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WITTIG-HORNER-EMMONS REACTIONS OF TRIETHYL 3-METHYL-PHOSPHONOCROTONATE WITH 3-FORMYLCHROMONES EN ROUTE TO BENZOPHENONE-BASED RETINOID CANDIDATES

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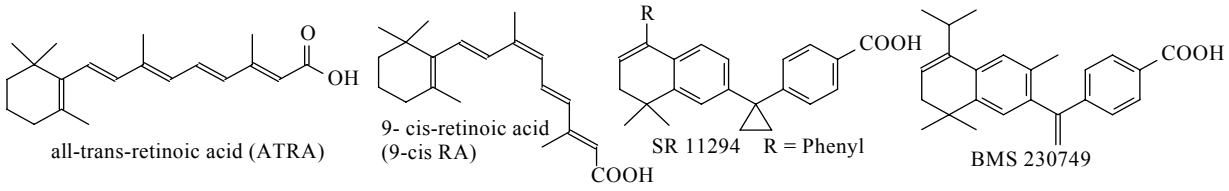
Abstract- Wittig-Horner-Emmons (WHE) reaction conditions were used in conjunction with other reactions to prepare benzophenone-based retinoid candidates. The chromone nucleus was reacted with triethyl 3-methyl-phosphonocrotonate to afford benzophenones following a known rearrangement of a reaction intermediate. Confirmations of the structure of rearranged products are provided in the form of the X-ray crystal structures and speculation regarding the mechanism for the rearrangements is included. The method provides a facile route to substituted benzophenone-based candidate ligands for retinoic acid receptors (RARs) or for a wide variety of other applications.

INTRODUCTION

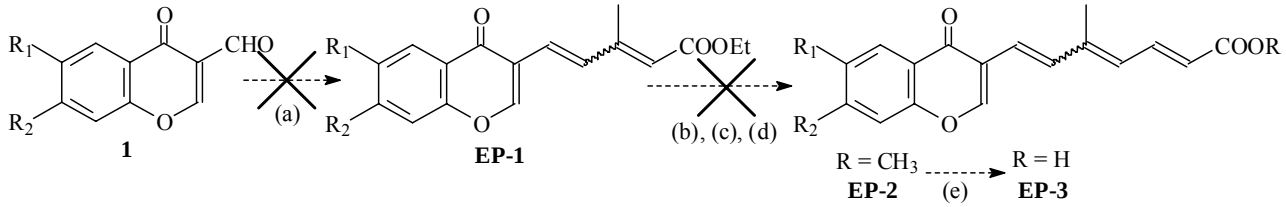
Our interest in the design and synthesis of ligands for retinoic acid receptors led to the synthesis of the benzophenone-based compounds reported herein. Vitamin A (retinol) and its biologically active analogs, collectively called retinoids, play a critical role in the development and homeostasis of vertebrate tissues.[1,2] All-trans retinoic acid (ATRA) and 9-cis retinoic acid (9-cis RA) (Figure 1) are endogenous ligands for retinoic acid receptors (RARs) and retinoid X receptors (RXRs). A variety of structurally diverse compounds have been developed that also bind to these receptors with high affinity (Figure 1).[3-5]

Figure 1. Structures of ATRA, 9-cis RA, SR 11294 (RAR ligand) and BMS 230749 (RXR ligand).



The aim of the present work is the preparation of novel RAR and/or RXR candidate ligands using the commercially available 3-formylchromones. The product of Wittig reactions between this chromone-aldehyde and commercially available phosphoranes might be expected to be chromones with poly-olefinic side chains (Scheme 1; **EP-1** and **EP-2**, **EP-3**).[6, 7] However, Wittig-Horner-Emmons (WHE) reactions involving triethyl 3-methylphosphonocrotonate and a series of 3-formylchromones resulted in the isolation of benzophenone-based compounds.[8] Similar rearrangements of the chromone nucleus have been reported in the literature. We herein report the use of the WHE reaction to synthesize benzophenone-based compounds following this predictable and reproducible rearrangement.[9, 10]

Scheme 1. Expected Products (EP) of Wittig and W-H-E Reactions.



Conditions: a) triethyl 3-methylphosphonocrotonate, *n*-BuLi, HMPA, -78°C, 1 h to rt 24 h; b) LAH; c) MnO_2, 0°C; d) methyl (triphenylphosphoranyl)acetate hydrobromide, *n*-BuLi, -78°C; e) LiOH, MeOH/THF/H_2O.

