Diastereoselective synthesis of chiral 1,3-cyclohexadienals

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Abstract

A novel approach to the production of chiral 1,3-cyclohexadienals has been developed. The organocatalysed asymmetric reaction of different β-disubstituted-α,β-unsaturated aldehydes with a chiral α,β-unsaturated aldehyde in the presence of a Jørgensen-Hayashi organocatalyst provides easy and stereocontrolled access to the cyclohexadienal backbone. This method allows for the synthesis of potential photoprotective chiral 1,3-cyclohexadienals and extra extended conjugation compounds in a simple manner.

Introduction

Organocatalysis is one of the fastest growing areas in organic chemistry [1–4]. The enantioselective organocatalytic Diels-Alder reaction from the seminal communication of Prof. MacMillan et al. [5] constitutes one of the most interesting research areas. The synthesis of enantiomerically enriched building blocks is an important task in organic synthesis, where cyclohexadienes [6–11] are of special interest due to their reactivity. Although the use of monosubstituted α,β-unsaturated aldehydes is more extended, in the last few years the use of β-disubstituted-α,β-unsaturated aldehydes has become more prevalent in this area. There are numerous examples of asymmetric synthesis by using organocatalysis, as shown by the work of Professor Serebryakov et al. in the synthesis of cyclohexa-1,3-dienes from prenal and unsaturated esters or derivatives, [12–16] Professor Hong et al. for the synthesis of aromatic aldehydes by organocatalytic [4+2] or [3+3] cycloaddition of α,β-unsaturated aldehydes [17–19] and Professor Watanabe et al. in citral, **1**, dimerization. [20–25] The cyclohexadienal scaffold has been shown to be bioactive in numerous cases throughout the literature. For example, the citral dimer shows antibiotic activity [26] and the retinal dimer could contribute to macular degeneration. [27] As chiral aldehyde **2** has been intensively used as a synthetic building block in the synthesis of bioactive natural products, [28–33] this study sought to obtain chiral cyclohexadienals using **2** in combination with different β-methyl disubstituted-α,β-unsaturated aldehydes in the presence of different catalysts (**5–10**), which avoid the dimerization of these compounds (Fig 1).

In the last few decades the potentially dangerous effects of UV radiation exposure have been extensively demonstrated [34–36]. While UVC light is filtered by the upper atmospheric layers, UVB and UVA light penetrate the upper layers of the atmosphere and reach the Earth's surface. Photoprotection against this radiation can prevent skin damage and deleterious effects on DNA. However, it is important not to overdo protection against UVB as this can reduce the biosynthesis of vitamin D[37,38]. Therefore, photoprotective agents that selectively absorb UVB and UVA radiation are the UV-filters needed for developing effective and safe sunscreens.

There are two groups of UV filters: inorganic and organic compounds. The inorganic filters scatter, reflect or absorb UV radiation, however, only TiO_2 and ZnO are FDA approved. The organic UV filters consist of structurally simple aromatic molecules that absorb in UVA and UVB. The organic UV filters used in sunscreens, and approved by the FDA (Fig 2)[39] can be classified as cinnamates, benzophenones, PABA and salicilate derivatives and others. Despite their use in sunscreens, there are several studies regarding the toxicity, and especially the phototoxicity, of these compounds [40–46].

In this work, cyclohexadienals containing different substitutions have been synthesized as easily accessible high-conjugated compounds with interesting UV-Vis properties, making them suitable for use as photoprotective UV-filters.

Materials and methods

All reactions were performed in oven-dried glassware under positive Ar pressure with magnetic stirring, unless otherwise noted. Air and moisture-sensitive liquids and solutions were transferred via a syringe or a stainless-steel cannula. TLC was performed on 0.25 mm E. Merck silica gel 60 F254 plates and visualized under UV light ($\lambda = 254$ nm) or by staining with potassium permanganate. Flash chromatography was performed on E. Merck 230–400 mesh silica gel 60. All reagents were purchased from commercial suppliers, and used without further purification unless otherwise noted. Solvents were distilled from suitable drying agents (CaH_2 or Na wire) under an Ar atmosphere at 760 mmHg. All moisture- and/or oxygen-sensitive solids were handled and stored in a glove box under N_2. The NMR spectra were recorded on Bruker AVANCE 400 MHz DRX and Varian Mercury 200 MHz using $CDCl_3$ as solvent. NMR data is reported as follows: chemical shift (δ) (parts per million, ppm); multiplicity: s (singlet), d (doublet), t (triplet), q (quartet) and br (broad); coupling constants (J) are given in Hertz (Hz). ^{1}H NMR chemical shifts were calibrated with respect to residual chloroform in $CDCl_3$ centered at 7.26 ppm, whereas for ^{13}C NMR, the center peak for $CDCl_3$, centered at 77.0 ppm, was used for the calibration. The IR spectra were obtained on a Shimadzu IR Affinity-1 (film over NaCl). All NMR and IR spectra can be found in S1 File. The HRMS spectra were obtained on an Applied Biosystems QSTAR XL mass spectrometer. The optical rotation was performed on a Perkin-Elmer 241 digital polarimeter using cuvette with l = 1 dm and $CHCl_3$ as the solvent. Absorbance measures were determined in 200–700 nm region using iPrOH as the solvent and an UV quartz cuvette (l = 1 cm) in a Shimadzu UV-2401PC spectrophotometer with thermostatic system at 20˚C. The UV-Vis spectra can be found in S4 File.

Results and discussion

First, the synthesis of chiral cyclohexadienals (Fig 3) with citral, **1**, and aldehyde, **2**, obtained from D-mannitol in the usual conditions was tested. [20–25].

The different experimental conditions of the catalyst, solvent and additives tested are shown in Table 1.
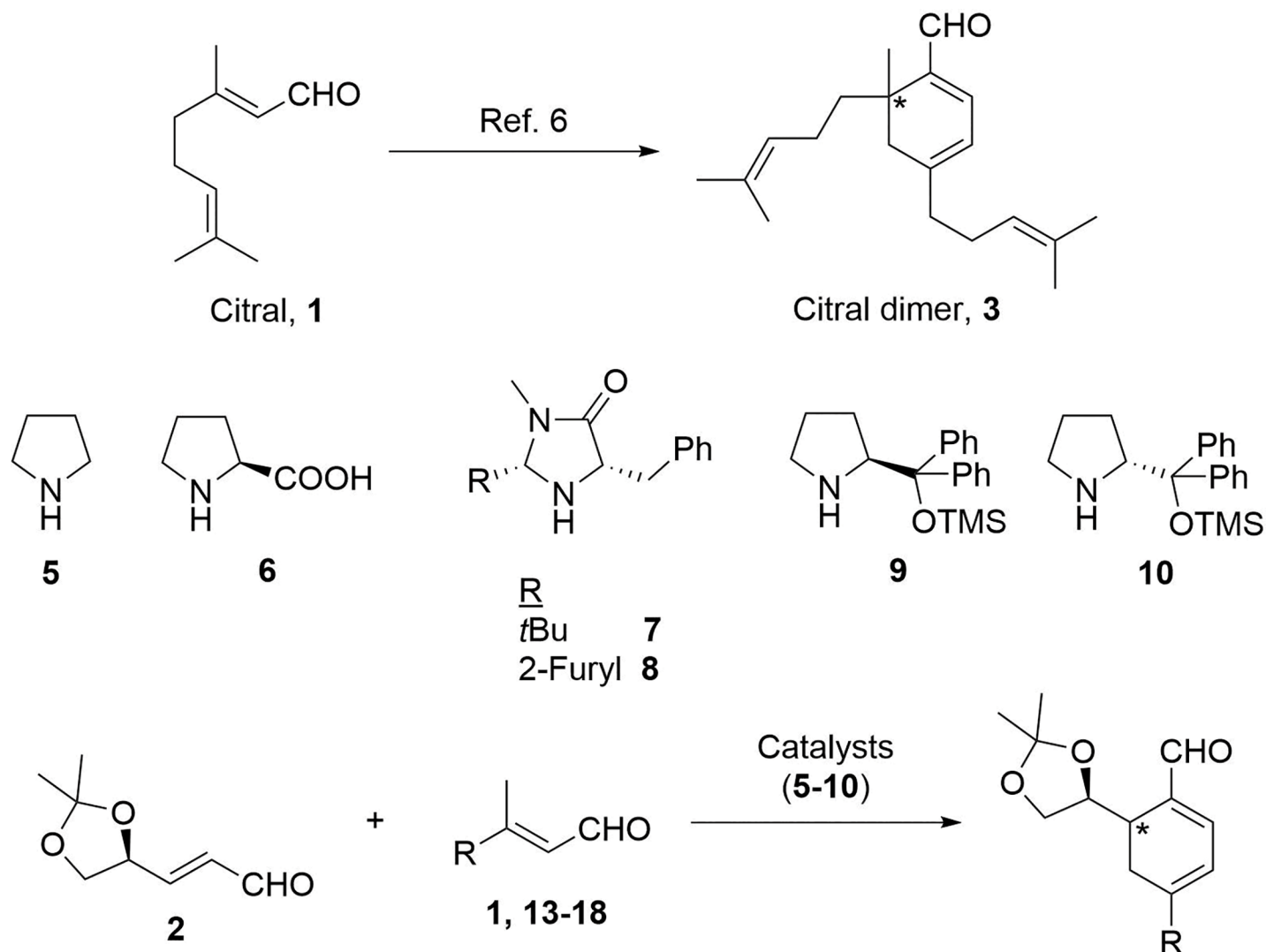
Fig 1. Proposal for the synthesis of new cyclohexadienal building blocks using different catalysts.

