The Aldol Reaction under High-Intensity Ultrasound: A Novel Approach to an Old Reaction

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We have employed high-intensity ultrasound (HIU) to reinvestigate the aldol reaction (AR) in water. A number of aldols that under usual conditions would undergo elimination were isolated in acceptable to good yields. Within 15–30 min, acetophenone reacted with non-enolizable aldehydes to afford the aldol exclusively, while under conventional conditions (stirring or heating under reflux) the same compounds either failed to react or gave, after several hours, the enone, often in complex product mixtures. A library of polyols was obtained starting from a series of acetophenones and excess formaldehyde. Benzaldehyde reacted with a series of 1,3-dicarbonyl compounds to afford the corresponding bis(benzylidene) adducts. The results proved to be highly reproducible because the relevant sonochemical parameters were rigorously controlled.

Introduction

The aldol reaction (AR), one of the oldest organic reactions,[1] has been extensively studied and exploited after Kane discovered in 1838 that mesityl oxide can be made by self-condensation of acetone;[2] the reaction still remains a common synthetic method and the most important reaction of enolate ions.[3] In the AR a new C−C bond is formed and up to two new adjacent stereocenters can be generated simultaneously. Because the aldol motif is present in many molecules of great interest, the AR has been widely used to prepare stereochemically complex products. In recent years, a number of methods have been developed to perform asymmetric ARs.[4] Although the AR can be catalysed by acids, and many variants employing neutral conditions have been described,[3] basic catalysis in protic solvent is used most commonly. Yields are often compromised by self-condensation, polycondensation, generation of regioisomeric enols, and dehydration of aldols, which is sometimes followed by Michael addition (e.g., Robinson annulation). To minimize competing processes, a useful modification, the Mukaiyama AR,[5] has been developed in which an enol silyl ether is reacted with carbonyl compounds in the presence of a Lewis acid. Recently, the focus has shifted to the use of transition metal catalysts (Rh, Ni, V),[6] to solvent-free reactions mediated by magnesium hydrogen sulfate,[7] to supported reagents[8] and anion-exchange resins.[9]

Aldols are raw materials for the production of lubricants, surface coatings and synthetic resins;[10] moreover, they are important intermediates in the synthesis of polyols.[11]

In the present work, we applied high-intensity ultrasound (HIU) to base-catalyzed AR in water to prepare a wide range of aldols and polyols, mainly from acetophenones as starting materials. In the last decade the use of water as a reaction solvent or co-solvent has attracted considerable attention in synthetic organic chemistry.[12] Aqueous media have several advantages for conventional procedures. Besides eliminating the need to dry solvents and substrates before use, they often bring out peculiar reactivities and selectivities that are not observed under anhydrous conditions. Reagents and catalysts have been developed that work well in aqueous media, and for the AR in particular.[13] For aqueous AR, Chan introduced a tin- or zinc-mediated cross-coupling of halo-ketones with aldehydes;[14] other authors have described aqueous Mukaiyama-type reactions.[15]

We found that, under HIU, these reactions take place with good yields in aqueous heterogeneous systems, generally without requiring any catalyst. Water is a common solvent in sonochemistry because its good cavitation energy has a maximal effect around room temperature.[16] It has been widely reported that ultrasound, when compared with conventional conditions, enhances reaction rates[17] and product yields in addition to sometimes changing the reaction pathway ("sonochemical switching").[18] Generally,

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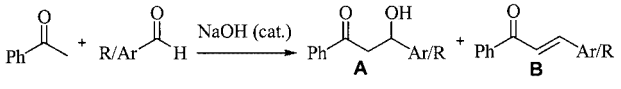
ultrasound accelerates a reaction by a more intimate mixing of reagents and enhances the activity of an insoluble catalyst by enlarging its surface area.[19] Reactions may also be accelerated because highly reactive radical species are formed during cavitation; in this case, sonochemical switching may occur. Although sonochemical ARs have appeared in the literature previously, starting in the early 1980s,[20] to the best of our knowledge, none has been reported to serve as a general method for the preparation of aldols. More recently, ultrasound has also been applied to closely related reactions, viz. the Knoevenagel condensation[21] and the Reformatsky reaction.[22] Our approach to the synthesis of aldols in water will hopefully contribute to the development of "green" procedures.[23]

Results and Discussion

We chose the well-known reaction between acetophenone and benzaldehyde (Scheme 1) as a suitable model to optimise conditions and to compare results with those from conventional methods. Because TLC did not afford a sufficient separation of reagents and products,[24] we followed the course of the reaction by HPLC (μ-Porasil®, Waters) and found that no 1,3-diphenylpropenone was formed. The results are displayed in Table 1. Addition of a surfactant[25] caused a dramatic effect: a very small amount of Aliquat® 336 (0.2−0.5%) sufficed to reverse the aldol/enone ratio, affording the former one exclusively in every case. Following this success, we reacted acetophenone with a series of non-enolizable aldehydes (Table 2, **1**−**13**).



