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HAMMET CONSTANTS EFFECTS IN MICROWAVE CASCADE ETHERIFICATION-CYCLIZATION-KRAPCHO REACTION TO ACCESS [2,3]-DIHYDROBENZOFURAN-3-ONES FROM SALICYLIC DERIVATIVES

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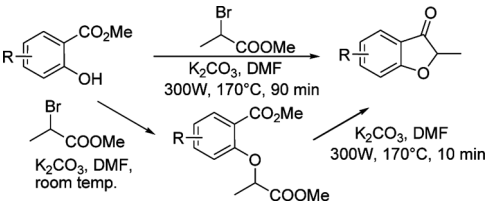
GRAPHICAL ABSTRACT



Abstract *Two methods were evaluated for the synthesis of substituted [2,3]-dihydro-2-methyl-benzofuran-3-ones from corresponding salicylate esters under microwave irradiation. A two-step sequence via ether intermediates was convenient for various substituted salicylate derivatives, while the second strategy involving a one-pot procedure was efficient for electron-donating substituted salicylates. Results allowed correlation of the Hammett constants effects in the intramolecular cyclization of O-ethoxycarbonyl ether of salicylic esters.*

Keywords Benzofuranone; Hammet constants; Krapcho reaction; microwave; salicylate

INTRODUCTION

Benzofuranes, dihydrobenzofuranes, and their corresponding 2,3-dihydro-3-one derivatives are structures found in a variety of molecules possessing biological activity such as the receptor α-2 antagonist efaroxan **1**[1] or the PPARα agonist **2** (Fig. 1).[2] These heterocycles are also part of natural products such as the insecticides rocaglamide **3**[3] and vasinfectins **4**.[4] An alternative and shorter synthesis of diversely substituted 2-methyl-2,3-dyhydro-benzofuran-3 is a major point of interest.

Benzofuranones **6** were prepared in several steps from triflate[5] or by Friedel–Crafts methodology with $AlCl_3$ or polyphosphoric acid (PPA).[6] However, a more

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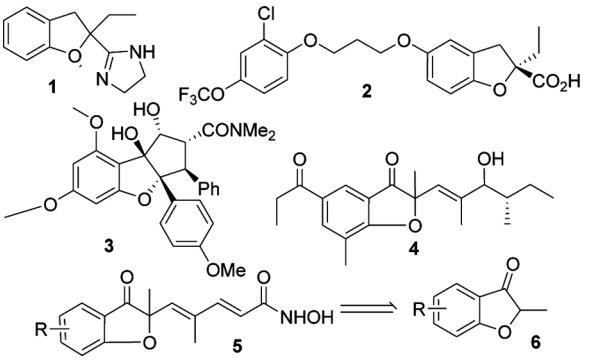
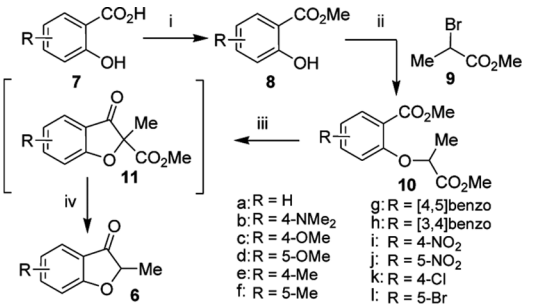


Figure 1. Natural and synthetic benzofurane derivatives.



Scheme 1. Conventional preparation of benzofuranones **6** from salicylate derivatives **7a**. (i) Esterification; (ii) etherification; (iii) cyclization; and (iv) decarboxylation.

classical synthesis (Scheme 1) involves etherification of salicylic derivatives **8** with esters under alkaline conditions to yield ethers **10**. Subsequent ether side-chain deprotonation using MeONa/MeOH or NaH/tetrahydrofuran (THF) led to the intramolecular attack of the carbonyl ester group to afford **11**.[7] Finally, the desired benzofuranone **6** was generated after decarboxylation on heating or via acidic hydrolysis.[8] In the case of aryl substituted benzofuranones, this strategy is particularly convenient as several salicylic acids **7** as well as esters **8** are commercially available. In addition, various 2-alkyl substituents can be easily introduced using appropriate α-halogenated esters **9**. This three-step synthesis was improved during our work on histone deacetylases (HDAC) inhibitor **5**, where a cascade etherification/cyclization/decarboxylation was developed.[9] We here report our attempts to generalize this reaction.

