Base-Catalyzed Condensation of 2-Hydroxybenzaldehydes with α,β-Unsaturated Aldehydes – Scope and Limitations

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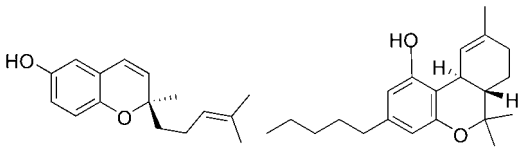
Abstract: The base-catalyzed condensation of α,β-unsaturated carbonyl compounds with 2-hydroxybenzaldehydes yielding tetrahydroxanthones and dihydrobenzopyrans has been investigated. A novel access to highly functionalized dihydrobenzopyrans *via* a mild generation of the dienol of senecialdehyde and subsequent conjugated aldol reaction has been reported.

Keywords: γ-aldol reaction; enols; enones; nucleophilic addition; oxygen heterocycles

Introduction

Benzopyrans are a common motif found in natural products and derived lead structures. Some examples are the cyclooxygenase inhibitior cordiachromene (**1**) and (−)-Δ^9-THC (**2**).[1] The development of new efficient processes for the construction of complex molecules using metal-free reagents has been receiving increasing attention over the last couple of years. Recently, carbon-carbon bond forming reactions using tertiary amines *via* an addition-aldol reaction mode (Baylis–Hillman reaction) were explored.[2]



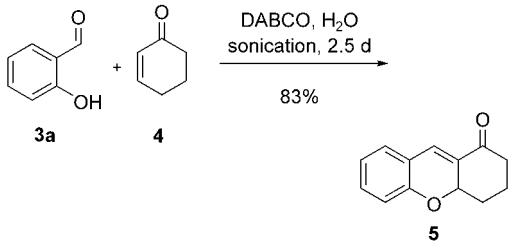
1 **2**

Results and Discussion

The condensation of Michael acceptors with 2-hydroxybenzaldehydes, as exemplified by **3a**, which in turn yields benzo[*b*]pyrans, has proven to be a versatile entry to this class of compounds. It should be noted that, albeit simple and high yielding, this reaction is sensitive due to the ambident nature of the starting materials, as both the 2-hydroxybenzaldehyde and the α,β-unsaturated system have an electrophilic and a nucleophilic site. Therefore different protocols have been described, varying in solvent (*t*-BuOH, $CHCl_3/H_2O$, dioxane, water only) and base (*t*-BuOK, K_2CO_3, DABCO) used.[3] The application of this concept on 2-cyclohexen-1-one (**4**) to yield tetrahydroxanthenones as seen in **5** has been recently and independently reported by us[4] (Scheme 1) and the Kim group.[5] Most closely related to these protocols is the procedure described by Ravichandran.[3e]

The aforementioned reaction conditions[4] were used to test 2-hydroxybenzaldehyde (**3a**) in the condensation reaction with senecialdehyde (**6a**) as a model system. The condensation product **7a** was isolated in 57% yield. Additionally, 22% of tricyclic species **8a** were separated from the reaction mixture (Scheme 2).[6]

By ^1H and ^{13}C NMR studies, the tricyclic hemiacetal structure **8a** was assigned to this compound. It was formed as a single diastereomer. Similar tricyclic hemiacetals have been synthesized from citraldienamine, 2-hydroxybenzaldehyde and 2-hydroxy-1-naphthaldehyde, respectively.[7] The latter reaction requires the synthesis and isolation of the dienamine, while the method presented here is a one-step procedure. In analogy to the



3a **4** **5**

Scheme 1. Synthesis of 2,3,4,4a–tetrahydroxanthen-1-ones.[4]

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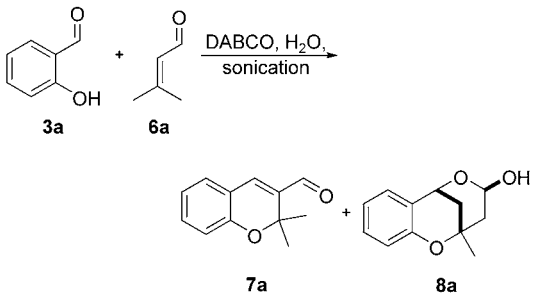
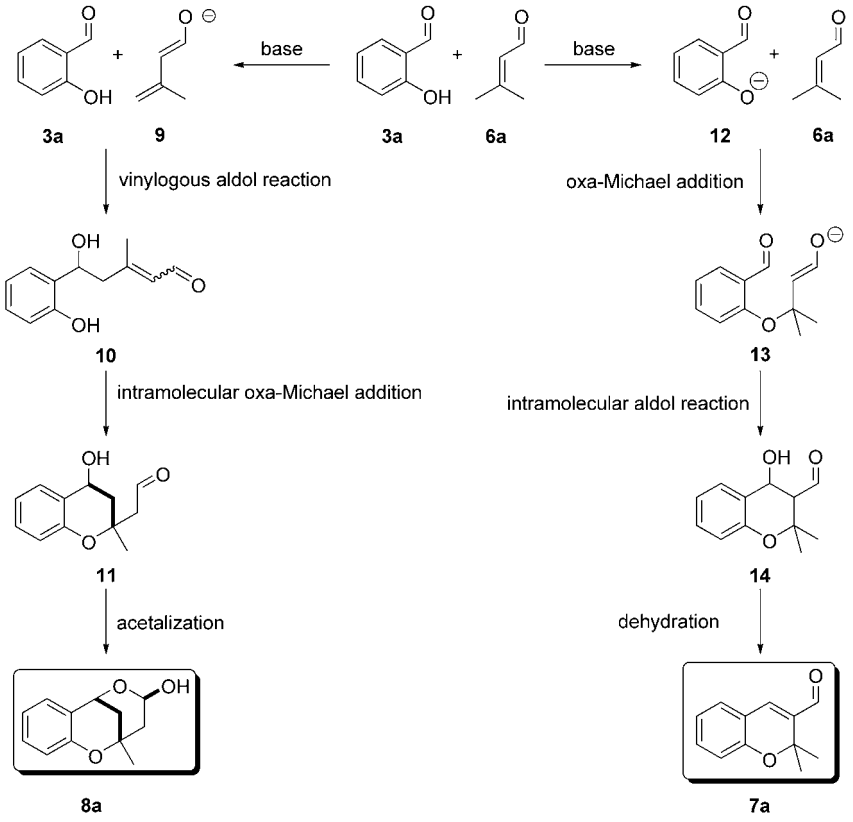


