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PAPER

Efficient proline and prolinol ether mediated 3-component synthesis of 3- and 3,4-substituted chromenone derivatives†

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A highly efficient route for the synthesis of valuable 3,4-substituted chromenone derivatives by the reaction of 1,3-diketones with aldehydes in the presence of L-proline was developed. The reactions take advantage of readily available starting materials and follow a Knoevenagel condensation/Michael addition/hemiacetalization domino process. Chiral 3-substituted chromenones are obtained with high enantioselectivities when a chiral diarylprolinol TMS-ether is applied in the reaction.

Introduction

The development of multicomponent reactions has attracted considerable attention due to the significant advantages this methodology offers to combinatorial and medicinal chemistry in the formation of complex structures in a few reaction steps.¹ Nowadays, the high atom-economy, the improvement of the reaction efficiency,² the reduction of waste and the high enantioselectivity represent important challenges in organic chemistry. In this respect, multicomponent metal-free domino reactions have the potential to address and fulfil all these aspects.^{3–5}

1,3-Dicarbonyl compounds have been widely employed in the synthesis of natural products and biologically active compounds through multicomponent reactions.⁶ Commonly, these transformations employ, beside simple 1,3-dicarbonyl compounds, aliphatic aldehydes as electrophiles and further nucleophilic partners and give rise to structurally different heterocyclic compounds by domino reactions.⁶

Chromenes or benzopyrans are an important group of heterocyclic compounds with various biological and pharmacological activities such as spasmolytic, diuretic, antiviral, antitumoral and antianaphylactic, among others.⁷ Furthermore, the chromene skeleton is present in numerous natural products which can be used as pigments, photoactive compounds and biodegradable agrochemicals (Fig. 1).⁷ Hence, their synthesis holds a special place and considerable efforts are devoted to the development of efficient methods for their synthesis.

Previously, we described an organocatalytic enantioselective addition–cyclization cascade reaction of 2-hydroxynaphthoquinone with α,β -unsaturated aldehydes. The diarylprolinol silyl ether catalyzed reaction provided 1,4-pyranonaphthoquinones in good yields and excellent enantioselectivities.⁸ Following this methodology, a very efficient and highly enantioselective organocatalytic synthesis of pyranocoumarins, quinolinones and pyranones was also reported starting from commercially available cyclic 1,3-dicarbonyl compounds and α,β -unsaturated aldehydes.⁹ In addition, we have studied the reaction of 1,3-cyclohexanedione and 5,5-dimethyl-1,3-cyclohexanedione with alkyl and aryl substituted α,β -unsaturated aldehydes. This reaction provides 4-substituted chromenes with excellent enantioselectivities starting from commercially available compounds using diarylprolinol TMS ether derivatives as catalysts (Scheme 1a).^{10–12} The usefulness of this class of compounds was subsequently evidenced in the synthesis of more complex fused polycyclic heterocycles.¹³

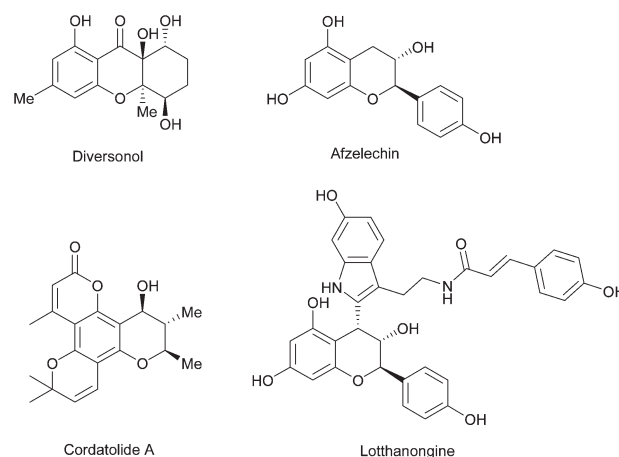
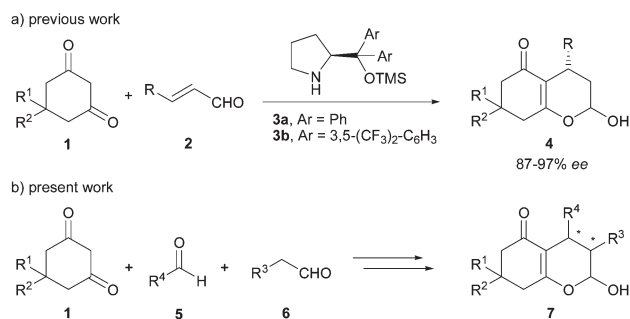


Fig. 1 Natural products with a chromene core.

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Scheme 1 Reaction of cyclic 1,3-diketones with aldehydes.

Table 1 Screening of solvents in the reaction of 1,3-cyclohexanedione (1a) and butanal (6a)

Entry ^a	Solvent	Yield (%)
1	CH ₂ Cl ₂	46
2	CHCl ₃	55
3	DMF	72
4	DMSO	64
5	Toluene	58
6	MeCN	86
7	THF	72
8	H ₂ O	28
9	Et ₂ O	65
10	MeOH	80

^a Reaction conditions: **1a** (1 equiv.), **6a** (4 equiv.) and L-proline (1 equiv.), 0.5 M.

Based on our previous results, we now envisioned that it might be possible to synthesize these compounds in one step by a multicomponent reaction employing 1,3-diketones and simple saturated aliphatic aldehydes as electrophiles and nucleophiles (Scheme 1b, R⁴ = R³CH₂). Furthermore, careful selection of the electrophilic partner (non-enolizable aldehyde) should allow the application of two different aldehydes in this process (Scheme 1b, R⁴ ≠ R³CH₂). Notably, this protocol would circumvent the additional purification procedures required in the case of sensitive α,β-unsaturated aldehyde substrates.^{8–10}

Results and discussion

In order to verify our proposal we first evaluated the effect of several solvents in the reaction of 1,3-cyclohexanedione (**1a**) with butanal (**6a**) promoted by L-proline (Table 1). The use of chlorinated solvents such as CH₂Cl₂ and CHCl₃ (Table 1, entries 1 and 2) afforded the desired product **7a** in moderate yields (46–55%). The yield slightly increased when DMSO, DMF or THF were employed in the reaction (Table 1, entries 3, 4 and 7). The best results were obtained when the reaction was carried out in MeCN or MeOH affording the desired product **7a** in 86 and 80% yield, respectively (Table 1, entries 6 and 10).

Table 2 Scope of the domino process

Entry ^a	1	6	R ¹ , R ²	R ³	8	d.r. ^b	Yield ^c (%)
1	1a	6a	H	C ₂ H ₅	8a ^d	4.6 : 1	47
2	1a	6b	H	C ₆ H ₁₃	8b ^d	4 : 1	65
3	1a	6c	H	CH ₂ Ph	8c	— ^e	69
4	1b	6a	CH ₃	C ₂ H ₅	8d	4 : 1	82
5	1b	6b	CH ₃	C ₆ H ₁₃	8e	4 : 1	90
6	1b	6d	CH ₃	CH ₃	8f	3 : 1	69
7	1b	6e	CH ₃	C ₃ H ₇	8g	4 : 1	80
8	1b	6f	CH ₃	C ₉ H ₁₉	8h	2 : 1	99
9	1b	6g	CH ₃	Ph	8i	— ^e	87
10	1c	6a	H, furyl	C ₂ H ₅	8j	— ^e	48

^a Reaction conditions: **1** (0.5 mmol), **6** (2 mmol) and L-proline (0.5 mmol) in acetonitrile (1 mL) at room temperature (40 h). The oxidation was carried out after column chromatography of the lactol intermediate **7**. ^b Diastereomeric ratio determined by ¹H NMR spectroscopy of the crude mixture. ^c Overall yield of both diastereoisomers after column chromatography. ^d Oxidation with TPAP/NMO. ^e Diastereoisomeric ratio could not be determined by ¹H NMR.

Having established that acetonitrile is the best solvent for the reaction of 1,3-cyclohexanedione (**1a**) with butanal (**6a**), we decided to explore the scope of this transformation by employing differently substituted cyclohexanediones and various aliphatic aldehydes (Table 2). In order to determine the diastereoselectivity, the hemiacetals **7** were converted into the corresponding lactones **8** by oxidation with TPAP/NMO or PCC.