RESULTS AND DISCUSSION

The thermal method used for the synthesis of 2-methyl-benzofuranones **6a** and **6b**[9] was extended to other substrates with results reported in Table 1. This method apparently suffered from some disadvantages, as the bromo- and nitro- derivatives

Table 1. Thermal preparation of [2,3]-dihydrobenzofuran-3-ones **6** from salicylate esters **8a**,**b**[a]

Entry	8	R	6	Yield[c] (%)
1	**8a**	H[b]	**6a**	42
2	**8b**	4-NMe_2[b]	**6b**	86
3	**8g**	[4,5]-benzo	**6g**	44[d]
4	**8h**	[3,4]-benzo	**6h**	30[d]
5	**8i**	4-NO_2	**6i**	Decomposition
6	**8l**	5-Br	**6l**	8[d]

[a]Reagents and conditions (see sequence in Scheme 1): (ii) K_2CO_3 (1 equiv.), **9** (1 equiv.), DMF, rt, overnight; (iii) DMF, reflux, 4 h; (iv) HCl 6 N.

[b]See reference 5 for more details.

[c]Yield of isolated product after flash chromatography.

[d]Yield after acidic hydrolysis.

gave poor yields (Table 1, entries 5 and 6). Moreover, different thermal behaviors were noticed during the cascade etherification/cyclization/decarboxylation, depending on the salicylate ring substitution. For compounds **8a**, **8 g**, **8 h**, and **8l**, a mixture of benzofuranones **6** and nondecarboxylated intermediates **11** was obtained. (Table 1, entries 1 and 3–5). In the case of **8b**, the reaction was complete (Table 1, entry 2). The process leading to this final decarboxylation is related to the Krapcho reaction.[10] Parameters have been reported for a powerful Krapcho decarboxylation: (i) methyl esters are easy to decarboxylate, (ii) dimethylsulfoxide (DMSO) must be chosen in preference to dimethylformamide (DMF), and (iii) LiCl, NaCN, or NaCl, are more efficient salts than KBr.[11] In this respect, the results obtained in our preliminary experiments were discordant as DMF was the solvent and formation of potassium bromide occurred during the etherification. The salicylate substituent emerged as an important issue to explore. An improved procedure is herein presented, leading to compounds **6**.

Studies were directed toward initial cyclization under microwave irradiation.[12] Bogdal et al. described the synthesis of phenol ethers such as **10** by microwave-assisted phase-transfer catalysis using tetrabutyl ammonium bromide.[13] Unfortunately, in our case, these conditions afforded a mixture from which no valuable compounds were detected, and ethers **10** were finally prepared under classical conditions (K_2CO_3, DMF, **9**). The conversion of ethers **10** into benzofuranones **6** was evaluated on derivative **10c** with a range of bases, additives, and solvents (Table 2). DMF appeared to be the most appropriate solvent, with DMSO furnishing complex mixtures (Table 2, entries 1 and 2). After 40 min at 300 W and 170 °C, the cyclization of ether **10c** was completed, giving a mixture of **6c**, **11c**, and an undetermined aromatic compound in a 1:0.27:0.56 ratio (Table 2, entry 3). The temperature of 170 °C was programmed for DMF (boiling point 154 °C) to artificially maintain the 300 W irradiation as long as possible during the experiments and to have the maximum possible cyclization to **6** or **11**. This was also the case for the other solvents used in this work, but depending on the solvent nature, the irradiation was not always at its maximum during the reactions. In the case of acetonitrile, for instance, which has a lower boiling point, the maximum irradiation was never reached (at least a maximum of 200–250 W was observed). However, for all solvents, we maintained 300 W. We postulated that the formation of compound **11c** released a methanolate

Table 2. 170 °C and 300 W microwave irradiation on 1 mmol of **10c**

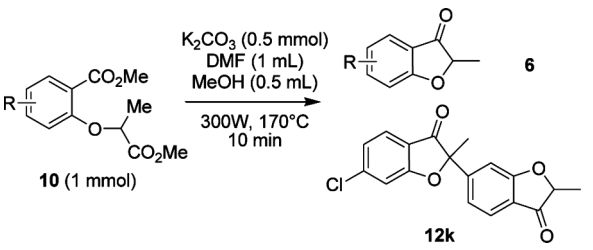
Entry	Time (min)	Solvent(s) (mL)	Additive(s) (equiv.)	**10c/11c/6c**[c]
1	10	DMF (1)	K_2CO_3 (1.5)	1:0.24:0.04
2	10	DMSO (1)	K_2CO_3 (1.5)	—[d]
3	40	DMF (1)	K_2CO_3 (1.5)	0:0.27:1.0
4	20	DMF (1)	K_2CO_3 (1.0) KBr (1.0)	0:0.45:1.0
5	20	DMF (1)	K_2CO_3 (0.25) KBr (1.0)	0:0.52:1.0
6	40	DMF (1)	K_2CO_3 (0.25) KBr (1.0)	0:0.57:1.0
7[a]	20	DMF (1)	K_2CO_3 (0.25) KBr (1.0)	1.0:0.13:0
8	40	DMF (1) MeOH (0.1)	K_2CO_3 (0.5), KBr (1.0) $KHCO_3$(1.0)	0:0.47:1.0
9	20	DMF (1) MeOH (0.1)	K_2CO_3 (0.5), KBr (1.0) $KHCO_3$ (1.0)	0:0.33:1.0
10	15	DMF (1) MeOH (0.1)	K_2CO_3 (0.5), KBr (1.0) $KHCO_3$ (1.0)	0:0.11:1.0
11	10	DMF (1) MeOH (0.5)	K_2CO_3 (0.5), KBr (1.0) $KHCO_3$ (1.0)	0:0.05:1.0
12	10	DMF (1) MeOH (1)	K_2CO_3 (0.5), KBr (1.0) $KHCO_3$ (1.0)	0:0.05:1.0
13	10	DMF (1)	K_2CO_3 (0.5), KBr (1.0) $KHCO_3$ (1.0)	1:0:0.03
14[b]	10	MeOH (1)	K_2CO_3 (0.5)	1:0:0
15	10	DMF (1) MeOH (0.5)	K_2CO_3 (0.5)	0:0.05:1.0