Scheme 2. Initial result: formation of 2,2-dimethyl-2*H*-chromene-3-carbaldehyde (**7a**) and 9-methyl-8,12-dioxatricyclo[7.3.1.0^{2,7}]trideca-2,4,6-trien-11-ol (**8a**).

published mechanism,[7] we propose that the formation of tricyclic compound **8a** involves the vinylogous addition of the dienolate **9** to the 2-hydroxybenzaldehyde **3a**. The phenolic hydroxy group of the α,β-unsaturated aldehyde **10** undergoes a base-promoted intramolecular stereoselective 1,4-addition to form the aldehyde **11**. This aldehyde cyclizes stereoselectively to give the hemiacetal **8a**.

Several mechanisms for the formation of **7a** have been proposed. On the one hand, in the presence of DABCO, a Baylis–Hillman reaction/Michael addition pathway has been postulated,[3f] on the other hand, **7a** may be formed by a Michael addition/aldol condensation sequence. In the case presented the Baylis–Hillman pathway is possible, as DABCO is used as a catalyst, but not probable, because sodium carbonate turned out to be the best reagent for the formation of **7a** (see below). Therefore, we postulate that the phenolate **12** undergoes a 1,4-addition to senecialdehyde. The resulting enolate **13** undergoes an intramolecular aldol addition with subsequent elimination of water from the aldol adduct **14** to yield **7a**.

Vinylogous aldol reactions of dienolates have gained attention due to their application in the synthesis of natural products.[8] The problem of regioselectivity, i.e., α-*versus* γ-substitution, has been a particular field of research.[9] While α-substitution usually occurs under kinetic control at low temperatures, the γ-substituted product as the thermodynamically stable isomer can be isolated when the reaction is performed at elevated temperatures.[8b] Recently, Katsuki and co-workers reported a chromium-salen catalyst for the γ-selective aldol addition of silicon dienol ethers.[10] Dienols were synthesized earlier, for example, by a ring opening of alkenyloxiranes.[11] But all reported procedures required the use of strong bases like lithium amides or organometallic intermediates, most notably the use of toxic reagents such as cadmium chloride.[8f] In contrast, our research suggests that even weak bases are sufficient to foster



Scheme 3. Mechanism rationale for the formation of **7a** and **8a**.

the deprotonation of senecialdehyde, as **8a** is probably formed by a vinylogous aldol reaction.

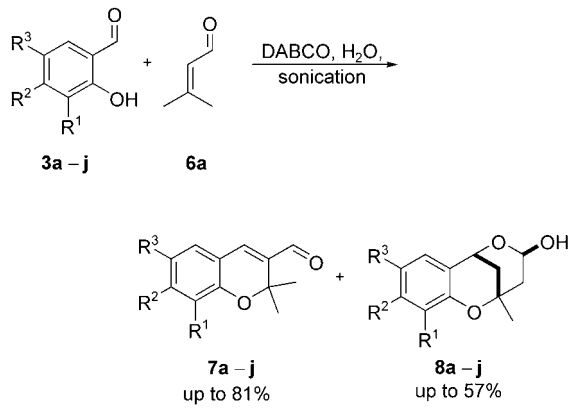
To optimize the product distribution either towards **7a** or **8a**, the type of catalyst was varied with respect to nucleophilicity and basicity. Triphenylphosphine was applied as a very weakly basic, but good nucleophilic catalyst. Potassium hydroxide was chosen as a very basic, but poorly nucleophilic catalyst. Within these margins, we also investigated several amines, ranging from weakly basic pyridines to very basic DBU.[12]