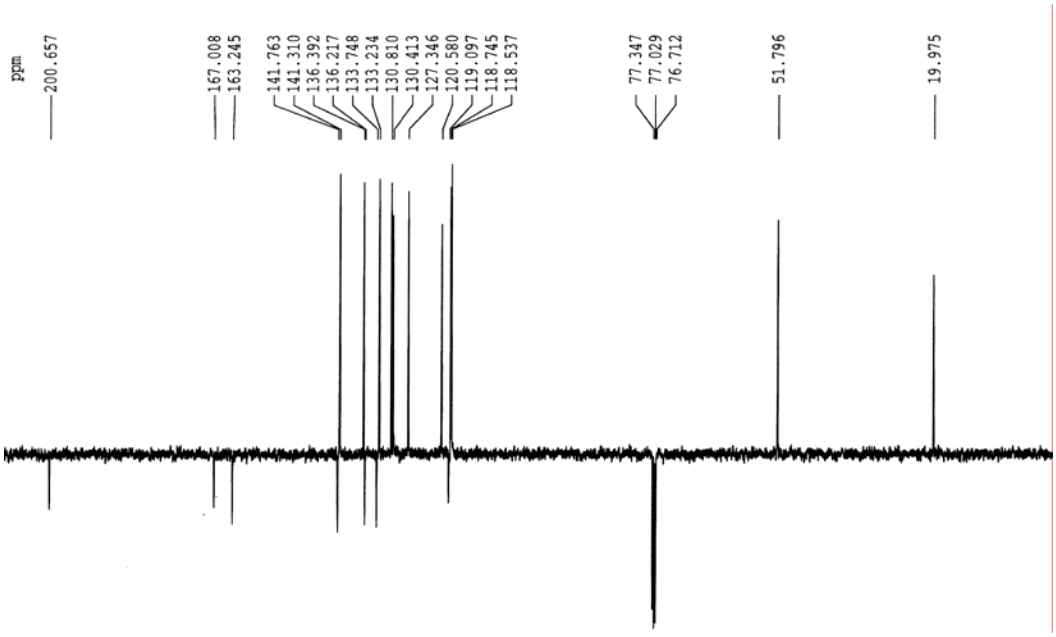
The structures of rearranged products are confirmed via X-ray crystal data. A mechanism for the rearrangement of the WHE reaction intermediate to the corresponding benzophenone is proposed. The facile synthetic routes reported herein are used to prepare RAR or RXR candidate ligands. The route has general applicability in the synthesis of a variety of substituted benzophenones (e.g., BMS 230749).[11]

RESULTS AND DISCUSSION

The product of a WHE reaction between 3-formylchromone (**1**) and triethyl 3-methyl-4-phosphonocrotonate might be predicted to be the diene (**EP-1**; see Scheme 1).[12, 13] This compound could be further elaborated as shown to provide expected chromone **EP-3** in acceptable yield (Scheme 1). Hence, **EP-1** was reduced to the alcohol with LAH and then oxidized to the corresponding aldehyde (MnO_2). The aldehyde was reacted with methyl (triphenylphosphoranyl)acetate hydrobromide under standard Wittig conditions to provide a methyl ester (**EP-2**; Scheme 1). However, ^{1}H NMR data of the

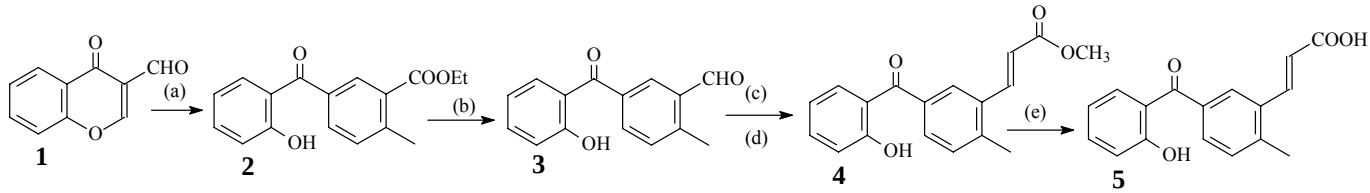
actual product (**4**; See Scheme 2) shows an exchangeable proton peak (CD_3OD) located at 11.8 ppm. In addition, DEPT ^{13}C NMR spectra show seven peaks for carbons with no protons attached consistent with compound (**4**) (**EP-2** would contain six such carbon peaks; Figure 2).

Figure 2. DEPT ^{13}C NMR of Compound (**4**).



Taken together, the data described above suggest that a rearrangement had occurred and a benzophenone intermediate (**2**) was obtained (see Scheme 2). Compound (**2**) then underwent reduction (LAH), oxidation (MnO_2), and a Wittig reaction to provide ester (**4**) in good yield. The target, (*E*)-3-(5-(2-hydroxybenzoyl)-2-methylphenyl)acrylic acid **(5),** was isolated in acceptable yield following basic hydrolysis.

