124 (44), 109 (20), 104 (68), 99 (84), 98 (20), 82 (28), 81 (35), 69 (18), 57 (27), 55 (48), 43 (37); molecular ion peak with m/z 372 was not detected. MS (ESI), m/z: 395 $[M + Na]^+$, 396 $[M + H + Na]^+$.

Diketone **3b** was also synthesized in 26—30% yields by method ***A*** from methyl ketones **7a—d** (pinacoline was used in a 5-fold excess). The combined filtrates obtained after separation of the precipitate contained compound **3b** and the corresponding hemiketal **6b** (R + R = $(CH_2)_5$, Ar = Ph) (10—15%) (^{1}H NMR data). Unfortunately, the chemical shifts of the $H_{(A)}$, $H_{(A')}$, $H_{(B)}$, and $H_{(B')}$ protons of hemiketal **6b** are close and partially overlap with the signals of cyclohexane ring protons. The signals of expected R-substituted 1,5-diketones **8a—d** were not found. Compound **3b** was obtained in 32% yield by method ***B*** from methyl ketone **1b** and benzaldehyde (2.5 : 1) and in 81% yield from enone **2b** (2 equiv.) by method ***C***.

Method *D*. To a stirred solution of α,β-enone **2b** (2 mmol) and methyl ketone **1b** in CH_2Cl_2 (15 mL), a finely powdered mixture of NaOH (4 mmol) and calcined K_2CO_3 (4 mmol) was added at 20 °C. The reaction mixture was stirred for 7 days maintaining temperature below 40 °C, diluted with water (10 mL), the organic layer was separated, washed with water (2×3 mL) and brine, and then dried with Na_2SO_4. The subsequent work up analogous to one described for method ***A*** afforded compound **3b** in 27% yield. The spectral data for the samples obtained by methods ***A—D*** are identical.

1,5-Bis(1-hydroxycyclohexyl)-3-(4-methylphenyl)pentane-1,5-dione (3c) was synthesized in 43% yield by method ***A*** and in 74% yield by method ***C***, m.p. 126 °C (AcOEt). Found (%): C, 74.41; H, 8.64. $C_{24}H_{34}O_4$. Calculated (%): C, 74.57; H, 8.87. IR, ν/cm^{-1}: 3438 sh., 3412, 1700. ^{1}H NMR (500 MHz, $CDCl_3$), δ: 1.14 (br.q, 2 H, CH_2, J = 3.3 Hz), 1.32—1.74 (m, 16 H, CH_2); 1.69 (td, 2 H, CH_2, J = 12.9 Hz, J = 4.5 Hz); 2.32 (s, 3 H, Me); 2.58, 3.00 (both ABX system, 2 H each, CH_2, J_{AB} = 18.0 Hz, J_{AX} = 8.4 Hz, J_{BX} = 7.0 Hz); 3.86 (q, 1 H, CH, J = 7.4 Hz); 7.11, 7.19 (both d, 2 H each, ArH, J = 8.0 Hz). MS (EI), m/z (I_{rel} (%)): 386 $[M]^+$ (2.0), 288 (21), 270 (24), 227 (26), 197 (64), 190 (100), 162 (38), 145 (68), 118 (82), 100 (38), 99 (54), 80 (74), 55 (24).