The amount of catalyst (0.5–1.5 equivs.) used has in essence no influence either on the yield or on the product distribution. Since the reaction is efficiently only catalyzed by bases with pK_b values between 3 (NEt_3: pK_b = 3.25, Na_2CO_3: pK_b = 3.70) and 5.5 (DABCO: pK_b = 5.18, DMAP: pK_b = 4.8)[13] the experimental pK_b value of the phenolate of 2-hydroxybenzaldehyde (pK_b = 5.2)[14] and the approximated pK_b value of dienolate **9** (pK_b = 3.7) are within this range.[15] Stronger bases like KOH (pK_b = −1.7) or DBU (pK_b = approx. 2) cause loss of yields, perhaps due to extensive decomposition of the starting materials, while weaker bases like pyridine (pK_b = 8.79) or *N*,*N*-dimethylaniline (pK_b = 8.8) fail to catalyze the reaction efficiently. Triphenylphosphine is not an active catalyst, making a nucleophilic role of the catalyst improbable. The best results for the formation of **7a** were obtained using sodium carbonate, while triethylamine favors the formation of **8a**. The benzopyran **7a** is most likely formed *via* an oxa-Michael addition, because non-nucleophilic bases like sodium carbonate are efficient catalysts for its generation.

As the reaction mixture contains two phases, the nature of the base exerts an important effect on the distribution of the postulated anionic species in the reaction mixture. To gain further insight into the problem of the solubility, we varied the solvent content for the two most successful catalysts, namely sodium carbonate for **7a** and triethylamine for **8a**, from pure water over mixtures of water and dioxane to pure dioxane. In the absence of water, no efficient turnover occurred, either with Na_2CO_3 or with NEt_3. In all other cases, the reactions proceeded to the desired products, with the best yields in a monophasic solution with a ratio of 3/1 dioxane/water (v/v). While the influence of the solvent on the product distribution was small when sodium carbonate was used, a distinctive effect could be observed for triethylamine. In the mixtures containing higher amounts of water, the yield of **7a** as well as the ratio **7a**:**8a** was diminished. Very small yields in pure dioxane are explained by the lack of stabilization of the anions, thus lowering the acidity of the 2-hydroxybenzaldehyde as well as that of the dienol. This is also in accordance with the observation that the color of the aqueous solvents turned to intense yellow after the addition of the catalyst, while the pure dioxane solution was much less colored after addition of triethylamine and remained colorless when sodium carbonate was used.

Although the results cannot explain the selectivities observed, it can be noted that triethylamine favors the formation of **8a** (yield **7a** 15%, **8a** 47%, according to GC), while sodium carbonate predominantly leads to the formation of **7a** (yield **7a** 59%, **8a** 18%, according to GC). Furthermore, it was possible to increase the ratio of **7a**:**8a** from 2.5 in the initial experiments to 3.3 under optimized conditions and to reverse the selectivity by choosing triethylamine as catalyst.

While the experiments described above were conducted using sonication to obtain consistent reaction conditions, this becomes obsolete in a homogeneous liquid phase. Therefore, the improved reaction conditions were used with the substrates **3a – j** with stirring at 55 °C for two days (Scheme 4). The substrate spectrum includes electron-rich (**3b**–**e**), electron-poor (**3g**, **h**) and sterically hindered (**3f**, **i**,[16] **j**) aldehydes. As can be seen from Table 1, the product distribution is strongly dependent on substrate. While it is mostly insensitive to steric demands on the 3-position (**3a**, **f**, **i**, **j**), it is strongly influenced by the electronic properties of the arene. When the electrophilicity of the aldehyde is lowered by donor substituents, the selectivity as well as the overall yield are diminished. As both products were obtained in mediocre yields for 4-methoxysalicylaldehyde (**3c**), only tricyclic product **8e** was isolated in very poor yields when 4-diethylaminosalicylaldehyde (**3e**) was used. The poor results of **3h** using sodium carbonate as base are due to the poor solubility of the sodium salt of the aldehyde: After addition of the base, a yellow precipitate was formed, presumably the sodium salt of anion **12**. After work-up and column chromatography, 90% of the starting material was recovered. Therefore, the catalyst was changed to the second best, DABCO, which was expected to be more soluble. Indeed, after an initial precipitation, the solution became clear within 16 h, leading to 27% of **7h** and 37% of **8h**. The involvement of a nucleophilic attack of the phenolate accounts for the low yields



Scheme 4. Synthesis of 2,2-dimethyl-2*H*-chromene-3-carbaldehydes **7a – j** and 9-methyl-8,12-dioxatricyclo[7.3.1.$0^{2,7}$]trideca-2,4,6-trien-11-ols **8a**–**j**.

Table 1. Yields of 2,2-dimethyl-2*H*-chromene-3-carbaldehydes **7** and 9-methyl-8,12-dioxatricyclo[7.3.1.$0^{2,7}$]trideca-2,4,6-trien-11-ols **8**.