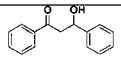
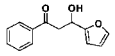
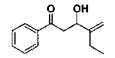
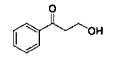
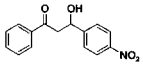
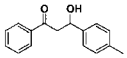
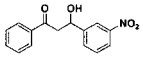
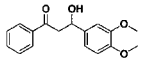
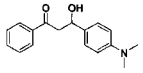
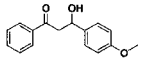
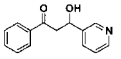
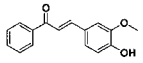
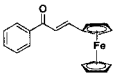
Scheme 1. AR of acetophenone with non-enolizable aldehydes

Table 1. AR conditions of acetophenone (4 mmol) and benzaldehyde (4 mmol) in water in the presence of NaOH (0.125 mmol)

Conditions	Time (min)	Yield ratio, A:B
Vigorous stirring, 20 °C	30	8:12
Vigorous stirring, 70 °C	30	0:30
Vigorous Stirring, 20 °C + Aliquat® 336[a]	15	trace:51
HIU 18 kHz, 20 °C, 280 W	15	73:0
U.S. 18 kHz, 20 °C, 280 W, Aliquat® 336	15	trace:82
HIU 18 kHz, 20 °C, 400 W	15	77: trace
HIU 20 kHz, 20 °C, 280 W	15	72:0
HIU 34 kHz, 20 °C, 250 W	30	49:0
HIU 34 kHz, 20 °C, 220 W, Aliquat® 336	30	0:31
US cleaner bath, 35 kHz, 20 °C, 140 W	60	17:0

[a] Methyltrioctylammonium chloride.

Table 2. AR of acetophenone (4 mmol) and non-enolizable aldehydes (4 mmol) in water in the presence of NaOH (0.125 mmol) under HIU (18 kHz, 280 W; 20 °C)

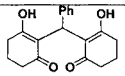
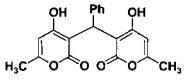
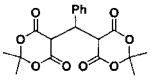
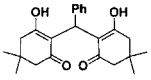
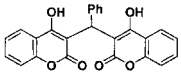
	Aldehyde	Product	Reaction time (min)	Yield %
1	Benzaldehyde		30	73
2	Furfural		45	59
3	Ethylacrolein		45	52
4	Formaldehyde		15 (under 5°C)	61
5	4-Nitrobenzaldehyde		45	78
6	*p*-Tolualdehyde		45	46
7	3-Nitrobenzaldehyde		45	76
8	3,4-Dimethoxybenzaldehyde		45	74
9	4-Dimethylaminobenzaldehyde		45	62
10	4-Methoxybenzaldehyde		45	37
11	Pyridine 3-carboxaldehyde		45	82
12	Vanillin		60 (NaOH 1.2 eq)	20
13	Ferrocenecarboxaldehyde		90	37

All of the aldehydes gave the aldol in acceptable to good yields, with two exceptions: vanillin (**12**) and ferrocenecarboxaldehyde (**13**) gave no aldol (for **12**, 1 equiv. of base was also added to convert the phenolic group to phenolate); after further addition of base and prolonged sonication, these reactions gave the enones instead. Because much information is available on the conventional AR with benzaldehyde, we used it to extend our comparative investigation further. In our hands, benzaldehyde reacted very fast with acetone to afford the corresponding aldol (4-hydroxy-4-phenylbutan-2-one) in good yield (72%); with acetaldehyde, surprisingly, it yielded cinnamaldehyde as the only product (79%). Reacting benzaldehyde with a number of 1,3-dicarbonyl compounds afforded, in all cases, the corresponding 2:1 adducts.

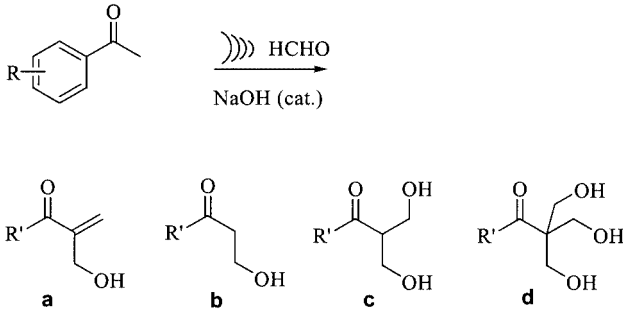
The present approach provides easy access to bis(benzylidene) derivatives (Table 3). Under these conditions, β-tetronic acid and ethyl acetylacetate gave no reaction or underwent hydrolysis, respectively.

The AR between acetophenones and excess formaldehyde (50 equiv.) is a convenient procedure for obtaining libraries of new polyols. We carried out these reactions at 20 kHz and 250 W because preliminary optimisation tests

Table 3. AR of benzaldehyde (4 mmol) with 1,3-dicarbonyl compounds (8 mmol) in water in the presence of NaOH (0.125 mmol) under HIU (18 kHz, 280 W; 20 °C)

	Reactant	Product	Reaction time (min)	Yield %
14	2,4-Cyclohexandione		60	71
15	4-Hydroxy-6-methyl-2-pyrone		60	83
16	Meldrum acid		60	65
17	Dimedone		90	68
18	4-Hydroxycoumarin		60	84

had shown that yields were somewhat higher under these conditions. After 1 h of sonication at 20 °C we isolated the derivatives listed in Scheme 2 and Table 4. Because of their dense functionalization, these compounds are potential starting materials for the synthesis of polymers and dendrimers. Longer reaction times caused an increase of **c** and even more of **d**; working at 5 °C reduced the formation of **a**.



Scheme 2. AR of different acetophenones with formaldehyde

Table 4. ARs of acetophenones and excess aq. formaldehyde (50 equiv.) under HIU (20 kHz, 250 W, 1 h, 20 °C)

Compound	R	Yield ratio (%) a	b	c	d
19	H	20	15	14	30
20	2-OCH_3	9	< 2[a]	11	14
21	2-Cl	19	2[a]	< 2[a]	22
22	4-Cl	5	4	11	39
23	4-NO_2	18	< 2[a]	10	34
24	3-CH_3CO	12	18	14	27

[a] Determined by HPLC ($CHCl_3$/acetone, 3:2; μ-Porasil® Waters).