1,5-Bis(1-hydroxycyclohexyl)-3-(4-methoxyphenyl)pentane-1,5-dione (3d) was synthesized in 59% yield by method ***A*** and in 82% yield by method ***C***, m.p. 117—118 °C (hexane—EtOAc). Found (%): C, 71.43; H, 8.49. $C_{24}H_{34}O_5$. Calculated (%): C, 71.61; H, 8.51. IR, ν/cm^{-1}: 3419, 1701. ^{1}H NMR (300 MHz, DMSO-d_6), δ: 1.04—1.56 (m, 20 H, CH_2); 2.81, 2.99 (both ABX system, 2 H each, CH_2, J_{AB} = 18.0 Hz, J_{AX} = 6.0 Hz, J_{BX} = 9.0 Hz); 3.45 (q, 1 H, CH, J = 7.4 Hz); 3.68 (s, 3 H, MeO); 4.97 (s, 2 H, OH); 6.77, 7.11 (both d, 2 H each, ArH, J = 6.0 Hz). ^{13}C NMR (DMSO-d_6), δ: 20.54, 20.69, 24.95, 32.66, 32.76, 33.83, 42.23, 54.86, 76.91, 113.30, 128.34, 136.95, 157.31, 214.33. MS (EI), m/z (I_{rel} (%)): 207 (24), 206 (47), 162 (28), 161 (64), 146 (24), 135 (72), 134 (100), 121 (34), 108 (23), 100 (23), 99 (42), 91 (21), 80 (74), 69 (31), 57 (28), 55 (39), 53 (39), molecular ion peak with m/z 402 was not detected. MS (ESI), m/z: 425 $[M + Na]^+$, 426 $[M + H + Na]^+$.

1,5-Bis(1-hydroxycyclohexyl)-3-(2,3,4-trimethoxyphenyl)-pentane-1,5-dione (3e) was synthesized in 47% yield by method ***A***, glassy oil. Found (%): C, 67.17; H, 8.52. $C_{26}H_{38}O_7$. Calculated (%): C, 67.51; H, 8.28. IR, ν/cm^{-1}: 3473 br., 1706. ^{1}H NMR (300 MHz, DMSO-d_6), δ: 1.02—1.74 (m, 20 H, CH_2); 2.83, 3.04 (both d, 2 H each, CH_2, J = 17.9 Hz, J = 6.0 Hz); 3.49 (t, 1 H, CH, J = 6.0 Hz); 3.59, 3.73 (both s, 3 H and 6 H, MeO); 4.99 (s, 2 H, OH); 6.48, 6.50 (both s, 1 H each, ArH). ^{13}C NMR (DMSO-d_6), δ: 20.63, 20.74, 24.98, 32.78, 32.87, 34.96 (CH), 41.95 (2 CH_2), 55.80 (2 MeO), 59.84 (1 MeO), 79.96 (2 CO), 104.76 (2 CH, Ar), 140.86 (2 C, Ar), 152.43 (2 C, Ar), 214.24 (2 C=O). MS (EI), m/z (I_{rel} (%)): 464 $[M + 2 H]^+$ (2), 463 $[M + H]^+$ (18), 462 $[M]^+$ (38), 320 (20), 266 (100), 221 (32), 210 (41), 196 (27), 195 (34), 194 (76), 179 (95), 99 (94), 80 (83), 55 (62), 43 (39), 42 (24).

2,8-Dihydroxy-2,8-dimethyl-5-(4-methoxyphenyl)nonane-3,7-dione (3f) was synthesized in 57% yield by method ***A*** and in 81% yield by method ***C***, m.p. 92—93 °C (hexane—EtOAc). Found (%): C, 67.47; H, 8.04. $C_{18}H_{26}O_5$. Calculated (%): C, 67.06; H, 8.13. IR, ν/cm^{-1}: 3474 br., 1709. ^{1}H NMR (500 MHz, DMSO-d_6), δ: 0.99, 1.11 (both s, 6 H each, Me); 2.83, 3.02 (both ABX system, 2 H each, CH_2, J_{AB} = 18.2 Hz, J_{AX} = 6.2 Hz, J_{BX} = 8.0 Hz); 3.49 (q, 1 H, CH, J = 7.0 Hz); 3.68 (s, 3 H, OMe); 5.14 (s, 2 H, OH); 6.78, 7.13 (both d, 2 H each, ArH, J = 8.6 Hz). ^{13}C NMR (DMSO-d_6), δ: 26.00, 26.12 (both Me), 33.96 (CH), 42.02 (2 CH_2), 54.85 (CH_3O), 75.73 (2 CO), 113.31, 128.36 (both CH, Ar), 136.77 (C, Ar), 157.37, 213.92 (2 C=O). MS (EI), m/z (I_{rel} (%)): 206 (43), 135 (21), 134 (62), 59 (100), 43 (36), molecular ion peak with m/z 322 was not detected. MS (ESI), m/z: 345 $[M + Na]^+$, 346 $[M + H + Na]^+$.

