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PAPER

Direct *anti* and regio-specific aldol reactions of cyclododecanone catalyzed by alkali metal hydroxides: implications for supramolecular helical design†

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The direct aldol condensation of benzaldehyde to cyclododecanone (CDD), catalyzed by NaOH is expected to yield bis-benzylidene cyclododecanone, but we interestingly ended up with novel β-hydroxy carbonyl compounds and monobenzylidene cyclododecanone derivatives in the cases of 2-halo substituted benzaldehydes. This exceptional behaviour is due to the capability of the CDD ring to exist in the zwitter ionic form. The formation of monobenzylidine derivatives can be due to less stable hydrogen bonds between –OH and –C═O groups, electrostatic interaction between aldehyde substituents and metal enolates and the bulkiness of the benzaldehyde ring substituents. We extensively optimized the reaction conditions using different solvents and alkali metal hydroxide catalysts and we are getting high yield, regio-specificity and high diastereoselectivity (*anti*-aldol) in β-hydroxy carbonyl compounds. The representative crystal structures were examined and they suggest the tendency of *anti*-aldol compounds to form supramolecular helical motifs. The β-hydroxyl carbonyl derivatives form supramolecular helices *via* O–H···O hydrogen bonds with two *anti*-aldol units per turn and a pitch of ∼6 Å. The cyclododecanone ring adopts the minimum energy [3333] square conformation. The nucleophile will attack only from the less hindered side of the carbonyl group in the CDD ring.

Introduction

The synthesis of *anti*-aldol products has assumed a great deal of interest in recent times, as many of the synthesis of natural products require stereospecificity.[1a–c] The aldol condensation reaction is well known for acyclic and cyclic ketones (5, 6, 7 & 8 member rings) using different metal hydroxides,[2a] metal complexes[2b] and polymer supported acid catalyst[2c] reactions. However, the previous reports show only the formation of bis-benzylidene cycloalkanones in all the cases so far. In our case, which is completely different from previous methods, the reaction has not proceeded after the formation of the β-hydroxy carbonyl compound (dehydration) due to the unique conformational property of CDD (Fig. 1). Herein we are obtaining diastereoselective β-hydroxy carbonyl compounds (only the *anti* isomer which is interesting and hence we proceeded to form further derivatives) and monobenzylidene cyclododecanone derivatives in the case of 2-Cl, 2-Br, 2,4-diCl substituted benzaldehydes (dehydrated products). Many methods have been proposed for aldol reactions, the addition of acyclic and cyclic ketones to aldehydes using preformed enolates such as silyl enol ethers.[3a–c] Ytterbium triflate (Yb OTf)$_3$,[3d] lithium enolate,[3e] gallium enolates[3f] and trichlorosilyl triflate[3h–i] have been reported to give low yields (16–90%), require higher reaction times (more than 15 hours) and give very low diastereoselectivity

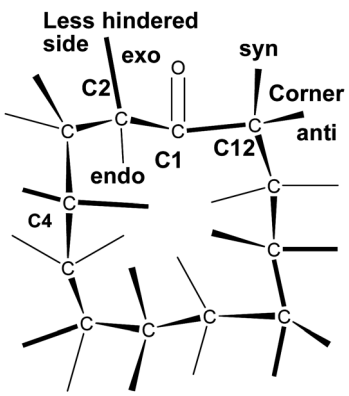

Fig. 1 [3333]-2-One conformation of cyclododecanone.

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(dr. ≈ 50 : 50), while the *anti*-selective product was obtained when MgI_2 was used as promoter.[4a] Several methodologies have been developed for getting single diastereomers (either *anti* or *syn* isomers), such as boron reagents and metal complexes in the presence of a tertiary amine, where the amine was mainly used to convert the ketone into an enol. Conventionally the selectivity has been achieved in two steps, for example, the reaction with boron followed by hydrogen peroxide oxidization. In view of this, ytterbium trifluoromethanesulfonate and tertiary amines systems were tried.[5] Attempts were also made to obtain *anti*-aldol products in high selectivity using dicyclohexylboron chloride and triethylamine.[6a,b] High *anti*-selectivity can be obtained in the case of sterically hindered aldehyde like trimethylacetaldehyde.[7] However, on the ketone side, the steric hindrance has not been studied extensively and the sterically hindered ketone was rarely used to get the *anti*-selective product in aldol additions. Only one report is available on using specially modified ketones to obtain high *anti*-selective product.[4] In all the cases, the reactions proceed smoothly, if the enolate ion is formed from the ketone. Even after the formation of the enol, there is no control over the product selectivity. For instance, the products formed were in ratio of 70 : 30 (*anti*/*syn*) in the reaction between cyclohexanone and benzaldehyde using MgI_2 as the promoter. While considering CDD, there is only one report available for diastereoselectivity, using α-halocyclododecanone subjected to reduction by TiCl4-*n*-Bu4NI[8] through a pinacol coupling reaction. However, they achieved only 89% selectivity and found only parent benzaldehyde. Earlier methods of aldol condensations suffered from multiple limitations, such as long reaction times, use of air and moisture-sensitive[5,6a,7] reagents, two step reactions that require the enolate to be formed before the aldehyde can be added, and the random *anti*/*syn* selectivity of products.[5,7] Therefore, we have chosen a ketone which is more sterically hindered and is known for its existence in the zwitter ionic form.[9a]

In the present work, we have developed a direct aldol addition reaction in cyclododecanone (CDD) with aromatic benzaldehydes, by using various alkali metal hydroxides to yield novel β-hydroxy carbonyl compounds. The *anti*-selective and regio-specific products were obtained in high yield. In contrast to earlier methods, the present method does not require any drastic conditions or any toxic catalysts or promoters. We designed a supramolecular helix of *anti*-aldol products.

Results and discussion

Optimization of the catalyst loading and solvent screening

A direct one-pot addition of CDD, benzaldehyde and NaOH followed by stirring at room temperature is expected to yield bis-benzylidine substituted cyclododecanone, but interestingly the reaction yields predominantly *anti*-β-hydroxy carbonyl compounds.

Herein we desire to communicate that cyclododecanone can efficiently generate an *anti*-aldol product. Whereas the role of the metal hydroxide enhances the enolate formation in the zwitter ionic medium of the CDD ring. Even though NaOH is a known catalyst for aldol condensations, this is the first time that the exclusive formation of *anti*-β-hydroxy carbonyl compounds has been reported. Although some reports are available on aldol additions using NaOH, LiOH and KOH as catalyst, they also use inclusion complexes with an optically active compound.[2a] We studied the effect of catalysts on this reaction. We chose three different alkali metal hydroxides such as NaOH, LiOH and KOH. With only 1 mol% the reaction proceeded smoothly in NaOH and LiOH, but in the case of KOH, the reaction took slightly longer. Hence, all three alkali metal hydroxides are able to catalyze the reaction, as shown in Table 1. All metal hydroxides induce CDD (**1**) to form the enolate. When CDD is present in solution, it is in the W-shaped zwitter ion[9a] form with a dynamic equilibrium.[9b]

Further, we studied the reaction with different solvents, such as non polar, polar, protic aprotic. Out of these solvents, only methanol was found to be suitable for the reaction to take place. No product was formed in the case of *t*-BuOH and PEG 400. The yields are shown in Table 2. In all the metal hydroxide catalysts and solvents tested, we obtained the β-hydroxyl ketone

Table 1 Screening of metal hydroxide catalysts in the direct *anti*-aldol addition of CDD with parent benzaldehydes (product **4a**) and *o*-Cl benzaldehydes (product **5a**), separately, in the presence of metal hydroxide

		Time (h)		Yield[b] (%)	
Metal hydroxides	Cat. loading[a] (mol%)	**4a**	**5a**	**4a**	**5a**
NaOH	0.50	60	60	—	—
	0.75	35	35	35	20
	1	1	3.5	86	75
LiOH	0.50	60	60	—	—
	0.75	42	42	30	20
	1	1.5	7	80	75
KOH	0.50	72	72	—	—
	0.75	60	60	30	10
	1	24	24	78	65

[a] The reaction was performed with parent benzaldehyde, *o*-chlorobenzaldehyde (0.01 M) and cyclododecanone (0.01 M) in the presence of three different metal hydroxide concentrations at room temperature (28 °C) with vigorous stirring, where methanol was used as solvent. [b] The reported yield is after purification by column chromatography.

