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Neighboring Heteroatom Effect Unique to Aqueous Aldol Reactions of Water-Insoluble Substrates

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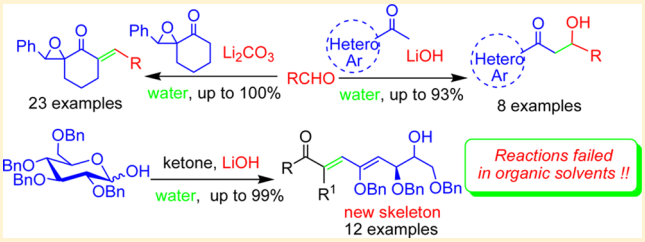
Supporting Information

ABSTRACT: The reactions of ketones and aldehydes in the presence of Li^+ and in the presence or absence of PTC mediated by water were performed to produce aldol products. Several advantages of the aqueous reactions over organic solvent-mediated ones have been demonstrated including higher yields, shorter reaction times, simpler purifications, and better functional group tolerance. Some reactions that do not take place in organic solvents have been realized in water. The successes are attributed to the neighboring heteroatom effect. In the aqueous aldol condensations, Li_2CO_3 was an efficient catalyst, and therefore base-liable groups such as epoxides, esters, and silyl groups could survive. For heteroaromatic ethanones, the aqueous aldol reactions were accomplished without PTC to give β-hydroxyketones in good yields. The water-mediated condensations of aldosyl hemiacetals with aromatic ketones led to a new carbohydrate-derived skeleton in quantitative yields. To some extent, this research has expanded the applicablities of aldol condensations and reactions.



INTRODUCTION

Aldol reaction is a powerful means of forming carbon−carbon bonds in organic chemistry. Classically, the reaction is performed by treating aldehydes and ketones in ethanol or methanol with bases or acids. One problem is the substrates bearing base-labile groups like ester, halide, epoxide, and sulfonate cannot survive such conditions. Another problem is the severe self-condensations of alkyl aldehydes bearing α-hydrogen atoms, which consume excess aldehydes, leading to substantial amounts of side products. The modifications of aldol reaction such as antibody-catalyzed and enzyme-catalyzed aldol reactions and the Mukaiyama aldol reaction have greatly expanded its applicabilities.[1] However, the problems associated with these modifications are the high costs for enzymes and antibodys and the substrate ketone has to be converted to boron or silicon enolates. In our continuing research on aqueous reactions, we have discovered that some aldol reactions could only be accomplished in water and not in organic solvents. The neighboring heteroatom effect (NHE) on these reactions was also investigated. Herein, we wish to report these results.

RESULTS AND DISCUSSION

In our previous work, the aqueous reactions of very sparing soluble high-melting-point (VSSHMP) substrates were accelerated by polytetrafluoroethylene (PTFE) sand (70 pieces/g) and agitated by a standard two-blade stirring rod.[2] In that work, it was noted that occasionally small amounts of the sticky reactant adhered to the reaction flask, and this reactant could not be reached by the standard stirring rod. This can lead to incomplete reactions. To solve this problem, the stirring rod was modified by inserting two PTFE wires (about 25 cm long with a diameter of about 1 mm in the middle and 2 mm along the rest of the wire) between the two blades (Supporting Information). This design effectively expands the reach of the stirring rod and worked well for reactions in a 100 mL flask.

The modified stirring rod was used in the following reactions. VSSHMP ketone **1a** was stirred at 80 °C with PTFE sand, Aliquat 336 (8 mol %), benzaldehydes (1.05 equiv), NaOH (20 mol %), and water for 2−5.5 h to yield **1aa**−**1ac** quantitatively (Table 1, entries 1−3). The substitution of Aliquat 336 with solid benzyltriethylamonium chloride, solid tetraethylamonium chloride, liquid *N*-butyl-*N*-methyl imidazolium chloride, solid sodium dodecyl sulfate, or liquid PEG 400 all ended in failure. This indicates that Aliquat 336 functions as both a phase transfer catalyst (PTC) and a reaction medium for the VSSHMP ketone. The PTFE sand functions as hundreds of stirrers to efficiently promote the dissolution of the VSSHMP substrate in Aliquat 336. Similarly, VSSHMP ketones **1b**−**1d** reacted with aromatic aldehydes to yield the corresponding α,β-unsaturated ketones **1ba**−**1db** in quantitative yields (Table 1, entries 4−10). Because products **1aa**−**1db** are VSSHMP, they were collected simply by filtration and washing with a small amount of aqueous acetone. The base, water, Aliquat 336, and sand were all recyclable for eight cycles for the condensation of **1c** with *p*-methoxybenzaldehyde to yield **1cc**. For comparison, a single wire-modified stirring rod (Supporting Information, page S4) was used instead of the double wire-modified one (Supporting Information, page S5) in the preparations of **1aa** and **1ac** with the reaction yields and times. The reason that the

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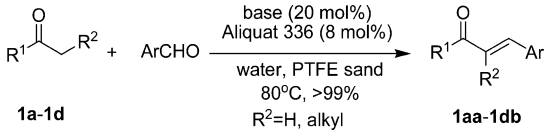
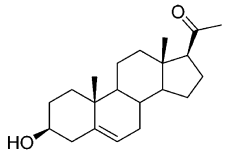
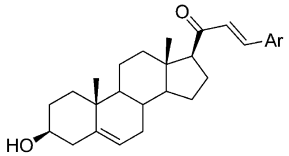
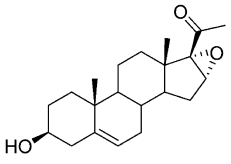
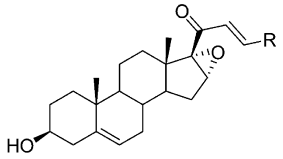
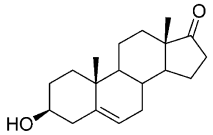
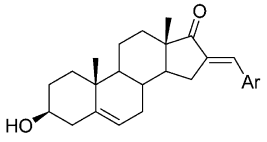
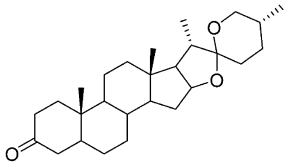
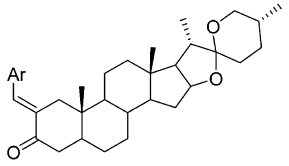
Table 1. Quantitative Aqueous Aldol Condensations of VSSHMP Ketones with Aromatic Aldehydes[a]



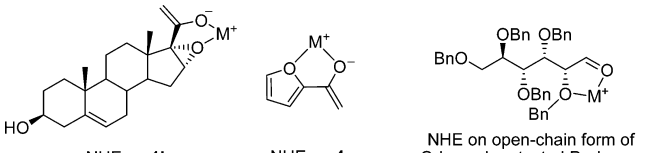
entry	ketone	*t* (h)	product
1[b]	 **1a**	2	 **1aa**: Ar=4-$NO_2C_6H_4$
2[b]		3	**1ab**: Ar=Ph
3[b]		5.5	**1ac**: Ar=4-$MeOC_6H_4$
4[b]	 **1b**	0.4	 **1ba**: Ar=4-$NO_2C_6H_4$
5[c]		1.3	**1ca**: Ar=4-$NO_2C_6H_4$
6[c]	 **1c**	2.5	 **1cb**: Ar=Ph
7[c]		3	**1cc**: Ar=4-$MeOC_6H_4$
8[c]		1	**1cd**: Ar=2-furanyl
9[b]	 **1d**	2	 **1da**: Ar=Ph
10[b]		7	**1db**: Ar=4-$MeOC_6H_4$

[a]Reaction conditions: ketone (1 g), aromatic aldehyde (1.05 equiv), base (20 mol %), Aliquat 336 (8 mol %), PTFE sand (5 g), and water (8 mL), mechanical stirring (400 rmp) at 80 °C. [b]NaOH as the base. [c]Na_2CO_3 as the base.

double wire-modified stirring rod was selected is that the wire is handmade and not always robust. In the preparation of **1cc**, the reaction time was 6.5 h at a stirring rate of 100 rmp, much longer than that in Table 1, entry 7 (3 h, 400 rmp). The reaction time was 3.0 h at 600 rmp, the same as in Table 1, entry 7. Stirring rate 400 rmp was appropriate.

The aqueous reaction of **1b** with *p*-nitrobenzaldehyde (Table 1, entry 4) catalyzed by NaOH was much faster than that of **1a** (Table 1, entry 1). It is speculated that the α-oxygen atom in **1b** chelated with the enolate M^+, which stabilized the intermediate and accelerated the reaction (Scheme 1). To verify this speculation, experiments (reactions **A**-**D**) were carried out in water versus in methanol, and the results are summarized in Table 2. The condensations of **1a** and *p*-nitrobenzaldehyde were performed in the presence of water, Aliquat 336, and PTEF sand and catalyzed by Li_2CO_3, Na_2CO_3, K_2CO_3, or Cs_2CO_3. The strongest base, Cs_2CO_3, gave a 29% yield of **1aa**;

Scheme 1. The NHE That Is Unique to the Aqueous Systems and Not Effective in Organic Solvents



the other ones did not give any products or led to trace products (Table 2, entries 2−4). The methanol-mediated reactions for **1a** catalyzed by these carbonates were successful in 90−96% yields of **1aa** (entries 1−4). For **1a**, the catalytic efficiency orders of the carbonates and their basicities were the same in water or in methanol. When **1b** which bears an α-oxygen atom was also subjected to the same aqueous reaction

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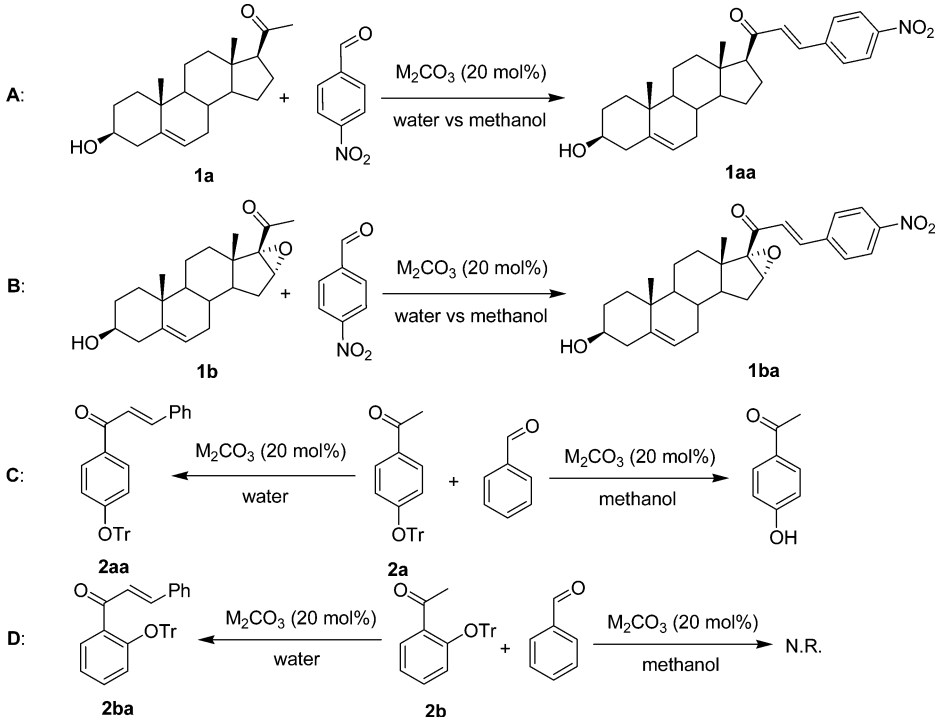
Table 2. Comparison of Carbonate-Catalyzed Condensations of Ketones and Heteroatom-Bearing Ketones with Aldehydes in Methanol versus in Water[a]



			water		methanol	
entry	reaction[b]	M	*t* (h)	yield	*t* (h)	yield
1	**A**	Li	9	NR[c]	20	90%
2	**A**	Na	9	trace	5.8	96%
3	**A**	K	9	trace	2	93%
4	**A**	Cs	9	29%	1	93%
5	**B**	Li	0.5	>99%	20	92%
6	**B**	Na	0.7	>99%	6	93%
7	**B**	K	2	>99%	2	94%
8	**B**	Cs	6	>99%	1	94%
9	**C**	Li	36	>99%	10	65%[c]
10	**C**	Na	23	>99%	10	73%[c]
11	**D**	Li	9	>99%	10	NR[d]
12	**D**	Na	14	>99%	10	NR[d]

[a]Reaction conditions in water:ketone (**1a**, **1b**, **2a**, or **2b**, 0.5 g), aldehyde (1.05 equiv), M_2CO_3 (20 mol %), Aliquat 336 (8 mol %), PTFE sand (5 g), and H_2O (4 mL), mechanical stirring (400 rmp); reaction conditions in methanol:ketone (**1a**, **1b**, **2a**, or **2b**, 0.5 g), aldehyde (1.05 equiv), M_2CO_3 (20 mol %), and methanol (4 mL), reflux. [b]Reaction temperatures in water: 80 °C for **A** and **B**, 70 °C for **C** and **D**. [c]The yield of 1-(4-hydroxyphenyl)ethanone. [d]NR, no reaction.