When using a non-chiral organocatalyst, such as pyrrolidine, **5**, cyclohexadienal **4** was obtained in low yields, although without diastereoselectivity (entry 1). The use of L-proline, **6** (entries 2–3), using different solvents, or no solvent at all, gave the required cyclohexadienal **4** in very low yields and the citral dimer **3**, as a subproduct. Then, MacMillan´s organocatalysts **7** and **8** were tested, but no result was obtained (entries 4–5). In addition, the Jørgensen-Hayashi catalysts **9** and **10** were used in different solvent conditions, obtaining different results depending on the solvent used, ranging from moderate yields of cyclohexadienal **4** (entries 6–9 and 22) to no reaction at all (entries 10–14). As can be seen in Table 1, in some cases the reaction was carried out in presence of additives such as acids (BzOH, *o*-nitro-BzOH, AcOH, TsOH, (±)-1,19-binaphthyl-2,29-diyl hydrogenphosphate[(±) BINAP-OH] or TFA) and bases (DBU) (entries 15–21) with improved yields. The best result was obtained when the Jørgensen-Hayashi catalyst **9** in CHCl₃ as the solvent, was used without any additional additive (entry 8) and produced a moderate yield and a good d.r.
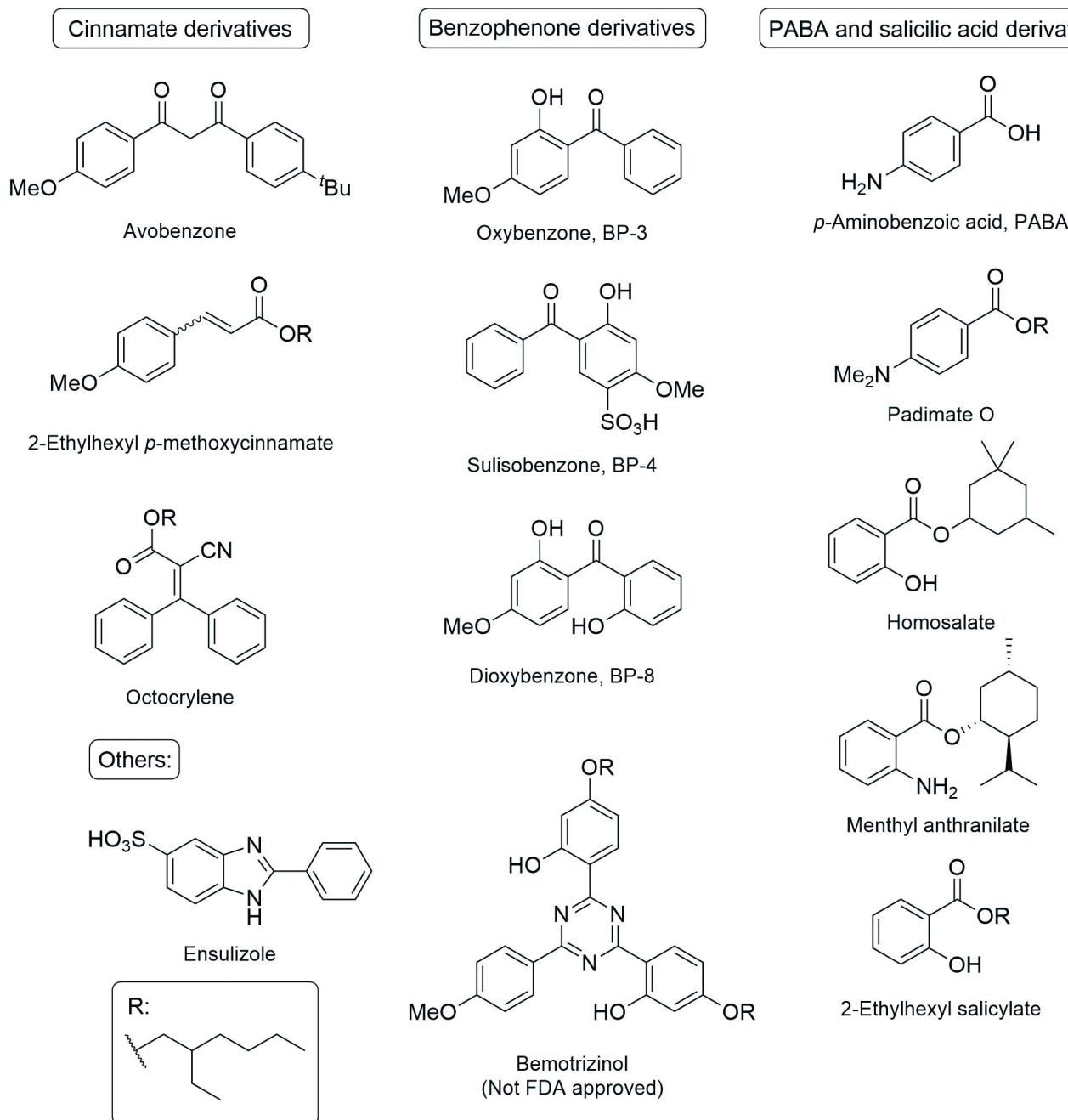
Fig 2. FDA approved UV-filters and bemotrizinol, approved only in Europe. The main UV filters structurally related to cinnamate esters, benzophenone, *p*-aminobenzoic acid (PABA) and salicilate derivatives, and two additional structures that can be found in ensulizole and bemotrizinol.

Determination of stereochemistry of stereocenter created by NMR

An extra cycle was made to introduce more conformational rigidity (Fig 4), in order to establish the stereochemistry of cyclohexadienal **4**. Aldehyde **4a** was oxidized using the usual conditions [47] to obtain the acid **11**; deprotection of the acetonide gave the desired lactone ring, **12**. After studying the NOE (Nuclear Overhauser Effect) on this compound, the configuration of
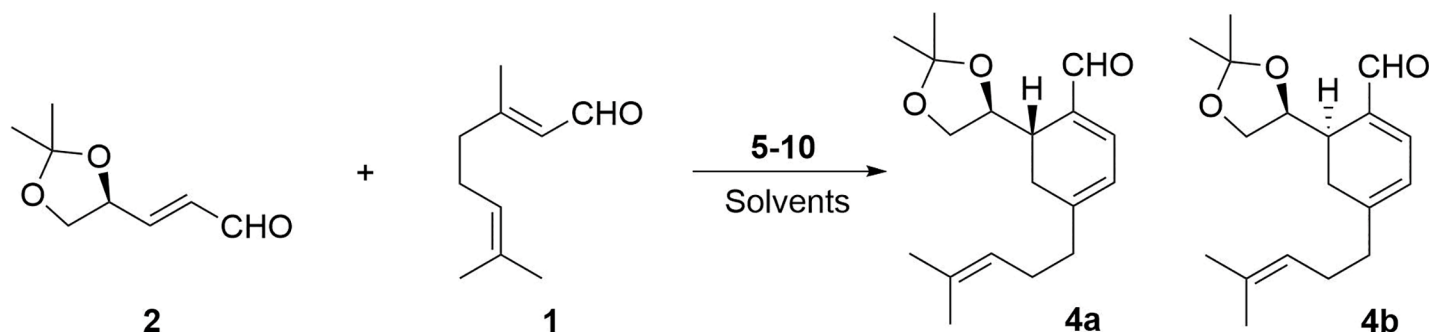
Fig 3. General reaction to obtain chiral cyclohexadienals.

