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Nathan Trometer, Matthieu Roignant, Elisabeth Davioud-Charvet. Efficient Multigram-Scale Synthesis of 7-Substituted 3-Methyltetral-1-ones and 6-Fluoromenadione. *Organic Process Research and Development*, 2022, acs.oprd.1c00421. <10.1021/acs.oprd.1c00421>. <hal-03584209>

**HAL Id: hal-03584209**

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Submitted on 22 Feb 2022

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# An Efficient Multigram Scale Synthesis of 7-Substituted-3-Methyltetral-1-ones and 6-Fluoromenadione

Nathan Trometer,<sup>1,‡</sup> Matthieu Roignant,<sup>1,‡</sup> Elisabeth Davioud-Charvet<sup>1,\*</sup>

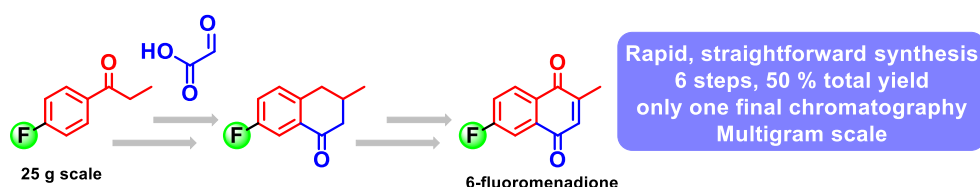
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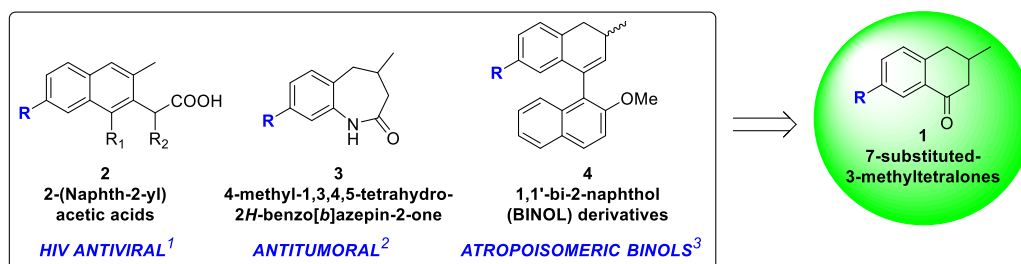
**ABSTRACT:** Herein is reported a safe and economical multigram synthesis of 6-fluoromenadione, an intermediate in the synthesis of novel antiparasitic agents. The keys to this 6-steps sequence process involves the condensation of the readily available starting 4'-fluoropropiophenone and glyoxylic acid, a bromination-elimination sequence from the 7-fluoro-3-methyltetral-1-one allowing the aromatization of the naphthol intermediate, which is then oxidized into the corresponding 6-fluoromenadione. The multigram process has been demonstrated from 25 g starting material scale with an improved overall yield of 50%, and then applied to five other 7-substituted-3-methyltetralones and their corresponding 6-substituted-menadiones.

**KEYWORDS:** glyoxylic acid, gram-scale synthesis, menadione, 3-methyltetralone, propiophenone.

## ■ INTRODUCTION

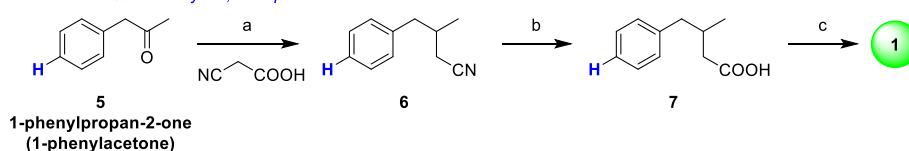
3-Methyltetral-1-one **1** (or 3-methyl-3,4-dihydronaphthalen-1(2*H*)-one, Scheme 1) is a useful compound known as a key synthetic intermediate for the preparation of numerous molecules active in therapeutic applications or of high interest for chemical applications (Scheme 1), such as the antiviral 2-(naphth-2-yl)acetic acids **2** against HIV,<sup>1</sup> the diversely substituted 4-methyl-1,3,4,5-tetrahydro-2*H*-benzo[*b*]azepin-2-one **3**,<sup>2</sup> active against various tumours, or the 1,1'-bi-2-naphthol (BINOL) derivatives **4**.<sup>3</sup> In most of these studies, structure-activity relationships were limited because diversely substituted aromatic starting materials are expensive and scarce, justifying the development of new synthetic methodologies to prepare 7-substituted-3-methyltetral-1-one **1a-f**.

a. High interest molecules

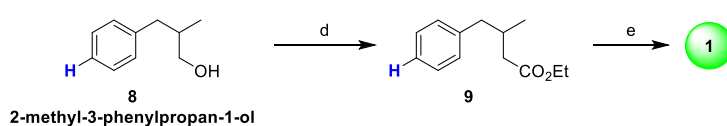


b. Previous work

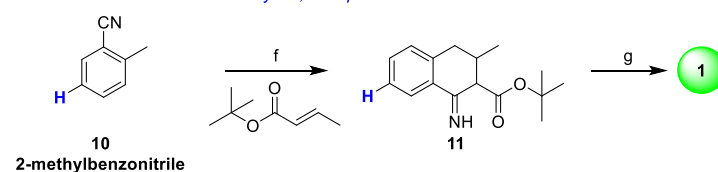
Route A: 71% overall yield, 4 steps<sup>3,5</sup>



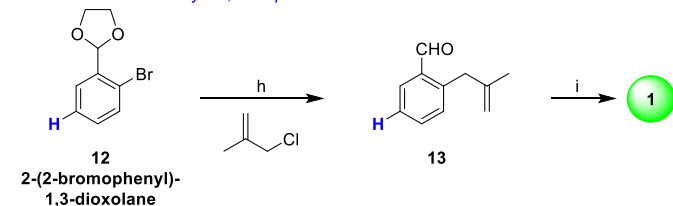
Route B: 54% overall yield, 4 steps<sup>4</sup>



Route C: undetermined overall yield, 2 steps<sup>2</sup>

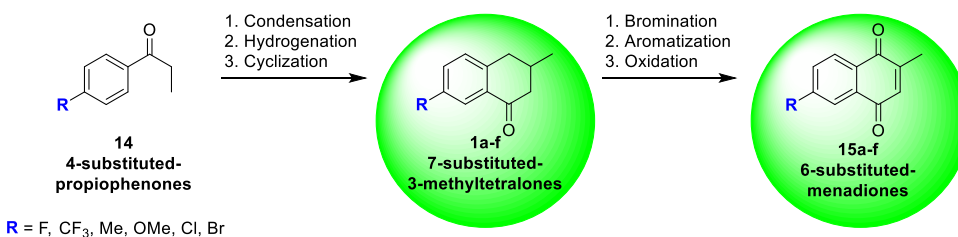


Route D: 25% overall yield, 3 steps<sup>6</sup>



**Reagents and conditions:** (a) i. cyanoacetic acid, ammonium acetate, acetic acid, benzene, reflux, 21 h, 79% ; ii. Pd/C, H<sub>2</sub>, 54 h, 99%. (b) KOH, ethanol/water (9/1, v/v), reflux, 48 h, 97%. (c) PPA, 90 °C, 2 h, 93%. (d) i. TsCl, pyridine ; ii. NaCN, methyl cellosolve, reflux ; iii. conc. H<sub>2</sub>SO<sub>4</sub>, ethanol, reflux, 68% overall. (e) 75% aq. H<sub>2</sub>SO<sub>4</sub>, 100 °C, 79%. (f) *N,N*-diisopropylamine, *n*-BuLi, diglyme, -78 °C to 0 °C, 10 min then **10**, (*E*)-*tert*-butyl but-2-enoate, -78 °C to r. t., 1 h. (g) HCl 6M, methanol, r. t. for 1 h then 70 °C for 1.5 h. (h) Mg, iodine, THF, reflux, 2 h then **12**, isobutenyl chloride, CuI, 0 °C for 2 h then r. t., overnight, 43%. (i) 3-methyl-5-(pyrrolidin-1-yl)pyridin-2-amine, aniline, benzoic acid, triphenylphosphine, PhCF<sub>3</sub>, chlorobis(cyclooctene)rhodium(I) dimer, 100 °C, 15 h, 65% (NMR yield).

c. This work



**Scheme 1.** Structure of 3-methyltetral-1-one **1** and 7-substituted-3-methyltetral-1-one **1a-f**, as key intermediates of active derivatives **2-4**, and 6-substituted-menadiones **15a-f** respectively.

Previously reported routes to efficiently synthesize 3-methyltetral-1-one **1** in the fewest possible steps, four main multi-step routes (routes A<sup>3,5</sup> – B<sup>4</sup> – C<sup>2</sup> – D<sup>6</sup>) have been widely used. Among the four routes, route A<sup>3,5</sup> is the most efficient with 71% overall yield of 3-methyltetral-1-one **1**, through 4 steps from 1-phenylpropan-2-one **5**. 3-Methyltetral-1-one **1** was prepared *via* subsequent condensation, reduction, hydrolysis, and finally acidic cyclization. In most cases of prepared 7-substituted-3-methyltetral-1-ones, the intermediates had to be isolated and purified through several column chromatography purifications and/or crystallizations.

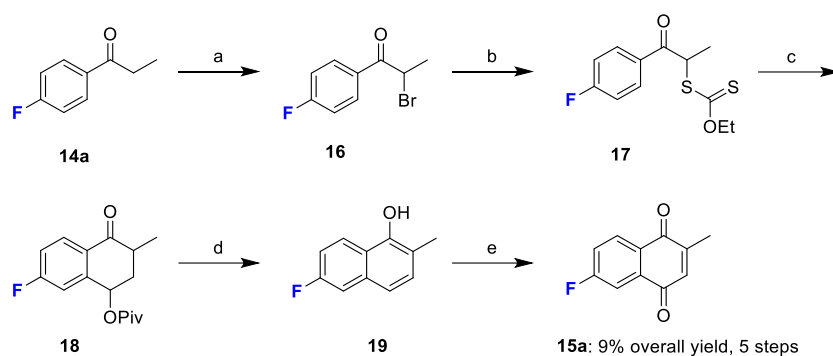
Only three 7-substituted 3-methyltetral-1-ones were produced by distinct routes: the 7-fluoro-3-methyltetral-1-one **1a** *via* a rhodium-catalyzed enantioselective hydroacylation of the 5-fluoro-2-(2-methylallyl)benzaldehyde (Route D, 9% in 5 steps from the 2-bromo-4-fluorotoluene),<sup>7</sup> the 7-methoxy-3-methyltetral-1-one **1b** (*via* a 4 steps-long sequence including a Grignard reaction with an undetermined overall yield from the available *p*-methoxybenzyl chloride),<sup>8</sup> and the 7-bromo-3-methyltetral-1-one **1c** (*via* a 3 steps Heck reaction–oxidation–acidic cyclisation sequence, 38% from the 1-bromo-4-iodobenzene), respectively.<sup>9</sup> The four methodologies are straightforward as long as the starting material is not a rare trisubstituted benzene, otherwise they are scope-limited whatever the presence of electron-withdrawing groups (fluorine, bromine) or electron-donating groups (methoxy) in the starting materials 1-phenylpropan-2-one **5** (route A), 2-methylbenzotrile **10** (route C), or the 2-bromobenzaldehyde as precursor of **12** (route D).

In this work we anticipated that the 7-substituted-3-methyltetral-1-one **1a-f** could represent useful starting-blocks to prepare complex natural compounds and synthetic analogues, various naphthalenes, or a series of 6-substituted-menadiones **15a-f** as key intermediates for the synthesis of 6-substituted-analogues of the 3-(4'-trifluoromethyl)benzylmenadione, called plasmodione through benzylation.<sup>10,11</sup> Herein, the

study was focused on the development of an efficient and robust method to enable the access to varying 7-substituted-3-methyltetralones **1a-f** and 6-substituted-menadiones **15a-f** from 4'-substituted propiophenones or 1-substituted-4-iodo-benzenes as starting materials.

