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Efficient Tandem Morita–Baylis–Hillman/Double Cross-Aldol Reaction between Cyclic Enones and Formaldehyde Promoted by *N*-Methylpyrrolidine

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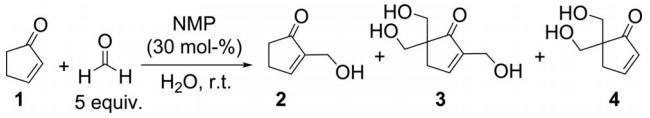
The Lewis base *N*-methylpyrrolidine acts in water as an efficient promoter of tandem reactions between 2 cyclopenten-1-one and aqueous formaldehyde. The reaction pathway includes, as consecutive independent steps, a MBH reaction and a double cross-aldol reaction to furnish the new 2,5,5-tris(hydroxymethyl)-2-cyclopenten-1-one in excellent yield. A range of cyclic enones and 4-nitrobenzaldehyde undergo the tandem reaction similarly. The reaction mechanism was also investigated.

Introduction

The Morita–Baylis–Hillman (MBH) and aldol addition reactions furnish important molecules with aldol and/or allylic alcohol motifs.[1,2] The development of asymmetric methodologies from classical variants using small-molecule organocatalysts, which display several advantages over metal catalysts including a lower toxicity, tolerance to water and air, low cost and accessibility, and operational simplicity, are of interest to the pharmaceutical industry.[3] The concept of the organocatalytic domino reaction consists of a transformation in which conversion of the starting materials triggers production of a transiently formed product that is used as a substrate for the next reaction, which, upon completion, affords stable final products. The tandem reaction notion becomes more appealing because it offers the possibility of enlarging molecular complexity with economy of reagent consumption and purification.[4] Thus far, a number of two-step domino reactions have been reported.[5] Sequences that include the MBH reaction as an independent cycle have been explored,[6] and important natural products such as chromenes, coumarins,[6a,6f] and tetrahydroxanthones[6b] have been obtained in good yields using such approaches.

In a prior stage of our work we investigated the direct hydroxymethylation of cyclopentenone with 36% HCHO in water promoted efficiently by *N*-methylpyrrolidine/Ba-$(OH)_2$ keeping in mind the prospect of further synthetic application of MBH derivative **2**.[7] We observed the emergence of new products **3** and **4** from the reaction mixture along with previously reported **2** (Scheme 1). The production of abnormal products using MBH conditions with different types of alkenes, electrophiles, catalysts, and solvents has been observed by several groups.[8]



Scheme 1. Tandem MBH–cross-aldol reaction.

The formation of aldol-type derivatives of cyclic enones has been reported. These types of products have been characterized and their formation found often to be independent of the MBH pathways activated by specific reaction conditions.[9] Notably, the polyol cyclopentenone structural motif is frequently found in biologically active substances such as antibiotics and antitumor agents and represents an excellent target opportunity to develop a new diastereo- and enantioselective route to this important class of compounds.[7] We envisioned an efficient, cheap, and environmentally safe reaction based on a domino MBH–cross-aldol pathway to prepare compound **3**. We report here initial studies into the application of this domino reaction as a means to produce **3** in optimized yields; details disclosed also provide insight into the reaction mechanism.

Results and Discussion

HPLC Optimization Studies

Reaction catalyst, starting solvent, and the amount of 36% HCHO were evaluated on the basis of product formation as realized by HPLC, and the results are outlined in

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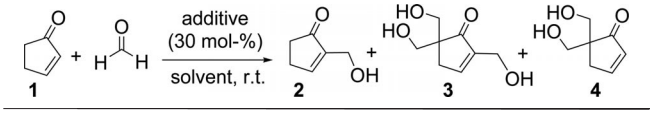
Table 1. Based on recent reports of the MBH reaction mechanism, we employed DMSO as a polar aprotic solvent and CH_3OH and H_2O as protic media; the expectation was that an acceleration of the reaction would result due to stabilization of the ionic transition states or promotion of a proton-transfer step.[10] Barbas and co-workers as well as Janda and co-workers and various other authors have described H_2O as an efficient medium for direct aldol reactions.[11] DMSO has been reported to favor cross-aldol asymmetric hydroxymethylation.[11d] Low-costing commercially available compounds such as the Lewis base *N*-methylpyrrolidine (NMP)[12a] and the inorganic base $Ba(OH)_2$[12b] at 30 mol-% were selected among others to promote the reaction. Both additives promote the reaction depicted in Table 1 and promote the formation of compounds **2** and **3**; addition of NMP allows formation of **4**. The use of 5 equiv. of 36% HCHO increases the yield of **3**, whereas **2** (MBH derivative) is the major product when 1.2 equiv. of aldehyde is used. Superior yields of **3** were achieved in H_2O, and NMP showed better reaction-promoting activity than $Ba(OH)_2$ (Table 1, Entry 14 vs. 11). In the case of $Ba(OH)_2$, precipitate formation was observed, which might be due to the insolubility of its microcrystalline structure.[12b] The low yields of compound **3** observed in DMSO and CH_3OH reflect the potential resistance to product formation in these solvents. HPLC analyses revealed the optimal conditions for reaction of **1** and 36% HCHO to be: NMP (30 mol-%), HCHO (5 equiv.), and H_2O as the solvent.

Table 1. HPLC screening results.