C-6 in compound **12** was established as *S*, because of NOE between H1' and H6 did not appear. Later on, the absolute configuration was confirmed by X-Ray of an analogue (**24a**).

Synthesis of chiral cyclohexadienals with different substituents

The mechanism could be understood by a Diels-Alder reaction, as suggested by Serebryakov et al. [12–16] and Watanabe et al. [20]. Similarly, this will would explain that the stereochemistry

Table 1. Experimental optimization of synthesis of chiral cyclohexadienals (4a, 4b) from citral (1) and α,β-unsaturated aldehyde 2.

Entry	Cat.	Solvent[a]	Addit.[c]	Product[d]	d.r.[e]
1	5	CHCl₃	-	**4a,b** (17)	50:50
2	6	-	-	**3** (8), **4a,b** (3)	n.d.
3	6	CHCl₃	-	**3** (12), **4a,b** (10)	50:50
4	7	*i*PrOH	-	-	-
5	8	*i*PrOH	-	-	-
6	9	Hexane	-	**4a,b** (5)	80:20
7	9	Toluene	-	**4a,b** (20)	75:25
8	9	CHCl₃[b]	-	**4a,b** (37)	85:15
9	9	DCM	-	**4a,b** (4)	n.d.
10	9	Et₂O	-	-	-
11	9	THF	-	-	-
12	9	*i*PrOH	-	-	-
13	9	EtOH	-	-	-
14	9	MeOH	-	-	-
15	9	CHCl₃	BzOH	**4a,b** (19)	60:40
16	9	CHCl₃	*o*-NO₂-BzOH	**4a,b** (27)	80:20
17	9	CHCl₃	AcOH	-	-
18	9	CHCl₃	TFA	-	-
19	9	CHCl₃	TsOH	**4a,b** (2)	n.d.
20	9	CHCl₃	(±) BINAP-OH	**4a,b** (4)	n.d.
21	9	CHCl₃	DBU	-	-
22	10	CHCl₃	-	**4a,b** (18)	33:66

[a] All reactions were carried out with 0.5 equiv. of catalyst, solvent (0.2M), for 48 hours.

[b] 20% and 30% of the catalyst produced lower yields in the same reaction time.

[c] 0.2 equiv. of the additive were added and the reaction was carried out following the general procedure.

[d] In parentheses, the yield of the isolated mixture in %.

[e] The relation of the diastereoisomers was established by integrating ¹H NMR in crude mixture.
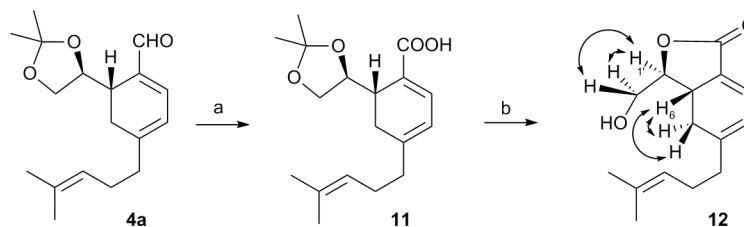
Fig 4. Synthesis of bicycle 12 from cyclohexadienal 4a. Reagents: a) NaH$_2$PO$_4$·H$_2$O (2.2 equiv.), NaClO$_2$ (5%, 2.2 equiv.), 2-methyl-2-butene, *t*BuOH, r.t., 2h, 99%; b) *p*-TsOH, MeOH, r.t., 30%.

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obtained in the final product does not depend on the Z or E stereochemistry of the α,β-unsaturation of the aldehyde used in the reaction. The same result was obtained with E-citral or a mixture E/Z-citral. E-citral was obtained from geraniol as described in the literature.[48] Once the conditions for the synthesis of cyclohexadienals were obtained, the generality of the reaction using different β-disubstituted-α,β-unsaturated aldehydes and **2** as starting materials was then observed, Fig 5 and Table 2.

The reaction was initiated using a simple α,β-unsaturated aldehyde such as **13**. When catalysts **9** or **10** were used, both produced a good yield and diastereoselection. When catalyst **10** was used, instead of **9**, the yield slightly decreased but diastereoselection remained complete. When using aromatic aldehydes, the reaction worked very well, especially with the *p*-methoxyphenyl group (entries 5–6) which produced excellent yields and diastereoselection with both catalysts **9** and **10**. When a bromophenyl group was used (entries 7–10), the yield and diastereoselection decreased but when a *p*-nitrophenyl group (entries 11–12) was used the yield increased with both catalysts and the diastereoselection was excellent, especially with catalyst **10**. When the reaction was run using an aliphatic cyclic aldehyde,
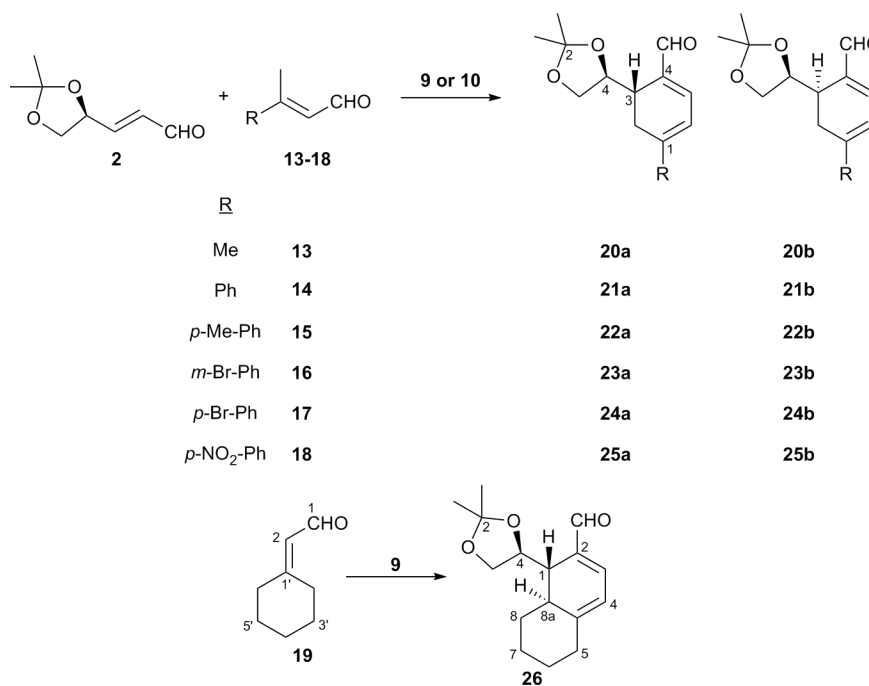
Fig 5. Synthesis of different chiral cyclohexadienals aromatic and non-aromatic compounds.

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Table 2. Synthesis of chiral cyclohexadienals (20a-26) from other β-disubstituted-α,β-unsaturated aldehydes (13–19)[a].

Entry[b]	S.M.	Cat.	Product	Yield (%)[c]	d.r.[d]
1	**13**	**9**	**20a**	60	85:15
2	**13**	**10**	**20b**	52	>95
3	**14**	**9**	**21a**	72	90:10
4	**14**	**10**	**21b**	35	>95
5	**15**	**9**	**22a**	99	>95
6	**15**	**10**	**22b**	83	>95
7	**16**	**9**	**23a**	48	85:15
8	**16**	**10**	**23b**	50	>95
9	**17**	**9**	**24a**	45	90:10
10	**17**	**10**	**24b**	45	>95
11	**18**	**9**	**25a**	90	90:10
12	**18**	**10**	**25b**	88	>95
13	**19**	**9**	**26**	4	>95

[a]General procedure for the synthesis of **14–19** can be found in the S2 File.