2,8-Dihydroxy-2,8-dimethyl-5-(4-dimethylaminophenyl)nonane-3,7-dione (3g) was synthesized in 27% yield by method ***B***, light yellow pasty oil. Found (%): N, 4.37. $C_{19}H_{29}NO_4$. Calculated (%): N, 4.18. IR, ν/cm^{-1}: 3440 sh., 1712. ^{1}H NMR (300 MHz, DMSO-d_6), δ: 1.01, 1.13 (both s, 6 H each, Me); 2.81 (s, 6 H, NMe); 2.83, 3.00 (both ABX system, 2 H each, CH_2, partially overlaps, J_{AB} = 18.0 Hz, J_{AX} = 5.7 Hz, J_{BX} = 7.7 Hz); 3.45 (q, 1 H, CH, J = 7.0 Hz); 5.13 (q, 2 H, OH); 6.60, 7.04 (both d, 2 H each, HAr, J = 8.4 Hz). ^{13}C NMR (DMSO-d_6), δ: 26.04, 26.14, 33.76, 40.24 (NMe), 42.09 (CH_2), 75.74, 112.73, 127.78, 132.54, 148.77, 213.96 (C=O). MS (EI), m/z (I_{rel} (%)): 206 (43), 135 (21), 134 (62), 59 (100), 43 (36), molecular ion peak with m/z 322 was not detected. Purification of compound **3g** by silica gel column chromatography (elution with CH_2Cl_2—AcOEt) lead to enone **2g** in 20% yield.

(4*E*)-2-Hydroxy-2-methyl-5-(4-dimethylaminophenyl)pent-4-ene-3-one (2g). Yield 27%, yellow powder, m.p. 124 °C (from EtOH—EtOAc). Found (%): C, 72.05; H, 8.18; N, 5.99. $C_{14}H_{19}NO_2$. Calculated (%): C, 72.07; H, 8.21, N, 6.00. IR, ν/cm^{-1}: 3420 (OH), 1656 (C=O), 1616 (CH=CH). UV, λ_{max}/nm (ε): 250 (4800), 392 (10200). ^{1}H NMR (300 MHz, DMSO-d_6), δ: 1.26 (s, 6 H, Me); 2.98 (s, 6 H, NMe); 5.23 (br.s, OH); 6.73, 7.56 (both d, 2 H each, ArH, J = 8.4 Hz); 7.26, 7.51 (both d, 1 H each, *trans*-CH=CH, J = 16.0 Hz).

2,8-Dihydroxy-2,8-dimethyl-5-(2-furyl)nonane-3,7-dione (3h) was synthesized in 22% yield by method ***B***; chemically inhomogeneous (purity of ~94%) dark oil isolated by silica gel column chromatography (elution with CH_2Cl_2—AcOEt). IR, ν/cm^{-1}: 3460 br., 1716. ^{13}C NMR (500 MHz, DMSO-d_6), δ: 1.09, 1.15 (both s, 6 H each, Me); 2.82, 3.09 (both ABX system, 2 H each, CH_2, J_{AB} = 18.2 Hz, J_{AX} = 6.2 Hz, J_{BX} = 7.6 Hz); 3.64 (q, 1 H, CH, J = 6.6 Hz); 5.26 (s, 2 H, OH); 5.99 (d, 1 H, furyl, J = 3.2); 6.29 (dd, 1 H, furyl, J = 3.2 Hz, J = 1.8 Hz); 7.46 (br.d, 1 H, furyl, J = 1.8 Hz).