The reaction of 1,3-cyclohexanedione (**1a**) with butanal and octanal and subsequent oxidation with TPAP/NMO afforded the corresponding chromenones **8a** and **8b** in 47 and 65% yield, with a diastereoisomeric ratio of 4.6 : 1 and 4 : 1 respectively (Table 2, entries 1 and 2). When 3-phenyl-propionaldehyde (**6c**) was used, the product **8c** was isolated in 69% overall yield. The reaction of 5,5-dimethyl-1,3-cyclohexanedione (**1b**) with aliphatic and aromatic aldehydes provided the chromenones **8d–i** in good to excellent yields (69–99%) and diastereoisomeric ratios in the range of 2 : 1 to 4 : 1 (Table 2, entries 4–9). In the case of 5-furyl-1,3-cyclohexanedione (**1c**) reaction with butanal (**6a**) afforded chromenone **8j** in 48% yield (Table 2, entry 10).

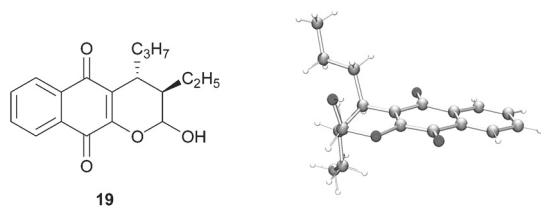
Next, we decided to explore the scope of the reaction with respect to other 1,3-diketones. The reaction of 1,3-cyclopentanedione (**9**) with butanal afforded, after oxidation, the product **14** in 53% overall yield (Table 3, entry 1). In the case of 2-hydroxynaphthoquinone (**10**), reaction with butanal and subsequent oxidation afforded the product **15** in 64% yield and 8 : 1 diastereomeric ratio (Table 3, entry 2). A similar result was obtained with the 4-hydroxy-6-methyl-2-pyrone **11**. In this case we isolated the product **16** in 65% yield and 7 : 1 diastereomeric ratio (Table 3, entry 3). Furthermore, 4-hydroxycoumarin (**12**) and its lactam analog **13** reacted with butanal (**6a**) giving the products **17** and **18** in 57 and 99% yield, respectively (Table 3, entries 4 and 5).

The *trans* relative configuration of the 3,4-disubstituted chromenones was determined by single crystal X-ray analysis of the

Table 3 Reaction of different 1,3-diketones with butanal (**6a**)

Entry ^a	1,3-Diketone	Product	d.r. ^b	Yield ^c (%)	
1 ^{d,e}			—	53	
2			8 : 1	64	
3			7 : 1	65	
4			3 : 1	57	
5			2 : 1	99	

^a Reaction conditions: 1,3-diketone (0.5 mmol), **6a** (2 mmol) and L-proline (0.5 mmol) in acetonitrile (1 mL) at room temperature (40 h). The oxidation was carried out after column chromatography of the lactol intermediate. ^b Diastereomeric ratio determined by ¹H NMR spectroscopy of the crude mixture. ^c Overall yield of both diastereoisomers after column chromatography. ^d Diastereomeric ratio could not be determined by ¹H NMR. ^e Oxidation with PCC.

**Fig. 2** X-ray crystal structure of 3-ethyl-2-hydroxy-4-propyl-3,4-dihydro-2H-benzo[*g*]chromene-5,10-dione **19**.

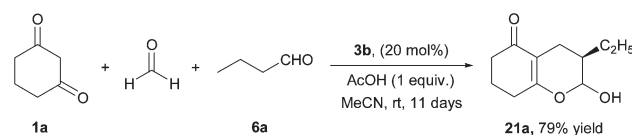
lactol **19** obtained in the reaction of 2-hydroxynaphthoquinone (**10**) and butanal (**6a**) (Fig. 2).

A challenging task consists in the use of two different aldehydes. In this case, in order to succeed, the reaction was performed by reacting benzaldehyde with 5,5-dimethyl-1,3-cyclohexanedione (**1b**), with subsequent addition of a second aldehyde **6** after 2 h. The corresponding 3,4-disubstituted chromenes **20a–f** were obtained in good yields (Table 4).

Table 4 Scope of the domino process using two different aldehydes

Entry ^a	6	R	20	d.r. ^b	Yield ^c (%)
1	6a	C ₂ H ₅	20a	1.3 : 1	71
2	6b	C ₆ H ₁₃	20b	1.4 : 1	84
3	6c	CH ₂ Ph	20c	— ^d	78
4	6d	CH ₃	20d	1 : 1	50
5	6e	C ₃ H ₇	20e	1.4 : 1	81
6	6f	C ₉ H ₁₉	20f	2 : 1	83

^a Reaction conditions: **1b** (0.5 mmol), benzaldehyde (2 mmol), **6** (2 mmol) and L-proline (0.5 mmol) in acetonitrile (1 mL) at room temperature (40 h). The oxidation was carried out after column chromatography of the lactol intermediate. ^b Diastereomeric ratio determined by ¹H NMR spectroscopy of the crude mixture. ^c Overall yield of both diastereoisomers after column chromatography. ^d Diastereomeric ratio could not be determined by ¹H NMR.

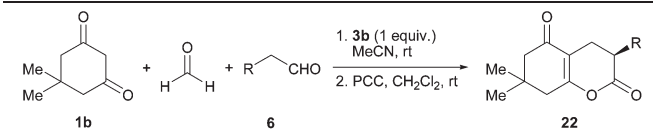
**Scheme 2** Organocatalyzed reaction between 1,2-cyclohexanedione (**1a**) with formaldehyde and butanal (**6a**).

Finally, we were interested in the enantioselective synthesis of this type of compounds. For this purpose, the reaction between 1,3-cyclohexanedione (**1a**), formaldehyde and butanal (**6a**) was carried out in the presence of diarylprolinol TMS-ether derivative **3b** as catalyst^{12,14} (20 mol%) and acetic acid (1 equiv.). After an extended reaction time of 11 days the corresponding lactol **21a** was isolated in 79% yield (Scheme 2).

With the goal to decrease the reaction time, one equivalent of the prolinol derivative **3b** was applied in the reaction. In order to circumvent the racemization of lactol **21**, oxidation to the corresponding lactones **22** was performed.

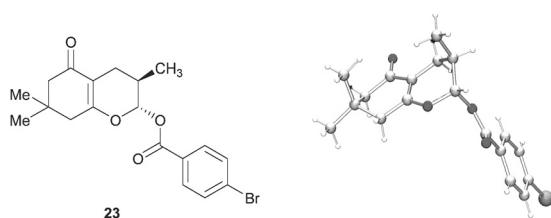
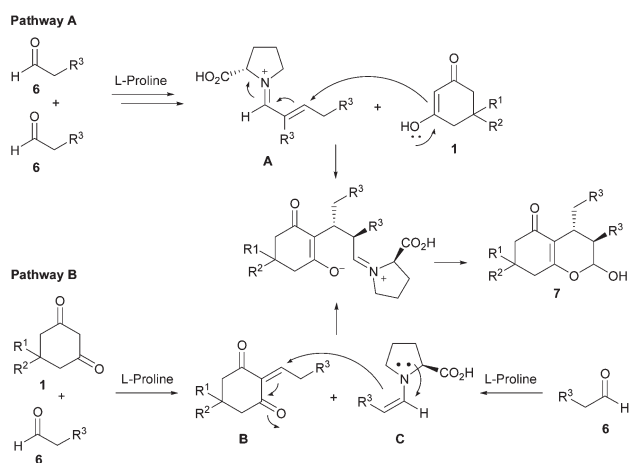
The reaction of 5,5-dimethyl-1,3-cyclohexanedione (**1b**) with formaldehyde and aliphatic aldehydes **6** gave rise, after oxidation with PCC, to chromenones **22** in moderate yields (49–52%) and good enantioselectivities (Table 5). The absolute configuration of the chromenones **22** was determined by single crystal X-ray analysis of derivative **23**. Based on this structure, the configuration of compounds **22** was assigned as (3*R*) (Fig. 3).