[b]All reactions were carried out in CHCl$_3$ (0.2M), 0.5 equiv. of catalyst, for 48 hours at r.t.

[c] Isolated yield of major diastereomer.

[d] Relation of the diastereoisomers was stablished by integrating ^{1}H NMR in crude mixture.

such as catalyst **19**, the yield was very poor (entry 13) but diastereoselection was complete. As can be seen in Table 2, the reaction proceeded quite well, especially when using aromatic aldehydes.

Crystallographic analysis of cyclohexadienal 24a

Compound **24a** was crystallized. In Fig 6, the X-ray crystal structure of compound **24a** [49] is shown and confirms the stereochemistry of compound **24a** at C-6. The stereochemistry of this compound was previously predicted by the NMR of compound **12**, and by analogy, the stereochemistry of compounds **20** to **26** was established.

UV-Vis absorption analysis

The UV-Vis absorbance of different photostable cyclohexadienals was measured (Table 3 and S4 File) in order to test the possible application of these compounds as photoprotective agents.

The majority of the compounds at concentrations in the order of 10^{-6} absorbed UVA and UVB. Compound **21b** exhibited values suitable for photoprotection against UVA owing to the higher area under the curve (AUC) at that particular wavelength region and its molar extinction coefficient (ε = 13200 M^{-1}cm^{-1}). The best results found in the UVB region were shown by compound **23b** which had an extinction coefficient of 34700 M^{-1}cm^{-1} at 288nm. However, the compound that was able to better absorb UVA and UVB was **23a**, with molar extinction coefficients of 8000 M^{-1}cm^{-1} in UVA and 10900 M^{-1}cm^{-1} in UVB.

A global view of UV absorption of this chiral aromatic cyclohexadienal can be seen in Fig 7.

Synthesis

General procedure for the optimization of conditions for cyclohexadienals (4a,b). Catalyst **5–10** (0.5 eq) were added to a solution containing **2** (0.3 mmol, 1 equiv.) and **1** (0.3
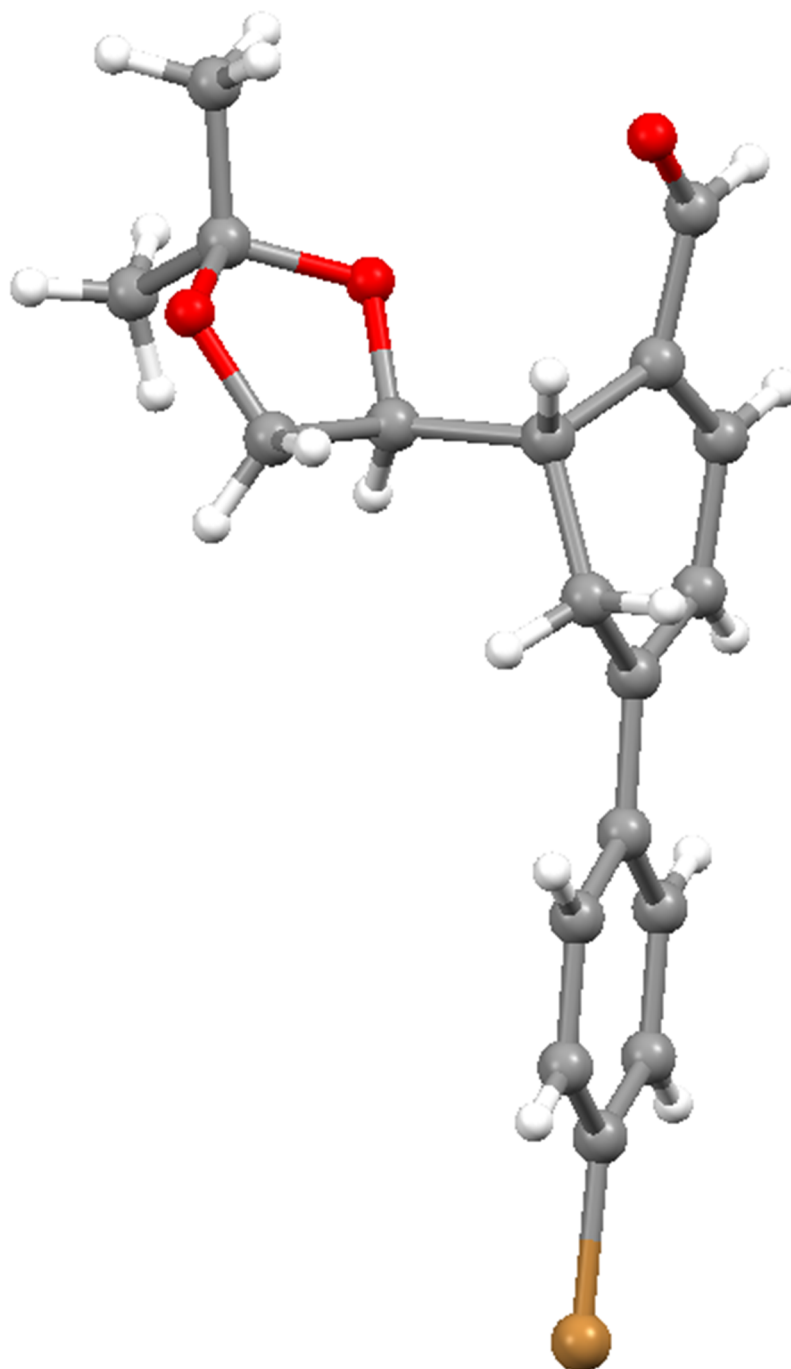
Fig 6. X-ray crystal structure of 24a. Displacement ellipsoids are drawn at the 30% probability level. Hydrogen atoms are shown as spheres of arbitrary radius (S3 File).

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mmol, 1 equiv.) in solvent (1.5 mL, 0.2M) at r.t. The reaction mixture was stirred at r.t. for 48h. The solution was concentrated in and the residue was purified by flash column chromatography (EtAcO:hexane) to obtain cyclohexadienals **4a** and **4b** as a yellow oil and dimer **3** as a colourless oil.

Table 3. The area of regions UVA (315–400 nm) and UVB (280–315 nm) and molar extinction coefficient of some cyclohexadienals (4a, 20b, 21b, 22b, 23a, 23b) dissolved in *i*PrOH.

Entry	Product	Concentration (M/10^{-6})	λ_{nm} (ε M^{-1} cm^{-1})	AUC (UVA)[a]	λ_{nm} (ε M^{-1} cm^{-1})	AUC (UVB)
1	**4a**	1.8	-	0.305	-	0.318
2	**20b**	5.3	341.3 (3000)	1.034	-	0.510
3	**21b**	8.5	351.5 (13200)	7.013	283.0 (2000)	2.370
4	**22b**	4.2	360.3 (4300)	1.194	274.8 (8900)	0.594
5	**23a**	7.4	336.3 (8000)	3.708	282.3 (10900)	2.310
6	**23b**	1.7	341.3 (2000)	2.374	287.8 (34700)	1.838

[a] Area Under Curve (AUC).