2-Hydroxy-7-(1-hydroxycyclohexyl)-2-methyl-5-phenylheptane-3,7-dione (3i) was synthesized in 17% yield by method ***A*** from enone **2b** and methyl ketone **1a** (see Scheme 4); chemically inhomogeneous (purity of ~92%) pasty oil isolated by silica gel column chromatography (elution with CH_2Cl_2—AcOEt). IR, ν/cm^{-1}: 3400 br., 1708. ^{1}H NMR (300 MHz, DMSO-d_6), δ: 0.98, 1.10 (both s, 3 H each, Me); 2.87 (dt, 2 H, CH_2, J = 18.2 Hz, J = 5.6 Hz); 3.03 (dd, 1 H, CH_2, J = 18.2 Hz, J = 3.6 Hz); 3.04

(dd, 1 H, CH_2, J = 18.2 Hz, J = 3.6 Hz); 3.54 (q, 1 H, CH, J = 7.0 Hz); 4.98, 5.16 (both s, in a 1 : 2 intensity ratio, 2 H, OH); 7.10 (q, 1 H, Ph, J = 4.0 Hz); 7.21 (d, 4 H, Ph, J = 3.6 Hz). ^{13}C NMR (DMSO-d_6), δ: 20.55, 20.71, 24.96 (all CH_2), 25.99, 26.12 (both Me); 32.67, 32.77 (both CH_2); 34.73 (CH), 41.9, 42.01 (both CH_2), 75.75, 76.94 (both CO), 126.82, 127.44, 127.92 (all CH, Ph), 144.98 (C, Ph), 213.89, 214.27 (both C=O). ME, (ESI), m/z: 355 $[M + Na]^+$, 356 $[M + H + Na]^+$. Ketodiol **3i** was also isolated in 18% yield from the reaction mixture obtained by the reaction of enone **2a** and methyl ketone **1b** (method ***A***).

Synthesis of diketo diacetates 4 (general procedure). To a solution of the corresponding diketo diol **3** (1 mmol) in CH_2Cl_2 (15—20 mL) containing trimethylamine (2 mL) and 4-dimethylaminopyridine (2 mg), acetic anhydride (0.6 mL) was added dropwise, the reaction mixture was maintained at 20—25 °C for 2 days, and then gently refluxed for 30 min. The reaction mixture was suspended in an ice-cold aqueous $NaHCO_3$ and extracted with benzene—ethyl acetate. The organic layer was filtered through a silica gel pad (a 3 cm thick). The target acetates were isolated as described in method ***A***.

2,8-Diacetoxy-2,8-dimethyl-5-phenylnonane-3,7-dione (4a). Yield 82%, m.p. 114—115 °C (hexane—EtOAc, 1 : 1). Found (%): C, 67.02; H, 7.41. $C_{21}H_{28}O_6$. Calculated (%): C, 67.00; H, 7.50. IR, ν/cm^{-1}: 1738, 1707 sh., 1256 (C—O). ^{1}H NMR (300 MHz, $CDCl_3$), δ: 1.28, 1.37 (both s, 6 H each, Me); 2.06 (s, 6 H, MeCO); 2.81, 2.91 (both ABX system, 2 H each, CH_2, J_{AB} = = 18.0 Hz, J_{AX} = 8.0 Hz, J_{BX} = 6.0 Hz); 3.74 (q, 1 H, CH, J = 6.8 Hz); 7.14—7.29 (m, 5 H, Ph). ^{13}C NMR (DMSO-d_6), δ: 20.83, 22.65, 22.83, 35.28, 41.30, 82.82, 126.09, 127.62, 127.91, 144.00, 169.81, 206.47. MS, m/z (I_{rel} (%)): 376 $[M]^+$ (1), 316 (26), 276 (20), 275 (50), 256 (24), 216 (22), 215 (74), 187 (26), 145 (24), 132 (23), 131 (100), 117 (24), 104 (73), 100 (68), 71 (31), 70 (43), 69 (61), 59 (74), 43 (37).