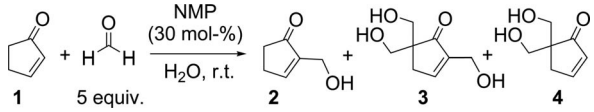
Entry[a]	Additive	HCHO [equiv.]	*t* [min]	Yield [%][b] 2	3	4	1
			CH_3OH				
1	$Ba(OH)_2$[c]	10	20	1	58.7	–	0.6
2	$Ba(OH)_2$[c]	5	40	n.d.	27.8	–	n.d.
3	$Ba(OH)_2$[c]	1.2	40	23	6.4	–	3.5
4	NMP	5	4.5[d]	31.4	50	5	11.5
5	NMP	1.2	15[d]	41	2	5	38
			DMSO				
6	$Ba(OH)_2$[c]	5	55	0.63	44.2	1.4	1.2
7	$Ba(OH)_2$[c]	1.2	20	2.3	1.8	12.8	19
8	NMP	5	24[d]	12.3	6.4	27.3	43.4
9	NMP	5	20[e]	8	40.7	33.3	5.2
10	NMP	1.2	4[d]	2.8	9.3	1.8	38
			H_2O				
11	$Ba(OH)_2$[c]	5	40	0.7	71.4	–	1.7
12	$Ba(OH)_2$[c]	1.2	40	n.d.	29	–	n.d.
13	NMP	5	15	27	56	11	4
14	NMP	5	45	2	85	10	1
15	NMP	1.2	45	23.4	22.5	26.6	14.6
16	NMP	1.2	2.5[d]	25	29	31.6	14

[a] Reaction conditions: **1** (10.5 μL, 0.12 mmol), 36% HCHO (1.2 or 5 equiv.; 11 μL, 0.144 mmol or 46 μL, 0.580 mmol) and NMP (3.87 μL, 0.036 mmol, 30 mol-%) in different solvents (0.250 mL) at r.t. [b] Determined by HPLC; n.d. = not determined. [c] Precipitate formation. [d] Hours. [e] Days.

Preparative Synthetic Experiments

We next performed several preparative synthetic experiments to verify the optimized reaction conditions identified by using HPLC to generate **3** (Table 1, Entries 11 and 14); the resulting data is depicted in Table 2. The best isolated yields of **3** were attained by using NMP as a reaction promoter (Table 2, Entries 6 and 7). Efforts to optimize the reaction conditions with $Ba(OH)_2$ as the catalyst were unsuccessful, possibly due to the formation of a precipitate (Table 2, Entries 1–5). Interestingly, after 15 min, TLC analysis of the reaction showed the presence of **2** together with unconsumed **1** and a light spot of a more-polar product with an R_f value characteristic of **3**. The spot representing compound **2** was imperceptible, whereas the spot representative of **3** became stronger after a reaction time of 1 h. When the reaction was complete, the spot for **3** appeared to be unique. Apparently, the reaction leading to **3** was carried out under the catalytic action of NMP (30 mol-%) in water and was a consequence of the formation of **2**.

Table 2. Examples of preparative syntheses of **3** and **4** based on HPLC optimized conditions.[a]



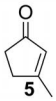
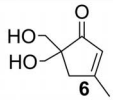
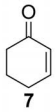
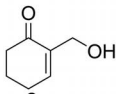
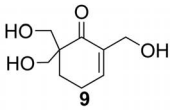
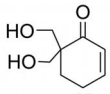
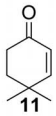
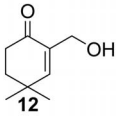
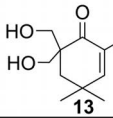
Entry	Additive	HCHO [equiv.]	**1** [mg]	*t* [min]	Yield [%][b] 2	3	4
1	$Ba(OH)_2$[c]	5	100	40	–	66	–
2	$Ba(OH)_2$[c]	5	200	80	–	63	–
3	$Ba(OH)_2$[c]	5	100	35	–	64	–
4	$Ba(OH)_2$[c]	5	80	240	–	58	–
5	$Ba(OH)_2$[c,d]	10	100	110	–	52	–
6	NMP	5	300	150	–	91	2
7	NMP	5	100	110	–	89	6
8	NMP	5	400	90[e]	30	46	3
9	NMP	1.2	200	230[e]	42	6	7

[a] Reaction conditions: 36% HCHO (5 equiv.) and additive (30 mol-%) in H_2O at r.t. [b] Isolated yield. [c] Precipitate formation increased with time. [d] CH_3OH was used as solvent. [e] Hours.

Scope of MBH and Tandem MBH–Aldol Reactions to Other Cyclic Enones

The next step was to explore the reaction scope with other cyclic enones (Table 3). Enones **5**, **7**, and **11**[9e] were found to participate in the reaction in H_2O or H_2O/CH_3OH (5:1) in a manner identical to that for the reaction of **1**. Bisaldol derivative **6** (Table 3, Entry 1) and MBH–aldol derivatives **9** and **13** (Table 3, Entries 4, 5, and 7) were obtained in good yields. A better yield of **9** was obtained by

Table 3. MBH and MBH–aldol reactions with formaldehyde and other cyclic enones.

Entry[a]	Substrate	*t* [h]	Identified products	Isolated yield [%]
1	 **5**	62	 **6**	58
2	**5**	130	**6**	45
3[b]	 **7**	24	 **8**	89
4	**7**	24	**8**	7
			 **9**	65
			 **10**	21
5[c]	**7**	110	**8**	17
			9	50.5
			10	30
6[d]	 **11**	120	 **12**	42
7	**11**	120	**12**	9
			 **13**	50

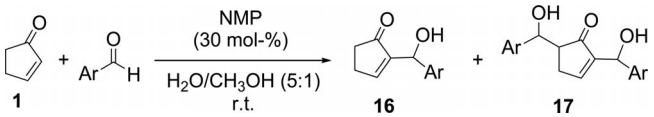
[a] Substrate (200 mg), 36% HCHO (5 equiv.), NMP (30 mol-%), and H_2O/CH_3OH (5:1) at r.t. [b] Substrate (100 mg), 36% HCHO (1.2 equiv.), NMP (5 mol-%)/$Ba(OH)_2$ (1.5 mol-%) as catalytic system at 0 °C. [c] Substrate (100 mg), 36% HCHO (5 equiv.), NMP (30 mol-%) in H_2O at r.t. [d] 36% HCHO (1.2 equiv.) and NMP (15 mol-%)/$Ba(OH)_2$ (7.5 mol-%).

using H_2O/CH_3OH (5:1) as the solvent (Table 3, Entry 4 vs. 5). Respective MBH derivatives **8** and **12** were isolated in very low yield (Table 3, Entries 4, 5, and 7) when an excess amount of formaldehyde was used. When 1.2 equiv. of 36% HCHO was employed, products **8** and **12** (Table 3, Entries 3 and 6) were obtained in high (89%) and moderate (42%) yield, respectively. The bisaldol hydroxymethyl derivative of **7** (i.e., **10**) was isolated in fairly good yield (21–30%; Table 3, Entries 4 and 5). The MBH reaction and the tandem MBH–double aldol reaction with disubstituted enone **11** were sluggish most likely due to steric factors.[9d] The bisaldol analogue of **11** was not isolated, whereas the corresponding analog of **5** (i.e., **6**; Table 3, Entry 1) was attained in good yield (58%). Substrate **5** cannot undergo the 1,4-addition step of the MBH pathway owing to steric hindrance at the β-position of the α,β-unsaturated 3-methyl-2-cyclopentenone ring. Accordingly, substrate **5** participates only in the aldol reaction route.[9c–9e]