Only 12 of the 42 aldols and polyols here reported have been described previously.[26] We have also examined some stereochemical aspects of these reactions in a few preliminary experiments. Our operating conditions did not influence the diastereoselectivity of the AR: although propiophenone reacted with 4-nitrobenzaldehyde, 3-nitrobenzaldehyde and pyridine 3-carboxaldehyde[27] to afford the corresponding aldols in good yields (30 min; 69, 77 and 72%, respectively), the poor diastereoisomeric excess (monitored by GC: OV1, film 0.4 μm) observed previously[28] was hardly improved (10−13% vs. 7−8%).

We attempted to use L-proline as a chiral catalyst for sonochemical asymmetric ARs both in water and, more conventionally, in DMSO. In either case, the aldols arising from acetophenone reacting with 4-nitrobenzaldehyde, 3-nitrobenzaldehyde and pyridine 3-carboxaldehyde (**5**, **7** and **11**, respectively; Table 2) exhibited uniformly poor values of *ee* (< 20%), a result at variance with a published report.[29] We achieved separation of enantiomers, which had failed when using various chiral GC columns, by chiral HPLC using hexane/2-propanol as eluent.[30]

Conclusion

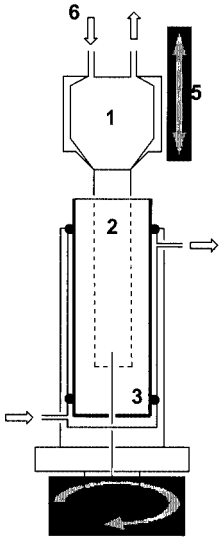
The above series of ARs, when carried out in aqueous suspension under HIU, afforded a number of aldols that usually cannot be isolated in practical yields because they undergo elimination immediately. Our approach offers ready access to polyols and bis-benzylidene adducts.

Experimental Section

General: Reactions were monitored by TLC on Merck 60 F_{254} (0.25 mm) plates, which were visualized by UV inspection and/or staining with 5% H_2SO_4 in ethanol and heating. Merck silica gel was used for column chromatography (CC). Melting points: Büchi SMP-20 (uncorrected). IR: Shimadzu FT-IR 8001 spectrophotometer. NMR: Bruker 300 Advance (300 MHz and 75 MHz for ^1H and ^{13}C, respectively). For ^1H NMR: $CDCl_3$ as solvent, $CHCl_3$ at δ = 7.26 ppm as reference. For ^{13}C NMR: $CDCl_3$ as solvent, $CDCl_3$ at δ = 77.0 ppm as reference. The chemical shifts (δ) are given in ppm, and the coupling constants (*J*) in Hz. Low-resolution mass spectra (LRMS): Finnigan-MAT TSQ70 in chemical ionization mode with isobutane as the reactant gas. GC analysis: Shimadzu GC-14 B equipped with a Shimadzu C-R6A Chromatopac integrator. HPLC analysis: Thermo-Quest Spectra Series P200, equipped with a UV-Vis Jasco 875-UV detector or a Gilson 133 refractive index refractometer, and a Millipore 740 Waters integrator. Commercially available reagents and solvents were used without further purification unless otherwise noted. All the reactions were performed on a flat-bottomed tube, made in Teflon® (diameter: 35 mm; thickness: 1 mm; volume: 40 mL), inserted in the thermostatic bath (for temperatures as low as −20 °C) of the sonochemical reactor. For some comparison of sonication effects, we used an Elma TS540 cleaner bath at 35 kHz (nominal operating frequency: 140 W).

The sonochemical apparatus (Scheme 3) used in the present work was designed for stringent control of the reaction conditions. The

transducer, consisting of two high-efficiency pre-stressed piezoelectric rings, is lodged in a Delrin® housing that can be cooled by a flow of refrigerated oil. Indeed, the whole probe system (comprising the transducer, the booster and the immersion horn) is refrigerated by an oil forced-circulation circuit connected to an oil−freon heat exchanger; this system is cooled in turn by a refrigerator unit. The frequency can be tuned between 17 and 45 kHz and the power can be varied up to a maximum output of 1000 W. To achieve optimal acoustic efficiency, the reactor can rotate eccentrically around the horn and the probe can be made to move alternatively up and down by a predetermined excursion at a chosen speed. Transducer resonance is maintained by a true motional feedback network. Electrical and acoustic parameters may be monitored thereby to give full process information. Reactions were performed in a Teflon® tube (thickness: 1 mm) inserted in a Delrin® reactor that was thermostatted by four Peltier modules.



Scheme 3. Sonochemical reactor: 1) transducer and booster, 2) horn, 3) thermostatted reactor, 4) eccentric rotation, 5) vertical excursion, 6) refrigeration system with oil forced-circulation circuit

General Procedure for 1−13: Both reactants (acetophenone and aldehyde, 4 mmol each), water (6 mL) and 0.25 M NaOH (0.5 mL, 0.125 mmol) were added to the above-mentioned Teflon® tube. The mixture was sonicated for 15−30 min at 18 kHz and 280 W using an immersion horn, whilst maintaining the temperature at 20 °C. The reactions were monitored by TLC using hexane/EtOAc or $CHCl_3$/MeOH as eluents. After extraction with $CHCl_3$ or EtOAc (10 mL, 3 times), a wash with brine (10 mL), drying ($MgSO_4$) and removal of the solvent, the residue was purified by CC (PE/EtOAc).