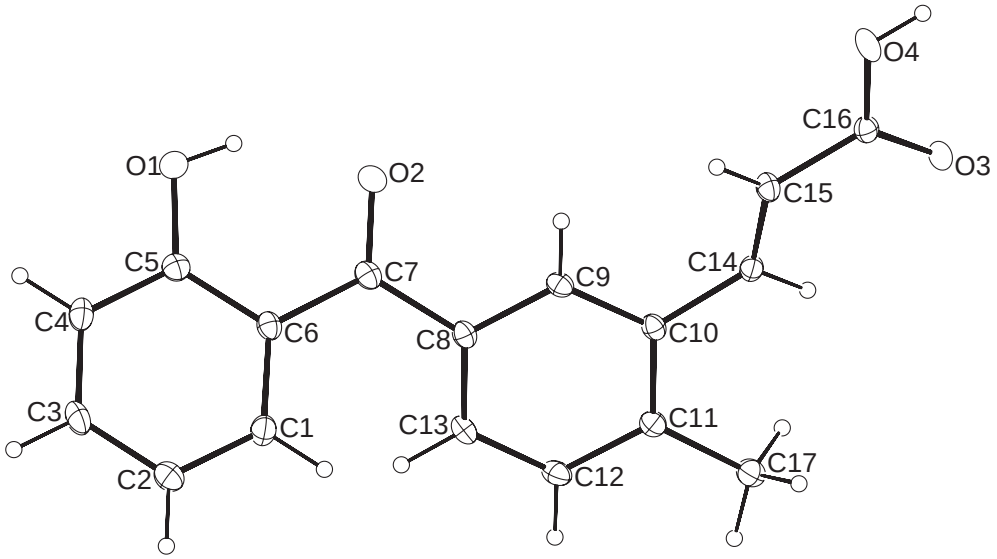
Scheme 2. Synthesis of Compound (**5**).



Conditions: a) triethyl 3-methyl-4-phosphonocrotonate, *n*-BuLi, HMPA, -78°C; b) LAH; c) MnO_2, five portions over 2 h, 0 °C; d) (methoxycarbonylmethyl) triphenylphosphonium bromide, *n*-BuLi, -78 °C; e) LiOH, MeOH/THF/H_2O, 2 h.

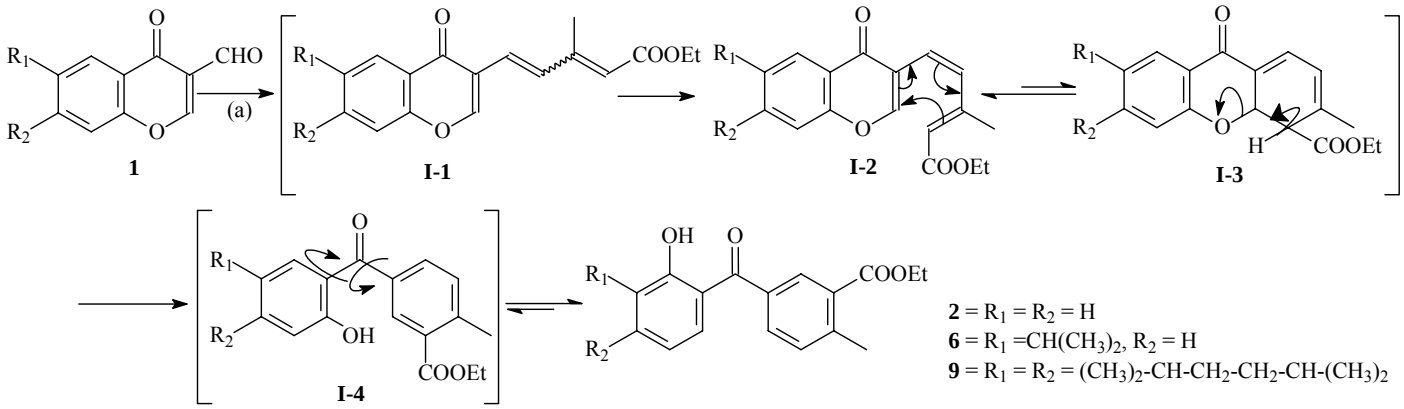
All spectroscopic data for (**5**) was consistent with the presence of the benzophenone system. In addition, the crystal structure shown in Figure 3 clearly demonstrates the formation of the benzophenone product. Hence, the initial WHE reaction provides the triene intermediate (**I-1**; Scheme 3) which undergoes cyclization to the more stable aromatic structure compound (**2**) (Scheme 3). Once the benzophenone nucleus is formed, it undergoes the reactions shown in Scheme 2 to provide the target acid (**5**).

Figure 3. ORTEP representation of crystal structure of compound (**5**) with 30% probability thermal ellipsoids.



To test the general applicability of this approach several chromones were used to prepare novel retinoid candidate ligands using the same synthetic route. In order to introduce aliphatic substituents into the lipophilic region of retinoid ligands, alkyl substituted chromones were used. For example, 6-isopropyl-3-formylchromone was reacted with triethyl 3-methyl-4-phosphonocrotonate under similar WHE reaction conditions as shown in Scheme 4. As seen with compound (**5**) above, ^{1}H and ^{13}C DEPT NMR data for the product of this reaction suggested a hydroxyl group was present.