Tandem MBH–Aldol Reaction with 1 and Representative Aryl Aldehydes

The scope of the reaction was also investigated with aryl aldehydes. Complex reaction mixtures were observed and only half of the initial amount of aldehyde was recovered when benzaldehyde (5 equiv.) and 2-furaldehyde (5 equiv.) were used (Table 4, Entries 2 and 8). The reactions for which an excess amount of 4-methoxybenzaldehyde and 2-naphthaldehyde was employed were sluggish, although MBH derivatives **16**-iv and **16**-ix were isolated in good yield (Table 4, Entries 4 and 9). When 1.2 equiv. of aldehyde was used, MBH products **16**-i, **16**-iii, **16**-v, and **16**-vii were formed in very good yields (Table 4, Entries 1, 3, 5, and 7). When the active electrophile 4-nitrobenzaldehyde was used in excess amount, MBH–aldol product **17**-vi was isolated in 20% yield and the MBH derivative **16**-vi was formed in 31% yield after a 5-h reaction time (Table 4, Entry 6).[9b]

Table 4. Scope of MBH and tandem MBH–aldol reactions between **1** and representative aldehydes.[a]



1 **16** **17**

Entry	Aldehyde	ArCHO [equiv.]	*t* [h]	Yield [%][b] **16**	**17**	**1**
1	benzaldehyde	1.2[c,d]	47	**16**-i, 73	–	–
2	benzaldehyde	5	91	–[e]	–[e]	42
3	4-methoxybenzaldehyde	1.2[c,d]	50	**16**-iii, 83	–	–
4	4-methoxybenzaldehyde	5	133	**16**-iv, 73	–	20
5	4-nitrobenzaldehyde	1.2[c]	4	**16**-v, 65	–	–
6	4-nitrobenzaldehyde	3	5	**16**-vi, 31	**17**-vi, 20	22
7	2-furaldehyde	1.2	10	**16**-vii, 77	–	–
8	2-furaldehyde	5	91	–[e]	–[e]	58
9	2-naphthaldehyde	2.5	14	**16**-ix, 67	–	15
10	2-naphthaldehyde	1.2[c]	20	**16**-x, 45		10

[a] Reaction conditions: **1** (100 mg, 1.22 mmol) and NMP (30 mol-%) at r.t. [b] Isolated yield. [c] CH_3OH/CH_2Cl_2 (3:1) was employed. [d] Reaction was performed at 0 °C. [e] Unidentified mixture was observed.

HPLC and NMR Studies of Tandem MBH–Aldol Reaction Mechanism

The reaction depicted in Table 1 was monitored with HPLC to understand better the phenomenon we had in our hands. The chromatograms of the reaction mixtures taken at reaction times of 15 and 45 min are shown in Figure 1. After a reaction time of 15 min (Figure 1, top) the existence of a mixture of species **2** (MBH derivative), **3** (MBH–aldol product), and a small amount of **4** (aldol derivative) is apparent. Compound **4** is formed readily from the starting products together with considerable fractions of **2** and **3**. The amount of **4** was found not to vary during the course of the reaction (see the area numbers). After a reaction time of 45 min (Figure 1, bottom) the peak representative of **2** was found to almost disappear although the peak representative of **3** was found to increase. Thus, the reaction might progress with **2** as the principal precursor to **3**. The quantitative data is listed in Table 1, Entries 13 and 14. An identical pattern of behavior was observed by following the reaction with ^{1}H NMR spectroscopy (Figure S8, Supporting Information).

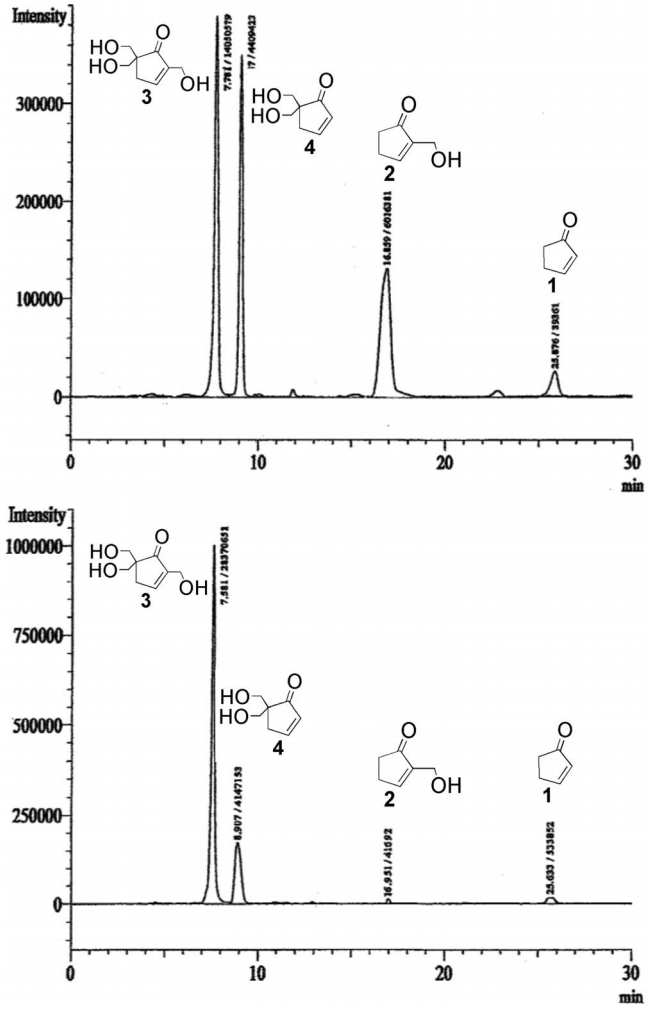
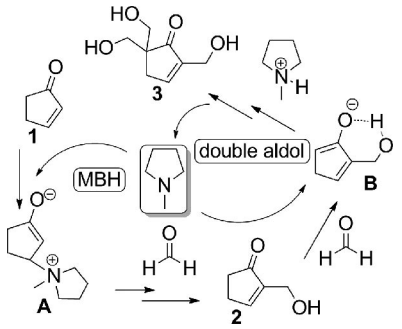


Figure 1. HPLC analyses of the reaction between **1** and formaldehyde (5 equiv.) in H_2O at r.t. catalyzed by NMP (30-mol-%) after a reaction time of 15 (top) and 45 min (bottom).