Regarding the mechanism of this transformation, two different pathways are possible. On one hand proline can mediated the autocondensation of the aldehyde with the formation of an iminium ion intermediate **A**. Attack of the 1,3-dicarbonyl nucleophile **1** on the iminium ion electrophile **A** and subsequent cyclization affords the desired product **7** (Scheme 3, pathway A). On the other hand, the 1,3-dicarbonyl compound can react with a molecule of aldehyde in a Knoevenagel condensation affording product **B**, which can undergo Michael addition with the enamine intermediate **C** formed by the condensation of the

Table 5 Enantioselective synthesis of 3-substituted chromenones


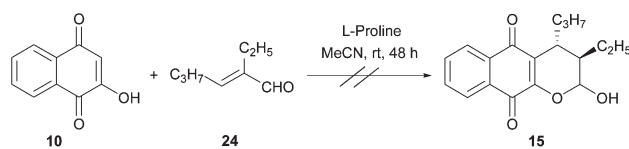
Entry ^a	6	R	22	Yield ^b (%)	Ee ^c (%)
1	6a	C ₂ H ₅	22a	49	89
2	6b	C ₆ H ₁₃	22b	50	87
3	6d	CH ₃	22d	51	83
4	6e	C ₃ H ₇	22e	52	88

^a Reaction conditions: **1b** (1 equiv.), formaldehyde (4 equiv.), **6** (4 equiv.) and **3b** (1 equiv.) in acetonitrile (0.5 M) at room temperature (40 h). The oxidation was carried out after column chromatography of the lactol intermediate. ^b Overall yield of both diastereoisomers after column chromatography. ^c Enantiomeric excesses were determined by HPLC.

**Fig. 3** X-ray crystal structure of (3*R*)-3,7,7-trimethyl-5-oxo-3,4,5,6,7,8-hexahydro-2*H*-chromen-2-yl-4-bromobenzoate **23**.**Scheme 3** Proposed mechanistic pathways for the reaction of 1,3-dicarbonyl compounds with aldehydes.

second molecule of aldehyde with L-proline. Finally, cyclization provides lactol **7** (Scheme 3, pathway B).

In order to determine the mechanism, the reaction was carried out employing 2-ethyl-2-hexenal **24** as aldehyde. Condensation of aldehyde **24** with L-proline gives rise to the intermediate **A**, present in pathway A (Scheme 3). After 48 h, no reaction was observed for the 2-hydroxynaphthoquinone **10** (Scheme 4). In view of these results we propose pathway B as plausible reaction mechanism for this transformation.

**Scheme 4** Reaction of 2-hydroxynaphthoquinone (**10**) with 2-ethylhexenal (**24**).

Conclusions

In summary, we have described a highly efficient one-pot synthesis of 3,4-disubstituted chromenones in very good yields, under mild conditions starting from 1,3-dicarbonyl compounds and aldehydes in the presence of L-proline. Notably, the reaction can be performed either with the same aldehyde as electrophile and nucleophile or as a three component reaction with two different aldehydes. The reaction mechanism involves first a Knoevenagel condensation between the 1,3-dicarbonyl compound and one molecule of aldehyde with subsequent Michael addition and hemiacetalization. Chiral 3-substituted derivatives are obtained with high enantioselectivities when (*S*)-2-[bis-(3,5-bistrifluoromethylphenyl)trimethylsilyloxyethyl]pyrrolidine is applied in the reaction.

Experimental section

General

All commercially available compounds were distilled or recrystallized prior to use. Solvents for chromatography were technical grade and distilled prior to use. MeCN used in reactions was analytical grade. Analytical thin-layer chromatography (TLC) was performed on Merck silica gel aluminium plates with F-254 indicator, visualized by irradiation with UV light. Column chromatography was performed using silica gel Merck 60 (particle size 0.040–0.063 mm). Solvent mixtures are understood as volume/volume. ¹H NMR and ¹³C NMR were recorded on a Bruker AM 250 spectrometer in CDCl₃. Data are reported in the following order: chemical shift (δ) in ppm; multiplicities are indicated s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet); coupling constants (*J*) are in Hertz (Hz). Mass spectra (MS-EI, 70 eV) were conducted on GC-MS Shimadzu QP2010 (column: Equity®-5, length × I.D. 30 m × 0.25 mm, *d_f* 0.25 μm, lot#28089-U, Supelco). IR spectra were recorded on a Jasco FT/IR-420 spectrometer and are reported in terms of frequency of absorption (cm⁻¹). The enantiomeric excesses were determined by HPLC analysis using a chiral stationary phase column. The chiral HPLC methods were calibrated with the corresponding racemic mixtures. Optical rotations were measured on a Perkin Elmer 241 polarimeter.

General procedure A

To a solution of L-proline (1 equiv.) and the corresponding 1,3-dicarbonyl compound in MeCN (0.5 M) was added the corresponding aldehyde (4 equiv.) at room temperature. The resulting solution was stirred for 40 h. The crude reaction mixture was directly charged on silica gel and purified by column

chromatography using hexane–ethyl acetate = 3 : 1 to afford the corresponding product as a mixture of two diastereomers.

General procedure B

To a solution of L-proline (1 equiv.) and the corresponding 1,3-dicarbonyl compound in MeCN (0.5 M) was added benzaldehyde (4 equiv.) at room temperature. The resulting solution was stirred for 2 h. After this time, the corresponding aliphatic aldehyde (4 equiv.) was added and the reaction was stirred for 40 h. The crude reaction mixture was directly charged on silica gel and purified by column chromatography using hexane–ethyl acetate = 3 : 1 to afford the corresponding product as a mixture of two diastereomers.

General procedure C

To a solution of 2(*S*)-[(bis(3,5-bis(trifluoromethyl)phenyl)trimethylsilyloxy)methyl]pyrrolidine **3b** (1 equiv.) and 5,5-dimethyl-1,3-cyclohexanedione (1 equiv.) in MeCN (0.5 M) was added formaldehyde (4 equiv.) and the corresponding aliphatic aldehyde (4 equiv.) at room temperature. The resulting solution was stirred for 40 h. The crude reaction mixture was directly charged on silica gel and purified by column chromatography using hexane–ethyl acetate = 3 : 1 to afford the corresponding product.

General procedure D (oxidation with tetrapropylammonium perruthenate, TPAP, and *N*-methylmorpholine *N*-oxide, NMO)

Solid TPAP (20 mol%) is added to a stirred mixture of the lactol obtained according to the general procedure A (1 equiv.), NMO (1.5 equiv.) and 4 Å molecular sieves (500 mg mmol⁻¹) in CH₂Cl₂ or MeCN (0.2 M) at room temperature. The reaction was followed by TLC until completed (in some cases additional amounts of TPAP and NMO were necessary). The crude reaction mixture was directly charged on silica gel and purified by column chromatography using hexane–ethyl acetate = 3 : 1 to afford the corresponding product as a mixture of two diastereomers.

General procedure E (oxidation with pyridinium chlorochromate, PCC)

To a solution of the corresponding lactol obtained according to the general procedure A, B or C was added PCC (10 equiv.). The resulting solution was stirred at room temperature (in some cases an additional amount of PCC was necessary). The reaction was followed by TLC until completed. Celite was added and filtered. The solvent was removed *in vacuo* and the residue was directly charged on silica gel and purified by column chromatography using hexane–ethyl acetate = 3 : 1 to afford the corresponding product as a mixture of two diastereomers in the case of lactols obtained according to methods A and B.

3-Ethyl-4-propyl-3,4,7,8-tetrahydro-6*H*-chromene-2,5-dione (8a)

The title compound was obtained according to the general procedure A. The isolated product was subsequently oxidized

according to the general procedure D; overall yield: 47%; d.r. (*cis/trans*) = 1 : 4.6; pale yellow oil. Major diastereoisomer: ¹H NMR (250 MHz, CDCl₃): δ = 2.86–2.82 (m, 1H), 2.59–2.49 (m, 3H), 2.45–2.32 (m, 2H), 2.07–1.93 (m, 2H), 1.61–1.40 (m, 2H), 1.34–1.06 (m, 4H), 1.01–0.91 (m, 3H), 0.87–0.82 (m, 3H); ¹³C NMR (62.5 MHz, CDCl₃): δ = 197.2, 169.1, 165.7, 116.9, 45.9, 36.7, 36.2, 33.4, 27.0, 24.1, 20.7, 19.5, 13.9, 11.7; IR (neat): ν̄ = 2960, 2874, 1774, 1652, 1457, 1381, 1171, 1129, 1065, 1002, 923, 841, 734 cm⁻¹; MS (EI) *m/z* (%) = 236 (54) [M]⁺, 218 (9), 207 (24), 193 (54), 179 (26), 166 (88), 151 (16), 137 (100), 125 (21), 109 (17), 95 (12), 70 (16), 55 (35).