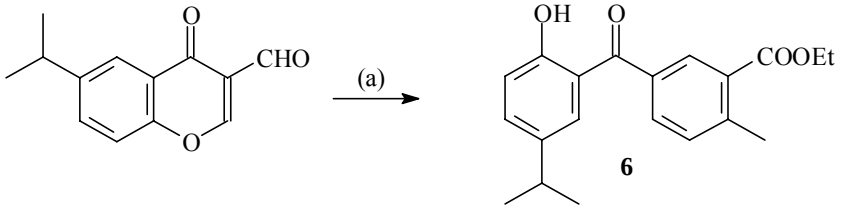
Scheme 3. Proposed mechanism for the rearrangement/cyclization to form key intermediates **2**, **6**, **9**.



Conditions: a) triethyl 3-methyl-4-phosphonocrotonate, *n*-BuLi, HMPA, -78°C, 1 h to rt 24 h.

Hence, cyclization of the intermediate triene (**I-1**) and ring opening of the chromone nucleus provides benzophenone (**6**) (Scheme 4) which is consistent with all spectroscopic data for the compound. Hydrolysis of the ester provides the target acid as a potential RAR candidate ligand.

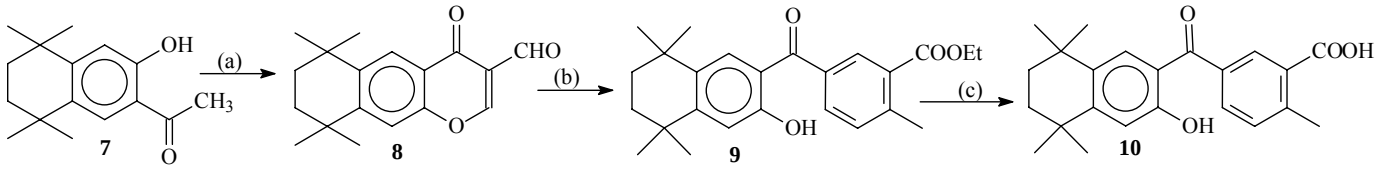
Scheme 4. WHE reaction of 6-isopropyl-3-formylchromone with triethyl 3-methyl-4-phosphonocrotonate.



Conditions: a) triethyl 3-methyl-4-phosphonocrotonate, *n*-BuLi, HMPA, -78°C, 1 h to rt 24 h.

Lastly, 6,6,9,9-tetramethyl-4-oxo-6,7,8,9-tetrahydro-4*H*-benzo[*g*]chromene-3-carbaldehyde (**8** below) was reacted with triethyl 3-methyl-4-phosphonocrotonate under WHE reaction conditions. In this case, the key starting intermediate (**7**) was prepared using known published procedures.[14-17]

Scheme 5. Synthesis of Compound (**10**).



Conditions: a) $POCl_3$, DMF; b) triethyl 3-methyl-4-phosphonocrotonate, *n*-BuLi, HMPA, -78°C, 1 h to rt 24 h; c) LiOH, MeOH/THF/H_2O, 2 h.

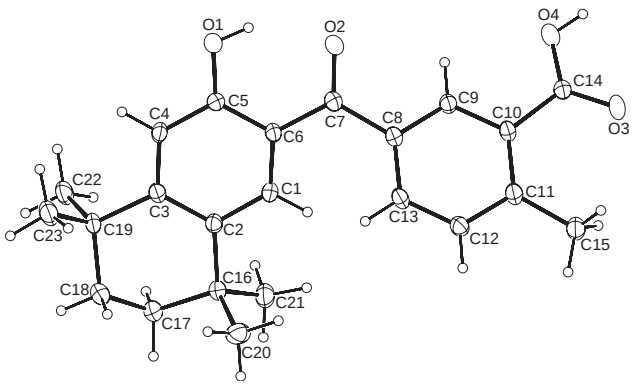
In the first reaction in the sequence, 2,5-dimethyl-2,5-hexanediol and concentrated HCl were stirred vigorously at rt for 3 - 4 h to afford 2,5-dichloro-2,5-dimethylhexane in good yield (90%).[14] Phenol and 2,5-dichloro-2,5-dimethylhexane were then reacted under Friedel Craft reaction conditions to provide intermediate which was acetylated using $AlCl_3$ in dried CH_2Cl_2 to yield (**7**).[15,16] Compound (**7**) was converted to the chromone aldehyde (**8**) using freshly distilled phosphorus oxy-chloride ($POCl_3$) in anhydrous DMF at rt. Compound (**8**) (6,6,9,9-tetramethyl-4-oxo-6,7,8,9-tetrahydro-4*H*-benzo[*g*]chromene-3-carbaldehyde) was used in the synthesis of the target benzophenone (**10**) as shown in Scheme 5.