2-Hydroxybenzaldehyde	R^1	R^2	R^3	pK_b[b]	Conditions[d]	Yield of **7** [%][a]	Yield of **8** [%][a]
3a	H	H	H	5.83 [5.2][c]	A	65	19
3a	H	H	H	5.83 [5.2][c]	B	19	46
3b	OMe	H	H	6.21	A	58	23
3b	OMe	H	H	6.21	B	13	36
3c	H	OMe	H	5.34	A	36	15
3c	H	OMe	H	5.34	B	4	44
3d	H	H	OMe	6.21	A	81	10
3d	H	H	OMe	6.21	B	36	46
3e	H	NEt_2	H	5.71	A	0	6.1
3e	H	NEt_2	H	5.71	B	0	3.5
3f	OMe	H	Br	6.38	A	44	27
3f	OMe	H	Br	6.38	B	10	57
3g	Br	H	Cl	7.80	A	58	17
3g	Br	H	Cl	7.80	B	17	51
3h	H	H	NO_2	8.92	A	0	8.9
3h	H	H	NO_2	8.92	B	0	47
3h	H	H	NO_2	8.92	C	27	37
3i	Allyl	H	H	5.50	A	52	23
3i	Allyl	H	H	5.50	B	19	61
3j	Ph	H	H	5.80	A	65	24[e]
3j	Ph	H	H	5.80	B	23	44[e]

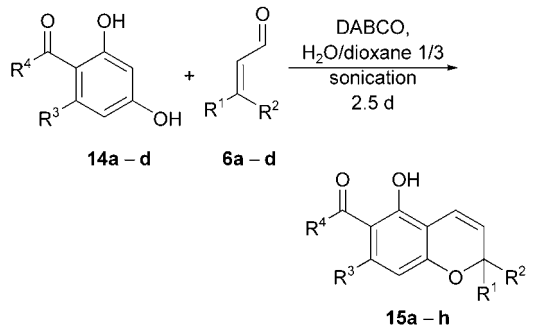
[a] Isolated yields.
[b] pK_b of the phenolate in water. Calculated using Advanced Chemistry Development (ACD) Software Solaris V4.76.
[c] Experimental value.
[d] Conditions: A: 0.5 equivs. Na_2CO_3, stirring, 55 °C, 2.5 d. B: 0.5 equivs. NEt_3, stirring, 55 °C, 2.5 d. C: 0.5 equivs. DABCO, stirring, 55 °C, 2.5 d.
[e] While all other compounds were single diastereomers, **8j** was obtained as a 1/1 mixture, probably differing in the relative stereochemistry of the lactol hydroxy group.

in **7h**, as the nitro group in the *para* position lowers the nucleophilicity of the oxygen.

In spite of these drawbacks, this method remains a convenient, one-step procedure for the synthesis of these heterocycles. It is applicable over a wide range of substrates, from modestly electron-rich to modestly electron-poor 2-hydroxybenzaldehydes, although the reaction conditions must be adjusted in some difficult cases.

When the arene becomes even more electron-rich, as it is the case with 2,4-dihydroxybenzaldehyde (**14**), none of the described reactions is observed and the formation of the dihydrobenzopyran **15** becomes predominant. This reaction has been reported as giving access to the dihydrobenzopyran moiety[17] from senecialdehyde, crotonaldehyde, cinnamaldehyde and citral and was extensively studied by Crombie et al. during their work on a synthesis of cannabinoids.[18] Although the reaction has proven to be very useful, the harsh reaction conditions required (typically refluxing pyridine)[19] and unsatisfactory yields in certain cases are drawbacks for this route to chromenes. We decided to investigate the scope and limitations of the mild catalytic method described which allows reaction temperatures below 60 °C, by applying these conditions to several α,β-unsaturated aldehydes and acceptor-substituted resorcins. In contrast to the reactions of senecialdehyde with 2-hydroxybenzaldehydes as above, all cases formed dihydrobenzopyrans with a high degree of chemoselection due to an aldol-type condensation of the phenolate and a subsequent ring closure.[18a] While unsubstituted resorcin failed to give any of the desired product, resorcin-carbaldehydes and other acceptor-substituted resorcin derivatives condensed with senecialdehyde and several α,β-unsaturated aldehydes. We reasoned that the higher acidity of the phenol hence increases the nucleophilicity at the carbon of the phenolate. Crotonaldehyde and cinnamaldehyde react with the resorcin-aldehyde **14a** to give dihydrobenzopyrans **15c** and **15d**, respectively, in low yields.

As our results in Scheme 5 indicate, all desired products **15a**–**h** could be obtained, albeit in moderate to low yields. In order to optimize the reaction, resorcin aldehyde (**14a**) was chosen as the model compound and screening of bases was performed (DABCO, DMAP, NEt_3, *i*-Pr_2EtN, KOH, NaOH, K_2CO_3, Na_2CO_3, Cs_2CO_3). DABCO was found to be superior to all bases tested. Potassium hydroxide was the second and cesium carbonate was the third best yielding 24% and 20% of product, respectively. During the reactions, a considerable amount of insoluble substance was formed. In order to



Scheme 5. Reaction of resorcin derivatives **14** with α,β-unsaturated aldehydes **6**.

Table 2. Reaction of resorcin derivatives **14** with α,β-unsaturated aldehydes **6a**–**d**.