4-Heptyl-3-hexyl-3,4,7,8-tetrahydro-6*H*-chromene-2,5-dione (8b)

The title compound was obtained according to the general procedure A. The isolated product was subsequently oxidized according with the general procedure D; overall yield: 65%; d.r. (*cis/trans*) = 1 : 4; pale yellow oil. Major diastereoisomer: ¹H NMR (250 MHz, CDCl₃): δ = 2.82–2.78 (m, 1H), 2.68–2.63 (m, 1H), 2.56–2.48 (m, 2H), 2.46–2.36 (m, 2H), 2.08–2.01 (m, 2H), 1.49–1.13 (m, 22H), 0.86–0.81 (m, 6H); ¹³C NMR (62.5 MHz, CDCl₃): δ = 197.2, 169.3, 165.7, 117.0, 44.1, 36.7, 34.0, 33.7, 31.7, 31.4, 30.7, 29.4, 29.0, 28.7, 27.0, 26.9, 26.3, 22.5, 22.4, 20.7, 14.0, 13.9; IR (neat): ν̄ = 2927, 2856, 1782, 1653, 1457, 1382, 1129, 737 cm⁻¹; MS (EI) *m/z* (%) = 348 (55) [M]⁺, 330 (15), 320 (20), 263 (45), 249 (58), 235 (26), 222 (100), 207 (22), 193 (19), 179 (13), 165 (27), 152 (20), 125 (48), 55 (33).

3-Benzyl-4-phenethyl-3,4,7,8-tetrahydro-6*H*-chromene-2,5-dione (8c)

The title compound was obtained according to the general procedure A. The isolated product was subsequently oxidized according with the general procedure E; overall yield: 69%; pale yellow oil. Mixture of diastereoisomers: ¹H NMR (250 MHz, CDCl₃): δ = 7.24–6.96 (m, 10H), 2.96 (ddd, *J* = 8.3, 5.8 and 1.1 Hz, 1H), 2.89–2.76 (m, 2H), 2.71–2.64 (m, 1H), 2.57–2.16 (m, 6H), 1.96–1.80 (m, 2H), 1.67–1.43 (m, 2H); ¹³C NMR (62.5 MHz, CDCl₃): δ = 196.8, 168.6, 165.9, 141.0, 136.7, 128.9 (2C), 128.7, 128.7 (2C), 128.3 (2C), 128.1 (2C), 127.1, 125.9, 116.5, 45.9, 37.4, 36.6, 35.6, 32.4, 32.3, 26.9, 20.4; IR (neat): ν̄ = 3061, 3029, 2948, 1782, 1653, 1456, 1381, 1266, 1112, 737, 701 cm⁻¹; MS (EI) *m/z* (%) = 360 (87) [M]⁺, 342 (6), 269 (93), 241 (10), 227 (12), 207 (14), 165 (91), 137 (98), 104 (21), 91 (100).

3-Ethyl-7,7-dimethyl-4-propyl-3,4,7,8-tetrahydro-6*H*-chromene-2,5-dione (8d)

The title compound was obtained according to the general procedure A. The isolated product was subsequently oxidized according with the general procedure E; overall yield: 82%; d.r. (*cis/trans*) = 1 : 5; gummy white solid. Major diastereoisomer: ¹H NMR (250 MHz, CDCl₃): δ = 2.83 (t, *J* = 5.4 Hz, 1H), 2.59–2.53 (m, 1H), 2.37 (s, 2H), 2.28–2.26 (m, 2H), 1.56–1.39 (m, 2H), 1.37–1.16 (m, 4H), 1.07 (s, 6H), 0.94 (t, *J* = 7.5 Hz, 3H), 0.87–0.81 (m, 3H); ¹³C NMR (62.5 MHz, CDCl₃): δ = 197.0, 169.2, 164.0, 115.7, 50.6, 45.9, 40.7, 36.2, 33.3, 32.5,

28.2, 28.1, 24.1, 19.6, 13.9, 11.7; IR (neat): $\tilde{\nu}$ = 3057, 2963, 2874, 1772, 1652, 1458, 1377, 1266, 1171, 1124, 1066, 738 cm^{-1} ; MS (EI) m/z (%) = 264 (51) $[\text{M}]^+$, 246 (9), 235 (30), 221 (50), 207 (29), 194 (100), 179 (15), 165 (73), 151 (17), 137 (8), 123 (9), 109 (12), 95 (10), 83 (17), 69 (11), 55 (25).

4-Heptyl-3-hexyl-7,7-dimethyl-3-propyl-3,4,7,8-tetrahydro-6H-chromene-2,5-dione (8e)

The title compound was obtained according to the general procedure A. The isolated product was subsequently oxidized according with the general procedure E; overall yield: 90%; d.r. (*cis/trans*) = 1 : 4; pale yellow oil. Major diastereoisomer: ^1H NMR (250 MHz, CDCl_3): δ = 2.82–2.77 (m, 1H), 2.69–2.63 (m, 1H), 2.37 (s, 2H), 2.28–2.27 (m, 2H), 1.26–1.19 (m, 22H), 1.08 (s, 6H), 0.85–0.80 (m, 6H); ^{13}C NMR (62.5 MHz, CDCl_3): δ = 197.0, 169.4, 164.1, 115.8, 50.7, 44.1, 40.7, 34.0, 33.7, 32.5, 31.7, 31.4, 30.7, 29.4, 29.0, 28.7, 28.2, 28.1, 26.9, 26.3, 22.5, 14.0; IR (neat): $\tilde{\nu}$ = 2929, 2857, 1782, 1653, 1383, 1128, 910, 735 cm^{-1} ; MS (EI) m/z (%) = 376 (74) $[\text{M}]^+$, 358 (14), 348 (30), 333 (14), 319 (11), 306 (17), 291 (70), 277 (90), 263 (38), 250 (100), 235 (75), 221 (27), 207 (32), 193 (41), 180 (28), 153 (49), 137 (18), 123 (17), 97 (77), 83 (58), 69 (40), 55 (82).

4-Ethyl-3,7,7-trimethyl-3,4,7,8-tetrahydro-6H-chromene-2,5-dione (8f)

The title compound was obtained according to the general procedure A. The isolated product was subsequently oxidized according with the general procedure E; overall yield: 69%; d.r. (*cis/trans*) = 1 : 3; pale yellow oil. Major diastereoisomer: ^1H NMR (250 MHz, CDCl_3): δ = 2.87–2.77 (m, 1H), 2.71–2.63 (m, 1H), 2.40 (s, 2H), 2.30 (s, 2H), 1.42–1.24 (m, 2H), 1.17 (d, J = 7.3 Hz, 3H), 1.10 (s, 6H), 0.84 (t, J = 7.5 Hz, 3H); ^{13}C NMR (62.5 MHz, CDCl_3): δ = 197.2, 170.1, 164.1, 115.1, 50.7, 40.8, 38.2, 37.0, 32.5, 28.3, 28.1, 27.0, 16.8, 10.7; IR (neat): $\tilde{\nu}$ = 2963, 2935, 2876, 1783, 1656, 1457, 1379, 1181, 1125, 1055, 991, 915, 734 cm^{-1} ; MS (EI) m/z (%) = 236 (44) $[\text{M}]^+$, 218 (7), 207 (39), 193 (13), 180 (100), 165 (68), 147 (20), 137 (30), 124 (20), 109 (20), 95 (27), 83 (26), 55 (49).

4-Butyl-7,7-dimethyl-3-propyl-3,4,7,8-tetrahydro-6H-chromene-2,5-dione (8g)

The title compound was obtained according to the general procedure A. The isolated product was subsequently oxidized according with the general procedure E; overall yield: 80%; d.r. (*cis/trans*) = 1 : 4; yellow oil. Major diastereoisomer: ^1H NMR (250 MHz, CDCl_3): δ = 2.84–2.79 (m, 1H), 2.74–2.68 (m, 1H), 2.40 (s, 2H), 2.31 (d, J = 1.4 Hz, 2H), 1.51–1.19 (m, 10H), 1.10 (s, 6H), 0.90 (t, J = 6.8 Hz, 3H), 0.85 (t, J = 7.0 Hz, 3H); ^{13}C NMR (62.5 MHz, CDCl_3): δ = 197.0, 169.3, 164.1, 115.8, 50.6, 43.8, 40.7, 33.7, 33.6, 32.8, 32.5, 28.4, 28.3, 28.1, 22.5, 20.2, 13.8, 13.5; IR (neat): $\tilde{\nu}$ = 2958, 2872, 1783, 1654, 1383, 1127 cm^{-1} ; MS (EI) m/z (%) = 292 (37) $[\text{M}]^+$, 274 (10), 264 (11), 249 (29), 235 (60), 221 (25), 208 (100), 193 (18), 179 (28), 165 (53), 153 (44), 137 (14), 123 (19), 109 (13), 97 (27), 83 (45), 69 (24), 55 (85).