## ■ RESULTS

**Previous works for the formation of 6-fluoromenadione 15a.** The choice of commercially available 6-substituted-menadiones is very limited and therefore, they are difficult to access. The previously reported synthesis to afford 6-fluoromenadione used in our laboratory was based on a 5-steps synthesis (Scheme 2).<sup>12</sup> Starting from commercial 4'-fluoropropiophenone **14a**, the 2-bromo-4'-fluoropropiophenone **16** was prepared in the presence of bromine in acetic acid,<sup>13</sup> and the corresponding xanthate **17** was formed by using potassium ethylxanthate. Then, the synthesis of the 7-fluoro-3-methyl-4-oxo-1,2,3,4-tetrahydronaphthalen-1-yl pivalate **18** was achieved, but in moderate yields, by using a xanthate-mediated free-radical addition/cyclization sequence based on the methodology pioneered by Zard and coworkers,<sup>14</sup> following radical addition of xanthate **17** to vinyl pivalate and using dilauroyl peroxide as initiator. The bicyclic molecule **18** was then treated with *p*-toluenesulfonic acid (PTSA) to form the corresponding naphthol **19**, which was then oxidized using a hypervalent iodine, diacetoxyiodobenzene (PIDA) to give the desired 6-fluoromenadione **15a**. Although, this 5-steps-long synthesis was elegant, the overall yield is only about 9% due to the very low yield of the cyclization step. In addition, the use of dilauroyl peroxide, a known hazardous reagent,<sup>15</sup> led to an unsustainable method, when it comes to multigram scale synthesis of 6-fluoromenadione. Noteworthy is to mention that the synthesis of 6-fluoromenadione **15a** through the radical addition/cyclization sequence was the only one successful process among the different approaches attempted in the first generation route.<sup>12</sup>



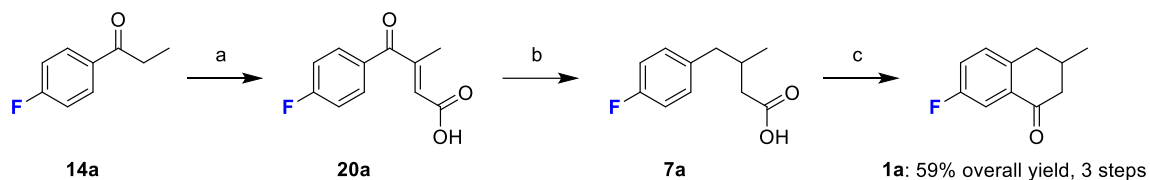
**Reagents and conditions:** (a) Bromine, acetic acid, 1-2 h, r. t., 99%. (b) Potassium *O*-ethyl xanthate, acetone, 0 °C, 57%. (c) Dilauroyl peroxide, vinyl pivalate, dichloroethane, reflux, 6-8 h, 26%. (d) PTSA, toluene, reflux, 3-4 h, 98%. (e) PIDA, MeCN, H<sub>2</sub>O, 0 °C to r. t., 65%.

## Scheme 2. First generation synthesis of 6-fluoromenadione **15a**.

Thus, it has been crucial to set up an efficient and more versatile synthetic route affording compound **15a**, using readily available starting materials. A *fac*-Ir(ppy)<sub>3</sub>-catalyzed photoredox process has recently been described to prepare naphthol **19**,<sup>16</sup> but its preparation has proved difficult in our hands under sustainable conditions (see supporting information, Scheme S1).

**7-fluoro-3-methyltetralone 1a as an intermediate for the formation of 6-fluoromenadione 15a.** An improved second generation synthesis to get access to compound **15a** has been considered by starting from 4'-fluoropropiophenone **14a** and glyoxylic acid (Scheme 3).<sup>17</sup> When added under acidic conditions, the two substrates underwent an aldolization giving a mixture of the *E* and *Z* isomers (ratio *E/Z*: 6/1) of the  $\alpha,\beta$ -unsaturated carboxylic acid **20a**. This mixture was then reduced using palladium on charcoal under a hydrogen atmosphere to obtain compound **7a** (see supporting information, Table S1 for optimization conditions).<sup>18</sup> Finally, the latter was cyclized in the presence of polyphosphoric acid (PPA) by forming an activated species,<sup>18</sup> the carboxylic-phosphoric anhydride,<sup>19</sup> which was then reactive enough to react with the aromatic ring by an electrophilic aromatic substitution and to form the tetralone **1a** in an overall yield of 59%. Through these three simple steps, it is possible to explore a library of new

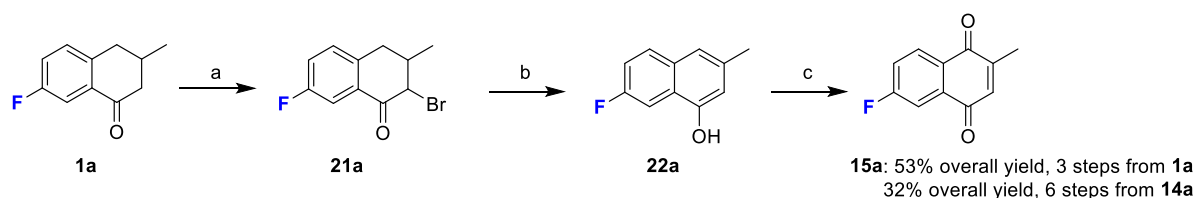
7-substituted-3-methyltetral-1-one derivatives **1a-f**, as potential starting-blocks for complex compound chemistry.



**Reagents and conditions:** (a) Glyoxylic acid, sulfuric acid, dioxane, reflux, 83%. (b) Pd/C, H<sub>2</sub>, acetic acid, 70 °C, overnight, 94%. (c) PPA, 90 °C, overnight, 76%.

**Scheme 3.** Three synthetic steps towards 7-fluoro-3-methyltetral-1-one **1a**.

**Synthetic pathway to obtain 6-fluoromenadione 15a.** The 7-fluoro-3-methyltetral-1-one **1a** was treated with *N*-bromosuccinimide (NBS) and PTSA to brominate the alpha position of the ketone giving the 2-bromo-7-fluoro-3-methyltetral-1-one **21a** (Scheme 4).<sup>20</sup> This bromoketone was then aromatized in the presence of lithium carbonate based on previously described procedures but slightly modified (see supporting information, Table S2 for optimization conditions) to form naphthol **22a**.<sup>21,22</sup> Finally, the 6-fluoromenadione **15a** was obtained after oxidation with PIDA (see supporting information, Table S3 for optimization conditions).<sup>12</sup> Noteworthy is to mention that each step was followed by a chromatographic purification during the optimization of the methodology, despite the little amount of side products giving an overall yield of 32% over six steps, versus 9% using the first generation route.



**Reagents and conditions:** (a) *N*-bromosuccinimide, PTSA, dichloromethane, reflux, 3.5 h, 94%. (b) Lithium carbonate, dimethylformamide, 100 °C, 2 h, 71%. (c) PIDA, acetonitrile, water, 0 °C to r. t., 1.5 h, 80%.

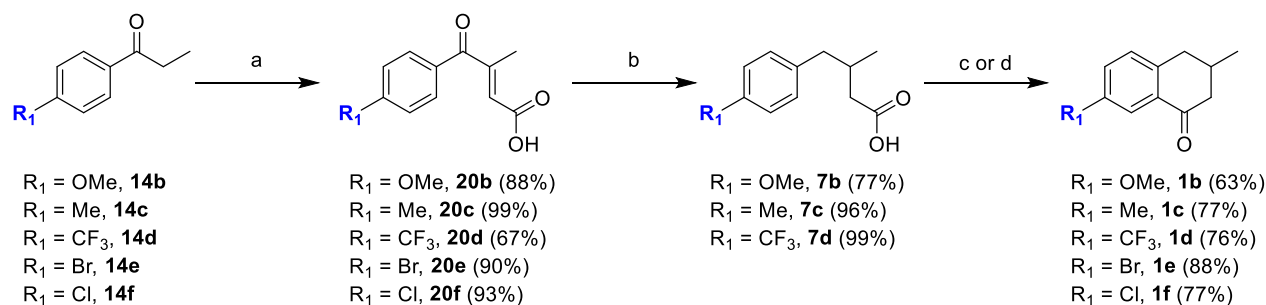
**Scheme 4.** Synthesis of 6-fluoromenadione **15a** by successive aromatization then oxidation.

Next, the synthesis was then performed with only one purification step after the final oxidation to get the 6-fluoromenadione with an overall yield of 50% and starting from 25 g of 4'-fluoropropiophenone **14a**. It has been shown that this new straightforward synthesis enables the access to bulk 6-fluoromenadione **15a** by using readily available starting materials, being timesaving because of almost no purification step and scalability. Further investigations have also led to expand the scope of this new methodology, which the previous approaches fell short of, to access an array of 7-substituted-3-methyltetral-1-one derivatives **1b-f** and 6-substituted-menadione derivatives **15b-f** from various commercially available electron-rich and -poor substrates.

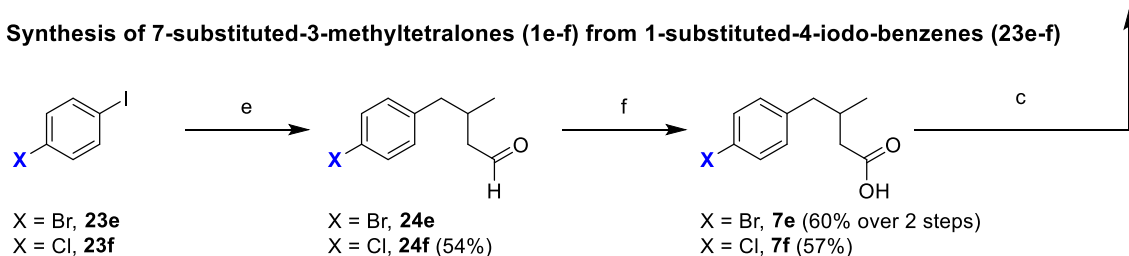
**Application to other 7-substituted-3-methyltetralones 1b-f and 6-substituted-menadiones 15b-f.** Gram scale synthesis of 6-methoxymenadione **15b** and 6-methylmenadione **15c** was performed according to this strategy from commercially available 4'-methoxypropiophenone **14b** and 4'-methylpropiophenone **14c**, with 12% and 35% over 6 steps, respectively (Scheme 5), versus 33% and 70% through the first generation route.<sup>12</sup> Nevertheless, the scope of the second generation route lies mainly to the generation of 7-substituted-3-methyl-naphthols **20b** and **20c** (e.g. 7-methoxy and 7-methyl groups, produced with 35% and 43% yield, respectively), which are regioisomers of the reported 7-substituted-2-methyl-naphthols produced in the first generation route.

In order to highlight trends of the second generation route we applied the synthesis to a variety of menadiones substituted at C-6 by electron-withdrawing groups such as the trifluoromethyl group and other halogens, chlorine and bromine.

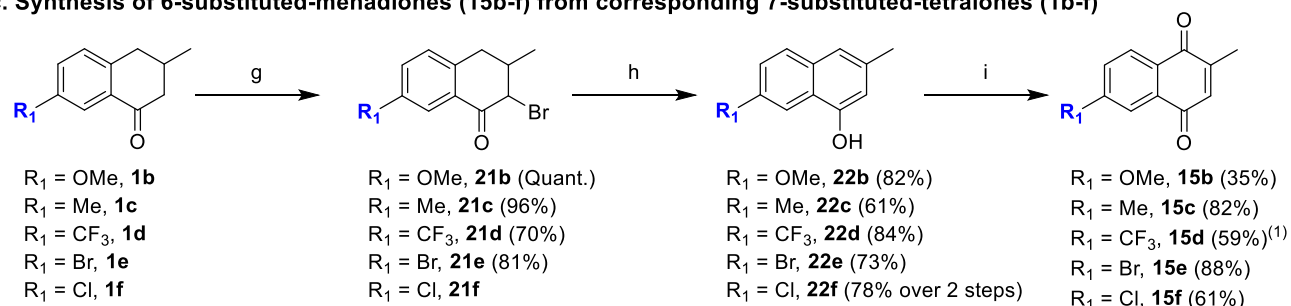
**a. Synthesis of 7-substituted-3-methyltetralones (1b-d) from 4'-substituted propiophenones (14b-d)**



**b. Synthesis of 7-substituted-3-methyltetralones (1e-f) from 1-substituted-4-iodo-benzenes (23e-f)**



**c. Synthesis of 6-substituted-menadiones (15b-f) from corresponding 7-substituted-tetralones (1b-f)**



**Reagents and conditions:** (a) Glyoxylic acid, sulfuric acid, dioxane, reflux. (b) Pd/C, H<sub>2</sub>, acetic acid, 70 °C, 18 h. (c) PPA, 90 °C, 18 h. (d) TFAA, trifluoromethanesulfonic acid, dichloromethane, r. t., 1 h. (e) 3-methyl-3-buten-1-ol, lithium acetate, lithium chloride, Bu<sub>4</sub>NCl, PdOAc<sub>2</sub>, dimethylformamide, 70 °C, 72 h. (f) Periodic acid, PCC, acetonitrile, 0 °C to r. t., 3.5 h. (g) *N*-bromosuccinimide, PTSA, dichloromethane, reflux, 3.5 h. (h) Lithium carbonate, dimethylformamide, 100 °C, 2 h. (i) PIDA, acetonitrile, water, 0 °C to r. t., 1.5 h.

<sup>(1)</sup> Done at -5 °C instead of r. t.