conditions as for **1a**, a quantitative yield of **1ba** was produced (Table 2, entries 5−8). The aqueous catalytic efficiency order of the carbonates for **1b** was Li_2CO_3 (0.5 h) > Na_2CO_3 (0.7 h) > K_2CO_3 (2 h) > Cs_2CO_3 (6 h), which is opposite to their basicity order and in accordance with their hardness order of M^+. When methanol was used instead of water as the solvent, the most efficient catalyst was Cs_2CO_3 (entry 8). However, the yield in this case was not quantitative (94%). In the case of **2a**, the aqueous condensation catalyzed by Na_2CO_3 was faster than that catalyzed by Li_2CO_3 (entries 9 and 10). For ketone **2b** with a *β*-oxygen atom (entries 11 and 12), the aqueous reaction catalyzed by Li_2CO_3 was faster than that by catalyzed Na_2CO_3, both in quantitative yields. In contrary, a methanol-mediated aldol condensation for **2a** or **2b** did not occur. These extraordinary performances of the aqueous reactions for **1b** and **2b** are attributed to the NHE. Although this effect has been documented in other organic solvent-mediated reactions,[3] it is unique to the aqueous systems in this report. In the control experiments (**1a** vs **1b**), this effect was not observed in other organic solvent-mediated reactions: in *N*,*N*-dimethylformamide (DMF) and tetrahydrofuran-water. The aqueous reaction is heterogeneous and the methanol-mediated one homogeneous. It is therefore believed that in the aqueous systems, Li^+ can be efficiently transferred into the phase of the substrate dissolved in Aliquat 336 to chelate with the *α*- or *β*-oxygen atom and the carbonyl group of **1b** or **2b** without competition. Another possible explanation is that these "on-water" reactions are catalyzed by the small intense Li^+ ions which can congregate at the water−organic interface and can complex with both neighboring oxygen atoms and the carbonyl groups of reactants which approach the barrier under vigorous stirring.[4] However, in polar solvents such as methanol, the oxygen atoms of the

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Table 3. Aqueous Aldol Condensations of Neighboring Heteroatom-Bearing Ketones with Aldehydes[a]

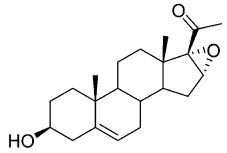
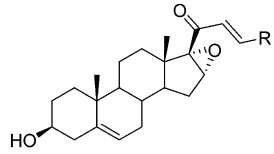
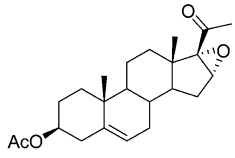
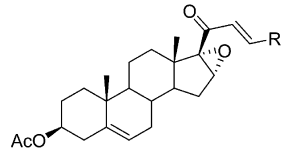
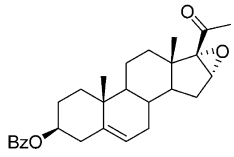
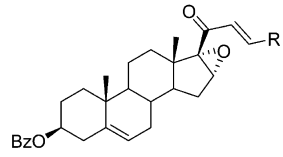
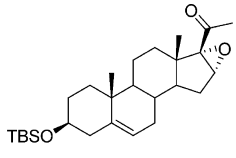
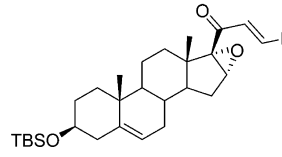
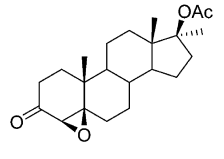
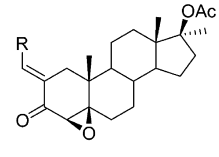
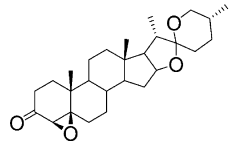
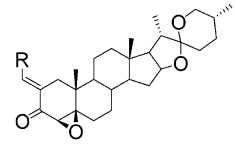
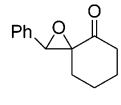
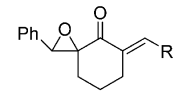
entry	ketone	T, t	yield	product	
1	 **1b**	80°C, 1 h	>99%		**3aa**: R=Ph
2		80°C, 3 h	>99%		**3ab**: R= 4-MeOC$_6$H$_4$
3	 **3b**	80°C, 1.5 h	>99%		**3ba**: R= 4-NO$_2$C$_6$H$_4$
4		80°C, 2.5 h	>99%		**3bb**: R=Ph
5	 **3c**	80°C, 8 h	>99%		**3ca**: R= 4-NO$_2$C$_6$H$_4$
6		90°C, 1.2 h	>99%		**3cb**: R=Ph
7	 **3d**	80°C, 9 h	>99%		**3da**: R= 4-NO$_2$C$_6$H$_4$
8		60°C, 13 h	>99%		**3db**: R=Ph
9	 **3e**	60°C, 1.3 h	>99%		**3ea**: R= 4-NO$_2$C$_6$H$_4$
10		60°C, 3 h	>99%		**3eb**: R=Ph
11	 **3f**	rt, 4 h	>99%		**3fa**: R= 4-NO$_2$C$_6$H$_4$
12		80°C, 0.8 h	>99%		**3fb**: R=Ph
13	 **3g**	rt, 0.7 h	>99%		**3ga**: R= 4-NO$_2$C$_6$H$_4$
14		rt, 3 h	>99%		**3gb**: R=Ph
15		rt, 6 h	83%[d]		**3gc**: R=iBu

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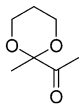
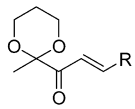
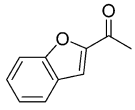
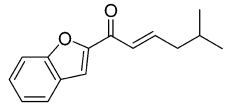
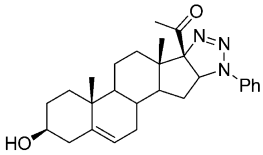
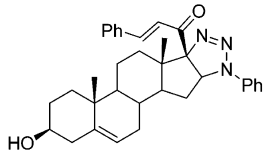
Table 3. continued

16	 **3h**	80°C, 1.3 h	>99%		**3ha**: R= 4-$NO_2C_6H_4$
17		80°C, 3 h	91%		**3hb**: R=Ph
18		80°C, 12 h	93%		**3hc**: R= 4-$MeOC_6H_4$
19[b]	 **3i**	0°C, 1 h	32%[d]		**3ia**
20[c]	 **3j**	80°C, 2.5 h	>99%		**3ja**

[a]Reaction conditions: ketone (**1b** or **3b**−**3j**, 1 g), aldehyde (2.0 equiv for entries 15 and 19; 1.05 equiv for the others), Li_2CO_3 (20 mol %), Aliquat 336 (5 mol % for **3g**−**3i**; 8 mol % for the others), PTFE sand (5 g), and water (8 mL), mechanical stirring (400 rmp). [b]1.0 equiv LiOH was used as catalyst. [c]The flask was covered with aluminum foil. [d]Yield after chromatographic purification.

solvent are in excess and are predominately associated with Li^+ which prevents the chelation of Li^+ with the α- or β-oxygen atom and the carbonyl group.

The aldol reactions of a series of neighboring heteroatom-bearing ketones with aldehydes catalyzed by Li_2CO_3 were carried out in the presence of Aliquat 336 and PTFE sand (Table 3). As most of the substrates used in "on-water" reactions are liquid or liquid plus solid, the aqueous reactions of very sparing soluble high-melting-point substrates are not common and challenging.[2,5] Most of the ketones (**1b**, **3b**−**3g**, **3i**, and **3j**) are VSSHMP (mp: 81−210 °C; solubility: 6.6×10^{-3} to 1.1×10^{-7} mol L^{-1}; data from SciFinder). The condensation yields were up to quantitative, and the products were simply collected by filtration except for entries 15 and 19. The advantage of using Li_2CO_3 as the catalyst is that base-liable groups such as epoxides (entries 1−15), esters (entries 3−6, 9, and 10), and silyl groups (entries 7 and 8) can survive the reaction. However, it is well documented that in the organic solvent-mediated aldol reactions, substrate ketones bearing these base-liable groups either partially or completely decomposed in the presence of NaOH or MeONa or do not condense with the aldehydes catalyzed by Li_2CO_3 or Na_2CO_3.[6] Although the epoxide, ketal, heteroaromatic ketones, and carbohydrates (Table 5) were successful in aqueous aldol reactions, the aqueous reactions of 2-methoxycyclohenanone and 3-methoxybutanone with benzaldehyde led to decomposition of the former and rather low reaction rate for the latter. Diacetyl (unprotected) and pyruvatesters could not survive the basic conditions. In the control experiments, treating **3g** and benzaldehyde or isovaleraldehyde with NaOH or LiOH or Na_2CO_3 in methanol did not furnish any desired products (**3gb** or **3gc**) because stronger bases NaOH and LiOH decomposed the α,β-epoxy carbonyl group and weak base Na_2CO_3 was not capable of catalyzing the reaction. Although the aldol condensation between aromatic ethanone **3i** and aromatic aldehydes is known, the aldol condensation using aliphatic aldehydes leading to **3ia** type of skeleton has never been reported. Ketones **3ga** and **3gb** have been prepared twice with the same outcomes (the same reaction rates and quantitative yields), demonstrating that these reactions are reproducible.

The NHE was also successfully applied to heteroaromatic ethanones (Scheme 1). For **4a**−**4c**, the aqueous direct aldol reactions in the presence of LiOH were accomplished without PTC, to give β-hydroxyketones **4aa**−**4cb** in good yields (Table 4, entries 1−7). Further this reaction was easily scaled up to 20 g. In the literature, these reactions have often been conducted in the presence of BuLi or LDA at a low temperature (−78 °C) in anhydrous solvents (ether or tetrahydrofuran).[7] In the control experiments, these aldol reactions in methanol or DMF catalyzed by NaOH, Cs_2CO_3, or DBU failed completely. The direct aqueous aldol reaction between **3i** and isovaleraldehyde in the presence of LiOH in the presence of Aliquat 336 was realized in a 41% yield of **4da** at 0 °C. The yield of **4da** was improved to 93% at −18 °C. There is only one known compound with the skeleton represented by **4da**, which was synthesized via the Mukaiyama aldol reaction starting from the corresponding silyl enol ether in 75% yield.[8]

Carbohydrates play an essential role in life and chemistry and are versatile intermediates in organic synthesis.[9] However, utilizing protected aldosyl hemiacetals in aldol reactions remains challenging. The only example is the condensation of *O*-benzyl-protected aldosyl hemiacetals with excess acetone to yield (3*E*,5*Z*,7*S*,8*R*)-5,7,9-tribenzyloxy-8-hydroxynona-3,5-dien-2-one and two other analogs in 68−70% yields.[10] The open-chain form of carbohydrates contains a neighboring oxygen atom for the carbonyl group; although it is only found in minute amounts because of the equilibrium with the cyclic hemiacetal form. It would be interesting to test if the NHE can be used for carbohydrates (Scheme 1). A series of ketones was found to react well with *O*-benzyl-protected D-glucosyl and D-xylosyl hemiacetals, in the presence of LiOH and tetrabutylammonium bromide (TBAB) in water (Table 5). All the reactions only took 15 min and gave good to quantitative

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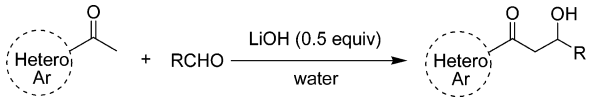
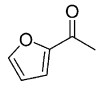
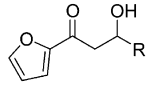
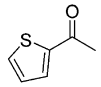
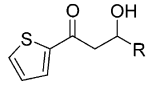
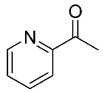
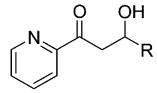
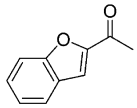
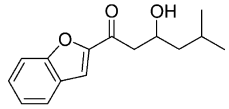
Table 4. Aqueous Aldol Reaction of Heteroaromatic Ethanones with Aliphatic Aldehydes[a]



entry	ketone	T, t	yield (%)	product
1	 **4a**	rt, 1 h	79	 **4aa**: R=iPr
2		0°C, 2 h	69	**4ab**: R=Pr
3	 **4b**	rt, 1 h	76	**4ba**: R=iPr
4		0°C, 2 h	63	 **4bb**: R=Pr
5		0°C, 2 h	58	**4bc**: R=Me
6	 **4c**	rt, 1 h	65	 **4ca**: R=iPr
7		0°C, 1 h	38	**4cb**: R=Pr
8[b]	 **3i**	-18°C, 1.5 h	93	 **4da**

[a]Reaction conditions (entries 1–7): ketone (**4a–4c**, 1 g), aldehyde (1.5 equiv for entries 1, 3, and 6; 2.0 equiv for entries 2, 4, and 7; 5.0 equiv for entry 5), LiOH (0.5 equiv), water (3 mL), magnetic stirring (400 rmp). [b]Reaction conditions (entry 8): **3i** (1.0 g), aldehyde (2.0 equiv), LiOH (2.0 equiv), Aliquat 336 (5 mol %), water (8 mL), and PTFE sand (5 g), mechanical stirring (400 rmp).

yields. The reactions of *O*-benzyl-protected D-glucosyl and D-xylosyl hemiacetals with liquid aliphatic ketones **5a** and **5b** and VSSHMP steroidal ketones **1c** and **5d** all produced chiral conjugated dienones **5aa–5db** containing a free hydroxyl group. The reactions with aromatic ketones **5e** and **5f** produced chiral diketones **5ea–5fb** with an enolether and a free hydroxyl group. Two sequential reactions, the aldol condensation and a BnOH elimination, took place in one pot for **5aa–5db**, and the two sequential reactions plus a Michael addition took place for **5ea–5fb**. The possible reason is that aromatic methyl ketones are less hindered and more acidic than steroidal and aliphatic ones and are capable of adding to the dienones to form **5ea–5fb**. The reactions for products **5aa–5bb** and **5ea–5fb** were so clean that chromatography was not necessary. In the control experiments, the preparation of **5eb** in refluxing organic solvent (methanol or $CHCl_3$) catalyzed by M_2CO_3 or MOH (M: Li, Na, and K) or DBU for 8 h ended in failure. These aqueous condensations provide a facile method for the synthesis of carbohydrate derivatives with a new type of skeleton (**5ea–5fb**) containing enolether, carbonyl, and free hydroxyl groups. It is easily to envisage the usefulness of this new type of skeleton. For example, the free hydroxyl groups could be transformed into tosylate or halide and substituted with amine or azide, which after a reductive ring closure would give deoxy miglitol derivatives. Miglitol is widely used clinically in treating diabetes.[11] The carbohydrate diketones could also lead to heterocyclic compounds bearing chiral hydroxyl groups. This research is currently underway in our laboratory.