4-Decyl-7,7-dimethyl-3-nonyl-3,4,7,8-tetrahydro-6H-chromene-2,5-dione (8h)

The title compound was obtained according to the general procedure A. The isolated product was subsequently oxidized according with the general procedure E; overall yield: 99%; d.r. (*cis/trans*) = 1 : 2; pale yellow oil. Major diastereoisomer: ^1H NMR (250 MHz, CDCl_3): δ = 2.79–2.75 (m, 1H), 2.66–2.60 (m, 1H), 2.35 (s, 2H), 2.26–2.24 (m, 2H), 1.22–1.14 (m, 34H), 1.05 (s, 6H), 0.84–0.79 (m, 6H); ^{13}C NMR (62.5 MHz, CDCl_3): δ = 197.0, 169.4, 164.1, 115.9, 50.7, 44.1, 40.8, 34.1, 33.7, 32.6, 31.8, 31.8, 30.8, 29.5, 29.5, 29.4, 29.3, 29.2, 29.2, 29.2, 29.1, 28.3, 28.1, 26.9, 26.3, 22.6, 14.0; IR (neat): $\tilde{\nu}$ = 2926, 2855, 1783, 1653, 1457, 1383, 910, 735 cm^{-1} ; MS (EI) m/z (%) = 460 (86) $[\text{M}]^+$, 432 (35), 348 (26), 333 (79), 319 (76), 305 (35), 292 (89), 277 (97), 221 (30), 207 (53), 193 (35), 180 (27), 153 (61), 137 (23), 97 (100), 83 (72), 69 (47), 55 (71).

3-Benzyl-7,7-dimethyl-4-phenethyl-3,4,7,8-tetrahydro-6H-chromene-2,5-dione (8i)

The title compound was obtained according to the general procedure A. The isolated product was subsequently oxidized according with the general procedure E; overall yield: 87%; pale yellow oil. Mixture of diastereoisomers: ^1H NMR (250 MHz, CDCl_3): δ = 7.34–7.06 (m, 10H), 3.17–3.05 (m, 1H), 3.00–2.89 (m, 2H), 2.85–2.70 (m, 1H), 2.68–2.48 (m, 1H), 2.47–2.41 (m, 1H), 2.37 (s, 2H), 2.33–2.27 (m, 2H), 1.83–1.53 (m, 2H), 1.16 (s, 3H), 1.13 (s, 3H); ^{13}C NMR (62.5 MHz, CDCl_3): δ = 196.6, 168.6, 164.3, 140.9, 136.6, 128.8, 128.7, 128.6, 128.3, 128.3, 128.1, 127.0, 125.8, 115.3, 50.5, 46.0, 40.6, 37.1, 35.6, 32.5, 32.2, 32.1, 28.6, 27.8; IR (neat): $\tilde{\nu}$ = 2959, 2871, 1782, 1654, 1455, 1381, 1266, 1104, 740, 701 cm^{-1} ; MS (EI) m/z (%) = 388 (35) $[\text{M}]^+$, 297 (48), 269 (7), 255 (7), 222 (4), 207 (3), 193 (69), 165 (51), 131 (8), 117 (4), 104 (15), 91 (100), 83 (9), 65 (6), 55 (6).

3-Ethyl-7-(furan-2-yl)-4-propyl-3,4,7,8-tetrahydro-6H-chromene-2,5-dione (8j)

The title compound was obtained according to the general procedure A. The isolated product was subsequently oxidized according with the general procedure D; overall yield: 48%; d.r. (*cis/trans*) = 1 : 5; yellow oil. Major diastereoisomer: ^1H NMR (250 MHz, CDCl_3): δ = 7.35–7.33 (m, 1H), 6.32–6.28 (m, 1H), 6.08–6.06 (m, 1H), 3.61–3.45 (m, 1H), 2.93–2.54 (m, 6H), 1.64–1.13 (m, 6H), 1.04–0.81 (m, 6H); ^{13}C NMR (62.5 MHz, CDCl_3): δ = 195.5, 168.9, 164.2, 155.0, 141.8, 117.0, 110.2, 105.2, 45.9, 40.9, 36.4, 33.2, 32.3, 31.8, 23.9, 19.6, 13.9, 11.6; IR (neat): $\tilde{\nu}$ = 2964, 2935, 2875, 1783, 1653, 1386, 1131, 1065, 738 cm^{-1} ; MS (EI) m/z (%) = 302 (100) $[\text{M}]^+$, 284 (17), 273 (31), 259 (37), 245 (22), 232 (71), 217 (19), 203 (52), 189 (24), 147 (17), 138 (33), 123 (18), 110 (19), 94 (28), 81 (22), 55 (20).

3-Ethyl-4-propyl-3,4,6,7-tetrahydrocyclopenta[b]pyran-2,5-dione (14)

The title compound was obtained according to the general procedure A. The isolated product was subsequently oxidized

according with the general procedure E; overall yield: 53%; pale yellow oil. Mixture of diastereoisomers: ^1H NMR (250 MHz, CDCl_3): δ = 2.71–2.52 (m, 6H), 1.62–1.47 (m, 2H), 1.44–1.14 (m, 4H), 0.97 (t, J = 7.4 Hz, 3H), 0.87 (t, J = 7.2 Hz, 3H); ^{13}C NMR (62.5 MHz, CDCl_3): δ = 202.5, 178.9, 169.1, 120.2, 46.2, 36.4, 34.1, 33.3, 25.1, 24.8, 19.5, 13.9, 11.6; IR (neat): $\tilde{\nu}$ = 2960, 2928, 2874, 1792, 1702, 1653, 1558, 1541, 1457, 1393, 1266, 1134, 1056, 734 cm^{-1} ; MS (EI) m/z (%) = 222 (32) $[\text{M}]^+$, 204 (8), 193 (58), 179 (34), 165 (11), 152 (100), 137 (17), 125 (22), 111 (33), 95 (11), 70 (19), 55 (31).

3-Ethyl-4-propyl-3,7-dihydrobenzo[*g*]chromene-2,5,10-trione (15)

The title compound was obtained according to the general procedure A. The isolated product was subsequently oxidized according with the general procedure D; overall yield: 64%; d.r. (*cis/trans*) = 1 : 8; yellow solid. Major diastereoisomer: ^1H NMR (250 MHz, CDCl_3): δ = 8.13–8.06 (m, 2H), 7.79–7.71 (m, 2H), 3.21 (t, J = 6.2 Hz, 1H), 2.75 (t, J = 7.5 Hz, 1H), 1.73–1.23 (m, 6H), 0.99 (t, J = 7.4 Hz, 3H), 0.89 (t, J = 7.0 Hz, 3H); ^{13}C NMR (62.5 MHz, CDCl_3): δ = 183.3, 176.9, 166.9, 150.2, 134.3, 133.9, 131.4, 130.8, 126.6, 126.4, 126.3, 45.2, 35.8, 34.7, 24.0, 19.7, 13.8, 11.6; IR (neat): $\tilde{\nu}$ = 2965, 2935, 2875, 1792, 1716, 1655, 1598, 1397, 1195, 1130, 1064, 991, 737 cm^{-1} ; MS (EI) m/z (%) = 298 (100) $[\text{M}]^+$, 270 (62), 256 (29), 241 (34), 227 (96), 213 (100), 199 (87), 185 (17), 173 (26), 159 (21), 144 (16), 128 (27), 115 (27), 104 (23), 76 (23), 55 (26).