**Scheme 5. Synthesis of 7-substituted-3-methyltetralones 1b-f and 6-substituted-menadiones 15b-f.**

The condensation between 4'-(trifluoromethyl)propiophenone **14d** and glyoxylic acid was performed to build the enoic acid **20d**. Then, the hydrogenation using palladium on charcoal led to acid **7d** with an excellent yield. During the cyclization step, a low yield (23%) was obtained using PPA. Several conditions were tested to increase this yield (Table 1). First, PPA was replaced by phosphoryl chloride (entry 2) but no reaction was observed.<sup>23</sup> Triflic acid was used

instead of PPA, at room temperature, and the yield was increased to 34% (entry 3).<sup>24</sup> Finally, the combination of triflic acid and trifluoroacetic anhydride gave us the best result for the cyclization of **7d** with 95% yield (entry 4).<sup>25</sup>

**Table 1.** Optimization of the cyclization step.

Entry	Reactant	Temperature	Time (h)	Yield (%)
1	PPA	90 °C	18	23
2	POCl <sub>3</sub>	r. t.	120	0
3	TfOH	r. t.	4	34
<b>4</b>	<b>TfOH, TFAA</b>	<b>r. t.</b>	<b>1</b>	<b>95</b>

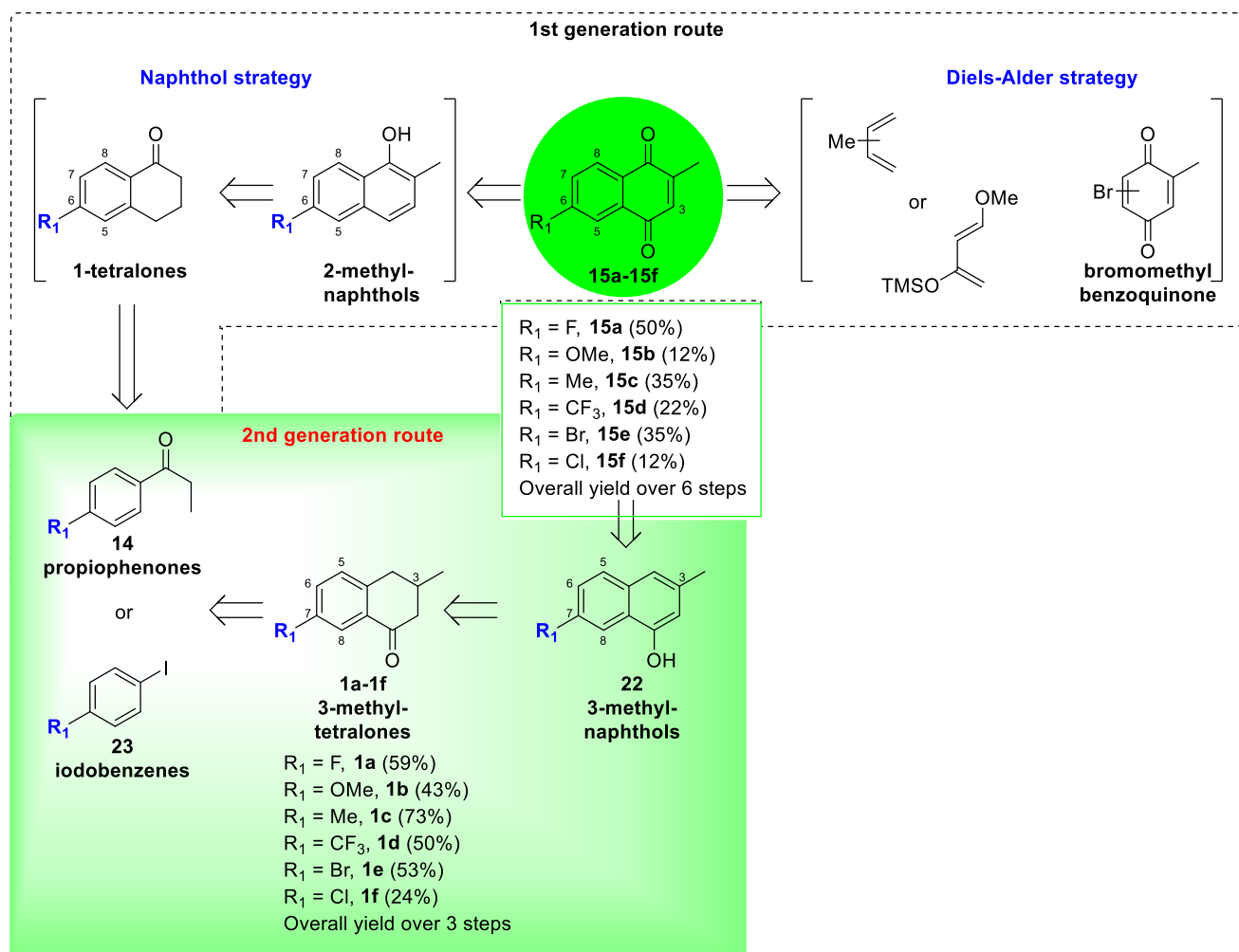
After the cyclization, 3-methyl-7-(trifluoromethyl)tetral-1-one **1d** was brominated with NBS and transformed in naphthol **23d**. Finally, 6-(trifluoromethyl)menadione **15d** was obtained by oxidation with PIDA. Nevertheless, at room temperature, **15d** was obtained with 24% yield only while decreasing the temperature to -5 °C allowed us to improve the yield to 59%. Thus, the 6-(trifluoromethyl)menadione **15d** was obtained with 22% overall yield in 6 steps.

The synthesis of both 6-bromomenadione **15e** and 6-chloromenadione **15f** from 4'-bromopropiophenone **14e** and 4'-chloropropiophenone **14f** were also considered. The aldolisation step with glyoxylic acid led to the corresponding acids **20e** and **20f**, with 90% and 93% yields, respectively. However, during the hydrogenation step, a mixture of several inseparable products was obtained. The substitution of bromide/chloride atom by a hydrogen atom was observed upon NMR spectra analysis. To avoid this problem, another strategy was investigated following Sleeb's *et al.*'s method.<sup>9</sup> A Heck coupling between 1-bromo-4-iodobenzene **23e** and 3-methyl-3-buten-1-ol was applied to form aldehyde **24e**, which was

oxidized by pyridinium chlorochromate (PCC) to obtain the corresponding acid **7e** with 60% yield over 2 steps. An independent preparation of **24e** followed by a chromatography column purification showed that the compound **24e** was isolated with 35% yield. This Heck coupling was also performed with 1-chloro-4-iodobenzene **23f** giving aldehyde **24f** (54%). Acid **7f** was obtained with 57% yield by oxidation of **24f** using PCC. From both acids **7e** and **7f**, 7-bromo-3-methyltetralone **1e** and 7-chloro-3-methyltetralone **1f** were obtained through cyclisation by PPA with 88% and 77% yield, respectively. Then, 6-bromomenadione **15e** and 6-chloromenadione **15f** were synthesized by following the 6 steps-sequence with 35% and 12% overall yields, respectively. Both will represent useful key intermediates in future medicinal chemistry schemes. Noteworthy is to mention that the synthesis of 6-(trifluoromethyl)menadione **15d** is reported for the 1<sup>st</sup> time and that of 6-chloromenadione **15f** gave 7% yield over 5 steps in the first generation route.

## ■ DISCUSSION

In our previous strategies, we studied two key routes (Scheme 2 of ref. 12): the Diels-Alder route and the 1-naphthol route, as part of the so-called "first generation route" to produce polysubstituted 2-methyl-1,4-naphthoquinones. This pioneering work allowed us to draw the first trend of synthetic methodologies to produce menadiones substituted at C-6 or C-7 with electron-donating groups (Me, OMe) *via* the one-step Diels-Alder reaction, or the 2-methyltetralone route from the only commercial tetralones or propiophenones readily available at that time (Scheme 6). In the case of electron-withdrawing groups (halogens), the C-6 or C-7 substituted menadiones could only be produced by the xanthate route,<sup>14</sup> albeit in low yields (F, Cl), *via* the key 2-methylnaphthols intermediates. But there was no versatile methodology to produce a wide variety of polysubstituted 2-methyl-1,4-naphthoquinones through the same synthetic pathway.



**Scheme 6.** Overview of the synthetic approaches developed in both, the first and second generation routes to prepare the 6-substituted-menadione analogues ( $R_1 = \text{F}$ , OMe, Me,  $\text{CF}_3$ , Br, Cl).

Herein, in the “second generation route”, we developed a new strategy to produce polysubstituted 2-methyl-1,4-naphthoquinones regardless the presence of electron-donating (Me, OMe) or -withdrawing groups (F, Cl, Br,  $\text{CF}_3$ ), over six steps in a more sustainable and high-yielding process (Scheme 6, green box). The route was designed via two key intermediates, the 7-substituted-3-methyl tetralones and 3-methylnaphthols, which are also of high value starting-blocks for natural product and medicinal chemistry. This new 6-step-long process allowed us to produce, in addition to the corresponding diverse 7-substituted-3-methyltetral-1-ones and 3-methylnaphthols, the 6-fluoromenadione with 50% yield from 25 g

starting material, the 6-bromomenadione ready for post-functionalization at C-6, the 6-chloromenadione and, for the first time, the 6-trifluoromethylmenadione.

## ■ CONCLUSIONS

In conclusion, we have developed efficient and convergent synthetic pathways for the multigram preparation of diverse 7-substituted-3-methyltetral-1-ones and 6-substituted-menadiones. This second generation strategy led to a broader substrate scope for the synthesis of new 6-substituted-menadiones over six steps and could be applied with a wide variety of electron-withdrawing or -donating substituents on 4'-substituted-propiophenones or 1-substituted-4-iodo-benzenes. Only one purification was required at the end of the synthesis. The main advantages include the use of readily available reagents, and the possibility to produce key building-blocks under sustainable conditions to potentially access to active pharmaceutical ingredients on scale through post-functionalization and introduction of structural diversity.

## ■ EXPERIMENTAL SECTION

**General Information.** Starting materials and reagents were obtained from Sigma-Aldrich, ABCR GmbH & Co., Alfa Aesar, Fluorochem and Apollo Scientific and used without further purification. Solvents were obtained from Carlo Erba, VWR and Fisher Scientific. All reactions were performed in standard glassware. Thin-layer chromatography (TLC) were performed using Merck silica gel plates (60 F-254, 0.25 mm) on aluminum sheets and revealed under UV lamp (325 and 254 nm). Crude mixtures were purified by flash column chromatography on silica gel 60 (230-400 mesh, 0.040-0.063 mm) purchased from VWR. NMR spectra were recorded on a Bruker Avance 400 apparatus ( $^1\text{H}$  NMR, 400 MHz -  $^{13}\text{C}$  NMR, 101 MHz -  $^{19}\text{F}$  NMR, 377 MHz) or Bruker Avance III HD 500 MHz apparatus ( $^1\text{H}$  NMR, 500 MHz -  $^{13}\text{C}$  NMR, 126 MHz -  $^{19}\text{F}$  NMR, 471 MHz) at the ECPM. All chemical shifts ( $\delta$ ) are quoted in parts per million (ppm). The chemical shifts are referred to the used partial deuterated NMR solvent ( $\text{CDCl}_3$ :  $^1\text{H}$  NMR, 7.26 ppm and  $^{13}\text{C}$  NMR, 77.16 ppm -  $\text{CD}_3\text{CN}$ :  $^1\text{H}$  NMR, 1.94 ppm and  $^{13}\text{C}$  NMR, 1.32 ppm and 118.26 ppm). The coupling constants (J) are given in Hertz (Hz). Resonance patterns are reported with the following notations: br (broad), s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), dd (doublet of doublets). High-resolution mass spectrometry (HRMS) analyses were performed with a Bruker MicroTOF mass analyzer under ESI in the positive or negative ionization mode detection or APCI in the positive ionization mode detection (measurement accuracy  $\leq 15$  ppm) at the Service de Spectrométrie de Masse Fédération Chimie Le Bel in Strasbourg. Melting point are measured on Stuart SMP10 with temperature accuracy of  $\pm 1.0$  °C at 20 °C and  $\pm 2.5$  °C at 300 °C.

### **General procedure A. Aldol condensation between propiophenone and glyoxylic acid.**

To a solution of 4'-substituted-propiophenone **14** (1.0 equiv.) and glyoxylic acid monohydrate (1.5 equiv.) in dioxane (0.8 M) was added dropwise sulfuric acid (3.6 equiv.). The solution was

stirred overnight at reflux. The resulting mixture was cooled down at room temperature and poured into water. The aqueous phase was extracted with diethyl ether, then the organic layer was washed 5 times with a 10% K<sub>2</sub>CO<sub>3</sub> aqueous solution. The pH of the aqueous layer was adjusted to acidic (pH 1) with a 3 M aqueous solution of hydrochloric acid and extracted three times with diethyl ether. The organic layer was dried over MgSO<sub>4</sub> and evaporated under reduced pressure. Dioxane was removed by a filtration on silica gel (cyclohexane then methanol) to afford the expected product as a mixture of isomers *E/Z*.