Entry	**6**	R^1	R^2	**14**	R^3	R^4	Product	Yield [%]
1	**6a**	Me	Me	**14a**	H	H	**15a**	53
2	**6b**	Me	H	**14a**	H	H	**15b**	35
3	**6c**	*n*-Pr	H	**14a**	H	H	**15c**	34
4	**6d**	Ph	H	**14a**	H	H	**15d**	10
5	**6a**	Me	Me	**14b**	H	Me	**15e**	18
6	**6a**	Me	Me	**14c**	H	OMe	**15f**	24
7	**6a**	Me	Me	**14d**	Me	H	**15g**	40
8	**6b**	Me	H	**14d**	Me	H	**15h**	21

Conditions: DABCO, H_2O, sonication, 4 d.

circumvent the polymerization of senecialdehyde, the reaction was performed without sonication at 45 °C with intense stirring. This procedure provided the product in 44% yield but did not prevent the formation of the insoluble side product. A last attempt was made by adding senecialdehyde at a very slow rate and in large excess. In this experiment, six equivalents of senecialdehyde were added to the reaction mixture under intense stirring over a period of 18 hours. The yield, however, was determined to be 45%. Finally, various solvents and mixtures of solvents were investigated, but none provided the desired increase in yield. Even though our method does not provide chromenes in high yields, it should be considered as an alternative to the established methods and applied when temperature sensitive compounds are involved.

Conclusion

In conclusion, we have demonstrated that the reaction of substituted 2-hydroxybenzaldehydes with α,β-unsaturated aldehydes gives rise to dihydrobenzopyrans depending on the catalyst used. In future studies, we will explore asymmetric variants of these reactions and their use in the synthesis of complex natural products.

Experimental Section

GC (gas chromatography) analytical: Hewlett-Packard HP 5890 Series II 12 m × 0.25 mm capillary column HP I (carrier gas N_2). TLC (thin layer chromatography): silica gel coated aluminium plates (Merck, silica gel 60, F_{254}). Detection under UV light at 254 nm, displayed with molybdatophosphate (5% phosphomolybdic acid in ethanol, dipping solution) and potassium permanganate (0.45 g potassium permanganate and 2.35 g of sodium carbonate in 90 mL of water, dipping solution). Solvent mixtures are understood as volume/volume. Abbreviations: cyc = cyclohexane, EtOAc = ethyl acetate, Pen = pentane, and PE = light petroleum ether. Descriptions without a nominated temperature were done by room temperature (rt). Solid materials were powdered. Solvents, reagents and chemicals were purchased from Aldrich, Fluka, Janssen, and Merck. Ethyl acetate, light petroleum ether and dichloromethane were distilled prior to use. All other solvents, reagents and chemicals were used as purchased.

General Procedure for the Optimization by GC Analysis

The solvent was treated with ultrasound for 15 min. while a stream of argon was passed through it. In 1 mL, the given amount of catalyst, 0.20 mL (0.18 g, 2.1 mmol) of senecialdehyde (**6a**) and 0.22 mL (0.23 g, 2.1 mmol) of 2-hydroxybenzaldehyde (**3a**) were suspended. The mixture was subjected to ultrasound for 36 hours, diluted with a saturated solution of sodium carbonate and extracted three times with ethyl acetate. A weighed amount of *n*-decane was added and the combined organic phases were dried over anhydrous magnesium sulfate. The mixture was analyzed by GC.

General Procedure for Base-Catalyzed Condensation of Senecialdehyde with 2-Hydroxybenzaldehydes on a Preparative Scale

The solvent was subjected to ultrasound for 15 min. while a stream of argon was passed through it. In an amount of solvent needed for a two molar solution of the reactants, 0.5 equivs. of catalyst, 1.0 equiv. of senecialdehyde and 1.0 equiv. 2-hydroxybenzaldehyde were suspended. The mixture was stirred at 55 °C for 2.5 days, diluted with a saturated solution of sodium carbonate, and extracted three times with ethyl acetate. The combined organic phases were dried over anhydrous magnesium sulfate and purified as described below.

***2,2-Dimethyl-2H-chromene-3-carbaldehyde* (7a) *and 9-Methyl-8,12-dioxatricyclo[7.3.1.0^{2,7}]trideca-2,4,6-trien-11-ol* (8a):** Synthesized from 1.00 mL (875 mg, 10.4 mmol) of senecialdehyde (**6a**), 1.11 mL (1.27 g, 10.4 mmol) of 2-hydroxybenzaldehyde (**3a**) and 551 mg (5.22 mmol) of sodium carbonate in 5 mL dioxane/water, 3/1. The crude product was purified by column chromatography (eluent EtOAc/PE for **7a**, then 1/1 for **8a**) to yield 1.27 g (65%) of **7a** as a yellow oil and 397 mg (19%) of **8a** as colorless crystals. Compound **7a**: R_f (EtOAc/PE, 1/5) = 0.68; compound **8a**: mp 153–155 °C, R_f (EtOAc/PE, 1/1) = 0.38.