3-Ethyl-4-propyl-3,4-dihydropyrano[3,2-*c*]chromene-2,5-dione (16)

The title compound was obtained according to the general procedure A. The isolated product was subsequently oxidized according with the general procedure D; overall yield: 57%; d.r. (*cis/trans*) = 1 : 3; gummy white solid. Major diastereoisomer: ^1H NMR (250 MHz, CDCl_3): δ = 7.85–7.81 (m, 1H), 7.62–7.55 (m, 1H), 7.37–7.30 (m, 2H), 3.09 (m, 1H), 2.80 (m, 1H), 1.77–1.26 (m, 6H), 1.02 (t, J = 7.4 Hz, 3H), 0.96–0.84 (m, 3H); ^{13}C NMR (62.5 MHz, CDCl_3): δ = 167.4, 161.5, 155.9, 153.0, 132.5, 124.4, 122.5, 116.7, 113.5, 106.2, 45.8, 36.1, 35.8, 24.4, 19.5, 13.8, 11.7; IR (neat): $\tilde{\nu}$ = 2964, 2935, 2875, 1793, 1717, 1647, 1457, 1388, 1145, 1043, 906, 760, 738 cm^{-1} ; MS (EI) m/z (%) = 286 (38) $[\text{M}]^+$, 257 (18), 243 (100), 216 (54), 187 (15), 175 (10), 128 (11), 121 (22), 92 (7).

3-Ethyl-6-methyl-4-propyl-3,4-dihydro-6*H*-pyrano[3,2-*c*]quinoline-2,5-dione (17)

The title compound was obtained according to the general procedure A. The isolated product was subsequently oxidized according with the general procedure D; overall yield: 99%; d.r. (*cis/trans*) = 1 : 2; colourless oil. Major diastereoisomer: ^1H NMR (250 MHz, CDCl_3): δ = 7.98 (dd, J = 8.0 and 1.3 Hz, 1H), 7.64–7.57 (m, 1H), 7.39 (d, J = 8.3 Hz, 1H), 7.31–7.25 (m, 1H), 3.74 (s, 3H), 3.28–3.23 (m, 1H), 2.82–2.76 (m, 1H), 1.70–1.26 (m, 6H), 1.00 (t, J = 7.5 Hz, 3H), 0.90 (t, J = 7.1 Hz,

3H); ^{13}C NMR (62.5 MHz, CDCl_3): δ = 168.6, 161.7, 152.2, 138.9, 131.1, 122.6, 122.1, 114.0, 113.5, 111.2, 45.8, 35.9, 35.6, 29.5, 24.1, 19.4, 13.8, 11.6; IR (neat): $\tilde{\nu}$ = 2964, 2935, 2874, 1783, 1653, 1600, 1465, 1391, 1150, 1066, 737 cm^{-1} ; MS (EI) m/z (%) = 299 (21) $[\text{M}]^+$, 270 (4), 256 (48), 242 (4), 228 (100), 213 (5), 200 (36), 188 (5), 134 (3), 77 (3).

3-Ethyl-7-methyl-4-propyl-3,4-dihydropyrano[4,3-*b*]pyran-2,5-dione (18)

The title compound was obtained according to the general procedure A. The isolated product was subsequently oxidized according with the general procedure D; overall yield: 65%; d.r. (*cis/trans*) = 1 : 7; colourless oil. Major diastereoisomer: ^1H NMR (250 MHz, CDCl_3): δ = 5.88 (s, 1H), 2.89 (t, J = 6.6 Hz, 1H), 2.68 (t, J = 7.5 Hz, 1H), 2.24 (s, 3H), 1.63–1.22 (m, 6H), 0.96 (t, J = 7.4 Hz, 3H), 0.87 (t, J = 7.0 Hz, 3H); ^{13}C NMR (62.5 MHz, CDCl_3): δ = 167.8, 163.4, 162.6, 160.5, 103.1, 98.6, 45.9, 36.0, 35.1, 24.3, 19.9, 19.4, 13.8, 11.6; IR (neat): $\tilde{\nu}$ = 2965, 2935, 2875, 1792, 1716, 1655, 1598, 1397, 1195, 1130, 1064, 991, 737 cm^{-1} ; MS (EI) m/z (%) = 250 (23) $[\text{M}]^+$, 221 (11), 207 (100), 180 (24), 165 (22), 151 (19), 139 (9), 123 (4), 85 (8), 69 (5), 55 (7).

3-Ethyl-7,7-dimethyl-4-phenyl-3,4,7,8-tetrahydro-6*H*-chromene-2,5-dione (20a)

The title compound was obtained according to the general procedure B. The isolated product was subsequently oxidized according with the general procedure E; overall yield: 71%; d.r. (*cis/trans*) = 1 : 1.3; colourless oil. Mixture of diastereoisomers: ^1H NMR (250 MHz, CDCl_3): δ = 7.31–7.03 (m, 10H), 4.21 (d, J = 7.0 Hz, 1H), 4.09 (s, 1H), 2.79–2.68 (m, 2H), 2.63–2.45 (m, 4H), 2.32–2.26 (m, 4H), 1.81–1.64 (m, 3H), 1.31–1.19 (m, 1H), 1.15 (s, 3H), 1.14 (s, 3H), 1.13 (s, 3H), 1.10–0.99 (m, 9H); ^{13}C NMR (62.5 MHz, CDCl_3): δ = 196.4, 195.7, 169.0, 168.1, 164.8, 164.8, 140.8, 137.5, 129.0, 128.7, 127.8, 127.4, 127.2, 126.5, 117.9, 114.2, 50.6, 50.4, 49.2, 45.7, 40.8, 39.8, 38.0, 32.6, 32.5, 28.4, 28.4, 28.1, 27.9, 25.2, 19.8, 11.7, 11.7; IR (neat): $\tilde{\nu}$ = 2963, 2876, 1782, 1654, 1456, 1374, 1267, 1162, 1121, 1062, 736, 700 cm^{-1} ; MS (EI) m/z (%) = 298 (12) $[\text{M}]^+$, 270 (59), 255 (4), 241 (100), 227 (26), 185 (3), 171 (8), 165 (7), 153 (4), 128 (14), 115 (18), 102 (19), 91 (14), 83 (11), 69 (7), 55 (22).

3-Hexyl-7,7-dimethyl-4-phenyl-3,4,7,8-tetrahydro-6*H*-chromene-2,5-dione (20b)

The title compound was obtained according to the general procedure B. The isolated product was subsequently oxidized according with the general procedure E; overall yield: 84%; d.r. (*cis/trans*) = 1 : 1.4; gummy pale yellow solid. Mixture of diastereoisomers: ^1H NMR (250 MHz, CDCl_3): δ = 7.32–7.11 (m, 10H), 4.20 (d, J = 7.0 Hz, 1H), 4.09 (s, 1H), 2.89–2.76 (m, 2H), 2.64–2.47 (m, 4H), 2.34–2.20 (m, 5H), 1.78–1.61 (m, 4H), 1.47–1.23 (m, 15H), 1.17 (s, 3H), 1.15 (s, 3H), 1.14 (s, 3H), 1.09–1.06 (m, 4H), 0.93–0.85 (m, 6H); ^{13}C NMR (62.5 MHz, CDCl_3): δ = 196.4, 195.8, 169.2, 168.3, 164.8, 164.8, 140.9,

137.6, 129.0 (2C), 128.7 (2C), 127.8 (2C), 127.4, 127.2, 126.5 (2C), 118.0, 114.3, 50.6, 50.4, 47.4, 44.1, 40.8, 39.9, 38.3, 32.6, 32.5, 31.8, 31.4, 28.9, 28.7, 28.5, 28.4, 28.1, 27.9, 27.9, 26.9, 26.9, 26.4, 22.4, 22.4, 13.9; IR (neat): $\tilde{\nu}$ = 2959, 2930, 2859, 1783, 1653, 1374, 1266, 1161, 1124, 1087, 1070, 737, 700 cm^{-1} ; MS (EI) m/z (%) = 354 (17) $[\text{M}]^+$, 326 (99), 311 (10), 269 (34), 255 (11), 241 (100), 227 (35), 213 (3), 207 (8), 185 (4), 173 (14), 165 (6), 145 (6), 129 (17), 117 (20), 102 (13), 91 (25), 83 (23), 69 (9), 55 (36).