**General procedure B. Hydrogenation.** Under argon, palladium on carbon (0.05 equiv.) was poured into a round bottom flask followed by a solution of enoic acid **20** (1.0 equiv.) in acetic acid (0.3 M). Then, a hydrogen atmosphere was created and the mixture reaction was vigorously stirred overnight at 70 °C. After cooling down at room temperature, the mixture reaction was poured on celite, filtrated and washed using acetic acid. The organic phase was concentrated under reduced pressure and purified by flash chromatography on silica gel to give the expected product.

**General procedure C. Intramolecular cyclization with PPA.** Polyphosphoric acid was added into a flask containing acid **7** (1.0 equiv.). The reaction mixture was stirred slowly overnight at 90 °C. After TLC check, the mixture was poured on ice water until PPA was completely dissolved by using sonicator. Then, the aqueous phase was extracted with ethyl acetate (3 times). The re-united organic phases were washed with brine, dried over MgSO<sub>4</sub> and concentrated under reduced pressure. The crude residue was purified by flash chromatography on silica gel affording the expected product.

**General procedure D. Bromination with *N*-bromosuccinimide.** A solution of 7-substituted-3-methyltetral-1-one **1** (1.0 equiv.) in dichloromethane (0.7 M) was added dropwise to a solution

of *N*-bromosuccinimide (1.0 equiv.) and *p*-toluenesulfonic acid monohydrate (0.1 equiv.) in dichloromethane (0.7 M) at 0 °C. The reaction mixture was stirred at reflux for 3.5 h. After addition of water, the organic layer was separated and the aqueous layer was extracted with dichloromethane. The combined organic layers were washed with a saturated aqueous solution of NaHCO<sub>3</sub> and brine, dried over MgSO<sub>4</sub> and concentrated under reduced pressure. The crude residue was purified by flash chromatography on silica gel to afford the expected product as a mixture of isomers.

**General procedure E. Naphthol formation.** To a solution of 2-bromotetral-1-one **21** (1.0 equiv.) in dimethylformamide (0.2 M) was added lithium carbonate (1.1 equiv.). The reaction mixture was stirred at 100 °C for 4.5 h. After cooling down at room temperature, this reaction mixture was treated with ice-cold water and extracted with diethyl ether (3x). The combined extracts were washed with a 1M aqueous solution of HCl, then with brine, dried over MgSO<sub>4</sub>, and concentrated under reduced pressure. The crude was purified by flash chromatography on silica gel to give the expected product.

**General procedure F. Oxidation with PIDA.** A solution of naphthol **22** (1.0 equiv.) in a mixture of acetonitrile and water (3/1, v/v, 0.05 M) was prepared. At 0 °C, (diacetoxyiodo)benzene (2.1 equiv.) was added portionwise to the stirring solution. The mixture reaction was stirred for 30 minutes at 0 °C then at room temperature for 1 h. A saturated aqueous solution of NaHCO<sub>3</sub> was added to the yellow mixture and it was extracted with ethyl acetate. The organic phases were washed with brine, dried over MgSO<sub>4</sub> and concentrated under reduced pressure. The crude mixture was purified by flash chromatography on silica gel giving the expected product.

**4-(4-fluorophenyl)-3-methyl-4-oxobut-2-enoic acid (20a).** According to the general procedure A, 4'-fluoropropionic acid **14a** was used. 559 mg (83% yield, beige solid, ratio *E/Z*:

6/1) of **20a** were isolated after filtration. **<sup>1</sup>H NMR (500 MHz, CD<sub>3</sub>CN)**: (\*refers to the minor isomer when unambiguous distinction is possible) δ 7.90-7.84 (m, 2H), 7.48\* (t, *J* = 7.1 Hz, 0.36H), 7.27-7.20 (m, 2H), 7.15\* (t, *J* = 8.7 Hz, 0.36H), 6.08 (q, *J* = 1.6 Hz, 1H), 5.90\* (s, 0.16H), 2.32 (d, *J* = 1.6 Hz, 3H), 1.84\* (s, 0.48H). **<sup>13</sup>C {<sup>1</sup>H} NMR (126 MHz, CD<sub>3</sub>CN)**: (\*refers to the minor isomer when unambiguous distinction is possible) δ 197.4, 167.2, 166.7 (d, <sup>1</sup>*J*<sub>C-F</sub> = 252.6 Hz), 152.8, 133.6 (d, <sup>3</sup>*J*<sub>C-F</sub> = 9.5 Hz, 2C), 133.3 (d, <sup>3</sup>*J*<sub>C-F</sub> = 3.0 Hz, 2C), 128.9\*, 125.7, 117.6\*, 116.6 (d, <sup>2</sup>*J*<sub>C-F</sub> = 22.3 Hz, 2C), 116.3\* (d, <sup>2</sup>*J*<sub>C-F</sub> = 21.8 Hz, 2C), 15.7, 12.5\*. **<sup>19</sup>F NMR (471 MHz, CD<sub>3</sub>CN)**: (\*refers to the minor isomer when unambiguous distinction is possible) δ -106.90 – -107.05 (m), -114.38\* – -114.47\* (m). **HRMS (ESI+)** *m/z*: [M+Na]<sup>+</sup> calculated for C<sub>11</sub>H<sub>9</sub>FNao<sub>3</sub>: 231.042793, found 231.042751.

**4-(4-fluorophenyl)-3-methylbutanoic acid (7a)**. According to general procedure B, 463 mg (94% yield, colourless oil) of **7a** were isolated by flash chromatography on silica gel (Dichloromethane then ethyl acetate). **<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)**: δ 7.14-7.09 (m, 2H), 7.00-6.95 (m, 2H), 2.63 (dd, *J* = 13.6, 6.6 Hz, 1H), 2.50 (dd, *J* = 13.6, 7.4 Hz, 1H), 2.36 (dd, *J* = 14.7, 5.5 Hz, 1H), 2.30-2.16 (m, 2H), 0.98 (d, *J* = 6.5 Hz, 3H). **<sup>13</sup>C {<sup>1</sup>H} NMR (126 MHz, CDCl<sub>3</sub>)**: δ 179.8, 161.6 (d, <sup>1</sup>*J*<sub>C-F</sub> = 243.7 Hz), 135.8 (d, <sup>4</sup>*J*<sub>C-F</sub> = 3.3 Hz), 130.7 (d, <sup>3</sup>*J*<sub>C-F</sub> = 7.7 Hz, 2C), 115.2 (d, <sup>2</sup>*J*<sub>C-F</sub> = 21.1 Hz, 2C), 42.1, 40.9, 32.3, 19.6. **<sup>19</sup>F NMR (471 MHz, CDCl<sub>3</sub>)**: δ -117.17 – -117.25 (m). **HRMS (ESI-)** *m/z*: [M-H]<sup>-</sup> calculated for C<sub>11</sub>H<sub>12</sub>FO<sub>2</sub>: 195.082681, found 195.083335.

**7-fluoro-3-methyl-3,4-dihydronaphthalen-1(2H)-one (1a)**. According to general procedure C, 304 mg (76% yield, yellow-beige solid) of **1a** were isolated by flash chromatography on silica gel (Toluene/ethyl acetate, 9/1, v/v, UV). **M.p.** = 50-54 °C. **<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)**: δ 7.63 (dd, *J* = 9.1, 2.8 Hz, 1H), 7.20 (dd, *J* = 8.3, 5.3 Hz, 1H), 7.14 (td, *J* = 8.3, 2.8 Hz, 1H), 2.96-2.92 (m, 1H), 2.73-2.68 (m, 1H), 2.64-2.59 (m, 1H), 2.33-2.23 (m, 2H), 1.12 (d, *J* = 6.3 Hz, 3H). **<sup>13</sup>C {<sup>1</sup>H} NMR (126 MHz, CDCl<sub>3</sub>)**: δ 197.5 (d, <sup>4</sup>*J*<sub>C-F</sub> = 1.9 Hz), 161.6 (d, <sup>1</sup>*J*<sub>C-F</sub> = 246.1 Hz), 139.5 (d,

$^4J_{C-F} = 3.1$  Hz), 133.8 (d,  $^3J_{C-F} = 6.2$  Hz), 130.7 (d,  $^3J_{C-F} = 7.1$  Hz), 120.8 (d,  $^2J_{C-F} = 22.2$  Hz), 112.9 (d,  $^2J_{C-F} = 21.9$  Hz), 46.8, 37.3, 30.6, 21.3.  **$^{19}\text{F}$  NMR (471 MHz,  $\text{CDCl}_3$ ):**  $\delta$  -115.26 – -115.31 (m). **HRMS (ESI+)**  $m/z$ :  $[\text{M}+\text{H}]^+$  calculated for  $\text{C}_{11}\text{H}_{12}\text{FO}$ : 179.086670, found 179.085306.

**2-bromo-7-fluoro-3-methyl-3,4-dihydronaphthalen-1(2H)-one (21a).** According to general procedure D, 132 mg (94 % yield, yellowish oil) of **21a** were isolated by flash chromatography on silica gel (Toluene/cyclohexane, 8/2, v/v, UV).  **$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):** (\*refers to the minor isomer when unambiguous distinction is possible)  $\delta$  7.77-7.73 (m, 1H), 7.28-7.24 (m, 2H), 4.55 (dd,  $J = 2.7, 1.2$  Hz, 0.62H), 4.47\* (br d,  $J = 4.0$  Hz, 0.38H), 3.44\* (ddd,  $J = 16.8, 4.5, 1.3$  Hz, 0.38H), 2.98-2.88 (m, 0.62H), 2.81-2.72 (m, 1H), 2.70-2.63\* (m, 0.38H), 2.28 (dddt,  $J = 11.1, 6.4, 4.7, 2.4$  Hz, 0.62H), 1.25 (d,  $J = 6.5$  Hz, 1.8H), 1.23\* (d,  $J = 7.0$  Hz, 1.2H).  **$^{13}\text{C}$  { $^1\text{H}$ } NMR (101 MHz,  $\text{CDCl}_3$ ):** (\*refers to the minor isomer when unambiguous distinction is possible)  $\delta$  190.1 (d,  $^4J_{C-F} = 2.0$  Hz), 189.7\* (d,  $J = 1.9$  Hz), 161.7 (d,  $^1J_{C-F} = 247.0$  Hz), 138.6 (d,  $^4J_{C-F} = 3.1$  Hz), 137.0\* (d,  $^4J_{C-F} = 3.1$  Hz), 131.3\* (d,  $^3J_{C-F} = 6.5$  Hz), 131.2 (d,  $^3J_{C-F} = 7.2$  Hz), 131.0\* (d,  $^3J_{C-F} = 6.5$  Hz), 130.7 (d,  $^3J_{C-F} = 7.2$  Hz), 121.9\* (d,  $^2J_{C-F} = 22.2$  Hz), 121.6 (d,  $^2J_{C-F} = 22.2$  Hz), 114.4 (d,  $^2J_{C-F} = 22.1$  Hz), 114.1\* (d,  $^2J_{C-F} = 22.2$  Hz), 58.1, 55.9\*, 37.2\*, 34.6, 33.3\*, 32.8, 19.02\*, 18.95.  **$^{19}\text{F}$  NMR (377 MHz,  $\text{CDCl}_3$ ):**  $\delta$  -114.23 – -114.39 (m). **HRMS (APCI+)**  $m/z$ :  $[\text{M}+\text{H}]^+$  calculated for  $\text{C}_{11}\text{H}_{11}\text{BrFO}$ : 256.9972, found 256.9985.

**7-fluoro-3-methylnaphthalen-1-ol (22a).** According to general procedure E, 288 mg (71% yield, brown-cream solid) of **22a** were obtained by flash chromatography on silica gel (Toluene/cyclohexane, gradient from 7/3 to 10/0, v/v, UV). **M.p.** = 119-120 °C.  **$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):**  $\delta$  7.73 (dd,  $J = 10.3, 2.6$  Hz, 1H), 7.69 (dd,  $J = 9.0, 5.5$  Hz, 1H), 7.27-7.17 (m, 2H), 6.68 (s, 1H), 5.12 (s, 1H), 2.43 (s, 3H).  **$^{13}\text{C}$  { $^1\text{H}$ } NMR (101 MHz,  $\text{CDCl}_3$ ):**  $\delta$  160.1 (d,  $^1J_{C-F} = 243.9$  Hz), 150.8 (d,  $^4J_{C-F} = 5.3$  Hz), 135.1 (d,  $^4J_{C-F} = 2.6$  Hz), 132.0, 129.4 (d,  $^3J_{C-F} = 8.7$  Hz),

123.4 (d,  $^3J_{C-F} = 8.8$  Hz), 119.8 (d,  $^5J_{C-F} = 1.3$  Hz), 116.9 (d,  $^2J_{C-F} = 25.3$  Hz), 111.7, 105.6 (d,  $^2J_{C-F} = 22.1$  Hz), 21.7.  **$^{19}\text{F}$  NMR (377 MHz,  $\text{CDCl}_3$ ):**  $\delta$  -116.11 – -116.17 (m). **HRMS (ESI-)  $m/z$ :** [M-H]<sup>-</sup> calculated for  $\text{C}_{11}\text{H}_8\text{FO}$ : 175.056467, found 175.057008.