6,6,9,9-Tetramethyl-4-oxo-6,7,8,9-tetrahydro-4*H*-benzo[*g*]chromene-3-carbaldehyde (**8**) was reacted with the commercially available triethyl 3-methyl-4-phosphonocrotonate in the presence of *n*-BuLi in dried THF to give compound (**9**) following the previously observed rearrangement. The target ligand (**10**) was obtained following basic hydrolysis.

As anticipated, the product of this reaction had an exchangeable proton at 11.5 ppm in the ^{1}H NMR spectrum. In addition, IR spectra showed carbonyl and carboxylate bands expected of benzophenone-

containing compounds possessing a carboxylic acid. These data suggest that the rearrangement had occurred as previously observed for the ligands reported above. The structure of (**10**) was confirmed via X-ray crystal analysis as shown in Figure 4.

Figure 4. ORTEP representation of crystal structure of compound (**10**) with 30% probability thermal ellipsoids.



CONCLUSION

Rearrangements of chromones under similar reaction conditions have been reported in the literature. The data provided herein provides further evidence for this useful, yet unanticipated synthetic route to substituted benzophenones. The reaction of 3-formylchromone with phosphoranes under WHE reaction conditions is a generally applicable route to substituted benzophenones. These cyclization reactions proceed at low temperatures, under mild conditions and provide facile routes to a variety of substituted benzophenones.

EXPERIMENTAL

General. Reactions were carried out in oven-dried glassware under a nitrogen atmosphere and were magnetically stirred and monitored by thin-layer chromatography (TLC) with Analtech 250 micron pre-coated silica gel plates. Tetrahydrofuran (THF) were freshly distilled from sodium/benzophenone under nitrogen and dichloromethane (CH_2Cl_2) distilled from calcium hydride. Except as otherwise indicated, all reagents were purchased and used without purification. Flash column chromatography was performed using silica gel 60 (particle size 230-400 mesh) supplied by Aldrich. Yields refer to chromatographically pure compounds. Melting points were obtained on a Thomas-Hoover apparatus and are not corrected. Nuclear magnetic resonance spectra were recorded on a Bruker Avance 400 at 400MHz for ^{1}H NMR (some on a GE at 500 MHz) and 100MHz for ^{13}C NMR. Chemical shifts were reported relative to solvents or an internal standard (TMS). Low- and high- resolution mass spectrometry data were recorded by the Department of Chemistry, Drexel University using a VG70-SE high resolution magnetic sector instrument operating at 7 KV acceleration voltages. Samples are dissolved in a matrix of nitrobenzoyl alcohol (NBA) doped with NaBr and bombarded with a 35 KV Cs ion beam (LSI, API, EPI-MS).

Elemental analyses were performed by Atlantic Micro lab Inc, Norcross, GA. X-ray crystallographic analysis was performed at Department of Chemistry, University of Pennsylvania.

Ethyl 5-(2-hydroxybenzoly)-2-methylbenzoate (2)

To a solution of triethyl 3-methyl-4-phosphonocrotonate (1.3 mL, 5.4 mmol) in dry THF (15 mL) was added *n*-butyllithium (2M in heptane, 4.5 mL, 9 mmol) and HMPA (0.16 mL, 0.9 mmol). The mixture was cooled to -78°C, stirred under N_2 for 30 min and 3-formylchromone (0.85 g, 4.9 mmol) in dry THF (5 mL) was added dropwise. The resulting mixture was stirred at -78°C for 1 h and allowed to warm to rt and stirred for 24 h. The reaction mixture was quenched with saturated aqueous NH_4Cl (20 mL) and extracted with EtOAc (50 mL × 3). The organic layer was washed with brine, dried over $MgSO_4$, condensed and purified by flash chromatography (silica gel; 10:1 to 3:1, hexane/EtOAc) to afford compound (**2**) (0.82 g; yield: 56%) as colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$): δ 11.9 (s, 1 H), 8.16 (s, 1 H), 7.62 (d, *J* = 7.9 Hz, 1 H), 7.48 (d, *J* = 8.0 Hz, 1 H), 7.44 (t, *J* = 7.9 Hz, 1 H), 7.30 (d, *J* = 7.9 Hz, 1 H), 6.99 (d, *J* = 8.4 Hz, 1 H), 6.81 (t, *J* = 7.6 Hz, 1 H), 4.27-4.33 (q, *J* = 7.1 Hz, 2 H), 2.62 (s, 3 H), 1.31 (t, *J* = 7.1 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 200.8, 167.1, 163.6, 144.9, 136.9, 135.9, 133.7, 132.6, 132.2, 131.9, 130.6, 119.4, 119.2, 118.9, 61.6, 22.3, 14.7.