***8-Methoxy-2,2-dimethyl-2H-chromene-3-carbaldehyde* (7b) and *6-Methoxy-9-methyl-8,12-dioxatricyclo[7.3.1.0^{2,7}]-trideca-2,4,6-trien-11-ol* (8b):** Synthesized from 1.58 g

(10.4 mmol) of 2-hydroxy-3-methoxybenzaldehyde (**3b**), 1.00 mL (0.875 g, 10.4 mmol) of senecialdehyde (**6a**) and 551 mg (5.20 mmol) of sodium carbonate in 5 mL of dioxane/water, 3/1. The crude product was purified by column chromatography (eluent EtOAc/PE for **7b**, then 1/1 for **8b**) to yield 1.31 g (58%) of **7b** as a yellow solid and 566 mg (23%) of **8b** as colorless crystals. Compound **7b**: mp 53–56 °C, R_f (EtOAc/PE, 1/5) = 0.36; compound **8b**: mp 173–175 °C, R_f (EtOAc/PE, 1/1) = 0.26.

***7-Methoxy-2,2-dimethyl-2H-chromene-3-carbaldehyde* (7c) and *5-Methoxy-9-methyl-8,12-dioxatricyclo[7.3.1.0^{2,7}]-trideca-2,4,6-trien-11-ol* (8c):** Synthesized from 576 mg (3.79 mmol) of 2-hydroxy-4-methoxybenzaldehyde (**3c**), 319 mg (3.79 mmol) of senecialdehyde (**6a**) and 201 mg (1.90 mmol) of sodium carbonate in 2 mL of dioxane/water 3/1. The crude product was purified by column chromatography (eluent EtOAc/PE for **7c**, then 1/1 for **8d**) to yield 445 mg (36%) of **7c** as a yellow oil and 134 mg (15%) of **8c** as colorless crystals. Compound **7c**: R_f (cyc/EtOAc, 5/1) = 0.32; compound **8c**: mp 128–130 °C, R_f (cyc/EtOAc, 5/1) = 0.05.

***6-Methoxy-2,2-dimethyl-2H-chromene-3-carbaldehyde* (7d) *and 4-Methoxy-9-methyl-8,12-dioxatricyclo[7.3.1.0^{2,7}]-trideca-2,4,6-trien-11-ol* (8d):** Synthesized from 1.30 mL (1.58 g, 10.4 mmol) of 2-hydroxy-5-methoxybenzaldehyde (**3d**), 1.00 mL (0.875 g, 10.4 mmol) of senecialdehyde (**6a**) and 584 mg (5.20 mmol) of sodium carbonate in 6 mL of dioxane/water 1/2. The crude product was purified by column chromatography. First, EtOAc/PE (1/5) was used as eluent to yield 1.67 g (74%) **7d** as a yellow solid, then eluent was changed to EtOAc/PE (1/1) to obtain 343 mg (14%) **8d** as a colorless solid. Compound **7d**: mp 50–54 °C, R_f (EtOAc/PE, 1/5) = 0.31; compound **8d**: mp 118–119 °C, R_f (EtOAc/PE, 1/1) = 0.33.

***5-N,N-Dimethylamino-9-methyl-8,12-dioxatricyclo[7.3.1.0^{2,7}]trideca-2,4,6-trien-11-ol* (8e):** Synthesized from 1.01 g (5.22 mmol) of 2-hydroxy-4-*N*,*N*-dimethylamino benzaldehyde (**3e**), 0.500 mL (439 mg, 5.22 mmol) of senecialdehyde and 277 mg of sodium carbonate. The crude product was purified by column chromatography (eluent Et_2O/Pen, 2/1) to afford **8e** as a colorless solid; yield: 87.7 g (6.4%), mp 149–149 °C, R_f (Et_2O/Pen, 2/1) = 0.27.

***6-Bromo-8-methoxy-2,2-dimethyl-2H-chromene-3-carbaldehyde* (7f) *and 4-Bromo-6-methoxy-9-methyl-8,12-dioxatricyclo[7.3.1.0^{2,7}]trideca-2,4,6-trien-11-ol* (8f):** Synthesized from 1.21 g (5.22 mmol) of 5-bromo-2-hydroxy-3-methoxybenzaldehyde (**3f**), 0.500 mL (439 mg, 5.22 mmol) of senecialdehyde (**6a**) and 277 mg (5.20 mmol) of sodium carbonate in 4 mL of dioxane/water, 3/1. The crude product was purified by column chromatography (eluent Et_2O/Pen, 1/5, for **7f**, then Et_2O for **8f**) to yield 689 mg (44%) of **7f** as a yellow solid and 447 mg (27%) of **8f** as colorless crystals. Compound **7f**: mp 101–104 °C, R_f (Et_2O/Pen, 1/5) = 0.36; compound **8f**: mp 155–158 °C; R_f (Et_2O) = 0.60.