General Procedure for 14−18: Benzaldehyde (4 mmol), a 1,3-dicarbonyl compound (8 mmol), water (6 mL) and 0.25 M NaOH (0.5 mL, 0.125 mmol) were added to the Teflon® tube. The mixture was sonicated for 1 h at 18 kHz and 280 W using an immersion horn, whilst the temperature was maintained at 20 °C. The reactions were monitored by TLC using hexane/EtOAc or $CHCl_3$/MeOH as eluents. In most cases, the product was recovered easily by filtration through a sintered disc filter funnel; sometimes a further extraction with $CHCl_3$ or EtOAc was needed. The residue was purified by crystallization or by CC (PE/EtOAc).

General Procedure for 19−22: Acetophenone (4.0 mmol), formaldehyde [37% (w/w) solution in water (20 mL)] and 0.25 M NaOH (0.5 mL, 0.125 mmol) were added to the Teflon® tube. The mixture was sonicated for 1 h using an immersion horn operating at 20 kHz and 250 W, whilst the temperature was maintained at 20 °C. The reactions were monitored by TLC using mixtures of hexane/EtOAc or $CHCl_3$/MeOH as eluents. The products were recovered by filtration through a sintered disc filter funnel and extracted with $CHCl_3$/MeOH (49:1). The residue was purified by CC (PE/EtOAc or $CHCl_3$/MeOH).

4-Ethyl-3-hydroxy-1-phenylpent-4-en-1-one (3): Yield: 424 mg (52%). Yellow oil. IR (liquid film): $\tilde{\nu}$ = 3374, 1682, 1356, 1279, 1211, 1086, 1026 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 7.98 (d, J = 7.1 Hz, 2 H), 7.60 (m, 1 H), 7.49 (t, J = 7.7 Hz, 2 H), 5.18 (s, 1 H), 4.95 (s, 1 H), 4.74 (m, 1 H), 3.24 (m, 2 H), 2.16 (m, 2 H), 1.13 (t, J = 7.4 Hz, 3 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 200.95, 152.13, 137.18, 133.98, 129.10, 128.54, 109.35, 71.10, 44.60, 25.23, 12.61 ppm. R_f = 0.15 (hexane/EtOAc, 9:1). CIMS: m/z = 205 $[M + H]^+$, 187 $[M + H - H_2O]^+$. $C_{13}H_{16}O_2$ (204.1): calcd. C 76.44, H 7.90; found C 76.50, H 7.86.

3-Hydroxy-3-(3-nitrophenyl)-1-phenylpropan-1-one (7): Yield: 823 mg (76%). White crystals. M.p. 124 °C. IR (KBr disk): $\tilde{\nu}$ = 3513, 1674, 1524, 1350, 1213, 760, 691 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 8.33 (s, 1 H), 8.16 (d, J = 8.1 Hz, 1 H), 7.96 (d, J = 7.3 Hz, 2 H), 7.80 (d, J = 7.7 Hz, 1 H), 7.69 (t, J = 8.2 Hz, 1 H), 7.55 (d, J = 7.9 Hz, 1 H), 7.47 (t, J = 7.5 Hz, 2 H), 5.46 (m, 1 H), 3.42 (m, 2 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 199.91, 148.76, 145.68, 136.64, 134.34, 132.45, 129.91, 129.20, 128.59, 122.92, 121.28, 69.47, 47.43 ppm. R_f = 0.19 (hexane/EtOAc, 7:3). CIMS: m/z = 272 $[M + H]^+$, 254 $[M + H - H_2O]^+$. $C_{15}H_{13}NO_4$ (271.1): calcd. C 66.41, H 4.83; found C 66.50, H 4.81.

3-(3,4-Dimethoxyphenyl)-3-hydroxy-1-phenylpropan-1-one (8): Yield: 846 mg (74%). White solid. M.p. 124 °C. IR (KBr disk): $\tilde{\nu}$ = 3511, 1684, 1595, 1516, 1262, 1140, 1022, 764, 698 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 7.98 (d, J = 8.1 Hz, 2 H), 7.58 (t, J = 7.5 Hz, 1 H), 7.47 (t, J = 7.6 Hz, 2 H), 7.02 (s, 1 H), 6.96 (d, J = 8.2 Hz, 1 H), 6.87 (d, J = 8.2 Hz, 1 H), 5.30 (m, 1 H), 3.92 (s, 3 H), 3.89 (s, 3 H), 3.38 (d, J = 6.5 Hz, 2 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 200.67, 149.57, 148.94, 137.03, 136.11, 134.06, 129.12, 128.56, 118.33, 111.55, 109.44, 70.34, 56.38, 56.31, 47.86 ppm. R_f = 0.21 (hexane/EtOAc, 7:3). CIMS: m/z = 287 $[M + H]^+$, 269 $[M + H - H_2O]^+$. $C_{17}H_{18}O_4$ (286.1): calcd. C 71.31, H 6.34; found C 70.69, H 6.41.

3-[(4-Dimethylamino)phenyl]-3-hydroxy-1-phenylpropan-1-one (9): Yield: 667 mg (62%). Yellow oil. IR (liquid film): $\tilde{\nu}$ = 3510, 1649, 1564, 1377, 1344, 1167, 1016, 816 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 7.98 (d, J = 8.1 Hz, 2 H), 7.59 (d, J = 7.3 Hz, 1 H), 7.48 (t, J = 7.5 Hz, 2 H), 7.33 (d, J = 8.4 Hz, 2 H), 6.77 (d, J = 8.5 Hz, 2 H), 5.28 (m, 1 H), 3.38 (m, 2 H), 2.97 (s, 6 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 197.42, 140.64, 137.40, 132.91, 130.82, 128.64, 128.42, 128.21, 113.34, 69.23, 48.83, 43.6 ppm. R_f = 0.20 (hexane/EtOAc, 8:2). CIMS: m/z = 251 $[M + H - H_2O]^+$. $C_{17}H_{19}NO_2$ (269.1): calcd. C 75.81, H 7.11; found C 75.95, H 7.16.