In summary, the NHE has been proven, and this effect is uniquely applicable to the aqueous reactions for a series of substrates; some of these results are unachievable via organic solvent-mediated reactions. In addition, the aqueous reactions have advantages of higher yields, shorter reaction times, simpler purifications, and better functional group tolerance. Especially, the condensation reactions between aldosyl hemiacetals and ketones gave multifunctionalized compounds, among which the carbohydrate diketones with a new type of skeleton were formed. This methodology is also useful in endeavors to replace organic solvents with water in organic synthesis.

■ EXPERIMENTAL SECTION

General Information. All of the chemicals were obtained from commercial sources or prepared according to standard methods. NMR spectra were recorded with a 400 or 600 MHz spectrometer for ^{1}H NMR and NOESY and 100 or 151 MHz for $^{13}C\{^1H\}$ NMR using TMS as an internal standard. Chemical shifts (δ) are reported relative to TMS (^{1}H) or $CDCl_3$ (^{13}C). Multiplicities are reported as follows: singlet (s), doublet (d), triplet (t), quartet (q), and multiplet (m). Melting points were recorded with a micromelting-point apparatus. Infrared analyses (KBr pellet) were performed by FT-IR. Elemental analyses for C, H, N, and Si were performed on an elemental analyzer. High-resolution spectra (HRMS) were recorded on a QTOF mass analyzer with electrospray ionization (ESI). All the aqueous reactions except for the preparations of **4aa–4cb** were conducted in 100 mL flasks and agitated by the modified stirring rod. The size of PTFE sand is 70 pieces/g.

General Procedures for the Aqueous Aldol Reactions (Procedures A–D). Procedure **A**: A mixture of ketone (1.000 g), Aliquat 336, PTFE sand (5 g), aldehyde, water (8 mL), and base was mechanically stirred (400 rmp). After TLC indicated completion of the reaction, it was stopped, and the crude product was suspended in water, while the PTFE sand precipitated on the bottom. The

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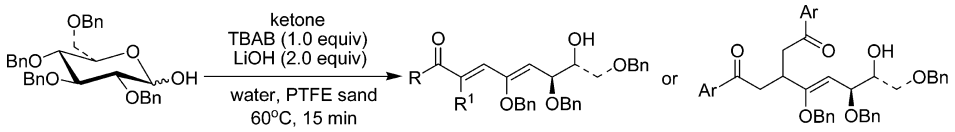
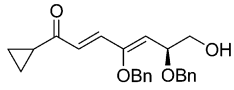
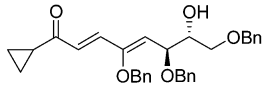
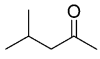
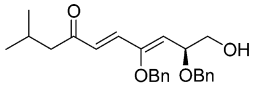
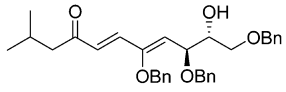
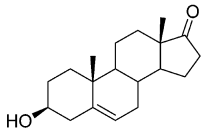
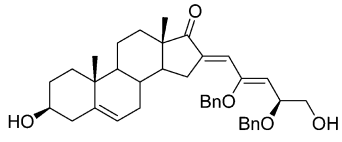
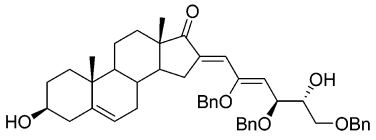
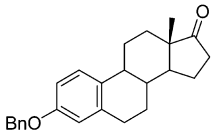
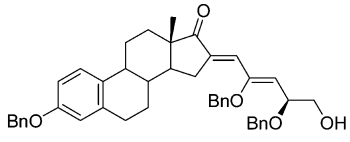
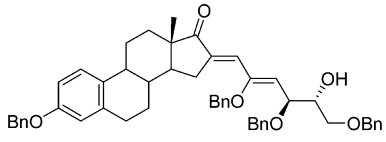
Table 5. Aqueous Aldol Reactions of Ketones and Protected Aldosyl Hemiacetals[a]



entry	ketone	product	yield (%)
1	 **5a**	 **5aa**	98
2		 **5ab**	97
3	 **5b**	 **5ba**	98
4		 **5bb**	99
5	 **1c**	 **5ca**	64
6		 **5cb**	68
7	 **5d**	 **5da**	58
8		 **5db**	61

[a]Reaction conditions: aldosyl hemiacetal (1 mmol), TBAB (1.0 equiv), ketone (1.0 equiv for **1c** and **5d**; 6.0 equiv for the others), LiOH (2.0 equiv), PTFE sand (5 g), and water (2.5 mL), mechanical stirring (400 rmp) at 60 °C for 15 min.

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suspension was filtrated and washed with cold aqueous acetone (3 mL, 75% v/v) to give the corresponding products, leaving the PTFE sand to be recovered.

Procedure **B**: After magnetically stirring (400 rmp) a mixture of heteroaromatic ethanone, LiOH (0.5 equiv), and water (3 mL per gram of ketone) for 15 min, aldehyde was added dropwisely within 20 min. The mixture was stirred for an additional period of time and then extracted with ethyl acetate three times, washed with water, and dried over Na_2SO_4. The unreacted heteroaromatic ethanone was recovered using bulb to bulb distillation, leaving the desired product to be collected.

Procedure **C**: A mixture of ketone (6 mmol), aldosyl hemiacetal (1 mmol), TBAB (322 mg), LiOH (48 mg), PTFE sand (5 g), and water (2.5 mL) was mechanically stirred (400 rmp) at 60 °C for 15 min. The crude product was extracted with ethyl acetate (3 × 8 mL), washed with water (2 × 10 mL), and dried over Na_2SO_4. The starting material (ketone) and byproduct (BnOH) were removed by bulb-to-bulb distillation under reduced pressure at about 60 °C.

Procedure **D**: A mixture of **1c** or **5d** (1 mmol), aldosyl hemiacetal (1 mmol), TBAB (322 mg), LiOH (48 mg), PTFE sand (5 g), and water (2.5 mL) was mechanically stirred (400 rmp) at 60 °C for 15 min. The reaction was stopped and extracted with ethyl acetate (3 × 8 mL), dried over Na_2SO_4, and purified by flash chromatograph on silica gel to afford the corresponding product.

Products **1ab**,[12] **1ac**,[12] **1ca**,[13] **1cb**,[14] **1cc**,[14] **1 cd**,[15] **3aa**,[16] and **3bb**[16] are known compounds and were synthesized quantitatively according to procedure **A**.

*(E)-3β-Hydroxy-21-(4-nitrobenzal)pregn-5-en-20-one (**1aa**).* Procedure **A**: 1.425 g, quantitative yield; white solid; mp 213−216 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.26 (d, J = 8.5 Hz, 2H), 7.71 (d, J = 8.5 Hz, 2H), 7.58 (d, J = 15.9 Hz, 1H), 6.88 (d, J = 15.9 Hz, 1H), 5.38 (d, J = 3.9 Hz, 1H), 3.60−3.50 (m, 1H), 2.90−2.86 (m, 1H), 2.41−2.23 (m, 3H), 1.02 (s, 3H), 0.67 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 199.8, 148.5, 141.1, 140.8, 138.4, 130.2, 128.8, 124.1, 121.3, 71.6, 62.6, 57.2, 50.0, 45.2, 42.2, 39.2, 37.3, 36.5, 32.0, 31.8, 31.6, 24.6, 22.7, 21.1, 19.4, 13.5; IR (KBr): ν 3611, 2940, 1677, 1608, 1518, 1344, 1112, 1056, 849, 756 cm^{-1}; elemental analysis calcd (%) for $C_{28}H_{35}NO_4$: C 74.80, H 7.85, O 14.23, N 3.12; found: C 75.23, H 7.79, N 3.07.

*(E)-3β-Hydroxy-16α,17α-epoxy-21-(4-nitrobenzal)pregn-5-en-20-one (**1ba**).* Procedure **A**: 1.400 g, quantitative yield; white solid; mp 202−204 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.25 (d, J = 8.4 Hz, 2 H), 7.72−7.68 (m, 3H), 6.92 (d, J = 15.9 Hz, 1H), 5.36 (d, J = 3.7 Hz, 1H), 3.80 (s, 1H), 3.60−3.50 (m, 1H), 2.35−2.22 (m, 2H), 2.19 (s, 1H), 2.12−2.03 (m, 2H), 1.98 (d, J = 12.9 Hz, 1H), 1.86 (d, J = 10.9 Hz, 2H), 1.15 (s, 3H), 1.06 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 194.5, 148.6, 141.2, 140.9, 140.4, 129.0, 124.6, 124.1, 120.9, 71.6, 71.3, 60.4, 50.3, 45.6, 42.2, 42.1, 37.2, 36.7, 31.6, 31.5, 29.8, 27.8, 20.5, 19.3, 15.2; IR (KBr): ν 3626, 3409, 3104, 3075, 2938, 1681, 1615, 1595, 1516, 1342, 1055, 1001, 979, 833, 755 cm^{-1}; elemental analysis calcd (%) for $C_{28}H_{33}NO_5$: C 72.55, H 7.18, N 3.02, O 17.26; found: C 72.37, H 7.11, N 3.07.

*(E)-2-Benzaltigogenone (**1da**).* Procedure **A**: 1.218 g, quantitative yield; white solid; mp 228−230 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.58 (d, J = 1.5 Hz, 1H), 7.43−7.34 (m, 5H), 4.43 (dd, J = 14.8, 7.4 Hz, 1H), 3.50 (dd, J = 10.4, 3.0 Hz, 1H), 3.39 (t, J = 10.9 Hz, 1H), 3.12 (d, J = 15.7 Hz, 1H), 2.48 (dd, J = 18.7, 5.2 Hz, 1H), 2.30−2.18 (m, 2H), 2.06−2.00 (m, 1H), 0.99 (d, J = 6.9 Hz, 3H), 0.82 (s, 3H), 0.81 (d, J = 6.4 Hz, 3H), 0.78 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 201.2, 137.2, 135.7, 135.3, 130.3, 128.5, 128.4, 109.2, 80.7, 66.9, 62.3, 56.2, 53.6, 42.8, 42.4, 41.8, 41.6, 40.4, 39.9, 36.0, 35.0, 31.8, 31.7, 31.4, 30.3, 28.8, 28.6, 21.2, 17.2, 16.4, 14.5, 11.9; IR (KBr): ν 2945, 1679, 1591, 1450, 1242, 1184, 1060, 981, 900, 699, 521 cm^{-1}; elemental analysis calcd (%) for $C_{34}H_{46}O_3$: C 81.23, H 9.22, O 9.55; found: C 81.43, H 9.17.

*(E)-2-(4-Methoxybenzal)tigogenone (**1db**).* Procedure **A**: 1.279 g, quantitative yield; white solid; mp 215−217 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.57 (d, J = 1.2 Hz, 1H), 7.40 (d, J = 8.5 Hz, 2H), 6.94 (d, J = 8.5 Hz, 2H), 4.43 (dd, J = 14.7, 7.3 Hz, 1H), 3.86 (s, 3H), 3.50 (dd, J = 10.1, 3.2 Hz, 1H), 3.40 (t, J = 10.9 Hz, 1H), 3.08 (d, J = 15.7 Hz, 1H), 2.46 (dd, J = 18.7, 5.2 Hz, 1H), 2.27−2.19 (m, 2H), 2.07−2.00 (m, 1H), 0.99 (d, J = 6.8 Hz, 3H), 0.82 (s, 3H), 0.80 (d, J = 6.3 Hz, 3H), 0.78 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 201.1, 160.0, 137.3, 133.1, 132.3, 128.3, 113.9, 109.2, 80.8, 66.9, 62.2, 56.2, 55.3, 53.7, 42.6, 42.1, 41.6, 40.4, 40.0, 35.9, 35.0, 31.8, 31.7, 31.4, 30.3, 28.8, 28.6, 21.3, 17.1, 16.4, 14.5, 12.0; IR (KBr): ν 3060, 2944, 1681, 1588, 1567, 1511, 1255, 1178, 1052, 983, 834, 534 cm^{-1}; elemental analysis calcd (%) for $C_{35}H_{48}O_4$: C 78.91, H 9.08, O 12.01; found: C 78.71, H 9.10.

*(E)-3-Phenyl-1-(4-(trityloxy)phenyl)prop-2-en-1-one (**2aa**).* Procedure **A**: 500 mg of **2a** was used; 615 mg, quantitative yield; white solid; mp 191−192 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.79−7.74 (m, 3H), 7.63−7.60 (m, 2H), 7.50−7.40 (m, 10H), 7.34−7.25 (m, 9H), 6.84 (d, J = 8.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 193.8, 154.7, 143.5, 143.4, 135.0, 130.8, 130.2, 130.0, 128.9, 128.5, 127.9, 127.6, 127.4, 121.1, 120.5, 91.9; IR (KBr): ν 3059, 3027, 1662, 1596, 1474, 1446, 1221, 975, 751, 700 cm^{-1}; elemental analysis calcd (%) for $C_{34}H_{26}O_2$: C 87.52, H 5.62, O 6.86; found, C 87.71, H 5.68.

*(E)-3-Phenyl-1-(2-(trityloxy)phenyl)prop-2-en-1-one (**2ba**).* Procedure **A**: 500 mg of **2b** was used; 613 mg, quantitative yield; white solid; mp 120−121 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.61−7.46 (m, 9H), 7.40−7.31 (m, 5H), 7.25−7.19 (m, 9H), 6.99 (t, J = 7.2 Hz, 1H), 6.89 (t, J = 7.4 Hz, 1H), 6.60 (d, J = 8.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 188.8, 160.8, 143.8, 143.6, 135.1, 131.2, 130.4, 129.7, 129.0, 128.8, 128.7, 128.4, 128.0, 127.8, 127.5, 121.9, 120.1, 91.1; IR (KBr): ν 3058, 3028, 1662, 1598, 1494, 1447, 1218, 977, 751, 699 cm^{-1}; elemental analysis calcd (%) for $C_{34}H_{26}O_2$: C 87.52, H 5.62, O 6.86; found, C 87.45, H 5.65.