[a]Experiment performed at 140 °C.
[b]Experiment performed at 70 °C (higher temperature was not accessible with our apparatus because of high-pressure limitation).
[c]Ratio evaluated on ^{1}H NMR spectrum of the crude material.
[d]Decomposition was observed.

anion able to promote the reaction and the amount of K_2CO_3 was reduced. In the same time, KBr was added for its potential role in the decarboxylation. At 170 °C, although cyclization of **10c** was complete, decarboxylation was not totally achieved (Table 2, entries 4–6). At lower temperature (140 °C), small amounts of **11c** were formed and compound **6c** was not detected (Table 2, entry 7). Taking into consideration the mechanism of the full sequence, etherification produces $KHCO_3$ and KBr while decarboxylation leads to the formation of methanolate. This prompted us to explore the use of a K_2CO_3/KBr/$KHCO_3$/MeOH mixture (Table 2, entries 8–10). Surprisingly, under these conditions, decreasing the reaction time remarkably improved the formation of **6c** vs. **11c**. The next series of attempts suggested that the presence of both DMF and methanol was critical, ideally in a 1:0.5 ratio (Table 2, entries 11–14). Entry 13 showed also that additive salts finally were not required, and we were pleased to establish efficient conditions for the conversion of ether **10c** into benzofuranone **6c** (Table 2, entry 15).

Several ethers **10** were then submitted to this protocol. The simplest ether **10a** gave **6a** as the single product in greater yield than reported[9] (Table 3, entry 1).

Table 3. Conversion of ethers **10** into benzofuranones **6** using microwave irradiation



Entry	**10**	R	Product(s)	Yield[a] (%)
1	**10a**	H	**6a**	71
2	**10b**	4-NMe_2	**6b**	85
3	**10c**	4-OMe	**6c**	79
4	**10d**	5-OMe	**6d**	46
5	**10h**	[3,4]-benzo	**6h**	0
6	**10i**	4-NO_2	—	Decomposition
7	**10k**	4-Cl	**6k/12k**	7/22
8	**10l**	5-Br	**6l**	44

[a]Yield of isolated product after flash chromatography.

Compounds **10** bearing electron-donating groups on the aromatic moiety were easily converted into corresponding benzofuranones (Table 3, entries 2–4). Compound **10h** gave no reaction and was recovered (Table 3, entry 5). Introduction of an electron-withdrawing group on the aromatic ring was detrimental for the reaction, with decomposition being observed for the nitro derivative **10i** (Table 3, entry 6). The bromide derivative **10l** gave the benzofuranone **6l** in moderate yield (Table 3, entry 8). Unexpectedly, in the case of **10k**, the major product resulted from a SN_{Ar} reaction between two molecules of **6k** to give **12k** (Table 3, entry 7). This undesired reaction suggested that the presence of an electron withdrawing group in compound **6** reinforced the acidity of the α hydrogen of the carbonyl group. In the case of nitro derivative **10i**, it could lead to polymerization and explain the difficulty of isolating the corresponding benzofuranone.

We then examined the preparation of benzofuranones **6** from derivatives **8** under microwave irradiation using compound **8b** as the model (Table 4, entry 1),

Table 4. 300 W microwave irradiation on 2 mmol of **8b**[a]

				Product ratio[b] (%)			
Entry	**9** (equiv.)	Temperature (°C)	Time (min)	**8b**	**10b**	**11b**	**6b**
1	1	155	30	16	—	4	45
2	1	145	30	—	50	—	5
3	1.1	160	90	8	—	—	74
4	1.25	170	90	—	—	—	83

[a]Reagents: DMF (1 mL), K_2CO_3 (1.5 equiv.).
[b]Ratio evaluated on ^1H NMR spectrum of the crude material.