3-Hydroxy-3-(4-methoxyphenyl)-1-phenylpropan-1-one (10): Yield: 379 mg (37%). White solid. M.p. 112 °C. IR (KBr disk): $\tilde{\nu}$ = 3515, 1686, 1590, 1520, 1268, 1140, 1025, 765, 695 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 7.98 (d, J = 8.1 Hz, 2 H), 7.57 (t, J = 7.5 Hz, 1 H), 7.46 (t, J = 7.5 Hz, 2 H), 6.95 (d, J = 8.2 Hz, 2 H), 6.85 (d, J = 8.2 Hz, 2 H), 5.29 (m, 1 H), 3.90 (s, 3 H), 3.38 (d, J = 6.5 Hz, 2 H) ppm. R_f = 0.24 (hexane/EtOAc, 7:3). CIMS: m/z = 257 $[M + H]^+$. $C_{16}H_{16}O_3$ (256.1): calcd. C 74.98, H 6.29; found C 74.96, H 6.40.

3-Ferrocenyl-1-phenylprop-2-en-1-one (13): Yield: 467 mg (37%). Dark yellow oil. IR (liquid film): $\tilde{\nu}$ = 1663, 1601, 1591, 1578, 1224,

1015, 696 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 7.99 (d, *J* = 7.1 Hz, 2 H), 7.77 (d, *J* = 15.4 Hz, 1 H), 7.58 (m, 1 H), 7.50 (t, *J* = 7.7 Hz, 2 H), 7.14 (d, *J* = 15.4 Hz, 1 H), 4.61 (s, 2 H), 4.50 (s, 2 H), 4.19 (s, 6 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 189.78, 146.73, 138.54, 128.38, 119.07, 69.55 ppm. R_f = 0.45 (hexane/EtOAc, 8:2). CIMS: *m*/*z* = 317 $[M + H]^+$.

1,1′-Dihydroxy-2,2′-(phenylmethylene)bis(cyclohex-1-ene)-3,3′-dione (14): Yield: 886 mg (71%). White solid. M.p. 193 °C. IR (KBr disk): ṽ = 1721, 1633, 1603, 1377, 1192, 1030, 949 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 7.20−7.11 (m, 3 H), 6.99 (m, 2 H), 5.97 (s, 1 H), 3.39 (br. s, OH, 2 H), 2.50−1.78 (m, 12 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 192.51, 191.29, 138.25, 128.56, 126.88, 126.25, 116.84, 33.97, 33.31, 33.40, 20.52 ppm. R_f = 0.62 (hexane/EtOAc, 1:1). CIMS: *m*/*z* = 313 $[M + H]^+$, 215. $C_{19}H_{20}O_4$ (312.1): calcd. C 73.06, H 6.45; found C 73.20, H 6.37.

4,4′-Dihydroxy-6,6′-dimethyl-3,3′-(phenylmethylene)bis(pyran)-2,2′-dione (15): Yield: 1.128 g (83%). White solid. M.p. 176 °C. IR (KBr disk): ṽ = 1676, 1610, 1566, 1410, 993, 835, 725 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 7.55 (t, *J* = 6.9 Hz, 2 H), 7.46 (t, *J* = 7.1 Hz, 1 H), 7.33 (d, *J* = 7.8 Hz, 2 H), 6.38 (s, 2 H), 6.29 (s, 1 H), 2.52 (s, 6 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 162.11, 135.98, 128.84, 127.01, 126.81, 103.71, 35.17, 20.01 ppm. R_f = 0.23 (hexane/EtOAc, 1:1). CIMS: *m*/*z* = 341 $[M + H]^+$, 201. $C_{19}H_{16}O_6$ (340.1): calcd. C 67.05, H 4.74; found C 67.22, H 4.70.

1,1′-Dihydroxy-5,5,5′,5′-tetramethyl-2,2′-(phenylmethylene)bis-(cyclohex-1-ene)-3,3′-dione (17): Yield: 1.001 g (68%). White solid. M.p. 191 °C. IR (KBr disk): ṽ = 3400, 1595, 1375, 1250, 1045, 870, 694 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 12.18 (br. s, OH, 2 H), 7.37 (m, 2 H), 7.28 (d, *J* = 6.8 Hz, 1 H), 7.21 (d, *J* = 7.7 Hz, 2 H), 5.69 (s, 1 H), 2.45 (m, 8 H), 1.34 (s, 6 H), 1.21 (s, 6 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 195.7, 148.8, 133.4, 132.0, 130.3, 128.3, 128.2, 117.1, 116.8, 111.7, 106.2, 55.6, 40.0 ppm. R_f = 0.71 (hexane/EtOAc, 3:7). CIMS: *m*/*z* = 369 $[M + H]^+$, 231 and 229 [M − dimedone unit]$^+$. $C_{23}H_{28}O_4$ (368.2): calcd. C 74.97, H 7.66; found C 74.68, H 7.46.