The combined information allows us to propose a plausible mechanism for the reaction between HCHO and **1** (Scheme 2). The MBH pathway[10] is catalyzed by the nucleophilic base NMP, which undergoes initial 1,4-addition to the enone, thereby producing intermediate **A**, the enolate of which reacts with HCHO to afford MBH product **2**. Intermediate dienolate **B**[9d,9e] forms under moderately basic conditions (NMP pK = 10.18)[13a] and is stabilized intramolecularly by the adjacent hydroxy group.[13b] From dienolate **B** final product **3** is then formed following double aldol reaction with HCHO. Notably, the MBH monoaldol product has never been isolated under our experimental conditions. The catalyst may therefore play a dual role; NMP activates the first cycle of formation for the MBH adduct, which serves as the substrate for a second one in moderately basic aqueous solution. 4-Nitrobezaldehyde is a good electrophile and might enter into an aldol condensation process too.



Scheme 2. Plausible mechanism of domino MBH/double cross-aldol reaction.

Conclusions

In conclusion, a unique reaction between 2-cyclopenten-1-one (**1**) and formaldehyde, promoted by the simple catalyst NMP in water as a medium, was accomplished, and **3**, a new polyhydroxymethyl derivative of cyclopentenone **1**, was isolated in 91% yield. Other cyclic enones were found to behave similarly. The reaction tentatively described as a MBH–cross-aldol tandem reaction creates three new C–C bonds in the polyhydroxymethyl derivative, one of which is a quaternary C center. The reaction scope with **1** was extended to include aryl aldehydes. However, of the aryl aldehydes investigated, only 4-nitrobenzaldehyde was found to react with **1** in the desired fashion. Further applications of the methodology, including an asymmetric version, are currently under study.

Experimental Section

General Remarks: Dichloromethane (CH_2Cl_2), ethyl ether (Et_2O), and methanol (CH_3OH) were freshly distilled prior to use. Ethyl acetate (EtOAc) was distilled from potassium carbonate. The water used for HPLC studies was Milli-Q grade and the acetonitrile was HPLC grade. Preparative thin-layer chromatography plates were prepared with silica gel 60 GF254 Merck (Ref. 1.07730.1000), whereas flash chromatography was carried out on silica gel 60M

purchased from MN (Ref. 815381). Reaction mixtures were analyzed by TLC using ALUGRAM SIL G/UV254 from MN (Ref. 818133, silica gel 60), and visualization of TLC spots was effected by using UV and ninhydrin (2,2-dihydroxyindane-1,3-dione) or phosphomolybdic acid (PMA) staining. The additives used on TLC and HPLC screening studies were purchased from Aldrich, Merck, and Fluka and used without further purification. 36% HCHO with methanol as a stabilizer was purchased from Fluka, and the 2-cyclopenten-1-one, (**1**) 2-cyclohexen-1-one (**7**), 3-methyl-2-cyclopenten-1-one (**5**), and 4,4 dimethyl-2-cyclohexen-1-one (**11**) were purchased from Aldrich. *N*-Methylpyrrolidine, 4-nitrobenzaldehyde, and 2-naphthaldehyde were obtained from Aldrich and used as received. Benzaldehyde, 4-methoxybenzaldehyde, and furan-2-carbaldehyde were used after purification by distillation under vacuum. NMR spectra were recorded with a Bruker AMX 400 using $CDCl_3$ and D_2O as solvents. HPLC studies were done with a Shimadzu Prominence system apparatus using a C_{18} Kromasil 100 5 μm column, 250 × 4.6 mm and 5% CH_3CN in Milli-Q water as the mobile phase. A SPD-20A UV/Vis detector was used with sensitivity to the limit [Noise level 0.5 × 10(–5) AU], wide linearity (2.5 AU) and wavelength range from 190 to 700 nm. IR spectra were obtained with a Shimadzu FTIR-8400S spectrometer and GC–MS spectra with a Shimadzu GC 2010 gas chromatograph combined with GC–MS-QP 201008 mass spectrometer. GC program: column oven temperature: 50.0 °C; injection temperature: 250.00 °C; pressure: 77.9 kPa, total flow: 17.7 mL/min; column flow: 1.34 mL/min; linear velocity: 42.0 cm/sec; purge flow: 3.0 mL/min split ratio: 10.0, high press. inj. pressure: 100.0 kPa, high press. inj. time: 1.00 min. GC–MS program: start time: 3.00 min; end time: 50.00 min; event time: 0.50 s; scan speed: 666; start: *m*/*z* = 40.00; end: *m*/*z* = 350.00.

General Procedure for the MBH–Cross-Aldol Reaction with Different Additives: Reactions were performed with a homemade carousel reaction station apparatus in appropriately sized reaction flasks by using 2-cyclopenten-1-one (**1**; 10 mg, 10.5 μL, 0.12 mmol) and aqueous formaldehyde (11 μL, 0.144 mmol OR 46 μL, 0.58 mmol) in the solvent (0.250 mL). For every reaction, catalytic amount (30 mol-%) of each respective additive was employed. The reactions were allowed to proceed at room temperature and reaction times normally varied from minutes to 2–3 h; some reactions were carried out for 11–48 h, as the major amount of substrate was found to disappear as revealed by TLC (EtOAc/hexane, 9:1).