Table 2 Screening of different organic solvents

		Time (h)		Yield[b] (%)	
Entry	Solvent[a]	**4a**	**5a**	**4a**	**5a**
1	CH_3OH	1	3.5	86	79
2	C_2H_5OH	1.5	5	68	60
3	*i*PrOH	3	8	62	54
4	*n*BuOH	5	8	< 50	< 50
5	*t*BuOH	3.5	3.5	—	—
6	CH_2Cl_2	2	4	78	65
7	CH_3CN	4.5	6	72	58
8	$CHCl_3$	4.5	6	65	58
9	THF	4	5.5	65	56
10	PEG 400	9	24	—	—
11	*n*-Hexane	3	5	40	30

[a] The reaction was performed with different solvents as indicated in table parent benzaldehyde, *o*-chlorobenzaldehyde (0.01 M) and cyclododecanone (0.01 M) in the presence of NaOH (1 mol%) at room temperature (28 °C) with vigorous stirring. [b] % Yield after the column chromatography.

in the case of parent benzaldehyde (*anti*-selective) and mono-benzylidene derivatives in case of *o*-chlorobenzaldehyde.

The scope of the regio-specific and *anti*-product formation in the aldol reaction

The unexpected behaviour of CDD is due to ring strain and bad transannular interaction observed in higher cyclic ketones ($n > 7$).[9a] The CDD takes part in the reaction in the form of a zwitter ion. The Newman projection[9c] along with the C_S-symmetry show –CO–C_α and –C_α–C_β bonds of the [3333]-2-one square conformation of CDD, which has α-methylene groups at either a corner (C) or less hindered side (S) position, as shown in Fig. 2. One of the two hydrogens (C-12) of the corner α-CH_2 group is eclipsed with the –C═O bond, represented as α-H_{syn}, and the other hydrogen of the corner α-CH_2 will be referred to as H_{anti}. The inner and outer hydrogens (C-2) of the less hindered side (non-corner) of α-CH_2 groups are represented as α-H_{endo} and α-H_{exo} respectively.[9d] The corner α-CH_2 groups (C) differ from the side α-CH_2 (S), since the projection angle between the p-orbital on the carbonyl group and two C–H bonds are quite different in the cases of the corner being 90° and 30°.[9c] So these (C) α-CH_2 groups are affected by torsional angle strain, and there is probably no large vicinal coupling constants between this α-proton and either of the two β-protons.

Hence the corner of the α-H_{anti} and β-CH_2 group (either one of two β-hydrogens) overlap, and the formation of the carbocation or carbanion is restricted or negligible. Only the less hindered side (S) α-CH_2 groups facilitate the formation of a carbanion or carbocation, since α-H_{exo} (outer) and α-H_{endo} (inner) protons are at the same angle (30°). Hence we conclude that regio-specificity was present in the CDD ring itself. This bond angle is steadily increasing for the large ring ketones, reaching a maximum value above 10-ring cyclic ketones, which is true for inside-carbonyl-conformation.[9e,f]

This is quite different from cyclohexanone and other cyclic ketones (n = 5–8). The previous NMR studies at −140 °C and

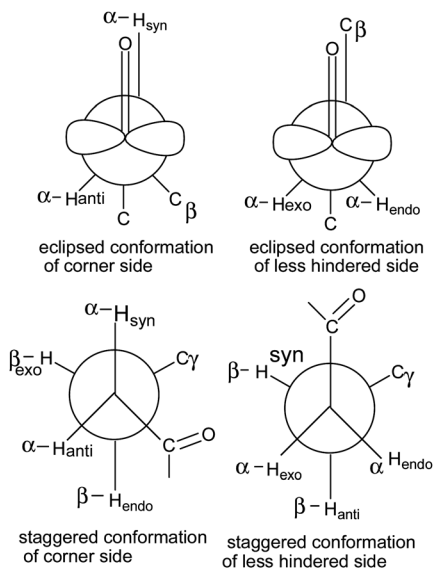


Fig. 2 Newman projection for the [3333]-2-one conformation of cyclododecanone.[9c]

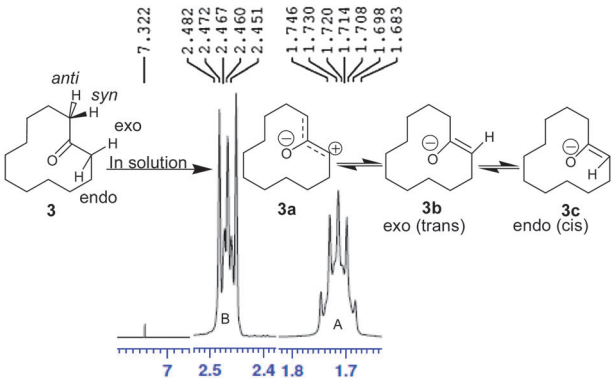


Fig. 3 Dynamic ^{1}H NMR spectra in the solution phase.

−100 °C of CDD shows the dynamic equilibrium (Fig. 3) associated with a conformational barrier of 7.3–7.6 Kcal mol^{-1}.[9c,d] Herein we analyzed the NMR spectra at room temperature (25 °C), and we also observed a dynamic NMR effect in the CDD ring. (See ESI†) This consists of two pentets AB and this will give a different coupling constant and different chemical shift J = 9.4, 6.4 Hz (**A**), J = 8.8, 4 Hz (**B**). The A pentet gave a large vicinal coupling constant. In the CDD ring, the corner proton α-H_{syn} is more shielded than its germinal counterpart compared to α-H_{anti}.

Stereochemical outcome of the reaction aldol molecules

In the CDD ring, out of two hydrogens (C-2) (Fig. 1) at the less hindered side (S), the *exo*-hydrogen (*trans*-enolate) will be involved in the enolate ion formation in CDD, this was favourable for *anti*-aldol product formation *via* a metal involving boat-metal-like transition state **TS1** (*anti* isomer up to 96–100%) Fig. 4a. If the other *endo*-hydrogen (*cis*-enolate) is involved in the enolate ion formation, the *syn*-aldol product will be formed through the metal involving boat-metal-like transition state **TS2** (*syn* isomer up to 4%), which is much less favourable, as we have shown in Fig. 4a. However, the *syn*-aldol adopts a staggered conformation, the phenyl group (R) is affected by gauche hydrogens on both sides, hence the aldehydic carbon is away from the keto group of the carbonyl oxygen, for this reason the dihedral angle increases (more than 60°), consequently the transition state will be destabilized. Obviously we are getting more stable stereoselective *anti*-aldol products.

The configuration of aldol is associated to the conformation of the transition state. Previous studies show that proton transfer from the amine or the carboxylic acid group of proline to form the alkoxide is essential for charge stabilization and to facilitate C–C bond formation in the transition state.[1c] In this reaction the proton transfer occurs from the solvent. The oxygen of benzaldehyde forms a hydrogen bond with the proton (solvent) in the C═O plane along the direction of the sp^2 lone pair of the oxygen atom. When the stereochemistry at C-2 is inverted from *R* to *S*, there is a possibility of C–H–π interaction between the hydrogen at C-2 and the substituent (either hydrogen or other substituents) of the aromatic ring of the benzaldehydes. We proposed a transition state model to explain the stereochemical outcome of the reaction, which is shown in Scheme 1.