2-Hydroxymethyl-1-phenylprop-2-en-1-one (19a): Yield: 129 mg (20%). Yellow oil. IR (liquid film): ṽ = 3306, 1651, 1447, 1321, 978, 741 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 7.77 (d, *J* = 7.2 Hz, 2 H), 7.58 (m, 1 H), 7.47 (t, *J* = 7.7 Hz, 2 H), 6.17 (s, 1 H), 5.83 (s, 1 H), 4.52 (m, 2 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 198.42, 146.65, 137.75, 132.95, 129.84, 128.74, 127.82, 63.63 ppm. R_f = 0.67 ($CHCl_3$/acetone, 1:1). CIMS: *m*/*z* = 163 $[M + H]^+$. $C_{10}H_{10}O_2$ (162.1): calcd. C 66.65, H 6.71; found C 66.50, H 6.58.

3-Hydroxy-2-hydroxymethyl-1-phenylpropan-1-one (19c): Yield: 100 mg (14%). Yellow oil. IR (liquid film): ṽ = 3400, 1676, 1597, 1449, 1258, 1217, 1041, 963 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 7.96 (d, *J* = 8.2 Hz, 2 H), 7.58 (m, 1 H), 7.47 (td, *J* = 8.7, 2.6 Hz, 2 H), 4.03 (m, 4 H), 3.78 (m, 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 202.19, 136.54, 134.00, 129.24, 129.20, 62.49, 50.75 ppm. R_f = 0.32 ($CHCl_3$/acetone, 1:1). CIMS: *m*/*z* = 181 $[M + H]^+$ 163 $[M + H - H_2O]^+$. $C_{10}H_{12}O_3$ (180.1): calcd. C 66.65, H 6.71; found C 66.00, H 7.61.

3-Hydroxy-2,2-bis(hydroxymethyl)-1-phenylpropan-1-one (19d): Yield: 252 mg (30%). Yellow oil. IR (liquid film): ṽ = 3400, 1674, 1597, 1464, 1234, 1026, 955, 700 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 7.76 (m, 2 H), 7.46 (m, 3 H), 4.06 (br. s, 6 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 207.36, 135.41, 132.76, 130.11, 128.95, 62.14, 51.83 ppm. R_f = 0.28 ($CHCl_3$/acetone, 1:1). CIMS: *m*/*z* = 211 $[M + H]^+$. $C_{11}H_{14}O_4$ (210.1): calcd. C 62.85, H 6.71; found C 63.27, H 7.59.

2-Hydroxymethyl-1-(2-methoxyphenyl)prop-2-en-1-one (20a): Yield: 69 mg (9%). Yellow oil. IR (liquid film): ṽ = 3400, 1663, 1597, 1464, 1248, 1022, 758 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 7.78 (d, *J* = 7.7 Hz, 1 H), 7.50 (t, *J* = 8.3 Hz, 1 H), 7.00 (m, 2 H), 6.12 (s, 1 H), 5.76 (s, 1 H), 4.49 (br. s, 2 H), 3.80 (s, 3 H) ppm. R_f = 0.62 ($CHCl_3$/acetone, 1:1). CIMS: *m*/*z* = 193 $[M + H]^+$. $C_{11}H_{12}O_3$ (192.1): calcd. C 68.74, H 6.29; found C 68.00, H 6.33.

3-Hydroxy-1-(2-methoxyphenyl)propan-1-one (20b): Yellow oil. R_f = 0.55 ($CHCl_3$/acetone, 1:1). CIMS: *m*/*z* = 181 $[M + H]^+$.

3-Hydroxy-2-hydroxymethyl-1-(2-methoxyphenyl)propan-1-one (20c): Yield: 92 mg (11%). Yellow oil. IR (liquid film): ṽ = 3400, 1651, 1455, 1265, 1100, 1025, 800 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 7.44 (m, 2 H), 7.10 (m, 2 H), 3.94 (m, 4 H), 3.88 (s, 3 H), 3.51 (m, 1 H) ppm. R_f = 0.31 ($CHCl_3$/acetone, 1:1). CIMS: *m*/*z* = 211 $[M + H]^+$,193 $[M + H - H_2O]^+$. $C_{11}H_{14}O_4$ (210.1): calcd. C 62.85, H 6.71; found C 62.82, H 6.59.

3-Hydroxy-2,2-bis(hydroxymethyl)-1-(2-methoxyphenyl)propan-1-one (20d): Yield: 134 mg (14%). Yellow oil. IR (liquid film): ṽ = 3400, 1684, 1597, 1456, 1260, 1022, 800 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 7.64 (d, *J* = 7.7 Hz, 1 H), 7.49 (m, 1 H), 6.99 (m, 2 H), 4.08 (m, 6 H), 3.87 (s, 3 H) ppm. R_f = 0.29 ($CHCl_3$/acetone, 1:1). CIMS: *m*/*z* = 241 $[M + H]^+$. $C_{12}H_{16}O_5$ (240.1): calcd. C 59.99, H 6.71; found C 58.39, H 6.89.

1-(2-Chlorophenyl)-2-hydroxymethylprop-2-en-1-one (21a): Yield: 149 mg (19%). Yellow oil. IR (liquid film): ṽ = 3400, 1663, 1591, 1433, 1094, 1053, 980, 756 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 7.41 (m, 2 H), 7.34 (m, 2 H), 6.26 (s, 1 H), 5.75 (s, 1 H), 4.52 (br. s, 2 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 197.50, 147.43, 138.46, 131.50, 131.15, 130.97, 129.77, 129.42, 126.93, 62.01 ppm. R_f = 0.69 ($CHCl_3$/acetone, 1:1). CIMS: *m*/*z* = 197 $[M + H]^+$. $C_{10}H_9ClO_2$ (196.0): calcd. C 61.08, H 4.61; found C 60.79, H 4.57.