1,5-Bis(1-acetoxycyclohexyl)-3-phenylpentane-1,5-dione (4b). Yield 79%, m.p. 116 °C (hexane—EtOAc, 1 : 1). Found (%): C, 70.83; H, 7.94. $C_{27}H_{36}O_6$. Calculated (%): C, 71.02; H, 7.95. IR, ν/cm^{-1}: 1736, 1702. ^{1}H NMR (300 MHz, DMSO-d_6), δ: 1.12, 1.34, 1.51, 1.67, 1.82 (all m, 4 H, 6 H, 6 H, 2 H, 2 H, CH_2); 2.06 (s, 6 H, Ac); 2.69, 2.81 (both ABX system, 2 H each, CH_2, J_{AB} = 17.8 Hz, J_{AX} = 6.1 Hz, J_{BX} = 7.9 Hz); 3.53 (q, 1 H, CH, J = 6.7 Hz); 7.13 (q, 1 H, Ph, J = 3.6 Hz); 7.20, 7.22 (both s, 2 H, Ph). ^{13}C NMR (DMSO-d_6), δ: 20.55, 20.64, 20.72, 24.32, 29.57, 30.24, 35.17, 41.32, 84.24, 126.01, 127.63, 127.88, 144.13, 169.78, 206.79. MS, (ESI), m/z: 479 $[M + Na]^+$, 480 $[M + H + Na]^+$.

2,8-Diacetoxy-2,8-dimethyl-5-(4-methoxyphenyl)nonane-3,7-dione (4d). Yield (80%), m.p. 112 °C (hexane—EtOAc, 1 : 1). Found (%): C, 65.10; H, 7.63. $C_{22}H_{30}O_7$. Calculated (%): C, 65.01; H, 7.44. IR, ν/cm^{-1}: 1738, 1706. ^{1}H NMR (300 MHz, DMSO-d_6), δ: 1.15, 1.27, 2.01 (all s, 6 H each, Me); 2.68—2.75 (m, 4 H, CH_2), 3.49 (br.t, 1 H, CH, J = 6.0 Hz); 3.69 (s, 3 H, Me); 6.78, 7.14 (both d, 2 H each, ArH, J = 8.6 Hz). ^{13}C NMR (DMSO-d_6), δ: 20.84, 22.66, 22.86, 34.51, 41.49, 54.83, 82.87, 113.31, 128.58, 135.92, 157.57, 169.83, 206.55. MS, m/z (I_{rel} (%)): 407 $[M + H]^+$ (8), 406 $[M]^+$ (63), 346 (13), 305 (19), 292 (39), 287 (16), 286 (41), 263 (15), 246 (17), 245 (30), 216 (22), 203 (43), 175 (72), 161 (16), 134 (46), 129 (28), 101 (48), 91 (100).

Synthesis of dioximes 5 (general procedure). To a stirred solution of the corresponding diketo diol **3** (1—2 mmol) and $NH_2OH \cdot HCl$ (0.49 g, 7 mmol) in aqueous (1 : 4) MeOH (20 mL), NaOH (0.3 g) was added in one portion at 28—30 °C. The reaction mixture was refluxed for 5—7 h, cooled, and the solvent was removed *in vacuo*. The semi-dry residue was triturated with ethyl acetate—hexane. Solid oximes were recrystallized.

1,5-Bis(1-hydroxycyclohexyl)-3-phenylpentane-1,5-dione dioxime (5b). Yield 67%, m.p. 179 °C (hexane—EtOAc, 1 : 2). Found (%): C, 68.47; H, 6.39; N, 6.58. $C_{23}H_{34}N_2O_4$. Calculated (%): C, 68.63; H, 8.51; N, 6.96. IR, ν/cm^{-1}: 3540, 3360, 3212, 1648. ^{1}H NMR (300 MHz, DMSO-d_6—$CDCl_3$ (1 : 4)), δ: 1.03, 1.14—1.65 (both m, 2 H and 18 H, CH_2); 2.36 (br.s, 2 H, overlaps with the OH group proton); 2.42, 2.89 (both ABX system, 2 H each, CH_2, J_{AB} = 12.8 Hz, J_{AX} = 4.4 Hz, J_{BX} = 6.8 Hz); 3.72 (q, 1 H, CH, J = 7.5 Hz); 7.06—7.22 (m, 5 H, Ph); 9.58 (br.s, 2 H, NOH). ^{13}C NMR (DMSO-d_6—$CDCl_3$ (1 : 4)), δ: 21.39, 21.48, 25.33, 31.61, 35.45, 35.81 (all CH_2), 39.59 (CH), 73.58 (CO), 126.46, 127.95, 128.05 (all CH, Ph); 145.30 (C, Ph); 163.39 (C=N). MS, m/z (I_{rel} (%)): 403 $[M + H]^+$ (2), 402 $[M]^+$ (13), 385 (17), 384 (24), 367 (16), 352 (14), 319 (18), 269 (100), 229 (18), 228 (33), 226 (19), 171 (24), 139 (19), 131 (27), 130 (67), 124 (23), 122 (25), 103 (20), 99 (82), 98 (36), 81 (62), 69 (20), 55 (78), 43 (20).