**6-fluoro-2-methylnaphthalene-1,4-dione (15a).** According to general procedure F, 77 mg (80% yield, yellow solid) of **15a** were obtained by flash chromatography on silica gel (Cyclohexane/ethyl acetate, 9/1, v/v, UV). **M.p.** = 90-93 °C.  **$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):**  $\delta$  8.14 (dd,  $J = 8.6, 5.2$  Hz, 1H), 7.69 (dd,  $J = 8.5, 2.7$  Hz, 1H), 7.38 (ddd,  $J = 8.6, 8.0, 2.7$  Hz, 1H), 6.87 (qd,  $J = 1.6, 0.5$  Hz, 1H), 2.20 (d,  $J = 1.6$  Hz, 3H).  **$^{13}\text{C}$  { $^1\text{H}$ } NMR (101 MHz,  $\text{CDCl}_3$ ):**  $\delta$  184.4, 183.9 (d,  $^4J_{C-F} = 1.6$  Hz), 166.1 (d,  $^1J_{C-F} = 257.3$  Hz), 148.7, 135.8 (d,  $^5J_{C-F} = 2.0$  Hz), 135.0 (d,  $^3J_{C-F} = 7.8$  Hz), 130.0 (d,  $^3J_{C-F} = 8.9$  Hz), 128.9 (d,  $^4J_{C-F} = 3.3$  Hz), 120.9 (d,  $^2J_{C-F} = 22.5$  Hz), 113.0 (d,  $^2J_{C-F} = 23.4$  Hz), 16.5.  **$^{19}\text{F}$  NMR (377 MHz,  $\text{CDCl}_3$ ):**  $\delta$  -102.06 – -102.12 (m). **HRMS (ESI+)  $m/z$ :** [M+H]<sup>+</sup> calculated for  $\text{C}_{11}\text{H}_8\text{FO}_2$ : 191.050284, found 191.050891.

**4-(4-methoxyphenyl)-3-methyl-4-oxobut-2-enoic acid (20b).** According to the general procedure A, 4'-methoxypropionic acid **14b** was used. 2.8 g (88% yield, white solid, ratio *E/Z*: 3.9/1) of **20b** were isolated after filtration.  **$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):** (\*refers to the minor isomer when unambiguous distinction is possible)  $\delta$  7.83 (d,  $J = 8.9$  Hz, 2H), 6.93 (d,  $J = 8.9$  Hz, 2H), 6.92\* (d,  $J = 8.9$  Hz, 0.8H), 6.06 (d,  $J = 1.9$  Hz, 1H), 5.92\* (s, 0.26H), 3.88 (s, 3H), 3.84\* (s, 1H), 2.41 (s, 3H), 2.05\* (s, 1H).  **$^{13}\text{C}$  { $^1\text{H}$ } NMR (126 MHz,  $\text{CDCl}_3$ ):** (\*refers to the minor isomer when unambiguous distinction is possible)  $\delta$  196.5, 171.2, 164.2, 155.6\*, 132.5 (2C), 128.0, 122.4, 114.2 (2C), 114.1, 55.7, 55.6\*, 16.5. **HRMS (ESI+)  $m/z$ :** [M+Na]<sup>+</sup> calculated for  $\text{C}_{12}\text{H}_{12}\text{NaO}_4$ : 243.062780, found 243.062339.

**4-(4-methoxyphenyl)-3-methylbutanoic acid (7b).** According to general procedure B, 2.0 g (77% yield, orange oil) of **7b** were isolated by flash chromatography on silica gel (Cyclohexane, then dichloromethane, then ethyl acetate).  **$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):**  $\delta$  7.08 (d,  $J = 8.5$  Hz,

2H), 6.85-6.81 (m, 2H), 3.79 (s, 3H), 2.58 (dd,  $J = 13.6, 6.8$  Hz, 1H), 2.48 (dd,  $J = 13.6, 7.2$  Hz, 1H), 2.37 (dd,  $J = 14.6, 5.2$  Hz, 1H), 2.27-2.21 (m, 1H), 2.15 (dd,  $J = 14.6, 8.0$  Hz, 1H), 0.97 (d,  $J = 6.5$  Hz, 3H).  **$^{13}\text{C}$  { $^1\text{H}$ } NMR (101 MHz,  $\text{CDCl}_3$ ):**  $\delta$  179.6, 158.1, 132.3, 130.3 (2C), 113.8 (2C), 55.4, 42.1, 40.8, 32.4, 19.7. **HRMS (ESI+)**  $m/z$ :  $[\text{M}+\text{Na}]^+$  calculated for  $\text{C}_{12}\text{H}_{16}\text{NaO}_3$ : 231.099165, found 231.098129.

**7-methoxy-3-methyl-3,4-dihydronaphthalen-1(2H)-one (1b).** According to general procedure C, 1.1 g (63% yield, orange oil) of **1b** were isolated by flash chromatography on silica gel (Cyclohexane/ethyl acetate, 9/1, v/v, UV).  **$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):**  $\delta$  7.50 (d,  $J = 2.8$  Hz, 1H), 7.15 (d,  $J = 8.4$  Hz, 1H), 7.05 (dd,  $J = 8.4, 2.8$  Hz, 1H), 3.83 (s, 3H), 2.94-2.89 (m, 1H), 2.73-2.70 (m, 1H), 2.64-2.58 (m, 1H), 2.33-2.23 (m, 2H), 1.13 (d,  $J = 6.1$  Hz, 3H).  **$^{13}\text{C}$  { $^1\text{H}$ } NMR (101 MHz,  $\text{CDCl}_3$ ):**  $\delta$  197.9, 158.1, 136.1, 132.8, 129.8, 121.4, 108.8, 55.1, 46.8, 37.0, 30.5, 21.2. **HRMS (ESI+)**  $m/z$ :  $[\text{M}+\text{Na}]^+$  calculated for  $\text{C}_{12}\text{H}_{14}\text{NaO}_2$ : 213.088600, found 213.088658.

**2-bromo-7-methoxy-3-methyl-3,4-dihydronaphthalen-1(2H)-one (21b).** According to general procedure D, 1.6 g (Quant., orange oil) of **21b** were isolated by flash chromatography on silica gel (Toluene, UV).  **$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):** (\*refers to the minor isomer when unambiguous distinction is possible)  $\delta$  7.55 (d,  $J = 2.8$  Hz, 0.55H), 7.53\* (d,  $J = 2.8$  Hz, 0.45H), 7.17\* (br s, 0.35H), 7.15 (br s, 0.65H), 7.11 (dd,  $J = 5.2, 2.8$  Hz, 0.55H), 7.09\* (dd,  $J = 5.2, 2.8$  Hz, 0.45H), 4.53 (dd,  $J = 2.6, 1.2$  Hz, 0.55H), 4.45-4.43\* (m, 0.45H), 3.83 (s, 3H), 3.37\* (dd,  $J = 16.4, 4.2$  Hz, 0.45H), 2.86 (ddd,  $J = 16.9, 10.7, 1.0$  Hz, 0.55H), 2.75-2.56 (m, 1.45H), 2.30-2.19 (m, 0.55H), 1.21 (d,  $J = 6.4$  Hz, 1.65H), 1.20 (d,  $J = 6.8$  Hz, 1.35H).  **$^{13}\text{C}$  { $^1\text{H}$ } NMR (101 MHz,  $\text{CDCl}_3$ ):** (\*refers to the minor isomer when unambiguous distinction is possible)  $\delta$  191.2, 190.7\*, 158.7, 135.6, 133.9\*, 130.7\*, 130.5, 130.2\*, 130.0, 123.0\*, 122.9, 110.3, 110.1\*, 58.8, 56.7\*, 55.6, 37.6\*, 35.0, 33.4\*, 32.8, 19.2\*, 19.1. **HRMS (ESI+)**  $m/z$ :  $[\text{M}+\text{H}]^+$  calculated for  $\text{C}_{12}\text{H}_{14}\text{BrO}_2$ : 269.017168, found 269.016447.

**7-methoxy-3-methylnaphthalen-1-ol (22b)**. According to general procedure E, 899 mg (82% yield, white solid) of **22b** were obtained by flash chromatography on silica gel (Toluene/cyclohexane, gradient from 9/1 to 10/0, then toluene/ethyl acetate, 9/1, v/v, UV). **M.p.** = 92-95 °C. **<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)**: δ 7.63 (d, *J* = 9.0 Hz, 1H), 7.43 (d, *J* = 2.6 Hz, 1H), 7.17 (q, *J* = 1.1 Hz, 1H), 7.15 (dd, *J* = 8.9, 2.6 Hz, 1H), 6.64 (d, *J* = 1.4 Hz, 1H), 5.27 (s, 1H), 3.94 (s, 3H), 2.42 (s, 3H). **<sup>13</sup>C {<sup>1</sup>H} NMR (101 MHz, CDCl<sub>3</sub>)**: δ 156.9, 150.4, 133.3, 130.6, 128.8, 123.5, 119.8, 119.4, 111.5, 100.0, 55.5, 21.6. **HRMS (ESI+)** *m/z*. [M+H]<sup>+</sup> calculated for C<sub>12</sub>H<sub>13</sub>O: 189.091006, found 189.091766.

**6-methoxy-2-methylnaphthalene-1,4-dione (15b)**.<sup>12</sup> According to general procedure F, 328 mg (35% yield, yellow solid) of **15b** were obtained by flash chromatography on silica gel (Toluene/ethyl acetate, gradient from 10/0 to 9/1, v/v, UV). **M.p.** = 150-153 °C. **<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)**: δ 8.04 (d, *J* = 8.6 Hz, 1H), 7.49 (d, *J* = 2.7 Hz, 1H), 7.18 (dd, *J* = 8.6, 2.7 Hz, 1H), 6.79 (q, *J* = 1.5 Hz, 1H), 3.94 (s, 3H), 2.18 (d, *J* = 1.5 Hz, 3H). **<sup>13</sup>C {<sup>1</sup>H} NMR (101 MHz, CDCl<sub>3</sub>)**: δ 185.2, 184.7, 164.1, 148.7, 135.4, 134.5, 129.2, 125.9, 120.4, 109.4, 56.0, 16.6.

**3-methyl-4-oxo-4-(*p*-tolyl)but-2-enoic acid (20c)**. According to the general procedure A, 4'-methylpropionic acid **14c** was used. 2.7 g (99% yield, white solid, ratio *E/Z*: 1.5/1) of **20c** were isolated after filtration. **<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)**: (\*refers to the minor isomer when unambiguous distinction is possible) δ 7.70 (d, *J* = 8.1 Hz, 2H), 7.49\* (br s, 1.4H), 7.25 (d, *J* = 8.4 Hz, 2H), 7.20\* (d, *J* = 8.0 Hz, 1.4H), 6.09 (s, 1H), 5.87\* (s, 0.7H), 2.41 (s, 3H), 2.36 (s, 5.1H), 1.98\* (s, 2.1H). **<sup>13</sup>C {<sup>1</sup>H} NMR (126 MHz, CDCl<sub>3</sub>)**: (\*refers to the minor isomer when unambiguous distinction is possible) δ 197.7, 171.4, 171.1\*, 154.1\*, 144.6, 132.9, 130.1 (2C), 129.6, 129.5 (2C), 124.2\*, 117.4, 21.8, 21.5\*, 16.1. **HRMS (ESI+)** *m/z*. [M+Na]<sup>+</sup> calculated for C<sub>12</sub>H<sub>12</sub>NaO<sub>3</sub>: 227.067865, found 227.068137.

**3-methyl-4-(*p*-tolyl)butanoic acid (7c).** According to general procedure B, 2.4 g (96% yield, yellowish oil) of **7c** were isolated by flash chromatography on silica gel (Cyclohexane, then dichloromethane, then ethyl acetate). **<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):** δ 7.10 (d, *J* = 8.0 Hz, 2H), 7.06 (d, *J* = 8.1 Hz, 2H), 2.61 (dd, *J* = 13.5, 6.8 Hz, 1H), 2.50 (dd, *J* = 13.5, 7.3 Hz, 1H), 2.38 (dd, *J* = 14.8, 5.4 Hz, 1H), 2.33 (s, 3H), 2.27 (dt, *J* = 13.3, 6.8 Hz, 1H), 2.17 (dd, *J* = 14.8, 8.1 Hz, 1H), 0.99 (d, *J* = 6.5 Hz, 3H). **<sup>13</sup>C {<sup>1</sup>H} NMR (101 MHz, CDCl<sub>3</sub>):** δ 179.7, 137.1, 135.7, 129.2 (2C), 129.1 (2C), 42.6, 40.9, 32.3, 21.1, 19.7. **HRMS (ESI<sup>+</sup>) *m/z*:** [M+Na]<sup>+</sup> calculated for C<sub>12</sub>H<sub>16</sub>NaO<sub>2</sub>: 215.104250, found 215.104381.