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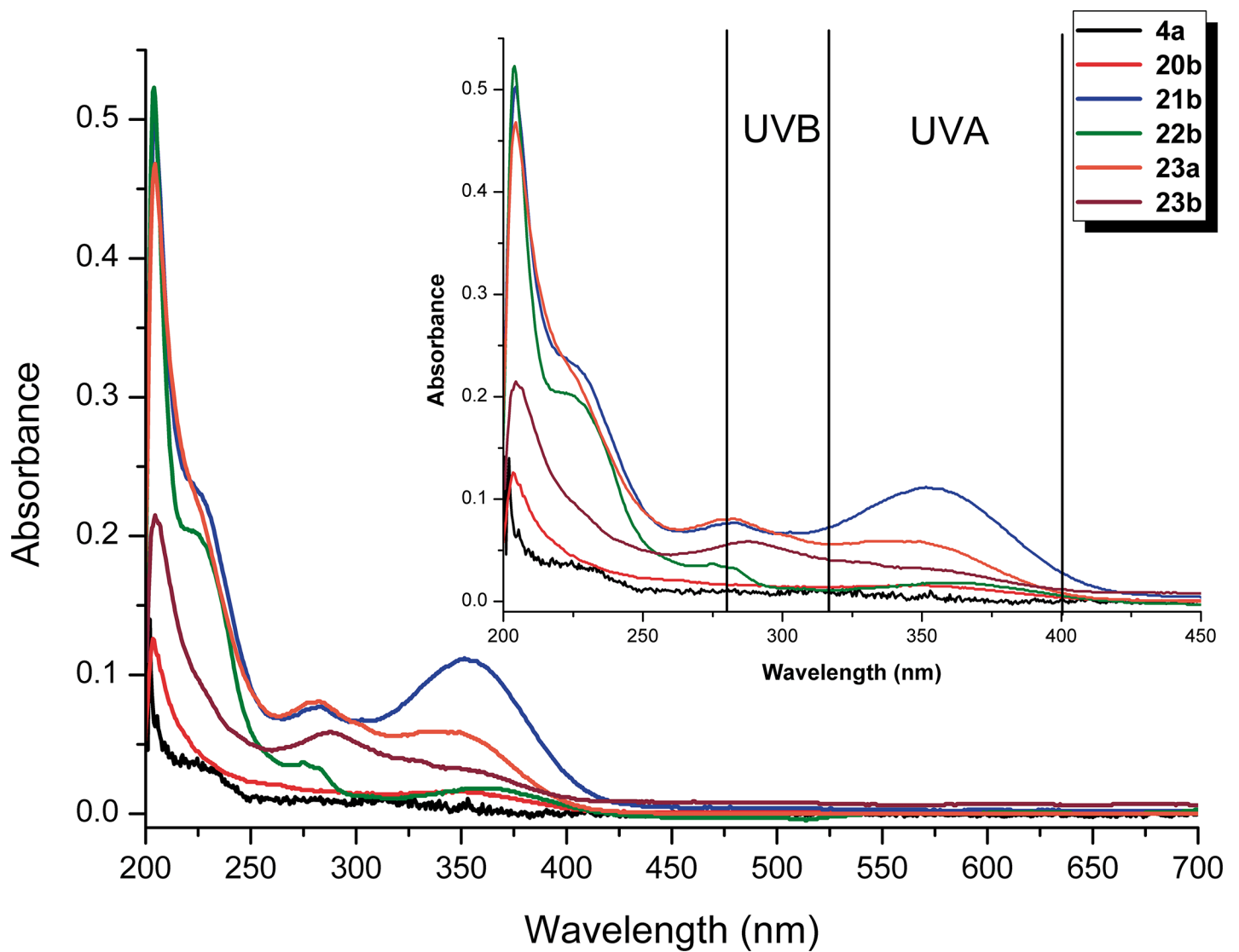
Fig 7. UV-Vis absorbance spectra at different λ of 4a, 20b, 21b, 22b, 23a, 23b. Amplification of the 200–450 nm region and the delimited UVA and UVB regions (ISO-21348).

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Catalyst **9** (0.5 eq) was added to a solution containing **2** (0.15 mmol, 1 equiv.) and E-citral (0.15 mmol, 1 equiv.) in $CHCl_3$ (0.75 mL, 0.2M) at r.t. The reaction mixture was stirred at r.t. for 48h. The solution was concentrated in vacuum and the residue was purified by flash column chromatography (EtAcO:hexane) to obtain a mixture of cyclohexadienals **4a** and **4b** as a yellow oil (yield 37%; d.r. 85:15).

6-Methyl-4,6-bis(4-methylpent-3-en-1-yl)cyclohexa-1,3-diencarbaldehyde(3).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 9.41 (1H, s), 6.67 (1H, d, J = 5.5 Hz), 5.92 (1H, d, J = 5.5 Hz), 5.10–5.03 (2H, m), 2.38–2.33 (1H, m), 2.19–2.18 (4H, m), 2.04–1.77 (4H, m, H-5), 1.69 (3H, s), 1.65 (3H, s), 1.62 (3H, s), 1.55 (3H, s), 1.41–1.32 (1H, m), 1.19 (3H, s).

(S)-6-((S)-2,2-Dimethyl-1,3-dioxolan-4-yl)-4-(4-methylpent-3-en-1-yl)cyclohexa-1,3-dien-1-carbaldehyde(4a).

$[α]_D^{25}$ = -43.3 (c = 0.54, $CHCl_3$).

IR (film): 2981, 2929, 1670, 1570, 1379, 1213, 1066, 842 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 9.47 (1H, s), 6.81 (1H, d, J = 5.7 Hz), 5.95–5.90 (1H, m), 5.10–5.00 (1H, m), 4.18 (1H, q, J = 6.4 Hz), 3.86 (1H, dd, J = 8.4, 6.4 Hz), 3.67 (1H, dd, J = 8.4, 6.4 Hz), 3.20–3.10 (1H, m), 2.44–2.37 (2H, m), 2.36–1.80 (4H, m), 1.68 (3H, s), 1.61 (3H, s), 1.42 (3H, s), 1.27 (3H, s).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 192.4, 151.8, 145.2, 135.1, 132.8, 123.2, 118.7, 109.0, 75.9, 66.7, 38.0, 31.7, 28.8, 26.4, 25.9 (2), 25.5, 18.0.

HRMS (ESI): Calculated for $C_{18}H_{26}O_3Na$ ([M+Na]$^+$): 313.1774; found 313.1775.

(R)-6-((S)-2,2-Dimethyl-1,3-dioxolan-4-yl)-4-(4-methylpent-3-en-1-yl)cyclohexa-1,3-dien-1-carbaldehyde(4b).

$[α]_D^{25}$ = 33.5 (c = 0.45, $CHCl_3$).

IR (film): 2981, 2929, 1670, 1570, 1379, 1213, 1066, 842cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 9.46 (1H, s), 6.84 (1H, d, J = 5.7 Hz), 6.00–5.97 (1H, m), 5.13–5.08 (1H, m), 3.92 (1H, q, J = 6.7 Hz), 3.75 (1H, dd, J = 15.6, 8.0 Hz), 3.72 (1H, dd, J = 15.6, 6.7 Hz), 2.94 (1H, t, J = 8.5 Hz), 2.66 (1H, d, J = 18.0), 2.37 (1H, dd, J = 18.0, 8.5 Hz), 2.33–2.10 (4H, m), 1.69 (3H, s), 1.62 (3H, s), 1.54 (3H, s), 1.30 (3H, s).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 192.3, 152.6, 146.5, 134.9, 132.4, 123.1, 118.6, 108.6, 74.8, 68.0, 37.9, 32.2, 29.6, 26.8, 25.8, 25.7, 25.6, 17.7.

HRMS (ESI): Calculated for $C_{18}H_{26}O_3Na$ ([M+Na]$^+$): 313.1774; found 313.1775.

6-((S)-2,2-dimethyl-1,3-dioxolan-4-yl)-4-(4-methylpent-3-en-1-yl)cyclohexa-1,3-dien-1-carboxilic acid(11).

2-methyl-2-butene (0.097 mL, 0.92 mmol), a 0.65M solution of $NaH_2PO_4^.H_2O$ in H_2O (0.97 mL, 0.81 mmol) and 5% $NaClO_2$ in H_2O (0.91 mL, 0.72 mmol) were added to a solution containing **4a** (105 mg, 0.36 mmol) in tBuOH (3.8 mL). The reaction mixture was stirred at r.t. for 22h. The reaction was quenched with H_2O and 1M HCl was added until acid pH was reached. The reaction mixture was extracted with EtOAc (3x10 mL). The combined organic layers were washed with H_2O until neutral pH was reached, dried over Na_2SO_4, filtered and concentrated under vacuum to obtain acid **11** (109 mg, 0.36 mmol, 99%).

$[α]_D^{25}$ = -63.0, (c = 0.684, $CHCl_3$).