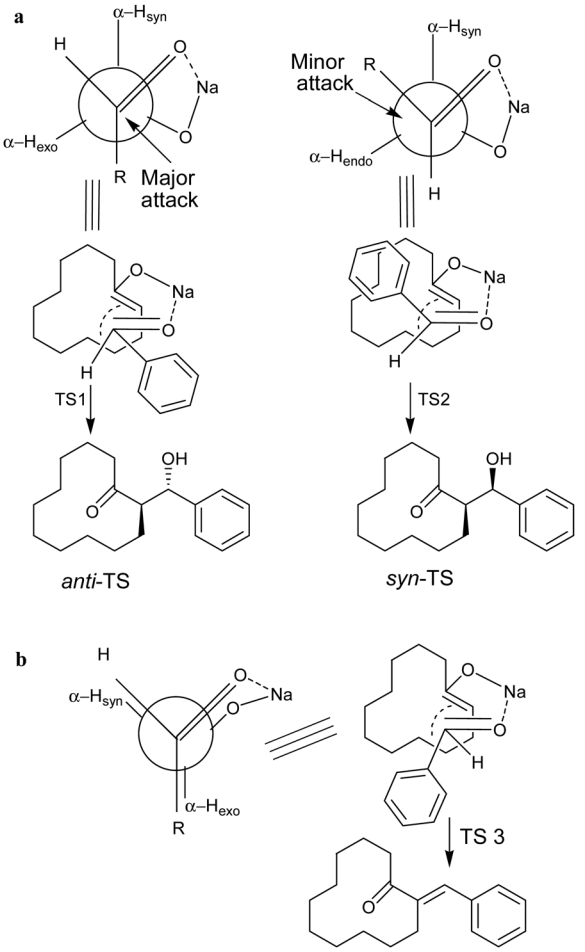
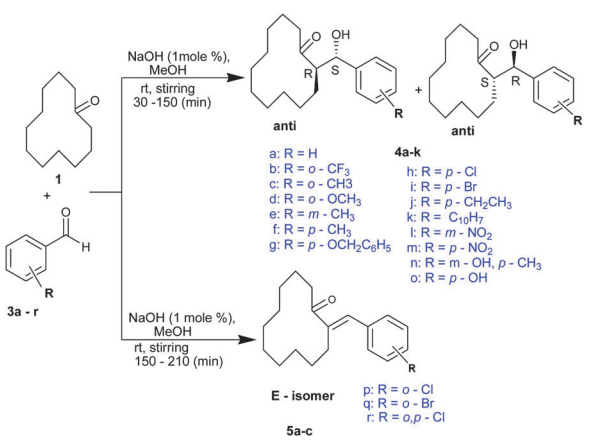


Fig. 4 (a) Plausible boat-metal-like transition state for the formation of aldol products. (b) Plausible transition state for the dehydrated product.



Scheme 1 Synthesis of *anti*-aldol and monobenzylidene products **4a–o** and **5a–c** from cyclododecanone catalyzed by sodium hydroxide.

In the case of the monobenzylidene, cyclododecanone derivatives (dehydrated products in Scheme 1) were formed in the case of 2-Cl, 2-Br and 2,4-Cl benzaldehydes (Table 3 entries 16–18). The electrostatic attractive force between the electron-withdrawing halogens (Cl, Br) and the sodium ion of the CDD enolate (*e.g.* Na–Cl, Na–Br), in addition to the bulkiness, plays a major

Table 3 *anti*-Selective and regio-selective aldol addition of cyclododecanone with aldehyde using sodium hydroxide as catalyst

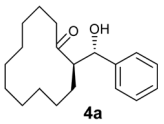
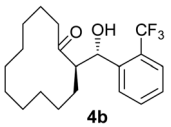
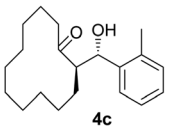
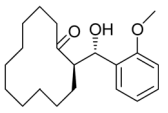
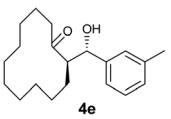
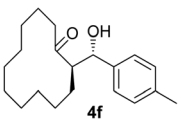
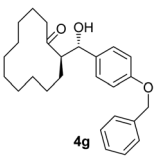
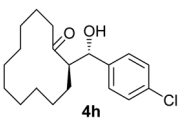
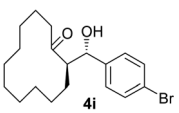
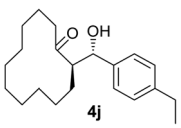
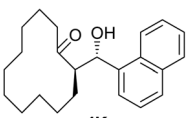
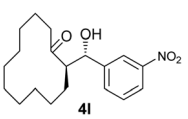
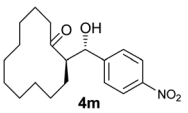
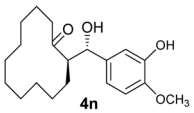
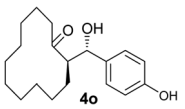
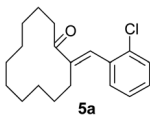
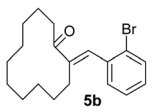
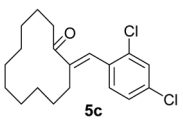
Entry	R[a]	Aldol product[b]	Yield (%)	Time[d] (min.)	*Anti*/*syn*[e,f] (%)
1	H	 **4a**	86	60	100
2	*o*-CF_3	 **4b**	86	45	98/2
3	*o*-CH_3	 **4c**	87	30	100
4	*o*-OCH_3	 **4d**	84	90	100
5	*m*-CH_3	 **4e**	85	30	97/3
6	*p*-CH_3	 **4f**	97[c]	45	100
7	*p*-OC_7H_7	 **4g**	80	120	100
8	*p*-Cl	 **4h**	94[b]	30	98/2
9	*p*-Br	 **4i**	89[c]	45	100
10	*p*-C_2H_5	 **4j**	85[c]	150	100
11	$C_{10}H_7$	 **4K**	82	180	100
12	*m*-NO_2	 **4l**	—	2880	+
13	*p*-NO_2	 **4m**	—	2880	—

Table 3 (*continued*)

Entry	R[a]	Aldol product[b]	Yield (%)	Time[d] (min.)	*Anti*/*syn*[e,f] (%)
14	*m*-OH, *p*-OCH_3	 **4n**	—	2880	—
15	*p*-OH	 **4o**	—	2880	—
16	*o*-Cl	 **5a**	79	210	96/4[f]
17	*o*-Br	 **5b**	75	180	98/2[f]
18	*o*-Cl, *p*-Cl	 **5c**	70[c]	150	100[f]

[a] The reaction was performed with different benzaldehydes (**3a–r**) (0.01 M), and cyclododecanone (0.01 M) in the presence of NaOH (1 mol%) at room temperature (28 °C) with vigorous stirring and methanol was used as solvent. [b] Isolated yield of **4a–o** and **5a–c**. [c] Crystal structure analysis. [d] All the products are regioselective. [e] The *anti*/*syn* ratio of **4a–o**. [f] *E*/*Z* ratio of **5a–c** was determined by ^{1}H NMR and chiral column HPLC (see the ESI†).

role in preventing the staggered conformation. Hence, the dehydrated product is obtained due to the eclipsed conformation of the intermediate, as shown figure in **4b**. The β-carbonyl compounds were stabilized by hydrogen bond interaction between the –OH group and –C═O. However, in case of aldehydes yielding benzylidene derivatives, the hydrogen of the –OH group is not available to form the hydrogen bond with the carbonyl group due to the strong interaction between the strong electron-withdrawing halogen (Cl, Br) and the hydrogen of the –OH group. As a result, the β-carbonyl compound is destabilized, leading to the formation of monobenzylidene derivatives.

This forms the well known chair Zimmerman–Traxler transition state.[1a,c] These are depicted by a chair-like conformation. This could be adopted, in which a nucleophilic group should be oriented gauche to the aldehydic hydrogen for steric reasons.[10a,b] Gaudemer, Evans, and Heathcock, suggested that the stiles-house method[1d–f] should be carefully used for aldol reactions, with compounds that have a bulky substituent at the β-position, where the enhanced gauche interaction destabilizes the hydrogen-bonded six-membered ring as shown in (Fig. 5) (Table 3, entries 16–18).