General Procedures for HPLC Screening of the MBH–Cross-Aldol Reaction between 2-Cyclopenten-1-one and 36% HCHO with Different Additives: These experiments were performed on the basis of prior TLC results obtained for each reaction. From each reaction was taken 10 μL of the reaction solution, and each aliquot was diluted in 1 mL H_2O (Milli-Q)/acetonitrile (95:5). From these solutions, 20 μL was injected on the Shimadzu Prominence system apparatus with the C_{18} Kromasil 100 5 μm column, 250 × 4.6 mm and 5% of CH_3CN in water as a mobile phase was used. The detection of the analyzed samples took place at 206 nm. The flow rate employed was 0.7 mL/min. Under these experimental conditions, the retention time (t_R) observed for BH product **2** was between 17 and 18.5 min. HPLC retention times for reactions using 2-cyclopenten-1-one (**1**) were between 23 and 24.5 min depending of the column equilibrium and temperature. The retention times (t_R) for compounds **3** and **4** were between 7.3 and 8.0 min and between 8.50 and 9.40 min, respectively. The column temperature was approximately 25 °C. To obtain reproducible results with HPLC, daily "back flushes" were performed. The daily work proceeded for slightly longer than 10 h and at the finish of each work day the column was cleaned with the same solvent gradient used to do reaction analyses. The time between each injection was 10 to 15 min. The routine sample calculations were based on the comparison of peak areas of BH product **2** and **1**, with external standard peak area from previously obtained calibration curves at equal working conditions. Six samples with concentrations ranging from 0.0036 to 0.0001 mg for **1** were used, whereas the seven samples for the BH product ranged in concentration between 0.005 and 0.0003 mg. Also, six samples of compound **3** and seven of compound **4** were employed with concentrations from 0.00098 to 0.0071 mg and from 0.00002 to 0.0051 mg, respectively. Each calibration curve was obtained based of the ratio area of respective peak and concentration on the sample.

General Procedure for the MBH–Cross-Aldol Reaction between 2-Cyclopenten-1-one and 36% HCHO for the Preparation of Compounds 3 and 4: To a stirred mixture of *N*-methylpyrrolidine (38.7 μL, 30 mol-%, 0.363 mmol) in H_2O (2.5 mL) was added sequentially 36% HCHO (0.5 mL, 6.1 mmol) and 2-cyclopenten-1-one (100 mg, 104.2 μL, 1.21 mmol). The resulting mixture was stirred at room temperature. Upon completion or after the time indicated in Table 2 (Entry 6), the reaction was quenched with 1 N HCl until pH 3. To the mixture was added $NaHCO_3$ to achieve a pH of about 7, and samples were then concentrated under reduced pressure. The resulting residue was taken up in CH_3OH (1 mL) and purified by preparative silica gel TLC eluted with EtOAc/hexane/CH_3OH (9.0:0.75:0.25). 2,5,5-Tris(hydroxymethyl)-2-cyclopenten-1-one (**3**; 190 mg, 91% yield) and 5,5-bis(hydroxymethyl)-2-cyclopenten-1-one (**4**; 3.5 mg, 2% yield) were obtained as colorless oils. The spectral characteristics of known compound **2** (Table 2, Entry 8) were found to be in agreement with previously reported data.

2-(Hydroxymethyl)-2-cyclopenten-1-one (2):[14] Translucent crystals, R_f = 0.36 (silica; EtOAc/hexane, 9:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.259–2.298 (t, *J* = 8 Hz, 1 H), 2.458–2.466 (m, 2 H), 2.482–2.651, (m, 2 H), 4.383–4.403 (d, *J* = 8 Hz, 2 H), 7.535, (m, 1 H) ppm. ^{13}C NMR (400 MHz, $CDCl_3$): δ = 26.86, 35.01, 57.57, 144.91, 159.05, 209.98 ppm.

2,5,5-Tris(hydroxymethyl)-2-cyclopenten-1-one (3): Colorless oil, R_f = 0.04 (silica; EtOAc/hexane, 9:1). IR (film, KBr/CH_3OH): $\tilde{\nu}$ = 3373, 2943, 2518, 1693, 1636, 1448, 1423, 1113, 1030, 663 cm^{-1}. ^{1}H NMR (400 MHz, D_2O, 25 °C): δ = 2.733–2.749 (m, 2 H, $C^3HC^4H_2C^5$), 3.578–3.606 (d, *J* = 11.2 Hz, 2 H, C^5CH_2OH), 3.695–3.723, (d, *J* = 11.2 Hz, 2 H, C^5CH_2OH), 4.252–4.264 (m, 2 H, C^2CH_2OH), 7.866–7.873, (m, 1 H, $C^2C^3HC^4H_2$) ppm. ^{13}C NMR (400 MHz, D_2O): δ = 34.522 ($C^3HC^4H_2C^5$), 55.305 (C^2CH_2OH), 56.253 [$C{=}OC^5(CH_2)_2$], 62.997 [$C^5(CH_2)_2(OH)_2$], 144.036 ($C{=}OC^2CH_2$), 163.855 ($C^2C^3HC^4H_2$), 213.340 (C=O) ppm. The spectroscopic data were assigned on the basis of 2D HMQC and 2D COSY NMR spectroscopy. GC–MS: *m*/*z* = 172 [M].

5,5-Bis(hydroxymethyl)-2-cyclopenten-1-one (4): Colorless oil, R_f = 0.08 (silica; EtOAc/hexane, 9:1). IR (film, KBr/CH_2Cl_2): $\tilde{\nu}$ = 3356, 2944, 2518, 1693, 1636, 1448, 1419, 1115, 1028, 659 cm^{-1}. ^{1}H NMR (400 MHz, D_2O, 25 °C): δ = 2.802–2.814 (t, 2 H, $C^3HC^4H_2C^5$), 3.574–3.602 (d, *J* = 11.2 Hz, 2 H, C^5CH_2OH), 3.686–3.714 (d, *J* = 11.2 Hz, 2 H, C^5CH_2OH), 6.238–6.263 [m, 1 H, ($C{=}OC^2HC^3H$)], 8.064–8.092 (m, 1 H, $C^2HC^3HC^4H_2$) ppm. ^{13}C NMR (400 MHz, D_2O): δ = 37.253 ($C^3HC^4H_2C^5$), 56.071 [$C{=}OC^5(CH_2)_2$], 63.718 [$C^5(CH_2)_2(OH)_2$], 133.904 ($C{=}OC^2CH_2$), 170.764 ($C^2C^3HC^4H_2$), 216.815 (C=O) ppm. The spectroscopic data were assigned on the basis of 2D HMQC and 2D COSY NMR spectroscopy. GC–MS: *m*/*z* = 142 [M].