*(E)-3β-Hydroxy-16α,17α-epoxy-21-(4-methoxybenzal)pregn-5-en-20-one (**3ab**).* Procedure **A**: 1.364 g, quantitative yield; white solid; mp 187−189 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.68 (d, J = 15.8 Hz, 1H), 7.52 (d, J = 8.6 Hz, 2H), 6.90 (d, J = 8.6 Hz, 2H), 6.72 (d, J = 15.8 Hz, 1H), 5.36 (d, J = 4.6 Hz, 1H), 3.85 (s, 3H), 3.75 (s, 1H), 3.59−3.49 (m, 1H), 2.34−2.21 (m, 2H), 2.10 (d, J = 10.6 Hz, 1H), 2.03−1.95 (m, 2H), 1.13 (s, 3H), 1.05 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 194.9, 161.7, 143.5, 141.2, 130.3, 127.4, 121.0, 118.9, 114.4, 71.6, 71.3, 60.2, 55.4, 50.4, 45.7, 42.2, 42.0, 37.2, 36.7, 31.6, 31.6, 31.5, 29.9, 27.7, 20.6, 19.3, 15.3; IR (KBr): ν 3550, 2939, 1675, 1602, 1577, 1513, 1247, 1178, 997, 810 cm^{-1}; elemental analysis calcd (%) for $C_{29}H_{36}O_4$: C 77.64, H 8.09, O 14.27; found, C 77.77, H 8.16.

*(E)-3β-Acetoxy-16α,17α-epoxy-21-(4-nitrobenzal)pregn-5-en-20-one (**3ba**).* Procedure **A**: 1.349 g, quantitative yield; white solid; mp 226−228 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.25 (d, J = 8.1 Hz, 2H), 7.72−7.69 (m, 3H), 6.92 (d, J = 15.9 Hz, 1H), 5.39 (d, J = 2.8 Hz, 1H), 4.66−4.57 (m, 1H), 3.80 (s, 1H), 2.41−2.29 (m, 2H), 2.05 (s, 3H), 1.15 (s, 3H), 1.07 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 194.5, 170.4, 148.5, 140.9, 140.3, 140.1, 129.0, 124.6, 124.1, 121.9, 73.7, 71.2, 60.3, 50.2, 45.6, 42.1, 38.1, 36.9, 36.8, 31.5, 29.7, 27.73, 27.68, 21.4, 20.4, 19.2, 15.2; IR (KBr): ν 2941, 1728, 1685, 1613, 1519, 1345, 1245, 1030, 984, 755 cm^{-1}; elemental analysis calcd for $C_{30}H_{35}NO_6$: C 71.27, H 6.98, N 2.77, O 18.99; found, C 71.07, H 6.90, N 2.80.

*(E)-3β-Benzoyloxy-16α,17α-epoxy-21-(4-nitrobenzal)pregn-5en-20-one (**3ca**).* Procedure **A**: 1.314 g, quantitative yield; white solid; mp 249−251 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.25 (d, J = 8.7 Hz, 2H), 8.06 (d, J = 7.3 Hz, 2H), 7.73−7.69 (m, 3H), 7.57 (t, J = 7.4 Hz, 1H), 7.45 (t, J = 7.6 Hz, 2H), 6.93 (d, J = 16.0 Hz, 1H), 5.44 (d, J = 4.8 Hz, 1H), 4.92−4.84 (m, 1H), 3.81 (s, 1H), 2.54−2.45 (m, 2H), 2.14−1.92 (m, 5H), 1.17 (s, 3H), 1.13 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 194.5, 165.9, 148.5, 140.9, 140.3, 140.1, 132.8, 130.8, 129.5, 129.0, 128.3, 124.6, 124.1, 122.0, 74.4, 71.2, 60.3, 50.2, 45.6, 42.1, 38.2, 36.9, 36.8, 31.5, 29.8, 27.81, 27.78, 20.5, 19.3, 15.2; IR (KBr): ν 3086, 2940, 1705, 1614, 1526, 1345, 1274, 1115, 985, 716 cm^{-1}; elemental analysis calcd for $C_{35}H_{37}NO_6$: C 74.05, H 6.57, N 2.47, O 16.91; found, C 74.25, H 6.62, N 2.42.

*(E)-3β-Benzoyloxy-16α,17α-epoxy-21-benzalpregn-5-en-20-one (**3cb**).* Procedure **A**: 1.207 g, quantitative yield; white solid; mp 252−254 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.07 (d, J = 7.5 Hz, 2H), 7.72 (d, J = 15.9 Hz, 1H), 7.58−7.55 (m, 3H), 7.45 (t, J = 7.6 Hz, 2H), 7.41−7.39 (m, 3H), 6.85 (d, J = 15.9 Hz, 1H), 5.44 (d, J = 4.4 Hz, 1H), 4.93−4.84 (m, 1H), 3.78 (s, 1H), 2.51−2.49 (m, 2H), 2.13 (d, J = 10.4 Hz, 1H), 1.16 (s, 3H), 1.12 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 194.9,

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165.9, 143.5, 140.0, 134.7, 132.7, 130.8, 130.5, 129.5, 128.9, 128.5, 128.3, 122.1, 121.0, 74.4, 71.2, 60.2, 50.3, 45.6, 42.0, 38.2, 36.9, 36.8, 31.6, 31.5, 29.8, 27.8, 27.7, 20.5, 19.3, 15.3; IR (KBr): ν 2943, 1712, 1679, 1604, 1276, 1115, 985, 758, 714 cm^{-1}. elemental analysis calcd for $C_{35}H_{38}O_4$: C 80.43, H 7.33, O 12.24; found, C 80.19, H 7.34.

*(E)-3β-(Tert-butyldimethylsilyloxy)-16α,17α-epoxy-21-(4-nitrobenzal)pregn-5-en-20-one (**3da**).* Procedure **A**: 1.298 g, quantitative yield; white solid; mp 255−257 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.25 (d, J = 8.6 Hz, 2H), 7.72−7.68 (m, 3H), 6.92 (d, J = 16.0 Hz, 1H), 5.33 (d, J = 4.7 Hz, 1H), 3.79 (s, 1H), 3.54−3.45 (m, 1H), 2.29 (t, J = 12.1 Hz, 1H), 2.19 (dd, J = 13.3, 3.3 Hz, 1H), 2.12−1.96 (m, 3H), 1.74 (d, J = 12.8 Hz, 1H), 1.15 (s, 3H), 1.05 (s, 3H), 0.91 (s, 9H), 0.08 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 194.4, 148.5, 141.9, 140.9, 140.3, 129.0, 124.6, 124.1, 120.4, 72.5, 71.3, 60.3, 50.4, 45.6, 42.8, 42.1, 37.3, 36.8, 32.0, 31.5, 29.8, 27.8, 25.9, 20.5, 19.4, 18.2, 15.2, −4.6; IR (KBr): ν 3117, 2931, 2856, 1682, 1602, 1516, 1344, 1251, 1099, 996, 834, 773 cm^{-1}; elemental analysis calcd (%) for $C_{34}H_{47}NSiO_5$: C 70.67, H 8.20, N 2.42, Si 4.86, O 13.84; found, C 70.79, H 8.25, N 2.45, Si 4.79.

*(E)-3β-(Tert-butyldimethylsilyloxy)-16α,17α-epoxy-21-benzal-pregn-5-en-20-one (**3db**).* Procedure **A**: 1.206 g, quantitative yield; white solid; mp 173−175 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.72 (d, J = 15.9 Hz, 1H), 7.58−7.56 (m, 2H), 7.40−7.39 (m, 3H), 6.85 (d, J = 15.9 Hz, 1H), 5.33 (d, J = 4.7 Hz, 1H), 3.76 (s, 1H), 3.54−3.46 (m, 1H), 2.29 (t, J = 12.1 Hz, 1H), 2.20 (dd, J = 12.1, 4.1 Hz, 1H), 2.05−1.95 (m, 2H), 1.82 (d, J = 13.3 Hz, 1H), 1.74 (d, J = 12.4 Hz, 1H), 1.14 (s, 3H), 1.05 (s, 3H), 0.91 (s, 9H), 0.08 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 194.7, 143.4, 141.8, 134.7, 130.5, 128.9, 128.5, 121.0, 120.6, 72.5, 71.2, 60.1, 50.4, 45.7, 42.9, 42.0, 37.3, 36.8, 32.1, 31.6, 31.6, 29.8, 27.8, 26.0, 20.5, 19.4, 18.2, 15.3, −4.5; IR (KBr): ν 3036, 2940, 2854, 1682, 1611, 1461, 1375, 1334, 1250, 1200, 1088, 981, 836, 761 cm^{-1}; elemental analysis calcd (%) for $C_{34}H_{48}SiO_3$: C 76.64, H 9.08, Si 5.27, O 9.01; found, C 76.57, H 9.15, Si 5.20.

*(E)-2-(4-Nitrobenzal)-4β,5β-epoxy-17α-methyl-17β-acetoxy-androstan-3-one (**3ea**).* Procedure **A**: 1.368 g, quantitative yield; white solid; mp 197−199 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.28 (d, J = 8.7 Hz, 2H), 7.74 (d, J = 2.1 Hz, 1H), 7.52 (d, J = 8.6 Hz, 1H), 3.28 (s, 1H), 2.71 (d, J = 16.0 Hz, 1H), 2.66 (dd, J = 16.0, 2.9 Hz, 2H), 2.29 (td, J = 13.3, 4.2 Hz, 1H), 1.94 (s, 3H), 1.36 (s, 3H), 1.22 (s, 3H), 0.77 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 195.5, 170.3, 147.5, 141.5, 135.0, 133.7, 130.5, 123.7, 90.3, 70.7, 62.5, 48.3, 48.1, 46.4, 38.5, 36.3, 35.7, 31.6, 31.3, 30.1, 29.6, 23.5, 21.9, 21.3, 21.2, 18.9, 14.2; IR (KBr): ν 2923, 1735, 1685, 1515, 1449, 1368, 1257, 1151, 1093, 940, 875 cm^{-1}; elemental analysis calcd (%) for $C_{29}H_{35}NO_6$: C 70.57, H 7.15, N 2.84, O 19.45; found, C 70.95, H 7.03, N 2.78.

*(E)-2-Benzal-4β,5β-epoxy-17α-methyl-17β-acetoxy-androstan-3-one (**3eb**).* Procedure **A**: 1.241 g, quantitative yield; white solid; mp 162−164 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.76 (d, J = 2.4 Hz, 1H), 7.43−7.34 (m, 5H), 3.25 (s, 1H), 2.83 (d, J = 15.9 Hz, 1H), 2.58 (dd, J = 15.9, 2.9 Hz, 1H), 2.28 (td, J = 13.2, 4.2 Hz, 1H), 1.94 (s, 3H), 1.36 (s, 3H), 1.22 (s, 3H), 0.77 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 196.2, 170.4, 138.0, 134.9, 130.7, 129.9, 128.8, 128.4, 90.5, 70.3, 62.7, 48.4, 47.9, 46.5, 38.4, 36.4, 35.7, 31.5, 31.4, 30.2, 29.6, 23.6, 22.0, 21.3, 21.0, 18.9, 14.2; IR (KBr): ν 2982, 2943, 1725, 1681, 1607, 1449, 1372, 1262, 1154, 1092, 1022, 761, 695, 547 cm^{-1}; elemental analysis calcd (%) for $C_{29}H_{36}O_4$: C 77.64, H 8.09, O 14.27; found, C 77.36, H 8.09.

*(E)-2-(4-Nitrobenzal)-4β,5β-epoxytigogenone (**3fa**).* Procedure **A**: 1.306 g, quantitative yield; white solid; mp 220−223 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.26 (d, J = 8.4 Hz, 2H), 7.72 (s, 1H), 7.50 (d, J = 8.4 Hz, 2H), 4.37 (dd, J = 14.7, 7.3 Hz, 1H), 3.47−3.45 (m, 1H), 3.34 (t, J = 10.9 Hz, 1H), 3.26 (s, 1H), 2.70−2.59 (m, 2H), 2.33−2.26 (m, 1H), 1.21 (s, 3H), 0.91 (d, J = 6.7 Hz, 3H), 0.78 (d, J = 6.1 Hz, 3H), 0.71 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 195.4, 147.5, 141.6, 134.9, 133.8, 130.4, 123.7, 109.2, 80.4, 70.6, 66.8, 62.5, 62.0, 55.3, 48.2, 41.5, 40.5, 39.0, 38.5, 34.8, 31.7, 31.6, 31.3, 30.5, 30.2, 29.6, 28.8, 21.4, 19.0, 17.1, 16.3, 14.4; IR (KBr): ν 2947, 1711, 1686, 1599, 1517, 1454, 1343, 1243, 1055, 982, 861 cm^{-1}; elemental analysis calcd (%) for $C_{34}H_{43}NO_6$: C 72.70, H 7.72, N 2.49, O 17.09; found, C 72.56, H 7.83, N 2.49.