**3,7-dimethyl-3,4-dihydronaphthalen-1(2H)-one (1c).** According to general procedure C, 1.6 g (77% yield, white solid) of **1c** were isolated by flash chromatography on silica gel (Toluene/ethyl acetate, 8/2, v/v, UV). **<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):** δ 7.81 (s, 1H), 7.27 (dd, *J* = 7.5, 2.0 Hz, 1H), 7.11 (d, *J* = 7.8 Hz, 1H), 2.97-2.86 (m, 1H), 2.69 (dd, *J* = 12.8, 1.9 Hz, 1H), 2.61 (dd, *J* = 16.4, 10.5 Hz, 1H), 2.34 (s, 3H), 2.31-2.21 (m, 2H), 1.11 (d, *J* = 6.2 Hz, 3H). **<sup>13</sup>C {<sup>1</sup>H} NMR (101 MHz, CDCl<sub>3</sub>):** δ 198.8, 141.0, 136.3, 134.5, 132.0, 128.8, 127.1, 47.3, 37.7, 30.7, 21.4, 21.0. **HRMS (ESI<sup>+</sup>) *m/z*:** [M+Na]<sup>+</sup> calculated for C<sub>12</sub>H<sub>14</sub>NaO: 197.093686, found 197.094299.

**2-bromo-3,7-dimethyl-3,4-dihydronaphthalen-1(2H)-one (21c).** According to general procedure D, 210 mg (96%, orange oil) of **21c** were isolated by flash chromatography on silica gel (Cyclohexane/toluene, 6/4, v/v, UV). **<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):** (\*refers to the minor isomer when unambiguous distinction is possible) δ 7.89 (br s, 0.7H), 7.87\* (br s, 0.3H), 7.36-7.32 (m, 1H), 7.16 (br s, 0.6H), 7.14\* (br s, 0.4H), 4.53 (dd, *J* = 2.6, 1.0 Hz, 0.7H), 4.44\* (m, 0.3H), 3.40\* (dd, *J* = 16.8, 4.5 Hz, 0.3H), 2.90 (m, 0.71H), 2.72 (m, 1H), 2.62\* (m, 0.3H), 2.37 (s, 3H), 2.25 (m, 0.7H), 1.22 (d, *J* = 6.5 Hz, 2.1H) 1.20\* (d, *J* = 7.0 Hz, 0.9H). **<sup>13</sup>C {<sup>1</sup>H} NMR (101 MHz, CDCl<sub>3</sub>):** (\*refers to the minor isomer when unambiguous distinction is possible) δ

191.3, 190.8\*, 140.0, 138.4\*, 136.8, 135.5\*, 135.2, 129.6\*, 129.13\*, 129.09, 128.7, 128.7, 128.3\*, 128.2\*, 59.1, 57.0\*, 37.4\*, 34.7, 33.7\*, 33.1, 21.0, 19.2\*, 19.1. **HRMS (ESI+)** *m/z*: [M+Na]<sup>+</sup> calculated for C<sub>12</sub>H<sub>13</sub>BrNaO: 275.004198, found 275.004086.

**3,7-dimethylnaphthalen-1-ol (22c)**. According to general procedure E, 971 mg (61% yield, white solid) of **22c** were obtained by flash chromatography on silica gel (Toluene, UV). **M.p.** = 93-96 °C. **<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)**: δ 7.86 (s, 1H), 7.62 (d, *J* = 8.4 Hz, 1H), 7.29 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.18 (s, 1H), 6.64 (d, *J* = 1.2 Hz, 1H), 5.05-5.03 (m, 1H), 2.51 (s, 3H), 2.43 (s, 3H). **<sup>13</sup>C {<sup>1</sup>H} NMR (101 MHz, CDCl<sub>3</sub>)**: δ 150.7, 134.9, 134.2, 133.3, 128.9, 127.1, 122.8, 120.3, 119.8, 111.0, 21.9, 21.8. **HRMS (ESI+)** *m/z*: [M+H]<sup>+</sup> calculated for C<sub>12</sub>H<sub>13</sub>O: 173.096091, found 173.096314.

**2,6-dimethylnaphthalene-1,4-dione (15c)**. According to general procedure F, 857 mg (82% yield, yellow solid) of **15c** were obtained by flash chromatography on silica gel (Toluene/cyclohexane, 8/2, v/v, UV). **M.p.** = 130-132 °C. **<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)**: δ 7.98 (d, *J* = 7.9 Hz, 1H), 7.84 (dd, *J* = 1.2, 0.6 Hz, 1H), 7.51 (ddd, *J* = 7.8, 1.8, 0.8 Hz, 1H), 6.80 (q, *J* = 1.6 Hz, 1H), 2.48 (s, 3H), 2.18 (d, *J* = 1.6 Hz, 3H). **<sup>13</sup>C {<sup>1</sup>H} NMR (101 MHz, CDCl<sub>3</sub>)**: δ 185.5, 185.4, 148.3, 144.9, 135.6, 134.4, 132.3, 130.1, 126.8, 126.5, 21.9, 16.6. **HRMS (ESI+)** *m/z*: [M+H]<sup>+</sup> calculated for C<sub>12</sub>H<sub>11</sub>O<sub>2</sub>: 187.075356, found 187.076313.

**3-methyl-4-oxo-4-(4-(trifluoromethyl)phenyl)but-2-enoic acid (20d)**. According to the general procedure A, 4'-trifluoromethylpropionic acid **14d** was used. 4.3 g (67% yield, white solid, ratio *E/Z*: 4.4/1) of **20d** were isolated after filtration. **<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)**: (\*refers to the minor isomer when unambiguous distinction is possible) δ 11.27 (br s, 1H), 7.89 (d, *J* = 8.0 Hz, 2H), 7.74 (d, *J* = 8.1 Hz, 2H), 7.66-7.58\* (m, 0.9H), 6.17 (d, *J* = 1.6 Hz, 1H), 5.88\* (s, 0.23H), 2.43 (s, 3H), 1.92\* (s, 0.68H). **<sup>13</sup>C {<sup>1</sup>H} NMR (101 MHz, CDCl<sub>3</sub>)**: (\*refers to the minor isomer when unambiguous distinction is possible) δ 196.8, 171.9\*, 171.0, 168.8\*, 153.7, 140.2\*,

138.7, 134.8 (q,  $^2J_{C-F} = 32.8$  Hz), 131.8\* (q,  $^2J_{C-F} = 32.9$  Hz), 130.1 (2C), 126.4\*, 125.8 (q,  $^3J_{C-F} = 3.7$  Hz, 2C), 125.6, 123.9\* (d,  $^1J_{C-F} = 272.7$  Hz), 123.5 (q,  $^1J_{C-F} = 272.8$  Hz), 117.0\*, 106.9\*, 15.7, 12.6\*.  **$^{19}\text{F}$  NMR (377 MHz,  $\text{CDCl}_3$ ):**  $\delta$  -62.86\*, -63.24. **HRMS (ESI+)  $m/z$  [M+Na] $^+$**  calculated for  $\text{C}_{12}\text{H}_9\text{F}_3\text{NaO}_3$ : 281.039600, found 281.039775.

**4-(4-trifluoromethylphenyl)-3-methylbutanoic acid (7d).** According to general procedure B, 3.8 g (99% yield, yellowish oil) of **7d** were isolated.  **$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):**  $\delta$  11.97 (s, 1H), 7.56 (d,  $J = 7.9$  Hz, 2H), 7.30 (d,  $J = 7.9$  Hz, 2H), 2.75 (dd,  $J = 13.5, 6.0$  Hz, 1H), 2.58 (dd,  $J = 13.5, 7.1$  Hz, 1H), 2.43-2.29 (m, 2H), 2.24 (dd,  $J = 13.9, 6.4$  Hz, 1H), 1.00 (d,  $J = 6.2$  Hz, 3H).  **$^{13}\text{C}$  { $^1\text{H}$ } NMR (101 MHz,  $\text{CDCl}_3$ ):**  $\delta$  179.9, 144.4, 129.6 (2C), 128.7 (q,  $^2J_{C-F} = 33.3$  Hz), 125.4 (d,  $^3J_{C-F} = 3.7$  Hz, 2C), 124.5 (q,  $^1J_{C-F} = 271.8$  Hz), 42.7, 40.9, 32.0, 19.6.  **$^{19}\text{F}$  NMR (377 MHz,  $\text{CDCl}_3$ ):**  $\delta$  -62.34. **HRMS (ESI+)  $m/z$  [M+H] $^+$**  calculated for  $\text{C}_{12}\text{H}_{14}\text{F}_3\text{O}_2$ : 247.094041, found 247.093769.

**3-methyl-7-(trifluoromethyl)-3,4-dihydronaphthalen-1(2H)-one (1d).** To a solution of **7d** (3.4 g, 13.9 mmol, 1.0 equiv.) and TFAA (11.6 mL, 83.6 mmol, 6 equiv.) in dichloromethane (34 mL) was added triflic acid (1.9 mL, 20.9 mmol, 1.5 equiv.). The reaction mixture was stirred for 1 h at room temperature. After this time, a saturated aqueous solution of sodium bicarbonate was added to the mixture. The aqueous phase was extracted with dichloromethane (3x). The organic phase was dried over  $\text{MgSO}_4$  and concentrated under reduced pressure. The crude residue was purified by flash chromatography on silica gel (Toluene/ethyl acetate, 7/3, v/v) to afford **1d** as a white solid (3.0 g, 95% yield). **M.p.** = 55-58 °C.  **$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):**  $\delta$  8.27 (s, 1H), 7.67 (dd,  $J = 8.1, 2.2$  Hz, 1H), 7.37 (d,  $J = 8.0$  Hz, 1H), 3.03 (br d,  $J = 17.5$  Hz, 1H), 2.80-2.67 (m, 2H), 2.40-2.28 (m, 2H), 1.15 (2d,  $J = 6.3$  Hz, 3H).  **$^{13}\text{C}$  { $^1\text{H}$ } NMR (101 MHz,  $\text{CDCl}_3$ ):**  $\delta$  197.2, 147.4, 132.6, 129.8, 129.7 (q,  $^3J_{C-F} = 3.6$  Hz), 129.3, 124.3 (q,  $^3J_{C-F} = 3.6$  Hz),

124.0 (d,  $^1J_{C-F}$  = 272.2 Hz), 46.9, 37.9, 30.3, 21.3.  **$^{19}\text{F}$  NMR (377 MHz,  $\text{CDCl}_3$ ):**  $\delta$  -62.74. **HRMS (ESI+)**  $m/z$ .  $[\text{M}+\text{H}]^+$  calculated for  $\text{C}_{12}\text{H}_{12}\text{F}_3\text{O}$ : 229.083476, found 229.083453.

**2-bromo-3-methyl-7-(trifluoromethyl)-3,4-dihydronaphthalen-1(2H)-one (21d)**. According to general procedure D, 576 mg (70%, yellowish oil) of **21d** were isolated by flash chromatography on silica gel (Toluene/cyclohexane, 7/3, v/v, UV).  **$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):** (\*refers to the minor isomer when unambiguous distinction is possible)  $\delta$  8.34 & 8.32 (2s, 1H), 7.74 (m, 1H), 7.41\* (d,  $J$  = 7.8 Hz, 0.35H), 7.40 (d,  $J$  = 8.1 Hz, 0.65H), 4.55 (br s, 0.65H), 4.46\* (d,  $J$  = 5.9 Hz, 0.35H), 3.52\* (dd,  $J$  = 17.4, 4.6 Hz, 0.35H), 2.99 (2d,  $J$  = 10.8 Hz, 0.65H), 2.83 (m, 1H), 2.70-2.64\* (m, 0.35H), 2.33-2.27 (m, 0.65H), 1.24 (d,  $J$  = 6.4 Hz, 1.95H), 1.20\* (d,  $J$  = 7.0 Hz, 1.05H).  **$^{13}\text{C}$   $\{^1\text{H}\}$  NMR (101 MHz,  $\text{CDCl}_3$ ):** (\*refers to the minor isomer when unambiguous distinction is possible)  $\delta$  189.9, 189.5\*, 146.4, 144.8\*, 130.5\* (q,  $^3J_{C-F}$  = 3.7 Hz), 130.3\*, 130.2 (q,  $^3J_{C-F}$  = 3.6 Hz), 130.0, 129.8, 129.7, 125.9 (q,  $^3J_{C-F}$  = 4.2 Hz), 125.5\* (q,  $^3J_{C-F}$  = 3.6 Hz), 123.7 (q,  $^1J_{C-F}$  = 272.3 Hz), 58.0, 55.2\*, 36.8\*, 34.3, 33.6\*, 33.4, 18.9, 18.8\*.  **$^{19}\text{F}$  NMR (377 MHz,  $\text{CDCl}_3$ ):**  $\delta$  -62.83. **HRMS (ESI+)**  $m/z$ .  $[\text{M}+\text{H}]^+$  calculated for  $\text{C}_{12}\text{H}_{11}\text{BrF}_3\text{O}$ : 306.993988, found 306.993449.