General Procedure for the MBH–Cross-Aldol Reaction between 3-Methyl-2-cyclopenten-1-one (5), 2-Cyclohexen-1-one (7), or 4,4-Di-

methyl-2-cyclohexen-1-one (11) and 36% HCHO for the Preparation of Compound 6, 9, 10, and 13: To a stirred mixture of *N*-methylpyrrolidine (30 mol-%; 64.86 μL, 0.624 mmol for **5** and **7**; 49.8 μL, 0.480 mmol for **11**) in H_2O (5.0 mL for **5** and **7**) or H_2O/CH_3OH (5:1 for **11**) was added sequentially 36% HCHO (0.8 mL, 10.4 mmol for **5** and **7**; 0.62 mL, 8 mmol for **11**) and 0.205 mL (2.1 mmol) of 3-methyl-2-cyclopenten-1-one (**5**) or 2-cyclohexen-1-one (**7**) or 4,4-dimethyl-2-cyclohexen-1-one (**11**, 0.22 mL, 1.61 mmol). The resulting mixture was stirred at room temperature. Upon completion or after the time indicated in Table 3, the reactions were quenched with brine (100 mL) and then extracted 4× with EtOAc/hexane (9:1). The organic layers were dried with anhydrous $MgSO_4$ and concentrated under reduced pressure. The reaction mixture of compound **5** was quenched with 1 N HCl until pH 3. To the mixture was added $NaHCO_3$ to a pH of about 7, and the mixture was concentrated under reduced pressure. The resulting residue was taken up in CH_3OH (1 mL) and purified by preparative silica gel TLC (EtOAc/hexane, 9:1). The concentrated residues of the reaction mixtures of **7** and **11** also were purified by silica gel TLC (EtOAc/hexane, 4:1). Compounds **6**, **9**, **10**, and **13** were obtained as oils in the following yields: **6**, 58% (190 mg); **9**, 65% (260 mg); **10**, 21% (70 mg); and **13**, 50% (180 mg). The corresponding known BH products of **7** and **11**, compounds **8** and **12**, were obtained in the following yields: **8**, 7% (20 mg) and **12**, 9% (22 mg). The spectral characteristics of known compounds **8** and **12** were found to be in agreement with previously reported data.

5,5-Bis[(hydroxy(3-methyl)methyl)]-2-cyclopenten-1-one (6): Colorless oil, R_f = 0.13 (silica; EtOAc/hexane, 2:1). IR (film, KBr/CH_2Cl_2): $\tilde{\nu}$ = 3455, 3053, 2986, 2373, 2308, 1684, 1616, 1421, 1265, 1026, 895, 744, 704 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, TMS, 25 °C): δ = 2.18 (s, 3 H, C^3CH_3), 2.310–2.339 {t, J = 5.6 Hz, 2 H, [$C^5(CH_2)_2(OH)_2$]}, 2.542 (s, 2 H, $C^3HC^4H_2C^5$), 3.766–3.780 {d, J = 5.6 Hz, 4 H, [$C^5(CH_2OH)_2$]}, 5.906 (s, J = 1.6 Hz, 1 H, $C{=}OC^2HC^3$) ppm. ^{13}C NMR (400 MHz, $CDCl_3$, TMS, 25 °C): δ = 19.825 (C^3CH_3), 40.860 ($C^3HC^4H_2C^5$), 55.699 [$C{=}OC^5(CH_2)_2$], 64.679 [$C^5(CH_2)_2(OH)_2$], 129.354 ($C{=}OC^2HC^3$), 180.521 ($C^2HC^3CH_3$), 213.050 (C=O) ppm. The spectroscopic data were assigned on the basis of 2D HMQC and 2D COSY NMR spectroscopy. GC–MS: m/z = 156 [M].

2-(Hydroxymethyl)-2-cyclohexen-1-one (8):[14b,14c,15] White powder, R_f = 0.28 (EtOAc/hexane, 1:1). ^1H NMR (400 MHz, $CDCl_3$): δ = 1.970–2.034 (m, J = 6.0 Hz, 2 H), 2.370–2.411 (m, 4 H), 2.424 (t, 1 H), 4.222–4.241 (d, J = 5.2 Hz, 2 H), 6.920–6.940 (t, J = 6.0 Hz, 1 H) ppm. ^{13}C NMR (400 MHz, $CDCl_3$): δ = 22.81, 25.72, 38.31, 62.17, 138.35, 147.10, 200.78 ppm.

2,6,6-Tris(hydroxymethyl)-2-cyclohexen-1-one (9): Colorless oil, R_f = 0.055 (silica; EtOAc/hexane, 2:1). IR (film, KBr/CH_2Cl_2): $\tilde{\nu}$ = 3344, 2944, 2831, 2521, 2364, 2044, 1664, 1453, 1415, 1113, 1032, 659 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, TMS, 25 °C): δ = 2.043–2.074 (t, 2 H, $C^4HC^5H_2C^6$), 2.527–2.568 (m, 2 H, $C^3C^4H_2C^5H_2$), 3.613–3.642 (d, J = 11.6 Hz, 2 H, C^6CH_2OH), 3.834–3.863 (d, J = 11.6 Hz, 2 H, C^6CH_2OH), 4.200, (s, 2 H, C^2CH_2OH), 7.144–7.164 (t, J = 4 Hz 1 H, $C^2C^3HC^4H_2$) ppm. ^{13}C NMR (400 MHz, TMS, $CDCl_3$, 25 °C): δ = 22.246 ($C^3HC^4H_2C^5$), 25.566 ($C^4H_2C^5H_2C^6$), 52.159 [$C{=}OC^6(CH_2)_2$], 59.492 ($C^2CH_2OH)_2$, 62.795 [$C^6(CH_2)_2(OH)_2$], 136.660 ($C{=}OC^2CH_2OH$), 150.569 ($C^2C^3HC^4H_2$), 203.420 (C=O) ppm. Spectral data were assigned on the basis of 2D HMQC and 2D COSY NMR spectroscopy. GC–MS: m/z = 185 [M – 1].