In Table 3, entries 1–11, we get regio-specific and highly diastereoselective β-hydroxy carbonyl compounds in moderate to good yield, whereas in the case of 3-NO_2, 4-NO_2, vanillin and 4-OH benzaldehydes (Table 3, entries 12–15) we are not able to obtain the β-hydroxy carbonyl compounds, even

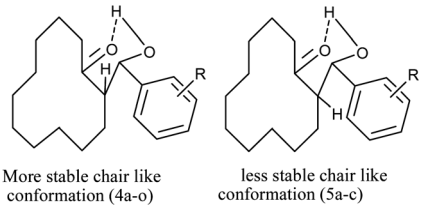
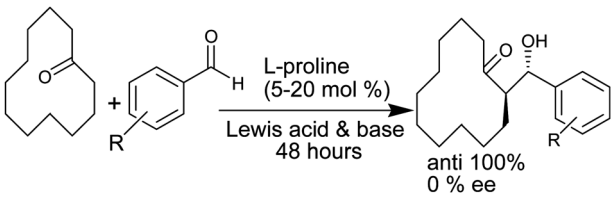


Fig. 5 Possible conformations of aldol and monobenzylidene products.



Scheme 2 L-Proline catalyzed aldol reactions.

though we tried all three alkali metal hydroxides, and at different temperatures (15 °C and 0 °C).

L-Proline as a catalyst for the aldol reaction

We also tried to obtain enantioselectivity of the β-hydroxy carbonyl compounds using L-proline (5–20 mol%) in the presence of Lewis acid ($ZnCl_2$ and I_2) and Lewis base catalysts (*N*,*N*-diisopropyl ethylamine and triethylamine) as shown in Scheme 2. However, we only achieved the *anti* isomer, and we failed to get enantiomeric excess because, in the most stable conformation of CDD, the carbonyl group (C═O) pointed inwards of ring showing no room for the incoming L-proline, as shown in Fig. 2. Hence the enolate formation is restricted or steric strain is increased when the L-proline moiety is introduced. So this will need to be specially modified for optically active chiral catalysts.

Crystal structure analysis of representative compounds 4f, 4h–4j and 5c

Crystal structures of the representative compounds were examined from each category, namely β-hydroxy carbonyl (**4f**, **4h–4j**) and monobenzylidene derivatives (**5c**).

The overall structures of **4f** and **5c** are illustrated in (Fig. 6), while the ORTEPs of **4h–j** are included in Fig. S1, ESI.† In **4f**, and in the reported centro symmetric structures of **4h–4j**, the stereogenic centers, C2 and C13, adopt *R* and *S* configurations, respectively.[11a] The cyclododecanone ring in all the compounds, adopts the [3333] square conformation, possessing 422 symmetry.[11b,c] The numbers in the square brackets indicate the number of ring bonds between the four corner atoms of the cyclododecanone ring. The [3333] square conformation is the most favoured conformation of cyclododecane and is predominantly observed in the reported structures.[11d] Based on theoretical calculations, the other three lowest energy conformations for the 8-membered ring were found to be – [2334], [1434], and [2343].[11e] In all the investigated CDD rings, the intra-annular bond distances and angles vary in the 1.496(3)–1.540(2) Å and 111.5(1)–120.6(1)° ranges, respectively. The average

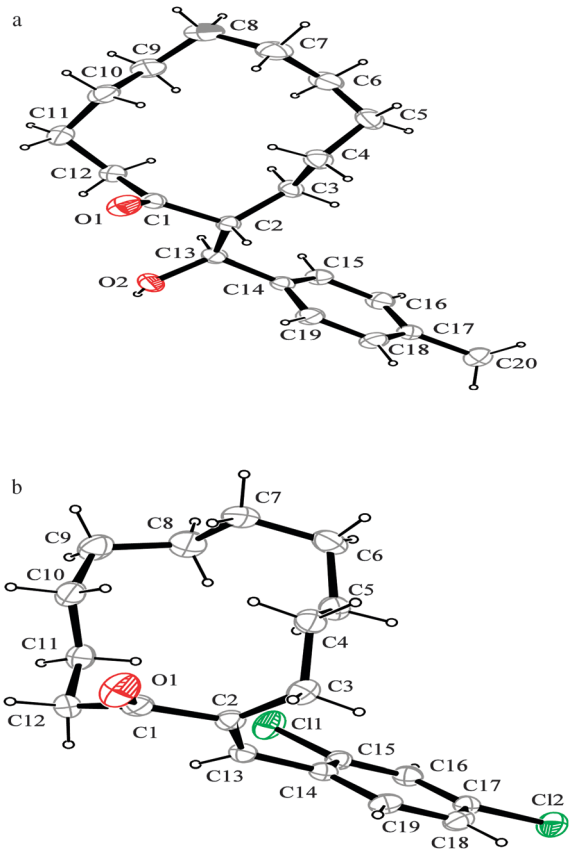


Fig. 6 (a) ORTEP for (**5c**). (b) ORTEP for (**4f**). A view of **4f** and **5c** with non-H atoms shown as probability ellipsoids at 30% levels drawn with ORTEP (Farrugia, 1997). H atoms radii are on an arbitrary scale.

distance and angle have been observed to be 1.53(2) Å and 114(2)°, respectively. The absolute value of the average torsion angles, corresponding to the synclinal and antiperiplanar conformations are 69(5)° and 161(8)°, respectively, for a cyclodecanone ring. In the present structures, these angles vary in the absolute 64(1)–75(1)° and 148(1)°–172(1)° ranges.

anti-Aldol products forms supramolecular helices

Intermolecular interactions are described in (Table 4). The β-hydroxy carbonyl compounds (**4f**, **4h–4j**) form supramolecular helices. In these *anti*-aldol compounds, (hydroxyl) O–H···O (carbonyl) hydrogen bonds form helices. The helical network is characterized by a C_6 pattern and the direction of the helix is along the 2^1-screw axis, as shown in (Fig. 7). The helices are characterized by two β-hydroxy carbonyl units per turn with an average pitch (rise per turn) of 6 Å (6.0 Å in **4f**, **4h** and **4i**, 5.8 Å in **4j**). The inner circle axes are approximately 5 Å and 2 Å, respectively.

The intra-helical O–H···O interactions are accompanied by (CDD) C12–H12A···O2 (hydroxyl) interactions (Table 4). The O–H···O and C–H···O interactions together generate a $R2^2$ (12) ring-pattern. The helical outer surface is hydrophobic, and helices are packed together by hydrophobic forces and also C–H···π and π···π interactions (Table 4). Earlier efforts have been made to design supramolecular architectures, especially helical motifs, using weak noncovalent interactions. Few examples of the

Table 4 Intermolecular interactions observed in **4f**, **4h–4j** and **5c**[a]

Interaction	D–H···A	D–H (Å)	H···A (Å)	D···A (Å)	D–H···A (A°)
4f	O2–H2O···O1^{i}	0.86 (3)	2.04 (3)	2.8659 (19)	160 (2)
	C12-H12A···O2^{i}	0.97	2.40	3.367(2)	174
4h	O2–H2O···O1^{ii}	0.90 (2)	1.99 (2)	2.8621 (16)	166 (2)
	C12–H12A···O2^{ii}	0.97	2.43	3.403 (2)	178
4i	O2–H2O···O1^{iii}	0.81 (2)	2.10 (2)	2.8863 (18)	164 (2)
	C12–H12A···O2^{iii}	0.97	2.46	3.431 (2)	177
4j	O2–H2O···O1^{iv}	0.91 (5)	2.04 (5)	2.921 (4)	164 (4)
	C12–H12A···O2^{iv}	0.97	2.50	3.475 (5)	178
5c	C19–H19···O1^{v}	0.93	2.38	3.259 (2)	157

[a] Symmetry codes: (i) $1-x, -1/2+y, 1-z$, (ii) $1/2-x, -1/2+y, 1/2-z$, (iii) $2-x, 1/2+y, 1/2-z$, (iv) $1-x, 1/2+y, 1/2-z$, (v) $1-x, 2-y, 1-z$. An inter-helical C–H···π interaction associated with methyl hydrogen was observed in **4f**, C20–H20A···Cg1 [symmetry code (vi): $-x, 1/2+y, 1-z$], H···A, 2.89 Å, D···A, 3.843(2) Å, D–H···A 173°. Cg1 is the centroid of the (C14–C19) ring.