IR (film): 2984, 2930, 1678, 1582, 1422, 1260, 1217, 1070, 1049 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.20 (1H, d, J = 5.8 Hz), 5.82 (1H, d, J = 5.8 Hz), 5.07 (1H, bs), 4.27 (1H, q, J = 6,2 Hz), 3.92 (1H, dd, J = 8.4, 6.2 Hz), 3.72 (1H, dd, J = 8.4, 7.4 Hz), 3.06 (1H, t, J = 8.0 Hz), 2.45 (1H, d, J = 8.0 Hz), 2.37 (1H, bs), 2.17 (4H, bs), 1.68 (3H, s), 1.61 (3H, s), 1.41 (3H, s), 1.31 (3H, s).

^{13}C NMR (50 MHz, $CDCl_3$): δ = 172.6, 148.8, 137.6, 132.7, 132.7, 124.1, 118.3, 109.0, 76.4, 66.9, 37.7, 33.6, 28.8, 26.4, 25.9 (2), 25.5, 18.0.

HRMS (ESI): Calculated for $C_{18}H_{27}O_4$ ([M+H]$^+$): 307.1904; found 307.1908.

(3*S*,3a*R*)-3-(Hydroxymethyl)-5-(4-methylpent-3-en-yl)-3a,4-dihydroisobenzofuran-1(3H)-one(**12**).

p-TsOH (21 mg, 0.11 mmol) was added to a solution containing **11** (35mg, 0.11 mmol) and MeOH (1.5 mL). The reaction mixture was stirred at r.t. for 14h. The reaction was quenched with H_2O. The crude mixture was extracted with EtOAc (3x10 mL). The combined organic layers were washed with H_2O, sat. $NaHCO_3$ solution and brine, dried over Na_2SO_4, filtered and concentrated under vacuum to yield **12** (8 mg, 0.033 mmol, 30%).

IR (film): 2959, 2924, 1749, 1217, 1030 cm^{-1}.

^{1}H NMR (400 MHz, CDCl$_3$): δ = 6.94 (1H, dd, J = 5.4, 3.3 Hz), 6.02(1H, bs), 5.07 (1H, bs), 4.24 (1H, dt, J = 8.2, 3.9 Hz), 3.98 (1H, d, J = 12.6 Hz), 3.76 (1H, d, J = 12.6 Hz), 2.99 (1H, dtd, J = 17.6, 8.2, 3.9 Hz), 2.36 (2H, dd, J = 17.6, 8.2 Hz), 2.28–2.14 (5H, m), 1.69 (3H, s), 1,61 (3H, s).

^{13}C NMR (50 MHz, CDCl$_3$): δ = 169.3, 147.6, 132.9, 131.1, 124.3, 123.2, 120.3, 85.9, 63.0, 37.8, 35.0, 31.7, 26.3, 25.9, 18.0.

HRMS (ESI): Calculated for $C_{15}H_{21}O_3$ ([M+H]$^+$): 249.1485; found 249.1491.

General procedure for the synthesis of cyclohexadienals (20a,b-26). Catalyst **9** or **10** (0.5 equiv.) was added to a solution of **2** (1 mmol, 1 equiv.) and aldehyde (1 mmol) in CHCl$_3$ (5 mL) at r.t. The reaction mixture was stirred at r.t. for 48h. The solution was concentrated under vacuum and the residue was purified by flash column chromatography (EtOAc:hexane) to obtain cyclohexadienal as a yellow oil.

(*S*)-3-((*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl)-1-methylcyclohexa-4,6-dien-4-carbaldehyde (**20a**).

Catalyst **9** used.

Yield: 60% (133 mg, 0.60 mmol).

$[\alpha]_D^{25}$ = -114.5 (c = 0.53, CHCl$_3$).

IR (film): 2916, 2848, 1672, 1059 cm^{-1}.

^{1}H NMR (200 MHz, CDCl$_3$): δ = 9.48 (1H, s), 6.82 (1H, d, J = 5.6 Hz), 5.92 (1H, d, J = 5.6 Hz), 4.21 (1H, q, J = 6.4 Hz), 3.87 (1H, dd, J = 8.4, 6.4 Hz), 3.68 (1H, dd, J = 8.4, 6.4 Hz), 3.17 (1H, ddd, J = 8.4, 6.4, 3.4 Hz), 2.41 (2H, d, J = 3.4 Hz), 1.91 (3H, s), 1.43 (3H, s), 1.30 (3H, s).

^{13}C NMR (50 MHz, CDCl3): δ = 192.4, 148.6, 145.5, 134.8, 119.3, 109.0, 76.1, 66.6, 31.7, 30.0, 26.4, 25.5, 24.2.

HRMS (ESI): Calculated for $C_{13}H_{18}O_3Na$ ([M+Na]$^+$): 245.1148; found 245.1146.

(*R*)-3-((*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl)-1-methylcyclohexa-4,6-dien-4-carbaldehyde (**20b**).

Catalyst **10** used.

Yield: 52% (116 mg, 0.52 mmol).

$[\alpha]_D^{25}$ = +12.7 (c = 1.65, CHCl$_3$).

IR (film): 2985, 2933,1666, 1573, 1192, 1155, 1066, 860 cm^{-1}

^{1}H NMR (200 MHz, CDCl$_3$): δ = 9.46 (1H, s), 6.83 (1H, d, J = 5.5 Hz), 6.01–5.95 (1H, m), 4.03–3.88 (1H, m), 3.85–3.65 (2H, m), 2.94 (1H, dt, J = 8.4, 1.7 Hz), 2.61 (1H, dd, J = 18.4, 1.7 Hz), 2.38 (1H, dd, J = 18.4, 8.4 Hz), 1.95 (3H, s), 1.39 (3H, s), 1.31 (3H, s).

^{13}C NMR (50 MHz, CDCl$_3$): δ = 192.6, 149.3, 147.0, 136.5, 119.4, 108.9, 75.5, 68.0, 32.5, 31.0, 27.0, 25.9, 24.3.

HRMS (ESI): Calculated for $C_{13}H_{19}O_3Na$ ([M+Na]$^+$): 223.1328; found 223.1326.

(*S*)-3-((*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl)-2,3-dihydro-[1,1'-biphenyl]-4-carbaldehyde (**21a**).

Catalyst **9** used.

Yield: 72% (205 mg, 0.72 mmol).

$[\alpha]_D^{25}$ = -34.1 (c = 0.16, CHCl$_3$).

IR (film): 2983, 2931, 1668, 1554, 1172, 756 cm^{-1}.

^{1}H NMR (200 MHz, CDCl$_3$): δ = 9.60 (1H, s), 7.53 (2H, dd, J = 8.0, 1.6 Hz), 7.39 (2H, d, J = 8.0 Hz), 7.41–7.37 (1H, m), 7.01 (1H, d, J = 6.0 Hz), 6.57 (1H, d, J = 6.0 Hz), 4.30 (1H, q, J = 6.4 Hz), 3.90 (1H, dd, J = 8.4, 6.4 Hz), 3.76 (1H, dd, J = 8.4, 6.4 Hz), 3.36–3.27 (1H, m), 2.95–2.86 (2H, m), 1.29 (3H, s), 1,40 (3H, s).

^{13}C NMR (50 MHz, CDCl$_3$): δ = 192.3, 146.4, 144.4, 139.3, 136.2, 129.4, 129.0 (2), 126.0 (2), 119.6, 109.2, 76.0, 66.8, 32.0, 27.3, 26.5, 25.6.

HRMS (ESI): Calculated for C$_{18}$H$_{20}$O$_3$Na ([M+Na]$^+$): 307.1305; found 307.1300.

(*R*)-3-((*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl)-2,3-dihydro-[1,1'-biphenyl]-4-carbaldehyde (21b).

Catalyst **10** used.

Yield: 35% (100 mg, 0.35 mmol).

[α]$_D^{25}$ = -27.3 (c = 0.07, CHCl3).

IR (film): 2985, 2933, 1666, 1548, 1170, 756 cm^{-1}.

^{1}H NMR (200 MHz, CDCl$_3$): δ = 9.56 (1H, s), 7.38 (2H, dd, J = 8.0 Hz, 1.6 Hz), 7.37–7.35 (1H, m), 7.20 (1H, d, J = 9.0 Hz), 7.19 (2H, dd, J = 8.0 Hz, 1.6 Hz), 6.59 (1H, dd, J = 9.0 Hz, 2.2 Hz), 4,07–3.97 (1H, m), 3.86–3.74 (2H, m), 3.25 (1H, d, J = 17.9 Hz), 3.05 (1H, dt, J = 8.4, 1.5 Hz), 2.68 (1H, ddd, J = 17.9, 8.4, 2.9 Hz, H-6), 1.36 (3H, s), 1.28 (3H, s).