***6-Bromo-8-chloro-2,2-dimethyl-2H-chromene-3-carbaldehyde* (7 g) *and 4-Bromo-6-chloro-9-methyl-8,12-dioxatricyclo[7.3.1.0^{2,7}]trideca-2,4,6-trien-11-ol* (8g):** Synthesized from 1.23 g (5.22 mmol) of 5-bromo-3-chloro-2-hydroxybenzaldehyde (**3g**), 0.500 mL (439 mg, 5.22 mmol) of senecialdehyde (**6a**) and 277 mg (2.61 mmol) of sodium carbonate in 4 mL of dioxane/water, 3/1. The crude product was purified by column chromatography (eluent Et_2O/Pen, 1/5, for **7 g**, then Et_2O for **8g**) to yield 934 mg (58%) of **7g** as a yellow oil and 123 mg (7.4%) of **8g** as colorless crystals. Compound **7g**: R_f (Et_2O/Pen, 1/5) = 0.51 ; compound **8g**: mp 148–151 °C, R_f (Et_2O) = 0.70.

***6-Nitro-2,2-dimethyl-2H-chromene-3-carbaldehyde* (7h) *and 4-Nitro-9-methyl-8,12-dioxatricyclo[7.3.1.0^{2,7}]trideca-2,4,6-trien-11-ol* (8h):** Synthesized from 871 mg (5.22 mmol) of 5-nitro-2-hydroxybenzaldehyde (**3h**), 0.500 mL (439 mg, 5.22 mmol) of senecialdehyde (**6a**) and 292 mg (2.61 mmol) of DABCO in 4 mL of dioxane/water, 3/1. The crude product was purified by column chromatography (eluent Et_2O/Pen, 1/1) to yield 331 mg (27%) of **7h** as a pale yellow solid and 490 mg (37%) of **8h** as colorless crystals. Compound **7h**: mp 111–115 °C, R_f (Et_2O/Pen, 1/1) = 0.64; compound **8h**: mp = 127–131 °C, R_f (Et_2O/Pen, 1/1) = 0.13.

***8-Allyl-2,2-dimethyl-2H-chromene-3-carbaldehyde* (7i) *and 6-Allyl-9-methyl-8,12-dioxatricyclo[7.3.1.0^{2,7}]trideca-2,4,6-trien-11-ol* (8i):** Synthesized from 846 mg (5.22 mmol) of 3-allyl-2-hydroxy-benzaldehyde (**3i**), 0.500 mL (439 mg, 5.22 mmol) of senecialdehyde (**6a**) and 277 mg (2.61 mmol) of sodium carbonate in 4 mL of dioxane/water, 3/1. The crude product was purified by column chromatography (eluent Et_2O/Pen, 1/10, for **7i**, then Et_2O for **8i**) to yield 616 mg (52%) of **7i** as a yellow oil and 296 mg (23%) of **8i** as colorless crystals. Compound **7i**: R_f (Et_2O/Pen, 1/10) = 0.36; compound **8i**: mp 102–104 °C, R_f (Et_2O) = 0.71.

***8-Phenyl-2,2-dimethyl-2H-chromene-3-carbaldehyde* (7j) *and 9-Methyl-6-phenyl-8,12-dioxatricyclo[7.3.1.0^{2,7}]trideca-2,4,6-trien-11-ol* (8j):** Synthesized from 1.03 g (5.22 mmol) of 2-hydroxy-3-phenylbenzaldehyde (**3j**), 0.500 mL (439 mg, 5.22 mmol) of senecialdehyde (**6a**) and 277 mg (2.61 mmol) of sodium carbonate in 4 mL of dioxane/water, 3/1. The crude product was purified by column chromatography (eluent Et_2O/Pen, 1/5, for **7j**, then Et_2O for **8j**) to yield 900 mg (65%) of **7j** as a yellow oil and 251 mg (24%) of **8j** as colorless crystals. Compound **7j**: mp 71–75 °C; R_f (Et_2O/Pen, 1/5) = 0.46; compound **8j** (both isomers): mp 160–162 °C, R_f (Et_2O) = 0.70.

5-Hydroxy-2,2-dimethyl-2*H*-chromene-6-carbaldehyde (15a)

Under an argon atmosphere, 5.00 g (36.2 mmol) of 2,4-dihydroxybenzaldehyde (**14a**) and 2.03 g (18.1 mmol) of DABCO were dissolved in 20 ml of water/dioxane, 1/3. Senecialdehyde (**6a**; 3.05 g, 36.2 mmol), was added and the mixture was placed in a sonication bath for 2.5 days. The product was extracted with 3 × 75 mL of Et_2O. The combined organic phases were dried over $MgSO_4$. The solvent was removed by evaporation under reduced pressure. The crude product was purified by column chromatography (EtOAc/PE, 1/5) providing **15a** as a yellow solid; yield: 3.95 g (53%). Recrystallization from heptane yielded light yellow needles, mp 70–71 °C, R_f (heptane/EtOAc, 5/1) = 0.31.

5-Hydroxy-2-methyl-2*H*-chromene-6-carbaldehyde (15b)

Under an argon atmosphere, 500 mg (3.62 mmol) of 2,4-dihydroxybenzaldehyde (**14a**) and 203 mg (1.81 mmol) of DABCO were dissolved in 2 mL of dioxane/water, 1/3. Crotonaldehyde (**6b**; 252 mg, 3.62 mmol), was added and the mixture was

placed in a sonication bath for 60 h. The crude product was extracted with 3 × 15 mL of Et_2O and the combined organic phases were dried over $MgSO_4$. Purification by column chromatography (EtOAc/PE, 1/5) gave **15b** as a yellow oil; yield: 242 mg (35%). R_f (cyc/EtOAc, 5/1) = 0.43.