Table 5. Influence of the cation of carbonate salts and solvent on decarboxylation of **8a**[a]

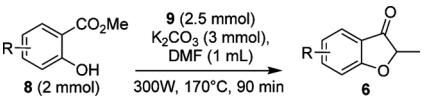
Entry	Cation	Solvent	**11a:6a**[b]
1	Li^+	DMF	9:1
2	Na^+	DMF	1:1
3	Cs^+	DMF	1.06:1
4	K^+	DMF	0.18:1
5	K^+	DMSO	2.67:1

[a]Reagents and conditions: **8a** (2 mmol), methyl 2-bromopropionate **9** (2.5 mmol), carbonate salt (3 mmol), solvent (1 mL), 170 °C, 300 W, 90 min.
[b]Ratio evaluated on ^{1}H NMR spectrum of the crude material.

at 300 W and 170 °C in DMF. The initial etherification of phenol **8b** appeared as a limiting step and a compromise was found between reaction time and complete etherification. An excess of bromide **9** (1.25 equivalents) finally gave compound **6b** as the sole product (Table 4, entries 3 and 4). Lower temperatures furnished mainly the ether **10b** (Table 4, entry 2). According to Krapcho,[11] several carbonate salts were examined to improve the decarboxylation of **8a** (R=H, Table 5). Only Na_2CO_3 or Cs_2CO_3 gave interesting results, although K_2CO_3 remained the most efficient salt in our cases. DMSO was the best solvent for the Krapcho reaction but gave no improvement in our case (Table 5, entry 5). The best conditions for direct formation of benzofuranones **6** from **8** remained K_2CO_3, DMF, 300 W, and 170 °C and were applied to other salicylate methyl esters **8** (Table 6).

Compounds bearing electron-donating groups were easily converted into corresponding benzofuranones **6** in moderate to good yields (Table 6, entries 1–7). Some

Table 6. Microwave assisted direct preparation of [2,3]-dihydro-benzofuran-3-ones **6** from **8**



			Products yield[a] (%)			
Entry	**8**	R	**8**	**10**	**11**	**6**
1	**8a**	H	—	—	11	60
2	**8b**	4-NMe_2	—	—	—	83
3	**8c**	4-OMe	—	—	—	80
4	**8e**	4-Me	—	—	17	71
5	**8f**	5-Me	—	—	—	52
6	**8g**	[4,5]-benzo	—	—	—	50
7	**8h**	[3,4]-benzo	—	—	—	30
8	**8i**	4-NO_2		Decomposition		
9	**8j**	5-NO_2		Decomposition		
10	**8k**	4-Cl	—	—	—	10
11	**8l**	5-Br	—	—	—	10

[a]Yield of isolated product after flash chromatography.

Table 7. 300 W microwave irradiation on halogenated and nitro salicylates[a]

Entry	**8**, R	Time (min.)	Temp. (°C)	Solvent	Products yield[c] (%)				
					8	**10**	**11**	**6**	**12**
1	**8k**, 4-Cl	60	170	DIPEA	Mixture[d]				
2	**8l**, 5-Br	60	170	DIPEA	Mixture[d]				
3	**8k**,4-Cl	60	100	NMM	—	19	—	15	30
4	**8l**,5-Br	60	130	NMM	—	39	3	4	—
5	**8l**,5-Br	60	100	CH_3CN	—	100	—	—	—
6	**8i**,4-NO_2	5	60	DMF	—	100	—	—	—
7	**8i**,4-NO_2	5 + 30[b]	155	DMF	—	—	—	2	—

[a]Reagents: K_2CO_3 (1.5 equiv.), **9** (1.25 equiv.).
[b]5 min at 60 °C followed by 30 min at 155 °C.
[c]Yield of isolated product after flash chromatography.
[d]We were not able to analyze this complex mixture.

amounts of nondecarboxylated intermediate **11** were generated with less donating groups (Table 6, entries 1 and 4). However, this microwave-assisted one-pot procedure gave better yields than the respective thermal experiments and ratios **11** vs. **6** were highly in favor of decarboxylated derivatives. No traces of benzofuranones were detected in mixtures obtained from nitro derivatives **8i** and **8j** (Table 6, entries 8 and 9). For halogenated compounds, benzofuranones **6k** and **6l** were isolated in poor yields (Table 6, entries 10 and 11), and it is noteworthy that the two-step strategy was more efficient in these cases.

To optimize microwave reactions in the nitro and halogenated series, other solvents were investigated (Table 7). Attempts with diisopropylethylamine (DIPEA) at 170 °C failed, leading to complex mixtures (Table 6, entries 1 and 2). Despite our efforts, N-methylmorpholine (NMM) did not furnish a significant improvement

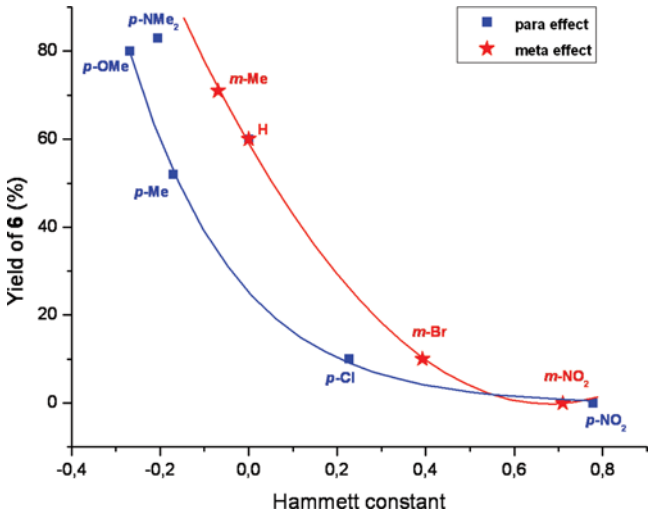


Figure 2. Yield of **6** = f (Hammett constant). (Figure is provided in color online.)