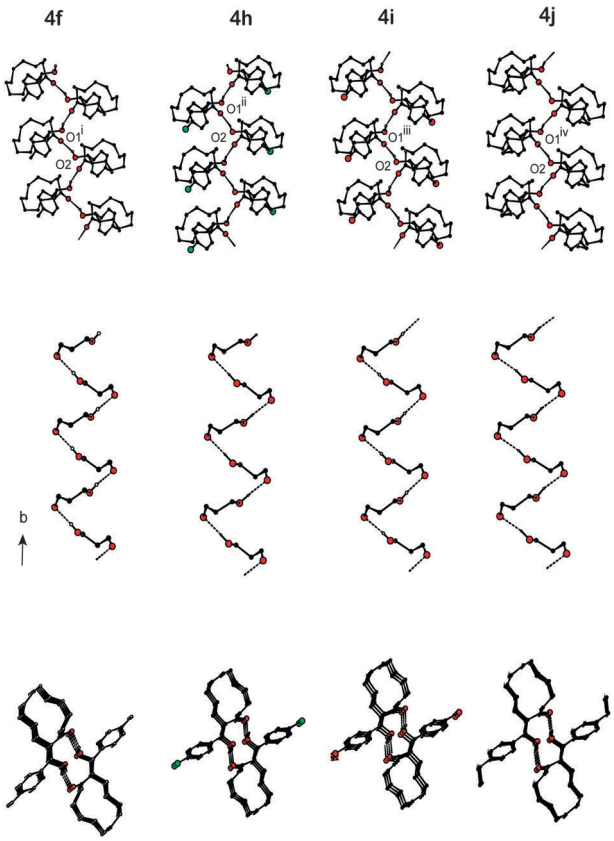


Fig. 7 Top row: Side-on view of hydrogen bonded supramolecular helices observed in **4f** and **4h–j**. Only relevant hydrogens have been shown and the symmetry codes are with respect to (Table 4). Middle row: Curtailed side-on view of the helices schematically showing helical chain along the *b*-axis. Bottom row: Cross-sectional view of the helices.

design of supramolecular helices have been reported.[12a–c] These supramolecular architectures have been designed with a purpose, for use as functional materials such as artificial ion channels or nonlinear optical (NLO) materials.[13a–d] The present O–H···O network serves as a supramolecular synthon[14a–d] for supramolecular helical design. In monobenzylidene derivative

(**5c**), the C–H···O interaction (Table 4) forms a molecular dimer, as shown in Fig. S2 (ESI†). Significant π···π interactions are also observed in the packing of **5c**. Cg1 makes a stacking interaction with Cg1^{i} [symmetry code (i): $1-x$, $1-y$, $1-z$] with a centroid-to-centroid distance of 3.6776(10) Å, a perpendicular distance of 3.4309(6) Å and a slippage of 1.324 Å. Cg1 is the centroid of the (C14–C19) ring.

X-Ray diffraction

Suitable single crystals for data collection were grown from a mixture of ethanol and tetrahydrofuran (1 : 1). Data were obtained from Oxford Diffraction *Xcalibur Eos Gemini* diffractometer.[15] The structure was solved by applying the direct phase-determination technique using SHELXS-97, and refined by full-matrix least square on F^2 using SHLEXL-97.[16a–c] All structural calculations were performed with WinGX suit of programs (version 1.85.05).[16b] Hydrogen atoms were placed in the geometrically expected positions and refined with the riding options. Hydroxyl hydrogen atoms were isotropically refined and methyl hydrogen atoms were fixed with reference to the local electron density maps. The O–H distances were observed in 0.81(2)–0.91(5) Å range. Distances with the rest of the hydrogen atoms are: aromatic/sp^2 C–H = 0.93 Å, methyl C–H = 0.96 Å, methylene C–H = 0.97 Å, methine C–H = 0.98 Å, and Uiso = 1.2 Ueq (parent) or 1.5 Ueq (for methyl). Essential crystal data are listed (Table S1 see the ESI†) Crystallographic data for the structures in this paper (CCDC 843588–843592, for **4f**, **4h–4j** and **5c**, respectively) is provided.†

Conclusions

We have synthesized a new series of *anti*-aldol addition products using NaOH as catalyst. The reaction stops half-way due to steric strain in the ketone, except in the case of three benzaldehydes, namely *o*-chloro, *o*-bromo, *o*,*p*-dichloro. Cyclododecanone (CDD) suffers from ring strain and bad transannular interactions, unlike ordinary ketones such as cyclohexanone. As a result, the method yields β-hydroxyl carbonyl compounds because CDD is already present in the zwitterionic form in the solution phase. We also observed the dynamic NMR spectra of the cyclododecanone ring at room temperature (25 °C) in $CDCl_3$ solvent.

We proposed a transition-state model to rationalize the outcome of the product selectivity. We have established that these *anti*-aldol molecules possess the tendency to assemble into helices. Such molecules could be used for the tailor-made design of supramolecular helices by altering the C13-side groups and substituents on CDD. The present study therefore also serves as an example of a rational design approach[14a–d] for assembling interesting supramolecular assemblies. This concept may be applicable to other metal hydroxides, which we are investigating, along with the asymmetric catalyst, in our laboratory.

Experimental section

General information

All chemicals were purchased from commercial sources and they were used without further purification unless otherwise specified. Thin layer chromatography (TLC), was performed on pre-coated silica gel on alumina plates. Melting points were obtained using microprocessor digital melting point apparatus and are uncorrected. IR spectra were recorded in the range 4000–400 cm^{-1} using the KBr pellet technique. The solution IR spectra were recorded at 4000–560 cm^{-1} using analytical grade dichloromethane as solvent. ^{1}H NMR and ^{13}C NMR spectra were recorded at 300 and 400 MHz using $CDCl_3$ as the solvent with TMS as an internal standard. HRMS analysis was obtained from the double focusing electron impact method. HPLC was performed using a chromatography equipped with a dual wavelength UV detector (Deuterium lamp, 192–600 nm) and the column were used as a *CHIRALPAK IC* (250 mm × 4.6 mm) 5 μm HPLC grade acetonitrile and water.

General procedure for Scheme 1

To a solution of aromatic benzaldehyde (0.01 mol), cyclododecanone (0.01 mol) was added at room temperature (28 °C) in methanol (10 ml) followed by an aqueous solution of NaOH (1 mol%) drop wise for a period of 10–15 min. The reaction mixture was stirred for 1 h at room temperature (28 °C). After the completion of the reaction, mixture was washed thrice with water. The white crude solid was subjected to column chromatography on silica gel (hexane : EtOAc).

HPLC data for all compounds

Analytical high performance liquid chromatography (HPLC) was performed on a water's liquid chromatography equipped with a dual wavelength UV detector (Deuterium lamp, 192–600 nm), using a *CHIRALPAK IC* (250 mm × 4.6 mm) 5 μm HPLC grade acetonitrile and water (80 : 20) were used as the eluting solvents, flow rate: 1.00 ml min^{-1}, injection volume 20 μL column temperature 25 °C, Run time: 12 min.