*(E)-2-Benzal-4β,5β-epoxytigogenone (**3fb**).* Procedure **A**: 1.198 g, quantitative yield; white solid; mp 209−211 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.74 (d, J = 2.3 Hz, 1H), 7.42−7.33 (m, 5H), 4.38 (dd, J = 14.9, 7.5 Hz, 1H), 3.50−3.46 (m, 1H), 3.36 (t, J = 10.9 Hz, 1H), 3.24 (s, 1H), 2.81 (d, J = 15.9 Hz, 1H), 2.56 (dd, J = 15.9, 2.9 Hz, 1H), 2.29 (td, J = 13.2, 4.1 Hz, 1H), 1.21 (s, 3H), 0.92 (d, J = 6.9 Hz, 3H), 0.79 (d, J = 6.3 Hz, 3H), 0.71 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 196.0, 137.9, 135.0, 130.7, 129.9, 128.8, 128.4, 109.1, 80.5, 70.2, 66.8, 62.6, 62.0, 55.4, 47.9, 41.5, 40.5, 39.1, 38.4, 34.8, 31.7, 31.4, 31.3, 30.6, 30.2, 29.6, 28.8, 21.2, 19.0, 17.1, 16.3, 14.4; IR (KBr): ν 2943, 2903, 1686, 1616, 1449, 1377, 1175, 1052, 983, 901, 868, 697 cm^{-1}; elemental analysis calcd (%) for $C_{34}H_{44}O_4$: C 79.03, H 8.58, O 12.39; found, C 79.41, H 8.74.

*(E)-2-Phenyl-5-(4-nitrobenzal)-1-oxaspiro⟨2,5⟩octan-4-one (**3ga**).* Procedure **A**: 1.658 g, quantitative yield; yellow solid; mp 159−160 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.28 (d, J = 8.7 Hz, 2H), 7.70 (s, 1H), 7.59 (d, J = 8.6 Hz, 2H), 7.43−7.34 (m, 5H), 4.32 (s, 1H), 3.02−2.98 (m, 1H), 2.83−2.76 (m, 1H), 2.17−2.09 (m, 1H), 1.92−1.84 (m, 1H), 1.76−1.71 (m, 1H), 1.62−1.51 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 196.6, 147.4, 141.7, 138.9, 134.6, 133.8, 131.0, 128.5, 128.3, 126.8, 123.6, 65.5, 64.9, 28.5, 25.7, 21.4; IR (KBr): ν 3033, 2938, 1680, 1597, 1515, 1342, 1155, 1111, 929, 852, 712, 690 cm^{-1}; HRMS calcd for $C_{20}H_{17}NO_4Na$ [M + Na^+]: 358.1055; found: 358.1055.

*(E)-2-Phenyl-5-benzal-1-oxaspiro⟨2,5⟩octan-4-one (**3gb**).* Procedure **A**: 1.429 g, quantitative yield; white solid; mp 112−114 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.74 (s, 1H), 7.48−7.34 (m, 10H), 4.33 (s, 1H), 3.05 (d, J = 16.4 Hz, 1H), 2.85−2.77 (m, 1H), 2.15−2.07 (m, 1H), 1.89−1.81 (m, 1H), 1.73−1.69 (m, 1H), 1.60−1.49 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 196.8, 137.8, 135.8, 135.3, 134.2, 130.6, 129.2, 128.5, 128.3, 126.8, 65.2, 64.8, 28.5, 25.9, 21.6; IR (KBr): ν 3058, 3030, 2930, 2856, 1679, 1588, 1450, 1397, 1277, 1157, 934, 860, 762, 694 cm^{-1}; HRMS calcd for $C_{20}H_{18}O_2Na$ [M + Na^+]: 313.1204; found: 313.1205.

*(E)-2-phenyl-5-(3-methyl-butylidene)-1-oxaspiro⟨2,5⟩octan-4-one (**3gc**).* A mixture of **3g** (1.00 g), Aliquat 336 (100 mg, 5 mol %), isovaleraldehyde (640 mg, 2.0 equiv), Li_2CO_3 (73 mg, 20 mol %), PTFE sand (5 g), and water (8 mL) was mechanically stirred (400 rmp) at room temperature for 6 h. After TLC indicated completion of the reaction, it was stopped and extracted with ethyl acetate (3 × 8 mL), dried over Na_2SO_4 and purified by flash chromatograph on silica gel to afford 1.107 g of **3gc**: 83% yield; oil; ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.38−7.30 (m, 5H), 6.89 (tt, J = 7.6, 1.8 Hz, 1H), 4.25 (s, 1H), 2.67 (d, J = 16.2 Hz, 1H), 2.40 (t, J = 12.7 Hz, 1H), 2.07−1.96 (m, 3H), 1.85−1.77 (m, 2H), 1.63−1.60 (m, 1H), 1.52−1.45 (m, 1H), 0.95 (d, J = 6.7 Hz, 6H); ^{13}C NMR (151 MHz, $CDCl_3$): δ 196.2, 141.6, 136.3, 134.2, 128.2, 126.7, 65.0, 64.6, 37.4, 28.2, 26.3, 25.7, 22.6, 21.1; IR (KBr): ν 2958, 2872, 1729, 1608, 1454, 1387, 1277, 1172, 761, 702 cm^{-1}; HRMS calcd for $C_{18}H_{22}O_2Na$ [M + Na^+]: 293.1517; found: 293.1519.

*(E)-1-(2-Methyl-1,3-dioxan-2-yl)-3-(4-nitrophenyl)prop-2-en-1-one (**3ha**).* Procedure **A**: 1.931 g, quantitative yield; yellow solid; mp 138−140 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.27 (d, J = 8.7 Hz, 2H), 7.85 (d, J = 16.0 Hz, 1H), 7.78 (d, J = 8.7 Hz, 2H), 7.31 (d, J = 16.0 Hz, 1H), 4.02 (ddd, J = 12.5, 4.6, 1.9 Hz, 2H), 3.84 (td, J = 12.2, 2.5 Hz, 2H), 2.16−2.08 (m, 1H), 1.48 (s, 3H), 1.42 (d, J = 13.4 Hz, 1H); ^{13}C NMR (151 MHz, $CDCl_3$): δ 198.5, 148.7, 142.1, 140.6, 129.2, 124.2, 123.9, 101.0, 62.9, 24.9, 24.6; IR (KBr): ν 2983, 2933, 1702, 1615, 1524, 1347, 1197, 1069, 1043, 837 cm^{-1}; HRMS calcd for $C_{14}H_{15}NO_5Na$ [M + Na^+]: 300.0842, found: 300.0843.

*(E)-1-(2-Methyl-1,3-dioxan-2-yl)-3-phenylprop-2-en-1-one (**3hb**).* Procedure **A**: 1.466 g, 91% yield; white solid; mp 81−82 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.86 (d, J = 16.0 Hz, 1H), 7.63 (dd, J = 6.9, 2.2 Hz, 2H), 7.42−7.40 (m, 3H), 7.22 (d, J = 15.9 Hz, 1H), 3.99 (ddd, J = 11.0, 4.8, 1.4 Hz, 2H), 3.85 (td, J = 12.3, 2.3 Hz, 2H), 2.12 (qt, J = 12.4, 4.9 Hz, 1H), 1.46 (s, 3H), 1.37 (d, J = 13.4 Hz, 1H); ^{13}C NMR (151 MHz, $CDCl_3$): δ 198.3, 144.9, 134.4, 130.7, 128.8, 128.5, 120.3, 100.9, 62.6, 24.9, 24.7; IR (KBr): ν 2960, 2927, 2884, 2847, 1698, 1613, 1142, 1080, 1046, 769 cm^{-1}; HRMS calcd for $C_{14}H_{16}O_3Na$ [M + Na^+]: 255.0997, found: 255.0998.

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*(E)-3-(4-Methoxyphenyl)-1-(2-methyl-1,3-dioxan-2-yl)prop-2-en-1-one (**3hc**).* Procedure **A**: 1.692 g, 93% yield; white solid; mp 120−121 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.82 (d, J = 15.9 Hz, 1H), 7.58 (d, J = 8.7 Hz, 2H), 7.10 (d, J = 15.9 Hz, 1H), 6.93 (d, J = 8.7 Hz, 2H), 3.98 (ddd, J = 11.0, 4.8, 1.4 Hz, 2H), 3.88−3.84 (m, 5H), 2.11 (qt, J = 12.4, 4.9 Hz, 1H), 1.45 (s, 3H), 1.36 (d, J = 13.3 Hz, 1H); ^{13}C NMR (151 MHz, $CDCl_3$): δ 198.3, 161.9, 144.8, 130.4, 127.1, 117.9, 114.3, 101.0, 62.6, 55.3, 55.2, 24.9; IR (KBr): ν 2978, 2853, 1682, 1597, 1568, 1511, 1251, 1045, 800, 551 cm^{-1}; HRMS calcd for $C_{15}H_{18}O_4Na$ [M + Na$^+$]: 285.1103, found: 285.1108.

*Preparation of (E)-1-(2-benzofuranyl)-5-methylhex-2-en-1-one (**3ia**).* A mixture of **3i** (1.00 g), isovaleraldehyde (2.0 equiv), Aliquat 336 (5 mol %), LiOH (1.0 equiv), PTFE sand (5 g), and water (5 mL) was mechanically stirred (400 rmp) at 0 °C for 1 h. After stopping the reaction by adding 1.2 equiv of acetic acid in 1 mL of water, it was extracted with ethyl acetate (3 × 10 mL), dried over Na_2SO_4, and purified by flash chromatograph on silica gel to afford the starting material **3i** (149 mg) and **3ia** (382 mg, 32% yield). **3ia**: Yellow solid; mp 68−70 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.71 (d, J = 7.8 Hz, 1H), 7.60 (dd, J = 8.4, 0.6 Hz, 1H), 7.56 (d, J = 0.8 Hz, 1H), 7.49−7.46 (m, 1H), 7.32−7.30 (m, 1H), 7.23 (dt, J = 15.2, 7.5 Hz, 1H), 6.94 (dt, J = 15.4, 1.4 Hz, 1H), 2.24 (td, J = 7.1, 1.4 Hz, 2H), 1.91−1.82 (m, 1H), 0.98 (d, J = 6.7 Hz, 6H). ^{13}C NMR (151 MHz, $CDCl_3$): δ 179.7, 155.7, 153.4, 148.9, 128.1, 127.2, 126.0, 123.9, 123.2, 113.2, 112.4, 42.1, 28.0, 22.5; IR (KBr): ν 3120, 3088, 1675, 1611, 1553, 1293, 1174, 1107, 1076, 847, 755 cm^{-1}; elemental analysis calcd (%) for $C_{15}H_{16}O_2$: C 78.92, H 7.06, O 14.02; found: C 78.73, H 7.14.

*(E)-3β-Hydroxy-3′-phenyl-4′,5′-dihydro-3′H-[16,17-d]triazol-21-benzalpregn-5-en-20-one (**3ja**).* As both the starting material and the product are photosensitive, the reaction flask was covered with aluminum foil, and the filtration was conducted in the dark. Procedure **A**: 1.209 g, quantitative yield; white solid; mp 140−151 °C (decomposition); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.77 (d, J = 15.9 Hz, 1H), 7.68−7.66 (m, 2H), 7.50 (d, J = 15.9 Hz, 1H), 7.44−7.33 (m, 7H), 7.07 (t, J = 6.7 Hz, 1H), 5.28 (d, J = 3.8 Hz, 1H), 5.00 (d, J = 6.4 Hz, 1H), 3.56−3.48 (m, 1H), 2.31−2.22 (m, 3H), 1.01 (s, 3H), 0.88 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 192.5, 144.0, 140.9, 139.3, 134.6, 130.8, 129.4, 129.0, 128.8, 123.4, 122.7, 120.8, 114.7, 107.5, 71.5, 57.3, 51.5, 50.5, 49.3, 42.1, 37.2, 36.5, 33.2, 33.0, 31.8, 31.5, 31.3, 26.9, 20.6, 19.3, 15.9; IR (KBr): ν 3306, 2931, 1735, 1679, 1600, 1499, 1444, 1360, 1331, 1114, 1024, 910, 731, 649 cm^{-1}; elemental analysis calcd (%) for $C_{34}H_{39}N_3O_2$: C 78.28, H 7.54, N 8.05, O 6.13; found, C 78.08, H 7.59, N 8.11.

Product **4aa** (6.91 g, 79% yield) were synthesized according to procedure **B** (6.00 g of **4a** was used and 0.72 g was recovered) and is known.[7a]

*1-(2-Furanyl)-3-hydroxyhexan-1-one (**4ab**).* Procedure **B**: (6.00 g of **4a** was used and 2.70 g was recovered); 3.77 g, 69% yield; oil; ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.61 (d, J = 2.5 Hz, 1H), 7.23 (s, 1H), 6.57−6.54 (m, 1H), 4.20 (s, 1H), 3.04 (d, J = 17.0 Hz, 1H), 2.91 (ddd, J = 17.0, 9.2, 2.3 Hz, 1H), 1.58−1.41 (m, 4H), 0.97−0.93 (m, 3H); ^{13}C NMR (151 MHz, $CDCl_3$): δ 188.7, 152.4, 146.8, 117.9, 112.2, 67.4, 45.2, 38.8, 18.5, 13.7; IR (KBr): ν 3443, 3132, 2961, 2931, 2872, 1666, 1568, 1467, 1395, 1016, 768 cm^{-1}; HRMS calcd for $C_{10}H_{14}O_3Na$ [M + Na$^+$]: 205.0841, found: 205.0846.

*3-Hydroxy-4-methyl-1-(2-thiophenyl)pentan-1-one (**4ba**).* Procedure **B**: (6.00 g of **4b** was used and 0.78 g was recovered); 6.24 g, 76% yield; oil; ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.75 (dd, J = 3.7, 1.0 Hz, 1H), 7.69−7.67 (m, 1H), 7.16−7.14 (m, 1H), 3.99−3.97 (m, 1H), 3.19 (s, 1H), 3.11 (dt, J = 16.8, 2.4 Hz, 1H), 2.99 (ddd, J = 16.8, 9.6, 1.4 Hz, 1H), 1.82−1.77(m, 1H), 1.01 (dd, J = 6.8, 2.2 Hz, 3H), 0.99 (dd, J = 6.8, 2.1 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$): δ 193.5, 144.2, 134.2, 132.8, 128.3, 72.5, 43.0, 33.3, 18.5, 17.6; IR (KBr): ν 3470, 3094, 2962, 1653, 1517, 1415, 1233, 1059, 727 cm^{-1}; HRMS calcd for $C_{10}H_{14}O_2SNa$ [M + Na$^+$]: 221.0612, found: 221.0618.