1-(2-Chlorophenyl)-3-hydroxypropan-1-one (21b): Yellow oil. IR (liquid film): ṽ = 3400, 1690, 1535, 1413, 1199, 1070, 870, 710 cm^{-1}. R_f = 0.64 ($CHCl_3$/acetone, 1:1). CIMS: *m*/*z* = 185 $[M + H]^+$.

1-(2-Chlorophenyl)-3-hydroxy-2-hydroxymethylpropan-1-one (21c): Yellow oil. R_f = 0.48 ($CHCl_3$/acetone, 1:1). CIMS: *m*/*z* = 215 $[M + H]^+$.

1-(2-Chlorophenyl)-3-hydroxy-2,2-bis(hydroxymethyl)propan-1-one (21d): Yield: 214 mg (22%). Yellow oil. IR (liquid film): ṽ = 3400, 1701, 1591, 1431, 1026, 970, 762 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 7.45 (m, 1 H), 7.36 (m, 3 H), 3.93 (br. s, 6 H) ppm. R_f = 0.44 ($CHCl_3$/acetone, 1:1). CIMS: *m*/*z* = 245 $[M + H]^+$. $C_{11}H_{13}ClO_4$ (244.1): calcd. C 54.00, H 5.36; found C 53.78, H 5.26.

1-(4-Chlorophenyl)-2-hydroxymethylprop-2-en-1-one (22a): Yield: 38 mg (5%). Yellow oil. IR (liquid film): ṽ = 3260, 1649, 1587, 1312, 1094, 1073, 984, 789 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 7.72 (d, *J* = 8.5 Hz, 2 H), 7.45 (d, *J* = 8.5 Hz, 2 H), 6.17 (s, 1 H), 5.80 (s, 1 H), 4.50 (m, 2 H) ppm. R_f = 0.67 ($CHCl_3$/acetone, 1:1). CIMS: *m*/*z* = 197 $[M + H]^+$. $C_{10}H_9ClO_2$ (190.0): calcd. C 61.08, H 4.61; found C 60.52, H 4.66.

1-(4-Chlorophenyl)-3-hydroxypropan-1-one (22b): Yield: 29 mg (4%). Yellow oil. IR (liquid film): ṽ = 3360, 1693, 1589, 1464, 1261, 1093, 820, 719 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 7.92 (d, *J* = 8.5 Hz, 2 H), 7.58 (m, 1 H), 7.47 (d, *J* = 8.6 Hz, 2 H), 4.05 (t, *J* = 5.3 Hz, 2 H), 3.22 (t, *J* = 5.3 Hz, 2 H) ppm. R_f = 0.59 ($CHCl_3$/acetone, 1:1). CIMS: *m*/*z* = 185 $[M + H]^+$, 167 $[M + H - H_2O]^+$. $C_9H_9ClO_2$ (184.0): calcd. C 58.55, H 4.91; found C 58.50, H 4.78.

1-(4-Chlorophenyl)-3-hydroxy-2-hydroxymethylpropan-1-one (22c): Yield: 94 mg (11%). Yellow oil. IR (liquid film): $\tilde{\nu}$ = 3400, 1676, 1589, 1402, 1252, 1093, 1045, 960, 841 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 7.92 (d, *J* = 8.6 Hz, 2 H), 7.47 (d, *J* = 8.6 Hz, 2 H), 4.06 (d, *J* = 7.8 Hz, 4 H), 3.78 (m, 1 H), 2.78 (br. s, 1 H) ppm. R_f = 0.38 ($CHCl_3$/acetone, 1:1). CIMS: *m*/*z* = 215 $[M + H]^+$, 187 $[M + H - H_2O]^+$. $C_{10}H_{11}ClO_3$ (214.0): calcd. C 55.96, H 5.17; found C 56.03, H 5.30.

1-(4-Chlorophenyl)-3-hydroxy-2,2-bis(hydroxymethyl)propan-1-one (22d): Yield: 380 mg (39%). Yellow oil. IR (liquid film): $\tilde{\nu}$ = 3536, 1728, 1678, 1591, 1460, 1280, 1074, 1035, 833, 743 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 7.74 (d, *J* = 8.4 Hz, 2 H), 7.42 (d, *J* = 8.5 Hz, 2 H), 4.04 (s, 6 H) ppm. R_f = 0.31 ($CHCl_3$/acetone, 1:1). ^{13}C NMR ($CDCl_3$): δ = 206.11, 140.86, 138.20, 133.93, 129.35, 58.85, 56.01 ppm. CIMS: *m*/*z* = 245 $[M + H]^+$. $C_{11}H_{13}ClO_4$ (244.1): calcd. C 54.00, H 5.36; found C 54.05, H 5.30.

2-Hydroxymethyl-1-(4-nitrophenyl)prop-2-en-1-one (23a): Yield: 149 mg (18%). Yellow oil. IR (liquid film): $\tilde{\nu}$ = 3526, 1651, 1522, 1354, 988, 739 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 8.28 (d, *J* = 8.7 Hz, 2 H), 7.87 (d, *J* = 8.7 Hz, 2 H), 6.30 (s, 1 H), 5.83 (s, 1 H), 4.53 (br. s, 2 H) ppm. R_f = 0.70 ($CHCl_3$/acetone, 1:1). CIMS: *m*/*z* = 208 $[M + H]^+$. $C_{10}H_9NO_4$ (207.1): calcd. C 57.97, H 4.38; found C 57.52, H 4.56.

3-Hydroxy-1-(4-nitrophenyl)propan-1-one (23b): Yellow oil. R_f = 0.62 ($CHCl_3$/acetone, 1:1). CIMS: *m*/*z* = 196 $[M + H]^+$.