**3-methyl-7-trifluoromethylnaphthalen-1-ol (22d)**. According to general procedure E, 319 mg (84% yield, brown solid) of **22d** were obtained by flash chromatography on silica gel (Toluene/cyclohexane, 7/3, v/v, UV). **M.p.** = 88-91 °C.  **$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):**  $\delta$  8.48 (s, 1H), 7.79 (d,  $J$  = 8.6 Hz, 1H), 7.61 (dd,  $J$  = 8.7, 1.9 Hz, 1H), 7.25 (s, 1H), 6.71 (s, 1H), 5.43 (s, 1H), 2.46 (s, 3H).  **$^{13}\text{C}$   $\{^1\text{H}\}$  NMR (101 MHz,  $\text{CDCl}_3$ ):**  $\delta$  151.9, 138.8, 136.1, 128.0, 126.3 (q,  $^2J_{C-F}$  = 33.3 Hz), 124.8 (d,  $^1J_{C-F}$  = 273.7 Hz), 122.2 (q,  $^3J_{C-F}$  = 3.2 Hz), 121.7, 120.1 (q,  $^3J_{C-F}$  = 4.5 Hz), 119.8, 112.0, 22.0.  **$^{19}\text{F}$  NMR (377 MHz,  $\text{CDCl}_3$ ):**  $\delta$  -62.02. **HRMS (ESI+)**  $m/z$ .  $[\text{M}+\text{H}]^+$  calculated for  $\text{C}_{12}\text{H}_{10}\text{F}_3\text{O}$ : 227.067826, found 227.067355.

**2-methyl-6-(trifluoromethyl)naphthalene-1,4-dione (15d).** According to general procedure F, realized at -5 °C, 1.5 g (59% yield, yellow solid) of **15d** were obtained by flash chromatography on silica gel (Toluene/cyclohexane, 6/4, v/v, UV). **M.p.** = 97-99 °C. **<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):** δ 8.33 (s, 1H), 8.23 (d, *J* = 8.1 Hz, 1H), 7.98 (dd, *J* = 8.1, 1.8 Hz, 1H), 6.93 (q, *J* = 1.6 Hz, 1H), 2.23 (d, *J* = 1.5 Hz, 3H). **<sup>13</sup>C {<sup>1</sup>H} NMR (101 MHz, CDCl<sub>3</sub>):** δ 184.5, 183.6, 148.8, 136.0, 135.4 (q, <sup>2</sup>*J*<sub>C-F</sub> = 33.3 Hz), 134.3, 132.7, 130.0 (q, <sup>3</sup>*J*<sub>C-F</sub> = 3.7 Hz), 127.4, 123.5 (q, <sup>3</sup>*J*<sub>C-F</sub> = 3.9 Hz), 123.3 (d, <sup>1</sup>*J*<sub>C-F</sub> = 273.3 Hz), 16.6. **<sup>19</sup>F NMR (377 MHz, CDCl<sub>3</sub>):** δ -63.38. **HRMS (ESI+) *m/z*:** [M+H]<sup>+</sup> calculated for C<sub>12</sub>H<sub>8</sub>F<sub>3</sub>O<sub>2</sub>: 241.047091, found 241.046381.

**4-(4-bromophenyl)-3-methyl-4-oxobut-2-enoic acid (20e).** According to the general procedure A, 4'-bromopropionic acid **14e** was used. 2.3 g (90% yield, white solid, ratio *E/Z*: 3.7/1) of **20e** were isolated after filtration. **<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):** (\*refers to the minor isomer when unambiguous distinction is possible) δ 7.67 (d, *J* = 8.6 Hz, 2H), 7.62 (d, *J* = 8.6 Hz, 2H), 7.52\* (d, *J* = 8.6 Hz, 0.5H), 7.34\* (d, *J* = 8.5 Hz, 0.5H), 6.15 (br d, *J* = 1.4 Hz, 1H), 5.86\* (br d, *J* = 1.0 Hz, 0.25H), 2.42 (d, *J* = 1.3 Hz, 3H), 1.91\* (d, *J* = 0.8 Hz, 0.8H). **<sup>13</sup>C {<sup>1</sup>H} NMR (101 MHz, CDCl<sub>3</sub>):** (\*refers to the minor isomer when unambiguous distinction is possible) δ 196.8, 171.0, 168.6\*, 154.3, 135.5\*, 134.2, 132.2 (2C), 132.0\*, 131.4 (2C), 130.3\*, 129.0\*, 127.6, 124.3\*, 116.8, 106.8\*, 16.1, 12.6\*. **HRMS (ESI+) *m/z*:** [M+Na]<sup>+</sup> calculated for C<sub>11</sub>H<sub>9</sub>BrNaO<sub>3</sub>: 290.962727, found 290.963532.

**4-(4-chlorophenyl)-3-methyl-4-oxobut-2-enoic acid (20f).** According to the general procedure A, 4'-chloropropionic acid **14f** was used. 2.5 g (93% yield, white solid, ratio *E/Z*: 1.8/1) of **20f** were isolated after filtration. **<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):** (\*refers to the minor isomer when unambiguous distinction is possible) δ 7.75 (d, *J* = 8.4 Hz, 2H), 7.50\* (d, *J* = 8.5 Hz, 1H), 7.45 (d, *J* = 8.4 Hz, 2H), 7.39\* (d, *J* = 8.5 Hz, 1H), 6.12 (s, 1H), 5.88\* (s, 0.5H), 2.39 (s, 3H), 1.96\* (d, *J* = 0.8 Hz, 1.5H). **<sup>13</sup>C {<sup>1</sup>H} NMR (101 MHz, CDCl<sub>3</sub>):** (\*refers to the minor isomer

when unambiguous distinction is possible)  $\delta$  196.8, 171.4, 171.1\*, 153.1\*, 140.2, 136.8\*, 134.3\*, 133.8, 131.3 (2C), 129.11 (2C), 129.06, 128.0, 125.1\*, 117.5\*, 15.9, 14.8\*. **HRMS (ESI+)**  $m/z$ :  $[M+Na]^+$  calculated for  $C_{11}H_9ClNaO_3$ : 247.013243, found 247.013594.

**4-(4-bromophenyl)-3-methylbutanoic acid (7e)**. A mixture of 1-bromo-4-iodobenzene **23e** (10.0 g, 35.35 mmol, 1.0 equiv.), lithium acetate (5.8 g, 88.0 mmol, 2.5 equiv.), lithium chloride (1.5 g, 35.4 mmol, 1.0 equiv.), 3-methyl-3-buten-1-ol (3.6 mL, 35.4 mmol, 1.0 equiv.), tetrabutylammonium chloride hydrate (21.0 g, 70.8 mmol, 2.0 equiv.) and palladium diacetate (450 mg, 2.0 mmol, 0.06 equiv.) in dimethylformamide (68 mL) was stirred at 70 °C for 72 h. After this time, the reaction mixture was quenched with a saturated aqueous solution of ammonium chloride. Then, the reaction mixture was extracted three times with diethyl ether. The combined organic layers were washed with brine, dried over  $MgSO_4$  and concentrated under reduced pressure. No further purification was required and the crude product **24e** was used in the next step directly. Acetonitrile (280 mL) was added to periodic acid (8.1 g, 35.5 mmol, 1.1 equiv.) and the resulting mixture was stirred for 15 min. At 0 °C, a solution of 4-(4-bromophenyl)-3-methylbutanal **24e** (7.9 g, 32.7 mmol, 1.0 equiv.) in acetonitrile (35 mL) was added followed by pyridinium chlorochromate (140 mg, 0.7 mmol, 0.02 equiv.) in acetonitrile (35 mL). The reaction mixture was then stirred at room temperature for 3.5 h. After this time, ethyl acetate was added. The organic phase was washed with a mixture of water and brine (1/1, v/v), a saturated aqueous of sodium hydrogen sulfate solution and brine. It was then dried over  $MgSO_4$  and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel (Dichloromethane/methanol, gradient from 98/2 to 95/5, v/v, UV) to afford **7e** as a colourless oil (5.46 g, 60% yield over 2 steps).  **$^1H$  NMR ( $CDCl_3$ , 400 MHz):**  $\delta$  7.44-7.37 (m, 2H), 7.04 (d,  $J$  = 8.3 Hz, 2H), 2.62 (dd,  $J$  = 13.5, 6.4 Hz, 1H), 2.47 (dd,  $J$  = 13.5, 7.3 Hz, 1H), 2.35 (dd,  $J$  = 14.3, 5.2 Hz, 1H), 2.30-2.15 (m, 3H), 0.97 (d,  $J$  = 6.4 Hz, 3H).  **$^{13}C$  { $^1H$ }**

**NMR (CDCl<sub>3</sub>, 101 MHz):**  $\delta$  179.2, 139.1, 131.5 (2C), 131.1 (2C), 120.1, 42.3, 40.7, 32.1, 19.6.

**HRMS (ESI-) *m/z*** [M-H]<sup>-</sup> calculated for C<sub>11</sub>H<sub>12</sub>BrO<sub>2</sub>: 255.002615, found 255.001185.

**7-bromo-3-methyl-3,4-dihydronaphthalen-1(2H)-one (1e).** According to general procedure C, 4.5 g (88% yield, white solid) of **1e** were isolated by flash chromatography on silica gel (Toluene/ethyl acetate, 8/2, v/v, UV). **M.p.** = 59-61 °C. **<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):**  $\delta$  8.11 (d, *J* = 2.2 Hz, 1H), 7.55 (dd, *J* = 8.2, 2.2 Hz, 1H), 7.12 (d, *J* = 8.2 Hz, 1H), 2.92 (dd, *J* = 16.3, 3.6 Hz, 1H), 2.71 (dd, *J* = 13.0, 1.8 Hz, 1H), 2.60 (dd, *J* = 16.3, 10.0 Hz, 1H), 2.34-2.25 (m, 2H), 1.13 (d, *J* = 6.2 Hz, 3H). **<sup>13</sup>C {<sup>1</sup>H} NMR (101 MHz, CDCl<sub>3</sub>):**  $\delta$  197.2, 142.5, 136.3, 133.8, 130.8, 129.9, 120.7, 46.9, 37.5, 30.4, 21.4. **HRMS (ESI+) *m/z*** [M+H]<sup>+</sup> calculated for C<sub>11</sub>H<sub>12</sub>BrO: 239.006604, found 239.006402.

**2,7-dibromo-3-methyl-3,4-dihydronaphthalen-1(2H)-one (21e).** According to the general procedure D, 103 mg (81%, yellowish oil) of **21e** were isolated by flash chromatography on silica gel (Toluene/cyclohexane, 8/2, v/v, UV). **<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):** (\*refers to the minor isomer when unambiguous distinction is possible)  $\delta$  8.17 (d, *J* = 2.2 Hz, 0.6H), 8.16\* (d, *J* = 2.2 Hz, 0.4H), 7.60 (td, *J* = 8.2, 2.2 Hz, 1H), 7.14 (2d, *J* = 3.5 Hz, 1H), 4.50 (br dd, *J* = 2.4, 0.8 Hz, 0.6H), 4.42\* (d, *J* = 8.0 Hz, 0.4H), 3.38\* (dd, *J* = 16.8, 4.0 Hz, 0.4H), 2.86 (m, 0.6H), 2.76-2.51 (m, 1.4H), 2.25 (dtdq, *J* = 10.6, 6.4, 3.8, 2.3, 1.8 Hz, 0.6H), 1.21 (d, *J* = 6.5 Hz, 1.8H), 1.18\* (d, *J* = 6.9 Hz, 1.2H). **<sup>13</sup>C {<sup>1</sup>H} NMR (CDCl<sub>3</sub>, 101 MHz):** (\*refers to the minor isomer when unambiguous distinction is possible)  $\delta$  189.8, 189.4\*, 141.5, 139.9\*, 137.2\*, 136.9, 132.5\*, 131.34, 131.28\*, 131.1\*, 130.98\*, 130.95, 130.6, 130.3\*, 121.1, 58.1, 55.6\*, 36.9\*, 34.4, 33.4\*, 33.0, 19.0. **HRMS (ESI+) *m/z*** [M+H]<sup>+</sup> calculated for C<sub>11</sub>H<sub>11</sub>Br<sub>2</sub>O: 316.917116, found 316.915206.

**7-bromo-3-methylnaphthalen-1-ol (22e).** According to general procedure E, 49 mg (73% yield, white solid) of **22e** were obtained by flash chromatography on silica gel

(Toluene/cyclohexane, 8/2, v/v, UV). **M.p.** = 105-107 °C. **<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):** δ 8.30 (s, 1H), 7.60-7.49 (m, 2H), 7.17 (s, 1H), 6.65 (s, 1H), 5.24 (s, 1H), 2.42 (s, 3H). **<sup>13</sup>C {<sup>1</sup>H} NMR (CDCl<sub>3</sub>, 101 MHz):** δ 150.4, 136.6, 133.4, 130.0, 128.8, 124.3, 123.9, 119.8, 118.4, 111.8, 21.9. **HRMS (ESI+)** *m/z*: [M+H]<sup>+</sup> calculated for C<sub>11</sub>H<sub>10</sub>BrO: 236.990953, found 236.990412.