^{13}C NMR (50 MHz, CDCl$_3$): δ = 197.3, 192.5, 146.2, 139.7, 136.1, 129.3,128.9 (2), 126.4 (2),119.8, 109.0,75.2, 68.1, 32.8, 27.1, 25.9, 21.4.

HRMS (ESI): Calculated for C$_{18}$H$_{21}$O$_3$Na ([M+Na]$^+$):285.1461; found 285.1485.

(*S*)-3-((*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl)-4'-methyl-2,3-dihydro-[1,1'-biphenyl]-4-carbaldehyde(22a).

Catalyst **9** used.

Yield: 99% (295 mg, 0.99 mmol).

[α]$_D^{25}$ = - 51.2 (c = 0.16, CHCl$_3$).

IR (film): 3030, 2985, 2873, 2720, 1675, 1170, 1061, 858, 810 cm^{-1}

^{1}H NMR (200 MHz, CDCl$_3$): δ = 9.58 (1H, s), 7.44 (2H, d, J = 8.0 Hz), 7.21 (2H, d, J = 8.0 Hz), 6.99 (1H, d, J = 5.8 Hz), 6.53 (1H, dd, J = 5.8, 2.5 Hz), 4.28 (1H, q, J = 6.3 Hz), 3.89 (1H, dd, J = 8.2, 6.3 Hz), 3.73 (1H, dd, J = 8.2, 6.3 Hz), 3.31 (1H, ddd, J = 9.2, 6.0, 2.3 Hz), 3.11–2.68 (2H, m), 2.38 (3H, s), 1.40 (2H, s), 1.29 (3H, s).

^{13}C NMR (50 MHz, CDCl3): δ = 192.0, 146.2, 144.4, 139.4, 136.1, 135.7, 129.5 (2), 125.7 (2), 118.5, 108.9, 75.8, 66.6, 31.8, 27.0, 26.3, 25.4, 21.3.

HRMS (ESI): Calculated for C$_{19}$H$_{23}$O$_3$ ([M+H]$^+$): 299.1642; found 299.1645.

(*R*)-3-((*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl)-4'-methyl-2,3-dihydro-[1,1'-biphenyl]-4-carbaldehyde(22b).

Catalyst **10** used.

Yield: 83% (248 mg, 0.83 mmol).

[α]$_D^{25}$ = +23.1 (c = 0.08, CHCl$_3$).

IR (film): 3030, 2984, 2873, 2717, 1668, 1170, 1067, 854, 810 cm^{-1}.

^{1}H NMR (200 MHz, CDCl$_3$): δ = 9.55 (1H, s), 7.48 (2H, d, J = 8.0 Hz), 7.21 (2H, d, J = 8.0 Hz), 7.01 (1H, d, J = 5.9 Hz), 6.55 (1H, dd, J = 5.9, 2.8 Hz), 4.02 (1H, q, J = 7.5 Hz), 3.90–3.68 (2H, m), 3.28 (1H, d, J = 17.9 Hz), 3.10 (1H, dt, J = 8.2, 1.4 Hz), 2.71 (1H, ddd, J = 17.9, 8.2, 2.8 Hz), 2.38 (3H, s), 1.37 (3H, s), 1.27 (3H, s).

^{13}C NMR (50 MHz, CDCl$_3$): δ = 192.2, 147.2, 146.2, 139.3, 136.6, 135.6, 129.4 (2), 126.1 (2), 118.8, 108.8, 75.1, 67.9, 32.7, 28.1, 26.8, 25.7, 21.3.

HRMS (ESI): Calculated for C$_{19}$H$_{23}$O$_3$ ([M+H]$^+$): 299.1642; found 299.1642.

(*S*)-3'-bromo-3-((*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl)-2,3-dihydro-[1,1'-biphenyl]-4-carbaldehyde(23a).

Catalyst **9** used.

Yield: 48% (174mg, 0.48 mmol).

$[\alpha]_D^{25}$ = -35.4 (c = 0.38, CHCl$_3$).

IR (film): 2984, 2876, 2814, 2718, 1670, 1551, 1211, 1173, 1069, 847, 781 cm^{-1}.

^{1}H NMR (200 MHz, CDCl$_3$): δ = 9.55 (1H, s), 7.61 (1H, t, J = 1.9 Hz), 7.48–7.34 (2H, m), 7.20 (1H, d, J = 7.9 Hz), 6.95 (1H, d, J = 5.9 Hz), 6.50 (1H, dd, J = 5.9, 2.4 Hz), 4.23 (1H, q, J = 6.3 Hz), 3.86 (1H, dd, J = 8.4, 6.3 Hz), 3.68 (1H, dd, J = 8.4, 6.3 Hz), 3.25 (1H, ddd, J = 9.1, 6.0, 3.1 Hz), 2.95–2.65 (2H, m), 1.36 (3H, s), 1.24 (3H, s).

^{13}C NMR (50 MHz, CDCl$_3$): δ = 192.2, 144.5, 143.7, 141.5, 136.7, 132.0, 130.5, 129.0, 124.5, 123.2, 120.6, 109.1, 78.1, 77.5, 76.8, 76.0, 66.7, 31.9, 27.3, 26.5, 25.5.

HRMS (ESI): Calculated for C$_{18}$H$_{19}$O$_3$NaBr ([M+Na]$^+$): 385.0410 and 387.0389; found 385.0405 and 387.0384.

(*R*)-3'-bromo-3-((*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl)-2,3-dihydro-[1,1'-biphenyl]-4-carbaldehyde(23b).

Catalyst **10** used.

Yield: 50% (192 mg, 0.50mmol).

$[\alpha]_D^{25}$ = -5.7 (c = 0.07, CHCl$_3$).

IR (film): 2984, 2934, 2878, 2815, 1670, 1549, 1169, 1067, 847, 782, 515 cm^{-1}.

^{1}H NMR (400 MHz, CDCl$_3$): δ = 9.56 (1H,s), 7.67 (1H, t, J = 1.9 Hz), 7.46 (1H, dd, J = 8.2, 1.9 Hz), 7.25 (1H, t, J = 8.2 Hz), 7.00 (1H, d, J = 5.8 Hz), 6.55 (1H, dd, J = 5.8, 2.9 Hz), 3.98 (1H, dt, J = 8.4, 6.4 Hz), 3.89–3.70 (2H, m), 3.19 (1H, dd, J = 17.9, 1.5 Hz), 3.08 (1H, dt, J = 8.4, 1.5 Hz), 2.70 (1H, ddd, J = 17.9, 8.4, 2.9 Hz), 1.36 (3H, s), 1.27 (3H, s).

^{13}C NMR (100 MHz, CDCl$_3$): δ = 192.2, 145.3, 145.1, 141.6, 136.5, 131.7, 130.1, 129.1, 124.7, 122.9, 120.5, 108.9, 74.9, 67.8, 32.5, 28.0, 26.7, 25.6.

HRMS (ESI): Calculated for C$_{18}$H$_{19}$O$_3$NaBr ([M+Na]$^+$): 385.0410 and 387.0389; found 385.0405 and 387.0386.

(*S*)-4'-bromo-3-((*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl)-2,3-dihydro-[1,1'-biphenyl]-4-carbaldehyde(24a).

Catalyst **9** used.

Yield: 45% (163 mg, 0.45 mmol).

$[\alpha]_D^{25}$ = -23.1 (c = 1.10, CHCl$_3$), this optical rotation was obtained from chromatographed fraction.

$[\alpha]_D^{25}$ = -23.2 (c = 0.10, CHCl$_3$), this optical rotation was obtained from a solution of crystals.

IR (film): 2987, 2875, 2718, 1668, 1171, 1072, 853, 813 cm^{-1}.