3-Hydroxy-2-hydroxymethyl-1-(4-nitrophenyl)propan-1-one (23c): Yield: 90 mg (10%). Yellow oil. IR (liquid film): $\tilde{\nu}$ = 3400, 1682, 1526, 1350, 1042, 855 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 8.33 (d, *J* = 8.9 Hz, 2 H), 8.12 (d, *J* = 8.9 Hz, 2 H), 4.07 (d, *J* = 5.0 Hz, 4 H), 3.78 (m, 1 H), 2.76 (br. s, 1 H) ppm. R_f = 0.55 ($CHCl_3$/acetone, 1:1). CIMS: *m*/*z* = 226 $[M + H]^+$. $C_{10}H_{11}NO_5$ (225.1): calcd. C 53.33, H 4.92; found C 54.01, H 4.90.

3-Hydroxy-2,2-bis(hydroxymethyl)-1-(4-nitrophenyl)propan-1-one (23d): Yield: 347 mg (34%). Yellow oil. IR (liquid film): $\tilde{\nu}$ = 3484, 1686, 1528, 1350, 1015, 860, 718 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 8.28 (d, *J* = 8.8 Hz, 2 H), 7.85 (d, *J* = 8.3 Hz, 2 H), 3.98 (s, 6 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 204.30, 155.36, 144.96, 130.71, 127.55, 60.31, 54.21 ppm. R_f = 0.32 ($CHCl_3$/acetone, 1:1). CIMS: *m*/*z* = 256 $[M + H]^+$. $C_{11}H_{13}NO_6$ (255.1): calcd. C 51.77, H 5.13; found C 51.65, H 5.37.

1-(3-Acetylphenyl)-2-hydroxymethylprop-2-en-1-one (24a): Yield: 98 mg (12%). Yellow oil. IR (liquid film): $\tilde{\nu}$ = 3450, 1700, 1651, 1597, 1360, 1259, 1022, 785 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 8.30 (s, 1 H), 8.14 (d, *J* = 7.7 Hz, 1 H), 7.93 (d, *J* = 6.9 Hz, 1 H), 7.57 (d, *J* = 7.7 Hz, 1 H), 6.22 (s, 1 H), 5.81 (s, 1 H), 4.53 (s, 2 H), 2.64 (s, 3 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 197.66, 146.64, 138.23, 137.59, 134.01, 132.30, 129.55, 129.23, 128.25, 63.25, 26.12 ppm. R_f = 0.68 ($CHCl_3$/acetone, 1:1). CIMS: *m*/*z* = 205 $[M + H]^+$. $C_{12}H_{12}O_3$ (204.1): calcd. C 70.57, H 5.92; found C 70.01, H 5.76.

1-(3-Acetylphenyl)-3-hydroxypropan-1-one (24b): Yield: 138 mg (18%). Yellow oil. IR (liquid film): $\tilde{\nu}$ = 3354, 1680, 1668, 1597, 1360, 1197, 1055, 787 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 8.45 (s, 1 H), 8.10 (d, *J* = 7.7 Hz, 2 H), 7.53 (m, 1 H), 4.00 (t, *J* = 5.36 Hz, 2 H), 3.25 (m, 2 H), 2.59 (s, 3 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 200.03, 197.59, 137.91, 137.45, 133.27, 132.64, 129.57, 128.20, 58.32, 41.1, 27.1 ppm. R_f = 0.57 ($CHCl_3$/acetone, 1:1). CIMS: *m*/*z* = 193 $[M + H]^+$, 175 $[M + H - H_2O]^+$. $C_{11}H_{12}O_3$ (192.1): calcd. C 68.74, H 6.29; found C 68.03, H 6.28.

1-(3-Acetylphenyl)-3-hydroxy-2-hydroxymethylpropan-1-one (24c): Yield: 124 mg (14%). Yellow oil. IR (liquid film): $\tilde{\nu}$ = 3400, 1682, 1597, 1361, 1200, 1047, 816 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 8.39 (s, 1 H), 8.03 (m, 2 H), 7.46 (t, *J* = 7.7 Hz, 1 H), 3.91 (m, 4 H), 3.80 (m, 1 H), 2.52 (s, 3 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 202.33, 198.12, 137.82, 137.23, 133.34, 133.14, 129.66, 128.55, 62.24, 51.36, 27.10 ppm. R_f = 0.38 ($CHCl_3$/acetone, 1:1). CIMS: *m*/*z* = 223 $[M + H]^+$, 205 $[M + H - H_2O]^+$. $C_{12}H_{14}O_4$ (222.1): calcd. C 64.85, H 6.35; found C 65.00, H 6.48.

1-(3-Acetylphenyl)-3-hydroxy-2,2-bis(hydroxymethyl)propan-1-one (24d): Yield: 272 mg (27%). Yellow oil. IR (liquid film): $\tilde{\nu}$ = 3400, 1685, 1597, 1427, 1362, 1211, 1022, 687 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 8.31 (s, 1 H), 8.06 (d, *J* = 7.4 Hz, 1 H), 7.93 (d, *J* = 7.5 Hz, 1 H), 7.53 (t, *J* = 7.6 Hz, 1 H), 4.02 (s, 6 H), 2.62 (s, 3 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 207.59, 198.28, 133.11, 131.96, 131.18, 129.65, 127.36, 64.58, 50.83, 23.06 ppm. R_f = 0.29 ($CHCl_3$/acetone, 1:1). CIMS: *m*/*z* = 253 $[M + H]^+$. $C_{13}H_{16}O_5$ (252.1): calcd. C 61.90, H 6.39; found C 61.65, H 6.30.

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