1,5-Bis(1-hydroxycyclohexyl)-3-(4-methylphenyl)pentane-1,5-dione dioxime (5c). Yield 46%, m.p. 166—167 °C (EtOH—EtOAc, 1 : 3). Found (%): C, 69.06; H, 8.62; N, 6.54. $C_{24}H_{36}N_2O_4$. Calculated (%): C, 69.20; H, 8.71; N, 6.73. IR, ν/cm^{-1}: 3560, 3360, 3228, 1652, 1636. ^{1}H NMR (500 MHz, DMSO-d_6), δ: 1.06, 1.22, 1.37, 1.49 (all m, 2 H, 4 H, 4 H, 10 H, CH_2); 2.23 (s, 3 H, Me); 2.54, 2.68 (both ABX system, 2 H each, CH_2, J_{AB} = 13.2 Hz, J_{AX} = 8.2 Hz, J_{BX} = 7.3 Hz); 3.94 (q, 1 H, CH, J = 7.6 Hz); 4.19 (s, 2 H, OH); 7.02, 7.13 (both d, 2 H each, ArH, J = 8.2 Hz); 10.32 (s, 2 H, NOH). MS, (ESI), m/z: 439 $[M + Na]^+$, 455 $[M + K]^+$.

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References

1. (a) C. H. Heathcock, in *Comprehensive Organic Synthesis*, Eds B. M. Trost, I. Fleming, New-York, 1993, Vol. **2**, Part 2, p. 133; (b) R. H. Wiley, *Org. Synth.*, Coll. Vol. **3**, 1995, 853; (c) J.-C. Plaquevent, D. Cahard, F. Guillen, *Sci. Synth.*, 2004, **26**, 513; (d) *Modern Aldol Reactions*, Ed. R. Mahrwald, Wiley—VCH, Weinheim, 2004.
2. (a) A. L. Marzinzik, E. R. Felder, *J. Org. Chem.*, 1998, **63**, 723; (b) V. Henryon, L. W. Liu, R. Lopez, J. Prunet, J. P. Ferezou, *Synthesis*, 2001, 2401; (c) R. Antonioletti, P. Bovicelli, S. Malancona, *Tetrahedron*, 2002, **58**, 589; (d) C. Simon, T. Constantieux, J. Rodriguez, *Eur. J. Org. Chem.*, 2004, 4957; (e) V. Cadierno, J. Diez, S. E. Garcia-Garrido, J. Gimeno, N. Nebra, *Adv. Synt. Catal.*, 2006, **348**, 2125; (f) H.-M. F. Madkour, A. S. Elgazwy, *Curr. Org. Chem.*, 2007, **11**, 853.
3. (a) H.-C. Guo, J.-A. Ma, *Angew. Chem., Int. Ed.*, 2006, **45**, 354; (b) N. Krause, A. Hoffman-Roder, *Synthesis*, 2001, 171; (c) *Domino Reactions in Organic Synthesis*, Eds L. F. Tietze, G. Brasche, K. M. Gericke, Wiley-WCH, Weinheim, 2006, 631 pp.