5-(2-Hydroxybenzoly)-2-methylbenzaldehyde (3)

To a solution of ester (**2**) (0.82 g, 2.7 mmol) in dry THF (25 mL) was added LAH powder (0.5 g, 12.9 mmol) with stirring at rt. The reaction mixture was treated in order with H_2O (10 mL), 10% NaOH (10 mL) and H_2O (10 mL), condensed under reduced pressure and the remaining residue was extracted with EtOAc (50 mL × 2). The EtOAc layer was washed with brine, dried over $MgSO_4$, condensed and purified by flash chromatography (silica gel; 1:1, hexane/EtOAc) to afford colorless oil. To a solution of the oil (0.45 g, 1.7 mmol) in dry CH_2Cl_2 (25 mL) was added MnO_2 (in five portions; 1.5 g, 17 mmol) and 0.5 g of molecular sieve (4 Å) powder. The mixture was chilled in an ice bath and stirred for 2 h. Another 1.5 g of MnO_2 was added in five portions over 2 h. After stirring for 30 min, the resulting mixture was filtered through Celite 450 and washed with CH_2Cl_2. The collected CH_2Cl_2 solution was condensed and purified by flash chromatography (silica gel; 1:1, hexane/EtOAc) to afford compound (**3**) (0.22 g, 40% for two steps) as a yellow solid: ^{1}H NMR (500 MHz, $CDCl_3$): δ 11.8 (s, 1 H), 10.3 (s, 1 H), 8.13 (s, 1 H), 7.82 (d, *J* = 7.5 Hz, 1 H), 7.53-7.57 (m, 2 H), 7.44 (d, *J* = 8.0 Hz, 1 H), 7.10 (d, *J* = 8.0 Hz, 1 H), 6.91 (t, *J* = 7.5 Hz, 1 H), 2.79 (s, 3 H).

(*E*)-Methyl 3-(5-(2-hydroxybenzoyl)-2-methylphenyl)acrylate (4)

To a solution of (methoxycarbonylmethyl) triphenylphosphonium bromide (0.37 g, 0.8 mmol) in dry THF

(20 mL) was added *n*-butyllithium (2M in heptane, 0.4 mL, 0.8 mmol) and HMPA (0.05 mL). The mixture was cooled to -78°C and stirred under N_2 for 30 min, followed by the dropwise addition of the aldehyde (**3**) (0.16 g, 0.6 mmol) in dry THF (5 mL). The resulting mixture was stirred at -78°C for 1 h and allowed to warm to rt. After 24 h, the reaction mixture was quenched with saturated aqueous NH_4Cl (20 mL) and extracted with EtOAc (30 mL × 3). The organic layer washed with brine, dried over $MgSO_4$, condensed and purified by flash chromatography (silica gel; 10:1 to 3:1, hexane/EtOAc) to afford compound (**4**) (0.1 g; yield: 51%) as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.9 (s, 1 H), 7.92 (d, *J* = 15.9 Hz, 1 H), 7.77 (s, 1 H), 7.48-7.52 (t, *J* = 7.8 Hz, 2 H), 7.42-7.46 (t, *J* = 8.6 Hz, 1 H), 7.27 (d, *J* = 7.9 Hz, 1 H), 7.00 (d, *J* = 8.4 Hz, 1 H), 6.79-6.83 (t, *J* = 8.2 Hz, 1 H), 6.32 (d, *J* = 15.9 Hz, 1 H), 3.74 (s, 1 H), 2.45 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 200.7, 167.0, 163.2, 141.8, 141.3, 136.4, 136.2, 133.7, 133.2, 130.8, 130.4, 127.3, 120.6, 119.1, 118.7, 118.5, 51.8, 19.9. NOE.

(*E*)-3-(5-(2-Hydroxybenzoyl)-2-methylphenyl)acrylic acid (5)

To a solution of the methyl ester (**4**) (20 mg, 0.06 mmol) in MeOH/THF/H_2O (6 mL; 1:1:1) was added LiOH (15 mg) and the mixture was stirred at rt for 2 h. The reaction was acidified to pH 1.5 by dropwise addition of 5 N HCl. The mixture was condensed and purified by chromatography (silica gel; 5:5:1, EtOAc/CH_2Cl_2/MeOH) to afford acid (**5**) as a pale yellow solid in quantitative yield: ^{1}H NMR (400 MHz, CD_3OD): δ 7.90 (d, *J* = 15.9 Hz, 1 H), 7.78 (s, 1 H), 7.49-7.53 (m, 2 H), 7.46 (t, *J* = 8.3 Hz, 1 H), 7.29 (d, *J* = 7.9 Hz, 1 H), 6.99 (d, *J* = 8.4 Hz, 1 H), 6.84 (t, *J* = 8.1 Hz, 1 H), 6.31 (d, *J* = 15.9 Hz, 1 H), 2.45 (s, 3 H). ^{13}C NMR (100 MHz, CD_3OD): δ 202.7, 171.1, 164.3, 143.7, 143.1, 138.2, 137.9, 135.7, 135.1, 132.6, 132.1, 129.1, 123.4, 121.0, 120.8, 119.6, 21.5. LC-MS (API-ESI): 297.3 (M-1), 298.4 (M+).