2-[Hydroxy (phenyl) methyl] cyclododecanone (4a)

The white crude solid was subjected to column chromatography on silica gel (*n*-hexane/EtOAc, 4 : 1) to afford the *anti*-aldol product **4a** (2.48 g, 86% *dr* = 100 : 0); R_f 0.48 (*n*-hexane/EtOAc, 4 : 1); Mp: 107–109 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.385–7.258 (m, 5H, CH_{Ar}); 4.823–4.783 (dd, J = 8, 3.2 Hz, 1H, CH*(OH)); 2.953–2.897 (td, J = 8.8, 4 Hz, 1H, CH_{ali}); 2.804–2.728 (qd, J = 9.6, 3.2 Hz, 1H, CH_{ali}); 2.628–2.617 (d, J = 4.4 Hz, 1H, CH_{ali}); 2.425–2.353 (qd, J = 8, 3.2 Hz, 1H, CH_{ali}); 1.892–1.825 (m, 1H, CH_{ali}); 1.606–1.571 (m, 1H, CH_{ali}); 1.531–1.473 (m, 1H, CH_{ali}); 1.392–1.160 (m, 15H, CH_{ali}). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 214.9, 142.1, 128.5, 128.0, 126.6, 75.3, 59.1, 39.5, 27.3, 26.3, 25.9, 24.2, 23.8, 23.8, 22.8, 22.3, 21.5; FTIR (KBr) ν = 3418.95, 3058.06, 2934.39, 2858.58, 1688.30, 1460.32, 1282.08, 951.33; HRMS (EI) m/z: Calc. for $C_{19}H_{28}O_2$ 288.2081 $[M]^+$; Found 288.2089.

2-{[2-(Trifluoromethyl) phenyl] (hydroxy) methyl} cyclododecanone (4b)

The crude residue was then purified by column chromatography on silica gel (*n*-hexane/EtOAc, 8 : 2) to afford the *anti*-aldol product **4b** (3.058 g, 86%, *dr* = 100 : 0) as a white crystalline solid; Mp: 143–145 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.672–7.654 (d, J = 6.4 Hz, 2H, CH_{Ar}); 7.615–7.577 (t, J = 15.2 Hz, 1H,

CH_{Ar}); 7.431–7.393 (t, J = 15.2 Hz, 1H, CH_{Ar}); 5.279–5.247 (dd, J = 8, 4.8, 1H, CH*(OH)); 3.080 (t, J = 12H, 1H, CH_{ali}); 2.914–2.903 (d, J = 4.4 Hz, 1H, CH_{ali}); 2.620–2.558 (m, 2H, CH_{ali}); 1.720, (bs, 1H, OH, CH_{2ali}), 1.308–1.129 (m, 15H, CH_{ali}). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 214.7, 141.1, 132.5, 128.0, 127.9, 125.7, 125.7, 70.4, 58.7, 39.2, 27.6, 26.3, 25.8, 24.3, 24.0, 23.9, 23.5, 22.4, 21.6. FTIR ν = 3448.25, 3048.06, 2984.29, 2878.38, 1708.20, 1453.42, 1356.45, 1272.08, 957.43, 835.48, 755.34. HRMS (EI) m/z: Calc. for $C_{20}H_{27}F_3O_2$ 356.1963 $[M]^+$; Found 356.1963.

2-[Hydroxy (2-tolyl) methyl] cyclododecanone (4c)

The crude residue was then purified by column chromatography on silica gel (*n*-hexane/EtOAc, 4 : 1) to afford the *anti*-aldol product **4c** (2.642 g, 87%, *dr* = 100 : 0) as a white crystalline solid; Mp: 127–129 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.364.7.341 (d, J = 8.2 Hz, 1H, CH_{Ar}); 7.213–7.154 (m, 3H, CH_{Ar}); 5.083–5.050 (dd, J = 9, 4.4 Hz, 1H, CH*(OH)); 3.102–3.056 (td, J = 4.1, 2.4 Hz, 1H, CH_{ali}); 2.740–2.668 (qd, J = 8.4, 3.6 Hz, 1H, CH_{ali}); 2.604–2.593 (d, 4.4 Hz, 1H, CH_{ali}); 2.589–2.459 (qd, J = 8.4, 3.2 Hz, 1H, CH_{ali}); 2.398 (s, 3H, C_{Ar}–CH_3); 1.832 (s, 1H, OH); 1.780–1.619 (m, 2H, CH_{2ali}); 1.315–1.135 (m, 15H, CH_{ali}). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 215.3, 140.2, 135.4, 130.6, 127.7, 126.4, 126.2, 71.7, 58.3, 39.9, 27.3, 26.3, 25.8, 24.3, 24.2, 24.1, 23.4, 22.4, 21.7, 19.4. FTIR (KBr) ν = 3452.42, 3052.25, 2942.35, 2857.27, 1675.17, 1435.19, 1255.44, 1375.46, 1124.25, 1041.27, 825.48, 715.34. HRMS (EI) m/z: Calc. for $C_{20}H_{30}O_2$; 302.2245 $[M]^+$; Found 302.2246.

2-[Hydroxy (2-methoxy phenyl) methyl] cyclododecanone (4d)

The crude residue was then purified by column chromatography on silica gel (*n*-hexane/EtOAc, 8 : 2) to afford the *anti*-aldol product **4d** (2.683 g, 84%, *dr* = 100 : 0) as a white crystalline solid; Mp: 123–125 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.337–7.314 (dd, J = 7.6, 1.6 Hz, 1H, CH_{Ar}); 7.263–7.216 (td, 6, 1.2 Hz, 1H, CH_{Ar}); 6.960–6.922 (t, J = 14.8 Hz, 1H, CH_{Ar}); 6.881–6.860 (d, J = 8.4, 1H, CH_{Ar}); 5.058–5.030 (t, J = 11.2 Hz, 1H, CH*(OH)); 3.273–3.134 (m, 1H, CH_{ali}); 3.148–3.134 (d, J = 5.6 Hz, 1H, CH_{ali}); 2.632–2.559 (qd, 9.2, 3.2 Hz, 1H, CH_{ali}); 2.220–2.149 (qd, J = 8.4, 3.6, 1H, CH_{ali}); 1.893 (ms, 1H, OH); 1.667 (s, 3H, OCH_3); 1.298–1.238 (m, 15H, CH_{2ali}). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 215.3, 156.0, 129.7, 128.4, 128.0, 120.7, 110.4, 70.8, 70.7, 55.1, 40.3, 26.1, 25.4, 25.2, 24.6, 24.5, 24.4, 23.5, 22.5, 22.0. FTIR (KBr) ν = 3418.93, 3041.28, 2937.42, 2851.54, 1695.28, 1490.27, 1291.54, 1239.26, 1025.42, 761.37. HRMS (EI) m/z: Calc. for $C_{20}H_{30}O_3$; 318.2194 $[M]^+$; Found 318.2195.

2-[Hydroxy (3-tolyl) methyl] cyclododecanone (4e)

The crude residue was then purified by column chromatography on silica gel (*n*-hexane/EtOAc, 7 : 3) to afford the *anti*-aldol product **4e** (2.58 g, 85%, *dr* = 97 : 3) as a white crystalline solid; Mp: 136–138 °C; 1H NMR (400 MHz, CDC_{l3}): δ = 7.251–7.213 (t, J = 15.2 Hz, 1H, CH_{Ar}); 7.152 (s, 1H, CH_{Ar}); 7.118–7.099 (d, J = 7.6 Hz, 2H, CH_{Ar}); 4.775–4.743 (dd, J = 9.2, 3.6 Hz, 1H, CH*(OH)); 2.978–2.923 (td, J = 4.1, 3.6 Hz, 1H, CH*–CHOH) 2.782–2.708 (qd, J = 8, 3.2 Hz, 1H, CH_{ali}); 2.611–2.604 (d, J = 2.8 Hz, 1H, CH_{ali}); 2.519–2.454 (qd, J = 8.4, 3.2 Hz, 1H, CH_{ali}); 2.356 (s, 3H, C_{Ar}–CH3); 1.794–1.759 (m, 1H, OH); 1.698–1.670 (m, 1H, CH_{ali}); 1.550–1.490 (m, 1H, CH_{ali}); 1.307–1.117 (m, 15H, CH_{ali}). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 215.0, 142.1, 138.2, 128.8, 128.4, 127.3, 123.8, 75.3, 59.2, 39.2, 27.3, 26.4, 26.0, 24.2, 23.8, 23.7, 22.8, 22.3, 21.6. FTIR (KBr) ν = 3464.32, 3043.25, 2952.25, 2867.37, 16687.17, 1433.29, 1251.54, 1365.11, 1136.30, 1045.47, 830.58, 725.24. HRMS (EI) m/z: Calc. for $C_{20}H_{30}O_2$; 302.2245 $[M]^+$; Found 302.2246.