(Table 7, entry 4). Nevertheless, some interesting results were noticed at lower temperatures. At 100 °C, **8k** underwent an intermolecular reaction to yield the dimer **12k** already seen in the two-step approach (Table 7, entry 3). The same temperature in acetonitrile allowed a quantitative conversion of **8l** into ether **10l**, which affords an alternative to Bogdal's procedure (Table 7, entry 5).[13] A complete etherification, carried out in DMF with mild heating, was also observed for nitro derivative **8i** (Table 7, entry 6). This crude material was then subjected to extra microwave irradiation at a higher temperature and decomposition occurred (Table 7, entry 7). These results confirmed that temperature around 150–170 °C was necessary for an efficient cyclization into benzofuranone but nitro and halogenated compounds were not stable in these conditions. The yield variability in benzofuranone **6** prompted us to correlate our results by the Hammett constants.[14] The methyl ester group on the aromatic moiety was chosen as reference, and *meta* and *para* effects were considered. A graphical representation of these data clearly indicated that a relation between isolated yields for the direct preparation of **6** from **8** and Hammett constants can be proposed (Fig. 2).

CONCLUSION

In conclusion, a new microwave-assisted route for the preparation of [2,3]-dihydrobenzofuran-3-ones **6** is reported. A two-step methodology involving a preliminary etherification of salicylate esters allowed the access to benzofuranones. This approach is particularly attractive for halogenated derivatives as it opens the way to various substituents using organometallic chemistry. A direct and easy conversion of salicylate esters into benzofuranones **6** was also developed. This one-pot protocol was suitable for compounds bearing electron-donating groups. An alternative microwave-assisted method is proposed to prepare ethers **10**. The reactivity of salicylate derivatives has been correlated by the Hammett constants, and this study may be used as a predictive tool. Further studies are currently devoted to the use of these benzofuranones as valuable scaffolds for the synthesis of biologically relevant compounds.

EXPERIMENTAL

Salicylate Ethers 10

K_2CO_3 (0.152 g, 1.1 mmol) and methyl 2-bromopropionate **9** (0.14 mL, 1.25 mmol) were added to a solution of salicylate ester **8** (1 mmol) in dry DMF (1 mL). After 12 h, the mixture was diluted with AcOEt (5 mL), washed with 1 N HCl (5 mL), and dried ($MgSO_4$). The crude residue was then concentrated and purified by column chromatography (petroleum ether/EtOAc; 85/15), providing **10**.

4-Methoxy-2-(1-methoxycarbonyl-ethoxy)-benzoic acid methyl ester 10c. Prepared from **8c** (5.12 g, 28 mmol) and isolated as oil (7.66 g, 94%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.67 (d, 3H, $J = 6.8$ Hz), 3.78 (s, 3H), 3.80 (s, 3H), 3.86 (s, 3H), 4.77 (q, 1H, $J = 6.8$ Hz), 6.40 (s, 1H), 6.56 (d, 1H, $J = 8.4$ Hz), 7.86 (d, 1H, $J = 8.4$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.5, 51.7, 52.4, 55.5, 74.6,

102.3, 106.5, 113.7, 133.95, 159.3, 163.9, 165.9, 172.3; HR-EIMS MNa^+, found: 291.0846. $C_{13}H_{16}O_6Na$ requires 291.08446.

5-Methoxy-2-(1-methoxycarbonyl-ethoxy)-benzoic acid methyl ester 10d. Prepared from **8d** (1.25 g, 6.87 mmol) and isolated as oil (1.65 g, 90%). ^1H NMR (400 MHz, $CDCl_3$): δ 1.69 (d, 3H, $J = 6.8$ Hz), 3.71 (s, 3H), 3.75 (s, 3H), 3.86 (s, 3H), 4.64 (q, 1H, $J = 6.8$ Hz), 6.88 (d, 1H, $J = 9.0$ Hz), 6.94 (dd, 1H, $J = 3.1$, 9.0 Hz), 7.30 (d, 1H, $J = 3.1$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.6, 52.2, 52.3, 55.8, 76.3, 115.8, 119.3, 119.5, 122.9, 151.4, 154.5, 166.3, 172.7; HR-EIMS MNa^+, found: 291.0844. $C_{13}H_{16}O_6Na$ requires 291.08446.