6,6-Bis(hydroxymethyl)-2-cyclohexen-1-one (10): Colorless oil, R_f = 0.14 (silica; EtOAc/hexane, 2:1). IR (film, KBr/CH_2Cl_2): $\tilde{\nu}$ = 3053, 2365, 1419, 1265, 895, 740, 705, 671 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, TMS, 25 °C): δ = 1.818–1.849 (t, 2 H, $C^4HC^5H_2C^6$), 2.440–2.486 (m, 2 H, $C^3C^4H_2C^5H_2$), 2.926–2.958 {q, 2 H, [$C^6(CH_2OH)_2$]}, 3.642–3.690 (m, 2 H, C^6CH_2OH), 3.876–3.915 (m, 2 H, C^6CH_2OH), 5.979–6.014 (tt, J = 2 Hz, 1 H, $C{=}OC^2HC^3H$), 6.979–7.024 [m, 1 H, ($C^2HC^3HC^4H_2$)] ppm. ^{13}C NMR (400 MHz, $CDCl_3$, TMS, 25 °C): δ = 22.790 ($C^3HC^4H_2C^5$), 25.730 ($C^4H_2C^5H_2C^6$), 50.410 [$C{=}OC^6(CH_2)_2$], 65.386 [$C^6(CH_2)_2(OH)_2$], 128.883 ($C{=}OC^2HCH_2OH$), 150.786 ($C^2C^3HC^4H_2$), 204.479 (C=O) ppm. The spectroscopic data were assigned on the basis of 2D HMQC and 2D COSY NMR spectroscopy. GC–MS: m/z = 156 [M].

2-(Hydroxymethyl)-4,4-dimethyl-2-cyclohexen-1-one (12):[16] Colorless oil, R_f = 0.72 (EtOAc/hexane, 1:2). ^1H NMR (400 MHz, $CDCl_3$): δ = 1.173 (s, 6 H), 1.878–1.844 (t, J = 6.8 Hz, 2 H), 2.501–2.467 (t, J = 8 Hz, 2 H), 4.216–4.202 (d, J = 5.6 Hz, 2 H), 6.587 (s, 1 H) ppm. ^{13}C NMR (400 MHz, $CDCl_3$): δ = 27.89, 33.02, 34.75, 36.06, 62.48, 135.43, 156.35, 201.03 ppm.

2,6,6-Tris[hydroxy(4,4-dimethyl)methyl]-2-cyclohexen-1-one (13): Colorless crystalline oil, R_f = 0.18 (silica; EtOAc/hexane, 2:1). IR (film, KBr/CH_2Cl_2): $\tilde{\nu}$ = 3053, 2988, 2365, 1419, 1265, 895, 740, 705, 671 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, TMS, 25 °C): δ = 1.219–1.224 {ss, 6 H, [$C^4(CH_3)_2$]}, 1.734 (s, 2 H, $C^4C^5H_2C^6$), 3.085 {br., 2 H, [$C^6(CH_2OH)_2$]}, 3.636–3.664 [d, J = 11.2 Hz, 2 H, (C^6CH_2OH)], 3.857–3.885 [d, J = 11.2 Hz, 2 H, (C^6CH_2OH)], 4.030–4.033 (d, J = 1.2 Hz, 2 H, C^2CH_2OH), 6.677 (s, 1 H, $C^2C^3HC^4$) ppm. ^{13}C NMR (400 MHz, $CDCl_3$, TMS, 25 °C): δ = 31.049 [$C^4(CH_3)_2$], 32.425 ($C^3HC^4C^5H_2$), 38.181 ($C^4C^5H_2C^6$), 50.884 [$C{=}OC^6(CH_2OH)_2$], 61.620 (C^2CH_2OH), 65.826 [$C^6(CH_2)_2(OH)_2$], 134.117 ($C{=}OC^2CH_2OH$), 155.960 ($C^2C^3HC^4H_2$), 205.043 (C=O) ppm. The spectroscopic data were assigned on the basis of 2D HMQC and 2D COSY NMR spectroscopy. GC–MS: m/z = 213 [M – 1].

General Procedure for MBH–Cross-Aldol Reaction between 2-Cyclopenten-1-one and Aryl Aldehydes: To stirred separate mixtures of *N*-methylpyrrolidine (38.7 μL, 30 mol-%) in H_2O/CH_3OH (5:1, 2.5 mL) was added benzaldehyde (610 μL, 6.05 mmol or 150 μL, 1.46 mmol), 4-methoxyphenylaldehyde (750 μL, 6.05 mmol or 158 μL, 1.46 mmol), 4-nitrophenylaldehyde (546 mg 3.6 mmol or 220 mg, 1.46 mmol); furan-2-carbaldehyde (0.5 mL, 6.05 mmol or 0.12 mL, 1.46 mmol), and 2-naphthaldehyde (470 mg, 3.1 mmol or 220 mg, 1.46 mmol) previously dissolved in a small amount CH_3OH. Afterwards, **1** (0.105 mL, 1.2 mmol) was added to each solution. The resulting mixtures were stirred at room temperature. Upon completion or after the time indicated in Table 4 saturated NaCl was added (100 mL), and the reaction mixtures were extracted with CH_2Cl_2 (4×). The organic fractions were dried with anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to afford slurry residues. The residues were purified by silica gel flash column chromatography (EtOAc/hexane, 1:4 to 1:2). The combined organic layers were concentrated under reduced pressure and dried under vacuum. The isolated compounds were obtained as follows: **16**-i in 73% yield (165 mg, pale yellow solid), **16**-iii in 83% (220 mg), and **16**-iv in 73% (194 mg) as light yellow solids; **16**-v in 65% (187 mg) and **16**-vi in 31%, (84 mg) as yellow solids; **16**-vii in 77% (167 mg), **16**-ix in 67% (190 mg), and **16**-x in 45% (127 mg) as light yellow crystalline solids; and compound **17**-vi in 20% (95 mg) as an oil. The spectral characteristics of the prepared known compounds were found to be in agreement with previously reported data.

2-(Hydroxyphenylmethyl)-2-cyclopenten-1-one (16-i):[9b,9e,14c,15,17] Pale yellow solid, R_f = 0.31 (silica; EtOAc/hexane, 1:1). ^1H NMR (400 MHz, $CDCl_3$): δ = 2.43–2.459 (m, 2 H), 2.575 (m, 2 H), 3.56–3.57 (d, J = 4.4 Hz, 1 H), 5.546 (s, 1 H), 7.26–7.38 (m, 6 H) ppm.