^{1}H NMR (200 MHz, CDCl$_3$): δ = 9.60 (1H, s), 7.53 (2H, d, J = 8.6 Hz), 7.39 (2H, d, J = 8.6 Hz), 6.99 (1H, d, J = 6.0 Hz), 6.54 (1H, dd, J = 6.0, 2.3 Hz), 4.28 (1H, q, J = 6.3 Hz), 3.89 (1H, dd, J = 8.4, 6.3 Hz), 3.71 (1H, dd, J = 8.4, 6.3 Hz), 3.31 (1H, ddd, J = 9.1, 5.9, 3.2 Hz), 3.02–2.66 (2H, m), 1.39 (3H, s), 1.29 (3H, s).

^{13}C NMR (50 MHz, CDCl$_3$): δ = 192.2, 145.0, 144.0, 138.2, 136.5, 132.2, 127.5, 123.5, 119.9, 109.2, 76.0, 66.7, 32.0, 27.2, 26.5, 25.5.

HRMS (ESI): Calculated for C$_{18}$H$_{20}$O$_3$Br ([M+H]$^+$): 363.0590 and 365.0570; found 363.0596 and 365.0581.

(*R*)-4'-bromo-3-((*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl)-2,3-dihydro-[1,1'-biphenyl]-4-carbaldehyde(24b).

Catalyst **10** used.

Yield: 45% (164 mg, 0.45 mmol).

$[\alpha]_D^{25}$ = -27.3 (c = 0.02, CHCl$_3$).

IR (film): 2984, 2872, 2718, 1668, 1169, 1072, 853, 815 cm^{-1}.

^{1}H NMR (200 MHz, CDCl$_3$): δ = 9.56 (1H, s), 7.52 (2H, d, J = 8.6 Hz), 7.41 (2H, d, J = 8.6 Hz), 7.00 (1H, d, J = 5.8 Hz), 6.55 (1H, dd, J = 5.8, 2.8 Hz), 4.11–3.88 (1H, m), 3.79 (2H, dd, J = 6.3, 2.0 Hz), 3.20 (1H, d, J = 17.9 Hz), 3.08 (1H, t, J = 8.2 Hz), 2.70 (1H, ddd, J = 17.9, 8.2, 2.8 Hz), 1.35 (3H, s), 1.27 (3H, s).

^{13}C NMR (50 MHz, CDCl$_3$): δ = 192.5, 146.0, 145.7, 138.6, 136.5, 132.1 (2), 127.9 (2), 123.4, 120.1, 109.1, 75.2, 68.1, 32.8, 28.1, 27.0, 25.8.

HRMS (ESI): Calculated for C$_{18}$H$_{20}$O$_3$Br ([M+H]$^+$): 363.0590 and 365.0570; found 363.0594 and 365.0582.

(S)-3-((S)-2,2-Dimethyl-1,3-dioxolan-4-yl)-4'-nitro-2,3-dihydro-[1,1'-biphenyl]-4-carbaldehyde(25a).

Catalyst **9** used.

Yield: 90% (296 mg, 0.90 mmol).

$[α]_D^{25}$ = -19.5 (c = 0.02, CHCl$_3$).

IR (film): 2983, 2931, 1668, 1554, 1172, 756 cm^{-1}.

^{1}H NMR (200 MHz, CDCl$_3$): δ = 9.64 (1H, s), 8.25 (2H, d, J = 9.1 Hz), 7.66 (2H, d, J = 9.1 Hz), 7.03 (1H, d, J = 5.9 Hz), 6.67 (1H, d, J = 5.9 Hz), 4.33–4.24 (1H, m), 3.92 (1H, dd, J = 8.5, 6.4 Hz), 3.73 (1H, dd, J = 8.5, 6.4 Hz), 3.37–3.28 (1H, m), 2.94–2.90 (2H, m), 1.38 (3H, s), 1.28 (3H, s).

^{13}C NMR (50 MHz, CDCl$_3$): δ = 192.3, 147.9, 145.7, 143.5, 143.0, 137.7, 126.6 (2), 124.3 (2), 122.8, 109.4, 76.1, 66.7, 32.0, 27.4, 26.4, 25.3.

HRMS (ESI): Calculated for C$_{18}$H$_{19}$NO$_5$Na ([M+Na]$^+$): 352.1155; found 352.1151.

(R)-3-((S)-2,2-Dimethyl-1,3-dioxolan-4-yl)-4'-nitro-2,3-dihydro-[1,1'-biphenyl]-4-carbaldehyde(25b).

Catalyst **10** used.

Yield: 88% (290 mg, 0.88 mmol).

$[α]_D^{25}$ = -27.6 (c = 0.04, CHCl$_3$).

IR (film): 2983, 2931, 1668, 1554, 1172, 756 cm^{-1}.

^{1}H NMR (200 MHz, CDCl$_3$): δ = 9.61 (1H, s), 8.25 (2H, d, J = 8.8 Hz), 7.69 (2H, d, J = 8.8 Hz), 7.04 (1H, d, J = 5.8 Hz), 6.69 (1H, dd, J = 5.8, 2.9 Hz), 4.06–3.92 (1H, m), 3.90–3.72 (2H, m), 3.25 (1H, dd, J = 17.7, 1.5 Hz), 3.12 (1H, td, J = 8.1, 1.5 Hz), 2.77 (1H, ddd, J = 17.7, 8.1, 3.0 Hz), 1.35 (3H, s), 1.27 (3H, s).

^{13}C NMR (50 MHz, CDCl$_3$): δ = 192.5, 147.8, 146.1, 144.7, 144.3, 137.7, 127.1 (2), 124.2 (2), 122.9, 109.2, 75.4, 68.0, 32.8, 28.0, 27.0, 25.7.

HRMS (ESI): Calculated for C$_{18}$H$_{19}$NO$_5$Na ([M+Na]$^+$): 352.1155; found 352.1150.

(1S)-1-((S)-2,2-Dimethyl-1,3-dioxolan-4-yl)-1,5,6,7,8,8a-hexahydronaftalen-2-carbaldehyde(26).

Catalyst **9** used.

Yield: 4% (11 mg, 0.04 mmol).

$[α]_D^{25}$ = -198.5 (c = 0.33, CHCl$_3$).

IR (film): 2930, 2855, 1672, 1582, 1059 cm^{-1}

^{1}H NMR (200 MHz, CDCl$_3$): δ = 9.45 (1H, s), 6.73 (1H, d, J = 5.8 Hz), 5.84 (1H, d, J = 5.8 Hz), 4.34–4.27 (1H, m), 3.83 (1H, dd, J = 8.6, 6.8 Hz), 3.67 (1H, dd, J = 8.6, 6.8 Hz), 2.95–2.85 (1H, m), 2.60–2.40 (1H, m), 2.30–1.27 (8H, m), 1,25 (6H, s).

^{13}C NMR (50 MHz, CDCl$_3$): δ = 193.0, 159.4, 144.9, 133.7, 114.6, 109.0, 66.3, 40.3, 38.5, 38.1, 37.1, 32.0, 29.9, 27.4, 26.4, 25.3.

HRMS (ESI): Calculated for C$_{16}$H$_{22}$O$_3$Na ([M+Na]$^+$): 285.1461; found 285.1466.

Conclusions

A new method for the synthesis of photoprotective chiral cyclohexadienals is described. The Jørgensen-Hayashi catalyst produced a good yield of these compounds by using a chiral α,β-unsaturated aldehyde, **2**. Further reactivity of the corresponding cyclohexadienals is under study.

According to the UV-Vis spectra of **4a**, **20b**, **21b**, **22b**, **22a** and **23b** it can be concluded that the cyclohexadienals containing systems with upper conjugation (**21b**, **22b**, **23a** and **23b**) present better absorbance properties than low conjugation cyclohexadienals **4a**, **20b**. In addition, the influence of the aryl substituent provides an important tool for modulating maximum absorbance. In this work, the influence of *p*-methylphenyl, *m*-bromophenyl and phenyl substituent on the cyclohexadienal backbone is shown, where the phenyl and *m*-bromophenyl substituents prove to be the best choice for UVA-filters and UVB-filters, respectively.

Supporting information

S1 File. NMR and IR data.
(DOCX)

S2 File. Experimental procedure for the synthesis of α,β-aldehyde intermediates.
(DOCX)

S3 File. X-Ray crystallographic data.
(DOCX)

S4 File. UV-Vis spectra.
(DOCX)

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