*3-Hydroxy-1-(2-thiophenyl)hexan-1-one (**4bb**).* Procedure **B**: (20.00 g of **4b** was used and 9.81 g recovered); 10.10 g, 63%; oil; ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.74 (s, 1H), 7.68 (d, J = 3.0 Hz, 1H), 7.15 (d, J = 2.6 Hz, 1H), 4.22 (s, 1H), 3.21 (s, 1H), 3.11 (d, J = 17.0 Hz, 1H), 3.00 (dd, J = 17.0, 9.1 Hz, 1H), 1.61−1.41 (m, 4H), 0.96 (t, J = 6.7 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$): δ 193.6, 144.1, 134.3, 132.6, 128.3, 67.7, 45.7, 38.7, 18.8, 14.0; IR (KBr): ν 3446, 3100, 2959, 2971, 2871, 1653, 1517, 1415, 1359, 1234, 1063, 726 cm^{-1}; HRMS calcd for $C_{10}H_{14}O_2SNa$ [M + Na$^+$]: 221.0612, found: 221.0617.

Product **4bc** (2.54 g, 58% yield) were synthesized according to procedure **B** (6.00 g of **4b** was used and 2.82 g was recovered) and is known.[7b]

*3-Hydroxy-4-methyl-1-(2-pyridinyl)pentan-1-one (**4ca**).* Procedure **B**: (500 mg of **4c** was used, 519 mg of **4ca** was obtained); oil; ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.69 (d, J = 3.2 Hz, 1H), 8.08 (d, J = 7.8 Hz, 1H), 7.88 (t, J = 7.6 Hz, 1H), 7.52−7.50 (m, 1H), 3.95−3.93 (m, 2H), 3.35 (d, J = 16.4 Hz, 1H), 3.28 (dd, J = 16.5, 9.2 Hz, 1H), 1.88−1.78 (m, 1H), 1.02 (t, J = 6.3 Hz, 6H); ^{13}C NMR (151 MHz, $CDCl_3$): δ 202.1, 153.2, 148.7, 137.2, 127.3, 122.0, 72.6, 42.6, 33.6, 18.4, 17.7; IR (KBr): ν 3447, 3058, 2962, 1694, 1621, 1467, 1384, 1044, 998, 778, 616 cm^{-1}; HRMS calcd for $C_{11}H_{15}NO_2Na$ [M + Na$^+$]: 216.1000, found: 216.0999.

*3-Hydroxy-1-(2-pyridinyl)hexan-1-one (**4cb**).* A mixture of **4c** (300 mg), butyraldehyde (2.0 equiv), LiOH (0.5 equiv), and water (0.9 mL) was magnetically stirred (400 rmp) at 0 °C for 1.5 h. The reaction was stopped and extracted with ethyl acetate (3 × 5 mL), dried over Na_2SO_4, and purified by flash chromatograph on silica gel to afford **4cb** (182 mg, 38% yield); oil; ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.68 (s, 1H), 8.07 (d, J = 7.4 Hz, 1H), 7.88 (t, J = 7.1 Hz, 1H), 7.51 (s, 1H), 4.18 (s, 1H), 3.90 (s, 1H), 3.41 (d, J = 16.8 Hz, 1H), 3.26 (dd, J = 16.6, 9.0 Hz, 1H), 1.62−1.44 (m, 4H), 0.96 (t, J = 6.1 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$): δ 202.0, 153.1, 148.8, 137.2, 127.4, 122.0, 67.7, 45.5, 39.2, 18.8, 14.0; IR (KBr): ν 3429, 3056, 2959, 2931, 2872, 1695, 1623, 1585, 1570, 1465, 1215, 997, 773 cm^{-1}; HRMS calcd for $C_{11}H_{13}NONa$ [M − H_2O + Na$^+$]: 198.0895, found: 198.0899.

*1-(2-Benzofuranyl)-3-hydroxy-5-methylhexan-1-one (**4da**).* A mixture of **3i** (1.0 g), isovaleraldehyde (2.0 equiv), Aliquat 336 (5 mol %), LiOH (2.0 equiv), PTFE sand (5 g), and water (8 mL) was mechanically stirred (400 rmp) at −18 °C for 1.5 h. After stopping the reaction by adding 2.2 equiv of acetic acid in 1 mL of water, it was extracted with ethyl acetate (3 × 10 mL), dried over Na_2SO_4, and purified by flash chromatograph on silica gel to afford the starting material **3i** (492 mg) and **4da** (726 mg, 93% yield). **4da**: white solid; mp 63−64 °C; ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.71 (d, J = 7.9 Hz, 1H), 7.58 (dd, J = 8.4, 0.7 Hz, 1H), 7.54 (d, J = 0.9 Hz, 1H), 7.49 (t, J = 7.8 Hz, 1H), 7.32 (t, J = 7.6 Hz, 1H), 4.37−4.32 (m, 1H), 3.14 (ddd, J = 17.1, 2.6, 2.0 Hz, 1H), 3.06 (dd, J = 17.2, 8.9 Hz, 1H), 2.99−2.96 (m, 1H), 1.92−1.83 (m, 1H), 1.63−1.58 (m, 1H), 1.32−1.27 (m, 1H), 0.96 (dt, J = 6.7, 1.3 Hz, 6H); ^{1}H NMR (600 MHz, $CDCl_3$-D_2O): δ 7.71 (d, J = 7.9 Hz, 1H), 7.57 (d, J = 8.4 Hz, 1H), 7.54 (d, J = 0.6 Hz, 1H), 7.50−7.47 (m, 1H), 7.32 (t, J = 7.5 Hz, 1H), 4.35−4.31 (m, 1H), 3.14 (dd, J = 17.1, 2.9 Hz, 1H), 3.06 (dd, J = 17.1, 8.9 Hz, 1H), 1.90−1.85 (m, 1H), 1.62−1.58 (ddd, J = 14.3, 9.0, 5.6 Hz, 1H), 1.32−1.27 (m, 1H), 0.96 (dd, J = 6.7, 1.5 Hz, 6H); ^{13}C NMR (151 MHz, $CDCl_3$): δ 191.4, 155.7, 152.4, 128.5, 126.9, 124.0, 123.4, 113.5, 112.4, 66.0, 46.0, 45.9, 24.5, 23.3, 22.1; IR (KBr): ν 3502, 2953, 2916, 1668, 1554, 1400, 1288, 1138, 1012, 746, 657 cm^{-1}; HRMS calcd for $C_{15}H_{18}O_3Na$ [M + Na$^+$]: 269.1154, found: 269.1158.

*(S,2E,4Z)-4,6-Bis(benzyloxy)-1-cyclopropyl-7-hydroxyhepta-2,4-dien-1-one (**5aa**).* Procedure **C**: 371 mg, 98% yield; syrup; ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.39−7.26 (m, 10H), 7.03 (d, J = 15.7 Hz, 1H), 6.58 (d, J = 15.7 Hz, 1H), 5.44 (d, J = 9.2 Hz, 1H), 4.81 (d, J = 11.4 Hz, 1H), 4.75 (d, J = 11.5 Hz, 1H), 4.48 (d, J = 11.6 Hz, 1H), 4.36 (ddd, J = 9.5, 7.3, 3.8 Hz, 1H), 4.26 (d, J = 11.6 Hz, 1H), 3.45−3.37 (m, 2H), 2.16−2.12 (m, 2H), 1.14 (dt, J = 7.3, 3.5 Hz, 2H), 0.99−0.95 (m, 2H); ^{13}C NMR (151 MHz, $CDCl_3$): δ 200.1, 154.8, 138.1, 136.9, 136.5, 128.7, 128.53, 128.46, 128.4, 128.0, 127.8, 127.4, 124.9, 74.4, 74.3, 70.8, 64.7, 20.2, 11.7; IR (KBr): ν 3450, 3062, 3031, 2923, 2871, 1674, 1645, 1599, 1496, 1452, 1390, 1207, 1181, 1082, 1027, 739, 699 cm^{-1}; HRMS calcd for $C_{24}H_{26}O_4Na$ [M + Na$^+$]: 401.1723, found: 401.1721.

*(2E,4Z,6S,7R)-4,6,8-Tris(benzyloxy)-1-cyclopropyl-7-hydroxyocta-2,4-dien-1-one (**5ab**).* Procedure **C**: 484 mg, 97% yield; syrup; ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.36−7.25 (m, 15H), 7.08 (d, J = 15.8 Hz, 1H), 6.57 (d, J = 15.7 Hz, 1H), 5.57 (d, J = 9.5 Hz, 1H), 4.77 (d, J = 11.8 Hz, 1H), 4.75 (d, J = 11.8 Hz, 1H), 4.49 (s, 2H), 4.46 (d, J = 11.8 Hz, 1H), 4.43 (dd, J = 9.6, 5.8 Hz, 1H), 4.24 (d, J = 11.8 Hz, 1H),

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3.88 (p, J = 4.7 Hz, 1H), 3.54 (dd, J = 9.7, 4.0 Hz, 1H), 3.50 (dd, J = 9.7, 6.1 Hz, 1H), 2.41 (d, J = 4.8 Hz, 1H), 2.16−2.12 (m, 1H), 1.15−1.12 (m, 2H), 0.99−0.96 (m, 2H); ^{13}C NMR (151 MHz, $CDCl_3$): δ 200.1, 155.8, 138.1, 138.0, 137.1, 136.8, 128.6, 128.5, 128.4, 128.3, 128.2, 128.0, 127.83, 127.79, 127.7, 127.4, 124.7, 74.5, 73.7, 73.4, 72.2, 70.9, 70.6, 20.0, 11.7; IR (KBr): ν 3458, 3063, 3031, 2915, 2867, 1675, 1650, 1599, 1497, 1454, 1389, 1206, 1182, 1084, 1027, 737, 698 cm^{-1}; HRMS calcd for $C_{32}H_{34}O_5Na$ [M + Na$^+$]: 521.2298, found: 521.2298.

*(S,5E,7Z)-7,9-Bis(benzyloxy)-10-hydroxy-2-methyldeca-5,7-dien-4-one (**5ba**).* Procedure **C**: syrup; 387 mg, 98% yield; ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.39−7.26 (m, 10H), 6.97 (d, J = 15.8 Hz, 1H), 6.43 (d, J = 15.8 Hz, 1H), 5.44 (d, J = 9.2 Hz, 1H), 4.78 (d, J = 11.4 Hz, 1H), 4.72 (d, J = 11.4 Hz, 1H), 4.48 (d, J = 11.6 Hz, 1H), 4.35 (ddd, J = 9.3, 7.2, 3.9 Hz, 1H), 4.26 (d, J = 11.6 Hz, 1H), 3.44 (dd, J = 11.5, 7.1 Hz, 1H), 3.40 (dd, J = 11.4, 3.5 Hz, 1H), 2.45 (d, J = 7.0 Hz, 2H), 2.21−2.14 (m, 1H), 0.96 (d, J = 6.6 Hz, 1H); ^{13}C NMR (151 MHz, $CDCl_3$): δ 200.2, 154.8, 138.1, 137.2, 136.5, 128.7, 128.53, 128.45, 128.4, 128.0, 127.8, 127.6, 125.0, 74.42, 74.41, 70.8, 64.7, 50.3, 25.1, 22.7; IR (KBr): ν 3445, 3063, 3032, 2957, 2929, 2871, 1685, 1658, 1631, 1600, 1496, 1456, 1295, 1091, 1057, 739, 698 cm^{-1}; HRMS calcd for $C_{25}H_{30}O_4Na$ [M + Na$^+$]: 417.2042, found: 417.2042.

*(5E,7Z,9S,10R)-7,9,11-Tris(benzyloxy)-10-hydroxy-2-methylundeca-5,7-dien-4-one (**5bb**).* Procedure **C**: 510 mg, 99% yield; syrup; ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.36−7.24 (m, 15 H), 7.00 (d, J = 15.8 Hz, 1H), 6.42 (d, J = 15.8 Hz, 1H), 5.56 (d, J = 9.6 Hz, 1H), 4.74 (d, J = 11.6 Hz, 1H), 4.72 (d, J = 11.6 Hz, 1H), 4.48 (s, 2H), 4.46 (d, J = 11.8 Hz, 1H), 4.42 (dd, J = 9.5, 5.8 Hz, 1H), 4.24 (d, J = 11.8 Hz, 1H), 3.91−3.85 (m, 1H), 3.54 (dd, J = 9.7, 4.1 Hz, 1H), 3.50 (dd, J = 9.7, 6.1 Hz, 1H), 2.45 (d, J = 6.9 Hz, 2H), 2.21−2.14 (m, 1H), 0.95 (d, J = 6.6 Hz, 6H); ^{13}C NMR (151 MHz, $CDCl_3$): δ 200.3, 155.7, 138.2, 138.0, 137.6, 136.8, 128.7, 128.5, 128.42, 128.35, 128.2, 128.0, 127.84, 127.80, 127.75, 127.0, 124.8, 74.6, 73.7, 73.4, 72.2, 70.9, 70.7, 50.2, 25.2, 22.8; IR (KBr): ν 3444, 3063, 3032, 2956, 2926, 2878, 1685, 1660, 1599, 1496, 1455, 1365, 1297, 1204, 1063, 1026, 739, 698 cm^{-1}; HRMS calcd for $C_{33}H_{38}O_5Na$ [M + Na$^+$]: 537.2617, found: 537.2617.