^{13}C NMR (400 MHz, $CDCl_3$): δ = 26.73, 35.32, 69.86, 126.42, 127.93, 128.57, 141.41, 147.80, 159.59, 209.77 ppm.

2-[Hydroxy(4-methoxyphenyl)methyl]-2-cyclopenten-1-one (16-iv):[9b,9e,15,17] Yellow solid, R_f = 0.25 (silica; EtOAc/hexane, 1:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.441–2.463 (m, 2 H), 2.508–2.590 (m, 2 H), 3.36–3.37 (d, J = 4 Hz, O*H*), 5.506 (s, 1 H), 6.869–6.898 (m, 2 H), 7.268–7.2309 (m, 3 H) ppm. ^{13}C NMR (400 MHz, $CDCl_3$): δ = 26.727, 35.417, 55.409, 69.740, 114.010, 127.804, 133.647, 148.052, 159.228, 209.783 ppm.

2-[Hydroxy(4-nitrophenyl)methyl]-2-cyclopenten-1-one (16-vi):[9b,9e,15,18] Slightly yellow crystalline solid, R_f = 0.44 (silica; EtOAc/hexane, 1:1), ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.46–2.48 (m, 2 H), 2.61–2.63 (m, 2 H), 3.76 (s, 1 H), 5.66 (s, 1 H), 7.302–7.309 (m, 1 H), 7.564–7.586 (d, J = 8.8 Hz, 2 H), 8.186–8.208 (d, J = 8.8 Hz, 2 H) ppm. ^{13}C NMR (400 MHz, $CDCl_3$): δ = 26.96, 35.26, 69.06, 123.84, 127.21, 146.81, 147.57, 148.65, 160.06, 209.47 ppm.

2-[1-Hydroxy(2-furyl)methyl]-2-cyclopenten-1-one (16-vii):[14c] Yellow solid, R_f = 0.28 (silica; EtOAc/hexane, 1:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.47–2.50 (m, 2 H), 2.65 (m, 2 H), 3.450–3.468 (d, J = 7.2 Hz, 1 H), 5.58 (s, 1 H), 6.28–6.29 (d, J = 4.4 Hz, 1 H), 6.33–6.34 (m, 1 H), 7.38 (m, 1 H), 7.52 (m, 1 H) ppm. ^{13}C NMR (400 MHz, $CDCl_3$): δ = 26.92, 35.21, 64.01, 107.48, 110.52, 142.63, 144.84, 153.82, 160.27, 209.38 ppm.

2-[(Hydroxy(naphthalene-1-yl)methyl)]-2-cyclopenten-1-one (16-ix):[19] Colorless oil, R_f = 0.725 (silica, Et_2O/CH_2Cl_2, 1:1). ^{1}H NMR (400 MHz, $CDCl_3$, TMS, 25 °C): δ = 2.410–2.466 (m, 2 H, $C^3HC^4H_2C^5$), 2.494–2.560 (br. m, 2 H, $C^4C^5H_2C$=O), 3.688–3.698 (d, J = 4 Hz, 1 H, C^2CHOH), 5.723 (s, 1 H, C^2CHOH), 7.271–7.276 (t, 1 H, $C^2C^3HC^4H_2$), 7.464–7.484 (d, J = 8 Hz, 3 H, βC*H*, Ar), 7.8.15–7.939 (m, 4 H, αC*H*, Ar) ppm. ^{13}C NMR (400 MHz, $CDCl_3$, TMS, 25 °C): δ = 26.780, ($C^3HC^4H_2C^5$), 35.348 ($C^4H_2C^5H_2C$=O), 69.994 (C^2CHOH), 124.462, 125.249, 126.131, 126.304 (βAr*C*H), 127.772, 128.176, 128.391 (αAr *C*H), 133.142, 133.348, 138.802 (Ar *C*), 147.742 (C=OC^2CH_2), 159.794 ($C^2C^3HC^4H_2$), 209.798 (C=O) ppm. Spectral data were assigned on the basis of 2D HMQC and 2D COSY NMR spectroscopy.

***syn*-2,5-Bis[hydroxy(4-nitrophenyl)methyl]cyclopent-2-enone (17-vi):**[9b] Pale yellow solid, m.p. 81–83 °C, R_f = 0.39 (silica; EtOAc/hexane, 1:2). ^{1}H NMR (400 MHz, $CDCl_3$, TMS, 25 °C): δ = 2.252–2.482 (m, 1 H, $C^3HC^4HC^5$), 2.636–2.689 (m, 1 H, 1 H, $C^3HC^4HC^5$), 2.785–2.803 (m, 1 H, $C^4H_2C^5HC$=O), 3.444–3.478 (t, 1 H, O*H*), 3.502–3.698 (br. m, 1 H, O*H*), 5.481–5.512 (d, J = 12.4 Hz, 1 H, $C^5HCHCAr$), 5.675, (s, 1 H, C^2CHCAr), 7.402–7.420 (m, 1 H, $C^2C^3HC^4H_2$), 7.481–7.585 (m, 4 H, Ar), 8.135–8.196 (m, 4 H, Ar) ppm. ^{13}C NMR (400 MHz, $CDCl_3$, TMS, 25 °C): δ = 27.673 ($C^3HC^4H_2C^5H$), 53.421 ($C^4H_2C^5HC$=O), 69.023, ($C^5HCHCAr$), 70.806 (C^2CHCAr), 123.929, 126.375, 127.224, 127.368 (4 *C*H Ar), 146.632, 146.945, 147.458, 148.249 (4 C Ar), 149.665 (C=OC^2C^3H), 161.323 ($C^2C^3HC^4H_2$), 208.489 (C=O) ppm. The spectroscopic data were assigned on the basis of 2D HMQC and 2D COSY NMR spectroscopy.

Supporting Information (see footnote on the first page of this article): Chromatograms of the reaction optimization experiments, ^{1}H NMR spectral details of the tandem reaction, and ^{1}H and ^{13}C 2D NMR spectroscopic data of all isolated compounds together with GS–MS spectra.

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