2-[Hydroxy (4-tolyl) methy] cyclododecanone (4f)

The crude residue was then purified by column chromatography on silica gel (*n*-hexane/EtOAc, 8 : 2) to afford the *anti*-aldol product **4f** (2.942 g, 97%, *dr* = 100 : 0) as a white crystalline solid; Mp: 164–166 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.253–7.212 (t, J = 15.2 Hz, 1H, CH_{Ar}); 7.155 (s, 1H, CH_{Ar}); 7.116–7.098 (d, J = 7.6 Hz, 2H, CH_{Ar});4.781–4.736 (dd, J = 9, 3.6 Hz, 1H, CH *(OH)); 2.964–2.916 (td, J = 9.6, 3.6 Hz, 1H, CH*–CHOH); 2.805–2.715 (qd, J = 9, 3.6 Hz, 1H, CH_{ali}); 2.558–2.547 (d, J = 4.4 Hz, 1H, CH_{ali}); 2.523–2.456 (qd, J = 6.7, 3.2 1H, CH_{ali}); 2.345 (s, 3H, C_{Ar}–CH_3); 1.836 (m, 1H, OH); 1.694–1.636 (m, 1H, CH_{ali}); 1.552–1.477 (m, 1H, CH_{ali}); 1.346–1.165 (m, 15H, CH_{2ali}). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 214.8, 139.1, 137.6, 129.1, 126.5, 75.1, 59.2, 39.2, 27.3, 26.3, 25.9, 24.2, 23.8, 23.7, 22.8, 22.3, 21.5, 21.0. FTIR (KBr) ν = 3422.35, 3088.15, 2932.45, 2857.67, 1687.87, 1463.49, 1291.54, 1375.91, 1139.40, 1043.57, 819.57, 730.54. HRMS (EI) m/z: Calc. for $C_{20}H_{30}O_2$; 302.2245 $[M]^+$; Found 302.2246.

2-{[(4-Benzyloxy) phenyl] (hydroxy) methyl} cyclododecanone (4g)

The crude residue was then purified by column chromatography on silica gel (*n*-hexane/EtOAc, 8 : 2) to afford the *anti*-aldol product **4g** (3.165 g, 80%, *dr* = 100 : 0) as a white crystalline solid; Mp: 137–140 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.442–7.240 (m, 7H, CH_{Ar}); 6.978–6.941 (dt, J = 11.6, 2.8 Hz, 2H, CH_{Ar}); 5.059 (s, 1H, OCH_2); 4.790–4.758 (dd, J = 9.2, 3.6 Hz, 1H, CH*(OH)); 2.961–2.906 (td, J = 9.2, 3.6 Hz, 1H, CH*–CHOH); 2.802–2.727 (qd, J = 8.8, 3.6 Hz, 1H, CH_{ali}); 2.515–2.417 (m, 2H, CH_{2ali}); 1.807 (m, 1H, OH); 1.674 (m, 1H, CH_{ali}); 1.674–1.162 (m, 15H, CH_{2ali}). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 214.9, 158.6, 136.8, 134.6, 128.6, 128.0, 127.9, 127.4, 114.9, 74.8, 70.0, 59.3, 39.2, 27.3, 26.4, 26.0, 24.2, 23.8, 23.7, 22.7, 22.3, 21.6. FTIR (KBr) ν = 3515.72, 3033.39, 2924.34, 2857.33, 1699.07, 1604.36, 1506.40, 1377.38, 1226.07, 1007.30, 819.42, 738.04, 695.95. HRMS (EI) m/z: Calc. for $C_{26}H_{34}O_3$; 394.2507 $[M]^+$; Found 394.2508.

2-[(4-Chlorophenyl) (hydroxy) methyl] cyclododecanone (4h)

The crude residue was then purified by column chromatography on silica gel (*n*-hexane/EtOAc, 8 : 2) to afford the *anti*-aldol product **4h** (3.165 g, 80%, *dr* = 98 : 2)) as a white crystalline solid; Mp: 146–148 °C; ^{1}H NMR (400 MHz,

$CDCl_3$): δ = 7.343–7.338 (d, J = 2 Hz, 1H, CH_{Ar}); 7.327–7.316 (t, J = 4.4 Hz, 1H, CH_{Ar}); 7.286–7.280 (t, J = 2.4 Hz, 1H, CH_{Ar}); 7.267–7.262 (d, J = 2 Hz, 1H, CH_{Ar}); 4.835–4.802 (dd, J = 9.2, 4 Hz, 1H, CH*(OH)); 2.954–2.896 (td, J = 8.8, 4 Hz, 1H, CH_{ali}); 2.814–2.738 (qd, J = 9.6, 3.2 Hz, 1H, CH_{ali}); 2.628–2.617 (d, J = 4.4 Hz, 1H, CH_{ali}); 2.425–2.353 (qd, J = 8, 3.2 Hz, 1H, CH_{ali}); 1.892–1.825 (m, 1H, CH_{ali}); 1.606–1.571 (m, 1H, CH_{ali}); 1.531–1.473 (m, 1H, CH_{ali}); 1.392–1.160 (m, 15H, CH_{ali}). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 214.7, 140.6, 133.7, 128.7, 128.0, 74.4, 58.9, 39.7, 27.3, 26.4, 25.9, 24.2, 23.8, 23.7, 22.6, 22.4, 21.5. FTIR (KBr) ν = 3411.89, 3055.80, 2932.90, 2857.00, 1687.46, 1596.64, 1375.43, 1291.41, 1139.02, 822.98, 731.68, 602.81. HRMS (EI) m/z: Calc. for $C_{19}H_{27}ClO_2$; 322.1699 $[M]^+$; Found 322.1700.

2-[(4-Bromophenyl) (hydroxy) methyl] cyclododecanone (4i)

The crude residue was then purified by column chromatography on silica gel (*n*-hexane/EtOAc, 7 : 2) to afford the *anti*-aldol product **4i** (3.165 g, 89%, *dr* = 100 : 0) as a white crystalline solid; Mp: 154–156 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.49–7.46 (m, 2H, CH_{Ar}); 7.22–7.20 (d, J = 8 Hz, 2H, CH_{Ar}); 4.80–4.77 (dd, J = 8, 4 Hz, 1H, CH*(OH)); 2.93–2.89 (td, J = 8, 4 Hz, 1H, CH_{ali}); 2.80–2.74 (qd, J = 8, 4 Hz, 2H, CH_{2ali}); 2.43–2.36 (qd, J = 12, 4 Hz, 1H, CH_{ali}); 1.88–1.81 (m, 1H, CH_{ali}); 1.63–1.45 (m, 2H, CH_{2ali}); 1.37–1.20 (m, 15H, CH_{ali}). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 214.7, 141.1, 131.6, 128.3, 121.8, 74.5, 58.8, 39.7, 27.3, 26.3, 25.9, 24.2, 23.7, 23.7, 22.68, 22.3, 21.5. FTIR (KBr) ν = 3408.00, 3056.76, 2931.76, 2856.76, 1686.10, 1589.96, 1373.30, 1290.54, 1139.00, 1043.02, 821.01, 730.46, 599.60. HRMS (EI) m/z: Calc. for $C_{19}H_{27}BrO_2$; 366.1194 $[M]^+$; Found 366.1194.