1-(1-Methoxycarbonyl-ethoxy)-naphthalene-2-carboxylic acid methyl ester 10h. Prepared from **8h** (2.02 g, 10 mmol) as light brown solid (2.2 g, 75%). ^1H NMR (400 MHz, $CDCl_3$): δ 1.61 (d, 3H, $J = 6.9$ Hz), 3.71 (s, 3H), 3.93 (s, 3H), 4.85 (q, 1H, $J = 6.8$ Hz), 7.50–7.59 (m, 2H), 7.61 (d, 1H, $J = 8.7$ Hz), 7.81 (dd, 1H, $J = 1.8$, 7.4 Hz), 7.87 (d, 1H, $J = 8.7$ Hz), 8.41 (br d, 1H, $J = 7.4$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.6, 52.2, 52.4, 80.2, 118.8, 124.0, 124.5, 126.5, 126.8, 127.6, 128.6, 129.3, 136.7, 155.6, 166.7, 172.1; HR-EIMS MNa^+, found: 311.0887. $C_{16}H_{16}O_5Na$ requires 311.08954.

4-Nitro-2-(1-methoxycarbonyl-ethoxy)-benzoic acid methyl ester 10i. Prepared from **8i** (8.27 g, 42 mmol) and isolated as white solid (9.6 g, 81%).^1H NMR (400 MHz, $CDCl_3$): δ 1.74 (d, 3H, $J = 6.8$ Hz), 3.82 (s, 3H), 3.96 (s, 3H), 4.93 (q, 1H, $J = 6.8$ Hz), 7.70 (d, 1H, $J = 1.9$ Hz), 7.90 (dd, 1H, $J = 1.9$, 8.5 Hz), 7.94 (d, 1H, $J = 8.5$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.3, 52.6, 52.7, 74.3, 109.4, 116.1, 127.3, 132.4, 150.4, 157.3, 165.1, 171.1; HR-EIMS MNa^+, found: 306.0590. $C_{12}H_{13}NO_7Na$ requires 306.05897.

4-Chloro-2-(1-methoxycarbonyl-ethoxy)-benzoic acid methyl ester 10k. Prepared from **8k** (11.1 g, 59.5 mmol) and isolated as pale orange solid (14.0 g, 86%). ^1H NMR (400 MHz, $CDCl_3$): δ 1.67 (d, 3H, $J = 6.8$ Hz), 3.78 (s, 3H), 3.89 (s, 3H), 4.77 (q, 1H, $J = 6.8$ Hz), 6.85 (d, 1H, $J = 1.9$), 7.02 (dd, 1H, $J = 1.9$, 8.4 Hz), 7.77 (d, 1H, $J = 8.4$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.6, 52.3, 52.6, 74.7, 115.9, 120.0, 122.1, 133.1, 139.2, 158.0, 165.7, 171.9; HR-EIMS MNa^+, found: 295.0349. $C_{12}H_{13}O_5\ ^{35}ClNa$ requires 295.03492.

5-Bromo-2-(1-methoxycarbonyl-ethoxy)-benzoic Acid Methyl Ester 10l. Prepared from **8l** (10.32 g, 44.7 mmol) and isolated as yellow solid (12.2 g, 86%). ^1H NMR (400 MHz, $CDCl_3$): δ 1.67 (d, 3H, $J = 6.8$ Hz), 3.78 (s, 3H), 3.89 (s, 3H), 4.77 (q, 1H, $J = 6.8$ Hz), 6.85 (d, 1H, $J = 1.9$), 7.02 (dd, 1H, $J = 1.9$, 8.4 Hz), 7.77 (d, 1H, $J = 8.4$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.5, 52.3, 52.5, 74.7, 117.3, 123.3, 134.5, 136.0, 156.4, 165.1, 172.0; HR-EIMS MNa^+, found 338.9844. $C_{12}H_{13}O_5\ ^{79}BrNa$ requires 338.9844.

Ether 10 preparation by microwave procedure. K_2CO_3 (0.207 g, 1.5 mmol) and methyl 2-bromopropionate **9** (0.14 mL, 1.25 mmol) were added to a solution of salicylate ester **8i** (0.197 g, 1 mmol) in DMF (1 mL). The mixture was heated at 60 °C for 5 min under stirring and 300 W microwave irradiation power. After cooling to ambient temperature, AcOEt (5 mL) was added. The resulting organic layer was washed with 1 N HCl (5 mL) and dried on $MgSO_4$. The crude

residue was then concentrated and purified by column chromatography (petroleum ether/AcOEt; 85/15), providing **10i** as a white solid (0.283 g, 100%).

Compound **10l** also prepared as **10i** from ester **8l** (0.230 g, 1 mmol) in acetonitrile (1 mL), K_2CO_3 (0.207 g, 1.5 mmol) and methyl 2-bromopropionate **9** (0.14 mL, 1.25 mmol) as a yellow solid (0.316 g, 100%).