Ethyl 5-(2-hydroxy-5-isopropylbenzoyl)-2-methylbenzoate (6)

A solution of triethyl 3-methyl-phosphonocrotonate (0.14 mL, 0.5 mmol) in dried THF (15 mL) was cooled in an ice bath, stirred and treated with *n*-butyllithium (2 M in heptane, 0.5 mL, 1.0 mmol). The reaction mixture was stirred at 0°C for 30 min and a solution of 3-formylisopropylchromone (0.1 g, 0.46 mmol) in dried THF (5 mL) added dropwise. The resulting mixture was stirred for 2 h at 0°C and allowed to warm to rt. After two days at rt the mixture was quenched with saturated aqueous NH_4Cl and extracted with EtOAc (20 mL × 3). The combined organic layer was washed with brine, dried over $MgSO_4$, condensed and purified by flash chromatography (silica gel; 10:1, hexane/EtOAc) to afford compound (**6**) (60 mg; yield: 40%) as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.8 (s, 1 H), 8.27 (d, *J* = 1.9 Hz, 1 H), 7.74-7.76 (dd, *J* = 1.9, 7.9 Hz, 1 H), 7.40 (m, 3 H, H_2, H_4 and H_5), 7.02 (d, *J* = 7.2 Hz, 1 H), 4.35 (q, *J* = 7.1 Hz, 2 H), 2.84 (m, 1 H), 2.70 (s, 3 H), 1.40 (t, *J* = 7.1 Hz, 3 H), 1.19 (d, *J* = 6.9 Hz, 6 H); ^{13}C NMR: δ 200.5, 167.0, 161.7, 144.9, 139.5, 136.0, 135.4, 132.6, 132.3, 132.1, 131.2, 130.8, 119.0, 118.6, 61.5,

33.6, 24.3, 22.2, 14.7. (400 MHz, Pyridine-d5): δ 13.33 (s, 1 H), 9.71 (d, *J* = 1.9 Hz, 1 H), 9.09-9.11 (dd, *J* = 1.9, 7.9 Hz, 1 H), 8.75 (d, *J* = 2.3 Hz, 1 H, H_2), 8.53-8.56 (dd, J = 2.3, 8.5 Hz, H_4), 8.47 (d, *J* = 7.9 Hz, 1 H), 8.34 (d, *J* = 8.2 Hz, 1 H, H_5), 5.40-5.46 (m, 2 H), 3.93 (m, 1 H), 3.78 (s, 3 H), 2.29-2.35 (m, 9 H). MS *m/z* (CI): 326 (M^+); (FAB): 327 (M+H); HR-MS (FAB): 327.1593 (Calcd for $C_{20}H_{23}O_4$ 327.1596); Anal. [$C_{20}H_{22}O_4$] C, H. Found: C, 73.46; H, 7.00.

1-(3-Hydroxy-5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphthalen-2-yl)ethanone (7)

To 2,5-dimethyl-2,5-hexanediol (2 g, 2.67 mmol) was added concentrated HCl (20mL) with vigorous stirring at rt for 3 - 4 h. Chloroform ($CHCl_3$; 25 mL) was added to the solution and the two layers were separated. The aqueous layer was extracted with $CHCl_3$ (2 x 25 mL), the organic layers were combined, dried over $MgSO_4$ and condensed under reduced pressure. This was purified by flash chromatography (silica gel; 10:1, hexane/EtOAc) to afford a tan amorphous solid of 2,5-dichloro-2,5-dimethylhexane (1.90g, yield: 90%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.0 (s, 4H), 1.6 (s, 12H). To a solution of the 2,5-dichloro-2,5-dimethylhexane (1g, 5.46 mmol) and phenol (0.616g, 6.55 mmol) was added $AlCl_3$ (1.09g, 8.19mmol) in small portions and the mixture stirred at rt for 12 h. The reaction was quenched by dropwise addition of water and extracted with EtOAc (3 x 30mL). The combined organic layers were washed with brine, dried over $MgSO_4$, condensed under reduced pressure and purified by flash chromatography (silica gel; 11:1, hexane/EtOAc) to afford 5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphthalen-2-ol (0.82g; yield: 82%): ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.16 (d, J = 8.50 Hz, 1H, Ar), 6.75 (d, J = 2.76 Hz, 1H, Ar), 6.62 (dd, J = 2.77, 8.49 Hz, 1H, Ar), 4.65 (s, 1H), 1.65 (m, 4H), 1.24 (d, J = 2.58 Hz, 12H). A solution of 5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphthalen-2-ol (0.48g, 2.35 mmol) in dried CH_2Cl_2 was added slowly to $AlCl_3$ (0.313g, 2.35 mmol). To this mixture CH_3COCl (0.22g, 2.82mmol) was added dropwise and the reaction refluxed for 8-12h. Water was added and the layers separated. The aqueous phase was extracted with EtOAc (3 x 25mL) and the combined organic layers were dried over $MgSO_4$, reduced under pressure and purified by flash chromatography (silica gel; 10:1, hexane/EtOAc) to afford (**7**) (0.3g; yield: 51%): ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.4 9 (d, 1H), 6.98 (d, 1H), 2.4 (s, 3H), 1.8 (s, 4H), 1.4 (s, 12H).