*(16E)-16-((S,Z)-2,4-Bis(benzyloxy)-5-hydroxypent-2-enylidene)-3β-hydroxy-androst-5-en-17-one (**5ca**).* Procedure **D**: 373 mg, 64% yield; white powder; ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.36−7.25 (m, 10H), 6.92 (s, 1H), 5.37 (d, J = 1.8 Hz, 1H), 5.21 (d, J = 8.7 Hz, 1H), 4.83 (d, J = 11.6 Hz, 1H), 4.65 (d, J = 11.6 Hz, 1H), 4.44−4.41 (m, 1H), 4.34 (d, J = 11.5 Hz, 1H), 4.13 (d, J = 11.9 Hz, 1H), 3.56−3.49 (m, 3H), 2.78 (dd, J = 16.4, 6.0 Hz, 1H), 2.33−2.17 (m, 4H), 2.03−2.95 (m, 2H), 1.05 (s, 3H), 0.93 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$): δ 209.1, 154.0, 141.3, 138.3, 138.2, 136.4, 128.6, 128.52, 128.45, 127.81, 127.76, 127.6, 121.0, 120.7, 75.1, 73.3, 71.3, 70.7, 64.8, 50.2, 49.4, 47.5, 42.1, 37.1, 36.7, 31.5, 31.4, 31.1, 30.8, 29.2, 20.4, 19.5, 14.1; IR (KBr): ν 3423, 3031, 2932, 2859, 1717, 1624, 1496, 1455, 1398, 1090, 1058, 738, 698 cm^{-1}; HRMS calcd for $C_{38}H_{46}O_5Na$ [M + Na$^+$]: 605.3243, found: 605.3242.

*(16E)-16-((4S,5R,Z)-2,4,6-Tris(benzyloxy)-5-hydroxyhex-2-enylidene)-3β-hydroxy-androst-5-en-17-one (**5cb**).* Procedure **D**: 478 mg, 68% yield; white powder; ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.33−7.26 (m, 13H), 7.21 (d, J = 7.1 Hz, 2H), 6.96 (s, 1H), 5.34 (d, J = 2.3 Hz, 1H), 5.32 (d, J = 9.2 Hz, 1H), 4.83 (d, J = 11.6 Hz, 1H), 4.62 (d, J = 11.6 Hz, 1H), 4.52 (d, J = 11.7 Hz, 1H), 4.50 (d, J = 11.7 Hz, 1H), 4.46 (dd, J = 8.6, 5.6 Hz, 1H), 4.30 (d, J = 11.6 Hz, 1H), 4.10 (d, J = 11.6 Hz, 1H), 3.94−3.90 (m, 1H), 3.57 (dd, J = 9.3, 2.6 Hz, 1H), 3.54−3.48 (m, 2H), 2.76 (dd, J = 16.4, 6.0 Hz, 1H), 2.61 (d, J = 3.1 Hz, 1H), 2.29 (dd, J = 13.2, 4.2 Hz, 1H), 2.25−2.16 (m, 2H), 1.87−1.82 (m, 3H), 1.03 (s, 3H), 0.92 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$): δ 209.0, 154.7, 141.3, 138.34, 138.33, 138.2, 136.7, 128.6, 128.5, 128.40, 128.36, 128.3, 127.8, 127.74, 127.68, 127.6, 120.7, 120.4, 74.4, 73.4, 73.3, 72.6, 71.4, 71.1, 70.6, 50.3, 49.5, 47.5, 42.1, 37.2, 36.7, 31.6, 31.5, 31.1, 30.9, 29.2, 20.4, 19.5, 14.2; IR (KBr): ν 3442, 3063, 3031, 2932, 2860, 1716, 1627, 1496, 1455, 1376, 1090, 1025, 910, 733, 698 cm^{-1}; HRMS calcd for $C_{46}H_{54}O_6$ [M + Na$^+$]: 725.3818, found: 725.3817.

*(E)-16-((S,Z)-2,4-Bis(benzyloxy)-5-hydroxypent-2-enylidene)-O-benzyl-estrone (**5da**).* Procedure **D**: 380 mg, 58% yield; white powder; ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.36−7.20 (m, 16H), 6.95 (s, 1H), 6.80 (dd, J = 8.5, 2.5 Hz, 1H), 6.74 (d, J = 2.3 Hz, 1H), 5.22 (d, J = 8.8 Hz, 1H), 5.03 (s, 2H), 4.85 (d, J = 11.7 Hz, 1H), 4.67 (d, J = 11.4 Hz, 1H), 4.43 (ddd, J = 8.6, 7.0, 4.6 Hz, 1H), 4.36 (d, J = 11.6 Hz, 1H), 4.14 (d, J = 11.6 Hz, 1H), 3.53−3.51 (m, 1H), 2.89−2.85 (m, 3H), 2.44−2.40 (m, 1H), 2.31−2.24 (m, 2H), 2.18 (s, 1H), 2.07−2.04 (m, 1H), 1.90−1.88 (m, 1H), 1.66−1.39 (m, 6H), 0.94 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$): δ 209.0, 157.0, 154.2, 138.5, 138.4, 137.8, 137.3, 136.6, 132.3, 128.70, 128.67, 128.61, 128.57, 128.5, 128.0, 127.8, 127.7, 127.6, 127.0, 126.4, 120.8, 115.0, 112.5, 75.1, 73.4, 70.8, 70.0, 65.0, 48.2, 48.0, 44.1, 37.9, 31.7, 29.7, 29.0, 26.8, 26.0, 14.6; IR (KBr): ν 3552, 3343, 3063, 3032, 2929, 2858, 1716, 1646, 1629, 1499, 1454, 1228, 1085, 1047, 1013, 750, 730 cm^{-1}; HRMS calcd for $C_{44}H_{46}O_5Na$ [M + Na$^+$]: 677.3243, found: 677.3247.

*(E)-16-((4S,5R,Z)-2,4,6-Tris(benzyloxy)-5-hydroxyhex-2-enylidene)-O-benzyl-estrone (**5db**).* Procedure **D**: 473 mg, 61% yield; white powder; ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.44−7.22 (m, 21H), 6.99 (s, 1H), 6.80 (d, J = 7.8 Hz, 1H), 6.74 (s, 1H), 5.34 (d, J = 8.9 Hz, 1H), 5.04 (s, 2H), 4.86 (d, J = 11.6 Hz, 1H), 4.65 (d, J = 11.5 Hz, 1H), 4.52 (s, 2H), 4.48−4.45 (m, 1H), 4.32 (d, J = 11.5 Hz, 1H), 4.12 (d, J = 11.4 Hz, 1H), 3.93 (s, 1H), 3.59−3.54 (m, 2H), 2.85 (s, 2H), 2.87 (s, 1H), 2.47−2.42 (m, 2H), 2.30−2.25 (m, 2H), 2.06 (d, J = 8.8 Hz, 1H), 1.87 (d, J = 11.3 Hz, 1H), 1.68−1.38 (m, 6H), 0.94 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$): δ 209.0, 157.0, 154.8, 138.54, 138.50, 138.3, 137.8, 137.4, 136.9, 132.4, 128.73, 128.71, 128.6, 128.51, 128.45, 128.1, 128.0, 127.90, 127.86, 127.82, 127.76, 127.6, 127.0, 126.5, 120.6, 115.1, 112.6, 74.5, 73.5, 73.4, 72.7, 71.2, 70.6, 70.0, 48.2, 48.1, 44.1, 37.9, 31.8, 29.8, 29.1, 26.9, 26.1, 14.6; IR (KBr): ν 3446, 3062, 3031, 2927, 2863, 1717, 1611, 1498, 1454, 1252, 1231, 1082, 1021, 910, 735, 698 cm^{-1}; HRMS calcd for $C_{52}H_{54}O_6Na$ [M + Na$^+$]: 797.3813, found: 797.3813.

*(S,Z)-3-(1,3-Bis(benzyloxy)-4-hydroxybut-1-enyl)-1,5-diphenylpentane-1,5-dione (**5ea**).* Procedure **C**: 519 mg, 97% yield; syrup; ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.97 (t, J = 7.2 Hz, 4H), 7.57 (t, J = 7.3 Hz, 2H), 7.46 (t, J = 7.7 Hz, 4H), 7.35−7.21 (m, 10H), 4.84 (d, J = 11.8 Hz, 1H), 4.81 (d, J = 11.8 Hz, 1H), 4.60 (d, J = 9.0 Hz, 1H), 4.42−4.39 (m, 2H), 4.19 (d, J = 11.7 Hz, 1H), 3.82 (p, J = 6.8 Hz, 1H), 3.42 (ddd, J = 12.0, 7.3, 5.0 Hz, 1H), 3.36 (ddd, J = 11.6, 7.9, 3.9 Hz, 1H), 3.30−3.20 (m, 4H), 2.18 (dd, J = 7.8, 5.1 Hz, 1H); ^{13}C NMR (151 MHz, $CDCl_3$): δ 198.74, 198.68, 160.7, 138.6, 137.2, 136.9, 133.5, 133.4, 128.82, 128.80, 128.6, 128.4, 128.27, 128.26, 128.11, 128.08, 128.0, 127.6, 108.6, 74.2, 72.3, 70.0, 65.3, 41.9, 41.7, 33.8; IR (KBr): ν = 3492, 3062, 3032, 2919, 2870, 1681, 1598, 1450, 1391, 1277, 1215, 1155, 1056, 752, 695 cm^{-1}; HRMS of **5ea** + 4H obtained from the reduction of **5ea** using $NaBH_4$ in methanol: calcd for $C_{35}H_{38}O_5Na$ [M + Na$^+$]: 561.2611; found: 561.2610.

*3-((3S,4R,Z)-1,3,5-Tris(benzyloxy)-4-hydroxypent-1-enyl)-1,5-diphenylpentane-1,5-dione (**5eb**).* Procedure **C**: 650 mg, 99% yield; syrup; ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.98−7.95 (m, 4H), 7.58−7.55 (m, 2H), 7.47−7.44 (m, 4H), 7.33−7.16 (m, 15H), 4.83 (d, J = 11.5 Hz, 1H), 4.80 (d, J = 11.5 Hz, 1H), 4.75 (d, J = 9.3 Hz, 1H), 4.50−4.45 (m, 2H), 4.42 (dd, J = 8.8, 5.6 Hz, 1H), 4.38 (d, J = 11.9 Hz, 1H), 4.17 (d, J = 11.8 Hz, 1H), 3.84−3.80 (m, 1H), 3.49−3.42 (m, 2H), 3.33−3.19 (m, 4H), 2.46 (s, 1H); ^{13}C NMR (151 MHz, $CDCl_3$): δ 198.73, 198.72, 161.4, 138.7, 138.4, 137.4, 136.9, 133.44, 133.42, 128.8, 128.5, 128.4, 128.33, 128.31, 128.28, 127.99, 127.97, 127.9, 127.8, 127.6, 127.5, 107.8, 73.5, 73.4, 72.8, 72.3, 71.1, 69.9, 42.0, 41.8, 34.0; IR (KBr): ν 3430, 3153, 1682, 1631, 1597, 1449, 1400, 1215, 1181, 1023, 1001, 754, 690 cm^{-1}; HRMS calcd for $C_{43}H_{42}O_6Na$ [M + Na$^+$]: 677.2874, found: 677.2876.

*(S,Z)-3-(1,3-Bis(benzyloxy)-4-hydroxybut-1-enyl)-1,5-bis(4-fluorophenyl)pentane-1,5-dione (**5fa**).* Procedure **C**: 564 mg, 99% yield; syrup; ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.05−7.97 (m, 4H), 7.35−7.19 (m, 10H), 7.14−7.11 (m, 4H), 4.84 (d, J = 11.6 Hz, 1H), 4.82 (d, J = 11.6 Hz, 1H), 4.60 (d, J = 9.0 Hz, 1H), 4.44−4.38 (m, 2H), 4.21 (d, J = 11.7 Hz, 1H), 3.77 (p, J = 6.8 Hz, 1H), 3.43 (dd, J = 11.2, 7.4 Hz, 1H), 3.38 (dd, J = 11.3, 4.0 Hz, 1H), 3.24−3.17 (m, 4H), 2.18 (s, 1H); ^{13}C NMR (151 MHz, $CDCl_3$): δ 197.1, 197.0, 165.90 (d, $^1J_{CF}$ = 255.1 Hz), 165.89 (d, $^1J_{CF}$ = 255.1 Hz), 160.5, 138.5, 137.1, 133.22 (d, $^4J_{CF}$ = 2.6 Hz), 133.21 (d, $^4J_{CF}$ = 2.6 Hz), 130.91 (d, $^3J_{CF}$ = 9.3 Hz), 130.88 (d, $^3J_{CF}$ = 9.3 Hz,), 128.6, 128.4, 128.1, 128.0, 127.9, 127.6, 115.9 (d, $^2J_{CF}$ = 21.8 Hz), 108.7, 74.1, 72.4, 70.0, 65.3, 41.7, 41.5, 33.9; IR (KBr): ν 3064, 3031, 2919, 2865, 1682, 1597, 1504,

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1453, 1231, 1156, 1089, 1068, 838, 739, 698 cm^{-1}; HRMS of **5fa** + 4H obtained from the reduction of **5fa** using $NaBH_4$ in methanol: calcd for $C_{35}H_{36}F_2O_5Na$ [M + Na^+]: 597.2423; found: 597.2427.