2-[(4-Ethylphenyl) (hydroxy) methyl] cyclododecanone (4j)

The crude residue was then purified by column chromatography on silica gel (*n*-hexane/EtOAc, 7 : 3) to afford the *anti*-aldol product **4j** (3.165 g, 85%, *dr* = 100) as a white crystalline solid; Mp: 123–125 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.262–7.242 (d, J = 8 Hz, 2H, CH_{Ar}); 7.196–7.176 (d, J = 8 Hz, 2H, CH_{Ar}); 4.800–4.771 (dd, J = 9.2, 6.4 Hz, 1H, CH*(OH)); 2.983–2.928 (td, J = 9.2, 3.6 Hz, 1H, CH*–CHOH); 2.797–2.723 (qd, J = 9.2, 3.2 Hz, 1H, CH_{ali}); 2.753–2.619 (q, J = 15.2, 7.6 Hz, 2H, $CH_{2ethylic}$); 2.531–2.458 (qd, J = 8.4, 3.2 Hz, 1H, CH_{ali}); 1.801–1.770 (ms, 1H, OH); 1.706–1.651 (m, 1H, CH_{ali}); 1.315–1.253 (m, 1H, CH_{ali}); 1.235–1.207 (t, J = 11.2 Hz, 3H, $CH_{3ethylic}$); 1.199–1.182 (m, 16, CH_{2ali}). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 214.9, 144.1, 139.4, 128.0, 126.6, 75.2, 59.3, 39.1, 28.5, 27.3, 26.4, 26.0, 24.2, 23.8, 23.7, 22.8, 22.3, 21.6, 15.5. FTIR (KBr) ν = 3437.90, 3015.26, 2930.95, 2856.69, 1690.00, 1509.83, 1465.65, 1372.63, 1314.23, 1140.29, 1038.80, 831.36, 732.13. HRMS (EI) m/z: Calc. for $C_{21}H_{32}O_2$; 316.2402 $[M]^+$; Found 316.2402.

2-[Hydroxy (napthalen-1-yl) methyl] cyclododecanone (4k)

The crude residue was then purified by column chromatography on silica gel (*n*-hexane/EtOAc, 7 : 3) to afford the *anti*-aldol product **4k** (3.165 g, 82%, *dr* = 100) as a white crystalline solid; Mp: 131–133 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.253–8.233 (d, J = 8 Hz, 1H, CH_{Ar}); 7.888–7.865 (d, J = 8.8 Hz, 1H, CH_{Ar}); 7.807–7.787 (d, J = 8 Hz, 1H, CH_{Ar}); 7.562–7.431 (m, 4H, CH_{Ar}); 5.566–5.536 (dd, J = 8, 4 Hz, 1H, CH*(OH)); 3.412–3.367 (td, 4.5, 3.2 Hz, 1H, CH*–CHOH); 2.910 (s, 1H, OH); 2.714–2.640 (qd, J = 8, 3.2 Hz, 1H, CH_{ali}); 2.433–2.360 (qd, J = 8.4, 3.2 Hz, 1H, CH_{ali}); 1.784–1.606 (m, 3H, CH_{2ali}); 1.299–1.075 (m, 15H, CH_{ali}). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 215.4, 137.7, 134.0, 130.8, 129.0, 128.6, 126.2, 125.6, 125.3, 124.6, 123.4, 73.0, 57.7, 40.4, 28.2, 26.4, 25.8, 24.3, 24.1, 23.4, 22.4, 21.6. FTIR (KBr) ν = 3417.40, 3065.26, 2920.95, 2846.49, 1696.30, 1517.53, 1453.65, 1365.83, 1324.23, 1140.69, 1036.67, 830.66, 736.13, HRMS (EI) m/z: Calc. for $C_{23}H_{30}O_2$; 338.2245 $[M]^+$; Found 338.2246.

(*E*)-1-(2-Chlorobenylidene) cyclododecanone (5a)

The white crude solid was subjected to column chromatography on silica gel (*n*-hexane/EtOAc, 7 : 3) to afford the monobenzylidene product **5a** (2.42 g, 79% E/Z = 96/4), R_f 0.4 (*n*-hexane/EtOAc, 4 : 1); white crystalline solid; Mp: 93–95 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.464 (s, 1H, $CH_{vinylic}$); 7.445–7.421 (td, 4.4, 1.2 Hz, 1H, CH_{Ar}); 7.288–7.256 (m, 3H, CH_{Ar}); 2.873–2.842 (m, 2H, CH_{2ali}); 2.549–2.519 (t, 12 Hz, 2H, CH_{2ali}); 1.866 (bs, 2H, CH_{2ali}); 1.318 (s, 11H, CH_{2ali}); 1.245 (s, 1H, CH_{ali}); 1.136–1.110 (t, J = 10.4 Hz, 2H, CH_{2ali}). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 205.0, 143.2, 136.0, 134.7, 133.8, 130.3, 129.4, 129.2, 126.4, 38.8, 26.5, 26.4, 25.4, 24.4, 24.2, 24.1, 23.9, 23.1, 22.5. FTIR (KBr) ν = 3515.35 [(broad peak) absence of OH peak], 3066.80, 2939.97, 2855.73, 1661.73, 1465.48, 1361.77, 1239.93, 1157.74, 939.21, 870.34, 767.87, 692.52. HRMS (EI) m/z: Calc. for $C_{19}H_{25}ClO$; 304.1593 $[M]^+$; Found 304.1594.

(*E*)-1-(2-Bromobenylidene) cyclododecanone (5b)

The crude residue was then purified by column chromatography on silica gel (*n*-hexane/EtOAc, 8 : 2) to afford the monobenzylidene product **5b** (2.624 g, 75%, E/Z = 98/2) as a white crystalline solid; Mp: 111–113 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.635–7.615 (m, 1H, CH_{Ar}); 7.288–7.256 (s, 1H, $CH_{vinylic}$); 7.344–7.168 (m, 3H, CH_{Ar}); 2.877–2.846 (m, 2H, CH_{2ali}); 2.539–2.509 (t, J = 12 Hz, 2H, CH_{2ali}); 1.893 (bs, 2H, CH_{2ali}); 1.318 (s, 11H, CH_{2ali}); 1.241 (s, 1H, CH_{ali}); 1.132–1.107 (t, J = 10 Hz, 2H, CH_{2ali}). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 205.1, 142.8, 138.0, 136.5, 132.6, 130.5, 129.3, 127.1, 124.0, 38.8, 26.5, 26.5, 25.4, 24.4, 24.2, 24.1, 24.0, 23.1, 22.5. FTIR (KBr) ν = 3483.16 [(broad peak) absence of OH peak], 3064.86, 2938.19, 2860.89, 1661.57, 1464.88, 1358.90, 1239.37, 1113.73, 765.70, 742.36. HRMS (EI) m/z: Calc. for $C_{19}H_{25}BrO$ 348.1088 $[M]^+$; Found 348.1089.

(*E*)-1-(2,4-Dichlorobenylidene) cyclododecanone (5c)

The crude residue was then purified by column chromatography on silica gel (*n*-hexane/EtOAc, 8 : 2) to afford themonobenzylidene product **5c** (2.386 g, 70%, E/Z = 100) as a white crystalline solid; Mp: 140–142 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.464–7.459 (d, J = 2 Hz, 1H, $CH_{vinylic}$); 7.375 (s, 1H, CH_{Ar}); 7.284–7.258 (dd, 8, 2 Hz, 1H, CH_{Ar}); 7.231–7.210 (d, 8.4 Hz, 1H, CH_{Ar}); 2.862–2.831 (m, 2H, CH_{2ali}); 2.517–2.831 (t, 12 Hz, 2H, CH_{2ali});1.859–1.852 (s, 2H,

CH_{2ali}); 1.373–1.236 (m, 12H, CH_{2ali}); 1.117–1.091 (t, 10.4 Hz, 2H, $CH2_{ali}$). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 204.7, 143.8, 134.4, 133.2, 131.1, 129.4, 126.9, 38.8, 26.5, 26.4, 25.5, 24.3, 24.2, 24.1, 24.0, 23.0, 22.5. FTIR (KBr) ν = 3429.57 [(broad peak) absence of OH peak], 3072.08, 2930.28, 2856.31, 1667.90, 1581.91, 1466.23, 1373.53, 1236.79, 1107.15, 854.61, 755.08, 698.29. HRMS (EI) *m*/*z*: Calc. for $C_{19}H_{24}Cl_2O$; 338.1204 $[M]^+$; Found 338.1206.

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