6,6,9,9-Tetramethyl-4-oxo-6,7,8,9-tetrahydro-4*H*-benzo[*g*]chromene-3-carbaldehyde (8)

To a solution of (**7**) (0.3g, 1.217 mmol) in anhydrous DMF (15 mL), freshly distilled $POCl_3$ (0.933g, 6.085 mmol) was added dropwise. The mixture was refluxed overnight and monitored by TLC. Solvent was removed under vacuum and ice cold water was added. The aqueous phase was extracted with CH_2Cl_2 (3 x 25 mL), and the organic layers combined, washed with brine, dried over $MgSO_4$, reduced under pressure and purified by flash chromatography (silica gel; 12:1 to 7:1, hexane/EtOAc) to afford

compound (**8**) (0.2g; yield: 57%): ^{1}H NMR (500 MHz, $CDCl_3$): δ 10.4 (s, 1H), 8.5 (s, 1H), 8.23 (s, 1H), 7.45 (s, 1H), 1.75 (s, 4H), 1.36 (s, 12H).

Ethyl 5-(3-hydroxy-5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphthalene-2-carbonyl)-2-methylbenzoate (9)

To a solution of triethyl 3-methyl-phosphonocrotonate (0.465 g, 1.76 mmol) in dry THF (20 mL) was added dropwise *n*-butyllithium (2M in heptane, 1.76 mL, 3.52 mmol) and the mixture cooled to -78°C and stirred under N_2 for 30 min. A solution of aldehyde (**8**) (0.5g, 1.76 mmol) in dry THF (5 mL) was added dropwise to the mixture. The reaction was stirred at -78°C for 1-2 h and allowed to warm to rt and stirred over 24 h. The reaction was quenched with saturated aqueous NH_4Cl (20 mL) and extracted with EtOAc (3 x 30 mL). The organic layers were washed with brine, dried over $MgSO_4$, condensed and purified by flash chromatography (silica gel; 15:1 to 7:1, hexane/EtOAc) to afford compound (**9**) (0.2g; yield: 28%) as a yellowish solid: ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.57 (s, 1H), 8.27 (d, J = 1.94, 1H), 7.76 (dd, J = 1.94, 7.87, 1H), 7.54 (s, 1H), 7.41 (d, J = 7.95, 1H) 7.0 (s, 1H), 4.37 (q, 2H), 2.72 (s, 3H), 1.68 (m, 4H), 1.37 (t, 3H), 1.31 (s, 6H), 1.20 (s, 6H).

5-(3-Hydroxy-5,5,8,8-tetramethyl-5,6,7,8-tetrahydronaphthalene-2-carbonyl)-2-methylbenzioc acid (10)

To a solution of the ethyl ester (**9**) (0.12g, 0.3041 mmol) in MeOH/THF/H_2O (6 mL; 1:1:1) was added LiOH (14mg, 0.6082 mmol) and the mixture stirred at rt for 2-6 h. The reaction was acidified to pH 1.5 – 2.0 by dropwise addition of 5 N HCl and extracted with EtOAc (2 x 25 mL). The combined organic layers was dried over $MgSO_4$, condensed under reduced pressure and purified by flash chromatography (silica gel; 10:1: 0.1, hexane/ EtOAc/ HCOOH) to afford acid (**10**) as a yellow solid in quantitative yield (0.1g, yield: 89%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.5 (s, 1H), 8.43 (d, J = 1.9 Hz, 1H), 7.83 (dd, J = 1.93, 7.88 Hz, 1H), 7.53 (s, 1H), 7.45 (d, J = 7.96 Hz, 1H), 7.01 (s, 1H), 2.77 (s, 3H), 1.68 (m, 4H), 1.31 (s, 6H), 1.20 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 199.55, 172.24, 160.60, 155.98, 145.98, 136.40, 133.57, 132.66, 132.06, 128.58, 117.66, 115.85, 35.22, 34.05, 32.08, 22.59. Anal. [$C_{23}H_{26}O_4$] C, H. Found: C, 75.09; H, 7.34.

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