*1,5-Bis(4-fluorophenyl)-3-((3S,4R,Z)-1,3,5-tris(benzyloxy)-4-hydroxypent-1-enyl)pentane-1,5-dione (**5fb**).* Procedure **C**: 687 mg, 99% yield; syrup; ^1H NMR (600 MHz, $CDCl_3$): δ 7.97−7.80 (m, 4H), 7.30−7.17 (m, 15H), 7.13−7.09 (m, 4H), 4.83 (d, J = 11.5 Hz, 1H), 4.80 (d, J = 11.5 Hz, 1H), 4.74 (d, J = 9.4 Hz, 1H), 4.49 (d, J = 11.9 Hz, 1H), 4.47 (d, J = 11.9 Hz, 1H), 4.43 (dd, J = 9.4, 5.5 Hz, 1H), 4.38 (d, J = 11.9 Hz, 1H), 4.18 (d, J = 11.9 Hz, 1H), 3.84−3.80 (m, 1H), 3.79−3.74 (m, 1H), 3.49 (dd, J = 9.8, 3.7 Hz, 1H), 3.44 (dd, J = 9.8, 6.4 Hz, 1H), 3.26−3.14 (m, 4H), 2.49 (d, J = 3.4 Hz, 1H); ^{13}C NMR (151 MHz, $CDCl_3$): δ 197.14, 197.13, 165.9 (d, $^1J_{CF}$ = 254.8 Hz), 161.2, 138.7, 138.4, 137.4, 133.3, 131.00 (d, $^3J_{CF}$ = 9.2 Hz), 130.97 (d, $^3J_{CF}$ = 9.2 Hz), 128.5, 128.43, 128.36, 128.0, 127.9, 127.8, 127.7, 127.6, 115.9 (d, $^2J_{CF}$ = 21.8 Hz), 108.0, 73.6, 73.4, 72.7, 72.5, 71.2, 69.9, 41.8, 41.7, 34.2; IR (KBr): ν 3065, 3032, 2907, 2867, 1683, 1597, 1504, 1453, 1231, 1157, 1090, 1068, 838, 739, 699 cm^{-1}; HRMS calcd for $C_{43}H_{40}F_2O_6Na$ [M + Na^+]: 713.2691, found: 713.2685.

Stereochemistry for 5aa−5fb. The configurations of the conjugated diene or enolether groups for **5aa−5fb** were indicated by the NOESY spectra.

Recycling Procedures for the Aqueous Reactions for 1cc. A mixture of **1c** (1 g), Aliquat 336 (10 mol %), *p*-methoxybenzaldehyde (1.05 equiv), Na_2CO_3 (0.8 equiv), PTFE sand (5 g), and water (10 mL) was mechanically stirred at 80 °C for 2.5 h. After TLC indicated completion of the reaction, the suspension in water was filtrated to gave crude product **1cc**, leaving the PTFE sand in the flask. After crystallization in aqueous acetone (6 mL, 75% v/v), 96% yield of **1cc** was obtained. The mother liquor was concentrated and combined with water from the previous pot, to which were again added **1c** (1 g) and *p*-methoxybenzaldehyde (1.05 equiv). The mixture was treated as in the first pot. This is the second cycle. In this manner, the reaction was cycled from the third to the eighth. The yields were quantitative starting from the second cycle. The durations extended from 2.5 to 4 h from first to eighth cycles.

Recycling Procedures for the Aqueous Reactions for 4ba. The recycling procedure for the aqueous reaction of **4b** (2.00 g) with isobutyraldehyde (Table 4, entry 3) was conducted according to procedure **B**. After direct in-flask extraction with ethyl acetate (2 × 5 mL), the aqueous phase was directly reused for the next aldol event for three times. The yields of **4ba** were 1.92 g (69%), 2.31 g (78%), 2.04 g (72%), and 2.13 g (75%). The amounts of recovered starting material were 217, 105, 203, and 192 mg. The average yield was 2.10 g, 73%, close to that in Table 4 (76%).

Recycling Procedures for the Aqueous Reactions for 5bb. The recycling procedure for the aqueous reaction for **5bb** (Table 5, entry 4) was a direct in-flask extraction one, according to procedure **C**. The aqueous phase was recycled three times. All three aldol events were completed in 15 min and in quantitative yields.

Organic Solvent-Mediated Aldol Reactions for 1a and 1b. A mixture of **1a** (158 mg) or **1b** (165 mg), 4-methoxybenzaldehyde (71 mg, 1.05 equiv), MOH (M: Li or Na, 2.0 equiv), and DMF (4 mL) or THF-water (3:1, 4 mL) was magnetically stirred (400 rmp) at room temperature. TLC indicated that no reaction took place in DMF. For both **1a** and **1b**, the reaction times were the same in THF-water (3.5 h for NaOH and 6 h for LiOH).

Organic Solvent-Mediated Aldol Reactions of Ketone with a Base-Liable Group Epoxyketone. A mixture of **3g** (200 mg), aldehyde (1.05 equiv for benzaldehyde, 2.0 equiv for isovaleraldehyde), K_2CO_3 (138 mg, 1.0 equiv), and methanol (4 mL) was magnetically stirred (400 rmp) at room temperature for 6 h. TLC indicated that no reaction took place. Another carbonate, Li_2CO_3 or Na_2CO_3, gave the same result. When the reaction was catalyzed by NaOH (1.0 equiv) at 10 °C in methanol, no desired product was formed in 1 h and most of **3g** decomposed in 8 h. When the reaction temperature was 40−45 °C, the decomposition took only 2 h. In other organic solvents (DMF or $CHCl_3$), this reaction catalyzed by M_2CO_3 or MOH (M: Li, Na, and K) also failed completely. For $CHCl_3$-mediated reaction, no desired product **3gb** or **3gc** was observed in 8 h at room temperature or at reflux. For DMF-mediated reaction, no aldol product was formed in 8 h with M_2CO_3; the starting material **3g** decomposed completely in 8 h at room temperature or in 3 h at 40−45 °C with MOH.

Organic Solvent-Mediated Aldol Reactions of Heteroaromatic Ethanones with Aliphatic Aldehydes. A mixture of heteroaromatic ethanone (**4a−4c**, 200 mg), butyraldehyde or isobutyraldehyde (2.0 equiv), base (1.0 equiv), and organic solvent (5 mL) was magnetically stirred (400 rmp) at 0 °C or room temperature for 8 h. The organic solvents used include methanol, DMF, and $CHCl_3$. The base was NaOH, K_2CO_3, Cs_2CO_3, or DBU. For K_2CO_3-catalyzed or $CHCl_3$-mediated reactions, no desired aldol products were formed. A stronger base (Cs_2CO_3, NaOH or DBU) gave only a trace amount of β-hydroxyketones in 8 h in methanol or in DMF. For the reaction of **4b** and excess isobutyraldehyde (5.0 equiv) in methanol, a longer reaction time (24 h) also ended in a poor conversion and gave complicated products.

A mixture of **3i** (200 mg), isovaleraldehyde (2.0 equiv), LiOH (1.0 equiv), and methanol (5 mL) was magnetically stirred (400 rmp) at 0 °C or room temperature for 1 h. TLC indicated that complicated products (at least eleven products) were formed with a poor conversion of **3i** and there were not major products.

Organic Solvent-Mediated Condensation of Acetophenone and *O*-Benzyl-Protected D-Glucosyl Hemiacetal. A mixture of acetophenone (180 mg), *O*-benzyl-protected D-glucosyl hemiacetal (135 mg), base (2.0 equiv), TBAB (0 mg or 40 mg), and organic solvent (methanol or $CHCl_3$, 2.5 mL) was magnetically stirred (400 rmp) at reflux for 8 h. The bases used include M_2CO_3, MOH (M: Li, Na, and K), and DBU. For $CHCl_3$-mediated or M_2CO_3-catalyzed reactions, no reaction took place. For methanol-mediated reactions catalyzed by MOH or DBU, the desired product **5eb** was not formed.

■ ASSOCIATED CONTENT

Supporting Information

The modification of the standard two-blade stirring rod. Copies of ^1H NMR, ^{13}C NMR and NOESY spectra for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ REFERENCES

(1) For comprehensive reviews, see: *Modern Aldol reactions*; Mahrwald, R., Ed.; Wiley-VCH: Weinheim, Germany, 2004.

(2) (a) Cui, X.; Li, B.; Liu, T.; Li, C. *Green Chem.* **2012**, *14*, 668−672. (b) He, G.; Li, B.; Li, C. *J. Agric. Food Chem.* **2013**, *61*, 2913−2918.

(3) Ikegami, S.; Ohishi, J.; Akaboshi, S. *Chem. Pharm. Bull.* **1975**, *23*, 2701−2710.

(4) (a) Narayan, S.; Muldoon, J.; Finn, M. G.; Fokin, V. V.; Kolb, H. C.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2005**, *44*, 3275−3279. (b) Butler, R. N.; Coyne, A. G. *Chem. Rev.* **2010**, *110*, 6302−6337. (c) Beattie, J. K.; McErlean, C. S. P.; Phippen, C. B. W. *Chem.—Eur. J.* **2010**, *16*, 8972−8974. (d) Li, C.-J. *Chem. Rev.* **2005**, *105*, 3095−3165. (e) Chanda, A.; Fokin, V. V. *Chem. Rev.* **2009**, *109*, 725−748. (f) Jung, Y.; Marcus, R. A. *J. Am. Chem. Soc.* **2007**, *129*, 5492−5502.

(5) (a) Butler, R. N.; Coyne, A. G.; Moloney, E. M. *Tetrahedron Lett.* **2007**, *48*, 3501−3503. (b) Badone, D.; Baroni, M.; Cardamone, R.; Ielmini, A.; Guzzi, U. *J. Org. Chem.* **1997**, *62*, 7170−7173.

(6) For examples, see: (a) Paquette, L. A.; Wang, T-Z; Vo, N. H. *J. Am. Chem. Soc.* **1993**, *115*, 1676−1683. (b) Lau, S. Y. W. *Org. Lett.* **2011**, *13*, 347−349. (c) Hong, B.-C.; Hsu, C.-S.; Lee, G.-H. *Chem. Commun.* **2012**, *48*, 2385−2387. (d) Davies, J. S.; Higginbotham, C. L.; Tremeer, E. J.; Brown, C.; Treadgold, R. C. *J. Chem. Soc., Perkin Trans. 1* **1992**, 3043−3048. (e) You, Y.-J.; Kim, Y.; Nam, N.-H.; Ahn, B.-Z. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 3137−3140. (f) Djurendić, E. A.;

Ajduković, J. J.; Sakač, M. N.; Csanádi, J. J.; Kojić, V. V.; Bogdanović, G. M.; Gaši, K. M. P. *Eur. J. Med. Chem.* **2012**, *54*, 784−792. (g) Hurst, D. T.; McInnes, A. G. *Can. J. Chem.* **1965**, *43*, 2004−2011.
(7) (a) Menche, D.; Arikan, F.; Li, J.; Rudolph, S. *Org. Lett.* **2007**, *9*, 267−270. (b) Abed, H. B.; Mammoliti, O.; Bande, O.; Lommen, G. V.; Herdewijn, P. *J. Org. Chem.* **2013**, *78*, 7845−7858. (c) Blay, G.; Fernández, I.; Muñoz, M. C.; Pedro, J. R.; Vila, C. *Eur. J. Org. Chem.* **2013**, 1902−1907. (d) Liu, R.; Li, Z.; Zhu, H.; Sun, W. *Inorg. Chim. Acta* **2012**, *387*, 383−389. (e) Molleti, N.; Rana, N. K.; Singh, V. K. *Org. Lett.* **2012**, *14*, 4322−4325. (f) Trost, B. M.; Ito, H. *J . Am. Chem. Soc.* **2000**, *122*, 12003−12004. (g) Trost, B. M.; Yeh, V. S. C. *Org. Lett.* **2002**, *4*, 3513−3516. (h) Crawford, C.; Nelson, A.; Patel, I. *Org. Lett.* **2006**, *8*, 4231−4234. (i) Singh, P. K.; Singh, V. K. *Org. Lett.* **2010**, *12*, 80−83. (j) Dodd, K.; Morton, D.; Worden, S.; Narquizian, R.; Nelson, A. *Chem.—Eur. J.* **2007**, *13*, 5857−5861. (k) Nagafuji, P.; Cushman, M. *J. Org. Chem.* **1996**, *61*, 4999−5003.
(8) Richard, F.; Carreyre, H.; Coustard, J. M.; Bachmann, C.; Perot, G. *Tetrahedron* **1998**, *54*, 14757−14766.
(9) (a) Casiraghi, G.; Zanardi, F. *Chem. Rev.* **1995**, *95*, 1677−1716. (b) Nicolaou, K. C.; Mitchell, H. J. *Angew. Chem., Int. Ed.* **2001**, *40*, 1576−1624. (c) Reddy, L. V. R.; Kumar, V.; Sagar, R.; Shaw, A. K. *Chem. Rev.* **2013**, *113*, 3605−3631. (d) Wang, C.-C.; Lee, J.-C.; Luo, S.-Y.; Kulkarni, S. S.; Huang, Y.-W.; Lee, C.-C.; Chang, K.-L.; Hung, S.-C. *Nature* **2007**, *446*, 896−899. (e) Romeo, G.; Chiacchio, U.; Corsaro, A.; Merino, P. *Chem. Rev.* **2010**, *110*, 3337−3370.
(10) (a) Calvo-Mateo, A.; Camarasa, M.-J.; Diaz-Ortiz, A.; De las Heras, F. G.; Alemany, A. *J. Chem. Soc., Pekin Trans. I* **1988**, 2861−2863. (b) Anastasia, M.; Allevi, P.; Ciuffreda, P.; Fiecchi, A.; Scala, A. *J. Org. Chem.* **1991**, *56*, 3054−3058.
(11) Winchester, B. G. *Tetrahedron: Asymmetry* **2009**, *20*, 645−651.
(12) Banday, A. H.; Zargar, M. I.; Ganaie, B. A. *Steroids* **2011**, *76*, 1358−1362.
(13) Dubey, S.; Jindal, D. P.; Piplani, P. *Indian J. Chem. B* **2005**, *44*, 2126−2137.
(14) Huang, L. H.; Zheng, Y. F.; Song, C. J.; Wang, Y. G.; Xie, Z. Y.; Lai, Y. W.; Lu, Y. Z.; Liu, H. M. *Steroids* **2012**, *77*, 710−715.
(15) Stefanović, M.; Miljković, D.; Miljković, M.; Jokić, A.; Stipanovic, B. *Tetrahedron Lett.* **1966**, *7*, 3891−3895.
(16) Dory, I.; Lanyi, G. *Acta Chim. Acad. Sci. Hung.* **1962**, *30*, 71−75.