5-Hydroxy-2-propyl-2*H*-chromene-6-carbaldehyde (15c)

Under an argon atmosphere, 500 mg (3.62 mmol) of 2,4-dihydroxybenzaldehyde (**14a**) and 203 mg (1.81 mmol) of DABCO were dissolved 2 mL of water/dioxane, 1/3. 355 mg (3.62 mmol) of *trans*-hex-2-enal (**6c**) were added and the mixture was placed in a sonication bath for 2.5 days. The crude product was extracted with 3 × 15 mL of Et_2O and the combined organic phases were dried over $MgSO_4$. Purification by column chromatography (EtOAc/PE, 1/5) afforded **15c** as an yellow oil; yield: 0.270 g (34%). R_f (heptane/EtOAc, 5/1) = 0.47.

5-Hydroxy-2-phenyl-2*H*-chromene-6-carbaldehyde (15d)

Under an argon atmosphere, 500 mg (3.62 mmol) of 2,4-dihydroxybenzaldehyde (**14a**) and 203 mg (1.81 mmol) of DABCO were dissolved in 2 mL of water/dioxane, 1/3. *trans*-Cinnamaldehyde (**6d**; 476 mg, 3.62 mmol), was added and the mixture was placed in a sonication bath for 2.5 days. The crude product was extracted with 3 × 15 mL of Et_2O and the combined organic phases were dried over $MgSO_4$. Purification by column chromatography (EtOAc/PE, 1/9) gave **15d** as a light yellow solid; yield: 91 mg (10%); mp 65–67 °C, R_f (heptane/EtOAc, 5/1) = 0.28.

1-(5-Hydroxy-2,2-dimethyl-2*H*-chromen-6-yl)-ethanone (15e)

Under an argon atmosphere, 500 mg (3.29 mmol) of 2,4-dihydroxyacetophenone (**14b**) and 185 mg (1.65 mmol) of DABCO were dissolved in 2 mL of water/dioxane, 1/3. Senecialdehyde (**6a**; 276 mg, 3.29 mmol) was added and the mixture was placed in a sonication bath for 2.5 days. The crude product was extracted with 3 × 15 mL of Et_2O and the combined organic phases were dried over $MgSO_4$. Purification by column chromatography (EtOAc/PE, 1/5) gave **15e** as a yellow solid; yield: 131 mg (18%), mp 93–96 °C, R_f (cyc/EtOAc, 5/1) = 0.48.

Methyl 5-Hydroxy-2,2-dimethyl-2*H*-chromene-6-carboxylate (15f)

Under an argon atmosphere, 500 mg (2.97 mmol) of methyl 2,4-dihydroxybenzoate (**14c**) and 167 mg (1.49 mmol) of DABCO were dissolved in 2 mL of water/dioxane, 1/3, followed by addition of 250 mg (2.97 mmol) of senecialdehyde (**6a**). The mixture was placed in a sonication bath for 2.5 days. The crude product was extracted with 3 × 15 mL of Et_2O and the combined organic phases were dried over $MgSO_4$. Purification by column chromatography (EtOAc/PE, 1/5) afforded **15f** as a yellow oil; yield: 170 mg (24%), R_f (cyc/EtOAc, 5/1) = 0.53.

5-Hydroxy-2,2,7-trimethyl-2*H*-chromene-6-carbaldehyde (15g)

Under an argon atmosphere, 750 mg (4.93 mmol) of 2,4-dihydroxy-6-methyl-benzaldehyde (**14d**) and 276 mg (2.46 mmol) of DABCO were dissolved in 3 mL of water/dioxane, 1/3. After adding 415 mg (4.93 mmol) of senecialdehyde (**6a**) the mixture was placed in a sonication bath for 2.5 days. The crude product was extracted with 3 × 15 mL of Et_2O and the combined organic phases were dried over $MgSO_4$. Purification by column chromatography (EtOAc/PE, 1/5) gave **15g** as yellow needle-shaped crystals; yield: 434 mg (40%), mp 56–58 °C, R_f (cyc/EtOAc, 5/1) = 0.55.

5-Hydroxy-2,7-dimethyl-2*H*-chromene-6-carbaldehyde (15h)

Under an argon atmosphere, 750 mg (4.93 mmol) of 2,4-dihydroxy-6-methylbenzaldehyde (**14d**) and 276 mg (2.46 mmol) of DABCO were dissolved in 3 ml of water/dioxane, 1/3. Crotonaldehyde (**6b**; 346 mg, 4.93 mmol) was added and the mixture was placed in a sonication bath for 2.5 days. The crude product was extracted with 3 × 15 mL of Et_2O and the combined organic phases were dried over $MgSO_4$. Purification by column chromatography (EtOAc/PE, 1/5) provided **15h** as a yellow oil; yield: 215 mg (21%), R_f (cyc/EtOAc, 5/1) = 0.48.

Supporting Information

Characterization data for the compounds made and the results of the optimization studies are contained in the Supporting Information.

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