Synthesis of [2,3]-Dihydro-benzofuran-3-ones 6 from Salicylate Ethers 10

K_2CO_3 (0.069 g, 0.5 mmol) were added to a solution of salicylate ether **10** (1 mmol) in DMF/MeOH (1 mL/0.5 mL). The mixture was heated at 170 °C for 10 min under stirring and 300 W microwave irradiation power. After cooling to ambient temperature, the mixture was diluted with EtOAc (5 mL). The resulting organic layer was washed with 1 N HCl (5 mL) and dried ($MgSO_4$). The crude residue was then concentrated and purified by column chromatography (petroleum ether/EtOAc; 85/15), providing **6**.

5-Methoxy-2-methyl-benzofuran-3-one 6d. Prepared from **10d** (0.268 g, 1 mmol) and isolated as a colorless oil (0.083 g, 46%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.50 (d, 3H, $J = 7.2$ Hz), 3.77 (s, 3H), 4.62 (q, 1H, $J = 7.2$ Hz), 6.99–7.03 (m, 2H), 7.22 (dd, 1H, $J = 2.9$, 8.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.3, 56.0, 82.7, 104.2, 114.5, 120.3, 128.2, 155.0, 167.9, 202.9; HR-EIMS MNa^+, found 201.0530. $C_{10}H_{10}O_3Na$ requires 201.05276.

6-Chloro-2-methyl-benzofuran-3-one 6k. Prepared from **10k** (0.273 g, 1 mmol) and isolated as a colorless oil (0.013 g, 7%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.51 (d, 3H, $J = 7.2$ Hz), 2.43 (s, 3H), 4.62 (q, 1H, $J = 7.1$ Hz), 6.89 (m, 2H), 7.54 (dd, 1H, $J = 1.2$, 7.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.4, 83.7, 111.0, 117.7, 119.8, 130.9, 141.4, 170.0, 203.9; HR-EIMS MNa^+, found 205.0041. $C_9H_7O_2$ ^{35}ClNa requires 205.00323.

Dimer 12k[15]. Prepared from **10k** (0.273 g, 1 mmol) and isolated as a colorless oil (0.072 g, 22%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.51 (d, 3H, $J = 8.0$ Hz), 2.40 (s, 3H), 4.64 (q, 1H, $J = 8.0$ Hz), 6.54 (d, 1H, $J = 2.0$ Hz), 6.78 (dd, 1H, $J = 4.0$, 8.0 Hz), 7.13 (m, 2H), 7.42 (dd, 1H, $J = 4.0$, 8.0 Hz), 7.60 (d, 1H, $J = 8$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 16.9, 17.5, 86.1, 94.8, 112.3, 114.4, 120.0, 123.3, 127.6, 129.9, 132.9, 135.2, 139.0, 140.9, 169.3, 170.2, 200.8, 201.6; HR-EIMS MNa^+, found 351.0406. $C_{18}H_{13}O_4$ ^{35}ClNa requires 351.04001.

5-Bromo-2-methyl-benzofuran-3-one 6l. Prepared from **10l** (0.316 g, 1 mmol) and isolated as a colorless oil (0.099 g, 44%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.45 (d, 3H, $J = 7.2$ Hz), 4.60 (q, 1H, $J = 7.2$ Hz), 6.94 (d, 1H, $J = 8.7$ Hz), 7.60 (dd, 1H, $J = 2.2$, 8.7 Hz), 7.69 (d, 1H, $J = 2.2$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 16.5, 82.8, 114.5, 115.5, 122.3, 127.1, 140.7, 171.3, 201.1; HR-EIMS MNa^+, found 249.0231. $C_9H_7O_2$ ^{79}BrNa requires 249.01972.

Synthesis of [2,3]-Dihydro-benzofuran-3-ones 6 from Salicylate Esters 8

K_2CO_3 (0.414 g, 3 mmol) and methyl 2-bromopropionate **9** (0.28 mL, 2.5 mmol) were added to a solution of salicylate ester **8** (2 mmol) in DMF (1 mL). The mixture was heated at 170 °C for 90 min under stirring and 300 W microwave irradiation power. After cooling to ambient temperature, EtOAc (5 mL) was added. The resulting organic layer was washed with 1 N HCl (5 mL) and dried ($MgSO_4$). The crude residue was then concentrated and purified by column chromatography (petroleum ether/EtOAc; 85/15), providing **6**.

6-Methoxy-2-methyl-benzofuran-3-one 6c. Prepared from **8c** (0.268 g, 1 mmol) and isolated as a colorless oil (0.142 g, 80%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.52 (d, 3H, $J = 6.7$ Hz), 3.80 (s, 3H), 3.86 (s, 3H), 3.89 (s, 3H), 4.65 (q, 1H, $J = 6.7$ Hz), 6.51 (s, 1H), 6.4 (d, 1H, $J = 8.3$ Hz), 7.55 (d, 1H, $J = 8.3$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 16.6, 55.9, 82.8, 96.2, 111.7, 113.5, 125.5, 168.4, 174.9, 200.2; HR-EIMS MNa^+, found 201.0528. $C_{10}H_{10}O_3Na$ requires 201.05276.