4. (a) F. Silva, M. Sawicki, V. Gouverneur, *Org. Lett.*, 2006, **8**, 5417; (b) Y. Qian, S. Xiao, L. Liu, Y. Wang, *Tetrahedron: Asymmetry*, 2008, **19**, 1515; (c) M. Thirumalaikumar, *Org. Prep. Proced. Int.*, 2011, **43**, 67; (d) M. P. Sibi, M. Manyem, *Tetrahedron*, 2000, **56**, 8033; (e) H. Y. Xie, S. R. Ban, J. N. Liu, Q. S. Li, *Tethedron Lett.*, 2012, **53**, 3865.
5. (a) T. Harada, N. Kumagai, T. Kinoshita, S. Matsunaga, M. Shibasaki, *J. Am. Chem. Soc.*, 2003, **125**, 2582; (b) R. Gnaneshwar, P. P. Wadgaonkar, S. Sivaram, *Tetrahedron Lett.*, 2003, **44**, 6047; (c) K. Miura, T. Nakagawa, A. Hosomi, *Synlett*, 2003, 2068; (d) K. Miura, N. Nakagawa, A. Hosomi, *Synlett*, 2005, 1917; (e) X. Wang, S. Adachi, S. Iwai, H. Takatsuki, K. Fujita, M. Kubo, A. Oku, T. Harada, *J. Org. Chem.*, 2003, **68**, 10046; (f) T. Harada, S. Adachi, X. Wang, *Org. Lett.*, 2004, **6**, 4877; (g) T. Harada, T. Yamauchi, S. Adachi, *Synlett*, 2005, 2151; (h) N. Jaber, M. Assie, J.-C. Fiaud, J. Colin, *Tetrahedron*, 2004, **60**, 3075; (i) T. Nakagawa, H. Fujisawa, Y. Nagata, T. Mukaiyama, *Bull. Chem. Soc. Jpn.*, 2005, **78**, 236; (j) G. Kumaraswamy, N. Jena, M. N. V. Sastry, M. Padmaja, B. Markondaiah, *Adv. Synth. Catal.*, 2005, **347**, 867; (k) W. Wang, H. Li, J. Wang, *J. Org. Lett.*, 2005, **7**, 1637; (l) A. Yanagisawa, A. Shinohara, H. Takahashi, T. Arai, *Sinlett.*, 2007, 141; (m) K. Ende, M. Ogawa, T. Shibata, *Angew. Chem.*, *Int. Ed.*, 2010, **49**, 2410; (n) A. Di Mola, A. Massa, *Curr. Org. Chem.*, 2012, **16**, 2290.
6. (a) B. Branchi, G. Doddi, G. Ercolani, *J. Org. Chem.*, 2005, **70**, 6422; (b) M. O. Edema, Ch. C. Okoye, *J. Chem. Soc. Niger.*, 2006, **31**, 49; (c) H. Wu, L. Lu, Y. Shen, Y. Wan, K. Yu, *Synth. Commun.*, 2006, **36**, 1193.
7. (a) J. An, L. Bagnell, T. Gablewski, C. R. Strauss, R. W. Trainor, *J. Org. Chem.*, 1997, **62**, 2505; (b) C.-J. Li, *Chem. Rev.*, 2005, **105**, 3095.
8. M. V. Mavrov, C. I. Firgang, *Russ. Chem. Bull.* (*Int. Ed.*), 2012, **61**, 606 [*Izv. Akad. Nauk*, *Ser. Khim.*, 2012, 604].
9. (a) M. V. Mavrov, S. G. Zlotin, *Chem. Heterocycl. Compd*, (*Enql. Transl.*), 2006, **42**, 591 [*Khim. Geterotsikl. Soedin.*, 2006, 677]; (b) Sh.-ichi Matsuoka, S. Shimakawa, K. Takagi, M. Suzuki, *Tetrahedron Lett.*, 2011, **52**, 6835; (c) A. O. Terent´ev, I. A. Yaremenko, V. V. Chernyshev, V. M. Dembitsky, G. I. Nikishin, *J. Org. Chem.*, 2012, **77**, 1833.

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