3-Benzyl-7,7-dimethyl-4-phenyl-3,4,7,8-tetrahydro-6H-chromene-2,5-dione (20c)

The title compound was obtained according to the general procedure B. The isolated product was subsequently oxidized according with the general procedure E; overall yield: 78%; white solid. Mixture of diastereoisomers: ^1H NMR (250 MHz, CDCl_3): δ = 7.36–6.97 (m, 20H), 4.08–4.05 (m, 2H), 3.25–2.99 (m, 4H), 2.83 (dd, J = 13.4 and 9.1 Hz, 1H), 2.56–2.37 (m, 5H), 2.28–2.20 (m, 4H), 1.15 (s, 3H), 1.10 (s, 6H), 1.00 (s, 3H); ^{13}C NMR (62.5 MHz, CDCl_3): δ = 196.1, 195.6, 168.9, 167.9, 164.9, 164.6, 140.6, 138.1, 137.4, 136.4, 128.9 (2C), 128.9 (2C), 128.9 (2C), 128.8 (2C), 128.5 (2C), 128.2 (2C), 127.6, 127.2, 126.6, 126.5 (2C), 118.0, 114.0, 50.5, 50.4, 49.1, 45.7, 40.8, 38.3, 38.0, 37.9, 32.4, 32.4, 28.5, 28.1, 27.8; IR (neat): $\tilde{\nu}$ = 2961, 1783, 1654, 1373, 1266, 1099, 736, 700 cm^{-1} ; MS (EI) m/z (%) = 360 (9) $[\text{M}]^+$, 332 (26), 281 (4), 269 (41), 241 (100), 227 (12), 207 (12), 171 (5), 157 (3), 131 (26), 115 (12), 104 (12), 91 (26), 83 (10), 55 (8).

3,7,7-Trimethyl-4-phenyl-3,4,7,8-tetrahydro-6H-chromene-2,5-dione (20d)

The title compound was obtained according to the general procedure B. The isolated product was subsequently oxidized according with the general procedure E; overall yield: 50%; d.r. (*cis/trans*) = 1 : 1; colourless oil. Mixture of diastereoisomers: ^1H NMR (250 MHz, CDCl_3): δ = 7.31–7.20 (m, 6H), 7.13–7.07 (m, 4H), 4.08 (d, J = 7.2 Hz, 1H), 3.96 (s, 1H), 3.07–2.95 (m, 2H), 2.57–2.47 (m, 4H), 2.33 (s, 2H), 2.27 (d, J = 3.1 Hz, 2H), 1.15 (d, J = 7.3 Hz, 3H), 0.95–0.91 (m, 9H), 0.86–0.82 (m, 6H); ^{13}C NMR (62.5 MHz, CDCl_3): δ = 196.6, 195.8, 169.6, 169.1, 165.0, 164.7, 140.8, 137.3, 129.0 (2C), 128.8 (2C), 127.8 (2C), 127.5, 127.3, 126.5 (2C), 117.8, 114.1, 50.6, 50.4, 41.8, 41.7, 40.9, 40.3, 39.0, 32.6, 32.5, 28.5, 28.4, 28.1, 28.0, 17.6, 12.3; IR (neat): $\tilde{\nu}$ = 2961, 2873, 1791, 1653, 1455, 1374, 1165, 1119, 1054, 1035, 735, 701 cm^{-1} ; MS (EI) m/z (%) = 284 (21) $[\text{M}]^+$, 269 (4), 256 (100), 241 (84), 227 (35), 223 (16), 200 (6), 185 (5), 171 (9), 157 (6), 145 (5), 129 (18), 115 (19), 102 (20), 91 (9), 83 (9), 55 (16).

7,7-Dimethyl-4-phenyl-3-propyl-3,4,7,8-tetrahydro-6H-chromene-2,5-dione (20e)

The title compound was obtained according to the general procedure B. The isolated product was subsequently oxidized according with the general procedure E; overall yield: 81%; d.r. (*cis/trans*) = 1 : 1.4; colourless oil. Mixture of diastereoisomers:

^1H NMR (250 MHz, CDCl_3): δ = 7.31–7.20 (m, 6H), 7.13–7.09 (m, 4H), 4.17 (d, J = 7.1 Hz, 1H), 4.07 (s, 1H), 2.89–2.77 (m, 2H), 2.55–2.52 (m, 4H), 2.32 (m, 2H), 2.25 (d, J = 2.9 Hz, 2H), 1.73–1.41 (m, 8H), 1.15–1.12 (m, 9H), 1.04 (s, 3H), 0.95 (t, J = 7.0 Hz, 3H), 0.88 (t, J = 7.3 Hz, 3H); ^{13}C NMR (62.5 MHz, CDCl_3): δ = 196.4, 195.7, 169.2, 168.3, 164.8, 164.8, 140.8, 137.56, 128.9 (2C), 128.7 (2C), 127.7 (2C), 127.4, 127.2, 126.5 (2C), 117.9, 114.2, 50.5, 50.4, 47.1, 43.7, 40.7, 39.9, 38.3, 33.7, 32.5, 32.5, 28.6, 28.5, 28.3, 28.1, 27.9, 20.2, 20.1, 13.7, 13.4; IR (neat): $\tilde{\nu}$ = 2960, 2872, 1784, 1655, 1374, 1162, 1122, 1083, 737, 699 cm^{-1} ; MS (EI) m/z (%) = 312 (15) $[\text{M}]^+$, 284 (77), 269 (18), 255 (11), 241 (100), 227 (35), 207 (4), 193 (8), 171 (8), 165 (7), 144 (5), 131 (25), 115 (19), 102 (17), 91 (17), 83 (17), 55 (33).

7,7-Dimethyl-3-nonyl-4-phenyl-3,4,7,8-tetrahydro-6H-chromene-2,5-dione (20f)

The title compound was obtained according to the general procedure B. The isolated product was subsequently oxidized according with the general procedure E; overall yield: 83%; d.r. (*cis/trans*) = 1 : 2; gummy pale yellow solid. Mixture of diastereoisomers: ^1H NMR (250 MHz, CDCl_3): δ = 7.22–7.11 (m, 6H), 7.04–7.01 (m, 4H), 4.10 (d, J = 7.1 Hz, 1H), 3.99 (s, 1H), 2.78–2.66 (m, 2H), 2.47–2.44 (m, 4H), 2.24 (s, 2H), 2.18–2.15 (m, 2H), 1.68–1.50 (m, 4H), 1.18–1.16 (m, 28H), 1.07–1.04 (m, 6H), 0.99 (s, 3H), 0.96 (s, 3H), 0.82–0.77 (m, 6H); ^{13}C NMR (62.5 MHz, CDCl_3): δ = 196.4, 195.8, 169.2, 168.4, 164.8, 164.8, 140.9, 137.6, 129.0 (2C), 128.7 (2C), 127.8 (2C), 127.4, 127.2, 126.5 (2C), 118.0, 114.3, 50.6, 50.4, 47.4, 44.1, 40.8, 39.9, 38.3, 32.6, 32.5, 31.8, 29.3, 29.3, 29.2, 29.1, 29.0, 28.5, 28.4, 28.1, 28.0, 27.9, 27.0, 26.9, 26.4, 22.6, 14.0; IR (neat): $\tilde{\nu}$ = 2957, 2927, 2856, 1784, 1655, 1374, 734 cm^{-1} ; MS (EI) m/z (%) = 396 (16) $[\text{M}]^+$, 368 (100), 353 (15), 269 (33), 255 (9), 241 (81), 227 (28), 207 (5), 185 (4), 173 (8), 165 (5), 145 (5), 129 (12), 117 (14), 105 (8), 91 (20), 83 (18), 69 (9), 55 (25).

(3R)-3,7,7-Trimethyl-3,4,7,8-tetrahydro-6H-chromene-2,5-dione (22a)

The title compound was obtained according to the general procedure C. The isolated product was subsequently oxidized according with the general procedure E; overall yield: 51%; white solid, m.p. = 82–84 °C. ^1H NMR (250 MHz, CDCl_3): δ = 2.85 (ddt, J = 16.3, 7.2 and 1.5 Hz, 1H), 2.73–2.57 (m, 1H), 2.41–2.39 (m, 2H), 2.30 (s, 2H), 2.16 (ddt, J = 16.3, 12.0 and 2.7 Hz, 1H), 1.32 (d, J = 6.7 Hz, 3H), 1.11 (s, 3H), 1.10 (s, 3H); ^{13}C NMR (62.5 MHz, CDCl_3): δ = 198.9, 170.2, 165.5, 112.9, 50.4, 40.8, 33.6, 32.5, 28.4, 28.2, 24.2, 15.3; IR (neat): $\tilde{\nu}$ = 2962, 1772, 1749, 1653, 1636, 1376, 1114, 1071, 1047, 1015, 738 cm^{-1} ; MS (EI) m/z (%) = 208 (21) $[\text{M}]^+$, 193 (4), 180 (100), 165 (95), 147 (22), 138 (16), 124 (52), 109 (23), 96 (44), 82 (15), 55 (19); $[\alpha]_{\text{D}}^{25} = +11.67$ (c = 0.48, CHCl_3 , 83% ee); HPLC conditions: AD-H column, *n*-hexane–2-propanol = 80 : 20, flow rate = 0.6 mL min^{-1} , minor enantiomer: t_{R} = 12.24 min; major enantiomer: t_{R} = 17.16 min.