**6-bromo-2-methylnaphthalene-1,4-dione (15e).** According to general procedure F, 39 mg (88% yield, yellow solid) of **15e** were obtained by flash chromatography on silica gel (Toluene/cyclohexane, 8/2, v/v, UV). **M.p.** = 129-130 °C. **<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):** δ 8.16 (d, *J* = 2.0 Hz, 1H), 7.94 (d, *J* = 8.3 Hz, 1H), 7.83 (dd, *J* = 8.3, 2.0 Hz, 1H), 6.83 (q, *J* = 1.5 Hz, 1H), 2.19 (d, *J* = 1.5 Hz, 3H). **<sup>13</sup>C {<sup>1</sup>H} NMR (CDCl<sub>3</sub>, 101 MHz):** δ 184.9, 183.8, 148.6, 136.7, 135.5, 133.4, 130.8, 129.34, 129.29, 128.4, 16.6. **HRMS (ESI+)** *m/z*: [M+H]<sup>+</sup> calculated for C<sub>11</sub>H<sub>8</sub>BrO<sub>2</sub>: 250.970218, found 250.970402.

**4-(4-chlorophenyl)-3-methylbutanal (24f).** A mixture of 1-chloro-4-iodobenzene **23f** (10.0 g, 41.9 mmol, 1.0 equiv.), lithium acetate (6.9 g, 104.4 mmol, 2.5 equiv.), lithium chloride (1.8 g, 42.0 mmol, 1.0 equiv.), 3-methyl-3-buten-1-ol (4.3 mL, 42.0 mmol, 1.0 equiv.), tetrabutylammonium chloride hydrate (24.9 g, 84.0 mmol, 2.0 equiv.) and palladium diacetate (530 mg, 2.4 mmol, 0.06 equiv.) in dimethylformamide (81 mL) was stirred at 70 °C for 72 h. After this time, the reaction mixture was quenched with a saturated aqueous solution of ammonium chloride. Then, the reaction mixture was extracted three times with diethyl ether. The combined organic layers were washed with brine, dried over MgSO<sub>4</sub> and concentrated under reduced pressure. The crude residue was purified by flash chromatography on silica gel (Cyclohexane, UV) to afford **24f** as an orange oil (4.4 g, 54% yield). **<sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz):** δ 9.75-9.71 (m, 1H), 7.30-7.25 (m, 2H), 7.13-7.07 (m, 2H), 2.60 (dd, *J* = 13.5, 6.7 Hz, 1H), 2.51 (dd, *J* = 13.5, 7.1 Hz, 1H), 2.46-2.38 (m, 1H), 2.38-2.31 (m, 1H), 2.27 (ddd, *J* = 15.6, 7.2, 2.2 Hz, 1H), 0.98 (d, *J* = 6.5 Hz, 3H). **<sup>13</sup>C {<sup>1</sup>H} NMR (CDCl<sub>3</sub>, 101 MHz):** δ 202.2, 138.6, 132.0, 130.6

(2C), 128.5 (2C), 50.2, 42.5, 30.1, 19.8. **HRMS (APCI+)** *m/z*: [M] calculated for C<sub>11</sub>H<sub>13</sub>OCl: 196.09, found 196.06.

**4-(4-chlorophenyl)-3-methylbutanoic acid (7f)**. 200 mL of acetonitrile was added to periodic acid (5.5 g, 24.1 mmol, 1.1 equiv.) and the resulting mixture was stirred for 15 min. At 0 °C, a solution of 4-(4-bromophenyl)-3-methylbutanal **24f** (4.4 g, 22.2 mmol, 1.0 equiv.) in acetonitrile (15 mL) was added followed by pyridinium chlorochromate (0.1 g, 0.4 mmol, 0.02 equiv.) in 15 mL of acetonitrile. The reaction mixture was then stirred at room temperature for 4 h. After this time, ethyl acetate was added. The organic phase was washed with a mixture of water and brine (1/1, v/v), a saturated aqueous of sodium hydrogen sulfate solution and brine. It was then dried over MgSO<sub>4</sub> and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel (Dichloromethane/methanol, gradient from 98/2 to 95/5, v/v, UV) to afford **7f** as a brown oil (2.7 g, 57% yield). **<sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz)**: δ 7.41-7.37 (m, 2H), 7.25-7.21 (m, 2H), 2.77 (dd, *J* = 13.5, 6.6 Hz, 1H), 2.62 (dd, *J* = 13.5, 7.4 Hz, 1H), 2.48 (dd, *J* = 14.7, 5.5 Hz, 1H), 2.39 (tt, *J* = 12.6, 6.5 Hz, 1H), 2.32 (m, 1H), 1.10 (d, *J* = 6.5 Hz, 3H). **<sup>13</sup>C {<sup>1</sup>H} NMR (CDCl<sub>3</sub>, 126 MHz)**: δ 179.5, 138.6, 132.1, 130.7 (2C), 128.6 (2C), 42.3, 40.8, 32.1, 19.6. **HRMS (ESI-)** *m/z*: [M-H]<sup>-</sup> calculated for C<sub>11</sub>H<sub>12</sub>ClO<sub>2</sub>: 211.053131, found 211.052909.

**7-chloro-3-methyl-3,4-dihydronaphthalen-1(2H)-one (1f)**. According to general procedure C, 1.8 g (77% yield, brown solid) of **1f** were isolated by flash chromatography on silica gel (Toluene/ethyl acetate, gradient from 7/3 to 9/1, v/v, UV). **M.p.** = 49-51 °C. **<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)**: δ 7.95 (d, *J* = 2.3 Hz, 1H), 7.40 (dd, *J* = 8.2, 2.3 Hz, 1H), 7.18 (d, *J* = 8.2 Hz, 1H), 2.94 (dd, *J* = 16.2, 3.6 Hz, 1H), 2.72 (dd, *J* = 13.0, 1.8 Hz, 1H), 2.63 (dd, *J* = 16.4, 10.0 Hz, 1H), 2.36-2.24 (m, 2H), 1.13 (d, *J* = 6.2 Hz, 3H). **<sup>13</sup>C {<sup>1</sup>H} NMR (CDCl<sub>3</sub>, 101 MHz)**: δ 197.3, 142.1, 133.5, 133.4, 132.9, 130.5, 126.9, 46.9, 37.5, 30.4, 21.4. **HRMS (APCI+)** *m/z*: [M+H]<sup>+</sup> calculated for C<sub>11</sub>H<sub>12</sub>ClO: 195.0571, found 195.0561.

**2-bromo-7-chloro-3-methyl-3,4-dihydronaphthalen-1(2H)-one (21f).** According to general procedure D, 2.3 g of **21f** (yield determined after the next step due to the presence of inseparable unknown by-product - ratio product/by-product, 16/1) were obtained and engaged directly in the next step without further purification. **<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):** (\*refers to the minor isomer when unambiguous distinction is possible)  $\delta$  8.05 (d,  $J$  = 2.3 Hz, 0.62H), 8.03\* (d,  $J$  = 2.3 Hz, 0.38H), 7.49\* (dd,  $J$  = 8.1, 2.3 Hz, 0.38H), 7.47 (dd,  $J$  = 8.2, 2.3 Hz, 0.62H), 7.22\* (d,  $J$  = 8.2 Hz, 0.38H), 7.21 (d,  $J$  = 8.2 Hz, 0.62H), 4.53 (dd,  $J$  = 2.7, 1.2 Hz, 0.62H), 4.44\* (br d,  $J$  = 5.9 Hz, 0.38H), 3.42\* (2dd,  $J$  = 16.9, 4.5 Hz, 0.38H), 2.90 (dd,  $J$  = 17.1, 10.7 Hz, 0.62H), 2.78-2.67 (m, 1H), 2.67-2.59\* (m, 0.38H), 2.31-2.22 (m, 0.62H), 1.23 (d,  $J$  = 6.5 Hz, 1.86H), 1.20\* (d,  $J$  = 7.0 Hz, 1.14H). **<sup>13</sup>C {<sup>1</sup>H} NMR (CDCl<sub>3</sub>, 101 MHz):** (\*refers to the minor isomer when unambiguous distinction is possible)  $\delta$  190.1, 189.6\*, 141.1, 139.5\*, 134.4\*, 134.1, 133.4, 131.1\*, 130.9, 130.8\*, 130.4, 128.4, 128.1\*, 58.1, 55.6\*, 37.1\*, 34.5, 33.4\*, 33.0, 19.03, 19.01\*. **HRMS (APCI+)**  $m/z$ : [M+H]<sup>+</sup> calculated for C<sub>11</sub>H<sub>11</sub>BrClO: 272.9676, found 272.9671.

**7-chloro-3-methylnaphthalen-1-ol (22f).** According to general procedure E, 1.4 g (78% yield over 2 steps, orange solid) of **22f** were obtained by flash chromatography on silica gel (Toluene/cyclohexane, 8/2, v/v, UV). **M.p.** = 105-106 °C. **<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):**  $\delta$  8.12 (s, 1H), 7.63 (d,  $J$  = 8.7 Hz, 1H), 7.42-7.34 (m, 1H), 7.18 (s, 1H), 6.65 (s, 1H), 5.36 (s, 1H), 2.42 (s, 3H). **<sup>13</sup>C {<sup>1</sup>H} NMR (CDCl<sub>3</sub>, 101 MHz):**  $\delta$  150.5, 136.4, 133.2, 130.3, 128.7, 127.5, 123.5, 121.0, 119.7, 111.8, 21.8. **HRMS (APCI+)**  $m/z$ : [M] calculated for C<sub>11</sub>H<sub>9</sub>ClO: 192.0336, found 192.0320.

**6-chloro-2-methylnaphthalene-1,4-dione (15f).** According to general procedure F, 860 mg (61% yield, yellow solid) of **15f** were obtained by flash chromatography on silica gel (Toluene/cyclohexane, gradient from 7/3 to 9/1, v/v, UV). **M.p.** = 115-116 °C. **<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):**  $\delta$  8.04 (d,  $J$  = 8.3 Hz, 1H), 8.01 (d,  $J$  = 1.9 Hz, 1H), 7.67 (dd,  $J$  = 8.3, 2.0 Hz, 1H),

6.85 (br d,  $J = 1.0$  Hz, 1H), 2.20 (d,  $J = 0.8$  Hz, 3H).  $^{13}\text{C}$  { $^1\text{H}$ } NMR ( $\text{CDCl}_3$ , 101 MHz):  $\delta$  184.6, 183.8, 148.6, 140.8, 135.6, 133.7, 133.5, 130.4, 128.4, 126.2, 16.6. HRMS (APCI+)  $m/z$ :  $[\text{M}+\text{H}]^+$  calculated for  $\text{C}_{11}\text{H}_8\text{ClO}_2$ : 207.0207, found 207.0221.

## ■ ASSOCIATED CONTENT

### Supporting Information.

The Supporting information is available free of charge at <https://pubs.acs.org/doi/>: Optimization screening and  $^1\text{H}$ ,  $^{13}\text{C}$  and  $^{19}\text{F}$  NMR spectra of all compounds (PDF).

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## **Funding Sources**

This work was supported by the University of Strasbourg (PhD salary from the French Ministry of Research (MENRT) to N. T.) and CNRS innovation program (grant to E. D.-C., and the Postdoctoral salary to M. R.), and the Laboratoire d’Excellence (LabEx) ParaFrap (grant LabEx ParaFrap ANR-11-LABX-0024 to E.D.C.).

## **Notes**

The authors declare no competing financial interest.

## **■ ACKNOWLEDGMENTS**

The authors wish to thank the Laboratoire d’Excellence (LabEx) ParaFrap consortium for funding and creating a proper framework for this scientific research, and CNRS<sub>innovation</sub> for the “Industrial prematuration” grant including the postdoc salary (M. R.). The authors are grateful to Tran-Hoang-Lan Le and Loris Locquet for exemplifying the protocols of the preparation of certain 7-substituted-3-methyltetral-1-ones and 6-substituted menadiones. Maxime Donzel is acknowledged for helpful supervision of N. T. during the M2 training and start of the PhD studies.

## **ABBREVIATIONS**

BINOL: 1,1'-bi-2-naphthol; HIV: human immunodeficiency virus; NBS: *N*-bromosuccinimide; PD: Plasmodione; PPC: Pyridinium chlorochromate; PIDA: Phenyliodine(III) diacetate; PPA: Polyphosphoric acid; PTSA: *p*-toluenesulfonic acid; TFAA: Trifluoroacetic anhydride; TLC: thin layer chromatography.

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