2,6-Dimethyl-benzofuran-3-one 6e. Prepared from **8e** (0.252 g, 1 mmol) and isolated as a yellow solid (0.115 g, 71%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.44 (d, 3H, $J = 7.2$ Hz), 2.27 (s, 3H), 4.54 (q, 1H, $J = 7.1$ Hz), 6.93 (dd, 1H, $J = 1.6$, 7.4 Hz), 7.35 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 16.4, 20.6, 82.0, 113.1, 120.3, 123.7, 131.5, 139.3, 170.9, 202.6; HR-EIMS MNa^+, found 185.0580. $C_{10}H_{10}O_2Na$ requires 185.05785.

2,6-Dimethyl-3-oxo-2,3-dihydro-benzofuran-2-carboxylic acid methyl ester 11e. Prepared from **8e** (0.252 g, 1 mmol) and isolated as a colorless oil (0.037 g, 17%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.38 (s, 3H), 2.43 (s, 3H), 3.92 (s, 3H), 7.00 (dd, 1H, $J = 0.5$, 7.3 Hz), 7.14 (t, 1H, $J = 0.4$ Hz), 7.39 (d, 1H, $J = 7.9$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 17.3, 22.0, 52.0, 91.0, 109.8, 117.7, 120.4, 129.7, 147.0, 161.6, 170.6, 203.1; HR-EIMS MNa^+, found 243.0731. $C_{12}H_{12}O_4Na$ requires 243.07356.

2,5-Dimethyl-benzofuran-3-one 6f. Prepared from **8f** (0.252 g, 1 mmol) and isolated as a colorless oil (0.084 g, 52%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.51 (d, 3H, $J = 7.2$ Hz), 2.43 (s, 3H), 4.62 (q, 1H, $J = 7.1$ Hz), 6.89 (m, 2H), 7.54 (dd, 1H, $J = 1.2$, 7.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 16.5, 22.5, 82.1, 113.5, 118.0, 123.5, 124.0, 150.0, 173.0, 201.9; HR-EIMS MNa^+, found 185.0577. $C_{10}H_{10}O_2Na$ requires 185.05785.

2-Methyl-naphtho[2,3-b]furan-3-one 6g. Prepared from **8g** (0.288 g, 1 mmol) and isolated as a colorless oil (0.99 g, 50%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.58 (d, 3H, $J = 7.2$ Hz), 4.72 (q, 1H, $J = 7.2$ Hz), 7.38 (m, 2H), 7.55 (td, 1H, $J = 1.2$, 6.8 Hz), 7.78 (d, 1H, $J = 8.5$ Hz), 7.91 (d, 1H, $J = 8.4$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 16.8, 81.9, 107.6, 121.3, 124.7, 126.1, 127.4, 129.7, 130.9, 139.7, 140.7, 165.7, 203.1; HR-EIMS MNa^+: found 221.0576. $C_{13}H_{10}O_2Na$ requires 221.05785.

2-Methyl-naphtho[1,2-b]furan-3-one 6h. Prepared from **8h** (0.288 g, 1 mmol) and isolated as a colorless oil (0.59 g, 30%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.64 (d, 3H, $J = 7.2$ Hz), 4.85 (q, 1H, $J = 7.2$ Hz), 7.45 (d, 1H, $J = 8.5$ Hz), 7.56

(d, 1H, $J = 8.5$ Hz), 7.60 (td, 1H, $J = 1.1$, 7.0 Hz), 7.71 (td, 1H, $J = 1.3$, 7.0 Hz), 7.88 (d, 1H, $J = 8.3$ Hz), 8.25 (md, 1H, $J = 7.1$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 16.8, 81.9, 105.6, 118.6, 123.9, 124.2, 124.8, 125.8, 127.5, 129.4, 137.2, 171.5, 203.1; HR-EIMS MNa^+, found 221.0581. $C_{13}H_{10}O_2Na$ requires 221.05785.

6-Nitro-2-methyl-benzofuran-3-one 6l. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.45 (d, 3H, $J = 7.2$ Hz), 4.60 (q, 1H, $J = 7.2$ Hz), 6.94 (d, 1H, $J = 8.7$ Hz), 7.60 (dd, 1H, $J = 2.2$, 8.7 Hz), 7.69 (d, 1H, $J = 2.2$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 16.5, 82.8, 114.5, 115.5, 122.3, 127.1, 140.7, 171.3, 201.1; HR-EIMS MNa^+, found: 249.0231. $C_9H_7O_2$ ^{79}BrNa requires 249.01972.

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(Ether **10k** furnished **12k** as major product under these conditions.)