(3R)-3-Ethyl-7,7-dimethyl-3,4,7,8-tetrahydro-6H-chromene-2,5-dione (22b)

The title compound was obtained according to the general procedure C. The isolated product was subsequently oxidized according with the general procedure E; overall yield: 49%; colourless oil. ^1H NMR (250 MHz, CDCl_3): δ = 2.81 (ddt, J = 16.4, 6.9 and 1.7 Hz, 1H), 2.54–2.42 (m, 1H), 2.39 (t, J = 2.0 Hz, 2H), 2.29 (s, 2H), 2.28–2.15 (m, 1H), 1.99–1.82 (m, 1H), 1.65–1.48 (m, 1H), 1.11 (s, 3H), 1.09 (s, 3H), 1.01 (t, J = 7.5 Hz, 3H); ^{13}C NMR (62.5 MHz, CDCl_3): δ = 196.9, 169.4, 165.2, 112.7, 50.4, 40.7, 39.8, 32.5, 28.4, 28.2, 23.0, 21.5, 11.1; IR (neat): $\tilde{\nu}$ = 2963, 2876, 1782, 1654, 1377, 1165, 1119, 1077, 756 cm^{-1} ; MS (EI) m/z (%) = 222 (13) $[\text{M}]^+$, 194 (82), 179 (32), 165 (100), 153 (14), 138 (25), 123 (11), 110 (12), 95 (15), 70 (14), 55 (29); $[\alpha]_{\text{D}}^{\text{RT}}$ = +10.39 (c = 1.03, CHCl_3 , 89% ee); HPLC conditions: AD-H column, n -hexane–2-propanol = 80 : 20, flow rate = 0.6 mL min^{-1} , minor enantiomer: t_{R} = 10.43 min; major enantiomer: t_{R} = 15.15 min.

(3R)-7,7-Dimethyl-3-propyl-3,4,7,8-tetrahydro-6H-chromene-2,5-dione (22c)

The title compound was obtained according to the general procedure C. The isolated product was subsequently oxidized according with the general procedure E; overall yield: 52%; pale yellow oil. ^1H NMR (250 MHz, CDCl_3): δ = 2.81 (ddt, J = 16.5, 7.0 and 1.7 Hz, 1H), 2.62–2.50 (m, 1H), 2.39 (t, J = 1.9 Hz, 2H), 2.30 (s, 2H), 2.28–2.15 (m, 1H), 1.93–1.80 (m, 1H), 1.56–1.34 (m, 3H), 1.11 (s, 3H), 1.10 (s, 3H), 0.94 (t, J = 7.2 Hz, 3H); ^{13}C NMR (62.5 MHz, CDCl_3): δ = 197.0, 169.6, 165.3, 112.7, 50.5, 40.8, 38.2, 32.6, 32.0, 28.4, 28.2, 21.9, 19.8, 13.8; IR (neat): $\tilde{\nu}$ = 2962, 2874, 1771, 1733, 1716, 1455, 1181, 1070, 930, 734 cm^{-1} ; MS (EI) m/z (%) = 236 (11) $[\text{M}]^+$, 208 (94), 193 (15), 179 (100), 165 (50), 153 (42), 137 (11), 123 (11), 109 (11), 97 (18), 83 (11), 55 (40); $[\alpha]_{\text{D}}^{\text{RT}}$ = –29.63 (c = 0.27, CHCl_3 , 88% ee); HPLC conditions: AD-H column, n -hexane–2-propanol = 80 : 20, flow rate = 1.0 mL min^{-1} , minor enantiomer: t_{R} = 9.09 min; major enantiomer: t_{R} = 13.29 min.

(3R)-3-Hexyl-7,7-dimethyl-3,4,7,8-tetrahydro-6H-chromene-2,5-dione (22d)

The title compound was obtained according to the general procedure C. The isolated product was subsequently oxidized according with the general procedure E; overall yield: 50%. Gummy yellow solid. ^1H NMR (250 MHz, CDCl_3): δ = 2.80 (ddt, J = 16.4, 7.0 and 1.7 Hz, 1H), 2.60–2.47 (m, 1H), 2.39 (t, J = 2.0 Hz, 2H), 2.29 (s, 2H), 2.27–2.15 (m, 1H), 1.94–1.80 (m, 1H), 1.56–1.35 (m, 3H), 1.36–1.27 (m, 6H), 1.11 (s, 3H), 1.09 (s, 3H), 0.87 (t, J = 6.8 Hz, 3H); ^{13}C NMR (62.5 MHz, CDCl_3): δ = 197.0, 169.6, 165.3, 112.7, 50.5, 40.8, 38.4, 32.5, 31.5, 29.9, 29.0, 28.4, 28.2, 26.6, 22.5, 21.9, 14.0; IR (neat): $\tilde{\nu}$ = 2955, 1700, 1653, 1596, 1457, 1388, 1266, 1069, 895, 740 cm^{-1} ; MS (EI) m/z (%) = 278 (25) $[\text{M}]^+$, 250 (83), 235 (100), 221 (19), 207 (24), 193 (37), 179 (56), 165 (47), 154 (61), 137 (17), 97 (25), 83 (27), 69 (15), 55 (34); $[\alpha]_{\text{D}}^{\text{RT}}$ = –23.15 (c = 0.42, CHCl_3 , 87% ee); HPLC conditions: OD-H column, n -hexane–2-propanol = 90 : 10, flow rate = 0.3 mL min^{-1} , minor enantiomer: t_{R} = 31.02 min; major enantiomer: t_{R} = 28.27 min.

min $^{-1}$, minor enantiomer: t_{R} = 31.02 min; major enantiomer: t_{R} = 28.27 min.

(3R)-3,7,7-Trimethyl-5-oxo-3,4,5,6,7,8-hexahydro-2H-chromen-2-yl-4-bromobenzoate (23)

The title compound was obtained according to the general procedure C. The isolated product was subsequently dissolved in pyridine. Dimethylaminopyridine and 4-bromobenzoyl chloride were dissolved in dichloromethane and the solution added to the alkaloid solution. The solution was made up to 6 mL with dichloromethane and stirred at room temperature overnight. The reaction mixture was poured into 20 mL 1 M NaHCO_3 and extracted with 3 \times 10 mL CH_2Cl_2 . The combined extracts washed with water and dried over Na_2SO_4 . The solvent was removed *in vacuo* and the residue was subjected to column chromatography; overall yield: 27%; white solid, m.p. = 181–184 $^{\circ}\text{C}$; ^1H NMR (250 MHz, CDCl_3): δ = 7.88/7.60 (AB system, J = 8.6 Hz, 4H), 6.26 (d, J = 4.2 Hz, 1H), 2.58–2.49 (m, 1H), 2.33–2.19 (m, 6H), 1.06–1.03 (m, 9H); ^{13}C NMR (62.5 MHz, CDCl_3): δ = 190.1, 165.6, 164.1, 132.0 (2C), 131.4 (2C), 129.0, 128.1, 109.4, 94.6, 50.6, 41.7, 32.3, 28.7, 28.7, 27.9, 20.9, 15.7; IR (neat): $\tilde{\nu}$ = 2962, 2878, 1734, 1635, 1590, 1396, 1265, 1079, 1011, 737 cm^{-1} ; MS (EI) m/z (%) = 393 (30) $[\text{M}]^+$, 299 (16), 267 (63), 255 (15), 223 (23), 211 (100), 193 (44), 183 (9), 141 (8); $[\alpha]_{\text{D}}^{\text{RT}}$ = –141.44 (c = 1.18, CHCl_3).

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